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# Capmatinib plus nazartinib in patients with *EGFR*-mutated non–small cell lung cancer

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ABSTRACT

*Purpose:* This phase 1b/2 trial evaluated the efficacy and safety of capmatinib plus nazartinib in patients with advanced *EGFR*-mutated non–small cell lung cancer (NSCLC).

*Methods:* In phase 1b, patients with progression on first-/second-generation EGFR-TKIs received escalating doses of capmatinib 200–400 mg bid plus nazartinib 50–150 mg qd. Once the MTD/RP2D was declared, phase 2 commenced with patient enrollment into groups according to mutation status and prior lines of treatment: group 1 (fasted; EGFR-TKI resistant; 1–3 prior lines; $EGFR^{L858R/ex19del}$; any T790M/MET); group 2 (fasted; EGFR-TKI naïve; 0–2 prior lines; de novo T790M+; any MET); group 3 (fasted; treatment-naïve; $EGFR^{L858R/ex19del}$; T790M−; any MET); group 4 (with food; 0–2 prior lines; $EGFR^{L858R/ex19del}$; any T790M/MET). Primary endpoints in phase 2 were investigator-assessed overall response rate (ORR) per RECIST v1.1 (groups 1–3), safety, and tolerability of the combination with food (group 4). Efficacy was assessed by T790M and MET status for a subgroup of patients.

*Results:* The RP2D was capmatinib 400 mg bid plus nazartinib 100 mg qd. In phase 2 (n = 144), the ORR was 28.8 %, 33.3 %, 61.7 %, and 42.9 % in groups 1 (n = 52), 2 (n = 3), 3 (n = 47), and 4 (n = 42), respectively. In group 1 +phase 1b RP2D, the ORR was 45.8 %, 26.2 %, 37.9 %, and 32.4 % in MET+ (n = 24), MET− (n = 42),

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T790M+ (n = 29), and T790M− (n = 34) patients. Most common any-grade treatment-related adverse events (≥25 %; n = 144) were peripheral edema (54.9 %), nausea (41.7 %), diarrhea (34.0 %), and maculopapular rash (25.0 %).

*Conclusion:* Capmatinib plus nazartinib showed antitumor activity in patients with EGFR-TKI-resistant, *EGFR*-mutated NSCLC. The overall safety profile was acceptable.

*Clinical trial registration:* ClinicalTrials.gov NCT02335944

## 1. Introduction

The majority of patients with advanced epidermal growth factor receptor (*EGFR*)-mutated non–small cell lung cancer (NSCLC) acquire resistance to treatment with EGFR-tyrosine kinase inhibitors (TKIs). *MET* amplification can arise as a mechanism of acquired resistance to EGFR-TKIs, occurring in ~5–26 % of patients with EGFR-TKI-resistant, *EGFR*-mutated NSCLC.[1–7] Targeting *MET* amplification, in addition to treatment with EGFR-TKIs, may therefore be a promising therapeutic strategy for circumventing acquired resistance.[8–13].

Capmatinib is a selective MET inhibitor (METi) that is approved (400 mg bid) in many countries worldwide for treating patients with metastatic *MET* exon 14 (*MET*ex14) skipping NSCLC.[14] The GEOMETRY mono-1 study showed the efficacy and safety of capmatinib monotherapy in pretreated and treatment-naïve patients with advanced NSCLC and *MET*ex14, including those with brain metastases.[15] In a phase 1b/2 study, capmatinib plus gefitinib demonstrated encouraging clinical activity (phase 2 overall response rate [ORR]: 29 % regardless of MET status; 47 % with MET gene copy number [GCN] ≥ 6) and manageable safety in patients with *EGFR*-mutated, MET-dysregulated NSCLC who had disease progression while receiving EGFR-TKIs.[10].

Nazartinib is a novel, third-generation irreversible EGFR-TKI that selectively inhibits *EGFR*-activating and T790M resistance mutations, while sparing wild-type EGFR.[16] In a phase 1 study, an ORR of 51 % and a median progression-free survival (PFS) of 9.1 months were observed with nazartinib in patients with *EGFR* T790M+ NSCLC who were naïve to third-generation EGFR-TKIs and had received ≤ 3 prior lines of therapy.[17,18].

Here, we report the results of a study investigating the efficacy and safety of capmatinib plus a third-generation EGFR-TKI in patients with advanced *EGFR*-mutated NSCLC.

## 2. Methods

### 2.1. Study design

This was a phase 1b/2, multicenter, open-label study (NCT02335944). Phase 1b (dose-escalation) established the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of capmatinib plus nazartinib. Phase 2 (dose-expansion) characterized the antitumor activity, safety, tolerability, and pharmacokinetics (PK) of the combination when administered at the selected dose, for four groups classified by mutation status, prior lines of treatment and fasting status (Figure 1).

This study was undertaken in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, following the ethical principles in the Declaration of Helsinki. The study protocol and amendments were reviewed by the Independent Ethics Committee or Institutional Review Board. All patients provided written informed consent.

### 2.2. Patients

Key eligibility criteria included age ≥ 18 years, stage IIIB/IV NSCLC per AJCC version 7, ≥ 1 measurable lesion per RECIST v1.1, ECOG performance status ≤ 1, and no prior treatment with METi or hepatocyte growth factor-targeting therapies. Patients were required to have locally documented *EGFR* L858R and/or ex19del mutations (or other activating mutations that confer sensitivity to first-/second-generation EGFR-TKIs) or a de novo T790M mutation. Patients with asymptomatic or controlled brain metastases were also eligible (Supplementary Methods).

