Exploratory Analysis of Factors Influencing Efficacy and Safety of Camidanlumab Tesirine: Data From the Open-Label, Multicenter, Phase 2 Study of Patients With Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL)

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INTRODUCTION

- Despite most patients with classical Hodgkin lymphoma (cHL) being cured with standard therapies, a proportion of patients are refractory or relapse after first- and second-line treatments, including stem cell transplantation. Treatment options are limited after failure of brentuximab vedotin (BV) and programmed cell death protein 1 (PD-1) blockade.
- Camidanlumab tesirine (Cami) is an antibody-drug conjugate comprising an anti-CD25 monoclonal antibody conjugated through a cleavable linker to a pyrrolobenzodiazepine (PBD) dimer cytotoxin.
- Cami has shown notable single-agent antitumor activity and manageable toxicity in the phase 2 study of patients with relapsed/refractory (R/R) cHL.[1]

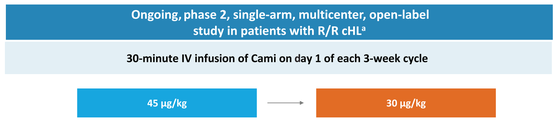
OBJECTIVE

To assess the clinical response and safety of Cami in subgroups of patients enrolled in the phase 2 study based on demographics, known risk factors affecting outcomes in patients with R/R cHL, and factors with potential relevance to the mechanism of action of Cami.

METHODS

- This analysis was based on the open-label, multicenter, phase 2 study of Cami monotherapy in patients with R/R cHL after ≥3 prior lines of therapy (NCT04052997).
- Cami was administered (30-minute infusion) on day 1 of each 3-week cycle at 45 µg/kg for 2 cycles and then 30 µg/kg for subsequent cycles (**Figure 1**).
- Efficacy outcomes included the overall response rate (ORR) and median duration of response (mDOR); statistical significance was assessed by comparison of 95% confidence intervals (CIs).
  - The 95% CI for ORR was based on an exact (Clopper–Pearson) method; the mDOR was estimated using the Kaplan–Meier method.
- Safety was assessed by incidence of treatment-emergent adverse events (TEAEs).

Figure 1. Cami ADCT-301-201 study design



[a]Primary analyses of efficacy and safety in the all-treated population, defined as all patients who received ≥1 dose of Cami; [b]Or until discontinuation due to disease progression, unacceptable toxicity, or other reasons. Patients deriving clinical benefit at 1 year may be able to continue treatment on a case-by-case basis.

Cami, camidanlumab tesirine; cHL, classical Hodgkin lymphoma; IV, intravenous; R/R, relapsed or refractory.

- Key eligibility criteria are listed in **Table 1**.
- Primary endpoint: ORR (per 2014 Lugano classification) assessed by central review.
- Secondary endpoints: duration of response (DOR), progression-free survival (PFS), and safety (frequency and severity of adverse events).

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Male or female • ≥18 years (≥16 years in the United States) • Pathologic diagnosis of cHL • Patients with R/R cHL who received ≥3 prior lines of systemic therapy (or ≥2 lines if ineligible for HSCT) • Prior treatment with BV and PD-1 blockade therapy • Measurable disease (2014 Lugano classification) • Eastern Cooperative Oncology Group performance status score of 0-2 • Adequate organ function	• Allogeneic/autologous HSCT ≤60 days before start of Cami treatment • History of neuropathy considered of autoimmune origin (eg, polyradiculopathy including GBS and myasthenia gravis) or other CNS autoimmune disease, such as poliomyelitis or MS • Recent infection (<4 weeks of cycle 1, day 1) considered caused by prespecified pathogens • HIV, HBV, or HCV infection needing antiviral therapy/prophylaxis • Clinically significant third-space fluid accumulation (ie, ascites requiring drainage or pleural effusion requiring drainage or associated with shortness of breath)

BV, brentuximab vedotin; Cami, camidanlumab tesirine; cHL, classical Hodgkin lymphoma; CNS, central nervous system; GBS, Guillain–Barré syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; MS, multiple sclerosis; PD-1, programmed cell death protein 1; R/R, relapsed or refractory.

