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LETTER TO THE EDITOR

Impact of prior chemotherapy with two different fluoropyrimidines on the efficacy of capecitabine plus irinotecan or FOLFIRI with or without bevacizumab in metastatic colorectal cancer: a post hoc analysis of the AXEPT study

Dear Editor,

Recently, the phase III Asian XELIRI (capecitabine plus irinotecan) ProjecT (AXEPT) study demonstrated the non-inferiority of modified capecitabine plus irinotecan (mXELIRI) ± bevacizumab (Bev) to fluorouracil plus leucovorin with irinotecan (FOLFIRI) ± Bev in terms of overall survival (OS) as a second-line treatment for patients with metastatic colorectal cancer [1, 2]. In the past decade, oral prodrugs of fluorouracil-containing regimens have shown similar efficacies to intravenous fluorouracil-containing regimens. However, no data supporting a change in the type of fluoropyrimidine administered as the first- and second-line treatments in a sequential strategy for the treatment of metastatic colorectal cancer has been obtained since the GERCOR study, which compared FOLFIRI followed by fluorouracil plus leucovorin with oxaliplatin (FOLFOX) to FOLFOX followed by FOLFIRI [3].

Our phase III trial, AXPET, was designed to determine whether fluorouracil plus leucovorin could be replaced by capecitabine combined with irinotecan for metastatic colorectal cancer. Here, we report data from an exploratory analysis that evaluated the impact of prior chemotherapy with two different fluoropyrimidine types, intravenous fluorouracil and leucovorin (IV) versus oral fluoropyrimidine (PO, per os), on the efficacy of mXELIRI and FOLFIRI as second-line chemotherapy regimens. The study protocols are found in the Supplementary Materials.

Abbreviations: AXEPT, Asian XELIRI (capecitabine plus irinotecan) ProjecT; Bev, bevacizumab; CI, confidence interval; FOLFIRI, fluorouracil plus leucovorin with irinotecan; FOLFOX, fluorouracil plus leucovorin with oxaliplatin; HR, hazard ratio; IRIS, irinotecan plus S-1; IV, intravenous; OS, overall survival; PFS, progression-free survival; PO, per os; XELIRI, capecitabine plus irinotecan.

Among the 650 patients included in the AXEPT phase III trial, data on the prior fluoropyrimidine regimen were not available for 8 patients (6 in the mXELIRI arm and 2 in the FOLFIRI arm) in this exploratory analysis (Supplementary Figure S1). In the intention-to-treat population ($n = 642$), 161, 190, 157, and 134 patients were categorized into the IV-IV (first-line treatment with an intravenous fluorouracil-containing regimen followed by FOLFIRI), IV-PO (first-line treatment with an intravenous fluorouracil-containing regimen followed by mXELIRI), PO-IV (first-line treatment with oral fluoropyrimidine-containing regimen followed by FOLFIRI), and PO-PO (first-line treatment with oral fluoropyrimidine-containing regimen followed by mXELIRI) groups, respectively. Thirty patients (16 in the mXELIRI arm and 14 in the FOLFIRI arm) were identified as ineligible after enrollment or did not receive any study treatment, and data on the prior fluoropyrimidine regimen were not available for analysis in 3 patients. In the per-protocol and safety population ($n = 617$), 159, 183, 148, and 127 patients were categorized into the IV-IV, IV-PO, PO-IV, and PO-PO groups, respectively (Supplementary Figure S1). The characteristics of the study population are presented in Supplementary Table S1. No significant differences were observed between mXELIRI and FOLFIRI groups among each prior fluoropyrimidine regimen (All $P > 0.05$).

All adverse events are listed in Supplementary Table S2. No significant differences in safety according to prior fluoropyrimidine regimen were seen in the two treatment arms. The median relative dose intensities were also similar to the prior fluoropyrimidine regimen in the FOLFIRI and mXELIRI arms (Supplementary Table S3).

In the prior oral 5-FU groups, the median OS was 16.7 months for mXELIRI and 17.0 months for FOLFIRI (PO-

