Phase 3 AMPLITUDE Trial: Niraparib and Abiraterone Acetate Plus Prednisone for Metastatic Castration-Sensitive Prostate Cancer Patients With Alterations in Homologous Recombination Repair Genes

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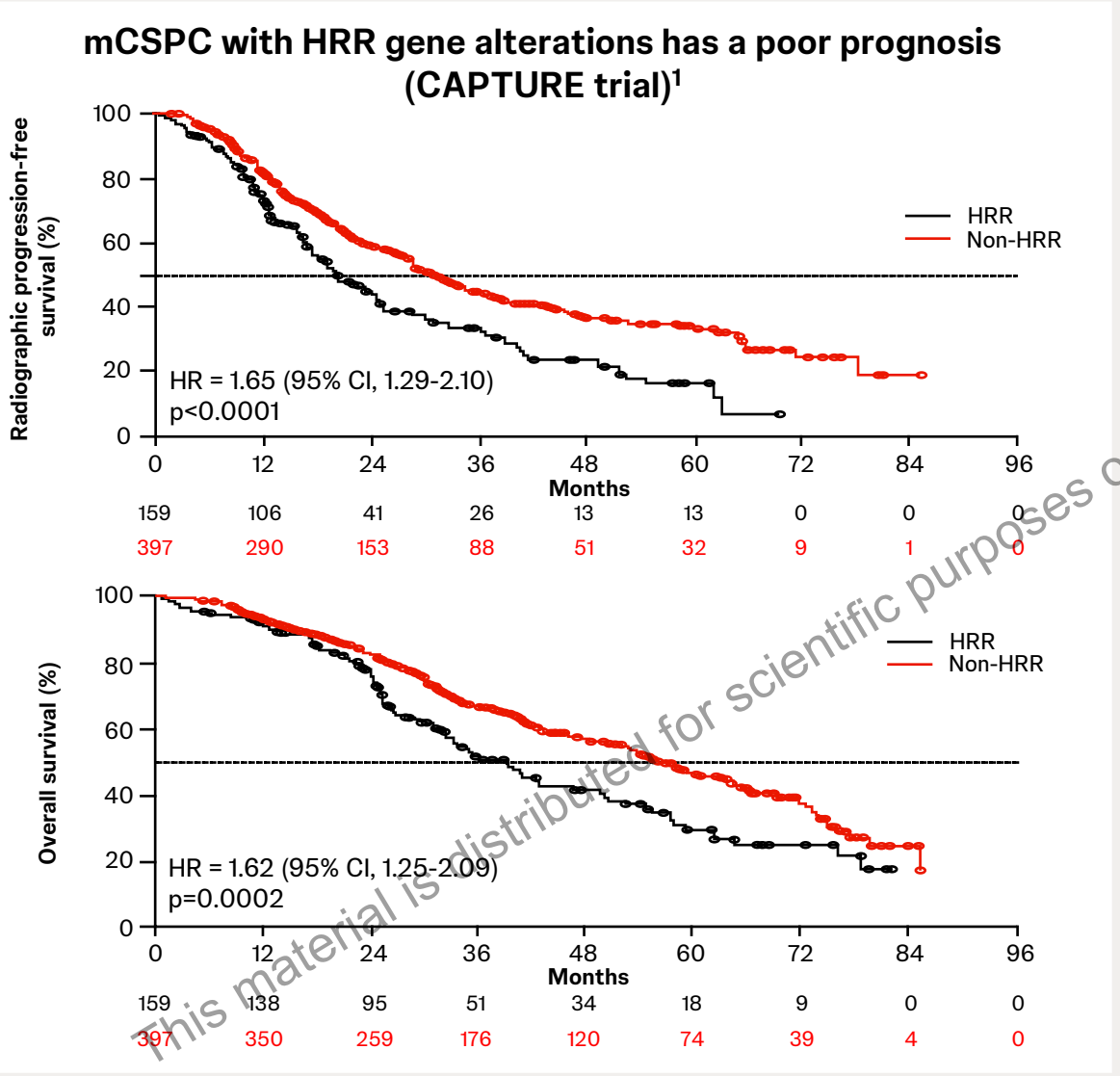
AMPLITUDE: Key Takeaways

- AMPLITUDE met its primary end point of rPFS
- AMPLITUDE is the first trial to show efficacy of the combination of a PARPi and an ARPI in mCSPC with HRR alterations, with greatest benefit in patients with BRCA alterations
- Improvements in rPFS are supported by a statistically significant benefit in time to symptomatic progression
- The safety profile of niraparib + abiraterone acetate plus prednisone was consistent with that previously observed in the MAGNITUDE trial,[1] with a <5% increase in patients discontinuing treatment due to toxicity versus those receiving placebo + abiraterone acetate plus prednisone

ARPI, androgen receptor pathway inhibitor; BRCA, breast cancer gene; HRR, homologous recombination repair gene; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PARPi, poly ADP-ribose polymerase inhibitor; rPFS, radiographic progression-free survival.

