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Camidanlumab Tesirine in Relapsed or Refractory Classic Hodgkin Lymphoma: A Phase 2 Study

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Abstract:
Outcomes in classic Hodgkin lymphoma (cHL) have steadily improved; however, additional therapies are needed for patients who relapse or do not respond to novel agents. Here, we report the efficacy and safety of camidanlumab tesirine (Cami), an anti-CD25 antibody-drug conjugate, in patients with relapsed/refractory cHL following brentuximab vedotin/programmed cell death protein 1 inhibitor therapies from the phase 2 ADCT-301-201 study. Eligible patients were adults with cHL who had received ≥3 prior lines of systemic therapy (or ≥2 if ineligible for hematopoietic stem cell transplant). Patients received 45 µg/kg Cami (intravenously, once every 3 weeks [Q3W]) in cycles 1 to 2, followed by 30 µg/kg IV Q3W for ≤1 year. The primary endpoint was overall response rate (ORR) per 2014 Lugano Classification. Secondary endpoints included complete response rate (CRR), progression-free survival (PFS), and overall survival (OS). In total, 117 patients were enrolled with a median age of 37.0 (range, 19, 87) years. The ORR was 70.1% (95% CI, 60.9, 78.2) with a CRR of 33.3% (24.9, 42.6). The median PFS was 9.13 (95% CI, 5.3, 15.0) months; median OS was not reached. Thirty-three (28.2%) patients discontinued treatment because of treatment-emergent adverse events; the most common reasons were skin and subcutaneous tissue disorders (10 [8.5%] patients), infections and infestations (5 [4.3%]), and nervous systems disorders (5 [4.3%]). Guillain-Barré- or polyradiculopathy-type events occurred in 8 (6.8%) patients. Cami was efficacious in this heavily pretreated population; however, the efficacy was overshadowed by substantial issues with the safety profile. NCT04052997

Conflict of interest: COI declared - see note

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Camidanlumab Tesirine in Relapsed or Refractory Classic Hodgkin Lymphoma: A Phase 2 Study

Running title (47/50 characters, including spaces): An anti-CD25 antibody–drug conjugate in R/R cHL

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Key points (up to 140 characters, including spaces)

- Camidanlumab tesirine produced an overall and complete response rate of 70% and 33% in relapsed/refractory classic Hodgkin lymphoma
- Substantial safety issues including skin toxicities and neurologic immune-related adverse events, were observed with camidanlumab tesirine

Keywords: Cami, antibody–drug conjugate, CD25, classic Hodgkin lymphoma, safety

Data sharing statement: Proposals requesting deidentified participant data collected for the study following publication can be sent to clinical.trials@adctherapeutics.com and will be evaluated on a case-by-case basis.

Explanation of Novelty (492/500 characters): This study evaluated camidanlumab tesirine (Cami), an anti-CD25 antibody–drug conjugate, in patients with relapsed/refractory classic Hodgkin lymphoma.

63 Patients received 45 μg/kg Cami every 3 weeks for 2 cycles, followed by 30 μg/kg for subsequent cycles
64 for ≤1 year. Responses were promising, with an overall response rate of 70.1% and a complete response
65 rate of 33.3%. However, substantial safety issues, notably neurologic immune-related adverse events,
66 overshadowed the benefits of Cami.

67

Abstract:

Outcomes in classic Hodgkin lymphoma (cHL) have steadily improved; however, additional therapies are needed for patients who relapse or do not respond to novel agents. Here, we report the efficacy and safety of camidanlumab tesirine (Cami), an anti-CD25 antibody–drug conjugate, in patients with relapsed/refractory cHL following brentuximab vedotin/programmed cell death protein 1 inhibitor therapies from the phase 2 ADCT-301-201 study. Eligible patients were adults with cHL who had received ≥3 prior lines of systemic therapy (or ≥2 if ineligible for hematopoietic stem cell transplant). Patients received 45 µg/kg Cami (intravenously, once every 3 weeks [Q3W]) in cycles 1 to 2, followed by 30 µg/kg IV Q3W for ≤1 year. The primary endpoint was overall response rate (ORR) per 2014 Lugano Classification. Secondary endpoints included complete response rate (CRR), progression-free survival (PFS), and overall survival (OS). In total, 117 patients were enrolled with a median age of 37.0 (range, 19, 87) years. The ORR was 70.1% (95% CI, 60.9, 78.2) with a CRR of 33.3% (24.9, 42.6). The median PFS was 9.13 (95% CI, 5.3, 15.0) months; median OS was not reached. Thirty-three (28.2%) patients discontinued treatment because of treatment-emergent adverse events; the most common reasons were skin and subcutaneous tissue disorders (10 [8.5%] patients), infections and infestations (5 [4.3%]), and nervous systems disorders (5 [4.3%]). Guillain–Barré– or polyradiculopathy-type events occurred in 8 (6.8%) patients. Cami was efficacious in this heavily pretreated population; however, the efficacy was overshadowed by substantial issues with the safety profile.

Introduction

Classic Hodgkin lymphoma (cHL) typically presents in young adults and accounts for approximately 10% of cases of newly diagnosed lymphoma.[1-4] While outcomes have steadily improved over the years, approximately 10%-20% of patients with cHL do not respond to treatment or experience relapse.[5] There is no consensus on preferred late-line salvage regimens, and choice of therapy depends on previous treatments the patient has already received.[6,7] Patients who have previously received brentuximab vedotin (BV) and programmed cell death protein 1 (PD-1) inhibitor therapies have limited options, and novel agents are needed to improve patient outcomes.[8-11]

Camidanlumab tesirine (Cami) is an anti-CD25 antibody–drug conjugate (ADC) with a pyrrolobenzodiazepine (PBD) payload (SG3199) that has demonstrated encouraging efficacy as a single agent in a phase 1 study in relapsed/refractory (R/R) lymphomas.[12] The maximum tolerated dose was not reached; the dose levels of 45 μg/kg and 30 μg/kg were identified as the recommended doses for expansion for patients with cHL. The most common observed adverse events (AEs), such as elevated liver enzymes, rash, fatigue, edema, and effusion, were consistent with other studies using the SG3199 PBD payload and were generally reversible and manageable with dose delays or reductions.[12-14] Approximately 6% of patients (5/77 patients) with cHL developed Guillain–Barré syndrome (GBS) or polyradiculopathy following treatment with Cami. Further investigation of these events demonstrated that GBS events were not associated with dose, cycle number, or prior immune checkpoint inhibitor treatment.[12,15] In terms of efficacy, Cami showed high response rates in a heavily pretreated population. Of the 37 evaluable patients with R/R cHL who received a dose of 45 μg/kg, the overall response rate (ORR) was 86.5%, of whom 48.6% had a complete response (CR).[12]

Here, we report results from the ADCT-301-201 phase 2 study, which was conducted to further evaluate the efficacy and safety of Cami in R/R cHL.

