Results of a phase 1b study of the selective BRAF V600 inhibitor encorafenib in combination with cetuximab alone or cetuximab + alpelisib for treatment of patients with advanced BRAF-mutant metastatic colorectal cancer


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Introduction: Patients with BRAF-mutated colorectal cancer (CRC) have been shown to have a poor prognosis compared with those patients with wild-type BRAF; however, BRAF inhibitors have demonstrated little activity in BRAF-mutated CRC. Preclinical data suggest that this activity may be increased by combining BRAF inhibitor treatment with EGFR and/or PI3K inhibitors. Herein, we describe results of a phase 1b clinical study of combinations of the selective BRAF inhibitor encorafenib with the EGFR monoclonal antibody cetuximab with or without the α-specific PI3K inhibitor alpelisib for the treatment of patients with metastatic BRAF-mutated CRC.

Methods: Patients with metastatic BRAF-mutated CRC were treated with either encorafenib + cetuximab or encorafenib + cetuximab + alpelisib. The primary objective of this study was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of encorafenib. Secondary objectives included investigation of safety, assessment of antitumor activity and determination of the pharmacokinetic profile of encorafenib ± alpelisib. Tumor samples were also studied to investigate genetic determinants of response and explore potential mechanisms of resistance.

Results: Patients were enrolled in either the dual arm (encorafenib + cetuximab; n = 26) or the triple arm (encorafenib + cetuximab + alpelisib; n = 28) of the dose escalation phase of the study. The MTD was not reached in either arm; the RP2D was established as 200 mg encorafenib qd + 250 mg/m² cetuximab qw ± 300 mg alpelisib qd. The most common treatment-related grade 3/4 AEs were fatigue and hypophosphatemia (8%) each in the dual arm and hyperglycemia (11%) and increased lipase (7%) in the triple arm. Percentage change in the target lesion from baseline by best response is presented in Figure 1. The best overall response rates, as determined by RECIST v1.1, were 23.1% in the dual arm (1 CR, 4 PR and 1 unconfirmed [u] PR) and 32.1% in the triple arm (4 PR and 5 uPR). Patients in the dual arm had a median PFS of 3.7 months (95% CI: 2.8–10.6) compared with 4.3 months (95% CI: 4.1–5.4) for patients in the triple arm. Exploratory analyses of biomarkers showed that BRAF amplification appeared to correlate with longer PFS. PI3K activation did not appear to correlate with response and there was no clear relationship between MAPK pathway activation and mutations related to WNT signaling and PFS. PK data were not available at the time of this analysis.

Conclusion: Results from this study suggest that either a dual combination of encorafenib with cetuximab or a triple combination of encorafenib with cetuximab and alpelisib are well tolerated with promising activity in patients with metastatic BRAF-mutant CRC. Further biomarker analyses may assist with the clarification of the relationship between gene alterations and clinical outcomes. Enrollment in the phase 2 part of this study is currently ongoing.