Results: We identified that Th CD4 subset appeared to be primary target of CTLA-4 therapy. The effect consisted of increased ratio of ThCD4 and skew of Th cells from IFNγ-secreting towards proliferating cells within the tumor. Analysis of major lymphocyte subsets from LN revealed an increased percentage of activated CD69+/CD25+ cells from Th, CD8+ and B cells and IFNγ+ secretion by Th. We found that the number of TCR clusters significantly increased in Th after therapy. This indicates proliferation of certain Th clones, yet with unknown specificities. To identify the antigen specificity of these clones we immunized mice with melanoma peptide neo-antigens and harvested T-cells from LN. Then T-cells were cocultured with APCs loaded with different melanoma peptides. We identified up to 75% CD69+/CD25+ activated T-cells to the specific peptides. We detected clones of TCR, which were found with a high frequency in cells reactivated to specific peptides and were not found in the control. Now the data set is in progress. Future experiments will be directed to compare B16F0-specific TCRs with proliferative clones after anti-CTLA4 blockade.

Conclusions: We found that anti-CTLA-4 immunotherapy leads to activation and clonal expansion of lymphocytes with similar TCRs. For detailed analysis, we developed the approach to identify the TCR specificity to specific B16F0 peptides.

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8P The characterization of tumors associated with the antitumor activity of lenvatinib plus anti-PD-1 antibody combination therapy in a mouse syngeneic model panel

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Background: Lenvatinib is a multiple receptor tyrosine kinase inhibitor targeting mainly vascular endothelial growth factor and fibroblast growth factor receptors. We also reported that lenvatinib has immunomodulatory activity that contributes to the antitumor activity of lenvatinib and enhances the antitumor activity in combination treatment with anti-PD-1 antibody (anti-PD-1). In this study, we investigated the characteristics of tumors associated with the antitumor activity of lenvatinib plus anti-PD-1 combination treatment.

Methods: We evaluated the antitumor activities of lenvatinib (10 mg/kg, Q.D.), anti-PD-1 (200mg/head, twice weekly), and their combination in 12 mouse syngeneic tumor models. To define the characteristics of tumors, we conducted RNA-seq analysis to examine T cell inflamed GEP (GEP) score using mouse tumors before treatment. We also stained CD31 in the same tumors and calculated micro-vessel density (MVD) score by dividing CD31 positive blood vessels number by tumor area. Then, the correlation analysis among gene expression levels of GEP, IHC-based MVD score and the antitumor activity of each administration was investigated.

Results: We confirmed that lenvatinib plus anti-PD-1 inhibited tumor growth more than each single treatment in this mouse syngeneic model panel. Regarding the relationship between tumor characters and antitumor activities of each treatment, we found that antitumor activities of lenvatinib were correlated with MVD scores of pretreatment tumors. MVD-high group was significantly more sensitive to lenvatinib than MVD-low group. On the other hand, antitumor activities of anti-PD-1 were correlated with GEP score. Lenvatinib plus anti-PD-1 combination demonstrated significant enhancement of antitumor activity compared with each single agent treatment in MVD-low / GEP-high tumors.

Conclusions: In this study, we found that MVD combined with GEP might be the important predictive biomarkers reflecting the antitumor activities of lenvatinib monotherapy and lenvatinib plus anti-PD-1 combination therapy.

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9P Click Activated Protodrugs Against Cancer (CAPAC) platform enhances the safety, pharmacokinetics, and antitumor efficacy of cancer therapies in vivo

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Background: The Click Activated Protodrugs Against Cancer (CAPAC™) platform aims to beat cancer without poisoning the body by activating powerful cancer therapies at the tumor site(s). CAPAC’s mechanism of activation is based on click chemistry and is therefore agnostic to tumor characteristics, biomarker expression, or other biological factors that vary across patients. This allows the CAPAC platform to be readily applicable to diverse tumor types. The lead candidate, SQ3370, is being evaluated in a phase I study in patients with advanced solid tumors (NCT04106492). We describe the safety, pharmacokinetics (PK), and therapeutic benefits of SQ3370, the lead candidate of the CAPAC Platform, in vivo.

Methods: SQ3370 consists of 2 components, SQ70 biopolymer, and SQP33 proto-drug. First, SQ70, a tetrazine-modified sodium hyaluronate biopolymer, is injected at the tumor site. Then, SQP33, a trans-cyclooctene (TCO)-modified protodrug of Doxorubicin (Dox) is given systemically as 5 daily doses. SQP33 has attenuated toxicity and is converted to active Dox by SQ70 at the tumor site through an efficient covalent reaction between tetrazine and TCO moieties.

Results: In canines, the highest non-severely toxic dose of SQ3370 was found to be 8.95 times higher when compared to the conventional dose of Dox. There were minimal and reversible systemic adverse events, with no evidence of cardiotoxicity. The PK analysis in dogs showed that SQ70 efficiently captures SQP33 from circulation and releases active Dox throughout the treatment period. In the absence of SQ70, SQP33 was found to be stable and did not spontaneously activate. In mice, at least 50% of the SQ70 remains at the injection site for 2-4 weeks, and plasma levels of SQP33 and Dox are similar across SQ70 injection locations. SQ3370 elicited dose-dependent anti-tumor responses in three syngeneic dual tumor models.

Conclusions: SQ3370 enhances higher concentrations of the active drug at the tumor site and minimizes systemic adverse effects associated with conventional chemotherapies. The CAPAC Platform represents a new therapeutic modality to treat solid tumors by using a drug with known efficacy, such as Dox, and expanding its pharmacological capabilities.

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10P DS-6000a, a novel CD6-targeting antibody-drug conjugate with a novel DNA topoisomerase I inhibitor DXd, demonstrates potent antitumor activity in preclinical models

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Background: Human Cadherin 6 (CD6) is a single transmembrane protein consisting of 790 amino acids classified in the type 2 cadherin family. Human CD6 is specifically expressed in the brain and kidneys during the development phase and has been reported to systemically decrease CDH6 expression in the adult body. CDH6 expression is increased specifically in renal cell carcinoma (RCC) and ovarian cancer (OVC). Therefore, CD6H could be an attractive target for cancer therapy. We created DS-6000a, a CD6H-targeting antibody-drug conjugate (ADC) using an enzymatically cleavable tetrapeptide-based linker, and a high drug-to-antibody ratio (DAR 7 to 8) with a novel DNA topoisomerase I inhibitor (DXd). In this study, the pharmacological activity and the mechanism of action of DS-6000a were evaluated in preclinical in vitro and in vivo models.

Methods: CD6H expression was assessed by immunohistochemistry and FCM analysis. Induction of DNA damage and apoptosis to tumor cells by DXd released from DS-6000a were assessed using CDH6-high and -low RCC and OVC cell lines, xenograft mouse models and patient derived xenograft (PDX) models.

Results: CD6H is highly expressed in RCC and OVC patient samples. DS-6000a demonstrated in vitro cell growth inhibitory activity in CDH6-high tumor cells, but not in CDH6-low tumor cells. DNA damage and apoptosis were induced in CDH6-high tumor cells after the in vitro treatment with DXd and DS-6000a, but not with isotype control IgG ADC. DS-6000a exhibited strong antitumor activity with tumor regression in CDH6-high cell lines in mouse xenograft models. DS-6000a also showed high efficacy against PDX models.

Conclusions: Based on these preclinical results, DS-6000a could provide a valuable therapy with a potential benefit in CDH6-expressing cancers at the clinical setting.