AstraZeneca

Statistical Analysis Plan

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A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

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Study Statistician

PPD

Date

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Global Product Statistician

PPD

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
DTC	Differentiated Thyroid Cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
FNA	Fine Needle Aspiration
IM	Intramuscular
ITT	Intention To Treat
LLOQ	Lower Limit Of Quantification
MRI	Magnetic Resonance Imaging
MTP	Multiple Testing Procedure
MUGA	Multi Gated Acquisition Scan
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
OAE	Other Adverse Event
PK	Pharmacokinetics
PR(PQ)	ECG interval measured from the beginning of the P wave to the beginning of the Q wave (or the R wave in the absence of Q wave). PR (PQ) represents the time interval from start of a trial depolarisation to the start of ventricular depolarisation.
QRS	Interval on the ECG from the start of ventricular electrical activation of the heart to the J point, with start taken as start of Q wave or R wave (when a Q wave is missing); the time interval of ventricular depolarisation.
QT	ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the end of the T wave; the time interval of ventricular depolarisation and repolarisation.
QTcF	Corrected Qt interval according to Fredericia's formula
RAI	Radioactive Iodine (131I)

Abbreviation or special term	Explanation
rhTSH	Recombinant human Thyroid Stimulating Hormone
RR	The time between corresponding points on 2 consecutive R waves on ECG; the interval from one ventricular depolarisation to the next
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SOC	System Organ Class
TSH	Thyroid Stimulating Hormone
ULOQ	Upper Limit of Quantification
US	Ultrasound
WBS	Whole Body Scintigraphy

AMENDMENT HISTORY

Date	Brief description of change
03 April 2018	Updated list of protocol violations Updated efficacy variables to indicate that any abnormalities seen in US, CT or MRI unless confirmed by FNA/biopsy will be considered benign. Added that a separate document to describe the algorithmic steps to determine the biochemical, clinical and complete remission status of each patient based on CSP will be provided by AZ to the designee. Updated the analysis windows for biochemical, clinical and complete remission to include patients that had any part the composite endpoint assessment for Stage 1 (suppressed Tg, TgAb, US and/or FNA/Biopsy) evaluated before 75 weeks (i.e. prior to 525 days) post RAI-treatment and the remaining composite endpoint assessments for Stage 2 (stimulated Tg, WBS) and Stage 3 (CT and MRI) evaluated at least 75 weeks (525 days) post RAI-treatment, in the derivation of biochemical, clinical and complete remission. Added sensitivity analysis on complete remission to include patients as per the CSP window. Updated the analysis to indicate that the two-sided p-value will be based on profile likelihood.
23SEP2016	Updated Tables 1 and 2 to match CSP. Updated the analysis windows to include patients that composite endpoint assessments for Stage 1, Stage 2 (stimulated Tg, WBS) and Stage 3 (CT and MRI) evaluated at least 75 weeks (525 days) post RAI-treatment, in the derivation of biochemical, clinical and complete remission. Removed the requirement that all necessary primary endpoint assessments must be completed within a 8 week period. Added description of outputs needed for demographic and baseline characteristics.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

- To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the intention to treat (ITT) study population. Complete remission is defined in Section 3.2.1.

1.1.2 Secondary objectives

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for v-raf murine sarcoma viral oncogene homolog B1 (BRAF) or neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS). Complete remission is defined in Section 3.2.1.

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in section 3.2.2.

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for BRAF or NRAS. Clinical remission is defined in section 3.2.2.

- To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

- To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

1.1.3 Exploratory objectives

- To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

- To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

- To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to Differentiated Thyroid Cancer (DTC) and response and resistance to study treatments.

- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

1.2 Study design

This is a double-blind, randomised, placebo-controlled, multi-centre study comparing the efficacy of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) with adjuvant RAI, to placebo with RAI.

Following recovery from surgery (1 or 2-stage total thyroidectomy), and screening to determine study eligibility, patients will be randomised and will take their assigned study treatment (selumetinib or placebo) twice daily for a period of approximately 5 weeks. Study treatment will begin approximately 4 weeks prior to the planned day of single dose RAI therapy, and will be continuous until 5 days following RAI therapy. Patients will be required to adhere to a standardised low iodine diet prior to their RAI therapy. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a 0.9 mg intramuscular (IM) recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodide uptake (patients or clinicians choosing to prepare for RAI ablation by withdrawal of thyroid hormone treatment will be ineligible for this study). Following the 2 consecutive days of rhTSH injections, patients will receive their planned RAI therapy as a fixed single 100 mCi (3.7 GBq) dose of ^{131}I the immediate next day. Study treatment will be taken as normal on the day of RAI therapy, and will be discontinued 5 days following the patient's RAI therapy.

Following RAI therapy, each patient will be followed up for a period of 18 months until the primary endpoint assessment of complete remission. The biochemical analysis contributing to the 18 month primary endpoint of complete remission will be performed by standardised central methodology, and the radiological imaging (Whole Body Scintigraphy (WBS), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI)) contributing to the 18 month primary endpoint assessment will be subject to a blinded independent central review to minimise the risk of bias. Additional thyroid cancer therapy (eg, surgery or RAI treatment) must only be given during the 18 month primary endpoint follow up period according to the pre-specified study re-treatment criteria (see protocol Section 5.9 for details). Patients who do receive re-treatment in the 18 months following their initial RAI therapy, will not have any 18 month primary endpoint assessments performed, though they will be included in the ITT population (as not being in remission) and they will remain in the study and enter standard of care follow up according to local practice.

Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at least 3 years following their initial RAI treatment.

1.3 Number of subjects

The primary objective of this study is to compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of the complete remission rate at 18 months post RAI treatment in the ITT study population.

Patients will be randomised into this study in a 2:1 ratio. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, 228 patients (152 and 76 patients randomised to the selumetinib and placebo-containing arms, respectively) provides at least 80% power to demonstrate a statistically significant difference at the 5% (2-sided) significance level.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Intention to treat (ITT) analysis set

The ITT analysis set will include all randomised patients. The ITT analysis set will be used for all efficacy analyses and treatment arms will be compared on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the ITT analysis set.

2.1.2 BRAF/NRAS mutation positive analysis set

For the analysis of the *BRAF* and *NRAS* mutation positive population (secondary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included. Treatment arms will be compared on the basis of randomised treatment, regardless of the treatment actually received.

2.1.3 Treatment-compliant (TC) analysis set

The treatment-compliant analysis set will be a subset of the ITT population containing patients that adhered to the minimum study treatment requirements specified in Section 3.1.1 of the protocol, i.e. patients who take study treatment twice daily for a **minimum** of 7 consecutive days prior to RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. Patients must also have had their RAI dose.

The TC analysis set will be used as a sensitivity analysis for the primary endpoint.

2.1.4 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomised treatment. Safety data will not be formally analysed but summarised using the safety analysis set according to the treatment combination received, i.e., erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

2.1.5 Pharmacokinetic (PK) analysis set

PK data will be analysed according to treatment received. This population will comprise all patients where at least one PK concentration has been generated and who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be further defined by the

AstraZeneca Study Team Physician, Pharmacokineticist and Statistician prior to breaking of the blind for any analyses being performed.

2.2 Important deviations

Important deviations are defined as deviations that could impact the interpretation of study data. Important deviations will be listed and summarised by randomised treatment group. Patients randomised but not dosed (with selumetinib/placebo) will lead to exclusion from the Safety analysis set. None of the other deviations will lead to patients being excluded from any of the analysis sets described in Section 2.1 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK). A per-protocol analysis excluding patients with significant protocol deviations is not planned.
If the deviations are serious enough to have the potential to impact the primary analysis, sensitivity analyses may be performed. Some deviations may be important from safety point of view but these may not affect the interpretation of the study results.

A list of important protocol deviations are defined in sections 2.2.1, 2.2.2, 2.2.3, 2.2.4. Note that the contents of these sections are not an exhaustive list. The study team physician and statistician will identify, adjudicate and classify a complete list of important deviations from monitor reports and programmatic checks prior to database lock and unblinding.

2.2.1 Important Inclusion Criteria Deviations

Inclusion Criteria	Description
03	Subject without histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer.
05	Subject not presenting at least one of the following staging categories post-surgery: a) Primary tumour greater than 4 cm b) Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease) c) N1a or N1b disease with at least 1 lymph node ≥ 1 cm d) N1a or N1b disease involving 5 or more lymph nodes (of any size)
06	Subject has not had a one or two-stage **total** thyroidectomy with therapeutic neck dissection of any clinically apparent metastatic lymph nodes (levels I to VII of the lateral and central neck) and all known tumour has not been resected. For Subject who has had a two-stage thyroidectomy, the second surgical procedure has taken place more than 12 weeks after the first procedure. Subject having undergone a robotic or endoscopic thyroidectomy, or any other novel or remote access surgical technique.
07	Subject had all of the following post-operative assessments performed sooner than 4 weeks post-surgery (post their last surgery if it was a 2-stage thyroidectomy): a) Neck US exam b) Neck MRI with contrast c) Chest CT without contrast Results from at least one of below assessments did not confirm the absence of macroscopic disease: a) Neck US exam b) Neck MRI with contrast c) Chest CT without contrast
08	Subject not suitable for radioactive iodine therapy.
09	Subject not suitable for TSH suppression with a goal of ≤0.5 mIU/L TSH for the duration of the study
10	Subject is not willing and able to start study treatment within 6-16 weeks after thyroid cancer surgery (last surgery if it was a 2-stage thyroidectomy).
11	WHO or ECOG Performance Status not 0 or 1.

2.2.2 Important Exclusion Criteria Deviations

Exclusion Criteria	Description
01	Known distant metastatic disease at study entry.
02	Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (apart from Hürthle variant with oncocytic cells having the nuclear features of papillary carcinoma).
03	Presence of anti-Tg antibodies at screening
04	Previous treatment with 131I (RAI) or external beam radiation therapy (EBRT) at any time in the past.
06	Subject has received an investigational drug during the last 4 weeks prior to first dose of study treatment.
08	Subject not willing to use rhTSH prior to their RAI treatment.
18	History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.
21	Previous treatment with any MEK or BRAF inhibitor.
22	Previous enrolment or treatment in the present study.

