Camidanlumab tesirine efficacy and safety in an open-label, multicenter, Phase 2 study of patients with relapsed or refractory classical Hodgkin lymphoma (R/R cHL)

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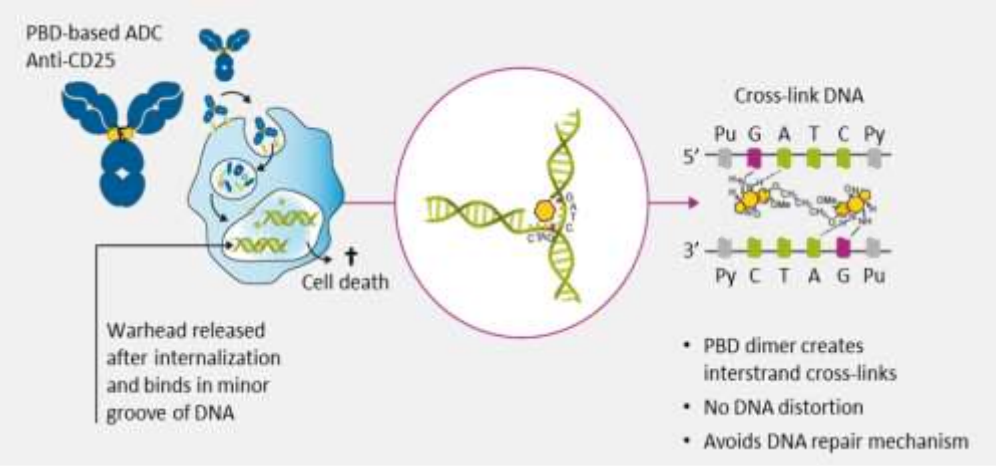
Introduction

Limited therapeutic options are available for patients with R/R cHL who are unresponsive to, or whose disease progresses after, BV and PD-1 blockade therapy.[1–5] Novel treatments are required to address this unmet need

Camidanlumab tesirine (Cami) is an Ab-drug conjugate comprising a human IgG1 anti-CD25 monoclonal Ab conjugated to a potent PBD dimer warhead[6]



Treatment with Cami demonstrated encouraging antitumor activity and manageable toxicity:

- In a Phase 1 trial that included patients with R/R cHL who received Cami at a dose of 45 µg/kg and achieved an overall response rate (ORR; CR + PR) of 86.5%[7]
- In the initial findings of this Phase 2 study of patients with R/R cHL, who achieved an ORR of 83.0%[8]

Here, we present preliminary results from this Phase 2 study of patients with R/R cHL (NCT04052997) after meeting target enrollment (100 patients)

1. Mehta-Shah N, et al. *Blood* 2018;131:1698–1703; 2. Mottok A, et al. *Blood* 2018;131:1654–1665; 3. Glimelius I, et al. *J Intern Med* 2017;281:247–260; 4. Eichenauer DA, et al. *Ann Oncol* 2018;29:iv19–29; 5. Shanbhag S, et al. *CA Cancer J Clin* 2018;68:116–132; 6. Flynn MJ, et al. *Mol Cancer Ther* 2016;15;2709–2721; 7. Hamadani M, et al. *Lancet Haematol* 2021;8(6):e433-e445 [doi:10.1016/S2352-3026(21)00103-4, Epub May 25, 2021]; 8. Herrera A, et al. Oral presentation, ASH Virtual Meeting, Dec 5–8, 2020 [data cut-off Aug 24, 2020; initial findings reported with target recruitment almost 50% complete].
Ab, antibody; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; Ig, immunoglobulin; PBD, pyrrolobenzodiazepine; PD-1, programmed cell death protein 1; R/R, relapsed or refractory.

Study Design

Ongoing, Phase 2, single-arm, multicenter, open-label study in patients with R/R cHL[a]

30-minute IV infusion of Cami on Day 1 of each 3-week cycle

[a] Safety analysis set comprises all patients who received ≥1 dose of Cami; efficacy analysis set comprises patients who started treatment ≥12 weeks before data cut-off (Mar 26, 2021) or with ≥2 post-baseline disease assessments, or who died before the second disease assessment; [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.
cHL, classical Hodgkin lymphoma; IV, intravenous; R/R, relapsed or refractory.

