PLATIPARP: A Phase 2 study of Induction Docetaxel and Carboplatin followed by maintenance rucaparib in treatment of patients with mCRPC with homologous recombination DNA repair deficiency

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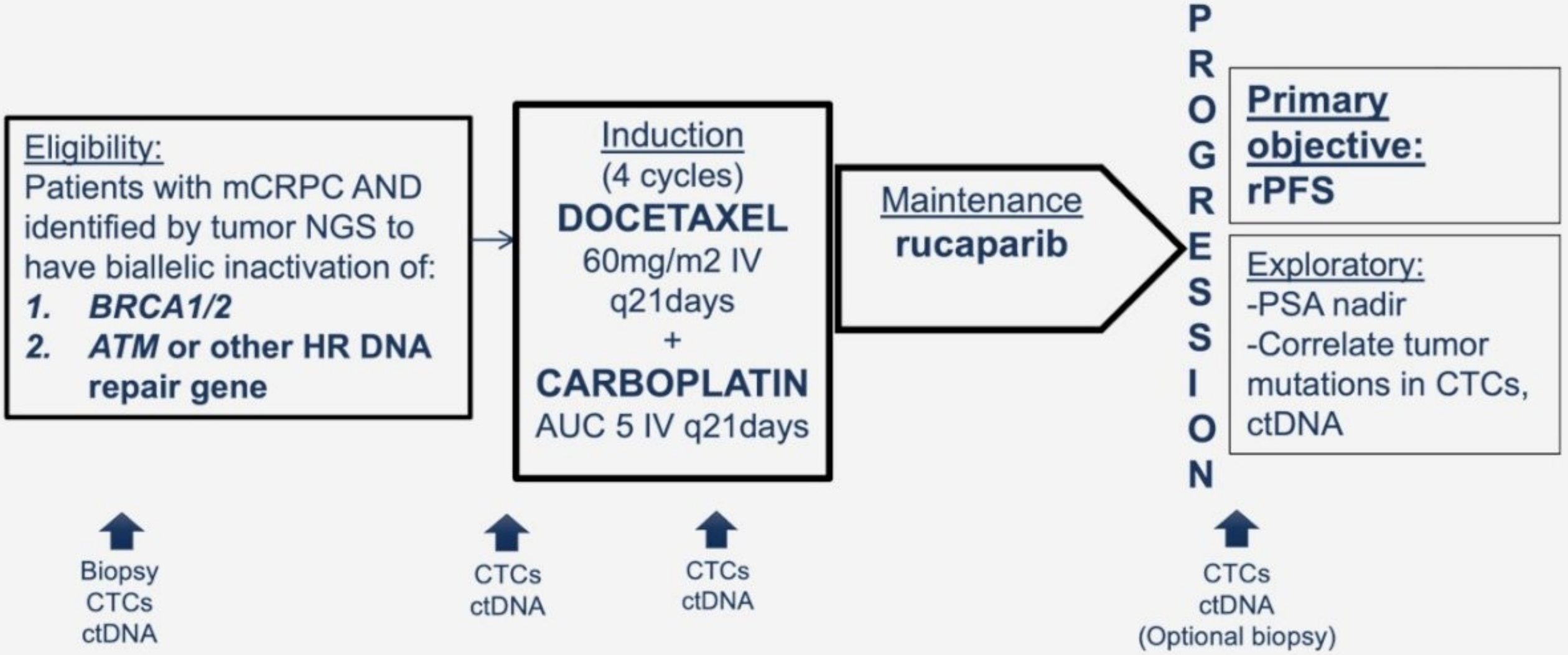
Background

- Genes of homologous recombination DNA repair (HRR) are **inactivated in ~25%of patients with mCRPC**
- Associated with sensitivity to DNA damage by platinum chemotherapy and PARP inhibitors (PARPi)→ as in Ovarian and Pancreatic cancers
- Synergestic efficacy, also resistance +/- cumulative dose-limiting toxicities seen
- Single-center phase 2 study : **whether induction chemotherapy (IC) with docetaxel and carboplatin followed by maintenance PARPi would provide prolonged disease control**

Method- Inclusion Criteria

- mCRPC tumors harboring a pathogenic alteration in an HR gene
- Have received prior taxane and/or androgen receptor pathway inhibitor (ARPI), but not prior PARPi

- Treatment - IC : 4 cycles of Docetaxel 60mg/m2 + Carboplatin AUC 5 IV q21 days, followed by PARPi rucaparib 600mg BID continuously as maintenance therapy until disease progression or unacceptable toxicity