2.2.3 Important Investigational Treatment Deviations

Description
Study medication is not administered according to the CSP
Received wrongly randomized treatment.
Compliance rate less than 80% (less than 4 weeks or 28 days).

2.2.4 Important Prohibited Concomitant Medication Deviations

Description
Subject received other anti-cancer agents, or investigational drugs whilst receiving study medication or during follow-up in this study (not including scenario when the patient withdraws from the study, or meets the re-treatment criteria).

2.2.5 Important Protocol-required Procedures Deviations

Description

Therapeutic RAI dose (131I) administered not according to CSP [100 mCi (3.7 GBq) 131I (+/- 10% at the time of administration)]
Diagnostic WBS dose (131I) administered not according to CSP [5 mCi (185 MBq) 131I (+/- 10% at the time of administration)]
Visit procedures of Visit 10/Month 18 - primary endpoint not performed within the visit window and/or assessment window defined in the SAP.
Visit procedures of Visit 10/Month 18 - primary endpoint not done according to the description in the CSP e.g.: - missing central lab testing for TgAb and/or Tg - rhTSH injection not administered on two consecutive days (Day 1 and Day 2) - Diagnostic RAI administration not 2 days prior to the WBS (either Day 2 or Day 3) - missing central lab testing result for stimulated Tg (Day 5 of rhTSH injection) - missing US - missing biopsy with positive US results of lesion >= 5 mm - missing chest CT and/or neck MRI

3. PRIMARY AND SECONDARY VARIABLES

3.1 General principles

Unless otherwise stated, baseline will be defined as the last available measurement prior to dosing with study treatment. For laboratory data and vital signs data, pre-dose assessments will be performed at screening.

Unless otherwise specified, data summaries and listings will be presented by the initial treatment arm a patient was assigned to, i.e., initial randomised treatment.

3.1.1 Study Day

In some cases, where data is summarised over time, study day will be calculated based on the actual assessment date. Efficacy data will be summarised using the ITT analysis set, so study day is derived in relation to the date of randomisation (study day 1 for efficacy data). Safety data will be summarised using the Safety analysis set, so study day is derived in relation to the date of first treatment (study day 1 for safety data).

3.1.2 Visit Windows

For summaries of vital signs, laboratory data, ECGs, Echo scans and ophthalmological examination, assessments will be assigned to calculated visit windows (using study day for safety data).

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits.

If more than 1 assessment falls into a visit window, the value nearest the protocol defined assessment time point will be used for the summaries by visit, as this is most representative of the patients' assessment at that time point. If two or more values fall within a time window and are equidistant to the protocol defined assessment time point, the value from the first time point will be used. For summaries showing the maximum or minimum values on study, the maximum/minimum value recorded during the time period being summarised (e.g. 18 months or 3 years) will be used (regardless of where it falls in the interval). Listings will display all values contributing to a time point for a patient; and also highlight the value for that patient that went into the table, wherever feasible.

See Section 3.2.3 for definition of visit windows for complete and clinical remission.

3.1.3 Handling of missing data

Safety assessment values of the form of "<x" (ie, below the lower limit of quantification (LLOQ)) or >x (i.e., above the upper limit of quantification (ULOQ)) will be imputed as "x" in the calculation of summary statistics but displayed as "<x"or ">x" in the listings.

For the sensitivity analyses using covariate (mutation status, histology status and age) adjusted logistic regression models, the following missing data approach for each covariate will be adopted:

- Missing mutation status; add an additional 'unknown' category to make 3 categories (positive, not detected, and unknown)
- Missing histology status; add an additional 'unknown' category to make 4 categories (papillary, follicular, poorly differentiated, and unknown)
- Missing age; impute the mean of observed ages

3.2 Efficacy variables

3.2.1 Complete remission rate at 18 months post-RAI treatment

Complete remission rate is defined as the proportion of randomised patients who are alive and meet the following criteria at 18 months post-RAI treatment:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.
2. No confirmed evidence of thyroid cancer[a] by neck ultrasound (US), as assessed by investigator site review.
3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.
4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

The complete remission rate will be calculated using all randomised patients (ITT population) as the denominator.

There are two main components to complete remission: biochemical remission and structural remission. Biochemical remission is measured by Tg and structural remission is assessed by the imaging assessments US, MRI, CT and WBS in conjunction with biopsy/FNA.

[a] Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease. In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

I.e. Any abnormalities seen in US, CT or MRI unless confirmed by FNA/biopsy will be considered benign.

Staged approach to primary endpoint assessments

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further therapy prior to the primary assessment, and for those patients not in biochemical remission (as determined by serum Tg levels in the absence of interfering Tg antibodies).

Full details of the staged approach to the primary endpoint assessments are outlined in the Clinical Study Protocol and Medical Imaging Independent Review Charter. There will be 3 stages of assessments. Patients that have been re-treated for thyroid cancer will not have any further primary endpoint assessments performed, though they will be included in the ITT population (as not being in remission). All patients who have not been re-treated for thyroid cancer will have stage 1 assessments performed. The decision on whether to proceed to stage 2 and 3 assessments for patients that have not been re-treated will be made at site, based on centrally analysed biochemical data (Tg and TgAb data). Patients identified as not in biochemical remission will not be required to have all remaining imaging assessments. For patients that have imaging assessments performed, the appropriate data will be sent to the imaging CRO for blinded independent central review to identify presence or absence of structural disease.

