Study Results Synopsis for Public Disclosure

Name of product: TNO155 (batoprotafib), EGF816 (nazartinib)

Protocol identification number: EudraCT: 2016-001861-10 / CTIS: 2023-508925-29-00 / ClinicalTrials.gov: NCT03114319

Title of study: An open-label, multi-center, phase I, dose finding study of oral TNO155 in adult patients with advanced solid tumors

Study center(s): This study was conducted in 18 centers in 9 countries: Canada (1 site, 10 participants), Korea, Republic of (2 sites, 18 participants), Netherlands (2 sites, 33 participants), Italy (1 sites, 3 participants), Singapore (1 site, 18 participants), United States (4 sites, 53 participants), Spain (5 sites, 74 participants), Taiwan (1 site, 8 participants), Japan (1 site, 10 participants).

Publication (reference): None

Study period

Study initiation date: 26-May-2017 (first participant first visit)

Early termination date: 04-Jul-2025 (last patient last visit)

Phase of development (phase of this clinical study): Ib

Objectives:

Primary objective: To characterize safety and tolerability of TNO155 as a single agent and in combination with nazartinib and identify recommended regimens for future studies in adult patients with advanced solid tumors.

Secondary objectives:

- To evaluate the preliminary anti-tumor activity of TNO155 as a single agent and in combination with nazartinib
- To evaluate the pharmacokinetic (PK) profile of TNO155 as a single agent and of TNO155 and nazartinib when administered in combination
- To assess pharmacodynamic (PD) response of SHP2 inhibition in tumors and of combined SHP2 and mutant EGFR inhibition in tumors

Study design and methodology: This study was a Phase Ib, multi-center, open-label study with a dose escalation part followed by a dose expansion part in adult patients with advanced solid tumors. The study treatment was administered until the patient experienced unacceptable toxicity, progressive disease, and/or had discontinued the treatment at the discretion of the Investigator or the patient, or due to withdrawal of consent.

The study is divided into two parts – dose escalation and dose expansion. The initial dosing schedule for TNO155, as a single agent or in combination with nazartinib, was 2 weeks on/1 week off on a 21-day cycle. Multiple schedules of TNO155 were explored in the escalation as

well as in the expansion parts for both single agent TNO155 and the combination to identify and assess the optimal regimen for safety, tolerability, and efficacy. Nazartinib was dosed once daily continuously, regardless of the schedule of TNO155.

Diagnosis and main criteria for inclusion:

The study population consisted of adult patients, with advanced non-small cell lung cancer (NSCLC) harboring a sensitizing EGFR mutation, advanced head and neck squamous cell carcinoma (HNSCC), advanced esophageal SCC, advanced gastrointestinal stromal tumor (GIST), advanced KRAS G12-mutant NSCLC, advanced cutaneous melanoma lacking activating mutations in NRAS and BRAF, and patients with other advanced solid malignancies that are RAS/BRAF- wild-type.

The key inclusion criteria were as follows:

1. Able to understand and voluntarily sign the informed consent form (ICF) and able to comply with the study visit schedule and the other protocol requirements.
2. Patient (male or female) ≥18 years of age willing to agree to not father a child/become pregnant and comply with effective contraception criteria.
3. Must have progressed following standard therapy, or for whom, in the opinion of the Investigator, no effective standard therapy exists, is tolerated or is appropriate.
4. ECOG (Eastern cooperative oncology group) performance status ≤2
5. Additional criteria only applying to TNO155 in combination with EGF816: Patients must be screened for Hepatitis B virus and Hepatitis C virus

The key exclusion criteria were as follows:

1. Tumors harboring known activating KRAS, NRAS, HRAS, BRAF or PTPN11 (SHP2) mutations. (Exceptions are KRAS G12-mutant NSCLCs)
2. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO.
3. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
4. Clinically significant cardiac disease.
5. Active diarrhoea or inflammatory bowel disease
6. Insufficient bone marrow function
7. Insufficient hepatic and renal function.
8. Additional criteria only applying to TNO155 in combination with EGF816:
    - Patients with a known history of human immunodeficiency virus (HIV) seropositivity.
    - Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry.
    - Patients who have undergone a bone marrow or solid organ transplant
    - Patients with a history or presence of interstitial lung disease or interstitial pneumonitis

- Bullous and exfoliative skin disorders at screening of any grade
- Presence of clinically significant ophthalmological abnormalities that might increase the risk of corneal epithelial injury

Test and reference therapies, dose and mode of administration, batch number:

The term "study treatment" referred to the following treatments:

- TNO155 as single agent.
- TNO155 in combination with Nazartinib.

