Targeted doublet therapy with encorafenib and cetuximab for BRAF V600E-mutant metastatic colorectal cancer: A systematic review and meta-analysis

Muhammad Ansab[a], *Shree Rath*[b], *Eiman Araib*[c], *Ghazal Ishaque*[d], *Noor Ul Huda Ramzan*[e], *Soban Ali Qasim*[f], *Ibrahim Halil Sahin*[g]*

[a] Faculty of Medicine, Services Institute of Medical Sciences, Lahore, Pakistan; [b] Faculty of Medicine, All India Institute of Medical Sciences, Bhubaneswar, India; [c] Faculty of Medicine, Dow University of Health Sciences, Karachi, Pakistan; [d] Faculty of Medicine, Shaheed Mohtarma Benazir Bhutto Medical College, Lyari, Karachi, Pakistan; [e] Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, US; [f] Faculty of Medicine, Multan Medical and Dental College, Multan, Pakistan; [g] Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan Medical School, US

Introduction

BRAF V600E-mutated metastatic colorectal cancer (mCRC) represents a biologically aggressive
subset with poor prognosis and limited response to conventional therapies. While dual inhibition of BRAF and
EGFR with encorafenib and cetuximab has emerged as a promising therapeutic strategy, a comprehensive
quantitative synthesis of its efficacy and safety has been lacking.

Methods and Materials

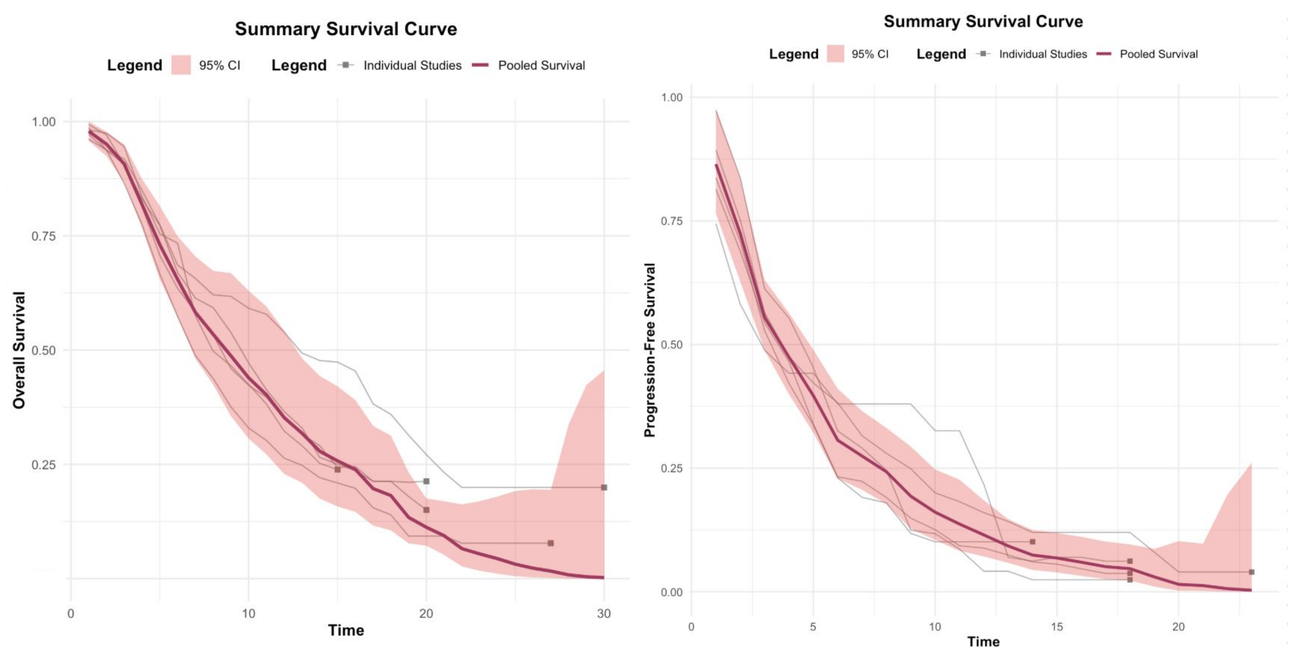
We conducted a systematic review and meta-analysis of studies evaluating the efficacy and safety of encorafenib combined with cetuximab in BRAF V600E-mutated mCRC. Nine studies were included: three randomized trials, one non-randomized early-phase interventional study, and five real-world cohort studies. Data were extracted from randomized controlled trials and cohort studies. A random-effects model was used to pool survival data through reconstructed KM-curves data, treatment response rates, and adverse events. Heterogeneity and publication bias were assessed using I2 statistics, Baujat plots, and LFK indices.

