



NDA 206162

Olaparib

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Accelerated Approval

- Serious or life-threatening condition
- Meaningful therapeutic benefit over existing treatments
- Endpoint
 - surrogate endpoint reasonably likely to predict clinical benefit
 - endpoint measured earlier than irreversible morbidity or mortality (IMM), reasonably likely to predict an effect on IMM or other clinical benefit
- Confirmatory trial to verify and describe clinical benefit

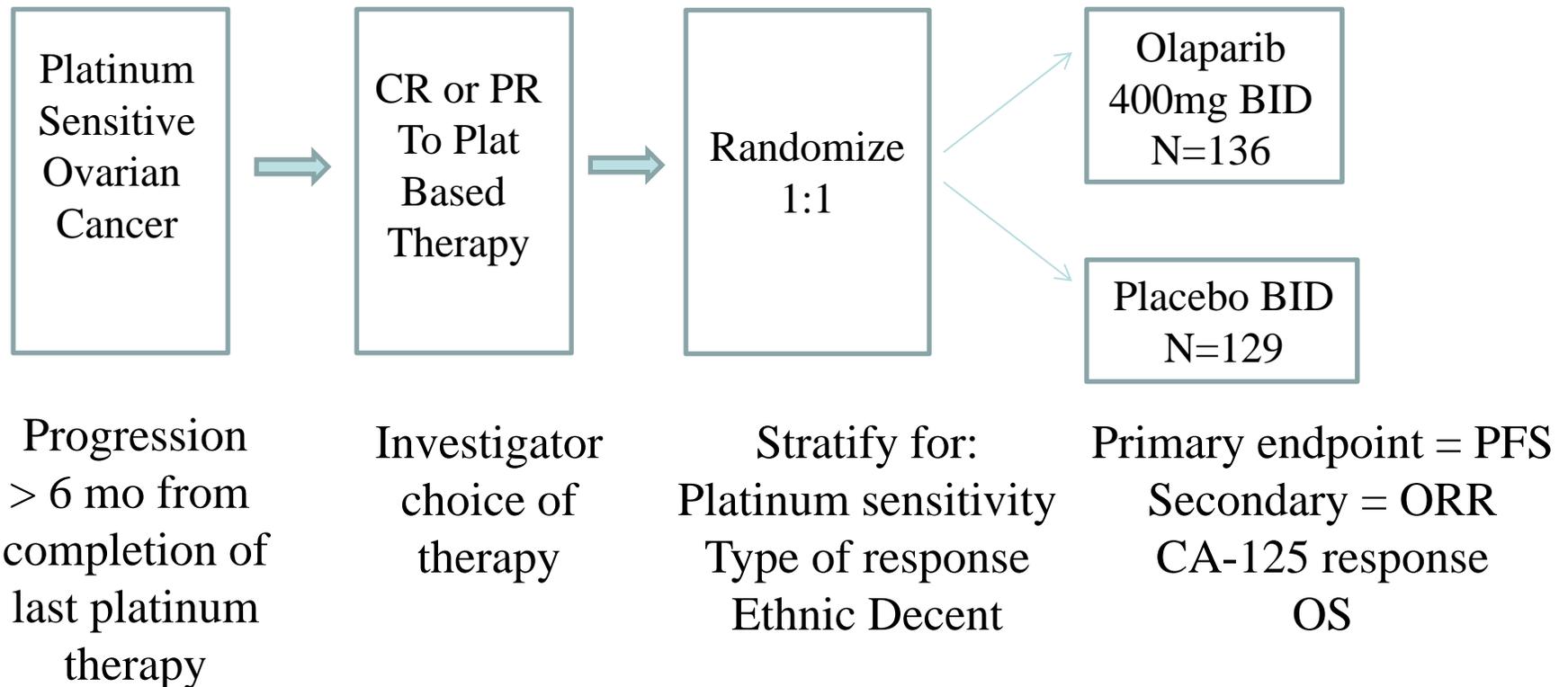


Applicant's Proposed Indication:

Olaparib is a PARP (poly ADP ribose polymerase) inhibitor indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (*gBRCA*) mutation as detected by an FDA approved test who are in response (complete response or partial response) to platinum-based chemotherapy

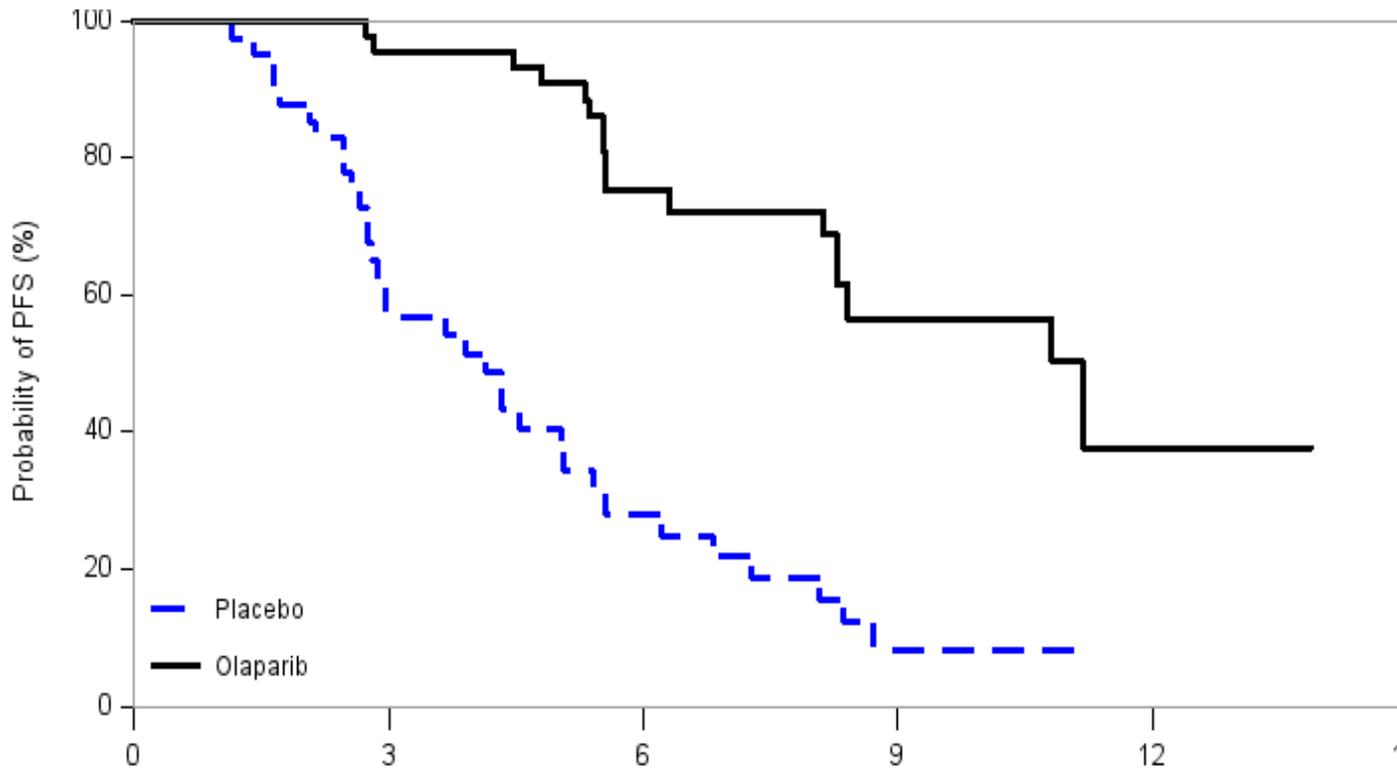


Pivotal Trial – Study 19



CR=Complete Response
PR=Partial Response
PFS=Progression-free Survival
ORR=Overall Response Rate
OS=Overall Survival

Kaplan-Meier Curves for PFS (INV) in gBRACm Population



	Olaparib	Placebo
Median PFS (months)	11.2	4.1
HR (95% CI)	0.17 (0.09, 0.32)	



Key Issues

- Prospectively planned analysis of retrospectively identified subpopulation
- Confirmatory trial
 - Statistical design
 - Formulation change
- MDS/AML safety signal

gBRCAmutated (gBRCAm) population

- Study 19 enrolled all comers with platinum sensitive ovarian cancer in response to second-line platinum therapy
- Statistical analysis plan amended prior to unblinding to include a gBRCAm subgroup analysis
- gBRCA status was recorded on the original Case Reports Forms, if known



gBRCAm population

- gBRCA status initially known for 37% of the intent-to-treat (ITT) population
- When efficacy signal in gBRCAm population noted, applicant made effort to find gBRCA status in all patients in ITT population
- 53/136 on olaparib arm and 43/129 on placebo identified with gBRCAm status



Key Issues

- Prospectively planned analysis of retrospectively identified subpopulation
- **Confirmatory trial**
 - Statistical design
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Confirmatory trial SOLO-2

- SOLO-2 design replicates Study 19
 - Exception is that only patients with gBRCAm eligible
- Statistical design may find a statistically significant difference but questionable if clinically meaningful



Key Issues

- Prospectively planned analysis of retrospectively identified subpopulation
- **Confirmatory trial**
 - Statistical design
 - Formulation change
- MDS/AML safety signal



