Synergy Between SEA-CD40 and Chemotherapeutics Drives Curative Anti-tumor Activity in Pre-clinical Models

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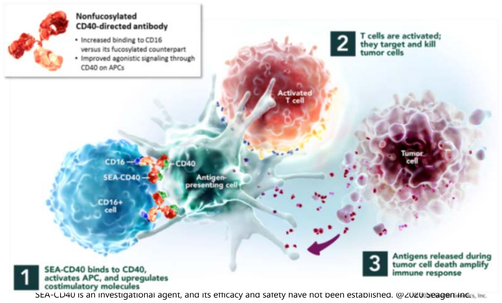
SEA-CD40 Proposed Mechanisms of Action

- SEA-CD40 is an agonistic nonfucosylated CD40 directed humanized monoclonal IgG1 antibody
- Increased binding of SEA-CD40 to FcgRIIIa/CD16 results in a robust innate immune signature characterized by:
  - CD40 directed induction of cytokines and chemokines that up-regulate co-stimulatory receptors
  - Kick-starting an anti-tumor immune responses and enhanced CD8 T cell response
  - Increasing NK cell-mediated ADCC of CD40+ tumor cells
- The immune signature driven by SEA-CD40 exposure has translated from early preclinical models through the clinical trial



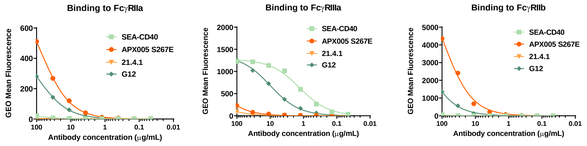
SEA-CD40 is an investigational agent, and its efficacy and safety have not been established. ©2020 Seagen Inc.

SEA-CD40 is Differentiated Based on FcγR Binding

	SEA-CD40*	APX005M	ADC-1013	Selicrelumab
Developer	Seagen	Apexigen	Alligator	Roche
Antibody Class	Humanized IgG1	Humanized rabbit IgG1	Fully human IgG1	Fully human IgG2
Fc backbone modification	↑FcRγIIIa binding	↑FcγRIIa&b ↓FcγRIIIa binding	Native	Native
Antibody used for activity	SEA-CD40	APX005M S267E[1]	G12[2]	21.4.1[3]

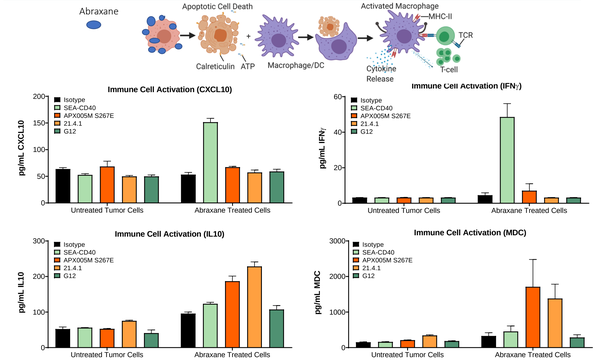
*parent antibody is dacetuzumab; [1]Based on sequence in US patent US9676861B2; [2]Based on sequence in South Korea patent SK20170041790A, [3]Based on clone described in Cancer Immunology Research March 2015 3; 236.

Activating FcγReceptors | Inhibitory FcγReceptor

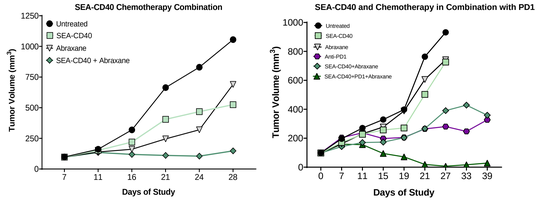


Antibodies were assessed for FcγR binding using flow cytometry to CHO cells transfected with human FcγRIIa, IIb or IIIa. As expected, APX005 S267E exhibited the highest affinity for FcγRIIa and FcγIIb. SEA-CD40 had the highest affinity for FcγRIIIa with lowest affinity for FcγRIIb These data highlight the differential activity for FcγRs and potential for differential impact on activity.

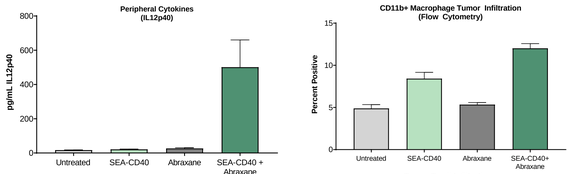
SEA-CD40 Induces Robust Immune Cell Activation to Abraxane Treated Tumor Cells



In vitro, pancreatic tumor cells treated with Abraxane for 18hrs and human PBMCs with various CD40 agonists were added and immune activation assessed. SEA-CD40 uniquely drove release of immune activating cytokines (CXCL10, IFNγ) when combined with Abraxane. In contrast other CD40 agonists amplified immune suppressive cytokines (IL-10, MDC).

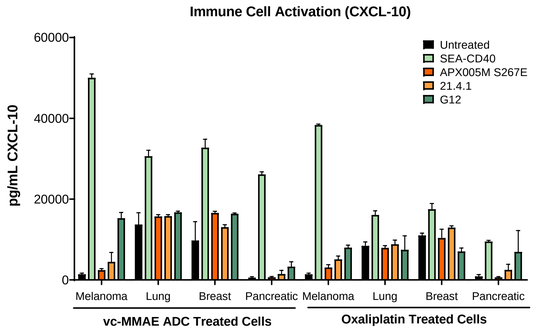


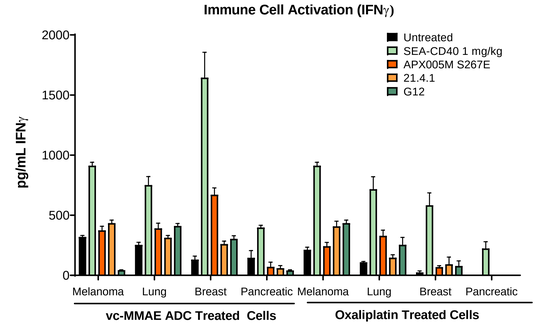
hCD40 TG mice bearing syngeneic tumors were treated when tumors reached 100 mm^3 with either Abraxane, SEA-CD40 or the combination (Q3XD3) +/- anti-PD1. Single agent treatment resulted in tumor growth delay, the combination of SEA-CD40 and Abraxane resulted in significant anti-tumor activity which was enhanced with anti-PD1 treatment.

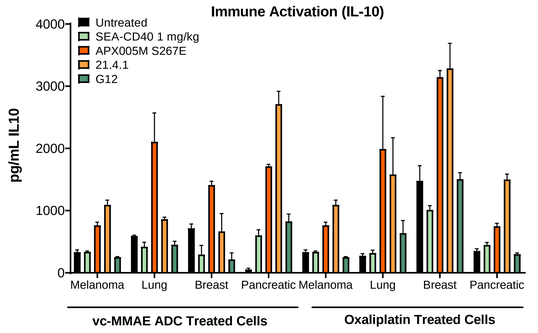


Peripheral cytokines or tumors from animals treated with single agents, or the combination, were taken 24hrs after the third treatment. Cytokines associated with APCs were increased in animals receiving SEA-CD40 plus Abraxane. Cytokine production was associated with influx of immune cells (Macrophages & T cells) into tumors as assessed by Flow Cytometry and IHC.

SEA-CD40 Enhance ICD Agent Activity in Multiple Indications

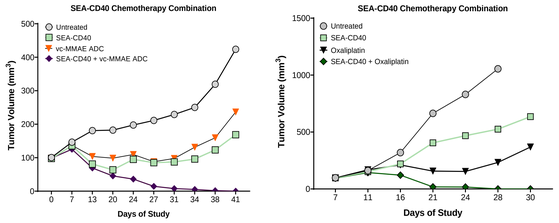






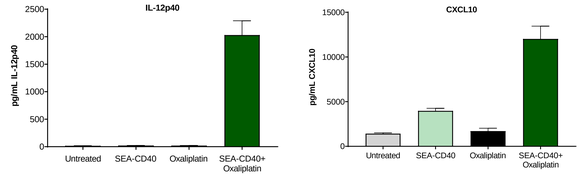
Tumor cells lines from multiple indications were treated in vitro with oxaliplatin or a vc-MMAE ADC for 18hrs and then added to human PBMCs plus various CD40-directed agonists. immune activation was assessed. SEA-CD40 combined with MMAE ADC or oxaliplatin drove release of immune activating cytokines (CXCL10, IFNγ) while other CD40 agonists amplified the immune dampening cytokine (IL-10).

SEA-CD40 Plus ADC or ICD Chemotherapeutic Agent Drive Curative Responses

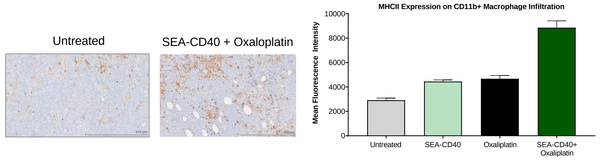


Tumor bearing human CD40 Tg mice were treated when tumors reached 100 mm^3 with single agent or the combination (Q3XD3). Single agent treatment resulted in tumor growth delay, the combination of SEA-CD40 and Vedotin-based ADC or an ICD chemotherapeutic agent drove curative anti-tumor responses.

SEA-CD40 + ICD-inducing Agents Engage Immune Cells *In Vivo*



Peripheral cytokines were examined following treatment of tumor-bearing animal. Increases in cytokines associated with APC activation were further increased in animals treated with the combination of SEA-CD40 and an ICD-inducing agent.



Tumors from animals treated with single agents or the combination were dissociated, and immune infiltration assessed by flow cytometry 24 hrs after the third treatment. Increases in macrophage infiltration and their activation state were significantly enhanced in tumors from animals treated with SEA-CD40 in combination with an ICD-inducing agent. IHC analysis confirmed increase in macrophage recruitment.

Conclusions

- SEA-CD40 is a differentiated CD40-targeted antibody that drives robust innate cell activation in combination with Abraxane that results in robust antitumor responses.
- SEA-CD40 in combination with Vedotin-based ADCs or ICD chemotherapeutic agents drives robust immune cell activation to a broad array of tumor types and results in curative responses *in vivo*.
- A Phase 1 open-label study of currently enrolling a cohort to evaluate the combination of SEA-CD40, gemcitabine, nab-paclitaxel, and pembrolizumab in PDAC in the United States (NCT02376699).

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