Signature Page for GCT1029-01_SAP
Study GCT1029-01 v2.0

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Study GCT1029-01 v2.0

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Statistical Analysis Plan

Sponsor:	Genmab
Protocol Title:	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1029 in patients with malignant solid tumors
Protocol Version:	Version 9.0, 24 October 2019
Trial Code:	GCT1029-01

[redacted]

Author: [redacted], [redacted] Biostatistician

Reviewer: [redacted], [redacted] Biostatistician

For Sponsor:

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[redacted]

Table of Contents

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[redacted]

1. List of Abbreviations and Definition of Terms

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALT	Alanine Aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLLOQ	Below Lower Limit of Quantification
BMI	Body Mass Index
BOIN	Bayesian Optimal Interval
BP	Blood Pressure
bpm	Beats per Minute
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum Concentration
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DDS	Dose-Determining Set
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DoR	Duration of Response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
EOTrial	End of Trial
EOTrt	End of Treatment

[redacted]

FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FU	Follow-Up
GGT	Gamma-Glutamyl Transferase
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantification
mBOIN	Modified Bayesian Optimal Interval
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
[redacted]	[redacted]
NSCLC	Non-Small Cell Lung Cancer
PD	Progressive Disease
PERCIST	Positron Emission Tomography Response Criteria In Solid Tumors
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PMD	Progressive Metabolic Disease
PMR	Partial Metabolic Response
PR	Partial Response
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
Scr	Screening
SD	Stable Disease
SMD	Stable Metabolic Disease
SMQ	Standardized MedDRA Query
SOD	Sum of Diameters
Subj FU	Subject Follow Up
SUL	Standardized uptake volume corrected for body lean mass
TNBC	Triple Negative Breast Cancer
TBIL	Total Bilirubin
TNM	Tumor Nodes Metastasis
ULN	Upper Limit of Normal

[redacted]

WHO	World Health Organization
WHO-DD	WHO Drug Dictionnary

[redacted]

2. Introduction

This Statistical Analysis Plan was written for the clinical trial GCT1029-01 conducted in a maximum of five to ten sites in Spain, United Kingdom and the US, with up to 20-30 additional sites to be included in Europe. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

3. Trial Design and Objectives

The present SAP covers the escalation part only as the expansion part of the trial was not initiated. [redacted]

3.1 Trial Objectives

3.1.1 Primary Objectives

- To determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of GEN1029.
- To establish the safety profile of GEN1029.

3.1.2 Secondary Objectives

- To establish the pharmacokinetic (PK) profile and evaluate immunogenicity of GEN1029 after single and multiple infusions.
- To evaluate the antitumor activity of GEN1029.

3.1.3 Exploratory Objectives

- To assess biomarkers predictive of response or resistance to GEN1029.
- To assess potential pharmacodynamic biomarkers of GEN1029.
- To assess the metabolic response in tumors.
- [redacted]

3.2 Trial Design

The trial design details are available in section 4 Trial Design of the protocol final version 9.0 dated 24 October 2019.

Unless other events, subjects are intended to receive GEN1029 until PD. Note that the treatment may be stopped due to other reasons.

In the dose escalation part, up to 3 dose regimens were evaluated:

- The Biweekly Regimen: subjects are dosed once every 14 days (Q2W)
- The Priming Regimen: in the first cycle, subjects receive a priming dose; after 14 days and thereafter, they are dosed with the full dose once every 14 days (Priming/Q2W).
- The Intensified Regimen (protocol v8.0): 8xQ1W/Q2W: subjects are dosed every week for the first 8 weeks and then they are dosed once every 14 days.

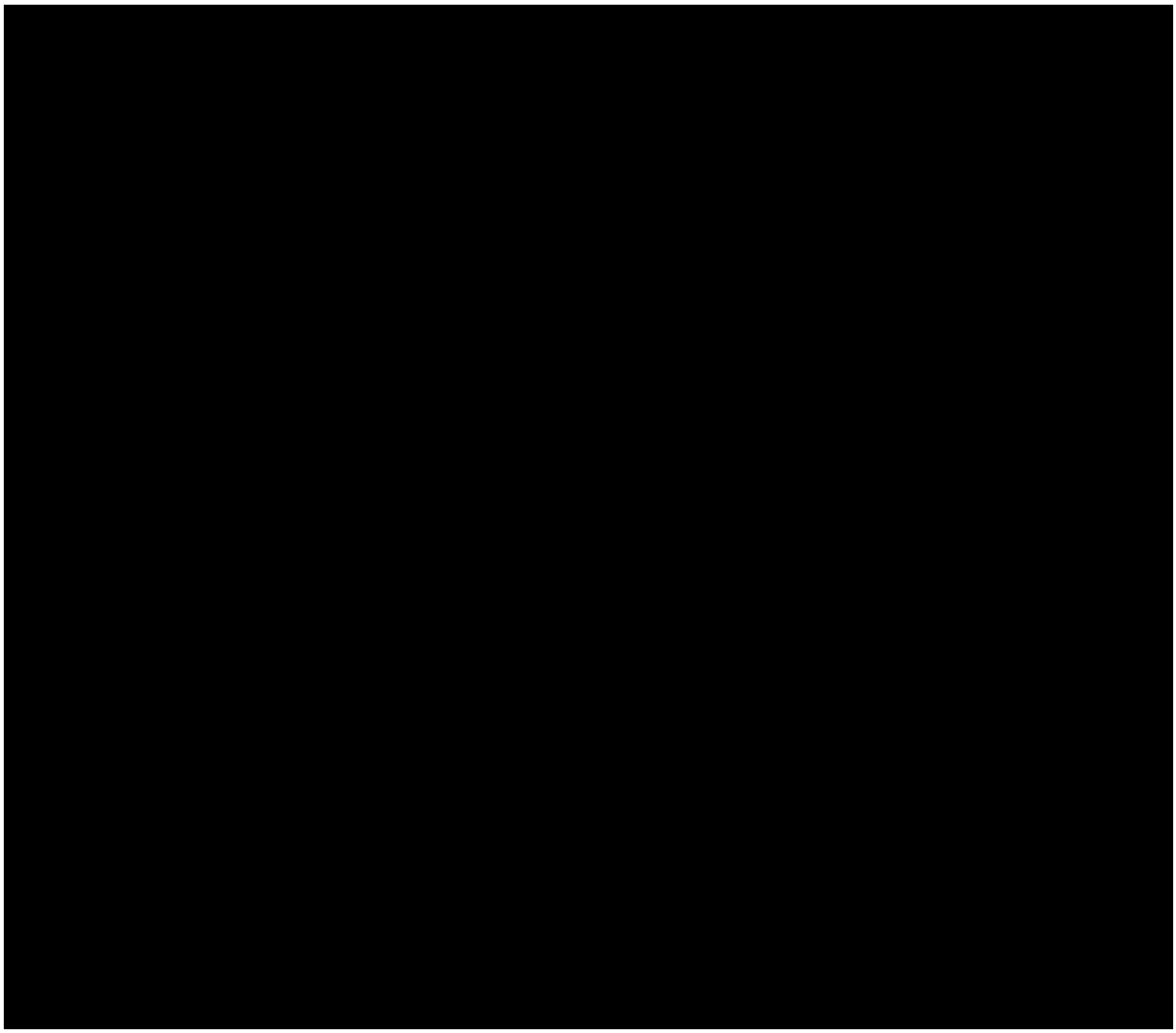
[redacted]

For the assessments of each cohort the dose limiting toxicities (DLT) will be collected for the first two cycles i.e. DLT period of 28 days.

The dose escalation part will be performed as a modified Bayesian Optimal Interval (mBOIN) design[3].

More details can be found in section 4.3 of the protocol final version 9.0 dated 24 October 2019.

Figure 1. [redacted]



3.3 Sample Size Justification

The protocol v9.0 planned to enroll up to approximately 100 subjects shared between the Regimens. As the MTD was found earlier than the highest dose level planned in the protocol and the expansion will not be initiated, only 48 subjects will be recruited.

Of those 48 subjects:

[redacted]

- Two subjects were assigned to the priming regimen:

  - One received the priming dose and then continued on a lower dose level. This subject is considered as treated on the 'biweekly regimen'.

  - The second subject received the priming dose and continued with a higher dose level, this subject will be analysed as treated in the priming regimen.

- Three subjects were also planned in an Intensified Regimen (8xQ1W/Q2W) all of whom experienced DLTs and, consequently, this dosing regimen was permanently discontinued.

[redacted] The Intensified Regimen was discontinued per protocol v9.0.

More details on sample size can be found in section 11.8 Sample Size Calculation of the protocol final version 9.0 dated 24 October 2019.

4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.4 or higher). For graphs R (RStudio, Version 3.5.0 or higher) can be used in addition.

Depending on the nature of the reported endpoint, the following type of summary statistics will be used:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages. Response rates will be presented as the number and percentage of subjects including exact 95% confidence interval using the Clopper-Pearson method.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values.
- Time to event parameters will be summarized using Kaplan-Meier estimates: median time, first and third quartiles along with approximate 95% confidence intervals (the default conftype=loglog in proc lifetest will be used). The 3, 6, 9, 12 and 24 month event-free rates will also be presented together with the 95% confidence intervals.

In general, in plots where subject data are grouped together (e.g. plots of means), the ticks on the time-axis will denote the nominal visit numbers (e.g. Scr, C1D1, C1D2 etc.) separated with distances proportionate to the difference between the time-points of the corresponding visits in the relevant dose level (cf. the Visit Number and Day/Week rows of table of assessments in section 1 Visit Schedule of the protocol final version 9.0 dated 24 October 2019).

