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

Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy in relapsed/refractory classical Hodgkin lymphoma

Tracking no: BLD-2022-019386R1

Philippe Armand (Dana-Farber Cancer Institute, United States) Pier Zinzani (IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia, Italy) Hun Lee (MDACC, United States) Nathalie Johnson (Jewish General Hospital, Montreal, Canada) Pauline Brice (HOPITAL SAINT LOUIS, France) John Radford (University of Manchester and the Christie NHS Foundation Trust, United Kingdom) Vincent Ribrag (Institut Gustave Roussy, France) Daniel Molin (Uppsala University, Sweden) Theodoros Vassilakopoulos (National and Kapodistrian University of Athens, Greece) Akihiro Tomita (Nagoya University School of Medicine, Japan) Bastian v. Tresckow (Department I of Internal Medicine, Medical Faculty and University Hospital Cologne, University of Cologne, Germany) Margaret Shipp (Dana-Farber Cancer Institute, United States) Alex Herrera (City of Hope, United States) Jianxin Lin (Merck & Co., Inc., United States) Eunhee Kim (Merck & Co., Inc., United States) Samhita Chakraborty (Merck & Co., Inc., United States) Patricia Marinello (Merck & Co., Inc., United States) Craig Moskowitz (University of Miami Sylvester Comprehensive Cancer Center, United States)

Abstract:
Previous analyses from the phase 2 KEYNOTE-087 (NCT02453594) trial of pembrolizumab monotherapy demonstrated effective antitumor activity with acceptable safety in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL), but longer-term response durability and outcome of patients who receive a second course after treatment discontinuation after complete response (CR) remain of clinical interest. We present KEYNOTE-087 data after >5 years of median follow-up. Patients with R/R cHL and progressive disease (PD) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV; cohort 1); after salvage chemotherapy and BV without ASCT (cohort 2); or after ASCT without subsequent BV (cohort 3) received pembrolizumab for ≤2 years. Patients in CR who discontinued treatment and subsequently experienced PD were eligible for second-course pembrolizumab. Primary end points were objective response rate (ORR) by blinded central review and safety. Median follow-up was 63.7 months. ORR was 71.4% (95% confidence interval [CI], 64.8-77.4; CR, 27.6%; partial response, 43.8%). Median duration of response (DOR) was 16.6 months; median progression-free survival was 13.7 months. A quarter of responders, including half of complete responders, maintained response ≥4 years. Median overall survival was not reached. Among 20 patients receiving second-course pembrolizumab, ORR for 19 evaluable patients was 73.7% (95% CI, 48.8-90.8); median DOR was 15.2 months. Any-grade treatment-related adverse events occurred in 72.9% of patients and grade 3 or 4 in 12.9%; no treatment-related deaths occurred. Single-agent pembrolizumab can induce very durable responses, especially in patients achieving CR. Second-course pembrolizumab frequently reinduced sustained responses after relapse from initial CR.

Conflict of interest: COI declared - see note

COI notes: P.A. reports grants or contracts from Merck, BMS, Affimed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM, and Kite; consulting fees from Merck, BMS, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome, Regeneron, Epizyme, AstraZeneca, and Genentech; and honoraria from Merck and BMS. P.L.Z. reports honoraria from Roche, Takeda, Gilead, Sanofi, Incyte, Novartis, Merck, BMS, AstraZeneca, and Kyowa Kirin. H.J.L. reports grants or contracts from BMS, Seagen, Oncternal, Merck, and Takeda; consulting fees from Century Therapeutics; and honoraria from Aptitude Health and the Korean Society of Cardio-Oncology. N.A.J. reports consulting fees from Merck, AbbVie, Beigene, Roche, BMS, and Kite; and honoraria from Roche, AbbVie, and Beigene. P.B. has no conflicts of interest to declare. J.R. has no conflicts of interest to declare. V.R. reports advisory board roles with Gilead, Infinity, MSD, BMS, Nanostring, Incyte, Roche, and AstraZeneca; and research funding from Astex, Argen-X, and GSK. D.M. reports honoraria from MSD and BMS. T.P.V. reports grants or contracts from Merck, Takeda, Amgen, Pfizer, and Dr Reddy's; consulting fees from Takeda, Roche, Genesis Pharma, and Novartis; honoraria from Takeda, Roche, Genesis Pharma, Merck, Novartis, Amgen, GSK, AbbVie, Integris, and AstraZeneca; and stock or stock options in Merck. A.T. reports grants or contracts from Chugai Pharmaceutical, Kyowa Kirin, Perseus Proteomics, Pfizer Japan, and Novartis Pharma K.K.; and honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Nippon Shinyaku, Ono Pharmaceutical, and Eisai. B.V.T. reports grants or contracts from Novartis, Takeda, and Merck Sharp & Dohme; consulting fees from Allogene, BMS/Celgene, Cerus, Incyte, Mitlenyi, Novartis, Pentixafarm, Roche, Amgen, Pfizer, Takeda, Merck Sharp & Dohme, and Gilead Kite; honoraria from AstraZeneca, Novartis, Roche Pharma AG, Takeda, and Merck Sharp & Dohme; and support for attending meetings and/or travel from AbbVie, AstraZeneca, Kite-Gilead, Merck Sharp & Dohme, Takeda, and Novartis. M.A.S. reports grants or contracts from BMS, Bayer, AbbVie, and AstraZeneca; and consulting fees from AstraZeneca. A.F.H. reports grants or contracts from BMS, Genentech, Merck, Seattle Genetics, AstraZeneca, Karyopharm, Kite Pharma, Gilead Sciences, AstraZeneca, and ADC Therapeutics; and consulting fees from BMS, Genentech, Merck, Seattle Genetics, AstraZeneca, Karyopharm, ADC Therapeutics, Takeda, Tubulis, Regeneron, Genmab, and Pfizer. J.L. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA. E.K. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of this analysis S.C. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA. P.M. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA. C.H.M. reports research funding from Merck & Co., Inc.

Preprint server: No;

Author contributions and disclosures: P.A., P.B. B.V.T., M.A.S., P.M., and C.H.M. contributed to conception, design, or planning of the study. P.A., N.A.J., J.R., V.R., D.M., T.P.V., A.T., B.V.T., A.H., S.C., and C.H.M. contributed to acquisition of the data. P.L.Z., V.R., M.A.S., J.L., E.K., S.C., P.M., and C.H.M. contributed to analysis of the data. P.A., P.L.Z., H.J.L., J.R., V.R., T.P.V., B.V.T., M.A.S., A.H., E.K., S.C., P.M., and C.H.M. contributed to interpretation of the results. H.J.L., P. B. S.C., and C.H.M. contributed to drafting the manuscript. P.A., P.L.Z., H.J.L., N.A.J., J.R., V.R., D.M., T.P.V., A.T., B.V.T., M.A.S., A.H., J.L., S.C., P.M., and C.H.M. contributed to critically reviewing or revising the manuscript for important intellectual content.

