Retrospective Analysis of Germline and Somatic Aberrations and Corresponding Outcomes Associated with the Use of Poly(ADP-ribose) Polymerase (PARP) Inhibitors

Crystal Wright, PharmD, BCPS
PGY-2 Oncology Pharmacy Resident
Avera Cancer Institute
Sioux Falls, SD

Disclosure

- The speaker has no actual or potential conflict of interest in relation to this presentation.
- I will be discussing off-label indications

Avera

Objective

- Describe patient populations which may benefit from poly(ADP-ribose) polymerase (PARP) inhibitor therapy based on germline and somatic aberrations.

Avera

PARP Inhibitors

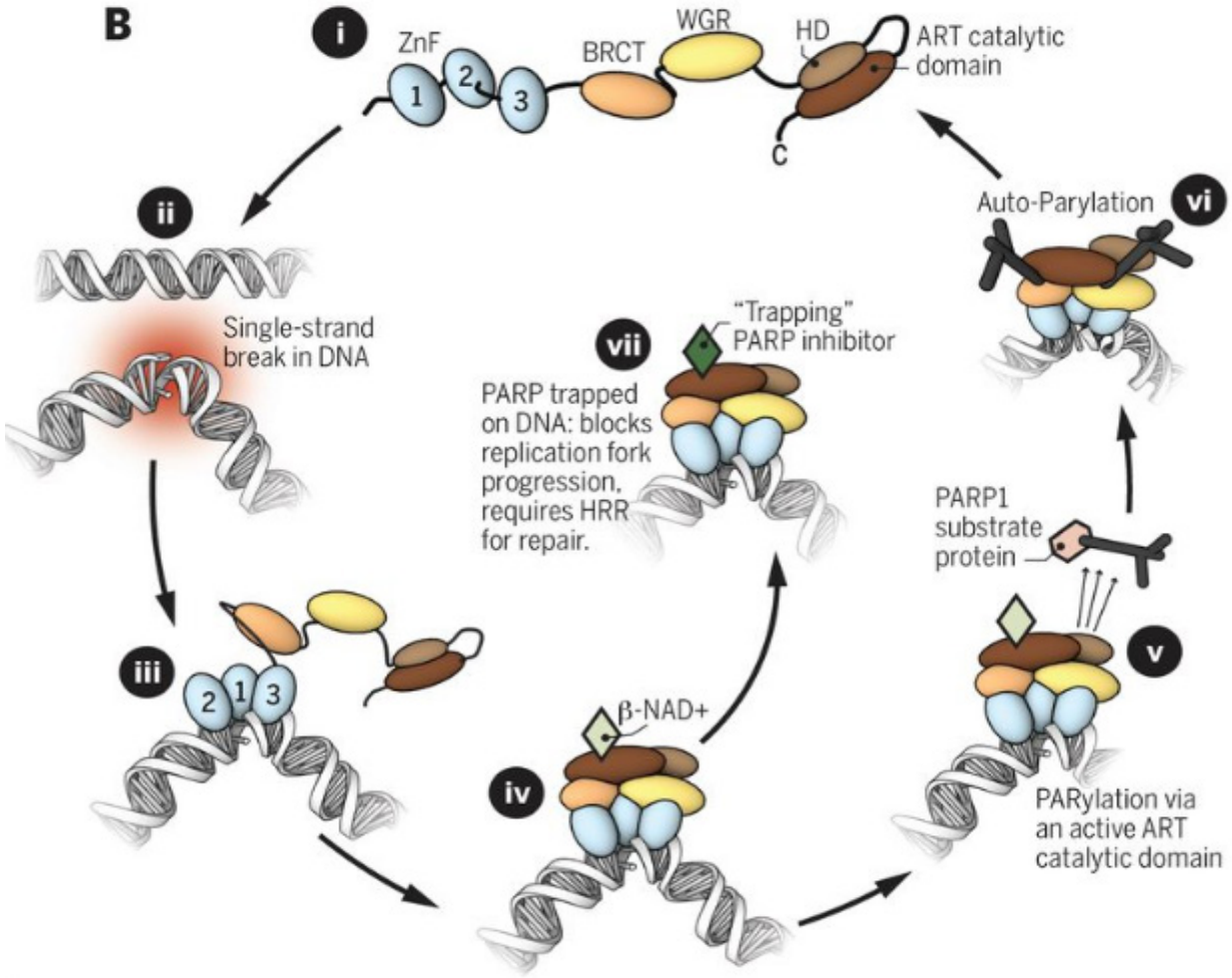
- Indicated for treatment and/or maintenance therapy for ovarian or breast cancer
  - Olaparib
  - Niraparib
  - Rucaparib
  - Talazoparib
  - Veliparib (investigational)
- Generally well-tolerated
  - Decreased blood counts
  - Nausea/vomiting/ diarrhea
  - Fatigue
  - Abdominal pain

Zejula [package insert] 2018
Talzenna [package insert] 2018
Lynparza [package insert] 2018
Rubraca [package insert] 2018

PARP: poly(ADP-ribose) polymerase

Avera

PARP Inhibitor Mechanism of Action



Adapted from: Lord Science 2017

PARP: poly(ADP-ribose) polymerase

Avera

PARP Inhibitors

Primary Cancer	Treatment Arms	Patient Cohorts	Outcome
Metastatic breast (n=302)	Olaparib vs standard therapy	gBRCA	PFS: 7.0 vs 4.2 months
Recurrent ovarian (n=533)	Niraparib vs placebo for maintenance	gBRCA	PFS: 21.0 vs 5.5 months
		HR deficiency	PFS: 12.9 vs 3.8 months
Recurrent ovarian (n=196)	Rucaparib vs placebo for maintenance	gBRCA	PFS: 16.6 vs 5.4 months
		HR deficiency	PFS: 13.6 vs 5.4 months
Advanced breast (n=431)	Talazoparib vs standard therapy	gBRCA	PFS: 8.6 vs 5.6 months
Ovarian, breast, pancreas, & prostate (n=298)	Olaparib (single arm)	gBRCA	ORR: 26.2% Stable disease: 42%

Robson NEJM 2017; Mirza NEJM 2016; Coleman Lancet 2017; Litton NEJM 2018; Kaufman J Clin Oncol 2014

PARP: poly(ADP-ribose) polymerase; PFS: progression-free survival; gBRCA: germline breast cancer susceptibility gene; HR: homologous repair; ORR: overall response rate

Rationale for Study

- PARP inhibitors have demonstrated efficacy in patients with germline BRCA mutations in several tumor types
- Preclinical data has suggested efficacy of PARP inhibitors in patients with genetic mutations in the DNA damage repair system
- Further clinical data are needed to assess efficacy of PARP inhibitors in patients with other DNA mutations which may confer PARP inhibitor sensitivity via homologous repair deficiency

Avera

PARP: poly(ADP-ribose) polymerase; BRCA: breast cancer susceptibility gene

Study Design

- Single-center, retrospective review

- Assessment of safety and efficacy of PARP inhibitors comparing:
  - Patients with known deleterious germline BRCA mutations
  - Patients with other known germline or somatic mutations

PARP: poly(ADP-ribose) polymerase; BRCA: breast cancer susceptibility gene

Avera

Study Criteria

Inclusion

- Adults age 18 or older
- Patients receiving at least one dose of a PARP inhibitor for a solid tumor malignancy at the Avera Cancer Institute at any time from January 1st, 2013 – June 30th, 2018

Exclusion

- Patients who had neither germline nor somatic tumor mutation testing results

PARP: poly(ADP-ribose) polymerase

Objectives

- Primary
  - Compare PFS in patients treated with a PARP inhibitor with germline BRCA mutations against those without germline BRCA mutations

PFS: progression-free survival; PARP: poly(ADP-ribose) polymerase;
BRCA: breast cancer susceptibility gene

