NDA 208558 s10: Olaparib

FDA Opening Remarks

Oncologic Drugs Advisory Committee Meeting

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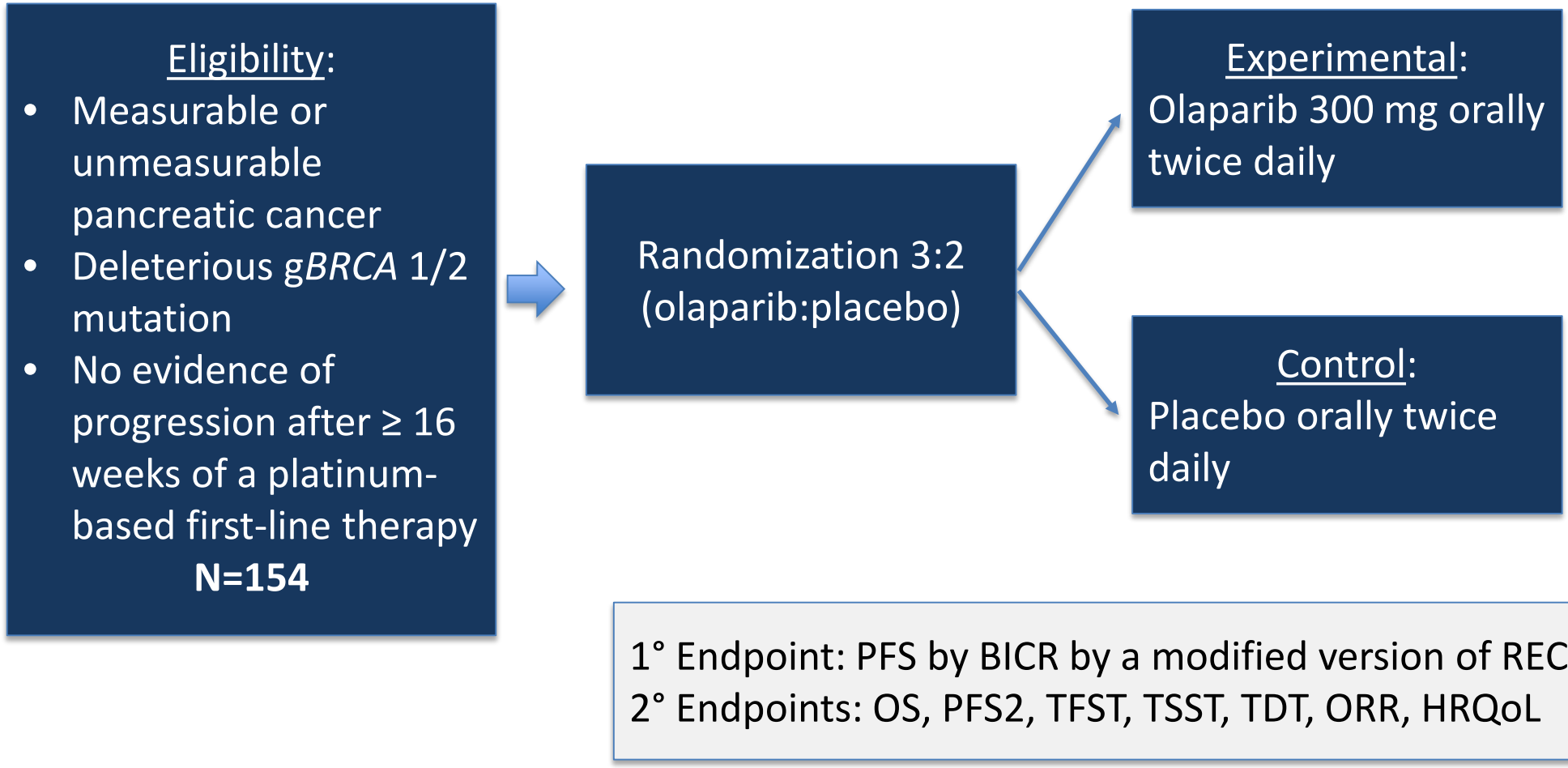
Proposed Indication

