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Sequential treatment of AML patients with alvocidib followed by cytarabine and mitoxantrone is highly effective through a mechanism dependent on MCL1 expression and function

Multiple phase I/II studies have shown alvocidib to be highly effective in both frontline and relapsed/refractory AML when sequentially administered before cytarabine and mitoxantrone (ACM). In frontline patients, ACM resulted in a complete remission (CR) rate of 70% versus 46% CR with ara-C and daunorubicin (7+3). The clinical activity of alvocidib in AML is significantly correlated with inhibition of cyclin-dependent kinase-9 (CDK9) and disruption CDK-9 mediated transcription. The MCL1 gene is regulated by CDK-9 transcriptional control and its expression is tightly regulated by alvocidib. Studies with AML cell lines to model the sequential treatment of the ACM regimen have shown that MCL1 expression and apoptosis are tightly connected to treatment with alvocidib. To further investigate the correlation of MCL-1 mediated survival, mitochondrial profiling (BH3 priming) was conducted on 63 archived ACM-treated samples taken directly from patients bone marrow or circulating blasts. Analysis of the BH3 priming states in AML clinical samples revealed NOXA priming was significantly higher in CR bone marrow samples (44.5% primed) compared with samples from non-responders (NR) (5.2% primed) (p=0.006). NOXA is known to interact directly with MCL1, suggesting that the AML samples that are most responsive to ACM treatment may have a high survival dependence on MCL1. The correlation between NOXA and ACM response is distinct from priming states predicting response to other ara-C regimens in samples from AML patients. This work reveals a potential biomarker for identification of patients likely to respond to ACM and this biomarker is currently being prospectively tested in a phase II clinical trial.

Biography

David J Bearss, PhD, brings a consistent and successful track record of drug discovery and development that spans the last 17 years in both academic and industrial settings. He is an expert in small-molecule drug development and in the use of genetic model systems in drug discovery and has deep experience in translational research focused on drug development and the use of genetic markers to predict drug sensitivity. He served as Chief Scientific Officer at SuperGen overseeing early drug discovery and development and subsequently as Co-Director of the Center for Investigational Therapeutics at the Huntsman Cancer Institute, Associate Professor in the Department of Oncological Sciences at the University of Utah and Associate Professor of Physiology & Developmental Biology at Brigham Young University. He has published more than 70 manuscripts and book chapters, has over 30 patents issued or pending and has won several awards for his scientific achievements.

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