# 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 (1,2).

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.

1. Lewis KA et al. Molecular cancer therapeutics. 2009 Apr;8(4):855-63. PubMed PMID: 19372558.
2. Cliby WA et al. The EMBO journal. 1998 Jan 2;17(1):159-69. PubMed PMID: 9427750.

## METHODS

- **Key eligibility criteria:** patients aged ≥16 years with advanced solid tumours, ECOG PS 0-1, adequate organ function and life expectancy of at least 12 weeks.
- **Trial design:** single arm, multicentre, open-label, phase I dose escalation trial. Time-To-Event Continual Reassessment Method (TiTE-CRM) was used to assess the optimal treatment schedule.

### TiTE-CRM
### (Time-To-Event Continual Reassessment Method)*

- Explicitly *models* the dose-toxicity relationship (cf. rule-based designs, e.g. 3+3; rolling 6).
- Uses information from <u>all</u> participants (including those that have not completed toxicity follow-up, using weighting) to calculate next dose allocation.
- More efficient, particularly for radiotherapy trials with long observation periods, as allows for continual accrual vs 3+3 design.
- Requires close collaboration between clinicians, data managers and statisticians throughout the trial.

*van Werkhoven E. *BMC Med Res Methodol* 20, 162 (2020); doi: 10.1186/s12874-020-01012-z

- **Trial treatments:** cisplatin (60mg/m$^2$ IV Day 1) and capecitabine (625mg/m$^2$ po bd Days 1-21) were administered q3w for 6 cycles. Berzosertib was administered concomitantly, IV, as per allocated dose schedule (Table 1).
- **Primary objective:** to determine the recommended phase II dose (RP2D) of berzosertib when administered concomitantly with cisplatin and capecitabine. Endpoint: highest treatment schedule resulting in <30% dose limiting toxicity (DLT) rate.
- **Secondary objectives**: safety/toxicity, feasibility and efficacy of the combination.

| Treatment schedule | Dose of berzosertib and days of the schedule it will be delivered |
|---|---|
| 1 | 90 mg/m$^2$ once a week for 18 weeks (Tuesdays) |
| 2 | 90 mg/m$^2$ twice a week for 18 weeks (Tuesdays and Fridays) |
| 3 | 140 mg/m$^2$ once a week for 18 weeks (Tuesdays) |
| 4 | 140 mg/m$^2$ twice a week for 18 weeks (Tuesdays and Fridays) |

**Table 1: Berzosertib dose escalation schedule**

## RESULTS

- Eighteen patients started treatment on study between December 2018 and August 2021. Figure 1 shows the number of patients enrolled by tumour type.
- Figure 2 is a schematic of patient flow in cohort A2.

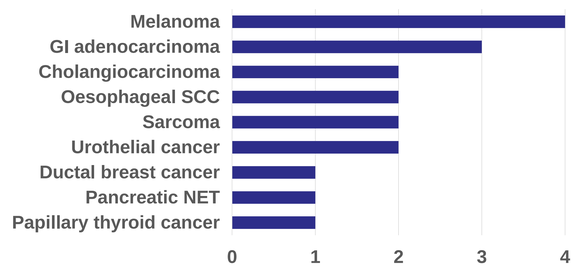
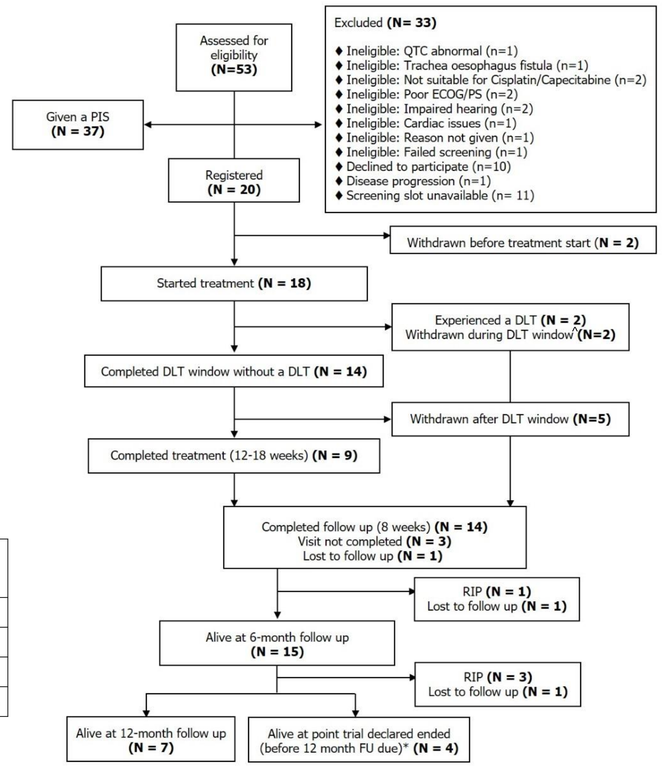



**Figure 1: Number of patients by tumour type**




^DLT window = 4 weeks.
*Patients in this category were alive at the last health status check in March 2022 (end of trial) but did not complete the full 12 month follow up period.

**Figure 2: Patient flow diagram**

- **Adverse events (AEs):** the most common grade ≥3 treatment-related AEs were neutropenia (38.9%) and thrombocytopenia (11.1%).
- **Serious adverse events (SAEs)**: there were 5 SAEs in the cohort, occurring in 3 patients: pyrexia, neutropenia, sepsis, vomiting and chest pain. There were no treatment-related deaths.
- **Dose-limiting toxicities:** two patients experienced DLTs; grade 3 neutropenia and grade 3 pyrexia in the first patient and sepsis, vomiting and dehydration (all grade 3) in the second patient. See figure 3.

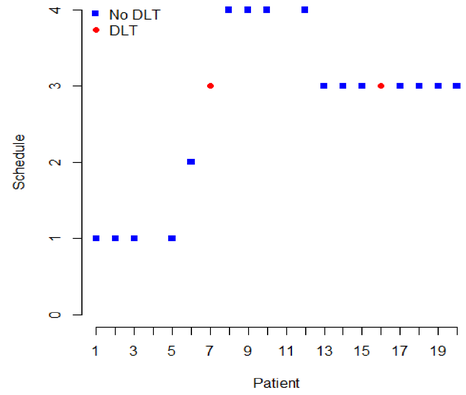



**Figure 3: Schedule allocation and DLTs**

Berzosertib 140mg/m$^2$ once weekly (dose level 3) was identified as the RP2D in this combination. This was a dose level lower than that identified by TiTE-CRM and was selected based on clinical judgement due to clinically unacceptable toxicities, not reaching DLT definition, with dose level 4.

## CONCLUSION

Weekly berzosertib administration at a dose of 140mg/m$^2$, with cisplatin (60mg/m$^2$ IV Day 1) and capecitabine (625mg/m$^2$ po bd Days 1-21), is feasible and well tolerated.

## ACKNOWLEDGEMENTS

CHARIOT trial was sponsored by the University of Oxford. Trial management was provided by the Oncology Clinical Trials Office (OCTO) at the University of Oxford as part of the UKCRC Oxford Clinical Trials Research Unit (OCTRU). Funding was provided by Cancer Research UK (Grant Ref: C43735/A20874). Merck provided free berzosertib to support the study.

S. El Badri has no conflict of interests to declare.

Clinical trial identification Protocol Version & date:
CHARIOT_Protocol_V5.0_26Oct2020
EudraCT Number: 2015-003965-27