Eribulin Monotherapy Versus Treatment of Physician’s Choice in Patients with Metastatic Breast Cancer (EMBRACE): A Phase III Open-label Randomised Study


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For Halaven™ prescribing information see [slide 29](#)
An Unmet Need in Metastatic Breast Cancer

- The prognosis for women with metastatic breast cancer (MBC) remains poor and there is no consensus regarding the optimal standard of care for women requiring therapy after taxanes and anthracyclines\(^1\)\(^-\)\(^3\)
  - As these agents are increasingly used in the neo- and adjuvant settings, many patients either do not respond, or become resistant to them\(^4\)\(^,\)\(^5\)

- Until recently capecitabine was the only chemotherapy specifically approved as monotherapy in Europe for MBC resistant to both an anthracycline and a taxane,\(^6\) resulting in an unmet need for well-tolerated treatment options for these patients

- With the approval of Halaven\(^\text{TM}\) (eribulin), women with locally advanced or MBC who have progressed after receiving at least two chemotherapeutic regimens for advanced disease and have previously received both an anthracycline and a taxane (unless they were not suitable for these treatments) have a well-tolerated treatment option which extends overall survival\(^7\)\(^,\)\(^8\)

Eribulin is a Non-taxane Microtubule Targeted Chemotherapy

- Eribulin is a non-taxane inhibitor of microtubule dynamics, with a mode of action distinct from other tubulin-targeting agents\textsuperscript{1-5}
  - It inhibits mitotic spindle formation by irreversibly binding to microtubules by an end poisoning mechanism thereby inhibiting the microtubule growth phase without affecting the shortening phase, preventing cell proliferation and increasing apoptosis

- Preclinical studies demonstrated that eribulin has activity against various taxane-resistant tumour cell lines\textsuperscript{6}

The Eribulin Binding Site Differs From Other Microtubule Inhibitors

Eribulin

- Binds to (+) ends of microtubules
- Inhibits only growth

Vinblastine

- Binds to (+) ends and along sides of microtubules
- Inhibit microtubule growth and shortening

Paclitaxel, docetaxel and epothilone B

- Bind to subunits inside of microtubules

Phase II Studies Confirmed Activity of Eribulin in Patients with Heavily Pre-treated MBC

- Phase I studies suggested that eribulin was active with a predictable side effect profile\(^1-4\)

201 Study\(^5\) (N=103):
Prior taxane & anthracycline\(^*\)

211 Study\(^6\) (N=299):
Prior taxane, anthracycline, & capecitabine\(^*\)

Primary Endpoint:
- ORR with independent review

Secondary Endpoints:
- DOR, PFS, OS, AEs

- ORR: 11.5%
- Median DOR: 5.6 months
- Median PFS: 2.6 months
  - 6-month PFS 25.9% (95% CI, 15.5, 36.3)
- Median OS: 9 months (range 15–826 days)
  - 6-month survival 67.8% (95% CI, 58.0, 77.6)
  - 1-year survival 45.7% (95% CI, 35.2, 56.2)

- ORR: 9.3%
- Median DOR: 4.1 months
- Median PFS: 2.6 months
  - 6-month PFS 15.6% (95% CI, 10.7, 20.5)
- Median OS: 10.4 months
  - 6-month survival 72.3% (95% CI, 66.9, 77.6)

AEs, adverse events; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

* MBC patients with progression of disease ≤6 months of last chemotherapy and, if present, pre-existing neuropathy ≤ grade 2.

