PHASE I STUDIES

A phase 1b study of the MET inhibitor capmatinib combined with cetuximab in patients with MET-positive colorectal cancer who had progressed following anti-EGFR monoclonal antibody treatment

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Summary

Background Overcoming resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) in patients with *KRAS* wildtype (WT) metastatic colorectal cancer (mCRC) could help meet the needs of patients with limited treatment options. *Methods* In this phase 1b study, patients with *N/KRAS* WT, *MET*-positive mCRC who had progressed following anti-EGFR mAb treatment received escalating oral doses of capmatinib (150, 300, and 400 mg) twice daily plus weekly intravenous cetuximab (at the approved dose). The primary objective was to establish a recommended dose for expansion (RDE) of capmatinib in combination with cetuximab. Safety, preliminary activity, pharmacokinetics, and pharmacodynamics were also explored. *Results* Thirteen patients were enrolled. No patients experienced a dose-limiting toxicity at investigated doses; the RDE was established as capmatinib 400 mg twice daily plus cetuximab. All patients experienced adverse events (AEs) suspected to be related to the study treatment. Five patients (38.5%) reported study-drug–related AEs of grade 3/4 in severity. No patients achieved a complete or partial response according to RECIST v1.1; however, tumor shrinkage of 29–44% was observed in 4 patients. *Conclusions* Capmatinib plus cetuximab was well tolerated. Preliminary signs of activity were observed. Further investigation is warranted to obtain efficacy data and refine predictive biomarkers of response. *Clinical trial registration* NCT02205398.

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Background

Colorectal cancer (CRC) is the third most common cancer worldwide; in 2012, there were 1.4 million new cases and 694 000 deaths from this disease globally [1]. Current treatment options for patients with metastatic unresectable CRC revolve around a backbone of chemotherapy with fluoropyrimidine used in various combinations with irinotecan or oxaliplatin [2]. Monoclonal antibodies (mAbs) bevacizumab (anti-VEGF), cetuximab, and panitumumab (anti-EGFRs) may be combined with these chemotherapy regimens to improve clinical outcomes [3–8] depending on *RAS* mutational status [9]. Treatment with inhibitors of EGFR is hampered by the development of acquired resistance [10] and further therapeutic options are limited for these patients. Mechanisms of *de novo* and acquired resistance to anti-EGFR mAbs are under investigation and studies in lung cancer have demonstrated that amplification of *MET* can drive resistance to EGFR inhibitors [11, 12]. Moreover, the link between *MET* amplification and resistance to EGFR inhibition has been reported for metastatic CRC (mCRC) [13–16]. *MET* encodes a receptor tyrosine kinase MET with the ligand hepatocyte growth factor (HGF) [17]. On binding with HGF, MET activates downstream signaling pathways leading to cell migration, proliferation, and angiogenesis [17]. Preclinical studies have explored the MET ligand HGF and demonstrated that this also drives resistance to EGFR inhibition [18, 19], further highlighting the importance of the MET pathway in anti-EGFR resistance. Taken together, these results point towards the utility of combining a MET inhibitor with an anti-EGFR mAb in treating certain patients to overcome resistance to anti-EGFR mAbs.

Capmatinib (INC280) is a small adenosine triphosphate competitive, reversible, highly selective inhibitor of the MET receptor tyrosine kinase [20]. In preclinical assessments, capmatinib demonstrated inhibition of MET activation in cancer cells whose growth is driven by the activated MET pathway [20, 21]. In clinical trials, capmatinib was well tolerated, with the majority of adverse events (AEs) being mild or moderate in severity [22, 23]. Antitumor activity has been observed in patients with non-small cell lung cancer treated with single-agent capmatinib and the combination of capmatinib with the EGFR inhibitor gefitinib [22, 24].

This study combines capmatinib with the anti-EGFR mAb cetuximab and was designed for patients with mCRC or head and neck squamous cell carcinoma (HNSCC) whose tumors have become resistant to anti-EGFR treatment and with evidence of MET pathway activation. Herein we report results from the dose-escalation part of the study; the dose-expansion part of the study was not initiated.

