Phase II Study of Tivantinib and Cetuximab in Patients With *KRAS* Wild-type Metastatic Colorectal Cancer With Acquired Resistance to EGFR Inhibitors and Emergence of MET Overexpression: Lesson Learned for Future Trials With EGFR/MET Dual Inhibition

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Abstract

There is a major need for therapeutic strategies able to overcome resistance to available treatments for patients with metastatic colorectal cancer. In this phase II study, we evaluated the combination of tivantinib and cetuximab in 41 molecularly selected patients with acquired resistance to anti-epidermal growth factor receptors and MET overexpression. Overall, our results suggest that this combination is not worth of further development.

Background: MET overexpression/amplification has been associated with resistance to anti- epidermal growth factor receptor therapies in patients with metastatic colorectal cancer (mCRC). Combining tivantinib, an inhibitor of the MET receptor tyrosine kinase, and cetuximab may be effective in patients with epidermal growth factor receptor-resistant MET-high mCRC. **Patients and Methods:** This multicenter, single-arm, Simon 2-stage, phase II study enrolled patients with MET-high, *KRAS* wild-type mCRC, who were treated with $\geq$ 1 prior systemic therapy, with at least stable disease on the last treatment regimen containing cetuximab or panitumumab. Patients were enrolled if they presented tumor progression on cetuximab or panitumumab within 3 months before enrollment. Patients received tivantinib (360 mg twice daily) plus cetuximab (500 mg intravenously every 2 weeks). The primary endpoint was objective response rate; secondary endpoints included progression-free survival, overall survival, and safety. The treatment would be considered effective if $\geq$ 5 confirmed partial responses were observed among 41 patients. **Results:** In total, 41 patients were evaluated, 4 patients (9.8%) achieved an objective response, the median progression-free survival was 2.6 months (95% confidence interval, 1.9-4.2 months), and the median overall survival was 9.2 months (95%

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confidence interval, 7.1-15.1 months). Among 13 patients with tested *MET* amplification, 2 responding patients had *MET* amplification compared with none of the nonresponding patients. The most common grade ≥ 3 treatment-emergent adverse events were neutropenia (14.6%), skin toxicity (12.2%), and fatigue (9.8%). **Conclusion:** Although the study did not meet its primary endpoint, efficacy results suggest some activity of the tested combination, with almost 10% of patients achieving objective response in a difficult-to-treat setting. Treatment-emergent adverse events were consistent with the known safety profile of tivantinib and cetuximab.

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Introduction

Two anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, cetuximab and panitumumab, proved to be effective in *RAS* wild-type metastatic colorectal cancer (mCRC).[1] However, the disease invariably becomes secondarily resistant to therapy owing to several mechanisms, including activation/overexpression/amplification of MET, the receptor tyrosine kinase for hepatocyte growth factor,[2-4] which plays a role in tumor growth, angiogenesis, invasion, and metastases. MET overexpression has been identified in 30% to 70% of CRC, and *MET* amplification is associated with sensitivity to MET inhibition.[5]

Tivantinib, a non-ATP-competitive, oral, MET receptor tyrosine kinase inhibitor, inhibits growth and induces apoptosis in human tumor cell lines expressing MET, including MET-high CRC lines.[6,7]

A randomized, placebo-controlled, phase I/II trial in 131 patients with *KRAS* wild-type mCRC, treated with 1 to 2 lines of systemic therapy, demonstrated that tivantinib in combination with full doses of irinotecan and cetuximab was well-tolerated. Although this study did not meet its primary endpoint of improved progression-free survival (PFS) in the tivantinib arm compared with the placebo arm, a trend towards improved overall response rate (ORR), PFS, and overall survival (OS) in the tivantinib group was demonstrated among patients with MET-high tumors.[8]

Recently, the potential role of anti-EGFRs reintroduction or rechallenge in mCRC has been extensively evaluated, showing encouraging ORRs (22%-54%), although in small studies with heterogeneous designs.[9-12] Recently, Rossini et al prospectively tested the activity of cetuximab and irinotecan as third-line treatment in 28 patients with *RAS/BRAF* wild-type mCRC with acquired resistance to cetuximab and irinotecan-based first-line therapy. They observed a promising ORR of 21% and showed that no patients with objective response had acquired *RAS* mutation in circulating tumor DNA.[13] In parallel, anti-EGFR-resistant patients with acquired MET overexpression/amplification may be the optimal candidates for dual EGFR and MET blockade.

Given the strong preclinical rationale of adding tivantinib to cetuximab following MET-driven acquired resistance to anti-EGFRs, we conducted a phase II study evaluating this combination in patients with molecularly selected *KRAS* wild-type mCRC with acquired resistance to anti-EGFRs and MET overexpression.

Patients and Methods

Study Design and Population

This was an investigator-initiated, multicenter, single-arm, Simon 2-stage, phase II trial.

Eligible patients (aged ≥ 18 years) had histologically confirmed *KRAS* wild-type (exon 2), unresectable mCRC; previous treatment with ≥ 1 line of systemic therapy for advanced or metastatic disease; objective response or stable disease (SD) to the last treatment line containing cetuximab or panitumumab, and then progression (PD) on cetuximab or panitumumab ≤ 3 months before enrollment; MET-high tumors (staining intensity ≥ 2+ in ≥ 50% of tumor cells); measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; Eastern Cooperative Oncology Group performance status ≤ 2; and adequate bone marrow, liver, and renal function. The study was performed in accordance with the International Conference on Harmonization and Good Clinical Practice standards, and the local ethical committees approved the study design. All patients signed an informed consent form before inclusion. The study was registered in ClinicalTrials.gov (NCT01892527).

Procedures, Treatment, and Endpoints

Tumor MET expression was tested centrally using the CONFIRM anti-total MET (SP44) antibody (Ventana Medical Systems, Tucson, AZ). Staining intensity (0, 1+, 2+, 3+) and percentage of cells stained were independently scored. Samples that scored ≥ 2+ in ≥ 50% of tumor cells were considered as having high MET expression (MET-high). The H-score was determined by multiplying the percentage of cells stained by the intensity of the stain.[14] A recent tumor biopsy after progression on prior anti-EGFRs was preferred at screening for biomarker analysis, but archival tumor samples were accepted for a patients' subgroup capped at a 30% of target accrual. Extended *RAS* and *BRAF* mutation status were assessed centrally by Sequenom MassArray (Myriapod Colon Status Kit, Diatech Pharmacogenetics, Jesi, Italy). *MET* amplification was tested by silver in situ hybridization, as previously described.[15,16]

Patients received tivantinib tablets, 360 mg twice daily (BID) orally in a continuous manner and cetuximab, 500 mg/m^2 intravenously every 2 weeks. The overall treatment period was divided into 28-day cycles without treatment interruption. Tivantinib dose delays (maximum, 14 days) and/or reductions (240 mg BID, 120 mg BID) were allowed for drug-related toxicity. Cetuximab-related toxicity was managed according to standard practice. Treatment was

Table 1 Responding Patient Characteristics

Characteristics	Patient #001001	Patient #001002	Patient #001007	Patient #001013
Gender, age, y	F, 60	M, 68	F, 74	M, 67
Prior therapies	FOLFOX, FOLFIRI + Bev, irinotecan + Cet	FOLFIRI + Pmab	FOLFIRI + Cet	XELOX + Bev, irinotecan + Cet, FOLFIRI + Cet
Primary tumor sidedness	Left	Left	Left	Right
Metastatic sites	Liver, lung, nodes	Liver, lung	Colon, liver, lung, nodes	Liver, lung
Baseline CEA levels, ng/mL	61	50	604	8
Biopsy timing, pre- post-prior anti-EGFRs	Pre	Post	Pre	Pre
MET H-score	200	300	200	200
MET amplification, SISH	Amplified	Amplified	NA	Non-amplified
Extended *RAS, BRAF*	Wild-type	Wild-type	Wild-type	Wild-type
Objective response	PR (−53%)	PR (−42%)	PR (−49%)	CR
CEA levels at best radiologic response, ng/mL	57	Not reported	168	2
Time on treatment, mos	19.8	2.1	6.2	25.5
Dose reduction	No	Yes	Yes	Yes

Abbreviations: Bev = bevacizumab; CEA = carcinoembryonic antigen; Cet = cetuximab; CR = complete response; FOLFIRI = 5-fluorouracil, folinic acid, and irinotecan; FOLFOX = 5-fluorouracil, folinic acid, and oxaliplatin; NA = not available; Pmab = panitumumab; PR = partial response; SISH = silver in situ hybridization; XELOX = capecitabine and oxaliplatin.

administered until PD, unacceptable toxicity, or withdrawal from the study. Patients discontinuing from study treatment were followed for survival.