EMBRACE Compared Eribulin with ‘Real-life’ Treatment Choices

**Global, open-label, randomised, phase III study**

**Patients (N=762)**
- Locally recurrent or MBC
- 2–5 prior chemotherapies
  - ≥ 2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤ 6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG PS ≤ 2

**Eribulin mesylate (n=508)**
1.4 mg/m\(^2\)* IV over 2–5 minutes on Day 1,8 q21 days

**RANDOMISATION 2:1***

**TPC (n=254):**
- Any monotherapy (cytotoxic, hormonal, biological)**; or
- Palliative treatment; or
- Radiotherapy

**Primary Endpoint:**
- OS

**Secondary Endpoints:**
- PFS
- ORR
- Safety

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ECOG PS, Eastern Cooperative Oncology Group performance status

- *Equivalent to 1.23 mg/m\(^2\) eribulin
- **Approved for treatment of cancer and administered according to local practice
- ***Patients were stratified by geographic region, prior capecitabine treatment, and human epidermal growth factor receptor 2 (HER2/neu) status before randomisation
- Patients were treated with eribulin mesylate or TPC until disease progression, unacceptable toxicity, patient/physician request to discontinue or serious protocol non-compliance
- Exploratory subgroups: Hormone receptor expression status (ER, PgR, HER2, triple-negative); number of organs involved; sites of disease

ER, oestrogen receptor; HER2/neu, human epidermal growth factor receptor 2; PgR, progesterone receptor; TPC, treatment of physician’s choice

The Primary Endpoint of EMBRACE was Overall Survival

**Overall survival**
- Primary analysis planned at 411 (50%) events (but actually took place at 422 (55%) events)
  - Updated analysis conducted at 589 (77%) events
- Determined from date of randomisation to death, or last date known alive (censored)
- Stratified log-rank by randomisation parameters (ITT population)

**Progression-free survival**
- Protocol pre-specified
- Assessed from randomisation to the earliest date of progression or death (or censored as per OS)
- Stratified log-rank (ITT and PP population)

**Tumour response**
- ORR and DOR were protocol pre-specified, CBR was not
- Tumour response was assessed using RECIST every 8 weeks (+1 week) until progression
- Investigator and independent review
- ORR assessed using exact Pearson Clopper two-sided 95% CI in patients with measurable disease per RECIST (version 1.0)

**Safety**
- Assessed according to NCI CTCAE criteria (version 3.0)

CBR, clinical benefit rate; CI, confidence intervals; ITT, intent to treat; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PP, per protocol; RECIST, Response Evaluation Criteria in Solid Tumours

Patients in the TPC Arm Received a Wide Range of Chemotherapy Agents

- 96% of patients in the TPC arm received chemotherapy
  - No patient received best supportive care or biological therapies

*Taxanes: paclitaxel, docetaxel, abraxane (ixabepilone).
**Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone.

Baseline Characteristics were Well Balanced Across Both Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Eribulin n=508</th>
<th>TPC n=254</th>
<th>Total N=762</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55 (28–85)</td>
<td>56 (27–81)</td>
<td>55 (27–85)</td>
</tr>
<tr>
<td>Ethnic origin, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Geographical region, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 1. North America, Western Europe, Australia</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Region 2. Eastern Europe, Russia</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Region 3. Latin America, South Africa</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>43</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

Tumour Characteristics were Similar Across Both Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Eribulin (n=508)</th>
<th>TPC (n=254)</th>
<th>Total (N=762)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER/PgR status, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER and/or PgR+</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>ER and/or PgR-</td>
<td>24</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>ER/PgR/HER2 negative, %</strong></td>
<td>18</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td><strong>HER2 status, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>73</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Positive</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>Number of organs involved, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>≥4</td>
<td>20</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td><strong>Most common metastatic sites, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>60</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Liver</td>
<td>58</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>43</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Lung</td>
<td>39</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

Patients had Received a Median of Four Prior Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Number of prior chemotherapy regimens*</th>
<th>Eribulin, % (n=508)</th>
<th>TPC, % (n=254)</th>
<th>Total, % (N=762)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>4 (median)</td>
<td>33</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>≥6</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Prior capecitabine, %</td>
<td>73</td>
<td>74</td>
<td>73</td>
</tr>
</tbody>
</table>

*Received for the treatment of locally recurrent or metastatic breast cancer.