Non-author contributions and disclosures: Yes; The authors would also like to thank May Tang (employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) for her contribution to the statistical analysis for the manuscript. This work was supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing and editorial assistance were provided by Dominic Singson, MD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Agreement to Share Publication-Related Data and Data Sharing Statement: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Clinical trial registration information (if any): ClinicalTrials.gov, NCT02453594

Original Article

Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy in relapsed/refractory classical Hodgkin lymphoma

(111/120 characters including spaces)

Philippe Armand,[1] Pier Luigi Zinzani,[2] Hun Ju Lee,[3] Nathalie A. Johnson,[4] Pauline Brice,[5] John Radford,[6] Vincent Ribrag,[7] Daniel Molin,[8] Theodoros P. Vassilakopoulos,[9] Akihiro Tomita,[10] Bastian von Tresckow,[11,12] Margaret A. Shipp,[1] Alex F. Herrera,[13] Jianxin Lin,[14] Eunhee Kim,[14] Samhita Chakraborty,[14] Patricia Marinello,[14] and Craig H. Moskowitz[15]

Affiliations

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli" and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna Italy; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Jewish General Hospital, Montreal, QC, Canada; [5]Hôpital Saint-Louis, Paris, France; [6]NIHR Clinical Research Facility, the Christie NHS Foundation Trust and University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; [7]Gustave Roussy, Villejuif, France; [8]Uppsala University, Uppsala, Sweden; [9]National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece; [10]Nagoya University Graduate School of Medicine, Nagoya, Japan; [11]Department I of Internal Medicine, Medical Faculty and University Hospital Cologne, University of Cologne, Cologne, Germany; [12]West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen,

Germany; [13]City of Hope, Duarte, CA, USA; [14]Merck & Co., Inc., Rahway, NJ, USA;

[15]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA

Corresponding Author:

Philippe Armand, MD, PhD

Dana-Farber Cancer Institute

450 Brookline Ave.

Boston, MA 02215

Email: philippe_armand@dfci.harvard.edu; parmand@partners.org

Phone: +1-617-632-6844

Fax: +1-617-632-4422

Data sharing

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval

in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Running head: 5-Yr FU of Pembrolizumab Monotherapy in R/R cHL (**47/50 characters with spaces**)

Scientific category: Primary: Clinical trials and observations

Subject area: Neoplasia: Lymphomas and other lymphoproliferative conditions: Immunotherapeutic approaches.

Text: 2766 words (≤4000)
Abstract: 250 words (≤250)
Tables/figures: 2/4 (≤7)
References: 12
Supplementary tables/figures: 6/3

Key Points: (1-2 key points; <140 characters each)

- Pembrolizumab monotherapy can produce very durable responses in a subset of patients with R/R cHL (**100/140**)
- Second-course pembrolizumab frequently reinduced sustained response in patients relapsing from CR (**100/140**)

Abstract (250/250)

Previous analyses from the phase 2 KEYNOTE-087 (NCT02453594) trial of pembrolizumab monotherapy demonstrated effective antitumor activity with acceptable safety in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL), but longer-term response durability and outcome of patients who receive a second course after treatment discontinuation after complete response (CR) remain of clinical interest. We present KEYNOTE-087 data after >5 years of median follow-up. Patients with R/R cHL and progressive disease (PD) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV; cohort 1); after salvage chemotherapy and BV without ASCT (cohort 2); or after ASCT without subsequent BV (cohort 3) received pembrolizumab for ≤2 years. Patients in CR who discontinued treatment and subsequently experienced PD were eligible for second-course pembrolizumab. Primary end points were objective response rate (ORR) by blinded central review and safety. Median follow-up was 63.7 months. ORR was 71.4% (95% confidence interval [CI], 64.8-77.4; CR, 27.6%; partial response, 43.8%). Median duration of response (DOR) was 16.6 months; median progression-free survival was 13.7 months. A quarter of responders, including half of complete responders, maintained response ≥4 years. Median overall survival was not reached. Among 20 patients receiving second-course pembrolizumab, ORR for 19 evaluable patients was 73.7% (95% CI, 48.8-90.8); median DOR was 15.2 months. Any-grade treatment-related adverse events occurred in 72.9% of patients and grade 3 or 4 in 12.9%; no treatment-related deaths occurred. Single-agent pembrolizumab can induce very durable responses, especially in patients achieving CR. Second-course pembrolizumab frequently reinduced sustained responses after relapse from initial CR.

Key words: classical Hodgkin lymphoma; pembrolizumab; immunotherapy

INTRODUCTION

Previous studies have shown that immune checkpoint inhibition targeting programmed death 1 (PD-1) is an effective therapeutic option in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) who are ineligible for or progress after autologous stem cell transplant (ASCT) with or without treatment with brentuximab vedotin (BV).[1-4] As a result, the National Comprehensive Cancer Network treatment guidelines recommend use of the anti–PD-1 checkpoint inhibitor, pembrolizumab, as an option for second-line treatment in patients ineligible for ASCT or for patients with R/R cHL after ≥2 lines of systemic therapy.[5] Pembrolizumab is approved by the US Food and Drug Administration for the treatment of various solid and hematologic malignancies, including R/R cHL.[6] KEYNOTE-087 is a phase 2 study of pembrolizumab in patients with R/R cHL who are ineligible for or progressing after ASCT and/or BV that demonstrated effective antitumor activity and a favorable safety profile in previous analyses.[1,2] With additional follow-up, it is now possible to assess the potential for long-term benefit and the ability to discontinue therapy for patients in complete remission (CR) and restart treatment upon subsequent disease progression. To this end, we present data from the KEYNOTE-087 study after >5 years of follow-up.

