NCT
NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Study Title:

Continuous ReAssessment with Flexible ExTension in Rare Malignancies – CRAFT: The NCT PMO-1602 Phase II Trial

The trial is designed as an Open-label, multi-arm, multicenter phase II trial to gain evidence of antitumor activity of specific treatments in each study arm separately in adult patients with (locally) advanced or metastatic solid tumors with distinct molecular characteristics. The primary endpoint is DCR on day 110 (± 5).

Short Title/ Acronym: NCT-PMO-1602 (CRAFT)

Final Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.0, 19.12.2025
Investigational Product:	Vemurafenib, Cobimetinib, Atezolizumab, Trastuzumab, Pertuzumab, Alectinib, Ipatasertib, Inavolisib
EudraCT Number:	2019-003192-18
Protocol-Number:	Version 4.0, 18.03.2024

Sponsor:
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg, Germany
Phone: 06221 / 42-2850
Fax: 06221 / 42-2840
E-Mail: michael.baumann@dkfz-heidelberg.de
u.weyrich@dkfz-heidelberg.de

Coordinating Investigator:
Prof. Dr. Richard F. Schlenk
National Center for Tumor Diseases (NCT)
Im Neuenheimer Feld 460
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 6228
Fax: +49 (0)6221 56 5863
E-Mail: richard.schlenk@nct-heidelberg.de

Author of Trial Report:
Dr. Erli Wang
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg, Germany
Phone: +49 6221 / 56-37858
E-Mail: erli.wang@nct-heidelberg.de

Initiation and Completion Dates:
First Patient in: 13 October 2021
Last Patient in: 07 August 2024
Last Patient Last Visit: 30 December 2024
Database lock: 25 August 2025

CONFIDENTIAL

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Coordinating Investigator as representative of Sponsor (Review)	Title, Name	Date	Signature
Biostatistician (Author)	Title, Name	Date	Signature

List of abbreviations:

AE	Adverse Event
AESI	Adverse Event of Special Interest
AST	Aspartate aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Toxicity Criteria for Adverse Events
ECHO	Echocardiogram
ECG	Electrocardiography
EOS	End of Study
EOT	End of Treatment
FAP	Full Analysis Population
FPI	First patient in
GGT	Gamma-Glutamyltransferase
i.v.	intravenous
LDH	Lactate dehydrogenase
IMP	Investigational Medicinal Product
LPI	Last patient in
LPO	Last patient out
MRI	Magnetic resonance imaging
MTB	Molecular tumor board
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
p.o.	per os/ oral
PR	Partial Response
PRO	Patient-reported outcome
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard deviation
SD	Stable Disease
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRAE	Treatment-related adverse event
TSH	Thyroid-stimulating hormone
UMVUE	Uniformly minimum variance unbiased estimator

Name of Sponsor:
German Cancer Research Center
Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
Phone: +49-6221 / 42 2850
Fax: +49-6221 / 42 2840
E-Mail: michael.baumann@dkfz-heidelberg.de,
u.weyrich@dkfz-heidelberg.de

Title of Study:
Continuous ReAssessment with Flexible ExTension in Rare Malignancies – CRAFT: The NCT PMO-1602 Phase II Trial

Name of IMP(s) incl. Active Ingredient:
Atezolizumab (Tecentriq®):
Arm 1, 2, 4, 6, 7

Vemurafenib (Zelboraf®):
Arm 1

Cobimetinib (Cotellic®):
Arm 1, 6

Trastuzumab (Herceptin®):
Arm 2

Pertuzumab (Perjeta®):
Arm 2

Alectinib (Alecensa®):
Arm 3

Ipatasertib:
Arm 4

Inavolisib:
Arm 5

Phase of Development:
Phase II

Protocol Version:
Version 4.0, 18.03.2024

Study Center(s) and Principal Investigator(s):
For a detailed list of all study centers and principal investigators see appendix 1.

Reference:

Bartlett, J. W., Seaman, S. R., White, I. R., Carpenter, J. R., for the Alzheimer's Disease Neuroimaging Initiative (2015). Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. Statistical Methods in Medical Research, 24(4), 462-487. doi:10.1177/0962280214521348

Edelmann, D., Terzer, T., Horak, P., Schlenk, R., Benner, A. (2025). The Progression-Free-Survival Ratio in molecularly aided tumor trials: A critical examination of current practice and suggestions for alternative methods. Biometrical Journal, 67, e70028. doi:10.1002/bimj.70028

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., . . . Verweij, J. (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer, 45(2), 228-247. doi:https://doi.org/10.1016/j.ejca.2008.10.026

Jung, S.-H. (1999). Rank tests for matched survival data. Lifetime Data Analysis, 5(1), 67-79. doi:10.1023/A:1009635201363

Simon, R. (1989). Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials, 10(1), 1-10. doi:https://doi.org/10.1016/0197-2456(89)90015-9

Heilig CE, Horak P, Kreutzfeldt S, et al. Rationale and design of the CRAFT (Continuous ReAssessment with Flexible ExTension in Rare Malignancies) multicenter phase II trial. ESMO Open. 2021 Dec;6(6):100310. DOI: 10.1016/j.esmoop.2021.100310. PMID: 34808524; PMCID: PMC8609144.

Studied Period (years):

First patient in (FPI): 13 October 2021

Last patient in (LPI): 07 August 2024

Last patient out (LPO): 30 December 2024

Objectives:

Primary Objective:

- To evaluate the efficacy of entity-informed, genomics-guided treatment in adult patients with advanced/metastatic tumors in each study arm.

Secondary Objectives:

- To assess Progression Free Survival (PFS) observed with genomic guided treatment (PFS2) in comparison to PFS observed directly before genomic guided treatment (PFS1), if three or more study arms go to the second stage according to Simon's two stage design.

Exploratory Objectives:

- To assess PFS observed with genomic guided treatment (PFS2) in comparison to PFS observed directly before genomic guided treatment (PFS1), if less than three arms reach second stage according to Simon's two stage design.
- To assess PFS in each study arm
- To assess overall survival (OS) in each study arm
- To assess Tumor Response Rate (TRR) including complete response (CR) and partial response (PR) according to RECIST v1.1 criteria after 16 weeks of specific treatment in each study arm
- To evaluate patient-reported outcomes overall and in each study arm
- To assess the clinical value of liquid biopsies in the study context

Safety Objective

- To assess safety/tolerability of specific treatments in each study arm

Methodology:

The NCT-PMO-1602 (CRAFT) trial was an open-label, multicenter phase-II basket study in subjects with previously treated advanced or recurrent solid tumors with treatment allocation according to results from whole genome/exome and RNA sequencing and validation by a multidisciplinary molecular tumor board (MTB). After molecular characterization of the tumor, eligible patients were assigned in the MTB to one of the seven study arms accordingly. Aim of this trial was to investigate the efficacy of targeted-therapy plus immune checkpoint inhibition in patients with advanced tumors exhibiting one of the following genetic alterations detected within the NCT/DKTK MASTER study: (i) BRAF V600E/K, (ii) ERBB2 amplification and/or overexpression or activating ERBB2 mutation, (iii) ALK rearrangement or activating ALK mutation, (iv) activating mutations or amplification of AKT, loss of PTEN, (v) activating PIK3CA mutations, (vi) aberrations predicting increased RAF-MEK-ERK pathway activity; (vii) patients with high tumor mutational burden and/or specific alterations predicting sensitivity to PD-1/PD-L1 inhibition are eligible within this study. An additional aim was the reduction of the cumulative hazard of progression-free survival observed within the study (PFS2) compared to the cumulative hazard of the progression-free time before inclusion into the study (PFS1). For the design of the trial, Simon's two-stage design was used.

Overall surveillance time:

Arm 1, Arm 3, Arm 4, Arm 5 and Arm 6: 28 days cycle, at least four cycles plus safety observation;
Arm 2 and Arm 7: 21 days cycle, at least five cycles plus safety observation
The time can vary depending on disease progression.

The schedule of treatment visits is provided in the following table 1.

Table 1. Schedule of treatment visits

Arm	Treatment	Visit
Arm 1 - BRAF V600E/K	Dispensation of Vemurafenib and Cobimetinib	2, 6, 8, 10, V-ExT
	Atezolizumab-Infusion	6, 7, 8, 9, 10, 11, V-ExT
Arm 2 - ERBB2	Trastuzumab-Infusion, Pertuzumab-Infusion, Atezolizumab-Infusion	2, 6, 7, 9, 10, V-ExT
Arm 3 - ALK	Dispensation of Alectinib	2, 6, 8, 10, V-ExT
Arm 4 - AKT	Dispensation of Ipatasertib	2, 6, 8, 10, V-ExT
	Atezolizumab-Infusion	2, 5, 7, 9, 10, 11, V-ExT
Arm 5 - PI3K	Dispensation of Inavolisib	2, 6, 8, 10, V-ExT
Arm 6 - MAPK	Dispensation of Cobimetinib	2, 6, 8, 10, V-ExT
	Atezolizumab-Infusion	2, 4, 6, 7, 8, 9, 10, 11, V-ExT
Arm 7 - Immune evasion	Atezolizumab-Infusion	2, 6, 7, 9, 10, V-ExT

* V-ExT: extended treatment

Imaging (local assessment): Visit 1 (imaging data from clinical routine), 8 (Week 8), 12 (Week 16), V-ExT

Vital signs and physical examination: Visit 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, V-ExT

ECHO: Visit 1 (for Arm 2, also performed at some of the subsequent visits at investigator's discretion)

ECG: Visit 1, 2, 3, 4, thereafter at investigator's discretion depending on treatment arm.

Concomitant medication:
Visit 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, V-ExT, safety observation, follow up

Laboratory assessments:
Hematology and blood chemistry: Visit 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, V-ExT
Coagulation: Visit 1, thereafter at investigator's discretion

Pregnancy Test: Visit 1, 2, and then varied between arms

Samples for biobanking: Visit 2, and then varied between arms

AEs: Visit 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, V-ExT, safety observation

PRO assessment: Visit 1, 8, 12, V-ExT

Number of Patients (planned and analyzed):

Number of patients planned:
In each study arm, 25 patients evaluable for the primary endpoint were planned. In the first stage, 14 patients were accrued. If there were 3 or fewer patients with an objective response of at least stable disease (confirmed radiologically), the respective study arm was stopped. Otherwise, 11 additional patients were accrued for a total of 25 patients.

Number of patients analyzed:
Full analysis population (FAP): 72

(Arm 1: 2; Arm 2: 15; Arm 3: 2; Arm 4: 13; Arm 5: 25; Arm 6: 9; Arm 7: 6)

Diagnosis and Main Criteria for Inclusion:

Indication
Metastatic or locally advanced malignancies

Main Inclusion criteria (valid for all arms):

1. Provision of written informed consent
2. Ability of patient to understand and comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations
3. Diagnosis of a metastatic or locally advanced malignancy
4. Progressive disease
5. At least one measurable lesion according to RECIST 1.1 that can be accurately assessed at baseline by computed tomography or magnetic resonance imaging and is suitable for repeated assessment
6. Prior administration of at least one standard chemotherapy for primary and/or relapsed malignancy according to current guidelines. Patients must have received standard therapy or have no standard therapy available. Or, in the opinion of investigator have been considered ineligible for a particular form of standard therapy on medical reasons.
7. ECOG Performance Status ≤2
8. Age ≥18 years, no upper age limit
9. a) Women of childbearing potential:
   Negative urine or blood pregnancy test *at baseline* as well as confirmed negative urine or blood pregnancy test *prior to study treatment*.
   A woman is considered of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
   Post-menopausal or evidence of non-childbearing status is defined within this clinical trial as follows:

- Amenorrheic for 1 year or more without an alternative medical cause following cessation of exogenous hormonal treatments PLUS follicle stimulating hormone (FSH) levels in the postmenopausal range in women not using hormonal contraception or hormonal replacement therapy
- Surgical sterilisation (bilateral oophorectomy, adnexectomy, hysterectomy or bilateral salpingectomy)

b) Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active: Consent to the use of two highly effective forms of contraception in place that result in a low failure rate of less than 1% per year when used consistently and correctly started after signing the informed consent form and continued throughout the period of study treatment plus at least seven months for both sexes after taking the last dose of study drug. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10. Availability of complete information about the last medical treatment given before study participation, i.e. remission status before start of treatment, dosage and timing of drugs applied, remission status and date of progression after treatment (in order to calculate PFS 1)

Molecular Inclusion criteria (as determined by Whole Genome or Exome Sequencing (WGS) and RNA Sequencing in NCT/DKTK MASTER validated or identification by gene panel performed in an accredited lab):

- **Arm 1 (BRAF V600E/K):** *BRAF* V600E/K mutation
- **Arm 2 (ERBB2):** *ERBB2* amplification and/or overexpression and/or activating ERBB2 mutation with overexpression
- **Arm 3 (ALK):** *ALK* rearrangement or activating *ALK* mutations including alternative transcription initiation (ALK-ATI)[26] or *RET*-fusions
- **Arm 4 (AKT/PTEN):** Activating *AKT1/2/3* mutations or amplifications; *PTEN* loss[a]
- **Arm 5 (PI3K):** Activating *PIK3CA* mutations without concurrent activating *KRAS/NRAS/HRAS*-alterations
- **Arm 6 (MAPK):** Aberrations predicting increased RAF-MEK-ERK pathway activity, excluding *BRAF* V600E/K mutations and activating *KRAS/NRAS/HRAS* alterations[a]
- **Arm 7 (Immune evasion):** High tumor mutational burden (defined as ≥10 mut/Mb based on panel sequencing or WES other than NCT/DKTK MASTER and ≥5 Mut/Mb based on WES/WGS in NCT/DKTK MASTER and/or specific alterations predicting sensitivity to PD1/PDL1 inhibition (e.g. DNA mismatch repair deficiency or *PDL1* amplification and/or overexpression), ineligibility for the six specific arms[a,b]

[a] Tumor board recommendations including associated evidence levels, and prioritization based on multidisciplinary discussion are included in tabular form for each study arm in the study report.
[b] Detailed inclusion criteria according to molecular tumor board recommendation

STUDY TREATMENT

Investigational Product, Dose and Mode of Administration, Batch Numbers:

Vemurafenib (Arm 1):

- Mode of administration: p.o.
- Batch numbers: 1167401, 1174232

Cobimetinib (Arm 1, 6):

- Mode of administration: p.o.
- Batch numbers: 1167396, 1174266

Atezolizumab (Arm 1, 2, 4, 6, 7):

- Mode of administration: i.v.
- Batch numbers 1200 mg: 1167389, 1174269, 1178032
  840 mg: 1167395, 1174264, 1177989, 1183425

Trastuzumab (Arm 2):
- Mode of administration: i.v.
- Batch numbers: 1167402, 1174249, 1178018

Pertuzumab (Arm 2):
- Mode of administration: i.v.
- Batch numbers: 1167397, 1171199, 1174689, 1178111, 1183680

Alectinib (Arm 3):
- Mode of administration: p.o.
- Batch numbers: 1167390, 1174243, 1178125

Ipatasertib (Arm 4):
- Mode of administration: p.o.
- Batch numbers: 1167403, 1174237, 1178005, 1183051

Inavolisib (Arm 5):
- Mode of administration: p.o.
- Batch numbers: 1176918, 1177167, 1181533, 1182234, 1184943

Dose:

Arm 1: 28-day run in phase of Vemurafenib (960 mg twice daily) and Cobimetinib (60 mg once daily for 21 days in a 28-day cycle.) followed by Vemurafenib (720 mg twice daily), Cobimetinib (60 mg once daily for 21 days in a 28-day cycle), and Atezolizumab (840 mg every 2 weeks)

Arm 2: Trastuzumab (8 mg/kg of body weight as a loading dose, followed by 6 mg/kg every 3 weeks), Pertuzumab (840 mg as a loading dose, followed by 420 mg every 3 weeks), and Atezolizumab (1200 mg every 3 weeks)

Arm 3: Alectinib (600 mg twice daily)

Arm 4: Ipatasertib (400 mg once daily for 21 days in a 28-day cycle) and Atezolizumab (1200 mg in the first cycle, followed by 840 mg every 3 weeks)

Arm 5 Inavolisib (9 mg once daily during a 28-days cycle)

Arm 6: Cobimetinib (60 mg once daily for 21 days in a 28-day cycle) and Atezolizumab (840 mg every 2 weeks)

Arm 7: Atezolizumab (1200 mg every 3 weeks)

Duration of Treatment:

The duration of the trial for each patient was expected to be 110 days treatment plus 28 days safety follow-up, plus a continuous survival follow-up every 12 weeks until end of study

(EOS). In case of clinical benefit, treatment continuation beyond week 16 was possible until clinical progress with subsequent safety follow-up or at the longest End of Study, defined as 110 days treatment plus 28 days after last patient first visit (LPFV).

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

Not applicable.

Criteria for Evaluation:

Efficacy analyses:

Primary efficacy endpoint

- Disease control rate (DCR) on day 110 (± 5), defined as the presence of a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1.

Secondary efficacy endpoints

- Overall Paired Progression Free Survival observed with genomic guided treatment (PFS2) and Progression Free Survival observed directly before genomics-guided treatment (PFS1).

PFS1 is defined as the time from start of the last chemotherapy line (start of first sequence) prior to inclusion in the CRAFT trial until progression observed directly after therapy. If the last treatment prior to inclusion in the trial was surgery, PFS1 is defined as the time from surgery (date of surgery) to progression observed directly after surgery. If no pre-treatment was performed ending with disease progression, the patient is not included in this analysis.

PFS2 is defined as the time from start of study therapy until clinically or radiologically confirmed disease progression or death from any cause, whichever occurs first. Patients without a PFS event at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.

Exploratory efficacy endpoint

- Progression-free survival (PFS), defined as the time from start of study therapy until clinically or radiologically confirmed disease progression or death from any cause, whichever occurs first. Patients without a PFS event at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- Overall survival (OS), defined as the time from start of study therapy to time of death from any cause. Patients still alive at the end of the study or lost to follow up will be censored at the time they were last known to be alive.
- Tumor Response Rate (TRR) including CR and PR according RECIST v1.1 criteria on day 110 (±5) as well as every 12 weeks during an extended treatment period in responding patients. Patients who discontinue treatment without progression and receive a subsequent anti-cancer therapy during the time of the respective observation period (day 110 (±5), day 110 (±5) + 12 weeks, etc.) are defined as failures. Patients are also defined as failures if progressive disease is documented during the respective observation period. If stable disease is documented during the observation period, but CR or PR is present at the end of the observation period, the patient is counted as responder.
- Patient reported outcomes (PRO), collected at baseline, week 8 (± 3 days) and week 16 (± 3 days), and during extended treatment period every 12 weeks; including
    - Health-related QoL is calculated as the new EORTC QLQ-C30 Summary Score recommended by the EORTC Quality-of-Life Group. In addition, the EORTC QLQ Function and Symptom Scores are calculated according to the actual EORTC Scoring Manual.

- Fatigue is calculated from the EORTC QLQ-FA12 according to the EORTC Scoring Manual.
- Sleep problems are calculated from the PSQI according to the corresponding scoring guidelines.
- Perceived cognitive impairment and impact of cognitive changes are calculated from the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) function scale according to the corresponding scoring manual.
- Anxiety is calculated from the Patient Health Questionnaire for Anxiety and Depression (PHQ-4) according to the corresponding scoring manual.
- Depression is calculated from the PHQ-4 according to the corresponding scoring manual.
- Pain interference is calculated from the Brief Pain Interference (BPI) according to the corresponding scoring manual.

- Mutational level measured in liquid biopsies at baseline and during trial treatment

Safety analysis:

Safety assessment comprises continuous recording of all adverse events (AE) and their severity, including serious adverse events (SAE), adverse events of special interest (AESI), suspected unexpected serious adverse reactions (SUSAR) as well as the relation of AEs to the study treatment; dose modifications for toxicity; and discontinuation of study treatment during the trial phase. The assessment of safety is mainly based on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline (i.e. are reported as AEs).

Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, the duration, whether the AE was serious, the intensity, the relationship to the study drug, actions taken, and the clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, SAEs, AESIs, SUSARs, special situations, AEs by intensity, and AEs by the relationship to the study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) are determined.

Toxic effects are graded according to NCI CTCAE (v5.0). The cases of disease progression which are not fatal or life-threatening and do not require hospitalization are not considered AEs and have not to be reported as SAEs.

Statistical methods:

Definition of study populations:

- Full analysis Population (FAP): all patients included in the study who received at least one dose of the study medication. The FAP serves as the population for all efficacy and safety analyses.
- Screening Population: treated patients as well as patients who were screened in the study, but have not received any study treatment.
- Sensitivity Population Arm 4: due to a protocol amendment (October 7th 2022) molecular markers for inclusion in arm 4 were restricted from PI3K/AKT and AKT/PTEN to only AKT/PTEN. In this set, only patients of arm 4 with markers AKT/PTEN are included who received at least one dose of study medication. This set may be used for sensitivity analysis of endpoints for Arm 4.

General analysis principles:

Binary endpoints (DCR, TRR) are described by the binomial proportion together with a 95% Clopper-Pearson confidence interval (CI).

Concerning the primary efficacy endpoint, the null hypothesis H_0: DCR ≤ 0.2 is tested by means of Simon's optimal two-stage design, separately for each study arm.

The distribution of time-to-event endpoints (PFS and OS) is estimated non-parametrically using the method of Kaplan and Meier.

To address the secondary efficacy objective, the null hypothesis of equal cumulative hazards of PFS2 and PFS1 are compared using a one-sided paired log-rank test (Jung, 1999). In sensitivity analysis, the PFS2/PFS1 ratio is assessed using the approach by Edelmann et al. (2025).

Analyses for all remaining endpoints (patient reported outcomes, safety endpoints) are analyzed descriptively.

All endpoints are analyzed separately for each study arm and for all study arms combined.

SAS Version 9.4 and R 4.5.1 were used to conduct the analyses presented in this report.

Analysis of efficacy endpoints

DCR

The analysis of the primary endpoint, DCR, is performed according to Simon's OTSD for each study arm separately using the FAP. More explicitly, n_1=14 patients are accrued in the first stage. If there are r_1=3 or fewer patients with an objective response of at least stable disease (confirmed radiologically), the respective study arm is stopped. Otherwise, 11 additional patients will be accrued for a total of n=25 patients. In the final analysis, the null hypothesis is rejected and the treatment strategy recommended for further development if eight or more patients with an objective response of at least stable disease are observed among the 25 patients. This corresponds to binomial testing at a significance level of 10%.

PFS2/ PFS1

The analysis compares the cumulative hazard of PFS2 with the cumulative hazard of PFS1 using a one-sided paired log-rank test (Jung, 1999) with a significance level of 5% based on the FAP. In sensitivity analysis, also based on the FAP, PFS2/PFS1 ratio is assessed using the approach by Edelmann et al. (2025).

Tumor response

Tumor response is analyzed based on the FAP. Descriptive statistics and patient data listing are used for the presentation of all response data. The treatment effect is evaluated by calculating the binomial proportion and 95% Clopper-Pearson CI of the TRR.

OS and PFS

OS and PFS are analyzed based on the FAP. The method of Kaplan and Meier is used to estimate the distributions of OS and PFS. The number of patients who died and causes of death are summarized overall and by study arm.

Patient Reported Outcomes (PRO)

The scores of the questionnaires concerning quality of life (QoL), fatigue, sleep problems, perceived cognitive impairment and impact of cognitive changes, anxiety, depression and pain interference are computed according to the EORTC scoring manual. As per EORTC scoring manual the scores are only calculated if at least 50% of the items have been answered (Fayers et al. 2001). Scores are analyzed for all patients in the FAP according to the corresponding EORTC guidelines. QoL subscales and single item sub-scores are summarized by the mean, standard deviation, median, minimum and maximum, and tabulated by visit. The change from baseline for all domains is examined descriptively.

Analysis of the safety endpoints:

AEs

AEs with start date after start of study medication are reported based on the full analysis population per arm and overall. The number and percentage of patients having AEs is reported overall and by severity graded according to the National Cancer Institute CTCAE version 5.0. Patients with multiple occurrences of the same AE are counted once, and only the maximum severity level is presented in the severity summaries. AESIs and AEs that are related to one of the study drugs are tabulated separately. All AEs are tabulated by SOC.

In addition, the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle during the study phase is determined and summarized. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) are determined. Regarding SAEs, the following information is summarized for each study arm based on the full analysis population:

- the total number of SAEs,
- the proportion of SAEs leading to death,
- the number of SAEs reported per patient,
- the number of patients with SAE by relationship with any study drug (related, not related, unknown)

Adverse events with start date after written informed consent and prior to start of study medication are listed separately.

Clinical laboratory evaluation

The number of laboratory values including blood counts and blood chemistry that fall outside of normal ranges and/or show prominent worsening from baseline during the study phase are reported. Laboratory data is summarized by presenting summary statistics of raw data and change from baseline values.

Vital signs and physical examination findings related to safety

The number of values related to vital signs and physical examination that fall outside of normal ranges and/or show prominent worsening from baseline during the study phase are reported. Data is summarized by presenting summary statistics of raw data and change from baseline values.

Study populations:

A total of 101 patients were screened at 7 trial sites. Of these, 28 were screening failures and 73 were enrolled into 7 treatment arms. One patient in Arm 6 withdrew informed consent before start of treatment. Therefore, 72 patients received study treatment and were included in the FAP. Sensitivity Population Arm 4 was not analyzed, because Arm 4 was stopped in stage 1 (according to Simon's two-stage design) with only 13 patients, making such an analysis not meaningful.

Details on baseline demographics and clinical characteristics for the FAP are provided in table 2.

Table 2. Demographic and clinical characteristics of the patients at baseline (FAP)

Arm (N)	**Arm 1 (2)**	**Arm 2 (15)**	**Arm 3 (2)**	**Arm 4 (13)**	**Arm 5 (25)**	**Arm 6 (9)**	**Arm 7 (6)**	**All (72)**
Sex, n (%)								
Female	0	5 (33.3)	1 (50.0)	7 (53.8)	15 (60.0)	3 (33.3)	3 (50.0)	34 (47.2)
Male	2 (100.0)	10 (66.7)	1 (50.0)	6 (46.2)	10 (40.0)	6 (66.7)	3 (50.0)	38 (52.8)
Age categorical (years), n (%)								

18 - 44	0	2 (13.3)	2 (100.0)	4 (30.8)	6 (24.0)	4 (44.4)	0	18 (25.0)
45 - 64	2 (100.0)	7 (46.7)	0	3 (23.1)	11 (44.0)	3 (33.3)	3 (50.0)	29 (40.3)
>=65	0	6 (40.0)	0	6 (46.2)	8 (32.0)	2 (22.2)	3 (50.0)	25 (34.7)
Race, n (%)								
Caucasian/ White	2 (100.0)	15 (100.0)	2 (100.0)	12 (92.3)	25 (100.0)	9 (100.0)	6 (100.0)	71 (98.6)
Other	0	0	0	1 (7.7)	0	0	0	1 (1.4)
Age continuous (years)								
Mean (SD)	60.5 (4.95)	60.1 (10.53)	38.5 (4.95)	58.2 (14.83)	56.4 (12.67)	45.1 (15.67)	61.8 (8.68)	56.1 (13.36)
Median	60.5	60.0	38.5	57.0	58.0	45.0	64.0	58.0
Min - Max	57.0 - 64.0	39.0 - 72.0	35.0 - 42.0	40.0 - 82.0	37.0 - 79.0	21.0 - 68.0	51.0 - 71.0	21.0 - 82.0
BMI (kg/m^2)								
Mean (SD)	22.1 (1.37)	26.3 (5.20)	21.6 (3.66)	24.3 (3.32)	23.8 (5.44)	27.3 (11.96)	24.6 (4.38)	24.8 (6.09)
Median	22.1	26.4	21.6	23.7	21.0	23.3	24.8	23.5
Min - Max	21.1 - 23.1	19.4 - 35.3	19.0 - 24.2	18.6 - 30.5	18.4 - 41.0	17.0 - 57.5	18.2 - 31.4	17.0 - 57.5
Height (cm)								
Mean (SD)	181.5 (4.95)	174.8 (9.47)	169.5 (13.44)	174.2 (10.89)	172.6 (8.09)	174.3 (12.21)	173.2 (9.99)	173.8 (9.46)
Median	181.5	178.0	169.5	172.0	174.0	174.0	176.0	174.5
Min - Max	178.0 - 185.0	155.0 - 187.0	160.0 - 179.0	158.0 - 192.0	159.0 - 191.0	156.0 - 190.0	156.0 - 183.0	155.0 - 192.0
Weight (kg)								
Mean (SD)	73.0 (8.49)	80.6 (18.28)	61.5 (0.71)	74.0 (14.26)	71.2 (18.95)	72.5 (15.10)	74.0 (15.07)	73.8 (16.76)
Median	73.0	82.0	61.5	68.0	67.0	75.0	73.5	71.4
Min - Max	67.0 - 79.0	55.8 - 122.0	61.0 - 62.0	55.0 - 102.0	49.0 - 130.0	51.0 - 102.0	57.5 - 94.0	49.0 - 130.0
Grading - primary diagnosis, n (%)								
G1	0	1 (6.7)	0	0	1 (4.0)	1 (11.1)	0	3 (4.2)
G2	0	7 (46.7)	0	4 (30.8)	8 (32.0)	3 (33.3)	2 (33.3)	24 (33.3)
G3	1 (50.0)	5 (33.3)	0	4 (30.8)	9 (36.0)	3 (33.3)	2 (33.3)	24 (33.3)
G4	0	1 (6.7)	0	2 (15.4)	0	0	0	3 (4.2)
Missing	1 (50.0)	1 (6.7)	2 (100.0)	3 (23.1)	7 (28.0)	2 (22.2)	2 (33.3)	18 (25.0)
Grading - last recurrence, n (%)								
G1	0	0	0	0	1 (4.0)	1 (11.1)	0	2 (2.8)
G2	0	4 (26.7)	0	3 (23.1)	9 (36.0)	2 (22.2)	2 (33.3)	20 (27.8)
G3	1 (50.0)	6 (40.0)	0	3 (23.1)	6 (24.0)	3 (33.3)	3 (50.0)	22 (30.6)
G4	0	1 (6.7)	0	2 (15.4)	0	0	0	3 (4.2)
Missing	1 (50.0)	4 (26.7)	2 (100.0)	5 (38.5)	9 (36.0)	3 (33.3)	1 (16.7)	25 (34.7)
Previous radiotherapy, n (%)								
Yes	0	4 (26.7)	1 (50.0)	8 (61.5)	17 (68.0)	5 (55.6)	4 (66.7)	39 (54.2)
No	2 (100.0)	11 (73.3)	1 (50.0)	5 (38.5)	8 (32.0)	4 (44.4)	2 (33.3)	33 (45.8)
Previous chemotherapy, n (%)								
Yes	2 (100.0)	14 (93.3)	2 (100.0)	13 (100.0)	24 (96.0)	9 (100.0)	6 (100.0)	70 (97.2)
No	0	1 (6.7)	0	0	1 (4.0)	0	0	2 (2.8)
Previous surgery, n (%)								

Yes	0	12 (80.0)	2 (100.0)	9 (69.2)	19 (76.0)	8 (88.9)	6 (100.0)	56 (77.8)
No	2 (100.0)	3 (20.0)	0	4 (30.8)	6 (24.0)	1 (11.1)	0	16 (22.2)

58.3% (42/72) of patients had the same tumor grade at primary diagnosis and last recurrence.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Two arms, Arm 2 and Arm 5, met the predefined criteria to proceed to stage two, whereas the other arms did not. In Arm 2, one patient withdrew informed consent after Cycle 2 and thus one more was recruited leading to 15 patients treated as part of stage 1. Among them, five patients achieved at least disease control; however, no additional patients were recruited thereafter due to overall EOS. In Arm 5, four patients achieved at least disease control among the first 12 treated patients. Therefore, this arm proceeded to stage 2 and the planned total sample size of 25 patients was reached.

