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ORCA-2

A phase I study of olaparib in addition to cisplatin-based concurrent chemoradiotherapy for patients with high risk locally advanced squamous cell carcinoma of the head and neck (HNSCC)

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Background and objectives

Standard care for locally advanced squamous cell carcinoma of the head and neck (HNSCC) is cisplatin-based chemoradiotherapy (C-CRT). Use of intensity modulated radiotherapy (IMRT) increases the accuracy of RT delivery, reducing toxicity to normal tissue and potentially allowing higher doses to be delivered to the tumour. However, despite aggressive primary management many patients with high risk disease develop recurrence.

The PARP-1 inhibitor olaparib inhibits DNA damage repair and may potentiate the anti-tumour activity of C-CRT. Preclinical data demonstrate potent radio-sensitisation but the optimal dosing schedule to enhance anti-tumour activity, whilst allowing normal tissue recovery, has not been investigated clinically.

ORCA-2 is a dose finding phase I study which will use a two dimensional dose escalation design to determine the maximum tolerated dose and schedule (MTD) of olaparib + cisplatin-based chemoradiotherapy (C-CRT). The total exposure to olaparib will be escalated both by increasing the dose over a fixed duration and increasing duration of a fixed dose.

An expansion cohort of 10-15 patients will be recruited at the MTD in order to define the recommended phase II dose and schedule (RP2D). If more than one MTD is defined, up to two cohorts will be chosen for expansion.

Expected recruitment for the trial is between 30 and 50 patients from up to 6 sites across the UK.

Endpoints

Primary Endpoint:

- Occurrence of Dose Limiting Toxicities (DLTs) during the DLT review period (treatment phase to 6 weeks post completion of C-CRT).

Secondary Endpoints:

- Frequency & severity of adverse events
- Time to loco-regional & any progression (TLP and TTP),
- Progression free survival (PFS),
- Overall survival (OS),
- Best overall response,
- Exploratory translational PK / PD endpoints

Current Status *(as at April 2016)*

Number of site activated: 1

First patient entered into the trial on 04/Feb/2016

Recruitment: 1 patient

Trial Design

Treatment

Week 0: Patients receive olaparib alone for the purposes of the exploratory biological studies. The weekly dose and schedule is assigned according to dose escalation scheme.

Weeks 1-7 (olaparib + C-CRT): Combination treatment is administered in a weekly schedule over 7 weeks as follows:

- Oral olaparib taken twice daily as per week 0
- Cisplatin 35 mg/m^2 IV day 1 every week (total dose 245 mg/m^2)
- IMRT is delivered on days 1-5 each week at a fixed total dose of 70 Gy in fractions. IMRT on day 1 of each week should begin after completion of cisplatin administration.

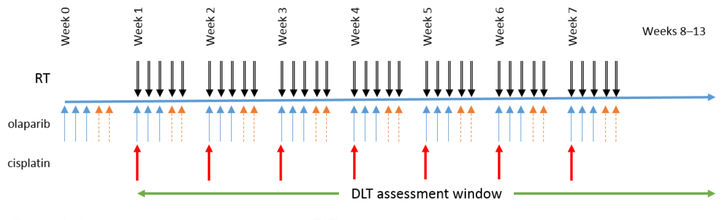

Figure 1: Schematic of treatment plan and DLT window

Dose Escalation Scheme

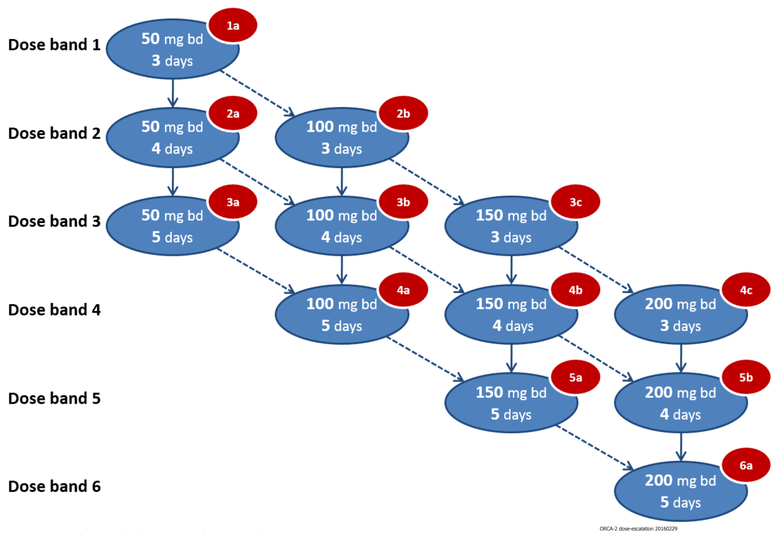

Figure 2: Olaparib dose escalation scheme.
The dose of olaparib per day will be increased over a fixed number of days (dotted arrows) and the number of days increased for a fixed dose of olaparib per day (solid arrows). Approximately equivalent doses have been grouped into dose bands. The small red oval indicates the cohort number.

All patients will receive the same dose of cisplatin + IMRT. Olaparib will be escalated by increasing both the dose (50, 100, 150 & 200 mg bd) and duration (3, 4 & 5 days). A Baysian dose escalation method, the Product of Independent Beta Probabilities Escalation (PIPE), is being used to guide dose escalation, which incorporates a target toxicity level of 33%. This design allows flexibility and adaptability to provide better estimates of the recommended dose-duration combinations for further investigation than a standard 3+3 design.

Eligibility

Key Inclusion Criteria

- Histologically confirmed high risk locally advanced HNSCC (TNM staging T_{any} N2/3 M0, bulky T3 or T4 N_{any} M0)
- WHO performance status 0 or 1
- Aged ≥18 years of age
- Adequate major organ function
- Patients must be able to swallow olaparib tablets
- Able to give informed consent

Key Exclusion Criteria

- Head and neck cancers of the following types:
  - Nasopharyngeal and paranasal sinus tumours
  - Oral squamous cell carcinomas (tumours of the oral cavity)
  - Low risk Human Papilloma Virus (HPV) positive oropharyngeal tumours (tonsillar and tongue base tumours)
- Confirmed distant metastatic disease
- Previous chemotherapy or radiotherapy for the treatment of HNSCC tumour
- Previous therapy with a PARP inhibitor
- Pre-existing gastrointestinal disorders that may interfere with the delivery or absorption of olaparib
- The current use of drugs which are known to inhibit or induce CYP3A4
- Resting ECG with QTc >480 msec or family history of long QT syndrome
- Contraindications to cisplatin treatment

Exploratory Biological Studies

- Assessment of target inhibition in peripheral mononuclear blood cells (PBMCs)
- Evaluation of other pharmacodynamic (PD) and predictive biomarkers in PBMCs, archival tumour tissue, and snap frozen tumour tissue
- Measurement of plasma concentrations of olaparib for correlation with PD markers
- Evaluation of plasma circulating biomarkers
- Enumeration of circulating tumour cells.
- Functional multi-parametric MRI assessments in expansion cohorts

Acknowledgements

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