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BYON4228, A PAN-ALLELIC SIRP α BLOCKING ANTIBODY WITH A FAVORABLE PRE-CLINICAL SAFETY PROFILE, ENHANCES ANTI-TUMOR IMMUNITY IN VITRO AND IN VIVO

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Background Preclinical data have established CD47-SIRP α interactions as a myeloid immune checkpoint in cancer, which is corroborated by preliminary evidence from the first clinical studies with CD47 blockers.

Methods However, the ubiquitously expressed CD47 mediates functional interactions with other ligands as well, and therefore targeting of the primarily myeloid cell-restricted inhibitory immunoreceptor SIRP α may represent a better strategy.

Results Here, we present preclinical results on a novel clinical candidate, BYON4228. BYON4228 is an antibody directed against SIRP α and recognizes both of the common allelic variants of human SIRP α which maximizes its potential clinical application in the broad human population. Notably, in contrast to several other anti-SIRP α antibodies in development, BYON4228 does not recognize the closely related T cell-expressed SIRP γ that has been reported to mediate interactions with CD47 as well, which are known to be instrumental in T cell extravasation and activation. BYON4228 binds to the N-terminal part of SIRP α and its epitope overlaps with the CD47-binding site. BYON4228 therefore prevents binding of CD47 to SIRP α and thus blocks inhibitory signaling through the CD47-SIRP α axis. Functional studies show that BYON4228 potentiates both macrophage- and neutrophil-mediated elimination of hematologic and solid cancer cells *in vitro* in the presence of several different tumor targeting antibodies like trastuzumab, rituximab, daratumumab and cetuximab, illustrating the broad potential clinical benefit and application of BYON4228. BYON4228 enhanced the efficacy of rituximab treatment *in vivo* when administered to human Non-Hodgkin lymphoma (NHL)-engrafted transgenic mice with a selective expression of huSIRP α_{BIT} on myeloid cells (huSIRP α_{BIT} -scid mice). Single intravenous infusion of up to 100 mg/kg BYON4228 to male and female cynomolgus monkeys was well tolerated and did not elicit any adverse effects.

Conclusions Collectively, this defines BYON4228 as a pan-allelic anti-SIRP α antibody without T cell SIRP γ recognition that promotes the destruction of antibody-opsonized cancer cells. Clinical studies are planned to start in 2022.

Ethics Approval Appropriate ethics approvals were present before commencing studies *in vivo*.

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