Methods

Study oversight

ADCT-301-201 (NCT04052997) was an open-label, single-arm, multicenter study to evaluate the efficacy and safety of Cami in patients with R/R cHL conducted at 73 sites in 11 countries (Supplemental Table 1). All patients provided written informed consent in accordance with the Declaration of Helsinki. The study protocol and amendments were approved by the appropriate institutional review board for each study site. The study was conducted according to Good Clinical Practice, as outlined by the International Council of Harmonisation, except for 1 serious breach in which the sponsor recommended implementation of a prolonged contraception period (9.5 months instead of 6.5 months for women and 6.5 months instead of 16 weeks for men) prior to obtaining regulatory approval of this change. This change was later included within a protocol amendment, which was approved by regulatory bodies of all participating countries.

Eligibility criteria

Eligible patients were aged ≥18 years (or ≥16 years for sites in the United States); had a diagnosis of cHL with measurable disease per the 2014 Lugano Classification[16]; received ≥3 prior lines of systemic therapy, including hematopoietic stem cell transplant (HSCT), BV, checkpoint inhibitors approved for cHL, or ≥2 prior lines in patients who were ineligible for HSCT; had an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 to 2; and had adequate organ function (absolute neutrophil count ≥1.0 × 10^3/μL, platelet count ≥75 × 10^3/μL without transfusion in the past 2 weeks; alanine aminotransferase [ALT], aspartate aminotransferase [AST], or gamma-glutamyl transferase ≤2.5 × the upper limit of normal [ULN] without liver involvement [ALT or AST ≤5.0 × ULN in cases of liver involvement]; total bilirubin ≤1.5 × ULN [total bilirubin ≤3.0 × ULN with direct bilirubin ≤1.5 × ULN in patients with known Gilbert's syndrome]; and blood creatinine ≤3.0 × ULN or calculated creatinine clearance ≥30 mL/min by the Cockcroft–Gault equation[17]). Patients were excluded in cases of history of hypersensitivity or positive

serum human antidrug antibody to a CD25 antibody; allogenic or autologous HSCT ≤60 days prior to the start of study drug; active graft-versus-host disease (GVHD), except for non-neurologic symptoms as a manifestation of grade ≤1 chronic GVHD; post-HSCT lymphoproliferative disorders; active second primary malignancy (other than nonmelanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast); history of symptomatic autoimmune disease; history of neuropathy considered of autoimmune origin or cHL with central nervous system involvement; history of Stevens–Johnson syndrome or toxic epidermal necrolysis; or other significant medical comorbidities.

Study treatment and procedures

Patients received 45 μg/kg Cami (intravenously [IV], once every 3 weeks [Q3W]) in cycles 1 to 2 (21-day cycles), followed by 30 μg/kg IV Q3W for subsequent cycles for ≤1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria. Patients who experienced clinical benefit could continue the treatment past 1 year on a case-by-case basis. Patients were premedicated with dexamethasone (4 mg orally, twice daily) to mitigate PBD-associated toxicities the day before Cami infusion, the day of the Cami infusion (≥2 h prior to infusion if it was not possible to give the day before; otherwise, any time prior to infusion), and the day after each Cami infusion, unless contraindicated. Disease assessments used positron emission tomography-computed tomography and were conducted at screening, at 6 weeks and 12 weeks after the first infusion, every 9 weeks throughout treatment, at the end of treatment, every 12 weeks for 1 year after the end of treatment, and then every 6 months until disease progression or initiation of other anticancer therapy except for HSCT or chimeric antigen receptor T-cell therapy.

Outcomes

The primary endpoint of the ADCT-301-201 study was ORR according to the 2014 Lugano Classification,[16] as determined by central review in all treated patients. Central imaging review was performed by 2

158 blinded independent reviewers with adjudication by a third blinded independent reviewer in cases of
159 discordance. Secondary endpoints included the CR rate (CRR), duration of response (DOR), progression-
160 free survival (PFS), and overall survival (OS). The safety of Cami was assessed via frequency and severity
161 of AEs, as well as changes from baseline of safety laboratory values, vital signs, ECOG performance
162 status, and 12-lead electrocardiograms. Treatment-emergent AEs (TEAEs) were defined as an AE that
163 occurred or worsened in the period extending from the first dose of Cami to either 30 days after the last
164 dose of Cami in this study or the start of a new anticancer therapy/procedure. Non-TEAEs were defined
165 as occurring >30 days after the last dose of Cami or after the start of subsequent anticancer therapy. The
166 following AEs, regardless of seriousness or causality, were considered AEs of special interest (AESIs): GBS
167 (including variants such as acute motor and sensory axonal neuropathy), polyradiculopathy, autonomic
168 nervous system imbalance, nerve palsy, grade ≥3 neurologic and immune-mediated toxicities, and
169 autoimmune events. Rashes were not defined as AESIs as they are well-described toxicities of PBD
170 dimers,[13] with the exception of Stevens–Johnson syndrome, toxic epidermal necrolysis, acute generalized
171 exanthematous pustulosis, exfoliative dermatitis, and drug reaction with eosinophilia and systemic
172 symptoms. A protocol specified interim safety enrollment pause was triggered after the occurrence of ≥2
173 cases of GBS or other relevant severe neurologic toxicity. During the safety pause, a detailed
174 independent review was performed by the Data and Safety Monitoring Board (DSMB) and it was
175 recommended that the study resume. The impact of Cami on health-related quality of life was assessed
176 via EuroQoL–5 Dimensions–5 Levels (EQ-5D-5L) and the Functional Assessment of Cancer Therapy –
177 General (FACT-G), including the lymphoma-specific subscale (FACT-Lym). CD25 expression was assessed
178 by immunohistochemistry (IHC) and histoscore (H-score) in tumor biopsy samples. H-score was reported
179 as a composite score of the percent of positive cells and the degree of positivity as follows: negative (0),
180 weakly (1+), moderately (2+), and strongly (3+) stained membranes. The H-score, with a potential range
181 of 0 to 300, was calculated as follows: H-score = [(1 × % weakly stained cells) + (2 × % moderately stained

cells) + (3 × % strongly stained cells)].[18] Additionally, soluble CD25 (sCD25) and CCL17 levels were measured in serum via immunoassays; patients with values falling outside of quantifications levels were excluded from analyses.