Tumor assessments per RECIST 1.1 were performed by computed tomography or magnetic resonance imaging every 8 weeks and at the end of treatment. Complete response (CR) and partial response (PR) were confirmed $\geq$ 4 weeks after the initial observation. Safety assessments were performed weekly for the first 2 cycles, then every 2 weeks. Adverse events (AEs) were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

The primary endpoint was ORR (the proportion of patients reaching a confirmed CR or PR among those who received $\geq$ 1 dose of the study drugs). Secondary endpoints included PFS (time from enrollment to disease progression or death from any cause, whichever occurred first), OS (time from enrollment to death from any cause), and safety.

Statistical Analysis

The sample size and stopping rules were determined according to a Simon 2-stage optimal design. Stage 1 had a planned sample size of 21 patients. After having observed $\geq$ 2 PRs, the enrollment was planned to be extended to 41 subjects. After stage 2, the treatment would be considered effective if $\geq$ 5 patients showed confirmed CR or PR among the 41 subjects enrolled. This design would effectively reject the null hypothesis of true response rates of $\leq$ 5% with a type I error rate of 0.05 and a statistical power $>$ 0.90 at the alternative hypothesis of true response rates of $\geq$ 20%. The probability of early stopping under the null hypothesis is 0.72.

Data were summarized by descriptive statistics. The association was tested by the Fisher exact test. The Kaplan-Meier method was used to estimate PFS and OS. Hazard ratios (HRs) with their 95% confidence intervals (CIs) were estimated. A *P*-value $<$ .05 was considered statistically significant for all secondary estimations. All analyses were performed using SAS software version 9.4 and STATA software v.13.

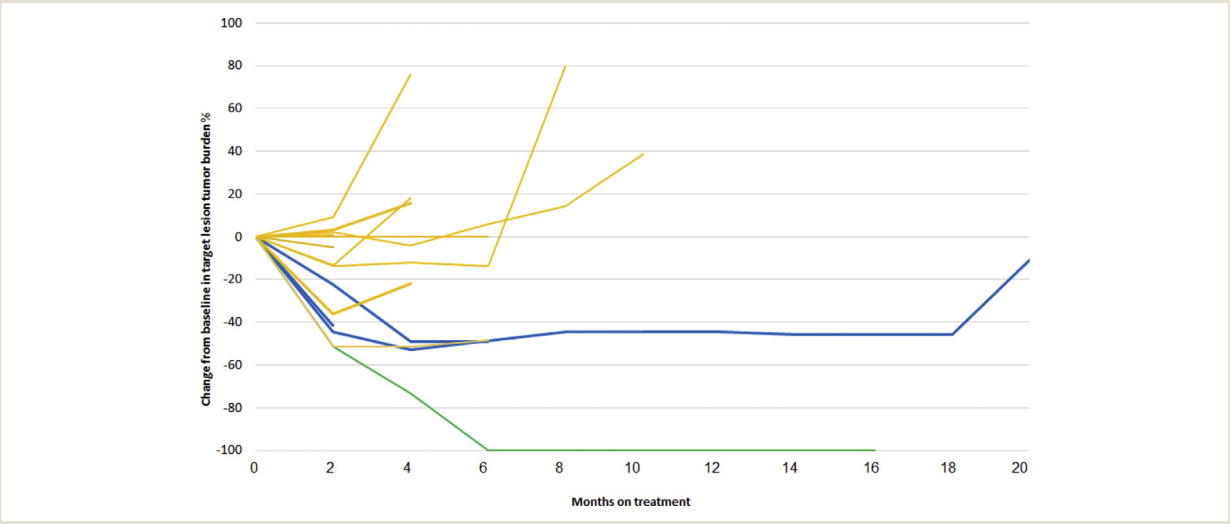
Results

Between April 2013 and June 2015, 69 anti−EGFR-resistant patients were consented at 9 Italian centers: 45 patients were MET-high, and, following 4 screening failures, 41 patients were treated and evaluated. Here we report the final results of the study. Positive results from stage 1 have been presented elsewhere.[17] The median time on therapy was 2.8 months (range, 0.4-25.5 months). The most common reasons for treatment discontinuation were PD (82.9%), AEs (9.8%), and death (4.9%). At the data cutoff date (January 2017), no patient was on treatment.

