blood

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma

Tracking no: BLD-2022-017951R2

Armando Santoro (Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy) Alison Moskowitz (Memorial Sloan Kettering Cancer Center, United States) Silvia Ferrari (Ospedale Papa Giovanni XXIII, Italy) Carmelo Carlo-Stella (IRCCS Humanitas Research Hospital-Humanitas Cancer Center, Italy) Julie Lisano (Seagen, Inc., United States) Stephen Francis (Bristol Myers Squibb, United States) Rachael Wen (Bristol Myers Squibb, United States) Alev Akyol (Bristol Myers Squibb, United States) Kerry Savage (BC Cancer, Centre for Lymphoid Cancer, Canada)

Abstract:

Conflict of interest: COI declared - see note

COI notes: A.S.: Advisory board: Bayer, Bristol Myers Squibb, Eisai, Gilead Science Inc, Merck Sharp & Dohme, Pfizer, Servier; Consultant/advisory role: Arqule, Incyte, Sanofi; Speaker's bureau: AbbVie, Amgen, Arqule, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, Eisai, Eli Lilly, Gilead, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, Takeda A.J.M.: Consultant/advisory role and honoraria: Affirmed, Imbrium Therapeutics, Janpix Ltd, L.P./Purdue, Merck, Seagen, Takeda; Research support/funding: ADC Therapeutics, Beigene, Bristol Myers Squibb, Incyte, Merck, Miragen, Seagen, SecuraBio; SAB member: Lymphoma Hub; Scientific Review Committee Member: Gilead Science Inc. S.F.: Nothing to disclose C.C.-S.: Consultant/advisory role: ADC Therapeutics, Celgene, a Bristol-Myers Squibb Company, Genenta Science, Karyopharm Therapeutics, Roche, Sanofi; Honoraria: ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Incyte, Janssen Oncology, Merck Sharp & Dohme, Novartis, Takeda; Research support/funding: ADC Therapeutics, Roche, Sanofi J.L.: Employee and equity ownership via stock: Seagen S.F.: Employee and stock ownership: Bristol Myers Squibb R.W.: Employee and stock ownership: Bristol Myers Squibb A.A.: Employee and stock ownership: Bristol Myers Squibb K.J.S.: Data and safety monitoring committee: Regeneron; Honoraria/consulting: Bristol Myers Squibb, Janssen, Kyowa, Merck, Novartis, Seagen; Research support/funding: Bristol Myers Squibb, Roche; Steering committee: Beigene

Preprint server: No;

Author contributions and disclosures: A.S., J.L., S.F., K.J.S. made the conception or design; A.S., A.J.M., S.F., C.C.-S., K.J.S. performed data acquisition; A.S., A.J.M., S.F., C.C.-S., J.L., S.F., R.W., A.A., K.J.S. performed data analysis and interpretation. All authors contributed to the writing of the manuscript.

Non-author contributions and disclosures: Yes; The authors thank the patients and families who made this study possible and the clinical study teams who participated in the trial. The authors also thank Mariana Sacchi, funded by Bristol Myers Squibb, for participating in the data review process. This study was supported by Bristol Myers Squibb and Seagen. Professional medical writing support for this manuscript was provided by Richard Sora, PhD, of Caudex, funded by Bristol Myers Squibb.

Agreement to Share Publication-Related Data and Data Sharing Statement: BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Seagen policy on data sharing may be found at https://www.seagen.com/healthcare-professionals/clinical-data-requests.

