eAn Open-label, Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-cell Malignancies

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List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AIDS	acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_t	area under the concentration-time curve from time 0 to last measurable concentration
βhCG	beta human chorionic gonadotropin
BAFF	B-cell activating factor
BCR	B-cell receptor
BM	bone marrow
CD	cluster of differentiation
CHO	Chinese hamster ovary (cell line)
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form
CT	computed tomography
DHAP	dexamethasone-cytarabine-cisplatin
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC_{90}	90% effective concentration
ECG	electrocardiogram
EOT	end of treatment
EU	European Union
FcγR	crystalline fragment gamma receptor
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FL	follicular lymphoma
GCP	Good Clinical Practices
GGT	gamma glutamyl transferase
HAHA	human anti-human antibodies

Abbreviation	Definition
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSC	hematopoietic stem cell
huCD19	human CD19
ICE	ifosfamide-carboplatin-etoposide
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	immunogenicity
IRB	Institutional Review Board
IRR	infusion-related reaction and infusion reaction
IV	intravenous(ly)
IVRS	interactive voice response system
Kd	dissociation constant
MAb	monoclonal antibody
MCL	mantle cell lymphoma
MEDI-551	a humanized monoclonal antibody directed against CD19
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MM	multiple myeloma
MRD	minimal residual disease
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NaCl	sodium chloride
NCI CTCAE V4.03	National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
NHL	non-Hodgkin lymphoma
NK	natural killer
NMO	neuromyelitis optica
OBD	optimal biologic dose
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
PR	partial response
QTc	corrected QT interval
RNA	ribonucleic acid

Abbreviation	Definition
SAE	serious adverse event
SC	subcutaneous
SCT	stem cell transplant(ation)
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
SPEP	serum protein electrophoresis
SLL	small lymphocytic lymphoma
$t_{½}$	terminal phase half-life
Tg	transgenic
TTR	time to response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
WBC	white blood cell
WHO	World Health Organization

Study Abstract

TITLE

An Open-label, Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-cell Malignancies

OBJECTIVES

Primary Objectives:

Arm A (MEDI-551 monotherapy in advanced B-cell malignancies)

- To determine the maximum tolerated dose (MTD) or optimal biologic dose (OBD) of MEDI-551 in subjects with relapsed or refractory advanced B-cell malignancies (chronic lymphocytic leukemia [CLL], including small lymphocytic lymphoma [SLL], diffuse large B-cell lymphoma [DLBCL], and follicular lymphoma [FL])
- To determine the preliminary safety profile of MEDI-551

Arm B (MEDI-551 monotherapy in CLL)

Dose Escalation

- To determine the MTD or highest protocol-defined dose of MEDI-551 in the absence of exceeding the MTD in subjects with relapsed or rituximab-refractory CLL (defined as those with less than a partial response [PR] or progression within 6 months after completing therapy with rituximab)

Dose Expansion

- To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL
- To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL

Arm C (MEDI-551 combined with rituximab in aggressive lymphoma)

Dose Escalation

- To determine the safety and tolerability of MEDI-551 in combination with rituximab at the MTD or the highest protocol-defined dose in the absence of exceeding the MTD in subjects with aggressive lymphomas

Dose Expansion

- To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in combination with rituximab in subjects with aggressive lymphomas
- To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in combination with rituximab in relapsed and rituximab-refractory population (defined as those with less than a PR or progression within 6 months after completing therapy with rituximab)

Arm D (MEDI-551 monotherapy in any anti-CD20-refractory aggressive lymphoma)

- To evaluate the clinical activity of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas (defined as any subject with less than a PR to any prior anti-CD20-based therapy or progression within 6 months after completing therapy with any anti-CD20-based regimen, including maintenance rituximab)

Secondary Objectives:

Arm A

- To determine the preliminary efficacy profile of MEDI-551 in subjects with advanced B-cell malignancies (CLL [including SLL], DLBCL, and FL)
- To determine the pharmacokinetics (PK) of MEDI-551 in subjects with advanced B-cell malignancies
- To determine the effect of treatment with MEDI-551 on circulating lymphocyte populations and immunoglobulin (Ig) levels, including time to recovery after treatment

- To determine the immunogenicity (IM) of MEDI-551 in subjects with advanced B-cell malignancies

Arm B

- To evaluate the PK and IM of MEDI-551 at doses studied in subjects with relapsed or rituximab-refractory CLL
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm C

- To evaluate the PK and IM of MEDI-551 when administered in combination with rituximab in subjects with aggressive lymphomas
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm D

- To determine the safety and tolerability of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas
- To evaluate the PK and IM of MEDI-551
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Exploratory Objective:

Arm B

- [redacted]

STUDY DESIGN

This is a Phase 1/2, multicenter, international, open-label, dose-escalation and expanded cohort study to evaluate the safety, tolerability, and potential antitumor activity of MEDI-551 as single agent or in combination with rituximab in adult subjects with advanced B- cell malignancies. The study design of Arm A comprises a dose-escalation phase followed by a dose-expansion phase in subjects with advanced B-cell malignancies receiving single-agent MEDI-551. This study arm included participants from 21 investigational sites in the United States (US), Canada, and European Union (EU). As of Version 10.0 of the protocol, the study design also includes dose escalation and expansion in subjects with CLL receiving single-agent MEDI-551 (Arm B), and dose escalation and expansion in subjects with aggressive lymphoma receiving MEDI-551 combined with rituximab (Arm C). As of Version 11.0 of the protocol, the study design also includes subjects with any anti-CD20-refractory aggressive lymphoma receiving single-agent MEDI-551 (Arm D). Arms B, C, and D were to include participants from 20 investigational sites in the US and 10 to 15 sites in the EU.

Enrollment in the study was closed as of 30Sep2015. As of 19Jan2017, 9 subjects remain on treatment; all have completed at least 1 year of treatment. All subjects who are currently receiving MEDI-551 treatment may continue to receive MEDI-551 until disease progression, unacceptable toxicity, complete response (CR), withdrawal of consent, or another reason to discontinue therapy intervenes. Subjects who achieve CR (complete response) may receive 2 additional cycles at the same dose prior to EOT (End of Treatment). A simplified schedule of evaluations focused on safety will be used. Safety follow-up assessments will be conducted at the EOT Visit (defined as the last day of the last cycle of investigational product administration) as well as at the 90-Day Post Last Dose Visit, which will serve as the End of Study Visit. Long-term follow-up for progression-free survival and overall survival will not be performed following implementation of Version 13.0.

Arm A

Enrollment in the dose-escalation and expansion phases of Arm A is complete. Protocol Version 4.0 was amended to make the study population for dose-escalation inclusive of subjects with FL, multiple myeloma (MM), CLL, or DLBCL. Dose escalation in Arm A began in subjects with FL or MM per protocol Versions 1.0 through 4.0. Subjects were enrolled into the first 2 cohorts under these versions of the protocol. Starting with Version 5.0 of the protocol, enrollment in dose-escalation Cohorts 3 and higher was open to subjects with the following advanced B-cell malignancies: FL, MM, CLL, or DLBCL. Subjects in Cohorts 1 and 2 continued to follow the protocol Version 4.0 dose schedule of 0.5 mg/kg (Cohort 1) or 1 mg/kg (Cohort 2) MEDI-551 administered intravenously (IV) once every week in 4-week cycles. Subjects enrolled in Cohorts 3 and higher received 2, 4, 8, or 12 mg/kg MEDI-551 (Cohorts 3 to 6, respectively) IV once per week on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle. As per Cohorts 1 and 2, dosing in Cohorts 3 and higher followed a standard 3+3 dose-escalation scheme. Subjects in Arm A were not to receive a MEDI-551 dose greater than 12 mg/kg. No intrasubject dose escalation was allowed.

A total of approximately 18 to 36 evaluable subjects were required for the dose-escalation phase; 26 were enrolled. Subjects were considered evaluable if they received at least 1 full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completed the safety follow-up through the dose-limiting toxicity (DLT) evaluation period, or experienced any DLT. Non-evaluable subjects were to be replaced in the same dose cohort. Dose escalation continued until the MTD (if ≤ 12 mg/kg), the 12-mg/kg maximum dose, or a lower dose (optimum biological dose or the OBD) was reached.

Following determination of the MTD or OBD, approximately 60 subjects total, 20 subjects each with FL, CLL, or DLBCL, were to be enrolled in the expansion phase of Arm A to determine the preliminary efficacy profile of MEDI-551 in the treatment of advanced B-cell malignancies. A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled. Under previous versions of the protocol, the expansion phase was to also include 20 subjects with MM. Enrollment of subjects with MM into the expansion phase was discontinued based on data from this study and recent nonclinical studies suggesting a lack of activity in the advanced/refractory MM setting. As of Version 8.0 of the protocol (and following enrollment of 1 MM subject), subjects with MM were not to be enrolled. Subjects in the expansion phase were treated on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle at the maximum dose tested in the dose-escalation phase, 12 mg/kg or OBD as determined in the dose escalation phase.

A preplanned interim safety analysis, as defined in the statistical analysis plan, was undertaken after reaching the maximum dose in the escalation phase to examine treatment effects on key safety endpoints. The analysis was performed and the protocol was amended (Version 7.0) to include the results of the analysis. An MTD or OBD was not identified in the dose-escalation phase of Arm A, so the maximum dose of 12 mg/kg was used for the expansion phase of this arm. Different dose levels or dosing schedules could be evaluated in the expansion phase if all available safety, PK, pharmacodynamic, and efficacy data suggested that evaluation of different dose levels, dosing schedules and/or duration of treatment would be beneficial.

All subjects who are currently receiving MEDI-551 treatment may continue to receive MEDI-551 until disease progression, unacceptable toxicity, CR, withdrawal of consent, or another reason to discontinue therapy intervenes. Subjects who achieve CR may receive 2 additional cycles at the same dose prior to EOT. Once Version 13.0 is in effect, re-treatment will not be available for subjects who achieve a CR and subsequently relapse while off treatment. Prior to Version 13.0, the US Food and Drug Administration was to be consulted concerning the possibility of additional treatment with MEDI-551 for subjects within the US and US subjects enrolled in Arm A could have been retreated at the 12-mg/kg dose at the discretion of the investigator and after discussion with the sponsor. Non-US subjects in Arm A were not to be retreated with MEDI-551 on subsequent relapse.

Safety follow-up assessments will be conducted at the EOT Visit (defined as the last day of the last cycle of investigational product administration) as well as at the 90-Day Post Last Dose Visit (defined as 90 days after the last dose of MEDI-55), which will serve as the End of Study Visit. In addition, prior to implementation of Version 13.0, all subjects were followed for disease evaluation every 3 months after the 90-Day Post Last Dose Visit until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study and for survival every 3 months until death, withdrawal of consent, or end of the study. Once Version 13.0 is in effect, all subjects who have completed treatment and safety follow-up will be considered to have completed the study.

Arm B

Enrollment in Arm B is complete. Based on evaluation of the PK data in CLL subjects (n = 26) from Arm A, there appeared to be lack of full exposure and numerically lower response rate compared to non-CLL subjects using the monthly dosing regimen at the highest dose evaluated (ie, 12 mg/kg). This arm of the study evaluated further dose escalation in CLL subjects utilizing a new schema, designed to saturate the potential B-cell sink, achieve full exposure, and maximize clinical activity, by employing weekly dosing of MEDI-551 for 4 weeks during Cycle 1 and then monthly dosing on Day 1 of each subsequent 28-day cycle to determine the MTD or the highest protocol-defined dose in the absence of exceeding the MTD, which would be evaluated subsequently in a dose-expansion phase. To further minimize infusion-related reactions at higher dose levels, for the 24 and 48 mg/kg dose levels of MEDI-551, the initial weekly doses were to be administered over 2 days on Day 1 and Day 2 in Cycle 1. Subsequent doses at the 24 and 48 mg/kg dose levels were to be administered in an identical fashion to lower dose levels (ie, weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond). Note that the 48 mg/kg cohort was not enrolled.

Using a standard 3+3 design, 3 to 6 subjects with CLL were to be enrolled per cohort, starting at a dose of 6 mg/kg and escalating to 3 additional dose levels (12, 24, and 48 mg/kg) in the dose-escalation phase of this arm. If 0 of 3 or ≤1 of 6 subjects treated at the previous dose level experienced a DLT, dose escalation could continue. The MTD was defined as the dose at which no more than 1 of 6 subjects experienced a DLT during Cycle 1. No intra-subject dose escalation was allowed. Subjects were considered evaluable for a DLT if they completed the first cycle of therapy or discontinued therapy during Cycle 1 due to a DLT. Nonevaluable subjects would be replaced in the same dose cohort. A total of up to 24 subjects were to be enrolled in the dose-escalation portion of this arm. Dose escalation was permitted after all investigators reviewed the available data and unanimously agreed during a data review meeting to proceed with enrollment into the next cohort. The outcome from this meeting was documented in writing and shared with all participating sites.

Once an MTD was identified or the maximum planned dose not exceeding the MTD was reached, additional CLL subjects were to be enrolled at the selected dose in the dose-expansion phase to ensure a total of 26 efficacy evaluable subjects were available for analysis after completing one post-treatment disease evaluation. The dose-expansion phase was to include subjects treated at the MTD or maximum planned dose enrolled in the dose-escalation phase of this arm.

Based on emerging PK and pharmacodynamic data, a dose of 12 mg/kg, administered weekly during Cycle 1 and then monthly in subsequent cycles, was determined to be sufficient to saturate the B-cell sink and achieve

full exposure. A single subject was enrolled in the 24 mg/kg cohort; at the sponsor's discretion and not due to any safety issues, no further dose-escalation was conducted and Arm B dose-expansion was not conducted. The MTD was not reached.

Arm C

Enrollment in Arm C is complete. Given the high unmet medical need in patients with multiply relapsed aggressive lymphoma, the synergistic activity observed in preclinical studies with MEDI-551 and rituximab, as well as the promising clinical activity seen with other dual monoclonal antibody (MAb) combinations in patients with B-cell malignancies, this arm of the study evaluated the safety and efficacy of MEDI-551 in combination with rituximab in subjects with aggressive lymphoma (relapsed or refractory DLBCL, Grade 3b FL, FL transforming to DLBCL and mantle cell lymphoma [MCL]). Using a standard 3+3 design, 3 to 6 subjects with aggressive non-Hodgkin lymphoma (NHL) were enrolled per cohort in the dose-escalation portion of this arm, starting at a MEDI-551 dose of 8 mg/kg and escalating to 12 mg/kg. This population received 8 mg/kg of MEDI-551 on Days 2 and 8 of Cycle 1 and Day 1 of Cycle 2, and beyond in 28-day cycles along with weekly rituximab for 8 weeks beginning on Day 1 of Cycle 1. Dose escalation continued to 12 mg/kg if 0 of 3 or $\leq$ 1 of 6 subjects treated at the lower dose experienced a DLT. The MTD was defined as the dose at which no more than 1 of 6 subjects experienced a DLT. No intrasubject dose escalation was allowed. Subjects were considered evaluable for a DLT if they completed the first cycle of therapy or discontinued therapy during Cycle 1 due to a DLT. Nonevaluable subjects were to be replaced in the same dose cohort. A total of up to 12 subjects were to be enrolled in the dose-escalation portion of this arm of the study. Dose escalation was permitted after all investigators reviewed the available data during a data review meeting and unanimously agreed to proceed with enrollment into the next cohort. The outcome from this meeting was documented in writing and shared with all participating sites.

Once an MTD was identified or the maximum planned dose not exceeding the MTD was reached, additional subjects would be enrolled and treated at the selected dose of MEDI-551 in combination with rituximab in the dose-expansion portion of this arm to ensure a total sample size of 26 efficacy evaluable subjects were available for analysis after completing one post-treatment disease evaluation. The 26 subjects were to include subjects treated at the selected dose during the dose-escalation portion of this arm.

The maximum planned dose of 12 mg/kg was evaluated and MTD was not reached. Further enrollment was halted at the sponsor's discretion (and not due to any safety issues) after enrollment of 19 subjects (3 in the 8 mg/kg MEDI-551 cohort and 16 subjects who received 12 mg/kg MEDI-551). Of the 19 subjects there were only 7 responders, and there was approximately a 13% probability of meeting the protocol-specified target response rate of 50%.

Subjects in Arm C were stratified by their responsiveness to any prior anti-CD20-based therapy with the option of ensuring a minimum number of 7 subjects who were refractory to any anti-CD20-based therapies were enrolled if clinical data from Arm D or emerging preclinical data suggested that the combination of anti-CD20 and anti-CD19 therapies improve response in this subpopulation.

Arm D

Enrollment in Arm D is complete. Given the high unmet medical need in patients with refractory aggressive lymphoma and in light of preservation of CD19 expression on the surface of these malignant cells, MEDI-551 may represent a salvage therapy option for anti-CD20-refractory patients. With evidence of clinical activity and safety of MEDI-551 established in an unselected relapsed refractory lymphoma population (Arm A), Arm D was added to investigate MEDI-551 in the anti-CD20-refractory population. Arm D evaluated the efficacy of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphoma (refractory DLBCL, Grade 3b FL, FL transforming to DLBCL, and MCL).

Since the safety and tolerability of the 12-mg/kg dose of MEDI-551 had been verified in Arm A, approximately 26 subjects with any anti-CD20-refractory disease were to be enrolled and treated with single-agent MEDI-551 at the dose and schedule used in the expansion cohort of Arm A (ie, 12 mg/kg of MEDI-551 on Days 1 and 8 of Cycle 1, and on Day 1 of Cycle 2 and beyond in 28-day cycles).

Further enrollment was halted at the sponsor's discretion (and not due to any safety issues) after enrollment of 16 subjects. Of the 16 subjects there were only 3 responders, and there was approximately a 1% probability of meeting the protocol-specified target response rate of 50%.

SUBJECT POPULATION

The subjects in this study are adults with relapsed or refractory B-cell malignancies: CLL, including SLL, DLBCL, FL, MCL, and transformed indolent lymphoma.

SUMMARY OF ELIGIBILITY CRITERIA

Select Inclusion Criteria

- Men or women at least 18 years of age or older at time of study entry
- Diagnosis
  - Arm A: CLL (including SLL), DLBCL, or FL; SLL, DLBCL, and FL must be histologically confirmed
  - Arm B: Histologically-confirmed SLL or previous confirmation of B-cell CLL with a characteristic immunophenotype by flow cytometry
  - Arm C: Histologically-confirmed aggressive B-cell DLBCL, including FL transforming to DLBCL, transformed indolent lymphoma, MCL, or Grade 3b FL, according to the World Health Organization (WHO)/American Joint Committee on Cancer (AJCC) criteria
  - Arm D: Histologically confirmed anti-CD20-refractory (defined as any subject with less than a PR to any prior anti-CD20-based therapy or progression within 6 months after completing therapy with any anti-CD20-based regimen, including maintenance rituximab) aggressive B-cell DLBCL, including FL transforming to DLBCL, transformed indolent lymphoma, MCL, or Grade 3b FL according to the WHO/AJCC criteria
- Evaluable/measurable disease
  - Non-CLL B-cell malignancies (Arms A, C, and D):
    - Histologically-confirmed B-cell NHL (FL or DLBCL), transformed indolent lymphoma, and MCL: Measurable disease defined as ≥ 1 lesion ≥ 20 mm in 1 dimension or ≥ 15 mm in 2 dimensions as measured by conventional or high resolution (spiral) computed tomography (CT). For Arms C and D: disease evaluable by the International Working Group criteria (Cheson et al, 2007).
    - Baseline positron emission tomography (PET) or PET/CT scans must show positive lesions compatible with CT-defined anatomical tumor sites (only applicable for FL, DLBCL, MCL, transformed indolent lymphoma, and FL transforming to DLBCL)
  - CLL (Arms A and B):
    - Confirmed B-cell CLL/SLL with a characteristic immunophenotype by flow cytometry, and symptomatic disease requiring treatment
    - CT scans showing involvement of ≥ 1 clearly demarcated lesions measuring ≥ 1.5 cm
- Prior therapy
  - Arm A
    - Histologically-confirmed B-cell NHL (FL or DLBCL): Relapsed from or refractory to ≥ 1 prior regimen containing rituximab, either alone or in combination, and not be a candidate for hematopoietic stem cell transplant at (SCT) or bone marrow (BM) transplant
    - B-cell CLL: Relapsed from or refractory to ≥ 2 prior lines of treatment, at least one of which must have contained rituximab
  - Arm B: Relapsed from or refractory to ≥ 2 prior chemotherapy regimens with ≥ 1 regimen containing rituximab
  - Arm C: Relapsed from or refractory to ≥ 2 prior chemotherapy regimens with ≥ 1 regimen containing rituximab or failed 1 prior rituximab-containing regimen and unable to tolerate additional multiagent chemotherapy
  - Arm D: Refractory to ≥ 1 regimen containing any anti-CD20-based therapy, including salvage regimens and maintenance rituximab. Refractory subjects are defined as any subject with less than a PR to any prior anti-CD20-based therapies or progressed within 6 months after completing therapy with any anti-CD20-based regimens, including maintenance rituximab. These subjects must not be eligible for hematopoietic SCT or BM transplant
- Prior radiation therapy is allowed provided exposure does not exceed an area of 25% of marrow space and occurred ≥ 6 weeks prior to the first dose of MEDI-551 (Arm A only)
- Karnofsky performance status ≥ 70
- Life expectancy of ≥ 12 weeks

- Adequate hematological function defined as:
  - Arm A (except for CLL subjects with significant BM involvement by biopsy): hemoglobin ≥ 9 g/dL (≥ 8 g/dL for subjects who are transfusion dependent), absolute neutrophil count ≥ 1500/mm^3, and platelet count ≥ 75,000/mm^3
  - Arms B, C, and D must meet the following criteria: hemoglobin ≥ 8 mg/dL, absolute neutrophil count ≥ 1000/mm^3, and platelet count ≥ 75,000/mm^3. In the event of significant BM involvement, these hematologic criteria will not be required for enrollment eligibility
- Adequate organ function defined as:
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2 × institutional upper limit of normal (ULN); bilirubin ≤ 1.5 × ULN except in the case of subjects with documented Gilbert's disease, ≤ 2.5 × ULN; serum creatinine ≤ 1.5 mg/dL or a calculated creatinine clearance of ≥ 60 mL/min as determined by the Cockcroft-Gault equation

Select Exclusion Criteria

- Any available standard line of therapy known to be life-prolonging or life-saving
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for treatment of cancer
- Receipt of any chemotherapy or small molecule targeted therapy (such as imatinib or other tyrosine kinase inhibitors, and including any experimental therapies) or radiation therapy within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of MEDI-551
- Receipt of any biological or immunological-based therapies (including experimental therapies) for leukemia, lymphoma, or myeloma (including, but not limited to, MAb therapy such as rituximab, or cancer vaccine therapies) within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of MEDI-551
- Previous therapy directed against CD19, such as MAbs or MAb conjugates
- Live or attenuated vaccines (other than experimental cancer vaccine therapy) within 28 days prior to receiving the first dose of MEDI-551
- Evidence of significant active infection requiring antimicrobial, antifungal, antiparasitic, or antiviral therapy or for which other supportive care is given
- Autologous SCT within 12 weeks prior to study entry (Arms A and D only)
- Prior allogeneic SCT or organ transplant (Arms A and D only)
- Human immunodeficiency virus (HIV) positive serology or AIDS
- Active hepatitis B as defined by seropositivity for hepatitis B surface antigen (HBsAg) or positive hepatitis B core antibody. Subjects with hepatitis C antibody will be eligible provided that they do not have elevated liver transaminases or other evidence of active hepatitis.
- Ongoing ≥ Grade 2 toxicities from previous cancer therapies unless specifically allowed in the Inclusion/Exclusion criteria
- Use of immunosuppressive medication other than steroids within 28 days before the first dose of MEDI-551
- Documented current central nervous system involvement by leukemia or lymphoma
- Pregnancy or lactation
- Previous medical history, or evidence, of an intercurrent illness that at the discretion of the principal investigator may compromise the safety of the subject in the study
- Clinically significant abnormality on electrocardiogram (ECG). The corrected QT interval (QTc, Fridericia) must be < 470 milliseconds for men and < 490 milliseconds for women (Must be confirmed by at least 2 additional 12-lead ECGs at least 2 minutes apart such that average manually over-read QTcF based on 3 ECGs exceeds stated thresholds)

TREATMENT

Subjects in Arms A, B, and C were treated in one of two phases: dose escalation or cohort expansion. Subjects in Arm D were treated at the dose and schedule used in the expansion cohort of Arm A.

Arm A

Subjects enrolled in the dose-escalation phase of Arm A were treated with 1 of 6 doses (0.5, 1, 2, 4, 8, or 12 mg/kg) of MEDI-551. Dose escalation began in subjects with FL or MM per protocol Versions 1.0 through 4.0. Under these versions of the protocol, subjects were enrolled into the first 2 cohorts. Starting with Version 5.0 of the protocol, enrollment in Cohorts 3 and higher was open to subjects with FL, MM, CLL or DLBCL. Subjects in Cohorts 1 and 2 received 0.5 or 1 mg/kg MEDI-551, respectively, IV once every week in 4-week cycles. Subjects enrolled in Cohorts 3 to 6 received 2, 4, 8, or 12 mg/kg MEDI-551, respectively, IV once per week on Days 1 and 8 during Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle. Subjects who do not experience a DLT or do not otherwise become ineligible to receive MEDI-551 continue to receive MEDI-551 until CR, disease progression, toxicity, or another reason for treatment discontinuation is observed. Subjects who achieve a CR could receive an additional 2 cycles of MEDI-551 at the same dose prior to EOT.

Following determination of the MTD or OBD or completion of dose escalation to 12 mg/kg, approximately 80 subjects total, 20 subjects each with FL, MM, CLL, or DLBCL, were to be enrolled in the expansion phase of Arm A. As of Version 8.0 of the protocol, and following enrollment of 1 MM subject, enrollment of additional MM subjects was discontinued. Twenty subjects each with FL, CLL (including SLL), or DLBCL were to be enrolled in the expansion phase. A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled. Subjects enrolled in the expansion phase were required to have evaluable disease as described in the inclusion criteria. Subjects in the expansion phase were treated with MEDI-551 on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle unless evaluation of different schedule(s) was needed as described above. Subjects who did not complete 2 cycles of treatment for reasons other than toxicity to MEDI-551, disease progression, or death due to disease were to be replaced until a total of 20 subjects in each cohort were evaluable.

Arm B

During the dose-escalation phase of Arm B, MEDI-551 was administered IV at 6 mg/kg weekly for 4 weeks during Cycle 1. For Cycle 2 and beyond, MEDI-551 6 mg/kg was administered on Day 1 of each 28-day cycle. Subsequent sequential cohorts were to evaluate doses of 12, 24, and 48 mg/kg administered weekly for 4 weeks during Cycle 1 and then on Day 1 of each 28-day cycle starting with Cycle 2 and beyond.

To further minimize infusion-related reactions at higher dose levels in Arm B, for the 24 and 48 mg/kg dose levels of MEDI-551, the initial weekly doses were to be administered over 2 days on Day 1 and Day 2 in Cycle 1. Additionally, mandatory premedication against IRR was required on both Day 1 and Day 2 of Cycle 1.

1. At the 24 mg/kg dose level, MEDI-551 was administered as follows:
   a. On Day 1, 12 mg/kg as an infusion over a minimum of 81 minutes
   b. On Day 2, 12 mg/kg as an infusion over a minimum of 60 minutes
2. At the 48 mg/kg dose level MEDI-551 was to be administered as follows:
   a. On Day 1, 12 mg/kg as an infusion over a minimum of 81 minutes
   b. On Day 2, 36 mg/kg as an infusion over a minimum of 60 minutes (or over a minimum of 90 minutes if the subject experienced an infusion reaction on Day 1)

Subsequent doses at the 24 and 48 mg/kg dose levels were to be administered in an identical fashion to lower dose levels (ie, weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond).

During the dose-expansion phase of Arm B, the MTD or highest protocol-defined dose not exceeding the MTD was to be administered IV weekly for 4 weeks during Cycle 1 and then on Day 1 of each 28-day cycle starting with Cycle 2 and beyond.

Treatment may continue until the subject experiences unacceptable toxicity, progression of disease, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

Arm C

During the dose-escalation phase of Arm C, MEDI-551 was administered IV at 8 mg/kg on Days 2 and 8 in combination with rituximab 375 mg/m^2 administered IV on Days 1, 8, 15, and 22 of Cycle 1 (28-day cycle). In Cycle 2, MEDI-551 was administered at 8 mg/kg on Day 1 and rituximab 375 mg/m^2 was administered on

Days 1, 8, 15, and 22. In Cycle 3 and beyond, only MEDI-551 8 mg/kg was administered on Day 1 of each 28-day cycle. As the MTD was not exceeded at 8 mg/kg, the MEDI-551 dose was escalated to 12 mg/kg administered in combination with a fixed dose of rituximab on the same schedule as noted above.

During the dose-expansion phase of Arm C, the selected MEDI-551 dose was administered IV on Days 2 and 8 in combination with rituximab 375 mg/m^2 administered IV on Days 1, 8, 15, and 22 of Cycle 1 (28-day cycle). In Cycle 2, the selected dose of MEDI-551 was administered on Day 1 and rituximab 375 mg/m^2 was administered on Days 1, 8, 15, and 22. In Cycle 3 and beyond, only MEDI-551 (at the MTD or highest protocol-defined not exceeding the MTD) was administered on Day 1 of each 28-day cycle.

Treatment may continue until the subject experiences unacceptable toxicity, disease progression, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

Arm D

MEDI-551 was administered IV at 12 mg/kg on Days 1 and 8 of Cycle 1 and on Day 1 of Cycle 2 and beyond in 28-day cycles. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

ASSESSMENT OF ENDPOINTS

The primary endpoints of each study arm are as follows: Arm A—MTD defined as the highest dose where ≤ 1 out of 6 subjects experience a DLT during the DLT evaluation period or OBD, and safety of MEDI-551 in relapsed or refractory advanced B-cell malignancies; Arms B and C—MTD defined as the highest dose where ≤ 1 out of 6 subjects experience a DLT during Cycle 1 or highest protocol-specified dose not exceeding MTD: DLTs , safety and tolerability, and clinical activity/efficacy of MEDI-551 as single agent in CLL or combined with rituximab in aggressive lymphomas; and Arm D—clinical activity/efficacy of single-agent MEDI-551 in any anti-CD20-refractory aggressive lymphomas. MTD or OBD/highest protocol-specified dose evaluation was based on the evaluable population for DLT during Cycle 1. The number and percentage of subjects with a DLT will be presented by dose level, and as a group overall. Safety endpoints include assessment of adverse events, serious adverse events, clinical laboratory evaluations, vital signs, physical examinations, and ECGs from the first administration of MEDI-551 through 60 days post-EOT (approximately 90 days after the last dose of MEDI-551). These assessments will be summarized for all subjects who received any MEDI-551. Clinical activity/efficacy will be assessed using CR, duration of CR, objective response, disease control, time to response, duration of objective response, duration of disease control, progression-free survival, and overall survival.

The secondary endpoints of each study arm are as follows: Arm A—clinical activity/efficacy, PK, and IM of MEDI-551 and effect of MEDI-551 on Ig levels and circulating B-lymphocyte populations; Arms B and C—PK and IM of MEDI-551 as single agent or combined with rituximab, and effect of MEDI-551 on lymphocyte populations, including time to recovery of lymphocyte levels; and Arm D—safety and tolerability, PK and IM of single-agent MEDI-551, and effect of MEDI-551 on lymphocyte populations, including time to recovery of lymphocyte levels. Efficacy in Arm A will be assessed as described above for Arms B, C, and D. Safety in Arm D will be assessed as described above for Arms A, B, and C. The PK parameters of MEDI-551 will be estimated using non-compartmental analysis. A population PK analysis may also be performed to obtain additional PK parameters. Anti-MEDI-551 antibodies will be assessed and summarized descriptively by dose cohort for each arm.

Exploratory endpoints of the study arms include the [redacted]

SAMPLE SIZE AND POWER CALCULATIONS

Arm A

For the dose-escalation phase, a minimum of 18 evaluable subjects (3 subjects each in Dose Cohort 1 through 6) or up to approximately 36 evaluable subjects (3+3 subjects per dose cohort) were required to determine the MTD. A subject was considered evaluable for assessment of DLT if the subject received at least one full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completed the safety follow-up through the DLT evaluation period (ie, the first 28-day cycle), or the subject experienced a DLT. Any non-evaluable subject was to be replaced in the same dose cohort.

A total of 26 subjects were enrolled in Arm A dose-escalation.

For the dose-expansion phase, approximately 20 subjects were to be entered into each of 3 arms to determine the preliminary efficacy profile of MEDI-551 in the treatment of advanced CLL (including SLL), DLBCL, and FL. The primary objective of the dose-expansion phase was to determine the preliminary efficacy profile of MEDI-551 in subjects with the advanced B-cell malignancies: CLL (including SLL), DLBCL, and FL. The sample size estimation was based on the CR rate and exact binomial test. A total of 20 subjects per arm were required to have approximately 80% power for testing the null hypotheses of 5% CR rate against the alternative of 20% CR rate at a 1-sided significance level of 0.1.

A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled in Arm A dose-expansion.

Arms B and C

Dose escalation: There were 4 planned dose levels (6, 12, 24, and 48 mg/kg) for MEDI-551 in the Arm B dose-escalation phase and 2 planned dose levels (8 and 12 mg/kg) for the Arm C dose-escalation phase. Using a standard 3+3 design, approximately 24 to 36 subjects were to be enrolled during the dose-escalation phase in Arms B and C depending on the observed safety profile and total number of dose levels evaluated.

A total of 7 subjects were enrolled in Arm B dose-escalation, including 1 at a dose of 24 mg/kg. The dose escalation continued in Arm C as planned (8 mg/kg and 12 mg/kg) based on emerging PK and pharmacodynamic data that suggested a dose of 12 mg/kg, administered weekly during Cycle 1 and then monthly in subsequent cycles, was determined to be sufficient to saturate the B-cell sink and achieve full exposure. At the sponsor's discretion and not due to any safety issues, no further dose-escalation was conducted. The MTD was not reached and dose expansion was not conducted in Arm B.

