Clinical Validity of FoundationOne® CDx Assay to Identify *HRR*-Positive or *BRCA*-Positive mCSPC Patients in the Phase 3 AMPLITUDE Study

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Key Takeaway

This study demonstrated the clinical validity of F1CDx® as an effective companion diagnostic to identify patients with mCSPC and *HRR* gene alterations, and to help guide treatment decisions regarding NIRA+AAP

Conclusions

In the AMPLITUDE study, rPFS outcomes with NIRA+AAP in patients with mCSPC and *HRR+* and *BRCA+* alterations identified by F1CDx® were consistent with those in the overall patient population

Reduced risk of radiographic disease progression or death with NIRA+AAP vs PBO+AAP was observed in all *HRR+* subgroups identified by F1CDx® (all *HRR+*, *HRR* effector+, *BRCA+*)

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Disclosures

US, VZ, KB, LF, FS, SM, CV, DS, SMc, and SW: are employees of Johnson & Johnson; employees may own stock/stock options in Johnson & Johnson. YL and T-CN are employees of Foundation Medicine, Inc. and may own stock/stock options of Roche Holding AG. This study was supported by Johnson & Johnson.

Introduction

- Approximately one fourth of patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) carry *HRR* alterations (with *BRCA1/2* being most frequent), leading to poor prognosis[1]
- Poly-adenosine diphosphate-ribose polymerase (PARP) inhibition has demonstrated significant efficacy and clinical benefit in pts with mCRPC and *HRR* alterations, particularly *BRCA1/2*-mutations[2-4]
- Niraparib (NIRA) is a highly selective and potent PARP inhibitor, approved in combination with abiraterone acetate and prednisone (AAP) for pts with *BRCA+* mCRPC, as identified by an approved companion diagnostic tissue test (FoundationOne®CDx [F1CDx®])
- The phase 3 AMPLITUDE study evaluated the safety and efficacy of NIRA+AAP in pts with *HRR+* mCSPC[5]
- NIRA+AAP significantly improved radiographic progression-free survival (rPFS) vs AAP, meeting the primary endpoint[5]

Methods

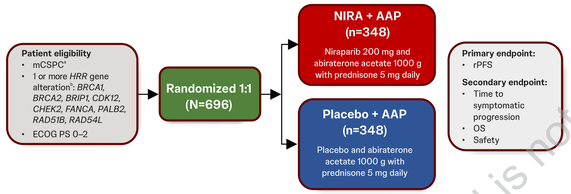
Objectives

- To evaluate the clinical utility of the tissue F1CDx® test to identify *HRR+ or BRCA+* mCSPC pts in the AMPLITUDE study

Study Design

- AMPLITUDE is a phase 3, randomized, double-blind, placebo-controlled study (NCT04497844) evaluating NIRA+AAP vs placebo (PBO)+AAP in pts with *HRR+* mCSPC (**Figure 1**)

Figure 1: AMPLITUDE Study design



*Pts with lymph node only disease are not eligible. †Based on central testing of tumor tissue (FoundationOne CDx), plasma (FoundationOne Liquid CDx) or germline (Invitae Multi-Cancer Panel, Invitae). Positive test results were also permitted from sponsor-approved local tests or from the PREVALENCE study[6] (NCT03784948).
AAP, abiraterone acetate and prednisone; *BRCA1*, breast cancer gene 1; *BRCA2*, breast cancer gene 2; *BRIP1*, BRCA1-interacting protein 1; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *FANCA*, fanconi anemia; *HRR+*, homologous recombination repair positive; mCSPC, metastatic castration-sensitive prostate cancer; NIRA, niraparib; OS, overall survival; *PALB2*, partner and localizer of BRCA2; rPFS, radiographic progression-free survival.