Clinical trial registration information (if any): clinicaltrials,gov, NCT02581631

Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma

Running head

Nivolumab plus BV in R/R MGZL

Authors

Armando Santoro,[1] Alison J. Moskowitz,[2] Silvia Ferrari,[3] Carmelo Carlo-Stella,[1] Julie Lisano,[4] Stephen Francis,[5]* Rachael Wen,[5] Alev Akyol,[5] Kerry J. Savage[6]

Corresponding author

Kerry J. Savage MD MSc FRCP(C)

600 W 10th Ave, Vancouver, BC V5Z 4E6, Canada

+1 604-877-6000

ksavage@bccancer.ba.ca

Author affiliations

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; IRCCS Humanitas Research Hospital–Humanitas Cancer Center, Rozzano, Milan, Italy

[2]Memorial Sloan Kettering Cancer Center, New York, NY, USA

[3]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

[4]Seagen Inc., Bothell, WA, USA

[5]Bristol Myers Squibb, Princeton, NJ, USA

[6]Centre for Lymphoid Cancer, Division of Medical Oncology, BC Cancer, Vancouver, BC, Canada

*Affiliation at the time of the study

Article type: Letter

Word limit: 1197/1200

Figure/table limit: 2/2

Reference limit: 22/25

Introduction

Mediastinal gray zone lymphoma (MGZL) is a rare non-Hodgkin lymphoma predominantly occurring in young men.[1] MGZL exhibits pathologic characteristics intermediate between nodular-sclerosis classical Hodgkin lymphoma (NSCHL) and primary mediastinal large B-cell lymphoma (PMBL), and is characteristically CD30-positive.[2,3] MGZL tumors, like NSCHL and PMBL, harbor frequent 9p24.1 copy-number alterations and expression of programmed death-1 (PD-1) ligands 1 and (less commonly) 2.[4-7] In a small case series of relapsed/refractory (R/R) MGZL, the PD-1 inhibitor pembrolizumab induced a complete metabolic response in 2 patients.[6] Gene expression profiling showed MGZL clusters between NSCHL and PMBL; whole exome sequencing supports a common cell of origin.[8,9] The 5th edition update of the World Health Organization and the International Consensus classification exclude cases arising outside the anterior mediastinum, which harbor different gene expression profiles and DNA alterations.[10,11] Optimal therapy for MGZL is unknown and outcomes remain unsatisfactory, with a 2-year progression-free survival (PFS) of 46% and overall survival (OS) of 92% in 1 multicenter study.[12] In another study, patients with MGZL treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCHR), had worse outcomes than patients with PMBL, with a 5-year event-free survival of 62% (PMBL, 93%) and OS of 74% (PMBL, 97%).[13] Nivolumab is a fully human immunoglobulin G4 anti–PD-1 immune checkpoint inhibitor monoclonal antibody that restores T-cell–mediated antitumor responses by interrupting PD-1 receptor–ligand interactions.[14] The antibody–drug conjugate brentuximab vedotin (BV) consists of monomethyl auristatin E, protease-cleavable linker, and a CD30 antibody, and induces apoptosis of CD30-positive tumor cells.[15] BV may also induce an immunogenic environment, contributing to depletion of T regulatory cells and potentiating the effect of PD-1 inhibition.[16-19] Nivolumab plus BV has a high objective response rate (ORR) as second-line treatment of R/R classical Hodgkin lymphoma (cHL) in transplant-eligible adults (85%).[20] In Checkmate 436 (NCT02581631), a phase 1/2 study evaluating nivolumab plus BV in R/R

non-Hodgkin lymphomas (n = 30), ORR was 73% in patients with R/R PMBL.[21] Previously, ORR with BV alone was 13%.[22] Simultaneously targeting PD-1 and CD30 may be effective in MGZL. We report efficacy and safety of nivolumab plus BV from the CheckMate 436 R/R MGZL expansion cohort.

Methods

Patients ≥18 years old with ECOG performance status scores of 0–1 and R/R MGZL after autologous hematopoietic stem cell transplantation (auto-HCT) or, if transplant ineligible, following ≥2 multi-agent chemotherapy regimens were enrolled. CD30 expression on ≥1% of the tumor or tumor-infiltrating lymphocytes before first treatment dose, per local immunohistochemistry on a relapsed specimen (if available) or primary diagnosis was required. Patients with active, known, or suspected autoimmune disease, a condition requiring systemic corticosteroid treatment (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose, were excluded. Patients previously treated with BV, other anti-CD30 treatment, allogeneic hematopoietic stem cell transplantation (allo-HCT), radiation therapy within 3 weeks (or chest radiation within 12 weeks) of the first dose, or chemotherapy or therapeutic antibodies within 4 weeks of the first dose were also excluded.