The dose and treatment schedules are presented in Table 2-1.

Table 2-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
TNO155	Capsule for oral administration	As assigned	Daily on continuous or intermittent schedule; Once daily (QD) or twice daily (BID) regimen
TNO155	Tablet for oral administration	As assigned	Daily on continuous or intermittent schedule; QD or BID regimen
Nazartinib (EGF816)	Capsule for oral administration	As assigned	Daily on continuous schedule

Source: Appendix 16.1.1-Protocol-Table 6-1

Protocol amendments and other changes to study conduct:

Novartis decided to halt the study enrollment of new patients on 13 May 2024 for business reasons. Importantly, this decision was not based on any safety/tolerability concerns. At the time of enrollment halt, the escalation part of the study was completed for both the single-agent and combination treatment arms. The single-agent and combination expansion arms were initiated and ongoing at the time when enrollment halt was declared. The already enrolled patients were allowed to continue their treatment as per protocol. The global last patient last visit occurred on 04-Jul-2025. This report presents the results of the combined dose escalation and dose expansion part of the study.

This synopsis describes the conduct of the study according to the final protocol (including all 8 amendments). The final protocol was dated 14-Nov-2023. The key changes of each amendment are presented in a table below (Table 2-2):

Table 2-2 Protocol amendments

Amendment	Date	Key Changes
Amendment 8	14-Nov-2023	The primary purpose of amendment was to update the required duration of condom use for sexually active male patients from 10 to 12 days after the last dose of study treatment, based on TNO155's terminal elimination half-life of 57.1 hours from the CTNO155A12104 hADME study. Updated drug interaction guidance based on in vitro data showing TNO155 and its metabolite NIH741 as substrates/inhibitors of BCRP, MRP2, MATE1, and MATE2K. Allowed use of liquid biopsy for KRAS G12 mutation testing in place of tumor biopsy, if locally approved and discussed with Novartis.
Amendment 7	16-Dec-2022	The purpose of the amendment was to remove the specific name of the electronic data capture (EDC) system used in the clinical trial. Novartis decided to discontinue use of the Oracle Clinical–Remote Data Capture (OC-RDC) system due to evolving technology and regulatory requirements. As a result, the specific system name was replaced with the broader term "Electronic Data Capture tools/systems.
Amendment 6	04-Feb-2022	The primary purpose of amendment was to remove the requirement for tumor HRAS mutation testing during molecular pre-screening when local testing was unavailable, due to discontinuation of the central assay. All molecular testing was performed locally. Removed the requirement for BRAF and RAS isoform testing on post-treatment samples to reduce biopsy burden; archival tissue or existing results were accepted. Discontinued screening and monitoring of NT-proBNP and Troponin I/T, and removed related eligibility criteria, as no correlation with LVEF changes was observed. Removed the food effect assessment from the study, as a dedicated clinical pharmacology study was planned. Added an exclusion criterion prohibiting live or live attenuated vaccines within 4 weeks prior to starting TNO155 plus nazartinib. Discontinued collection of serum biomarkers (FGF19, C4, bile acids, fasting total cholesterol, LDL-C, HDL-C) due to sufficient data availability. Updated the list of drugs to be used with caution to include sensitive CYP3A4/5 substrates, based on in vitro CYP3A4 induction data. Allowed use of a tablet formulation of TNO155, pending local health authority approval. Aligned HBV/HCV (Hepatitis B Virus/ Hepatitis C Virus) monitoring frequency with cycle length; retained "at least every 4 weeks" for continuous dosing schedules. Updated protocol sections to comply with enhanced health authority reporting and data protection regulations.