Key Study Endpoints

Primary endpoint	Efficacy of single-agent Cami by ORR (per 2014 Lugano classification; complete + partial response) assessed by central review
Secondary endpoint	Duration of response[a], progression-free survival[b], and proportion of patients who receive hematopoietic stem cell transplantation
	Safety per frequency and severity of adverse events

[a] Defined as time from first documentation of tumor response to disease progression or death; [b] Defined as time from first dose of study drug until first date of either disease progression or death due to any cause.
ORR, overall response rate.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Male or female
- ≥18 years (≥16 years in US)
- Pathologic diagnosis of cHL
- Patients with R/R cHL who received ≥3 prior systemic therapy lines (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

Exclusion Criteria

- Previous Cami treatment
- Hypersensitive to or positive serum for ADA to CD25 antibody
- Allogeneic/autologous HSCT ≤60 days before start of Cami treatment
- History of neuropathy considered of autoimmune origin (e.g., 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 pre-specified pathogens
- HIV, HBV, or HCV infection needing antiviral therapy/prophylaxis
- Clinically significant third-space fluid accumulation (i.e., ascites requiring drainage, or pleural effusion requiring drainage or associated with shortness of breath)

ADA, anti-drug antibody; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; 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.

Baseline Characteristics

Characteristic		Total (N=117)
Sex, n (%)	Male	73 (62.4)
	Female	44 (37.6)
Age, years, median (min, max)		37 (19, 87)
Histology, n (%)	Nodular sclerosis cHL	91 (77.8)
	Other/unknown/not evaluable[a]	26 (22.2)
ECOG status, n (%)	0	63 (53.8)
	1	48 (41.0)
	2	6 (5.1)
No. prior systemic therapies[b], median (range)		6 (3–19)
Prior BV and PD-1 blockade, n (%)	BV	116 (99.1)
	PD-1 blockade therapy	117 (100)
	BV and PD-1 blockade therapy	116 (99.1)[c]
Prior HSCT, n (%)	Autologous	58 (49.6)
	Allogeneic	3 (2.6)
	Both	12 (10.3)
No. of cycles, mean (SD)		4.6 (2.5)
Disease status after first-line systemic therapy, n (%)	Relapsed	77 (65.8)
	Refractory	29 (24.8)
	Other[d]	11 (9.4)
Disease status after last-line systemic therapy, n (%)	Relapsed	38 (32.5)
	Refractory	66 (56.4)
	Other[d]	13 (11.1)

At data cut-off (Mar 26, 2021):

No. of patients enrolled
117

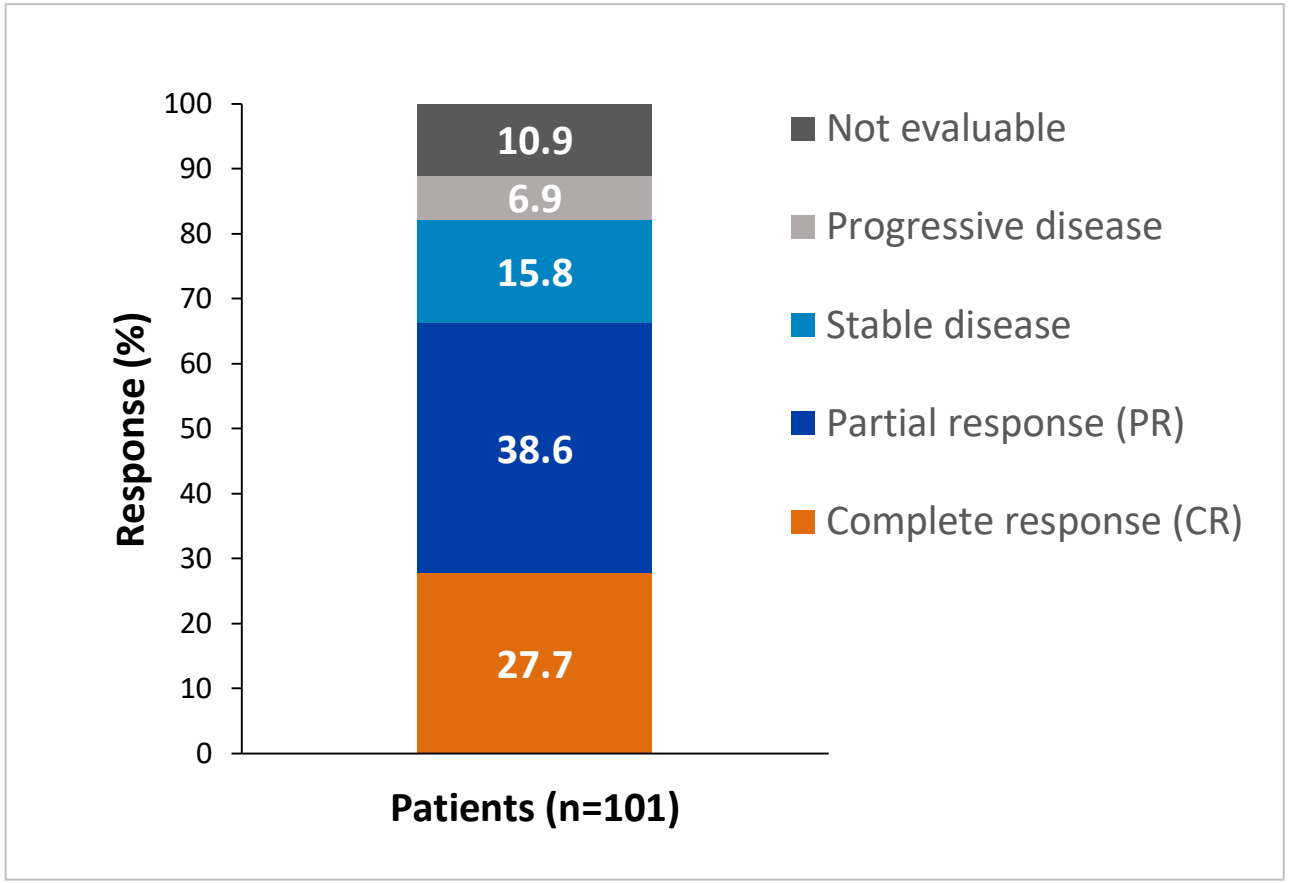
Mean (SD) No. of cycles
4.6 (2.5)

Heavily pre-treated patients; median (range) prior lines of systemic therapy
6 (3–19)

No. of patients with prior brentuximab vedotin and PD-1 blockade therapy
116 (99.1%)[c]

[a] Includes mixed cellularity and lymphocyte-rich cHL (n=11), cHL subtype not specified (n=1) or unknown (n=12), cHL Epstein-Barr virus-associated (n=1), and missing (n=1); [b] Includes prior HSCT; [c] One patient did not receive BV owing to a protocol deviation; [d] Missing or not evaluable.
BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; PD-1, programmed cell death protein 1; SD, standard deviation.

Overall Response Rate[a]