Avera

Objectives

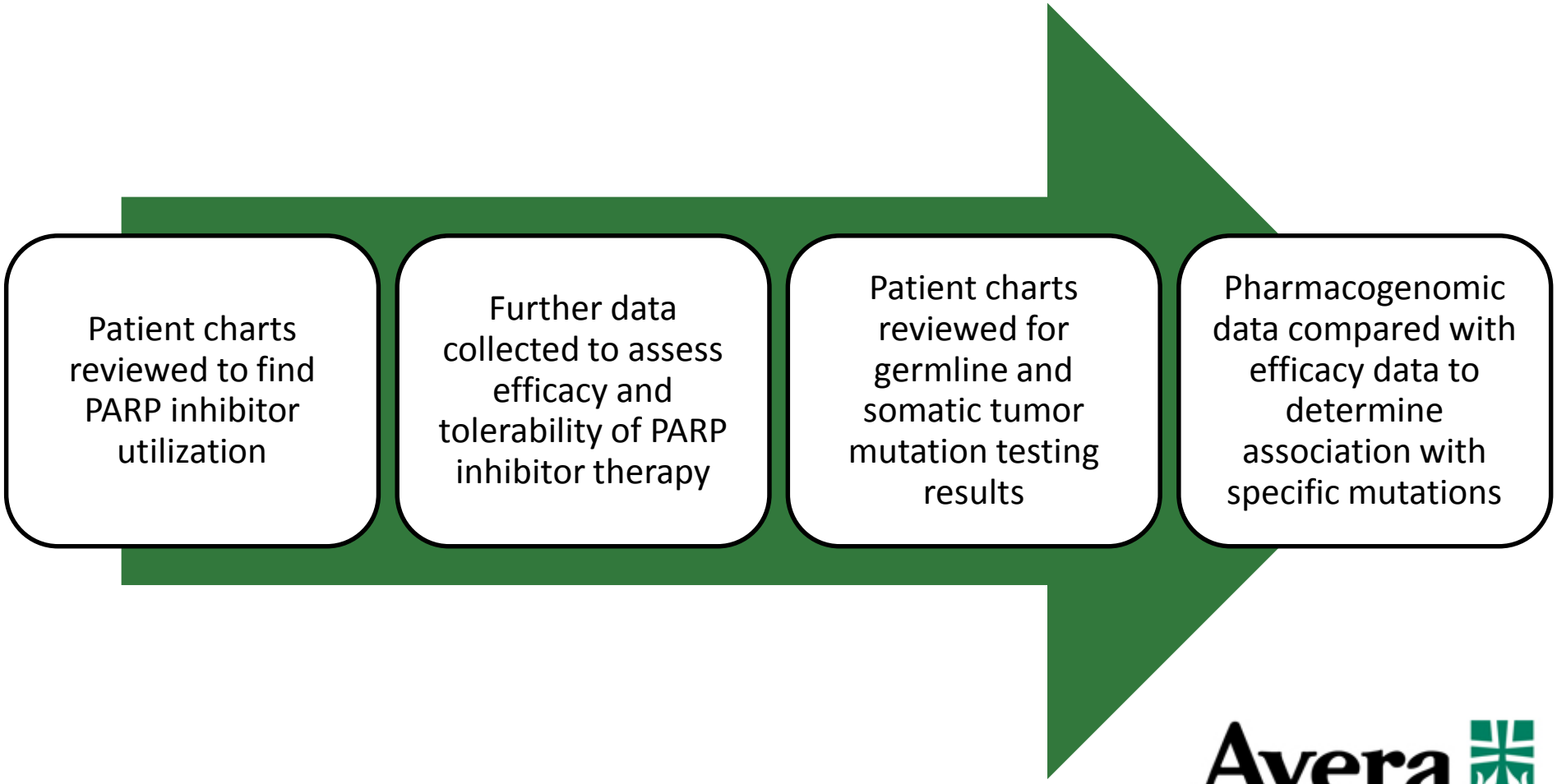
- Secondary
  - Compare PFS in patients treated with a PARP inhibitor with germline BRCA against those with other known genetic mutations
  - Compare best response between cohorts
  - Assess the rate of adverse effects which required discontinuation of PARP inhibitor therapy
  - Report the tolerability of PARP inhibitors as monotherapy and in combination with other agents

PFS: progression-free survival; PARP: poly(ADP-ribose) polymerase;
BRCA: breast cancer susceptibility gene