Patients received nivolumab 240 mg and BV 1.8 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. For cycle 1, BV was administered on day 1 and nivolumab on day 8. For cycle 2 and beyond, both were administered on day 1. Primary endpoints were investigator-assessed ORR and safety. Response was assessed according to the Lugano Classification 2014 with PET-CT at week 6 and 12, then every 9 weeks for the subsequent 4 assessments, and every 12 weeks after the first year. With an assumed ORR of 50%, the two-sided 80% confidence interval (CI) was 11.6%–55.2%; the lower bound of the 80% CI excluded 10%, which was the null hypothesis ORR. Secondary endpoints included complete remission (CR) rate, OS, PFS, and duration of response (DOR). For OS,

patients who were alive or had unknown vital status were censored at the last date they were known to be alive. For other secondary outcomes, patients who received subsequent therapy before documented progression, including auto-HCT or allo-HCT, were censored on the last tumor assessment date before subsequent therapy. All patients provided written informed consent. At each site, approval from the appropriate institutional review board and independent ethics committee was obtained.

Data Sharing Statement

BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Seagen policy on data sharing may be found at https://www.seagen.com/healthcare-professionals/clinical-data-requests.

Results and Discussion

Among the 10 patients in the MGZL cohort, there were 6 men and 4 women. Median age was 35 years (range, 25–72) (**Table 1**). Seven had refractory disease (absence of CR after frontline therapy or absence of CR/partial remission [PR] with any salvage therapy) at study entry, 1 each had relapsed disease after frontline or salvage therapy, and disease status for the remaining patient was not reported. In addition to CD30, 8 cases were also positive for CD15 and CD20; 2 were negative for both. Patients received a median of 2 (range, 1–3) prior lines of systemic cancer therapy; none included auto-HCT.

Patients received a median of 7 doses each of nivolumab (range, 5–26) and BV (range, 1–29). At database lock (DBL) (February 28, 2020), all had discontinued treatment due to disease progression (n = 5), allo-HCT (n = 4), or auto-HCT (n = 1). One was not evaluable for response because they died before receiving nivolumab (received 1 BV dose); this patient was included in the ORR calculation. At a median follow-up of 12.4 months (range,

0.1–25.5) ORR per investigator was 70% (80% CI, 45–88) with 5 achieving CR, 2 achieving PR, and 2 exhibiting progressive disease (**Figure 1**, **Supplemental Figure 1**). Among those who achieved CR, time to CR ranged from 1.2 to 4.8 months and duration of CR from 1.5 to 3.2 months. All patients who discontinued treatment due to maximum clinical benefit achieved CR and were censored, as they subsequently received allo-HCT (n = 4) or auto-HCT (n = 1), and all were alive at DBL. Median DOR, therefore, could not be assessed.

At DBL, median PFS was 21.9 months (95% CI, 0.07–21.9), with 5 patients experiencing events (4 PD and 1 death from disease progression after 1 cycle of BV) (**Supplemental Figure 2**). The 6-month OS rate was 80.0% (95% CI, 40.9–94.6). Median OS was not reached.

Treatment-related adverse events (TRAEs) occurred in 9 patients, with 3 exhibiting grade 3 TRAEs (1 each of neutropenia, febrile neutropenia, and thrombocytopenia) (**Supplemental Table 1**). TRAEs in ≥2 patients were neutropenia (n = 3), peripheral sensory neuropathy (n = 3), paresthesia (n = 2), thrombocytopenia (n = 2), and anemia (n = 2). Grade 3 febrile neutropenia was the only serious TRAE (n = 1). One patient each experienced an infusion-related reaction (grade 1) and an immune-mediated AE (grade 2 maculo-papular rash, resolved without systemic steroids). All 3 deaths were from disease progression.

