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A phase II study of pembrolizumab and eribulin in patients with HR-positive/HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes: KELLY study

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BACKGROUND

- Studies of checkpoint inhibitor monotherapy have shown only modest activity in hormone receptor (HR)–positive (+)/ human epidermal growth factor receptor 2 (HER2)–negative (-) metastatic breast cancer (MBC) [1].
- However, pembrolizumab (P) added to standard neoadjuvant therapy significantly improved the pathologic complete response rate in HR+/HER2- early breast cancer in the I-SPY-2 trial [2].
- The KELLY trial aimed to evaluate the efficacy and safety of P in combination with eribulin (E) in anthracycline- and taxane-pretreated patients (pts) with HR+/HER2- inoperable locally recurrent or MBC irrespective of programmed death-ligand 1 (PD-L1) status.

METHODS

Study design:

- This is an open-label, single-arm, multicenter phase IIA clinical trial.
- Pts received E 1.23 mg/m2 intravenously (IV) on days 1 and 8 with P 200 mg fixed dose IV on day 1 of a 21-day cycle until unacceptable toxicity, disease progression or study withdrawal.

Key selection criteria:

1. HR+/HER2-, inoperable locally recurrent or MBC.
2. Previously treated with endocrine therapy and at least one, but not more than two, prior chemotherapeutic regimens for treatment of locally recurrent or MBC.
3. Prior anthracycline/taxane exposure either in the early or metastatic setting, unless contraindicated.
4. Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1.

Primary endpoint:

- Clinical benefit rate (CBR) defined as total number of objective responses (complete response [CR] and partial response [PR]) plus stable disease (SD) lasting at least 24 weeks divided by the number of pts in the total population according to RECIST v.1.1.

Secondary endpoints:

- CBR in subjects with PD-L1–positive tumors according to RECIST v.1.1.
- Progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), and overall survival (OS) both in the overall population and in subjects with PD-L1–positive tumors according to RECIST v.1.1.
- Safety and tolerability of the E–P combination, according to the US National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.3.

Exploratory endpoints:

- The analysis of PFS and ORR based on immune-related RECIST (irRECIST).
- The associations of PFS to PD-L1 status, endocrine sensitivity, and prior exposure to inhibitors of cyclin-dependent kinase (CDK)4/6, mammalian Target Of Rapamycin (mTOR), and phosphatidylinositol 3-kinase (PI3K).

RESULTS

Patient's characteristics

- Between January 29, 2018, and October 17, 2018, a total of 44 pts were enrolled in the study, with a median follow-up of 7.7 months (mo.) (range: 1–18 mo.). The patient's characteristics at baseline are described in **Table 1.**

Table 1. Patient baseline characteristics in the PD-L1–negative and PD-L1–positive subgroups, and the overall population.

	PD-L1		
Characteristic	Negative* (n=22)	Positive* (n=21)	All patients** (n=44)
Age			
Median (range), years	55 (40–75)	51 (32–77)	52.5 (32–77)
ECOG performance status, n (%)			
0	15 (68.2)	15 (71.4)	31 (70.5)
1	7 (31.8)	6 (28.6)	13 (29.5)
Time from primary diagnosis to study enrollment			
Median (range), months	94.9 (11.1–290.1)	74 (18.4–360.3)	84.6 (11.1–360.3)
Number of metastatic sites, n (%)			
1-2	12 (54.5)	7 (33.3)	20 (45.5)
≥3	10 (45.5)	14 (66.7)	24 (54.5)
Visceral disease, n (%)			
No	1 (4.5)	3 (14.3)	4 (9.1)
Yes	21 (95.5)	18 (85.7)	40 (90.9)
Liver disease, n (%)			
No	2 (9.1)	4 (19)	6 (13.6)
Yes	20 (90.9)	17 (81)	38 (86.4)
Prior neoadjuvant or adjuvant chemotherapy, n (%)			
No	7 (31.8)	3 (14.3)	11 (25)
Yes	15 (68.2)	18 (85.7)	33 (75)
Previous lines of chemotherapy in metastatic disease, n (%)			
1	9 (40.9)	13 (61.9)	22 (50)
2	13 (59.1)	8 (38.1)	22 (50)
Previous treatment in advanced disease, n (%)			
Any CDK4/6 inhibitor	10 (45.5)	10 (47.6)	21 (47.7)
Any PI3K inhibitor	4 (18.2)	2 (9.5)	6 (13.6)
Any mTOR inhibitor	8 (36.4)	7 (33.3)	15 (34.1)
Lines of endocrine therapy			
Median (range)	2 (1–7)	2 (1–4)	2 (1–7)
Endocrine sensitivity ***, n (%)			
No	13 (59.1)	11 (52.4)	25 (56.8)
Yes	8 (36.4)	10 (47.6)	18 (40.9)

