# PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

# First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1029 in patients with malignant solid tumors

| | |
|---|---|
| **Protocol no.:** | GCT1029-01 |
| **Sponsor:** | Genmab* |
| **Clinical Research Organization:** | [redacted], [redacted], [redacted], USA |
| **EudraCT No.:** | 2017-001394-16 |
| **IND No.:** | 134822 |
| **NCT No.** | NCT03576131 |
| **Trial Drug Name:** | GEN1029 (HexaBody®-DR5/DR5) |

*Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab B.V; or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following contact information page.

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# 1 OVERVIEW OF PROTOCOL AMENDMENTS

| Protocol/Amendment No; Version | Issue Date |
|---|---|
| Version 9.0 (incorporating protocol amendment 07); | 24-Oct-2019 |
| Version 8.0 (incorporating protocol amendment 06) | 13-Sep-2019 |
| Version 7.0 (incorporating protocol amendment 05) | 18-Mar-2019 |
| Version 6.0 (incorporating protocol amendment 04) | 07-Feb-2019 |
| Version 5.0 (incorporating protocol amendment 03) | 15-Mar-2018 |
| Version 4.0 (incorporating protocol amendment 02) | 13-Dec-2017 |
| Version 3.0 (incorporating protocol amendment 01) | 07-Dec-2017 |
| Version 2.0 | 04-Oct-2017 |

# 2 SUMMARY OF PROTOCOL AMENDMENTS

Seven protocol amendments have been made to the original protocol (dated 04-Oct-2017, protocol version 2.0). A summary of key changes with each amendment is provided in Table 1.

**Table 1 Protocol Amendments**

| Amendment Number/ Protocol Version | Document Date | Key Changes |
|---|---|---|
| Amendment 7, v9.0 | 24-Oct-2019 | A health authority raised concerns that the current dose levels (0.3, 1.0, 3.0, [redacted] mg/kg) were too steep for dose escalation, which was the main reason for the present protocol amendment. As an additional precaution, the proposed optional intermediate dose levels [redacted] 2.0[redacted] mg/kg) were made mandatory.<br>• Footnotes on monitoring of liver parameters were edited for clarity.<br>• The PK sampling schedule of the Dose Escalation part was aligned with the overall visit schedule.<br>• For completeness, time to response was added as a secondary endpoint.<br>• Because optional intermediate dose levels were no longer applicable, any reference to these have been deleted.<br>• Clarified to emphasize that the PET scans are exploratory and treatment decisions must be made based on the results of the CT portion of the scans according to RECIST v1.1.<br>• Progression-free survival was redefined according to new guidance. |
| Amendment 6, v8.0 | 13-Sep-2019 | As of the 20-Aug-2019, 27 subjects had been exposed to GEN1029 at dose levels ranging from 0.3 to 3 mg/kg: 24 subjects on the Biweekly Regimen (Q2W) and 3 subjects on the Intensified Regimen (8×Q1W/Q2W). All 3 subjects exposed in the Intensified Regimen experienced DLTs, [redacted] Consequently, the Intensified Regimen was permanently discontinued and, with this amendment, removed from the protocol.<br><br>Additional precautionary measures were implemented including:<br>• Monitoring of liver laboratory parameters at Day 3 of Cycles 1 and 2. To be repeated at least once more, ie, at Day 5, if Day 3 AST or ALT ≥grade 1 and >1.5×baseline.<br>• Restart dosing at 0.3 mg/kg. One subject had been dosed with 0.3 mg/kg and the patient showed no signs of transaminase elevations.<br>• The Priming Regimen was modified so that the priming dose was reduced from 2 doses to 1 dose, with the full dose administered 14 days after the priming dose. The priming regimen was being evaluated as it may mitigate the hepatotoxicity, since clinical data from the trial demonstrated that hepatotoxicity was primarily a first dose effect, and if hepatotoxicity is observed after the first dose, then it is often absent or at least less severe upon re-exposure of the subject.<br>• PET-CT was implemented to better evaluate anti-tumor activity and allow for a better benefit/risk assessment.<br>• Performing liver ultrasound at Screening to explore potential correlation between findings and efficacy/safety.<br><br>Diarrhea was reported in more than 40% of the patients and was the most frequently reported SAE; the majority of these events were considered to be related to the trial drug. Therefore, a guidance on managing diarrhea has been included in the protocol. |

| Amendment Number/ Protocol Version | Document Date | Key Changes |
|---|---|---|
| Amendment 5, v7.0 | 18-Mar-2019 | A detailed evaluation and analysis of transaminase levels for all subjects in the trial led to observations regarding the opportunity to introduce steroid premedication in potentially mitigating these events. Thus, with the present amendment, a mitigation plan to prevent transaminase elevations was introduced.<br>• Prophylactic premedication with dexamethasone (10 mg IV) became mandatory for at least the first 2 cycles.<br>• If a ≥ grade 2 increase of ALT or AST was observed during the second cycle, or at any time thereafter, premedication with dexamethasone was to be continued/reintroduced.<br>• Furthermore, paracetamol (acetaminophen) as premedication was to be considered to be omitted and used with caution during all treatment cycles.<br>• Antihistamines, diphenhydramine (50 mg po preferred) or dexchlorpheniramine (5 mg IV), could be part of the premedication regimen as per protocol. |
| Amendment 4, v6.0 | 07-Feb-2019 | Initial PK data suggested that PK appears to be very similar for the 2 antibodies (1029-01 and 1029-05). However, human PK predictions based on the nonclinical model appear to have significantly underestimated the observed human clearance of both 1029-01 and 1029-05. Predictions for $C_{max}$ have been very accurate and increase of $C_{max}$ appeared to be dose-proportional. However, since the clearance in humans appeared to be significantly higher than predicted, $C_{trough}$ values for both GEN1029 component antibodies were below the lower level of quantification (based on 14 days dosing interval) and $AUC_{0\text{-}14days}$ was also below the predicted values. Thus, based on limited PK data from 10 subjects at doses of 0.3-3 mg/kg in dose escalation cohorts, plasma half-life ($T_{1/2}$) appeared to be relatively short, ranging from 15 to 63 hours. To achieve higher exposures in subjects and potentially provide opportunity to achieve the best therapeutic response, 2 additional dose regimens were introduced with this amendment:<br>• An Intensified Regimen: subjects dosed once weekly for the first 8 weeks then once every 14 days thereafter (8×Q1W/Q2W) to obtain higher drug exposures and thereby potentially improve the anti-tumor efficacy.<br>• A Priming Regimen: in the first cycle, subjects received 2 weekly priming doses. Thereafter, they were dosed once every 14 days (Priming/Q2W) to potentially enable tolerance of increased dose levels and consecutively providing higher exposures. The concept of a priming dose has been successfully implemented for multiple drugs to desensitize the system to prevent eg, tumor lysis syndrome, cytokine release and infusion reactions. This may potentially lead to tolerance of higher dose levels as well as increasing the therapeutic window.<br><br>The total maximum planned number of subjects was increased from 188 to 549, partly because of the additional dose regimens and partly because of the introduction of a Bayesian predictive probability approach for the Expansion. |
| Amendment 3, v5.0 | 15-Mar-2018 | The original protocol version 2.0 dated 04 October 2017 was submitted to the FDA and MHRA. In order to address the recommendations and requests from the FDA, amendment 1, dated 06-Dec-2017, was prepared. Similarly, amendment 2, dated 13-Dec-2017, was prepared to address the comments and requests from MHRA.<br><br>The purpose of amendment 3 was to combine the two regional amendments 1 and 2 into one global amendment. |

| Amendment Number/ Protocol Version | Document Date | Key Changes |
|---|---|---|
| Amendment 2, v4.0 | 13-Dec-2017 | The original protocol version 2.0 dated 04 October 2017 was submitted to the MHRA. In order to address the recommendations and requests from the MHRA, the Amendment 2 was prepared.<br>• The trial objectives and trial design were updated to clarify that only 1 recommended phase 2 dose will be tested in the expansion part.<br>• The investigational and reference therapy were modified to clarify that the absolute maximum dose of GEN1029 would be [redacted]<br>• Clarified that the safety follow-up visit must be performed 70 days rather than 30 days after last dosing.<br>• Clarified that all AEs would be collected from the time where the subject signed the informed consent form.<br>• Added rationale for the highest pre-planned dose level.<br>• Inclusion criterion #10 was expanded to include recommendations on highly effective methods of contraception.<br>• Since attribution of an observed toxicity to a new drug can be uncertain, the word "related" was modified to "at least possibly related."<br>• Modified DLT definition to clarify that a grade ≥2 AST or ALT elevation with concomitant grade ≥2 bilirubin elevation lasting for > 7 days should be considered a DLT.<br>• Modified DLT definition to clarify that non-hematologic laboratory abnormalities that had no clinical consequences and that resolved to grade ≤1 within 7 days should not be considered DLTs.<br>• Clarified that grade 4 AEs fulfilling the DLT criteria should always lead to IMP discontinuation. |

| Amendment Number/ Protocol Version | Document Date | Key Changes |
|---|---|---|
| Amendment 1, v3.0 | 07-Dec-2017 | The original protocol version 2.0 dated 04 October 2017 was submitted to the FDA. In order to address the recommendations and requests from the FDA, Amendment 1 was prepared.<br>• Modified inclusion criterion to clarify that subjects should only be included in the Dose Escalation part of the trial if there was no other available therapy likely to confer a clinical benefit or if they were not candidates for such therapy.<br>• Modified inclusion criterion for clarity by removing "a taxane" from the list of acceptable prior treatment failures.<br>• Modified inclusion criterion for the urothelial Expansion cohort to more clearly state that subjects should have metastatic disease after failure of at least 1 platinum-containing regimen and a checkpoint inhibitor, since both have a survival advantage in this setting. In addition, "a taxane or pemetrexed" was omitted from the end of this criterion, as this wording was not appropriate in this setting.<br>• Clarified that if a subject was withdrawn prematurely from a cohort without experiencing a DLT, another subject should be enrolled in the cohort to bring the number to 3 evaluable subjects.<br>• Modified DLT definition to clarify that a grade ≥3 thrombocytopenia associated with bleeding was considered a DLT.<br>• Since attribution of an observed toxicity to a new drug can be uncertain, the word "related" was modified to "at least possibly related."<br>• Modified DLT definition to clarify that grade ≥3 amylase and/or lipase elevations with significant clinical symptoms that did not resolve to grade ≤1 or baseline within 7 days should be considered a DLT.<br>• Modified DLT definition to clarify that a grade ≥2 AST or ALT elevation with concomitant grade ≥2 bilirubin elevation lasting for > 7 days should be considered a DLT.<br>• Modified DLT definition to clarify that non-hematologic laboratory abnormalities that have no clinical consequences and that resolved to grade ≤1 within 7 days should not be considered DLTs.<br>• Modified safety stopping rule related to drug-related grade 4 AEs that did not fulfill the DLT criteria, so that if such events did not resolve to grade ≤1 or baseline within 14 days, this would be considered a safety stopping rule. |
| Original protocol v2.0 | 04-Oct-2017 | Original protocol, v2.0 distributed |
| v1.0 | 04-Oct-2017 | Original protocol, v1.0 internal document at Genmab, not distributed |

# 3 REDACTED PROTOCOL VERSION 9.0, LATEST VERSION

# CLINICAL TRIAL PROTOCOL

# First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1029 in patients with malignant solid tumors

| | |
|---|---|
| **Protocol no.:** | GCT1029-01 |
| **Sponsor:** | Genmab* |
| **Clinical Research Organization:** | [redacted], [redacted], USA |
| **Coordinating Investigator:** | Professor [redacted]<br>Newcastle Hospitals NHS Foundation Trust<br>Sir Bobby Robson Cancer Trials Research Centre<br>Newcastle upon Tyne, NE7 7DN<br>England |
| **EudraCT No.:** | 2017-001394-16 |
| **IND No.:** | 134822 |
| **Trial Drug Name:** | GEN1029 (HexaBody®-DR5/DR5) |
| **Date of Protocol:** | Version 9.0; 24-Oct-2019 (incorporating protocol amendment 07)<br>Version 8.0, 13-Sep-2019 (incorporating protocol amendment 06)<br>Version 7.0, 18-Mar-2019 (incorporating protocol amendment 05)<br>Version 6.0, 07-Feb-2019 (incorporating protocol amendment 04)<br>Version 5.0, 15-March-2018 (incorporating protocol amendment 03)<br>Version 4.0, 13-Dec-2017 (incorporating protocol amendment 02)<br>Version 3.0, 07-Dec-2017 (incorporating protocol amendment 01)<br>Version 2.0, 04-Oct-2017 |

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| **Sponsor information for all countries except the USA** | |
|---|---|
| **Sponsor** | Genmab B.V.<br>Uppsalalaan 15<br>3584 CM Utrecht<br>The Netherlands |
| **Sponsor information for the USA** | |
| **Sponsor** | Genmab US, Inc.<br>902 Carnegie Center<br>Suite 301<br>Princeton, NJ 08540<br>USA |

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## STATEMENT OF COMPLIANCE

**GCP Compliance:** This trial will be conducted in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP E6 (R2)), and applicable regulatory requirements.

## Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

## ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BOIN | Bayesian Optimal Interval |
| BOR | Best Overall Response |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| CFR | Code of Federal Regulations |
| Cmax | Maximum Concentration |
| CMV | Cytomegalovirus |
| CR | Complete response |
| CRC | Colorectal Cancer |
| CRO | Contract Research Organisation |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DDS | Dose-Determining Set |
| DLT | Dose limiting toxicity |
| DMC | Data Monitoring Committee |
| DoR | Duration of Response |
| DR5 | Death Receptor 5 |
| DRF | Dose-range finding |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EGFR | Epidermal growth factor receptor |
| EoT | End of Trial |
| FAS | Full analysis set |
| FDA | U.S. Food and Drug Administration |
| FDG | Fluoro-Deoxy-Glucose |
| FIH | First-in-human |
| FFPE | Formalin Fixed Paraffin Embedded |

| | |
|---|---|
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GFR | Glomerular filtration rate |
| GLP | Good Laboratory Practice |
| HBsAg | Hepatitis B surface antigen |
| HED | Human equivalent dose |
| HNSTD | Highest Non-Severely Toxic Dose |
| i.v. | Intravenous |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| LD | Longest Diameter |
| mAbs | monoclonal antibodies |
| mBOIN | modified Bayesian Optimal Interval |
| mCRC | Metastatic colorectal cancer |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOA | Mode of Action |
| MRSD | Maximum Recommended Starting Dose |
| MTD | Maximum tolerated dose |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NOAEL | No Observable Adverse Effect Level |
| NS | Non serious |
| NSCLC | Non-small cell lung cancer |
| ORR | Objective Response Rate |
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive disease |
| PET | Positron Emission Tomography |
| PERCIST | Positron Emission Tomography Response Criteria In Solid Tumors |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PR | Partial response |
| RCC | Renal Cell Carcinoma |
| RDFD | Recommended Dose for Further Development |

| | |
|---|---|
| RECIST | Response Evaluation Criteria In Solid Tumors |
| [redacted] | [redacted] |
| RP2D | Recommended Phase 2 Dose |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCC | Squamous cell carcinomas |
| SD | Stable disease |
| SUL | Standardized uptake volume |
| SUSAR | Serious unexpected suspected adverse reactions |
| SUVmax | Maximum tumor standardized uptake value |
| SUVpeak | Peak tumor standardized uptake value |
| TEAE | Treatment-emergent adverse event |
| TLG | Total lesion glycolysis |
| TLS | Tumor lysis syndrome |
| TNBC | Triple Negative Breast Cancer |
| TNFRSF | Tumor Necrosis Factor Receptor Superfamily |
| TNM | Tumor Nodes Metastasis |
| TRAIL | TNF Related Apopotosis Induced Ligand |
| TTR | Time to response |
| ULN | Upper Limit of Normal |
| VEGF | Vascular Endothelial Growth Factor |
| WHO | World Health Organization |

## TRIAL SYNOPSIS

<table>
<tr><td>Title</td><td>First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1029 in patients with malignant solid tumors.</td></tr>
<tr><td>Brief Title</td><td>GEN1029 Safety Trial in Patients With Malignant Solid Tumors.</td></tr>
<tr><td>Clinical Phase</td><td>Phase I/IIa</td></tr>
<tr><td>Countries and Sites</td><td>The Dose Escalation part is planned to be performed in a maximum of 5-10 sites in Spain, United Kingdom and the US, with up to 20-30 additional sites to be included in Europe and the US for the Expansion part.</td></tr>
<tr><td>Purpose and Rationale</td><td>Death receptor 5 (DR5) is a receptor for TRAIL, which initiates the extrinsic apoptosis pathway leading to apoptotic cell death of TRAIL-sensitive cancer cells. GEN1029 is a mixture of two HexaBody® molecules which targets two distinct epitopes on DR5.</td></tr>
<tr><td>Objectives and Endpoints</td><td>Dose Escalation Part
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>• Determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D)</td><td>• Dose Limiting Toxicities (DLTs)</td></tr>
<tr><td>• Establish the safety profile of GEN1029</td><td>• Adverse events (AEs) and safety laboratory parameters (hematology and biochemistry)</td></tr>
<tr><td>Secondary</td><td></td></tr>
<tr><td>• Establish the pharmacokinetic (PK) profile and evaluate immunogenicity of GEN1029 after single and multiple infusions</td><td>• PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve [$AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$], AUC0_14d, CL. maximum concentration [$C_{max}$], time of $C_{max}$ [$T_{max}$], pre-dose values, and half-life of GEN1029)<br>• Immunogenicity of GEN1029</td></tr>
<tr><td>• Evaluate the anti-tumor activity of GEN1029</td><td>• Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations)<br>• Objective Response, Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DoR), and Time to Response (TTR)</td></tr>
<tr><td>Exploratory</td><td></td></tr>
</table></td></tr>
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|---|---|
| • To assess biomarkers predictive of response or resistance to GEN1029<br>• To assess potential pharmacodynamic biomarkers of GEN1029<br>• To assess the metabolic response in the tumors<br>• [redacted] | • DR5 expression (protein, [redacted]) in tumor biopsies<br>• Circulating protein profiles<br>• Immune cells levels<br>• Biomarker profile<br>• Standardized uptake volume corrected for body lean mass (SUL)<br>• [redacted] |

**Expansion Part**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the Objective Response Rate (ORR) by indication | • ORR |
| Secondary | |
| • Evaluate the anti-tumor activity of GEN1029 | • Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations)<br>• Objective Response, Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DoR), and Time to Response (TTR) |
| • To further describe the safety profile of GEN1029 | • Adverse events (AEs) and safety laboratory parameters (hematology and biochemistry) |
| • Evaluate the pharmacokinetic (PK) profile as feasible, evaluate immunogenicity of GEN1029 after single and multiple infusions | • PK parameters<br>• Immunogenicity of GEN1029 |
| Exploratory | |
| • To assess biomarkers predictive of response or resistance to GEN1029<br>• To assess potential pharmacodynamic biomarkers of GEN1029<br>• To assess the metabolic response in the tumors<br>• [redacted] | • DR5 expression (protein, [redacted]) in tumor biopsies<br>• Circulating protein profiles<br>• Immune cells levels<br>• Biomarker profile<br>• Standardized uptake volume corrected for body lean mass (SUL)<br>• [redacted] |

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| **Trial Design** | This is an open-label, multi-center phase I/IIa safety trial of GEN1029 in patients with malignant solid tumors. The trial consists of two parts; a dose-escalation part (phase I, first-in-human (FIH)) and an expansion part (phase IIa). The expansion part of the trial will be initiated once the MTD or the Recommended Phase 2 Dose (RP2D) has been determined.<br><br>In the dose escalation part, up to 2 dose regimens may be evaluated:<br>• The Biweekly Regimen: patients are dosed once every 14 days (Q2W).<br>• The Priming Regimen: in the first cycle, patients receive a priming dose. After 14 days and thereafter, they are dosed with the maximum starting dose once every 14 days (Priming/Q2W).<br><br>These regimens may also be evaluated in the expansion part. If two regimens are available for patients with a specific indication they will be randomized in a 1:1 fashion. Randomization will be stratified by the Eastern Cooperative Oncology Group performance status at screening (0 or 1). |
| **Planned Number of Patients** | Up to 520 patients can be enrolled in this trial.<br><br>The dose escalation part will enroll up to approximately 100 patients, shared between the Biweekly and Priming Regimens. Three patients were exposed in an Intensified Regimen (8×Q1W/Q2W) all of whom experienced DLTs and, consequently, this dosing regimen was permanently discontinued.<br><br>In the expansion part, each cohort will enroll between 10 and 60 patients. If all seven cohorts are opened, between 70 and 420 patients may be enrolled. |
| **Population** | Patients with the following indications: patients with advanced and/or metastatic colorectal cancer (CRC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), renal cell carcinoma (RCC), gastric (incl. esophagogastric junction) cancer, pancreatic cancer or urothelial cancer who have failed available standard therapy or who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1029 may be beneficial.<br><br>The following indication specific cohorts are considered for the expansion part: CRC, NSCLC, TNBC, RCC, gastric, pancreas or urothelial cancer who have failed anticancer therapy for metastatic disease (as defined in the inclusion criteria). |
| **Key Inclusion Criteria** | • Patients with advanced and/or metastatic CRC, NSCLC, TNBC, RCC, gastric (incl. esophagogastric junction), pancreas or urothelial cancer who have no available standard therapy or who are not candidates for available standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1029 may be beneficial.<br>• Patient must be ≥ 18 years of age |

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|---|---|
| | • Patients must have measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1<br>• In the dose escalation part all patients must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded (FFPE) blocks/slides) from either archival tissue (preferably derived from advanced disease stage) or a fresh biopsy collected before Cycle 1, Day 1. In the expansion part a mandatory fresh biopsy (FFPE tissue blocks/slides) at screening (aspirates are not acceptable) is to be provided for all patients which is taken after failure/stop of last prior treatment, unless not clinically feasible as documented by the investigator. In case it is not feasible to meet the required criteria for a fresh tumor biopsy, the sponsor medical officer's approval of enrollment is needed. Furthermore, the latest available archival tumor tissue sample has to be collected if available.<br>• Have an acceptable hematological status<br>• Have an acceptable renal function<br>• Have an acceptable liver function<br>• Have an Eastern Cooperative Oncology Group performance status of 0 or 1<br>• Body weight ≥ 40 kg |
| **Key Exclusion Criteria** | • Acute deep vein thrombosis or clinically relevant pulmonary embolism, not stable for at least 8 weeks prior to first IMP administration<br>• Have clinically significant cardiac disease<br>• Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management<br>• Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (younger than 6 months) or progressive brain metastases or stroke<br>• History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of IMP<br>• Have received a cumulative dose of corticosteroid ≥ 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks before the first IMP administration<br>• History of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial<br>• Radiotherapy within 14 days prior to first IMP administration<br>• Any prior therapy with a compound targeting DR4 or DR5 |
| **Investigational and Reference Therapy** | GEN1029 at dose levels: 0.3, [redacted], 1.0, 2.0, 3.0, [redacted] mg/kg. |

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| **Statistics** | MTD and/or RP2D will be determined using a modified (mBOIN) algorithm.<br><br>Patients eligible for an expansion cohort will be entered in a stage-wise fashion. For each stage, the success of the stage is predicted. If the predictive probability of success is less than 10% the stage is not further explored. Success is evaluated on the basis of the objective responder rate.<br><br>Adverse events will be presented using summary statistics<br><br>Individual curves of plasma/serum concentration of each component of GEN1029 including information on actual dose, will be presented for all patients.<br><br>PK parameters will be calculated based on non-compartmental methods and will be calculated separately for Cycle 1, Cycle 2 and Cycle 3.<br><br>RECIST criteria (v1.1) will be used to define response. Summaries of objective response, best overall tumor response and disease control will be presented by dose cohort/indication and total.<br><br>PFS, OS, and DoR will be summarized using survival analysis methods. 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) will be presented. TTR will be summarized using descriptive statistics. |

# 1 VISIT SCHEDULE

## 1.1 Dose Escalation Part

In the dose escalation part, up to 2 dose regimens may be evaluated:

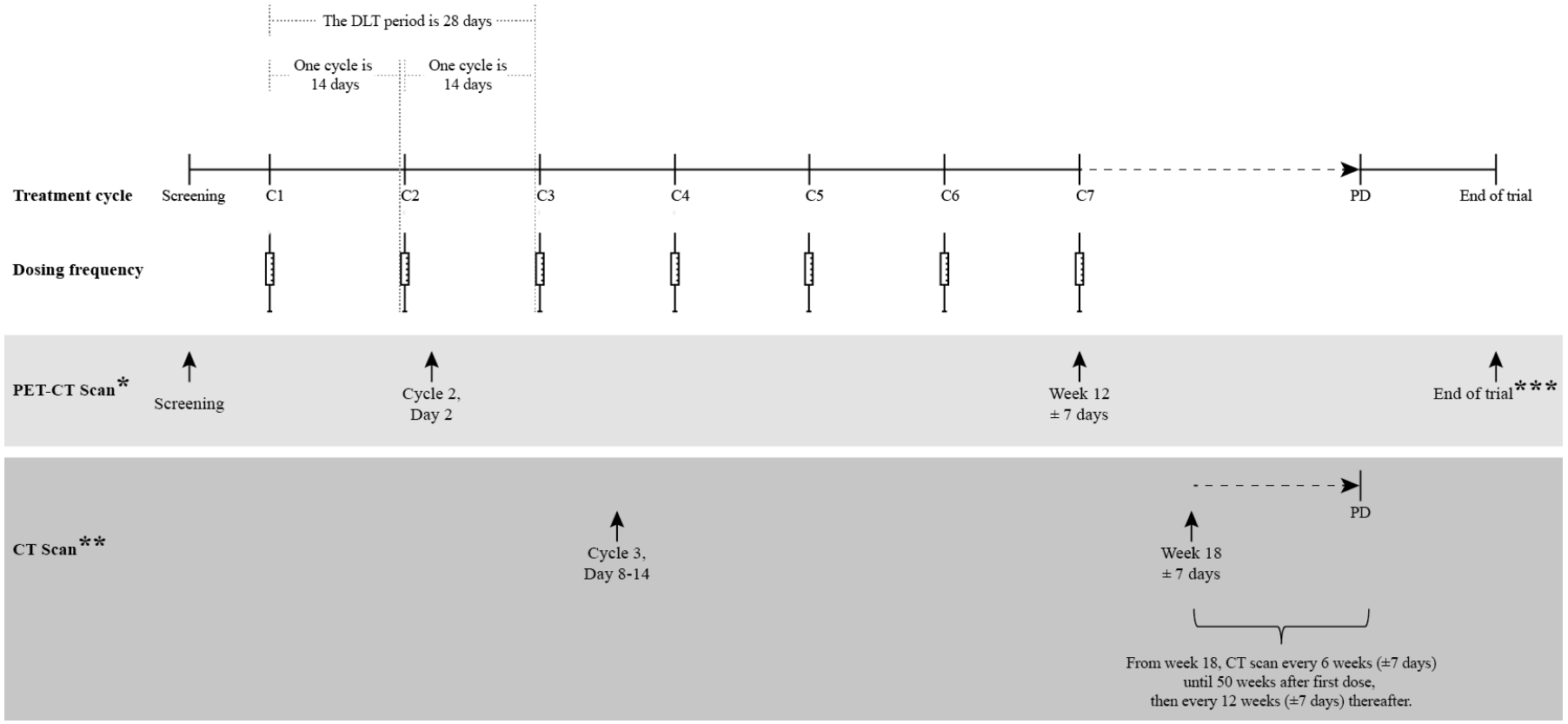
- The Biweekly Regimen: patients are dosed once every 14 days (Q2W).
- The Priming Regimen: in the first cycle, patients receive a priming dose. After 14 days and thereafter, they are dosed with the maximum starting dose once every 14 days (Priming/Q2W).

