Gene-by-Gene Analysis in the MAGNITUDE Study of Niraparib With Abiraterone Acetate and Prednisone in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Repair Gene Alterations

Shahneen Sandhu (Shahneen.Sandhu@petermac.org)[1], Gerhardt Attard[2], David Olmos[3], Eleni Efstathiou[4], Elena Castro[5], Dana E Rathkopf[6], Matthew R Smith[7], Guilhem Roubaud[8], Eric J Small[9], Andrea J Pereira de Santana Gomes[10], Marniza Saad[11], Deniz Tural[12], Shibu Thomas[13], Karen Urtishak[13], Michael Gormley[13], Gary E Mason[13], Brooke Diorio[14], George Wang[13], Angela Lopez-Gitlitz[15], Kim N Chi[16]

[1]Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia; [2]University College London, London, UK; [3]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; [4]Houston Methodist Cancer Center, Houston, TX, USA; [5]University Hospital Virgen de la Victoria, Málaga, Spain; [6]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; [7]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [8]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [9]University of California San Francisco, San Francisco, CA, USA; [10]Liga Norte Riograndense Contra o Câncer, Natal, Brazil; [11]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [12]Department of Medical Oncology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Zuhuratbaba District, Bakirkoy, Istanbul, Turkey; [13]Janssen Research & Development, LLC, Spring House, PA, USA; [14]Janssen Research & Development, LLC, Titusville, NJ, USA; [15]Janssen Research & Development, LLC, Los Angeles, CA, USA; [16]University of British Columbia, BC Cancer - Vancouver Center, Vancouver, British Columbia, Canada.

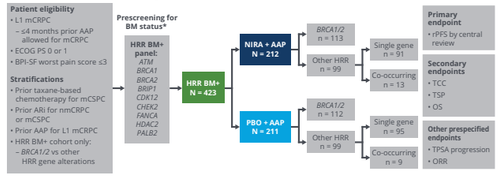
INTRODUCTION

- Radiographic progression free survival (rPFS) was statistically significantly and clinically meaningfully improved with niraparib (NIRA) + abiraterone acetate and prednisone (AAP) in patients with metastatic castration resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations in the phase 3 MAGNITUDE study (ClinicalTrials.gov Identifier: NCT03748641), with improvement also observed in secondary and other endpoints
- A paucity of data supports the use of poly (ADP-ribose) polymerase (PARP) inhibitors in patients with HRR gene alterations other than *BRCA1/2*
- Here, we report the efficacy of NIRA + AAP in patients with mCRPC and a qualifying (by plasma, tissue, and/or saliva/whole blood assays) single-gene HRR alteration other than *BRCA1/2*

METHODS

- A prespecified analysis was undertaken of the primary endpoint (rPFS by blinded independent central review), secondary endpoints (time to cytotoxic chemotherapy [TCC], time to symptomatic progression [TSP], and overall survival [OS]), as well as time to prostate-specific antigen progression (TPSA) and objective response rate (ORR) across 186 patients (91 randomized to NIRA + AAP; 95 to placebo [PBO] + AAP) with a single alteration in the *ATM*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, or *PALB2* gene (excluding co-occurring alterations)
  - CDK12 alterations were added to the MAGNITUDE HRR positive cohort eligibility mid-way through study enrollment, therefore patients with CDK12 alterations are included in this analysis regardless of which cohort they were enrolled (**Figure 1**)
- This analysis of individual alterations was not powered for formal statistical inference
- Data on co-occurring mutations are not reported here due to the small sample size per tumor genotype and the inability to draw meaningful conclusions
- Given the rarity of some single-gene alterations, groups based on functional similarity (HRR-Fanconi group [*BRIP1*, *FANCA*, *PALB2*] and HRR-associated group [*CHEK2*, *HDAC2*]) are also presented. Double-strand breaks can be detected by different proteins, such as the FANC complex, which recruit HRR effectors including BRCA1, BRCA2, and PALB2 (**Figure 2**)