		Added language for collection of race and ethnicity data to assess population diversity and safety/efficacy variations. Included protocol provisions for mitigation procedures during public health emergencies (e.g., pandemics, natural disasters).
Amendment 5	14-Apr-2020	The primary purpose of amendment was to add a dose escalation followed by a dose expansion arm of TNO155 in combination with nazartinib (EGF816) in advanced EGFR-mutant NSCLC post-EGFR TKI progression. The combination targeted SHP2-mediated resistance mechanisms and included exploratory objectives for brain metastases. CRC patients were excluded due to limited response to single-agent TNO155, to enrich for responsive populations. NSCLC patients with KRAS G12 mutations were included in the single-agent dose escalation. Patients with BRAF/NRAS wild-type melanoma (potential NF1 loss) were included in dose escalation, with a new expansion group added. The food effect study was moved to dose escalation to confirm minimal impact on TNO155 exposure and potentially remove fasting requirements. The number of single-agent TNO155 regimens tested in expansion groups was increased from two to three. The DLT criterion for asymptomatic LVEF decrease ≥15% was removed to avoid unnecessary dose modifications in patients with normal LVEF. The requirement for Cardiologist consultation before resuming treatment after LVEF normalization was removed to prevent treatment delays. The exclusion criterion was clarified to allow patients with permanent, controlled toxicities (e.g., vitiligo, endocrinopathies) from prior immunotherapy. FDG-PET scans were added to efficacy assessments for GIST patients.
Amendment 4	21-Feb-2019	To address a health authority request by specifying in the inclusion criteria that certain patient groups must have progressed on or been intolerant to standard-of-care therapy per local guidelines, in addition to prior specified therapies. Added a 5 mg dose strength of TNO155 to allow greater flexibility in dosing regimens. Included blood collections for exploratory immune-related biomarkers to assess SHP2's role in immunomodulation and tumor microenvironment interactions. Modified DLT criteria to clarify that asymptomatic Grade 3 amylase/lipase elevations >7 days and Grade 4 elevations suspected to be drug-related were considered DLTs only if baseline values were normal. Updated pregnancy follow-up timeframes.

		Revised the list of prohibited and cautionary medications. Allowed the statistical model to incorporate DLT data from all completed and ongoing schedules to guide dose escalation more efficiently. Added a provision for re-escalation of TNO155 after dose reduction if the adverse event was later deemed unrelated, with Novartis approval. Revised withdrawal of consent language to reflect global regulatory differences in sample use. Extended the screening period from 14 to 28 days to improve logistical flexibility for sites and patients.
Amendment 3	09-May-2018	Addressed health authority requests to require women of child-bearing potential to use highly effective contraception while on study treatment and for 30 days (previously 10 days in Amendment 2) after the last dose of TNO155.
Amendment 2	23-Jan-2018	The amendment addressed the inclusion of Japanese patients in a separate dose escalation group, added esophageal squamous cell cancers and selected KRAS G12C-mutant cancers to the eligible population, clarified eligibility criteria, included pre- and on-treatment skin biopsies, and relaxed contraception requirements following permanent discontinuation of TNO155.
Amendment 1	22-Feb-2017	Addressed health authority requests through the following updates Specified required prior anti-neoplastic therapies by replacing “standard of care” with approved chemotherapies. Grade 3 thrombocytopenia with bleeding was added to the dose-limiting toxicity definition. Modified Cycle 2 visit schedule to increase safety monitoring; added hematology and biochemistry assessments. Added exclusion criterion for unresolved toxicities (<=Grade 1) from prior therapy, excluding alopecia. Updated QTc prolongation management to include electrolyte evaluation and medication review. Added progressive disease as a reason for treatment discontinuation. Required informing patients continuing treatment post-progression about alternative therapies. Restricted high-risk tumor biopsies for molecular pre-screening due to investigational device regulations.

Other changes in study conduct

On 30-Oct-2023, during the conduct of this study, the electronic data Case Record Form (CRF) system was transitioned, with no impact on the data flow or data quality.

Changes in planned analysis

The following protocol specified analyses were not performed and decisions related to these changes were made prior database lock:

- Exploratory objectives
- Separate analyses of Japanese vs rest of the world (ROW)
- As of Protocol Amendment 6, the effect of food was not investigated

Changes in the conduct of the study and/or planned analyses due to COVID-19

Due to the COVID-19 pandemic, some general advice in regard to the study conduct was provided to the investigators to ensure the safety and well-being of study patients, and to enable trial oversight and compliance with the Health Authority (HA) guidance. Examples of such guidance included:

- Patients not visiting the site based on the investigator's clinical judgment or patient decision
- Conducting study visits by telephone may be possible in some cases

These deviations in study conduct were reported during the study as COVID-19 related protocol deviations and reported in protocol deviation section; however, there was no impact on overall interpretation of efficacy and safety results.

Criteria for evaluation:

- **Efficacy**: Efficacy was evaluated measuring Overall Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), Progression Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The local investigator's assessment was used for the evaluation of the preliminary antitumor activity of the study treatment and for treatment decision making.
- **Safety**: Safety assessments included physical examination including vital signs, body weight, performance status, hematology, chemistry, urinalysis, coagulation, pregnancy, myoglobin and viral hepatitis markers, electrocardiogram (ECG), multiple gated acquisition (MUGA) scan/ trans-thoracic echocardiography (TTE), ophthalmic examination as well as collection of adverse events (AEs). Tolerability was evaluated in terms of dose interruptions, dose reductions and dose intensity.
- **Pharmacodynamics assessments**: For assessment of pharmacodynamic effects in tumor, pre- and post- treatment tumor biopsies were examined for the expression of Dual Specificity Phosphatase 6 (DUSP6) for patients enrolled in the study.
- **Pharmacokinetics:** Serial blood samples were collected at timepoints specified in the protocol from all patients in the dose escalation and the dose expansion parts of the study in order to characterize the single dose, combination dose and steady-state plasma PK of TNO155. The following key PK parameters were assessed: AUClast, AUCtau, AUCinf, Cmax, Tmax, CL/F, Racc, T1/2, and T½eff from the plasma concentration-time data.

