Research article

Eribulin Plus Pembrolizumab in Patients With Metastatic Triple-Negative Breast Cancer (ENHANCE 1): A Phase 1b/2 Study

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Running title: Phase 1b/2 Study of Eribulin + Pembrolizumab in mTNBC

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Translational Relevance:

This phase 1b/2 study assessed eribulin plus pembrolizumab as a potential treatment for patients with metastatic triple-negative breast cancer (mTNBC). The combination demonstrated activity in patients with mTNBC and 0 or 1-2 prior systemic therapies, and those with PD-L1+ or PD-L1− tumors. While the anticancer activity of the study drugs appeared most robust in patients with PD-L1+ tumors and no prior therapy, the study-drug combination also demonstrated promising anticancer activity in previously treated patients and those with PD-L1− tumors. The safety profile for the combination of eribulin plus pembrolizumab was comparable to historical data for the individual drugs with no new safety signals. These study results support further development of eribulin plus pembrolizumab as a potential first-line to third-line therapy for patients with mTNBC.
Abstract

Purpose
As monotherapies, eribulin (chemotherapy) and pembrolizumab (immunotherapy) have shown promise for patients with metastatic triple-negative breast cancer (mTNBC). This phase 1b/2 study examined eribulin plus pembrolizumab as a potential mTNBC treatment in first-line and later-line settings.

Experimental design
In this open-label, single-arm, phase 1b/2 study, eligible patients had mTNBC, measurable disease, and ≤2 prior systemic anticancer therapies in the metastatic setting. Patients were enrolled by number of prior systemic anticancer therapies (stratum 1: 0 vs stratum 2: 1–2) in the metastatic setting and further analyzed by tumor PD-L1-expression status. All patients received intravenous eribulin 1.4 mg/m² on day 1 and day 8, plus intravenous pembrolizumab 200 mg on day 1, of 21-day cycles. The primary objectives were the safety, tolerability, and objective response rate (ORR) of this combination.

Results
The study included 167 patients (phase 1b, n=7; phase 2, n=160). The most common treatment-emergent adverse events were fatigue (66%), nausea (58%), peripheral sensory neuropathy (41%), alopecia (40%), and constipation (37%). ORRs were 25.8% (95% CI: 15.8-38.0) for stratum 1 (n=66) and 21.8% (95% CI: 14.2-31.1) for stratum 2 (n=101). Patients with PD-L1+ tumors (combined positive score ≥1) had numerically higher ORR than those with PD-L1− tumors, particularly in stratum 1 (stratum 1: 34.5%
[95% CI: 17.9-54.3] vs 16.1% [95% CI: 5.5-33.7]; stratum 2, 24.4% [95% CI: 12.9-39.5] vs 18.2% [95% CI: 8.2-32.7]).

**Conclusion**

Eribulin plus pembrolizumab was generally well tolerated and showed promising antitumor activity in mTNBC. Efficacy outcomes appeared influenced by line of therapy and PD-L1 status.

ClinicalTrials.gov identifier: NCT02513472
INTRODUCTION

Triple-negative breast cancer (TNBC) is characterized by aggressive clinicopathologic features (eg, larger tumor size, higher grade tumors) (1), a poorer prognosis, earlier recurrence, and high death rates (1,2). While some combination therapies have recently shown promise in the first-line (1L) setting for metastatic TNBC (mTNBC), limited data are available for second-line and later (2L+) therapeutics. The median overall survival (OS) for patients with mTNBC treated in the 2L+ is 8 to 15 months (2). There is, therefore, an unmet clinical need to identify new and more effective treatments for improving the prognosis of patients with mTNBC, especially in the later-line setting.

