PROTOCOL	
TITLE:	A phase II study of brentuximab vedotin and lenalidomide in relapsed and refractory T-cell lymphomas
STUDY NUMBER:	OSU-17204
IND NUMBER:	137831
TEST PRODUCTS:	Brentuximab vedotin (Adcetris®) Lenalidomide (Revlimid®)
INDICATION:	Cutaneous T-cell lymphomas (CTCL) Peripheral T-cell lymphomas (PTCL)
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BACKGROUND

Background on T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are uncommon disorders accounting for 10-15% of all non-Hodgkin lymphomas (NHL). The NHL classification project represents the first attempt to systematically study the distribution of NHL subtypes based on a collaborative international effort and it confirmed the wide geographic variation in the frequency of different subtypes of PTCL. Subsequently, the International T-cell Lymphoma Project (ITLP), the largest collaborative international effort to date, reported prevalence and outcomes of 1314 cases of PTCL from 22 institutions worldwide with central pathology review. The ITLP consortium launched a prospective study, the T-cell project, in September 2006 aimed at collecting an exhaustive clinical and biologic data set on 1000 patients with PTCL for better definition of prognostic factors that would influence outcomes of these patients. This review aims to describe the difference in frequency and outcomes for various subtypes of PTCL based on these studies (William and Armitage 2013). Cutaneous T-cell lymphomas (CTCLs) are rare non-Hodgkin lymphomas that involve the skin and frequently the peripheral blood and lymph nodes. In the United States, only 2,000-3,000 new cases of CTCL are diagnosed yearly (Criscione and Weinstock 2007).

CTCL Classification

In western countries ~75% of PCL are of T-cell origin (primary cutaneous T-cell lymphoma (CTCL)) and 20-25% of B-cell origin. In addition, a small subset of cutaneous lymphomas originates from Natural Killer (NK) cells, e.g. Epstein-Barr-Virus associated Natural Killer cell (NK)/T-cell lymphoma. Other small groups of temporarily unclassifiable lymphomas with undefined phenotypic characteristics are collated also in the current classification system (Willemze et al. 2005; Jaffe 2006).

Cutaneous T-cell Lymphomas (CTCL) represent a rare disease entity. Although the distribution of CTCL subtypes varies between different regions, the incidence of CTCL is comparable between different regions of the world. For example, in the US Criscione (Criscione and Weinstock 2007) observed an annual incidence of CTCL of 9.6 new cases per one million persons for the time period of 1998-2002.

The current classification of CTCL was developed by a collaborative effort of the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) (Willemze et al. 2005; Jaffe 2009; Campo et al. 2011). This WHO- EORTC classification of CTCLs enlists 14 entities (Campo et al. 2011). Approximately 90% of CTCLs are represented by 2 subtypes; mycosis fungoides (MF) and primary cutaneous CD30+ lymphoproliferative disorders (LPD).

CTCL with Indolent clinical behavior:

- Mycosis fungoides (MF), the most frequent form of CTCL that accounts for 50 to 60% of all cases

- Mycosis fungoides variants and subtypes:
  - folliculotropic MF,
  - pagetoid reticulosis,
  - granulomatous slack skin
- Primary cutaneous CD30+ lymphoproliferative disorders (LPD), the second most frequent CTCL subtype (20-30% of CTCLs)
  - primary cutaneous anaplastic large cell lymphoma (pCALCL)
  - lymphomatoid papulosis (LyP).
  - Subcutaneous panniculitis-like T-cell lymphoma (TCL)
  - Primary cutaneous CD4+ small/medium-sized pleomorphic TCL (PCSM) (provisional)

CTCL with Aggressive clinical behavior:

- Sézary syndrome (SS), the distinctive leukemic variant of MF that represents 2 to 5% of all CTCL cases
- Adult T-cell leukemia/lymphoma (ATL) (approximately 2% of CTCL cases in Western countries
- Extranodal NK/TCL, nasal type (approximately 5% of CTCL cases in Western countries
- Primary cutaneous peripheral TCL, unspecified (or not otherwise specified, NOS including all provisional entities;
  - Primary cutaneous aggressive epidermotropic CD8+ TCL (provisional)
  - Cutaneous gamma/delta-positive (PCGD) TCL (provisional)

Thus, CTCL comprise a group of heterogeneous T cell lymphomas with a clinical behavior that is distinct from that of systemic/nodal non-Hodgkin´s lymphomas, including those with a similar histological subtype. Characteristics of CTCL vary widely in skin appearance (patches, plaques, tumors), aggressiveness, biological behavior, blood involvement, histological and immunophenotypic aspects and, consequently, in prognosis and survival (Yamashita et al. 2012; Cerroni and Wiesner 2009)
Classification and treatment guidelines specific for MF/SS and Non-MF/SS CTCL have been developed separately. In 2007, the latest revision for MF and SS staging was published by the International Society for Cutaneous Lymphomas (ISCL)/ EORTC that incorporated advances in tumor cell biology and diagnostic techniques and updated guidance for standardized assessment and categorization of tumor (T), node (N), metastases (M) and blood (B) involvement (Olsen et al. 2007). The most recent classification of non-MF/SS CTCL has been proposed by the ISCL and the Lymphoma Task Force of the EORTC in 2007 (Kim et al. 2007). In contrast to the MF/SS classification, no stages had been allocated to the proposed non-MF/SS CTCL TNM classification, since the working group came to the conclusion that for the non-MF/CTCL entities a lack of specific survival information prevented prognostic categorization.

<u>Prognosis and Clinical Presentation of CTCL</u>

In 1997, survival data were derived by the Cutaneous Lymphoma Study Group of the EORTC from the registry of the Dutch Cutaneous Lymphoma Working Group (DCLWG) that included 626 PCL patients from 1986 to 1994 (CTCL: 508 patients, CBCL: 118 patients). Although CTCL is generally considered incurable, the majority of patients (~90%) presents initially with an indolent form of the disease and will live for several years. Independent survival data for each subtype of CTCL are scarce, essentially due to the limited number of patients *per* subtype and to the historical evolution in their classification. Overall, prognosis and survival vary significantly by subtype of CTCL (Willemze et al. 2005) survival data for 1476 CTCL patients registered between 1986 and 2002 by the Dutch and Austrian Cutaneous Lymphoma Group. Indolent CTCL subtypes displayed 5 year survival rates of 75-100%, whereas 5-year survival rates of aggressive subtypes ranged between 15-25% (Willemze et al. 2005).

With 50%-60% of CTCL cases, Mycosis Fungoides (MF) represents the most common CTCL subtype. Sézary syndrome (SS) is a leukemic variant of MF and is diagnosed in approximately 3% of CTCL patients (Willemze et al. 2005). Adult T-cell leukemia/lymphoma (ATL) and extranodal NK/TCL, nasal type represent approximately 2% (ATL) and 5% (extranodal NK/TCL) of CTCL cases, respectively, in Western countries, although they are more prevalent in Asia (Suzumiya et al. 2009).

Mycosis Fungoides (MF) presents clinically with patches (flat, scaly skin lesion), plaques (raised, palpable skin lesions) and/or tumors (thick, deep skin infiltrating, sometimes ulcerating lesions) of the skin. With clinical progression, the dermal infiltrates become more diffuse and epidermotropism may be lost. MF may present with blood involvement (MF with leukemic involvement).

Although MF overall shows an indolent behavior with a median survival of more than 15 years when it is diagnosed at early stages (Stages IA-IIA), approximately 20% of these patients will experience progression to higher stages (Stages IIB-IVB), characterized by presence of tumors, erythema, lymph node or blood involvement. The prognosis at these higher stages worsens to a median survival of less than 5 years (Agar et al. 2010; Kaye et al. 1989; Diamandidou, Cohen, and Kurzrock 1996; Zackheim 1999; Zackheim et al. 1999; Kim et al. 2003; Arulogun et al. 2008) The worst prognosis is seen for patients with visceral involvement (M1, stage IVB) with a median survival of less than 2 years.

	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB
N	438	583	40	167	100	56	67	37	14
%	29.2	38.8	2.7	11.1	6.7	3.7	4.5	2.5	0.9
Median survival (yr)	35.5	21.5	15.8	4.7	4.7	3.4	3.8	2.1	1.4
5-yr DSS (%)	98	89	89	56	54	48	41	23	18
10-yr DSS (%)	95	77	67	42	45	45	20	20	-
5-yr OS (%)	94	84	78	47	47	40	37	18	18
10-yr OS (%)	88	70	52	34	37	25	18	15	-

Table 1: Five and 10-year Survival for Mycosis Fungoides/Sézary Syndrome
Adapted from (Agar et al. 2010); DSS: disease-free survival; OS: overall survival

Advanced disease and in particular the presence of tumors or elevation of both LDH and β2-microglobulin is associated with an increased incidence of transformation of MF to a diffuse large-cell lymphoma. The incidence of large cell transformation increases with MF stage, with a rate of approximately 1.5 % in early stage MF increasing up to approximately 60% in stage IV MF (Arulogun et al. 2008).

Transformed MF (tMF) cells may be either CD30- or CD30+ (Diamandidou et al. 1998). Outcome is poor if transformation takes place within 2 years from initial diagnosis or if advanced stage is present at time of transformation. The median overall survival at diagnosis of tMF is approximately 19 months, if tumors are present, median survival drops to less than 1 year (Diamandidou et al. 1998; Jawed et al. 2014). Transformation of MF in general is associated with increased resistance to aggressive therapies (Kennedy et al. 2003; de Masson et al. 2014; Willemze 2011).

Sézary syndrome (SS) is characterized clinically by pruritic erythroderma, generalized lymphadenopathy, and blood involvement with circulating Sézary cells. Patients with this syndrome often experience intractable pruritus, which is typically the most significant life- altering symptom (Horwitz et al. 2008). Histological features of affected skin in SS may be similar to those in MF. However, the cellular infiltrates in SS are more often monotonous, and epidermotropism may be absent. In addition to morphologic identification of Sézary cells in blood for diagnosis of SS and MF with leukemic involvement, the characterization by flow cytometry distinguishes more precisely malignant Sézary cells from atypical lymphocytes with cerebriform nuclei that can be present in blood of healthy individuals and individuals with benign inflammatory skin diseases. The typical immunophenotype of Sézary cells is CD3+, CD4+, CD7- and CD8-, similar to epidermotropic MF cells.

Non-MF/SS CTCL presents with distinct clinical features compared to MF/SS.

CD30+ LPD represents approximately 20-30% of CTCL cases and comprises two subtypes: Lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (pCALCL). Typically patients with LyP are younger at first diagnosis

compared to patients diagnosed with pCALCL (median age 45 vs. 60). In addition LyP and pCALCL present with different clinical features.

Lymphomatoid papulosis is characterized by recurrent papulonodular and papulonecrotic skin eruptions, plaques and tumors are rare. The skin eruptions disappear normally without treatment and treatment does not prevent recurrence. Secondary lymphomas, either concurrent or sequential, are frequent: In 2000 the Dutch Cutaneous Lymphoma Group reported associated lymphomas in approximately 20% of cases (23 patients) out of 118 LyP patients, half of them were MF (Bekkenk et al. 2000). Patients with LyP rarely develop extra-cutaneous disease, only 4% (7 patients) were described by Bekkenk. In the 4 cases in which regional lymph nodes were involved the disease completely disappeared in all cases either with or without systemic therapy. In the other 3 cases LyP transformed to a large T-cell lymphoma with lung involvement (1 patient) or to Hodgkin disease (2 patients). Life expectancy is similar to the normal population due to the self-healing character of LyP. Sixty percent of **primary cutaneous ALCL** present clinically with skin tumors concurrently with papulonodular and papulonecrotic skin lesions. In the report from Bekkenk spontaneous remissions were observed in only 42% of cases (33 patients out of 79). In 10% (8 patients) of the 79 patients the disease recurred extra-cutaneous. Four of these patients died within 5 years of follow up due to lymphoma. Patients with multi-focal skin disease developed extracutaneous disease more often than patients with skin lesions limited to one skin area. The prognosis for patients with pCALCL is excellent, the disease related 5- and 10 year survival rates are greater than 95% and 90% respectively.

Treatment of CTCL

Treatment guidelines for CTCL, MF/SS, primary cutaneous lymphomas or CD30+ LPD have been published by the NCCN, the NCI; the ESMO guidelines Working Group and the EORTC-ISCL-USCLC (Horwitz et al. 2016). In general, treatment guidelines distinguish CTCL by clinical appearance and localization, histological subtype, extent and type of extracutaneous disease, aggressiveness and prior treatment response.

Due to the self-healing but chronically recurring nature and benign character of LyP, treatment is not recommended unless the patient presents with numerous, disseminated or stigmatizing lesions. Therapeutic strategies for pCALCL and for MF/SS depend on size and extend of tumors (pCALCL) or on the clinical stage of the disease (MF) (Willemze et al. 2005; Horwitz et al. 2008). In addition the extent and type of skin involvement and the presence of extracutaneous disease in lymph nodes, blood and/or viscera is taken into account.