CDK: Cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group; mTOR: Mammalian Target Of Rapamycin; n: Number of patients; PD-L1: Programmed death-ligand 1; PI3K: Phosphatidylinositol 3-kinase.
* PD-L1 expression was centrally assessed using the PD-L1 IHC 22C3 pharmDx kit (Agilent, Carpinteria, CA, USA). The measure of expression was the combined positive score (CPS), defined as the ratio of PD-L1– positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells x 100. PD-L1 positivity was defined as CPS ≥1.
** PD-L1 status was not evaluable in one patient because of low tumor cellularity.
*** Endocrine sensitivity was defined according to either of the following criteria: 1) Relapse that occurred after at least 24 mo. while the patient was receiving adjuvant endocrine therapy. 2) Progression that occurred after at least 24 weeks while the patient was receiving endocrine therapy in the context of metastatic disease.

Efficacy

Primary analysis

- Based on RECIST v.1.1 as assessed by investigator review, 16 of 44 pts had PR and 8 of 44 pts had SD lasting at least 24 weeks for a CBR of 54.4% (95% confidence interval [CI]: 38.8–69.6%) **(Table 2)**. KELLY study met its primary endpoint because CBR was significantly higher than null hypothesis that was defined as 30% CBR (two-sided $P = 0.001$).

Table 2. Response in all patients according to local assessment *.

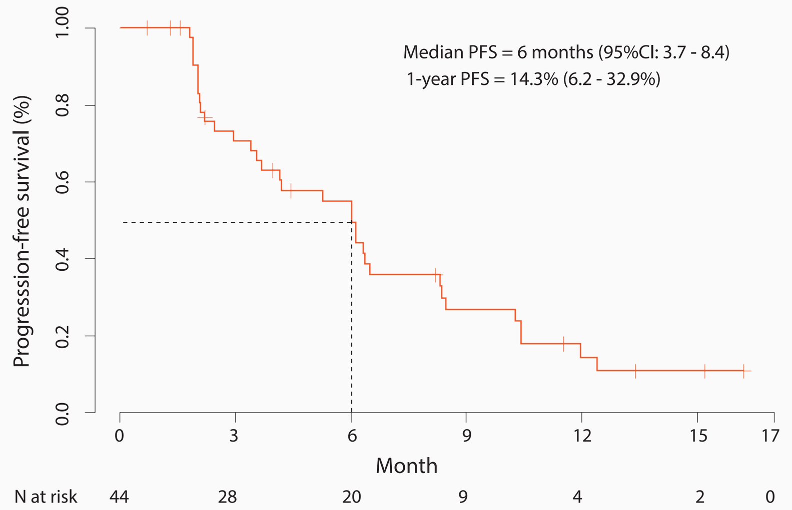
Best response	All patients (n=44)	95%CI
Age		
CBR **, n (%)	24 (54.5)	38.8–69.6
CR	0 (0)	-
PR	16 (36.4)	22.4–52.2
SD ≥24 weeks	8 (18.2)	8.2–32.7
SD <24 weeks	6 (13.6)	13.2–40.3
PD	11 (25)	13.2–40.3
NE ***	3 (6.8)	1.4–18.7

95%CI: 95% confidence interval; CR: Complete response; CBR: Clinical benefit rate; n: Number of patients; NE: Not evaluated; PR: Partial response; PD: Progressive disease; SD: Stable disease.
* Final results include patients with measurable disease at baseline based on RECIST v.1.1 as assessed by investigator review who received ≥1 cycle of E–P combination.
** CR + PR + SD ≥24 weeks in all patients.
*** A total of three patients discontinued the treatment prior to the first tumor evaluation. Two of them due to adverse events (hypertriglyceridemia and respiratory infection). The other patient withdrew informed consent.

Secondary analysis

- ORR was 36.4% (95%CI: 22.4–52.2%). Median PFS was 6.03 mo. (95%CI: 3.7–8.4 mo.). Among responders, DoR was 6.14 mo. (95%CI: 3.04 mo.–Not achieved [NA]) **(Figure 1 and Table 3)**. OS data are immature (15 deaths, 34.1%).

Figure 1. Progression-free survival in all patients.



95%CI: 95% confidence interval; N: Number of patients; PFS: Progression-free survival.

- In PD-L1–positive subgroup, CBR and ORR were 38.1% (95%CI: 18.1–61.6%) and 28.6% (95%CI: 11.3–52.2%), respectively. Median PFS was 4.2 mo. (95%CI: 2.2–8.5 mo.). Among responders, DoR was 5.2 mo. (95%CI: 3 mo.–NA) **Table 3.**

Table 3. Response in the PD-L1–negative and PDL1–positive subgroup, and the overall population according to local assessment.