Formulation change

- Study 19 used a 50 mg capsule formulation
 - Dose 400 mg BID
- Potential confirmatory trial (SOLO-2) to use a tablet formulation
 - Dose 300 mg BID
 - Greater exposure than 400 mg BID capsule dose



Key Issues

- Prospectively planned analysis of retrospectively identified subpopulation
- Confirmatory trial
 - Statistical design
 - Formulation change
- **MDS/AML safety signal**



Myelodysplastic syndrome (MDS)/ Acute Myelogenous Leukemia (AML) Safety Signal

- Investigator's Brochure updated July 2011 to include MDS/AML events
 - Additional instruction to investigators to obtain regular complete blood counts in patients on olaparib and consult hematologist if MDS/AML suspected



MDS/AML

- 22/2618 (0.8%) suspected or confirmed cases identified to date in entire olaparib safety database
- Unable to determine if gBRCAm patients more susceptible



Key Issues

- Prospectively planned analysis of retrospectively identified subpopulation
- Confirmatory trial
 - Statistical design
 - Formulation change
- MDS/AML safety signal



NDA 206162 Olaparib Capsules

FDA Presentation
ODAC Meeting
June 25, 2014



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Major Issues for Discussion

- Loss of Randomization for gBRCAm Subgroup
- Estimation of the Treatment Effect of Olaparib Therapy
- Risks of Olaparib therapy in the Platinum-Sensitive Maintenance Setting
- Reproducibility of Results in a Larger Trial



gBRCA Status for Study 19

	Olaparib (N=136)	Placebo (N=129)	All (N=265)
gBRCA Status Known at Time of Randomization	37%	37%	37%
gBRCA Status Known at time of Subpopulation Analysis	76%	83%	79%
gBRCAm (total)	39%	33%	36%
gBRCAwt (total)	37%	50%	43%



Loss of Randomization

- Issue 1: Did the retrospective identification of the gBRCAm population lead to an imbalance of known prognostic factors in the treatment arms?



Time to Progression on Penultimate Platinum Regimen

- Defined as time interval from the date of last platinum treatment until documented progression
- Also known as the Platinum Free Interval (PFI)
- Longer PFIs are associated with higher responses to subsequent platinum-based therapies



Time to Progression on Penultimate Platinum Regimen; gBRCAm Population

Platinum Free Interval	Olaparib N=53 %	Placebo N=43 %
6 - 12 months	42	49
> 12 months	58	51



Number of Prior Chemotherapy Regimens; gBRCAm Subpopulation

Number of Prior Chemotherapy Regimens	Olaparib N=53 %	Placebo N=43 %
≤ 3	79	72
> 3	21	28



Type of Response to Platinum Regimen Immediately Preceding Randomized Treatment; gBRCAm Subpopulation

