Clinical Study Report Synopsis	
Drug Substance	Monalizumab (IPH2201) Durvalumab (MEDI4736)
Study Code	D419NC00001
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A Phase I/II Study of Durvalumab and Monalizumab in Adult Participants with Select Advanced Solid Tumors

Study Dates: First participant enrolled: 07 March 2016
Last participant last visit: 29 October 2021
The analyses presented in this report are based on a clinical data lock date of 22 December 2021

Phase of Development: Clinical pharmacology (I)
Therapeutic exploratory (II)

International Co-ordinating Investigator: PPD
PPD
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Sponsor's Responsible Medical Officer: PPD
Early Oncology, AstraZeneca R&D
PPD
PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

SYNOPSIS

Study centers

This was a multicenter study was conducted at 47 sites in 11 countries.

Publications

Banerjee S, Oaknin A, Sanchez-Simon I, Salgado AC, Patel SP, Oza A, et al. Phase 1b trial of monalizumab (NKG2A inhibitor) plus durvalumab: Safety and efficacy in patients with metastatic ovarian, cervical, and microsatellite-stable endometrial cancers [abstract 518] Int J Gynecol Cancer 2020;30 (suppl 4):A86-A87

Wainberg Z, Diamond J R, Curgliano G, Deva S, Bendell J, Han S-W, et al. First-line durvalumab plus monalizumab, mFOLFOX6, and bevacizumab or cetuximab for metastatic microsatellite-stable colorectal cancer [abstract 128] J Clin Oncol 2020;38(suppl 4):128

Cho M, Bendell J, Han S-W, Naidoo J, Lieu C, Carneiro B, et al. Durvalumab + monalizumab, mFOLFOX6, and bevacizumab in patients (pts) with metastatic microsatellite-stable colorectal cancer (MSS-CRC) [abstract 1201P]. Ann Oncol 2019;30(suppl 5): v490-1

Diamond J, Standifer N, Ascierto M, Morehouse C, Ghadially H, Rodriguez Canales J, et al. Translational endpoints in patients with metastatic microsatellite-stable colorectal cancer (MSS-CRC) treated with durvalumab plus monalizumab (anti-NKG2A) [abstract 1194P] Ann Oncol 2018;29(suppl 8):viii425

Segal N, Naidoo J, Curigliano G, Patel S, Sahebjam S, Papadopoulos K, et al. First-in-human dose escalation of monalizumab plus durvalumab, with expansion in patients with metastatic microsatellite-stable colorectal cancer [abstract 3540]. J Clin Oncol 2018;36(suppl 15):3540

Song, X. Population pharmacokinetics and dose regimen evaluation of monalizumab, a monoclonal antibody targeting NKG2a, in patients with advanced solid tumors [abstract 3029]. Cancer res 2020:80(Suppl 16):3029

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Type	Objective	Endpoints
	Primary	
Safety	• **Part 1:** To assess safety and tolerability, describe the DLTs, and determine the MTD or the highest protocol-defined dose level in the absence of establishing an MTD of durvalumab in combination with monalizumab in participants with advanced solid tumors • **Part 2:** To assess further the safety and tolerability of either the MTD or the highest protocol-defined dose level, in the absence of establishing an MTD, of durvalumab in combination with monalizumab in participants with selected advanced solid tumors • **Part 3 (Cohorts A[CCI]):** To assess safety and tolerability of durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in participants with 1L or 2L [CCI] CRC • **Part 3 (Cohorts C1A and C2A):** To assess safety and tolerability of durvalumab in combination with monalizumab plus cetuximab in participants with [CCI] CRC which are [CCI] (C1A) or [CCI] (C2A) • **Part 3 (Cohorts C1B and C2B):** To assess safety and tolerability of monalizumab in combination with cetuximab in participants with [CCI] CRC which are [CCI] (C1B) or [CCI] (C2B)	• AEs • SAEs • DLTs • Abnormal laboratory parameters, vital signs, and ECG results
Clinical activity	• **Part 3 (Cohort C1A):** To evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in participants with [CCI] CRC that is [CCI] • **Part 3 (Cohort C1B):** To evaluate the antitumor activity of monalizumab in combination with cetuximab in participants with [CCI] CRC that is [CCI]	• OR by investigator assessment per RECIST v1.1
	Secondary	
Clinical activity	• **Parts 1 and 2:** To evaluate the preliminary antitumor activity of durvalumab in combination with monalizumab in participants with advanced solid tumors • **Part 3 (Cohorts A[CCI]):** To evaluate the preliminary antitumor activity of durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in participants with 1L or 2L [CCI] CRC • **Part 3 (Cohort C2A):** To evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in participants with [CCI] CRC that is [CCI]	• OR, DC, DoR, PFS by investigator assessment per RECIST v1.1 • OS