Methods

Study design

In this phase 1b multicenter, open-label, dose-finding study (NCT02205398), patients who received at least one previous line of treatment for metastatic disease and received cetuximab or panitumumab with the last regimen were treated with escalating doses of capmatinib + cetuximab. Dose-escalation decisions were based on all relevant data from all dose levels evaluated in the ongoing study, including safety information, dose-limiting toxicities (DLTs), and pharmacokinetic (PK) data from evaluable patients. The recommended dose for the next cohort of patients was guided by a Bayesian Logistic Regression Model following the principle of escalation with overdose control (EWOC) [25–27]. Following the determination of the maximum tolerated dose and/or recommended dose for expansion, two expansion groups were planned: one comprising patients with mCRC and the other comprising patients with HNSCC (Supplementary Fig. S1).

Study objectives

The primary objective of the study was to estimate the maximum tolerated dose and/or recommended dose of capmatinib in combination with cetuximab in *MET*-positive patients with mCRC or HNSCC who developed resistance to previous EGFR therapy. Secondary objectives included safety, preliminary antitumor activity, and PK of the combination of capmatinib with cetuximab. Exploratory objectives included: assessment of the effect of the treatment combination on relevant signaling pathways (HGF/MET, EGFR/PI3K/AKT, and MAPK) in tumor tissue, assessment of the effect of the combination on markers of tumor response in the blood, and assessment of genetic alterations in multiple cancer-related genes in newly and previously obtained tumor samples, including evaluating their relationship with clinical outcomes.

Study population

Adult patients with *K/NRAS* wildtype (WT) and *MET*-positive mCRC, and *MET*-positive recurrent/metastatic HNSCC who had received at least one prior line of treatment for metastatic disease were eligible for study enrollment. *MET* positivity was initially defined as *MET* immunohistochemistry (IHC) intensity score 2 + or 3 + in ≥ 50% of tumor cells; however, this was amended to IHC intensity score 2 + in ≥ 50% of tumor cells and *MET* gene copy number (GCN) ≥ 5 by fluorescence *in situ* hybridization (FISH), or IHC intensity score 3 + in ≥ 50% of tumor cells, based on response data from a study of capmatinib + gefitinib [28]. Analyses were performed on a newly obtained or the most recent previously obtained tumor

sample available. The last line of treatment had to include an anti-EGFR antibody and patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 2. Patients were excluded if they had received prior treatment with MET/HGF inhibitors.

Study treatment

Patients received oral tablets of capmatinib on a continuous twice-daily dosing regimen alongside weekly intravenous infusions of cetuximab (Erbitux®; 400 mg/m^2 initial infusion and 250 mg/m^2 subsequent infusions). Study treatment was administered during 28-day cycles. The starting dose of capmatinib was 150 mg twice daily and was selected based on available safety, PK, pharmacodynamics (PD), and preliminary efficacy data from completed and ongoing studies of capmatinib. This starting dose was below the recommended dose of single-agent capmatinib, determined as 400 mg twice daily for the tablet formulation. The cetuximab dose was fixed and followed the recommended dosing for patients with mCRC or HNSCC according to the cetuximab label. Patients received treatment until they experienced unacceptable toxicity, disease progression, or death or if they prematurely withdrew from the study or withdrew consent.

Study assessments

Efficacy assessments

Tumor response was assessed locally by investigators based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Each patient was evaluated for all potential sites of tumor lesions at screening and every 8 weeks after starting study treatment until disease progression. Computed tomography or MRI scans were made at screening to assess the primary tumor and presence of metastases. The same method of assessment of each lesion that was measured at screening was recommended to be used throughout the study to enable consistent comparisons.

Safety assessments

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 and Medical Dictionary for Regulatory Activities Version 20 was used. DLT criteria included grade ≥ 4 hematologic AEs; febrile neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L or 1000/mm^3 and a single temperature of > 38.3 °C or a sustained temperature of ≥ 38 °C for more than 1 h); any neurologic disorder of grade ≥ 2; or any non-hematologic AEs of grade ≥ 3 except for rash, diarrhea, nausea, or vomiting (these became DLTs if they persisted

following adequate treatment) occurring within the first cycle of treatment with capmatinib plus cetuximab.