Derivation of primary endpoint of complete remission

The complete remission status of each patient will be determined programmatically by AstraZeneca or designee, by incorporating data on assessment dates, re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, and structural disease assessment from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in complete remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer, all imaging data will be sent to the imaging CRO. Determination of presence or absence of structural thyroid cancer will be made by the imaging CRO only for biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

The imaging CRO will assess the WBS, MRI and CT and also review the site assessment of neck US and biopsy findings for US, CT and MRI (if performed) to provide an overall assessment: presence or absence of structural thyroid cancer, or not evaluable based on all of the available information. For the derivation of the complete remission endpoint, patients that are not evaluable for structural disease assessment will be considered as not achieving complete remission, regardless of the result of other assessments.

AstraZeneca or designee will programmatically combine information on assessment dates, further therapy, biochemical data, and the determination of structural disease from the central imaging CRO, to determine the complete remission status of each patient as shown in Table 1.

A separate document to describe the algorithmic steps to determine the complete remission status of each patient based on Table 1 and CSP will be provided by AZ to the designee.

Table 1 Programmatic derivation of complete remission status

Further thyroid cancer therapy[a] (re-treatment)	Biochemical data[b]		Structural disease assessment[c]	Complete remission
	Stimulated Tg	TgAb		
Yes	Any	Any	Any	No
No	< 1 ng/mL	Negative[d]	Absence of disease	Yes
No	≥ 1ng/mL	Any	Any	No
No	Any	Positive[d]	Any	No
No	Any	Any	Presence of disease	No
No	NE	Any	Any	No
No	Any	NE	Any	No
No	Any	Any	NE	No

[a] As assessed by investigator at site

[b] As assessed by standardised central laboratory analysis
[c] As assessed by blinded, independent central review
[d] If the stage 1 and stage 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3days) is required. Only if the third sample is negative for TgAb will the overall result be considered negative.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments)

3.2.2 Clinical remission rate at 18 months post-RAI treatment

Clinical remission rate is defined as the proportion of randomised patients who are alive and meet the following criteria at 18 months post-RAI treatment:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer by neck US, as assessed by investigator site review.

3. No evidence of thyroid cancer by diagnostic WBS, as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal US findings, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

The clinical remission rate will be calculated using all randomised patients (ITT population) as the denominator.

Derivation of clinical remission status

The clinical remission status of each patient will be determined programmatically by AstraZeneca or designee, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, structural disease assessment based on US by investigator site review and structural disease assessment based on WBS from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in clinical remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer:

- A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on US and biopsy.

- A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on WBS for only biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

AstraZeneca or designee will programmatically combine information on further therapy, biochemical data, determination of structural disease from the investigator site assessment of US and determination of structural disease from the central imaging CRO of WBS, to determine the clinical remission status of each patient as shown in Table 2.

A separate document to describe the algorithmic steps to determine the clinical remission status of each patient based on Table 2 and CSP will be provided by AZ to the designee.

Table 2 Programmatic derivation of clinical remission status

Further thyroid cancer therapy[a]	Biochemical data		Structural disease assessment		Clinical remission
	Stimulated Tg[b]	TgAb[b]	US/biopsy[a]	WBS[c]	
Yes	Any	Any	Any	Any	No
No	<1 ng/mL	Negative[d]	Negative	Absence of disease	Yes
No	<1 ng/mL	Negative[d]	NE	Absence of disease	Yes
No	≥1 ng/mL	Any	Any	Any	No
No	Any	Positive[d]	Any	Any	No
No	Any	Any	Positive	Any	No
No	Any	Any	Any	Presence of disease	No
No	NE	Any	Any	Any	No
No	Any	NE	Any	Any	No
No	Any	Any	Any	NE	No

[a] As assessed by investigator at site
[b] As assessed by standardised central laboratory analysis
[c] As assessed by blinded, independent central review
[d] If the stage 1 and stage 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3days) is required. Only if the third sample is negative for TgAb will the overall TgAb result be considered negative.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments)

3.2.3 Visit windows for complete and clinical remission assessment

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further therapy prior to the primary assessment and for those patients not in biochemical remission, therefore the assessments that contribute to primary endpoint will be performed on different dates. These assessments are stimulated Tg (and TgAb using the same blood draw), US scan, MRI scan, CT scan and WBS.

The derivation of the primary endpoint is based on data on further therapy, biochemical data and a single overall assessment of structural disease from all of the available imaging modalities of local US results plus MRI, CT and WBS from the blinded, independent central review, as shown in Table 1. However, the dates on which these components were performed will be incorporated into the derivation of the primary endpoint to ensure patients are assessed at least 18 months post-RAI treatment as follows.

Any patient that has been re-treated for thyroid cancer prior to scheduled assessment at 18 months post-RAI treatment (i.e. prior to 525 days) will be considered **not** to be in complete remission.