FIGURE 1: Study design



L1, first-line; mCRPC, metastatic castration-resistant prostate cancer; AAP, abiraterone acetate and prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; BPI-SF, Brief Pain Inventory–Short Form; mCSPC, metastatic castration-sensitive prostate cancer; ARi, androgen receptor inhibitor; nmCRPC, nonmetastatic castration-resistant prostate cancer; HRR, homologous recombination repair; BM, biomarker; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival; TCC, time to cytotoxic chemotherapy; TSP, time to symptomatic progression; OS, overall survival; TPSA, time to prostate-specific antigen; ORR, overall response rate.
*Patients were prospectively tested by plasma, tissue, and/or saliva/whole blood. Patients who were negative by plasma were also confirmed negative on tissue whenever possible.
Note: The 91 patients with single-gene alterations in the NIRA group included 6 patients with single *CDK12* gene alterations from the HRR BM– cohort; the 95 patients with single-gene alterations in the PBO group included 8 patients with single *CDK12* gene alterations from the HRR BM– cohort.

FIGURE 2: HRR-Fanconi group (FANCA, BRIP1, PALB2)

HRR, homologous recombination repair; DSB, double-strand break.
Adapted from Teyssonneau D, et al. 2021[1] under the Creative Commons (CC) by license (http://creativecommons.org/licenses/by/4.0/).
Note: The FANC complex contains FANCA.

PROSTATE CANCER

RESULTS

- When combined into functional groups, patients with an alteration in the HRR-Fanconi pathway (*BRIP1*, *FANCA*, or *PALB2*) as well as patients with an HRR-associated alteration (*CHEK2* or *HDAC2*) showed improvement in all endpoints (**Table 1**)
- Patients with gene alterations in *PALB2*, *CHEK2*, and *HDAC2* showed benefit across all endpoints, similar to results seen in patients with *BRCA1/2* gene alterations
- Additionally, *BRIP1* showed a compelling benefit in rPFS (**Table 1**)
- In patients with *ATM* alterations, benefit was observed in TCC, TSP, TPSA, and ORR (**Table 1**)
- There was benefit in TPSA and ORR for patients with *CDK12* alterations but not for the primary or secondary endpoints (**Table 1**)
- With the exception of *CDK12*, all individual genes showed improvement in the primary endpoint and/or ≥1 of the secondary endpoints (**Table 1**)

TABLE 1: Combined functional groups of primary, secondary, and other endpoints

Single-gene alteration, HR (95% CI)	NIRA + AAP (N)	PBO + AAP (N)	rPFS, HR (95% CI)	TCC, HR (95% CI)	TSP, HR (95% CI)	OS, HR (95% CI)	TPSA progression, HR (95% CI)	ORR (risk ratio) NIRA vs PBO
BRCA1/2	113	112	0.53 (0.36, 0.79)	0.58 (0.33, 1.01)	0.68 (0.42, 1.11)	0.96 (0.57, 1.63)	0.46 (0.30, 0.69)	1.65 (1.02, 2.71); 29/56 (52%) vs 15/48 (31%)
HRR-Fanconi group	17	14	0.59 (0.23-1.45)	0.68 (0.17-2.74)	0.90 (0.24-3.37)	0.43 (0.12-1.50)	0.65 (0.27-1.59)	1.5 (0.38-6.00); 3/6 (50%) vs 2/6 (33%)
BRIP1	4	4	0.23 (0.02-2.26)	NE	1.14 (0.10-13.27)	NE	0.98 (0.14-7.00)	0.5 (0.13-2.00); 1/2 (50%) vs 1/1 (100%)
FANCA	5	6	1.07 (0.18-6.44)	0.51 (0.05-5.16)	1.23 (0.17-8.74)	NE	0.66 (0.13-3.47)	NE; 0/1 (0%) vs 0/2 (0%)
PALB2	8	4	0.59 (0.15-2.22)	0.39 (0.02-6.19)	0.41 (0.03-6.62)	0.27 (0.05-1.66)	0.59 (0.16-2.20)	2 (0.33-11.97); 2/3 (67%) vs 1/3 (33%)
HRR-associated group	20	23	0.64 (0.26-1.58)	0.72 (0.19-2.69)	0.58 (0.17-2.00)	0.43 (0.13-1.38)	0.43 (0.17-1.10)	6.4 (0.96-43.25); 5/7 (71%) vs 1/9 (11%)
CHEK2	18	20	0.66 (0.25-1.75)	0.36 (0.07-1.88)	0.54 (0.14-2.25)	0.44 (0.12-1.71)	0.37 (0.14-0.99)	NE; 5/7 (71%) vs 0/6 (0%)
HDAC2	2	3	0.71 (0.06-8.02)	NE	0.71 (0.04-11.79)	0.44 (0.04-5.13)	NE	NE; 0/0 (0%) vs 1/3 (33%)
ATM	43	42	1.11 (0.63-1.99)	0.26 (0.08-0.80)	0.75 (0.28-2.00)	1.07 (0.44-2.65)	0.73 (0.39-1.36)	3 (1.12-8.13); 14/17 (82%) vs 3/11 (27%)
CDK12	11	16	1.32 (0.43-3.92)	1.13 (0.27-5.70)	1.05 (0.28-3.94)	1.61 (0.49-5.33)	0.66 (0.24-1.80)	2.25 (0.64-7.97); 3/4 (75%) vs 2/6 (33%)

