Phase 1b study of gedatolisib plus palbociclib and endocrine therapy in women with hormone receptor-positive advanced breast cancer: updated results in treatment-naïve patients

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204P

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BACKGROUND

It is hypothesized that the addition of a pan-PI3K/mTOR inhibitor after progression on a CDK4/6 inhibitor and endocrine therapy (ET) in estrogen receptor-positive (ER+), HER2-negative advanced breast cancer (ABC) can:

- Potentially restore sensitivity to a CDK4/6 inhibitor; and
- Prevent adaptive activation of the PI3K/mTOR pathway.[1-5]

- To evaluate this hypothesis, a Phase Ib study combining gedatolisib, a dual inhibitor of PI3K/mTOR; palbociclib, a CDK4/6 inhibitor; and endocrine therapy (letrozole or fulvestrant) to treat women with ER+/HER2- ABC was conducted.
- Manageable toxicity and preliminary antitumor activity were observed in 35 patients enrolled in the dose escalation portion of the study[6] and 103 patients enrolled in the expansion portion of the study.[7]
- In this subgroup analysis, we report updated efficacy and safety data in treatment-naïve patients from Escalation Arm A and Expansion Arm A with a June 29, 2022, database lock. Median progression-free survival (mPFS) and Duration of Response (DOR) are updated as of March 16, 2023.

B2151009 OVERALL STUDY DESIGN

- Patients with ER+/HER2- ABC were treated in two different Arms as shown. Pre-/peri-menopausal women received ovarian suppression therapy.
- 11 treatment-naïve patients (Escalation Arm A) and 30 treatment-naïve patients (Expansion Arm A) were pooled for the sub-group analysis.
- Treatment regimen: gedatolisib 180 mg IV weekly; palbociclib 125 mg PO daily for 21 days followed by seven days off; letrozole 2.5 mg PO daily.
- Tumor assessment was performed at baseline and every 8 weeks until disease progression or the start of a new anti-cancer therapy. Twelve months after enrollment was completed, the protocol was amended to allow tumor assessments every 12–16 weeks. All patients had tumors assessed every eight weeks for at least the first 18 months from their start of therapy.
- Endpoints: Primary - objective response assessed by the investigator; Secondary - safety, duration of response (DOR), and PFS.

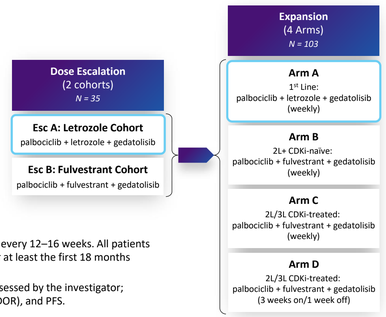


Table 1: Baseline Characteristics (Full Analysis Set)

Parameter	Escalation Arm A (n = 11)	Expansion Arm A (N = 30)	Total Treatment-Naïve (n = 41)
Age			
Median years (range)	50.0 (37.0–74.0)	54.5 (28.0–78.0)	54.0 (28.0–78.0)
Tumor, Node, Metastasis (TNM) Stage, n (%)			
Stage III	1 (9.1)	0 (0.0)	1 (2.4)
Stage IV	10 (90.9)	29 (96.7)	39 (95.1)
Stage unknown	0 (0.0)	1 (3.3)	1 (2.4)
Number of Prior Therapies - Advanced Breast Cancer, n (%)			
0	11 (100.0)	30 (100.0)	41 (100.0)
Measurable Baseline Disease, n (%)			
Yes	8 (72.7)	30 (100)	38 (92.7)
No	3 (27.3)	0	3 (7.3)
Prior Adjuvant Endocrine Therapy, n (%)			
Yes	2 (18.2)	16 (53.3)	18 (43.9)
No	9 (81.8)	14 (46.7)	23 (56.1)

Parameter	Escalation Arm A (n = 11)	Expansion Arm A (N = 30)	Total Treatment-Naïve (n = 41)
Disease Site Involved, n (%)			
Bone	9 (81.8)	17 (56.7)	26 (63.4)
Brain	0	0	0
Liver	1 (9.1)	14 (46.7)	15 (36.6)
Lung	0	7 (23.3)	7 (17.1)
Lymph node	4 (36.4)	8 (26.7)	12 (29.3)
Pleural effusion	1 (9.1)	3 (10.0)	4 (9.8)
Skin	0	1 (3.3)	1 (2.4)
Other	10 (90.9)	25 (83.3)	35 (85.4)
Number of Disease Sites Involved, n (%)			
≤ 3	10 (90.9)	25 (83.3)	35 (85.4)
≥ 4	1 (9.1)	5 (16.7)	6 (14.6)
***PIK3CA*, n (%)[1]**			
Wild type	7 (63.6)	24 (80.0)	31 (75.6)
Mutation	4 (36.4)	5 (16.7)	9 (22.0)
Unknown/missing	0	1 (3.3)	1 (2.4)

[1]*PIK3CA* status confirmed by liquid biopsy using a central lab.