	PD-L1		
Response	Negative (n=22)	Positive (n=21)	All patients (n=44)
Best response per RECIST v.1.1			
ORR, n (%)	9 (40.9)	6 (28.6)	16 (36.4)
95%CI for response rate	20.7–63.6	11.3–52.2	22.4–52.2
P	0.396		
CBR	15 (68.2)	8 (38.1)	24 (54.6)
95%CI	45.1–86.1	18.1–61.6	38.8–69.6
P	**0.048**		
DoR*, median, months	6.1	5.2	6.1
95%CI	6 – NA	3 – NA	3 - NA
P	0.423		
Patients with PFS events, n (%)	16 (72.7)	15 (71.4)	32 (72.7)
95%CI	49.8–89.3	47.8–88.7	57.2–85
P	0.924		
PFS, median, months	6.5	4.2	6.0
95%CI	4.2–NA	2.2–8.5	3.7–8.4
P	0.307		

95%CI: 95% confidence interval; CBR: Clinical benefit rate; DoR: Duration of Response; n: Number of patients; NA: Not achieved; ORR: Overall response rate; *P*: P-value; PD: Progressive disease; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors.
* Evaluated in patients who had overall response (n = 9 for the PD-L1–negative population, n = 6 for the PD-L1–positive population, and n = 16 for the total population).

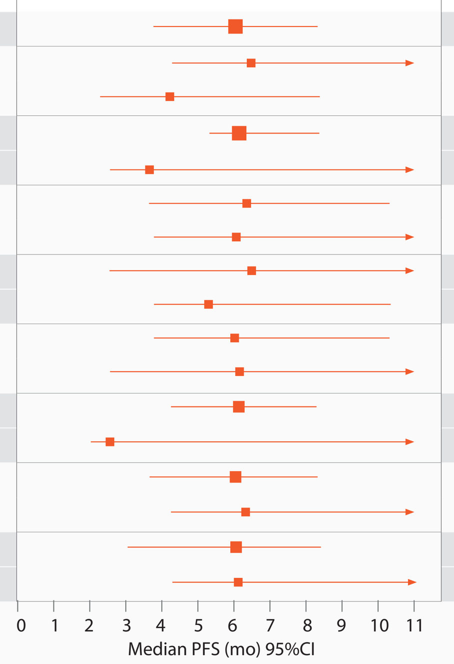
Exploratory analyses

- ORR and median PFS based on irRECIST were 36.4% (95%CI: 22.4–52.2%) and 6.1 mo. (95%CI: 4.2–8.4 mo.), respectively.
- PD-L1, ECOG performance status, number of metastatic sites, and prior antineoplastic therapies were not associated with significant differences in PFS **(Figure 2)**.

95%CI: 95% confidence interval; CDK: Cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group; mo.: months; mTOR: Mammalian Target Of Rapamycin; NA: Not achieved; P: P-value; PD-L1: Programmed death-ligand 1, PFS: Progression-free survival; PI3K: Phosphoinositide 3-kinase.
Horizontal Bars Represent 95%CI for the median PFS in each subgroup. The median PFS and hazard ratio were estimated using Kaplan-Meier method and log-rank test, respectively.

Figure 2. Forest-plot analyses of progression-free survival in key subgroups.

Subgroup		PFS events (%)	Number of patients	Median PFS (mo) 95%CI	Hazard ratio 95%CI	*P*
Overall		33 (75%)	44	6.03 (3.7 - 8.37)		
PD-L1 status	Negative	16 (72.7%)	22	6.5 (4.2 - NA)	1.6 (0.8 - 3.1)	0.213
	Positive	16 (76.2%)	21	4.17 (2.2 - 8.47)		
ECOG performance status	0	23 (74.2%)	31	6.13 (5.27- 8.47)	1.4 (0.7 - 3)	0.386
	1	10 (76.9%)	13	3.57 (2.47 - NA)		
Number of organs involved	1-2	16 (80%)	20	6.37 (3.57 - 10.43)	1.2 (0.6 - 2.3)	0.672
	≥3	17 (78.8%)	24	6.03 (3.7 - 12.4)		
Lines of chemotherapy in advanced disease	First	15 (68.2%)	22	6.5 (2.47 - NA)	1.2 (0.6 - 2.4)	0.575
	Second	18 (81.8%)	22	5.27 (3-7 - 10.43)		
Any CDK 4/6 inhibitor	No	17 (73.9%)	23	6.03 (3.7 - 10.43)	1 (0.5 - 1.9)	0.947
	Yes	16 (76.2%)	21	6.13 (2.47 - NA)		
Any PI3K inhibitor	No	29 (76.3%)	38	6.13 (4.17 - 8.37)	0.9 (0.3 - 2.7)	0.894
	Yes	4 (66.7%)	6	2.47 (1.9 - NA)		
Any mTOR inhibitor	No	22 (75.9%)	29	6.03 (3.57 - 8.37)	0.8 (0.4 - 1.6)	0.498
	Yes	11 (73.3%)	15	6.33 (4.2 - NA)		
Endocrine sensitivity	No	21 (84%)	25	6.03 (2.97 - 8.47)	0.8 (0.4 - 1.5)	0.431
	Yes	12 (66.7%)	18	6.03 (4.17 - NA)		



