According to current guidelines, doublet chemotherapy plus an anti–epidermal growth factor receptor (EGFR) agent is the recommended upfront treatment option in patients with RAS or BRAF wild-type metastatic colorectal cancer (mCRC), specifically in left-sided tumors.\textsuperscript{1,2} Although these combinations have significantly improved overall survival (OS), up to approximately 3 years, the duration of first-line therapy is still a matter of debate. Disabling and cumulative adverse effects, especially oxaliplatin-related neuropathy, can worsen during prolonged treatment, severely affecting quality of life. The need to limit these toxic effects in patients with disease not amenable to local treatment after achieving maximum tumor response has led to the idea of intermittent or maintenance therapy. Several randomized clinical trials have investigated different therapeutic approaches, such as observation or deescalation of treatment intensity, instead of continuing induction therapy until disease progression. Data are more robust with bevacizumab used as the targeted agent in maintenance setting. A 2020 network meta-analysis\textsuperscript{3} found no benefit from continuing bevacizumab-based induction therapy until progressive disease (PD), while a significant progression-free survival (PFS) benefit was documented with fluoropyrimidine (5-FU) and leucovorin (LV) plus bevacizumab as maintenance therapy vs observation. However, no significant trend for overall survival (OS) was observed in favor of maintenance therapy.\textsuperscript{3}

Maintenance strategies with anti-EGFR agents have been long debated, especially due to their peculiar adverse events; while bevacizumab has a relatively manageable toxicity profile, skin rash or gastrointestinal toxic effects induced by EGFR inhibition may negatively impact quality of life and hinder a prolonged maintenance strategy. The TIME-PRODIGE-28 study by Boige et al\textsuperscript{4} addressed the efficacy of maintenance therapy with single-agent cetuximab vs a treatment-free interval after a 4-month induction treatment with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) and cetuximab in patients with RAS wild-type mCRC. In this phase 2 noncomparative trial, patients were randomized 1:1 to maintenance therapy with biweekly cetuximab or observation after achieving disease control with 8 cycles of induction therapy. After PD, reinduction with FOLFIRI and cetuximab was recommended and was followed by maintenance or observation according to the original randomization group. The primary end point was the progression-free rate at 6 months from randomization. The sample size calculation was based on a Fleming 1-step design, and cetuximab maintenance therapy was considered effective if more than 50% of patients (34 of 67 patients) were alive and without PD at 6 months after randomization. Among 214 included patients, 139 achieved disease control and were randomized to either maintenance therapy with biweekly cetuximab or observation after achieving disease control with 8 cycles of induction therapy. At a median follow-up of 40.5 months, 26 patients (38.8%) receiving maintenance therapy and 4 patients (5.6%) in the observation control group were alive without PD at 6 months after randomization, not reaching the prespecified threshold in either group. Although not powered for comparison, results were disappointing, with a median PFS from randomization of 2.0 months vs 5.3 months in the observation vs maintenance group, and a median OS from randomization of 19.7 months vs 24.8 months, respectively. In terms of safety, the incidence of adverse effects was expectedly increased in the maintenance therapy group, particularly skin rash (11.9% of patients) and diarrhea (6% of patients). Interestingly, next-generation sequencing analysis on available tumor samples showed activating alterations in the mitogen-activated protein kinases pathway (≥1 alteration in RAS, BRAF, MAP2K1, or RTK genes) in 28.6% of patients, with the expected
enrichment in right-sided tumors and significant association with inferior PFS, regardless of treatment group (hazard ratio, 1.63 [95% CI, 1.01-2.62]; P = .04).

