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Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial

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1 **Pembrolizumab combined with pomalidomide and dexamethasone for treatment of**
2 **relapsed or refractory multiple myeloma: randomised phase 3 KEYNOTE-183 study**

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52

53 **Research in context**

54 **Evidence before this study:** An initial PubMed search using the search terms “relapsed” and
55 “multiple myeloma” filtered by article type (clinical trial) and publication dates (01/01/2013 to
56 11/27/2018) yielded 70 articles. Treatment of relapsing/refractory multiple myeloma (RRMM)
57 poses the unique challenge of balancing efficacy and safety in patients who tend to be heavily
58 treated and older. Thus, several ongoing phase 1 and 2 trials are evaluating combinations of the
59 following drugs: bendamustine, tivantinib, bortezomib, carfilzomib, ixazomib, delanzomib,
60 venetoclax, ricolinostat, vorinostat, lenalidomide, pomalidomide, daratumumab, isatuximab,
61 elotuzumab and pembrolizumab. The phase 2 ELOQUENT-3 study by Dimopoulos et al (*New*
62 *Engl J Med* 2018) in patients with RRMM is noteworthy, demonstrating significantly higher
63 progression-free survival (PFS) in patients treated with immunostimulatory antibody against
64 SLAMF7 (elotuzumab) plus pomalidomide and dexamethasone versus pomalidomide and
65 dexamethasone alone (10.3 months vs 4.7 months; HR 0.54; p=0.008). This led to the recent
66 US Food and Drug Administration (FDA) approval of the elotuzumab combination in RRMM.

67 Narrowing of our search by adding filters for the terms “multiple myeloma” and “PD-1” yielded
68 only two results relevant to RRMM (and a third article on melanoma), both involving a PD-1
69 inhibitor. Badros et al (*Blood* 2017; phase 2, single arm) reported acceptable safety (grade 3 or
70 4 adverse events [AEs] in 40% of patients) and promising efficacy (response rate 60% and
71 median PFS 17.4 months) with the combination of pembrolizumab and the immunomodulator
72 pomalidomide and dexamethasone in patients with RRMM. Lesokhin et al (*J Clin Oncol* 2016;
73 phase 1b) demonstrated acceptable safety (drug-related AEs in 63% of patients) and anti-
74 tumour activity (complete response following radiotherapy in one of 27 patients) with nivolumab
75 in patients with RRMM. These results provide a promising backdrop for the KEYNOTE-183
76 study, which was designed to assess the efficacy and safety of a combination of pomalidomide
77 and dexamethasone with or without pembrolizumab.

78 **Added value of this study:** The phase 3 KEYNOTE-183 study (ClinicalTrials.gov identifier,
79 NCT02576977) was conducted to evaluate the efficacy, via analysis of survival outcomes and
80 tumour response, and safety of the checkpoint inhibitor pembrolizumab with pomalidomide and
81 dexamethasone in patients with RRMM. In a phase 2 study (Badros et al *Blood* 2017), this
82 combination provided a response rate of 60%, median response duration of 14.7 months, and
83 manageable safety, supporting its evaluation in KEYNOTE-183. However, an interim analysis
84 conducted at a median follow-up of 8.1 months showed an unfavourable benefit-risk profile of
85 the pembrolizumab-pomalidomide-dexamethasone combination in patients with RRMM. These
86 results led to the FDA decision to halt KEYNOTE-183.

87 **Implications of all the available evidence:** Given the unfavourable benefit to risk profile of the
88 pembrolizumab combination with pomalidomide and dexamethasone, KEYNOTE-183 is unlikely
89 to change clinical practice. However, this study may provide valuable information to guide the
90 design of future clinical studies involving checkpoint inhibitors in RRMM.

91

92 **Abstract**

93 **Background:** KEYNOTE-183 (ClinicalTrials.gov ID: NCT02576977) evaluated the efficacy and
94 safety of pomalidomide-dexamethasone with or without pembrolizumab in patients with
95 relapsed/refractory multiple myeloma (MM).

96 **Methods:** In this phase 3, randomised, open-label, multicentre study (97 medical centres in 11
97 countries across Europe, North America, the Middle East, Asia and Australasia), 249 patients
98 with active MM treated with at least two prior lines of anti-myeloma therapy (excluding
99 pomalidomide) and refractory to the last line of therapy were randomised 1:1 to receive
100 pembrolizumab 200 mg every 3 weeks plus 4 mg pomalidomide on days 1–21 and 40 mg
101 dexamethasone weekly in 28-day cycles or pomalidomide plus dexamethasone. Randomisation
102 occurred via an interactive voice response system/integrated Web response system;
103 randomised allocation schedules were generated by the sponsor. Dual primary endpoints in
104 patients receiving pembrolizumab-pomalidomide-dexamethasone and pomalidomide-
105 dexamethasone were progression-free survival (PFS; per International Myeloma Working Group
106 2011 criteria) and overall survival (OS); secondary endpoints in the two treatment arms were
107 overall response and safety. Efficacy was assessed in all randomised patients, and safety in
108 patients who received at least one dose of study treatment. On July 3, 2017 the US Food and
109 Drug Administration (FDA) determined that the risks of the pembrolizumab-pomalidomide-
110 lenalidomide combination outweighed the benefits and that the study should be halted. The
111 findings of the unplanned, ad hoc interim analysis that led to this decision are presented.

112 **Findings:** Between January 5, 2016 and June 2, 2017, 125 patients were randomised to the
113 triple-therapy group, and 124 to the double-therapy group, of whom 120 and 121 patients,
114 respectively, were included in the analyses. At data cut-off (June 2, 2017), with median follow-
115 up of 8.1 months (range 0.1–16.2), median PFS was 5.6 months (95% CI 3.7–7.5) with
116 pembrolizumab-pomalidomide-dexamethasone versus 8.4 months (5.9–not reached) with

117 pomalidomide-dexamethasone, (hazard ratio [HR] 1.53; 95% CI 1.05–2.22; p=0.98). Median
118 time to progression was 8.1 months (95% CI 5.6–not reached) with pembrolizumab-
119 pomalidomide-dexamethasone versus 8.7 months (95% CI 6.6–not reached) with
120 pomalidomide-dexamethasone. Median OS was not reached (95% CI 12.9–not reached) with
121 pembrolizumab-pomalidomide-dexamethasone versus 15.2 months (95% CI 12.7–not reached)
122 with pomalidomide-dexamethasone (HR 1.61; 95% CI 0.91–2.85; p=0.95). Response rates
123 were 34% (95% CI 26–43%) versus 40% (95% CI 32–50%). Overall, 29 (23%) patients (16
124 progression, 13 adverse events) versus 21 (17%) patients (18 progression, three adverse
125 events) died. Four (3%) deaths were considered by the investigator to be related to
126 pembrolizumab-pomalidomide-dexamethasone (myocarditis, sepsis, Stevens-Johnson
127 syndrome, death of unknown cause); myocarditis and Stevens-Johnson syndrome were
128 attributed to pembrolizumab.

129 **Interpretation:** The unfavourable benefit-risk profile of the pembrolizumab-pomalidomide-
130 dexamethasone combination in patients with relapsed/refractory MM reported here led to the
131 decision by the US FDA to halt the KEYNOTE-183 trial. Additional studies are needed to identify
132 patients who would benefit from programmed death 1 inhibition in combination with
133 pomalidomide.

134 **Funding:** Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

135

136 **Introduction**

137 Multiple myeloma, a malignant disorder of clonal plasma cells characterised by monoclonal
138 protein, osteolytic bone lesions, renal disease and immunodeficiency, accounts for
139 approximately 1% of all cancers and 10% of haematological cancers.^{1,2} Introduction of the
140 immunomodulatory imide (IMiD) agents lenalidomide and pomalidomide, proteasome inhibitors
141 such as bortezomib and carfilzomib, and effective combination with novel therapies with
142 different mechanisms of action, such as daratumumab, have significantly improved survival in
143 multiple myeloma.³⁻¹⁰ However, most patients still undergo cycles of remission and relapse until
144 the disease becomes refractory. Prognosis is particularly poor in patients who are refractory to
145 IMiDs or proteasome inhibitors.^{11,12} Effective combination of novel therapies with different
146 mechanisms of action remains an unmet need.

147 Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed
148 death 1 (PD-1) that blocks interaction between PD-1 and its ligands PD-L1 and PD-L2, with anti-
149 tumour activity across multiple tumour types.¹³⁻¹⁶ In a phase 1 study, pembrolizumab plus
150 lenalidomide and low-dose dexamethasone had anti-tumour activity with manageable safety in
151 patients with relapsed/refractory multiple myeloma.¹⁷ Moreover, in a phase 2 study,
152 pembrolizumab plus pomalidomide-dexamethasone provided a response rate of 60%, median
153 response duration of 14.7 months, and manageable safety, supporting pembrolizumab-based
154 therapy in patients with relapsed/refractory multiple myeloma.¹⁸

155 In KEYNOTE-183, we evaluated the clinical impact of combining pembrolizumab with
156 pomalidomide and dexamethasone (pembrolizumab-pomalidomide-dexamethasone) in patients
157 with relapsed/refractory multiple myeloma. On July 3, 2017, the US Food and Drug
158 Administration (FDA) halted KEYNOTE-183 based on interim data presented to the data
159 monitoring committee, which indicated that the risks associated with the pembrolizumab

160 combination outweighed the benefits.¹⁹ We present the results of the unplanned, interim efficacy
161 (survival outcomes and tumour response) and safety analyses leading to this decision.

162 **Methods**

163 KEYNOTE-183 was a phase 3, randomised, open-label trial comparing triple therapy with
164 pembrolizumab-pomalidomide-dexamethasone with pomalidomide-dexamethasone alone in
165 patients with relapsed/refractory multiple myeloma (ClinicalTrials.gov ID: NCT02576977).
166 Patients were enrolled at 97 medical centres across 11 countries (Australia, Canada, France,
167 Germany, Israel, Italy, Japan, New Zealand, Norway, Spain and the United States of America).
168 A full account of the trial protocol and key changes made to it after the start of the study is
169 provided in the appendix (table S1).

170 **Patients**

171 Eligible patients were aged ≥ 18 years; had confirmed diagnosis of active multiple myeloma;
172 measurable disease; received at least two prior lines of anti-myeloma therapy, including IMiDs
173 (lenalidomide or thalidomide) and proteasome inhibitors (bortezomib, ixazomib or carfilzomib);
174 and were refractory to the last line of therapy (primary refractory or documented progression
175 within 60 days of completing IMiD and/or proteasome inhibitor-based treatment; relapsed and
176 refractory [relapse <6 months after stopping treatment with an IMiD or proteasome inhibitor-
177 containing regimen]); pomalidomide-naïve; had Eastern Cooperative Oncology Group (ECOG)
178 performance status 0 or 1; and were able to provide bone marrow biopsy or aspirate material for
179 disease assessment and biomarker analysis.

180 **Trial design and treatment**

181 **Procedures**

182 Patients were randomised 1:1 to receive intravenous pembrolizumab 200 mg every 3 weeks
183 plus oral pomalidomide 4 mg daily on days 1–21 and oral low-dose dexamethasone 40 mg

184 (20 mg for patients aged >75 years) on days 1, 8, 15, and 22 in 28-day cycles or pomalidomide
185 and low-dose dexamethasone. Treatment was continued until confirmed progression,
186 unacceptable toxicity, or physician/patient decision. Adverse events were graded according to
187 Common Terminology Criteria for Adverse Events, version 4.0, and monitored throughout the
188 study and for 30 days (90 days for serious adverse events) after treatment end. Patients who
189 discontinued for reasons other than progression had post-treatment follow-up every 4 weeks for
190 disease status until progression, initiation of non-study cancer treatment, withdrawal of consent,
191 or loss to follow-up.

192 The trial was to be terminated prematurely if the quality or quantity of data recording was
193 inaccurate or incomplete, adherence to the protocol and regulatory requirements were poor,
194 there were plans to modify or discontinue development of pembrolizumab, or in response to a
195 request by the US FDA or other health authority due to safety concerns.

196 **Randomisation and masking**

197 Treatment allocation to the pembrolizumab-pomalidomide-dexamethasone and pomalidomide-
198 dexamethasone arms occurred using an interactive voice response system/integrated Web
199 response system (randomised allocation schedules were generated by the sponsor).

200 Randomisation was stratified by number of prior lines (two vs at least three) and disease status
201 (lenalidomide-refractory or sensitive). This was an open-label study, and therefore masking was
202 not performed.

203 Patients were immediately discontinued from pembrolizumab following the FDA decision to halt
204 the trial and were transferred to available standard of care therapies at their individual
205 physician's discretion and according to local institutional regulations.

206 **Trial oversight**

207 The study was designed by academic advisors and employees of Merck Sharp & Dohme Corp.,
208 a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Data were collected by investigators and
209 their site personnel and analysed by statisticians employed by Merck. Results were interpreted
210 by academic authors and authors who were Merck employees. An external data monitoring
211 committee assessed safety and efficacy at interim timepoints and made recommendations
212 regarding patient safety and study integrity. The study was conducted in accordance with the
213 protocol and amendments, Good Clinical Practice Guidelines, and the Declaration of Helsinki.
214 All patients provided written informed consent.

215 **Endpoints and assessments**

216 The dual primary endpoints were progression-free survival per International Myeloma Working
217 Group 2011 (IMWG 2011)²⁰ criteria by blinded independent central review and overall survival.
218 Progression-free survival was defined as time from randomisation to first documented disease
219 progression or death from any cause, and overall survival as time from randomisation to death
220 from any cause. Secondary efficacy endpoints included overall response rate by central review
221 (at least a partial response per IMWG 2011), duration of response (time from first documented
222 partial response until progression or death), and disease control rate per IMWG 2011
223 (percentage of patients with confirmed complete response, very good partial response, partial
224 response, minimal response or stable disease for at least 12 weeks before confirmed
225 progression), and the safety and tolerability of both treatments. Complete response was defined
226 as negative immunofixation on serum and urine, disappearance of any soft-tissue
227 plasmacytomas and $\leq 5\%$ plasma cells in the bone marrow. Very good partial response was
228 defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis
229 or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours. Partial
230 response was defined as $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary
231 M-protein by $\geq 90\%$ or to < 200 mg in 24 hours. Patients not meeting the criteria for complete,

232 very good partial, or partial response or progressive disease were determined to have stable
233 disease. Progressive disease required any one or more of the following criteria: an increase of
234 $\geq 25\%$ from baseline in serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL);
235 urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours); only in patients
236 without measurable serum and urine M-protein levels: the difference between involved and
237 uninvolved free light chain levels (the absolute increase must be > 10 mg/dL); bone marrow
238 plasma cell percentage (the absolute percentage must be $\geq 10\%$); definite development of new
239 bone lesions or soft-tissue plasmacytomas or definite increase in the size of existing bone
240 lesions or soft-tissue plasmacytomas; development of hypercalcaemia (corrected serum calcium
241 > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative
242 disorder. Because of premature study termination, progression-free survival and response
243 endpoints were evaluated by confirmed investigator assessment. Median time to progression
244 (time from randomisation to first documented progression) was also evaluated. Immune-
245 mediated adverse events, defined as adverse events (non-serious and serious) associated with
246 pembrolizumab exposure that were consistent with immune phenomena and that had a
247 potentially immunologic aetiology, were pre-specified as events of interest.

248 Efficacy was assessed in the intention-to-treat population of all patients assigned to a treatment
249 group. Safety was assessed in patients who received at least one dose of study treatment.

250 Attribution of adverse events to the study drugs was determined by the site investigators.

251 Disease response assessments were performed every 4 weeks. Patients were contacted for
252 assessment of survival status every 12 weeks after the end of treatment.

253 **Statistical analysis**

254 Hypothesis testing of objective response rate, progression-free survival and overall survival was
255 strongly controlled by a familywise type I error rate of 2.5% (one-sided). A sample size of 300
256 patients was planned (with approximately 210 subjects at the first interim assessment, the study

257 would have approximately 88.7% power for detecting a 25% difference in objective response
258 rate [55% vs 30%] at a 0.5% level of significance [one-sided]). For progression-free survival,
259 based on 236 events (estimated to occur approximately 20 months after the first patient
260 enrolled), the study had 90.6% power to detect a hazard ratio of 0.635 with pembrolizumab-
261 pomalidomide-dexamethasone versus pomalidomide-dexamethasone (assuming median
262 progression-free survival of 4.0 months) at a one-sided alpha of 1.5%. For overall survival,
263 based on 182 events (estimated to occur 10 months after progression-free survival analysis),
264 the study had 80.5% power to detect a hazard ratio of 0.6 for pembrolizumab-pomalidomide-
265 dexamethasone versus pomalidomide-dexamethasone (assuming median overall survival of
266 12.7 months) at one-sided alpha of 0.5%. For overall response rate, based on the first 210
267 randomly assigned patients, the study had 88.7% power to show a 25% difference for
268 pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone (55% vs
269 30%) at a one-sided alpha of 0.5%. Immune-mediated adverse events were summarized
270 separately by toxicity and grade (including counts, percentages, and 95% confidence intervals).
271 Although two interim analyses were protocol-specified before final analysis (the first a final
272 analysis of objective response rate and the second a final progression-free survival analysis and
273 interim overall survival analysis; details available in the redacted protocol), neither was
274 conducted since the trial was halted prematurely. Statistical analyses were done with SAS
275 (version 9.4).

276 **Multivariable analysis**

277 After study termination, an ad hoc analysis was conducted to identify potential factors
278 associated with the imbalance in deaths in the two treatment arms. Towards that goal, factors
279 associated with prognostic and/or predictive of death were first evaluated by retrospective
280 random forest analysis. A multivariable Cox regression analysis was subsequently used to

281 calculate differences between groups with factors associated with risk for death identified from
282 the random forest analysis.

283 **Role of the funding source**

284 Merck representatives and academic advisors designed the study. Authors and sponsor
285 representatives analysed and interpreted the data. An external data monitoring committee
286 monitored the interim data and made recommendations to the executive oversight committee
287 about the overall risk and benefit to trial participants. Investigators and site personnel collected
288 data. Authors and Merck representatives analysed and interpreted the data. All authors attest
289 that the study was conducted in accordance with the protocol and all amendments, they had
290 access to the data used for writing of the manuscript and vouch for the accuracy of the data and
291 analyses. The first and last authors wrote the first draft with input from authors who were
292 employees of the sponsor. A medical writer employed by the sponsor assisted with manuscript
293 preparation. All authors reviewed and edited the manuscript and made the decision to submit for
294 publication.

295 **Results**

296 **Patients**

297 Between January 5, 2016, and June 2, 2017, 348 patients were screened and 249 were
298 randomly assigned to receive pembrolizumab-pomalidomide-dexamethasone (N=125) or
299 pomalidomide-dexamethasone (N=124). Of these, 120 patients in the pembrolizumab-
300 pomalidomide-dexamethasone group and 121 in the pomalidomide-dexamethasone group were
301 treated. The 20-mg dose of dexamethasone was administered from the start of treatment in 81
302 patients (37, pembrolizumab-pomalidomide-dexamethasone; 44, pomalidomide-
303 dexamethasone). The most common reasons for screen failure (in $\geq 10\%$ of patients) were prior
304 treatments did not conform to the inclusion criteria (i.e. patients had not received prior treatment
305 with ≥ 2 lines of anti-myeloma therapy and had failed the last line or else prior anti-myeloma

306 treatment did not include an IMiD; n=31/97, 32%), inadequate organ function (n=30, 31%),
307 received prior excluded therapies (i.e. pomalidomide, antibodies or drugs specifically targeting
308 T-cell co-stimulation or checkpoint pathways; monoclonal antibody ≤ 4 weeks prior to day 1, anti-
309 myeloma therapy ≤ 2 weeks prior to day 1, n=14, 14%), no confirmed diagnosis of active multiple
310 myeloma and measurable disease (n=12, 12%), lack of informed consent (n=11, 11%), and
311 ECOG performance status >1 (n=10, 10%).

312 Baseline patient and disease characteristics were generally similar between groups (table 1).
313 More patients in the pembrolizumab-pomalidomide-dexamethasone group had high-risk
314 cytogenetics (28 [22%] versus 17 [14%] with pomalidomide-dexamethasone), including deletion
315 17p13 in 15 (12%) versus six (5%) patients, and plasmacytoma in 15 (12%; six of 15 [40%]
316 extramedullary) versus six (5%; three of six [50%] extramedullary) patients (table 1). At the time
317 of the unplanned interim analysis, the overall median follow-up was 8.1 months (range 0.1–
318 16.2), and was 7.8 months (range 0.3–16.2) with pembrolizumab-pomalidomide-
319 dexamethasone versus 8.6 months (range 0.1–15.6) with pomalidomide-dexamethasone (table
320 S3). A total of 44 (37%) patients versus 55 (45%) were on treatment; 76 (63%) patients versus
321 66 (54%) had discontinued (figure 1). Disease progression was the most common reason for
322 study discontinuation in both treatment arms (43 [36%] patients in the pembrolizumab-
323 pomalidomide-dexamethasone arm and 40 [33%] patients in the pomalidomide-dexamethasone
324 arm), followed by adverse events (24 [20%] vs 10 [8%]) (table 2). Eighteen (15%) and five (4%)
325 patients in the pembrolizumab-pomalidomide-dexamethasone and pomalidomide-
326 dexamethasone groups, respectively, discontinued due to treatment-related adverse events.

327 **Efficacy**

328 As of June 2, 2017, median progression-free survival was 5.6 months (95% CI 3.7–7.5) with
329 pembrolizumab-pomalidomide-dexamethasone versus 8.4 months (95% CI, 5.9–not reached)
330 with pomalidomide-dexamethasone; hazard ratio for disease progression or death was 1.53

331 (95% CI 1.05–2.22; $p=0.98$; figure 2A). Median time to progression was 8.1 months (95% CI
332 5.6 months–not reached) with pembrolizumab-pomalidomide-dexamethasone versus 8.7
333 months (95% CI 6.6 months–not reached) with pomalidomide-dexamethasone. The estimated
334 6-month progression-free survival rate was 48% (95% CI 37–58%) versus 60% (95% CI 49–
335 69%), respectively (figure 2A). Median overall survival was not reached (95% CI 12.9 months–
336 not reached) with pembrolizumab- pomalidomide-dexamethasone and was 15.2 months (95%
337 CI 12.7 months–not reached) with pomalidomide-dexamethasone; hazard ratio for death was
338 1.61 (95% CI 0.91–2.85; $p=0.95$). The estimated 6-month overall survival rate was 82% (95%
339 CI 74–88%) versus 90% (95% CI 82–95%; figure 2B). The hazard ratio for comparison of
340 overall survival was similar among subgroups, except for the ECOG performance status 0,
341 disease stages 1 and 2, and Japan subgroups (figure S1). The hazard ratio for comparison of
342 progression-free survival was similar among subgroups, except for the race (other) and Japan
343 subgroups (figure S2).

344 The overall response rate with pembrolizumab-pomalidomide-dexamethasone was
345 34% (95% CI 26.1–43.4), with 43 patients having partial response or better, versus 40%
346 (95% CI 31.6–49.5) with pomalidomide-dexamethasone, with 50 patients having partial
347 response or better. The disease control rate was approximately 85% in both groups (table S4).
348 Median duration of response was 8.2 months (range 0+ to 14.8+) with pembrolizumab-
349 pomalidomide-dexamethasone versus not reached (range 0.9+ to 13.8+) with pomalidomide-
350 dexamethasone. The percentage of patients with response duration ≥ 6 months was 60% versus
351 72%, respectively (table S3).

352 **Adverse events**

353 Median duration of study treatment in all treated patients was 123.5 days (range 5–477 days)
354 with pembrolizumab-pomalidomide-dexamethasone versus 127.0 days (range 2–463 days) with
355 pomalidomide-dexamethasone (table S5); at analysis, patients had received a median of 4.4

356 cycles of treatment. Adverse events of any grade were reported in 119 (99%) patients in the
357 pembrolizumab-pomalidomide-dexamethasone group versus 116 (96%) in the pomalidomide-
358 dexamethasone group (table 2), grade 3 or 4 adverse events were reported in 90 (75%) versus
359 77 (63%) patients (table 2), and serious adverse events were reported in 75 (63%) versus 56
360 (46%) patients, respectively (table 3). Grade 5 adverse events were reported in 13 (11%)
361 patients in the pembrolizumab-pomalidomide-dexamethasone group versus three (2%) patients
362 in the pomalidomide-dexamethasone group (table 4). Any-grade adverse events with $\geq 5\%$
363 difference in incidence between groups were neutropenia (38% with pembrolizumab-
364 pomalidomide-dexamethasone vs 27% with pomalidomide-dexamethasone), pneumonia (23%
365 vs 15%), nausea (17% vs 12%), headache (13% vs 4%), and increased alanine
366 aminotransferase level (10% vs 3%). Grade 3 or 4 adverse events with $\geq 5\%$ difference between
367 groups were neutropenia (34% vs 21%) and thrombocytopenia (12% vs 7%). There were no
368 serious adverse events with $\geq 5\%$ difference between groups. Immune-mediated adverse events
369 (most commonly pneumonitis, hyperthyroidism, and rash in 3% of patients each) occurred in 21
370 (18%) patients in the pembrolizumab-pomalidomide-dexamethasone group (table 2). Of note,
371 only one patient had immune-mediated neutropenia and there were no cases of immune-
372 mediated thrombocytopenia.

