haematologica
Journal of the Ferrata Storti Foundation

# Anti-CD47 antibody magrolimab with pembrolizumab in patients with relapsed/refractory classic Hodgkin lymphoma

*by Joseph G. Schroers-Martin, Reid Merryman, Michael A. Spinner, Austin Yeung, Cheryl Chang, Chandley Silin, May Powell, Philippe Armand, Margaret Shipp and Ranjana Advani*

*Received: March 20, 2026.*
*Accepted: June 25, 2026.*

*Citation: Joseph G. Schroers-Martin, Reid Merryman, Michael A. Spinner, Austin Yeung, Cheryl Chang, Chandley Silin, May Powell, Philippe Armand, Margaret Shipp and Ranjana Advani. Anti-CD47 antibody magrolimab with pembrolizumab in patients with relapsed/refractory classic Hodgkin lymphoma. Haematologica. 2026 July 2. doi: 10.3324/haematol.2026.300899 [Epub ahead of print]*

# Anti-CD47 antibody magrolimab with pembrolizumab in patients with relapsed / refractory classic Hodgkin lymphoma

Joseph G Schroers-Martin[1], Reid Merryman[2], Michael A. Spinner[3], Austin Yeung[1], Cheryl Chang[4], Chandley Silin[1], May Powell[1], Philippe Armand[2], Margaret Shipp[2], Ranjana Advani[1]

[1] Department of Medicine, Division of Oncology, Stanford University Medical Center, Stanford, CA

[2] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

[3] Division of Hematology/Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA

[4] Duke University, Durham, NC

*Correspondence should be addressed to:
Ranjana Advani
Stanford University, Stanford CA, United States
radvani@stanford.edu

**Running head**: Magrolimab with Pembrolizumab in Hodgkin Lymphoma

**Trial Registration**: ClinicalTrials.gov identifier: NCT04788043

**Data Sharing Statement**: The clinical trial protocol and the data that support the findings of this study are available from the corresponding author upon reasonable request.

**Acknowledgements**

The authors thank the patients, their families, and the investigators who participated in this study. This study was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme LLC, and by Gilead Sciences. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme LLC or Gilead Sciences.

**Contributions**

R.A., M.A.S., and M.S. conceived and designed the overall study; R.A. and all other authors enrolled and treated patients on study; and all authors contributed to writing and editing the manuscript.

**Disclosure of Potential Conflicts of Interest:**

J.S.M.: Consulting: Pierre Fabre, Pfizer, and Navya. Advisory board: Pierre Fabre, Pfizer, Incyte.
R.M.: Consulting: Abbvie. Advisory board: Genmab, Bristol Myers Squibb, Abbvie, Ipsen, KITE, Pfizer, AstraZeneca. Honoraria: Genmab, Abbvie. Institutional research funding: Merck, Bristol Myers Squibb, Genmab, Genentech/Roche.
M.A.S.: Consulting: Gilead/Kite, Pfizer, and Bristol Myers Squibb. Institutional research funding: Pfizer and Allogene Therapeutics.
P.A.: Consulting: Merck, BMS/Celgene, GenMab, Enterome, Genentech/Roche, ATB Therapeutics, Regeneron, Pfizer, Lilly Loxo. Research funding: Kite. Institutional research funding: Merck, BMS/Celgene, Adaptive, Genentech, IGM, Astra Zeneca, Lilly Loxo
M.S.: Consulting: AstraZeneca. Research funding: Bristol-Myers Squibb, Merck, AstraZeneca, Novartis, and Genentech.
R.A.: Consulting: Genentech/Roche, Gilead, and ADCT. Institutional research funding: Genentech/Roche, Gilead, Merck, Millennium, BeiGene, and Seagen Inc

Outcomes remain suboptimal for patients with relapsed/refractory classic Hodgkin lymphoma (R/R cHL) who experience progression after autologous stem cell transplantation (ASCT) or are transplant-ineligible due to age or comorbidities(1). Molecular profiling of Hodgkin Reed-Sternberg (HRS) cells has demonstrated overexpression of the programmed cell death-1 (PD-1) ligands PD-L1 and PD-L2, conferring therapeutic vulnerability to anti-PD-1 checkpoint inhibitors (CPIs)(2). While the overall response rate (ORR) to single agent CPIs in R/R cHL is high (69-87%), complete response rates (CRR) are variable(3-6).