EMBRACE was a Large Phase III Trial that Randomised 762 Patients to Treatment

**Total patients randomised (N=762)**

2:1

**Eribulin**
- ITT: n=508
- Safety*: n=503
- Response evaluable**: n=468

**TPC**
- ITT: n=254
- Safety*: n=247
- Response evaluable**: n=214

**Reasons for discontinuation (n=479)**
- Progression: 82.5%
- Adverse events: 10.2%
- Physician’s decision to stop treatment: 3.8%
- Withdrew consent: 1.9%
- Death: 0.6%
- Other: 1.0%

**Reasons for discontinuation (n=238)**
- Progression: 79.0%
- Adverse events: 10.1%
- Physician’s decision to stop treatment: 4.6%
- Withdrew consent: 2.1%
- Death: 0.8%
- Other: 3.4%

*Safety population consists of all subjects who were dosed.
**Patients were not required to have measurable disease at baseline.

Median Duration of Eribulin Treatment was 3.9 Months

<table>
<thead>
<tr>
<th>Drug exposure</th>
<th>Eribulin n=503</th>
<th>TPC Chemotherapy n=238</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of exposure, months (range)</td>
<td>3.9 (0.7–16.3)</td>
<td>2.1 (0.03–21.2)</td>
</tr>
<tr>
<td>≥ 5 cycles, % (range)</td>
<td>59 (1–23)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dose interruptions, %</strong></td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><strong>Dose delays, %</strong></td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td><strong>Dose reductions, %</strong></td>
<td>29</td>
<td>26</td>
</tr>
</tbody>
</table>

NA, not applicable

Patients were treated with eribulin or TPC until disease progression, unacceptable toxicity, patient/physician request to discontinue or serious protocol non-compliance

Eribulin Significantly Extended Median Overall Survival Compared with TPC

- Eribulin significantly extended median OS compared with TPC (13.1 vs. 10.6 months; P=0.041)

HR, hazard ratio
Analysis occurred at 422 events (deaths), representing 55% of the ITT population
*HR Cox model including geographic region, HER2/neu status, and prior capecitabine therapy as strata.
†P value from stratified log-rank test (pre-defined primary analysis).

Updated Overall Survival Analysis Requested by Regulators Validated the Primary Analysis

- Updated OS analysis requested by European and US regulatory authorities validated the statistically significant increase in OS for eribulin compared with TPC (13.2 vs. 10.5 months)

Analysis occurred at 589 events (deaths), representing 77% of the ITT population

*HR Cox model including geographic region, HER2/neu status, and prior capecitabine therapy as strata.
†Nominal P value from stratified log-rank test.

A pre-specified exploratory OS subset analysis demonstrated a significantly longer median OS in Region 1 with eribulin (13.1 months) vs. TPC (10.1 months) – HR 0.72 (95% CI, 0.57, 0.92); P=0.009

Based upon a stratified Cox analysis.
Survival Benefit with Eribulin was Observed in Both Capecitabine Pre-treated and Capecitabine-naïve Patients

- Analysis of OS showed a survival benefit for the eribulin group compared with TPC in both capecitabine pre-treated patients (HR 0.77; 95% CI 0.61, 0.97), and capecitabine-naïve patients (HR 0.94; 95% CI, 0.62, 1.44)\(^1\)

Based upon a stratified Cox analysis.\(^2\)

- Analysis of updated OS showed a survival benefit for the eribulin group compared with TPC in both capecitabine pre-treated patients (HR 0.787; 95% CI, 0.645, 0.961), and capecitabine-naïve patients (HR 0.865; 95% CI, 0.606, 1.233)\(^3\)

The Median PFS was 3.7 and 2.2 Months with Eribulin and TPC Respectively

- PFS (ITT population) was longer with eribulin vs. TPC in both the independent (3.7 vs. 2.2 months) and investigator (3.6 vs. 2.2 months) review
  - Statistically significant by investigator (but not independent) review

- PFS (PP population) was longer with eribulin vs. TPC, reaching statistical significance by both independent (P=0.02) and investigator review (P<0.001)

ITT, intent-to-treat (ITT population=all randomised patients); PP, per protocol (PP population=patients who met key inclusion criteria and no major protocol violation)

No Differences were Observed Between Treatment Groups with Regards to First Post-trial Anti-cancer Treatment

- Comprehensive data on post-trial treatments were not required per protocol, except for the first anti-cancer treatment after the study treatment for the purpose of censoring for PFS.