Approximately 40% of TNBC tumors express programmed death-ligand 1 (PD-L1) (3). Binding of PD-L1 to programmed death receptor-1 (PD-1) may facilitate tumor immunity by suppressing cytotoxic T-cell responses (4). Pembrolizumab, a monoclonal anti-PD-1 antibody, is approved for the treatment of several advanced cancers (5). In a randomized, phase 3 study in patients with PD-L1–positive (PD-L1+) TNBC (KEYNOTE-355), patients with a combined positive score (CPS) ≥10, treated with 1L pembrolizumab plus chemotherapy had improved progression-free survival (PFS) compared with chemotherapy alone (9.7 vs 5.6 months; hazard ratio [HR] = 0.65, 95% CI: 0.49–0.86) (6,7). Patients with mTNBC who received pembrolizumab monotherapy as 2L+ (KEYNOTE-086 cohort A) achieved an objective response rate (ORR) of 5%, regardless of PD-L1 status (8). A randomized, phase 3 clinical trial comparing nab-paclitaxel with or without atezolizumab (an anti-PD-L1 antibody) in patients with previously untreated advanced TNBC revealed that the addition of atezolizumab...
significantly improved median PFS compared with chemotherapy alone in both the intent-to-treat population (7.2 vs 5.5 months, respectively, *P*=0.002) and in the PD-L1+ subgroup of patients (7.5 vs 5.0 months, *P*<0.001) (3), and was associated with a clinically relevant improvement in median OS in the PD-L1+ subgroup (21 vs 19 months) (9).

Eribulin mesylate (“eribulin”) is a synthetic analogue of halichondrin B that inhibits microtubule dynamics (10-12). Preclinical studies suggest that eribulin reverses epithelial-to-mesenchymal transition, induces vascular remodeling, and suppresses cancer cell migration and invasion (12). In the United States, eribulin is indicated for patients with metastatic breast cancer (MBC) following ≥2 prior lines of chemotherapy for metastatic disease (13). Prior therapy should include an anthracycline and a taxane in the adjuvant or metastatic setting (13). Eribulin monotherapy has shown promise for patients with mTNBC. In a retrospective subgroup analysis of a phase 3 clinical trial (Study 301), eribulin prolonged median OS versus capecitabine as first-to-third-line (1–3L) treatment for mTNBC (14.4 vs 9.4 months; 95% CI: 0.54–0.91; *P*=0.01) (14). In a pooled analysis from 2 large-scale, phase 3 MBC trials (Study 301 and EMBRACE), eribulin prolonged median OS versus capecitabine or treatment of physician’s choice (12.9 vs 8.2 months; HR: 0.74; *P*=0.006) in the mTNBC subgroup (15).

Both eribulin and pembrolizumab monotherapies have shown promising antitumor activity in patients with mTNBC (8,14-17). This open-label, single-arm, phase 1b/2 study
evaluated the safety and efficacy of eribulin plus pembrolizumab combination as 1–3L treatment in patients with mTNBC.

METHODS

Study design and procedures

This analysis (data cutoff date: July 31, 2019) of an ongoing, open-label, single-arm, phase 1b/2 study evaluated the safety and efficacy of eribulin plus pembrolizumab in patients with mTNBC (ClinicalTrials.gov identifier: NCT02513472) (18). The study was conducted across 18 sites in the United States, in accordance with the World Medical Association Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and the United States code of federal regulations. The protocol was approved by each Institutional Review Board. All participants provided written informed consent prior to study enrollment.

In the initial, safety run-in cohort (phase 1b), patients received intravenous eribulin 1.4 mg/m² on day 1 and day 8 of each 21-day cycle, plus intravenous pembrolizumab 200 mg on day 1 of each 21-day cycle. This dose became the recommended phase 2 dose if ≤1 patient had a dose-limiting toxicity (DLT) in the first cycle. If ≥2 patients experienced a DLT at this first dose level, then the dose of eribulin would be lowered to 1.1 mg/m². Patients in the phase 2 part of the study were enrolled into 2 strata based on the number of prior systemic therapies in the metastatic setting (stratum 1, no prior treatment or stratum 2, 1–2 prior treatments).
Patients

Eligible adults aged ≥18 years had mTNBC, as defined by the American Society of Clinical Oncology/College of American Pathologists (19,20), and measurable disease according to Response Evaluation Criteria In Solid Tumors version 1.1 (21), as assessed locally by investigators. Additional inclusion criteria were an Eastern Cooperative Oncology Group performance status of ≤1, life expectancy of ≥3 months, ≤2 prior systemic anticancer therapies in the metastatic setting, and adequate bone marrow, renal, and hepatic function. Patients were excluded if they had received prior treatment with eribulin or an agent targeting the PD-1–signaling pathway, or adjuvant therapy in the last 6 months. Additional exclusion criteria are detailed in the Online Resource Materials (online resource: Methods). Patients with previously treated stable brain metastasis were allowed (exclusions apply, see online resource: Methods).

Study endpoints and assessments

The primary objectives of the phase 1b portion of the study were to evaluate the safety and tolerability of eribulin plus pembrolizumab. All adverse events (AEs) were recorded and monitored. Treatment-emergent AEs (TEAEs) were graded using Common Terminology Criteria for Adverse Events (version 4.03) and characterized using the Medical Dictionary for Regulatory Activities (version 22.0). AEs were evaluated as related or unrelated to the study drugs by the investigator. DLTs were assessed in the first dosing cycle (further details in online resource: Methods). Treatment-related AEs
that resulted in study-drug discontinuations, or study-drug delays of ≥2 weeks, were also considered a DLT.

The primary efficacy endpoint of the phase 2 portion of the study was the ORR, defined as the percentage of patients with best overall response of complete response (CR) or partial response (PR) as assessed by independent imaging review. Secondary efficacy endpoints were PFS, OS, duration of response (DOR), and clinical benefit rate (CBR; the percentage of patients with CRs, PRs, and durable [≥24 weeks] stable disease [SD]). Subgroup analyses of efficacy by PD-L1 expression status (ie, positive or negative) were also performed.

Tumor assessments were performed at baseline, then every 9 weeks after the first dose, using computed tomography or magnetic resonance imaging scans. CRs or PRs were confirmed by a second examination performed ≥4 weeks after the first observation of response. Best overall response of SD required ≥1 posttreatment assessment that met the SD criteria >8 weeks after the start of treatment. For patients with a history of stable brain metastases, brain scans were repeated if clinically indicated at tumor assessment time points. PD-L1-expression status was determined using tissue samples collected at screening. PD-L1+ was defined as a CPS of ≥1 using an investigational version of the PD-L1 assay (IHC 22C3 pharmDx [Agilent, Carpinteria, CA, USA]) (22).
Statistical analyses

The study planned an initial run-in cohort of ≥6 patients in phase 1b and then a total sample size of approximately 170 patients, including 100 in stratum 2. With 100 patients, the 95% CI for ORR would be 16.9%–34.7% for an observed ORR of 25% based on the binomial distribution. Analyses were performed after all ongoing patients had completed ≥24 weeks of treatment or discontinued from treatment.

DLTs were assessed in the DLT evaluable set (patients who completed the first treatment cycle and had a safety evaluation in phase 1b). Safety, PFS, and OS were assessed in the full analysis set (all patients who received study drugs). Efficacy analyses on ORR and CBR were performed in the evaluable analysis set (all patients, including those in phase 1b who received the phase 2 dose, with evaluable tumor assessments at baseline and postbaseline, unless discontinued early or died).

The Clopper–Pearson method was used to calculate 95% CIs for ORR and CBR. Median PFS, OS, and DOR were estimated using Kaplan–Meier product limit method, and their corresponding 95% CIs were calculated using a generalized Brookmeyer and Crowley method. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Between September 21, 2015, and July 31, 2019 (data cutoff date), 167 patients were
enrolled and treated (phase 1b, n=7; phase 2, n=160). At the data cutoff date, 158 patients had discontinued and 9 remained on treatment. As noted in Table 1, 44% of patients had PD-L1+ tumors, 45% had PD-L1-negative (PD-L1−) tumors, and 11% had unknown tumor PD-L1 status. Overall, 66 (40%) patients were enrolled into stratum 1 (no prior systemic anticancer therapies for metastatic disease) and 101 (60%) patients were enrolled into stratum 2 (1–2 prior systemic anticancer therapies for metastatic disease) (Table 1).

**Recommended phase 2 dose**
None of the 7 patients in the phase 1b part of the study experienced a DLT. As such, the recommended phase 2 dose was eribulin 1.4 mg/m² on days 1 and 8 plus pembrolizumab 200 mg on day 1 of each 21-day cycle.

**Safety**
The 5 most common TEAEs (all grades) were fatigue (66%), nausea (58%), peripheral sensory neuropathy (41%), alopecia (40%), and constipation (37%) (Table 2). The only grade 3 or higher TEAE occurring in >10% of patients was neutropenia (26%) (Table 2). Overall, 21% of patients in this study received growth-factor support (filgrastim and/or pegfilgrastim). TEAEs led to study-drug discontinuation of eribulin, pembrolizumab, or both in 6%, 9%, and 11% of patients, respectively. Life-threatening treatment-related TEAEs were experienced by 2 patients (hemophagocytic lymphohistiocytosis and pyrexia, n=1; neutropenia, n=1). Overall, 15 patients experienced a fatal TEAE(s) but none of these deaths were considered treatment related (Supplemental Table 1).
TEAEs of clinical interest for pembrolizumab occurred in 43% of patients (Supplemental Table 2). The most commonly reported among these were hypothyroidism (18%), pneumonitis (11%), hyperthyroidism (8%), and infusion-related reaction (3%) (Supplemental Table 2). Immune-related TEAEs were of grade 3–4 severity in a minority of patients (12%; Supplemental Table 2).