Pharmacokinetic assessments

Serial blood samples were collected to assess single-dose and steady-state plasma PK of capmatinib. Samples were taken pre-dose and at 0.5, 1, 2, 4, 6, and 8 h post-dose on Day 1 and Day 15 of Cycle 1, and pre-dose on Day 1 of Cycles 2, 3, and 4. Noncompartmental PK parameters were estimated from each evaluable individual plasma concentration–time profile.

Biomarker assessments

Patients were required to provide a recent, previously obtained tumor sample and/or a newly obtained tumor sample taken during the molecular prescreening visit. On-treatment tumor samples could also be collected on Day 15 of Cycle 1, where feasible. The following markers were assessed in tumor tissue: protein expression and/or GCN of *MET* (by IHC and/or FISH); *K/NRAS* mutational status of patients with mCRC; DNA sequence of multiple known cancer genes, including markers known to be related to resistance to EGFR inhibitors; and phosphorylation level of markers related to MET, PI3K/AKT, and MAPK signaling pathways in paired newly obtained biopsies (Day 1 and Day 15 of Cycle 1). MET assessment by FISH was implemented after protocol amendment 2 (where the definition of MET positivity was updated based on preliminary data from ongoing clinical studies with capmatinib).

Statistical methods

An adaptive Bayesian Logistic Regression Model guided by the EWOC principle was used to guide the dose escalation. Data from the study were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (*n*, mean, standard deviation, median, minimum, and maximum) for quantitative data, and contingency tables (frequencies and percentages) for qualitative data. The PK analysis set consisted of all patients who provided an evaluable PK profile.

Results

Preclinical data supporting combined targeting of EGFR and MET in HNSCC and CRC

The impact of cetuximab treatment on growth of two HNSCC cell lines (YD-38, CAL-33) and one CRC cell line (CCK-81)

was assessed in the presence or absence of activated MET. The cell lines selected have no *MET* amplification; however, MET expression was present and likely to be representative of their lineages. All three cell lines were *RAS (KRAS, NRAS*, and *HRAS)* WT, and a *PIK3CA* mutation was noted in the CAL-33 cell line. Growth of all cell lines was inhibited with cetuximab treatment with varying degrees; however, activation of MET by exposure to HGF reversed this inhibition. HGF/MET-mediated resistance to cetuximab was fully blocked by co-treatment with capmatinib (Supplementary Fig. S2). Capmatinib and cetuximab acted synergistically in the presence of HGF in HNSCC (Supplementary Fig. S3) and CRC cell lines (Supplementary Fig. S4), but not when HGF was lacking. Methods associated with this preclinical experiment are provided in the Supplementary Methods.

Patient population

A total of 98 patients with targeted indications were prescreened to check for KRAS, NRAS, and MET status between July 28, 2014 and January 20, 2017, and 13 patients with mCRC meeting the inclusion criteria were enrolled into the study. All patients had *K/NRAS* WT and *MET*-positive mCRC, and no patients with HNSCC were enrolled. Patients received capmatinib 150 mg + cetuximab ($n = 4$), capmatinib 300 mg + cetuximab ($n = 3$), or capmatinib 400 mg + cetuximab ($n = 6$). All 13 patients discontinued treatment; 12 of those as a result of disease progression and 1 patient in the capmatinib 400 mg + cetuximab group due to grade 1/2 asthenia, folliculitis, and skin infection. The median age of patients enrolled in the study was 60 years (range: 35–77 years; Table 1). The majority of patients were male (84.6%) and most patients (92.4%) had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Patients had received a median of four prior lines of antineoplastic therapy, which included cetuximab in 5 patients and panitumumab in 7 patients. One patient had received both cetuximab and panitumumab in different lines of prior therapy.

The sponsor decided to halt recruitment to this study after the phase 1b dose-finding part. This decision was based on the difficulty in identifying patients most likely to benefit from this combination, and the expectation that further clinical development in CRC would necessitate a different study design.

