gastrointestinal tumours, colorectal

A PHASE I TRIAL OF IRINOTECAN (IRI) AND BUPARLISIB IN PREVIOUSLY TREATED PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC): FINAL RESULTS

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Aim: Buparlisib is an oral pan-class PI3K inhibitor. A phase I trial established the safety and recommended dose of single agent Buparlisib, and promising preliminary anti-tumor activity was seen. It is currently being studied in combinatorial trials in several different malignancies. The primary objective of this phase I trial was to identify the maximum tolerated dose (MTD) for Iri plus Buparlisib in patients with previously treated mCRC, with or without previous exposure to Iri. The secondary objectives were to determine the PK of each drug alone and in combination, to determine clinical response to the combination, and to correlate biomarkers of PI3K signaling with clinical response.

Methods: A conventional 3 + 3 dose titration scheme was used. Iri was administered intravenously every 14 days and Buparlisib given orally daily. The first dose of Iri was administered on cycle 1 day 1, with Buparlisib starting 24 hours after the first dose of Iri. Pts were assessed for safety and toxicities every cycle (q14 days).

Results: Twenty patients were enrolled: 14 were evaluable for DLT: 3 in cohort 0 (Iri 120 mg/m2 + Buparlisib 50 mg/d), 7 in cohort 1 (Iri 150 mg/m2 + Buparlisib 50 mg/d), 4 in cohort 2 (Iri 150 mg/m2 + Buparlisib 80 mg/d). The most common adverse events (all grades) were nausea, vomiting, diarrhea, fatigue, hyperglycemia, and transaminitis. The MTD was Iri 150 mg/m2 + Buparlisib 50 mg/d. One dose limiting toxicity (DLT), grade 2 genital mucositis, was observed in a male pt in cohort 1. In cohort 2 one pt had DLT of grade 3 diarrhea and another had DLT with asymptomatic grade 3 hyponatremia. One pt in cohort 1 experienced grade 2 delirium and a pt in cohort 2 had grade 3 psychosis. Of the 4 pts who received 4 cycles of therapy 2 had stable and 2 had progressive disease. No objective responses were observed. PK data and molecular correlates will be presented in the meeting.

Conclusions: This first human trial established that Buparlisib (50 mg qd) and Iri (150 mg/m2 q14d) are tolerable in combination. The efficacy of this regimen will need to be tested in future studies.

Disclosure: J.C. Baranda: Research Funding from Novartis. All other authors have declared no conflicts of interest.