HR, hazard ratio; CI, confidence interval; PBO, placebo; AAP, abiraterone acetate and prednisone; NIRA, niraparib; rPFS, radiographic progression-free survival, TCC, time to cytotoxic chemotherapy; TSP, time to symptomatic progression; OS, overall survival; TPSA, time to prostate-specific antigen; ORR, overall response rate; HRR, homologous recombination repair; NE, not estimable.

KEY TAKEAWAYS

- The prognostic impact of *BRCA1/2* altered prostate cancer and response to PARP inhibitors is well characterized; however, PARP inhibition activity in other HRR gene alterations is not as well characterized
- A gene-by-gene analysis in patients with mCRPC showed benefit for treatment with NIRA + AAP for rPFS, secondary endpoints, and other efficacy endpoints both in patients with *BRCA1/2* mutations and in selected other HRR gene alterations

CONCLUSIONS

- Clinical benefit was seen in primary, secondary, and other endpoints in patients with HRR gene alterations, both *BRCA1/2* and beyond *BRCA1/2*, who were treated with NIRA + AAP
- In addition to improvements in rPFS, improvement in the secondary endpoints, such as delaying time to cytotoxic chemotherapy and prolonging time to symptomatic progression, are particularly relevant for improving the experience of patients with mCRPC
- These data support the overall conclusions of the MAGNITUDE primary analysis and support the benefit of NIRA + AAP in patients with HRR gene alterations, both *BRCA1/2* and beyond *BRCA1/2*

ACKNOWLEDGMENTS

This study (ClinicalTrials.gov Identifier: NCT03748641) is funded by Janssen Research & Development. Medical writing and editorial assistance were provided by Kristen Exaul, PhD, and Ashley Davis, PhD, of Cello Health Communications/MedErgy.

© 2022 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2022 ASCO Annual Meeting. All rights reserved.

