Updated results of a Phase 1b study of gedatolisib plus palbociclib and endocrine therapy in women with hormone receptor positive advanced breast cancer: Subgroup analysis by *PIK3CA* mutation status

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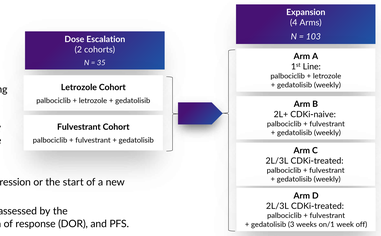
BACKGROUND

- The addition of a PI3K/mTOR inhibitor after progression on CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) in estrogen receptor positive (ER+), HER2-negative advanced breast cancer (ABC) can
  - potentially restore sensitivity to CDK4/6i and
  - prevent adaptive activation of the PI3K/mTOR pathway[1-5].
- To evaluate this hypothesis, a Phase Ib study of gedatolisib (G), a dual inhibitor of PI3K/mTOR, palbociclib (P) a CDK4/6i, and ET (with letrozole [LET] or fulvestrant [FUL]) in women with estrogen receptor positive (ER+)/HER2- ABC was conducted.
- Manageable toxicity and preliminary antitumor activity were observed in 35 patients(pts) enrolled in the dose escalation portion of the study[6], and 103 pts enrolled in the expansion portion of the study[7].
- In this analysis, we report updated efficacy and safety data, and sub-group analysis by *PIK3CA* mutation status in the four expansion study arms with a June 29, 2022, database lock.

STUDY DESIGN

- Patients with ER+/HER2- MBC were treated in four-arms as shown in "Expansion" panel. Pre-/peri-menopausal women received ovarian suppression.
- Dosing information: Palbociclib: 125 mg/day in a 3 week on, 1 week off schedule; Letrozole: 2.5 mg/day; Fulvestrant: 500 mg intramuscular injection on cycle 1 days 1 and 15, and every 28 days ± 3 days thereafter; Gedatolisib: 180 mg IV weekly (Arms A, B, and C) or three weeks on/one week off (Arm D).
- Tumor assessment performed at baseline and every 12-16 weeks until disease progression or the start of a new anti-cancer therapy.
- Endpoints: Primary – objective response assessed by the investigator; Secondary – safety, duration of response (DOR), and PFS.



RESULTS

Table 1: Baseline Characteristics

All data as of 29-June-2022 database lock date

Parameter	Expansion Arm A (N=31)	Expansion Arm B (N=13)	Expansion Arm C (N=32)	Expansion Arm D (N=27)
Age				
Median Years (range)	54 (28-78)	62 (41-71)	59 (41-74)	59 (34-79)
Prior Therapies – Advanced Breast Cancer, n (%)				
Prior Chemotherapy	1 (3.2)	4 (30.8)	15 (46.9)	5 (18.5)
Prior SERD or SERM Therapy[1]	0	5 (38.5)	14 (43.8)	10 (37.0)
Prior Aromatase Inhibitor Therapy	0	7 (53.8)	25 (78.1)	19 (70.4)
Prior CDK4/6 inhibitor	0	0	32 (100)	26 (96.3)
Number of Prior Therapies – Advanced Breast Cancer, n (%)				
0	30 (96.8)	2 (15.4)	0	0
1	1 (3.2)	9 (69.2)	15 (46.9)	18 (66.7)
2	0	2 (15.4)	11 (34.4)	8 (29.6)
3 or more	0	0	6 (18.8)	1 (3.7)
Measurable Baseline Disease, n (%)				
Yes	31 (100)	13 (100)	32 (100)	27 (100)
No	0	0	0	0
Disease Site Involved, n (%)				
Bone	18 (58.1)	11 (84.6)	25 (78.1)	18 (66.7)
Brain	0	0	1 (3.1)	0
Liver	14 (45.2)	10 (76.9)	20 (62.5)	17 (63)
Lung	7 (22.6)	3 (23.1)	7 (21.9)	6 (22.2)
Lymph Node	8 (25.8)	2 (15.4)	9 (28.1)	2 (7.4)
Pleural Effusion	4 (12.9)	0	3 (9.4)	2 (7.4)
Skin	1 (3.2)	0	1 (3.1)	0
Other	26 (83.9)	10 (76.9)	20 (62.5)	21 (77.8)
Number of Disease Sites Involved, n (%)				
1 – 3	26 (83.9)	11 (84.6)	26 (81.2)	24 (88.9)
≥4	5 (16.1)	2 (15.4)	6 (18.8)	3 (11.1)
***PIK3CA*, n (%)[2]**				
Wild Type	25 (80.6)	9 (69.2)	24 (75.0)	15 (55.6)
Mutation	5 (16.1)	4 (30.8)	8 (25.0)	11 (40.7)
Unknown/Missing	1 (3.2)	0	0	1 (3.7)

[1]Across 4 arms, 27 subjects received SERD and 2 subjects received SERM as a primary systemic therapy for advanced breast cancer. No subjects received both therapies

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

EFFICACY

Table 2: Efficacy Summary (All Expansion Arms)

	Total Expansion Arms (N=103, full analysis set)			
	Expansion			
Arm	**A**	**B**	**C**	**D**
Prior Therapy	1L: CDKi- naive	2L+: CDKi- naive	2L/3L: CDKi -pretreated	2L/3L: CDKi- pretreated
n (Full, response evaluable)	31, 27	13, 13	32, 28	27, 27
Study Treatment	P + L + G	P + F + G	P + F + G	P + F + G
Gedatolisib schedule	weekly	weekly	weekly	3 weeks on/1 week off
Median DOR, months (95% CI)[3]	NR (22.2, NR)	12.2 (3.7, 40.6)	16.6 (3.7, 30.3)	12.6 (7.3, 21.2)
ORR[1] (evaluable)	85%	77%	36%	63%
mPFS[2], mos (range)	NR (16.9, NR)	12.9 (7.6, 38.3)	5.1 (3.3, 7.5)	12.9 (7.4, 16.7)
Median Follow Up[2], mos (range)	33.1 (0.0+, 40.3+)	NE (2.1+, 42.5)	NE (0.0+, 32.1)	29.0 (1.7, 31.6+)
PFS % at 12 mos[2]	72.1%	54.5%	23.6%	53.2%

[1]Response evaluable analysis set per RECIST v1.1 including uPR; [2]full analysis set; [3]Kaplan Meier method and confidence intervals by the Brookmeyer and Crowley Method; Abbreviations: 1L= first line, 2L= second line; mos= months; NR = not reached; NE = could not be estimated per reverse KM method; DOR, duration of response; ORR, objective response rate; PFS, progression free survival; +=censored

SAFETY

Table 3: Treatment Related and Emergent Adverse Events (≥20% of subjects, by SOC and preferred term)

	All Expansion Arms (n=103)			
Adverse Event	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders				
Stomatitis[1]	19.4	41.7	27.2	0
Nausea	42.7	34.0	0	0
Vomiting	32.0	12.6	1.0	0
Diarrhea	23.3	8.7	2.9	0
Dry mouth	25.2	1.9	0	0
Constipation	20.4	4.9	1.0	0
General disorders and administration site conditions				
Fatigue	21.4	35.9	10.7	0
Skin and subcutaneous tissue disorders				
Rash[1,2]	21.4	10.7	20.4	0
Pruritus	13.6	7.8	4.9	0
Investigations				
White blood cell count decreased	1.9	15.5	11.7	2.9
Lymphocyte count decreased	2.9	4.9	11.7	1.0
Blood and lymphatic system disorders				
Anemia	10.7	17.5	11.7	0
Neutropenia/Neutrophil count decreased[3,4]	1.0	11.7	53.4	9.7
Nervous system disorders				
Dysgeusia	42.7	2.9	0	0
Headache	18.4	5.8	0	0
Metabolism and nutrition disorders				
Decreased appetite	23.3	8.7	0	0
Hyperglycemia	12.6	5.8	3.9	1.9
Injury, poisoning and procedural complications				
Infusion related reaction	16.5	5.8	0	0

