CONFIDENTIAL INFORMATION

Statistical Analysis Plan (SAP)

FINAL Version 3.0
15th February 2024

EudraCT Number	2019-001739-29
Protocol Number	MedOPP243 (DEBBRAH)
Protocol Version Date	V5.0, 18-JAN-2022
Title	A Multicenter, Open-Label, Single-Arm, Multicohort Phase II Clinical Trial of Trastuzumab Deruxtecan (DS-8201a) in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer with Brain Metastases and/or Leptomeningeal Carcinomatosis. DS-8201a for trEatment of aBc, BRain mets, And Her2[+] disease –The DEBBRAH Study–
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STATISTICAL ANALYSIS PLAN (SAP)

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Signature Page

EudraCT Number: **2019-001739-29**
Protocol Number: **MedOPP243**

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SAP Revision History:

Version Number	Date	Changes
1.0	08th February 2021	New
2.0	11th June 2021	Changes according to protocol version 4.0, 30 Dec 2020
3.0	15th February 2024	Changes according to protocol version 5.0, 18 Jan 2022

LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced Breast Cancer
AE	Adverse Event
AESI	Adverse Event of Special Interest
ARO	Academic Research Organization
ATC	Anatomical Therapeutic Chemical
BC	Breast Cancer
BM	Brain Metastases
BPM	Beats Per Minute
CB	Clinical Benefit
CBR	Clinical Benefit Rate
CI	Confidence Interval
CNS	Central nervous Nervous System
CPMP	Committee for proprietary Proprietary medicinal Medicinal productsProducts
CR	Complete Response
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ER	Endocrine Receptors
EUDRACT	European Clinical Trials Database
FAS	Full Analysis Set
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IQR	Interquartile Range
LMC	Leptomeningeal Carcinomatosis
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MEDDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression Disease
PFS	Progression-Free Survival
PP	Per Protocol set
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred Term
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases criteria
RD	Recommended Dose
RDI	Relative Dose Intensity

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Relative Risk
RS	Recurrence Score
SAE	Serious Adverse Event
SAIL	SAIL S.L.L.
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Steering Committee
SD	Stable Disease / Standard Deviation
SI	International System of Units
SOC	System Organ Class
SRS	Stereotactic Radiosurgery
TEAE	Treatment emergent adverse event
TLF	Tables, listings and figures
TTP	Time To Progression
TTR	Time To Response
UMVUE	Uniformly Minimum Variance Unbiased Estimator
WBRT	Whole Brain Radiation Therapy
WHO	World Health Organization

TABLE OF CONTENTS

1 INTRODUCTION

1.1 General

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Protocol version Date: version 4.0, 30 Dec 2020
- eCRF release version date: version 5.0, 06-Nov-2020

1.2 Type of Study

This is a multicenter, international, open-label, single-arm, multicohort, two-stage optimal Simon's design, phase II clinical trial.

1.3 Study Design

This is a multicenter, open-label, single-arm, multicohort, two-stage optimal Simon's design, phase II clinical trial that is designed to evaluate the safety, tolerability, and efficacy of trastuzumab deruxtecan (DS-8201a) for pretreated patients with unresectable locally advanced or metastatic HER2-positive or HER2-low expressing BC with untreated or treated BMs or LMC.

Patients will be assigned to one of the following five study cohorts:

- **Cohort 1 (N=8):** HER2-positive BC with non-progressing BM (after WBRT and/or SRS and/or surgery)
- **Cohort 2 (N=10):** HER2-positive or HER2-low BC with asymptomatic, untreated BMs
- **Cohort 3 (N=7):** HER2-positive BC with progressing BMs after local treatment
- **Cohort 4 (N=7):** HER2-low expressing BC with progressing BMs after local treatment
- **Cohort 5 (N=7):** HER2-positive or HER2-low expressing BC with LMC

Enrolment will start for all cohorts at the same time.

A futility interim analysis has been planned in cohorts 1, after the recruitment of 4 patients. At the interim analysis, if the number of patients achieving the primary endpoint is equal or less than futility boundary in each cohort, the accrual in the cohort must be stopped. The stopping rules for each cohort are:

- **Cohort 1:** All 4 patients with progressive disease or death at 16 weeks.

Additionally, a feasibility interim analysis has been planned in each cohort. At the halfway point of the recruitment period, the Steering Committee will evaluate if the accrual objective for the first stage was achieved in each study cohorts (4, 5, 3, 3 and 3 patients for cohorts 1, 2, 3, 4 and 5, respectively). If this accrual objective has not achieved in a cohort, the Steering Committee will propose a corrective action plan or finalize the study in this cohort.

For estimation of PFS, TTR, ORR, DOR, CBR, OS, 12-week CNS disease stabilization, and best percentage of change in target tumor lesions, tumor assessment will be based on RANO-BM criteria and on RECIST v.1.1 criteria for estimation in non-target tumor lesions (Brain MRI and chest/pelvis and abdomen CT) (see Appendix 1) and will be performed every six weeks (± 3 days) for the first six months and, thereafter, every nine weeks (± 5 days) until disease progression. If patient interrupts treatment without confirmation

on disease progression, tumor assessment will continue until event is confirmed unless patient starts new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

In addition, for patients allocated in the study cohort 5, CSF analysis will be performed at base line, every three weeks for 12 weeks (corresponding to the first 5 cycles of treatment) and every six weeks thereafter and at the time of disease progression, treatment discontinuation, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

Bone scans will be only performed every 24 weeks (± 7 days) for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression.

Safety assessments will include the incidence, nature, and severity of AEs and laboratory abnormalities graded per the NCI-CTCAE v.5.0. Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry, coagulation, and pregnancy test (see Appendix 1 of the protocol).

To perform exploratory studies, patients must have consented to provide sufficient newly obtained tumor biopsy tissue except for patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. Patients will also be given the option of providing a tissue biopsy sample obtained at disease progression for exploratory analyses; this decision will not affect overall study eligibility. Furthermore, patients have agreed to give blood samples (liquid biopsy) at the time of inclusion, after two cycles of study treatment, and upon progression or study termination. Moreover, patient allocated in the study cohort 5, must have consented to provide CSF samples for their analysis at baseline, every three weeks for 12 weeks (corresponding to the first 5 cycles of treatment) and every six weeks thereafter and at the time of disease progression or study termination.

1.4 Study Flow Chart

Summary of study assessments is reported in Appendix 1 (schedule of Assessments) of the protocol.