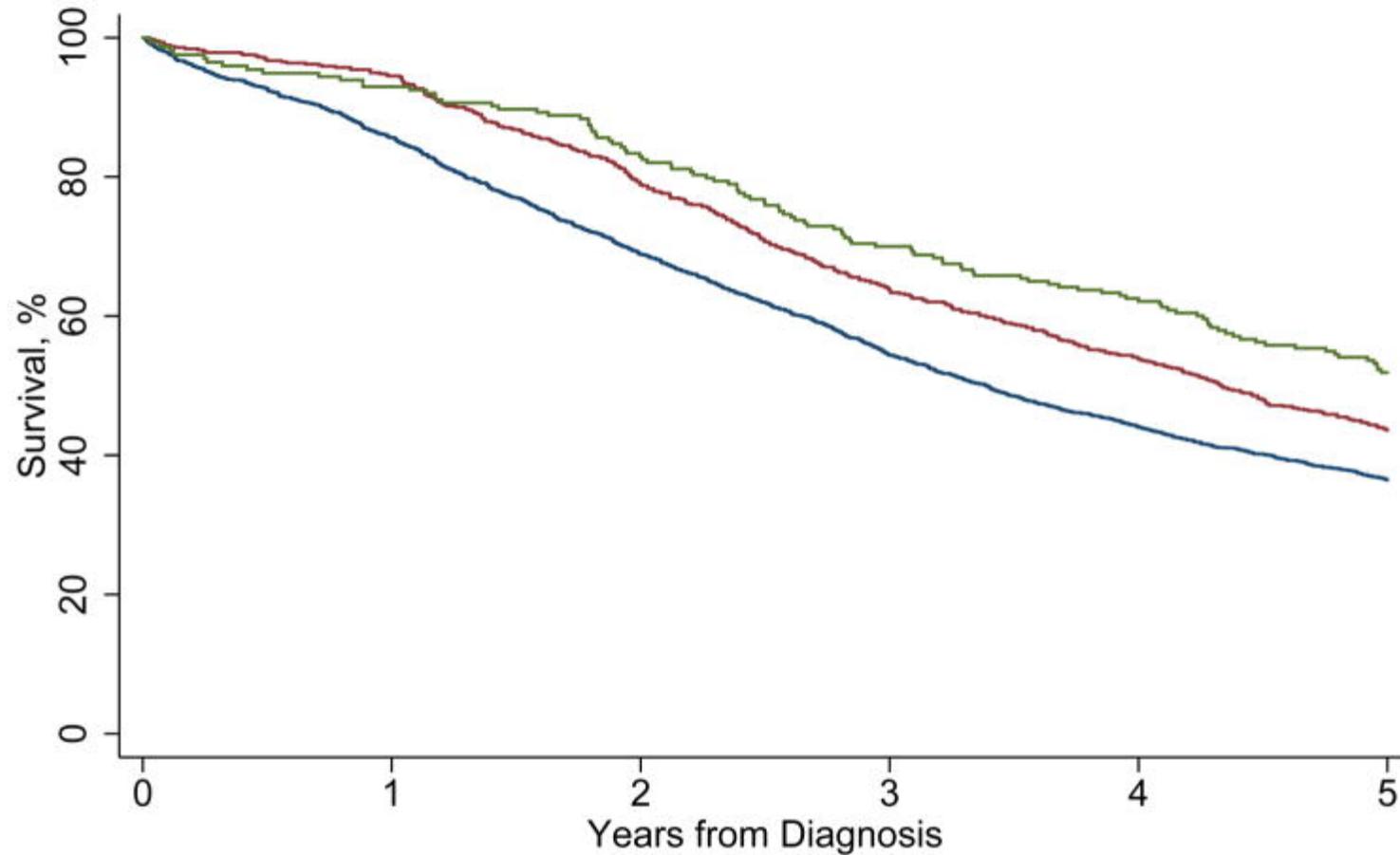
Type of Response	Olaparib N=53 %	Placebo N=43 %
Complete Response	55	51
Partial Response	45	49



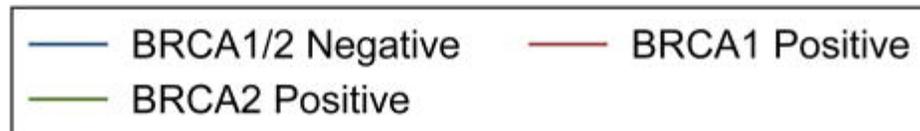
Chemotherapy Regimen Immediately Prior to Randomized Therapy: gBRCAm Population

Platinum Regimen Immediately Prior to Olaparib Treatment	Olaparib (N=53) %	Placebo (N=43) %
Platinum and Taxane	30	33
Platinum and Gemcitabine	25	33
Platinum and Anthracycline	11	14
Other Platinum Combination	11	7
Single Agent Platinum	23	14

BRCA as a Prognostic Marker



Bolton et. Al.
JAMA. 2012;307(4):382-389.





BRCA Mutations

	Randomized to Olaparib (N=53) %	Randomized to Placebo (N=43) %
BRCA1 Mutation ^{1,2}	75	70
BRCA2 Mutation ³	25	30

1 Most frequent mutations were 187delAG (n=16) and 5835insC (n=15)

2 One patient on the placebo arm had both a BRCA1 and BRCA2 mutation

3 Most frequent mutation was 6174delT (n=5)



Loss of Randomization

- It does not appear that there was an inadvertent unequal distribution of known prognostic factors in the gBRCAm subpopulation



Loss of Randomization

- Issue 2: Did the retrospective identification of the gBRCAm population lead to an imbalance of unknown prognostic factors in the treatment arms?



Multiple Comparisons

- Statistically significant improvement in PFS in the Intent-To-Treat population
- gBRCAm was one of 12 subgroups that were pre-specified in the Statistical Analysis Plan
- No adjustments for multiplicity were planned for these multiple subgroup comparisons
- The p-values are not interpretable



Small Sample Size

- gBRCA known in 79% ITT population
 - 96 gBRCAm patients (Case Report Form+Myriad):
 - 53 patients in olaparib arm with 17 PFS events
 - 43 patients in placebo arm with 33 PFS events



Treatment Effect

	Median PFS (months) Olaparib (N=53)	Median PFS (months) Placebo (N=43)
Primary analysis	11.2 (95% CI: 8.3 - NE)	4.1 (95% CI: 2.8 – 5.1)
Sensitivity analysis to assess reliability of estimate of treatment effect	8.4 (95% CI: 8.3 - NE)	4.3 (95% CI: 2.8 – 5.6)