An overview of the dosing frequency as well as treatment cycle duration and dose limiting toxicity (DLT) period duration, and scanning frequency is shown in Figure 1-1. A cycle is always 14 days and the DLT period is always 28 days, irrespective of which dose regimen the patients are following.

Further details on when the 2 dose regimens will be available and open for enrollment are described in Section 4.2.

Table 1-1 lists all of the assessments in the dose escalation part and indicates with an "X" the visits at which they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Table 1-2 shows the timing of the ECG assessments, Table 1-3 shows the timing of the PK sampling, Table 1-4 shows the timing of cytokine and complement sampling, and Table 1-5 shows the timing for measurement of vital signs in relation to infusions.




*: Mandatory PET-CT scans must be taken at screening and, if avid at screening, also at Cycle 2 Day 2, and week 12 (±7 days). If PET-CT at screening showed no avidity, a CT scan has to be done instead of a PET-CT in week 12 (±7 days).
**: A CT scan must be performed at Cycle 3, Day 8-14 after first dose. From week 18 (±7 days) until week 50 after first dosing, CT scans must be performed every 6 weeks (±7 days), and every 12 weeks (±7 days) thereafter. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts.
***: Only if a patient, who has been exposed to GEN1029, did not have any PET-CT scans while on treatment and displayed avidity at screening.

**Figure 1-1 Overview of Dosing and Scanning Frequency, DLT and Cycle Duration – Dose Escalation Part**

## Table 1-1 Visit evaluation schedule Dose Escalation Part – Biweekly Regimen (Q2W) and Priming Regimen (Priming/Q2W)

| **Treatment Cycle** | **Screening** | **Cycle 1-3[1]** | | | | **Cycle 4-PD[1]** | | **End of treatment[2]** | **Safety Follow-up[21]** | | **Patient follow-up** | **End of trial** | **Unscheduled** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **≤ 21 days prior to Visit C1-D1** | **1d** | **2d** | **3d[24,28]** | **8d** | **1d** | **8d[22]** | **-** | **30 days after last dosing** | **70 days after last dosing** | **13W, 26W, 39W + 52W after last dosing** | **-** | **-** |
| **Visit window[3]** | | **±1d** | **-** | **-** | **±1d** | **±3d** | **±1d** | **-** | **±7d** | **±7d** | **±14d** | **-** | **-** |
| Informed Consent[4] | X | | | | | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | | | | | |
| Demographics, disease status | X | | | | | | | | | | | | |
| Prior cancer therapy/surgery | X | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | |
| Body Weight[6] | X | X | | | | X | | X | | | | | |
| Physical Examination[25] | X | X | | | | X | | X | | | | | |
| Vital Signs[7] | X | X | X | | X | X | X | X | | | | | X[14] |
| Liver ultrasound | X | | | | | | | | | | | | |
| ECG | Please see Table 1-2 for details of ECG assessments | | | | | | | | | | | | |
| PET-CT scan[29] | X[29] | X[8] | | | | X[8] | | | | | | X[30] | |
| Efficacy assessment (CT-Scan) | | X[9] | | | | X[9] | | X[23] | | | | | X[14] |
| ECOG status | X | X | | | | X | | X | | | | | X[14] |
| Adverse Events[5] | X | X | X | X | X | X | X | X | X | X | X[18] | | X[14] |
| Concomitant Medication | X | X | X | X | X | X | X | X | X[19] | X[19] | X[19] | | X[14] |
| Pre-medication[33] | | X | X | | | | | | | | | | |
| IMP administration | | X | | | | X | | | | | | | |
| End of trial | | | | | | | | | | | | X[20] | |
| **Laboratory assessments[10]** | | | | | | | | | | | | | |
| Hematology | X | X | X | | X | X | X | X | X | X | | | X[14] |
| Biochemistry[26] | X | X | X | X[27] | X | X | X | X | X | X | | | X[14] |
| Urinalysis | X | X | | | | X | | X | X | X | | | X[14] |
| [redacted] | | | | | | | | | | | | | |
| Pregnancy Test[11] | X | X | | | | X | | X | | | | | X[14] |
| ADA (Immunogenicity) | X | X | | | | X | | X | X | X | | | X[14] |
| Hepatitis B, C, CMV[12] | X | | | | | | | X | | | | | X[14] |
| PK Sampling | Please see Table 1-3 for details of PK sampling | | | | | | | | | | | | |
| Tumor biopsy | X[13] | | | | | | | X[14] | | | | | X[14] |
| Immunophenotyping | | X[15] | | | X[15] | | X[17] | X | | | | | X[14] |
| Cytokine and circulating factors | Please see Table 1-4 for details of cytokine and complement sampling | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |

| **Footnotes to Trial Flowchart: Dose Escalation Part - Biweekly Regimen (Q2W) and Priming Regimen (Priming/Q2W)** |
|---|
| [1] The duration of one cycle is 14 days. Treatment can continue until PD. |
| [2] If the patient shows PD, starts a new anti-cancer treatment or withdraws from treatment due to another reason, the end of treatment visit should be performed as soon as possible after decision of discontinuation. |
| [3] The specified visit windows are in accordance with the previous visit. However, within 28 days from treatment start (corresponding to the DLT period), max. 2 doses of GEN1029 in the Q2W regimen and in the priming regimen can be administered. At Cycles 2 and 3, Day 1 of the next cycle should be performed 7 days ± 1 day after Day 8 of the previous cycle and from Cycle 4 and onwards, Day 1 of the next cycle should be performed 7 days ± 3 days after Day 8 of the previous cycle. |
| [4] Informed consent must be obtained before or at Screening prior to making any screening assessments. |
| [5] Adverse Events should be reported from the time the informed consent is signed. |
| [6] During the trial, body weight is measured on the dosing day, as part of the dose calculation. Please see section 9.4.1. |
| [7] Temperature, blood pressure and heart rate. Please see Table 1-5 and section 9.4.2. |
| [8] Mandatory PET-CT scans must be taken at screening and, if avid at screening, also at Cycle 2 Day 2, and week 12 (±7 days). Please see section 9.2. |
| [9] A CT scan must be performed at Cycle 3, Day 8-14 after first dose. If PET-CT at screening showed no avidity, a CT scan has to be done instead of a PET-CT in week 12 (±7 days). From week 18 (±7 days) until week 50 after first dosing, CT scans must be performed every 6 weeks (±7 days), and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. |
| [10] All laboratory parameters will be analyzed centrally, except urinalysis. In the first 3 cycles, all biochemistry safety parameters must be assessed locally as well to monitor liver function. At treatment visits, laboratory parameters will also be analyzed at local laboratory prior to treatment of IMP please see section 9.5. |
| [11] Serum (beta-hCG) laboratory test should be taken at screening. A urine pregnancy test should be taken before every treatment of IMP. |
| [12] HbsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients. At end of treatment, only antibodies to CMV antigen will be assessed. Please see section 9.5 for further details. |
| [13] The latest archived biopsy can be used preferably derived from advanced disease stage. If no sample is available, a new tumor biopsy must be obtained. |
| [14] Optional. |
| [15] All patients must have a sample taken at Day 1 and 8 of Cycle 1 and at Day 8 of Cycle 3. If the visit occurs on an infusion day, the sample must be taken before IMP treatment. |
| [16] Sample to be taken at Cycle 3. |
| [17] Sample to be taken at Cycle 6. |
| [18] Only non-serious AEs ≥ 3 possibly related to IMP and SAEs (independent of causality). |
| [19] Only new anticancer treatments. |
| [20] Patient status at withdrawal. |
| [21] If the patient withdraws sooner than 70 days after the last dosing, the safety follow-up visit should take place at the time of withdrawal unless there has been a safety follow-up visit within the last 14 days. |
| [22] The day 8 visit can be omitted after approval by the sponsor medical monitor if there have been no AEs fulfilling the DLT criteria in the previous 6 cycles. |
| [23] To be completed as indicated to confirm response, new symptoms, end of treatment visit or at the physician discretion, see Section 9.2. |
| [24] Cytokine, complement and PK sampling to be taken at Cycles 1 and 2 Day 3 after infusion, see Table 1-3 and Table 1-4. |
| [25] A complete, general physical examination will be done at the screening and Cycle 1 Day 1 visits. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed. |
| [26] Any AST, ALT, and/or bilirubin ≥ grade 2 needs to be checked 2×/week for up to 4 weeks and until resolution or return to baseline. |
| [27] Repeat at least once more, i.e. on Day 5 if AST, ALT, or bilirubin ≥ grade 1 and > 1.5×baseline. |
| [28] If no AST, ALT, and/or bilirubin ≥ grade 2 elevations are observed in Cycle 1 and 2, the visit at Cycle 3 Day 3 can be omitted |
| [29] The PET must be combined with CT and the CT portion must be of similar diagnostic quality to CT alone. The PET-CT must be performed before any optional tumor biopsy to avoid potential false positive findings. The baseline PET-CT assessment during screening should be performed at the closest date as possible from start of trial treatment, at least one week before tumor biopsy. Of note, if tumor lesions showed no avidity at baseline, no further PET scans should be performed, but CT scans only. |
| [30] To be performed only if a patient, who has been exposed to GEN1029, did not have any PET-CT scans while on treatment and displayed avidity at screening. |
| [redacted] |
| [redacted] |
| [33] Dexamethasone 4 mg/p.o. one day before dosing at Cycles 1 and 2 and 10 mg. i.v. at Day 1 before dosing and at Day 2 in Cycles 1 and 2. If a drug-related ≥ grade 2 elevation of ALT and/or AST is observed during the second cycle or thereafter, Dexamethasone pre-medication should be continued/re-introduced. In this case, Dexamethasone can be given orally on the day after the dosing day (Section 6.4.1). |

## Table 1-2 ECG Assessments in Dose Escalation Part – Applicable for Both Regimens

| Treatment Cycle | Screening | Cycle 1-3 | | | Cycle 4-PD | End of Treatment | Unscheduled |
|---|---|---|---|---|---|---|---|
| **Day** | **-** | **1d** | **2d** | **8d** | **1d** | **-** | |
| Before Infusion (on infusion days) | 1 | 3 | 3 [a] | 3 | 3 | 1 | 1 [b] |
| End of infusion (+15 minutes) | | 3 | | | 3 | | |
| End of infusion + 2 hours (± 15 minutes) | | 3 | | | | | |
| End of infusion + 4 hours (± 30 minutes) | | 3 | | | | | |

1 – Single ECG assessment
3 – Triplicate ECG assessments

[a] Time window for the Day 2 sampling in the dose escalation part is 24 hours ± 2 hours after the end of infusion on Day 1
[b] Optional

## Table 1-3 PK Sampling in Dose Escalation Part – Applicable for Both Regimens

| Treatment Cycle | Screening | Cycle 1-3 | | | | Cycle 4-PD | Unscheduled |
|---|---|---|---|---|---|---|---|
| **Day/Week** | **-** | **1d** | **2d** | **3d** | **8d** | **1d** | |
| Before Infusion (on infusion days) | X | X | X[1] | X[2] | X | X | X[3] |
| End of infusion (+15 minutes) | | X | | | X | X | |
| End of infusion + 2 hours (± 15 minutes) | | X | | | | | |
| End of infusion + 4 hours (± 30 minutes) | | X | | | | | |

[1] Time window for the Day 2 sampling in the dose escalation part is 24 hours ± 2 hours after the end of infusion on Day 1
[2] Sample to be taken at Day 3 of Cycles 1 and 2. If a patient comes for a visit at Day 5 to have safety laboratory samples taken, a sample for PK assessments should also be taken.
[3] Optional

## Table 1-4 Cytokine and Circulating Factors Sampling in Dose Escalation Part – Applicable for Both Regimens

| Treatment Cycle | Cycle 1-3 | | | | Unscheduled |
|---|---|---|---|---|---|
| **Day** | **1d** | **2d** | **3d** | **8d** | |
| Before infusion (on infusion days) | X | X | X[2] | X | X[3] |
| End of infusion + 4 hours (± 30 minutes) | X | | | | |

[1] Time window for the Day 2 sampling in the dose escalation part is 24 hours ± 2 hours after the end of infusion on Day 1
[2] Sample to be taken at Cycles 1 and 2 Day 3
[3] Optional

## Table 1-5 Vital Signs during the Dose Escalation Part – Applicable for Both Regimens

| |
|---|
| Pre-infusion (up to 30 min before infusion) |
| 15 min after start of infusion (± 5 min)* |
| At the end of infusion (± 5 min) |
| 15 min after end of infusion (± 5 min) |
| 30 min after end of infusion (± 5 min) |
| 1 hour after end of infusion (± 10 min) |
| 2 hours after end of infusion (± 10 min) |
| 4 hours after end of infusion (± 30 min) (first 3 cycles) |

*If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (± 5 minutes) for the remaining duration of the infusion.

## 1.2 Expansion Part

In the expansion part, up to 2 dose regimens may be evaluated:

- The Biweekly Regimen: patients are dosed once every 14 days (Q2W).
- The Priming Regimen: in the first cycle, patients receive a priming dose. After 14 days and thereafter, they are dosed with the maximum starting dose once every 14 days (Priming/Q2W).

An overview of the dose, dosing frequency, and cycle duration is shown in Figure 1-2. A cycle is always 14 days, irrespective of which dose regimen the patients are following.

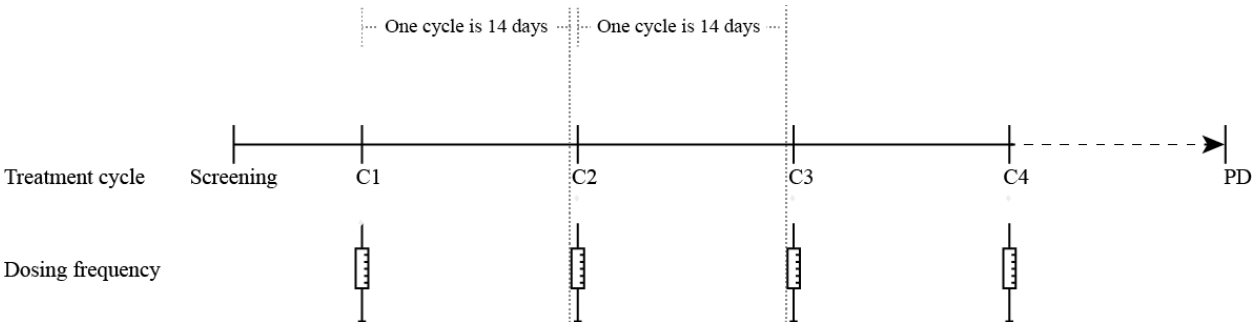



**Figure 1-2 Overview of Dosing Frequency and Cycle Duration – Expansion Part**

Further details on when the 2 dose regimens are available and open for enrollment are described in Section 4.2.

Table 1-6 lists all of the assessments in the expansion part and indicates with an "X" the visits at which they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Table 1-7 shows the timing of the ECG assessments, Table 1-8 shows the timing of the PK sampling and Table 1-9 shows the timing for measurement of vital signs in relation to infusions.

## Table 1-6 Visit Evaluation Schedule in Expansion Part – Biweekly Regimen (Q2W) and Priming Regimen (Priming/Q2W)

| **Treatment Cycle** | **Screening** | **Cycle 1-3[1]** | | | **Cycle 4-PD[1]** | | **End of treatment[2]** | **Safety Follow-up[20]** | | **Patient follow-up** | **End of trial** | **Un-scheduled** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **≤ 21 days prior to Visit C1-V1** | **1d** | **3d[31]** | **8d** | **1d** | **8d[21]** | **-** | **30 days after last dosing** | **70 days after last dosing** | **13W, 26W, 39W + 52W after last dosing** | **-** | **-** |
| **Visit window[3]** | | **±1d** | **-** | **±1d** | **±1d** | **±1d** | **-** | **±7d** | **±7d** | **±14d** | **-** | **-** |
| Informed Consent[4] | X | | | | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | | | | |
| Demographics, Disease status | X | | | | | | | | | | | |
| Prior cancer therapy/surgery | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Height | X | | | | | | | | | | | |
| Body Weight[6] | X | X | | | X | | X | | | | | |
| Physical Examination[24] | X | X | | | X | | X | | | | | |
| Vital Signs[7] | X | X | | X | X | X | X | | | | | X[15] |
| Liver ultrasound | X | | | | | | | | | | | |
| ECG | Please see Table 1-7 for details of ECG assessments | | | | | | | | | | | |
| Efficacy assessment ([PET]-CT-Scan/MRI) | X[8] | X[9] | | | | | X[22] | | | | | X[15] |
| ECOG status | X | X | | | X | | X | | | | | X[15] |
| Adverse Events[5] | X | X | | X | X | X | X | X | X | X[17] | | X[15] |
| Concomitant Medication | X | X | | X | X | X | X | X[18] | X[18] | X[18] | | X[15] |
| IMP administration | | X | | | X | | | | | | | |
| Pre-medication[30] | | X | | | | | | | | | | |
| End of trial | | | | | | | | | | | X[19] | |
| **Laboratory assessments[10]** | | | | | | | | | | | | |
| Hematology | X | X | | X | X | X | X | X | X | | | X[15] |
| Biochemistry[23] | X | X | X[25] | X | X | X | X | X | X | | | X[15] |
| Urinalysis | X | X | | | X | | X | X | X | | | X[15] |
| [redacted] | | | | | | | | | | | | |
| Pregnancy Test[11] | X | X | | | X | | X | | | | | X[15] |
| ADA (Immunogenicity) | X | X | | | X | | X | X | X | | | X[15] |
| Hepatitis B, C, CMV[12] | X | | | | | | X | | | | | X[15] |
| PK Sampling | Please see Table 1-8 for details of PK sampling | | | | | | | | | | | |
| Tumor biopsy | X[13] | | | | | | X[15] | | | | | X[15] |
| Immunophenotyping and PBMC | | X[28] | | X[28] | | X[16] | X | | | | | X[15] |
| Cytokines and circulating factors | | X | X[27] | X | X[14] | X[14] | | | | | | X[15] |
| [redacted] | | | | | | | | | | | | |

| **Footnotes to Trial Flowchart: Expansion Part - Biweekly Regimen (Q2W) and Priming Regimen (Priming/Q2W)** |
|---|
| [1] The duration of one cycle is 14 days. Treatment can continue until PD. |
| [2] If the patient shows PD, is starting new anti-cancer treatment or withdraws from treatment due to another reason the end of treatment visit should be performed as soon as possible after decision of discontinuation. |
| [3] The specified visit windows are in accordance with the previous visit. From Cycle 2-12, Day 1 of the next cycle should be performed 7 days ± 1 day after Day 8 of the previous cycle and from Cycle 13 and onwards, Day 1 of the next cycle should be performed 7 days ± 3 days after Day 8 of the previous cycle. |
| [4] Informed consent must be obtained before or at Screening prior to making any screening assessments. |
| [5] Adverse Events should be reported from the time the informed consent is signed. |
| [6] During the trial, body weight is measured on the dosing day as part of the dose calculation. If body weight is assessed ≤ 7 days before the first day of the planned dosing in a cycle, this value can be used to calculate dose. |
| [7] Temperature, blood pressure and heart rate. Please see Table 1-9 and Section 9.4.2 |
| [8] Within 4 weeks prior to Cycle 1 Day 1. If a (PET)-CT-scan/MRI has been performed within 4 weeks prior to Cycle 1 Day 1 as part of standard procedure, it is acceptable as screening CT-scan/MRI for the trial. If there is suggestion of brain metastases/tumors, a (PET)-CT-scan/MRI of the head and neck will be performed before inclusion. Please see section 9.2. At the discretion of the investigators and after approval of the sponsor, combined PET-CT may be performed for tumor assessments. |
| [9] On-trial imaging will be performed at Week 6 (-7 days), every 6 weeks (±7 days) for 50 weeks, and every 12 weeks (±7 days) thereafter from the date of first dose until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. |
| [10] All laboratory parameters will be analyzed centrally, except urinalysis. In the first 3 cycles, all biochemistry safety parameters must be assessed locally as well to monitor liver function. At infusion visits laboratory parameters will be analyzed at local laboratory prior to IMP treatment please see section 9.5. |
| [11]Serum (beta-hCG) laboratory test should be taken at screening. A urine pregnancy test should be taken before every treatment of IMP. |
| [12] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients. At end of treatment, only antibodies to CMV antigen will be assessed. |
| [13] A mandatory fresh biopsy (FFPE tissue blocks/slides) at screening (aspirates are not acceptable) is to be provided for all patients which is taken after failure/stop of last treatment, unless not clinically feasible as assessed and documented by investigator. In case it is not feasible to meet the required criteria for fresh tumor biopsy, the sponsor medical officer's approval of enrollment is needed. Furthermore the latest available archival tumor tissue sample has to be collected if available. |
| [14] All patients must have a sample taken at Day 1 and 8 of Cycles 4, 5 and 6. If the visit occurs on an infusion day, the sample must be taken before IMP treatment. If the Day 8 visit on Cycle 4 and/or 5 is omitted according to footnote 21, the sample does not need to be taken (sample at Cycle 6 Day 8 is mandatory). |
| [15] Optional. |
| [16] Sample to be taken Cycles 3 and 6. |
| [17] Suspected IMP related AEs only. |
| [18] Only new anticancer treatments. |
| [19] Patient status at withdrawal. |
| [20] If the patient withdraws sooner than 70 days after the last dosing, the safety follow-up visit should take place at the time of withdrawal unless there has been a safety follow-up visit within the last 14 days. |
| [21] The Day 8 visit can be omitted after approval by the sponsor medical monitor if there have been no AEs fulfilling the DLT criteria in the previous 3 cycles. |
| [22] To be completed as indicated to confirm response, new symptoms, end of treatment visit or at the physician discretion, see Section 9.2. |
| [23] Any AST, ALT, and/or bilirubin ≥ grade 2 needs to be checked 2×/week for up to 4 weeks and until resolution or return to baseline. |
| [24] A complete, general physical examination will be done at the screening and Cycle 1 Day 1 visits. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed. |
| [25] Repeat at least once more, i.e. on Day 5 if AST, ALT, or bilirubin > grade 1 and > 1.5×baseline. |
| [redacted] |
| [27] Only required at Cycles 1 and 2 |
| [28] All patients must have a sample taken at Day 1 and 8 of Cycle 1 and at Day 8 of Cycle 3. If the visit occurs on an infusion day, the sample must be taken before IMP treatment. |
| [redacted] |
| [30] Dexamethasone 4 mg/p.o. one day before dosing at Cycles 1 and 2 and 10 mg. i.v. at Day 1 before dosing and orally at Day 2 in Cycles 1 and 2. If a drug-related ≥ grade 2 elevation of ALT and/or AST is observed during the second cycle or thereafter, Dexamethasone pre-medication should be continued/re-introduced. In this case, Dexamethasone can be given orally on the day after the dosing day (Section 6.4.1). |
| [31] If no AST, ALT, and/or bilirubin ≥ grade 2 elevations are observed in Cycle 1 and 2, the visit at Cycle 3 Day 3 can be omitted. |

## Table 1-7 ECG Assessments in Expansion Part – Applicable for Both Regimens

| Treatment Cycle | Screening | Cycle 1-3 | | Cycle 4-PD | End of Treatment | Unscheduled |
|---|---|---|---|---|---|---|
| **Day** | **-** | **1d** | **8d** | **1d** | **-** | |
| Before Infusion (on infusion days) | 1 | 3 | 3 | 3 | 1 | 1[a] |
| End of infusion (+15 minutes) | | 3 | | 3 | | |

1 – Single ECG assessment
3 – Triplicate ECG assessments
[a] Optional.

## Table 1-8 PK Sampling in Expansion Part – Applicable for Both Regimens

| Treatment Cycle | Screening | Cycle 1-3 | | Cycle 4-PD | Unscheduled |
|---|---|---|---|---|---|
| **Day/Week** | **-** | **1d** | **8d** | **1d** | |
| Before Infusion (on infusion days) | X | X | X | X | X[1] |
| End of infusion (+15 minutes) | | X | | X | |

[1] Optional.

## Table 1-9 Vital Signs during the Expansion Part – Applicable for Both Regimens

| |
|---|
| Pre-infusion (up to 30 min before infusion) |
| At the end of infusion (± 10min)* |
| 1 hour after end of infusion (± 10 min) |
| 2 hours after end of infusion (± 15 min) |

*If infusion lasts for more than 60 minutes, vital signs should be assessed every 30 minutes (± 5 minutes) for the remaining duration of infusion.

# 2 INTRODUCTION

## 2.1 Background

GEN1029 is being developed primarily for intravenous (i.v.) treatment of selected malignant solid tumors. The medical need is high for innovative anti-cancer therapies with improved efficacy and safety profiles, including therapies for patients with advanced and/or metastatic Colorectal Cancer (CRC), Non-small Cell Lung Cancer (NSCLC), Triple Negative Breast Cancer (TNBC), Renal Cell Carcinoma (RCC), gastric, pancreas or urothelial cancer. Additional tumor types might be selected based on ongoing preclinical research and initial experience to be generated in this first-in-human trial, primarily focusing on the safety and tolerability of GEN1029 being administered as a monotherapy.

GEN1029 targets DR5 (TRAILR2, CD262), which is expressed in a variety of human cancer tissues (Burvenich et al., 2013; Ichikawa et al., 2001; Koornstra et al., 2003; Wang et al., 2003). DR5 is a member of the Death Receptor subgroup of the Tumor Necrosis Factor Receptor Superfamily (TNFRSF) (MacFarlane et al., 1997; Pan et al., 1997; Schneider et al., 1997; Walczak et al., 1997). The mechanism of action of GEN1029 resembles DR5 activation by its natural ligand, trimeric TNF-related apoptosis-inducing (TRAIL, Apo-2L) (Sessler et al., 2013), resulting in DR5 hyperclustering and induction of caspase-dependent apoptosis.

The level of DR5 protein expression on the cell surface required for efficacy of GEN1029 is not known. Preclinical activity of GEN1029 was observed at low levels of DR5 expression, and there was no correlation between DR5 expression levels and GEN1029 preclinical efficacy. The threshold of DR5 expression for clinical efficacy may be well below the detection limit of immunohistochemical methods, and target expression could thus not be used as a basis for indication selection. Instead, indication selection for this FIH trial was based on a comprehensive preclinical efficacy data package. In an *in vitro* screening of a cell line panel consisting of 240 DR5-positive cell lines representing 16 different tumor types, GEN1029 induced strong inhibition of tumor cell viability in cell lines representing renal, colorectal, gastric, urothelial and pancreatic cancer as well as TNBC, NSCLC and brain tumors. These *in vitro* screening results were validated *in vivo* in a patient-derived xenograft (PDX) clinical trial, in which large sets of CRC and NSCLC PDX models were screened for sensitivity to GEN1029.

Based on these *in vitro* and *in vivo* efficacy screenings for GEN1029, CRC, NSCLC, TNBC, RCC, gastric, pancreas and urothelial cancer have been selected to be explored in this trial. For more comprehensive information regarding the cytotoxicity of GEN1029 *in vitro* and *in vivo*, please refer to the Investigator's Brochure.

### 2.1.1 Overview of Disease

#### *2.1.1.1 Colorectal Cancer*

In the US, 134,490 new cases of colorectal cancer and 49,190 deaths due to/related to CRC are estimated in 2016. Five-year relative survival rates in the US were 71% for patients with regional disease at diagnosis and only 13% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012).

