Neuropilin-1 as a potential biomarker of progression-free survival benefit for tivozanib + mFOLFOX6 versus bevacizumab + mFOLFOX6 in metastatic colorectal cancer: post-hoc biomarker analysis of BATON-CRC Phase 2 trial

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Background

Tivozanib is a selective oral small molecular weight inhibitor of tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3). Tivozanib in combination with FOLFIRI (flurouracil, leucovorin, and irinotecan) plus oxaliplatin (FOLFOX) has been studied in patients with previously untreated metastatic colorectal cancer (mCRC) and was associated with significantly reduced levels of serum VEGF-A, VEGF-C, and VEGF-D compared with bevacizumab plus FOLFOX. Tivozanib is a high affinity receptor antagonist that blocks the receptor tyrosine kinases VEGF receptors 1-3 (VEGFRs) with a long half-life and activity against all 3 VEGF receptors (VEGFRs) (165,121)

Methods

OBJECTIVE

• The objective of this study was to provide final results of the BATON-CRC Phase 2 trial of tivozanib + mFOLFOX6 (Arm A) vs bevacizumab + mFOLFOX6 (Arm B), including results from predefined subgroups.

Patients and methods

Eligible patients

Patients were randomized 2:1 and stratified by lactate dehydrogenase (LDH), origin of metastasis, and NRP-1 low and high were defined as above and below the median of 298.5 pg/mL. All patients received mFOLFOX6 every 2 weeks of each 28-day cycle.

No prior VEGF therapy (including bevacizumab) was permitted, nor a history of significant thromboembolic or vascular disorders within 6 months of study entry. Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and an overall health status consistent with the study criteria. Patients had ≥1 target lesion (one or multiple measurable lesions on CT scans) and a minimum of 1 extralesional target in 2 different anatomic sites. All patients had adequate renal, hepatic, and hematologic function. Patients had ≤12 prior lines of chemotherapy for metastatic CRC (mCRC) initiated to expand treatment or bevacizumab 5 mg/kg every 2 weeks on days 1 and 15.

Results

Overall Efficacy

Patients who had low NRP-1 levels showed an improved PFS at the interim analysis in BATON-CRC. A potential hypothesis for the NRP-1 effect may be that:

• Tivozanib + mFOLFOX6 may be superior to treatment with bevacizumab in patients with low NRP-1 levels, potentially due to the broader VEGF pathway inhibitory activity of tivozanib

Conclusions

• Patients with low NRP-1 treated with tivozanib + FOLFOX6 had an increased PFS compared with patients treated with bevacizumab, whereas PFS was comparable for both treatment groups in patients with high NRP-1 levels.

Figure 5. Kaplan-Meier Plot of PFS: Investigator Assessed

Figure 6. PFS of Patients With NRP-1 Low (A) and NRP-1 High (B) Levels Based on a Median Cut-Off

Patients with low NRP-1 treated with bevacizumab + FOLFOX6 had an increased PFS compared with patients treated with bevacizumab, whereas PFS was comparable for both treatment groups in patients with high NRP-1 levels. (A) PFS of patients with NRP-1 low treated with tivozanib + mFOLFOX6 (n=52; Arm A) vs bevacizumab + mFOLFOX6 (n=28). (B) PFS of patients with NRP-1 high treated with tivozanib + mFOLFOX6 (n=127; Arm A) vs bevacizumab + mFOLFOX6 (n=37).

Figure 7. Kaplan-Meier Plot of OS: Investigator Assessed

Figure 8. OS of Patients With NRP-1 Low (A) and NRP-1 High (B) Levels Based on a Median Cut-Off

Patients with low NRP-1 treated with tivozanib + FOLFOX6 had an increased OS compared with patients treated with bevacizumab, whereas OS was comparable for both treatment groups in patients with high NRP-1 levels. (A) OS of patients with NRP-1 low treated with tivozanib + mFOLFOX6 (n=52; Arm A) vs bevacizumab + mFOLFOX6 (n=28). (B) OS of patients with NRP-1 high treated with tivozanib + mFOLFOX6 (n=127; Arm A) vs bevacizumab + mFOLFOX6 (n=37).

Table 1. Baseline Patient Characteristics

Table 2. All-Grade Treatment-Related AE - All % of Patients in Either Treatment and Grade 3/4 Treatment-Related AE - All Patients in either treatment

Table 3. Treatment-Related TEAE - Any Grade % of Patients

Table 4. Adverse Events and TEAE - Any Grade % of Patients