First disclosure of frontline treatment (1L tx) with the selective CDK4 inhibitor BGB-43395 in combination with letrozole for metastatic HR+/HER2− breast cancer (BC): a phase 1 safety expansion

Background:

BGB-43395, a highly selective CDK4i, showed preclinical antitumor activity characterized by improved CDK4 target coverage and selectivity over CDK6. This enhanced selectivity may reduce off-target toxicity and the need for tx modifications. BGB-43395 is being evaluated as monotherapy or with endocrine therapy in patients (pts) with HR+/HER2− BC and other advanced solid tumors in an ongoing phase 1a/1b open-label, international study (NCT06120283). We report on the safety, preliminary anti-tumor activity, and pharmacodynamics (PD) of BGB-43395 + letrozole as 1L tx for BC.

Methods:

In safety expansion cohort 2, CDK4/6i-naive pts with advanced/metastatic HR+/HER2− BC were randomized to receive BGB-43395 240, 400, or 600 mg PO BID + letrozole to determine the recommended dose for further development. The objectives were to assess safety, preliminary anti-tumor activity, and PD.

Results:

As of Nov 11, 2025, 58 pts received study tx (240 mg n=19; 400 mg n=19; 600 mg n=20).

Treatment emergent adverse events (TEAEs) occurred in 98% of pts; grade (G)≥3 TEAEs in 32%, 37%, and 65% of pts on 240 mg, 400 mg, and 600 mg, respectively. The most common TEAEs (mostly G1/2) were (240 mg / 400 mg / 600 mg): diarrhea (79% / 95% / 90% [G3 5% / 11% / 30%]), nausea (53% / 68% / 85% [G3 0% / 5% / 0%]), and vomiting (26% / 47% / 60% [G3 0% / 0% / 0%]). Rates of TEAE hematologic toxicities (mostly G1/2) were low; neutrophil count decreased/neutropenia (240 mg 26% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 10%]); anemia (240 mg 5% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 5%]); platelet count decreased/thrombocytopenia ([all G1 or 2] 240 mg 5%; 400 mg 0%; 600 mg 5%).

TEAEs led to dose modification in 53% of pts (median relative dose intensity: 240 mg 100%; 400 mg 97%; 600 mg 69%), tx discontinuation in 3% (240 mg, 1 pt; 600 mg, 1 pt), and 0 deaths.

BGB-43395 + letrozole demonstrated early efficacy (Table) and strong PD effects, indicated by TK1 reduction and ctDNA decrease. Median study follow-up was 6.8 (range 3.2-9.7) mo, median time-to-response was 3.6 (range 1.6-8.4) mo, and median PFS was not reached.

Table

BGB-43395 BID dose + letrozole	**240 mg (n=19)**	**400 mg (n=19)**	**600 mg (n=20)**
Median tx follow-up, mo	7.0	7.1	5.2
Best overall response, %			
PR[a]	58	68	40
SD	37	32	55
PD	5	0	0
NE	0	0	5
Objective response rate (CR + PR), % (95% CI)	58 (33-80)	68 (43-87)	40 (19-64)
Disease control rate (CR + PR + SD), % (95% CI)	95 (74-100)	100 (82-100)	95 (75-100)

RECIST v1.1 (investigator). [a]Unconfirmed.

Conclusions:

The CDK4-selective inhibitor BGB-43395, in combination with letrozole, demonstrated a favorable safety profile, with low hematologic and manageable gastrointestinal toxicity. Antitumor activity in 1L tx of pts with advanced HR+/HER2− BC was promising. Doses of 400 mg and 240 mg BID demonstrated efficacy and safety that support further development in combination with letrozole.