reported in 47% of patients across doses. TEAEs seen in ≥30% of patients included (all grade, grade ≥3) nausea (52%, 1%), stomatitis (48%, 2%), alopecia (39%, 0%), and fatigue (32%, 1%). Select TEAEs (all grade, grade ≥3) of decreased neutrophil count/neutropenia (6%, 1%) and diarrhea (16%, 0%) observed with another TROP2-directed ADC were infrequent with Dato-DXd. Drug-related interstitial lung disease, by independent adjudication, occurred in 19 patients (11%): 4 mg/kg (10%, 1 grade 1, 3 grade 2, 1 grade 3); 6 mg/kg (4%, 2 grade 2); 8 mg/kg (15%, 3 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). TEAEs leading to dose reductions/interruptions occurred in 16% and 18% of patients, respectively: 4 mg/kg, 2% and 14%; 6 mg/kg, 8% and 18%; 8 mg/kg, 30% and 21%. Treatment discontinuations due to TEAEs were observed in 15% of patients (4 mg/kg, 14%; 6 mg/kg, 10%; 8 mg/kg, 19%), including some patients with prior dose reductions/interruptions. Primary analysis results from the NSCLC cohort will be presented. **Conclusion:** Dato-DXd continues to demonstrate promising efficacy and a generally manageable safety profile in heavily pretreated patients with advanced/metastatic NSCLC for whom treatment options are limited. **Keywords:** antibody drug conjugate, NSCLC, metastatic

MA03.03
NBTXR3 Activated by SBRT Combined with Nivolumab or Pembrolizumab in Patients With Advanced Cancers: Phase I Trial

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Introduction: Immune checkpoint inhibitors (ICIs) have led to durable responses and improved outcomes in patients with lung cancer who respond to treatment, however many patients exhibit resistance to ICIs. Overcoming this resistance is a major challenge in immuno-oncology. Emerging evidence suggests that radiation therapy (RT) can enhance the antitumor response to ICIs by producing an immunomodulatory effect. RT dose and ultimate efficacy are however limited by toxicity related to exposure of healthy tissues. NBTXR3, composed of functionalized hafnium oxide nanoparticles, is injected intratumorally and activated by RT. NBTXR3 increases RT energy deposit inside tumor cells and subsequent tumor cell death, without adding toxicity to healthy tissues. Preclinical data demonstrate NBTXR3/RT can trigger both a local and systemic anti-tumor immune response, overcome resistance to anti-PD-1 in mice bearing resistant lung tumors, and reduce development of spontaneous lung metastases. We hypothesize that NBTXR3/RT, combined with anti-PD-1 may prime the immune system to increase the proportion of ICI responders or convert ICI non-responders to responders. **Methods:** This multicenter, open-label, phase I trial [NCT03589339] is evaluating NBTXR3/SBRT/anti-PD-1 (nivolumab or pembrolizumab) in 3 cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to HN re-irradiation and (2) lung or (3) liver metastases from any primary cancer eligible for anti-PD-1. Stereotactic body RT (SBRT) is delivered at tumor-site specific doses per standard practice. The primary objective is to determine the NBTXR3/SBRT/anti-PD-1 recommended phase 2 dose in each cohort. Secondary objectives are anti-tumor response (objective response rate), safety, and feasibility of NBTXR3 injection. **Results:** Nine patients have been treated at the 22% NBTXR3 dose level, 3 with HNSCC, 4 with lung metastases and 2 with liver metastases. NSCLC was the primary cancer in 2 lung patients and 1 liver patient. HNSCC was the primary cancer in 2 lung patients and 1 liver patient. Overall tumor regression was observed in 8/9 patients, 7 of whom were anti-PD-1 non-responders, including 4 lung patients. Of particular interest, the combination of NBTXR3/SBRT/anti-PD-1 resulted in tumor regression in 6/7 patients who had progressed on prior anti-PD-1, including 3 lung patients. A complete response lasting over 1 year has been observed in the injected lymph node in 1 anti-PD-1 naïve HNSCC patient. 2 SAEs related to anti-PD-1 and possibly related to NBTXR3 (G5 pneumonitis, G4 hyperglycemia) were observed in 1 anti-PD-1 naïve HNSCC patient and considered DLTs. This patient also experienced two other SAEs (G4 diabetic ketoacidosis, G4 acute kidney injury) related to anti-PD-1. SBRT-related safety profile was as expected. NBTXR3 injection in the lung was well tolerated. Updated safety and efficacy results with additional patients and longer follow-up will be presented. **Conclusion:** Safety data from this first-in-human phase I trial evaluating NBTXR3/SBRT/anti-PD-1 in patients with advanced cancers, show NBTXR3 intratumoral injection is feasible and well-tolerated in HNSCC, lung, and liver metastases. NBTXR3/SBRT/anti-PD-1 demonstrated promising signs of efficacy and led to tumor regression in patients having progressed on prior anti-PD-1. These data support further development of NBTXR3/SBRT in combination with anti-PD-1 as well as other ICIs. **Keywords:** NBTXR3, Nivolumab, Pembrolizumab

MA03.05
DNA Damage Response (DDR) Gene Mutations and Correlation With Immunotherapy Response in NSCLC Patients

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Introduction: Previous studies have shown that gene mutations in the DDR pathway are related to the efficacy of immunotherapy for advanced NSCLC. However, whether there are key genes in the DDR pathway that are positively related to the efficacy of immunotherapy in advanced NSCLC remains unclear. **Methods:** We first used a published cohort of 350 NSCLC patients from MSKCC to screen the gene mutations in the DDR pathway potentially related to the efficacy of advanced NSCLC immunotherapy, defined as the DDR-IO gene set. Then, we included 64 patients with advanced NSCLC who received PD-(L)1 inhibitor monotherapy in SYSUCC to test the predictive value of the DDR-IO gene mutations. Further, we used another cohort consisted of 137 lung cancer patients to validate our findings. In addition, we tried to explore the potential mechanism using TCGA data. **Results:** We identified a DDR-IO gene set consisting of 7 DDR pathway genes, which included ATM, BRCA2, BRIP1, MRE11, POLE, MSH2 and PARP1. In the MSKCC cohort, we found that patients with DDR-IO mutations tended to gain more survival benefit from anti-PD-(L)1 immunotherapy than DDR-IO wild-type patients (Median OS: unreached vs 9 months, $p < 0.001$; median PFS: 5.40 months vs 3.17 months, $p = 0.029$, Fig. A-B). Furthermore, we examined the predictive value of DDR-IO gene set in the SYSUCC cohort. We found that the median PFS of DDR-IO gene mutant patients was significantly better than that of DDR-IO wild-type patients (Median PFS: 256 days vs. 63 days, $p = 0.039$, Fig. C). In the 137 validation cohort, we also found that the PFS (Fig. D), ORR, DCR, and DCB rates of patients with DDR-IO gene mutations were significantly better than those DDR-IO gene mutations ($p < 0.05$). We have made a preliminary exploration of the potential mechanism by which the DDR-IO gene mutations affect immunotherapy. We found that TMB and TNB were significantly higher in NSCLC patients with DDR-IO gene mutations (TMB, $p = 0.012$; TNB, $p = 0.009$) in the SYSUCC cohort. Similar results were found in TCGA data ($p < 0.05$). In addition, the proportion of CD8+ T cells, M1 macrophages, T lymphoid follicular helper cells and activated NK cells were significantly higher in NSCLC patients with DDR-IO gene mutations ($p < 0.05$).