In phase 1b, patients with *EGFR*-activating mutations (any MET/T790M) who had progressed on first-/second-generation EGFR-TKIs were enrolled. In phase 2, patients were enrolled into groups according to mutational status, treatment history, and fasting status, detailed in Figure 1 and Supplementary Methods. MET+ was defined as *MET* GCN

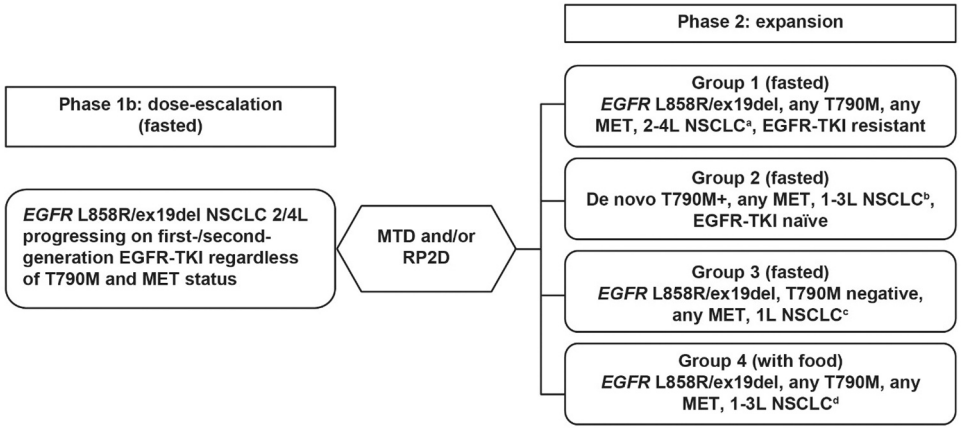


**Fig. 1.** Study Design. [a]1–3 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry, including 1 line maximum of first-/second-generation EGFR-TKI; [b]0–2 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry without any line of therapy known to inhibit EGFR; [c]No prior line of systemic antineoplastic therapies in the therapeutic setting before study entry (maximum 1 cycle of chemotherapy allowed); [d]0–2 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry; prior treatment with first-/second-generation EGFR-TKIs was permitted, but not required. *EGFR*, epidermal growth factor receptor; L, line of therapy; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

≥ 4 by FISH and/or immunohistochemistry score 3 + (defined as ≥50 % of tumor cells staining with high intensity). In phase 1b, the MET and T790M status were either locally documented or centrally determined. In phase 2, central tests for the MET and T790M status were performed (see Supplementary Methods for more details).

### 2.3. Brain metastases-related eligibility criteria

Patients with asymptomatic or controlled brain metastases were allowed to participate in the trial. These patients should have completed any planned radiotherapy and/or surgery, if required, > 2 weeks prior to the first dose of study treatment and have remained asymptomatic. Patients were required to be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging. Patients taking steroids must have been on a stable dose for 2 weeks prior to the first dose of study treatment.

### 2.4. Study treatment

In phase 1b, the starting dose for the first cohort of patients was 50 mg once daily (qd) nazartinib and 200 mg twice daily (bid) capmatinib. Patients were enrolled into 5 cohorts with the following capmatinib (bid)/nazartinib (qd) dose levels: 200 mg/50 mg, 200 mg/100 mg, 400 mg/75 mg, 400 mg/100 mg, and 400 mg/150 mg. Patients in phase 2 received the RP2D. Treatment was administered in 28-day cycles.

### 2.5. Efficacy assessments

Tumor response was determined locally by the investigators according to Response Evaluation in Solid Tumors (RECIST) version 1.1. Computed tomography/magnetic resonance imaging (CT/MRI) scans were performed at baseline within 28 days prior to the start of treatment and subsequently every 8 weeks ( ± 7 days) from the start of cycle 3 until disease progression and every 12 weeks ( ± 7 days) from cycle 13 day 1 until disease progression. CT/MRI scans were also performed at the end of treatment (EOT) if not conducted within 30 days prior to EOT. Brain CT/MRI was mandated for all patients prior to study treatment. Subsequent brain scans were conducted every 8 weeks ( ± 7 days) and every 12 weeks ( ± 7 days) from cycle 13 day 1 if brain lesions were documented at baseline for eligible patients or in patients that developed symptoms indicative of brain metastases.

### 2.6. Study endpoints

Primary endpoints included the incidence of dose-limiting toxicities (DLTs; phase 1b); investigator-assessed ORR per RECIST v1.1 (phase 2 groups 1–3), safety, and tolerability of the combination when taken with food (phase 2 group 4). Secondary endpoints in phases 1b and 2 included ORR (phase 1b and phase 2 group 4 only), disease control rate (DCR), duration of response (DOR), time to response (TTR), PFS, overall survival (OS), safety, tolerability, and PK.

In an exploratory analysis, efficacy was assessed by T790M and MET status for a combined patient subgroup with known MET and T790M status from phase 1b at RP2D and phase 2 group 1 (group 1 +phase 1b RP2D). These patients from phase 1b matched the group 1 inclusion criteria.

### 2.7. Statistical analysis

In phase 1b, an adaptive, 5-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control principle was used to make dose recommendations for the proposed combination treatment and to estimate the MTD or RP2D. The use of Bayesian response adaptive models for phase 1 studies has been advocated by the EMEA guideline on small populations[19] and other groups [20,21] and is one of the key elements of the FDA's Critical Path Initiative. For MTD or RP2D determination, ≥ 6 patients were treated at that dosage, only 1 of the 2 investigational drugs was escalated at a time, and clinical assessments of safety and PK were conducted.

For phase 2 primary analysis, a Bayesian approach was used to estimate the ORR by patient group and preliminary antitumor activity was judged based on predefined criteria. For data presented here (cutoff: October 26, 2021), ORR and DCR were summarized using descriptive statistics by dose (phase 1b) or patient (phase 2) groups. The Kaplan-Meier method was used to analyze the time-to-event endpoints (DOR, TTR, PFS, OS). Study assessments and details regarding statistical analyses are presented in Supplementary Methods.

## 3. Results

Thirty-three patients were treated in phase 1b with escalating doses of capmatinib 200–400 mg bid and nazartinib 50–150 mg qd. In phase 2, 144 patients were treated at the RP2D.

### 3.1. Phase 1b

#### 3.1.1. Baseline characteristics

Baseline characteristics are shown in Table S1. Median age was 58 years; majority female, with no smoking history, adenocarcinoma histology. All patients had stage IV disease at study entry. Data on prior therapies are presented in **Supplementary Results**.