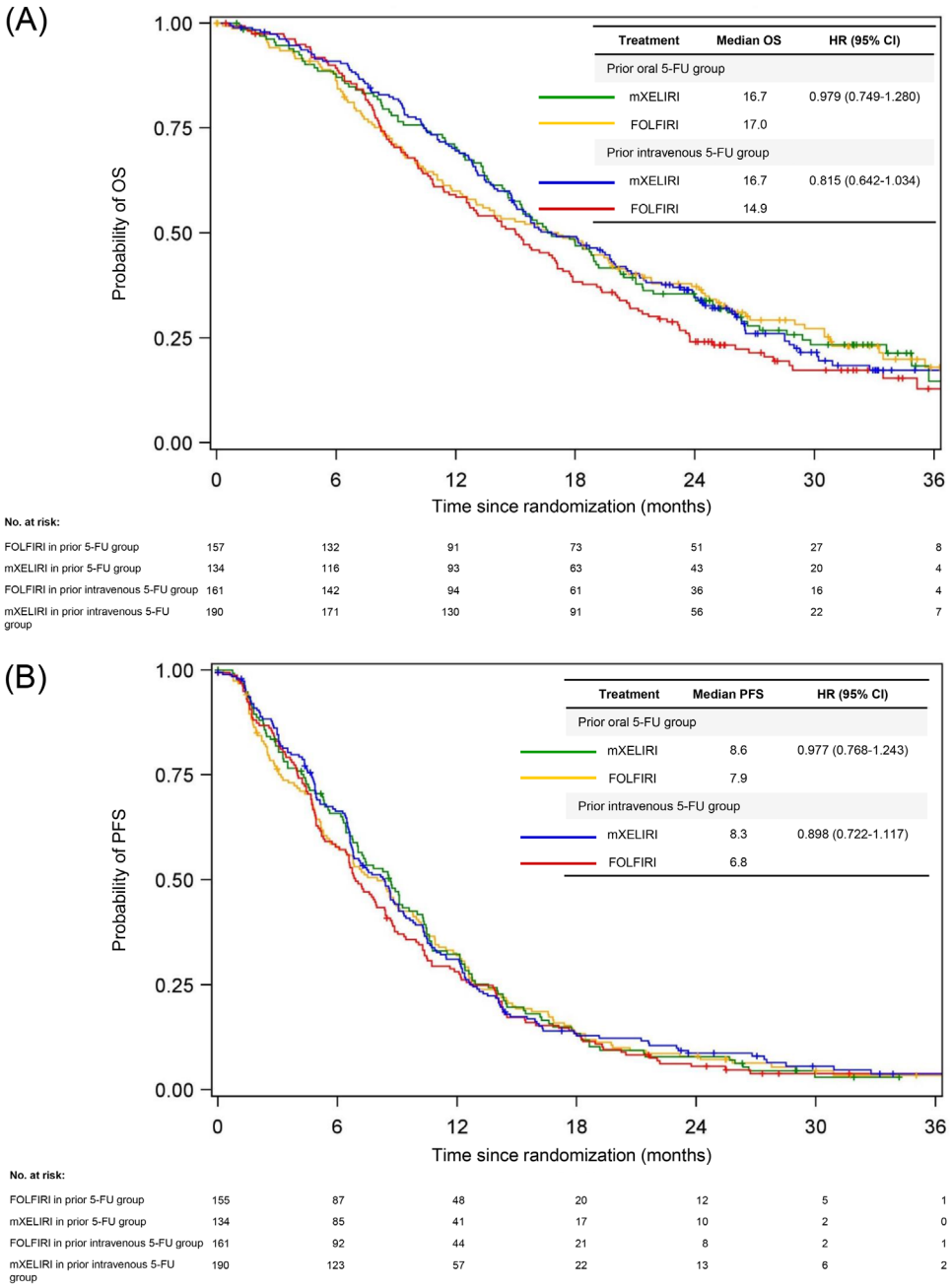

FIGURE 1 Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival in the full analysis set. Abbreviations: FOLFIRI = fluorouracil plus leucovorin with irinotecan; XELIRI = capecitabine plus irinotecan.

IV vs. PO-PO: HR, 0.979; 95% CI, 0.749–1.280; $P = 0.877$) (Figure 1A), whereas the median progression-free survival (PFS) was 8.6 months for mXELIRI and 7.9 months for FOLFIRI (HR, 0.977; 95% CI, 0.768–1.243; $P = 0.851$) (Figure 1B). In the prior intravenous 5-FU group, the median OS was 16.7 months for mXELIRI and 14.9 months for FOLFIRI (IV-IV vs. IV-PO: HR, 0.815; 95% CI, 0.642–1.034; $P = 0.092$) (Figure 1A), whereas the median PFS was 8.3 months for mXELIRI and 6.8 months for FOLFIRI (HR, 0.898; 95% CI, 0.722–1.117; $P = 0.332$) (Figure 1B). The objective response rates were 18.9% in the first-line oral 5-FU group and 27.9% in the intravenous 5-FU group for mXELIRI (PO-PO and IV-PO), and 20.3% in the prior oral 5-FU group and 17.0% in the intravenous 5-FU group for FOLFIRI (PO-IV and IV-IV) (Supplementary Table S4).

The results revealed no relevant difference in efficacy between second-line XELIRI and FOLFIRI, regardless of the first-line fluoropyrimidine regimens. These results showed two clear options for second-line chemotherapy in clinical practice: intravenous (FOLFIRI) or orally administered fluoropyrimidine, such as capecitabine (XELIRI), combined with irinotecan.