Determination of recommended dose

None of the patients treated across the three dose levels experienced a DLT. PK analyses demonstrated that exposures of capmatinib at 400 mg twice daily in combination with cetuximab were comparable with the exposures at the single-agent recommended dose of capmatinib (400 mg twice daily). The Bayesian model confirmed that the combination of capmatinib 400 mg twice daily + cetuximab satisfied the EWOC specified in the study protocol. Based on the model estimation, the available safety data, and preliminary PK analysis, the recommended dose was established as capmatinib 400 mg twice daily in combination with weekly cetuximab (400 mg/m^2 initial infusion and 250 mg/m^2 subsequent infusions).

Treatment duration

The overall median duration of exposure to treatment was 56 days (range: 21–221 days). The median duration of exposure was higher in patients treated with capmatinib 400 mg + cetuximab (83.5 days) compared with those treated with capmatinib 150 mg + cetuximab (44.5 days) or capmatinib 300 mg + cetuximab (49.0 days). Two patients (33.3%) in the capmatinib 400 mg combination arm received treatment for longer than 24 weeks (Fig. 1).

Safety

All 13 patients experienced at least one AE suspected to be related to the study treatment; for 5 of these patients, the AEs were grade 3/4 in severity (Table 2); there were no deaths as a result of treatment-related AEs. The most common (occurring ≥ 30% of all patients) AEs suspected to be related to study treatment were fatigue, hypomagnesemia (5 patients each, 38.5%), elevated alanine aminotransferase (ALT), decreased appetite, dermatitis acneiform, and nausea (4 patients each, 30.8%). The most frequently reported AEs regardless of cause (occurring in ≥ 30% of all patients; Supplementary Table S1) were fatigue, hypoalbuminemia, hypomagnesemia, nausea, pyrexia (7 patients each, 53.8%), peripheral edema (6 patients, 46.2%), elevated ALT, decreased appetite (5 patients each, 38.5%), elevated aspartate aminotransferase, dermatitis acneiform, elevated lipase, and rash (4 patients each, 30.8%). Five patients experienced grade 3/4 AEs suspected to be related to study treatment; these were fatigue, elevated amylase (2 patients each, 15.4%), elevated ALT, and elevated lipase (1 patient each, 7.7%). Eight patients reported grade 3/4 AEs regardless of cause; these included fatigue, elevated lipase, elevated amylase (2 patients each, 15.4%), hypomagnesemia, elevated ALT, elevated blood bilirubin, and hepatic failure (1 patient each, 7.7%). Five patients (38.5%) experienced 11 serious AEs regardless of cause; these were elevated blood bilirubin, dehydration, device-related infection, fatigue, hepatic failure, lung infection, pneumonia, pneumothorax, renal failure, sepsis, and stomatitis. One patient with folliculitis (grade 2), skin infection (grade 2), and asthenia (grade 1) decided to discontinue study

Table 1 Patient demographics by treatment group

Demographic	Capmatinib 150 mg + cetuximab $n = 4$	Capmatinib 300 mg + cetuximab $n = 3$	Capmatinib 400 mg + cetuximab $n = 6$	All patients $N = 13$
Median age, years (range)	52.5 (35–77)	64.0 (40–74)	60.5 (54–73)	60.0 (35–77)
Sex, n (%)				
Female	1 (25.0)	1 (33.3)	0	2 (15.4)
Male	3 (75.0)	2 (66.7)	6 (100.0)	11 (84.6)
ECOG PS, n (%)				
0	0	1 (33.3)	5 (83.3)	6 (46.2)
1	4 (100.0)	1 (33.3)	1 (16.7)	6 (46.2)
2	0	1 (33.3)	0	1 (7.7)
Median prior lines of antineoplastic therapy, n	3.5	4.0	4.0	4.0
Prior EGFR mAb, n (%)	4 (100.0)	3 (100.0)	6 (100.0)	13 (100.0)
Cetuximab	1 (25.0)	2 (66.7)	2 (33.3)	5 (38.5)
Panitumumab	3 (75.0)	0 (0)	4 (66.7)	7 (53.8)
Both cetuximab and panitumumab[a]	0 (0)	1 (33.3)	0 (0)	1 (7.7)

[a] Received by the same patient in different therapy lines

ECOG PS Eastern Cooperative Oncology Group performance status; *EGFR* epidermal growth factor receptor; *mAb* monoclonal antibody

treatment. One patient died due to disease progression during the study.

