SURVIVAL OUTCOMES AND TOXICITY AMONG PATIENTS TREATED WITH CONCOMITANT RADIOTHERAPY AND IMMUNOTHERAPY FOR ADVANCED MELANOMA: TWO FACES OF THE ABSOCAPAL EFFECT?

Background Combined treatment with radiotherapy (RT) and checkpoint inhibition (CPI) can theoretically increase both treatment response and toxicity. We recently reported a high rate of immune-mediated adverse events (irAEs) among patients with advanced melanoma and Merkel cell carcinoma (MCC) treated with concomitant RT and CPI. We now present survival data from the same cohort.

Methods The original study population consisted of 30 patients with advanced melanoma and 5 with MCC who underwent RT within 30 days of CPI; eligible patients were identified via an institutional retrospective registry. Information on the development of new irAEs diagnosed within 3 months of RT initiation was collected. Overall survival (OS) was calculated by the Kaplan-Meier method. Outcomes of patients who did or did not develop new irAEs after RT were compared via the log-rank test. To limit heterogeneity, the survival analysis was restricted to patients with melanoma.

Results Of the 30 patients with melanoma included in the survival analysis, 25 had died and 5 remained alive when data were censored in August 2020. Median follow-up was 18 months. Treatment with concomitant RT and CPI constituted first-line therapy for most patients (21/30); 8 patients had received one previous line of treatment and 1 patient had progressed on multiple regimens. Thirteen patients (43.3%) experienced at least one new irAE following RT in the context of concomitant CPI. Patients who experienced new irAEs post-RT demonstrated longer median OS of 25 months (95% confidence interval (CI): 8.6 - 41.4 months) in comparison to a median OS of 11 months for patients who did not develop post-RT irAEs (95% CI: 0.0 - 24.4 months). In the post-RT irAE group, 1-year and 2-year OS (69.2% and 53.8%, respectively) were higher compared to patients without irAEs (47.1% and 23.5%, respectively). These differences in survival did not reach statistical significance within this limited cohort size (figure 1; p = 0.076).

Conclusions The use of concomitant RT and CPI was associated with an elevated rate of new irAEs. Patients who developed new irAEs following RT experienced a substantial absolute increase in median OS of 14 months, an observation from a limited cohort which warrants further investigation. These data support prior reports of increased OS among patients experiencing irAEs and may suggest that RT and CPI in combination can meaningfully potentiate immune response in certain clinical contexts.

Ethics Approval The study was approved by the Cleveland Clinic Foundation Institutional Review Board, approval number 18–1225

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ENHANCED IMMUNE RESPONSES IN HUMAN BREAST AND COLON CANCER FOLLOWING CHECKPOINT THERAPY IN A CD34+ STEM CELL HUMANIZED NCG (HUCD34NCG) MOUSE MODEL

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Background Breast and colon cancer rank second and third, respectively, in world-wide prevalence of malignancies and present a large unmet medical need. The correlation between lymphocyte infiltration into the tumor microenvironment and efficacy of anti-cancer immunotherapies has been established. Therefore, relevant and cost-saving pre-clinical models are needed for developing new treatment approaches to predominant human tumor types. HuCD34NCG mice facilitate studying human immune responses in vivo elicited by experimental therapeutic antibodies. We characterized growth kinetics and human immune responses to checkpoint blockade in human breast and colon tumor-bearing HuCD34NCG mice. Aging, non tumor-bearing HuCD34NCG mice were also monitored for indicators of spontaneous hematopoietic cancer formation.

Methods HSC engraftment was quality controlled prior to inoculating HuCD34NCG mice with either colon adenocarcinoma (COLO 205) or triple negative breast cancer (MDA-MB-436) cells (both purchased from American Type Culture Collection, Manassas, VA). Mice were randomized into treatment groups based on tumor size, and checkpoint inhibitor antibodies were dosed twice weekly (anti-human PD-1, BioXcell clone: RMP1-14 or Keytruda; anti-human CTLA-4, BioXcell clone: BN13; and combination therapy). Body weights, general health status and survival were monitored. Peripheral blood (PB) and selected tissues were analyzed for the presence and composition of human immune cells by acoustic focusing flow cytometry. Non tumor-bearing aged HuCD34NCG mice (27 weeks post-engraftment) were sampled biweekly over ten weeks for lymphoma immunophenotyping.