Typically in localized early stages of **MF** (stages IA – IB) and, if indicated, in LyP local skin-directed therapy is used. Corticosteroids, nitrogen mustard or carmustin applied to skin lesions can induce response rates of >90% (Zackheim 1998; Zackheim, Kashani-Sabet, and Amin 1998; Zackheim 2003a, 2003c, 2003b; Kim 2003). Although topical corticosteroids result in faster regression of skin lesions in LyP, oral

corticosteroids appear to have no activity in LyP (Kempf et al. 2011). Retinoids can be used for plaques and also combined with phototherapy, when widespread involvement of the skin is present. Response rates of 45 – 75% can be achieved by these agents in MF (Breneman et al. 2002; Lessin et al. 2013). Total skin electron beam therapy can be considered for stage IB and IIA MF since it has been shown to be active for plaques and tumors, in particular in combination with topical nitrogen mustard (Chinn et al. 1999). In initial intermediate and advanced stage, refractory MF, large cell transformation, blood involvement or Sézary syndrome a combination of different local therapies or local with systemic therapy is beneficial. Local steroids, retinoids or nitrogen mustard can be used in combination with systemic retinoids, interferon, the histone deacetylase inhibitor Romidepsin, denileukin-difitox, extra-corporeal photophoresis (ECP) or chemotherapy such as methotrexate. These treatments achieve complete remissions only infrequently in advanced stages (<10%) of MF, but response rates range between ~35 and 90% and may last for years.

Patients with advanced or relapsed disease can be treated with more aggressive chemotherapy such as Gemcitabine, liposomal doxorubicin or with combination chemotherapy. Combination chemotherapy should be considered only for patients who have failed several treatment lines with local and systemic agents, or patients with bulky lymph nodes or visceral involvement per NCCN and ESMO guidelines (Horwitz et al. 2016; Willemze et al. 2013). For the treatment of solitary tumors or grouped lesions in pCALCL, surgical excision and radiotherapy is recommended and result in a >95% CR rate. Relapses limited to the skin do not affect prognosis and can be treated similarly to initial tumors. In multi-focal pCALCL use of MTX, retinoids, Interferon and thalidomide with varying effect have been reported. For young patients in advanced stage CTCL, allogeneic stem cell transplantation (SCT) may be a promising therapy, since a graft-versus tumor effect could play an important role for disease control (Duarte et al. 2010). Investigational drugs such as mogamulizumab (defucosylated anti-CCR4-antibody) are currently explored in clinical studies of MF/SS. Phase 2 studies showed complete and partial responses in MF/SS. In a phase 2 study of mogamulizumab in CTCL (only MF/SS) patients who had failed at least one systemic therapy, a response rate of 37% was observed. The response rate in SS tended to be higher in SS compared to MF (47% vs. 29%) (Duvic, Evans, and Wang 2016). Based on this result a phase 3 study in CTCL has been initiated and results are awaited in 2017. Romidepsin, a histone deacetylase inhibitor, has modest activity with an ORR of 37% and is now FDA approved for treatment of advanced stage CTCL (Whittaker et al. 2010).

Overview on peripheral T-cell lymphoma

Peripheral (systemic) T cell lymphomas (PTCL) is a rare disease with poor outcome (William and Armitage 2013). Furthermore, the outcome for PTCL patients who relapsed after initial treatment is dismal with a median survival after relapse of 2.5 months (William and Vose 2013). There is no standard treatment for PTCL. Agents that are active in this disease include anthracycline-based, gemcitabine-based, etoposide and others (Moskowitz, Lunning, and Horwitz 2014). Recently,

pralatrexate and romidepsin have been approved by the FDA to treat relapsed refractory PTCL (Piekarz et al. 2011; O'Connor et al. 2011). Novel agents with activity against relapsed/refractory PTCL are urgently needed. NCCN guidelines recommend that all patients with PTCL should be treated on clinical trials (Horwitz et al. 2016).

Background on Bretuximab Vedotin (BV)

The CD30 molecule is a member of the TNF superfamily and is a surface receptor expressed predominantly on activated B- and T-cells in healthy individuals (Younes 2011). However, CD30 is nearly universally present on Hodgkin Reed-Sternberg (HRS) cells and in anaplastic large-cell lymphoma (ALCL), making it an attractive therapeutic target. Brentuximab vedotin (BV) is an antibody-drug conjugate that consists of three components: a chimeric CD30-specific monoclonal antibody attached to the microtubule- disrupting agent monomethyl auristatin E (MMAE) by a protease-cleavable covalent linker. Upon binding to CD30, BV is internalized and MMAE is released via proteolytic cleavage in the lysosome, leading to apoptotic cell death. In the phase II setting, BV provided an impressive overall response rate (ORR) of 75% in relapsed/refractory (rel/ref) patients with Hodgkin lymphoma (HL) (Younes et al. 2010b) and 86% in ALCL (Pro et al. 2012) and is now FDA-approved for these indications. Variable levels of CD30 expression are also seen in other NHL subtypes, including 14% of patients with DLBCL (Hu et al. 2013). Preliminary data from an ongoing phase II trial shows that BV in rel/ref patients with CD30+ DLBCL (n = 50) has single-agent activity with an overall response rate (ORR) of 42%, including 8 complete responses (CR), with a median duration of response of 46 weeks for patients who achieved CR (range of 1.4+ to 22.7+ weeks) (Sharman et al. 2013). Interestingly, responses have been seen in DLBCL patients with variable levels of CD30 expression (range 0-90%), with no statistical correlation between CD30 expression and response (Sharman et al. 2013).

Krathen, et al. have shown that multispectral imaging is able to detect CD30 expression in tumors judged to be CD30-negative by immunohistochemistry, suggesting that targeting even low levels of this molecule may be sufficient to show clinical benefit (Krathen et al. 2012). BV has been very well tolerated, with the most common adverse events being peripheral neuropathy, nausea, fatigue, and neutropenia, with febrile neutropenia being rare (Younes et al. 2010a; Younes et al. 2012; Sharman et al. 2013).

Clinical Studies of BV in T-Cell Lymphomas

Systemic Anaplastic Large Cell Lymphoma (sALCL)

There are five phase I, three phase II studies, and three case reports totaling 124 patients with sALCL (Berger et al. 2017b).

Phase I studies

The Younes et al. phase I study looked at $CD30^+$ relapsed HL (n = 42), angioimmunoblastic TCL (n = 1) and sALCL (n = 2) patients treated with BV (Younes et al. 2010a). No gender or age data are specified for these patients. CD30 positivity was seen in 100% (n = 2) and 100% (n = 2) were ALK^+. All patients (n = 2) achieved CR (median duration 36 weeks). In the Gibb et al. phase I study, refractory $CD30^+$ lymphoma patients were treated with BV as a bridge to allogeneic SCT (Gibb et al. 2013). Of the 24 patients in this study, 18 had HL, five had sALCL and one had TCL. Gender and age data are not specified for this subset of patients. CD30 positivity was seen in 100% (n = 5), 40% (n = 2) were ALK^-, and 60% (n = 3) had unknown ALK status. Complete remission leading to transplant was achieved by 60% (n = 3). Data is not available for the remaining two patients regarding SD versus PD (Gibb et al. 2013). The Fanale et al. phase I trial studied the efficacy of BV as a front-line treatment in peripheral TCL patients including sALCL (n = 32). Of the 32 patients, 50% (n = 16) were male (median age of 35 years). CD30 positivity was seen in 100% (n = 32) and 19% (n = 6) were ALK^+. An OR was experienced by 94% (n = 30) (median duration 52·8 weeks). Of these patients, 75% (n = 24) achieved CR (median duration 105.2 weeks) and 19% (n = 6) experienced a PR. Progressive disease was suffered by 6% (n = 2) (Fanale et al. 2014). Bartlett et al. published a phase I dose-escalation study. Four patients had sALCL. There are no available data separating the gender and age for this subset of patients. CD30 positivity was seen in 100% (n = 4). There were no available ALK expression data. Complete remission was achieved by 75% (n = 3) (median duration N/A). The remaining 25% (n = 1) experienced SD (Bartlett et al. 2009). Fanale et al. published a phase I dose-escalation study with refractory HL (n = 38), sALCL (n = 5) and peripheral T-cell lymphoma (PTCL) (n = 1). There are no available data separating the gender and age for this subset of patients. CD30 positivity was seen in 100% (n = 5) and 20% (n = 1) were ALK^+. An OR was experienced by 80% (n = 4) (median duration N/A). Complete remission was achieved by 80% (n = 4) (median duration N/A) and 20% (n = 1) experienced SD (Fanale et al. 2012).

Phase II studies

The Pro et al. phase II study included 58 relapsed/refractory sALCL patients of which 57% (n = 33) were male and the median age was 52 years. CD30 positivity was seen in 100% (n = 58) and 72% (n = 42) were ALK^+. An OR was experienced by 86% (n = 50) (median duration 50.4 weeks). Fifty seven percent (n = 33) achieved CR (median duration 52·8 weeks) and 29% (n = 17) experienced a PR. Stable disease was maintained by 3% (n = 2) and 5% (n = 3) experienced PD (Pro et al. 2012). In the Ogura et al. phase I/II study looking at $CD30^+$ patients with HL (n = 14) or sALCL (n = 5), 100% (n = 5) were male (median age 41 years). The CD30 biomarker was expressed in 100% (n = 5) and 20% (n = 1) were ALK^+. Of these patients, 100% (n = 5) experienced an OR (median duration 38·80 weeks). Eighty percent (n = 4) achieved CR (median duration N/A) and 20% (n = 1) achieved a PR (Ogura et al. 2014). In the Bartlett et al. phase II study looking at retreatment of $CD30^+$patients with HL (n = 21) or sALCL (n = 8) who initially achieved an OR with BV, the median age of sALCL patients was 51·5 years and male patients made up 50% (n = 4). All sALCL patients were $CD30^+$ (n = 8) and 38% (n = 3) of them were ALK^+. An OR was

experienced by 88% (n = 7) (median duration 28 weeks). Five patients (63%) achieved CR (median duration 20 weeks) and 25% (n = 2) experienced PR (Bartlett et al. 2014).

Sézary Syndrome (SS)/Mycosis Fungoides (MF)

There is one recent phase 3 trial, three phase II studies and four case reports totaling 91 patients with MF (n = 79) and SS (n = 13) (Berger et al. 2017a).

Phase III trial

Kim et al (Kim et al. 2016) recently presented the final results of ALCANZA trial. Adults with CD30-expressing (≥10% of infiltrate by central review) mycosis fungoides (MF) who received ≥1 prior systemic therapy or primary cutaneous anaplastic large cell lymphoma (pcALCL) who received ≥1 prior systemic therapy or radiotherapy were enrolled. Patients were stratified by diagnosis and randomized 1:1 to receive BV 1.8 mg/kg IV, once every 3 weeks, or physician choice (PC) of either methotrexate (MTX) 5–50 mg PO, once weekly, or bexarotene (Bex) 300 mg/m² (target dose) PO, once daily, for up to 16 three-week cycles, until disease progression or unacceptable toxicity. Primary endpoint was ORR4, defined as ORR lasting ≥4 months, an endpoint that captures response rate and duration as a single measurement. ORR4 was determined by independent review of global response using the ISCL/EORTC consensus guidelines (Olsen et al. 2011). 131 patients were randomized with 128 patients in the intent-to-treat population (97 MF, 31 pcALCL; 3 excluded for insufficient CD30 expression) and assigned to BV (n=64) or PC (n=64). Baseline characteristics were generally balanced between arms with the exception of more patients with extracutaneous disease in the BV arm (Table-2). In BV vs PC arms, respectively, median age was 62 (22–83) vs 58 (22–83) years; ECOG performance status 0–1 was 95% vs 97%. Patients in each arm had a median of 2 prior systemic therapies. At a median follow-up of 17.5 months, ORR4 (primary endpoint) and PFS strongly favored BV vs PC with ORR4 of 56% vs 13% ($p<0.0001$) and median PFS of 16.7 vs 3.5 months (HR 0.270; 95% CI, 0.169–0.430; $p<0.0001$), respectively (Fig 1, 2). ORR was 67% (n=43) with CR 16% for BV, compared with ORR of 20% (n=13) with CR 2% for PC (ORR, $p<0.0001$; CR, $p=0.0046$). Skindex-29 showed significantly greater symptom reduction for BV compared with PC (-27.96 vs -8.62; $p<0.0001$). Patients received a median of 12 (1–16) cycles of BV vs 5.5 (1–16) Bex and 3 (1–16) cycles of MTX. Grade 3–4 AEs, all cause / drug-related, were seen in 41% / 29% with BV vs 47% / 29% with PC. Serious AEs were seen in 29% of patients in each arm. Peripheral neuropathy (PN), any grade, was seen in 67% in the BV arm (32% grade 2, 9% grade 3) and 6% in the PC arm. At last follow-up, 36/44 (82%) patients in the BV arm had improvement or resolution of PN. Discontinuation due to AEs occurred in 24% (BV) vs 8% (PC). Four deaths in the BV arm (3 unrelated to study drug) occurred within 30 days of the last dose. Other AEs were consistent with reported safety profiles for the individual agents. In this first report of a randomized phase 3 trial evaluating a new agent vs standard-of-care options in CTCL, the clinical outcome of BV was far superior to PC (MTX or Bex). Highly statistically significant improvements in ORR4 (44%) and median PFS (13.2 months) were observed with

BV. Greater ORR with higher CR rate and reduction in symptoms per Skindex-29 symptom domain were also observed in the BV arm. Safety data for BV were consistent with the established tolerability profile. The data from this randomized trial provide compelling evidence favoring BV over PC of Bex or MTX in CD30-expressing CTCL (Kim et al. 2016).