Efficacy

Based on Investigator review per RECIST v1.1 criteria, no patients achieved a complete or partial response over the course of the study (Table 3). Six patients achieved stable disease, resulting in a disease control rate of 46.2%. Tumor shrinkage was observed in 6 patients in the study; 2 patients had target lesion reduction of 29% (1 at the 300 mg capmatinib dose level and 1 at the 400 mg capmatinib dose level), and 2 patients had target lesion reductions greater than 30% (both patients were at

the 400 mg capmatinib dose level; Fig. 2). Confirmation criteria of RECIST v1.1 were not met for objective response in any of the 4 patients with tumor shrinkage ≥ 29%.

Biomarker analyses

IHC data ($n = 13$) and FISH data ($n = 9$) from tumor samples taken prior to treatment initiation revealed a range of MET overexpression and *MET* amplification (Supplementary Table S2). The majority of patients had IHC scores of 3 + in ≥ 50% of tumor cells by centrally or locally assessed IHC; however, 3 patients were recruited

Fig. 1 Duration of exposure to capmatinib + cetuximab alongside MET status. *Abbreviations: BID* twice daily; *PD* progressive disease; *PR* partial response; *SD* stable disease
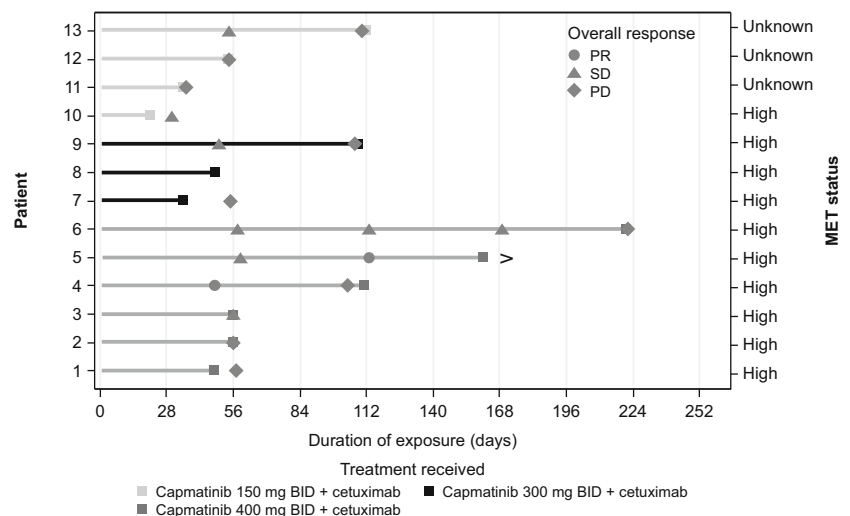
Table 2 AEs suspected to be study treatment related in at least 10% of all patients

AE, n (%)	Capmatinib 150 mg + cetuximab n = 4		Capmatinib 300 mg + cetuximab n = 3		Capmatinib 400 mg + cetuximab n = 6		All patients N = 13	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Fatigue	1 (25.0)	1 (25.0)	2 (66.7)	1 (33.3)	2 (33.3)	0	5 (38.5)	2 (15.4)
Hypomagnesemia	2 (50.0)	0	1 (33.3)	0	2 (33.3)	0	5 (38.5)	0
Elevated ALT	3 (75.0)	1 (25.0)	0	0	1 (16.7)	0	4 (30.8)	1 (7.7)
Decreased appetite	3 (75.0)	0	0	0	1 (16.7)	0	4 (30.8)	0
Dermatitis acneiform	2 (50.0)	0	2 (66.7)	0	0	0	4 (30.8)	0
Nausea	1 (25.0)	0	1 (33.3)	0	2 (33.3)	0	4 (30.8)	0
Elevated amylase	1 (25.0)	1 (25.0)	0	0	2 (33.3)	1 (16.7)	3 (23.1)	2 (15.4)
Elevated AST	2 (50.0)	0	0	0	1 (16.7)	0	3 (23.1)	0
Rash	0	0	0	0	3 (50.0)	0	3 (23.1)	0
Elevated blood alkaline phosphatase	0	0	0	0	2 (33.3)	0	2 (15.4)	0
Dermatitis	0	0	1 (33.3)	0	1 (16.7)	0	2 (15.4)	0
Diarrhea	0	0	0	0	2 (33.3)	0	2 (15.4)	0
Folliculitis	0	0	0	0	2 (33.3)	0	2 (15.4)	0
Elevated lipase	0	0	0	0	2 (33.3)	1 (16.7)	2 (15.4)	1 (7.7)
Peripheral edema	1 (25.0)	0	0	0	1 (16.7)	0	2 (15.4)	0
Stomatitis	1 (25.0)	0	1 (33.3)	0	0	0	2 (15.4)	0
Vomiting	1 (25.0)	0	0	0	1 (16.7)	0	2 (15.4)	0