**Efficacy**

Treatment with eribulin plus pembrolizumab resulted in an ORR of 23.4% (95% CI: 17.2–30.5; Table 3). CR and PR were observed in 8 (4.8%) and 31 (18.6%) patients, respectively. In addition, 53 patients (31.7%) had SD lasting ≥8 weeks (Table 3). The median DOR (in patients with CR or PR) was 8.3 months (95% CI: 6.5–22.2; Table 3). Subgroup analyses by prior lines of therapy indicated a numerically higher ORR among patients in stratum 1 who had no prior systemic therapy compared with those patients in stratum 2 who had 1–2 prior lines (25.8% [95% CI: 15.8–38.0] vs 21.8% [95% CI: 14.2–31.1], respectively) (Table 3). The overall median PFS was 4.1 months (95% CI: 3.5–4.2), which was similar across strata (Table 3). The overall median OS was 16.1 months (95% CI: 13.3–18.5), with a median OS of 17.4 months (95% CI: 13.2–21.0) for stratum 1 versus 15.5 months (95% CI: 12.5–18.7) for stratum 2 (Table 3).

Subgroup analysis by PD-L1 tumor-expression status indicated better efficacy outcomes in patients with PD-L1+ tumors versus those with PD-L1− tumors (ORR, 28.4% [95% CI: 18.5–40.1] vs 17.3% [95% CI: 9.6–27.8]; PFS, 4.2 months [95% CI: 3.5–
6.1] vs 3.9 months [95% CI: 2.3–4.4]; and OS, 16.3 months [95% CI: 12.7–24.2] vs 15.2 months [95% CI: 13.3–18.0], respectively). Most patients showed a decrease in target lesion size regardless of PD-L1-expression status (Figure 1A and 1B).

Efficacy outcomes stratified by both stratum and PD-L1-expression status are shown in Table 4. Among patients in stratum 1, the median PFS was higher for patients who had PD-L1+ tumors compared with those who had PD-L1− tumors (6.1 months [95% CI: 4.1–10.2] vs 3.5 months [95% CI: 2.0–4.2], respectively; Figure 2A). In contrast, patients in stratum 2 had similar median PFS results, regardless of PD-L1-expression status (Figure 2B). Patients with PD-L1+ tumors in stratum 1 had a median OS that was numerically longer than the median OS among those with PD-L1− tumors (21.0 months [95% CI: 8.3–29.0] vs 15.2 months [95% CI: 12.8–19.4], respectively; Figure 2C); however, a trend toward longer OS was not observed in patients with PD-L1+ tumors in stratum 2 (Figure 2D).

To further assess PD-L1 tumor-expression status as an indicator of greater anticancer activity of eribulin when combined with pembrolizumab, we compared efficacy outcomes for patients with PD-L1+ tumors based on an immunohistochemistry-staining CPS cutoff of either 1 (CPS≥1) or 10 (CPS≥10). In the 1L setting (stratum 1), the ORR for patients with PD-L1+ tumors was higher than for those with PD-L1− tumors, regardless of whether the CPS cutoff was 1 or 10 (CPS≥1, ORRs 34.5% vs 16.1%; CPS≥10, ORRs 30.8% vs 23.4%, respectively; Supplemental Table 3A). In the 2–3L setting (stratum 2), the ORR for patients with PD-L1+ tumors was also numerically higher versus those
with PD-L1− tumors by both CPS cutoffs (CPS≥1, ORR 24.4% vs 18.2%; CPS≥10, ORR 23.8% vs 20.6%, respectively) (**Supplemental Table 3B**).

**DISCUSSION**

In this analysis of an ongoing open-label, single-arm, phase 1b/2 study, the combination of eribulin plus pembrolizumab was generally well tolerated and showed encouraging antitumor activity as 1–3L therapy for patients with mTNBC, resulting in an ORR of 23.4%. The safety profile of eribulin plus pembrolizumab was similar to what was seen in previous monotherapy studies (16,23,24). Neutropenia was the only TEAE of grade ≥3 occurring in >10% of patients. The rate of neutropenia observed in this study (all grades, 36%; grade 3/4, 26%) compared favorably to that observed in the pivotal EMBRACE study (all grades, 52%; grade 3/4, 45%) (23).

Acknowledging the limitations of cross-study comparisons, in this current study, patients with mTNBC who received eribulin plus pembrolizumab in the 1L setting (stratum 1) achieved an ORR of 26% (95% CI: 16–38) versus an ORR of 21% (95% CI: 14–31) for patients treated with pembrolizumab monotherapy (KEYNOTE-086 cohort B) (17) and an ORR of 10% for patients receiving eribulin monotherapy (2). Moreover, patients treated in the 2–3 L setting (stratum 2) in the current study had an ORR of 22% (95% CI: 14–31), which compares favorably to the ORRs of 5% to 12% observed in the 2L+ for pembrolizumab monotherapy ([KEYNOTE-086 cohort A] (8); [KEYNOTE-119] (25)).

Although no ORR for eribulin monotherapy in patients with mTNBC has been reported for the 2L+ setting, the median PFS and median OS observed in the current study for
patients with mTNBC who were treated with eribulin plus pembrolizumab compared favorably to historical reports for eribulin monotherapy (1-2L+, PFS: 4.1 months in this study vs 2.8 months (15); OS: 16.1 months in this study vs 12.9 months (15)). Similarly, higher median PFS and OS were observed in patients with PD-L1+ mTNBC in this study versus pembrolizumab monotherapy (KEYNOTE-012; 1-2L+, PFS: 4.2 vs 1.9 months, OS: 16.3 vs 11.2 months, respectively, (16)). These results suggest that eribulin plus pembrolizumab has promising antitumor activity in patients with mTNBC and that this activity appears greater than in historical reports of either agent alone.

Limitations of the current study are typical of an early-phase study: this is a nonrandomized, single-arm clinical trial, and the patient population in this study was rather heterogeneous with regard to the number of prior systemic therapies (0–2) and tumor PD-L1-expression status. The lack of a direct comparator arm with immunotherapy or eribulin alone limits interpretation, especially as it has been suggested that immunotherapy may stabilize disease but later impact OS. Additionally, this study was not powered to assess efficacy based on PD-L1 status. Further study is warranted to delineate which patients with mTNBC might derive the most benefit from this treatment combination.

A subgroup analysis of patients with human epidermal growth factor receptor-2-negative MBC treated with eribulin, showed that receiving eribulin in the earlier setting (1L) resulted in higher ORRs compared with later-line (2–3L) therapy (26% vs 8%, respectively) (26). Interestingly, while the ORR in this study was higher in the earlier-line
setting (stratum 1, 26%), much of the antitumor benefit conferred by eribulin plus pembrolizumab was still retained in the later-line setting (stratum 2, 22%). Moreover, previous studies indicated that patients who had PD-L1+ mTNBC and who were treated with pembrolizumab monotherapy had an ORR of 21% for 1L versus 5% in 2L+ use (8,17). In this study, patients with PD-L1+ mTNBC achieved an ORR of 34.5% in 1L (stratum 1) compared with 24.4% in the 2–3L setting (stratum 2), which further demonstrates that this combination therapy of eribulin plus pembrolizumab may have promising antitumor efficacy even in the later-line settings.