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Design of POLO[1]



1° Endpoint: PFS by BICR by a modified version of RECIST 1.1[2]
2° Endpoints: OS, PFS2, TFST, TSST, TDT, ORR, HRQoL

[1] Acronym for "Pancreas Cancer Olaparib Ongoing" trial
[2] RECIST 1.1 was modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline.
PFS = progression free survival; OS = overall survival; PFS2 = time to second progression; TFST = time to first subsequent therapy or death; TSST = time to second subsequent therapy or death; TDT = time to study treatment discontinuation or death; ORR = overall response rate; HRQoL = health-related quality of life

Primary Efficacy Results (PFS) in POLO

Progression Free Survival	Olaparib N = 92	Placebo N = 62
Number of Events n (%)	60 (65)	44 (71)
Progression	55	44
Death	5	0
Median PFS in months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio (95% CI)	0.53 (0.35, 0.81)	
p-value (log-rank)	0.0035	

Interim Analysis of OS in POLO

	Olaparib N=92	Placebo N=62
Number of Events, n (%)	41 (45)	30 (48)
Median OS in Months (95% CI)	18.9 (14.9, 26.2)	18.1 (12.6, 26.1)
Hazard Ratio (95% CI)	0.91 (0.57, 1.45)	
p-value (log-rank)	0.683*	

**Not significant based on 67% information using O'Brien-Fleming method*

Olaparib Safety Profile

- In general, consistent with known toxicities of olaparib
- Compared to placebo, higher incidence of fatigue, gastrointestinal toxicities, anemia, decreased appetite, and rash
- Increased incidence of serious adverse events (24% vs. 15%)

Efficacy Endpoints in Pancreatic Cancer

- Overall survival gold standard for demonstrating clinical benefit in pancreatic cancer
  - Direct measure of clinical benefit
  - Limitations to assessment of progression-free survival in pancreatic cancer

- Prior approvals in pancreatic cancer have been supported by demonstrated improvement in OS

Issues

1. Uncertainty about the magnitude of improvement in PFS conferred by olaparib
   - 95% CI for the point estimate of the PFS HR is (0.35, 0.81)
   - Imaging challenges

Issues

2. Limitations of POLO trial

   - Small sample size
   - Likelihood of demonstrating OS improvement is low based on interim results and no additional trials are planned
   - Improvement in patient quality of life not demonstrated

Risk:Benefit Assessment Considerations

- Unmet medical need
- Demonstrated effectiveness of olaparib for gBRCAm ovarian and breast cancer
- Toxicities of olaparib
- Uncertainty regarding benefit of olaparib for the proposed indication
  - Magnitude of PFS improvement
  - POLO trial limitations (e.g., lack of demonstrated improvement in OS or other measure of direct clinical benefit)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sNDA 208558 s10: Olaparib
FDA Presentation

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Office of Oncologic Diseases

December 17, 2019

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- Richard Pazdur, M.D., Director, (Acting) OOD

Outline

- Overview of Pancreas Cancer Olaparib Ongoing (POLO) trial results
- Issues identified during FDA review
- Summary
- Question for ODAC

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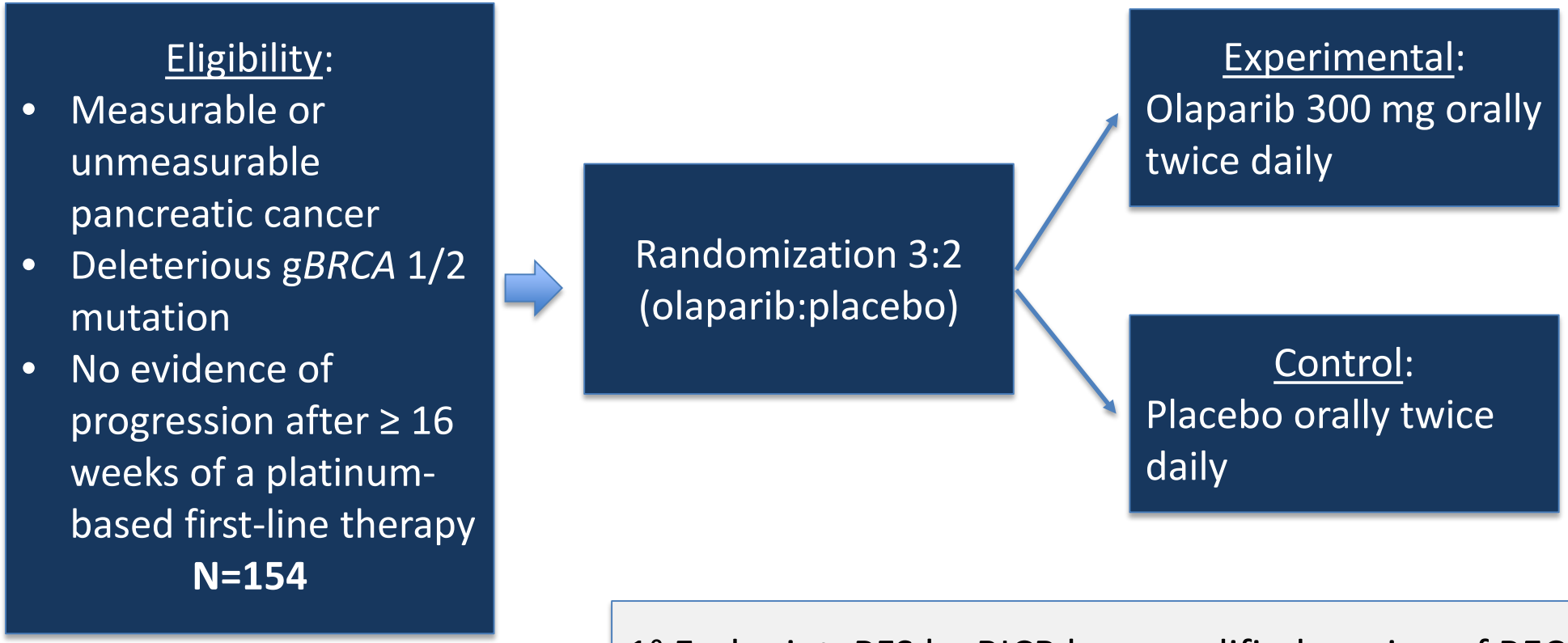
Design of POLO



