



P3.364: Phase II Trial of Olaparib in Patients with Mesothelioma

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Introduction

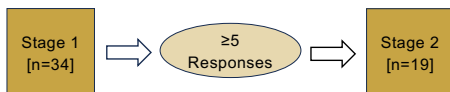
- Homologous recombination deficiency (HRD) is a phenotype defined by the inability of cells to properly repair double-stranded DNA breaks.
- Solid tumors, such as breast, prostate or pancreatic cancers, that are known to be HRD are susceptible to treatment with a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor.
- Mesothelioma has few effective treatment options once a patient has failed both immunotherapy and chemotherapy
- BRCA1-associated protein (BAP1) is the most commonly mutated gene in mesothelioma and is a key regulator of several cellular processes, including DNA repair.
- We hypothesized that mesothelioma patients with BAP1 loss and/or other germline or acquired HR pathway mutations have defective HR DNA repair which will also result in sensitivity to PARP inhibition.
- We therefore evaluated the PARP inhibitor olaparib in a phase II single-center trial in patients with relapsed, platinum-sensitive mesothelioma and germline or somatic HR deficits.

Methods

Key Inclusion Criteria

- HR pathway genetic abnormality** by BAP1 loss via immunohistochemistry and/or heterozygous germline and/or somatic mutation in HR pathway related gene
- Platinum-sensitive disease** defined as no progression ≥ 3 months following completion of chemotherapy
- Diagnosis of mesothelioma (any site or histology)
- Measurable disease per mRECIST 1.1 or RECIST 1.1
- Normal liver, renal and bone marrow function
- ECOG Performance status of 0 or 1

Schema



- Treatment:** Olaparib 300mg PO BID
- Imaging:** CT Scans q8 weeks for 24 weeks then q12 weeks thereafter
- Statistics:** The Simon minimax two-stage design required ≥ 5 responses in the first 34 patients to expand to a second stage for a total of 53 patients

Objectives

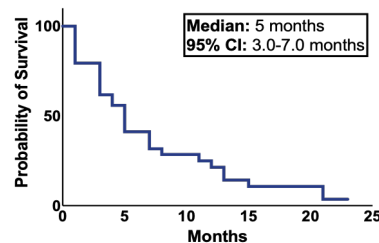
- Primary**
 - Determine the objective response rate (ORR) of olaparib in patients with platinum-sensitive mesothelioma harboring germline or acquired HR pathway mutations or BAP1 loss by IHC
- Secondary**
 - Overall survival (OS)
 - Progression free survival (PFS)
 - Toxicity of olaparib
- Exploratory**
 - Determine the range and mean Homologous Recombination Deficiency (HRD) scores and whether the HRD score positively correlates with olaparib response
 - Assess the safety of PARP inhibition on serious hematopoietic toxicities in patients with and without germline BAP1 mutations
 - Correlate ctDNA levels with olaparib response

Demographics

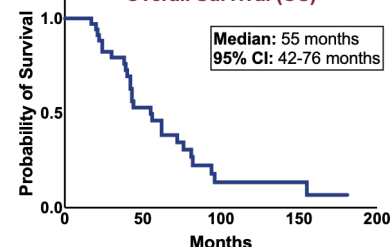
	[n=34]	%
Gender		
Male	17	50%
Median Age (range)	68.5 years (45-83)	
Race & Ethnicity		
White, Non-Hispanic	34	100%
Site of Disease		
Pleural	21	62%
Peritoneal	12	35%
Bicavitary	1	3%
Histology		
Epithelioid	33	97%
Baseline ECOG		
0	19	56%
1	15	44%
Prior Platinum		
Cisplatin	7	21%
Carboplatin	27	79%
Last Platinum to Olaparib		
0-1 year	10	29%
1-3 years	18	53%
≥ 3 years	6	18%
BAP1 IHC		
Lost	32	94%
BAP1 Somatic NGS		
Pathogenic Variant	29	79%
Germline Mutations		
Yes	9	26%
No	21	62%

Results

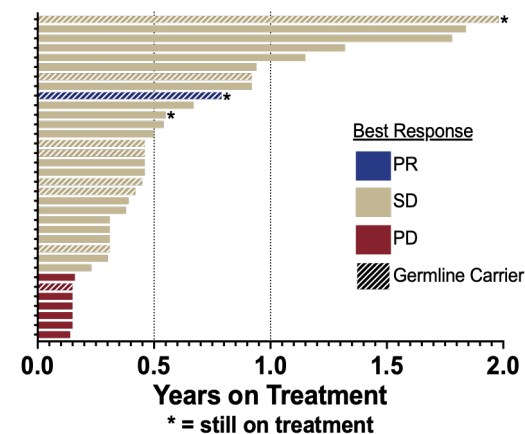
Progression Free Survival (PFS)



Overall Survival (OS)



Time on Treatment



Response Summary

Median Overall Survival	55 months
Median Progression Free Survival	5 months
Disease Control Rate (DCR)	79%
Objective Response Rate (ORR)	3% [1]*

*Response occurred in an individual with a BRCA2 germline mutation

Conclusions & Future Directions

- In this study of patients with platinum-sensitive mesothelioma who progressed on or after prior therapy, olaparib treatment failed to meet the pre-specified response endpoint to proceed to a second stage.
- Olaparib was safe, and well-tolerated
- The study achieved a disease control rate of 79%.
- These data suggest that BAP1 loss by IHC does not select for olaparib sensitivity in mesothelioma.
- Evaluation of correlative endpoints is ongoing.
- The partial response in the single case with a germline BRCA2 mutation mirrors olaparib response in other solid tumors and warrants confirmation in larger studies.

Treatment Related AEs

	Grade 1 or 2	Grade 3
Anemia	27 [79%]	5 [15%]
Nausea	10 [29%]	1 [3%]
Vomiting	4 [12%]	1 [3%]
Fatigue	4 [12%]	0 [0%]

*No Grade 4 or 5 TRAEs occurred

Germline Mutations