Type	Objective	Endpoints
	• **Part 3 (Cohort C2B):** To evaluate the antitumor activity of monalizumab in combination with cetuximab in participants with CCI CRC that is CCI	
	• **Part 3 (Cohort C1A):** To further evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in participants with CCI CRC that is CCI • **Part 3 (Cohort C1B):** To further evaluate the antitumor activity of monalizumab in combination with cetuximab in participants with CCI CRC that is CCI	• DC, DoR, PFS by investigator assessment per RECIST v1.1 • OS
PK	• **Parts 1 and 2:** To describe the PK of durvalumab and monalizumab when administered in combination in participants with advanced solid tumors	• Individual participant durvalumab, monalizumab, and cetuximab concentrations in serum at different time points after administration of these agents were summarized
	• **Part 3 (Cohorts A CCI):** To describe the PK of durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in participants with 1L or 2L CCI CRC • **Part 3 (Cohorts C1A and C1B):** To describe the PK of the following when administered in combination in participants with CCI CRC that is CCI 1.1. Durvalumab, monalizumab, and cetuximab (C1A) 1.2. Monalizumab and cetuximab (C1B) • **Part 3 (Cohorts C2A and C2B):** To describe the PK of the following when administered in combination with cetuximab in participants with CCI CRC that is CCI 1.3. Durvalumab and monalizumab (C2A) **1.4.** Monalizumab (C2B)	
Immunogenicity	• **Parts 1 and 2:** To describe the immunogenicity of durvalumab and monalizumab when administered in combination in participants with advanced solid tumors	CCI
	• **Part 3 (Cohorts A CCI):** To describe the immunogenicity of durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in participants with 1L or 2L CCI CRC • **Part 3 (Cohorts C1A and C1B):** To describe the immunogenicity of the following when administered in combination in participants with CCI CRC that is CCI 1.5. Durvalumab, monalizumab, and cetuximab (C1A) 1.6. Monalizumab and cetuximab (C1B) • **Part 3 (Cohorts C2A and C2B):** To describe the immunogenicity of the following when administered in combination with cetuximab in participants with CCI CRC that is CCI 1.7. Durvalumab and monalizumab (C2A) 1.8. Monalizumab (C2B)	

Type	Objective	Endpoints
	CCI	
CCI	CCI	CCI
	CCI	

1L = first-line; 2L = second-line; CCI AE = adverse event; DC = disease control; DoR = duration of response; DLT = dose-limiting toxicity; ECG = electrocardiogram; CCI CRC = CCI colorectal cancer; MTD = maximum tolerated dose; OR = objective response; OS = overall survival; CCI PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

NOTE: Part 1 was dose escalation/expansion (expansion in Part 1 was restricted to cervical cancer and CCI CRC); Part 2 was tumor type dose expansion in select advanced solid tumor malignancies; Part 3 was dose exploration in CCI CRC.

NOTE: Cohort A participants were systemic therapy naïve in the recurrent/metastatic setting. CCI was not opened. Cohort C participants were CCI.

Study design

This was a Phase I/II, multicenter, open-label, dose escalation, dose expansion, and dose exploration study to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics, and antitumor activity of monalizumab in combination with durvalumab in adult participants with advanced solid tumor malignancies. The study

consisted of 3 parts: dose escalation/expansion (Part 1), tumor type dose expansion (Part 2), and dose exploration in participants with CCI colorectal cancer (CCI CRC) (Part 3).

Target subject population and sample size

Part 1 evaluated dose escalation/expansion of durvalumab in combination with monalizumab in participants with select advanced solid tumor malignancies. Participants with recurrent or metastatic CCI CRC, ovarian cancer, CCI endometrial cancer, cervical cancer, castration-resistant prostate cancer, pancreatic adenocarcinoma, or non-small cell lung cancer (NSCLC) were enrolled. At the sponsor's discretion, expansion in Part 1 at a given dose level was restricted to specific tumor types (cervical and CCI CRC) in order to provide additional PK, pharmacodynamic, and safety data for optimal dose level selection of dose expansion in Part 2 and subsequent clinical studies.

Part 2 (tumor type dose expansion) further evaluated the identified dose of durvalumab in combination with monalizumab from Part 1. Participants with CCI CRC, ovarian cancer, CCI endometrial cancer, and NSCLC were enrolled.