Macrophages are an attractive novel immunotherapeutic target. In the cHL tumor microenvironment, tumor-associated macrophages (TAMs) have been associated with inferior outcomes(7). HRS cells express CD47, limiting macrophage-mediated phagocytosis, and TAMs in proximity to HRS cells express SIRP-alpha, the CD47 ligand(8). Magrolimab, an anti-CD47 monoclonal antibody, impairs macrophage immune evasion by blocking the CD47/SIRP-alpha interaction and has been evaluated in R/R B-cell lymphomas(9).

Together, these findings provide a preclinical rationale for dual targeting of the PD-1/PD-L1 & CD47/SIRP-alpha immune checkpoints. In this phase II trial we assessed the safety & preliminary efficacy of magrolimab with pembrolizumab in R/R cHL.

This was a single arm phase II study (NCT04788043) conducted at two US medical centers. The study protocol and amendments were approved by the institutional review board for each site, and all patients provided written informed consent in accordance with the Declaration of Helsinki. Eligible patients were adults with R/R cHL after ≥2 lines of systemic therapy, ECOG performance status 0-1, and adequate hematopoietic and end organ function. Prior anti-PD-1 immunotherapy was initially permitted if the last dose was administered ≥6 months prior to study enrollment; this window was reduced to ≥3 months in a protocol amendment 11/2023. Prior allogeneic transplantation; active infections; and immunodeficiency, autoimmune disease, or non-infectious pneumonitis requiring corticosteroids within 6 months were excluded.

Patients received magrolimab 1mg/kg priming dose on C1D1, 30mg/kg weekly during C1/C2, then 45mg/kg every 3 weeks from C3. Pembrolizumab was administered at 200mg every 3 weeks in combination with magrolimab. Treatment continued for up to 24 months or until progression of disease, unacceptable toxicity, or planned SCT. The primary outcome was CR rate assessed via positron emission tomography / computed tomography (PET/CT) utilizing the Lugano and LYRIC criteria(10). Key secondary endpoints included safety, tolerability, and the ORR. Exploratory objectives included the duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Safety was continuously assessed per the Common Terminology Criteria for Adverse Events (CTCAE) criteria version 5.

Based on an estimated CRR 18% to CPi monotherapy in historical cohorts of anti-PD-1 naïve and exposed patients with R/R cHL, we hypothesized that magrolimab with pembrolizumab could increase the CRR to 40% (3, 4, 11). Setting a null hypothesis of 18% and an alternative hypothesis of 40%, a sample size of 24 subjects was estimated to provide 80% power with a 1-sided alpha error rate of 0.10. Due to sponsor-mandated study closure before planned accrual, results are reported as observational data. The data cutoff was August 29, 2025.

Eight patients were enrolled prior to the early termination of the study due to the discontinuation of magrolimab clinical development. Patients were 50% female with median age 34 years (range 25-59). At relapse prior to study enrollment, all patients had advanced stage disease, with 75% (n=6) having extranodal involvement of lung or osseous sites. Two patients had bulky disease defined as any site >7.0cm. Details regarding pre-treatment patient characteristics are provided in **Supplementary Table 1**.

Patients had received a median of 2 prior lines of systemic therapy (range 2-18) and most had undergone ASCT (n=7, 87.5%). Overall, 75% of patients (n=6) had previously received a novel agent. Five patients (62.5%) received prior CPi as either a combination regimen (n=3), monotherapy (n=1), or multiple lines (n=1). The median interval from prior CPi to study treatment was 19 months (range 6-34). Two patients were CPi-refractory, defined as disease progression while receiving most recent immunotherapy. Five patients (62.5%) had received brentuximab vedotin (BV). Two patients without novel agent exposure had each received frontline adriamycin, bleomycin, vinblastine, and dacarbazine; followed by salvage ifosfamide, carboplatin, etoposide and ASCT. Details regarding prior treatment and responses for each patient are provided in **Supplementary Table 2**.

A planned interim safety analysis after the first 6 patients were treated found no dose-limiting toxicities. Overall toxicity was predominantly G1-2 (**Table 1**). The class effect of anticipated transient anemia occurred in 75% of patients (n=6, G1-2 62.5%, G3 12.5%). Two patients required RBC transfusions during initial magrolimab loading. Increased alkaline phosphatase, ALT, and bilirubin were common (87.5, 75%, 25% respectively) but typically G1-2. While lymphopenia occurred in most patients (G1 37.5%, G2 50%, G3 25%, G4 12.5%), neutropenia was G≤2 and infectious complications were manageable. These included lung infections treated with outpatient oral antibiotics (n=3, G2), and episodes of shingles (n=1, G2) and otitis externa, upper respiratory infection, and viral gastroenteritis (n=1 for each, all G1).