The date of the first assessment that contributes to the complete remission definition, i.e., the date that the stimulated Tg was performed, must be at least 75 weeks (525 days) post-RAI treatment. However, if a patient has any part of the composite endpoint assessment for Stage 1 (suppressed Tg, TgAb, US and/or FNA/Biopsy) evaluated before 75 weeks (i.e. prior to 525 days) post RAI-treatment and the remaining composite endpoint assessments for Stage 2 (stimulated Tg, WBS) and Stage 3 (CT and MRI) evaluated at least 75 weeks (525 days) post RAI-treatment, then the patient will be considered in the derivation of biochemical, clinical and complete remission. In addition, there is no restriction on the date that the last assessment/scan that contributes to the complete remission definition must be performed.

If a patient has at least one part of the composite endpoint for Stage 2 or Stage 3 assessed before 75 weeks post-RAI treatment, and not repeated after this time point, or fails to complete the full set of primary endpoint assessments, then the patient will be considered **not** to be in complete remission, regardless of the assessment of disease status.

3.3 Safety variables

3.3.1 Adverse events (AE)

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4. The CTCAE grade will be assigned by the investigator.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as serious adverse events (SAEs) or discontinuation of investigational product due to adverse event (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

The denominator for AE summaries will be the Safety population.

3.3.2 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

Change from baseline in vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination variables will be calculated for each post-dose visit during follow-up where this data was collected. The baseline value will be the latest result obtained prior to the start of study treatment.

For laboratory data, CTCAE grade will be calculated at each visit. The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination data will include only patients in the Safety population with recorded data.

For ECG data, the Investigator's assessment of the ECG (normal, borderline or abnormal) and heart rate, QRS, PR and QT will be recorded at each time-point. QTcF (Fredericia) will be calculated programmatically by AstraZeneca or designee using the reported ECG values (RR and QT).

$$QTcF = QT / RR^{(1/3)} \text{ where RR is in seconds}$$

3.4 PK data

The plasma concentration-time data for selumetinib and N-desmethyl selumetinib will be analysed using non-linear mixed effects modelling. The primary aims of that modelling will

be to characterise the pharmacokinetics of selumetinib and N-desmethyl selumetinib in the population studied, generate population and individual patient estimates of pharmacokinetic parameters, quantify the variability in those parameters and investigate covariates which may explain that variability. In addition, if the data are suitable, potential relationships between plasma selumetinib/N-desmethyl selumetinib concentrations and efficacy and safety endpoints will be investigated using a graphical approach and/or appropriate PK/PD modelling techniques. A detailed pharmacokinetic analysis plan will be written prior to database lock. The results of the analysis will be reported separately from the clinical study report (CSR).

3.5 Other data

3.5.1 Thyroid cancer recurrence

The occurrence and date of any thyroid cancer recurrence will be recorded for patients who have previously entered remission, either complete or clinical (at any point during the study or follow up periods). The rate of thyroid cancer recurrence will be calculated using only patients who have achieved remission as the denominator.

3.5.2 Survival status

The survival status and survival assessment date of all patients will be recorded. Survival time will be calculated as the time from the date of randomisation to the date of death. Patients who have not died at the time of the final study follow up will be censored at the last date the patient was known to be alive.

3.5.3 Further therapy

The dates and type of any further therapy for thyroid cancer will be recorded during the study and follow up periods.

4. ANALYSIS METHODS

4.1 General principles

Statistical analyses will be performed by, or under the guidance of, Biometrics and Information Sciences, AstraZeneca using SAS version 9.1.3 or later and, where appropriate, additional validated software. These analyses will be performed in accordance with this Statistical Analysis Plan (SAP), which will detail analyses to be performed and summaries to be produced for the CSR.

The database will be cleaned, locked and released for analysis after all patients have completed their 18 month assessments. A CSR will be developed for this analysis, including the result of the primary endpoint analysis. An updated CSR will be released upon completion of analyses after all patients have completed the study (3 years of follow-up), however the primary analysis will not be repeated at this point. Table 3 details the time points of analysis for each endpoint.

4.2 Analysis methods

Since there is only one primary endpoint/comparison of interest (complete remission rate at 18 months for selumetinib vs. placebo in the ITT population), the primary endpoint will be considered statistically significant if the two-sided p-value is less than 0.05.

A summary of the endpoints to be analysed and analyses to be performed is shown in Table 3.

Table 3 Statistical analyses and pre-planned sensitivity analyses

Endpoint	Analysis Population	Analyses	Analysis at:	
			18 months	3 years
Complete Remission Rate	ITT	**Primary analysis:**		
		Logistic regression with treatment as the only covariate.	✓	✓
		Sensitivity analyses:		
		Logistic regression adjusted for mutation status, histology status and age	✓	
		Logistic regression with treatment as the only covariate, using the treatment compliant population.	✓	
		Logistic regression with treatment as the only covariate using protocol defined 8 week window	✓	
		Logistic regression with treatment as the only covariate ignoring any window	✓	
		Logistic regression with treatment as the only covariate, excluding patients with high TSH.	✓	
		Other analyses:		
		By treatment descriptive summaries	✓	
		Subgroup analyses (see Section 4.2.4)	✓	
	BRAF/*NRAS* mutation positive	**Secondary analysis:**		
		Logistic regression with treatment as the only covariate.	✓	
		Sensitivity analysis:		
		Logistic regression adjusted for histology status and age	✓	

