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LETTER TO THE EDITOR

A phase Ib/II study of fruquintinib in combination with paclitaxel as the second-line therapy for advanced gastric cancer

Dear Editor,

In the first-line setting for advanced gastric cancer (AGC), a combination of nivolumab and fluoropyrimidine/platinum has become the standard treatment [1]. However, treatment options are limited after failure of first-line therapy, particularly in China. Ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR)-2, was associated with significant improvements in progression-free survival (PFS) when combined with paclitaxel in the second-line setting [2, 3]. Further, ramucirumab has not yet been approved by the National Medical Products Administration; hence, it is still inaccessible in China. Therefore, single-agent paclitaxel is still a standard-of-care second-line treatment for AGC in China.

Currently, there is no acknowledged active combination of cytotoxic chemotherapy with small-molecule inhibitors of tyrosine kinases involved in angiogenesis for AGC. Fruquintinib is a highly selective small-molecule inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine and has shown an encouraging anti-tumor activity against multiple cancer types [4]. Notably, in the recent phase III FRESCO trial (NCT02314819), single-agent fruquintinib significantly prolonged overall survival (OS) and PFS in patients with refractory metastatic colorectal cancer [5]. Here we report data of a phase Ib/II trial (NCT02415023) that aimed to evaluate the efficacy and safety profiles of fruquintinib in combination with paclitaxel as the second-line therapy for Chinese patients with AGC. The study design is detailed in Supplementary Methods.

Between September 2014 and March 2017, 34 patients with AGC were enrolled in this study (Supplementary Figure S1), with 15 patients recruited in the dose-escalation stage and 19 in the dose-expansion stage. All patients had received prior fluoropyrimidine/platinum-based combination therapy, in which three patients (8.8%) had an additional anthracycline (Supplementary Table S1).

The dose-escalation stage, which followed a 3+3 design, evaluated the safety and identified the recommended phase II dose (RP2D) of the study regimen. Supplementary Table S2 summarizes the incidence of adverse events (AEs) in the dose-escalation stage. No dose-limiting toxicity (DLT) was detected in the fruquintinib 2 mg or 3 mg dose cohort. Two DLTs (one grade 3 febrile neutropenia, lasting for 5 days, and one grade 3 upper respiratory tract infection, lasting for 12 days) were reported in the 9 patients enrolled in the fruquintinib 4 mg dose cohort, 7 of whom were evaluable for DLT. The reason for enrolling 9 patients in the 4 mg dose cohort is detailed in Supplementary Table S3. In view of the DLT incidence of 2/7, which was between 1/6 and 2/6, the steering committee acknowledged that fruquintinib at 4 mg was at risk of exceeding the maximum tolerated dose. After careful discussion, the steering committee decided to further evaluate the safety of the 4 mg dose level during the first treatment cycle for the first six patients recruited in the dose expansion stage before recruiting subsequent patients. During the first cycle, one of the first six patients in the dose expansion stage developed a DLT (grade 3 hand-foot syndrome). After carefully evaluating these safety data, the steering committee established RP2D as fruquintinib 4 mg once daily in combination with paclitaxel 80 mg/m^2 once weekly for 3 weeks in a 28-day cycle. It continued the recruitment of subsequent patients in the dose expansion stage to further verify this RP2D.

The dose expansion stage aimed to further investigate the safety and preliminary efficacy of RP2D. The baseline characteristics of the patient cohort at RP2D (n = 28, nine in the dose-escalation stage and 19 in the dose-expansion stage) are summarized in Supplementary Table

Abbreviations: AGC, advanced gastric cancer; VEGFR, vascular endothelial growth factor receptor; PFS, progression-free survival; OS, overall survival; DLT, dose-limiting toxicity; RP2D, recommended phase II dose.

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S4. Among the 28 patients who were evaluable for safety, the most common all-grade AEs were leukopenia (100%), neutropenia (96.4%), alopecia (75.0%), and anemia (35.7%) (Supplementary Table S5). Grade ≥3 AEs occurred in 23 (82.1%) patients. The most common grade ≥3 AEs were neutropenia (64.3%) and leukopenia (28.6%) (Supplementary Table S6). Grade ≥3 hypertension was observed in two (7.1%) patients, and grade ≥3 hand-foot syndrome occurred in two (7.1%) patients. Two (7.1%) patients reported grade ≥3 hemorrhagic events (one gastrointestinal hemorrhage and one hematuria). No patient had grade ≥3 proteinuria. No thromboembolic event, cardiac toxicity, or gastrointestinal perforation at any grade was observed. Seventeen (60.7%) patients required dose modification or dose interruption due to AEs, mostly neutropenia (46.4%). Ten (35.7%) patients discontinued fruquintinib and/or paclitaxel due to AEs. One (3.6%) death not otherwise specified was recorded.

After a median follow-up duration of 10.8 (range, 9.9-21.9) months among patients at RP2D, the median OS was 8.5 (95% confidence interval [CI], 5.6-10.0) months (Figure 1A). The median PFS was 4.0 (95% CI, 3.0-4.8) months (Figure 1B). Fourteen patients (50%) remained progression-free at month 4 and the Kaplan-Meier estimated 4-month PFS rate was 56.5% (95% CI, 35.3-73.2). As the lower boundary of the 95% CI of the 4-month PFS rate at RP2D exceeded 25% and fulfilled the pre-specified statistical requirement (Supplementary Methods), the combination regimen of fruquintinib at 4 mg and paclitaxel was considered worthy of further investigation.

Twenty-seven patients in the 4 mg dose cohort were evaluable for tumor response. The best responses included a confirmed partial response in seven patients (objective response rate, 25.9% [95% CI, 11.1-46.3]) and stable disease in 11 patients (40.7%; disease control rate, 66.7% [95% CI, 46.1-83.5]). Tumor shrinkage was observed in 22 (81.5%) patients (Figure 1C).

