Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma

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Key Points

- Treatment options for relapsed/refractory PMBCL are limited, and prognosis is generally poor.
- Pembrolizumab had a manageable safety profile and promising antitumor activity in heavily pretreated rrPMBCL patients.

Treatment options for relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL) are limited, and prognosis is generally poor (overall response rate [ORR] 0% to 25%; 2-year overall survival 15%). PMBCL frequently involves PD-1 ligand overexpression, potentially making PMBCL particularly susceptible to PD-1 blockade. We evaluated safety and antitumor activity of pembrolizumab, an anti–PD-1 antibody, in rrPMBCL as part of the KEYNOTE-013 multicohort phase 1b trial. At time of data cutoff, 20 patients (median age 30 years; median 3 prior lines of therapy) had been enrolled and treated, of whom 17 were included in the efficacy analyses. Eleven patients (61%) experienced drug-related adverse events (mostly grade 1-2); none discontinued treatment due to adverse events. ORR was 41% (7/17); 6 additional patients (35%) had stable disease. Of patients evaluable by imaging, 13 out of 16 (81%) had decreases in target lesions. With a median follow-up of 11.3 months, median duration of response was not reached. Two patients reached the maximum 2-year treatment duration and remain in remission. Median overall survival was not reached for treated patients overall; all responders were still alive at data cutoff. These results in heavily pretreated rrPMBCL patients demonstrate that PD-1 blockade with pembrolizumab has a manageable safety profile and promising antitumor activity. This trial was registered at www.clinicaltrials.gov as #NCT01953692. (Blood. 2017;130(3):267-270)

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a diffuse large B-cell lymphoma (DLBCL) subtype occurring mostly in young women.1 While most patients with PMBCL are cured with standard frontline therapy,2 ~200 patients per year in the United States are diagnosed with relapsed/refractory PMBCL (rrPMBCL),3 which has a poor prognosis with limited treatment options.2,4 The rarity of rrPMBCL limits the ability to conduct clinical trials, and no standard of care has been identified; rrPMBCL is generally treated like other relapsed/refractory DLBCL (rrDLBCL) subtypes.2,4 National Comprehensive Cancer Network guidelines recommend that patients who relapse after autologous stem cell transplantation (SCT) or are ineligible for high-dose therapy be enrolled in clinical trials or receive second-line chemotherapy regimens, palliative radiation, or supportive care. These treatment options generally yield poor outcomes. In a study of 106 PMBCL patients, outcomes in both primary refractory and relapsed PMBCL after doxorubicin-containing therapy were poor: 0% of 35 primary refractory and 4 out of 18 relapsed patients (22%) responded to salvage treatment.5 In a retrospective study among 180 patients relapsed/refractory to 1 line of anthracycline-based chemotherapy, salvage chemotherapy resulted in significantly worse overall response rate (ORR) in rrPMBCL (25%) than in rrDLBCL overall (48%); 2-year overall survival after diagnosis of relapsed/refractory disease was 15% and 34%, respectively (also significantly different).5 There is an urgent medical need for more effective treatment options in rrPMBCL.

Like classical Hodgkin lymphoma, PMBCL frequently exhibits 9p24.1/PD-L1/PD-L2 copy-number alterations and rearrangements and associated PD-L1 and/or PD-L2 overexpression, potentially facilitating immune evasion.7,11 The genetics of PMBCL could thus make it particularly susceptible to PD-1 blockade.11 Pembrolizumab is a humanized anti–PD-1 monoclonal antibody blocking interaction of PD-1 with its ligands, PD-L1 and PD-L2. Pembrolizumab has demonstrated efficacy against solid tumors2,13 and promising antitumor activity in Hodgkin lymphoma.14 Here, we report results from the PMBCL cohort of an ongoing phase I trial of pembrolizumab in patients with hematologic malignancies.
Study design

KEYNOTE-013 is a multicenter, international, multicohort, open-label phase 1b trial evaluating safety, tolerability, and antitumor activity of pembrolizumab in patients with selected hematologic malignancies. Adults with rrPMBCL who failed, were ineligible for, or refused autologous SCT formed an independent trial cohort. Key eligibility criteria were Eastern Cooperative Oncology Group performance status 0-1, no active autoimmune disease, no allogeneic SCT within the past 5 years, no symptomatic central nervous system disease, no active infection requiring intravenous therapy, and no prior therapy with agents targeting T-cell costimulation or checkpoint pathways. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. (The complete Study Protocol is available in the supplemental Material, available on the Blood Web site.)

