Safety and Tolerability of Neoadjuvant Inavolisib Combined with Endocrine Therapy and Dual HER2 Blockade in Early HR+/HER2+/PIK3CA-Mutant Breast Cancer: 2nd preplanned Safety Interim Analysis of the Chemotherapy-free GeparPiPPa Study

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Background

The modern management of early breast cancer (BC) increasingly aims at therapeutic de-escalation without compromising efficacy. In HER2-positive, hormone receptor (HR)-positive BC, the presence of *PIK3CA* mutations, observed in approximately 25–30% of cases, has been associated with reduced sensitivity to standard anti-HER2 therapy and chemotherapy. Targeting the PI3K pathway therefore represents a promising strategy to overcome resistance.

The GeparPiPPa study evaluates the addition of the PI3K-inhibitor Inavolisib to neoadjuvant endocrine therapy combined with dual HER2 blockade (trastuzumab and pertuzumab as PH-FDC SC), and therefore if a biomarker-driven approach can enhance efficacy while enabling a promising chemotherapy-free treatment option.

Patients and Methods

GeparPiPPa (NCT05306041) is an international, randomized, multicenter phase II trial recruiting in Germany, Italy, Spain, and Romania. Patients with early HR+/HER2+ BC and centrally confirmed *PIK3CA* mutation are randomized to neoadjuvant endocrine therapy (ET) + PH-FDC SC with vs. without inavolisib for 6 cycles. The present safety set includes 48 treated patients (inavolisib n=23; control n=25). **The trial design is depicted on Figure 1.** Patients with no evidence of a *PIK3CA* mutation were asked to participate in the observational cohort study to collect data on real world treatment approaches.

The primary objective of the GeparPiPPa study is to compare the pathological complete response (pCR) rates between HR+/HER2+ *PIK3CA* mutant early BC treated with inavolisib concurrently to ET + PH-FDC SC vs. ET + PH-FDC SC alone. Further objectives include the assessment of safety, tolerability, overall treatment adherence, as well as the rate of breast-conserving surgery and the proportion of patients requiring additional chemotherapy.

Key inclusion criteria were early, non-metastatic HR+/HER2+ BC with central confirmation of receptor status and *PIK3CA* mutation, clinical stage cT1b–cT3 irrespective of nodal status, and adequate glycemic control defined as HbA1c ≤6.5%.

Adverse events (AE) were assessed per patient (NCI-CTCAE v5.0). **Key AEs of special interest (AESIs)** included diarrhea, hyperglycemia, stomatitis, and rash. The **2nd pre-planned Safety Interim Analysis (SIA)** after the first 40 patients completed ≥2 cycles is presented. All statistical tests were two-sided, with α=0.05. All p-values were considered exploratory and reported without adjustment for multiple comparisons.

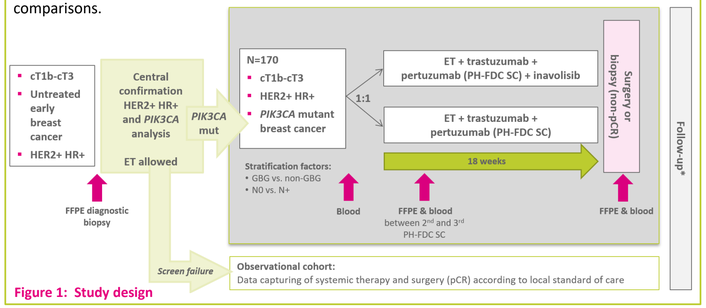

Figure 1: Study design

Results

Median age was 53 years (yrs) (37-71) in the inavolisib and 51 yrs (23-79) in the control arm. Baseline characteristics are summarized in **Table 1**. AEs occurred in 100% of patients in the inavolisib vs. 95.8% in the control arm; grade ≥3 events appeared in 17.4% vs. 8.3% (p=0.416), respectively, serious AE (SAE) in 13.0% vs. 4.2% (p=0.348), respectively. The key adverse events are presented in **Figure 2**. Dose reductions and interruptions >3 days were required in nine (39.1%) of inavolisib-treated patients, mainly due to non-hematologic toxicity. Two patients (4.2%) discontinued treatment because of investigators' decision (one in each arm), and one patient (2.1%) due to cardiac toxicity (in control arm). Recommended premedication according to the protocol were loperamide in patients with diarrhea ≥ grade 1 and metformin in patients with a fasting glucose levels ≥ grade 2 and antihistamine in patients with rush ≥ grade 1. 18 patients receiving inavolisib developed diarrhea ≥ grade 1; four required no treatment, while 14 received loperamide; five of these continued prophylactic loperamide until cycle 6. One patient received prophylactic loperamide, developed diarrhea ≥grade 1, and continued loperamide thereafter. **Figure 3** shows individual patient trajectories of fasting glucose levels over time, demonstrating a greater variability and occasional higher peaks in the inavolisib group. **Figure 4** provides an overview of treatment compliance in patients treated with inavolisib, demonstrating an increasing frequency of dose reductions over time; however, 6 (42.9%) of 14 patients completed therapy without dose modification.