Results

A total of 1,063 patients from 9 studies (3 randomized trials, 1 early-phase interventional study, 5 real-world cohorts) were included. The pooled median overall survival (OS) was 8.7 months (95% CI: 6.7–12.0), with survival rates at 6, 12, and 18 months of 65%, 35%, and 18%, respectively. The median progression-free survival (PFS) was 3.7 months (95% CI: 2.8–4.6). The objective response rate (ORR) was 25% (95% CI: 22–30%), comprising a partial response rate (PRR) of 22%and a complete response rate (CRR) of 2%. The disease control rate (DCR) was 67% (95% CI: 58–76%).

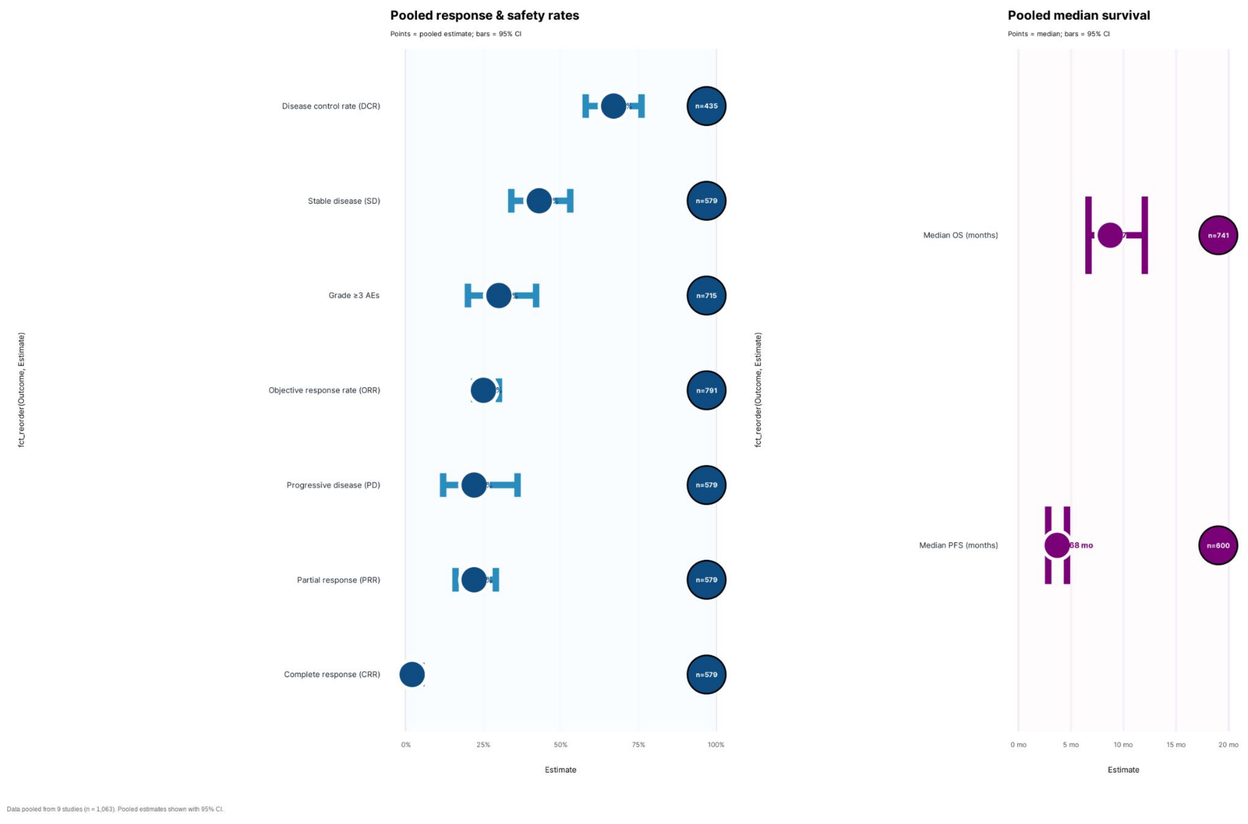
Approximately 30% of patients experienced grade ≥ 3 adverse events (95% CI: 20–42%), most commonly fatigue, diarrhea, and anemia.

Heterogeneity for most endpoints was moderate ($I^2 < 60\%$), and no major publication bias was detected for safety outcomes.



Summary of pooled outcomes — encorafenib + cetuximab (meta-analysis, n = 1,063)

Left: response & safety rates (percent). Right: pooled median survival (months). Error bars = 95% CI.



Data pooled from 9 studies (n = 1,063). Pooled estimates shown with 95% CI.

Conclusion

This meta-analysis supports the use of encorafenib plus cetuximab as an effective and tolerable
regimen in patients with BRAF V600E-mutated mCRC, offering modest improvements in survival and disease
control. Future trials should prioritize biomarker-guided treatment, explore triplet and first-line combinations,
and address mechanisms of resistance to enhance durable clinical benefit.