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A multi-centre phase I trial of the PARP inhibitor olaparib in patients with relapsed chronic lymphocytic leukaemia, T-prolymphocytic leukaemia or mantle cell lymphoma.

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Relapsed chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL) and T-prolymphocytic leukaemia (T-PLL) remain incurable despite the availability of novel agents. Genetic alterations in the ATM-p53 DNA damage response (DDR) pathway represent an important mechanism of chemoresistance to conventional chemotherapeutic agents and also drive genomic instability.

The ataxia telangiectasia-mutated (ATM) protein plays a critical role in the DNA damage response to double strand breaks (DSBs) (Shiloh & Ziv 2013). Poly (ADP-ribose) polymerase (PARP) plays a central role in single strand break (SSB) repair and when the activity of this enzyme is inhibited unrepaired SSB lesions are converted into DSBs during DNA replication. Tumour cells deficient in homologous recombination repair (HRR) proteins, such as BRCA or ATM, may develop lethal amounts of DNA damage when treated with PARP inhibitors. We have demonstrated the efficacy of PARP inhibition on growth of ATM-defective CLL and MCL in vitro (Weston, et al 2010). Olaparib (Lynparza™) is an oral PARP inhibitor licensed as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (Kaufman, et al 2015; Ledermann, et al 2016; Tutt, et al 2010; Mateo et al, 2015). Olaparib is well tolerated and demonstrates significant activity in combination with chemotherapy (Bang, et al 2015) but myelosuppression may be a potentially limiting factor.

We report the results of a phase I conventional dose escalation trial using a cumulative 3+3 design to assess safety and maximum tolerated dose (MTD) of the PARP-inhibitor olaparib in patients with relapsed CLL, T-PLL or MCL unsuitable for further conventional treatment. The initial 3 cohorts (9 patients) received the original
capsule formulation of olaparib (Supplementary Figure 1). During the trial AstraZeneca developed a tablet formulation to improve drug loading, bioavailability and reduce the number of tablets. Consequently, a further 2 cohorts received the new tablet formulation (6 patients). A total of 15 patients with relapsed CLL (n=9), MCL (n=4) or T-PLL (n=2) were treated (Supplementary Table 1). The median age of patients was 69 years (range 53–77) and the median number of previous lines of therapy was 3 (range 1-7). The median duration of olaparib treatment was 71 days with an interquartile range of 26–93 days (Table I). Myelosuppression was the most common haematological grade 3-4 toxicity and was seen in 8 patients. Overall, both formulations of olaparib were generally well tolerated with the most common AEs being anaemia (66%), thrombocytopenia (53%), fatigue (53%), nausea (33%) and neutropenia (33%). Grade ≥3 AEs were seen in 10 patients (66%), (anaemia (33%), thrombocytopenia (33%), neutropenia (20%)). Of the 6 patients dosed at 200mg bd (capsule), 3 patients experienced grade ≥3 adverse events (AEs) and all 3 patients who were dosed at 400mg bd (capsule) experienced at least 1 grade ≥3 AE. For the tablet formulation of olaparib, 4 of the 6 patients dosed at 100mg bd experienced grade ≥3 AEs (Table II). As regards development of DLTs, 1 out of 6 patients receiving olaparib 200mg bd capsules developed a DLT (grade 4 thrombocytopenia). All three patients who received the higher dose of 400mg bd capsules developed DLTs which were possibly attributable to olaparib within 8 weeks of treatment initiation (Grade 3 maculo-papular rash, grade 4 anorexia/weight loss and grade 4 thrombocytopenia). The MTD for olaparib capsules was therefore defined as 200mg bd using the 3+3 dose-escalation design. The tablet formulation of olaparib was introduced at a treatment dose of 100mg bd and was administered to 6 patients. One patient from the initial cohort developed a fatal DLT which presented as an infective
episode, renal failure (acute kidney injury) and bleeding with a high International Normalised Ratio on warfarin. No DLT was experienced in the subsequent cohort but one patient was not evaluable due to early disease progression. Unfortunately, recruitment ceased after this cohort (mainly due to the availability of BTK inhibitor trials) and we were therefore unable to define an MTD for the tablet formulation. The tablet formulation dose of 300mg bd is now used in most studies for monotherapy in solid tumours (Mateo et al, 2016). The median OS from the start of treatment for all 15 patients (9 deaths in trial period) was 129 days (Supplementary Figure 2A). The median OS for patients treated with capsules (106 days) was not dissimilar to that for patients treated with tablets (129 days) (Supplementary Figure 2B).

Specific primers for targeted deep sequencing of ATM (exons 4-65), SF3B1 (exons 13-16), TP53 (exons 4-10), BIRC3 (exons 2-9), and MyD88 (exon 5) were designed with the D3 Assay Design web-based tool (https://www.fluidigm.com/assays). Twelve patients (80%) had evidence of a mutation in at least one of the 6 well-established CLL 'driver' genes: ATM, TP53, BIRC3, SF3B1, NOTCH1 and MyD88. (Supplementary Figure 3A). A further patient, TNO13, presented with monoallelic ATM loss due to an 11q deletion (Supplementary Figure 3A, Table I). SF3B1 gene alterations have similar functional consequences to that of ATM loss (Te Raa, et al 2015), justifying our strategy to observe ATM and SF3B1 mutant tumours as a single group of 9 patients (60%) (Supplementary Figure 3A, Table I). Duration of olaparib treatment ranged from 8 to 133 days with a median of 83 days in patients whose tumours harboured mutations within ATM or SF3B1 ('mutated') compared to 37.5 days in those lacking such alterations ('unmutated') (Supplementary Figure 3B). Although not significant, a longer median survival time of 192 days was also seen in patients with a 'mutated' genotype compared to 89 days in the 'unmutated' group.
(Supplementary Figure 3C). Therefore, aberrations in the ATM pathway may be associated with improved responses and overall survival with PARP inhibitor treatments even among heavily pre-treated and relapsed patients with CLL, MCL and T-PLL. Future studies would be needed to better define the optimal dosage in haematological tumours but this early data suggest that olaparib could have potential clinical utility in patients with a defective ATM pathway.
References:


Registration

The trial is registered with ISRCTN registry (ISRCTN34386131)

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Author Contributions: