**1178P** Tackling fratricide to manufacture clinical grade NKG2D-CAR T cells

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Background: The NKG2D receptor is a type II transmembrane glycoprotein playing an important role in anti-tumor responses. In humans, NKG2D binds to eight ligands, MHC class I-related chain MICA and B and unique long 16 (UL16)-binding proteins ULBP 1-6. The surface expression of NKG2D ligands (NKG2DL) is highly regulated to avoid inappropriate immune responses in physiological conditions but is induced by various stress situations such as malignant transformation or inflammation. NKG2DL expression on tumors has been reported in the literature. However, a systematic study on all NKG2DL in a large array of normal tissues and tumor samples is lacking. Celyad is pursuing the clinical development of NKG2D based chimeric antigen receptor (CAR) T cell therapy and robust data are thus required to adequately support this work.

Methods: We performed an extensive immunohistochemistry study on primary tumors and normal adjacent tissues from patients suffering from pancreatic, breast, ovarian, bladder, colorectal and lung carcinomas and on a series of normal tissues from non-cancer patients.

Results: MICA/B were the most frequently and highly expressed. Interestingly the subset of triple negative breast cancers (TNBC) showed strong membranous staining for all NKG2DL on tumor cells making this patient subpopulation a very attractive therapeutic target for NKG2D-based therapies. There was no clear correlation between the expression of NKG2DL and the clinical stage of the tumors indicating that every stage of the diseases could be targeted. In bladder, TNBC, CRC and pancreatic tumors, tumor cells were frequently stained for multiple NKG2DL implying that these tumors would not be susceptible to immune escape. Tumor-associated fibrovascular structures displayed generally membranous staining within the endothelial compartment suggesting that NKG2D-based CAR T therapy can target simultaneously both the tumor and the tumor microenvironment.

Conclusions: In conclusion, this extensive immunohistochemistry study supports the concept of targeting NKG2DL for cancer therapy.

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