

Clinical Validation of a Tissue-Based Next-Generation Sequencing Kit for Identifying Patients with *BRCA1/2*-Mutated Prostate Cancer for Niraparib + Abiraterone Acetate and Prednisone Therapy

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Key Takeaway



This companion diagnostic (CDx) clinical validation study demonstrates the clinical utility of HRD Complete assay to identify mPC patients with *BRCA1/2* mutations who might benefit from the Niraparib+AAP treatment

Conclusions



The CDx clinical validation study indicates high concordance in *BRCA1/2* mutation detection capability between HRD Complete and the clinical trial assay used to enroll patients



The clinical validity results provided evidence that patients with *BRCA1/2* gene mutations identified by HRD Complete demonstrated similar efficacy as with MAGNITUDE *BRCA* subgroup patients



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Disclosures

Xin Ye, Yaji Xu, Victoria Zadorozhny, Usha Singh, Xiaofang Zhuo, Lesley Farrington, Yuping Chen, Tingting Wu, Lichao Luo, Han Yang, Katherine Bell, Xuesong Lyu, Yanmei Liu, Fei Shen, Longen Zhou, and Flora Berisha: Employees of Johnson & Johnson and may hold stock/shares options in Johnson & Johnson. Lida Zhang, and Zhijie Zheng: Employees of AmoyDx and may own stock/shares options in AmoyDx. Xiaolin Lu and Dingwei Ye: No competing interests.

Introduction

- The phase 3 MAGNITUDE study (NCT03748641) evaluated Niraparib + Abiraterone Acetate plus Prednisone (AAP) for treatment of patients with metastatic prostate cancer (mPC) and mutations in homologous recombination repair genes, including *BRCA1/2*¹
- The homologous recombination deficiency (HRD) Complete Kit has been developed as a tissue-based next-generation sequencing assay for the detection of homologous recombination repair (HRR) gene mutations, including *BRCA1/2* mutations (single nucleotide variants, InDel, homozygous deletions), in patients with prostate cancer²
- This companion diagnostic (CDx) clinical validation study was performed to assess the concordance between HRD Complete and clinical trial assays (CTAs, that were used to enroll patients in the trial and included both tissue and plasma assays) for *BRCA1/2* mutations, and clinical efficacy of Niraparib + AAP in *BRCA1/2*-positive patients tested by HRD Complete

Results

Demographics characteristics

- The demographics of HRD Complete evaluable population and HRD Complete unevaluable population closely resembled those of the primary efficacy analysis set of the MAGNITUDE study (**Table 1**)

Table 1. Summary of demographics

	CDx Evaluable N=117	CDx Unevaluable N=108	All patients N=225
Age, years			
Mean (SD)	67.7 (8.18)	68.0 (9.63)	67.9 (8.88)
Median (range)	68.0 (49–88)	68.0 (43–100)	68.0 (43–100)
Age group, n (%)			
<65 years	39 (33.3)	37 (34.3)	76 (33.8)
65-74 years	53 (45.3)	43 (39.8)	96 (42.7)
≥75 years	25 (21.4)	28 (25.9)	53 (23.6)
Sex, male, n (%)	117 (100.0)	108 (100.0)	225 (100)
Race, n (%)			
Asian	14 (12.0)	24 (22.2)	38 (16.9)
Black	1 (0.9)	2 (1.9)	3 (1.3)
White	91 (77.8)	71 (65.7)	162 (72.0)
Unknown	11 (9.4)	11 (10.2)	22 (9.8)
Ethnicity, n (%)			
Hispanic or Latino	14 (12.0)	12 (11.1)	26 (11.6)
Not Hispanic or Latino	91 (77.8)	83 (76.9)	174 (77.3)
Not reported	12 (10.3)	13 (12.0)	25 (11.1)
Weight, kg			
Mean (SD)	86.3 (17.11)	84.0 (17.31)	85.2 (17.21)
Median (range)	83.0 (53–140)	82.8 (49–160)	83.0 (49–160)
Height, cm			
Mean (SD)	172.6 (8.20)	171.6 (7.92)	172.1 (8.07)
Median (range)	172.7 (152–196)	170.8 (155–194)	172.0 (152–196)

Note: CDx evaluable population were tested by HRD Complete and received valid *BRCA1/2* results, while the CDx unevaluable population were those not tested by HRD Complete or tested by HRD Complete but received invalid results. *BRCA*=breast cancer gene, CDx=companion diagnostic, HRD=homologous recombination deficiency, SD=standard deviation.

Methods

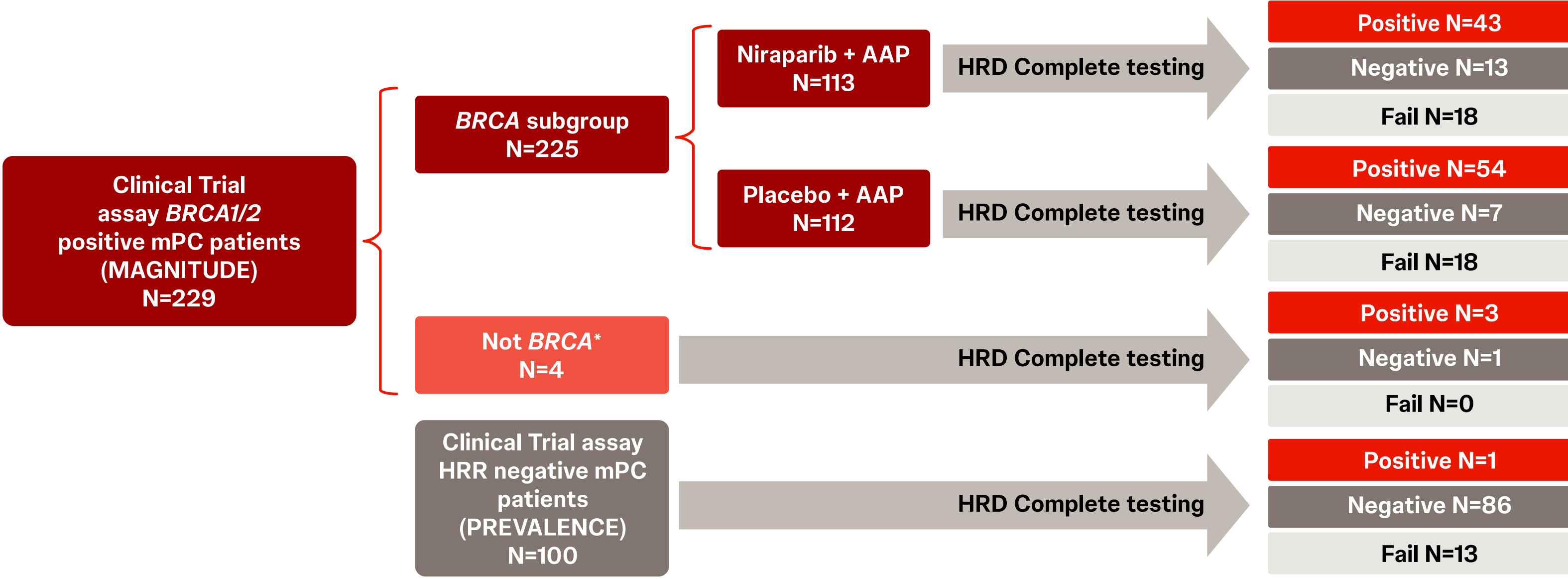
Study design (Figure 1)

- Residual tissue DNA of patients from MAGNITUDE with *BRCA*-positive results were retrospectively tested with the HRD Complete assay
 - Samples from PREVALENCE (NCT03871816) that were HRR-negative with the same CTAs were additionally tested with HRD Complete to assess the negative percent agreement (NPA)