1. Chi KN. *J Clin Oncol*. 2023;41:3339-3351.

Background: Metastatic Castration-Sensitive Prostate Cancer



- Addition of an ARPI, such as abiraterone, to ADT ± docetaxel is standard of care for mCSPC[2-5]
- Niraparib, a highly selective and potent inhibitor of PARP-1/2, is approved in combination with AAP for BRCA-mutated metastatic castration-resistant prostate cancer[6,7]
- Phase 1b trial identified no drug-drug interaction between niraparib and AAP[8]
- The AMPLITUDE trial was conducted to evaluate niraparib in combination with AAP in patients with HRRm mCSPC

AMPLITUDE trial registration NCT04497844.
AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; HRRm, HRR mutation.
1. Olmos D, et al. Presented at ASCO 2025. Abstract 5094. 2. Fizazi K, et al. *N Engl J Med.* 2017;377:352-360. 3. James ND, et al. *N Engl J Med.* 2017;377:338-351. 4. Fizazi K, et al. *Lancet.* 2022;399:1695-1707. 5. Smith MR, et al. *N Engl J Med.* 2022;386:1132-1142. 6. Chi KN. *J Clin Oncol.* 2023;41:3339-3351. 7. Chi KN, et al. *Ann Oncol.* 2023;34:772-782. 8. Saad F, et al. *Cancer Chemother Pharmacol.* 2021;88, 25-37.

AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC

First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival.
Median follow-up: 30.8 months

Key inclusion criteria:
- mCSPC[a]
- Alteration in ≥1 HRR eligible gene: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*[b]
- ECOG PS 0-2

Key exclusion criteria:
- Any prior
  - PARPi
  - ARPI other than AAP

Prior allowed treatments in mCSPC:
- ADT ≤6 months
- Docetaxel ≤6 cycles[c]
- AAP ≤45 days
- Palliative RT

Randomized 1:1 (N=696)

Nira (200 mg QD) + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

PBO + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

Stratifications:
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Primary end point
- rPFS by investigator review

Key secondary end points
- Time to symptomatic progression
- OS
- Safety

Clinical data cutoff: January 7, 2025

[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.

AMPLITUDE Statistical Analysis Plan

- Graphical approach with group sequential design of one primary and two key secondary end points
- End points analyzed with overall type I error of 0.05

Primary end point (1st and final analyses)

rPFS by investigator review

Key secondary end points (1st interim analysis)

Time to symptomatic progression

Overall survival

Populations of interest for formal statistical evaluation[a]

BRCAm
Participants with *BRCA1/2* alterations[b]

HRRm (ITT)
All randomized participants

[a]HRR effectors group (*BRCA1/2* + *BRIP1*, *PALB2*, *RAD51B*, *RAD54L*) also prespecified for formal statistical analysis after BRCAm and prior to HRRm. [b]Includes co-occurring *BRCA1* or *BRCA2* alterations. ITT, intent-to-treat.