AST aspartate aminotransferase; *AE* adverse event; *ALT* alanine aminotransferase

prior to the change in eligibility criteria and had IHC scores of 2 + in ≥ 50% of cells but GCN was not available. The GCN ranged from 2 to 16 by central FISH assessment; 3 patients had GCN > 5. The level of *MET* amplification or MET overexpression did not appear to correlate with tumor response; tumor regression was observed in the presence and absence of high-level *MET* amplification (Fig. 2 and Supplementary Table S2).

Data from next-generation sequencing of tumor samples taken prior to treatment initiation (n = 6), Day 15 of Cycle 1 (n = 6), and relapse (n = 1) revealed that the most common mutations observed at prescreening and during treatment were in the *TP53* and *APC* genes (Supplementary Table S2). *BRAF* V600E mutations were detected in tumor samples from 2 patients prior to and during treatment, but there was no apparent correlation between the presence of the *BRAF* V600E mutation and tumor response; both patients had stable disease and 1 had a reduction in tumor size of 29% from baseline. A previously uncharacterized *BRAF* translocation (*UACA-BRAF* fusion) was observed in the one tumor sample that was available for analysis by next-generation sequencing upon relapse.

Pharmacodynamics

Phosphorylation of MET, AKT, ERK, and S6 (Supplementary Fig. S5a) were assessed in tumor biopsies at screening and

during treatment. In 2 patients with significant tumor shrinkage, levels of most phosphorylated proteins reduced from screening to Day 15 of Cycle 1 (Supplementary Fig. S5b and c). In 4 patients with progressive disease, the levels of phosphorylated proteins were more variable with some increases and some decreases in levels following treatment (Supplementary Fig. S5d-g).

Pharmacokinetics

The geometric mean plasma exposures (maximum concentration and area under the concentration–time curve) of capmatinib generally increased with dose in a dose-proportional manner (Supplementary Table S3). Capmatinib exposures at 400 mg in combination with cetuximab were comparable with those exposures reported from previous studies of single-agent capmatinib treatment, indicating no PK drug–drug interaction was observed. Capmatinib was rapidly absorbed after oral administration with the median time to reach maximum drug concentration of 1.1 h at the 400 mg dose (Supplementary Table S3).