Table 3 Statistical analyses and pre-planned sensitivity analyses

Endpoint	Analysis Population	Analyses	Analysis at: 18 months	Analysis at: 3 years
		Other analyses:		
		By treatment descriptive summaries	✓	
		Subgroup analyses (see Section 4.2.4)	✓	
Clinical Remission Rate	ITT	**Secondary analysis:**		
		Logistic regression with treatment as the only covariate.	✓	
		Sensitivity analysis:		
		Logistic regression adjusted for mutation status, histology status and age	✓	
		Other analyses:		
		By treatment descriptive summaries	✓	
		Subgroup analyses (see Section 4.2.4)	✓	
	BRAF/*NRAS* mutation positive	**Secondary analysis:**		
		Logistic regression with treatment as the only covariate.	✓	
		Sensitivity analysis:		
		Logistic regression adjusted for histology status and age	✓	
		Other analyses:		
		By treatment descriptive summaries	✓	
		Subgroup analyses (see Section 4.2.4)	✓	
Thyroid cancer recurrence	ITT	By treatment descriptive summaries		✓
		Kaplan-Meier plot if sufficient data		✓
Overall survival	ITT	By treatment descriptive summaries		✓
		Kaplan-Meier plot if sufficient data		✓
Use of further thyroid cancer therapy	ITT	By treatment descriptive summaries	✓	✓
Adverse events	Safety	By treatment descriptive summaries of any AEs occurring between treatment start and 30 days after last treatment dose.	✓	

Table 3 Statistical analyses and pre-planned sensitivity analyses

Endpoint	Analysis Population	Analyses	Analysis at:	
			18 months	3 years
		By treatment descriptive summaries of any treatment-related AEs occurring between 30 days after last treatment dose and end of follow-up.	✓	
		By treatment descriptive summaries of any serious AEs occurring between treatment start and end of follow-up.	✓	
Vital signs	Safety	By treatment descriptive summaries	✓	
Laboratory data	Safety	By treatment descriptive summaries	✓	✓
ECGs	Safety	By treatment descriptive summaries	✓	
ECHO/MUGA	Safety	By treatment descriptive summaries	✓	
Physical examination	Safety	By treatment descriptive summaries	✓	
Ophthalmologic examination	Safety	By treatment descriptive summaries	✓	
PK	PK	Population PK analyses (to be described in a separate PK analysis plan).	✓	

4.2.1 Primary analysis

The primary analysis will be an analysis of complete remission rate at 18 months and will compare selumetinib in combination with RAI vs. placebo in combination with RAI in the ITT population using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio together with its associated 95% profile likelihood CI and two-sided p-value based on profile likelihood.

A summary table will also be produced showing the number of patients that are in complete remission, not in complete remission due to re-treatment for thyroid cancer prior to scheduled assessment at 18 months post-RAI treatment or due to missing assessments (i.e. local lab,

wrong lab kit, no stage 2 or 3, missed visit, withdraw consent etc.). In addition, a listing of assessments/scans that contribute to the complete remission definition were performed will be presented.

4.2.2 Secondary analyses

Secondary analyses will be performed using a logistic regression model including treatment as the only covariate for the following endpoints and populations.

- Complete remission rate at 18 months post RAI treatment (BRAF/NRAS positive population)
- Clinical remission rate at 18 months post RAI treatment (ITT population)
- Clinical remission rate at 18 months post RAI treatment (ITT and BRAF/NRAS positive population)

Results will be presented in terms of the odds ratio, together with its associated 95% profile likelihood CI and two-sided p-value based on profile likelihood.

4.2.3 Sensitivity analyses

4.2.3.1 Logistic regression model including treatment and adjusted for covariates

A sensitivity analysis for each of the primary and secondary analyses will be performed using a logistic regression model including treatment and adjusted for the covariates mutation status (ITT population only), histology status, and age, provided there are enough data points for a meaningful analysis. If the model fails to converge, levels of the problematic covariate may be collapsed or if necessary excluded from the model. Specifically, this sensitivity analysis will be performed for each of the following:

- Complete remission rate at 18 months post RAI treatment (ITT population)
- Complete remission rate at 18 months post RAI treatment (BRAF/NRAS positive population)
- Clinical remission rate at 18 months post RAI treatment (ITT population)
- Clinical remission rate at 18 months post RAI treatment (BRAF/NRAS positive population)

The logistic regression model will be fitted with the following effects (where specified) regardless of whether the inclusion of the effects significantly improves the fit of the model. PROC LOGISTIC (SAS®) will be used for the statistical analysis. The variables shown in Table 4 will be used.

Table 4 Data specification for variables in logistic regression models and/or subgroup analyses

Variable	Variable Type	Variable Specification
Complete or Clinical Remission[a]	Dichotomous outcome	1=Yes 0=No
Treatment[b]	Unordered categorical covariate	1=selumetinib + RAI 0=placebo + RAI
BRAF/*NRAS* mutation status[c]	Unordered categorical covariate	A= *BRAF* mutation positive or *NRAS* mutation positive B= *BRAF* mutation not detected and *NRAS* mutation not detected C=unknown
BRAF mutation status[d]	Unordered categorical covariate	A= *BRAF* mutation positive B= *BRAF* mutation not detected C=unknown
NRAS mutation status[d]	Unordered categorical covariate	A= *NRAS* mutation positive B= *NRAS* mutation not detected C=unknown
Histology status	Unordered categorical covariate	A=papillary B=follicular C=poorly differentiated D=unknown
Age	Continuous covariate	Number in years
Gender[e]	Unordered categorical covariate	A=female B=male
Race[e]	Unordered categorical covariate	A=Caucasian B=Oriental C=other

[a] For definitions of complete and clinical remission refer to Sections 3.2.1 and 3.2.2 respectively. PROC LOGISTIC will use the DESCENDING option in order to model the probability of remission = 1 (yes).