Study Period	**Screening Period**		**Treatment Period***		**EoT**	**Post-Treatment Follow-Up Period**
Day	**-28 to -1**	**-14 to -1**	**Cycle 1 Day 1**	**Cycle X Day 1**	**Within 40 days (± 7 days) after last dose of study treatment**	**Follow-up every 12 weeks (±14 days)[19]**
Informed Consent Form[1]	X					
HER2 status[2]	X					
Medical history[3]	X					
Physical examination		X	X	X	X	
ECOG performance status		X	X	X	X	
Weight and vital signs[4]		X	X	X	X	
Concomitant medication reporting[5]		X	X	X	X	
AE reporting[6]		X	X	X	X	
12-lead ECG[7]		X	X[7]	X[7]	X[7]	
ECHO or MUGA scan[8]	X			X[8]		
Troponin[9]		X			X	
Ophthalmologic assessments[10]	X				X	
pSO_2[11]		X	X	X	X	
Tumor assessments[12]	X			X[12]	X[12]	
Tumor samples (for exploratory study)[13]	X (if feasible)				At the time of progression (if feasible)	
Blood samples (for exploratory study)[14]	X			X	At the time of progression	
Hematology		X	X	X	X	
Chemistry[15]		X	X	X	X[15]	

Study Period	Screening Period		Treatment Period*		EoT	Post-Treatment Follow-Up Period
Day	-28 to -1	-14 to -1	Cycle 1 Day 1	Cycle X Day 1	Within 40 days (± 7 days) after last dose of study treatment	Follow-up every 12 weeks (±14 days)[19]
INR/PT and aPTT		X	X	X	X	
Urinalysis		X				
Pregnancy test[16]		X	X	X	X[16]	
Viral serology[17]		X				
Trastuzumab deruxtecan (DS-8201a) administration			X	X		
Review patient diary			X	X		
PRO assessments[18]		X	X	X	X	X
Survival status					X	X
Post-study anticancer therapy					X	X

AEs = Adverse events; aPTT = Activated partial thromboplastin time; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; HER2 = Human Epidermal Growth Factor Receptor 2; INR = International normalized ratio; MUGA = Multiple-Gated Acquisition; PRO QOL: Patient reported outcome-Quality of life; PT = Prothrombin time.
***** All visits must occur within ± 2 working days. Assessments scheduled for Days 1 each cycle must be performed within 48 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, to confirm to the patient if treatment can be followed up.

1. **Informed Consent Form:** Signed written Informed Consent Form obtained prior to any trial-specific procedure.
2. **HER2 status:** Local confirmation of HER2-positive status.
3. **Medical history:** Complete medical history and demographics (including age, gender, and ethnic origin). All medications taken in the last 28 days prior to enrolment will be collected.
4. **Weight and vital signs**: Weight, height (only at screening), respiratory rate, blood pressure measurements (systolic and diastolic), pulse rate, and body temperature (oral, axillary, or tympanic temperature). Vital signs should be measured before and after the end of the infusion on Day 1 of cycle 1 to 3 and only before infusion on Day 1 of subsequent cycles.
5. **Concomitant medication reporting:** Relevant concomitant medication will be recorded at screening and on an ongoing basis.
6. **AE reporting:** All AEs occurring during the trial and until 30 days after treatment discontinuation visit (EoT visit) have to be recorded with grading according to the NCI–CTCAE v.5.0 criteria.
7. **12-lead ECG:** ECGs (will be taken in triplicate, in close succession, while in a supine/semi-recumbent position) to be collected at screening (within 14 days before enrollment). Subsequent ECGs will be performed in triplicate in close succession if an abnormality is noted. ECGs will be taken at every 4th cycle.
8. **ECHO or MUGA scan:** LVEF assessment will be performed at screening (within 28 days before enrollment), Cycle 5 Day 1, and on Day 1 of every four cycles (±7 days) thereafter (e.g., Cycles 9, 13, 17, etc.) while on treatment, and at the EoT visit. *Note: the same test must be used for the subject throughout the study.*
9. **Troponin**: Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening, EOT, and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. Subjects may also have local troponin testing as clinically indicated during the treatment phase based on subject reported cardiac symptoms. If ECG is abnormal, follow institutional guidelines. If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3.
10. **Ophthalmologic assessments**: They will include visual acuity testing, slit lamp examination and fundoscopy will be performed at screening (within 28 days before enrollment), at EoT and if patient present sign or symptoms of ophthalmologic problems.
11. **pSO_2:** pulse oximetry will be performed on Day 1, of every cycle, and until the safety follow-up visit 40 days after last dose. During Cycle 1, pulse oximetry will be assessed on Day 1 prior and after infusion of trastuzumab deruxtecan, on Day 8 and Day 15. On Day 1 pre-dose measurements will be taken thereafter.
12. **Tumor assessments:** Baseline assessments of the chest, abdomen, and pelvis (preferably CT or MRI in case of contrast allergy) must be performed no more than 28 days before the first dose of study treatment. Post-baseline assessments will be performed every 6 weeks (± 3 working days) from the first dose of study treatment for the first 6 months of treatment and every 9 weeks (± 5 working days) thereafter using the same imaging method and where possible obtained at the same institution for an individual patient as used during screening until progression disease or EoS. Bone scans will be only performed every 24 weeks (± 7 working days) for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression. If a bone scan was performed > 28 days but ≤ 60 days prior to start of study treatment, the bone scan does not need to be repeated. Brain imaging (MRI) during the trial should be performed every 6 weeks [± 3 working days] from the first dose of study treatment for the first 6 months, and, thereafter, every 9 weeks [± 5 working days]) unless clinically suspected brain progression. Patients who discontinue treatment without evidence of disease progression will be followed every nine weeks (± 5 days) for tumor assessments until documented progression, elective withdrawal from the study, the start of new anti-cancer treatment, or study completion or termination. *Note: For patients included in the study cohort 5, axis MRI and spinal tap for CSF collection must also be performed, at baseline, every 3 weeks for 12 weeks (corresponding to the first 5 cycles of treatment), every 6 weeks thereafter, and at the time of treatment progression or study termination.*
13. **Tumor samples (for exploratory study):** A tissue sample should be provided at baseline (if feasible) from breast primary tumor or metastases amenable to biopsy (at sites of locoregional recurrence [skin, chest wall, breast or lymph nodes], or distant recurrence [bone, liver, lung or abdomen]) that will be obtained between progression to the prior regimen and inclusion in the study. Patients for whom tissue sample cannot be obtained (e.g., non-measurable disease, inaccessible tumor or subject safety concern) may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. If feasible, an additional tissue sample should be collected at the end of treatment visit for patients who discontinue treatment due to disease progression.
14. **Blood samples (for exploratory study):** Blood samples are required for all patients at the time of inclusion, after two cycles of study treatment, and upon progression or study termination.
15. **Hematology/chemistry:** Cycle 1 Day 1 hematology and chemistry panel assessments are not required if the screening hematology and chemistry panel was performed at screening within 48 hours prior to start of study treatment. On cycle 1, hematology, chemistry and coagulation assessment must be repeated on day 8 and day 15.
16. **Pregnancy test:** A serum pregnancy test at screening to confirm eligibility in the trial and within one week prior to start of study medication (with result available prior to dosing). This assessment does not need to be repeated at Cycle 1 Day 1 if it was performed at screening within 48 hours prior to start of study treatment. Thereafter, repeat pregnancy tests (urine or serum test per institutional guideline) before infusion of each cycle and at end of treatment. A serum test should be performed to confirm any positive urine pregnancy test during the trial.

17. **Viral serology:** Human Immunodeficiency Virus, Hepatitis B surface Antigen (HBsAg), total Hepatitis B core Antibody (HBcAb), Hepatitis C Virus antibody; additional tests for Hepatitis B Virus DNA or Hepatitis C Virus RNA will be required within 28 days before enrollment to confirm eligibility. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
18. **PRO Assessments:** The EORTC-QLQ-C30 and the EORTC-QLQ-BR23 questionnaires will be completed at baseline, Day 1 of cycles 2-4, then on Day 1 of every other subsequent cycle starting with cycle 6 (e.g., cycles 6, 8, 10, etc.), End of Treatment visit and during follow-up period until start of anticancer therapy.