For the other arms, Arm 4 was terminated for futility according to Simons two-stage design after 13 patients had been treated, of whom only two achieved at least disease control; therefore, the planned sensitivity analysis was not meaningful and was not performed. Arm 1, 3, 6, and 7 were terminated early without reaching the planned number of patients due to overall EOS.

DCR and TRR (week16 assessment)

Table 3 provides the overall response data according to RECIST v1.1 at week 16 or EOT of the FAP.

Table 3. Overall Response per RECIST v1.1 at Week 16 or EOT (FAP)

RECIST result / reason of EOT		**Number of patients N (%)**							
	Arm (N)	**Arm 1 (2)**	**Arm 2 (15)**	**Arm 3 (2)**	**Arm 4 (13)**	**Arm 5 (25)**	**Arm 6 (9)**	**Arm 7 (6)**	**All (72)**
Overall Response (RECIST v1.1) at Week 16 or EOT *	NE	0	1 (6.7)	0	0	0	0	0	1 (1.4)
	PD	0	5 (33.3)	1 (50.0)	10 (76.9)	12 (48.0)	6 (66.7)	3 (50.0)	37 (51.4)
	PR	2 (100.0)	4 (26.7)	0	1 (7.7)	3 (12.0)	1 (11.1)	1 (16.7)	12 (16.7)
	SD	0	1 (6.7)	1 (50.0)	1 (7.7)	5 (20.0)	1 (11.1)	1 (16.7)	10 (13.9)
Not available, reason of EOT	AE other than undue toxicity	0	0	0	0	2 (8.0)	0	0	2 (2.8)
	Clinical PD, no MRI/CT done	0	2 (13.3)	0	1 (7.7)	1 (4.0)	0	0	4 (5.6)
	Death	0	1 (6.7)	0	0	0	0	0	1 (1.4)
	Investigator's decision	0	0	0	0	1 (4.0)	0	0	1 (1.4)
	Other reason(s)	0	0	0	0	0	1 (11.1)	0	1 (1.4)
	Undue Toxicity	0	0	0	0	1 (4.0)	0	1 (16.7)	2 (2.8)
	Withdrawal of informed consent (patient's decision)	0	1 (6.7)	0	0	0	0	0	1 (1.4)

Undue Toxicity: 01-036 (Arm 7), hepatitis grade 3; 03-004, (Arm 5), hyperglycemia

Investigator's decision: 11-006 (Arm 5), deterioration of general condition, suspected disease progression

Other reason(s): 11-012 (Arm 6), clinical and biochemical progress

* including patients with radiological PD occurring before Week 16 that led to EOT.

The results of binomial proportion together with 95% Clopper-Pearson CI for DCR and TRR after 16 weeks of specific treatment in each study arm are presented in the following table 4.

Table 4. Overview of DCR and TRR at week 16 (FAP)

			DCR				TRR			
					95% CI				95% CI	
Arm	**last Stage**	**N (FAP)**	**Responder**	**Proportion**	**Lower**	**Upper**	**Responder**	**Proportion**	**Lower**	**Upper**
Arm 1	Stage 1	2	2	1.0000	0.1581	1.0000	2	1.0000	0.1581	1.0000
Arm 2	Stage 1	15	5	0.3333	0.1182	0.6162	4	0.2667	0.0779	0.5510
Arm 3	Stage 1	2	1	0.5000	0.0126	0.9874	0	0		
Arm 4	Stage 1	13	2	0.1538	0.0192	0.4545	1	0.0769	0.0019	0.3603
Arm 5	Stage 2	25	8	0.3200	0.1495	0.5350	3	0.1200	0.0255	0.3122
Arm 6	Stage 1	9	2	0.2222	0.0281	0.6001	1	0.1111	0.0028	0.4825
Arm 7	Stage 1	6	2	0.3333	0.0433	0.7772	1	0.1667	0.0042	0.6412
All arms		72	22	0.3056	0.2024	0.4253	12	0.1667	0.0892	0.2730

Overall, DCR was 30.6% (22 /72, 12 PR and 10 SD) and TRR was 16.7% (12/72) in the FAP. Eight patients in Arm 5 achieved disease control (3 PR and 5 SD). According to Simon's optimal two-stage design, the null hypothesis DCR ≤ 0.2 could be rejected at the one-sided 10% significance level. The estimated DCR, calculated using the uniformly minimum variance unbiased estimator (UMVUE) was 0.3505 (90% CI: 0.2031–0.4483), and the *p*-value was 0.0933.

Details on the status at EOT/EOS are shown in table 5.

Table 5. Status at EOT/EOS

FAP		**Number of patients N (%)**							
	Arm (N)	**Arm 1 (2)**	**Arm 2 (15)**	**Arm 3 (2)**	**Arm 4 (13)**	**Arm 5 (25)**	**Arm 6 (9)**	**Arm 7 (6)**	**All (72)**
Status at EOT									
EOT due to	Disease Progression	2 (100.0)	11 (73.3)	2 (100.0)	12 (92.3)	18 (72.0)	8 (88.9)	4 (66.7)	57 (79.2)
	Overall end of study	0	2 (13.3)	0	1 (7.7)	2 (8.0)	0	0	5 (6.9)
Premature termination of trial treatment	AE other than undue toxicity	0	0	0	0	2 (8.0)	0	0	2 (2.8)
	Death	0	1 (6.7)	0	0	0	0	0	1 (1.4)
	Investigator's decision	0	0	0	0	2 (8.0)	0	0	2 (2.8)
	Other reason(s)	0	0	0	0	0	1 (11.1)	0	1 (1.4)
	Undue Toxicity	0	0	0	0	1 (4.0)	0	1 (16.7)	2 (2.8)
	Withdrawal of informed consent (patient's decision)	0	1 (6.7)	0	0	0	0	1 (16.7)	2 (2.8)

Details about premature EOT: AE other than undue toxicity: 01-037 (Arm 5), febrile infection; 13-005 (Arm 5), daytime sleepiness, memory disorder, changes in character Investigator's decision: 03-003 (Arm 5), persistent infectious situation, poor general condition, progressive disease 11-006 (Arm 5), deterioration of general condition, suspected disease progression Other reason(s): 11-012 (Arm 6), clinical and biochemical progress Undue Toxicity: 01-036 (Arm 7), hepatitis grade 3; 03-004 (Arm 5), hyperglycemia									
Status at EOS									
EOS due to	AE other than undue toxicity	0	0	0	0	1 (4.0)	0	0	1 (1.4)
	Death	2 (100.0)	8 (53.3)	1 (50.0)	11 (84.6)	12 (48.0)	6 (66.7)	1 (16.7)	41 (56.9)
	Investigator's decision *	0	0	0	0	1 (4.0)	0	0	1 (1.4)
	Lost to Follow-Up	0	0	0	0	0	1 (11.1)	0	1 (1.4)
	Overall end of study	0	7 (46.7)	1 (50.0)	2 (15.4)	11 (44.0)	2 (22.2)	5 (83.3)	28 (38.9)
Details about EOS reason: Investigator's decision: 13-004 (Arm 5), disease progression AE other than undue toxicity: 13-005 (Arm 5), daytime sleepiness, memory disorder, changes in character									

Survival analyses

The follow-up time for patients in the FAP was calculated from the date of first treatment to the date of last known contact. Patients who died during the study were censored. The median follow-up was 15.9 months (95% CI 11.6–21.1) overall, 8.2 months (95% CI 6.8–not estimable) for Arm 2, and 17.7 months (95% CI 9.4–21.1) for Arm 5.

PFS (PFS2)

Patients without progression or death were censored at last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments. In the FAP, the number of patients with an event PD/death was 66 (91.7%) overall, 13 (86.7%) in Arm 2, 12 (92.3%) in Arm 4, 22 (88.0%) in Arm 5, and 19 (100.0%) in other arms (1, 3, 6, 7). The median PFS was 2.5 months (95% CI 1.9–3.7) overall, 3.5 months (95% CI 1.5–6.2) for Arm 2, 1.9 months (95% CI 1.2–2.8) for Arm 4, 3.6 months (95% CI 1.9–5.4) for Arm 5, and 1.9 months (95% CI 1.7–5.8) for other arms. For more information see table 6.

Table 6. Time to progression from date of first treatment (in Months)

Parameter	Arm 2	Arm 4	Arm 5	Other arms (1,3,6,7)	All
Number of Patients	15	13	25	19	72
Number (%) of Patients with the Event	13 (86.7)	12 (92.3)	22 (88.0)	19 (100.0)	66 (91.7)
25 Percent Point Estimate (95% CI) *	1.9 (0.1, 2.3)	1.8 (1.1, 1.9)	1.8 (0.5, 3.4)	1.7 (0.8, 1.8)	1.8 (1.2, 1.9)
Median (95% CI) *	3.5 (1.5, 6.2)	1.9 (1.2, 2.8)	3.6 (1.9, 5.4)	1.9 (1.7, 5.8)	2.5 (1.9, 3.7)
75 Percent Point Estimate (95% CI) *	6.2 (3.5, .)	2.8 (1.9, .)	6.1 (3.7, 10.2)	6.4 (1.9, 11.5)	5.8 (3.9, 9.1)
6-month event free rate (95% CI) **	0.320 (0.109, 0.557)	0.154 (0.025, 0.388)	0.250 (0.102, 0.431)	0.263 (0.096, 0.468)	0.248 (0.154, 0.353)
9-month event free rate (95% CI) **	0.000 (., .)	0.154 (0.025, 0.388)	0.167 (0.052, 0.337)	0.211 (0.066, 0.410)	0.155 (0.081, 0.251)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points were displayed

PFS2/ PFS1

PFS1 was available for 71 patients in the FAP and PFS2 was available for 72 patients. Consequently, data from 71 patients were included in the paired analysis.

In the primary analysis, PFS2 was compared with PFS1 using a one-sided paired log-rank test at a significance level of α = 5% according to Jung (1999). The resulting value of the test statistic W was -1.196 with a *p*-value of 0.884. As sensitivity analysis, the PFS2/PFS1 ratio was assessed using a marginal Cox model with robust variance estimate as proposed by Edelmann et al. (2025). The hazard ratio (HR) comparing PFS2 with PFS1 was tested using the one-sided null hypothesis H_0: HR ≥ 1 against the alternative H_1: HR < 1. The estimated HR was 1.224, with a one-sided *p*-value of 0.886.

The results of the primary analysis and the sensitivity analysis were almost identical. Neither showed any advantage for PFS2 over PFS1.

OS

In the FAP, the number of patients who died was 41 (56.9%) overall, 8 (53.3%) in Arm 2, 11 (84.6%) in Arm 4, 12 (48.0%) in Arm 5, and 10 (52.6%) in other arms (1, 3, 6, 7). The median OS was 10.1 months (95% CI 7.4–21.5) overall, 8.0 months for Arm 2, 8.6 months (95% CI 2.2–21.5) for Arm 4, 10.1 months for Arm 5, and 11.1 months for other arms. The upper limits of the 95% CIs for Arm 2, Arm 5 and other arms were not estimable. Following table 7 provides the detailed information.

Table 7. Time to death from date of first treatment (in Months)

Parameter	Arm 2	Arm 4	Arm 5	Other arms (1,3,6,7)	All
Number of Patients	15	13	25	19	72
Number (%) of Patients with the Event	8 (53.3)	11 (84.6)	12 (48.0)	10 (52.6)	41 (56.9)
25 Percent Point Estimate (95% CI) *	2.1 (0.4, 8.0)	2.4 (1.1, 8.6)	3.9 (1.2, 6.9)	4.6 (1.1, 10.4)	3.0 (1.7, 6.9)
Median (95% CI) *	8.0 (1.5, .)	8.6 (2.2, 21.5)	10.1 (4.7, .)	11.1 (4.6, .)	10.1 (7.4, 21.5)
75 Percent Point Estimate (95% CI) *	. (7.9, .)	21.5 (3.4, .)	. (., .)	33.8 (11.1, .)	27.1 (21.5, .)
6-month event free rate (95% CI) **	0.733 (0.436, 0.891)	0.538 (0.248, 0.760)	0.659 (0.432, 0.813)	0.737 (0.479, 0.881)	0.672 (0.549, 0.769)
9-month event free rate (95% CI) **	0.290 (0.055, 0.589)	0.462 (0.192, 0.696)	0.527 (0.310, 0.705)	0.675 (0.414, 0.840)	0.526 (0.399, 0.638)
12-month event free rate (95% CI) **	0.290 (0.055, 0.589)	0.462 (0.192, 0.696)	0.475 (0.261, 0.661)	0.478 (0.230, 0.690)	0.453 (0.326, 0.570)
18-month event free rate (95% CI) **	0.290 (0.055, 0.589)	0.308 (0.095, 0.554)	0.475 (0.261, 0.661)	0.478 (0.230, 0.690)	0.406 (0.279, 0.529)

*corresponding to time to death in months
**Kaplan-Meier estimates for the respective time points were displayed

Kaplan–Meier plots of PFS and OS are shown in the following figure 1 and 2.