Dose expansion: A sample size of 26 subjects was planned for each dose-expansion cohort in Arms B and C. Given an expected response rate of 50% for both cohorts, this would provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30%, and associated 80% confidence intervals for the response rate would have a precision of ± 13%. The 30% historical response rate was selected for both Arms B and C expansion cohorts based on the following reported data:

- In relapsed CLL patients, objective response rates between 15% and 30% were reported for rituximab monotherapy (O'Brien et al, 2001; Mavromatis and Cheson, 2003).
- In DLBCL patients with 2 prior lines of therapy, response rates were only about 30% with single-agent rituximab (Coiffier et al, 1998; Wang et al, 2013; Churpek et al, 2013).

A total of 19 subjects were enrolled in Arm C. Of these 19 subjects there were only 7 responders, and there was about a 13% probability of meeting the protocol-specified target response rate of 50%; further enrollment to Arm C was therefore halted at the sponsor's discretion. The MTD was not reached and enrollment in Arm C was discontinued prior to dose expansion at the sponsor's discretion and not due to any safety issues.

Arm D

A sample size of approximately 26 subjects was planned for Arm D. Given an expected response rate of 50% for this cohort, this would provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30% (Zinzani et al, 2013; Witzig et al, 2011), and associated 80% confidence intervals for the response rate would have a precision of ± 13%.

A total of 16 subjects were enrolled in Arm D. Of these 16 subjects there were only 3 responders, and there was about a 1% probability of meeting the protocol-specified target response rate of 50%; further enrollment was therefore halted at the sponsor's discretion and not due to any safety issues.

1 INTRODUCTION

1.1 Disease Background

CD19 Function and Expression

Cluster of differentiation (CD) 19 is a B-cell-restricted transmembrane protein member of the immunoglobulin (Ig) superfamily encoded by the *CD19* gene (Cooper et al, 2004). This cell surface antigen is first expressed by early pre-B cells from the time of heavy chain rearrangement and is down-regulated during terminal differentiation into plasma cells (Nadler et al, 1983). CD19 is a component of the B-cell receptor (BCR) complex and controls the signaling threshold for B-cell development and humoral immunity (Sato et al, 1995; Sato et al, 1997). Knockout mice lacking CD19 do not show defective B-cell development within the bone marrow (BM), but have reduced B-cell numbers in peripheral lymphoid organs and reduced serum Ig levels (Engel et al, 1995). Conversely, mice overexpressing CD19 within the B-cell compartment have a defect in early B-cell development in the BM, an increased response of B cells to mitogens, and elevated levels of serum Igs (Engel et al, 1995). CD19 is not expressed on hematopoietic stem cells or B cells before the pro-B-cell stage (Nadler et al, 1983; Loken et al, 1987).

Expression of CD19 in B-cell leukemias and lymphomas is widespread. CD19 is expressed in chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), and B-cell non-Hodgkin lymphoma (NHL) (Uckun et al, 1988; D'Arena et al, 2000; Ginaldi et al, 1998; Anderson et al, 1984). Histologically, the vast majority of NHL subtypes are derived from B cells and express common B-cell antigens such as CD19, CD20, and CD22 (Armitage and Weisenburger, 1998; The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993; Harris et al, 1994; Masir et al, 2006). Compared to CD20, which is also expressed in multiple B-cell malignancies, CD19 is expressed at lower levels, but on a broader range of B cells; CD19 expression occurs earlier during B-cell development and continues for longer than does CD20 expression (Cooper et al 2004; D'Arena et al, 2000). In multiple myeloma (MM), CD19 is not expressed on malignant plasma cells, but an increasing population of CD19-positive cells appears following chemotherapy (Rasmussen et al, 2002; Bergsagel et al, 1995; Kiel et al, 1999). It is thought that this CD19-positive population represents a stem cell population that is resistant to available chemotherapies (Huff and Matsui, 2008).

Treatment of B-cell Malignancies

Treatment of B-cell CLL and NHL, the largest groups of hematologic malignancies, relies primarily on a combination of chemotherapy and biotherapy based on the monoclonal antibody (MAb) rituximab, directed against CD20 (Robak, 2007). While many patients achieve long-lasting remissions with this combination in both CLL and NHL, patients whose disease progresses after treatment with rituximab and/or commonly used chemotherapies have few effective options (Robak, 2007; Coiffier, Sep2005; Coiffier, Mar2005). With each subsequent treatment, the duration of remission usually becomes shorter and, eventually, most CLL and NHL patients die from their disease (Hennessy et al, 2004). Once patients become refractory to rituximab (ie, achieve less than partial response [PR] or relapse within 6 months of rituximab therapy), limited biologic agents are available as adjunctive treatment to chemotherapy. While treatment with ofatumumab, an anti-CD20 MAb, has resulted in an objective response rate (ORR) of approximately 58% in CLL patients, there are currently no approved agents for NHL patients (Wierda et al, 2010). Furthermore, it is unclear whether ofatumumab offers similar activity in CLL patients considered to be rituximab refractory. Therefore, an unmet medical need exists for patients who have relapsed or refractory NHL or CLL that is no longer responsive to rituximab or chemotherapy. The broad expression profile of CD19 on B-cell malignancies, including ALL, CLL, and NHL, makes this an attractive target both for patients in whom therapy with rituximab has failed and as a potential first-line treatment (Uckun et al, 1988). In MM, patients who are not candidates for a stem cell transplant (SCT) can achieve durable remissions with first-line chemotherapeutic regimens (San Miguel et al, 2008), but nearly all patients will eventually relapse and require subsequent therapy (Richardson et al, 2003). As with other B-cell malignancies, in MM, subsequent lines of therapy have a lower effectiveness and shorter duration (Richardson et al, 2003). Multiple myeloma patients who have received multiple lines of therapy likely have higher percentages of CD19-expressing cells (Matsui et al, 2008) and, because this may represent a stem cell population that is resistant to available chemotherapies, these patients have an unmet medical need.

1.2 Description of MEDI-551

The following sections provide a brief description of MEDI-551. Refer to the current Investigator's Brochure for details.

MEDI-551 Pharmacology

MEDI-551 is a humanized IgG1 kappa MAb directed against human CD19 (huCD19). Affinity maturation of the parental humanized antibody 3649 resulted in antibody 16C4,

which has superior binding characteristics. MEDI-551 is generated by expression of MAb 16C4 in a fucosyltransferase-deficient Chinese hamster ovary (CHO) producer cell line (BioWa Potelligent® Technology) generating a homogeneously afucosylated antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC). MEDI-551 shows potent in vitro ADCC against multiple B-cell leukemia and lymphoma cell lines, as well as patient-derived CLL and ALL cells. MEDI-551 efficiently depletes blood and tissue B cells in huCD19 transgenic (Tg) mice and has antitumor activity in severe combined immunodeficiency mouse models of human B-cell leukemia, lymphoma, and MM. MEDI-551 does not bind CD20, and thus activity of MEDI-551 should be independent of activity of rituximab or other CD20-targeted therapies. MEDI-551 is expected to selectively target B cells, with antitumor activity in a variety of B-cell-derived malignancies.

1.3 Nonclinical Experience with MEDI-551

MEDI-551 Toxicology

A pharmacologically relevant Tg animal model, huCD19 Tg mouse, was developed and used to evaluate the potential toxicity of MEDI-551 in animals. Because MEDI-551 binds neither rodent nor non-human primate CD19, these standard toxicology models were not considered pharmacologically relevant, and the Tg model was used instead.

The Tg model expresses huCD19 in a murine C57BL6 genetic background under the control of human regulatory elements, resulting in huCD19 expression that is restricted to B-lineage cells as it is in humans (Zhou et al, 1994; Yazawa et al, 2005). MEDI-551 binds to and depletes huCD19+ B cells in these huCD19 Tg mice with a similar affinity and by the same mechanism of action as is expected in humans. Nonclinical toxicology studies with this model demonstrated that there were no adverse effects after either a single dose (up to 50 mg/kg), 5 weekly doses (up to 36.6 mg/kg), or 13 or 26 weekly doses (up to 30 mg/kg). The only findings in these toxicology studies were related to the pharmacologic action of B-cell depletion. The time to recovery of B cells appears to be dose dependent. An additional study to investigate subcutaneous (SC) dosing (13 weekly SC or intravenous [IV] doses up to 30 mg/kg) was recently conducted and an increased incidence of background bronchioloalveolar adenomas (benign) was noted in the 30-mg/kg IV group at the recovery necropsy. Given that this finding is isolated to this study and was not observed in the longer 26-week chronic toxicity study at the same dose, the relevance to overall risk assessment for patients is unknown. In addition, MEDI-551 was evaluated in an embryofetal development study in huCD19 Tg mice. The only adverse findings in the study were treatment-related reduction in fertility index and the number of mice that were pregnant or in cohabitation.

Importantly, MEDI-551 had no impact on embryofetal development. Treatment with MEDI-551 resulted in expected pharmacologic depletion of total B lymphocytes in peripheral blood of adult mice. In fetal livers, the site of B-cell development in mice, there was a dramatic difference in huCD19+ B cells between progeny of dosed mice and vehicle-treated mice. Overall, the results suggest that MEDI-551 crosses the placenta and depletes B cells. An additional study to evaluate the recovery of B cells in infants from treated mice, as well as an assessment of immune function in these infants, will be performed at a future date.

Maximum Dose Selection

Nonclinical studies were conducted with normal donor peripheral blood mononuclear cells to predict the 90% effective concentration (EC_{90}) for ADCC. Other studies were conducted to assess the binding affinity (dissociation constant [Kd]) of MEDI-551 to CD19-expressing cells. Serum MEDI-551 concentrations were simulated for the planned doses and compared to the determined EC_{90} for ADCC and Kd. It was determined that a dose beyond 12 mg/kg MEDI-551 is unlikely to result in added pharmacologic activity and clinical benefit. At 12 mg/kg, MEDI-551 levels in subjects are projected to be far in excess of the in vitro EC_{90} and Kd for binding to the target (CD19).

Review of pharmacokinetic (PK) results for each histology enrolled in Arm A suggested that unlike follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) subjects, CLL subjects had limited exposure due to a large B-cell sink even at the highest dose tested (12 mg/kg). Lack of saturation of the B-cell sink may have limited the clinical activity of MEDI-551 noted in CLL subjects. Consequently, Arm B will explore higher doses of MEDI-551 and a more frequent dosing schedule to determine if saturation of the B-cell sink may be maximized.

1.4 Clinical Experience with MEDI-551

The clinical development of MEDI-551 is ongoing in subjects with B-cell malignancies, systemic scleroderma, relapsing/remitting multiple sclerosis, and neuromyelitis optica (NMO) and NMO spectrum disorders. There are 5 clinical studies of MEDI-551, including MI-CP204, in subjects with B-cell malignancies; these studies are described below, based on a data cutoff date of 31Mar2015.

In the current Phase 1/2 study, MI-CP204, enrollment in the dose-escalation and expansion phases in adult subjects with relapsed and refractory advanced B-cell malignancies (CLL, DLBCL, FL, or MM) has been completed (enrollment of MM subjects was discontinued

after the start of the dose-expansion phase due to lack of activity based on nonclinical and preliminary clinical data). Subjects in the dose-escalation phase received MEDI-551 at doses of 0.5, 1, 2, 4, 8, or 12 mg/kg (3 to 6 subjects per dose cohort), or 12 mg/kg (a total of 75 subjects in the combined dose-escalation and dose-expansion portions of this arm of the study received 12 mg/kg). Two dose-limiting toxicities (DLTs) were reported as infusion-related reactions; one occurred at the 4 mg/kg cohort and the other at 12 mg/kg dose level. The protocol was amended to add 3 arms to the study: Arm B applies dose escalation to determine the maximum tolerated dose (MTD) or maximum dose that will saturate the B-cell sink in subjects with CLL; Arm C combines rituximab and MEDI-551 in treating subjects with aggressive lymphomas; and Arm D assesses the activity of MEDI-551 monotherapy in subjects with anti-CD20- refractory aggressive lymphomas. The protocol was further amended to include mandatory steroid prophylaxis and graded infusions consistent with Studies CD-ON-MEDI-551-1019 and CD-ON-MEDI-551-1088 (see below). A total of 111 subjects have been treated with MEDI-551 in MI-CP204. The most commonly reported adverse events (AE) (> 20% of subjects) were infusion-related reaction, fatigue, cough, and nausea. The most commonly reported related AEs (in ≥ 5% of subjects in the overall study population) were infusion-related reaction, nausea, neutropenia, fatigue, and vomiting. Deaths were reported for 27 of 111 (24.3%) subjects in MI-CP204. Progressive disease (PD) was the most common cause. All 27 deaths were considered unrelated to MEDI-551. Twenty-eight subjects (25.2%) in MI-CP204 experienced serious adverse events (SAEs); SAEs were noted in every dose cohort except the 2 dose cohorts in Arm B (6 mg/kg or 12 mg/kg every week for 4 weeks, then every 4 weeks, N = 6 for the combined cohorts). In Study MI-CP204, mean serum MEDI-551 PK concentration-time profiles following IV administration declined in a bi-exponential manner, with an initial rapid distribution followed by a slower elimination phase. In general, MEDI-551 PK was dose proportional between 0.5 and 12 mg/kg following the first dose. Thirty of 111 subjects (27.0 %) in MI-CP204 experienced objective response (OR), defined as complete response (CR) or partial response (PR). Three subjects, 2 subjects who achieved CR and 1 subject who achieved a very good PR, were retreated following relapse.

Study D2850C00001, sponsored by AstraZeneca Japan, is a Phase 1, open-label, dose-escalation study of MEDI-551 in adult Japanese subjects with advanced B-cell malignancies. Twenty subjects were enrolled and have received doses of 2, 4, 8, or 12 mg/kg. The AEs most commonly reported (in ≥ 15% of subjects) were infusion-related reaction (IRR), hypertriglyceridemia, white blood cell (WBC) count decreased, leukopenia, nasopharyngitis, lymphocyte count decreased, neutrophil count decreased, and rash. Following Cohort 1, premedication with non-steroidal agents and antihistamines was permitted. After Grade 3 infusion-related reactions occurred in Cohort 2, premedication with steroids was also

permitted if a subject had experienced infusion reactions with other drugs, had rapid bulky tumor growth, high cytokine levels, and/or CLL. Two DLTs of infusion-related reaction occurred at the 12 mg/kg dose; hence the MTD was determined to be 8 mg/kg in this population.

Two Phase 2 clinical studies are evaluating MEDI-551 for the treatment of B-cell malignancies. Study CD-ON-MEDI-551-1019, which is closed to enrollment but still ongoing, is a Phase 2, multicenter, international, randomized, 3-arm, active-control, open label study evaluating the antitumor activity, safety, tolerability, immunogenicity (IM), pharmacokinetics (PK), and pharmacodynamics of MEDI-551 when used in combination with bendamustine versus rituximab in combination with bendamustine in adult subjects with progressive CLL (also known as relapsed or refractory CLL). A total of 150 subjects have been treated with one of 3 regimens: MEDI-551 2 mg/kg, MEDI-551 4 mg/kg, or rituximab, each in combination with bendamustine. A total of 90 subjects have been treated with MEDI-551. The most common AEs reported in the combined MEDI-551 groups (in > 20% of subjects) were infusion-related reaction, nausea, fatigue, neutropenia, pyrexia, cough, and constipation. The most common AEs (in ≥ 10%) of subjects in the combined MEDI-551 groups judged related to MEDI-551 were infusion-related reaction, nausea, neutropenia, fatigue, chills, and vomiting. Deaths were reported for 18 of 90 subjects (20.0%) who received MEDI-551 in CD-ON-MEDI-551-1019 (6 of 33 subjects [18.2%] in the 2 mg/kg group and 12 of 57 subjects [21.1%] in the 4 mg/kg group) and in 6 of 60 subjects (10.0%) in the rituximab + bendamustine group. All except for 1 of the deaths (4 mg/kg MEDI-551 + bendamustine group) were considered not related to study drug. Thirty-five of 90 subjects (38.9%) in the combined MEDI-551 groups and 19 of 60 subjects (31.7%) in the rituximab group experienced SAEs. The SAE of infusion-related reaction occurred more frequently in the combined MEDI-551 groups (10 of 90 subjects [11.1%]) than in the rituximab group (1 of 60 subjects [1.7%]). Febrile neutropenia occurred more frequently in the rituximab group (7 of 47 subjects [11.7%]) than in the combined MEDI-551 groups (2 of 90 subjects [2.2%]).

The CD-ON-MEDI-551-1019 study protocol was amended in May 2013 to mitigate the risk of infusion-related reactions by requiring premedication with steroids, antihistamines, and antipyretics before the initial MEDI-551 dose; using a reduced infusion rate during the initial administration of MEDI-551; and moving the first MEDI-551 dose to Day 2 of Cycle 1.

Study CD-ON-MEDI-551-1088 is a Phase 2 study of MEDI-551 when used in combination with ifosfamide-carboplatin-etoposide (ICE) or dexamethasone-cytarabine-cisplatin (DHAP) versus rituximab in combination with ICE or DHAP in adult subjects with relapsed or

refractory DLBCL. Subjects were initially assigned to one of three regimens: MEDI-551 2 mg/kg, MEDI-551 4 mg/kg, or rituximab, each in combination with ICE or DHAP. Enrollment was stopped in November 2012 following 2 deaths in subjects in the 4 mg/kg arm of MEDI-551. These events were evaluated by the sponsor's internal safety review committee and a Data Monitoring Committee. The safety review and data monitoring committees concluded that the role of MEDI-551 in these events was unclear and advised that enrollment at a higher dose of MEDI-551 may be reopened only after more safety information on the MEDI-551 2 mg/kg dose in combination with chemotherapy was obtained. As a result of the review and recommendations of these groups, the protocol was amended. The study was re-opened for enrollment in the 4 mg/kg arm in December 2012 after review of the safety data for the MEDI-551 2 mg/kg combination arm by the safety review committee. A total of 119 subjects in CD-ON-MEDI-551-1088 have received at least 1 dose of study treatment, including 71 subjects in the combined MEDI-551 groups. Adverse events reported for > 20% of subjects in the combined MEDI-551 groups were anemia, thrombocytopenia, nausea, fatigue, neutropenia, constipation, vomiting, asthenia, and diarrhea. The most common AEs judged related to MEDI-551 (in > 10% of subjects in the combined MEDI-551 groups) were anemia, thrombocytopenia, nausea, neutropenia, fatigue, and leukopenia. Deaths were reported for 9 of 71 subjects (12.7%) receiving MEDI-551 (7 of 48 subjects [14.6%] in the 2 mg/kg group and 2 of 23 subjects [8.7%] in the 4 mg/kg group) and 8 of 48 subjects (16.7%) receiving rituximab in CD-ON-MEDI-551-1088. Two deaths in the MEDI-551 group and 1 death in the rituximab group were considered to be related to investigational product. Thirty of 71 subjects (42.3%) in the combined MEDI-551 groups and 20 of 48 subjects (41.7%) in the rituximab group experienced SAEs in CD-ON-MEDI-551-1088.

A Phase 1b/2, multicenter, open-label study of MEDI0680 (AMP-514), a MAb directed against human programmed cell death 1, in combination with MEDI-551, D2852C00004, is evaluating the safety, tolerability, clinical activity, MTD, PK, and anti-drug antibodies (ADAs) in subjects with relapsed and refractory aggressive B-cell lymphoma. Subjects receive MEDI-551 at 12 mg/kg (with possible dose de-escalation to 8 mg/kg) and MEDI0680 (AMP-514) at 2.5 or 10 mg/kg. A total of 8 subjects have been enrolled. Adverse events reported by more than 1 subject were fatigue, constipation, diarrhea, nausea, vomiting, peripheral edema, paresthesia, and rash. Two subjects, both in the MEDI-551 12 mg/kg + MEDI0680 (AMP-514) 2.5 mg/kg dose group died. Both deaths were attributed to progressive disease and neither death was considered to be related to either study drug. Serious adverse events were reported for 2 subjects in the MEDI-551 12 mg/kg + MEDI0680 (AMP-514) 2.5 mg/kg group. One subject suffered Grade 3 hydronephrosis from which he

recovered. The verbatim language for the second subject's SAE (not yet coded) was hospitalization and disease progression.

One externally-sponsored scientific research study (J1340) initiated by a collaborator at Johns Hopkins University is ongoing. Fifteen subjects with MM have been enrolled; no significant safety concerns have been reported. The accrual is completed but the study is ongoing.

1.5 Rationale for Study

Patients with B-cell leukemia or lymphoma who have received rituximab either alone or in combination with chemotherapy have no available therapies after progression while on rituximab or treatment with approved or standard of care chemotherapies. For these patients, there are no curative therapies available. For patients with advanced MM, there are similarly no curative therapies, and CD19 expression on malignant cells appears to increase with increasing lines of therapy. Targeting CD19 is an attractive alternative in patients with rituximab-refractory B-cell leukemia or lymphoma and in advanced MM.

This Phase 1/2 study has 4 treatment arms. The objective of Arm A was to determine the MTD or optimal biologic dose (OBD; one of which will be further tested as the recommended Phase 2 dose) and preliminary safety profile of MEDI-551 in subjects with advanced B-cell malignancies (CLL, DLBCL, FL, and MM). The study design employed in Arm A was used in earlier versions of the protocol and will be continued in Version 10.0 of the protocol. Subjects received MEDI-551 at doses ranging from 0.5 to 12 mg/kg delivered either weekly (Cohorts 1 and 2) or monthly (Cohorts 3 to 6, and expansion). Based on nonclinical studies and preliminary clinical data from this study suggesting a lack of activity in the advanced/refractory MM setting, MM subjects were excluded from enrollment as of Version 8.0 of the protocol.

A second arm (Arm B) was added because PK data from the ongoing Phase 1/2 study demonstrated a lack of full exposure (ie, the dose of antibody is insufficient to saturate the B-cell antigens) in CLL subjects treated with the current monthly dosing regimen and at doses tested. Therefore, as of Version 10.0 of the protocol, Arm B investigated a new dosing schema and higher doses of MEDI-551 in CLL subjects to determine if full exposure could be achieved and clinical activity maximized. A third arm (Arm C) was added to the Phase 1/2 study to investigate the safety, tolerability, and clinical activity of MEDI-551 in combination with rituximab in subjects with aggressive lymphomas. The rationale for this combination was based on nonclinical data suggesting synergistic activity with rituximab and a PK-maximized dose of MEDI-551. As of Version 11.0 of the protocol, a fourth arm (Arm

D) was added to this study to evaluate the clinical activity of MEDI-551 monotherapy in subjects with any anti-CD20-refractory aggressive lymphoma. The rationale for this arm was based on data from Arm A, demonstrating the activity of single-agent MEDI-551 in a heavily pretreated relapsed refractory patient population that had received prior rituximab. Detailed justification for these study arms is provided below.

Rationale for Arm B

Clinical and PK data from Arm A of the Phase 1/2 study suggest that the lack of full exposure in CLL subjects compared with FL and DLBCL subjects may have resulted in reduced clinical activity in CLL (response: 19% CLL [n = 26] vs 29% FL [n = 34] and 23% DLBCL [n = 26]). The number of circulating malignant B cells is much higher in CLL patients than in those with other B-cell malignancies. Therefore, to maximize tumor cell killing, the dose of antibody should be sufficient to saturate the B-cell antigens (B-cell sink). Subjects with CLL treated with MEDI-551 at the 12-mg/kg dose demonstrate lower plasma concentrations of MEDI-551 than other subjects treated at that dose (mean minimum observed concentration at steady state is 89.5 ± 45.7 µg/mL for CLL and 134 ± 40.6 µg/mL for non-CLL), suggesting that the B-cell sink may not be saturated at the 12-mg/kg dose. Moreover, studies of rituximab have reported markedly lower rituximab concentrations/exposure and a low response rate (13%) in patients with SLL or CLL compared to patients with FL (60%) treated at the same dose of 375 mg/m^2 weekly for 4 weeks (McLaughlin et al, 1998). A greater response rate (50%) was seen in CLL patients given rituximab at 375 mg/m^2 three times weekly for 4 weeks (Byrd et al, 2001), suggesting that dose intensity established via frequent dosing may also improve response rates. Additionally, dose intensity with higher doses of the MAb may be effective in improving responses as suggested by a response rate of 75% in patients receiving a rituximab dose of 2250 mg/m^2 weekly for 4 weeks (O'Brien et al, 2001). These data suggest that higher response rates with MEDI-551 may be achieved with increased dose density by using higher doses and/or more frequent dosing. Therefore, additional dose escalation with MEDI-551 was warranted in CLL subjects to determine the MTD or the effective dose that may overcome the B-cell sink.

Arm B of this study was added to investigate further dose escalation using a dosing regimen that may maximize saturation of the B-cell sink in CLL subjects. In Arm B, CLL subjects received MEDI-551 weekly for the first 4 weeks followed by monthly infusions to ensure rapid saturation of the B-cell sink. The maximum ME~~D~~I-551 dose that subjects had previously received in a 1-month period was 24 mg/kg for those treated in the 12-mg/kg dose cohort using the earlier dosing schema (ie, loading dose on Days 1 and 8 of the first month,

followed by monthly dosing). Safety data were available for the maximum dose. Doses of 4, 8, and 12 mg/kg per month had been established as safe in this patient population. Therefore, dose escalation in Arm B was started at 6 mg/kg per week for 4 weeks followed by 6 mg/kg on Day 1 of every 28-day cycle from Cycle 2 and beyond, so that a maximum dose of 24 mg/kg per month would not be exceeded in the first dose cohort tested. Weekly doses of 12, 24, and 48 mg/kg were to be assessed in sequential dose-escalation cohorts based on the new dosing regimen. Dose escalation was allowed to continue until the MTD is defined or the highest protocol-defined dose not exceeding the MTD was reached. A 48-mg/kg maximum dose was proposed based on a review of rituximab data, which suggest that complete saturation of the B-cell sink in CLL occurs with approximately 4 to 5 g of the MAb. The maximum dose of MEDI-551 suggested corresponds to this antibody level.

Rationale for Arm C

B-cell markers including CD20 and CD19 are expressed in various B-cell malignancies and have served as targets for B-cell-directed therapies. The density of CD19 expression on the surface of B-cells is lower than that of CD20; however, prior therapy with CD20-targeted agents has been shown to reduce the percentage of CD20 expression on cells (Chu et al, 2002). Therefore, using agents that target both CD19 and CD20 simultaneously may maximize tumor cell killing by ensuring that malignant cells with low levels of either CD19 or CD20 are effectively eliminated. This hypothesis is supported by nonclinical data of MEDI-551 in combination with rituximab in the treatment of lymphoma cell lines, including rituximab-resistant lines, showing a 5 times greater increase in the percentage of tumor cell killing compared with either agent alone.

Arm A of the ongoing Phase 1/2 study has successfully determined a MEDI-551 dose and dosing schema that permits full exposure and maximizes the clinical activity of MEDI-551 in non-CLL NHL subjects. Therefore, based on nonclinical evidence showing that MEDI-551 and rituximab may act synergistically, Arm C was added to investigate the combination of these 2 agents in the treatment of subjects with aggressive B-cell lymphoma. The addition of this dual-antibody arm to the protocol was warranted to further explore the activity of MEDI-551 in NHL. Evaluation of MEDI-551 combined with rituximab may facilitate future studies utilizing this combination either alone or in combination with chemotherapy.

While the majority of patients with aggressive B-cell malignancies will be cured, at least 30% of those with DLBCL will relapse after first-line therapy, and a cure is still unattainable for patients with mantle cell lymphoma (MCL) or high-grade FL. For MCL, lenalidomide has been approved as a treatment option after second relapse, but there are no approved

therapies for patients with high-grade FL after second relapse. For those patients able to undergo allogeneic transplant, cure may be possible but the transplant process (regardless of disease course or treatment response) is associated with 30% mortality. Therefore, new therapies with better toxicity profiles than traditional cytotoxic chemotherapy are needed for this patient population. Furthermore, in an aging population where the median age of diagnosis of lymphoma is 65 years, chemotherapy-free regimens are attractive as they minimize organ toxicities, myelosuppression, and infection risk inherent to conventional chemotherapy regimens. Nevertheless, these non-traditional chemotherapeutic agents may have other toxicities that complicate treatment in this elderly population. This older population and multiply relapsed patients often have multiple medical comorbidities resulting from cumulative toxicity from prior chemotherapy that prevent repeat multiagent chemotherapy administration. In addition, dual-antibody combinations have already been successfully and safely used in the management of patients with B-cell malignancies as demonstrated by high response rates with the combination of rituximab and epratuzumab with (96%) or without (67%) chemotherapy (Micallef et al, 2011; Leonard et al, 2005). Given the high unmet medical need in patients with multiply relapsed aggressive lymphoma, the synergistic activity observed in nonclinical studies with MEDI-551 and rituximab, as well as the promising clinical activity seen with other dual MAb combinations in patients with B-cell malignancies, evaluation of the combination of rituximab and MEDI-551 was warranted in patients with multiply relapsed aggressive lymphoma in the current study.

Rituximab monotherapy in a multiply relapsed population has resulted in responses ranging from 15% to 30% (Coiffier et al, 1998; Wang et al, 2013) and other therapies (including chemotherapy options) being developed in this population have demonstrated response rates of approximately 30% (Wang et al, 2013; Churpek et al, 2013). At present, single-agent MEDI-551 has demonstrated an ORR of approximately 23%. Consequently, a dual-antibody combination that achieves a response rate ≥ 50% would warrant further investigation.

Unlike the CLL population, PK data suggest that a 12-mg/kg dose of MEDI-551, administered once every 28 days, offers adequate exposure to malignant B cells in DLBCL and FL and, therefore, further dose escalation is not warranted in this patient population. Based on the hypothesis that dual-antibody therapy may be more effective at eliminating malignant B cells, a dose-escalation cohort of aggressive lymphoma subjects was initially treated with a MEDI-551 dose of 8 mg/kg, one dose below the maximum dose tested along with a standard dose of rituximab (375 mg/m^2). Dose escalation of MEDI-551 continued to 12 mg/kg. Once an MTD had been achieved or safety of the maximum proposed dose had been established, an expansion cohort was enrolled to confirm the activity of this dose of MEDI-551 in combination with rituximab.

Rationale for Arm D

The literature indicates that subjects who have received CD20-targeted agents such as rituximab develop resistance via several mechanisms, including "shaving" of CD20 off the surface of malignant cells upon repeated exposure to rituximab. Data from both cell lines and patient samples indicate a loss of CD20 with recurrent exposure to CD20-targeted agents (Tsai et al, 2012; Martin et al, 2008; Hagberg et al, 2006). Loss of CD20 may contribute to rituximab resistance in patients who become refractory to rituximab therapy following repeated exposure (ie, achieving less than a PR with rituximab-based regimens or progression within 6 months of having completed rituximab-based therapy). The percentage of patients considered refractory to rituximab is unknown. Nevertheless, data from the CORAL study suggested that approximately 20% of patients will develop rituximab resistance (Hagberg et al, 2006; Gisselbrecht et al, 2010). That study reported response rates of 50% in those who received rituximab as first-line therapy and 70% response rates in those with no prior rituximab exposure. Furthermore, Gisselbrectht and colleagues reported 3-year event-free survival rates of 21% versus 47% in those with and without prior rituximab exposure (Gisselbrecht et al, 2010). However, despite a loss of CD20 after rituximab exposure, CD19 expression remains on the surface of malignant B cells, offering a potential target to salvage rituximab-refractory patients (Chu et al, 2002).

At present, there are no approved therapies for patients with aggressive lymphoma who are refractory to rituximab or any anti-CD20-based therapies and thus, this is a population with high unmet need. Lymphoma therapies generally incorporate a MAb in combination with either a cytotoxic regimen, an immunomodulatory molecule, or small targeted molecule. Due to a lack of approved non-CD20-targeted treatment options for aggressive lymphoma, retreatment with rituximab has continued, resulting in the administration of a regimen that appears to have reduced efficacy. CD19 expression, therefore, offers a promising target for treatment with CD19-targeted therapies such as MEDI-551.

MEDI-551 has demonstrated activity in the current study (Arm A) in a heavily pretreated patient population, all of whom received prior rituximab. Subjects in Arm A, with multiply relapsed aggressive lymphomas including DLBCL and high-grade FL, had received a median of 5 prior lines of therapy and demonstrated response rates of 23% with a preliminary duration of response of approximately 5 months. Based on the rationale above, it was possible that an even better response rate may have been seen in subjects refractory to any anti-CD20-based therapies, including rituximab.

To evaluate the clinical activity of MEDI-551 in the refractory population, Arm D was added, to enroll adult subjects with any anti-CD20-refractory aggressive lymphoma (refractory DLBCL, Grade 3b FL, FL transforming to DLBCL, and MCL). The same dose used in the expansion cohort of Arm A, 12 mg/kg, was tested in Arm D. This dose and schedule of MEDI-551 provided adequate exposure and was well tolerated based on data from Arm A. A total of approximately 26 refractory subjects were to be enrolled and treated with MEDI-551 at 12 mg/kg given IV on Days 1 and 8 of Cycle 1 and then on Day 1 of every subsequent 28-day cycle with continuation of dosing until unacceptable toxicity, disease progression, or withdrawal of consent.

1.6 Risk-benefit Summary

MEDI-551 may offer a benefit to patients with CD19-expressing hematologic malignancies who have failed standard therapies. Nonclinical and clinical data support the antitumor activity of MEDI-551 in a variety of B-cell malignancies. Specifically, MEDI-551 showed response rates of 19% in CLL, 29% in FL, and 23% in DLBCL subjects who had received a median of 5 prior lines of therapy. Currently, infusion reactions are an identified risk of MEDI-551 treatment. Potential risks, based on the mechanism of action of MEDI-551, and data from nonclinical safety and pharmacology studies and published literature on relevant or similar therapies (primarily rituximab) include the following: acute hypersensitivity reactions, tumor lysis syndrome, IM-related reactions, immunosuppression with increased risk of infection, and adverse reproductive effects. There are, however, no clinical or nonclinical data to suggest that the toxicity profile of MEDI-551 will compare unfavorably to rituximab. Clinical data suggest the toxicities observed are consistent with the toxicity profile of other MAbs and B-cell-depleting agents.

