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# 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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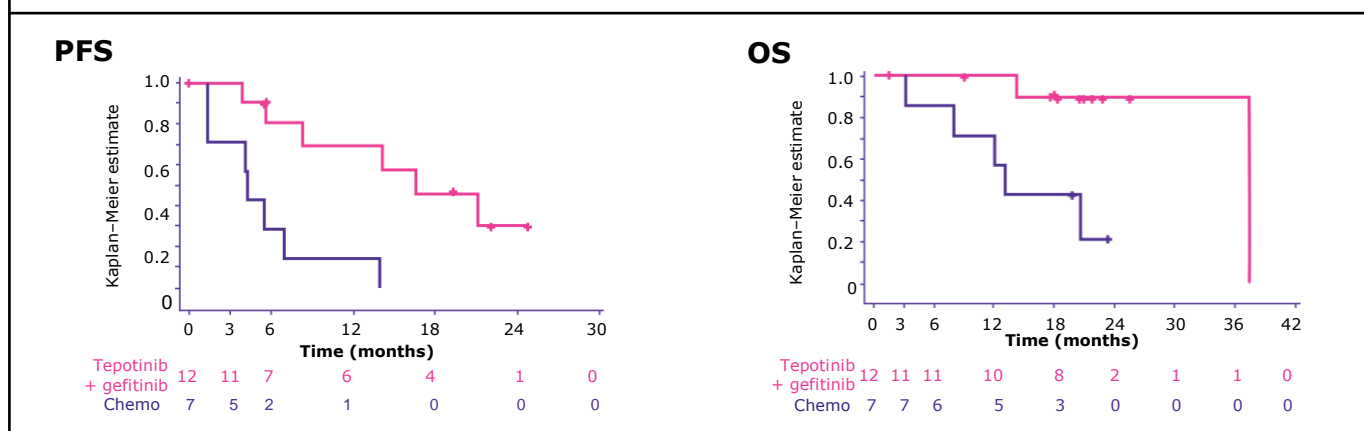
## INTRODUCTION

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

## TEPOTINIB

- Tepotinib is an oral, once-daily, highly selective, potent MET inhibitor (IC<sub>50</sub> ~1.7 nM)<sup>12</sup>
- 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)<sup>12</sup>
- In patients with MET amplification (n=19), treatment with tepotinib plus gefitinib improved investigator-reported PFS and OS (**Figure 1**) as well as ORR<sup>13</sup>
  - 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<sup>13</sup>**



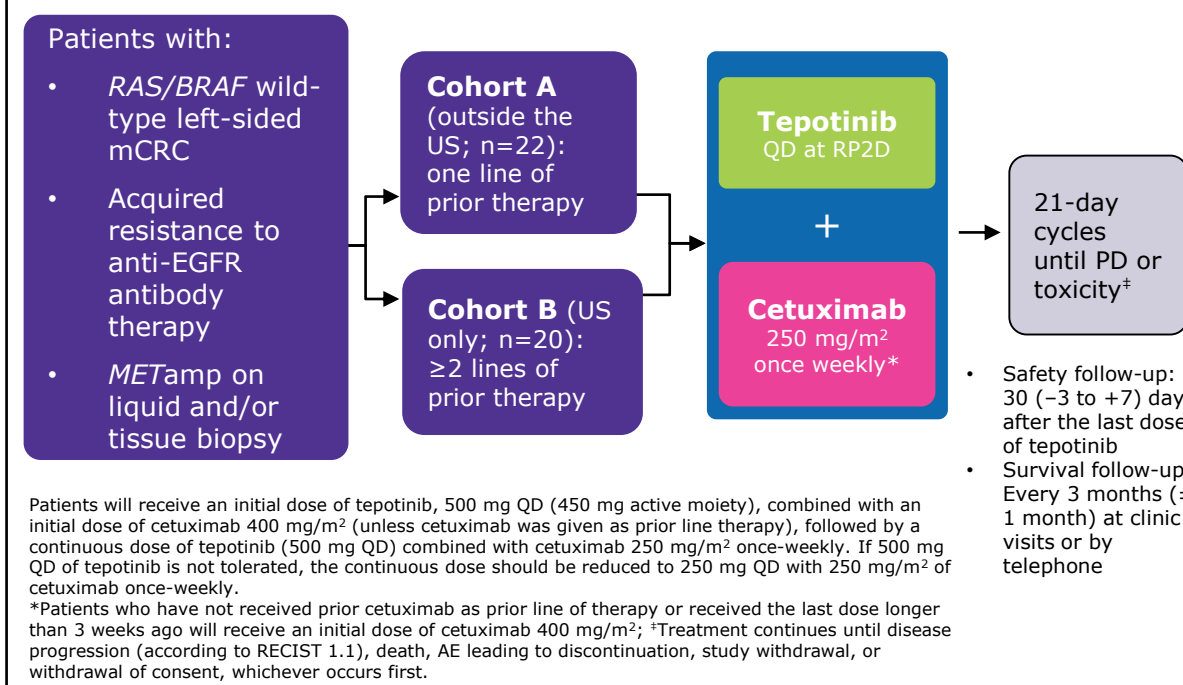
- The objective of the PERSPECTIVE study is to investigate whether a dual approach of MET inhibition (tepotinib) plus an anti-EGFR (cetuximab) can achieve disease control in patients with mCRC by targeting emerging MET pathway activation and maintaining EGFR pathway inhibition