METHODS

Study design

KEYNOTE-087 is a multicenter, single-arm, multicohort, nonrandomized, phase 2 study of pembrolizumab in patients with R/R cHL. Detailed study inclusion and exclusion criteria have been previously described.[1,2] Eligible adult patients had to have R/R cHL that had progressed after the most recent therapy or without a response to most recent ASCT, with adequate performance status and organ function. All patients provided written informed consent. The study was approved by the independent institutional review boards at each study

site and conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Patients were enrolled into 3 cohorts: patients whose disease did not respond or progressed after ASCT and subsequent BV (cohort 1); patients who were unable to achieve a response (ie, complete response [CR] or partial response [PR]) to salvage chemotherapy, did not receive ASCT and progressed after BV (cohort 2); and patients who did not respond to or whose disease progressed after ASCT and did not receive subsequent BV (cohort 3). All patients in the study received pembrolizumab 200 mg intravenously every 3 weeks for up to 2 years or until disease progression (PD), unacceptable adverse events (AEs), illness preventing further treatment administration, or investigator/patient withdrawal. Patients who achieved CR and had received at least 6 months of treatment with at least 2 doses after CR was confirmed were allowed to discontinue study treatment before 2 years; those who subsequently experienced PD and did not receive any anti-cancer treatment since the last dose of pembrolizumab were eligible for a second course of pembrolizumab for up to an additional 17 cycles (~1 year).

Assessments

Response assessments were performed using positron emission tomography and computed tomography scan starting at screening. Computed tomography scans were performed every 12 weeks for subsequent response assessments, and positron emission tomography scans were performed at weeks 12 and 24 and to confirm CR and PD and as clinically indicated. Disease assessments were performed until PD, start of new anticancer treatment, death, patient withdrawal of consent, or end of study. Primary end points were safety and objective response rate (ORR) assessed per the 2007 International Working Group Revised Response Criteria for Malignant Lymphomas (IWG 2007) by blinded independent central review

(BICR).[7] Secondary end points included ORR per the Lugano 2014 Criteria by BICR,[8] duration of response (DOR) and progression-free survival (PFS) per the IWG 2007 criteria by BICR, and overall survival (OS). Second-course treatment ORR, DOR and PFS per the IWG 2007 criteria by investigator assessment as well as second-course OS was exploratory. AEs were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0, until 30 days after the last study dose for all AEs and 90 days after the last study dose for serious AEs.

Statistical analyses

Efficacy and safety were analyzed in all patients who received at least 1 dose of study treatment. ORR and CR were assessed for the overall population and by each cohort. The ORR by BICR involved the point estimate and 95% 2-sided binomial exact confidence interval (CI) using the Clopper-Pearson method. PFS, OS, and DOR were estimated using the Kaplan-Meier method. Summary statistics were provided for safety end points. The data cutoff date was March 15, 2021.

RESULTS

Patients

Baseline patient characteristics have been previously presented.[1,2] Forty-six percent of patients in the overall population were female. Median age was 35 years (range, 18-76), 46.2% were female, 91.4% were aged <65 years, median prior lines of systemic therapy was 4 (range, 1-12), and 83.3% had prior treatment with BV. Seventy-one patients (33.8%) had primary refractory disease,[9] and 122 patients (58.1%) were refractory to their last line of therapy. A total of 210 patients were enrolled into the 3 cohorts (69 in cohort 1, 81 in cohort 2, and 60 in cohort 3), 46 patients (21.9%) completed study treatment, and 164 (78.1%)

discontinued from the study, most commonly because of progressive disease (41.0%), achievement of CR (13%), AEs (9%), or physician decision (5%) (supplemental Table 1).

Efficacy for the total population and by cohort

At data cutoff, the median follow-up (time from first study dose to data cutoff) was 63.7 months (range, 59.8-68.7). The ORR for the overall population per the IWG 2007 criteria by BICR was 71.4% (95% CI, 64.8-77.4), with a CR rate of 27.6% and a PR rate of 43.8% (Figure 1). ORRs for cohorts 1-3 were 78.3%, 64.2%, and 73.3%, respectively. Results per the Lugano 2014 criteria by BICR were similar to ORR by IWG 2007 criteria in the total population (ORR, 73.3% [95% CI, 66.8-83.9] and by cohort (Figure 1).

The median DOR for the overall population per IWG 2007 criteria was 16.6 months (95% CI, 11.8-27.1), and 24.8% of patients maintained responses for ≥ 4 years per Kaplan-Meier estimates (Figure 2A). The median DOR for patients in cohorts 1-3 was 25.0, 11.1, and 24.4 months, respectively. The median PFS for the overall population was 13.7 months (95% CI, 11.1-19.4), and the 5-year PFS rate was 14.2% (Figure 2B). The median PFS for patients in cohorts 1-3 was 16.4, 11.1, and 19.7 months, respectively. The median OS was not reached (NR) for all patients and for patients in each respective cohort, and the 5-year OS rate for the overall population was 70.7% (Figure 2C).

Efficacy by best objective response

A total of 58 patients across the 3 cohorts achieved CR (cohort 1, n = 17; cohort 2, n = 21; cohort 3, n = 20) (supplemental Table 2). The median DOR for all patients who achieved CR was not reached (95% CI, 16.1 months-not reached [NR]), and the proportion of patients remaining in complete response after ≥4 years was 51.6%, per Kaplan-Meier estimates (Figure 3A, supplemental Table 2). The median PFS was 56.5 months (95% CI, 21.7-NR),

and the 5-year PFS rate was 44.3% (Figure 3b). The median OS was not reached, and the 5-year OS rate was 82.8% (Figure 3C. supplemental Table 2).

Among the 58 patients who achieved CR, 10 patients received allogeneic stem-cell transplant (SCT). Five patients achieved a CR with pembrolizumab and then proceeded to allogeneic SCT. The other 5 patients achieved a CR to pembrolizumab, subsequently progressed, and then went on to receive allogeneic SCT. The median DOR for patients who received allogeneic stem-cell transplant was 13.6 months (95% CI, 2.8-NR) (supplemental Figure 1A) and the median PFS was 36.9 months (95% CI, 5.3-57.6) (supplemental Figure 2A). Of the 48 patients who achieved CR and did not undergo subsequent allogeneic SCT, the median DOR was NR (95%CI, 16.8 months to NR) (supplemental Figure 1B) and the median PFS was 56.5 months (95% CI, 27.6-NR) (supplemental Figure 2B).

For patients with CR who received pembrolizumab for <1 year (21 patients), ≥1 year to <2 years (32 patients), and ≥2 years (5 patients), the median (95% CI) duration of CR was 14.5 (8.5-16.8), not reached (31.2-NR) and 13.8 (5.6-NR) months, respectively; 62.2% in the ≥1 year to <2 years group and 40.0% in the≥ 2 years group had a response ≥4 years per Kaplan-Meier estimates (supplemental Table 3)

Forty-six patients who achieved CR per BICR did not receive a second course of pembrolizumab. Of those patients 13 (28.3%) had an ongoing response at data cutoff. Median (95% CI) DOR was not reached (26.8-NR); 67.4% of patients had a response ≥4 years per Kaplan-Meier estimates (supplemental Table 4).