The proposed Phase 1/2 trial will characterize both the safety and antitumor activity of MEDI-551 in B-cell malignancies, with the goal of more fully elucidating its risk-benefit profile. The exclusion criteria, safety monitoring, starting dose, dose-escalation scheme, and stopping criteria will minimize the risks for subjects participating in the monotherapy and combination therapy arms of the study.

The combination of rituximab and MEDI-551 has the potential for additive toxicities including acute hypersensitivity reactions, tumor lysis syndrome, IM-related reactions, immunosuppression with increased risk of infection, and potential adverse reproductive effects. The dosing schema for MEDI-551 and rituximab has been altered to minimize the risk of infusion-related AEs by separating MEDI-551 and rituximab dose administration on Day 1 of Cycle 1. Additional changes to the administration of MEDI-551, including change in the infusion rate and additional steroid premedication together with administration of an

anti-pyretic and H2-blocker, have been mandated to further minimize this risk. To further reduce the risk of additive toxicities, the dose-escalation schema in the combination arm (Arm C) starts with a 33.3% lower dose of MEDI-551 (ie, 8 mg/kg) than the maximum dose demonstrated as safe (ie, 12 mg/kg) in the single-agent treatment of subjects with B-cell malignancies. Finally, DLT criteria and dose-modification schemas have been adjusted to address the potential for increased hematologic and non-hematologic toxicities. Additional follow-up has been implemented to further ensure the safety of subjects (Section 6.3).

Based on the observed pharmacologic activity and mechanism of action of MEDI-551, as well as the considerable clinical experience with marketed products such as rituximab, which has a similar mechanism of action, the risk-benefit profile is considered acceptable for the single-agent arms (Arms A, B, and D) of the clinical study. In addition, with the safety provisions listed above and the knowledge that B-cell-targeted MAbs have been successfully and safely combined to treat this population, the risk-benefit profile is considered acceptable for the dual-antibody arm (Arm C) of this study.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are listed by study arm.

Arm A

1. To determine the MTD or OBD of MEDI-551 in subjects with relapsed or refractory advanced B-cell malignancies (CLL, including SLL, DLBCL, and FL)
2. To determine the preliminary safety profile of MEDI-551

Arm B

Dose escalation

1. To determine the MTD or highest protocol-defined dose of MEDI-551 in the absence of exceeding the MTD in subjects with relapsed or rituximab-refractory CLL (defined as those with less than a PR or progression within 6 months after completing therapy with rituximab)

Dose expansion

1. To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL

2. To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL

Arm C

Dose escalation

1. To determine the safety and tolerability of MEDI-551 in combination with rituximab at the MTD or the highest protocol-defined dose in the absence of exceeding the MTD in subjects with aggressive lymphomas

Dose expansion

1. To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in subjects with aggressive lymphomas
2. To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in combination with rituximab in relapsed and rituximab-refractory population (defined as those with less than a PR or progression within 6 months after completing therapy with rituximab)

Arm D

1. To evaluate the clinical activity of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas (defined as any subject with less than a PR to any prior anti-CD20-based therapy or progression within 6 months after completing therapy with any anti-CD20-based regimen, including maintenance rituximab)

2.2 Secondary Objectives

The secondary objectives of this study are listed by study arm.

Arm A

1. To determine the preliminary efficacy profile of MEDI-551 in subjects with advanced B-cell malignancies (CLL [including SLL], DLBCL, and FL)
2. To determine the PK of MEDI-551 in subjects with advanced B-cell malignancies
3. To determine the effect of treatment with MEDI-551 on circulating lymphocyte populations and Ig levels, including time to recovery after treatment
4. To determine the IM of MEDI-551 in subjects with advanced B-cell malignancies

Arm B

1. To evaluate the PK and IM of MEDI-551 at doses studied in subjects with relapsed or rituximab-refractory CLL
2. To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm C

1. To evaluate the PK and IM of MEDI-551 when administered in combination with rituximab in subjects with aggressive lymphomas
2. To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm D

1. To determine the safety and tolerability of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas
2. To evaluate the PK and IM of MEDI-551
3. To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

2.3 Exploratory Objectives

The exploratory objectives of this study are listed by study arm.

Arm A

1. [redacted]

Arm B

1. [redacted]
2. [redacted]
3. [redacted]

Arm C

1. [redacted]
2. [redacted]

Arm D

1. [redacted]
2. [redacted]

3 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1/2, multicenter, international, open-label, dose-escalation and expanded cohort study to evaluate the safety, tolerability, and potential antitumor activity of MEDI-551 as single agent or in combination with rituximab in adult subjects with advanced B-cell malignancies. The study design of Arm A comprised a dose-escalation phase followed by a dose-expansion phase in subjects with advanced B-cell malignancies receiving single-agent MEDI-551.

As of Version 10.0 of the protocol, the study design also includes dose escalation and expansion in subjects with CLL receiving single-agent MEDI-551 (Arm B), and dose escalation and expansion in subjects with aggressive lymphoma receiving MEDI-551 combined with rituximab (Arm C). As of Version 11.0 of the protocol, the study design also includes subjects with any anti-CD20-refractory aggressive lymphoma receiving single-agent MEDI-551 (Arm D).

This study included participants from 21 investigational sites in the United States (US), Canada, and European Union (EU).

Enrollment in the study was closed as of 30Sep2015. As of 19Jan2017, 9 subjects remain on treatment; all have completed at least 1 year of treatment. All subjects who are currently receiving MEDI-551 treatment may continue to receive MEDI-551 until disease progression, unacceptable toxicity, CR, withdrawal of consent, or another reason to discontinue therapy intervenes. Subjects who achieve CR may receive 2 additional cycles at the same dose prior to EOT Visit. A simplified schedule of evaluations focused on safety will be used. Safety follow-up assessments will be conducted at the EOT Visit (defined as the last day of the last

cycle of investigational product administration) as well as at the 90-Day Post Last Dose Visit (defined as 90 days after the last dose of study medication), which will serve as the End of Study Visit. Long-term follow-up for PFS and OS will not be performed following implementation of Version 13.0.

Arm A

Enrollment in the dose-escalation and dose-expansion phases of Arm A is complete. Protocol Version 4.0 was amended to make the study population for dose-escalation inclusive of subjects with FL, MM, CLL, or DLBCL. Dose escalation in Arm A began in subjects with FL or MM per protocol Versions 1.0 through 4.0. Under these versions of the protocol, subjects were enrolled into the first 2 cohorts. Starting with Version 5.0 of the protocol, enrollment in dose-escalation Cohorts 3 and higher was open to subjects with the following advanced B-cell malignancies: FL, MM, CLL, or DLBCL. Subjects in Cohorts 1 and 2 continued to follow the protocol Version 4.0 dose schedule of 0.5 mg/kg (Cohort 1) or 1 mg/kg (Cohort 2) MEDI-551 administered IV once every week in 4-week cycles. Subjects enrolled in Cohorts 3 and higher received 2, 4, 8, or 12 mg/kg MEDI-551 (Cohorts 3 to 6, respectively) IV once per week on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle. Rules for dose escalation are provided in Section 4.5.5. As per Cohorts 1 and 2, dosing in Cohorts 3 and higher followed a standard 3+3 dose-escalation scheme. No intrasubject dose escalation was allowed. The dose cohorts for the dose-escalation phase in Arm A are shown in Figure 3.1-1.

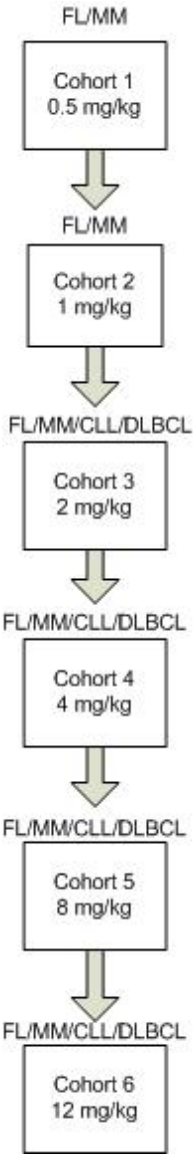


Figure 3.1-1 Flow Diagram for Dose Escalation in Arm A

CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MM = multiple myeloma.

Note: Subjects in Cohorts 1 and 2 were treated as per Version 4.0 of the protocol. Subjects in Cohorts 3 and beyond were as per Version 5.0 and subsequent versions of the protocol.

Subjects continued to receive MEDI-551 until disease progression, toxicity, or another reason to discontinue therapy intervened. All subjects (US and non-US) who achieved a CR could have received an additional 2 cycles of MEDI-551 at the same dose. Rules for dose escalation are described in Section 4.5.5. A total of approximately 18 to 36 evaluable subjects were required for the dose-escalation phase; 26 were enrolled. Subjects were considered evaluable if they received at least one full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completed the safety follow-up through the

DLT evaluation period as defined in Section 4.5.6, or experienced any DLT. Non-evaluable subjects were replaced in the same dose cohort. Dose escalation continued until the MTD (if ≤ 12 mg/kg), the 12-mg/kg maximum dose, or a lower dose (the OBD) as determined by a combination of safety, PK, pharmacodynamic, and response data was reached.

Following determination of the MTD or OBD, approximately 80 subjects total, 20 subjects each with FL, MM, CLL, or DLBCL, were to be enrolled in the dose-expansion phase of Arm A to determine the preliminary efficacy profile of MEDI-551 in the treatment of advanced B-cell malignancies. As of Version 8.0 of the protocol, enrollment of MM subjects in the expansion phase was discontinued based on data from this study and recent nonclinical studies suggesting a lack of activity in the advanced/refractory MM setting. Twenty subjects each with FL, CLL (including SLL), or DLBCL were enrolled in the dose-expansion phase for a total of approximately 60 evaluable subjects. A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled.

Subjects in the dose-expansion phase of Arm A were treated on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle at the MTD, maximum dose of 12 mg/kg, or OBD as determined in the dose-escalation phase. A preplanned interim safety analysis, as defined in the statistical analysis plan, was undertaken when the maximum dose was reached to examine treatment effects on key safety endpoints. As of Version 7.0 of the protocol, the dose-escalation phase of Arm A had been completed. No MTD or OBD was identified during the dose-escalation phase; therefore the expansion phase of Arm A proceeded using the previously selected maximum dose of 12 mg/kg. The preplanned interim safety analysis was conducted at the completion of the dose-escalation phase. No significant safety findings were noted and no changes were made to the protocol as a result of these findings.

If evaluation of available safety, PK, pharmacodynamic, and efficacy data suggest that increased safety and/or efficacy is possible with a longer dosing interval, an extended interval may be evaluated. Subjects who achieved a CR may receive an additional 2 cycles of MEDI-551 at the same dose. Once Version 13.0 is in effect, re-treatment will not be available for subjects who achieve a CR and subsequently relapse while off treatment. Prior to Version 13.0, the US FDA was to be consulted concerning the possibility of additional treatment with MEDI-551 for subjects within the US, and US subjects enrolled in Arm A could have been retreated at the 12-mg/kg dose at the discretion of the investigator and after discussion with the sponsor. Non-US subjects in Arm A were not to be retreated with MEDI-551 on subsequent relapse.

Arm B

Enrollment in Arm B is complete. Based on evaluation of the PK data in CLL subjects (n = 26) from Arm A, there appeared to be lack of full exposure and numerically lower response rate compared to non-CLL subjects using the current monthly dosing regimen at the highest dose evaluated (ie, 12 mg/kg). This arm of the study evaluated further dose escalation in CLL subjects utilizing a new schema, designed to saturate the potential B-cell sink, achieve full exposure, and maximize clinical activity, by employing weekly dosing of MEDI-551 for 4 weeks during Cycle 1 and then monthly dosing on Day 1 of each subsequent 28-day cycle to determine the MTD or the highest protocol-defined dose in the absence of exceeding the MTD, which would be evaluated in a dose-expansion phase. To further minimize infusion-related reactions at higher dose levels, for the 24 and 48 mg/kg dose levels of MEDI-551, the initial weekly doses were to be administered over 2 days on Day 1 and Day 2 in Cycle 1. Subsequent doses at the 24 and 48 mg/kg dose levels were to be administered in an identical fashion to lower dose levels (ie, weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond). Note that the 48 mg/kg cohort was not enrolled. A flow diagram for Arm B is provided in Figure 3.1-2.

Using a standard 3+3 design, 3 to 6 subjects with CLL were to be enrolled per cohort, starting at a dose of 6 mg/kg and escalating to 3 additional dose levels (12, 24, and 48 mg/kg) in the dose-escalation phase of this arm. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, achieves CR (2 additional cycles at the same dose may be given prior to EOT) or withdraws consent. If 0 of 3 or ≤ 1 of 6 subjects treated at the previous dose level experienced a DLT, dose escalation could continue. The MTD was defined as the dose at which no more than 1 of 6 subjects experienced a DLT during Cycle 1. No intrasubject dose escalation was allowed. Subjects were considered evaluable for a DLT if they completed their first cycle of therapy or discontinued therapy during Cycle 1 due to a DLT. Nonevaluable subjects were to be replaced in the same dose cohort. A total of up to 24 subjects were to be enrolled in the dose-escalation portion of this arm. Dose escalation was permitted after all investigators reviewed the available data after a data review meeting and unanimously agreed to proceed with enrollment into the next cohort. The outcome from this meeting was documented in writing and shared with all participating sites.

Once an MTD was identified or the maximum planned dose not exceeding the MTD was reached, additional CLL subjects were to be enrolled at the selected dose in the dose-expansion phase to ensure a total of 26 efficacy evaluable subjects were available for analysis after completing one post-treatment disease evaluation. The dose-expansion phase

included subjects treated at the MTD or maximum planned dose enrolled in the dose-escalation phase of this arm. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, withdraws consent, or achieves CR (2 additional cycles at the same dose may be given prior to EOT).

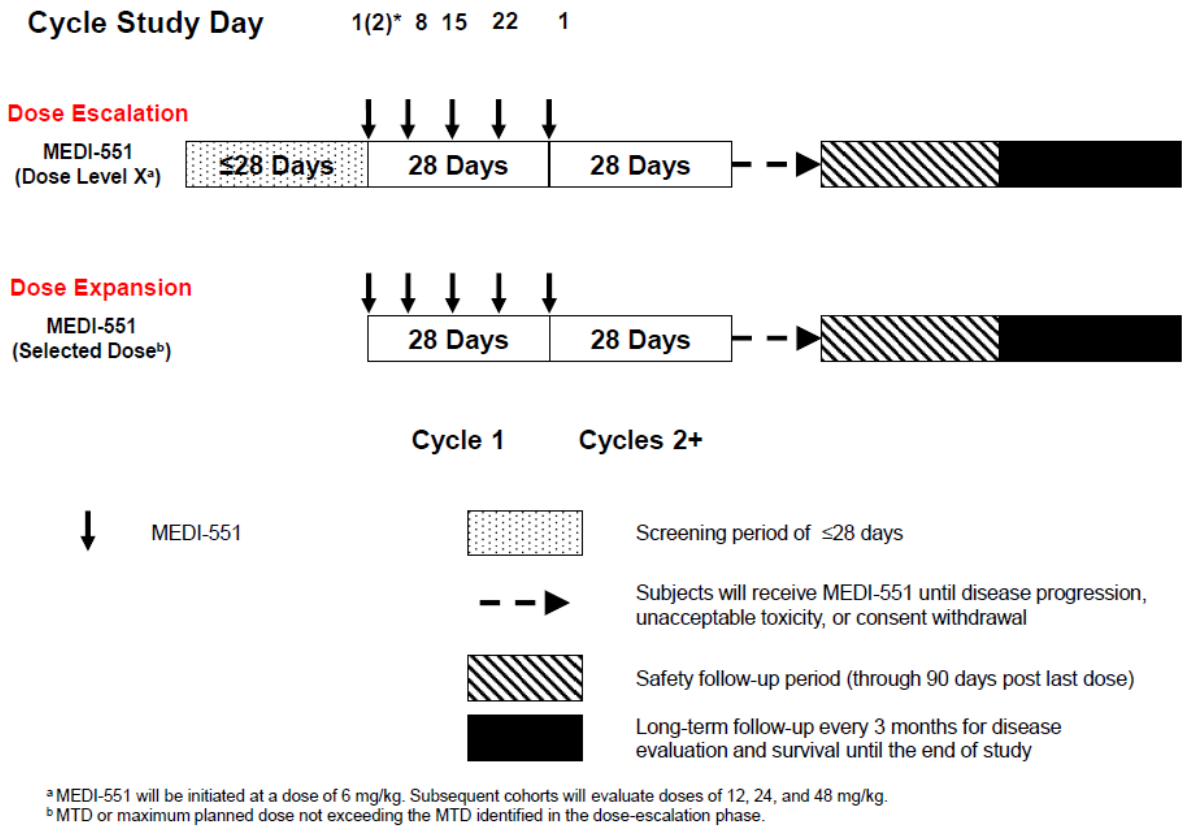


Figure 3.1-2 Flow Diagram for Dose Escalation and Expansion in Arm B

MTD = maximum tolerated dose.

* Note: For the 24 and 48 mg/kg cohorts, the initial weekly doses were administered over 2 days on Day 1 and Day 2 in Cycle 1. Subsequent doses for the 24 and 48 mg/kg cohorts were to be administered weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond. Note that the 48 mg/kg cohort was not enrolled.

Arm C

Enrollment in Arm C is complete. Given the high unmet medical need in patients with multiply relapsed aggressive lymphoma, the synergistic activity observed in preclinical studies with MEDI-551 and rituximab, as well as the promising clinical activity seen with other dual MAb combinations in patients with B-cell malignancies, this arm of the study evaluated the safety and efficacy of MEDI-551 in combination with rituximab in subjects with aggressive lymphoma (relapsed or refractory DLBCL, Grade 3b FL, FL transforming to

DLBCL and MCL) in dose-escalation and dose-expansion cohorts. A flow diagram for Arm C is provided in Figure 3.1-3.

Using a standard 3+3 design, 3 to 6 subjects with aggressive NHL were enrolled per cohort in the dose-escalation portion of this arm, starting at a MEDI-551 dose of 8 mg/kg and escalating to 12 mg/kg. Subjects in this arm received weekly rituximab for 8 weeks beginning on Day 1 of Cycle 1 along with MEDI-551 8 mg/kg on Days 2 and 8 of Cycle 1, and on Day 1 of Cycle 2 and beyond in 28-day cycles. Dose escalation continued to 12 mg/kg as 0 of 3 or ≤ 1 of 6 subjects treated at the lower dose experienced a DLT. The MTD was defined as the dose at which no more than 1 of 6 subjects experienced a DLT. No intrasubject dose escalation was allowed. Subjects were considered evaluable for a DLT if they completed their first cycle of therapy or discontinued therapy during Cycle 1 due to a DLT. Nonevaluable subjects were to be replaced in the same dose cohort. A total of up to 12 subjects were to be enrolled in the dose-escalation portion of this arm of the study. Dose escalation was permitted after all investigators reviewed the available data during a data review meeting and unanimously agreed to proceed with enrollment into the next cohort. The outcome from this meeting was documented in writing and shared with all participating sites.

Once an MTD was identified or the maximum planned dose not exceeding the MTD was reached, additional subjects were to be enrolled and treated at the selected dose of MEDI-551 in combination with rituximab in the dose-expansion portion of this arm to ensure a total sample size of 26 efficacy evaluable subjects were available for analysis after completing one post-treatment disease evaluation. The 26 subjects were to include subjects treated at the selected dose during the dose-escalation portion of this arm. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, withdraws consent, or achieves a CR (2 additional cycles of MEDI-551 at the same dose may be administered before EOT). A total of 19 subjects were enrolled in Arm C.

Subjects in Arm C were stratified based on their responsiveness to any prior anti-CD20-based therapy with the option of ensuring a minimum number of 7 subjects who are refractory to any prior anti-CD20-based therapy are enrolled if clinical data from Arm D or emerging preclinical data suggest that the combination of anti-CD20 and anti-CD19 therapies improve response in this subpopulation.

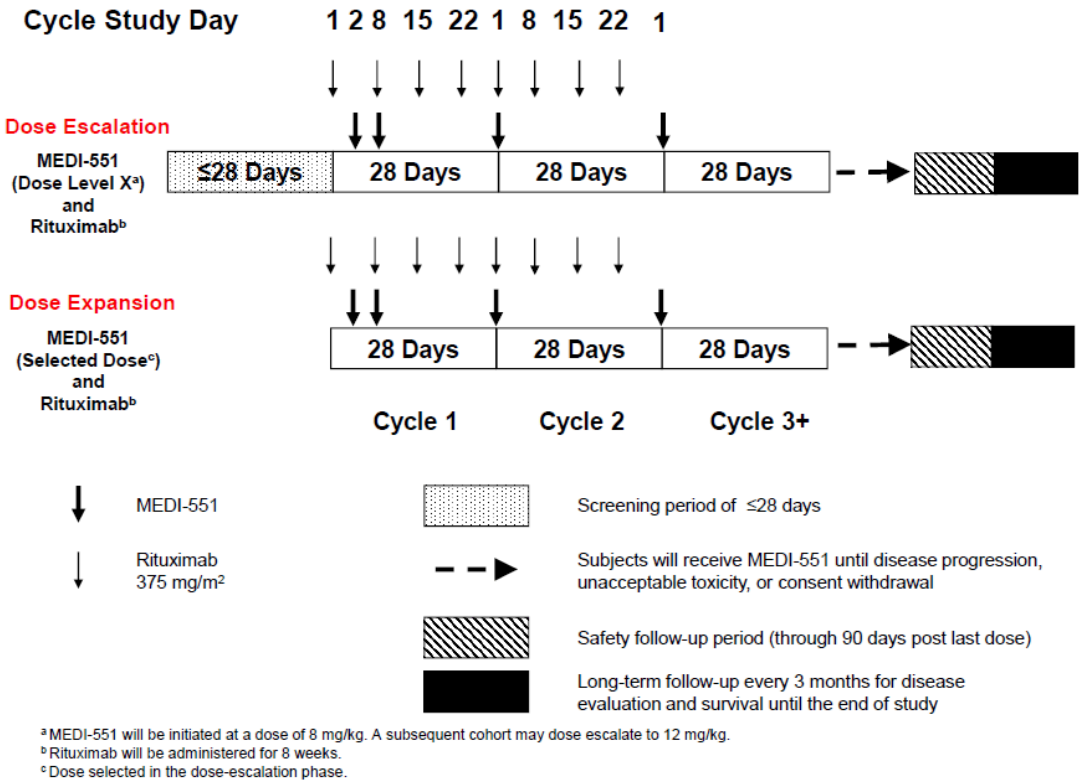


Figure 3.1-3 Flow Diagram for Dose Escalation and Expansion in Arm C

MTD = maximum tolerated dose.

Arm D

Enrollment in Arm D is complete. Given the high unmet medical need in patients with refractory aggressive lymphoma and in light of preservation of CD19 expression on the surface of these malignant cells, MEDI-551 may represent a salvage therapy option for anti-CD20-refractory patients. Evidence of clinical activity and safety of MEDI-551 in an unselected patient population (Arm A) supported investigating MEDI-551 in the anti-CD20-refractory population. Arm D evaluated the clinical activity of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphoma (refractory DLBCL, Grade 3b FL, FL transforming to DLBCL, and MCL). A flow diagram for Arm D is provided in Figure 3.1-4.

Since the safety and tolerability of the 12-mg/kg dose of MEDI-551 has been verified in Arm A, approximately 26 subjects with any anti-CD20-refractory disease were to be enrolled and treated with single-agent MEDI-551 at the dose and schedule used in the expansion cohort of Arm A (ie, 12 mg/kg of MEDI-551 on Days 1 and 8 of Cycle 1, and on Day 1 of Cycle 2 and beyond in 28-day cycles). A total of 16 subjects were enrolled in Arm D. Treatment may continue until the subject experiences unacceptable toxicity, disease

progression, withdraws consent, or achieves a CR (2 additional cycles of MEDI-551 at the same dose may be administered before EOT).

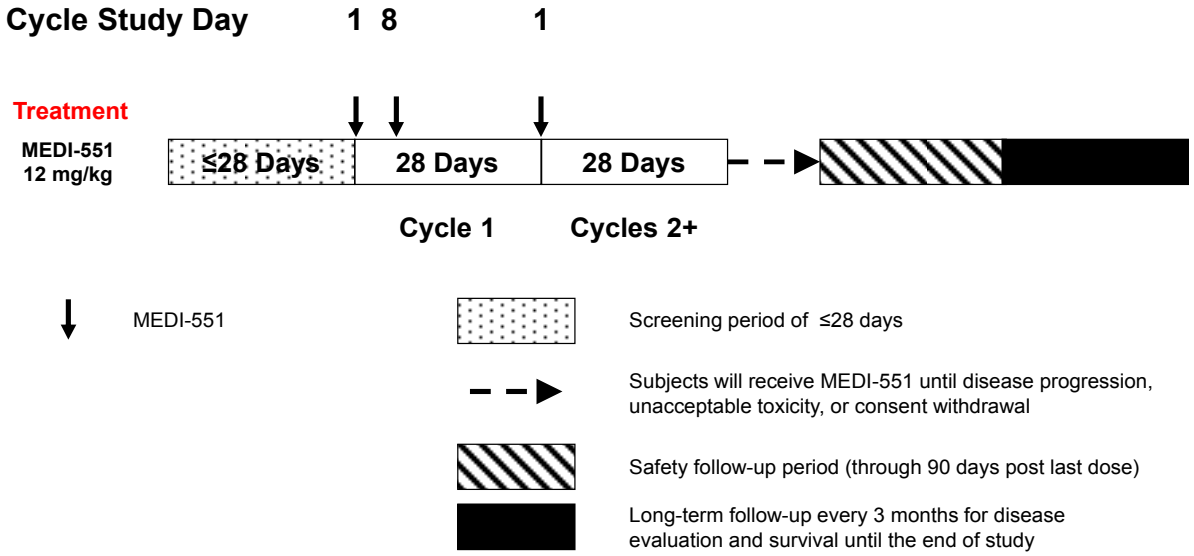


Figure 3.1-4 Flow Diagram for Treatment in Arm D

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Study Duration

The duration of investigational product treatment will be determined by disease response and safety. Safety follow-up assessments will be conducted through approximately 90 days after the last dose of investigational product, which is equivalent to approximately 60 days post-EOT Visit. The estimated study duration is approximately 8 to 10 years from the time the first subject is enrolled in the study. Study completion is defined as the date of the last protocol-specified visit for the last subject in the study.

4 STUDY PROCEDURES

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice response system [IVRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The

SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log will be maintained of all consented subjects and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria).

4.2 Subject Selection

The subjects enrolled in this study were adults with relapsed or refractory B-cell malignancies: CLL (including SLL), DLBCL, FL (as of protocol Version 8.0), MCL (as of protocol Version 10.0), and transformed indolent lymphoma (as of protocol Version 11.0).

The investigator (physician) or qualified designee was to discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study and provide the subject/legal representative with the study-specific informed consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The investigator or designee was to address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, was to secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the US, European Union [EU] Data Privacy Directive authorization in the EU), and written informed assent was to be obtained prior to conducting any protocol-related procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Men or women at least 18 years of age or older at time of study entry
2. Written informed consent and HIPAA authorization (applies to covered entities in the USA only) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
3. Diagnosis
    - Arm A: CLL (including SLL), DLBCL, or FL; SLL, DLBCL, and FL must be histologically confirmed
    - Arm B: Histologically confirmed SLL or previous confirmation of B-cell CLL with a characteristic immunophenotype by flow cytometry
    - Arm C: Histologically confirmed aggressive B-cell DLBCL, including FL transforming to DLBCL, transformed indolent lymphoma, MCL, or Grade 3b FL,

according to the World Health Organization (WHO)/American Joint Committee on Cancer (AJCC) criteria

- Arm D: Histologically confirmed anti-CD20-refractory (defined as any subject with less than a PR to any prior anti-CD20-based therapy or progression within 6 months after completing therapy with any anti-CD20-based regimen, including maintenance rituximab) aggressive B-cell DLBCL, including FL transforming to DLBCL, transformed indolent lymphoma, MCL, or Grade 3b FL, according to the WHO/AJCC criteria

4. Optional: Willing to provide a fresh tumor sample if a sufficient quantity of archival tumor sample is not available (Arms B, C, and D).
5. Evaluable/measurable disease
   - Non-CLL B-cell malignancies (Arms A, C, and D):
     - Histologically confirmed B-cell NHL (FL or DLBCL), transformed indolent lymphoma, and MCL: Measurable disease defined as ≥ 1 lesion ≥ 20 mm in one dimension or ≥15 mm in 2 dimensions as measured by conventional or high-resolution (spiral) computed tomography (CT). For Arms C and D: disease evaluable by the International Working Group criteria (Cheson et al, 2007)
     - Baseline PET or PET/CT scans must show positive lesions compatible with CT-defined anatomical tumor sites (only applicable for FL, DLBCL, MCL, transformed indolent lymphoma, and FL transforming to DLBCL)
   - CLL (Arms A and B):
     - Confirmed B-cell CLL/SLL with a characteristic immunophenotype by flow cytometry, and symptomatic disease requiring treatment
     - CT scans showing involvement of ≥ 1clearly demarcated lesions measuring ≥ 1.5 cm
6. Prior therapy
   - Arm A:
     - Histologically confirmed B-cell NHL (FL or DLBCL): Relapsed from or refractory to ≥ 1 prior regimen containing rituximab, either alone or in combination, and not be a candidate for hematopoietic SCT or BM transplant
     - B-cell CLL: Relapsed from or refractory to ≥ 2 prior lines of treatment, ≥ 1 of which must have contained rituximab
   - Arm B: Relapsed from or refractory to ≥ 2 prior chemotherapy regimens with ≥ 1 regimen containing rituximab
   - Arm C: Relapsed from or refractory to ≥ 2 prior chemotherapy regimens with ≥ 1 regimen containing rituximab or failed 1 prior rituximab-containing regimen and unable to tolerate additional multiagent chemotherapy
   - Arm D: Refractory to ≥ 1 regimen containing any anti-CD20-based therapy, including salvage regimens and maintenance rituximab. Refractory subjects are defined as any subject with less than a PR to any prior anti-CD20-based therapies or progressed within 6 months after completing therapy with any anti-CD20-based regimens, including maintenance rituximab. These subjects must not be eligible for hematopoietic SCT or BM transplant

7. Prior radiation therapy is allowed provided exposure does not exceed an area of 25% of marrow space and occurred ≥ 6 weeks prior to the first dose of MEDI-551 (Arm A only)
8. Karnofsky performance status ≥ 70
9. Life expectancy of ≥ 12 weeks
10. Adequate hematologic function

    Arm A (except for CLL subjects with significant BM involvement by biopsy) must meet the following criteria:

    - Hemoglobin ≥ 9 g/dL, (≥ 8 g/dL for subjects who are transfusion dependent)
    - Absolute neutrophil count ≥ 1500/mm^3
    - Platelet count ≥ 75,000/mm^3

    Arms B, C, and D must meet the following criteria:

    - Hemoglobin ≥ 8 g/dL
    - Absolute neutrophil count ≥ 1000/mm^3
    - Platelet count ≥ 75,000/mm^3
    - In the event of significant BM involvement, the above hematologic criteria will not be required for enrollment eligibility
11. Adequate organ function defined as follows:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2 × institutional upper limit of normal (ULN)
    - Bilirubin ≤ 1.5 × ULN except for subjects with documented Gilbert's disease, ≤ 2.5 × ULN;
    - Serum creatinine ≤ 1.5 mg/dL or a calculated creatinine clearance of ≥ 60 mL/min as determined by the Cockcroft-Gault equation[1]
12. Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use highly effective contraception from screening and must agree to continue using such precautions for at least 180 days after the last dose of investigational product. Depending on the investigational product received, this period may be longer. Cessation of birth control after this point should be discussed with a responsible physician
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are postmenopausal (defined as 12 months with no menses without an alternative medical cause or follicle-stimulating hormone/luteinizing hormone levels consistent with a menopausal state)
    - A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Acceptable methods of contraception are described in Table 4.2.1-1. Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception

[1] Cockcroft-Gault equation: (140 - age) × weight in kg / (serum creatinine × 72). Multiply by 0.85 for females.

13. Non-sterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (Table 4.2.1-1) from at least Day 1 through 90 days after the last dose of investigational product
14. Negative serum beta human chorionic gonadotropin (βhCG) test (for women of childbearing potential only)
15. Females or female partners not of childbearing potential must have been surgically sterilized or postmenopausal (as defined above in inclusion criterion #12). Sterilized males must be at least 1 year post vasectomy

Table 4.2.1-1 Recommended Methods of Contraception

Barrier Methods	Intrauterine Devices	Hormonal Contraceptives
Male condom plus spermicide Cap (plus spermicidal cream or jelly) plus male condom Diaphragm (plus spermicidal cream or jelly) plus male condom	Copper T Progesterone T plus condom or spermicide	Implants Hormone shot/injection Combined pill Minipill Patch

4.2.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Any available standard line of therapy known to be life-prolonging or life-saving
2. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for treatment of cancer
3. History of allergy or reaction to any component of the MEDI-551 formulation
4. Receipt of any chemotherapy or small molecule targeted therapy (such as imatinib or other tyrosine kinase inhibitors, and including any experimental therapies) or radiation therapy within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of MEDI-551
5. Receipt of any biological or immunological-based therapies (including experimental therapies) for leukemia, lymphoma, or myeloma (including, but not limited to, MAb therapy such as rituximab, or cancer vaccine therapies) within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of MEDI-551
6. Previous therapy directed against CD19, such as MAbs or MAb conjugates
7. Live or attenuated vaccines (other than experimental cancer vaccine therapy) within 28 days prior to receiving the first dose of MEDI-551
8. Evidence of significant active infection requiring antimicrobial, antifungal, antiparasitic, or antiviral therapy or for which other supportive care is given
9. Autologous SCT within 12 weeks prior to study entry (Arms A and D only)
10. Prior allogeneic SCT or organ transplant (Arms A and D only)
11. Human immunodeficiency virus (HIV) positive serology or AIDS
12. Active hepatitis B as defined by seropositivity for hepatitis B surface antigen or positive hepatitis B core antibody. Subjects with hepatitis C antibody will be eligible provided

that they do not have elevated liver transaminases or other evidence of active hepatitis (Villadolid et al, 2010)

13. Ongoing ≥ Grade 2 toxicities from previous cancer therapies unless specifically allowed in the Inclusion/Exclusion criteria. Use of immunosuppressive medication other than steroids within 28 days before the first dose of MEDI-551
14. Use of systemic steroids within 7 days before the first dose of MEDI-551 (inhaled and topical corticosteroids are permitted). Subjects may take replacement doses of steroids (defined as ≤ 30 mg/day hydrocortisone or the equivalent) if on a stable dose for at least 2 weeks prior to the first dose of MEDI-551. This does not include required steroid prophylaxis prior to the first infusion of MEDI-551
15. Documented current central nervous system involvement by leukemia or lymphoma
16. Pregnancy or lactation
17. Previous medical history, or evidence, of an intercurrent illness that at the discretion of the principal investigator may compromise the safety of the subject in the study
18. Clinically significant abnormality on electrocardiogram (ECG). The corrected QT interval (QTc, Fridericia) must be < 470 milliseconds for men and < 490 milliseconds for women (Must be confirmed by at least 2 additional 12-lead ECGs at least 2 minutes apart such that average manually over-read QTcF based on 3 ECGs exceeds stated thresholds)
19. Any physical, social, or psychiatric condition that would prevent effective cooperation or participation in the study
20. Concurrent enrollment in another clinical study, unless in a follow-up period or it is an observational study
21. Employees of the clinical study site who are directly involved with the conduct of the study, or immediate family members of such individuals. These subjects may be treated at another site participating in the study
22. History of other invasive malignancy within 5 years except for localized/in situ carcinomas.

4.3 Study Entry and Treatment Assignment

An IVRS was used to both document participation and to assign a dose cohort (dose-escalation phase) or treatment arm (expansion phase) to the subject. A subject was considered entered into the study when the investigator notified the IVRS that the subject met eligibility criteria and the IVRS provided the assignment of investigational product.

The procedure for using IVRS was as follows:

- Once the subject had signed the informed consent form, the investigator or designee contacted the IVRS and the IVRS provided the assignment of the SID number
- After confirmation of eligibility, the investigator or designee contacted the IVRS and provided the SID number and subject's baseline characteristic(s) used to verify that it is the same subject

- The IVRS assigned a dose cohort or treatment arm to the subject based on disease type
- A confirmatory fax/email with this information was sent to the investigator/designee who dispensed the investigational product to the subject and recorded the appropriate information in the subject's medical records and investigational product accountability log

Details for using IVRS were provided in the IVRS manual.

Investigational product (MEDI-551) must be administered after the dose cohort or treatment arm is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the MedImmune study monitor and/or its designee must be notified immediately.

4.4 Blinding

This study was not blinded.

4.5 Study Treatment

4.5.1 Investigational Product (MEDI-551)

MEDI-551 is manufactured by MedImmune, LLC. Investigational product will be distributed to clinical sites using designated distribution centers. The sponsor will provide the investigators with adequate quantities of investigational product. Investigational product will be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product will be supplied to the investigational product manager in vials with identical appearances. The clinical site staff will order investigational product from the investigational product manager using the site's normal ordering procedures. The investigational product manager will prepare the investigational product. MEDI-551 is supplied as a sterile liquid solution at a dosage strength of [redacted] at MEDI-551 concentrations of [redacted]. Investigational product will be supplied as described below:

[redacted]: The [redacted] Drug Products are supplied in vials with a nominal [redacted] solution of MEDI-551 at a concentration of [redacted] MEDI-551, and contain a nominal [redacted] of MEDI-551.

The Drug Product solution at the [redacted] strength contains [redacted].

[redacted]: The [redacted] Drug Products are supplied in vials with a nominal [redacted] solution of MEDI-551 at a concentration of [redacted], and contain a nominal [redacted] of MEDI-551.

The Drug Product solution at the [redacted] strength contains [redacted]

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.5.1.1 Investigational Product Inspection

Each vial of investigational product selected for dose preparation should be inspected. MEDI-551 is supplied as [redacted]), clear, colorless, liquid solutions that are free from visible particles. If any defects in the investigational product are noted, the investigator and site monitor should be notified immediately (see Section 4.5.1.2).

4.5.1.2 Reporting Product Complaints

Any defects in the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com
Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)
Fax: +1-301-398-8800
Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Treatment Regimens

Arm A

Subjects enrolled in the dose-escalation phase of Arm A were treated with 1 of 6 doses (0.5, 1, 2, 4, 8, or 12 mg/kg) of MEDI-551. Subjects in Cohorts 1 and 2 received 0.5 or 1 mg/kg MEDI 551, respectively, IV once every week in 4-week cycles. Subjects enrolled in Cohorts 3, 4, 5, and 6 will receive 2, 4, 8, or 12 mg/kg MEDI-551, respectively, IV once per week on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle. Subjects who did not experience a DLT or did not otherwise become ineligible to receive MEDI-551 may continue to receive MEDI-551 until CR, disease progression, toxicity, or another reason for treatment discontinuation is observed. Subjects who achieve a CR may receive an additional 2 cycles of MEDI-551 at the same dose. Once Version 13.0 is implemented, re-treatment will not be available for subjects who achieve a CR and subsequently relapse while off treatment.

Following determination of the MTD or OBD or completion of dose escalation to 12 mg/kg as described in Section 4.5.5, additional subjects with FL, CLL, or DLBCL were enrolled in the dose-expansion phase of Arm A. A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled. One subject with MM was enrolled before the MM group was removed from the dose-expansion phase of the study. Enrollment of MM subjects was discontinued due to a lack of activity based on nonclinical and preliminary clinical data. Subjects in these dose-expansion cohorts were treated at a dose of 12 mg/kg in the absence of establishing a MTD. Different dose levels or dosing schedules may be evaluated if all available safety, PK, pharmacodynamic, and efficacy data suggest that evaluation of different dose levels, dosing schedules and/or duration of treatment would be beneficial. Subjects in the expansion phase were treated with MEDI-551 on Days 1 and 8 of Cycle 1 (loading doses) and then on Day 1 of every subsequent 28-day cycle unless evaluation of different schedule(s) was needed as described above.

Arm B

During the dose-escalation phase of Arm B, MEDI-551 was administered IV at 6 mg/kg weekly for 4 weeks during Cycle 1. For Cycle 2 and beyond, MEDI-551 6 mg/kg was administered on Day 1 of each 28-day cycle. Subsequent sequential cohorts were to evaluate doses of 12, 24, and 48 mg/kg administered weekly for 4 weeks during Cycle 1 and then on Day 1 of each 28-day cycle starting with Cycle 2 and beyond.

To further minimize infusion-related reactions at higher dose levels, for the 24 and 48 mg/kg dose levels of MEDI-551, the initial weekly doses were to be administered over 2 days on Day 1 and Day 2 in Cycle 1. Additionally, as detailed in Section 4.5.3, mandatory premedication against IRR was required on both Day 1 and Day 2 of Cycle 1.

1. At the 24 mg/kg dose level MEDI-551 was administered as follows:
   a. On Day 1, 12 mg/kg as an infusion over a minimum of 81 minutes as detailed in Section 4.5.3
   b. On Day 2, 12 mg/kg as an infusion over a minimum of 60 minutes as detailed in Section 4.5.3
2. At the 48 mg/kg dose level MEDI-551 was to be administered as follows:
   a. On Day 1, 12 mg/kg as an infusion over a minimum of 81 minutes as detailed in Section 4.5.3
   b. On Day 2, 36 mg/kg as an infusion over a minimum of 60 minutes as detailed in Section 4.5.3

Subsequent doses at the 24 and 48 mg/kg dose levels was to be administered in an identical fashion to lower dose levels (ie, weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond).

During the dose-expansion phase of Arm B, the selected MEDI-551 dose was to be administered IV weekly for 4 weeks during Cycle 1 and then on Day 1 of an every 28-day cycle starting with Cycle 2 and beyond.

Treatment may continue until the subject experiences unacceptable toxicity, disease progression, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

Arm C

During the dose-escalation phase of Arm C, MEDI-551 was administered IV at 8 mg/kg on Days 2 and 8 in combination with rituximab 375 mg/m^2 administered IV on Days 1, 8, 15,

and 22 of Cycle 1 (28-day cycle). In Cycle 2, MEDI-551 was administered at 8 mg/kg on Day 1 and rituximab 375 mg/m^2 was administered on Days 1, 8, 15, and 22. For Cycle 3 and beyond, only MEDI-551 8 mg/kg was administered on Day 1 of each 28-day cycle. As the MTD was not exceeded at 8 mg/kg, the MEDI-551 dose was escalated to 12 mg/kg administered in combination with a fixed dose of rituximab on the same schedule as noted above.

Treatment during the dose-escalation phase may continue until the subject experiences unacceptable toxicity, disease progression, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

Arm D

MEDI-551 was be administered IV at 12 mg/kg on Days 1 and 8 of Cycle 1 and on Day 1 of Cycle 2 and beyond in 28-day cycles. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, reaches CR (2 additional cycles may be given prior to EOT) or withdraws consent.

4.5.2.1 Dose Modification for Toxicity Management

Arm A

In rare circumstances and under the authority of the Medical Monitor, subjects were retreated following a DLT as described in Section 6.4.1.

During the DLT period, dose modification was not permitted. However, a delay in therapy due to a reversible non-DLT toxicity was permitted as long as the total delay within the cycle is ≤ 5 days total. Any toxicity leading to a delay > 5 days in duration during the DLT period was be considered a DLT.

Following the DLT period, subsequent cycles of MEDI-551 were delayed or modified based on hematologic and nonhematologic toxicities observed during each subsequent cycle of treatment as described in Table 4.5.2.1-1. Both hematologic and nonhematologic toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE V4.03; CTCAE, 2010).

The following AEs are exceptions to the dose modification and stopping rules described below in Table 4.5.2.1-1 and require NO modification of MEDI-551 dosing: lymphopenia (any grade) and hematologic abnormalities equal in severity to the subject's baseline grade. Dose modification for Grade 2, 3, or 4 AEs will occur as described in Table 4.5.2.1-1. For

Grade 4 hematologic toxicity (other than lymphopenia), resolution to ≤ Grade 2 or subject's baseline is required to re-initiate treatment.

Adverse events for which a cause other than MEDI-551 can be clearly attributed (such as an accident) will not result in a dose delay or reduction.

Table 4.5.2.1-1 MEDI-551 Dose Modifications for Arm A

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-551
Grade ≤ 1	None
Grade 2 [a]	**First Occurrence**: • For AEs present before the next dose of MEDI-551 is to be given, delay the next dose of MEDI-551 for up to 7 days until resolution to ≤ Grade 1 or baseline, and resume at current dose level. • Reduce the dose of MEDI-551 to 50% and restart therapy if AE does not resolve to ≤ Grade 1 or baseline within 7 days. • For Grade 2 infusion reaction, infusion rate may be decreased by 50% or interrupted for up to 4 hours and symptomatic care instituted as clinically indicated. Following interruption, infusion should be resumed at 50% of original rate for remainder of infusion. • For allergic reactions ≥ Grade 2 or any allergic reaction necessitating the use of pressors, permanently discontinue MEDI-551. **Second Occurrence:** • For second occurrence of Grade 2 AE, delay for up to 7 days until resolution to ≤ Grade 1 or baseline and initiate next dose at 50% of current dose level. The exceptions are as follows: ◦ For Grade ≥ 2 allergic reactions, MEDI-551 is to be permanently discontinued at the first occurrence. ◦ Grade 2 infusion reactions do not necessitate dose reduction. • Permanently discontinue MEDI-551 if AE does not resolve to ≤ Grade 1 or baseline within 7 days or if the dose has previously been reduced.

Table 4.5.2.1-1 MEDI-551 Dose Modifications for Arm A

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-551
Grade 3 or 4 [b, c]	**First Occurrence:** • For AEs present before the next dose of MEDI-551 is to be given, delay next dose of MEDI-551 for up to 7 days until resolution to ≤ Grade 1 or baseline, and resume at 50% of current dose level. • If next dose is delayed for > 7 days due to failure of toxicity to resolve to ≤ Grade 1 or baseline, discontinue MEDI-551. • For Grade 3 infusion reaction, infusion rate may be decreased by 50% or interrupted for up to 4 hours and symptomatic care instituted as clinically indicated; steroid prophylaxis must be employed for all subsequent doses of MEDI-551. Following interruption, infusion should be resumed at 50% of original rate for remainder of infusion. For Grade 3 infusion reaction that does not respond to medical therapy (including interruption of infusion for ≤ 4 hours) or that occurs despite steroid prophylaxis, permanently discontinue MEDI-551. • For any Grade 4 infusion or allergic reaction that necessitates the use of systemic pressor agents, permanently discontinue MEDI-551. **Second Occurrence:** • Permanently discontinue MEDI-551.

See Section 6.4.1 for additional details on dose interruption and study discontinuation criteria.

[a] Hematologic abnormalities equal in severity to the subject's baseline and lymphopenia (any grade) do not require dose modification.

[b] Except Grade 3 or 4 toxicities noted as exceptions to the DLT criteria (see Section 4.5.6).

[c] For ≥Grade 3 hematologic toxicities other than lymphopenia, resolution to ≤ Grade 2 or subject's baseline is required to re-initiate treatment.

Arms B, C, and D

During the DLT period, dose modification was not permitted. However, a delay in therapy due to reversible non-DLT toxicity was permitted as long as the total delay within the cycle is ≤ 7 days total. Any toxicity leading to a delay > 7 days in duration during the DLT period was considered a DLT.

Following the DLT period, subsequent cycles of MEDI-551 could be delayed or modified based on hematologic and nonhematologic toxicities observed during each subsequent cycle of treatment as described in Table 4.5.2.1-2. Both hematologic and nonhematologic toxicities were graded according to the NCI CTCAE V4.03 (CTCAE, 2010).

The following AEs were exceptions to the dose modification and stopping rules described in Table 4.5.2.1-2 and required NO modification of MEDI-551 dosing: lymphopenia (any grade) or hypogammaglobulinemia. Dose modification for Grade 2, 3, or 4 AEs occurred as described in Table 4.5.2.1-2. Laboratory changes within a cycle did not require prompt dose modification or delay unless clinically indicated in the investigator's opinion. Adverse events

for which a cause other than MEDI-551 could be clearly attributed (such as an accident) did not result in a dose delay or reduction. If more than one dose reduction was needed for the same toxicity, the subject was required to permanently discontinue treatment.

For subjects in the dose-escalation portion of Arms B and C, if the start of Cycle 2 was delayed for toxicity-related reasons beyond 7 days, the subject was considered to have had a DLT and was required to resume dosing at a dose level below which they were enrolled. If the subject was unable to recover from toxicity within 7 days despite the dose modification indicated in Table 4.5.2.1-2, they were required to permanently discontinue treatment. The start of Cycle 3 and beyond was allowed to be delayed by up to 7 days to permit resolution of toxicity or for logistical reasons. If a subject delayed 2 consecutive cycles by >7 days each, they were to be withdrawn from therapy even if delays are due to different toxicities.

For all subjects in the dose-expansion portion of Arms B and C, and for all subjects enrolled in Arm D, any cycle could be delayed by 7 days to permit resolution of toxicity or for logistical reasons. For a given subject, a single cycle was allowed to be delayed by up to 28 days to permit recovery from toxicity. Upon recovery of toxicity, dose modification was required to be performed according to the guidelines provided in Table 4.5.2.1-2. If a cycle was delayed by > 28 days, the subject was required to permanently discontinue treatment. If a subject had received 1 dose reduction and a subsequent cycle was delayed by > 7 days to permit recovery from toxicity, the subject was required to permanently discontinue treatment. If 2 consecutive cycles were delayed by 7 days each, the subject was required to permanently discontinue therapy even if delays are due to different toxicities.

Table 4.5.2.1-2 MEDI-551 Dose Modifications for Nonhematologic and Hematologic Toxicity in Arms B, C, and D

Toxicity Grade	Dose Modification of MEDI-551
	Nonhematologic Toxicity
Grade ≤ 1	None
Grade 2	**First Occurrence:** • For Adverse Events (AEs) present before the next dose of MEDI-551 is to be given: • If resolution to ≤ Grade 1 or baseline within 7 days, then resume at current dose level a) If resolution to ≤ Grade 1 or baseline within 8-28 days, then resume dose at 50% of current dose level • If resolution to ≤ Grade 1 or baseline exceeds 28 days, then discontinue MEDI-551 • For Grade 2 infusion reaction, infusion rate may be decreased by 50% or interrupted for up to 4 hours and symptomatic care instituted as clinically indicated. Following interruption, infusion should be resumed at 50% of original rate for remainder of infusion. • For allergic reactions ≥ Grade 2 or any allergic reaction necessitating the use of pressors, permanently discontinue MEDI-551. **Second Occurrence:** • For AEs present before the next dose of MEDI-551 is to be given: a) If resolution to ≤ Grade 1 or baseline within 7 days, then initiate next dose at 50% of current dose level with the following exceptions: i) For ≥ Grade 2 allergic reactions, MEDI-551 is to be permanently discontinued at the first occurrence ii) Grade 2 infusion reactions do not necessitate dose reduction iii) For Grade 2 AE that previously required dose reduction but resolves within 7 days on 2nd occurrence, resume at current dose level (ie, 50% of original dose) b) If resolution to ≤ Grade 1 or baseline beyond 7 days, then permanently discontinue MEDI-551 c) If resolution to ≤ Grade 1 or baseline takes exactly 7 days in two consecutive cycles, then permanently discontinue MEDI-551 **Third Occurrence:** • For AEs present before the next dose of MEDI-551 is to be given, permanently discontinue MEDI -551

Table 4.5.2.1-2 MEDI-551 Dose Modifications for Nonhematologic and Hematologic Toxicity in Arms B, C, and D

Toxicity Grade	Dose Modification of MEDI-551
Grade 3 or 4 [a,b]	**First Occurrence:** • For AEs present before the next dose of MEDI-551 is to be given, delay next dose of MEDI-551 for up to 7 days until resolution to ≤ Grade 1 or baseline, and resume at 50% of current dose level. • If next dose is delayed for > 7 days due to failure of toxicity to resolve to ≤ Grade 1 or baseline, permanently discontinue MEDI-551. • For Grade 3 infusion reaction, infusion must be stopped for up to 4 hours until the subject recovers. An additional dose of steroids will be given and the infusion may resume but the infusion rate must be decreased by 50% for remainder of infusion. For Grade 3 infusion reaction that does not respond to medical therapy (including interruption of infusion for ≤ 4 hours) or that occurs despite steroid prophylaxis, discontinue MEDI-551. • For any Grade 4 infusion or allergic reaction that necessitates the use of systemic pressor agents, permanently discontinue MEDI-551. **Second Occurrence:** • For AEs present before the next dose of MEDI-551 is to be given, permanently discontinue MEDI-551.
Hematologic Toxicity [c,d]	
Grade 1 or 2	None
Grade 3 [a,b]	**First Occurrence:** • Delay dose by up to 7 days until resolution to ≤ Grade 2 and resume at current dose level. If subject does not recover to ≤ Grade 2 within that time, permanently discontinue MEDI-551. **Second Occurrence:** • Delay dose by up to 7 days until resolution to ≤ Grade 2 and decrease dose by 50%. If subject does not recover to ≤ Grade 2 within that time, permanently discontinue MEDI-551. **Third Occurrence:** • Permanently discontinue MEDI-551.
Grade 4 [a,b]	**First Occurrence:** • Delay dose by up to 7 days until resolution to ≤ Grade2 and decrease dose by 50%. If subject does not recover to ≤ Grade 2 within that time, permanently discontinue MEDI-551. **Second Occurrence:** • Permanently discontinue MEDI-551.

See Section 6.4.1 for additional details on dose interruption and study discontinuation criteria.

[a] Except Grade 3 or 4 toxicities noted as exceptions to the Dose Limiting Toxicity (DLT) criteria (see Section 4.5.6).

[b] Please note that for laboratory findings observed in the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings before implementing dose modification.

[c] For advanced B-cell malignancy dose escalation/expansion, hematologic abnormalities equal in severity to the subject's baseline and lymphopenia (any grade) do not require dose modification.

[d] For subjects in Arms B, C, and D, lymphopenia or changes in lymphocyte counts will not be considered hematologic toxicities. Hematologic abnormalities equal in severity to the subject's baseline grade will not warrant dose modification unless they recur after normalization or improvement in the counts to ≤ Grade 2. Thereafter, hematologic abnormalities will require dose modification or cessation of dosing as indicated in

Table 4.5.2.1-2 MEDI-551 Dose Modifications for Nonhematologic and Hematologic Toxicity in Arms B, C, and D

Toxicity Grade	Dose Modification of MEDI-551

this table.

4.5.3 Investigational Product Preparation and Administration

The day of receipt of the first dose of investigational product is considered Day 1. The weight used to calculate the dose will be the weight on Day 1 of each cycle. The weight at screening may be used for Cycle 1, Day 1 if the weight on Day 1 is within 10% of the screening weight. No change in dose should be made during a particular cycle unless a change in weight of greater than 10% is observed from the weight used to calculate the dose for that cycle. An equation for weight-based dose calculation is provided below.

Drug Volume (mL) = Dose (mg/kg) × Patient Weight (kg) ÷ Product Concentration (mg/mL)

The dose of investigational product for administration must be prepared by the investigators or site's designated investigational product manager using aseptic technique. The investigational product manager will select the appropriate number of vials of investigational product required to prepare the subject's dose. Allow the vial(s) to come to room temperature.

To prepare investigational product for administration, the investigational product manager should remove the tab portion of the vial cap and clean the rubber stopper with 70% ethyl alcohol or equivalent. To avoid foaming, the vial should not be shaken. A vial should only be used one time to prepare a single dose.

Arm A

The dose of MEDI-551 must be prepared using aseptic technique. MEDI-551 must be diluted for IV administration in a PVC-, DEHP-, and latex-free infusion bag containing a total volume of 250 mL of 0.9% sodium chloride for injection. An amount of 0.9 % sodium chloride equal to the volume of MEDI-551 solution to be added should be removed from the infusion bag, and then the calculated amount of MEDI-551 should be added to the infusion bag. The prepared solution may be stored at room temperature prior to being administered to the subject. MEDI-551 must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial, as the MEDI-551 product contains no bacteriostatic agents.

MEDI-551 will be administered as an IV infusion over 60 minutes (+ 15 minutes) using a 0.2 micron filter. Subjects will be monitored during and after infusion with assessment of vital signs every 15 minutes during infusion, at the end of infusion, and 30 and 60 minutes after the infusion.

In the event of an IRR, the infusion of MEDI-551 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen and/or an antihistamine (eg, diphenhydramine) may be administered at the discretion of the investigator. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. For subsequent infusions in subjects who experience an infusion reaction and do not require discontinuation of MEDI-551 (see Section 6.4.1), acetaminophen and an antihistamine may be administered prior to initiation of the MEDI-551 infusion. If a subject experiences a Grade 3 infusion reaction, all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent) 30 minutes prior to initiation of MEDI-551 infusion. Investigators may administer steroids during any cycle at their discretion as clinically indicated and per their institution's guidelines.

Arms B, C, and D

The use of the 2 dosage strengths, [redacted], will be specified by the sponsor. Subjects who begin therapy with the [redacted] form will continue therapy with that dosage form. Subjects in cohorts of Arms B, C and D receiving MEDI-551 at dose levels of 12 mg/kg or less will receive the [redacted] dosage form. However, the [redacted] ([redacted]) investigational product must be used for the 24 and 48 mg/kg cohorts of Arm B. The dose of MEDI-551 must be prepared using aseptic technique. MEDI-551 has been shown to be compatible with PVC-, DEHP-, and latex-free infusion bags containing a total volume of 250 mL of 0.9% sodium chloride for injection. An amount of 0.9 % sodium chloride equal to the volume of MEDI-551 solution to be added should be removed from the infusion bag, and then the calculated amount of MEDI-551 should be added to the infusion bag. The prepared solution may be stored at room temperature prior to being administered to the subject. MEDI-551 infusion must begin within 4 hours after preparation. If the infusion of the dose is not initiated within 4 hours, a new dose must be prepared using a new vial, as the MEDI-551 product contains no bacteriostatic agents. MEDI-551 will be administered by IV infusion using a 0.2-micron in-line filter.

All subjects must receive mandatory premedication consisting of a minimum dose of 60 mg of IV methylprednisolone (or its equivalent) as well as 500 to 650 mg oral acetaminophen (or

paracetamol equivalent) and 50 mg IV diphenhydramine (or its equivalent) before the start of the initial MEDI-551 infusion. The initial infusion of MEDI-551 will be administered a minimum of 30 to 60 minutes after administration of mandatory premedications (as described in this section) according to the following sequence of infusion rates, regardless of dosage form:

- 1 mL/minute for a minimum of 15 minutes, then
- 2 mL/minute for a minimum of 15 minutes, then
- 4 mL/minute to complete the infusion

The minimum infusion time will be 81 minutes. Subjects receiving doses ≥ 24 mg/kg in Arm B will receive the initial infusion over 2 days on Day 1 and Day 2 of Cycle 1. The Day 1 infusion will be administered over a minimum of 81 minutes as described above. The Day 2 infusion will be administered over a minimum of 60 minutes (+ 15 minutes at the investigator's discretion). If the subject experiences an infusion reaction on Day 1, the Day 2 infusion will be administered over a minimum of 90 minutes. Subjects will be monitored closely during the initial infusion of MEDI-551, with vital signs recorded every 5 minutes over the first 30 minutes of the infusion and then every 15 minutes for the remainder of the infusion duration. Additional details regarding vital signs monitoring during the initial infusion of MEDI-551 are provided in Section 6.4.3. For subsequent infusions, MEDI-551 will be administered over 60 minutes (+ 15 minutes at the investigator's discretion). Vital signs will be monitored as described in Section 6.4.3. The initial infusion of MEDI-551 will be administered on Day 1 of Cycle 1 for Arms B and D, and Day 2 of Cycle 1 for Arm C.

In the event of an IRR, the infusion of MEDI-551 may be interrupted until resolution of the event (up to 4 hours) and re-initiated at the 1-mL/minute rate. MEDI-551 infusion must be completed within 4 hours after the initial start of the infusion (NOTE: This is in addition to the 4 hours permitted from preparation of MEDI-551 solution to start of infusion). A new IP solution is required to be prepared if MEDI-551 infusion is not able to be completed within 4 hours after the initial start of the infusion. The rate may be increased slowly (by 50% every 15 minutes) until completion of the infusion. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) may be administered in addition to acetaminophen (or institutional equivalent) and/or an antihistamine at the discretion of the investigator for management of the IRR (Simons, 2010; Sampson et al, 2006). In the event of a Grade 4 IRR, MEDI-551 should be permanently discontinued (see Section 4.5.2.1 and Section 4.5.6).

If a subject experiences a Grade 3 IRR and does not require permanent discontinuation of MEDI-551 (see Section 4.5.2.1 and Section 4.5.6), all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent), oral acetaminophen 500 to 650 mg (or equivalent dose of paracetamol), and IV diphenhydramine (or its equivalent) 50 mg 30 to 60 minutes prior to initiation of MEDI-551 infusion. Subjects who only experience a Grade 1 or 2 IRR and do not require permanent discontinuation of MEDI-551 (see Section 4.5.2.1) may receive methylprednisolone (or the equivalent), acetaminophen (or paracetamol equivalent), and diphenhydramine 30 to 60 minutes prior to initiation of the MEDI-551 infusion at the investigator's discretion.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

For Arm C only: Rituximab will be administered per institutional guidelines (see Appendix 2 for rituximab prescribing information). All subjects must receive mandatory premedication consisting of a minimum dose of 60 mg IV methylprednisolone (or its equivalent) as well as 500 to 650 mg oral acetaminophen (or paracetamol equivalent), and 50 mg IV diphenhydramine 30 to 60 minutes before the start of the initial rituximab infusion on Day 1 of Cycle 1. The initial infusion of rituximab will be administered over a minimum of 30 to 60 minutes after administration of mandatory premedications. On Day 2 of Cycle 1, MEDI-551 will be administered over a minimum of 81 minutes following mandatory premedications as indicated above under "Arms B, C, and D". On Day 8 of Cycle 1 and Day 1 of Cycle 2, MEDI-551 should be administered first with rituximab administration a minimum of 30 minutes after completion of the MEDI-551 infusion.

4.5.4 Concomitant Medications

Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician. The use of pre-medication prior to administration of MEDI-551, in the absence of a previously documented reaction to MEDI-551, is permitted when it is clinically indicated or in accordance with institutional guidelines for administration of a MAb. Premedication with acetaminophen, diphenhydramine, and corticosteroids is mandatory before the first MEDI-551 infusion for Arms B, C, and D. The infusion rate should be reviewed and adjusted to minimize infusion reactions as detailed in Section 4.5.3. In addition, the following concomitant medications are allowed: 1) hematopoietic growth factors to treat anemia and cytopenias as per usual institutional practice following consultation with the Medical Monitor; 2) red cell and platelet transfusions in subjects who

are transfusion-dependent; 3) prophylactic intravenous Ig to prevent infections; 4) intrathecal prophylaxis with either methotrexate or cytarabine, if clinically indicated; and 5) prophylactic antibiotics. No transfusions are permitted during the DLT period for all dose-escalation cohorts in Arms B and C. For subjects with large tumor burden or elevated LHD (ie, at high risk for tumor lysis syndrome), prophylaxis against tumor lysis syndrome may be given according to institutional guidelines prior to initiation of study treatment (eg, hydration, urine alkalinization, administration of hypouricemic agent). Subjects' hydration status should be assessed to reduce risks of infusion-related hypotension; laboratory abnormalities that could complicate management if tumor lysis syndrome were to develop should be managed according to institutional standards.

All concomitant medications given to the subject from the time the subject signs the informed consent form through 90-Day Post Last Dose Visit will be recorded on the source document.

4.5.5 Dose Escalation

Rules for dose escalation in Arms A, B, and C are described below. This section is not relevant to Arm D.

Arm A

1. The MTD was to be determined based on the assessment of DLT during the DLT period (see Section 4.5.6). Subjects were considered evaluable for assessment of DLT if they received at least 1 full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completed the safety follow-up through the DLT evaluation period, or experienced any DLT. Non-evaluable subjects were to be replaced. Any MEDI-551 treatment-related toxicity (regardless of grade) leading to an inability to receive a full cycle of MEDI-551 was to be considered a DLT.
2. Per protocol Version 4.0, dose escalation was initiated in 3 subjects with FL or MM treated at the 0.5 mg/kg dose, once a week for 4-week cycles. No DLTs were observed in the first 3 subjects during the DLT period; therefore, enrollment in the next higher dose cohort (Cohort 2) began. Subjects in Cohorts 1 and 2 continued to receive MEDI-551 weekly in 4-week cycles.
3. If no DLTs are observed in Cohort 2, dose escalation into Cohort 3 will proceed with enrollment of subjects with advanced B-cell malignancies (CLL, DLBCL, FL, or MM). If a DLT is observed in Cohort 2, expansion and evaluation will occur per Rule 5 below. Three subjects will be treated at the Cohort 3 dose on Days 1 and 8 in the 1st cycle (loading doses) and then once every 28 days at the start of each subsequent cycle. If no DLTs are observed in the first 3 subjects during the DLT period, enrollment in the next higher dose cohort will begin.

4. For the first two dose cohorts only, subject enrollment was staggered so that no fewer than 7 days (including the day of treatment of the first subject) separates treatment start dates for each subject. A staggered enrollment achieves an observation period between subjects such that an adequate safety evaluation, including the assessment for cytokine release syndrome and tumor lysis syndrome, could be performed prior to entry of additional subjects. If no Grade ≥ 2 cytokine release syndrome or tumor lysis syndrome was observed in the subjects in the first two cohorts during the first 7 days of treatment, enrollment and treatment of subjects in subsequent cohorts (Cohorts 3 and higher) was allowed to proceed concurrently.
5. If 1 of 3 subjects in a dose cohort experienced a DLT during the DLT period, that dose cohort was allowed be expanded to a total of 6 subjects. If 1 of 6 subjects experienced a DLT, dose escalation continued in the next higher dose cohort.
6. If ≥ 2 subjects in a dose cohort experienced a DLT during the DLT period, the MTD would have been exceeded and no further subjects would be enrolled into that dose cohort. If this occurred, the preceding dose cohort would be evaluated for the MTD and a total of 6 subjects would be treated at the preceding dose. If ≤ 1 of 6 subjects experienced a DLT at the preceding dose, then this dose level would be the MTD.
7. If the MTD is not reached, either the maximum dose of 12 mg/kg or a lower dose (OBD) as determined by PK, pharmacodynamic, biomarker, and safety data will be used for cohort expansion.
8. At the discretion of the sponsor, an intermediate dose could have been chosen for dose escalation. Situations that might have prompted selection of an intermediate dose included unexpected toxicities that did not meet the definition of DLT or multiple similar toxicities in a cohort that did not meet the definition of a DLT. If an intermediate dose was chosen, subsequent dose escalation would be to the next predetermined dose provided all the criteria for dose escalation in Rules 2-6 above were met. Further dose escalation would be based on toxicities observed at each dose level, and would be allowed to proceed according to the original dosing schedule or would be allowed to include additional intermediate dosing steps based on accumulated safety data.

Arms B and C

1. The MTD was to be determined based on the assessment of DLT during the DLT period (see Section 4.5.6). Subjects were considered evaluable for assessment of DLT if they completed Cycle 1 of MEDI-551 or discontinued MEDI-551 treatment during Cycle 1 due to a DLT. Non-evaluable subjects were to be replaced. Any MEDI-551 treatment-related toxicity (regardless of grade) leading to an inability to complete the first cycle of MEDI-551 was considered a DLT.
2. If 0 of 3 or ≤ 1 of 6 subjects treated at the previous dose level experienced a DLT, dose escalation was allowed to continue.
3. If ≥ 2 of 6 subjects in a dose cohort experienced a DLT during the DLT period, the MTD would have been exceeded and no further subjects would be enrolled into that dose cohort. If this occurred, the preceding dose cohort would be evaluated for the MTD and a total of 6 subjects would be treated at the preceding dose. If ≤ 1 of 6 subjects experienced a DLT at the preceding dose, then this dose level would be the MTD.

4. If the MTD was not reached, the highest protocol-specified dose will be used for cohort expansion. The highest protocol-specified dose is 48 mg/kg for Arm B and 12 mg/kg for Arm C.

A study-specific Dose Escalation Committee consisting of all study investigators and the sponsor's medical monitor provided ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee was responsible for dose-escalation decisions and making recommendations regarding further conduct of the study. The sponsor notified sites when enrollment into each dose cohort had been completed and when enrollment into the next dose cohort was permitted. Details of the composition and role of the Dose Escalation Committee are presented in Section 6.4.

4.5.6 Dose-limiting Toxicities

Dose-limiting toxicities for Arms A, B, and C are described below. This section is not relevant to Arm D.

Arm A

The period for evaluating DLTs was from the time of first administration of MEDI-551 through the first 28-day cycle. Delays of ≤ 5 days within a cycle due to reversible non-DLT toxicities were allowed during the DLT period; in that case, the DLT period was no greater than 33 days. Subjects who did not receive 2 doses (subjects enrolled under protocol Version 5.0) or 4 doses (subjects enrolled under protocol Version 4.0) of MEDI-551 during this time for reasons other than toxicity were to be replaced with another subject at the same dose level. Grading of DLTs was according to the NCI CTCAE V4.03 (CTCAE, 2010).

A DLT was defined as:

- A MEDI-551 treatment-related AE of any toxicity grade that led to an inability to receive a full cycle of MEDI-551 or
- Any Grade 3 or higher toxicity as described below that could not be reasonably ascribed to another cause, such as disease progression or accident.

During the DLT period, a delay in therapy due to a reversible non-DLT toxicity lasting ≤ 5 days total was not considered a DLT as long as the subject received the full intended dose.

Nonhematologic DLTs were any Grade 3 or higher diagnosis or laboratory finding with the following exceptions:

- Grade 3 fever that lasts ≤ 24 hours with or without medical therapy and is not considered an SAE
- Transient Grade 3 rigors or chills that responds to optimum medical therapy
- Grade 3 tumor lysis syndrome that resolves to ≤ Grade 2 within 72 hours after initiation of treatment
- Any Grade 3 or 4 electrolyte alteration that is reversible to ≤ Grade 1 within 24 hours after it occurs
- Any Grade 3 liver function test elevation that resolves to ≤ Grade 1 within 24 hours after it occurs

Grade 3 or higher hematologic toxicities were considered DLTs with the following exceptions:

- ≥ Grade 3 lymphopenia or leukopenia in the absence of neutropenia
- ≤ Grade 4 neutropenia in the absence of fever that resolves within 5 days
- ≤ Grade 4 thrombocytopenia that resolves within 5 days
- ≤ Grade 4 anemia in a subject who was transfusion dependent at study entry, or had a history of hemolysis

Arms B and C

The period for evaluating DLTs was from the time of first administration of MEDI-551 through the first 28-day cycle. Grading of DLTs was according to the NCI CTCAE V4.03 (CTCAE, 2010).

A DLT was defined as:

- A MEDI-551 (or rituximab for Arm C) treatment-related AE of any toxicity grade that led to an inability to receive a full cycle of MEDI-551 (or rituximab for Arm C).
- **NOTE**: During the DLT period, a delay in therapy due to a reversible non-DLT toxicity lasting ≤ 7 days total would not be considered a DLT as long as the subject received the full intended dose.

Nonhematologic DLTs were any Grade 3 or higher MEDI-551 (or rituximab for Arm C) treatment-related toxicity not attributable to another cause with the following exceptions:

- Grade 3 fever that lasted≤ 24 hours with or without medical therapy and is not considered an SAE
- Grade 3 rigors or chills lasting < 6 hours that respond to optimum medical therapy

- Grade 3 IRR (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 tumor lysis syndrome that resolves to ≤ Grade 2 within 72 hours after initiation of treatment
- Any Grade 3 electrolyte alteration that is reversible to ≤ Grade 1 within 72 hours after it occurs
- Any Grade 3 liver function test elevation up to 8 × ULN and total bilirubin up to 5 × ULN that resolves to ≤ Grade 1 within 72 hours after it occurs. Any liver function test elevation > 8 × ULN or total bilirubin elevation > 5 × ULN that is attributed to investigational product requires discontinuation of investigational product.

Hematologic DLTs were any Grade 3 or higher MEDI-551 (or rituximab for Arm C) treatment-related toxicity not attributable to another cause, with the following exceptions:

- Grade 3 or 4 neutropenia in the absence of fever or infection that resolves to Grade 2 within 7 days
- Grade 3 or 4 thrombocytopenia that resolves to Grade 2 within 7 days and does not require a transfusion
- Grade 3 anemia that resolves to Grade 2 within 7 days and does not require a transfusion
- Grade 3 or 4 lymphopenia

4.6 Monitoring Subject Compliance

Investigational product is administered by study site personnel; subject compliance and investigational product administration will be reviewed during monitoring visits to the site and to the pharmacy.

4.7 Subject Status

Subject Completion

An individual subject will be considered to have completed the study if the subject was followed for survival until death or end of the study, regardless of the number of doses of investigational product that was received. Once Version 13.0 is in effect, all subjects who have completed treatment and the 90-Day Post Last Dose Visit for safety follow-up will be considered to have completed the study.

Until Version 13.0, is in effect, subjects will be considered not to have completed the study if one of the following conditions applies:

- Withdrawal of consent: If consent for follow-up is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.
- Lost to follow-up: Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on the last day of the study.

Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol at the point that they would be if no evaluations had been skipped.

Permanent Discontinuation of Investigational Product

Subjects who do not receive all protocol-specified doses of the investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

4.8 Study Completion

Study completion is defined as the date of the last protocol-specified visit for the last subject in the study. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor, and/or destroyed by the site/IRB/IEC instructions. The investigator will notify the IRB/IEC when the study has been completed.

5 ASSESSMENT OF EFFICACY AND CLINICAL PHARMACOLOGY

5.1 Efficacy and Clinical Pharmacology Parameters

The efficacy of MEDI-551 will be evaluated in subjects with advanced B-cell malignancies, including CLL (including SLL), DLBCL, FL, MCL, and other transformed indolent lymphomas. The efficacy profile will be assessed using CR, duration of CR, OR, disease control, time to response (TTR), duration of objective response, duration of disease control, progression-free survival (PFS), and overall survival (OS). Clinical activity in subjects in Arms B, C, and D will also be assessed by the percentage of MRD-negative CRs achieved with single-agent MEDI-551 in Arms B and D, and with the combination of MEDI-551 and rituximab in Arm C.

MEDI-551 PK will be described by area under the concentration-time curve from time 0 to last measurable concentration (AUC_t), area under the concentration-time curve from time 0 to infinity (AUC_∞), clearance, steady-state volume of distribution, and terminal-phase half-life ($t_{½}$) estimated by non-compartmental analysis. Circulating levels of blood mononuclear cells, including T cells, B cells, natural killer (NK) cells, and monocytes will be determined using standard clinically available flow cytometry. The production of human anti-human antibodies (HAHA) will be evaluated during treatment and in follow-up.

5.2 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent for follow-up is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects/legal representatives will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

The purpose of Protocol Version 13.0 is discontinue participation for all subjects who are no longer dosing and have completed at least the 90-day post treatment safety follow-up, while allowing subjects who are benefiting from MEDI-551 to continue treatment. Subjects who are currently on treatment will be allowed to continue to receive MEDI-551 with a simplified schedule of evaluations focused on safety. The 90-Day Post Last Dose Visit for safety follow-up (approximately 90 days after last dose of study drug[s]) will be conducted when subjects come off treatment. Long-term follow-up for PFS and OS will be discontinued. Once Version 13.0 is in effect, all subjects who have completed treatment and safety follow-up through at least the 90-Day Post Last Dose Visit will be considered to have completed the study.

A summary of changes implemented in Version 13.0 is provided in Section 15 of the protocol. Key safety assessments relevant to MEDI-551 are retained. Table 5.2.1-1

describes the frequency and type of procedure to be conducted for subjects who remain on treatment:

5.2.1 Schedule of Study Procedures - All Subjects Approved for Version 13.0 of the Protocol

Table 5.2.1-1 Schedule of Evaluations

Evaluations	Day 1, All Cycles Once Version 13.0 Is In Effect (± 7 Days)	EOT Visit (± 7 Days)	EOS or 90-Day Post Last Dose Visit (± 7 Days)
Verify eligibility criteria	X		
Medical history	X		
Concomitant medications	X	X	X
Pregnancy test (females of childbearing potential)	X		
Karnofsky performance status	X	X	X
Physical examination (focused)	X	X	X
AE/SAE assessment	X	X	X
Weight	X	X	
Vital signs	Pre and post dose	X	X
ECG (single)		X	X
Serum chemistry	X	X	X
Hematology	X	X	X
Coagulation tests		X	X
Urinalysis		X	X
Quantitative IgM, IgG, IgA		X	X
Flow cytometry of whole blood for T/B cell and effector cell subsets		X	X
MEDI-551 serum concentrations		X	X
Anti-MEDI-551 antibodies		X	X
Disease assessment [a]	Every 2-6 months	X[b]	
MEDI-551 administration	X		

AE = adverse event; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; Ig= immunoglobulin; SAE = serious adverse event;

[a] Subjects with FL, DLBCL, MCL, and transformed indolent lymphoma: Assess by CT scan (FDG-PET or PET-CT if clinically indicated) and physical exam every 2 months during the first year of treatment and then every 6 months. Additional scans may be performed if clinically indicated. Subjects with CLL "(including SLL)" will perform chest, abdomen, pelvis, and neck (if applicable). CT scans are only required after the first year of treatment if clinically indicated (eg previous indication to treat was based on predominantly nodal disease) or if indicated based on hematology findings.

[b] Disease assessment not required if performed within 8 weeks prior to the EOT visit.

5.3 Description of Study Procedures

Simplified study procedures implemented in Version 13.0 are described in this section.

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

5.3.1 Medical History and Physical Examination, ECG, Weight, and Vital Signs

In Arms A, B, C, and D, medical history, physical examinations, ECG, weight, and vital signs will be evaluated according to the schedule in Section 5.2. Physical examination should be focused (symptom-directed).

Findings from medical history and physical exam shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to at or below the pre-study baseline.

As of Version 13.0, single ECGs will be obtained at the specified time points in the Schedule of Study Procedures in Section 5.2.1 . Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry.

Body weight will be recorded at Screening, and on Day 1 of each treatment cycle, and at EOT Visit.

5.3.2 Clinical Laboratory Tests

In Arms A, B, C, and D, clinical laboratory safety tests will be performed in a licensed clinical laboratory following the schedule shown in Section 5.2.1. Urine pregnancy tests (women of childbearing potential only) on Day 1 of each cycle prior to dosing will be performed in the clinic using a licensed test (dipstick). New abnormal laboratory results that are clinically significant should be repeated as soon as possible (preferably within 24 to 48 hours). Tests for AST, ALT, alkaline phosphatase, and total bilirubin must be conducted concurrently and assessed concurrently. The following clinical laboratory tests will be performed.

Serum Chemistry

• Bicarbonate	• Lactate dehydrogenase
• Calcium	• Blood urea nitrogen
• Chloride	• Uric acid
• Magnesium	• Creatinine
• Potassium	• Total bilirubin
• Sodium	• Glucose
• Aspartate aminotransferase	• Albumin
• Alanine aminotransferase	• Total protein
• Alkaline phosphatase	• Triglycerides
• Gamma glutamyl transferase	• Cholesterol

Hematology

• WBC count with differential	• Platelet count
• Red blood cell count	• Mean corpuscular volume
• Hematocrit	• Mean corpuscular hemoglobin concentration
• Hemoglobin	

Urinalysis

• Glucose
• Ketones
• Blood
• Bilirubin
• Protein

Pregnancy Test (females of childbearing potential only)

• Urine human chorionic gonadotropin

Other Safety Tests

• Coagulation tests: prothrombin time, partial thromboplastin time, fibrinogen

5.3.3 T/B-cell and Immunoglobulin Levels

For Arms A, B, C, and D, flow cytometry performed at a central laboratory will be used to determine circulating T/B-cell levels and effector cell subsets. Samples for quantitative IgM, IgG, and IgA levels will be collected and local clinical laboratories will determine Ig levels.

5.3.4 Pharmacokinetic Evaluation and Methods

For Arms A, B, C, and D, blood samples for MEDI-551 PK evaluation will be collected according to the schedule shown in Section 5.2.1. MEDI-551 concentrations in serum samples will be measured using a validated immunoassay.

5.3.5 Immunogenicity Evaluation and Methods

For Arms A, B, C, and D, anti-MEDI-551 antibodies will be assessed according to the schedule shown in Section 5.2.1. Samples will be assessed for the presence of anti-MEDI-551 antibodies using a validated drug-tolerant solution -phase bridging assay. Tiered analysis will be performed to include screening, confirmatory and titer assay components, and positive-negative cutpoints, which were statistically determined from drug-naïve validation samples, will be employed.

5.3.6 Disease Evaluation and Methods

Subjects with FL, DLBCL, MCL, or transformed indolent lymphoma will be assessed by CT scan and physical examination according to the schedule shown in Section 5.2. Fluorodeoxyglucose-positron emission tomography (FDG-PET) or positron emission tomography (PET-CT) are not required unless clinically indicated. Criteria for CR and PR will be according to the International Working Group criteria (Cheson et al, 2007). Complete response unconfirmed will not be used to assess response.

Subjects with CLL (including SLL) will be assessed by hematology and disease assessment according to the schedule shown in Section 5.2.1. CT scans are only required after the first year of treatment if clinically indicated (eg previous indication to treat was based on predominantly nodal disease) or if indicated based on hematology findings. Assessment of disease response for CLL (including SLL), will be determined according to the National Cancer Institute - Working Group (NCI-WG) guidelines on CLL (Hallek et al, 2008).

5.3.7 Estimate of Blood Volume Collection

Beginning with Version 13.0, subjects will have approximately 15 mL of blood drawn on any single visit during the treatment period. The estimated volume of blood to be collected during the EOT Visit or the 90-Day Post Last Dose Visit will be no more than 20 mL each visit. The total volume of blood to be collected for a subject will depend on the number of cycles completed.

6 ASSESSMENT OF SAFETY

6.1 Safety Parameters

6.1.1 Adverse Events

The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after the subject/legal representative signs the informed consent form but before the subject has received investigational product.

Elective treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE.

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death

- Is immediately life-threatening

  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in offspring of the subject

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.1.3 Other Events of Special Interest

6.1.3.1 Hepatic Function Abnormality

A 'hepatic function abnormality' of special interest to the sponsor is defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality, where the etiology is unknown, follow-up investigations and inquiries should be initiated promptly by the investigational site based on medical judgment to make an informed decision regarding the etiology of the event.

6.1.3.2 Infusion Reactions

Any IRR resulting in permanent discontinuation of investigational product must be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety or designee using the Fax Notification Form. See Section 6.2.5 and Section 6.3.5.5 for instructions.

6.2 Assessment and Recording of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as generally defined below.

Grade 1	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject. The event poses a significant risk of harm to the subject, and hospitalization may be required.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or is with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5	The termination of life as a result of an event.

Severity will be graded according to the NCI CTCAE V4.03 (CTCAE, 2010).

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the seriousness criteria and would be considered an AE, whereas a Grade 2 myocarditis requiring hospitalization for pain management would be considered an SAE.

6.2.2 Assessment of Relationship

An event is considered "product-related" for the purposes of regulatory reporting if the investigator, the MedImmune medical monitor, or the MedImmune Patient Safety Physician assesses the event as possibly, probably, or definitely related to the investigational product. This is not a conclusive determination of causal association between the product and the event.

Whenever the investigator's assessment is unknown or unclear, the event is treated as product-related for the purposes of reporting to regulatory authorities.

An event may be deemed to be not related to the product for purposes of regulatory reporting only if the investigator, MedImmune medical monitor, and MedImmune Patient Safety physician, if applicable, agree that the event is not product-related.

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of investigational product; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The following guidelines should be used by investigators to assess the relationship of an event to investigational product administration.

Relationship assessments that indicate an **"Unlikely Relationship"** to investigational product:

None: The event is related to an etiology other than the investigational product (the alternative etiology must be documented in the study subject's medical record).

Remote: The event is unlikely to be related to the investigational product and likely to be related to factors other than investigational product.

Relationship assessments that indicate a "**Likely Relationship**" to investigational product:

Possible: There is an association between the event and the administration of the investigational product, and there is a plausible mechanism for the event to be related to investigational product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Probable: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to

the investigational product, and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product, and causes other than the investigational product have been ruled out and/or the event re-appeared on re-exposure to the investigational product.

6.2.3 Recording of Adverse Events

Adverse events will be recorded on the case report form (CRF) using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification of the sponsor. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form (Section 6.2.4).

6.2.4 Recording of Serious Adverse Events

Serious adverse events will be recorded on the SAE Report Form using a recognized medical term or diagnosis that accurately reflects the event. Serious adverse events will be assessed by the investigator for severity, relationship to the investigational product, and possible etiologies. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 regarding guidelines for assessment of severity and relationship, respectively.

For all SAEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made by the investigator. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

6.2.5 Recording of Other Events of Special Interest

Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 6.1.3.1) should be recorded according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

If an event of hepatic function abnormality is a pre-existing condition, the event does not meet the definition of an AE and does not need to be recorded as such.

If the etiology of the hepatic function abnormality is known (including progression of primary or metastatic malignancy) and/or not a pre-existing condition, the diagnosis should be recorded as an AE/SAE per Section 6.2.3 and Section 6.2.4.

If the hepatic function abnormality remains unexpected, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.2.3 and Section 6.2.4.

Infusion-related Reactions

Infusion reactions meeting the criteria noted in Section 6.1.3.2 should be recorded using recognized medical terms or diagnosis that accurately reflects the event in the same manner all AEs and SAEs (Section 6.1.1 and Section 6.1.2, respectively). See Section 6.3.5.5 for additional reporting requirements. Infusion reactions and related signs and symptoms should only be recorded on the infusion reaction eCRF.

6.3 Reporting Requirements for Safety Parameters

6.3.1 Study Reporting Period for Adverse Events

All AEs that occur after a subject has signed the written informed consent form through the 90-Day Post Last Dose Visit must be reported by the investigator.

Any new sign or symptom, disease, or other untoward medical event that occurs after the subject/legal representative signs the informed consent form must be reported by the investigator as an AE in the same way as AEs that occur after the subject receives investigational product.

6.3.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through the 90-Day Post Last Dose Visit. After the initial SAE report the investigator is required to follow each subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

All SAEs should be followed up to resolution by the investigator, even if this extends beyond the study reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event should be reported to MedImmune Patient Safety.

6.3.3 Notification of Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax to MedImmune Patient Safety or designee (ie, contract research organization).

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: 1 301 398 4205

MedImmune will provide international fax numbers to the sites in countries outside of the US.

MedImmune, as sponsor of the study is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. MedImmune may be required to report certain SAEs to regulatory authorities within

7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.3.4 Notification of Institutional Review Board or Independent Ethics Committee of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC. The IRB/IEC must be informed in a timely manner by the investigator of SAEs occurring at their site during the study. The sponsor will submit information on serious unexpected and related events to any EU IECs. Investigators must also submit safety information provided by MedImmune to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.3.5 Other Events Requiring Immediate Reporting

6.3.5.1 Pregnancy and Overdose

The following events are not necessarily considered to be AEs but are considered immediately reportable events and are required to be reported in real time (i.e., within 24 hours of learning about the event) to MedImmune Patient Safety using the Fax Notification Form:

1. Pregnancy
2. Investigational product overdose (whether or not the overdose is associated with an AE or SAE)

Subjects who become pregnant during the study period must not receive additional doses of investigational product. If the subject requests to know which treatment she received, this information will be provided to her. After obtaining the subject's consent, the subject will be followed for the duration of the pregnancy. A pregnancy should be followed for outcome and any premature terminations reported. In addition, the health status of the mother and child, including date of delivery, and the child's gender and weight should be reported to MedImmune Patient Safety after delivery.

6.3.5.2 Other Protocol-specific Events

The following events are also considered IREs and must be reported ***within 24 hours*** to MedImmune Patient Safety using the Fax Notification Form:

1. Any withdrawal of consent during the study
2. Any event resulting in discontinuation of investigational product

6.3.5.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3.1) in a study subject, with or without associated clinical manifestations, where the etiology is unknown, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.3.3 for contact information). The investigator shall review the data with the medical monitor. The investigator should use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated. If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, discontinuation of dosing for this subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune safety review committee (see Section 6.4) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune safety review committee is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.3.5.4 Hepatitis Reactivation

Any event of hepatitis reactivation must be reported immediately (i.e., within 24 hours of learning about the event), regardless of the amount of time that has passed since the subject's last MEDI-551 dose.

6.3.5.5 Infusion-related Reactions

Any infusion-related reaction of a study subject with the investigational product causing permanent discontinuation of dosing with investigational product, with or without associated

AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety or designee using the Fax Notification Form (see Section 6.3.3 for contact information). An infusion reaction does not automatically make an AE serious, but if the consequences of the reaction are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.2.4 and Section 6.3).

6.3.5.6 Progressive Multifocal Leukoencephalopathy

Any suspected case of PML should be immediately reported (i.e., within 24 hours of learning about the event) to MedImmune and discussed with the medical monitor.

6.4 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and "other events" reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate review, investigation, and follow-up of SAEs reported from the clinical study sites.

A study-specific Dose-Escalation Committee will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee will be responsible for dose-escalation decisions and making recommendations regarding further conduct of the study. The Dose-Escalation Committee includes the MedImmune medical monitor for the study, the MedImmune Patient Safety physician for the study, and the principal investigator from each actively enrolling study site. This committee will review data, including all AEs, laboratory parameters, PK, and pharmacodynamic data, following the full enrollment of any dose-escalation cohort and completion of the DLT evaluation period. This committee will also review data at other time points in response to AEs assessed as medically relevant by the medical monitor. Dose-escalation decisions and outcomes of reviews of safety and other relevant data will be communicated to the MedImmune safety review committee. The sponsor will notify sites when enrollment into each dose cohort has been completed and when enrollment into the next dose cohort is permitted.

A MedImmune safety review committee provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. Committee members include, but are not limited to, appropriate representatives from Patient Safety, Clinical Development, and Regulatory Affairs. The committee reviews protocol-specific safety data and assesses changes to the benefit/risk profile of the molecule during early phases of development. Based on review of safety data,

the committee may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

6.4.1 Interruption or Permanent Discontinuation of Study Dosing in Individual Subjects

Dosing of MEDI-551 may be interrupted for up to 4 hours in subjects experiencing Grade 2 or 3 infusion reactions as described in Section 4.5.2.

An individual subject will not receive any further investigational product (i.e., permanent discontinuation) if any of the following occur in the subject in question:

1. Withdrawal of consent;
2. Allergic reactions ≥ Grade 2 or any allergic reaction that necessitates the use of systemic pressors.
   - Grade 3 infusion reactions that do not respond to medical therapy (including interruption of infusion for ≤ 4 hours) or that occur despite steroid prophylaxis. Any Grade 4 infusion reaction or any infusion reaction that necessitates the use of systemic pressors.
3. Grade 3 infusion reactions that respond to medical therapy or slowing the infusion rate and that are of limited duration will not necessitate dose interruption or discontinuation.
4. Pregnancy;
5. DLT (see Section 4.5.6 for definition of DLTs). The Medical Monitor may decide that certain events meeting the criteria for DLT are controllable and that retreatment is considered safe.
   a. Subjects whose DLT resolves to ≤ Grade 1 or baseline within 7 days can be retreated during the DLT period at one dose level below the subject's prior dose for all arms of the study except the first dose-escalation cohort of Arms B and C.
   b. Subjects with toxicities considered DLTs that persist beyond 7 days will not be retreated for Arm A only.
   c. Recurrence of the DLT following retreatment will necessitate permanent discontinuation of treatment with MEDI-551 for Arm A only.
6. Delay in administration of MEDI-551 for more than 21 days for reason of toxicity within any 3 consecutive cycles for Arm A or delay in cycles as dictated in Section 6.4.1 for Arms B, C, and D;
7. Recurrence of any ≥ Grade 3 toxicity not attributable to other causes unless otherwise specified in Section 6.4.1;
8. Documentation of disease progression;
9. Any event which, in the opinion of the investigator, contraindicates further dosing such as intercurrent illnesses, significant drug toxicities or complications if judged by the investigator to be in the best interest of the subject;
10. Subject non-compliance;

11. Treatment with another investigational agent;
12. Initiation of alternative anticancer therapy;
13. Achievement of a CR and a maximum of 2 additional cycles after CR. For the purposes of discontinuation of drug, CR shall be defined as the time of hematological and radiological CR without necessity of BM confirmation.

Subjects who are permanently discontinued from investigational product will be followed for safety for approximately 90 days post last dose. In addition, until Version 13.0, subjects were to be followed for disease evaluation every 3 months after the 90-Day Post Last Dose Visit until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study. Upon disease progression, subjects were to be followed only for survival every 3 months until death, withdrawal of consent, or end of study.

6.4.2 Study Stopping Criteria

If any of the following occur, no further administration of investigational product will take place and no further subjects will be entered into the study:

1. The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects in the current study, determined after review of relevant information through internal MedImmune safety data review procedures.
2. Subject enrollment is unsatisfactory.
3. Non-compliance that might significantly jeopardize the validity or integrity of the study.
4. Sponsor decision to terminate development.

In case a safety event requiring enrollment suspension occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the medical monitor and the MedImmune safety review committee to determine whether dosing and study entry/randomization should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. The relevant competent health authorities in participating countries and IRB/IEC will be notified of any event that triggers suspension of enrollment in this study. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

Decisions regarding ongoing treatment for any subjects who have already received investigational product and are currently in the study at the time study-stopping criteria are met will be made on a case-by-case basis after discussion with the subject, principal investigator, and the sponsor. In the case that a safety event requiring enrollment suspension

occurs, all subjects on treatment will be re-consented. Regardless of whether dosing is continued or not, all subjects who were on treatment at the time study-stopping criteria were met will continue to be followed by the principal investigator for safety until the end of the study.

Withdrawal criteria for individual subjects are provided in Section 6.4.1.

6.4.3 Monitoring of Dose Administration

Arm A

Vital signs will be evaluated prior to infusion and at the end of infusion only; additional monitoring may be performed if clinically indicated. Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

In the event of an IRR, the infusion of MEDI-551 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen and/or an antihistamine (eg, diphenhydramine), or institutional equivalents, may be administered at the discretion of the investigator. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. For subsequent infusions in subjects who experience an IRR and do not require discontinuation of MEDI-551 (see Section 6.4.1), acetaminophen and an antihistamine may be administered prior to initiation of the MEDI-551 infusion. If a subject experiences a Grade 3 IRR, all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent) 30 minutes prior to initiation of MEDI-551 infusion.

Arms B, C, and D

Vital signs are evaluated prior to infusion and at the end of infusion as well as at the EOT and 90-Day Post Last Dose visits; additional monitoring may be performed if clinically indicated.

As described in Section 6.4.1, all subjects receiving MEDI-551 in Arms B, C, and D must receive mandatory premedication consisting of a minimum dose of 60 mg IV

methylprednisolone (or its equivalent), 500 to 650 mg oral acetaminophen (or paracetamol equivalent), and 50 mg IV diphenhydramine (or its equivalent) before the initial MEDI-551 infusion on Day 1 of Cycle 1 in Arms B and D, and on Day 2 of Cycle 1 in Arm C.

In the event of an IRR, the infusion of MEDI-551 may be interrupted until resolution of the event (up to 4 hours) and re-initiated at the 1 mL/minute rate. The rate may be slowly increased by 50% every 15 minutes until completion of the infusion. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) may be administered in addition to acetaminophen (or institutional equivalent) and/or an antihistamine at the discretion of the investigator for management of the IRR (Simons, 2010; Sampson et al, 2006). In the event of a Grade 4 IRR, the subject should have MEDI-551 permanently discontinued (see Sections 4.5.2.1 and 4.5.6).

If a subject experiences a Grade 3 IRR and does not require permanent discontinuation of MEDI-551 (see Sections 4.5.2.1 and 4.5.6), all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent), oral acetaminophen 500 to 650 mg (or equivalent dose of paracetamol), and IV diphenhydramine 50 mg 30 to 60 minutes prior to initiation of MEDI-551 infusion. Subjects who only experience a Grade 1 or 2 IRR and do not require permanent discontinuation of MEDI-551 (see Section 4.5.2.1) may receive methylprednisolone (or the equivalent), acetaminophen (or paracetamol equivalent), and diphenhydramine 30 to 60 minutes prior to initiation of the MEDI-551 infusion at the investigator's discretion.

Monitoring of the administration of rituximab in Arm C will be performed according to institutional protocols.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Details of endpoint analyses will be described in the statistical analysis plan.

7.2 Analysis Populations

The **Evaluable population for DLT** will include all subjects in the dose-escalation phase who receive at least 1 full cycle of MEDI-551 and complete safety follow-up through the DLT evaluation period (defined in Section 4.5.6) or experience any DLT during the DLT evaluation period. The Evaluable population for DLT will be used for the MTD analysis.

The **Safety population** will include all subjects who receive any treatment of MEDI-551. The Safety population will be used to evaluate baseline characteristics as well as all endpoints for safety.

The **Evaluable population for efficacy** will include all subjects who receive any treatment of MEDI-551 and complete at least one post-baseline disease assessment. The Evaluable population for efficacy will be used to evaluate the efficacy endpoints.

7.3 Endpoints

The primary, secondary, and exploratory endpoints are listed in this section, and assessment of the endpoints is described in Section 7.4.

7.3.1 Primary Endpoints

Arm A

1. MTD or OBD: DLTs
2. Safety: AEs, SAEs, laboratory evaluations, vital signs, physical examinations, and ECGs

Arms B and C

1. MTD is defined as the highest dose where ≤ 1 out of 6 subjects experience a DLT during the DLT evaluation period or the highest protocol-specified dose not exceeding MTD: DLTs
2. Safety: AEs, SAEs, laboratory evaluations, vital signs, physical examinations, and ECGs
3. Clinical activity/efficacy: CR, duration of CR, PR, objective response, disease control, TTR, duration of objective response, duration of disease control, PFS, and OS

Arm D

1. Clinical activity/efficacy: CR, duration of CR, PR, objective response, disease control, TTR, duration of objective response, duration of disease control, PFS, and OS

7.3.2 Secondary Endpoints

Arm A

1. Clinical activity/efficacy: CR, duration of CR, PR, objective response, disease control, TTR, duration of objective response, duration of disease control, PFS, and OS
1. Effect of MEDI-551 on circulating lymphocyte populations: circulating levels of blood mononuclear cells, including T-cells, B-cells, NK cells and monocytes
2. Pharmacokinetics: PK profiles and parameters, including maximum observed concentration (C_{max}), AUC, clearance (CL), and $t_{½}$, of MEDI-551
3. Incidence of anti-MEDI-551 antibodies based on samples obtained from each subject at multiple timepoints before and after dosing

Arms B and C

1. Pharmacokinetics: PK profiles and parameters, including C_{max}, AUC, CL, and $t_{½}$, of MEDI-551
1. Incidence of anti-MEDI-551 antibodies based on samples obtained from each subject at multiple timepoints before and after dosing
2. Effect of MEDI-551 on B-lymphocyte levels in peripheral blood, including time to recovery of B-lymphocyte level

Arm D

1. Safety: AEs, SAEs, laboratory evaluations, vital signs, physical examinations, and ECGs
2. Pharmacokinetics: PK profiles and parameters, including C_{max}, AUC, CL, and $t_{½}$, of MEDI-551
3. Incidence of anti-MEDI-551 antibodies based on samples obtained from each subject at multiple timepoints before and after dosing
4. Effect of MEDI-551 on B-lymphocyte levels in peripheral blood, including time to recovery of B-lymphocyte level

7.3.3 Exploratory Endpoints

Descriptive statistics will be used to describe the exploratory analyses when possible. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well. The variables likely to be included in the exploratory analyses are described below.

Arm B

1. [redacted]

7.4 Assessments

7.4.1 MTD or OBD/Highest Protocol-defined Dose

The MTD was based on the evaluable population for DLT and was defined as the highest dose at which ≤ 1 out of 6 subjects experience a DLT during the DLT evaluation period. The number and percentage of subjects with a DLT will be presented by dose level and overall. Since the MTD was not reached, the OBD (Arm A) or highest protocol-defined dose (Arms B and C) was determined based upon analysis of all available data, including safety, PK, pharmacodynamic, and response.

7.4.2 Safety Assessments

Safety endpoints will be summarized descriptively. The occurrence of AEs, abnormal laboratory values, and SAEs reported from the time that written informed consent is obtained through approximately 90 days post last dose will be summarized for all subjects who received any MEDI-551. Adverse events and SAEs will be graded according to the NCI CTCAE V4.03 and described by system organ class and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to MEDI-551. Frequency rates will be calculated for each system organ class and MedDRA preferred term.