Avera

METHODS

Data Collection and Analysis



PARP: poly(ADP-ribose) polymerase

Methods

- Patient information collected
  - Diagnosis
  - PARP inhibitor received
  - Purpose of therapy
    - Treatment
    - Maintenance
  - Prescribed dose & maximum tolerated dose
  - Duration of therapy/progression data
  - Best response to therapy
  - Germline and somatic genetic mutations

PARP: poly(ADP-ribose) polymerase

Methods

- Germline testing
  - Multigene panel
  - Individual gene testing
- Somatic tumor testing
  - Biopsy
    - Samples may be taken from either original tumor specimen or metastatic site
    - FoundationOne®
  - Cell-free DNA test
    - FoundationOne ACT®, Guardant360®

Avera

Methods

- Mutations selected for analysis
  - ATM
  - BRCA1/2
  - CHEK2
  - PALB2
  - PTEN
  - BRIP1
  - CDH1
  - CDKN2A
  - MSH2
  - NF1
  - RAD50
  - ARID1A
  - ARID1B
- Excluded variants of unknown significance

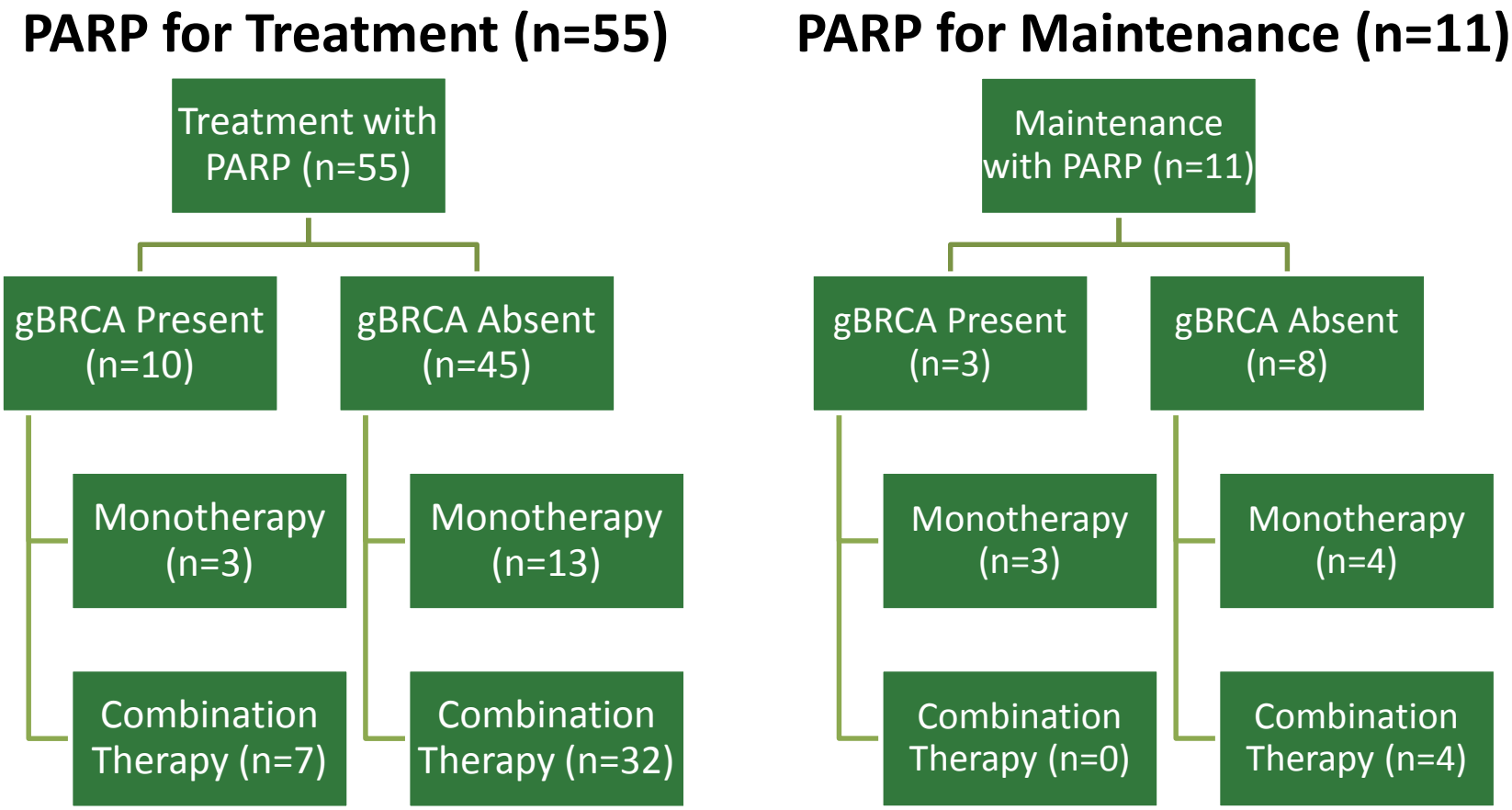
Konstantinopoulos Cancer Discov. 2015
Shimelis J Natl Cancer Inst. 2018