Statistical methods

A sample size of 100 was estimated to provide >98% power to distinguish between an active therapy with a 55% true response rate and a therapy with a response rate of <35% with a 1-sided α of 0.025. The all-treated population consisted of all patients who received ≥1 dose of Cami. Time-to-event endpoints were analyzed via the Kaplan–Meier method. Responses were analyzed via percentages and 95% CIs. Differences between biomarker levels in responders and nonresponders were assessed via box plots and statistical significance of differences was inferred using Wilcoxon's rank sum test with continuity correction (threshold for significance, $P = 0.05$). Receiver operating characteristic (ROC) analyses were performed to evaluate the predictive potential of biomarker variables. Area under the curve and maximum Youden's index (0–1) were used to measure the sensitivity and specificity of the predictive responses. Biomarker and ROC analyses were performed using the statistical program R, version 4.3.1, packages stats and pROC.

Results

Patients

In total, 117 patients were enrolled in ADCT-301-201 and received ≥1 dose of Cami (Figure 1). The median age was 37.0 (range, 19, 87) years, and the median number of prior lines of systemic therapy was 6 (range, 3, 19). Thirty-six (30.8%) patients relapsed following the last prior line of therapy, and 66 (56.4%) patients were refractory to the last prior line of therapy (Table 1). One patient was included in the all-treated population who did not receive prior BV treatment; this was recorded as a protocol deviation. The median follow-up was 20.1 (range, 1.2, 39.4) months. Among all patients, the median

treatment duration was 85.0 (range, 1, 349) days and the median number of treatment cycles was 5.0 (range, 1, 15). Fifty-eight (49.6%) patients reported ≥1 dose delay, while 22 (18.8%) reported ≥1 dose decrease. The most common primary reasons for treatment discontinuation were disease progression (48 [41.0%] patients), unacceptable toxicity (34 [29.1%] patients), and transition to transplant (14 [12.0%] patients; Figure 1). After discontinuing Cami treatment, 18 (15.4%) patients received HSCT without any intervening anticancer therapy (allogeneic, 14 [12.0%] patients; autologous, 4 [3.4%] patients). After the completion of planned accrual, the ADCT-301-201 study was stopped by the Sponsor with the data cutoff date of 27 January 2023, as the data were considered mature, and continued data collection was not expected to substantially impact the overall conclusions of the study. All ongoing patients were in follow-up at that time. For responders, at least 20 months had elapsed since their initial response.

Efficacy

Among all treated patients, the ORR was 70.1% (82/117 patients; 95% CI, 60.9, 78.2) and the CRR was 33.3% (39/117 patients; 95% CI, 24.9, 42.6; Supplemental Table 2). The median DOR was 13.7 (95% CI, 7.9, 14.7) months (Figure 2A), with a 54.4% (95% CI, 35.8, 69.6) probability of maintaining response for 12 months. Among patients with a CR, the median DOR was 14.5 (95% CI, 7.9, not estimable [NE]) months (Figure 2B), with a 62.1% (95% CI, 36.4, 79.9) probability of maintaining response for 12 months. The median time to first response (either CR or partial response) was 41.0 (range, 32, 148) days, while the median time to first response of CR was 45.0 (range, 36, 222) days, and the median time to best overall response was 43.0 (range, 32, 222) days. The median PFS was 9.1 (95% CI, 5.3, 15.0) months (Figure 2C). When analyzed by best overall response, the median PFS was 15.9 (95% CI, 10.1, NE) months for patients who achieved a CR, 9.2 (95% CI, 5.1, NE) months for patients with a PR, 4.2 (95% CI, 2.8, 5.1) months in patients with stable disease, and 1.3 (95% CI, 1.1, 1.4) months for patients with progressive disease or who were not evaluable (Figure 2D). The median OS was not reached (95% CI, NE, NE; Figure

2E). The ORR and CRR were generally consistent across clinically relevant subgroups included in the analysis compared with the overall population (Figure 3). Notably, patients who were refractory to frontline treatment had an ORR of 72.4% (95% CI, 52.8, 87.3) and a CRR of 34.5% (95% CI, 17.9, 54.3); patients who had received ≥8 prior lines of therapy had an ORR of 73.8% (95% CI, 58.0, 86.1%) and a CRR of 38.1% (95% CI, 23.6, 54.4); and patients who had received prior stem cell transplant had an ORR of 74.3% (95% CI, 62.8, 83.8) and a CRR of 41.9% (95% CI, 30.5, 53.9). Demographic and baseline disease characteristics for North American and European patients are provided in Supplemental Table 3.

Safety

A summary of TEAEs is given in Supplemental Table 4. All Cami infusions, with the exception of 1 that was interrupted owing to a grade 2 infusion-related reaction, were completed and well tolerated; no severe or serious instances of hypersensitivity were reported. Infusion-related reactions of any grade occurred in 5 (4.3%) patients, all grade 1 or 2. The most common TEAEs of any grade were fatigue (45 [38.5%] patients), maculo-papular rash (38 [32.5%] patients), and pyrexia (35 [29.9%] patients; Table 2). The most common TEAEs of grade ≥3 were lymphopenia (12 [10.3%] patients), thrombocytopenia (11 [9.4%] patients), and anemia (10 [8.5%] patients; Table 2, Supplemental Table 5). A summary of TEAEs reported in patients who received allogeneic transplant prior to enrollment (n = 15) is given in Supplemental Table 6.

Skin and subcutaneous tissue disorders of any grade were experienced by 92 (78.6%) patients, most commonly maculo-papular rash (38 [32.5%] patients), rash (31 [26.5%] patients), pruritus (28 [23.9%] patients), and erythema (14 [12.0%] patients). The median time to onset for skin and subcutaneous tissue disorders of any grade was 39 (range, 3, 302) days, while the median time to onset was 99 (range 40, 302) days for grade ≥3. Thirty-three (28.2%) patients required dose delays and 12 (10.3%) patients discontinued treatment owing to skin or subcutaneous tissue disorders. The median number of days to resolution of skin toxicity after dose reduction or delay was 32.5 days (range 8-666 days). Thirty-seven

(31.6%) patients had hepatic events, mainly comprising laboratory abnormalities. The median number of days to resolution of hepatic toxicity after dose reduction or delay was 29.5 days (range 7-320 days). Two cases of drug-induced liver injury (both grade 3) were reported (mixed [n = 1]; hepatocellular type [n = 1]); both patients recovered. Fifty-one (43.6%) patients had cytopenias, with grade 4 events occurring in 8 (6.8%) patients.