	Brentuximab Vedotin				Physician's Choice Bexarotene or Methotrexate			
	Total N=64 n (%)	ORR4[a]	ORR	CR	Total N=64 n (%)	ORR4[a]	ORR	CR
MF	48 (75%)	50%	65%	10%	49 (77%)	10%	16%	0
Stage[b,c] , n (%)								
IA-IIA	15 (31%)	40%	53%	7%	18 (37%)	22%	28%	0
IIB	19 (40%)	63%	68%	16%	19 (39%)	5%	16%	0
IIIA-IIIB	4 (8%)	50%	75%	0	2 (4%)	0	0	0
IVA	2 (4%)	100%	100%	50%	9 (18%)	0	0	0
IVB	7 (15%)	29%	57%	0	0	NA	NA	NA
pcALCL	16 (25%)	75%	75%	31%	15 (23%)	20%	33%	7%
Disease involvement[b], n (%)								
Skin-only	9 (56%)	89%	89%	44%	11 (73%)	27%	45%	9%
Extracutaneous disease	7 (44%)	57%	57%	14%	4 (27%)	0	0	0

[a]ORR4 is defined as response lasting at least 4 months.
[b]Percentage in each subcategory in the Total column is based on the number of patients in each disease subtype.
[c]One patient in each arm had incomplete staging data and are not included in the table: 1 patient in the BV arm had PR, 1 patient in the PC arm had no response.
ORR4, ORR, CR rates are based on the number of patients in the Total column.
CR, complete response; MF, mycosis fungoides; NA, not applicable; ORR, overall global response rate; pcALCL, primary cutaneous anaplastic large cell lymphoma

Table 2: Clinical Characteristics of patients treated on the ALCANZA trial (Kim et al. 2016)

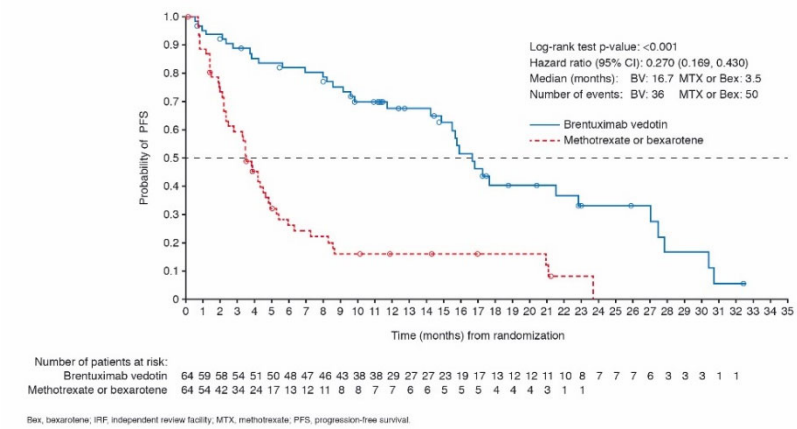


Figure 1: PFS of patients treated on the ALCANZA trial (Kim et al. 2016)

Phase II studies

Bashey et al. published a phase II abstract detailing BV in the treatment of MF (n = 14) and SS (n = 1) with variable CD30 expression Median age was 64 years. Gender data are not available. An OR was observed in 60% (n = 9) (not specified CR versus PR). Median duration is unknown. Of the patients who did not experience an OR, the data do not specify SD versus PD (Bashey et al. 2012). Kim et al. published a phase II study observing BV in 22 patients with MF and 10 patients with SS (Kim et al. 2015). CD30 expression was variable. Gender differentiating data are not

available. The median age was 62-years-old. An OR was experienced by 70% (n = 21) in which CR was achieved by 3% (n = 1; SS) and 66% (n = 20) experienced PR. Stable disease was maintained by 13% (n = 4) and 17% (n = 5) experienced PD. Duvic et al. published a phase II study observing BV activity in CD30$^+$ cutaneous TCL and lymphoproliferative disorders. Of the 48 total patients, there were 28 with CD30$^+$ MF and seven with CD30$^+$ MF with LyP. Gender and age information are not specified for these subpopulations. Of these patients, 60% (n = 21) achieved an OR (median duration 14·4 weeks). Eight patients (23%) achieved CR (median duration not reported) and 37% (n = 13) experienced a PR (Tetzlaff et al. 2013).

Peripheral T-cell lymphoma/Angioimmunoblastic T-cell lymphoma

Phase I studies

There are four phase I studies totaling 10 patients with PTCL. Younes et al. published a phase I study and one patient in this study had a diagnosis of CD30$^+$ angioimmunoblastic TCL (Younes et al. 2010b). Age and gender of this patient are not detailed separately. This patient experienced PD. Of note, this patient had the best response of those in the low dose cohort. Gibb et al. published a phase I study looking at BV as bridge therapy for allogenic SCT in patients with HL, ALCL or CD30$^+$ TCL (Gibb et al. 2013). One patient in this study had CD30$^+$ TCL. The age and gender of this patient are not detailed separately. This patient experienced either PD or death prior to follow-up PET after 4 cycles (1 of 4 in this category; results not specific to TCL). Fanale et al. published a phase I study looking at BV as front-line therapy for patients with TCL. Seven patients fall into the category of PTCL [PTCL-NOS (n = 2), angioimmunoblastic TCL (n = 2); enteropathy associated TCL (n = 1), TCL (n = 2)]. Of these patients, 14% (n = 1) were male (median age 55 years). All patients (n = 7) were CD30$^+$. An OR was observed in 100% (n = 7) of patients (median duration 56·7 weeks). All patients (n = 7) achieved CR as well (median duration 56·7 weeks). An additional phase I study performed by Fanale et al. details one patient, diagnosed with CD30$^+$ TCL, who experienced a PR for an unknown duration (Fanale et al. 2012).

Phase II studies

Horwitz et al. published a phase II study observing BV efficacy in relapsed TCL. This study included a total of 35 patients with PTCL (PTCL-NOS [n = 22], angioimmunoblastic TCL [n = 13]). Males comprised 77% (n = 27) (median age 64 years). All of these patients were CD30$^+$. An OR was observed in 41% (n = 14) (median duration 30·4 weeks). Complete remission was achieved in 24% (n = 8) (median duration 30·4 weeks) and 18% (n = 6) experienced a PR. Stable disease was maintained in 18% (n = 6) and 41% (n = 14) experienced PD (Horwitz et al. 2014).

Lymphatoid Papulosis (LyP)

Duvic et al. published a phase II study observing BV activity in CD30$^+$ cutaneous TCL

and lymproliferative disorders. Of the 48 total patients, there were nine with $CD30^+$ LyP alone. Gender and age information are not specified for this subpopulation. All of these patients (n = 9) achieved an OR (median duration 23 weeks). Complete remission was achieved by 56% (n = 5) and 44% (n = 4) experienced a PR (Tetzlaff et al. 2013).

Primary Cutaneous ALCL

There is one phase II study and two case reports totaling six patients with primary cutaneous ALCL (pc-ALCL) (Berger et al. 2017a).

Phase II studies

Duvic et al. published a phase II study observing BV activity in $CD30^+$ cutaneous TCL and lymphoproliferative disorders. Of the 48 total patients, there were two with $CD30^+$ pc-ALCL and two with $CD30^+$ pc-ALCL and LyP. Gender and age information are not specified for these subpopulations. All of these patients (n = 4) achieved an OR (median duration 18 weeks). All four patients achieved CR (median duration 10 weeks) (Tetzlaff et al. 2013).

Case reports

Patsinakidis et al. detailed a case report of a 56-year-old male with $CD30^+$ and ALK^- pc-ALCL.The patient achieved PR after four weeks and CR after another four weeks. No follow-up data is available (Patsinakidis et al. 2015). Kaffenberger et al. detailed a case report of a 60-year-old male with $CD30^+$, ALK^- refractory pc-ALCL. After two cycles (six weeks) the patient experienced CR, which continued through follow-up at 56 weeks (Kaffenberger et al. 2013).

Lenalidomide Background

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and anti-angiogenic effects.

Lenalidomide demonstrates pleiotropic activities in distinct cell types that result in direct antitumor effects on cancer cells, inhibition of stromal growth factor support, and enhancement of host anticancer immunity (Heise et al. 2010; Kotla et al. 2009; Martiniani et al. 2012; Zeldis et al. 2011; Zhu, Kortuem, and Stewart 2013). The clinical activity of lenalidomide has been most notable in B-cell malignancies including multiple myeloma (MM), MCL, DLBCL, FL, and B-cell CLL (Davies and Baz 2010; Schey et al. 2010; Dawar and Hernandez-Ilizaliturri 2012; Ferrajoli et al. 2008).

The activity of lenalidomide may be further subdivided into the following categories: direct antiproliferative activity against hematopoietic tumor cells; immunomodulatory activity including upregulation of T cell and NK cell responses;

and inhibition of monocyte responses, antiangiogenic activity, and pro-erythropoietic activity.

Lenalidomide's pleiotropic activities in a range of cell types including multiple myeloma (MM) cells and immune effector cells suggest modulation of multiple molecular pathways. Studies conducted to identify the molecular target(s) of lenalidomide have shown that it physically associates with the protein cereblon (encoded by the *CRBN* gene), a protein required for the teratogenic effects of thalidomide in zebrafish and chicken embryos (Ito et al. 2010). Cereblon is a substrate receptor for an ubiquitin E3-ligase complex containing deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1) proteins ($CRL4^{cereblon}$) (Ito et al. 2010). Upon binding to Cereblon, lenalidomide induces the ubiquitination of substrate proteins, including Ikaros (encoded by the gene *IKZF1*) and Aiolos (encoded by the gene *IKZF3*), thus targeting them for proteasomal-dependent degradation (Gandhi et al. 2013; Kronke et al. 2013; Lu et al. 2014). It was also demonstrated that the expression of Cereblon in MM cells is linked to the anti-proliferative effects of lenalidomide and to the acquired resistance in vitro (Zhu, Kortuem, and Stewart 2013; Lopez-Girona et al. 2012). The downstream anti-proliferative and pro-apoptotic effects of Ikaros and Aiolos are linked to the subsequent downregulation of the MM growth-promoting factors c-Myc and IRF4 (Bjorklund et al. 2014).

Ikaros and Aiolos are zinc finger transcription factors initially discovered as regulators of the T cell receptor and are required for proper hematopoiesis particularly lymphocyte development and plasma cell maturation. Cereblon expression also mediates the T-cell response to lenalidomide through the targeted degradation of Ikaros and Aiolos (Lopez-Girona et al. 2012; Gandhi et al. 2013). In activated T cells in which cereblon was transiently decreased, interleukin-2 (IL-2) and TNF- α induction by lenalidomide was markedly reduced. Since IL-2 and TNF-α are important for tumor surveillance by activated T cells, these results indicate that some of the immunomodulatory effects of lenalidomide are mediated via initial binding to cereblon. Specifically, upon engagement with the $CRL4^{cereblon}$, lenalidomide induced ubiquitination and proteasomal degradation of Ikaros and Aiolos in T cells in a time- and concentration-dependent manner (Gandhi et al. 2013; Kronke et al. 2013). Because Ikaros and Aiolos are known repressors of the IL-2 promoter, their degradation in response to lenalidomide and other IMiDs® compounds, explains the enhanced T cell IL-2 production .

In summary, lenalidomide exhibits potent anti-tumor activity in B cell malignancies, which appears to be mediated through the protein target, cereblon. While specific cereblon interaction networks are still to be defined, these results are key for further understanding of the mechanism of lenalidomide effects.

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: Leukopenia, Neutropenia, Febrile

neutropenia, Granulocytopenia, Lymphopenia; Anemia; Thrombocytopenia; Vision Blurred; Diarrhea; Upper abdominal pain, Abdominal pain, Toothache, Constipation; Dyspepsia; Nausea; Vomiting; Asthenia; Fatigue; Edema, Peripheral edema; Pyrexia; Chills; Pneumonia, Bronchitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Gastroenteritis, Herpes simplex, Herpes zoster, Influenza, Lower respiratory tract infection, Sinusitis, Sepsis, Bacteremia; Nasopharyngitis, Pharyngitis; Rhinitis; Weight loss; Decreased appetite; Hyperglycemia; Hypokalemia, Hypocalcemia, Hypophosphatemia, Hypomagnesemia, Hyponatremia; Pain in extremity, Pain in limb, Arthralgia, Back pain, Bone pain, Muscle spasms, Musculoskeletal pain, Muscle cramp, Chest pain and Myalgia; Dizziness; Dysgeusia, Headache; Cataract; Hypoaesthesia; Neuropathy, Peripheral neuropathy, Peripheral sensory neuropathy; Tremor; Cough; Dyspnea; Epistaxis; Pulmonary embolism, Deep vein thrombosis; Dry skin; Pruritus; Rash, Hypersensitivity (in uncommon category); Depression; Insomnia and recently Vertigo.

Overall, lenalidomide has been shown to be well-tolerated in patients with rel/ref DLBCL, with the most common grade 3 or 4 adverse events seen in phase II trials being neutropenia (41%), thrombocytopenia (19%), and anemia (9.2%) (Witzig et al. 2011) (Witzig et al., 2011). In another trial in patients with rel/ref HL, changing the dosing frequency from an interrupted schedule of Days 1-21 of a 28-day cycle to continuous dosing resulted in only a modest increase in patients that had to discontinue treatment (5.3% prior to Cycle 2 and 10.5% after Cycle 2, compared with 9.5% and 19%, respectively) (Fehniger et al. 2011).
Complete and updated adverse events are available in the Investigational Drug Brochure.

Clinical Studies of lenalidomide in T-cell lymphomas

Lenalidomide is less studied in T-cell lymphomas compared to B-cell lymphomas however few studies confirmed a single agent activity in both CTCL and PTCL.