Figure 1. PFS (FAP)

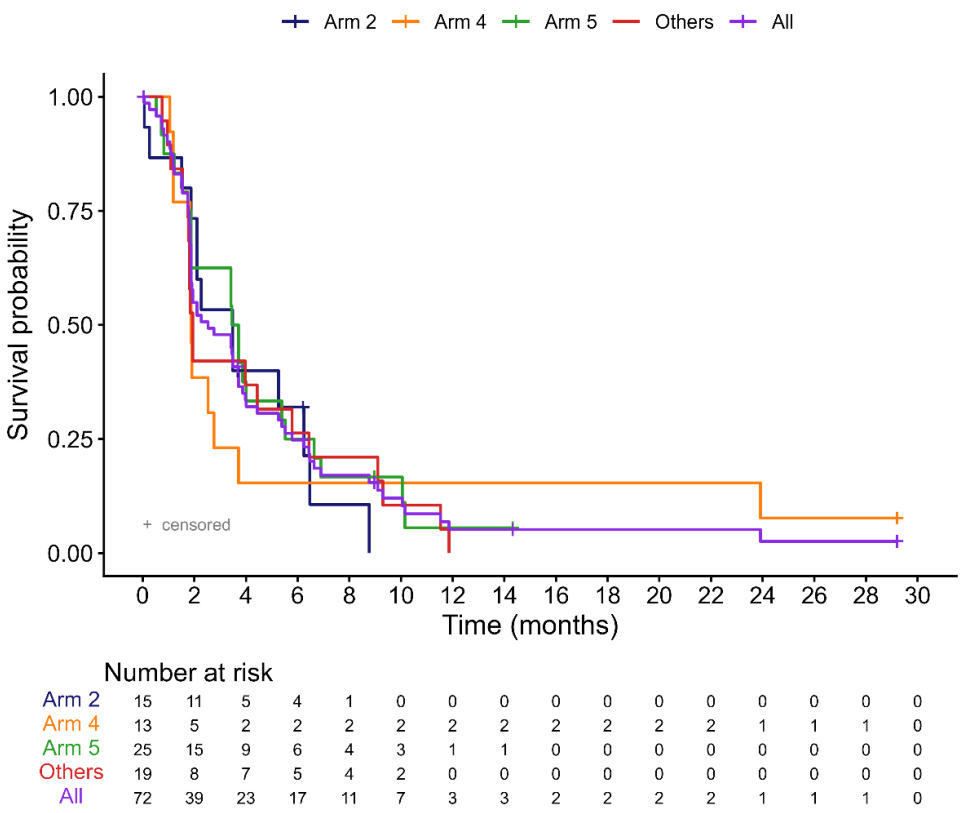
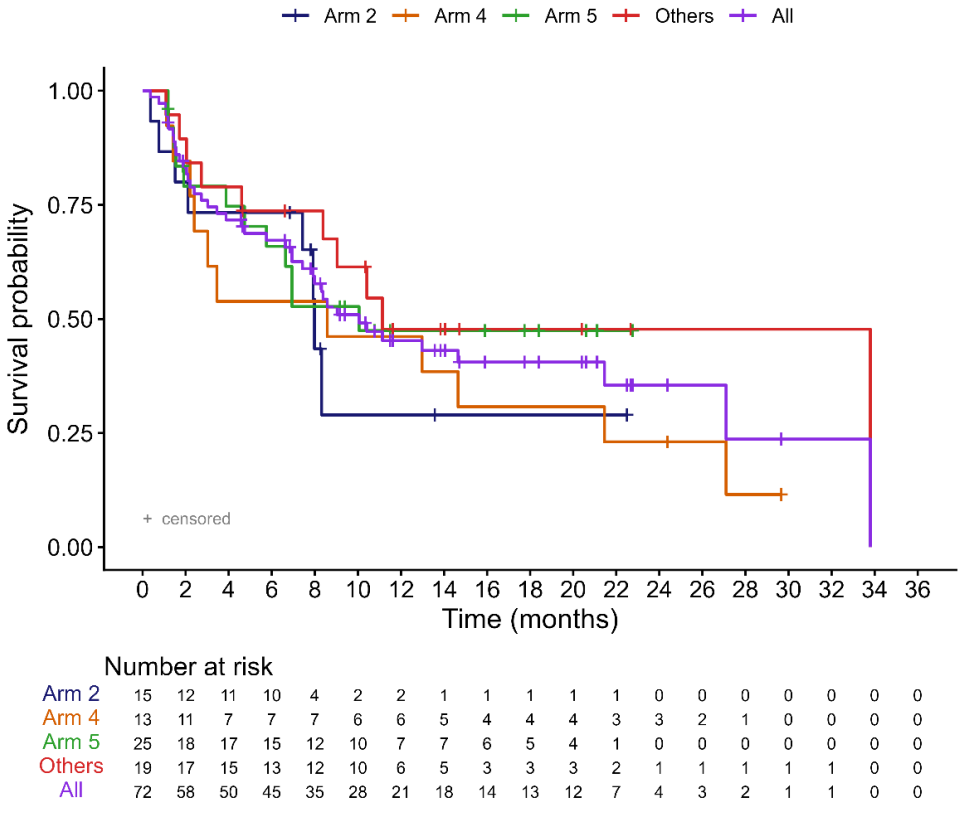


Figure 2. OS (FAP)



SAFETY RESULTS:

In the following results, only AEs or tests/examinations on or after the date of first treatment were included. No special situation has been reported.

Adverse events (AEs)

The total drug exposure was 540 days for patients in Arm 1, 1603 days in Arm 2, 339 days in Arm 3, 2233 days in Arm 4, 3285 days in Arm 5, 678 days in Arm 6, and 522 days in Arm 7.

A total of 70 (97.2%) treated patients experienced at least one AE of any causality, whereas one patient in Arm 2 and one patient in Arm 4 had no AEs documented. AEs were reported in 2 patients in Arm 1, 14 patients in Arm 2, 2 patients in Arm 3, 13 patients in Arm 4, 25 patients in Arm 5, 9 patients in Arm 6, and 6 patients in Arm 7 (Table 8). AEs resulting in death occurred in 16 patients, all of which were attributed to disease progression. Overview of all SAEs see table 9.

The most frequently reported AEs by SOC across all treatment arms were “Gastrointestinal disorders” (48/72, 66.7%), “General disorders and administration site conditions” (45/72, 62.5%), “Investigations” (41/72, 56.9%), and “Infections and infestations” (39/72, 54.2%). Details of all AEs, SAEs and AEs ≥ Grade 3 by SOC are provided in the following table 10-12. The most frequently reported AEs by PT were diarrhea (14/72, 19.4%), hyperglycaemia (12/72, 16.7%), and fatigue (10/72, 13.9%), which occurred in at least 10% of the patients.

Table 8. Overview of all AEs

	Number of patients N (%)							
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All**
Any AE	2 (100.0)	14 (93.3)	2 (100.0)	12 (92.3)	25 (100.0)	9 (100.0)	6 (100.0)	70 (97.2)
Any SAE	2 (100.0)	3 (20.0)	2 (100.0)	5 (38.5)	7 (28.0)	4 (44.4)	1 (16.7)	24 (33.3)
Any Severe AE (CTCAE v5.0 Grade 3 or 4)	2 (100.0)	7 (46.7)	2 (100.0)	9 (69.2)	12 (48.0)	6 (66.7)	3 (50.0)	41 (56.9)
Any AE Grade>=3	2 (100.0)	8 (53.3)	2 (100.0)	9 (69.2)	13 (52.0)	6 (66.7)	3 (50.0)	43 (59.7)
Dose of Study Drug Reduced or Temporarily Discontinuation Due to AE	Atezolizumab: 1 (50.0) Cobimetinib: 2 (100.0) Vemurafenib: 2 (100.0)	Atezolizumab: 2 (13.3) Pertuzumab: 2 (13.3) Trastuzumab: 3 (20.0)	Alectinib: 1 (50.0)	Atezolizumab: 4 (30.8) Ipatasertib: 3 (23.1)	10 (40.0)	Atezolizumab: 3 (33.3) Cobimetinib: 6 (66.7)	2 (33.3)	Alectinib: 1 (1.4) Atezolizumab: 12 (16.7) Cobimetinib: 8 (11.1) Vemurafenib: 2 (2.8) Pertuzumab: 2 (2.8) Trastuzumab: 3 (4.2) Ipatasertib: 3 (4.2) Inavolisib: 10 (13.9)
Study Drug Discontinued Due to AE	Atezolizumab: 1 (50.0) Cobimetinib: 1 (50.0) Vemurafenib: 1 (50.0)	Atezolizumab: 3 (20.0) Pertuzumab: 2 (13.3) Trastuzumab: 2 (13.3)	0	Atezolizumab: 5 (38.5) Ipatasertib: 5 (38.5)	8 (32.0)	Atezolizumab: 3 (33.3) Cobimetinib: 2 (22.2)	1 (16.7)	Atezolizumab: 13 (18.1) Cobimetinib: 3 (4.2) Vemurafenib: 1 (1.4) Pertuzumab: 2 (2.8) Trastuzumab: 2 (2.8) Ipatasertib: 5 (6.9) Inavolisib: 8 (11.1)

AE Resulting in Death	0	4 (26.7)	1 (50.0)	4 (30.8)	4 (16.0)	2 (22.2)	1 (16.7)	16 (22.2)
AESI	2 (100.0)	2 (13.3)	0	0	4 (16.0)	2 (22.2)	1 (16.7)	11 (15.3)

Table 9. Overview of all SAEs

	Number of patients N (%)							
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All**
Any SAE	2 (100.0)	3 (20.0)	2 (100.0)	5 (38.5)	7 (28.0)	4 (44.4)	1 (16.7)	24 (33.3)
Any Severe SAE (CTCAE v5.0 Grade 3 or 4)	1 (50.0)	3 (20.0)	2 (100.0)	5 (38.5)	6 (24.0)	3 (33.3)	1 (16.7)	21 (29.2)
Any SAE Grade>=3	1 (50.0)	3 (20.0)	2 (100.0)	5 (38.5)	6 (24.0)	3 (33.3)	1 (16.7)	21 (29.2)
Dose of Study Drug Reduced or Temporarily Discontinuation Due to SAE	Cobimetinib: 2 (100.0) Vemurafenib: 2 (100.0)	Pertuzumab: 1 (6.7)	Alectinib: 1 (50.0)	Atezolizumab: 1 (7.7) Ipatasertib: 1 (7.7)	2 (8.0)	Atezolizumab: 2 (22.2) Cobimetinib: 3 (33.3)	0	Alectinib: 1 (1.4) Atezolizumab: 3 (4.2) Cobimetinib: 5 (6.9) Vemurafenib: 2 (2.8) Pertuzumab: 1 (1.4) Ipatasertib: 1 (1.4) Inavolisib: 2 (2.8)
Study Drug Discontinued Due to SAE	Atezolizumab: 1 (50.0) Cobimetinib: 1 (50.0) Vemurafenib: 1 (50.0)	Atezolizumab: 1 (6.7) Pertuzumab: 1 (6.7) Trastuzumab: 1 (6.7)	0	Atezolizumab: 1 (7.7) Ipatasertib: 1 (7.7)	6 (24.0)	0	1 (16.7)	Atezolizumab: 4 (5.6) Cobimetinib: 1 (1.4) Vemurafenib: 1 (1.4) Pertuzumab: 1 (1.4) Trastuzumab: 1 (1.4) Ipatasertib: 1 (1.4) Inavolisib: 6 (8.3)
SAE Resulting in Death	0	0	0	0	0	0	0	0
AESI	0	0	0	0	3 (12.0)	0	1 (16.7)	4 (5.6)

Table 10. All AEs by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Blood and lymphatic system disorders	1 (50.0)	3 (20.0)	1 (50.0)	5 (38.5)	7 (28.0)	4 (44.4)	2 (33.3)	23 (31.9)
Cardiac disorders	0	0	1 (50.0)	2 (15.4)	2 (8.0)	0	0	5 (6.9)
Congenital, familial and genetic disorders	0	0	1 (50.0)	0	0	0	0	1 (1.4)
Ear and labyrinth disorders	0	0	0	1 (7.7)	1 (4.0)	1 (11.1)	0	3 (4.2)
Endocrine disorders	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Eye disorders	0	1 (6.7)	0	1 (7.7)	2 (8.0)	2 (22.2)	0	6 (8.3)
Gastrointestinal disorders	2 (100.0)	5 (33.3)	2 (100.0)	10 (76.9)	21 (84.0)	7 (77.8)	1 (16.7)	48 (66.7)

General disorders and administration site conditions	2 (100.0)	10 (66.7)	2 (100.0)	7 (53.8)	17 (68.0)	4 (44.4)	3 (50.0)	45 (62.5)
Hepatobiliary disorders	1 (50.0)	1 (6.7)	1 (50.0)	3 (23.1)	2 (8.0)	2 (22.2)	1 (16.7)	11 (15.3)
Immune system disorders	0	1 (6.7)	0	1 (7.7)	1 (4.0)	0	0	3 (4.2)
Infections and infestations	2 (100.0)	4 (26.7)	1 (50.0)	9 (69.2)	18 (72.0)	4 (44.4)	1 (16.7)	39 (54.2)
Injury, poisoning and procedural complications	0	6 (40.0)	0	1 (7.7)	0	0	0	7 (9.7)
Investigations	2 (100.0)	6 (40.0)	2 (100.0)	9 (69.2)	11 (44.0)	8 (88.9)	3 (50.0)	41 (56.9)
Metabolism and nutrition disorders	2 (100.0)	3 (20.0)	1 (50.0)	1 (7.7)	14 (56.0)	1 (11.1)	0	22 (30.6)
Musculoskeletal and connective tissue disorders	2 (100.0)	2 (13.3)	1 (50.0)	3 (23.1)	9 (36.0)	2 (22.2)	3 (50.0)	22 (30.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (50.0)	1 (6.7)	0	2 (15.4)	2 (8.0)	0	1 (16.7)	7 (9.7)
Nervous system disorders	1 (50.0)	1 (6.7)	1 (50.0)	2 (15.4)	9 (36.0)	1 (11.1)	0	15 (20.8)
Product issues	0	0	0	0	0	1 (11.1)	0	1 (1.4)
Psychiatric disorders	0	0	1 (50.0)	0	3 (12.0)	0	0	4 (5.6)
Renal and urinary disorders	0	0	0	2 (15.4)	7 (28.0)	0	0	9 (12.5)
Reproductive system and breast disorders	0	0	0	1 (7.7)	1 (4.0)	0	0	2 (2.8)
Respiratory, thoracic and mediastinal disorders	0	5 (33.3)	0	7 (53.8)	7 (28.0)	4 (44.4)	1 (16.7)	24 (33.3)
Skin and subcutaneous tissue disorders	2 (100.0)	5 (33.3)	1 (50.0)	4 (30.8)	11 (44.0)	3 (33.3)	0	26 (36.1)
Surgical and medical procedures	0	1 (6.7)	0	0	1 (4.0)	0	0	2 (2.8)
Vascular disorders	0	2 (13.3)	0	2 (15.4)	6 (24.0)	0	0	10 (13.9)
All patients	2	15	2	13	25	9	6	72