The high investigator-assessed ORR and CR rate are consistent with those reported with nivolumab plus BV in PMBL (73% ORR, 37% CR) and cHL as first salvage (85% ORR, 67% CR).[20,21] The tolerable safety profile is generally consistent with those established for nivolumab plus BV.[18,21] Based on the favorable efficacy and safety profile, this regimen may represent a salvage option for transplant-eligible patients with R/R MGZL.

Acknowledgments

The authors thank the patients and families who made this study possible and the clinical study teams who participated in the trial. The authors also thank Mariana Sacchi, funded by Bristol Myers Squibb, for participating in the data review process. This study was supported

by Bristol Myers Squibb and Seagen. Professional medical writing support for this manuscript was provided by Richard Sora, PhD, of Caudex, funded by Bristol Myers Squibb.

Authorship Contributions

Contribution: A.S., J.L., S.F., K.J.S. made the conception or design; A.S., A.J.M., S.F., C.C.-S., K.J.S. performed data acquisition; A.S., A.J.M., S.F., C.C.-S., J.L., S.F., R.W., A.A., K.J.S. performed data analysis and interpretation. All authors contributed to the writing of the manuscript.

Disclosure of Conflicts of Interest

A.S.: Advisory board: Bayer, Bristol Myers Squibb, Eisai, Gilead Science Inc, Merck Sharp & Dohme, Pfizer, Servier; Consultant/advisory role: Arqule, Incyte, Sanofi; Speaker's bureau: AbbVie, Amgen, Arqule, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, Eisai, Eli Lilly, Gilead, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, Takeda

A.J.M.: Consultant/advisory role and honoraria: Affirmed, Imbrium Therapeutics, Janpix Ltd, L.P./Purdue, Merck, Seagen, Takeda; Research support/funding: ADC Therapeutics, Beigene, Bristol Myers Squibb, Incyte, Merck, Miragen, Seagen, SecuraBio; SAB member: Lymphoma Hub; Scientific Review Committee Member: Gilead Science Inc.

S.F.: Nothing to disclose

C.C.-S.: Consultant/advisory role: ADC Therapeutics, Celgene, a Bristol-Myers Squibb Company, Genenta Science, Karyopharm Therapeutics, Roche, Sanofi; Honoraria: ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Incyte, Janssen Oncology, Merck Sharp & Dohme, Novartis, Takeda; Research support/funding: ADC Therapeutics, Roche, Sanofi

J.L.: Employee and equity ownership via stock: Seagen

S.F.: Employee and stock ownership: Bristol Myers Squibb

R.W.: Employee and stock ownership: Bristol Myers Squibb

A.A.: Employee and stock ownership: Bristol Myers Squibb

K.J.S.: Data and safety monitoring committee: Regeneron; Honoraria/consulting: Bristol Myers Squibb, Janssen, Kyowa, Merck, Novartis, Seagen; Research support/funding: Bristol Myers Squibb, Roche; Steering committee: Beigene

Clinical Trials # NCT02581631

References

1. Quintanilla-Martinez L, Fend F. Mediastinal gray zone lymphoma. *Haematologica*. 2011;96(4):496-499.

2. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. *Haematologica*. 2011;96(4):558-566.

3. Dunleavy K, Wilson WH. Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: do they require a unique therapeutic approach? *Blood*. 2015;125(1):33-39.

4. Eberle FC, Salaverria I, Steidl C, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. *Mod Pathol*. 2011;24(12):1586-1597.

5. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3277.

6. Melani C, Major A, Schowinsky J, et al. PD-1 blockade in mediastinal gray-zone lymphoma. *N Engl J Med*. 2017;377(1):89-91.

