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Results from a Phase II study of nanoliposomal irinotecan (nal-IRI) with 5-fluorouracil (5-FU)/leucovorin in refractory advanced high-grade neuroendocrine cancer (HG-NEC)

Sarbajit Mukherjee, Robert Ramirez, Christos Fountzilas, Deepak Vadehra, Mary Lynne Tarquini, Kristopher Attwood, Renuka Iyer.

BACKGROUND

Metastatic neuroendocrine carcinomas (NECs) have a poor prognosis, and standard first-line chemotherapy combines etoposide (E) and platinum (P) has limited benefit. Currently, there is no standard second-line therapy. Irinotecan-based regimens have shown benefits; hence we explored nanoliposomal Irinotecan (nal-IRI) efficacy in this patient population.

METHODS

In this open-label, single-arm, multi-center Phase 2 study, advanced GEP or unknown origin HG-NEC patients with progressive disease/intolerance to 1st line treatment with EP received nal-IRI 70 mg/m2, leucovorin 400 mg/m2 followed by 5-FU 2400 mg/m2 (over 46 hours) every other week till disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Baseline tissue or blood sample was submitted for Next Generation Sequencing (NGS). Subsequently, on treatment, blood samples were collected for circulating tumor DNA (CtDNA) measurement using Foundation One® Liquid assay. The study had Simon's minimax design with a plan to enroll 18 patients in stage 1. Unfortunately, it was closed to accrual due to non-clinical reasons after enrolling 11 patients.

RESULTS

There were n=11 treated pts enrolled at two sites, of which nine were evaluable for the primary endpoint. In the overall population, 64% were male, median age (range): 66.7 years (50-87.8), median Ki-67 90% (range 50-100%), primary site: 27% colorectal 18% esophageal, 18% ampullary, 9% pancreatic, 28% other; 73% had liver mets. Among evaluable pts, one (11.1%) had a partial response, and 5 (55.6%) had stable disease, with a disease control rate of 67%. Median PFS was 4.4 months (95% CI: 1.7, 6.7). Median OS was 9.4 months (95% CI: 2.9, 29.3) (with one patient alive at 33 months). Among all treated pts (n=11), 9 (82%) had a treatment-related adverse event (AE), with 8 (73%) having grade 3 or higher AEs. The most common AEs were diarrhea (45%), nausea (45%%), vomiting (45%), and fatigue (45%)—no treatment discontinuation due to side effects. Subsequent chemotherapy was administered in 5 (45%) patients. On NGS, the most common variants were: TP53 (89%), CHEK2 (78%), APC (22%), and NF1(22%), and they remained mostly detectable throughout treatment.

CONCLUSIONS

A combination of 5-FU and nal-IRI showed efficacy and manageable toxicity in refractory HG-NEC, consistent with NET-02 study results (McNamara, 2022). Ongoing biomarker analysis using CtDNA may identify patients likely to benefit most from this combination. Ipsen Pharmaceuticals and the North American Neuroendocrine Tumor Society funded the trial. Clinical trial information: NCT03736720.

ABSTRACT ID 23469