BLU-222, an investigational, potent, and selective CDK2 inhibitor, demonstrated robust antitumor activity in CCNE1-amplified ovarian cancer models

Victoria Brown,1,2 Phil Ramsden,3 Nealla House,4 Richard Vargass,5 Jian Guo,6 Roudan Wang,6 Riadh Lobbar,7 Maxine Chen,1 Douglas Wilson,1 Joseph Kim,8 Neil Bifulco,9 Michelle Maynard,9 Emanuele Perola,9 Dean Zhang,1 Steve Wenglowski1, Yoon Jong Choil1

1Blueprint Medicines Corporation, Cambridge, MA, USA

Background

• A broad range of aggressive cancers harbor cyclin E1 (CCNE1) gene amplification (Figure 1A).
• CCNE1 amplification has been associated with poor survival in ovarian cancer, representing an unmet medical need (Figure 1B).
• Cyclin E1 is the canonical binding partner of cyclin-dependent kinase 2 (CDK2) and the cyclin E1-CDK2 complex drives G1/S progression of the cell cycle (Figure 2).
• CCNE1 is a driver of disease that, along with their regulatory cyclin binding partners, drive cell cycle progression.
• Cyclin-dependent kinases (CDKs) are a family of enzymes that, along with their regulatory cyclin binding partners, drive cell cycle progression.
• Cyclin E1 is the canonical binding partner of cyclin-dependent kinase 2 (CDK2).
• Selectively inhibiting CDK2 for CCNE1 amplification drives cancer cell proliferation (amplifications of CCNE1 are prevalent across various tumor types).
• Amplification of CCNE1 in tumors is now enrolling patients (Figure 1C).

Methods

• BLU-222 selection was determined by enzyme assays and cellular target engagement assays (Figure 3).
• Data from Project Achilles® and preclinical assays from a panel of cancer cell lines were used to determine CDK2 sensitivity based on CCNE1 copy number.
• In vitro cellular potency was assessed by phospho-Rb levels.
• Mechanism of action was determined using CRISPR-Cas9 generated Rb knockdown cell lines.
• In vivo antitumor activity of BLU-222 as a single agent or in combination with standard of care (SOC) agents was measured in the OVCAR-3 cell line-derived xenograft (CDK2) tumor model harboring a CCNE1 amplification (Figure 4).

Results

• Table 1: BLU-222 is a selective and potent CDK2 inhibitor.

Conclusions and future directions

• CCNE1 copy number increase was a strong predictor of response to CDK2 inhibition across tumor types in cellular systems.
• BLU-222 is a selective and potent CDK2 inhibitor that amplified the CDK2/CCNE1 axis in an Rb-dependant manner.
• BLU-222 and olaparib induced tumor regression that persisted even after treatment cessation.
• Combination treatments with BLU-222 and standard of care therapies induced tumor regression (Figure 8).

References


Disclosures

• All authors contributed to the preparation of this manuscript. No other disclosures were reported.

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