ORR (CR + PR)
66.3% (67/101)
95% CI: 56.2, 75.4

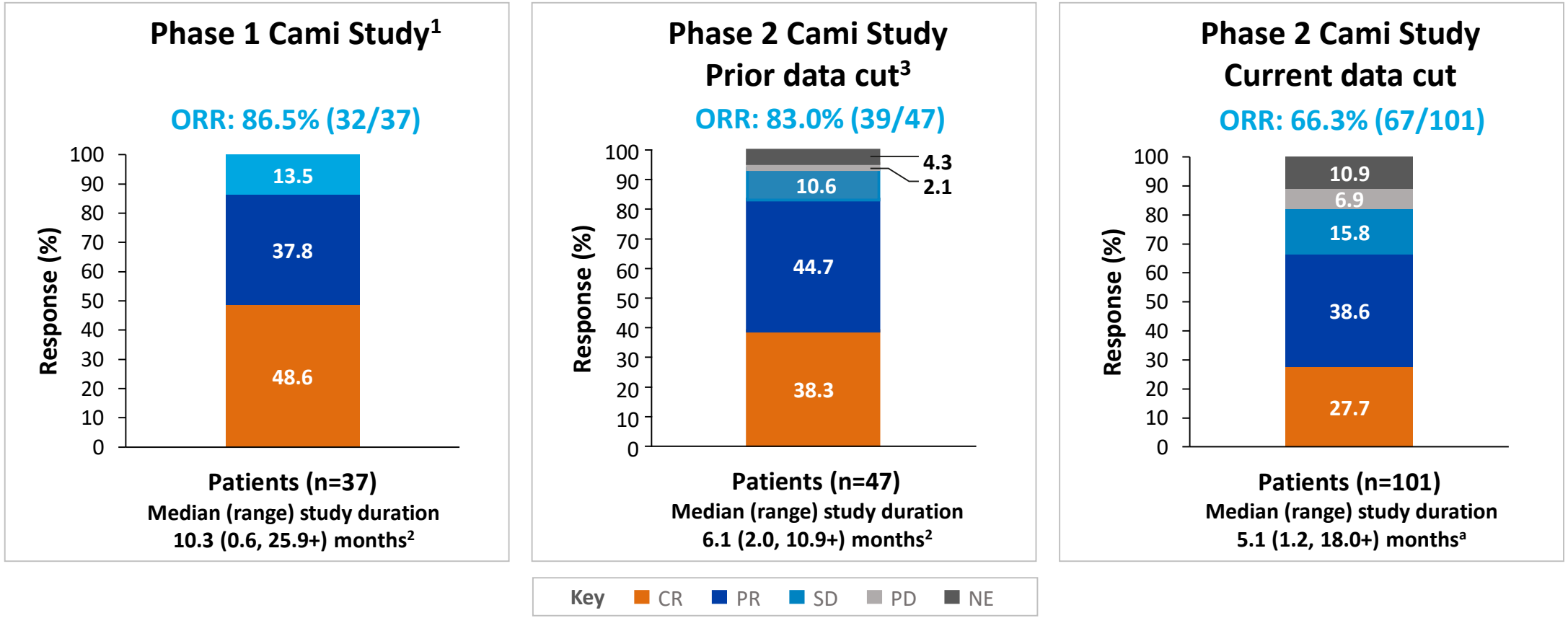
No. of patients with CR
28 (27.7%)

No. of patients with PR
39 (38.6%)

No. of patients reporting HSCT as reason for discontinuation
9 (7.7%)[b]

[a] Per central review. Efficacy analysis set (n=101) defined as patients with ≥12 weeks of follow-up since first dose or ≥2 post-baseline disease assessments, or who died prior to their second disease assessment. Five (5.0%) patients died prior to second disease assessment: 2 of whom did not have a scan/new anticancer therapy; 1 who had no scan following new anticancer therapy, 1 who had no second scan/new anticancer therapy, and 1 who had no second scan following new anticancer therapy; [b] Of these 9 patients, 1 died due to disease progression (1 year post haploidentical transplant) and 8 were alive and being followed-up at the time of data cut-off. CI, confidence interval; HSCT, hematopoietic stem cell transplantation; ORR, overall response rate.