#### 3.1.2. Safety

Capmatinib 400 mg bid plus nazartinib 100 mg qd was selected as the RP2D based on the summary of doses satisfying the overdose control criterion allowing further enrollment at this dose level; the BLRM assessing the probability of DLTs in cycle 1; and the clinical assessment of safety and PK in the dose-determining set. Five DLTs were reported in 4/28 patients in the dose-determining set: grade 3 maculopapular rash (n = 3; 2 at capmatinib 400 mg/nazartinib 150 mg and 1 at capmatinib 400 mg/nazartinib 100 mg); grade 3 rash (n = 1 at capmatinib 400 mg/nazartinib 150 mg); and grade 3 increased alanine aminotransferase (ALT; n = 1 at capmatinib 200 mg/nazartinib 50 mg). Based on the BLRM, the probability of overdose (<25 % probability that the DLT rate was >35 %) was 1.4 % at the capmatinib 400 mg/nazartinib 100 mg dose level. Phase 1b adverse event (AE) data are presented in **Supplementary Results,** Table S2**,** and Table S3**.** PK data are presented in **Supplementary Results** and Table S4.

#### 3.1.3. Efficacy

An overall response was observed in all dose groups, except capmatinib 200 mg/nazartinib 50 mg (Table S5). Median DOR, PFS, and OS are presented in Table S5. The median follow-up time for PFS (from the start of treatment to the event or censoring date) was 5.6 months (range: 0.0 to 60.6). The median follow-up time for OS (from the start of treatment to the date of death or censoring, i.e. last contact date on or prior to the data cut-off date) was 11.9 months (range: 1.1 to 60.6). Kaplan-Meier median TTR was not reached for all patients, and most responses occurred within 2 months. Percentage changes from baseline in sum of longest lesion diameters are shown in Fig. S1.

### 3.2. Phase 2

#### 3.2.1. Patients

The majority were female, with no smoking history, had adenocarcinoma histology, and stage IV disease at study entry; median age 60.5 years (Table 1 and **Supplementary Results)**. Group 1 +phase 1b RP2D consisted of 68 patients (group 1 [n = 52]; phase 1b RP2D [n = 16]), of whom 66 had known MET status (Table 1).

**Table 1**
Patient Demographics and Disease Characteristics – Phase 2 and MET+ and MET− Patients in Group 1 +Phase 1b RP2D (Full Analysis Set).

| Characteristic | Phase 2 | | | | | Group 1 +Phase 1b RP2D[a] | |
|---|---|---|---|---|---|---|---|
| | Group 1 N = 52 | Group 2 N = 3 | Group 3 N = 47 | Group 4 N = 42 | All Patients N= 144 | MET+ N = 24[b] | MET− N = 42[b] |
| **Median (range) age, years** | 61.0 (31-80) | 66.0 (53-83) | 60.0 (31-84) | 59.5 (42-82) | 60.5 (31-84) | 64.0 (41-80) | 60.0 (31-77) |
| **Sex, n (%)** | | | | | | | |
| Female | 38 (73.1) | 2 (66.7) | 33 (70.2) | 24 (57.1) | 97 (67.4) | 18 (75.0) | 28 (66.7) |
| Male | 14 (26.9) | 1 (33.3) | 14 (29.8) | 18 (42.9) | 47 (32.6) | 6 (25.0) | 14 (33.3) |
| **Race, n (%)** | | | | | | | |
| Caucasian | 26 (50.0) | 2 (66.7) | 30 (63.8) | 20 (47.6) | 78 (54.2) | 11 (45.8) | 18 (42.9) |
| Asian | 22 (42.3) | 1 (33.3) | 16 (34.0) | 21 (50.0) | 60 (41.7) | 10 (41.7) | 22 (52.4) |
| Black | 1 (1.9) | 0 | 0 | 0 | 1 (0.7) | 0 | 1 (2.4) |
| Missing | 3 (5.8) | 0 | 1 (2.1) | 1 (2.4) | 5 (3.5) | 3 (12.5) | 1 (2.4) |
| **ECOG PS, n (%)** | | | | | | | |
| 0 | 22 (42.3) | 1 (33.3) | 22 (46.8) | 17 (40.5) | 62 (43.1) | 9 (37.5) | 17 (40.5) |
| 1 | 29 (55.8) | 2 (66.7) | 25 (53.2) | 25 (59.5) | 81 (56.3) | 14 (58.3) | 23 (54.8) |
| 2 | 1 (1.9) | 0 | 0 | 0 | 1 (0.7) | 1 (4.2) | 2 (4.8) |
| **Smoking history, n (%)** | | | | | | | |
| Never smoked | 36 (69.2) | 3 (100) | 26 (55.3) | 23 (54.8) | 88 (61.1) | 17 (70.8) | 26 (61.9) |
| Former smoker | 13 (25.0) | 0 | 19 (40.4) | 18 (42.9) | 50 (34.7) | 7 (29.2) | 13 (31.0) |
| Current smoker | 3 (5.8) | 0 | 2 (4.3) | 1 (2.4) | 6 (4.2) | 0 | 3 (7.1) |
| **Tumor histology/cytology, n (%)** | | | | | | | |
| Adenocarcinoma | 50 (96.2) | 3 (100) | 45 (95.7) | 40 (95.2) | 138 (95.8) | 23 (95.8) | 41 (97.6) |
| Other | 1 (1.9) | 0 | 1 (2.1) | 0 | 2 (1.4) | 1 (4.2) | 0 |
| Squamous cell carcinoma | 1 (1.9) | 0 | 1 (2.1) | 2 (4.8) | 4 (2.8) | 0 | 1 (2.4) |
| **Stage at time of study entry, n (%)** | | | | | | | |
| IIIB | 0 | 0 | 0 | 2 (4.8) | 2 (1.4) | - | - |
| IV | 52 (100) | 3 (100) | 47 (100) | 40 (95.2) | 142 (98.6) | 24 (100) | 42 (100) |
| **Key metastatic sites, n (%)** | | | | | | | |
| Bone | 27 (51.9) | 2 (66.7) | 22 (46.8) | 19 (45.2) | 70 (48.6) | 13 (54.2) | 21 (50.0) |
| CNS | 19 (36.5) | 1 (33.3) | 13 (27.7) | 14 (33.3) | 47 (32.6) | 6 (25.0) | 16 (38.1) |
| Liver | 12 (23.1) | 3 (100) | 11 (23.4) | 6 (14.3) | 32 (22.2) | 6 (25.0) | 9 (21.4) |
| **Prior antineoplastic therapies, n (%)** | | | | | | | |
| 1 | 35 (67.3) | 1 (33.3) | 3 (6.4)[c] | 21 (50.0)[d] | 60 (41.7) | 13 (54.2) | 30 (71.4) |
| 2 | 13 (25.0) | 1 (33.3) | 0 | 9 (21.4) | 23 (16.0) | 7 (29.2) | 10 (23.8) |
| 3 | 4 (7.7) | 0 | 0 | 0 | 4 (2.8) | 4 (16.7) | 2 (4.8) |
| **Molecular profile, n (%)** | | | | | | | |
| MET[e] | 19 (36.5) | 1 (33.3) | 18 (38.3) | 14 (33.3) | 52 (36.1) | 24 (100) | 0 |
| T790M[f,g] | 22 (42.3) | 3 (100) | 0 | 5 (11.9) | 30 (20.8) | 9 (37.5) | 19 (45.2) |
| Ex19del[g] | 33 (63.5) | 0 | 17 (36.2) | 25 (59.5) | 75 (52.1) | 14 (58.3) | 29 (69.0) |
| L858R[g] | 19 (36.5) | 3 (100) | 21 (44.7) | 14 (33.3) | 57 (39.6) | 9 (37.5) | 12 (28.6) |

