Abstract 4340

CHARIOT trial (cohort A2): A phase I dose escalation study combining the ATR inhibitor Berzosertib with cisplatin and capecitabine

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Background

Berzosertib is a potent inhibitor of ataxia telangiectasia-mutated and Rad3-related protein kinase (ATR). Preclinical studies have shown that ATR inhibition enhances the cytotoxic effects of DNA damaging drugs. Cohort A2 of the CHARIOT trial (NCT03641547) explored the combination of berzosertib with cisplatin and capecitabine in advanced solid tumours to assess the optimal treatment schedule, safety and preliminary efficacy.

Methods

In this single arm, mulicentre, open-label, phase I dose escalation trial, adult patients with advanced solid tumours received six cycles of chemotherapy with three weekly cisplatin (60mg/m^2 IV Day 1) and capecitabine (625mg/m^2 po bd Days 1-21) combined with berzosertib. A Time-To-Event Continual Reassessment Method (TiTE-CRM) design was used to assess the optimal treatment schedule. Highest treatment schedule resulting in <30% dose limiting toxicity (DLT) rate was selected as recomended dose. Berzosertib was administered across four dose levels, 90mg/mg^2 IV once weekly escalating to a dose of 140mg/m^2 IV twice weekly.

Results

Eighteen patients received treatment on study between December 2018 and August 2021 (commonest tumour sites, melanoma (5) and esophageal (2) cholangiocarcinoma (2). The most common grade ≥3 treatment-related adverse events were neutropenia (38.9%) and thrombocytopenia (11.1%). There were no treatment-related deaths. Two patients experienced dose limiting toxicities (DLTs): grade 3 neutropenia and grade 3 pyrexia in the first patient and sepsis, vomiting and dehydration (all grade 3) in the second patient. Nine patients completed 6 cycles of treatment. Berzosertib 140mg/m^2 once weekly was identified as the recommended phase II dose in this combination.

Conclusions

Weekly Berzosertib administration with Cisplatin and Capecitabine is feasible and well tolerated. Preliminary efficacy data to follow.

Clinical trial identification

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Editorial acknowledgement

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