Three patients died because of TEAEs (respiratory failure following multipathogen infection, myocardial infarction, and cardiac arrest/left ventricular failure in 1 patient each), none of which were considered related or possibly related to Cami (Supplemental Table 7). Three patients experienced fatal non-TEAEs that were considered related or possibly related to Cami: 1 patient each with sepsis, aplastic anemia, and respiratory failure owing to pneumonia. Overall, 33 (28.2%) patients had TEAE(s) leading to treatment discontinuation. The most common types of TEAEs that led to treatment discontinuation were skin and subcutaneous tissue disorders (10 [8.5%] patients), infections and infestations (5 [4.3%] patients), and nervous systems disorders (5 [4.3%] patients).

AEs of special interest

Thirty-nine (33.3%) patients reported an AESI of any grade (Table 3). The most commonly reported post-treatment AESIs (≥2% of patients overall) were hypothyroidism (14 [12.0%] patients), hyperthyroidism (9 [7.7%] patients), thyroiditis (8 [6.8%] patients), GBS (6 [5.1%] patients), noninfectious pneumonitis (4 [3.4%] patients), and autoimmune thyroiditis (3 [2.6%] patients). The median time to manifestation of an AESI of any grade was 78 (range, 17, 264) days and the median time to manifestation of grade ≥3 AESIs was 105 (range, 28, 393) days.

Of the 117 patients in the safety population, GBS- or polyradiculopathy-type events were reported in 8 (6.8%) patients (Supplemental Table 8). These patients had no common demographic characteristics or medical antecedents, although 3 patients had an immune-related AE (irAE) affecting the thyroid gland

prior to GBS/polyradiculopathy. The onset of GBS/polyradiculopathy was most common after 2 cycles of treatment, though in some patients it occurred after 6 or 7 cycles. Initial symptoms in patients were nonspecific, at times delaying intervention, and in 7 of 8 patients the first symptom was pain, including painful paresthesia, radicular pain, abdominal pain, and headache. Sensory symptoms (including paresthesia) and weakness were also common. Cerebrospinal fluid analysis was reported in 5 patients and generally showed elevated white blood cell counts as well as elevated protein levels. Antiganglioside panel results were reported as positive in 1 patient. Electromyoneurography was positive for signs consistent with GBS/polyradiculopathy in 6 patients; abnormal MRI results (gadolinium enhancement of the cauda equina and/or lumbosacral plexus) were reported in 4 patients. All 8 patients who experienced GBS discontinued study therapy. They all received intravenous immunoglobulins; 5 patients received plasma exchange; 6 patients received steroids; and 1 patient was administered rituximab. Five of 8 patients had reported resolution of GBS prior to study closure.

Additional immune-related adverse events of interest included one patient who developed grade 4 type 1 diabetes mellitus after 2 cycles of Cami treatment, one patient who experienced grade 3 autoimmune hemolytic anemia (AIHA) after 12 cycles of Cami, and two patients who developed tubulointerstitial nephritis, both confirmed by kidney biopsy.

Exploratory biomarker analyses

In patients with valid biomarker data, no statistically significant differences in tumor cell CD25 H-score were observed between responders and nonresponders ($P = 0.54$; Supplemental Figure 1); however, baseline sCD25 levels were statistically significantly higher in nonresponders than responders ($P = 0.0037$; Supplemental Figure 2A). From baseline to cycle 3, day 1 pre-Cami infusion (end of cycle 2), there was a significantly greater decrease in sCD25 in nonresponders compared with responders ($P = 0.025$; Supplemental Figure 2B); this trend was already visible at cycle 2, day 1 pre-Cami infusion (end of cycle 1), but it was not statistically significant (data not shown). There was no statistically significant

difference in baseline CCL17 levels between responders and nonresponders (P = 0.22; Supplemental Figure 3A), but from baseline to cycle 2, day 1 pre-Cami infusion (end of cycle 1), there was a statistically significant decrease in CCL17 in responders compared with nonresponders (P = 0.0031; Supplemental Figure 3B); although this trend remained at cycle 3, day 1 pre-Cami (end of cycle 2), it was not statistically significant (data not shown).

ROC analyses were performed to assess the ability to predict response to Cami of baseline sCD25 alone or as part of models incorporating CD25 IHC, baseline CCL17, and pharmacodynamic changes of sCD25 and CCL17 observed at the end of cycle 1 and cycle 2. Baseline sCD25 alone or in combination with CD25 IHC or CCL17 baseline values had a modest predictive value for response to Cami treatment (Supplemental Table 8). Slightly better predictive values were obtained by adding the changes from baseline of sCD25 and CCL17 to these models; however, the predictive level reached was still not satisfactory (Supplemental Table 8 and Supplemental Figure 4).

Patient-reported outcomes

The patient-reported outcomes (PRO) population included 116 patients. PRO results are described in detail in the Supplemental Materials. The mean change from baseline in EQ-5D-5L visual analog scale (VAS) score and mean scores on the FACT-Lym lymphoma subscale generally improved with treatment (Supplemental Figure 5A and 5B).

Discussion

With novel agents advancing into earlier treatment lines, there is an increasing number of patients exposed to both BV and checkpoint inhibitors, yet for patients who relapse after or who have disease refractory to these treatments, there are limited treatment options.[8-11] In this study, Cami demonstrated efficacy in a highly pretreated population, with >60% of patients in the post-transplant setting, including, in some cases, allogeneic stem cell transplant. The exploratory biomarker analyses conducted did not

identify predictive biomarker(s) or models allowing for the early identification of patients more likely to respond to Cami with satisfactory sensitivity and specificity. Generally, patients reported a trend in improvement regarding overall health and lymphoma-related symptoms throughout the study. However, the majority of patients (62.9%) were at least somewhat bothered by the side effects of treatment, reflective of the burden of Cami-related toxicities. Because of the single-arm design of this study, there is no comparison for Cami-related impact on PROs, limiting the conclusions that can be drawn from the PRO data collected during the trial.

Use of Cami in this heavily pretreated population was associated with a high rate of AEs, as almost all (94.9%) patients reported ≥1 TEAE considered related to Cami and the majority experienced ≥1 grade ≥3 TEAE; however, toxicities were generally manageable with monitoring and dose modifications. The observed safety profile can be viewed as a combination of PBD-associated AEs (abnormal liver tests, cytopenias), anti–CD25-associated AEs (likely GBS or polyradiculopathy), and possibly toxicities that are caused by both components (likely skin toxicities). Skin toxicities represent the most common challenge for Cami delivery; skin and subcutaneous disorders were the most common TEAEs that led to dose modifications. They were often triggered by sun exposure and generally occurred within the first 2 cycles of treatment.