Of the 92 patients who achieved PR (37 in cohort 1, 31 in cohort 2, and 24 in cohort 3), 2 patients underwent SCT, 15 patients started new anticancer treatment, 4 patients were lost to follow-up, and 5 patients had disease progression or died after ≥2 missed visits. The median DOR for all patients who achieved PR was 11.1 months (95% CI, 8.2-16.8), and the proportion of patients remaining in PR ≥3 years was 3.0%, per Kaplan-Meier estimates (Figure 3A, supplemental Table 2). Among the patients who achieved PR, the median PFS was 13.8 months (95% CI, 12.0-22.1) and the 3-year PFS rate was 10.3% (Figure 3B supplemental table 2). The median survival for all patients who achieve PR was not reached (95% CI: NR-NR), and the 5-year OS rate was 75.5% (Figure 3C, supplemental Table 2).

Among the 23 patients who achieved stable disease, the median PFS was 8.3 months (95% CI, 5.6-11.1) and the 3-year PFS rate was 5.3% (Figure 3B). The median OS was not reached (95% CI, 26.8-NR), and the 5-year OS rate was 53.7% (Figure 3C). Among the 33 patients whose disease progressed, the median PFS was 2.8 months (95% CI, 2.7-2.8) (Figure 3B). The median OS was 62.9 months (95% CI, 36-NR), and the 5-year OS rate was 50.6% (Figure 3C).

Efficacy in patients who received second-course treatment per investigator review

A total of 20 patients who achieved CR per investigator assessment (12 of these patients also achieved CR by BICR) and experienced disease progression received second-course pembrolizumab (10 in cohort 1, 7 in cohort 2, and 3 in cohort 3) (supplemental Figure 3). The median duration of the initial response before second-course treatment was 27.2 months (95% CI, 16.8-30.2). Ten patients completed the 17 additional cycles of pembrolizumab, and 1 patient was still in second treatment at data cutoff. One patient was not included in the response analysis of patients who received second-course pembrolizumab because response

data were not available at the time of data cutoff. The ORR per IWG 2007 criteria for the 19 evaluable patients was 73.7% (95% CI, 48.8-90.9), with 7 patients (36.8%) achieving CR and 7 patients (36.8%) achieving PR (Table 1). The ORR for patients in cohorts 1-3 per IWG 2007 criteria was 77.8%, 85.7%, and 33.3%, respectively. The median DOR for all patients who received second-course treatment was 15.2 months (95% CI, 3.9-32.9) (Figure 4A). Of patients who experienced a CR to second-course treatment (n = 7), the median DOR was 21.8 months (95% CI, 7.3-NR), The median PFS was 17.2 months (95% CI, 6.6-25.2), and the 2-year PFS rate was 38.1% (Figure 4B). The median OS was not reached, and the 2-year and 3-year OS rates were 94.1% and 87.4%, respectively (Figure 4C). Two patients received a subsequent allogeneic stem-cell transplant after second-course pembrolizumab.

Safety

Adverse events occurred in 205 patients (97.6%), and 153 patients (72.9%) experienced treatment-related AEs. The most commonly reported treatment-related AEs occurring in >10% of patients were hypothyroidism (14.3%), pyrexia (11.4%), fatigue (11.0%), and rash (11.0%) (Table 2, supplemental Table 5). Grade 3 or 4 treatment-related AEs occurred in 27 patients (12.9%); most commonly reported (occurring in ≥2 patients) were neutropenia (2.4%), pericarditis (1.0%), and diarrhea (1.0%). Fourteen patients (6.7%) discontinued from the study because of treatment-related AEs. No treatment-related deaths were reported. Treatment-related AEs by cohort are presented in supplemental Table 3.

For patients who received second-course pembrolizumab (n = 20), 19 (95.0%) experienced a treatment-related AE, most common (≥15%) were fatigue (20.0%) and diarrhea, muscle spasms, and rash (15.0% each) (supplemental Table 6). Seven grade 3 treatment-related AE

were experienced by 6 patients; no grade 4 or 5 events occurred. No patients discontinued second-course pembrolizumab or died because of treatment-related AEs.

DISCUSSION

Previous studies have demonstrated the robust antitumor activity and manageable safety of pembrolizumab in R/R cHL.[1,2,4,10] The superior PFS associated with this therapy, compared with BV, was demonstrated in the phase 3 randomized, open-label KEYNOTE-204 study of pembrolizumab or BV in patients with R/R cHL who were refractory to or ineligible for ASCT (N = 304).[10] The present results confirm that the safety profile of pembrolizumab is maintained with additional follow-up, with no new toxicity signal. In addition, this study allows us to address the important clinical question of response durability for patients with R/R cHL. With long-term follow-up, we report that a subset of patients, comprising a quarter of responders and half of complete responders, can obtain very durable benefit (with more than 4 years of response duration) regardless of prior receipt and timing of brentuximab vedotin. Although it is still too early to speculate on an even longer time horizon, the shape of the DOR curves (**Figures 2A and 3A**) at least suggests the provocative possibility that those responders may remain in remission for an extended period of time even beyond the currently reported 5-year time point.

In this context, it is very important to understand the predictors of such long-term benefit. Consistent with prior studies,[3] the best predictor of long-term benefit to date is the depth of radiographic response. In fact, all patients in long-term response (>4 years) were complete responders, and conversely among patients achieving CR, more than half remained in CR beyond 4 years. This provides actionable information for patients considering additional therapy, such as stem cell transplantation, while in pembrolizumab-induced remission. Our

results also raise the question of whether CR rate may be a useful surrogate of long-term benefit with PD-1 blockade–based combination therapies, although this hypothesis will require validation. Conversely, patients who did not achieve a CR with pembrolizumab had poorer outcomes, with very few long-term remissions maintained. This raises the question of whether those patients may best be served by consolidation strategies. Of note, the outcomes of patients in our cohort who received an allogeneic stem cell transplant appeared less favorable than in larger series[11]; this likely reflects the small number of patients concerned and limited follow-up.

An additional benefit of the long-term follow-up of KEYNOTE-087 patients is the ability to report outcome for patients who enter CR and whose disease subsequently progresses. Although the numbers are small and the follow-up for second course is short, our results suggest that retreatment with pembrolizumab provides a high probability (74%) of achieving a second remission, making this an excellent choice of therapy for such patients; they also support the ability to stop treatment before 2 years in patients achieving CR with first-course pembrolizumab. However, the DOR curve (Figure 4A) suggests that few patients in this setting will maintain remission beyond ~3 years, which again may be relevant to decisions regarding stem cell transplantation consolidation. Additionally, promising antitumor activity with second-course therapy raises the possibility that combining pembrolizumab with other agents in this setting (eg, chemotherapy) may provide another important salvage option.