Statistical methods: All statistical analyses were performed by Novartis. The study data were analyzed and reported in the clinical study report (CSR).

- **Analysis sets:**
  - **Full Analysis Set (FAS):** comprised all patients to whom study treatment had been assigned and who received at least one dose of TNO155 as a single agent, or at least

one dose of TNO155 or nazartinib if assigned to the combination arm. Patients were analyzed according to the TNO155 or TNO155 in combination with nazartinib dosing regimen (dose and dosing schedule) they had been assigned to.

- **Safety Set (SS):** included all patients to whom study treatment had been assigned and who received at least one dose of TNO155 as a single agent, or at least one dose of TNO155 or nazartinib if assigned to the combination arm and had at least one valid post-baseline safety assessment.

  Patients were analyzed according to the study treatment and dosing regimen they actually received.

  The actual treatment received corresponded to:

  1. The treatment assigned if it was received at least once, or
  2. The first treatment received when starting therapy with study treatment, if the assigned treatment was never received.

- **Dose determining set (DDS):** The Dose-determining set consisted of all patients from the Safety set in the dose escalation part of the study who either meet the minimum exposure criteria and have sufficient safety evaluations as determined by the Investigator and Novartis or experienced a dose limiting toxicity (DLT) during the first cycle of treatment.
- **Pharmacokinetic analysis set (PAS):** included all patients who provided evaluable PK data of TNO155 or nazartinib. PK data were considered evaluable if all of the following conditions were satisfied:
  1. The patient received one of the planned treatments;
  2. The patient provided at least one primary PK parameter;
  3. The patient did not vomit within 4 hours after dosing of TNO155 or nazartinib.

Primary endpoint: To characterize the safety and tolerability of TNO155 as a single agent and in combination with nazartinib in solid tumors and identify recommended regimen included: incidence of DLT for dose escalation, incidence and severity of AEs, serious adverse events (SAEs) as mentioned in safety assessments, including changes in laboratory values, vital signs and ECGs, and dose interruptions, reductions, and dose intensity.

Separate adaptive Bayesian models guided by the escalation with overdose control (EWOC) principle were applied for the DLT analyses in each dose escalation part and the estimation of the maximum tolerated dose/recommended dose (MTD/RD) using DDS for the single agent treatment or combination treatment, respectively. Tolerability of study treatment was assessed by summarizing dose intensity and dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons were summarized for each of the study drugs separately by treatment for tumor indication and treatment combination. The incidence of treatment-emergent adverse events (new or worsening from baseline) were summarized by system organ class and/or preferred term, severity based on Common Terminology Criteria for Adverse Events (CTCAE) grades, and relation to study treatment. All CTCAE grades and grades ≥3 will be summarized. Summary tables for AEs included only AEs that started or worsened during the on-treatment period, the treatment- emergent AEs. Serious adverse events and non-serious adverse events during the on-treatment period were tabulated. All deaths (on-treatment and post-treatment) were summarized by treatment groups, system organ class (SOC) and preferred term (PT). Summary statistics were provided by treatment and visit/time for each laboratory data, vital signs, and ECG variables. The number and percentage of patients

with worst post baseline values for liver function parameters of interest (ALT, AST, and ALP), notable vital sign values (low/high), and notable ECG values were also summarized.

Secondary endpoints: The endpoints for the secondary objectives included efficacy endpoints, ORR, DCR, DOR, PFS, PK analyses, changes of PD marker DUSP6 in tumor and in blood. The assessment of efficacy endpoints was based on RESIST v1.1. Data for demographic and baseline characteristics, and efficacy, safety, pharmacokinetic and pharmacodynamics measurements were summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data). All summaries, listings, figures, and analyses were performed by treatment group for each single and combination agent separately. Patients treated with the same dosing regimen (dose and dosing schedule) of TNO155 were pooled into a single treatment group.

Pharmacokinetic parameters: They were determined by non-compartmental method(s) using the PK profile of TNO155X or TNO155 and nazartinib. Descriptive statistics were presented for all pharmacokinetic parameters (AUClast, AUCtau, AUCinf, Cmax, Tmax, Cmin, CL/F, Racc, T1/2, and T½eff).

