Brentuximab Vedotin in Combination With Nivolumab, Doxorubicin, and Dacarbazine in Newly Diagnosed Patients With Advanced Stage Hodgkin Lymphoma (Trial in Progress)

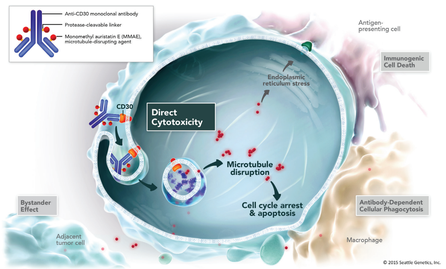
Judah Friedman[1], Hun Ju Lee[2], Linda Ho[3], Ian Flinn[4]

[1]Case Western Reserve University, Cleveland, OH; [2]MD Anderson Cancer Center, Houston, TX; [3]Seattle Genetics, Inc., Bothell, WA; [4]Sarah Cannon Research Institute, Nashville, TN

Brentuximab Vedotin Description and Mechanism of Action

- Brentuximab vedotin (BV, ADCETRIS®) 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), allowing for targeted delivery of MMAE to CD30-expressing cells
- Binding of MMAE to tubulin disrupts the microtubule network within the cell, inducing cell cycle arrest and apoptosis
- Direct cytotoxicity associated with BV may be augmented by secondary effects, including the bystander effect[1] on adjacent tumor cells, immunogenic cell death[2,3] mediated by antigen presenting cells, antibody-dependent cellular phagocytosis[4] by macrophages, and the depletion of CD30-expressing T regulatory cells[5,6]

BV Primary Mechanism of Action and Proposed Secondary Effects



Background and Rationale

BV approval for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) is based on the results of the ECHELON-1 study[7] (NCT01712490)

Part A

- Designed to further assess the impact of primary prophylaxis with granulocyte colony stimulating factor (G-PP) on safety and efficacy of the A+AVD regimen

Rationale

- The subset of patients in ECHELON-1 who received G-PP had lower rates of Grade 3 or higher neutropenia (29% vs 70% without G-PP) and febrile neutropenia (FN [11% vs 21% without G-PP])[8]

Parts B and C

- Designed to assess the safety and efficacy of the combination of BV with nivolumab, doxorubicin, and dacarbazine (AN+AD)

Rationale:

- BV in combination with doxorubicin and dacarbazine, omitting vinblastine, preserved high activity rates with low toxicity in 34 patients with previously untreated nonbulky Stage I/II cHL, suggesting that vinblastine may not be required for efficacy[9]
- Nivolumab is approved as monotherapy for relapsed/refractory (R/R) cHL* and has shown to be well tolerated with promising activity when combined with multi-agent chemotherapy (N+AVD) in newly diagnosed advanced-stage cHL[10]
- BV + Nivolumab in combination is an active and well tolerated investigational regimen in R/R cHL in the first salvage setting[6,11] and in newly diagnosed cHL patients over 60 years of age ineligible for or declining conventional combination chemotherapy[12]
- The combination with BV and nivolumab with doxorubicin and dacarbazine should hypothetically result in high response rates and be well tolerated, with potentially less toxicity than vinblastine-containing regimens

*Adult patients with cHL that has relapsed or progressed after 1) autologous hematopoietic stem cell transplantation (HSCT) and BV; or, 2) 3 or more lines of systemic therapy that includes autologous HSCT (OPDIVO USPI).

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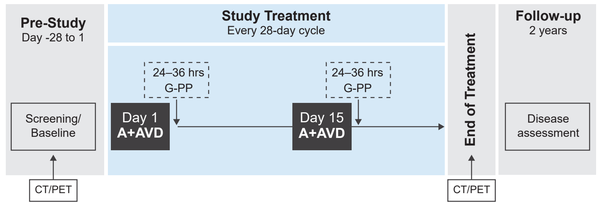
The combination of BV, nivolumab, doxorubicin, and dacarbazine (AN+AD) is being studied for treatment naïve patients with advanced stage (Part B) and early stage (Part C) cHL in new additions to the SGN35-027 trial

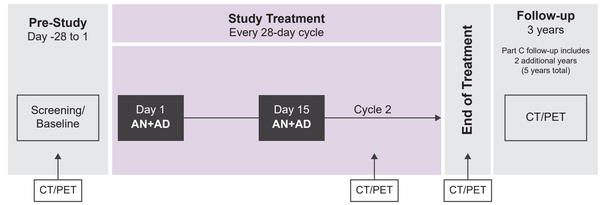
Study Design: Part A

- Part A of the study is designed to evaluate the rate of treatment-emergent FN following G-PP plus A+AVD in patients with previously untreated, advanced stage cHL
- Patients will be administered A+AVD consisting of BV 1.2 mg/kg (A), doxorubicin 25 mg/m² (+A), vinblastine 6 mg/m² (V), and dacarbazine 375 mg/m² (D). A+AVD will be administered by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle for up to 6 cycles
- G-PP (filgrastim or pegfilgrastim) will be administered 24–36 hours following A+AVD administration, beginning with Cycle 1 and continuing throughout all treatment cycles
- Approximately 40 patients will be enrolled in Part A



Study Design: Parts B and C

- Designed to assess the CR rate at end of treatment (EOT) with AN+AD in patients with previously untreated advanced cHL (Part B) and in patients with previously untreated early stage cHL (Part C)
- Patients will be administered AN+AD consisting of BV 1.2 mg/kg (A), nivolumab 240 mg (N), doxorubicin 25 mg/m² (+A), and dacarbazine 375 mg/m² (D). Each will be administered separately by IV infusion on Days 1 and 15 of each 28-day cycle for up to 6 cycles in Part B and 4 cycles in Part C
- Approximately 50 patients and 150 patients will be enrolled in Part B and Part C, respectively.



Study Objectives

Part A	Parts B and C
Primary Objective	**Primary Objective**
• To assess the treatment-emergent FN rate in patients with previously untreated, advanced stage cHL treated with A+AVD and G-PP	• To assess the CR rate at EOT with AN+AD in patients with previously untreated advanced stage (Part B) and early stage (Part C) cHL
Secondary Objectives	**Secondary Obejctives**
• To assess the incidence and severity of adverse events of clinical interest • To assess dose intensity, dose reductions, and dose delays related to any component of A+AVD • To assess primary refractory disease rates • To assess subsequent anticancer therapy utilization • To assess end of treatment (EOT) complete response (CR) rate • To assess physician-reported progression-free survival (PFS) rate at 2 years	• To assess safety and tolerability of AN+AD • To assess overall response rate • To assess duration of response • To assess duration of complete response • To assess event-free survival • To assess PFS • To assess overall survival

Eligibility

Key Inclusion Criteria

- Treatment-naïve, cHL patients with Ann Arbor Stage III or IV disease (Parts A and B)
  - Patients enrolling in Part B may also have Ann Arbor Stage II with bulky disease
- Treatment-naïve, cHL patients with Ann Arbor Stage I or II with nonbulky disease (Part C)
- Histologically confirmed cHL according to the current World Health Organization Classification
- Bidimensional measurable disease as documented by positron emission tomography/computed tomography (PET/CT) or CT imaging
  - Must have at least one lesion >1.5 cm in the longest diameter on cross-sectional imaging, measurable in 2 perpendicular dimensions on CT (or magnetic resonance imaging; MRI), and fluorodeoxyglucose (FDG) avid by PET
- An Eastern Cooperative Oncology Group performance status ≤2
- Age 12 years or older

Key Exclusion Criteria

- Nodular lymphocyte predominant HL
- History of another malignancy within 3 years of the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy
  - Exceptions are malignancies with a negligible risk of metastasis or death
- Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy within 4 weeks of the first study drug dose, unless underlying disease has progressed on treatment
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Active cerebral/meningeal disease related to the underlying malignancy
- Current therapy with other systemic anti-neoplastic or investigational agents

Safety Assessments

- Surveillance and recording of adverse events (AEs) and serious adverse events
- Recording of concomitant medication
- Measurements of protocol-specified physical examination findings
- Measurements of protocol-specified laboratory tests

Part A

- Assess rate of FN
- Assess incidence and severity of AEs of clinical interest

Parts B and C

- Assessment by safety monitoring committee after at least 10 patients have completed treatment
- Assess type, incidence, severity, seriousness, and relatedness of AEs
- Assess type, incidence, and severity of laboratory abnormalities
- Final safety visit 100 days ±2 wks after last dose of nivolumab or 30 days after last dose of BV, whichever is later

Response Assessments

Part A (Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas[13]):

- EOT (within 30–37 days of last dose)
  - CT of the neck, chest, abdomen, and pelvis
  - PET scan
  - B symptom assessment

Parts B and C (Lugano and Lymphoma Response to Immunomodulatory Therapy Criteria [LYRIC][14])

- Cycle 2 (Day 25–28) and EOT (within 30–37 days of last dose):
  - CT of the neck, chest, abdomen, and pelvis
  - PET scan

Study Sites and Completion Dates

- 21 sites in the United States
- Parts A and B currently enrolling; Part C expected to open enrollment in 2Q 2020

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