Results in Context with Prior Analyses

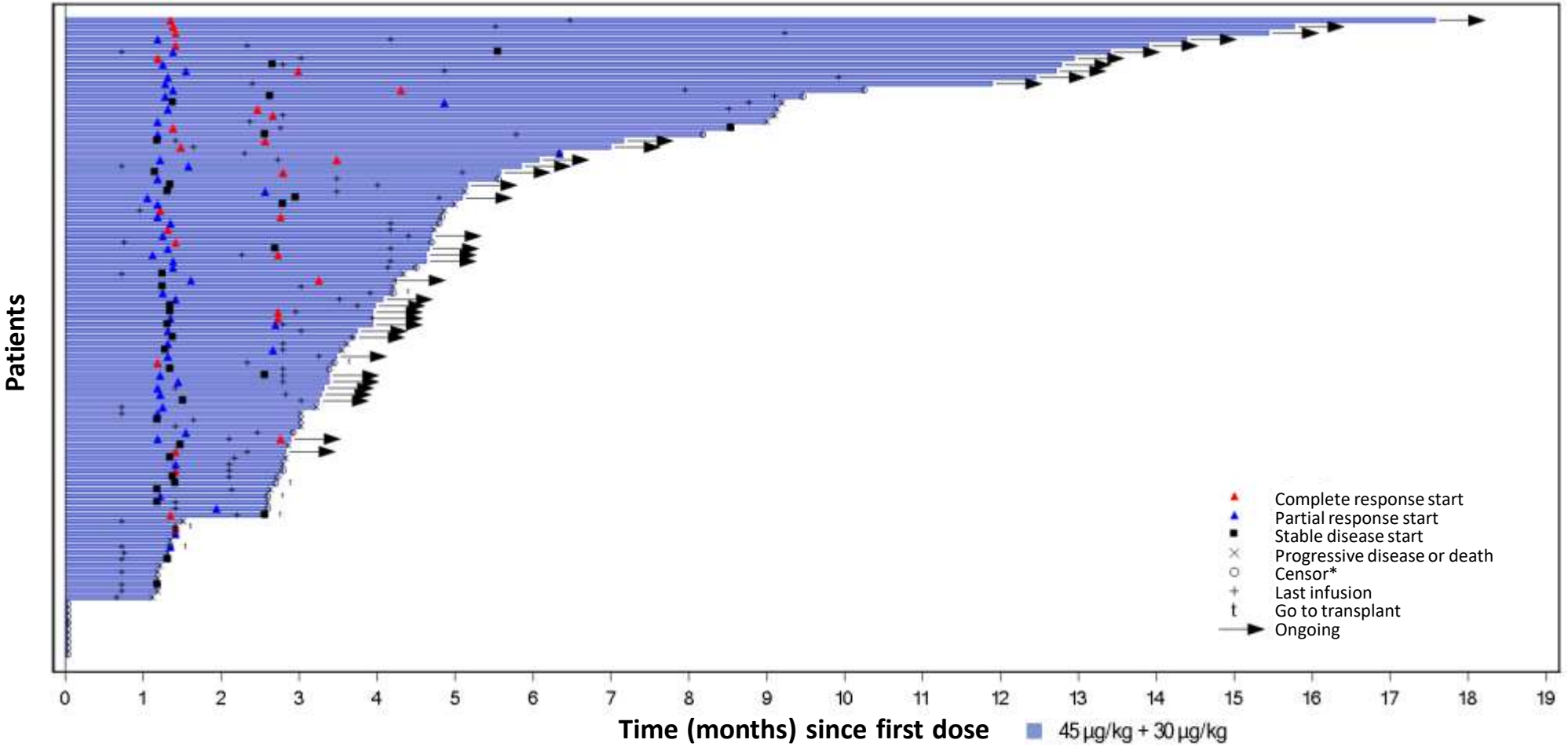


[a] Versus the Phase 1 study and prior data cut of this Phase 2 study, median study duration is shorter. Potential reasons include patient enrollment in this data cut having an unusual distribution; likely due to a prior enrollment pause that, when lifted, meant many patients enrolled, impacting median duration (calculated using each patient's individual study duration).

1. Hamadani M, et al. *Lancet Haematol* 2021;8(6):e433-e445 [doi:10.1016/S2352-3026(21)00103-4, Epub May 25, 2021]; for data shown, patients with R/R cHL received Cami 45 µg/kg Q3W; 2. Data on file, ADCT Therapeutics 2021; 3. Originally presented at the 62nd ASH Annual Meeting and Exposition Virtual Meeting, Dec 5–8, 2020, by Herrera A, et al. *Preliminary Results of a Phase 2 Study of Camidanlumab Tesirine (Cami), a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients With Relapsed or Refractory Hodgkin Lymphoma*. © American Society of Hematology. Patients received 45 µg/kg Q3W for first 2 cycles, then 30 µg/kg for subsequent cycles; data cut-off Aug 24, 2020.

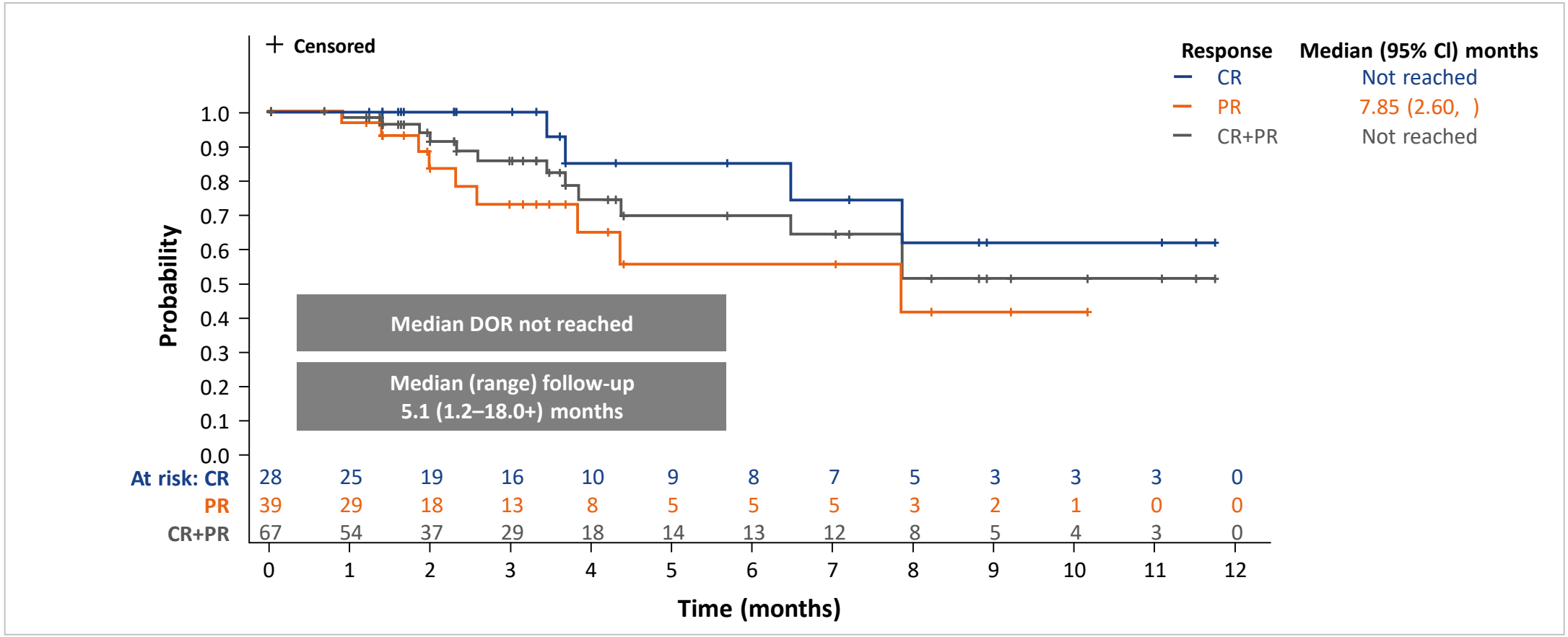
+ denotes censored (study duration was calculated from first dose date to end of study visit for completed patients or to data cut-off date for ongoing patients); CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease.