7. Sarkozy C, Chong L, Takata K, et al. Gene expression profiling of gray zone lymphoma. *Blood Adv*. 2020;4(11):2523-2535.

8. Pittaluga S, Nicolae A, Wright GW, et al. Gene expression profiling of mediastinal gray zone lymphoma and its relationship to primary mediastinal B-cell lymphoma and classical Hodgkin lymphoma. *Blood Cancer Discov*. 2020;1(2):155-161.

9. Sarkozy C, Hung SS, Chavez EA, et al. Mutational landscape of gray zone lymphoma. *Blood*. 2021;137(13):1765-1776.

10. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748.

11. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022;140(11):1229-1253.

12. Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: characteristics, outcomes, and prognostication among a large multicenter cohort. *Am J Hematol*. 2015;90(9):778-783.

13. Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. *Blood*. 2014;124(10):1563-1569.

14. Bristol Myers Squibb. Opdivo® (nivolumab) prescribing information. July 2022.

15. Seattle Genetics. Adcetris® (brentuximab vedotin) prescribing information. November 2022.

16. Heiser RA, Grogan BM, Manlove LS, Gardai SJ. CD30+ T regulatory cells, but not CD30+ CD8 T cells, are impaired following brentuximab vedotin treatment in vitro and in vivo. AACR. Vol. 78. Presented at: the AACR Annual Meeting. Chicago, IL, USA; April 14–18, 2018: Abstract 1789.

17. Cao AT, Law C-L, Gardai SJ, Heiser RA. Brentuximab vedotin-driven immunogenic cell death enhances antitumor immune responses, and is potentiated by PD1 inhibition in vivo. AACR. Vol. 77. Presented at: the AACR Annual Meeting. Washington, DC, USA; April 1–5, 2017: Abstract 5588.

18. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183-1194.

19. Gardai SJ, Epp A, Law C-L. Brentuximab vedotin-mediated immunogenic cell death. *Cancer Res*. 2015;75(15 suppl): Abstract 2469.

20. Advani R, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood*. 2021;138:427-438.

21. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. *J Clin Oncol*. 2019;37(33):3081-3089.

22. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. *Blood*. 2017;129(16):2328-2330.

Tables

Table 1. Baseline characteristics

Characteristic	MGZL (N = 10)
Age, median (range), years	35 (25–72)
>65 years (%)	1* (10)
Male, n (%)	6 (60)
ECOG performance status, n (%)	
0–1	9 (90)
≥2	1 (10)
Refractory disease†, n (%)	7 (70)
Bulky disease ≥10 cm, n (%)	3 (30)
Prior systemic cancer therapies, median (range)	2 (1–3)‡
Prior therapies, n (%) R-CHOP	3 (30)
DA-EPOCHR	4 (40)
Prior auto-HCT, n	0
Time from completion of most recent prior systemic therapy to study treatment, n (%)	
<3 months	8 (80)
3–6 months	1 (10)
>6 months	1 (10)

Unless noted otherwise, data are n (%).

*Patient was 72 years old.

†No CR following frontline therapy and no CR/PR to any salvage therapy.

‡One patient received 2 prior regimens, but 1 regimen was unknown. This patient met the study inclusion criteria, as it was known that they had received 2 prior regimens.

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Figures

Figure 1. Best overall response and tumor reduction.