Reliability of the Estimation of the Treatment Effect of Olaparib

- PFS results of gBRCAm subpopulation held up to multiple sensitivity analyses including:
 - Full independent radiology review
 - Evaluation-time bias
 - Attrition bias



Supportive Efficacy

- Primary analysis of PFS in the randomized population of Study 19 (N=265) was positive
- Response rate of ~30-35% as monotherapy in gBRCAm population in other studies

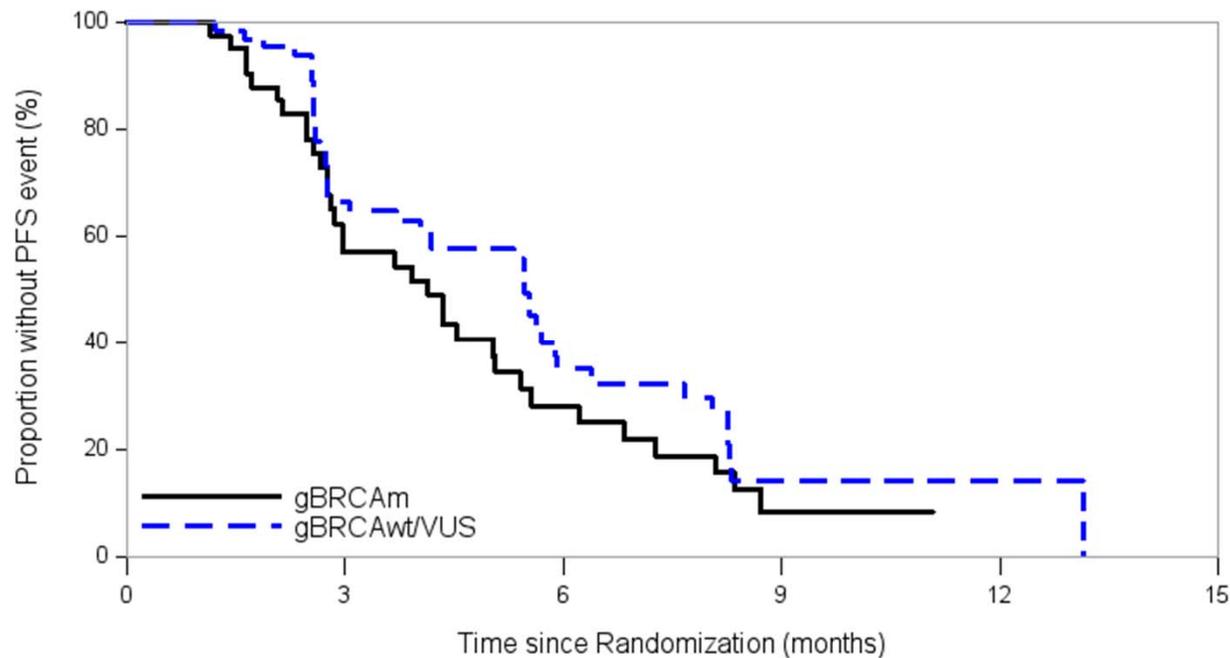


Reliability of Treatment Effect

- Performance of gBRCAm in context of other trials
- Would expect longer PFS due to:
 - Better prognosis due to gBRCAm
 - All patients were in CR or PR to platinum therapy

