Phase I/II study of pembrolizumab in combination with oral binimetinib in patients with unresectable locally advanced or metastatic triple-negative breast cancer

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Presentation ID
PO3-06-14

San Antonio Breast Cancer Symposium
December 5-9, 2023

Abstract

Background: Activation of the RAS/MAPK pathway is associated with reduced tumor-infiltrating lymphocytes and poor outcomes in triple-negative breast cancer (TNBC). This trial evaluated the efficacy of pembrolizumab in combination with binimetinib, an MEK inhibitor.

Methods: Patients with unresectable locally advanced or metastatic TNBC with ≤ 3 prior lines of therapy were enrolled. Treatment includes a 2-week run-in with binimetinib followed by pembrolizumab. There were 2 dose levels (DL) with binimetinib at 45 mg at DL 0 and 30 mg at DL -1. A standard 3+3 design was used in Phase I, and Simon's two-stage Optimal design was used in Phase II. PD-L1 22C3 was performed in archival samples with CPS ≥ 10 considered as positive (PD-L1+). Tumor-infiltrating lymphocytes (TILs) were quantified into 0, 1, 2, and 3+. Circulating tumor cells (CTC) and circulating cancer-associated macrophage-like cells (CAML) were isolated using CellSieve microfilters and immunofluorescently labeled with PD-L1 and p-ERK. Wilcoxon rank sum test, Chi-square test, Cox regression model, and Spearman correlation were used for analysis.

Results: 22 patients were enrolled with a median age of 58 years old. Dose-limiting toxicity (DLT) was observed in 2 out of 4 patients in DL 0, with grade 3 ALT abnormality, flank pain, and nausea. In the next 6 patients in DL -1, there was 1 DLT with grade 3 AST/ALT abnormality. There were 18 patients treated with DL -1 and were evaluable for response. The objective response rate (ORR) was 27.8% (95% CI: 9.7%-53.5%) with 1 complete response (CR) and 4 partial responses (PR). The clinical benefit rate (CBR ≥ 24 weeks) was 33.3% (95% CI: 13.3%-59.0%). ORR in patients without liver metastases was 45.5% (95% CI: 16.7%-76.6%), and CBR was 54.5% (95% CI: 23.4%-83.3%). No response was observed in all 5 patients with liver metastases. There were 40.9% of patients with PD-L1 CPS ≥ 10. ORR in patients with PD-L1+ was 66.7%. Patients with PD-L1 negative tumors had an ORR of 8.3% and a clinical benefit ≥ 24 weeks of 16.7%. PD-L1 expression in archival tissue was associated with ORR (p = 0.009) and CBR (p = 0.034) but not progression-free survival (PFS, p = 0.373) or overall survival (p = 0.396). TILs in archival tissue were also not associated with CBR (p = 0.166) and PFS (p = 0.157). All patients with CR or PR had TILS greater than 1+. We further evaluated blood-based biomarkers with CTC and CAML. We further evaluated blood-based biomarkers with mean CAML expression, count, and size. No association between CBR and baseline PD-L1 measure was identified: mean CAML expression (p = 0.06), CAML size (p = 0.52), and CAML count (p = 0.71). Similarly, no associations in CBR were identified between the decline in CAML measures: mean CAML expression, CAML size, and CAML count (all with p = 0.09). However, a decrease in CAML count (p = 0.01), a decrease in CAML size (p = 0.009), and a decrease in CAML mean expression (p = 0.02) were associated with longer overall survival. No significant differences were observed in PFS. PD-L1 expression in CAML is not associated with PD-L1 expression in archival tissue (Spearman ρ = 0.13). Only a decrease in p-ERK CAML count (p = 0.04) was significantly associated with CBR. No association was identified between CBR and any of the following: decrease in CAML size (p = 0.33), decrease in CAML mean expression (p = 0.09), baseline CAML count (p = 0.94), baseline CAML size (p = 0.94), or baseline CAML mean expression (p = 0.06). There were also no associations identified for OS or PFS.

Conclusions: Pembrolizumab and binimetinib at 30 mg are safe with manageable toxicities. Consistent with the preclinical data that MEKi can restore T cell function, promising activity was observed even in patients with low TILs and PD-L1 negative, particularly in patients without liver metastases. PD-L1 expression in peripheral blood CAML, rather than archival tumor tissue, may serve as a better biomarker to predict the clinical benefit of this combination. Early reductions in CAML count and size were also significantly associated with responses. Future larger clinical trials are warranted to further evaluate the efficacy of this chemotherapy-free combination.