GBS- and polyradiculopathy-type events are a major concern for patients treated with Cami. Neurologic irAEs have also been reported with immune checkpoint inhibitors at a rate of 1% to 12% for any grade of neurologic irAEs and a rate of <1% for grades 3 to 4.[19-22] With Cami, GBS/polyradiculopathy was seen at a rate of 6.8% in the current study, which is consistent with the prior phase 1 study (5 [6.5%] of 77 patients with cHL).[12] Of note, almost all cases of GBS/polyradiculopathy in Cami-treated patients were in patients with cHL, suggesting it may be disease associated. Cases of GBS occurring in patients with cHL have been previously reported in the literature.[23-25] Recent studies suggest a role of $CD25^+$ T-suppressor cells in GBS pathogenesis.[26] Although the pathogenesis of GBS/polyradiculopathy events in Cami-treated patients

remains unclear, it is plausible that reduction in the T-regulatory cell population triggers an immune-related polyneuropathy in susceptible patients with cHL. A case of GBS was reported in a patient treated with for ipilimumab, an anti-CTLA-4 agent.[27] The presentation of GBS and/or polyradiculopathy events in this study showed substantial interpatient variability, with no clear clinical correlate, which challenges the prospect of proactive identification of patients who could be at risk for developing GBS/polyradiculopathy following treatment with Cami. Other irAEs were observed in this study, including type 1 diabetes, tubulointerstitial nephritis, and a fatal event of aplastic anemia.

Other AESIs of particular note included tubulointerstitial nephritis, type 1 diabetes mellitus, and autoimmune hemolytic anemia. In 2 of the 4 patients who experienced these AESIs, the events developed following cycle 2 of Cami. All events were considered at least probably related to Cami and led to permanent discontinuation of treatment. These immune-related AEs were likely due to CD25 (ie, also expressed on regulatory T cells) targeting of Cami and reflect tolerability challenges with Cami that impact its clinical application.

In conclusion, Cami was efficacious in a heavily pretreated population of patients with R/R cHL, highlighting the value of targeting CD25. Objective responses to Cami were observed in a majority of patients; although, a limitation of the ADCT-301-201 study was the single-arm design. However, the efficacy of Cami was overshadowed by the substantial issues in its safety profile. Cami is no longer being pursued at any dose or in combination treatment at this time.

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535

536 Table 1. Demographic and baseline disease characteristics of the all-treated population.

Characteristic	N = 117
Sex, n (%)	
Male	73 (62.4)
Female	44 (37.6)
Median (range) age, y	37.0 (19, 87)
Age group, n (%)	
<60 years	91 (77.8)
≥60 years	26 (22.2)
Region, n (%)	
North America	56 (47.9)
Europe	61 (52.1)
Race, n (%)	
White	101 (86.3)
Black or African American	5 (4.3)
Asian	3 (2.6)
Native Hawaiian or Pacific Islander	1 (0.9)
Other	5 (4.3)
Missing	2 (1.7)
Ethnicity, n (%)	
Hispanic or Latino	7 (6.0)
Not Hispanic or Latino	104 (88.9)
Missing	6 (5.1)
ECOG performance status score, n (%)	
0	64 (54.7)
1	47 (40.2)
2	6 (5.1)
Extranodal, n (%)	47 (40.2)
Constitutional symptoms, n (%)	
Absence of B symptoms	62 (53.0)
B symptoms	50 (42.7)
Missing	5 (4.3)
Disease stage as study entry, n (%)	
I/II	28 (23.9)
III/IV	89 (76.1)
Median (range) prior systemic therapies	6.0 (3, 19)
Prior systemic therapies, n (%)	
≤5 prior lines	45 (38.5)
6–7 prior lines	30 (25.6)
≥8 prior lines	42 (35.9)
Prior radiotherapy, n (%)	55 (47.0)
Prior HSCT, n (%)	74 (63.2)
Only autologous	59 (50.4)
Only allogeneic	3 (2.6)
Both	12 (10.3)

None	43 (36.8)
Response to first line of systemic therapy,[a] n (%)	
Relapse	79 (67.5)
Refractory[b]	29 (24.8)
Response to most recent line of systemic therapy,[a] n (%)	
Relapse	36 (30.8)
Refractory[b]	66 (56.4)
Response to last checkpoint inhibitor,[a] n (%)	
Relapse	33 (28.2)
Refractory[b]	71 (60.7)

537 [a]Missing or non-evaluable responses are not included.

538 [b]Refractory was defined as having a best response to a line of treatment of stable disease or progressive
539 disease.

540 ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant.

541

542 Table 2. Most common TEAEs (any grade, ≥10% incidence or grade ≥3, ≥3% incidence) by system organ
543 class and severity in the all-treated population

Any grade TEAE,[a] n (%)	N = 117		
	Any grade	Grade 2	Grade ≥3
Skin and subcutaneous tissue disorders	92 (78.6)	29 (24.8)	26 (22.2)
Maculo-papular rash	38 (32.5)	12 (10.3)	8 (6.8)
Rash	31 (26.5)	11 (9.4)	3 (2.6)
Pruritus	28 (23.9)	6 (5.1)	4 (3.4)
Erythema	14 (12.0)	1 (0.9)	6 (5.1)
General disorders and administration site conditions	84 (71.8)	33 (28.2)	9 (7.7)
Fatigue	45 (38.5)	19 (16.2)	5 (4.3)
Pyrexia	35 (29.9)	7 (6.0)	1 (0.9)
Peripheral edema	14 (12.0)	2 (1.7)	1 (0.9)
Chills	12 (10.3)	2 (1.7)	0
Gastrointestinal disorders	64 (54.7)	24 (20.5)	9 (7.7)
Nausea	32 (27.4)	8 (6.8)	1 (0.9)
Constipation	20 (17.1)	5 (4.3)	0
Diarrhea	19 (16.2)	3 (2.6)	3 (2.6)
Vomiting	13 (11.1)	6 (5.1)	0
Abdominal pain	12 (10.3)	8 (6.8)	1 (0.9)
Investigations	56 (47.9)	18 (15.4)	19 (16.2)
Increased GGT	20 (17.1)	9 (7.7)	6 (5.1)
Increased ALT	15 (12.8)	2 (1.7)	3 (2.6)
Increased AST	14 (12.0)	2 (1.7)	1 (0.9)
Increased lipase	9 (7.7)	3 (2.6)	5 (4.3)
Increased amylase	9 (7.7)	1 (0.9)	4 (3.4)
Metabolism and nutrition disorders	56 (47.9)	8 (6.8)	17 (14.5)
Hypophosphatemia	21 (17.9)	2 (1.7)	9 (7.7)
Hyperglycemia	14 (12.0)	4 (3.4)	4 (3.4)
Hypokalemia	14 (12.0)	4 (3.4)	3 (2.6)
Decreased appetite	12 (10.3)	2 (1.7)	0
Nervous system disorders	54 (46.2)	11 (9.4)	8 (6.8)
Headache	19 (16.2)	4 (3.4)	0
Dizziness	12 (10.3)	2 (1.7)	0
GBS	4 (3.4)	0	4 (3.4)
Blood and lymphatic system disorders	51 (43.6)	14 (12.0)	32 (27.4)
Anemia	29 (24.8)	14 (12.0)	10 (8.5)
Thrombocytopenia	24 (20.5)	3 (2.6)	11 (9.4)
Neutropenia	19 (16.2)	8 (6.8)	9 (7.7)
Lymphopenia	18 (15.4)	2 (1.7)	12 (10.3)
Respiratory, thoracic, and mediastinal disorders	39 (33.3)	16 (13.7)	5 (4.3)
Dyspnea	16 (13.7)	5 (4.3)	3 (2.6)
Cough	12 (10.3)	3 (2.6)	0
Musculoskeletal and connective tissue disorders	38 (32.5)	12 (10.3)	3 (2.6)
Arthralgia	19 (16.2)	8 (6.8)	0