Most patients were male (N = 24; 58%); the median age was 61 years (range, 37-68 years) (see Supplemental Table 1 in the online version). In total, 28 patients had an Eastern Cooperative Oncology Group performance status of 0. The median number of prior systemic treatments was 2 (range, 1-7), including fluoropyrimidines, irinotecan, and oxaliplatin in most patients, and bevacizumab in slightly less than 50%. A total of 17 (41.5%) patients received $\geq$ 3 prior treatment lines. Primary tumor sidedness was left in 29 (70.7%) patients and right in 8 (19.5%) patients. The median number of metastatic sites was 2 (range, 1-4), and 20 (48.8%) patients had $\geq$ 2 metastatic sites.

At data cutoff (median follow-up, 20.5 months; range, 0.4-39.0 months), 10 (24.4%) patients were alive, and 4 (9.8%) patients achieved an objective response, including 3 confirmed PRs and 1 confirmed CR, with a median duration of 11 months (range, 1.6-17.8 months) (see Supplemental Table 2 and Supplemental Figure 1 in the online version). Characteristics of the responding patients are summarized in Table 1. In addition, 1 unconfirmed PR was observed, 13 (34.1%) more patients had SD (median duration, 3.3 months; range, 1.2-7.5 months), and 4 patients had a SD longer than 4 months (4.3, 4.6, 5.5, and 7.5 months). The disease control rate

Figure 1 Percentage Change in Tumor Burden. Percentage Change in Tumor Lesion Size From Baseline Over Time in Patients (N = 16*) With Objective Response (Complete Response: Green; Partial Response: Blue) and Stable Disease (Yellow)



*Data Available for 16 of 18 Patients.

(DCR) (ORR + SD) was 43.9% (N = 18), with a median duration of control of 3.6 months (range, 1.2-17.8 months) (Figure 1). The median PFS was 2.6 months (95% CI, 1.9-4.2 months), and the median OS was 9.2 months (95% CI, 7.1-15.1 months) (Figure 2). Carcinoembryonic antigen (CEA) was the only baseline factor associated with PFS (HR_{median}, 1.45; 95% CI, 1.01-2.078; $P = .045$) and OS (HR_{median}, 2.20; 95% CI, 1.44-3.36; $P < .001$).

No correlation was observed between MET status and timing of biopsy, before versus after prior anti-EGFR treatment (data not shown). The median H-score was 200 (range, 120-300) in the MET-high cohort and 30 (range, 0-120) in the MET-low cohort. Among treated patients, 15 (37%) had MET status assessed on biopsies taken before anti-EGFRs, and no correlation was found between median H-score and outcome (PR + CR vs. SD + PD; DCR vs. PD; data not shown).

At a non-preplanned post-hoc assessment of extended *RAS* and *BRAF* mutation status, 3 (7.3%) patients showed *NRAS* mutations, 2 of them on biopsies taken after and 1 on a biopsy taken before prior anti-EGFR therapy. Also, 1 (2.4%) patient had a *BRAF* mutation on a biopsy taken after previous anti-EGFRs. One patient with *NRAS* mutation detected prior anti-EGFRs and the *BRAF*-mutant patient achieved SD, whereas the other 2 patients had PR as best response.

MET amplification was tested in a subgroup of 13 *RAS* and *BRAF* wild-type patients with available tumor tissue (Figure 3). Of the 4 responding patients, 2 had *MET* amplification with multiple copies and small clusters (1 patient had a biopsy taken before and the other after, prior anti-EGFRs), 1 was non-amplified, and 1 had no more tumor tissue available (Table 1; Figure 3). All non-responders who were tested were analyzed on post-progression tumor re-biopsies, and none of them showed *MET* amplification ($P = .039$).

Most (82.9%) patients experienced ≥ 1 treatment-emergent AE (TEAE). Grade ≥ 3 TEAEs occurred in 53.7% of patients, and were more frequently neutropenia (14.6%), skin toxicity (12.2%), and fatigue (9.8%) (Table 2).

