282 BISPECIFIC ANTIBODIES (BSABS) TARGETING ABCB1/PGP AND CD47 PROVIDE A MULTI-MODAL, TUMOR SPECIFIC APPROACH TO COMBAT DRUG RESISTANT CANCERS

[1]Robert Arathoon*, [1]Raffaella Briante, [1]Alissa O'Connor, [1]Cindy Tan, [2]Pamela Klein, [1]Jessica Morgan, [1]Paul Ponath, [3]Leonard Presta, [4]Qianting Zhai, [5]Suchismita Mohanty, [1]Pinping Zhang. *[1]Kenjockety Biotechnology Inc., South San Francisco, CA, USA; [2]PMK BioResearch, San Francisco, CA, USA; [3]Consultant, San Francisco, CA, USA; [4]Abiosciences Inc., South San Francisco, CA, USA; [5]ArsenalBio, South San Francisco, CA, USA*

Background Bispecific antibodies (BsAbs) are gaining momentum in several immunotherapeutic[1 2 3] and immuno-oncology settings.[4] Certain designs of BsAbs enable tumor-specific targeting when two targets are concurrently expressed on tumor but not normal tissue. Judicious choice of bispecific immunotherapeutic targeting enables separate effects that are simultaneously beneficial and specific against tumor cells. This provides a multi-modal approach to the previously intractable problem of counteracting Efflux Pump (EP) mediated drug resistance in tumors. EP mediated drug resistance (EPMDR) adversely impacts a broad range of therapeutics including antineoplastics, TKIs, ADC-toxins and others. Elevated EP activity can also promote cancer cell growth by expelling catabolites and inhibitory substances from tumor cells. Prior efforts to combat EPMDR have focused on small molecule antagonists to EP intracellular domains; although some showed early promise[5 6] these ultimately failed mainly for lack of tumor specificity and off-target toxicity. In contrast, BsAbs targeting extracellular domains of efflux pumps together with other tumor associated antigens (TAA) provide for: a) Tumor specific targeting b) Specific masking or antagonizing of the TAA target c) Concurrent counteraction of tumor cell efflux mechanismsd) Invoking an Fc-mediated immune attack on tumor cells Use of the Kenjockety BASE PlatformTM (Bispecific Antibodies Specific to Efflux Pumps) has yielded BsAbs that have successfully targeted four different EPs together with several TAAs.

Methods Monoclonal antibodies to EPs have been raised and engineered into BsAbs with a common light chain[7 8] in IgG frameworks. These concurrently target an EP and a TAA. By design, each arm of the antibody binds with relatively weak affinity to its target on normal tissue. However, when both targets are displayed together on tumor cells, their concurrent engagement results in stronger, efficacious binding.

Results A prototype BsAb that concurrently targets CD47 and the EP, P-glycoprotein, provided compelling, dose-dependent proofs of concept in various in vitro studies and in drug-resistant hematologic and solid tumor xenograft models. Efficacy was shown with and without additional therapeutics. In cynomolgus studies the BsAb also demonstrated a lack of off-tumor toxicities typically associated with each target.

Conclusions BsAbs concurrently targeting EPs and TAAs (including immuno-oncology targets) provide promising new tumor-specific therapies for treatment of patients with drug resistant cancers.

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