NOVARTIS

Clinical Development

LDK378

LDK378A2203 / NCT01685138

A phase II, multicenter, single-arm study of oral LDK378 in crizotinib na..-ve adult patients with ALK-activated non-small cell lung cancer

Statistical Analysis Plan (SAP) for Final Analysis

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Table of contents

Table of contents 3
List of tables 5
I Introduction 6
1.1 Study design 6
1.2 Objectives 6
1.2.1 Primary objective 6
1.2.2 Secondary objectives 6
[redacted] 7
2 Statistical methods 7
2.1 Data analysis. 7
2.2 Analysis sets 8
2.3 Patient demographics and other baseline characteristics... 9
2.4 Protocol deviations 0
2.5 Patient disposition 10
2.6 Treatments (study drng, concomitant therapies, compliance) 11
2.7 Anal ysis of the prima1y variable 13
2.7.1 Variable 13
2.7.2 Statistical hypothesis, model, and method of analysis 13
2.7.3 Handling of missing values/censo1ing/discontinua tions 14
2.7.4 Supportive analyses 14
2.8 Analysis of secondaly va1iables 14
2.8.1 Efficacy 14
2.8.2 Safety 18
- 24
24
2.8.5 Phannacogenetics/phannacogenomics 24
[redacted] 24
24
2.9 Samp le size calculation 24
2.10 Power for analysis of key secondary variables 25
2.11 Intelil11 anal ys is 25
3 Ch anges to protocol specified analyses 25
4 Additional details on implementation of statistical methodology 27
4.1 Data included in the analyses 27

4.2 Patient Classification into Analysis Sets 27
4.3 Last contact date....28
4.4 Month derivation 28
4.5 Dose inten11ptions and dose changes....28
4.6 Efficacy endpoints 29
4.6.1 Implementation of RECIST Guidelines....29
4.6.2 Sources for overall lesions response 33
4.6.3 Kaplan-Meier estimates 33
4.6.4 Confidence inte,val and p-value for response rate. 34
4.7 Safety evaluations 35
4.7.1 Multiple assessments within post-baseline visits....35
4.7.2 Baseline 35
4.8 Handling of missing or paitial dates 36
4.8.1 AE date imputation 36
4.8.2 hlcomplete date of initial diagnosis of cancer, da.te of most recent recmTence and date ofanti-neoplastic therapies....38
4.8.3 Incompl ete assess ment dates for tumor assessment....38
4.8.4 Incomplete date for death....39
[redacted] 39
5 Reference....40

List of tables

Table 2-1 Outcome and event dates for DOR and PFS analyses 16
Table 2-2 ECOGpe1fo1mance scale 23
Table 2-3 Operating characteristics of Simon's optimal two-stage design 25
Table 3-1 Changes to protocol specified analysis or descriptions and rationale ... 25
Table 4-1 Patient classification rnles 27
Table 4-2 hlclusion/exclusion of assessments used in waterfall graph 32
Table 4-3 SOlu·ces for overall lesion response 33
Table 4-4 AE/treatment date abbreviations 37
Table 4-5 AE pa1tial date imputation algo1itlun 37
Table 4-6 AE/treatment date relationship and imputation legend 38
Table 4-7 AE imputation example scenarios 38

1 Introduction

This SAP desc1ibes the planned statistical methods for the final analysis for study LDK378A2203.

1.1 Study design

This is a prospective, multi-center, open-label, single am1, phase II study with a Simon two-stage design to evaluate the efficacy and safety of single-agent LDK378 in patients with ALK-reammged NSCLC not previously treated with crizotinib. Patients must have received cytotoxic chemotherapy (1 to 3 p1ior lines of which I must be a platinum doublet), and must have progressed during the most recent chemotherapy prior to emollment in the trial. Patients will receive treatment with LDK378 750 mg administered orally on a once-daily dosing schedule. Treatment with LDK378 750 mg once daily will continue until the patient experiences unacceptable toxicity that precludes ftuther treatment, discontinues treatment at the discretion of the investigator or at patient's request, starts a new anticancer therapy, or dies. LDK378 may be continued beyond RECIST-defined disease progression (PD) as assessed by the investigator if, in the judgment of the inves tigator, there is evidence of continued clinical benefit. In these patients tumor assessment should continue as per the schedule of assessments until treatment with LDK378 is pennanently discontinued. Patients who discontinue study drng in the absence of progression will continue to be followed for tumor assessments until the time of PD as assessed by the investigator.

1.2 Objectives

1.2.1 Primary objective

The prinia1y object ive is to demonstrate the anti-tumor activity of LDK378, as measmed by overall response rate (ORR), by investigator assessment per RECIST 1.1.

1.2.2 Secondary objectives

Toe key seconda1y objectives are to evaluate response related endpoints as assessed by both investigator and Blinded Independent Review Committee (BIRC), tmless otherwise specified, asperRECIST 1.1:

- duration ofresponse (DOR)
- disease control rate (DCR)
- tin1e to response (TTR)

and to assess

- ORR by BIRC assessment.

Other secondary obje ctives are to evaluate:

- the safety profile ofLDK378
- progression-freesurvival(PFS) as assessed by both investigator and BIRC
- Overall smvival (OS).

2 Statistical methods

This section and its subsections will be imported to section 9.7 of the CSR after the analyses have been conducted. This section of the RAP follows the CSR template stmcture of Section 9.7 as of the release date of this document.

The text will be changed to the past tense when impo1ted into the CSR; references to Section 4, where additional details are provided for programming implementation, may be removed in the CSR.

In what follows, study drng refers to LDK378/Cerit:inib.

2.1 Data analysis

Data will be analyzed by Novartis Oncology Biostatistics and programming personnel according to the data analysis section 10 of the LDK378A2203 protocol. hnpo11ant infom1ation is given in the following sections and details are provided, as applicable, in Section 4 from which Appendix 16.1.9 of the CSR will be extracted.

SAS® version 9.4 (or later version if available at time of database lock) will be used in all analyses.

Data from all patients who signed informed consent in centers that participate in this study will be used in the analysis; due to expected small size of emolhnent at individualcenters, no center effect will be assessed. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock.

As described in Section 1.1 this study has a Simon two-stage design. If the study stops at the end of Stage 1 (see Section 2.11), the data available will be smnmarized in an abbreviated CSR. Otherwise, the analysis cut-off date for the primary analysis of sn1dy da.ta will be established once all patients have either completed at least six treatment cycles, i.e., 168 days (1 cycle =28 days), or discontinued study dmg earlier. The data will be summarized in the primary CSR. Following the primary analysis time point, the study will remain open. Patients still being followed on the study will continue as per the schedule of assessments.

The analysis cutoff date for the final analysis of study data will be 22-Jan-2018 con-espondi.ng to last patient last visit date.

Section 4.1 provides futther details regarding data to be included in the analyses.

General presentation of descriptive summaries

Qualitativ e data (e.g., gender, race) will be su!lllnat·ized by frequency co1mts an d percen tages. Percentages will be calculated using the number of patients in the relevant populaiton or subgroup as the denominator.

Continuous da.ta (e.g. , age, body weight) will be su!lllnat·ized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximtnn).

2.2 Ana l ysis sets

A patient is considered to be enrolled into the sn1dy if they have signed informed consent. Only patients who have signedinfom1ed consent will be included in the analysis data sets.

Full Analysis Set

Tue Full Analysis Set (FAS) consists of all patients who received at least one dose of study drng. All efficacy endpoints will be analyzed using FAS.

Tue FAS will be used for all listings. Unless othenvise specified the FAS will be the default analysis set used for all analyses.

Safety Set

The Safety Set consists of all patients who received at least one dose of study drng. All safety data will be analyzed using the SafetySet.

The FAS and Safety Set in this study are identical.

Per-Protocol Set

For the definition refer to CLDK378A2203 RAP Module 3 Amendment 1. No analyses will be pe1fonned based on patients in this analysis set in this CSR.

2.3 Patient demographics and other baseline characteristics

Tue FAS will be used for all patient demographic and baseline characteristic summaries and listings, unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be smumarized and listed. Categorical data (e.g. gender, race, ethnicity, WHO perfonnance status) will be summarized by frequency count and percentages. Continuous data (i.e. age) will be summarized by desc1ptivestatistics (as defined in Section 2.1) including quartiles.