DISCLOSURES

SS received honoraria from Merck Sharp & Dohme and AstraZeneca; received consulting or advisory fees from Bristol Myers Squibb and AstraZeneca; received speakers bureau fees from AstraZeneca; and received research funding from Novartis, Amgen, Merck Sharp & Dohme, AstraZeneca, and Genentech. GA received honoraria from Astellas Pharma and Janssen; received consulting or advisory fees from Abbott Laboratories, Astellas Pharma, AstraZeneca, Bayer, ESSA, Ferring, Janssen-Cilag, Medivation, Millennium, Novartis, Pfizer, Ventana Medical Systems, and Veridex; received speakers bureau fees from Astellas Pharma, AstraZeneca, Ferring, Ipsen, Janssen, Sanofi, Takeda, and Ventana Medical Systems; received research funding from Arno Therapeutics, Innocrin Pharma, and Janssen; has patents or other intellectual property or received royalties for abiraterone acetate; received travel, accommodations, or expense reimbursement from Abbott Laboratories, Astellas Pharma, Bayer, ESSA, Ferring, Janssen, Medivation, Pfizer, and Ventana Medical Systems; and is affiliated with the Institute of Cancer Research. DO received honoraria from Astellas Pharma, Bayer, and Janssen; received consulting or advisory role fees from AstraZeneca, Bayer, Clovis Oncology, Daiichi Sankyo, Janssen, and Merck Sharp & Dohme Oncology; received research funding from Astellas Medivation, AstraZeneca, Bayer, Genentech/Roche, Janssen, Merck Sharp & Dohme Oncology, Pfizer, and Tokai Pharmaceuticals; and received travel, accommodations, or expense reimbursement from Astellas Pharma, AstraZeneca Spain, Bayer, Ipsen, Janssen, and Roche. EE received consulting or advisory fees from Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis; received speakers bureau fees from Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis; and received research funding from Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis. EC received honoraria from AstraZeneca, Astellas, Janssen, Clovis, and Merck Sharp & Dohme; received consulting or advisory fees from AstraZeneca, Astellas, Bayer, Janssen, Merk, Merck Sharp & Dohme, and Pfizer; received speakers bureau fees from AstraZeneca and Janssen; received research funding from AstraZeneca, Bayer, Janssen, and Merck Sharp & Dohme; and received travel, accommodations, or expense reimbursement from AstraZeneca and Janssen. DER received research funding from Janssen, Celgene/Bristol Myers Squibb, Bayer, Taiho, Genentech/Roche, and Phosplatin. MRS received consulting or advisory fees from Amgen, Astellas Pharma, Bayer, Janssen Oncology, Lilly, Novartis, and Pfizer; received research funding from Bayer, ESSA, Janssen Oncology, Lilly, and ORIC Pharmaceuticals; and received travel, accommodations, or expense reimbursements from Amgen, Bayer, Janssen, and Lilly. GR received consulting or advisory role fees from Astellas, Janssen, Pfizer, Merck Sharp & Dohme, and AstraZeneca; received research funding from Bayer; and received travel, accommodations, or expense reimbursements from Janssen. EJS has stock or other ownership of Fortis, Harpoon, and Teon; received honoraria from Janssen and Johnson & Johnson; and received consulting or advisory role fees from Janssen, Fortis, Teon, and Ultragenyx. AJPG received consulting or advisory fees from Janssen; received speakers bureau fees from Janssen, Bayer, and Astellas; received research funding from Janssen, Bayer, Merck Sharp & Dohme, and Roche; and received travel, accommodations, or expense reimbursement from Astellas. MS received honoraria from Johnson & Johnson, Merck Sharp & Dohme, AstraZeneca, Pfizer, Ipsen, and Eisai; received consulting or advisory role fees from Johnson & Johnson, Merck Sharp & Dohme, AstraZeneca, Pfizer, Ipsen, and Eisai; and received research funding from Johnson & Johnson and Merck Sharp & Dohme. DT has nothing to disclose. ST is employed by; has stock or other ownership in; received research funding from; has patents, royalties, or other intellectual property from; and received travel, accommodations, or expense reimbursement from Johnson & Johnson. KU and MG are employed by; have stock or other ownership in; and have patents or other intellectual property or received royalties from Janssen Research & Development. GEM is employed by Janssen Research & Development. BD is employed by Janssen (Johnson & Johnson). GW is employed by and has stock or other ownership in Janssen (Johnson & Johnson). ALG is employed by Janssen (Johnson & Johnson) and has stock or other ownership in Johnson & Johnson. KNC received honoraria from Astellas Pharma, AstraZeneca, Bayer, Janssen, Merck, and Roche; received consulting or advisory fees from Amgen, Astellas Pharma, AstraZeneca, Bayer, Constellation Pharmaceuticals, Daiichi Sankyo, ESSA, Janssen, Merck, POINT Biopharma, Roche, and Sanofi; received research funding from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, ESSA, Janssen, Merck, Novartis, Pfizer, Roche, and Sanofi; and gave expert testimony for AstraZeneca and Novartis.

REFERENCE:

1. Teyssonneau D, et al. *J Hematol Oncol*. 2021;14(1):51.

Presented at JADPRO Live 2022, October 20-23, 2022, Aurora, CO