Consistent with results from a previous study (9), patients with mTNBC, no prior systemic anticancer therapy, and PD-L1+ tumors in this study had the most robust response to the combination of immunotherapy and chemotherapy (median OS, 21 months). Based on both CPS cutoffs (≥1 and ≥10), the ORR was higher in patients with PD-L1+ tumors versus those with PD-L1- tumors in both stratum 1 and stratum 2; the benefit appears to be more pronounced for patients with PD-L1+ tumors in the 1L setting (stratum 1). Interestingly, among patients with evaluable PD-L1 status, based on a cutoff CPS of ≥1, all 6 patients who had a CR had PD-L1+ tumors. Whereas, only 2 of 6 patients with a CR had PD-L1+ tumors based on a cutoff CPS of ≥10 (Supplemental Table 3). While ORR was higher among the PD-L1+ cohort, how we optimally select patients who are likely to benefit from eribulin plus pembrolizumab therapy requires further investigation.
Atezolizumab in combination with paclitaxel protein-bound was approved by the FDA for patients with mTNBC and PD-L1+ tumors (defined as PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area) (27). Additionally, the FDA recently approved pembrolizumab in combination with chemotherapy (ie, paclitaxel, paclitaxel protein-bound, or gemcitabine plus carboplatin) for the treatment of patients with mTNBC whose tumors express PD-L1 (CPS≥10) (5). Given these recent FDA approvals, many patients with mTNBC and PD-L1+ may be treated with immunotherapy plus chemotherapy in the 1L setting. It should be noted that those patients with PD-L1+ tumors in this study derived a clinical benefit in the 2L+ setting (ORR, 24.4%). Importantly, those patients with PD-L1− tumors in this study also derived benefit from the combination of eribulin plus pembrolizumab in both the 1L and 2L+ settings (ORRs, 16.1% to 18.2%). Thus, while the immediate clinical utility of the study-drug combination requires further investigation, the combination of eribulin plus pembrolizumab may be a potential treatment option for those patients with mTNBC and PD-L1+ tumors who are either treatment-naïve or have experienced disease progression on a previous line of therapy, and/or those patients with mTNBC who have PD-L1− tumors.

Eribulin has well-documented efficacy in the 2L+ setting for patients with MBC, including mTNBC (13-15). However, a recent clinical study of patients with pretreated (2−3L) mTNBC (KEYNOTE-119) failed to prove superiority of pembrolizumab versus standard chemotherapy regimens (including eribulin) (25). In the current study, eribulin plus pembrolizumab shows promising antitumor activity for patients with mTNBC in the 2−3L
setting. However, caution is warranted in interpreting these data as it remains to be determined whether the addition of immunotherapy to standard chemotherapy in the 2–3L setting confers a greater benefit for patients with mTNBC than chemotherapy alone. Nonetheless, the median OS of 15.5 months and median PFS of 4.1 months observed in this study for patients with mTNBC and treated with eribulin plus pembrolizumab in the 2–3L setting is encouraging and warrants further investigation.

**Conclusion**

Eribulin plus pembrolizumab was generally well tolerated with a predictable safety profile in patients with mTNBC. The study-drug combination showed promising antitumor activity in the 1-3L setting. While the activity appeared enhanced in patients with PD-L1+ tumors, the study-drug combination also demonstrated promising antitumor activity in patients with PD-L1− tumors. These results support further clinical development of eribulin plus pembrolizumab as a potential antitumor strategy for patients with mTNBC.
Compliance with ethical standards / Research involving human participants /

Ethical approval:
All experiments comply with the current laws of the country in which they were performed.
Informed consent: Informed consent was obtained from all individual participants included in the study.
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (IRB; Dana Farber Cancer Institute IRB, Organization number: IORG0000035IRB; federal-wide assurance number: FWA00001121) and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
This article does not contain any studies with animals performed by any of the authors.

Data availability: The data will not be available for sharing at this time as the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.
REFERENCES


TABLES

Table 1. Patient demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eribulin + Pembrolizumab</th>
<th>Phase 1b (n = 7)</th>
<th>Phase 2 (n = 160)</th>
<th>Total (N = 167)</th>
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<td>Age, years</td>
<td>Median (range)</td>
<td>54 (44–65)</td>
<td>56 (32–88)</td>
<td>56 (32–88)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>7 (100)</td>
<td>160 (100)</td>
<td>167 (100)</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>7 (100)</td>
<td>134 (83.8)</td>
<td>141 (84.4)</td>
</tr>
<tr>
<td></td>
<td>Black or African American</td>
<td>0</td>
<td>19 (11.9)</td>
<td>19 (11.4)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>0</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0</td>
<td>6 (3.8)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>0</td>
<td>4 (57.1)</td>
<td>102 (63.8)</td>
<td>106 (63.5)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3 (42.9)</td>
<td>57 (35.6)</td>
<td>60 (35.9)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>PD-L1 expression status*, n (%)</td>
<td>Positive</td>
<td>3 (42.9)</td>
<td>71 (44.4)</td>
<td>74 (44.3)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>2 (28.6)</td>
<td>73 (45.6)</td>
<td>75 (44.9)</td>
</tr>
<tr>
<td></td>
<td>Not available</td>
<td>2 (28.6)</td>
<td>16 (10.0)</td>
<td>18 (10.8)</td>
</tr>
<tr>
<td>Phase 2 enrollment strata, n (%)</td>
<td>Stratum 1</td>
<td>3 (42.9)</td>
<td>63 (39.4)</td>
<td>66 (39.5)</td>
</tr>
<tr>
<td></td>
<td>Stratum 2</td>
<td>4 (57.1)</td>
<td>97 (60.6)</td>
<td>101 (60.5)</td>
</tr>
</tbody>
</table>