Unscheduled visit data will not be tabulated unless otherwise specified. In plots where individual subject data are plotted vs. time, the time on the horizontal axis will denote the actual time since C1D1. Unscheduled visit data will be included in these plots.

In tables and listings presenting data by visit, the visit labels (Screening, Cycle 1 Day 1, Cycle 1 Day 2, …, End of Treatment, Safety Follow-up, Subject Follow-up and End of Trial, Unscheduled) or their abbreviated term (Scr, C1D1, C1D2, …, EOTrt, Saf FU, Subj FU, EOTrial, UNS) will be used.

In tables and listings presenting coded data (e.g. medical history, concomitant medication, adverse events …), the dictionary and the version used will be mentioned in the footnote.

[redacted]

In tables and listings displaying derived endpoints based on RECIST v1.1, this RECIST version will be mentioned in the output.

4.1 Trial Period and Visit Window Definitions

4.1.1 Trial Periods

Screening period will be defined as the period between signature of the ICF and the date of first IMP administration.

On-Treatment period will be defined as the period between first IMP administration (included) and last IMP administration, including the safety follow-up period (taking the maximum of date of last IMP +70 days, end of treatment visit and safety FU visit).

Follow-up period will be defined as the period after the On-Treatment period (that includes the safety FU period) +1 day until the date of last contact.

4.1.2 Visit Windows

Visit windows are defined in the protocol. Those will not be used in the analysis to avoid excluding important data due to dates outside visit windows. Tables will assume that observations are from the recorded visit irrespective of the date specified.

4.2 Planned Analyses

Safety results will be summarized for the DMC after each cohort in the dose escalation part.

The final analysis of trial data will be performed when the trial is completed and will be based on all subject data of the dose escalation part.

The final analysis will be based on locked database with clean data. A full integrated clinical trial report will be produced when the trial is completed.

4.3 Definition of Populations (Analysis Sets)

Populations will be finalized at the pre-database lock meeting.

4.3.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who received at least one dose of GEN1029. Subjects will be analyzed according to the actual trial treatment received. The FAS and the Safety Set (SAF) are defined the same way.

4.3.2 Safety Set

The Safety Set (SAF) consists of all subjects who received at least one dose of GEN1029. Subjects will be analyzed according to the actual trial treatment received. The FAS and the Safety Set (SAF) are defined the same way.

4.3.3 Dose-Determining Set

The Dose-Determining Set (DDS) consists of all subjects from the Safety Set who either have received between 80% and 125% of the planned dose and have completed the DLT observation period (day 1-28), or have experienced a DLT during cycle 1. This constitutes an evaluable subject for the determination of MTD Statistical Analyses. Subjects with a

[redacted]

dose reduction (below 80% of the planned dose) due to abnormal ALT/AST measurements will also be considered evaluable for MTD and be included in the DDS.

Details of the analysis sets definition will be included in a separate document, the "Classifications of Analysis Populations" plan.

4.3.4 Immunogenicity Set

The Immunogenicity Set consists of all subjects from the Safety Set and who have at least one immunogenicity measurement taken.

4.3.5 PK Analysis Set

The PK Analysis Set consists of all subjects who have been exposed to GEN1029 (i.e. at least one dose of IMP) and who have at least 1 post-dose PK measurement. PK parameters like Cmax, AUC, ... at Cycle 1 Day 1 will be considered as post-baseline measurements as in the calculation post-baseline and baseline (pre-dose) concentrations are included.

4.4 Subgroup Definitions

If at least 5 subjects per subgroup per dose level are available, subgroup analyses by ADA-positivity are planned.

Other sub-group analyses may be performed post-hoc. Due to the low expected number of subjects per site no investigation of site effects is planned.

4.5 Treatment Assignment and Treatment Arms

Data will be grouped according to treatment dose level in the biweekly regimen, as described below, rather than by 'treatment arm'. Intensified and Priming regimen only have 1 subject per regimen and will be provided only in listings (cf. section 3.3).

In biweekly regimen, subjects will receive one infusion of GEN1029 every second week. The following doses are planned: 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 2.0 mg/kg and 3.0 mg/kg. Other dose levels were planned in the protocol v9.0, as the MTD was identified, those were not investigated.

Results will be grouped according to dose-level and total.

All data will be listed by dose level, subject ID (subject treatment number), site ID and visit (if applicable). Data related to screen failures will be listed by screening number.

4.6 Calculated Variables

- Baseline is defined as the available data from the latest recorded measurement made before the first IMP administration (trial day 1). Measurements done on the same date as the first IMP administration will be considered as done before the first IMP administration unless specified otherwise (i.e the time associated with the date implies that the measurement was done after the first IMP, even if it is during the same day). For PK variables, the IMP administration on Day 1 of each cycle will be time 0.

[redacted]

- Change from baseline is defined as the post-baseline value – baseline value. Change from baseline will be missing when either post-baseline or baseline value is missing.
- For laboratory data, local change from baseline will be calculated as the post-baseline local value – local baseline value. Local change from baseline will be missing when either local post-baseline or local baseline value is missing.
- For laboratory data, central change from baseline will be calculated as the post-baseline central value – central baseline value. Central change from baseline will be missing when either central post-baseline or central baseline value is missing.
- Percent change from baseline is defined as 100*(post-baseline value – baseline value)/baseline value. If the baseline value is 0 and the post-baseline value is 0, the change from baseline and the percent change from baseline are both 0. If the baseline value is 0 and the post-baseline value is not 0, the percent change from baseline will be undefined (missing value).
- Time (in months) from first diagnosis of primary site to start date of IMP: (start date of IMP – date of first diagnosis)/30.4375.
- Time (in months) since most recent recurrence/relapse or progression to start date of IMP: (start date of IMP – date of most recent recurrence/relapse or progression)/30.4375.
- Time (in months) since last biopsy: (start date of IMP – date of most recent biopsy)/30.4375.
- Total number of days in trial: max (last contact date, date of death) – start date of IMP + 1.
- Total treatment duration (days): (end date of IMP – start date IMP) +1,

  End date of IMP related to

  - **Biweekly and Priming regimen**:
    - min (last IMP+13[a], last contact date, cut-off date)
  - **Intensified Regimen**:
    - min (last IMP+6[b], last contact date, cut-off date) up to Cycle 4 included
    - min (last IMP+13, last contact date, cut-off date) after cycle 4
- Actual cumulative dose (mg): sum of all actual doses administered.
- Dose intensity (mg/cycle): actual cumulative dose divided by the number of cycles initiated.
- Relative dose intensity (%): 100 * ratio of actual cumulative dose and planned cumulative dose.

[a] 13= 2 weeks – 1 day taken into account in the +1

[b] 6= 1 week – 1 day taken into account in the +1

[redacted]

- Planned cumulative dose (mg) – only used for calculation of relative dose intensity: Allocated dose level * weight in kg * number of cycles initiated. For subjects whose body mass index (BMI) is greater than 30 kg/m2, the formula should use a weight that, based on the subject's height, corresponds to a maximum BMI of 30. When a cycle is missed/skipped, this cycle is also included to count the number of cycles initiated.

4.7 Partial/Missing Dates

Partial or missing dates in general will not be imputed (medical history, previous cancer treatment).

For the calculation of the time (in months) from initial diagnosis of primary site to first date of IMP and time since most recent recurrence/relapse or progression to start date of IMP, the following imputation rules will be applied when the date of first diagnosis or date of most recent recurrence/relapse or progression is incomplete:

- If the day is missing: first day of the month
- If the day and month are missing: first day of July.
- If the day and month are missing and if the year is the same as the start year of IMP: leave missing.

For the assignment to prior or concomitant medication the following rules will be applied in case of incomplete or missing dates:

- If medication is ongoing or end date is missing, then medication will be considered as concomitant and missing date(s) will not be imputed.
- If end date is incomplete: if the day is missing: the end date will be imputed with the last day of the month; if the day and month are missing: the end date will be imputed with min (31 December of the year, last contact date, date of death).

The imputed dates will only be used for the assignment to prior or concomitant medication and will not be used in any other calculation and will not be listed.

For new anti-cancer therapy, when the start date is partial or missing, the date will be imputed:

- if start date is missing, but end date is not missing: the start date will be set to the end date.

- if start date remains missing, the start date will be set to the minimum of (last contact date and date of death).

- if start date is incomplete: if the day is missing: the start date will be imputed with the last day of the month; if the day and month are missing: the start date will be imputed with min (31 December of the year, the last contact date, date of death, end date if not missing).

The imputed dates will only be used to define the start of the new anti-cancer therapy for progression free survival and will not be used in any other calculation and will not be listed.

[redacted]

For the assignment of adverse events (AE) the following rules will be applied in case of incomplete or missing start date:

- if end date is before the date of first IMP administration, the start date will remain missing (medical history);
- If start date is missing and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed by the date of first IMP administration (AE).
- If start date is incomplete and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed as follow:
    - if the day is missing and if the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start date month is after the month of first dose, day will be imputed as the first (i.e. 01-MMM-YY);
    - if the day and month are missing and if the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start date year is after the year of first dose, the month and day will be imputed as January first (i.e. 01-JAN-YY).

The imputed date will only be used for the assignment of the treatment-emergent flag to adverse events and will not be used in any other calculation (unless specified otherwise) and will not be listed (i.e. only date as recorded will be listed).

4.8 Methods to Be Used for Handling Missing Data

All available data will be included in data listings and tabulations. Imputed dates will not be included in the listings.

No imputation of missing data is planned for safety endpoints, PK or biomarker endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

Any subjects with missing information regarding response to treatment will be counted as non-responders. This also includes subjects with response that cannot be confirmed according to RECIST v1.1[2] criteria.

For PK data, missing concentration values will be reported as is in data listings. Concentration values below the lower limit of quantification will be handled as LLOQ/2 in summary statistics and reported as is in data listings. Any missing concentration data will not be imputed.