Results Both tumor-bearing models showed significant anti-hPD-1 and anti-hCTLA-4 responses, but combination therapy only enhanced growth reduction significantly in MDA-MB-436 tumors. Flow cytometric analysis identified viable human leukocytes in tumor and spleen at study termination. These tumor-infiltrating lymphocytes (TIL) and splenocytes from surviving COLO 205 and MDA-MB-436 mice consisted of a total T-cell phenotype (CD3+) with proliferating (Ki67+), CD4+, CD8+ and Treg subsets. Additionally, myeloid cells (CD11b+, CD11c+) and M1/M2 macrophages were detected within these infiltrates. Splenic and tumor-infiltrating T-cells readily secreted human cytokines (IFN-γ, IL-2, TNF-α) and granzyme B upon ex vivo activation exhibiting polyfunctional and cytotoxic capabilities in all treatment groups. Baseline murine and human cytokine levels were distinguished in plasma from aging, non tumor-bearing HuCD34NCGs. Their phenotypes also showed no conclusive indicators of abnormal blood cells developing or graft failure.

Conclusions Breast and colon tumor cell-line derived models were established in HuCD34NCG mice. Standard checkpoint inhibitor treatment promoted human T-cell infiltration into tumor microenvironments inhibiting growth. These results demonstrate that HuCD34NCGs are a robust and relevant host for various human cell xenotransplants to advance preclinical immuno-oncology drug development.

Ethics Approval Animal studies were executed in compliance with local Charles River IACUC guidelines, IACUC number I-033. 

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200 NBTXR3 NANOPARTICLE WITH IMMUNORADIATION IMPROVES SURVIVAL AND GENERATES LONG-TERM ANTI-TUMOR MEMORY IN AN ANTI-PD1 RESISTANT MURINE LUNG CANCER MODEL

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Background Although treatment with high-dose (HD) radiation (XRT) and NBTXR3 on primary tumors in combination with sparking ongoing clinical trials, including those targeting TIGIT in combination with anti-PD-1 or anti-PD-L1. The INTASYL™ platform is a self-delivering RNAi technology that (1) provides efficient delivery into target cells bypassing the need for specialized formulations, mechanical perturbation, or drug delivery systems; and (2) specifically and durably silence target gene expression when administered intratumorally (IT), providing in vivo tumor control. IT administration restricts target gene expression when administered intratumorally (IT), alone or in combination in a CT26 model of murine colorectal carcinoma.

Methods To assess silencing activity, activated human pan-T cells were incubated in vitro with INTASYL compounds either alone or in combination and mRNA silencing was determined by qRT-PCR and protein silencing by flow cytometry. To assess in vivo tumor efficacy CT-26 cells were implanted subcutaneously into BALB/c mice. INTASYL compounds were administered IT at 1 mg/dose on Days 1, 3, 7, and 10 either as single agents (mPH-804, mPH-762, mPH-790) or in combination (mPH-804 + mPH-762 or mPH-804 + mPH-790). Controls consisted of PBS (vehicle; (IT)), and anti-TIGIT, anti-PD-1, or anti-PD-L1 antibodies (0.2 mg/dose) administered via intraperitoneal injection (IP). Tumor volumes and body weight were recorded throughout the study. Tumors were taken at the end of the study for analysis.

Results Single and combination knockdown of target molecules was validated at the mRNA level (≥90%) by qRT-PCR and at the protein level (≥80%) in activated human pan-T cells. In vivo, combination treatment with mPH-804 + mPH-762 or mPH-790 improved tumor control compared to individual monotherapies providing evidence of potential synergy. All treatments were well tolerated.

Conclusions n/a

Acknowledgements We demonstrate the potential of INTASYL-mediated combination therapy targeting TIGIT and PD-1/PD-L1. These findings indicate that combination of TIGIT + PD-1/PD-L1 silencing improves tumor control compared to monotherapy. As INTASYL IT is efficacious and may mitigate irAEs needed for developing new treatment approaches to predominant human tumor types, HuCD34NCG mice facilitate studying human immune responses in vivo elicited by experimental therapeutic antibodies. We characterized growth kinetics and human immune responses to checkpoint blockade in human breast and colon tumor-bearing HuCD34NCG mice. Aging, non tumor-bearing HuCD34NCG mice were also monitored for indicators of spontaneous hematopoietic cancer formation.

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