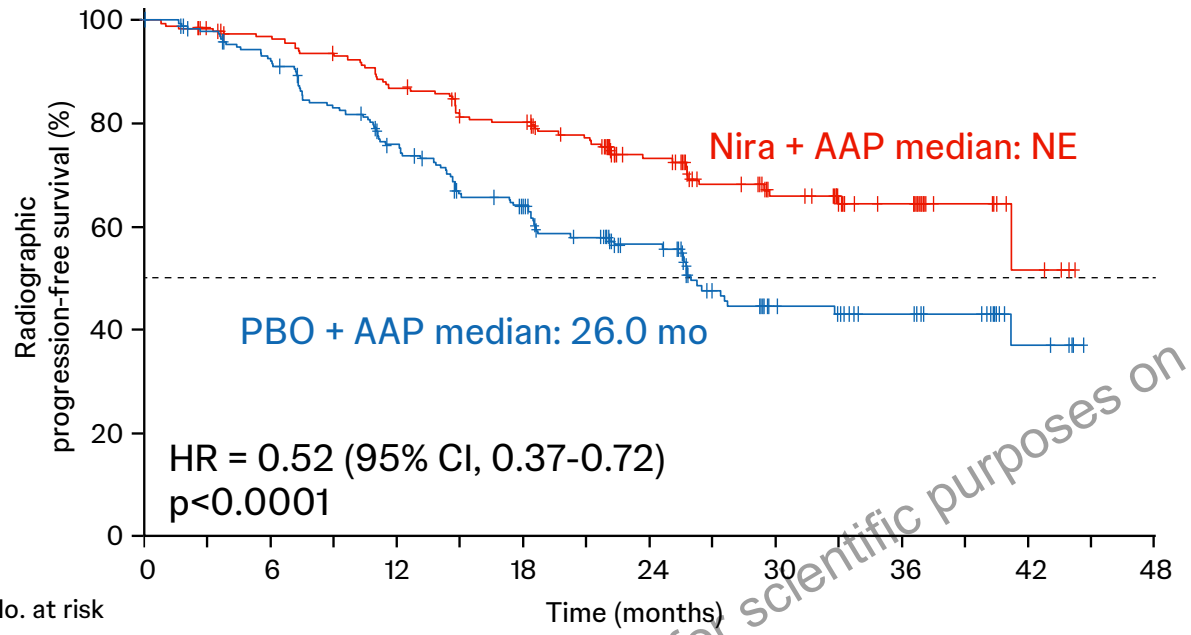
Baseline Characteristics

		Nira + AAP (n=348)	PBO + AAP (n=348)
Median age (range), y		68 (40-88)	67 (40-92)
Median PSA at initial diagnosis (range), ng/mL		112 (0.1-17475)[a]	102 (0.1-15900)[b]
ECOG PS score, n (%)	0	242 (70)	218 (63)
	≥1	106 (30)	130(37)
Gleason score at initial diagnosis, n (%)	≥8	276 (79)	262 (75)
Metastatic stage at diagnosis, n (%)	M1 (Synchronous)	301 (86)	302 (87)
Disease volume, n (%)	High	269 (77)	271 (78)
Prior docetaxel use in mCSPC, n (%)		54 (16)	56 (16)
Site of metastases[c], n (%)	Bone only	146 (42)	154 (44)[d]
	Visceral	57 (16)	54 (16)[d]
	Lymph nodes	173 (50)	161 (46)[d]
BRCA alteration, n (%)		191 (55)	196 (56)

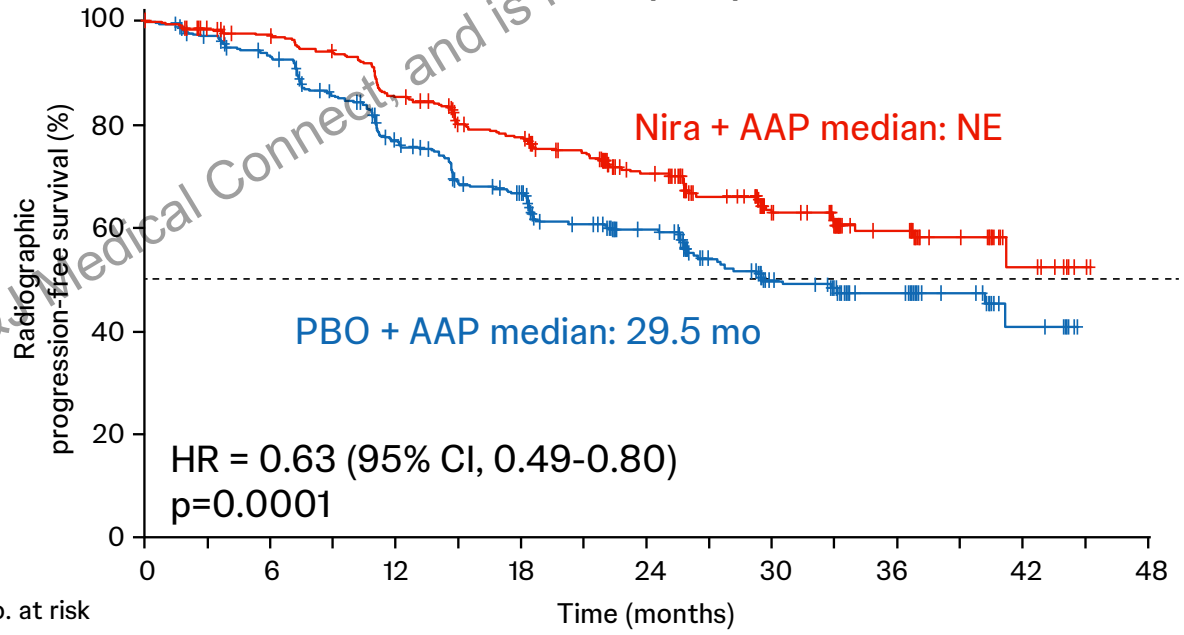
- Characteristics were well balanced between treatment groups

[a]n=258. [b]n=275. [c]Non-mutually exclusive. [d]n=347.
PSA, prostate-specific antigen.

Primary End Point: Radiographic Progression-Free Survival



No. at risk									
Nira + AAP	191	177	158	142	95	55	30	4	0
PBO + AAP	196	174	137	109	73	33	22	6	0



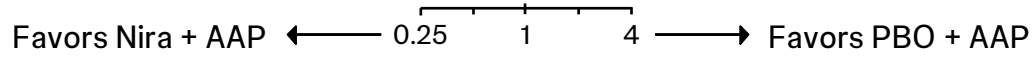
No. at risk									
Nira + AAP	348	321	280	246	164	91	54	9	0
PBO + AAP	348	312	245	201	135	70	43	9	0

AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm population.
NE, not estimable.