Diagnosis and extent of cancer

Descriptive statistics and frequency counts and percentages will be tabulated, as approp1iate, for diagnosis and extent of cancer based on the data collected on the electronic Case Report Fonn (eCRF) including primary site of cancer, details of tumor histology/cytology, histological grade, time since initial diagnosis of primary site, stage at initial diagnosis, time from initial diagnosis to first recunence/progression, time since most recent relapse/progression, metastatic sites, and (based on the <la.ta collected on the RECIST eCRFs on the individual target and non-target lesion codes) presence/absenceof target and non-target lesions.

Time since initial diagnosis, time since most recent relapse/progression and time since initial diagnosis to first recwTence/ progression will be swnmarized in months.

Medical history

Medic.al histo1yand ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate sm111uaries will be presented for ongoing and histo1ical medical conditions. The summa1ies will be presented by prima1y system organ class and preferred tenu. Medical history and current medical conditions are coded using the Medical Dictionaiy for Regnlato1yActivities (MedDRA) tenninology.

Prior anti-cancer therapy

Prior anti-neoplastic (anti-cancer) therapy will be listed in three separate catego1ies: 1. medications,2. radiotherapy, and 3. sm·gery.

Tue nwnber and percentage of patients who received ai1y prior anti-neoplastic medications, prior anti-neoplasticradiotherapy or prior anti-neoplasitc stll'gery will be stll11narized.

Prior anti-neoplastic medications will be stmnuaiized by chemotherapy(medication) setting, other therapy (medication) setting, munber of p1ior regimens of chemothe rapy, prior anticancer medications including cisplatin, cai·boplatinpemetrexed docetaxel gemcitabine bevacizumab erlotinib and gefitinib. Prior ailtineoplastic medications will also be summarized by ATC class, and prefell'ed tenn.

Screen failures

Screen failures will comprise patients wbo have been enrolled and have failed to meet inclusion or exclusion criteria.. These patients are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled patients as follows:

- Number (%) of patients who completed screening phase (based on the presence of srudy phase completion date and the 'Next phase entered' is 'Treatment' in the 'Screening Phase Disposition' page);
- Number (%) of patients who discontinued dtni.ng screening phase (based on thepresence of date of discontinuation and discontinuation/ "subjectstatus" reason entered and ' Will the subject continue into the next phase of the tiial' is ' No' in the 'Screening Phase Disposition' page) ;
- Reasons for screening phase discontinuation(based on reasons recorded in Screening Phase Disposition' page).

All screen failure patients with reasons for screen failure will be listed. Violations of inclusion/ exclusion criteria leading to screen failures will be smnma.rized by criteria.

2.4 Protocol deviations

Frequency counts and percentages of patients in the FAS with any protocol deviations (inclusion/exclusioncriteria not met, patient not withdrawn as per protocol, key procedures not perfo1med as per protocol, treatment deviation, prohibited concomitant medication, Good Clinical Practice (GCP) deviation) will be tabulated by the deviation catego1y Major protocol deviations will be tabulated separately. Toe full list of protocol deviations are documented in the data handling plan.

Protocol deviations will be listed.

2.5 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment (based on the absence of the ' End of Treatment Phase Completion' page);
- Number(%) of patients who discontinued treatment (based on completion of the ' End of Treatment Phase Completion' page with date of discontinuation and reason of discontinuation/ ' Subject Status' entered);
- Number (%) of patients who entered post treatment efficacy follow-up (based on 'Next Phase Entered' is ' Post-treatmentfollow-up' on the ' End of Treatment Phase Completion' page for patients who discontinued tl·ea.tme nt);
- Number(%) of patients who entered stnvival follow-up (based on ' Next Phase Entered' is 'Survival follow-up' on the 'End of Treatment Phase Completion' page for patients who discontinued treatment);
- Number (%) of patients who discontinued from study (based on 'Will subject continue into the next phase of the trial' is 'No' as entered on the 'End of Treatment Phase Completion' page for patients who discontinued treatment;)

- Primaiy reasons for srudy treatment discontinuation (based ou discoutiuuatiou reasons entered under 'Subject Status' in the 'End of Treatment Phase Completion' page);
- Number (%) of patients who are still in the post-treatment srudy phase (based on presence of 'End of Treatment Phase Completion' and absence of 'Sn1dy Phase Completion' page);
- Number (%) of patients who discontinued from the post-treatment efficacy follow-up (based ou completion of 'Study Phase Completion' page with date of discontinuation and discontinuation reasons entered under 'Subject Status');
- Ntunber (%) of patients who entered stuvival follow-up (based on completion of 'Study Phase Completion' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Next Phase Entered' is 'Smvival follow-up' for patients who discontinuedfrom the post-treatment efficacy follow-up);
- Number (%) of patients who discontinued from study (based on completion of 'Study Phase Completion' page with date of discontinuation and discontinuation reasons entered tmder 'Subject Stanis' and 'Will subject continue into the next phase of the ttial' is 'No ', for patients who discontinued from the post-treatment efficacy follow-up);
- Plimaly reasons for discontinuation from the post-treatment efficacy follow-up (based on discontinuation reasons entered under 'Subject Status' in the 'Study Phase Completion' page).

2.6 Treatments (study drug, concomitant therapies, compliance)

The Safety Set will be used for all medication data sumrna1ies ai1d listings unless othe1wise speci fied.

Study drug and study treatment

Sn1dy drng and study treatmentboth refer to LDK378 and will be used interchangeably.

Date of first/last administrationof studydrug

The date of first administration of study chug is defined as the first date when a non-zero dose of study ch11g was achninisteredand recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first administration of study ch11g will also be refe1Ted as start date of srudy chug.

The date of last administration of study ch11g is defined as the last date when a non-zero dose of studydrng was administered and recorded on DAR eCRF. This date will also be refen-ed as last da.te of study dmg.

Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, pe1fonnance status, adverse event onset, laboratory abnonnality occunen,ce vital sign measm·emeut, dose intem1ption) will be calculated using the sta11 date of srudy drug as the origin. For assessments occuning after or on the sta1t date of srudy ch11g, s tud y day will be calculated as:

Study Day =Event date - sta1t date of study chug + I .

The first day of study drng is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occuning plior to the sta11 of the sn1dy chug, study day will be negative and will be calculated as:

Study Day= Event date• staJ1date of study ch11g.

Tue stu dy day will be displayed in the data listings.

Dose exposure and intensity

Definitions of duration of exposure, cumulative dose, average daily dose, acn1al dose intensity (DD, relat ive dose intensity (RDD, as well as intermediate calculations, include:

- Duration of exposure (days): last date of study clrng - first date of study dmg + 1 (periods of inte1rnption are not excluded)
- Ctunulative dose(mg): total dose of study ch11g taken by a patient in the study
- Number of dosing days(days): duration of expostu·e - number of zero dose days
- Average daily dose (mg/day): cmuulative dose (mg)/ nmuberof dosing days (days)
- DI (mg/day): ctunulative dose (mg)/ duration of exposure (days)
- RD!(%): 100 x [DI (mg/day)/ plalllled dose (750 mg)]

Note: given the plaiilled LDK378 dose of 750mg/day, the plaiilled dose intensity can be calculated as PDI (mg/day) = cumulative planned dose (mg)/Dura tion of expostu-e (days), where Cllllllulative plalllled dose (mg) = Protocol plam1ed dose of 750 (mg)* Duration of exposme. RDI (%) which is calculated as I00*DI/PDI can be simplified as shown above.

Dm-ation of srudy exposme to srudy ch11g, cumulativ e dose , average daily dose, DI and RDI will be sununarized. In addition, the dmation of exposure to study chug will be categorized into time inte1vals; frequency counts and percentages of patients with exposure in each time interval will be presented. Frequency counts and percentages of patients who have dose chaJ1ges, reduc tions or intenu ptions , and the con-esponding reasons, will be stllllllnarized.

Listings of all doses of the sn1dy ch11g along with dose change/intenup tion reasons will be produced.

Section 4.5 provides futther details on the definition of dose changes and inte1n1ptions.

Concomitant therapy

Concomitant therapies are defined as any medica tions (excluding study chug, p1ior antineoplastic treatments and blood transfosions), surgeries or procedures (including physical therapy) administered in the sn1dy and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

These therapies will be coded using the WHO Drng Reference Listing (WHO DRL) dictiona1y that employs the WHO Anatomical Therapeutic Chemical (\VHO ATC) classification system. All stunma1ies will be tabulated using frequency counts and percentages.

Concomitant therapies will be smnmarized by ATC class and prefen-ed term. These smmuaries will include 1) medications sta1ting on or after the sta1t of study dmg but sta1ting

no later than 30 days after last dose of study drng and 2) medications start ing prior to the start of study drng but continuing after the start of study drng.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the s tart of study drng or starting more than 30 days after the last date of study drng will be flagged in the listing.

Antineoplastic therapy after discontinuation of study drug

The FAS will be used for all listings and summa1ies of antineoplastic therapies initiated after discontinuation of srudy chug. All stuumaries will be tabulated using frequency counts and percentages.

Antineoplastic medications initiated after discontinuation of study drng will be smumarized and listed by Anatomical Therapeutic Chemical (ATC) class and prefen-ed tenu .

Antineoplastic radiotherapy since discontinuation of study treatment will be stUD1ua1ized and listed by setting.

Anti.neoplastic smgery since discontinuation of srudy treatment will be stuumarized and listed by procedm·e.

2.7 Analysis of the primary variable

The pri mar y objective is to demonstrate the antitumor activity of LDK378, as measured by ORR by investigator assessment.

2.7.1 Variable

The pri mary endpoint used to evaluate the anti-tumor activity of LDK378 is the overall response rate (ORR), defined as the propo1tion of patients with a best overall confinned complete response (CR) or partial response (PR), as assessed per RECIST 1.I by the investigator.

2.7.2 Statistical hypothesis, model and method of analysis

The primary efficacy analysis will be performed on the FAS.

The study targets an ORR of 50%. A response rate of 35% or Jess is considered as insufficient level of activity for the proposed patient population. Therefore,

Ho: ORR .:'o35% will be tested vs H1: ORR > 50%

using a one-sided test with o.=0.05 based on Simon's optimal t\vo-stage design (Simon 1989). If 45 or more responses are seen in 105 total patients (estimated ORR of 42.9%), then Ho will be rejected and the ttial declared positive.

Stage 1 will enroll 43 patients. If the sn1dy is terminated early at the end of Stage l (16 or fewer responses among 43 patients enrolled to Stage 1), then the study will be considered to have failed to reject Ho See Section 2.11 for fi.uther details of the stopping criteria for fotility. Stage 2 will include an additional 62 patients. The prim ar y analysis will occur when all l 05 patients have completed 6 cycles of treatment or discontinued treatment earlier.

The ORR will be estimated and the 90% and 95% Clopper-Pearson (Clopper and Pearson 1934) confidence inte1vals (Cls) will be provided. The uniformly minimum variance tmbiased estimator (UMVUE) and the 90% two-stage CI (Atkinson and Brown 1985) will also be presented. Refer to Section 4.6.4 for additional details.

Clopper-Pearson confidence inte,vaJs will be used since the confidence limits based on the nonnaJ approximation are not bounded by the [O, 1] interval , meaning that for rates close to 0 or I, the upper limit of the nonuaJ approximation inte,val for the proportion could exceed I or the lower limit could be negative. The 90% two-stage CI will be presented to conespond to the Simon two-stage p-value.

2.7.3 Handling of missing values/censoring/discontinuations

Confirmed PR or CR repo11ed prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR in espective of the number of missed assessments before response.

Patients with a best overall response (BOR) of 'Unknown' or 'Not Assessed per RECIST I.I will be considered as non-responders when estimating ORR.

Patients who have disease progression and continue to receive study drng after progression will qualify for PD at the time of progression and will be co1mted as PD in the de1ivation of ORR and any other efficacy endpoints.

2.7.4 Supporitve analyses

Listings of calculated overall lesion response based on raw measurements repo11ed by the investigator (Source 2 in Table 4-3) will be generated. Waterfall plots representing the best percentage change from baseline in the smn of the longest tumor diameters for target lesions will be produced.

2.8 Analysis of secondary variables

2.8.1 Efficacy

All tllllor response related endpoints tmder the secondary efficacy objectives (DOR, TTR, DCR, PFS) will be analyzed as per investigator assessment and as per the BIRC. Confirmation of response is required for all response endpoints, as per RECIST 1.1.

All secondary endpoint analyses will be performed based on the FAS, unless otherwise specified.

No adjustment for multiple testing will be made.

The key secondary effic cy endpoints are

- ORR byBIRC
- DOR by investigator assessment and by BIRC
- DCR by investigator assessment and by BIRC
- TTR by investigator assessment and by BIRC

Other secondary efficacy endpoints are

- PFS by investigator assessment and by BIRC
- OS

The definitions and details on the derivation of the secondary endpoints are given in the LDK378A2203 protocol. Fmther details and mies needed for programmatic implementation of RECIST 1.I guidelines are provided in Section 4.6.1.

Overall Response Rate

ORR as assessed by the BIRC, per RECIST 1.1, will be estimated and Cls will be provided per all methods desc1ibed in Section 2.7.2.

Bestoverall response

The BOR will be assessed based on reported lesion responses at different evaluation time points. Both CR and PR require confinnation at least 4 weeks after its initial obse1vation.

Only tumor assessments pe1fonned before the start of any finther anti-neoplastic therapies (i.e. any additional seconda1y anti-neoplastic therapy or anti-cancersurgery) will be considered in the assessment of BOR. If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR detem1ination. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on ' Anti-neoplastic therapies since last date of study dmg' as appropriate. Clinical dete1ioration will not be considered as documented disease progression. Patients with BOR ' unknown' will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall responseUNK
- New anti-neoplastictherapy staited before first post-baseline assessment
- Stable disease (SD) too early (<= 6 weeks after start date of study dmg)
- PD too late (> 12 weeks after start date of study drng)

Special (and rare) cases where BOR is 'unknown' due to both early SD and late PD will be classifiedas 'SD too early'.

Duration of response

Among patients with a confumed response (PR or CR), DOR is defined as the time from first documented response (PR or CR) to the date of first doclllllented PD or death due to underlying cancer. If a patient has not had an event, DOR is censored at the date of last adequate trnnor assessment.

The censoring and event date options to be considered for the main anal ysis are presented in Table 2-1.

Table 2-1 Outcome and event dates for DOR and **PFS** analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug•	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment•	Censored
D	No progression	Date of last adequate assessment •	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Date of last adequate assessment •	Censored
G	Deaths due to reason other than deterioration of 'Study indication'	Date of last adequate assessment •	Censored (only applicable to DOR)

• The rare excepiton to this is tt thepatient dies no later than the time of the second scheduled assessment as definedin the protocol in whichcase this is a PFS event at the dateof death

• After the last adequate rumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7 of Section 14 (Appendix II) of the LDK378A2203 protocol

DOR will be described in tabular and graphical fom1at using Ka plan-Meier methods including estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 2005) and Kaplan-Meier estimated probabilities with co1Tes p ondin g 9 5 % C ls (K albfleisch and Prentice 2002) at several time points (including at least 4, 8, 12, 15, 18 months).

These analyses will be pe1formed se parately based on investigator assessment and based on BIRC assessment.

Refer to Section 4.6.3 for ftuther details regarding derivation of Kaplan - Meier estimates.

Diseasecontrol rate

DCR, defined as the propo1tion of patients with BOR of CR, PR, SD, or Non-CR/Non-PD, per RECIST 1.1, will be estimated and the exact binomial 95% CI provided.

These analyses will be perform ed separately based on investigator assessment and based on BIRC assessment.