In Part 3, cohorts A CCI were added to evaluate dose exploration of durvalumab in combination with monalizumab and chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in participants with metastatic first line (1L) or second line (2L) CCI CRC. Participants with CCI CRC systemic therapy-naïve in the recurrent/metastatic setting were enrolled into cohort A. CCI

Part 3 (cohorts C1 and C2) evaluated dose exploration of 1) durvalumab in combination with monalizumab plus cetuximab (cohorts C1A and C2A) and 2) monalizumab in combination with cetuximab (cohorts C1B and C2B) in participants with CCI CRC which were CCI (cohort C1) or CCI (cohort C2).

CCI

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Durvalumab was manufactured by MedImmune on behalf of AstraZeneca, as 500 mg (nominal) durvalumab solution per vial. Each mL of solution contains 50 mg durvalumab.

Durvalumab solution 1500 mg was administered intravenously (IV) every 4 weeks (Q4W).
CCI [redacted]

Monalizumab was manufactured by MedImmune on behalf of AstraZeneca, CCI [redacted]

Cetuximab (Part 3 cohorts C1A and C1B only) was manufactured by Merck Serono on behalf of AstraZeneca, as 500 mg (nominal) cetuximab solution per vial. Each mL of solution contained 5 mg cetuximab. Cetuximab was administered as 500 mg/m^2 IV infusion Q2W. CCI [redacted]

Duration of treatment

Study treatment was administered up to 3 years, until unacceptable toxicity, documentation of confirmed progressive disease (PD), or documentation of participant withdrawal for another reason. Any participants still receiving investigational product at the time of this data cut-off were able to continue to receive investigational product within the current study, as long as, in the investigator's opinion, the participant was deriving clinical benefit and had not fulfilled any discontinuation criteria. All participants were followed for survival until the end of study (approximately 5 years after the final participant was enrolled) or when the sponsor stopped the study, whichever occurred earlier.

Statistical methods

Tolerability and safety were assessed by summarizing adverse events (AEs) and serious adverse events (SAEs), laboratory assessments, electrocardiogram (ECG) results, and vital signs during the study. The safety evaluation was based on the as-treated population.

Objective response rate (ORR) was estimated with a CCI [redacted]% confidence interval (CI) using the exact binomial method. Participants that had missing overall response assessments were considered non-responders, and were counted in the denominator, but not in the numerator, of ORR.

The efficacy endpoints included best overall response (BoR); objective response (OR); disease control (DC); time to response (TTR); duration of response (DoR); progression-free survival (PFS); overall survival (OS); and change from baseline in tumor size. Efficacy endpoints were summarized based on the as-treated population. Due to randomization in cohort C, efficacy endpoints in cohort C were summarized per intent to treat (ITT) population instead of

as-treated population. In addition, for time-to-event efficacy endpoints the calculation started at date of randomization.

Efficacy analyses were based on an application of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al 2009) according to investigator assessed tumor measurements.

Study population

The study was conducted at study sites located in North America, Europe, and Asia Pacific, across 47 sites and 11 countries. CCI [redacted] The first participant was enrolled on 07 March 2016 and the last participant completed the last visit on 29 October 2021. A total of 537 participants were screened for enrollment, 154 failed screening: 135 participants did not meet the inclusion/exclusion criteria, 5 withdrew consent, and 14 participants failed due to other reasons. A total of 383 participants were included in this study, of which 382 participants received treatment.

- Part 1: The as-treated population included 45 participants across 5 dose-defined groups.
- Part 2: The as-treated population included 140 participants across 4 cancer defined groups.
- Part 3: The as-treated population included 197 participants; 36 participants in cohort A, 83 participants in cohorts C1A + C2A, and 78 participants in cohorts C1B and C2B.

By the end of the primary completion study, one participant in the CCI CRC cohort of the tumor type expansion group (Part 2) was on retreatment schedule receiving monalizumab plus durvalumab, and one participant in the A1 cohort of the dose exploration in CCI CRC group (Part 3) was on treatment schedule receiving only monalizumab plus durvalumab while chemotherapy (modified regimen comprised of folinic acid, fluorouracil, and oxaliplatin [mFOLFOX6]) and bevacizumab were discontinued. The primary reason for discontinuation of study treatment was PD. The primary reason for study discontinuation was death.

Summary of efficacy results

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Tumor Type Expansion Group (Part 2)

CCI [redacted]

CCI [redacted]

In the ovarian cohort, CCI [redacted] The median PFS was 1.8 months and the median OS was 16.7 months. CCI [redacted]

In the CCI [redacted] endometrial cohort, CCI [redacted] The median PFS was 1.8 months CCI [redacted]. The ORR was 0.0%.