Avera

RESULTS

Avera

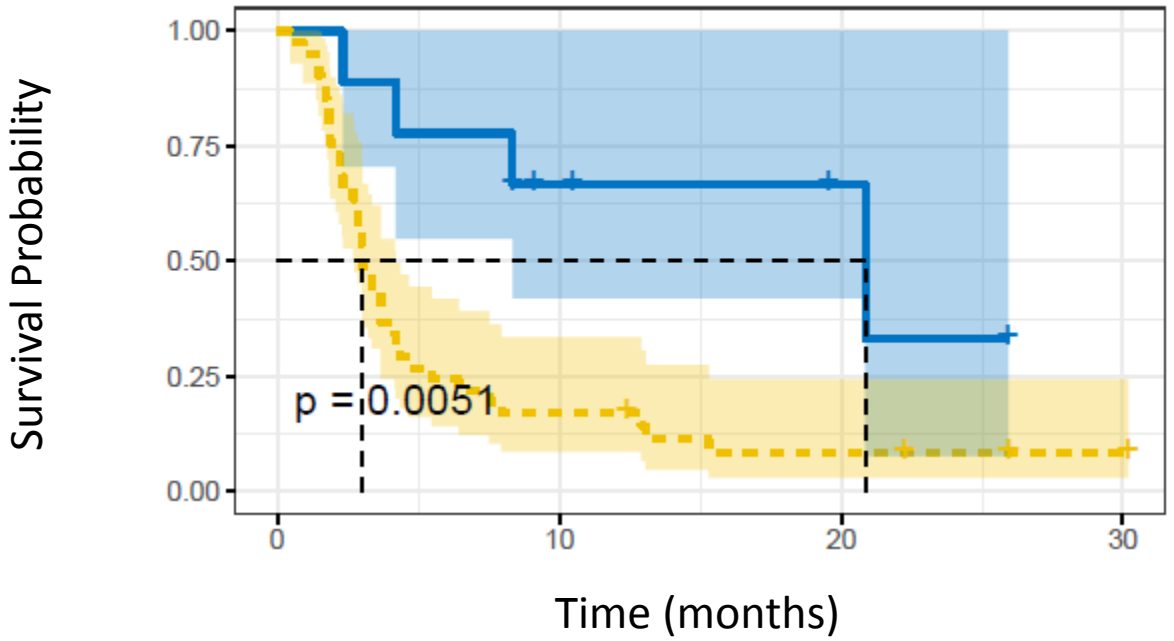
Patient Characteristics



PARP: poly(ADP-ribose) polymerase

Primary Outcome

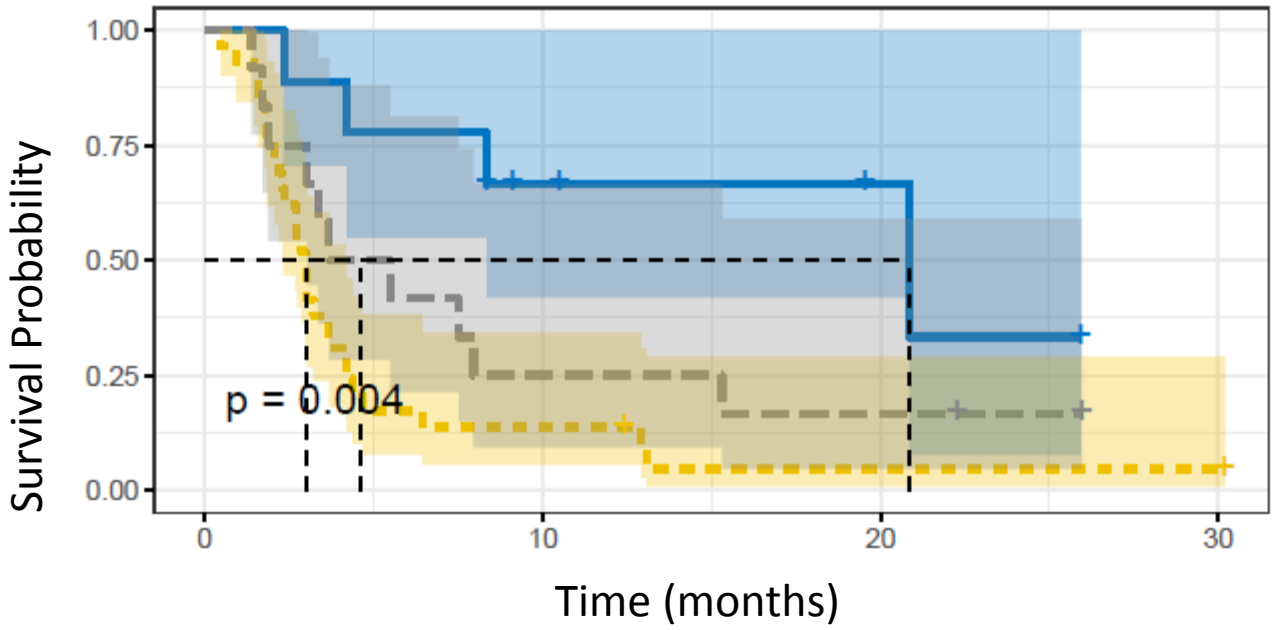
- Progression-free survival



Cohort	PFS (months)	95% CI
Germline BRCA Mutation (n=9)	20.9	8.34-NR
No Germline BRCA Mutation (n=41)	3.0	2.73-4.21

Primary Outcome

- Progression-free survival by BRCA mutation status



Cohort	PFS (months)	95% CI
Germline BRCA Mutation (n=9)	20.9	8.34-NR
Somatic BRCA Mutation (n=12)	4.6	3.02-NR
No BRCA Mutation (n=29)	3.0	2.33-4.17