Time to response

Time to overall response of CR or PR (TTR) is defined as the time from sta1t of study drng to first documented response (CR or PR, which must be confumed st1bsequently). Patients who did not achieve a response (i.e. confumed response) will be censored as follows:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis), for patients who ha.d a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond;
- At last adequate ttuuor assessment date, otherwise. In this case the patient has not yet progressed so he/she theoretically still has a.cha.nee of responding.

TTR will be summarized by frequency counts using descriptive statistics for patients with confinued CR or PR. These analyses will be pe1fonned separntely based on investigator assessment and based on BIRC assessment.

Progression-freesurvival

PFS is defmed as the time from the slart date of study drng to the date of the fust radiologicaly doclllllented PD or death due to any cause.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any ftuther anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date or before the sta11 of the new anticancer therapy date, whichever is earlier. Clinical deterioration will not be considered as a qualifying event for progression. Refer to Table 2-1 for censoring and event date options and outcomes forPFS.

In particular, PFS will be censored at the last adequate tumor assessment: **if** one of the following occurs: absence of event; the event occuffed after a new anticancer therapy is given; the event occuned after two or more missing tumor assessments (see Section 4.6.1). See also Section 4.6.1 describing the special case of a missing baseline tllllllor assessment.

PFS will be described in tabular and graphical fonna.t using Kaplan-Meier methods as desc1ibed for DOR, including estimated median (in months) with *95%* CI, 25 th and 75th percentiles and Kaplan-Meier estimated probabilities with con-esponding 95% Cls at several time points (including a.t least 4, 8, 12, 15 and 18 months). Censo1ing reason s will also be summarized.

These analyses will be performed separately based on investigator assessment and based on BIRC assessment.

Overall survival

OS is defined as the time from the stan date of snidy drng to the date of death due to any cause. lf the patient is alive at the date of the anal ysis cut-off or lost to follow-up, then OS will be censored a.t the last contact date p1ior to data. cutoff date (see Section 4.3 for funher details on derivation of last contact date).

OS will be described in tabular and graphical fonnat using Kaplan-Meier methods as desc1ibed for DOR, including estimated median (in months) with *95%* CI, 25 th and 75th

percentiles and Kaplan-Meier estimated probabilities with co1responding95% Cls at several time points (including at least 4, 8, 12, 18 and 24 months).Censoring reasons will also be sununa1ized.

Duration of Follow-up and Gap Analyses

The duration of treatment pe1iod will be reported:

Treatmeut period=Last patient last date of ti-eatment- Firstpatient sta1tdate of treatment+1

In addition, descriptive statistics including qua1tiles will be tabulated for the duration of follow-up in the study:

- Duration between sta1t date of study drng and cut-off da.te = (Cut-off date - Start date of study drng +I)).
- Follow-up time for PFS/OS= (Date of event or censoring - Stait date of sn1dy drug + 1)..

All stmnnarieswill be reported in months (see Sec tion 4.4). The calculations for PFS will be based on the investigator and BIRC assessments. Date of censoring is the same as the one defined for thePFS and OS analyses.

2.8.2 Safety

All safety analyses will be pe1formed based on the Safety Set.

Baseline

Baseline is the result of an investigation desc1ibing the "trne" mlinfluenced state of the pa tient. The las t available assessment before or on the startdate of study drng is defined as "baseline" value or" baseline" assessmen.t If an assessment is planned to be perfonned prior to the first dose of study drng in the protocol and the assessment is perfonned on the same day as the first administration of srudy drng, it will be assmned that it was perfonned prior to study drng administration, if assessment time point is not collected or is missing. If assessment time points are collected, the obse1ved time point will be used to dete1mine pre-dose on studyday I for baseline calculation. Unscheduled assessments will be used in the detennination of baseline. See Section 4.7.2 for forther details on derivation of baseline for laborato1y data and ECGs.

Patients who stait treatment and discontinue from the study on the same day may have 2 different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reponed to the end of treatment (EOT) visit. Data reported at the EOT visit are not eligible for baselineselection.

Groupingfor the analyses

The overall observation period will be divided into three mutually exclusivesegments:

- Pre-treatment period: from day of patient' s infonned consent to the day before first dose of studydrng
- On-treatment pe1iod:

- For discontinued patients, from day of first dose of study drng to 30 days after last dose of srudy drug
- For ongoing patients, from day of first dose of study chug to the data cut-off date

- Post-treatment period: starting at day 31 after last dose of study drug

The safety SUlllllary tables will include only assessments collected no later than 30 days after study ch11g discontinuation and assessments prior to the data cut-off date for on-going patients, unless otherwise specified.

For select items, shift tables or change from baseline summaries generated for laboratory, ECG, vital signs and change score generation may use data from pre-treatment period for baseline calculations.

All data, regardless of obse,vation period, will be listed and assessments collected in the pre-treatment and post-treatment period will be flagged in all I.be listings .

Adver se e vent s (AE s)

AEs will be coded using the MedDRA 20.1 corresponding to the latest version available prior to planned date of clinical database lock (in case, the setting is changed, SAP will need to be amended) and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 coll'espondingto I.be se ve1ity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected on I.be "End of Treatment Phase completion", "Study Phase Completion" or "Death" eCRF pages.

All AE smrnnaries will be smnmarized (frequency com1ts and percentages) by system orgar1 class and/or prefe!1'ed term, and maxi.mum severity grades, except where otherwise noted. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will beproduced:

- AEs regardless of study dJug relationship
- AEs suspected to be sn1dy chug related
- On-treatment deaths, by primary system organ class and prefened te1m
- SAEs regardless of study dJug relationship
- SAEs suspected to be study drng related
- AEs leading to discontinuation of study chug
- AEs requiring dose adjustment
- AEs requiring study ch11g inten11ption
- AEs requiring dose adjustment or study chug interruption
- AEs requiring significant additional therapy

Adverse events of specialinterest

Adverse events of special interest (AESis) are defined as AEs within the following categories/ groupings of prefen-ed terms:

- Hepatotoxicity
- Interstitial Jungdisease/Pneumonitis
- QT inte1val prolongation
- Bradycardia
- Hyperglycemia
- Gastrointestinal toxicity (nausea, vomiting and dianhea)
- Pancreatitis (including lipase and amylase elevations)

The AESI defmitions will be based on the electronic case retii eval strategy (eCRS) for **LDK378** program based on MedDRA 20.1-

[redacted]

In case, the setting is changed, SAP will need to be amended.

These AESis will be summarized for each grouping, by prefened tem1, as follows:

- AllAESis
- CTC grade 3/4 AESis
- AESis suspected to be study drug related
- CTC grade 3/4 AESis suspected to be study drng related
- Serious AESis
- AESis leading to study drng discontinuation
- AESis requiringdose adjustment
- AESis requiling study drng intenuption
- AESis leading to dose adjustlnentor study drng intenuption

Laboratory data

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summa1ies will include all laboratory assessments collected no later than 30 days after study drng discontinuation. All Jaborato1y assessments will be listed and those collected later than 30 days after study drng discontinuation will be flagged in the listings.

Laboratory data will be classified (by Novartis Oncology CORR) into CTC grades according to the NCI CTCAE v4.03. For all repo1ts, CTC grade is always obtai11ed on the converted

measurement in SI unit. A seve1ity grade of 0 will be assigned when the val ue is within nonnal limits. Grade 5 will not beused.

The following sulllJlia1ies will be produced for the hematology and biochem.islly labo ratory data (by laboratory parameter):

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laborato1y parameters with CIC grades
- Shift tables using low, nonnal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are notdefined.

The following lab parameters will be summarized:

- Hematology: absoh1te lymphocytes (decreased), absolute neutrophils (decreased), hemoglobin (anemia) (decreased), WBC (decreased); platelet counts (decreased)
- Biochemist1y: alkaline phosphatase (APT) (increased), SGPT (ALT) (increased), SGOT (AST) (increased), total bilirnbin (increased), amylase (increased), potassium (hyper and hypo), sodium (hyper and hypo), creatinine (increased), glucose (hyper and hypo), phosphate (hypo)

The following laboratory parameters will be presented in listings and will not be smnmarized: absolute basophils, absolute eosinophils, absolute monocytes, RBC, albumin, calcium, magnesium, creatinine clearance, direct bilirnb,in blood urea nitrogen (BUN) or urea, GGT, urinalysis macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity), Urinalysis Microscopic panel (RBC WBC casts), Honnones (males only) Testosterone, LH, FSH, sex hormone binding globulin (SHBG), coagulation INR, pro-tluombinti.me (PT) or Quick Test.