Table 11. All SAEs by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Blood and lymphatic system disorders	1 (50.0)	0	0	0	0	0	0	1 (1.4)
Cardiac disorders	0	0	1 (50.0)	0	0	0	0	1 (1.4)
Gastrointestinal disorders	1 (50.0)	0	1 (50.0)	1 (7.7)	2 (8.0)	1 (11.1)	0	6 (8.3)
General disorders and administration site conditions	0	0	0	1 (7.7)	0	1 (11.1)	0	2 (2.8)
Hepatobiliary disorders	0	1 (6.7)	0	2 (15.4)	0	1 (11.1)	1 (16.7)	5 (6.9)
Infections and infestations	1 (50.0)	0	1 (50.0)	2 (15.4)	4 (16.0)	1 (11.1)	0	9 (12.5)
Injury, poisoning and procedural complications	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Investigations	2 (100.0)	0	1 (50.0)	1 (7.7)	0	1 (11.1)	0	5 (6.9)

Metabolism and nutrition disorders	1 (50.0)	1 (6.7)	0	0	1 (4.0)	0	0	3 (4.2)
Nervous system disorders	0	0	0	2 (15.4)	1 (4.0)	0	0	3 (4.2)
Psychiatric disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Renal and urinary disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (7.7)	1 (4.0)	1 (11.1)	0	3 (4.2)
All patients	2	15	2	13	25	9	6	72

Table 12. AEs ≥ Grade 3 by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Blood and lymphatic system disorders	1 (50.0)	1 (6.7)	0	2 (15.4)	2 (8.0)	0	0	6 (8.3)
Eye disorders	0	0	0	0	0	1 (11.1)	0	1 (1.4)
Gastrointestinal disorders	1 (50.0)	0	2 (100.0)	2 (15.4)	3 (12.0)	1 (11.1)	0	9 (12.5)
General disorders and administration site conditions	0	5 (33.3)	1 (50.0)	4 (30.8)	5 (20.0)	2 (22.2)	1 (16.7)	18 (25.0)
Hepatobiliary disorders	0	1 (6.7)	1 (50.0)	1 (7.7)	1 (4.0)	1 (11.1)	1 (16.7)	6 (8.3)
Infections and infestations	2 (100.0)	0	1 (50.0)	4 (30.8)	6 (24.0)	1 (11.1)	0	14 (19.4)
Injury, poisoning and procedural complications	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Investigations	2 (100.0)	2 (13.3)	2 (100.0)	5 (38.5)	3 (12.0)	5 (55.6)	1 (16.7)	20 (27.8)
Metabolism and nutrition disorders	1 (50.0)	1 (6.7)	0	1 (7.7)	2 (8.0)	0	0	5 (6.9)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (16.7)	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (6.7)	0	1 (7.7)	2 (8.0)	0	1 (16.7)	5 (6.9)
Nervous system disorders	0	1 (6.7)	0	1 (7.7)	2 (8.0)	0	0	4 (5.6)
Psychiatric disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Renal and urinary disorders	0	0	0	1 (7.7)	4 (16.0)	0	0	5 (6.9)
Respiratory, thoracic and mediastinal disorders	0	1 (6.7)	0	4 (30.8)	0	1 (11.1)	0	6 (8.3)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Vascular disorders	0	0	0	0	2 (8.0)	0	0	2 (2.8)
All patients	2	15	2	13	25	9	6	72

Within each treatment arm, AEs documented as related to at least one IMP were considered treatment-related. Overall, treatment-related adverse events (TRAE) were observed across all treatment arms while treatment-related SAEs were not observed in Arm 3 (Table 13 and 14). In Arm 1, TRAEs were reported in 2 patients (100.0%), including treatment-related SAEs in both patients. In Arm 2, TRAEs occurred in 9 patients (60.0%), with one treatment-

related SAE reported. Two patients (100.0%) in Arm 3 experienced TRAEs, and no treatment-related SAEs were documented. In Arm 4, TRAEs were reported in 7 patients (53.8%), including one patient with 3 treatment-related SAEs. In Arm 5, TRAEs occurred in 23 patients (92.0%), and treatment-related SAEs occurred in 5 patients. In Arm 6, TRAEs occurred in 7 patients (77.8%), and one patient had treatment-related SAEs. In Arm 7, TRAEs were reported in 4 patients (66.7%), with one treatment-related SAE documented. TRAEs with grade 3 or 4 occurred in 16 patients (22.2%) overall and in 6 patients (24.0%) in Arm 5. None of the fatal events were assessed as treatment related.

TRAEs leading to dose reduction or temporary discontinuation occurred in 1 of 72 patients (1.4%) for Alectinib, 2 (2.8%) for Atezolizumab, 8 (11.1%) for Cobimetinib, 9 (12.5%) for Inavolisib, 1 (1.4%) for Pertuzumab, 2 (2.8%) for Trastuzumab, and 2 (2.8%) for Vemurafenib (Table 13). TRAEs leading to permanent discontinuation occurred in 5 patients (6.9%) receiving Atezolizumab, 4 (5.6%) receiving Inavolisib, and 2 (2.8%) receiving Ipatasertib. In Arm 5, 9 patients (36.0%) had Inavolisib dose reduction or temporary discontinuation due to TRAEs, and 4 patients (16.0%) permanently discontinued Inavolisib for the same reason.

The most frequently reported TRAEs by SOC were "Gastrointestinal disorders" (33.3%), "Investigations" (25%), "General disorders and administration site conditions" (19.4%), "Metabolism and nutrition disorders" (19.4%), and "Skin and subcutaneous tissue disorders" (18.1%). In terms of PT, diarrhoea (19.4%), hyperglycaemia (16.7), and fatigue (13.9) were the most common, occurring in at least 10% of patients, followed by rash (9.7%), nausea (9.7%), and blood creatine phosphokinase increased (9.7%). For more information about treatment-related AEs, SAEs and AEs ≥ Grade 3 by SOC see table 15-17.

Table 13. Overview of AEs related to IMP

	Number of patients N (%)							
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All**
Any AE	2 (100.0)	9 (60.0)	2 (100.0)	7 (53.8)	23 (92.0)	7 (77.8)	4 (66.7)	54 (75.0)
Any SAE	2 (100.0)	1 (6.7)	0	1 (7.7)	5 (20.0)	1 (11.1)	1 (16.7)	11 (15.3)
Any Severe AE (CTCAE v5.0 Grade 3 or 4)	1 (50.0)	3 (20.0)	1 (50.0)	2 (15.4)	6 (24.0)	2 (22.2)	1 (16.7)	16 (22.2)
Any AE Grade>=3	1 (50.0)	3 (20.0)	1 (50.0)	2 (15.4)	6 (24.0)	2 (22.2)	1 (16.7)	16 (22.2)
Dose of Study Drug Reduced or Temporarily Discontinuation Due to AE	Cobimetinib: 2 (100.0) Vemurafenib: 2 (100.0)	Atezolizumab : 1 (6.7) Pertuzumab: 1 (6.7) Trastuzumab : 2 (13.3)	Alectinib: 1 (50.0)	0	9 (36.0)	Atezolizumab : 1 (11.1) Cobimetinib: 6 (66.7)	0	Alectinib: 1 (1.4) Atezolizumab : 2 (2.8) Cobimetinib: 8 (11.1) Vemurafenib: 2 (2.8) Pertuzumab: 1 (1.4) Trastuzumab : 2 (2.8) Inavolisib: 9 (12.5)
Study Drug Discontinued Due to AE	0	Atezolizumab : 1 (6.7)	0	Atezolizumab : 2 (15.4) Ipatasertib: 2 (15.4)	4 (16.0)	Atezolizumab : 1 (11.1)	1 (16.7)	Atezolizumab : 5 (6.9) Ipatasertib: 2 (2.8) Inavolisib: 4 (5.6)
AE Resulting in Death	0	0	0	0	0	0	0	0
AESI	2 (100.0)	2 (13.3)	0	0	4 (16.0)	2 (22.2)	1 (16.7)	11 (15.3)

Table 14. Overview of SAEs related to IMP

	Number of patients N (%)							
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All**
Any SAE	2 (100.0)	1 (6.7)	0	1 (7.7)	5 (20.0)	1 (11.1)	1 (16.7)	11 (15.3)
Any Severe AE (CTCAE v5.0 Grade 3 or 4)	0	1 (6.7)	0	1 (7.7)	4 (16.0)	0	1 (16.7)	7 (9.7)
Any AE Grade>=3	0	1 (6.7)	0	1 (7.7)	4 (16.0)	0	1 (16.7)	7 (9.7)
Dose of Study Drug Reduced or Temporarily Discontinuation Due to AE	Cobimetinib: 2 (100.0) Vemurafenib: 2 (100.0)	Pertuzumab: 1 (6.7)	0	0	2 (8.0)	Cobimetinib: 1 (11.1)	0	Cobimetinib: 3 (4.2) Vemurafenib: 2 (2.8) Pertuzumab: 1 (1.4) Inavolisib: 2 (2.8)
Study Drug Discontinued Due to AE	0	0	0	Atezolizumab : 1 (7.7) Ipatasertib: 1 (7.7)	3 (12.0)	0	1 (16.7)	Atezolizumab : 2 (2.8) Ipatasertib: 1 (1.4) Inavolisib: 3 (4.2)
AE Resulting in Death	0	0	0	0	0	0	0	0

Table 15. AEs related to IMP by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Blood and lymphatic system disorders	0	0	0	0	2 (8.0)	1 (11.1)	0	3 (4.2)
Cardiac disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Ear and labyrinth disorders	0	0	0	0	0	1 (11.1)	0	1 (1.4)
Endocrine disorders	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Eye disorders	0	0	0	0	0	2 (22.2)	0	2 (2.8)
Gastrointestinal disorders	0	2 (13.3)	1 (50.0)	6 (46.2)	11 (44.0)	3 (33.3)	1 (16.7)	24 (33.3)
General disorders and administration site conditions	0	3 (20.0)	1 (50.0)	0	7 (28.0)	2 (22.2)	1 (16.7)	14 (19.4)
Hepatobiliary disorders	0	0	0	0	0	0	1 (16.7)	1 (1.4)
Immune system disorders	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Infections and infestations	1 (50.0)	0	0	0	4 (16.0)	0	0	5 (6.9)
Injury, poisoning and procedural complications	0	2 (13.3)	0	0	0	0	0	2 (2.8)
Investigations	2 (100.0)	1 (6.7)	1 (50.0)	3 (23.1)	5 (20.0)	5 (55.6)	1 (16.7)	18 (25.0)
Metabolism and nutrition disorders	0	1 (6.7)	0	0	13 (52.0)	0	0	14 (19.4)
Musculoskeletal and connective tissue disorders	2 (100.0)	1 (6.7)	1 (50.0)	0	1 (4.0)	1 (11.1)	0	6 (8.3)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (50.0)	0	0	0	0	0	0	1 (1.4)
Nervous system disorders	1 (50.0)	0	1 (50.0)	0	3 (12.0)	1 (11.1)	0	6 (8.3)
Psychiatric disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Renal and urinary disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Reproductive system and breast disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	2 (13.3)	0	0	2 (8.0)	0	0	4 (5.6)
Skin and subcutaneous tissue disorders	2 (100.0)	2 (13.3)	0	0	6 (24.0)	3 (33.3)	0	13 (18.1)
Vascular disorders	0	1 (6.7)	0	0	1 (4.0)	0	0	2 (2.8)
All patients	2	15	2	13	25	9	6	72

Table 16. SAEs related to IMP by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Gastrointestinal disorders	0	0	0	1 (7.7)	1 (4.0)	0	0	2 (2.8)
Hepatobiliary disorders	0	0	0	0	0	0	1 (16.7)	1 (1.4)
Infections and infestations	0	0	0	0	2 (8.0)	0	0	2 (2.8)
Injury, poisoning and procedural complications	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Investigations	2 (100.0)	0	0	0	0	1 (11.1)	0	3 (4.2)
Metabolism and nutrition disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Nervous system disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Psychiatric disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
All patients	2	15	2	13	25	9	6	72

Table 17. AEs ≥ Grade 3 related to IMP by SOC

	Number of patients N (%)							
System organ class (MedDRA 28.0)	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Arm 5**	**Arm 6**	**Arm 7**	**All arms**
Eye disorders	0	0	0	0	0	1 (11.1)	0	1 (1.4)
Gastrointestinal disorders	0	0	0	1 (7.7)	2 (8.0)	0	0	3 (4.2)
Hepatobiliary disorders	0	0	0	0	0	0	1 (16.7)	1 (1.4)
Infections and infestations	1 (50.0)	0	0	0	2 (8.0)	0	0	3 (4.2)
Injury, poisoning and procedural complications	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Investigations	0	1 (6.7)	1 (50.0)	1 (7.7)	0	2 (22.2)	0	5 (6.9)
Metabolism and nutrition disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)

Nervous system disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Psychiatric disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Renal and urinary disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	1 (6.7)	0	0	0	0	0	1 (1.4)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
Vascular disorders	0	0	0	0	1 (4.0)	0	0	1 (1.4)
All patients	2	15	2	13	25	9	6	72

Two patients experienced SUSARs, both in Arm 5. One patient developed infectious pleural effusion (CTCAE Grade 4; duration 32 days), which led to drug withdrawal. The other patient had personality change, somnolence, and memory impairment (CTCAE Grade 3; duration 6 days), which led to drug temporarily discontinuation. Both events recovered/resolved, and were assessed as related to Inavolisib by the investigator and the sponsor.

AESIs were reported in 11 patients across the study arms, including 2 patients in Arm 1, 2 patients in Arm 2, 4 patients in Arm 5, 2 patients in Arm 6, and 1 patient in Arm 7 (Table 18).