Similarly favorable results have been preliminarily reported with long-term follow-up of the PD-1 inhibitor nivolumab in the phase 2 CheckMate-205 study.[12] One notable difference between the 2 studies is that patients on CheckMate-205 continued treatment until PD, whereas patients on KEYNOTE-087 received a maximum of 2 years of treatment (for first-course therapy). Given the overall similarity of long-term PFS and DOR between the studies, and acknowledging the perils of cross-trial comparisons, one may reasonably conclude that

there is no apparent benefit to continuing PD-1 blockade treatment beyond 2 years for patients with R/R cHL.

In conclusion, the current analysis reports the longest-term data so far on patients with R/R cHL treated with PD-1 blockade. It confirms the strong activity of pembrolizumab in this setting without any new safety concern. More importantly, it demonstrates the ability for some patients (approximately one-quarter of responders and one-half of complete responders) to maintain very durable remissions, the importance of radiographic depth of response as a predictor of long-term benefit, and the feasibility of stopping treatment for patients in CR and resuming following disease progression. Such information may be valuable in guiding therapy choice for patients with R/R cHL as well as for informing decisions regarding possible consolidation of remission for responders.

ACKNOWLEDGMENTS

The authors thank the patients and their families and all investigators and site personnel integral to the study's completion. The authors would also like to thank May Tang (employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) for her contribution to the statistical analysis for the manuscript. This work was supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Medical writing and editorial assistance were provided by Dominic Singson, MD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

AUTHORSHIP

Contributions

P.A., P.B. B.V.T., M.A.S., P.M., and C.H.M. contributed to conception, design, or planning of the study.

P.A., N.A.J., J.R., V.R., D.M., T.P.V., A.T., B.V.T., A.H., S.C., and C.H.M. contributed to acquisition of the data.

P.L.Z., V.R., M.A.S., J.L., E.K., S.C., P.M., and C.H.M. contributed to analysis of the data.

P.A., P.L.Z., H.J.L., J.R., V.R., T.P.V., B.V.T., M.A.S., A.H., E.K., S.C., P.M., and C.H.M. contributed to interpretation of the results.

H.J.L., P. B. S.C., and C.H.M. contributed to drafting the manuscript.

P.A., P.L.Z., H.J.L., N.A.J., J.R., V.R., D.M., T.P.V., A.T., B.V.T., M.A.S., A.H., J.L., S.C., P.M., and C.H.M. contributed to critically reviewing or revising the manuscript for important intellectual content.

All authors approved the final manuscript for submission

Conflict-of-interest disclosure

P.A. reports grants or contracts from Merck, BMS, Affimed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM, and Kite; consulting fees from Merck, BMS, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome, Regeneron, Epizyme, AstraZeneca, and Genentech; and honoraria from Merck and BMS.

P.L.Z. reports honoraria from Roche, Takeda, Gilead, Sanofi, Incyte, Novartis, Merck, BMS, AstraZeneca, and Kyowa Kirin.

H.J.L. reports grants or contracts from BMS, Seagen, Oncternal, Merck, and Takeda; consulting fees from Century Therapeutics; and honoraria from Aptitude Health and the Korean Society of Cardio-Oncology.

N.A.J. reports consulting fees from Merck, AbbVie, Beigene, Roche, BMS, and Kite; and honoraria from Roche, AbbVie, and Beigene.

P.B. has no conflicts of interest to declare.

J.R. has no conflicts of interest to declare.

V.R. reports advisory board roles with Gilead, Infinity, MSD, BMS, Nanostring, Incyte, Roche, and AstraZeneca; and research funding from Astex, Argen-X, and GSK.

D.M. reports honoraria from MSD and BMS.

T.P.V. reports grants or contracts from Merck, Takeda, Amgen, Pfizer, and Dr Reddy's; consulting fees from Takeda, Roche, Genesis Pharma, and Novartis; honoraria from Takeda, Roche, Genesis Pharma, Merck, Novartis, Amgen, GSK, AbbVie, Integris, and AstraZeneca; and stock or stock options in Merck.

A.T. reports grants or contracts from Chugai Pharmaceutical, Kyowa Kirin, Perseus Proteomics, Pfizer Japan, and Novartis Pharma K.K.; and honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Nippon Shinyaku, Ono Pharmaceutical, and Eisai.

B.V.T. reports grants or contracts from Novartis, Takeda, and Merck Sharp & Dohme; consulting fees from Allogene, BMS/Celgene, Cerus, Incyte, Mitlenyi, Novartis, Pentixafarm, Roche, Amgen, Pfizer, Takeda, Merck Sharp & Dohme, and Gilead Kite; honoraria from AstraZeneca, Novartis, Roche Pharma AG, Takeda, and Merck Sharp & Dohme; and support for attending meetings and/or travel from AbbVie, AstraZeneca, Kite-Gilead, Merck Sharp & Dohme, Takeda, and Novartis.

M.A.S. reports grants or contracts from BMS, Bayer, AbbVie, and AstraZeneca; and consulting fees from AstraZeneca.

A.F.H. reports grants or contracts from BMS, Genentech, Merck, Seattle Genetics, AstraZeneca, Karyopharm, Kite Pharma, Gilead Sciences, AstraZeneca, and ADC Therapeutics; and consulting fees from BMS, Genentech, Merck, Seattle Genetics, AstraZeneca, Karyopharm, ADC Therapeutics, Takeda, Tubulis, Regeneron, Genmab, and Pfizer.

J.L. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA.

E.K. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of this analysis.

S.C. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA.

P.M. reports employment at Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and is a share/stockholder or has stock options in Merck & Co., Inc., Rahway, NJ, USA.

C.H.M. reports research funding from Merck & Co., Inc.

REFERENCES

1. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic hodgkin lymphoma. *J Clin Oncol*. 2017;35(19):2125-2132.
2. Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood*. 2019;134(14):1144-1153.
3. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: Extended follow-up of the multicohort single-arm phase ii checkmate 205 trial. *J Clin Oncol*. 2018;36(14):1428-1439.
4. Armand P, Kuruvilla J, Michot JM, et al. KEYNOTE-013 4-year follow-up of pembrolizumab in classical Hodgkin lymphoma after brentuximab vedotin failure. *Blood Adv*. 2020;4(12):2617-2622.
5. Hoppe RT, Advani RH, Weiyun ZAi et al. NCCN Guidelines® Insights: Hodgkin Lymphoma, Version 2.2022. *J Natl Compr Canc Netw*. 2022;20:322-334.
6. Merck Sharp & Dohme LLC. KEYTRUDA® (pembrolizumab) injection, for intravenous use. 01/2023. Merck Sharp & Dohme Corp.,: Whitehouse Station, NJ; 2023.
7. Cheson BD. The International Harmonization Project for response criteria in lymphoma clinical trials. *Hematol Oncol Clin North Am*. 2007;21(5):841-854.
8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
9. Zinzani PL, Chen R, Armand P, et al. Pembrolizumab monotherapy in patients with primary refractory classical Hodgkin lymphoma who relapsed after salvage autologous

stem cell transplantation and/or brentuximab vedotin therapy: KEYNOTE-087 subgroup analysis. *Leuk Lymphoma*. 2020;61(4):950-954.

10. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22(4):512-524.
11. Merryman RW, Castagna L, Giordano L, et al. Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma. *Leukemia*. 2021;35(9):2672-2683.
12. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed or refractory (R/R) classical hodgkin lymphoma (CHL) after autologous transplantation: 5-year overall survival from the phase 2 CheckMate 205 study. *Hematol Oncol*. 2021;39(suppl 2):122-125.

Table 1. Summary of overall response per the IWG 2007 criteria by investigator assessment in patients who received second-course treatment and had response data at data cutoff[a]

	Cohort 1 n = 9	Cohort 2 n = 7	Cohort 3 n = 3	Total n = 19
ORR, % (95% CI)	77.8 (40.0-97.2)	85.7 (42.1-99.6)	33 (0.8-90.6)	73.7 (48.8-90.8)
BOR, n (%)				
CR	1 (11.1)	6 (85.7)	0 (0)	7 (36.8)
PR	6 (66.7)	0 (0)	1 (33.3)	7 (36.8)
SD	1 (11.1)	0 (0)	2 (66.7)	3 (15.8)
PD	1 (11.1)	1 (14.3)	0 (0)	2 (10.5)

[a]One patient was not included because response data were not available at the time of data cutoff.

BOR, best overall response.

Table 2. Treatment-related adverse events

n (%)	Overall Population, N = 210
Any-grade TRAE	153 (72.9)
TRAEs ≥5%	
Hypothyroidism	30 (14.3)
Pyrexia	24 (11.4)
Fatigue	23 (11.0)
Rash	23 (11.0)
Diarrhea	17 (8.1)
Headache	16 (7.6)
Nausea	15 (7.1)
Arthralgia	13 (6.2)
Cough	13 (6.2)
Pruritus	13 (6.2)
Infusion-related reaction	11 (5.2)
Neutropenia	11 (5.2)
Grade 3 or 4 TRAEs	27 (12.9)
Grade 3 or 4 TRAEs in ≥2 patients	
Neutropenia	5 (2.4)
Pericarditis	2 (1.0)
Diarrhea	2 (1.0)

TRAE, treatment-related adverse event.

FIGURE LEGENDS

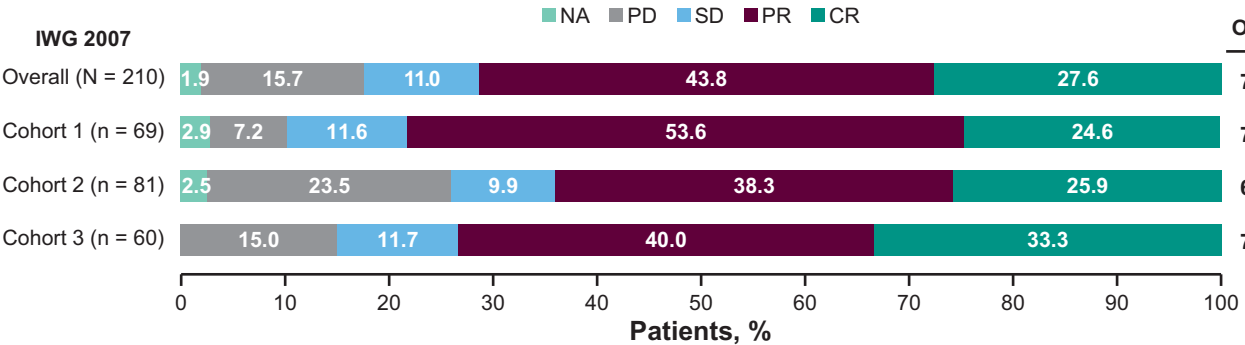
Figure 1. Objective response rate per the IWG 2007 and Lugano 2014 criteria for the overall population. CR, complete response; NA, not assessed; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Kaplan-Meier estimates for the overall population. (A) Response duration, (B) progression-free survival, and (C) overall survival. DOR, duration of response; NR, not reached; OS, overall survival; PFS, progression-free survival.

Figure 3. Kaplan-Meier estimates for the overall population by best objective response. (A) Response duration, (B) progression-free survival, and (C) overall survival. CR, complete response; DOR, duration of response; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Figure 4. Kaplan-Meier Estimates for patients who received second-course treatment. (A) Duration of the second response, (B) progression-free survival, and (C) overall survival. OS, overall survival; PFS, progression-free survival.