7.4.3 Efficacy Assessments

The efficacy will be assessed based on CR, duration of CR, objective response, disease control, TTR, duration of objective response, duration of disease control, PFS, and OS.

- **Complete response:** The definition of CR varies by disease type (see Section 5.3.6).
- **MRD-negative CR:** Subjects with CR and negative MRD defined as the proportion of subjects with a best response of CR and without MRD.
- **Duration of complete response:** Duration of CR will be measured from the first documentation of a CR to the time of PD/relapse. Duration of CR will be censored on the date of last disease assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of CR will only be calculated for the subgroup of subjects with CR using the Kaplan-Meier method.
- **Objective response:** Objective response includes CR and PR.
- **Disease control:** Disease control includes CR, PR, or SD for at least 8 weeks.
- **Time to response:** Time to response will be measured from the start of MEDI-551 administration to the first documentation of response (CR or PR) and will only be assessed in subjects who have achieved objective response.

- **Duration of objective response:** Duration of objective response will be measured from the first documentation of objective response to the event of PD/relapse. Duration of objective response will be censored on the date of last disease assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of objective response will only be calculated for the subgroup of subjects with an objective response.
- **Duration of disease control:** Duration of disease control will be defined as the time period from start of MEDI-551 administration to the event of PD/relapse. Duration of disease control will be censored on the date of last disease assessment for subjects who have no documented PD/relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of disease control will only be calculated for the subgroup of subjects with best response of CR, PR, or SD.
- **Progression-free survival:** Progression-free survival will be measured from start of MEDI-551 administration until the first documentation of PD/relapse or death, whichever occurs first. Progression-free survival will be censored on the date of last disease assessment for subjects who have no documented PD/relapse or death prior to data cutoff, dropout, or the initiation of alternative anticancer therapy.
- **Overall survival:** Overall survival will be determined as the time from the start of MEDI-551 administration until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive.

The analysis methods will differ by the types of endpoints. For categorical endpoints, proportions will be summarized, 80% and 95% confidence intervals will be calculated using the Clopper-Pearson exact method. For time-to-event endpoints, Kaplan-Meier method will be used to describe the endpoints graphically and to estimate the median or the event rates at time of interest.

7.4.4 Pharmacokinetic Assessment

The PK of MEDI-551 will be estimated by non-compartmental analysis. A population PK analysis may also be performed to obtain additional PK parameters. Those PK parameters will be summarized by descriptive statistics including N, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean.

7.4.5 Assessment of Effect on Circulating Lymphocyte Populations

Circulating levels of blood mononuclear cells, including T-cells, B-cells, NK cells and monocytes will be determined using standard clinically available flow cytometry. B-cell levels will be monitored from start of treatment until recovery or study discontinuation due to initiation of alternative anticancer therapy or subject withdrawal. Recovery will be defined as a B-cell count of ≥ 200 cells/μL in subjects with baseline B-cells of ≥ 200 cells/μL or two

consecutive B-cell counts within ± 20% of baseline in subjects with baseline B-cell counts of < 200 cells/μL. Time to B-cell recovery will be analyzed. The correlation between Ig levels and B cell counts during treatment and recovery will also be evaluated.

7.4.6 Immunogenicity Assessment

Immunogenicity of MEDI-551 will be assessed and summarized descriptively by dose cohort.

7.5 Sample Size and Power Calculations

Arm A

For the dose-escalation phase, a minimum of 18 evaluable subjects (3 subjects each in Dose Cohort 1 through 6) or up to approximately 36 evaluable subjects (3+3 subjects per dose cohort) were required to determine the MTD; 26 were enrolled. A subject was considered evaluable for assessment of DLT if the subject received at least one full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completed the safety follow-up through the DLT evaluation period (as defined in Section 4.5.6), or the subject experienced a DLT. Any nonevaluable subject would be replaced in the same dose cohort. Table 7.5-1 provides the probability of dose escalation to the next higher lever for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Table 7.5-1 True Underlying DLT Rate at a Given Dose Level

True Underlying DLT Rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

DLT = dose-limiting toxicity.

For the dose-expansion phase, approximately 20 subjects were to be entered into each of 3 arms to determine the preliminary efficacy profile of MEDI-551 in the treatment of advanced CLL (including SLL), DLBCL, and FL. A total of 69 subjects (24 CLL, 21 DLBCL, 23 FL, and 1 MM) were enrolled. The primary objective of the dose-expansion phase was to determine the preliminary efficacy profile of MEDI-551 in these subjects. The sample size estimation was based on the CR rate and the exact binomial test. A total of 20 subjects per arm would be required to have approximately 80% power for testing the following hypotheses at 1-sided significance level of 0.1.

- Null hypothesis: undesirable CR rate = 5%
- Alternative hypothesis: desirable CR rate = 20%

Arms B and C

Dose Escalation

There were 4 planned dose levels (6, 12, 24, and 48 mg/kg) for MEDI-551 in the Arm B dose- escalation phase and 2 planned dose levels (8 and 12 mg/kg) for Arm C dose escalation. Using a standard 3+3 design, approximately 24 to 36 subjects were to be enrolled during the dose-escalation phase in Arms B and C depending on the observed safety profile and total number of dose levels evaluated.

A total of 7 subjects were enrolled in Arm B; all were in dose escalation (n = 3 each for 6 and 12 mg/kg, n = 1 for 24 mg/kg). Based on emerging PK and pharmacodynamic data, a dose of 12 mg/kg, administered weekly during Cycle 1 and then monthly in subsequent cycles, was determined to be sufficient to saturate the B-cell sink and achieve full exposure. At the sponsor's discretion and not due to any safety issues, no further dose-escalation was conducted. The MTD was not reached.

Arm C dose escalation was completed as planned, with 3 subjects each in the 8 and 12 mg/kg cohorts.

Dose Expansion

A sample size of 26 subjects was planned for each dose-expansion cohort in Arms B and C. Given an expected response rate of 50% for both cohorts, this would provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30%, and associated 80% confidence intervals for the response rate would have a precision of ± 13%. The 30% historical response rate was selected for both Arms B and C expansion cohorts based on the following reported data:

- In relapsed CLL patients, OR rates between 15% and 30% were reported for rituximab monotherapy (O'Brien et al, 2001; Mavromatis and Cheson, 2003).
- In DLBCL patients with 2 prior lines of therapy, response rates were only about 30% with single-agent rituximab (Coiffier et al, 1998; Wang et al, 2013; Churpek et al, 2013).

Enrollment in Arm B was discontinued prior to dose expansion at the sponsor's discretion and not due to any safety issues..

Further enrollment in Arm C was halted at the sponsor's discretion (and not due to any safety issues) after enrollment of 19 subjects (3 in the 8 mg/kg MEDI-551 cohort and 16 who received 12 mg/kg MEDI-551). Of the 19 subjects there were only 7 responders, and there was about a 13% probability of meeting the protocol-specified target response rate of 50%.

Arm D

A sample size of approximately 26 subjects was planned for Arm D. Given an expected response rate of 50% for this cohort, this would provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30% (Zinzani et al, 2013; Witzig et al, 2011), and associated 80% confidence intervals for the response rate would have a precision of ± 13%.

Further enrollment was halted at the sponsor's discretion (and not due to any safety issues) after enrollment of 16 subjects. Of the 16 subjects there were only 3 responders, and there was about a 1% probability of meeting the protocol-specified target response rate of 50%.

8 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable government regulations, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that any problems noted in the course of the monitoring are resolved.

9.3 Audit and Inspection of the Study

During the conduct of the study, the sponsor or its representative may conduct audits of any data and facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, Quality Assurance monitors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 ETHICS

10.1 Regulatory Considerations

The study will be conducted in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki. Good Clinical Practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the sponsor and to the IRB/IEC, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed consent form will be given to every subject/legal representative, and the original will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the

change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legally authorized representative, if the subject is unable to provide informed consent) in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. Subjects or their legal representatives must be informed of the following:

- The study involves research.
- The aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or the fetus of the subject, if the subject should become pregnant) that are currently unforeseeable.
- The study procedures to be followed and alternative treatment available to them. Subjects or their legal representatives must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- Who to contact for answers to any questions relating to the research project.
- Participation is voluntary and that they are free to withdraw or withdraw their child from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled.
- The extent of the confidentiality of subject records must be defined, and subjects or their legal representatives must be informed that applicable data protection legislation will be complied with.
- The monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the

extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

The consent form generated by the investigator must be approved by the IRB/IEC and be acceptable to MedImmune. Consent forms must be written so as to be understood by the prospective subject/legal representative. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by regulatory authorities and/or MedImmune professional and regulatory compliance persons. The subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

11 DATA HANDLING AND RECORD KEEPING

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by an SID number or coded number and date of birth. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the informed consent form (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with MedImmune policies and applicable regulatory requirements for a period of 2 years following the last regulatory authority approval of a marketing application of MEDI-551 and until there are no pending or contemplated marketing applications, or for 2 years after centers have been notified that clinical development of MEDI-551 has been discontinued, or as otherwise required by local requirements, whichever is longer. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

12 FINANCING AND INSURANCE

Financing and insurance are addressed in the individual site contracts.

13 PUBLICATION POLICY

Publication by the site of any data from this study must be carried out in accordance with the clinical study agreement.

14 REFERENCES

Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood. 1984;(63):1424-33.

Armitage JO, Weisenburger DD for the Non-Hodgkin's Lymphoma Classification Project. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. J Clin Oncol. 1998;16:2780-95.

Bargou R, Leo E, Zugmaier G, Klinger M, Goebeler M, Knop S, et al. Regression in cancer patients by very low doses of a T cell-engaging antibody. Science. 2008;321(5891):974-7.

Bergsagel PL, Smith AM, Szczepek A, Mant MJ, Belch AR, Pilarski LM. In multiple myeloma, clonotypic B lymphocytes are detectable among CD19+ peripheral blood cells expressing CD38, CD56, and monotypic lg light chain [published erratum appears in Blood. 1995 Jun 1;85(11):3365]. Blood. 1995;85:436-47.

Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol. 2001;19:2153-64.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86. Available at: http://jco.ascopubs.org/cgi/content/full/25/5/579.

Chu PG, Chen YY, Molina A, Arber DA, Weiss LM. Recurrent B-cell neoplasms after rituximab therapy: an immunophenotypic and genotypic study. Leuk Lymphoma. 2002;43(12):2335-41.

Churpek JE, Pro B, van Besien K, Kline J, Conner K, Wade JL 3rd, et al. A phase 2 study of epothilone B analog BMS-247550 (NSC 710428) in patients with relapsed aggressive non-Hodgkin lymphomas. Cancer. 2013;119(9):1683-9.

Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood. 1998;92(6):1927-32.

Coiffier B. Monoclonal antibodies in the treatment of indolent lymphomas. Best Practice & Research Clinical Haematology. 2005 Mar;18(1):69-80.

Coiffier B. State-of-the-art therapeutics: diffuse large B-cell lymphoma. J Clin Oncol. 2005 Sep 10;23:6387-93.

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Published on May 28, 2009 (v4.03: June 14, 2010). Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Cooper LJN, Al-Kadhimi Z, DiGiusto D, Kalos M, Colcher D, Raubitschek A, et al. Development and application of CD19-specific T cells for adoptive immunotherapy of B cell malignancies. Blood Cells, Molecules, and Diseases. 2004;33:83-9.

D'Arena G, Musto P, Cascavilla N, Dell'Olio M, Di Renzo N, Carotenuto M. Quantitative flow cytometry for the differential diagnosis of leukemic B-cell chronic lymphoproliferative disorders. Am J of Hematology. 2000;64:275-81.

Durie M, Harousseau J-L, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(10):1-7. Available at: http://www.nature.com/leu/journal/v20/n9/full/2404284a.html.

Engel P, Zhou L, Ord DC, Sato S, Koller B, Tedder TF. Abnormal B lymphocyte development, activation, and differentiation in mice that lack or overexpress the CD19 signal transduction molecule. Immunity. 1995;3:39-50.

Ginaldi L, De Martinis M, Matutes E, Farahat N, Morilla R, Catovsky D. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol. 1998;(51):364-9.

Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28:4184-90.

Hagberg H, Gisselbrecht C, CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol. 2006;17 Suppl 4:iv31-2.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute - Working Group 1996 Guidelines. Blood. 2008 Jun 15;111(12):5446-56. Available at: http://bloodjournal.hematologylibrary.org/content/111/12/5446.long.

Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary MLet al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84:1361-92.

Hennessy BT, Hanrahan EO, Daly PA. Non-Hodgkin lymphoma: an update. Lancet Oncol. 2004;5:341-53.

Huff CA, Matsui W. Multiple myeloma cancer stem cells. J Clin Oncol. 2008;26:2895-2900.

Kiel K, Cremer FW, Rottenburger C, Kallmeyer C, Ehbrecht E, Atzberger A, et al. Analysis of circulating tumor cells in patients with multiple myeloma during the course of high-dose therapy with peripheral blood stem cell transplantation. Bone Marrow Transplantation. 1999;23:1019-27.

Leonard JP, Coleman M, Ketas J, Ashe M, Fiore JM, Furman RR, et al. Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol. 2005;23(22):5044-51.

Loken MR, Shah VO, Dattilio KL, Civin CI. Flow cytometric analysis of human bone marrow. II. Normal B lymphocyte development. Blood. 1987;70:1316-24.

Martin A, Conde E, Arnan M, Canales MA, Deben G, Sancho JM, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica. 2008;93:1829-36.

Masir N, Marafioti T, Jones M, Natkunam Y, Rudiger T, Hansmann ML, et al. Loss of CD19 expression in B-cell neoplasms. Histopathology. 2006;48:239-46.

Matsui W, Wang Q, Barber JP, Brennan S, Smith BD, Borrello I, et al. Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. Cancer Res. 2008 Jan 01;68:190-7.

Mavromatis B, Cheson BD. Monoclonal antibody therapy of chronic lymphocytic leukemia. J Clin Oncol. 2003;21(9):1874-81.

McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825-33.

Micallef IN, Maurer MJ, Wiseman GA, Nikcevich DA, Kurtin PJ, Cannon MW, et al. Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previously untreated diffuse large B-cell lymphoma. Blood. 2011;118(15):4053-61.

Nadler LM, Anderson KC, Marti G, Bates M, Park E, Daley JF, et al. B4, a human B lymphocyte-associated antigen expressed on normal, mitogen-activated, and malignant B lymphocytes. J Immunol. 1983;(131):244-50.

O'Brien SM, Kantarjian H, Thomas DA, Giles FJ, Freireich EJ, Cortes J, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol. 2001;19:2165-70.

Rasmussen T, Jensen L, Johnsen HE. The CD19 compartment in myeloma includes a population of clonal cells persistent after high-dose treatment. Leuk Lymphoma. 2002;43(5):1075-7.

Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003 Jun 26;348(26):2609-17.

Robak T. Recent progress in the management of chronic lymphocytic leukemia. Cancer Treatment Reviews. 2007;(33):710-28.

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008 Aug 28;359(9):906-17.

Sato S, Steeber DA, Tedder TF. The CD19 signal transduction molecule is a response regulator of B-lymphocyte differentiation. Proc Natl Acad Sci.1995;92:11558-62.

Sato S, Steeber DA, Jansen PJ, Tedder TF. CD19 expression levels regulate B lymphocyte development: human CD19 restores normal function in mice lacking endogenous CD19. \J Immunol 1997;158:4662-9.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al, Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

Simons FE. Anaphylaxis. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S161-81.

The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-94.

Tsai PC, Hernandez-llizaliturri FJ, Bangia N, Olejniczak SH, Czuczman MS. Regulation of CD20 in rituximab-resistant cell lines and B-cell non-Hodgkin lymphoma. Clin Cancer Res. 2012;18:1039-50.

Uckun FM, Jaszcz W, Ambrus JL, Fauci AS, Gajl-Peczalska K, Song CW et al. Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins. Blood. 1988;71:13-29.

Villadolid J, LaPlant KD, Markham MJ, Nelson DR, George TJ. Hepatitis B reactivation and rituximab in the oncology practice. The Oncologist. 2010 Oct;15(10):1113–21. doi: 10.1634/theoncologist.2010-0106.

Wang M, Fowler N, Wagner-Bartak N, Feng L, Romaquera J, Neelapu SS, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia. 2013 Apr 02. Epub ahead of print.

Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1749-55.

Witzig TE, Vose JM, Zinzani PL, Reeder CB, Buckstein R, Polikoff JA, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22:1622-7.

Yazawa N, Hamaguchi Y, Poe JC, Tedder TF. Immunotherapy using unconjugated CD19 monoclonal antibodies in animal models for B lymphocyte malignancies and autoimmune disease. PNAS. 2005;102(42):15178-83.

Zhou L, Smith HM, Waldschmidt TJ, Schwarting R, Daley J, Tedder TF. Tissue-specific expression of the human CD19 gene in transgenic mice inhibits antigen-independent B-lymphocyte development. Mol Cell Biol. 1994;14(6):3884-94.

Zinzani PL, Vose JM, Czuczman MS, Reeder CB, Haioun C, Polikoff J, et al. Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: subset analysis of the NHL-003 study. Ann Oncol. 2013;24:2892-7.

15 SUMMARY OF PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

Protocol Version 2.0, 28 May 2009

Version 1.0 of protocol MI-CP204, dated 01Apr2009, has been amended to create Version 2.0, dated 28 May 2009. This protocol was amended in response to requests from the FDA following review of CP204 after submission of the IND on 29 April 2009. The language in the requested changes was agreed to by the FDA following submission of proposed changes on 26 May 2009.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 2.0. Major changes to the protocol are described below. Added text is shown bolded and underlined (eg, **text**) and deleted text is shown with strikethrough (eg, ~~**text**~~).

- Section 4.2.1 (Inclusion Criteria) and Study Abstract:

2) Bilirubin ≤ 1.5 × ULN except in the case of subjects with documented Gilbert's disease, ≤ **2.**5 × ULN;

- Section 4.2.2 (Exclusion Criteria) and Study Abstract:

2. **Any available standard line of therapy known to be life-prolonging or life-saving;**

- Section 4.5.2 (Treatment Regimens)

Dose Modification for Toxicity Management

In rare circumstances and under the authority of the Medical Monitor, subjects may be retreated following a DLT as described in Section 6.4.1.

The following AEs are exceptions to the dose modification and stopping rules described below in Table 4.5.2.1-1 and require NO modification of MEDI-551 dosing: lymphopenia (any grade) and ~~≤Grade 3~~ **baseline** hematologic ~~toxicity~~ **abnormalities.**

Dose modification for Grade 4 hematologic toxicity (other than lymphopenia) will occur as described in Table 4.5.2.1-1 with the exception that resolution only to ≤ Grade 2 **or subject's baseline,** and not to Grade 1**,** will be required to re-initiate treatment.

- Table 4.5.2-1 (MEDI-551 Dose Modification Table) – Footnotes

[a] Except Grade ~~≤3~~ **< 2 or subject's baseline** hematologic toxicity, which requires no dose modification~~, or lymphopenia (any grade)~~. **Lymphopenia (any grade) also will not require modification of treatment.**

[b] Except Grade 3 or 4 toxicities noted as exceptions to the DLT criteria. **Lymphopenia (any grade) will not require modification of treatment.**

[c] For Grade 4 hematologic toxicities other than lymphopenia, resolution only to ≤ Grade 2 **or subject's baseline,** and not to Grade 1**,** will be required to re-initiate treatment.

- Section 4.5.3 (Investigational Product Preparation and Administration)

In the event of an infusion-related reaction, the infusion of MEDI-551 may be interrupted until resolution of the event, and the infusion re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen (750-1000 mg) and/or an antihistamine (eg, diphenydramine 25-50 mg) may be administered. **If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well.** For subsequent infusions in subjects who experience an infusion reaction and do not require discontinuation of MEDI-551 (see Section 6.4.1), acetaminophen and an antihistamine may be administered prior to initiation of the MEDI-551 infusion. **If a subject experiences a Grade 3 infusion reaction, all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent) 30 minutes prior to initiation of MEDI-551 infusion.**

- Section 5.3.9 (Disease Evaluation and Methods)

CLL

Subjects will be assessed by hematology and physical exam every cycle. For subjects who achieve hematological CR and had evidence of nodal disease by CT scan at screening, a repeat CT scan will be performed. Bone marrow biopsy will be performed 3 months following CR to confirm CR. **A repeat BM biopsy will be performed 4 weeks later in subjects where the initial BM biopsy is considered hypocellular.** Subjects who do not achieve CR need not have a follow-up BM biopsy.

- Section 6.4.1 (Interruption or Permanent Discontinuation of Study Dosing in Individual Subjects)

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent;
2. Allergic reactions ≥ Grade 2. Infusion reactions ≤ Grade 3 that respond to medical therapy or slowing the infusion rate and that are of limited duration will not necessitate dose interruption or discontinuation. **Infusion reactions ≥ Grade 3 that do not respond to medical therapy or that occur despite steroid prophylaxis will require permanent discontinuation of MEDI-551 in that subject.** Any **Grade 4** infusion or allergic reaction **or one** that necessitates the use of systemic pressor agents will cause **permanent** ~~dose~~ discontinuation **of MEDI-551** in that subject;
3. Pregnancy or intent to become pregnant;
4. DLT (see Section 4.5.6 for definition of DLTs). The Medical Monitor may decide that certain events meeting the criteria for DLT are controllable and that retreatment is considered safe.
5. If such subjects are retreated during the DLT period, they will be treated at one dose level below the subject's prior dose provided that the DLT resolves to ≤ Grade 1 or baseline within 7 days.
6. Subjects with toxicities considered DLTs that persist beyond 7 days will not be retreated.
7. Recurrence of the DLT following retreatment will necessitate permanent discontinuation of treatment with MEDI-551.

- Section 6.4.3 (Monitoring of Dose Administration)

If a subject experiences an infusion reaction during administration of MEDI-551, diphenhydramine (Benadryl®) 50 mg and acetaminophen (Tylenol®) 650 mg, or the institutional equivalents, may be administered. **If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well.** Alternatively, or in addition, the rate of the MEDI-551 infusion may be diminished. Any such activities must be recorded appropriately. For patients who experience an infusion reaction, prophylactic administration of acetaminophen and/or diphenhydramine or the equivalents may be considered prior to subsequent administrations of MEDI-551. **If a subject experiences a Grade 3 infusion reaction, all subsequent administration of MEDI-551 must be preceded by IV methylprednisolone 100 mg (or the equivalent) 30 minutes prior to initiation of MEDI-551 infusion.**

Protocol Version 3.0, 06Nov2009

Version 2.0 of protocol MI-CP204, dated 28 May 2009, has been amended to create Version 3.0, dated 06Nov2009. The protocol was amended to add clarification to certain sections, perform minor copyedits, and to add specific language for non-US studies.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 3.0. Major changes to the protocol are described below.

Title Page:

- The EudraCT Number was added for EU compliance.
- A new Medical Monitor was assigned to this study. Therefore, the name, title, and contact information for the Medical Monitor was updated (also in the Sponsor Agreement section on Page 2).
- The protocol title was changed to more accurately reflect the study design (ie, added "open-label and Phase 1/2" and deleted "dose-escalation."

Section 1.0:

A risk-benefit summary was added per EU regulatory guidance.

Section 3.1 and the Study Abstract:

- Text was added to clarify that FL/MM and CLL/DLBCL are grouped separately based upon differences in tumor burden and aggressiveness.
- Text was added to indicate that an interim safety analysis will be conducted when the MTD or OBD has been established. This analysis is being done to examine treatment effects on key safety endpoints. This information was also added to a new *Interim Analysis* section (Section 7.6).
- For clarity, text was added to specify that FDA will be consulted concerning the possibility of additional treatment with MEDI-551 for subjects *within the United States* who achieve CR and subsequently relapse.

Section 3.2 and Study Abstract

For clarity, text was revised to state that subjects may continue to receive MEDI-551 until CR, disease progression, toxicity, or another reason to discontinue therapy intervenes.

Section 4.2.1 and the Study Abstract:

- Inclusion Criterion 3 was edited to specify that the CLL population is to include subjects with SLL.
- The units for anemia were corrected to g/dL.
- Inclusion Criterion 10 was edited to specify platelet count ≥ 75,000/mm^3 (except for CLL subjects with evidence of bone marrow disease, who must have a platelet count ≥ 50,000/mm^3).
- Inclusion Criterion 12 was edited to clarify the recommended methods of contraception and to state that subjects must use adequate contraception methods through 90 days after the last dose of MEDI-551.
- Inclusion Criterion 13 was edited to specify that for subjects with DLBCL or FL only, disease is to be evaluable by the International Working Group criteria (formerly RECIST criteria; references to RECIST criteria were thus removed from the List of Abbreviations and from Appendix 1.

Section 4.3:

Paragraph 1 was edited to clarify that a subject is considered entered into the study when the investigator notifies the IVRS that the subject meets eligibility criteria and the IVRS provides the assignment of a *dose cohort or treatment arm* to the subject. The text formerly specified study entry upon subject receipt of a kit number; however, the IVRS assigns a dose cohort or treatment arm and not a kit number.

Section 4.5.2

Table 4.5.2-1 was revised to make it consistent with Section 6.4.1. Text was added to the table to state that (1) for Grade 2 infusion reaction, infusion rate may be decreased by 50% or interrupted for up to 4 hours and symptomatic care instituted as clinically indicated; (2) following interruption, infusion should be resumed at 50% of original rate for remainder of infusion.

Sections 4.5.3 and 6.4.3:

The text was edited to clarify that in the event of an infusion reaction, diphenhydramine and/or acetaminophen administration would be at the investigator's discretion. Further, references to specific doses of both drugs were removed. The text was changed because the investigator will determine the circumstances under which these drugs would be used, and at what dose. Added a clarification to the text to state that in the event of an infusion-related

reaction, the infusion of MEDI-551 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours).

Section 4.5.5:

- Rule 1 was modified to add a definition of subjects evaluable for DLT assessment.
- Rule 3 was modified to provide the rationale behind using a staggered enrollment.
- Rule 7 was modified to specify that if a lower dose than the MTD is used for dose expansion, that dose is the OBD.
- Text was added to clarify the role and composition of the Dose Escalation Committee and to add a reference to the SMC (also in Section 6.4).

Sections 5.2, 5.2.1, 5.2.2, and 5.2.3:

Lymph node palpation was removed from the Schedule of Assessments because subjects already undergo CT scans which are considered more accurate for assessing lymph node size and disease progression.

Section 5.2.4:

Added visit window of ± 48 hours for the 30-day post-therapy visit and ± 1 week for the every 3 months post-therapy follow-up visit.

Section 5.3.6:

The text was edited to clarify that the additional sampling to be performed in the first 10 subjects in the expansion cohorts is planned in order to obtain additional PK data.

Section 6.2.1 and the Study Abstract:

The text was edited to specify that AE severity will be graded according to the NCI CTCAE V4.0 (formerly V3.0), since the CTCAE version was updated subsequent to the finalization of Version 2.0 of this protocol. The CTCAE version number was also updated in the List of Abbreviations.

Section 6.4.1 and 6.4.3

Language concerning interruption or discontinuation of treatment due to infusion reactions was clarified and updated:

- Added text to state that dosing of MEDI-551 may be interrupted for up to 4 hours in subjects experiencing Grade 2 or 3 infusion reactions.
- List item #3 was revised to state that discontinuation of treatment would result from Grade 3 infusion reactions that do not respond to medical therapy (including interruption of infusion for ≤ 4 hours) or that occur despite steroid prophylaxis, or from any Grade 4 infusion reaction or any infusion reaction that necessitates the use of systemic pressors.

Section 6.4.3

Added text to clarify that in the event of an infusion-related reaction, the infusion of MEDI-551 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion.

Section 7.2

An additional analysis population, the Per-Protocol population (defined as all subjects who complete 2 cycles of treatment or who discontinue treatment for toxicity due to MEDI-551, disease progression, or death due to disease) was added for evaluation of efficacy endpoints.

Section 7.4.1:

References to confirmatory or confirmed CR and confirmed PR were removed. The text was modified to include the 80% CI in estimations of CR rate.

Section 7.4.3

Added language to clarify recovery of B-cell counts.

Appendices:

Appendix 1 was changed to provide a link to the International Working Group criteria. Appendix 5 (formerly the link to the International Working Group criteria) was removed.

Other Text Edits:
Throughout the document, MedImmune Product Safety was changed to MedImmune Patient Safety.

Protocol Version 4.0, 27Jan2010

Version 3.0 of protocol MI-CP204, dated 06Nov2009, has been amended to create Version 4.0, dated 27Jan2010. The protocol was amended to add FDA requested DLT

language, add clarification to certain sections, update the Medical Monitor, and make minor copy edits.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 4.0. Major changes to the protocol are described below.

Title Page:

A new Medical Monitor was assigned to this study. Therefore, the name, title, and contact information for the Medical Monitor was updated (also in the Sponsor Agreement section on Page 2)

Study Abstract and Section 4.2.2:

Exclusion criterion 13 was edited to clarify that subjects with active hepatitis B or C infection as defined by seropositivity for hepatitis B (HBsAg) or hepatitis C antibody, and elevated liver transaminases are not eligible to participate in the study.

Sections 4.5.2

Added text to clarify that dose modification is not permitted during the DLT period; however, a delay in therapy due to a reversible non-DLT toxicity is permitted as long as the total delay within the cycle is ≤ 5 days total. Any toxicity leading to a delay > 5 days in duration during the DLT period will be considered a DLT.

Section 4.5.5 and 4.5.6:

The text was edited to specify that during the DLT period, any MEDI-551 treatment-related toxicity (regardless of grade) leading to an inability to receive a full cycle of MEDI-551 would be considered a DLT. Further, the text was edited to clarify that during the DLT period, a delay in therapy due to a reversible non-DLT toxicity lasting ≤ 5 days total would not be considered a DLT as long as the subject was able to receive the full intended dose of MEDI-551. Added clarification that delays of up to 5 days total within a cycle due to reversible non-DLT toxicities are allowed during the DLT period; in that case, the DLT period will be no greater than 33 days.

Study Abstract, Sections 2.3, and 7.5
Revised one of the exploratory objectives to state that the effect of [redacted]

Protocol Version 5.0, 23Sep2010

Version 4.0 of protocol MI-CP204, dated 27Jan2010, has been amended to create Version 5.0, dated 23Sep2010. The protocol was amended to make the study population for dose-escalation inclusive of subjects with FL, MM, CLL, and DLBCL and to add FDA requests for monitoring of post-treatment hepatitis reactivation. In addition, clarification was added to certain sections, and minor copyedits were performed.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 4.0. Major changes to the protocol are described below.

Title Page:
The name, title, and contact information for the Medical Monitor was updated (also in the Sponsor Agreement section on Page 2).

Study Abstract and Sections 3.1 and 4.5.2

Study Design and Treatment Sections

- The Study Design and treatment sections were updated to specify that dose escalation began in subjects with FL or MM per protocol Version 4.0 (27Jan2010) through Cohort 2, and that Cohorts 3 to 6 will enroll subjects with FL, MM, CLL or DLBCL with a modified dosing schedule. Specifically, subjects in Cohorts 1 and 2 will continue to follow the protocol Version 4.0 dose schedule of 0.5 mg/kg (Cohort 1) or 1 mg/kg (Cohort 2) MEDI-551 IV infusion once every week in 4-week cycles. Subjects enrolled in Cohorts 3 and higher will receive 2, 4, 8, or 12 mg/kg MEDI-551 (Cohorts 3 to 6, respectively) IV once per week on Days 1 and 8 in the 1st cycle (loading doses) and then once every 28 days at the start of each subsequent cycle.
- The number of evaluable subjects required for dose-escalation was changed to 18 to 36.
- The treatment schedule for the expansion phase was modified to specify that subjects will be treated on Days 1 and 8 in the 1st cycle (loading doses) and then once every 28 days at the start of each subsequent cycle at the MTD or OBD as determined in the dose-escalation phase.
- Text regarding the possibility of different MTDs/OBDs in different tumor types was deleted.

Section 4.5.3

The following text was added: “MEDI-551 must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial, as the MEDI-551 product contains no bacteriostatic agents.”

Section 4.5.5

The rules for dose escalation were modified to reflect the change in study design as discussed above.

Section 4.5.6

The text was updated to specify that subjects who do not receive at least one full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 during the first treatment cycle for reasons other than toxicity will be replaced with another subject at the same dose level.

Section 5.2

The study schedule for Cohorts 1 and 2 and a new schedule of assessments for Cohorts 3 to 6 were added. Text regarding monitoring post treatment hepatitis reactivation was added as per FDA request.

Section 6.3.5 (Other Events Requiring Immediate Reporting)

A subsection for hepatitis reactivation was added to this section as per FDA request.

Section 6.4.1

Rule #6 was modified to specify that delay in administration of MEDI-551 for more than 21 days for reason of toxicity within any 3 consecutive cycles would lead to dose interruption or discontinuation.

Section 7.3.1

Text regarding the conduct of additional studies to determine MTD in different disease indication was removed from this section.

Appendix 2

The link to the National Cancer Institute CTCAE Version 4.0 was updated.

Protocol Version 6.0, 18Jul2011

Version 5.0 of protocol MI-CP204, dated 23Sep2010, has been amended to create Version 6.0, dated 18Jul2011. The protocol was amended to allow for subjects who achieve a CR to be dosed with 2 additional cycles of MEDI-551 per FDA request. In addition, clarification was added to certain sections, and minor copyedits were performed.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 5.0. Major changes to the protocol are described below.

Title Page

A new Medical Monitor was assigned to this study. Therefore, the name, title, and contact information for the Medical Monitor was updated (also in the Sponsor Agreement section on Page 2).

Study Abstract and Sections 3.0, 4.5.2, 6.4.1

Study Design and Treatment Sections

- The text was updated to specify that all subjects (US and non-US) who achieve a CR may receive an additional 2 cycles of MEDI-551 at the same dose level per the FDA. The FDA will be consulted concerning the possibility of additional treatment with MEDI-551 for subjects within the US who achieve a CR and subsequently relapse; however, non-US subjects will not be re-treated on subsequent relapse.