*aTumor samples with evaluable PD-L1 status were available from 149 patients, of which 63% were primary tumor samples and 37% were metastatic. PD-L1 status was considered positive if the CPS was ≥1 and negative if CPS was <1.

bNo prior systemic anticancer therapy for metastatic disease.

c1–2 Prior systemic anticancer therapies for metastatic disease.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1.
Table 2. Summary of TEAEs that occurred in ≥ 10% of patients.

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Eribulin + Pembrolizumab (N = 167)</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>110 (65.9)</td>
<td>12 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>96 (57.5)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>69 (41.3)</td>
<td>12 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>66 (39.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>61 (36.5)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60 (35.9)</td>
<td>44 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>54 (32.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>53 (31.7)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52 (31.1)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51 (30.5)</td>
<td>6 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>47 (28.1)</td>
<td>10 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>46 (27.5)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (26.9)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>41 (24.6)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>41 (24.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>41 (24.6)</td>
<td>5 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32 (19.2)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31 (18.6)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>30 (18.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>30 (18.0)</td>
<td>6 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>28 (16.8)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>28 (16.8)</td>
<td>9 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>27 (16.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>27 (16.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>26 (15.6)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>25 (15.0)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (14.4)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>24 (14.4)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22 (13.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>21 (12.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>21 (12.6)</td>
<td>13 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>21 (12.6)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>21 (12.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>20 (12.0)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>20 (12.0)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>19 (11.4)</td>
<td>9 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>18 (10.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>18 (10.8)</td>
<td>9 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>18 (10.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>18 (10.8)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>18 (10.8)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>17 (10.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (9.6)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Adverse event terms were coded using Medical Dictionary for Drug Regulatory Affairs version 22.0 per protocol and were graded using Common Terminology Criteria for Adverse Events version 4.03. Patients who experienced different grades for a single preferred term were counted only once per preferred term using the highest severity grade.

TEAE, treatment-emergent adverse event.
Table 3. Summary of tumor responses overall, and by prior systemic anticancer therapy strata.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stratum 1 (n = 66)</th>
<th>Stratum 2 (n = 101)</th>
<th>Total (N = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*, n (%)</td>
<td>17 (25.8)</td>
<td>22 (21.8)</td>
<td>39 (23.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.8–38.0</td>
<td>14.2–31.1</td>
<td>17.2–30.5</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>5 (7.6)</td>
<td>3 (3.0)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>12 (18.2)</td>
<td>19 (18.8)</td>
<td>31 (18.6)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>24 (36.4)</td>
<td>29 (28.7)</td>
<td>53 (31.7)</td>
</tr>
<tr>
<td>mOS, months</td>
<td>17.4</td>
<td>15.5</td>
<td>16.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.2–21.0</td>
<td>12.5–18.7</td>
<td>13.3–18.5</td>
</tr>
<tr>
<td>mPFS, months</td>
<td>4.2</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.5–5.5</td>
<td>2.3–4.4</td>
<td>3.5–4.2</td>
</tr>
<tr>
<td>mDOR*,d, months</td>
<td>9.0</td>
<td>8.6</td>
<td>8.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.2–22.2</td>
<td>6.2–25.</td>
<td>6.5–22.2</td>
</tr>
</tbody>
</table>

*aORR = CR + PR.
*b95% CIs were calculated by Clopper–Pearson method.
*cMedians for PFS, OS, and DOR were estimated using the Kaplan–Meier method and their corresponding 95% CIs were calculated using a generalized Brookmeyer and Crowley method.
*dIn patients with confirmed CR or PR.
CI, confidence interval; CR, complete response; DOR, duration of response; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
Table 4. Summary of tumor responses stratified by both prior systemic anticancer therapy strata and PD-L1-expression status.

