PERSPECTIVE: Tepotinib + cetuximab in patients with *RAS/BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) and acquired resistance to anti-EGFR antibody therapy due to *MET* amplification

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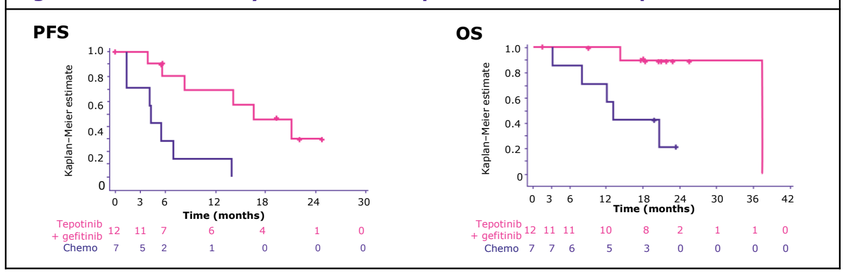
INTRODUCTION

- CRC is the third most common cancer worldwide, with >1.8 million new cases and 881,000 deaths estimated in 2018[1,2]
- *MET*amp is a secondary or co-driver genetic change in mCRC patients with acquired resistance to anti-EGFR therapy, contributing to disease progression[3,4]
- The estimated incidence of *MET*amp in EGFR-resistant CRC is 4–23%[5–10]
- Inhibition of the MET downstream signaling pathways may prevent cancer cell proliferation, survival and metastasis[11,12]

TEPOTINIB

- Tepotinib is an oral, once-daily, highly selective, potent MET inhibitor (IC_{50} ~1.7 nM)[12]
- The INSIGHT study was a Phase Ib/II randomized trial that compared tepotinib plus gefitinib with chemotherapy in relapsed *EGFR*-mutant NSCLC with MET overexpression (IHC2+ and IHC3+) and/or *MET* amplification (NCT01982955)[12]
- In patients with *MET* amplification (n=19), treatment with tepotinib plus gefitinib improved investigator-reported PFS and OS (**Figure 1**) as well as ORR[13]
  - Median PFS was 16.6 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43) compared with chemotherapy
  - Median OS was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51) compared with chemotherapy
  - ORR was 67% vs 43% (odds ratio = 2.67; 90% CI: 0.37, 19.56)

Figure 1. INSIGHT study: PFS and OS of patients with *MET* amplification[13]



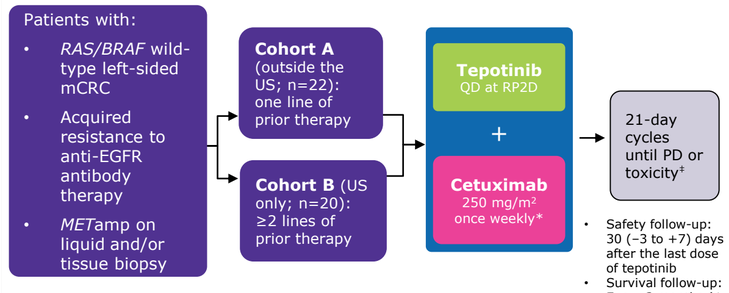
- The objective of the PERSPECTIVE study is to investigate whether a dual approach of MET inhibition (tepotinib) plus an anti-EGFR (cetuximab) can achieve disease control in patients with mCRC by targeting emerging MET pathway activation and maintaining EGFR pathway inhibition

PERSPECTIVE

Study design and methods

- PERSPECTIVE (NCT04515394) is a multicenter, open-label, Phase II, single arm study (**Figure 2**)
- An initial safety run-in period (n≥6) will confirm the safety and tolerability of tepotinib in combination with cetuximab
- The study is anticipated to enroll approximately 48 patients: 6 in safety run-in, 22 in Cohort A and 20 in Cohort B

Figure 2. PERSPECTIVE study design



Patients will receive an initial dose of tepotinib, 500 mg QD (450 mg active moiety), combined with an initial dose of cetuximab 400 mg/m² (unless cetuximab was given as prior line therapy), followed by a continuous dose of tepotinib (500 mg QD) combined with cetuximab 250 mg/m² once-weekly. If 500 mg QD of tepotinib is not tolerated, the continuous dose should be reduced to 250 mg QD with 250 mg/m² of cetuximab once-weekly.
*Patients who have not received prior cetuximab as prior line of therapy or received the last dose longer than 3 weeks ago will receive an initial dose of cetuximab 400 mg/m²; ‡Treatment continues until disease progression (according to RECIST 1.1), death, AE leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

- PERSPECTIVE aims to assess preliminary antitumor activity, safety and tolerability, and explore pharmacokinetic profiles of tepotinib in combination with cetuximab
- Study endpoints are shown in **Table 1**
- Retrospective assessment of study endpoints (OR, DoR and PFS) may be conducted by an independent review committee
- Analyses for Cohorts A and B will be performed separately
- No formal statistical hypothesis will be tested in this exploratory study

