Synergistic Anticancer Activity of Eribulin Plus Palbociclib in Patient-Derived Xenograft (PDX) Models of ER+/Her2- Human Breast Cancer

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Abstract

Eribulin is a synthetic analog of the marine sponge natural product halichondrin B. Its clinical formulation is currently approved in numerous countries for treating certain patients with advanced breast cancer or advanced soft tissue sarcomas. Its anticancer mechanisms include relatively fast antimitotic effects that lead to cell death by apoptosis, and slower complex changes in tumor phenotype that result from actions on the tumor microenvironment, such as inducing migratory/apoptotic-dependent invasion. For this reason, eribulin action can induce phenotypic changes and hypoxia in processes associated with decreased migration and invasiveness in vitro. Such changes in tumor phenotype led us to ask whether eribulin could be successfully combined with inhibitors of cyclin-dependent kinases 4 and 6 (CDK 4/6), which work at the G1/S cell cycle checkpoint where phenotypic changes are typically regulated. It is now recognized that patient-derived xenograft (PDX) models recapitulate human tumor biology and drug responsiveness better than standard xenograft models derived from established human tumor cell lines. According to our recent study (Eri-PH-704-2-192), PDX models developed from patients with luminal B breast cancers, OD-BRE-BRE-0192 and OD-BRE-0745, recapitulate breast cancer patient characteristics, such as basal expression of Ki67, halichondrin E7389 is suppression of microtubule growth. Mol. Cancer Ther., 4:1086-1092. Jordan RM, et al. (2005) Clinical verification of antitumor autoimmune response in eribulin chemotherapy for breast cancer. Poster at 2005 ASCO Annual Meeting, Abstract 2027. Towle MJ et al. (2011) Eribulin induces irreversible mitotic blockade: implications of cell cycle checkpoint sensitivity and microtubule stability. Mol. Cancer Ther., 10:909-920. Ueda et al., 2016; Goto et al., 2016; Prat et al., 2015, Kobayashi et al., 2016).

Introduction

Eribulin mesilate (Halaven®) is currently approved in >40 countries worldwide for treatment of certain patients with advanced breast cancer and/or advanced liposarcoma (or soft tissue sarcoma). In Japan, it is approved for metastatic breast cancer and/or unresectable metastatic liposarcoma, with its antimitotic effects and activity on the glucocorticoid receptor (GluCR) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer cell lines, in combination with the ERBB2 inhibitor lapatinib. We have previously shown that combining eribulin with lapatinib in breast cancer xenograft models can lead to novel antitumor mechanisms, including synergistic antitumor effects (Okayama et al., 2014). In addition, we have demonstrated that eribulin has antimitotic and antiangiogenic effects on human liposarcoma xenograft models (Nomoto et al., 2014). In vitro, eribulin exerts its antimitotic activity by inducing mitotic arrest at the G2/M checkpoint, with only limited effects by CDK4/6 inhibitors. In the OD-BRE-BRE-0192 model, eribulin and palbociclib dose levels were chosen that led to only minimal effects at the G1/S checkpoint. One such drug is palbociclib (Ibrance®), a cyclin-dependent kinase inhibitor that exerts its cdk 4/6 inhibitory activity at the G1/S checkpoint where palbociclib exerts its cdk 4/6 inhibitory activity, and palbociclib's dose levels were chosen that led to only minimal effects at the G1/S checkpoint. Thus, in the current study, we hypothesized that combining eribulin and palbociclib would lead to superior anticancer activity compared to either agent alone.

Dosing Scheme Using 48 h Palbociclib Holiday to Avoid Cell Cycle-Based Antagonism

Table 1: Breast Cancer PDX Models

<table>
<thead>
<tr>
<th>Designation</th>
<th>ER PR/HER2 Status</th>
<th>Patient and Cancer Details</th>
<th>Patient Prior Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD-BRE-0192</td>
<td>Eri-PH-704-2-192</td>
<td>45 year old female patient with luminal B invasive lobular breast carcinoma, with lymph node metastases</td>
<td>Patient responded poorly to prior therapies including epirubicin, SFU, cyclophosphamide, taxol, paclitaxel, bevacizumab and gemcitabine</td>
</tr>
<tr>
<td>OD-BRE-0745</td>
<td>Eri-PH-704-2-192</td>
<td>78 year old female patient with luminal B invasive ductal breast carcinoma, with lymph node metastases</td>
<td>Patient had no prior chemotherapy or radiation therapies prior to surgery</td>
</tr>
</tbody>
</table>

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Eribulin and palbociclib show synergetic anticancer activity in two patient-derived xenograft (PDX) models of ER+/HER2- luminal B human breast cancer.

All doses and combinations were at or below empirically determined MTD dose levels (based on standard criteria of <20% reversible body weight loss and <10% lethality).

In both models, synergy was seen with doses intentionally selected to show only minimal anticancer activity when administered alone, with a 48 h ‘palbociclib holiday’ dosing strategy was employed to avoid potential cell cycle-based antagonism. Further studies are currently underway to test the hypothesis that the palbociclib holiday is required to see synergy.

In the OD-BRE-BRE-0192 PDX model, synergy was optimally seen with 0.25 mg/kg eribulin plus 150 mg/kg palbociclib.

In the OD-BRE-0745 PDX model, synergy was optimally seen with 0.25 mg/kg eribulin plus 75 mg/kg palbociclib.

The current results provide a preclinical foundation for exploring an eribulin plus palbociclib combination strategy in appropriate breast cancer patients.

References