Lynparza® in Combination With Abiraterone and Prednisone or Prednisolone for the Treatment of Adults With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

United States Food and Drug Administration
Oncologic Drugs Advisory Committee

April 28, 2023

AstraZeneca MERCK

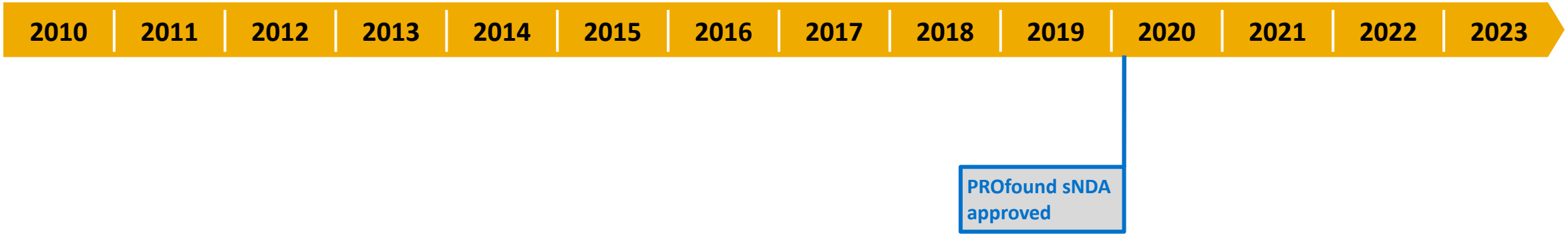
Introduction

Cristian Massacesi, MD
Chief Medical Officer and
Oncology Chief Development Officer
AstraZeneca

Proposed Indication

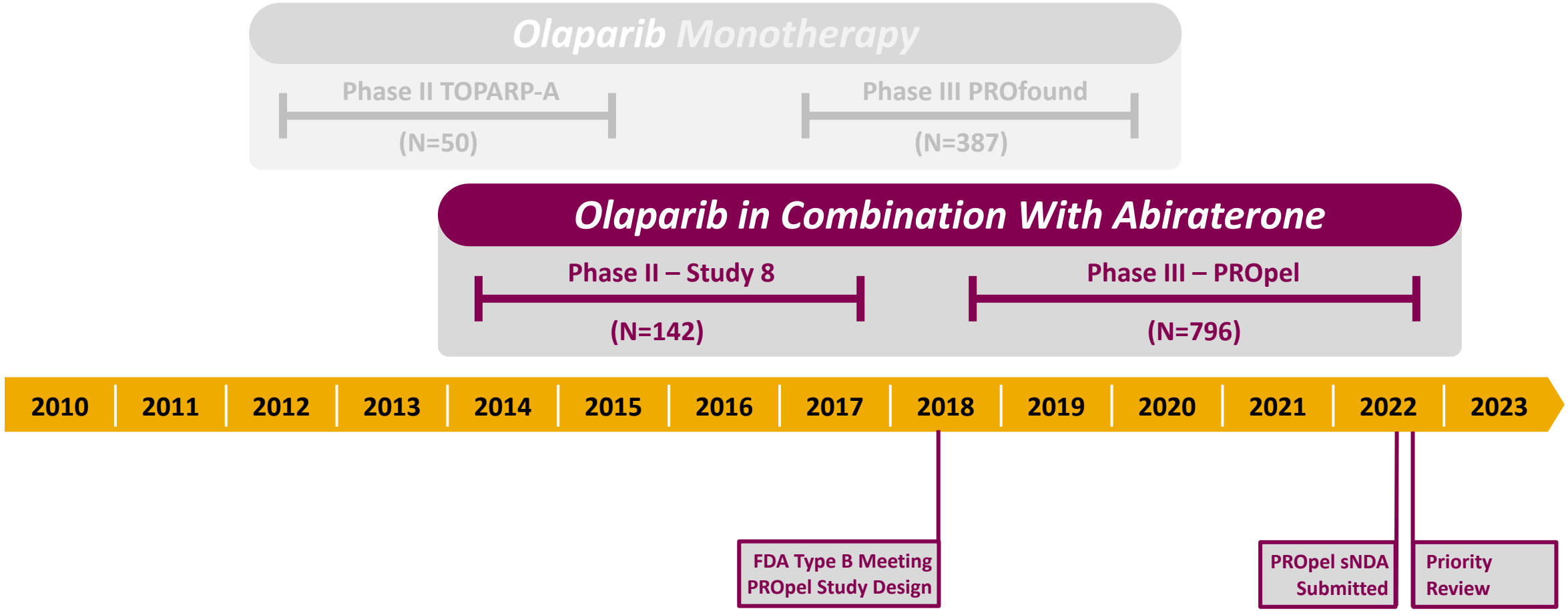
Lynparza in combination with abiraterone and prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)

Clinical Development Program for Monotherapy in Homologous Recombination Repair (HRR) Gene Mutated mCRPC



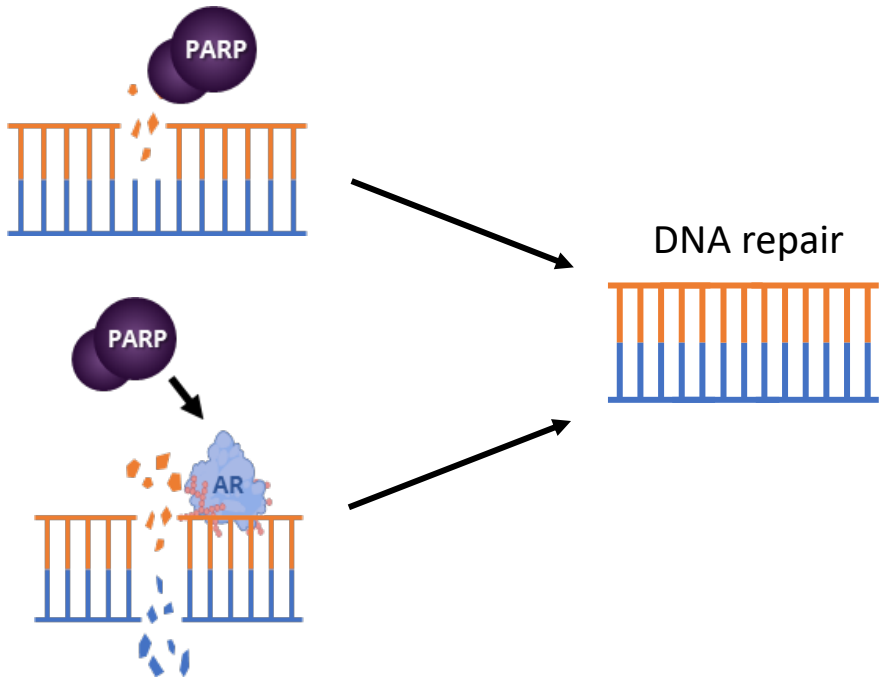
[a] Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza (approved May 19, 2020). Gene panel includes *ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm,* and *RAD54Lm.*

Clinical Development Program for Combination in All-Comer mCRPC



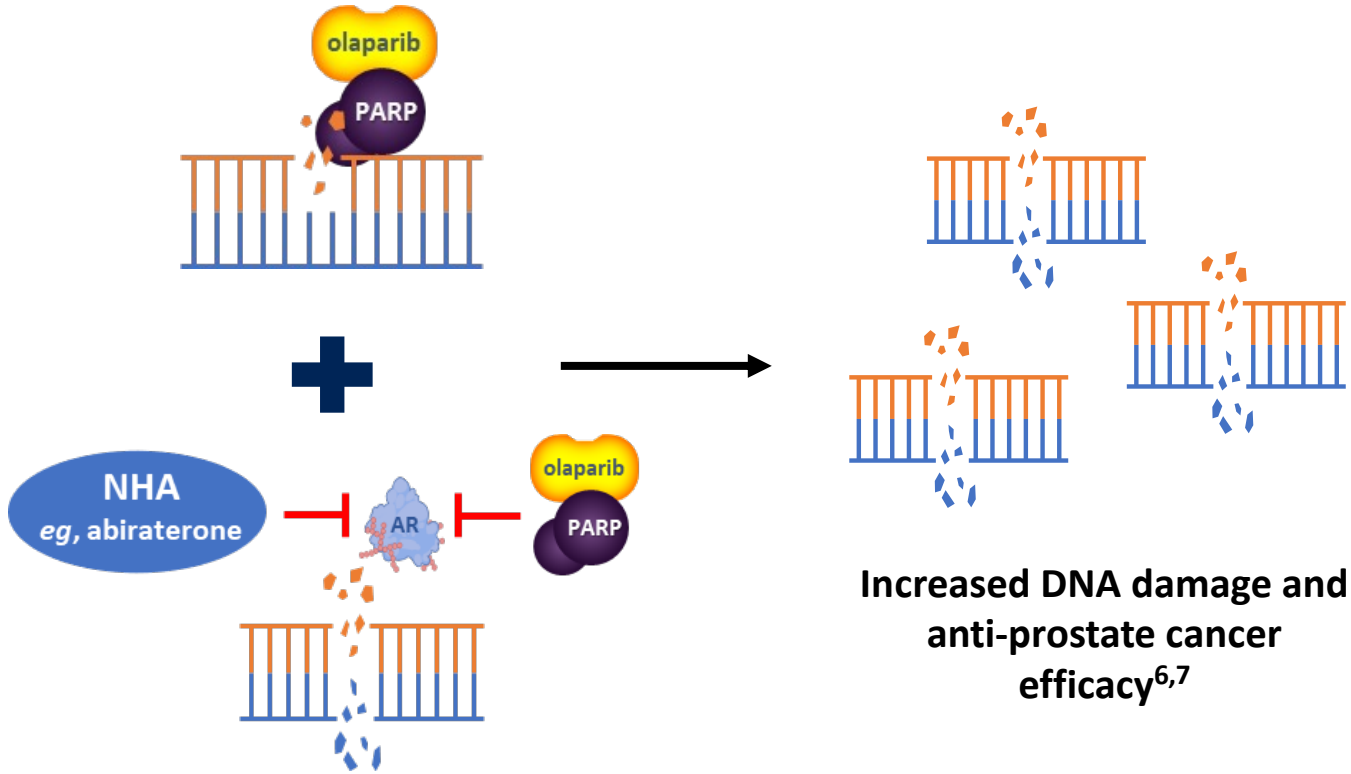
Olaparib + Abiraterone in Non-HRRm Prostate Cancer Generates More DNA Damage Than Each Single Agent Alone

PARP activity facilitates DNA repair[1]



AR binds damaged DNA through PARP activity[2] and facilitates repair through multiple pathways[3,4]

PARP inhibition and trapping on damaged DNA[5]



Reduction of AR protein levels and prevention of DNA binding and repair[2]

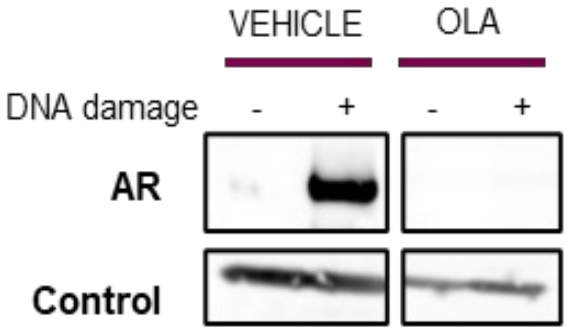
Increased DNA damage and anti-prostate cancer efficacy[6,7]

AR, activated androgen receptor; NHA, novel hormonal agent.

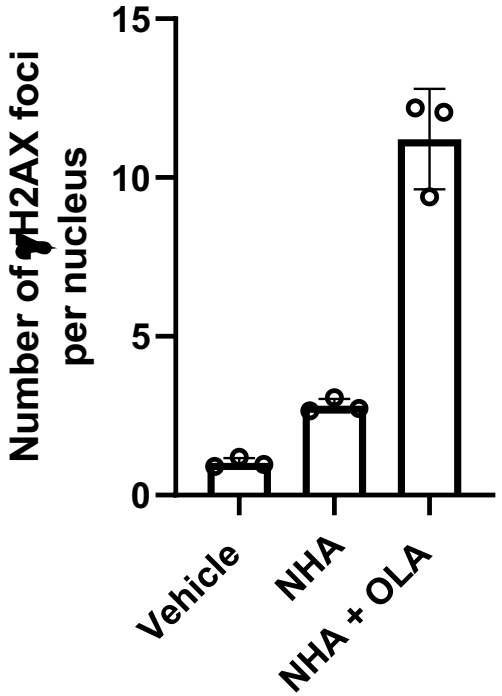
1. Chaudhuri AR, Nussenzweig A. *Nat Rev Mol Cell Biol*. 2017;18(10):610-621; 2. Data on file. AstraZeneca; 3. Goodwin JF, et al. *Cancer Discov*. 2013;3(11):1254-1271; 4.Polkinghorn WR, et al. *Cancer Discov*. 2013;3(11):1245-1253; 5. Pommier Y, et al. *Sci Transl Med*. 2016;8(362):362ps17; 6. Asim M, et al. *Nat Commun*. 2017;8(1):374; 7. Li L, et al. *Sci Signal*. 2017;10(480):eaam7479.

Olaparib + NHA Results in More DNA Damage and More Antitumor Activity Than NHA Alone in Non-HRRm Prostate Models

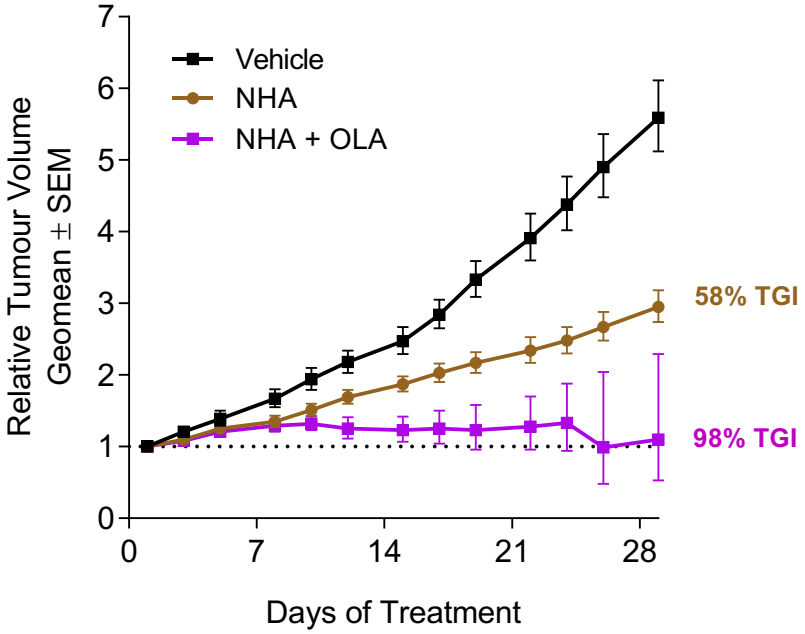
AR binding to damaged DNA inhibited by olaparib



DNA damage increased with addition of olaparib to NHA



Increased antitumor activity with addition of olaparib to NHA

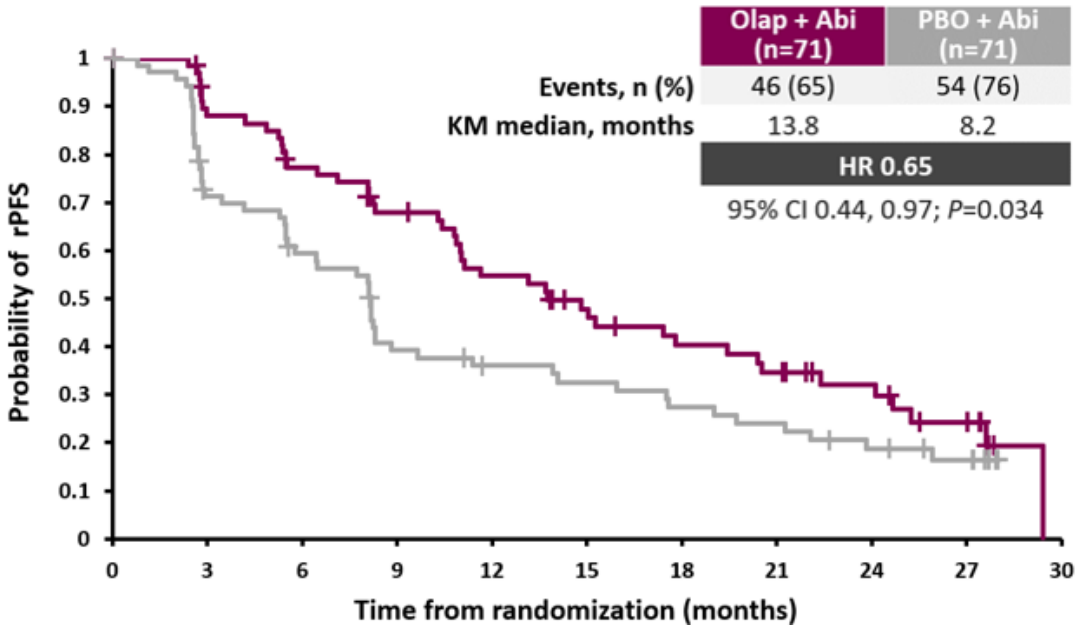


AR, activated androgen receptor; NHA, novel hormonal agent.
Data on file. AstraZeneca.

Outcome of Two Randomized Trials Support the Combination of Olaparib + Abiraterone in an All-Comer mCRPC Population

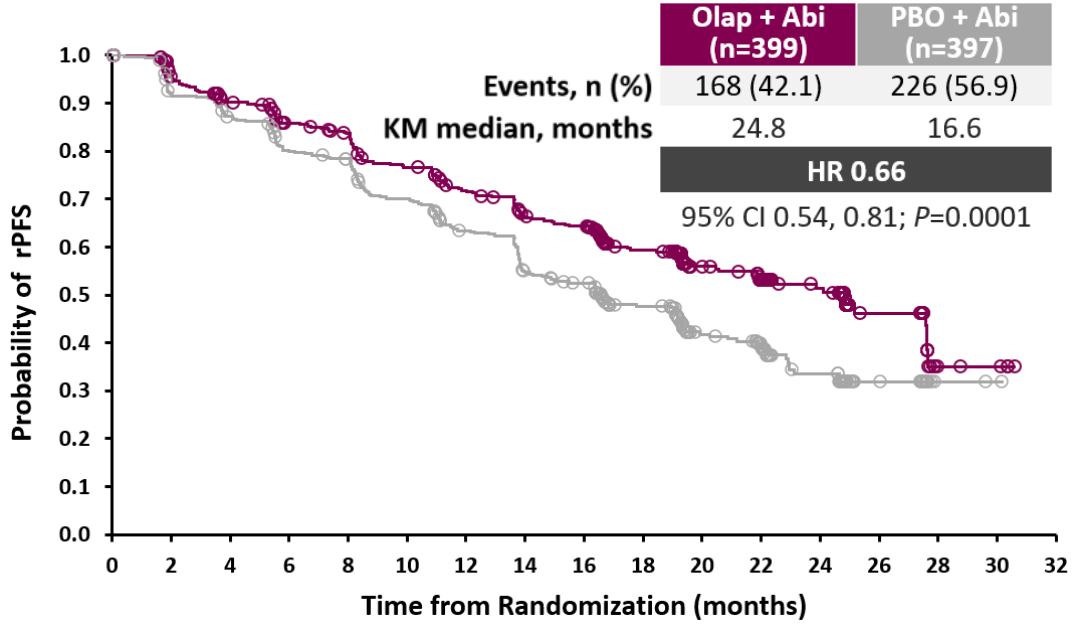
Phase II – Study 8 (N=142)

Primary Endpoint: rPFS (INV)



Phase III – PROpel Trial (N=796)

Primary Endpoint: rPFS (INV)



INV, investigator.

Agenda

Unmet Need
Neal Shore, MD, FACS
GenesisCare, US

mCRPC is a fatal disease with no meaningful improvements in first-line treatment outcomes in ~10 years

Efficacy
Laurence Toms, MD
AstraZeneca

PROpel was a positive study in an all-comer population, with demonstrated benefit across multiple endpoints

Safety
Simon Turner, PhD
AstraZeneca

Safety of olaparib and abiraterone was manageable, tolerable, and consistent with established safety profiles

Clinical Perspective
Daniel George, MD
Duke Cancer Institute

PROpel results support a new first-line treatment option, with a favorable benefit-risk in *BRCAm* and non-*BRCAm* patients

Conclusions
Cristian Massacesi, MD
AstraZeneca

Totality of evidence in PROpel including statistically significant and clinically meaningful rPFS, with no overall survival detriment, supports an all-comer indication

Consultants

Andrew J. Armstrong, MD, ScM, FACP
Professor of Medicine, Surgery, Pharmacology, and Cancer Biology
Director of Research, the Duke Cancer Institute Center for Prostate and Urologic Cancers
Divisions of Medical Oncology and Urology, Duke Cancer Center

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Janet Wittes, PhD
Biostatistics
Wittes LLC

Disease Background and Unmet Needs in mCRPC

Neal Shore, MD, FACS
Chief Medical Officer
Surgical Oncology and Urology
GenesisCare

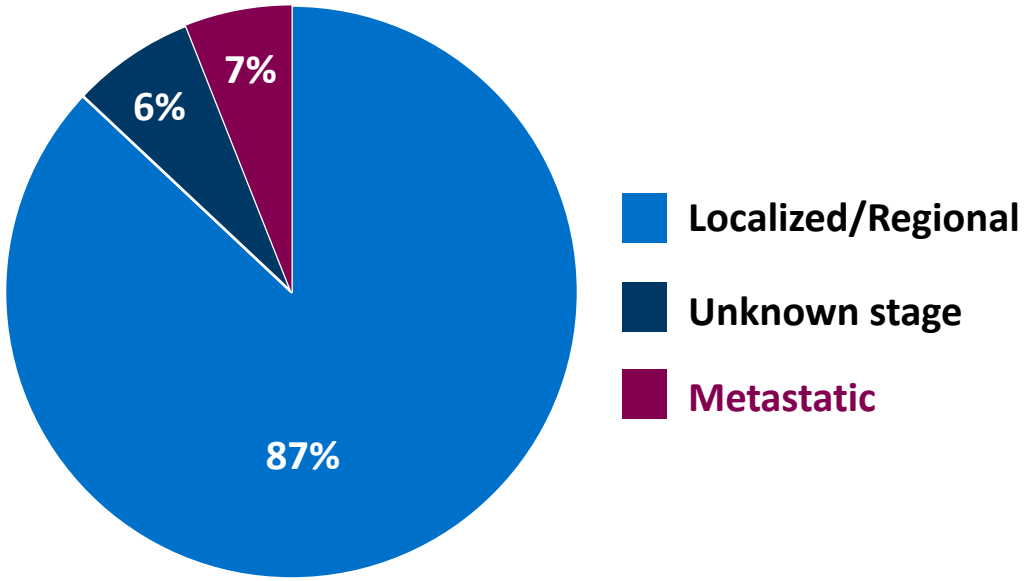
Prostate Cancer: Second Leading Cause of Cancer Death in Men

2022

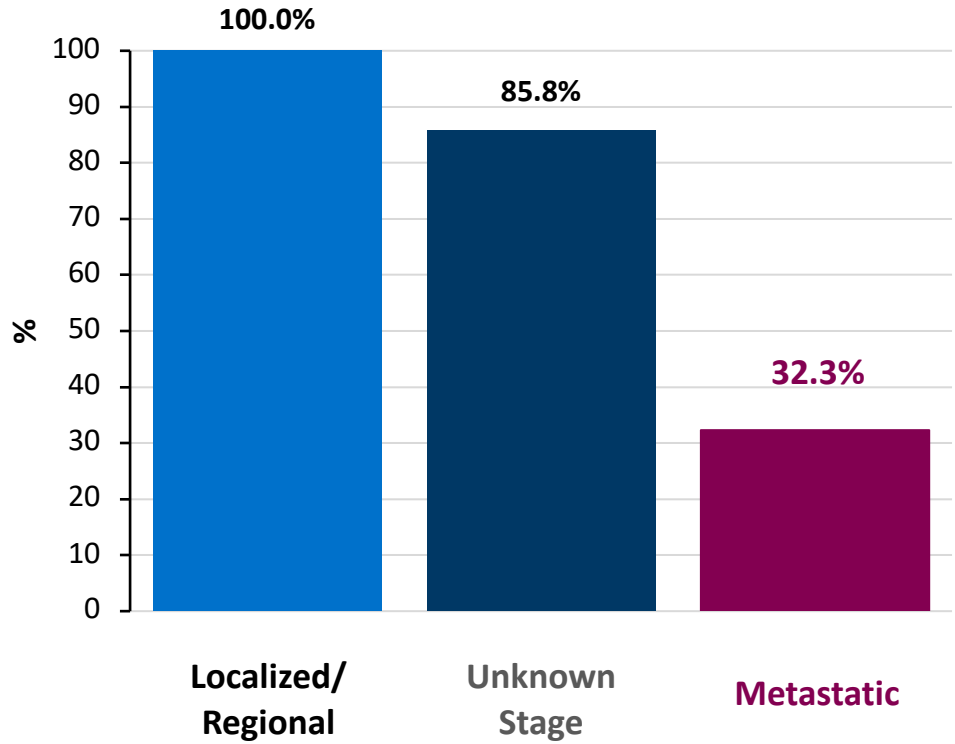
268,490 new cases of prostate cancer

34,500 deaths from prostate cancer

Percent of Cases by Stage at Diagnosis



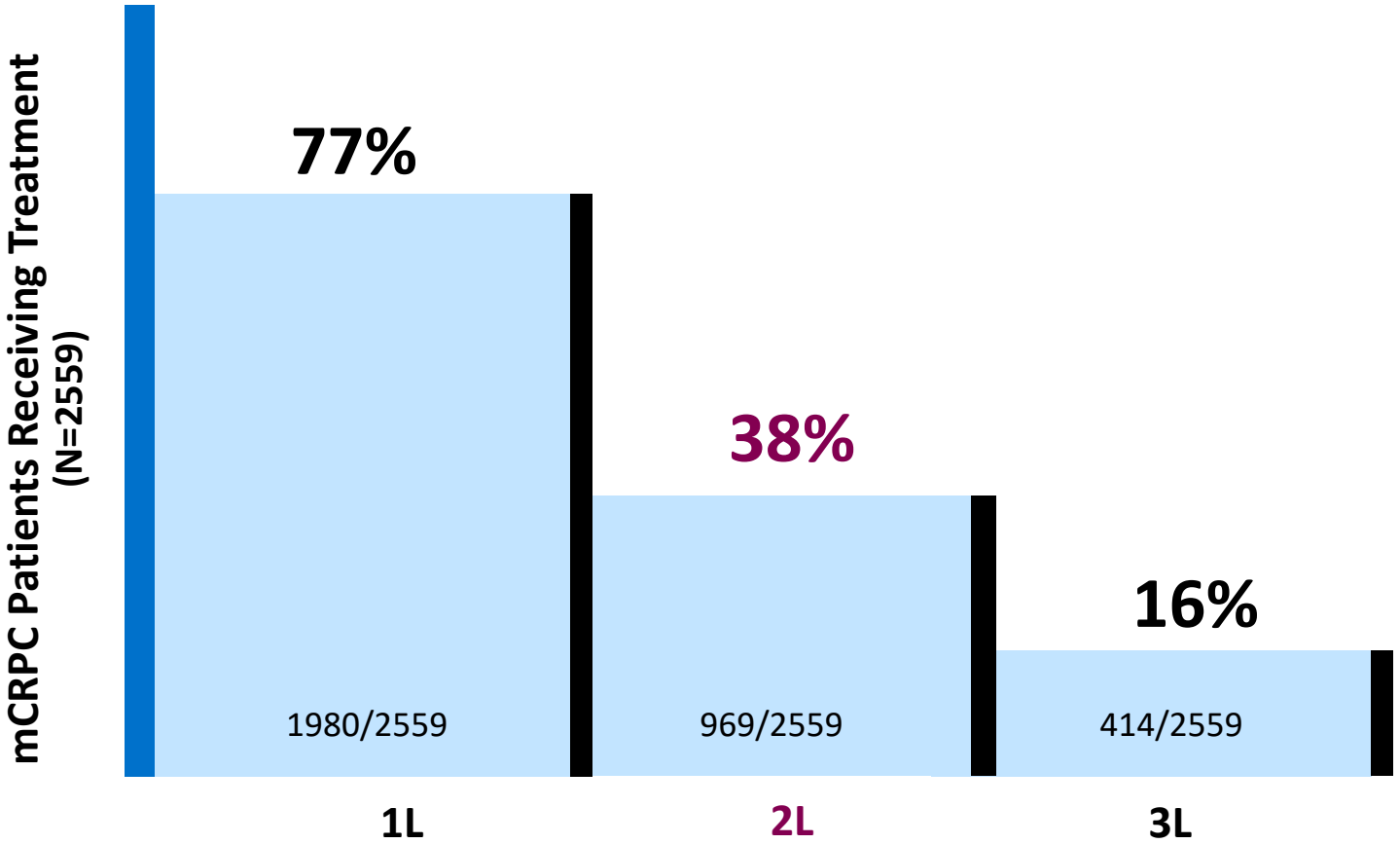
5-Year Relative Survival



SEER. https://seer.cancer.gov/statfacts/html/prost.html. Accessed March 31, 2023.

<50% of Patients With mCRPC Receive a 2L Therapy

Improving 1L treatment outcomes is critical



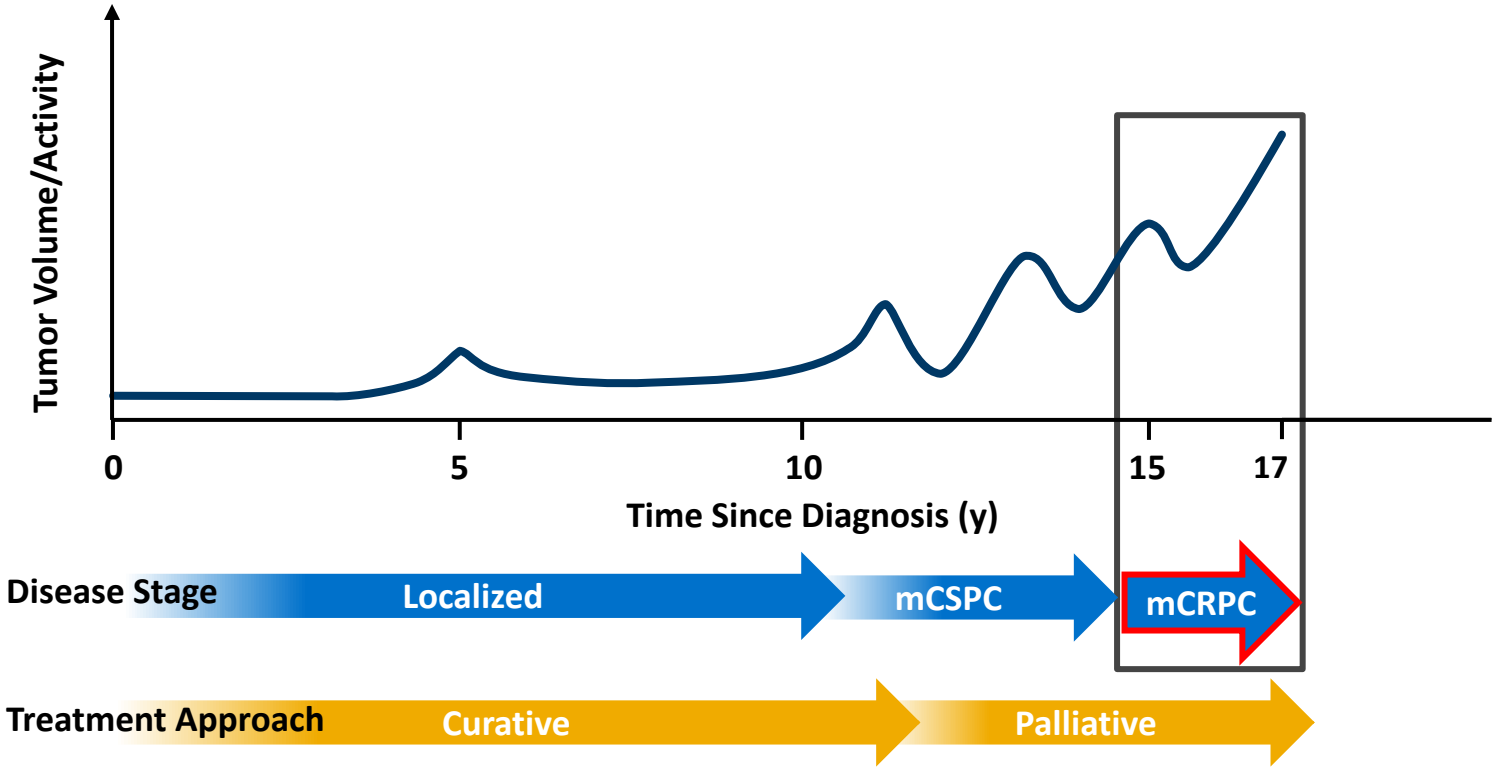
Reasons for not receiving additional lines of therapy[1]:

- Death
- Early disease progression
- Poor performance status or fitness level
- Preexisting comorbidities
- Lack of access to subsequent therapies
- Poor disease prognostic factors

Adapted from *Clin Genitourin Cancer*, Vol. 18(4), George DJ, et al, Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States, Pages 284-294, Copyright 2020, with permission from Elsevier.

1. Shore ND, et al. *Adv Ther*. 2021:38(8):4520-4540.

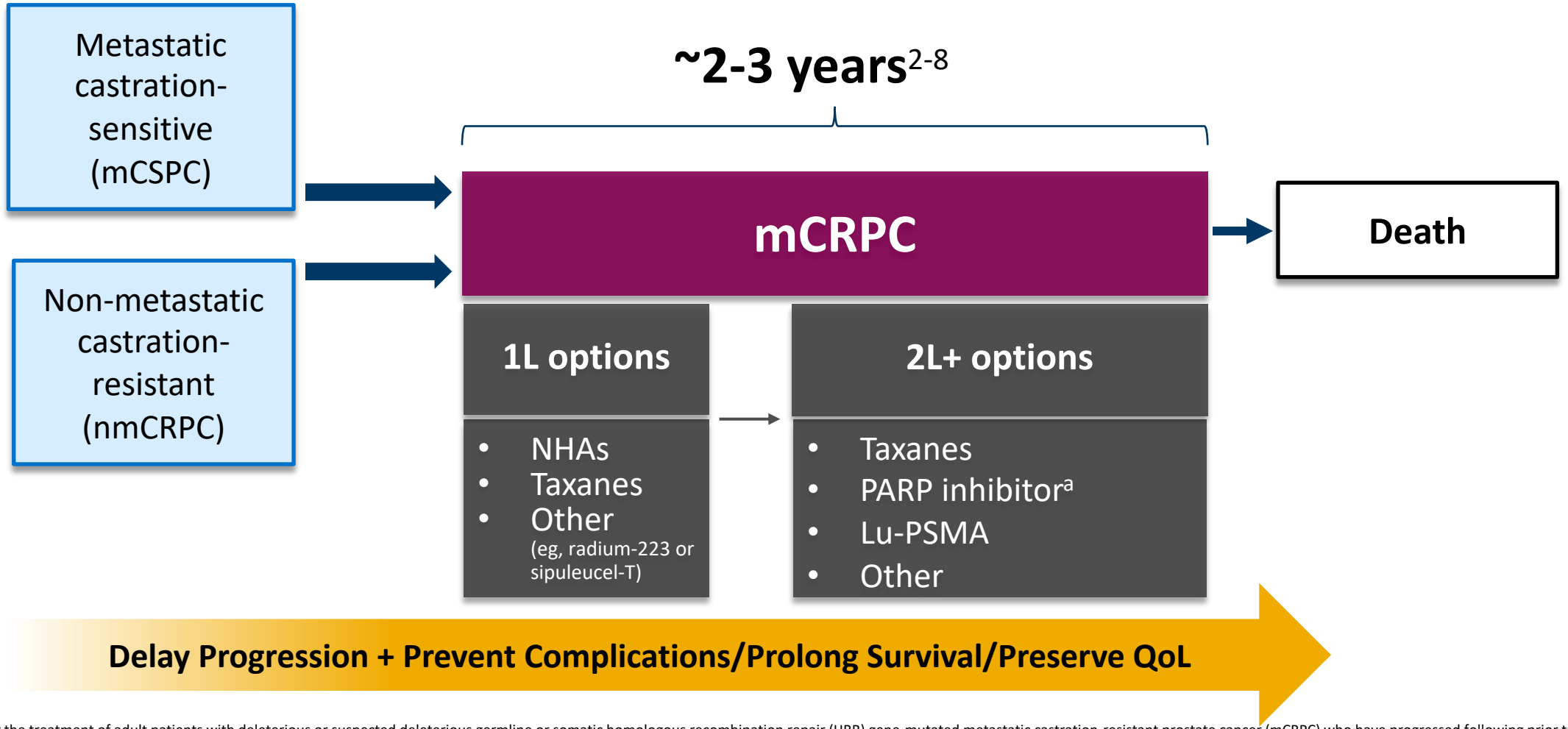
Delaying Disease Progression Is Fundamental[1,2]



- Delay the time to new metastases
- Reduce the need for palliative radiation for painful bone lesions
- Reduce the complications of visceral metastases
- Delay the time before chemotherapy
- Preserve quality of life

Reprinted from *Nat Rev Dis Primers*, Vol. 7(1), Rebello RJ, et al, Prostate cancer, Page 9, Copyright 2021, with permission from Springer Nature.
mCSPC, metastatic castration-sensitive prostate cancer.
1. Eliasson L, et al. *Clin Ther*. 2017;39(4):723-737; 2. George DJ, et al. *Cancer Med*. 2023;12(5):6040-6055.

mCRPC Is Fatal, Despite Currently Available Therapies[1]



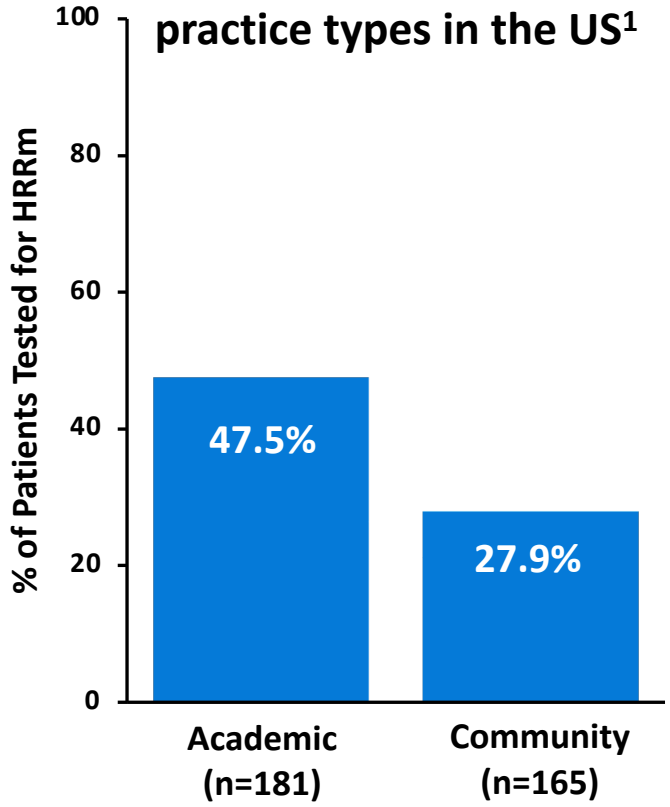
[a] Olaparib is approved for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.[9]

Lu-PSMA, lutetium-177 prostate-specific membrane antigen; mCSPC, metastatic castration-sensitive prostate cancer; NHAs, novel hormonal agents.

1. Scher HI, et al. *J Clin Oncol*. 2016;34(12):1402-1418; 2. Ryan CJ, et al. *Lancet Oncol*. 2015;16(2):152-160; 3. Beer TM, et al. *Eur Urol*. 2017;71(2):151-154; 4. Berthold DR, et al. *J Clin Oncol*. 2008;26(2):242-245; 5. Parker C, et al. *N Engl J Med*. 2013;369(3):213-223; 6. Kantoff PW, et al. *N Engl J Med*. 2010;363(5):411-422; 7. Shore ND, et al. *Adv Ther*. 2021;38(8):4520-4540; 8. George DJ, et al. *Clin Genitourin Cancer*. 2020;18(4):284-294; 9. Lynparza [US prescribing information]. AstraZeneca: Wilmington, DE; 2020.

HRR Testing Is Important but Underutilized in Real-World Practice

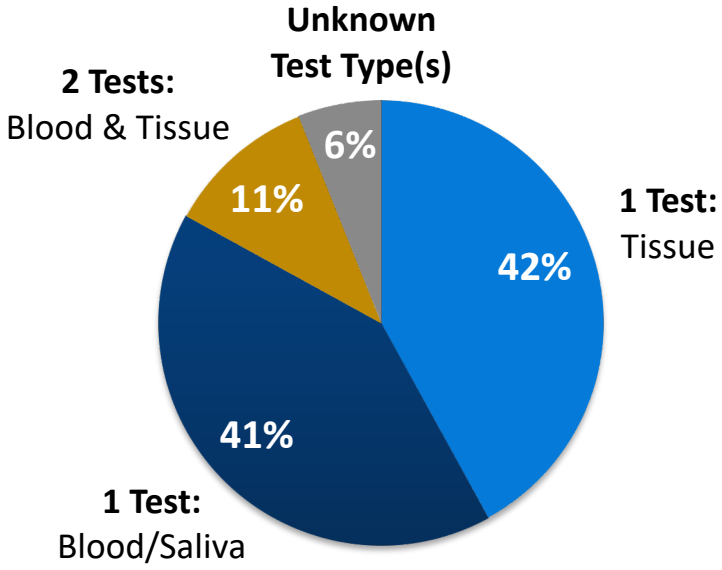
Disparity of testing across practice types in the US[1]



Multitude of barriers to testing[1]

- Germline testing misses ~50% of *BRCAm* in mCRPC[2]
- Inadequate sample available
- ~30% tissue test failure rate[3,4]
- Patient refusal
- Time required to receive test results
- HRR test interpretation is evolving for variants of uncertain significance, which are more common in underrepresented populations[5]
- Reimbursement challenges

Of patients who are tested, vast majority only have 1 test performed[6]



1. Leith A, et al. *Future Oncol*. 2022;18(8):937-951; 2. Lai Z, et al. *BMC Cancer*. 2022;22(1):13; 3. Hussain M, et al. *Clin Cancer Res*. 2022;28(8):1518-1530; 4. Armstrong AJ, et al. Presented at ESMO Annual Congress 2022. 9-13 September 2022; Paris, France. Poster #1370P; 5. Shore ND. Presented at ASCO Annual Congress 2022. June 3-7, 2022; Chicago, IL. Oral presentation 10500; 6. Shore N, et al. *Future Oncol*. 2021;17(22):2907-2921.

Advancing First-Line mCRPC Treatment Options

- **mCRPC is a heterogeneous and lethal disease**
- **Despite multiple available treatment options, outcomes remain poor**
- **Delaying radiographic progression in the first-line is meaningful to patients**
  - <50% receive a subsequent therapy
- **Genetic testing is important but not optimally implemented**
- **Physicians and patients should have the opportunity to choose the treatment option that is right for them**

Clinical Efficacy

Laurence Toms, MD
Global Clinical Head
Late Development Oncology
AstraZeneca

PROpel: Pivotal Phase III Study in All-Comer

N=796

Key eligibility criteria:

- 1L mCRPC: No prior treatment for mCRPC
- No prior abiraterone
  - Other NHAs stopped ≥12 mo
- ECOG 0-1
- Candidate for abiraterone

R 1:1

Olaparib + abiraterone (n=399)

Placebo + abiraterone (n=397)

Stratification factors:

- Site of distant metastases: Bone only vs visceral vs other
- Prior docetaxel at mHSPC: Yes vs no

Primary:

- rPFS (investigator)
  - Sensitivity (BICR)

Key secondary (alpha control):

- OS

Other secondary/exploratory:

- Time to first subsequent therapy or death (TFST)
- HRQoL, PFS2, ORR, PSA response, PSA progression
- HRRm status

Dosage:

- Olaparib/placebo: 300 mg bid
- Abiraterone: 1000 mg qd
- Prednisone or prednisolone: 5 mg bid

Schedule of imaging assessments:

- CT/MRI and bone scans: Q8W for the first 24 weeks, then Q12W

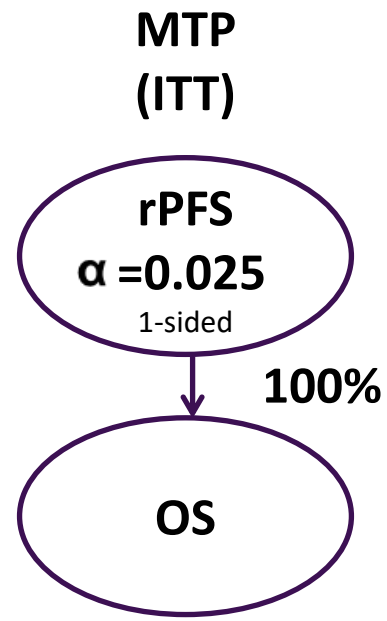
BICR, blinded independent central review; mHSPC, metastatic hormone-sensitive prostate cancer; NHAs, novel hormonal agents; PFS2, time from randomization to second progression or death; PSA, prostate-specific antigen.

PROpel: Clinical Assumptions and Statistical Analysis

Clinical assumptions:

- **rPFS**: Target HR 0.68; median, 24.3 vs 16.5 mo (**Δ 7.8 mo**)

	DCO1 July 30, 2021	DCO2 March 14, 2022	DCO3 October 12, 2022
Time after first patient randomized, mo	**33**	**40**	**47**
rPFS			
Analysis	**Interim**	**Final**	**N/A**
Events, n (%)	394 (49.5)	457 (57.4)	
OS[a]			
Analysis	**Interim**	**Interim**	**Final**
Events, n (%)	228 (28.6)	319 (40.1)	381 (47.9)



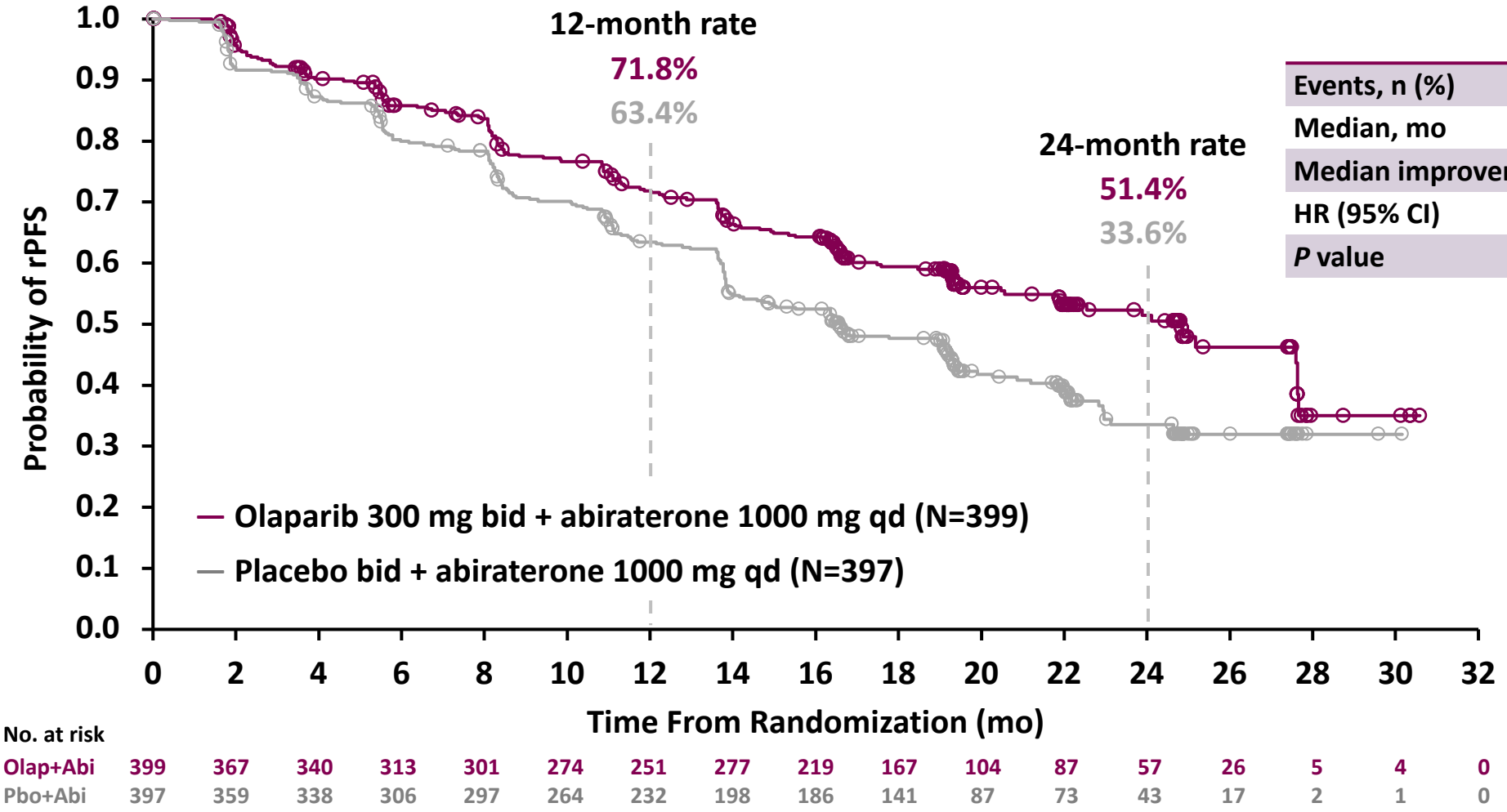
[a] OS power: 55.3% (assumption = median OS in the control arm of 36 mo; HR 0.8).
DCO, data cutoff; MTP, multiple testing procedure; N/A, not available.

PROpel: Key Baseline Disease Characteristics Were Balanced

		Patients, %	
		Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Age, y	Median (min, max)	69.0 (43, 91)	70.0 (46, 88)
	<65	32.6	24.4
	≥65	67.4	75.6
ECOG performance status	(0) Normal activity	71.7	68.5
	(1) Restricted activity	28.1	31.2
Total Gleason score	≤7	30.4	33.8
	8 to 10	66.4	64.9
Baseline S-prostate specific antigen, µg/L	Median	17.9	16.8
Prior docetaxel at mHSPC	Yes	22.6	22.4
Site of metastases	Bone only	54.4	54.7
	Visceral (eg, lung/liver)	13.3	13.1
	Other	32.3	32.2
Baseline pain score (BPI-SF Item 3 score)	0 to <4 (no/mild pain)	71.1	78.1
	4 to ≥6 (moderate/severe pain)	21.3	16.2

Data on missing values are provided in the briefing document.
BPI-SF, Brief Pain Inventory-Short Form; mHSPC, metastatic hormone-sensitive prostate cancer.

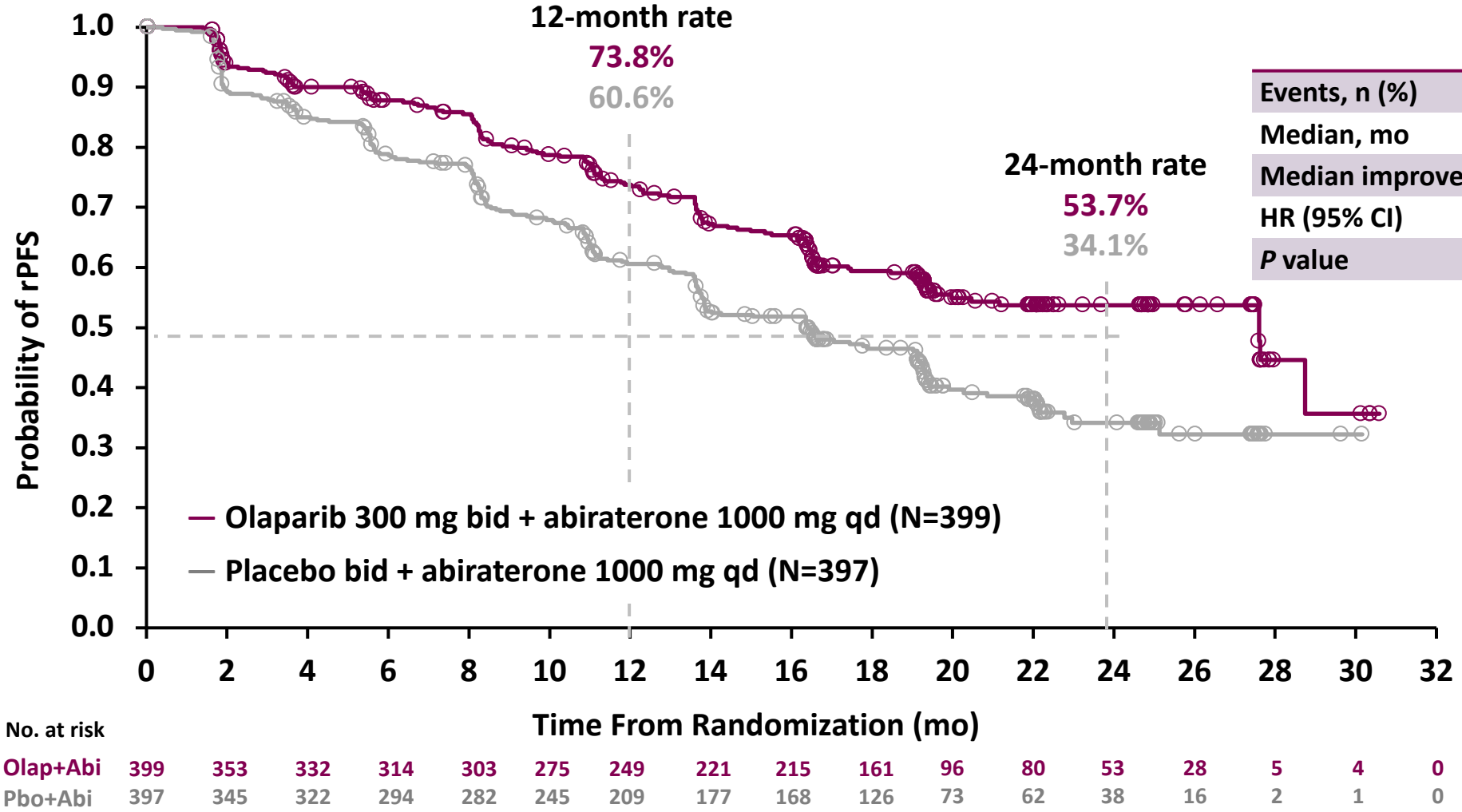
PROpel Showed a Statistically Significant and Clinically Meaningful Benefit in the Primary Endpoint of rPFS (INV)



	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median, mo	24.8	16.6
Median improvement	**8.2 months**	
HR (95% CI)	**0.66** (0.54, 0.81)	
P value	**<0.0001**	

INV, investigator.

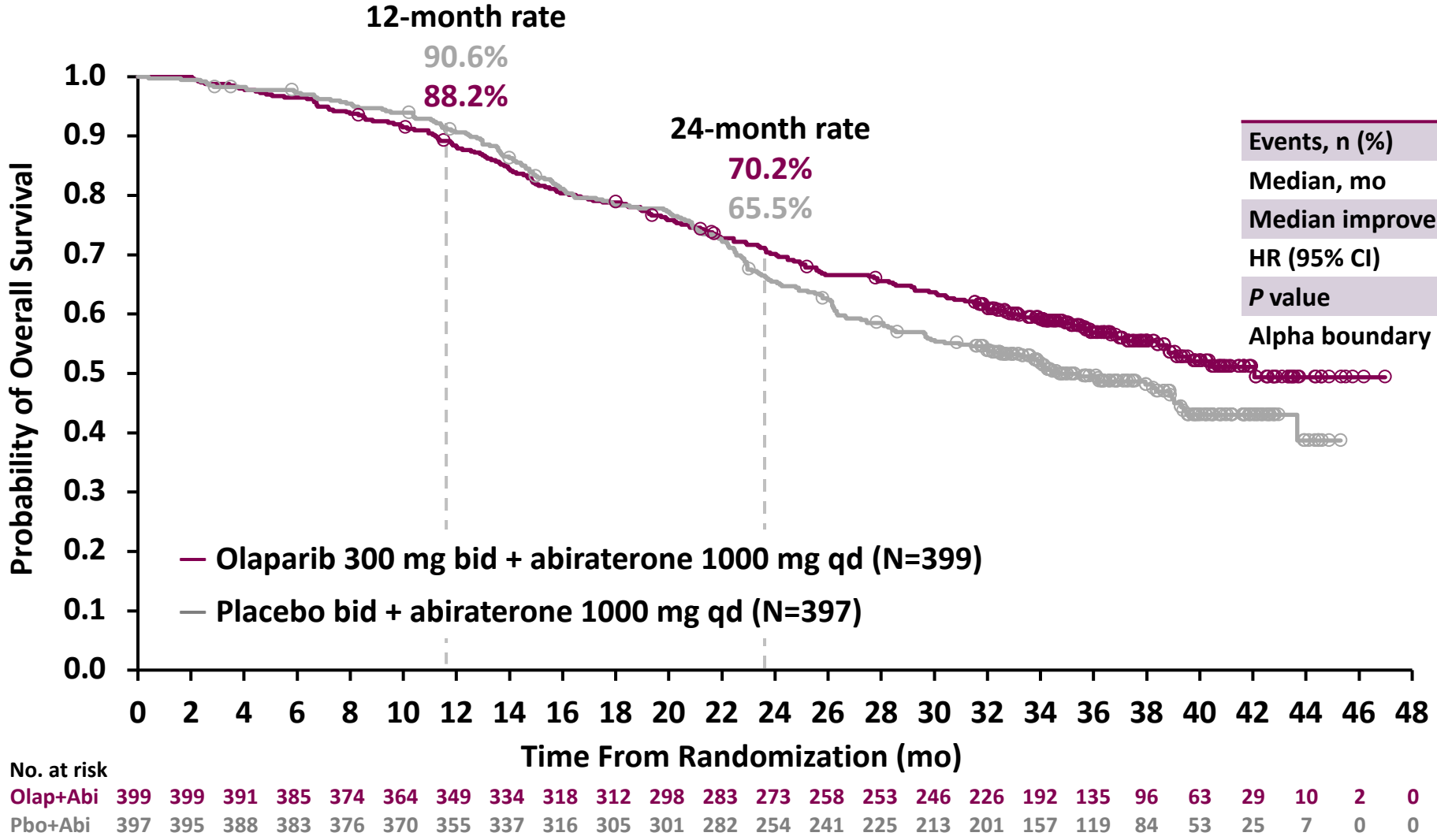
PROpel: BICR Result Confirms the Clinical Benefit Demonstrated by Investigator rPFS



	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median, mo	27.6	16.4
Median improvement	**11.2 months**	
HR (95% CI)	**0.61** (0.49, 0.74)	
***P* value**	<0.0001	

BICR, blinded independent central review.

PROpel: Overall Survival Showed a Clinically Meaningful 19% Reduction in the Risk of Death



	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, mo	42.1	34.7
Median improvement	**7.4 months**	
HR (95% CI)	**0.81** (0.67, 1.00)	
***P* value**	0.0544	
Alpha boundary	0.0377	

No. at risk

Olap+Abi	399	399	391	385	374	364	349	334	318	312	298	283	273	258	253	246	226	192	135	96	63	29	10	2	0
Pbo+Abi	397	395	388	383	376	370	355	337	316	305	301	282	254	241	225	213	201	157	119	84	53	25	7	0	0

Full analysis set (upper bound CI=0.996).

PROpel: Meaningful Clinical Effect Across Endpoints in the ITT Population

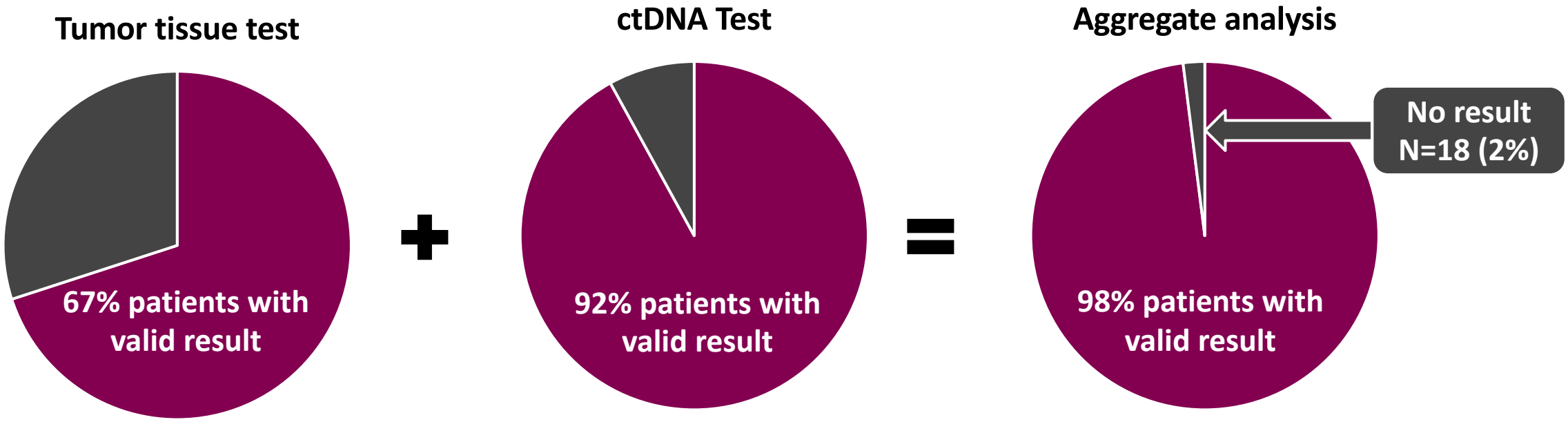
	ITT (N=796)		
	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)	HR (95% CI)
Confirmed PSA 50 response,[a] %	79.3[b]	69.2[c]	
Confirmed ORR,[a] %	52.2[d]	43.8[e]	
Median time to (mo):			
PSA progression[a]	NC	12.0	0.55 (0.45, 0.68)
First subsequent therapy[f]	24.6	19.4	0.76 (0.64, 0.90)
First cytotoxic chemotherapy[f]	32.0	22.4	0.72 (0.61, 0.87)
PFS2,[f] median (mo)	NC	NC	0.76 (0.59, 0.99)
FACT-P overall change from baseline[f,g]	-5.8	-5.3	

[a] At DCO1. [b] Value represents 315/399 patients. [c] Value represents 274/397 patients. [d] Value represents 84/161 patients. [e] Value represents 70/160 patients. [f] At DCO3. [g] Reported as LS means values and based on N=278 for olaparib + abiraterone and N=295 for placebo + abiraterone.

DCO, data cutoff; FACT-P, Functional Assessment of Cancer Therapy – Prostate Cancer; LS, least-squares; NC, not calculable/calculated; ORR, objective response rate; PFS2, time from randomization to second progression or death; PSA, prostate-specific antigen.

PROpel: Aggregate Results From Tissue and ctDNA Provide the Most Complete and Valid Data Set

98% of patients provided both tissue and ctDNA samples



- Reference standard
- Dependent on high-quality sample
- ~30% failure rate reported across prostate cancer studies

- Complements tissue test
- Identifies mutations from any tumor lesion shed into the blood

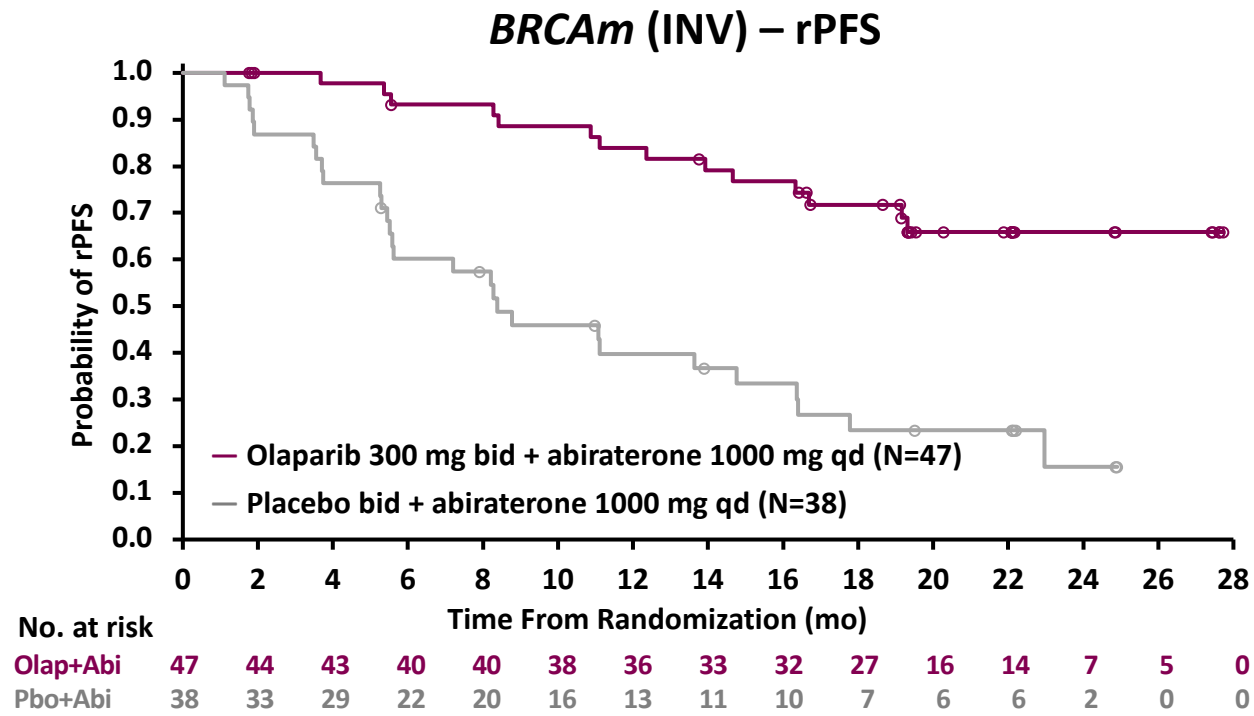
- Maximizes biomarker information
- Minimizes patients with unknown status

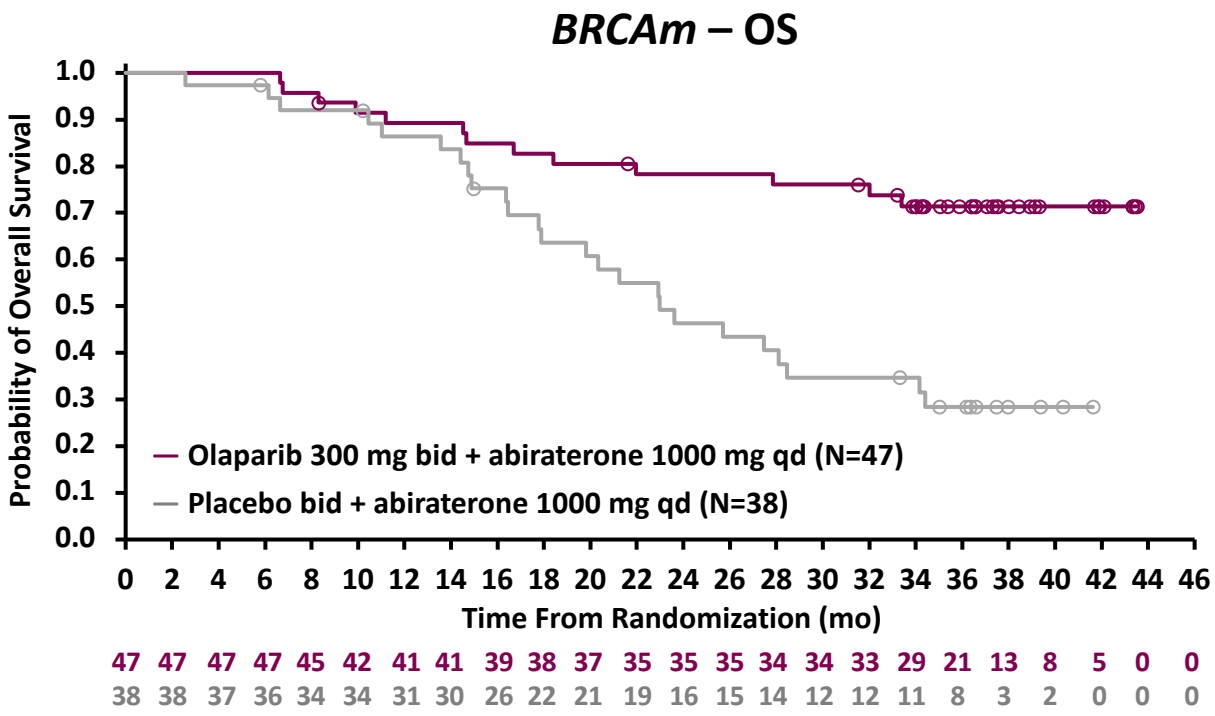
PROpel: Baseline Disease Characteristics in Non-*BRCAm* Subgroup Were Balanced

		Patients, %			
		***BRCAm* (N=85)**		**Non-*BRCAm* (N=693)**	
		Olaparib + Abiraterone (N=47)	**Placebo + Abiraterone (N=38)**	**Olaparib + Abiraterone (N=343)**	**Placebo + Abiraterone (N=350)**
Age, y	Median (min, max)	67.0 (43, 83)	70.0 (46, 85)	69.0 (45, 91)	70.0 (49, 88)
	<65	36.2	28.9	32.4	24.0
	≥65	63.8	71.1	67.6	76.0
ECOG performance status	(0) Normal activity	76.6	52.6	71.4	70.6
	(1) Restricted activity	23.4	47.4	28.3	29.4
Total Gleason score	≤7	21.3	31.6	31.8	33.7
	8-10	72.3	65.8	65.3	65.1
Baseline S-prostate specific antigen, µg/L	Median	29.0	22.5	17.7	16.8
Prior docetaxel at mHSPC	Yes	17.0	26.3	23.0	21.7
Site of metastases	Bone only	53.2	52.6	54.5	55.1
	Visceral (eg, lung/liver)	10.6	21.1	12.8	12.0
	Other	36.2	26.3	32.7	32.9
Baseline pain score (BPI-SF Item 3 score)	0 to <4 (no/mild pain)	66.0	68.4	72.3	78.9
	4 to ≥6 (moderate/severe pain)	31.9	26.3	19.8	15.4

Data on missing values are provided in the briefing document.
BPI-SF, Brief Pain Inventory-Short Form; mHSPC, metastatic hormone-sensitive prostate cancer.

PROpel: Substantial Clinical Benefit of Both rPFS and OS in *BRCAm* Subgroup



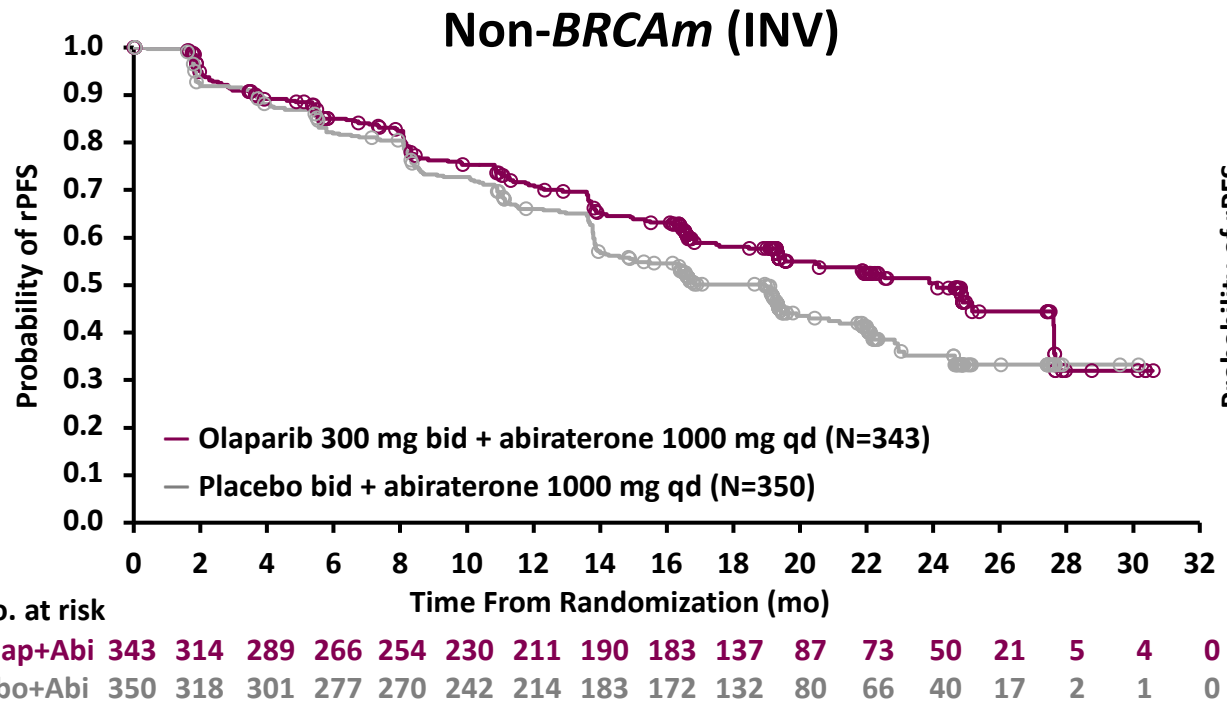


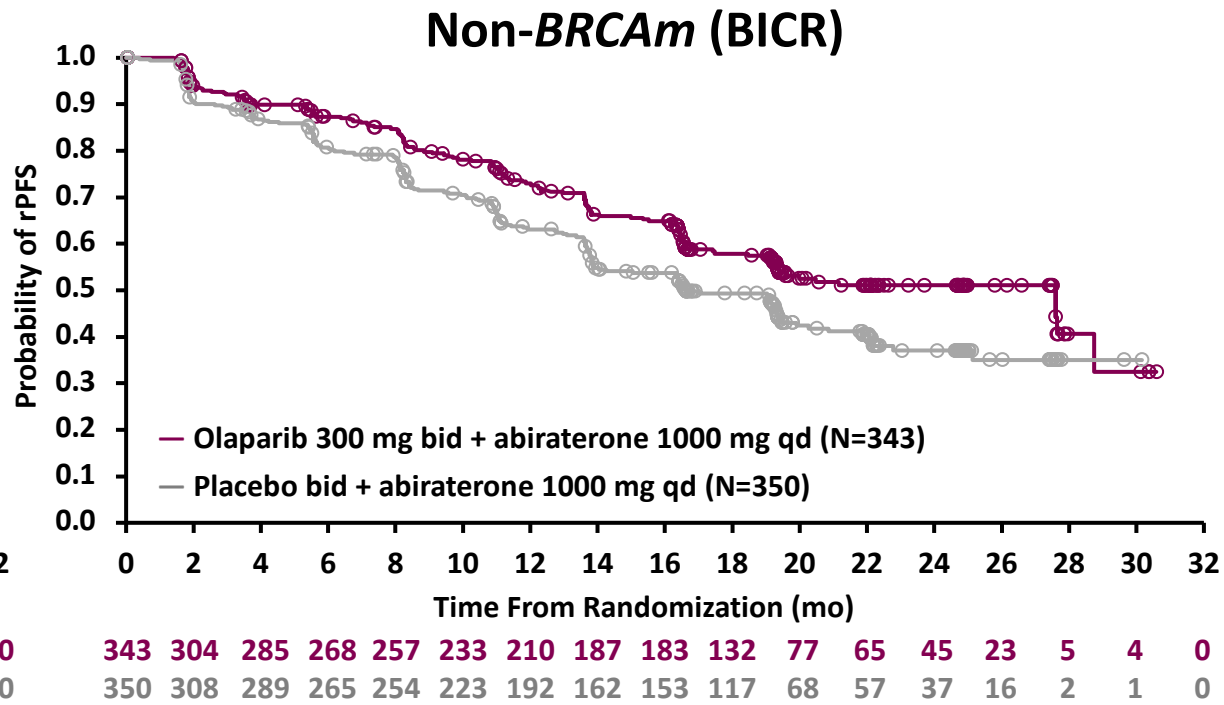
	Olaparib + Abiraterone (N=47)	Placebo + Abiraterone (N=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median, mo	NC	8.4
Median improvement	**NC**	
HR (95% CI)	**0.23** (0.12, 0.43)	

	Olaparib + Abiraterone (N=47)	Placebo + Abiraterone (N=38)
Events, n (%)	13 (27.7)	25 (65.8)
Median, mo	NC	23.0
Median improvement	**NC**	
HR (95% CI)	**0.29** (0.14, 0.56)	

INV, investigator; NC, not calculable/calculated.

PROpel: Clinically Meaningful Benefit in rPFS in Non-*BRCAm* Subgroup





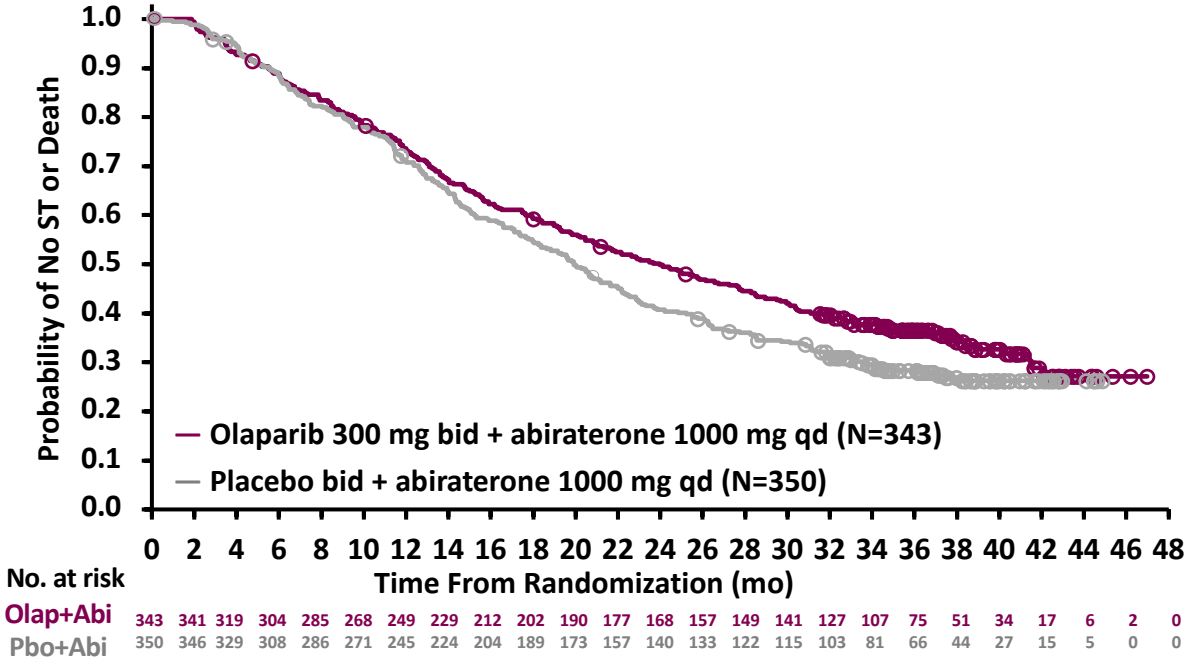
	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	148 (43.1)	194 (55.4)
Median, mo	24.1	19.0
Median improvement	**5.1 months**	
HR (95% CI)	**0.76** (0.61, 0.94)	

	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	141 (41.1)	183 (52.3)
Median, mo	27.6	16.6
Median improvement	**11.0 months**	
HR (95% CI)	**0.72** (0.58, 0.90)	

BICR, blinded independent central review; INV, investigator.

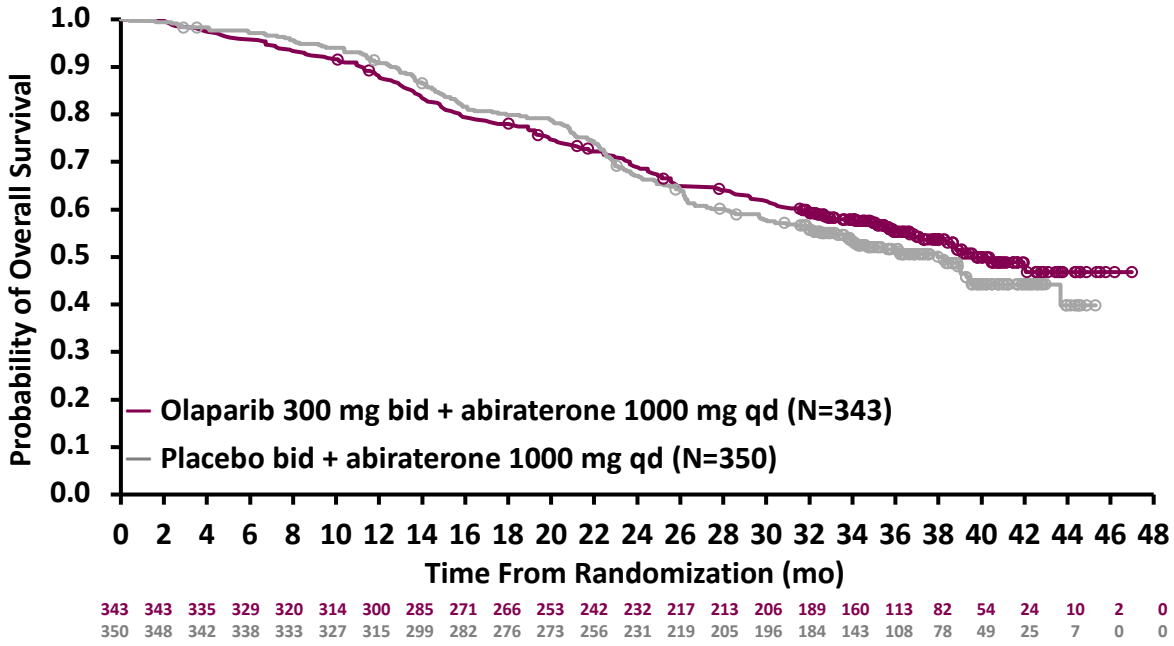
PROpel: TFST and Overall Survival in Non-*BRCAm* Subgroup

Non-*BRCAm*: Time to First Subsequent Therapy



	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	224 (65.3)	250 (71.4)
Median, mo	24.0	19.9
Median improvement	**4.1 months**	
HR (95% CI)	**0.84** (0.70, 1.01)	

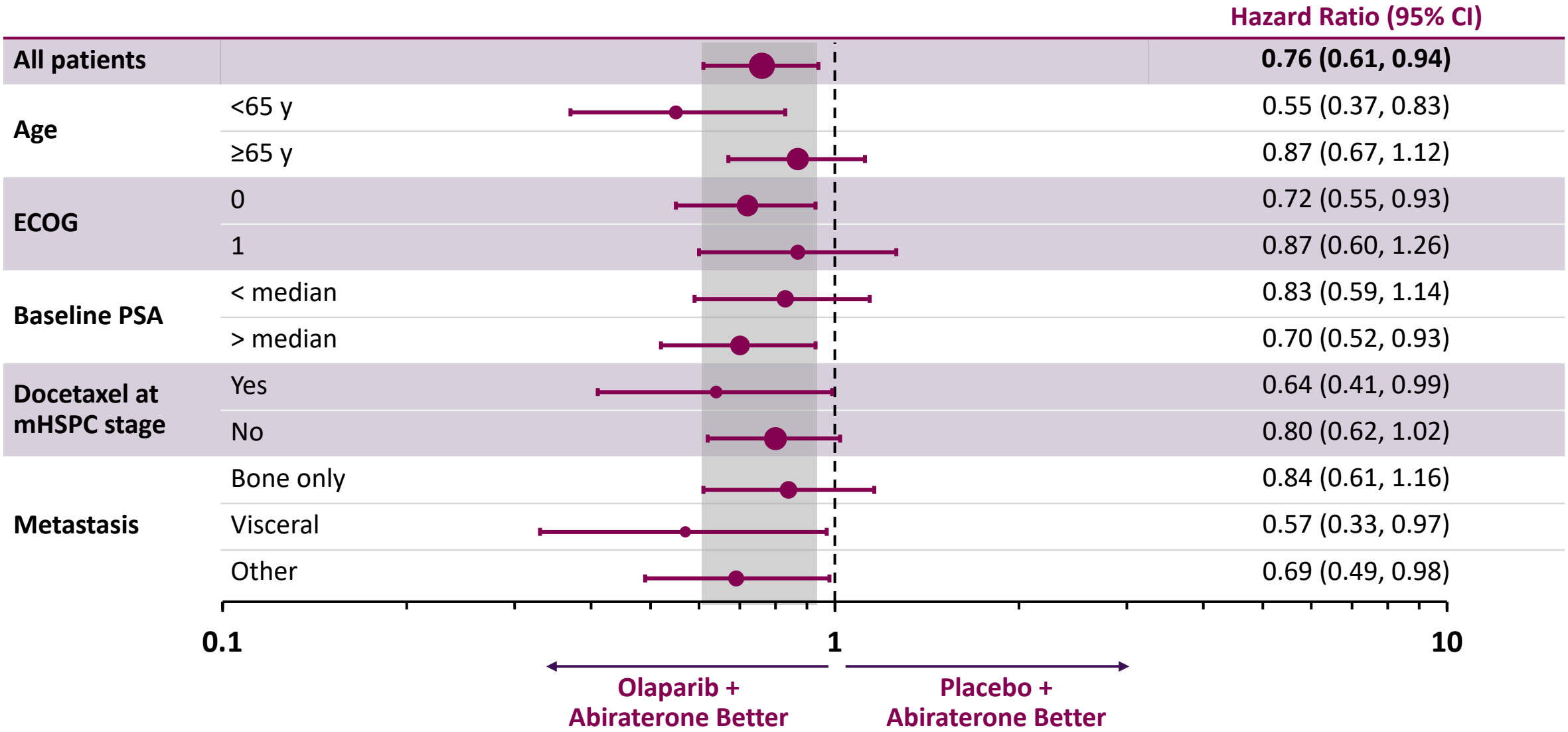
Non-*BRCAm*: Overall Survival



	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	158 (46.1)	176 (50.3)
Median, mo	39.6	38.0
Median improvement	**1.7 months**[a]	
HR (95% CI)	**0.91** (0.73, 1.13)	

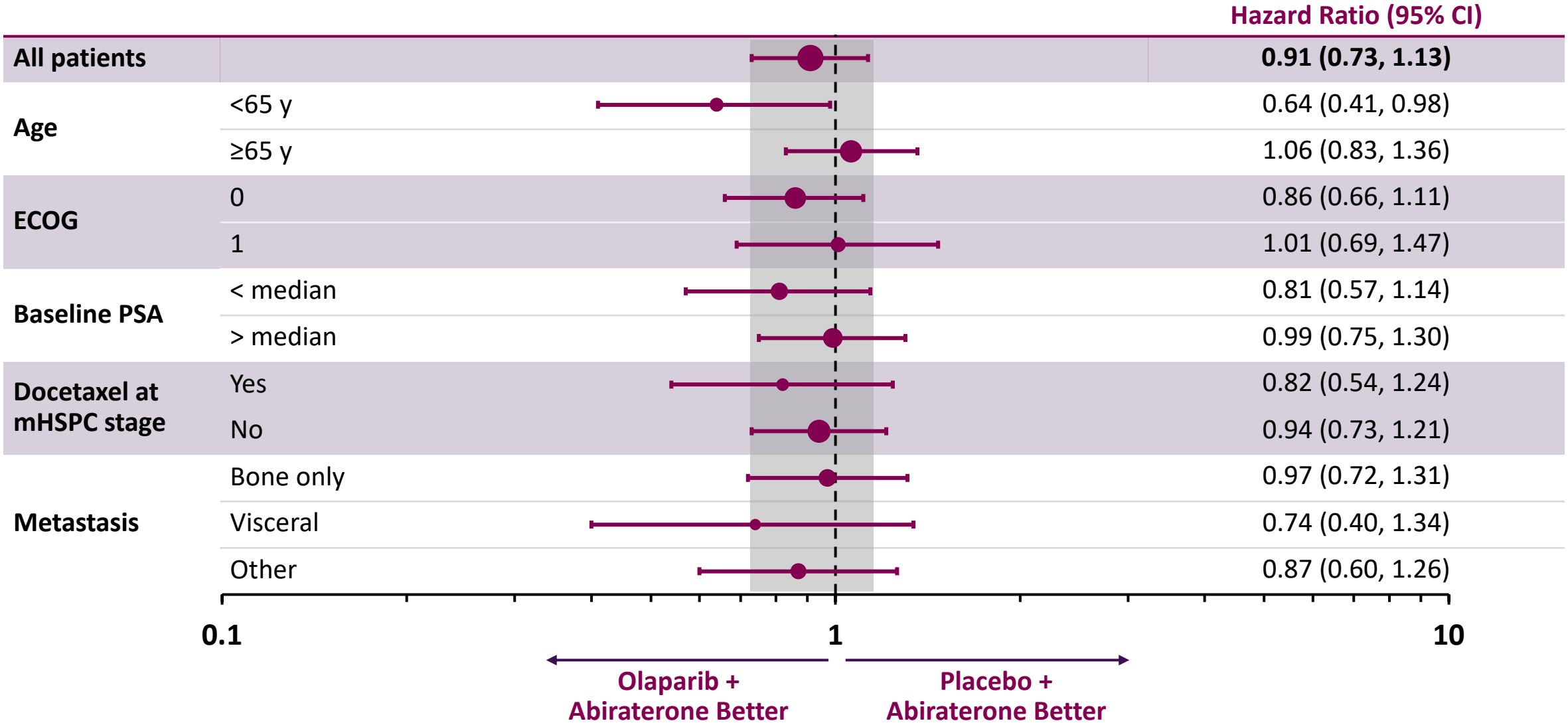
[a] Based on rounded value of 1.67 mo (using unrounded values of 39.62 mo – 37.95 mo).

PROpel: rPFS (INV) Subgroup Analysis for Non-*BRCAm*



INV, investigator; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

PROpel: OS Subgroup Analysis for Non-*BRCAm*



mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

PROpel: Meaningful Clinical Effect Across Endpoints in the Non-*BRCAm* Subgroup

	Non-*BRCAm* (N=693)		
	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)	HR (95% CI)
Confirmed PSA 50 response,[a] %	78.6[b]	71.4[c]	
Confirmed ORR,[a] %	51.1[d]	45.4[e]	
Median time to (mo):			
PSA progression[a]	22.1	13.1	0.63 (0.50, 0.79)
First subsequent therapy[f]	24.0	19.9	0.84 (0.70, 1.01)
First cytotoxic chemotherapy[f]	30.1	22.7	0.80 (0.66, 0.97)
PFS2,[f] median (mo)	NC	NC	0.86 (0.65, 1.14)
FACT-P overall change from baseline[f,g]	-6.3	-5.3	

[a] At DCO1. [b] Value represents 268/341 patients. [c] Value represents 250/350 patients. [d] Value represents 70/137 patients. [e] Value represents 64/141 patients. [f] At DCO3. [g] Reported as LS means values and based on N=236 for olaparib + abiraterone and N=261 for placebo + abiraterone.

DCO, data cutoff; FACT-P, Functional Assessment of Cancer Therapy – Prostate Cancer; NC, not calculable/calculated; PFS2, time from randomization to second progression or death; PSA, prostate-specific antigen.

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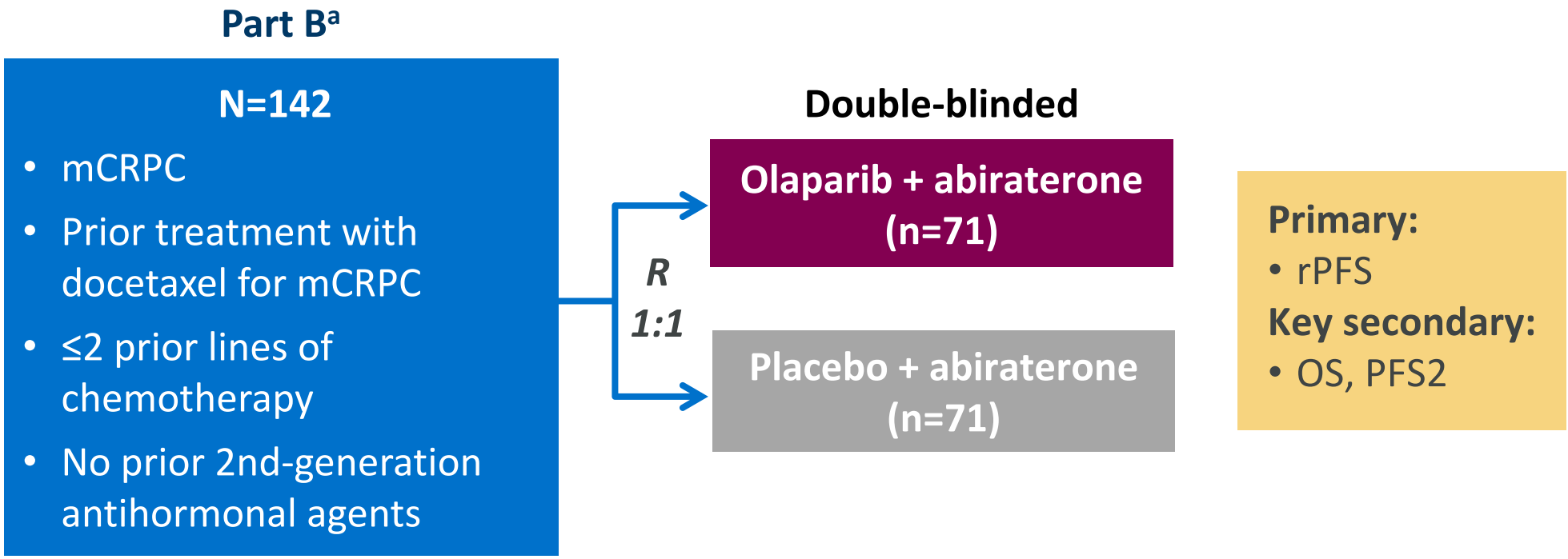
Issue #1

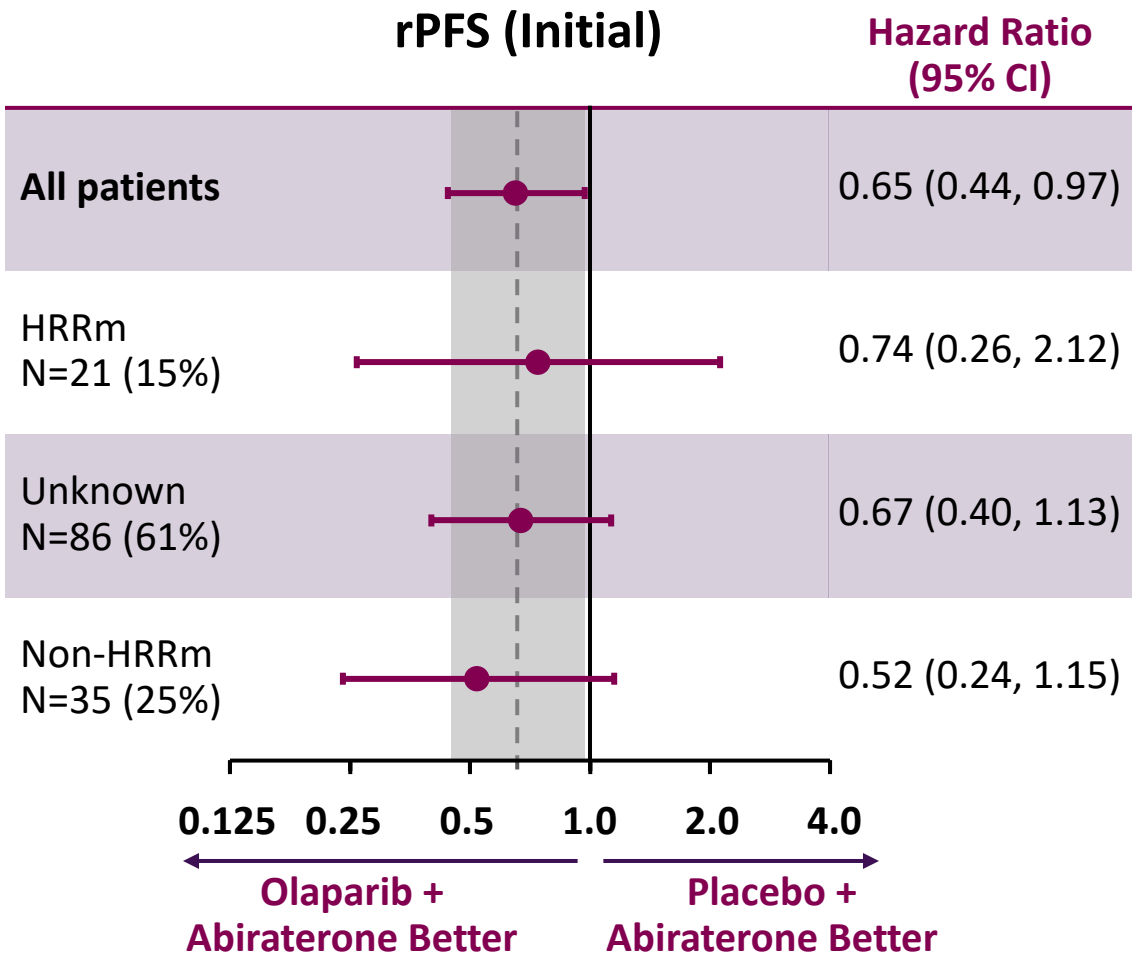
PROpel Population and Stratification

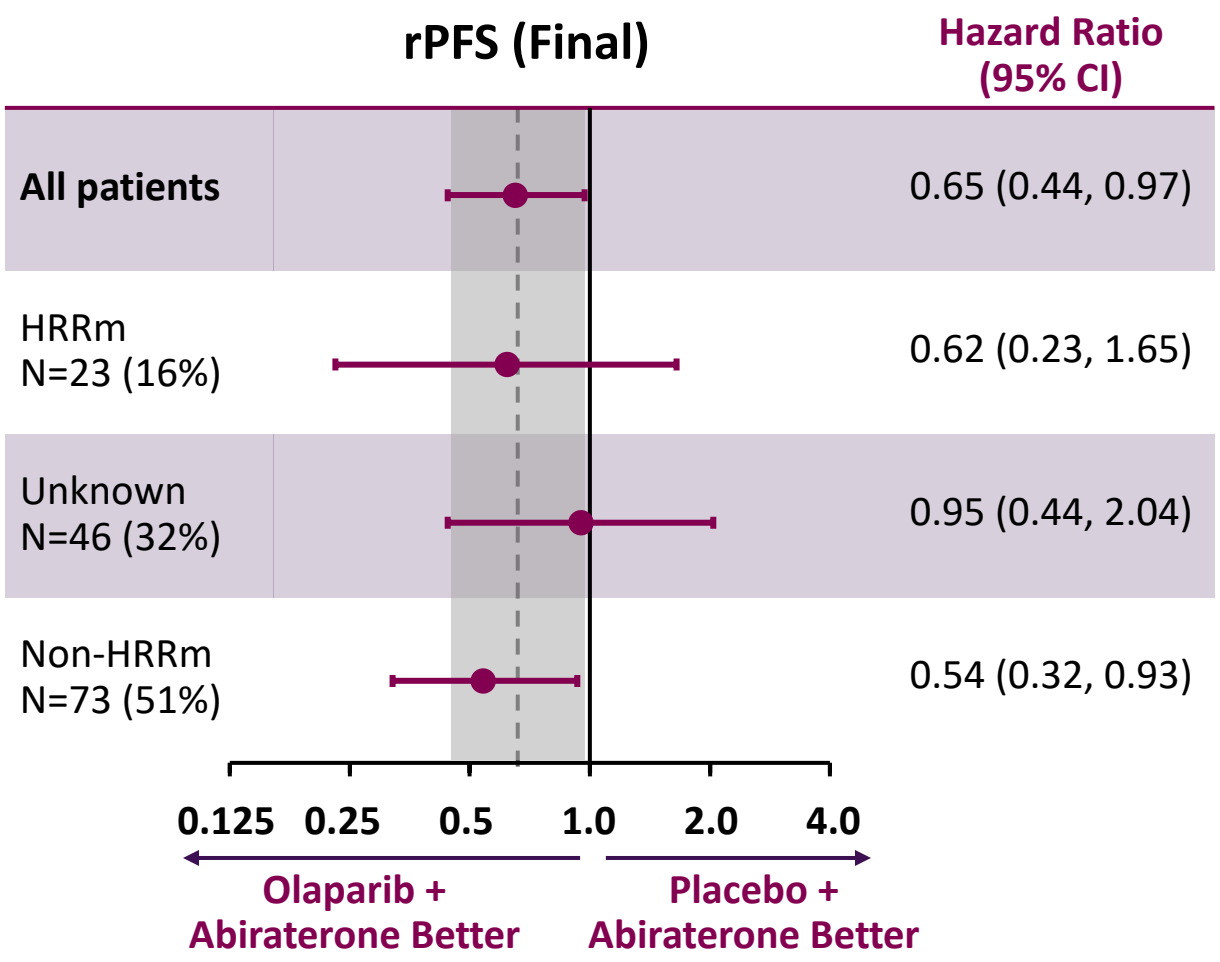
Study 8: Proof of Concept for Olaparib + Abiraterone Combination



[a] First patient in = November 25, 2014; last patient in = July 14, 2015.
PFS2, time from randomization to second progression or death.

Study 8 Did Not Demonstrate HRRm Was a Predictive Biomarker for Clinical Benefit





PROpel: Decision to Not Stratify by HRRm/*BRCAm* Was Evidence Based, Data Remain Interpretable

- **Why did we not stratify by HRRm/*BRCAm*?**
  - Study 8 did not demonstrate HRRm was predictive
  - Limited evidence of HRRm/*BRCAm* as prognostic factors in mCRPC in 2018
  - Stratified by known prognostic factors
- **Reliable estimation of treatment effects**
  - *BRCAm* and non-*BRCAm* distribution were well balanced between arms
  - Baseline characteristics were well balanced within non-*BRCAm* groups

Prospective stratification would not have affected tissue test failure rate

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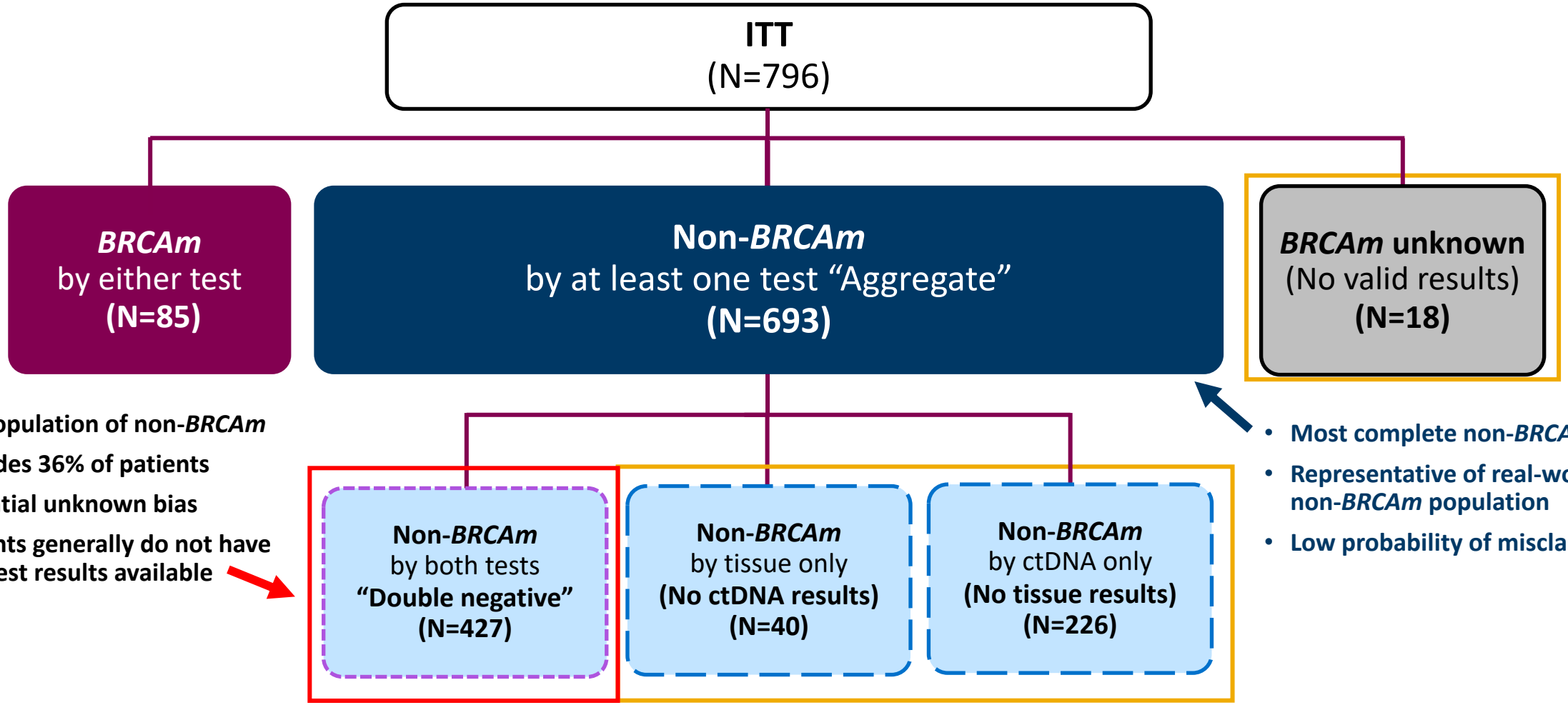
Issue #2

PROpel Biomarker Status

PROpel: Aggregate Non-*BRCAm* Includes Patients Negative by Either or Both Tests



- Subpopulation of non-*BRCAm*
- Excludes 36% of patients
- Potential unknown bias
- Patients generally do not have two test results available

- Most complete non-*BRCAm* dataset
- Representative of real-world non-*BRCAm* population
- Low probability of misclassification

FDA: "Non-*BRCAm*"

FDA: "Undetermined *BRCA* status"

PROpel: Clinical Benefit Demonstrated Beyond *BRCAm* Subgroup

FDA Briefing Document:
Table 1: PROpel: rPFS and OS by *BRCA* Mutation Status

Aggregate Non*-BRCAm

	ITT (N=796, 100%)		*BRCAm*[1] (N=85, 11%)		Undetermined *BRCA* status[2] (N=284, 35%)		non-*BRCAm*[3] (N=427, 54%)	
	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P
rPFS (INV)								
Median in months (range)	25 (20, 28)	17 (14, 19)	NR (19, NR)	8 (6, 15)	NR (10, NR)	19 (14, 22)	22 (17, 25)	17 (14, 19)
HR[4] (95%CI)	0.66 (0.54, 0.81)		0.24 (0.12, 0.46)		0.66 (0.46, 0.94)		0.85 (0.66, 1.11)	
rPFS (BICR)								
Median in months (range)	28 (20, NR)	16 (14,19)	NR (NR, NR)	8 (4,16)	NR (19, NR)	19 (14, 22)	20 (17,28)	17 (14,19)
HR[4] (95%CI)	0.61 (0.49, 0.74)		0.19 (0.1, 0.37)		0.59 (0.41, 0.85)		0.82 (0.62, 1.08)	
OS								
Median in months (range)	42 (38, NC)	35 (31, 39)	NR (NR, NR)	23 (18,34)	NR (40, NR)	38 (28, 39)	37 (33, NR)	38 (31, NR)
HR[4] (95%CI)	0.81 (0.67, 1.00)		0.3 (0.15, 0.6)		0.73 (0.52, 1.03)		1.06 (0.81, 1.39)	

***Double negative Non*-BRCAm**

[*] 18 patients unknown by either test included in FDA undetermined group. [1] Either ctDNA or tissue test positive. [2] Either ctDNA or tissue test negative & other test unknown or both tests unknown. [3] Both ctDNA & tissue tests negative.

PROpel: Low Probability of Misclassification of *BRCAm* Patients by ctDNA

- High overall agreement (94%) between tissue and ctDNA tests
- ~3% probability of misclassification is estimated based on:
  - Positive percent agreement for *BRCAm* is 74%
  - *BRCAm* prevalence in mCRPC is 11%
- **Out of 226 patients with ctDNA negative and tissue test unknown, ~6 *BRCAm (3%)* patients could have been misclassified as non-*BRCAm***

Multiple sensitivity analyses, reclassifying and removing patients from the non-*BRCAm* analysis populations, show minimal impact on the estimated treatment effect

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Issue #3

Overall Survival in *BRCAm*-Negative Patients Across Trials

External Evidence Does Not Support OS Detriment in PROpel

Prostate Cancer – Study 8 Double Negative OS >1[a]

- **Significant limitations of this analysis:**
  - Limited tissue availability: 38 patients (27%) had valid results
  - High variability: Small sample size (n=23), sparse events (n=18) limit interpretation (OS HR 2.77 [95% CI: 1.06, 8.06])
- ***BRCA*-undetermined patients show clinical benefit**
  - OS HR 0.71 (95% CI: 0.43, 1.16); 112 patients, 65 events

Ovarian Cancer – Indication Restrictions Due to OS Detriment[b]

- Different tumor type and line of therapy
- Different treatment regimens (mono- vs combination therapy)
  - PROpel based on potential for combination to drive benefit outside of *BRCAm*/HRRm

[a] From Table 10 (Pg 21) of FDA Briefing Document. [b] From Table 4 (Pg 15) of FDA Briefing Document.

PROpel: Subsequent Anticancer Therapies in Non-*BRCAm* Subgroup

- No clinically significant differences in use of subsequent therapies
- Most common subsequent therapies are taxanes and novel hormonal agents

Non-*BRCAm* (Aggregate)	n/N (%)	
	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Patients with any subsequent anticancer therapy	**157/343 (45.8)**	**191/350 (54.6)**
Patients with any subsequent anticancer therapy, *in patients who discontinued all study treatment*	**157/255 (61.6)**	**191/276 (69.2)**

Non-*BRCAm* (Double Negative)	Olaparib + Abiraterone (N=214)	Placebo + Abiraterone (N=213)
Patients with any subsequent anticancer therapy	**109/214 (50.9)**	**121/213 (56.8)**
Patients with any subsequent anticancer therapy, *in patients who discontinued all study treatment*	**109/173 (63.0)**	**121/167 (72.5)**

Efficacy Conclusions

- **PROpel met its predefined primary endpoint**
  - 34% reduction in risk of progression or death
- **There was a trend to improved OS in the ITT population**
  - 19% reduction in risk of death
- **The aggregate non-*BRCAm* subgroup is the most complete and relevant to the real-world population**
  - 5 months as assessed by investigators and 11 months by BICR
  - No evidence that OS is compromised (HR 0.91)
  - Totality of evidence support a meaningful clinical benefit in non-*BRCAm* patients

Clinical Safety

Simon Turner, PhD

Executive Director, Patient Safety Oncology

AstraZeneca

Olaparib and Abiraterone Have Well-Established Safety Profiles

Olaparib

Extensive exposure across multiple tumor types

- >20,000 patients in the clinical program
- >140,000 patient-years in marketed use

Safety profile includes:

- Hematologic effects (predominantly anemia)
- Gastrointestinal disturbances (nausea/vomiting, diarrhea)
- Fatigue/asthenia

Abiraterone

Approved for use in mCRPC (2011)

- Used with prednisone (5 mg bid)

Safety profile includes:

- Bone/muscle pain
- CV effects (hypertension, edema, hypokalemia, heart failure/MI, arrhythmia)
- Infections (eg, upper respiratory tract and urinary tract infections)

MI, myocardial infarction.

PROpel: Olaparib Increases Duration of Exposure to Abiraterone

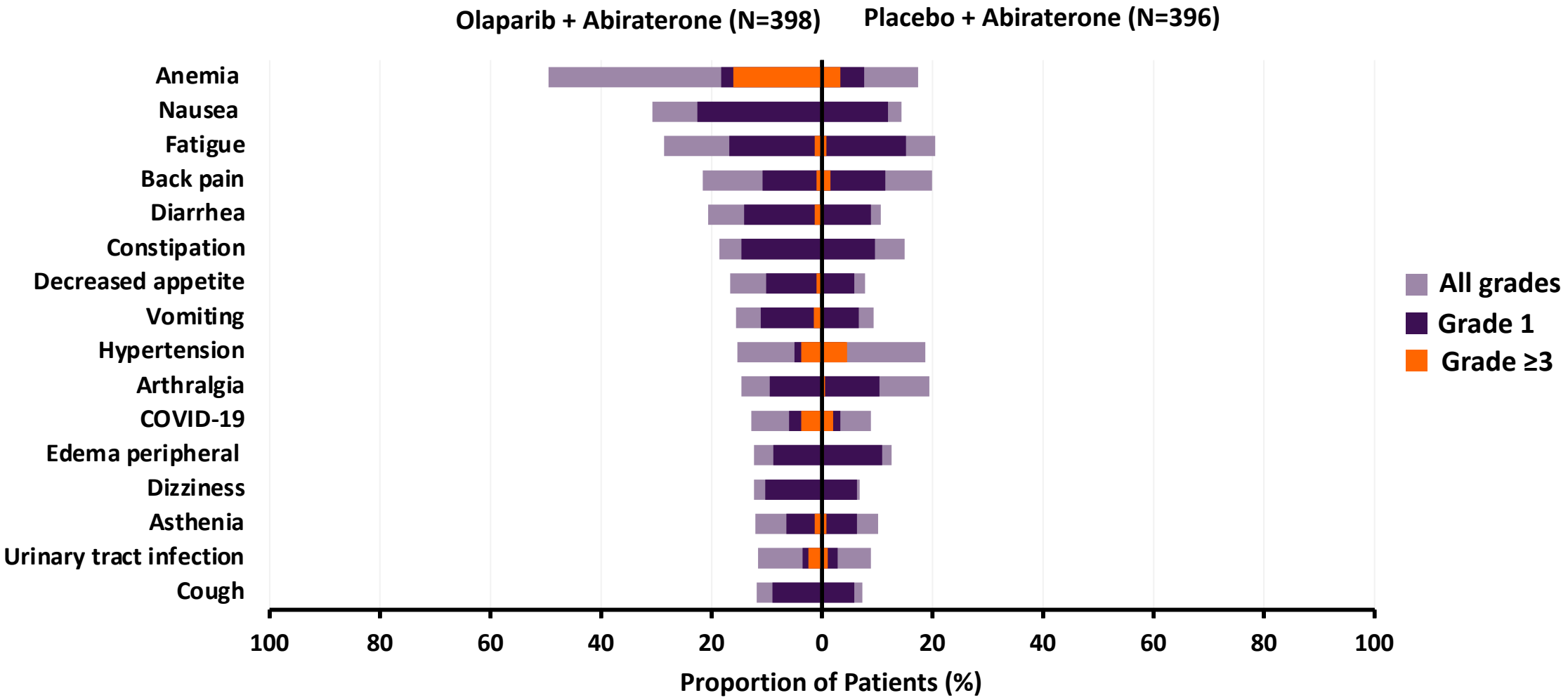
		Olaparib + Abiraterone		Placebo + Abiraterone	
		Olaparib (N=398)	Abiraterone (N=398)	Placebo (N=396)	Abiraterone (N=396)
Median total treatment duration (mo)		**18.5**	**20.1**	**15.7**	**15.7**
Cumulative exposure over time (% patients on treatment)	**≥12 mo**	62.3	66.1	59.8	60.1
	≥24 mo	40.2	43.5	30.8	31.6
	≥36 mo	16.1	17.8	14.6	14.9

PROpel: Safety Summary

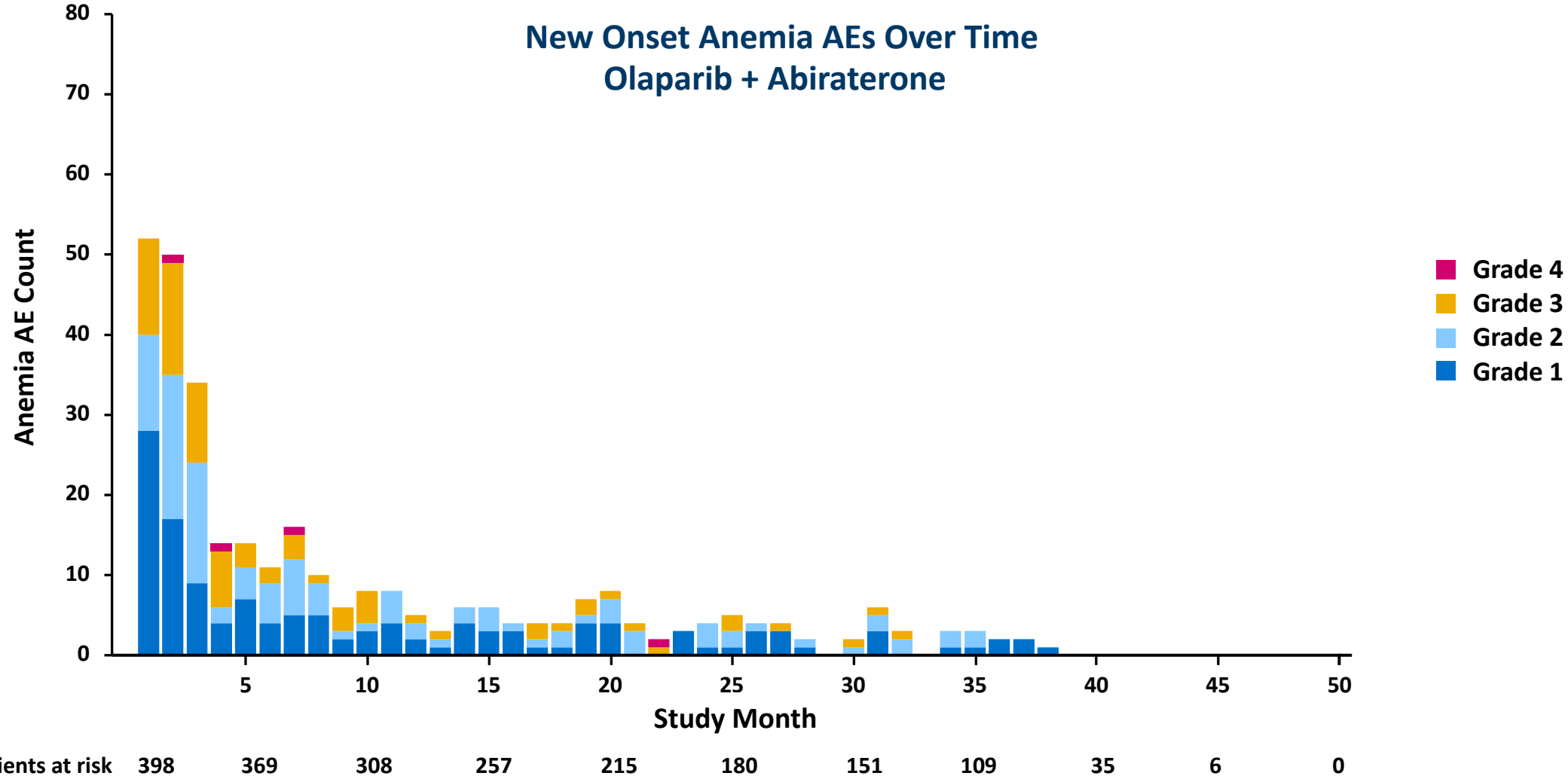
	Patients, n (%)	
	Olaparib + Abiraterone (N=398)	Placebo + Abiraterone (N=396)
Any AE	389 (97.7)	380 (96.0)
Any AE of CTCAE grade ≥3	222 (55.8)	171 (43.2)
Any SAE	161 (40.5)	126 (31.8)
Any AE with outcome of death	26 (6.5)	20 (5.1)
Any AE leading to dose interruption of olaparib/placebo	195 (49.0)	112 (28.3)
Any AE leading to dose reduction of olaparib/placebo	90 (22.6)	24 (6.1)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3)	34 (8.6)
Any AE leading to dose interruption of abiraterone	145 (36.4)	95 (24.0)
Any AE leading to dose reduction of abiraterone	10 (2.5)	17 (4.3)
Any AE leading to discontinuation of abiraterone	45 (11.3)	37 (9.3)

CTCAE, Common Terminology Criteria for Adverse Events.

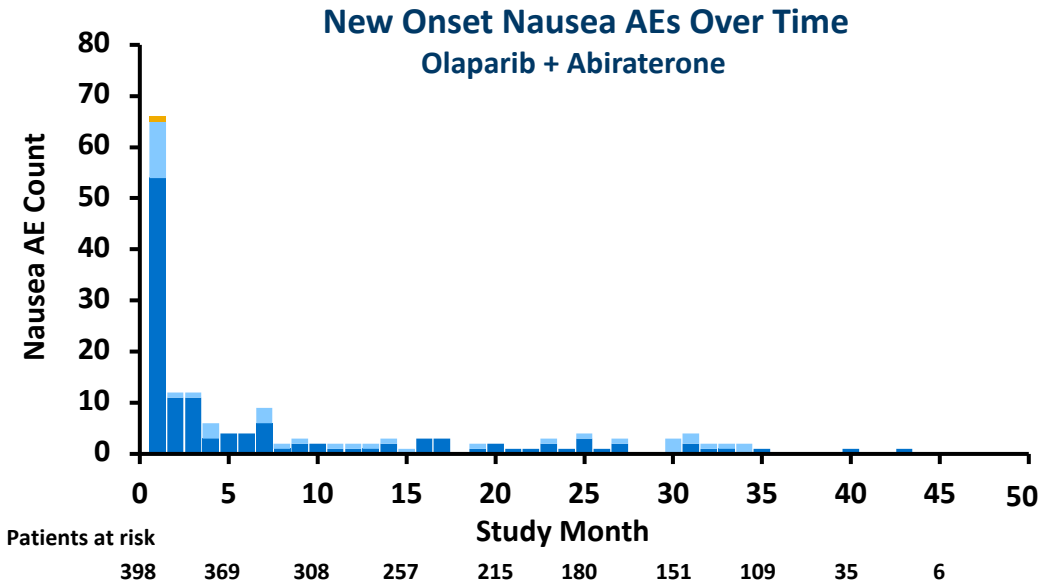
PROpel: Safety of Olaparib and Abiraterone Consistent With Their Known Safety Profiles

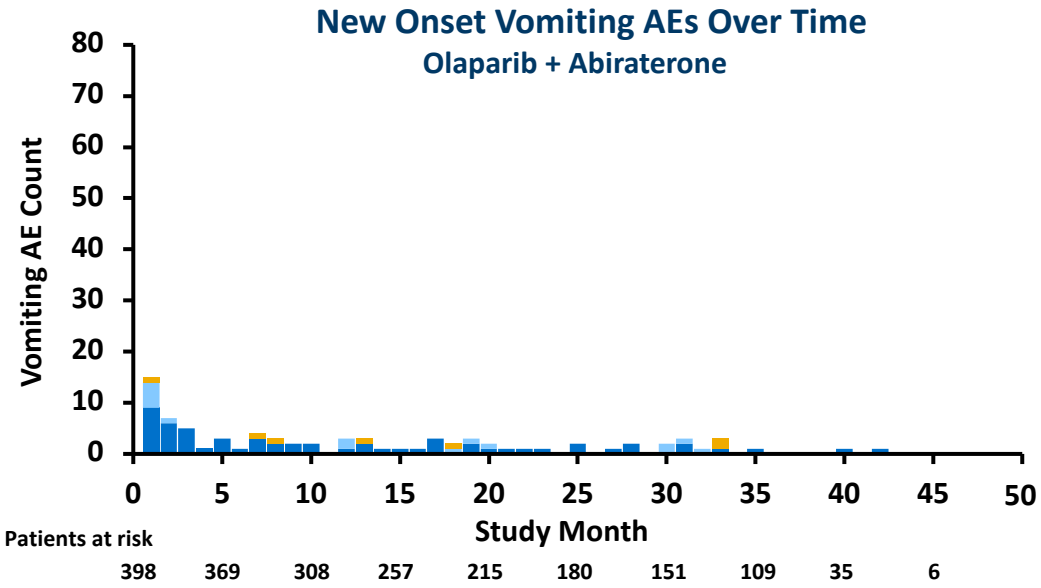


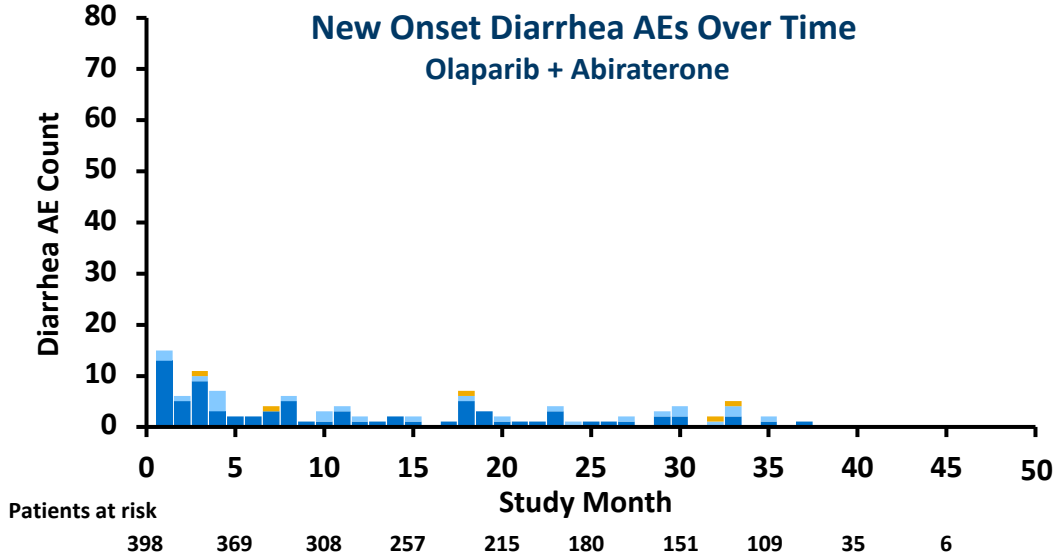
PROpel: Most Anemia AEs Occur Early and Were Manageable



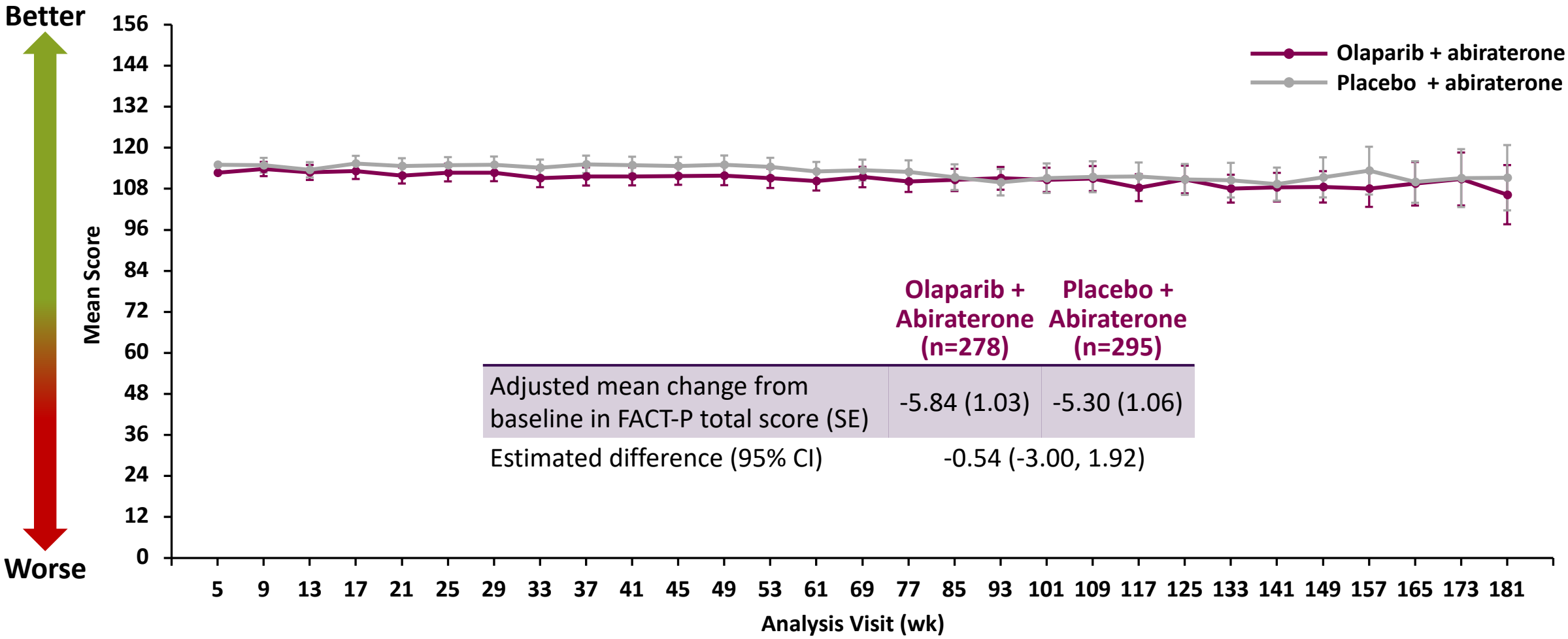
PROpel: Most GI AEs Occur Early and Were Manageable







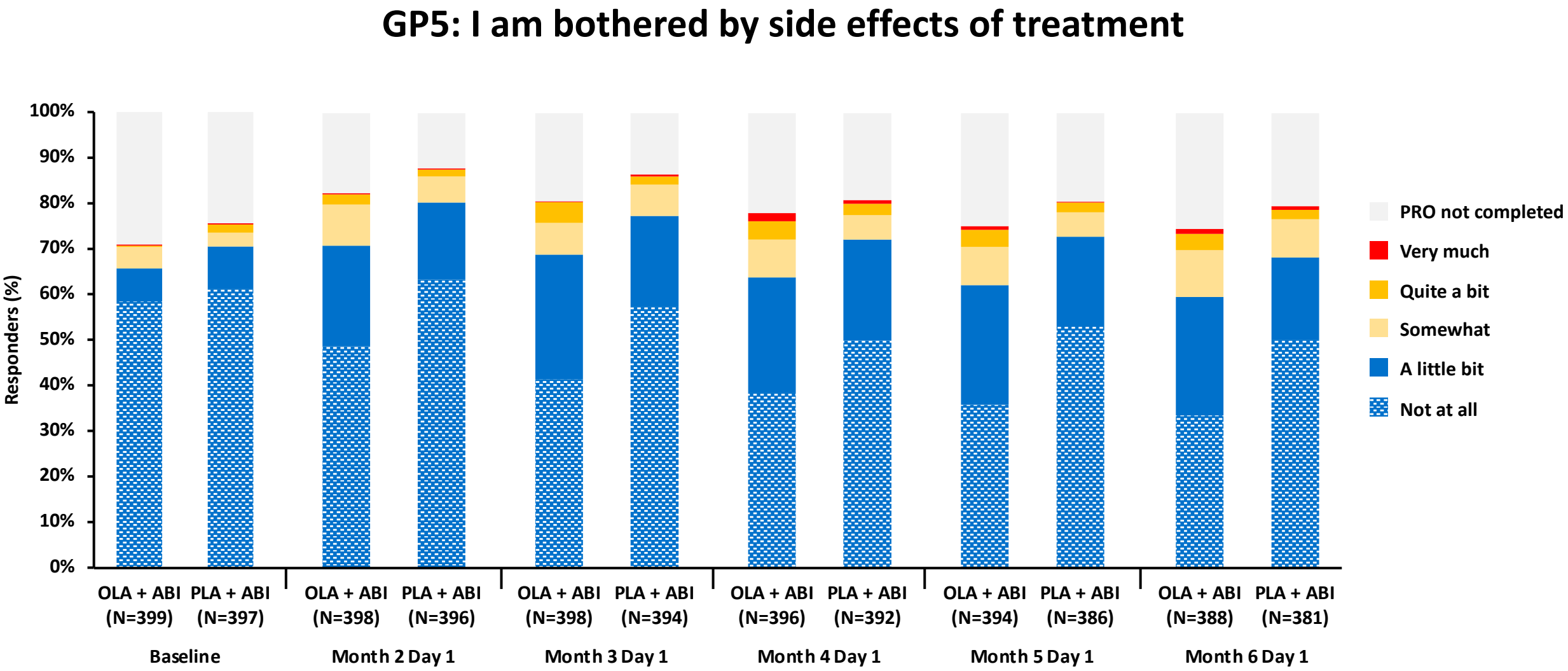
PROpel: Adding Olaparib to Abiraterone Had No Clinically Meaningful Impact on HRQoL



	Olaparib + Abiraterone (n=278)	Placebo + Abiraterone (n=295)
Adjusted mean change from baseline in FACT-P total score (SE)	-5.84 (1.03)	-5.30 (1.06)
Estimated difference (95% CI)	-0.54 (-3.00, 1.92)	

FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156. A clinically meaningful change in FACT-P total score is 10.
FACT-P, Functional Assessment of Cancer Therapy – Prostate Cancer.

PROpel: Most Patients Had Little/No Bother by Side Effects

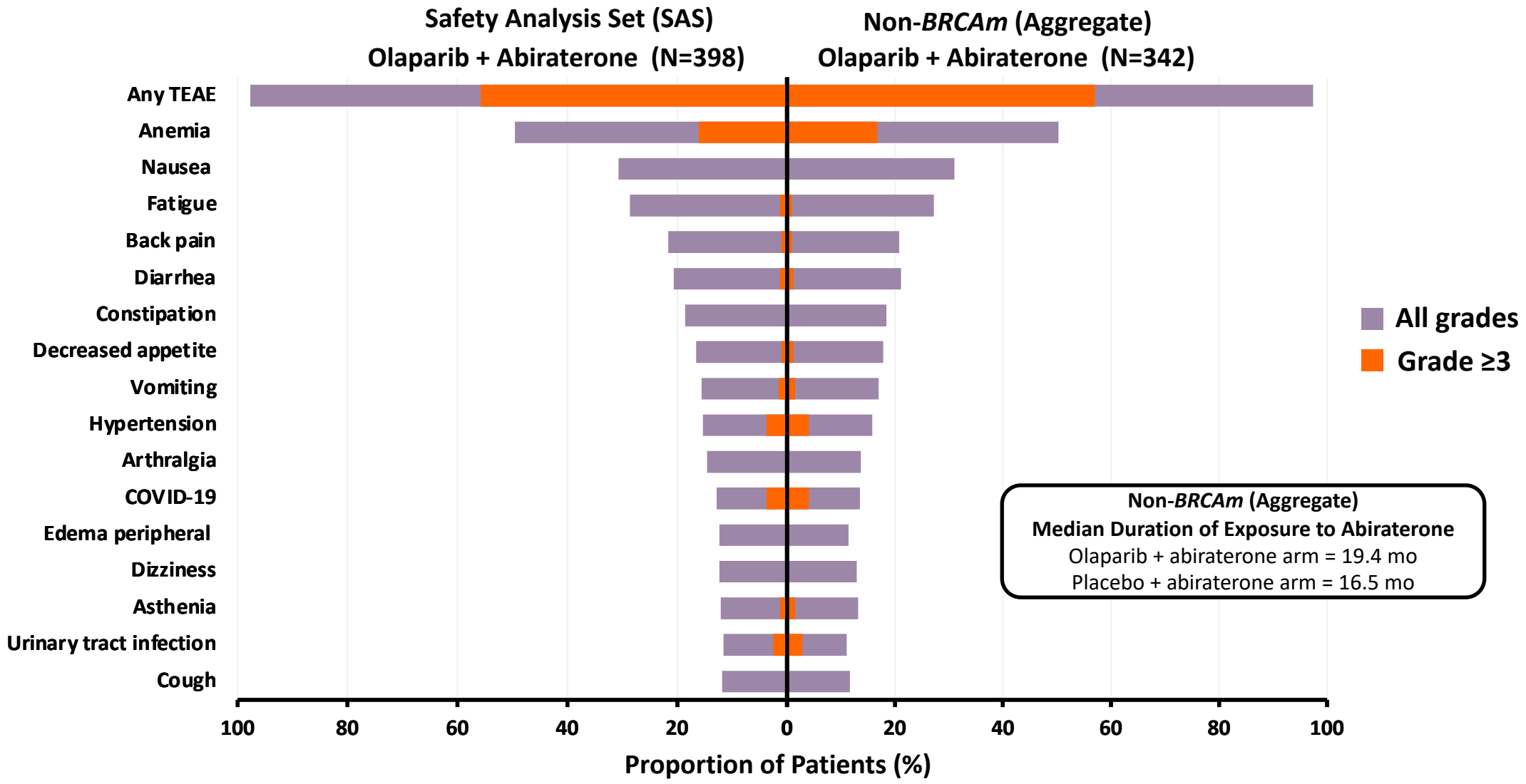


PROpel: Grade 5 Adverse Events (>1 Patient in Either Arm)

Preferred term	Number (%) of Patients	
	Olaparib + Abiraterone (N=398)	Placebo + Abiraterone (N=396)
Any grade 5 adverse event	**26 (6.5)[a]**	**20 (5.1)[b]**
COVID-19[c]	12	3
Pneumonia[d]	3	1
Infection/Sepsis[e]	0	4
Death/Sudden death	2	4
Acute pulmonary edema	0	2

[a] Occurring in a single patient: Malignant melanoma, mitral valve disease, pulmonary embolism, respiratory failure, duodenal ulcer, general physical health deterioration, myocardial ischemia, craniocerebral injury, and subdural hematoma. [b] Occurring in a single patient: Diffuse B-cell lymphoma, interstitial lung disease, acute kidney injury, intraventricular hemorrhage, ischemic stroke, and coronary artery disease. [c] Includes COVID-19, COVID-19 pneumonia, and suspected COVID-19. [d] Includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia bacterial. [e] Includes infection, pneumococcal sepsis, staphylococcal sepsis, and sepsis.

PROpel: Safety in Non-*BRCAm* Subgroup Is Consistent With SAS



PROpel: Grade 5 Adverse Events in Non-*BRCAm* (Aggregate) Subgroup (>1 Patient in Either Arm)

Preferred Term	Number (%) of Patients	
	Olaparib + Abiraterone (N=342)	Placebo + Abiraterone (N=350)
Any grade 5 adverse event	**24 (7.0)[a]**	**17 (4.9)[b]**
COVID-19[c]	11	3
Pneumonia[d]	3	1
Infection/Sepsis[e]	0	3
Death/Sudden death	2	3

[a] Grade 5 AEs occurred in a single patient: Mitral valve disease, pulmonary embolism, respiratory failure, duodenal ulcer, general physical health deterioration, myocardial ischemia, craniocerebral injury, and subdural hematoma. [b] Grade 5 AEs occurred in a single patient: Diffuse B-cell lymphoma, interstitial lung disease, acute kidney injury, intraventricular hemorrhage, ischemic stroke, coronary artery disease, and acute pulmonary edema. [c] Includes COVID-19, COVID-19 pneumonia, and suspected COVID-19. [d] Includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia bacterial. [e] Includes infection, staphylococcal sepsis, and sepsis.

Safety Conclusions

- Safety of olaparib and abiraterone was manageable, tolerable, and consistent with established safety profiles
- Olaparib increased the duration of exposure to abiraterone, with no clinically meaningful impact on overall HRQoL
- No evidence of substantive toxicity that could adversely affect OS

Clinical Perspective

Daniel George, MD

Professor of Medicine and Surgery

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Director, Genitourinary Oncology

Duke Cancer Institute

Duke University School of Medicine

rPFS Benefit Seen Across Multiple PARPi + NHA Studies

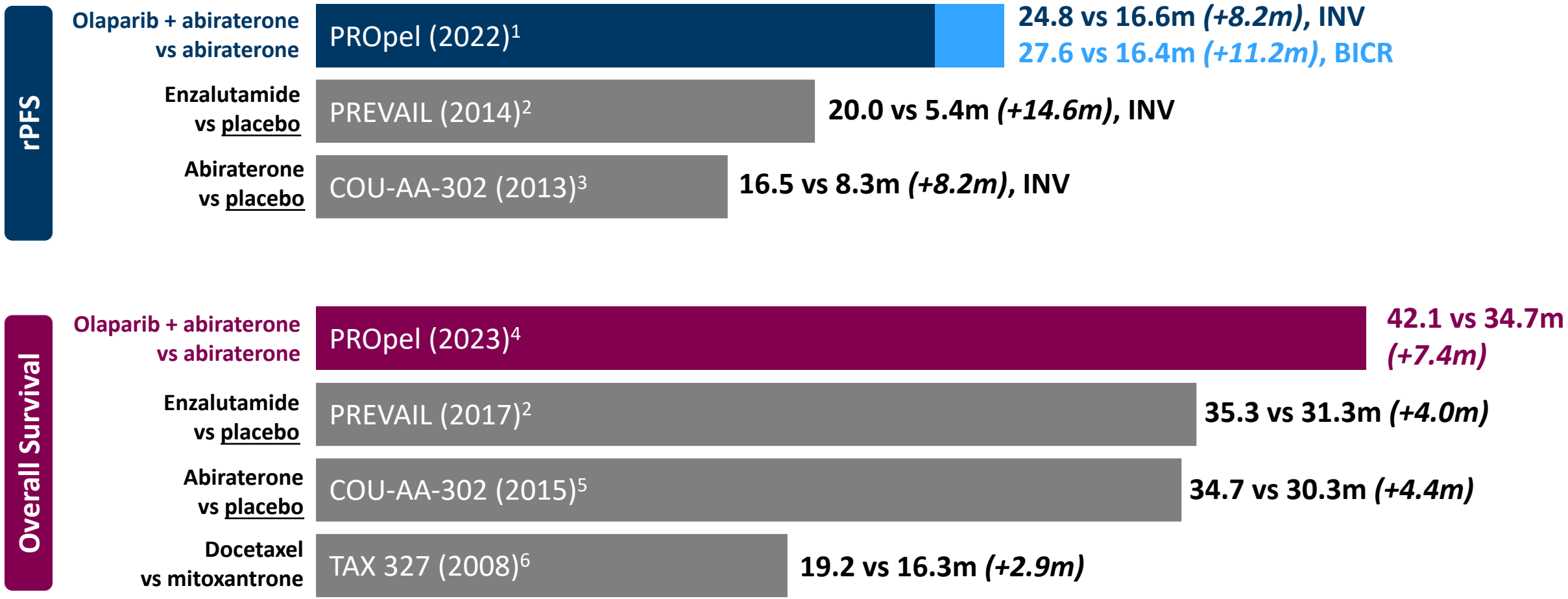
- **3 randomized trials show consistent activity of PARPi + NHA** in a biomarker-unselected patient population

	STUDY 8[1] (N=142)	**PROpel[2] (N=796)**	**TALAPRO-2[3] (N=805)**
	Olaparib + abiraterone vs abiraterone (post docetaxel) in mCRPC	Olaparib + abiraterone vs abiraterone in 1L mCRPC	Talazoparib + enzalutamide vs enzalutamide in 1L mCRPC
Primary endpoint: rPFS, HR in ITT	**0.65**	**0.66**	**0.63**

NHA, novel hormonal agent.

1. Clarke N, et al. *Lancet Oncol*. 2018;19(7):975-986; 2. Clarke NW, et al. *NEJM Evid*. 2022;1(9); 3. Agarwal N, et al. *J Clin Oncol.* 41(suppl 6); Abstract LBA17.

Olaparib + Abiraterone Extends 1L rPFS and OS Benchmarks Beyond Currently Available Therapies; First Major Improvement in ~10 Years



BICR, blinded independent central review; INV, investigator.

1. Clarke NW, et al. *NEJM Evid*. 2022;1(9); 2. Beer TM, et al. *Eur Urol*. 2017;71(2):151-154; 3. Ryan CJ, et al. *N Engl J Med*. 2013;368(2):138-148; 4. Clarke NW, et al. *J Clin Oncol*. 2023;41(suppl 6): Abstract LBA16; 5. Ryan CJ, et al. *Lancet Oncol*. 2015;16(2):152-160; 6. Berthold DR, et al. *Ann Oncol*. 2008;19(10):1749-1753.

Genetic Testing Informs Decision-Making but Can Be Challenging

- **Genetic testing is important and recommended**

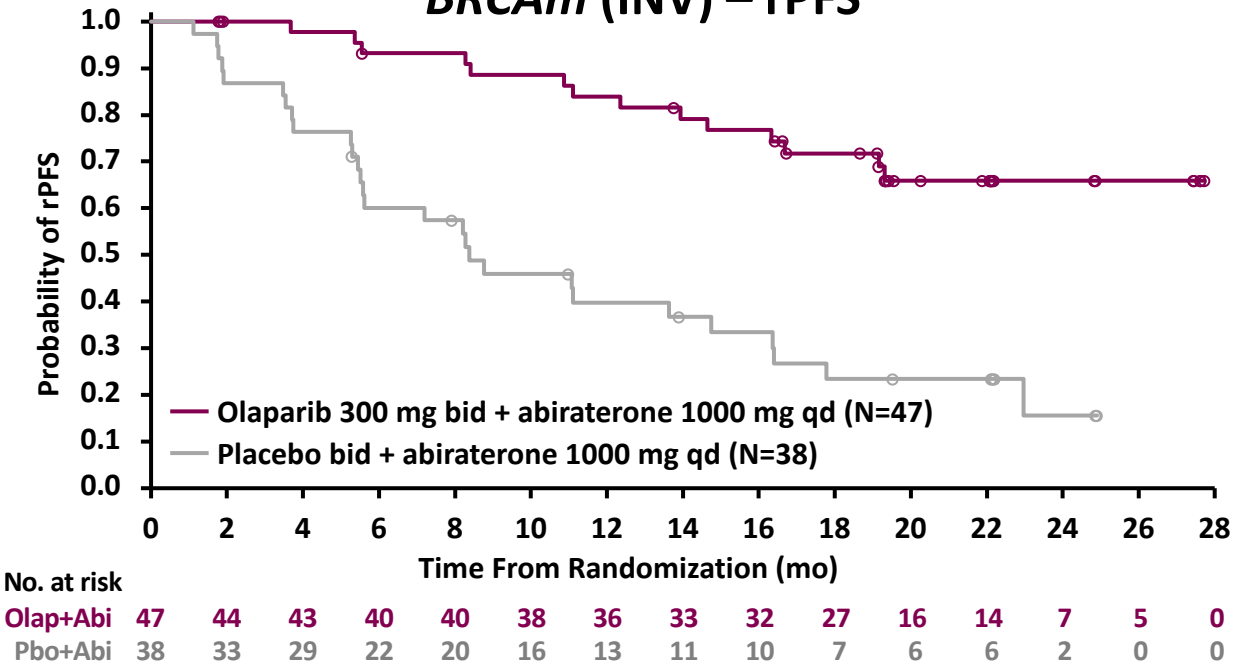
- **Majority of US mCRPC patients may have an unknown *BRCAm* or HRRm** status due to[1]:
  - Lack of testing
  - Uninformative test results
  - Cost and/or access
  - Patient refusal

- In light of this, there are **three patient scenarios in clinical practice**:
  1. Patient has a positive test for *BRCAm*/HRRm
  2. Patient has a negative test for *BRCAm*/HRRm
  3. Patient's biomarker status is unknown

1. Leith A, et al. *Future Oncol*. 2022;18(8):937-951.

BRCAm Status Matters in mCRPC

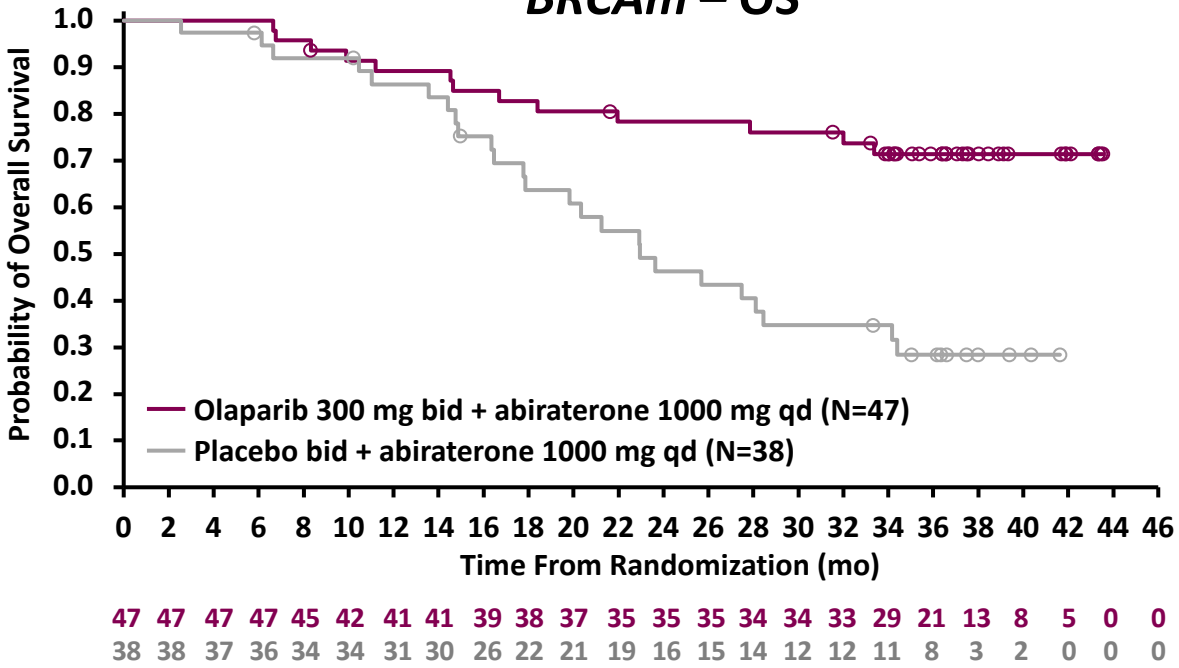
BRCAm (INV) – rPFS



No. at risk															
Olap+Abi	47	44	43	40	40	38	36	33	32	27	16	14	7	5	0
Pbo+Abi	38	33	29	22	20	16	13	11	10	7	6	6	2	0	0

	Olaparib + Abiraterone (N=47)	Placebo + Abiraterone (N=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median, mo	NC	8.4
Median improvement	**NC**	
HR (95% CI)	**0.23** (0.12, 0.43)	

BRCAm – OS



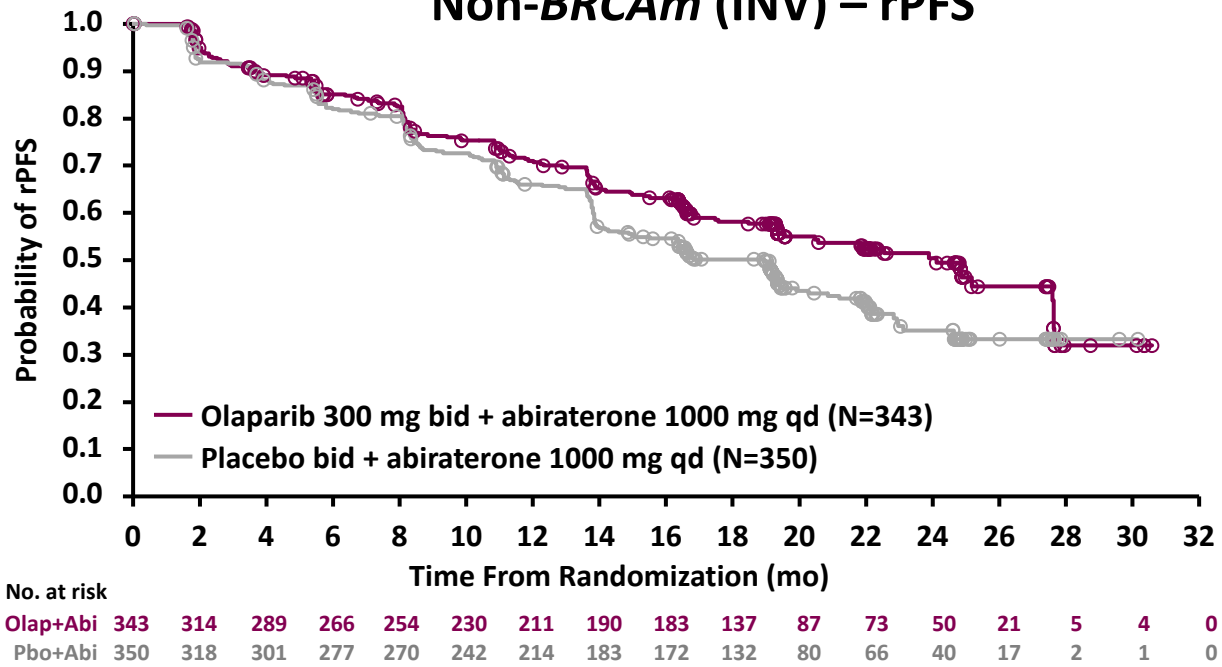
Olap+Abi	47	47	47	47	45	42	41	41	39	38	37	35	35	35	34	34	33	29	21	13	8	5	0	0
Pbo+Abi	38	38	37	36	34	34	31	30	26	22	21	19	16	15	14	12	12	11	8	3	2	0	0	0

	Olaparib + Abiraterone (N=47)	Placebo + Abiraterone (N=38)
Events, n (%)	13 (27.7)	25 (65.8)
Median, mo	NC	23.0
Median improvement	**NC**	
HR (95% CI)	**0.29** (0.14, 0.56)	

INV, investigator.

Patients With a Negative *BRCAm* Test Also Derive Clinical Benefit

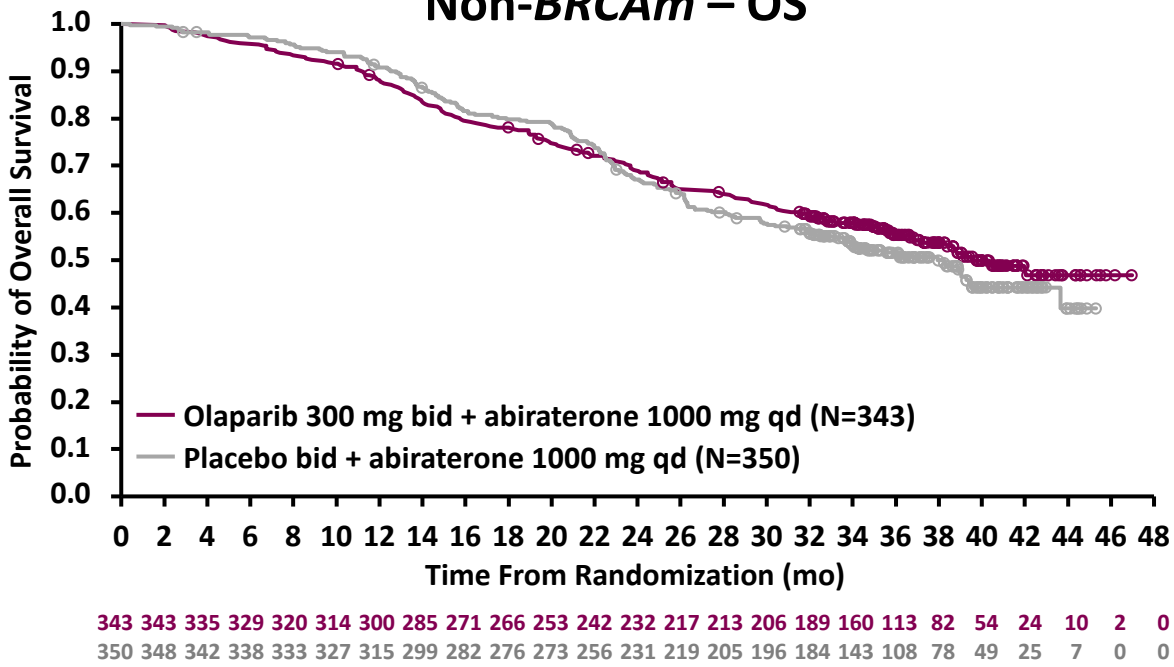
Non-*BRCAm* (INV) – rPFS



No. at risk

Olap+Abi	343	314	289	266	254	230	211	190	183	137	87	73	50	21	5	4	0
Pbo+Abi	350	318	301	277	270	242	214	183	172	132	80	66	40	17	2	1	0

Non-*BRCAm* – OS



Olap+Abi	343	343	335	329	320	314	300	285	271	266	253	242	232	217	213	206	189	160	113	82	54	24	10	2	0
Pbo+Abi	350	348	342	338	333	327	315	299	282	276	273	256	231	219	205	196	184	143	108	78	49	25	7	0	0

	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	148 (43.1)	194 (55.4)
Median, mo	24.1	19.0
Median improvement	**5.1 months**	
HR (95% CI)	**0.76** (0.61, 0.94)	

	Olaparib + Abiraterone (N=343)	Placebo + Abiraterone (N=350)
Events, n (%)	158 (46.1)	176 (50.3)
Median, mo	39.6	38.0
Median improvement	**1.7 months**[a]	
HR (95% CI)	**0.91** (0.73, 1.13)	

[a] Based on rounded value of 1.67 mo (using unrounded values of 39.62 mo – 37.95 mo).
INV, investigator.

Patients with an Undetermined BRCA Status Derive Clinical Benefit and Represent a Significant Proportion of Patients in Clinical Practice

FDA Briefing Document: Table 7

	BRCAm N= 85 (11%) Olaparib vs Placebo	Sponsor Aggregate Non-BRCAm[a] — Negative/Unknown[a] Non-BRCAm: Undetermined *BRCAm* status N= 284 (35%) Olaparib vs Placebo	Sponsor Aggregate Non-BRCAm[a] — Double Negative Non-BRCAm: Non-*BRCAm* N= 427 (54%) Olaparib vs Placebo	Non-*BRCAm* Aggregate analysis[b] N= 693 (87%) Olaparib vs Placebo
rPFS by INV				
Median, months	NR vs 8	NR vs 19	22 vs 17	24 vs 19
HR (95% CI)	0.24 (0.12, 0.46)	0.66 (0.46, 0.94)	0.85 (0.66, 1.11)	0.76 (0.61, 0.94)
rPFS by BICR				
Median, months	NR vs 8	NR vs 19	20 vs 17	28 vs 17
HR (95% CI)	0.19 (0.1, 0.37)	0.59 (0.41, 0.85)	0.82 (0.62, 1.08)	0.72 (0.58, 0.90)
OS				
Median, months	NR vs 23	NR vs 38	37 vs 38	40 vs 38
HR (95% CI)	0.3 (0.15, 0.6)	0.73 (0.52, 1.03)	1.06 (0.81, 1.39)	0.91 (0.91, 1.13)
ORR by BICR				
Patients with evaluable disease at baseline	N= 20 vs 18	N= 50 vs 51	N= 92 vs 81	N= 138 vs 128
ORR % (95% CI)	60% (36, 81) vs 28% (10, 53) (Δ = 32%)	60% (45, 74) vs 43% (29, 58) (Δ = 17%)	52% (42, 63) vs 48% (37, 60) (Δ = 4%)	54% (45, 62) vs 46% (37, 55) (Δ = 8%)

[a] 18 patients with unknown BRCA status by either test included in FDA undetermined subgroup but not included in the Sponsor aggregate non-*BRCAm* analysis.
[b] Aggregate results are reported from various DCOs, to correspond with FDA Briefing Document Table 7: rPFS from DCO1, OS from DCO3, ORR from DCO2.
BICR, blinded independent central review; INV, investigator.

Olaparib + Abiraterone Should Be a Treatment Option for Patients With mCRPC

- *BRCAm* patients derive greatest proportional benefit from olaparib and abiraterone
- Patients without a known *BRCA* mutation can benefit from this combination with manageable side effects
- **Treatment decision-making is personal** and needs to account for individual patient factors, including patient preference
- **Patients and their physicians should be allowed to decide** the optimal treatment for mCRPC

AstraZeneca MERCK

Summary

Cristian Massacesi, MD
Chief Medical Officer and
Oncology Chief Development Officer
AstraZeneca

Propel Confirms Combination Therapy as First-Line Option in mCRPC

Efficacy Discussion Points	Sponsor Supporting Evidence
PROpel Population and Stratification	**Population reflective of a real-world first-line mCRPC population** • All-comer design supported by MOA, non-clinical data, and Study 8 results • Stratified by known prognostic factors; prespecified HRRm subgroup analysis • HRRm and *BRCAm* distribution balanced, allowing for reliable estimation of treatment effect
PROpel Biomarker Status	**Aggregate non-*BRCAm* represents the most complete dataset for estimation of treatment effect** • PROpel provided rigorous testing, with >98% patients tested by both validated and FDA-approved tissue and ctDNA tests with 94% concordance for *BRCAm* • Low probability of misclassification; sensitivity analysis confirmed minimal impact on OS HR for aggregate non-*BRCAm* • Aggregate non-*BRCAm* population consistent with clinical practice
Overall Survival in Non-*BRCAm*	**PROpel primary and secondary endpoints confirm a meaningful clinical benefit in non-*BRCAm* population** **PROpel shows no evidence of substantive toxicity that could result in OS detriment (*JCO* 2023 publication)[1]** • No increase in treatment-related deaths • No impact on ability to receive subsequent therapy • Increased exposure to abiraterone in combination **Evidence presented by FDA to support external validity is of limited relevance** • Different tumor type, different PARPi, used as monotherapy

1. Merino M, et al. *J Clin Oncol*. 2023;JCO2300225.

PROpel Demonstrated a Positive Benefit-Risk in an All-Comer Population

mCRPC is a fatal disease

- 2-year median OS[1]
- <50% of patients receive a 2L therapy[1]

Benefit across multiple endpoints

	HR (95% CI)	
Endpoint	**ITT**	**Non-*BRCAm***
rPFS (INV)	**0.66** (0.54, 0.81)	**0.76** (0.61, 0.94)
rPFS (BICR)	**0.61** (0.49, 0.74)	**0.72** (0.58, 0.90)
OS	**0.81** (0.67, 1.00)	**0.91** (0.73, 1.13)
TFST	**0.76** (0.64, 0.90)	**0.84** (0.70, 1.01)

Manageable and tolerable safety

- Safety of olaparib + abiraterone was consistent with their individual established profiles
- Most AEs occur early and are manageable
- Combination with olaparib resulted in longer exposure to abiraterone
- No clinically meaningful impact on HRQoL

BICR, blinded independent central review; INV, investigator; TFST, time from randomization to start of first subsequent therapy or death.

1. George DJ, et al. *Clin Genitourin Cancer*. 2020;18(4):284-294.

Conclusions

- PROpel met its primary objective
- The greatest benefit is seen in *BRCAm* patients
- There is a positive benefit-risk profile in non-*BRCAm* patients
- A complementary diagnostic may inform patients and physicians of the expected benefit-risk
- The totality of evidence including statistically significant and clinically meaningful rPFS, with no overall survival detriment, supports the proposed indication:

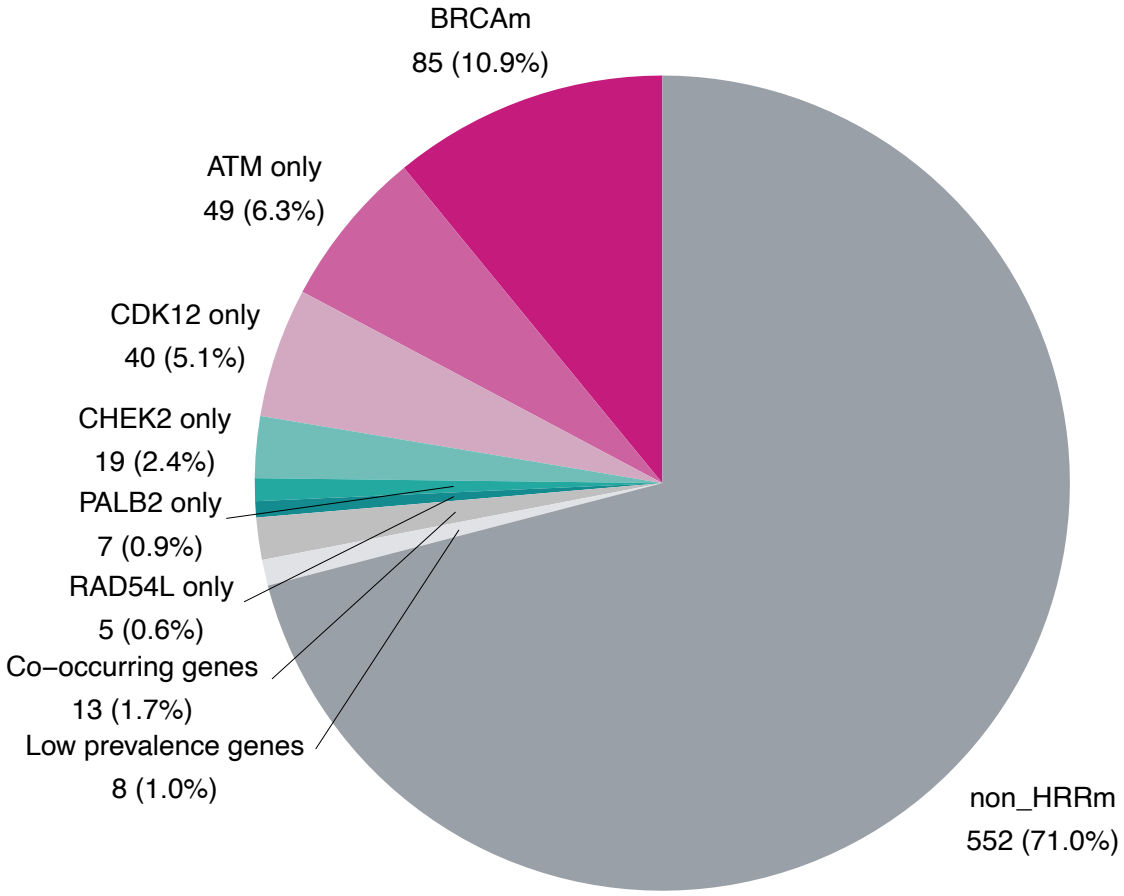
  "Lynparza in combination with abiraterone and prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)"

Supportive Slides

PROpel: Prevalence of BRCAm and Other HRRm Genes

- The prevalence in PROpel is 11% for BRCAm and 29% for HRRm which is similar to other published studies and indicates that PROpel is representative of the mCRPC patient population

- BRCAm are the most prevalent mutations, followed by ATM and CDK12 at 6 and 5% respectively. Alterations in other genes occur less frequently.



Overall HRRm prevalence 226 (29.0%)

Non-*BRCAm*/HRRm Subgroups Perform Similarly to Non-*BRCAm* (by Aggregate)

	rPFS by INV (DCO1)			OS (DCO3)		
		Median (mo)			Median (mo)	
	Hazard Ratio/ (95% CI)	Olaparib + Abiraterone	Placebo + Abiraterone	Hazard Ratio/ (95% CI)	Olaparib + Abiraterone	Placebo + Abiraterone
FAS (N=796)	0.66 (0.54, 0.81)	24.8	16.6	0.81 (0.67, 1.00)	42.1	34.7
Non-HRRm (N=552)	0.76 (0.60, 0.97)	24.1	19.0	0.89 (0.70, 1.14)	42.1	38.9
HRRm including *BRCAm* (n=226)	0.50 (0.34, 0.73)	NC	13.9	0.66 (0.45, 0.95)	NC	28.5
HRRm excluding *BRCAm* (n=141)	0.80 (0.50, 1.27)	NC	19.2	1.01 (0.64, 1.57)	31.9	33.7
Non-*BRCAm* (n=693)	0.76 (0.61, 0.94)	24.1	19.0	0.91 (0.73, 1.13)	39.6	38.0
***BRCAm* (n=85)**	0.23 (0.12, 0.43)	NC	8.4	0.29 (0.14, 0.56)	NC	23.0

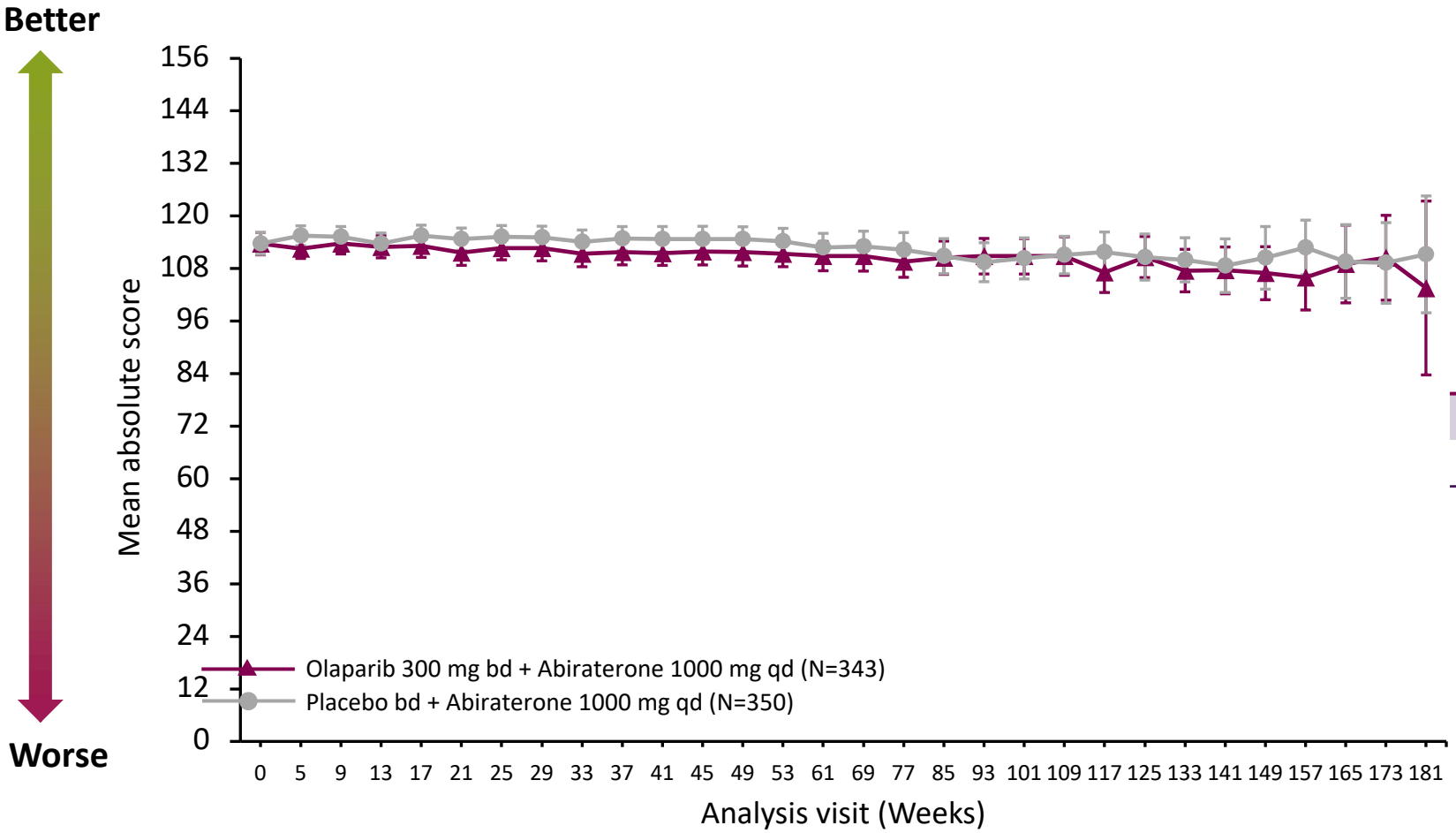
PROpel Subsequent Anti-Cancer Therapy – BRCAm (Aggregate)

	Olaparib + abiraterone (N=47)	Placebo + abiraterone (N=38)
Patients with any subsequent anticancer therapy, [a] n (%)	**18 (38.3)**	**22 (57.9)**
New hormonal agents	7 (14.9)	6 (15.8)
Taxanes	11 (23.4)	17 (44.7)
PARP inhibitors	1 (2.1)	1 (2.6)
Other anticancer therapies [b]	4 (8.5)	9 (23.7)

[a] Patients can be counted in >1 anticancer therapy.
[b] Other anticancer therapies e.g. immunotherapy, targeted therapy, non-taxane chemotherapy etc

Mean FACT-P[1] Total Score and Change From Baseline Values For Non-BRCAm (Aggregate) Subgroup Are Comparable in Both Treatment Arms and Consistent with Full Analysis Set

EQ-30



	Non-BRCAm (Aggregate)	
Overall	**Olaparib + Abiraterone N=236**	**Placebo + Abiraterone N=261**
LS means (SE)	-6.27 (1.11)	-5.27 (1.13)
Difference (95% CI)	**-0.99 (-3.62, 1.63)**	

[1]FACT-P, Functional Assessment of Cancer Therapy – Prostate

Note: FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156. A clinically meaningful change in FACT-P total score is 10.

PROpel: Low Incidence of Missing *BRCAm* Patients in Aggregate Non-*BRCAm* Subgroup by ctDNA Test

693 patients assigned to the non-*BRCAm* subgroup in PROpel

467 non-*BRCAm* patients had a tissue result (427 also had a ctDNA result)	**226 non-*BRCAm* patients by ctDNA only (no tissue results)**

How many ***BRCAm*** patients **might be missed** in this subgroup by ctDNA test?

Method One

By Non-concordance and Prevalence

- **Non-concordance rate** between ctDNA and tissue test is **26.1%** (=100%-73.9%(PPA))
- Prevalence of *BRCAm* in PROpel is **11%** (9%-12% in mCRPC studies)
- **~2.9% (11% × 26.1%)** of potential *BRCAm* patients could be missed by ctDNA test

Method Two

By Negative Predictive Value (NPV)

- **NPV** for **ctDNA testing** is 97.3 %
- **~2.7%** (=100%-97.3%) of potential *BRCAm* patients could be missed by ctDNA test

~6 of 226 patients with negative ctDNA only might have unidentified *BRCA* mutations, representing 1% of the 693 aggregate non-*BRCAm* subgroup.

OS HR in Non-*BRCAm* Negative/Unknown Subgroup Is Minimally Impacted by Potentially Misclassified *BRCAm* Patients

# of Patients Removed*	HR (95% CI) FDA Method	HR (95% CI) Most Conservative
0: Primary analysis	0.70 (0.49, 1.00)	
6 (2.7%)	0.70 (0.49, 1.01)	0.76 (0.53, 1.08)
12 (5.3%)	0.70 (0.49, 1.02)	0.82 (0.57, 1.18)

Two sensitivity analyses:

FDA Method = Randomly reclassifying patients; number of patients removed are averaged over simulations

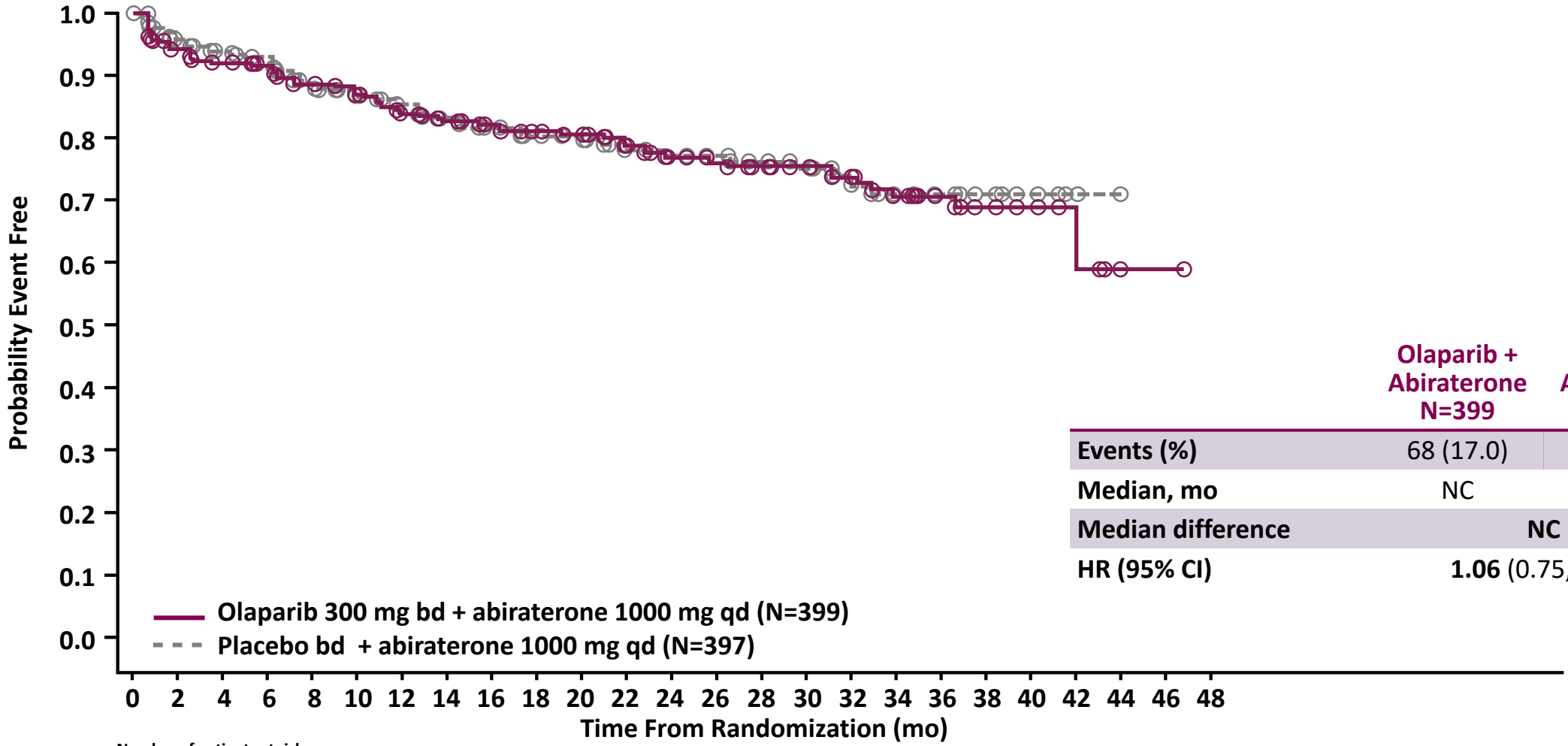
Most Conservative = Reclassifying best-performing patients in test arm and worst-performing patients in control arm

* From ctDNA non-*BRCAm* and tissue unknown population.

Time to Pain Progression in Non-BRCAm (Aggregate) Subgroup

	FAS		Non-BRCAm (Aggregate)	
	Ola + abi (N=399)	Pla + abi (N=397)	Ola + abi (N=343)	Pla + abi (N=350)
Time to Pain Progression, TTPP (DCO3)				
No. of patients with events / N (%)	68/399 (17.0)	60/397 (15.1)	62/343 (18.1)	56/350 (16.0)
Median TTPP (months)	NC	NC	NC	NC
HR (95% CI)	1.06 (0.75, 1.50)		1.13 (0.78, 1.62)	

No Differential Outcome for Time to Pain Progression Between Treatment Arms but Analysis Limited by Small Number of Events



	Olaparib + Abiraterone N=399	Placebo + Abiraterone N=397
Events (%)	68 (17.0)	60 (15.1)
Median, mo	NC	NC
Median difference	**NC**	
HR (95% CI)	**1.06** (0.75, 1.50)	

Number of patients at risk

399	294	270	249	229	210	188	176	161	150	140	122	112	103	98	93	79	55	39	26	16	6	1	1	0	Ola 300 mg bd + Abi 1000 mg qd
397	308	281	253	228	197	174	155	139	123	112	89	86	82	73	68	55	41	33	24	11	4	0	0	0	Pla bd + Abi 1000 mg qd

PROpel: Retesting for Biomarker Unknown Population

- Of the 261 patients that were biomarker unknown based on tumour tissue testing, after database lock, a request was sent to clinical sites for potentially receiving an additional tumour tissue sample
- After database lock, for 24% (62/261) of patients, an additional sample was sent for diagnostic tumor tissue testing
- For 10/62 (16%) of these cases a known biomarker status was obtained
  - 1 patient had BRCAm and 1 patient had another HRRm (PALB2). Both of these mutations were detected in ctDNA, therefore these patients were already included in the BRCAm / HRRm subgroup in the aggregate analysis

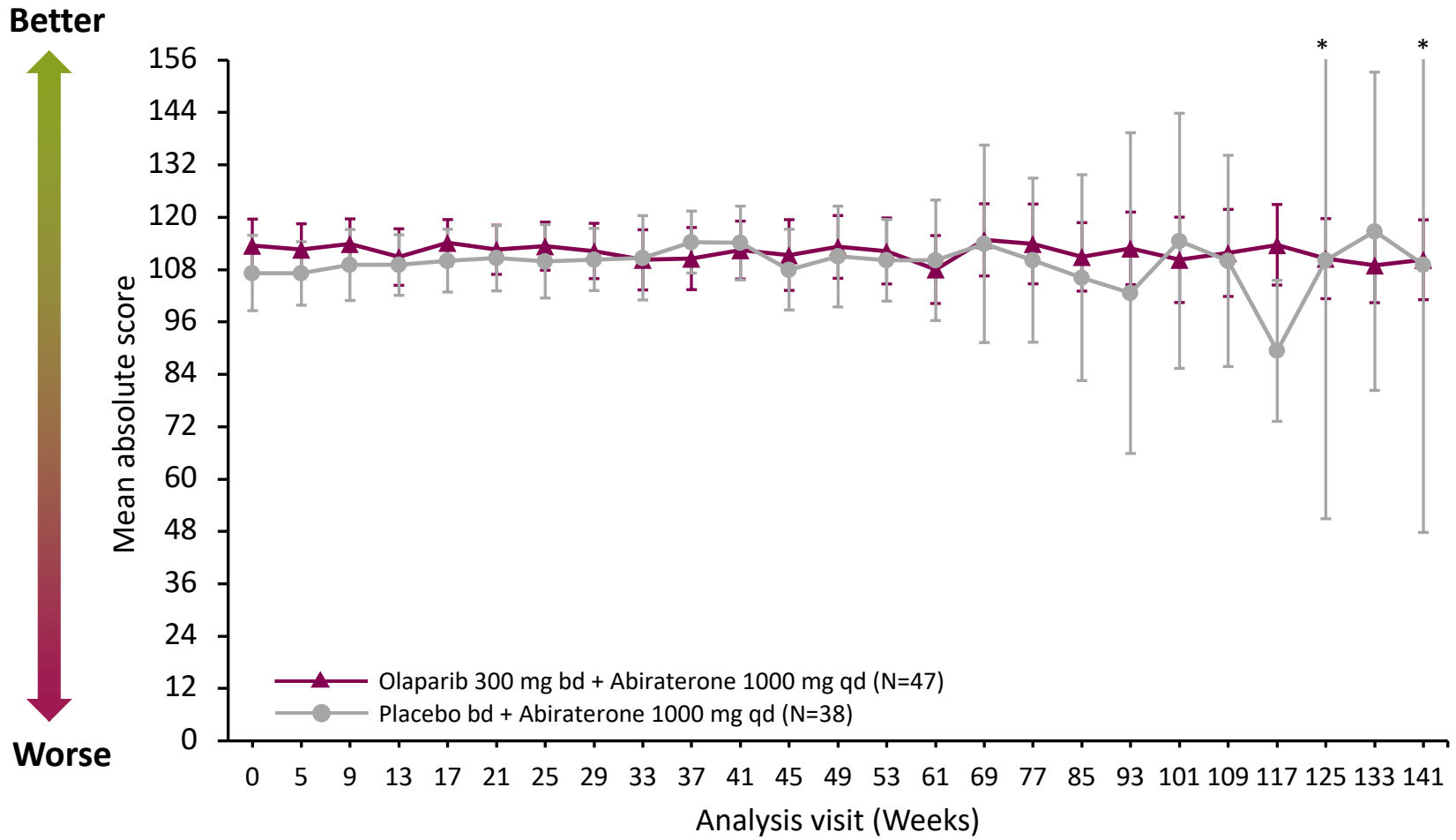
PROpel: >99% of Non-*BRCAm* Patients by Tumor and ctDNA Are Non-*BRCAm* by Germline

- 100% of patients who were non-*BRCAm* by ctDNA only were negative for *BRCAm* in the germline assay (Myriad Genetics MyRisk® hereditary cancer assay), (202/202 evaluable)

- 99.8% of patients classified as non-*BRCAm* by aggregate tumor and ctDNA test results were negative for *BRCAm* in the germline assay (617/618 evaluable)

- No patient with an unknown biomarker status by ctDNA or tumor test had a germline mutation reported in *BRCA* or HRR (13/13 evaluable)

Mean FACT-P[1] Total Score for BRCAm (Aggregate) Subgroup



	BRCAm (Aggregate)	
Overall	**Olaparib + Abiraterone N=36**	**Placebo + Abiraterone N=28**
LS means (SE)	2.43 (2.95)	-1.21 (3.09)
Difference (95% CI)	**3.64 (-4.05, 11.33)**	

* Top end of the confidence limits is beyond the range of the score scale

[1]FACT-P, Functional Assessment of Cancer Therapy – Prostate

Note: FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156. A clinically meaningful change in FACT-P total score is 10.

Hematological Adverse Events

	Number (%) patients			
	Olaparib + Abiraterone (N=398)		Placebo + Abiraterone (N=396)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Blood and lymphatic system disorders	**216 (54.3)**	**73 (18.3)**	**96 (24.2)**	**23 (5.8)**
Anemia*	198 (49.7)	64 (16.1)	70 (17.7)	13 (3.3)
Neutropenia*	40 (10.1)	19 (4.8)	14 (3.5)	7 (1.8)
Lymphopenia*	56 (14.1)	21 (5.3)	26 (6.6)	10 (2.5)
Thrombocytopenia*	27 (6.8)	3 (0.8)	17 (4.3)	2 (0.5)

*grouped terms

PROpel Time to First Cytotoxic Chemotherapy or Death – FAS

	Olaparib + abiraterone (N=399)	Placebo + abiraterone (N=397)
Time to first cytotoxic chemotherapy		
Total patients receiving subsequent therapy or death, n (%)	223 (55.9)	265 (66.8)
Subsequent cytotoxic chemotherapy, n (%)	124 (31.1)	167 (42.1)
Death (in absence of first subsequent cytotoxic chemotherapy) , n (%)	99 (24.8)	98 (24.7)
Median (months)	**32.0**	**22.4**
HR (95% CI)	**0.72 (0.61, 0.87)**	

Venous Thromboembolic Events in PROpel: Summary Table

	Number (%) Patients	
	Olaparib + Abiraterone (N=398)	Placebo + Abiraterone (N=396)
Any AE[a]	34 (8.5)	16 (4.0)
Any AE CTCAE grade 3	31 (7.8)	10 (2.5)
Any AE CTCAE grade 4	2 (0.5)	2 (0.5)
Any AE with outcome of death	1 (0.3)	0
Any SAE	17 (4.3)	4 (1.0)
Any AE leading to discontinuation of study treatment	0	1 (0.3)

[a] Embolic and thrombotic events, venous SMQ grouped term.

PROpel: Sensitivity Analysis Censoring COVID-19 Deaths

rPFS and OS – Subgroups by *BRCAm* Status

HR (95% CI)	FAS (N=796)	*BRCAm* (N=85)	Non-*BRCAm* (Aggregate) (N=693)	Non-*BRCAm* (Double Negative) (N=427)
rPFS (INV)[a]				
Primary analysis	0.66 (0.54, 0.81)	0.23 (0.12, 0.43)	0.76 (0.61, 0.94)	0.86 (0.66, 1.12)
Sensitivity censoring COVID deaths	0.65 (0.53, 0.79)	0.23 (0.12, 0.43)	0.74 (0.59, 0.92)	0.83 (0.64, 1.09)
Overall survival[b]				
Primary analysis	0.81 (0.67, 1.00)	0.29 (0.14, 0.56)	0.91 (0.73, 1.13)	1.06 (0.81, 1.39)
Sensitivity censoring COVID deaths	0.77 (0.62, 0.94)	0.27 (0.13, 0.52)	0.86 (0.69, 1.07)	0.99 (0.75, 1.31)

[a] DCO1, Death where primary/secondary cause of death was due to COVID-19 infection or a COVID-19 infection reported as a fatal AE.
[b] DCO3, Deaths (due to COVID-19) in the absence of progression were censored at the last evaluable RECIST assessment before date of death.

Study 8: Grade 5 Adverse Events

	SAS		Non-BRCAm (Neg/Neg)	
	Olaparib + Abiraterone (N=71)	Placebo + Abiraterone (N=71)	Olaparib + Abiraterone (N=13)	Placebo + Abiraterone (N=10)
Patients with AE with outcome of death	**4 (5.6)**	**1 (1.4)**	**1 (7.7)**	**0**
Cardiac failure	1	0	0	0
Ischemic stroke	1	0	0	0
Mediastinitis	1	0	0	0
Pneumonitis	1	0	1	0
Pyelonephritis/Sepsis	0	1	0	0