<table>
<thead>
<tr>
<th>Eribulin + Pembrolizumab</th>
<th>PD-L1+ Stratum 1 (n = 29)</th>
<th>PD-L1− Stratum 1 (n = 31)</th>
<th>PD-L1+ Stratum 2 (n = 45)</th>
<th>PD-L1− Stratum 2 (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR ( ^{b} ), %</td>
<td>34.5</td>
<td>16.1</td>
<td>24.4</td>
<td>18.2</td>
</tr>
<tr>
<td>95% CI ( ^{b} )</td>
<td>17.9–54.3</td>
<td>5.5–33.7</td>
<td>12.9–39.5</td>
<td>8.2–32.7</td>
</tr>
<tr>
<td>mOS ( ^{c} ), months</td>
<td>21.0</td>
<td>15.2</td>
<td>14.0</td>
<td>15.5</td>
</tr>
<tr>
<td>95% CI ( ^{c} )</td>
<td>8.3–29.0</td>
<td>12.8–19.4</td>
<td>11.0–19.4</td>
<td>12.4–18.7</td>
</tr>
<tr>
<td>mPFS ( ^{c} ), months</td>
<td>6.1</td>
<td>3.5</td>
<td>4.1</td>
<td>3.9</td>
</tr>
<tr>
<td>95% CI ( ^{d} )</td>
<td>4.1–10.2</td>
<td>2.0–4.2</td>
<td>2.1–4.8</td>
<td>2.3–6.3</td>
</tr>
<tr>
<td>mDOR ( ^{c,d} ), months</td>
<td>8.3</td>
<td>15.2</td>
<td>8.2</td>
<td>8.6</td>
</tr>
<tr>
<td>95% CIs</td>
<td>3.2–NE</td>
<td>6.5–22.2</td>
<td>5.1–25.1</td>
<td>3.5–13.2</td>
</tr>
</tbody>
</table>

\(^{a}\)Excludes 18 patients who had unknown tumor PD-L1 status.

\(^{b}\)ORR = CR + PR; 95% CIs were calculated by Clopper–Pearson method.

\(^{c}\)Medians for PFS, OS, and DOR were estimated using the Kaplan–Meier method and their corresponding 95% CIs were calculated using a generalized Brookmeyer and Crowley method.

\(^{d}\)In patients with confirmed CR or PR.

CI, confidence interval; CR, complete response; DOR, duration of response; m, median; NE, not estimable; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response.
FIGURES

**Fig. 1** Maximum percentage change from baseline to postbaseline nadir in total sum of target lesion diameters in stratum 1 (A) and stratum 2 (B)

\(^a\)This analysis included evaluable patients with both baseline and at least 1 postbaseline target lesion assessment.

Stratum 1: no prior systemic anticancer therapy for metastatic disease.

Stratum 2: 1-2 prior systemic anticancer therapies for metastatic disease

PD-L1, programmed death-ligand 1.

**Fig. 2** Kaplan–Meier curves of progression-free survival (A and B) and overall survival (C and D) in stratum 1 and stratum 2, respectively

Stratum 1: no prior systemic anticancer therapy for metastatic disease.

Stratum 2: 1–2 prior systemic anticancer therapies for metastatic disease.

CI, confidence interval; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
A. Stratum 1

B. Stratum 2

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Figure 2

A  
PD-L1 Positive  
Median PFS (95% CI), months = 6.1 (4.1–10.2)  
PD-L1 Negative  
Median PFS (95% CI), months = 3.5 (2.0–4.2)

B  
PD-L1 Positive  
Median PFS (95% CI), months = 4.1 (2.1–4.8)  
PD-L1 Negative  
Median PFS (95% CI), months = 3.9 (2.3–6.3)

C  
PD-L1 Positive  
Median OS (95% CI), months = 21.0 (8.3–29.0)  
PD-L1 Negative  
Median OS (95% CI), months = 15.2 (12.8–19.4)

D  
PD-L1 Positive  
Median OS (95% CI), months = 14.0 (11.0–19.4)  
PD-L1 Negative  
Median OS (95% CI), months = 15.5 (12.4–18.7)
Clinical Cancer Research

Eribulin Plus Pembrolizumab in Patients With Metastatic Triple-Negative Breast Cancer (ENHANCE 1): A Phase 1b/2 Study

Sara M Tolaney, Kevin Kalinsky, Virginia Kaklamani, et al.

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