activity in mouse models. The combination of SEA-CD40 and chemotherapeutic agents with a T cell targeted anti-PD1 antibody could deepen and extend these anti-tumor responses.

**Conclusions** These data support continued clinical evaluation of SEA-CD40 in combination with chemotherapeutic agents and potentially in the future MMAE based ADCs. A phase 1 clinical trial is actively enrolling (NCT02376699) and includes a cohort in pancreatic cancer assessing the combination of SEA-CD40, gemcitabine, nab-paclitaxel, and pembrolizumab.

**Ethics Approval** Studies with human samples were performed according to institutional ethics standards. Animal studies were approved by and conducted in accordance with Seattle Genetics Institutional Care and Use Committee protocol #SGE-029.

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Abstracts

439  **DUAL MODES OF ACTION FOR ANTI-TIM-3 ANTIBODY MBG453 IN MYELODYSPLASTIC SYNDROMES (MDS) AND ACUTE MYELOID LEUKEMIA (AML): PRECLINICAL EVIDENCE FOR IMMUNE-MEDIATED AND ANTI-LEUKEMIC ACTIVITY**

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**Background** TIM-3 is expressed on leukemic stem cells (LSCs) and blasts in AML, 1, 2 and TIM-3 expression on MDS blasts correlates with disease progression. 3 Functional evidence for TIM-3 in AML was established with an anti-TIM-3 antibody which inhibited engraftment and development of human AML in immuno-deficient murine hosts. 1 TIM-3 promotes an auto- stimulatory loop via the TIM-3/Galectin-9 interaction, supporting LSC self-renewal. 4 In addition to its cell-autonomous role on LSCs/blasts, TIM-3 also has a critical role in innate (macrophages, regulatory T cells) and innate (macrophages, dendritic cells, NK cells) immune responses. 5 MBG453 is a high-affinity, humanized anti-TIM-3 IgG4 antibody (Ab) (stabilized hinge, S228P), which blocks the binding of TIM-3 to phosphatidylinerine (PtdSer). Recent results from a multi-center, open label phase Ib dose-escalation study (NCT03066648) in patients with high-risk MDS and no prior hypomethylating agent therapy evaluating MBG453 in combination with decitabine demonstrated encouraging preliminary efficacy with an overall response rate of 58%, 6 and MBG453 combined with azacitidine also showed encouraging response rates. 7 Preclinical experiments were undertaken to define the mechanism of action of the hypomethylating agent and anti-TIM-3 combination.

**Methods** THP-1 cells (a human monocytic AML cell line) were pre-treated with decitabine and co-cultured with anti-CD3 activated human donor peripheral blood mononuclear cells (PBMCs) in an Incucyte-based assay to measure cell killing. The ability of MBG453 to mediate antibody-dependent cellular phagocytosis (ADCP) was measured by determining the phagocytic uptake of an engineered TIM-3-overexpressing Raji cell line in the presence of MBG453 by phorbol 12-myristate 13-acetate (PMA)-activated THP-1 cells. Patient-derived AML xenograft studies were undertaken in immune-deficient murine hosts to evaluate the combination of decitabine and MBG453.

**Results** MBG453 was determined to partially block the TIM-3/Galectin-9 interaction in a plate-based MSD (Meso Scale Discovery) assay, supported by a crystal structure of human TIM-3. 8 Pre-treatment of THP-1 cells with decitabine enhanced sensitivity to immune-mediated killing in the presence of MBG453. MBG453 was determined to mediate modest ADCP, relative to controls. MBG453 did not enhance the anti-leukemic activity of decitabine in patient-derived xenograft studies in immuno-deficient hosts.

**Conclusions** Taken together, these results support both direct anti-leukemic effects and immune-mediated modulation by MBG453. Further studies are ongoing to determine: (1) whether MBG453 can mediate physiologically relevant ADCP of TIM-3-expressing leukemic cells; and (2) the potential of MBG453 to impact the autocrine feedback loop of TIM-3/Galectin-9.

**Ethics Approval** The human tissue used in these studies was under the Novartis Institutes of BioMedical Research Ethics Board IRB, Approval Number 201252867.

**REFERENCES**


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440  **ACTIVITY AND SAFETY OF CAMRELIZUMAB, AN ANTI-PD-1 IMMUNE CHECKPOINT INHIBITOR, FOR PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER**

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**Background** Effective options are limited for patients with non–small-cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy. Camrelizumab is a potent anti-PD-1 monoclonal antibody and has shown promising activity in NSCLC. We assessed the activity and safety of camrelizumab for patients with previously treated, advanced NSCLC patients with negative oncogenic drivers.

**Methods** Patients who progressed during or following platinum-based doublet chemotherapy were enrolled. All patients received camrelizumab(200 mg)every 3 weeks or in combination with chemotherapy until loss of clinical benefit. The primary endpoint was objective response rate (ORR), other