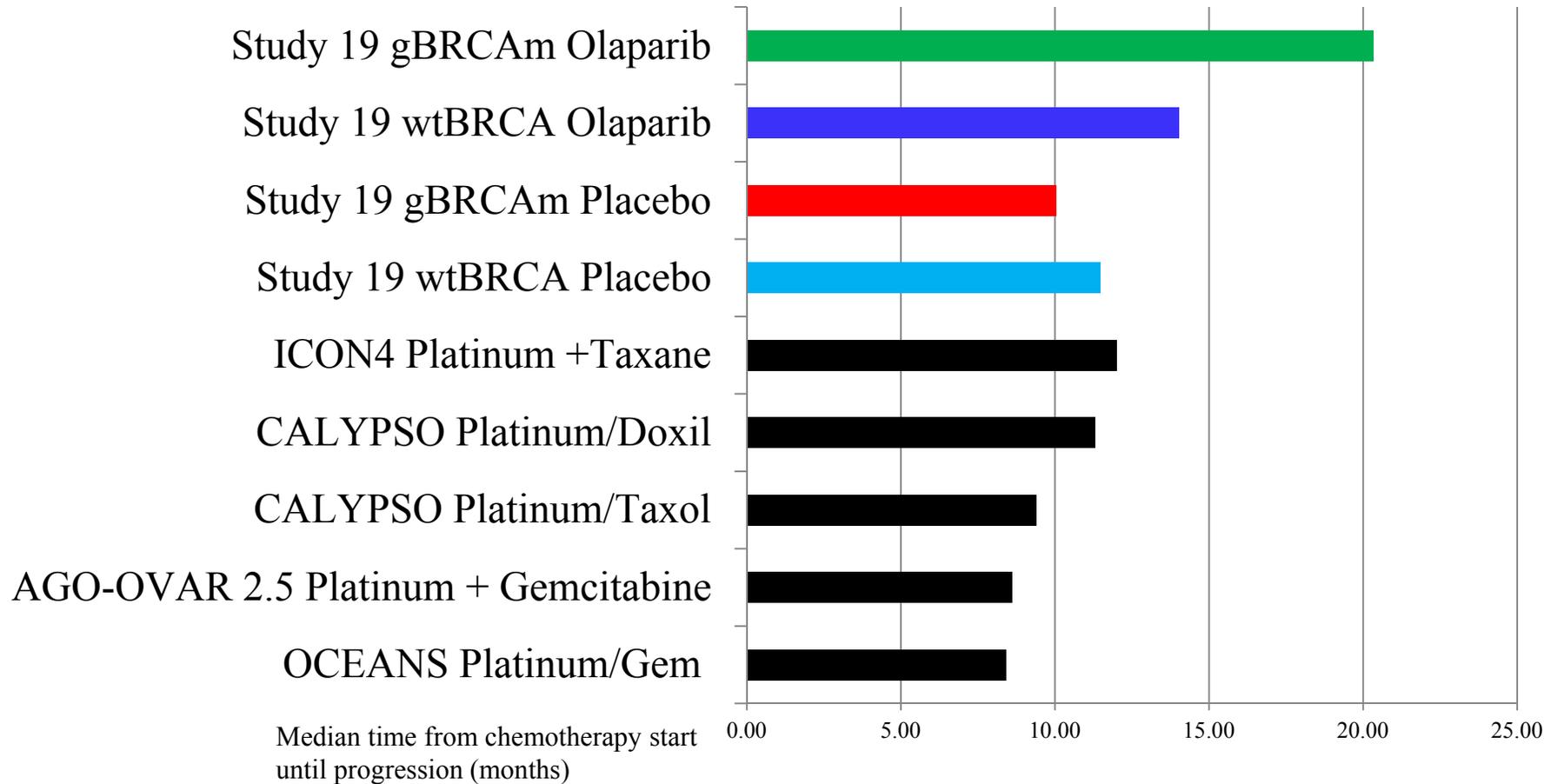


PFS: gBRCAwt vs. gBRCAm Treated with Placebo





Study 19 in Context of Other Platinum Sensitive Trials





Efficacy Summary

- Enrichment by gBRCAm status appears to be associated with a larger magnitude of effect on PFS
- Known Prognostic Factors
- Unknown Prognostic Factors
- Needs Confirmation in a Larger Study



Clinical Safety



Deaths due to Adverse Event

	Olaparib N=136	Placebo N=128
Deaths due to Adverse Event (per Investigator)	3	0
Hemorrhagic stroke/AML (gBRCAm)	1	0
Cholestatic jaundice and PD (gBRCA unk)	1	0
PD and MDS (gBRCA wild type)	1	0



Four Cases MDS or AML Study 19 (n=265)

Arm	MDS/AML	Confirmed	gBRCA	Outcome
Olaparib	MDS	Yes	Wild type	Death
Olaparib	AML	Yes	Mutant	Ongoing
Olaparib	AML	No	Mutant	Death
Placebo	MDS	Yes	Unknown	Ongoing

MDS or AML

- 22 cases MDS or AML in olaparib treated patients in safety database of 2618 patients (0.8%).
 - 9 presented with or progressed to AML
 - 17 have died
- 17/22 patients had known BRCA mutation
- All had received multiple prior chemo regimens including olaparib, and some prior XRT
- 6 of 7 with cytogenetic reports had chromo 5 and/or 7 abnormalities.

MDS or AML

- Estimated annual incidence MDS in US is approx. 3.3/100,000 (0.0033%).
- Incidence in large case-control study of almost 29,000 ovarian cancer patients treated with platinum was 0.3%
- Unknown incidence in gBRCAm population
- MDS/AML incidence in Study 19 on olaparib was 2.2%.
- MDS/AML incidence in olaparib safety database was 0.8%.



