PHASE 2 TRIAL OF PEMBROLIZUMAB AND BRENTUXIMAB VEDOTIN IN PATIENTS WITH METASTATIC SOLID MALIGNANCIES AFTER PROGRESSION ON PRIOR PROGRAMMED CELL DEATH PROTEIN-1 INHIBITORS (SGN35-033, TRIAL IN PROGRESS)

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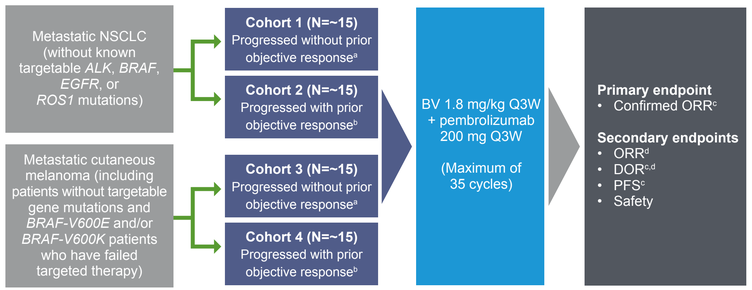
Background and Clinical Rationale

- Intratumoral Tregs contribute to resistance to checkpoint inhibition through various mechanisms including the overexpression of immune checkpoints, upregulation of immunosuppressive molecules, and apoptotic Treg-induced immunosuppression.[1]
- Tumor-infiltrating Tregs have a unique phenotype expressing higher levels of CD30 than other T cells and non-tumor infiltrating Tregs in several malignancies including NSCLC.[2,3]
- BV (ADCETRIS®) was the first antibody-drug conjugate to be approved in multiple cancer types.[4]
- The unique combination of a CD30-directed monoclonal antibody, a protease-cleavable linker, and the microtubule-disrupting agent MMAE drives the anticancer activity of BV.[5]
  - MMAE-mediated microtubule disruption induces cell cycle arrest and apoptosis.[5]
  - BV has been shown to induce immunogenic cell death and promotes activation and recruitment of immune cells to tumors.[5–11]
- BV has been shown to reduce Tregs in clinical trials of classical Hodgkin's lymphoma and cutaneous T-cell lymphoma, to be uniquely toxic to CD30-expressing Tregs, and to allow for expansion of co-cultured CD8+ T cells in vitro.[11,12]
- Pembrolizumab is a PD-1-directed monoclonal antibody, which binds to PD-1 on T cells and blocks the interaction between PD-1 and PD-L1, allowing reactivation of T cells.[13]
  - PD-1 blockade has been shown to enhance Treg proliferation and immunosuppressive activity in humans and mice.[14]
- Preclinically, the combination of BV with PD-1 inhibitors in CD30+ lymphomas resulted in greater antitumor activity than either agent alone.[15]
- Taken together, these preclinical data support the rationale for combining BV with pembrolizumab to overcome resistance to checkpoint inhibition.

Study Design

- SGN35-033 (NCT04609566) is a multi-cohort, open-label, multicenter, phase 2 study investigating the safety and antitumor activity of BV in combination with pembrolizumab for the treatment of patients with metastatic NSCLC or cutaneous melanoma who have progressed on or following treatment with PD-1 inhibitor therapy.
- Patients will be divided into 4 cohorts (~15 patients per cohort) based on indication (NSCLC or melanoma) and disease state (relapsed/refractory to prior PD-1 inhibitor therapy; **Figure 1**).
- Patients will receive BV 1.8 mg/kg in combination with pembrolizumab 200 mg IV Q3W for up to 35 cycles.
- Based on antitumor activity and safety data, each cohort may have an expansion phase (~40 additional patients per cohort) to further characterize the safety and antitumor activity of BV with pembrolizumab.

Figure 1: SGN35-033 Study Design



[a]During or after PD-1 inhibitor therapy ≤3 months or SD for <6 months. [b]CR/PR for ≥3 months or SD for ≥6 months. [c]By INV per RECIST 1.1. [d]By INV per iRECIST.

