TRIAL STATISTICAL ANALYSIS PLAN

c33744236-02

BI Trial No.:	1280-0022
Title:	Xenera™ 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease Including Protocol Amendment 5 <1280-22>-protocol-version-05 [c18323506-08]
Investigational Product:	Xentuzumab (BI 836845)
Responsible trial statistician:	[redacted] Phone: [redacted]
Date of statistical analysis plan:	23 AUG 2021 SIGNED
Version:	2

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[redacted]

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
AQA	Analgesic Quantification Algorithm
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA Queries
BOR	Best Overall Response
BPI-SF	Brief Pain Inventory – Short Form
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
DC	Disease Control
DLM	Database Lock Meeting
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQoL 5-dimension health status self-assessment questionnaire
HLT	High Level Term
HR	Hazard Ratio
ICH	International Conference on Harmonisation
iPD	Important Protocol Deviation
IRT	Interactive Response Technology
ITT	Intention-to-Treat
KM	Kaplan-Meier
Max	Maximum

Min	Minimum
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MQRM	Medical Quality Review Meeting
nAb	Neutralising antibody
NFBSI-16	Network Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index
OR	Objective response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival
PPS	Per Protocol Set
PR	Partial Response
PRO	Patient Reported Outcome
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
PT	Preferred Term
Q1	Lower quartile
Q3	Upper quartile
RECIST	Response Evaluation Criteria in Solid Tumours
RPM	Report Planning Meeting
RS	Randomised Set
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Stable Disease
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SSC	Special Search Categories
TFST	Time to First Subsequent Therapy
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSST	Time to Second Subsequent Therapy
TTE	Time to Event
ULN	Upper Limit of Normal
WHO-DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9 guidance (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including protocol amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

This TSAP currently covers the Phase II part of the study, for the scenario that the criterion for expanding the trial seamlessly into Phase III has not been met. In such an instance, the trial will be unblinded and the results evaluated in an explorative manner to see if they are sufficient for further development of this compound in this indication.

SAS® Version 9.4 or a later version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following changes to the statistical methods described in the CTP and subsequent amendments are detailed in this TSAP:

- Where considered appropriate, the potential impact of Coronavirus Disease 2019 (COVID-19) on the study will be assessed by producing additional summaries of disposition, protocol deviations, treatment compliance, efficacy, treatment exposure and adverse events (AEs). The start date for COVID-19 having an impact on the trial will be taken as the earliest date of a COVID-19 related protocol deviation, discontinuation due to COVID-19, onset of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related AE or COVID-19 related global BI recruitment hold (17 MAR20).

5. ENDPOINTS

Time to event (TTE) endpoints, unless stated otherwise, will be calculated as follows:

For patients with ‘event’ as an outcome:

- TTE [days] = date of outcome – date of randomisation + 1

For patients with ‘censored’ as an outcome:

- TTE (censored) [days] = date of outcome – date of randomisation + 1

Derivations will be calculated in days but will be presented as months in the respective outputs [Months = (Days x 12) / 365.25].

All references to the Response Evaluation Criteria in Solid Tumours (RECIST) are according to Version 1.1 in combination with MD Anderson criteria (refer to Section 5.1 of the CTP for further details). Unless stated otherwise, all imaging-related endpoints detailed below will primarily be derived from blinded independent assessment data, derivations using investigator assessment data will also be performed but will be supportive in nature.

5.1 PRIMARY ENDPOINT

The primary endpoint is progression-free survival (PFS) calculated as the time from randomisation until progressive disease (PD) according to RECIST or death from any cause, whichever occurs earlier. The date of PD will be based upon blinded independent assessment.

The rules to determine the PFS outcome (event or censored) along with the date of outcome are specified in Table 5.1: 1. These rules will be applied to the independent assessment data prior to analysis.

In order to identify whether radiological imaging assessments are missing, a nominal time-point based on the scheduling detailed in the CTP will be assigned to each assessment according to Table 6.7: 1. If a patient does not have an assessment for one of the scheduled time-points, it will count as a missed assessment. Any assessment with an overall tumour

response of Not Evaluable (NE) will be considered as a missed assessment and cannot be used as an outcome date.

Table 5.1: 1 Derivation rules for PFS

Status at time of analysis	Outcome	Date of outcome
No baseline radiological assessment and/or no post-baseline radiological assessments		
Death on or before the second planned radiological assessment	Event*	Date of death
Vital status is unknown or alive or death after second radiological assessment	Censored	Date of randomisation
With baseline and at least one post-baseline radiological assessment		
Alive and non-PD, no more than one consecutively missed radiological assessment	Censored*	Date of last radiological assessment
Alive and non-PD, two or more consecutively missed radiological assessments	Censored*	Date of last radiological assessment prior to missed radiological assessments
PD, no more than one consecutively missed radiological assessment prior to PD	Event*	Date of radiological assessment of PD
PD, two or more consecutively missed radiological assessments prior to PD	Censored*	Date of last radiological assessment prior to missed radiological assessments
Death and non-PD, no more than one consecutively missed prior radiological assessment prior to death	Event*	Date of death
Death and non-PD, two or more consecutively missed radiological assessments prior to death	Censored*	Date of last radiological assessment prior to missed radiological assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before the outcomes flagged with a '*' above	Censored	Date of last radiological assessment before subsequent anti-cancer therapy (or date of randomisation if none exist)

* For these outcomes if initiation of subsequent anti-cancer therapy occurred prior to the outcome date then the rule for the final row of table will be used instead

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

There are no key secondary endpoints defined for the trial.

5.2.2 Secondary endpoints

Overall survival

Overall survival (OS) will be calculated as the time from randomisation to death from any cause. Patients without evidence of death will be censored at the date of last contact when known to be alive.

Disease control

Disease control (DC), defined as a best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD) or Non-CR/Non-PD. SD and Non-CR/Non-PD must have been observed up until at least the Week 24 tumour assessment.

BOR is defined according to RECIST based on all evaluable tumour assessments from randomisation until the earliest of PD, start of subsequent anti-cancer therapy, loss to follow-up, withdrawal of consent or death. To be aligned with the primary endpoint derivation, tumour assessments after two or more consecutively missed assessments will not be considered.

Duration of disease control

Duration of DC will be calculated as the time from randomisation until the earliest of PD (according to RECIST) or death from any cause, among patients with DC.

The outcome rules defined in Table 5.1: 1 will be used for the calculation.

Objective response

Objective response (OR), defined as a BOR (as detailed for DC) of CR or PR.

Time to pain progression or intensification of pain palliation

Time to pain progression or intensification of pain palliation, defined as the time from randomisation until the earliest of:

- ≥2 point increase from baseline in the Brief Pain Inventory – Short Form (BPI-SF), Item 3 (worst pain), without a decrease (of ≥1 point) from baseline analgesics use (via the 8-point Analgesic Quantification Algorithm [AQA]), or
- ≥2 point increase from baseline in the AQA, or
- Death

The rules to determine outcome (event or censored) along with the date of outcome are specified in Table 5.2.2: 1. These rules will be applied to the independent assessment data prior to analysis.