The first 11 patients were to receive intravenous pembrolizumab 10 mg/kg every 2 weeks for the trial’s duration (1 patient withdrew shortly after enrollment and was not dosed); after a study amendment, the subsequent 8 patients received a fixed dose of IV pembrolizumab 200 mg every 3 weeks, based on pharmacokinetic/pharmacodynamic evaluations that demonstrated the regimens provided similar exposure. Treatment continued up to 2 years, until unacceptable toxicity, or until confirmed disease progression. Treatment response was evaluated using International Working Group 2007 criteria for malignant lymphoma. Adverse events (AEs) were collected throughout the study and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary end points were safety and ORR by investigator assessment. Key secondary end points included complete response (CR) rate, duration of response (DOR), and overall survival. Patients were censored for DOR at the time of starting another anticancer therapy. Safety was evaluated in all patients who received ≥1 dose of study drug; those patients who also had ≥1 postbaseline tumor assessment, or disease progression before first tumor assessment, were included into the efficacy analyses.

Table 1. Clinical outcomes in patients evaluated for efficacy: response to treatment

<table>
<thead>
<tr>
<th>n (%) (N = 17)</th>
<th>90% confidence interval</th>
</tr>
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<tbody>
<tr>
<td>ORR</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>No assessment</td>
<td>1 (5.9)*</td>
</tr>
</tbody>
</table>

*Patient discontinued pembrolizumab therapy prior to the first radiologic tumor assessment because of clinical disease progression.

Figure 1. Treatment response in the 16 pembrolizumab-treated patients with rrPMBCL who were evaluable (by imaging) for efficacy at the time of data cutoff. (A) Best percentage change from baseline in target lesions. (Number at the end of each bar indicates the patient identification number.) (B) Transplant eligibility, treatment duration, investigator-assessed response to treatment, and duration of response. (Unless indicated otherwise, patients had stable disease.) PD, progressive disease; PR, partial response; SD, stable disease.
Table 2. Clinical outcomes in patients evaluated for efficacy: duration of response to prior therapy and to pembrolizumab

<table>
<thead>
<tr>
<th>Complete responders</th>
<th>Duration of response to prior therapy, mo (type of response)</th>
<th>Duration of response to pembrolizumab, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2 (SCT ineligible)</td>
<td>ACVBP — (PR) 2</td>
<td>20.5* (response ongoing)</td>
</tr>
<tr>
<td>Patient 7 (prior autologous SCT)</td>
<td>R-CHOP — (SD)</td>
<td>2.4 (response ongoing)</td>
</tr>
<tr>
<td>Patient 3 (SCT ineligible)</td>
<td>IP-NVB — (SD)</td>
<td>—</td>
</tr>
<tr>
<td>Patient 8 (prior autologous SCT)</td>
<td>R-DHAP — (PD)</td>
<td>—</td>
</tr>
<tr>
<td>Patient 5 (SCT ineligible)</td>
<td>BEAM — (PD)</td>
<td>—</td>
</tr>
<tr>
<td>Patient 6 (SCT ineligible)</td>
<td>R-DHAP — (PD)</td>
<td>—</td>
</tr>
</tbody>
</table>

Patient numbers refer to Figure 1.
ACVBP, bleomycin, cyclophosphamide, doxorubicin, prednisone, and vindesine; AraC, cytarabine; BEAM, melphalan, carmustine, cytarabine, and etoposide; BV, brentuximab vedotin; CCNU-EAM, cytarabine, etoposide, lomustine, and melphalan; CHO-MTX, doxorubicin, cyclophosphamide, vincristine sulfate, methotrexate, etoposide, and ifosfamide; DA-EPOCH, cyclophosphamide, doxorubicin, etoposide, prednisone, and vincristine sulfate; IE, etoposide and ifosfamide; IP-NVB, ifosfamide, methylprednisolone, and vinorelbine tartrate; MTX, methotrexate; PD, progressive disease; PR, partial response; R-IE, rituximab, etoposide, and ifosfamide; R-ACVB, rituximab, doxorubicin, vindesine, bleomycin, and cyclophosphamide; R-DHAP, cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine sulfate; R-DAC, carboplatin, cytarabine, dexamethasone, and rituximab; R-DHAX, rituximab, cytarabine, cisplatin, and dexamethasone; R-DHAP, rituximab, dexamethasone, oxaliplatin, and rituximab; R-EPOCH, cyclophosphamide, doxorubicin, etoposide, prednisone, rituximab, and vincristine sulfate; R-VACOP-B, etoposide, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

*Patient initially presented with partial response, and the time shown represents the total duration of response since the date partial response was first observed.

Results and discussion

By the analysis cutoff date (27 May 2016), 19 patients had been enrolled, and 18 received ≥1 dose of study drug. One patient had not yet reached the first response assessment at time of data cutoff; the remaining 17 comprised the efficacy analysis population. Median age was 30 years, and 72% were female (supplemental Table 1). Patients were heavily pretreated and had relapsed on multiple treatments; pembrolizumab was the median fourth line of therapy (range, 3rd to 7th). Most patients (94%) previously received rituximab, 33% had prior autologous SCT, and 61% had prior radiation. Twelve patients were transplant ineligible because of chemotherapy-resistant disease.