- Subgroup analyses were conducted based on demographics, known risk factors affecting outcomes in patients with R/R cHL, and factors with potential relevance to the mechanism of action of Cami (**Table 2**).
- Additional exploratory analyses were conducted to try identifying factors associated with Guillain–Barré syndrome (GBS)/polyradiculopathy observed in some cHL patients treated with Cami:
  - A machine learning-based retrospective exploratory analysis integrating laboratory, biomarkers, exposure, and clinical and demographic data was conducted in cHL patients to identify potential predictors of GBS/polyradiculopathy using a combined dataset from the phase 1 study in lymphoma ADCT-301-001 and phase 2 study ADCT-301-201.
    - This analysis was based on 194 patients in total, of which 13 developed GBS/polyradiculopathy: 7 female and 6 male patients, with a median age (range) of 37 (20-68) years.
    - A negative association between GBS/polyradiculopathy and baseline lactate dehydrogenase (LDH) levels was found.
  - Following the observation for LDH, a more focused exploratory analysis, integrating a smaller number of variables, was performed to identify a potential model that could predict a subgroup of patients with more elevated risk of developing GBS/polyradiculopathy.
    - This new analysis used receiver operating characteristic (ROC) curves and a linear model integrating baseline levels of LDH, sCD25, and 7 cytokines (IL-2, IL-4, IL-6, IL-8, IL-10, IFNγ, and TNFα).
    - The analysis was based on the 184 cHL patients (out of the 194 of the original analysis) that had values for all the variables mentioned above in the data set used. For this reason and because of the lack of an independent validation cohort, resulting models could be overfitted.
- As of January 29, 2021, enrollment was complete (N = 117), and the data cutoff was March 16, 2022.

RESULTS

EFFICACY

- No significant differences were noted in primary efficacy outcomes among subgroups for patients enrolled in the phase 2 study.
- No significant differences were noted in efficacy outcomes between demographic subgroups based on age or sex (**Table 2**).
  - The ORR was similar for patients who were refractory or relapsed after first-line therapy (72.4% vs 72.2%).
  - Despite the higher number of patients who were refractory after last-line therapy versus patients who relapsed, the ORR was not significantly different between the two groups (68.2% vs 78.4%).
- Response to Cami did not depend on the prior response to PD-1 inhibition or the time since the last PD-1 inhibitor use.
  - The ORR was similar for patients who were refractory to PD-1 inhibition or relapsed (66.2% vs 75.8%) and for patients who were treated with Cami ≤4 months and >4 months since the last PD-1 inhibitor (69.0% vs 71.7%).
- No significant differences in the ORR were observed based on the number of prior lines of therapy, prior hematopoietic stem cell transplantation (HSCT), or region.
  - However, the complete response rate (CRR) for patients who received prior HSCT was 41.9% vs 18.6% in patients without HSCT; the mDOR was 13.73 months in patients with prior HSCT versus 5.85 months in patients without prior HSCT.
- Median DOR was similar between North American (NA) and European (EU) patients (13.77 vs 13.73 months).
  - However, NA patients had higher CRR than EU patients (44.6% vs 23%), and differences were more pronounced in NA versus EU patients with prior HSCT (52.4% vs 28.1%).

Table 2. Subgroups and corresponding overall response rates

Subgroup	Patients, n	Overall response rate (CR+PR) (95% CI)	Complete response rate (CR) (95% CI)
Region			
North America	56	75.0 (61.6, 85.6)	44.6 (31.3, 58.5)
Europe	61	65.6 (52.3, 77.3)	23.0 (13.2, 35.5)
Age			
<50 years	82	70.7 (59.6, 80.3)	34.1 (24.0, 45.4)
≥50 years	35	68.6 (50.7, 83.1)	31.4 (16.9, 49.3)
Sex			
Female	44	79.5 (64.7, 90.2)	29.5 (16.8, 45.2)
Male	73	64.4 (52.3, 75.3)	35.6 (24.7, 47.7)
Disease stage			
I-II	25	84.0 (63.9, 95.5)	28.0 (12.1, 49.4)
III-IV	91	67.0 (56.4, 76.5)	35.2 (25.4, 45.9)
Extranodal involvement			
Yes	51	68.6 (54.1, 80.9)	33.3 (20.8, 47.9)
No	66	71.2 (58.7, 81.7)	33.3 (22.2, 46.0)
Number of prior systemic therapies			
≤5 lines	46	69.6 (54.2, 82.3)	23.9 (12.6, 38.8)
6-7 lines	31	67.7 (48.6, 83.3)	41.9 (24.5, 60.9)
≥8 lines	40	72.5 (56.1, 85.4)	37.5 (22.7, 54.2)
Response to first-line systemic therapies			
Refractory	29	72.4 (52.8, 87.3)	34.5 (17.9, 54.3)
Relapse	79	72.2 (60.9, 81.7)	32.9 (22.7, 44.4)
Response to last-line systemic therapies			
Refractory	66	68.2 (55.6, 79.1)	33.3 (22.2, 46.0)
Relapse	37	78.4 (61.8, 90.2)	37.8 (22.5, 55.2)
Prior HSCT			
Yes	74	74.3 (62.8, 83.8)	41.9 (30.5, 53.9)
No	43	62.8 (46.7, 77.0)	18.6 (8.4, 33.4)
Region by prior HSCT			
North America with HSCT	42	76.2 (60.5, 87.9)	52.4 (36.4, 68.0)
North America without HSCT	14	71.4 (41.9, 91.6)	21.4 (4.7, 50.8)
Europe with HSCT	32	71.9 (53.3, 86.3)	28.1 (13.7, 46.7)
Europe without HSCT	29	58.6 (38.9, 76.5)	17.2 (5.8, 35.8)
Response to last PD-1 inhibitor			
Refractory	71	66.2 (54.0, 77.0)	32.4 (21.8, 44.5)
Relapse	33	75.8 (57.7, 88.9)	36.4 (20.4, 54.9)
Time from last PD-1 inhibitor			
≤4 months	58	69.0 (55.5, 80.5)	32.8 (21.0, 46.3)
>4 months	53	71.7 (57.7, 83.2)	32.1 (19.9, 46.3)

Relapse was defined as the best overall response (BOR) of a complete or partial response (CR/PR), refractory was defined as stable or progressive disease (SD/PD), and other was defined as not evaluable (NE)/missing.
CR, complete response; HSCT, hematopoietic stem cell transplantation; PD-1, programmed cell death protein 1; PR, partial response.

SAFETY

- The tolerability of Cami was similar across most subgroups.
  - A similar incidence of TEAEs overall, grade ≥3 TEAEs, and groupings by system organ class was reported in older (≥50 years) compared with younger (<50 years) patients (**Table 3**).
  - The incidence of any grade TEAEs was similar between NA and EU patients (100% vs 98.4%). Patients with prior HSCT had more grade ≥3 TEAEs versus those without prior HSCT (73% vs 58.1%).

Table 3. Subgroups and corresponding treatment-emergent adverse events

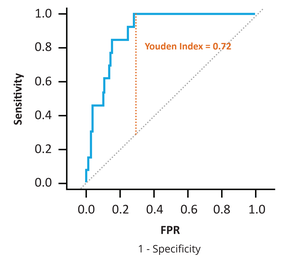
Subgroup	Patients, n	All-grade TEAEs (%)	Grade ≥3 TEAEs (%)
Region			
North America	56	56 (100)	40 (71.4)
Europe	61	60 (98.4)	39 (63.9)
Age			
<50 years	82	81 (98.8)	54 (65.9)
≥50 years	35	35 (100)	25 (71.4)
Sex			
Female	44	43 (97.7)	25 (56.8)
Male	73	73 (100)	54 (74.0)
Prior HSCT			
Yes	74	73 (98.6)	54 (73.0)
No	43	43 (100)	25 (58.1)

HSCT, hematopoietic stem cell transplantation; TEAE, treatment-emergent adverse event.