- Based on the limited available data, no differences were observed between the treatment groups with regards to this first anti-cancer treatment.

- The first anti-cancer treatment received after the study by patients in the eribulin and TPC arms were:

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Eribulin</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy, %</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Hormonal therapy, %</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Radiotherapy, %</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Objective Response Rate Significantly Improved with Eribulin Compared with TPC

- ORR was significantly improved with eribulin vs. TPC (independent and investigator review).
- The median DOR for eribulin and TPC was 4.2 and 6.7 months, respectively by independent review (P=0.159) and was similar by investigator review.

<table>
<thead>
<tr>
<th></th>
<th>Independent Review</th>
<th>Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eribulin (n=468)</td>
<td>TPC (n=214)</td>
</tr>
<tr>
<td>ORR (CR+PR), %</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>P value</td>
<td>0.002</td>
<td>0.028</td>
</tr>
<tr>
<td>CR, %</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PR, %</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>SD, %</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>PD, %</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>NE, %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Clinical benefit rate (CR+PR+SD ≥6 months), %</td>
<td>23</td>
<td>17</td>
</tr>
</tbody>
</table>

Response evaluable population (n=682)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Overall Incidence of Adverse Events was Similar in Both Treatment Groups

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Eribulin (n=503)</th>
<th>TPC (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>AEs leading to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>interruption</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>discontinuation</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>dose reduction</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>dose delay</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Fatal AEs (treatment-related)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The Most Common Haematological Adverse Event with Eribulin was Neutropenia

- Febrile neutropenia occurred at low incidence with eribulin (5%) and TPC (2%)
- Mean time to nadir within a cycle was approximately 13 days; mean time to recovery (≤ grade 2) was approximately 8 days
- Neutropenia was managed with dose delays, dose reductions and G-CSF (administered to 18% and 8% of patients in the eribulin and TPC arms, respectively)
  - Administration of prophylactic G-CSF was not permitted in the study
- <1% of eribulin patients discontinued treatment due to haematological AEs

<table>
<thead>
<tr>
<th>Haematological, %</th>
<th>Eribulin (n=503)</th>
<th>TPC (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Anaemia</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

Events are those that occurred in at least 20% of safety population patients (consisting of all patients who were dosed) in either arm.

G-CSF, granulocyte colony stimulating factor.

The Most Common Grade 3/4 Adverse Event with Eribulin was Neutropenia

- Neutropenia was the most common grade 3/4 AE with eribulin and the TPC subgroups of vinorelbine, taxanes and gemcitabine

<table>
<thead>
<tr>
<th></th>
<th>Eribulin (n=503)</th>
<th>Vinorelbine (n=61)</th>
<th>Taxanes (n=38)</th>
<th>Gemcitabine (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3, %</td>
<td>21</td>
<td>30</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Grade 4, %</td>
<td>24</td>
<td>10</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

Non-haematological Adverse Events were those Commonly Associated with Chemotherapy

<table>
<thead>
<tr>
<th>Non-haematological, %</th>
<th>Eribulin (n=503)</th>
<th>TPC (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>Alopecia*</td>
<td>45</td>
<td>N/A</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral neuropathy**</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>22</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>

Events shown are those that occurred in at least 20% of safety population patients (consisting of all patients who were dosed) in either arm. 
*In the eribulin group alopecia was grade 1 in 26% and grade 2 in 17%; the number of patients by grade do not equal number of AEs since a small proportion of patients were reported as mild, moderate or severe rather than by grade. 
**This term includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
Peripheral Neuropathy Occurred in 35% of Patients who Received Eribulin

- 8% of patients receiving eribulin experienced grade 3 peripheral neuropathy, <1% experienced grade 4.

- Peripheral neuropathy was the most common AE leading to discontinuation from eribulin (5%).