Prespecified Subgroup Analysis of rPFS

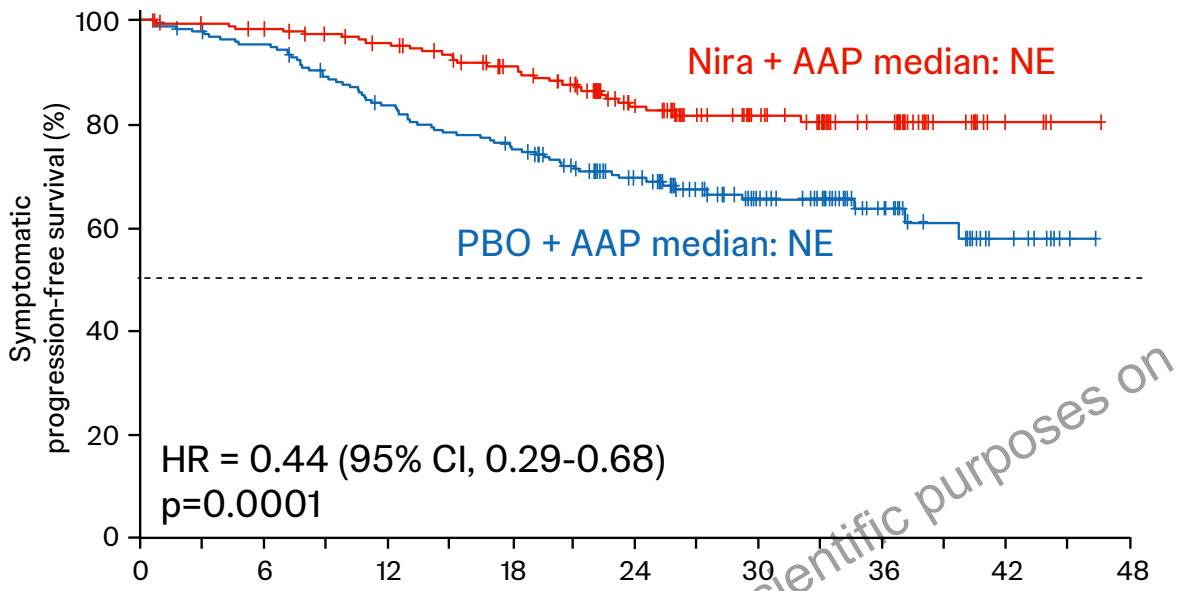
Variable	Subgroup	Median, mo		HR (95% CI)	Events/N	
		Nira + AAP	PBO + AAP		Nira + AAP	PBO + AAP
All participants		NE	29.5	0.65 (0.51-0.83)	113/348	151/348
Age	<65 yr	41.2	29.3	0.51 (0.34-0.77)	35/116	62/135
	65-74 yr	NE	NE	0.74 (0.50-1.11)	45/148	52/139
	≥75 yr	NE	26	0.74 (0.46-1.19)	33/84	37/74
ECOG PS at baseline	0	NE	40.2	0.60 (0.44-0.82)	72/242	93/218
	≥1	34	29.5	0.76 (0.51-1.14)	41/106	58/130
Prior docetaxel use	Yes	41.2	NE	0.75 (0.40-1.40)	18/54	23/56
	No	NE	29.5	0.62 (0.48-0.82)	95/294	128/292
Visceral metastases	Yes	NE	18.5	0.57 (0.33-0.99)	22/57	30/54
	No	NE	33.2	0.67 (0.51-0.87)	91/291	121/294
Bone-only metastases at baseline	Yes	NE	41.2	0.71 (0.46-1.10)	36/146	48/154
	No	41.2	25.6	0.60 (0.45-0.81)	77/202	103/194
Metastases stage at diagnosis	M0	NE	NE	0.96 (0.29-3.17)	5/32	6/36
	M1	NE	27.4	0.60 (0.47-0.78)	100/301	142/302
Disease volume at baseline	High	41.2	26.3	0.65 (0.50-0.85)	100/269	130/271
	Low	NE	40.2	0.55 (0.27-1.10)	13/79	21/77
Regions	Asia	36.8	NE	1.11 (0.62-1.97)	26/72	21/63
	Europe	NE	26.3	0.56 (0.40-0.78)	56/168	86/177
	North America	NE	33.2	0.51 (0.25-1.04)	14/45	18/44
	Rest of world	NE	NE	0.65 (0.35-1.20)	17/63	26/64