Table 18. Listing of adverse events of special interest (AESIs) - FAP

Arm	Patient ID	Gender	Age	Description	Preferred Term	CTCAE Grade	Outcome	IMP	Action on IMP	Related to IMP?
Arm 1	01-011	Male	64	photosensitivity	Photosensitivity reaction	Grade 1 (mild AE)	unknown	Atezolizumab	Dose not changed	No
								Cobimetinib	Dose not changed	Yes
								Vemurafenib	Dose not changed	Yes
	01-013	Male	57	photosensitivity	Photosensitivity reaction	Grade 1 (mild AE)	recovered /resolved	Atezolizumab	Dose not changed	No
								Cobimetinib	Dose not changed	Yes
								Vemurafenib	Dose not changed	Yes
				skin infection	Skin infection	Grade 3 (severe AE)	recovered /resolved	Atezolizumab	Dose not changed	No
								Cobimetinib	Dose not changed	No
								Vemurafenib	Dose not changed	Yes
Arm 2	03-006	Male	71	Myositis	Myositis	Grade 1 (mild AE)	recovered /resolved	Atezolizumab	Drug withdrawn	Yes
								Pertuzumab	Dose not changed	No
								Trastuzumab	Dose not changed	No
	06-021	Female	39	Hypothyroism	Hypothyroidism	Grade 2 (moderate AE)	recovered /resolved	Atezolizumab	Dose not changed	Yes
								Pertuzumab	Dose not changed	No
								Trastuzumab	Dose not changed	No
Arm 5	03-003	Female	48	Colitis	Colitis	Grade 3 (severe AE)	not recovered /not resolved	Inavolisib	Drug withdrawn	Yes

	03-004	Female	60	Hyperglycemia	Hyperglycaemia	Grade 3 (severe AE)	recovered /resolved	Inavolisib	Drug withdrawn	Yes
	06-016	Female	59	Pneumonnitis	Pneumonitis	Grade 2 (moderate AE)	recovered /resolved	Inavolisib	Temporary discontinuation	Yes
	13-004	Male	53	inflammatory rash	Rash	Grade 3 (severe AE)	recovered /resolved	Inavolisib	Temporary discontinuation	Yes
Arm 6	06-006	Female	45	Central serous retinopathy	Central serous chorioretinopathy	Grade 1 (mild AE)	recovered /resolved	Atezolizumab	Dose not changed	No
								Cobimetinib	Temporary discontinuation	Yes
	13-002	Male	38	Myositis	Myositis	Grade 1 (mild AE)	recovered /resolved	Atezolizumab	Temporary discontinuation	Yes
								Cobimetinib	Dose not changed	No
				neurosensory retinal detachment	Retinal detachment	Grade 3 (severe AE)	recovered /resolved	Atezolizumab	Dose not changed	No
								Cobimetinib	Temporary discontinuation	Yes
Arm 7	01-036	Female	61	suspected autoimmune Hepatitis	Autoimmune hepatitis	Grade 3 (severe AE)	recovered /resolved	Atezolizumab	Drug withdrawn	Yes

Other Safety Data

Most recorded laboratory values were normal or classified as not clinically significant aberrant. The most frequently observed clinically significant hematology parameters included lymphocytes (absolute count), hemoglobin and platelets. For clinical chemistry, commonly reported clinically significant parameters involved gamma-glutamyl transferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST/SGOT), among others. With respect to endocrinology, the clinically significant abnormality was thyroid-stimulating hormone (TSH).

No clinically relevant values were observed for numeric urinalysis parameters, including pH value, follicle stimulating hormone (FSH). For categorical urinalysis parameters (protein, glucose, and pregnancy test), protein at baseline in three patients was assessed as clinically relevant. One patient in Arm 5 was reported as protein positive, and two patients in Arm 1 had protein values of 30 mg/dl and 100 mg/dl, respectively.

Two patients had positive pregnancy test results. One patient in Arm 2 tested positive at Cycle 2 Day 1; pregnancy termination was performed immediately thereafter; subsequent ß-HCG tests were negative. The other patient in Arm 4 had a positive pregnancy test during the safety follow-up period (about one year after EOT). However, this patient was not pregnant, and the positive test result was related to tumor progression with ß-HCG elevation.

Nine patients had abnormal ECHO at baseline, including two patients with abnormal left ventricular ejection fraction. Another two patients had abnormal ECHO result at follow-up. The majority of electrocardiogram (ECG) assessments were reported as normal. Clinically significant abnormal ECG findings included (sinus) tachycardia and bradycardia.

Physical examination revealed diverse clinically significant findings, most frequently involving the skin (e.g., dry/red/ulcera), extremities (e.g., edema, pain), and abdomen (e.g., acute renal failure, infection, liver palpable or hardened/enlarged).

In the following table 19, hematology and clinical chemistry data at baseline and changes from baseline for all arms are presented.

Table 19. Laboratory test data: Hematology and clinical chemistry baseline values and change from baseline (FAP)

			All Patients (N=72)					
Variable		**Unit**	**N***	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
Hematology								
Red Blood Cell Count	Baseline 1)	10E12/L	70	4.0	0.6	3.9	3.0	5.3
	Change 2)	10E12/L	70	0.1	0.5	0.1	-1.1	1.1
Platelets	Baseline 1)	10E9/L	70	254.5	105.3	239.5	90.0	598.0
	Change 2)	10E9/L	70	36.6	100.7	26.0	-154.0	336.0
White Blood Cell Count	Baseline 1)	10E9/L	70	7.1	3.3	6.6	2.6	26.1
	Change 2)	10E9/L	70	0.8	3.5	0.9	-17.0	12.6
Hemoglobin	Baseline 1)	g/L	70	118.6	16.3	117.0	81.0	151.0
	Change 2)	g/L	70	-0.8	13.2	-1.0	-35.0	28.0
Neutrophils (abs)	Baseline 1)	10E9/L	70	5.0	3.0	4.4	0.6	22.4
	Change 2)	10E9/L	70	0.5	3.3	0.6	-15.7	12.8
Lymphocytes (abs)	Baseline 1)	10E9/L	70	1.1	0.6	1.1	0.0	3.1
	Change 2)	10E9/L	70	0.2	0.6	0.1	-1.2	2.2
Monocytes (abs)	Baseline 1)	10E9/L	70	0.6	0.4	0.5	0.0	2.5
	Change 2)	10E9/L	70	0.0	0.3	0.1	-1.0	0.7
Eosinophils (abs)	Baseline 1)	10E9/L	70	0.2	0.2	0.1	0.0	0.8
	Change 2)	10E9/L	70	0.0	0.1	0.0	-0.3	0.4
Basophils (abs)	Baseline 1)	10E9/L	70	0.0	0.0	0.0	0.0	0.1
	Change 2)	10E9/L	70	0.0	0.0	0.0	-0.1	0.1
Clinical chemistry								
Urea	Baseline 1)	mmol/L	50	4.8	2.1	4.2	1.7	9.3
	Change 2)	mmol/L	50	0.1	1.5	0.5	-3.8	3.8
Fasting glucose	Baseline 1)	mmol/L	19	5.0	0.5	4.8	4.2	6.1
	Change 2)	mmol/L	19	1.5	2.2	0.8	-0.5	7.9
Sodium	Baseline 1)	mmol/L	70	137.9	3.8	138.0	127.0	146.0
	Change 2)	mmol/L	70	-0.6	3.3	0.0	-8.0	9.0
Potassium	Baseline 1)	mmol/L	70	4.1	0.4	4.1	3.2	5.0
	Change 2)	mmol/L	70	0.1	0.4	0.0	-1.0	1.1
Glucose	Baseline 1)	mmol/L	53	5.6	0.8	5.4	3.1	7.2
	Change 2)	mmol/L	53	0.5	2.2	-0.2	-1.9	13.3
Magnesium	Baseline 1)	mmol/L	69	0.8	0.1	0.8	0.5	1.1
	Change 2)	mmol/L	69	0.0	0.1	0.0	-0.3	0.2
Serum Uric acid	Baseline 1)	µmol/l	69	299.9	94.9	279.6	148.7	535.4
	Change 2)	µmol/l	69	-22.9	70.7	-29.7	-166.6	249.8
Calcium	Baseline 1)	mmol/L	70	2.3	0.2	2.3	0.6	2.6
	Change 2)	mmol/L	70	0.0	0.3	0.0	-0.2	1.9
Total protein	Baseline 1)	g/L	69	68.7	9.5	69.0	5.5	88.0
	Change 2)	g/L	69	0.6	4.8	1.6	-18.0	8.8
LDH	Baseline 1)	µmol/s*L	70	5.9	5.3	4.1	1.3	37.6

	Change 2)	µmol/s*L	70	0.6	4.4	0.2	-12.1	22.3
Creatinine	Baseline 1)	µmol/L	70	70.5	20.9	67.2	40.7	146.7
	Change 2)	µmol/L	70	4.9	12.8	4.0	-18.6	61.0
Albumin	Baseline 1)	g/L	69	39.8	5.0	41.4	28.5	49.0
	Change 2)	g/L	69	-0.1	5.3	-0.4	-8.0	32.0
Total bilirubin	Baseline 1)	µmol/L	70	11.3	17.4	6.9	3.4	143.4
	Change 2)	µmol/L	70	3.4	13.5	0.0	-8.6	87.6
Direct bilirubin	Baseline 1)	µmol/L	37	7.1	21.2	2.9	1.7	131.2
	Change 2)	µmol/L	37	3.8	13.9	0.0	-3.4	73.9
ALT (SGPT)	Baseline 1)	µmol/s*L	70	0.6	0.5	0.4	0.1	2.3
	Change 2)	µmol/s*L	70	0.2	1.0	0.1	-2.0	5.5
AST (SGOT)	Baseline 1)	µmol/s*L	69	0.9	1.0	0.6	0.2	5.2
	Change 2)	µmol/s*L	69	0.1	1.0	0.1	-4.5	4.0
GGT	Baseline 1)	µmol/s*L	69	3.1	4.3	1.2	0.2	19.7
	Change 2)	µmol/s*L	69	0.6	3.7	0.1	-13.7	16.8
Alkaline phosphatase	Baseline 1)	µmol/s*L	70	2.9	2.4	2.1	0.8	12.8
	Change 2)	µmol/s*L	70	0.9	2.5	0.1	-4.7	10.2
Fasting insulin	Baseline 1)	mU/L	21	7.8	5.5	6.6	1.1	22.0
	Change 2)	mU/L	21	23.9	27.2	13.9	0.0	98.4
HbA1C	Baseline 1)	%	19	5.4	0.4	5.5	4.3	5.9
	Change 2)	%	19	0.7	0.8	0.5	-0.1	2.9

1) Last value before or on date of first medication
2) Change calculated as latest available value during study - last value before or on date of first medication
* Only Patients with baseline and last value during study were counted for change.

Vital signs at baseline and changes from baseline for all arms are presented in the following table 20. The results showed that the average changes in systolic blood pressure, diastolic blood pressure, heart rate, temperature, and body weight from baseline were all minimal.

Table 20. Vital signs: baseline values and change from baseline (FAP)

		All Patients (N=72)					
Variable		**N**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
Systolic BP (mmHg)	Baseline 1)	72	127.1	19.7	121.0	95.0	196.0
	Change 2)	69	-0.7	18.1	2.0	-50.0	41.0
Diastolic BP (mmHg)	Baseline 1)	72	81.1	9.8	80.5	60.0	104.0
	Change 2)	69	-0.9	11.6	0.0	-32.0	29.0
Heart Rate (bpm)	Baseline 1)	72	84.4	15.8	83.0	52.0	124.0
	Change 2)	69	0.0	15.1	-1.0	-47.0	30.0
Temperature (°C)	Baseline 1)	72	36.7	0.5	36.7	35.5	38.0
	Change 2)	69	0.0	0.6	0.0	-1.8	1.2
Body weight (kg)	Baseline 1)	72	73.4	16.8	71.2	47.0	130.0
	Change 2)	70	-1.5	4.9	-0.7	-27.0	10.0

1) Last value before or on date of first medication
2) Change calculated as latest available value during study - last value before or on date of first medication
* Only Patients with baseline and last value during study were counted for change.

OTHER ENDPOINTS

PRO

The EORTC QLQ-C30, Fatigue Module (FA12), Pittsburgh Sleep Quality Index (PSQI), Brief Pain Inventory (BPI), Functional Assessment of Cancer Therapy (FACT), and Patient Health Questionnaire-4 (PHQ-4) scores were calculated according to the respective scoring manuals and summarized descriptively at baseline, week 8, week 16, and extended treatment, including changes from baseline.

The QLQ-C30 results for all arms and Arm 5 at baseline, week 8, and week 16, including changes from baseline, were shown in table 21 and 22 respectively. For all arms, global health status/QoL and all functional scales exhibited an upward trend, suggesting improved overall well-being. For symptom scales, fatigue, pain, dyspnea, constipation, and financial difficulties steadily decreased over time, while nausea/vomiting and diarrhea tended to increase. Appetite loss and insomnia decreased from baseline to week 8 but rose slightly by week 16. Overall, these results indicate a positive impact of the intervention from baseline to weeks 8 and 16, with enhanced functional capacity, improved global quality of life, and reduced severity of several symptoms.

Table 21. EORTC QLQ-C30 and change from baseline, all arms (FAP)

Visit	Variable	N	Mean	SD	Median	Minimum	Maximum
Baseline	Global health status/QoL (revised)	67	51.6	21.6	50.0	0.0	100.0
	Physical functioning (revised)	70	66.5	27.3	73.3	0.0	100.0
	Role functioning (revised)	65	52.6	30.5	50.0	0.0	100.0
	Emotional functioning	70	55.4	23.7	58.3	0.0	100.0
	Cognitive functioning	70	73.1	27.3	83.3	0.0	100.0
	Social functioning	70	55.8	33.7	66.7	0.0	100.0
	Fatigue	70	51.6	28.8	44.4	0.0	100.0
	Nausea and vomiting	70	9.8	14.6	0.0	0.0	50.0
	Pain	69	35.0	32.6	33.3	0.0	100.0
	Dyspnoea	69	32.4	33.3	33.3	0.0	100.0
	Insomnia	70	36.7	36.0	33.3	0.0	100.0
	Appetite loss	69	25.6	30.3	33.3	0.0	100.0
	Constipation	70	18.6	30.4	0.0	0.0	100.0
	Diarrhoea	69	17.4	29.5	0.0	0.0	100.0
	Financial difficulties	69	21.5	34.4	0.0	0.0	100.0
Week 8	Global health status/QoL (revised)	48	57.8	22.0	58.3	16.7	100.0
	Change from Baseline	45	2.5	21.1	0.0	-50.0	41.7
	Physical functioning (revised)	48	70.1	25.2	73.3	13.3	100.0
	Change from Baseline	47	-1.4	18.5	0.0	-40.0	46.7
	Role functioning (revised)	46	59.1	29.1	66.7	0.0	100.0
	Change from Baseline	42	2.0	25.6	0.0	-33.3	66.7
	Emotional functioning	48	65.9	26.5	70.8	0.0	100.0
	Change from Baseline	47	10.2	25.2	8.3	-41.7	66.7
	Cognitive functioning	47	77.3	26.8	83.3	0.0	100.0