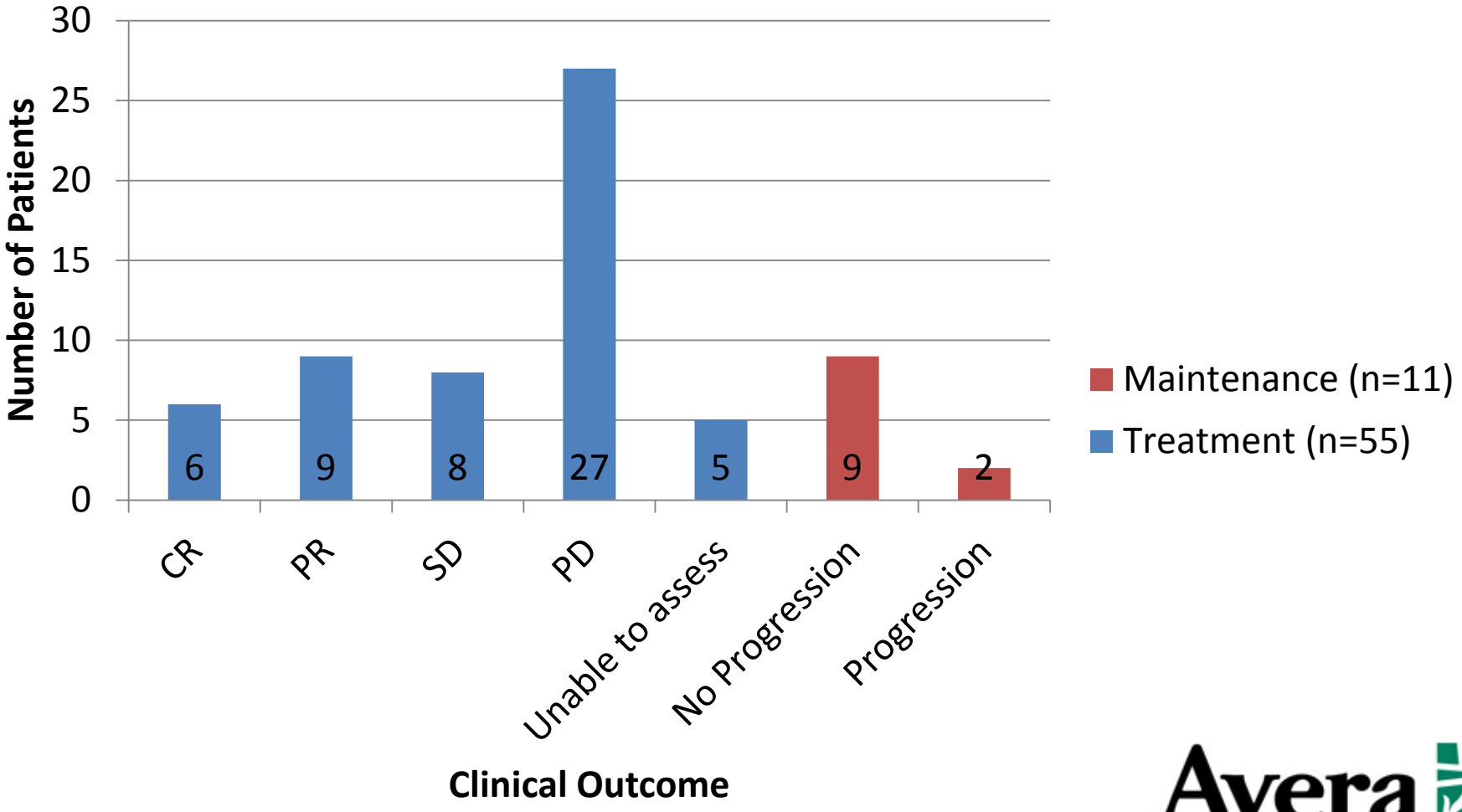
Secondary Outcome

- Progression-free survival: exploratory analyses

Cohort	PFS (months)	95% CI	P-value
BRCA1/BRCA2 Analysis			
Germline BRCA2 Mutation (n=6)	20.86	NA-NA	0.0094
Germline BRCA1 Mutation (n=3)	4.21	2.33-NA	
Somatic BRCA Mutation (n=12)	4.58	3.02-NA	
No Germline BRCA Mutation (n=41)	2.99	2.33-4.17	
Monotherapy versus Combination Therapy			
mBRCA, Combination therapy (n=13)	15.31	3.68-NA	0.0024
mBRCA, Monotherapy (n=8)	6.72	3.02-NA	
wtBRCA, Combination therapy (n=23)	2.99	2.69-4.37	
wtBRCA, Monotherapy (n=6)	1.81	1.58-NA	

mBRCA: mutant BRCA, either germline or somatic; wtBRCA: wild-type BRCA

Secondary Outcome: Best Response



CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

Avera

Secondary Outcomes

Early Discontinuation of Therapy				
Therapy	Concomitant Agents	Diagnosis	Duration of Therapy	Discontinuation Reason
Niraparib 200 mg daily	None	IIIC recurrent ovarian	2 weeks	Thrombocytopenia
Olaparib 200 mg capsule BID given days 1-10 of a 21-day cycle	Paclitaxel 80 mg/m^2 weekly & carboplatin AUC 5 every 3 weeks	IA triple-negative invasive ductal carcinoma	3 days	Rash which resolved after drug discontinuation
Olaparib 200 mg tablet BID given days 2-8 of a 21-day cycle	Paclitaxel 80 mg/m^2 & carboplatin AUC 1.5 weekly	IA triple-negative invasive ductal carcinoma	8 weeks	Thrombocytopenia, neutropenia
Niraparib 300 mg daily	None	IIIC recurrent ovarian	3 days	Malaise
Niraparib 100 mg daily	Nab-paclitaxel 62.5 mg/m^2 & gemcitabine 500 mg/m^2 weekly	IV pancreatic	39.5 weeks	Fatigue

