Pembrolizumab combined with carfilzomib and low-dose dexamethasone for relapsed or refractory multiple myeloma: Cohort 2 of the phase I KEYNOTE-023 study

Prognosis for patients with treatment-refractory or relapsed multiple myeloma (MM) is extremely poor, and new treatment approaches are urgently sought. Characterised by multifaceted immune suppression, MM can develop resistance to therapy, which makes it particularly difficult to treat.[1] Like other cancers that evade immune detection through the production of checkpoint proteins, MM cells show increased expression of programmed death 1 (PD-1) ligand (PD-L1).[2] Pembrolizumab is a highly selective monoclonal antibody against PD-1 that has shown efficacy in some haematological malignancies.[3–5] Preliminary evidence suggests that pembrolizumab may be a promising therapeutic option for patients with MM,[6] particularly as combination therapy with an immunomodulatory agent and dexamethasone. In Cohort 1 of KEYNOTE-023 (NCT02036502), pembrolizumab plus low-dose dexamethasone and the immunomodulatory drug lenalidomide demonstrated promising safety and efficacy in patients with relapsed or refractory MM (rrMM).[7] In parallel, two phase III randomised controlled studies were initiated to evaluate pembrolizumab combined with dexamethasone plus either lenalidomide (KEYNOTE-185, NCT02579863) or pomalidomide (KEYNOTE-183, NCT02576977) compared with dexamethasone plus lenalidomide or pomalidomide alone.[8,9] Interim analysis by the internal data monitoring committee responsible for the KEYNOTE-183 and KEYNOTE-185 studies, however, determined there was a higher risk for death among patients receiving the pembrolizumab combinations.[8,9] The United States Food and Drug Administration determined that the benefit–risk ratio of these regimens did not allow continuation, and a clinical hold was placed on all active studies, including Cohort 1 of KEYNOTE-023.[10]

KEYNOTE-023 had begun enrolling a second cohort for its expansion phase on 31 October 2016 to evaluate safety and preliminary efficacy of pembrolizumab in combination with carfilzomib and low-dose dexamethasone in patients with rrMM. The proteasome inhibitor carfilzomib was approved as monotherapy in patients with rrMM who received one or more lines of therapy and as combination therapy with lenalidomide and dexamethasone or daratumumab and dexamethasone in the second to fourth lines of therapy.[11] A partial clinical hold was placed on Cohort 2 of KEYNOTE-023 on 15 September 2017, at which time enrolment was halted and treatment was discontinued except in patients who were deriving clinical benefit. In the present study, we report the results from the cohort of patients treated with pembrolizumab plus carfilzomib.

Eligible adults (aged ≥18 years) had rrMM with measurable disease and were previously treated with one to three lines of therapy (planned enrolment, 30–45 patients). All patients received intravenous (IV) pembrolizumab 200 mg every 3 weeks starting on day 1 of cycle 1. Oral or IV dexamethasone 20 mg was administered on days 1, 2, 8, 9, 15, 16, 22 and 23 of each 23-day cycle. Carfilzomib (starting at 20 mg/m^2 on days 1 and 2 of cycle 1 and escalating to 56 mg/m^2 thereafter as tolerated) was administered 30 min to 4 h after dexamethasone treatments on days 1, 2, 8, 9, 15 and 16 of each cycle followed by a 12-day rest period. Treatment continued until confirmed disease progression, unacceptable toxicity, investigator decision or withdrawal of consent. The study was approved by applicable Institutional Review Boards or Ethics Committees and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

The primary objective was to determine the safety of pembrolizumab in combination with carfilzomib and low-dose dexamethasone in patients with rrMM. Adverse events (AEs), including immune-mediated AEs, were recorded and graded based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Secondary objectives were to evaluate efficacy through the objective response rate (ORR) and disease control rate (DCR) based on investigator assessment per International Myeloma Working Group 2006 criteria.[12] Duration of response (DOR), progression-free survival (PFS), time to progression and overall survival (OS) were exploratory endpoints. Safety and efficacy were analysed in patients who received ≥1 dose of study treatment. The point estimates and confidence intervals (CIs) of the ORRs were evaluated using the Clopper–Pearson method, and DOR, PFS and OS were evaluated using the Kaplan–Meier method for censored data.

From 31 October 2016 to 15 September 2017, 10 patients were enrolled and treated. Four were women, and nine were between 18 and 69 years of age [median (range) age 61·0 (42–85) years; Table SI). Seven of the 10 patients had Stage III disease (Table SI). Patients received a median (range) of 9·5 (2–21) cycles of pembrolizumab, 42·0 (10–93) cycles of

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Table I. Incidence of all-cause adverse events (AEs) in two or more patients, Grade 3–5 AEs in all patients and corresponding treatment-related AEs for both groups.*

	Any grade		Grade 3–5	
Patients experiencing AEs,† *n/N*	All cause	Treatment-related	All cause	Treatment-related
Anaemia	5/10	0/10	1/10	0/10
Pneumonia	5/10	3/10	5/10	3/10
Diarrhoea	4/10	2/10	1/10	1/10
Pyrexia	4/10	0/10	0/10	0/10
Acute kidney injury	3/10	0/10	1/10	0/10
Asthenia	3/10	1/10	0/10	0/10
Headache	3/10	2/10	1/10	0/10
Muscle spasms	3/10	2/10	0/10	0/10
Thrombocytopenia	3/10	3/10	2/10	2/10
Blood creatinine increased	2/10	1/10	1/10	0/10
Bronchitis	2/10	1/10	0/10	0/10
Insomnia	2/10	1/10	0/10	0/10
Nausea	2/10	1/10	1/10	1/10
Neutropenia	2/10	1/10	2/10	1/10
Rash	2/10	0/10	0/10	0/10
Rhinitis	2/10	0/10	0/10	0/10
Tinnitus	2/10	2/10	0/10	0/10
Vomiting	2/10	2/10	1/10	1/10
Agitation	1/10	1/10	1/10	1/10
Alanine aminotransferase increased	1/10	0/10	1/10	0/10
Bacteraemia	1/10	0/10	1/10	0/10
γ-glutamyltransferase increased	1/10	0/10	1/10	0/10
Hepatocellular injury	1/10	1/10	1/10	1/10
Hypokalaemia	1/10	0/10	1/10	0/10
Influenza	1/10	1/10	1/10	1/10
Hypopituitarism	1/10	1/10	1/10	1/10
Liver injury	1/10	0/10	1/10	0/10
Multiple organ dysfunction syndrome‡	1/10	1/10	1/10	1/10
Prostatitis	1/10	0/10	1/10	0/10

AE, adverse event.

*For each Grade 3–5 AE, the corresponding all-grade AE frequency is provided even if the event did not occur in two or more patients.

†Preferred terms from Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.

‡Grade 5.

carfilzomib and 51·0 (12–124) cycles of dexamethasone. The median (range) follow-up (defined as the time from first dose to the date of death or to the end-of-study date if the patient was still alive) was 26·0 (2·0–35·2) months. At the final database cut-off (31 March 2020) all patients had discontinued treatment, six because of AEs (Grade 1 cardiac amyloidosis, Grade 3 hypopituitarism, acute kidney injury, liver injury, hepatocellular injury and Grade 5 multiple organ dysfunction syndrome), two because of physician decision and one each because of progressive disease and study termination by the sponsor.

All 10 patients experienced one or more AE (Table SII). Treatment-related AEs were reported in eight of the 10 patients; one patient experienced a serious treatment-related AE (multiple organ dysfunction syndrome), which was fatal (Table SII). The fatal AE was considered related to both treatments based on investigator assessment. The most common Grade 3–5 AEs were pneumonia, which occurred in five of the 10 patients (three Grade 3, two Grade 4), followed by neutropenia (Grade 3) and thrombocytopenia (Grade 4) in two patients each (Table I). Two of the 10 patients experienced immune-mediated AEs: one experienced Grade 2 hypothyroidism and Grade 3 hypophysitis and the other experienced Grade 2 nephritis.

The ORR was 70·0% (95% CI 34·8–93·3) with a median DOR of 14·1 months, and the DCR was 100% (Table II). The median PFS and OS were 14·3 (95% CI 2·0–19·6) and 22·5 (95% CI 2·0–not available) months respectively (Table II; Figure S1).

Although the first randomised controlled studies of pembrolizumab-containing combination therapies for rrMM were unsuccessful, further study with close consideration of

Table II. Summary of efficacy outcomes.

	Pembrolizumab + carfilzomib + dexamethasone (N = 10)
Patients achieving an outcome, *n/N* (%)	
Objective response rate*	7/10 (70, 95% CI 34·8–93·3)
Stringent complete response	0/10
Complete response	0/10
Very good partial response	4/10 (40)
Partial response	3/10 (30)
Disease control rate†	10/10 (100)
Stable disease	3/10 (30)
Progressive disease	0/10
Progression-free survival, months, median (95% CI)	14·3 (2·0 – 19·6)
Time to response, months, median (range)	1·1 (0·9 – 1·9)
Duration of response, months, median (range)	14·1 (3·7 – 17·7)
Overall survival, months, median (95% CI)	22·5 (2·0 – NR)

CI, confidence interval; NR, not reached.
*Objective response rate = stringent complete response + complete response + very good partial response + partial response.
†Disease control rate = stringent complete response + complete response + very good partial response + partial response + stable disease.

patient and disease backgrounds may yet improve prognoses.[2,13] Although the truncated size and duration of Cohort 2 of the KEYNOTE-023 study precludes drawing definitive conclusions, the data suggest that combination therapies with a PD-1 inhibitor may still be a potential therapeutic option for patients with MM.

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Conflict of interest

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Research design: Razi Ghori, Patricia Marinello, Jesus San Miguel. Acquisition of data: Razi Ghori, Mohammed Farooqui. Analysis or interpretation of data: Philippe Moreau, Razi Ghori, Mohammed Farooqui, Jesus San Miguel. Draft or critically revise manuscript: all authors. Approve final version for submission: all authors.

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Data availability statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised 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 USA and European Union 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.

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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 SI. Baseline demographic and disease characteristics.

Table SII. Summary of adverse events.

Fig S1. Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival.

References

1. Neri P, Bahlis NJ, Lonial S. New strategies in multiple myeloma: immunotherapy as a novel approach to treat patients with multiple myeloma. *Clin Cancer Res*. 2016;**22**:5959–65.
2. Paiva B, Azpilikueta A, Puig N, Ocio EM, Sharma R, Oyajobi BO, et al. PD-L1/PD-1 presence in the tumor microenvironment and activity of PD-1 blockade in multiple myeloma. *Leukemia*. 2015;**29**:2110–3.
3. *KEYTRUDA® (pembrolizumab) for injection, for intravenous use*. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp, 2020.
4. Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: two-year follow-up of KEYNOTE-087. *Blood*. 2019;**134**:1144–53.
5. Armand P, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. *J Clin Oncol*. 2019;**37**:3291–9.
6. Ribrag V, Avigan DE, Green DJ, Wise-Draper T, Posada JG, Vij R, et al. Phase 1b trial of pembrolizumab monotherapy for relapsed/refractory multiple myeloma: KEYNOTE-013. *Br J Haematol*. 2019;**186**:e41–4.
7. Mateos MV, Orlowski RZ, Ocio EM, Rodriguez-Otero P, Reece D, Moreau P, et al. Pembrolizumab combined with lenalidomide and low-dose dexamethasone for relapsed or refractory multiple myeloma: phase I KEYNOTE-023 study. *Br J Haematol*. 2019;**186**:e117–21.
8. Mateos M, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, et al. Pembrolizumab combined with pomalidomide and dexamethasone for treatment of relapsed or refractory multiple myeloma: randomised phase 3 KEYNOTE-183 study. *Lancet Haematol*. 2019;**6**:e459.
9. Usmani SZ, Schjesvold F, Oriol A, Karlin L, Cavo M, Rifkin RM, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2019;**6**:e448–58.
10. FDA places clinical hold on three studies evaluating pembrolizumab in multiple myeloma [press release]. The ASCO Post; July 7, 2017. http://www.ascopost.com/News/57813. Accessed January 4, 2021.
11. *KYPROLIS® (carfilzomib) for injection, for intravenous use*. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc., 2020.
12. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;**20**:1467–73.
13. Gormley NJ, Pazdur R. Immunotherapy combinations in multiple myeloma—known unknowns. *N Engl J Med*. 2018;**379**:1791–5.

Characterisation of Asp669Tyr Piezo1 cation channel activity in red blood cells: an unexpected phenotype

Human red blood cells (RBCs) have a unique capacity to deformability linked to volume preservation via membrane permeability control. Most notably, defects in proper cation permeability maintenance are implicated in several diseases.[1] Dehydrated hereditary stomatocytosis (DHS), also termed hereditary xerocytosis [Online Mendelian Inheritance in Man (OMIM®) 194380], is a rare autosomal dominant congenital haemolytic anaemia, characterised by decreased intracellular K^+ concentration, uncompensated by Na^+ increase. The RBCs are dehydrated with resulting increased mean corpuscular haemoglobin (Hb) concentration (MCHC) and decreased osmotic fragility.[1] Ektacytometry reveals a characteristic profile with a normal maximal Elongation Index (EI_{max}) and largely decreased O_{min} (osmolality at which EI reaches a minimum in the hypotonic region) and O_{hyper} (osmolality at 50% of EI_{max} in the hypertonic region).[1] Mutations affecting two cation channels have been linked to the disease: the Piezo1, a mechanosensitive non-selective cation channel[2] and Gárdos channel [potassium calcium-activated channel subfamily N member 4 (KCNN4)], a K^+-selective channel activated by intracellular Ca^{2+}.[3,4] However, recent case reports tend to discriminate Piezo1 and Gárdos channel-related pathologies.[5] Multiple mutations on the Piezo1 channel leading to DHS symptoms have been recently described;[6,7] however, functional characterisation of mutant channels is often restricted to heterologous expression. In the present study,