A Significant Number of Patients Experience Long-lasting Treatment Effects



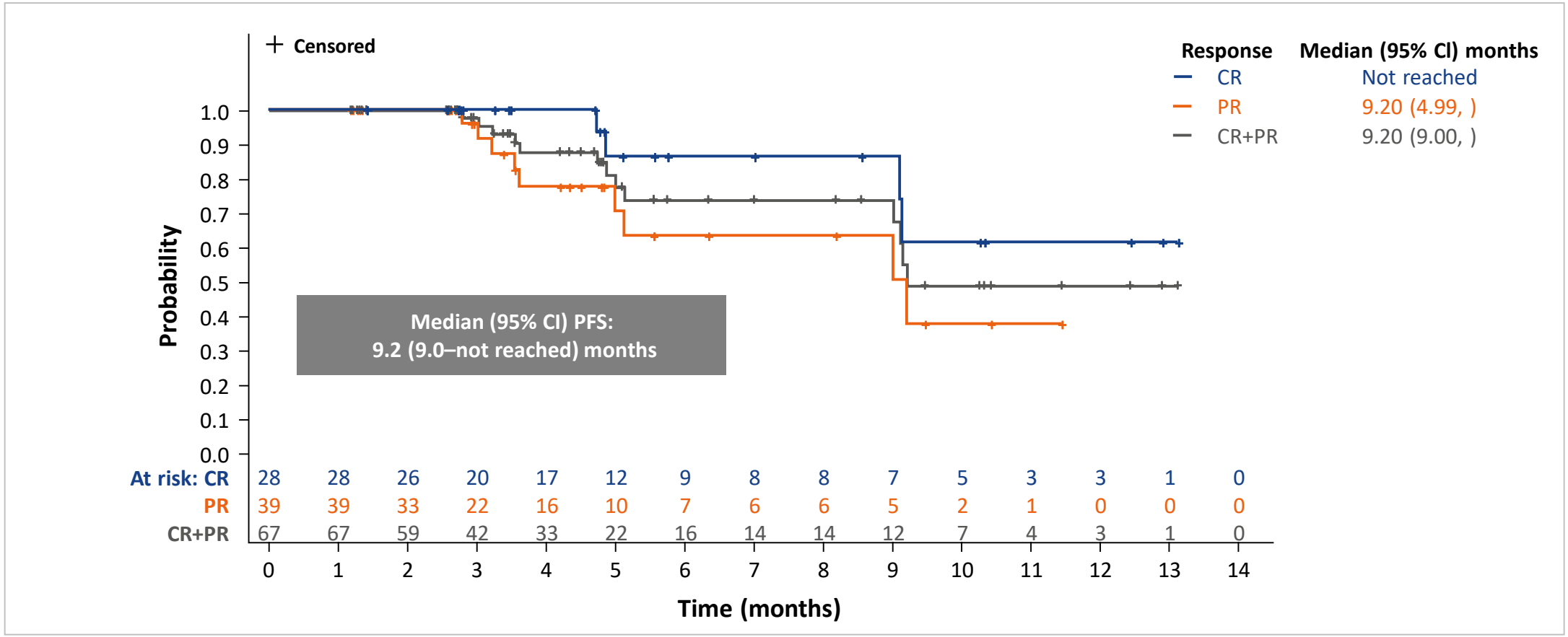
Each bar represents one patient in the study. Response is determined by independent reviewer. Efficacy analysis set includes patients who started treatment at least 12 weeks before data cut-off date or with at least two post-baseline disease assessment results from independent reviewer or death prior to the second scheduled disease assessment according to protocol schedule.
* Only for censored patients who discontinued the study due to reasons other than progression, or who went on to a different anticancer treatment other than transplant, or who are ongoing but have no disease assessment yet.

Duration of Response



No. of events: CR, n=4; PR, n=9; CR+PR, n=13. Efficacy analysis (n=101) set defined as patients with ≥12 weeks of follow-up since first dose or ≥2 post-baseline disease assessments or who died prior to their second disease assessment.
CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response.

Progression-free Survival



No. of events: CR, n=4; PR, n=9; CR+PR, n=13. Efficacy analysis set (n=101) defined as patients with ≥12 weeks of follow-up since first dose or ≥2 post-baseline disease assessments or who died prior to their second disease assessment.
CI, confidence interval; CR, complete response; DOR, duration of response; PFS, progression-free survival; PR, partial response.

