Clinical Development

INC280

Protocol CINC280X2205 / NCT02276027

A Phase II, open label, multiple arm study of single agent AUY922, BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced non-small cell lung cancer (NSCLC)

RAP Module 3 – Detailed Statistical Methodology

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Table of contents

Amendment 1

Amendment rationale

To align the statistical analysis description with the latest protocol amendment 7 (dated on 22nd of May 2019).

Changes to the RAP M3:

Changes to specific sections of the RAP Module 3 are shown in the track changes version of the RAP M3 using strike through font for deletions and underlined for insertions.

The following main changes were made:

- Section 3.1.3 – Update the definition of Per-Protocol Set as per protocol amendment.
- Section 3.1.4 – Update the table 3-1 for patient classification into analysis sets.
- Section 8.1 – Update the definition of BOR as per protocol amendment.
- Section 8.2 – Update the description of statistical analysis as per protocol amendment.
- Section 9.2.1.1 – Update the adverse events of special interest

1 Introduction

This document provides detailed statistical methodology for the analysis of data from study INC280X2205 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in RAP module 7. RAP module 8 provides the programming specifications for derived variables, datasets and outputs.

All changes to the planned analysis described in RAP modules 3, 7 and 8 required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in RAP module 7 without the need to amend these modules.

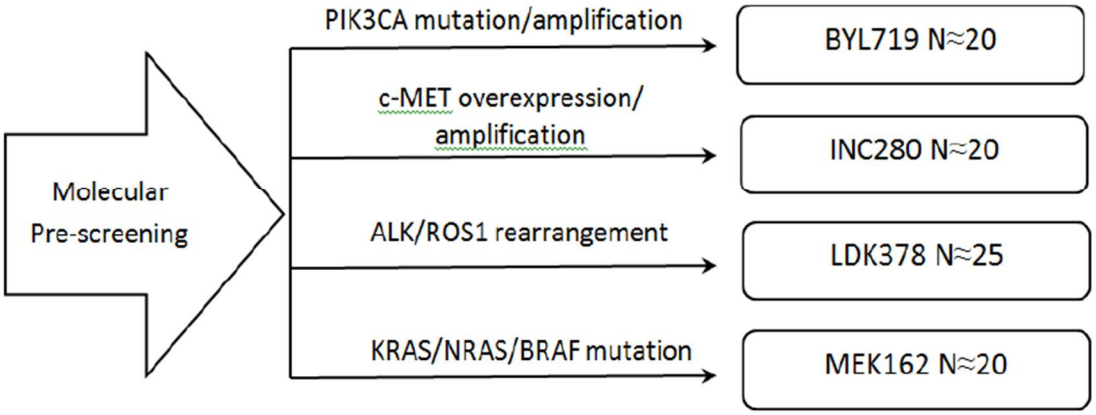
RAP modules 3, 7 and 8 may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts, management updates.

RAP modules 3, 7 and 8 are created based on final protocol version 03 released on 22-May-2019.

1.1 Study design

This is a Phase II, multiple arm, open-label study of single agent BYL719, INC280, LDK378 and MEK162. This study will enroll approximately 20-25 advanced NSCLC patients to each treatment arm according to their molecular alterations (Figure 1-1). Each treatment arm is independent from one another and will be analyzed separately. Despite the title of this study, AUY922 was decided not to be included for investigation as detailed in protocol Amendment 3.

Figure 1-1 Study Design



The multiple arm design was chosen, with objective response rate (ORR) as primary endpoint, to evaluate the efficacy of single agent BYL719, INC280, LDK378 and MEK162 in advanced

NSCLC patients. In addition, safety, tolerability, PK and gene alterations that may be related with resistance will also be evaluated for each agent.

For each treatment arm the sample size was calculated based on a Bayesian approach using either a minimally informative prior (BYL719, INC280 and MEK162) or an informative prior using relevant historical data (LDK378). The proposed sample size will allow detecting with high likelihood statistically and clinically relevant anti-tumor activity.