- *HRR* status was prospectively evaluated using central (tissue-F1CDx®) and/or local tests as clinical trial assays (CTAs)
- Clinical utility of F1CDx® was explored by comparing the primary endpoint of rPFS between treatment arms in *HRR+* and *BRCA+* pts identified by F1CDx® and overall enrolled by CTAs
- Analysis was performed in three target *HRR+* patient subgroups defined by the altered *HRR* genes in **Table 1**

Table 1: *HRR*-positive patient subgroups

HRR-positive patient subgroup	Altered *HRR* gene(s)
All *HRR*	*BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, CHEK2, CDK12, FANCA*
HRR effectors	*BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L*
BRCA	*BRCA1, BRCA2*

- Several *HRR* gene alterations defined as *HRR+* by F1CDx® are identified as potentially benign variants of unknown significance, which may not predict clinical response to PARP inhibition and do not meet the criteria for clinical actionability. Supplemental analyses were performed excluding these benign variants: *BRIP1: P47A; CHEK2: I157T, D438Y; PALB2: P8L, R37H*

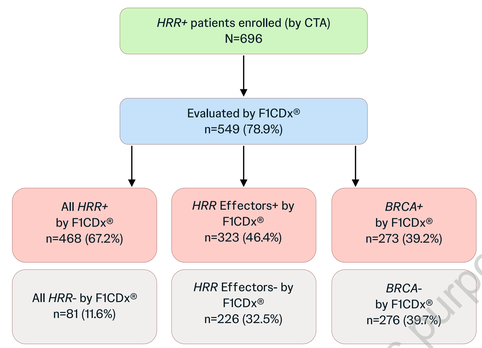
Statistical Analysis

- The Kaplan-Meier product-limit method and a stratified Cox model were used to estimate rPFS and to obtain hazard ratios (HRs) with associated confidence intervals (CIs)

Results

- Of 696 CTA-identified *HRR+* pts enrolled in AMPLITUDE, 549 (78.9%) were evaluated by the F1CDx® assay (**Figure 2**)
- Based on F1CDx®, 468 (67.2%) pts were all *HRR+*, 323 (46.4%) pts were *HRR* effectors+, and 273 (39.2%) pts were *BRCA+*
- In **all *HRR+* pts identified by F1CDx®**, HR for rPFS was 0.56 (95% CI: 0.42–0.76) compared with 0.63 (95% CI: 0.49–0.80) in all *HRR+* pts identified by CTA (**Table 2**)
- Efficacy based on rPFS in the F1CDx®-positive subgroup of pts with NIRA+AAP treatment versus PBO+AAP was comparable to the pts in CTA subgroups (**Figure 3**)

Figure 2: Patient disposition



BRCA, breast cancer gene; *HRR+*, homologous recombination repair-positive; F1CDx®, FoundationOne® CDx assay; n, number of patients; %, percentage.

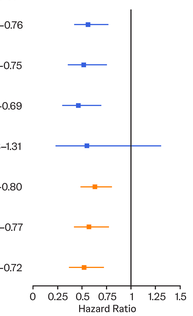
Table 2: rPFS in all *HRR+* patients

	All *HRR+* by F1CDx®		All *HRR+* by CTA	
	NIRA+AAP (n=234)	PBO+AAP (n=234)	NIRA+AAP (n=348)	PBO+AAP (n=348)
Number of events	75	108	113	151
rPFS, median (95% CI), mo	NE (41.2–NE)	29.3 (25.6–NE)	NE (41.2–NE)	29.5 (25.8–NE)
rPFS rate (95% CI), %				
6 mo	94.0 (90.2–96.4)	91.9 (87.7–94.7)	97.3 (94.9–98.6)	93.5 (90.3–95.7)
12 mo	80.8 (75.2–85.3)	70.1 (63.9–75.6)	85.4 (81.1–88.8)	77.0 (72.1–81.2)
24 mo	50.0 (43.7–56.4)	41.0 (34.9–47.4)	70.6 (65.1–75.3)	59.7 (54.0–64.9)
30 mo	29.9 (24.4–36.1)	22.2 (17.4–27.9)	63.0 (56.8–68.6)	49.9 (43.6–55.9)
Hazard ratio (95% CI)	0.56 (0.42–0.76)		0.63 (0.49–0.80)	

For hazard ratio, the stratified Cox proportional-hazard model was used for time-to-event endpoints.
AAP, abiraterone acetate and prednisone; CI, confidence interval; *HRR+*, homologous recombination repair positive; mo, months; NIRA, niraparib; NE, not estimable; PBO, placebo; rPFS, radiographic progression-free survival.