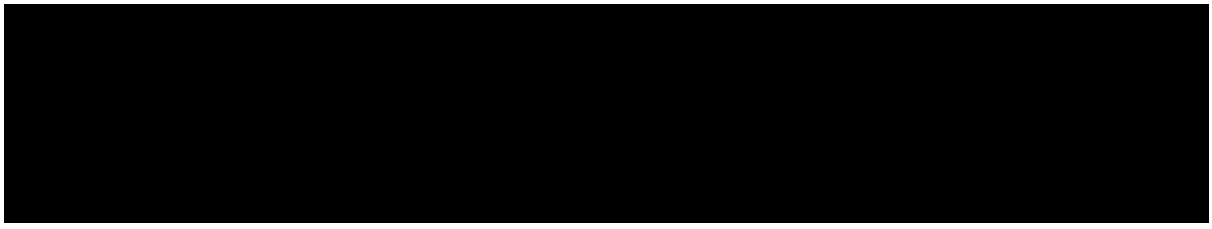
In order to identify whether questionnaire assessments are missing, a nominal time-point based on the scheduling detailed in the CTP will be assigned to each assessment according to Table 6.7: 2. If a patient does not have an assessment for both the BPI-SF, Item 3 and the AQA score at one of the scheduled time-points, it will count as a missed assessment;

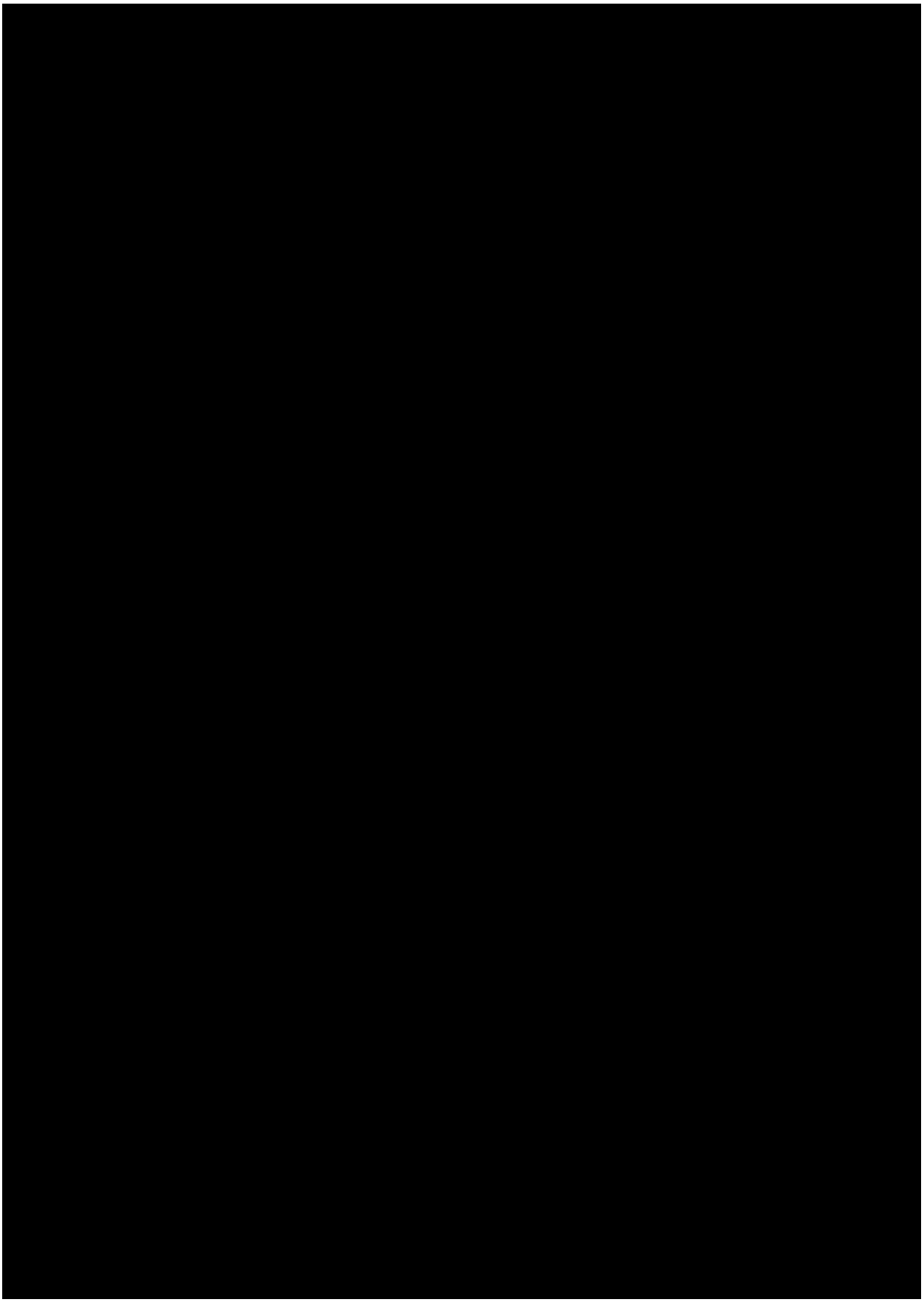
otherwise, a response will be derived. If a ≥2 point increase from baseline in the BPI-SF, Item 3 is observed but the AQA score is missing, it will be assumed that no decrease in analgesics use has taken place.

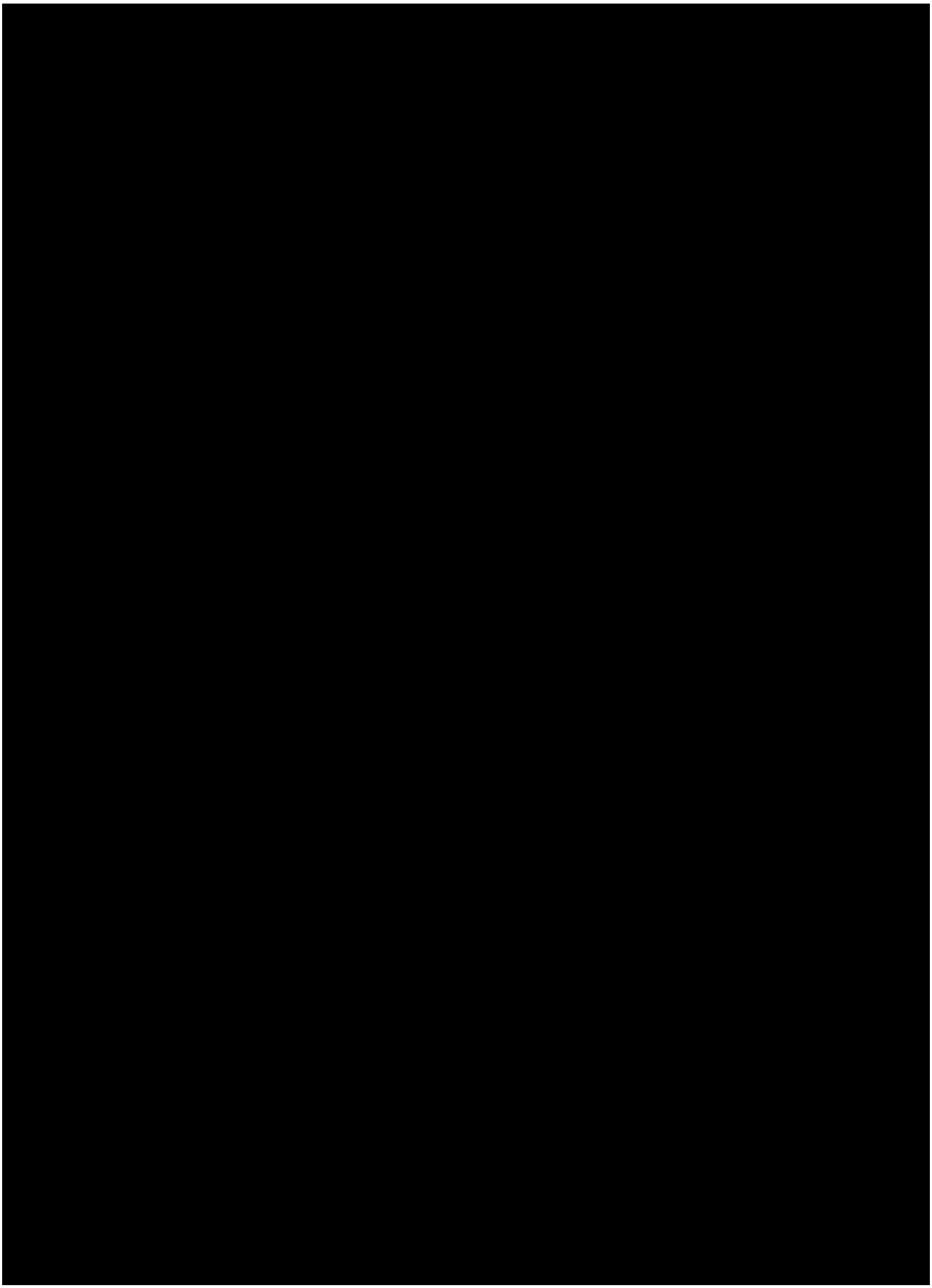
Table 5.2.2: 1 Derivation rules for pain progression or intensification of pain palliation