Psychiatric disorders	23 (19.7)	11 (9.4)	1 (0.9)
Insomnia	16 (13.7)	5 (4.3)	1 (0.9)
Endocrine disorders	22 (18.8)	15 (12.8)	0
Hypothyroidism	12 (10.3)	7 (6.0)	0

[a]Adverse events coded using MedDRA v22.0.

ALT, alanine aminotransferase; AST aspartate aminotransferase; GBS, Guillain–Barré syndrome; GGT, gamma-glutamyl transferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

549 Table 3. AESI by system organ class in the all-treated population

AESI,[a] n (%)	N = 117					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Patients with any AESI	6 (5.1)	17 (14.5)	9 (7.7)	6 (5.1)	1 (0.9)	39 (33.3)
Endocrine disorders	8 (6.8)	16 (13.7)	0	0	0	24 (20.5)
Hypothyroidism	6 (5.1)	8 (6.8)	0	0	0	14 (12.0)
Hyperthyroidism	5 (4.3)	4 (3.4)	0	0	0	9 (7.7)
Thyroiditis	3 (2.6)	5 (4.3)	0	0	0	8 (6.8)
Autoimmune thyroiditis	0	3 (2.6)	0	0	0	3 (2.6)
Nervous system disorders	0	3 (2.6)	4 (3.4)	2 (1.7)	0	9 (7.7)
Guillain–Barré syndrome	0	1 (0.9)	3 (2.6)	2 (1.7)	0	6 (5.1)
Facial paralysis	0	0	1 (0.9)	0	0	1 (0.9)
Myelitis transverse	0	1 (0.9)	0	0	0	1 (0.9)
Polyneuropathy	0	0	1 (0.9)	0	0	1 (0.9)
Radiculopathy	0	1 (0.9)	0	0	0	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	3 (2.6)	1 (0.9)	0	0	5 (4.3)
Pneumonitis	1 (0.9)	3 (2.6)	0	0	0	4 (3.4)
Interstitial lung disease	0	0	1 (0.9)	0	0	1 (0.9)
Hepatobiliary disorders	0	0	2 (1.7)	1 (0.9)	0	3 (2.6)
Drug-induced liver injury	0	0	2 (1.7)	0	0	2 (1.7)
Autoimmune hepatitis	0	0	0	1 (0.9)	0	1 (0.9)
Blood and lymphatic system disorders	0	0	1 (0.9)	0	1 (0.9)	2 (1.7)
Aplastic anemia	0	0	0	0	1 (0.9)	1 (0.9)
Autoimmune hemolytic anemia	0	0	1 (0.9)	0	0	1 (0.9)
Metabolism and nutrition disorders	0	0	0	2 (1.7)	0	2 (1.7)
Diabetic ketoacidosis	0	0	0	2 (1.7)	0	2 (1.7)
Type I diabetes mellitus	0	0	0	1 (0.9)	0	1 (0.9)
Renal and urinary disorders	0	0	2 (1.7)	0	0	2 (1.7)
Tubulointerstitial nephritis	0	0	2 (1.7)	0	0	2 (1.7)
Eye disorders	1 (0.9)	0	0	0	0	1 (0.9)
Blepharitis	1 (0.9)	0	0	0	0	1 (0.9)
Infections and infestations	0	0	1 (0.9)	0	0	1 (0.9)
Meningitis aseptic	0	0	1 (0.9)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	0	1 (0.9)	0	0	0	1 (0.9)
Myositis	0	1 (0.9)	0	0	0	1 (0.9)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.9)	0	1 (0.9)
Generalized dermatitis exfoliative	0	0	0	1 (0.9)	0	1 (0.9)
Lichenoid keratosis	0	0	0	1 (0.9)	0	1 (0.9)

550 [a]Adverse events coded using MedDRA v22.0.

551 AESI, adverse events of special interest; MedDRA, Medical Dictionary for Regulatory Activities.

552

553 Figure Legends

554 Figure 1. Patient enrollment and disposition.

555 Figure 2. Kaplan–Meier of (A) DOR in the all-treated population, (B) DOR by best overall response, (C) PFS
556 in the all-treated population, (D) PFS by best overall response, and (E) OS in the all-treated population.

557 Figure 3. Subgroup analysis of (A) ORR and (B) CRR in the all-treated population.

558

Figure 1. Patient enrollment and disposition.

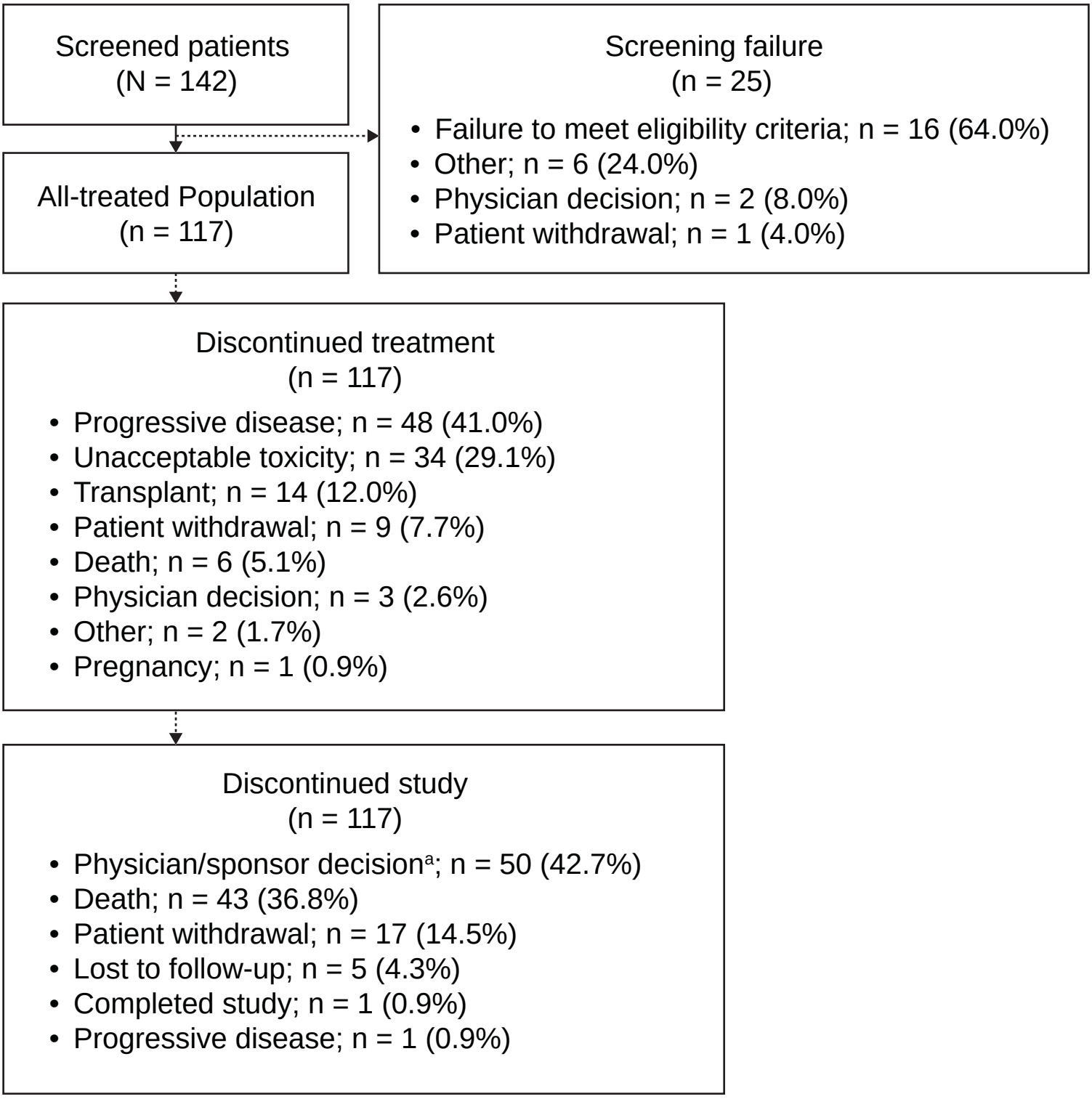


Figure 2

Figure 2. Kaplan–Meier of (A) DOR in the all-treated population, (B) DOR by best overall response, (C) PFS in the all-treated population, (D) PFS by best overall response, and (E) OS in the all-treated population.

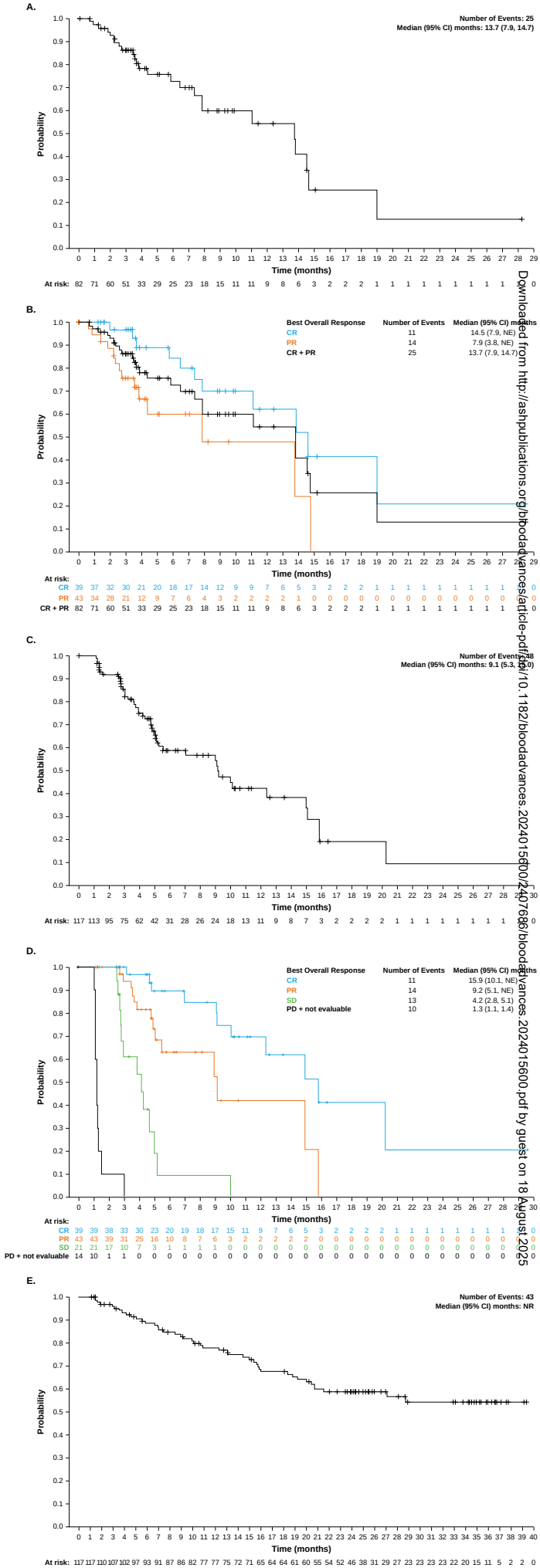
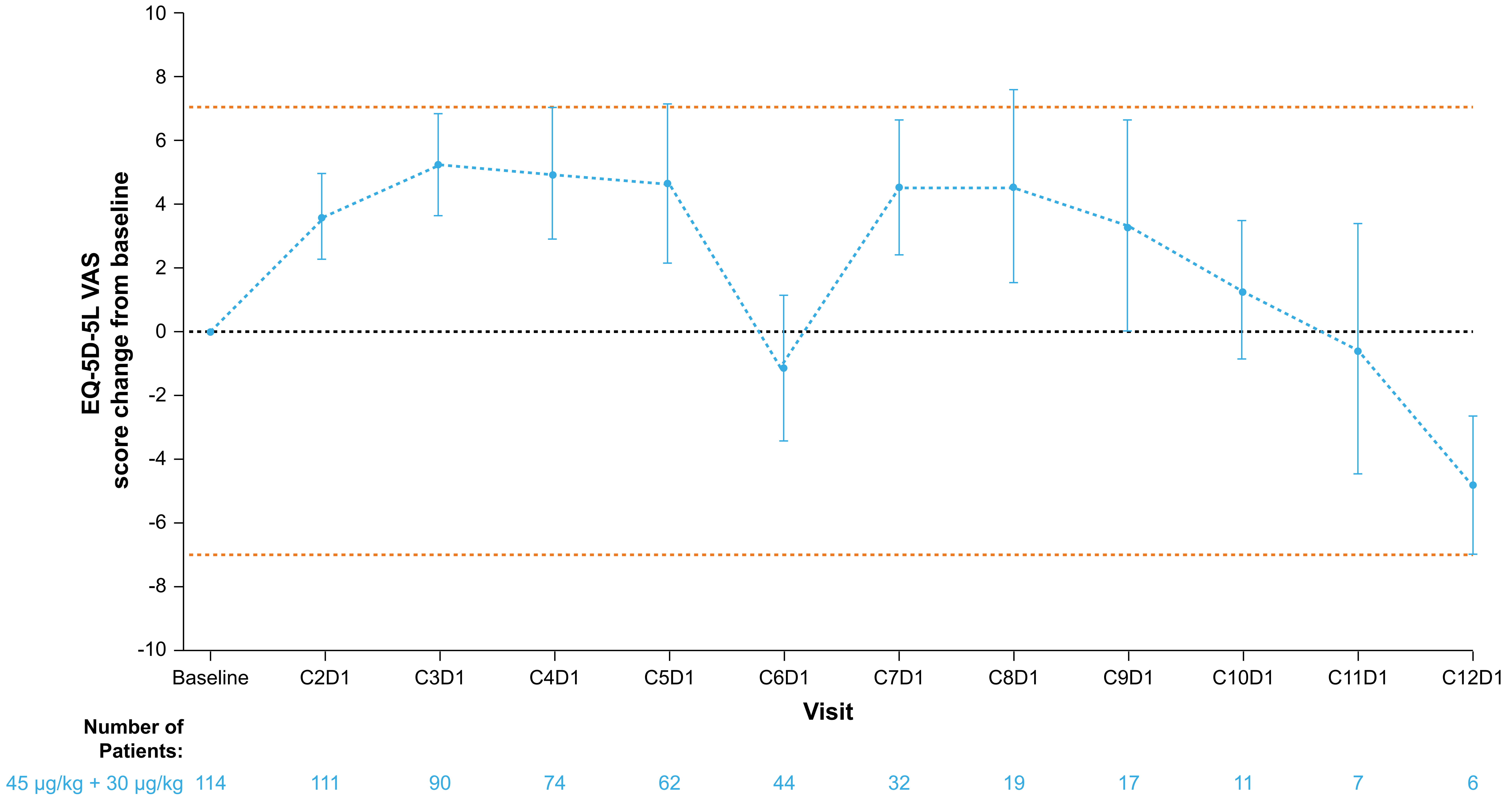