1.2 Objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint	
Primary		
To investigate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162	ORR per RECIST v1.1	
Secondary		
To further assess the clinical activity of single agent BYL719, INC280, LDK378 and MEK162	OS, PFS, DCR, duration of overall response per RECIST v1.1	
To characterize the safety and tolerability of single agent BYL719, INC280, LDK378 and MEK162	Frequency/severity of AEs and SAEs; laboratory abnormalities Dose interruptions and dose reductions	
To characterize the pharmacokinetic profiles of single agent BYL719, INC280, LDK378 and MEK162	PK parameters including but not limited to AUC0-t, Cmax, Tmax, T1/2, CL/F and Vz/F	

[redacted]

2 Data Analysis

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version *9.4*. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.2 or above.

The study data will be analyzed and reported based on all patients' data up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. The CSR will include all outputs planned within RAP module 7.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

3 Analysis sets

The patients who are screen failure will not be included in any of these sets. They will be listed with the reason for screening failure.

3.1 Analysis sets

3.1.1 Full Analysis Set

For each treatment arm the Full Analysis Set (FAS) comprises all patients who received at least one dose of the respective study treatment. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

3.1.2 Safety Set

For each treatment arm the Safety Set includes all patients who received at least one dose of the respective study medication and had at least one valid post-baseline safety assessment. Please note: A **"no"** to indicate that the patient had no AEs (on the AE eCRF) constitutes a valid safety assessment.

Patients will be classified according to treatment received, where treatment received is defined as:

- The treatment assigned if it was received at least once, or
- If the assigned treatment was never received, then the first treatment received when starting therapy with study treatment will be used for classification

The safety set will be used for all the safety summary of the study.

3.1.3 Per-Protocol Set

For each treatment arm the Per-Protocol Set (PPS) consists of a subset of the patients in the respective FAS who are compliant with requirements of the clinical study protocol (CSP).
Protocol deviations potentially leading to exclusion from the PPS are:

- type of indication different from those required in protocol Section 5 (e.g., incorrect histology/cytology, incorrect molecular alteration etc.)
- prior therapy does not match with requirements in protocol Section 5 in terms of number and types of previous therapy regimens
- missing or incomplete documentation of stage of disease
- ECOG>2
- another anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment
- study treatment received different from treatment assigned
- patient without measurable lesions

Any other protocol deviations leading to exclusion from the PPS will be described in the RAP prior to clinical database lock.

Patients will be classified according to treatment as assigned.

The PPS will define the patients used in the sensitivity analysis of the primary endpoint. If the PPS and the FAS are identical, then analyses described using the PPS below will not be performed.

3.1.4 Pharmacokinetic analysis set

For each treatment arm the PK analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK concentration. The PAS will be used for summaries of PK concentration (Tables and Figures). For a concentration to be evaluable, subjects are required to:

- Take a dose of the treatment prior to sampling (expect pre-dose samples);
- For post-dose samples, do not vomit with the specified hours after the treatment;
- For steady state trough concentrations, take the same dose of the treatment for at least the required consecutive days prior to sampling.

The PAS for PK parameter calculations includes all subjects who provide an evaluable PK profile. The PAS will be used for summaries as well as listings of derived PK parameters. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments;
- Subject provides at least one primary PK parameter;
- Subject follows the specified meal instructions for the treatment;
- Subject does not vomit within the specified period of the treatment.

Note: patients may be removed from the estimation of certain PK parameters on an individual basis depending on the PK profiles. These patients will be identified at the time of the analyses along with the reason for their removal.

3.2 Additional criteria

Table 3-1 gives additional details to those included in Section 3.

Patients are excluded from the analysis populations based on the protocol deviations entered in the database and/or on specific patient classification rules as shown in Table 3-1 below.

Table 3-1: Patient classification into analysis sets

Analysis Population	Additional patient classification rules leading to exclusion
Full Analysis Set	Patient who did not receive at least one dose of study treatment component
Safety Set	Patient who did not receive at least one dose of study treatment component
Per Protocol Set	Protocol deviations that will lead to removal of patients from Per Protocol Set (defined in Section 3.1.3)
Pharmacokinetic Analysis Set	Patients who do not have at least one evaluable PK sample as defined in Section 3.1.4

4 Patient demographics and other baseline characteristics

Unless noted otherwise, summaries described in this section will be based on the FAS. Summaries will be produced by treatment arm and overall. Data will be listed individually by patient based on the FAS.

4.1 Basic demographic and background data

Demographic data, including age, sex, height, baseline weight, body mass index, medical condition, and disease characteristics will be listed and summarized.

