MITAZALIMAB – A CD40 AGONIST TO UNLEASH DENDRITIC CELLS IN IMMUNO-ONCOLOGY

Peter Ellmark, PhD, Assoc. Prof., VP Discovery, Alligator Bioscience
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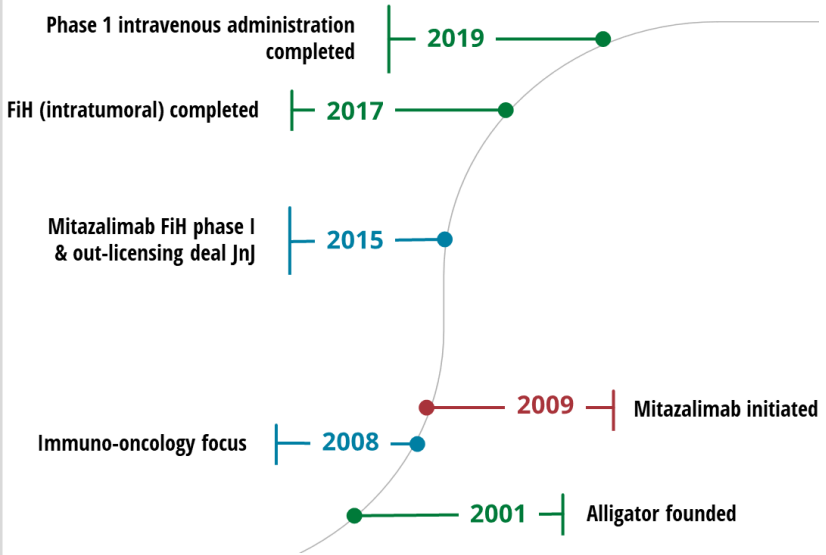
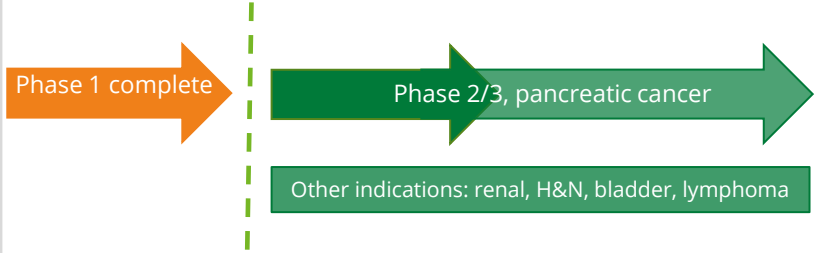
Mitazalimab: Phase II ready CD40 antibody

Mitazalimab – from idea to phase2-ready drug product





Clinical	Proof of mechanism confirmed in patients Safe and tolerable up to 1.2mg/Kg
Drug supply	Clinical material available for Ph2 & initial Ph 3
Launch	Possible launch 2026
BD	Available for Global or Regional License or clinical collaboration to expand indications

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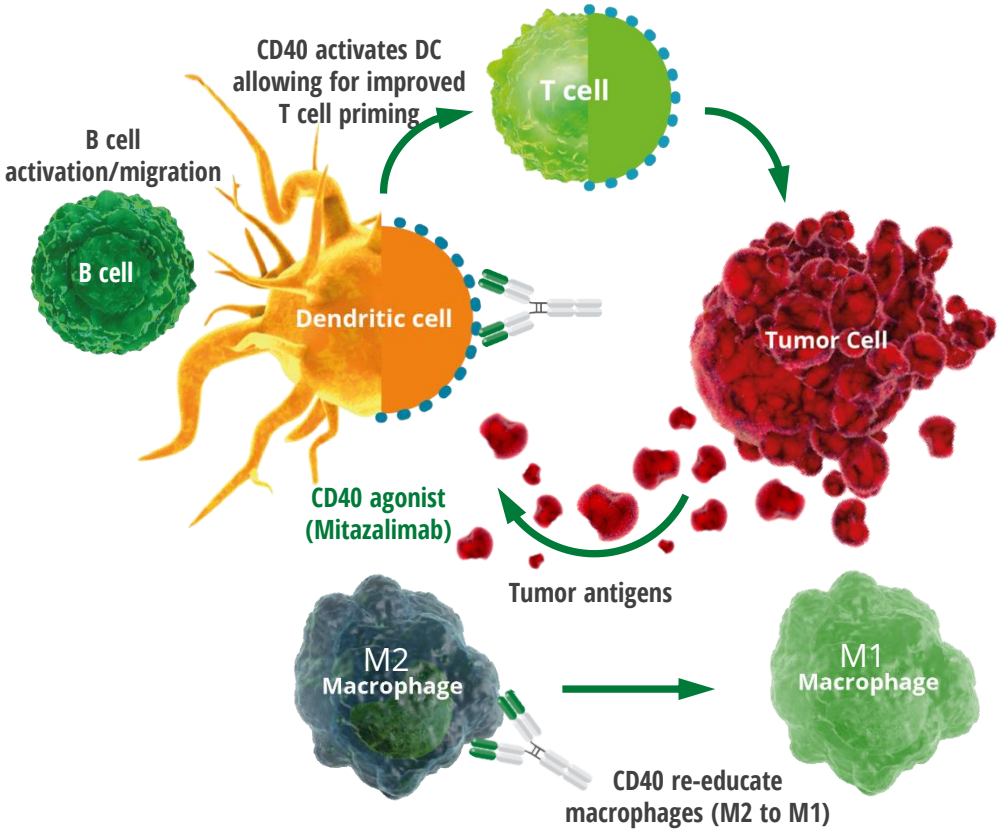
Mitazalimab – Unleashing Dendritic cells in Immuno-Oncology



- Mitazalimab binds to CD40, the key activation receptor on antigen presenting cells, e.g. dendritic cells (DC), B cells and macrophages
- Mitazalimab activates DC (and B cells) allowing for improved T cell priming
- Mitazalimab re-educates macrophages from a tumor promoting (M2) to a tumor suppressing (M1) phenotype
- The mode of action provides opportunities for use in combination with chemotherapy, vaccines and checkpoint inhibitors

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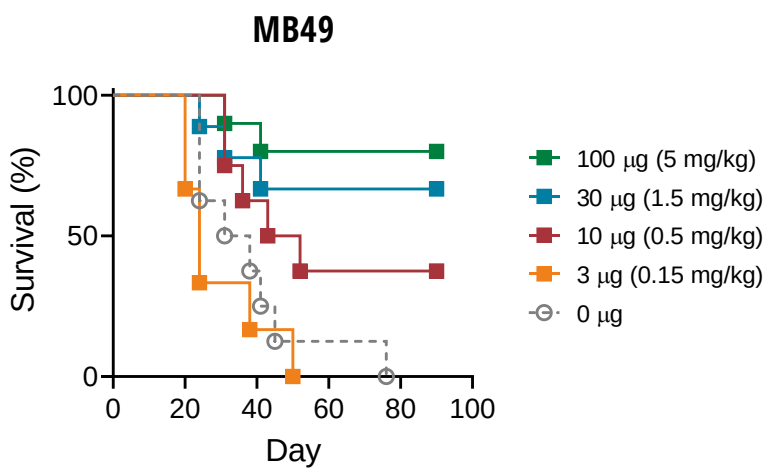
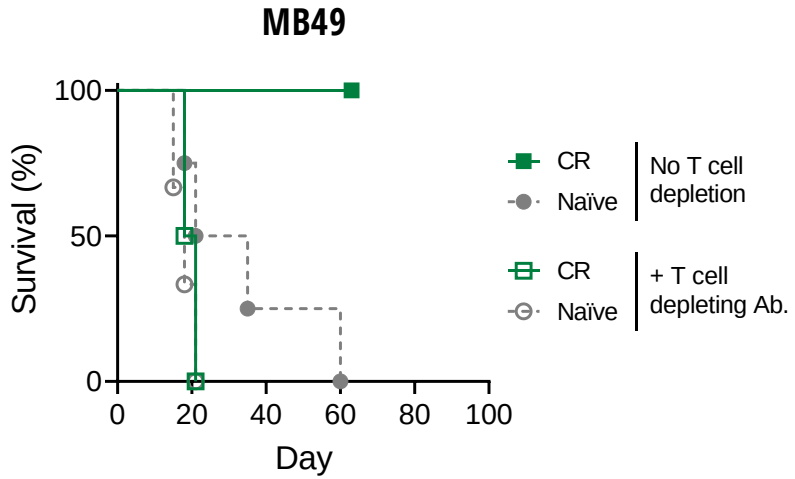
Mitazalimab demonstrates anti-tumor effect

Effective dose in mouse model approx 1 mg/kg



hCD40tg mice were inoculated with MB49 tumors s.c. The mice received the indicated doses of Mitazalimab p.t. on days 7 and 10.

Induce T cell-dependent memory



hCD40tg mice previously cured from MB49 tumors by Mitazalimab (complete responders, CR), were rechallenged with MB49 tumors. Alternatively, naïve mice were used. One cohort among both CR and naïve mice also received anti-CD4 and anti-CD8 antibody in order to deplete T cells.

Mitazalimab administered peritumorally or systemically reduces growth of a bladder carcinoma tumor.

Mangsbo *et al*, 2015, Clinical Cancer Research

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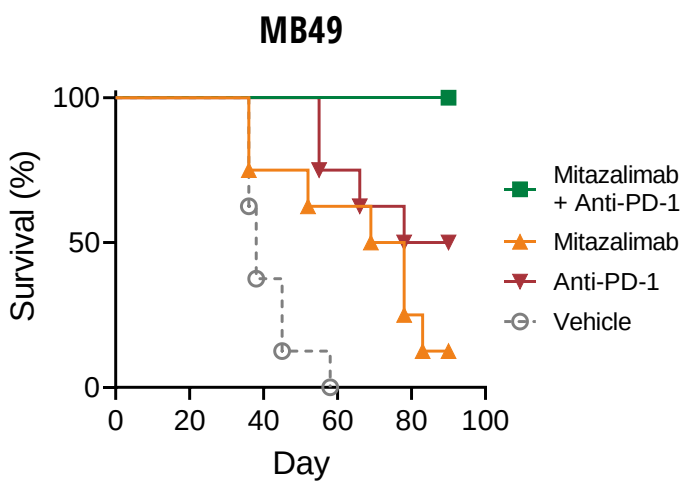
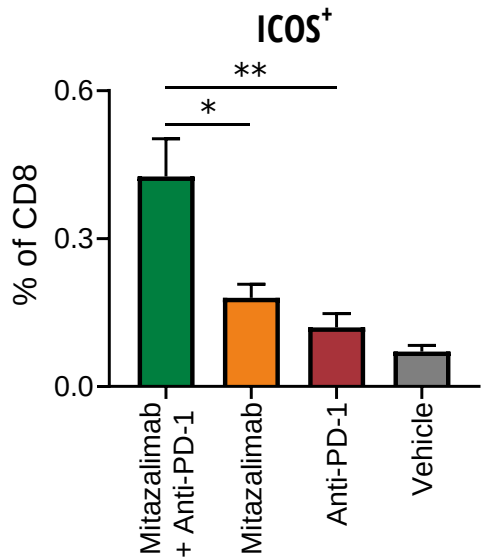
Mitazalimab synergizes with PD-1 blockade

Anti-tumor effect



hCD40tg mice were inoculated with MB49 tumors s.c. The mice received 100 µg Mitazalimab i.p. every 2-3 days from day 7 until day 20 or 250 µg anti-PD-1 surrogate antibody (RMP1-14) i.p. on days 7, 10 and 13. Alternatively, mice received a combination of the two therapies.

T cell activation



hCD40tg mice were inoculated with E.G7-OVA tumors s.c. The mice received 100 µg Mitazalimab i.p. or/and 250 µg anti-PD-1 surrogate antibody (RMP1-14) i.p. on days 0, 3, 5, 7 and 10. Activation of splenic $CD8^+$ T cells was assessed by determining frequency of $ICOS^+$ cells by flow cytometry.

Mitazalimab combined with a surrogate anti-PD-1 antibody results in improved anti-tumor effect and T cell activation.

Irenaeus *et al*, 2019, International Journal of Cancer

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Mitazalimab: Strong competitive position

Compound	Company	Phase
APX005M	Apexigen	II
Mitazalimab	Alligator	I/II
Selicrelumab	Roche	I/II
CDX-1140	Celldex	I/II
ABBV-927	Abbvie	I
SEA-CD40	Seattle Genetics	I

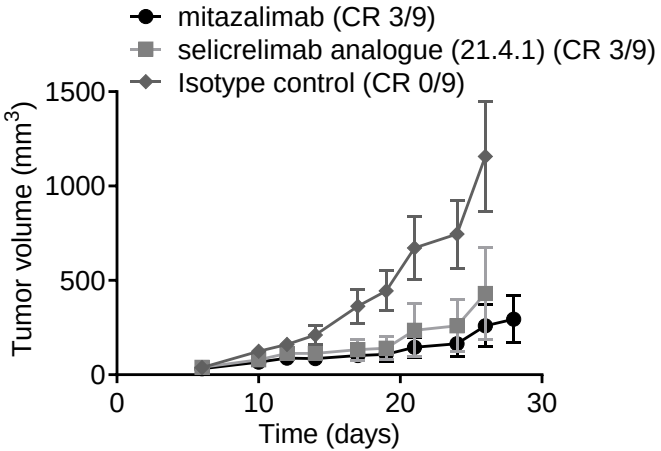
- Several CD40-targeting antibodies are in clinical development
- Mitazalimab has potential to be first in class and best in class

CD40 agonists:
Selective CD40 activation
FcgR dependent

CD40 superagonists:
General CD40 activation
FcgR independent

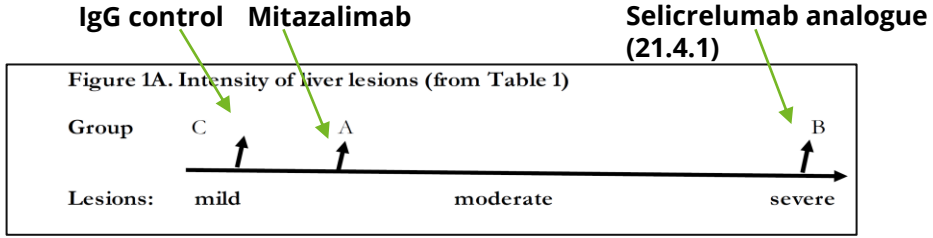
Mitazalimab vs superagonist – preclinical efficacy

> Mitazalimab compares well to reference superagonist antibody

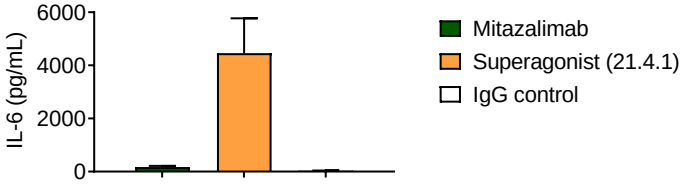


hCD40tg mice were challenged with syngeneic bladder tumors (MB49, hCD40-). Mitazalimab (30 µg), selicrelumab (30 µg), or isotype control (30 µg), were administered day 7 and 10, (n=9). IL-6 was measured in serum taken 4 h post treatment on day 7.

> Mitazalimab causes less pathology in liver



> Mitazalimab induces lower IL-6 release



Top: Blinded histopathology examination by independent assessors at the Swedish National veterinary institute. Bottom: IL-6 levels measured from blood samples collected 4 h post treatment day 6 A) mitazalimab, B) superagonist (21.4.1) and C) isotype control. B16 tumor bearing hCD40tg mice treated with 100 µg at day 3, 6 and 9 (n = 6), sacrificed at day 15

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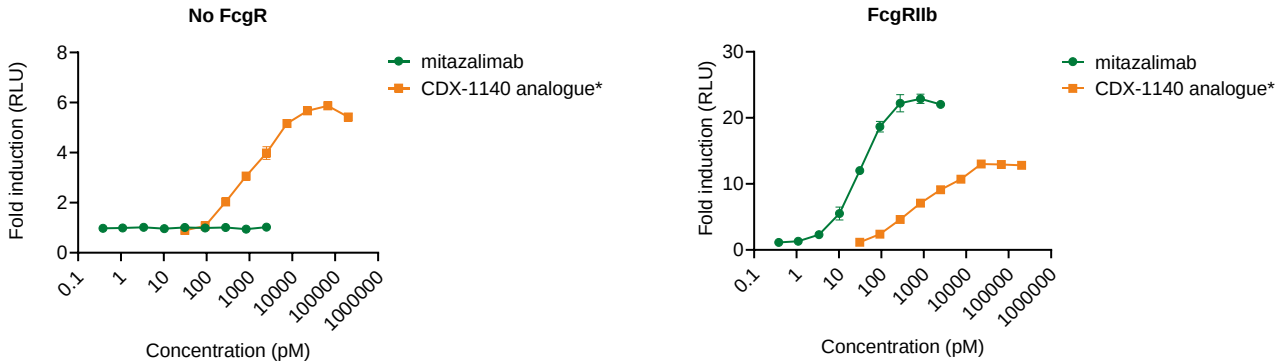
Mitazalimab vs FcyR independent CD40 agonists

- FcyR independent antibodies activate also in the abscence of FcyR
- The IgG2 format of CDX-1140 provides weak FcyR-mediated cross linking and agonistic effect compared to mitazalimab



In vitro activity of CD40 mAbs in CD40 reporter assay cocultured with CHO cells transfected with FcyRIIb or without FcyR

* Seq from Pat no US 2019/0322743 A1

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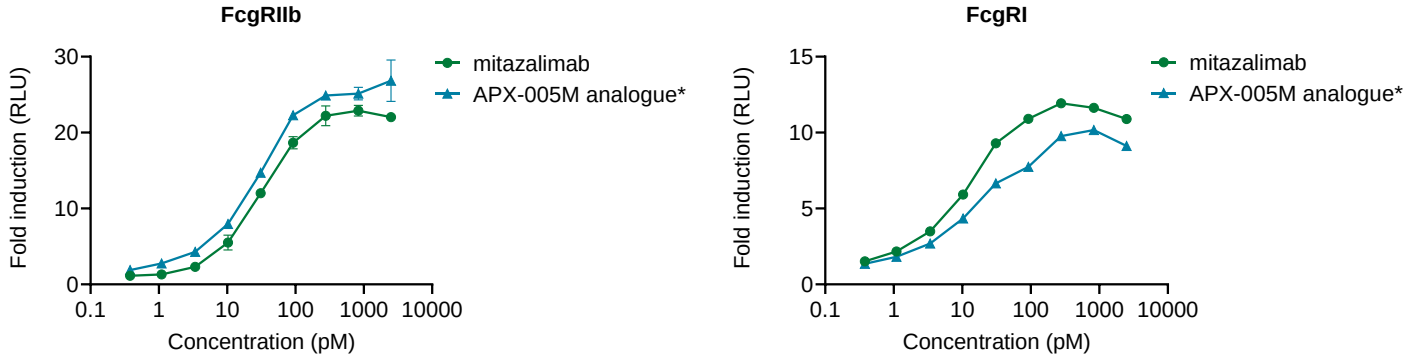
FcyR dependent CD40 agonists – role of Fc

- Differences in FcyR affinity modify the CD40 agonistic activity
- Maximal agonistic effect dictated by FcyR distribution (1, 2a, 2b, 3) in different compartments



In vitro activity of CD40 mAbs in CD40 reporter assay cocultured with CHO cells transfected with FcgRI or FcgRIIb.

* Seq from Pat no US_9676861_B2

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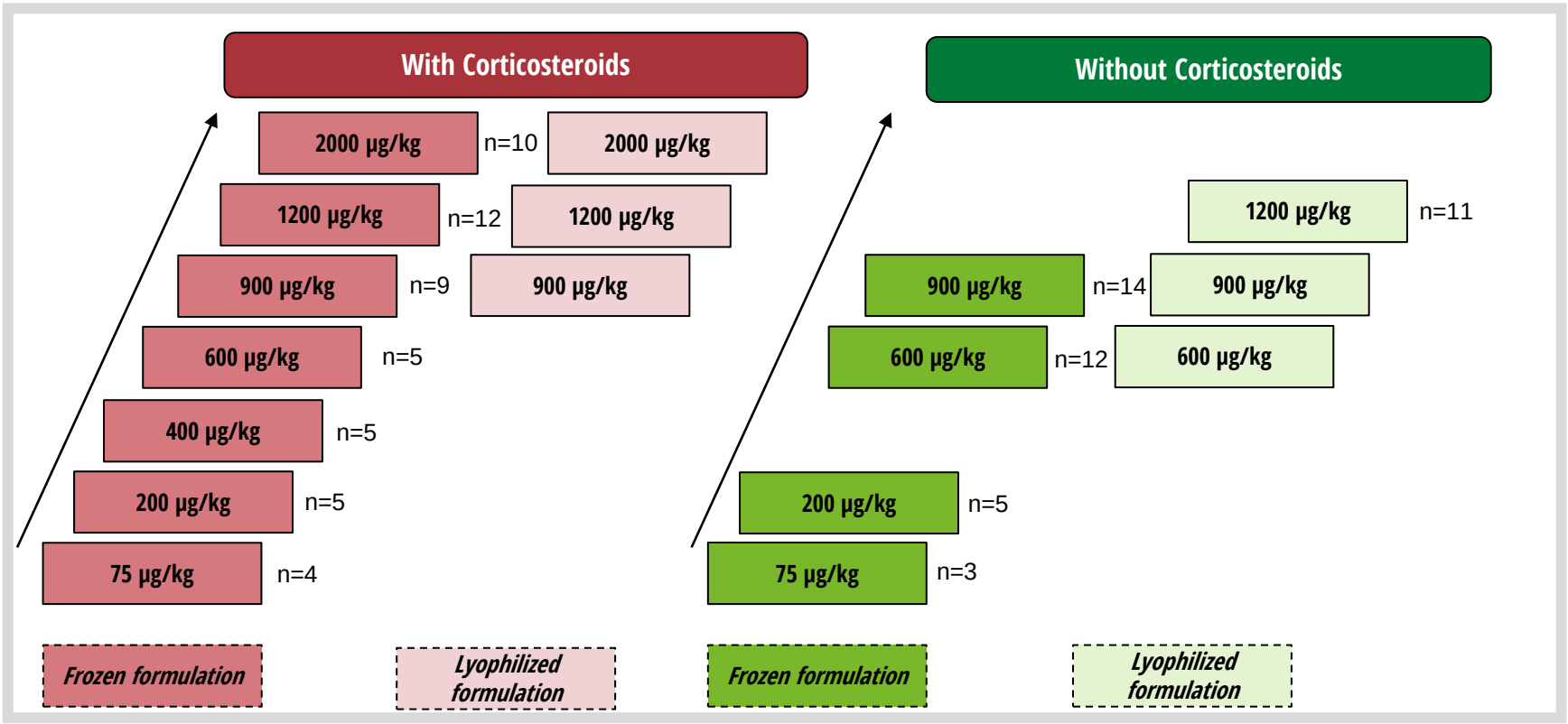
Phase 1 i.v. study (NCT02829099)



Calvo *et al*., JCO 2019;37;15 suppl:2527

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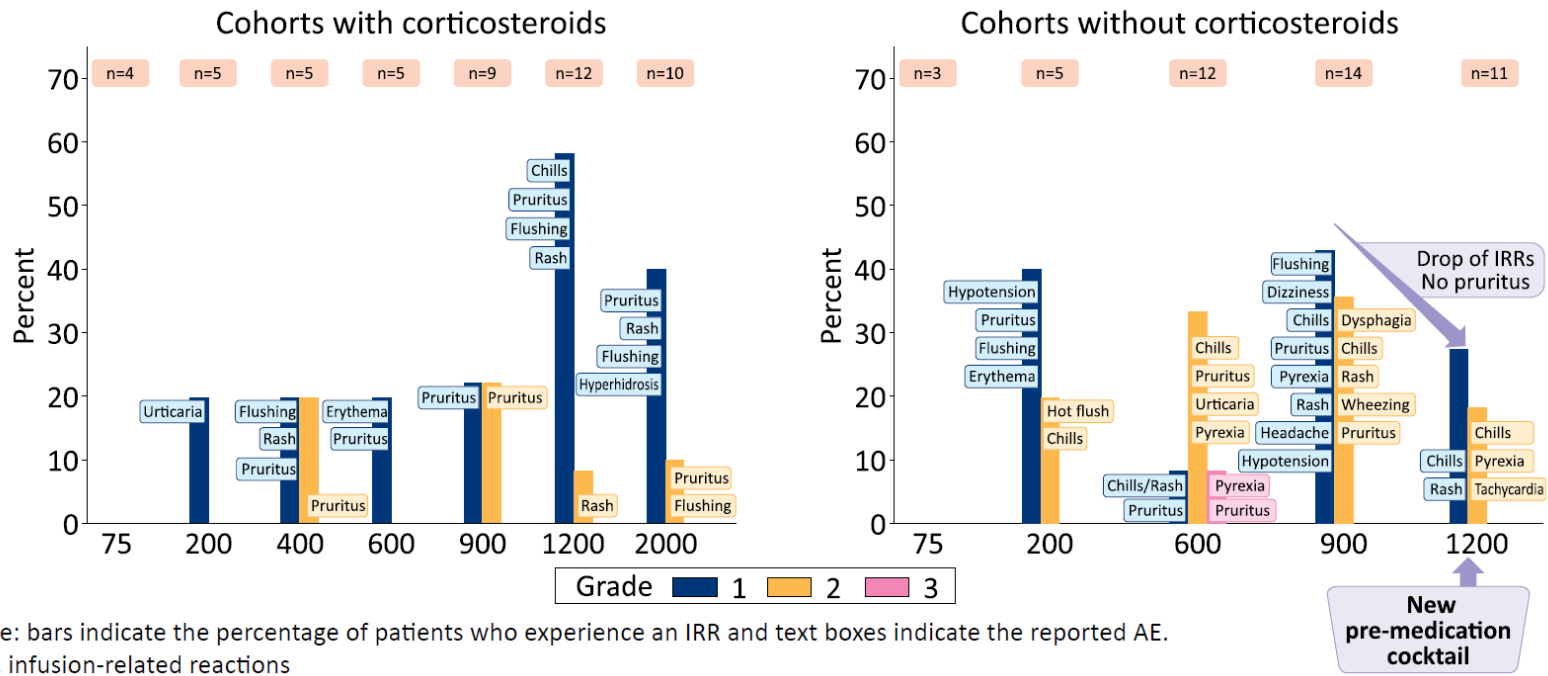
Infusion related reactions – i.v. study

Figure 3: IRR nature and incidence per dose level (cohorts w/ & w/o corticosteroids)



Note: bars indicate the percentage of patients who experience an IRR and text boxes indicate the reported AE.
IRR, infusion-related reactions

Calvo *et al*., JCO 2019;37;15 suppl:2527

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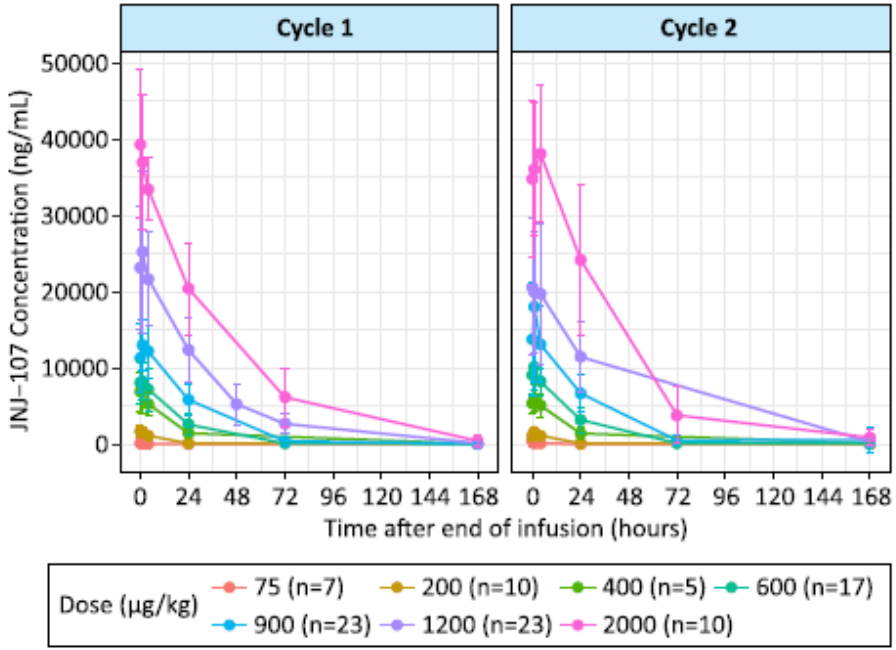
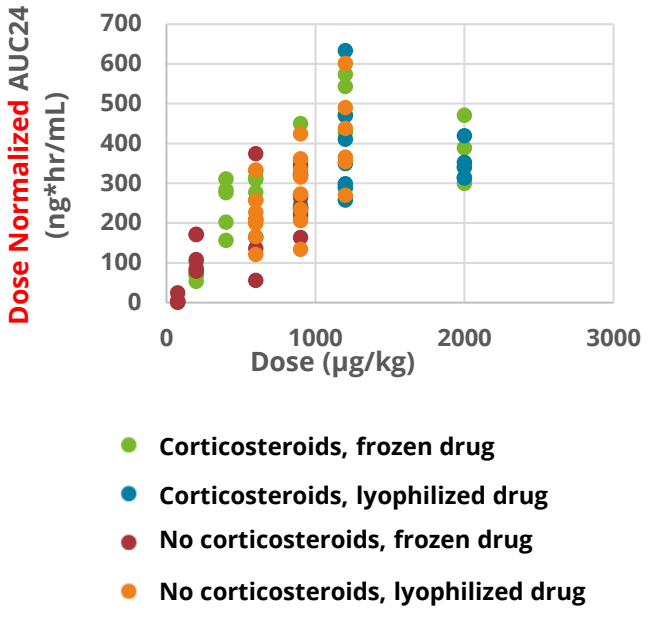
Pharmacokinetics

- Target mediated drug disposition ($t_{1/2}$: 16-24h)
- Target saturation at ~1200 µg/kg.





Calvo et al., JCO 2019;37;15 suppl:2527

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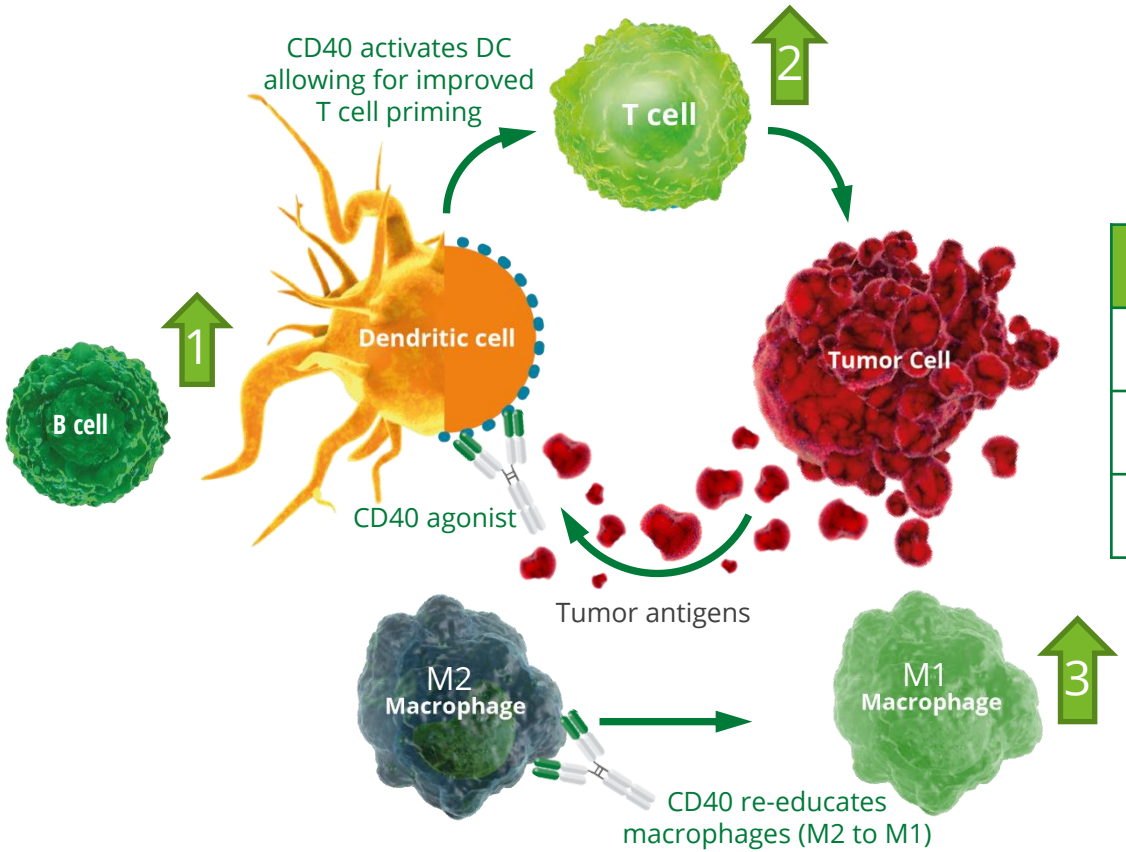
Conclusions i.v. study on safety and anti-tumor activity

- Mitazalimab has a manageable safety profile both with and without corticosteroid premedication when administered once every 2 weeks
- Preliminary PK data showed moderate variability and short half-life.
- Antitumor activity
  - A partial response was observed in one patient with renal cell cancer who was in the study for 9 months
  - 10 (11%) patients showed stable disease lasting ≥ 6 months
- Future clinical development will require combination therapy

Mitazalimab – Pharmacodynamic Biomarkers



	Cell type	Activation marker	Cytokine/ Chemokine
1	B cells	• CD80/86 • HLA-DR	• IL-6 • IL-12
2	T cells		• IFNγ, TNFα • IL-10, IP-10
3	Macrophages	• CD80/86	• MCP-1 • IL-8

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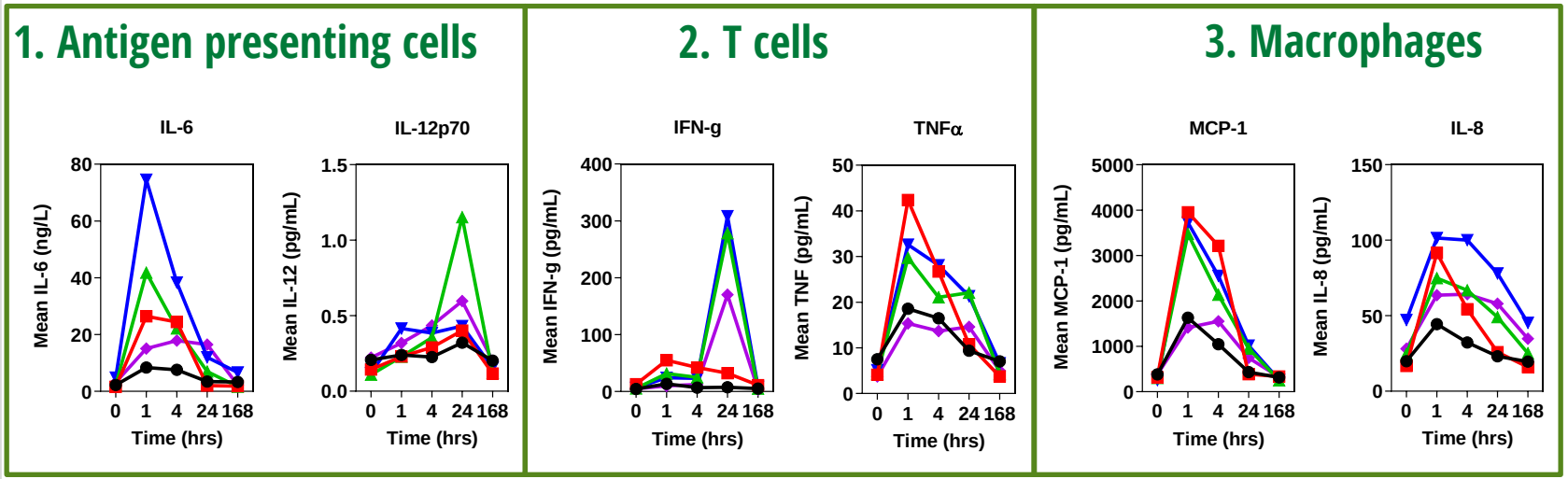
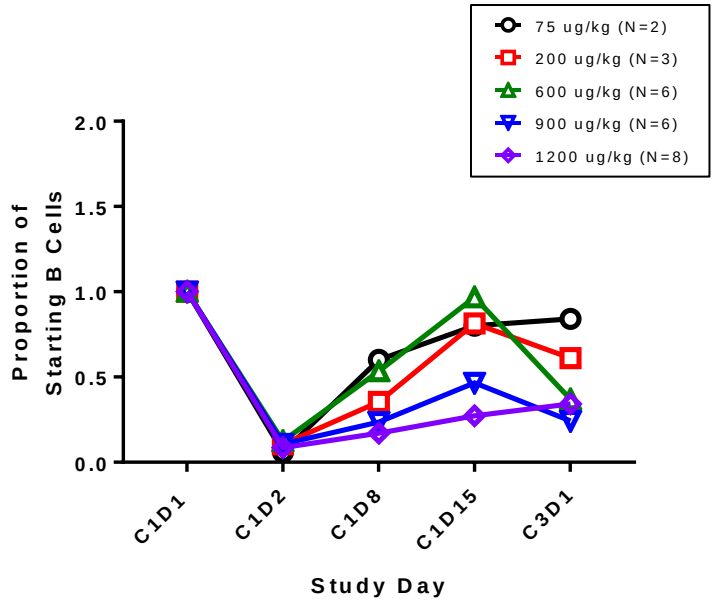
PD-markers – cytokines and chemokines

> Mitazalimab induce cytokines and chemokines as expected from a CD40 agonist

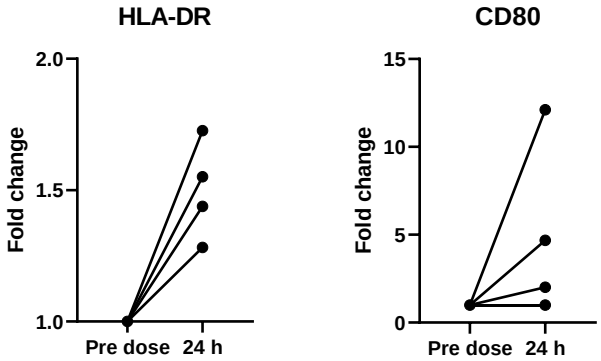


Activation of B cells in circulation – i.v. study

> B cell margination



> B cell activation markers



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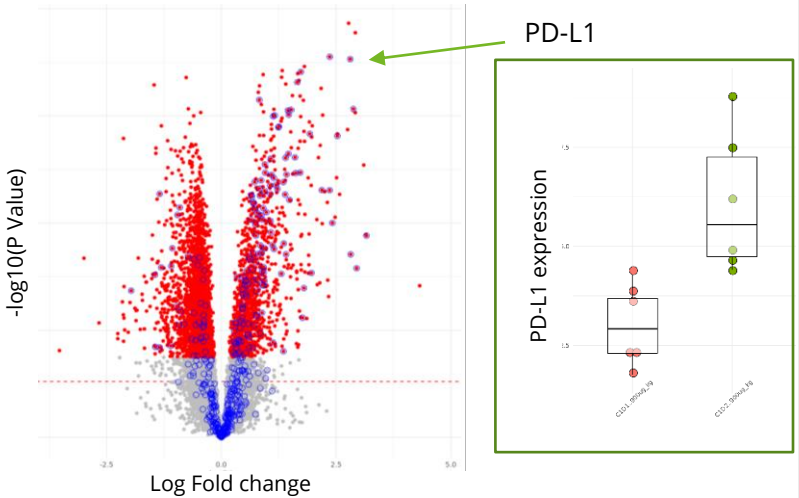
CD40 activation – RNA seq data

- RNA seq on samples collected from whole blood before and after (1 day) treatment
- Treatment groups w/o steroids at 75, 200, 600 and 900 µg/kg analyzed
- Unsupervised analysis:
  - post- vs pre-treatment
  - dose-dependent effects
- Supervised analysis:
  - Evaluate the expression of several markers known to be deregulated with CD40 activity to validate the mechanism of action for the CD40 agonist

Differentially expressed genes (900µg/kg)



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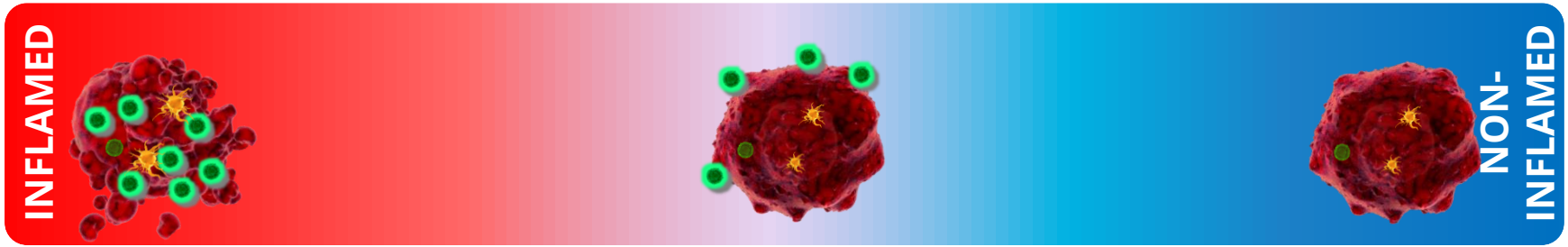
Conclusion - RNAseq analysis

- Dose dependent expression of relevant genes pre vs post treatment
- Pre-selected gene signatures related to known CD40 biology including signatures related to IFN-gamma signaling show the expected changes in expression
- Supports activation of antigen presenting cells/macrophages
- High correlation between genes shown to be upregulated with treatment
- Upregulation of PD-1 ligands supports combination with PD-(L)1 therapy

Future development - CD40 drive efficacy also in non-inflamed tumors



CD40 stimulation enhance priming, quantity and quality of tumor specific T cells

- Impaired dendritic cells/T cell priming
- MΦ (M2) suppressed

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CD40 agonists and Pancreatic cancer

Pancreatic cancer is an immunologically "cold" tumor

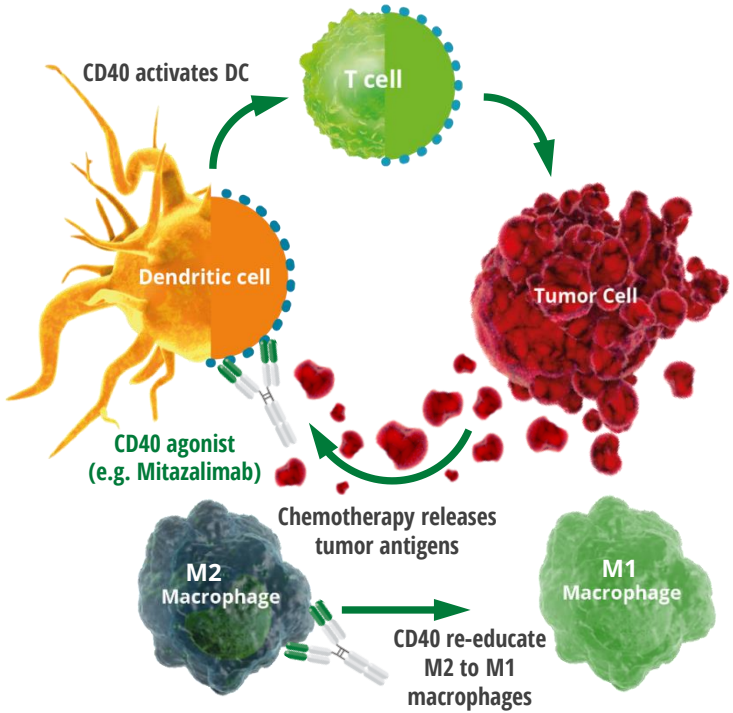
- Low immune cell infiltration
- Suppressive tumor stroma
- Low immunogenicity

CD40 agonistic antibodies

- Activates dendritic cells, enabling them to prime tumor specific T cells
- Re-educate macrophages, from tumor promoting (M2) to tumor suppressive (M1) type

CD40 agonist plus chemotherapy release the brakes

- Chemotherapy releases tumor antigens which are taken up by DCs stimulated by CD40
- Tumor antigen loaded DCs activates cytotoxic T cells leading to tumor cell killing



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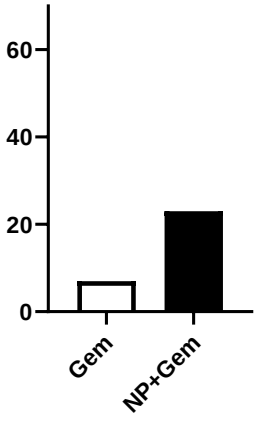
Pancreatic Cancer: Promise of chemo+ CD40 (and PD-1)

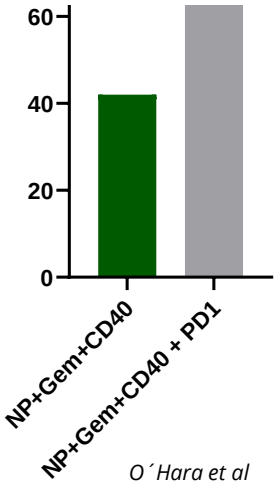
> CD40 agonistic antibodies increase ORR in pancreatic cancer (phase 1 studies)

Overall response rate (%)

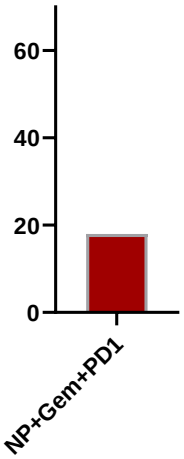


Von Hoff et al
NEJM 2013

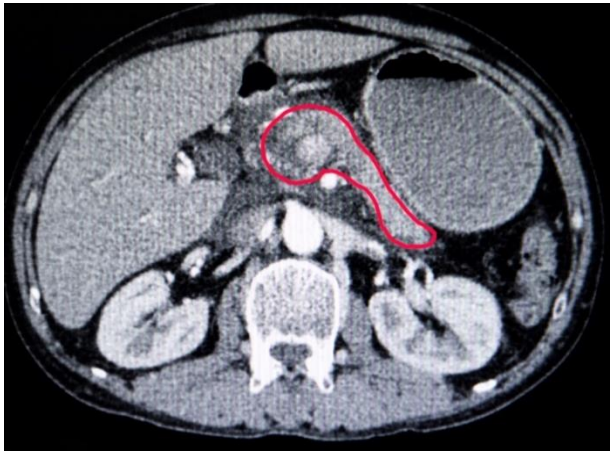
Apexigen



O´Hara et al
AACR, 2019



Wainberg et al
J Clin Onc 2019



Promising data in pancreatic cancer with CD40 agonist from Apexigen in combination with chemo (despite no single agent responses in ph1 dose escalation)

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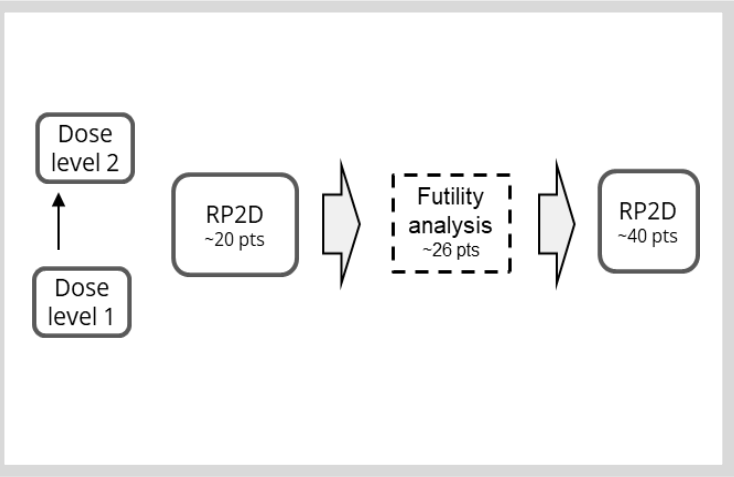
OPTIMIZE-1: Mitazalimab in Pancreatic Cancer

Establish safety and efficacy with Folfirinox



Dosing regimen: Folfirinox 2 days before mitazalimab

- Run-in part to demonstrate safety of mitazalimab in combination with standard of care
- Expansion at selected dose (RP2D) with an additional 20 patients for interim efficacy evaluation followed by further expansion upon positive signal
- Dosing schedule of mitazalimab based on mechanism of action

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Acknowledgments

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Alligator team

Partners