699 PHASE 2 TRIAL OF BRENTUXIMAB VEDOTIN (BV) WITH PEMBROLIZUMAB (PEMBRO) IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER OR METASTATIC CUTANEOUS MELANOMA AFTER PROGRESSION ON ANTI-PD-1 THERAPY

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Background Anti-PD-1 therapy is the mainstay of frontline treatment for NSCLC and melanoma. However, the majority of these patients become refractory/resistant. BV is hypothesized to selectively deplete a subset of activated effector intratumoral regulatory T-cells (Tregs) that express CD30, potentially re-sensitizing tumors to anti-PD-1 therapy. SGN35–033 (NCT04609566) is an ongoing, multi-cohort, multicenter, open-label trial evaluating the efficacy and safety of BV+pembro in anti-PD-1 refractory solid tumors.

Methods Patients with primary refractory (progression without response or SD for <6 months) or secondary refractory (progression after response for ≥3 months or SD for ≥6 months) NSCLC or melanoma that progressed on anti-PD-1 therapy were included. Patients received 21-day cycles of BV (1.8 mg/kg) and pembro (200 mg). The primary endpoint is confirmed ORR per investigator assessment (RECIST v1.1). Exploratory biomarker analyses include T cell subsets by flow cytometry of peripheral blood at baseline and during treatment, IHC (CD8 and Foxp3) and RNAseq of tumor biopsies collected at baseline and cycle 3 day 1.

Results 54 patients with NSCLC (11 primary and 43 secondary refractory) and 58 patients with melanoma (17 primary and 41 secondary refractory) were enrolled. All patients were heavily pretreated (median prior lines of therapy: 3 [range: 1–10]). All patients' cancer had progressed on anti-PD-1 therapy, and all patients' melanoma had confirmed progression on anti-PD1 therapy within the last 90 days. ORR was up to 20% across cohorts and DCR ranged from 64%-80% (table 1). In an exploratory analysis, numerically higher response rates were observed in patients with tumors with higher PD-L1 expression. No new safety signals were observed. Preliminary IHC and RNAseq analysis of paired tumor biopsies from responders demonstrated increased tumor-infiltrating CD8 T cells at C3D1 post-treatment. Exploratory analyses of transcriptome-wide RNA expression indicated that responders exhibited enrichment of genes related to T cell signaling, Treg biology, and antigen presentation in baseline tumor biopsies, consistent with the hypothesized immune modulatory effects of BV.

Conclusions These data support the potential for BV to re-sensitize anti-PD-1 resistant/refractory tumors to PD1 through CD30-directed depletion of Treg cells. Treatment with BV +pembro was associated with selective depletion of CD30+ Tregs and modulation of the tumor microenvironment to relieve Treg immunosuppression. These data support further exploration of this combination for treatment of relapsed/refractory melanoma and NSCLC. SGN35–033 is currently enrolling cohorts to investigate the activity of BV+Pembro in frontline NSCLC and head and neck cancer.

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Trial Registration NCT04609566

Ethics Approval Ethics approval was obtained from the central IRB (WCG, 20202815) prior to enrollment of patients; all protocol amendments have received IRB approval and the study is renewed annually. Patients provided informed consent prior to study enrollment.

Abstract 699 Table 1 Objective response rate, disease control rate, median progression-free survival, and median duration of response

	NSCLC (95% CI)			Melanoma (95% CI)	
Refractory	Primary n=11	Secondary n=43	Refractory	Primary n=17	Secondary n=41
ORR (CR+PR), %	9 (0.2, 41.3)	14 (5.3, 27.9)	ORR (iCR+iPR),* %	18 (3.8, 43.4)	20 (8.8, 34.9)
DCR (CR+PR+SD), %	64 (30.8, 89.1)	72 (56.3, 84.7)	DCR (iCR+iPR+iSD),* %	71 (44.0, 89.7)	80 (65.1, 91.2)
mPFS, mo	2.8 (1.4, 4.0)	5.3 (2.8, 7.1)	miPFS,* mo	3.9 (1.8, 5.6)	4.2 (3.4, 5.6)
mDOR, mo	3.6 (NR)	5.9 (4.63, NR)	miDOR,* mo	4.2 (4.17, NR)	4.9 (2.86, NR)

Table includes all treated patients
CR: complete response; DCR: disease control rate; DOR: duration of response; iRECIST: immune-RECIST; m: median; mo: months; NR: not reached; NSCLC: non-small cell lung cancer; ORR: overall response rate; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors.
*One patient with melanoma experienced pseudoprogression but consolidated to an iCR; hence iRECIST is reported for these cohorts.

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