The current management of metastatic colorectal cancer involves various drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, trifluridine-tipiracil,

pembrolizumab, and nivolumab. Recommended initial therapy options for advanced or metastatic disease depend on whether the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOx, and FOLFOXIRI. Addition of a biological agent (e.g., bevacizumab, cetuximab, panitumumab) is an option in combination with some of these regimens. Systemic therapy options for patients with progressive disease depend on the choice of initial therapy. The NCCN panel endorses the concept that treating patients in a clinical trial has priority over standard treatment regimens. In the currently established treatment algorithm clinical trials are at least to be considered in the fourth line setting. The approval of targeted agents, like Avastin® and Erbitux®, has improved outcomes for patients with metastatic colorectal cancer (mCRC). However, all targeted agents currently approved to treat mCRC patients either target the Vascular Endothelial Growth Factor (VEGF) pathway or the Epidermal Growth Factor Receptor (EGFR) pathway. This highlights the need for new agents with novel mechanisms of action. The medical need appears to be given especially for patients with RAS (KRAS, NRAS) or BRAF mutant disease, and those patients who have failed all available treatment options.

#### *2.1.1.2 Lung Cancer - NSCLC*

In the US, 224,390 new cases and 158,080 deaths from lung and bronchial cancer are estimated in 2016. At least 57% of patients had metastatic disease at initial diagnosis. Five-year relative survival rates in the US are 27% for patients with regional disease at diagnosis and only 4% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012). NSCLC represents approximately 80% of lung cancers and includes adenocarcinomas which account for approximately 50% of lung cancers, squamous cell carcinomas (SCC) which account for approximately 20% and large cell carcinomas which account for approximately 10% of lung cancers.

Several drugs are approved for treatment of NSCLC including alkylators, antimetabolites, tubulin inhibitors and monoclonal antibodies. Bevacizumab (anti-VEGF), ramucirumab (anti-VEGFR-2) and tyrosine kinase inhibitors are reserved for patients who are EGFR or Anaplastic lymphoma kinase (ALK) positive. Recently the immune checkpoint inhibitor nivolumab and pembrolizumab (a human and humanized IgG4 monoclonal antibodies, respectively) that target PD-1 have both gained approval as 2$^{nd}$ line therapy for SCCs and as subsequent therapy for patients with metastatic non-squamous NSCLC which has progressed on or after first-line chemotherapy or targeted agents. In patients with sensitizing EGFR mutations, erlotinib is recommended as 1$^{st}$ line treatment (gefitinib and afatinib are also indicated in this patient population); and for patients with an ALK mutation crizotinib is 1$^{st}$ line therapy. For other patients diagnosed with NSCLC stage III or IV, chemotherapy is 1$^{st}$ line treatment and tubulin inhibitors, paclitaxel, docetaxel, vinorelbine and nab-paclitaxel, in combination with platinum based chemotherapy is standard of care treatment. Despite multiple treatment options, patients with stage IV NSCLC ultimately have a poor prognosis - lung cancer is the leading cause of cancer death for both men and women. The treatment rate diminishes with each line of therapy, as patients succumb to their cancer or experience deterioration of their health that makes further treatment impossible. This poor prognosis highlights the need for more effective agents, across all lines of therapy and especially in later lines. Squamous histology patients are the least likely to receive multiple lines of treatment, while those with EGFR or ALK mutations are more likely to receive additional lines, reflecting differences in the availability of approved treatment options for each population.

#### *2.1.1.3 Breast Cancer - TNBC*

In the US, 249,260 new cases and 40,890 deaths from breast cancer are estimated in 2016. Five-year relative survival rates in the US are 85% for patients with regional disease at diagnosis and only 26% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012). Overall, about 12% of breast cancers are triple negative.

Metastatic breast cancer patients generally have a number of treatment options. Breast cancer is particularly sensitive to cytotoxic therapy, with several types of agents with different mode of actions (MOA), active for first-line therapy including anthracyclines and taxanes. Median survival with chemotherapy is approximately two and a half years. Long-term responses to 1st line therapy are rare; however, breast cancer is sensitive to later lines of therapy as well. Slightly fewer than three-quarters of patients receive 2nd line therapy, and approximately two-thirds of these 2nd line patients receive 3rd line therapy. Classes of agents such as fluoropyrimidines, antimetabolites, and vincaalkaloids are common agents for the chemotherapy backbone in later lines of therapy. Nearly two-thirds of patients overexpress one of the hormone receptors, estrogen (ER) or progesterone (PR), making them sensitive to endocrine therapy. With at least five endocrine agents available, combined with the recent successes of the mTOR inhibitor everolimus and the CDK4/6 inhibitor palbociclib in this setting, physicians are able to treat patients sequentially through multiple lines of therapy. The medical need for patients that overexpress HER2 is partially addressed by trastuzumab, lapatinib, pertuzumab, and T-DM1. HER2-positive patients represent approximately one-third of all breast cancers. With the recent introduction of novel HER2-targeted agents in the 1st line and relapsed setting, sequencing and combinations of agents in later lines of therapy appears to provide promising options.

A huge unmet medical need remains for women with metastatic TNBC, as this disease usually progresses rapidly following three to five lines of chemotherapy. To date, only one targeted drug, bevacizumab, has been registered in this setting, however bevacizumab has limited clinical value as no overall survival gain was demonstrated. Considerable interest has been generated by the encouraging results obtained with the immune-checkpoint inhibitors pembrolizumab and atezolizumab in heavily pre-treated women with advanced-stage TNBC. The overall response rate to these agents remains modest (~18%), but the median duration of response had not been reached at the time of publication, indicating sustained responses rarely observed in patients with heavily pre-treated TNBC (Piccart et al., 2016).

#### *2.1.1.4 Renal Cell Cancer*

In the US, 62,700 new cases and 14,240 deaths from renal cell cancer are estimated in 2016. Five-year relative survival rates in the US were 65% for patients with regional disease at diagnosis and only 13% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012). Approximately 90% of renal tumors are RCC, and approximately 80% of these are clear cell tumors.

For the treatment of RCC, multiple targeted agents (two mTOR inhibitors, i.e. everolimus and temsirolimus; six VEGF pathway inhibitors, i.e. bevacizumab, cabozantinib, axitinib, sorafenib, sunitinib, and pazopanib) and the immune checkpoint inhibitor nivolumab are available. There are numerous treatment possibilities through multiple lines of therapy. With so many options, prognosis is relatively good: in the 1st line setting, median survival of -2-3 years is achieved, and

most patients achieve a PFS of approximately a year. The relatively long survival obscures the fact that, even with best therapy, patients are not cured.

#### *2.1.1.5 Gastric Cancer*

In the US, 26,370 new cases of stomach cancer and 10,730 deaths are estimated in 2016. Approximately 50% of patients present with advanced disease at diagnosis and have a poor outcome. Five-year relative survival rates in the US are 30% for patients with regional disease at diagnosis and only 5% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012).

In HER2-negative patients cytotoxic regimens such as FOLFOX (folinic acid, 5-fluorouracil (5-FU), oxaliplatin) and EOX (epirubicin, oxaliplatin, capecitabine) are established treatments for 1st line. In HER2-positive patients, trastuzumab, has become the standard of care, either in combination with cisplatin plus 5-FU or with cisplatin plus capecitabine. Ramucirumab, as single agent or in combination with paclitaxel is an option for 2$^{nd}$ line therapy. However, with approximately a one-year survival reported in the 1$^{st}$ line setting for either HER2-negative or HER2-positive patients, there is a significant unmet need for more efficacious therapies for metastatic gastric cancer patients.

#### *2.1.1.6 Pancreas Cancer*

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States and expected to become the second by 2020. In the US, 53,070 new cases of pancreatic cancer and 41,780 deaths are estimated in 2016. Five-year relative survival rates in the US are 27% for patients with local disease at diagnosis and only 2% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012).

FOLFIRINOX and gemcitabine alone or in combination with albumin-bound paclitaxel, are the predominant systemic therapeutic regimens used as 1$^{st}$ line treatments in this setting, although other regimens containing agents such as irinotecan liposome injection (combined with 5-FU and leucovorin), bevacizumab, or erlotinib and FOLFOX may be utilized as 2$^{nd}$ and 3$^{rd}$ line treatments. The use of FOLFIRINOX in patients with good performance status has significantly increased in recent years. However, despite the increased number of treatments available in this setting, many patients continue to opt for no therapy at this stage. The low objective response rate and lack of survival benefit with current chemotherapy and combined modalities indicate that clinical trials are crucial options for newly diagnosed, late-stage patients.

#### *2.1.1.7 Urothelial Cancer*

In US, 76,900 new urinary bladder cancer cases and 16,390 deaths are estimated in 2016. Five-year relative survival rates in the US are 34% for patients with regional disease at diagnosis and only 5% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012).

Treatment for advanced bladder cancer has historically included gemcitabine- or taxane-based chemotherapy regimens besides DDMVAC and chemoradiotherapy. A clear unmet need is the paucity of approved targeted agents for the treatment of bladder cancer. That has started to change with the recent approval of atezolizumab as well as several other novel agents currently in pivotal

clinical development for advanced disease. Atezolizumab's accelerated approval came along with a Breakthrough Therapy Designation and priority review from the U.S. FDA, highlighting the need for new treatment options in bladder cancer.

### 2.1.2 Introduction to Investigational Treatment

GEN1029 is an equimolar mixture of two non-competing DR5-specific humanized IgG1κ antibodies, with an E430G HexaBody® mutation in their Fc domains. This is the first time that an antibody product exploiting Genmab's HexaBody technology will be tested in humans. HexaBody molecules are monomeric IgG1 antibodies that have an engineered Fc-region harboring a single mutation, such as E430G, that significantly enhances the natural process of forming ordered hexameric antibody structures through intermolecular Fc-Fc interactions upon cell surface antigen binding (de Jong et al., 2016; Diebolder et al., 2014). In the case of GEN1029, this results in DR5 hyperclustering and activation of the cell death inducing signaling pathway, leading to programmed cell death of the target cells.

The mechanism of GEN1029-mediated DR5 clustering through antibody hexamerization is different from conventional, bivalent DR5-specific IgG1 antibodies, such as conatumumab, tigatuzumab, drozitumab, lexatumumab, and LBY-135 that depend on additional FcγR-mediated crosslinking in order to induce DR5 hyperclustering and apoptosis. Despite promising preclinical activity and a generally good safety profile (for the majority of the compounds, the MTD was not reached – please also refer to the benefit-risk assessment in Section 2.3), these conventional IgG1 antibodies against DR5 failed to show convincing anti-tumor efficacy in clinical trials (Amarante-Mendes et al., 2015; Ashkenazi, 2015). The low efficacy of conventional anti-DR5 antibodies has been attributed to lack of proper FcγR-mediated crosslinking, for example due to competition with endogenous serum IgG and/or absence of FcγR-expressing cells in the tumor microenvironment (Gieffers et al., 2013).

Of note, TAS266 is a particular multivalent anti-DR5 antibody fragment-based compound that was tested in humans. TAS266 is a tetravalent Nanobody®, consisting of four humanized llama-derived VHH antibody fragments linked through 35-aa linkers (Huet et al., 2014). The TAS266 study was terminated after three out of four patients showed reversible liver toxicity at starting dose, which correlated with the presence of pre-existing anti-drug antibodies (ADA), suggesting that TAS266 toxicity was caused by an atypical antigenicity of the tetravalent Nanobody (Papadopoulos et al., 2015).

The unique concept and mechanism of action of GEN1029 supports the notion that GEN1029 is a promising therapeutic agent with potential anti-tumor effect in many different cancer types.

### 2.1.3 Summary of Nonclinical Studies

A comprehensive nonclinical data package is available supporting the mechanism of action (MoA) of GEN1029 to induce cell killing of DR5-positive cancer cells by DR5 hyperclustering and downstream caspase activation.

The individual antibody components of GEN1029, drug substances 1029-01 and 1029-05, bind different epitopes on DR5 but have comparable apparent binding affinities with EC50 values in the high picomolar/low nanomolar range. It was shown both *in vitro* and *in vivo* that GEN1029 induced more potent cytotoxicity compared to the single HexaBody molecules and to the mixture of wild type (WT) antibodies without the E430G mutation. These data demonstrated that both the mixture of the two different HexaBody molecules and the HexaBody format were required for the efficacy of GEN1029. Furthermore, it was demonstrated both *in vitro* and *in vivo* that the efficacy

of GEN1029 was independent of secondary FcγR-mediated crosslinking, which was in contrast to the conventional DR5-targeting antibody conatumumab. GEN1029 induced cytotoxicity *in vitro* in a range of cell lines derived from different solid cancers, with loss of cell viability starting at a median concentration (IC20) of 0.083 μg/mL (0.554 nM). *In vivo*, GEN1029 showed potent anti-tumor activity in a broad range of human cancer cell line-derived xenograft (CDX) models and consistently outperformed conatumumab in all responsive models. Maximal anti-tumor activity was observed at doses of 2 mg/kg or higher, and 0.5 mg/kg was the lowest dose at which anti-tumor activity was observed. Importantly, GEN1029 also showed strong anti-tumor activity in patient-derived xenograft (PDX) models, which are thought to represent the genetic and histological heterogeneity observed in human tumors.

The cytotoxic activity of GEN1029 was shown to be caspase-mediated. GEN1029 induced rapid and potent caspase-3/7 activation in DR5-positive cancer cells.

*In vitro* studies indicated that GEN1029 did not induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) on tumor cell lines, and did not induce fluid-phase complement activation *in vitro*.

[redacted]

[redacted]

For more comprehensive information regarding nonclinical studies for GEN1029, please refer to the current version of Investigator's Brochure.

### 2.1.4 Summary of Clinical Trials

This will be the first administration of GEN1029 in humans; therefore, no clinical experience is available.

## 2.2 Rationale

Death Receptor 5 (DR5) is a receptor for Tumor Necrosis Factor Related Apoptosis-Inducing Ligand (TRAIL), which upon binding to the ligand, initiates an 'outside-in' signaling pathway leading to apoptotic cell death of TRAIL-sensitive cancer cells. While previously tested human DR5 monoclonal antibodies (mAbs) showed compelling pre-clinical anti-tumor activity, human DR5 mAbs did not perform well in clinical trials.

Receptor clustering and activation of apoptosis by human DR5 mAbs appeared not to be potent enough in patients, possibly due to insufficient crosslinking of DR5 via FcγR expressing immune cells in the tumor micro-environment. FcγR-mediated crosslinking is considered to be a key factor for the anti-tumor activity of human DR5 mAbs. Therefore, GEN1029 targeting of two distinct epitopes on DR5 with a mixture of two DR5-specific HexaBody molecules that organize into hexameric antibody structures upon surface target binding to increase FcγR-independent clustering is a rational novel approach to overcome this issue for the therapy of cancer patients.

Based on promising pre-clinical results this trial is planned to explore the safety, PK and biomarker profile as well as the anti-tumor activity of GEN1029 in patients with advanced and/or metastatic CRC, NSCLC, TNBC, RCC, gastric, pancreas or urothelial cancer who have failed available standard therapy or who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1029 may be beneficial.

## 2.3 Benefit-Risk Assessment

Several human DR5 mAbs have been clinically tested but their anti-tumor effect has been rather limited presumably as a consequence of insufficient FcγR-immune cell-mediated crosslinking of DR5 and a less potent apoptosis triggering signal (Micheau et al., 2013; Forero et al., 2017; Gieffers et al., 2013). GEN1029 targets two distinct epitopes on DR5 and enhances hexamer formation/receptor clustering in an FcγR-independent manner and is therefore a rational novel approach to overcome this issue.

Previous clinically tested human DR5 mAbs have as described above generally been well tolerated and most adverse events (AEs) have been mild to moderate (CTCAE grade 1-2). The most frequently reported AEs across human DR5 mAb mono-therapy trials (Herbst et al., 2010; Doi et al., 2011; Camidge et al., 2010; Forero-Torres et al., 2010; Plummer et al., 2007; Wakelee et al., 2010; Forero et al., 2017) conducted in adult patients with advanced cancer disease are listed below (order reflecting reported frequency (x out of 7 trials)), independent of CTCAE grading:

- Fatigue (among the most frequent reported AEs in 7/7 clinical trials)
- Nausea (6/7)
- Vomiting (6/7)
- Pyrexia (5/7)
- Anorexia (4/7)
- Anemia (3/7)
- Chills (3/7)
- Constipation (3/7)
- Cough (3/7)
- Diarrhea (3/7)
- Dyspnea (3/7)
- Headache (3/7)

The most frequent reported clinical significant and possibly drug related adverse event ≥ grade 3 has been elevation of amino transferase liver enzymes (Camidge et al., 2010; Plummer et al., 2007). A mitigation plan for handling AEs of elevated liver parameters has been prepared for this trial in order to closely monitor, dose-delay, dose-reduce or withdraw patients with liver enzyme elevations (please see Section 7.2.2.1).

There are so far no specific experimental observations or knowledge about the reproductive or fetal developmental toxicity of GEN1029. However, DR5 mRNA has been described to be expressed in the reproductive system and reproductive effects of GEN1029 in humans can therefore not be ruled out. More detailed information about DR5 receptor expression, nonclinical and clinical results as well as potential safety aspects of GEN1029 therapy can be found in the Investigator's Brochure.

Based on nonclinical and clinical data available to date, and published data from other human DR5 mAbs, the conduct of the trial GCT1029-01 is regarded as justifiable. Furthermore, the patient population eligible for the current trial is patients with selected advanced and/or metastatic cancer, who have failed available standard therapy or who are not candidates for standard therapy, and for whom in the opinion of the investigator, experimental therapy with GEN1029 may be beneficial. All patients enrolled in this trial will be controlled frequently by qualified health care professional(s) who will provide care and closely monitor and evaluate the patient's response to the trial drug, in terms of its safety and efficacy.

As of the 20-Aug-2019, 27 patients have been exposed to GEN1029 at dose levels ranging from 0.3 to 3 mg/kg: 24 patients on the Biweekly Regimen (Q2W) and 3 patients on the Intensified Regimen (8×Q1W/Q2W). Based on this experience, two AEs have been identified as risks and AEs of special interest (AESIs). These are elevated transaminase levels and diarrhea (Section 10.3). As a result, a mitigation plan for handling AEs of diarrhea has been prepared for this trial to guide diagnostic steps and treatment.

Of note, all 3 patients exposed in the Intensified Regimen experienced DLTs due to transaminase elevations, [redacted] Consequently, the Intensified Regimen is permanently discontinued.

More detailed information about the known and expected benefits and risks including reasonably expected AEs of GEN1029 can be found in the Investigator's Brochure.

# 3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 3-1.

## Table 3-1 Objectives and Endpoints

### Dose Escalation Part

| Objectives | Endpoints |
|---|---|
| Primary | |
| • Determine the MTD and/or the recommended Phase 2 dose (RP2D)<br>• Establish the safety profile of GEN1029 | • Dose limiting Toxicities (DLTs)<br>• Adverse events (AEs) and safety laboratory parameters (hematology and biochemistry) |
| Secondary | |
| • Establish the PK profile and evaluate immunogenicity of GEN1029 after single and multiple infusions | • PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve [$AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$], AUC0_14d, CL. maximum concentration [$C_{max}$], time of $C_{max}$ [$T_{max}$], pre-dose values, and half-life of GEN1029<br>• Immunogenicity of GEN1029 |
| • Evaluate the anti-tumor activity of GEN1029 | • Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations)<br>• Objective Response, Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DoR), and Time to Response (TTR) |
| Exploratory | |
| • To assess biomarkers predictive of response or resistance to GEN1029<br>• To assess potential pharmacodynamic biomarkers of GEN1029<br>• To assess the metabolic response in the tumors<br>• [redacted] | • DR5 expression (protein, [redacted]) in tumor biopsies<br>• Circulating protein profiles<br>• Immune cells levels<br>• Biomarker profile<br>• Standardized uptake volume corrected for body lean mass (SUL)<br>• [redacted] |

## Expansion Part

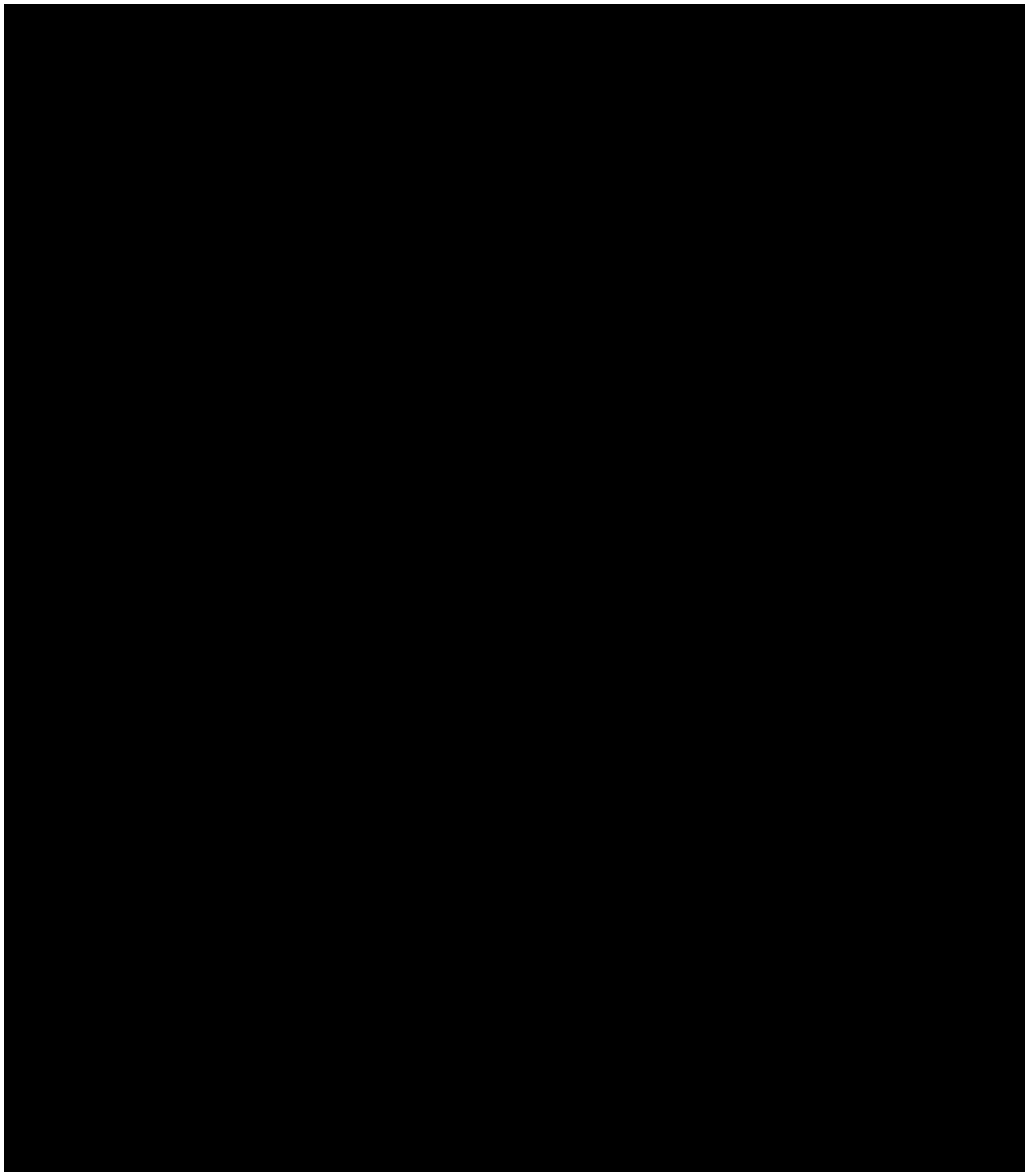
| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the Objective Response Rate (ORR) by indication | • ORR |
| Secondary | |
| Evaluate the anti-tumor activity of GEN1029 | • Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations)<br>• Objective Response, Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DoR), and Time to Response (TTR) |
| • To further describe the safety profile of GEN1029 | • Adverse events (AEs) and safety laboratory parameters (hematology and biochemistry) |
| • Evaluate the pharmacokinetic (PK) profile as feasible, evaluate immunogenicity of GEN1029 after single and multiple infusions | • PK parameters<br>• Immunogenicity of GEN1029 |
| Exploratory | |
| • To assess biomarkers predictive of response or resistance to GEN1029 | • DR5 expression (protein, [redacted]) in tumor biopsies |
| • To assess potential pharmacodynamic biomarkers of GEN1029 | • Circulating protein profiles<br>• Immune cells levels<br>• Biomarker profile |
| • To assess the metabolic response in the tumors | • Standardized uptake volume corrected for body lean mass (SUL) |
| • [redacted] | • [redacted] |

# 4 TRIAL DESIGN

## 4.1 Description of Trial Design

This is an open-label, multi-center phase I/IIa safety trial of GEN1029 in a mixed population of patients with solid tumor types. The trial consists of two parts; a dose escalation part (phase I, FIH) and an expansion part (phase IIa) as depicted in Figure 4-1.

**Figure 4-1** [redacted]



In the dose escalation part, up to 2 dose regimens may be evaluated; these are described in Section 4.2. Those dose regimens, that are considered to be safe by the Data Monitoring Committee (DMC) and the sponsor safety committee, and for which a recommended phase 2 dose (RP2D) is established, may be further explored in the expansion part. Each expansion cohort will only include patients with one selected indication who are to be treated with one selected dose regimen. More than one dose regimen may be evaluated per indication, but in different cohorts.

Patients in both parts of the trial will receive treatment until disease progression. Thus, the treatment period will last until unacceptable toxicity or disease progression is observed. Efficacy will be assessed every six weeks primarily based on CT-scans. The RECIST 1.1 criteria will be used for response evaluation (Eisenhauer et al., 2009).

## 4.2 Dose regimens

This trial will evaluate a Biweekly Regimen (Q2W) and a Priming Regimen (Priming/Q2W), as described in Table 4-1. For both regimens, one cycle is 14 days.

**Table 4-1: Dosing Frequencies in the Two Dose Regimens**

| Biweekly Regimen (Q2W) | Priming Regimen (Priming/Q2W) |
|---|---|
| Cycle 1–End of treatment Q2W | Cycle 1 – Priming dose on Day 1 |
| | Cycle 2– End of treatment Q2W |

### 4.2.1 Biweekly Regimen (Q2W)

The trial is initiated with the Biweekly Regimen. In this dose regimen, patients are treated on day 1 of each cycle. The escalation of this regimen is started at 0.3 mg/kg and may thereafter evaluate GEN1029 at the following dose levels:

- 0.3, [redacted] 1.0, 2.0, 3.0, [redacted] mg/kg

Dose escalations (and de-escalations) in the escalation part will follow the modified Bayesian Optimal Interval (mBOIN) design; see Section 4.3.

### 4.2.2 Priming Dose Regimen

Dose escalation based on a priming dose may be considered, applying dose levels that have been declared safe by the DMC and endorsed by the sponsor safety committee. The priming dose will be administered on Day 1 of the first cycle, and thereafter dosed with the maximum starting dose once every 14 days.

Scenarios for different priming and starting dose levels are covered in Table 4-2. The priming dose and the starting dose in Cycle 2 will be determined based on the totality of the available data and selected as recommended by the DMC and confirmed by the sponsor safety committee.

**Table 4-2:** [redacted]

Dose escalation based on priming doses may potentially evaluate GEN1029 at the following dose levels in the second cycle (dependent on data collected during the trial):

- 0.3, [redacted], 1.0, 2.0, 3.0, [redacted] mg/kg

Dose escalation (and de-escalations) in the escalation part will follow the mBOIN design; see Section 4.3.

### 4.3 Dose Escalation Part

In the dose-escalation part, there will be a minimum of 2 nights between the first and second patient in each dose cohort to account for any safety signals at each new dose level. This might be modified according to recommendations from the DMC and as endorsed by the sponsor safety committee. In addition, the first cohort of the Biweekly Regimen will be a single patient cohort. Furthermore, no other patients within a dose cohort will receive their first treatment simultaneously, i.e. on the same day, during the dose escalation part of the trial, unless apparently efficacious dose levels which are declared safe by the DMC are further investigated. During treatment, safety assessments will initially be performed on a weekly basis. For the assessments of each cohort, the DLTs will be collected for the first two cycles i.e. DLT period of 28 days. For the priming regimen, the DLT period must contain 14 days evaluation of one full dose administered after the priming dose have been administered. A patient is defined as "evaluable" if a DLT is observed prior to completing the DLT period, or if the DLT period is completed without any DLTs.