Biomarkers: Correlation between biomarkers and clinical response as well as exposure was evaluated. For change-from-baseline analyses, calculations were only performed on patients with evaluable samples from both baseline and post-treatment time points. If either of the baseline or post-baseline values were below the lower limit of quantification (LLOQ), percent change, absolute change, or fold-change from baseline was not imputed.

Summary - Results

Demographic and background characteristics:

A total of 227 patients completed the screening across 18 sites and were treated with varying doses of TNO155 as single agent and TNO155 in combination with EGF816.

- **TNO155 as single agent (N=183; Escalation + Expansion parts):** The median age of patients was 61.0 years (range 18–83 years). The majority of the patients (68.3%) were from the age category of 18 to <65 years. There were 57.9% male and 42.1% female patients in the FAS. The majority of the patients were of Caucasian race (57.4%) and of non-Hispanic and non-Latino ethnicity (34.4%).
- **TNO155 as combination (TNO155 + EGF816) (N=44; Escalation + Expansion parts):** The median age of the patients was 57.0 years (range 38–84 years). The majority of the patients (68.2%) were from the age category of 18 to <65 years. There were 34.1% male and 65.9% female patients in the FAS. Most of the patients were of Asian race (59.1%) and of non-Hispanic and non-Latino ethnicity (34.1%).

Protocol deviations:

- **TNO155 as single agent (N=183; Escalation + Expansion parts):** Protocol deviations were reported for 92 patients (50.3%). The most frequent protocol deviations were "Other deviation" (53 patients, 29.0%) and "Study Treatment Deviation" (23 patients, 12.6%).

  Deviations due to COVID-19 related changes as "Other", lockdown / quarantine of subject and site issue were affecting 1.6%, 0.5%, and 0.5% of patients, respectively.
- **TNO155 as combination (TNO155 + EGF816) (N=44; Escalation + Expansion parts):** Protocol deviations were reported for 25 patients (56.8%). The most frequent protocol

deviations were "Other deviation" (15 patients, 34.1%) and "Study Treatment Deviation" (9 patients, 20.5%).

Deviation due to COVID-19 related health status was reported in one patient (2.3%).

Due to operational issues during conduct on the trial and transition across two clinical databases, some potential protocol deviations were identified after closure of the sites, that did not transition from OCRDC to RAVE, which were neither documented nor confirmed, on the database. All these potential protocol deviations were reviewed outside the database and were assessed to have no impact on the patient's safety or the study conduct.

There were another 5 potential protocol deviations that were not confirmed in the database. However, among the 5 protocol deviations, 2 protocol deviations were deemed not protocol deviations after the review. Additionally, 3 more protocol deviations missed medical review. However, all the protocol deviations were medically reviewed outside the database to assess any impact on patient safety and study conduct. It was assessed to have no impact. A memorandum on the above protocol deviations was sent to specific sites, where the issues were identified.

Exposure:

- **TNO155 as single agent (N=183; Escalation + Expansion parts):** The median exposure to TNO155 was 7.00 weeks (range 0.1 to 248.1 weeks) in 183 patients, across different dosage regimens. Overall, 55 patients (escalation plus expansion) received the recommended dose of TNO155 as single agent (RD: 60 mg QD 2 weeks on/1 week off (2/1)). The median duration of exposure to TNO155 at RD for single agent was 8.0 weeks (range: 0.1 to 39.9 weeks). The duration of exposure to TNO155 at RD for ≥32 weeks was 5.5%. Median duration of TNO155 exposure varied across dosage groups.

  The majority of the patients (33.9%) were treated for 4–<8 weeks, 22.4% for 8–<12 weeks, and 21.3% for <4 weeks, with only 4.4% exposed for ≥32 weeks. The total cumulative exposure time for TNO155 as a single agent for all patients was 2181.9 weeks.
- **TNO155 as combination (TNO155 + EGF816) (N=44; Escalation + Expansion parts):** The median exposure to the combinations of TNO155 and EGF816 was 9.57 weeks (range 0.7 to 161.1 weeks) in 44 patients, across different dosage regimens. Overall, 22 patients (escalation plus expansion) received the RD of TNO155 in combination with EGF816 (RD: TNO155 40 mg QD 2/1 + EGF816 100 mg QD continuous). The median duration of exposure to the combination at RD was 10.0 weeks (range: 0.7 to 153.0 weeks). The percentage of patients with a duration of exposure to the combination ≥32 weeks was 18.2%. Median duration of TNO155 and EGF816 exposure varied across dosage groups.