Interestingly, FOLFIRI, after the failure of the first-line intravenous 5-FU chemotherapy (IV-IV), tended to have a worse survival outcome than other regimens (Figure 1). In contrast, mXELIRI, after the failure of an oral fluoropyrimidine (PO-PO), showed better efficacy results (Figure 1). These findings might be similar to those of the subgroup analyses in the FIRIS trial, which compared irinotecan plus S-1 (IRIS) vs. FOLFIRI as the second-line chemotherapy for metastatic colorectal cancer [4]. Although previous chemotherapy with or without oxaliplatin was used as one of the stratifying factors, the IRIS arm had a longer PFS and OS than the FOLFIRI arm in a subgroup analysis of patients who had received previous chemotherapy with oxaliplatin. The resistance to fluorouracil and leucovorin that occurs with the FOLFOX and FOLFIRI regimens might be partly overcome by the inhibition of dihydropyrimidine dehydrogenase. These results suggest the potential benefit of a treatment strategy that switches from fluorouracil and leucovorin to S-1. Sensitivity to fluorouracil could be restored using different modes of modulation. Although the possibility of cross-resistance between fluorouracil and capecitabine has not been clinically excluded, predictors of sensitivity to capecitabine and doxifluridine in xenograft models appear to differ from those for fluorouracil [5]. Thus, switching to capecitabine after fluorouracil and leucovorin or the administration of the agents in the reverse order might be beneficial.

Because the difference in the impact of treatment dose and duration between the mXELIRI and FOLFIRI regimens does not seem to be easily explained by treatment adherence or differences in the overall percentage of the standard drug doses delivered, other potential reasons for this finding should be considered. Differences in the efficacy of oral prodrugs and fluorouracil have been suggested by the results of the recent IDEA trial[6]. In the XELOX regimen, the dose of oxaliplatin administered at one time is higher than that given with FOLFOX, and we therefore presume that higher peak doses of oxaliplatin are achieved. Additionally, although the maximum plasma concentration of fluoropyrimidine is lower with XELOX (capecitabine is given twice daily orally for 2 out of 3 weeks) than with FOLFOX (where the fluoropyrimidine is given as a bolus and then infused over 2 days every 2 weeks), the area under the curve is greater with XELOX than with FOLFOX. The continuity of fluoropyrimidine exposure in the form of capecitabine means that there is a greater overall chance that the tumor cells will be exposed to fluoropyrimidine at a critical part of the cell cycle, compared with the administration of fluorouracil as a bolus over 2 days every 2 weeks. These findings also apply to the differences between mXELIRI and FOLFIRI in the AXEPT trial, although the dose intensity of irinotecan in the mXELIRI regimen given with each cycle was lower than that given in FOLFIRI. It is very difficult to confirm which sequential therapy is most appropriate, but the presently available results will certainly continue to be a focus of strong debate.

In conclusion, no significant differences in efficacy were identified between patients who received the prior fluoropyrimidine regimens in either treatment group. Therefore, mXELIRI ± Bev could be a good treatment option after the failure of an oral fluoropyrimidine-based treatment, such as XELOX ± Bev.

AUTHOR CONTRIBUTIONS

Conception and design: Kei Muro, Satoshi Morita, Young Suk Park, Yasuhide Yamada, Junichi Sakamoto, Tae Won Kim

Provision of study patients: Satoru Iwasa, Zi-Xian Wang, Kei Muro, Young Suk Park, Dongsheng Zhang, Yasuhide Yamada, Junichi Sakamoto, Tae Won Kim

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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CONFLICT OF INTEREST DISCLOSURES

Dr. Iwasa reported receiving personal fees from Taiho, ONO, BMS, Daiichi-Sankyo, Eli Lilly, and Chugai; and research fundings from Bayer, BMS, Daiichi Sankyo, Taiho, Eisai, Pfizer, and ONO outside the submitted work. Dr. Muro reported receiving personal fees from AstraZeneca, Amgen, ONO, Sanofi, Taiho, Eli Lilly, BMS, Chugai, Takeda, BMS, and Bayer; and research fundings from ONO, Sanofi, Taiho, Daiichi Sankyo, Parexel International, Solasia Pharma, Pfizer, Merck Serono, Amgen, Astellas, and MSD outside the submitted work. Dr. Morita reported receiving personal fees from BMS, Chugai, and Taiho outside the submitted work. Dr. Yamada reported receiving personal fees from Janssen, Chugai, Behringer Ingelheim, and ONO outside the submitted work. The remaining authors have declared no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the ECRIN data center upon reasonable request.

DECLARATIONS

ETHICS APPROVAL AND CONSENT

The study was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was reviewed and approved by the institutional review board of each study site prior to the initiation of the study. All patients provided written informed consent.

CONSENT FOR PUBLICATION

Not applicable

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SUPPORTING INFORMATION

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