The dose escalation part will be performed as a mBOIN design (Yuan et al., 2016). This is in many ways similar to a traditional 3+3 design (even more similar to its 3+3+3 variant) except that the mBOIN design may allow re-escalation to an already investigated dose level. Re-escalation is allowed when the previous dose level is considered safe (based on data from additional patients). Re-escalation is not allowed to dose levels that have been terminated.

Specifically for this trial a target toxicity level of 30% has been chosen leading to escalation and de-escalation borders of lambda1=0.24 and lambda2=0.36.

According to the mBOIN design each time a cohort of patients has been completed, it is evaluated whether the next cohort should stay on the same dose, escalate to the dose level above or de-escalate to the dose level below. This evaluation is based on the frequency of DLTs on the current dose level in the following way:

- DLT frequency at current dose level <= 0.24: Escalate
- DLT frequency at current dose level >0.24 and <0.36: Stay at same dose level

- DLT frequency at current dose level >= 0.36: De-escalate

After completion of the DLT period for each cohort, based on the safety data and the recommendation from the mBOIN design algorithm (Table 4-4), the DMC will recommend the dose-level for the next cohort of patients, see Table 4-3. As a precaution, the DMC can also recommend lower dose levels than the mBOIN design algorithm recommends and even below 0.3 mg/kg; i.e. 0.1 mg/kg.

**Table 4-3 Number of DLTs Leading to Dose Escalation, De-escalation or Remaining at the Same Dose Level**

| Number of patients in a cohort | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|
| Escalate | 0 | 0 | <=1 | <=1 | <=1 | <=1 | <=2 |
| Stay at same level | 1 | 1 | - | 2 | 2 | 2 | 3 |
| De-escalate | 2 | 2 | 2 | 3 | 3 | 3 | 4 |
| Terminate a dose level | 3 | >=3 | >=3 | >=4 | >=4 | >=4 | >=5 |

***First-in-Human Cohort:***

In order to limit patients being treated at a dose of possibly limited efficacy (i.e. [redacted]), the Biweekly Regimen (the initial regimen to be explored) will begin by evaluating GEN1029 with the initial cohort consisting of one evaluable patient (i.e. at 0.3 mg/kg). If this patient has experienced a DLT or ≥ grade 3 toxicity (at least possibly drug-related), the cohort size will be increased to at least 3 evaluable patients.

***Dose Level Termination:***

A potential drawback of the basic BOIN design is that, theoretically, a very toxic dose level could be investigated in multiple cohorts, if the dose level just below it is not toxic. To avoid this problem, a dose level termination criterion is implemented (see Table 4-4).

Other mBOIN specific parameters are detailed in Table 4-4.

**Table 4-4: Design Parameters of the mBOIN Design for the Two Dose Regimens**

| | Biweekly Regimen (Q2W) | Priming Regimen (Priming/Q2W) |
|---|---|---|
| Target toxicity rate | 30% | |
| [lambda1; lambda2] | [0.24; 0.36] | |
| DLT period | Day 1-28 | |
| Stopping criteria | If the BOIN algorithm recommends that the next cohort should be run on a dose level that has already investigated 9 patients (to ensure that the trial will not keep enrolling patients on a dose level already adequately investigated) | |
| Dose level termination due to toxicity | A certain dose level can no longer be investigated if an additional DLT-free cohort would lead to de-escalation | |
| Default cohort size | 3 patients | |
| Initial cohort size | 1 patient | 3 patients |
| Possibly modified cohort size | In case a cohort had less than 3 patients evaluable the next cohort on the same dose level may be enlarged to bring the number of patients on the dose level up to a multiple of 3 | |
| Algorithm may be used if | There are at least 3 evaluable patients on a dose level (except the initial dose level) | There are at least 3 evaluable patients on a dose level |
| Replacement of in-evaluable patients | If needed (to bring number of patients on the dose level up to 3) in-evaluable patients will be replaced. | |
| Over-recruitment on safe doses | Apparently efficacious dose levels which are declared safe by the DMC may be further investigated, augmenting the mBOIN design, by adding up to a total of max. 9 patients to such dose levels | |
| Maximum number of patients to add on safe doses | 18 | |
| DLT consideration in over-recruited patients | Do not contribute to mBOIN algorithm, but will be reported to DMC. (If the mBOIN algorithm later stipulates de-escalation to an over-recruited dose level, all patients on that dose will be counted as part of the mBOIN algorithm.) | |

***Determination of MTD and RP2D:***

After the mBOIN algorithm has completed (for a given regimen), the DMC and the sponsor safety committee will determine the MTD and the RP2D which may be the same as the algorithm recommends for the next cohort or it may be a lower dose. In any case the RP2D will be a dose with a lower observed DLT rate than the target toxicity level of 30%.

If there is evidence that a dose level lower than the MTD (which might not have been reached at this stage) has adequate efficacy (whether determined by CT scan data or by pharmacodynamic endpoints or predicted efficacious dose) the DMC and sponsor safety committee may decide that the RP2D has been determined and may decide to stop the dose escalation.

## 4.4 Expansion Part

The aim of the expansion part is to provide further data on the safety, tolerability, PK and anti-tumor activity of the selected dose regimen(s).

The expansion cohorts may run in parallel. Each cohort will only contain one selected indication on a specific dose regimen. More than one dose regimen per indication may potentially be evaluated, depending on the outcome from the escalation part. Within an indication these would all constitute different expansion cohorts, and patients would in this case be randomized between the available dose regimens (see Section 6.1.2 on treatment assignment for more information). A total of up to seven expansion cohorts will be opened.

In each expansion cohort, an analysis after at least 10 evaluable patients will be performed. If there is evidence of anti-tumor activity such as tumor shrinkage or prolonged disease stabilization, and without safety concerns, up to 60 patients will be allocated to an expansion cohort in a stage wise fashion, primarily testing pre-specified futility criteria (see Section 11.7 for further details), but also taking the totality of the data into account. The data will be evaluated by the sponsor safety committee which decides on further recruitment into the cohort.

A DMC review of safety data will be performed when 12 patients have been recruited and have been followed for at least two cycles (regardless of indication and dose regimen). DMC safety review will be performed after 36 patients have been recruited and followed for at least two cycles (regardless of indication). Thereafter, DMC safety review will be performed at least quarterly. The DMC and the sponsor safety committee will evaluate the safety profile with particular emphasis on any safety signals.

Patients in the expansion part will be treated on the dose regimen(s) from the dose escalation part recommended by the DMC and confirmed by the sponsor safety committee based on a positive benefit-risk assessment. If deemed appropriate, and based on data available, the expansion part may be initiated before the MTD has been reached. Furthermore, different doses and regimens might be explored in the expansion cohorts.

## 4.5 Planned Number of Patients

The dose escalation part will enroll up to approximately 100 patients shared between the Biweekly and Priming Regimens. Three patients were exposed in an Intensified Regimen (8xQ1W/Q2W) all of whom experienced DLTs and, consequently, this dosing regimen was permanently discontinued.

In the expansion part, the planned number of patients depends on how many indications and regimens that will be evaluated. Each opened cohort (which is indication and regimen specific) will enroll between 10 and 60 patients. Opening all seven cohorts would allocate between 70 (minimum 10 in each) and 420 (maximum 60 in each) patients in the expansion part.

## 4.6 Trial Design Rationale

Part I of this trial is a FIH, open-label, dose-escalation, safety trial studying the DR5-specific agonistic hexamer-forming antibody GEN1029 in patients with different types of malignant solid tumors in order to determine the MTD and/or RP2D the safety profile of GEN1029.

Escalation and de-escalation in the dose escalation part will be guided by a mBOIN design, which is very similar to the 3+3 design but with the possibility to investigate a dose level again that would have been closed in a 3+3 design after de-escalation to a lower dose level and observing that level to not be toxic. This greatly enhances the probability of identifying the correct MTD level.

Part II of this trial is the expansion part including up to seven indications for further investigation. The aim of the expansion part is to provide further data on the safety, tolerability, pharmacokinetic and anti-tumor activity of the selected dose.

## 4.7 First-in-Human Clinical Trial Starting Dose, dose increments and highest pre-planned dose level

A First-in-Human clinical trial starting dose of **0.3 mg/kg** is proposed for GEN1029. This dose level is considered to be safe and in the lower end of the potential therapeutically active dose range, based on considerations from the following preclinical pharmacology, pharmacokinetic and toxicology studies:

- [redacted]
  [redacted]
  [redacted]:
  [redacted]

[redacted]

[redacted]

[redacted]

## 4.8 End of Trial and End of Treatment Definitions

### 4.8.1 End of Trial

The trial is considered completed with the last safety follow-up visit (70 days after last dose) for the last patient participating in the trial. The final data from the trial site will be sent to the sponsor (or designee) after completion of the final patient visit within the time frame specified in the clinical trial agreement. The trial will run for a maximum of three years after the last patient first treatment.

### 4.8.2 End of Treatment

For each patient the treatment period will be until progression (cycles of 14 days) unless the patient fulfills one of the discontinuation of treatment criteria (see Section 8.1).

### 4.8.3 Trial Termination

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or ICH-GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further trial drug development

# 5 TRIAL POPULATION(S)

## 5.1 Inclusion Criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Patient must be ≥ 18 years of age, at the time of signing the informed consent.
2. **For the dose escalation part:**

   Patients with advanced and/or metastatic CRC, NSCLC, TNBC, RCC, gastric (incl. esophagogastric junction), pancreas or urothelial cancer who have no available standard therapy likely to confer clinical benefit or who are not candidates for such available therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1029 may be beneficial.

   **For the expansion part:**

   Patients with advanced and/or metastatic cancer in up to seven of the following indications: CRC, NSCLC, TNBC, RCC, gastric, pancreas or urothelial cancer who have failed the following anticancer therapy for metastatic disease (if patients were eligible for the respective treatments):

   - CRC: CRC patients after failure of at least 2 prior systemic regimens but not more than 4 for advanced and/or metastatic disease (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to oxaliplatin- and irinotecan-containing regimens as well as EGRF and VEGF-A targeting antibodies, immune checkpoint inhibitors (PD-1 or PD-L1 inhibitor), capecitabine, ziv-aflibercept, ramucirumab, regorafenib, vemurafenib, and trifluridine-tipiracil.
   - NSCLC: NSCLC patients after failure of at least 1 prior systemic regimens but not more than 3 for advanced and/or metastatic disease (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to one platinum-containing regimen (or alternative chemotherapy due to platinum ineligibility, e.g. a gemcitabine-containing regimen) and failure of an immune checkpoint inhibitor (patients must have been treated with an approved PD-1 or PD-L1 inhibitor according to the established local label and access). Patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) / c-ros oncogene 1 receptor tyrosine kinase (ROS1) rearrangement, or B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) mutations should have been treated with appropriate targeted therapy before trial entry.
   - TNBC: TNBC patients after failure of at least 1 prior systemic regimen for advanced and/or metastatic disease but not more than 4 (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to anthracycline-, antimetabolite- or microtubule inhibitor-containing regimens, or PARP inhibitors
   - RCC: RCC patients after failure of at least 2 prior systemic regimens for advanced and/or metastatic disease but not more than 3 (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to anti-angiogenic agents, mTOR inhibitors and immune checkpoint inhibitors (patients must

have been treated with an PD-1 or PD-L1 inhibitor according to the established local label and access; unless contraindicated).

- Gastric cancer (incl. esophagogastric junction): gastric cancer patients after failure of at least 2 prior systemic regimens for advanced and/or metastatic disease but not more than 3 (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to one platinum-containing regimen (or alternative chemotherapy due to platinum ineligibility) and failure of a taxane-containing regimen, ramucirumab or an irinotecan-containing regimen. Patients with PD-L1 positive tumors or HER2 overexpression should have been treated with appropriate targeted therapy before trial entry according to the established local label and access.
- Pancreas cancer: pancreas cancer patients after failure of at least 1 prior systemic regimen for advanced and/or metastatic disease but not more than 2 (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to taxane-, antimetabolite- or platinum-containing regimens, or immune check-point inhibitors according to the established local label and access.
- Urothelial cancer: patients after failure of at least 1 prior systemic regimen for advanced and/or metastatic disease but not more than 3 (adjuvant and maintenance treatment is considered being part of one treatment regimen) including but not limited to one platinum-containing regimen (or alternative chemotherapy due to platinum ineligibility, e.g. a gemcitabine-containing regimen) and failure of an immune checkpoint inhibitor (patients must have been treated with an approved PD-1 or PD-L1 inhibitor according to the established local label and access).

3. Patients must have measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
   - A minimum of one lesion ≥ 10 mm (or twice the slice thickness if slices are not 5 mm thick) in the longest diameter (LD) from a non-irradiated area.
     1. Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area.
     2. If target lesion(s) are located within previously irradiated area patients can be enrolled if:
        i. target lesions have not been irradiated within the last 3 months.
        ii. there has been demonstrated progression in the "in field" target lesion and after sponsor acceptance.
4. In the dose escalation part all patients must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded (FFPE) blocks/slides) from either archival tissue (preferably derived from advanced disease stage) or a fresh biopsy collected before Cycle 1, Day 1.

   In the expansion part a mandatory fresh biopsy (FFPE tissue blocks/slides) at screening (aspirates are not acceptable) is to be provided for all patients which is taken after failure/stop of last prior treatment, unless not clinically feasible as documented by investigator. In case it is not feasible to meet the required criteria for a fresh tumor biopsy, the sponsor medical officer's approval of enrollment is needed. Furthermore, the latest available archival tumor tissue sample has to be collected if available.
5. Have an acceptable hematological status defined as:

- Hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL).
- Absolute neutrophil count (ANC) ≥ 1500/µL ($1.5\times10^9$/L).
- Platelet count ≥ $75\times10^9$/L.

6. Have an acceptable renal function defined as:
   - Glomerular filtration rate (GFR) ≥50 mL/min/1.73 m² – e.g., according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation:

     $GFR = 186 \times (SCr^{-1.154}) \times (age^{-0.203})$

     (where SCr, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the patient is female; multiply it by 1.212, if the patient is African-American (Levey et al., 1999).
   - Not being on dialysis.
7. Have an acceptable liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the ULN (independent of liver involvement).
   - Bilirubin ≤ 1.5 × ULN (except in patients diagnosed with Gilbert's syndrome, who can have total bilirubin < 3.0 mg/dL), direct bilirubin ≤ 2 × ULN.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Body weight ≥ 40kg.
10. Patients, both females and males, of childbearing or reproductive potential must agree to use adequate contraception as described below from the screening visit until six months after the last infusion of IMP.
    - Female trial participants of childbearing or reproductive potential must agree to use one of the highly effective methods of contraception described in Table 5-1 from the screening visit until six months after the last infusion of IMP.

**Table 5-1 Highly Effective Contraceptive Methods (from Appendix 1)**

| **Highly Effective Contraceptive Methods**<br>*Failure rate of <1% per year when used consistently and correctly.* |
|---|
| Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable<br>• Implantable |
| Intrauterine device (IUD) |
| Intrauterine hormone-releasing system (IUS) |
| Bilateral tubal occlusion |

| |
|---|
| **Vasectomized partner**<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female trial participant and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| **Sexual abstinence**<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* |

- Male trial participants with female partners of childbearing or reproductive potential must agree to use a condom during sexual intercourse from the time of the screening visit until six months after the last infusion of IMP.

11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Patient must have life expectancy of greater than three months.
12. A female patient of childbearing potential (see Appendix 1 for definition) must have a negative serum (beta-hCG) pregnancy test at screening.
13. A female patient must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction while included in the trial and for six months after the last infusion of IMP. Male patients must agree not to donate sperm while included in the trial and for six months after the last infusion of IMP.
14. Patient must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
15. Each patient must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the trial and are willing to participate in the trial.

## 5.2 Exclusion Criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Acute deep vein thrombosis or clinically relevant pulmonary embolism, not stable for at least 8 weeks prior to first IMP administration.
2. Have clinically significant cardiac disease, including:
   - Onset of unstable angina up to six months prior to signing the ICF.
   - Acute myocardial infarction up to six months prior to signing the ICF.
   - Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/ or a known decreased cardiac ejection fraction of < 45%.
   - A baseline QT interval as corrected by Fridericia's formula (QTcF) > 480 msec or a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form).
3. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.

4. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (younger than 6 months) or progressive brain metastases or stroke.
    - Transient ischemic attack > 1 month prior to screening is allowed.
    - Patients with a history of symptomatic metastatic brain or meningeal tumors may be included, if the end of definitive therapy is > 6 months before the first dose of trial drug and the patient is having clinically or radiologically no evidence of tumor growth. Patients with brain metastases must not be undergoing acute corticosteroid therapy or steroid taper. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 days prior to screening.
    - Patients with central nervous system symptoms should undergo a Computed Tomography (CT) scan or Magnetic Resonance Imaging of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, patients with spinal cord compression should be excluded.
5. History of chronic liver disease or evidence of hepatic cirrhosis.
6. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of IMP.
7. Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support 4 weeks prior to first IMP administration or being chronically transfusion dependent.
8. Have received a cumulative dose of corticosteroid ≥ 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks before the first IMP administration.
9. History of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial.
10. Radiotherapy within 14 days prior to first IMP administration. (Palliative radiotherapy will be allowed as described in Section 6.4.2).
11. Any anticancer therapy (including: small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug) given within five half-lives before first infusion.
    - For anti-cancer therapies with half-lives greater than 5.5 days, a washout period of at least four weeks is acceptable (six weeks for nitrosureas or mitomycin).

    Accepted exceptions are bisphosphonates (e.g. pamidronate, zoledronic acid, etc.) and denosumab.
    - Toxic effects of prior anti-cancer therapy considered as chronic, such as chemotherapy-induced fatigue, alopecia, or anorexia of ≤ grade 2, where anymore resolution is not expected, does not prevent the patient from participation in the trial.
12. Any prior therapy with a compound targeting DR4 or DR5.
13. Known past or current malignancy other than inclusion diagnosis, except for:
    - Cervical carcinoma of Stage 1B or less.
    - Non-invasive basal cell or squamous cell skin carcinoma.
    - Non-invasive, superficial bladder cancer.

- Prostate cancer with a current PSA level < 0.1 ng/mL.
- Any curable cancer with a complete response (CR) of > 2 years duration.

14. Known human immunodeficiency virus seropositivity.
15. Known history / positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    - Positive test for antibodies to hepatitis B core antigens (anti-HBc)

      **and**

    - Negative test for antibodies to hepatitis B surface antigens (anti-HBs).
16. Known history / positive serology for hepatitis C (unless due to immunoglobulin therapy), which has not been cured.
17. Ongoing significant, uncontrolled medical condition including:
    - Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
18. Clinically significant active viral, bacterial or fungal infection requiring:
    - Intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose.
19. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result.

### 5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once only. The rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

If rescreening is approved, complete new screening must be performed and all eligibility criteria must be re-assessed. If more than 4 weeks have passed since the initial screening failed the patient must be re-consented. Also a new ICF should be signed if updates have been made since signing of the first ICF.

# 6 TREATMENT

## 6.1 Treatment Assignment

### 6.1.1 Patient Numbering

After obtaining informed consent, patients will be given a screening number before they undergo any screening procedure. A screening ID consists of the letter "S" followed by a three-digit sequence number that uniquely identifies a patient at a screening visit e.g. S004.

When screening has been completed and the patient satisfies the eligibility criteria, the patient is given a patient ID. A patient ID consists of a four-digit number that uniquely identifies a patient, e.g., patient 0012.

### 6.1.2 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Allocation of patients will be controlled by the CRO.

***Escalation Part:***
When a potential patient in the dose escalation is identified at a site, the site personnel must contact the CRO for allocation in accordance to Section 4.3. If there is an opening in the currently enrolling cohort, the site will be given approval to start the screening process. If there is no opening in the currently enrolling cohort, the CRO will place the patient on a list of potential patients. If another patient fails the screening process, the CRO will alert the site that has the next patient on the waiting list. If the patient is still eligible, the site will be given approval to start the screening process.

***Expansion Part:***
In the expansion part, treatment assignment will be done through an electronic system, for example, the interactive response technology (IRT) system. The CRO will oversee the recruitment and notify the sites when cohorts are complete. If only one dose regimen is opened within an indication, eligible patients will be allocated to this. In the situation where more than one dose regimen is available to eligible patients within an indication, patients will be allocated as follows to available regimens:

- If two dose regimens are available within the indication, patients will be randomized in a 1:1 fashion, stratified by ECOG score at screening
- Should one dose regimen within an indication be stopped during the expansion phase, the allocation mechanism will switch to allocation into the one regimen left.

## 6.2 Dosage and Administration

GEN1029 should be diluted into a 0.9% NaCl (saline) 100 mL (or 250 mL dependent on total dose) infusion bag according to the dose assigned to the patient and administered within 24 hours of preparation.

GEN1029 should be administered intravenously over a minimum of 60 minutes and the infusion must be completed within 90 minutes using a 0.2 μm in-line filter. The entire infusion volume from the prepared infusion bag needs to be administered, no dead volume is provided. The infusion is complete when the infusion line has been flushed with minimum 15 mL saline.

The dose will be calculated based on the patient's weight rounded to the nearest kilogram, i.e., assigned cohort dose in mg/kg x body weight in kg.

For patients whose body mass index (BMI) is greater than 30 kg/m$^2$, the investigator should use a weight that, based on the patient's height, corresponds to a maximum BMI of 30.

Please refer to the IMP manual for dose calculation and additional information regarding IMP administration.

## 6.3 Compliance

Trial drug will be administered by site personnel to assure compliance with trial requirements. The date and time of each trial drug administration will be recorded in the eCRF.

## 6.4 Concomitant Medications and Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than GEN1029 the patient is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including route, dose and frequency

The patient must be told to notify the investigational site about any new medications he or she takes after the start of the trial drug.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.4.1 Prophylactic Concomitant Medication

Fourteen out of 27 patients (11 out of 24 patients in the Biweekly Regimen and 3 out of 3 patients in the Intensified Regimen) have experienced transaminase elevations ≥ grade 2. These elevations seem to be primarily a first-dose effect, and independent of dose level or presence of liver metastasis. Preliminary data from the ongoing dose escalation suggests that pre-medication with steroids may prevent elevations of transaminases.

Therefore, mandatory pre-medication with Dexamethasone must be administered as follows:

- 4 mg/p.o. one day before dosing at Cycles 1 and 2.
- Dose escalation part: 10 mg. i.v. at Day 1 before dosing and at Day 2 in Cycles 1 and 2. Expansion part: 10 mg. i.v. at Day 1 before dosing and orally at Day 2 in Cycles 1 and 2.

If a drug-related ≥ grade 2 elevation of ALT and/or AST is observed during the second cycle or thereafter, dexamethasone pre-medication should be continued/re-introduced. In this case, Dexamethasone can be given orally on the day after the dosing day.

Furthermore, the below guidance should be followed throughout the trial:

- Paracetamol (Acetaminophen) and antihistamines (Diphenhydramine, 50 mg p.o. preferred, or Dexchlorpheniramine (5 mg i.v.), can be part of the pre-medication regimen as judged necessary by the investigator.

All pre-medication must be reported on the concomitant medication page in the eCRF.

### 6.4.2 Permitted Concomitant Medications and Therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.4.3). Administration of concomitant medications must be reported in the appropriate section of the eCRF.

- Palliative radiotherapy during the trial will be allowed for local pain control provided that:

  (i) in the opinion of the investigator, the patient does not have progressive disease (PD) AND (ii) no more than 10% of the patient's bone marrow is irradiated AND (iii) the radiation field does not encompass a target lesion.

- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. Patients are permitted to be taking chronic erythropoietin provided that no dose adjustment was made within two months before the first dose of IMP.
- Blood-cell transfusion is allowed if clinically indicated.
- Chronic steroid therapy is acceptable provided that the dose was stable for at least 2 weeks before the first administration of GEN1029 and remains stable thereafter. The cumulative dose of corticosteroid within two weeks before the first infusion should not have been ≥ 150 mg prednisone (or equivalent doses of corticosteroids). Short-term steroid treatment is permitted at the discretion of the investigator.
- Tumor lysis syndrome (TLS): For patients at risk of developing a TLS, prophylaxis according to standard local practice with (aggressive) hydration, allopurinol, and/or rasburicase is recommended.
- Bisphosphonates (e.g. pamidronate, zoledronic acid, etc.) and denosumab.
- Multivitamins, vitamin D and calcium.

### 6.4.3 Prohibited Concomitant Therapy

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications and substances are prohibited during the trial:

- Any other investigational therapy.
- No dietary supplements are allowed during the trial period (except for multivitamins, vitamin D, calcium and supplements in prevention of weight loss). The use of traditional medicines is not permitted.

If a patient receives any of these during the trial, the sponsor must be notified for evaluation of whether the patient can continue treatment or not.

## 6.5 Trial Drug Information

### 6.5.1 Physical Description of Trial Drug

GEN1029 – 20 mg/mL formulated in [redacted] - is a clear colorless solution supplied as a concentrate for solution for infusion to be diluted (at site) in 0.9% NaCl (saline).

### 6.5.2 Packaging

IMP will be provided in a 10R/I tubular colorless glass vial containing 7 mL or 10 mL of GEN1029 (140 mg/vial or 200 mg/vial, respectively).

### 6.5.3 Labeling

IMP labels will contain information to meet the applicable regulatory requirements.

### 6.5.4 Preparation, Handling, and Storage

Each dose of IMP must be prepared by the site pharmacy using aseptic techniques.

All IMP must be stored at controlled temperatures ranging from 35.6 °F to 46.4 °F (2 °C to 8 °C).

Refer to the pharmacy manual or trial site investigational product manual for additional guidance on trial drug preparation, handling, and storage.

### 6.5.5 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of IMP in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

At trial close-out, and as appropriate during the course of the trial, the investigator will destroy all used and unused IMP, packaging, drug labels, and a copy of the completed drug accountability log to the monitor or to the address provided in the investigator folder at each site (unless otherwise agreed with sponsor).

## 6.6 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

### 6.6.1 Procedures

All initial technical complaints must be reported to the sponsor by the trial-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the trial-site personnel must report the technical complaint to the sponsor according to the serious adverse event reporting timelines (Section 10.4.4). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

### 6.6.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the contact information page(s), which will be provided as a separate document.

# 7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

## 7.1 Dose-limiting Toxicity

For the purpose of dose escalation, SAEs, non-serious (NS) ≥ grade 3 AEs and clinically significant abnormal lab values will be collected and assessed by the DMC for DLTs (in each cohort during the first two cycles; i.e. DLT period of 28 days). National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 will be used to grade the intensity of adverse events.

DLT criteria are defined below:

***Hematological***

- Grade 4 neutropenia (i.e., ANC $< 0.5 \times 10^9$ cells/L) for minimal duration of seven days.
- Grade 3 and 4 febrile neutropenia (i.e., ANC $< 1.0 \times 10^9$ cells/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour).
- Grade 4 thrombocytopenia ($\leq 25.0 \times 10^9$ platelets/L) for minimal duration of seven days.
- ≥ Grade 3 thrombocytopenia associated with bleeding.
- Grade 4 anemia.

  *Note: Any grade 4 hematological AE should be checked 2x/ week for up to 4 weeks until a repeated value below grade 2 is reported.*

***Non-hematological***

- Grade 4 infusion-related reactions.
- Grade 4 anaphylaxis.
- Grade 3 infusion-related reactions that do not resolve to ≤ grade 1 within 24 hours.
- At least possibly related grade 4 AST, ALT or bilirubin elevations.
- At least possibly related grade 3 AST, ALT or bilirubin elevations that do not resolve to ≤ grade 1 within 7 days.
- At least possibly related AST, ALT or bilirubin elevations by more than one grade from baseline (e.g. grade 0→grade 2 as defined in the NCI-CTCAE Version 4.03) that do not resolve to ≤ grade 1 within 7 days.
- At least possibly related ≥ grade 2 AST or ALT elevations with concomitant bilirubin >2.0×ULN with no signs of cholestasis, i.e. a Hy's law case.
- Re-occurring of at least possibly related AST, ALT or bilirubin elevations ≥ grade 3, observed in cycle 1 and again in cycle 2 independent of resolution.
- At least possibly related ≥ grade 3 amylase and/or lipase elevations with significant clinical symptoms that do not resolve to ≤ grade 1 or baseline within 7 days.
- Grade ≥ 3 diarrhea that does not respond to optimal antidiarrheal treatment within 2 days
- Grade ≥ 3 vomiting that does not respond to optimal antiemetic treatment within 2 days
- Grade 3 nausea that does not respond to optimal antiemetic treatment within 7 days

- Any ≥ grade 3 at least possibly related non-hematological AE, which occurs during the first two cycles ***excluding***:
  - Non-hematological laboratory abnormalities that have no clinical consequences and resolve to ≤ grade 1 or baseline within 7 days (this also includes electrolyte abnormalities that respond to medical intervention).
  - Grade 3 fatigue persisting for less than 72 hours (optimal medical management must be applied).

**Dose-escalation part of the trial:**

- Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 28 days) must discontinue trial drug immediately.
- Meetings with the DMC will follow after completion of each cohort. Safety data for the specific cohort as well as cumulative safety data for all cohorts (SAEs, NS AEs, laboratory data and DLTs where applicable) will be evaluated.

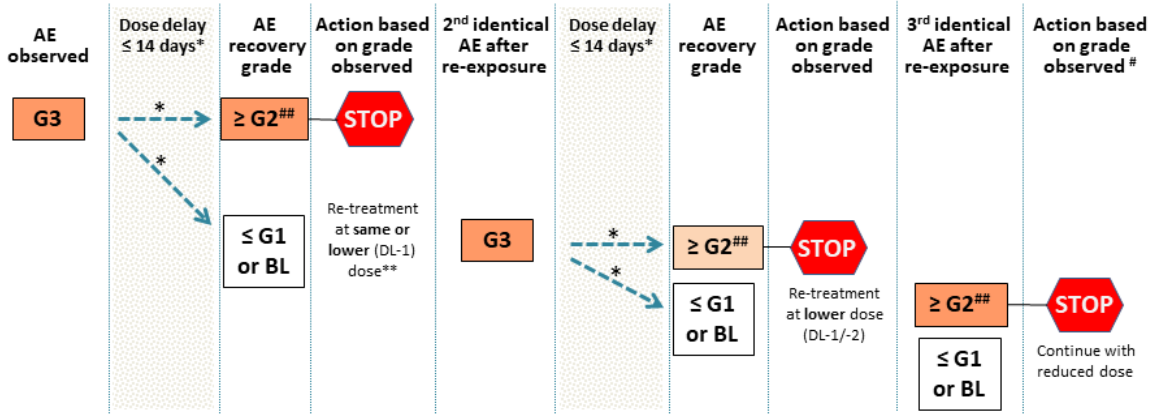
## 7.2 Dose Modification Guidance and Mitigation Plans for Specific Adverse Events

### 7.2.1 Dose modification Guidance

#### *7.2.1.1 Handling of adverse events fulfilling the DLT criteria*

Adverse events that fulfill the DLT criteria (after the DLT period has ended in the dose-escalation part of the trial or during the expansion part of the trial) should be handled as shown in Figure 7-1. *Please note that specific rules apply for elevated liver parameters (see Section 7.2.2.1).*

**Figure 7-1**: **Handling of adverse events fulfilling the DLT criteria**




BL=Baseline.
*Dose delay: Next dose of IMP can maximally be delayed 14 days unless approved otherwise by the sponsor medical monitor.
** If sponsor and investigator disagree, DMC should approve.
# No delay for recovery from ≥ G2 allowed.
## Unless grade at BL was ≥ G2 and AE has resolved to baseline grade.

***Grade 4 AEs fulfilling DLT criteria will always lead to IMP discontinuation.***

First occurrence of AE fulfilling DLT criteria grade 3:

- Investigator must contact sponsor for thorough discussion in order to decide whether the patient should be withdrawn from treatment or next dosing should be delayed.
- Administration of GEN1029 can be delayed for up to 14 days (i.e. one cycle). If the intensity resolves to ≤ grade 1 or baseline within this period, re-treatment may be considered under the following conditions:
    - Sponsor and investigator (DMC may be consulted) will discuss any safety concerns in order to decide whether next dose of IMP should be administered at same dose level or one dose level lower (DL-1). In case investigator and sponsor disagree, the DMC must be consulted.

Second occurrence of an identical AE grade 3 after re-exposure to IMP:

- If re-treatment leads to an identical adverse event with same intensity, the next administration of GEN1029 can be delayed for up to 14 days. If the intensity of the AE resolves to ≤ grade 1 or baseline within this period, re-treatment may be considered under the following conditions:
    - Next dose of IMP should be administered at one dose level lower (DL-1 or DL-2) than the dose level causing the recurrence of the adverse event.

Third occurrence of an identical AE ≥ grade 2 after re-exposure to IMP:

- If re-treatment at a lower dose leads to a third identical adverse event with intensity ≥ grade 2, the subject must permanently discontinue trial drug. No dose delay is allowed. However, if the adverse event is ≤ grade 1 or baseline, re-treatment may be considered under the following condition:
    - Next dose of IMP should be administered at same reduced dose level (DL-1 or DL-2).

Please note:

- Re-escalation of treatment dose is not allowed for patients that previously have been dose-reduced.
- IMP must be permanently discontinued if the patient experiences an adverse event fulfilling the DLT criteria (after the DLT period has ended for the dose-escalation part of the trial or during the expansion part of the trial) that fails to resolve to ≤ grade 1 or baseline within 14 days after the planned dosing date.
- IMP must be permanently discontinued if more than two dose reductions are required.
- IMP must be permanently discontinued in case of a dose delay of more than 14 days due to toxicity possibly related to GEN1029 unless otherwise approved by the sponsor medical monitor.

#### *7.2.1.2 Handling of adverse events not fulfilling the DLT criteria:*

Adverse events that do not fulfill the DLT criteria should be handled as following (*specific rules apply for elevated liver parameters. Please see Section 7.2.2.1*):

- The investigators are encouraged to contact sponsor in case of any safety concern that need thorough discussion and evaluation.

### 7.2.2 Mitigation Plan for Specific Adverse Events

#### *7.2.2.1 Elevated Liver Parameters*

All possibly IMP related events of elevated liver parameters must be managed as shown in Table 7-1 (except for DLTs that lead to permanent discontinuation of IMP).

**Note:** In case of a drug-related ≥ grade 2 elevation of ALT and/or AST, pre-medication with dexamethasone must be administered to the patient upon subsequent dosings (see Section 6.4.1).

**Table 7-1 Handling of Adverse Events Involving Elevated Liver Parameters**

| Baseline | Transaminases [a] | | Bilirubin [a] | Action with IMP |
|---|---|---|---|---|
| G0-G1 | G2: >3.0 - 5.0 x ULN | or | G2: >1.5 - 3.0 x ULN | Delay dosing [b, c] |
| G0-G1 | G3: >5.0 - 20.0 x ULN | or | G3: >3.0 - 10.0 x ULN | Delay dosing [d, e] |
| G0-G1 | G4: >20.0 x ULN | or | G4: >10.0 x ULN | Stop dosing |
| G0-G1 | ≥G2: >3.0 x ULN | and | >2.0 x ULN | Stop dosing[f] |

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, G = grade, ULN = upper limit of normal.

a Any AST, ALT, and / or bilirubin ≥ grade 2 elevation needs to be checked 2x/week for up to 4 weeks.

b Re-start at same dose level at 1st occurrence when resolved to ≤ grade 1 within 7 days / re-start at a reduced dose level at 2nd occurrence when resolved to ≤ grade 1 within 7 days.

c Stop dosing at 3rd occurrence in case of unfavorable benefit-risk assessment by the DMC.

d Re-start at a reduced dose level, but only when resolved to ≤ grade 1 within 7 days.

e Stop dosing at 2nd occurrence.

f Patients with ALT/AST>3.0 x ULN and bilirubin >2.0 x ULN with no signs of cholestasis, and for which the cause is at least possibly linked to study drug (i.e. a Hy's law case), must permanently discontinue trial drug.

- If a patient experiences AST, ALT or bilirubin elevations by more than one grade from baseline (grade 0→grade 2 as defined in the NCI-CTCAE Version 4.03), next dose of GEN1029 must be delayed until resolution to ≤ grade 1. Upon resolution to ≤ grade 1 within 7 days, treatment with GEN1029 may be re-started at same dose level for patients with 1st occurrence but at a reduced dose level (DL-1) for patients with 2nd occurrence. If requested by the investigator, the DMC and the sponsor may allow a patient with a favorable benefit-risk assessment to continue in the trial on a reduced dose even if the resolution to grade 1 occurs within 4 weeks. In case of 3rd occurrence a benefit-risk assessment should be conducted by the DMC. In case of an unfavorable benefit-risk assessment GEN1029 therapy should be permanently discontinued.
- If a patient experiences grade 3 AST, ALT or bilirubin elevations, GEN1029 therapy must be delayed until resolution to ≤ grade 1. Upon resolution to ≤ grade 1 within 7 days treatment with GEN1029 may be re-started at reduced dose level (DL-1). If requested by the investigator, the DMC and the sponsor may allow a patient with a favorable benefit-risk assessment to continue in the trial on a reduced dose even if the resolution to grade 1

occurs within 4 weeks. In case of 2nd occurrence GEN1029 therapy should be permanently discontinued.

- Patients with grade 4 AST (>20.0 x ULN), grade 4 ALT (>20.0 x ULN) and / or grade 4 bilirubin (>10.0 x ULN) elevations, or other grade 4 liver toxicity must permanently discontinue trial drug.
- Patients with ALT/AST >3.0 x ULN and bilirubin >2.0 x ULN with no signs of cholestasis, and for which the cause is at least possibly linked to study drug (i.e. a Hy's law case), must permanently discontinue trial drug.

Please note:

- In case of elevated liver parameters ≥ grade 2, AST, ALT, and bilirubin laboratory values must be checked (unscheduled visits) twice a week for up to 4 weeks until a repeated value below grade 2 is reported.

**Table 7-2 Guidance for Supportive Care in Case of Elevated Liver Parameters**

| On-treatment levels | Supportive Care |
|---|---|
| Transaminases > 3 – 5 x ULN or bilirubin > 1.5 – 3 x ULN | Consider administering corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper. |
| Transaminases >5.0 x ULN or bilirubin >3.0 x ULN | Consider administering corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. |

#### *7.2.2.2 Infusion-Related Reactions*

- Pre-medication to prevent infusion-related reactions may be administered at the investigator's discretion according to local guidelines (e.g., antihistamine, acetaminophen/paracetamol and corticosteroids). The use of paracetamol (acetaminophen) as pre-medication should be considered to be omitted to prevent transaminase elevations, and used with caution during all treatment cycles.
- Grade 1: If an infusion-related reaction grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- Grade 2-3: If an infusion-related reaction grade 2 or 3 occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to ≤ grade 1 within an hour.
    - Patients who have experienced prior infusion related grade 2 or 3 reactions in the trial should be pre-medicated (antihistamine, acetaminophen and corticosteroids are recommended).
    - If the patient has a second Grade 3 infusion-related reaction despite pre-medication, the infusion should be stopped and the patient should be withdrawn from treatment.
- Grade 4: If anaphylaxis or grade 4 infusion-related reactions occur, administration of IMP should be discontinued immediately and permanently and appropriate medical therapy should be administered.

Please note:

- As a routine precaution, patients enrolled in this trial must be observed for 2 hours after each infusion, in an area with resuscitation equipment and emergency agents.
- At all times during GEN1029 infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All pre-medication must be reported on the concomitant medication page in the eCRF

#### *7.2.2.3 Diarrhea*

Due to the observation that diarrhea may be associated with GEN1029 treatment in a dose independent manner and can be severe, the following guidance is introduced to manage diarrhea events as they occur (Table 7-3).

**Table 7-3 Guidance for Managing Diarrhea**

| Toxicity Grade (CTCAE) | Dose Modification | Investigations | Management |
|---|---|---|---|
| Grade 1 | Continue treatment | No specific diagnostic work-up recommended.<br>The investigations described below may be considered if the event is prolonged or progressive. | Close monitoring and consider the following treatments if needed:<br>• Loperamide or diphenoxylate/atropine<br>• Fluid and electrolyte supplementation |
| Grade 2 | Hold treatment until event improves to ≤ G1 | Blood work-up (including complete blood count, electrolytes, urea, creatinine and C-reactive protein)<br>Stool evaluation to rule out infectious etiology (e.g. stool culture and tests for *Clostridium difficile* toxin, parasite, CMV or other viral etiology, ova and parasite)<br>Stool calprotectin and lactoferrin to assess intestinal inflammation<br>Consider CT scan of abdomen/pelvis<br>GI consultation for further evaluation (i.e. capsule endoscopy, colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy with biopsy from stomach, duodenum, terminal ileum, colon)<br>*NB - Treatment for the event can be initiated while awaiting test results* | Close monitoring and administration of corticosteroids.<br>For G2, unless diarrhoea is transient, treat with 3 mg oral budesonide once daily. Budesonide may be increased to 6 mg once daily if there is no response in 2-3 days.<br>Consider if in-patient care is required for G3/G4 diarrhoea.<br>For G3, treat with 3-6 mg oral budesonide once daily. May administer IV methylprednisolone (2mg/kg/day) if symptoms persist for ≥ 3-5 days*.<br>For G4, administer IV methylprednisolone (2mg/kg/day)*.<br>Corticosteroids should be continued until the event improves to ≤ G1 and then tapered. |
| Grade 3 | Hold treatment until event improves to ≤ G1 | | |
| Grade 4 | Permanently discontinue treatment | | |

*Patients who respond to IV methylprednisolone can be switched to oral budesonide for continued treatment and taper.
Patients should be made aware of the potential for diarrhoea to occur and to inform the investigator immediately if they experience changes in bowel habits, nausea, vomiting, abdominal pain, cramping, fever and blood or mucus in the stool.

## 7.3 Safety Stopping Rules

Treatment with IMP should be discontinued due to safety concerns under the following conditions:

- Patients experiencing a DLT (an adverse event fulfilling DLT criteria within the DLT period during the dose-escalation part of the trial).

- If the patient experiences an adverse event fulfilling the DLT criteria after the DLT period has ended in the dose-escalation part of the trial or during the expansion part of the trial, that fails to resolve to ≤ grade 1 or baseline within 14 days after the planned dosing date. N.B. Grade 4 AEs fulfilling DLT criteria will always lead to IMP discontinuation.
- If more than two dose reductions are required.
- Dose delay of more than 14 days due to toxicity possibly related to GEN1029.
- Possibly related event of elevated liver parameters
    - Patients with grade 4 AST (>20.0 x ULN), grade 4 ALT (>20.0 x ULN) and / or grade 4 bilirubin (>10.0 x ULN) elevations, or other grade 4 liver toxicity.
    - 2nd occurrence of a grade 3 AST, ALT or bilirubin elevation (if first occurrence resolved to ≤ grade 1 within 7 days).
    - Patients with ALT/AST>3.0 x ULN bilirubin >2.0 x ULN with no signs of cholestasis, and for which the cause is at least possibly linked to study drug (i.e. a Hy's law case).
    - In case of a negative benefit-risk assessment performed by DMC due to 3rd occurrence of AST, ALT or bilirubin elevations by more than one grade from baseline (grade 0→grade 2; if it resolved to grade 0 at prior occurrences).
- 2nd occurrence of a grade 3 infusion-related reaction despite pre-medication prior to infusion.
- 1st occurrence of anaphylaxis or grade 4 infusion-related reactions.

Please note:

- Observation procedures and assessments are to be continued for the rest of the cycle. Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible (specified as the end of treatment visit).

# 8 DISCONTINUATION, FOLLOW UP AND COMPLETION

## 8.1 Discontinuation of Treatment

Patients will be withdrawn from treatment for the following reasons:

- Safety Stopping Rules (as defined in Section 7.3)
- Pregnancy
- Patient choice
- Investigator or sponsor decision due to individual patient safety issues not covered by other withdrawal criteria
- Disease progression
- Initiation of other anti-cancer treatment (the expansion part only)
- Intercurrent illness that precludes further participation or requires a prohibited concomitant treatment

Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible at the end of treatment visit.

## 8.2 Withdrawal from the Trial

Patients will be withdrawn from the trial (dose escalation or expansion parts), including safety follow-up evaluations and follow-up contact, for the following reasons:

- A patient may withdraw from the trial at any time at his or her own request
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- Lost to Follow-Up (see Section 8.4)
- Patient died
- Trial closure
- Initiation of other anti-cancer treatment (the dose-escalation part only)

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

The sponsor will make any effort to ensure patients are followed up for completion of safety assessment in the trial. See Table 1-1 and Table 1-6 for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

When a patient withdraws before completing the trial, the reason for withdrawal is to be documented in the eCRF and in the source document. Trial drug assigned to the withdrawn patient may not be assigned to another patient.

Patients who withdraw will not necessarily be replaced.

### Withdrawal From the Use of Samples in Future Research

The patient may withdraw consent for use of samples for research (refer to Section 13.2.5). In this case, samples will be destroyed after they are no longer needed for the clinical trial. Details of the sample retention for research are presented in the ICF.

## 8.3 Safety Follow up Evaluations

Patients discontinuing from treatment for any reason will have safety follow-up visits 30 and 70 days after last treatment and will also be contacted every 13 weeks after last dose until end of trial.

Data collected should be added to the adverse events eCRF and the concomitant medications eCRF.

## 8.4 Lost to Follow-up

For patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent form and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). Patients lost to follow-up should be recorded as such on the appropriate disposition eCRF.

# 9 ASSESSMENTS

## 9.1 Demography and Baseline Characteristics

### 9.1.1 Demographics

Date of birth and/or age, race, ethnic origin, gender and smoking and drinking habits will be recorded at screening in the eCRF.

### 9.1.2 Disease Status

Primary site of cancer and initial and current disease stage [Tumor Nodes Metastasis (TNM) staging system] will be recorded at screening in the eCRF.

For patients with:

- NSCLC, the patients' tumor status with respect to EGFR mutations and ALK / ROS1 rearrangement.
- CRC, the patients' tumor status with respect to BRAF and RAS mutations, and gastric cancer, the patients' tumor status with respect to HER2-neu expression mutations will be also recorded (incl. date of the assessment).

### 9.1.3 Medical History

Relevant past and all current disease data will be recorded in the eCRF. Any past surgery not related to cancer should be recorded in the medical history.

### 9.1.4 Concomitant Medication

Any medication or therapy other than GEN1029 is considered concomitant medication and should be recorded in the eCRF with the following information:

- Start date
- Route of administration
- Stop date of administration or ongoing at trial termination
- Indication/reason for use
- The total daily dose should be filled in whenever possible.

Relevant prior concomitant medication given within 4 weeks prior to screening and all medication given from visit 0 (Screening) until the 70-day safety follow-up must be recorded.

During the patient follow-up period only new anti-cancer treatment will be collected.

### 9.1.5 Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies and surgeries must be reported in the appropriate section of the eCRF. Number of cycles, best response and stop reason along with dates of administration and progression should be reported.

Radiotherapy should be recorded if the indication is cancer.

### 9.1.6 Liver Ultrasound

All patients will need to have an ultrasound of the liver at screening to investigate potential underlying factors related to potential liver toxicity of GEN1029. This will cover the assessment of liver morphology, i.e. size, capsular contour (smooth, coarse, lobulated), parenchymal echogenicity, vascularity, biliary tree, and masses or collections.

Ideally, fast the patient for 6 hours to reduce bowel gas and prevent gall bladder contraction. A patient may take small amounts of still water by mouth prior to scan, particularly for taking any medications.

Equipment selection:
- Depending on the size of the patient a curved linear array 2-6Mhz.
- If there is nodularity of the liver border then a linear array with a 7-12MHZ frequency will better appreciate this.
- Good colour / power / Doppler capabilities when assessing vessels or vascularity of a structure.

The normal anatomy and any pathology found, including measurements and vascularity should be documented.

Doppler evaluation should be used to document blood flow characteristics and blood flow direction, which is crucial in the diagnosis of portal hypertension.

Common pathology to be assessed at minimal should contain:
- Hepatic steatosis
- Fatty liver
- Fibrosis
- Cirrhosis
- Liver cysts
- Haemangioma
- Portal hypertension
- Portal vein thrombosis
- Hepatic vein thrombosis
- Liver abscess/collection
- Trauma
- Tumor / metastases
- Abscess

The basic hard copy imaging should cover the following:
- Longitudinal
  - Left lobe
  - Caudate lobe
  - IVC
  - Porta hepatis
  - Comparison to Rt Kidney
- Transverse
  - Left lobe
  - Left hepatic vein
  - Left portal vein
  - Right portal vein

- Middle and Right hepatic vein
- Demonstrate hepatopetal flow in portal vein
- Demonstrate hepatic vein flow
- Document the normal anatomy. Any pathology found in 2 planes, including measurements and any vascularity

## 9.2 Efficacy Assessment

The RECIST 1.1 criteria will be used for response evaluation (Eisenhauer et al., 2009).

The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression.

As an exploratory analysis the metabolic response in the tumors will be assessed by PET scan in selected patients as described below. The metabolic response will not be used for efficacy assessments, and hence the patient's ability to stay on treatment will be based on the RECIST 1.1 response only

Chest x-rays and ultrasound should not be used to measure tumor lesions.

### 9.2.1 Dose Escalation Part

In the dose escalation part, PET-CT scans must be taken at screening and, if avid at screening, also at Cycle 2 Day 2, and week 12 (±7 days). If a patient, who has been exposed to GEN1029, did not have any PET-CT scans while on treatment and the PET-CT scan at screening displayed avidity, a PET-CT scan should be taken at the end of trial visit (please refer to Section 9.2.3 for additional details on PET-CT scans).

The PET-CT scan at screening is with contrast of thorax, abdomen and pelvis. If there is suspicion of brain metastases or tumors, a scan of the head will be performed before inclusion.

Up to five target lesions (maximum two per organ) will be defined at screening and these must be followed throughout the trial. Non-target lesions will also be assessed throughout the trial.

A CT scan must be performed at Cycle 3, Day 8-14 after first dose. If PET-CT at screening showed no avidity, a CT scan has to be done instead of a PET-CT scan in week 12 (±7 days). From week 18 (±7 days) until week 50 after first dosing, CT scans must be performed every 6 weeks (±7 days), and every 12 weeks (±7 days) thereafter. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts.

Additional CT-scans may be performed at the investigators discretion to confirm response or new symptoms. The intervals should not be shorter than four weeks. In this case the investigator must choose the imaging technology based on the clinical indication. Information from additional scans should be added to an unscheduled visit in the eCRF

### 9.2.2 Expansion Part

In the expansion part, all patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed during screening. If there is suspicion of brain metastases or tumors, a CT-scan of the head will be performed before inclusion.

Up to five target lesions (maximum two per organ) will be defined at screening and these must be followed throughout the trial. Non-target lesions will also be assessed throughout the trial.

Scans will be performed at week 6 (-7 days), every 6 weeks (±7 days) for 50 weeks, and every 12 weeks (±7 days) thereafter from the date of first dose until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts.

Additional CT-scans may be performed at the investigators discretion to confirm response or new symptoms. The intervals should not be shorter than four weeks. In this case the investigator must choose the imaging technology based on the clinical indication. Information from additional scans should be added to an unscheduled visit in the eCRF.

Magnetic resonance imaging can consistently be performed instead of CT scan if the patient is allergic to iodine contrast or at the discretion of the investigator, after approval of the sponsor.

At the discretion of the investigators and after approval of the sponsor, combined PET-CT may be performed for tumor assessments in the expansion part, but only if the CT portion is of similar diagnostic quality to CT alone. Please refer to Section 9.2.3 for additional details on PET-CT.

### 9.2.3 PET-CT

FDG (18F-Fluoro-Deoxy-Glucose) imaging (or dual-phase fluorodeoxyglucose positron emission tomography [dual-phase **18**F-FDG-PET]) will be performed according to Table 1-1. **The PET shall be combined with CT and the CT portion must be of similar diagnostic quality to CT alone**.

The patient needs to fast for 4 to 6 hours prior to the FDG-PET scan. The patient can drink water freely during the fast and should be encouraged to do so. He/she may also take regular medications as scheduled during the fast. Blood glucose level will be checked on the day of the FDG-PET scan and results assessed prior to the administration of FDG. The patient should have a blood glucose level ≤ 180 mg/dL (≤ 10 mmol/L) in order to have the FDG-PET scan. If the level is higher, the scan should be rescheduled if possible. Regular diet can be resumed after the scan. The interval between FDG administration and scanning must be 60 minutes +/- 10 minutes and it is particularly important that the time interval between injection and start of the scan is the same at on treatment as compared to baseline.

All patients should be encouraged to increase fluid intake for a few hours after the scan to promote excretion of the FDG. A diuretic (furosemide, typically 20-40 mg IV) may be administered at the discretion of the Investigator before or during the FDG-PET scan in order to accelerate elimination of the [18F] FDG from the renal collecting system.

Diazepam may be used to promote muscle relaxation and reduce muscular uptake if tumor deposits are in the neck or shoulder girdle area. Diazepam administration and diuretic administration must be recorded in the Concomitant Medications eCRF page.

Note that the PET must be performed before any tumor biopsy to avoid potential false positive findings. The baseline FDG-PET assessment during screening should be performed at the closest date as possible from start of study treatment, at least one week before tumor biopsy.

#### *9.2.3.1 Ad PET Scan Acquisition:*

Attenuation corrected FDG-PET scans (from skull base to mid-thigh) will be performed. The patient will be administered 370–740MBq (10-20mCi) 2-[F-18]-fluoro-2-deoxy-D glucose (FDG) intravenously (dose is dependent on local practice and scanner type). The administered activity and time of FDG administration must be recorded ).

Approximately one hour following the administration of FDG, a whole body PET scan (base of skull to thighs) is performed and the time of the commencement of the scanning is recorded. The sequence of the scan must be the same for the baseline scan and all on treatment scans, and the interval between FDG administration and scanning should be as similar as practical.

Preferably for a given patient the same scanner should be used at all time-points. The FDG-PET images will be analyzed by the site.

#### *9.2.3.2 Local Scan Interpretation*

The PET-CT scans will be analyzed by an experienced reader (the same reader should interpret all scans for each subject).

Of note, if tumor lesions showed no avidity at baseline, no further PET scans should be performed.

### 9.2.4 Reading of the Scans

In the dose escalation and expansion parts, the reading of the scans will be done by a local radiologist. Sites should attempt to maintain the same radiologist throughout the trial. Results from the radiology evaluations shall be recorded in the eCRF and a copy of the evaluation reports should be kept in the patient's file.

## 9.3 Pharmacokinetics

### 9.3.1 Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of Hx-DR5-01 plus Hx-DR5-05 as specified in Table 1-3 and Table 1-8. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of GEN1029. Venous blood samples will be collected and each plasma sample will be divided into aliquots. Samples collected for analyses of plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. [redacted] Patient confidentiality will be maintained. At visits where plasma concentration will be evaluated, one blood draw of sufficient volume can be used.

### 9.3.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of Hx-DR5-01 and Hx-DR5-05 using validated methods. Samples may also be used to determine anti-drug antibodies or neutralizing antibodies.

## 9.4 Clinical Safety Assessments

### 9.4.1 Physical Examination

A complete physical examination will at a minimum include general appearance of the following body systems: lymph node regions, mouth and throat, respiratory, cardiovascular system, abdomen, extremities, muscular-skeletal system, neurological system, and skin.

Height (without shoes) must be measured at visit 0 (Screening) and rounded to nearest centimeter.

Body weight (without overcoat and shoes) will be measured at visit 0 (Screening), at day 1 of each cycle, as part of the dose calculation, and at end of treatment visit, and will be recorded in the eCRF.

If body weight is assessed seven days or less (using the site scale) before the day of the planned dosing, this weight can be used for dose calculation and is to be is recorded in the eCRF.

### 9.4.2 Vital Signs

Vital signs, including temperature, blood pressure and heart rate, should be measured with the patient in a supine or reclined position and recorded in the eCRF. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed just before and no longer than 30 minutes before infusion start, during and after the infusions until 4 hours after end of infusion of the three first infusions (dose escalation part only) and until 2 hours after the remaining infusions, as indicated in Table 1-5 and Table 1-9 for the dose escalation and expansion parts, respectively.

### 9.4.3 Electrocardiograms

The electrocardiograms (ECGs) will be recorded digitally at the sites by using the standard 12-leads as outlined in Table 1-2 and Table 1-7 for the dose escalation and expansion parts, respectively. ECGs will be performed in accordance with the ECG manual issued by the vendor. The digital ECGs will be transmitted from the sites electronically to a central laboratory for a treatment-blinded measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the print out. In case of discrepancy between central and the investigator ECG readings, the central reading will be used for trial analysis purposes.

For the ECG recordings, the patients must be resting and in a supine or reclined position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (e.g., vomiting, cough) should either induce a repeat of the ECG or be annotated on the eCRF with the description and time of the occurrence.

### 9.4.4 ECOG Performance Status

The eastern cooperative oncology group (ECOG) performance status will be assessed by the investigator at screening, on Day 1 of each cycle, and at the end of treatment visit. Performance status will be scored using the ECOG performance status scale index

**Table 9-1 ECOG performance status**

| Score | Description |
|---|---|
| 0 | Fully active, able to carry out all normal activity without restriction. |
| 1 | Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities.<br>Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## 9.5 Clinical Laboratory Assessments

The tests detailed in Table 9-2 will be drawn and shipped for centralized testing, except urinalysis which will be analyzed locally, and results will be reported to the investigators by the central laboratory as described in the laboratory manual. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the CRF.

Local laboratory values for biochemistry and hematology must be obtained within 24 hours prior to each IMP administration and reviewed by the investigator prior to each IMP administration to ensure the patient can be dosed in line with the dosing instructions as defined in the protocol. In the first 3 cycles, all biochemistry safety samples must be assessed locally as well to monitor liver function. Furthermore, local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions of the patient with the exception of evaluation of patient eligibility, which must be evaluated based on central laboratory data. However, if the central laboratory values obtained during screening are unexpectedly unavailable when the patient is scheduled for the first administration of GEN1029, local laboratory values may be used following agreement with the sponsor's Medical Monitor.

For clinical treatment decisions, *e.g.* IMP administration or safety reasons, for an individual patient, local laboratory values take precedence over central laboratory values. Local laboratory values must be recorded in the eCRF if they are of clinical importance, *e.g.* if they result in a clinical laboratory AE, used as supportive information on an AE or lead to dose modifications/delays of the IMP. Furthermore local laboratory values of clinical significance will be assessed for the evaluation of DLT. If a central laboratory value indicates dose modification/delay, but the local laboratory value does not, the medical officer should be contacted and the site will be asked to retrospectively record the corresponding local laboratory value in the eCRF. Any local or central laboratory values leading to a dose modification/delay should be recorded as an AE (Section 10.2.6).

For the analyses and reporting of the trial results, the central laboratory values will be used. All recorded local laboratory values will be listed.

A manual with detailed description of the procedures for sampling, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels for central analysis will be provided by the central laboratory. The manual and the result reports will include all reference ranges.

Laboratory equipment may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be included in the database, but must be reported to the investigator.

**Table 9-2 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit<br>mean corpuscular volume<br>mean corpuscular hemoglobin<br>mean corpuscular hemoglobin concentration<br>coagulation factors prothrombin time, (international normalized ratio and activated partial thromboplastin time) | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC Count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Biochemistry | BUN (Blood Urea Nitrogen) | Potassium | Aspartate Aminotransferase (AST) | Total and direct bilirubin |
| | Creatinine (GFR calculation) | Sodium | Alanine Aminotransferase (ALT) | albumin |
| | Glucose | Calcium | Alkaline phosphatase | Magnesium |
| | lactate dehydrogenase | uric acid | C-reactive Protein | Lipase |
| | Amylase | gamma-glutamyl transferase | glycosylated hemoglobin | Chloride |
| | Cholesterol | Triglycerides | High density lipoprotein | low density lipoprotein |
| Urinalysis* | protein, leukocyte pregnancy test (as needed in women of childbearing potential only) by dipstick | | | |
| Other Screening Tests | Follicle-stimulating hormone and estradiol (as needed in women of childbearing potential only)<br>Hepatitis B and C<br>CMV | | | |
| [redacted] | [redacted] | | | |
| NOTES :<br>*Urinalysis will be analyzed at the local laboratory.<br>For the Cytomegalovirus (CMV), anti-IgG and IgM will be assessed. In case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. | | | | |

In case of discrepancies leading to protocol deviations, this will be reported, reviewed and discussed with the sponsor medical team and documented.

## 9.6 Immunogenicity

### 9.6.1 Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of anti-drug antibodies as specified in Table 1-1 and Table 1-6.

Samples will be used to evaluate the presence of antibodies to GEN1029. Venous blood samples will be collected and each plasma sample will be divided into 2 aliquots (one for ADA and a back-up). Samples collected for ADA to GEN1029 may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity. Genetic analyses will not be performed on these serum samples. Patient confidentiality will be maintained. At visits where antibodies to GEN1029 will be evaluated, one blood draw of sufficient volume can be used.

### 9.6.2 Analytical Procedures

The detection and characterization of antibodies to GEN1029 will be performed using a validated assay methods under the supervision of the sponsor. All samples collected for detection of antibodies to GEN1029.

### 9.6.3 Immunogenicity Assessments

Antibodies to GEN1029 will be evaluated in plasma samples collected from all patients according to the visit schedule. These samples will be tested by the sponsor or sponsor's designee.

Plasma samples will be screened for antibodies binding to GEN1029 and the titer of confirmed positive samples will be reported. Two titer methods will be used; one method will determine the response against Hx-DR5-01 and the other against Hx-DR5-05. Other analyses may be performed to verify the stability of antibodies to GEN1029 and/or further characterize the immunogenicity of GEN1029.

## 9.7 Biomarkers

Biomarker investigations in this study will include both candidate stratification biomarkers, that may predict drug response to the treatment, and pharmacodynamic biomarkers, to further understand the mechanism of action, potential mechanisms of resistance, dynamic changes over time and the understanding of DR5 biology in cancer and the pathomechnism of disease.

### 9.7.1 Biomarker assessments in tumor samples

Tumor biopsies will be collected at screening from each patient according to inclusion criteria and must be in accordance with the collection and processing guidance provided in the laboratory manual:

- To ensure sufficient tumor tissue, it is mandatory to collect core needle biopsies, which should be CT-guided for internal solid tumor lesions and performed by experienced interventionalists. It should be noted that it is not allowed to take biopsies from target lesions at baseline and during treatment. Archival biopsies should be FFPE. Fresh biopsies should be collected as both mandatory FFPE tissue (blocks/slides) and optional fresh frozen tissue.

Biomarker analyses in tumor samples at baseline, during and at end of treatment visit may help to confirm GEN1029’s mechanism of action, enable the identification of biomarkers predictive of response or resistance to GEN1029, study dynamic changes over time, gain insight in the evolution of disease and tumor immune microenvironment.

[redacted]

[redacted]

***Protein expression analyses***
DR5 expression and expression of other proteins related to GEN1029's mechanism of action (for example; caspases as a measure of apoptotic activity) may be evaluated in tumor biopsies by immunohistochemistry on an automated staining platform. Tumor sections will be scored by a certified pathologist, and digital images will be made from stained tumor sections in order to be used for exploratory digital pathology analyses.

### 9.7.2 Biomarker assessments in blood samples

Biomarker assessments will also be performed using whole blood samples to investigate potential pharmacodynamic markers and explore the relationship to efficacy and/or mechanism of action of GEN1029. Assessments will be performed at baseline (before infusion at C1D1) and at later cycles during treatment including visits in close proximity with a planned CT scan, and at the end of treatment in order to enable correlation analyses with response to treatment or disease progression.

***Protein expression analyses***
Levels of proteins related to GEN1029's mechanism of action, including levels and activation status of complement components and cytokines, may be measured so changes associated with the mechanism of action of GEN1029 can be monitored.

***Immunophenotyping analyses***
Immunophenotyping, including single cell sorting/sequencing, may be performed (for example; measurement of [redacted]) at baseline and during treatment so changes associated with the mechanism of action of GEN1029 can be monitored.

[redacted]

### 9.7.3 Additional analyses

In addition to the biomarker analyses listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about GEN1029 (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing trials and/or literature data. Biomarker samples may further be used to help address emerging issues and to enable the development of safer, more effective, and, ultimately, individualized therapy.

Moreover, biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

# 10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

## 10.1 Adverse Event Definitions

### 10.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

### 10.1.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that meets one of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is “medically important”
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

[1] The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

[2] Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition during trial that has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient’s general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above

### 10.1.3 Definition of Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 10.3 and in the investigator's brochure.

### 10.1.4 Definition of Infusion-Related Reactions

Infusion-related AEs are defined as any AEs occurring during infusion or where the onset of the event occurs within 24 hours after the end of infusion and is coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred term as:

"Arthralgia", "Asthenia", "Bronchospasm", "Chills", "Cough", "Hyperhidrosis", "Dizziness", "Pyrexia", "Fatigue", "Flushing", "Headache", "Hypertension", "Hypotension", "Infusion related reaction", "Lethargy", "Malaise", "Myalgia", "Nausea", "Pruritus", "Tachycardia", "Tumor pain", or by MedDRA High Level term as "Exfoliative conditions" or "Dyspneas", "Dyspnoeas", "Breathing abnormalities" or by MedDRA High Level Group Term as "Allergic conditions".

Investigators should consider the clinical picture and isolated events, such as "Fatigue", occurring within 24 hours after the end of infusion, might be considered not to constitute an infusion-related reaction, if judged not to be infusion-related by the investigator.

For infusion-related reactions the causality of the event (Section 10.2.11) should be judged as "at least possibly related" by the investigator.

## 10.2 Adverse Event Reporting

Non-serious Adverse Events:

Non-serious AEs should be reported from the time the patient signs the ICF until the safety follow up visit (at 70 days after the last IMP dose) or the end of trial (EOT)/withdrawal visit), whichever comes first.

Serious Adverse Events

SAEs should be reported from the time the patient signs the ICF until the safety follow up visit (at 70 days after the last IMP dose) or the end of trial (EOT)/withdrawal visit, whichever comes first.

Please note:

- Final assessment of AEs must be performed by a medically qualified person, i.e., a medical doctor.
- All AEs that occur in patients during the AE reporting period must be reported, whether or not the event is treatment-related.
- All AEs should be entered in the eCRF and assessment should be made at each visit (or more frequently, if necessary) of changes in severity, the suspected relationship to the trial treatment, action taken to trial drug, and the outcome. Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the eCRF completion guideline.
- If an AE becomes grade 3 or results in an SAE it should be reported both in the eCRF and on the relevant paper form (SAE paper form or non-serious grade 3 form).
- All AEs should be followed until they are resolved or until end of trial, whichever comes first. At least possibly related non-serious ≥ grade 3 AEs and SAEs still ongoing after end of trial should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

### 10.2.1 Pre-existing Condition

In this trial, a pre-existing condition (i.e. a disorder present before the AE reporting period started and noted on the medical history/physical examination form) is not to be reported as an AE. If a pre-existing condition worsens during the IMP treatment period, the event should be reported as an AE.

### 10.2.2 Diagnosis

The diagnosis/cause of an AE should be recorded rather than the symptoms of the AE. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

### 10.2.3 Study Disease

Signs and symptoms, which according to the investigator are expected and well known consequences of the indication, both in intensity and frequency, should not be reported as AEs or SAEs. Any unexpected change in the intensity or frequency should be reported as an AE (or SAE if applicable).

### 10.2.4 Disease Progression or Death

Progression of malignancy, if documented by use of an appropriate method (as per RECIST criteria), should not be reported as an SAE. However all deaths (including death caused by disease progression) should be reported as SAEs.

### 10.2.5 Unrelated Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, should however be reported if it meets the definition of an AE. For example, an acute appendicitis should be reported as the AE and not the appendectomy.

### 10.2.6 Laboratory test abnormalities

Laboratory abnormalities that are considered clinically significant, i.e. induce clinical signs or symptoms, require concomitant therapy or require changes in trial treatment should be recorded as an AE in the eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

NOTE: A CTCAE grade 3 or 4 event (severe) does not automatically indicate an SAE.

### 10.2.7 Start Date and Time

Start date for an (S)AE is the date of occurrence of the first symptom of the disease, e.g. if chest pain occurs on 01 April 2016 and the patient is hospitalized with myocardial infarction on 04 April 2016, then the onset date of the SAE myocardial infarction is 01 April 2016.

The time should be filled in if the event starts on a dosing day or if the duration of the event is less than 24 hours.

### 10.2.8 Information about infusion-related reactions

If the start date of an AE is the same as an infusion date, the investigator is to assess whether the AE is related to the infusion.

### 10.2.9 Seriousness Criteria

Indicate whether or not the AE is determined to be "serious" based on the criteria defined in Section 10.1.2.

### 10.2.10 Intensity

The investigator will use the NCI's CTCAE version 4.03 to describe the severity of AEs.

### 10.2.11 Relationship to Investigational Medicinal Product

A suspected adverse reaction is one in which there is a reasonable possibility that the IMP caused the adverse event, this means there is evidence to suggest a causal relationship between the IMP and the adverse event.

The investigator must assess whether or not the event is related to the IMP. The relationship is to be judged using the following terms:

- At least possibly related
- Not related

If the relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the AE is being reported.

### 10.2.12 Action Taken with Investigational Medicinal Product

The action taken with the IMP should be noted as:

- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

Drug interrupted should be use if the infusion is interrupted or if a treatment is postponed due to mitigation of AEs.

Not applicable should only be used if the AE occurs before first treatment or in the follow-up period.

### 10.2.13 Outcome

The outcome of the AE must be judged by investigator using the following terms:

- Fatal
- Not recovered/not resolved
- Recovered/resolved

- Recovered/resolved with sequelae
- Unknown

#### 10.2.14 End Date and Time

The end date should be filled in if the outcome of an event is fatal, recovered/resolved or recovered/resolved with sequelae. The time should be filled in if the event starts on a dosing day or if the duration of the event is less than 24 hours.

### 10.3 Adverse Events of Special Interest

#### 10.3.1 Elevation of Transaminases

Alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased have been reported in more than 50% of the patients. The majority of these were considered to be related to the IMP and appeared to be independent of the dose level. Guidance for managing elevated transaminases has been included in Section 7.2.2.1.

#### 10.3.2 Diarrhea

Diarrhea has been reported in more than 40% of the patients and was the most frequently reported SAE. The majority of these were considered to be related to the IMP. Guidance for managing diarrhea has been included in Section 7.2.2.3.

### 10.4 Events Requiring Immediate Reporting

#### 10.4.1 Serious Adverse Events and Non-Serious ≥ Grade 3 Adverse Events

SAEs and non-serious ≥ grade 3 AEs must be reported from the investigational site to the sponsor no later than 24 hours following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or other information at, or from which, such development was reported, noted or recognized.

Grade 3 and 4 abnormal laboratory test results must be reported as AEs when these are assessed as clinically significant by the reporting investigator.

All events fulfilling the definition of Hy's Law (i.e. ALT/AST > 3×ULN and Bilirubin > 2×ULN) must be reported as SAEs.

#### 10.4.2 Overdose and Medication Errors

For this trial, an overdose is defined as a patient receiving a dose of the IMP 10% in excess of the intended dose specified in this protocol.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

Medication errors include infusion rate errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All events of overdose and/or medication errors with IMP must be reported from the investigational site to the sponsor within 24 hours of awareness whether associated with an adverse event or not.

In addition, overdose and/or medication errors with IMP must also be recorded in the AE page of the eCRF whether associated with an AE or not.

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalizations, the event is serious and must be reported as an SAE.

Rescue medication to reverse the action of GEN1029 is not available. In case of overdose, medication errors, misuse and/or abuse of trial drug patients should receive supportive care according to local guidelines and potential side effects of GEN1029 should be treated symptomatically.

In the event of an overdose, the investigator should:

i. Contact the Medical Monitor immediately.

ii. Closely monitor the patient for any AE/SAE and laboratory abnormalities until GEN1029 can no longer be detected systemically.

iii. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).

iv. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

### 10.4.3 Pregnancy

Any pregnancy that occurs during trial participation must be reported. Pregnant trial patients must be withdrawn from treatment immediately, whereas male patients may continue in the trial should pregnancy of female partners occur. In this case, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy.

Each pregnancy must be reported to sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of one month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the trial and considered by the investigator as possibly related to the IMP, must be promptly reported to sponsor or designee.

### 10.4.4 Timelines for Immediate Reporting

The required timeframes and reporting forms for reporting of serious adverse events (SAEs), non-serious ≥ grade 3 adverse events (NS ≥ grade 3 AEs), overdose, medication errors and pregnancies are presented in Table 10-1.

**Table 10-1 Timeframes for Reporting SAEs, NS ≥ Grade 3 AEs, Overdose, Medication errors and Pregnancies**

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs and NS ≥ grade 3 AEs*** | 24 hours* | Safety Reporting Form | 24 hours* | Site DCF |
| | | | 3 days ** | CDS DCF |
| All events of Overdose and/or Medication errors with IMP | 24 hours* | Safety Reporting Form | 24 hours* | Site DCF |
| | | | 3 days ** | CDS DCF |
| Pregnancy | 24 hours* | Pregnancy Form | 3 days | Updated Pregnancy Form |

DCF=Data Clarification Form; CDS=Corporate Drug Safety

* All new information regarding SAEs (initial and follow-up) must be reported from sites to sponsor within 24 hours.

** Sites should make every effort to respond to follow-up queries from sponsor within 3 business days if information is available.

*** AESIs that are serious or NS ≥grade 3 AEs should follow these reporting timelines.

Completed Safety Reporting Forms, Pregnancy Forms, DCFs or any IMP related SAE occurring any time after the patient has terminated trial participation, must immediately be forwarded to the Safety CRO:

[redacted]

If you have access to a secured email you may forward completed forms to

**Email to:** [redacted]

If you do not have access to a secured email, please forward completed forms to

**Fax: Europe:** [redacted]**, US:** [redacted]

## 10.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is recorded and reported as soon as possible, but within a maximum of 15 calendar days (fatal or life-threatening SUSARs within a maximum of seven days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow–up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional eight days.

The investigator should be aware of local reporting regulations to the IEC/IRB. The safety CRO will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations.

## 10.6 Follow-Up on Adverse Events

All AEs should be followed until they are resolved or until the safety follow-up visit, whichever comes first. At least possibly related non-serious ≥ grade 3 AEs and SAEs still ongoing after end of trial should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

## 10.7 Warnings and Precautions

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided investigator's brochure (IB). Additional safety information collected between IB updates will be communicated in the form of investigator notifications. This information will be included in the patient informed consent and should be discussed with the patient during the trial as needed.

## 10.8 Data Monitoring Committee

This trial will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the trial. The DMC will consist at a minimum of two physicians with appropriate disease area qualifications and, where applicable, a statistician. The functions and responsibilities of the DMC will be described in the DMC Charter, which will be approved by the DMC.

During the dose escalation phase, the DMC will be responsible for reviewing safety and pharmacokinetic data after completion of the cohort on each dose-level. A DMC meeting including both an open and closed session will be held in order to discuss data. During the open session, sponsor employees and investigators will participate together with the DMC. During the closed session, only DMC members will participate. After the closed session, the sponsor will be informed of the DMC's recommendations. The sponsor safety committee will hereafter meet to evaluate the recommendations provided by the DMC and decide whether the dose of IMP should be escalated, de-escalated or held at same dose-level.

During the expansion phase of the trial, the DMC may meet at regular intervals, as defined in the DMC charter.

The DMC will also review the safety, pharmacokinetic and efficacy data at the end of the trial in order to provide an overall Risk Benefit assessment, as defined in the DMC charter.

# 11 STATISTICS

All statistical analyses will be performed by a Contract Research Organization (CRO), under the direction of sponsor personnel.

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All presentations will be done separately for the dose escalation part and the expansion part.

In the reporting of the dose escalation part tables will report by cohort while in the expansion part tables will report by indication.

All data will be listed. Baseline is defined as the latest available measurement made before the first treatment with IMP.

A patient will be considered as having completed the trial when all planned trial visits have been performed.

## 11.1 Analysis Sets

### 11.1.1 Full Analysis Set

The full analysis set (FAS) and safety set are defined in the same way and comprise all subjects who received at least 1 dose of trial treatment. Subjects will be analyzed according to the actual trial treatment received.

### 11.1.2 Safety Set

See the definition of the FAS.

### 11.1.3 Per-Protocol Set

Not applicable.

### 11.1.4 Dose-Determining Analysis Set

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

## 11.2 Patient Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term.

## 11.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to GEN1029 as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the IMP will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system, by dose cohort.

## 11.4 Analysis of Dose Escalation Part

### 11.4.1 Primary Objectives

The primary objectives are to:

- Determine the MTD and the recommended Phase 2 dose (RP2D)
- Establish the safety profile of GEN1029.

#### *11.4.1.1 Primary Endpoints*

- Number of DLTs during the DLT period (initial 28 days of treatment). See Section 4.3 for how the MTD will be determined.
- Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

  The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by System Organ Class (SOC) and or Preferred Term (PT), severity (CTCAE grade), type of adverse event, and relationship to IMP.

  SAEs, non-serious AEs and AEs of special interest (AESI) during the on-treatment period will be tabulated.

  All deaths (on-treatment and post-treatment) will be summarized.

  All AEs, deaths and SAEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

  Further summaries of AEs will be specified in the statistical analysis plan.

### 11.4.2 Secondary Safety Objectives

#### *11.4.2.1 Clinical Safety Data*

Liver toxicity will be described separately as *a priori* this is the most relevant potential safety concern.

#### *11.4.2.2 Laboratory Safety Data*

Grading of laboratory values will be assigned programmatically as per the National Cancer Institute's CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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 CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by the CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by the CTCAE:

- Shift tables using the low/normal/high/ (low and high) (or other project-specific) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

#### *11.4.2.3 Other Safety Data*

**ECG**

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each patient during the trial in accordance with Table 1-2 (dose escalation part) and Table 1-7 (expansion part). ECG data will be read and interpreted centrally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced.

**Vital signs**

Data on vital signs will be tabulated and listed; notable values will be flagged.

### 11.4.3 Pharmacokinetics

Individual curves of plasma/serum concentration of each component of GEN1029 including information on actual dose, will be presented for all patients. All available data will be shown in these figures. Concentrations below the limit of quantitation will be set to LLOQ/2.

PK parameters (Table 11-1) will be calculated based on non-compartmental methods and will be calculated separately for Cycle 1, Cycle 2 and Cycle 3.

The relation between derived PK parameters and covariates such as actual dose, weight and dose, and selected laboratory parameters will be evaluated graphically.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Further exploratory analyses of PK data may be performed.

**Table 11-1 Non-compartmental Pharmacokinetic Parameters**

| | |
|---|---|
| $AUC_{0\text{-}14days}$ | The AUC from time zero to day 14 (mass x time x volume-1) |
| $AUC_{inf}$ | The AUC from time zero to infinity (mass x time x volume-1) |
| $AUC_{last}$ | The AUC from time zero to last quantifiable measurement |
| $C_{max}$ | The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration |
| $T_{max}$ | The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration |
| $T_{1/2}$ | The elimination half-life associated with the terminal slope ($\lambda z$) of a semi logarithmic concentration-time curve |
| CL | The total body clearance of drug from the plasma |

### 11.4.4 Immunogenicity of GEN1029

As a result of Immunogenicity analysis samples will be scored ADA positive or ADA negative and subsequently reported. From positive ADA samples titer values and neutralizing antibody scores (postivie or negative) will be determined and reported. ADA negative samples with drug on board above the drug tolerance limits of the ADA method will be scored inconclusive due to possible drug intereference. The association between positive/non-positive ADA and PK (pre-dose, AUC, Cmax), major safety signals (CTCAE ≥ grade 3) and efficacy information (change in tumor size by CT scan) will be explored.

### 11.4.5 Secondary Efficacy Objective

The secondary efficacy objective is to further evaluate the anti-tumor activity of GEN1029.

#### *11.4.5.1 Secondary Efficacy Endpoints*

##### *11.4.5.1.1 Definition of Response*

RECIST criteria (v1.1) will be used to define response. Based on the definition of response (Table 11-2) and the combined evaluation (see Table 1 in Eisenhauer et al., 2009), each patient will be assigned 1 of the following categories at each CT scan visit and as Best Overall Response (BOR):

1) CR

2) PR

3) SD

4) PD or

5) Not Evaluable

BOR is the best response recorded from the start of the treatment until disease progression/recurrence (the smallest measurements recorded since the treatment started will be used as the reference for PD).

**Table 11-2 Definition of Response (RECIST Criteria v1.1)**

| | Category | Criteria |
|---|---|---|
| *Based on target lesions* | Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm. |
| | Partial Response (PR) | ≥ 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LDs. |
| | Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of LDs while in trial. |
| | Progressive Disease (PD) | ≥ 20% (and ≥ 5 mm) increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the target LDs recorded while in trial or the appearance of 1 or more new lesions. |
| | NE | Not evaluable |
| *Based on non-target lesions* | CR | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). |
| | SD | Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits. |
| | PD | Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. |
| | NE | Not evaluable |

LD =Longest Diameter; SD for non-target lesions defined as "Non-CR/Non-PD" by Eisenhauer et al., 2009.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation

SD: follow-up measurements occurring at least 6 weeks (± 7 days) after first treatment must have met the SD criteria at least once.

PR and CR: no formal confirmation response is required. However, a repeat CT-scan may be performed no less than 4 weeks after the criteria for response is met to substantiate/confirm CT response. If the response is still present this will be called confirmed response/confirmed complete response.

Reporting of Objective Response Rate (ORR) results:

Patients in response categories 1 and 2 are considered responders and patients in response categories 4 and 5 are considered as failing to respond to treatment. Patients in response categories 1, 2 and 3 are considered to be in disease control.

Individual patient data listings and summaries of objective response, best overall tumor response and disease control will be presented by dose cohort/indication and total.

The maximal response (maximal reduction in the sum of the LD in the target lesions) in target lesions at any time on trial will be reported using waterfall plots.

*11.4.5.1.2 Progression-free Survival*

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

(Eisenhauer et al., 2009). PFS will be censored in accordance with Table C1 in Appendix C in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-small Cell Lung Cancer Drugs and Biologics (FDA 2015).

Progression-free survival will be derived for all patients and presented graphically as well as summarized using survival analysis methods.

The quartile estimates of PFS from the Kaplan Meier product limit algorithm will be presented. The 2-sided 95% confidence interval will be presented as well. 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.

