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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Potent *in Vitro* and *In Vivo* Efficacy of BYON4413, a Duba-Based Antibody-Drug Conjugate Targeting CD123 in Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) and myelodysplasia (MDS) result from a differentiation impairment driving an accumulation of immature myeloid cells in the bone marrow and peripheral blood. A widely reported feature of these neoplastic myeloid cells is an increased cell surface expression of CD123, the IL3 receptor α subunit. This observation has established CD123 as an attractive target for precision therapy. Here, we describe BYON4413, a novel antibody-drug conjugate (ADC) that binds with high affinity to CD123. BYON4413 comprises a humanized IgG1 antibody directed at CD123 that is site-specifically conjugated to Byondis' proprietary duocarmazine linker-drug (LD) technology, ByonZine® and ByonShieLD®. This LD, when cleaved upon internalization and lysosomal routing, releases a potent duocarmycin payload that alkylates DNA, generating damage that results in replication stress and cell death. *In vitro* studies with AML cell lines demonstrate that BYON4413 is highly effective in eradicating CD123-positive cells while having little impact on CD123-negative cells. Similar results are observed when we test BYON4413 on AML patient-derived BMMCs/PBMCs in *ex vivo* assays (n=50), indicating that the specificity of BYON4413 cytotoxicity is largely limited to CD123-positive cells. *Ex vivo* experiments also reveal a stronger potency of BYON4413 in AML patient-derived blasts compared to healthy CD34 $^{+}$ hematopoietic stem/progenitor cells. *In vivo* PK/PD studies demonstrate that BYON4413 is remarkably efficient at reducing the tumor burden in multiple AML patient- and cell line-derived xenograft models. Studies in non-human primates suggest that BYON4413 has a favorable toxicity profile and a high maximum tolerable dose, features that should enable combination strategies with other oncolytics. In sum, BYON4413 shows great potential to be an effective targeted therapy against AML, MDS, and other CD123 $^{+}$ hematological malignancies such as blastic plasmacytoid dendritic cell neoplasm (BPDCN). Readied with these promising pre-clinical results, we have designed a first-in-human dose-escalation and expansion trial enrolling AML and high-risk MDS patients scheduled to begin in Q12024.

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