4.2 Medical History

Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for current and historical medical conditions by primary system organ class and preferred term. Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Lastest MedDRA version available at time of reporting will be used.

4.3 Prior antineoplastic therapy

Prior anti-neoplastic therapy will be summarized for three distinct subtypes (medication, radiotherapy and surgery).

The number (%) of patients who received, separately, any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting at last medication, time (in *days*) between end of last medication to start of study treatment, best response at last medication (defined to be the best response during the last treatment regimens recorded), duration (in months) of last best response (last best response is the best response at last medication), reason for discontinuation at last medication and time (in months) from start of last medication to progression. The last medication is defined based on the last end date of all prior regimen components. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include a summary of radiotherapy locations, including all locations recorded for each subjects. Setting at last radiotherapy, and method also be summarized. The time between the last radiotherapy to start of treatment will be summarized in category (< 1 month, 1 - <6 months, 6 - <12 months, and >=12 month). Last radiotherapy is based on end date.

The summary of prior anti-neoplastic surgeries will include the time between the last surgery to start of treatment and procedure applied in last surgery. Last surgery (non-biopsy procedure) is based on the date of surgery. The time between the last surgery to start of treatment will be summarized in category (< 1 month, 1 - <6 months, 6 - <12 months, and >=12 month).

4.4 Diagnosis and extent of cancer

The summary of diagnosis and extent of cancer will include details of primary site of cancer, tumor histology/cytology, histological grade, stage at initial diagnosis, time (in months) from initial diagnosis of primary site to start of study treatment, time (in months) since most recent recurrence/relapse or progression to start of study treatment, time (in months) from initial diagnosis of primary site to first recurrence/relapse or progression, current stage of cancer, current extent of disease (metastatic sites), types of lesions (target and non-target lesions) at baseline, and disease burden at baseline for target lesion.

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 discontinued treatment (based on completion of the ‘End of Treatment Disposition’ page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the ‘End of Treatment Disposition’ page),

- Number (%) of patients no longer being followed for study evaluation (based on completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date and reason entered),
- Number (%) of patients continued to be followed for study evaluation(based on non-completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date and reason entered)
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

A listing of study completion by treatment group will be produced separately using the FAS. Patients are considered to be ongoing if they have not discontinued due to any reason (e.g., disease progression, AE, withdrawn consent).

6 Protocol deviations

The number and percentage of patients with any protocol or non-protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the *SSD*. Major protocol deviations will be tabulated separately by treatment.

All protocol deviations will be listed by treatment.

7 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

Unless otherwise noted, the Safety set will be used for all medication data summaries.

Study drug and study treatment

Study drug and study treatment both refer to the following four investigational drugs in this study:

A: BYL719

B: INC280

C: LDK378

D: MEK162

To maintain consistency, we will only use the term "study treatment" throughout the remaining document.

Date of first/last administration of study treatment

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of study treatment was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

Last date of exposure to study treatment

Last date of exposure to study treatment is the last date of study treatment.

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1.

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment.

On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment + *30* days inclusive.

Definition of end of the study
The end of study is defined as the earliest occurrence of one of the following:

- All patients have completed 30-day safety follow up and a minimum of 12 months has elapsed since last patient first treatment, or patients have been transferred to another Novartis study that they can continue to receive study drug
- Study is terminated early

7.1 Study treatment exposure

Duration of exposure to study treatment will be summarized by treatment arm.

The duration of exposure to study treatment (including categories: <10, 10-<20, 20-<30, ≥30 weeks) will be summarized. In addition, the cumulative dose, average daily dose, DI, and RDI (including categories: <0.5, 0.5-<0.75, 0.75- <0.9, 0.9-<1.1, ≥1.1) will be summarized by treatment arm. Frequency counts and percentages of patients who have dose reductions or delays, percentage of actual days dosed, and the corresponding reasons, will be provided.

All doses of the study treatment along with reasons for any dose change will be listed.

The number of dose delays will be summarized by treatment arm.

Duration of study drug/treatment exposure

The following algorithm will be used to calculate the duration of study treatment exposure (in days) for patients who take at least 1 dose of the study treatment:

Duration of exposure of any study treatment (days) = last date of exposure to the study treatment – date of first administration of the study treatment + 1

In case patient has died, discontinued the treatment, or there is a data cut-off date, use the following definition for the duration of exposure for both the study treatments for all arms
Duration of exposure in days = date of death/date of discontinuation(from EOT disposition page)/data cut-off date − first date of dose administration of the study treatment + 1

For patients who did not take any drug, the duration of drug exposure is by definition equal to zero.

