Klinikum der Universität München. D. Briukhovetska: A. Employment (full or part-time); Significant; Klinikum der Universität München. J. Jobst: None. P.J. Müller: None. M. Seifert: None. R. Grü NEW E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Patents in the field of immuno-oncology. C. Klein: A. Employment (full or part-time); Significant; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Stocks and patents with Roche. S. Kobold: A. Employment (full or part-time); Significant; Klinikum der Universität München. B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Elite Network of Bavaria, LMU Munich’s Institutional Strategy LMUexcellent. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Patents in the field of immuno-oncology. 09.03 CD122-DIRECTED IL-2/ANTI-IL-2 COMPLEXES ENHANCE ABSOCAL RESPONSES TO RADIATION COMBINED WITH ANTI-PD-1 1,2,3,K Onyshchenko*, 1,2,3,R Luo, 1,3,G Niedermann. 1Department of Radiation Oncology, Faculty of Medicine, University of Freiburg, Freiburg, Germany; 2Faculty of Biology, University of Freiburg, Freiburg, Germany; 3German Cancer Consortium (DKTK), Partner Site Freiburg, Freiburg, Germany; 4German Cancer Research Center (DKFZ), Heidelberg, Germany 10.1136/jitc-2022-ITOC9.8 Background Early clinical trials have provided evidence for RT-induced systemic effects in conjunction with αPD-1 or IL-2 in metastatic patients, but strong abscopal responses are clinically rare. Dual combinations of αPD-1 with more effective and less toxic IL-2 derivatives, e.g., CD122-directed pegylated IL-2, are also currently under investigation. Whether a combination of RT, αPD-1, and CD122-directed IL-2/anti-IL-2 complexes (IL-2c) can increase abscopal effects against established non-irradiated tumors is unknown. Also, in-depth analyses of the differentiation of tumor-specific CD8+ T cells have not yet been reported for αPD-1/IL-2c in combination with RT. We investigated how adding IL-2c to hRT/αPD-1 affects tumor-specific CD8+ T cell differentiation in mouse tumor models and the potential of this triple combination to enhance the abscopal effect compared to the respective dual treatments. Materials and Methods Mice bearing bilateral tumors were treated with two fractions of 8 Gy (C51 colon carcinoma model) or 12 Gy (B16 melanoma model); αPD1 was given weekly; IL-2c was given for five consecutive days. CD8 T cell-depleting and CXCR3-blocking antibodies were used to determine if the therapeutic effects depend on CD8+ and CXCR3+ T cells. Differentiation stages of tumor-specific CD8+ T cells in tumor-draining lymph nodes, spleen, blood, and tumors were determined by flow cytometry using MHC-I tetramers and various antibodies. Results The abscopal effect was significantly stronger in triple-treated mice compared to mice treated with RT/αPD-1 (C51 model: P < 0.01; B16 model: P < 0.05), RT/IL-2c (C51 model: P < 0.01; B16 model: P < 0.001) or αPD-1/IL-2c (C51 model: P < 0.0001, B16 model: P < 0.01). Moreover, triple therapy improved survival and resulted in complete cures of 3/12 mice in the C51 model and 2/12 mice in the B16 model. These anti-tumor effects were associated with dramatic expansion of tumor-specific CD8+ T cells. Undifferentiated stem-like and effector-like but not terminally differentiated exhausted cells particularly strongly increased. Moreover, IL-2c induced CXCR3 expression on tumor-specific CD8+ T cells. Both CD8+ (C51 model: P < 0.0001; B16 model: P < 0.01) and CXCR3+ (C51 model: P < 0.0001) T cells were crucial for the RT-induced abscopal effect upon RT/αPD-1/IL-2c treatment. Conclusions RT/αPD-1/IL-2c triple treatment resulted in superior local and systemic expansion of tumor-specific CD8+ T cells with stem- and effector-like phenotypes. Also, IL-2c strongly increased CXCR3+ CD8+ T cells that were associated with pronounced abscopal responses in models with an established metastasis resistant to αPD-1/IL-2c and only transiently responding to RT/αPD-1 or RT/IL-2c. Therefore, such triple combinations appear promising for clinical evaluation in metastatic patients. Disclosure Information K. Onyshchenko: None. R. Luo: None. G. Niedermann: None. 09.04 SECONDARY RESISTANCE TO IMMUNOTHERAPY IS ASSOCIATED WITH DEATH AND DE-DIFFERENTIATION OF ACTIVATED T CELLS 1C Qing*, 2E Ghorani, 1K Foster, 2M Amann, 1Uddin, 1G Beattie, 1Solomon, 1F Arce-Vargas, 1K Peggs, 1Quezada. 1Cancer Institute, University College London, London, UK; 2Roche Innovation Center Zurich, Zurich, Switzerland 10.1136/jitc-2022-ITOC9.9 Background Immunotherapies have transformed the care of patients with multiple tumor types, but the majority who respond eventually progress after a period of stabilization. The reasons for this are not well known. We set out to explore mechanisms of immunotherapy failure in this setting, using a murine model of melanoma treated with a regulatory T cell (Treg)-depleting antibody combined with a cancer cell vaccine. Materials and Methods C57BL/6 mice were injected subcutaneously with B16 cells. Treatment with a mouse IgG2a depleting αCD25 antibody was given on day 5, followed by a B16
tumor vaccine (GVAX) given intradermally on days 6, 9, and 12. Tumors were harvested for single-cell RNA sequencing (scRNAseq) or flow cytometry using panels designed to interrogate the activation and differentiation landscape of infiltrating T cells.