## 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**



- 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**

Phase	Objective/Endpoint	Description
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
	Secondary endpoints	PFS
	Secondary endpoints	OS
	Secondary endpoints	Tolerability and safety
Additional endpoints	Additional endpoints	Immunogenicity of cetuximab
	Additional endpoints	Pharmacokinetics
Additional endpoints	Additional endpoints	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**)

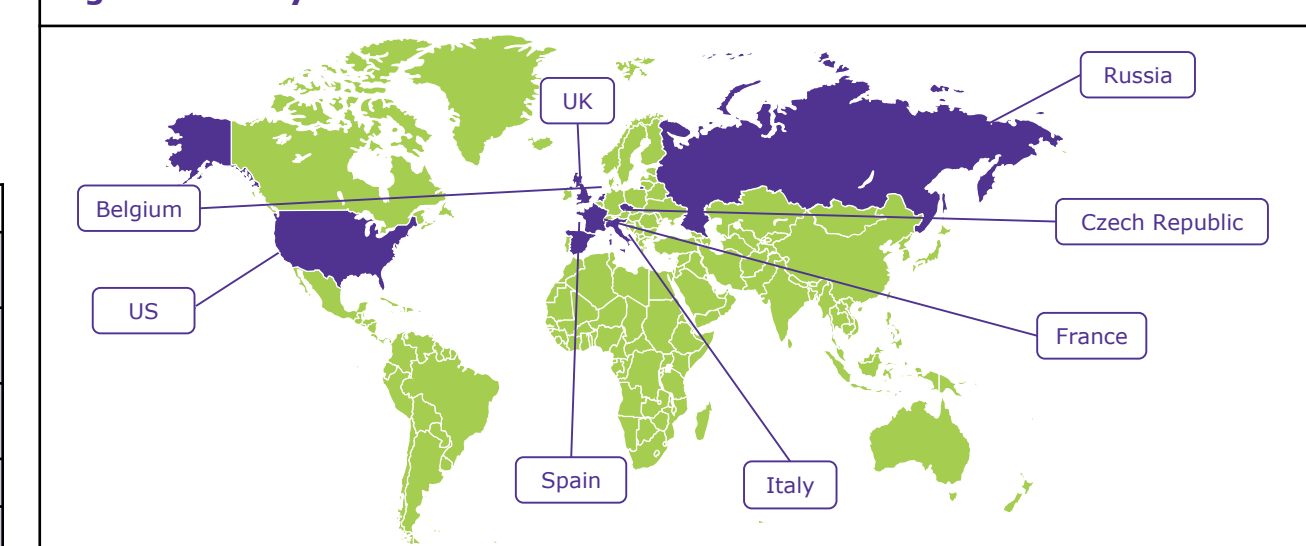
**Table 2. Key inclusion and exclusion criteria**

Key inclusion criteria	Key exclusion criteria <sup>†</sup>
<ul style="list-style-type: none"> <li>• ≥18 years of age</li> <li>• 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</li> <li>• METamp positive by liquid and/or tissue biopsy with appropriate regulatory status</li> <li>• Measurable disease by investigator per RECIST 1.1</li> <li>• &lt;2 months between last administration of the most recent EGFR containing regimen and the first study dose</li> <li>• ECOG performance status 0–1</li> <li>• Life expectancy &gt;3 months</li> <li>• Adequate hematological function, hepatic and renal functions as defined in the protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic CNS metastases, neurologically unstable with increasing doses of steroids within 2 weeks prior to study entry</li> <li>• Carcinomatous meningitis</li> <li>• Brain metastasis as the only measurable lesion</li> <li>• Anticancer therapy within 21 days prior to first study dose, except anti-EGFR containing regimen associated chemotherapy</li> <li>• Any unresolved NCI-CTCAE Grade ≥2 or higher toxicity from previous therapies</li> <li>• Known severe hypersensitivity reactions to monoclonal antibodies, any anaphylaxis or uncontrolled asthma</li> <li>• Discontinuation of the most recent cetuximab or panitumumab therapy due to an adverse event</li> <li>• Prior HGF/MET pathway-targeted therapy</li> <li>• Impaired cardiac function</li> <li>• History of other prior neoplasms other than mCRC, ILD or other interstitial pneumonitis</li> <li>• Major surgery within 28 days prior to Day 1 of study intervention</li> <li>• Participation on another study within 3 weeks of the first dose of intervention</li> </ul>

\*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](http://www.ClinicalTrials.gov) (NCT04515394) or contact Merck KGaA, Darmstadt, Germany (Tel: +49 6151720; [www.merckgroup.com](http://www.merckgroup.com))



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