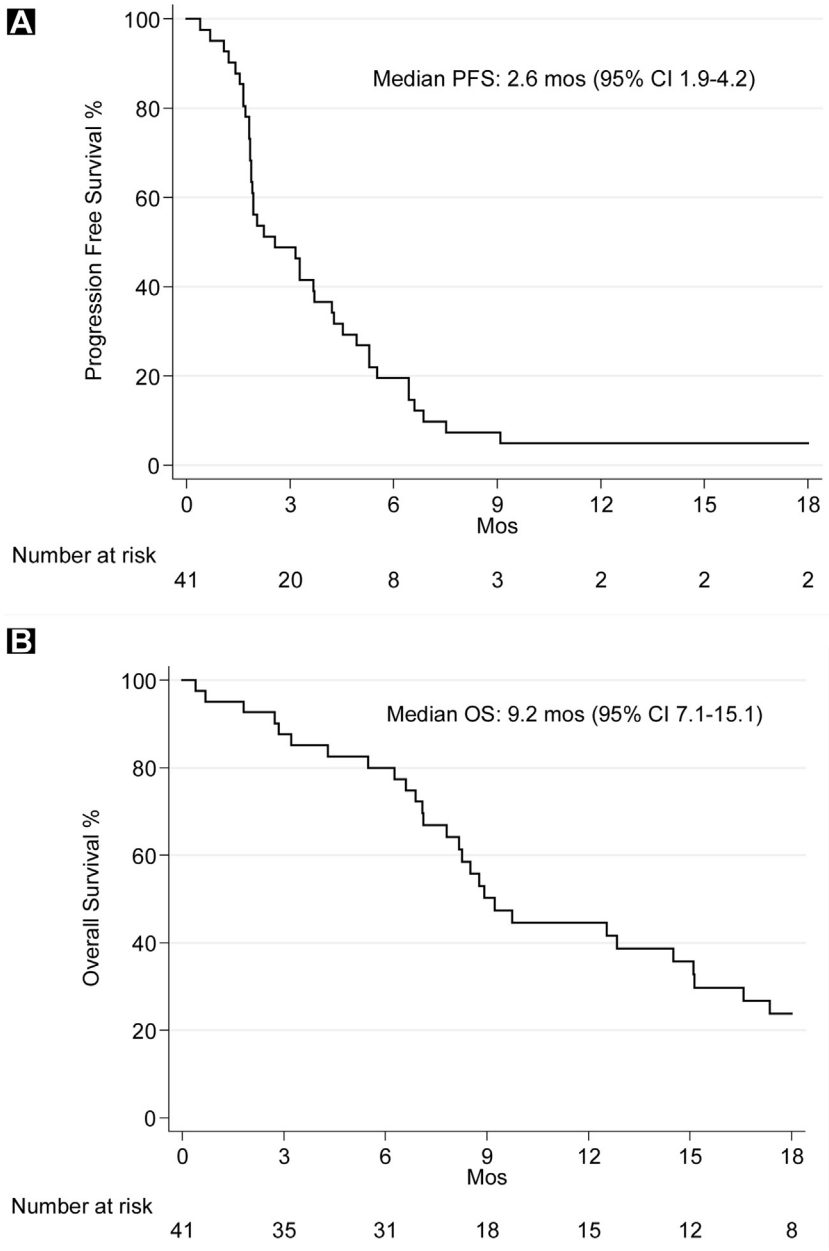
A total of 12 (29.3%) patients experienced serious AEs. The most common serious AE was febrile neutropenia (4 events in 3 patients, included 1 grade 5). Overall, 34.1% of patients needed a dose reduction/interruption, and 9.8% discontinued treatment owing to TEAEs, in most cases (35.7%), hematologic toxicity.

Discussion

Recently, only regorafenib and TAS-102 have been approved for the treatment of patients with refractory mCRC, based on limited OS gains.[18,19] Therefore, there is a major need for other therapeutic strategies able to overcome resistance to available treatments.

MET activation promotes tumor growth and aggressiveness in CRC and is associated with more advanced disease stage; however, de novo *MET* amplification is rarely found as potential mechanism of primary resistance to anti-EGFR therapies.[20] Indeed, the negative results obtained for tivantinib in the second-line trial for anti−EGFR-naive patients with *KRAS* wild-type mCRC can be explained by its low prevalence as oncogenic driver (1% of all mCRCs). Notably, the involvement of *MET* is much more relevant in the setting of acquired resistance to anti-EGFR monoclonal antibodies,[2,15] because *MET* amplification may be present in tumor subclones positively selected during anti−EGFR-based therapy.[1,5,21] Therefore, dual MET and EGFR blockade could provide clinical benefit to patients with mCRC with MET-driven acquired resistance to EGFR blockade.[2,21,22] On these bases, our phase II study tested whether MET inhibition might overcome acquired resistance to anti-EGFRs, by evaluating the activity of tivantinib plus cetuximab in 41 heavily-pretreated patients with *KRAS* wild-type mCRC with acquired resistance to EGFR inhibitors and MET overexpression. The study showed promising results during its first stage (N = 21), with a DCR of 52.4%.[17] However, during its