Group 1: Fasted; EGFR-TKI resistant; 1-3 prior lines of systemic therapy [including maximum 1 line of first-/second-generation EGFR-TKI]; EGFRL858R/ex19del; any T790M/MET; Group 2: Fasted; EGFR-TKI naïve; 0-2 prior lines; de novo T790M+ ; any MET; Group 3: Fasted; treatment naïve; EGFRL858R/ex19del; T790M− ; any MET; Group 4: With food; 0-2 prior lines; EGFRL858R/ex19del; any T790M/MET.

[a]Group 1 +phase 1b RP2D consisted of 68 patients, of whom 66 had known MET status (24 MET+, 42 MET−), 2 patients had unknown MET status.

[b]5 of 24 patients in the MET+ (IHC 3 + and/or *MET* GCN ≥4 by FISH) subgroup and 10 of 42 patients in the MET− subgroup were treated at the RP2D in the dose-escalation part and also matched the group 1 inclusion criteria.

[c]All 3 patients received chemotherapy at their last treatment (2 in the adjuvant setting and 1 in the therapeutic setting, allowed per protocol).

[d]Systemic antineoplastic therapy administered as adjuvant or neo-adjuvant treatment more than six months prior to study enrollment was not considered a prior line of therapy for purpose of this study. They were considered as treatment naive, here the count includes 3 such patients.

[e] In phase 2, 7 patients (4.9 %) had unknown MET status (group 1 [n = 1], group 3 [n = 3], and group 4 [n = 3]).

[f] In phase 2, 18 patients (12.5 %) had unknown T790M status (group 1 [n = 5], group 3 [n = 6], and group 4 [n = 7]). In group 1 +phase 1b RP2D, 5 patients had unknown T790M status (1 MET+ patient and 4 MET− patients).

[g]*EGFR* mutation status was recorded as "missing" for 4 patients in phase 2 (group 3 [n = 2] and group 4 [n = 2]) and for 1 MET− patient in group 1 +phase 1b RP2D.

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GCN, gene copy number; IHC, immunohistochemistry; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor

### 3.2.2. *Efficacy*

In groups 1, 3, and 4, investigator-assessed ORRs were 28.8 % (95 % CI 17.1–43.1), 61.7 % (46.4–75.5), and 42.9 % (27.7–59.0). The median DORs were 6.5 months (3.7–10.8), 11.6 months (6.6–17.5), and 14.5 months (9.2-not estimable [NE]). The best percentage changes from baseline in sum of longest lesion diameters for groups 1, 3, and 4 are shown in Figure 2. The median TTR was NE in groups 1 and 4 and 1.9 months (1.8–5.9) in group 3. Median PFS was 5.6 months (3.7–7.4), 10.1 months (7.6–13.8), and 10.9 months (5.6–19.2), and median OS was 18.8 months (14.9–26.0), 25.6 months (18.8–33.0), and 28.9 months (20.5-NE) for groups 1, 3, and 4, respectively (Table 2). Group 2 (n = 3) efficacy results are presented in Table 2. The median follow-up time for PFS (from the start of treatment to the event or censoring date) was 5.6 months (range: 0.0 to 47.1). The median follow-up time for OS (from the start of treatment to the date of death or censoring) was 20.6 months (range: 0.4 to 49.4).

Exploratory analysis across all groups (N = 144) showed 29 patients had baseline brain metastasis (target lesions only [n = 3]; nontarget and target lesions [n = 26]). Absence or normalization of brain nontarget lesions was observed in 7 of 26 patients (26.9 %); 18 of 29 patients (62.1 %) had ≥ 30 % reduction of their baseline brain target lesion diameters. Approximately half of all patients with baseline brain metastases did not develop new metastases during the study, and patients without baseline metastases remained metastasis-free. No new brain metastases were reported during the study (Table S6).