SAFETY

Table 2: Treatment Related and Emergent Adverse Events (≥ 20% of Subjects, by SOC and Preferred Term)

Adverse Event	Treatment-Naïve (N = 41) Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %
Gastrointestinal disorders				
Stomatitis[1]	9 (22.0)	13 (31.7)	12 (29.3)	0
Nausea	15 (36.6)	16 (39.0)	1 (2.4)	0
Diarrhoea	12 (29.3)	5 (12.2)	1 (2.4)	0
Vomiting	13 (31.7)	5 (12.2)	0	0
Constipation	11 (26.8)	2 (4.9)	0	0
Dry mouth	10 (24.4)	0	0	0
Blood and lymphatic system disorders				
Neutropenia/Neutrophil count decreased[2,3]	0	7 (17.1)	21 (51.2)	4 (9.8)
Anaemia	4 (9.8)	9 (22.0)	4 (9.8)	0
Skin and subcutaneous tissue disorders				
Rash[2,4]	11 (26.8)	6 (14.6)	15 (36.6)	0
Pruritus	8 (19.5)	3 (7.3)	4 (9.8)	0
General disorders and administration site conditions				
Fatigue	10 (24.4)	12 (29.3)	4 (9.8)	0
Nervous system disorders				
Dysgeusia	19 (46.3)	2 (4.9)	0	0
Headache	6 (14.6)	5 (12.2)	0	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	11 (26.8)	0	0	0
Investigations				
White blood cell count decreased	1 (2.4)	7 (17.1)	5 (12.2)	0
Alanine aminotransferase increased	6 (14.6)	1 (2.4)	3 (7.3)	0
Aspartate aminotransferase increased	7 (17.1)	2 (4.9)	0	0
Lymphocyte count decreased	1 (2.4)	4 (9.8)	4 (9.8)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	7 (17.1)	2 (4.9)	0	0
Metabolism and nutrition disorders				
Hyperglycaemia	6 (14.6)	4 (9.8)	2 (4.9)	0
Decreased appetite	7 (17.1)	2 (4.9)	0	0
Vascular disorders				
Hot flush	11 (26.8)	0	0	0
Injury, poisoning and procedural complications				
Infusion related reaction	5 (12.2)	6 (14.6)	0	0

There were no Grade 5 treatment related TEAEs.
[1]Majority of the pts in this subgroup did not receive prophylactic treatment for stomatitis; [2]Number of patients with at least one of the terms. If a patient experienced multiple terms, it will be counted once for the highest grade; [3]Neutropenia and neutrophil count decrease were reported interchangeably for many patients. In this table, neutropenia (SOC-blood and lymphatic system disorders) and neutrophil count decreased (SOC-investigations) were combined; [4]Rash, rash macular-papular, rash pruritic, rash pustular, rash papular, rash erythematous, or rash vesicular.

Table 3: Patient Treatment Discontinuation (Full Analysis Set)

	Total Treatment-Naïve Patients (n = 41)
Patients Who Discontinued Treatment, n (%)	
Reasons other than AEs	36 (87.8)
Progression or relapse	15 (36.6)
Study terminated by sponsor[1]	9 (22.0)
Other[2]	12 (29.3)
Adverse events[3]	
Treatment related	4 (9.8)
Unknown	1 (2.4)

[1]After study termination, 9 patients in this subgroup rolled over to an expanded access protocol (EAP) and continued treatment. As of March 16, 2023, 5 of these patients remain enrolled in the EAP; [2]Other includes: withdrawal by subject, lost to follow up, global deterioration, PI decision, new diagnosis-renal cell carcinoma; [3]Treatment related AEs: stomatitis, psoriasis, rash maculo-popular, fatigue (n=1 each).

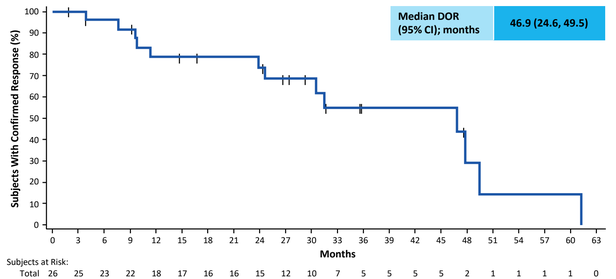
EFFICACY

Table 4: Efficacy Summary – Treatment-Naïve Population (1L)

	Escalation Arm A	Expansion Arm A	Total Treatment-Naïve
Responses (Evaluable and Measurable Disease),[1] n (%)	**n = 7**	**n = 26**	**n = 33**
CR	0	1 (3.8)	1 (3.0)
PR	4 (57.1)	21 (80.8)	25 (75.8)
SD	3 (42.9)	3 (11.5)	6 (18.2)
Unconfirmed PR	0	0	0
Durable SD (≥ 24 weeks)	1 (14.3)	2 (7.7)	3 (9.1)
PD	0	1 (3.8)	1 (3.0)
ORR[1]	4 (57.1)	22 (84.6)	26 (78.8)
Median DOR, mos (95% CI)[2]	39.7 (30.5, NR)	46.9 (11.3, NR)	46.9 (24.6, 49.5)
Progression-Free Survival (Full Analysis Set)	**n = 11**	**n = 30**	**n = 41**
Median PFS, mos (95% CI)	45.8 (32.3, NR)	48.6 (11.6, NR)	48.6 (30.4, NR)
Median follow-up,[3] mos, range	18.2 (1.5, NR)	37.8 (12.9, 51.6)	37.8 (14.9, 51.6)

The 2 arms were not randomized.
[1]Subjects with measurable disease in response evaluable analysis set per RECIST v1.1; [2]Confirmed responders in the full analysis set; [3]Median follow-up for PFS is per reverse Kaplan-Meier method including two censored patients with a short follow up time.
CR, complete response; DOR, duration of response; mos, months; NR, not reached; ORR, objective response rate; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

Figure 1: Duration of Response for Confirmed Responders in Treatment-Naïve Subgroup (Full Analysis Set)

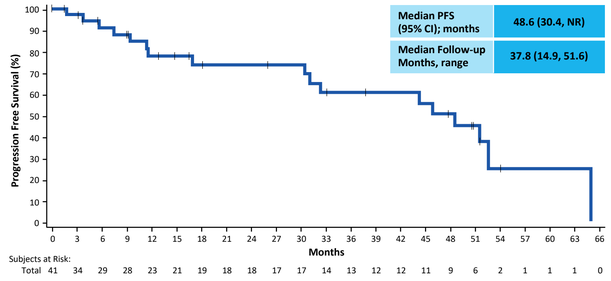


Note: Duration of Response (DOR) was investigator-assessed according to RECIST v1.1.

Figure 2: Treatment-Naïve (1L) Patients' Best Response (Maximum Percent Change in Sum of Target Lesion Diameters from Baseline; n = 33, Measurable Disease Population)

6 patients had 100% reduction in sum of target lesion diameters; 1 patient had CR, 5 patients had PR due to the presence of non-target lesions.
Note: The dose escalation portion of the study allowed patients with bone-only disease, while the dose expansion portion required subjects to have measurable disease. This figure represents maximum changes in sum of target lesions diameters from baseline in patients with measurable disease only: seven from Dose Escalation Arm A and 26 from Dose Expansion Arm A.

Figure 3: Progression-Free Survival for Treatment-Naïve Patients (n = 41, Full Analysis Set)



Note: PFS was investigator-assessed according to RECIST v1.1.

CONCLUSIONS

- Gedatolisib in combination with letrozole and palbociclib demonstrated encouraging efficacy and durable responses in the subgroup of treatment-naïve patients with ER+/HER2- advanced breast cancer.
- Promising efficacy results, with a median PFS of 48.6 months and ORR of 79%, in patients with measurable and evaluable disease, was very encouraging and compares favorably to published data with other therapies in this setting.
- The study regimen was well tolerated, with < 10% (4/41) patients discontinuing due to treatment-related adverse events.
- A Phase 3 study evaluating gedatolisib (3 weeks on/1 week off) with palbociclib and fulvestrant in HR+/HER2- ABC is currently enrolling.
- These preliminary results are very encouraging and warrant further evaluation of gedatolisib in treatment-naïve ER+/HER2- ABC.

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Disclosures

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Poster

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