The following listings will be produced for the laborato1ydata for all laborato1yparameters where CTC grades are defined:

- Listing of patients with laborato1y abno1malities of CIC grade 3 or 4
- Listing of all laboratory data with values flagged to show the conesponding CTC grades and the classifications relative to the laboratory reference ranges.

Liver function tests (LFTs) of interest for LDK378 are total bilirubin (TBILn, ALT, AST and ALP. In what follows, AT refers to ALT or AST values. LFTs will be smnmarized as follows:

- Shift tables of baseline vs. worst post-baselineon-treatment values for the categories:
  - TBILI$ 2xULN, TBILI > 2xULN and missing TBILI
  - ALT$ 3xULN, ALT > 3xULN and missing ALT
  - AST$ 3xULN, AST > 3xULN and missing AST
  - ALP:;; 2x ULN, ALP > 2xULN and missing ALP
- Frequency counts and percentages of patients with worst post-baselineon-treatment values in the categories:
  - ALT > 3xULN, ALT> SxULN, ALT> IOxULN, ALT>20xULN
  - AST > 3xULN, AST > SxULN, AST> I0xULN, AST> 20xULN
  - AT> 3xULN, AT> 5xULN, AT > I0xULN, AT > 20xULN

- TBILI > 2xULN
- ConcmTent ALT > 3xULN and TBILI > 2xULN
- ConcmTent AST > 3xULN and TBILI > 2xULN
- ConcmTent AT > 3xULN and TBILI > 2xULN
- ConcmTent AT > 3xULN and TBILI > 2xULN and ALP :;; 1.5xULN
- ConcmTent AT > 3xULN and TBILI > 2xULN and ALP >= 2xULN

ConctUTent mea surements are those occmTing on the same date.

In addition , a listing of all TBILI, ALT, AST and ALP values for patients wilh a post-baseline TBILI > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

ECGs

ECG data will be analysed based on central laboratory reported results. The smmuaries will include all ECG assessments perfonued no later than 30 days after lhe last da.te of stud y drug. All ECG assessments will be listed, and those collected later than 30 days after study drug discontiima.tion will be flagged in the listing.

The following analyses will be perfonned for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate, QTcB QTcF, and QTcP) as noted.

- For each of lhe QTcF, QTcB, QTcP, and QT iI1te1v als , desctiptive statistics a.t b aseline, a.t eac h post-baseline tiine poiI1t and changes from baseline at each post-baseline tin1e point
- For each of lhe QTcF, QTcB, QTcP, and QT iI1te1v als , shift tables based on notable parameter categories (g50, >450g 80, >480• $500, >500ms) at baseline and the worst post-baseline value obse1ved
- Frequency cotmts and percentages of patients having notable ECG values according to lhe following categories:
  - QT parameter (QT, QTcF, QTcB, QTcP) increase from baseliI1e >30 ms, >60 ms
  - Newly occm1111g post-baseliI1e QT parameter > 450 ms, > 480 ms, > 500 ms
  - HR increase from baseline> 25% and value> I00 bpm
  - HR decrease from baseline > 25% and value < 50 bpm
  - PR increase from baseliI1e > 25% and value > 200 ms
  - Newly occm1111g post-baseliI1e PR > 200 ms, > 220 ms
  - QRS increase from baseliI1e > 25% and value> 110 ms
  - Newly occun111g post -base liI1e QRS > 110 ms, > 120 ms

  The denominator to calcula.te pe rc en tages for each category is lhe number of pa.tients with both a baseline and a post-baseline evaluation. A newly occur1111g post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the c1ite1ion at baseliI1e
- Frequency counts and percentages of patients with newly occtm111g post-baselme qualitative ECG abnormalities (mo1pbology) will be smnmarized. The denominator to calcula.te percen tages is the number of patients with botha baseline and a post-baseline evaluation. A newly occtm-ing post-baseliI1equalitative ECG abnonnality is defined as a post-baseline abnonual finding which was not present a.t baseline

Patients with notable ECG interval values and newly occuning qualitative ECG abnonnalities will be listed and the coffesponding notable values and abnonuality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

Vital signs

Vital sign assessments will be perfonued in order to characterize basic body function. Tue parameters collected are weight (kg), body temperan·ue (°C), pulse ra.te (beats per minute), systolic and diastolic blood pressure (nmtllg), and respiration rate (breaths per minute).

Clinically notable elevated values are defined as:

- Systolic BP: 2. 160 nunHg and an increase 2. 20 nunHg from baseline
- Diastolic BP: 2. 100 mmHg and an increase 2. 15 nmtllg from baseline.
- Body temperan·ue: 2. 39.1°C
- Weight: increase from baseline of 2. 10%
- Pulse rate: 2. 120 bpm with increase from baseline of 2.1S bpm

Clinically notable below nomial values are defined as:

- Sys tolic BP: ,s; 90 nunHg and a decrease 2. 20 nnnHg from baseline
- Diastolic BP: ,s; 50 mmHg and a decrease 2. 1S mmHg from baseline
- Body temperan·ue: S: 35 °C
- Weight: decrease from baseline of 2. 10%
- Pulse rate: S: 50 bpm with decrease from baseline of 2. 15 bpm

Vital signs shift table based on values classified as notable low, 1101mal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP.

Descriptive statistics will be tabulated for baseline and change from baseline to worst post-baseline value for each vital sign measure.

Patients with clinically notable vital sign ab1101malities will be listed. All vital sign assessmentswill be listed by patient and vilal sign parameter.

In the listings, clinically notable values will also be flagged.

ECOG performance status

ECOG Perfonnance Scale is provided in Table 2-2 and is used to assess physical health of patients, ranging from O (most active) to *5* (dead):

Table 2-2 ECOG performance scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-carebut unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled.Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift tables of ECOG pe1fonnance status at baseline to worst post-baseline ECOG status by score. ECOG pe1fo1mance stan1s at each time point will be listed.

[redacted]

[redacted]

2.8.5 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

[redacted]

2.9 Sample size calculation

Based on Simon's (1989) optimal two-stage design, approximately 105 total patients are required to test a null hypothesis of ORR .:'o 35% vs. an altemative hypothesis of ORR of 50% or more with a one-sided cr=0.05 and 90% power. If at least 17 confnmed responses are

observed among 43 patients enrolled into Stage 1, an additional 62 patients will be enrolled into Stage 2. If 45 or more confirmed responses are obse1ved among I05 total patients, the nial will bedeclared positive.

The operating characteristics of the design are desc1ibed in Tab le 2-3.

Table 2-3 Operating characteristics of Simon's optimal two-stage design

	True ORR			
	35% (null hypothes is)	40%	45%	50% (alternative hypothesis)
Probabilrty stop for futility at Stage 1 (16 or fewer responses out of 43 patients enrolled at Stage 1)	0.683	0.418	0.192	0.063
Probabilrty trial is success (45 or more responses out of 105 total patients)	0.049	0.268	0.642	0.900

2.10 Power for analysis of key secondary variables

Not applicable.

2.11 Interim analysis

In order to info1m the recommendation to proceed to Stage 2 of the study, a data monitoring committee (DMC) will periodically review response data during Stage I, based on local investigator assessment, as defined in the DMC chal er. The DMC may request data of assessment of response by the BIRC if deemed necessary to provide its recommendation. As per Simon's optimal two-stage design, the nial will be stopped at Stage 1 for futility if 16 or fewer responses are obse1ved in the 43 patients enrolled to Stage 1. According to this rnle, the DMC will make the reco1mnendaiton to transition into the Stage 2 of the study. If at the time that the last patient is enrolled to Stage 1 a minimmn of 17 responses have not yet been obse1ved, accrnal may be temporarily suspended until either the minimmn number of 17 responses are obse1ved or all 43 patients have been followed for at least 6 cycles of LDK378 or discontinued treatment.