  The majority of the patients (25.0%) were treated for 8-<12 weeks, 20.5% for >= 32 weeks, and 18.2% for 4-<8 weeks. The total cumulative exposure time to TNO155 and EGF816 in combination for all patients was 1045.3 weeks.

Efficacy Results

- **TNO155 Single Agent:** Among all subjects treated with TNO155 monotherapy, the ORR was 0.5%, with Best Overall response (BOR) of stable disease (SD) in 20.2% and partial response (PR) only in 0.5%, while progressive disease was noted as BOR in 65.6%. A DCR of 20.8% and median PFS of 1.8 months was observed. The Kaplan-Meier estimate of the PFS rate at 6 months was 8.0%, and at 12 months was 1.5%. The overall event rate was 89.6%, with 10.4% of patients censored.

At the RD, ORR was zero and the DCR was 29.1%. A total of 87.3% had disease progression, and 9.1% died. The median PFS observed was 1.9 months (95% CI: 1.81- 2.04).

- **TNO155 in combination with EGF816**: **TNO155 in combination with EGF816:** In the combination arm, the ORR was 9.1% with a BOR of SD in 27.3%, and 9.1% achieved a PR, while progressive disease was seen in 54.5% patients. A DCR of 36.4% and Median PFS was 1.97 months was observed.

  At RD in combination arm, the ORR was 9.1% and the DCR was 36.4%. A total of 86.4% had disease progression, and 4.5% died. The median PFS observed was 1.97 months (95% CI: 1.45-5.45).

Pharmacokinetic Results

- **TNO155 QD dosing**: Median Tmax on Cycle 1 Day 1 (C1D1) ranged from 1.0 to 1.63 hours and on Cycle 1 Day 14 (C1D14) ranged from 1.1 to 3.1 hours across doses, indicating rapid absorption. Systemic exposure, both AUC0-24 and Cmax increased with dose from 1.5 to 70 mg QD on C1D1 and C1D14. Both AUC0-24 and Cmax increased in approximately dose proportional manner over the evaluated dose range. PK variability was moderate (geo-CV up to 56% for Cmax and up to 67.0% for AUC0-24). Racc values ranging from approximately 1.9 to 3.0 across doses. Effective half-life was ~28.7 to 40.8 hours.
- **TNO155 BID dosing**: Median Tmax on C1D1 ranged from 0.9 to ~3.1 hours and on C1D14 ranged from 2.1 to 2.1 h, indicating rapid absorption. Systemic exposure, both AUC0-12 and Cmax increased with dose from 30 mg to 60 mg BID (C1D1) and from 30 mg to 50 mg BID (C1D14). Both AUC0-12 and Cmax increased in approximately dose proportional manner over the evaluated dose range. PK variability was moderate (geo-CV up to 53% for Cmax and up to 48.0% for AUC0-12). Racc (AUC0-12h) was ranging from 3.5 to 4.3 across doses. Effective half-life was 25 to 31 hours.
- **TNO155 (Combination QD):** Median Tmax on C1D14 ranged from 2.3 to 4.5 hours, indicating rapid absorption. TNO155 plasma exposure increased with dose across Arms A– D (Geo-mean AUClast ranged from 1010 to 2740 h*ng/mL and geo-mean Cmax ranged from 154 to 399 ng/mL). PK variability was moderate (CV up to 29.0% for Cmax and up to 24.0% for AUClast). When compared with single-agent TNO155, exposure in the combination arms observed were within the range at the same dose levels, indicating that co-administration with EGF816 did not alter the pharmacokinetics of TNO155.
- **EGF816 (Combination QD):** Median Tmax on C1D14 ranged from 2.2 to 3.1 hours, indicating rapid absorption. Geo-mean AUClast ranged from 1300 to 3960 h*ng/mL; geo-mean Cmax ranged from 215 to 614 ng/mL across Arms A–D. No consistent dose- dependent increase in EGF816 exposure was observed. PK variability was moderate (CV

up to 53.0% for Cmax and up to 57.0% for AUClast). When compared with single agent EGF816, exposure in the combination arms observed were within the range at the same dose levels, indicating that coadministration with TNO155 did not alter the pharmacokinetics of EGF816.

