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LETTER TO THE JOURNAL

# SALIRI-based (raltitrexed plus irinotecan) therapy as a second-line treatment for patients with metastatic colorectal cancer (SALLY): A prospective, multicenter, non-interventional, registry study

Primary chemotherapy options for colorectal cancer (CRC) involve four key drugs: fluorouracils (5-FU), oxaliplatin, irinotecan and raltitrexed. The first-line regimen consists of 5-FU and leucovorin combined with oxaliplatin (FOLFOX), while the second-line regimen involves 5-FU and leucovorin combined with irinotecan (FOLFIRI) for metastatic CRC (mCRC) in China [1]. Efficacy findings for FOLFOX and FOLFIRI as first-line treatments reported overall response rates (ORRs) of 54% and 56%, with median progression-free survival (mPFS) of 8.0 and 8.5 months, respectively. In the second-line setting, ORRs decreased to 15% and 4%, with mPFS of 4.2 and 2.5 months, respectively, possibly indicating induced drug resistance due to repeated 5-FU infusions in both first-line and second-line treatments [2]. Our present research was a prospective, non-interventional clinical trial conducted in 58 centers across China. The design and procedures are shown in the Supplementary Material. From April 2018 to March 2021, a total of 1,067 mCRC patients were enrolled for second-line treatment with raltitrexed plus irinotecan (SALIRI regimen) following unsuccessful 5-FU combined with platinum-based drug treatment, of whom 1,066 were included in the full analysis set (FAS) and 1,042 in the per-protocol set (PPS). The demographics, baseline and clinical characteristics of the patients are detailed in Supplementary Table S1.

The primary outcome revealed a mPFS of 7.3 months (range: 0.8-40.7, 95% confidence interval [CI]: 7.0-7.6) and a median overall survival (mOS) of 17.8 months (range: 1.4-47.3, 95% CI: 17.0-19.2) in both the FAS and PPS cohorts (Figure 1A-D, Supplementary Table S2).

Regarding secondary outcomes, mPFS and mOS were 5.8 (range: 0.8-34.5) and 17.0 (range: 1.8-47.3) months in the SALIRI group ($n$ = 268), whereas in the SALIRI + targeted therapy (TAR; $n$ = 795), including cetuximab ($n$ = 103), bevacizumab ($n$ = 678) or post-cetuximab + bevacizumab ($n$ = 9) or the other targeted drug group ($n$ = 5), mPFS and mOS were 7.6 (range: 0.8-40.7) and 18.1 (range: 1.4-40.7) months. A significant difference only in OS was found between SALIRI and the SALIRI + TAR groups ($P$ = 0.045) (Figure 1E-F).

Subsequently, the ORR and disease control rate (DCR) for the entire cohort were 19.5% and 84.2%, respectively. The best tumor response comprised 1 patient achieving a complete response (0.1%), 207 with partial responses (19.4%), 690 attaining stable disease (64.7%) and 144 experiencing progressive disease (13.5%). However, in the SALIRI + TAR group, the ORR and DCR were 20.9% (95% CI: 18.1-23.9) and 85.8% (95% CI: 83.2-88.1), whereas in the SALIRI group, the ORR and DCR were 15.7% (95% CI: 11.5-20.6) and 80.6% (95% CI: 75.4-85.2), respectively (Supplementary Table S2).

In addition, an exploration of PFS and OS among patients with diverse genotypes, including mutation states of rat sarcoma viral oncogene homolog *(RAS)*, v-raf murine sarcoma viral oncogene homolog B1 *(BRAF)* and microsatellite stability (MSS)/high microsatellite instability (MSI-H), was conducted. MSS/MSI-H status was measured by immunohistochemistry (IHC) or the capillary electrophoresis-based multiplex polymerase

**Abbreviations:** AEs, adverse events; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CI, confidence interval; DCR, disease control rate; dMMR, mismatch repair deficient; FAS, full analysis set; FOLFIRI, fluorouracil and leucovorin combined with irinotecan; FOLFOX, fluorouracil and leucovorin combined with oxaliplatin; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, high microsatellite instability; MSS, microsatellite stability; ORRs, overall response rates; pMMR, mismatch repair proficient; PPS, per protocol set; *RAS*, rat sarcoma viral oncogene homolog; SALIRI, raltitrexed in combination with irinotecan; TAR, targeted therapy; XELIRI, capecitabine plus irinotecan; 5-FU, fluorouracil.