5. Changes to Protocol

The definition of the DDS differs from the protocol v9.0: The DDS includes subjects with a dose reduction (below 80% of the planned dose) due to abnormal ALT/AST measurements, those are evaluable for MTD and included in the DDS.

The PK analysis set was not specified in the protocol v9.0. PK analysis set needs to be defined as PK is essential to correctly select the RP2D and can only be evaluated based on the dosed subjects.

[redacted]

The protocol (section 4.1) opened for the possibility to further explore dose regimens in an expansion part. This possibility is not used.

[redacted]

6. Trial Subjects

6.1 Subject Disposition

Screening failures including failure reason, protocol version and re-screening information will be presented in a listing. Subjects who were screened but never started trial treatment will be included in the same listing. The number of screen failure and the screen failure reasons will be tabulated. Reason for not receiving the treatment will be listed.

The number of subjects in each analysis set will be tabulated as defined in section 4 and overall.

The frequency of subjects treated, of subjects who discontinued the trial treatment ('end of treatment') and of subjects who terminated the trial ('end of trial') will be given for the full analysis set (FAS). A subject will be considered as having completed the trial when all planned trial visits have been performed, including end-of-treatment visit and safety FU visit. The primary reason for discontinuation of treatment and the primary reason for withdrawal from the trial will both be summarized. The details of the 'other reason' will be included in the listing together with other discontinuation details.

A listing of all subjects screened including site, country, ICF date and version, screening number, ICF form date, [redacted] and population flags will be presented.

Subject dispositions and reasons for discontinuation (of treatment or the trial) will also be presented in a flow diagram in accordance with the current CONSORT statement[1].

6.2 Important Protocol Deviations

The important major protocol deviations will be summarized by dose-level and overall for all subjects. The details of all deviations will be listed.

In addition, Covid-19 related PDs will be listed separately:

- All important PDs related to Covid-19;
- All non important PDs related to Covid-19 (major, minor);
- Subject listing of missed/changed visits;
- Subject listing of efficacy assessments missed due to visits impacted by Covid-19.

A summary table of the above might be added to evaluate the impact of Covid-19.

Protocol violations will be defined in the protocol deviations plan.

6.3 Inclusion and Exclusion Criteria

Listing of all inclusion and exclusion criteria not met will be listed.

Information on informed consent [redacted] will be presented in the disposition listing.

[redacted]

7. Demographic Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed for the FAS. Those outputs may be displayed for the DDS set and PK set if those population sets differ from more than 20% compared to the FAS.

The variables to be summarized are:

- Gender (Male/Female)
- Age (years, continuous and categorical: age < 65 years and age ≥ 65 years)
- Race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska native, Other)
- Country (Spain, United Kingdom, United States)
- Ethnic origins (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg) at baseline
- Height (cm)
- BMI (kg/m²) at baseline
- Contraception data, only for female subjects:
    - Subject considered as sterilized or infertile (Yes, No)
    - Reason (Surgical sterilization, Postmenopausal, Other)
    - Subject practice adequate contraception (Yes, No)
    - Type of contraception (pills/implant/vaginal device/injections/transdermal patches/other)

Smoking and drinking history will be presented in listings as individual data. Details of the 'other' categories mentioned above will be added to the listings.

8. Baseline Disease Characteristics

Descriptive statistics with respect to subject disease characteristics at baseline will be displayed for the FAS.

- Type of cancer at time of diagnosis (Advanced and/or metastatic CRC, NSCLC, TNBC, RCC, Gastric (incl. esophagogastric junction) cancer, Pancreatic cancer, Urothelial cancer)
- ECOG performance status (0-5). Note: at entry only subjects with an ECOG performance status of 0 and 1 are allowed.
- Tumor stage at screening (I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, IVB, IVC) by indication.
- Histological results (see CRF for the details) by indication
- Histological subtype (see CRF for the details) by indication
- Histological grade (GX, G1, G2, G3, G4)
- Mutational status (e.g.: EGFR mut, ALK rearrangement, BRAF, NRAS, None) and mutational sub-term (T790M, L858R, …) combined
- Receptor status (ER+, ER-, PR+, PR-, HER2+, HER2-, Other, None)
- Time (in months) from initial diagnosis to start date of IMP

[redacted]

- Time (in months) since most recent recurrence/relapse or progression to start date of IMP

Tumor stage at time of diagnosis (I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, IVB, IVC), reason tumor staging not performed, tumor classification (TNM), target and non-target lesions details at time of diagnosis, and details of the other categories mentioned above will be added to the listings.

9. Biopsy

Descriptive statistics with respect to the biopsy information at baseline will be displayed for the FAS.

The variables to be summarized are:

- Biopsy performed (Yes, No) at screening*
- Type of biopsy (Fresh, Archived, both) available at screening*
- Time since last biopsy before first date of IMP (months)

* independent if at screening or re-screening visit.

Reason biopsy not done will be added to the listings. Time since biopsy to start date of IMP (months) will be added in the listing for each biopsy performed Reason for biopsy failure will be listed only (free text).

10. Medical Procedures and Surgical History

Medical conditions and Surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA[c]).

The medical conditions will be tabulated separately for active (ongoing at screening) and non-active conditions by system organ class (SOC) and preferred term (PT) for the FAS. Surgeries will be tabulated separately in the same way. SOC will be ordered by decreasing frequency and PT (within SOC) will be ordered by decreasing frequency in total. As mentioned in the section 17.3 of Adverse Events, the adverse events collected during the pre-treatment period will be tabulated together with the medical history.

All details will be listed.

11. Prior Anti-Cancer Therapies

Prior systemic anti-cancer therapies will be summarized for the FAS as described below.

Prior systemic therapies in the metastatic setting will be listed and tabulated by first and fourth Anatomical Therapeutic Chemical class (WHO-DD dictionary, ATC 1 name and ATC 4 name) for the FAS. ATC classes will be ordered by decreasing frequency.

Prior radiation therapies and anti-cancer surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented separately by system organ class and preferred term (both ordered by decreasing frequency in total).

[c] Most recent MedDRA version at the time of production

[redacted]

In addition, the number of prior systemic treatment lines will be summarized by means of descriptive statistics and by category (1, 2 and ≥3). Regimen consisting only of radiotherapy or surgery will not be counted as systemic treatment, but a regimen with systemic therapy and surgery/radiotherapy will be counted as systemic.

The number of subjects by combination of drugs as 1st line systemic regimen (first combination received), and the number of subjects by combination of drugs as 2nd line systemic regimen (second combination received) will be presented by indication.

The best response to the latest prior cancer therapy and to the second last prior cancer therapy will be tabulated.

In addition to the tabulation by dose a similar tabulation by tumor type (indication) will be presented.

All details will be listed.

12. Subsequent Anti-Cancer Therapies

Subsequent cancer therapies will be summarized for the FAS as described below.

Subsequent systemic cancer therapies will be listed and tabulated by first and fourth Anatomical Therapeutic Chemical class (WHO-DD dictionary, ATC 1 name and ATC 4 name) for the FAS. ATC classes will be ordered by decreasing frequency.

On-study radiation therapy and surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred term. SOC and PT (within SOC) will be ordered by decreasing frequency in total.

In addition to the tabulation by dose, a similar tabulation by tumor type (indication) will be presented.

All details will be listed.

13. Procedures

Procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The medical procedures will be tabulated by system organ class (SOC) and preferred term (PT) for the FAS. Table will be ordered by decreasing frequency of SOC and by decreasing frequency of PT within SOC in total. All procedures will be listed.

14. Prior and Concomitant Medication

Prior and Concomitant medications will be classified according to WHO-DD dictionary.

Medications will be reported according to the following two distinct categories:

- Prior when they start and end before the first day of trial treatment.
- Concomitant when they start before the first day of trial treatment and stop or continue after the first day of trial treatment, or when they start on or after first day of trial treatment. Concomitant medication should start or continue during the on treatment period.

The number and percentage of subjects receiving a concomitant medication will be displayed by first and fourth Anatomical Therapeutic Chemical class (WHO-DD dictionary, ATC 1 name and ATC 4 name) for the FAS. ATC classes will be ordered by decreasing frequency.

[redacted]

A listing of all medications recorded on the (prior and) concomitant medications CRF page will provide details including indication, dose, route, frequency, and start and stop dates. Prior and Concomitant medications will be listed separately. Also, the specific AE or medical history event will be included where applicable.

15. Efficacy Evaluation

Efficacy results will be presented on the full analysis set (FAS).

The RECIST v1.1 guidance[2] will be used to derive the response and progression endpoints. A confirmation is not required as such per protocol, but both categories of endpoints (confirmed and un-confirmed) will be derived.

15.1 Dose Escalation Part

The evaluations described in this section are part of the secondary objectives. The primary objective is described in the Safety Evaluation section 17.

15.2 Tumor Shrinkage

Anti-tumor activity measured by tumor shrinkage (based on sum of the diameter(s) of all target lesions from the CT-scan evaluations) will be listed and summarized graphically by:

- Individual plots (waterfall and spider plots)
- waterfall plots of the maximal response (maximal reduction in the sum of diameters in the target lesions) at any time on trial

Summaries will be presented as described in section 4 per assessment. The largest tumor shrinkage and its change from baseline will also be presented. Missing values are imputed using the method specified in section 4.8 (Table 3 in Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009;45(2):228-247.~~Eisenhauer et al., 2009~~).

15.3 Best overall response (BOR)

The time point (per visit) response categories per RECIST v1.1 guidance[2] are: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE).

The best overall response is the best response across all time points, where Table 3 in Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009;45(2):228-247.~~Eisenhauer et al. (2009~~) describes how a response is to be confirmed when possible.