Studies of lenalidomide in CTCL

A phase 2 multicenter trial was performed to evaluate single-agent lenalidomide in advanced, refractory mycosis fungoides/Sézary syndrome. Thirty-two patients were enrolled with a median of 6 prior treatment regimens, including a median of 4 systemic therapies. Patients achieved an overall response rate of 28% (9 patients), and all were partial responses. Median overall survival was 43 months, median progression-free survival was 8 months, and median duration of response was 10 months. No grade 4 toxicities occurred. Grade 3 adverse events included fatigue (22%), infection (9%), and leukopenia (3%). Patients were frequently unable to tolerate the 25-mg starting dose of lenalidomide used in other hematologic malignancies due to fatigue, pain, and transient flare reaction (TFR) as a contributory factor. TFR appeared to correlate with clinical response, but the small sample size limited definitive conclusions, and the underlying mechanisms of this reaction are not known. Data from correlative studies on peripheral blood samples suggest that the

effects of lenalidomide could be associated with decreased circulating CD25(+) T cells and CD4(+) T-cell numbers. Skin lesions showed a trend for increased CD8, CD25, and FoxP3 expression with decreased CD4:CD8 ratio. In conclusion, lenalidomide monotherapy demonstrated activity in refractory cutaneous T-cell lymphomas, along with acceptable toxicity (Querfeld et al. 2014)

Lenalidomide monotherapy studies in PTCL

Forty patients with recurrent and refractory T-cell lymphomas other than mycosis fungoides and patients with untreated T-cell lymphoma who were not candidates for combination chemotherapy were prescribed oral lenalidomide at a dose of 25 mg daily on days 1 to 21 of each 28-day cycle, with standardized dose reductions for toxicity. The primary endpoint was overall response rate (ORR), and secondary endpoints were complete and partial response rates, progression-free survival (PFS), overall survival (OS), and safety. The authors also determined duration of response (DoR). The ORR was 10 of 39 patients (26%); 3 patients (8%) achieved complete responses and 7 patients achieved partial responses. Three patients had stable disease for ≥5 cycles. The median OS was 12 months (range <1 month to ≥69 months), the median PFS was 4 months (range, <1 month to ≥50 months), and the median DoR was 13 months (range 2 months to ≥37 months), including 5 responses that lasted >1 year. Toxicity was in keeping with the known safety profile of lenalidomide. Among the patients who had recurrent/refractory peripheral T-cell lymphoma (29 patients), the ORR was 24%, the median OS was 12 months, the median PFS was 4 months, and the median DoR was 5 months (range, 2 months to ≥37 months) (Toumishey et al. 2015). Another multicentre, single-arm, open-label phase 2 trial investigated the efficacy and safety of lenalidomide monotherapy in patients with relapsed/refractory PTCL. Patients received oral lenalidomide 25mg once daily on days 1-21 of each 28-day cycle for a maximum of 24 months, until disease progression or development of unacceptable adverse events (AEs). A total of 54 patients with PTCL were treated. The overall response rate was 22% (12 of 54), including complete response (CR) or unconfirmed CR (CRu) in 11% of patients; 31% of patients with angioimmunoblastic T-cell lymphoma (AITL) responded (CR/CRu in 15% of patients). The median progression-free survival and median response duration were 2.5 and 3.6 months, respectively, in the intent-to-treat population, and 4.6 and 3.5 months, respectively, in patients with AITL. Thrombocytopenia and neutropenia were the most common grade 3 or 4 haematological AEs, in 11 (20%) and 8 (15%) patients, respectively. Overall, 19 patients (35%) experienced at least 1AE leading to study dose interruption or reduction (commonly neutropenia or thrombocytopenia). Serious AEs were observed in 54% of patients and 12 patients died during the study; lymphoma progression (n=6); and acute respiratory distress syndrome, dyspnea, lung infiltration, neutropenic sepsis, pneumonia and cerebral ischemia (n=1 each) (Morschhauser et al. 2013).

Combination Studies of Brentuximab Vedotin and Lenalidomide

The results of phase I/dose expansion trial of BV and lenalidomide in patients with

relapsed refractory diffuse large B-cell lymphomas (DLBCL) has been recently presented (Ward et al. 2015). Eligible patients had rel/ref de novo or transformed DLBCL after at least one prior systemic therapy and have previously received or are ineligible for SCT. Response assessments were performed after cycles 2, 4, 6, 9 and then every six months for two years by PET/CT scan and response determined per the Revised International Working Group Response Criteria for Malignant Lymphoma 2007. The study was in two parts, a dose-escalation portion using a 3+3 design to determine the MTD, followed by a dose-expansion cohort enrolling patients with either CD30 (+) or CD30 (-) DLBCL assessed by visual assessment using routine IHC per local laboratory. BV was administered every 21 days and lenalidomide was dosed continuously for a maximum of 16 cycles until disease progression or unacceptable toxicity. Eighteen patients were enrolled to date. The median age was 61 years (range 51-79), with 83% having an ECOG performance status of 0-1. Median number of prior therapies was 2 (range 1-6), with 39% undergoing a previous autoSCT, and one patient a previous alloSCT. 72% of patients were refractory to their last regimen. 13 patients had CD30 (-) and 5 CD30 (+) DLBCL. Treatment-related adverse events (AEs) occurring in >20% of patients included anemia (50%), elevated ALT (28%), hypocalcemia (22%), peripheral neuropathy (22%), neutropenia (28%), thrombocytopenia (33%), and hypokalemia (28%). Anemia, febrile neutropenia, thrombocytopenia, and hypokalemia were the only grade 3/4 related AEs observed in >10% of patients. Growth factors were not given during cycle 1 but were administered in 11 patients with subsequent cycles. One patient came off study for thrombocytopenia after completing 8 cycles, while in a CR. 47% have required at least one dose reduction. The DLTs per dose cohort are summarized in the table-3 below. The MTD of the combination is 1.2 mg/kg of BV Q21d with 20 mg Len given continuously. At the time of this analysis, 17 patients (1 too early) had restaging evaluations; 7 CR (41%), 2 PR, 3 SD, and 5 PD, for an overall RR of 53%. Five CRs occurred after C2, 1 after C6 and 1 after C8. All responses were ongoing with a range of 5 to 35 wks. Among the 7 CRs, 2 patients have CD30 (+) and 5 patients CD30 (-) DLBCL, 4 pts were GCB and 3 non-GCB. Of the four patients with CD30 (-) disease categorized as GCB, two achieved a CR. This Phase I study of BV plus lenalidomide identified the MTD of the combination at BV 1.2 mg/kg Q21d with lenalidomide 20 mg/d continuously. Dose expansion cohorts of 15 patients each for CD30 (-) and CD30(+) DLBCL are currently accruing. The predominant toxicity of the study regimen was related to cytopenias, consistent with prior experience. Although patient numbers were small, the high CR rate is intriguing (Ward et al. 2015).

# Patients	Assigned BV Dose	Assigned Len Dose	# of DLT	DLT Toxicity
9	1.2mg/kg	20mg	1	Neutropenia
6	1.2mg/kg	25mg	2	Neutropenia, DVT
3	1.8mg/kg	25mg	2	Fatigue, Neutropenia

Table 3: DLTs observed in BV and lenalidomide phase I trial in DLBCL (Ward et al. 2015)

Rational for Clinical Development of the Combination of Brentuximab Vedotin and Lenalidomide in T-Cell Lymphomas

Patients with advanced stage relapsed/refractory CTCL and PTCL have poor outcomes and new treatments are needed. There is sound rationale for combining BV and lenalidomide in the treatment of rel/ref CTCL/PTCL. As described above, both have single-agent activity in these diseases and unique mechanisms of action. Potential explanations for lenalidomide's activity include augmentation of innate and adaptive immune function, alterations of the cytokine profile of the tumor microenvironment, and effects on angiogenesis. Combinations of lenalidomide with agents that have minimal effect on the immune system, such as BV, are less likely to have antagonistic effects. Although BV is thought to act primarily through delivery of MMAE to the malignant cells, it is possible that lenalidomide may enhance the activity of the anti-CD30 antibody through immune-mediated mechanisms. Both lenalidomide and BV have very favorable safety profiles, making this an attractive combination in multiply relapsed and heavily pretreated patients. We hypothesize that the addition of lenalidomide to BV in patients with rel/ref CTCL/PTCL will increase the ORR. Moreover, both agents have been combined a recent phase I trial in DLBCL and were deemed safe and hence we can proceed with a phase II design utilizing the dose and schedule already established in this phase I trial (BV 1.2 mg/kg Q21d with lenalidomide 20 mg/d continuously) without a need for a formal dose escalation (Ward et al. 2015).

Correlative Studies Background

Correlation of Response to CD30 Expression

Objective responses have been observed in patients with all levels of CD30 expression, including levels interpreted as negative by routine immunohistochemistry (IHC). Correlation of CD30 expression with clinical response was evaluated in a phase 2, single-arm exploratory study of BV in relapsed or MF. In this study, CD30 expression levels from multiple intrapatient tumor biopsies were evaluated visually by routine IHC using the BerH2 antibody, with retrospective review of pre-treatment CD30 expression using quantitative, computer-assisted image analysis. Thirteen of 19 patients (68%) achieved an objective response. The majority of these patients had pre-treatment CD30 expression levels of less than 50% by IHC and visual analysis, including 37% of patients with CD30 expression <10%. Quantitative, computer-assisted assessment detected CD30 expression in all samples, including 12 interpreted as IHC negative by visual assessment. Results showed that CD30 expression levels did not correlate with response to BV treatment by routine IHC ($p=0.17$) or by image analysis ($p=0.74$); however, the zero to low CD30 expression by routine IHC may be attributed to low sensitivity of standard IHC detection (Ward et al. 2015).

To further characterize the correlation of CD30 expression with clinical response, this current study will therefore investigate the antitumor activity of the combination of

brentuximab vedotin and lenalidomide treatment in patients with CTCL/PTCL with CD30 expression on malignant cells both detectable (≥1%) and not detectable (<1%) by visual assessment using routine IHC.

Investigation of Immune Parameters in Patients Treated with Brentuximab Vedotin and Lenalidomide

Lenalidomide has multiple mechanisms of action, and the exact anti-tumor effect may differ depending on the malignancy exposed to the drug and the immune microenvironment present. It is unclear what the exact mechanism is that explains the activity of lenalidomide in CTCL/PTCL. Several mechanisms have been proposed to explain the activity of lenalidomide in hematologic malignancies, including changes in cytokine levels including TNF- , alteration of type I interferon levels, and pleiotropic effects on adhesion molecules. All of these effects would be expected to modulate T-cell and NK cell function. In addition to assessment of a maximal tolerated dose and related clinical outcomes, this study will also incorporate correlative studies examining lymphocyte subset numbers, phenotype, and function as well as measurement of plasma cytokines and other biomarkers of the NK cell and T-cell response. Expression profiling of peripheral blood mononuclear cell (PBMC) will be performed before, during, and after lenalidomide therapy. These studies will allow correlation of immune cell function with clinical response.

OBJECTIVES AND ENDPOINTS

Primary Objective

To determine the overall response rate (ORR) of the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed or refractory CTCL/PTCL

Secondary Objectives

1. To estimate the duration of response and 2 year progression-free survival (PFS) and overall survival (OS) associated with the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed or refractory CTCL/PTCL

2. Although safety of that combination has been established in a recent phase I trial in patients with DLBCL, we also aim to define the qualitative and quantitative toxicities of the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed or refractory CTCL/PTCL. Toxicity will be graded by the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0

Exploratory Objectives

1. To correlate between the expression of CD30 in neoplastic cells by IHC and

ORR of the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed or refractory CTCL/PTCL

2. To determine T-cell and NK cell subset numbers, phenotype, and functional status in rel/ref CTCL/PTCL patients, and whether the combination of brentuximab vedotin and lenalidomide alters these parameters during therapy.

3. To determine changes in plasma cytokine levels and other biomarkers in this patient population during therapy with the combination of brentuximab vedotin and lenalidomide.

PATIENTS AND METHODS

Inclusion Criteria

1. Able to understand and voluntarily sign an informed consent form.

2. Age ≥18 years at the time of signing the informed consent form.

3. Able to adhere to the study visit schedule and other protocol requirements.

4. Biopsy-proven, measurable, Stage IB-IVB relapsed or refractory cutaneous T-cell lymphoma after 2 lines of skin-directed therapy or one prior line of systemic therapy

    a. Note: extracorporeal photopheresis will be considered a systemic therapy for this study

5. Patients with large cell transformation of cutaneous T cell lymphoma are eligible.

6. Patients with advanced stage non-MF CTCL are eligible including, but not limited to, advanced stage LyP or pcALCL.

7. Patients with systemic T cell lymphoma of any stage and any subtypes. Patient must have had at least one standard chemotherapy and measurable disease at the time of enrollment. Bi-dimensional measurable disease of at least 1.5 cm in the greatest transverse diameter as documented by CT or PET/CT or PET positive disease (Deauville score=5)

8. Patients with systemic T cell lymphomas who relapsed after autologous transplant are eligible.

9. Prior treatment with brentuximab vedotin is allowed provided the patient did

not progress on BV or within 30 days of last dose of BV. Patients must be at least 3 months from the last dose of BV.

10. CD30 staining is to be performed on fresh biopsy or archival FFPE tissue however CD30 positivity is not required for eligibility

11. All cancer therapy, including radiation, topical steroid, and chemotherapy must have been discontinued at least 1 week or 3 half-lives whichever is the longest prior to treatment in this study. The only exceptions are participants who are symptomatic from their skin lesions and have been on corticosteroids for prolonged periods of time (>60 days) without change may continue use of either systemic steroids (equivalent to <10 mg per day of prednisone) or topical steroids are eligible for this study if the frequency and dosage steroids has not changed for 60 days prior to the study. These participants should continue on the same dose of systemic/topical steroid throughout the study period unless they achieve a complete response at which time steroids can be discontinued. Patients are allowed to continue any medications with known activity in T cell lymphomas at the pre-enrollment doses for conditions other than T cell lymphomas (ie, steroids for sarcoidosis) , as long as there is evidence of T cell lymphoma progression while patients were on these agents.

