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508P

Interim analysis of giredestrant (GIRE) + inavolisib (INAVO) in MORPHEUS breast cancer (BC): A phase Ib/II study of GIRE treatment (rx) combinations in patients (pts) with estrogen receptor-positive (ER+), HER2-negative, locally advanced/metastatic BC (LA/mBC)

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Background

Effective endocrine-based rx options post—cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) are limited. GIRE is a potent, oral, selective ER antagonist and degrader; INAVO is a potent and selective PI3Kα inhibitor that promotes mutant p110α degradation. *PIK3CA* mutations are truncal and persist after CDK4/6i rx. Based on encouraging preliminary results in this study (MORPHEUS BC; NCT04802759), GIRE + INAVO was expanded to enrol 40 pts; updated results are presented here.

Methods

Pts with *PIK3CA*-mutated (m) LA/mBC (determined by tissue-/blood-based assay) and progression on 1—2 lines of endocrine-based rx (including CDK4/6i) were randomised to GIRE (30 mg orally daily [PO QD]) or GIRE + INAVO (9 mg PO QD). After preliminary combination results, enrolment was prioritised to GIRE + INAVO; updated results for GIRE will not be presented. Primary endpoints were safety and objective response rate (ORR); progression-free survival (PFS) was also assessed.

Results

As of 9 January 2025, 40 pts with *PIK3CA*m tumours were enrolled in the GIRE + INAVO arm; 65% (26/40) had one prior line of therapy for LA/mBC; 35% (14/40) had two; 45% (18/40) had prior fulvestrant. Efficacy and safety are in the table. No clinically relevant drug–drug interactions were seen.

Conclusions

GIRE + INAVO showed impressive efficacy, particularly in pts whose tumours had *ESR1* co-mutation. With this expanded cohort (n = 40), we have confirmed preliminary results from SABCS 2023 (n = 15), comparing favourably with historical data including alpelisib, capivasertib, elacestrant, and imlunestrant in this post—CDK4/6i-treated population. Safety of GIRE + INAVO was consistent with known profiles, with good tolerability.Table: 508P

	GIRE + INAVO (N = 40)
Confirmed ORR, n (%)Complete responsePartial response	16 (40) 3 (8) 13 (33)
ORR (*ESR1* mutation), n/n (%)ORR (*ESR1* no mutation detected), n/n (%)	10/13 (77) 6/25 (24)
Clinical benefit rate, n (%)	28 (70)
Median PFS, mo (95% confidence interval)	9.5 (7.3, 14.0)
All-grade TRAEs, n (%)	39 (98)
Grade 3 AEs, n (%)*	15 (38)

	GIRE + INAVO (N = 40)
AE leading to any rx discontinuation, n (%)	4 (10)
Most common all-grade TRAEs with ≥20% incidence rate, n (%)	Hyperglycaemia 24 (60); Diarrhoea 22 (55); Nausea 18 (45); Fatigue 17 (43); Decreased appetite 11 (28); Alopecia 8 (20); Vomiting 8 (20)

* No grade 4/5.AE, adverse event; mo, months; TRAE, treatment-related adverse event.

Clinical trial identification

NCT04802759.

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