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Preliminary safety in the inavolisib + ribociclib or abemaciclib + fulvestrant or letrozole arms of MORPHEUS-pan breast cancer: A Phase 1b/2 study of efficacy and safety of multiple treatment combinations in patients with advanced breast cancer

PD10-08

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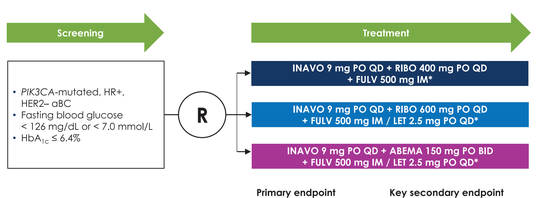
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BACKGROUND

- Endocrine therapy (ET) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) remains the recommended first-line treatment for patients with endocrine-sensitive, hormone receptor-positive, HER2-negative advanced breast cancer (HR+, HER2− aBC) that has no detectable *PIK3CA* mutations.[1,2]
  - However, resistance to ET is common, mediated through altered signaling in the estrogen receptor, CDK4/6, and phosphoinositide 3-kinase (PI3K) pathways.[3]
- *PIK3CA* mutations occur in ~ 40% of HR+ BCs and are associated with poor prognosis and endocrine resistance.[4,5]
  - These mutations predict sensitivity to PI3Kα inhibitors, including inavolisib (INAVO), a potent, oral, selective PI3Kα inhibitor that also promotes degradation of mutant p110α.[6]
- In the INAVO120 trial (NCT04191499), INAVO + fulvestrant (FULV) + palbociclib significantly improved progression-free and overall survival vs placebo + FULV + palbociclib in patients with *PIK3CA*-mutated, endocrine-resistant HR+, HER2− aBC.[7,8] The combination was well tolerated, with low rates of treatment discontinuation due to adverse events (AEs),[7,8] leading to its approval by the United States Food and Drug Administration.[9]
- MORPHEUS-pan BC (NCT03424005) is an ongoing umbrella study. We present data from the INAVO + ribociclib (RIBO) 400 mg + FULV, INAVO + RIBO 600 mg + FULV / letrozole (LET), and INAVO + abemaciclib (ABEMA) + FULV / LET groups.

METHODS

Figure 1: Study design



* INAVO on days 1–28; ABEMA on days 1–28; RIBO on days 1–21; FULV on days 1 and 15 of Cycle 1, then on day 1 of each subsequent cycle; LET on days 1–28. Data from the INAVO + RIBO 600 mg + FULV and INAVO + RIBO 600 mg + LET arms are combined due to later opening, resulting in smaller sample sizes and shorter follow-up, as are data from the INAVO + ABEMA + FULV and INAVO + ABEMA + LET arms.
† Investigator-assessed by Response Evaluation Criteria in Solid Tumours v1.1.
aBC, advanced breast cancer; ABEMA, abemaciclib; BID, twice daily; FULV, fulvestrant; HbA_{1c}, glycated hemoglobin; HER2−, HER2-negative; HR+, hormone receptor-positive; IM, intramuscularly; INAVO, inavolisib; LET, letrozole; PO QD, orally once daily; R, randomization; RIBO, ribociclib.

RESULTS

Patients

- As of data cut-off (August 11, 2025), 64 patients were enrolled across three treatment groups (patients who had completed at least one treatment cycle were included in the analysis): INAVO + RIBO 400 mg + FULV (n = 21), INAVO + RIBO 600 mg + FULV / LET (n = 19), and INAVO + ABEMA + FULV / LET (n = 24) (Table 1).
- Median duration of safety follow-up was:
  - 7.13 months (min–max: 2.6–16.3) in the INAVO + RIBO 400 mg + FULV arm.
  - 5.06 months (min–max: 1.4–6.9) in the INAVO + RIBO 600 mg + FULV / LET group.
  - 6.11 months (min–max: 0.2–19.4) in the INAVO + ABEMA + FULV / LET group.

Safety

- The median number of cycles of INAVO was 7 in the INAVO + RIBO 400 mg + FULV arm (min–max: 2–18), 6 (min–max: 2–8) in the INAVO + RIBO 600 mg + FULV / LET group, and 6 (min–max: 1–20) in the INAVO + ABEMA + FULV / LET group.
- A safety summary is provided in Table 2. There were no grade 5 AEs observed. One patient in the INAVO + RIBO 600 mg + FULV / LET group discontinued treatment due to an AE (peripheral edema).
- Figure 2 summarizes the most frequently reported AEs across treatment groups; hyperglycemia and diarrhea were the most common. It should be noted that unlike the INAVO120 trial, this study protocol used the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0, which defines grade 3 hyperglycemia as fasting blood glucose > 250–500 mg/dL or > 13.9–27.8 mmol/L, or hospitalization indicated.
- Key INAVO-specific selected grade 3–4 AEs are shown in Table 2; hyperglycemia was the most frequently reported.
- The most common AEs leading to interruption / reduction of INAVO only are presented in Table 2; hyperglycemia and diarrhea were the leading causes across any group.

Efficacy

- Confirmed best overall response rates ranged between 21–33% across treatment groups. Patient-level data in each treatment group is shown in Figure 3.

Table 1: Baseline patient demographics and clinical characteristics (safety population)

		INAVO + RIBO (400 mg) + FULV (n = 21)	INAVO + RIBO (600 mg) + FULV / LET pooled (n = 19)	INAVO + ABEMA + FULV / LET pooled (n = 24)
Sex, n (%)	Female	21 (100)	19 (100)	24 (100)
Race, n (%)	Asian	12 (57.1)	0	10 (41.7)
	White	9 (42.9)	19 (100)	14 (58.3)
Ethnicity, n (%)	Not Hispanic or Latino	21 (100)	19 (100)	23 (95.8)
	Not stated	0	0	1 (4.2)
BMI, n (%)	< 30 kg/m^2	18 (85.7)	14 (73.7)	23 (95.8)
	≥ 30 kg/m^2	3 (14.3)	5 (26.3)	1 (4.2)
HbA_{1c}, n (%)	< 5.7%	13 (61.9)	16 (84.2)	20 (83.3)
	5.7–6.4%	8 (38.1)	3 (15.8)	4 (16.7)
Prior chemotherapy in the metastatic/LA setting, n (%)	Yes	12 (57.1)	5 (26.3)	13 (54.2)
Prior lines of therapy for metastatic disease*, n (%)	0	0	5 (26.3)	1 (4.2)
	1	7 (33.3)	6 (31.6)	7 (29.2)
	2	4 (19.0)	4 (21.1)	0
	3	1 (4.8)	1 (5.3)	7 (29.2)
	4	2 (9.5)	2 (10.5)	0
	> 4	7 (33.3)	1 (5.3)	9 (37.5)
Median prior lines of therapy for metastatic disease (min–max)		2.0 (1.0–5.0)	1.0 (0–5.0)	3.0 (0–5.0)
Number of metastatic sites, n (%)	0	0	0	1 (4.2)
	1	1 (4.8)	2 (10.5)	5 (20.8)
	2	6 (28.6)	6 (31.6)	9 (37.5)
	3	10 (47.6)	6 (31.6)	5 (20.8)
	≥ 4	4 (19.0)	5 (26.3)	4 (16.7)
Metastatic sites at enrollment, n (%)	Non-visceral	4 (19.0)	2 (10.5)	4 (16.7)
	Visceral†	17 (81.0)	17 (89.5)	20 (83.3)
	Liver involvement	13 (61.9)	15 (78.9)	14 (58.3)

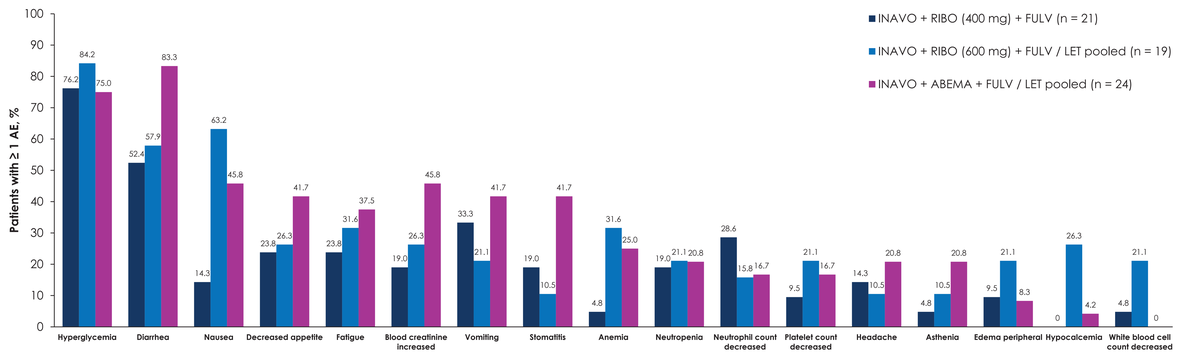
* Including endocrine therapy.
† Defined as any disease site beyond the bone, breast, lymph nodes, skin, muscle, and connective tissue.
ABEMA, abemaciclib; BMI, body mass index; FULV, fulvestrant; HbA_{1c}, glycated hemoglobin; INAVO, inavolisib; LA, locally advanced; LET, letrozole; RIBO, ribociclib.

Table 2: Safety summary (safety population)*,†

Patients with ≥ 1 AE, n (%)	INAVO + RIBO (400 mg) + FULV (n = 21)	INAVO + RIBO (600 mg) + FULV / LET pooled (n = 19)	INAVO + ABEMA + FULV / LET pooled (n = 24)
Any-grade AE	21 (100)	19 (100)	24 (100)
Related any-grade AE‡	21 (100)	19 (100)	24 (100)
Grade 3–4 AE	12 (57.1)	13 (68.4)	22 (91.7)
Grade 3 AE	11 (52.4)	13 (68.4)	21 (87.5)
Grade 4 AE	1 (4.8)§	0	1 (4.2)¶
INAVO-specific key selected grade 3–4 AEs	5 (23.8)	6 (31.6)	12 (50.0)
Hyperglycemia	5 (23.8)	5 (26.3)	10 (41.7)
Diarrhea	0	1 (5.3)	3 (12.5)
Stomatitis	0	0	2 (8.3)
Rash	0	0	0
Serious AE	5 (23.8)	1 (5.3)	6 (25.0)
Related serious AE‡	1 (4.8)	0	4 (16.7)
AE leading to withdrawal from any study drug	0	1 (5.3)¶	0
AE leading to dose interruption of any study drug	12 (57.1)	11 (57.9)	20 (83.3)
Related AE leading to dose interruption of any study drug‡	10 (47.6)	11 (57.9)	20 (83.3)
AE leading to interruption of INAVO	10 (47.6)	11 (57.9)	16 (66.7)
Most common AEs leading to interruption of INAVO			
Hyperglycemia	4 (19.0)	5 (26.3)	5 (20.8)
Diarrhea	1 (4.8)	0	7 (29.2)
AE leading to dose modification of any study drug**	8 (38.1)	12 (63.2)	22 (91.7)
Related AE leading to dose modification of any study drug‡,**	8 (38.1)	12 (63.2)	21 (87.5)
AE leading to modification of INAVO**	7 (33.3)	9 (47.4)	17 (70.8)
Most common AE leading to modification of INAVO**			
Hyperglycemia	6 (28.6)	9 (47.4)	8 (33.3)

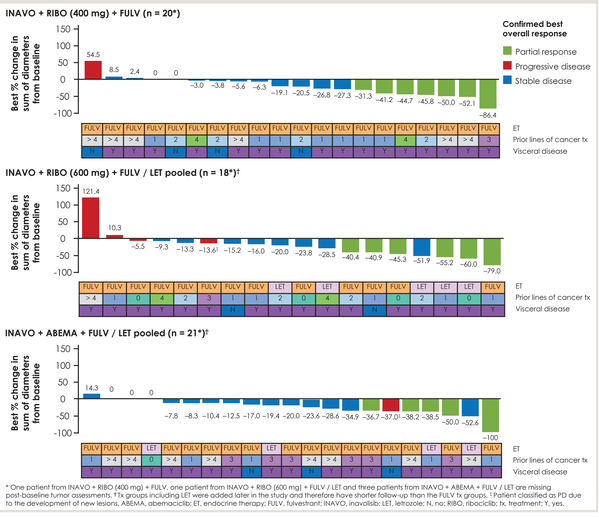
* No grade 5 AEs reported. † Per National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0. ‡ Investigator-determined study therapy attribution. § Hyperglycemia (serious, grade 4, resolved). ¶ Aspartate aminotransferase increased (non-serious, grade 4, resolved). ** Peripheral edema (non-serious, grade 2). ** Dose modifications were defined as dose reductions.
ABEMA, abemaciclib; AE, adverse event; FULV, fulvestrant; INAVO, inavolisib; LET, letrozole; RIBO, ribociclib.

Figure 2: Most common any-grade AEs (occurring in ≥ 20% of patients in any group; safety population)*



* Per National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0.
ABEMA, abemaciclib; AE, adverse event; FULV, fulvestrant; INAVO, inavolisib; LET, letrozole; RIBO, ribociclib.

Figure 3: Confirmed best overall response



* One patient from INAVO + RIBO (400 mg) + FULV, one patient from INAVO + RIBO (600 mg) + FULV / LET and three patients from INAVO + ABEMA + FULV / LET are missing post-baseline tumor assessments. † Tx groups including LET were added later in the study and therefore have shorter follow-up than the FULV tx groups. ‡ Patient classified as PD due to the development of new lesions. ABEMA, abemaciclib; ET, endocrine therapy; FULV, fulvestrant; INAVO, inavolisib; LET, letrozole; N, no; RIBO, ribociclib; tx, treatment; Y, yes.

CONCLUSIONS

- **Safety data observed with INAVO-containing triplet regimens in *PIK3CA*-mutated, HR+, HER2− aBC were consistent with the known safety profiles of the individual agents.**
- **No new safety findings were observed.**
- **Hyperglycemia and diarrhea were the most frequent AEs across all groups and were the leading causes of INAVO dose interruptions / reductions. Enhanced AE management to minimize dose reduction is important.**
- **Grade 4 AEs were infrequent, no grade 5 AEs were reported, and the incidence of AEs leading to study treatment discontinuation was low.**
- **Comparison of these triplet regimens with prior studies[7] is limited by the inclusion of late-line patients and those with prediabetes, as well as the use of NCI CTCAE v4.0 for AE grading.**
- **These data support continued evaluation of INAVO-based triplets in *PIK3CA*-mutated HR+, HER2− aBC.**

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CONFLICT OF INTEREST

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