Discussion

In this phase 1b dose-escalation study, no DLTs were experienced in any of the three dose levels investigated. The
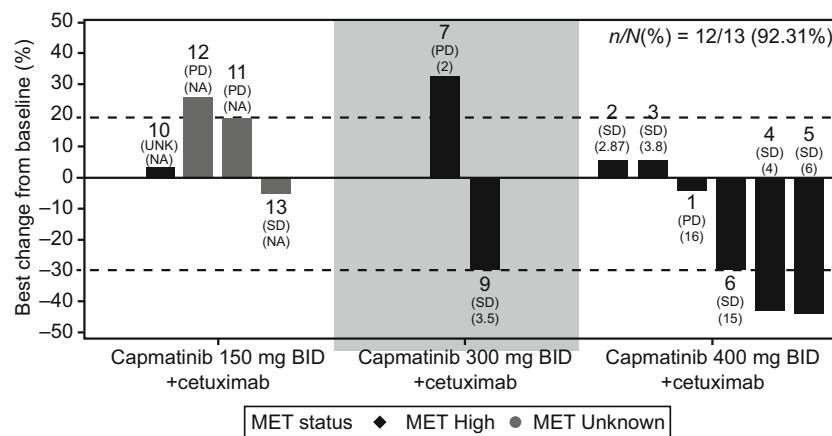
Fig. 2 Best percentage change from baseline in target lesions (RECIST v1.1) per Investigator assessment. MET unknown: IHC 2 +, GCN NA; MET high: IHC 3 + or IHC 2 + and GCN ≥ 5 by FISH. FISH GCN based on central laboratory data. Numbers above bars represent patient number (best overall response) (FISH GCN). *Abbreviations: BID* twice daily; *FISH* fluorescence *in situ* hybridization; *GCN* gene copy number; *IHC* immunohistochemistry; *NA* not available; *PD* progressive disease; *SD* stable disease; *UNK* unknown

recommended dose and schedule of capmatinib was established as 400 mg twice daily in combination with weekly cetuximab (400 mg/m^2 initial infusion and 250 mg/m^2 subsequent infusions). The capmatinib dose was identical to the recommended phase 2 dose of 400 mg that had previously been selected in studies of capmatinib based on safety and efficacy results [22, 24].

The combination of capmatinib and cetuximab was well tolerated; the most common AEs suspected to be related to treatment were fatigue, gastrointestinal issues (nausea and decreased appetite), skin conditions (dermatitis acneiform), and shifts in biochemistry (hypomagnesemia, elevated ALT). Safety results were consistent with single-agent safety profiles of capmatinib in patients with solid tumors [23, 29], and cetuximab or panitumumab in patients with mCRC [30, 31]. Fatigue, gastrointestinal issues, and skin conditions were also reported in these single-agent studies.

In our study, 6 patients (46.2%) achieved disease control over the course of the study. Two of these patients had tumor size reductions consistent with a partial response (≥ 30% reduction); however, they did not meet the confirmation criteria of RECIST v1.1 as they exhibited progressive disease at the next evaluation. This may suggest a transient evasion of EGFR resistance that was not sustained over the full treatment duration. Two other patients had stable disease with tumor size reductions of 29%. The limited patient numbers and short follow-up time make it difficult to fully assess the efficacy of the capmatinib + cetuximab combination in this patient population.

MET signaling is a promising target, and defining the populations of patients who may respond to treatment is increasingly important [32]. Nevertheless, defining biomarker assays and associated cut-offs that identify "*MET*-positive" tumors, which are responsive to MET inhibition, is challenging. Initially, patients whose tumors displayed MET IHC scores

Table 3 Best overall response by Investigator assessment as per RECIST v1.1

Response	Capmatinib 150 mg + cetuximab $n = 4$	Capmatinib 300 mg + cetuximab $n = 3$	Capmatinib 400 mg + cetuximab $n = 6$	All patients $N = 13$
BOR, *n* (%)				
CR	0	0	0	0
PR	0	0	0	0
SD	1 (25.0)	1 (33.3)	4 (66.7)	6 (46.2)
PD	2 (50.0)	1 (33.3)	2 (33.3)	5 (38.5)
Unknown[a]	1 (25.0)	1 (33.3)	0	2 (15.4)
ORR, *n* (%) [95% CI]	0 [0–60.2]	0 [0–70.8]	0 [0–45.9]	0 [0–24.7]
DCR, *n* (%) [95% CI]	1 (25.0) [0.6–80.6]	1 (33.3) [0.8–90.6]	4 (66.7) [22.3–95.7]	6 (46.2) [19.2–74.9]

BOR best overall response; *CI* confidence interval; *CR* complete response; *DCR* disease control rate; *ORR* overall response rate; *PD* progressive disease; *PR* partial response; *SD* stable disease; *RECIST* Response Evaluation Criteria In Solid Tumors