Section 1.4

The clinical experience with MEDI-551 was updated to include results from the MI-CP204 study as of 09 May 2011 and to provide information on any toxicities observed through Cohort 4 (4 mg/kg).

Section 4.5.4

The text was edited to specify that routine use of pre-medications prior to administration of MEDI-551 in the absence of documented prior reaction to MEDI-551 infusion is allowed when it is clinically indicated or in accordance with institutional guidelines for administration of a MAb.

Section 5.2

The study schedule for Cohorts 3 to 6 were updated to add the collection of exploratory post end of infusion biomarkers and updated the PK samples collected for the cohort expansion. The visit window for the Every 3 months post-therapy visits was modified from 7 to 14 days to allow for potential scheduling issues.

Sections 5.3.2 and 6.0

Text for hepatic function abnormality was added to these section as per revised MedImmune protocol template Version 14.1 and oncology-specific modifications.

Section 7.4.1

The objective response rate was revised from 12 weeks to 8 weeks in order to align with the disease assessment schedule.

Protocol Version 7.0, 04Oct2011

Version 6.0 of protocol MI-CP204, dated 18Jul2011, has been amended to create Version 7.0, dated **04Oct2011**. The protocol was amended to state that the maximum dose-escalation phase dose of 12 mg/kg was selected for the expansion phase of the study. An additional safety follow-up visit at 60 days after the last dose was also added. In addition, information about the selection of the maximum dose of 12 mg/kg and an updated clinical experience section were added to the introduction. Infusion reactions were added as an event of special interest. The date of the Version 5.0 protocol in this section was corrected to 23Sep2010.

Section 1.3

Information supporting the selection of 12 mg/kg as the maximum dose to be tested was provided.

Section 1.4

The completion of Cohort 6 and the number of subjects enrolled was noted. Safety information was updated.

Section 3.1

The completion of Cohort 6, selection of the dose for the expansion phase and the completion of the interim safety analysis were documented.

Section 5.2

The 60-day post-therapy visit was added. The procedures for Cohorts 3 to 6 were edited to show that they also apply to the expansion cohort.

Sections 5.3, 6.3, and 7.3

The addition of the 60-day post-therapy safety visit, and the extended safety monitoring period were noted. The estimate of blood volume collection in Section 5.3.11 was updated.

Sections 6.1.3.2, 6.2.5 and 6.3.5.5

Infusion reactions were added as an event of special interest.

The study abstract was updated as needed to reflect the changes in the protocol.

Protocol Version 8.0, 02May2012

Version 7.0 of protocol MI-CP204, dated 24Oct2011, has been amended to create Version 8.0, dated 02May2012.

All changes to the protocol were also made, if applicable, in the abstract

Sections 1.5, 3.1, 4.2, 4.5.2, 5.2.2, 5.3

Sections were modified to note discontinuation of enrollment of MM subjects based on data from this study and recent nonclinical studies, which suggest lack of activity in the advanced/refractory MM setting. The expansion phase will enroll approximately 60 subjects: 20 subjects each with FL, CLL (including SLL), or DLBCL.

Sections 3.1, 4.2, 5.1, 5.3.4, 5.3.9, 7.4 and 7.9

References to CLL in these sections were modified to say CLL (including SLL).

Section 4.2

All eligibility criteria pertaining to subjects with MM have been removed. The subjects enrolled in this study as of Protocol Version 8.0 will be adults with relapsed or refractory B-cell malignancies: CLL (including SLL), DLBCL, and FL.

Section 4.2.1

Inclusion criterion #3 was modified to state that subjects with a diagnosis of CLL (including SLL), DLBCL, or FL are included and that SLL, DLBCL, and FL must be histologically confirmed.

Inclusion criterion #6 for subjects with MM was removed; subsequent criteria were renumbered.

Inclusion criterion #8 was revised to specify that permitted prior radiation therapy must have occurred at least 6 weeks before the first dose of MEDI-551.

Inclusion criterion #9 was changed to provide different hematological criteria for CLL subjects with bone marrow involvement.

Inclusion criterion #10 was changed to modify the definition of adequate organ function.

Section 4.2.2

Exclusion criterion #4 was modified to note that radiation therapy is not permitted within 6 weeks prior to the first dose of MEDI-551.

Section 4.5.2

The size and composition of the expansion phase were updated to reflect approximately 60 subjects and removal of the MM group.

Section 4.5.3

Preparation information for MEDI-551 is provided. In addition, directions state that infusion will be done using a 0.2 micron filter.

Section 4.5.4

Both red cell and platelet transfusions are acceptable in subjects who are transfusion-dependent.

Section 5.2.2

Evaluations related to subjects with MM have been removed.

IgE testing has been removed

References to HIV-1 and HIV-2 are revised to read HIV, as it is not necessary for investigators to evaluate for HIV-2.

Section 5.2.1 refers only to subjects in Cohorts 1 and 2. All subjects in those cohorts have completed the study; therefore Section 5.2.1 has not been altered.

Section 5.3

Descriptions of procedures related to subjects with MM have been removed. Details of response criteria for subjects with MM have been removed.

Appendices

Appendix 1 includes the signatures of sponsor representatives to document approval of the protocol, according to the revised Clinical Study Protocol Standard Operating Procedure. Other appendices have been renumbered.

Protocol Version 9.0, 15Jul2013

Version 8.0 of protocol MI-CP204, dated 02May2012, has been amended to create Version 9.0, dated 15Jul2013. The purpose of the amendment is to redefine the end of study. All text revisions resulting from this amendment are incorporated in the body of protocol Version 9.0. Major changes to the protocol are described below.

Abstract and Sections 3.2, 4.7, 5.2.1.4, 5.2.2.4, 6.4.1, and 7.4.1

The definition of end of study, "defined as 1 year after the last subject begins treatment" was removed from these sections. The revised definition was added to the abstract and to Sections 1 and 4.8.

Abstract

The following sentence was added to the end of the study design section of the abstract: "The end of the study will occur after the deaths of 50% of all planned subjects or the date the sponsor stops the study."

Section 3.2 Estimated Study Duration

An estimated study duration of 8 to 10years, based on the revised end of study, was provided.

Section 4.8 Study Completion
The second, **bolded** sentence was added to this section: "Study completion is defined as the date of the last protocol-specified visit or assessment (including telephone contact) for the last subject in the study. **This date will be after the deaths of 50% of all planned subjects or the date the sponsor stops the study."**

Section 4.2.1 Inclusion Criterion # 4

The term SLL was removed from the expression beginning, "Subjects with histologically-confirmed B-cell NHL ..." as it was incorrect. The same correction was made in the abstract.

Protocol Version 10.0, 07Oct2013

Version 9.0 of protocol MI-CP204, dated 15Jul2013, has been amended to create Version 10.0, dated 07Oct2013. The purpose of the amendment is to add 2 arms to Study MI-CP204: dose escalation and expansion in subjects with CLL receiving MEDI-551 monotherapy (Arm B); and dose escalation and expansion in subjects with aggressive lymphoma receiving MEDI-551 in combination with rituximab (Arm C). Note that dose escalation and expansion in advanced B-cell malignancies from the original protocol are referred to as Arm A. All text revisions resulting from this amendment are incorporated in the body of protocol Version 10.0. Major changes to the protocol are described below.

Abstract

The abstract was revised to reflect the changes made to the body of the protocol.

Section 1.1 (Disease Background)

Under the subsection, "Treatment of B-cell Malignancies," a paragraph was added to provide background on the rituximab-refractory population.

Section 1.3 (Nonclinical Experience with MEDI-551)

A paragraph describing the findings from the nonclinical SC dosing and embryofetal development studies were added to this section.

Section 1.4 (Clinical Experience with MEDI-551)

This section was modified to reflect the updated data from Arm A of Study MI-CP204 and the other 3 ongoing MEDI-551 studies in advanced B-cell malignancies.

Section 1.5 (Rationale for Study)

This section was revised to include justification for the new study arms (Arms B and C).

Section 1.6 (Risk-benefit Summary)

The risk-benefit summary was revised to reflect the preliminary data from Study MI-CP204 and the potential for additive toxicities with the combination of MEDI-551 and rituximab.

Section 2 (Study Objectives)

The exploratory objectives (on biomarkers) of Arm A were simplified into a single objective, with the detail provided in Section 7.3 (Endpoints). In addition, primary, secondary, and exploratory objectives were added for Arms B and C.

Section 3 (Study Design)

The description of Arm A was revised to indicate that enrollment in the dose-escalation and expansion phases of this arm is complete. In addition, descriptions and flow diagrams of dose escalation and expansion in Arms B and C were added to the study design section.

Section 4.2.1 (Inclusion Criteria)

Inclusion criteria #3 through #13 were revised to reflect the subjects to be included in Arms B and C.

Section 4.2.2 (Exclusion Criteria)

Exclusion criterion #11 was modified to indicate that it applies only to Arm A.

Sections 4.5.1.1 (Investigational Product Inspection) and 4.5.1.2 (Reporting Product Complaints)

Two subsections were added under Section 4.5.1 (Investigational Product) to describe investigational product inspection and the reporting procedure for product complaints.

Sections 4.5.2 (Treatment Regimens)

The text for Arm A was edited to reduce repetition of study design information (presented in Section 3), focusing only on the treatment regimen. In addition, the treatment regimens for Arms B and C were added to this section.

Sections 4.5.2.1 (Dose Modification for Toxicity Management)

Dose modification criteria for Arms B and C were added to this section. In addition, the text for Arm A was edited to specify that AE severity will be graded according to the NCI

CTCAE V4.03 (formerly V4.0). The CTCAE version number was also updated in the List of Abbreviations.

Section 4.5.3 (Investigational Product Preparation and Administration)

The following equation for weight-based dose calculation was added:
Drug Volume (mL) = Dose (mg/kg) × Patient Weight (kg) ÷ Product Concentration (mg/mL)

In addition, descriptions for investigational production preparation and administration were added for Arms B and C.

Section 4.5.4 (Concomitant Medications)

The following text was added to the concomitant medications section: “Prophylactic intravenous Ig to prevent infections.”

Section 4.5.5 (Dose Escalation)

Dose-escalation criteria for Arms B and C were added. Additionally, in the last paragraph of this section, the first sentence was revised to indicate that the Dose Escalation Committee consists of all study investigators and the sponsor’s medical monitor. Reference to the MedImmune Safety Monitoring Committee was removed.

Section 4.5.6 (Dose-limiting Toxicities)

Dose-limiting toxicity criteria for Arms B and C were added to this section. In addition, the text for Arm A was edited to specify that AE severity will be graded according to the NCI CTCAE V4.03 (formerly V4.0).

Section 5.2 (Schedule of Study Procedures)

A sentence was added to indicate that the schedule of study procedures for Arms A, B, and C are presented in separate subsections. The schedule of study procedures and by-visit descriptions of procedures were added in Section 5.2.2 for Arm B and in Section 5.2.3 for Arm C.

Sections 5.3.1 (Medical History and Physical Examination, ECG, Weight, and Vital Signs), 5.3.2 (Clinical Laboratory Tests), 5.3.4 (Bone Marrow Biopsy), 5.3.6 (Pharmacokinetic Evaluation and Methods), 5.3.7 (Immunogenicity Evaluation and Methods), 5.3.8 (Biomarker Evaluation and Methods), and 5.3.11 (Estimate of Blood Volume Collection)

In each of these sections, descriptions of study procedures were added for Arms B and C.

Sections 6.2.1 (Assessment of Severity)

The text was edited to specify that AE severity will be graded according to the NCI CTCAE V4.03 (formerly V4.0).

Sections 6.3.5.3 (Hepatic Function Abnormality), 6.4 (Safety Management During the Study), and 6.4.2 (Study Stopping Criteria)

The "MedImmune Safety Monitoring Committee (SMC)" was replaced with the "MedImmune safety review committee." In Section 6.4, the last paragraph describing the MedImmune SMC was replaced with a description of the MedImmune safety review committee.

Section 7.2 (Analysis Populations)

The Per-Protocol Population was removed.

Section 7.3 (Endpoints)

This section was revised to align endpoints with the study objectives.

Section 7.4 (Assessments)

Assessment of the endpoints were removed from Section 7.3 and described in this section.

Sections 7.4.1 (MTD or OBD/Highest Protocol-defined Dose)

Assessments for Arms A, B, and C were specified.

Sections 7.4.2 (Safety Assessments)

Assessments for Arms A, B, and C were specified. In addition, the text was edited to specify that AE severity will be graded according to the NCI CTCAE V4.03 (formerly V4.0).

Section 7.5 (Sample Size and Power Calculations)

Sample size and power calculations were added for Arms B and C.

Section 14 (References)

New references cited in the protocol were added to the reference list.

Appendices 2 (International Working Group Criteria for Malignant Lymphoma), 3 (National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0), 4 (International Uniform Response Criteria for Multiple Myeloma), and 5 (National Cancer Institute - Working Group Guidelines)

Appendices 2 through 5 were deleted. These appendices only included a URL to guideline documents. These URLs were included in the reference list.

Appendix 2 (Rituximab Prescribing Information)

Given that Arm C will evaluate MEDI-551 in combination with rituximab, the prescribing information for rituximab was included in Appendix 2.

Protocol Version 11.0, 21Mar2014

Version 10.0 of protocol MI-CP204, dated 07Oct2013, has been amended to create Version 11.0, dated 21Mar2014. The purpose of the amendment is to add a fourth arm (Arm D) to Study MI-CP204: subjects with anti-CD20-refractory aggressive lymphomas receiving MEDI-551 monotherapy. All text revisions resulting from this amendment are incorporated in the body of protocol Version 11.0. Major changes to the protocol are described below.

Abstract

The abstract was revised to reflect the changes made to the body of the protocol.

Section 1.5 (Rationale for Study)

This section was revised to include justification for Arm D.

Section 1.6 (Risk-benefit Summary)

The risk-benefit summary was revised to reflect the addition of Arm D.

Section 2 (Study Objectives)

Primary, secondary, and exploratory objectives were added for Arm D.

Section 3 (Study Design)

A description and flow diagram of Arm D were added to the study design section.

Section 4.2.1 (Inclusion Criteria)

The following changes were made to the inclusion criteria:

- Inclusion criterion #3 (diagnosis) was revised to reflect the subjects to be included in Arm D.
- Inclusion criterion #4 was revised to indicate that the fresh tumor biopsy is optional
- Inclusion criterion #5 (evaluable/measurable disease) was revised to reflect the subjects to be included in Arm D.
- Inclusion criterion #6 (prior therapy) was revised to reflect the subjects to be included in Arm D.
- Inclusion criterion #10 (adequate hematologic function) was revised to reflect the subjects to be included in Arm D.
- Inclusion criterion #12 (contraception) was revised to further define "postmenopausal."

Section 4.2.2 (Exclusion Criteria)

The following changes were made to the exclusion criteria:

- Exclusion criteria #4 and #5 were revised to reflect a washout period of 28 days or 5 half-lives instead of 6 weeks.
- Exclusion criterion #7 was revised to indicate "live or attenuated" vaccines.
- Exclusion criterion #9 (history of other invasive malignancies) was removed.
- Exclusion criteria #18 (ECG abnormality) and #20 (concurrent enrollment in another study) were revised to provide additional clarification.
- Exclusion criterion #21 was modified to indicate that subjects related to employees of a clinical study site directly involved with the conduct of the study may be treated at another participating site.

Section 4.5.1 (Investigational Product [MEDI-551])

This section was updated to reflect the 2 manufacturing processes and the dosage strengths ([redacted] and [redacted] mg/mL).

Section 4.5.2 (Treatment Regimens)

The treatment regimen for Arm D was added to this section.

Section 4.5.2.1 (Dose Modification for Toxicity Management)

This section was revised to include Arm D, which will follow the same dose modification criteria as Arms B and C.

Section 4.5.3 (Investigational Product Preparation and Administration)

This section was revised to include Arm D, which will follow the same investigational product preparation and administration procedures as Arm B.

Section 4.5.4 (Concomitant Medications)

The following text was added to the concomitant medications section: “intrathecal prophylaxis with either methotrexate or cytarabine, if clinically indicated, and prophylactic antibiotics.”

Section 5.1 (Efficacy and Clinical Pharmacology Parameters)

This section was revised to reflect Arms B, C, and D.

Section 5.2 (Schedule of Study Procedures)

The schedule of study procedures and by-visit descriptions of procedures for Arm D were added in Section 5.2.4. In addition, the schedule of study procedures and by-visit descriptions of procedures for Arms B and C were updated to include Karnofsky performance status assessment and BM biopsy with MRD analysis.

Sections 5.3.1 (Medical History and Physical Examination, ECG, Weight, and Vital Signs), 5.3.2 (Clinical Laboratory Tests), 5.3.3 (B-cell and Immunoglobulin Levels), 5.3.4 (Bone Marrow Biopsy), 5.3.5 (Cytogenetic Analysis), 5.3.6 (Minimal Residual Disease Analysis), 5.3.7 (Pharmacokinetic Evaluation and Methods), 5.3.8 (Immunogenicity Evaluation and Methods), 5.3.9 (Biomarker Evaluation and Methods), 5.3.10 (Disease Evaluation Methods), and 5.3.12 (Estimate of Blood Volume Collection)

In each of these sections, descriptions of study procedures were added for Arm D. In addition, Sections 5.3.3, 5.3.5, and 5.3.12 were revised for Arms B and C.

Sections 5.3.6 (Minimal Residual Disease Analysis)

This section was added to describe MRD analysis for Arms B, C, and D.

Sections 6.4.1 (Interruption of Permanent Discontinuation of Study Dosing in Individual Subjects)

This section was revised to reflect Arms A, B, C, and D.

Section 6.4.2 (Study Stopping Criteria)

This section was revised to be consistent with the new protocol template (v16.2).

Sections 6.4.3 (Monitoring of Dose Administration)

This section was revised to reflect Arm D, which will follow the same monitoring procedures as Arms B and C.

Section 7.3 (Endpoints)

The primary, secondary, and exploratory endpoints of Arm D were added.

Section 7.4.3 (Efficacy Assessments)

The definition of MRD-negative CR was added to efficacy assessments.

Section 7.5 (Sample Size and Power Calculations)

Sample size and power calculations were added for Arm D.

Section 14 (References)

New references cited in the protocol were added to the reference list.

Protocol Version 12.0, 27Jan2015

Version 11.0 of protocol MI-CP204, dated 21Mar2014, has been amended to create Version 12.0, dated 12Jan2015. The purpose of the amendment is to add information regarding the [redacted] dosage strength and to remove references to the [redacted] dosage strength of MEDI-551. Modifications to CT/PET scan frequency were made to minimize radiation exposure. In Arm B, subjects receiving doses ≥ 24 mg/kg will receive the initial weekly doses in Cycle 1 over Days 1-2 as mitigation for infusion-related reactions.

This is being implemented in addition to existing safeguards of prophylactic medications (including antihistamines and corticosteroids) and the option to decrease infusion rate because 2 out of 3 subjects at the 6 mg/kg dose level experienced Grade 3 infusion-related reactions during the first infusion.

An allowance for prophylaxis against tumor lysis syndrome in subjects with large tumor burden was added. Appendix 2, Rituximab Prescribing Information, was updated. Other changes were made for clarity and consistency. In addition, changes from Administrative Change 1, dated 30Jun2014, were incorporated. All text revisions resulting from this amendment are incorporated in the body of protocol Version 12.0. Major changes to the protocol are described below.

1. Cover page – Change in medical monitor.
2. Study Abstract – The abstract was modified to mirror the changes made to the protocol body.
3. Section 3.1 (Overview of Study Design) – Language was added to describe the dosing schedule for subjects in Arm B receiving 24 or 48 mg/kg dose levels of MEDI-551. The initial doses will be administered over 2 days on Day 1 and Day 2 in Cycle 1. The flow diagram for Arm B was updated to be consistent with this change.
4. Section 4.2.2 (Exclusion Criteria) – Exclusion criterion 12 was modified to align with allowances for hepatitis B in other MEDI-551 studies. Exclusion criterion 22, history of other invasive malignancy within 5 years except for localized/in situ carcinomas, was added to align with other MEDI-551 studies.
5. Section 4.5.1 (Investigational Product [MEDI-551]) – References to the [redacted] dose were removed and the [redacted] dose was added.
6. Section 4.5.1.1 (Investigational Product Inspection) – References to the [redacted] dose were removed and the [redacted] dose was added.
7. Section 4.5.2 (Treatment Regimens) – Text was added to Arm B to specify that for MEDI-551 doses ≥ 24 mg/kg, the initial weekly doses will be administered over 2 days on Day 1 and Day 2 in Cycle 1. This change was made to minimize infusion-related reactions at higher dose levels. Subsequent doses at the 24 and 48 mg/kg dose levels will be administered weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond.
8. Section 4.5.3 (Investigational Product Preparation and Administration) –
   - Arms B, C, and D – Reference to the [redacted] dosage strength was removed. Added text to specify that subjects in cohorts of Arms B, C and D receiving MEDI-551 at dose levels of 12 mg/kg or less will receive the 10 mg/mL dosage form. Added text to specify that subjects receiving doses ≥ 24 mg/kg in Arm B will receive the initial infusion over 2 days on Day 1 and Day 2 of Cycle 1 and that the Day 1 infusion will be administered over a minimum of 81 minutes, and the Day 2 infusion will be administered over a minimum of 60 minutes (+ 15 minutes at the investigator's discretion). Added text to state that MEDI-551 infusion must be completed within 4 hours after the initial start of the infusion and that a new IP

solution is required to be prepared if MEDI-551 infusion is not able to be completed within 4 hours after the initial start of the infusion.

- For Arm C only: Added text to clarify the timing of MEDI-551 dosing and state that on Day 8 of Cycle 1 and Day 1 of Cycle 2, MEDI-551 should be administered first with rituximab administration a minimum of 30 minutes after completion of the MEDI-551 infusion**.**

9. Section 4.5.2.1 (Dose Modification for Toxicity Management) – The duration of infusion interruption was changed from 6 hours to 4 hours in Table 4.5.2.1-2 for Grade 3 infusion reactions that do not respond to medical therapy as follows: For Grade 3 infusion reaction that does not respond to medical therapy (including interruption of infusion for ≤ **~~6~~ 4** hours) or that occurs despite steroid prophylaxis, discontinue MEDI-551.
10. Section 4.5.3 (Investigational Product Preparation and Administration) – Text was modified in the section for Arms B, C, and D to indicate that [redacted] dosage strengths will be used as specified by the sponsor. Text was added to describe that subjects receiving doses ≥ 24 mg/kg in Arm B will receive the initial infusion over 2 days on Day 1 and Day 2 of Cycle 1. Text was added to indicate that the MEDI-551 infusion must be completed within 4 hours after the initial start of the infusion. Text was added for Arm C to reiterate that MEDI-551 will be administered over a minimum of 81 minutes after mandatory premedications, and that on Day 8 of Cycle 1 and Day 1 of Cycle 2, MEDI-551 should be administered first with rituximab administration a minimum of 30 minutes after completion of the MEDI-551 infusion.
11. (Section 4.5.4 (Concomitant Medications) – Text was added to recommend premedication with acetaminophen, diphenhydramine, and corticosteroids before the first infusion. A statement was added to allow for prophylaxis against tumor lysis syndrome according to institutional guidelines in subjects with large tumor burden.
12. Section 5.2.2 (Study Procedures for Arm B) and Table 5.2.2-1 (Schedule of Study Procedures for Dose Escalation and Expansion in Arm B) – A column was added for Cycle 1 Day 2 to accommodate the 2-day dosing for doses ≥ 24 mg/kg. Aspirate was added to BM biopsy. In Cycle 2+, CT scan and disease response was changed to Q3M. Footnote b was modified to indicate that only subjects who had a positive BM biopsy at baseline and achieve CR will be required to undergo repeat BM biopsy for confirmation of CR. Footnote c was modified to require CT scans every 3 months during treatment for the first 1 year to decrease radiation exposure while still allowing sufficient monitoring of disease response. Cycle 1, Day 2 and the associated assessments were added to the visit-by-visit lists of procedures. Windows around timing for completion of ECGs were added and standardized for clarity. Follow-up visits every 3 months after Day 60 post-EOT visit were changed to every 3 months post-EOT visit to align with the schedule for follow-up scans.
13. Section 5.2.3 (Study Procedures for Arm C) and Table 5.2.3-1 (Schedule of Study Procedures for Dose Escalation and Expansion in Arm C) - Aspirate was added to BM biopsy. Cycle 3+, Day 22 was added to allow for completion of CT/PET scans prior to Day 1 of every other cycle. Footnote b was modified to indicate that only subjects who had a positive BM biopsy at baseline and achieve CR will be required to undergo repeat BM biopsy for confirmation of CR. Footnote c was modified to require CT scans every 2 months during treatment for the first 1 year and every 3 months during the first year of follow-up to decrease radiation exposure while still allowing sufficient monitoring of

disease response. Text was modified to clarify that CTs are required, while FDG-PET scans are optional. Windows around timing for completion of ECGs were added and standardized for clarity. Follow-up visits every 3 months after Day 60 post-EOT visit were changed to every 3 months post-EOT visit to align with the schedule for follow-up scans.

14. Section 5.2.4 (Study Procedures for Arm D) and Table 5.2.4-1 (Schedule of Study Procedures for Arm D) - Aspirate was added to BM biopsy. Cycle 3+, Day 22 was added to allow for completion of CT/PET scans prior to Day 1 of every other cycle. Footnote b was modified to indicate that only subjects who had a positive BM biopsy at baseline and achieve CR will be required to undergo repeat BM biopsy for confirmation of CR. Footnote c was modified to require CT scans every 2 months during treatment for the first 1 year, then every 6 months and at EOT, and during follow-up every 3 months for the first 1 year to decrease radiation exposure while still allowing sufficient monitoring of disease response. Text was modified to clarify that CTs are required, while FDG-PET scans are optional. Windows around timing for completion of ECGs were added and standardized for clarity. Follow-up visits every 3 months after Day 60 post-EOT visit were changed to every 3 months post-EOT visit to align with the schedule for follow-up scans.
15. Section 5.3.1 (Medical History and Physical Examination, ECG, Weight, and Vital Signs) – Windows for completion of ECGs were added for each arm.
16. Section 5.3.7 (Pharmacokinetic Evaluation and Methods) – Blood samples for MEDI-551 serum concentrations were added at for Arm B at Cycle 1, Day 2 (newly added samples); and for Arm C at Cycle 1, Days 15 and 22 (to align with samples required in Table 5.2.3-1).
17. Section 5.3.10 (Disease Evaluation and Methods) – The section for FL, DLBCL, MCL, and Transformed Indolent Lymphoma was modified to require scans every 2 cycles beginning with Cycle 3 for a period of 1 year, then every 3 cycles during follow-up for a year.
18. Section 5.3.12 (Estimate of Blood Volume Collection) – The blood volume for Arm B was increased to 105 mL (7.1 tablespoons) for the 6 and 12 mg/kg cohorts and to less than 116 mL (7.8 tablespoons) for the 24 and 48 mg/kg cohorts.
19. Appendix 2, Rituximab Prescribing Information, was updated with the most recent version, dated 8/2014.

Protocol Version 13.0, 01Jun2017

Version 12.0 of protocol MI-CP204, dated 27Jan2015, has been amended to create Version 13.0, dated 01Jun2017. The purpose of Version 13.0 is to discontinue participation for all subjects who are no longer dosing and have completed at least the 90-Day Post Last Dose Visit, while allowing subjects who are benefiting from MEDI-551 to continue treatment.

Enrollment in the study was closed as of 30Sep2015. Arm A was completed as planned, with a total of 95 subjects enrolled (26 in dose-escalation and 69 in expansion). A total of 7 subjects were enrolled in Arm B dose-escalation, including one at a dose of 24 mg/kg.

Based on emerging PK and pharmacodynamic data, a dose of 12 mg/kg, administered weekly during Cycle 1 and then monthly in subsequent cycles, was determined to be sufficient to saturate the B-cell sink and achieve full exposure; at the sponsor's discretion and not due to any safety issues, no further Arm B dose-escalation was conducted and Arm B dose-expansion was not initiated. A total of 19 subjects were enrolled in Arm C. Of these 19 subjects there were only 7 responders, and there was about a 13% probability of meeting the protocol-specified target response rate of 50%. Further enrollment in Arm C was therefore halted at the sponsor's discretion and not due to any safety issues. A total of 16 subjects were enrolled in Arm D. Of these 16 subjects there were only 3 responders, and there was about a 1% probability of meeting the protocol-specified target response rate of 50%. Further enrollment in Arm D was therefore halted at the sponsor's discretion and not due to any safety issues.

As of 19Jan2017, 9 subjects remain on treatment; all have completed at least 1 year of treatment.

Subjects who are currently on treatment will be allowed to continue to receive MEDI-551 with a simplified schedule of evaluations focused on safety. The 90-Day Post Last Dose Visit (60 days post-EOT Visit) will be conducted when subjects come off treatment. Long-term follow-up for progression-free survival and overall survival will be discontinued. As of Version 13.0, all subjects who have completed treatment and safety follow-up will be considered to have completed the study.

- On treatment days, the schedule of evaluations is simplified.
  - Key safety assessments relevant to MEDI-551 are retained. Vital signs will be evaluated pre-dose and at end of infusion only.
  - Additional safety assessments that have not been informative during later cycles of MEDI-551 will not be required at each cycle (note these evaluations are retained at EOT). This includes (when applicable) ECG, coagulation, urinalysis; liver function will continue to be evaluated at each cycle), PK, ADA, and B-cell monitoring (B-cell levels in non-CLL subjects were generally very low at baseline, likely due to prior anti-cancer treatments. B-cell levels in CLL subjects were often elevated at baseline; however, this is likely reflects malignant rather than normal B cells. Across populations, B cells were nearly or fully depleted following > 6 cycles).
  - Exploratory evaluations are removed.
  - Disease evaluations will be performed at regular intervals to determine whether MEDI-551 is continuing to provide clinical benefit.
    - Subjects with DLBCL, FL, MCL, or transformed indolent lymphoma who have completed > 1 year of treatment: disease evaluation is required once every 6 months.

  - Subjects with CLL who have completed > 1 year of treatment: after which CT scans for disease evaluation are only required once every 6 months if clinically indicated (eg previous indication to treat was based on predominantly nodal disease) or if indicated based on hematology findings.

- At the EOT Visit, all safety assessments will be performed, but exploratory evaluations are removed. Evaluations used to confirm CR are removed (where applicable).
- Safety follow-up will be conducted at the 90-Day Post Last Dose Visit (also known as End of Study). All safety assessments will be performed; exploratory evaluations are removed. The 30 Days post-EOT visit is removed.
- Long-term follow-up for progression-free survival and overall survival will be discontinued once Version 13.0 is in effect. All subjects who have completed treatment and safety follow-up through at least the 90-Day Post Last Dose Visit (ie approximately 90 days post last dose), withdrawn consent, or been lost to follow-up will be considered to have completed the study.

Major changes to the protocol are described below.

1. Title Page: The Medical Monitor was changed from Dr. Boyd Mudenda to Dr. Nai Shun Yao as the primary medical monitor. Dr. Yao's title and contact information were updated.
2. Dr. Mohammed Dar was added as the secondary medical monitor.
3. Study Abstract:
    a. The abstract was modified to mirror the changes made to the protocol body.
    b. Subject numbers were updated to reflect actual enrollment
    c. Rationale for discontinuing enrollment in Arms B, C, and D added
    d. Exploratory Objectives amended
4. Section 1.4 (Clinical Experience with MEDI-551): Updated to be consistent with the current MEDI-551 Oncology Investigators Brochure.
5. Section 3.1 (Overview of Study Design):
    a. Number of subjects treated was updated as well as 90 Day Post Last Dose Visit added and defined.
    b. To make the protocol more consistent, subjects in all arms who achieve a CR may receive an additional 2 cycles of MEDI-551 at the same dose prior to EOT. Previously this applied to Arm A only. Subjects in Arm A who reached CR and then came off treatment had durable responses of > 1 year in all cases.
    c. Retreatment will not be provided for subjects who come off treatment in CR and later progress. Prior to implementation of Version 13.0, the option of retreatment would be considered for subjects in the US only.
6. Section 3.2 (Estimated Study Duration): Clarified to state that safety follow-up assessments will be conducted through approximately 90 days after the last dose of investigational product, which is equivalent to approximately 60 days post-EOT Visit, and revised to state that study completion is defined as the date of the last protocol-specified visit for the last subject in the study.
7. Section 4.5.2 (Treatment Regimens): Updated to reflect changes described above.
8. Section 4.5.5 (Dose Escalation): Updated to reflect actual enrollment.

9. Section 4.7 (Subject Status): The following statement was added: Once Version 13.0 is in effect, all subjects who have completed treatment and safety follow-up, withdrawn consent, or been lost to follow-up will be considered to have completed the study.
10. Section 4.8 (Study Completion): The following statement was updated. Study completion is defined as the date of the last protocol-specified visit for the last subject in the study. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor, and/or destroyed by the site/IRB/IEC instructions.
11. Section 5.2 (Schedule of Study Procedures): Added rationale and summary of changes in study procedures.