CCI [redacted]

CCI

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CCI

CCI

CCI [redacted]

CCI [redacted]

Summary of pharmacokinetic results

For serum concentrations of monalizumab, a total of 2563 samples collected from 382 participants were available for analysis. Overall, the results suggest that the co-administration of either cetuximab or durvalumab did not significantly impact the PK exposure of monalizumab. Similarly, participants with CCI [redacted] status did not significantly impact the PK exposure of monalizumab.

For serum concentrations of durvalumab, a total of 1358 samples were taken from 315 participants. It was concluded that the co-administration of monalizumab did not significantly impact the PK exposure of durvalumab.

For serum concentrations of cetuximab, 320 pre-dose samples were taken from 77 participants. It was concluded that the co-administration of monalizumab did not significantly impact the PK exposure of cetuximab.

Summary of pharmacodynamic results

No post-treatment tissue samples were obtained so pharmacodynamic effects could not be evaluated. Participating sites were encouraged to support exploratory study objectives but insufficient samples were provided to support this analysis, therefore it was not performedSummary of pharmacokinetic/pharmacodynamic relationships.

CCI [redacted]

CCI [redacted]

Summary of safety results

CCI [redacted]

[redacted]

CCI [redacted] One participant had a TEAE with an outcome of death CCI [redacted] this was not considered related to study treatment. CCI [redacted]

CCI [redacted]

Three participants (2.1%) had a TEAE with an outcome of death CCI [redacted]; none were related to study treatment.

CCI [redacted]
CCI

CCI [redacted] No participants had a TEAE with an outcome of death.

In the exploration cohort A2 (Part 3), CCI [redacted] No participants had a TEAE with an outcome of death.

In cohort C1A + C2A, CCI [redacted] One participant (1.2%) had a TEAE CCI [redacted] with an outcome of death.

In the exploration cohort C1B + C2B, CCI [redacted]

CCI [redacted] One participant (1.3%) had a TEAE CCI [redacted] with an outcome of death.

Overall, the majority of participants in all cohorts experienced Grade 3 or 4 events; however fewer events led to discontinuation. CCI [redacted] Safety findings were consistent with the corresponding treatment regimens and individual treatment components.

CCI [redacted] monalizumab plus durvalumab, with or without chemotherapy (mFOLFOX6), and with biologic agents (bevacizumab or cetuximab) (Part 3), were generally well tolerated with the exception of chemotherapy-related toxicities which were consistent with chemotherapy related safety profile, however, the number of participants in chemotherapy cohorts were relatively low to draw any definitive conclusions.

In this study, treatment regimens including monalizumab with durvalumab and monalizumab plus durvalumab in combination with chemotherapy (mFOLFOX6) and biologic agents were generally well tolerated with the exception of chemotherapy-related toxicities which were consistent with chemotherapy related safety profile.

Generally, changes in laboratory parameters were not suggestive of clinically significant hematologic (except chemotherapy related hematologic toxicities consistent with safety profile of chemotherapies), hepatic, metabolic, or renal toxicities. No clinically meaningful trends in vital signs, or electrocardiogram findings were observed, and there were no physical findings or observations related to safety.

Immune-mediated events were generally consistent with the known safety profile of durvalumab and were manageable in accordance with toxicity management guidelines.

No treatment related fatal TEAEs were reported in any study cohort.

The combination of monalizumab with durvalumab and other drugs did not lead to any safety signals for the combinations.

Conclusion(s)

- CCI [redacted]

CCI The dose selected for the expansion phase was monalizumab 750 mg Q2W.

- Monalizumab in combination with durvalumab (± bevacizumab) or with cetuximab appeared to be relatively well tolerated. In this study, treatment regimens including monalizumab plus durvalumab, in combination with chemotherapy (mFOLFOX6) and other agents were generally well tolerated with the exception of chemotherapy-related toxicities which were consistent with chemotherapy related safety profile. Overall, the safety profiles of the investigational products were consistent with the corresponding treatment regimens. The safety profile of the combination of monalizumab with durvalumab did not appear to lead to any new safety signals beyond what was known for monalizumab or the known safety profile of durvalumab.
- CCI
- Monalizumab, durvalumab, and cetuximab PK concentrations were within the expected exposure range and coadministration of monalizumab with durvalumab and cetuximab did not appear to impact exposure.
- CCI
- CCI

Overall, the risk/benefit of monalizumab with durvalumab in combination with chemotherapy and biologic agents in adult participants with advanced solid tumor malignancies explored in this study is considered favorable from a safety perspective, while no added clinical benefit from standard-of-care was observed.