Therapy was discontinued for 3 patients due to: 1) ongoing pre-existing radiotherapy-related mucositis complicated by G3 aspiration, dysphagia, and esophagitis, 2) G3 hepatotoxicity attributed to pembrolizumab, 3) planned allogeneic SCT after achieving CR. Other G≥3 TRAEs included lymphopenia (n=2) & increased ALT & bilirubin (n=1). There were no fatal AEs, G≥3 infectious AEs, or treatment-related deaths. One patient died off study due to PD.

The ORR was 75% (95% CI 0.41, 0.93; 3 CR, 3 PR) and two patients had stable disease (**Figure 1A**). The median duration of treatment was 7.1 months (range 2.5-18.0), median time to best response was 2.9 months, and the median DOR was 18.3 months. For the full cohort, at a median follow-up of 25.0 months (range 13.0-33.2) the median PFS was 20.7 months (**Figure 1B**) and median OS not reached **(Figure 1C)**.

Among patients with prior PD-1 exposure, the ORR was 60% (95% CI 0.29, 0.85; 1 CR, 2 PR, 2 SD) including responses in patients with bulky disease (**Figure 1D**) and both CPi-refractory patients. Among patients with PR, the median reduction in target lesions from baseline was 81% (**Figure 1E**). At study closure five patients were on active treatment.

Outcomes for cHL patients relapsing post-ASCT remain unsatisfactory. Intensive chemo-immunotherapy combinations evaluated for pre-transplant induction achieve high response rates at the cost of significant toxicity(12). Monotherapy approaches are suitable for longer maintenance, but with lower CR rates(3, 4). Additionally, anti-PD-1 immunotherapy is now a frontline standard of care, and the efficacy of CPi salvage regimens for pre-exposed patients is not fully characterized(13).

There is therefore an unmet need for novel immunotherapy combinations. The combination of magrolimab and pembrolizumab was intended as a rational approach based on preclinical data demonstrating dual dependence of the cHL microenvironment on the PD-1 and CD47 checkpoint axes.

Our results demonstrate excellent tolerability and promising response rates in post-ASCT and CPi-exposed patients. Anticipated anemia after initiation of magrolimab was transient and self-limited. The clinical development of magrolimab was discontinued after a planned interim safety analysis of the ENHANCE-3 study of magrolimab with azacitadine and venetoclax demonstrated an increased risk of death driven by infections and respiratory failure(14). In comparison to the morbidity seen in this highly immunosuppressed population, in our study there was no G≥3 infectious or pulmonary toxicity.

One limitation of our cohort was incomplete prior exposure to novel agents, making the individual contributions of magrolimab and pembrolizumab more difficult to assess. Three patients had not received CPi, and two patients received chemotherapy alone before

ASCT. However, a similar approach was recently explored in a Chinese phase II study of IBI322, an anti-CD47 / anti-PD-L1 bispecific antibody(15). Twenty-four patients with progression after prior anti-PD-1 or anti-PD-L1 immunotherapy were enrolled. The ORR rate was 47.8% with CRR 12.5%, and among primary refractory patients the ORR was 57.1%. Rates of lymphopenia (62.5%, with 29.2% G≥3) and anemia (62.5%) were similar to our study with no treatment-related AEs leading to drug discontinuation or death. These data in exclusively CPi-exposed patients provide further evidence for safety and efficacy.

Our study, although limited by cohort size and partial prior CPi exposure, suggests that dual anti-PD-1 & CD47-directed checkpoint blockade warrants further investigation in R/R cHL. Based on our experience, this combination could be utilized as a bridge to allogeneic transplantation or for maintenance therapy in transplant-ineligible patients.

## References


1. Mehta-Shah N, Bartlett NL. Management of relapsed/refractory classical Hodgkin lymphoma in transplant-ineligible patients. Blood. 2018;131(15):1698-1703.

2. Roemer MG, Redd RA, Cader FZ, et al. Major histocompatibility complex class II and programmed death ligand 1 expression predict outcome after programmed death 1 blockade in classic Hodgkin lymphoma. J Clin Oncol. 2018;36(10):942-950.

3. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from pivotal phase 2 CheckMate 205 study. Blood Adv. 2023;7(20):6266-6274.

4. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy in relapsed/refractory classical Hodgkin lymphoma. Blood. 2023;142(10):878-886.

5. Shi Y, Su H, Song Y, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. Lancet Haematol. 2019;6(1):e12-e19.

6. Song Y, Gao Q, Zhang H, et al. Tislelizumab for relapsed/refractory classical Hodgkin lymphoma: 3-year follow-up and correlative biomarker analysis. Clin Cancer Res. 2022;28(6):1147-1156.

7. Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med. 2010;362(10):875-885.

8. Carey CD, Gusenleitner D, Lipschitz M, et al. Topological analysis reveals a PD-L1-associated microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma. Blood. 2017;130(22):2420-2430.

9. Advani R, Flinn I, Popplewell L, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin’s lymphoma. N Engl J Med. 2018;379(18):1711-1721.

10. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-2496.

11. Manson G, Brice P, Herbaux C, et al. Efficacy of anti-PD1 re-treatment in patients with Hodgkin lymphoma who relapsed after anti-PD1 discontinuation. Haematologica. 2020;105(11):2664-2666.

12. Lynch RC, Cassaday RD, Smith SD, et al. Dose-dense brentuximab vedotin plus ifosfamide, carboplatin, and etoposide for second-line treatment of relapsed or

refractory classical Hodgkin lymphoma: a single centre, phase 1/2 study. Lancet Haematol. 2021;8(8):e562-e571.

13. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+ AVD in advanced-stage classic Hodgkin's lymphoma. N Engl J Med. 2024;391(15):1379-1389.

14. Daver N, Vyas P, Huls G, et al. The ENHANCE-3 study: venetoclax and azacitidine plus magrolimab or placebo for untreated AML unfit for intensive therapy. Blood. 2025;146(5):601-611.

15. Zhang H, Yu J, Li H, et al. Cd47/pd-L1 bispecific antibody (Ibi322) in anti-pd-1 or pd-L1 treatment-resistant classical hodgkin lymphoma: A phase I study. EHA Library. 2023;387916:S216