Confirmed objective response rate (ORR) is defined as an overall response (PR or better) confirmed by a subsequent overall response of PR or better at least four weeks later*. Of note, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or start of new anti-cancer therapy.

The date of the confirmed response is the date of first occurrence of response.

[* The following sequences will be counted as confirmed response:

- CR-CR = CR confirmed

[redacted]

- CR-PR = PD (confirmed) - because of reappearance of disease. with sas checks, we must make sure that prior scan is corrected to PR if believed when seeing the following scan to be only PR at subsequent scan. This way CR-PR should not occur if the reader interprets this as a PR confirmed, it would be corrected to PR-PR in this case. Otherwise, it would be CR-PD which would qualify as confirmed SD if minimum duration criteria for SD met.
- PR-PR = PR confirmed
- PR-CR = PR confirmed

NB: two intermediate missing (NE) scan evaluations between the response scan and the confirmation scan are allowed, e.g. the sequences PR-NE-PR and PR-NE-NE-PR will be considered PR confirmed.

In all cases the scan that confirms the first scan with CR/PR must occur no sooner than 4 weeks after the first scan.

A subject with sequences that qualify both as PR confirmed and CR confirmed, e.g. PR-PR-CR-CR would be considered a CR confirmed.

If PR or CR are not confirmed, the response will be SD when on or after 35 days after first IMP and NE when before 35 days. (The 35 days takes into account the minimal 6-weeks duration +/- 1 week window before first post baseline scan.)

Best overall response will be summarized descriptively. Subjects with no post-baseline data will be identified by NE for best response.

The best overall response is presented with exact 95% confidence interval using the Clopper-Pearson method.

As a supportive analysis, the best response including both confirmed and unconfirmed responses is presented similarly. (The unconfirmed response does not require a confirmatory scan for e.g. CR or PR.)
CR and PR should be confirmed for the final analysis. If any data should be published before the final database lock (i.e Interim analysis), CR pending confirmation and PR pending confirmation categories will be used.

15.4 Objective response rate (ORR)

The objective response rate is the proportion of subjects with either CR or PR as best overall response. This is presented as part of the BOR summaries.

Similarly, the ORR including both confirmed and unconfirmed responses will be presented as a supportive analysis.

In addition, ORR will be analyzed by subgroup (as described in section 4.4) using a forest plot.

15.5 Time to response (TTR)

Time to response (TTR) will be calculated on subjects responding. It is defined as the number of days from Day 1 in Cycle 1 to the first documented response of either CR or PR, which can be subsequently confirmed (although date of initial response is used, not date of confirmation).

[redacted]

TTR will be listed and summarized using descriptive statistics. Results will be graphically displayed as a Kaplan-Meier curve, starting from 0% (no responder) to 100% (all responders).

15.6 Progression free survival (PFS)

PFS is defined as the time from the date of C1D1 to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1[2].

PFS will be censored in accordance with Table A in Appendix 3 in the FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)". In summary, PFS will be censored if no event (progression or death) is observed before the first of (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy.

Subjects continuing without disease progression or death will be censored and the censoring date will be the date of the last adequate tumor assessment prior to data cut-off/start of new anti-cancer therapy. If there are no post-baseline scans available, then it will be censored at the date of the first IMP.

In case an event occurs after more than 2 missed scans, the censoring is done at last adequate assessment date before the missed scans. The definition of '2 missed scans' is equals to 98 days, the equivalent of 2 * (6 weeks + 1 week of windowing).

If last scan date before the PD or death date is less or equal to 350 days (50 weeks) after start of IMP and the PD or death date is greater than 98 days (6+1 weeks *2) after this last scan date, then it will be censored at last scan date.

If last scan date before PD or death date is greater than 350 days (50 weeks) and less or equal to 441 days (50+13 weeks) after start of IMP and the PD or death date is greater than 140 days (50+13 weeks) after this last scan date, then it will be censored at last scan date.

If last scan date before the PD or death date is greater than 441 days (7+13 weeks) after the start of IMP and PD or death date is greater than 182 (12+1 week *2) days after this last scan date, then it will be censored at last scan date.

Progression-free survival will be derived and listed for all subjects as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimate of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS PROC LIFETEST will be used).

The number of events may be small, and thereby limit use of the Kaplan Meier method to provide reliable information. In this case, descriptive statistics (e.g., n, mean, standard deviation, median, minimum, and maximum) for PFS will be presented.

15.7 Duration of response (DoR)

[redacted]

Duration of response (DOR) only applies to the subset of subjects in the FAS whose confirmed best overall response is CR or PR. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented disease progression.

DoR will be analysed using the censoring rules based on the FDA guideline, see section 15.3.
DOR (months) will be listed for all subjects in the FAS with best overall response of CR or PR, and presented graphically as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimate of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS PROC LIFETEST will be used), and the range.

The number of events may be small and limit use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented.

15.8 Overall survival (OS)

Overall survival (OS) is defined as the time (months) from the date of the first IMP administration to the date of death due to any cause.

If a subject is not known to have died, then OS will be censored, and the censoring date will be the latest date the subject was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population and presented graphically as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimates of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS PROC LIFETEST will be used).

16. Pharmacokinetic Evaluation

The pharmacokinetic evaluation described below is part of the secondary objective.

The calculation of the pharmacokinetic endpoints will be performed by [redacted].

Individual curves of plasma/serum concentration of each component of GEN1029 (Hx-DR5-01 and Hx-DR5-05), including information on actual dose, will be presented for all subjects in the PK set. All available data will be shown in these figures. Additional graphs of PK concentration will present the ADA values and the values of the titers.

The results will also be summarized descriptively over time according to the planned PK sampling schedule.

Mean graphs for the plasma/serum concentrations by cycle (for cycle 1, cycle 2 and cycle 3) and dose level will be presented both with and without error bars. The value <BLLoQ will be replaced by the numerical LLoQ value divided by 2 and mentioned in a footnote.

[redacted]

In addition, descriptive statistics for each clone will be calculated and presented for all non-compartmental PK parameters (e.g. C_{max}, T_{max}) for Cycle 1, Cycle 2 and Cycle 3. This will include mean (arithmetic and/or geometric), median, min, max, n, standard deviation (SD), and geometric coefficient of variation (CV%) of the PK parameters of GEN1029.

Geometric CV% will be calculated as follow:

Geometric CV% = (sqrt(exp(variance for log transformed data)-1))*100

Geometric mean and CV% will not be calculated for $T_{max}$and $T_{½}$.

Missing concentration values will be reported as it is in data listings. Concentration values below lower limit of quantitation (BLLOQ) will be handled as lower limit of quantitation (LLOQ)/2 in summary statistics and reported as it is in data listings. Any missing PK parameter data will not be imputed.

17. Safety Evaluation

All safety results will be presented on the safety set (SAF).

17.1 Primary Endpoint: Dose-limiting Toxicities (DLT)

DLT definition is provided in protocol V9.0 section 7.1.

All analyses on the primary endpoint will be done on the dose-determining set in the dose escalation part of the trial.

The number of subjects with a DLT will be presented for each dose-level.
All the DLT information will be included in a graph marking subjects who have no DLT and have a DLT in order of inclusion, also indicating the subjects which are not evaluable for DLT (not part of the DDS).

Subjects excluded from the DDS and the reasons will be listed.

17.2 Extent of Exposure

The actual cumulative dose, actual and relative dose intensities (continuous and in categories: >= 110%, 90% to < 110%, 70% to < 90%, 50% to < 70%, < 50%, missing), the number of subjects with a dose reduction and the reason of dose reduction (AE/Other) of GEN1029 will be listed and summarized by means of descriptive statistics together with the duration in days. Also, the number of subject days (total number of days in trial) and the number of days on treatment will be presented by means of descriptive statistics for each dose group. The duration of GEN1029 in days by ADA status will also be presented.

17.3 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA[d]) and will be graded according to the National Center Institute Common Terminology Criteria for AEs (NCI NCI-CTCAE criteria[e]).

Adverse events will be analyzed in terms of their type, incidence, severity, and relationship to the trial treatment as determined by the Investigator.

[d] MedDRA version current at the time of production of report

[e] NCI CTCAE version 4.03 as per protocol

[redacted]

Related AEs are defined as events with a relationship to trial treatment equal to 'possibly related' or 'related' as determined by the Investigator according to protocol v3. For subjects enrolled under the protocol v5 or subsequent versions, the relationship to trial treatment is defined as 'Not related' or 'At least possibly related', and related AES are events with a relationship to trial treatment equal to 'At least possibly related'.

Summary tables for AEs described below will only include AEs that are treatment-emergent, i.e., AEs that started or worsened (taking into account the dates of grade changes) during the on-treatment period.

Adverse events collected during the pre-treatment period that do not worsen after treatment is initiated will be tabulated together with the medical history, by System Organ Class (SOC) and Preferred Term (PT), and will be included in the AE listings (marked with a flag). Adverse events collected during the follow-up period will be tabulated separately from the treatment-emergent AEs and will be included in the AE listings (marked with a flag).

See section 4.1 for definition of pre-treatment, on-treatment and post-treatment periods.

A summary table will present the number and percentage of subjects with at least one:

- Adverse event (AE)
- AE related to GEN1029
- Grade ≥3 AE
- Grade ≥3 AE related to GEN1029
- Serious AE
- Serious AE related to GEN1029
- AE leading to drug discontinuation
- AE leading to drug interruption
- AE leading to dose reduction
- SAE leading to drug discontinuation
- Medication errors or overdose
- Serious congenital anomaly/birth defect
- Serious medically significant
- Fatal AE
- Fatal AE related to GEN1029
- AE of special interest[f]: Elevation of Transaminases[g]
- AE of special interest: Diarrhea

[f] Additional AESI's might be added.