Figure 3: Efficacy by CTA and F1CDx® subgroups (forest plot)

Subgroup	Patients (Events) NIRA+AAP	Patients (Events) PBO+AAP	HR	95% CI
F1CDx All *HRR+*	234 (75)	234 (108)	0.56	0.42–0.76
F1CDx *HRR* Effectors+	164 (47)	159 (71)	0.52	0.36–0.75
F1CDx *BRCA+*	136 (37)	137 (65)	0.46	0.30–0.69
F1CDx *HRR-*	37 (9)	44 (14)	0.55	0.23–1.31
CTA All *HRR+*	348 (113)	348 (151)	0.63	0.49–0.80
CTA *HRR* Effectors+	230 (71)	226 (102)	0.57	0.42–0.77
CTA *BRCA+*	191 (57)	196 (93)	0.52	0.37–0.72



AAP, abiraterone acetate and prednisone; *BRCA*, breast cancer gene; CI, confidence interval; *HRR+*, homologous recombination repair positive; NIRA, niraparib.

- In ***HRR+* effector pts identified by F1CDx®**, HR for rPFS was 0.52 (95% CI: 0.36–0.75) compared with 0.57 (0.42–0.77) in *HRR+* effector pts identified by CTA (**Table 3**)
- In ***BRCA+* pts identified by F1CDx®**, HR for rPFS was 0.46 (95% CI: 0.30–0.69) compared with 0.52 (0.37–0.72) in *BRCA+* pts identified by CTA (**Table 4**)
- Similar results were observed for the F1CDx®-identified all *HRR+* and *HRR* effectors+ subgroups after excluding potentially benign variants

Table 3: rPFS in *HRR* effector+ patients

	HRR effectors+ by F1CDx®		*HRR* effectors+ by CTA	
	NIRA+AAP (n=164)	PBO+AAP (n=159)	NIRA+AAP (n=230)	PBO+AAP (n=226)
Number of events	47	71	71	102
rPFS, median (95% CI), mo	NE (41.2–NE)	28.2 (25.8–NE)	NE (41.2–NE)	27.6 (25.6–NE)
rPFS rate (95% CI), %				
6 mo	94.5 (89.9–97.1)	92.5 (87.3–95.6)	96.9 (93.6–98.5)	93.6 (89.4–96.1)
12 mo	82.3 (75.8–87.4)	72.3 (64.9–78.7)	85.9 (80.6–89.9)	77.0 (70.8–82.1)
24 mo	48.8 (41.3–56.4)	42.8 (35.3–50.5)	71.8 (65.1–77.3)	58.6 (51.5–65.1)
30 mo	29.9 (23.4–37.3)	20.1 (14.6–27.0)	64.5 (56.8–71.1)	46.4 (38.6–53.9)
Hazard ratio (95% CI)	0.52 (0.36–0.75)		0.57 (0.42–0.77)	

For hazard ratio, the stratified Cox proportional-hazard model was used for time-to-event endpoints.
AAP, abiraterone acetate and prednisone; CI, confidence interval; *HRR+*, homologous recombination repair positive; mo, months; NIRA, niraparib; NE, not estimible; PBO, placebo; rPFS, radiographic progression-free survival.

Table 4: rPFS in *BRCA+* patients

	BRCA+ by F1CDx®		*BRCA+* by CTA	
	NIRA+AAP (n=136)	PBO+AAP (n=137)	NIRA+AAP (n=191)	PBO+AAP (n=196)
Number of events	37	65	57	93
rPFS, median (95% CI), mo	NE (41.2–NE)	26.5 (22.1–NE)	NE (41.2–NE)	26.0 (22.1–41.2)
rPFS rate (95% CI), %				
6 mo	94.9 (89.8–97.5)	92.0 (86.2–95.5)	96.8 (93.0–98.5)	92.6 (87.9–95.6)
12 mo	84.6 (77.6–89.7)	70.8 (62.7–77.7)	86.9 (81.1–91.0)	75.9 (69.0–81.4)
24 mo	51.5 (43.2–59.7)	39.4 (31.6–47.8)	73.2 (66.0–79.2)	56.5 (48.8–63.5)
30 mo	31.6 (24.4–39.9)	18.3 (12.7–25.6)	65.8 (57.5–72.9)	44.5 (36.2–52.5)
Hazard ratio (95% CI)	0.46 (0.30–0.69)		0.52 (0.37–0.72)	

For hazard ratio, the stratified Cox proportional-hazard model was used for time-to-event endpoints.
AAP, abiraterone acetate and prednisone; *BRCA*, breast cancer gene; CI, confidence interval; mo, months; NIRA, niraparib; NE, not estimible; PBO, placebo; rPFS, radiographic progression-free survival.

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