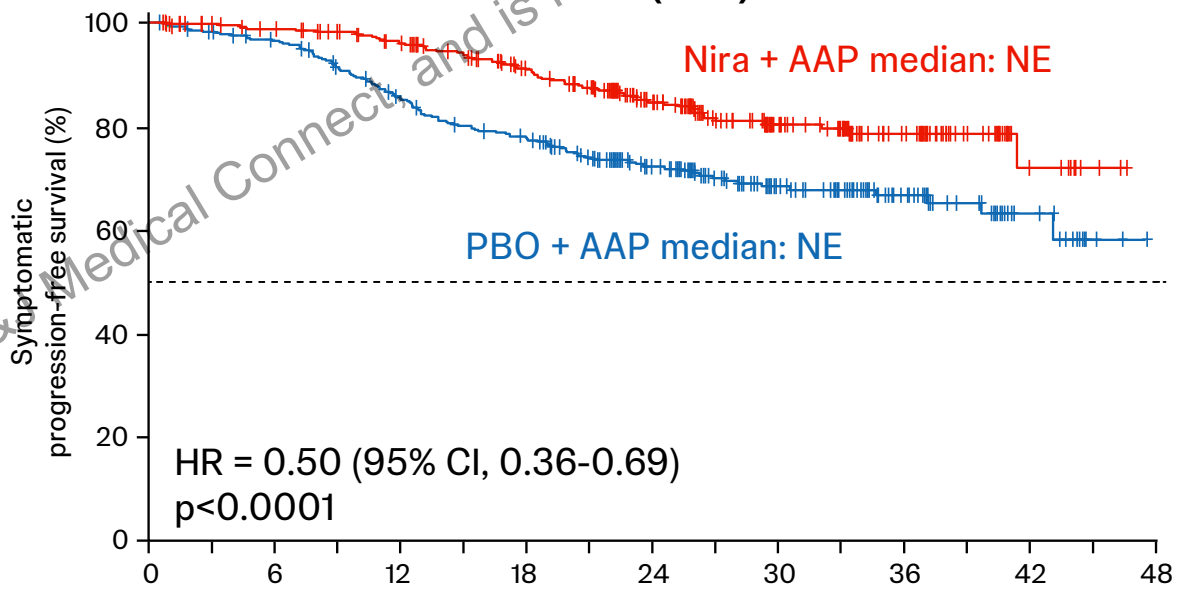
Benefit from Nira + AAP is generally consistent across prespecified subgroups

Results in small subgroups should be interpreted with caution.

Secondary End Point: Time to Symptomatic Progression



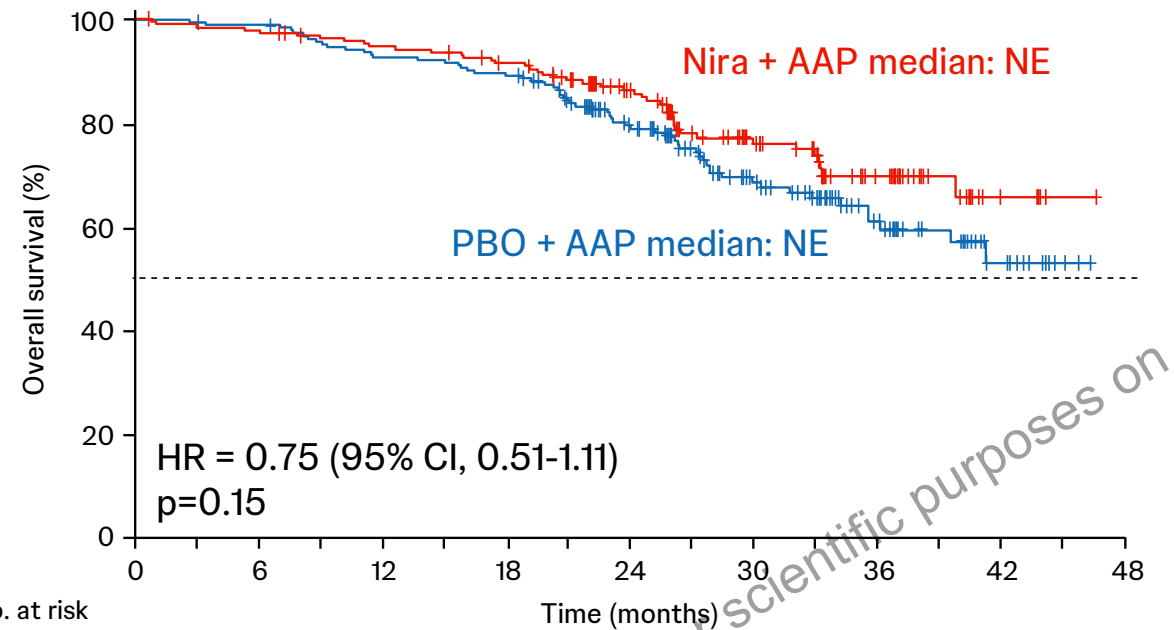
No. at risk									
Nira + AAP	191	183	172	154	108	65	37	5	0
PBO + AAP	196	185	159	144	101	59	32	9	0