Duration of dose delays or interruption (days): Sum of the duration (in days) of all dose delays/interruptions between the first and last non-zero dose. Definition of dose delay/interruption is given below.

Dose delay/interruption: For any of the treatments arms, when the actual total dose received of the corresponding study treatment is zero, it will be considered as dose delay. The algorithms for dose delay can be defined as follows.

The number of dose delays will be counted as the number of periods in the eCRF DAR page with actual total daily dose administered = 0 mg. For example, 2 dose delays correspond to two different records in which the actual total daily dose administered = 0 mg. Those records may involve more than 1 day. This will be identified using the start and end date of dosing on the corresponding eCRF DAR page. The last zero dose of each treatment arms followed by permanent discontinuation are not considered as dose interruption.

Cumulative dose

The actual cumulative dose for each study treatment is defined as the total dose for the corresponding study treatment given during the study treatment exposure and is expressed in mg. For patients who did not take any dose of this drug, the actual cumulative dose is by definition equal to zero.

The planned cumulative dose is defined as the total dose planned to be given during the study treatment exposure and is expressed in mg.

For all the arms, it is obtained by multiplication of the treatment exposure in appropriate unit (days) by the first planned total daily dose (e.g., treatment duration = 10 days => planned cumulative dose = 10 × daily dosing).

Number of dosing days is defined as the duration of exposure minus the number of zero dose days.

Dose intensity and relative dose intensity

Dose intensity

For each of the study treatments, the dose intensity (DI), expressed as mg/day, for patients with non-zero duration of exposure is defined as follows:

Actual dose intensity (DI) (dosing unit/unit of time) = actual cumulative dose (mg) / duration of *study treatment exposure* (days).

Planned dose intensity (PDI) (dosing unit/unit of time) = planned cumulative dose (mg) / duration of *study treatment exposure* (days).

Relative dose intensity (RDI) is the actual dose intensity (DI) divided by the planned dose intensity (PDI).

For patients who do not take any drug, the actual DI is by definition equal to zero.

Dose reduction

For each treatment arm, the corresponding eCRF allows the recording of dose changes including dose increase, dose reduction and dose delay. A dose change is defined as a change in dosing from one level to the next, however a dose interruption will not be counted as a dose change.

At time points at which the dose change flag is checked and the actual total daily dose received is non-zero, if the actual dose is lower than the previous last non-zero actual total daily dose then the dose change is identified as a dose reduction.

7.2 Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will be summarized by ATC class and preferred term. These summaries will include 1) medications starting on or after the start of study treatment but starting no later than 30 days after last dose of study treatment and 2) medications starting prior to the start of study treatment and continuing after the start of study treatment.

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

Anti-neoplastic therapies since discontinuation of study treatment will be listed and tabulated by ATC class and preferred term.

7.3 Compliance

Compliance to each of the study treatments will be assessed by the number of dose reductions and dose interruptions as mentioned in Section 7.1.

8 Analysis of the primary variable(s)

Evaluation of anti-tumor activity will be based on investigator assessment of overall lesion response according to RECIST v1.1 (see Protocol Appendix 14.4).

8.1 Definitions

Best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking the nadir of the sum of the diameter recorded since the treatment started as reference for PD assessment). The best overall response will be determined from response assessments undertaken while on treatment. However, any assessments taken more than 28 days after the last dose of study therapy will not be included in the best overall response derivation. Moreover, if any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.
The study requires that for a response PR or CR changes in tumor measurements must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for the response are first met.
The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation is required or one determination of CR prior to progression where confirmation is not required.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation is required or one determination of PR prior to progression where confirmation is not required.
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of study treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of study treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall response rate (ORR): For each treatment arm, individual lesion measurements and overall response at each assessment will be listed by patient, from which the best overall response (BOR) will be derived for all patients. The ORR is the proportion of patients with BOR of either CR or PR among all patients in the respective FAS.

Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to ‘Disease progression’ or death due to study indication.

A patient with documented PD as per RECIST will not be considered for clinical progression and their date of PD will always be the date of disease progression as per RECIST.

Clinical progression: Clinical progression will be considered for BOR.

