Frontline Brentuximab Vedotin in Hodgkin Lymphoma and CD30-Expressing Peripheral T-Cell Lymphoma for Older Patients and Those with Comorbidities (TRIAL IN PROGRESS)

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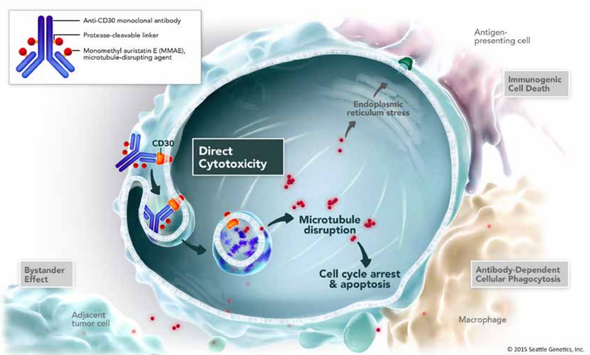
Background

- Favorable outcomes in patients with classical Hodgkin lymphoma (cHL) and, to a lesser degree, CD30-expressing peripheral T-cell lymphoma (PTCL) have not been attained in older patients or those with significant comorbidities[1]
  - 5-year progression-free survival (PFS) and freedom from treatment failure rates are 30% to 45% in older patients with HL, compared with 75% to 80% expected in younger patients[2,3]
  - Comorbidity is independently associated with higher mortality among patients with cHL[2]
- Patients with cHL and PTCL who are older or who have significant comorbidities have:
  - No standard treatment regimen
  - Limited ability to use combination chemotherapy
  - High unmet medical need

Brentuximab Vedotin

- Brentuximab vedotin (BV) has been approved for several indications, including US FDA frontline approval for treatment of adult patients with:
  - Previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine
  - Previously untreated systemic anaplastic large-cell lymphoma (ALCL) or other CD30-expressing PTCL including angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone
- BV is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent, monomethyl auristatin E (MMAE)
- Targeted delivery of MMAE to CD30-expressing cells is the primary mechanism of action of BV[4]
- Binding of MMAE to tubulin disrupts the microtubule network of the cell, subsequently inducing cell cycle arrest and apoptotic cell death

Proposed Mechanisms of Action of BV



Safety and Efficacy of BV Monotherapy

- BV monotherapy is active and well-tolerated in multiple clinical trials, including:
  - HL patients who are replapsed or refractory to several lines of chemotherapy[5]
  - Frontline HL patients ≥60 yrs (Part A Study SGN35-015)[6]
  - Relapsed or refractory patients with CD30-expressing PTCL[7]

Clinical Rationale

- Improvements in the prognosis of patients with HL and CD30-expressing PTCL have not been reflected in patients with significant comorbidities[1]
- Single-agent BV has the potential to be an active and well-tolerated frontline treatment for patients with cHL and PTCL who are not candidates for multi-agent chemotherapy due to comorbidities

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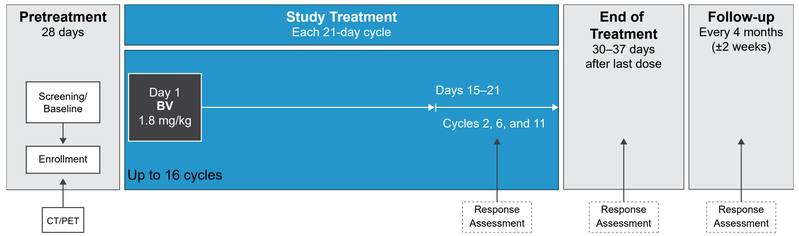
Parts E and F have been added to Study SGN35-015 to assess frontline brentuximab vedotin monotherapy in cHL and PTCL patients with significant cormorbidities

Study Design

- Evaluating the safety, efficacy, and tolerability of BV as frontline monotherapy in patients with comorbidities
- Currently enrolling:
  - ~50 patients with cHL (Part E)
  - ~50 patients with PTCL (Part F)



Study Parts E and F Objectives and Endpoints

Primary Objective	Primary Endpoints
To assess the ORR of single-agent BV as frontline therapy in patients ineligible for conventional combination chemotherapy due to comorbidities	ORR by BICR according to modified Lugano criteria[a]
Secondary Objectives	**Secondary Endpoints**
To evaluate safety and tolerability of single-agent brentuximab vedotin	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities
To assess duration of response, CR rate, and PFS	CR rate, disease control rate, duration of ORR, duration of CR, and PFS
To assess OS	OS
To assess resolution of B symptoms	B symptoms resolution rate
To assess pharmacokinetics and immunogenicity of BV	Incidence of antitherapeutic antibodies to BV

AE=adverse events; BICR=blinded independent central review; CR=complete response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
a. modified Lugano criteria require at least a PR by CT to achieve an overall response of CR in the setting of a complete metabolic response[8]

Safety and Response Assessments

Safety Assessments

- Type, incidence, severity, seriousness, and relatedness of AEs
- Type, incidence, and severity of laboratory abnormalities

Response Assessments

- Cycles 2, 6, and 11, and end of treatment (1 month after discontinuation of study treatment)
- CT of the neck, chest, abdomen, and pelvis
- PET scan (required until negative)
- Treatment decisions per Investigator assessment according to Lugano criteria[9]
- BICR assessments according to both modified[8] and unmodified[9] Lugano criteria

Eligibility

Key Inclusion Criteria

- Treatment-naive patients with histopathological diagnosis of cHL, which excludes nodular lymphocyte-predominant HL (Part E)
- Treatment-naive patients with CD30-expressing PTCL (Part F)
- Patients unsuitable or unfit for initial conventional combination chemotherapy for HL (Part E) or CD30-expressing PTCL (Part F) due to the presence of comorbidity-related factors as documented by:
  - Cumulative Illness Rating Scale (CIRS) score ≥10 (per criteria from Salvi et al[10]), or
  - Requiring assistance with or dependence on others for any instrumental activities of daily living (IADLs)
- An Eastern Cooperative Oncology Group (ECOG) performance status of ≤3
- FDG-PET-avid and bidimensional measurable disease ≥1.5 cm in longest axis documented by radiographic technique
- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m²
- Age 18 yrs or older

Key Exclusion Criteria

- Symptomatic neurologic disease compromising IADLs or requiring medication
- History of another malignancy within 1 year before the first dose of BV or any evidence of residual disease from a previously diagnosed malignancy

Eligible Histologic Subtypes of PTCL per WHO 2016 Classification of Lymphomas[11]

- PTCL, not otherwise specified
- ALCL, ALK-positive
- ALCL, ALK-negative
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal PTCL with TFH phenotype
- Breast implant–associated ALCL
- In addition, cases of T-cell leukemias with measurable disease may be eligible on a case by case basis. Contact the medical monitor for review of these cases.

Study Sites and Completion Dates

- US trial with 37 sites
- Enrollment in Parts E and F started October 2019
- Clinicaltrials.gov: NCT01716806
- Estimated study completion including long-term follow-up: September 2024

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