DBPR728: A kinase inhibitor targeting MYC driven cancers

A Precision Medicine strategy for Cancers

INDICATIONS:

Tumors with *c-MYC* or *N-MYC* amplification/ overexpression

PATENTS:

PCT filed
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PUBLICATIONS:

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DEVELOPMENT STATUS:

preclinical stage

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INVENTION DESCRIPTION

DBPR728 is an oral-available novel Aurora kinase A inhibitor which was selected based on its potency to reduce levels of c-MYC and N-MYC oncoproteins. DBPR728 efficiently induces cell apoptosis and inhibits proliferation of several cancer cell lines. Head-to-head comparison of DBPR728 with the phase II investigational drug alisertib demonstrated superiority of DBPR728 on the regression or suppression of multiple tumor xenografts (e.g. small cell lung cancer, triple-negative breast cancer, liver cancer, pancreatic cancer, medulloblastoma) overexpressing c-MYC and/or N-MYC. In addition, oral administration of DBPR728 at 300 mpk once a week or 200 mpk twice a week showed similar tumor regression potency, as compared to the dosage of 100 mpk 5W for 2 weeks. DBPR728 also showed synergy with everolimus (an mTOR inhibitor) in regressing MYC-overexpressing small cell lung cancer tumor xenografts. No significant hematological toxicity was observed in mice receiving DBPR728 at 300 mpk QW in a 21-day cycle.

COMPETITIVE ADVANTAGES

- Deregulation of MYC is frequently associated with poor prognosis and unfavorable patient survival. DBPR728 was designed based on its potency to reduce levels of c-MYC and N-MYC oncoproteins in addition to its inhibitory activity to Aurora A kinase.
- DBPR728 is superior to alisertib in degrading c-MYC oncoprotein in the tumor xenografts.
- Amplification or overexpression of c-MYC/N-MYC can serve as a biomarker for selection of patients who are potentially responsive to DBPR728.

MARKET POSITIONING/OPPORTUNITY

Amplification/overexpression of MYC-family oncogenes occurs in ~28% of human cancers, correlating with poor prognosis and aggressive disease conditions. In addition to the lack of effective binding pockets on its surface, the high turnover rate (<30 mins) of MYC-family oncoproteins increases difficulties for drug design. DBPR728 has long elimination half-life in the tumors; the tumor/plasma exposure ratio of DBPR728 was about 3.6-fold within 7 days after drug administration. This unique pharmacokinetic property of DBPR728 enables constitutive reduction of c-MYC protein level, leading to cell apoptosis and tumor regression with manageable hematology toxicities. The disease indications of DBPR728 may be expanded based on the genomic features of the cancers including c-MYC and N-MYC amplification.

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