Outcomes

- Concordance of HRD Complete with the CTAs was summarized as positive percent agreement (PPA), NPA, and overall percent agreement (OPA)
- Clinical efficacy of Niraparib + AAP compared to placebo + AAP in HRD Complete-tested patients was evaluated by radiographic progression-free survival (rPFS) using Cox proportional hazards model

Figure 1: Study design



*4 subjects who were not randomized into the *BRCA* subgroup were later found to carry *BRCA* gene mutation and were included in the study. AAP=abiraterone acetate plus prednisone, *BRCA*=breast cancer gene, HRD=homologous recombination deficiency, HRR=homologous recombination repair, mPC=metastatic prostate cancer.

Clinical efficacy

- In the patients from MAGNITUDE who were *BRCA1/2*-positive via HRD Complete, niraparib + AAP showed consistent clinical improvement in rPFS with a 45% reduction in the risk of radiographic progression/death compared with placebo + AAP (HR=0.549; 95% CI, 0.297–1.017; p=0.0534) (**Table 4**)
 - This efficacy is comparable to the efficacy demonstrated in the *BRCA*-positive subgroup population in MAGNITUDE (HR=0.533; 95% CI, 0.361–0.789; p=0.0014)

Table 4. Summary of radiographic progression-free survival by central review

Progression-free survival (95% CI)	<i>BRCA1/2</i> -positive HRD Complete		<i>BRCA1/2</i> -positive CTA+	
	Placebo+AAP N=54	Niraparib+AAP N=43	Placebo+AAP N=112	Niraparib+AAP N=113
Event, n (%)	29 (53.7)	17 (39.5)	64 (57.1)	45 (39.8)
Censored, n (%)	25 (46.3)	26 (60.5)	48 (42.9)	68 (60.2)
Time to event, months				
25 th percentile (95% CI)	5.55 (3.71, 8.31)	9.23 (3.68, 16.46)	5.36 (3.58, 8.05)	10.87 (8.05, 13.44)
Median (95% CI)	11.17 (8.08, 13.93)	18.43 (11.10, NE)	10.87 (8.31, 13.80)	16.56 (13.86, NE)
75 th percentile (95% CI)	NE (13.80, NE)	NE (18.43, NE)	NE (16.39, NE)	NE (21.95, NE)
Range	(0.5–24.9+)	(1.0–27.5+)	(0.5, 24.9+)	(0.0+, 27.5+)
6-months event free rate (95% CI)	0.718 (0.577, 0.820)	0.858 (0.710, 0.934)	0.711 (0.617, 0.786)	0.865 (0.786, 0.916)
12-months event free rate (95% CI)	0.482 (0.329, 0.620)	0.632 (0.455, 0.765)	0.444 (0.341, 0.542)	0.690 (0.584, 0.775)
18-months event free rate (95% CI)	0.344 (0.196, 0.498)	0.527 (0.328, 0.691)	0.327 (0.224, 0.433)	0.470 (0.344, 0.587)
24-months event free rate (95% CI)	0.344 (0.196, 0.498)	0.451 (0.240, 0.642)	0.297 (0.192, 0.410)	0.349 (0.199, 0.503)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
p-value ^a	0.0534		0.0014	
HR (95% CI) ^b	0.549 (0.297,1.017)		0.533 (0.361,0.789)	

^ap-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no). ^bHR is from stratified proportional hazards model. HR <1 favors niraparib + AAP treatment. Note: + = censored observation. Note: HRD Complete+ indicates subjects from cohort 1 which are tested by HRD Complete and get valid positive results of *BRCA1/2*; CTA+ indicates subjects from cohort 1 (*BRCA* randomized) with available *BRCA1/2* positive results by clinical trial assay, including tissue positive and/or plasma positive. AAP=abiraterone acetate plus prednisone, *BRCA*=breast cancer gene, CI=confidence interval, CTA=clinical trial assay, HR=hazard ratio, HRD=homologous recombination deficiency, NE=not estimable.

References

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