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. Grünmeier: None. M. Thomas: A. Employment (full or part-time); Significant; Helmholtz München. C. Marr: A. Employment (full or part-time); Significant; Helmholtz München. B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; European Research Council. M. Levesque: A. Employment (full or part-time); Significant; University Hospital Zurich. M. Heppt: A. Employment (full or part-time); Significant; Universitätsklinikum Erlangen. S. Endres: 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. 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; Volkswagen Foundation, European Research Council, Hector Foundation, Elite Network of Bavaria, Melanoma Research Alliance, Else Kröner-Fresenius-Stiftung, German Cancer Aid, Ernst-Jung-Stiftung, LMU Munich’s Institutional Strategy LMUexcellent, Bundesministerium für Bildung und Forschung, European Research Council Grant, Fritz-Bender Foundation, José-Carreras Foundation. C. Marr: None. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; TTCR2 Inc, Novartis, BMS, GSK. 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 ABDSCPAL RESPONSES TO RADIATION COMBINED WITH ANTI-PD-1

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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 < 0.01) 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-cell 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.


09.04 SECONDARY RESISTANCE TO IMMUNOTHERAPY IS ASSOCIATED WITH DEATH AND DE-DIFFERENTIATION OF ACTIVATED T CELLS

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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...