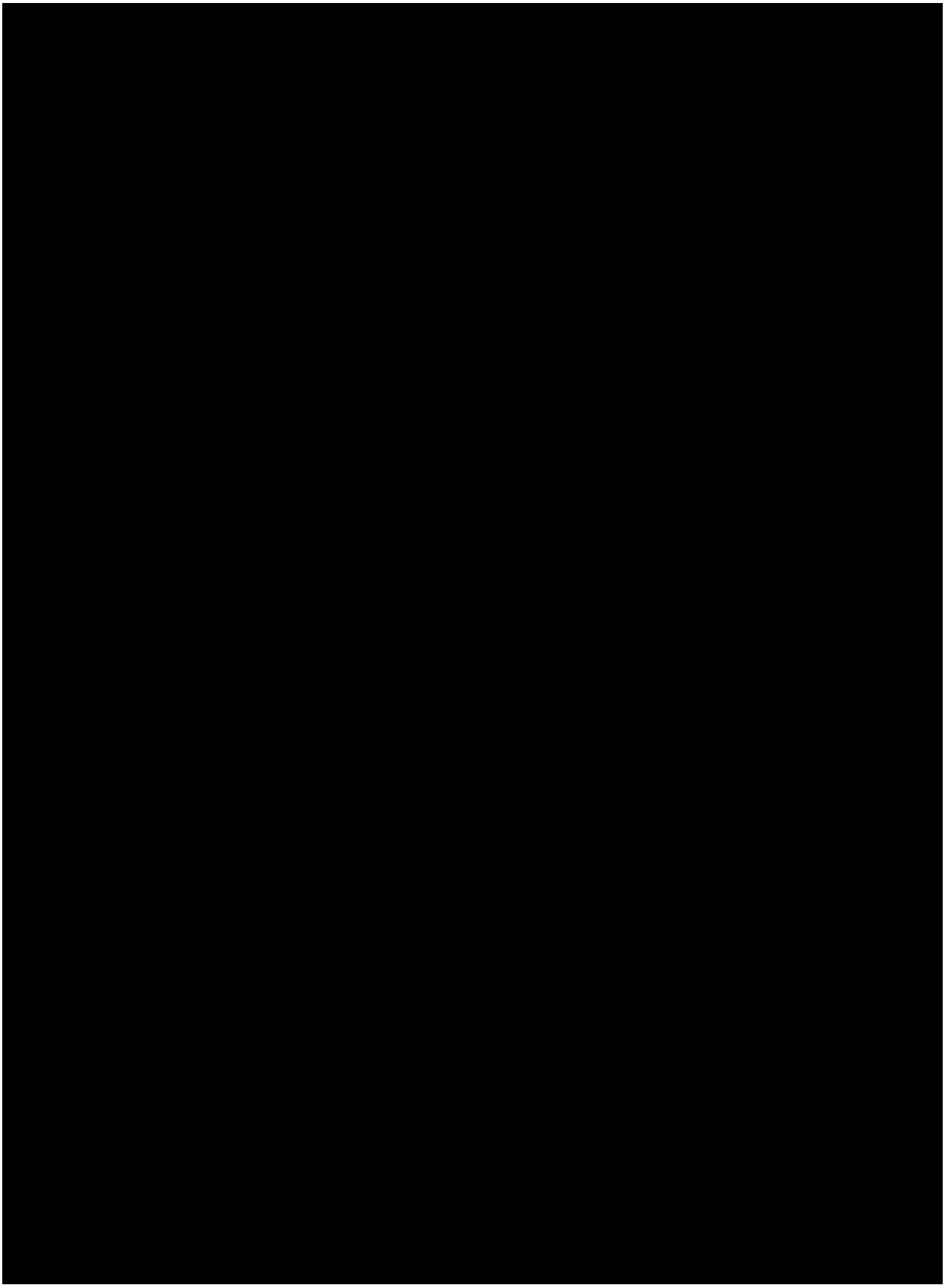
Status at time of analysis	**Outcome**	**Date of outcome**
No baseline assessment and/or no post-baseline assessments		
Death on or before the second planned assessment	Event*	Date of death
Vital status is unknown or alive or death after second planned assessment	Censored	Date of randomisation
With baseline and at least one post-baseline assessment		
Alive and event-free, no more than one consecutively missed assessment	Censored*	Date of last assessment
Alive and event-free, two or more consecutively missed assessments	Censored*	Date of last assessment prior to missed assessments
Alive with event, no more than one consecutively missed assessment prior to event	Event*	Date of assessment of event
Alive with event, two or more consecutively missed assessments prior to event	Censored*	Date of last assessment prior to missed assessments
Death and event-free, no more than one consecutively missed assessment prior to death	Event*	Date of death
Death and event-free, two or more consecutively missed assessments prior to death	Censored*	Date of last assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before outcomes flagged with a '*' above	Censored	Date of last assessment before subsequent anti-cancer therapy (or date of randomisation if none exist)

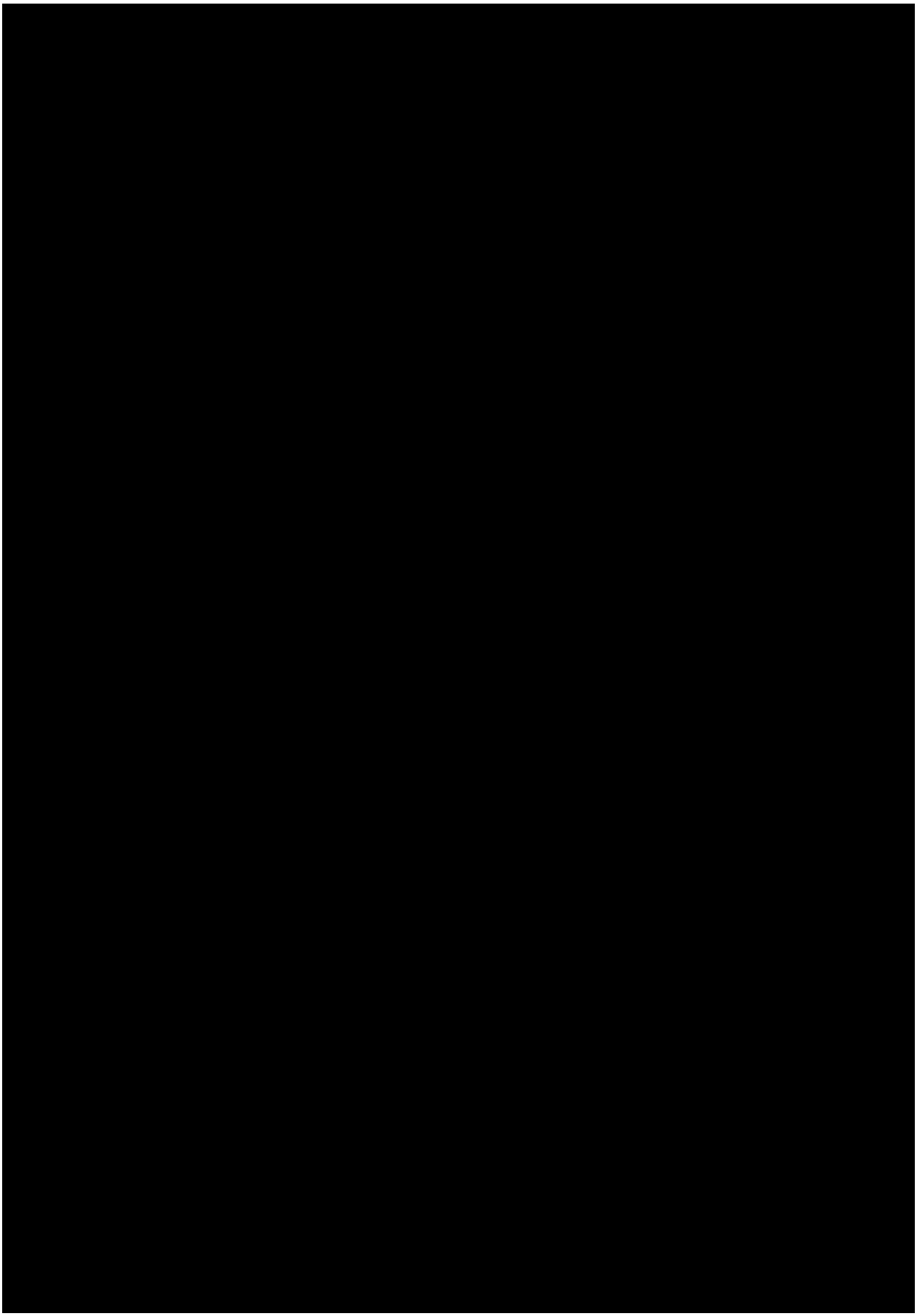
* For these outcomes if initiation of subsequent anti-cancer therapy occurred prior to the outcome date then the rule for the final row of table will be used instead

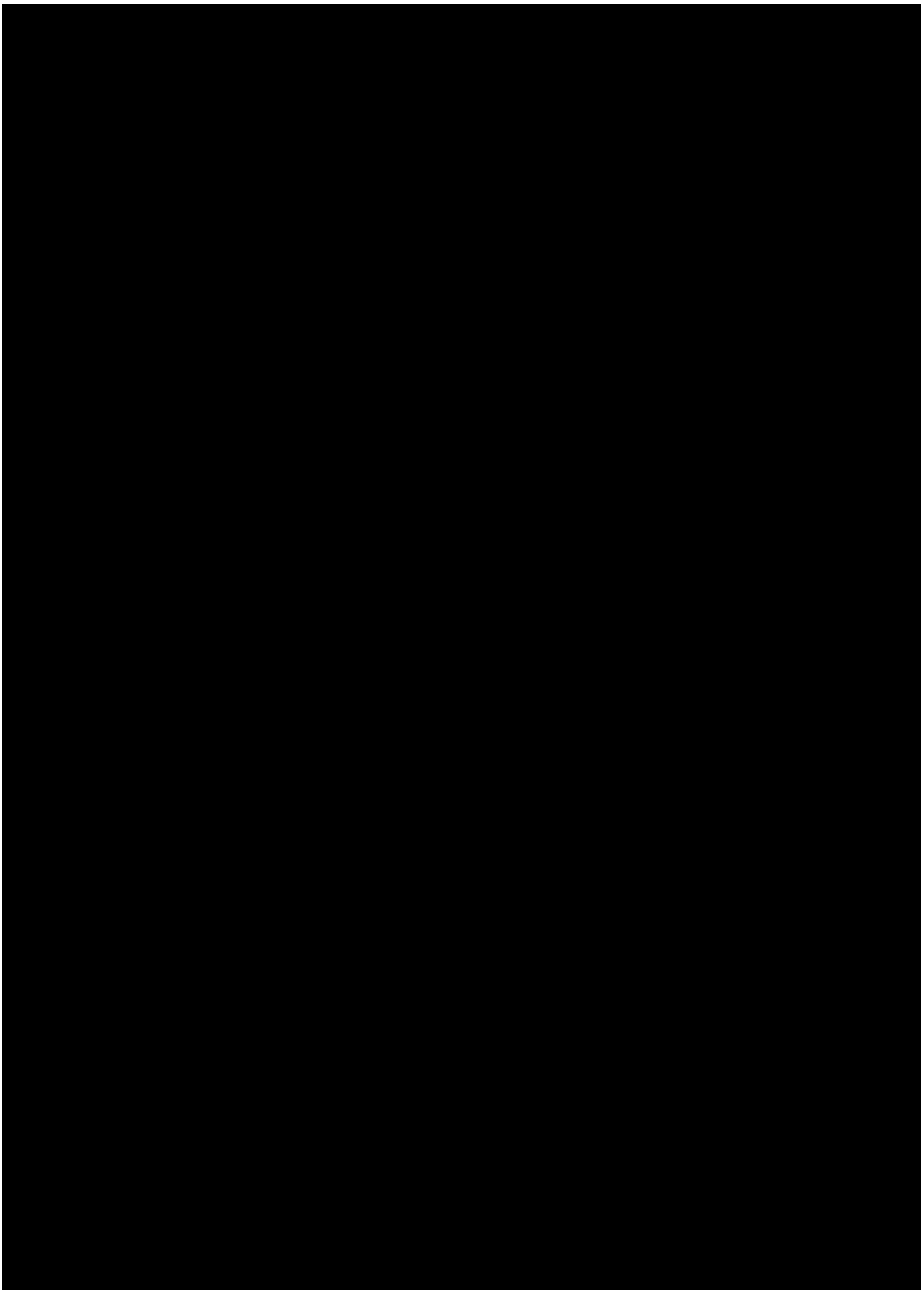


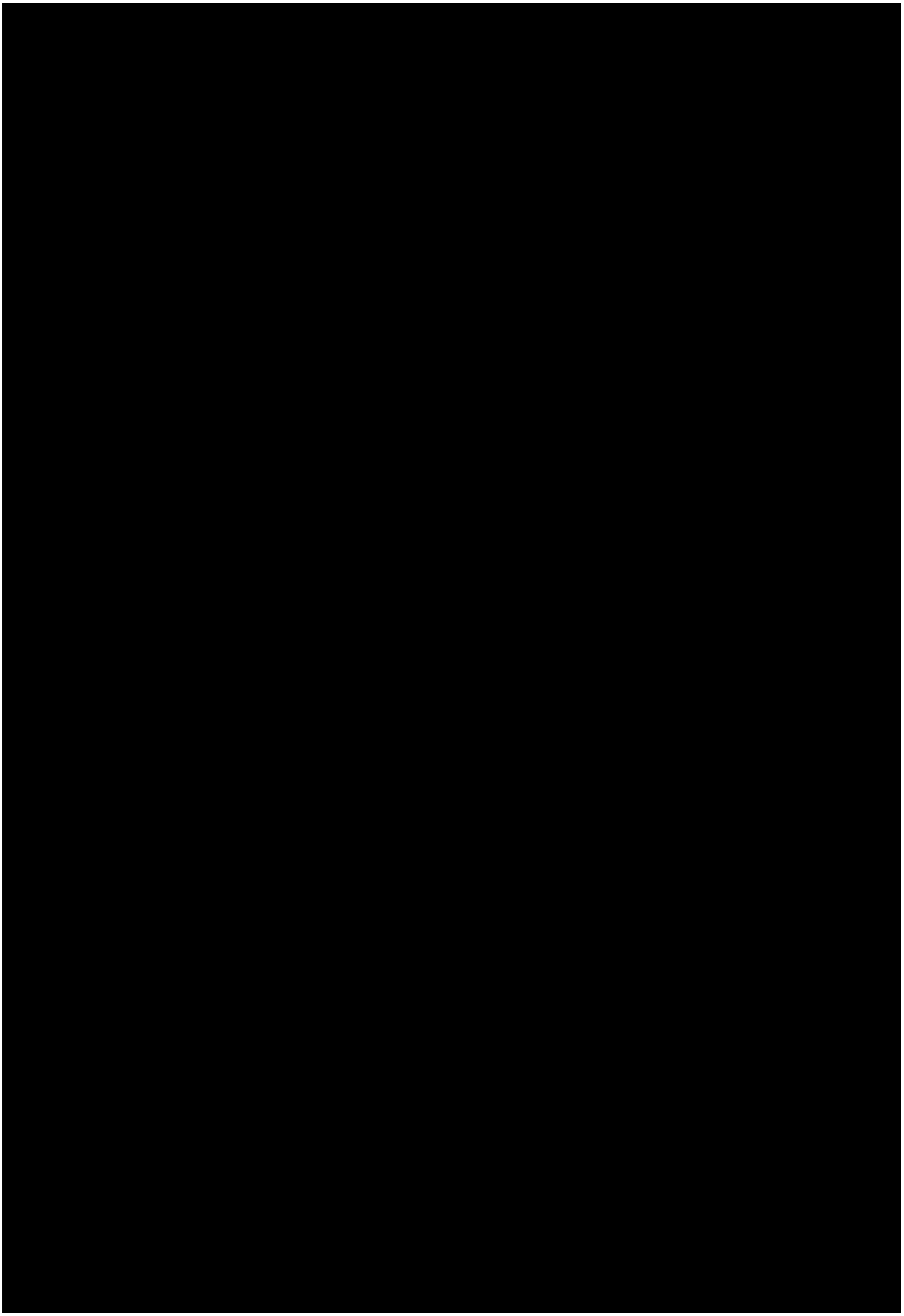












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, all randomised patients will be classified into either 'Xe1000+Ev10+Ex25' or 'Plc+Ev10+Ex25' as randomised. For efficacy analyses, the intent-to-treat (ITT) approach will be used, i.e. patients will be analysed according to the treatment group they were randomised to. All planned analyses will be presented by this randomised treatment group. Handling of patients where treatment group assignment has not been followed will be handled on a case-by-case basis, to be agreed at report planning meetings prior to database lock. The following study periods are defined:

- Screening: day of informed consent to day prior to first administration of study treatment
- Treatment: day of first administration of study treatment to day of last administration of study treatment
- Residual effect period (REP): day after last administration of study treatment, for a duration of 42 days
- Follow-up: day after the end of the REP to trial completion

For safety analyses, treated patients will be analysed according to the initial treatment taken, and for safety summaries, data recorded whilst taking study treatment and up to 42 days after last administration of study treatment (i.e. including the REP) will be considered as on-treatment. As the treatment arms are made up of a combination of individual treatments, a patient may have multiple last doses of treatment; therefore, the last dose of study medication is defined as the latest of these.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set (PPS) analysis will be performed, hence, no patient will be excluded from the analyses (with the exception of patients not providing informed consent). However, patients with potentially important protocol deviations (iPDs) will be documented to give an indication of the level of adherence to the protocol, refer to Table 6.2: 1. Note this is a working list and may not be finalised until the final Medical Quality Review Meeting (MQRM), Database Lock Meeting (DBLM) and Report Planning Meeting (RPM) have taken place prior to the database lock of the primary PFS analysis.

A frequency table of the above iPDs will be produced. In addition, a frequency table of all COVID-19 related non-important and important PDs will be produced.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Analysis Set Excluded from
A1	Diagnosis of trial disease questionable	None
A2	Prohibited baseline condition, diagnosis or treatment	None
A3	Laboratory result indicating inadequate organ function at screening	None
A4	Adequate archival tumour tissue not available	None
B1	Informed consent not available/not done	All
B2	Informed consent too late	None
B3	Age limit for patient inclusion not adhered to	None
C1	Time window violation for procedures performed at screening	None
C2	Trial medication not given according to protocol	None
C3	Infusion time for the investigational treatment outside of CTP specific boundaries	None
C4	Randomisation not followed	None
D1	Prohibited treatment during trial conduct phase	None
E1	Imaging assessments not done according to CTP instructions	None
F1	Other protocol violations affecting patient rights or safety	None

6.3 PATIENT SETS ANALYSED

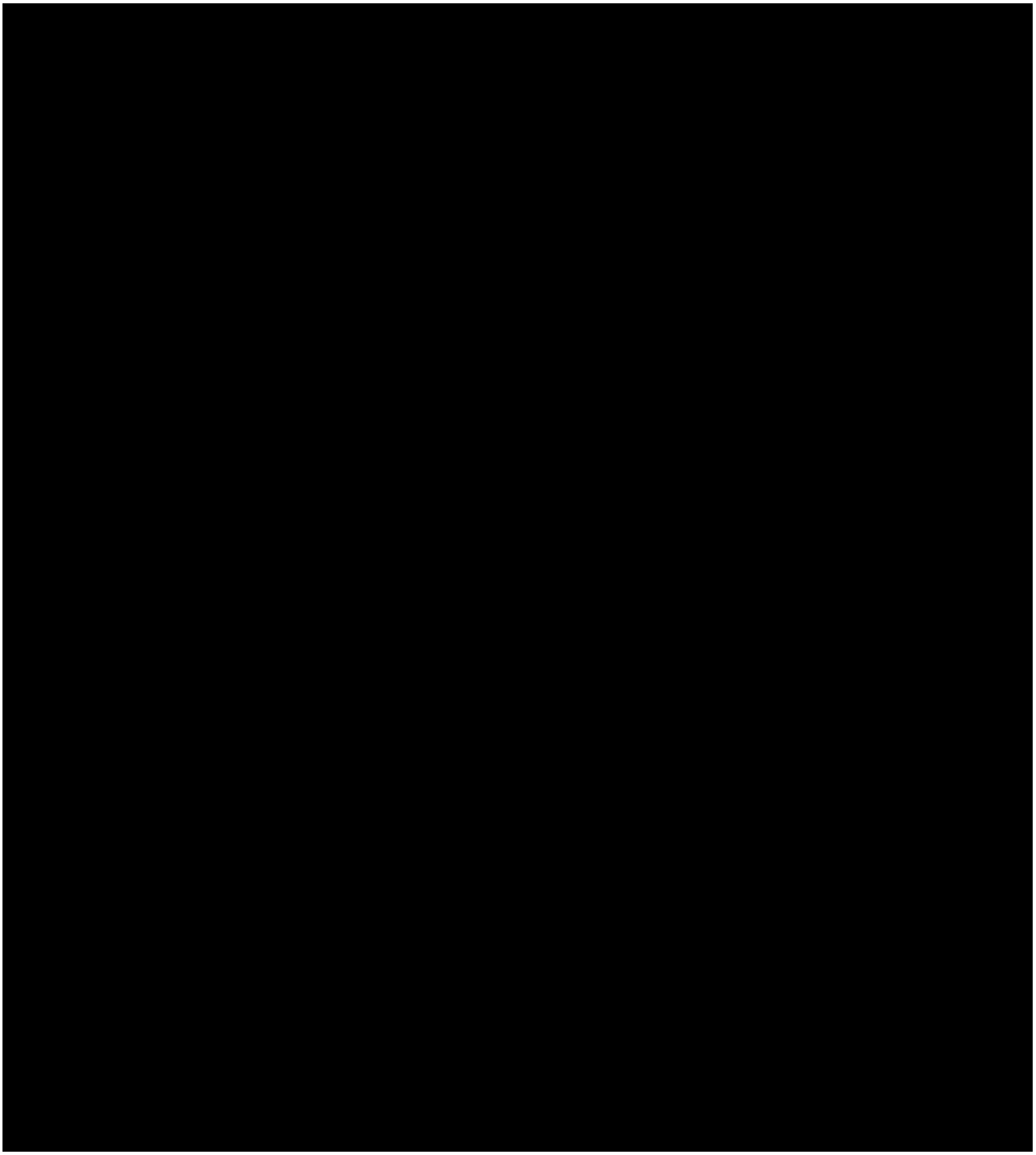
The following patient sets are defined:

- Enrolled set:
  This patient set includes all patients who have given informed consent. The enrolled set will be used for patient disposition summaries.

- Randomised set (RS):
  This patient set includes all randomised patients, regardless of whether they have received treatment or not. The RS will be used for demographic and baseline characteristic summaries and the evaluation of primary, secondary and further endpoints.

- Treated set (TS):
  This patient set includes all patients who are documented to have received and taken at least one dose of any study medication. The TS will be used for the evaluation of safety.

- PK parameter analysis set (PKS):
  This patient set includes all patients in the TS who have at least one valid drug plasma concentration available that was not excluded because of protocol deviations affecting PK evaluation.



6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed, unless required for the following analyses and definitions. Then the rules as described below apply.

For TTE endpoints, patients who are event-free but have dropped out of the trial prematurely or are not evaluable for other reasons will be censored according to the rules given in Sections 5.1, 5.2 and 5.3.

The BPI-SF pain interference aggregated score will only be calculated if 4 or more of the 7 individual item scores have been completed.

Missing or incomplete dates that affect the evaluation of endpoints will be imputed utilising a worst-case approach, which will be applied on a case-by-case basis (depending on the affected endpoint) and documented appropriately prior to database lock and unblinding.

For the purposes of potential PFS censoring incomplete start dates of subsequent anti-cancer therapy will be imputed. The earliest possible date will be assumed, if this results in a start date prior to the stop date of study treatment this will be defaulted to study treatment stop date + 1 day.

Missing or incomplete adverse event (AE) dates will be imputed according to BI standards (2).

For the calculation of time to first diagnosis, if the date of diagnosis is incomplete the 1st will be used for a missing day and January for a missing month.

In general, actual patient data as reported in the eCRF will be used for analyses. If the data relating to the assignment of stratification factors are missing in the eCRF then the values entered into the Interactive Response Technology (IRT) system will be used instead (note these entries are automatically transferred to the eCRF).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last measurement observed prior to start of trial medication will be assigned to baseline. Note that for some trial procedures this may be the value measured on the same day trial medication was started. In these cases, where time of measurement is not recorded, it will be assumed that the measurements were taken prior to the intake of any study medication.

For measurements where not only the examination date but also time are recorded, examination time will be taken into account when defining baseline. Therefore, a measurement recorded on the same date as the first study drug administration will be considered as the baseline value, if and only if, the recording time was before or the same as the time of first study drug administration. If any of these times are missing and the date of the measurement is equal to the date of first study drug administration, then the measurement will be considered according to what was planned in the protocol, i.e. for safety laboratory data prior to first study medication. Note this rule will be relaxed for PRO data, as long as the baseline assessment of PROs is performed on or prior to the date of first study drug administration it will be considered as a valid baseline.

For tumour assessments, baseline evaluations must be performed no more than 28 days prior to start of trial medication.

Study days and visits will be labelled according to the flow chart of the CTP. In alignment with the CTP, study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'. Hence, 'Day 0' will not exist.

In order to identify whether consecutive imaging time points are missing for a patient a nominal time point [8, 16, 24 weeks and every 8 weeks thereafter up to 80 weeks, and every 12 weeks thereafter] will be assigned to each image. This will be achieved by creating time windows for each assessment as detailed in Table 6.7: 1 below. If a patient does not have an image in one of the time windows when one is expected they will be considered as having 'missed an assessment' for that time-point. In case a patient has more than one assessment in one window, the assessment with the latest outcome will be used for the analysis unless progressive disease (PD) has been recorded earlier then PD will be used. Additionally, if a patient has multiple imaging dates within an assessment (e.g. a different target lesion imaging date to the non-target lesion imaging date), if the overall response is PD the earliest imaging date will be used, otherwise the latest imaging date will be used. Note for the slotting of imaging data and the derivation of time to efficacy events in general, ‘Day 1’ will be considered as the day of randomisation.

Table 6.7: 1 Nominal time-points and windows for imaging

Nominal time-point [Weeks]	Nominal time-point [Days]	Window [Days]
0	1	<=1
8	57	[2, 85]
16	113	[86, 141]
+8 weeks*	+56 days*	[+56 days, +56 days]*
80	561	[534, 603]
92	645	[604, 687]
+12 weeks*	+ 84 days*	[+84 days, +84 days]*

* For subsequent visits, add value to previous record in respective column

In a similar fashion to imaging time points, missed PRO assessments will be identified as detailed in Table 6.7: 2.

Table 6.7: 2 Nominal time-points and windows for PROs

Nominal time-point [Weeks]	Nominal time-point [Days]	Window [Days]
0	1	<=1[#]
4	29	[2, 43]
8	57	[44, 71]
+4 weeks*	+28 days*	[+28 days, +28 days]*
80	561	[548, 589]
88	617	[590, 645]
+8 weeks*	+56 days*	[+56 days, +56 days]*

* For subsequent visits, add value to previous record in respective column
# Note any Course 1, Visit 1 data recorded prior to starting study medication will be defaulted to Day 1 even if it was after the randomisation date

Note if a patient discontinues study treatment and enters the follow-up for progression then PRO assessments will follow the imaging assessment schedule, so will either be 8-weekly or 12-weekly dependent upon whether reached Week 80 (Cycle 20) or not.

7. PLANNED ANALYSIS

In general (unless specified elsewhere), BI standards (3) will be followed for the End-Of-Text tables. In summary:

- The set of statistics for continuous data is N / Mean / Standard Deviation / minimum (Min) / lower quartile (Q1) / Median / upper quartile (Q3) / Maximum (Max). Other than the Min and Max, all statistics will be presented to one more decimal place than the raw data.

- Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category 'missing' will only be displayed if there are actually missing values.

- Time-to-event endpoints will be summarised in months [Months = (Days x 12) / 365.25] to one decimal place. Hazard ratios (HRs) and corresponding confidence intervals (CIs) will be presented to two decimal places. P-values will be presented to four decimal places.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, for the RS of patients.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report, for the RS of patients.

Concomitant diseases will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarised by primary system organ class (SOC) and preferred term (PT). Concomitant medications will be coded using the most current version of WHO-DD and will be summarised by ATC3 class and PT. In situations where a therapy belongs to more than one ATC3 class all classes will be presented, along with explanatory footnotes. Separate summaries of concomitant medications started prior to and during the period of taking study medication will be produced.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report, for the TS of patients. Appropriate summaries of compliance before and from the start of the COVID-19 disruption will also be produced.

7.4 PRIMARY ENDPOINT

The primary endpoint of PFS as assessed by blinded independent assessment will be analysed using the RS of patients.

7.4.1 Primary analysis of the primary endpoint

The primary endpoint will be analysed using a stratified (presence of baseline bone-only metastases, prior CDK4/6 inhibitor treatment, menopause status) log-rank test to assess the effect of treatment.

A stratified Cox proportional hazards model will be used to estimate the HR of the treatment effect and the corresponding asymptotic two-sided 95% Wald CI. A HR of less than one will favour the xentuzumab arm. Breslow's method for handling ties will be used.

Kaplan-Meier (KM) estimates will be used to display the distribution of PFS for each treatment group on a KM curve. To support the plot, estimated survival probabilities at specific time points of interest (scheduled imaging time-points) will be tabulated along with 95% CIs, using Greenwood's variance estimate. In addition, the survival distribution will be used to provide estimates of the median, 25^{th} and 75^{th} percentiles.

Suitable methods will be used to check the assumption of proportional hazards.

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable, as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

Overall survival

The analysis of this endpoint will follow that of the primary endpoint, detailed in Section 7.4.1.

Disease control

A logistic regression model adjusting for the previously defined stratification factors will be used for the analysis of this binary endpoint. The treatment groups will be compared via the likelihood ratio test and presented along with the corresponding odds ratio and 95% CI. An odds ratio greater than one will favour the xentuzumab arm.

Duration of disease control

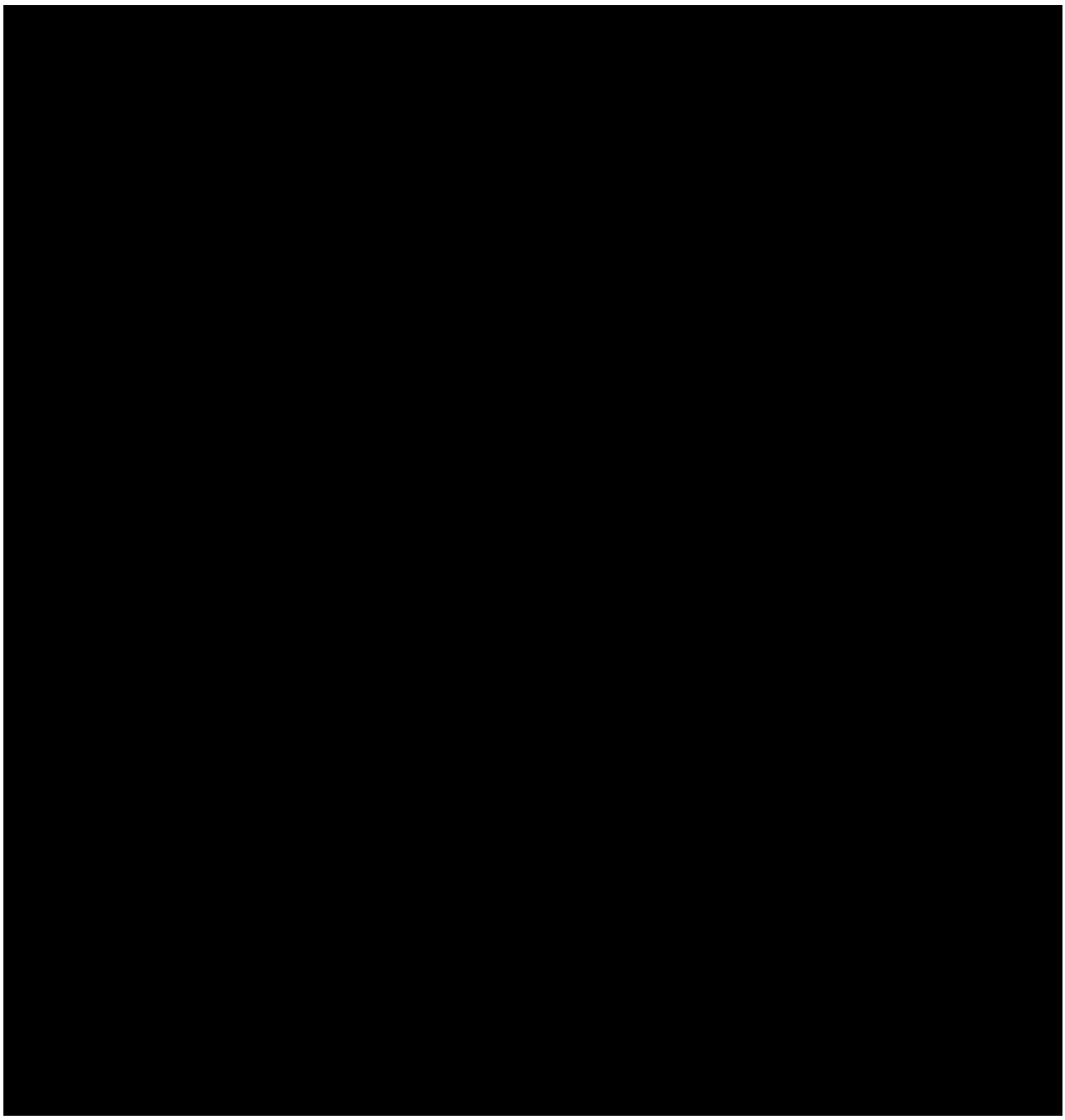
KM estimates will be calculated for each treatment group to provide estimates of the median, 25th and 75th percentiles and their corresponding 95% CIs.

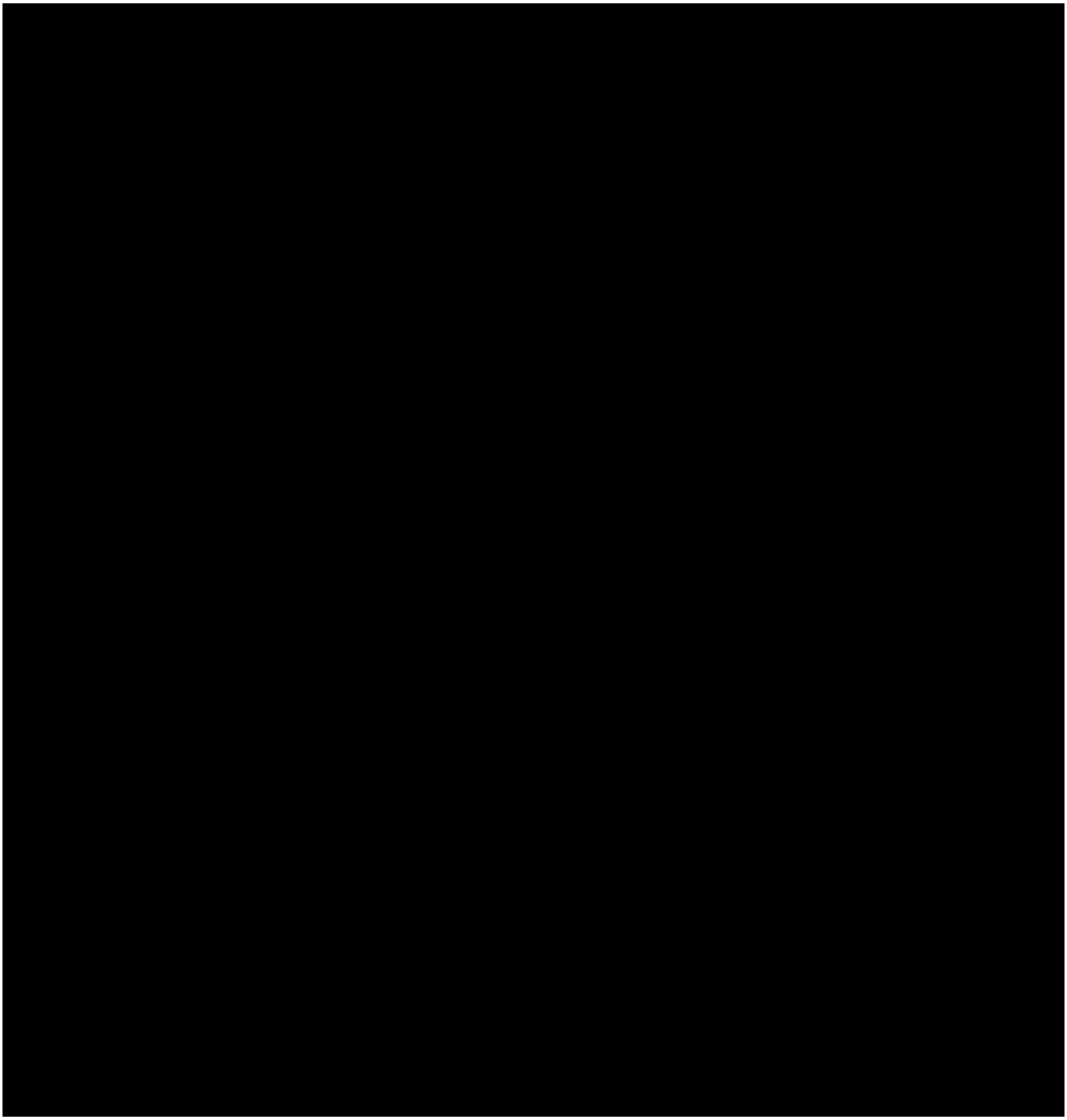
Objective response

OR will be analysed as for DC above.

Time to pain progression or intensification of pain palliation

The analysis of this endpoint will follow that of the primary endpoint, detailed in Section 7.4.1.





7.7 EXTENT OF EXPOSURE

A descriptive summary of total duration of study treatment will be produced both for the combined treatment and for each of the individual components. A dose reduction summary of everolimus will also be produced along with dose intensity summaries for each of the individual components of the study treatment. Refer to Section 5.4.2 for further details.

A Kaplan-Meier plot of the time to permanent discontinuation of all study medication (date of last administration of study medication – date of first administration of study medication + 1) will also be produced by treatment group. Patients who have not permanently discontinued study medication will be censored at the date of the snapshot for the analysis.

Appropriate summaries of exposure before and from the start of the COVID-19 disruption will also be produced.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. In addition to the summaries described below, standard tables required for the clinical trials disclosure process (ClinicalTrials.gov and EudraCT) will be produced (4).

7.8.1 Adverse Events

AEs will be coded with the most recent version of the MedDRA. The severity of AEs will be scaled according to Common Terminology Criteria (CTC) AE version 5.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

For analysis, multiple AE occurrence data on the eCRF will be collapsed into an AE if all of the following applies:

- All AE attributes are identical (Lowest Level Term [LLT], CTCAE grade, action taken with trial medication, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)

- The occurrences are time overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on the analysis and presentation of AE data refer to BI standards (5).