Safety will be reviewed by the DMC regularly during the conduct of the study.

3 Changes to protocol specified analyses

This section contains to protocol-specified analyses and associated rationale for inclusion in Appendix 16.1.9 (Docmnentaiton of statistical methods) of the CSR.

Table 3-1 Changes to protocol s pe c ified analysis or des c riptions and rationale

Protocol Section	Protocol Description	Change	Ra tionale
Section 10.1.2-Safety Set	The Safety Set will include all patients who receive at least one dose ofLDK378	Changed to "The Safety Set consists of all patients who received at least one	This change from the protocol wording for and has been introduced in Section 2.2 of lhe RAP for

Protocol Section	Protocol Descrietion	Change	Rationale
	and have at least one valid post-baseline safety assessment. The statement that a patient has no AE (on the Adverse Event eCRF) constitutes a valid safety assessment.	dose of srudy dmg"	progranumng cla1ific.ation/simplification. It does not constitute a de facto change given that the DAR eCRF where the infonnation on dosing is collected will also collect the reason for why the dmg was discontinued which in itself constitutes a safety assessment
Section 10.1.3 - Per Protocol Set	The PPS will include patients who have an adequate tumor assessment at baseline, a follow-up tumor assessment >8 weeks after starting treatment (unless disease progression is observed before that time), and no major protocol deviation"s	Changed to"The PPS will include patients who have au adequate rumor assessment at baseline, a follow-up tumor assessment >7 weeks after starting treatment (unless disease progression is obse1ved before that time), and no major protocol deviations"	This change was made to take into consideration the +/-1 week window associated with rumor assessments
Section 10.5.3.3 - Laborato1y abno1malities	Frequency tables for newlyoccuning on-treatmentgrades 3 or 4 will be provided separately for hematology and biochemistty laboratory tests	Deleted	One of the proposed analysis desc1ibed in Section 2.8.2 of the RAP tmder Laborato1y Abnonnalities, is a shift table usingCTC grades to compare baseline to the worst post-baselinevalue on treatment. The info1ma.tion thatwould be contained in the tabulation described in the protocol is similar to that contained within this shift table
Section 10.4 -	Reference is made to	The analysis for the	This change is ma.de given

Protocol Section	Protocol Description	Change	Rationale
Primary Objective; Section 10.5.1 - Key Secondary Objective(s)	the calculation of 90% Cls given that the primary endpoint is tested at one-sided 5% significance level	primary endpoint will show the 90% CI as per protocol as well as 95% nai:ve Cls. For other secondary endpoints only 95% Cls will be dis la ed	that across the LDK378 program, all efficacy endpoints are surmnarized using 95% Cls

4 Additional details on implementation of statistical methodology

Tue sec tions below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of statistical methods) of the CSR as well as rules details on programing mies that will be followed to in1plement the analyses desc1ibed in Section 2.

4.1 Data included in the analyses

This section provides additional details to those included in Section 2.1.

Final analysis of study data at the end of the study will include the data with an assessment date or event start date (e.g. vital sign assessment date or sta1t date of an adverse event) prior to or on the cut-off date. For example, if the cut-off date is 30DEC2008, an AE starting on 28DEC2008 will be reported, whereas an adverse event starting on 31DEC2008 will not be repo1ted.

4.2 Patient Classification into Analysis Sets

This section provides additional details to those included in Sec tion 2.2.

Patients are excluded from the analysis populations based on the protocol deviations entered in the data.base and/or on specific patient classification mies as shown in Table 4-1 below. No analyses based on Per Protocol Set are planned in this final CSR.

Table 4-1 Patient classification rules

Analysis Population	Protocol deviation severity codes leading to exclusion	Additional patient classification mies leading to exclusion
Full Ana lysis Set	1, 3, 511	Not applicable
Safety Set	2, 3, 511	Not applicable
Per Protocol Set	4,511	Protocol deviations that will lead to removal of pa tients from Per Protocol Set (defined in Section 2.2)

[redacted]

Severity code: 0= Include in everything, 1= Exclude from FAS, 2= Exclude from safety, 3= Exclude from FAS and safety, 4= Exclude from per-protocol, 511=exclude from all analysis

4.3 Last contact date

Tue last contact date is used for censoring in OS analyses and will be derived for patients not known to have died at the analysis cut-off using the latest complete date among lhe following:

- All patient assessment dates (e.g. blood draws, vital signs, perfomiance status, patient reported outcomes, ECG, ttuuor assessments, etc)
- Concomitant medication stait and end dates
- Start and end dates of antineoplastic therapies administered after stt1dy drng discontinuation.
- AE sta1t and end dates
- Last known date patient alive collected on lhe 'Su1vival info1mation' eCRF
- Study drng start ai1d end dates
- Dateof discontinuation on the 'End of treatment phase completion' and/or the 'Srudy phase completion' eCRFs.

If the last contact date as derived above is after the cut-off date then the cut-off date will be used. Only dates associated with patient visits or acttial examinations of the pa.tient will be used in the de1ivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used.

4.4 Month derivation

For all derivations, a month will be calculated as (365.25 *I* 12 } = 30.4375 days . If duration is to be repotted in months, dmation in days will be divided by 30.4375.

4.5 Dose interruptions and dose changes

This section provides additional details to those included in Section 2.6.

All calculations of dose iutenuptious and dose changes are based on the dose actually taken by lhe patient.

An intem1ption is defined as a O mg dose taken on one or more days. What follows defines how dose intenuptions will be co unted in the case of multiple dose inte111ptions .

- If an intenu ption occurs consecutively for at least two days due to the saine reason, then it will be counted only once *(example: If the actual dose on days 1-3 is 750 111g and actual dose 011 days 4-5 is O mg and dose i11te r n1pfio11 on days 4-5 is due to AE, then the total number of dose interruptions is* J).

- If an intenu ption occurs consecutively for at least two days due to different reasons, then it will be cotmted for each reason *(example: If the actual dose on days 1-3 is 750 mg and actual dose 011 days 4-5 is 0 mg and dose interruption 011 day 4 is due to AE and dose interr11ption on day 5 i.s due to dosing error, then the total number of dose interruptions is 2).*
- If an intenuption occurs for more than one day due to the same reason, but the days are not consecutive , i.e. there is at least one dosing day in between, then each dose inte1111ption will be counted as a different occunence *(example: if the actual dose on days 1, 3 and 5, is 750 mg and acfllal dose 011 days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 m·e borh due to dosing error, the toral number of dose inrerruprions is 2).*

A dose change is defined as a change to a lower or higher dose than the protocol planned dose e.g. 600 mg or 450 mg or 300 mg (reduction may be preceded by a O mg due to an inte1111ption) in the daily administered dose, with an associated reason for dose change documented in the DAR sununa1y eCRF page. *For example, in the sequence 750 mg - 0 mg - 600 mg, the 600 mg dose will be co11nted as a dose change, preceded by a 0 mg due ro interruption (with reason documented) and 600 111g due to change (with reason documented).*

A dose inten11ption will not be counted as a dose change.

If a patient moves from a higher than protocol planned dose down to the planned dose then this will not be counted as a dose change, however if they move directly from a higher than planned dose down to a lower than protocol planned dose, then lhis will be cotmted as a dose change (with reason documented).

Dose reductions are a subset of dose changes where dose changes to higher tlian protocol plam1ed dose are excluded.

4.6 Efficacy endpoints

For further details on efficacyendpoints, see Section 14 (Appendix II) of the protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator and BIRC according to RECIST I.I.

Response and progression evaluation will be perfonned according to the Nova1tis RECIST 1.1 guidelines, included in Section 14 (Appendix II) of the LDK378A2203 protocol.

The text below gives more detailed instrnctions and mies needed for programming of the analyses desc1ibed in Sections 2.7 and 2.8.1.

4.6.1 Implementation of RECISTGuidelines

Disease progression

PD should only be assigned if it is confumed by an objective assessment metl1od as per RECIST I.I (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions) If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST eCRF with appropriate method (or method='Other').