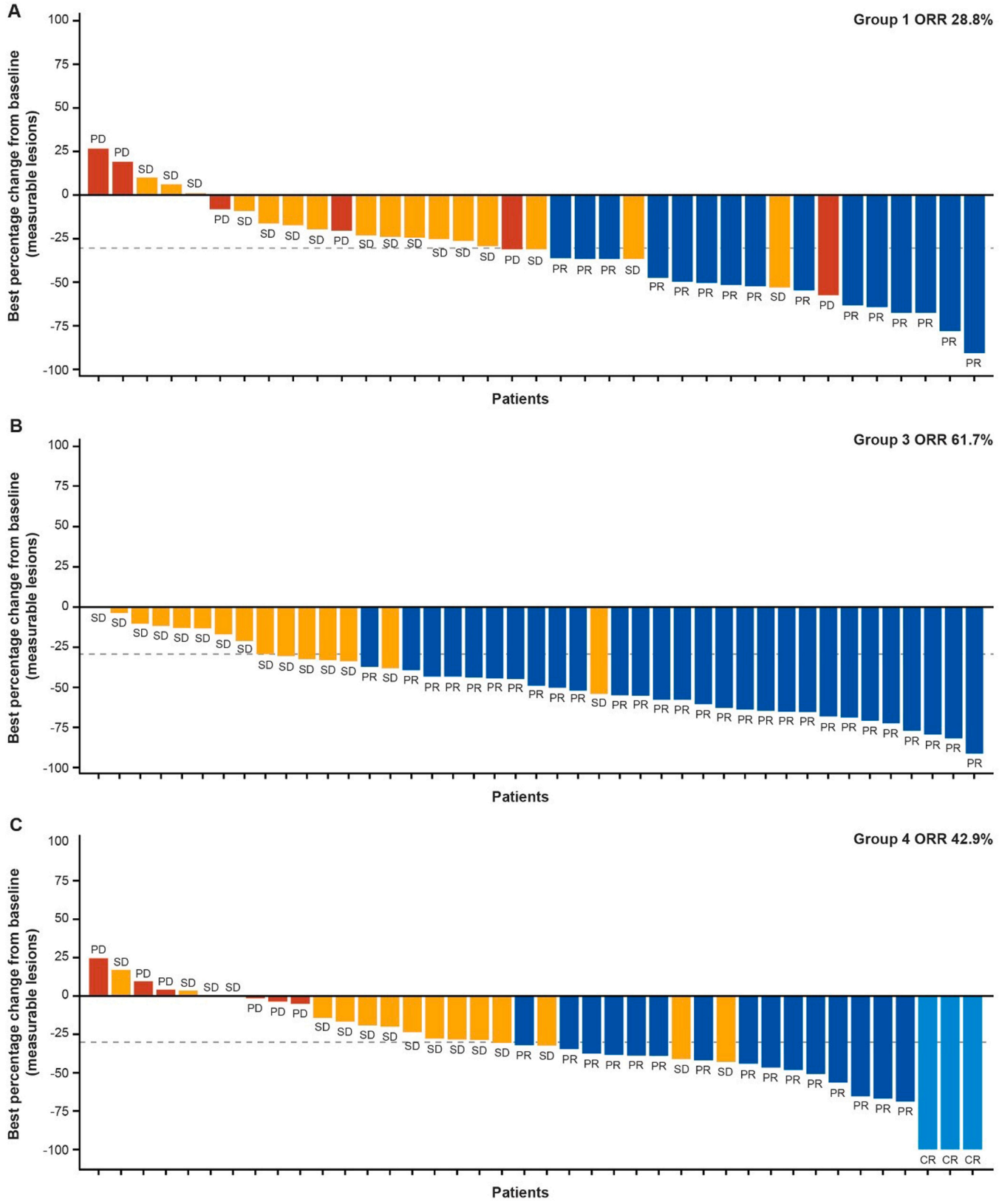


**Fig. 2.** Waterfall Plot for Best Percentage Change From Baseline in Sum of Longest Lesion Diameters Based on Investigator Assessment in (A) Group 1, (B) Group 3, and (C) Group 4 – Phase 2[a] (Full Analysis Set). Group 1: Fasted; EGFR-TKI resistant; 1–3 prior lines of systemic therapy [including maximum 1 line of first-/second-generation EGFR-TKI]; EGFRL858R/ex19del; any T790M/MET; n/N (%) = 37/52 (71.2); Group 3: Fasted; treatment naïve; EGFRL858R/ex19del; T790M− ; any MET; 43/47 (91.5) Group 4: With food; 0–2 prior lines; EGFRL858R/ex19del; any T790M/MET; 40/42 (95.2). [a]Patients in the phase 2 part of this study (dose-expansion) were enrolled into 4 parallel groups according to their mutation status and prior lines of treatment. n = number of patients with a baseline and ≥ 1 postbaseline assessment of target lesions based on investigator assessment. Percentage changes from baseline > 100 % are set to 100 %. CR, complete response; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

**Table 2**
Investigator-Assessed Efficacy and OS – Phase 2 (Full Analysis Set).

| Efficacy Parameter | Group 1 N = 52 | Group 2 N = 3 | Group 3 N = 47 | Group 4 N = 42 | All Patients N= 144 |
|---|---|---|---|---|---|
| **Best overall response, n (%)** | | | | | |
| CR | 0 | 0 | 0 | 3 (7.1) | 3 (2.1) |
| PR | 15 (28.8) | 1 (33.3) | 29 (61.7) | 15 (35.7) | 60 (41.7) |
| SD | 16 (30.8) | 2 (66.7) | 15 (31.9) | 16 (38.1) | 49 (34.0) |
| PD | 9 (17.3) | 0 | 0 | 6 (14.3) | 15 (10.4) |
| Unknown | 12 (23.1) | 0 | 3 (6.4) | 2 (4.8) | 17 (11.8) |
| **ORR, n (%) [95 % CI]** | 15 (28.8) [17.1-43.1] | 1 (33.3) [0.8-90.6] | 29 (61.7) [46.4-75.5] | 18 (42.9) [27.7-59.0] | 63 (43.8) [35.5-52.3] |
| **DCR, n (%) [95 % CI]** | 31 (59.6) [45.1-73.0] | 3 (100) [29.2-100] | 44 (93.6) [82.5-98.7] | 34 (81.0) [65.9-91.4] | 112 (77.8) [70.1-84.3] |
| **DOR** | | | | | |
| Events, n/M[a] (%) | 14/15 (93.3) | 1/1 (100) | 22/29 (75.9) | 13/18 (72.2) | 50/63 (79.4) |
| Median (95 % CI), months | 6.5(3.7-10.8) | 12.0 (NE) | 11.6(6.6-17.5) | 14.5(9.2-NE) | 11.6(9.2-12.8) |
| **PFS** | | | | | |
| Events, n/N (%) | 38/52 (73.1) | 3/3 (100) | 35/47 (74.5) | 30/42 (71.4) | 106/144 (73.6) |
| Median (95 % CI), months | 5.6(3.7-7.4) | 3.8(3.7-NE) | 10.1(7.6-13.8) | 10.9(5.6-19.2) | 7.7(7.1-9.9) |
| **OS** | | | | | |
| Events, n/N (%) | 35/52 (67.3) | 3/3 (100) | 30/47 (63.8) | 23/42 (54.8) | 91/144 (63.2) |
| Median (95 % CI), months | 18.8 (14.9-26.0) | 5.6(3.7-NE) | 25.6 (18.8-33.0) | 28.9 (20.5-NE) | 22.9 (19.2-28.3) |
| 36-month event-free probability, % (95 % CI) | 25.0 (13.3-38.6) | 0.0 | 27.4 (12.6-44.5) | 39.9 (23.1-56.3) | 30.6 (22.2-39.3) |
| 48-month event-free probability, % (95 % CI) | 20.0(9.6-33.1) | 0.0 | NE | NE | 25.7 (16.7-35.6) |