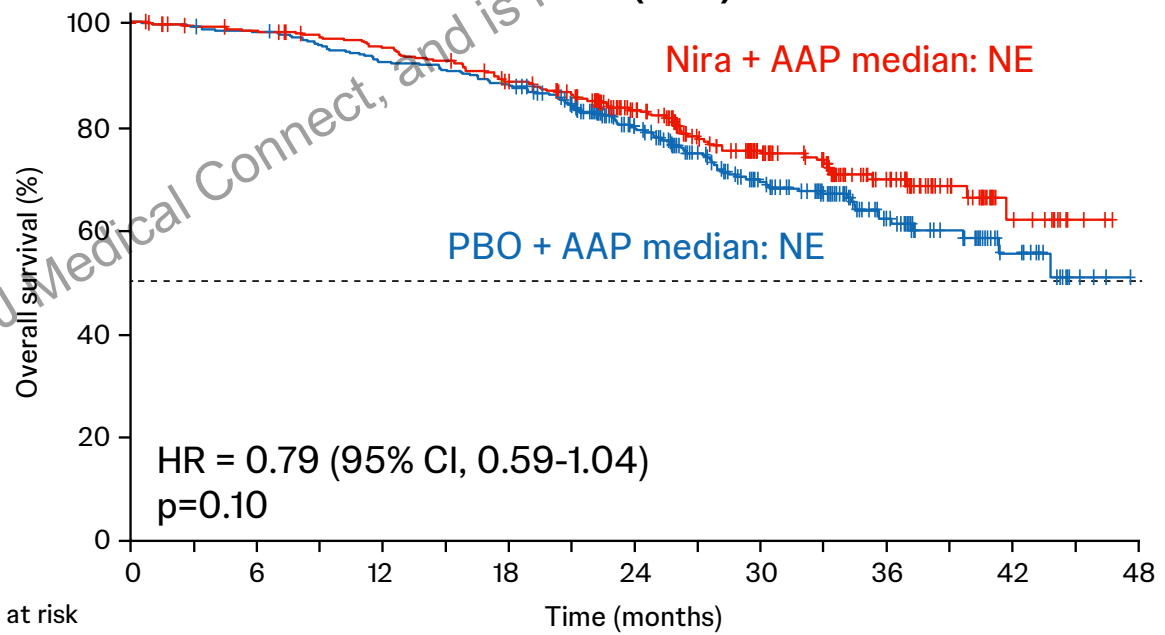
No. at risk									
Nira + AAP	348	331	310	272	193	115	66	10	0
PBO + AAP	348	328	284	256	180	110	62	15	0

Nira + AAP significantly reduced the risk of symptomatic progression by 56% in BRCAm group and by 50% in HRRm population

Secondary End Point: Overall Survival (First Interim Analysis)



No. at risk									
Nira + AAP	191	186	177	168	126	75	38	6	0
PBO + AAP	196	193	180	174	124	72	39	12	0



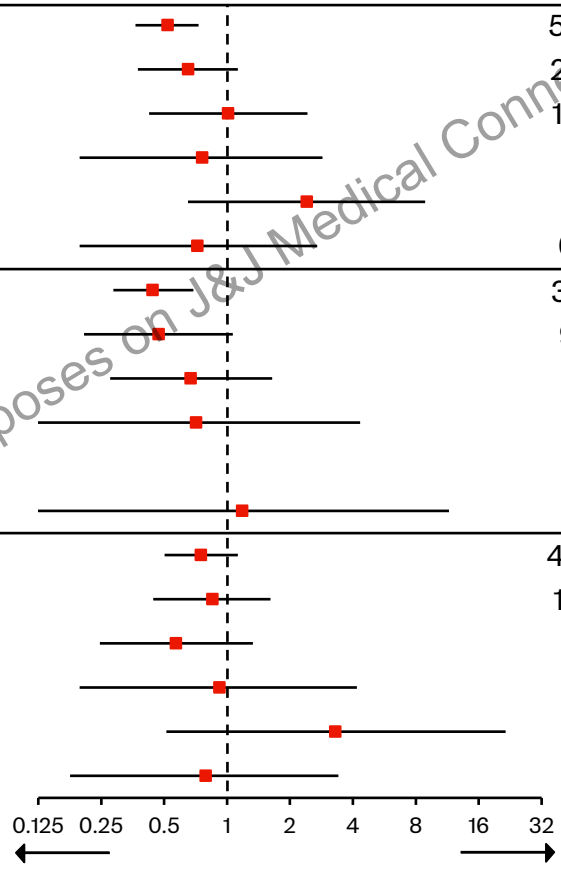
No. at risk									
Nira + AAP	348	335	320	293	218	133	71	13	0
PBO + AAP	348	340	319	304	219	131	70	18	0

The first interim analysis (≈50% of total needed events) estimates show Nira + AAP reduced risk of death by 25% in BRCAm group and by 21% in HRRm population

The first interim analysis for OS was conducted when 193 participants had died (of a target of 389, an information fraction of 50%), 85 of 348 (24%) in the Nira + AAP group and 108 of 348 (31%) in the PBO + AAP group.