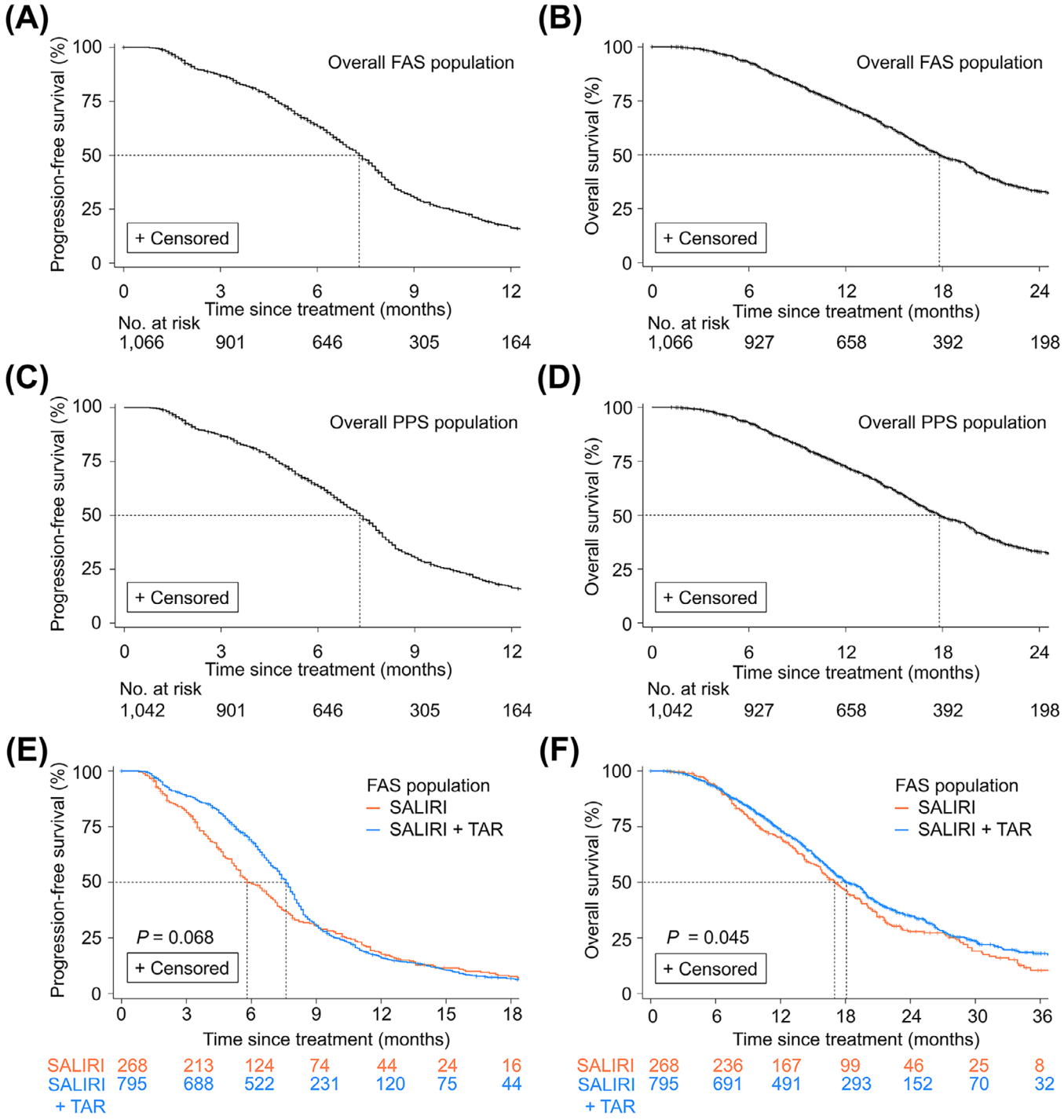


**FIGURE 1** **Efficacy analysis of the different populations**. PFS and OS in the FAS (A, B) and PPS (C, D) populations. PFS (E) and OS (F) times after treatment of SALIRI and SALIRI + TAR in the FAS population. Abbreviations: FAS, full analysis set; OS, overall survival; PPS, per protocol set; SALIRI, raltitrexed + irinotecan; TAR, targeted therapy.