MDS or AML

- Concern that olaparib may promote or cause MDS/AML
- Surveillance strategies in place in clinical trials
- Post-marketing requirement likely for further surveillance if approved



Adverse Event Duration

	Olaparib N=53	Placebo N=43	
AE	Median (Min-Max) days	Median (Min-Max) days	Δ median
Abd distention	147 (30-613)	34 (7-71)	113
Dysgeusia	114.5 (16-706)	11 (2-89)	103.5
Abd pain upper	99 (4-484)	8 (1-15)	91
Nausea	96 (1-1174)	26 (1-85)	70
Arthralgia	89 (14-850)	22 (7-51)	67
Abd pain	75 (8-1061)	18 (2-109)	57
Back pain	57 (5-191)	8 (3-101)	49
Musculosk. pain	57 (3-194)	9.5 (4-15)	47.5
Constipation	44 (16-675)	4 (2-6)	40



Safety Summary

- Few deaths due to AE
- Discontinuations/modifications due to AE
- Long term tolerability as maintenance therapy vs. treatment-free interval
- Increased risk of MDS/AML

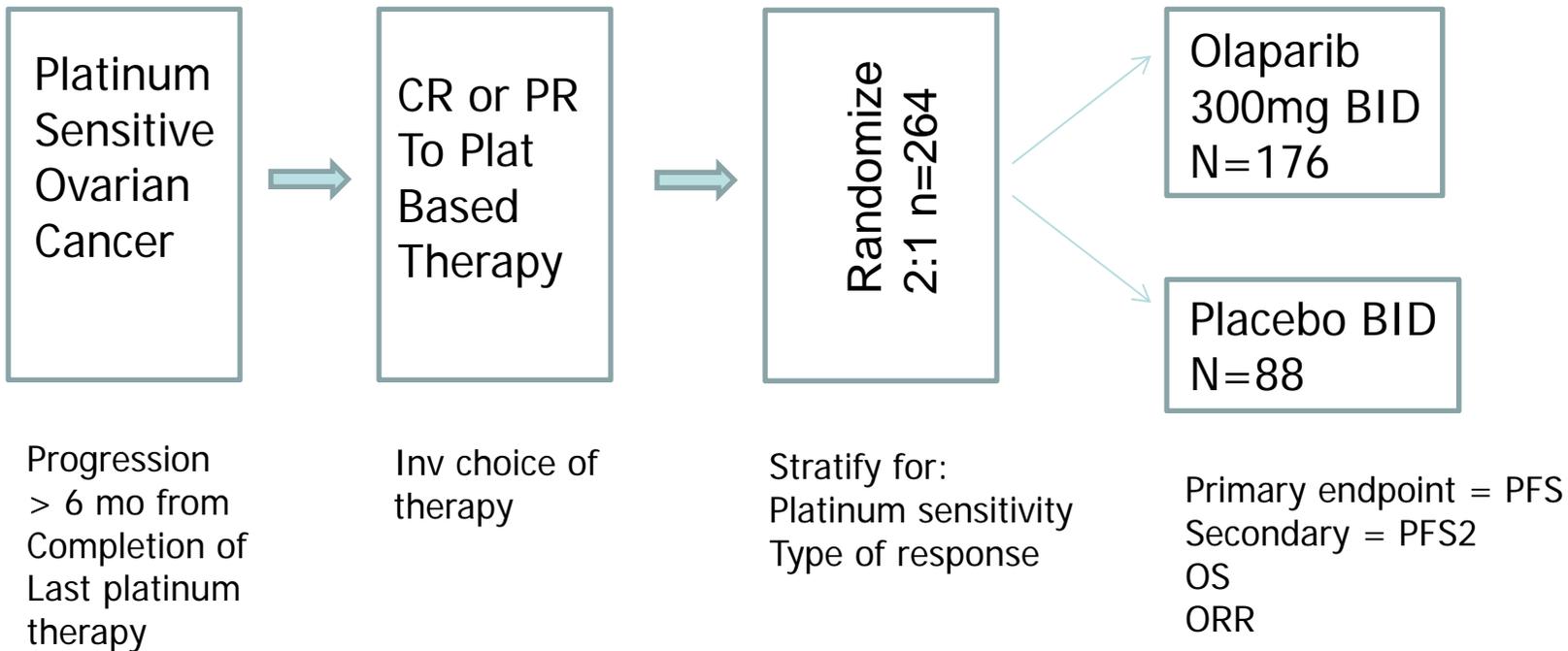


SOLO-2

- Using different, non-bioequivalent formulation
 - Concern regarding toxicity/tolerance
- Study is sized on having sufficient precision of estimated HR and thus overpowered