	Change from Baseline	46	4.3	20.3	0.0	-50.0	66.7
	Social functioning	47	68.1	30.9	66.7	0.0	100.0
	Change from Baseline	46	8.9	29.1	0.0	-66.7	66.7
	Fatigue	48	46.8	29.8	38.9	0.0	100.0
	Change from Baseline	47	-2.8	28.9	0.0	-77.8	55.6
	Nausea and vomiting	46	10.9	20.9	0.0	0.0	100.0
	Change from Baseline	45	2.2	24.0	0.0	-50.0	100.0
	Pain	46	28.6	27.1	33.3	0.0	100.0
	Change from Baseline	45	-1.9	26.6	0.0	-66.7	33.3
	Dyspnoea	48	29.9	29.4	33.3	0.0	100.0
	Change from Baseline	46	3.6	30.0	0.0	-66.7	66.7
	Insomnia	48	31.2	36.0	33.3	0.0	100.0
	Change from Baseline	47	-6.4	27.5	0.0	-100.0	66.7
	Appetite loss	48	22.2	31.8	0.0	0.0	100.0
	Change from Baseline	46	-1.4	28.1	0.0	-66.7	66.7
	Constipation	48	9.7	23.8	0.0	0.0	100.0
	Change from Baseline	47	-5.7	31.3	0.0	-100.0	66.7
	Diarrhoea	48	19.4	26.5	0.0	0.0	100.0
	Change from Baseline	46	2.9	32.1	0.0	-100.0	66.7
	Financial difficulties	47	20.2	34.0	0.0	0.0	100.0
	Change from Baseline	46	0.7	24.8	0.0	-66.7	100.0
Week 16	Global health status/QoL (revised)	31	62.6	24.5	66.7	0.0	100.0
	Change from Baseline	29	8.8	22.2	8.3	-45.8	50.0
	Physical functioning (revised)	31	75.6	25.1	86.7	6.7	100.0
	Change from Baseline	30	5.0	14.8	0.0	-33.3	40.0
	Role functioning (revised)	31	64.0	32.8	66.7	0.0	100.0
	Change from Baseline	28	7.7	28.1	0.0	-50.0	66.7
	Emotional functioning	31	68.5	27.4	75.0	0.0	100.0
	Change from Baseline	30	12.5	22.6	8.3	-16.7	66.7
	Cognitive functioning	30	77.2	29.8	100.0	0.0	100.0
	Change from Baseline	29	5.2	25.6	0.0	-33.3	83.3
	Social functioning	31	73.1	30.9	83.3	0.0	100.0
	Change from Baseline	30	13.6	27.0	4.2	-33.3	83.3
	Fatigue	31	41.9	30.7	33.3	0.0	100.0
	Change from Baseline	30	-9.3	25.1	0.0	-77.8	33.3
	Nausea and vomiting	31	15.1	24.5	0.0	0.0	100.0
	Change from Baseline	30	6.7	22.1	0.0	-33.3	83.3
	Pain	31	25.5	30.2	16.7	0.0	100.0
	Change from Baseline	30	-5.3	27.6	0.0	-83.3	33.3
	Dyspnoea	30	25.6	32.4	0.0	0.0	100.0
	Change from Baseline	28	-1.2	34.5	0.0	-66.7	66.7

	Insomnia	31	32.3	29.2	33.3	0.0	100.0
	Change from Baseline	30	-3.3	32.0	0.0	-100.0	66.7
	Appetite loss	31	23.7	28.8	0.0	0.0	100.0
	Change from Baseline	29	-1.1	33.9	0.0	-66.7	66.7
	Constipation	31	5.4	19.4	0.0	0.0	100.0
	Change from Baseline	30	-7.8	34.7	0.0	-100.0	100.0
	Diarrhoea	31	29.6	35.9	0.0	0.0	100.0
	Change from Baseline	29	10.3	47.2	0.0	-100.0	100.0
	Financial difficulties	31	15.6	25.4	0.0	0.0	66.7
	Change from Baseline	29	-1.7	26.9	0.0	-66.7	66.7

Table 22. EORTC QLQ-C30 and change from baseline, Arm 5

Visit	Variable	N	Mean	SD	Median	Minimum	Maximum
Baseline	Global health status/QoL (revised)	25	48.2	18.9	50.0	8.3	83.3
	Physical functioning (revised)	25	62.9	30.7	73.3	0.0	100.0
	Role functioning (revised)	22	47.0	33.6	41.7	0.0	100.0
	Emotional functioning	25	52.0	28.5	58.3	0.0	100.0
	Cognitive functioning	25	65.3	32.2	66.7	0.0	100.0
	Social functioning	25	53.0	32.2	66.7	0.0	100.0
	Fatigue	25	50.7	29.8	44.4	0.0	100.0
	Nausea and vomiting	25	10.0	15.2	0.0	0.0	50.0
	Pain	24	34.7	34.4	33.3	0.0	100.0
	Dyspnoea	25	29.3	33.8	33.3	0.0	100.0
	Insomnia	25	34.7	39.1	33.3	0.0	100.0
	Appetite loss	24	20.8	32.3	0.0	0.0	100.0
	Constipation	25	29.3	33.8	33.3	0.0	100.0
	Diarrhoea	25	10.7	18.6	0.0	0.0	66.7
	Financial difficulties	25	22.7	34.3	0.0	0.0	100.0
Week 8	Global health status/QoL (revised)	17	52.5	21.8	58.3	16.7	91.7
	Change from Baseline	17	0.7	22.4	0.0	-50.0	41.7
	Physical functioning (revised)	17	69.7	28.1	80.0	13.3	100.0
	Change from Baseline	17	1.9	17.3	0.0	-26.7	46.7
	Role functioning (revised)	17	57.8	29.5	66.7	0.0	100.0
	Change from Baseline	16	6.3	26.4	0.0	-33.3	66.7
	Emotional functioning	17	58.8	34.3	66.7	0.0	100.0
	Change from Baseline	17	8.8	22.3	8.3	-25.0	66.7
	Cognitive functioning	17	73.5	32.3	83.3	0.0	100.0
	Change from Baseline	17	8.8	20.5	0.0	-16.7	66.7
	Social functioning	16	63.5	37.6	75.0	0.0	100.0
	Change from Baseline	16	4.7	26.2	0.0	-50.0	66.7

	Fatigue	17	51.0	33.6	55.6	0.0	100.0
	Change from Baseline	17	0.7	23.7	0.0	-33.3	33.3
	Nausea and vomiting	16	9.4	18.2	0.0	0.0	66.7
	Change from Baseline	16	2.1	16.0	0.0	-16.7	50.0
	Pain	16	38.5	33.2	33.3	0.0	100.0
	Change from Baseline	16	5.2	19.9	0.0	-50.0	33.3
	Dyspnoea	17	25.5	32.3	0.0	0.0	100.0
	Change from Baseline	17	5.9	31.7	0.0	-33.3	66.7
	Insomnia	17	33.3	40.8	0.0	0.0	100.0
	Change from Baseline	17	-3.9	23.2	0.0	-33.3	66.7
	Appetite loss	17	19.6	31.3	0.0	0.0	100.0
	Change from Baseline	16	2.1	14.8	0.0	-33.3	33.3
	Constipation	17	11.8	26.2	0.0	0.0	100.0
	Change from Baseline	17	-9.8	25.7	0.0	-66.7	33.3
	Diarrhoea	17	17.6	23.9	0.0	0.0	66.7
	Change from Baseline	17	9.8	30.7	0.0	-33.3	66.7
	Financial difficulties	17	23.5	32.8	0.0	0.0	100.0
	Change from Baseline	17	3.9	28.6	0.0	-33.3	100.0
Week 16	Global health status/QoL (revised)	13	46.8	25.8	50.0	0.0	91.7
	Change from Baseline	13	-1.6	21.1	8.3	-45.8	16.7
	Physical functioning (revised)	13	67.9	30.5	80.0	6.7	100.0
	Change from Baseline	13	1.8	10.9	0.0	-20.0	26.7
	Role functioning (revised)	13	50.0	40.8	33.3	0.0	100.0
	Change from Baseline	12	1.4	32.9	0.0	-50.0	66.7
	Emotional functioning	13	59.6	35.3	66.7	0.0	100.0
	Change from Baseline	13	7.1	21.5	0.0	-16.7	66.7
	Cognitive functioning	12	63.9	38.2	75.0	0.0	100.0
	Change from Baseline	12	-2.8	19.9	0.0	-33.3	33.3
	Social functioning	13	64.1	36.5	66.7	0.0	100.0
	Change from Baseline	13	1.9	12.8	0.0	-33.3	16.7
	Fatigue	13	48.7	39.2	44.4	0.0	100.0
	Change from Baseline	13	-0.9	20.5	0.0	-44.4	33.3
	Nausea and vomiting	13	23.1	30.8	16.7	0.0	100.0
	Change from Baseline	13	16.7	24.5	16.7	0.0	83.3
	Pain	13	40.4	37.6	50.0	0.0	100.0
	Change from Baseline	13	0.6	27.3	0.0	-66.7	33.3
	Dyspnoea	13	35.9	39.6	33.3	0.0	100.0
	Change from Baseline	13	15.4	29.2	0.0	-33.3	66.7
	Insomnia	13	43.6	34.4	33.3	0.0	100.0
	Change from Baseline	13	2.6	28.7	0.0	-33.3	66.7
	Appetite loss	13	43.6	31.6	33.3	0.0	100.0

	Change from Baseline	12	22.2	25.9	16.7	0.0	66.7
	Constipation	13	5.1	12.5	0.0	0.0	33.3
	Change from Baseline	13	-12.8	29.0	0.0	-66.7	33.3
	Diarrhoea	13	43.6	39.4	66.7	0.0	100.0
	Change from Baseline	13	30.8	44.0	33.3	-33.3	100.0
	Financial difficulties	13	15.4	29.2	0.0	0.0	66.7
	Change from Baseline	13	0.0	23.6	0.0	-33.3	66.7

QLQ-C30 scores over time are shown in the following figure 3-7. t-based 95% CIs were calculated. For some arms and visits (especially week 16) with very small sample sizes, the 95% CIs tended to be wide and imprecise.

