CDK2 inhibition with BLU-222 in combination with ribociclib demonstrates robust antitumor activity in pre-clinical models of CDK4/6 inhibitor-naïve and -resistant HR+/HER2– breast cancer

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Background

CDK2 are regulatory proteins that, when partnered with cyclin-dependent kinases (CDKs), are critical for the regulation of cell growth and proliferation.

- CDK2 inhibition is a key target in combination with endocrine therapy in advanced hormone-naive prostate cancer (HPC) and human epidermal growth factor receptor 2 (HER2) cancers.

- Despite improved progression-free and overall survival, almost all patients with HER2-positive breast cancer develop CDK4/6 inhibitor resistance and disease progression on treatment.

- A recent study of CDK2 inhibition in cell lines demonstrated that CDK2 inhibition was the key resistance mechanism by which tumors were resistant to CDK4/6 inhibition.

- Patients with HR+/HER2– breast cancers could benefit from treatment with a selective CDK inhibitor in combination with endocrine therapy, which is in the clinical trial phase (NCT05315436).

- BLU-222, an investigational novel, potent, and selective small-molecule inhibitor of CDK2, is being developed as a potential new therapy.

- Here, we investigate the antitumor activity of BLU-222 in pre-clinical models of CDK2 inhibition-resistant and HR+/HER2– breast cancer.

Table 1: BLU-222 is a selective and potent CDK2 inhibitor6

<table>
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<th>IC50 (nM)</th>
<th>CDK2</th>
<th>CDK1</th>
<th>CDK4</th>
<th>CDK6</th>
<th>CDK7</th>
<th>CDK9</th>
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<td></td>
<td>0.005</td>
<td>1.000</td>
<td>40.00</td>
<td>10.00</td>
<td>1.000</td>
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</table>

Table 2: Results

- BLU-222 and ribociclib demonstrated activity in distinct subtypes of breast cancer (Figure 1).

Results

Figure 1: IC50 of breast cancer cell lines treated with BLU-222 or ribociclib

- BLU-222 and ribociclib demonstrated activity in distinct subtypes of breast cancer (Figure 1).

Conclusions

- This presentation supports that CDK2/cyclin E-activation is a key vulnerability in clinical CDK4/6 inhibitor-resistant, HR+/HER2– breast cancer.

- The improved durability of response when BLU-222 is combined with ribociclib in HPC is consistent with the rationale for the study of the combination of these agents in clinical trials.

- BLU-222 is currently being evaluated in combination with fulvestrant in HR+/HER2– breast cancer as well as with PAM50-identified, endometrial, and other cancers as well as with HER2+ and HER2– breast cancer with disease progression in clinical trials.

- BLU-222 in combination with fulvestrant in HR+/HER2– breast cancer.

- BLU-222 with ribociclib in HR+/HER2– breast cancer.

- BLU-222 with ribociclib in HR+/HER2– breast cancer with disease progression on a CDK4/6 inhibitor.

References


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Disclosures

The authors have no other relevant disclosures to disclose. Nealia House and Kerrie Fai are employees of Blueprint Medicines Corporation. The remaining authors are employees of Blueprint Medicines Corporation and have no conflicts of interest to disclose.