

**EDITORIAL**



## Positioning EGFR re-treatment in modern metastatic colorectal cancer: insights from PARERE

Over the past decade, the number of therapeutic options for metastatic colorectal cancer (mCRC) have substantially improved, resulting in an estimated 50%-63% of patients receiving third-line therapy. This necessitates judicious selection of therapy in later-line settings.<sup>1,2</sup> Landmark trials confirmed survival benefit with the addition of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies to cytotoxic therapy in first-line treatment of mCRC patients.<sup>3-7</sup> Provision of anti-EGFR therapy after progression, 'rechallenge', in subsequent treatment is a subject of investigation, due to the resolution of previous resistant clones, potentially reestablishing sensitivity to EGFR inhibition.<sup>8,9</sup> Given the recent approvals of late-line therapies,<sup>10,11</sup> it is paramount physicians understand the potential role of EGFR rechallenge in their treatment paradigm.

Previously, smaller phase II clinical trials have indicated the benefit of anti-EGFR therapy rechallenge in RAS/BRAF-V600E wild-type (wt) mCRC. The randomized VELO trial suggested improved progression-free survival (PFS), and the randomized phase II CITRIC trial indicated improved disease control rate (DCR) and objective response rate (ORR).<sup>12-17</sup> However, adoption of this rechallenge strategy has not been ubiquitously implemented due to a lack of a large, randomized trial. Ciraci et al. sought to confirm the benefit of anti-EGFR rechallenge, directed by circulating tumor DNA (ctDNA) analysis through the PARERE trial.<sup>2</sup>

PARERE is a large phase II, multicenter, open-label study evaluating the optimal treatment sequence of anti-EGFR therapy and regorafenib in patients with RAS/BRAF wt mCRC with  $\geq 6$  months previous exposure and response and/or disease stabilization from anti-EGFR therapy during first-line treatment; one or more interval-line of therapy;  $\geq 4$  months from prior anti-EGFR therapy; and previous treatment (or absolute contraindication) to fluoropyrimidines, oxaliplatin, irinotecan and anti-angiogenic agents. Patients did not harbor RAS, KRAS, NRAS and BRAF-V600E mutations based on ctDNA analysis. Patients were subsequently randomly assigned in a 1 : 1 ratio to receive panitumumab followed by regorafenib upon disease progression (arm A: pan—rego) or regorafenib followed by panitumumab (arm B: rego—pan). Notably, regorafenib could be initiated at lower doses, per the ReDOS trial, and escalated as tolerated.<sup>18</sup>

A total of 213 patients with RAS/BRAF-V600E wt disease were randomized with a median of two prior lines of therapy. Microsatellite instability was tested on nearly all patients; however, human epidermal growth factor receptor 2 (HER2) was only assessed in 56.8% of patients with six (5%) patients included.

After a median follow-up of 31.9 months, overall survival between the two arms was equivalent (11.6 versus 11.7 months). However, patients treated with panitumumab consistently demonstrated superior ORR, DCR and PFS. Specifically, the pan—rego arm had a significantly improved DCR (61% versus 36%), ORR (16% versus 2%) and PFS (4.2 versus 2.4 months). Furthermore, the opposing sequence of rego—pan resulted in improved second-line outcomes when anti-EGFR was provided (ORR: 18% versus 0%, DCR: 62% versus 38% and PFS: 3.9 versus 2.7 months). Median treatment durations for panitumumab and regorafenib were very similar regardless of arm. Additionally, a small percentage of patients (9%) demonstrated mutations that could pose resistance to anti-EGFR therapy; however, no survival differences were found. No new safety signals were identified; however, regorafenib had greater adverse events than panitumumab.

The PARERE trial is the first large, randomized trial demonstrating the efficacy and importance of ctDNA-guided anti-EGFR monotherapy rechallenge in those patients who do not exhibit RAS/BRAF-V600E mutations, and the superiority of anti-EGFR therapy over the later-line tyrosine kinase inhibitor regorafenib in ORR, DCR, PFS and, importantly, tolerability. Furthermore, the administration of panitumumab, regardless of being provided before or after regorafenib, resulted in favorable outcomes, underscoring that the sequence of anti-EGFR rechallenge in late-line settings may not be interdependent on concurrent or sequential cytotoxic therapy.

Despite the clear benefit, the option to pursue anti-EGFR rechallenge is predicated on two crucial elements: appropriate selection per ctDNA analysis and an anti-EGFR-free interval. The use of anti-EGFR antibodies in the first-line metastatic setting inescapably results in the development of mutational resistance within the EGFR signaling cascade, but these mutations can change or decay over time.<sup>8,9,19</sup> In the initial cohort of patients screened in the PARERE trial, 38% exhibited persistent RAS and/or BRAF-V600E mutations, rendering them ineligible for rechallenge therapy. This underscores the critical importance of ctDNA analysis and ongoing monitoring to detect the recurrence or emergence of resistance mutations during treatment.

Despite this selection, 40% of patients did not benefit from anti-EGFR rechallenge, highlighting that mutational resistance may be other than *RAS/BRAF* alterations and reminds us that ctDNA remains prognostic and not predictive. Additionally, it emphasizes the consideration of negative hyperselection which is discussed in the REMARRY and PURSUIT trials.<sup>16</sup> The authors of these studies reported greater benefit from anti-EGFR rechallenge in patients who consistently lacked resistant clones. For tumors that develop resistant clones, it is estimated alterations to EGFR have a half-life of ~4 months, to mitigate potential persistence-resistant clones.<sup>8,9,19</sup>

The authors recognize several limitations to their study. Firstly, the lack of survival difference between arms was likely attenuated by the fact that both arms received panitumumab. Improvement in all secondary endpoints were observed, regardless of sequence of administration. The authors recognize regorafenib would now be considered a suboptimal third-line therapy choice, given the SUNLIGHT trial which led to the approval of trifluridine/tipiracil plus bevacizumab. The authors acknowledge, considering the results of the SUNLIGHT trial and its approval in the third line setting, that the role of anti-EGFR rechallenge in this line of treatment should be largely based on individualized clinical needs for objective response. At the completion of PARERE, fruquintinib was recently approved by the Food and Drug Administration, allowing another treatment option.<sup>11</sup> Furthermore, only 56.8% of patients were tested for HER2, despite HER2 amplification being a known cause of resistance to anti-EGFR therapy and the current role of HER2-directed therapies in mCRC.<sup>20,21</sup> Lastly, assessment of response was locally determined and not centrally reviewed.

Regardless, the PARERE trial is a pivotal advancement in the spectrum of therapy options for chemorefractory mCRC. By providing a randomized validation of ctDNA-guided anti-EGFR rechallenge, it affirms that EGFR blockade can be strategically redeployed as part of a dynamic, biologically informed treatment continuum, rather than solely as first-line therapy. The PARERE trial also raises important questions about the optimal timing and sequencing of EGFR rechallenge in the context of recently approved therapies for refractory disease.

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## DISCLOSURE

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