12. ECOG performance status of ≤ 2 at study entry (see Appendix 11 for definitions).

13. Laboratory test results within these ranges:

    a. Absolute neutrophil count ≥1000/mm³

    b. Platelet count≥50,000/mm³

    c. Total bilirubin ≤ 2 x ULN

    d. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

        i. AST (SGOT) and ALT (SGPT) ≤ 5 x ULN in patients with documented hepatic involvement by lymphoma

    e. Calculated Creatinine Clearance ≥ 50 ml/min (by the Cockroft-Gault equation – please see appendix 12). Calculation will be based on actual body weight.

14. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix or breast. Patients with early stage of prostate cancer under

clinical surveillance without therapy are eligible. Patients with B-cell lymphomas treated with curative intent, and in remission for at least 2 years, may be in included (after discussion with PI).

15. Negative serum pregnancy test at the time of enrollment for females of childbearing potential (as defined in section 0).

16. Women of childbearing potential must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material. This is defined as either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of contraception (one highly effective method and one additional effective method (as defined in section **Women of Childbearing Potential**0) AT THE SAME TIME) at least 28 days prior to the start of lenalidomide, for the duration of study participation, and for 28 days following the last doses of brentuximab vedotin and lenalidomide. Women of childbearing potential must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a woman of childbearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

17. All study participants must be registered into the mandatory Revlimid REMS® program and be willing to comply with its requirements. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program. Refer to section 0.

18. Life expectancy ≥ 90 days.

Exclusion Criteria

1. Patients with active CNS involvement with lymphoma are not eligible

2. Patients with pre-existing grade ≥ 3 peripheral neuropathy

3. Patients with known HIV infection or are not eligible

4. Patients who had solid organ transplants are not eligible

5. Evidence of active hepatitis B infection, based on positive surface antigen or

Hepatitis B DNA PCR, or active hepatitis C infection. Patients who are Hepatitis B core antibody positive must take prophylaxis with lamivudine or equivalent and be willing to undergo monthly Hepatitis B DNA PCR testing.

6. Present or history of progressive multifocal leukoencephalopathy (PML)

7. Active grade II-IV acute or extensive chronic graft vs. host disease (GVHD)

8. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction likely to interfere with the delivery, absorption, or metabolism of lenalidomide.

9. Patients may take steroids for disease control up to 24 hours prior to study enrollment. Topical steroids are allowed for CTCL patients as described in inclusion criteria above.

10. Any illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of lenalidomide, or put the study outcomes at undue risk.

11. A cardiovascular disability status of New York Heart Association Class ≥ 2 (please see appendix 13)

12. History of severe allergic reactions to humanized monoclonal antibodies

13. History of other malignancy that could affect compliance with the protocol or interpretation of results. Patients with a history of curatively treated basal or squamous cell carcinoma or Stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible. Patients with early stage of prostate cancer under clinical surveillance without therapy are eligible

14. Known hypersensitivity to any of the study drugs or analogs

15. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior study therapy

16. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis

17. Receipt of live-virus vaccines within 28 days prior to the initiation of study treatment or need for live-virus vaccines at any time during study treatment

18. Recent major surgery (within 6 weeks prior to the start of study treatment) other than for diagnosis

19. Receiving immunosuppressive therapy.

20. Refractory to prior therapy with brentuximab vedotin (evidence of progression within 30 days of the last dose).

21. Prior therapy with lenalidomide.

22. Pregnant or lactating, or intending to become pregnant during the study

23. Inability to tolerate aspirin, or other forms of anticoagulation, due to bleeding diathesis.

Registration Procedures

General Registration Procedures

The patient must be aware of the nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required. Written informed consent will be obtained by a co-investigator or a specific designee previously approved by the OSU Institutional Review Board (IRB), using forms approved by the IRB.

The study will be coordinated by The Ohio State University (OSU). Dr. John Reneau, the lead principal investigator and will coordinate protocol management.

Patients will undergo an initial assessment to determine eligibility and to determine baseline disease status prior to study enrollment. Patients will be registered through the database of the OSU Clinical Trials Office (CTO) and provide written informed consent. All patients for whom questions arise relative to eligibility for the study should be discussed with the principal investigator prior to entry onto the study.

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator and OSUCCC-CTO MCTP as soon as possible.

To ensure timely communication of treatment tolerance, the progress of each patient

will be discussed with the principal investigator on a monthly basis with any adverse events being promptly communicated to the principal investigator by the treating physician or designee to ensure safe treatment of other patients in the study.

Subsite Patient Registration Procedures

For subsite patients, sites must send the signed consent form, documentation of the consent process, and the Screening Form (refer to Supplemental Forms Document) within 2 business days of initial consent.

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

OSU patients will be registered by the OSU research coordinator, as per CTO standard practice.

Subsite patients will have eligibility verified and will be entered on study centrally at The Ohio State University by the Multi-Center Trial Program (MCTP). All subsites must email the MCTP to verify slot availabilities prior to consenting patients. Once a patient signs consent, the signed consent document and documentation of the consenting process must be faxed or securely emailed to the MCTP. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the MCTP:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form, if not previously sent
- Signed Patient HIPAA Authorization Form (if separate), if not previously sent
- Consent Documentation Note, if not previously sent
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria

Upon receipt of registration documents, the MCTP will send an email confirming receipt. If confirmation of receipt is not received within 1 hour of submission, please contact the MCTP by phone and/or pager to confirm receipt.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the MCTP will:

- Assign the patient a study sequence ID, if not already provided at time of consent
- Register the patient on the study
- Fax and/or e-mail the subsite the completed Registration Form with the assigned study sequence ID and registration date as confirmation of patient

registration

Following registration, patients should begin protocol treatment within 28 calendar days. Issues that would cause treatment delays should be discussed with the Principal Investigator and MCTP as soon as possible. If a patient does not receive protocol therapy following registration, the PI and MCTP must be notified immediately within 1 business day.

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the required regulatory documents, including the initial IRB approval for the site, have been forwarded to the MCTP and all other study-specific requirements have been met (as outlined during site activation).

Collection of Specimens for Correlative Studies

About 12-15 ml of blood with be collected by venipuncture in 3 yellow-topped Acid citrate dextrose (ACD) tubes. Tubes will be kept at ambient temperature and will be delivered to the leukemia tissue bank (LTB) laboratory within 3 hours of venipuncture. Samples will be separated into plasma and cells and stored as per LTB standard procedure and will be frozen until batch analyzed as detailed in section 0 above. A separate 4-5 ml will be collected in a green-topped sodium heparin tube for cytokine assay where plasma is separated and frozen. Samples will be drawn at pretreatment (any time after consent but before first dose of BV or lenalidomide), on C2D1, and C6D1.

Refer to the Laboratory Manual for additional details.

STUDY TREATMENT

All patients will receive the same treatment in an open-label phase II design with dosage modifications planned based on toxicity (as described in section 0 below). Based on prior safety demonstrated in phase I trial in relapsed/refractory DLBCL (Ward et al. 2015), all patients will receive BV at a dose of 1.2 mg/kg IV q21 days along with lenalidomide 10 mg/day continuously (for a total of 16 cycles). Patients who sustain a PR or better may continue on a treatment extension with lenalidomide for a total duration of 2 years. Since the maximum duration of treatment with brentuximab, in prior clinical trials, was limited to 16 cycles, treatment beyond 16 cycles isnot permitted (on protocol).

Premedication Administration

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin. However, patients who experience a grade 1 or grade 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication as described in Section 0. Patients who experience a grade 3 or grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the

discretion of the Investigator. Patients should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Patients should receive prophylaxis as appropriate per institution standards.

Agent Administration

Brentuximab Vedotin

Brentuximab vedotin will be administered on Day 1 (± 2 days) at a fixed dose of 1.2 mg/kg of each 21-day cycle. The dose of brentuximab vedotin is administered by outpatient IV infusion given over approximately 30 minutes.

Lenalidomide

Lenalidomide will be taken at a dose of 10 mg by mouth once a day continuously during each 21-day cycle. Patients will be asked to maintain a diary (Appendix 14) that must be returned to clinic staff at the end of each cycle. Lenalidomide can be taken with or without food. The capsule should be swallowed whole with water and should not be opened, broken, or chewed. With cycle 1, lenalidomide may start up to 72 hours after start of brentuximab if patient needs to be urgently treated; at the discretion of treating physician.

Revlimib REMS® Program Requirements

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS®program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

General Concomitant medications and supportive care guidelines

Unless otherwise described below, all supportive measures consistent with optimal patient care should be provided throughout the study according to institutional standards.

Anticoagulation

All patients should take low-dose aspirin (81 mg daily) as prophylactic anticoagulation (unless already receiving anticoagulation therapy). Patients intolerant to ASA may use warfarin or low molecular weight heparin.

Medications for Infusion-Related Reactions

Medications for infusion-related reactions during BV administration, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a grade 1 or grade 2 infusion-related reaction may receive subsequent BV infusions with premedication consisting of acetaminophen and diphenhydramine administered 30-60 minutes prior to each 30-minute infusion or according to institutional standards. If anaphylaxis occurs, brentuximab vedotin administration should be immediately and permanently discontinued.

Medications that Aggravate Cytopenias

Medications that aggravate cytopenias (e.g., trimethoprim-sulfamethoxazole) should be avoided. All patients should be up-to-date on any recommended vaccinations prior to study entry. Additional vaccination(s) during each cycle of study treatment must be approved by the PI.

Prophylactic Intrathecal Therapy

Prophylactic intrathecal therapy is allowed only after discussion with the PI.

Blood Products

The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy. Prophylactic growth factors are allowed at the discretion of the investigator. Prednisone (or equivalent) ≤20 mg/day may be used for non-lymphomatous purposes.

Management of “tumor flare” reaction

Short course of systemic corticosteroids may be given for a maximum of 7 days to treat “tumor flare” reaction at the discretion of treating physician. Treatment with BV and lenalidomide must be suspended until tumor flare reaction regresses to ≤ grade 1. Further cycles may be delayed for maximum of 6weeks until regression of “tumor fare” before patients are to be re-challenged. Lenalidomide dose will be appropriately reduced as per section 6.3 below.

Women of Childbearing Potential

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced

malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

A woman of childbearing potential is defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months. Women of childbearing potential are required to have a negative serum or urine pregnancy test within 10-14 days prior to and again no more than 24 hours before the first dose of lenalidomide. Women of childbearing potential are required to use two forms of contraception at the same time, including one highly effective method (i.e., intrauterine device, hormonal (birth control pills, injections, or implants), tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e., latex condom, diaphragm, cervical cap), beginning 28 days prior to the first dose of lenalidomide, continuing through participation in the study and for 28 days following the last doses of brentuximab vedotin and lenalidomide. Male patients engaged in a sexual relationship with a woman of childbearing potential must agree to use a latex condom during sexual contact, even if he has had a successful vasectomy.

If a patient is suspected to be pregnant, both study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing. Please refer to section 9.13 for pregnancy reporting requirements.

Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for up to 16 cycles until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The James Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar. Patients with a CR, PR, or SD at the completion of 16 cycles may continue to receive treatment with BV and lenalidomide at the discretion of the treating physician.

For subjects who withdraw consent, there must be clear documentation of whether the subject withdraws consents to treatment only (i.e. agrees to follow-up) or withdraws consent to treatment and follow-up.

Duration of Follow-up

Patients will be followed for adverse events for approximately 28-35 days after last dose of study therapy (refer to Study Calendar for end of treatment assessment requirements). Patients removed from study for unacceptable toxicity will continue to be followed until resolution or stabilization of the event. Patients who receive at least one dose of BV and lenalidomide will be followed for survival and disease status every 3 months for the first 2 years after discontinuation of study treatment and per institutional standard of care thereafter until death, study closure, or withdrawal of consent. Patients will not be followed for disease status following disease progression. For patients who discontinue study drug for any reason other than disease progression or initiation of a non-protocol therapy for treatment of lymphoma, restaging scans will be done every 6 months for the first year and per institutional standard of care thereafter.

STUDY MEDICATIONS

Brentuximab Vedotin (Adcetris)

Brentuximab Vedotin Description

Brentuximab vedotin (available commercially as Adcetris) is a CD30-directed antibody-drug conjugate consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. It indicated for treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not autologous stem cell transplant candidates. It is also indicated for treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.

Clinical Pharmacology

Brentuximab vedotin is an ADC. The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of BV is due to the binding of the ADC to CD30-expressing cells,

followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells.

Pharmacokinetics and Drug Metabolism

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of BV, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of BV. MMAE exposures decreased with continued administration of BV with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. In vitro data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. In vitro studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during an ADCETRIS infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

Supplier(s)

Brentuximab vedotin will be obtained through commercial supply and billed to patient's insurance

Dosage Form and Preparation

Calculate the dose (mg) and number of vials of brentuximab vedotin required. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Reconstitute each 50 mg vial of BV with 10.5 mL of sterile water for injection, USP, to yield a single-use solution containing 5 mg/mL BV. Direct the

stream toward wall of vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. DO NOT SHAKE. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates. Following reconstitution, dilute immediately into an infusion bag, or store the solution at 2-8°C and use within 24 hours of reconstitution. DO NOT FREEZE.

Calculate the required volume of 5 mg/mL reconstituted BV needed and withdraw this amount from the vials. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100 mL to achieve the final concentration required (100-205 mL NS to a concentration of 0.4 – 1.8 mg/mL). BV can be diluted into 0.9% sodium chloride injection, 5% dextrose injection, or lactated ringer's injection. Gently invert the bag to mix the solution.