1.5 Sample Size

A maximum of 39 patients with pretreated unresectable locally advanced or metastatic HER2-positive or HER2-low expressing patients will be recruited following the five study cohorts:

Cohort 1: N = 8

Cohort 2: N = 10

Cohort 3: N = 7

Cohort 4: N = 7

Cohort 5: N = 7

The sample size calculations were described in the protocol using the following wording:

The primary endpoint for this study in the cohort of patients with stable BMs (cohort 1) is the PFS at 16 weeks. The primary endpoint for this study in the cohorts of patients with untreated or progression BMs (cohorts 2 to 4) is the best ORR-IC. The primary endpoint for this study, in the cohorts of patients with LMC (cohort 5) is the OS.

The trial uses a two-stage optimal Simon's design for the cohort 1, a one-stage A'Hern design for the cohorts 2 to 4, and a one-stage survival design for the cohort 5. The analysis in the cohort 1 will be one-sided, based on stochastic ordering of uniformly minimum variance unbiased estimator (UMVUE). The analyses in the cohorts 2 to 4 will be one-sided, based on stochastic binomial exact test. The sample size for the LMC cohort was based on a one arm time-to-event design. The analysis will be based on maximum likelihood exponential test.

The local type I and II errors for all designs will be 0.05 and 0.2, respectively.

- ***Cohort 1***

We hypothesized that excluding a rate of patients without PFS events ≤5% while targeting an improvement of patients without PFS events to ≥40% would be an optimal approach to evaluation of the study strategy. Non evaluable patients enrolled in the initial stage can be replaced. We will accrual 4 patients in the first stage. We will stop this cohort if all 4 patients progressed at 16 weeks. Otherwise, 4 additional patients will be accrued for a total of 8. At least 2 patients without progressive disease at 6 months among 8 patients enrolled will be adequate to justify the investigation of this strategy in further clinical trials.

- ***Cohort 2***

We hypothesized that excluding an ORR-IC ≤5% while targeting an improvement of the ORR to ≥40% would be an optimal approach to evaluation of the study strategy. At least 3 patients with overall response among 10 patients will be adequate to justify the investigation of this strategy in further clinical trials.

- ***Cohort 3***

We hypothesized that excluding an ORR-IC ≤5% while targeting an improvement of the ORR to ≥40% would be an optimal approach to evaluation of the study strategy. At least 2 patients with overall response among 7 patients will be adequate to justify the investigation of this strategy in further clinical trials.

- ***Cohort 4***

We hypothesized that excluding an ORR-IC ≤5% while targeting an improvement of the ORR to ≥40% would be an optimal approach to evaluation of the study strategy. At least 2 patients with overall response among 7 patients will be adequate to justify the investigation of this strategy in further clinical trials.

- ***Cohort 5***

The one-sided maximum likelihood exponential test has an 80% power to detect a 4-month increase in median OS over a 2-months median OS. We scheduled an 18-month accrual period and 6-month of follow-up period. At least 3 patients will be accrued in the first stage to evaluate the feasibility of this cohort. A total of 7 patients will be accrued in this cohort.

Stopping boundary based on accrual:

At the halfway point of the recruitment period, the steering committee will evaluate if the accrual objective for the first stage was achieved in every study cohorts (4, 5, 3, 3 and 3 patients for cohorts 1, 2, 3, 4 and 5, respectively). If this accrual objective has not achieved in a cohort, the Steering Committee will propose a corrective action plan or finalize the study in this cohort.

2 STUDY OBJECTIVES

2.1 Cohort 1

2.1.1 Primary Objective

- To assess efficacy –defined as 16 weeks PFS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 of trastuzumab deruxtecan (DS-8201a) in patients with pretreated unresectable locally advanced or metastatic HER2-positive BC with non-progressing BM (after WBRT and/or SRS and or surgery).

2.1.2 Secondary Objectives

- To assess efficacy –defined as PFS, ORR, CBR, time to response (TTR), duration of response (DOR), and best percentage of change in tumor burden per RANO-BM (for IC lesions) and RECIST 1.1 (extracranial lesions and overall lesions)–after treatment with trastuzumab deruxtecan (DS-8201a) in this population.
- To assess OS in this population.
- To assess the safety and tolerability of trastuzumab deruxtecan (DS-8201a) in this population by NCI-CTCAE v.5.0.

2.1.3 Exploratory Objectives

- To assess patient [redacted] using the [redacted] and its [redacted] this population.
- To evaluate predictive or prognostic biomarkers (plasma and/or tissue and/or CSF) associated with disease activity status or response to treatment in this population.
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression tumor and/or blood and/or CSF samples from this population.

2.2 Cohorts 2, 3 and 4

2.2.1 Primary Objective

- To assess efficacy -defined as intracranial overall response rate (ORR-IC) per RANO-BM of trastuzumab deruxtecan (DS-8201a) in patients with pretreated unresectable locally advanced or metastatic BC:
  - **Cohort 2:** HER2-positive or HER2-low expressing with untreated BMs
  - **Cohort 3:** HER2-positive with progressing BMs after local treatment
  - **Cohort 4:** HER2-low expressing with progressing BMs after local treatment.

2.2.2 Secondary Objectives

- To assess efficacy –defined as PFS, CBR, TTR, DOR, and best percentage of change in tumor burden per RANO-BM (for IC lesions) and RECIST 1.1 (for extracranial lesions and overall lesions); and ORR per RECIST 1.1 (for extracranial lesions and overall lesions).
- Time to WBR and/or SRS (only for cohort 2), defined as the time from the treatment initiation to time of CNS disease progression that requires treatment with WBR and/or SRS, and determined locally by the investigator through the use of RANO-BM and RECIST 1.1 criteria.
- To assess OS.
- To assess the safety and tolerability of trastuzumab deruxtecan (DS-8201a) by NCI-CTCAE v.5.0.

2.2.3 Exploratory Objectives

- To assess [redacted] using the [redacted] and its [redacted] in study cohorts 2, 3, and 4.
- To evaluate predictive or prognostic biomarkers (plasma and/or tissue and/or CSF) associated with disease activity status or response to treatment in study cohorts 2, 3, and 4.
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression tumor and/or blood and/or CSF samples from patients of study cohorts 2, 3, and 4.

2.3 Cohort 5

2.3.1 Primary Objective

- To assess efficacy –defined as OS– of trastuzumab deruxtecan (DS-8201a) in patients with pretreated unresectable locally advanced or metastatic HER2-positive or HER2-low expressing BC with LMC.

2.3.2 Secondary Objectives

- To assess efficacy -defined as PFS, ORR, CBR, TTR, DOR, and best percentage of change in tumor burden per RANO-BM (IC lesions) and RECIST 1.1 (extracranial lesions and overall lesions).
- To assess the safety and tolerability of trastuzumab deruxtecan (DS-8201a) by NCI-CTCAE v.5.0.

