Mitazalimab, a potent CD40 agonist in combination with chemotherapy redirects and activates tumor infiltrating myeloid cells

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

- Mitazalimab is an Fcγ-FcγR-dependent CD40 agonistic antibody (yG7) 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 has potential for superior clinical activity, since mitazalimab is the only Fcγ-FcγR-dependent CD40 agonist with tumor-directed activity that can be dosed >1 mg/kg

Mitazalimab in clinical development

- Phase I
  - Mitazalimab has shown clinical activity and a manageable safety profile in Phase I studies
  - Safety: Safe and tolerable up to response 1200 µg/kg i.v. and most drug-related adverse events grade 1-2
  - Responses: 1 patient with partial and 10 patients with stable disease (> 6 months)
- Phase 1/2
  - OPTIMIZE-1 (NCT04888312) is an ongoing phase 1b/2, open-label, multicenter study designed to evaluate safety, tolerability, and efficacy of mitazalimab in combination with chemotherapy (mFOLFIRINOX) in adults diagnosed with previously untreated metastatic pancreatic cancer

Mitazalimab activates tumor associated macrophages (TAMs) which have the ability to reshape the myeloid cell compartment in the tumor

- Mitazalimab binds to CD40, the key activation receptor on antigen presenting cells (APCs), i.e. dendritic cells (DCs), B cells and macrophages
- Mitazalimab activates tumor associated macrophages (TAMs) which have the ability to reshape the tumor infiltrating myeloid microenvironment leading to stromal degradation and enhanced chemo and immune cell penetration
- Mitazalimab activates DCs allowing priming of tumor specific T cells which results in more tumor specific T cells infiltrating and killing the tumor and improved anti-tumor efficacy

Mitazalimab in combination with chemotherapy, that kills tumor cells, improves the release of tumor antigens that are picked up by DCs enhancing priming and infiltration of tumor specific T cells

Mitazalimab activates TAMs from human tumor samples

- Mitazalimab activates TAMs purified from human prostate and ovarian tumor samples, into a more pro-inflammatory and less immunosuppressive phenotype

Mode of action - mitazalimab combined with chemotherapy

1. Mitazalimab activates macrophages (MΦ)
2. Chemotherapy induces tumor cell killing
3. Mitazalimab activates dendritic cells (DCs)
4. The combination enhances T cell infiltration

Mitazalimab activates DCs

- Mitazalimab activates tumoral and splenic DCs in human CD40- transgenic (hCD40tg) 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

Mitazalimab alters the composition of myeloid cells in the tumor

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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

Mitazalimab is effective in a chemotherapy resistant tumor model

- FOLFIRINOX inhibits tumor growth in a chemotherapy sensitive mouse tumor model, but not in a chemotherapy resistant tumor model which was developed by sensitizing the tumor cell line MB49 with continuous low dose treatment of FOLFIRINOX
- The combination of treatment of mitazalimab and FOLFIRINOX induces a strong anti-tumor response in the chemotherapy resistant tumors

Mitazalimab in combination with chemotherapy induces a potent anti-tumor response

- Mitazalimab combined with chemotherapy, checkpoint inhibitor (anti-PD-1) or vaccine has a synergistic effect on survival in preclinical tumor models
- Mitazalimab synergizes with other anti-cancer treatments, such as chemotherapy (FOLFIRINOX), vaccine and checkpoint inhibitor (anti-PD-1). The combined treatment of mitazalimab and FOLFIRINOX induces a potent anti-tumor response in chemotherapy resistant tumors demonstrating the opportunity for mitazalimab to overcome chemotherapy resistance in e.g. pancreatic cancer patients

Summary and conclusions

- Preclinical data demonstrate that mitazalimab activates DCs and alters the composition of tumor infiltrating myeloid cells, resulting in enhanced activation of T cells and improved anti-tumor responses
- Mitazalimab has the potential to reshape the myeloid cell compartment in the tumor microenvironment. This was demonstrated as activation of TAMs purified from human tumor samples and a reduction in the proportion of the tumor intratumoral immunosuppressive macrophages in preclinical tumor models
- Mitazalimab synergizes with other anti-cancer treatments, such as chemotherapy (FOLFIRINOX), vaccine and checkpoint inhibitor (anti-PD-1). The combined treatment of mitazalimab and FOLFIRINOX induces a potent anti-tumor response in chemotherapy resistant tumors demonstrating the opportunity for mitazalimab to overcome chemotherapy resistance in e.g. pancreatic cancer patients

- OPTIMIZE-1, a phase 1b/2 study with mitazalimab in combination with FOLFIRINOX in pancreatic cancer is currently ongoing