The current European Society for Medical Oncology (ESMO) guidelines identify the combination of 5-FU and LV plus an anti-EGFR agent as the maintenance regimen of choice after induction therapy with 5-FU, leucovorin, and oxaliplatin (FOLFOX) plus an anti-EGFR agent. Our 2023 individual patient data pooled meta-analysis of 4 phase 2 randomized clinical trials supported the same recommendation. This meta-analysis compared 3 different strategies (5-FU and LV plus anti-EGFR, anti-EGFR monotherapy, and 5-FU and LV alone) and found that monotherapy maintenance (either anti-EGFR or 5-FU and LV) was inferior to combination in terms of PFS. Again, despite the lack of statistical power to potentially detect OS differences, there was no statistically significant improvement of OS with 5-FU and LV plus an anti-EGFR agent. Importantly, this pooled analysis focused on the optimal anti-EGFR-based maintenance regimen, but the design of the available studies did not allow us to address the role of an intermittent stop and go strategy compared with treatment continuation. In this context, the TIME-PRODIGE-28 trial by Boige et al may represent a valuable contribution for clinical practice.

ESMO guidelines also recommend that patients treated with initial FOLFIRI plus a monoclonal antibody should continue with the same regimen until PD, considering its more favorable safety profile compared with FOLFOX. Indeed, there is a historical lack of academic trials investigating the optimal postinduction strategy after an irinotecan-based induction. The 2022 ERMES study evaluated the potential role of maintenance monotherapy with cetuximab after a 4-month induction with FOLFIRI and cetuximab compared with continuation of the same regimen until PD in patients with RAS or BRAF wild-type mCRC. The ERMES study failed to demonstrate the noninferiority of single-agent cetuximab in terms of PFS vs the continuation of FOLFIRI and cetuximab, although the latter was burdened by a higher incidence of grade 3 or higher adverse events. A different strategy was tested by the noncomparative, phase 2 IMPROVE study, which randomized patients with RAS or BRAF wild-type mCRC to either intermittent or continuous FOLFIRI and panitumumab: the median PFS during treatment was 18.1 months in the intermittent group vs 11.4 months in the continuation group, but the properly defined PFS and mature OS data are still pending. Interestingly, the intermittent FOLFIRI and panitumumab regimen was also associated with reduced skin toxic effects. Additionally, both ERMES and IMPROVE studies showed that the continuation of FOLFIRI and an anti-EGFR agent might be preferable in patients with right-sided tumors, whereas the intermittent or deintensified strategies may be feasible in left-sided subgroup with acceptable outcomes.

A thorough understanding of the biology underlying anti-EGFR resistance is of paramount importance, especially when it comes to identifying the best strategy (ie, continuation, treatment break, or drug deescalation) after achieving maximum response in the first-line setting. Rare genomic alterations have been associated with primary resistance to EGFR inhibitors, highlighting the relevance of comprehensive genomic profiling and hyperselection beyond RAS and BRAF. Patients with primary resistance or right-sided tumors may not derive the optimal benefit from intermittent or chemotherapy-free strategies after an anti-EGFR-based induction. In line with this hypothesis, the study by Boige et al found that alterations in the mitogen-activated protein kinases pathway were associated with extremely poor outcomes in both groups.

On the other hand, acquired resistance to anti-EGFR therapy may be linked to the emergence of RAS alterations and resistant clones during treatment, and the presence of such clones may decline when the anti-EGFR therapy is stopped. An intermittent anti-EGFR-based upfront strategy may delay the onset of acquired resistance mechanisms and be of particular interest in patients with EGFR-dependent RAS or BRAF wild-type and left-sided tumors.

Although novel findings are improving our understanding of this complex scenario, the clinical decision of treatment deescalation or treatment break should involve a comprehensive and dynamic evaluation of both patient and tumor's characteristics, as well as the achievement of an optimal cytoreduction, thus supporting a more individualized approach for the choice of treatment duration and intensity. Future phase 3 trials should investigate anti-EGFR-based intermittent strategies or
maintenance with anti-EGFR monotherapy in properly selected patients with predicted EGFR-dependency, such as those with proficient mismatch repair, microsatellite stable, RAS and BRAF wild-type, and ERBB2-negative tumors, with tumor response to induction therapy and low risk of symptomatic disease progression.

**ARTICLE INFORMATION**

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**Corresponding Author:** Filippo Pietrantonio, MD, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian 1, 20133 Milan, Italy (filippo.pietrantonio@istitutotumori.mi.it).

**Author Affiliations:** Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

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