Pembrolizumab in relapsed or refractory Richter syndrome

Approximately 10% of patients with chronic lymphocytic leukaemia (CLL) experience transformation to Richter syndrome (RS).\(^1\) Associated with an aggressive disease course often refractory to chemotherapy, RS demonstrates poor outcomes, especially for patients with prior CLL treatment and even more so for patients with relapsed/refractory (RR) disease.\(^2\) Pembrolizumab-containing combination chemotherapy is the most widely used first-line treatment in diffuse large B-cell lymphoma (DLBCL)-type RS, and stem cell transplantation (SCT) is often recommended as consolidation in suitable patients.\(^3,5\) Additionally, early-phase studies have shown activity of novel agents in patients with DLBCL-type RS.\(^6\)–\(^8\) Patients with classical Hodgkin lymphoma (cHL)-type RS are typically treated with conventional CHL regimens, yet their outcomes are inferior to those for de novo cHL.\(^2\)

The programmed death 1 (PD-1) pathway appears to play an important and therapeutically exploitable role in certain lymphoma subsets, especially cHL and primary mediastinal large B-cell lymphoma (PMBCL).\(^9\)–\(^10\) In which pembrolizumab, a PD-1 inhibitor, has already demonstrated activity.\(^11\)–\(^12\) RS may also be sensitive to PD-1 blockade. Indeed, results of a phase-2 study of pembrolizumab in 25 patients with CLL and RS (n = 9) demonstrated an objective response in four of nine patients with the DLBCL variant of RS and a median overall survival (OS) of 10–7 months, suggesting that PD-1 inhibition may be a viable treatment option in this disease.\(^13\)

KEYNOTE-170 (NCT02576990) was an open-label multicentre phase-2 trial evaluating efficacy and safety of pembrolizumab monotherapy in two cohorts: RR PMBCL and RS. The RS cohort was designed to validate findings from Ding et al. Adults (aged ≥ 18 years) with a pathologic diagnosis of RS who were either refractory to or relapsed after one or more previous treatments were included. Patients were required to have radiographically measurable disease, Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function. Patients were treated with pembrolizumab 200 mg intravenously every three weeks for up to 35 administrations (approximately two years). Additional therapies to treat the underlying CLL (according to treatment guidelines) could be added at the physician’s discretion. The study was approved by institutional review boards or ethics committees at each study site and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Primary endpoint was objective response rate (ORR) by independent central review, according to International Working Group 2007 response criteria for RS.\(^14\) Secondary endpoints were duration of response (DOR), progression-free survival (PFS), and OS. Efficacy and safety populations consisted of all patients who received one or more doses of study medication. ORR was analysed using point estimate and 90% two-sided exact confidence interval (CI) using the Clopper–Pearson method. DOR, PFS and OS were estimated using the Kaplan–Meier method. Disease response was assessed using PET and CT scans at week 12 and every 12 weeks thereafter. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events, version 4.0. Immune-mediated AEs were based on a list of terms specified by the sponsor and included by the investigator.
regardless of attribution to study treatment or immune relatedness. Data cut-off was 28 May 2019.

Twenty-three patients enrolled and received pembrolizumab. Most (78%) had DLBCL variant histology; two (9%) had cHL histology (Table SI). Most patients (83%) had received two or more lines of therapy for RS (Table SI). Most patients (96%) previously received rituximab and 48% previously received ibrutinib. At data cut-off, all patients discontinued treatment because of disease progression (n = 16, 70%), AEs regardless of treatment relatedness (n = 4, 17%), patient withdrawal (n = 2, 9%) or physician’s decision (n = 1, 4%). Median time on therapy was 0.7 months.

Table I. Best objective tumour response.

| Pembrolizumab | n = 23 |
|---------------|--------|
| Objective response rate, n (%) [95% CI] | 3 (13·0) [2.8–33.6] |
| Best objective response, n (%) | |
| Complete response | 1 (4·3) |
| Partial response | 2 (8·7) |
| Stable disease | 1 (4·3) |
| Progressive disease | 11 (47·8) |
| No assessment* | 8 (34·8) |

CI, confidence interval.

*Patients with no assessment either died or discontinued the study without having had imaging performed.

Table II. Treatment-related adverse events of any grade and of grade 3–4.

| Pembrolizumab | n = 23 |
|---------------|--------|
| One or more AE, n (%) | 13 (56·5) 6 (26·1) |
| Anaemia | 2 (8·7) 2 (8·7) |
| Hypothyroidism | 2 (8·7) 0 |
| Fatigue | 2 (8·7) 0 |
| Pyrexia | 2 (8·7) 0 |
| Rash | 2 (8·7) 1 (4·3) |
| Autoimmune haemolytic anaemia | 1 (4·3) 1 (4·3) |
| Febrile neutropenia | 1 (4·3) 1 (4·3) |
| Lymph node pain | 1 (4·3) 0 |
| Neutropenia | 1 (4·3) 1 (4·3) |
| Hyperthyroidism | 1 (4·3) 1 (4·3) |
| Colitis | 1 (4·3) 0 |
| Diarrhoea | 1 (4·3) 0 |
| Oral discomfort | 1 (4·3) 0 |
| Stomatitis | 1 (4·3) 0 |
| Chills | 1 (4·3) 0 |
| Herpes zoster | 1 (4·3) 0 |
| Urinary tract infection (bacterial) | 1 (4·3) 0 |
| Increased blood glucose | 1 (4·3) 0 |
| Decreased platelet count | 1 (4·3) 1 (4·3) |
| Hypokalaemia | 1 (4·3) 0 |
| Pneumonitis | 1 (4·3) 1 (4·3) |
| Maculopapular rash | 1 (4·3) 0 |

(range, 0·03–12·6); 13 patients (57%) had pembrolizumab exposure of less than one month, and four patients (17%) had exposure for three or more months. Median number of doses was two (range, 1–18).