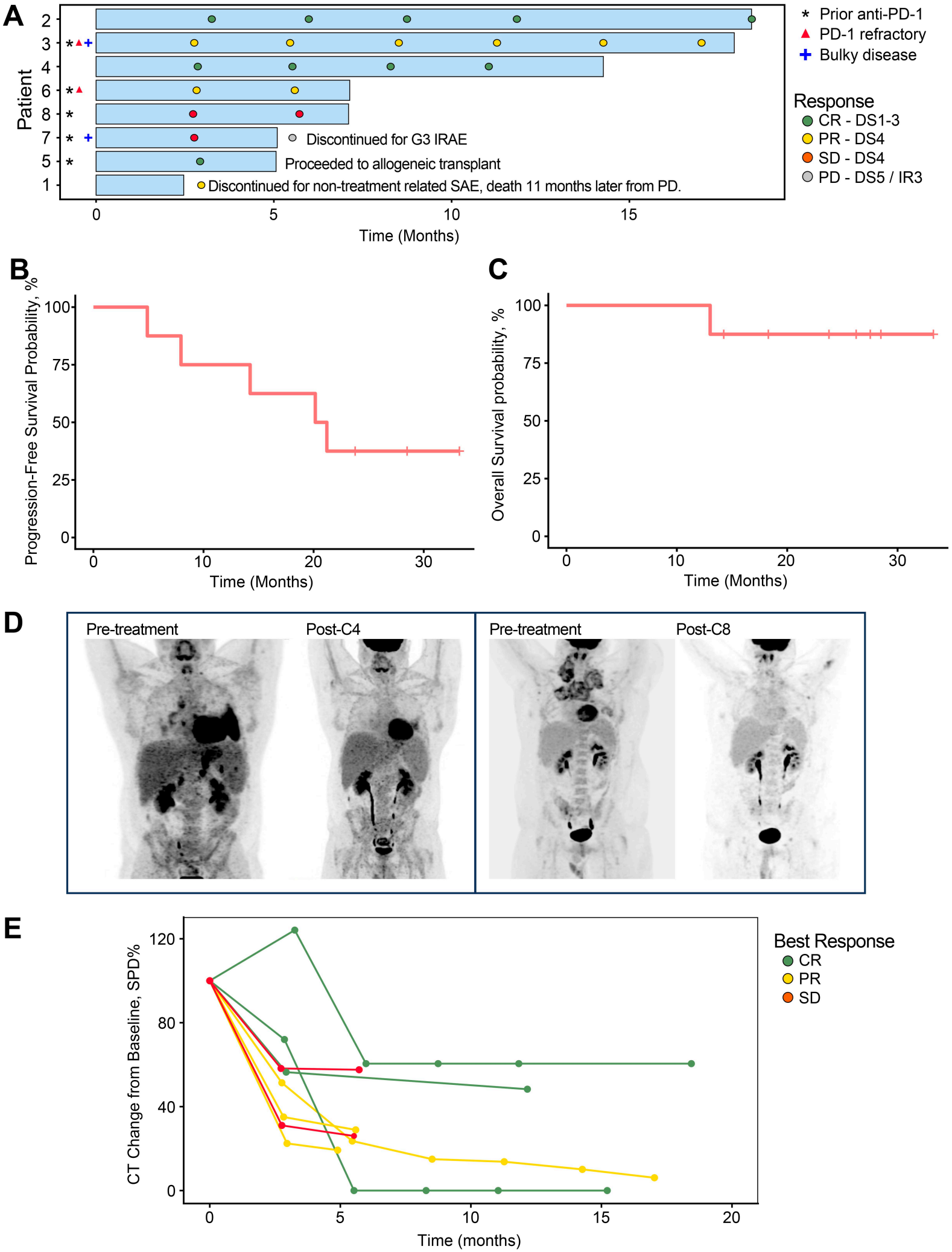
## Tables

**Table 1**. Most common treatment emergent adverse events (TEAEs) by severity in the study population: any grade, >25% incidence or G≥3, any incidence.

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | Patients Affected | Patients Affected | Patients Affected | Patients Affected |
| Alanine Aminotransferase Increased | 6 (75%) | 1 (12.5%) | 1 (12.5%) | 0 |
| Alkaline Phosphatase Increased | 7 (87.5%) | 0 | 0 | 0 |
| Allergic Rhinitis | 4 (50%) | 0 | 0 | 0 |
| Anemia | 5 (62.5%) | 6 (75%) | 1 (12.5%) | 0 |
| Aspartate Aminotransferase Increased | 3 (37.5%) | 1 (12.5%) | 0 | 0 |
| Aspiration, Dysphagia, Esophagitis | 0 | 0 | 1 (12.5%) | 0 |
| Blood Bicarbonate Decreased | 3 (37.5%) | 0 | 0 | 0 |
| Blood Bilirubin Increased | 2 (25%) | 0 | 1 (12.5%) | 0 |
| Chills | 3 (37.5%) | 0 | 0 | 0 |
| Diarrhea | 3 (37.5%) | 0 | 0 | 0 |
| Eosinophilia | 3 (37.5%) | 0 | 0 | 0 |
| Fatigue | 3 (37.5%) | 0 | 0 | 0 |
| Headache | 4 (50%) | 1 (12.5%) | 0 | 0 |
| Hyperglycemia | 7 (87.5%) | 0 | 0 | 0 |
| Hypoalbuminemia | 3 (37.5%) | 0 | 0 | 0 |
| Hyponatremia | 3 (37.5%) | 0 | 0 | 0 |
| Infusion-Related Reaction | 3 (37.5%) | 1 (12.5%) | 0 | 0 |
| Lung Infection | 0 | 3 (37.5%) | 0 | 0 |
| Lymphocyte Count Decreased | 3 (37.5%) | 4 (50%) | 2 (25%) | 1 (12.5%) |
| Mucositis Oral | 1 (12.5%) | 0 | 1 (12.5%) | 0 |
| Nasal Congestion | 3 (37.5%) | 0 | 0 | 0 |
| Nausea | 4 (50%) | 0 | 0 | 0 |
| Neutrophil Count Decreased | 2 (25%) | 2 (25%) | 0 | 0 |
| Platelet Count Decreased | 4 (50%) | 0 | 0 | 0 |
| White Blood Cell Decreased | 5 (62.5%) | 2 (25%) | 0 | 0 |

## Figures

**Figure 1**: Clinical responses and outcomes among patients receiving magrolimab and pembrolizumab. **(A)** Swimmer plot depicting treatment duration and radiographic responses for patients receiving magrolimab and pembrolizumab. **(B)** Kaplan Meier plot depicting progression free survival for patients on study. **(C)** Kaplan Meier plot depicting overall survival for patients on study. **(D)** Exemplary responses in patients with prior anti-PD-1 exposure. Left, complete response (CR, Deauville Score 3) in patient #5. Right, partial response (PR, Deauville Score 4) in patient #3 with bulky disease who had previously progressed on pembrolizumab. **(E)** A spider plot depicts volumetric response (change in sum of product diameters) over time of evaluable patients on treatment.