Figure 2 Progression-free Survival (A) and Overall Survival (B)

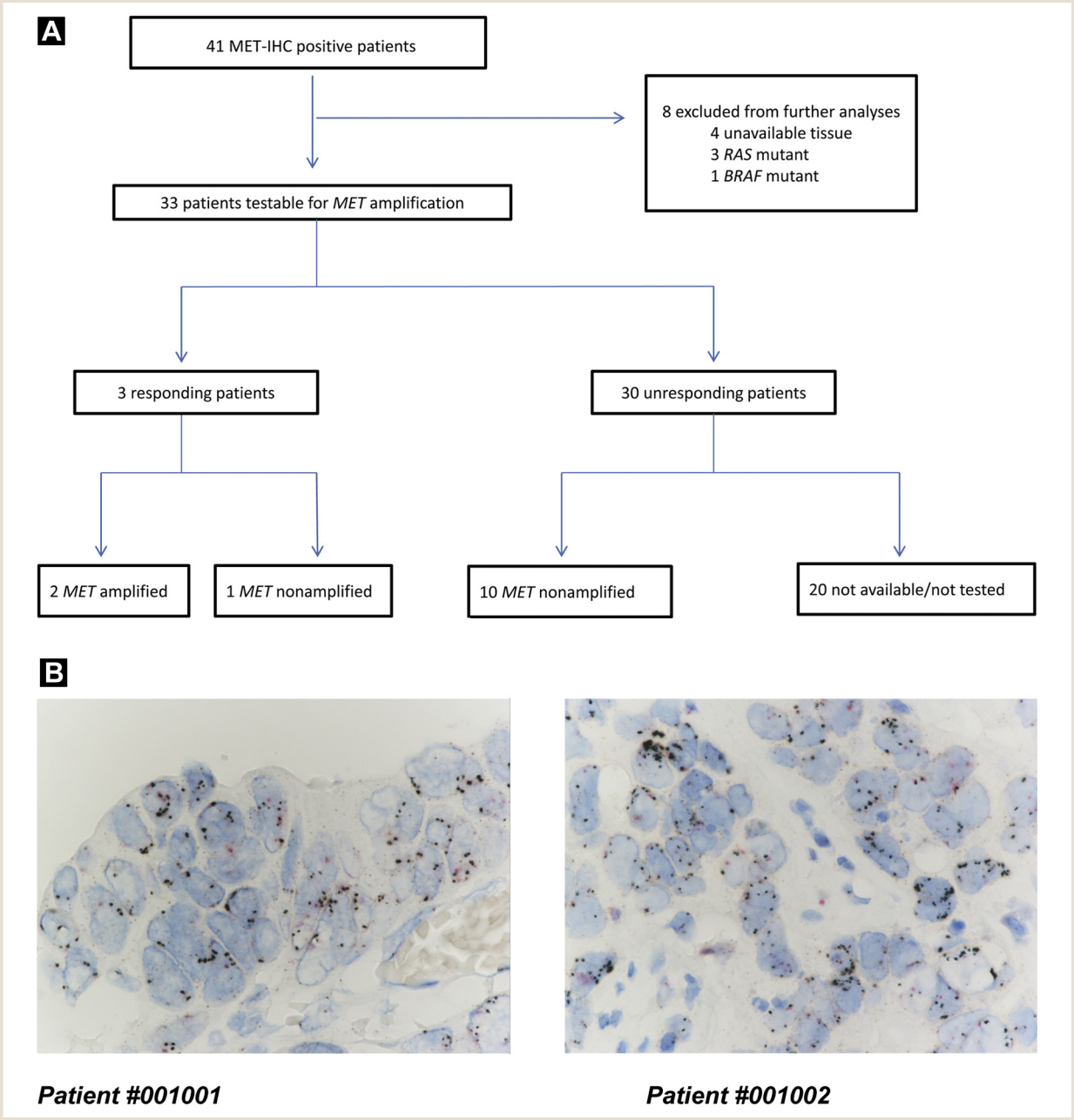


Abbreviations: CI = confidence interval; OS = overall survival; PFS = progression-free survival.

second stage, the study did not meet its primary endpoint, with 4 (9.8%) patients reporting confirmed responses instead of the 5 expected. On the other hand, PFS (2.6 months) and OS (9.2 months) were promising and compare well with the results of the Cricket study,[13] also given that patients were heavily pretreated.

