FRONTLINE BRENTUXIMAB VEDOTIN PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA WITH LESS THAN 10% CD30 EXPRESSION (SGN35-032, TRIAL IN PROGRESS)

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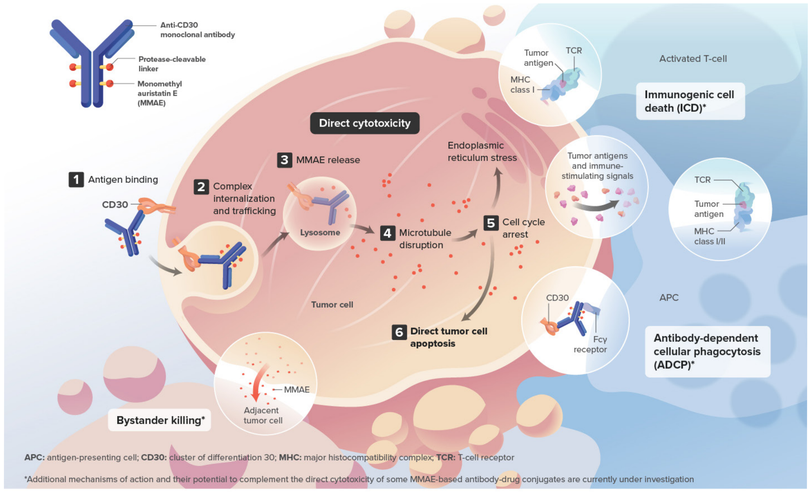
Background and Clinical Rationale

- BV (ADCETRIS®) was the first antibody–drug conjugate to be approved in multiple cancer types.[1]
- The unique combination of a CD30-directed monoclonal antibody, the protease-cleavable linker, and the microtubule-disrupting agent MMAE drives the anticancer activity (**Figure 1**).[2]
  - MMAE-mediated microtubule disruption induces cell cycle arrest and apoptosis as well as the bystander effect on adjacent cells.[2–4]
  - Direct cytotoxicity is at the heart of the multifaceted anticancer activity of BV, including the induction of immunogenic cell death, which promotes activation and recruitment of immune cells to tumors.[2–10]
- In the ECHELON-2 phase 3 clinical trial:
  - A+CHP showed clinically meaningful and statistically significant efficacy in patients with PTCL across a range of CD30 expression levels, including the lowest eligible level of 10% by IHC, when compared with patients treated with CHOP alone.[11]
  - No marked increase in toxicity was observed.[11]
- Results from ECHLEON-2 led to FDA approval of A+CHP as first-line treatment for adult patients with CD30-positive PTCL, regardless of CD30 expression level.[12]
- It is hypothesized that A+CHP will demonstrate efficacy in PTCL with <10% CD30 expression because:
  - Clinical responses to BV have been detected in patients with PTCL, cutaneous T-cell lymphoma, or B-cell lymphoma with low (<10%) or undetectable CD30 expression.[11,13,14]
  - In ECHELON-2, CD30 expression did not predict response to A+CHP in non-ALCL subtypes as responses were observed across all CD30 levels.[13]

Figure 1: Proposed Mechanism of Action of BV



APC: antigen-presenting cell; **CD30:** cluster of differentiation 30; **MHC:** major histocompatibility complex; **TCR:** T-cell receptor

*Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

Brentuximab vedotin is an investigational agent in some settings, and its safety and efficacy have not been established.

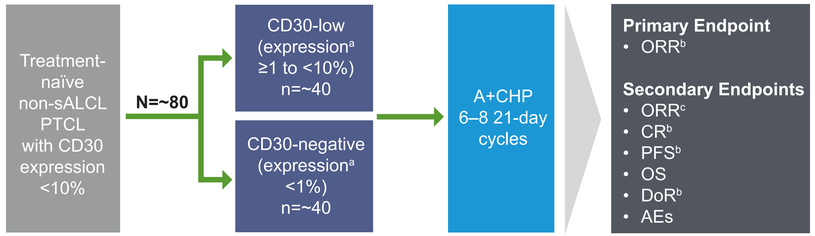
Study Design

- SGN35-032 (NCT04569032) is a dual-cohort, open-label, multicenter, phase 2 study investigating the efficacy and safety of frontline A+CHP in patients with non-sALCL PTCL subtypes with <10% CD30 expression on tumor cells (**Figure 2**).
- Patients will receive 6–8 cycles of A+CHP in 21-day cycles as follows: BV 1.8 mg/kg, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2, administered IV on Day 1 of each cycle, and prednisone 100 mg daily administered orally on Days 1−5 (±1 day window) of each cycle.