*11.4.5.1.3 Overall Survival*

Overall survival is defined as the number of days from Day 1 in Cycle 1 to death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

Overall survival will only be analyzed for the expansion part using the same techniques and presented in the same manner as PFS.

*11.4.5.1.4 Duration of Response*

Duration of response (DoR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) and is defined as the number of days from the first documentation of objective tumor response (CR or PR) to the date of first PD or death due to underlying cancer. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment.

DoR will be summarized in the same way as PFS.

*11.4.5.1.5 Time to Response*

Time to response (TTR) is defined as the number of days from Day 1 in Cycle 1 to the first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per local review and according to RECIST 1.1.

The TTR calculations is restricted to those subjects in the FAS with a confirmed PR or CR. TTR will be listed and summarized by treatment group.

*11.4.5.1.6 Tumor Shrinkage*

Tumor shrinkage (based on CT-scan evaluations) will be listed and summarized.

## 11.5 Analysis of Expansion Part

In general, the analysis methodology for the endpoints of the dose expansion part will be the same as the one used for the corresponding endpoints in the dose escalation part, only summarizing by cohort (which is regimen and indication specific).

### 11.5.1 Primary Objective

The primary objective of the expansion part is to evaluate the ORR by cohort.

#### *11.5.1.1 Primary Endpoint*

The primary endpoint for the dose expansion part is the ORR as defined in Section 11.4.5.1. The primary analysis will be based on the confirmed responses. Supportive to this, an analysis using both confirmed and unconfirmed response will be carried out.

#### *11.5.1.2 Statistical Hypothesis, Model and Method of Analysis*

If only one regimen is evaluated for an indication there is no formal hypothesis to be tested in the dose expansion part. The ORR will be estimated with exact 2-sided 95% confidence intervals (CIs) for each arm using the Clopper-Pearson method. Other response rates such as BOR and rate of disease control will be reported similarly.

Should there be more than one regimen evaluated for an indication the endpoints will be reported per regimen (and indication) as described above. In addition for each indication tested in multiple regimens, a logistic regression model, adjusted for screening ECOG score and regimen (with two possible levels) will be used to report the comparative efficacy of the evaluated regimens.

The odds ratio in response rates between two initiated regmeins within one indication will be tested at the two-sided 5% Type-I error rate level.

The totality of the data together with the planned comparison will guide the selection of a regimen for further development.

#### *11.5.1.3 Handling of Missing Values/Censoring/Discontinuations*

Any patients with missing information regarding response to treatment will be counted as non-responders.

### 11.5.2 Secondary Efficacy Objective

The secondary efficacy objectives and endpoints in the dose expansion part are (besides the ORR that is primary endpoint) those that are described in Section 11.4.4.

### 11.5.3 Secondary Safety Objective

The safety objective with the expansion part is to further describe the safety profile of GEN1029. AEs and laboratory parameters will be reported as described in 11.4.1 and 11.4.2. All listings and tables will be presented by cohort in the expansion part.

### 11.5.4 Pharmacokinetics

PK parameters will be calculated as feasible, depending on the availability of the data.

### 11.5.5 Immunogenicity of GEN1029

Immunogenicity of GEN1029 in the expansion part will be reported as described in Section 11.4.4. The association between positive/non-positive ADA and PK (pre-dose, AUC, Cmax), major safety signals (CTCAE ≥ grade 3) and efficacy information (change in tumor size by CT scan) will be explored and reported as feasible.

## 11.6 Explorative Analysis

### 11.6.1 Biomarkers

Biomarker analyses in this study are exploratory and focused on identifying potential pharmacodynamic (PD) or predictive markers that may be further validated in prospective trials with GEN1029 (HexaBody-DR5/DR5), as well as to further understand the biological impact of GEN1029 on downstream pathway activities and tumor cell processes.

Biomarkers, such as DR5 expression (protein or [redacted]) and immune cell populations, will be tabulated for all patients who had samples collected and testing performed. Biomarker assessments will be summarized by time point using descriptive statistics. Changes in biomarker parameters, as compared to baseline, will be calculated and analyzed for association with relevant clinical endpoints such as objectives response, PFS, OS. Subgroup analysis may be performed to evaluate differences between biomarker parameters in groups of responders and non-responders or other clinically relevant subgroups, and to evaluate the associations between biomarker parameters and specific clinical endpoints. Univariate and multivariate analyses, as well as pathway analyses may also be performed if applicable. Any pharmacodynamic measures will be listed, tabulated, and plotted as appropriate. Patients may be grouped by cohort, regimen, or clinical response.

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

### 11.6.2 Metabolic Response in the Tumors

As an exploratory analysis the metabolic response in the tumors will be evaluated following the Positron Emission Tomography Response Criteria In Solid Tumors (PERCIST 1.0), see (Wahl et al., 2009). The metabolic endpoint is the standardized uptake volume corrected for body lean mass (SUL). Percentage change from screening in SUL will be summarized by scan visit for the hottest lesion. 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).

### 11.6.3 [redacted]

[redacted]

## 11.7 Interim Analyses

In the expansion part each cohort will contain of up to 4 stages, targeting a maximum sample size of 60 patients. For each stage, the success of the stage is predicted. If the predictive probability of success is less than 10% the stage is not further explored in order not to expose patients to in-efficacious doses based on an interim futility analysis, as detailed in Table 11-3 and Table 11-7. The interim analysis divides each cohort into a maximum of 4 stages in total. The analysis will be based on both the uncomfirmed and confirmed CR or PR observed when the interim-sample size is accomplished.

**Table 11-3: Cohort stages and Sample Sizes**

| Stage | Sample size at interim (n) | Sample size at end of stage (N) |
|---|---|---|
| 1 | Not applicable | 10 |
| 2 | 10 | 20 |
| 3 | 20 | 40 |
| 4 | 40 | 60 |

At the interim, a Bayesian predictive probability approach will be used to evaluate the futility criteria (Lee and Liu, 2008). By using predictive probabilities, it is possible to directly assess the outcome of a trial (in this case stage), if continued to its end (Saville et al., 2014). Given the interim data, the predicted probability is a *weighted average* of posterior probabilities, as if calculated given the outcome at the end of the stage. The weights correspond to how likely each outcome is. The predictive probabilities may in fact be calculated at any time point during Stage 2, 3 and 4.

As originally suggested by Lee and Liu (Lee and Liu, 2008) the predictive probability approach is operated with respect to a historical response rate ($p_0$) only. However, as applied here, also a target response rate ($p_1$) that warrants further evaluation of the drug, is being used to evaluate futility. In general, this decreases the Type I error rate and increases the Type II error rate as more studies would be stopped. For more details, please see Section 11.8.2.

For Stage 2, the success criteria for each cohort is a posterior density (given completion of stage) of the responder rate that exceeds $p_0$ by [redacted] and $p_1$ by [redacted]. Stage 2 is further explored if the predictive probability of success, as calculated at end of Stage 1, is greater than [redacted]. Similar considerations yield for Stage 3 and 4, but the success criteria are a posterior density of the responder rate that exceeds $p_0$ by [redacted] and $p_1$ by [redacted]. The success criteria based on the posterior probabilities are illustrated in Figure 11-1, where the more conservative expansion strategy being used for Stage 3 and 4 as compared to Stage 2 becomes clear.

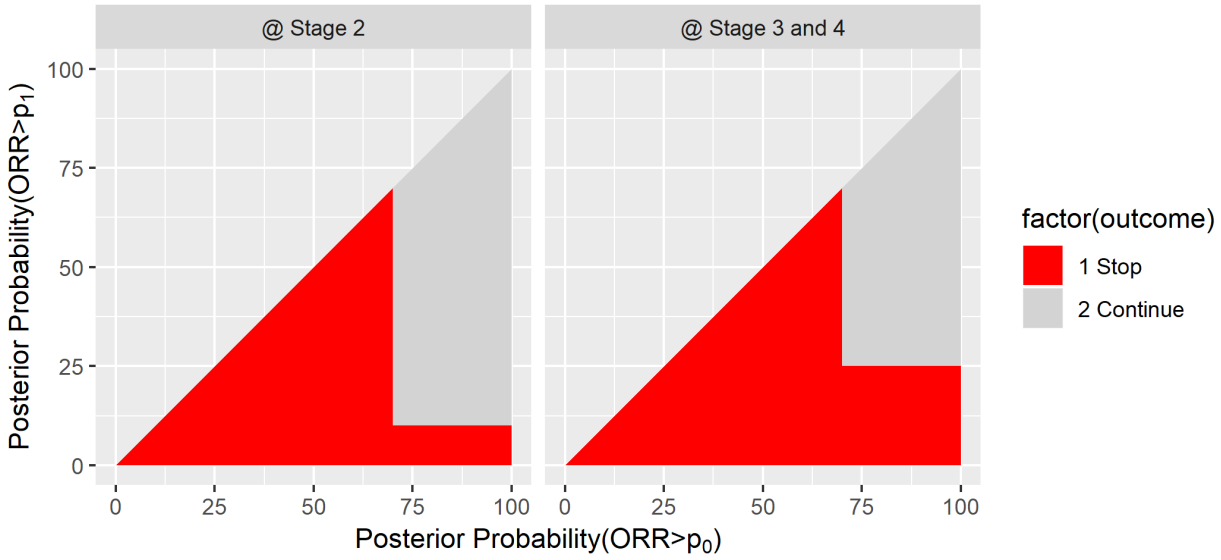



**Figure 11-1: Success criteria based on posterior probabilities**

In addition to the interim analysis for futility, interim data from the trial may be presented at scientific meetings.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

## 11.8 Sample Size Calculation

### 11.8.1 Dose Escalation Part

The actual number of patients depends on the true relationship between dose and DLT probability and could range between 10 to 25 patients for a given scenario, as presented below. Similarly, the number of dose levels explored depends on the toxicity profile. Up to 18 additional patients may be recruited to dose levels below MTD where it is found relevant to further explore the efficacy.

In total up to approximately 100 patients are planned to be recruited during the escalation part. The patients are shared between the Biweekly and Priming Regimens.

Table 11-4 below shows 6 different scenarios for the probability of a patient having a DLT at 6 dose levels, which in our case could be the 6 lowest dose levels. For each scenario the total expected number of patients, when following the mBOIN design, is shown in the rightmost column. For each of the dose levels and scenarios, first the probability of a DLT and then the expected number of patients at the dose level is shown. The mBOIN design algorithm behaves as intended with most patients exposed to the dose levels with DLT probability close to the target DLT rate and fewer patients exposed in total if the toxicity is high at the lowest dose levels.

**Table 11-4 Modified BOIN Design Characteristics for 6 Dose Levels**

| | | Probability(DLT) and expected number of patients at dose level | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| **Scenario** | | **Dose = 1** | **Dose = 2** | **Dose = 3** | **Dose = 4** | **Dose = 5** | **Dose = 6** | **No. Pat.** |
| 1 | Pr(DLT) | 0% | 1% | 2% | 4% | 8% | 16% | |
| | No. Pat. | 1.0 | 3.1 | 3.2 | 3.5 | 4.2 | 8.7 | 23.8 |
| 2 | Pr(DLT) | 1% | 2% | 4% | 8% | 16% | 32% | |
| | No. Pat. | 1.1 | 3.2 | 3.5 | 4.2 | 6.2 | 7.2 | 25.3 |
| 3 | Pr(DLT) | 5% | 15% | 25% | 40% | 50% | 60% | |
| | No. Pat. | 1.8 | 5.6 | 6.5 | 4.6 | 1.5 | 0.2 | 20.2 |
| 4 | Pr(DLT) | 20% | 35% | 50% | 60% | 65% | 70% | |
| | No. Pat. | 4.9 | 6.8 | 2.7 | 0.4 | 0.0 | 0.0 | 14.9 |
| 5 | Pr(DLT) | 30% | 40% | 50% | 60% | 70% | 75% | |
| | No. Pat. | 5.4 | 5.5 | 1.8 | 0.3 | 0.0 | 0.0 | 13.0 |
| 6 | Pr(DLT) | 1% | 1% | 1% | 60% | 65% | 70% | |
| | No. Pat. | 1.0 | 3.1 | 8.3 | 6.7 | 0.4 | 0.0 | 19.6 |

If 4 dose levels are explored the pattern identified repeats, but the total number of patients is lower, see Table 11-5.

**Table 11-5: Modified BOIN Design Characteristics for 4 Dose Levels**

| | | Probability (DLT) and expected number of patients* at dose level | | | | Total |
|---|---|---|---|---|---|---|
| **Scenario** | | **Dose = 1** | **Dose = 2** | **Dose = 3** | **Dose = 4** | **No. Pat.** |
| 1 | Pr(DLT) | 2% | 4% | 8% | 16% | |
| | No. Pat. | 3.2 | 3.5 | 4.2 | 8.6 | 19.5 |
| 2 | Pr(DLT) | 4% | 8% | 16% | 32% | |
| | No. Pat. | 3.4 | 4.2 | 6.1 | 6.9 | 20.6 |
| 3 | Pr(DLT) | 15% | 25% | 40% | 50% | |
| | No. Pat. | 5.2 | 6.4 | 4.3 | 1.3 | 17.3 |
| 4 | Pr(DLT) | 35% | 50% | 60% | 65% | |
| | No. Pat. | 6.4 | 2.9 | 0.5 | 0.0 | 9.9 |
| 5 | Pr(DLT) | 40% | 50% | 60% | 70% | |
| | No. Pat. | 6.0 | 2.3 | 0.4 | 0.0 | 8.7 |
| 6 | Pr(DLT) | 1% | 60% | 65% | 70% | |
| | No. Pat. | 8.3 | 6.6 | 0.4 | 0.0 | 15.4 |

* Based on 50,000 simulations

### 11.8.2 Expansion Cohorts

The maximum sample size for each expansion cohort is 60 patients, divided over up to 4 stages as described in Section 11.7. The historical ($p_0$) and target ($p_1$) response rates being used to evaluate the operating characteristics are presented in Table 11-6.

**Table 11-6: Response Rate Characteristics by Indication**

| | Colorectal Cancer (CRC) | Triple Negative Breast Cancer (TNBC) | Other indications* |
|---|---|---|---|
| Historical response rate ($p_0$) | 2% | 7.5% | 10% |
| Target response rate that warrants further evaluation of the drug ($p_1$) | 15% | 20% | 25% |

*NSCLC, RCC, gastric, pancreas or urothelial cancer

Given $p_0$ and $p_1$ it is possible to prospectively calculate the required number of responders to further explore each stage as presented in Table 11-7. A priori it is assumed that the response rate is distributed as Beta(0.2, 0.8).

**Table 11-7: Continuation Criteria in Terms of Number of Responders**

| Indication | Stage 2 (n=10; N=20) | Stage 3 (n=20; N=40) | Stage 4 (n=40; N=60) |
|---|---|---|---|
| CRC | ≥1/10 | ≥2/20 | ≥4/40 |
| TNBC | ≥1/10 | ≥2/20 | ≥6/40 |
| Other | ≥1/10 | ≥3/20 | ≥7/40 |

Numbers of responses serve as a guideline; however, the totality of efficacy data will be considered when making decisions to terminate or continue an arm.

The operating characteristics in terms of the probability for not exploring a stage, and the probability that the estimated response rate is greater than $p_1$ (if the stage is completed) are presented in Table 11-8. The operating characteristics are based on 50,000 simulations of each assumption of true response rate. For the colorectal cohort there is a high probability to stop under $p_0$ early on, which partly is due to the requirement to beat $p_1$ (15%) with some confidence as well. This requirement has less impact on the TNBC cohort and the other indications (NSCLC, RCC, gastric, pancreatic and urothelial cancer) for which the stopping rate is lower.

**Table 11-8: Operating Characteristics in Terms of a) Probability for not Exploring each Stage; and b) the Probability that the Estimated Response Rate is Greater than $p_1$ (if the Stage is Completed)**

| Indication | True ORR | Stage 2 (n=10; N=20) | | Stage 3 (n=20; N=40) | | Stage 4 (n=40; N=60) | |
|---|---|---|---|---|---|---|---|
| | | a) | b) | a) | b) | a) | b) |
| CRC ($p_0$=2%; $p_1$=15%) | 2% | 81% | 1% | 94% | 0% | 99% | 0% |
| | 15% | 20% | 56% | 18% | 54% | 13% | 55% |
| TNBC ($p_0$=7.5%; $p_1$=20%) | 7.5% | 46% | 6% | 55% | 1% | 92% | 0% |
| | 20% | 11% | 58% | 7% | 56% | 16% | 54% |
| Other* ($p_0$=10%; $p_1$=25%) | 10% | 35% | 4% | 68% | 1% | 90% | 0% |
| | 25% | 6% | 58% | 9% | 55% | 10% | 54% |

*NSCLC, RCC, gastric, pancreas or urothelial cancer

### 11.8.3 Statistical Power for Comparing Two Regimens within one Indication

If more than one regimen is evaluated for the same indication in two different cohorts in the expansion part, the response rates in the two cohorts will be compared as described in Section 11.5.1.2). The power (probability of being able to detect a statistically significant difference between two regimens *A* and *B* with underlying true response rates $\theta_A$, and $\theta_B$, respectively) for different stages of sample sizes, is presented in Table 11-9. It is noted that the sample sizes at the final analysis may not be equal.

For each scenario, 50,000 trials were simulated, and the logistic regression model (see Section 11.5.1.2) was estimated using SAS PROC GENMOD to test the significance (at the one-sided Type I error rate of 5%) of Regimen *B* being better than Regimen *A*. The power is the percentage of trials were the p-value of the regimen effect was <5% (one-sided). The simulations are constrained on having at least two responders in each cohort at N=20, and at least four responders in each cohort at N=40 and N=60. This reflects the expansion strategy within each cohort and implies that there is some similarity imposed on the realized trials that impacts the following power assessment.

**Table 11-9: Power (Probability to Detect a Significant Difference Between two Regimens)**

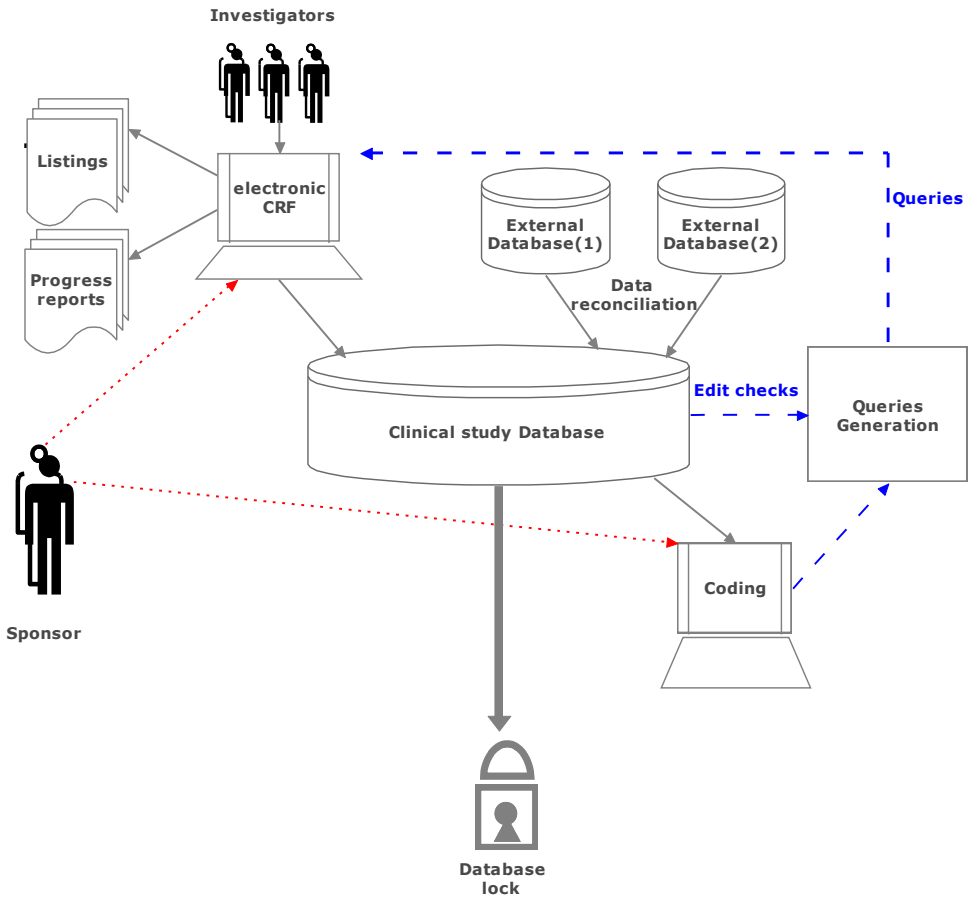
| $\theta_A$ | $\theta_B$ | Power @$N_A$=$N_B$=20 | Power @$N_A$=$N_B$=40 | Power @$N_A$=$N_B$=60 |
|---|---|---|---|---|
| 10% | 15% | 0% | 0% | 6% |
| 10% | 20% | 2% | 5% | 24% |
| 10% | 25% | 6% | 18% | 52% |
| 15% | 20% | 1% | 3% | 9% |
| 15% | 25% | 4% | 11% | 26% |
| 15% | 30% | 10% | 27% | 49% |
| 20% | 25% | 2% | 5% | 9% |
| 20% | 30% | 6% | 15% | 23% |
| 20% | 35% | 13% | 30% | 45% |
| 25% | 30% | 4% | 7% | 8% |
| 25% | 35% | 8% | 15% | 22% |

Due to foreseen scenarios and the constraint imposed on the simulations, the probability to conclude that there is a significant improvement with Regimen *B* over Regimen *A* is low to moderate. The power ranges from 0% up to 52%, depending on the underlying assumed response rates and the sample sizes. This can also be expressed as that the probability of not being able to detect a difference based on the statistical model lies between 48 and 100%.

# 12 DATA HANDLING AND RECORD KEEPING

## 12.1 Data Flow

**Figure 12-1 Outline of Data Flow**




## 12.2 Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: patient identification, eligibility, and trial identification; trial discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; trial drug administration information; and date of trial completion and reason for early discontinuation of trial drug or withdrawal from the trial, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document).

## 12.3 Case Report Form Completion

Case report forms are provided for each patient in electronic format.

Electronic data capture (EDC) will be used for this trial. The trial data will be transcribed by trial-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the trial site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the patient's source documentation. All data relating to the trial must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Trial site personnel must complete the eCRF as soon as possible after a patient visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements, such as ECOG will be completed by the same individual who made the initial baseline determinations whenever possible.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel. The investigator must verify that all data entries in the eCRFs are accurate and correct. If necessary, queries will be generated in the EDC tool.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in three different ways:

- Trial-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- The monitor can generate a query for resolution by the trial-site personnel.
- The clinical data manager can generate a query for resolution by the trial-site personnel.
- The sponsor can generate a query for resolution by the trial-site personnel.

## 12.4 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, periodic monitoring visits by the sponsor and direct transmission of clinical laboratory data from a central laboratory, ECG data from ECG vendor and CT-scans and reads from the scan vendor (expansion part only) into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed by the trial-site personnel before the start of the trial. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database they will be verified for accuracy and consistency with the data sources.

## 12.5 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each patient, as well as all trial documents as specified in ICH/GCP guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by

the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

# 13 ETHICS

## 13.1 Trial-Specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure.

This trial is being conducted to evaluate the multiple-dose pharmacokinetics of GEN1029 in patients with malignant solid tumors. The results of this trial will provide useful information on the pharmacokinetics of GEN1029. These data are also needed to assist in developing dosage adjustment guidance for future trials.

As with all clinical and pharmacokinetic trials, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of intravenous indwelling catheters is permitted in this trial. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacokinetics of GEN1029. This minimizes the total volume of blood (approximately 1300 mL for the first 24 cycles) collected from each patient during the trial.

Potential patients will be fully informed of the risks and requirements of the trial and, during the trial, patients will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only patients who are fully able to understand the risks, benefits, and potential adverse events of the trial, and provide their consent voluntarily will be enrolled.

## 13.2 Regulatory Ethics Compliance

### 13.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that originated in the Declaration of Helsinki 2013, and that the trial data are credible.

### 13.2.2 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the ICF, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

Where applicable, interim reports on the trial and/or reviews of trial progress will be submitted by the investigator to the IEC/IRB at intervals stipulated in the IEC/IRB guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

### 13.2.3 Informed Consent

Each patient must give written consent according to local requirements after the nature of the trial has been fully explained. The ICF(s) must be signed before performance of any trial-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the patient can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines including ICH-GCP E6(R2), applicable regulatory requirements, and sponsor policy.

Before enrollment in the trial, the investigator or an authorized member of the trial-site personnel must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care will receive for the treatment of their disease. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the patient is authorizing such access, and agrees to allow his or her trial physician to re-contact the patient for the purpose of obtaining consent for additional safety evaluations, if needed.

The patient will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the patient.

Patients will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the trial is appropriately obtained, the patient will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the trial. A copy of this signed ICF will be given to the patient.

Where local regulations require, a separate ICF may be used for the required DNA component of the trial.

### 13.2.4 Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this trial will be limited to those data that are necessary to fulfill the purpose and the objectives of the trial.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

The informed consent obtained from the patient includes explicit consent for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has a number of rights. Among these the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Further, the patient has the right to withdraw its consent to process his or her personal data. Personal data collected prior to the patients withdrawal will still be used and will not be withdrawn or deleted but no new personal data will be collected or processed for trial purposes unless it relates to an already reported side effect. Reasonable steps will be taken by the Investigator to respond to such requests, taking into consideration the nature of the request, the conditions of the trial, the applicable laws and regulations and the investigators obligations stated in the clinical trial agreement (including the data processor agreement).

Exploratory biomarker research is not conducted under standards appropriate for the return of data to patients. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to patients or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

### 13.2.5 Long-Term Retention of Samples for Additional Future Analyses

If it is determined at any time before trial completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. [redacted]

In this case, such analyses would be specific to research related to the trial drug or diseases being investigated in the clinical trial.

# 14 ADMINISTRATIVE PROCEDURES

## 14.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see contact information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

## 14.2 Regulatory Documentation

### 14.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A trial may not be initiated until all local regulatory requirements are met.

## 14.3 Patient Identification, Enrollment, and Screening Logs

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the trial. This document will be reviewed by the sponsor trial-site contact for completeness.

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the trial file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the trial will identify patients by patient identification and date of birth. In cases where the patient is not randomized into the trial, the date seen and date of birth will be used.

The investigator must also complete a patient screening log, which reports on all patients who were seen to determine eligibility for inclusion in the trial.

## 14.4 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the

monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet/talk with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, trial-site personnel will be available to provide an update on the progress of the trial at the site.

### 14.5 On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must, however, be respected. The investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

### 14.6 Publication

All information, including but not limited to information regarding GEN1029 or the sponsor's operations (e.g. patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1029, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be reported in a CTR generated by the sponsor and will contain eCRF data from all trial sites that participated in the trial and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the CTR has been issued will be reported in a separate report and will not require a revision of the CTR. Trial patient identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2016), the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish trial site-specific data after the primary data are published. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work (ICMJE, 2010).

## 14.7 Registration of Clinical Trials and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

## 15 REFERENCES

Amarante-Mendes, G. P. & Griffith, T. S. (2015). Therapeutic applications of TRAIL receptor agonists in cancer and beyond. *Pharmacol.Ther., 155,* 117-131.

Ashkenazi, A. (2015). Targeting the extrinsic apoptotic pathway in cancer: lessons learned and future directions. *J Clin Invest, 125,* 487-489.

Battisti, W. P., Wager, E., Baltzer, L., Bridges, D., Cairns, A., Carswell, C. I. et al. (2015). Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. *Annals of Internal Medicine (Philadelphia, PA), 163,* 461-464.