Eligibility:
Patients with mCRPC AND identified by tumor NGS to have biallelic inactivation of:
1. BRCA1/2
2. ATM or other HR DNA repair gene
Induction
(4 cycles)
DOCETAXEL
60mg/m2 IV
q21days
+
CARBOPLATIN
AUC 5 IV q21days
Maintenance
rucaparib
PROGRESSION
Primary objective:
rPFS
Exploratory:
-PSA nadir
-Correlate tumor mutations in CTCs, ctDNA
Biopsy
CTCs
ctDNA
CTCs
ctDNA
CTCs
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CTCs
ctDNA
(Optional biopsy)

Objectives

- **Primary endpoint**
  - Clinical/ Radiographic Progression Free Survival (PFS) compared to a historical control of 9.1 months with PARPi alone(no prior platinum)
    - 20 patients provided ~90% power to determine whether this treatment lowered risk of progression with a hazard ratio of 0.5 (implying PFS of 18.2 months), based on a 1-sided 1-sample log-rank test

- **Secondary endpoints**
  - PSA_{50} response rate
  - Safety
  - Overall Survival

- Post-hoc subgroup analysis-
  - BRCA complex group (alterations in BRCA1, BRCA2, and PALB2) and
  - Refractory to IC (no PSA decline)

Results

18 patients enrolled between November 2018 and November 2021

Under-enrollment occurred - loss of manufacturer support for Rucaparib prior to study completion

11/18 (61%) of patients had ≥2 prior ARPI, and 9/18 (50%) had previously received docetaxel

HR genes included - ATM (7), BRCA1 (3), BRCA2 (8), PALB2 (1), FANCA (1) and CHD1/SPOP (1) with 3 tumors harboring two alterations