In particu lar, discontinuation due to disease progression or death due to progressive disease, without suppo1t ing objective evidence (as defined above), will not be considered as PD in the determination ofBOR, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in teclmique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK (unknown) overall lesion response assessment. However, a response assessment other than the Nova1tis calculated UNK response may be accepted from the investigator or BIRC if a definitive response assessment can be jt1stified based on the available infonnation. Potential discrepancies between the modality used and overall lesion response repo1ted by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be que1ied dming the data validation process.

Determination of missing adequate tumor assessments

For the computation of ORR, patients without any radiological assessment after the sta1t date of study drng will be counted as failme.

Pa11iaJ or complete responses repo1t ed prior to any additional anticancer therapy will be considered for ORR computation in espective of the number of missed assessments before response. In this section, the 'missing adequate assessment' is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the 'missing adequate assessment' will also be refe1rnd as 'miss ing assessment'.

As detailed in Section 14 (Appendix II) of the LDK378A2203 protocol, the PFS censo1ing and event date options depend on the presence and the number of missing tumor assessments. *For example, an event occurring after two or more missing assessments is censored i11 the analysis of PFS at the last adequate tumor assessment before the event date.*

An exact rnle to dete1mine whether there is none, one or two missing assessments is therefore needed. This rnle will be based on the distance benveen the last adequate tumor assessment date and the event date.

If the distance is larger than threshold D1 or D2 then the analysis will assume one or two missing assessments, respectively. The threshold D1 will be defined as the protocol specified interval between the tmuor assessments plus the protocol allowed window around the assessments. Similarly, the tlu-esho ld D2 is defined as nvo times the protocol specified interval between the tumor assessments plus the protocol allowed window aro1md the assessments. In tl1is study, the protocol defined schedule of tumor assessment is eve1y 8 weeks and each assessment is expected to be perf01med at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than D1= 8+2 = 10 weeks means one missing assessment and any distance larger tl1an D2 = (2*8) + 2 = 18 weeks means two missing assessments.

The same definition of D2 will be used to determine the PFS censoring reason. If the distance between the last adequate tumor assessment date and one of the following dates is $\leq$ D 2:

1. Analysis cut-off date
2. Start date of farther anti-neoplastic therapy
3. Visit date of study treatment discontinuation due to consent withdrawal
4. Visit date of study treatment discontinuation due to loss to follow-up

then the associated censoring reason will be

1. Ongoing
2. New cancer therapy
3. Withdrew consent
4. Loss to follow-up

However, if this distance is larger than D2, then the censoring reason will be ' Adequate assessment no longer available'.

Non-measurable disease at baseline

As specified in Section 14 (Appendix II) of the LDK378A2203 protocol, the RECIST 1. 1 criteria imply that only patients with measurable disease at baseline should be included in the study. If a patient without measurable disease is em·olled, the intent-to-treat (ITT) p1inciple requires including these patients in the anal yses. Hence, analyses will be based on FAS including patients with either measurable or non-measurable disease. Therefore, a mle needs to be specified on how to handle these cases.

As specified in Table 3-1 of Section 14 (Appendix II) of the LDK378A2203 p rotocol, overall lesion response can be derived for patients without measurable disease at baseline.

Target lesion response will always be UNK due to missing baseline measurements. Therefore, a CR, PR or SD can never be assigned as an overall lesion response. However, a PD can still be determined from non-target lesions or from new lesions.

As a result, the overall lesion responses will always be UNK until PD occms. The BOR will either be UNK or PD depending on the tuning of PD (if PD is obse1ved > 17 weeks , it will be considered as UNK). The PFS censoring and event date options will depend on how many UNK.s precede the PD.

Missing baseline tumor assessment

As specified in Section 14 (Appendix II) of the protocol (see Table 4-1}, since the tuning of PD cannot be detennined for patients with missing baseline tmnor assessment, these patients are censored iJ1 the PFS analysis at the start date of treatment. This mle, however, only applies to the ' PD component' of the PFS or DOR assessment.

Patients without baseline tumor assessment who die within D2 distance from start date of treatment will be counted as having an event in the prinlary analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

Construction of waterfall graphs

The wate1fall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the smu of the longest diameter of all target lesions for each patient. The proportions of patients with valious degrees of tumor shtinkage or growth can then represent a useful efficacy meuic.

However, caution needs to be paid to the assessments, where an occmTence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measmements obtained on target lesions. These assessments will not be displayed as bars in the graph. If such a " contradicting" assessment represents lhe only post-baseline assessment for a patient, then the patient will be represented by a special symbol (e.g. *) in the wate1fall graph.

The assessments with unknown target response and also assessments with unknown overall response will be excluded. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph needs to be shown and this number will be used as a denominator when calculating the percentages of patients with tmnor shrinkage and nunor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are desc1 bedin Table 4-2.

Table 4-2 Inclusion/exclusion of assessments used in waterfall graph

Criteria for inclusion/exclusion			Possible source of conu·adictions	
Target response	Overall lesion resoonse	Include in waterfaJJ	Non-target resoonse	New lesion?
CR/PR/SD	PD	Yes but as* onlv	PD	anv
CR/PR/SD	PD	Yes but as* onlv	anv	Yes
UNK	UNKorPD	No	anv	anv
CR/PR/SD	UNK	No	UNK	No
CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
PD	PD	Yes as a bar	any	any

Tue following algorithm will be used to consu11ct the graph:

I. Select "valid" post-baseline assessments to be included, i.e. for each patient and each assessment repeat the following four steps:

1.1 Check the target lesion response and overaJJ lesion response at each assessment. If at least one of them is UNK then exclude the whole assessment. Otherwise, go to step 1.2.

1.2 Check the overall lesion response. If PD then go to step 1.3. Otherwise, go to step 1.4

1.3 Check target response. If it's PD then go to step 1.4. Otherwise flag the assessment *

1.4 Calculate the% change from baseline in target lesions.

2. For each patient, go through all valid assessments identified in step I and find the assessment with best % change from baseline in target lesions. The "best" means best for the patient, i.e. the largest shrinkage or if a patient only has assessments with tumor growth take the assessment where the growth is minimal. *(Example1:* Patient I has the following% changes from baseline at assessments 1, 2, 3, 4 and S, respectively: -10%; -25%; -13%; -4% and +6%. His/her best % change is then -25%. *Exa111ple 2:* Patient 2 has the following % changes from baseline at assessments I , 2 and 3, respectively: +5%; +18% and +35%. His/her best% change is then +5%.
3. Constnict the wate1fall graph displaying the best% change from baseline for each patient. Patients having only * flagged assessment(s) will bedisplayed separately.

Both investigatorassessment and BIRC will beused in the construction of wate1fall plot.

The recommended way of the display from left to1ight is:

1. Bars under the ho1izontal axis representingnunor slu·inkage
2. Bars above the ho1izontaJ axis representing nunor growth
3. "Zero" bars with * symbol representing patients with contradiction

4.6.2 Sources for overall lesionsresponse

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point will be providedfrom different som·ces as illustrated in Table 4-3.

Table 4-3 Sources for overall lesion response

Sow-ce 1	Investigator (local radiolo2v) reported overall lesion response
Source2	Calculated overall lesion response based on raw (i.e. individual lesion) measurements from Investigator (local radiolo2v)
Source 3	BIRC (Blinded Independent review co1111nittee) repor tedoverall lesion response

In this study, Source 1 will be used for the prinuuy endpoint derivation and other secondary endpoint calculations based on investigator assessment (ORR, DCR, DOR, TTR and PFS) and Sow-ce 2 will be listed against Somce 1 and discrepancies between calculated and reported responses assigned by investigator will be identified. Source 3 will be used to calculate ORR, DCR, DOR, TTR and PFS by BIRC.