Results Combined αCD25/GVAX therapy resulted in three different clinical response patterns - no response, partial response, and secondary resistance, with characteristic immune phenotypes. Amongst partially responsive tumors, about 90% of them relapsed between day 35–45. Reasoning that loss of immune control precedes clinical progression, we characterized the evolution of the immune landscape in pre-relapse tumors. We analyzed stable, partially responding tumors on days 28, 35, and 47. Over time, we found a decrease in the abundance of 4-1BB+TIM-3+TCF7- CD8+ effector memory T cells and Ki67+ CD4 effector cells (Teffs). In parallel, non-activated TCF7+ T cells rose in abundance. Treg abundance also recovered over time. ScRNAseq and scTCRseq analyses of pre-relapse and relapse tumors revealed that non-activated CD4 Teffs accumulating at relapse were transcriptionally equivalent to their activated counterparts at pre-relapse except for the expression of activation related genes. Overlaps were found in CDR3 usage between CD4 activated and non-activated populations at both pre-relapse and relapse, suggesting that the accumulating non-activated CD4 cells had been deactivated. In contrast, little overlap in CDR3 usage was found between CD8 activated and non-activated populations at relapse, indicating that the accumulating non-activated CD8 cells had been replaced by new, non-reactive clones. Additionally, we observed that in pre-relapse tumors, the percentage of Fas+ cells in activated Teffs is higher than that in non-activated cells. In activated Teffs, accumulating at relapse were transcriptionally equivalent to their activated counterparts at pre-relapse except for the expression of activation related genes. Overlaps were found in CDR3 usage between CD4 activated and non-activated populations at both pre-relapse and relapse, suggesting that the accumulating non-activated CD4 cells had been deactivated. In contrast, little overlap in CDR3 usage was found between CD8 activated and non-activated populations at relapse, indicating that the accumulating non-activated CD8 cells had been replaced by new, non-reactive clones. Additionally, we observed that in pre-relapse tumors, the percentage of Fas+ cells in activated Teffs is higher than that in non-activated Teffs. Blocking Fas/Fasl interactions with an αFasl antibody synergized with αCD25 on stable tumors to prevent relapse.

Conclusions Combined Treg depletion/whole tumor vaccine therapy is effective in a poorly infiltrated B16 model. Most mice that achieve partial response eventually relapse, mimicking what is often seen in human disease. By characterizing the evolution of the immune landscape within partially controlled tumors, we revealed that progression is associated with a loss of immune fitness characterized by deactivation and death of activated infiltrating Teffs.


Plenary symposium 12: combination therapy (with a special focus on local 10)

12.03 ISB 1442, A FIRST-IN-CLASS CD38 AND CD47 BISPECIFIC ANTIBODY INNATE CELL MODULATOR FOR THE TREATMENT OF CD38 POSITIVE HEMATOLOGIC MALIGNANCES

1. C Granclement, 1 C Estoppey, 1 E Dheilly, 1 M Panagopoulou, 1 E Martini, 1 V Labanca, 1 S De Angelis, 1 I Frei, 1 A Drake, 1 A Rubod, 1 G Gudi, 1 V Udupa, 1 I Olsen, 1 R Giovannini, 1 M Doucy, 1 E Feldman, 1 C Konto, 1 A Srivastava, 2 E Zhukovsky, 1 M Perro, 1 S Sammicheli
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Background ISB 1442 is a fully human first-in-class 2+1 biparatopic bispecific antibody targeting CD38 x CD47 using the BEAT2 2.0 (Bispecific Engagement by Antibodies based on the TCR) platform to target CD38 and CD47 as a treatment for CD38+ malignancies. ISB 1442 is designed with a bi-paratopic anti-CD38 arm that strongly binds two CD38 epitopes on tumor cells which do not functionally compete with daratumumab. The anti-CD47 arm is made of a single Fab designed to block interaction between CD47 and the signal-regulatory protein alpha (SIRPα) with low affinity. This approach enables CD47 binding only of proximal receptors on the same cell via avidity-induced binding of CD38 on tumor cells which is expected to induce minimal unintended effects on red blood cells (RBC) compared to anti-CD47 monoclonal antibody (mAb). The Fc portion of ISB 1442 is engineered to enhance antibody dependent cell phagocytosis (ADCP), antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

Materials and Methods ISB 1442 was tested for its capacity in vitro to induce ADCP, ADCC and CDC across a broad range of tumor cell lines expressing different levels of CD38 and CD47 relative. To assess the complex mechanisms of action of ISB 1442 in a single system, a multiple mode of action of killing (MMoAK) assay was established to allow for simultaneous killing by natural killer cells (ADCC), autologous macrophages (ADCP), and complement from human serum (CDC). In vivo, ISB 1442 was assessed in therapeutic tumor models, expressing high or low CD38 level, of subcutaneously established xenograft in CB17/SCID mice. On-target specificity was evaluated in vitro in human whole blood assays.

Results In vitro, ISB 1442 exhibited higher killing potency compared to daratumumab across a range of CD38-expressing tumor cells. Additionally, ISB 1442 showed in vitro tumor killing potency through phagocytosis comparable to anti-CD47 (5F9) mAb, acting mostly through ADCP. In the CDC, ADCC and MMoAK assays, ISB 1442 exhibited tumor cell killing that was twice as high as daratumumab in MM cell lines. In vivo, ISB 1442 induced higher tumor growth inhibition than daratumumab. ISB 1442 did not cause any detectable RBC depletion or binding to RBC suggesting a more favorable on-target specificity profile in humans as compared to anti-CD47 (5F9) mAb.

Conclusions We report a novel approach for the treatment for CD38 positive hematologic malignancies by co-targeting CD38 and CD47 using a first in class multispecific antibody. Based on its unique design and multiple mechanisms of action, ISB 1442 is anticipated to enhance antitumor activity in patients relative to anti-CD38 mAbs by overcoming primary and acquired tumor escape mechanisms of resistance.

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