chain reaction. The measurements of other genotype mutation states are described in the Supplementary Material. Patients with *RAS* mutations exhibited a comparatively shorter mPFS of 7.1 months (range: 1.1-22.1, 95% CI: 6.5-7.7), while those with the *RAS* wild-type had a mPFS of 7.8 months (range: 0.9-32.6, 95% CI: 7.1-8.2). The mPFS for patients with *BRAF* mutations was 5.4 months (range: 1.9-19.4, 95% CI: 2.6-12.1), in contrast to 7.4 months (range: 0.9-32.6, 95% CI: 6.8–7.8) for the *BRAF* wild-type. Similarly, it was also shown that the mOS of patients with *RAS* mutations was 16.4 months (range: 1.4-38.7, 95% CI: 14.4-18.9), while those with the *RAS* wild-type appeared to have a relatively longer mOS time of 19.4 months (range: 1.8-36.9, 95% CI: 17.0-21.2),. The mOS for patients with

*BRAF* mutations was 18.1 months (range: 5.7-22.7, 95% CI: 6.5-22.7) compared to 17.7 months (range: 1.8-38.7, 95% CI: 16.4-19.7) for the wild-type. However, all apparent differences between the mutations and wild-type groups were not statistically significant. In the subgroup analysis, for MSS/mismatch repair proficient (pMMR) mCRC patients who received SALIRI-based therapy, the mPFS was 7.7 months (range: 0.9-28.6, 95% CI: 7.1-8.0) and for those with MSI-H-related cases, it was 7.8 months (range: 2.0-14.3, 95% CI: 5.3-11.6). MSS/pMMR- or MSI-H-related mOS in mCRC patients were 18.1 months (range: 2.4-39.6, 95% CI: 16.3-19.9) and 19.9 months (range: 3.4-20.6, 95% CI: 5.3–not evaluable), respectively (Supplementary Table S3).

These findings contradict the prevailing reports that 95% of MSS/pMMR CRC patients exhibit poor responses to immune checkpoint inhibitors [3] and demonstrate that SALIRI-based treatment approaches may represent a promising option for managing MSS/pMMR CRC. Moreover, only 14 patients (1.3%) were identified as MSI-H in the present trial, and 711 (66.7%) remained undetermined (Supplementary Table S1), possibly due to limitations in current MSI-H status identification methods. Typically, IHC provides widely accessible protein expression analysis but necessitates high-quality tissue samples. MSI-H polymerase chain reaction analysis can evaluate specific microsatellite loci, albeit at a higher cost. Therefore, enhancing the capacity to detect accurately the MSI-H patient status in the future is paramount.

Furthermore, the analysis of risk factors for mPFS and mOS after treatment revealed significant correlations between excision of the primary site and mPFS and mOS as well as addition of TAR to SALIRI and mOS times. Age, gender or the primary tumor site location were not potential risk factors for mPFS and mOS of the patients (Supplementary Table S4).

In the present study, 5-FU and oxaliplatin were exchanged with SALIRI, which led to a series of outcomes in the real-life setting (mPFS and mOS of 7.3 and 17.8 months, an ORR of 19.5% and DCR of 84.2%). Compared with irinotecan monotherapy [4], the FOLFIRI regimen [4–6] and the regimen comprising capecitabine plus irinotecan (XELIRI) [7], the present outcomes may validate the problem of repeated use resistance to 5-FU-based regimens with raltitrexed as an alternative treatment for continued 5-FU application from a clinical point of view. In addition, mOS and mPFS were prolonged when SALIRI was used in combination with TAR, a finding in good agreement with those reported in previous studies in which the addition of bevacizumab to chemotherapy regimens was shown to be beneficial for mCRC treatment [8–10]. Regarding safety, in the present trial, an average relative dose intensity of 99.7% (SD 3.9%, range: 48.2%–154.5%; relative dose intensity = actual dose intensity / planned dose intensity * 100%) of raltitrexed for SALIRI-based chemotherapy regimens was achieved, and dose adjustment was not required for 80.7% (861/1,067) of patients in their overall treatment regimens. There were 13.1% (140/1,067) grade III/IV adverse events (AEs) and 7.2% (77/1,067) AEs which led to raltitrexed dose reductions or drug discontinuation, but no AEs were fatal (Supplementary Tables S5-S6). Raltitrexed requires only a 15-min intravenous infusion for its administration, which improves patient compliance compared to oral medication problems, such as misuse, missed doses or multiple doses. In addition, due to its safety profile, some patients can complete their treatment on the day ward, thereby improving their quality of life. An advantage of the present study was its prospective design, over a wide range of Chinese regions that included patients aged from 20 years to 80 years regardless of *RAS* genotype and thus, the results are likely to be representative of the overall Chinese population.

In summary, exchanging 5-FU and oxaliplatin with SALIRI after first-line chemotherapy led to favorable mPFS and mOS, especially when combined with targeted drugs for the treatment of mCRC, which may solve the problem of repeated use resistance to 5-FU analogs and thus improve therapeutic outcomes.

## AUTHOR CONTRIBUTIONS

*Conceptualization*: Shuqui Qin and Jin Li. *Formal analysis*: All authors. *Investigation*: All authors. *Writing—original draft*: Shuqui Qin and Jin Li. *Writing—review & editing*: All authors. *Manuscript approval*: All authors. *Supervision*: Jin Li. *Project administration*: Jin Li.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## FUNDING INFORMATION

None.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this work are available from the corresponding author upon reasonable request.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The trial was in accordance with the Helsinki Declaration and was approved by the ethics committees of

Tongji University Shanghai East Hospital (approval number: 2018-Research Review No. 12) and Bayi Hospital Nanjing Chinese Medicine University (approval number: 81YY-ZLLL-17-32). All patients signed informed consent forms. This study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR1800016185).

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## REFERENCES

1. Xu R, Wang W, Zhu B, Lin X, Ma D, Zhu L, et al. Disease characteristics and treatment patterns of Chinese patients with metastatic colorectal cancer: a retrospective study using medical records from China. BMC Cancer. 2020;20(1):131.
2. Francipane MG, Bulanin D, Lagasse E. Establishment and characterization of 5-fluorouracil-resistant human colorectal cancer stem-like cells: tumor dynamics under selection pressure. Int J Mol Sci. 2019;20(8):1817.
3. Yang W, Zheng H, Lv W, Zhu Y. Current status and prospect of immunotherapy for colorectal cancer. Int J Colorectal Dis. 2023;38(1):266.
4. Zhang X, Duan R, Wang Y, Liu X, Zhang W, Zhu X, et al. FOLFIRI (folinic acid, fluorouracil, and irinotecan) increases not efficacy but toxicity compared with single-agent irinotecan as a second-line treatment in metastatic colorectal cancer patients: a randomized clinical trial. Ther Adv Med Oncol. 2022;14:17588359211068737.
5. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-237.
6. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499-3506.
7. Cui C, Shu C, Yang Y, Liu J, Shi S, Shao Z, et al. XELIRI compared with FOLFIRI as a second-line treatment in patients with metastatic colorectal cancer. Oncol Lett. 2014;8(4):1864-1872.
8. Guan ZZ, Xu JM, Luo RC, Feng FY, Wang LW, Shen L, et al. Efficacy and safety of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of advanced metastatic colorectal cancer: a prospective, non-intervention and post-marketing multicenter clinical study (REACT). Chinese Clinical Oncology. 2016;21(10):865-873.
9. Wang F, Dai G, Deng Y, Tang Y, Wang W, Niu Z, et al. Efficacy and safety of chemotherapy combined with bevacizumab in Chinese patients with metastatic colorectal cancer: A prospective, multicenter, observational, non-interventional phase IV trial. Chin J Cancer Res. 2021;33(4):490-499.
10. Zhu JL, Li S, Zhu C. Efficacy and safety of the combination of bevacizumab with raltitrexed-based chemotherapy as second-line therapy in patients with metastatic colorectal cancer (mCRC): An interim analysis of a multicenter phase II trial. Ann Oncol. 2019;30:ix39.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.