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A Phase I Study of Olaparib in Addition to Cisplatin-Based Concurrent Chemoradiotherapy for Patients with High Risk Locally Advanced (LA) Squamous Cell Carcinoma of the Head and Neck (HNSCC)

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Background

Cisplatin-based chemoradiotherapy (C-CRT) is a standard of care for patients with locally advanced squamous cell carcinoma of the head & neck (LA HNSCC), but recurrence is common. Olaparib, a PARP-1 inhibitor inhibits DNA damage and may potentiate anti-tumour activity of C-CRT.

Methodology

This was a phase I trial designed to determine the recommended phase II dose and schedule of olaparib in combination with C-CRT

Entry required patients to be treatment-naïve, with high risk LA HNSCC (Tany N2/3 M0, bulky T3 or T4 Nany M0) and WHO performance status of 0 or 1.

A novel Product of Independent Beta Probabilities Escalation design was used. Escalation decisions were based on a pre-specified target toxicity level of 33%, prior probabilities of toxicity per dose-duration combination and cumulative toxicity data from at least 2 patients per cohort. Olaparib was escalated by dose (50 & 100 mg bd) and duration (3 & 4 days per week). A radiotherapy QA programme was conducted by the National RTTQA Group to monitor protocol compliance.

Primary endpoint was occurrence of dose limiting toxicity (DLT) over 13 weeks (7 weeks C-CRT, 6 weeks follow up). Secondary endpoints were best overall response (BOR) using RECIST, time to progression (TTP), progression free survival (PFS) and overall survival (OS).

The maximum tolerated dose and schedule of olaparib was determined from the escalation phase at cohort 1a (50mg bd for 3 days). The study entered the expansion phase to provide more "real-world" data on the tolerability of the combination and to establish the recommended phase II dose. The trial closed to recruitment at the end of 2019.

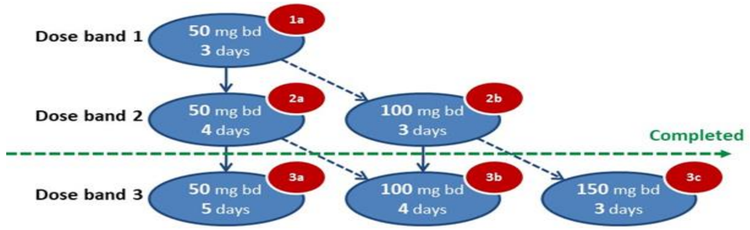


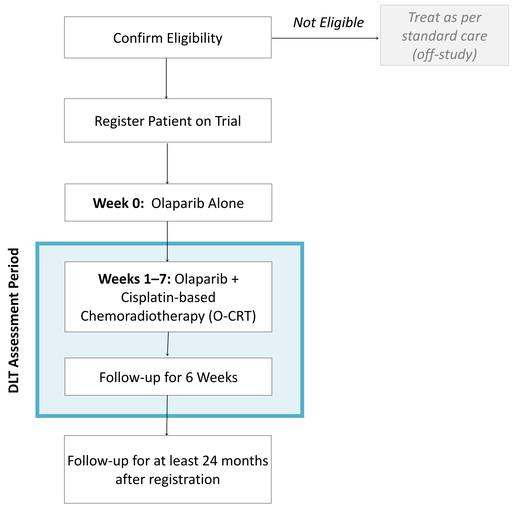
Figure 1: *Dose Escalation Design*

Baseline characteristics (n=15)

Age (in years)		**WHO status**	
Median	57 years (range 53-59)	0	14
		1	1
Sex		**Smoking status**	
Male	13	Ex-smoker	11
Female	2	Current smoker	4
Site of primary		Never smoked	0
Hypopharynx	2		
Oropharynx	13		

➢ 16 patients were registered but 1 patient did not start treatment and is not included in the analysis.

Trial Design



Combination treatment given as follows:

➢Oral olaparib – weeks 0 – 7 (dose/scheduled dependent on dose level recruiting at the time of enrolment)

➢Cisplatin – weeks 1 - 7 (35 mg/m^2 IV day 1; total dose 245 mg/m^2)

➢RT – weeks 1 -7 (days 1-5; total dose 70 Gy in 35 fractions; RT given after cisplatin on day 1 each week)

Figure 2: *Trial Schema*

Results

Toxicity

➢14 patients were eligible for DLT assessment.

➢No DLTs were observed in the initial 50 mg bd 3 days cohort (n=2).

➢DLTs were observed in all patients at 50 mg bd 4 days (n=2) & 100 mg bd 3 days (n=2) cohorts.

➢Expansion of 50 mg bd 3 days cohort (n=8) saw 4 DLTs, including 1 patient who died on treatment.

➢Posterior mean probability of DLT at 50 mg bd 3 days was 0.40 (90% credible interval 0.17-0.65).

➢Grade 3 Adverse Events were seen in 13 patients, Grade 4 in 6 patients and Grade 5 in 1 patient. All were related to at least 1 of the trial treatments.

Results /cont.

DLT summary (n=14 evaluable patients) DLT type	50mg bd 3 days	50mg bd 4 days	100mg bd 3 days
AR resulting in omission of cisplatin +/- olaparib for >2 weeks	1	0	1
Febrile neutropenia	0	2	0
G3 nausea despite optimal supportive care	1	0	0
G3 mucositis lasting >6 weeks	1	0	1
Other clinically significant occurrence (fatal MI, associated with neutropenic sepsis)	1	0	0
Total:	4	2	2

Response

Patients evaluable for Best Overall Response by RECIST (n= 12*) * of 15 patients registered	
Complete response	5 (42%)
Partial response	5 (42%)
Stable disease	1 (8%)
Progressive disease	1 (8%)

➢ Median time to progression was not estimable (NE; 95% confidence interval (CI) 23.8-NE months). Three patients died during follow up.

➢ 12-month PFS was 86% (95% CI 55-96); 24-month PFS was 78% (95% CI 45-92).

➢ Overall survival at 24-month was 76% (95% CI 42-92).

Best Overall Response

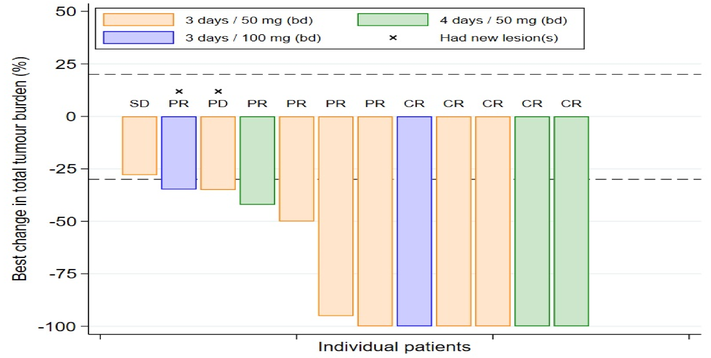


Figure 3: *Best change in total tumour burden from baseline measurements.*

Conclusion

Data suggest promising anti-tumour activity of olaparib in addition to cisplatin-based concurrent chemoradiotherapy for patients with high risk locally advanced HNSCC, but due to excess acute toxicity seen this combination will not be proposed for future investigative studies.

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Conflict of interest: First Author Martin Forster reports research grants from AstraZeneca, Boehringer Ingelheim, MSD and Merck and has conducted consulting and advisory services, speaking or writing engagements, or public presentations for Achilles, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Guardant Health, Merck, MSD, Nanobiotix, Novartis, Oxford VacMedix, Pfizer, PharmaMar, Roche and Takeda.
Third Author Teresa Guerrero Urbano reports conducting advisory services to TheraPanacea

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