Most Common TEAEs

All-grade TEAEs in ≥20% of patients	Total (N=117)
Any TEAE of any grade	116 (99.1)
Fatigue	43 (36.8)
Maculopapular rash	33 (28.2)
Nausea	32 (27.4)
Pyrexia	31 (26.5)
Anemia	24 (20.5)

Grade ≥3 TEAEs in ≥5% of patients	Total (N=117)
Any TEAE Grade ≥3	62 (53.0)
Hypophosphatemia	9 (7.7)
Maculopapular rash	8 (6.8)
Thrombocytopenia	8 (6.8)
Anemia	7 (6.0)
Lymphopenia	7 (6.0)

All-grade TEAEs leading to dose delay, reduction or discontinuation	Total (N=117)
Dose delay or reduction	56 (47.9)
Discontinuation	16 (13.7)

TEAE, treatment-emergent adverse event.

PBD-associated TEAEs and Fatal TEAEs

Categories of TEAEs considered PBD-associated

- Skin reactions/nail disorders in 76 (65.0%) patients[a]
- Liver function test abnormalities in 31 (26.5%) patients
- Edema or effusion in 14 (12.0%) patients

Fatal TEAEs

- Three patients (2.6%) had a fatal TEAE:
  - Myocardial infarction in 1 (0.9%) patient, considered not related to treatment
  - Respiratory failure in 1 (0.9%) patient, considered unlikely related to treatment
  - Adenovirus infection in 1 (0.9%) patient, considered unlikely related to treatment

[a] For Skin reactions/nail disorders category: Grade 1: n=30 (25.6%); Grade 2: n=26 (22.2%); Grade 3: n=19 (16.2%); Grade 4: n=1 (0.9%); Grade 5: n=0.
GBS, Guillain-Barré syndrome; PBD, pyrrolobenzodiazepine; TEAE, treatment-emergent adverse event.

GBS/Polyradiculopathy

Total: 7/117 (6.0%) patients. All events were deemed related or probably related to treatment

AE by preferred term	Study day event start–stop	Max grade	Grade at last assessment	Outcome at last assessment
Radiculopathy	Days 41–206	2	-	Recovered/resolved
GBS	Days 164–283	2	-	Recovered/resolved
GBS	Day 48–ongoing[b]	3	2	Not recovered/not resolved
Polyneuropathy (assessed as polyradiculopathy by Sponsor)[a]	Day 64–ongoing[b]	3	3	Recovering/resolving
GBS	Day 137–ongoing[b]	3	3	Not recovered/not resolved
GBS	Day 24–ongoing[b]	4	3	Not recovered/not resolved
GBS	Day 101–ongoing[b]	4	4	Not recovered/not resolved

[a] Additional events reported in the same patient included Grade 3 meningitis aseptic, which was recovering/resolving at last assessment; Grade 3 facial paralysis, not recovered/not resolved; and Grade 4 inappropriate antidiuretic hormone secretion, which recovered/resolved; all 3 events were considered related to treatment; [b] At last assessment prior to data cut-off.
AE, adverse event; GBS, Guillain-Barré syndrome.

Conclusions

Favorable ORR	In this Phase 2 study of heavily pre-treated patients with R/R cHL post BV and PD-1 blockade failure, preliminary data show Cami demonstrated a favorable ORR of 66.3%, with a CRR of 27.7%. ORR data continue to mature
Encouraging DOR	Patient DOR was encouraging; median DOR was not reached Time-to-event data continue to mature
Safety consistent with prior assessments	No new safety signals were identified; safety profile remains consistent with prior findings[1–3]
Management of GBS/polyradiculopathy	GBS/polyradiculopathy remains a concern and warrants swift counter-measures, such as intravenous Ig, plasma exchange, and/or high-dose steroids[4]

1. Collins G, et al. Oral presentation, ICML, Lugano, Switzerland, Jun 18–22, 2019; 2. Herrera A, et al. Oral presentation, ASH Virtual Meeting, Dec 5–8, 2020; 3. Hamadani M, et al. *Lancet Haematol* 2021;8(6):e433-e445 [doi:10.1016/S2352-3026(21)00103-4, Epub May 25, 2021]; 4. Haanen JBAG, et al. *Ann Oncol* 2017;28(Suppl. 4): i119–i142.
AE, adverse event; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CRR, complete response rate; DOR, duration of response; GBS, Guillain-Barré syndrome; Ig, immunoglobulin; ORR, overall response rate; PD-1, programmed cell death protein 1; R/R, relapsed or refractory.