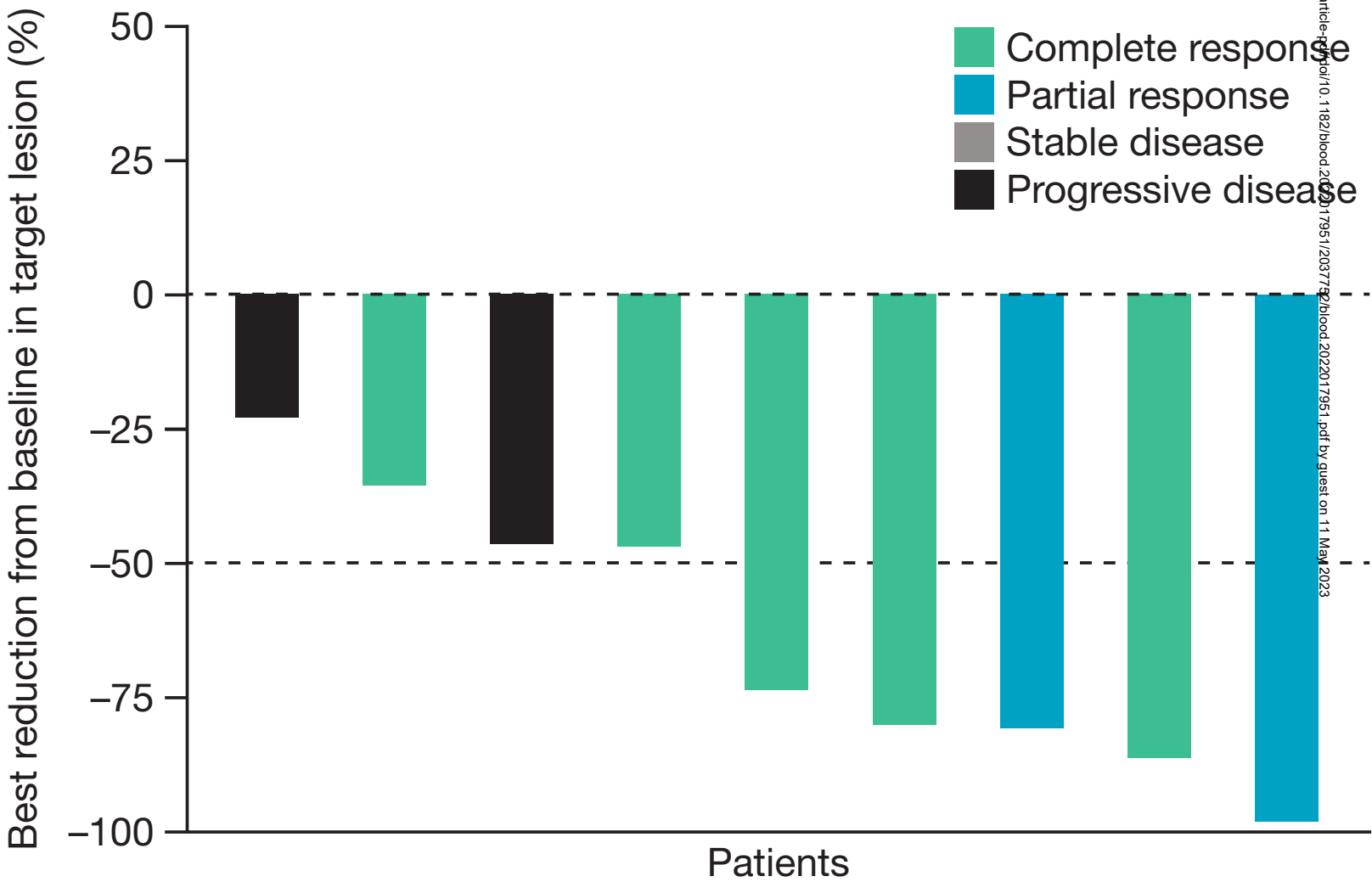
Figure 1

Best overall response per investigator (Primary endpoint)

Best overall response	MGZL (N = 10)
Objective response rate, % (80% CI)	70 (45–88)
Complete response	5 (50)
Partial response	2 (20)
Stable disease	0
Progressive disease	2 (20)
Death prior to disease assessment	1 (10)

Data are n (%) unless stated otherwise.

Best reduction in target lesion per investigator by best overall response



Response evaluable patients are those with target lesion(s) assessed at baseline and with all baseline target lesion(s) assessed at > 1 on-study timepoint. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy.