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Updated efficacy, safety, & PD-L1 status of patients with HR+, HER2- metastatic breast cancer administered abemaciclib plus pembrolizumab

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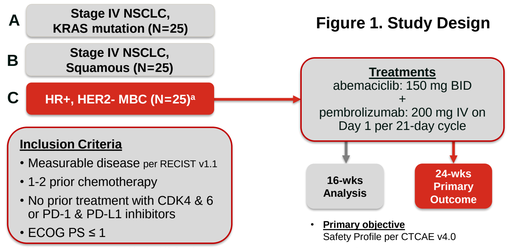
BACKGROUND

- In HR+ breast cancer, estrogen stimulates cyclin D1 expression and facilitates the activation of CDK4 & 6 and cell cycle progression[1,2]
- Abemaciclib is a CDK4 & 6 selective inhibitor administered twice-daily on a continuous schedule. It is 14 times more potent against cyclin D1/CDK4 than cyclin D3/CDK6 in enzymatic assays[3]
- Continuous inhibition of CDK4 & 6 with abemaciclib leads to sustained cell cycle arrest and subsequent senescence or apoptosis.[3] However, short term inhibition leads to G1 arrest that rebounds upon withdrawal[4]
- Abemaciclib is FDA-approved as monotherapy[5] as well as in combination with fulvestrant[6] or a nonsteroidal aromatase inhibitor (anastrozole or letrozole)[7] in patients with HR+, HER2-advanced breast cancer
- In preclinical models, abemaciclib monotherapy followed by treatment in combination with anti-programmed death-ligand 1 (PD-L1) antibody therapy enhanced anti-tumor response compared to monotherapy of either compound and induced immunological memory[8]
- In patients with HR+, HER2- metastatic breast cancer (MBC), administering the maximum tolerated dose[9] of abemaciclib (150 mg twice daily on continuous schedule) in combination with pembrolizumab, a programmed death receptor 1 (PD-1) antibody (200 mg on day one of a 21 day cycle), demonstrated a 14.3% objective response rate (ORR) at 16 weeks[10]
- Here, we report the updated efficacy and safety of abemaciclib in combination with pembrolizumab along with the baseline PD-L1 status at 24 weeks in patients with HR+, HER2- MBC

METHODS

Figure 1. Study Design



[a]28 patients were enrolled in the MBC cohort
[b]In patients presenting with initial radiologic progression, the investigator may elect to continue treatment and repeat imaging ≥4 weeks later for assessment per irRECIST

- **Primary objective**
  Safety Profile per CTCAE v4.0
- **Secondary objectives**
  Objective Response Rate (ORR), Progression-free Survival (PFS), Duration of Response (DoR), and Disease Control Rate (DCR) per RECIST v1.1[b]
  Overall Survival (OS)

RESULTS

Table 1. Baseline Characteristics of Patients with MBC

	N=28
Median age (range)	55 (31-76)
Age ≥65 years, n (%)	7 (25.0)
ECOG PS 0 / 1, %	57.1 / 35.7[a]
Metastatic sites, n (%)	
Visceral[b]	23 (82.1)
Liver	18 (64.3)
Lung	8 (28.6)
Bone	19 (67.9)
Bone-only	1 (3.6)
# of Metastatic Sites, n (%)	
1 site	4 (14.3)
2 sites	5 (17.9)
≥3 sites	19 (67.9)

[a]2 patients had missing ECOG PS data
[b]visceral includes: liver, lung, brain, CNS (non-brain),other (visceral), peritoneum, pleura

Table 2. Prior Therapies for Metastatic Disease[a]

Endocrine Therapy[b]	N=28, n (%)	Chemotherapy[c]	N=28, n (%)
# of Regimens		# of Regimens	
1	11 (39.3)	1	14 (50.0)
2	9 (32.1)	2	11 (39.3)
3	4 (14.3)	≥ 3[d]	2 (7.1)
≥ 4	1 (3.6)	Taxanes[e]	17 (60.7)
Prior fulvestrant	12 (42.9)	Capecitabine	14 (50.0)

[a]median number of prior systemic regimens for metastatic disease was 3 (range 1-7)
[b]1 patient had ET in the adjuvant setting and 2 patients did not have prior ET
[c]1 patient had missing prior chemotherapy data in metastatic setting
[d]at the time of data analysis, 1 patient had 3 prior chemotherapy regimens in metastatic setting and another patient had 5 chemotherapy regimens in metastatic setting
[e]82% of patients received taxanes in any setting

Table 3. Most Common Adverse Events

Investigator-assessed TEAE[a] in ≥ 25% of patients (N=28)	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grades 4-5 n (%)
Diarrhea	22 (78.6)	11 (39.3)	8 (28.6)	3 (10.7)	0
Fatigue	16 (57.1)	9 (32.1)	7 (25.0)	0	0
Headache	12 (42.9)	10 (35.7)	2 (7.1)	0	0
Neutropenia[b]	11 (39.3)	0	3 (10.7)	8 (28.6)	0
Pruritus	11 (39.3)	8 (28.6)	3 (10.7)	0	0
Nausea	10 (35.7)	9 (32.1)	0	1 (3.6)	0
AST increased	8 (28.6)	2 (7.1)	2 (7.1)	4 (14.3)	0
Decreased appetite	8 (28.6)	8 (28.6)	0	0	0
Vomiting	8 (28.6)	6 (21.4)	1 (3.6)	1 (3.6)	0
ALT increased	7 (25.0)	1 (3.6)	3 (10.7)	3 (10.7)	0
Abdominal pain	7 (25.0)	4 (14.3)	2 (7.1)	1 (3.6)	0
Cough	7 (25.0)	2 (7.1)	5 (17.9)	0	0
Additional TEAEs of Clinical Interest					
Hypothyroidism	5 (17.9)	1 (3.6)	4 (14.3)	0	0
Rash	4 (14.3)	2 (7.1)	1 (3.6)	1 (3.6)	0
Pneumonitis	2 (7.1)	0	2 (7.1)	0	0
Acute kidney injury (Renal failure)	2 (7.1)	0	2 (7.1)	0	0
Dermatitis acneiform	2 (7.1)	1 (3.6)	1 (3.6)	0	0
Hyperglycemia	1 (3.6)	0	0	1 (3.6)	0
Colitis	1 (3.6)	1 (3.6)	0	0	0
Laboratory Abnormalities of Clinical Interest (Safety Population)					
Creatinine increased[c]	28 (100.0)[d]	14 (50.0)	13 (46.4)	1 (3.6)	0
White Blood Cell decreased	25 (92.6)	5 (18.5)	16 (59.3)	4 (14.8)	0
Neutrophil count decreased[e]	21 (77.8)	5 (18.5)	7 (25.9)	9 (33.3)	0
Anemia[e]	20 (74.1)	12 (44.4)	8 (29.6)	0	0
Platelet count decreased[e]	18 (66.7)	18 (66.7)	0	0	0
ALT increased[b]	14 (51.9)	6 (22.2)	2 (7.4)	6 (22.2)	0
AST increased[f]	13 (50.0)	7 (26.9)	2 (7.7)	4 (15.4)	0

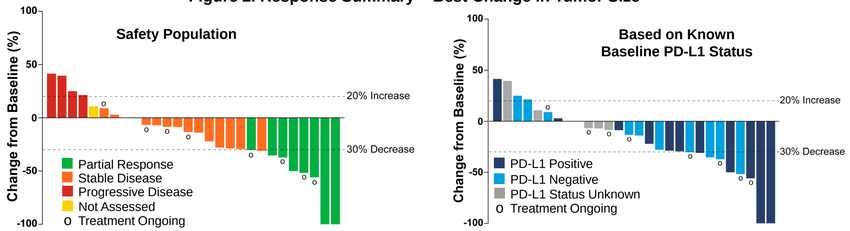
[a]per CTCAE v4.0
[b]1 patient had grade 1 febrile neutropenia and 1 patient had grade 3 febrile neutropenia
[c]abemaciclib is a known inhibitor of renal efflux transporters (OCT2, MATE1, and MATE2-K) causing increased creatinine unrelated to renal injury, insufficiency or impaired renal function[11,12]
[d]2 patients experienced grade 2 renal failure
[e]n=27; 1 patient had a missing baseline or post-baseline result
[f]n=26; 2 patients had a missing baseline or post-baseline result

Table 4. Safety Overview

All Adverse Events	N=28, n (%)
≥ 1 Serious AEs	8 (28.6)
Discontinuation due to AEs[a]	6 (21.4)
Deaths due to AEs[b]	1 (3.6)
During therapy[b]	1 (3.6)
Within 30 days after study treatment discontinuation	0 (0)

[a]patients discontinued due to sepsis (n=1), transaminitis (ALT and/or AST increased) (n=3), creatinine increased (n=1), renal insufficiency (n=1)
[b]death occurred due to sepsis

Figure 2. Response Summary – Best Change in Tumor Size



Investigator-assessed Response	N=28
Confirmed ORR (CR+PR) (95% CI)	28.6% (13.2-48.7)
CR	0%
PR (confirmed) (95% CI)	28.6% (13.2-48.7)
CBR (CR+PR+SD ≥6 months) (95% CI)	46.4% (27.5-66.1)

Investigator-assessed Response	PD-L1 Positive[a] n=12	PD-L1 Negative n=11	PD-L1 Unknown n=5[b]
Confirmed ORR (CR+PR) (95% CI)	33.3% (9.9 – 65.1)	36.4% (10.9 – 69.2)	0% (N/A)
CR (95% CI)	0% (N/A)	0% (N/A)	0% (N/A)
PR (95% CI)	33.3% (9.9 – 65.1)	36.4% (10.9 – 69.2)	0% (N/A)
CBR (CR+PR+SD ≥6 months) (95% CI)	50.0% (21.1 – 78.9)	54.5% (23.4 – 83.3)	20.0% (0.5 – 71.6)

[a]baseline PD-L1 status was determined using a CPS ≥1 provisional cutoff by IHC using an investigational version of the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA). The "combined positive score" (CPS) is the number of staining tumor and immune cells relative to total tumor cells. Positivity is defined by the number of staining cells per 100 tumor cells
[b]5 patients had undetermined PD-L1 status

Figure 3. Treatment Duration

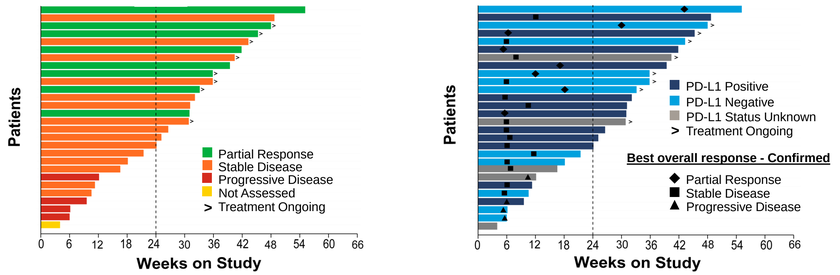
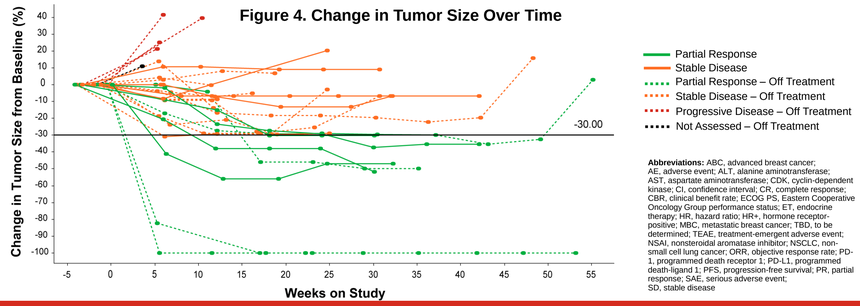


Figure 4. Change in Tumor Size Over Time



Abbreviations: ABC, advanced breast cancer; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDK, cyclin-dependent kinase; CI, confidence interval; CR, complete response; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hazard ratio; HR+, hormone receptor-positive; MBC, metastatic breast cancer; TBD, to be determined; TEAE, treatment-emergent adverse event; NSAI, nonsteroidal aromatase inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed death receptor 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SAE, serious adverse event; SD, stable disease

Table 5. Response Summary Over Time – Comparison with Abemaciclib Monotherapy (MONARCH 1)

Best Overall Response, n (%)	16 weeks		24 weeks		12 months	
	JPCE N=28	MONARCH 1 N=132	JPCE N=28	MONARCH 1 N=132	JPCE N=28	MONARCH 1 N=132
Confirmed ORR, (%)	14.3%	6.8%	28.6%	10.6%	TBD	19.7%
CR	0	0	0	0	TBD	0
PR	4 (14.3)	9 (6.8)	8 (28.6)	14 (10.6)	TBD	26 (19.7)
SD	17 (60.7)	80 (60.6)	15 (53.6)	75 (56.8)	TBD	63 (47.7)
PD	5 (17.9)	33 (25.0)	4 (14.3)	34 (25.8)	TBD	34 (25.8)
Not Assessed	2 (7.1)	10 (7.6)	1 (3.6)	9 (6.8)	TBD	9 (6.8)
Disease Control Rate (CR+PR+SD)	21 (75.0)	89 (67.4)	23 (82.1)	89 (67.4)	TBD	89 (67.4)
Patients Remaining on Study Treatment	17 (60.7)	68 (51.5)	8 (28.6)	48 (36.4)	TBD	13 (9.8)

CONCLUSIONS

- Continuous dosing of abemaciclib in combination with pembrolizumab demonstrated a manageable safety profile in patients with HR+, HER2- MBC
- No new safety signals were detected at the 24 week analyses as compared to the 16 week analyses[10]
- At 24 weeks, abemaciclib in combination with pembrolizumab demonstrated a confirmed ORR of 28.6%
- Baseline PD-L1 status was not predictive for response to abemaciclib in combination with pembrolizumab in patients who received treatment for up to 24 weeks

Study JPCE – Part D

Treatment of patients with HR+, HER2- MBC with abemaciclib in combination with aromatase inhibitors was approved based on the Phase 3 study, MONARCH 3, which established efficacy (median PFS 28.2 vs 14.8 months; HR: 0.540 and ORR 61% vs 45.5%), safety and tolerability of the combination in patients with measurable disease.[12] Since de novo or acquired resistance to adjuvant ET and MBC remain an important clinical challenge, we will explore the safety and efficacy of the novel triplet combination (abemaciclib + pembrolizumab + anastrozole) in patients with HR+, HER2- MBC in Part D

D

HR+, HER2- MBC (N = 25)

Treatments

abemaciclib: 150 mg Q12H + pembrolizumab: 200 mg IV on Day 1 per 21-day cycle + anastrozole: 1 mg Q24H

Inclusion Criteria

- Measurable disease per RECIST v1.1
- No chemotherapy in advanced setting
- Post menopausal due to surgical/natural menopause or ovarian suppression with GnRH agonist
- No ET or have previously received ET. Patients on neoadjuant ET or ≤ 2 weeks on NSAI were allowed
- No prior treatment with CDK4 & 6 or PD-1 & PD-L1 inhibitors
- ECOG PS ≤ 1

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Acknowledgements:

We thank the patients and their caregivers for their participation in this study, the study investigators and their staff, and the JPCE (NCT02779751) clinical trial team. This study is sponsored by Eli Lilly and Company, in collaboration with Merck & Co., Inc. Kenilworth, NJ, USA. Medical writing support was provided by Nirmala Xavier of Eli Lilly and company.

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Sponsored by Eli Lilly and Company