To the best of our knowledge, fruquintinib is the first small-molecule VEGFR inhibitor that can be effectively co-administrated with a cytotoxic agent for AGC and meets the pre-specified benchmark in phase II for further investigation. This is likely to be a result of the superior potency and kinase selectivity of fruquintinib compared with many first-generation small-molecule VEGFR inhibitors, such as sunitinib and sorafenib [6, 7], which guarantees high fruquintinib exposure that can provide sustained target inhibition and hence a substantial anti-tumor effect. [4] The PFS and objective response rate data in this study compared favorably to those for ramucirumab in combination with paclitaxel as in the RAINBOW and RAINBOW-Asia trials [2, 3]. These data corroborate other observations that taxanes and anti-angiogenic agents have a synergistic activity in various malignancies [8, 9]. Moreover, the overall safety profile at RP2D was consistent with that known for paclitaxel and fruquintinib [4, 10].

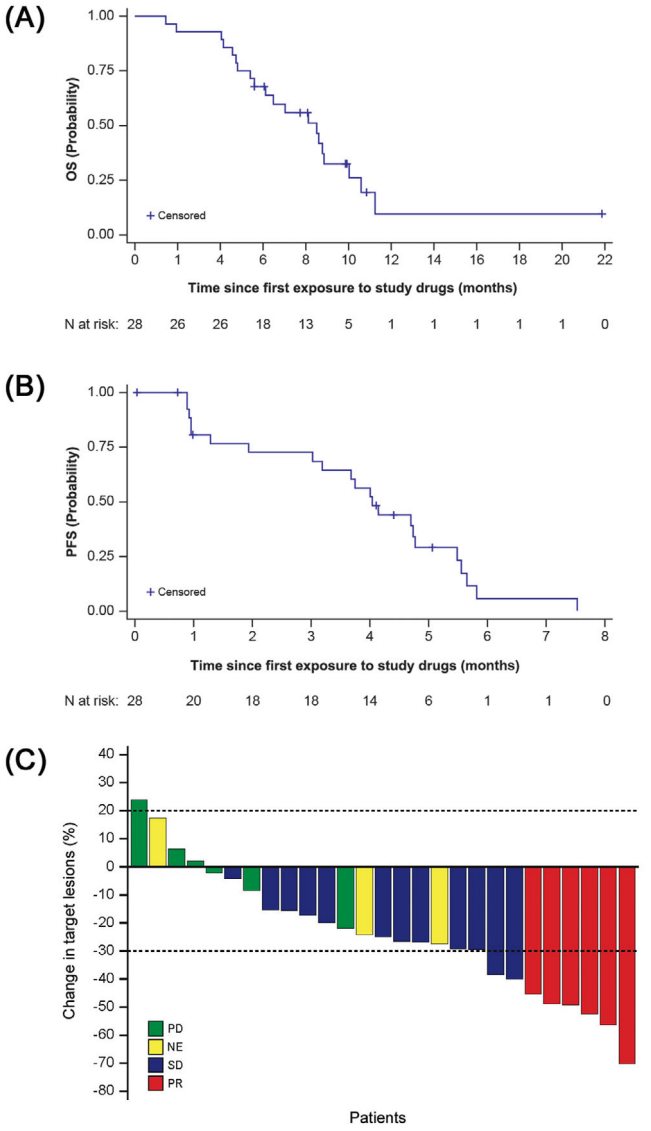

FIGURE 1 Efficacy analysis at the recommended phase II dose. (A) Kaplan-Meier curves for overall survival for patients at the recommended phase II dose. (B) Kaplan-Meier curves for progression-free survival for patients at the recommended phase II dose. (C) Waterfall plot of the maximum percent change from baseline in measurable target lesions for patients at the recommended phase II dose. The dashed lines indicate thresholds of changes in target lesions for evaluating PR and PD. PD, progressive disease; NE, non-evaluable; SD, stable disease; PR, partial response

We acknowledge that paclitaxel plus ramucirumab has become the standard-of-care second-line treatment for AGC, based on the results of the RAINBOW and RAINBOW-Asia studies. However, as shown in RAINBOW-Asia [2, 3], paclitaxel plus ramucirumab did not achieve significant OS improvements over paclitaxel alone as second-line treatment for Asian patients with

AGC, predominantly Chinese patients, highlighting the need to further develop more effective therapeutic regimens for these patients. Furthermore, as a small-molecule inhibitor, fruquintinib might be more suitable for the socioeconomic status of China as it has a lower price and is more conveniently administered than ramucirumab.

In summary, this phase Ib/II study demonstrates that the combination of fruquintinib at 4 mg once daily and paclitaxel weekly exhibited an acceptable safety profile and promising efficacy in patients with AGC who failed standard first-line therapy. The study outcomes warranted further investigation of such combination regimens in AGC and led to an ongoing randomized, double-blind, placebo-controlled, multicenter phase III confirmatory study (NCT03223376).

DECLARATIONS

AUTHORSHIP

Concept and design: RHX, DSZ

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: YZ, ZXW

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: ZXW

Obtained funding: RHX, WGS

Administrative, technical, or material support: RHX, WGS.

Study supervision: RHX, DSZ

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CONFLICTS OF INTEREST

Wei-Guo Su is an employee of HUTCHMED limited. All 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 corresponding authors upon reasonable request.

ETHICS APPROVAL AND CONSENT

The institutional review boards or independent ethics committees of all participating institutions approved the protocol (A2014-033-02). This study followed the guidelines of the Declaration of Helsinki, International Conference on Harmonization, and Good Clinical Practice. All participants provided written informed consent. The manuscript was in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

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.

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