[g] Includes the following PTs: Aspartate aminotransferase increased, Alanine aminotransferase increased and Transaminases increased

[redacted]

- Other AE of interest: Pyrexia
- Related AE of special interest: Elevation of Transaminases
- Related AE of special interest: Diarrhea[h]
- Other related AE of interest: Pyrexia
- Other AE of interest: Infusion-related AE

In addition, tabulations of the number of subjects who experienced at least one AE will be presented by PT, by PT and cycle, by SOC and PT and by SOC, PT and severity (sorted by decreasing frequency of PT, decreasing frequency of SOC and by decreasing frequency of PT within a SOC in total for table by SOC and PT). Subjects will only be counted once for each preferred term. In case a subject experienced the same event more than once, the highest severity grade will be presented.

The following tabulations will be presented for subjects experiencing at least on treatment emergent adverse event:

- All AEs
- AE related to GEN1029
- Grade ≥3 AE
- Grade ≥3 AE related to GEN1029
- Serious AE
- Serious AE related to GEN1029
- AE leading to drug discontinuation
- SAE leading to drug discontinuation
- AE leading to drug interruption
- AE leading to dose reduction
- Fatal AE
- Fatal AE related to GEN1029
- AE of special interest: Elevation of Transaminases
- AE of special interest: Diarrhea
- Other AE of interest: Pyrexia
- Other AE of interest: Infusion-related AE

All treatment emergent adverse events of interest will be summarized grouped by AESI category, preferred term, severity grade and in addition, also by cycle.

The categories of treatment emergent adverse events of interest will be defined using MedDRA SMQ lists or lists of PT's provided by sponsor at the time of the analysis

[h] Includes the following PTs: 'Diarrhoea' 'Enteritis', 'Gastrointestinal inflammation', 'Hepatitis' and 'Drug-induced liver injury'.

[redacted]

programming. The AESI indicator per eCRF data will be used as a data monitoring tool and provided in listing.

In addition, time to onset of first AESI event (for subjects with at least one event), total number of AESI events, total number and percentage of AESI events with outcome of resolution, and time to resolution of each AESI event (for events which are resolved) will be summarized by AESI category using descriptive statistics. AESI events with partial start date will be imputed accordingly to the rules described in section 4.7. The same outputs will be created for the other event of interest: Pyrexia.

Time to onset of first AESI event will also be presented graphically by AESI category using Kaplan-Meier curves (one plot for each AESI category); in these Kaplan-Meier curves, subjects with no AESI will be censored at the end of the treatment period. Time to onset of first other event of interest: Pyrexia, using Kaplan-Meier curves will also be displayed.

AESI will also be presented graphically using swim lane plots. Plots will be performed individually for each subject, by dose level, and will show the reported AESI by category on a time-based x-axis (arrow will be used to show ongoing AEs). Plots will also include lines to show start date in the study (i.e., informed consent date) and last contact date of subject, as well as start and end dates of on-treatment period. Other event of interest: Pyrexia, will also be displayed on those swim lane plots.

Listings of all adverse events (including those from the pre and post-treatment periods) will be provided including the screening number/patient number (including site and country), age, race, sex, regimen, dose level, tumor type, verbatim, PT, SOC, duration of the event, highest severity, action taken, outcome, causality, date of onset, cycle of onset, date of resolution, days since the first dose, days since the latest dose, serious (Y/N), DLT (Y/N), infusion reaction (Y/N) and the treatment-emergent flag. AEs collected during the pre-treatment and post-treatment period will be flagged. Similar listings will also be created for each adverse events of interest separately.

Adverse Event will also be presented in a table by ADA status as applicable.

17.4 Deaths and Serious Adverse Events

In addition to the tables presented in section 17.3, Fatal AEs, SAEs and NCI-CTCAE grade ≥ 3 AEs will be presented also by ADA positivity and by preferred term.

The number of deaths will be tabulated by source and total. The primary cause of death will be included in the listing. Number of deaths within 30 days of first dose of IMP, within 100 days of first IMP, and after 100 days after first IMP will also be tabulated.

17.5 Clinical Laboratory Data

The following laboratory parameters are measured:

- Biochemistry parameters: Sodium, potassium, magnesium, creatinine, calcium, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total bilirubin, direct bilirubin, lactate dehydrogenase, uric acid, C-reactive protein, lipase, amylase, gamma-glutamyl transferase, glycosylated hemoglobin, chloride, cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein (calculated).

[redacted]

- Hematology parameters: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, reticulocyte count and coagulation factors (prothrombin time, international normalized ratio and activated partial thromboplastin time).
- Urinalysis parameters: pH, density, protein, glucose, blood, leukocytes, bilirubin, and Beta-HCG

Safety laboratory assessments (biochemistry, hematology and urinalysis) will be graded using NCI-CTCAE v4.03 if possible. Grading will be assigned programmatically. The calculations of NCI-CTCAE grades will be based on the observed laboratory values. For local laboratory assessments, if a grade higher than 0 is attributed when the value is within normal range, then the grade will be put equal to 0. NCI-CTCAE grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by the NCI-CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges. All laboratory assessments will be converted to the corresponding international system of unit. Values >xx or <xx will be imputed with respectively 1 value lower or 1 value higher according precision. For example, <50 will be imputed by 49, >35.6 will be imputed by 35.7. Only central labs will be used in summary tables. Local and central laboratory assessments will be used for the subject profile plots. Normalized values can be presented with different symbols.

For uric acid, grade 1 and grade 3 are defined with overlapping boundaries: >ULN – 10 mg/dl (590 µmol/L); for grade 1 without physiologic consequences and for grade 3 with physiologic consequences (no grade 2). In all listings, tables (e.g., shift-tables based on NCI-CTCAE-grade), and graphs (if applicable) where uric acid is presented with NCI-CTCAE grade: a footnote will be added:

"A uric acid value >ULN-590 µmol/L is either NCI-CTCAE grade 1 if there is no physiological consequence or grade 3 if there is. In the absence of physiological consequence information and for the purpose of presentation in this listing/table/graph, such values are here considered to be grade 1".

All summaries described below will be generated separately for hematology, coagulation, and biochemistry tests. Each dose level will have its own color and pattern. Individual subject's data over time per parameter and dose level will be plotted in individual profiles plots for the liver parameters. Abbreviated subject numbers are put at the beginning of the profile. Liver parameters will be presented in individual plots: ALT, AST, ALP, Total bilirubin and GGT will be plotted, with normalized values. Those five parameters will be presented in panel plots simultaneously and by dose level.

For laboratory tests where grades are defined by the NCI-CTCAE V4.3, the number and percentage of subjects by highest post-baseline (on-treatment) NCI-CTCAE grade will be presented, regardless of baseline.

Shift tables will be produced for all laboratory parameters graded by NCI-CTCAE grading to compare baseline grade to the highest on-treatment grade per subject. These tables will summarize the number of subjects with each baseline NCI-CTCAE grade and changes to the maximum NCI-CTCAE grade. For the calculation of the maximum NCI-CTCAE grade, both scheduled and unscheduled values available post baseline will be used.

Shift tables in Low/Normal/High categories will be displayed when NCI-CTCAE grading is missing. These tables will summarize the number of subjects going from Normal/Low at

[redacted]

baseline to High at any post-baseline and going from Normal/High at baseline to Low at any post-baseline. Both scheduled and unscheduled values available during the treatment period will be used.
In addition, the frequency of subjects with incidence of drug induced liver laboratory abnormalities will be summarized descriptively and listed. Drug induced liver laboratory abnormalities will be defined as subjects meeting or exceeding one of the following predefined limits post-baseline:

- AST and/or ALT > 3xULN
- AST and/or ALT > 5xULN
- AST and/or ALT > 10xULN
- AST and/or ALT > 20xULN
- AST and/or ALT > 3xULN and Total Bilirubin > 2xULN
- AST and/or ALT > 3xULN and Total Bilirubin > 2xULN and ALP < 1.5xULN
- AST and/or ALT > 3xULN and INR > 1.5

subsequent to ALT/AST elevation will be included for the assessment of the incidence. Of note, total bilirubin, ALP and/or INR, total bilirubin and/or ALP measurements concurrent or within 30 days will be included for the assessment of the incidence.

The number of subjects with at least one post-baseline NCI-CTCAE grade 3 or 4 laboratory value will be presented overall and by laboratory parameter.

The following subject data listings will be produced for all laboratory parameters, separately for hematology and biochemistry, where NCI-CTCAE grades are defined:

- Listing of subjects with laboratory abnormalities of NCI-CTCAE grade 3 or 4 including a flag when clinically significant.
- Listing of all laboratory data by visit including NCI-CTCAE grades and flags marking clinical significance as well as values that are below or above the corresponding laboratory reference range.

All other laboratory parameters will be listed by laboratory parameter and subject. Percentage change in laboratory safety parameters from baseline to subsequent visits will be derived and presented in listings.

17.6 Vital Signs, Physical Findings and Other Observations Related to Safety

Abnormal physical examination results will be tabulated and listed over time by body system.

Descriptive statistics (actual values and changes from baseline) over time will be given for body weight as it is important for the dosing.

Vital signs results will be listed by subject with a flag marking the clinically notable values for each of the following parameters:

Clinically notable elevated values

- Systolic BP: >=180 mmHg and an increase >=20 mmHg from baseline
- Diastolic BP: >=105 mmHg and an increase >=15 mmHg from baseline
- Weight: Increase from baseline of >=10%
- Heart rate: >=120 bpm with increase from baseline of >=15 bpm
- Temperature: >38 °C

Clinically notable below normal values

[redacted]

- Systolic BP: <=90 mmHg and a decrease >=20 mmHg from baseline
- Diastolic BP: <=50 mmHg and a decrease >=15 mmHg from baseline
- Weight: decrease from baseline of >=10%
- Heart rate: <=50 bpm with decrease from baseline of >=15 bpm
- Temperature: <35 °C

The number of subjects with at least one clinically notable value as defined above will be summarized in a table.

