COMBINING BEMPEGALDESLEUKIN (CD122-PREFERENTIAL IL-2 PATHWAY AGONIST) AND NKTR-262 (TLR7/8 AGONIST) PAIRS LOCAL INNATE ACTIVATION WITH SYSTEMIC CD8+ T CELL EXPANSION TO ENHANCE ANTI-TUMOR IMMUNITY

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Background Previously, we demonstrated that radiation therapy (RT) combined with Bempegaldesleukin (BEMPEG;NKTR-214), a first-in-class CD122-prefeferential IL-2 pathway agonist, led to enhanced anti-tumor efficacy through a T cell-dependent mechanism. However, we observed only modest systemic responses to BEMPEG/RT across several murine tumor models. Therefore, we explored alternative approaches to improve systemic tumor-specific immunity. We evaluated whether intratumoral NKTR-262, a polymer-modified toll-like receptor (TLR) 7/8 agonist, combined with systemic BEMPEG treatment resulted in improved tumor-specific immunity and survival compared to BEMPEG combined with RT. We hypothesized that BEMPEG/NKTR-262 immunotherapy would promote synergistic activation of local immunostimulatory innate immune responses followed by systemic adaptive immunity to significantly improve tumor regression and overall survival.

Methods Tumor-bearing mice (CT26; EMT6) received BEMPEG (0.8 mg/kg; iv), RT (12 Gy x 1), and/or intratumoral NKTR-262 (0.5 mg/kg). Flow cytometry was used to evaluate CD4+ and CD8+ T cell activation status in the blood and/or tumor (7 days post-treatment) and NK activity in the tumor (1, 3 days post-treatment). The contribution of specific immune subsets was determined by depletion of CD4+, CD8+, or NK cells. CD8+ T cell activity was determined in vitro by tracking apoptosis in an Incucyte assay. Data are representative of 1–2 independent experiments (n=5–14/group) and statistical significance was determined by 1-way ANOVA (p-value cut-off of 0.05).

Results BEMPEG/NKTR-262 resulted in significantly improved survival compared to BEMPEG/RT. BEMPEG/NKTR-262 efficacy was NK and CD8+ T cell-dependent, while BEMPEG/RT primarily relied on CD8+ T cells. Response to BEMPEG/NKTR-262 was characterized by a significant expansion of activated CD8+ T cells (GzmA+; Ki-67+; ICOS+; PD-1+) in the blood, which correlated with reduced tumor size (p<0.05). In the tumor, NKTR-262/BEMPEG induced higher frequencies of GzmA+ CD8+ T cells exhibiting reduced expression of suppressive molecules (PD-1+, TIM-3+), compared to BEMPEG/RT. Indeed, CD8+ T cells isolated from BEMPEG/NKTR-262-treated tumors had greater cytolytic capacity than those from BEMPEG/RT-treated mice. CD8+ T cell expansion (blood) and activity (tumor) depended upon the initial NK response, as neither occurred in the absence of NK cells. BEMPEG/NKTR-262 uniquely induced the expansion of early and high effector NK cells.

Conclusions Combining BEMPEG with NKTR-262 lead to an early and robust NK cell expansion not observed in the BEMPEG/RT combination. The improved tumor regression and survival was dependent on the NKTR-262 driven expansion of NK cells. A clinical trial of BEMPEG/NKTR-262 for patients with metastatic solid tumors is in progress (NCT03435640).
interferon genes agonists (STINGα) were shown to induce a potent type I interferon response in preclinical studies. The intratumoral administration of STINGα, to promote tumor inflammation, was shown to result in a protective spontaneous immune response in several murine tumor models. However, the encouraging preclinical results are not supported by recent clinical data, challenging the efficacy of unspcific monotherapy. As it is more and more clear that an effective cancer immunotherapy will require the combination of different treatment strategies, we investigate here the efficacy of combining KISIMATM cancer vaccine with STINGα treatment.

Methods Mice were vaccinated with subcutaneous (s.c.) injection of KISIMATM vaccine combined with s.c. administration of STINGα. Safety and immunogenicity were assessed by measuring temperature, serum cytokines and the peripheral antigen-specific response. Anti-tumoral efficacy as well as in depth monitoring of TILs and tumor microenvironment modulation were assessed following therapeutic vaccination in a HPV16 E6 and E7 expressing TC-1 cold tumor model.

Results Combination treatment was well tolerated and promoted the development of circulating antigen-specific CD8 T cells. In TC-1 tumor bearing mice, KISIMATM therapeutic vaccination resulted in the infiltration of both antigen-specific CD8 and CD4 T cells within the tumor, as well as a switch of tumor associated macrophages polarization toward the more inflammatory type 1. Combination therapy further increased the tumor microenvironment modulation induced by KISIMATM vaccine, promoting the polarization of inflammatory Thelper 1 CD4 T cells and increasing the effector function of antigen-specific CD8 T cells. The profound modulation of the tumor microenvironment induced by combination therapy enhanced the beneficial effect of KISIMATM vaccination, resulting in a prolonged tumour control.

Conclusions Combination of KISIMA™ cancer vaccine with systemic STINGα treatment induces the development of a potent, tumor-specific immune response resulting in a profound modulation of the TME. As check-point inhibitor (CPI) therapy is ineffective on poorly infiltrated tumors, combination with therapies able to highly enhance tumor infiltration by T cells could expand CPI indications.

Ethics Approval The study was approved by the Canton of Geneva Ethic Board, under the license number GE165/19

REFERENCE

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453

NOVEL COMBINATION IMMUNOTHERAPY FOR BOOSTING AND PRIMING IMMUNE RESPONSES IN PANCREATIC CANCER: STRONG ANTI-TUMOUR EFFECTS WITH INTERLEUKIN-15 AND CD40 AGONIST TREATMENT

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Abstract 453 Figure 1 Tumour kinetics and survival in Panc02 (left) and KPC (right) pancreatic cancer mouse models

Background With the poorest 5-year survival of all cancers, improving treatment for pancreatic cancer is one of the biggest challenges in cancer research. In this era of combination immunotherapies, we sought to explore the potential of combining both priming and activation of the immune system. To achieve this, we combined a CD40 agonist with interleukin-15 and tested its potential in pancreatic cancer.

Methods Two different mouse models of pancreatic cancer were used to assess the potential of this combination regimen. Therefore, effects on tumour growth kinetics and survival were charted. Differential effects on immune signatures was investigated using RNA sequencing. Functional immune subset involvement was tested using different immune depletion experiments and multicolour flow cytometry in different relevant immune sites. Immune memory was checked using re-challenge experiments.

Results We demonstrated profound reduction in tumour growth and increased survival of mice with the majority of mice being cured when both agents were combined, including an unprecedented dose reduction of CD40 agonist without losing any efficacy (fig 1). RNA sequencing analysis showed involvement of natural killer cell and T cell mediated anti-tumour responses and the importance of antigen-presenting cell pathways. This combination resulted in enhanced infiltration of tumours by both cytotoxic T cells and natural killer cells, as well as a striking increase in the ratio of CD8+ T cells over T regulatory cells. We also observed a significant increase in numbers of dendritic cells in tumour draining lymph nodes, particularly CD103+ dendritic cells with cross-presentation potential. A critical role for CD8+ T cells and involvement of natural killer cells in the anti-tumour effect was highlighted. Importantly, strong immune memory was established, with an increase in memory CD8+ T cells only when both interleukin-15 and the CD40 agonist were combined.

Conclusions We demonstrated profound synergistic anti-tumour effects upon combination of CD40 agonist and interleukin-15 treatment in mouse models of pancreatic cancer. This preclinical data supports initiation of a first-in-human clinical trial