Subgroup Analysis by *BRCA* and non-*BRCA* Alterations

End Point	Subgroup	HR (95% CI)	Events/N	
			Nira + AAP	PBO + AAP
rPFS	*BRCA*	0.52 (0.37-0.72)	57/191	93/196
	CHEK2	0.65 (0.38-1.11)	24/72	32/76
	CDK12	1.01 (0.43-2.39)	13/28	10/28
	FANCA	0.76 (0.20-2.82)	4/15	5/15
	PALB2	2.41 (0.66-8.74)	6/9	4/13
	Other	0.72 (0.20-2.66)	6/25	4/15
Time to symptomatic progression	*BRCA*	0.44 (0.29-0.68)	31/191	66/196
	CHEK2	0.47 (0.21-1.05)	9/72	18/76
	CDK12	0.68 (0.28-1.62)	9/28	12/28
	FANCA	0.71 (0.12-4.27)	2/15	3/15
	PALB2	NE (NE-NE)	1/9	2/13
	Other	1.18 (0.12-11.36)	4/25	1/15
OS	*BRCA*	0.75 (0.51-1.11)	44/191	61/196
	CHEK2	0.85 (0.45-1.59)	18/72	21/76
	CDK12	0.57 (0.25-1.31)	9/28	15/28
	FANCA	0.92 (0.20-4.12)	3/15	4/15
	PALB2	3.30 (0.52-21.21)	3/9	2/13
	Other	0.79 (0.18-3.36)	5/25	3/15



Non-BRCA subgroups were not statistically powered for formal testing in this exploratory analysis. Hazard ratios were stratified by disease volume (high vs low).
Other: *RAD54L*, *BRIP1*, *RAD51B*.

Subsequent Therapy for Prostate Cancer

Patients, n (%)	Nira + AAP (n=347)[a]	PBO + AAP (n=348)
Discontinued treatment due to progressive disease (denominator for any subsequent therapy)	93 (27)	149 (43)
Any subsequent therapy (denominator for below)	72 (77)	120 (81)
Chemotherapy[b]	60 (83)	91 (76)
ARPI	19 (26)	27 (23)
PARPi	**8 (11)**	**43 (36)**
Radiopharmaceuticals	6 (8)	8 (7)
Immunotherapy	2 (3)	6 (5)
Other[c]	6 (8)	13 (11)

[a]One randomized patient never received the study treatment. [b]Of patients with any subsequent therapy, 14% in the Nira + AAP group and 11% in the PBO + AAP group also received carboplatin. [c]Capivasertib, ODM 208, AMG 509, vobramitamab duocarmazine, ZEN 3694, cabozantinib, datopotamab deruxtecan, enfortumab vedotin, investigational antineoplastic drugs, NUV 868, zanzalintinib.

Overview of AMPLITUDE Safety Profile

Safety population, n (%)	Nira + AAP (n=347)[a]	PBO + AAP (n=348)
TEAEs	346 (>99)	341 (98)
Treatment-related TEAEs[b]	309 (89)	257 (74)
Grade 3 or 4 TEAEs	261 (75)	205 (59)
Treatment-related grade 3 or 4 TEAEs	193 (56)	105 (30)
SAEs	136 (39)	96 (28)
Treatment-related SAEs	44 (13)	11 (3)
TEAEs leading to treatment discontinuation[c]	**51[d] (15)**	**36 (10)**
TEAEs leading to dose reduction	76 (22)	24 (7)
TEAEs leading to death[e]	14[f] (4)	7 (2)

<5% increase in rate of discontinuation due to toxicity of Nira + AAP versus PBO + AAP

Median duration of treatment was 25.3 months in the Nira + APP group and 22.5 months in the PBO + APP group.
[a]One randomized patient never received the study treatment. [b]AE is categorized as related if assessed by the investigator as related to study treatment (Nira/PBO or AA/PBO or prednisone). [c]An AE is counted as leading to discontinuation of study treatment if it leads to withdrawal of Nira/PBO or AA/PBO or prednisone. [d]Includes one case of MDS. [e]AE leading to death based on AE outcome of fatal. [f]TEAE leading to death included 4 cases of respiratory infection, including 2 attributed as related to COVID-19, 4 attributed to cardiac causes, 3 classified as sudden death, and 1 each of sepsis, subdural hematoma, and multiorgan dysfunction syndrome.
AE, adverse event; MDS, myelodysplastic syndrome; SAE, serious AE; TEAE, treatment-emergent AE.

Adverse Events of Special Interest

Selected categories of TEAEs of interest, n (%)		Nira + AAP (n=347)		PBO + AAP (n=348)	
		All grades	Grade ≥3	All grades	Grade ≥3
Participants with ≥1 AE of interest		306 (88)	217 (63)	261 (75)	132 (38)
Hematologic	**Anemia**	**179 (52)**	**101 (29)**	**83 (24)**	**16 (5)**
	Neutropenia	76 (22)	33 (10)	28 (8)	7 (2)
	Thrombocytopenia	66 (19)	24 (7)	20 (6)	1 (<1)
	MDS	1 (<1)	1 (<1)	0	0
Cardiovascular	**Hypertension**	**155 (45)**	**93 (27)**	**113 (33)**	**64 (18)**
	Arrhythmia	68 (20)	19 (5)	28 (8)	11 (3)
	Cardiac failure	20 (6)	9 (3)	6 (2)	4 (1)
Nonhematologic or cardiovascular	Hypokalemia	92 (27)	40 (12)	70 (20)	38 (11)
	Hepatotoxicity	46 (13)	8 (2)	71 (20)	19 (5)

- Other common AEs of any grade: constipation (35% vs 16%), nausea (31% vs 14%), fatigue (26% vs 18%), and arthralgia (21% vs 21%) in the Nira + AAP vs PBO + AAP groups, respectively

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the patient with the worst toxicity is used. If a patient has missing toxicity for a specific AE, the patient is only counted in the total column for that AE.