373 Adverse events resulted in treatment discontinuation in 24 (20%) and ten (8%) patients in the
374 pembrolizumab-pomalidomide-dexamethasone and pomalidomide-dexamethasone groups,
375 respectively. The most common (occurring in ≥ 2 patients in either group) were death (3 [3%] vs
376 3 [1%]), pneumonia (2 [2%] vs 3 [1%]), neutropenic sepsis (2 [2%] vs 2 [1%]), cerebrovascular
377 accident (2 [2%] vs 3 [1%]) and dyspnoea (2 [2%] vs 2 [1%]). Of these, neutropenic sepsis (2
378 [2%] vs 2 [1%]), pneumonia (2 [2%] vs 2 [1%]) and cerebrovascular accident (2 [2%] vs 2 [1%])
379 were considered by the investigator to be treatment related.

380 **Deaths**

381 As of June 2, 2017, a total of 50 patients had died: 29 (23%) with pembrolizumab-
382 pomalidomide-dexamethasone (16 from progressive disease, 13 from adverse events) versus
383 21 (17%) with pomalidomide-dexamethasone (18 from progressive disease, three from adverse
384 events). Table 5 summarises the adverse events leading to death. There were four treatment-
385 related deaths with pembrolizumab-pomalidomide-dexamethasone (death of unknown cause,
386 neutropenic sepsis, myocarditis, and Stevens-Johnson syndrome in one patient each). Deaths
387 from myocarditis and Stevens-Johnson syndrome were attributed to pembrolizumab by the
388 investigator. There were three non-treatment-related deaths with pomalidomide-
389 dexamethasone (death of unknown cause, anaemia and pneumonia in one patient each; table
390 5). A review of disease characteristics among patients who died showed that more patients in
391 the pembrolizumab-pomalidomide-dexamethasone group had International Staging System
392 stage 3 disease (15 [52%]) versus four (19%) in the pomalidomide-dexamethasone group),
393 high-risk cytogenetics (10 [34%] vs six [29%]), plasmacytoma (seven [24%] vs three [14%]), and
394 ECOG performance status of 1 (21 [72%] vs 13 [62%]) at baseline (table S6). The hazard ratio
395 for death was 1.23 (95% CI 0.57–2.66) when patients with high-risk disease characteristics
396 were excluded (figure S3). In the analysis, of 13 deaths in the pembrolizumab-pomalidomide-
397 dexamethasone group, four were from progression and nine were from AEs (myocardial
398 infarction, cardiac failure, pericardial haemorrhage, Stevens-Johnson Syndrome, sepsis [n=3]
399 and unknown death [n=2]); two of those AEs were considered related to pembrolizumab by the
400 investigator (Stevens-Johnson Syndrome and unknown death). Of 13 deaths in the
401 pomalidomide-dexamethasone group, 12 were from progression and one was from an AE
402 (unknown death).

403 In a retrospective random forest analysis, age, ECOG performance status, disease stage,
404 presence of plasmacytoma and double-refractory status were ranked as more relevant
405 contributors to death than treatment (figure S4). A subsequent multivariable analysis showed

406 that age, ECOG performance status, and plasmacytoma significantly contributed to the risk for
407 death. ECOG performance status was both prognostic and predictive of outcome. ECOG
408 performance status 0 was associated with reduced risk for death (hazard ratio 0.86; 95% Wald
409 confidence limits 0.32–2.29), whereas ECOG performance status 1 was associated with
410 increased risk for death (hazard ratio 2.3; 95% Wald confidence limits 1.11–4.76). The clinical
411 course of patients who died of adverse events in the pembrolizumab-pomalidomide-
412 dexamethasone group is summarised in the appendix (table S7).

413 **Discussion**

414 In this non-protocol-specified interim analysis of KEYNOTE-183, after a median follow-up of 8.1
415 months, an increased risk for death was observed with pembrolizumab-pomalidomide-
416 dexamethasone versus pomalidomide-dexamethasone alone in patients with relapsed/refractory
417 multiple myeloma. The early mortality signal led to a halt of enrolment by the data monitoring
418 committee and to subsequent study termination by the FDA July 3, 2017.¹⁹ The early study
419 termination resulted in incomplete data collection, and, at analysis, only 27.5% of the protocol-
420 specified events required for evaluation of overall survival (50 of 182 protocol-specified survival
421 events observed) and 48.7% required for analysis of progression-free survival (115 of 236
422 protocol-specified progression-free survival events observed) had accrued. Treatment exposure
423 was also shortened (median 4.5 treatment cycles in the pembrolizumab-pomalidomide-
424 dexamethasone group [37 (31%) patients with fewer than three cycles] vs median 5.0 treatment
425 cycles in the pomalidomide-dexamethasone group [29 (24%) with fewer than three cycles]).
426 Several studies have shown that longer follow-up is necessary to discern efficacy outcomes with
427 immunotherapies given the non-proportional hazard effect that leads to delayed clinical
428 response and late separation of Kaplan-Meier survival curves.²¹⁻²³ As such, although the
429 overlapping confidence intervals for both progression-free survival and overall response in this

430 premature analysis suggest no difference between the two treatment groups, this interpretation
431 is limited by the early termination of the study.

432 The acknowledged association between severity of disease and degree of immune system
433 dysfunction suggests that PD-1 blockade may be both safer and more effective in patients with
434 a lower burden of disease and less impaired immune system. Thus, the failure of
435 pembrolizumab to improve the outcome in patients with relapsed/refractory multiple myeloma in
436 the present study population may be attributable to the considerable immunodeficiency that
437 exists in these patients.