Table 1. Baseline characteristics

Parameter	Category	With Inavolisib N (%) = 23	Without Inavolisib N (%) = 25
Age, years	<40	5 (21.7)	2 (8.0)
	40-<50	4 (17.4)	10 (40.0)
	50-<65	11 (47.8)	9 (36.0)
	≥ 65	3 (13.0)	4 (16.0)
Menopausal Status	Pre/perimenopausal	14 (60.9)	15 (60.0)
	Postmenopausal	8 (34.8)	10 (40.0)
cT (sono)	cT1	14 (60.9)	17 (70.8)
	cT2	9 (39.1)	7 (29.2)
	cT3	0 (0.0)	0 (0.0)
	Missing	0	1
BMI, kg/m²	<18.5	0 (0.0)	0 (0.0)
	18.5- <25	14 (60.9)	17 (68.0)
	25- ≥ 30	7 (30.4)	7 (28.0)
	>30	2 (8.7)	1 (4.0)
Tumor grading	G1	0 (0.0)	2 (8.0)
	G2	13 (56.5)	13 (52.0)
	G3	10 (43.5)	10 (40.0)
Nodal Status (sono)	Negative	20 (87.0)	21 (84.0)
Histological tumor type	Invasive carcinoma of no special type (NST)	22 (95.7)	20 (80.0)
TILs	low (0-<10%)	16 (69.6)	17 (68.0)
	intermediate (10-60%)	7 (30.4)	8 (32.0)
	high (>60-100%)	0 (0.0)	0 (0.0)
Ki67 (central)	≤20%	8 (34.8)	10 (40.0)
	>20%	15 (65.2)	15 (60.0)

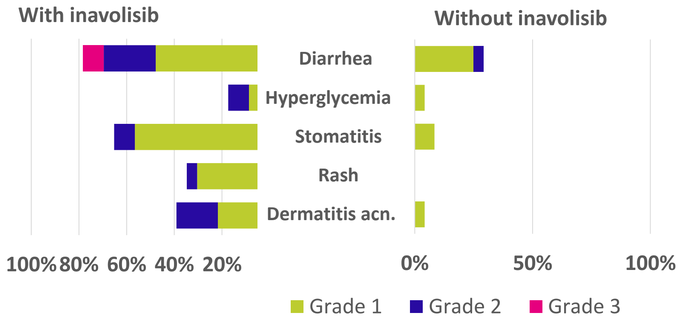

Figure 2: Key Adverse Events, max. grade per patient (inavolisib vs. control arm, respectively).

All grades p-values were descriptive in nature and no adjustment for alpha inflation was performed:
- Diarrhea: 78.3% vs. 29.2% (p=0.001)
- Hyperglycemia: 17.4% vs. 4.2% (p=0.188)
- Stomatitis: 65.2% vs. 8.3% (p<0.001)
- Rash: 34.8% vs. 4.2% (p=0.010)
- Acneiform dermatitis: 39.1% vs. 4.2% (p=0.004)

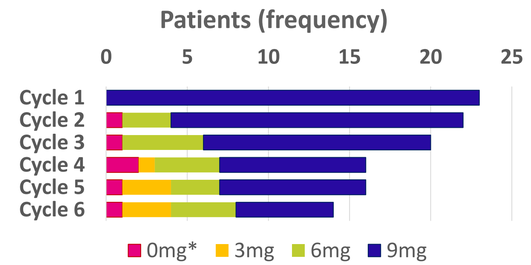

Figure 4: Changes of inavolisib dosing per patients over the study duration.

The length of the bars corresponds to the sum of patients who reached the cycle and those who discontinued study treatment. *treatment discontinuation or no intake in this cycle

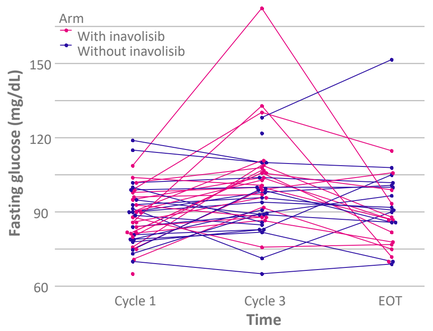

Figure 3: Levels of fasting glucose over the study duration

Conclusions

The observed safety profile is consistent with the known toxicity spectrum of inavolisib as reported in the INAVO120 study[1,2]. Gastrointestinal and mucocutaneous AEs, including diarrhea, stomatitis, rash, and acneiform dermatitis, appear more frequent compared to INAVO120, although they are predominantly low-grade and clinically manageable. In contrast, the incidence of hyperglycemia is comparable or even less pronounced, with no grade ≥3 events observed. This differences might be due to the differences of the allowed HbA1c level at study entry (Inavo120 HbA1c ≤ 6% versus GeparPiPPa ≤ 6.5%). 6.3% patients (n=1 in the inavolisib vs. n=2 in the control arm) discontinued study treatment and none of the discontinuations were related to the key AEs.

Overall, the safety findings support a manageable tolerability profile of inavolisib, with no unexpected toxicities identified. The study continues as planned.

References

1. Turner NC et al., Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer. N Engl J Med. 2024
2. Jhaveri KL et al., Overall Survival with Inavolisib in *PIK3CA*-Mutated Advanced Breast Cancer. N Engl J Med. 2025.

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