Grim reaping the benefits of the BCL-2 selective antagonist, Venetoclax, Venclexta™ for the treatment of hematological malignancies

Programmed cell death is governed by a complex interaction of BCL-2 (B-cell Lymphoma 2) family of pro-survival (BCL-2, BCL-XL and MCL-1) and pro-death proteins (BIM, PUMA, NOXA). BCL-2 family proteins share a common set of BCL-2 homology domains. Venetoclax (GDC-0199/ABT-199) is a first in-class BCL-2 selective antagonist that is currently approved for the treatment of Chronic Lymphocytic Leukemia. Current research efforts have focused on assessing the potential utility of venetoclax in other hematological malignancies such as multiple myeloma (MM) in which a high unmet medical need remains. In human MM cell lines (n=21) BCL-2 is expressed but sensitivity to venetoclax correlated with high BCL-2 and low BCL-XL or MCL-1 expression. MM cells that co-express BCL-2 and BCL-XL were resistant to venetoclax but sensitive to a BCL-XL selective inhibitor (A-1155463). MM xenograft models that co-expressed BCL-XL or MCL-1 with BCL-2 were also resistant to venetoclax in vivo. Resistance to venetoclax was mitigated by co-treatment with bortezomib in MM xenografts that co-expressed BCL-2 and MCL-1 due to upregulation of NOXA, a pro-apoptotic factor that neutralizes MCL-1. In contrast, xenografts that co-expressed BCL-XL and BCL-2 were more sensitive to the combination of bortezomib and BCL-XL selective inhibitor (A-1331852). Immunohistochemistry of MM patient bone marrow biopsies and aspirates (n=95) revealed high levels of BCL-2 and BCL-XL in 62% and 43% of evaluable samples, respectively. In addition to MCL-1, our data suggests that BCL-XL may also be a potential resistance factor to venetoclax monotherapy and in combination with standard of care drugs such as bortezomib.

Biography

Deepak Sampath is graduated from Washington University in St. Louis, Graduate School of Arts and Sciences earning a PhD in Molecular Cell Biology and Biomedical Sciences. Following a post-doctoral fellowship at Wyeth Research, Dr. Sampath joined the Department of Oncology at Wyeth Pharmaceuticals as Senior Scientist focusing on the discovery of orally bioavailable taxanes. Presently, Dr. Sampath is a Principal Scientist at Genentech in the Department of Translational Oncology and his lab focuses on the molecular and in vivo pharmacology of drugs that target the PI3K/Akt and BCL-2 apoptotic pathways in solid and hematological cancers.

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