Why did another study with a MET inhibitor fail to meet its primary endpoint in gastrointestinal cancers? First, a stringent molecular selection could have resulted in improved precision of our proof-of-concept trial, ideally through enrollment of patients with *RAS/BRAF* wild-type mCRC, showing objective response to the last anti−EGFR-based treatment line, and *MET* amplification detected in tumor re-biopsies obtained at disease progression. Moreover, *MET* amplification is found only in approximately 10% of cases, and might be heterogeneous and/or concomitant with other resistance mechanisms.[15] In addition, detection of MET overexpression, even if corroborated by the use of H-score, may lead to a less accurate molecular selection owing to the presence of a relevant proportion of cancers without MET-driven oncogene addiction and technical issues. Indeed, here we showed that *MET* amplification was detected in 2 of 3 patients with objective response

Figure 3 ***MET*** **Amplification. Consort Diagram Showing Tested Patients (A) and Silver in Situ Hybridization Results in 2 Responding Patients (B)**



Abbreviation: IHC = immunohistochemistry.

(1 responding patient had no tumor tissue available) compared with no amplifications in non-responding patients. In addition, the selection of ORR as primary endpoint may have been not appropriate; considering the setting and the fact that tivantinib induces more disease stabilizations than responses, a more adequate primary endpoint would have been PFS rate.[23] Furthermore, owing to aggressiveness and limited OS expectations of patients with acquired *MET* amplification,[15,24] dual MET and EGFR targeting might lead to short-lasting clinical responses missed by the first 8-week radiologic assessment; therefore, questioning the clinical importance of such strategy. Finally, although tivantinib has been developed as a MET inhibitor, preclinical findings suggested that tivantinib may also affect the cytoskeleton, via MET and paxillin inhibition.[25-27]

Despite these limitations, our study contributes in setting the optimal paradigm on how trials with MET inhibitors should be designed and gives novel insight on how drug development should be implemented. Although the issue of MET-driven acquired

Table 2 TEAEs Summary

Most Common (≥10%) TEAEs	All Grades, N (%)	Grade ≥ 3, N (%)	Treatment-related, *N* (%)
Skin toxicity	28 (68.3)	5 (12.2)	26 (63.4)
Fever	13 (31.7)	2 (4.9)	6 (14.6)
Fatigue	12 (29.3)	4 (9.8)	11 (26.8)
Neutropenia	9 (21.9)	6 (14.6)[a]	9 (21.9)
Hypomagnesemia	7 (17.1)	2 (4.9)	4 (9.8)

Forty-one patients were included in the analysis.
Abbreviation: TEAE = treatment-emergent adverse event.
[a]Including serious febrile neutropenia in 3 patients, 1 with grade 5.

resistance to anti-EGFRs has been evidenced by seminal studies, effective targeting of 'iatrogenic' tumor branched evolution remains an unresolved clinical scenario. The implementation of liquid biopsy-driven proof-of-concept trials could lead to a major refinement of the eligible population.[13]

AEs were in line with the known safety profile of tivantinib and cetuximab. However, approximately 30% of patients required tivantinib dose reduction, differing from the previous phase I/II study.[8] The first dose reduction level of 240 mg BID was well-tolerated, with no clinically relevant neutropenia, and equally active (tablets provide higher exposure than the previous capsule formulation). Interestingly, 3 of the 4 responding patients needed a reduction of tivantinib dose to 240 mg BID, and response was obtained with the lower dose. These findings suggest that tivantinib optimal dose in combination with cetuximab may be 240 mg BID.

Overall, our results suggest that the combination of tivantinib and cetuximab is not worthy of further development in patients with mCRC with acquired resistance to anti-EGFRs and MET-high status. However, further studies of MET inhibitors in mCRC are ongoing (eg, the European Commission-funded Framework 7 MErCuRIC program[28] and the NCT02205398 trial of capmatinib and cetuximab), given the well-established role of the hepatocyte growth factor/MET pathway and the poor prognosis of patients with MET overexpression/amplification.