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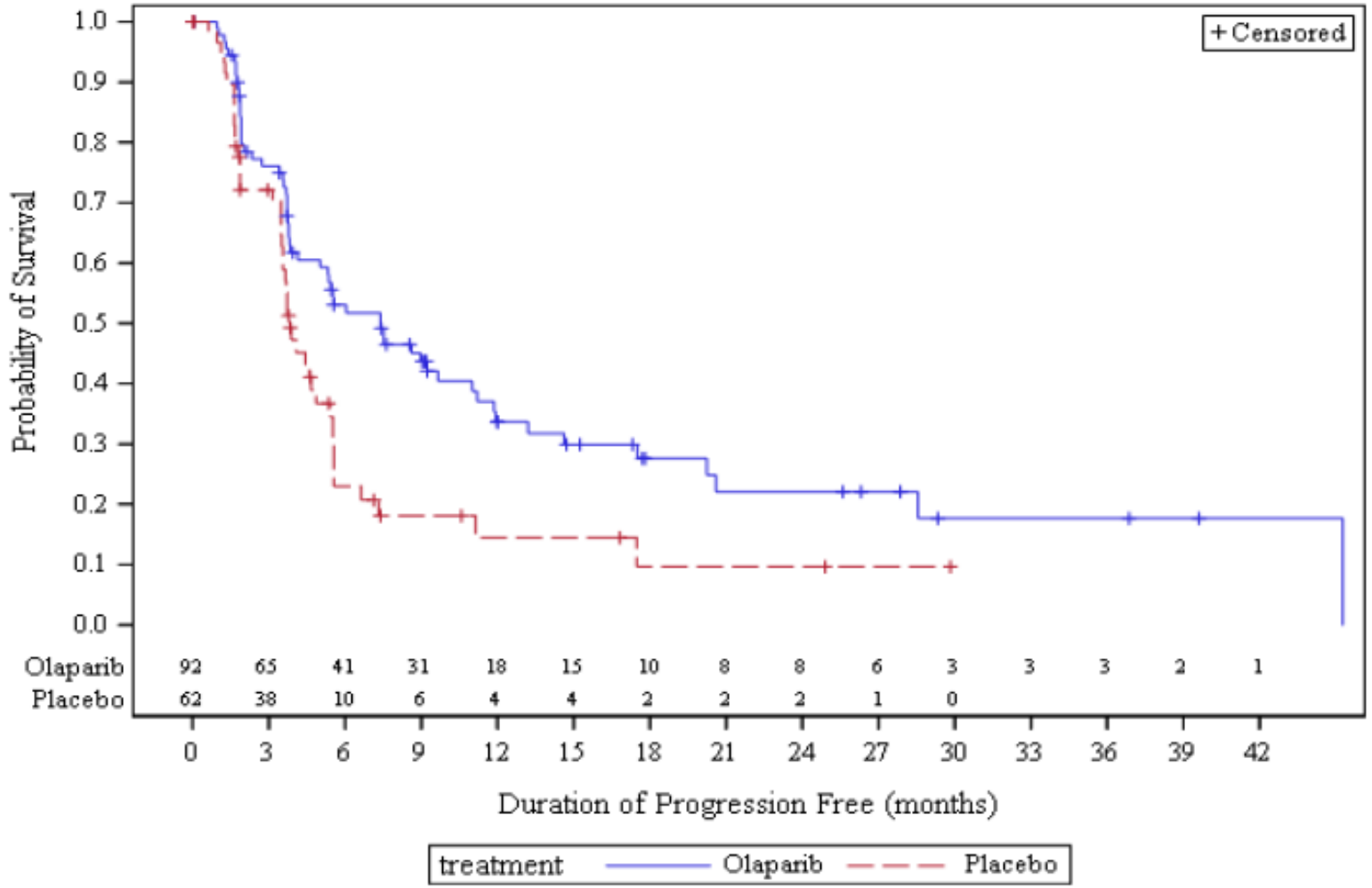
CI = confidence interval

Kaplan-Meier Curves for PFS (by Blinded Independent Central Review)



Treatment Emergent Adverse Events (POLO)

	Olaparib N=91		Placebo N=60	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General Disorders and Administration Site Conditions				
Fatigue	45%	4.4%	27%	0
Gastrointestinal Disorders				
Nausea	45%	0	23%	1.7%
Diarrhea	29%	0	15%	0
Constipation	23%	0	10%	0
Vomiting	20%	1.1%	15%	1.7%
Blood and Lymphatic System Disorders				
Anemia	27%	11%	17%	3.3%
Metabolism and Nutrition Disorders				
Decreased appetite	25%	3.3%	7%	0
Skin and Subcutaneous Tissue Disorders				
Rash	12%	0	3.3%	0

Serious Adverse Events (SAEs) in POLO

	Olaparib N=91	Placebo N=60
Patients with any SAE	24%	15%
Gastrointestinal disorders	11%	5%
Abdominal pain	3.3%	1.7%
Vomiting	1.1%	5%
Blood and lymphatic system disorders	7%	1.7%
Anemia	7%	0

Outline

- Overview of POLO results
- Issues identified during FDA review
- Summary
- Discussion topic and question for ODAC