If documented progression is present, then that data will always be used. If there is no documented progression but if the reason for end of treatment is disease progression or the reason for death is due to study indication, then that will also be considered as disease progression.

8.2 Statistical model, analysis and output

A Bayesian approach will be used to estimate ORR and to provide inferential statements in each arm.

Based on prior clinical assumption, the prior median of ORR of each treatment arm is obtained. For INC280, BYL719 and MEK162, a minimally informative unimodal Beta prior distribution for each arm i with parameters a_i and b_i (Neuenschwander et al. 2010) that reflects the degree of uncertainty around ORR before starting the current trial was elicited. Based on prior clinical assumption, the prior median of ORR of each treatment arm is obtained. If the prior median ORR is smaller than 50%, b_i =1 and a_i=ln(0.5)/ln(median$_i$); otherwise a_i =1 and b_i =ln(0.5)/ln(1-median$_i$). The values of prior median$_i$, a_i and b_i for the three treatment arms are listed in Table 8-1.

For BYL719 arm, based on the assumption that similar response is expected in adenocarcinoma and squamous cell carcinoma patients, primary analyses will be done using the pooled data from these two subgroups of patients.

For LDK378 arm, a mixture prior was considered. Table 8-1 gives the priors for all the treatment arms. Details of these priors are described in Section 10.4.2 of the Clinical study protocol (CSP).

At time of analysis, for each treatment arm, the posterior distribution will be derived using the prior and with all available data collected on study. Once the posterior distribution is derived, the posterior probabilities that the true ORR lies in the following efficacy intervals will be provided for each treatment arm:

- [0, L_i) unacceptable efficacy
- [L_i, M_i) limited efficacy
- [M_i, 100%] clinically relevant efficacy

The values of thresholds L_i and M_i for the five treatment arms are listed in Table 8-1.

If (i) the posterior mean ORR in arm i is equal to or greater than M_i and (ii) the posterior probability of being in the unacceptable efficacy category is lower than 5%, then the corresponding study treatment is declared efficacious for the patient population in that arm.

For each treatment arm, the estimated ORR will be the median value of the respective posterior distribution.

Table 8-1 Parameters of prior distributions and thresholds for posterior distributions of ORR

Arm	Prior distribution					Threshold	
i	Component	a	b	Median	90% Credible interval	L_i	M_i
1. LDK378	1** (80%) 2 (20%) Mixture	6.9374 1	5.2562 0.7565	57% 60% 58%	(34%, 79%) (7%, 98%) (26%, 87%)	40%	55%
2. INC280	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%
3. MEK162	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%
4. BYL719	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%

Arm	Prior distribution					Threshold	
i	Component	a	b	Median	90% Credible interval	L_i	M_i

** Component derived from MAP approach. Based on [CLDK378X1101] data with 2 responders in 5 patients at 750 mg QD, with cut-off date of 29-Apr-2013, and [CLDK378X2101] data with 47 responders in 78 patients at 750 mg QD, with cut-off date of 28-Feb-2013. This component received 80% weight and will be updated with additional data prior to the final analysis.

For each treatment arm the mean, median, and two-sided 90% credible interval for ORR from the posterior distribution will be presented. Individual tumor lesion assessments will be listed along with the overall response by assessment.

Supportive analyses for ORR

- For each treatment arm the Bayesian posterior estimate of median and two-sided 90% credible interval of ORR will be presented using PPS, if PPS is different from FAS.
- For each treatment arm, individual tumor lesion assessments will be listed along with the overall response by assessment. BOR will be listed by patient and summarized with frequency and percentage, together with the observed ORR and frequentist exact two-sided 90% confidence interval (CI) (Clopper and Pearson 1934) provided by treatment.
- For BYL719 arm, BOR summaries may be provided by subtypes of cancer (e.g. lung adenocarcinoma and lung squamous cell carcinoma)

8.2.1 Handling of missing values/censoring/discontinuations

Missing data will simply be noted as missing on appropriate tables/listings. Patients with missing best overall response will be considered as non- responders for the primary ORR analysis.