Burvenich, I. J., Lee, F. T., Cartwright, G. A., O'Keefe, G. J., Makris, D., Cao, D. et al. (2013). Molecular imaging of death receptor 5 occupancy and saturation kinetics in vivo by humanized monoclonal antibody CS-1008. *Clin Cancer Res., 19,* 5984-5993.

Camidge, D. R., Herbst, R. S., Gordon, M. S., Eckhardt, S. G., Kurzrock, R., Durbin, B. et al. (2010). A phase I safety and pharmacokinetic study of the death receptor 5 agonistic antibody PRO95780 in patients with advanced malignancies. *Clin Cancer Res., 16,* 1256-1263.

de Jong, R. N., Beurskens, F. J., Verploegen, S., Strumane, K., van Kampen, M. D., Voorhorst, M. et al. (2016). A Novel Platform for the Potentiation of Therapeutic Antibodies Based on Antigen-Dependent Formation of IgG Hexamers at the Cell Surface. *PLoS.Biol., 14,* e1002344.

Diebolder, C. A., Beurskens, F. J., de Jong, R. N., Koning, R. I., Strumane, K., Lindorfer, M. A. et al. (2014). Complement is activated by IgG hexamers assembled at the cell surface. *Science, 343,* 1260-1263.

Doi, T., Murakami, H., Ohtsu, A., Fuse, N., Yoshino, T., Yamamoto, N. et al. (2011). Phase 1 study of conatumumab, a pro-apoptotic death receptor 5 agonist antibody, in Japanese patients with advanced solid tumors. *Cancer Chemotherapy and Pharmacology (Berlin), 68,* 733-741.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R. et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur.J Cancer, 45,* 228-247.

FDA (2015). Clinical Trial Endpoints for the Approval of NonSmall Cell Lung Cancer Drugs and Biologics. Guidance for Industry. Available at: https://www.fda.gov/media/116860/download. Accessed October 2019.

Forero, A., Bendell, J. C., Kumar, P., Janisch, L., Rosen, M., Wang, Q. et al. (2017). First-in-human study of the antibody DR5 agonist DS-8273a in patients with advanced solid tumors. *Invest New Drugs*.

Forero-Torres, A., Shah, J., Wood, T., Posey, J., Carlisle, R., Copigneaux, C. et al. (2010). Phase I trial of weekly tigatuzumab, an agonistic humanized monoclonal antibody targeting death receptor 5 (DR5). *Cancer Biother.Radiopharm., 25,* 13-19.

Gieffers, C., Kluge, M., Merz, C., Sykora, J., Thiemann, M., Schaal, R. et al. (2013). APG350 induces superior clustering of TRAIL receptors and shows therapeutic antitumor efficacy independent of cross-linking via Fcgamma receptors. *Mol.Cancer Ther., 12,* 2735-2747.

Herbst, R. S., Kurzrock, R., Hong, D. S., Valdivieso, M., Hsu, C. P., Goyal, L. et al. (2010). A first-in-human study of conatumumab in adult patients with advanced solid tumors. *Clin Cancer Res., 16,* 5883-5891.

Huet, H. A., Growney, J. D., Johnson, J. A., Li, J., Bilic, S., Ostrom, L. et al. (2014). Multivalent nanobodies targeting death receptor 5 elicit superior tumor cell killing through efficient caspase induction. *MAbs., 6,* 1560-1570.

Ichikawa, K., Liu, W., Zhao, L., Wang, Z., Liu, D., Ohtsuka, T. et al. (2001). Tumoricidal activity of a novel anti-human DR5 monoclonal antibody without hepatocyte cytotoxicity. *Nat.Med., 7,* 954-960.

ICMJE (2010). Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication. *J.Pharmacol.Pharmacother., 1,* 42-58.

ICMJE (2016). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Koornstra, J. J., Kleibeuker, J. H., van Geelen, C. M., Rijcken, F. E., Hollema, H., De Vries, E. G. et al. (2003). Expression of TRAIL (TNF-related apoptosis-inducing ligand) and its receptors in normal colonic mucosa, adenomas, and carcinomas. *J Pathol., 200,* 327-335.

Lee, J. J., and Liu, D. D. (2008). A predictive probability design for phase II cancer clinical trials. *Clin Trials 5*, 93-106.

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern.Med., 130,* 461-470.

MacFarlane, M., Ahmad, M., Srinivasula, S. M., Fernandes-Alnemri, T., Cohen, G. M., & Alnemri, E. S. (1997). Identification and molecular cloning of two novel receptors for the cytotoxic ligand TRAIL. *J Biol.Chem., 272,* 25417-25420.

Micheau, O., Shirley, S., & Dufour, F. (2013). Death receptors as targets in cancer. *Br.J Pharmacol., 169,* 1723-1744.

Pan, G., Ni, J., Wei, Y. F., Yu, G., Gentz, R., & Dixit, V. M. (1997). An antagonist decoy receptor and a death domain-containing receptor for TRAIL. *Science, 277,* 815-818.

Papadopoulos, K. P., Isaacs, R., Bilic, S., Kentsch, K., Huet, H. A., Hofmann, M. et al. (2015). Unexpected hepatotoxicity in a phase I study of TAS266, a novel tetravalent agonistic Nanobody(R) targeting the DR5 receptor. *Cancer Chemotherapy and Pharmacology (Berlin), 75,* 887-895.

Piccart, M. J. & Gingras, I. (2016). Breast cancer in 2015: Academic research sheds light on issues that matter to patients. *Nat.Rev.Clin Oncol, 13,* 67-68.

Plummer, R., Attard, G., Pacey, S., Li, L., Razak, A., Perrett, R. et al. (2007). Phase 1 and pharmacokinetic study of lexatumumab in patients with advanced cancers. *Clin Cancer Res., 13,* 6187-6194.

[redacted]

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.

Schneider, P., Bodmer, J. L., Thome, M., Hofmann, K., Holler, N., & Tschopp, J. (1997). Characterization of two receptors for TRAIL. *FEBS Lett., 416,* 329-334.

Sessler, T., Healy, S., Samali, A., & Szegezdi, E. (2013). Structural determinants of DISC function: new insights into death receptor-mediated apoptosis signalling. *Pharmacol.Ther., 140,* 186-199.

[redacted]

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.

Wakelee, H. A., Patnaik, A., Sikic, B. I., Mita, M., Fox, N. L., Miceli, R. et al. (2010). Phase I and pharmacokinetic study of lexatumumab (HGS-ETR2) given every 2 weeks in patients with advanced solid tumors. *Ann.Oncol, 21,* 376-381.

Walczak, H., Degli-Esposti, M. A., Johnson, R. S., Smolak, P. J., Waugh, J. Y., Boiani, N. et al. (1997). TRAIL-R2: a novel apoptosis-mediating receptor for TRAIL. *EMBO J, 16,* 5386-5397.

Wang, S. & El-Deiry, W. S. (2003). TRAIL and apoptosis induction by TNF-family death receptors. *Oncogene, 22,* 8628-8633.

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.

# Appendix 1 Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials



## Recommendations related to contraception and pregnancy testing in clinical trials

### Introduction and scope

The aim of this document is to supplement existing guidelines related to embryofetal risk mitigation and to provide practical guidance on contraception use and pregnancy testing in clinical trials. It is not the aim of this document to discuss when women of childbearing potential may be included in clinical trials or to discuss treatment of pregnant women with investigational medicinal products (IMPs) in clinical trials. In this guidance document it is assumed that treatment with the IMP will be interrupted in case of pregnancy. For this reason the relevant data for risk assessment cover risks in the early stages of pregnancy only. The recommendations in this document are intended for sponsors of clinical trials seeking to meet regulatory expectations for submission of application dossiers for clinical trials with IMPs in accordance with Directive 2001/20/EC. Deviations from these recommendations should be justified by the sponsor. This guidance applies to all IMPs, with the exception of advanced therapy medicinal products (ATMP). For ATMP products, embryofetal risk assessment and the need for contraception and pregnancy testing recommendations should be considered on a case-by-case basis.

This document should be read in conjunction with the published guidelines and in particular the following:

- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3 (R2)), EMA/CPMP/ICH/286/95
- Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (ICH S6 (R1)), EMA/CHMP/ICH/731268/1998
- Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9), EMA/CHMP/ICH/646107/08
- Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2 (R1)), EMEA/CHMP/ICH/126642/2008
- General Considerations for Clinical Trials (ICH E8), CPMP/ICH/291/95
- Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11), CPMP/ICH/2711/99
- Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling, EMEA/CHMP/203927/2005
- Guideline on the Summary of Product Characteristics – SmPC (September 2009). In EUDRALEX – Volume 2C - Regulatory Guidelines in Notice to applicants and regulatory guidelines for medicinal products for human use

- Guideline for Good Clinical Practice (ICH E6), CPMP/ICH/135/95
- Note for Guidance on Development Safety Update Reports (ICH E2F), EMA/CHMP/ICH/309348/2008
- U.S. Medical Eligibility Criteria for Contraceptive Use, 2010; Adapted from the World Health Organization (WHO) May 28, 2010 / Vol. 59" – with special regard to table 1
- Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data, EMEA/CHMP/313666/2005
- Guideline on the Investigation of Drug Interactions, CPMP/EWP/560/95/Rev.1 Corr.
- U.S. Selected Practice Recommendations for Contraceptive Use, 2013
- Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products, EMEA/CHMP/SWP/28367/07
- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7, Step 3)

**Main text**

## 1 Definitions

### 1.1 Definition of women of childbearing potential and of fertile men

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

### 1.2 Definition of end of relevant systemic exposure

For the purpose of this document the end of relevant systemic exposure is defined as the time point where the IMP, including any active or major metabolites, has decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity. In case reproductive toxicity studies are available, this systemic exposure level should include a sufficient exposure margin to the no-observed adverse effect level (NOAEL) in the non-clinical reproductive toxicity studies. In the absence of reproductive toxicity studies, such considerations may be based on the principles of a minimal anticipated biological effect level (MABEL) or other accepted principles. In case of a genotoxic IMP the principle of threshold of toxicological concern (TTC) should be considered.

## 2 How to proceed from risk assessment to practical contraception recommendations

### 2.1 Risk Assessment

#### 2.1.1 IMPs with Marketing Authorisation

In case of clinical trials with authorised IMPs, the appropriate labelling (the SmPC, for medicinal products approved in the EU) should be reviewed when assessing contraception recommendations. In case of existing contraception recommendations, these should form the basis for the contraception recommendation with the IMP, but their relevance for the specific clinical trial needs to be assessed and justified by the applicant. In case of no contraception recommendations, the principles for IMPs without marketing authorisation (MA) should be applied.

#### 2.1.2 IMPs without Marketing Authorisation

In case of clinical trials with IMPs that have not yet received MA, there is usually limited or no information about the outcome of pregnancies in humans following in utero or gonadal exposure. Depending on the stage of clinical development there may also be limited or no information from non-clinical reproduction toxicity studies.

The general recommendation in the ICH M3(R2) guideline is that "all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of WOCBP not using highly effective birth control or whose pregnancy status is unknown".

The following non-clinical toxicological studies for risk assessment during preconception and early stages of pregnancy are considered necessary in order to allow a conclusion that non-clinical toxicological studies do not indicate a risk to the unborn that would necessitate the requirement for highly effective methods of contraception in clinical trials (the timings of these studies are included in the appropriate guidelines):

- A standard battery of genotoxicity testing (if applicable)
- Repeated dose toxicity of adequate duration
- Embryofetal development
- Fertility and early embryonic development

Given that it is assumed that treatment with the IMP will be interrupted in case of pregnancy, the pre- and postnatal development study is not considered necessary for assessment of risk to the unborn, except for IMPs with exceptionally long half-lives. Since the focus of this guidance is on the early stages of pregnancy, the main concern relates to evidence of teratogenicity.

Risk assessment should be based on all relevant available non-clinical and clinical data, including pharmacology and pharmacokinetic data, in accordance with the CHMP "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling". In order to specify the duration of the risk mitigation measures after discontinuation of treatment with the IMP, the risk assessment should include an estimation of the end of relevant systemic exposure (see section 1.2).

In the present guidance document the following three main risk categories for the early stages of pregnancy have been adapted from the risk categories set in table 1 of the above CHMP guideline:

- Demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy

- Possible human teratogenicity/fetotoxicity in early pregnancy

- Unlikely human teratogenicity/fetotoxicity in early pregnancy

In case of insufficient or unavailable non-clinical data, the impact on the risk categorization should be evaluated. Unavailable or insufficient non-clinical data should be considered as "effects detected", and the highest possible risk category assumed.

Genotoxicity / genetic damage at the level of the germ cells and/or conceptus may deserve particular attention due to its potential irreversible nature. If genotoxic effects take place in the germ cells that are undergoing or completing meiosis (spermatocytes, preovulatory oocytes), but not in the primordial spermatogonia or in the oocytes that are arrested in the first meiotic prophase, such effects may be considered reversible in the sense that new spermatocytes or arrested oocytes are unaffected. It is recommended that as a minimum one sperm cycle (here defined as 90 days) or menstruation cycle (here defined as 30 days) should be awaited after the relevant systemic exposure to the medicinal product has ended (see section 1.2).

Concerning the embryo-fetal risk posed from treatment of male subjects with IMPs capable of provoking embryo-fetal harm, there is a theoretical risk of human teratogenicity/fetotoxicity in a pregnant WOCBP partner through exposure to the ejaculate. Exposure levels in the WOCBP partner are, however, much smaller from exposure to semen compared with direct intake of the IMP by the WOCBP. Estimated exposure levels in WOCBP are three or more orders of magnitude lower than the plasma concentrations in the male subject (Klemmt & Scialli, The Transport of Chemicals in Semen. Birth Defects Research 2005; 74: 119-31).

A concern may, therefore, only apply to IMPs with demonstrated or suspected human teratogenicity/fetotoxicity in the early pregnancy (see section 2.2.2) at sub-therapeutic systemic exposure levels.

## 2.2 Birth Control and Pregnancy Testing Recommendations for WOCBP

### 2.2.1 General considerations

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test, except for IMPs where an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data.

The recommendations below, with respect to contraception and pregnancy testing, are provided in relation to the risk categories that have been adapted from the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling", and concern both authorized and unauthorized IMPs.

### 2.2.2 Contraception and pregnancy testing recommendations for IMPs with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs where a malformative effect has been demonstrated in humans or is suspected on the basis of class effects, IMPs with genotoxic potential, or IMPs where there is a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data.

- The inclusion of WOCBP requires use of a highly effective contraceptive measure (see sections 4.1 and 4.3). Contraception methods with low user dependency (see section 4.1, footnote 2) should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.
- Additional pregnancy testing should be performed at monthly intervals.
- The above mentioned risk mitigation measures (contraception and pregnancy testing) should be maintained during treatment and until the end of relevant systemic exposure (see section 1.2). This period should be extended by 30 days in case of genotoxicity (see section 2.1.2).

### 2.2.3 Contraception and pregnancy testing recommendations for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs, where human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and non-clinical reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/fetotoxicity.

- The inclusion of WOCBP requires use of a highly effective contraceptive measure (see sections 4.1 and 4.3). Contraception should be maintained during treatment and until the end of relevant systemic exposure (see section 1.2).

- Additional pregnancy testing should be considered taking into account, amongst others, the duration of the trial. As a minimum, a pregnancy test should be performed at the end of relevant systemic exposure.
- In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.

#### 2.2.4 Contraception and pregnancy testing recommendations for IMPs with unlikely human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs where assessment of the completed necessary non-clinical studies (see section 2.1.2) does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.

- The inclusion of WOCBP is possible using at least an acceptable effective contraceptive measure unless an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data (see sections 4.1, 4.2 and 4.3 for methods considered acceptable and section 4.4 for methods considered unacceptable). As a minimum contraception should be maintained until treatment discontinuation.
- Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary.

#### 2.2.5 Other factors to consider

The choice of contraceptive methods for WOCBP and the frequency of pregnancy testing may need to be adapted to special circumstances, which should be justified by the sponsor. Factors to consider when adapting the need for a specific clinical trial may include e.g. exposure to IMP, study duration, fertility of study population, and seriousness of the treated medical condition.

### 2.3 Recommendations for male subjects with pregnant or non-pregnant WOCBP partner

For IMPs with possible or unlikely risk of human teratogenicity/fetotoxicity in early pregnancy (see sections 2.2.3 and 2.2.4), no contraception measures are needed for male subjects with pregnant or non-pregnant WOCBP partner. Also for non-genotoxic IMPs with demonstrated, or suspected human teratogenicity/fetotoxicity in early pregnancy (see section 2.2.2), only at therapeutic or supratherapeutic systemic exposure levels, no contraception measures are needed. For non-genotoxic IMPs with demonstrated or suspected human teratogenicity/fetotoxicity (see section 2.2.2) in early pregnancy, at subtherapeutic systemic exposure levels, where it is theoretically possible that relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid, male contraception (condom) is recommended in order to avoid exposure of an existing embryo/fetus. Contraception should be continued until the end of relevant systemic exposure in WOCBP (see section 1.2).

For genotoxic IMPs, the male subject should use condom during treatment and until the end of relevant systemic exposure in the male subject (see section 1.2), plus a further 90-day period (see section 2.1.2). For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

## 3 Provision of information in the IB/appropriate label and trial protocol

### 3.1 Information to be provided in the IB/appropriate label

For clinical trials with IMPs that have not yet received MA the analysis of embryofetal risk should be provided in the Investigator's Brochure (IB). The "Summary of data and guidance for the investigator", or equivalent section as part of the reference safety information should contain the above mentioned risk assessment (see section 2.1) and the recommendations for the level of contraception and frequency of pregnancy testing (see sections 2.2 and 2.3). The information should be sufficiently detailed to indicate the duration of the need for contraceptive measures and pregnancy testing.

Regarding the content of this information, reference is made to the SmPC guideline. For clinical trials with authorised IMPs the SmPC is the basis for the analysis of embryofetal risk (see section 2.1.1).

Where hormonal contraception methods are recommended birth control methods, assessment should be made of the likelihood of possible interaction with IMP (see section 4.3).

### 3.2 Information to be provided in the trial protocol

The specific recommendations for contraception and pregnancy testing for a clinical trial in the study protocol should be adequate in relation to the information provided in the IB/appropriate label and any other factors to consider. They should encompass all IMPs as well as non-investigational medicinal products, e.g. background therapy and the measures to be followed should be based on the medicinal product with highest risk. The study protocol should contain detailed information on the level of contraception and the possibility for an interaction between the IMP or the non-investigational medicinal products and hormonal contraceptives, the frequency of pregnancy testing, and the duration of the need for contraceptive measures and pregnancy testing. The need for sexual counseling of study subjects, e.g. in adolescents, should be reflected in the protocol.

## 4 Birth control methods

### 4.1 Birth control methods which may be considered as highly effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system ( IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3).

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

### 4.2 Acceptable birth control methods which may not be considered as highly effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide [5]
- cap, diaphragm or sponge with spermicide [5]

[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

### 4.3 Assessment of pharmacokinetic interaction between the IMP and hormonal contraceptives and recommendations on the use of hormonal contraceptives

For hormonal contraception methods, caution should be taken to possible interaction with a (non-biologic) IMP. Interaction with the IMP leading to reduced efficacy of the hormonal contraception method can occur due to e.g. increased metabolism (enzyme induction).

A potential human teratogen needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless on the in vitro induction study results (see Guideline on the Investigation of Drug Interactions). For the purpose of this guidance, an IMP with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy (see section 2.2.2) is a potential human teratogen. For these IMPs, data from a clinical pharmacokinetic interaction study between the IMP and contraceptive steroids, if available, allow to conclude whether the efficacy of hormonal contraception is reduced. In the absence of such a clinical pharmacokinetic interaction study, any recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor.

For all other IMPs, recommendations should take into account both the evidence of the non-clinical reproductive toxicity data and available information related to the potential risk for interaction, e.g. in vitro enzyme induction results, signs of autoinduction and results from clinical interaction studies.

As a general rule, use of hormonal contraception is not recommended if a clinically relevant interaction with contraceptive steroids has been observed or is suspected. If an interaction with contraceptive steroids has been observed or is suspected, but the effect is considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom).

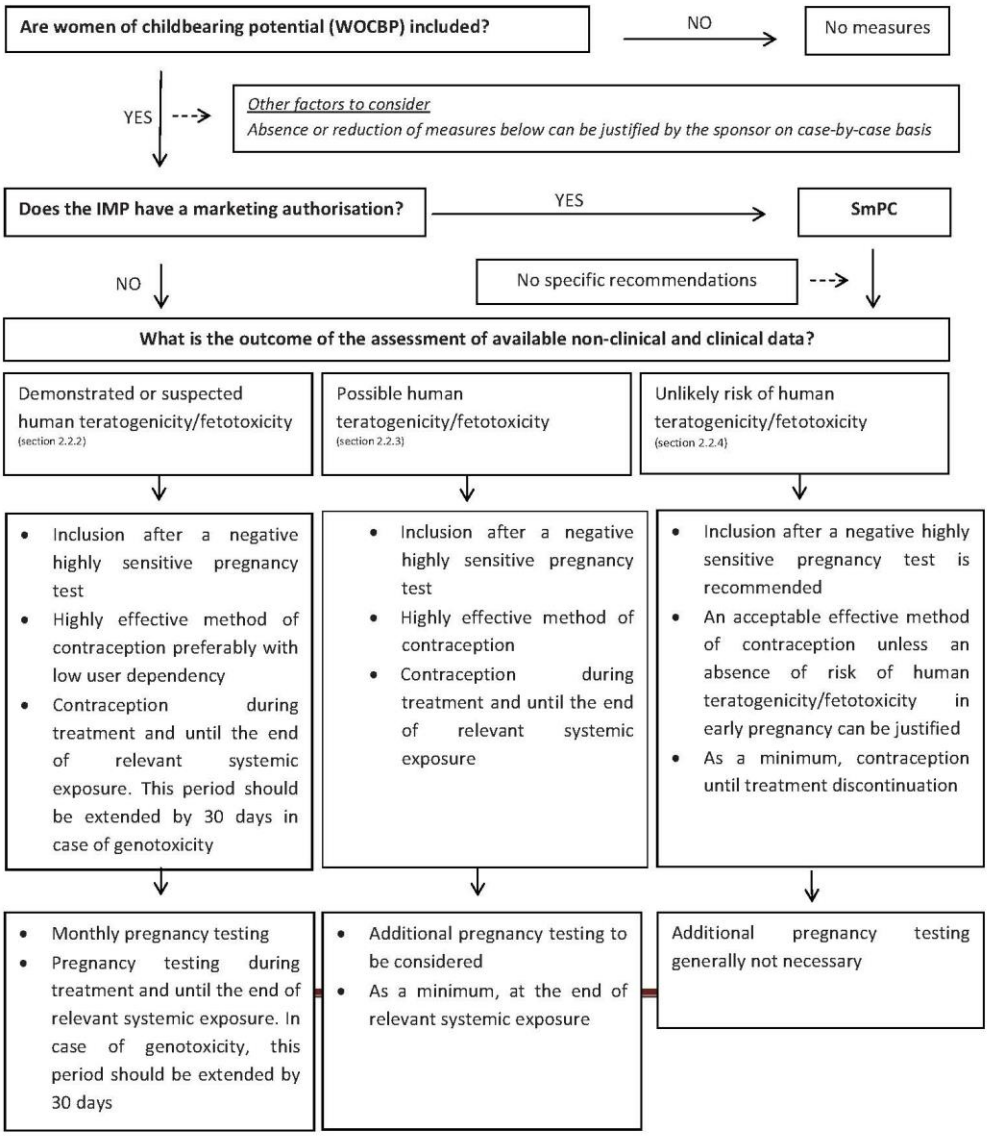
An assessment of the potential for interaction between the IMP and hormonal contraceptives should be provided in the IB, including a scientific rationale for the use of hormonal contraception methods with or without a supplementary barrier method (preferably male condom).

### 4.4 Birth control methods which are considered unacceptable in clinical trials

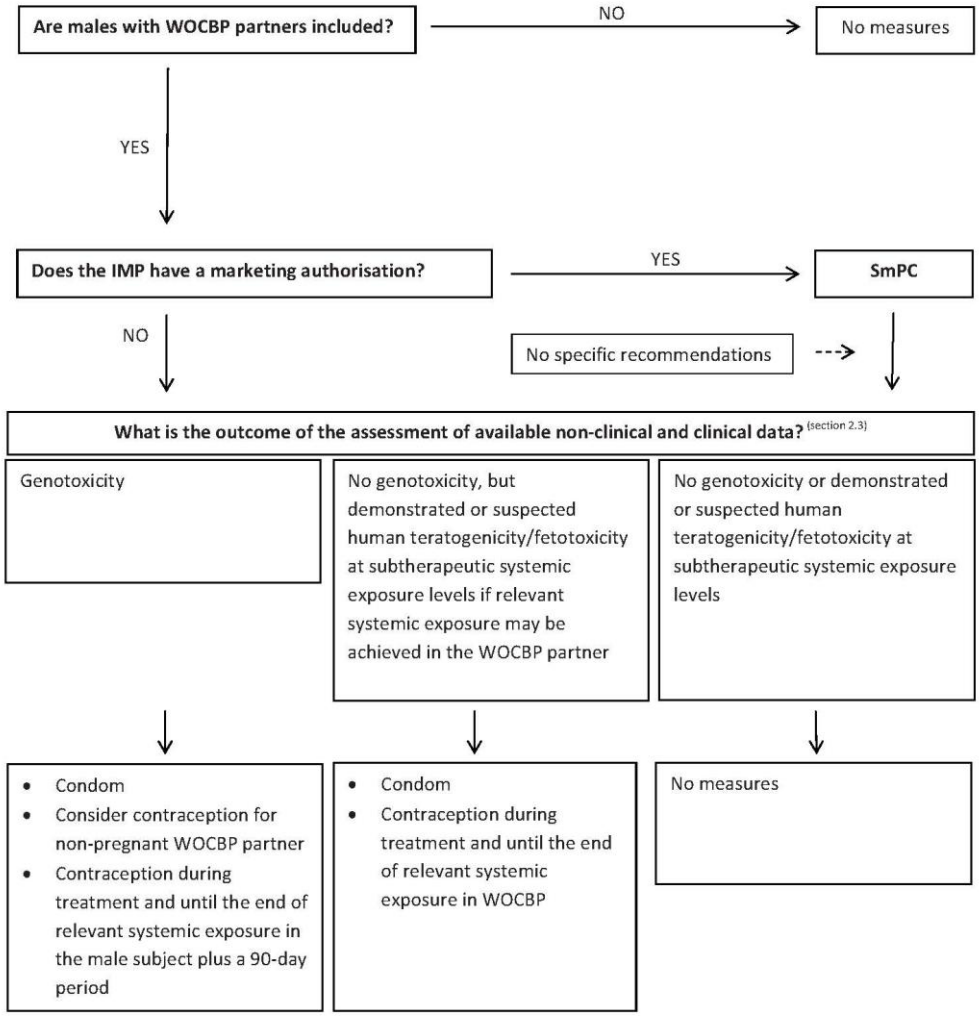
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

## Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

### Women of Childbearing Potential (WOCBP)



**Males with WOCBP Partners**



## Appendix 2 INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure that they are fully informed regarding the trial drug, the conduct of the trial, and the obligations of confidentiality.

*NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the EU.*

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): [redacted]

Institution: Genmab

Signature: [redacted] Date: [redacted]

(DD-Mmm-YYYY)

**Note:** If the address or telephone number of the investigator changes during the course of the trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature Page for [redacted]

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| Reason for signing: Approved | Name: [redacted]<br>Role: Clinical Operations - Biostatistics<br>Date of signature: 24-Oct-2019 09:27:44 GMT+0000 |

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| Reason for signing: Approved | Name: [redacted]<br>Role: Clinical Operations - Trial Management<br>Date of signature: 24-Oct-2019 10:54:59 GMT+0000 |

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