Steven L Warner, J Cancer Sci Ther 2017, 9:5(Suppl)
DOI: 10.4172/1948-5956-C1-101

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Defining and exploiting the clinical mechanism of activity for alvocidib in acute myeloid leukemia patients

Alvocidib drug development has largely focused on the inhibition of cell cycle regulating CDKs. However, recent clinical activity in leukemia is not fully accounted for by cell cycle inhibition. We set out to more fully understand the mechanism of alvocidib particularly in leukemia patients that were benefiting significantly from the treatment. In addition to the cell cycle regulating CDKs, alvocidib has very potent activity against CDK9 (IC50=1.5 nM). CDK9 is responsible for controlling the transcriptional pause release that is important for the expression of certain genes. One of the most universally regulated transcripts by CDK9 is the anti-apoptotic family member, MCL-1, a member of the BCL-2 family involved suppressing cell death. Alvocidib treatment results in a concentration and time-dependent inhibition of MCL-1 expression in cancer cells. To further validate the CDK9/MCL-1 axis as the therapeutic target of alvocidib in, we utilized an approach called mitochondrial profiling to interrogate the dependencies that leukemia cells have on BCL-2 family members and retrospectively screened archived patient samples from a previously completed phase II clinical trial. We discovered that the patients that had a strong dependency on MCL-1, identified by a high NOXA priming score, where those that showed profound benefits from alvocidib. These findings led us to conduct an on-going phase II prospective biomarker trial where we are prescreening patients for NOXA priming and enrolling patients with a score 40%. Taken together, these results highly support the conclusion that alvocidib works through a mechanism that targets CDK9 activity and MCL-1 expression.

Biography

Steven L Warner specializes in small molecule drug discovery, new screening platforms in drug discovery, and translational research focusing on cancer therapeutics. He is an expert in the discovery of novel cancer agents and has played integral roles in moving multiple compounds into clinical trials. He earned his graduate degree in Pharmaceutical Sciences at the University of Arizona. He completed a postdoctoral fellowship under the mentoring of Dan Von Hoff at the Translational Genomics Research Institute (TGen). He is currently the Vice President of Drug Discovery and Development at Tolero Pharmaceuticals.

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