- Patients with ≤ grade 2 neuropathy were permitted to enrol into the EMBRACE trial.
  - The incidence of grade 3/4 neuropathy was comparable in patients with and without pre-existing neuropathy.

<table>
<thead>
<tr>
<th>Patients with pre-existing grade 1/2 neuropathy at study entry (n=103)</th>
<th>Patients without pre-existing grade 1/2 neuropathy at study entry (n=386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3, n (%)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

The study met its primary endpoint of statistically significant improvement in OS with eribulin vs. ‘real-life’ treatment choices for women with MBC who had received a median of four prior chemotherapy regimens.

- An updated analysis of the OS requested by European and US regulatory authorities validated the statistically significant increase in OS for eribulin vs. TPC
  - ORR was significantly improved with eribulin vs. TPC
  - PFS was longer with eribulin vs. TPC and achieved statistical significance by investigator, but not independent review
EMBRACE: Conclusions (Safety)

Eribulin demonstrated a manageable toxicity profile,\(^1\) consistent with earlier studies\(^2-7\) and AEs were those commonly associated with chemotherapy agents.

- The overall incidence of AEs and serious AEs were almost identical in the two arms\(^1\)

- The most common haematological AE with eribulin was neutropenia; the incidence of febrile neutropenia was low\(^1\)

- The incidence of grade 3/4 neuropathy was comparable in patients with and without pre-existing neuropathy\(^1\)

EMBRACE: Summary

- EMBRACE demonstrated that eribulin is well-tolerated and significantly improves OS in women with heavily pre-treated MBC compared with available cytotoxic therapy\(^1\)

- These benefits are clinically meaningful – the 2.5 month prolongation of median OS represents an increase of 23\(^1\)\%
  - This is comparable to that reported with docetaxel vs. mitomycin + vinblastine* (31\(^2\)% and capecitabine + docetaxel vs. docetaxel* (26\(^3\)%

- It is rare for OS to be the primary endpoint in MBC trials – eribulin is the first monotherapy to provide a significant improvement in OS in heavily pre-treated MBC patients previously treated with an anthracycline and a taxane\(^1,4\)
  - The improved primary endpoint of OS seen in EMBRACE suggests that prolongation of OS is a realistic and achievable aim when evaluating new therapies in women with heavily pre-treated MBC\(^1\)

“The benefit that eribulin has shown as a single agent in this setting suggests that this drug could become a new standard of care”\(^1\)

EMBRACE study investigators

*Studies conducted in anthracycline refractory patients

HALAVEN™ (eribulin)

Please refer to the Summary of Product Characteristics (SPC) before prescribing.
Presentation: 2 ml vial containing 0.88 mg of eribulin (as mesylate).
Indication: Monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless not suitable.

Dose and administration: For use in units specialised in the administration of cytotoxic chemotherapy under the supervision of a qualified physician. Recommended dose in adults and elderly: 1.23 mg/m² eribulin as the ready to use solution (equivalent to 1.4 mg/m² eribulin mesylate) administered intravenously over 2-5 minutes on Days 1 and 8 of a 21-day cycle. Patients may experience nausea or vomiting. Antiemetic prophylaxis including corticosteroids should be considered. See SPC for guidelines on dose delay and reduction due to toxicity. Renal impairment: Dose reduction may be required for severe impairment (dose not established); no specific dose adjustment recommended in mild or moderate impairment. Hepatic impairment due to metastases: Reduce dose for mild or moderate impairment; severe impairment not studied. Hepatic impairment due to cirrhosis: Not studied; close monitoring recommended. Paediatrics: No information. Contra-Indications: Hypersensitivity to eribulin or any excipients. Contraindicated in breast feeding.