Storage and Stability

Store vial at 2-8°C in the original carton to protect from light.

Administration

BV shall be administered at 1.2 mg/kg as 30-minute IV infusion on Day 1 of every 21-day cycle.

Special Instructions

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. MMAE is primarily metabolized by CYP3A. Co-administration of BV with potent CYP3A inhibitors (i.e. ketoconazole) has been shown to increase exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors should be closely monitored for adverse reactions (please see Appendix 18).

Lenalidomide (Revlimid)

Lenalidomide Description

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino- 1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3. It indicated for the treatment of patients with multiple myeloma in combination with dexamethasone in patients who have received at least one prior therapy, transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities, or mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Clinical Pharmacology

Lenalidomide is an analogue of thalidomide with immunomodulatory, anti-angiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

Pharmacokinetics and Drug Metabolism

Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of lenalidomide in patients with MM or MDS, the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose.

In the trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. It can be administered with or without food.

Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

Elimination is primarily renal. Following a single oral administration of [14C]-lenalidomide to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within 10 days in urine and feces, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate. The mean half- life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS, or MCL.

Supplier(s)

Lenalidomide is supplied through the Revlimid REMS program by Celgene Corporation. Lenalidomide will be provided free of charge to patients

Dosage Form and Preparation

Lenalidomide is available in 2.5 mg, 5 mg, 10 mg, 15 mg, and 25 mg capsules for oral administration. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Storage and Stability

Store at 20-25°C; excursions permitted to 15-30°C.

Administration

Lenalidomide shall be administered at 10 mg daily (and dose may be decreased based on toxicity as detailed in section 0 below) by mouth once per day on Days 1 through 21 of each 21-day cycle.. Three patients with CTCL treated with 20 mg lenalidomide so far have experienced significant skin-related AEs; 2 have had grade 3 tumor flare and one experienced DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome necessitating decrease of starting lenalidomide dose for future patients for safety reasons.

Special Instructions

Care should be exercised in the handling of lenalidomide. Women of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

Lenalidomide capsules should not be opened or crushed. If powder from lenalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If lenalidomide contacts the mucous membranes, flush thoroughly with water.

Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen-containing therapies may have an increased risk of venous thromboembolism. These therapies should be used with caution in patients receiving lenalindomide and patients should be closely monitored.

DOSE DELAYS/DOSE MODIFICATIONS

If AEs are encountered attributable to lenalidomide, dose reductions will be allowed to a lowest permissible dose of 2.5 mg daily. If AEs are encountered attributable to brentuximab vedotin, dose reduction to 0.9 mg/kg will be allowed. **Doses of brentuximab vedotin should not be re-escalated after a dose reduction.**

Criteria for Starting a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- the ANC is ≥ 1000/cumm
- the platelet count is ≥50,000/cumm
- *For patients with pre-treatment platelets ≤ 100,000/cumm, may treat with platelets ≥ 25,000/cumm.
- Any non-hematologic treatment-related grade 3 or 4 adverse event has

resolved to ≤ grade 1 (except neuropathy as noted in the dose modification sections below)

The start of the next cycle may be delayed for up to 6 weeks if additional time is required for the patient to recover from study treatment associated toxicity experienced during the current cycle. Delays of greater than 6 weeks are prohibited without approval of the PI.

Brentuximab Vedotin Dose Delays or Modifications

Starting	Reduction 1	Reduction 2
1.2 mg/kg	0.9 mg/kg	Off study

There are no dose adjustments or modifications to brentuximab vedotin for infusion- related reactions (see Section 0). However, if anaphylaxis occurs, brentuximab vedotin administration should be immediately and permanently discontinued.

If a treating physician would like to modify or hold brentuximab vedotin not according to the following dose modifications, this action must be discussed with the OSU PI before the decision is made.

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 3 or 4 neutropenia (ANC < 1000/cumm)	• Hold lenalidomide until toxicity resolves to ≤ grade 2. • Follow CBC weekly. • Decrease lenalidomide per Section 0 for the remainder of the current cycle. Do not make up missed doses. • For subsequent cycles, use pegfilgrastim or filgrastim (minimum of 7 days). Resume lenalidomide at the starting dose from the previous cycle. • Omitted doses are not made up. • If neutropenia recurs with use of growth factors, decrease lenalidomide per Section 0. • If the lowest dose of lenalidomide is reached, start reducing brentuximab per Section 6.2 • If the patient is at the lowest allowed dose of both brentuximab vedotin and lenalidomide with pegfilgrastim or filgrastim, remove the patient from study

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 3 or 4 thrombocytopenia (platelet count < 50,000/cumm)*	• Hold lenalidomide until toxicity resolves to ≤ grade 2. Resume lenalidomide at the same dose level in the subsequent cycle. • Follow CBC weekly • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21 of the current cycle, decrease lenalidomide per Section 0 and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Decrease lenalidomide per Section 0 at the start of the next cycle. • Omitted doses are not made up. • If the patient is at the lowest allowed dose of lenalidomide, keep the same dose of lenalidomide and decrease the BV dose per Section 0. • If the patient is at the lowest allowed dose of both brentuximab vedotin and lenalidomide, remove the patient from study.
Grade 3 or 4 non- blistering rash	• If grade 3, hold lenalidomide. Clinical team to follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, decrease lenalidomide per Section 0 and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and decrease lenalidomide per Section 0 at the start of the next cycle. • Omitted doses are not made up. • If grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash - any grade	• Discontinue lenalidomide. Remove patient from study.

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 2, 3, or 4 sensory neuropathy	• If grade 2, decrease brentuximab vedotin dose per Section 0. • If grade 3, hold brentuximab vedotin until toxicity resolves to ≤ grade 1. Decrease brentuximab vedotin dose per Section 0. • Hold lenalidomide until toxicity resolves to < grade 2 and decrease lenalidomide per Section 0. • If grade 4, discontinue brentuximab vedotin and lenalidomide. Remove patient from study.
Grade 2, 3, or 4 motor neuropathy	• If grade 2, decrease brentuximab vedotin dose per Section 0. • If grade 3, discontinue brentuximab vedotin. • Hold lenalidomide until toxicity resolves to < grade 2 and decrease lenalidomide per Section 0. • If grade 4, discontinue brentuximab vedotin and lenalidomide. Remove patient from study.
Grade 3 or 4 venous thrombosis/embolism	• Hold lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at same dose or decrease per Section 0 at treating physician's discretion.
Other grade 3 or 4 non-hematologic toxicity	• Hold brentuximab vedotin and lenalidomide until toxicity resolves to ≤ grade 2. • For toxicity attributed to brentuximab vedotin, decrease brentuximab vedotin dose per Section 0 when restarting. If unrelated to brentuximab vedotin, resume at the previous dose level. • For toxicity attributed to lenalidomide, decrease per Section 0. • If the toxicity resolves to ≤ grade 2 prior to Day 21 of the current cycle, resume lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. • Omitted doses are not made up.

* For patients with pre-treatment platelets ≤ 100,000/cumm, may treat with platelets ≥ 25,000/cumm.

Lenalidomide Dose Delays or Modifications*

Starting dose	Reduction 1	Reduction 2	Reduction 3
10 mg	5 mg	2.5 mg**	Discontinue lenalidomide and remain on BV**

*Above dosing is for a continuous 21 day cycle unless otherwise noted.

For patients treated on earlier versions of the protocol, where higher doses of lenalidomide were employed, please follow this dose modification scheme:

Starting dose	Reduction 1	Reduction 2	Reduction 3	Reduction 4	Reduction 5	Reduction 6
20 mg	15 mg	10 mg	10 mg Days 1-14	5 mg	2.5 mg**	Discontinue lenalidomide and remain on BV**

*Above dosing is for a continuous 21 day cycle unless otherwise noted.
**The above proposed changes in lenalidomide dose modifications (in version 11 of protocol) are due to our increased experience with using the combination where have treated 17 patient so far (through July 2019) and we have observed that a fair number of patients have difficulty tolerating lenalidomide and may need lower doses and longer times to recover from AEs due to lenalidomide. One patient with Sezary syndrome who was treated on the higher dose of lenlidomide, in the earlier versions of the protocol, we had to remove from trial as he developed a serious Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome attributed to lenalidomide. We then continued him on on single agent BV, as FDA approved standard of care agent, and he was stable on that for an additional 9 months which is kind of unusual to have such duration of response to single agent BV in Sezary syndrome. Our observation suggests that in patients who seems to respond to lenalidomide + BV combination, but cannot tolerate lenalidomide, lenalidomide may favorably modulate future response to single BV so it would make sense to continue observing those patients, on protocol, while they are receiving single agents BV as long they seem to be deriving benefit from treatment.

If a treating physician would like to modify or hold lenalidomide not according to the dose modifications detailed in section 6.2 (above), this action **must be discussed with the PI** before the decision is made.

STUDY ASSESSMENTS

Please refer to the study calendar for complete information regarding study evaluations, **APPENDIX 10: Study Calendar**.

Pretreatment and screening evaluations

Pretreatment evaluations will include the following testing:

- History and physical examination
- ECOG PS
- Height, weight and BSA
- Concurrent medications
- For CTCL patients, baseline lesion assessments and disease staging must occur on Day 1 of protocol therapy as indicated in Section 0, Schedule of Study Assessments and should include:
    - mSWAT score (appendix 3)
    - Skindex-16 (appendix 4)
    - quantitation of absolute Sézary cell count by flow cytometry and/or manual count
    - lymph node regions, liver, and spleen clinical exam
    - Skin biopsy unless a diagnostic biopsy was obtained within 2 years from C1D1 of treatment
- Laboratory testing including: CBC with differential, Chemistry including calcium, magnesium and inorganic phosphorus; liver function tests, total protein, albumin uric acid, LDH, Hepatitis B, C, and HIV serologies
- Baseline contrasted CT scan of the chest, abdomen, and pelvis (or FDG-PET) should occur within 60 days prior to the start of therapy (Day 1). MRI can be substituted for CTs if indicated. Baseline imaging at screening may be omitted at the discretion of PI for patients with CTCL with limited skin involvement (based on NCCN standard of care guidelines). If scans are deemed required at screening; there is 60 day window before patient starts C1D1. If there is evidence of systematic disease on screening scans, restaging will occur on D15-21 of Cycles 2, 4, 6, and 9 and then every 6 months for 2 years. Note that restaging may occur on D1 of the following cycle (i.e. Cycles 3, 5, 7, and 10) provided it takes place prior to treatment and confirmation of absence of progression is documented prior to treatment. Re-imaging is only required for patients with PTCL and patients with CTCL only if there is evidence of visceral disease.
- Bone marrow biopsy and aspirate (May be collected up to 90 days prior to C1D1. If a positive bone marrow aspirate/biopsy was obtained more than 90 days prior to C1D1 and the patient has not received treatment

in the interim, the assessment does not need to be repeated. Results of the assessment do not have to be available prior to enrollment). Bone marrow biopsy is optional at the discretion of PI.

Evaluations during treatment

All patients will be assessed every 3 weeks by physical exam throughout 16 cycles of treatment.

Please refer to appendix 10 for full assessment schedule. All patients will be evaluated for toxicity utilizing the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (please see Appendix 15)

CTCL Patients

For CTCL patients, skindex-16 (appendix 4), mSWAT (appendix 3), skin photographs will be obtained and attached to electronic medical records (per standard of care), and immunophenotyping of peripheral blood (in patients with known circulating disease at screening) will be repeated every 6 weeks. Response will be assessed by a global response score (please see appendix 9) integrating change in skin disease as measured by the modified severity weighted assessment tool (mSWAT) score (please see appendix 5), change in lymph node size, change in visceral disease, and changes in peripheral blood Sézary cells by flow cytometry (please see appendices 6-8). CR/PR assignment requires confirmatory assessment in 4 weeks for skin scores only. Clinical lymph node, liver and spleen exam will occur on Day 1 of each cycle by physical exam. Skin scores and Sézary cell will be assessed every other cycle, Contrasted CT scan of the, chest, abdomen and pelvis (or FDG-PET) will be performed at screening for all patients. In patients with lymphadenopathy and/or organomegaly at screening, contrasted CT scans of the, chest, abdomen, and pelvis will occur at D15-21 od cycles 2, 4, 6, and 9, and then every 6 months for one year after maximal response, or until disease progression, or off study whichever comes first. CTCL patients, without extra cutaneous disease at screening, will have repeat imaging only at time of PR/CR confirmation, suspicion of new lesion or PD in lymph nodes, and at time of end of treatment visit.

PTCL Patients

For PTCL patients, response will be evaluated by the Cheson criteria (Cheson 2015), measured by CT or PET/CT at baseline, at D15-21 of cycles 2, 4, 6, and 9, and then every 6 months for one year after maximal response, or until disease progression, or off study whichever comes first. All patients will have contrasted CT scans of the chest, abdomen, and pelvis (or FDG-PET) at the time of concern for disease progression in lymph nodes and/or viscera. A bone marrow biopsy will be performed to confirm a complete response in patients with bone marrow involvement at the start of therapy.

Post-treatment evaluations

Reassessment off therapy will occur approximately 4 weeks from the last dose of study therapy. For patients removed from study for reasons other than disease progression or who complete 16 cycles of therapy, reassessment will then occur every 3 months while on lenalidomide maintenance, or every 6 months otherwise, until progression or an alternative therapy is started. End of treatment (EOT) assessments will take place 28-35 days after last dose of study drug; if completed before this time point, the patient will be contacted by phone 30-37 days following the last treatment to asses for adverse events. EOT assessments will be performed before any other therapeutic intervention, if possible.

If patients move on to the 2 year lenalidomide maintenance, lenalidomide will be ordered to cover 28 days of continuous dosing (instead of the 21 days during treatment), and dispensed every 28 days (-4 days). Patients will be evaluated for AEs by the Clinical Research Coordinator/Specialist (in person or by phone) once every 28 days (-4 days). During this time patients will have basic laboratory studies (complete metabolic profile, and CBC with differential) performed every 28 days (-4 days); locally if preferred. Patients will be evaluated by treating Physician every 12 weeks (-7 days) while on lenalidomide maintenance.

Assignment of response: the Global Response Score

Response (CR, PR, SD) and progression will be defined using the Global Response Score (see appendix 9 for definition). All partial and complete responses must be confirmed with another efficacy assessment no less than 4 weeks apart. The 4 week repeat efficacy assessment is to include determination of mSWAT score, physical exam of lymph node regions, liver and spleen, and peripheral blood flow cytometry for Sezary cells. Repeat CT scanning is not required at 4 weeks to confirm response (Olsen et al. 2011).

Time to response

Time to response (TTR) will be defined as the time from the first BV dose to the time of documented objective response (PR or CR).

Duration of response

Duration of response (DOR) will be defined as the time from first objective response until disease progression.

Time to progression

Time to progression (TTP) will be defined as the time from the first BV dose until disease progression.

Overall response at 4 months (ORR4); for CTCL patients only

ORR 4 is a novel endpoint that was introduced in the ALCANZA trial (Kim et al. 2016) and will likely become the new standard for efficacy in CTCL trials. ORR4 is defined as ORR lasting ≥4 months, an endpoint that captures response rate and duration as a single measurement. ORR4 will be based on the ISCL/EORTC consensus guidelines (as detailed above).

Disease control rate

Disease control rate (DCR) is defined as the proportion of patients with CR, PR, or SD.

Progression-Free Survival

Progression-free survival (PFS) is defined as the time from start of study treatment to first documentation of tumor progression (including radiographic and clinical progression) or to death due to any cause, whichever comes first. PFS data will be censored on the day following the date of the last disease assessment documenting absence of progressive disease for patients who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumor progression.

Overall Survival

Overall survival (OS) is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

STUDY DISCONTINUATION

In the absence of treatment delays due to adverse events, treatment may continue for up to 16 cycles or until one of the following criteria applies:

- Inability of patient to comply with study requirements
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Patient decides to withdraw from the study
- Determination by the investigator that it is no longer safe for the patient to continue therapy
- Pregnancy
- Active HBV infection or hepatitis
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

Patients who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

REGULATORY AND REPORTING REQUIREMENTS

Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

Unanticipated Problems Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious adverse events (SAEs)

An adverse event should be classified as a serious adverse event if the following criteria are met:

- It results in death (i.e., the adverse event actually causes or leads to death)
- It is life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Ohio State University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to the Ohio State University. IRB approval is not required for protocol exceptions occurring at secondary sites.

Reporting to the OSU IRB

NOTE: External participating sites are not permitted to report directly to the OSU IRB or FDA. All external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program (MCTP). The MCTP will facilitate submission of external site SAEs to the OSU IRB and FDA. Refer to section 0 for additional details.

The OSU PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at OSU, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within the time frames outlined in the IRB

policy.

Subsite SAE Reporting Requirements

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the OSU Principal Investigator and MCTP within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form. External participating sites must also submit the "SAE Submission Form" cover sheet (refer to the Supplemental Forms Document).

Copies of de-identified source documentation pertaining to the SAE must be submitted to OSU. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to OSU as soon as possible but no later than 5 calendar days.
Refer to section 0 for instruction on reporting SAEs to Celgene.

OSU Reporting to Subsites

The Ohio State University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Ohio State University and at other secondary sites, if applicable.

Reporting to the FDA

NOTE: External participating sites are not permitted to report directly to the OSU IRB or FDA. All external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program (MCTP). The MCTP will facilitate submission of external site SAEs to the OSU IRB and FDA. Refer to section 0 for additional details.

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR THE IRB**. It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than 7 calendar days after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the

subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information. A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
    - Death
    - A life-threatening adverse drug experience
    - Inpatient hospitalization or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
    - A congenital anomaly/birth defect
    - Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA (refer to the FDA website to obtain the current address and fax number for the Center for Drug Evaluation and Research Division of Oncology Drug Products).

Reporting to Celgene

All AE reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug, date and time of administration of test medications and all concomitant medications, and medical treatment provided. For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and "reasonably related" are present (refer to Sections 0 and 0).

SAEs as defined above must be reported to Celgene in writing using a MedWatch 3500A form within 24 hours of the investigator's knowledge of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report must be documented in a follow-up report. A final report to document resolution of the SAE

is required. The Celgene protocol number (pending) and the institutional protocol number should be included on the SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report should be attached to the SAE and retained with the patient's records.

Celgene Drug Safety Contact Information Celgene Corporation
Global Drug Safety and Risk Management Connell Corporate Park
300 Connell Dr., Suite 6000 Berkeley Heights, NJ 07922 Fax: (908) 673-9115
Email: drugsafety@celgene.com

Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

Deaths	
Any reportable death while on study or within 30 days of study	Immediately, within 24 hours, to PI and the IRB
Any reportable death while off study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	
Any reportable adverse events as described in Sections 0 and 0 (other than death) and 0	Immediately, within 24 hours to PI and within required time frame to the IRB (per local policy) and within 7 or 15 calendar days to the FDA
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance as described in Sections 0 and 0	Immediately, within 24 hours, to PI and within required time frame to the IRB (per local policy)

Overdose

Overdose, as defined for this protocol, refers to Revlimid® and brentuximab vedotin dosing only.

On a per dose basis, an overdose is defined as the following amount over the

protocol-specified dose of Revlimid® and brentuximab vedotin assigned to a given patient, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose
- IV 10% over the protocol-specified dose
- SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a woman occurring while on lenalidomide or within 28 days of her last dose of lenalidomide are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by fax or email using the Pregnancy Initial Report Form (Appendix 16). The patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity, for further evaluation and counseling.

The PI will follow the patient until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form (Appendix 17). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the PI should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by fax or other appropriate method within 24 hours of the investigator's knowledge of the event using the SAE Report Form.

Any suspected fetal exposure to lenalidomide must be reported to Celgene within 24 hours of the investigator's knowledge of the event. All neonatal deaths that occur within 28 days of birth should be reported without regard to causality as SAEs. In addition, any infant death after 28 days that the investigators suspects is related to the *in utero* exposure to lenalidomide should also be reported to Celgene Drug Safety immediately by fax or other appropriate method within 24 hours of the investigator's knowledge of the event using the SAE Report Form. In the case of a live "normal" birth, Celgene Drug Safety should be advised as soon as the information is available.

If a female partner of a male patient taking lenalidomide becomes pregnant, the male patient should notify the investigator and the pregnant woman should be advised to call her healthcare provider immediately.

Data and safety monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at the regular protocol review meeting at least monthly. The PI of the trial will review toxicities and responses of the trial where applicable and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will be reported to the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the MCTP protocol files. Teleconferences must minimally be held monthly and may be held more frequently, as needed. For studies closed to accrual with patients expected to remain on long-term treatment and/or follow-up, teleconferences may be extended to occur every two months or quarterly. Decreasing frequency of teleconferences requires OSU PI and MCTP approval.

Data Submission

The study will be managed per the Multi-Center Trial Program (MCTP) policies. Subsite data must be submitted to the MCTP as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the MCTP to external participating sites prior to site activation. Data will be submitted using case report forms and the Data Submission Form cover sheet (refer to Supplemental Forms Document) supplied by the MCTP. Access to the OSU OnCore database may be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan.

Auditing

As the study sponsor, The Ohio State University Comprehensive Cancer Center (OSUCCC) will audit each site as per OSU policies. Audits will be performed by the

OSUCCC Clinical Research Audit Team. For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the OSUCCC Multi-Center Trial Program (MCTP) and the Quality Assurance Oversight Committee.

Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Investigators and study staff will undergo training on Good Clinical Practice (GCP) through the Collaborative Institutional Training Initiative (CITI). GCP training sets the standard for the design, conduct, recording, and reporting of studies involving human subjects, ensuring that study subjects rights, safety, and well-being are protected. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochures, informed consent form, written information given to the patients (including pill diaries), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator, as allowable by local regulations. The principal investigator will ensure that the study will be conducted according to the protocol and all applicable regulations. The protection of each subject's rights and welfare will be maintained.

Retention of records

FDA regulations (21 CFR § 312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

STATISTICAL CONSIDERATIONS

Determination of sample size

The study will follow a Simon's two-stage optimal design. As patients will be accrued independent of CD30+ positivity and the study is likely to include CD30- patients, the true ORR to BV is likely lower than the recently reported 55% in the ALCANZA trial (Kim et al. 2016). Also the inclusion of PTCL patients in the same cohort will likely

lower the expected ORR. Therefore, an ORR of 50% in patients with relapsed/refractory PTCL/CTCL, independent of CD30 status, would be clinically meaningful and an ORR of 30% or less would not be, which translates to a null hypothesis of ORR≤0.3 and an alternative hypothesis of ORR≥0.5. With a type I error probability of 0.1 and 85% power, Simon's two-stage design allows an interim analysis after 14 patients are evaluated for response. If only 4 or less patients achieve response, then the trial will be terminated and no further development of this combination is warranted. If 5 or more patients achieve response, then study will continue to accrue to a total of 37 patients. Out of 37 patients, if the number of response is less than or equal to 14, we will conclude that the combination is not clinically promising enough to be explored in a phase III setting. If 15 or more responses are observed, the null hypothesis will be rejected and further study of the combination is warranted.

With anticipated accrual rate of around 3 patients each month, the accrual period will be 13 months to achieve the 37 total enrollment goal.

Primary objectives

The primary objective for this phase II trial is ORR to BV and lenalidomide. Definitions of responses are detailed in section 0 above. ORR is defined as the proportion of patients who achieve CR or PR at xx, where the numerator is the number of patients with CR/PR, and the denominator include all eligible patients who receive at least two cycles of the combination and are evaluable for response assessment. Patients who fail to have an assessment due to progression, death or toxicity will be considered evaluable and categorized as non-responders; patients who fail to have an assessment due to other reasons (e.g. withdraw consent or refusal) will be considered unevaluable. Patients who do not complete at least two cycles will be replaced. ORR and DCR will be calculated and presented together with 95% exact binomial confidence intervals.

Secondary objectives

The definitions of secondary endpoints including DOR, PFS and OS are defined in section 7. These time to event outcomes will be evaluated using the method of Kaplan-Meier. The estimates of survival distribution at certain time points will be provided with 95% confidence intervals, and the analyses will be mostly descriptive with a focus on graphical presentation due to limited sample size.

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy and had this confirmed, will not be evaluated for safety. Although safety of that combination has been established in a recent phase I trial in patients with DLBCL, we also aim to define the qualitative and quantitative toxicities of the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed or refractory CTCL/PTCL. Toxicity will be graded by the NCI Common Toxicity Criteria for Adverse

Events (CTCAE) version 4.0. The frequency of adverse events will be provided by grade and attribution.

Exploratory objectives

Correlative studies (peripheral blood mononuclear cells and serum): The analysis of correlative studies will be mainly descriptive as well and exploratory in nature due to the limited sample size. The correlative studies are mostly designed to determine their feasibility and the reproducibility of these tests in patients to aid in the design for future studies. When possible, results from control samples will be compared to test samples. For results that are dichotomous (e.g. staining present/absent), results will be compared using the Fisher's exact test to generate p value. For continuous results (e.g. percent cells positive), results will be compared using the non-parametric Wilcoxon rank sum test.

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APPENDIX 1: Modified ISCL/EORTC Revisions to the TNMB

Classification of MF/SS

Table 1. Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS[1]

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions[1] to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Table 2. ISCL/EORTC proposal on TNM classification of cutaneous lymphoma other than MF/SS

Classification
T
T1: Solitary skin involvement
T1a: a solitary lesion <5 cm diameter
T1b: a solitary >5 cm diameter
T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions*
T2a: all-disease-encompassing in a <15-cm-diameter circular area
T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area
T2c: all-disease-encompassing in a >30-cm-diameter circular area
T3: Generalized skin involvement
T3a: multiple lesions involving 2 noncontiguous body regions
T3b: multiple lesions involving ≥3 body regions
N
N0: No clinical or pathologic lymph node involvement
N1: Involvement of 1 peripheral lymph node region† that drains an area of current or prior skin involvement
N2: Involvement of 2 or more peripheral lymph node regions† or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes
M
M0: No evidence of extracutaneous non–lymph node disease
M1: Extracutaneous non–lymph node disease present

*Definition of body regions (see Figure 1): Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior

APPENDIX 2: Modified ISCL/EORTC Revisions to the Staging of MF/SS

Table 2. Modified ISCL/EORTC Revisions to the Staging of MF/SS[1]

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

APPENDIX 3: Modified Severity Weighted Assessment Tool (mSWAT)

Table 3. Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.
Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

APPENDIX 4: Skindex-16

Skindex16
©MMChren,1997

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often Have you been bothered by:	Never Bothered						Always Bothered
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item: Yes ☐ No ☐

APPENDIX 5: ISCL/USCLC EORTC Consensus: Response in Skin

Table 6. Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.
*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.
†Whichever criterion occurs first.

APPENDIX 6: ISCL/USCLC EORTC Consensus: Response in Lymph Nodes

Table 7. Response in Lymph Nodes*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Peripheral and central lymph nodes.
†Whichever criterion occurs first.

APPENDIX 7: ISCL/USCLC EORTC Consensus: Response in Viscera

Table 8. Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or New organ involvement or Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Whichever criterion occurs first.

APPENDIX 8: ISCL/USCLC EORTC Consensus: Response in Blood

Table 9. Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to $\geq B_1$ in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*As determined by absolute numbers of neoplastic cells/μL.

†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

§Whichever occurs first.

APPENDIX 9: ISCL/USCLC EORTC Consensus: Global Response Score

Table 10. Global Response Score

Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.
It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

APPENDIX 10: Study Calendar

Assessment	Screening[1]	Day 1 of each cycle[16]	2-year maintenance and higher***	End of Study[6]	Follow up[7]
Informed consent*	X				
Baseline conditions	X				
AE assessments		X[2]	X[2]	X	
Concomitant medications	X			X	
Archival tissue collection**	X				
Brentuximab Vedotin		X			
Lenalidomide		Daily D1-D21[18]	Daily D1-D28[18]		
Medical history	X				X
Physical examination, vital signs, weight, height	X	X	X	X	X
BSA	X	X	X	X	X
mSWAT score[17]		X	X	X	
Skindex-16[17]		X	X	X	
Skin photography[17]	X		X		
Lymph node biopsy[19]	X				
Bone marrow and organ biopsy[3]	X[3]	X[10]	X[10]		
Skin biopsy[17]	X				
Response Assessment		X[13]	X[13]		
CBC w/diff	X	X[4, 9]	X[4, 9]		
Serum chemistry	X	X[4, 9]	X[4, 9]		
Hepatitis B, C, HIV serology	X[14]				
Pregnancy testing	X[8]	X[8]	X[8]	X	
Peripheral blood flow		X[15]	X[15]	X	
PMBC collection		X[11]			

Assessment	Screening[1]	Day 1 of each cycle[16]	2-year maintenance and higher***	End of Study[6]	Follow up[7]
Plasma cytokines		X[11]			
Thyroid functions	X[12]	X[12]		X[12]	
CT chest abdomen pelvis and/or FDG-PET	X[5]	X[5]	X[5]	X	X[5]

* Informed Consent to be obtained within the time frame permissible per local policy.

** Archival tissue collection is optional and tissue from time of diagnosis is acceptable. Fresh biopsy at the discretion of the investigator if there is clinical suspicion for transformed disease

*** Lenalidomide will be picked up by Patient every 28 days during 2-year lenalidomide maintenance. Clinical Research Coordinator/Specialist will perform AE assessments in person or by phone every 28 days. All other assessments will be performed every 12 weeks during Clinic visit, or earlier as indicated by treating Physician.

1 Screening assessments may take place up to 28 days prior to C1D1

2 Baseline adverse events should be collected prior to treatment on C1D1 (may take place up to 7 days prior to C1D1). During 2-year lenalidomide maintenance and beyond, before EOT, adverse events will be evaluated by Clinical Research Coordinator/Specialist in person or by phone every 28 days. Patient will be evaluated by Treating Physician every 12 weeks.

3 May be collected up to 90 days prior to C1D1. If a positive bone marrow aspirate/biopsy was obtained more than 90 days prior to C1D1 and the patient has not received treatment in the interim, the assessment does not need to be repeated. Results of the assessment do not have to be available prior to enrollment (optional and at the discretion of the investigator). Bone marrow biopsy is optional at the discretion of PI.

4 If performed less than 7 days before C1D1, procedures do not need to be repeated on C1D1

5 Baseline imaging at screening may be omitted at the discretion of PI for patients with CTCL with limited skin involvement (based on NCCN standard of care guidelines). If scans are deemed required at screening; there is 60 day window before patient starts C1D1. If there is evidence of systematic disease on screening scans, restaging will occur on D15-21 of Cycles 2, 4, 6, and 9 and then every 6 months for 2 years. Note that restaging may occur on D1 of the following cycle (i.e. Cycles 3, 5, 7, and 10) provided it takes place prior to treatment and confirmation of absence of progression is documented prior to treatment. Re-imaging is only required for patients with PTCL and patients with CTCL only if there is evidence of visceral disease.

6 EOT assessments will take place 28-35 days after last dose of brentuximab vedotin; if completed before this time point, the patient will be contacted by phone 30-37 days following the last treatment to asses for adverse events. EOT assessments will be performed before any other therapeutic intervention, if possible. If patients move on to the 2 year lenalidomide maintenance, they need to be evaluated for AEs by CRC (in person or by phone once/month) and be evaluated by a physician every 3 months while on lenalidomide.

7 Patients will be followed for survival and disease status every 3 months for the first 2 years after discontinuation of treatment and per institutional standard of care thereafter.

8 Women of childbearing potential must have a negative pregnancy test 10-14 days prior to C1D1 and again no more than 24 hours before C1D1. Pregnancy tests must be done weekly during C1 and then on Day 1 of each cycle thereafter. For women with irregular menstruation, pregnancy tests must be done every 14 days while on therapy.

9 Also to be drawn on Days 8 and 15 of Cycle 1. During 2-year lenalidomide maintenance and beyond (before EOT), to be drawn every 28 days. Can be done locally.

10 If bone marrow is negative at baseline, no additional bone marrow biopsies need to be performed for restaging. Bone marrow biopsy will only be performed to confirm attainment of CR

11 To be drawn only at pretreatment (any time after consent but before first dose of BV or lenalidomide), C2D1, and C6D1

12 TSH with reflex to Free T4 to be drawn at screening, Day 1 of Cycles 4, 7, 10, 13, 16, and EOT.

13 Starting at D1 of C2 utilizing Global response score as outlined in section 0

14 No need to repeat if it was negative 2 years prior to start of treatment

15 Only repeated every cycle if a known T-cell clone is identified in the peripheral blood before (usually in patients with Sezary syndrome)

16 All visits +/- 4 days

17 CTCL patients only or PTCL patients with skin involvement. If skin biopsies were done within the prior 2 years, no need to be repeated if there is no suspicion for transformed disease.

18 With cycle 1, lenalidomide may start up to 72 hours after start of brentuximab if patient needs to be urgently treated; at the discretion of treating physician. During 2-year maintenance, lenalidomide will be dispensed every 28 days for continuous dosing.

19 Core or fine needle biopsies of lymph nodes may be considered in patients with CTCL at the discretion of PI if PET-CT shows FDG avid adenopathy to confirm nodal involvement by CTCL.

20 To be performed every 3 months (12 weeks) after cycle 16. After 2-year lenalidomide maintenance, to be performed every 6 months.

APPENDIX 11: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 12: Cockcroft-Gault Estimation of Creatinine Clearance

Males

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

Females

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg}) \times 0.85}{72 \times (\text{serum creatinine, mg/dL})}$$

APPENDIX 13: New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX 14: PATIENT'S MEDICATION DIARY

Today's Date:_____ Agent: Lenalidomide

Cycle: _____ Patient Name:_____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _ _ _ mg (_ _ _ capsules) of lenalidomide daily at approximately the same time each day. **Please note that the capsules can come in different strengths, so it is important that you read the label on the pill bottle.** Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Lenalidomide may be taken with or without food.
3. Record the date, the number of capsules taken, and when you took them.
4. If you forgot to take your dose and it is before 6:00PM, then take a dose. If it is after 6:00pm, then do not take a dose that day. Restart taking it the next day.
5. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
6. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				

21				

APPENDIX 15: NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX 16: Celgene Initial Pregnancy Form

Celgene Ref. # RV-CL-DLBCL-PI-003919 Page 1 of 1

Celgene

PREGNANCY INITIAL REPORT

Pregnancy reports must be sent to Celgene Drug Safety IMMEDIATELY

Protocol No.: _____

Date site first became aware of Pregnancy: dd mon yyyy

Investigator Name: _____

Subject Initials (F, M, L): | Site No.: | Subject No.: | Subject's Age:

Sex of Subject: ☐ Female ☐ Male

☐ Pregnancy of Subject ☐ Pregnancy of Subject's Partner
☐ Suspected Pregnancy ☐ Exposure of a Pregnant Female

Race: ☐ Black ☐ White ☐ Asian
☐ Other, specify _____

Screening Pregnancy Test: dd mon yyyy
Negative? ☐ Yes ☐ No
Last Menstrual Period: dd mon yyyy

Total # prior pregnancies: _____
Total # prior live births: _____
Total # terminations (spontaneous and elective): _____
History of congential anomalies with prior pregnancies? ☐ Yes ☐ No
History of familial congential anomalies? ☐ Yes ☐ No

Concomitant Medications: (at time of study entry, during study treatment and at conception) Attach additional sheets as necessary

Study Drug Name: _____

Date of First Dose: dd mon yyyy

Date of Last Dose: dd mon yyyy

Method of Birth Control: (Check (√) all that apply)

☐ Abstinence
☐ Condom
☐ Diaphragm
☐ Depo Contraceptive (e.g., Norplant, Depo-Provera)
☐ Intrauterine Device (IUD)
☐ Oral Contraceptive
☐ Rhythm Method
☐ Spermicide
☐ Sterilization (female)
☐ Sterilization (male)
☐ None
☐ Other: _____

Pregnancy Initially Diagnosed By: ☐ Home Urine Test ☐ Office Urine Test ☐ Serum Test

Date of Pregnancy Test: dd mon yyyy

Female is Currently: _____ weeks pregnant OR ☐ No longer Pregnant (If no longer pregnant, complete Pregnancy Follow-up Report)

Female has Elected to: ☐ Carry Pregnancy to Term (Expected Date of Delivery):
☐ Terminate Pregnancy (Date Performed or Pending): dd mon yyyy

Summarize Diagnostic Tests to Date (e.g., ultrasound, amniocentesis): ☐ None

Describe Complications with Pregnancy to Date ☐ None

Investigator's Name and Signature: Date: dd mon yyyy

Reporter's Name and Signature: Date: dd mon yyyy

Reporter's Phone Number: | Reporter's Fax Number: | Reporter's E-mail Address:

NOTE: Please use the first three letters of the month (e.g.: JAN)

INIT PREG Form 26 May 2010

APPENDIX 17: Celgene Pregnancy Follow-Up Form

Celgene Ref. # RV-CL-DLBCL-PI-003919 Page 1 of 1

PREGNANCY FOLLOW-UP REPORT

Pregnancy reports must be sent to Celgene Drug Safety IMMEDIATELY

Protocol No.: _____

Date site first became aware of Pregnancy: ___ ___ ___ (dd mon yyyy)

Investigator Name: _____

Subject Initials (F, M, L): ___ Site No.: ___ Subject No.: ___ Subject's Age: ___

Sex of Subject: ☐ Female ☐ Male

Race: ☐ Black ☐ White ☐ Asian ☐ Other, specify _____

Summarize Diagnostic Tests to Date (e.g., ultrasound, amniocentesis): ☐ None

Describe Complications with Pregnancy to Date
☐ None

If a pregnancy complication or abnormal outcome meets serious adverse event reporting criteria, an SAE form should be completed and faxed to Celgene Drug Safety IMMEDIATELY.

Female is Currently: _____ weeks pregnant OR

Date of Delivery/Termination: ___ ___ ___ (dd mon yyyy)

Birth Weight: _____

Method of Delivery:
☐ Vaginal ☐ C-section ☐ Forceps/Vacuum extraction

Gestational Age at Delivery: _____

Apgar Score: _____ 1 min. _____ 5 min. _____ 10 min.

Pregnancy Outcome
☐ Elective Termination, specify in Comments
☐ Premature birth/congenital anomaly *
☐ Premature birth/healthy infant
☐ Term birth/congenital anomaly *
☐ Term birth/healthy infant
☐ Spontaneous abortion
☐ Stillbirth
☐ Unknown/Lost to follow-up
** If anomaly, please provide comments below*

Comments: (Include changes in Concomitant Medications since previous report and medications at delivery, e.g., epidural)

Investigator's Name and Signature: Date: ___ ___ ___ (dd mon yyyy)

Reporter's Name and Signature: Date: ___ ___ ___ (dd mon yyyy)

Reporter's Phone Number: | Reporter's Fax Number: | Reporter's E-mail Address:

NOTE: Please use the first three letters of the month (e.g.: JAN)

FOLLOW-UP PREG Form 26 May 2010

APPENDIX 18: CYP3A4 inhibitors

PRESCRIPTION MEDICATIONS - INHIBITORS OF CYP3A4 Copyright EBM Consult www.ebmconsult.com			
Drug Class	**Weak 3A4 Inhibitors** (≥1.25 to < 2-fold ↑AUC) or (Clearance ↓ by 20-50%)	**Moderate 3A4 Inhibitors** (≥2 to < 5-fold ↑ AUC) or (Clearance ↓ by 50-80%)	**Strong 3A4 Inhibitors** (≥5-fold ↑ AUC) or (Clearance ↓ by >80%)
Antiarrhythmics		Amiodarone*	
Antibiotics		Erythromycin	Clarithromycin Telithromycin
Antidepressants			Nefazodone
Antifungals		Fluconazole Miconazole*	Itraconazole Ketoconazole
Calcium Channel Blockers		Diltiazem Verapamil	
H2 Receptor Antagonist	Cimetidine		
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)		Delavirdine	
Protease Inhibitors		Amprenavir Fosamprenavir	Atazanavir Darunavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir
Other		Conivaptan Grapefruit juice Cat's claw (*Uncaria tomentosa*)* *Echinacea angustifolia* Wild cherry (*Trifolium pratense*) Chamomile (*Matricaria chamomilla*) Licorice (*Glycyrrhiza glabra*)	

Note: The referenced change in area under the curve (AUC) and/or change in clearance of either midazolam (Versed; a specific substrate of CYP3A4) or a known sensitive CYP3A4 substrate. The use of an (*) reflects opinion of editorial board based on clinical experience since no data available with midazolam or other sensitive substrate.