BACKGROUND

Metastatic breast cancer (MBC) remains incurable, and few cytotoxic agents prolong overall survival (OS). Several cytotoxic therapies are approved for treating patients with MBC, and current clinical guidelines generally recommend sequential monotherapies, but not a preferred sequence of administration.1

Eribulin, a synthetic analogue of halichondrin B, inhibits microtubule growth, blocks cell-cycle progression, and induces apoptosis of tumor cells.2 In preclinical studies, eribulin induced vascular remodeling and increased tumor perfusion;3 similarly, noncytotoxic effects have been demonstrated clinically.4 Eribulin mesylate (eribulin) is approved in the United States for the treatment of patients with MBC after ≥2 prior chemotherapies for metastatic disease; additionally, it is approved in the European Union for locally advanced/MBC patients with ≥1 prior chemotherapies for advanced disease. Prior treatments should include a taxane and an anthracycline.

Two randomized, open-label, phase 3 trials (Study 305/EMBRACE and Study 301 [ClinicalTrials.gov: NCT00388726 and NCT00337103, respectively]) assessed the efficacy and safety of eribulin in pretreated patients with locally recurrent/MBC.5,6 In a previous pooled analysis of these 2 studies,7 median OS was 15.2 months (eribulin) versus 12.8 months (control arm; hazard ratio [HR], 0.85; 95% confidence interval [CI] 0.77-0.95; P = .003); OS favored eribulin in all analyzed subgroups including human epidermal growth factor receptor 2 (HER2)-negative disease (HR, 0.82; P = .002), and triple-negative disease (HR, 0.74; P = .006). These findings were supported by another pooled analysis in patients with ≥1 prior chemotherapy regimens.8 Here, we report an exploratory, post hoc, pooled subgroup analysis of the influence of the number of prior chemotherapy regimens on OS using data from EMBRACE and Study 301.

METHODS

Both trials enrolled women aged ≥18 years, with previously treated locally recurrent/MBC.5,6 OS was compared between eribulin and treatment of physician’s choice [TPC] (EMBRACE) or capecitabine (Study 301). Patients with ≤3 prior chemotherapies for locally advanced/MBC had longer median OS with eribulin (15.3 months) versus control (13.2 months; hazard ratio, 0.858; P = .01).

KEYWORDS
advanced breast cancer, efficacy analysis, eribulin, overall survival, safety
therapy regimens for locally advanced/MBC (eribulin, n = 391; TPC, nominally significantly different in patients with ≤3 prior chemo 11.7 versus 10.0 months, respectively; this improvement was again trend was emphasized in those patients with 0-3 prior lines of therapy regimens for locally advanced/MBC (15.3 vs 13.2 months, P = .039; Table 1). Median OS was adjusted by study (defined in Twelves et al, 2014) and P-values were estimated by stratified log-rank test. An exploratory comparative analysis of OS grouped by ≤3 versus >3 prior treatments, and by individual number of prior lines of treatment (ie, 0, 1, 2, 3, 4, 5, and 6), for locally advanced/MBC was completed using data pooled from both studies except as noted (ie, data on ≥5 prior lines of therapy are from EMBRACE only). A pooled analysis of safety data was not possible because the studies used different versions of the Medical Dictionary for Regulatory Activities (version 14.1 for Study 301).

3 | RESULTS

3.1 | Patients

In EMBRACE, patients were randomized 2:1 to receive eribulin (1.4 mg/m² [equivalent to 1.23 mg/m² when expressed as a free base] intravenously on days 1 and 8 every 21 days; n = 254). In Study 301, 554 patients were randomized to receive eribulin and 548 to receive capecitabine. Patient characteristics have been previously reported. Almost all (99%) patients had received prior anthracycline and taxane therapy. In EMBRACE, the median number of prior chemotherapy regimens for locally advanced/MBC was 3 (with approximately one-quarter having >3 and three-quarters having ≤3). In Study 301, only 1 patient (a protocol deviation) received >3 prior chemotherapy regimens for locally advanced/MBC.

3.2 | Post hoc efficacy analysis

This subgroup analysis demonstrated a nominally significant difference in median OS with eribulin treatment (ITT group, n = 945) versus control (n = 727) in patients who received ≤3 prior chemotherapy regimens for locally advanced/MBC (15.3 vs 13.2 months, respectively; HR, 0.858; P = .01; Table 1, Figure 1). In EMBRACE, patients with >3 prior regimens for locally advanced/MBC had a median OS in the eribulin (n = 117) versus TPC (n = 73) ITT groups of 11.7 versus 10.0 months, respectively; this improvement was again nominally significantly different in patients with ≤3 prior chemotherapy regimens for locally advanced/MBC (eribulin, n = 391; TPC, n = 180; 13.3 vs 10.7 months, respectively; P = .039; Table 1).

