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Phase Ia/Ib Study of BAY1895344 Plus Topoisomerase I Inhibitors with a Focus on Poorly Differentiated Neuroendocrine Carcinomas and Pancreatic Adenocarcinoma

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BACKGROUND

Advanced small cell lung cancer (SCLC), extra-pulmonary neuroendocrine carcinoma (EP-NEC) and pancreatic adenocarcinoma (PDA) are rapidly progressive cancers characterized by unbridled replication stress. Patients with these malignancies possess dismal prognoses with limited options after initial first-line chemotherapy. These tumors rely on the integrity of DNA damage repair pathways to ensure genomic stability. The ataxia telangiectasia and Rad3-related (ATR) protein kinase is a potential therapeutic target in these cancers and is activated by replication stress. The ATR inhibitor BAY 1895344 has demonstrated cytotoxic potential in SCLC and gastrointestinal cancer xenografts in combination with the topoisomerase I(TopI) inhibitors topotecan and irinotecan. We developed a phase I study combining BAY 1895344 with irinotecan or topotecan.

METHODS

NCT04514497 is a phase Ia/Ib study with 3 dose escalation cohorts (irinotecan IV D1 plus BAY 1895344 PO BID D1, D2 Q14 days; irinotecan IV D1,8,15 plus BAY 1895344 QD D1-D3, D8-10 and D15-17 Q21 days; topotecan IV D1-D5 plus BAY 1895344 PO QD D2, D5 Q21 days) and 3 dose expansion cohorts. Primary objectives are to assess safety and tolerability and estimate the maximum tolerated dose and recommended phase 2 dose of the combinations. Secondary objectives include estimating pharmacokinetic profiles and assessing anti-tumor activity of the combinations. In dose escalation, patients with refractory advanced solid tumors for whom TopI inhibitors are considered SOC are eligible. In dose expansion, patients must have SCLC, EP-NEC (large cell or small cell histology mandated) or PDA. Dose escalation will utilize a 3+3 design. Biopsies for pharmacodynamic DNA damage biomarker assessment are required in dose expansion. The tissue-based correlative studies are outlined in Table 1.

RESULTS

The trial is currently enrolling patients.

Biomarker	Phase of Study	Time of Collection	Purpose	Mandatory (M)/Optional (O)
γH2AX, pNBS1	Dose Expansion	D-7 C1D3	Measure DNA damage biomarkers	M
Whole Exome Sequencing, RNA Sequencing	Dose Expansion, Escalation	Archival	Determine if certain mutations or expression of DNA damage repair genes predict treatment sensitivity	O
ATM	Dose Expansion, Escalation	Archival	Identify pts with tumors responsive to ATR inhibition	O

CONCLUSIONS

Anti-tumor activity has been observed with the ATR inhibitor berzosertib in combination with topotecan in patients with SCLC and EP-NEC. Based upon the potential best-in-class cytoreductive capacity of BAY 1895344 preclinically compared with other ATR inhibitors, we are hopeful that TopI inhbitors plus BAY 1895344 will represent safe and meaningful treatment options for patients with SCLC and EP-NEC which can be carried forward to more definitive efficacy-assessing studies.

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