9 Analysis of the secondary variable(s)

9.1 Efficacy evaluation

For disease progression, beside documented radiological progression, clinical progression will also be used. When there is a documented progression, the radiological scan date will we used as date of progression. When there is no documented progression, and

(i) the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression

(ii) the patient died with reason for death is due to study indication, then death date will be used as date of progression

The secondary efficacy objective of this study is to further estimate clinical activity of single agent BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced NSCLC carrying specific molecular alterations. Tumor response will be evaluated based on RECIST v1.1. Disease control rate (DCR), duration of response, PFS and OS will be assessed and analyzed as follows:

- **DCR** is defined as the proportion of patients with a BOR of CR, PR or SD at any time on study. For each treatment arm the observed DCR with exact two-sided 90% confidence interval will be presented.

- **Duration of overall response** is defined as the time from the first documented CR or PR (confirmed by the subsequent assessment) to the date of the first documented progression or death due to underlying cancer. If a patient has not experienced a documented progression or death due to underlying cancer, duration of overall response is censored at the date of the last adequate tumor assessment. If a patient discontinued trial treatment and received a new anti-neoplastic therapy prior to disease progression, duration of overall response is censored at the start date of the new therapy. The Kaplan-Meier curve, median and quartile will be presented if a sufficient number of responses is observed. For each treatment arm the subset of patients with documented CR or PR in FAS will be used.
- **PFS** is defined as the time from start of study treatment to the date of the first documented progression or death due to any cause. If a patient has not experienced a documented progression or death, PFS is censored at the date of the last adequate tumor assessment. If a patient discontinued trial treatment and received a new anti-neoplastic therapy prior to disease progression, PFS is censored at the start date of the new therapy. The Kaplan-Meier estimate of PFS distribution function will be presented graphically using FAS. The resulting median and quartile estimates will be provided along with two-sided 90% confidence intervals.
- **OS** is defined as the time from start of study treatment to date of death due to any cause. If a patient is not known to have died, OS will be censored at the date of the last contact. The Kaplan-Meier estimate of OS distribution function will be presented graphically using FAS. The resulting median and quartile estimates will be provided along with two-sided 90% confidence intervals.

For BYL719 arm, based on the assumption that similar response is expected in adenocarcinoma and squamous cell carcinoma patients, analyses for the secondary endpoints will be done using the pooled data from these two subgroups of patients.

9.2 Safety evaluation

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for AEs [CTCAE] version *4.03* grading limits or normal ranges as appropriate). Other safety data includes electrocardiogram, vital signs and ECOG performance status.

The Safety set will be used for summaries and listings of safety data in Section 14 of the CSR. All listings and tables will be presented for each treatment arm separately. Unless otherwise, specified, data from all arms will not be pooled and “All patients” column will not be presented in any safety summary.

The safety summary tables will only include assessments collected no later than *30 days* after study treatment discontinuation. All safety assessments will be listed, and those collected later than *30 days* after study treatment discontinuation will be flagged.

9.2.1 Adverse event

AEs will be coded using the latest version of MedDRA available prior to clinical database lock 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 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE

grade 5 (death) will not be used in this study. Death information will be collected on the "End of Treatment" or "Survival Information" eCRF pages.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted.

The following AE summaries will be produced:

- AEs regardless of study drug relationship (including CTC grade 3/4)
- AEs suspected to be study drug related (including CTC grade 3/4)
- AEs leading to discontinuation of study drug regardless of study drug relationship.
- AEs leading to discontinuation of study drug suspected to be study drug related.
- AEs requiring dose adjustment and/or study drug interruption regardless of study drug relationship
- AEs requiring dose adjustment and/or study drug interruption suspected to be study drug related
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- All deaths and on-treatment deaths, with cause of death by preferred term

A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (system organ class, preferred term etc.).

Reporting of death: As mentioned above, summary tables will be produced separately for "All deaths" (post-text) and "on-treatment deaths" (in-text). All deaths will be listed with a flag to identify on-treatment deaths and with reasons of death.

9.2.1.1 Adverse events of special interest

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound INC280 and LDK378. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

All AESI definitions or AE grouping are specified in the electronic Case Retrieval Strategy (eCRS), in which they are identified by the flag "SP". Additional AESI may be reported if there are any updates to the eCRS at the time of the analyses.

