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Mitazalimab, a potent CD40 agonist with potential for combination with chemotherapy

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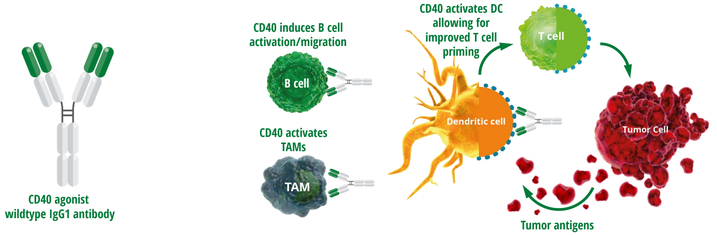
Tumor-directed activity and limited systemic immune activation

Mitazalimab – a CD40 agonist with best-in-class profile

- Mitazalimab is a FcγR crosslinking dependent CD40 agonistic antibody (IgG1) with a tumor-directed immune activation
- Mitazalimab binds with high affinity to a unique binding epitope on the CD40 receptor which allows for high efficacy and potency
- Mitazalimab is well tolerated with manageable side effects up to 1200 µg/kg (2000 µg/kg with corticosteroids) with early evidence of clinical activity from the phase 1 dose escalation study included one partial response (PR) and 10 patients with prolonged stable disease (SD) ≥6 months
- Mitazalimab has potential for superior clinical activity, since mitazalimab is the only FcγR-dependent CD40 agonist with tumor-directed activity that can be dosed >1 mg/kg



Mode of action

- Mitazalimab binds to CD40, the key activation receptor on antigen presenting cells, e.g., DCs, B cells and macrophages
- Mitazalimab activates DCs allowing priming of tumor specific T cells
- Mitazalimab activates TAMs and has the ability to reshape the tumor infiltrating myeloid microenvironment
- Mitazalimab has been shown in preclinical studies to provide synergistic efficacy with chemotherapy, vaccines and checkpoint inhibitors

Mitazalimab – a potent, FcγR crosslinking dependent CD40 agonist

- Mitazalimab and APX005M (sotigalimab) are both FcγR crosslinking dependent while CDX-1140 is FcγR crosslinking independent
- In contrast to FcγR cross linking independent antibodies, which activate CD40 broadly regardless of FcγR expression in the microenvironment, the FcγR crosslinking dependency of mitazalimab has the potential to direct the immune response to the tumor environment
- Differences in FcγR affinity and FcγR expression and bioavailability modulate the CD40 agonistic activity of FcγR crosslinking dependent antibodies

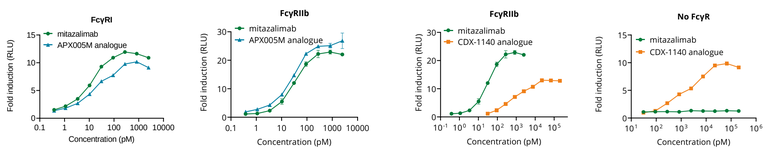


Figure 1. In vitro activity of CD40 mAbs in CD40 reporter assay co-cultured with CHO cells transfected with FcγRIIb, FcγRI or without FcγRs

Mitazalimab alters the composition of myeloid cells in the tumor

- Mitazalimab activates tumoral and splenic dendritic cells (DCs) in human CD40 transgenic mice in vivo, which results in improved activation of both splenic and intratumoral T cells
- Mitazalimab alters the composition of tumor myeloid cells such that monocytes and macrophages are reduced in favor of granulocytic cells

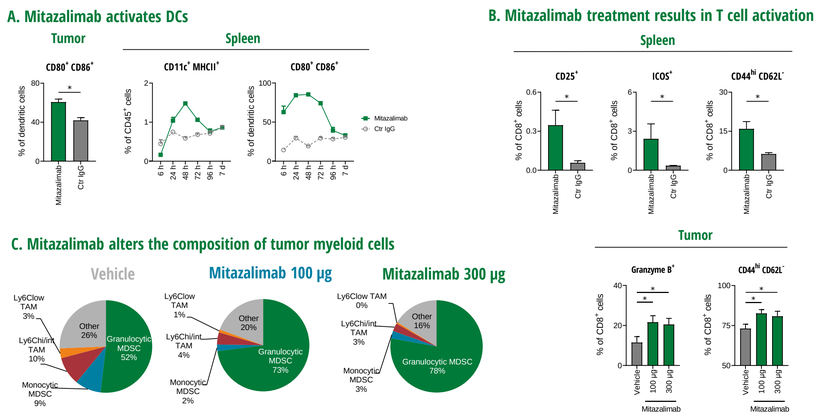


Figure 2. A. MB49 tumor-bearing hCD40tg mice received one dose of 100 µg Mitazalimab i.p. and 24 h later, tumors were collected and activation of dendritic cells (CD11c+ MHCII+) assessed by determining the frequency of CD80+ CD86+ cells. Alternatively, hCD40tg mice received one dose of 100 µg Mitazalimab i.p. and spleens were collected at the indicated time points following treatment. **B.** hCD40tg mice were inoculated with MB49 tumors s.c. On days 7, 10 and 13 post-inoculation, mice received 100 µg or 300 µg Mitazalimab i.p. Twenty-four hrs after the final treatment, mice were sacrificed, tumors collected, and analyzed by flow cytometry for T cell activation. **C.** hCD40tg mice were inoculated with MB49 tumors s.c. On days 7, 10 and 13 post-inoculation, mice received 100 µg or 300 µg Mitazalimab i.p. Twenty-four hrs after the final treatment, mice were sacrificed, tumors collected and analyzed by flow cytometry for various myeloid cell subpopulations. The pie charts show the composition of the tumor myeloid CD45+ CD11b+ cells.

Mitazalimab activates TAMs from human tumor samples

- Mitazalimab activates tumor associated macrophages (TAMs) purified from human prostate and ovarian tumor samples
- CD40 agonists have the capacity to activate myeloid immune cells, which thereby reshape the tumor microenvironment by reducing the effect from immunosuppressive immune cells

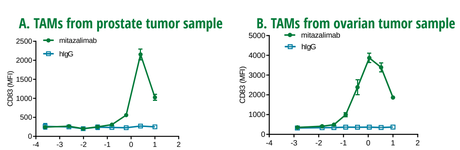


Figure 3. Human primary tumors, **A.** prostate and **B.** ovarian tumors were processed into single-cell suspensions and incubated with mitazalimab or isotype control. Expression levels of CD83 on TAMs were assessed by flow cytometry.

Mitazalimab synergizes with anticancer treatments

- Mitazalimab administered as monotherapy reduces tumor growth and induces survival in preclinical tumor models
- Mitazalimab combined with chemotherapy, checkpoint inhibitor (anti-PD-1) or vaccine has a synergistic effect on survival in preclinical tumor models
- These preclinical data demonstrate opportunities for combination of mitazalimab with other treatment modalities in immuno-oncology

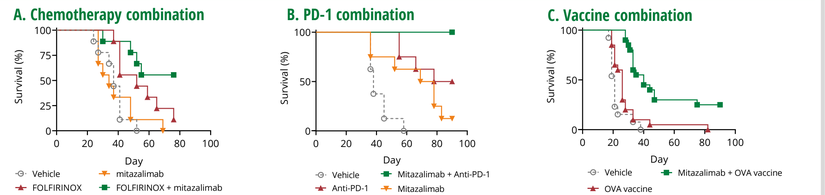


Figure 4. A. MB49 tumor-bearing hCD40tg mice received treatment with FOLFIRINOX (oxaliplatin, irinotecan, folinic acid and 5-fluorouracil) on days 7-8, 14-15 and 21-22, and/or 100 µg mitazalimab on days 10, 17 and 24. **B.** MB49 tumor-bearing hCD40tg mice received 100 µg mitazalimab every 2-3 days from day 7 until day 20, or 250 µg anti-PD-1 surrogate antibody on days 7, 10 and 13. **C.** hCD40tg mice received 100 µg mitazalimab and 200 µg ovalbumin protein (OVA) simultaneously on day 0 and 7. Controls received OVA only. Seven days following the second therapy dose, the mice were inoculated with E.G7-OVA tumors.

OPTIMIZE-1: Phase 1b/2 study in Pancreatic Cancer

OPTIMIZE-1: Phase 1b/2 study of mitazalimab in combination with mFOLFIRINOX in Pancreatic Cancer

- Phase 1b run-in to demonstrate safety of mitazalimab in combination with mFOLFIRINOX
- Phase 2 expansion at selected dose (RP2D) with an additional 21 patients for interim efficacy evaluation followed by further expansion upon positive signal
- CTA approved in France and Belgium, and FPI in Q2 2021

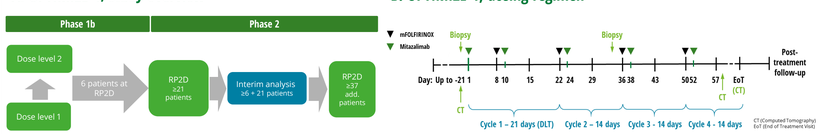


Figure 5. A. study overview and **B.** dosing regimen of OPTIMZE-1 with the aim to establish safety and efficacy of mitazalimab combined with mFOLFIRINOX

Summary and conclusions

- Mitazalimab is a FcγR crosslinking dependent CD40 agonist (IgG1) which binds to a unique epitope on the CD40 receptor that allows for tumor-directed immune activation as well as high efficacy and potency
- Preclinical data demonstrate that Mitazalimab activates DCs and alters the composition of tumor infiltrating myeloid cells, which results in improved activation of both splenic and intratumoral T cells
- Mitazalimab activates TAMs purified from human prostate and ovarian tumor samples, and thereby has the potential to reshape the myeloid cells in the tumor microenvironment
- Mitazalimab combined with chemotherapy, checkpoint inhibitor (anti-PD-1) or vaccine has a synergistic effect on survival in preclinical tumor models
- OPTIMIZE-1, a phase 1b/2 study with mitazalimab in combination with mFOLFIRINOX in pancreatic cancer is planned to be initiated in Q2 2021 and CTA has been approved in France and Belgium