Group 1: Fasted; EGFR-TKI resistant; 1-3 prior lines of systemic therapy [including maximum 1 line of first-/second-generation EGFR-TKI]; EGFRL858R/ex19del; any T790M/MET; Group
2: Fasted; EGFR-TKI naïve; 0-2 prior lines; de novo T790M+ ; any MET; Group
3: Fasted; treatment naïve; EGFRL858R/ex19del; T790M− ; any MET; Group
4: With food; 0-2 prior lines; EGFRL858R/ex19del; any T790M/MET.
aM is the number of patients with partial or complete response.
ORR = CR + PR.
DCR = CR + PR + SD.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

### 3.3. Efficacy by T790M and MET Status in Group 1 +Phase 1b RP2D

In MET+ (n = 24) and MET− (n = 42) patients, the ORR (95 % CI) was 45.8 (25.6–67.2) and 26.2 (13.9–42.0); median DOR was 6.8 months (5.6–10.8) and 8.3 months (3.4–40.4); median PFS was 8.0 months (5.4–11.0) and 5.3 months (3.5–5.7); and median OS was 18.6 months (14.0–21.3) and 20.4 months (11.9–31.8), respectively (Table 3). Kaplan-Meier curves for PFS are presented in Fig. S2.

In T790M+ (n = 29) and T790M− (n = 34) patients, the ORR was 37.9 % and 32.4 %; median DOR was 7.4 months (3.6–39.2) and 10.1 months (3.7–25.7); median PFS was 5.7 months (5.3–11.0) and 5.6 months (3.3–7.4); and median OS was 21.7 months (14.9–40.6) and 17.2 months (11.9–20.4), respectively (Table 3).

### 3.4. Safety

The median duration of exposure was 24.3 weeks (range, 0.3–188.6) for capmatinib and 33.4 weeks (0.3–214.1) for nazartinib. An overview of adverse events (AEs) is presented in Table S7. AEs (any grade or cause) were reported in all patients (n = 144); the most frequent events (≥10 %) are listed in Table S8. The most frequent grade ≥ 3 any-cause AEs (>5 %) were increased ALT (n = 20, 13.9 %), increased amylase (n = 16, 11.1 %), increased lipase (n = 14, 9.7 %), maculopapular rash (n = 12, 8.3 %), pleural effusion (n = 9, 6.3 %), and peripheral edema (n = 8, 5.6 %). The most common treatment-related AEs (TRAEs; any grade ≥10 %) are reported in Table 4. Most frequent grade ≥ 3 TRAEs (>5 %) were increased ALT (n = 19, 13.2 %), maculopapular rash (n = 12, 8.3 %), increased amylase, increased lipase (n = 11, 7.6 % each), and peripheral edema (n = 8, 5.6 %).

AEs (any grade or cause) leading to treatment discontinuation were reported in 48 patients (33.3 %) Table S7. The most frequent TRAEs leading to discontinuation (any grade, >3 %) were peripheral edema (n = 6, 4.2 %), increased ALT, and interstitial lung disease (n = 5, 3.5 % each), data not shown. AEs leading to dose adjustments/interruptions were reported in 115 patients (79.9 %). Of 13 fatal SAEs reported, two were considered treatment-related; one patient died due to hepatitis B reactivation, and a second with treatment-related embolism had deep vein thrombosis as a preexisting condition, a potential confounding factor. PK data are presented in **Supplementary Results** and Table S9.

### 3.5. Food effect evaluation

PK data were compared when taken with food (group 4) versus fasted conditions (phase 1b at RP2D and phase 2 group 3) (Table S10). Capmatinib showed a 23 % decrease in AUC with a geometric mean ratio (GMR) of 0.77 (90 % CI 0.60–0.99) and 32 % decrease in $C_{max}$, GMR 0.68 (0.52–0.90) when taken with food (n = 12) versus fasted (n = 20), but no change in $T_{max}$ on cycle 1 day 1 (C1D1). At steady state (cycle 2 day 1 [C2D1]), there was no difference observed in AUC, whereas a slightly lower $C_{max}$ (14 %) was observed when taken with food (n = 15) versus fasted (n = 18) however, the 90 % CI of the geometric mean ratio covered 1 (0.66–1.11). A ~2-hour delay in $T_{max}$ was observed when taken with food. Overall, no significant food effect was observed at the steady state.

Nazartinib showed a 43 % decrease in AUC with a GMR of 0.57 (90 % CI 0.42–0.77) and a 38 % decrease in $C_{max}$ with GMR of 0.62 (90 % CI 0.45–0.85) when taken with food (n = 12 for both) versus fasted on C1D1 (n = 17, n = 19, respectively). While for C2D1, the decrease in AUC was 23 % with GMR of 0.77 (90 % CI 0.55–1.08) and the decrease in $C_{max}$ was 25 % with GMR of 0.75 (90 % CI 0.56–1.00) when taken with food (n = 15) versus fasted (n = 16, n = 17). No changes in $T_{max}$ were observed on either cycle. Overall, lower exposure was seen when taken with food versus fasted state, suggesting a modest negative food effect.

## 4. Discussion

At the RP2D, capmatinib 400 mg bid plus nazartinib 100 mg qd demonstrated antitumor activity in patients with *EGFR*-mutated stage IIIB/IV NSCLC previously exposed to first-/second-generation EGFR-TKIs who later became EGFR-TKI resistant.

