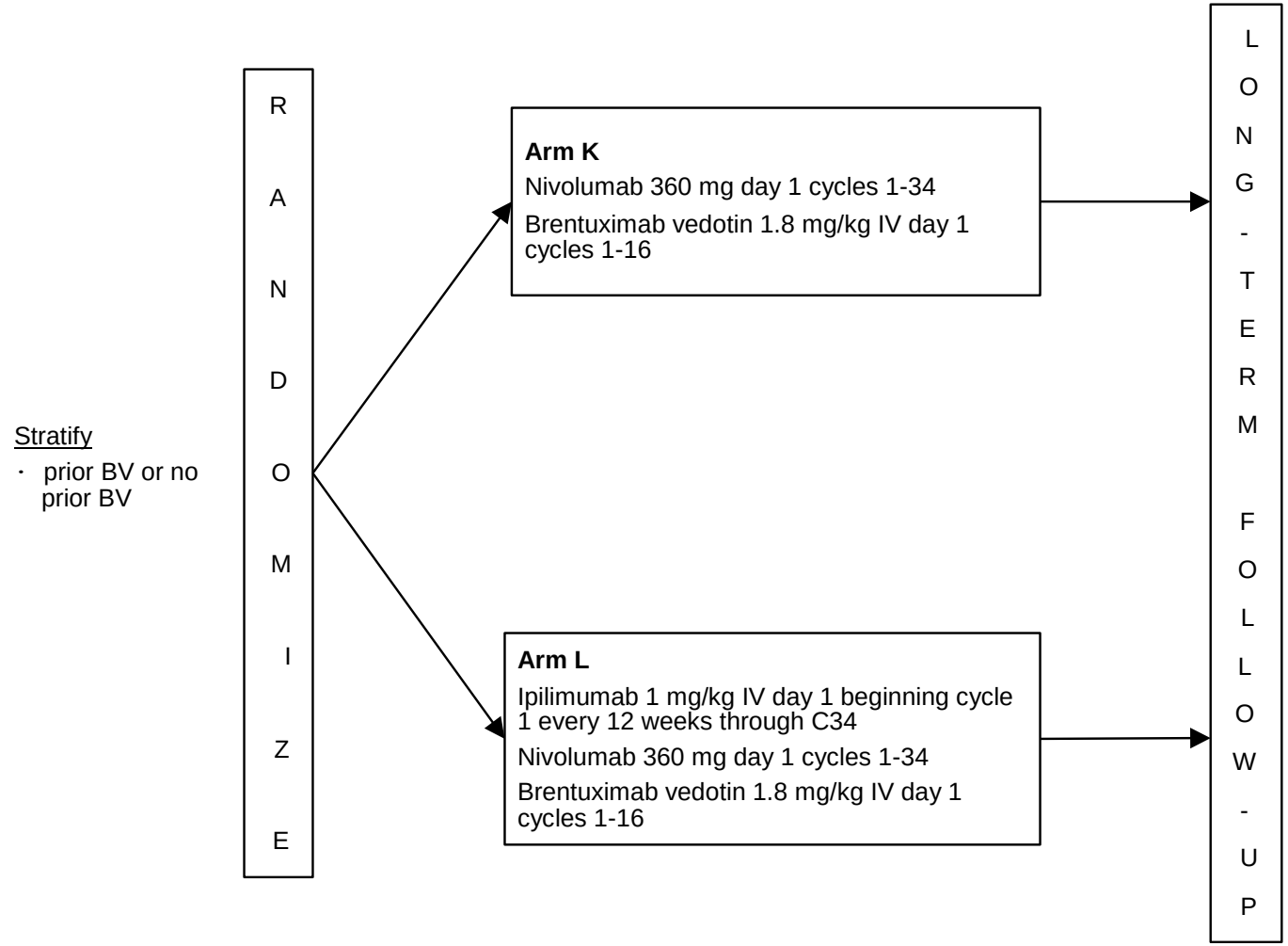
## Schema – Phase II




Phase II Accrual Goal=120 patients

Cycle=21 days

3.2 Randomized Phase II - Eligibility Criteria (Arms K and L)

_____3.2.1 Age ≥ 18 years.

_____3.2.2 Patients must have pathologically confirmed relapsed or refractory classical Hodgkin Lymphoma (cHL). A biopsy at any relapse is acceptable. Other histologies including lymphocyte predominant (LP) HL are not permitted.

_____3.2.3 Patients must have relapsed after first line chemotherapy. May have relapsed after autologous stem cell transplant, or have primary refractory disease. No upper limit for number of prior therapies. Patient must not have received a prior allogeneic stem cell transplant.

_____3.2.4 Patients may have received prior brentuximab vedotin, but must not have received brentuximab vedotin within 6 months prior to registration, and must not have relapsed within 6 months of receiving previous brentuximab vedotin. Patients may not have received prior nivolumab or PD1/PDL1 axis agents. Patients may not have received prior ipilimumab.

_____ 3.2.5 Patients may not have received other prior activating immunotherapies (i.e. checkpoint inhibitor therapies). For the purposes of this study monoclonal antibodies and antibody drug conjugates are not considered to be activating immunotherapies and there are no additional time restrictions on prior exposure to these agents (except prior brentuximab vedotin).

_____3.2.6 ECOG-ACRIN performance status between 0-2.

_____3.2.7 Patients must have measurable disease as defined in Section 6. Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease unless verified by a diagnostic quality CT scan. Patients must use the same imaging modality (CT or PET/CT) throughout the study.

_____3.2.8 Women must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

All females of childbearing potential must have a blood test or urine study within 24 hours prior to enrollment to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential? _____(Yes or No)

Date of blood or urine test: _____

_____ 3.2.9 Women of childbearing potential (WOCBP) and sexually active males must either abstain from sexual intercourse for the duration of their participation in the study or agree to use both double barrier

contraception and birth control pills or implants for at least one week prior to the start of the study drug and continuing for 5 months after the last dose of study drug (for female patients) and for 7 months after the last dose of study drug (for male patients who are sexually active with WOCBP).

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

_____3.2.10 Patients must have no evidence of dyspnea at rest and a pulse oximetry > 92% while breathing room air.

_____ 3.2.11 Patients must have FEV1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL. Carbon monoxide diffusion capacity (DLCO), FEV1, and FVC all >50% predicted value. All pulmonary function tests must be obtained within one month prior to registration.

_____3.2.12 Hematologic parameters (unless due to documented marrow involvement) obtained within 2 weeks prior to registration)

_____ 3.2.12.1 ANC $\geq$ 1500/mcL (1.5 x $10^9$/L)

_____ 3.2.12.2 Platelets $\geq$ 75,000/mcL (75 x $10^9$/L)

_____3.2.13 Liver/Renal function, obtained within 2 weeks prior to registration

_____ 3.2.13.1 AST/ALT $\leq$ 2.5 x upper limit of normal (ULN)

_____ 3.2.13.2 Bilirubin $\leq$ 2 x upper limit of normal (ULN) (unless documented Gilbert's Syndrome, for which Bilirubin $\leq$ 3 x upper limit of normal (ULN) is permitted)

_____ 3.2.13.3 Calculated creatinine clearance by Cockroft-Gault formula $\geq$ 30 ml/min

_____ 3.2.14 No evidence of prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical carcinoma or any surgically- or radiation-cured malignancy continuously disease free for $\geq$ 5 years so as not to interfere with interpretation of radiographic response.

_____ 3.2.15 Patient must have no current or prior history of CNS involvement.

_____ 3.2.16 All prior therapy must have been completed at least 21 days prior to enrollment (6 weeks for nitrosoureas or mitomycin C). No concomitant anti lymphoma therapy, including systemic corticosteroids for the purpose of treatment of lymphoma are allowed. Topical steroids are allowed.

_____3.2.17 No history of Steven's Johnson's syndrome, TENs syndrome, or motor neuropathy.

_____ 3.2.18 HIV positive patients are eligible provided they meet the other protocol criteria including the following:

- Long term survival expected were it not for the cHL
- HIV viral loads undetectable by standard clinical HIV testing

- Willing to adhere to effective combination antiretroviral therapy

_____ 3.2.19 Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (i.e., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids. A history of occasional (but not continuous) use of steroid inhalers is allowed.

Replacement doses of steroids for patients with adrenal insufficiency are allowed. Patients who discontinue use of steroid medication for at least 2 weeks prior to initiation of therapy are eligible if, in the judgment of the treating physician investigator, the patient is not likely to require resumption of treatment with these classes of drugs during the study.

Exclusion from this study also includes patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis); other CNS autoimmune disease (e.g., Multiple sclerosis). Patients with autoimmune hypothyroid disease or type I diabetes on replacement treatment are eligible.

Treatment with systemic corticosteroids (including oral steroids)?
Yes _____ No _____

Continuous use of topical steroid creams/ointments?
Yes _____ No _____

Continuous use of steroid containing inhalers?
Yes _____ No _____

Adrenal insufficiency?
Yes _____ No _____

Date of last dose of steroid containing medicines: _____

_____ 3.2.20 Patients must not have grade 2 or greater peripheral sensory neuropathy.

_____ 3.2.21 Patients must not have NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.

_____ 3.2.22 Patients must not have previously existing hypersensitivity to brentuximab vedotin or ipilimumab.

_____ 3.2.23 Patients must not have a serious medical or psychiatric illness likely to interfere with study participation.

_____ 3.2.24 Patients must not be participating in any other clinical trial or taking any other experimental medications within 21 days prior to registration.

_____ 3.2.25 Routine vaccinations, including seasonal influenza, should be given at least 2 weeks prior to study treatment. Vaccines are not prohibited on study, but must be given at least 6 weeks after cycle 1 and not within 7 days of treatment.

_____3.2.26 Patients must not currently be smoking tobacco or other agents.

_____ 3.2.27 Patients must not have a history of or evidence of cardiovascular risks including any of the following:

- QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.at baseline.
- History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to registration.
- History prior to registration or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system. (See Appendix IX)
- LVEF ≤ lower limit of normal on cardiac echo or MUGA.
- Intra-cardiac defibrillator.
- History of abnormal cardiac valve morphology (≥ grade 2) documented by ECHO; (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- History or evidence of current clinically significant uncontrolled cardiac arrhythmias; Clarification: Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.
- Treatment refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy

_____ _____

Physician Signature Date

**OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.