Figure 3. Arm 2

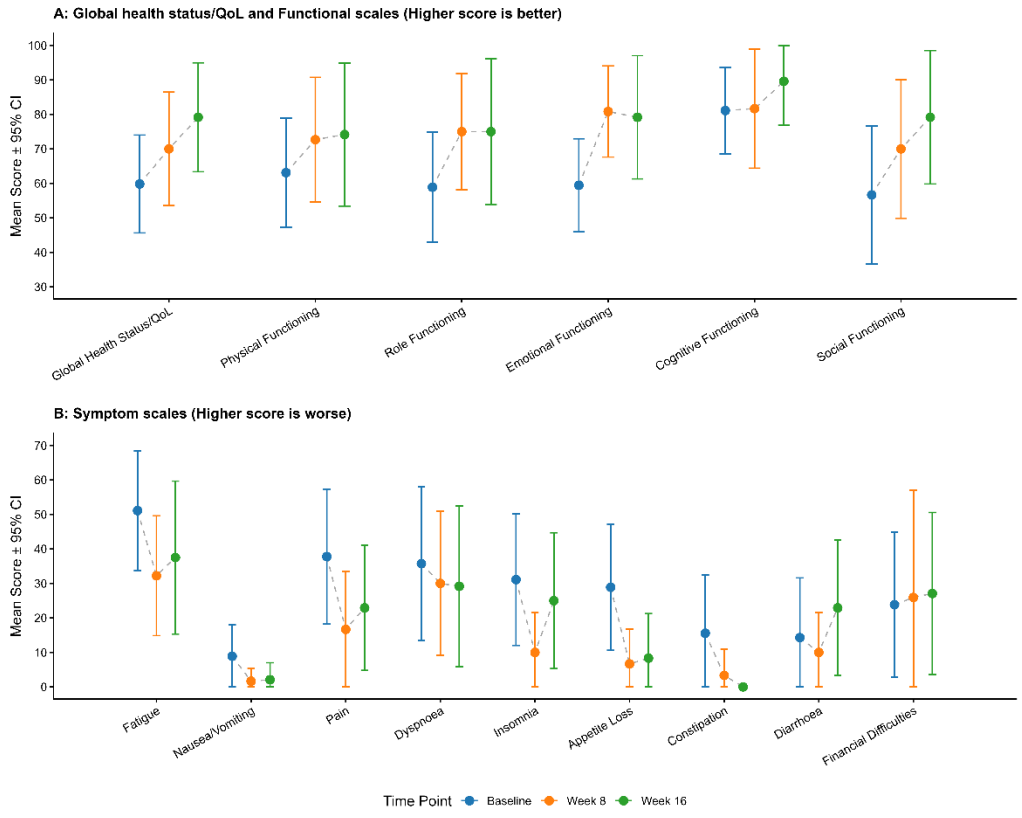


Figure 4. Arm 4

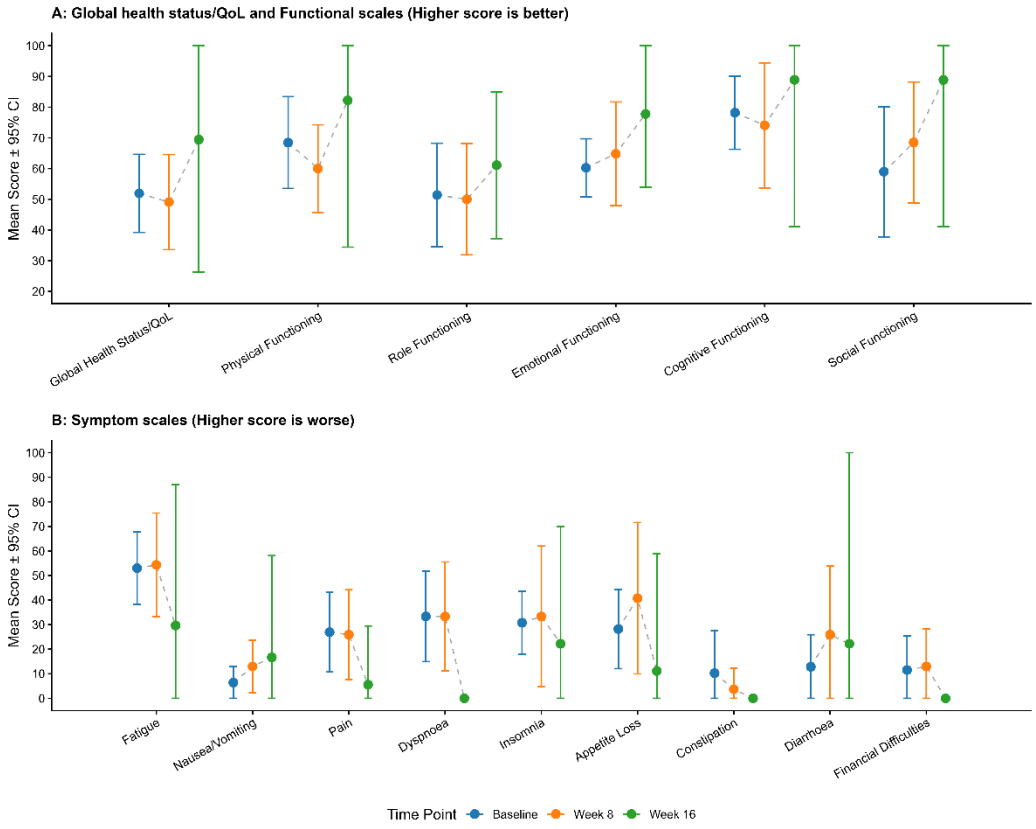


Figure 5. Arm 5

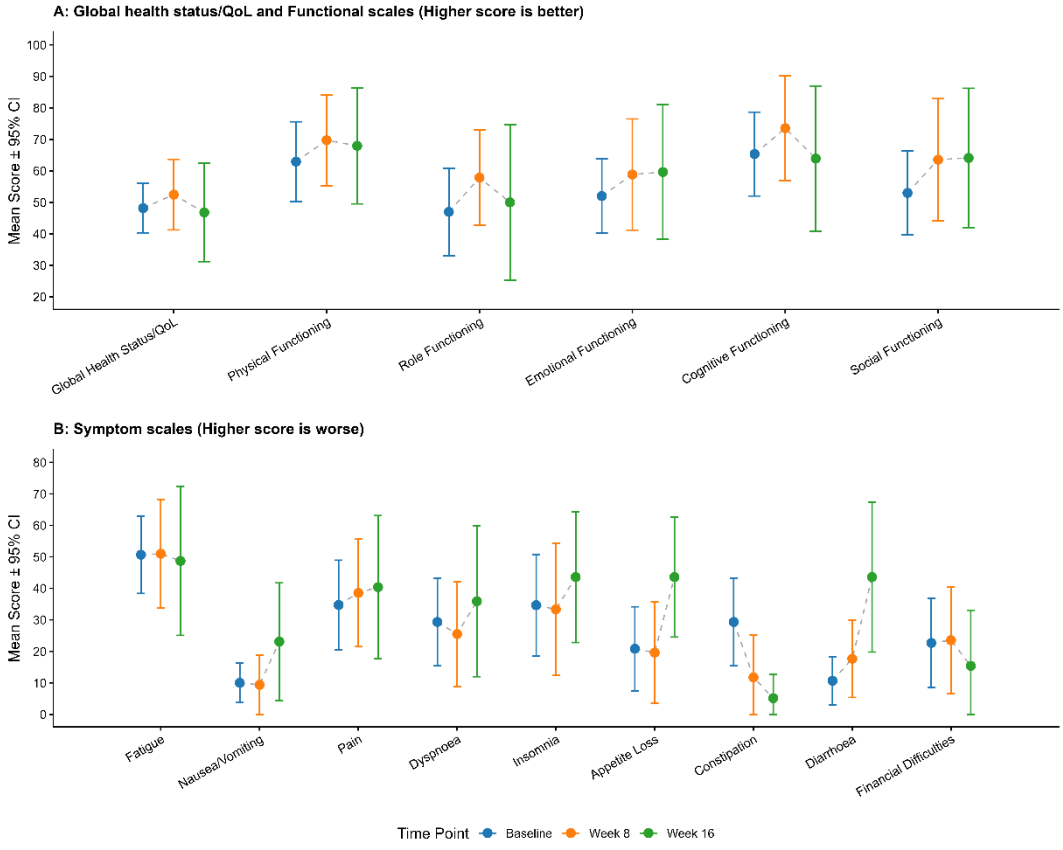


Figure 6. Other arms (1,3,6,7)

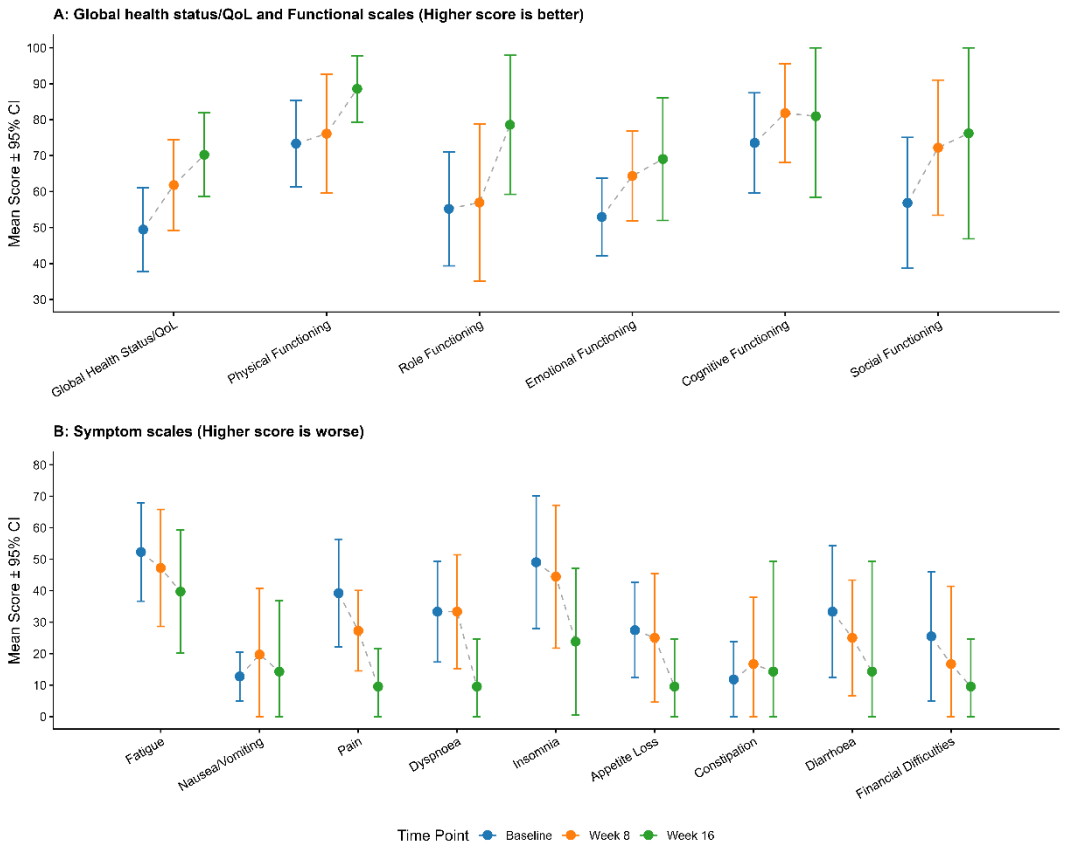
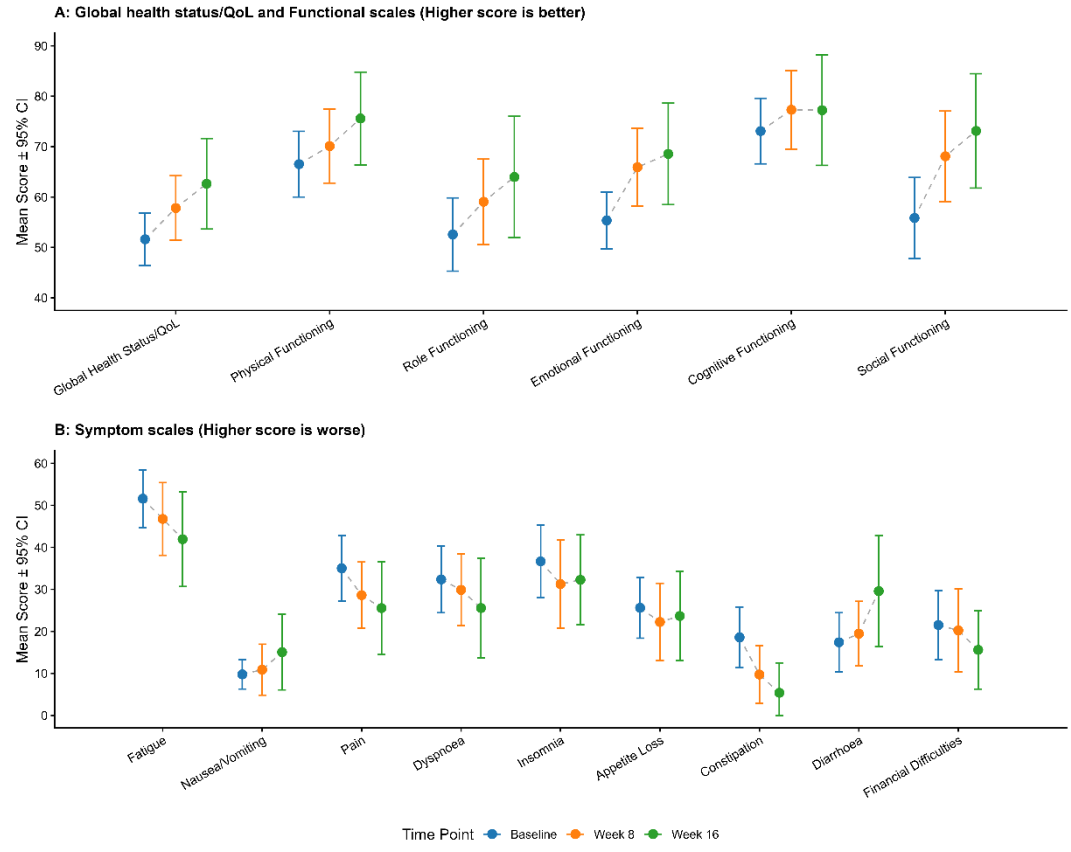


Figure 7. All arms



CONCLUSION:

In this phase II trial, seven treatment arms were included. The primary endpoint, DCR after 16 weeks of treatment, was 30.6% (22/72, 95% CI 0.2024–0.4253) among all treated patients. TRR was 16.7% (12/72, 95% CI 0.0892–0.2730), and the overall median PFS and OS were 2.5 months (95% CI 1.9–3.7) and 10.1 months (95% CI 7.4–21.5), respectively.

Arm 5 proceeded into stage 2, with 8 of 25 treated patients achieving disease control (UMVUE point estimate 0.3505). Therefore, the null hypothesis DCR ≤ 0.2 can be rejected at a significance level of α=10% (90% CI 0.2031–0.4483; p=0.0933). The TRR in Arm 5 was 12% (3/25, 95% CI 0.0255–0.3122), and the median PFS and OS were 3.6 months (95% CI 1.9–5.4) and 10.1 months (95% CI 4.7– not estimable), respectively. All other arms remained in stage 1. In Arm 2, the DCR was 33.3% (5/15, 95% CI 0.1182–0.6162) and the TRR was 26.7% (4/15, 95% CI 0.0779–0.5510), with the median PFS and OS of 3.5 (95% CI 1.5–6.2) and 8.0 months (95% CI 1.5–not estimable), respectively. In Arm 4, the DCR was 15.4% (2/13, 95% CI 0.0192–0.4545) and the TRR was 7.7% (1/13, 95% CI 0.0019–0.3603), with the median PFS and OS of 1.9 (95% CI 1.2–2.8) and 8.6 months (95% CI 2.2–21.5), respectively. When Arm 1, 3, 6, and 7 were considered together, the DCR was 36.8% (7/19, 95% CI 0.1629–0.6164) and the TRR was 21.1% (4/19, 95% CI 0.0605–0.4557), with the median PFS and OS of 1.9 (95% CI 1.7–5.8) and 11.1 months (95% CI 4.6– not estimable), respectively.

The safety profile was generally consistent with that in previous studies mentioned in the trial protocol. A total of 20 treatment-related SAEs were reported in 11 patients (15.3%) overall, including 1 event in Arm 2, 3 events in 1 patient in Arm 4, 9 events in 5 patients in Arm 5, and 6 events in 4 patients in other arms (1, 6, 7). In addition, 13 AESIs were reported in 11 patients (15.3%) overall, including 2 events in 2 patients in Arm 2, 4 events in 4 patients in Arm 5, and 7 events in 5 patients in other arms (1, 6, 7). Furthermore, two patients experienced SUSARs, both in Arm 5. No fatal AEs were assessed as treatment related.

Substantial amendments:

23 July 2021 Amendment protocol version 2.0

15 December 2021 IMPD Ipatasertib (Sept. 2021)

17 December 2021 IB Vemurefenib v19, IB Trastuzumab v22

25 November 2022 Amendment protocol version 3.0

06 January 2023 IB Ipatasertib v14, DIL Atezolizumab, PI-change Würzburg

06 February 2023 IB Trastuzumab v23

21 February 2023 New site Lübeck

05 June 2023 PI-change TU Munich, Updated IBs (IB Atezolizumab v19 + Addendum, IB Cobimetinib v15, IB Inavolisib v7, IB Pertuzumab v22) and SmPCs

13 February 2024 Updated IBs (IB Vemurafenib v20 + v21, IB Atezolizumab v19 + Addendum 2, IB Alectinib v12 + Addendum 1 + v13 + v14, IB Ipatasertib v15) and SmPCs (Vemurafenib, Atezolizumab, Pertuzumab)

23 May 2024 Amendment protocol version 4.0

18 June 2024 QIMPD Inavolisib (April 2024)

09 September 2024 Updated IBs (IB Vemurafenib v22, IB Pertuzumab v23, IB Ipatasertib v16) and SmPCs, Notification about end of recruitment

30 December 2024 Notification end of trial

06 January 2025 Updated IBs (IB Cobimetinib v17, IB Atezolizumab v21, IB Alectinib v15, IB Inavolisib v9) and SmPCs

Interruptions or early termination:

Early termination without reaching the planned sample size due to slow recruitment in December 2024

Date of the report:
19 December 2025

Appendix 1: List of study centers and Principal Investigators

No.	Study center	Principal Investigator
01	**University Hospital Heidelberg** National center for tumor diseases Im Neuenheimer Feld 460 69120 Heidelberg	Prof. Dr. Richard F. Schlenk Tel.: +49 (0)6221 56 6228 E-Mail: richard.schlenk@nct-heidelberg.de
02	**University Hospital Carl-Gustav-Carus** National center for tumor diseases Fetscherstraße 74 01307 Dresden	Dr. Christoph Heining Tel.: +49 (0)351 458 15532 E-Mail: christoph.heining@nct-dresden.de
03	**Charité – University medicine Berlin** Medical clinic haematology and oncology Hindenburgdamm 30 12203 Berlin	Dr. Damian Tobias Rieke Tel.: +49 (0)30 450-613 559 E-Mail: damian.rieke@charite.de
04	**University medicine of Johannes Gutenberg-university Mainz** III. Medical clinic Langenbeckstraße 1 55131 Mainz	Dr. Alexander Desuki Tel.: +49 (0)6131-17-5999 E-Mail: alexander.desuki@unimedizin-mainz.de
05	**Clinic Rechts der Isar of TU Munich** Haematology and oncology Ismaninger Str. 22 81675 München	Prof. Dr. Anna Lena Illert Tel.: +49 (0)89 – 4140-4111 E-Mail: lena.illert@mri.tum.de
06	**University Hospital Tübingen** Medical clinic I Otfried-Müller-Str. 10 72076 Tübingen	Prof. Dr. med. Michael Bitzer Tel.: +49 (0)7071-29-85415 E-Mail: m.bitzer@med.uni-tuebingen.de
07	**University Hospital Freiburg** Clinic for inner medicine I Hugstetter Str. 55 79106 Freiburg	PD Dr. Heiko Becker Tel.: +49 (0)761 270-32785 E-Mail: heiko.becker@uniklinik-freiburg.de
08	**University Hospital Würzburg** Interdisciplinary trial center Josef-Schneider-Straße 6 97080 Würzburg	PD Dr. Barbara Deschler-Baier Tel.: +49 (0)931-201-35060 E-Mail: deschler_b@ukw.de
09	**University Hospital Schleswig-Holstein** Haematology and oncology Ratzeburger Allee 160 23538 Lübeck	Prof. Dr. med. Nikolas von Bubnoff Tel.: +49 (0)451-500-44151 E-Mail: nikolas.vonbubnoff@uksh.de

Trial profile