Safety

- All-cause adverse events (AEs) occurred in 100% of pts (Grade 3-4, 61.4%), without treatment-related deaths.
- The combination of E plus P was administered for a median of 7.6 cycles.
- The average dose intensity and relative dose intensity for E were 0.74 mg/m²/week and 89.7%, respectively. For P the mean absolute and relative dose intensities were 0.648 mg/week and 97.2%, respectively.
- Dose interruptions and delays for any of treatments were required in 5 (11.4%) and 16 (36.4%) pts, respectively. A total of 9 (20.5%) pts had a dose reduction of E.
- Thirty-two (72.7%) pts discontinued the treatment during the study because of disease progression, 5 pts because AEs (13.6%), 1 patient withdrew her consent, 1 patient needed to use prohibited medication, and 1 patient died due to an AE unrelated to the study medication. The treatment is ongoing in 4 pts.
- The most frequent AEs are summarized in **Table 4**.

Table 4. Most frequent adverse events from any cause that occurred in at least 10% of the patients (N=44).

Adverse event, n (%)	Any Grade	Grade 3	Grade 4**
ANY*	44 (100)	26 (59.1)	6 (13.6)
Hematologic AEs			
Neutropenia	20 (45.45)	14 (31.82)	3 (6.82)
Anemia	19 (43.18)	1 (2.27)	0 (0)
Non-Hematologic AEs			
Asthenia	19 (43.18)	2 (4.55)	0 (0)
Diarrhea	15 (34.09)	1 (2.27)	0 (0)
Fatigue	14 (31.82)	1 (2.27)	0 (0)
Nausea	11 (25)	0 (0)	0 (0)
Peripheral sensory neuropathy	11 (25)	3 (6.82)	1 (2.27)
Alanine aminotransferase increased	10 (22.73)	2 (4.55)	0 (0)
Decreased appetite	10 (22.73)	0 (0)	0 (0)
Back pain	9 (20.45)	0 (0)	0 (0)
Constipation	9 (20.45)	0 (0)	0 (0)
Abdominal pain	8 (18.18)	0 (0)	0 (0)
Aspartate aminotransferase increased	8 (18.18)	1 (2.27)	0 (0)
Headache	8 (18.18)	0 (0)	0 (0)
Mucosal inflammation	8 (18.18)	1 (2.27)	0 (0)
Pyrexia	8 (18.18)	0 (0)	0 (0)
Cough	7 (15.91)	0 (0)	0 (0)
Dyspnea	7 (15.91)	0 (0)	0 (0)
Urinary tract infection	7 (15.91)	0 (0)	0 (0)
Arthralgia	6 (13.64)	0 (0)	0 (0)
Hypothyroidism	6 (13.64)	0 (0)	0 (0)
Lacrimation increased	6 (13.64)	0 (0)	0 (0)
Vomiting	6 (13.64)	0 (0)	0 (0)
Pain in extremity	5 (11.36)	0 (0)	0 (0)
Rash	5 (11.36)	0 (0)	0 (0)
Respiratory tract infection	5 (11.36)	1 (2.27)	0 (0)

AEs: Adverse events; n: Number of patients.
* N=1 patient had a cardiac arrest unrelated with study medication.
** Alopecia frequency was not reported in this Table.

CONCLUSIONS

- E plus P is a safe and active regimen for pts with previously treated HR+/HER2- locally recurrent or MBC.
- The preliminary antitumor activity of this combination seems encouraging when compared with historical controls from similar populations treated with eribulin monotherapy.
- Intriguingly, E plus P achieved higher antitumor activity in PD-L1-negative pts than PD-L1–positive pts. However, these findings should be interpreted cautiously because might reflect baseline imbalances in prognostic factors between the two subgroups.
- Further studies should be conducted to investigate potential biomarkers or other clinical characteristics that may be predictive of response to E plus P, or to understand the resistance mechanisms related to the therapy.

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Conflicts of interest:
https://medsir.org/kelly/

Trial Registration: NCT03222856 on July 19th, 2017. First patient included: January 29, 2018.