Therapeutic Targeting of Metabolic Dependencies in AML
Marina Konopleva MD Anderson Cancer center, Houston TX

Acute myeloid leukemia (AML) is initiated and maintained by a relatively rare leukemia stem cells (LSCs) capable of self-renewal and proliferation. Recent data showed that LSCs (Lagadinou et al. Cell Stem Cell 2013) and residual cytarabine (Ara-C)-resistant AML cells (representing minimal residual disease, MRD) (Farge et al. Cancer Discovery 2017) are highly dependent on mitochondrial function for survival. This unique metabolic biology makes chemoresistant LSCs and AML cells vulnerable to pharmacological blockade of the oxidative phosphorylation (OXPHOS). A novel OXPHOS inhibitor IACS-010759 potently inhibits mitochondrial complex I, suppresses OXPHOS and selectively inhibits the growth of AML cells in vitro and in vivo. OXPHOS inhibition with complex I inhibitor IACS-010759 is effective in reducing LSCs and MRD, alone and in combination with chemotherapy in vivo. We have further demonstrated that glutamine is required for growth of leukemic cells and supports OXPHOS in AML. Inhibition of glutaminolysis by glutaminase inhibitor CB-839 reduces mitochondrial respiration, NADH/NAD ratio and greatly enhances anti-leukemia efficacy of the hypomethylating agent azacitidine. In a Phase II study of CB-839 and Azacitidine the combination is well tolerated and induces responses in high-risk MDS patients.