Secondary Outcomes

- Average dose intensity
  - Monotherapy: Percentage of FDA-recommended dose which was tolerated by patients
  - Combination therapy: Percentage of prescribed dose which was tolerated by patients

	Monotherapy	Combination Therapy	Total
Olaparib (n=40)	87%	94%	92%
Niraparib (n=22)	81%	86%	84%
Rucaparib (n=4)	83%	N/A	83%

Discussion

Strengths

- Provides an assessment of clinical outcomes for patients with genomic mutations other than germline BRCA
- Assessed tolerability of PARP inhibitors in a clinical setting

Limitations

- Insufficient patient population to assess outcomes for individual PARP inhibitors
- Retrospective data
- Single-center analysis

PARP: poly(ADP-ribose) polymerase

Avera

Discussion

- Progression-free survival (PFS)
  - Patients with germline BRCA mutations had a significantly longer PFS
  - Patients with somatic BRCA mutations had longer PFS than patients without BRCA mutations
  - Analyses of other mutations of interest were performed, but were not found to be statistically significant
- Secondary outcomes
  - Patients with germline BRCA2 mutations may receive more benefit from PARP inhibitors than other groups
    - Limitations: small sample size and patient selection
  - Patients treated with PARP inhibitors had an overall response rate of 27%
  - Prescribed doses of PARP inhibitors were well tolerated as monotherapy and in combination

PARP: poly(ADP-ribose) polymerase; BRCA: breast cancer susceptibility gene; PFS: progression-free survival

Avera

Conclusions

- In this cohort of 66 patients treated with PARP inhibitors, patients with germline BRCA mutations had a significantly longer PFS
- Patients with germline BRCA2 mutations had improved PFS over those with other BRCA mutations, though external validity for this data is limited
- PARP inhibitor therapy was generally well tolerated

PARP: poly(ADP-ribose) polymerase; PFS: progression-free survival

Future Directions

- An expanded review is planned which will include patients without known genetic mutations
- The expanded review will also include patients who received talazoparib or veliparib
- Further studies with larger cohorts are needed to assess other genetic mutations which may be associated with improved outcomes

Avera

References

- Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390(10106):1949-61.
- Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. N Engl J Med 2009;361:123-34.
- Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib Monotherapy in Patients with Advanced Cancer and a Germline BRCA1/2 Mutation. J Clin Oncol 2014;33:244-50.
- Konstantiopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: Exploiting the fundamental vulnerability of ovarian cancer. Cancer Discov. 2015;5(11):1137-54.
- Kuchenbaecker KB , Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017 Jun 20;317(23):2402-2416.
- Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. New Engl J Med 2018;379(8):753-763.
- Lord CJ, Ashworth A. PARP Inhibitors: The First Synthetic Lethal Targeted Therapy. Science 2017; 355(6330):1152-8.

Avera

References

- Lynparza® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2018
- McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, et al. Deficiency in the Repair of DNA Damage by Homologous Recombination and Sensitivity to Poly(ADP-Ribose) Polymerase Inhibition. Cancer Res 2006;66(16):8109-15.
- Minchom A, Aversa C, Lopez J. Dancing with the DNA damage response: next-generation anti-cancer therapeutic strategies. Ther Adv Med Oncol 2018;10:1-18.
- Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016;375:2154-64.
- Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-33.
- Rubraca® [package insert]. Boulder, CO; Clovis Oncology, Inc.; 2018
- Shimelis H, LaDuca H, Hu C, Hart SN, Na J, Thomas A, et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. J Natl Cancer Inst 2018;110(8):855-62.
- Talzenna® [package insert]. New York, NY; Pfizer, Inc.; 2018
- Zejula® [package insert]. Waltham, MA; Tesaro, Inc.; 2018

Avera

Retrospective Analysis of Germline and Somatic Aberrations and Corresponding Outcomes Associated with the Use of Poly(ADP-ribose) Polymerase (PARP) Inhibitors

Crystal Wright, PharmD, BCPS
PGY-2 Oncology Pharmacy Resident
Avera Cancer Institute
Sioux Falls, SD