

P – 288 The role of sidedness in second-line therapy for RAS wild-type colorectal cancer: a network meta-analysis (NMA)

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Introduction: Primary tumor location (PTL) is a prognostic and potentially predictive factor in metastatic colorectal cancer (mCRC). Intriguingly, post-hoc analyses suggested limited benefit from the upfront use of anti-epidermal growth factor receptor antibodies (EGFR) in patients with RAS wild-type (wt) right-sided tumors. While the predictive impact of PTL on clinical outcome after first-line treatment in RAS wt mCRC is uncertain, the lack of head-to-head randomized controlled trials (RCTs) according to sidedness complicate the optimal treatment choice. We conducted a systematic review and NMA to evaluate the role of sidedness on the efficacy of second-line treatments.

Methods: The systematic review included all phase II/III randomized clinical trials (RCTs) published or presented at international conferences comparing different second-line treatments for RAS wt mCRC. Only trials with RAS wt mCRC were included. We performed a random-effect frequentist NMA to evaluate indirect comparisons of regimens including anti-EGFR or anti-vascular endothelial growth factor antibodies (VEGF) based, CT alone or best supportive care (BSC). Progression-free survival (PFS) and Overall Survival (OS) were the outcomes of interest. Analyses were performed for all patients on a trial-based level, regardless of or according to sidedness, when data were available. Surface under the cumulative ranking value (SUCRA) was applied to rank the effect size of treatments.

Results: Overall, 11 RCTs (3,384 patients) were included. In RAS wt patients, PFS was improved with anti-VEGF (HR = 0.63, 95% CI 0.52-0.76) and anti-EGFR (HR = 0.77, 95% CI 0.64-0.91) vs CT, regardless of side. Despite the lack of a statistically proven PFS superiority of anti-VEGF vs anti-EGFR (HR = 0.82, 95% CI 0.66-1.01), anti-VEGF showed the highest likelihood of being ranked as the best treatment in terms of PFS according to SUCRA (98.8% and 67.7% respectively). Conversely, anti-VEGF improved OS compared to both CT (HR = 0.72, 95% CI 0.63-0.83) and anti-EGFR (HR = 0.77, 95% CI 0.66-0.88). In 5 RCTs sidedness data were available. In patients with right-sided mCRC no improvement in OS or PFS was observed with either biologic added to CT vs CT alone. In patients with left-sided mCRC an improvement in PFS was observed with anti-VEGF vs both CT (HR = 0.51, 95% CI 0.33-0.80) and anti-EGFR (HR = 0.59, 95% CI 0.40-0.88). SUCRA favored anti-VEGF for PFS (99.8% and 63.5% respectively), while no improvement in OS was observed.

Conclusion: Through indirect comparisons, second-line regimens with CT and anti-VEGF or anti-EGFR improved PFS in RAS wt mCRC patients. Anti-VEGF based therapy appeared to have higher chances to have better efficacy results according to SUCRA compared to the others. Anti-VEGF could be considered the best second-line choice in left mCRC (specifically for patients who have received upfront EGFR-inhibitors), while no combination provided significant efficacy improvement for right-sided mCRC over CT alone.