Pharmacodynamic Results (DUSP6 Expression):

- **TNO155 Single Agent:** Thirteen patients (19.1%) with SD showed marked reductions in DUSP6 expression (mean change: −57.9%, median: −59.9%) and 48 patients (70.6%) with progressive disease as best response showed reductions in DUSP6 expression with mean change of −37.2% and a median of −48%).
- **TNO155 in combination with EGF816:** Two patients (33.3%) with PR showed mean (SD) change of −75.4% and median change of −75.4% and 4 patients (66.7%) with BOR of progressive disease were evaluable (patients with evaluable biopsy pairs) and showed reductions in DUSP6 with mean change of −65.7 % and median of −67%.

Safety results:

Dose- limiting toxicities

- **TNO155 as single agent (Escalation part)**
  - A total of 13 patients treated with TNO155 as a single agent across different dosage levels experienced DLTs, of which 8 patients had Grade ≥ 3 events.
  - The most commonly reported DLT was decrease in ejection fraction (n=5).
  - Based on an integrated assessment of summaries of DLT rates, safety, efficacy, PK and PD data, the RD for TNO155 as single agent was determined to be TNO155 60 mg QD 2/1.
- **TNO155 in combination with EGF816 (Escalation parts)**
  - Overall, 2 patients treated with TNO155 in combination with EGF816 experienced Grade ≥ 3 DLTs (one event each: diarrhoea and decreased platelet count), both occurring in the TNO155 60 mg QD 2/1 plus EGF816 100 mg QD continuous treatment group.
  - Based on an integrated assessment of summaries of DLT rates, safety, efficacy, PD and PK data, the RD for TNO155 as combination agent was determined to be TNO155 40 mg QD 2/1 + EGF816 100 mg QD continuous.

Overview of adverse events, SAEs and deaths

- **TNO155 Single Agent (Escalation + Expansion Parts)**
  - **Adverse events**: All patients (100%) experienced at least one adverse event (AE), with 117 patients (63.9%) experiencing Grade ≥ 3 AEs, regardless of relationship to study treatment. The most frequently reported AEs by system organ class (SOC), regardless of relationship to study drug were general disorders and administration site conditions (n=135; 73.8%), and investigations (n=134; 73.2%), followed by gastrointestinal disorders (n=129; 70.5%). The most commonly reported PTs within these SOCs were peripheral oedema (n=76; 41.5%), diarrhoea (n =64; 35.0%), increased aspartate

aminotransferase (n=52, 28.4%) and increased alanine aminotransferase (n=42; 23.0%). The most common treatment-related AEs (by PT) were peripheral oedema and diarrhea. These safety results are consistent with the known safety profile of TNO155, and similar patterns were observed at the recommended dose.

- **Deaths:** Overall, 38 deaths (20.8%) of which 16 deaths occurred while on treatment across all dosage groups, none of the deaths were considered treatment related, and most of the deaths reported due to other reasons were mainly considered due to underlying tumor progression. One death occurred due to COVID-19 during the COVID-19 pandemic period.

  At the RD for TNO155 as a single agent, 10 deaths (18.2%) were reported. Of these, 7 deaths (12.7%) were due to the study indication, and 3 deaths (5.5%) were due to other reasons and none of them related to study treatment.

- **SAEs:** SAEs (all Grades) were reported in 64 patients (35.0%). The most frequently reported SAEs by SOC were infections and infestations (n=22, 12.0%), with pneumonia being the most frequently reported PT (5.5%). None of the pneumonia events were considered treatment related.

  Overall, the incidence of any individual treatment-related SAE did not exceed 1 patient (≤0.5%). Similar trends were observed at the RD.

- Twelve patients (6.6%) discontinued study treatment due to AEs, regardless of study treatment relationship. Of these, 6 patients (3.3%, including one patient from RD) discontinued study treatment due to treatment related AEs and the incidence of any individual treatment-related AEs did not exceed 1 patient (≤0.5%).
- **AESIs**: The most common reported adverse events of special interest (AESIs) were peripheral oedema, hepatotoxicity followed by skin reaction. In patients treated at the RD, the most commonly reported AESIs were peripheral oedema and hematologic toxicity.

- **TNO155 in combination with EGF816 (Escalation + Expansion Parts)**
  - **Adverse events**: The majority of patients (97.7%) treated with TNO155 in combination with EGF816 experienced at least one AE, with 30 patients (68.2%) experiencing Grade ≥ 3 AEs, regardless of relationship to study treatment. Most AEs reported under SOC regardless of study drug was gastrointestinal disorders, with diarrhea being the most commonly reported PT (n=31, 70.5%). The most common treatment-related AEs (by PT) were peripheral edema and diarrhea. These findings are consistent with the known safety profiles of TNO155 and EGF816, and similar trends were observed at the RD.
  - **Deaths**: Overall, 5 deaths (11.4%) were reported across different dosage groups due to the study indication, of which 1 death was from the RD.
  - **SAEs:** SAEs (all Grades) were reported in 19 patients (43.2%). The most commonly reported SAEs were reported under SOC infections and infestations and respiratory, thoracic and mediastinal disorders (n=8, 18.2% each), with pneumonia being the most frequently reported PT (11.4%). None of the pneumonia SAEs were considered treatment related. The most common treatment related SAEs by PTs were reported in 4 patients (9.1%) for diarrhoea followed by 3 patients (6.8%) for hepatitis B

reactivation. The safety findings are aligned with known safety profile of TNO155 and EGF816.