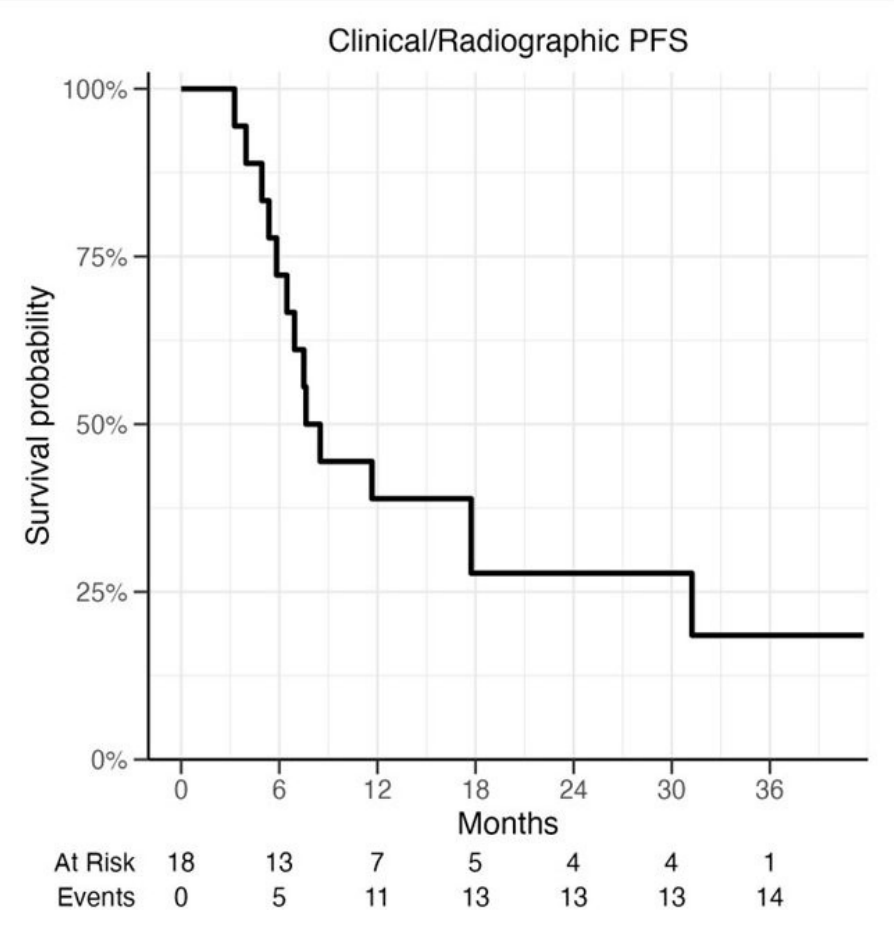
Results

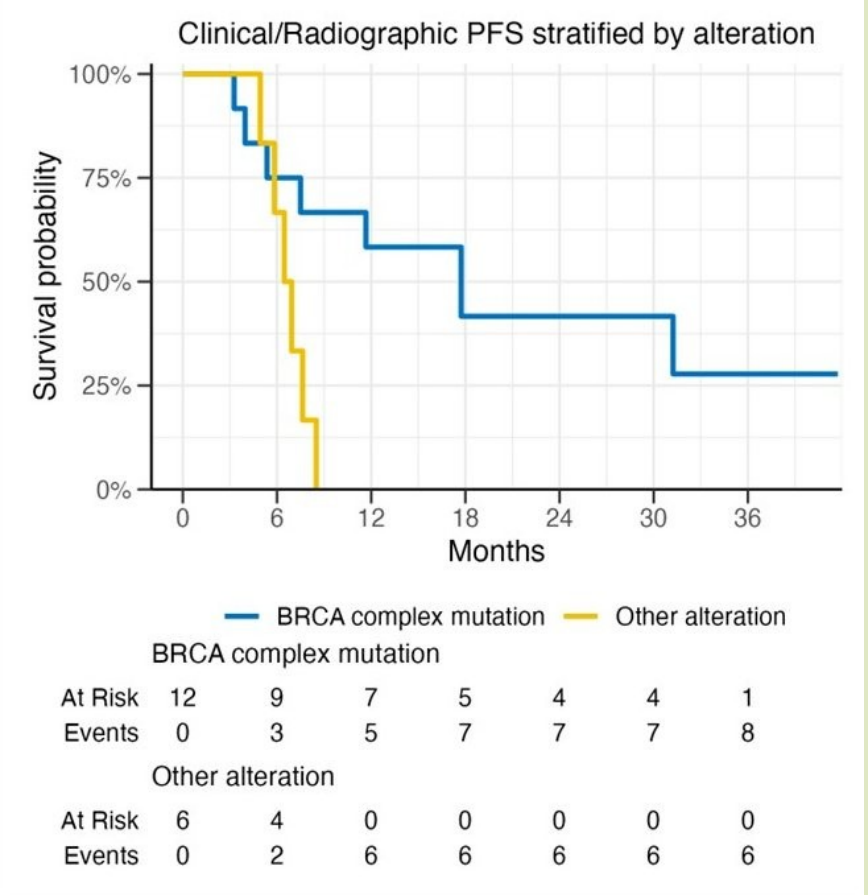
- Median follow up – 31.5 months

Group	PSA_{50}	PFS (months)	OS (months)
Overall	12/18 (67%)	8.1 (6.5- NR)	18 (12.8 – NR)
BRCA complex	8/12 (67%)	17.7 (7.5 – NR)	26.9 (14.0 – NR)
Other HR	4/6 (67%)	6.7 (5.8 – NR)	13.2 (10.9 – NR)
Refractory to IC	0/6 (0%) *(with subsequent rucaparib)*	5.9 (4.9 – NR)	11.2 (7.7 – NR)

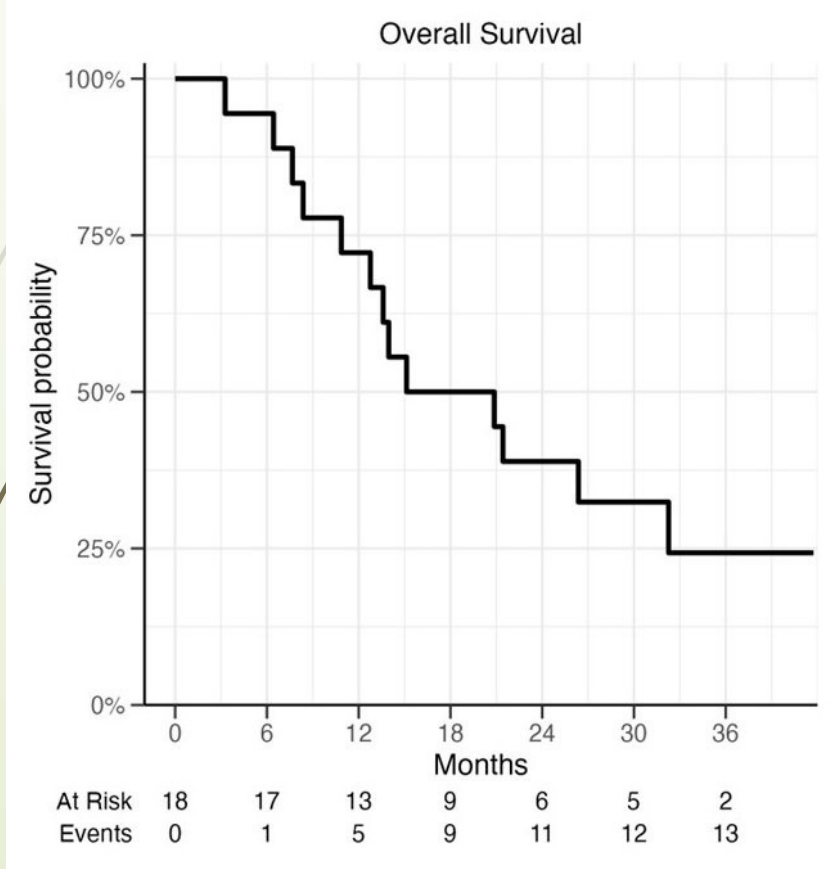
- 6/18 (33%) patients experienced grade ≥3 adverse events, including one with grade 4 thrombocytopenia

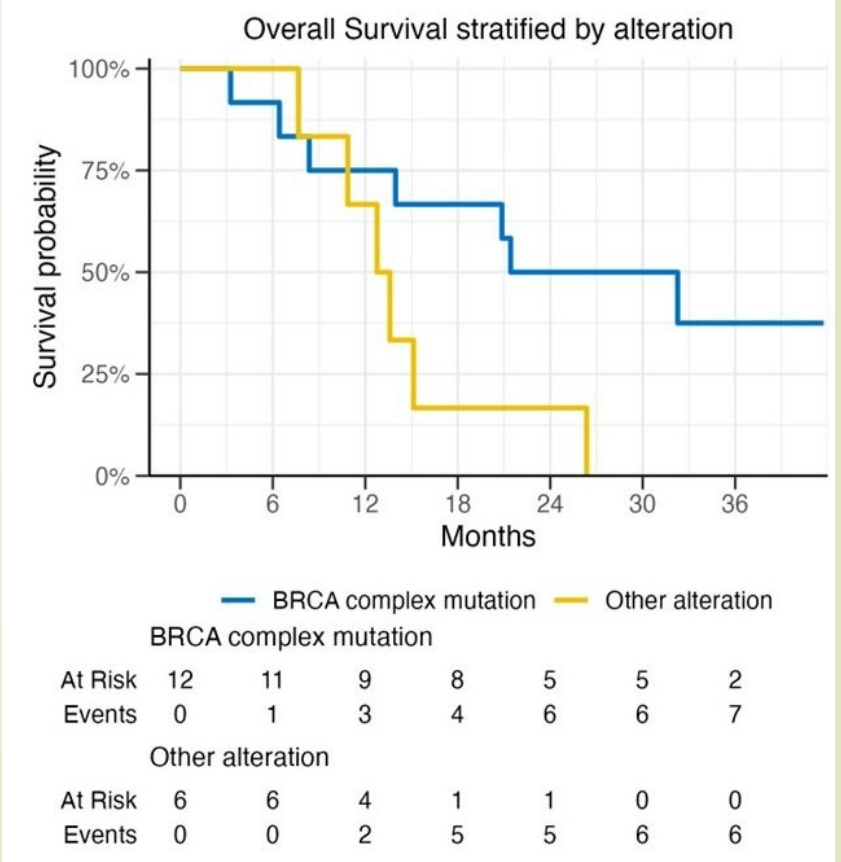
Primary endpoint





Secondary endpoint





Adverse events

Adverse Event	Grade 3	Grade 4
Anemia	2	0
Fatigue	2	0
Leukopenia	1	0
Ototoxicity	1	0
Thrombocytopenia	0	1

Conclusion

IC followed by maintenance rucaparib **did not** significantly increase PFS with HR alterations compared to historical control

Results more encouraging in BRCA complex group

IC refractory not rescued by subsequent PARPi → overlapping mechanisms of resistance when platinum is used prior to PARPi

Optimal use and sequencing of platinum with PARPi warrants further study with HRR alterations (especially in *BRCA* complex) → investigated in COBRA study (NCT04038502)

THANK YOU !