487P I TOP-ART / PMO-1603: Randomized Phase 2 Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies

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Rationale

Genomic aberrations affecting the repair of DNA double-strand breaks (DSB) by homologous recombination (HR) are found in various cancers and result in sensitivity to inhibitors of the DNA repair enzyme PARP1. Trabectedin induces DNA DSB and PARP1 activation and may thus increase the effect of PARP inhibitors in HR-deficient cancers. Whole-exome/genome sequencing (WES/WGS) can identify mutations in DNA repair pathways and mutational signatures generated by these aberrations.

Methods

TOP-ART is a randomized phase II trial comparing trabectedin (1.1 g/sqm q3w) and olaparib (150 mg bid) (TrO) with treatment of physician's choice (PC) in adults with advanced/metastatic cancers with defective HR DNA repair ("BRCAness"), as determined by WES/WGS (*Fig. 1*). Molecular eligibility is determined based on a newly developed BRCAness score, incorporating measures of genomic instability, mutational signatures and somatic as well as germline alterations of DNA repair genes. Main exclusion criteria are hematologic/primary brain cancers, ECOG PS >1, platinum-refractory disease, prior PARP inhibitor treatment. Patients are randomized 1:1 to TrO (days 1/1-21) vs. PC, until PD. Cross-over upon PD is allowed. The primary endpoint is the DCR (CR, PR and SD [RECIST 1.1]) at 16 weeks.

Fig. 1: Treatment Schedule

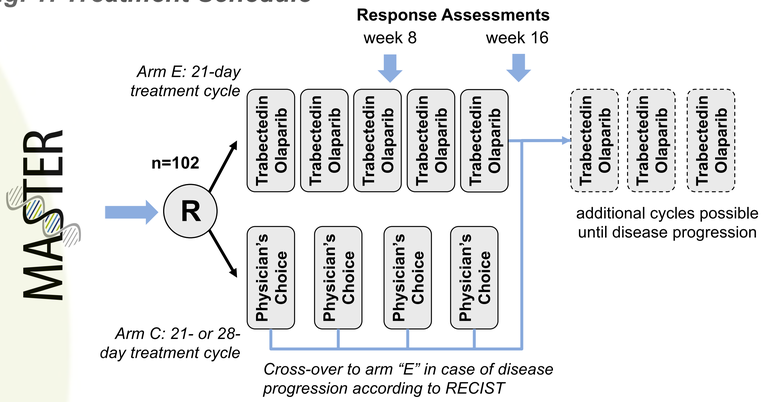
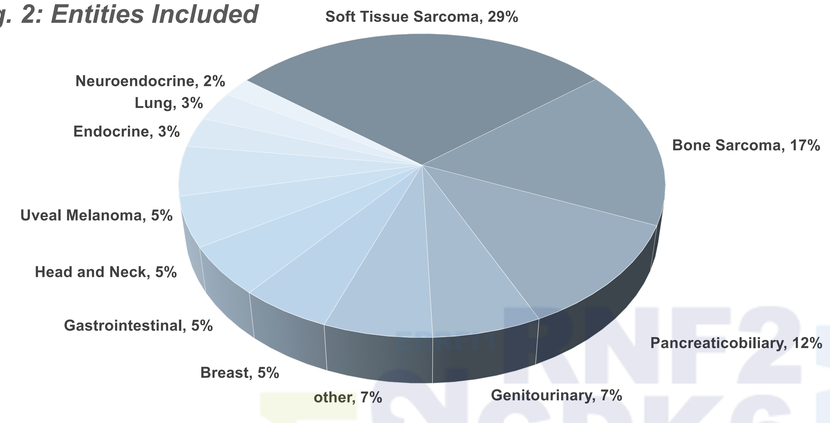


Fig. 2: Entities Included



Results

As of August 2022, 94 patients have been randomized (Arm E/TrO, n=46; Arm C/PC, n=48). Most frequent entities included were: soft tissue sarcoma, n=27; bone sarcoma, n=16; pancreaticobiliary cancers, n=11 (*Fig. 2*). Median age was 52 years (range, 21-70); 52% of patients were female. Prior treatments were balanced between both treatment arms: 13% and 17% (arm E and C, respectively) had prior surgery; 38% and 35% had prior radiotherapy. All patients had previous chemotherapy, with a median of 3 prior lines (range, 1-8 in arm E; range, 1-9 in arm C). In both arms, a median of 3 treatment cycles were applied; PD was the main cause of treatment termination. Cross-over from PC to TrO occurred in 58%. Main AEs associated with TrO were cytopenias, infections and gastrointestinal side effects, requiring dose reductions of trabectedin in more than 50%.

The planned interim analysis after assessment of the primary endpoint in the first 30 patients showed comparable DCR at week 16 in the TrO (38.5%) and PC (36.8%) arms while the DCR after cross-over to TrO was 55.6%. Based on a 51% conditional power to achieve superiority of TrO as initially planned, the study was continued.

Conclusion

The trial successfully passed the interim analysis and is expected to be completed in 2022.

Additional Information

Clinical Trial Identification: EudraCT 2017-001755-31, ClinicalTrials.gov Identifier NCT03127215

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Conflicts of Interest (Presenter): None

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