A Dual BH3-mimetic approach targeting BCL-2 and MCL1 is highly efficacious and well-tolerated in Acute Myeloid Leukemia

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Abstract Title: Dual BH3-mimetic targeting of BCL-2 and MCL1 is efficacious and well-tolerated in Acute Myeloid Leukemia

Aim
To determine the efficacy of targeting pro-survival proteins BCL-2 and MCL1 in pre-clinical models of AML.

Background
Identification of a chemotherapy-free option for AML represents a highly desired research objective. Perturbation of cell survival is a hallmark of cancer now amenable to precision targeting by BH3-mimetics able to inhibit BCL-2, BCL-X<sub>L</sub> and MCL1. We hypothesize that simultaneous targeting of BCL-2 and MCL1 will enhance apoptosis of AML blasts, without increased toxicity to non-malignant cells.

Methods
S55746 (BCL-2 inhibitor), S63845 (MCL1 inhibitor) were obtained from Servier and A1155463 (BCL-X<sub>L</sub> inhibitor) from WEHI. Primary AML cells were obtained from patients providing consent. In vivo: NOD.Cg-Prkdc<sup>scid</sup> Il2rg<sup>milWjl</sup>/SzJ (NSG) or NOD/Rag<sup>-/-</sup>Il2rg<sup>milWjl</sup> (NRGS) mice were used.

Results
S55746 and S63845 showed strong synergy in primary AML patient samples tested, suggesting that a dual BH3-mimetic approach was efficacious. Anti-leukemic activity across a spectrum of AML cases with diverse cytogenetic and molecular pathologies was observed. Bioluminescent imaging of NSG mice showed clearance of xenografted MV4;11 or OCI-AML3 cells, translating into prolongation of survival from combined S55746/S63845. Patient-derived xenograft models revealed rapid reduction of established AML in the bone marrow after one week of treatment. Tolerability of this approach was confirmed in normal CD34+ progenitor cells in short-term and long-term (2-3 weeks) clonogenic assays and from histological examination of mice treated for 8 weeks at doses shown to be efficacious against AML.

Conclusions
Dual BH3-mimetic targeting of BCL-2/MCL1 induces synergistic cyto-reduction of human primary AML samples in vitro and in vivo. We therefore report for the first time, that dual pharmacological inhibition of BCL-2/MCL1 represents a novel approach to treating AML with an acceptable therapeutic safety margin. Our results support the translational investigation of dual BH3-mimetic targeting in the clinic.