17.7 ECG

ECG interpretation (Normal / Abnormal, not clinically significant/ Abnormal, clinically significant) and ECG measurements (RQT, QTcF, QTcB, PR and QRS) will be tabulated/summarized by visit and ECG time point (Before IMP administration and End of IMP administration (+15 min)). The three 12-lead ECG performed at each visit/time point will be combined as one measurement using the average of the three results (for ECG measurements), and the worst outcome of the three results for ECG interpretation. If available, reason for ECG abnormality will be listed.

Categorical analysis of QT, QTcB and QTcF interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT, QTcB and QTcF intervals (>450 ms or >480 ms or >500 ms) or changes from baseline (change of >30 ms or >60 ms) will be presented at baseline and at any post-baseline visit.

Additionally, categorical analysis of PR interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute PR (>200 ms or >220 ms) or changes from baseline (change of >25%) will also be presented at baseline and at any post-baseline visit.

Lastly, categorical analysis of QRS interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QRS (>110 ms or >120 ms) or changes from baseline (change of >25%) will also be presented at baseline and at any post-baseline visit.

A listing of these subjects will be produced.

18. Other Safety Data

18.1 Immunogenicity (anti-drug antibodies) of GEN1029

Data on immunogenicity (anti-drug antibodies) of GEN1029 will be summarized as described below on the immunogenicity set.

Titers of GEN1029 will be listed additionally to their presentation in graphs of PK concentration and pharmacokinetic table

Positive/negative host immune response to GEN1029 will be tabulated by visit. For post-baseline results, a subject will have a positive ADA status if negative at baseline and at least one positive post-baseline result, or positive at baseline and at least one positive post-baseline result with a titer higher than baseline. Of note, subjects with no post-baseline ADA assessment will have a missing ADA status.

Of note, ADA positivity requires confirmation in 2 assay steps. First step has many false positive; the second assay step (confirmation) ensures specificity of the assay. Only confirmed ADA positivity results will be considered as positive.

[redacted]

The association between positive/non-positive ADA and PK (pre-dose, AUC, C_{max}), major safety signals (NCI-CTCAE ≥ grade 3) and efficacy information (change in tumor size by CT scan) will be explored in the corresponding sections: contingency tables and/or descriptive statistics will be presented by positive/non-positive ADA.

18.2 Pregnancy Test

All pregnancy test data will be listed

18.3 Cytomegalovirus (CMV)

Antibodies to CMV antigen assessed at screening and end of treatment will be listed.

19. Exploratory Objectives

The evaluations described below are part of the exploratory objectives.

19.1 Biomarkers

The exploration of biomarkers predictive of response or resistance, and the exploration of potential pharmacodynamic biomarkers are part of the explorative objectives. Biomarkers will be assessed both in tumor and laboratory samples.

Protein expression analysis (cytokines and complement sampling) and the immunophenotyping will be presented as per protocol 9.7.2.

[redacted]

Changes from baseline will be summarized by cytokine or complement component, dose-level, and time point. Summary statistics will be tabulated and displayed graphically (mean-se plot and boxplots). These tabulations and graphs may be subgrouped by type of clinical response to evaluate potential differences by responder groups and ADA-

[redacted]

[redacted]

19.2 Metabolic Response in the Tumors

The metabolic response in the tumors will be evaluated following the Positron Emission Tomography Response Criteria In Solid Tumors (PERCIST 1.0)[5]. The metabolic endpoint is the standardized uptake volume corrected for body lean mass (SUL).

The evaluation of SUL only applies to the subset of subjects in the FAS that presented an avid PET scan at screening.

Percentage change from screening in SUL will be summarized by scan visit for the hottest lesion (SULpeak). The hottest lesion site may vary over time. The metabolic response will also be classified and summarized (according to PERCIST 1.0) as

a) complete metabolic response (CMR);

b) partial metabolic response (PMR);

c) stable metabolic disease (SMD); and

d) progressive metabolic disease (PMD).

The metabolic response rate, and the best overall metabolic response (CMR, PMR, SMD or PMD) are presented with exact 95% confidence interval using the Clopper-Pearson method.

19.3 [redacted]

[redacted]

19.4 ECOG Performance Status

ECOG performance status assessments will be listed and summarized descriptively over time.

20. References

1. http://www.consort-statement.org/
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009;45(2):228-247.
3. Yuan, Y., Hess, K. R., Hilsenbeck, S. G., & Gilbert, M. R. (2016). Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. Clin Cancer Res., 22, 4291-4301.
4. FDA (2015). Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, Guidance for Industry.
5. Wahl, R. L., Jacene, H., Kasamon, Y., and Lodge, M. A. (2009). From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 50 Suppl 1, 122S-150S
6. Lee, J. J., and Liu, D. D. (2008). A predictive probability design for phase II cancer clinical trials. Clin Trials 5, 93-106.

7. Saville, B. R., Connor, J. T., Ayers, G. D., and Alvarez, J. (2014). The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. Clin Trials 11, 485-493.

[redacted]

21. List of Tables/Graphs/Listings

21.1 List of Statistical Tables

Output Number	Output Name	Population
General		
Table 14.01.01	Screen Failures	All screened subjects
Table 14.01.02.01	Analysis Sets	All enrolled Subjects
Table 14.01.02.02	Regimen Allocation	All dosed Subjects
Table 14.01.03.01	Subject Treatment Disposition	Full Analysis Set
Table 14.01.03.02	Subject Study Disposition	Full Analysis Set
Table 14.01.04.01	Important Protocol Deviations	Full Analysis Set
Table 14.01.04.02	Protocol Deviations due to Covid-19	Full Analysis Set
Table 14.01.05	Demographic Characteristics	Full Analysis Set
Table 14.01.06	Baseline Disease Characteristics	Full Analysis Set
Table 14.01.07	Biopsy Information	Full Analysis Set
Table 14.01.08.01	Medical History (Ongoing) – by SOC and Preferred Term	Full Analysis Set
Table 14.01.08.02	Medical History (Past) – by SOC and Preferred Term	Full Analysis Set
Table 14.01.08.03	Surgical History – By SOC and Preferred Term	Full Analysis Set
Table 14.01.09.01	Prior Anti-Cancer Therapies Summary	Full Analysis Set
Table 14.01.09.02	Prior Anti-Cancer Therapies by Indication	Full Analysis Set
Table 14.01.09.03	Prior Anti-Cancer Therapies – by ATC 1 Name and ATC 4 Name	Full Analysis Set
Table 14.01.09.04	Prior Anti-Cancer Surgeries - by SOC and Preferred Term	Full Analysis Set
Table 14.01.09.05	Prior Radiation Therapies - by SOC and Preferred Term	Full Analysis Set
Table 14.01.10.01	Subsequent Anti-Cancer Therapies - by ATC 1 Name and ATC 4 Name	Full Analysis Set
Table 14.01.10.02	Subsequent Anti-Cancer Therapies - by ATC 1 Name and ATC 4 Name and Indication	Full Analysis Set
Table 14.01.10.03	On-Study Cancer Surgeries – by SOC and Preferred Term	Full Analysis Set
Table 14.01.10.04	On-Study Radiation Therapies – by SOC and Preferred Term	Full Analysis Set
Table 14.01.11	Procedures – by SOC and Preferred Term	Full Analysis Set
Table 14.01.12.01	Prior Medications - by ATC 1 Name and ATC 4 Name	Full Analysis Set
Table 14.01.12.02	Concomitant Medications - by ATC 1 Name and ATC 4 Name	Full Analysis Set

[redacted]

Efficacy Evaluation		
Table 14.02.01.01	Tumor Shrinkage	Full Analysis Set
Table 14.02.01.02	Disease Response According to RECIST 1.1 - Confirmed Response	Full Analysis Set
Table 14.02.01.03	Disease Response According to RECIST 1.1 – All Responses	Full Analysis Set
Table 14.02.02.01	Time to Confirmed Response According to RECIST 1.1	Full Analysis Set patients with Confirmed CR or PR
Table 14.02.02.02	Progression Free Survival According to RECIST 1.1	Full Analysis Set
Table 14.02.02.03	Duration of Confirmed Response According to RECIST 1.1	Full Analysis Set patients with Confirmed CR or PR
Table 14.02.03.01	Overall Survival	Full Analysis Set
Pharmacokinetics		
Table 14.02.04.01	Plasma/Serum Concentration of Hx-DR5-01– Descriptive Statistics	PK Analysis Set
Table 14.02.04.02	Plasma/Serum Concentration of Hx-DR5-05– Descriptive Statistics	PK Analysis Set
Table 14.02.05.01	PK Parameters of Hx-DR5-01 – Descriptive Statistics	PK Analysis Set
Table 14.02.05.02	PK Parameters of Hx-DR5-05 – Descriptive Statistics	PK Analysis Set
Table 14.02.06.01	PK Parameters of Hx-DR5-01 by ADA Positivity	Immunogenicity Set
Table 14.02.06.02	PK Parameters of Hx-DR5-05 by ADA Positivity	Immunogenicity Set
Table 14.02.7	Immunogenicity of GEN1029	Immunogenicity Set
Safety Evaluation		
Table 14.03.01	Primary Endpoint: Summary of DLT	Dose-Determining Set
Table 14.03.02	GEN1029 Administration – Extent of Exposure	Safety Set
Table 14.03.03	Summary of Treatment Emergent Adverse Events	Safety Set
Table 14.03.04.01	Treatment Emergent Adverse Events – by Preferred Term	Safety Set
Table 14.03.04.02	Treatment Emergent Adverse Events – by Preferred Term and Cycle	Safety Set
Table 14.03.04.03	Treatment Emergent Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.04.04	Treatment Emergent Adverse Events - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.05.01	GEN1029 Related Treatment Emergent Adverse Events - by Preferred Term	Safety Set
Table 14.03.05.02	GEN1029 Related Treatment Emergent	Safety Set

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	Adverse Events - by Preferred Term and Cycle	
Table 14.03.05.03	GEN1029 Related Treatment Emergent Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.05.04	GEN1029 Related Treatment Emergent Adverse Events – by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.06.01	Treatment Emergent Adverse Events Grade ≥3 – by Preferred Term	Safety Set
Table 14.03.06.02	Treatment Emergent Adverse Events Grade ≥3 - by Preferred Term and Cycle	Safety Set
Table 14.03.06.03	Treatment Emergent Adverse Events Grade ≥3 - by SOC and Preferred Term	Safety Set
Table 14.03.06.04	Treatment Emergent Adverse Events Grade ≥3 - by Preferred Term and CTCAE Grade	Safety Set
Table 14.03.06.05	Treatment Emergent Adverse Events Grade ≥3 – by Preferred Term and ADA Positivity	Safety Set
Table 14.03.07.01	GEN1029 Related Treatment Emergent Adverse Events Grade ≥3 - by Preferred Term	Safety Set
Table 14.03.07.02	GEN1029 Related Treatment Emergent Adverse Events Grade ≥3 - by Preferred Term and Cycle	Safety Set
Table 14.03.07.03	GEN1029 Related Treatment Emergent Adverse Events Grade ≥3 - by SOC and Preferred Term	Safety Set
Table 14.03.07.04	GEN1029 Related Treatment Emergent Adverse Events Grade ≥3 - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.07.05	GEN1029 Related Treatment Emergent Adverse Events Grade ≥3 - by Preferred Term and ADA Positivity	Safety Set
Table 14.03.08.01	Serious Treatment Emergent Adverse Events - by Preferred Term	Safety Set
Table 14.03.08.02	Serious Treatment Emergent Adverse Events - by Preferred Term and Cycle	Safety Set
Table 14.03.08.03	Serious Treatment Emergent Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.08.04	Serious Treatment Emergent Adverse Events - by SOC and Preferred Term and CTCAE Grade	Safety Set

[redacted]

Table 14.03.08.05	Serious Treatment Emergent Adverse Events - by Preferred Term and ADA Positivity	Safety Set
Table 14.03.09.01	GEN1029 Related Serious Treatment Emergent Adverse Events - by Preferred Term	Safety Set
Table 14.03.09.02	GEN1029 Related Serious Treatment Emergent Adverse Events - by Preferred Term and Cycle	Safety Set
Table 14.03.09.03	GEN1029 Related Serious Treatment Emergent Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.09.04	GEN1029 Related Serious Treatment Emergent Adverse Events - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.09.05	GEN1029 Related Serious Treatment Emergent Adverse Events - by Preferred Term and ADA Positivity	Safety Set
Table 14.03.10.01	Treatment Emergent Adverse Event Leading to Drug Discontinuation - Preferred Term	Safety Set
Table 14.03.10.02	Treatment Emergent Adverse Event Leading to Drug Discontinuation - Preferred Term and by Cycle	Safety Set
Table 14.03.10.03	Treatment Emergent Adverse Event Leading to Drug Discontinuation - by SOC and Preferred Term	Safety Set
Table 14.03.10.04	Treatment Emergent Adverse Event Leading to Drug Discontinuation - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.11.01	Serious Treatment Emergent Adverse Event Leading to Drug Discontinuation - Preferred Term	Safety Set
Table 14.03.11.02	Serious Treatment Emergent Adverse Event Leading to Drug Discontinuation - Preferred Term and Cycle	Safety Set
Table 14.03.11.03	Serious Treatment Emergent Adverse Event Leading to Drug Discontinuation - by SOC and Preferred Term	Safety Set
Table 14.03.11.04	Serious Treatment Emergent Adverse Event Leading to Drug Discontinuation - by SOC and Preferred Term and CTCAE Grade	Safety Set

[redacted]

Table 14.03.12.01	Treatment Emergent Adverse Event Leading to Drug Interruption - Preferred Term	Safety Set
Table 14.03.12.02	Treatment Emergent Adverse Event Leading to Drug Interruption - Preferred Term and Cycle	Safety Set
Table 14.03.12.03	Treatment Emergent Adverse Event Leading to Drug Interruption - by SOC and Preferred Term	Safety Set
Table 14.03.12.04	Treatment Emergent Adverse Event Leading to Drug Interruption - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.13.01	Treatment Emergent Adverse Event Leading to Drug Reduction - Preferred Term	Safety Set
Table 14.03.13.02	Treatment Emergent Adverse Event Leading to Drug Reduction - Preferred Term and Cycle	Safety Set
Table 14.03.13.03	Treatment Emergent Adverse Event Leading to Drug Reduction - by SOC and Preferred Term	Safety Set
Table 14.03.13.04	Treatment Emergent Adverse Event Leading to Drug Reduction - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.14.01	Fatal Treatment Emergent Adverse Events - by Preferred Term	Safety Set
Table 14.03.14.02	Fatal Treatment Emergent Adverse Events - by Preferred Term and Cycle	Safety Set
Table 14.03.14.03	Fatal Treatment Emergent Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.14.04	Fatal Treatment Emergent Adverse Events - by Preferred Term and ADA Positivity	Safety Set
Table 14.03.15.01	GEN1029 Related Fatal Treatment Emergent Adverse Events - by Preferred Term	Safety Set
Table 14.03.16.01	Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term	Safety Set
Table 14.03.16.02	Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term and Cycle	Safety Set
Table 14.03.16.03	Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by SOC and Preferred Term	Safety Set

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Table 14.03.16.04	Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.16.05	Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term, CTCAE Grade and by Cycle	Safety Set
Table 14.03.16.06	Time to Onset of First Treatment Emergent Adverse Event of Special Interest: Elevation of Transaminases , with Outcome of Resolution and Time to Resolution	Safety Set
Table 14.03.17.01	Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term	Safety Set
Table 14.03.17.02	Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term and Cycle	Safety Set
Table 14.03.17.03	Treatment Emergent Adverse Events of Special Interest: Diarrhea - by SOC and Preferred Term	Safety Set
Table 14.03.17.04	Treatment Emergent Adverse Events of Special Interest: Diarrhea - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.17.05	Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term, CTCAE Grade and by Cycle	Safety Set
Table 14.03.17.06	Time to Onset of First Treatment Emergent Adverse Event of Special Interest: Diarrhea, with Outcome of Resolution and Time to Resolution	Safety Set
Table 14.03.18.01	Other Treatment Emergent Adverse Events of Interest: Pyrexia - by Preferred Term	Safety Set
Table 14.03.18.02	Other Treatment Emergent Adverse Events of Interest: Pyrexia - by Preferred Term and Cycle	Safety Set
Table 14.03.18.03	Other Treatment Emergent Adverse Events of Interest: Pyrexia - by SOC and Preferred Term	Safety Set
Table 14.03.18.04	Other Treatment Emergent Adverse Events of Interest: Pyrexia - by SOC and Preferred Term and CTCAE Grade	Safety Set
Table 14.03.18.05	Other Treatment Emergent Adverse Events of Interest:	Safety Set

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	Pyrexia - by Preferred Term, CTCAE Grade and by Cycle	
Table 14.03.18.06	Time to Onset of First Other Treatment Emergent Adverse Events of Interest: Pyrexia , with Outcome of Resolution and Time to Resolution	Safety Set
Table 14.03.19	Related Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term	Safety Set
Table 14.03.20	Related Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term	Safety Set
Table 14.03.21	Related Other Treatment Emergent Adverse Events of Interest: Pyrexia	Safety Set
Table 14.03.22	Serious Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term	Safety Set
Table 14.03.23	Serious Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term	Safety Set
Table 14.03.24	Serious Other Treatment Emergent Adverse Events of Interest: Pyrexia	Safety Set
Table 14.03.25	Related Serious Treatment Emergent Adverse Events of Special Interest: Elevation of Transaminases - by Preferred Term	Safety Set
Table 14.03.26	Related Serious Treatment Emergent Adverse Events of Special Interest: Diarrhea - by Preferred Term	Safety Set
Table 14.03.27	Related Serious Other Treatment Emergent Adverse Events of Interest: Pyrexia	Safety Set
Table 14.03.28.01	Other Treatment Emergent Adverse Events of Interest: Infusion-Related Adverse Events - Preferred Term	Safety Set
Table 14.03.28.02	Other Treatment Emergent Adverse Events of Interest: Infusion-Related Adverse Events - by SOC and Preferred Term	Safety Set
Table 14.03.28.03	Other Treatment Emergent Adverse Events of Interest: Infusion-Related Adverse Events - by Preferred Term and CTCAE Grade	Safety Set
Table 14.03.28.04	Other Treatment Emergent Adverse Events of Interest: Infusion-Related Adverse	Safety Set