[b] The PARAM=REF option on the CLASS statement will be used, so that parameter effects of class main effects using the reference coding scheme estimate the difference in the effect of each non-reference level compared to the effect of the reference level. The REF = first/last option will be used so that the placebo+RAI treatment group is the reference group. Parameter effects will not be presented in the results

[c] *BRAF*/*NRAS* mutation status variable will be included as covariates in the sensitivity and subgroup analyses on ITT population only

[d] The separate *BRAF* and *NRAS* mutation status variables will be included as covariates in the subgroup analyses on ITT population only, see Section 4.2.4

[e] Gender, race will be included as covariates in the subgroup analyses only, see Section 4.2.4

The results of all the logistic regression analyses will be presented in terms of an odds ratio for the treatment effect together with its associated 95% profile likelihood confidence interval and 2-sided p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above.

If there are any imbalances in the covariates defined above, adjusted response rates whose odds ratio exactly matches the odds ratio from the primary analyses (weighted in line with the prevalence of covariates) will be presented.

4.2.3.2 Additional sensitivity analyses

The primary endpoint analysis, a logistic regression model including treatment as the only covariate for complete remission at 18 months, will be repeated separately for the following:

- using the treatment-compliant population.
- classifying patients that had their first assessment started at 18 months ± 2 weeks [534 – 562 days] following the patient's RAI dose, and all necessary primary endpoint assessments were completed within a 8 week period to be in complete remission.
- to allow patients that were identified as being in complete remission outside of the specified time windows to be classed as being in complete remission, in order to investigate time bias between arms.
- excluding patients with high TSH. Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission, therefore this sensitivity analysis excludes patients with high TSH, which is defined as a value >10 mIU/L recorded, at any point from the start of treatment, by standardised central laboratory analysis.

4.2.4 Subgroup Treatment Effects

The complete and clinical remission rates at month 18 will be presented for each treatment arm, overall and by each covariate subgroup separately, for the ITT and BRAF/NRAS mutation positive population.

The extent to which the treatment effect is consistent across the subgroups mutation status (ITT population only), histology status, age, gender, and race will be assessed for the ITT population and in the BRAF/NRAS mutation positive population.

The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate

terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

- Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter estimate.

- Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data (BRAF or NRAS mutation status, BRAF mutation status, NRAS mutation status (ITT population only), histology status, age, gender, and race) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as $\leq$45 and >45 years. The treatment effect and 95% confidence intervals for each level of the subgroup will be obtained from a single logistic regression model that contains a treatment, factor and treatment-by-factor interaction term.

To assess the impact of known versus unknown covariate information separate logistic regression models will be performed containing treatment, factor and treatment-by-factor interaction term, for the following factors, if sufficient data, e.g., minimum 10 patients per treatment-by-factor level, to be meaningful to do so:

- BRAF or NRAS mutation status (known and unknown)

- BRAF mutation status (known and unknown)

- NRAS mutation status (known and unknown)

- Histology status (known and unknown)

The treatment effect and 95% confidence intervals for each level of the known subgroup will presented alongside the other categories in the appropriate forest plots; i.e. for each mutation

status there will be treatment odds ratios and 95% confidence intervals for positive, not detected, known (combined positive and not detected group) and unknown, and for histology status there will be treatment odds ratios and 95% confidence intervals for papillary, follicular, poorly differentiated, known (combined papillary, follicular, and poorly differentiated group) and unknown.

4.2.5 Demographic and baseline characteristics

The following baseline characteristics will be listed for each patient and summarised for all patients in the ITT analysis set by treatment group:

- Patient disposition
- Inclusion in analysis populations
- Important protocol deviations
- Demography (age (at informed consent), sex, race and thnic group)
- Patient characteristics including height and weight
- Patient recruitment by country and centre
- Past and current medical history
- Relevant surgical history
- Disease characteristics at baseline
- Primary tumor and TNM classification at original diagnosis
- Allowed and disallowed concomitant medications (presented by ATC classification system) for all patients in the safety analysis set

4.2.6 Safety

Safety data will not be formally analysed. The safety analysis set will be used for the reporting of safety data.

4.2.6.1 Adverse events

AE data will be listed for each patient and summarised by treatment received according to System Organ Class (SOC) and preferred term.

For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial treatment arm.

AE summaries will include all of the following:

- Any AEs occurring after commencement of study treatment and within 30 days of the last dose of study medication,
- Selumetinib or RAI related AEs occurring between 30 days after the last dose of study medication and the final study visit at 3 years following the initial RAI dose.
- All SAEs occurring after commencement of study treatment until the final study visit at 3 years following the initial RAI dose.