Median follow-up was 3·8 months (range, 0·2–31·0). ORR was 13·0% (95% CI, 2·8–33·6) with one complete response (CR) and two partial responses (PR, Table I). ORR for patients with non-cHL RS was 4·8% (1/21). Two responders (one CR and one PR) had cHL histology and did not receive prior ibrutinib, and one responder (PR) had DLBCL histology and received ibrutinib concomitantly with pembrolizumab. Five patients experienced tumour reduction from baseline (Fig S1A). One responder subsequently underwent allogeneic SCT and remained in remission at data cut-off, whereas two experienced disease progression after 2·7 and 6·2 months (Fig S1B) respectively. Median PFS and OS were 1·6 months (95% CI, 1·0–2·1) and 3·8 months (95% CI, 1·8–18·1) respectively (Fig S2). Three patients subsequently underwent allogeneic SCT [one in remission and two after additional therapy (venetoclax for one patient and venetoclax and ibrutinib for the other patient)]. Two were alive at data cut-off, and one died after disease progression.

Treatment-related AEs occurred in 57% of patients, with anaemia, hypothyroidism, fatigue, pyrexia and rash (two patients each, 9%) most commonly reported (Table II). Anaemia was the only grade 3–4 treatment-related AE reported in one or more patients (n = 2, 9%). Three patients (13%) discontinued because of treatment-related AEs (autoimmune haemolytic anaemia, pneumonitis and rash). Five patients (22%) experienced six immune-mediated AEs [one colitis (grade 1), two hypothyroidism (grade 2) and one each of hyperthyroidism, pneumonitis and rash (all grade 3)]. Median time to onset of first immune-related AE was 20 days (range, 7–168). Five patients died from AEs likely related to disease progression (hypercalcaemia, septic shock, hypercalcaemia of malignancy and subdural haematoma); one patient died of unknown cause after reporting disease progression. None of the deaths were considered treatment-related by the investigators.

The safety profile of pembrolizumab was manageable and consistent with that of previous reports. Although both patients with Hodgkin histology demonstrated a response to therapy, less activity was observed in the non-cHL histology. Most patients experienced disease progression early or died from AEs associated with underlying malignancy. It is conceivable that rapid disease progression limited their ability to benefit from longer pembrolizumab exposure. It is possible that co-targeting PD-1 and other signalling pathways could improve outcomes, a strategy that is currently being tested in several trials.

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Conflicts of interest

PA: Consultancy, research funding (institution) and personal fees from Merck and Bristol-Myers Squibb during the conduct of the study; consultancy outside the submitted work for Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, C4, GenMab; research funding outside the submitted work from Affimed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM. NM: No conflicts to disclose. DM: Clinical study support from Merck during the conduct of the study; personal fees (lectures) from Roche, Takeda, Merck and Bristol-Myers Squibb outside the submitted work. JZ: Consultancy role with Seattle Genetics, Mundi Pharma, Verastem and Kyowa Kirin; member of a speaker’s bureau for Seattle Genetics and Spectrum. BE: Grants from Janssen, Roche, AbbVie, Gilead and BeiGene; personal fees from Janssen, Roche, Novartis, Gilead, Celgene, AstraZeneca, Oxford Biomedica (UK), Adaptive Biotechnologies and ArQule. ZG: No conflicts to disclose. EH: Research funding/grants from Merck, AstraZeneca, Bristol-Myers Squibb, Celgene, Merck Serono; personal advisory board fees from AstraZeneca; advisory board payment to institution from Merck, Roche and Gilead. JMP: personal fees from Gilead, Pharmacies and AstraZeneca. TP: No conflicts to disclose. VR: Non-financial research funding from ArgenX; personal fees (advisory board) from Gilead, Infinity, Merck, Bristol-Myers Squibb, Epizyme, Nanostring, Incyte, Roche, AstraZeneca; personal fees (consulting) from Servier. JS: Clinical study support from Merck to institution during the conduct of the study; grants outside the submitted work from Seattle Genetics, Bristol-Myers Squibb, Pharmacyclics, AstraZeneca and Imbrium; personal fees outside the submitted work from Seattle Genetics, Bristol-Myers Squibb, Pharmacyclics and AstraZeneca. AC: Institutional research grant from Merck during the conduct of the study; institutional research grant outside the submitted work from Merck, Roche, Pfizer, Bayer, Novartis, MEI-Pharma and ADCT Therapeutics. AC: Employee at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stockholder for Merck & Co., Inc., Kenilworth, NJ, USA. RO: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stockholder for Merck & Co., Inc., Kenilworth, NJ, USA. PM: Employee at and received travel accommodations/expenses from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stockholder for Merck & Co., Inc., Kenilworth, NJ, USA. BC: Research support to institution for clinical trial from Merck, Genetech, Celgene, Triphase, Acerta, Seattle Genetics, Millennium, Immunomedics, Cephalon.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics and disease demographics.

Fig S1. Best tumour change from baseline per central review (A) and time to response and duration of response based on International Working Group per central review (B).

Fig S2. Kaplan–Meier analysis of progression-free survival (A) and overall survival (B).

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