2.3.3 Exploratory Objectives

- To assess [redacted] using the [redacted] and i[redacted], [redacted] in this population.
- To evaluate predictive or prognostic biomarkers (plasma and/or tissue and/or CSF) associated with disease activity status or response to treatment in this population.
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression tumor and/or blood and/or CSF samples from this population.

3 DEFINITION OF ENDPOINTS

3.1 Cohort 1

3.1.1 Primary Endpoint

- 16 weeks-PFS, defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first. Progression will be determined locally by the investigator through the use of Response Assessment in Neuro- Oncology Brain Metastases (RANO-BM) criteria (IC lesions) and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.

3.1.2 Secondary Endpoints

- PFS defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first. Progression will be determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- ORR, defined as a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- CBR, defined as an objective response (CR or PR), or stable disease (SD) for at least 24 weeks, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- TTR, defined as the time from the treatment initiation to time of the first objective tumor response observed for patients who achieved a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- OS, defined as the time from treatment initiation to death from any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.
- Maximum Tumor Shrinkage, best percentage of change from baseline in the size of tumors, defined as the biggest decrease, or smallest increase if no decrease will be observed and determined locally

by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.

3.1.3 Safety Endpoints

- Patient safety and AEs will be evaluated using the NCI-CTCAE v.5.0.

  All AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the treatment.

3.1.4 Exploratory Endpoints

- Overall change from baseline in [redacted], [redacted] and [redacted]; Time to [redacted] in [redacted]; Time to [redacted] in [redacted]; Time to [redacted].
- Relationship between tissue- and/or blood- and/or CSF-based biomarkers and patient clinical characteristics (e.g., baseline features) and outcome (e.g., duration of [redacted]).

3.2 Cohorts 2, 3 and 4

3.2.1 Primary Endpoint

- ORR-IC, defined as a complete response (CR) or partial response (PR), and determined locally by the investigator through the use of RANO-BM criteria.

3.2.2 Secondary Endpoints

- PFS, defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first. Progression will be determined locally per RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- ORR, defined as a CR or PR, determined locally by the investigator through the use of RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- CBR, defined as an objective response (CR or PR), or SD for at least 24 weeks, and determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- TTR, defined as the time from the treatment initiation to time of the first objective tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, determined locally by the investigator though the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1. for both extracranial lesions and overall (IC and extracranial) lesions.
- OS, defined as the time from treatment initiation to death from any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.
- Maximum Tumor Shrinkage, best percentage of change from baseline in the size of tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, and determined

locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.

- Only cohort 2: Time to WBRT and/or SRS, defined as the time from treatment initiation to CNS disease progression that requires treatment with WBRT and/or SRS, according RANO-BM and RECIST 1.1 criteria.

3.2.3 Safety Endpoints

- Patient safety and AEs will be evaluated using the NCI-CTCAE v.5.0.

  All AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the treatment.

3.2.4 Exploratory Endpoints

- Overall change from baseline in [redacted], [redacted] and [redacted]; Time to [redacted] in [redacted]; Time to [redacted] in [redacted]; Time to [redacted] [redacted].
- Relationship between tissue- and/or blood- and/or CSF-based biomarkers and patient clinical characteristics (e.g., baseline features) and outcome (e.g., duration of [redacted]).

3.3 Cohort 5

3.3.1 Primary Endpoint

- OS, defined as the time from treatment initiation to death from any cause.

  Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

3.3.2 Secondary Endpoints

- ORR, defined as a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- CBR, defined as an objective response (CR or PR), or SD for at least 24 weeks, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- PFS, defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first during at least first 12 months. Progression will be determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (ICand extracranial) lesions.
- TTR, defined as the time from the treatment initiation to time of the first objective tumor response observed for patients who achieved a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.

- Maximum Tumor Shrinkage, best percentage of change from baseline in the size of tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, and determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.

3.3.3 Safety Endpoints

- Patient safety and AEs will be evaluated using the NCI-CTCAE v.5.0.

  All AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the treatment.

3.3.4 Exploratory Endpoints

- Overall change from [redacted], [redacted] and [redacted]; Time to [redacted] in [redacted]; Time to [redacted] in [redacted]; Time to [redacted].
- Relationship between tissue- and/or blood- and/or CSF-based biomarkers and patient clinical characteristics (e.g., baseline features) and outcome (e.g., duration of [redacted]).

4 ANALYSIS SETS

The following sets will be analyzed:

- **Screening:** Patients who were present at the screening visit.
- **Safety and FAS (Full Analysis Set) Set:** The safety/FAS set includes patients who received at least one dose of study treatment.

  Efficacy and Safety endpoints will be analyzed on the Safety/FAS set.
- **Exploratory Analysis Set:** Exploratory analyses will be performed on those patients in the safety set who consented to participate in the exploratory research program and were evaluable for exploratory endpoints.

  Exploratory analysis will be performed on exploratory evaluable set.

5 STATISTICAL METHODS

5.1 General Methodology

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, maximum, and first and third quartiles, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places

reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n as the denominator, for frequency tables not assessed by time point the set will be used as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g., clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a p-value is only presented to four decimal places (by SAS) it will not be rounded again but will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001".

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 5% will be used for confidence intervals.

For binary endpoints, the 95% confidence intervals (CIs) will be constructed based on an exact binary distribution.

For time to event endpoints the Kaplan-Meier method will be applied. Number and proportion of events, median survival time and survival rates, with corresponding 95%Cl will be calculated.

All scores and change from baseline will be summarized in terms of the number of observations, mean, standard deviation, 95%CI of mean, median, range and interquartile range. We will examine the residuals to assess model assumptions.

All report outputs will be produced using SAS® version 9.4 version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document.

5.2 Subject Disposition

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening set, the number of patients eligible to participate in the study, and number of screen failures.
- Number and percent of subjects in each of the analysis sets.
- Number and percent of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of subjects excluded from each of the analysis sets along with reason for exclusion.
- Study termination:
  - Number and percent of subjects who completed the study.
  - Frequency of premature termination reasons.
  - Listing of all dropouts along with reason for termination, dose level and time of termination.
- Follow-up time (months), defined as the time from start dose until the last available follow-up date.
- Follow-up Dates:
  - Database cut-off date.

- Start date of treatment dose of the first patient.
- Start date of treatment dose of the last patient.
- End date of treatment dose of the last patient.
- End date of follow-up of the last patient.

No statistical tests are planned for these data.

5.3 Baseline Characteristics

Baseline characteristics will be provided by arm and overall, for the Safety/FAS set.

Descriptive statistics, including number of subjects, mean, standard deviation (SD), median and range for continuous variables and frequency and percent for categorical variables will be provided.

Baseline Characteristics:

- Demographic characteristics
- Oncological history
- Medical history
- History of Breast Cancer
- Previous early disease treatment
- Previous advanced/metastatic disease treatment
- HER2 and HR status
- Physical examination
- ECOG
- Vital Signs
- 12-lead electrocardiogram
- LVEF Evaluation
- Tumor assessment
- Prior concomitant medication

No statistical tests are planned for these data.

A by-subject listing of all demographic and other baseline characteristics will be provided.