EXPLORATORY ANALYSES

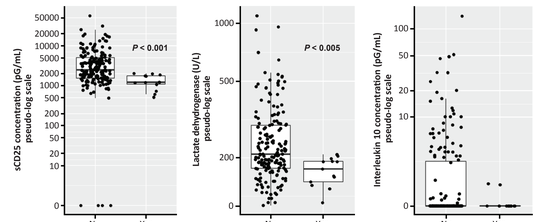
- The focused exploratory analysis based on a smaller number of variables and using ROC curves and linear models showed that the model integrating patient baseline LDH, IL-10, and sCD25 levels had the best area under the curve (AUC) of 0.90 (**Figure 2**).
- At the model cutoff corresponding to the Youden index, the following were noted (**Figure 2**):
  - The model would correctly predict all GBS/polyradiculopathy–affected patients (true positives) with 100% sensitivity and, importantly, would not select any false negatives (patients predicted negative who instead developed GBS) (**Table 4**).
  - In the patient group with no GBS/polyradiculopathy, the cutoff would predict 48/184 false positives (predicted GBS when absent) and 123/184 true negatives (predicted no GBS when absent).
- The separate box plots of sCD25, LDH, and IL-10 demonstrate that individual markers do not effectively differentiate patients with GBS/polyradiculopathy from the others (**Figure 3**).
- Considering potential model overfitting and that, because of the small number of GBS/polyradiculopathy cases (n = 13), all available data were used as a training cohort, a validation in an independent cohort is needed in order to confirm model predictivity.

Figure 2. ROC analysis for GBS prediction



AUC = 0.90; sensitivity = 100%; and specificity = 72%.
FPR, false positive rate; GBS, Guillain–Barré syndrome; ROC, receiver operating characteristic. ADCT-301-001 final database lock of March 31, 2020; ADCT-301-201 data cutoff of March 16, 2022 (data transfer April 20, 2022).

Figure 3. Boxplots of individual model biomarkers



GBS, Guillain–Barré syndrome; sCD25, soluble CD25.

Table 4. Model performance for exploratory biomarker analysis

	Patients who developed GBS/polyradiculopathy	Patients who did NOT develop GBS/polyradiculopathy
Predicted GBS/polyradiculopathy	13 (true positives)	48 (false positives)
No predicted GBS/polyradiculopathy	0 (false negatives)	123 (true negatives)

GBS, Guillain–Barré syndrome.

CONCLUSIONS

- Evidence from preliminary subgroup analyses suggests that the response to Cami was independent of age, sex, and response to and timing of the last PD-1 inhibitor.
- Differences in the safety and efficacy of Cami were noted by prior transplant and region.
  - Although a difference in CRR was observed between NA and EU, this did not result in a meaningful difference in mDOR or ORR between the two regions.
- These preliminary analyses should be interpreted with caution as subgroups were small and limited in statistical comparison.
- Retrospective exploratory analyses identified a potential predictive model based on baseline levels of LDH, sCD25, and IL-10, which might help identify patients more at risk of developing GBS/polyradiculopathy when treated with Cami.
  - If the model is successfully validated in an independent cohort, it might represent an aid to identify a subset of patients with increased risk of developing GBS/polyradiculopathy to be monitored more closely during Cami treatment.
- These results suggest that Cami shows antitumor activity across patient subgroups, including heavily pretreated and older patients.

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References

1. Carlo-Stella C, et al. *HemaSphere*. 2022;6:102-103.

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