

FAST FACTS

S1826 - A PHASE III, RANDOMIZED STUDY OF NIVOLUMAB (OPDIVO) PLUS AVD OR BRENTUXIMAB VEDOTIN (ADCETRIS) PLUS AVD IN PATIENTS (AGE \geq 12 YEARS) WITH NEWLY DIAGNOSED ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA

ELIGIBILITY CRITERIA

1. Disease Related Criteria

- a. All patients must have histologically confirmed newly diagnosed, previously untreated Stage III or IV classical Hodgkin lymphoma (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or not otherwise specified (NOS)). Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.
- b. Patients must have bidimensionally measurable disease (at least one lesion with longest diameter \geq 1.5 cm) documented on the Lymphoma Baseline Tumor Assessment Form in Rave.
- c. Patients must have a whole body or limited whole body PET-CT scan performed within 42 days prior to registration. (A contrast-enhanced (diagnostic) CT, MRI or MR-PET is acceptable in event that PET-CT is contra-indicated, however the same modality must be utilized through the trial.) NOTE: All images from PET-CT, CT, MRI or MR-PET scans performed as standard of care to assess disease (**within 42 days prior to registration**) must be submitted as indicated in Section 15.4 and associated radiology reports must be submitted as indicated in Section 14.4a.

2. Age criteria: Patients must be \geq 12 years of age..

3. Prior/Concurrent Therapy Criteria

- a. Patients must not have received any prior chemotherapy, radiation, or antibody-based treatment for classical Hodgkin lymphoma. Steroid pre-treatment is permitted as outlined in Section 5.4k
- b. Patients must not have had prior solid organ transplant
- c. Patients must not have had prior allogeneic stem cell transplantation
- d. Patients must not have received a live vaccine within 30 days prior to planned Day 1 of protocol therapy (e.g. measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid).
- e. At registration, investigator must declare intent-to-treat with Residual PET Radiation Therapy (Residual PET RT- RPRT) to be administered after patient completes 6 cycles of therapy if, after end of treatment, the patient meets criteria specified in Section 7.5 for receiving RT). Patients will be stratified by investigator's intent-to-treat with Residual PET RT.
 - All patients enrolled by COG-investigators will be considered intent-to-treat with Residual PET RT.

4. Clinical/Laboratory Criteria

- a. Patients must have a performance status corresponding to Zubrod scores of 0, 1 or 2. Use Lansky for patients \leq 17 years of age. *The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only. See Sections 10.3 and 18.4.
- b. Patients must have adequate renal function as indicated below:
Adults (age 18 or older):

- Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained within 28 days prior to registration. Estimated creatinine clearance is based on actual body weight.

Estimated creatinine clearance = $(140 - \text{age}) \times \text{wt (kg)} \times 0.85$ (if female)
 $72 \times \text{creatinine (mg/dl)}$

Pediatric Patients (age 12-17):

The following must have been obtained within 14 days prior to registration:

- Measured or calculated* creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m², or
- Serum creatinine ≤ 1.5 x institutional upper limit of normal (IULN), or a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
< 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
16 -17 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (96) utilizing child length and stature data published by the CDC.

*calculated based on institutional standard

- c. Patients must have adequate hepatic function, evidenced by the following*:
- Total bilirubin ≤ 2 x IULN, and
 - AST and ALT ≤ 3 x IULN
- * unless due to Gilbert's disease, lymphomatous involvement of liver or vanishing bile duct syndrome
- For adults (age 18 or older), above hepatic function must be documented within 28 days prior to registration.
- For pediatric Patients (age 12-17), above hepatic function must be documented within 14 days prior to registration.
- d. Patients must have adequate cardiac function defined as follows:
- Patients must have an echocardiogram (ECHO), MUGA, or functional cardiac imaging scan with a left ventricular ejection (LVEF) fraction $\geq 50\%$ or a shortening fraction of $\geq 27\%$.
- For adults (age 18 or older), the ECHO or MUGA be performed within 42 days prior to registration.
- For pediatric Patients (age 12-17)**, the ECHO, MUGA, or functional cardiac imaging scan must be performed **within 14 days** prior to registration.

- e. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable or unquantifiable viral load within 6 months prior to registration are eligible for this trial.
- f. Patients must not have known active Hepatitis B (HBV) or Hepatitis C Virus (HCV) at date of registration. Patients with previously treated HBV or HCV that have an undetectable viral load and no residual hepatic impairment are eligible.
- g. Patients must not have any known central nervous system lymphoma.
- h. Patients must not have a history of or active interstitial pneumonitis or interstitial lung disease.
- i. Patients must not have had a diagnosis of inherited or acquired immunodeficiency (unless allowed under Section 5.4e).
- j. Patients must not have any known uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, hemodynamically unstable cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- k. Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Steroid use for the control of Hodgkin lymphoma symptoms is allowable, but must be discontinued prior to Cycle1, Day1.
- l. Patients with peripheral neuropathy must have < Grade 2 at date of registration.
- m. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, immunosuppressive drugs, or corticosteroids with doses higher than prednisone 10 mg or equivalent). Autoimmune diseases include but are not limited to autoimmune hepatitis, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), as well as symptomatic disease (e.g.: rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis or glomerulonephritis). Vitiligo, alopecia, hypothyroidism on stable doses of thyroid replacement therapy, psoriasis not requiring systemic therapy within the past 2 years are permitted.
- n. No second prior malignancy is allowed except for adequately treated basal (or squamous cell) skin cancer, any in situ cancer or other cancer for which the patient has been disease free for two years.
- o. Females of childbearing potential must not be pregnant or nursing, and have a negative pregnancy test within 28 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method while receiving study drug and for women until 6 months after receiving the last dose of study drug or, for men, until 7 months after receiving the last dose of study drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5. Specimen Submission Criteria

- a. Patients must have sufficient diagnostic tissue specimens collected prior to registration as outlined in Section 12.1.

- b. Patients must be offered participation in banking for planned translational medicine and future research, as outlined in Section 15.2. With patient consent, any residuals from the mandatory tissue submission will also be banked for future research.