5.4 Response Evaluation Criteria

Lesions will be classified as target and non-target at baseline, in accordance with RANO-BM criteria (for CNS lesions) and RECIST v.1.1 criteria (in case of non-CNS lesions).

5.4.1 RANO-BM Criteria

Overall response evaluation according to RANO-BM Criteria (Lin et al. 2015) will be obtained from CNS target lesion response, CNS non-target lesion response, CNS new lesions, corticosteroids, clinical status as follows:

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 2: Summary of the response criteria for CNS metastases proposed by RANO-BM

CNS Target lesions:

- CR: Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.
- PR: At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- PD: At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
- SD: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

CNS Non-target lesions:

- CR: Requires all the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
- Non-CR or non-PD: Persistence of one or more non-target CNS lesion or lesions.
- PD: Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

5.4.2 RECIST v.1.1 Criteria

Overall response according RECIST v1.1 will be obtained from target lesion response, non-target lesion response and new lesions, as follows:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5.5 Response Efficacy Definitions

- Best Overall Response, defined as the best overall response recorded from the start of the study treatment until 35 days after last dose administration date and confirmation of response is not required.
    - When CR or PR is the best response across all time points, then best overall response will be CR or PR respectively.
    - When SD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
    - When SD is the best response for < 24 weeks the best overall response will be SD < 24 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for < 24 weeks the best overall response will be SD < 24 w.
    - When PD is the best response across all time points, best overall response will be PD.
    - When there is no evaluable tumor assessments best overall response will be NE.
- PFS is defined as the time from start dose until death by any cause or objective tumor progression or clinical disease progression. Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. Censoring rules are specified below:

Situation	Date of progression or censoring	Outcome
Progression documented between scheduled visits	Earliest of: • Date of assessment by investigator (if progression is based on clinical criteria); or • Date of assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).	Progressed
Death before first progression disease (PD) assessment	Date of death.	Progressed
Death between adequate assessment visits	Date of death.	Progressed
No progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions.	Censored
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions.	Censored

5.5.1 Primary Efficacy Endpoint Definitions

The primary endpoint for this study, in the cohort of patients with stable BMs (cohort 1) is the PFS at 16 weeks. PFS is defined as the number of patients without PD or death at 16 weeks (non- PFS event) divided by the number of patients in the analysis set. Progression will be assessed based on local Investigator's assessment according RANO-BM criteria (for IC lesions) and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions. We will consider a patient as PFS event if accomplish any of both criteria for progression or die from any cause in absence of documented progressive disease.

The primary endpoint for this study, in the cohorts of patients with untreated or progression BMs (cohorts 2 to 4) is the best ORR-IC. The ORR-IC is defined as the number of patients with CR or PR divided by the number of patients in the analysis set. Best overall response will be assessed based on local Investigator's assessment according RANO-BM criteria. We will consider a patient as responder if accomplish the criteria at the same tumor evaluation. Patients without tumor response evaluation will be considered as no responder.

The primary endpoint for this study, in the cohorts of patients with LMC (cohort 5) is the OS. OS is defined as the time from treatment initiation to death from any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

5.5.2 Secondary Efficacy Endpoints Definitions

The secondary efficacy variables are PFS, ORR, DOR, TTR, OS and Maximum Tumor reduction:

- ORR in cohort 1 to 4, as defined in secondary endpoint section.
- OS in cohorts 1 to 4, as defined in secondary endpoint section.

- PFS in cohorts 2 to 4, as defined in secondary endpoint section.
- PFS in cohorts 2 to 4, defined as time to event outcome. PFS is defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first. Progression will be determined locally per RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions. We will consider a patient as PFS event if accomplish any of both criteria for progression or die from any cause in absence of documented progressive disease.
- CBR in cohorts 1 to 4, CBR is defined as an objective response (CR or PR), or SD for at least 24 weeks, and determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- TTR in Study cohort 1. TTR, defined as the time from the treatment initiation to time of the first objective tumor response observed for patients who achieved a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- TTR in study cohorts 2 to 4. TTR defined as the time from the treatment initiation to time of the first objective tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a CR or PR, determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- DOR in study cohorts 1 to 4, DOR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined locally by the Investigator through the use of RANO-BM criteria for IC lesiosn and RECIST v.1.1 criteria, for both extracranial lesions and overall (IC and extracranial) lesions. In case of the patient first reaching PR and later CR, the duration of CR will be measured and reported separately, starting from the date when first documented, and ending when a progressive disease is diagnosed, or the patient dies.
- Best percentage of change from baseline in the size of tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, and determined locally by the investigator through the use of RANO-BM criteria for IC lesions and RECIST criteria v.1.1 for both extracranial lesions and overall (IC and extracranial) lesions.
- Maximum tumor reduction in study cohorts 1 to 4. Maximum tumor reduction is defined as the biggest decrease, or smallest increase if no decrease will be observed, as determined locally by the Investigator through the use of RANO-BM criteria.

5.6 Efficacy Analysis

5.6.1 Primary Efficacy Analysis

All primary efficacy analyses will be analyzed at feasibility interim (see section 5.8.2) and final analysis.

PFS at week 16 in cohort 1 will be calculated with UMVUE method (1). The p-value and 95% confidence will be calculated based on Koyama and Chen, 2017 (2). We will use the functions published on the R library "OneArmPhaseTwoStudy" November 13, 2017 (3). The R codes of these functions are described in

appendix 7.1.1 Additionally, the 95% exact (Pearson-Clopper) confidence intervals and p-value under exact binomial test will be reported.

In cohorts 2, 3, and 4 the ORR-IC with its 95% exact (Pearson-Clopper) confidence intervals and p-value under exact binomial test will be reported. At final analysis it will be declared positive if the null hypothesis (H0: ORR-IC ≤5%) is beyond the lower boundary of the confidence interval. The one-sided p-value will be obtained based on exact binomial test at a nominal alpha level of 0.025. The SAS code is described in appendix 7.1.2.

For overall survival (OS) in cohort 5 the p-value will be obtained from one-sided maximum likelihood exponential test. The R code function is described in appendix 7.1.3 Additionally, the number and proportion of events, median survival time and survival rates, with corresponding 95% CI, by Kaplan-Meier method will be reported.

5.6.2 Decision Rules and Adjustment of Alpha for Primary Endpoint

The study would be defined as positive at final analysis in the study **cohort 1** if the rate of patients without PFS events in the trastuzumab deruxtecan (DS-8201a) arm is statistically significantly greater ($p<0.05$) than expected under the null hypothesis (H0: % of pts without PFS events ≤ 5%). The analysis will be one-sided, based on stochastic ordering of UMVUE.

The UMVUE for the response rate, the p-value and the 95% confidence intervals will be calculated using the functions published on R library "OneArmPhaseTwoStudy" November 13, 2017 (3). The R codes of these functions are described in appendix section 7.1.

The study would be defined as positive at final analysis in the study **cohorts 2, 3 and 4,** if the ORR-IC in the trastuzumab deruxtecan (DS-8201a) arm is statistically significantly greater ($p<0.05$) than expected under the null hypothesis (H0: ORR-I-IC ≤ 5%). The analysis will be one-sided, based on binomial exact test.