438 The incidence of any-grade adverse events was similar between groups, with a higher incidence
439 of grade 3 or 4 and serious adverse events with pembrolizumab-pomalidomide-dexamethasone
440 versus pomalidomide-dexamethasone. All common, non-severe adverse events were
441 manageable, and no specific type led to treatment discontinuation. The most common immune-
442 mediated adverse events reported in the experimental group were pneumonitis, hyperthyroidism
443 and rash in 3% of patients each. There were two grade 5 immune-mediated adverse events of
444 myocarditis and Steven-Johnson syndrome, events expected as per the label for
445 pembrolizumab.²⁴ Overall, the type and incidence of immune-mediated adverse events in the
446 experimental group were consistent with those reported previously for pembrolizumab¹³⁻¹⁶ and
447 with those observed in KEYNOTE-185.

448 A total of 50 deaths occurred: 29 (23%) deaths with pembrolizumab-pomalidomide-
449 dexamethasone (13 from adverse events) versus 21 (17%) with pomalidomide-dexamethasone
450 (3 from adverse events). However, the number of patients who discontinued (43 vs 40) or died
451 from disease progression (16 vs 18) was similar between groups, suggesting that the risk for
452 progression was similar between groups. This suggests that progression-free survival in the

453 pembrolizumab-pomalidomide-dexamethasone group could have been influenced by the
454 imbalance in the number of deaths.

455 A review of alternatives for the difference in early death observed between the treatment groups
456 showed that the frequency of high-risk features at baseline among patients who died
457 prematurely was higher in the pembrolizumab-pomalidomide-dexamethasone than in the
458 pomalidomide-dexamethasone group, despite the safeguard of randomisation (it should be
459 noted that disease characteristics were generally not balanced between the treatment arms in
460 this study, likely due to the fact that patient enrolment was still ongoing at the time of early study
461 termination and to the unplanned ad-hoc nature of the analysis). Specifically, more patients in
462 the pembrolizumab-pomalidomide-dexamethasone group who died early had stage III disease,
463 high-risk cytogenetics and/or extramedullary plasmacytoma, factors typically associated with
464 poorer prognosis, an imbalance that might account for the difference in early death that led to
465 early termination of KEYNOTE-183. Moreover, when adverse-event-related death was
466 evaluated between the two treatment groups, after removal of patients with these high-risk
467 characteristics, there was no difference in overall deaths between groups with 13 deaths in each
468 group (hazard ratio for death 1.23; $p=0.69$). A multivariable analysis to identify factors
469 associated with risk for death indicated that only ECOG performance status 1 was predictive
470 and prognostic of risk for death. This might indicate that the performance status evaluation of
471 patients at study entry was underestimated considering that patients with ECOG performance
472 status of 2 are usually included in multiple myeloma clinical studies but was an exclusion
473 criterion in this study. Together, these analyses suggest that the imbalance in the number of
474 deaths observed may be driven by a diverse set of non-treatment-related adverse events and
475 not necessarily by exacerbation of any specific treatment-related safety signal.

476 The findings of this study are not generalizable to other indications; it is not possible to
477 determine whether the problems encountered in this study population receiving pembrolizumab

478 in combination with standard of care therapy would be observed in other indications. Moreover,
479 the present findings are limited by the early halting of this study, which rendered completion of
480 prespecified analyses impossible.

481 In summary, although these data showed an imbalance in the number of deaths between
482 treatment groups, because of the shortened follow-up at termination, the interim analyses were
483 underpowered and inconclusive. Additional studies are needed to optimise identification of
484 patients who would benefit from PD-1 inhibition in combination with pomalidomide. Furthermore,
485 given the efficacy of pembrolizumab combinations demonstrated in the treatment of other
486 diseases, checkpoint inhibitors deserve to be appropriately investigated with other treatment
487 backbones.

488 **Contributors**

489 MVM, JSM, UK, PM, contributed to study design or planning. HB, IA, NB, SZU, SJ, JSM, UK, JL
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495 MF, JF, PM, SL contributed to critical review or revision of the article drafts. All authors gave
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498 all aspects of the work and will ensure that questions related to accuracy or integrity of any part
499 of the work are appropriately investigated and resolved, and have reviewed the final version of
500 the manuscript to be submitted and agree with the content and submission.

501 **Declaration of interests**

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546 **Data-sharing statement**

547 Merck & Co., Inc.'s data sharing policy, including restrictions, is available at
548 http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study
549 data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

550

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613 **Figure Legends**

614 ***Figure 1: Randomisation and study disposition***

615 ***Figure 2: Progression-free survival based on confirmed investigator assessment (A) and***
616 ***median overall survival (B) in the intention-to-treat population***

617 SOC is pomalidomide and low-dose dexamethasone. SOC=standard of care.

618

619 **Table 1:** Baseline disease and patient characteristics in the intention-to-treat population

Characteristic	Pembrolizumab + SOC	SOC
	N=125	N=124
Median age (range), years	65 (45–94)	67 (22–90)
≥70 years	44 (35%)	48 (39%)
ECOG performance status		
0	60 (48%)	60 (48%)
1	65 (52%)	64 (52%)
ISS stage		
I	45 (36%)	45 (36%)
II	46 (37%)	39 (31%)
III	33 (26%)	33 (27%)
Missing	1 (1%)	7 (6%)
Median number of prior recurrences (range)	3 (1–8)	3 (2–7)
High-risk cytogenetics*		
Yes	28 (22%)	17 (14%)
Del17p13	15 (12%)	6 (5%)
t(4;14)	10 (8%)	8 (6%)
t(14;16)	8 (6%)	3 (2%)
Normal	52 (42%)	71 (57%)
Missing	45 (36%)	36 (29%)
Presence of plasmacytoma [†]	15 (12%)	6 (5%)
Bone, n/N (%)	9/15 (65%)	3/6 (50%)
Extramedullary, n/N (%)	6/15 (40%)	3/6 (50%)
Prior ASCT	77 (62%)	81 (65%)

Prior therapy		
Lenalidomide	119 (95%)	116 (94%)
Thalidomide	48 (38%)	41 (33%)
Bortezomib	121 (97%)	116 (94%)
Carfilzomib	34 (27%)	33 (27%)
Daratumumab	9 (7%)	8 (6%)
Lenalidomide refractory	107 (86%)	107 (86%)
Refractory [‡]		
Double	51 (41%)	50 (40%)
Triple	23 (18%)	29 (23%)
Quadruple	5 (4%)	2 (2%)

620 Data are n (%) unless otherwise specified. ASCT=autologous stem cell transplantation;

621 SOC=standard of care is pomalidomide and low-dose dexamethasone; intention-to-treat

622 population defined as all patients assigned to treatment.

