DARO-LIPID (ANZUP 2205): A randomised phase 2 study of sphingosine kinase inhibitor (opaganib) with darolutamide in poor prognostic metastatic castration resistant prostate cancer (mCRPC) based on a circulating lipid biomarker, PCPro

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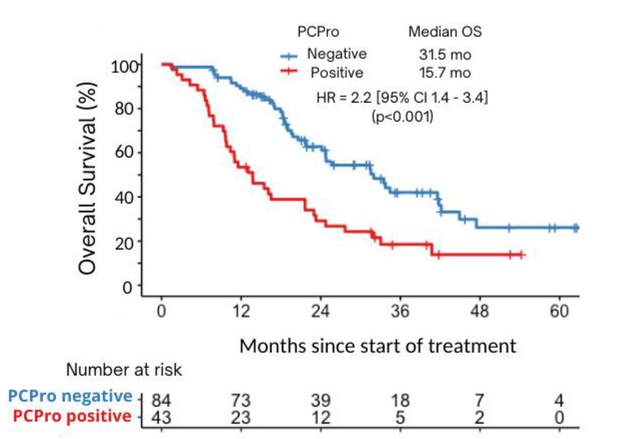
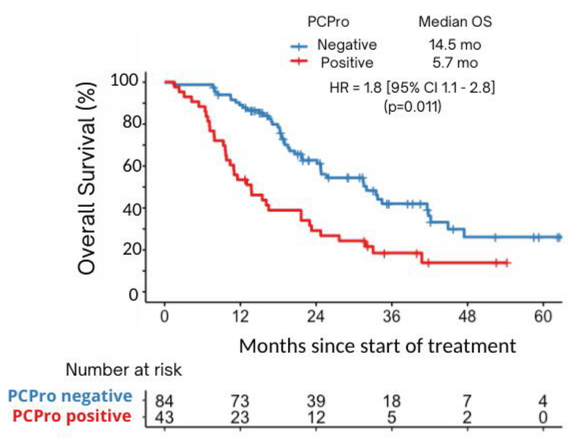
Background and Rationale

- Resistance to standard treatment for mCRPC is a problem
- Novel treatment strategies are needed
- Elevated circulating sphingolipids, including ceramides, are associated with shorter PFS and OS in mCRPC treated with docetaxel or ARPIs
- The NATA-compliant plasma lipid biomarker (PCPro), including ceramides, can prospectively identify people with mCRPC who have a poor prognosis and resistance to ARPIs.

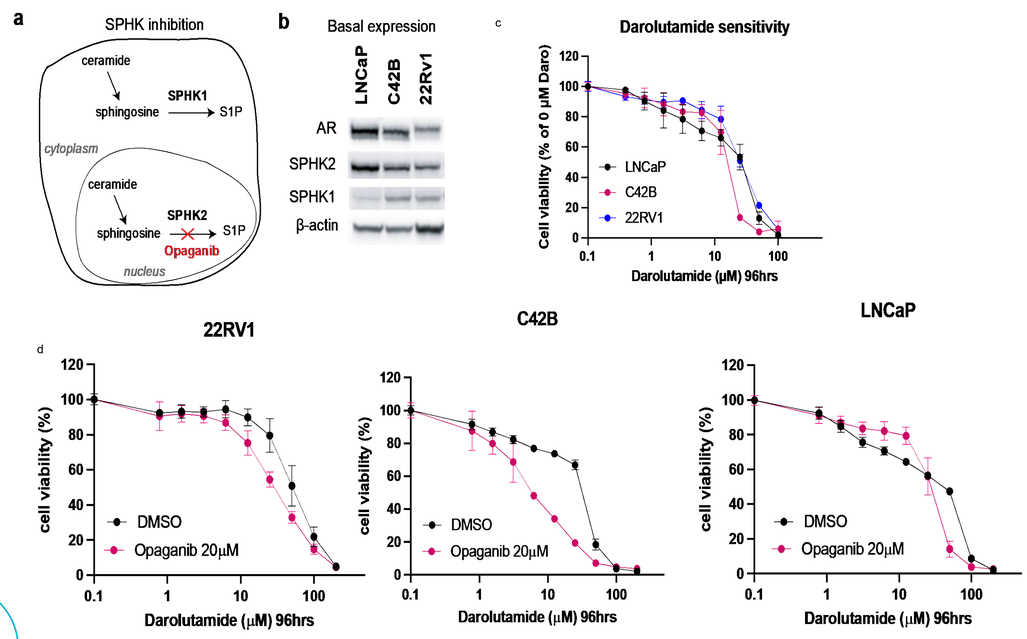
ARPI - Overall survival by PCPro



ARPI - rPFS by PCPro



- Ceramides are metabolised into sphingosine-1-phosphate, which promotes cancer growth, metastasis and drug resistance through regulation of cell proliferation, survival and immune processes.
- In PC cell line experiments, inhibition of ceramide-S1P axis, such as through the SPHK inhibitors like Opaganib, has been shown in vitro to suppress prostate growth, and overcome enzalutamide resistance.

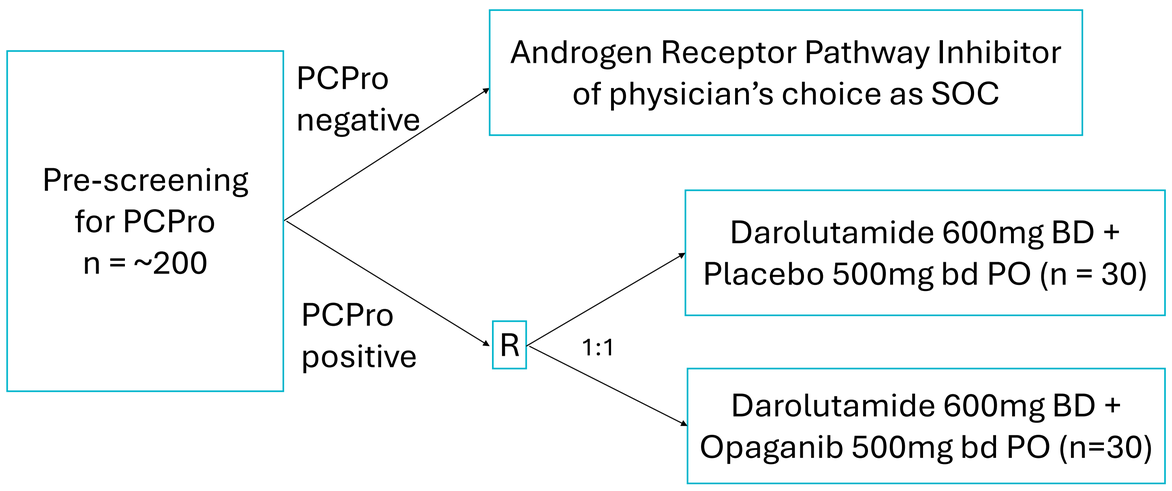


Study Aim

The DARO-LIPID study aims to evaluate whether the addition of opaganib to standard of care therapy with darolutamide improves rPFS in PCPro positive people with mCRPC receiving first line ARPI treatment.

- Opaganib is orally bioavailable and well-tolerated.

Study Schema



Key inclusion criteria

- mCRPC
- Disease progressing on current therapy
- No prior ARPI
- Docetaxel allowed in mHSPC
- Adequate liver, renal function

Key exclusion criteria

- Any prior ARPI
- Current opioid medications
- Known GI disease that could interfere with oral medication
- Significant neurological or psychological condition

Outcomes

Primary outcome

- 12-month radiographic progression free survival

Secondary outcomes

- PSA progression free-survival
- Overall survival
- Adverse events
- HR QOL
- Drug-drug interactions between opaganib and darolutamide
- Health economics
- Change in circulating lipid profile with opaganib treatment
- Exploratory biomarker studies

Opaganib Side Effects

- Nausea and vomiting
- Fatigue
- Insomnia
- Anxiety
- Gastrointestinal toxicity

Statistics

- A two-sided log rank test with 60 participants in total, split evenly between the control and treatment groups, will detect differences in survival distributions with 80% power at a 0.05 significance level
- Previous data show median rPFS for PCPro positive people treated with ARPI is 3.9 months, compared to median rPFS of 20 months for patients treated on the PREVAIL study
- The null hypothesis of this test is that there is no difference in survival curves between treatment arms, and the alternative hypothesis is the 12-mo rPFS will increase to 60% in the treatment group.

Progress

- The trial is currently recruiting at 2 sites (Chris O'Brien Lifehouse and Calvary Mater Newcastle).
- At least 10 additional sites in start up
- Three people screened to date, all with negative PC-Pro results

Trial queries please email:
darolipid.trial@anzup.org.au

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