Figure 1



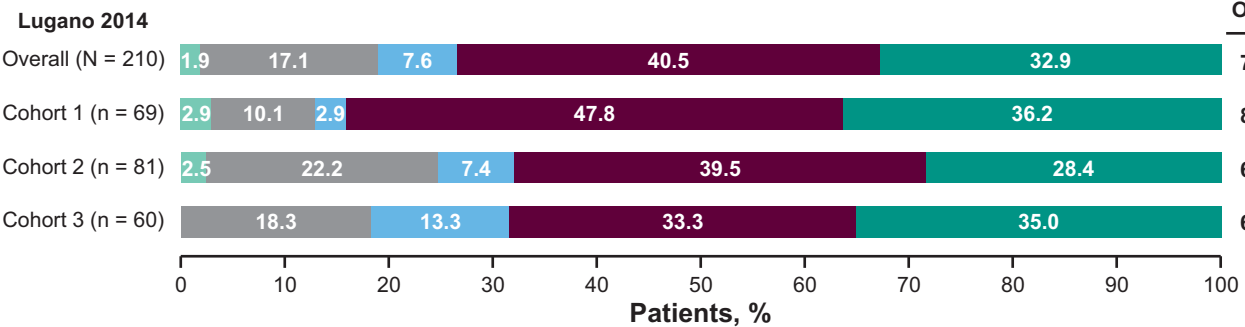
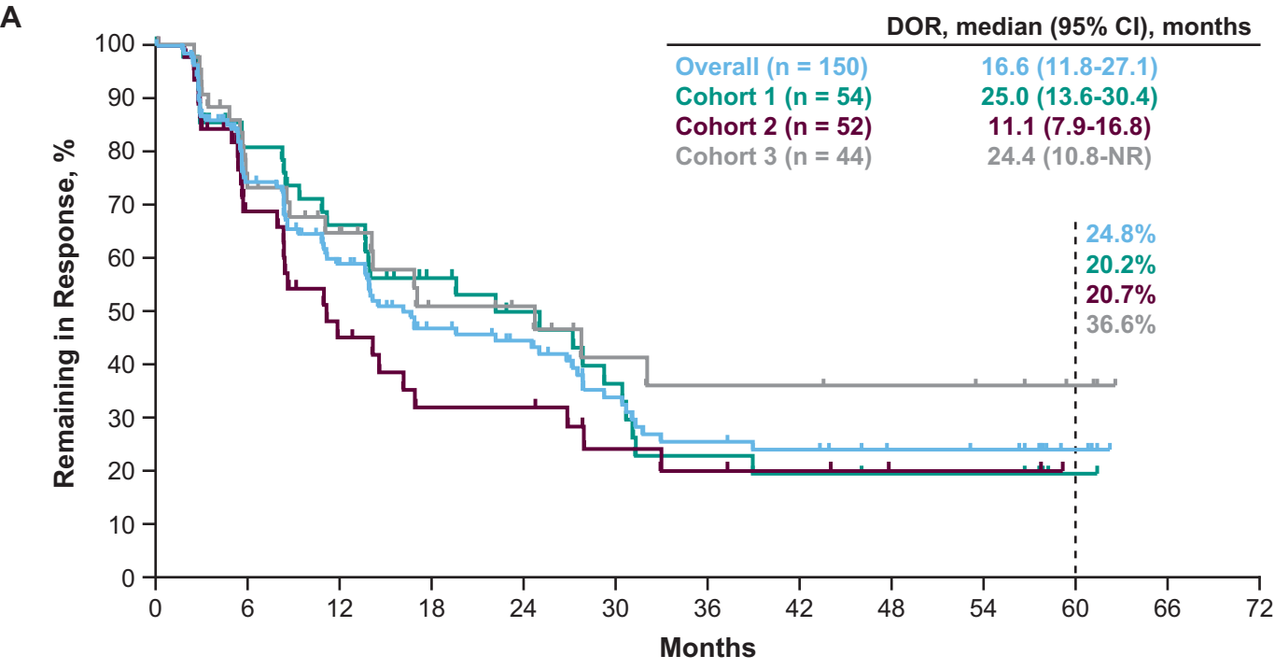
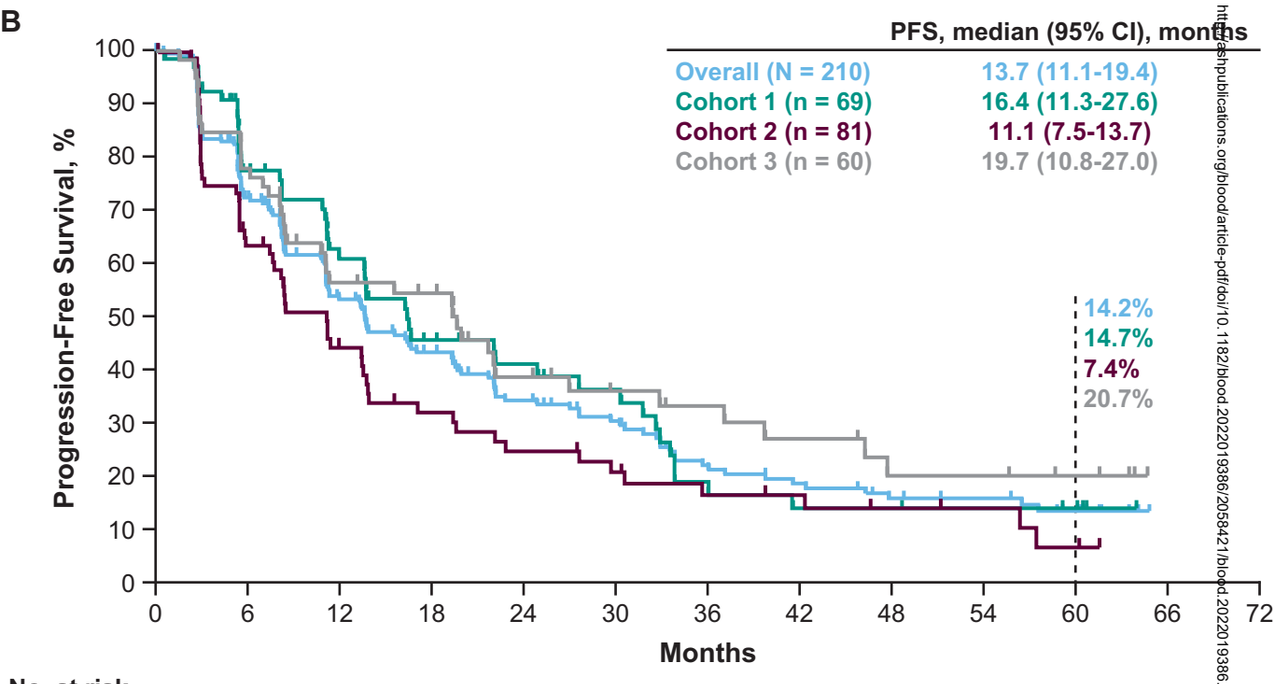