623 *Baseline cytogenetics was analysed in bone marrow aspirate sample by fluorescence in situ

624 hybridisation (FISH) or by standard karyotyping if FISH is not available, at local laboratories.

625 †Presence of extramedullary soft tissue plasmacytoma was evaluated by magnetic resonance

626 imaging or computed tomography (CT) or positron emission tomography/CT at screening.

627 ‡Patients were considered refractory if they had failed two (double; lenalidomide/bortezomib),

628 three (triple; lenalidomide/bortezomib/pomalidomide or lenalidomide/bortezomib/carfilzomib) or

629 four (quadruple; lenalidomide/bortezomib/pomalidomide/carfilzomib) prior lines of treatment,

630 defined as documented disease progression during or within 60 days of completing their last

631 anti-myeloma therapy.

632

633 **Table 2:** Adverse events in the as-treated population

Adverse event	Pembrolizumab + SOC	SOC
	N=120	N=121
Any adverse event	119 (99%)	116 (96%)
Grade 3 or 4	90 (75%)	77 (63%)
Serious	75 (63%)	56 (46%)
Leading to discontinuation of any drug	24 (20%)	10 (8%)
Leading to death	13 (11%)	3 (2%)
Any-grade adverse events occurring in ≥10% of patients in either arm		
Neutropenia*	46 (38%)	33 (27%)
Anaemia	34 (28%)	43 (36%)
Fatigue	29 (24%)	36 (30%)
Constipation	27 (23%)	24 (20%)
Pyrexia	27 (23%)	23 (19%)
Pneumonia*	28 (23%)	18 (15%)
Thrombocytopenia	25 (21%)	20 (17%)
Diarrhoea	21 (18%)	21 (17%)
Upper respiratory tract infection	20 (17%)	21 (17%)
Dyspnoea	21 (18%)	18 (15%)
Peripheral oedema	19 (16%)	19 (16%)
Cough	18 (15%)	18 (15%)
Nausea*	20 (17%)	14 (12%)
Back pain	13 (11%)	20 (17%)
Neutrophil count decreased	17 (14%)	16 (13%)

Asthenia	14 (12%)	14 (12%)
Dizziness	15 (13%)	13 (11%)
Headache*	15 (13%)	5 (4%)
Muscle spasms	12 (10%)	12 (10%)
White blood cell count decreased	12 (10%)	10 (8%)
Alanine aminotransferase increased*	12 (10%)	3 (2%)
Grade 3 or 4 adverse events with incidence \geq10% in either arm		
Neutropenia*	41 (34%)	26 (21%)
Anaemia	20 (17%)	16 (13%)
Thrombocytopenia*	14 (12%)	8 (7%)
Pneumonia	16 (13%)	15 (12%)
Neutrophil count decreased	15 (13%)	11 (9%)
Any-grade immune-mediated adverse events and infusion reactions		
	Pembrolizumab +SOC	
	N=120	
Any event	21 (18%)	
Pneumonitis	5 (4%)	
Hyperthyroidism	3 (3%)	
Rash	3 (3%)	
Hypothyroidism	2 (2%)	
Myopathy	2 (2%)	
Myocarditis	1 (1%)	
Iridocyclitis	1 (1%)	
Hepatitis	1 (1%)	
Anaphylaxis	1 (1%)	

Infusion-related reactions	1 (1%)
Exfoliative dermatitis	1 (1%)
Psoriasis	1 (1%)
Skin necrosis	1 (1%)
Stevens-Johnson syndrome	1 (1%)

634 Data are n (%). *Any-grade or grade 3-4 adverse events with $\geq 5\%$ difference between treatment
635 groups. The as-treated population includes all patients with at least one dose of study treatment.
636 SOC=standard of care (pomalidomide and low-dose dexamethasone)

637

638 **Table 3:** Serious adverse events $\geq 3\%$ in the as-treated population

Serious adverse event*	Pembrolizumab + SOC	SOC
	N=120	N=121
Pneumonia	21 (18%)	17 (14%)
Acute kidney injury	4 (3%)	4 (3%)
Pneumonitis	4 (3%)	0
Febrile neutropenia	3 (3%)	4 (3%)
Death	3 (3%)	0
Pyrexia	3 (3%)	5 (4%)
Sepsis	3 (3%)	3 (3%)
Influenza	1 (1%)	3 (3%)
Upper respiratory tract infection	1 (1%)	3 (3%)

639 Data are n (%). *There were no serious adverse events with $\geq 5\%$ difference between treatment
640 groups. The as-treated population includes all patients with at least one dose of study treatment.
641 SOC=standard of care (pomalidomide and low-dose dexamethasone)

642

643 **Table 4:** Adverse events leading to death in the as-treated population

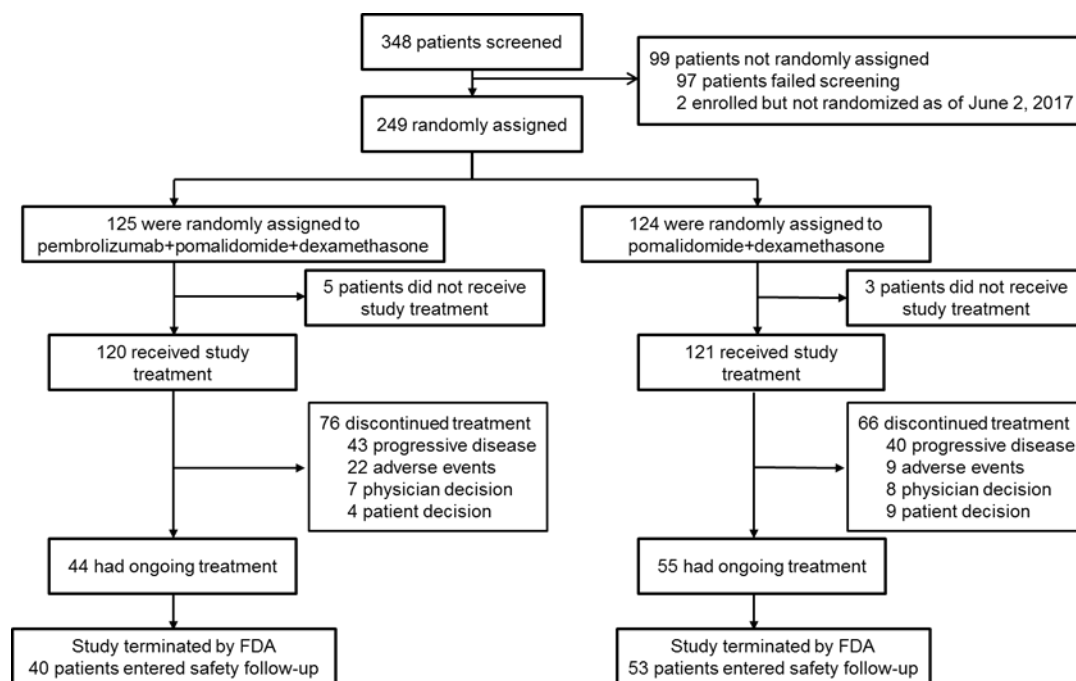
Adverse event	Pembrolizumab + SOC N=120	SOC N=121
Death of unknown cause	3 (3%)*	1 (1%)
Sepsis	3 (3%)	0
Anaemia	0	1 (1%)
Cardiac failure	1 (1%)	0
Myocardial infarction	1 (1%)	0
Myocarditis	1 (1%)*,†	0
Pericardial haemorrhage	1 (1%)	0
Neutropenic sepsis	1 (1%)*	0
Pneumonia	0	1 (1%)
Respiratory tract infection	1 (1%)	0
Stevens-Johnson syndrome	1 (1%)*,†	0

644 Data are n (%). *Treatment-related in one patient. †Attributed to pembrolizumab by investigator.

645 The as-treated population includes all patients with at least one dose of study treatment.

646 SOC=standard of care (pomalidomide and low-dose dexamethasone)

647

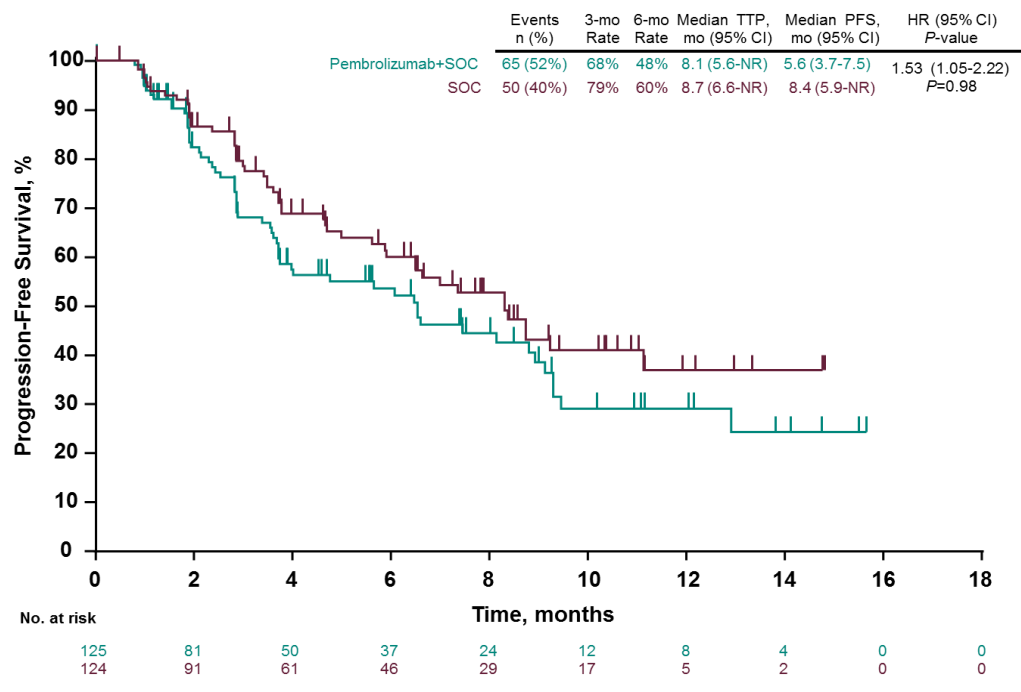
648 **Figure 1**

649

650

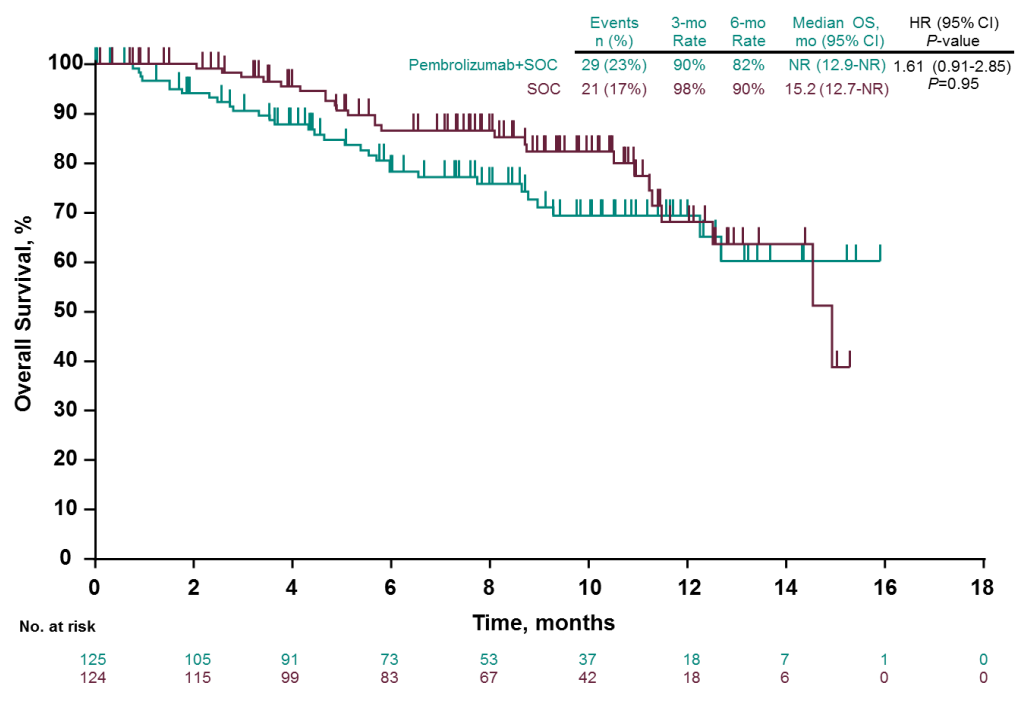
651 **Figure 2**

652 **A**



653

654 **B**



655