In an exploratory analysis of brain metastases, patients without baseline metastases remained metastasis-free, and most patients with baseline metastases experienced a > 30 % lesion diameter reduction after treatment, suggesting a protective effect of this drug combination against brain metastases. Furthermore, no new brain metastases were reported during the study.

An exploratory efficacy analysis by T790M and MET status in first-/second-generation EGFR-TKI–resistant patients from group 1 +phase 1b RP2D suggested that the combination had antitumor activity regardless

**Table 3**
Efficacy by T790M and MET Status in the Combined Group 1 +Phase 1b RP2D (Full Analysis Set).

| Efficacy Parameter | Group 1 +Phase 1b RP2D | | | | |
|---|---|---|---|---|---|
| | T790M+N = 29 | T790M−N = 34 | MET+N = 24 | MET−N = 42 | All Patients[a]N = 68 |
| **Best overall response, n (%)** | | | | | |
| CR | 0 | 2 (5.9) | 1 (4.2) | 1 (2.4) | 2 (2.9) |
| PR | 11 (37.9) | 9 (26.5) | 10 (41.7) | 10 (23.8) | 21 (30.9) |
| SD | 9 (31.0) | 8 (23.5) | 5 (20.8) | 13 (31.0) | 18 (26.5) |
| PD | 2 (6.9) | 10 (29.4) | 3 (12.5) | 10 (23.8) | 13 (19.1) |
| Unknown | 7 (24.1) | 5 (14.7) | 5 (20.8) | 8 (19.0) | 14 (20.6) |
| **ORR, % (95 % CI)** | 37.9 (20.7-57.7) | 32.4 (17.4-50.5) | 45.8 (25.6-67.2) | 26.2 (13.9-42.0) | 33.8 (22.8-46.3) |
| **DCR, % (95 % CI)** | 69.0 (49.2-84.7) | 55.9 (37.9-72.8) | 66.7 (44.7-84.4) | 57.1 (41.0-72.3) | 60.3 (47.7-72.0) |
| **DOR** | | | | | |
| Events, n/M[b] (%) | 11/11 (100) | 9/11 (81.8) | 11/11 (100) | 9 /11 (81.8) | 21/23 (91.3) |
| Median (95 % CI), months | 7.4 (3.6-39.2) | 10.1 (3.7-25.7) | 6.8 (5.6-10.8) | 8.3 (3.4-40.4) | 8.3 (5.6-11.1) |
| **PFS** | | | | | |
| Events, n/N (%) | 21/29 (72.4) | 27/34 (79.4) | 18/24 (75.0) | 32/42 (76.2) | 51/68 (75.0) |
| Median (95 % CI), months | 5.7 (5.3-11.0) | 5.6 (3.3-7.4) | 8.0 (5.4-11.0) | 5.3 (3.5-5.7) | 5.6 (5.3-7.4) |
| **OS** | | | | | |
| Events, n/N (%) | 21/29 (72.4) | 23/34 (67.6) | 16/24 (66.7) | 28/42 (66.7) | 46/68 (67.6) |
| Median (95 % CI), months | 21.7 (14.9-40.6) | 17.2 (11.9-20.4) | 18.6 (14.0-21.3) | 20.4 (11.9-31.8) | 18.8 (14.9-21.8) |
| 36-month event-free probability, % (95 % CI) | 34.0 (17.2-51.6) | 22.1 (9.1-38.8) | 15.9 (3.9-35.1) | 33.1 (18.6-48.4) | 28.1 (17.1-40.0) |
| 48-month event-free probability, % (95 % CI) | 30.2 (14.4-47.7) | 17.7 (6.1-34.2) | 15.9 (3.9-35.1) | 30.1 (16.2-45.3) | 24.3 (14.1-36.1) |

Group 1: Fasted; EGFR-TKI resistant; 1-3 prior lines of systemic therapy [including maximum 1 line of first-/second-generation EGFR-TKI]; EGFRL858R/ex19del; any T790M/MET.
aIncludes patients with unknown T790M or MET status.
bM is the number of patients with partial or complete response.
ORR = CR + PR.
DCR = CR + PR + SD.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; TKI, tyrosine kinase inhibitor.