Eligibility

Table 1: Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Relapsed/refractory metastatic squamous or nonsquamous NSCLC (without known targetable *ALK*, *BRAF*, *EGFR*, or *ROS1* mutations) or metastatic cutaneous melanoma (including patients without targetable gene mutations and *BRAF-V600E and/or BRAF-V600K* patients who have failed targeted therapy) • Measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology • Currently on PD-1 CPI therapy or received last dose of PD-1 CPI therapy ≤90 days prior to enrollment[b] • Progressed on treatment in the metastatic setting with an anti–PD-1 therapy administered either as monotherapy, or in combination with other CPIs or other therapies • ECOG performance status ≤1	• Active CNS metastases unless definitively treated and stable for ≥4 weeks • History of another malignancy ≤3 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy[a] • Prior treatment with BV • Current therapy with other systemic anti-neoplastic or investigational agents • Any uncontrolled ≥Grade 3 (per NCI CTCAE Version 5.0[16]) viral, bacterial, or fungal infection ≤2 weeks prior to first dose of study drug • Grade ≥2 peripheral sensory or motor neuropathy at baseline

[a]Excluding malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

[b]PD-1 inhibitor therapy must be last previous line of therapy.

Study Assessments

Baseline Assessments
- Blood samples and tumor biopsies will be collected for biomarker assessments.

Efficacy Assessments
- Efficacy assessments will be performed by INV per RECIST 1.1 and by iRECIST from Cycle 1 Day 1.
- Radiographic tumor evaluations, performed by CT scan of the chest, abdomen, and pelvis, will be made every 6 weeks until Week 48, then every 12 weeks thereafter until disease progression.
- A biopsy will be collected at baseline and 6 weeks after the first dose (±1 week), unless medically infeasible.

Safety Assessments
- Safety assessments will consist of the surveillance and recording of AEs, concomitant medications, physical examination findings, and laboratory tests.

Patient-Reported Outcomes Assessments
- Patient-reported outcomes assessments will be performed using the EQ-5D-5L questionnaire and will be collected at every cycle.

Endpoints

Table 2: Study Endpoints

Primary	Exploratory
• ORR by INV per RECIST 1.1	• OS • Treg and MDSC levels[a] • CD8+ T cell proliferation[a] • Efficacy outcomes in tumors with different expression levels of CD30 and PD-L1 • Patient-reported outcomes per EQ-5D-5L
Secondary	
• ORR by INV per iRECIST • DOR by INV per RECIST 1.1 and iRECIST • PFS by INV per RECIST 1.1 • Safety	

[a]In peripheral blood and tumor tissue before and after treatment.

Statistical Analysis

- Efficacy and safety endpoints will be summarized with descriptive statistics by cohort.
- The observed ORR per RECIST 1.1 and the 95% CI will be provided for the full analysis set (all patients who are enrolled and received any amount of study drug) using Clopper-Pearson methodology.
- Time-to-event endpoints will be estimated using Kaplan-Meier methodology, and Kaplan-Meier plots will be presented.
- Median values for time-to-event analyses will be presented, and 2-sided 95% CIs will be calculated using the log-log transformation method.

Summary

- Intratumoral Tregs express uniquely high levels of CD30[2,3] and provide a potential target for overcoming PD-1–refractory NSCLC and melanoma.
- BV in combination with pembrolizumab is a promising treatment for patients with metastatic solid tumors whose disease is relapsed or refractory to prior PD-1 inhibitor therapy.
- The SGN35-033 study will evaluate the safety and antitumor activity of BV in combination with pembrolizumab for the treatment of patients with metastatic NSCLC or cutaneous melanoma who have progressed on or following treatment with PD-1 inhibitor therapy.
- Enrollment is underway in 20 sites in the USA.
  - ~60 patients will be enrolled.

Abbreviations

AE, adverse event; *ALK*, anaplastic lymphoma kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; BV, brentuximab vedotin; CI, confidence interval; CNS, central nervous system; CPI, checkpoint inhibitor; CR, complete response; CT, computed tomography; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D-5L, EuroQol-5 dimension-5 level; INV, investigator; iRECIST, immune RECIST; IV, intravenous; MMAE, monomethyl auristatin E; MDSC, myeloid-derived suppressor cells; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; *ROS1*, Proto-oncogene tyrosine-protein kinase; SD, stable disease; Treg, T regulatory cell.

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