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	Events - by Preferred Term, CTCAE Grade and by Cycle	
Table 14.03.29	Deaths	Full Analysis Set
Table 14.03.30.xx	Biochemistry Laboratory Results - Shift Table from Baseline NCI-CTCAE Grade to Highest Post-Baseline NCI-CTCAE Grade	Safety Set
Table 14.03.31	Biochemistry Laboratory Results - Shift Table from Baseline to Maximum/Minimum Post-Baseline Abnormality	Safety Set
Table 14.03.32.xx	Hematology Laboratory Results - Shift Table from Baseline NCI-CTCAE Grade to Highest Post-Baseline NCI-CTCAE Grade	Safety Set
Table 14.03.33	Hematology Laboratory Results - Shift Table from Baseline to Maximum/Minimum Post-Baseline Abnormality	Safety Set
Table 14.03.34.xx	Coagulation factors Laboratory Results - Shift Table from Baseline NCI-CTCAE Grade to Highest Post-Baseline NCI-CTCAE Grade	Safety Set
Table 14.03.35	Coagulation factors Laboratory Results - Shift Table from Baseline to Maximum/Minimum Post-Baseline Abnormality	Safety Set
Table 14.03.36	NCI-CTCAE Grade 3/4 Laboratory Results	Safety Set
Table 14.03.37	Subject Incidence of Liver Laboratory Abnormalities	Safety Set
Table 14.03.38	Abnormal Physical Examination over Time - by Body System	Safety Set
Table 14.03.39	Body weight over Time - Descriptive Statistics	Safety Set
Table 14.03.40	Vital Signs - Abnormalities	Safety Set
Table 14.03.41.01	ECG Measurement over Time	Safety Set
Table 14.03.41.02	ECG Abnormalities	Safety Set
Exploratory Evaluation		
Table 14.04.01	Metabolic Response in Tumors According to PERCIST 1.0	Full Analysis Set (subset of subjects presenting an avid PET scan at screening)
Table 14.04.02	ECOG Performance Status Over Time	Full Analysis Set
Table 14.04.03.xx	Cytokine and Complement Sampling – By Category - Over Time	Full Analysis Set
Table 14.04.04.xx	Immunophenotype data – By Category - Over Time	Full Analysis Set

21.2 List of Graphs

Output Number	Output Name	Population

[redacted]

General		
Graph 14.01.01	Consort Diagram	All Subjects
Efficacy Evaluation		
Graph 14.02.01	Tumor Shrinkage: Change from Baseline in Tumor Size – Individual Profiles Plots	Full Analysis Set
Graph 14.02.02	Tumor Shrinkage: Change from Baseline in Tumor Size – Waterfall plot	Full Analysis Set
Graph 14.02.03	Peak SUL: Change from Baseline in Tumor Size – Individual Profiles Plots	Full Analysis Set (Subset of subject presenting an avid PET scan at screening)
Graph 14.02.04	Peak SUL: Change from Baseline in Tumor Size – Waterfall plot	Full Analysis Set (Subset of subjects presenting an avid PET scan at screening)
Graph 14.02.05.01	Time to Response According to RECIST 1.1– Kaplan-Meier Curves	Full Analysis Set (Responders)
Graph 14.02.05.02	PFS According to RECIST 1.1 – Kaplan-Meier Curves	Full Analysis Set
Graph 14.02.05.03	DoR According to RECIST 1.1– Kaplan-Meier Curves	Full Analysis Set (Responders)
Graph 14.02.06	Overall Survival - Kaplan Meier Curves	Full Analysis Set
Pharmacokinetics		
Graph 14.03.01	Plasma/Serum Concentration of Hx-DR5-01 - PK Profiles	PK Analysis Set
Graph 14.03.02	Plasma/Serum Concentration of Hx-DR5-01 – Mean-se by Cycle – With Error bars	PK Analysis Set
Graph 14.03.03	Plasma/Serum Concentration of Hx-DR5-01 – Mean by Cycle – Without Error bars	PK Analysis Set
Graph 14.04.01	Plasma/Serum Concentration of Hx-DR5-05 - PK Profiles	PK Analysis Set
Graph 14.04.02	Plasma/Serum Concentration of Hx-DR5-05 - Mean-se by Cycle – With Error bars	PK Analysis Set
Graph 14.04.03	Plasma/Serum Concentration of Hx-DR5-05 - Mean by Cycle – Without Error bars	PK Analysis Set
Graph 14.05	Plasma/Serum Concentration - PK Profiles – By Clones and ADA	PK Analysis Set
Safety Evaluation		
Graph 14.06.01	Summary of DLT – Dose-escalation Part	Safety Set
Graph 14.06.02	Time to First Treatment Emergent Adverse Event of Special Interest: Elevation of Transaminases - Kaplan-Meier Curves	Safety Set
Graph 14.06.03	Time to First Treatment Emergent Adverse Event of Special Interest: Diarrhea - Kaplan-Meier Curves	Safety Set
Graph 14.06.04	Time to Other Treatment Emergent Adverse Events of Interest: Pyrexia - Kaplan-Meier Curves	Safety Set
Graph 14.06.05	Time to First Treatment Emergent Adverse Event of Special Interest: Swim Lane Plot	Safety Set

[redacted]

Graph 14.07.xx	Laboratory Results – <Parameter>- Individual Profiles Plots – Safety Set	Safety Set
Graph 14.08.xx	Time profile of ALT, AST, ALP, GGT and TBIL	Safety Set
Exploratory Evaluation		
Graph 14.9.xx	Cytokines and Complement Sampling - <Parameter>– Mean-Se Plots	Full Analysis Set
Graph 14.10.xx	Cytokines and Complement Sampling - <Parameter>– Boxplot	Full Analysis Set
Graph 14.11.xx	Immunophenotype - <Parameter>– Mean-Se Plots	Full Analysis Set

21.3 List of Data Listings

Output Number	Output Name
General	
Listing 16.02.01.01.a	Screening Failures and Not-treated Subjects
Listing 16.02.01.01.b	Analysis sets
Listing 16.02.01.02	Subject Disposition
Listing 16.02.01.03.01	Protocol Deviations
Listing 16.02.01.03.02	Covid 19 Protocol Deviations - All important PDs related to Covid-19
Listing 16.02.01.03.03	Covid-19 Protocol Deviations - All non-important PDs related to Covid 19
Listing 16.02.01.03.04	Covid-19 Protocol Deviations - Subject listing of missed/changed visits
Listing 16.02.01.03.05	Covid-19 Protocol Deviations - Subject listing of assessments missed due to visits impacted by Covid-19
Listing 16.02.01.04	Inclusion and Exclusion Criteria not met
Listing 16.02.01.05	Demographic Characteristics
Listing 16.02.01.06	Baseline Disease Characteristics
Listing 16.02.01.07	Biopsy Information
Listing 16.02.01.08	Medical and Surgery History including Pre-Treatment Adverse Event
Listing 16.02.01.09	Prior Anti-Cancer Therapies
Listing 16.02.01.10	Subsequent Anti-Cancer Therapies
Listing 16.02.01.11	Procedures
Listing 16.02.01.12.01	Prior Medications
Listing 16.02.01.12.02	Concomitant Medications
Efficacy Evaluation	
Listing 16.02.02.01	Subjects Excluded from Dose Determing Set
Listing 16.02.02.02.a	RECIST: Lesions Information (Including All Assessments)
Listing 16.02.02.02.b	PERCIST: Lesions Information (Including All Assessments)
Listing 16.02.02.03	Response Information (including BOR, PFS, DoR, TOR, OS)
Listing 16.02.02.04	Immunogenicity
Pharmacokinetics	
Listing 16.02.02.05.01	Plasma/Serum Concentration of Hx-DR5-01
Listing 16.02.02.05.02	Plasma/Serum Concentration of Hx-DR5-05
Listing 16.02.02.06.01	PK Parameters of Hx-DR5-01
Listing 16.02.02.06.02	PK Parameters of Hx-DR5-05
Safety Evaluation	
Listing 16.02.03.01	DLTs
Listing 16.02.03.02	Exposure Data Including Dose Information, Adjustments, and Interruptions
Listing 16.02.03.03.01	Treatment-Emergent Adverse Events
Listing 16.02.03.03.02	Treatment-Emergent Adverse Events Leading to Treatment Discontinuation
Listing 16.02.03.04	Post-Treatment Period Adverse Events
Listing 16.02.03.05.01	Special Interest Treatment-Emergent Adverse Events: Elevation of Transaminases
Listing 16.02.03.05.02	Special Interest Treatment-Emergent Adverse Events: Diarrhea
Listing 16.02.03.05.03	Other Treatment Emergent Adverse Events of Interest: Pyrexia

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Listing 16.02.03.06.01	Fatal Treatment Emergent Adverse Events
Listing 16.02.03.06.02	Deaths
Listing 16.02.03.07.01	Laboratory Results - Hematology
Listing 16.02.03.07.02	Laboratory Results - Biochemistry
Listing 16.02.03.07.03	Laboratory Results – Coagulation Factors
Listing 16.02.03.07.04	Laboratory Results - Immunophenotyping
Listing 16.02.03.07.05	Laboratory Results – Serology
Listing 16.02.03.07.06	Laboratory Results – Urinalysis
Listing 16.02.03.07.07	Laboratory Results – Pregnancy Test
Listing 16.02.03.08.01	NCI CTCAE Grade ≥3 Laboratory Results - Hematology
Listing 16.02.03.08.02	NCI CTCAE Grade ≥3 Laboratory Results - Biochemistry
Listing 16.02.03.09	Vital Signs
Listing 16.02.03.10	Physical Examination Results
Listing 16.02.03.11	ECG Results
Listing 16.02.03.12	ECOG over Time
Exploratory Evaluation	
Listing 16.02.04	Laboratory Results - Cytokines and Complement Sampling
Listing 16.02.05	[redacted]

[redacted]

22. Version history

Version of the SAP and date	Changes
Final version 1.0, 24 April 2018	NA. First final version.
Final version 2.0, February 2022	Major changes: - Incorporate changes made to the protocol from V5.0 to V9.0. including design features such as cohorts' definition and interim analyses. - Remove the expansion part - [redacted]