4.6.3 Kaplan-Meier estimates

To analyze time to event variables (DOR, TTR, OS and PFS) an estimate of the smvival function will be constnicted using ***Kaplan-Meier*** *(product -limit) method* as iniplemented in PROC LIFETEST with METHOD=KM option (see example below). The median time to event and estimated event rates at different time points will be estimated, along with associated 90% or 95% two-sided Cls derived based on the complementa1y log-log

transfonnation. This will be conducted via the SAS procedure LIFETEST. The TIME statement will include a variable with survival times *(survti111e* in the example below) and a (iight) censo1ing va1iable *(censor* in the example below) with a valtle of 1, representing censoring (example code below for constmction of 90% Cls):

```
PROC LIFETEST data =dataset
    METHOD = KM
    ALPHA = 0.1
    ALPHAQT = 0 .1
    CONFTYPE=LOGLOG;
TIME survtime*censor(1);
RUN;
```

/* *survtime* represents variable containing event/censor times;
censor represents censoiing variable (I = censored, 0 = event); */

Kaplan-Meier sUtv iv aJ and failure ftmction estimates from this procedure will be used to construct the Kaplan-Meier figures

Median smvival will be obtained along with 2-sided 90% or 95% Cls calculated from PROC LIFETEST output using the method ofBrookmeyer & Crowley, 1982.

Kaplan-Meier estimates with 2-sided 90% or 95% Cis a.t sp ecific tim e points will be summarized. The time points can be expressed in weeks or in months depending on the time- to-event va1iable. The Cis will be constmcted using Greenwood's fo1mula [Collet , 1994 , p.23] for the standard enor of the Kaplan-Meier estimate.

The Kaplan-Meier graphs will be constrncted usingSAS software.

4.6.4 Confidence interval andp-value for response rate

ORR will be sununa1ized in te1ms of percentage rates with 90% and 95% Cis. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

SAS proced1u·e FREQ will be used to estimate tlle proportion of responders (bina1y outcome= 1 or "Yes"), along with the associated 90% or 95% (=100 x (1 - *two-sided alpha level))* two-sided Pearson-Clopper CI and exact one-sided p-value for tlle hypothesis test of the *null proporrion* (0.35). These estiniates are obtained as follows:

```
proc freq data= dataset;
      table binary event I
            b i nomi a l (
                  p = null proportion
                  level = " Yes " )
            alpha= two-sided alpha le vel;
      exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing Jeve1="No". From the

results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

LCLLEVEL="Yes" (%) = 100% · UCL1EVEL="No" (%)

UCLLEVEL="Yes" (%) = I00% • LCLLEVEL="No" (%)

4.7 Safety evaluations

Tue text below gives more detailed instrnctions and mies needed for programming of the analyses desc1ibed in Section 2.8.2.

4.7.1 Multiple assessments within post-baseline visits

For all analyses regarding abnomial assessments or analyses based on worst post-baseline value (laboratory, ECGs, vital signs, ECOG perfonnance status), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measw·ements will be included in listings.

Laboratory data

For laboratory data, assessments can be collected from both local and central laboratory on the same date. For shift tables using CTC grades to compare baseline to the worst post-baseline value, the assessment with worst post-baseline value is used for analyses i.nespective of the source. For LFT sunnnaries, where concunent measurements are used in the calculation of number and percentage of patients with worst post-baseline values, the assessment with worst post-baseline value is used (since worst values are based on the largest ratio of lab value to its ULN for each patient) although the worst values for the different parameters may be coming from different laborato1ies.

ECGs

For all patients, 3 ECGs are targeted to be measured at the protocol-defmed (nominal) ti.me-po ints. If a patient bas more than one measurement at a specific time point, the average of *all* available measurements associated with the nominal ti.me point will be used for the analyses.

4.7.2 Baseline

As defined in Section 2.8.2, the last available assessment before or on the date of sta1t of study dmg is defined as "baseline" value or "baseline" assessment.

Laboratory data

If both central and local laboratory assessments were pe1formed on the same date and co1Tespond ing to the baseline assessment date, then the central laboratory assessment will be used for the calculation ofbaseline.

ECGs

Baseline for ECG analysis is defined as the average of all available ECG measmements associated with the baseline assessment date. Study day 1 scheduled pre-dose ECGs will be consideredto have been obtained prior to study drng administration if dosing time is missing.

If a scheduled pre-dose measurement acmally occwTed post-dose, then the c01Tesponding measurement will be treated and analyzedsimilar to an unscheduled post-dose measurement.

4.8 Handling of missing or partial dates

For patients not known to have died prior to the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will be repo11ed as "co ntinuingat the cut-off date".
- This approach applies, in particular, to AEs and concomitantmedication repo1ts. For these events, theend date will not be imputed and therefore will not appear in the listings.

For patients known to have died p1ior to or on the cut-off date:

- All events with sta1t date before or on the cut-off date, and with end date missing or after the cut-off date will have the end da.te imputed to the death date.
- This approach applies, in particular, to AEs and concomitant medication repolts. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. for a dose administration record with missing end date or last date of study dtug after the cut-off date), the end date will be imputed to the cut-off date for the ptupose of calculating dm11tion of exposme to study drng and dose intensity. Tue imputed date will bedisplayed and flagged in the listings.

4.8.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algo1ithm. Missing date for AE will be handled according to mies specified below. A pa1 ial date is simply an incomplete date e.g. DDOCT2001: the days are missingfrom this DDMMMYYYY date.

Paitial AE sta1t dates, ifleft pai1ial, would ultimately mean the following

It would not be possible to place the AE in time.

Therefore the treatment/dosageat the time of the event would be unknown.

Therefore the event could not be repo1ted/sunnnarized appropriately - if at all.

Therefore it is impoltant to pe1fon11 date imputation to ensme that as many data events are represented as co1Tectly as possible. Of course pa1tial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

- **Missing** AE sta1t dates
- AE sta1 dates **missing the year**

- Pa1 1ial/missing AE **end date s**

The following Table 4-4 explains the abbreviations used.

Table 4-4 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date TRTSTD	<not used>	TRTM	TRTY

Tue following matrix Table 4-5 describes the possible combinations and their associated imputations. hl the light grey boxes the upper_ text indicates the imputation and the lower text the relationship of the AEstai1 date to the treatment start date (TRTSTD).

Tab le 4-5 **AE** partial date imputation algo rithm

	AEMMISSING	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEYMISSING	NC Uncertain (D)	NC Unce1tain (C}	NC Uncertain (C)	NC Unce1tain (C)
AEY < TRTY	Before 1R TSTD (B)	Before 1RTSTD (C}	Before 1RTSTD (B)	Before TRTSTD (A)
AEY=TRTY	Uncertain (D)	Before 1RTSTD (A)	Uncertain (A)	After 1RTSTD (A)
AEY> TRTY	After 1RTSTD	After 1RTSTD	After 1RTSTD	After1RTSTD

The following Table 4-6 is the legend to the above table.

Table 4-6 AE/treatme nt date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE sta1t date prior to Treatment Sta1 1 Date
After TRTSTD	h1dica.tes AE sta1t date after Treatment Sta1t Date
Uncertain	htsufficient to determine the relationship of AE start date to Treaunent Sta1t Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	0lMONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	OlJULYYYY
(E)	0lJANYYYY

The following Table 4-7 gives a few examples.

Tab le 4-7 **AE** imputatio n example scenarios

Partia l AE start date	Treatment start date	Relationship	Imputation Calcula tion	Imputed Date
12mmyyyy	20OCT2001	Unce rtain	NC	<blan k>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Unce rtain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Unce rtain	(B)	21OCT2010
ddNOV2001	20OCT2001	After	(A)	01 NOV2001

4.8.2 Incompletedate of initial diagnosis of cancer, date of most recent recurrence and date of anti-neoplastictherapies

Missing day is defaulted to the 151h of the month and missing month and day is defaulted to 01-Jan.

4.8.3 Incomplete assessment dates for tumor assessment

All investigation dates(e.g. X-r,ay CT sca.n) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, the incomplete date(s) are not co1tsidered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. X-ray, CT-scan) if the

overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise, if overall lesion response is PD, the assessment date is calcnlated as the earliest date of *all* investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1 *st* of the month is used.

If the month is not completed, for any of the investigations,the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for anycalculations.

4.8.4 Incomplete date for death

All dates must be completed with day, month and year.

If the day or montl1 is miss ing, death will be imputed to the maxinuuu of tl1e last coutact date (excluding the date of death) and the following:

- Missing day: Ist day of the month and year of death
- Missing day and month: July 1st of the year of deatll

[redacted]

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