[a] Patients were assessed as progressing clinically; however, no scan assessment was performed on or after 6 weeks on treatment

of 2 + or 3 + in ≥ 50% of tumor cells were included in our study; however, data from studies of single-agent capmatinib and capmatinib in combination with gefitinib suggested that more stringent MET biomarker criteria were needed to enrich for potential responders to capmatinib-based treatment regimens [23, 24]. Based on experience from these other studies, the criteria in our study were amended so that only patients with MET IHC scores of 3+, or 2 + with MET GCN > 5, were eligible. The low incidence of tumors matching these criteria made patient recruitment difficult, and as a result, only 13 patients with mCRC out of the 98 prescreened were enrolled. While initial publications that provided the concept for this study [12, 13] highlighted *MET* amplification as the critical *MET* alteration underlying resistance to anti-EGFR antibodies, it is noteworthy that tumor shrinkage in our study was observed in the absence or presence of high-level *MET* amplification. This finding suggests that MET protein status may have independent predictive value as a biomarker of response. Conversely, we reasoned that it would be difficult to robustly distinguish MET 2 + versus 3 + staining in the IHC assay across samples and therefore opted to consider the MET GCN (MET GCN ≥ 5) as an additional selection biomarker in cases where the IHC assay showed a 2 + result. Given the small number of recruited patients, we cannot judge how well this biomarker selection scheme performed compared to other methods of patient selection. In addition, we cannot exclude that the level of target inhibition attained with the tested doses was insufficient to achieve an optimal response to treatment, although based on preclinical measurements and clinical PK of capmatinib across studies, we consider this an unlikely scenario, at least for MET inhibition.

The most common gene mutations observed were in the *TP53* and *APC* genes; these were apparent at prescreening and during treatment and are expected in patients with CRC [33, 34]. *BRAF* V600E mutation was reported in 2 patients at screening and during treatment; *BRAF*-mutant CRC is associated with a significantly poorer prognosis and poor response to standard treatments [4, 35]. Both patients with *BRAF*-mutation in this study had stable disease as their best overall response and 1 patient exhibited tumor regression of 29% from baseline, suggesting that this mutation is not a clear marker of resistance to the capmatinib + cetuximab combination.

PD data from this study were variable and difficult to interpret as the number of patients from whom paired biopsies could be obtained was low and there may have been issues with the robustness of the assays used. Specifically, the robustness of the pMET IHC assay may be questionable as three prescreening tumor samples showed an implausible lack of pMET signal given their medium-to-high total *MET* expression (data not shown). This may indicate that preservation of the MET phospho-epitope was not optimal.

The study was planned for expansion in a CRC and an HNSCC cohort; however, it was temporarily halted prior to initiating the dose-expansion part. This decision was taken based on difficulties in identifying patients who met the eligibility criteria. The data obtained in this study may justify the further clinical evaluation of capmatinib + cetuximab in CRC. Given the challenges in the identification of patients with MET-dependent CRC, enrollment of a broader molecular patient population may be considered.

Compliance with ethical standards

Merck Sharpe & Dohme. S. Siena reports acting in an advisory role for Amgen, Bayer, Bristol-Myers Squibb, Roche, Merck, Merck Sharpe & Dohme, Novartis Pharmaceuticals Corporation, and Sanofi. R. Mesia reports an advisory role for Merck, Bristol-Myers Squibb, Merck Sharpe & Dohme, AstraZeneca, Roche, and Nanobiotix; speaker bureaus for Merck, Bristol-Myers Squibb, and Merck Sharpe & Dohme. A. Cervantes reports research grants to his institution form Novartis Pharmaceuticals Corporation to develop clinical trials on investigational compounds. J. Dekervel reports speaker fees, consulting fees or travel grants from Amgen, Bayer, Ipsen, Novartis Pharmaceuticals Corporation, Merck and Servier. L. Siu reports research funding for her institution from Novartis Pharmaceuticals Corporation for the conduct of this study. A. Myers, Y. Sun, H.-X. Hao, R. Tiedt, S. Vicente, and S. Zhao are all employed by Novartis Pharmaceuticals Corporation. R. Berardi declares that she has no conflict of interest.

Ethical approval   All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent   Informed consent was obtained from all individual participants included in the study.

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