Special warnings and precautions: Myelosuppression is dose dependent and primarily manifested as neutropenia. Monitoring of complete blood counts should be performed prior to each dose of eribulin. Treatment should only be initiated in patients with ANC values ≥1.5 x 10⁹/l and platelets >100 x 10⁹/l. Febrile neutropenia reported in <5% of breast cancer patients. Febrile neutropenia, severe neutropenia or thrombocytopenia requires dose delay or reduction. Patients with ALT or AST >3 x ULN or bilirubin >1.5 x ULN have a higher incidence of Grade 4 neutropenia and febrile neutropenia. Severe neutropenia may be managed with G-CSF or equivalent at the physician’s discretion in accordance with relevant guidelines. Monitor closely for signs of peripheral motor and sensory neuropathy. Severe peripheral neuropathy requires dose delay or reduction. QT prolongation on Day 8 has been observed. ECG monitoring recommended in patients with congestive heart failure, bradycardias, if also receiving medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalaemia or hypomagnesaemia prior to initiating eribulin and monitor during therapy. Eribulin should be avoided in patients with congenital long QT syndrome. No experience of using eribulin in combination with anti-HER2 therapy in clinical trials. Medicinal product contains small amounts of ethanol (<100 mg per dose).

Drug Interactions: Concomitant use with substances which are inhibitors of hepatic transport proteins or with enzyme inducing substances not recommended. Exercise caution with concomitant use with substances metabolised by CYP3A4; avoid concomitant use if substance has a narrow therapeutic window.

Pregnancy and lactation: Do not use during pregnancy unless clearly necessary. Contraception advised. Do not use during breast feeding.

Effects on ability to drive and use machines: Do not drive or use machines if experiencing tiredness or dizziness.

Undesirable effects: Adverse reactions reported with eribulin in breast cancer clinical trials: Very common (≥1/10): Neutropenia, leukopenia, anaemia; Decreased appetite; peripheral neuropathy, headache; Nausea, constipation, diarrhoea, vomiting; Alopecia; arthralgia and myalgia; Fatigue/asthenia, pyrexia. Common (≥1/100 to <1/10): Urinary tract infection, oral candidiasis, upper respiratory tract infection, nasopharyngitis, rhinitis; Febrile neutropenia, thrombocytopenia, lymphopenia; Hypokalaemia, hypomagnesaemia, dehydration, hyperglycaemia, hypophosphatemia; insomnia, depression; Dysgeusia, dizziness, hypoaesthesia, lethargy, neurotoxicity; Lactation increased, conjunctivitis; Vertigo; Tachycardia; Hot flush; Dyspnea, cough, oropharyngeal pain, epistaxis, rhinorrhea; Abdominal pain, stomatitis, dry mouth, dyspepsia, gastrooesophageal reflux disease, mouth ulceration, abdominal distention; Alanine aminotransferase increased, aspartate aminotransferase increased; Rash, pruritus, nail disorder, night sweats, palmar plantar erythrodysaesthesia, dry skin, erythema, hyperhidrosis; Pain in extremity, muscle spasms musculoskeletal pain and musculoskeletal chest pain, muscular weakness, bone pain, back pain; Mucosal Inflammation, peripheral oedema, pain, chills, influenza like illness, chest pain; Weight decreased. Medically significant but uncommon (≥1/1000 to <1/100): Pneumonia, neutropenic sepsis, oral herpes, Herpes zoster; Tinnitus; Deep vein thrombosis, pulmonary embolism; Intestinal lung disease; Hyperbilirubinaemia; Angioedema; Dysuria, haematuria, proteinuria, renal failure. Overdose: No known antidote. Closely monitor and manage with supportive medical interventions.

Shelf-life: 4 years.

Special precautions for storage: None. For storage conditions of the opened and diluted medicinal product, see SPC.

Legal Category: POM

Cost: Eribulin 0.44mg/ml 2ml vial: £313 per vial

Marketing authorisation (MA) number: Eribulin 0.44mg/ml 2ml vial x 1: EU/1/11/678/001, Eribulin 0.44mg/ml 2ml vial x 6: EU/1/11/678/002

MA holder: Eisai Europe Ltd.

Further information from: Eisai Ltd., Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, United Kingdom

Date of preparation: March 2011

Adverse events should be reported. Reporting forms and Information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Eisai Ltd on 0208 600 1400/0845 676 1400 or Lmedinfo@eisai.net