#5711 CHARIOT: A phase I dose escalation study combining ATR inhibitor Berzosertib with chemoradiotherapy in oesophageal cancer using time to event continual reassessment (TiTE-CRM) method: Results from A1 cohort (combination with palliative RT)

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Oesophagogastric cancer

Abstract

Background

Berzosertib (M6220) is a selective ATR protein kinase inhibitor. Preclinical studies in esophageal cancer cell lines show that combining M6220 with cisplatin increased tumour cell kill *in vitro* and caused tumour growth delay in combination with radiation *in vivo*. The A1 cohort of CHARIOT (NCT03641547) tested the feasibility of combining Berzosertib with radiation in esophageal cancer. Primary objective: establish recommended phase II dose (RP2D) in combination with palliative RT; secondary objectives: safety, toxicity and efficacy.

Methods

Design-Single arm, open label, phase I dose escalation trial using TiTE-CRM. Key inclusion/exclusion - Adenocarcinoma or Squamous carcinoma of thoracic oesophagus, not suitable for radical treatment, tumour length ≤15cm, no stent in-situ, life expectancy of ≥12 weeks, ECOG 0-1, without prior irradiation to mediastinum/upper abdomen. Radiation dose was 35gy/15 fractions/3 weeks. Six dose levels were tested (table 1), with a target Dose Limiting Toxicity (DLT) rate of 25% during an observation window of 24 weeks.

Table 1

Treatment schedule	Berzosertib Dose	Participants commencing treatment	Participants Receiving full dose
1	140mg/m^2 day 2,9,16	3	3
2	140mg/m^2 day 2,5,9,12,16	1	1
3	140mg/m^2 day 2,5,9,12,16,19	1	1
4	240mg/m^2 day 2,9,16	1	1
5	240mg/m^2 day 2,5,9,12,16	1	1
6	240mg/m^2 day 2,5,9,12,16,19	9	4*

** 4/9 received all 6 infusions; 4/9 received 5 infusions and 1/9 received 4 infusions*

Results

Between Dec 2018 and Jan 22, 16 patients were recruited from 4 UK centres. All completed final (week 12) visit. No DLTs were reported during the trial. The TiTE-CRM recommended dose escalation for each dose level until the maximum. This was the RP2D at trial end. Ten Grade 3 adverse events [rash (n=4), one each of oesophagitis, lymphoedema, hyponatremia, lymphopenia, constipation, RIG displacement] were reported. Seven deaths were reported (6 disease related; 1 – cause not documented).

Conclusions

Berzosertib plus radiotherapy was well tolerated in patients with advanced oesophageal cancer and warrants investigation in future trials evaluating efficacy.

Clinical trial identification

NCT03641547

Editorial acknowledgement

Legal entity responsible for the study

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Disclosure