Table 1. Key objectives and endpoints

Safety run-in	**Primary objectives**	Confirm the RP2D dose of tepotinib in combination with cetuximab
	Primary endpoint	Occurrence of dose-limiting toxicities
Overall study	**Primary endpoint**	OR (confirmed CR or PR) assessed by investigators per RECIST 1.1
	Secondary endpoints	DoR
		PFS
		OS
		Tolerability and safety
		Immunogenicity of cetuximab
	Additional endpoints	Pharmacokinetics
		Biomarkers of resistance

Eligibility criteria

- Participants enrolled in this study will have advanced left-sided CRC diagnosis, *RAS/BRAF* wild-type, documented previous anti-EGFR therapy, acquired resistance on the most recent anti-EGFR antibody, and METamp (**Table 2**)

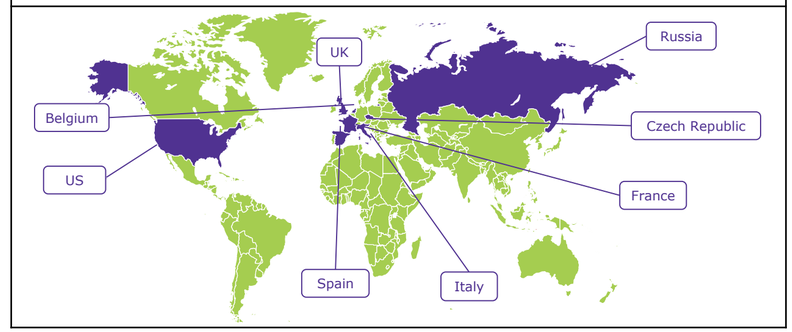
Table 2. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria†
• ≥18 years of age	• Symptomatic CNS metastases, neurologically unstable with increasing doses of steroids within 2 weeks prior to study entry
• Locally advanced or metastatic, unresectable, left-sided* CRC with *RAS/BRAF* wild-type, with previous anti-EGFR therapy and acquired resistance to anti-EGFR monoclonal antibody therapy (panitumumab or cetuximab) confirmed by PD according to RECIST 1.1	• Carcinomatous meningitis
	• Brain metastasis as the only measurable lesion
	• Anticancer therapy within 21 days prior to first study dose, except anti-EGFR containing regimen associated chemotherapy
• *MET*amp positive by liquid and/or tissue biopsy with appropriate regulatory status	• Any unresolved NCI-CTCAE Grade ≥2 or higher toxicity from previous therapies
	• Known severe hypersensitivity reactions to monoclonal antibodies, any anaphylaxis or uncontrolled asthma
• Measurable disease by investigator per RECIST 1.1	• Discontinuation of the most recent cetuximab or panitumumab therapy due to an adverse event
• <2 months between last administration of the most recent EGFR containing regimen and the first study dose	• Prior HGF/MET pathway-targeted therapy
	• Impaired cardiac function
• ECOG performance status 0–1	• History of other prior neoplasms other than mCRC, ILD or other interstitial pneumonitis
• Life expectancy >3 months	• Major surgery within 28 days prior to Day 1 of study intervention
• Adequate hematological function, hepatic and renal functions as defined in the protocol	• Participation on another study within 3 weeks of the first dose of intervention

*From splenic flexure to rectum - NCCN version 4.2020. †Other exclusion criteria include: Medical history of difficulty swallowing, malabsorption, or other gastrointestinal disease or conditions that may hamper compliance and/or absorption of the test products; known infection with HIV, hepatitis B or hepatitis C; substance abuse, active infection or psychiatric condition or laboratory abnormalities that may increase the risk associated with study participation; history of ILD or interstitial pneumonitis; uncontrolled hypertension (not stabilized to <150/90 mmHg).

- The study is being conducted at centers in Belgium, Czech Republic, France, Italy, Russia, Spain, UK, and the US. As of April 2021, there are 26 active centers in Spain (7 centers), France (6), the UK (2), Russia (7) and the US (4). (**Figure 3**)

Figure 3. Study sites



Study contacts

- The Coordinating Investigator for this study is Dr Josep Tabernero, (jtabernero@vhio.net)
- For further information, please visit www.ClinicalTrials.gov (NCT04515394) or contact Merck KGaA, Darmstadt, Germany (Tel: +49 6151720; www.merckgroup.com)

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Abbreviations: AE, adverse event; BRAF, proto-oncogene B-Raf; CI, confidence interval; CNS, central nervous system; CR, complete response; CRC, colorectal cancer; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; HR, hazard ratio; IC_{50}, half maximal inhibitory concentration; IHC, immunohistochemistry; ILD, interstitial lung disease; mCRC, metastatic colorectal cancer; MET, mesenchymal–epithelial transition factor; METamp, *MET* amplification; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RAS, rat sarcoma viral oncogene homolog; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase II dose.

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