Clinical Practice Points

- Combining MET-inhibitors and anti-EGFR agents may be effective in mCRC.
- In this study, patients with MET-high, KRAS wild-type mCRC received tivantinib + cetuximab.
- The study did not meet its primary endpoint.
- Some activity of the combination in a challenging setting was reported.

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Daiichi Sankyo provided the study drug tivantinib, funding to buy the study drug cetuximab, and funding to support clinical trial services. Daiichi Sankyo had no role in the study's conduct, in data collection and analysis, or in data interpretation. The sponsor, Humanitas Clinical and Research Center, collected the data through a contract research organization. All authors had unrestricted access to the final study data on request, were responsible for data interpretation, manuscript preparation, and the decision to submit for publication, and attest to the completeness and accuracy of the data and data analysis. Daiichi Sankyo reviewed the final manuscript before submission.

Disclosure

L. Rimassa reports a consulting or advisory role with Lilly, Sanofi, Bayer, ArQule, and Amgen. F. Pietrantonio reports a consulting or advisory role with Amgen, Merck, Bayer, Sanofi, and Roche. S. Lonardi reports a consulting or advisory role with Amgen, Bayer, Merck, and Lilly; speakers' bureau for Lilly, Roche, and BMS; and research funding from Amgen. R. Bordonaro reports a consulting or advisory role with Roche, Sanofi, Novartis, AstraZeneca, and Merck. A. Santoro reports a consulting or advisory role with Bayer, Takeda, Lilly, Amgen, ArQule, BMS, MSD, Celgene, Novartis, Roche, Servier, and Eisai. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.02.004.

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Supplemental Data

Supplemental Table 1 Baseline Demographics and Disease Characteristics

Baseline Demographics and Disease Characteristics	N = 41 (%)
Median age, y (range)	61 (37-78)
Gender	
Male	24 (58.5)
Female	17 (41.5)
ECOG performance status	
0	28 (68.3)
1	13 (31.7)
Primary tumor site	
Left colon	29 (70.7)
Right colon	8 (19.5)
Missing	4 (9.8)
Number of metastatic sites	
1	17 (41.5)
2	13 (31.7)
≥ 3	7 (17.0)
Missing	4 (9.8)
Median (range)	2 (1-4)
Metastatic sites	
Liver	33 (80.5)
Lung	17 (41.5)
Nodes	10 (24.4)
Peritoneum	4 (9.8)
Bone	2 (4.9)
Other	2 (4.9)
Mutation status	
NRAS mutant[a]	3 (8.1)
BRAF mutant[b]	1 (2.4)
Number of prior systemic treatments	
1	8 (19.5)
2	13 (31.7)
3	7 (17.1)
≥ 4	10 (24.4)
Missing	3 (7.3)
Median (range)	2 (1-7)
Prior systemic treatment	
Fluoropyrimidine	38 (92.7)
Irinotecan	35 (85.4)
Oxaliplatin	28 (68.3)
Bevacizumab	20 (48.8)
Median time between anti-EGFR and enrollment, d (range)	42 (2-279<u>d</u>)
Median CEA value, ng/mL (range)[c]	71 (2-4201)

Abbreviations: CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor.
[a]Data available for 37 patients.
[b]Data available for 39 patients.
[c]Data available for 35 patients.
[d]One protocol violation (time between anti-EGFR and enrollment > 3 months).

Supplemental Table 2 Best Overall Response

Best Overall Response	N = 41 (%)	Median Duration, mos (Range)
Best response		
CR	1 (2.4)	16.6[a]
PR	3 (7.3)	5.5 (1.6-17.8)
SD	14 (34.1)[b]	3.3 (1.2-7.5)
Progressive disease	21 (51.2)	–
Not evaluable	2 (4.9)	–
Overall response rate (CR + PR)	4 (9.8)	11 (1.6-17.8)
Disease control rate (CR + PR + SD)	18 (43.9)	3.6 (1.2-17.8)

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.
[a]This patient obtained PR at week 8, and CR at week 32.
[b]Including 1 PR for which confirmatory computed tomography scan was not performed.

Supplemental Figure 1 Patient #001007 Computed Tomography Scan Showing Partial Response. Left, Baseline; Right, Week 16