AEs occurring before commencement of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

Any AE with a missing onset date will be considered an on treatment AE unless the stop date of the AE indicates otherwise. Similarly, any AE with a partial onset date will be considered an on treatment AE unless the partial onset date or the stop date indicates otherwise.

4.2.6.2 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

No formal analyses of vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination data will be performed; this data will be summarised and listed.

4.2.7 Other analyses

4.2.7.1 Thyroid cancer recurrence

Very few thyroid cancer recurrences are expected on this study, therefore no formal analysis of thyroid cancer recurrence data will be performed; data will be listed and summarised by treatment arm for all patients in the ITT analysis set. Kaplan-Meier plots of time to recurrence (defined as a patient whose thyroid cancer has subsequently recurred, or the patient has a new malignancy) may be produced if appropriate, for those patients classed as being in complete remission at 18 months (or later).

4.2.7.2 Survival status

Very few deaths are expected on this study therefore no formal analysis of survival data will be performed; data will be listed by individual patients and summarised by treatment arm for all patients in the ITT analysis set. Kaplan-Meier plots of survival may be produced if appropriate.

4.2.7.3 Further therapy

No formal analysis of further therapy data will be performed; data will be listed and summarised by treatment arm for all patients in the ITT analysis set. Kaplan-Meier plots of time to further therapy may be produced if appropriate.

4.2.7.4 PK

Plasma selumetinib, N-desmethyl selumetinib plasma concentrations will be listed for each patient. A population PK analysis will be carried out. The results of this analysis will be reported outside of the CSR.

4.2.7.5 Genetics

Any genetic data analysis (other than *BRAF* and *NRAS*) will be planned outside this SAP and reported outside the CSR for this study.

4.2.7.6 Biomarker data

BRAF and *NRAS* mutation assessment of tumour biopsy will be used to identify patients for this primary patient population. The results of any other exploratory biomarker investigations will be planned outside this SAP and reported outside the CSR for this study.

5. INTERIM ANALYSES – NOT APPLICABLE

6. CHANGES OF ANALYSIS FROM PROTOCOL

In the protocol section 6.4.5 (Derivation of primary endpoint of complete remission) it is stated:

"The first assessment must be started at 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within a 8 week period. If a patient has assessments/scans that fall outside of these time windows, the patient will be considered not to be in complete remission, regardless of the assessment of disease status."

Change of analysis:

Patients who did not complete a full set of assessments within 8 weeks of commencing the 18 month primary endpoint assessments but who do have a full set of assessments at or following the time the 18 month assessment window began, will be considered for the primary endpoint. Specifically, patients whose any part of the composite endpoint assessment for Stage 1 (suppressed Tg, TgAb, US and/or FNA/Biopsy) was evaluated before 75 weeks (i.e. prior to 525 days) provided that all the composite endpoint assessments for Stage 2 (stimulated Tg, WBS) and Stage 3 (CT and MRI) were evaluated at least 75 weeks (≥525 days) post RAI-treatment will be considered for the primary endpoint.

The same time window derivations will be applied to the secondary analysis of clinical remission.

In addition the sensitivity analyses (SAP 4.2.3.2) were clarified in light of the change to programmatic derivation of the primary and secondary analyses.

Rationale:

During the study it became clear that some patients found it difficult to attend the site for all stages of the assessment in the study mandated time windows due to numerous reasons (e.g. work or personal commitments, difficulties scheduling with several different departments, equipment failure at the site requiring rescheduling, etc.). If the assessment shows that the patient has not relapsed at a time point beyond 18 months, then it is expected the patient would not have relapsed *at* the earlier 18 month time point. In an attempt to include as comprehensive an assessment for Complete Remission, the 8 week window to complete all assessment stages has been removed from the programming derivation (but not from the guidance given to sites).

It is considered that a patient who has not required retreatment and is in complete remission (e.g. no evidence of relapse) later than 18 months can be assumed to have been in complete remission at the 18 month timepoint. As such, in the programming definition, the upper window around 18 months has been removed.

'At least 75 weeks' will be used in the programming criteria for the start of the 18 month assessment window. This allows a slightly larger window than the guidance given in the CSP to the investigator (18 months +/- 2 weeks). This is because the calculation of 18 months may vary slightly depending whether the site using calendar months or 365.25 days x 1.5 to choose the 18 month visit date (and the specific definition of 18 months is not given in the CSP). The 'At least 75 weeks' criterion has also been extended to allow inclusion in the derivation of biochemical, clinical and complete remission of patients whose any part of the composite endpoint assessment for Stage 1 (suppressed Tg, TgAb, US and/or FNA/Biopsy) evaluated before 75 weeks (i.e. prior to 525 days) provided that all the composite endpoint assessments for Stage 2 (stimulated Tg, WBS) and Stage 3 (CT and MRI) were evaluated at least 75 weeks (≥525 days) post RAI-treatment. Rationale is that the Stage 2 and 3 are the main drivers to assess biochemical and structural remission provided though all assessments have been implemented.

7. REFERENCES

Gail & Simon 1985
Gail M & Simon R. Testing for qualitative interactions between treatment effects and subject subsets. Biometrics 1985; 41:361-72.

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