A
Patient
2
3
4
6
8
7
5
1
Discontinued for G3 IRAE
Proceeded to allogeneic transplant
Discontinued for non-treatment related SAE, death 11 months later from PD.
0
5
10
15
Time (Months)
Prior anti-PD-1
PD-1 refractory
Bulky disease
Response
CR - DS1-3
PR - DS4
SD - DS4
PD - DS5 / IR3
B
Progression-Free Survival Probability, %
100
75
50
25
0
0
10
20
30
Time (Months)
C
Overall Survival probability, %
100
75
50
25
0
0
10
20
30
Time (Months)
D
Pre-treatment
Post-C4
Pre-treatment
Post-C8
E
CT Change from Baseline, SPD%
120
80
40
0
0
5
10
15
20
Time (months)
Best Response
CR
PR
SD

## Supplementary Data

Supplementary Table 1: Stage at relapse for enrolled patients, with sites of disease bulk (defined as any site >7.0cm) and extranodal involvement.

| Subject ID | Stage at relapse | Disease bulk at relapse | Extranodal sites |
|---|---|---|---|
| **1** | III | Non-bulky | |
| **2** | IV | Non-bulky | Osseous |
| **3** | IV | **Bulky**<br>8.3cm mediastinal<br>7.1cm supraclavicular | Lung |
| **4** | IV | Non-bulky | Osseous |
| **5** | IV | Non-bulky | Lung 6.9cm |
| **6** | IV | Non-bulky | Lung<br>Liver |
| **7** | IV | **Bulky**<br>7.2cm pelvic/osseous | Osseous |
| **8** | III | Non-bulky | |

Supplementary Table 2: Prior treatment and responses for enrolled patients.

| Subject ID | Prior Lines of Therapy And Response | Interval from Prior CPI to Study Treatment (Months) | Cycles of Study Treatment | Best Response |
|---|---|---|---|---|
| **1** | 1) ABVD x3 (PD)<br>2) ICE (PR) + ASCT + RT (PD) | NA | 4 | PR |
| **2** | 1) ABVD x4 (CR)<br>2) BV-Bendamustine x2 (CR) + ASCT (PD) | NA | 24 | CR |
| **3** | 1) BV-AVD x5 (PR)<br>2) ICE x2 (PD)<br>3) Pembrolizumab x3 (PD)<br>4) BeGEV x3 (CR) + ASCT (CR) | 21<br>**Refractory** | 26 | PR |
| **4** | 1) ABVD x6 + RT (CR)<br>2) ICE (PR) + ASCT + RT (CR) | NA | 21 | CR |
| **5** | 1) BV-AVD x3 (PD)<br>2) Pembrolizumab-GND x4 (CR) + ASCT (CR) | 6 | 8 | CR |
| **6** | 1) ABVD x2 + AVD x4 (CR)<br>2) BV + Nivolumab + Ipilimumab (CR)<br>3) Nivolumab (PD)<br>4) GND (CR) | 14<br>**Refractory** | 11 | PR |
| **7** | 1) ABVD x 4 (PD)<br>2) ICE-Bortezomib (PD)<br>3) GND + ASCT (PD)<br>4) BV (PD)<br>5) Idelalisib (PD)<br>6) Bendamustine (PD)<br>7) AKT inhibitor (PD)<br>8) Vorinostat + Sirolimus (SD)<br>9) EBV cytotoxic T lymphocytes (PD)<br>10) Vorinostat + Sirolimus (PD)<br>11) Pembrolizumab + RT (PD)<br>12) BV + Pembrolizumab (PR)<br>13) CAR-T #1 (PD)<br>14) Nivolumab x1 + CAR-T #2 + Nivolumab x3 (PR)<br>16) BV + Nivolumab (CR)<br>17) BV + Nivolumab x5 (PD)<br>18) Ipilimumab x3 (PD)<br>19) Pembrolizumab (SD) | 34 | 9 | SD |
| **8** | 1) ABVD x6 (CR)<br>2) Pembrolizumab-GND x4 + ASCT (CR) | 19 | 11 | SD |