The safety and tolerability profile of pembrolizumab in rrPMBCL appeared manageable. Eleven patients (61%) experienced drug-related adverse events (DRAEs), most of which were grade 1 or 2 (supplemental Table 2). Most commonly reported DRAEs were hypothyroidism, diarrhea, nausea, fatigue, pyrexia, and decreased appetite (n = 2 patients each). The only grade 3 DRAE was neutropenia in 1 patient. The only grade 4 DRAE was veno-occlusive liver disease subsequent to allogeneic SCT during the follow-up period after pembrolizumab was discontinued; the patient recovered from veno-occlusive liver disease. Potential immune-related AEs (n = 1 each) were grade 2 aggravated diarrhea and grade 2 radiation pneumonitis. No patient discontinued treatment due to AEs. There were no treatment-related deaths.

At best response, the ORR was 41% (7/17), with 2 patients achieving a CR and 5 a partial response; an additional 35% (6/17) had stable disease as best response (Table 1). This ORR was higher than reported in prior retrospective studies, where it ranged from 0% to 25% in patients primary refractory to or relapsed after anthracycline-based chemotherapy.5,6 In our study, 81% (13/16) of patients evaluable by imaging had an overall decrease in target lesions; in 2 of these patients, reductions were <5% (Figure 1A). With a median follow-up duration of 11.3 months (range, 3.4 to 27.4 months), median DOR was not reached, and 6 of the 7 responses in patients evaluable by imaging were ongoing at the time of data cutoff (Figure 1B). DOR ranged from 2.3 to 22.5 + months; DOR in the 2 patients with CR was 2.3 + and 20.5 + months (patients 7 and 2 in Figure 1, respectively). Remissions achieved with pembrolizumab appeared to be long-lasting, while prior treatment responses to high-dose chemotherapy, including to first-line therapy, lasted a few months at most (Table 2). None of the responders received autologous SCT. Two patients, both with stable disease, received allogeneic SCT after pembrolizumab discontinuation (patients 9 and 10). Ten patients discontinued treatment: 5 due to progressive disease based on imaging (patients 4, 10, 11, 13, and 14), 4 for clinical progression (patients 12, 15, and 16 and 1 patient not depicted in Figure 1), and 1 due to physician decision (patient 9).
Two patients with objective response (CR or partial response) reached the maximum 2 years of treatment shortly before data cutoff and remain in remission (follow-up: 25.4 months [patient 1], 23.8 months [patient 2]). All patients who had an objective response to pembrolizumab were alive at time of data cutoff. While these outcomes are very encouraging overall, there exist few published studies specifically conducted in this rare patient population that can serve as accurate historical controls for efficacy comparisons with other treatment options for rPMBCL. \(^5,6\) A recent phase 2 trial with brentuximab vedotin in this specific setting was terminated early due to low ORR (2/15 [13%]). \(^7,8\)

These preliminary efficacy and safety findings indicate that pembrolizumab has potential to provide substantial clinical benefit in heavily pretreated patients with rPMBCL, particularly given the lack of effective alternatives. A global, multicenter, phase 2 trial (KEYNOTE-170) is currently evaluating single-agent pembrolizumab in this setting (www.clinicaltrials.gov #NCT02576990).

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References


Authorship

Contribution: P.A. and M.A.S. contributed to study inception and design; P.L.Z., P.A., V.R., C.H.M., J.-M.M., and J.K. enrolled patients into this study; Y.Z. conducted the statistical analysis of the data; P.A., J.K., M.A.S., P.L.Z., A.B., and S.C. contributed to data interpretation; P.A., P.L.Z., S.C., and A.B. contributed to writing the first draft of the manuscript; and all authors critically revised the manuscript for important intellectual content, reviewed the submitted version of the manuscript, and agree with its content and submission.

Conflict-of-interest disclosure: P.L.Z. has been a scientific advisor to Merck Sharp & Dohme, Bristol-Myers Squibb, Celgene, Gilead, Infinity, Janssen, Pfizer, Roche, and Takeda. V.R. has been a scientific advisor to Bristol-Myers Squibb, Eisai, Gilead, Infinity, Pharmamar, and NanoString; has received research funding from ArgenX; and has received consulting fees from Servier. C.H.M. has been a scientific advisor to and received research funding from Merck & Co., Inc., BMS, and Seattle genetics. J.-M.M. has received consulting fees from Bristol-Myers Squibb. J.K. has received research funding from Roche; consultancy fees from Bristol-Myers Squibb, Gilead, Janssen, Roche, and Seattle Genetics; and honoraria from Merck & Co., Inc., Amgen, Bristol-Myers Squibb, Celgene, Gilead, Roche, Janssen, Lundbeck, and Seattle Genetics. A.B., Y.Z., and S.C. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may own stock and/or hold stock options in the company. M.A.S. has been a scientific advisor to Merck & Co., Inc., and received research funding and consulting fees from Bristol-Myers Squibb. P.A. received institutional research funding from Merck & Co., Inc., Affimed, Bristol-Myers Squibb, Roche, and Pfizer and consultation fees from Merck & Co., Inc., Bristol-Myers Squibb, Infinity Pharmaceuticals, and Pfizer.

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