Overcoming PARP inhibitors drawbacks with a new generation PARP1 selective drug

Phase 1: A novel PARP1 selective inhibitor is effective in preclinical models of ovarian cancer

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BACKGROUND

Poly(ADP-ribose)polymerase inhibitors (PARPi) have demonstrated clinical effectiveness in a wide range of tumours, including ovarian cancer, and show greater efficacy in homologous recombination (HR) defective tumours.

They inhibit PARP1 and PARP2, as well as other members of the family, potentially responsible for adverse effects, mainly haematological and intestinal, which have limited their ability to be combined with chemotherapy.

AIM AND EXPERIMETAL DESIGN

Here, the antitumor activity of **PARP1i**, a novel inhibitor selective for PARP1 was investigated.

Patient-derived ovarian cancer xenografts (OC-PDXs) were transplanted subcutis or orthotopically (ip) to evaluate the dose response efficacy on tumour growth and dissemination.

PARP1i was administered orally (0.1-10 mg/Kg) for 8 weeks.

RESULT 1

In the BRCA wild-type **PDX84**, **PARP1i** did not affected tumour growth.

In the BRCA1 mutated **PDX106**, **PARP1i** induced tumour stabilization at doses higher than 0.1 mg/Kg.

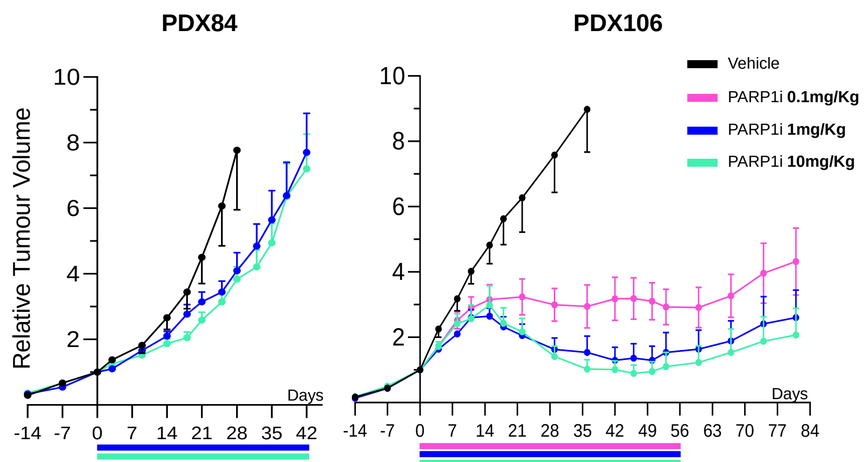


Figure 1
*Subcutaneously implanted tumour bearing mice were randomized at a tumour volume of approximately 170mm³ (PDX84) or 200mm³ (PDX106) and treated with **PARP1i** (0.1, 1 and 10 mg/kg) dosed orally once daily (5 days ON and 2 Off). Antitumor response was evaluated measuring the growing tumour. The minor (d) and the major (D) dimensions were recorded and the tumour volume calculated as [(D x d²)]/2. Relative tumour volume (RTV) was calculated for each mouse as [TV dayn/TV at day0] (day0=start treatment) and tumour growth curves were generated plotting each group mean RTV against time elapsed from treatment start.*

FUTURE PERSPECTIVES

i) Investigate **PARP1i** pharmacokinetics and pharmacodynamics to assess the target engagement, in accordance with the drug mechanism of action (MoA)

ii) Evaluate **PARP1i** in combination with the standard-of-care treatments for ovarian cancer

RESULT 2

Antitumor efficacy was also evident against two BRCA mutated yet resistant to Olaparib OC-PDXs.

A. In the subcutaneous model **PDX107**, **PARP1i** significantly slowed down tumour growth at 1 and 10 mg/Kg.

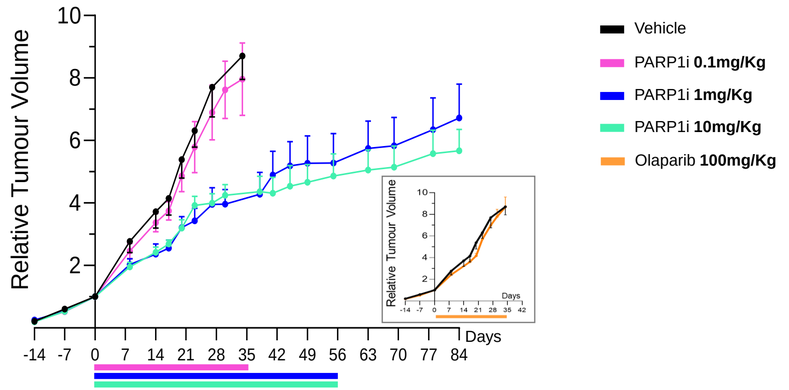
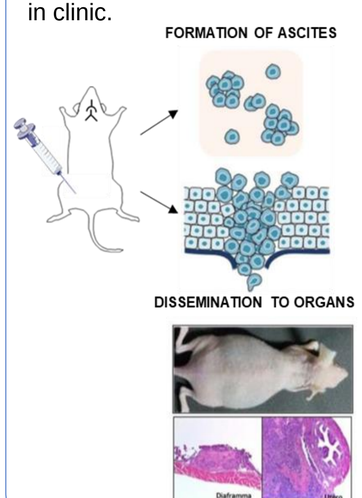
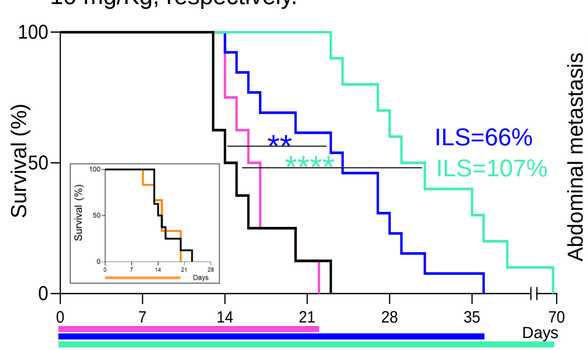


Figure 2.
*Subcutaneously implanted PDX107 tumour bearing mice were randomized at a tumour volume of approximately 200mm³ and treated with **PARP1i** (0.1, 1 and 10 mg/kg) dosed orally once daily (5 days ON and 2 Off). Antitumor response was evaluated as described in figure 1.*

Orthotopically implanted tumours recapitulate the process of metastatic spread after patients debulking surgery, reproducing the formation of ascites and the colonization of the peritoneal organs that could be observed in clinic.



B. In **PDX22**, **PARP1i** decelerated the development of abdominal disease at 1 and 10mg/Kg. This translated in an increment of lifespan of 66% and 107% for 1 and 10 mg/Kg, respectively.



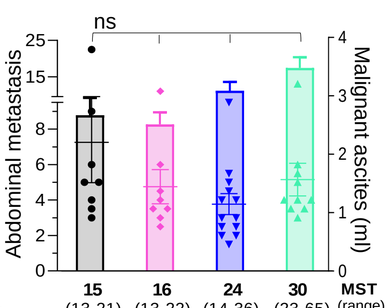


Figure 3.
*PDX22 tumour bearing mice were randomized and treated with **PARP1i** (0.1, 1 and 10 mg/kg) dosed orally once daily (5 days ON and 2 Off).*
According to animal welfare guidelines, disease-related deaths cannot be an ethical endpoint. Mice were monitored daily. The evidence for disease progression was the appearance of signs of distress, time at which mice were euthanized. The time-to-disease progression was recorded as survival time (ST; day 0 = start treatment) and Kaplan-Meier curves generated. For each treatment group, the median ST (MST) was determined and the increment of lifespan (ILS) calculated as 100 x [(treated mice MST- untreated mice MST)/untreated mice MST].
*Log Rank test ** p ≤ 0.01, **** p ≤ 0.001*

Figure 4.
Tumour burden was assessed at sacrifice. Malignant effusion was collected and the volume of cancer cells floating in the abdomen recorded.
Metastatic dissemination was assessed analyzing macroscopically representative organs and anatomical sites (ovary, liver, pancreas, diaphragm, omentum, and lymph nodes) and for each mouse the "metastatic score" calculated.
ANOVA and Tukey's post-test
ns: not significative