The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all AEs with an onset between first drug intake and last drug intake + REP (42 days) will be assigned to the randomised treatment. All AEs with an onset before first drug intake will be assigned to ‘screening’ and all AEs with an onset after the residual effect period will be assigned to ‘post-treatment’ (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of AEs will be presented; along with the standard categories presented additional categories for action taken and drug relationship with each compound, worst CTCAE grade and infusion related reaction response. The frequency of patients with AEs will be summarised by treatment, highest CTCAE grade, primary SOC and PT. The SOCs will be sorted alphabetically; PTs will be sorted by decreasing frequency (within SOC). Only AEs with a given CTCAE grade will be displayed in tables showing AEs by worst CTCAE grade. AEs with a missing CTCAE grade will not be displayed in these tables; a footnote will explain that these AEs are not included and a separate listing of them will be produced if required. The following tables will be produced for AEs during the on-treatment period:

- Patients with AEs
- Patients with any related AE

- Patients with related xentuzumab/placebo AEs
- Patients with related everolimus AEs
- Patients with related exemestane AEs
- Patients with SAEs
- Patients with related xentuzumab/placebo SAEs
- Patients with related everolimus SAEs
- Patients with related exemestane SAEs
- Patients with other significant AEs, defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of any study medication
- Patients with AEs leading to death (no CTCAE grade required)
- Patients with AEs leading to discontinuation of xentuzumab/placebo
- Patients with AEs leading to discontinuation of everolimus
- Patients with AEs leading to discontinuation of exemestane
- Patients with AEs leading to dose reduction of everolimus
- Patients with AEs leading to dose interruption of xentuzumab/placebo
- Patients with AEs of Special Interest (refer to Section 5.2.6.1 of the CTP)

In addition some AEs are considered to be of particular importance and special search categories (SSC) of groupings of PTs based on Standardised MedDRA Queries (SMQ), BI customised MedDRA Queries (BIcMQ) or MedDRA High Level Terms (HLT) are defined at the project level, the latest version of which will be used. Details of the current version are provided in the Table 7.8.1: 1 below.

SSCs summaries of patients with AEs and related AEs by treatment, highest CTCAE grade, grouped term and PT will be produced. Similar summaries will be produced for the BIcMQ SARS-COV-2-infections.

Table 7.8.1: 1 Overview of Special Search Categories

Grouped term	**Groupings**
Hepatic impairment	SMQ: Drug related hepatic disorders – comprehensive search
Hyperglycaemia narrow	SMQ: Hyperglycaemia / new onset diabetes mellitus (narrow terms only)
Infusion related reaction	SMQ: Hypersensitivity
Non-infectious pneumonitis	SMQ: Interstitial lung disease (narrow terms only)
Renal insufficiency	SMQ: Acute renal failure, SMQ: Proteinuria, HLT: Glomerulonephritis and nephrotic syndrome
Weight loss	BIcMQ: Weight loss
Neutropenia	SMQ: Haematopoietic leukopenia (narrow terms only)
Stomatitis	BIcMQ: Gastrointestinal mucositis (subsearch1: Stomatitis)

Table 7.8.1: 1 Overview of Special Search Categories (cont.)

Grouped term	Groupings
Asthenia	MedDRA PTs of Asthenia, Fatigue, Lethargy, Malaise, and Decreased activity
Haemorrhage	SMQ: Haemorrhage laboratory terms (narrow terms only), SMQ: Haemorrhage terms (excl. laboratory terms)
Anemia	SMQ: Haematopoietic erythropenia
Thrombocytopenia	SMQ: Haematopoietic thrombocytopenia (narrow terms only)
Thromboembolism	SMQ: Embolic and thrombotic, vessel type unspecified and mixed arterial and venous
Bradycardia	SMQ: Torsade de pointes/QT prolongation, PT of Bradycardia
Rash	BIcMQ: Skin eruptions (subsearch2: Skin rash potentially related to drug use)

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). The same on-treatment periods as considered for the analysis of AEs will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

The focus of the laboratory data analysis will be on the following primary laboratory parameters:

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glucose, creatinine, platelets, cholesterol, triglycerides, neutrophils, lymphocytes, haemoglobin and white blood cells.

Descriptive statistics including baseline, last value on-treatment and change from baseline to last value on-treatment will be produced. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE version 5. The following outputs will be presented for each of the above parameters:

- Transitions of CTCAE grade from baseline to worst on-treatment laboratory value
- Transitions of CTCAE grade from baseline to last on-treatment laboratory value

Patients with no CTCAE grade due to missing laboratory values will be displayed as ‘Missing’. Note with version 5 of the CTCAE grading some of laboratory parameters detailed above (ALT, AST and total bilirubin) can no longer be assigned a grade at baseline. For these parameters, the CTCAE shift tables will be replaced by shift tables of pre-defined categories

based on Upper Limit of Normal (ULN) values. A similar approach will also be adopted for creatinine due the ambiguity of CTCAE grading for grades 2 and 3. The pre-defined categories will follow BI standards (7).

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE Grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available (or CTCAE grading at baseline cannot be assigned) but the patient has a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Hepatic enzyme elevations (potential Hy's law cases):

The assessment of hepatic enzyme elevations will include frequencies of patients falling into the following categories:

- ALT and/or AST ≥ 3 x ULN with total bilirubin ≥ 1.5 x ULN
- ALT and/or AST ≥ 3 x ULN with total bilirubin ≥ 2 x ULN
- ALT and/or AST ≥ 3 x ULN with total bilirubin ≥ 2 x ULN and alkaline phosphatase ≥ 2 x ULN
- ALT and/or AST ≥ 3 x ULN with total bilirubin ≥ 2 x ULN and alkaline phosphatase < 2 x ULN
- Maximum ALT: ≥ 3, ≥ 5, ≥ 10 and ≥ 20 x ULN
- Maximum AST: ≥ 3, ≥ 5, ≥ 10 and ≥ 20 x ULN
- Maximum ALT and AST: ≥ 3, ≥ 5, ≥ 10 and ≥ 20 x ULN
- Maximum total bilirubin: ≥ 1.5 and ≥ 2 x ULN
- Maximum alkaline phosphatase: ≥ 1.5 and ≥ 2 x ULN

Where applicable for defining the above, events can occur in any order, but must occur within 30 days of each other, with an increase of either ALT or AST being the trigger for evaluations. Along with summaries of the above supportive eDISH plots will also be produced.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

In order to investigate potential bradycardia a shift table of heart rate (<60 bpm, ≥60 bpm) at baseline by lowest and last on-treatment heart rate (<60 bpm, ≥60 bpm) will be produced. Other suitable summaries may be produced to investigate potential bradycardia.

7.8.4 Electrocardiogram

Electrocardiogram (ECG) results will only be listed; any clinically significant abnormalities will be recorded as either a concomitant diagnosis or an AE.

7.8.5 Others

Not applicable.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-HTG-0035:* "How to Guide: Handling of Missing and Incomplete AE dates"
3.	*BI-KMED-BDS-HTG-0045:* "How to Guide: Standards for Reporting of Clinical Trials and Project Summaries"
4.	*BI-KMED-BDS-QRG-0010:* "Quick Reference Guide: Preparation of tables for results disclosure
5.	*BI-KMED-BDS-HTG-0066:* "How to Guide: Analysis and Presentation of Adverse Event Data from Clinical Trials"
6.	*BI-KMED-BDS-HTG-0042:* "How to Guide: Handling, Display and Analysis of Laboratory Data"
7.	*BI-KMED-BDS-HTG-0036:* "How to Guide: CTCAE Grading for Laboratory Values"

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**06-OCT-20**	[redacted]	None	This is the final TSAP
2	**23-AUG-21**		5.2.2	Clarified the minimum duration of DC.
			[redacted]	
			6.7	Allowing baseline PRO assessments measured on the same day of starting study treatment.
			[redacted]	
			[redacted]	
			7.8.1	Additional AE table added for 'any related' AEs. Update to SSCs.

APPROVAL / SIGNATURE PAGE

Document Number: c33744236 **Technical Version Number:2.0**

Document Name: 8-01-tsap

Title: XeneraTM 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Project Statistician	[redacted]	23 Aug 2021 11:45 CEST
Approval		23 Aug 2021 17:23 CEST
Approval		23 Aug 2021 23:01 CEST
Approval		24 Aug 2021 16:48 CEST
Author-Trial Statistician		24 Aug 2021 16:52 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed