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Otviciclib – a new pan-CDK inhibitor in oncology

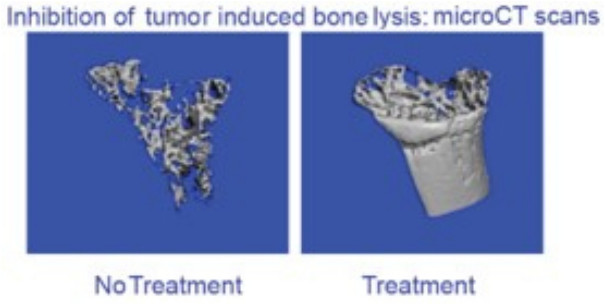
Otviciclib, pan-CDK inhibitor, multiple myeloma, colon cancer, breast cancer, cyclin-dependent kinases

INVENTION NOVELTY

Currently, numerous therapies for multiple myeloma with diverse mechanisms of action are under development. Most of the therapies in clinical development target patients who have exhausted existing treatment options, showing for instance bortezomib resistance or multiple drug resistance. The major unmet needs in multiple myeloma are novel treatment strategies for patients with high-risk disease. High unmet medical needs also remain for neoadjuvant or adjuvant treatments that can improve the cure rates of patients with early-stage resectable colorectal cancers and in invasive breast cancers resistant to radiotherapy, lapatinib or trastuzumab.

VALUE PROPOSITION

Otviciclib, a highly selective small molecule inhibitor for a subset of cyclin-dependent kinases (CDK), is orally available and in contrast to e.g., palbociclib, which has been approved for breast cancer, bioavailable in the low nanomolar range. Otviciclib has an interesting and unique CDK spectrum (CDK1/2/3/5/7/9/16) and importantly targets also wnt-signaling, with aberrant wnt-signaling being a hallmark of many cancers.



Otviciclib in an othotopic multiple myeloma tumor model (source: Prof. Huber, MUI)

TECHNOLOGY DESCRIPTION

Otviciclib was selected in a phenotypic assay involving cell-cell interactions with the tumor microenvironment after demonstrating its stem-cell killing capabilities. Because EC_{50} of otviciclib is in the low nanomolar range for most sensitive human cancer cell lines tested, the substance displays a comfortable window over “normal” cells in the tumor microenvironment. Its clear mode of action resulting in caspase-dependent cell death at G2/M transition, repression of Mcl-1, enhancement of p53 expression, induction of PARP cleavage and increase of Bcl-2 in tumor cells qualifies otviciclib as a pan-CDK inhibitor to overcome drug resistance in various tumor entities. Otviciclib kills bortezomib resistant cell lines, cells resistant to CDK4/6 inhibitors and radioresistant cell lines.

COMMERCIAL OPPORTUNITY

Otviciclib offers a combination of desirable properties unmatched by other CDK inhibitors. The technology is open for licensing, further pre-clinical and clinical co-development is highly welcomed.

DEVELOPMENT STATUS

Otviciclib was tested *in vivo* in three human tumor cell line derived xenograft models (colorectal cancer, multiple myeloma) in immunodeficient mice. Mice survived significantly longer and had significant delayed tumor growth in all models. Otviciclib treatment also increased survival of mice inoculated intro-tibially with a human multiple myeloma cell line and a significant increase in total bone volume was measured (see Figure). High efficacy of otviciclib was found in human colon cancer organoids derived from patients with mutations in the beta-catenin/APC pathway.

PATENT SITUATION

Notice of allowance has been issued by the US patent and trademark office. Patents are pending in EP, JP, CA, AU and HK (based on WO2018/099952, priority of 2016).

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