AMPLITUDE: Conclusions

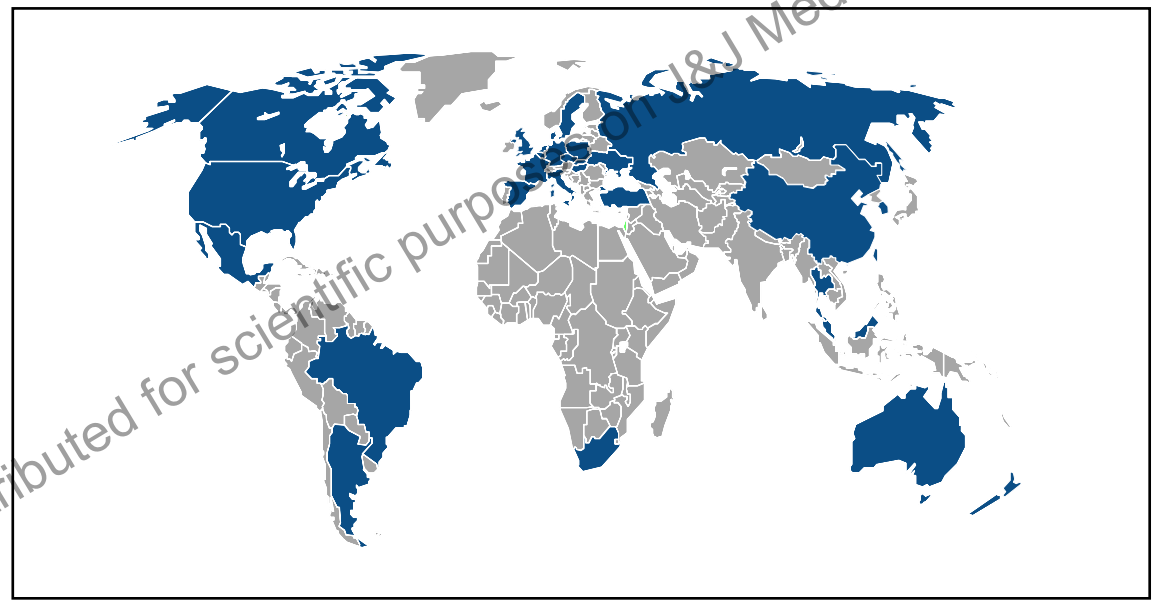
- The AMPLITUDE trial met its primary end point of rPFS and is the first trial to show efficacy of a PARPi + ARPI combination in mCSPC with HRR alterations, with likely greatest benefit in patients with BRCA alterations
- Improvements in rPFS are supported by a statistically significant benefit in time to symptomatic progression and a trend toward improved OS
- The safety profile of niraparib + AAP was consistent with that previously observed in the MAGNITUDE trial,[1] with a <5% increase in patients discontinuing treatment due to toxicity than in those receiving placebo
- AMPLITUDE supports niraparib + AAP as a new treatment option for patients with mCSPC and HRR gene alterations

1. Chi KN. *J Clin Oncol*. 2023;41:3339-3351.

Acknowledgments

Thank you to our patients, their families and caregivers, AMPLITUDE investigators, site staff, and clinical teams

A total of 696 patients from 32 countries were randomized in AMPLITUDE, with >6000 patients consenting to genomic testing



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AMPLITUDE: Lay Summary

- The AMPLITUDE study evaluated how well a combination of 3 medicines (niraparib, abiraterone, and prednisone) worked in a specific type of prostate cancer that has spread beyond the prostate, needs testosterone to grow, and has genetic changes that prevent cancer cells from fixing damaged DNA
  - Niraparib - further prevents cancer cells from fixing mistakes in DNA, causing the cancer cells to die
  - Abiraterone - reduces male hormones, slowing down tumor growth
  - Prednisone - further prevents tumor growth and reduces side effects of other medicines (abiraterone)
- The combination of niraparib, abiraterone, and prednisone helped patients have longer time before their cancer got worse and new symptoms developed, and may help them live longer compared with abiraterone and prednisone
- When side effects occurred, they could be managed by adjusting the dose and/or giving supportive care
- Based on these results, the researchers suggest that this drug combination could become a new standard treatment for patients with specific genetic changes in their prostate cancer

https://www.congresshub.com/Oncology/AM2025/Niraparib/Attard