The study would be defined as positive at final analysis in the study **cohort 5**, if the median overall survival in the DS-8310a arm is statistically significantly greater ($p<0.05$) than expected under the null hypothesis (H0: median OS ≤ 2 months). The analysis will be based on the one-sided maximum likelihood exponential test.

5.6.3 Secondary Efficacy Analysis

Secondary efficacy analyses will be reported in the FAS set and separately by each cohort.

For binary endpoints, the number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.

For time to event endpoints the Kaplan-Meier method will be applied. Number and proportion of events, median survival time and survival rates, with corresponding 95%CI, will be calculated.

Maximum tumor shrinkage will be described with the median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions will be provided.

For all tests, we will use two-sided p-values with alpha ≤ 0.05 level of significance. P-values emerging from these analyses will not be interpreted in a confirmative sense; they will be considered of descriptive nature only.

5.6.4 Handling of Missing Efficacy Data

Study variables could be missing for patients who withdrawn from the trial or for specific visits. We will report reasons for withdrawal.

Patient with missing in response outcomes (ORR and CBR or without PFS events at 6 months) will be considered as no responders, or last observation will be carried forward (maximum tumor reduction). Patients without any post-baseline assessment will be considered as non-responders or without clinical benefit.

For the analysis of maximum tumor shrinkage only observed cases will be used.

The analysis of timed endpoints is based on a Kaplan-Meier method (PFS, ORR, CBR, TTR, DOR, and OS), therefore, not affected by patient withdrawals (as they are censored) provided that dropping out is unrelated to prognosis.

For PFS, TTR and DOR, patients without a date of disease progression or death will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of treatment initiation + 1 day.

The other variables will be managed with simple imputations methods (last observation carried forward). The effect that any missing data might have on results will be assessed via sensitivity analysis.

5.6.5 Estimands

Estimands for the study are defined in the table 1:

Table 1. Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Primary Cohort 1	Full Analysis Set	PFS at week 16	- Patient with no progression or death at week 16 will considered as non-PFS at week 16. - Patients without any post-baseline assessment will be considered as non-PFS.	The 95% CI and p-value by UMVUE method.
Sensitivity to Primary Cohort 1	Full Analysis Set	PFS at week 16	- Patient with no progression or death at week 16 will considered as non-PFS at week 16. - Patients without any post-baseline assessment will be considered as non-PFS.	The 95% Pearson-Clopper CI and p-value under exact binomial test.
Primary Cohort 2,3,4	Full Analysis Set	ORR	- Patient with missing ORR outcomes will be considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The 95% Pearson-Clopper CI and p-value under exact binomial test.
Primary Cohort 5	Full Analysis Set	OS	- Patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI
Secondary 1	Full Analysis Set by cohorts 2 to 5	PFS	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time with corresponding 95% CI.
Secondary 2	Full Analysis Set by cohorts	PFS at week 16	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - PFS time irrespective of start of new therapies will be considered. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, week 16 survival rates with corresponding 95% CI.

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Secondary 3	Full Analysis Set by cohorts	PFS at week 24	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - PFS time irrespective of start of new therapies will be considered. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, week 24 survival rates with corresponding 95% Cl.
Secondary 4	Full Analysis Set by cohorts	ORR	- Patient with missing ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The 95% Pearson-Clopper CI and p-value under exact binomial test.
Secondary 5	Full Analysis Set by cohorts	CBR	- Patient with missing CBR outcomes will consider as non-clinical benefit. - Patients without any post-baseline assessment will be considered as non-clinical benefit.	The 95% Pearson-Clopper CI and p-value under exact binomial test.
Secondary 6	Full Analysis Set by cohorts	OS	- Patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Secondary 7	Full Analysis Set by cohorts	DOR	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-response tumor assessment is available, patients will be censored at the date of treatment response + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Secondary 8	Full Analysis Set by cohorts	TTR	- Patients with no response will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Secondary 9	Full Analysis Set by cohorts	Maximum Tumor Shrinkage	Only observed cases will be used	Median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Secondary 10 Cohort 2	Full Analysis Set Only Cohort 2	Time to WBRT/SRS	- Patients with no progression (according RANO-BM criteria) will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - Patients with no WBRT and/or SRS treatment will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI

5.6.6 Exploratory Analysis

These statistical analyses will be exploratory. Therefore, no pre-specified analyses are detailed in the SAP. Exploratory analyses will be performed on the exploratory analysis set.

Changes in biomarkers will be evaluated on a [redacted] level regarding their association with treatment. Baseline and post-treatment values of quantitative biomarkers will be described with [redacted] and [redacted] in [redacted]). Baseline and post-treatment values of categorical biomarkers ([redacted]) will be described with frequency and percentage.

Change from baseline between values of quantitative biomarkers will be analyzed with [redacted] and [redacted] differences. The corresponding 95% confidence intervals, applicable test statistics and p-values will be presented. P-values and 95%CI for [redacted] differences will be based on paired [redacted]. P-values for ranks will be based on [redacted]. The 95%CI for [redacted] difference will be based on [redacted]. Change from baseline between percentage of categorical biomarkers will be analyzed with [redacted].

Markers will be evaluated on a [redacted] level regarding their change over potential for prediction of the clinical endpoints ([redacted]. Biomarker and response correlations with clinical covariates will be investigated. It will be checked whether covariates can improve the prediction and whether there is an interaction with the biomarkers. Further [redacted] techniques (e.g., [redacted]) will be evaluated to study combinations of markers. Techniques to control false discovery rate and overfitting (cross-validation) will be also considered. Analysis will be performed on exploratory analysis set.

5.7 Safety Analysis

All safety tables will list or summarize subjects by cohort on the entire Safety set. These safety assessments will be subjected to clinical review and summarized by appropriate descriptive statistics.

5.7.1 Duration and Extent of Exposure

Duration and extent of exposure will be based on the safety set.

The following parameters will be calculated:

- b: "Actual Cycle Duration" is the treatment duration for a cycle per CRF. It is the length of time (days) between actual and next cycle start date dose. At the last cycle is the difference between start and stop date dose.
- c: "Actual Cycle Dose Days" is the number of days with dose administration in the cycle, considering the interruptions.
- d: "Actual Total Dose per Cycle" is the total dose a patient took in a cycle, considering interruptions and reductions.
- e: "Intended Daily Dose per Cycle" is equal to 60 mg/m2 every 2 weeks.
- f: "Intended Cycle Duration" is equal to 14 days +/- 2 days.
- g: "Intended Cycle Dose Days" is equal to 1 day for all cycles.
- A: "Total number of cycles".
- B: "Treatment Duration" = Sum over all cycles of (b).
- C: "Days on drug" = Sum over all cycles of (c).
- D: "Total Actual Total Dose" = Sum over all cycles of (d).
- E: "Mean Intended Daily Dose" = Mean over all cycles of (e).
- F: "Total Intended Duration" = Sum over all cycles of (f).
- G: "Total Intended Dose Days" = Sum over all cycles of (g).
- H: "Intended Total Dose" = G*E
- I: "Actual Average Daily Dose on Dose Days" = D/C
- J: "Ratio for Dose Interruption" = C/G
- K: "Ratio for Cycle Duration" = F/B
- L: "Actual Average Daily Dose Intensity" = I*J*K
- M: "Relative Dose Intensity (RDI)" = L/E*100

The treatment duration (days), number of cycles, and Treatment compliance (%) will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum and maximum, to each cohort.

Extent of exposure measured as RDI will be described with median, interquartile range (IQR) and range. The RDI will be dichotomized in different cutoffs (≥50%, ≥70%, ≥80%, ≥90%, ≥100%) and described with frequencies and percentages.

5.7.2 Concomitant Medications

The number and percent of unique patients taking concomitant medications will be summarized by therapeutic classification, coded term and dose level. Elective surgeries/procedures performed during the study will be presented in a listing.

The following are conventions that will be used to classify individual medications as prior and/or concomitant:

- Medications with stop dates prior to start dose will be considered prior.
- Medications with missing stop dates or stop dates the day of or after start dose will be considered concomitant, regardless of start date. Additionally, if the start date is prior to start dose or missing, the medication will also be considered prior.

Frequencies and by-subject listing of all prior and concomitant medications will be provided, containing variables listed on Prior/Concomitant Assessment eCRF, their corresponding categories (Prior or Concomitant), and WHO Anatomical Therapeutic Chemical (ATC) level 2 and preferred term if applicable.

5.7.3 Dose Delays, Reductions and Discontinuations

The following summaries will be provided by cohort:

- Subjects with at least one dose delay.
- Subjects with at least one dose delay due to adverse event.
- Subjects with at least one dose reduction.
- Subjects with at least one dose reduction due to adverse event.
- Subjects with permanently dose discontinuation.
- Subjects with permanently dose discontinuation due to adverse event.

5.7.4 Adverse Events

All AEs will be recorded on the eCRF "Adverse Events" page and will be coded using the current version of MedDRA® to give a system organ class (SOC) and preferred term (PT) for each event. All adverse event safety data will be updated to the version of MedDRA that is current at the time of the database lock and statistical analyses. Adverse events will be coded with grades defined according to CTCAE V5.0 criteria.

Treatment-emergent AEs (i.e., those events occur after the first study medication administration and were not present at baseline or worsened in severity following the start of treatment) will be tabulated. The TEAE will be tabulated according to intensity and causality. If intensity of an AE or causality of an AE to the study medication is missing, a worst-case scenario will prevail (severe in intensity or probably related will be assumed). In the summary tables the number of subjects with events and the number of events will be presented.

The onset date of an AE will be compared to the date of first dose of study drug to determine whether the AE is treatment emergent. Adverse events with an onset date on or after the date of first dose of study drug will be classified as treatment emergent.

All deaths and SAEs, regardless of cause, from treatment start until 28 days after final dose of treatment. Non-fatal AEs occurring after treatment start regardless of cause, up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first. Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment emergent adverse events with cause possibly, probably, or definitely related to treatment as judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

Descriptive statistics will be used to characterize the profiles of treatment-related AEs, treatment-related deaths, SAEs, treatment-related delays, dose reductions, and/or treatment discontinuations. All AEs will be graded according to the current version of the NCI-CTCAE v.5.0 and the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be graded according to the NCI-CTCAE v.5.0. Additionally, treatment compliance, in particular dose reduction requirements, skipped doses and/or cycle delays due to AEs, will be described.

The following summaries will be provided:

- Summary of Adverse Events
    - Subjects with at least one Adverse Event (AE)
    - Subjects with at least one Treatment Emergent AE (TEAE)
    - Subjects with at least one related study drug TEAE
    - Subjects with at least one grade 3 or 4 or 5 TEAE
    - Subjects with at least one related grade 3 or 4 or 5 TEAE
    - Subjects with at least one serious TEAE
    - Subjects with at least one related serious TEAE
    - Subjects with at least one non-serious TEAE
    - Subjects with at least one Adverse Event of Special Interest (AESI)
    - Deaths due to TEAE
    - Subjects with TEAE leading to Discontinuation of Study Treatment
    - Subjects dropped out due to AE
- Summary by SOC and PT of the number and percentage of subjects reporting each:
    - Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events by Treatment and Haematologic
    - Treatment Emergent Adverse Event Related to Study Drug
    - Related Treatment Emergent Adverse Event by Treatment and Haematologic
    - AESI Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events with Grade 3 or 4 or 5
    - Related Treatment-Emergent Adverse Event with Grade 3 or 4 or 5
    - Serious Treatment Emergent Adverse Event
    - Serious and Related Treatment Emergent Adverse Event
    - Treatment Emergent Adverse Event by Maximum Severity
    - Treatment Emergent Adverse Event Leading to Discontinuation of Study Drug

5.7.5 Clinical Laboratory Parameters

The following summaries will be produced for all hematology and biochemistry laboratory parameters:

- Shift tables of low, normal, high distribution (n; %) with respect normal ranges of center, at each post-baseline cycle by baseline (cycle 1 day 1) distribution.
- Shift tables of low, normal, high distribution (n; %) of clinically significant at each post-baseline cycle comparing with baseline (cycle 1 day 1) distribution.
- The value distribution will be displayed using a serial box plot at each cycle, for each treatment arm.

5.7.6 Vital Signs

The following summaries will be produced for all vital sign's parameters:

- Shift tables of low, normal, high distribution (n; %) at each post-baseline cycle by baseline (cycle 1 day 1) distribution.

5.7.7 Physical Examination

The following summaries will be produced for all physical examination's parameters:

- Shift tables of low, normal, high distribution (n; %) at each post-baseline cycle by baseline (cycle 1 day 1) distribution.

5.8 Interim Analysis

5.8.1 Futility Interim Analyses in Cohort 1

A futility interim analysis has been planned in cohort 1. The recruitment will not be stopped during the interim analysis. However, after the interim analysis, if the number of patients achieving the primary endpoint is equal or less than futility boundary in each cohort, the accrual in the cohort must be stopped. The stopping rule is:

Cohort 1: All 4 patients with progressive disease or death at 16 weeks.

5.8.2 Feasibility Interim Analyses

At the halfway point of the recruitment period, the steering committee will evaluate if the accrual objective for the first stage was achieved in each study cohorts (4, 5, 3, 3 and 3 patients for cohorts 1, 2, 3, 4 and 5, respectively).

If this accrual objective has not achieved in a cohort, the Steering Committee will propose a corrective action plan or finalize the study in this cohort.

Interim analyses report will summarize descriptively the following results by cohort on the Safety/FAS set.

- Subject disposition
- Baseline characteristics
- Efficacy analysis
    - PFS events at 16 weeks
    - Median PFS
    - Unconfirmed tumor response according RECIST v.1.1 Criteria
    - Maximum Tumor Shrinkage
    - Unconfirmed Tumor Response according RANO-BM Criteria
    - Waterfall Plot
    - DOR
    - TTR
    - Median OS
- Safety analysis
    - TEAEs
    - AESIs
    - Serious TEAEs
    - Dose delays, reductions, and discontinuations

No statistical tests are planned for these data.

5.9 Changes of Analysis from Protocol

In section 3.1, the method for calculating the primary endpoint of cohort 1 is specified in greater detail.

We have included the analyses of maximum Tumor Shrinkage in all lesions as secondary endpoint.

