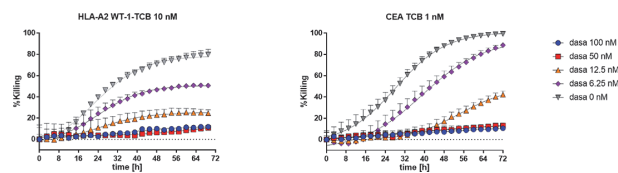


Abstracts

tumor cell killing.^{1 2} TCB treatment is sometimes associated with safety liabilities due to on-target on-tumor, on-target off-tumor cytotoxic activity and cytokine release. Patients treated with TCBs may experience a Cytokine Release Syndrome (CRS), characterized by fever, hypotension and respiratory deficiency and associated with the release of pro-inflammatory cytokines such as IL-6, TNF- α , IFN- γ , and IL-1 β .³ Off-tumor toxicity may occur if target antigens are expressed in healthy cells, which may potentially result in tissue damages and compromise the patient's safety. Rapid pharmacological blockade of T cell activation and proliferation is a promising approach to mitigate these life-threatening toxicities. Tyrosine kinases such as SRC, LCK or ZAP70 are involved in downstream signaling pathways after engagement of the T cell receptor and blocking these kinases might serve to abrogate T cell activation when required. Dasatinib was identified as a potent candidate that switches off CAR T cell functionality.^{4 5}

Methods Using an in vitro model of target cell killing by human peripheral blood mononuclear cells, we assessed the reversible effects of dasatinib combined with CEA-TCB or HLA-A2-WT1-TCB on T cell activation and proliferation, target cell killing and cytokine release. At assay endpoints, T cell phenotype and target cell killing were measured by flow cytometry and supernatants were analyzed by Luminex to assess cytokine release. To determine the effective dose of dasatinib, the Incucyte system was used to follow kinetics of target cells killing by TCB in the presence of a dose response of dasatinib concentrations.

Results 100 nM dasatinib prevented TCB-mediated target cell killing when added in the system upon restimulation of activated T cells (figure 1). Dasatinib concentrations above 50 nM fully switched off target cell killing (figure 2) which was restored upon removal of dasatinib. These data confirm that dasatinib act as a potent and reversible on/off switch for activated T cells at pharmacologically relevant doses as they are applied in patients according to the label.⁶



Abstract 653 Figure 2 Real time killing (Incucyte) of red fluorescent A375 cells loaded with RMF peptides by 10 nM HLA-A2 WT-1-TCB (left panel) and of red fluorescent MKN45 cells by 1 nM CEA-TCB (right panel) in the presence of different dasatinib concentrations ranging from 100 nM to 0 nM. Mean of technical duplicates + SEM

Conclusions Taken together, we provide evidence for the use of dasatinib as a pharmacological on/off switch to mitigate off-tumor toxicities or CRS by T cell engaging therapies. These data are being validated in vivo.

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654

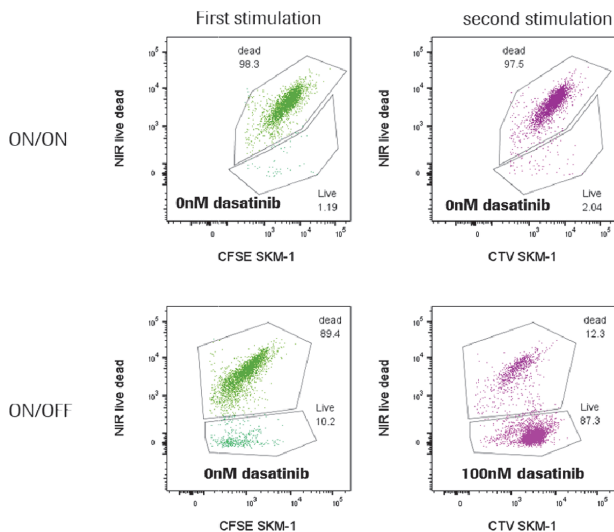
REAL WORLD INCIDENCE OF GRADE III AND HIGHER ADVERSE EFFECTS, EMERGENCY ROOM UTILIZATION AND HOSPITAL ADMISSIONS DURING TREATMENT WITH COMMONLY USED PD-1/PDL-1 TARGETING IMMUNE CHECK POINT INHIBITORS

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Background The landscape of cancer treatment has changed drastically since the development of Immune Checkpoint Inhibitors (ICI). ICIs have become the cornerstone to various cancer treatments.^{1 2} The adverse effect (AE) profile of ICI is different than conventional chemotherapy. Nivolumab and pembrolizumab target programmed cell death-1 T-cell receptor, whereas programmed death ligand-1 is targeted by atezolizumab and durvalumab.^{3 4} Easy tolerability and lack of myelosuppression make immunotherapy an attractive treatment option. Some AEs can be severe, life-threatening, or even fatal (grade III and higher).¹ Much of the data regarding AE profile is from clinical trials. The aim of our study is to review real world single institution AE data on the most commonly utilized ICIs.

Methods We reviewed a total of 229 patient charts who had received pembrolizumab, nivolumab, durvalumab or atezolizumab at Saint Francis Hospital in Hartford, CT, USA. 53

10nM HLA-A2 WT-1-TCB



Abstract 653 Figure 1 Representative flow cytometry experiment reporting SKM-1 target cell viability upon first stimulation with 10 nM HLA-A2 WT-1-TCB in the absence of dasatinib (left panel) and upon second stimulation with 10 nM HLA-A2 WT-1-TCB in the presence of 100 nM dasatinib (right panel)

patients were excluded given lack of records or because they received less than 2 cycles of treatment.

Results 176 patients were included in the final analysis. ICIs were discontinued in 25/176 (14.2%) patients secondary to AE. 24/176 (13.6%) patients had grade III or higher AEs reported. 10/95 (10.5%) patients who received pembrolizumab developed grade III/IV AEs (8 pneumonitis, 2 nephritis). 5/45 (11.1%) patients treated with nivolumab developed grade III/IV AEs (2 pneumonitis, 1 new-onset DKA, 1 nephritis, 1 myositis). 8/19 (42.1%) receiving durvalumab had grade III or higher AEs (6 pneumonitis, 1 sepsis, 1 colitis). Lastly, 1/17 (5.8%) in atezolizumab group developed grade III/IV AE (colitis). 96/176 (54.5%) patients had one or more ER visit and 91/176 (51.7%) were admitted to the hospital for various reasons one or more times.

Conclusions ICIs have a relatively safe drug profile. 86.4% of our studied population did not develop any grade III or higher AEs. The main reason for ICI discontinuation was disease progression rather than AE. The most common grade III/IV AE was pneumonitis. Durvalumab had the highest incidence of AE, pneumonitis, which is likely related to radiation use prior to immunotherapy.

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Ethics Approval Institutional Review Board approval - IRB#: SFH-19-72

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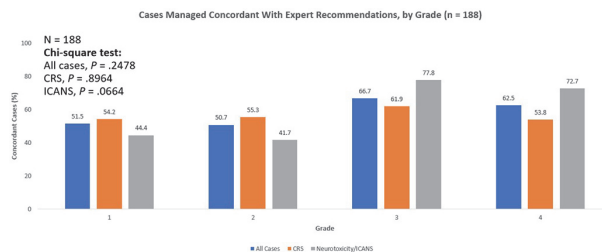
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655

CONCORDANCE BETWEEN HEALTHCARE PROVIDERS AND EXPERT CONSENSUS RECOMMENDATIONS IN THE MANAGEMENT, MONITORING, AND MITIGATION OF ADVERSE EVENTS ASSOCIATED WITH CAR T-CELL THERAPY: AN UPDATED ANALYSIS

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Background Chimeric antigen receptor (CAR) T-cell therapy has been a major innovative breakthrough for hematologic malignancies. These therapies are associated with unique and potentially serious toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS), that require vigilance, prompt recognition, and appropriate management to ensure patient safety and optimal therapeutic benefit. We developed an online tool to give



Abstract 655 Figure 1 Planned management of HCPs compared with expert recommendations, by grade

healthcare providers (HCPs) case-specific, evidence-based expert guidance on the management of adverse events (AEs) from CAR T-cell therapy. Here, we report an updated analysis comparing CAR T-cell toxicity management among HCPs using the tool vs the expert consensus recommendations.¹

Methods In March 2019, 5 experts provided consensus guidance for the screening, prophylaxis, monitoring, and management of CRS and ICANS in patients considering or receiving CAR T-cell therapy. This information was used to build the interactive online tool. To use this tool, HCPs enter the AE of interest, the severity of the event,² and their planned management approach. The HCPs were then shown the expert recommendation for that specific scenario. After viewing the expert recommendation, HCPs were asked if it affected their intended approach.

Results Between May 2019 and July 2020, 282 HCPs entered 431 unique case scenarios into the tool. Of the entered cases, 56% were HCPs seeking expert recommendations on pretreatment screening and prophylaxis/monitoring strategies for patients not yet experiencing an AE. Of 188 cases entered for patients who received CAR T-cell therapy and experienced an AE, 67% were CRS and 33% were neurotoxicity/ICANS. Overall the planned toxicity management strategy of HCPs matched the expert recommendations in 57% of cases, with a similar rate of concordance for both CRS and ICANS events. There was no significant difference in concordance rates with expert recommendations by toxicity severity (figure 1) nor among HCPs who indicated they practiced at authorized centers vs those who did not (P = 0.7184). Among HCPs who answered the optional survey on the impact of the tool on their management plan, 30% indicated that the expert recommendations changed their approach.

Conclusions These data suggest that many HCPs are challenged to optimally manage CAR T-cell therapy toxicities in concordance with expert recommendations. Use of an online tool providing easy access to evidence-based consensus expert recommendations may improve care and safety in patients treated with CAR T-cell therapy. A detailed analysis of the tool including planned management vs expert recommendations for each toxicity and grade will be presented.

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