Figure 2



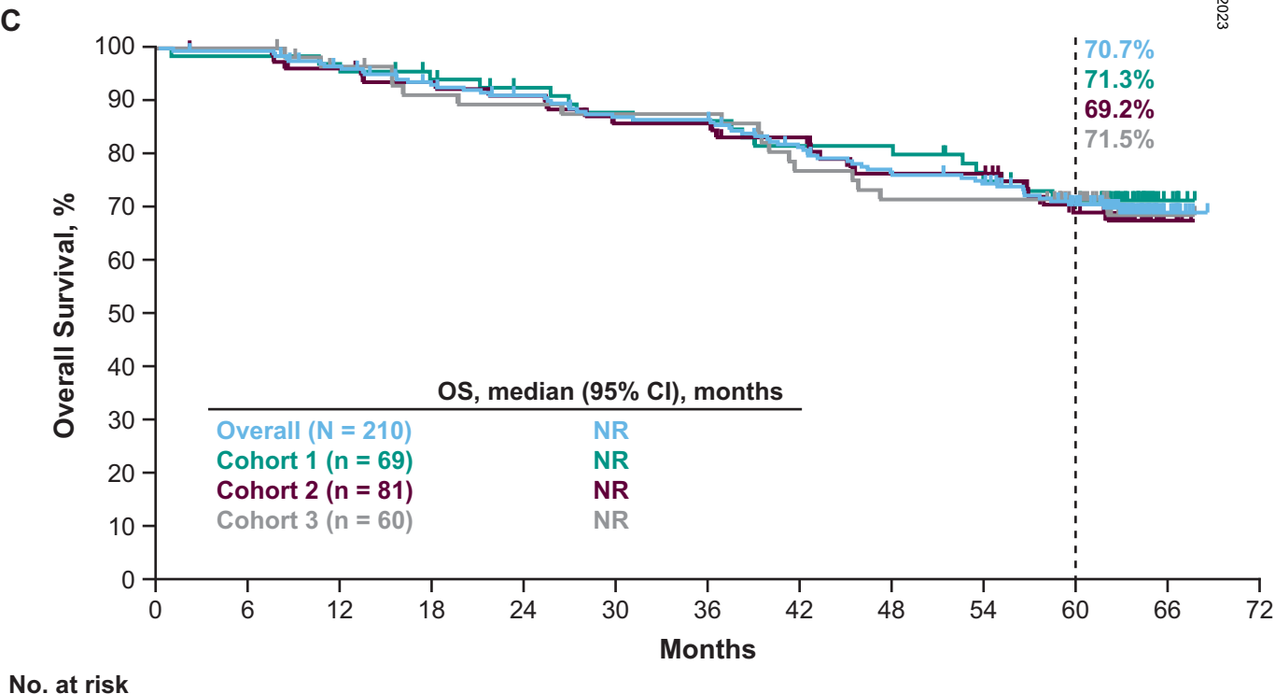
No. at risk

Overall	150	86	62	43	37	25	19	17	13	12	4	0	0
Cohort 1	54	34	27	19	15	11	7	6	5	5	1	0	0
Cohort 2	52	24	15	10	10	6	5	4	2	2	0	0	0
Cohort 3	44	28	20	14	12	8	7	7	6	5	3	0	0



No. at risk

Overall	210	134	8	67	49	39	27	22	17	15	10	0	0
Cohort 1	69	45	33	23	18	15	8	6	6	5	4	0	0
Cohort 2	81	43	26	18	14	11	8	7	5	4	2	0	0
Cohort 3	60	46	30	26	17	13	11	9	6	6	4	0	0



No. at risk

Overall	210	208	197	187	180	171	169	156	145	140	121	13	0
Cohort 1	69	68	66	63	59	56	55	50	49	44	40	6	0
Cohort 2	81	80	76	73	71	66	65	62	56	56	47	4	0
Cohort 3	60	60	55	51	50	49	49	44	40	40	34	3	0

Figure 3

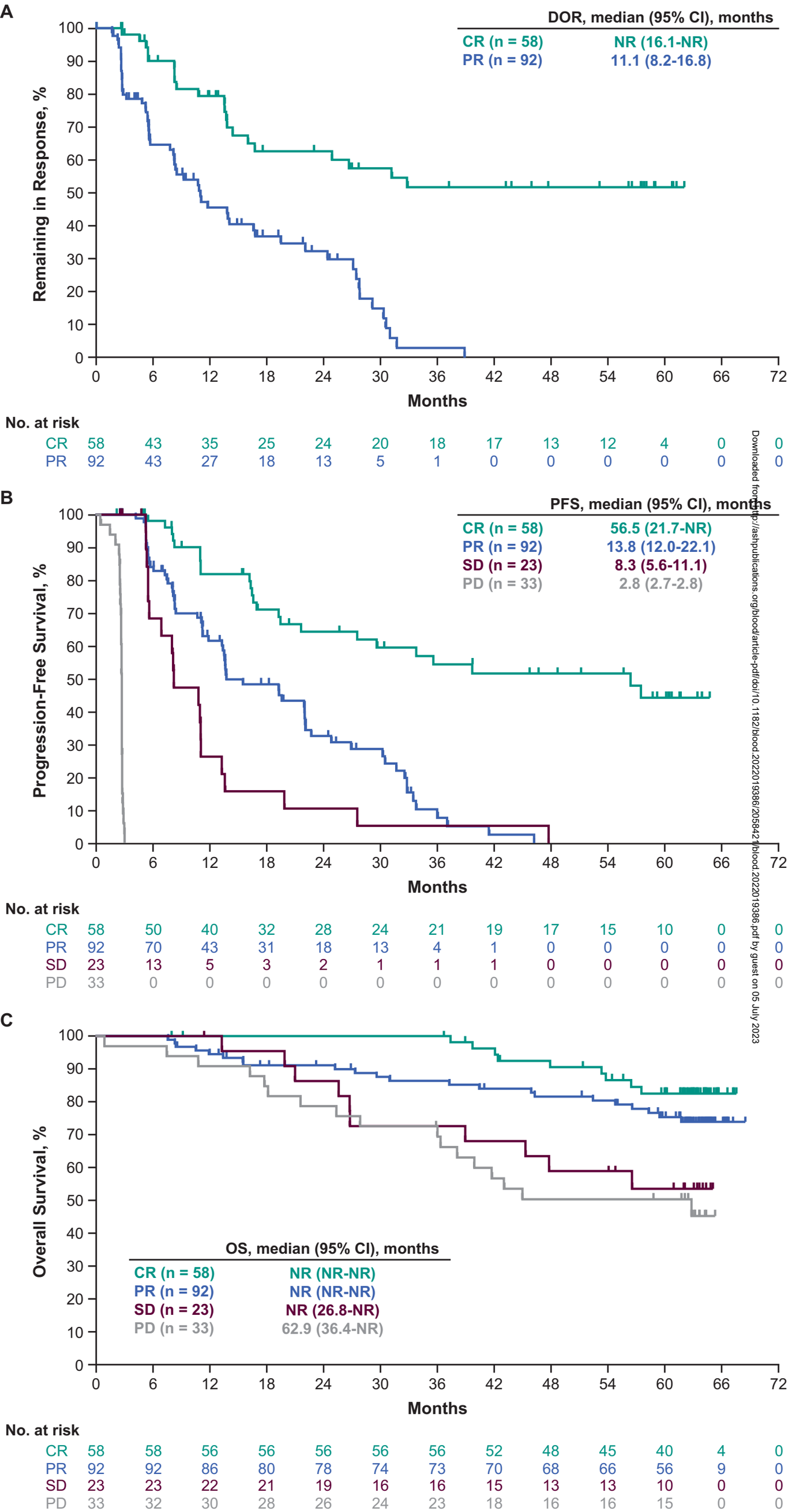


Figure 4