There were no Grade 5 treatment related TEAEs

[1]Prophylactic treatment for stomatitis was not implemented; [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]Rash, Rash maculo-papular, Rash pruritic, Rash pustular, Rash papular, Rash erythematous, or Rash vesicular; [4]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

Table 4: Patient Treatment Discontinuation

	Expansion Arm A (N=31)	Expansion Arm B (N=13)	Expansion Arm C (N=32)	Expansion Arm D (N=27)
Subjects who discontinued treatment	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Discontinuation of Study Treatment				
Reasons other than AEs	28 (90.3)	11 (84)	29 (90.6)	26 (96.3)
Progression or relapse	12 (38.7)	10 (76.9)	24 (75.0)	18 (66.7)
Death[1]	0	0	0	1 (3.7)
Study terminated by sponsor[2]	8 (25.8)	1 (7.7)	0	2 (7.4)
Other[3]	8 (25.8)	0	5 (15.6)	5 (18.5)
Adverse Event[4]	3 (9.7)	2 (15.4)	3 (9.4)	1 (3.7)

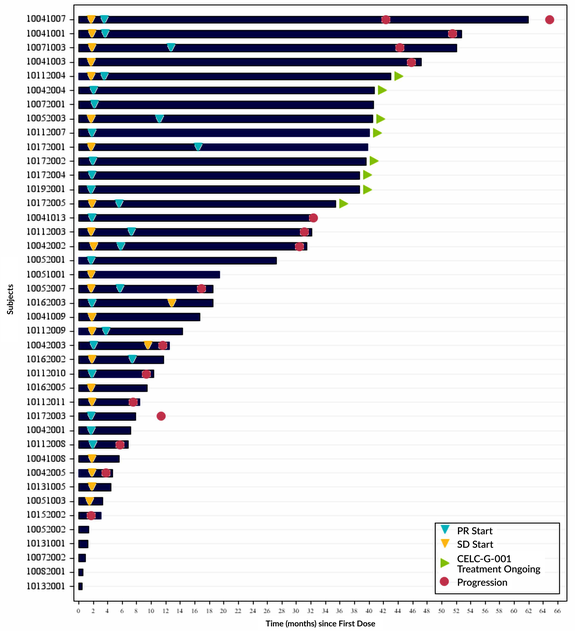
[1]Death due to non treatment related septic shock; [2]After study termination, as of database lock date of June 29, 2022, 11 subjects rolled over to an expanded access protocol and continued treatment; [3]Other includes global deterioration, protocol violation, no longer willing to participate in study; [4]Treatment related AEs: stomatitis (n=4); mucosal inflammation, pneumonitis, psoriasis, pulmonary embolism (n=1 each); Non-treatment related AEs: edema peripheral (n=1)

Table 5: Efficacy Summary (*PIK3CA* Mutation Status)

	Total Expansion Arms (N=103, full analysis set)							
	Expansion							
Arm	**A**		**B**		**C**		**D**	
Prior Therapy	1L: CDKi- naive		2L+: CDKi- naive		2L/3L: CDKi -pretreated		2L/3L: CDKi- pretreated	
n (Full, response evaluable)	31, 27		13, 13		32, 28		27, 27	
Study Treatment	P + L + G		P + F + G		P + F + G		P + F + G	
Gedatolisib schedule	weekly		weekly		weekly		3 weeks on/1 week off	
	WT	MT	WT	MT	WT	MT	WT	MT
***PIK3CA* Status**	81%[2,3]	16%[2,3]	69%	31%	75%[2]	25%[2]	56%[2,3]	41%[2,3]
ORR[1] (evaluable)	81%	100%	78%	75%	25%	63%	60%	73%
PFS % at 12 mos[2]	74%	60%	50%	67%	22%	29%	49%	60%

[1]Response evaluable analysis set per RECIST v1.1 including uPR; [2]full analysis set; [3]Baseline *PIK3CA* mutation status missing for one patient; 1L= first line, 2L= second line; mos= months; WT=wild type; MT= *PIK3CA* mutation; ORR, objective response rate; PFS, progression free survival

Figure 1: Treatment-Naive (1L) Subjects Time to First Response, Duration of Response and Treatment



Note: Each bar is presented for each subject starting from first dose date to last dose date, with time of disease progression. No subject died prior to experiencing disease progression. 8 subjects (green arrows) remained on treatment after transferring to an expanded access protocol (CELC-G-001) or individual IND as of June 29, 2022.

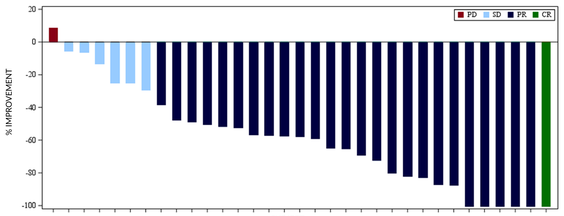
Table 6 : Efficacy Summary (Treatment-Naïve [1L] Population)

	Escalation Arm A	Expansion Arm A	Escalation Arm A + Expansion Arm A Total
n (full, response evaluable)	**(11, 10)**	**(30, 26)[3]**	**(41, 36)**
Responses (response evaluable)[1]	n (%)	n (%)	n (%)
CR	0	1 (3.8)	1 (2.8)
PR	4 (40.0)	21 (80.8)	25 (69.4)
SD	6 (60.0)	3 (11.5)	9 (25.0)
Unconfirmed PR	0	0	0
Durable SD (>=24 weeks)	3 (30.0)	2 (7.7)	5 (13.9)
PD	0	1 (3.8)	1 (2.8)
Not Evaluable	0	0	0
ORR[1]	4 (40.0)	22 (84.6)	26 (72.2)
Progression Free Survival (full analysis set)[2]			
Median PFS, mos (95%CI)[2]	44.2 (32.3, 51.4)	NR (11.6, NR)	42.3 (30.4, 45.8)[4]

Median time from the last prior therapy was 1 month for Escalation Arm A vs 26 months for Expansion Arm A.
These 2 arms were not randomized.

[1]Response evaluable analysis set per RECIST v1.1; [2]full analysis set; [3]one subject in expansion arm A was not treatment-naive and has been excluded in this evaluation; [4]median PFS follow up time was 33.1 months; CR, complete response; mos, months; NR, Not Reached; PFS, progression free survival; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate

Figure 2: Treatment-Naive (1L) Subjects Best Response (Maximum Improvement in Sum of Target Lesion Diameters from Baseline)



Note: Three patients in Escalation Arm A did not have measurable target lesions but had non-target lesions. In this study, they were considered evaluable and included in all analyses of efficacy. Based on evaluation of their non-target lesions, each of the three patients had SD as BOR.

CONCLUSIONS

- Gedatolisib in combination with ET and palbociclib demonstrated encouraging efficacy and durable responses in both treatment naïve ER+/HER2- ABC as well as in later line settings.
- Promising efficacy results compared favorably to published data for current standard of care.
- High response rates were observed in subjects regardless of *PIK3CA* mutation status.
- Therapy was well tolerated with few subjects (<10%) discontinuing due to adverse events.
- A Phase 3 study evaluating gedatolisib in patients with HR+/HER2- ABC is ongoing (NCT05501886; Poster-ID-OT3-26-02)
- Further study of gedatolisib in treatment naïve HR+/HER2- ABC is warranted.

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