Clinical trial information: NCT03106415

Trial Schema

Sample Size: 15-38 patients

Eligibility criteria

- Females ≥ 18 years
- ECOG PS ≤ 1
- ER/PR ≤10% and HER2 negative
- ≤3 prior lines of treatment in metastatic setting
- Measurable disease
- Adequate organ and cardiac functions

Dose Level	Dose	
	Pembrolizumab (mg)	Binimetinib (mg)
0	200 mg IV every 3 weeks	45 mg bid
-1	200 mg IV every 3 weeks	30 mg bid
-2	200 mg IV every 3 weeks	15 mg bid

Baseline Characteristics

	Dose Level -1 (N=18)	Dose Level 0 (N=4)	Total (N=22)
Age at Registration			
Mean (SD)	57.1 (11.3)	63.3 (6.5)	58.2 (10.8)
Number of Prior Treatments			
0	5 (27.8%)	0 (0.0%)	5 (22.7%)
1	3 (16.7%)	1 (25.0%)	4 (18.2%)
2	6 (33.3%)	2 (50.0%)	8 (36.4%)
3	4 (22.2%)	0 (0.0%)	4 (18.2%)
Ethnicity			
Black or African American	4 (22.2%)	3 (75.0%)	7 (31.8%)
Not Reported	1 (5.6%)	0 (0.0%)	1 (4.5%)
Unknown	2 (11.1%)	0 (0.0%)	2 (9.1%)
White	11 (61.1%)	1 (25.0%)	12 (54.5%)
Race			
Hispanic or Latino	1 (5.6%)	0 (0.0%)	1 (4.5%)
Not Hispanic or Latino	16 (88.9%)	4 (100.0%)	20 (90.9%)
Unknown	1 (5.6%)	0 (0.0%)	1 (4.5%)
Metastatic Liver			
No	11 (61.1%)	3 (75.0%)	14 (63.6%)
Yes	7 (38.9%)	1 (25.0%)	8 (36.4%)

Outcomes

Figure 1: Swimmer plot of tumor burden changes over time with pembrolizumab in combination with binimetinib.

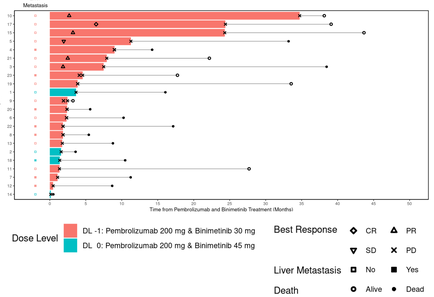
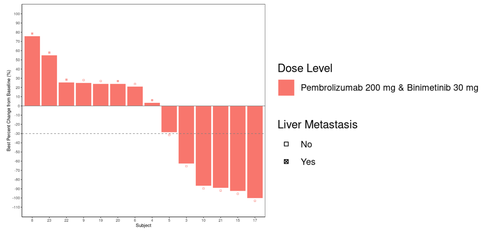


Figure 2: Waterfall plot of tumor burden changes over time with pembrolizumab in combination with binimetinib.



Dose Limiting Toxicities and AEs

Dose Levels	CTCAE Grading	Toxicities
0	3	Flank pain and nausea/vomiting > 48 hours
	3	ALT abnormality (no liver metastasis)
-1	3	ALT and AST abnormality (liver metastasis)

Other common toxicities

- Fatigue 81.8%, Other Blood and Lymphatic Disorders 77.3%, Nausea 72.7%, Anemia 68.2%, AST Increased 59.1%, Cardia Troponin T Increased 59.1%, CPK Increased 54.5%, Diarrhea 54.5%

CAML and Objective Responses

Figure 3: PD-L1 boxplots among patients with clinical benefit (CR, PR, and SD ≥ 6 months on the left) vs. PD (on the right) according to: **A.** Baseline numbers of CAML cell count. **B.** Baseline CAML size **C.** Baseline CAML PD-L1 expression.

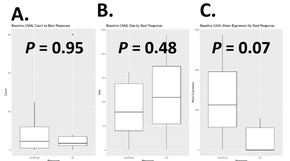
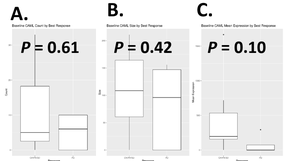
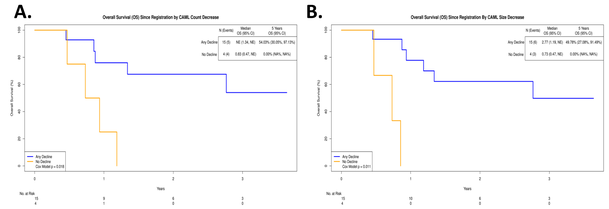


Figure 4: p-ERK boxplots among patients with clinical benefit (CR, PR, and SD ≥ 6 months on the left) vs. PD (on the right) according to: **A.** Baseline numbers of CAML cell count. **B.** Baseline CAML size **C.** Baseline CAML p-ERK expression.



CAML and Overall Survival

Figure 5: **A.** Kaplan-Meier (KM) curve for overall survival according to a reduction in the circulating cancer-associated macrophage-like (CAML) cell count after treatment initiation. **B.** KM curve for overall survival according to a reduction in the CAML size after treatment initiation.



Conclusions

- Pembrolizumab, in combination with binimetinib, appears safe with manageable toxicities.
- Promising activity was observed, particularly in patients without liver metastasis.
- Baseline PD-L1 expression on CAML, early reduction in CAML count, and CAML size, but not p-ERK in CAML, were significantly associated with subsequent responses and improvement in OS.

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