Adverse events of special interest (AESIs) INC280 are:

- Hepatotoxicity
- Pneumonitis/Interstitial lung disease
- Central nervous system toxicity
- Renal dysfunction
- Pancreatitis
- Teratogenicity

- Photosensitivity
- Drug-drug interactions with strong CYP3A4 inducers
- QTc interval prolongation

Adverse events of special interest (AESIs) LDK378 are:

- Hepatotoxicity
- Interstitial lung disease/pneumonitis
- QTc prolongation
- Hyperglycemia
- Bradycardia
- GI toxicity (nausea, diarrhea, vomiting)
- Pancreatitis

9.2.2 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis Oncology statistical programming) into CTC grades according to the NCI CTCAE v4.03 as applicable. Grade 5 will not be used. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For cases when the CTC grade definition includes change from baseline criteria (e.g., Creatinine, Ejection fraction, Fibrinogen, Hemoglobin, INR): When a lab value is of grade X based on threshold/ranges, but grade X+1 when considering change from baseline, the final Grade is set to X+1. For other cases, a Grade 0 CTC grade will be set when laboratory value is:

Within LLN and ULN and grading in both direction,

Below ULN and grading in hyper direction,

Above LLN and grading in hypo direction.

Laboratory data for which a CTC grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable.

The following listings will be produced:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4,
- Listing of all laboratory data with values flagged to show corresponding CTC grades and the classifications relative to the laboratory reference ranges (i.e., High (H) or Low (L))

9.2.3 Vital signs, weight and physical examinations

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 7-3.

Table 9-1 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values

Systolic blood pressure [mmHg]	≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥105 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥120 bpm/≤50 bpm with increase/decrease from baseline of ≥15 bpm
Respiratory rate	≥30 breaths per minute; ≤10 breaths per minute
Body temperature [°C]	≥ 39; ≤ 35
Weight [kg]	≥10% decrease/increase from baseline

Vital signs will be listed by subject, and visit/time. Clinically notable vital sign values will be flagged in the listings.

9.2.4 ECOG status

Shift tables of ECOG performance status at baseline to worst post-baseline ECOG status will be provided by cohort using safety set.

9.2.5 Electrocardiograms

9.2.5.1 ECG data descriptive statistics

Baseline for ECG analysis is defined as the average of all available ECG measurements associated with the baseline assessment. Scheduled study day 1 pre-dose ECGs will be considered to have been obtained prior to study treatment administration if dosing time is missing. If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

If a patient has more than one post-baseline measurement at a specific time point, the median of all available measurements associated with the nominal time point will be used for the analyses. The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing. All ECG data will be reported based on the local reading of the ECG.

The following summaries will be provided for each applicable ECG parameter:

- Frequency counts and percentages of patients having notable ECG values according to Table 9-4.

Table 9-2 Criteria for notable ECG values

ECG parameter	Criteria for ECG notable values
QT, QTcF	Increase from baseline >30 ms to 60ms, >60 ms
HR (bpm)	Increase from baseline >25% and value >100 bpm Decrease from baseline >25% and value <50 bpm
PR (ms)	Increase from baseline >25% and value >200 ms
QRS (ms)	Increase from baseline >25% and value >120 ms

Notable ECG values (including notable QT interval values) will be flagged in the listings.

9.2.6 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group. Cumulative dose, dose intensity and relative dose intensity of study treatment will be listed separately by patient and treatment group and summarized separately by treatment group. Categories for relative dose intensity of study treatment will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group.

9.2.7 Other safety analyses

9.2.7.1 Cardiac Imaging

LVEF data will be listed for BYL719 and MEK162 treatment arm.

9.2.7.2 Cardiac enzymes

For BYL719, MEK162 and LDK378 arms, troponin-I or troponin-T will be listed. For MEK162 treatment arm, CK will be listed.

9.2.7.3 Ophthalmology assessments (MEK162)

Full ophthalmic examination including slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially central serous retinopathy and RVO will be performed at the following time points:

- Screening/baseline
- Day 15, Cycle 1
- Day 1 of all subsequent Cycles
- End of Treatment

For patients with clinical suspicion of central serous retinopathy or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography and Electroretinogram (ERG) may be done.

For Fundoscopy, slit lamp, visual field testing and color vision test the incidence of abnormalities at baseline along with the incidence of new abnormalities reported at the timepoints given above will be summarized by type of abnormality for both eyes.

For the visual acuity, Landolt score values are captured in CRF for both eyes.

Ophthalmology examination data will be listed.

9.3 Pharmacokinetic data

All PK analyses will be performed based on the PAS unless otherwise specified. Listings will be generated using the FAS.

Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV.

9.3.1 Descriptive statistics

For each study treatment, concentration data will be listed and summarized by time point, patient and treatment group. Descriptive statistics will include arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum and maximum.

PK parameters will be calculated using noncompartmental methods for serial intensive PK sampling and summarized as described in Table 9-8. The PK parameters considered primary are AUClast, AUCtau, Cmax, and Tmax. Other PK parameters (CL/F, Vz/F, and T1/2) are considered as secondary. All PK parameters will be listed.
The geometric mean and arithmetic mean (SD) and individual concentration versus time profiles will be displayed by treatment arms separately graphically for the patients in PAS.

Table 9-8 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUC(1) , Cmax, CL/F, Vz/F, T1/2	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
Tmax	Median, minimum, and maximum.
(1) Includes AUClast and AUCtau CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100	

9.4.1 Analyses of next Generation Sequencing data:

If Next generation sequencing data is available, then they will be listed.

10 Interim analyses

NA

11 Definitions and general methodology

11.1 General definitions

11.1.1 Subgroup analyses

NA

11.1.2 Assessment windows, baseline and post baseline definitions, missing data handling

11.1.2.1 Baseline

Baseline is the last available and valid assessment performed or value measured within 28 days before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, [redacted]).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

11.1.2.2 Scheduled study visit and window for the analysis

Unless otherwise specified, when more than one assessment is available for a visit, all assessments will be listed under the visit while only the assessment closest to the planned day for the visit will used for summaries and analyses.

Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient.

Note: Patients without any valid assessments to calculate a percentage change from baseline value will be excluded from the graphs. Assessments with an unknown overall response will be included as long as the sum of diameters of target lesions is correctly computed on the same lesions assessed at baseline.

Patients will be ordered in the graph from left (worst change) to right (best change).

1. Bars above the horizontal axis (0%) representing tumor growth,

2. Bars under the horizontal axis (0%) representing tumor shrinkage.

A special symbol (e.g. ∗) will be added below the bottom of respective bars for confirmed RECIST response (CR or PR), with corresponding specifications in footnote. The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be shown. The best overall response (BOR) will be shown above each of the displayed bars in the graph. A horizontal threshold line at -30% will be shown.

11.1.3 Handling of missing and partial dates and imputation rules

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

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date. For these events, the end date will not be imputed.

For patients known to have died prior to or on the cut-off date used for reporting:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. 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. a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date in order to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.

11.1.3.1 Imputation Rules for AE

A missing AE start date will be imputed using the following logic matrix described in Table 11-2.

Table 11-2 Imputation rules for a partially missing AE start date

	AEM MISSING	**AEM < TRTM**	**AEM = TRTM**	**AEM > TRTM**
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started
TRTM: Month treatment started; TRTY: Year treatment started

Table 11-3 is the legend to the logic matrix shown in Table 11-2 and details the relationship of AE start date to study treatment start date.

Table 11-3 Imputation legend and AE/treatment start date relationship

	AE start date relationship	Imputation
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B)	Uncertain	TRTSTD+1
(C)	Before treatment start	15MONYYYY
(D)	Before treatment start	01JULYYYY
(E)	After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for AE end dates.

11.1.3.2 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial concomitant medication end dates will not be imputed.

11.1.3.3 Incomplete date of initial diagnosis of cancer and date of most recent recurrence

For incomplete date of initial diagnosis of cancer and date of most recent recurrence, missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan. If because of this imputation the chronology of the events is altered then the imputation should be made to the minimum value up to where chronology remains unchanged. E.g. if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

11.1.3.4 Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be ‘randomization date −1’.

End date:

Imputed date = min (study start date, last day of the month), if day is missing;

Imputed date = min (randomization date, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies

Start date:

Imputed date = max (last date of study treatment + 1, first day of the month), if day is missing;

Imputed date = max (last date of study treatment + 1, 01JAN), if day and month are missing.

End date: No imputation.

11.1.3.5 Incomplete date for death or last contact

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

If the day or month is missing, death will be imputed to the maximum of the full (non-imputed) last contact date (excluding the date of death) and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day is missing from the date of last contact it will be imputed to 15th day of the month and year of last contact only if derived from the 'Survival Information' page.

12 References

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, Biometrics 38, 29 - 41.

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.