Additional exploratory pooled post hoc analysis for patients receiving 0-6 prior lines of therapy showed a trend for higher OS in patients treated with eribulin compared with control (Table 2), and this trend was emphasized in those patients with 0-3 prior lines of therapy compared with those who had been more heavily pretreated.

| Parameter | Eribulin | Control | Median survival difference |
|-----------|----------|---------|----------------------------|
| ≤3 Prior chemotherapy regimens (EMBRACE) | | |
| n | 391 | 180 |
| Median overall survival | 13.3 mo | 10.7 mo |
| 95% CI, days | 404 d | 326 d |
| P-value | .039 |
| Hazard ratio (eribulin vs TPC) | 0.774 |
| 95% CI | 0.606-0.988 |

| Parameter | Patients randomized to receive | Median survival difference |
|-----------|-------------------------------|-----------------------------|
| >3 Prior chemotherapy regimens (EMBRACE) | | |
| n | 117 | 73 |
| Median overall survival | 11.7 mo | 10.0 mo |
| 95% CI, days | 355 d | 304 d |
| P-value | .607 |
| Hazard ratio (eribulin vs TPC) | 0.899 |
| 95% CI | 0.600-1.348 |

Note: CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; TPC, treatment of physician's choice. *A conversion factor of 30.4375 was used to convert number of days into months.
**Based on stratified log-rank test, for Study 301, strata included HER2/neu status (clinical database) and geographical region; for analyses of EMBRACE, strata included HER2/neu status (clinical database), geographical region, and prior capecitabine treatment; for pooled analyses, strata included study, geographical region, prior capecitabine use, and HER2/neu status.
*Hazard ratios and the corresponding 95% CI were generated based on a Cox regression model with stratification factors of: HER2/neu status (clinical database) and geographical region; for analyses of EMBRACE, strata included HER2/neu status (clinical database), geographical region, and prior capecitabine treatment; for pooled analyses, strata included study, geographical region, prior capecitabine use, and HER2/neu status.
*Hazard ratios and the corresponding 95% CI were generated based on the Cox regression model, with stratification factors of: study, geographical region (North America/Western Europe/Australia, Latin America/South Africa, Eastern Europe, Asia), prior capecitabine use, and HER2/neu status.
*The control treatments were TPC for EMBRACE and capecitabine for Study 301.
3.3 | Safety

The number of prior chemotherapies appeared not to affect the safety of eribulin in EMBRACE. Although neutropenia and asthenia/fatigue rates were higher with eribulin treatment compared with control, the incidences of both were similar regardless of whether patients had ≤3 or >3 prior regimens (neutropenia, 51.7% for both subgroups; asthenia/fatigue, 53.2% vs 55.1% for ≤3 vs >3, respectively). For patients in the TPC group, the incidences of neutropenia (30.9% vs 25%) and asthenia/fatigue (40.4% vs 36.8%) were numerically higher in patients having ≤3 prior regimens compared with those having >3 prior regimens.

4 | DISCUSSION

This exploratory subgroup analysis of EMBRACE and Study 301 shows that the OS benefit conferred by eribulin over TPC/capecitabine is predominantly seen in patients who had fewer prior regimens (≤3) for locally advanced/MBC with a median OS benefit of 2.1 months. This difference in OS was also observed in EMBRACE alone (≤3 prior regimens, 2.6 months; >3 prior regimens, 1.7 months); the number of prior regimens appeared not to affect the safety of eribulin.

The pooled subgroup analysis by number of prior regimens showed that eribulin conferred an OS benefit of 1.2, 1.6, and 1.5 months for patients treated with 0, 1, or 2 prior regimens for locally advanced/MBC, respectively, with a 5.0-month OS benefit observed for patients with 3 prior regimens (HR, 0.608; P = .0098). Patient numbers were, however, not large enough to draw conclusions regarding the relative efficacy of eribulin in patients who had received 0, 1, 2, or 3 prior chemotherapy regimens. Benefit from eribulin appeared reduced in more heavily pretreated patients, but patient numbers were small, especially for those with 6 prior regimens (9 patients).

The greater benefits of eribulin when used in earlier-line settings are supported by other studies. In a post hoc subgroup analysis of patients (n = 392) in Study 301, treated in the second-line setting, median OS was longer in those with HER2-negative MBC receiving eribulin versus capecitabine (16.1 vs 13.5 months, respectively; HR, 0.77; P = .026). A large-scale clinical study in patients with advanced/MBC, randomized to receive eribulin or vinorelbine, also achieved its primary end point of prolonged progression-free survival (HR, 0.80; P = .036). Again, the benefit in progression-free survival from eribulin was seen in patients who had received fewer prior regimens for metastatic disease (≤2; HR, 0.69; 95% CI 0.53-0.91) but not in those who had been more heavily pretreated (>2; HR, 0.91; 95% CI 0.66-1.25).
Despite the post hoc nature and small sample size (especially for patients with >3 prior regimens for locally advanced/MBC), this study suggests there may be potential benefit in using eribulin to treat patients with locally advanced/MBC sooner rather than later. As there is considerable attrition in patients receiving successive lines of therapy, it is appropriate that treatments demonstrating the greatest benefit are used earlier for patients with locally advanced/MBC.

## 5 | CONCLUSIONS

Patients who have received 3 or fewer regimens for locally advanced/MBC showed an improvement in OS if treated with eribulin rather than with TPC/capecitabine. Clinicians should consider the use of eribulin as indicated and available for the treatment of such patients.

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