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Peripheral blood biomarkers in 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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MAYO CLINIC

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 and the MEK inhibitor, binimetinib. Here we evaluated potential biomarkers in peripheral blood to predict response.

Methods: Patients with unresectable locally advanced or metastatic TNBC with ≤ 3 prior lines of therapy were enrolled. Treatment included 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. 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 and Cox regression model were used for analysis.

Results: A total of 22 patients were enrolled. The median age was 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 17 patients treated at DL -1 and were evaluable for response. The objective response rate (ORR) was 29.41% (95% CI: 10.31-55.96) with 1 complete response (CR) and 4 partial responses (PR). The clinical benefit rate (CBR ≥ 24 weeks) was 35.29% (95% CI: 14.21-61.67). ORR in patients without liver metastases was 55.56% (95% CI: 21.20 - 86.30), and CBR was 66.67% (95% CI: 29.93-92.51). There was no response observed in all 5 patients with liver metastases (Figure 1). The baseline mean CTC count was 1.3 cells, and CAML count was 8.9 cells/20 mL. Per 7.5 mL of blood, the baseline mean CTC count was 1.3 cells and 1.2 cells, while the CAML count was 8.9 cells and 8.1 cells for PD-L1 and p-ERK samples, respectively. Most samples had 0 CTCs present at baseline and during follow-up, so analysis of CTC was only explored as presence or absence of CTCs at baseline. The presence of CTCs in p-ERK at baseline was associated with worse PFS (p=0.04). Decreases in PD-L1 CAML count (p=0.02, Figure 4A), size (p=0.01, Figure 4B), and mean expression (p=0.03) were associated with better OS.

Conclusions: Pembrolizumab and binimetinib at 30 mg are safe with manageable toxicities. Promising activity was observed in patients without liver metastases. Baseline PD-L1 expression, early reduction in CAML count, size, and PD-L1 expression were significantly associated with overall survival, providing potential noninvasive biomarkers to predict response to this combination. Future larger clinical trials are warranted to further evaluate the predictive role of these biomarkers.

Trial Schema

Sample Size: 15-38 patients

Eligibility criteria

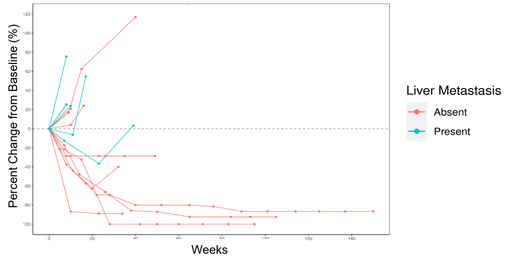
- Females ≥ 18 years
- ECOG PS ≤ 1
- ER/PR ≤10% and HER2 negative
- ≤3 prior lines of treatment in metastatic setting
- Measurable disease
- Adequate organ and cardiac functions

Table 1: Dose modification schema.

Dose Level	Dose	
	Pembrolizumab (mg)	Binimetinib (mg) daily
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

Outcomes

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



Dose Limiting Toxicities and Adverse Events

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

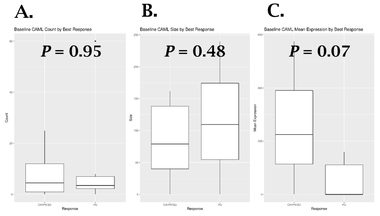
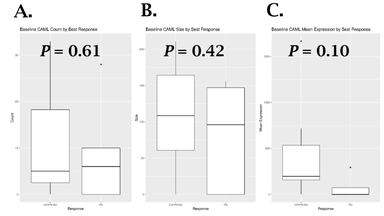
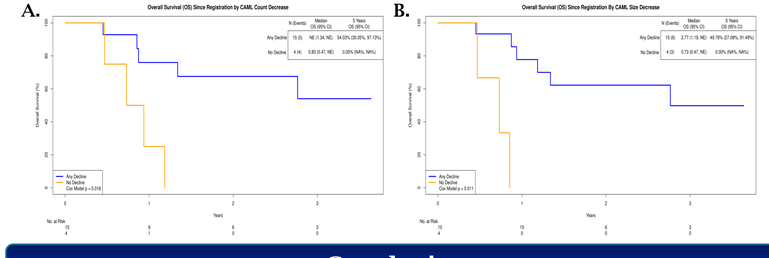


Figure 3: p-ERK boxplots among patients with clinical benefit (CR, PR, and SD ≥ 6 months) vs. PD according to: **A.** Baseline numbers of CAML cell count. **B.** Baseline CAML size **C.** Baseline CAML p-ERK expression.



CAML and Overall Survival

Figure 4: **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, early reduction in CAML count, size, and PD-L1 expression were significantly associated with subsequent responses and improvement in OS.
- Clinical trial information: NCT03106415