Issues

- #1: Uncertainty about the magnitude of improvement in PFS conferred by olaparib
  - 95% CI for the point estimate of the PFS HR is (0.35, 0.81)
  - Imaging challenges
- #2: POLO trial limitations
  - Small sample size: randomization may not guarantee balance in unknown prognostics factors
  - Lack of evidence of clinical benefit on key secondary endpoints

Issue #1

Uncertainty about the magnitude of PFS improvement

PFS as an endpoint

Advantages	Limitations
• Allows for early assessment of response	• Imaging-based endpoint
• Not confounded by subsequent therapy	• Improvement may not reflect a clinical benefit to patients, especially when small in magnitude

Primary PFS Analysis in POLO

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Assessment of Tumor-based Endpoints in Pancreatic Cancer

- 2018 FDA Guidance on Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics[1]:
  - Accuracy in measuring tumors can differ across tumor types
  - Can be imprecise in locations where there is a lack of demarcated margins
- In one meta-analysis, the authors concluded that computed tomography (CT) scanning has only a moderate diagnostic accuracy in the detection of recurrent disease.[2]

1. https://www.fda.gov/media/71195/download; 2. Daamen LA, Groot VP, Goense L, et al. The diagnostic performance of CT versus FDG PET-CT for the detection of recurrent pancreatic cancer: a systematic review and meta-analysis. Eur J Radiol, 2018; 106:128-136.

Overall Response Rate (ORR) in POLO (BICR)

	Olaparib N=92	Placebo N=62
Overall Response Rate* (95% CI) (%)	19.6 (12.0, 29.1)	9.7 (3.6, 19.9)
Complete Responders (CR) n (%)	2 (2.2)	0
Partial Responders (PR) n (%)	16 (17.4)	6 (9.7)

*Per RECIST 1.1

- Initial responses in the placebo arm occurred from Week 7 to Week 31

Single Sites of Progression

Organ	Olaparib N=92	Placebo N=62
Total Progressions, n (%)	60 (100)	44 (100)
Total Progressions in a Single Organ, n (%)	37 (62)	28 (64)
Liver, n	21	15
Pancreas, n	8	7
Peritoneum, n	4	2
Lymph node, n	1	2
Other, n	3	2

* 20% of patients across arms progressed in the pancreas or peritoneum only

Issue #2

POLO trial limitations

Small Sample Size of POLO

- Powered to demonstrate a large treatment effect on overall survival (OS)
  - 80% power to detect a HR of 0.57 for OS based on 106 events assuming a median OS of 8.0 months in the placebo arm and 14.0 months in the olaparib arm
- Randomization may not adequately control for all important prognostic factors

