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

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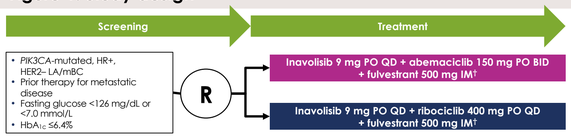
BACKGROUND

- Endocrine therapy combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor is a first-line standard of care for patients with hormone receptor-positive, HER2-negative metastatic breast cancer (HR+, HER2– mBC).[1]
- Treatment resistance may occur due to the crosstalk between the estrogen receptor, CDK4/6, and PI3K oncogenic pathways.[2–4]
- *PIK3CA* mutational status is associated with poor prognosis in HR+, HER2 – mBC[5] but is also predictive of response to PI3K inhibitor treatment.[6,7]
- Inavolisib is a potent, selective inhibitor of PI3Kα that also promotes the degradation of mutated p110α.[8,9]
- The INAVO120 study (NCT04191499) showed that the combination of inavolisib plus the CDK4/6 inhibitor palbociclib, and fulvestrant, resulted in significantly longer progression-free survival compared with placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2– locally advanced (LA)/mBC.[10] These data coupled with a low frequency of study treatment discontinuations due to adverse events (AEs)[10] led to approval of the combination by the United States Food and Drug Administration.[11]
- Here, we report preliminary safety and pharmacokinetic data from the inavolisib + abemaciclib/ribociclib + fulvestrant arms of the MORPHEUS-pan BC umbrella study (NCT03424005).

METHODS

- The study design is shown in Figure 1.

Figure 1: Study design



Primary endpoint
- ORR*

Key secondary endpoints
- PFS*, safety

Key exploratory endpoints
- To compare the PK of inavolisib, abemaciclib, and ribociclib with those of historic data

* Investigator-assessed by RECIST 1.1. † Inavolisib on Days 1–28 of 28-day cycles; abemaciclib on Days 1–28 of 28-day cycles; ribociclib on Days 1–21 of 28-day cycles; fulvestrant on Days 1 and 15 of Cycle 1, then on Day 1 of each 28-day cycle thereafter. BID, twice daily; HbA_{1c}, hemoglobin A_{1c}; HER2–, HER2-negative; HR+, hormone receptor-positive; IM, intramuscularly; LA, locally advanced; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patients
- As of data cut-off (September 9, 2024), six patients had been enrolled in the inavolisib + abemaciclib + fulvestrant arm and six in the inavolisib + ribociclib + fulvestrant arm (Table 1).
- Two of six patients in the inavolisib + abemaciclib + fulvestrant arm and three of six in the inavolisib + ribociclib + fulvestrant arm had discontinued all study drugs. All treatment discontinuations were due to progressive disease (none were due to AEs).
- Median duration of safety follow-up was 6.0 months (range: 2.3–10.1) in the inavolisib + abemaciclib + fulvestrant arm and 6.2 months (4.7–7.4) in the inavolisib + ribociclib + fulvestrant arm.

Safety
- The duration of the study drug treatment was generally similar between arms (Table 2).
- A safety summary is shown in Table 3. No grade 4 or 5 AEs or AEs leading to treatment withdrawal were seen. In the inavolisib + ribociclib + fulvestrant arm, one serious AE (upper respiratory tract infection) was seen within 30 days after last dose of study treatment, but it was not considered related to treatment.
- The most common AEs of any cause are shown in Figure 2. AEs occurring in four or more patients in either arm were hyperglycemia, diarrhea, nausea, and vomiting. It should be noted that the study protocol used the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, which defines grade 3 hyperglycemia as ">250–500 mg/dL; >13.9–27.8 mmol/L; hospitalization indicated." In contrast, NCI CTCAE version 5.0 uses "Insulin therapy initiated; hospitalization indicated."
- Key selected grade ≥3 AEs are shown in Table 4.
- All six patients in the inavolisib + abemaciclib + fulvestrant arm, and two of six in the inavolisib + ribociclib + fulvestrant arm had an AE leading to treatment modification/interruption (Table 5).

Pharmacokinetics
- The concentrations of inavolisib, abemaciclib, and ribociclib in this study were generally aligned with historic/literature data for inavolisib (Figure 3 and Table 6), abemaciclib (Table 6), and ribociclib (Table 6).
- Although mean inavolisib concentrations in the inavolisib + abemaciclib + fulvestrant arm appeared slightly higher than historic inavolisib data, individual inavolisib concentrations in this arm were within the observed range in the Phase 3 study as well as the population pharmacokinetics predicted exposure range (Figure 3). Given the small sample size in this arm, conclusions about drug–drug interactions cannot be made at this point.

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

		Inavolisib + abemaciclib + fulvestrant (n=6)	Inavolisib + ribociclib + fulvestrant (n=6)
Age, years	Median (range)	59.5 (33–67)	39.5 (33–75)
Age group, years, patients, n (%)	<65	4 (66.7)	5 (83.3)
	≥65	2 (33.3)	1 (16.7)
Sex, patients, n (%)	Female	6 (100)	6 (100)
Race, patients, n (%)	White	6 (100)	6 (100)
Ethnicity, patients, n (%)	Not Hispanic or Latino	5 (83.3)	6 (100)
	Not stated	1 (16.7)	0
Prior cancer surgery, patients, n (%)	Yes	4 (66.7)	3 (50.0)
Prior cancer radiotherapy, patients, n (%)	Yes	6 (100)	6 (100)
Prior lines of therapy for metastatic disease, patients, n (%)	1	1 (16.7)	3 (50.0)
	2	0	1 (16.7)
	3	1 (16.7)	0
	4	0	1 (16.7)
	>4	4 (66.7)	1 (16.7)
Number of metastatic sites*, patients, n (%)	0	1 (16.7)	0
	1	1 (16.7)	0
	2	2 (33.3)	2 (33.3)
	3	1 (16.7)	2 (33.3)
	≥4	1 (16.7)	2 (33.3)
Metastatic sites*, patients, n (%)	Bone	4 (66.7)	6 (100)
	Liver	4 (66.7)	3 (50.0)
	Breast	1 (16.7)	2 (33.3)
	Lung	1 (16.7)	2 (33.3)
	Lymph node	0	3 (50.0)
	Peritoneum	0	1 (16.7)
	Pleural effusion	0	1 (16.7)
	Adrenal gland	1 (16.7)	0
	Cervix	1 (16.7)	0
	Skin	1 (16.7)	0

* Refers to metastatic sites at enrollment.

Table 2: Exposure (safety population)

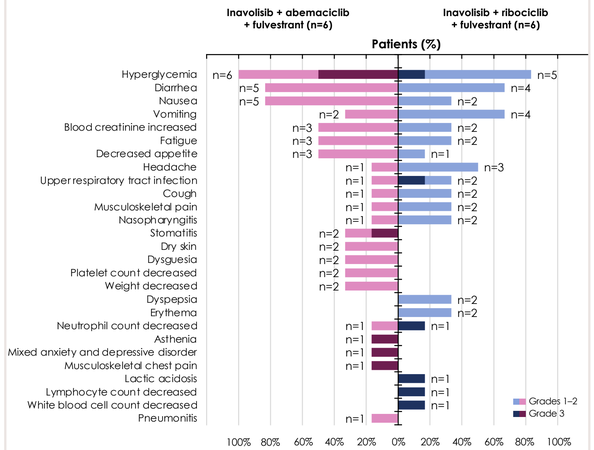
	Inavolisib + abemaciclib + fulvestrant (n=6)			Inavolisib + ribociclib + fulvestrant (n=6)		
	Inavolisib	Abemaciclib	Fulvestrant	Inavolisib	Ribociclib	Fulvestrant
Median number of cycles (range)	5.0 (2–10)	5.5 (2–10)	5.5 (2–10)	6.0 (4–7)	6.0 (4–7)	6.0 (4–7)

Table 3: Safety summary (safety population)

Patients, n (%)	Inavolisib + abemaciclib + fulvestrant (n=6)	Inavolisib + ribociclib + fulvestrant (n=6)
Any-grade AE	6 (100)	6 (100)
Related any-grade AE	6 (100)	5 (83.3)
Grade 3 AE	5 (83.3)	1 (16.7)
Related grade 3 AE	5 (83.3)	1 (16.7)
Grade 4 AE	0	0
Grade 5 AE	0	0
Serious AE	0	1 (16.7)*
Related serious AE	0	0
AE leading to withdrawal from any treatment or stage	0	0
AE leading to dose modification/interruption	6 (100)	2 (33.3)
Related AE leading to dose modification/interruption	6 (100)	2 (33.3)

Related AEs refer to AEs related to any study drug. * Upper respiratory tract infection (not deemed treatment-related) in a patient following treatment discontinuation during safety follow-up. AE, adverse event.

Figure 2: Most common AEs (safety population)*



* Includes all AEs occurring in ≥2 patients in either arm (all-grade AEs), all grade 3–4 AEs, and an additional AE of interest (pneumonitis). Patient n values outside of bars refer to AEs of all grades. AE, adverse event.

Table 4: Key selected grade ≥3 AEs (safety population)

Patients with ≥1 AE, n (%)	Inavolisib + abemaciclib + fulvestrant (n=6)	Inavolisib + ribociclib + fulvestrant (n=6)
All key selected grade ≥3 AEs	5 (83.3)	1 (16.7)
Hyperglycemia	3 (50.0)	1 (16.7)
Hyperglycemia (insulin-treated)	1 (16.7)	1 (16.7)
Stomatitis/mucosal inflammation	1 (16.7)	0
Diarrhea	0	0
Rash	0	0

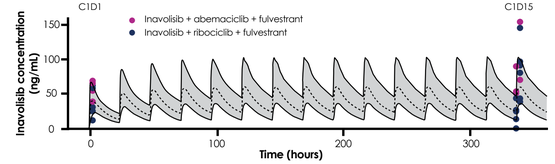
AE, adverse event.

Table 5: Most common AEs leading to treatment modification/interruption of any study drug (safety population)*

Patients with ≥1 AE, n (%)	Inavolisib + abemaciclib + fulvestrant (n=6)	Inavolisib + ribociclib + fulvestrant (n=6)
All	6 (100)	2 (33.3)
Hyperglycemia	4 (66.7)	2 (33.3)
Diarrhea	2 (33.3)	1 (16.7)

* Occurring in >1 patient in either arm. AE, adverse event.

Figure 3: Inavolisib population PK modeling



Observed vs. population PK predicted concentration–time profiles of inavolisib at C1D1 single dose and C1D15 dose at steady state. Dashed line represents population PK-predicted median, shaded area represents population PK-predicted 90% confidence intervals, and dots display observed plasma concentrations of inavolisib. C, cycle; D, day; PK, pharmacokinetics.

Table 6: Observed vs. historic PK concentrations

	Observed geometric mean (% geometric CV), ng/mL				Historic geometric mean (range or % geometric CV), ng/mL		
	Inavolisib + abemaciclib + fulvestrant arm (n=4)		Inavolisib + ribociclib + fulvestrant arm (n=6)				
Visit	Inavolisib	Abemaciclib	Inavolisib	Ribociclib	Inavolisib	Abemaciclib*,[12]	Ribociclib[13]
C1D1, 3 hr post-dose	55.5 (26.1)	110.0 (60.8)	35.2 (72.1)	537.0 (77.2)	36.0 (0.05–150.0)	N/A	559 (58.6)†
C1D15 pre-dose	50.2 (56.7)	293.0 (44.8)	10.3 (671.4)	543.0 (50.7)	13.6 (0.05–80.4)	N/A	N/A
C1D15, 3 hr post-dose	102.0 (41.2)	275.0 (56.0)	75.5 (54.5)	1,130.0 (65.1)	59.2 (0.05–173.0)	249.0 (N/A)†	1,040 (49.3; n=10)†

* Arithmetic mean. † C_{max} was reported. C, cycle; C_{max}, maximum serum concentration; CV, coefficient of variation; D, day; hr, hour; N/A, not available; PK, pharmacokinetics.

CONCLUSIONS

- **This analysis reporting data from the first six patients per arm showed that the safety profile of inavolisib + abemaciclib/ribociclib + fulvestrant for *PIK3CA*-mutated, HR+, HER2– LA/mBC was manageable and consistent with that of inavolisib and each individual CDK4/6 inhibitor. All treatment discontinuations were due to progressive disease, rather than AEs.**
- **Comparison of pharmacokinetics data from this study with historic/literature data suggested that clinically relevant drug–drug interactions between inavolisib and ribociclib are unlikely.**
- **In this analysis of inavolisib + abemaciclib/ribociclib + fulvestrant for *PIK3CA*-mutated, HR+, HER2– LA/mBC, no unexpected safety findings were observed in either arm. The study is ongoing and enrolling patients.**

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CONFLICT OF INTEREST

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