SOLO-2



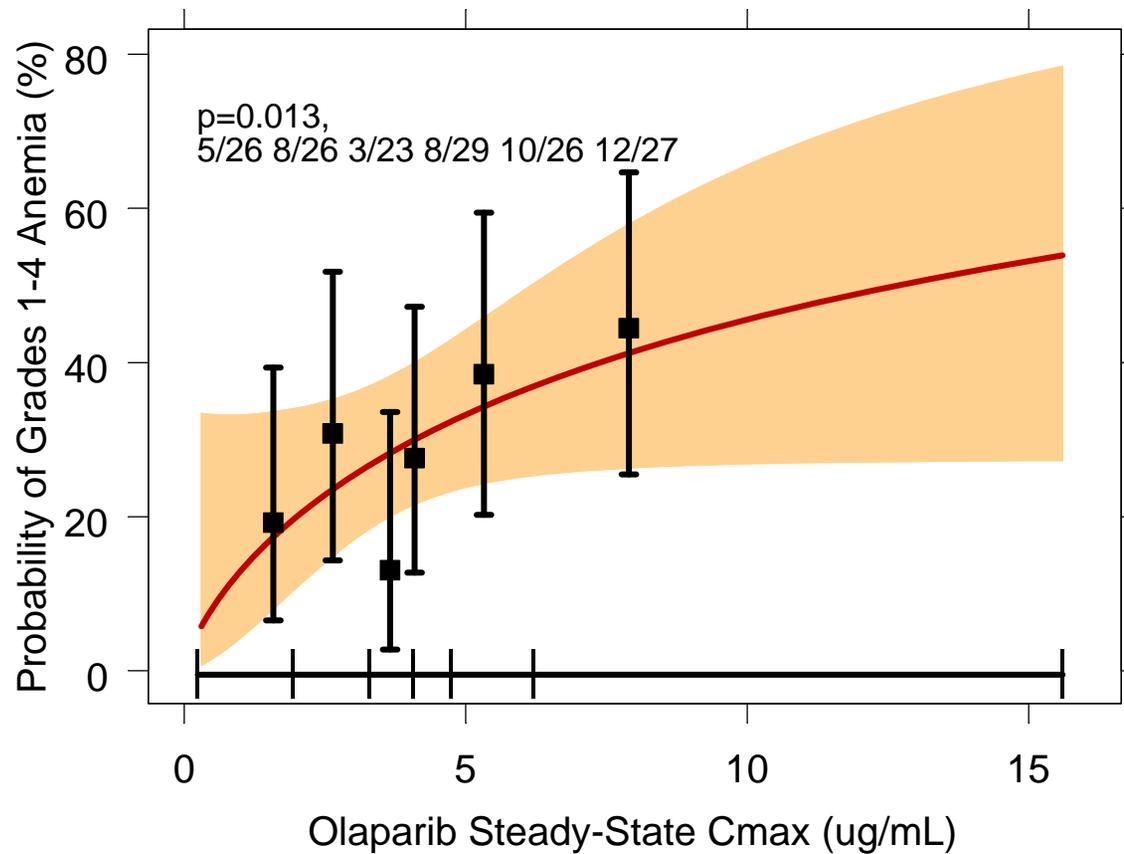


Olaparib Formulation

- Current Capsule Formulation
 - 16 capsules every day in divided dose
 - High variability in exposure
 - No exposure-response for PFS or response rate identified at the proposed dose in other trials
 - Exposure-response relationship identified for anemia



Exposure-Response Anemia





Olaparib Formulation

- Confirmatory Trial Tablet Formulation
 - Current dose being studied (300 mg BID) had 1.5x steady-state exposure of olaparib compared to capsule formulation in the relative bioavailability trial
 - Unknown impact on safety, efficacy, or tolerability in SOLO-2 compared to Study 19



What Accelerated Approval Entails

- Approval would be for capsule formulation
- If confirmatory trial demonstrates clinical benefit of tablet formulation, applicant will phase out capsule formulation



Statistical Issues Regarding Confirmatory Trial

- Study is sized to give sufficient precision of the hazard ratio
- If median PFS of control arm is 4 months, study can detect a statistically significant improvement in median PFS of 1.5 months (HR=0.72)



Summary

- Large treatment effect on PFS
- Mechanism of drug and mutation
- Supportive efficacy data from other trials
- Statistical issues
- Potential increase in MDS/AML
- Tolerability in maintenance setting
- New formulation in SOLO-2



Question 1 (vote)

- Do the safety and efficacy results from Study 19 in the gBRCAM population support an accelerated approval, or should marketing approval consideration be delayed until the results from SOLO-2 are available?



Question 2 (discuss)

- What is the appropriate magnitude of treatment effect on PFS in terms of median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to have a favorable risk-benefit profile in this patient population? Consider the safety profile of the tablet formulation to be similar to the currently observed safety profile.



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Backup Slides Shown



PFS KM for gBRCAwt/vus