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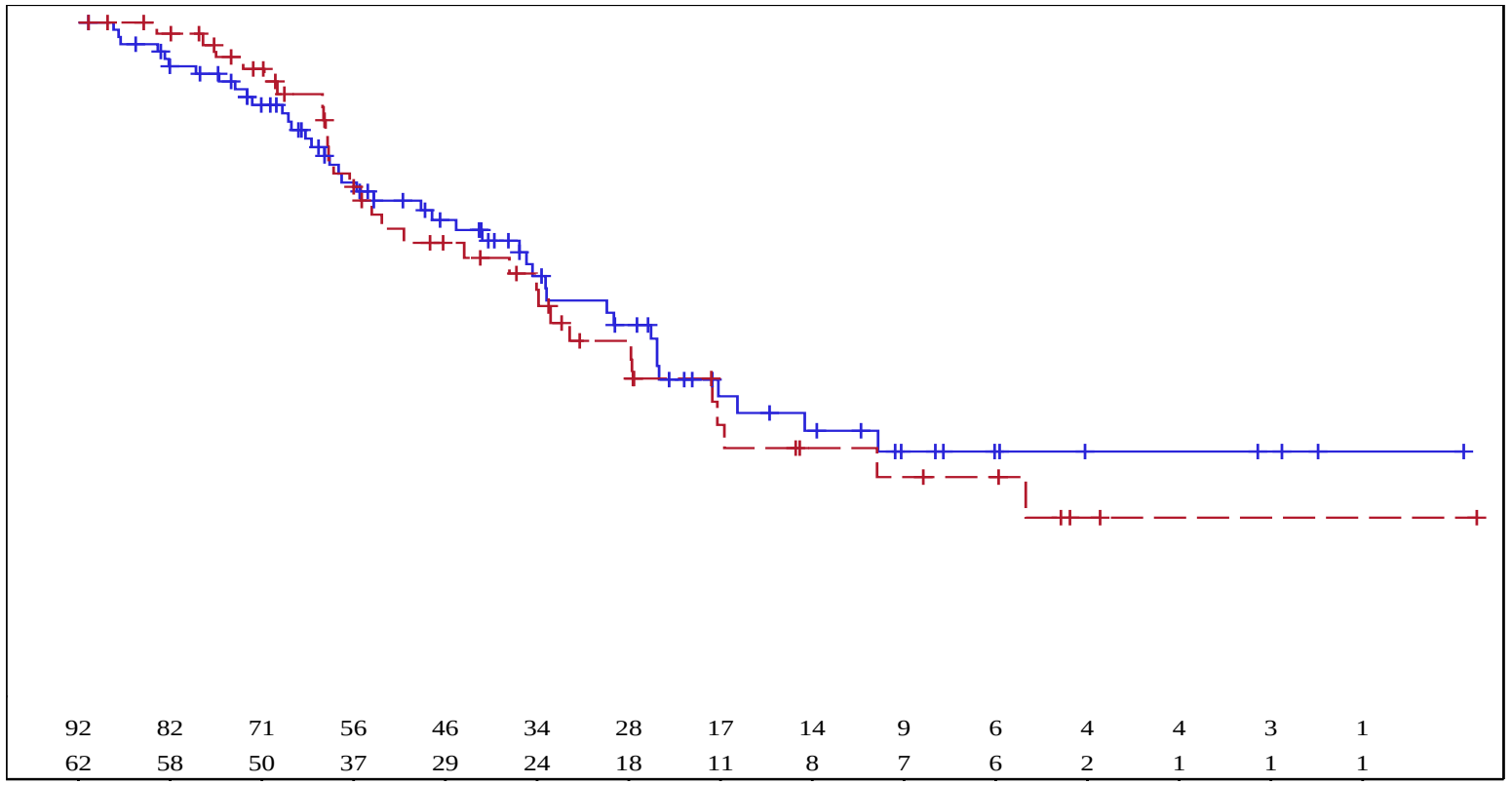
**Not significant based on 67% information using O'Brien-Fleming method*

- Crossover not permitted (olaparib: 1% vs. placebo: 15% received subsequent PARP inhibitor)

Kaplan-Meier Curves for OS



- Probability of final OS analysis showing a statistically significant difference: 5% to 16% (based on conditional or predictive power)

Health-Related Quality of Life (HRQoL) Analyses

- Comparisons are descriptive (no adjustment for multiplicity)
- Low patient numbers prevent reliable comparison between treatment arms
- POLO trial not designed to demonstrate preservation of HRQoL
- Analyses of QLQ-C30 pain domain and QLQ-PAN26 pancreatic pain domain did not show a treatment effect for olaparib

Time to First Subsequent Therapy or Death (TFST)

- Applicant's analyses of TFST indicates that patients randomized to olaparib had a median improvement in TFST of 2.9 months

- FDA does not consider this analysis meaningful due to use of a placebo comparator

Outline

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- Question for ODAC

Considerations for Maintenance Olaparib in Pancreatic Cancer

- Unmet medical need
- Demonstrated effectiveness of olaparib for gBRCAm ovarian and breast cancer
- Toxicities of olaparib
- Uncertainty regarding benefit of olaparib for the proposed indication
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ODAC Voting Question

Question: Is the risk-benefit assessment for olaparib as a maintenance therapy in patients with gBRCAm pancreatic cancer favorable?


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