    Section 5.2.1 (Schedule of Study Procedures – All Subjects Approved for Version 13.0 of the Protocol): This section title changed from Study Procedures for Arm A
12. 5.2.1 Title was Study Procedures for Arm A.
    a. The following tables and instructions were removed and all subjects are to follow newly entered Table 5.2.1-1:
        i. Table 5.2.1.1-1 (Schedule of Study Procedures for Dose-escalation Cohorts 1 and 2 [Screening and Cycles 1 - 3 and All Subsequent Odd Cycles] of Arm A) and Table 5.2.1.1-2 (Schedule of Study Procedures for Dose-escalation Cohorts 1 and 2 [Cycle 4, All Even Cycles, End of Treatment, and Post-therapy] of Arm A)
        ii. Tables 5.2.1.2-1 and 5.2.1.2-2 (Dose-Escalation Cohorts 3-6 and Expansion (Screening and Cycles 1-3) Arm A and (Cycle 4 and Follow up) Arm A
        iii. Table 5.2.2-1 Dose-Escalation and Expansion Arm B
        iv. Table 5.2.3-1 Dose-Escalation and Expansion Arm C
        v. Table 5.2.4-1 Procedures for Arm D

The following procedures were completely removed and are no longer collected:

a. Day 30 and Day 60 post dose visits were removed as well as all long term follow up visits, which were replaced with a single 90-Day Post Last Dose Visit (also defined as End of Study visit).
b. Hepatitis B, C; HIV-1 and HIV-2
c. Serum βhCG and Urine βhCG have been changed to “Pregnancy Test (females of childbearing potential)”
d. Triplicate ECGs were changed to single ECGs and are no longer collected during dosing visits. Single ECGs will be collected at the EOT visit and the 90-Day Post Last Dose Visit.
e. Physical examination is now only focused (symptom-directed)
f. Height
g. Cytogenetic analysis is no longer required
h. Liver and spleen palpation
i. Collection of bone marrow biopsy and aspirates as well as tumor tissue
j. Collection of exploratory post-infusion biomarkers
k. Collection of circulating biomarkers
l. Collection of RNA samples for analysis
m. Collection of DNA samples for analysis
n. Subsequent anticancer therapy

o. Collection of blood tumor biomarkers
p. Flow Cytometry for MRD
q. Peripheral blood for MRD
r. Molecular analysis of whole blood DNA

13. Section 5.3 Description of Study Procedures: This section was modified to mirror the changes described above in Section 5.2:
    a. 5.3.1 (Medical History and Physical Exam, ECG, Weight, and Vital Signs):
        i. Physical Examinations updated from "post-screening exams may be primarily focused on disease findings" to "Physical examination should be focused (symptom-directed)".
        ii. ECGs are no longer required on all dosing days (Day 1 of each treatment cycle) and are to be done as single ECGs, not triplicate.
        iii. On dosing days, vital signs will be monitored prior to MEDI-551 infusion and at End Of Infusion only.
    b. 5.3.2 (Clinical Laboratory Tests):
        i. The hyperlink was added for reference to Section 5.2 laboratory assessments schedule
        ii. Women of childbearing potential only added to clarify Day 1 urine pregnancy tests.
    c. 5.3.3 (B-cell and Immunoglobulin Levels):
        i. Separate paragraphs were consolidated into 1 paragraph for Arms A, B, C, and D.
    d. Sections 5.3.4 Bone Marrow Biopsy, 5.3.5 Cytogenetic Analysis, and 5.3.6 Minimal Residual Disease Analysis were all removed due to removal of all relevant samples and testing.
    e. 5.3.4 (Pharmacokinetic Evaluation and Methods):
        i. Most of this section was removed and a reference to Section 5.2 was added as well a statement that MEDI-551 concentrations in serum samples will be measured using a validated immunoassay.
    f. 5.3.5 (Immunogenicity Evaluation and Methods:
        i. The visits for assessing antibodies in Section 5.3.8 was simplified to refer to Section 5.2 and will only be collected at EOT and 90-Day Post Last Dose Visits.
    g. 5.3.9 Biomarker Evaluation and Methods was removed.
    h. 5.3.6 (Disease Evaluation and Methods) section was modified to a different frequency:
        i. FL, DLBCL, MCL, and transformed indolent lymphoma: Subjects will be assessed by CT scan (FDG-PET or PET-CT if clinically indicated) and physical . CLL (and SLL) : Subjects will be assessed by chest, abdomen, pelvis, and neck (if applicable) CT scan and disease response assessment (physical exam) if clinically indicated (eg previous indication to treat was based on predominantly nodal disease) or when indicated based on hematology findings.
    i. Section 5.3.11 Experimental Sample Collection was removed entirely.

    j. 5.3.7 (Estimate of Blood Volume Collection) was renumbered and all Arms were condensed to one section.

14. Section 6.3.2 (Study Reporting Period for Serious Adverse Events): Updated language to reflect that reporting period for SAEs is the period immediately following the time that written informed consent is obtained through the 90-Day Post Last Dose.
15. Section 6.4.1 (Interruption or Permanent Discontinuation of Study Dosing in Individual Subjects): Modified language to state that until Version 13.0 is implemented, the protocol required long-term follow-up of subjects who are permanently discontinued from investigational product.
16. Section 6.4.3 (Monitoring of Dose Administration): This section was modified to mirror the changes described above in Sections 5.2.1 - 5.2.4 and Section 5.3.1.
17. Section 7 (Statistical Considerations):
    a. Updated to include the actual numbers of subjects enrolled in each Arm.
    b. Added rationale for discontinuing enrollment in Arms B, C, and D.
    c. Updated the number of exploratory endpoints

Appendix 1 Signatures

Sponsor Signature

An Open-label, Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-cell Malignancies

I agree to the terms of this protocol and all amendments/administrative changes.

Signature and date: An electronic signature is appended

[redacted]

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [redacted]

Signature of Principal Investigator

An Open-label, Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-cell Malignancies I agree to the terms of this protocol and all amendments/administrative changes.

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available)_____

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Appendix 2 Rituximab Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITUXAN® safely and effectively. See full prescribing information for RITUXAN®.

RITUXAN® (rituximab) injection, for intravenous use
Initial U.S. Approval: 1997

WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

- **Fatal infusion reactions within 24 hours of Rituxan infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).**
- **Severe mucocutaneous reactions, some with fatal outcomes (5.2).**
- **Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).**
- **Progressive multifocal leukoencephalopathy (PML) resulting in death (5.4).**

RECENT MAJOR CHANGES

Boxed Warning	9/2013
Warnings and Precautions	9/2013

INDICATIONS AND USAGE
Rituxan® (rituximab) is a CD20-directed cytolytic antibody indicated for the treatment of patients with:
- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.5).

DOSAGE AND ADMINISTRATION
- Administer only as an intravenous infusion.
- Do not administer as an intravenous push or bolus.
- Rituxan should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.
- The dose for NHL is 375 mg/m^2 (2.2).
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with FC, administered every 28 days (2.3).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.4).
- The dose for RA in combination with methotrexate is two-1000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).
- The dose for GPA and MPA in combination with glucocorticoids is 375 mg/m^2 once weekly for 4 weeks (2.6).

DOSAGE FORMS AND STRENGTHS
- Injection: 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial (3)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function (5.5).
- Infections: Withhold Rituxan and institute appropriate anti-infective therapy (5.6).
- Cardiac arrhythmias and angina: Discontinue infusions in case of serious or life-threatening events (5.7).
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).
- Live virus vaccines: Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Cytopenias: Monitor blood counts at regular intervals (5.11, 6.1).

ADVERSE REACTIONS
Most common adverse reactions in clinical trials were:
- NHL (≥ 25%): infusion reactions, fever, lymphopenia, chills, infection and asthenia (6.1).
- CLL (≥ 25%): infusion reactions and neutropenia (6.1).
- RA (≥ 10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion reactions, serious infections, and cardiovascular events) (6.2).
- GPA and MPA (≥15 %): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (other important adverse reactions include infusion reactions) (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Renal toxicity when used in combination with cisplatin (5.8).

USE IN SPECIFIC POPULATIONS
- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of Rituxan to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion Reactions

Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue Rituxan infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion reactions [*see Warnings and Precautions (5.1), Adverse Reactions (6.1)*].

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan [*see Warnings and Precautions (5.2), Adverse Reactions (6)*].

Hepatitis B Virus (HBV) Reactivation

HBV reactivation can occur in patients treated with Rituxan, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with Rituxan. Discontinue Rituxan and concomitant medications in the event of HBV reactivation [*see Warnings and Precautions (5.3), Adverse Reactions (6)*].

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving Rituxan [*see Warnings and Precautions (5.4), Adverse Reactions (6)*].

1 INDICATIONS AND USAGE

1.1 Non-Hodgkin's Lymphoma (NHL)

Rituxan® (rituximab) is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

1.2 Chronic Lymphocytic Leukemia (CLL)

Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)

Rituxan® (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

1.4 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Rituxan® (rituximab), in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

1.5 Limitations of Use

Rituxan is not recommended for use in patients with severe, active infections.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Administer only as an Intravenous Infusion [*see Dosage and Administration (2.7)*].
Do not administer as an intravenous push or bolus.
Premedicate before each infusion [*see Dosage and Administration (2.7)*].
Rituxan should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur [see *Warnings and Precautions (5.1)*].

- **First Infusion**: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- **Subsequent Infusions**:
  Standard Infusion: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
  For previously untreated follicular NHL and DLBCL patients:
  If patients did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.
  Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).
  Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count $\geq 5000/mm^3$ before Cycle 2 should not be administered the 90-minute infusion [see Clinical Studies (14.4)].
- Interrupt the infusion or slow the infusion rate for infusion reactions [*see Boxed Warning, Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is:

- 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of cycles 2–6 (every 28 days).

2.4 Recommended Dose as a Component of Zevalin® for treatment of NHL

- Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin.
- Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90- Zevalin.
- Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.5 Recommended Dose for Rheumatoid Arthritis (RA)

- Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
- Rituxan is given in combination with methotrexate.

2.6 Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

- Administer Rituxan as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment.
- Safety and efficacy of treatment with subsequent courses of Rituxan have not been established [*see Warnings and Precautions (5.14)*].

2.7 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine. For patients administered Rituxan according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion [*see Clinical Studies (14.4)*].

For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

For GPA and MPA patients, glucocorticoids are given in combination with Rituxan [*see Dosage and Administration (2.6)*].

Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last Rituxan infusion.

2.8 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

3 DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/10 mL in a single-use vial
- 500 mg/50 mL in a single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)*].

5.2 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6)*].

5.3 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituxan. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with Rituxan. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituxan therapy. HBV reactivation has been reported up to 24 months following completion of Rituxan therapy.

In patients who develop reactivation of HBV while on Rituxan, immediately discontinue Rituxan and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop HBV reactivation. Resumption of Rituxan in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. [*See Boxed Warning, Adverse Reactions (6)*]

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [*See Boxed Warning, Adverse Reactions (6)*].

5.5 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Rituxan in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [*See Warnings and Precautions (5.8), Adverse Reactions (6)*].

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Rituxan-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute appropriate anti-infective therapy. [*See Adverse Reactions (6, 6.1)*].

5.7 Cardiovascular

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina. [*See Adverse Reactions (6)*].

5.8 Renal

Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and Precautions (5.5)*].

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean

time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur. [*See Adverse Reactions (6)*].

5.10 Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituxan.

The effect of Rituxan on immune responses was assessed in a randomized, controlled study in patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on MTX alone).

Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

5.11 Laboratory Monitoring

In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias [*See Adverse Reactions (6.1)*]. In patients with RA, GPA or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment with Rituxan.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While the efficacy of Rituxan was supported in four controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations. The use of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended [*See Clinical Studies (14.6)*].

5.14 Retreatment in Patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients with GPA and MPA. The safety and efficacy of retreatment with Rituxan have not been established [*See Dosage and Administration (2.6), Adverse Reactions (6.3), and Clinical Studies (14.7)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion reactions [*see Warnings and Precautions (5.1)*]
- Mucocutaneous reactions [*see Warnings and Precautions (5.2)*]
- Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.3)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.5)*]
- Infections [*see Warnings and Precautions (5.6)*]
- Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- Renal toxicity [*see Warnings and Precautions (5.8)*]
- Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

The most common adverse reactions of Rituxan (incidence ≥ 25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of Rituxan (incidence ≥ 25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

6.1 Clinical Trials Experience in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to Rituxan in 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials (n=356 and n=2427). The population included 1180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received Rituxan as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received Rituxan 375 mg/m^2 as an initial infusion followed by 500 mg/m^2 for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. [*See Boxed Warning, Warnings and Precautions (5.1)*]. In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of Rituxan at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.8%]). For Cycles 2-8, the incidence of Grade 3-4 infusion reactions on the day of or day after the 90-minute infusion, was 2.8% (95% CI [1.3%, 5.0%]). [*See Warnings and Precautions (5.1), Clinical Studies (14.4)*].

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%). [*See Warnings and Precautions (5.4), (5.5), (5.6)*].

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in patients treated with R-FC compared to patients treated with FC. Prolonged neutropenia is defined as Grade 3-4 neutropenia that has not resolved between 24 and 42 days after the last dose of study treatment. Late-onset neutropenia is defined as Grade 3-4 neutropenia starting at least 42 days after the last treatment dose.

In patients with previously untreated CLL, the frequency of prolonged neutropenia was 8.5% for patients who received R-FC (n=402) and 5.8% for patients who received FC (n=398). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% of 209 patients who received R-FC and 4.3% of 230 patients who received FC.

For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for patients who received R-FC (n=274) and 19.1% for patients who received FC (n=274). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 38.7% in 160 patients who received R-FC and 13.6% of 147 patients who received FC.

Relapsed or Refractory, Low-Grade NHL

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [*See Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m^2 weekly for 4 doses.

Table 1
Incidence of Adverse Reactions in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1

Table 2*

Incidence of All Adverse Reactions** Occurring in ≥2% and at Least 1% Greater than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo+MTX N=398 n (%)	Rituxan+MTX N=540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (<1)	12 (2)
Urticaria	3 (<1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (<1)	9 (2)
Asthenia	1 (<1)	9 (2)

*These data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo administered in combination with methotrexate.

**Coded using MedDRA.

Infusion Reactions

In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

Infections

In the pooled, placebo-controlled studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group.

In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (≥ 0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

Cardiac Adverse Reactions

In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over three courses of Rituxan.

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

Hypophosphatemia and hyperuricemia

In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

In the experience with Rituxan in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

Retreatment in Patients with RA

In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients having received at least two, three, and four courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of Rituxan were similar to rates and types seen for a single course of Rituxan.

In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who were retreated with Rituxan was similar to those who were retreated with placebo [*See Clinical Studies (14.6), and Dosage and Administration (2.5)*].

6.3 Clinical Trials Experience in Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented below reflect the experience in 197 patients with GPA and MPA treated with Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase. In the 6-month remission induction phase, 197 patients with GPA and MPA were randomized to either Rituxan 375 mg/ m^2 once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function, white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The primary analysis was at the end of the 6 month remission induction period and the safety results for this period are described below.

Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of greater than or equal to 10% in the Rituxan group. This table reflects experience in 99 GPA and MPA patients treated with Rituxan, with a total of 47.6 patient-years of observation and 98 GPA and MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation. Infection was the most common category of adverse events reported (47-62%) and is discussed below.

Table 3
Incidence of All Adverse Reactions
Occurring in ≥ 10% of Rituxan-treated GPA and MPA
Patients in the Clinical Study Up to Month 6*

Preferred Term	Rituxan N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion Reactions

Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on background oral corticosteroids which may have mitigated or masked an infusion reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.

Infections

In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group by Month 6. The most common infections in the Rituxan group were upper respiratory tract infections, urinary tract infections, and herpes zoster.

The incidence of serious infections was 11% in the Rituxan-treated patients and 10% in the cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia.

Hypogammaglobulinemia

Hypogammaglobulinemia (IgA, IgG or IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with Rituxan. At 6 months, in the Rituxan group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group.

Retreatment in Patients with GPA and MPA

In the active-controlled, double-blind study, subsequent courses of Rituxan were allowed for patients experiencing a relapse of disease. The limited data preclude any conclusions regarding the safety of subsequent courses of Rituxan with GPA and MPA [*See Dosage and Administration (2.6), and Warnings and Precautions (5.14)*].

6.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

A total of 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse reactions. Upon further treatment, the proportions of patients with infusion reactions were similar between HACA positive and negative patients, and most reactions were mild to moderate. Four HACA positive patients had serious infusion reactions, and the temporal relationship between HACA positivity and infusion reaction was variable.

A total of 23/99 (23%) Rituxan-treated patients with GPA and MPA tested positive for HACA by 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

6.5 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituxan.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged hypogammaglobulinemia [*See Warnings and Precautions (5.6)*].
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections [*See Warnings and Precautions (5.6)*].
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

- Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Rituxan. In patients with CLL, Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving Rituxan and for 12 months following treatment. Rituxan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on postcoitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system. Hypogammaglobulinemia has been observed in pediatric patients treated with Rituxan.

The safety and effectiveness of Rituxan in pediatric patients have not been established.

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Lymphocytic Leukemia

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 11 or in Study 12; there was also no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 65 years of age or older in Study 12 [*See Clinical Studies (14.5)*]. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of Rituxan. In Study 11, the dose intensity of Rituxan was similar in older and younger patients, however in Study 12 older patients received a lower dose intensity of Rituxan.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 11); 56% vs. 39% (Study 12)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 11); 21% vs. 10% (Study 12)], thrombocytopenia [19% vs. 8% (Study 12)], pancytopenia [7% vs. 2% (Study 11); 7% vs. 2% (Study 12)] and infections [30% vs. 14% (Study 12)].

Rheumatoid Arthritis

Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and 2% were 75 years old and older. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Of the 99 Rituxan-treated GPA and MPA patients, 36 (36%) were 65 years old and over, while 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over. The clinical study did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

There has been no experience of overdosage with Rituxan.

11 DESCRIPTION

Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the DHL 4 human B cell lymphoma cell line.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

12.2 Pharmacodynamics

Non-Hodgkin's Lymphoma (NHL)

In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/μl) within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid

protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of Rituxan, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with counts >10 cells/µL. By Month 18, most patients (87%) had counts >10 cells/µL.

12.3 Pharmacokinetics

Non-Hodgkin's Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 Rituxan weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Rheumatoid Arthritis

Following administration of 2 doses of Rituxan in patients with RA, the mean (± S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 × 500 mg and 2 × 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received Rituxan, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m^2 rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0. 312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have higher clearance. However, further dose adjustment based on gender or HACA status is not necessary.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Rituxan or to determine potential effects on fertility in males or females.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of Rituxan given as an intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with > 5000 lymphocytes/μL in the peripheral blood were excluded from the study.

Results are summarized in Table 4. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of Rituxan weekly for 8 doses. Results are summarized in Table 4.

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of Rituxan weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of Rituxan. Results are summarized in Table 4.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m^2 weekly for 4 doses. Results are summarized in Table 4.

Table 4
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting

	Study 1 Weekly×4 N=166	Study 2 Weekly×8 N=37	Study 1 and Study 3 Bulky disease, Weekly×4 N=39[a]	Study 3 Retreatment, Weekly×4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b, c, d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[a] Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.

[b] Kaplan-Meier projected with observed range.

[c] "+" indicates an ongoing response.

[d] Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 5. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 5
Efficacy Results in Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years)[a]	2.4	1.4
Hazard ratio (95% CI)[b]	0.44 (0.29, 0.65)	

[a] $p < 0.0001$, two-sided stratified log-rank test.
[b] Estimates of Cox regression stratified by center.

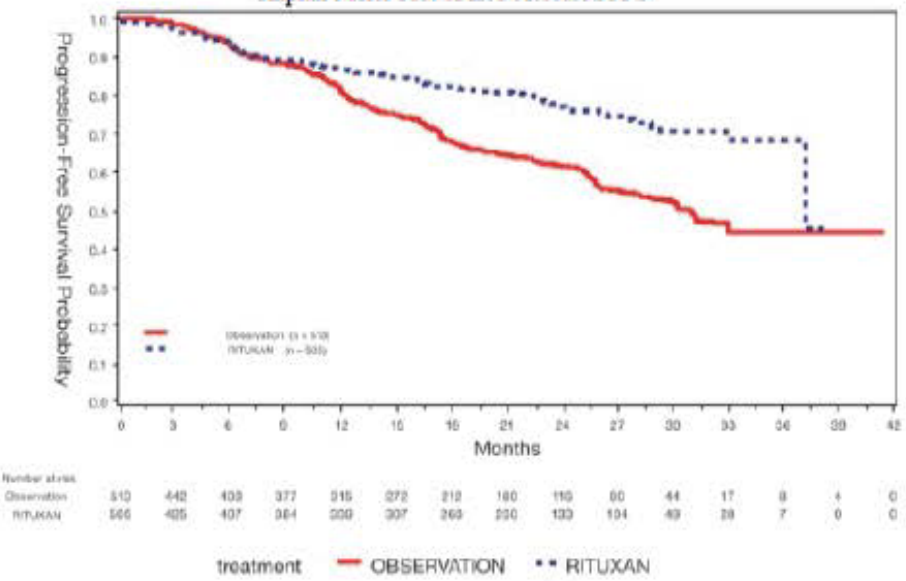
Study 5

An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy, 375 mg/m^2 every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Figure 1
Kaplan-Meier Plot of IRC Assessed PFS



Study 6

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m^2 intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

14.3 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 7

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m^2 on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥ 2, 86% had ECOG performance status of < 2, 57% had

elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 6. These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given after the second randomization.

Analysis of results after the second randomization in Study 7 demonstrates that for patients randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

Study 8

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance status scores < 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 6.

Study 9

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤ 1, 99% had ECOG performance status of < 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 6.

Table 6
Efficacy Results in Studies 7, 8, and 9

	Study 7 (n = 632)		Study 8 (n = 399)		Study 9 (n = 823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	74%	63%	69%	58%	95%	86%
Hazard ratio[d]	0.72[a]		0.68[a]		0.40[a]	

[a] Significant at $p < 0.05$, 2-sided.
[b] NE = Not reliably estimable.
[c] Kaplan-Meier estimates.
[d] R-CHOP vs. CHOP.

In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.4 Ninety-Minute Infusions in Previously Untreated Follicular NHL and DLBCL

In Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated in a prospective, open-label, multi-center, single-arm trial for the safety of 90-minute rituximab infusions. Patients with follicular NHL received rituximab 375 mg/m^2 plus CVP chemotherapy. Patients with DLBCL received rituximab 375 mg/m^2 plus CHOP chemotherapy. Patients with clinically significant cardiovascular disease were excluded from the study. Patients were eligible for a 90-minute infusion at Cycle 2 if they did not experience a Grade 3-4 infusion-related adverse event with Cycle 1 and had a circulating lymphocyte count $\leq$ 5000/mm^3 before Cycle 2. All patients were pre-medicated with acetaminophen and an antihistamine and received the glucocorticoid component of their chemotherapy prior to Rituxan infusion. The main outcome measure was the development of Grade 3-4 infusion-related reactions on the day of, or day after, the 90-minute infusion at Cycle 2 [*See Adverse Reactions (6.1)*].

Eligible patients received their Cycle 2 rituximab infusion over 90 minutes as follows: 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes [*See Dosage and Administration (2.1)*]. Patients who tolerated the 90-minute rituximab infusion at Cycle 2 continued to receive subsequent rituximab infusions at the 90-minute infusion rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8).

The incidence of Grade 3-4 infusion-related reactions at Cycle 2 was 1.1% (95% CI [0.3%, 2.8%]) among all patients, 3.5% (95% CI [1.0%, 8.8%]) for those patients treated with R-CVP, and 0.0% (95% CI [0.0%, 1.5%]) for those patients treated with R-CHOP. For Cycles 2-8, the incidence of Grade 3-4 infusion-related reactions was 2.8% (95% CI [1.3%, 5.0%]). No acute fatal infusion related reactions were observed.

14.5 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously untreated CLL [Study 11 (n=817)] or previously treated CLL [Study 12 (n=552)]. Patients received fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day on days 1, 2 and 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

In Study 11, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In Study 12, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (Study 11) or an independent review committee (Study 12). The investigator assessed results in Study 12 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 7.

Table 7
Efficacy Results in Studies 11 and 12

	Study 11* (Previously untreated)		Study 12* (Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	<0.01		0.02	
Response rate (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (37, 51)

*As defined in 1996 National Cancer Institute Working Group guidelines.

Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 8.

Table 8
Efficacy Results in Studies 11 and 12 in Subgroups Defined by Age*

	Study 11		Study 12	
Age subgroup	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)
Age < 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age ≥ 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age < 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age ≥ 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

* From exploratory analyses.

14.6 Rheumatoid Arthritis (RA)

Reducing the Signs and Symptoms: Initial and Re-Treatment Courses

The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1, patients were randomized to receive either Rituxan 2×1000 mg+MTX or placebo+MTX for 24 weeks. Further courses of Rituxan 2×1000 mg+MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 9.

In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 × 1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of

patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after retreatment, are shown in Table 9.

Table 9
ACR Responses in Study 1 and Study 2 (Percent of Patients)
(Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
	Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)		
Response	Placebo + MTX n = 201	Rituxan + MTX n = 298	Treatment Difference (Rituxan – Placebo)[c] (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo)[a,b,c] (95% CI)
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (–4%, 13%)
ACR70				ACR70			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

[a] In Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

[b] Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at Week 24.

[c] For Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive > 20 IU/mL, negative < 20 IU/mL) at baseline; For Study 2, weighted difference stratified by RF status at baseline and ≥ 20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 10.

Table 10
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

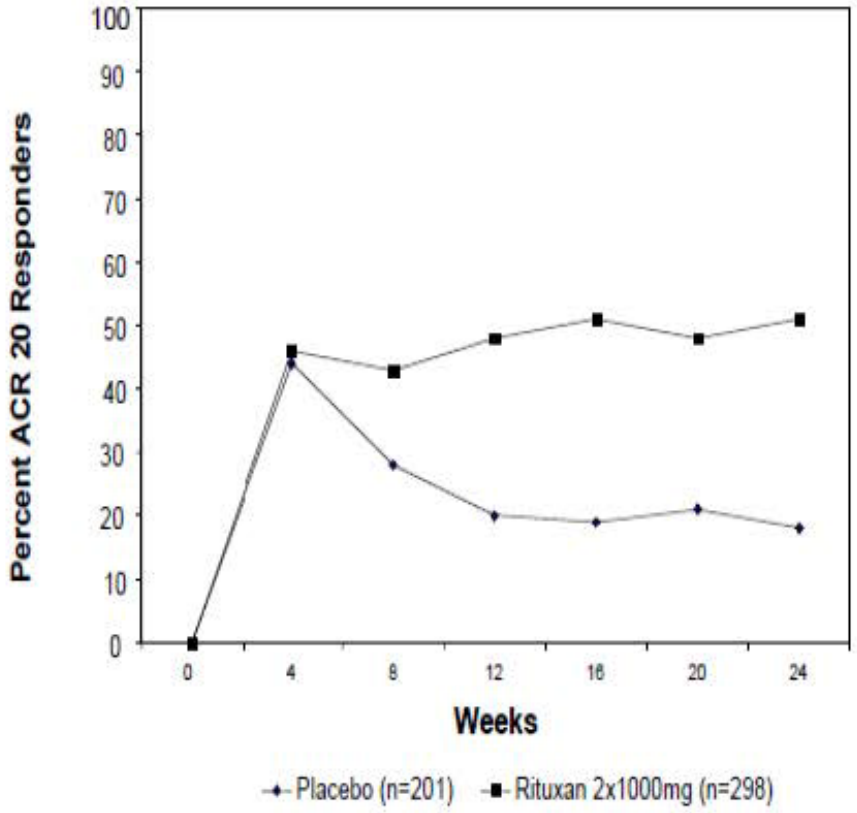
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	73.0	68.0	71.0	41.0
Pain[a]	68.0	68.0	67.0	38.5
Disability Index (HAQ)[b]	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

[a] Visual Analogue Scale: 0 = best, 100 = worst.

[b] Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar proportion of patients achieved these responses through Week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 2
Percent of Patients Achieving ACR 20 Response by Visit*
Study 1 (Inadequate Response to TNF Antagonists)



*The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage compared to placebo +MTX after 1 year as shown in Table 11.

Table 11
Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 × 1000 mg + MTX[b]	Placebo + MTX[c]	Treatment Difference (Placebo – Rituxan)	95% CI
Change during First Year				
TSS	0.66	1.77	1.11	(0.47, 1.75)
ES	0.44	1.19	0.75	(0.32, 1.19)
JSN Score	0.22	0.58	0.36	(0.10, 0.62)
Change during Second Year[a]				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

[a] Based on radiographic scoring following 104 weeks of observation.

[b] Patients received up to 2 years of treatment with Rituxan + MTX.

[c] Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with Rituxan + MTX from Week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 11, progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 × 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.

Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

Table 12
Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

	Placebo + MTX n = 172	Rituxan 2 × 1000 mg + MTX n = 170	Treatment Difference (Rituxan – Placebo)[b] (95% CI)
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of patients with "Improved" score (Change from Baseline ≥ MCID)[a]	48%	58%	11% (0%, 21%)

[a] Minimal Clinically Important Difference: MCID for HAQ = 0.22.

[b] Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥ 20 IU/mL, negative < 20 IU/mL) at baseline.

14.7 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

A total of 197 patients with active, severe GPA and MPA (two forms of ANCA Associated Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month remission induction phase and a 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either Rituxan 375 mg/m^2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months.

Table 13
Percentage of Patients Who Achieved
Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate	64%	53%	11%
95.1%[b] CI	(54%, 73%)	(43%, 63%)	(–3%, 24%)[a]

[a] non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (–3%> –20%).

[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months

In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment with Rituxan

Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the first course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent courses of Rituxan in patients with GPA and MPA [*see Warnings and Precautions (5.14)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. It is important that the patient's overall health be assessed at each visit and the risks of Rituxan therapy and any questions resulting from the patient's reading of the Medication Guide be discussed. See FDA approved patient labeling (Medication Guide).

Rituxan is detectable in serum for up to six months following completion of therapy. Individuals of childbearing potential should use effective contraception during treatment and for 12 months after Rituxan therapy.

RITUXAN® [rituximab]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License Number 1048

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MEDICATION GUIDE
Rituxan® (ri-tuk-san)
(rituximab)
injection

Read this Medication Guide before you start Rituxan and before each Rituxan infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Rituxan?

Rituxan can cause serious side effects that can lead to death, including:

- **Infusion reactions.** Infusion reactions are the most common side effect of Rituxan treatment. Serious infusion reactions can happen during your infusion or within 24 hours after your infusion of Rituxan. Your doctor should give you medicines before your infusion of Rituxan to decrease your chance of having a severe infusion reaction.

  Tell your doctor or get medical help right away if you get any of these symptoms during or after an infusion of Rituxan:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain
- **Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get any of these symptoms at anytime during your treatment with Rituxan:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules
- **Hepatitis B virus (HBV) reactivation.** Before Rituxan treatment, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving Rituxan could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive Rituxan if you have active hepatitis B liver disease. Your doctor will monitor you for hepatitis B infection during and for several months after you stop receiving Rituxan.
- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus. People with weakened immune systems can get PML. Your chance of getting PML may be higher if you are treated with Rituxan alone or with other medicines that weaken your immune system. PML can result in

death or severe disability. There is no known treatment, prevention, or cure for PML.

Tell your doctor right away if you have any of the following symptoms or if anyone close to you notices these symptoms:

- confusion or problems thinking
- loss of balance
- change in the way you walk or talk
- decreased strength or weakness on one side of your body
- blurred vision or loss of vision

See "**What are the possible side effects of Rituxan?**" for more information about side effects.

What is Rituxan?

Rituxan is a prescription medicine used to treat:

- **Non-Hodgkin's Lymphoma (NHL):** alone or with other chemotherapy medicines.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.
- **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.
- **Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA):** with glucocorticoids, to treat GPA and MPA.

People with serious infections should not receive Rituxan.

It is not known if Rituxan is safe or effective in children.

What should I tell my doctor before receiving Rituxan?

Before receiving Rituxan, tell your doctor if you:

- have had a severe infusion reaction to Rituxan in the past
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system.
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your household is scheduled to receive a vaccination. Some

types of vaccines can spread to people with a weakened immune system, and cause serious problems.

- have taken Rituxan for GPA or MPA in the past.
- have any other medical conditions
- are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.

  Women who are able to become pregnant should use effective birth control (contraception) while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about effective birth control.
- are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk. You and your doctor should decide the best way to feed your baby if you receive Rituxan.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

How will I receive Rituxan?

- Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of infusions such as fever and chills.
- Your doctor should do regular blood tests to check for side effects to Rituxan.

Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health. Tell your doctor or nurse about any new symptoms.

What are the possible side effects of Rituxan?

Rituxan can cause serious and life-threatening side effects, including:

See **"What is the most important information I should know about Rituxan?"**

- **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to help prevent TLS.
- **Serious infections.** Serious infections can happen during and after treatment with Rituxan, and can lead to death. Rituxan can lower the ability of your immune system to fight infections. Types of serious infections that can happen with Rituxan include bacterial, fungal, and viral infections. After receiving Rituxan, some patients

have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these patients with low antibody levels developed infections. Call your doctor right away if you have any symptoms of infection:

- fever
- cold symptoms, such as runny nose or sore throat that do not go away
- flu symptoms, such as cough, tiredness, and body aches
- earache or headache
- pain during urination
- white patches in the mouth or throat
- cuts, scrapes or incisions that are red, warm, swollen or painful

- **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need treatment, or your doctor may decide to stop your treatment with Rituxan.
- **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do blood tests to check how well your kidneys are working.
- **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy medicines to treat non-Hodgkin's lymphoma. Tell your doctor right away if you have any stomach area pain during treatment with Rituxan.
- **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check your blood cell counts.
  - **White blood cells.** White blood cells fight against bacterial infections. Low white blood cells can cause you to get infections, which may be serious. See "Increased risk of infections" above for a list of symptoms of infection.
  - **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - **Platelets.** Platelets are blood cells that help your blood to clot.

Common side effects during Rituxan treatment include:

- infusion reactions (see "**What is the most important information I should know about Rituxan?**")
- chills
- infections
- body aches
- tiredness
- low white blood cells

Other side effects with Rituxan include:

- aching joints during or within hours of receiving an infusion
- more frequent upper respiratory tract infection

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all of the possible side effects with Rituxan. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Rituxan

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide provides a summary of the most important information about Rituxan. If you would like more information, talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals.

For more information, go to www.Rituxan.com or call 1-877-474-8892.

What are the ingredients in Rituxan?

Active ingredient: rituximab

Inactive ingredients: polysorbate 80, sodium chloride, sodium citrate dihydrate, and water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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