Figure 3. Subgroup analysis of (A) ORR and (B) CRR in the all-treated population.


A.
Subgroup
No. of Patients
ORR (95% CI)
Overall 82/117 70.1 (60.9, 78.2)
Sex
Female 35/44 79.5 (64.7, 90.2)
Male 47/73 64.4 (52.3, 75.3)
Age
<60 years 63/91 69.2 (58.7, 78.5)
≥60 years 19/26 73.1 (52.2, 88.4)
Region
North America 42/56 75.0 (61.6, 85.6)
Europe 40/61 65.6 (52.3, 77.3)
Extranodal
Yes 31/47 66.0 (50.7, 79.1)
No 51/70 72.9 (60.9, 82.8)
Constitutional symptoms
A 49/62 79.0 (66.8, 88.3)
B 31/50 62.0 (47.2, 75.3)
Disease stage
I/II 21/28 75.0 (55.1, 89.3)
III/IV 61/89 68.5 (57.8, 78.0)
Response to first line
Relapse 57/79 72.2 (60.9, 81.7)
Refractory 21/29 72.4 (52.8, 87.3)
Response to most recent line
Relapse 28/36 77.8 (60.8, 89.9)
Refractory 45/66 68.2 (55.6, 79.1)
Prior systemic therapies
≤5 lines 32/45 71.1 (55.7, 83.6)
6–7 lines 19/30 63.3 (43.9, 80.1)
≥8 lines 31/42 73.8 (58.0, 86.1)
Prior stem cell transplant
Yes 55/74 74.3 (62.8, 83.8)
No 27/43 62.8 (46.7, 77.0)
Response to last checkpoint inhibitor
Relapse 25/33 75.8 (57.7, 88.9)
Refractory 47/71 66.2 (54.0, 77.0)
0 20 40 60 80 100
ORR (%)
B.
Subgroup
No. of Patients
CRR (95% CI)
Overall 39/117 33.3 (24.9, 42.6)
Sex
Female 13/44 29.5 (16.8, 45.2)
Male 26/73 35.6 (24.7, 47.7)
Age
<60 years 33/91 36.3 (26.4, 47.0)
≥60 years 6/26 23.1 (9.0, 43.6)
Region
North America 25/56 44.6 (31.3, 58.5)
Europe 14/61 23.0 (13.2, 35.5)
Extranodal
Yes 15/47 31.9 (19.1, 47.1)
No 24/70 34.3 (23.3, 46.6)
Constitutional symptoms
A 22/62 35.5 (23.7, 48.7)
B 15/50 30.0 (17.9, 44.6)
Disease stage
I/II 9/28 32.1 (15.9, 52.4)
III/IV 30/89 33.7 (24.0, 44.5)
Response to first line
Relapse 26/79 32.9 (22.7, 44.4)
Refractory 10/29 34.5 (17.9, 54.3)
Response to most recent line
Relapse 14/36 38.9 (23.1, 56.5)
Refractory 22/66 33.3 (22.2, 46.0)
Prior systemic therapies
≤5 lines 11/45 24.4 (12.9, 39.5)
6–7 lines 12/30 40.0 (22.7, 59.4)
≥8 lines 16/42 38.1 (23.6, 54.4)
Prior stem cell transplant
Yes 31/74 41.9 (30.5, 53.9)
No 8/43 18.6 (8.4, 33.4)
Response to last checkpoint inhibitor
Relapse 12/33 36.4 (20.4, 54.9)
Refractory 23/71 32.4 (21.8, 44.5)
0 20 40 60 80 100
CRR (%)

Figure 4. Mean (SE) change from baseline for (A) EQ-5D-5L VAS score and B) FACT-Lym lymphoma subscale in the PRO population.

A.



B.