Abbreviations

A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; AE, adverse event; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; BICR, blinded independent central review; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CI, confidence interval; CR, complete response; CT, computed tomography; DoR, duration of response; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; FDG, fluorodeoxyglucose; GI, gastrointestinal; IHC, immunohistochemistry; IV, intravenous; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MF, mycosis fungoides; MMAE, monomethyl auristatin E; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PML, progressive multifocal leukoencephalopathy; PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL–not otherwise specified; sALCL, systemic anaplastic large cell lymphoma; TFH, T-follicular helper; T-LPD, T-cell lymphoproliferative disorder.

Figure 2: SGN35-032 Study Design



[a]By centrally confirmed local assessment.
[b]Per BICR using Revised Response Criteria for Malignant Lymphoma.[15]
[c]Per BICR using modified Lugano criteria.[16]

Table 1: Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years	• Current diagnosis of sALCL, primary cutaneous T-cell lymphoproliferative disorders and lymphomas, or MF[a]
• Newly diagnosed PTCL[b]	• History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for ≥3 years[c]
• Non-sALCL subtypes: ◦ PTCL-NOS ◦ AITL ◦ ATLL positive for human T-cell leukemia virus 1 ◦ EATL ◦ Hepatosplenic T-cell lymphoma ◦ MEITL ◦ Indolent T-LPD of the GI tract ◦ Follicular T-cell lymphoma ◦ Nodal PTCL with TFH phenotype	• Current therapy with other systemic anti-neoplastic or investigational agents[d]
• CD30 expression <10% by local assessment in tumor containing lymph node or other extranodal soft tissue biopsy[e]	• History of PML
• FDG-avid disease by PET and measurable disease of ≥1.5 cm by CT, as assessed by the site radiologist	• Cerebral/meningeal disease related to the underlying malignancy
• ECOG performance status ≤2	• Prior treatment with BV or doxorubicin

[a]Including transformed MF.
[b]Per Revised European-American Lymphoma World Health Organization 2016 classification.
[c]Excluding malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%), such as carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
[d]Participation in other clinical trials for any condition is not allowed. Participation in observational studies is permitted.
[e]Patients will be enrolled based on local results but only patients with CD30 expression <10% per central confirmation will be analyzed for the primary and secondary endpoint.

Study Assessments

Screening/Baseline Assessments

- CD30 expression will be assessed by IHC; local pathology results will be confirmed centrally.

Efficacy Assessments

- Primary and secondary efficacy assessments will be performed by BICR, and additional efficacy assessments will be performed by the investigator using the Revised Response Criteria for Malignant Lymphoma and modified Lugano criteria.[15,16]
- Radiographic disease evaluations will be made at baseline, after Cycle 4 of treatment, after the completion of study treatment, at 9, 12, 15, 18, 21, and 24 months after initiation of study treatment, and every 6 months thereafter until disease progression, death, or analysis of the primary endpoint, whichever comes first.
- A PET scan will be performed at baseline, after Cycle 4, and at the completion of study treatment.
- Follow-up restaging CT scans will be performed over the next 2 years.

Safety Assessments

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

Endpoints

Table 2: Study Endpoints

Primary
- ORR per BICR[a]

Secondary
- ORR per BICR[b]
- CR rate per BICR[a]
- PFS per BICR[a]
- OS
- DoR per BICR[a]
- Safety and tolerability

Additional
- ORR, CR rate, PFS, and DoR as assessed by the investigator[a]

[a]Using Revised Response Criteria for Malignant Lymphoma.[15]
[b]Using modified Lugano criteria.[16]

Statistical Analyses

- Efficacy and safety endpoints will be summarized with descriptive statistics to describe continuous variables by cohort, for both the CD30-negative and the CD30-low cohorts.
- 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

- A+CHP is approved as first-line treatment for adult patients with CD30-positive PTCL, regardless of CD30 expression level.[12]
- The SGN35-032 study will evaluate the efficacy and safety of A+CHP in patients with non-sALCL PTCL and CD30 expression <10% on tumor cells.
- Enrollment is ongoing in 20 US sites and 11 European sites in France, Italy, Spain, and the UK.
  - ~80 patients will be enrolled.

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