**Table 4**
Treatment-Related AEs (Any Grade ≥10 % in All Patients) – Phase 2 (Safety Set).

| Preferred Term | Group 1 N = 52 | | Group 3 N = 47 | | Group 4 N = 42 | | All PatientsN= 144 | |
|---|---|---|---|---|---|---|---|---|
| | Any Graden (%) | Grade 3/4n (%) | Any Graden (%) | Grade 3/4n (%) | Any Graden (%) | Grade 3/4n (%) | Any Graden (%) | Grade 3/4n (%) |
| Number of patients with ≥ 1 event | 49 (94.2) | 31 (59.6) | 46 (97.9) | 27 (57.4) | 42 (100) | 22 (52.4) | 140 (97.2) | 82 (56.9) |
| Peripheral edema | 26 (50.0) | 3 (5.8) | 27 (57.4) | 4 (8.5) | 23 (54.8) | 1 (2.4) | 79 (54.9) | 8 (5.6) |
| Nausea | 22 (42.3) | 4 (7.7) | 23 (48.9) | 2 (4.3) | 15 (35.7) | 0 | 60 (41.7) | 6 (4.2) |
| Diarrhea | 12 (23.1) | 1 (1.9) | 22 (46.8) | 0 | 14 (33.3) | 1 (2.4) | 49 (34.0) | 2 (1.4) |
| Maculopapular rash | 12 (23.1) | 8 (15.4) | 14 (29.8) | 2 (4.3) | 9 (21.4) | 2 (4.8) | 36 (25.0) | 12 (8.3) |
| Increased ALT | 7 (13.5) | 4 (7.7) | 12 (25.5) | 7 (14.9) | 10 (23.8) | 6 (14.3) | 31 (21.5) | 19 (13.2) |
| Increased blood creatinine | 8 (15.4) | 0 | 11 (23.4) | 0 | 11 (26.2) | 0 | 31 (21.5) | 0 |
| Vomiting | 13 (25.0) | 2 (3.8) | 11 (23.4) | 1 (2.1) | 5 (11.9) | 2 (4.8) | 29 (20.1) | 5 (3.5) |
| Increased AST | 4 (7.7) | 0 | 12 (25.5) | 5 (10.6) | 9 (21.4) | 2 (4.8) | 27 (18.8) | 7 (4.9) |
| Fatigue | 14 (26.9) | 2 (3.8) | 6 (12.8) | 0 | 5 (11.9) | 0 | 26 (18.1) | 2 (1.4) |
| Pruritus | 4 (7.7) | 0 | 9 (19.1) | 0 | 12 (28.6) | 0 | 25 (17.4) | 0 |
| Increased amylase | 7 (13.5) | 6 (11.5) | 10 (21.3) | 3 (6.4) | 6 (14.3) | 2 (4.8) | 24 (16.7) | 11 (7.6) |
| Increased lipase | 11 (21.2) | 6 (11.5) | 7 (14.9) | 3 (6.4) | 6 (14.3) | 2 (4.8) | 24 (16.7) | 11 (7.6) |
| Asthenia | 5 (9.6) | 1 (1.9) | 10 (21.3) | 1 (2.1) | 6 (14.3) | 0 | 22 (15.3) | 2 (1.4) |
| Hypoalbuminemia | 7 (13.5) | 0 | 9 (19.1) | 0 | 6 (14.3) | 0 | 22 (15.3) | 0 |
| Muscle spasms | 2 (3.8) | 0 | 9 (19.1) | 0 | 10 (23.8) | 0 | 21 (14.6) | 0 |
| Rash | 4 (7.7) | 0 | 9 (19.1) | 2 (4.3) | 5 (11.9) | 0 | 18 (12.5) | 2 (1.4) |
| Decreased appetite | 9 (17.3) | 0 | 4 (8.5) | 0 | 2 (4.8) | 0 | 16 (11.1) | 0 |
| Dermatitis acneiform | 2 (3.8) | 1 (1.9) | 9 (19.1) | 0 | 4 (9.5) | 0 | 15 (10.4) | 1 (0.7) |
| Paronychia | 3 (5.8) | 0 | 5 (10.6) | 0 | 7 (16.7) | 0 | 15 (10.4) | 0 |

Group 1: Fasted; EGFR-TKI resistant; 1-3 prior lines of systemic therapy [including maximum 1 line of first-/second-generation EGFR-TKI]; EGFRL858R/ex19del; any T790M/MET; Group 3: Fasted; treatment naïve; EGFRL858R/ex19del; T790M−; any MET; Group 4: With food; 0-2 prior lines; EGFRL858R/ex19del; any T790M/MET. Group 2 data has not been included as N = 3 (only 3 patients).
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 4.03.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; MedDRA, Medical Dictionary for Regulatory Activities; TKI, tyrosine kinase inhibitor.

of T790M status, in line with similar observations from other third-generation EGFR TKIs e.g., osimertinib [9,22,23]. MET+ patients (n = 24), also showed antitumor activity (ORR 45.8 %, median PFS 8.0 months); of note, 45.8 % of these patients were treated in the third/fourth line, suggesting that MET inhibition may be useful in this setting. The retrospective nature of this analysis and the small sample sizes limit this interpretation, however similar observations have been made previously[24].

In T790M− patients unselected for MET and treated with first-line capmatinib plus nazartinib, the results (ORR: 61.7 %, median PFS: 10.1 months) do not seem to support the addition of a METi to an EGFR-TKI versus treatment with an EGFR-TKI alone. With the limitations of cross-trial comparisons, a blinded independent review committee-assessed ORR and median PFS (95 % CIs) of 69 % (53−82) and 18 months (15-NE) were reported in a phase 2 study evaluating first-line nazartinib (150 mg qd) in patients with advanced *EGFR*-mutated NSCLC (N = 45).[25] In the phase 1/2 AURA study, an investigator-assessed ORR and median PFS (95 % CIs) of 67 % (47−83) and 22.1 months (13.7–30.2) were observed with first-line osimertinib 80 mg qd in patients with locally advanced/metastatic *EGFR*-mutated NSCLC (N = 30)[26].

Capmatinib plus nazartinib demonstrated acceptable safety at the RP2D. The AE profile was largely in line with that reported in other studies combining METi with EGFR-TKIs, differing only in an absence of cardiac toxicity compared with osimertinib, and acceptable liver toxicity compared with savolitinib.[9–11,27] In this study, the most common any-grade TRAEs included gastrointestinal events (nausea, diarrhea), peripheral edema, and maculopapular rash. Peripheral edema is a common TRAE associated with METi, and its occurrence is likely a drug class effect [10,15][29,30]. Maculopapular rash has been reported previously with nazartinib and is usually acute, self-limiting, and different from the acneiform rash associated with wild-type EGFR inhibition.[17,25] We conclude that the incidence of peripheral edema and maculopapular rash is comparable with that observed for single-agent capmatinib and single-agent nazartinib, respectively. Overall, AEs were self-limiting, successfully managed by dose adjustments and/or use of concomitant medications. The safety profile for groups 1 and 3 was largely comparable, despite different lines of treatment. The combination was also well tolerated when administered with food, with safety profiles comparable to fasted states.

Patients who develop acquired resistance to EGFR-TKIs have limited treatment options. A combination of METi and EGFR-TKI may act synergistically in patients whose tumors bear alterations in both pathways, thereby preventing or overcoming acquired resistance to EGFR-TKIs. Our study findings support the concept of targeting EGFR and MET pathways in patients with third-generation EGFR-TKI resistant, EGFR-mutated NSCLC.

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## Declaration of Competing Interest

**Enriqueta Felip:** Consulting or Advisory Role: AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Roche, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, Turning Point Therapeutics, Daiichi Sankyo. Speakers' Bureau: Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Lilly, Roche, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, Merck Sharp & Dohme, Peervoice, Pfizer, Sanofi, Takeda, Touch Oncology. Travel, Accommodations, Expenses: AstraZeneca, Janssen, Roche. Other Relationship: Grifols. Uncompensated Relationships: Member of the Scientific Advisory Committee Hospital Universitari Parc Taulí , SEOM (Sociedad Española de Oncología Médica), President from 2021–2023, "ETOP IBCSG Partners" Member of the Scientific Committee.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114182.

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