In patients treated at the RD, the most commonly reported SAEs were reported under SOC respiratory, thoracic and mediastinal disorders and investigations (n=3, 13.6% each), with pleural effusion being the most frequently reported PT (n=2, 9.1%). Treatment related SAEs were reported in 5 patients (22.7%), and the frequency of any individual treatment-related SAE did not exceed 1 patient (≤4.5%).

- Three patients (6.8%) discontinued study treatment due to AEs (regardless of study treatment relationship). Of these, 2 patients (4.5 %; these two patients are from RD) discontinued study treatment due to treatment related AEs (blood creatine phosphokinase increased (n=2, 4.5%) and myopathy toxic (n=1, 2.3%)). The safety findings are aligned with known safety profile of TNO155.
- **AESIs**: Overall, diarrhea, skin reaction and hematologic toxicity were the most commonly reported AESIs. In patients treated at the RD, the most commonly reported AESIs were diarrhea, peripheral oedema, and hematologic toxicity.

Laboratory abnormalities (single agent and combination)

- **Hematology**: The most commonly observed abnormal hematology parameters in single agent were decreased lymphocytes and hemoglobin. No significant changes were observed in coagulation lab parameters. Similar patterns were observed for combination treatment.
- **Biochemistry**: The most commonly observed abnormal biochemical parameters were AST, ALT and ALP increased in both single agent and combination treatment, which was aligned with safety profile of TNO155. No other significant abnormalities were found for biochemical parameters under single agent and combination treatment.
- **ECG**: The most commonly observed abnormality was prolonged PR intervals for both single agent and combination treatment.
- **Left ventricular ejection fraction (LVEF):** Across all dosing regimens, 19 patients (10.4%) experienced a reduction in ejection fraction (EF); among them, 2 patients (1.1%) had a Grade 3 EF decrease, and 3 patients (1.6%) developed left ventricular dysfunction (LVD), all of them were Grade
  3. All were considered treatment related and none of them were serious.
- One patient with Grade 3 decrease in EF (SAE) was observed with TNO155 + EGF816 combination treatment and was considered not related to study treatment. No Grade 4 decrease in EF was observed with either single agent or TNO155 in combination with EGF816.

  Overall, the safety results from single agent and combination from the study were in line with the known safety profiles of TNO155 and EGF816. No new signals were identified.

Conclusions: A total of 141 patients were enrolled into the dose escalation part, across various doses and schedules for the single agent arm. At the end of the dose escalation part, based on the integrated assessment of summaries of DLT rates, safety, efficacy, PK, and PD data, the RD was determined to be TNO155 60 mg QD 2/1.

In the combination arm, a total of 44 patients were treated across several doses and schedules. At the end of the combination dose escalation part of the study, based on the integrated assessment of summaries of DLT rates, safety, efficacy, and PK data, the RD was determined to be TNO155 40 mg QD 2/1 + EGF816 100 mg QD continuous.

The expansion part was initiated with the determined RDs for the single agent and combination arms. However, the sponsor decided to halt the enrolment on 13 May 2024, for business reasons. This decision was not due to any safety reasons. The patients enrolled into the study were continued to be treated and were followed up according to the protocol.

At the time of enrollment halt, a total of 42 patients had been treated in the expansion part with TNO155 single agent and 15 patients had been treated in the expansion part for the combination arm. The number of patients that received the RD regimen including both escalation and expansion parts was 55 for single agent TNO155 and 22 patients for TNO155 in combination with EGF816.

Based on the analysis of clinical data results of CTNO155X2101 (An open-label, multi-center, phase I, dose finding study of oral TNO155 in adult patients with advanced solid tumors), TNO155 as a single agent and in combination with EGF816 could be safely administered to patients with advanced solid tumors at doses that led to evidence of MAPK pathway suppression in patient tumors. However, despite evidence of target engagement by TNO155, limited efficacy was observed in the enrolled population with advanced, heavily pre-treated malignancies. The safety data observed in the combination arm were consistent with those observed with each single agent, and no new safety signals were identified.