5.10 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

6 BIBLIOGRAPHY

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2.- Koyama T and Chen H (2008). Proper inference from Simon's two-stage designs. Statistics in Medicine, Jul 20; 27(16): 3145–3154. DOI: 10.1002/sim.3123

3.- Kieser M, et all (2017). OneArmPhaseTwoStudy: An R Package for Planning, Conducting, and Analysing Single-Arm Phase II Studies. Nov, 81(8). DOI:10.18637/jss.v081.i08

7 APPENDIX

7.1 Appendix 1 – Codes

All report outputs will be produced using SAS® version 9.4 (TS1M5) version in a secure and validated environment.

7.1.1 R Code - UMVUE

- **The UMVUE of the overall response rate, based on function "get_UMVUE_GMS":**

```
k<- Total number of responders in the study;
r1<-Futility boundary at interim analysis (number of events);
n1<-Accrued patients at first stage;
n2<-Accrued patients at second stage;
n<-Overall patients accrued in the two stages of the study;
p0<-Expected response rate;

get_UMVUE_GMS <-function (k, r1, n1, n)
{
  stopifnot(class(k) == "numeric" | class(k) == "integer",
    k >= 0)
  stopifnot(class(r1) == "numeric", r1 >= 0)
  stopifnot(class(n1) == "numeric", n1 >= 0, n1 > r1)
  stopifnot(class(n) == "numeric", n >= 0, n > n1)
  umvue <- numeric(0)
  if (k <= r1) {
    umvue <- k/n1
  }
  else {
    upper_boundry_dividend <- min(k - 1, n1 - 1)
    lower_boundry_dividend <- max(r1, k - 1 - n + n1)
    upper_boundry_divisor <- min(k, n1)
    lower_boundry_divisor <- max(r1 + 1, k - n + n1)
    i_upper <- lower_boundry_dividend:upper_boundry_dividend
    i_lower <- lower_boundry_divisor:upper_boundry_divisor
    umvue <- sum(choose(n1 - 1, i_upper) * choose(n - n1,
      k - 1 - i_upper))/sum(choose(n1, i_lower) * choose(n -
      n1, k - i_lower))
  }
  umvue }
```

- **Calculation of p-value based on function "get_p_KC":**

```
k<- Total number of responders in the study;
r1<-Futility boundary at interim analysis (number of events);
n1<-Accrued patients at first stage;
n2<-Accrued patients at second stage;
n<-Overall patients accrued in the two stages of the study;
p0<-Expected response rate;

get_p_KC<- function(k, r1, n1, n, p0)
{
  stopifnot(class(k) == "numeric" | class(k) == "integer",
    k >= 0)
  stopifnot(class(r1) == "numeric", r1 >= 0)
  stopifnot(class(n1) == "numeric", n1 >= 0, n1 > r1)
  stopifnot(class(n) == "numeric", n >= 0, n > n1)
  stopifnot(class(p0) == "numeric", p0 >= 0, p0 <= 1)
  p <- numeric(0)
  if (k > r1) {
    k1 <- (r1 + 1):n1
    k2 <- k - k1
    n2 <- n - n1
    p <- sum(dbinom(k1, n1, p0) * (1 - pbinom(k2 - 1, n2,
      p0)))
  }
  else {
    p <- 1 - pbinom(k - 1, n1, p0)
  }
  p
}
```

- **Calculation of 95% confidence intervals for response based on function "get_CI":**

k<- Total number of responders in the study;
r1<-Futility boundary at interim analysis (number of events);
n1<-Accrued patients at first stage;
n2<-Accrued patients at second stage;
n<-Overall patients accrued in the two stages of the study;
p0<-Expected response rate;
alpha= overall significance level the trial was planned for;
precision= gives the precision (in decimal numbers) to which the confidence interval should be calculated (should be less than 10).

```
get_CI<- function (k, r1, n1, n, alpha = 0.05, precision = 4)
{
  stopifnot(class(k) == "numeric" | class(k) == "integer",
    k >= 0)
  stopifnot(class(r1) == "numeric", r1 >= 0)
  stopifnot(class(n1) == "numeric", n1 >= 0, n1 > r1)
  stopifnot(class(n) == "numeric", n >= 0, n > n1)
  stopifnot(class(alpha) == "numeric", alpha > 0, alpha <=
    1)
  stopifnot(class(precision) == "numeric", precision >= 0,
    precision < 10)
  stopifnot(k > r1, precision > 1)
  eff <- seq(0, 1, 0.01)
  tmp <- sapply(eff, function(bla) get_p_KC(k = k, r1 = r1,
    n1 = n1, n = n, p0 = bla))
  index_low <- which(tmp >= alpha)[1]
  index_high <- which(tmp >= (1 - alpha))[1] - 1
  if (precision > 2) {
    eff_low <- seq(eff[index_low - 1], eff[index_low], (1/(10^(3))))
    eff_high <- seq(eff[index_high], eff[index_high + 1],
      (1/(10^(3))))
    for (i in 2:(precision)) {
      if (i > 2) {
        eff_low <- seq(eff_low[index_low - 1], eff_low[index_low],
          (1/(10^(i + 1))))
        eff_high <- seq(eff_high[index_high], eff_high[index_high +
          1], (1/(10^(i + 1))))
      }
      tmp_low <- sapply(eff_low, function(bla) get_p_KC(k = k,
        r1 = r1, n1 = n1, n = n, p0 = bla))
      tmp_high <- sapply(eff_high, function(bla) get_p_KC(k = k,
        r1 = r1, n1 = n1, n = n, p0 = bla))
      index_low <- which(tmp_low >= alpha)[1]
      index_high <- which(tmp_high >= (1 - alpha))[1] -
        1
    }
    result <- data.frame(CI_low = eff_low[index_low], CI_high = eff_high[index_high])
  }
  else {
    result <- data.frame(CI_low = eff[index_low], CI_high = eff[index_high])
  }
  result
}
```

7.1.2 SAS Code - Stochastic Binomial Exact Test

ORR

The number and proportion of patients with CNS-ORR, with its 95% exact (Pearson-Clopper) confidence intervals will be calculated.

```
proc freq data=ITT;
  tables CNSORR / binomial(exact p=.05) alpha=.025;
  title 'CNS-ORR (FAS)';
run;
```

7.1.3 R Code - Maximum Likelihood Method for Exponential Distribution

- **Calculation of p-value:**

######Maximum likelihood for exponential distribution, superiority.

mOSobs = observed median overall survival (OS).

mOS0 = null hypothesis (H0) of median overall survival.

HRobs = observed Hazard Rate (HR) = -log(0.5)/mOSobs

HR0 = H0 of HR = -log(0.5)/mOS0

Ev = events at the end of study

log() = natural logarithm in R

pnorm = The pnorm function is used to calculate the cumulative distribution function of the normal distribution.

Formula:

p-value = pnorm(sqrt(Ev)*(log(HRobs)-log(HR0)))

7.2 Appendix 2 - List of Tables, Listings, Figures

A complete list of tables, listings and figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output.

All statistical output will identify the underlying analysis sets and indicate the number of patients/events in this set (N) and the number of patient/events actuals contributing to the output (n). All statistical output will be presented per treatment (if applicable).

All patient listings will contain additionally to the patient identification the analysis set and the treatment.