SUPPLEMENT: Weight-based pembrolizumab dosing at 4 mg/kg every six weeks leads to exposures below approved doses with unestablished efficacy: A pharmacokinetic model-based simulation analysis

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Supplementary Methods

KEYNOTE-001 (NCT01295827) was a phase 1 study of pembrolizumab administered at a dose of either 2 mg/kg or 10 mg/kg Q3W or 10 mg/kg Q2W IV in participants with advanced non–small-cell lung cancer (N = 495).[1] KEYNOTE-002 (NCT01704287) was a randomized, active-controlled, phase 2 study of pembrolizumab 2 mg/kg (n = 180) or 10 mg/kg Q3W IV (n = 181) versus chemotherapy (n = 179) in participants with ipilimumab-refractory melanoma.[2] KEYNOTE-006 (NCT01866319) was a randomized, controlled, phase 3 study of pembrolizumab 10 mg/kg Q2W (n = 279) or Q3W (n = 277) versus 4 doses of ipilimumab at a dose of 3 mg/kg Q3W (n = 278) IV in participants with advanced melanoma.[3] KEYNOTE-010 (NCT01905657) was a randomized phase 2/3 study of pembrolizumab 2 mg/kg (n = 345) versus 10 mg/kg (n = 346) versus docetaxel 75 mg/m^2 (n = 343) Q3W IV in participants with previously treated advanced PD-L1–positive (PD-L1 tumor proportion score ≥1%) non–small-cell lung cancer.[4] KEYNOTE-024 (NCT02142738) was a randomized, open label, phase 3 study of pembrolizumab 200 mg Q3W IV (n = 154) versus platinum-based chemotherapy (n = 151) in participants with previously untreated advanced non–small-cell lung cancer with PD-L1 tumor proportion score ≥50%.[5] Cohort B of the open-label, phase 1 KEYNOTE-555 study (NCT03665597) enrolled participants with stage III or IV melanoma to evaluate the pharmacokinetic profile, efficacy, and safety of pembrolizumab 400 mg Q6W IV (n = 101).[6] MK-3475A-D77 (NCT05722015) was a randomized phase III study of pembrolizumab 790 mg Q6W administered subcutaneously (n = 251) versus 400 mg Q6W administered IV (n = 126), each given with platinum-doublet chemotherapy, in participants with metastatic non-small cell lung cancer.[7] MK-3475A-C18 (NCT05017012) was an open-label phase 1 study of pembrolizumab 650 mg Q6W (at 165 mg/ml or 130 mg/ml) or pembrolizumab 395 mg (at 165 mg/ml) Q3W administered subcutaneously (N = 140) in participants with melanoma, non–small-cell lung cancer, or renal cell carcinoma.[8]

Supplementary References

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Supplementary Table 1. Clinical trials sponsored by MSD evaluating weight-based and fixed dosing of pembrolizumab

	2 mg/kg Q3W		200 mg Q3W		400 mg Q6W		200 mg Q3W then 400 mg Q6W[a]		Total	
	No. of Trials	No. of participants	No. of Trials	No. of participants	No. of Trials	No. of participants	No. of Trials	No. of participants	No. of Trials	No. of participants
Biliary tract cancer	–	–	2	614	–	–	–	–	2	614
Bladder	–	–	6	1863	2	748	–	–	8	2611
Breast	–	–	8	3260			–	–	8	3260
Cervical	–	–	1	308	–	–	1	530	2	838
Colorectal	–	–	6	508	2	326	–	–	8	834
cSCC	–	–	1	159	1	556	–	–	2	715
Gastric/ esophageal	–	–	10	3438	1	455	–	–	11	3893
Endometrial	–	–	2	518	1	175	1	548	4	1241
Esophageal	–	–	3	456	1	862	1	352	5	1670
Hematology	–	–	6	694	1	66	1	146	8	906
HNSCC	–	–	11	2400			–	–	11	2400
Liver	–	–	8	1704	1	475	–	–	9	2179
MCC	–	–	1	55			–	–	1	55
Melanoma	6	607	8	1540	4	1685	1	115	19	3947
Mesothelioma	–	–	1	19	–	–	–	–	1	19
Myeloma	–	–	1	48	–	–	–	–	1	48

NSCLC	5	720	28	6928	–	–	–	–	33	7648
Ovarian	–	–	4	1478	1	322	–	–	5	1800
Prostate	–	–	3	996	–	–	–	–	3	996
RCC	1	295	5	1300	8	3941	–	–	14	5536
SCLC	–	–	3	353			1	448	4	801
Urothelial carcinoma	–	–	6	1571	1	24	–	–	7	1595
Total	**12**	**1622**	**124**	**30210**	**24**	**9635**	**6**	**2139**	**166**	**43606**
Tumor types[b]	3	3	22	22	12	12	6	6	22	22

Data from Trialtrove. Query used to extract the data: (Tested Drug contains pembrolizumab) AND [(Sponsor contains Merck & Co.) OR (Sponsor is Merck & Co./Merck Sharp & Dohme (MSD)) OR (Sponsor is Merck Sharp & Dohme LLC)]; included trials from phase 1 to post marketing stages for closed and/or completed trials. Some entries lacked actual enrollment numbers, so planned subject counts were used instead. The subject numbers are approximate and may not reflect exact counts, as detailed cohort sizes and dosing information are not always reported or accessible.

[a]Includes studies in which treatment with pembrolizumab was initiated at 200 mg Q3W then switched to 400 mg Q6W.

[b]Represents the distinct number of tumor types studied under each dose.

cSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; MSD, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

Supplementary Table 2. Clinical trials not sponsored by MSD evaluating weight-based and fixed dosing of pembrolizumab

	2 mg/kg Q3W		200 mg Q3W or 400 mg Q6W[a]		Total	
	No. of Trials	**No. of participants**	**No. of Trials**	**No. of participants**	**No. of Trials**	**No. of participants**
Phase 2/3	1	200	12	5286	13	5486
Phase 3	2	450	100	51091	102	51541
Total	3	**650**	**112**	**56287**	**115**	**56937**

Data from Trialtrove. Query used to extract the data: [(Tested Drug is pembrolizumab) OR (Tested Drug is Pembrolizumab IV)] AND [(Trial Phase is II/III) OR (Trial Phase is III)]; MSD-sponsored trials were excluded. Some entries lacked actual enrollment numbers, so planned subject counts were used instead. The subject numbers are approximate and may not reflect exact counts, as detailed cohort sizes and dosing information are not always reported or accessible.

[a]Includes studies that evaluated 200 mg Q3W, 200 mg Q3W or 400 mg Q6W, 200 mg Q3W then switched to 400 mg Q6W, or 400 mg Q6W.

MSD, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Q3W, every 3 weeks; Q6W, every 6 weeks.

Supplementary Table 3. Summary of C_{trough} and AUC after initial dosing (first 6 weeks) by dose and body weight group

	200 mg Q3W				400 mg Q6W				2 mg/kg Q3W				4 mg/kg Q6W			
	<50 kg n = 169	**50-80 kg n = 2109**	**>80 kg n = 1329**	**Overall N = 3607**	**<50 kg n = 169**	**50-80 kg n = 2109**	**>80 kg n = 1329**	**Overall N = 3607**	**<50 kg n = 169**	**50-80 kg n = 2109**	**>80 kg n = 1329**	**Overall N = 3607**	**<50 kg n = 169**	**50-80 kg n = 2109**	**>80 kg n = 1329**	**Overall N = 3607**
C_{trough}																
Geometric mean (95% CI), µg/mL	23.2 (21.6-24.9)	19.1 (18.8-19.5)	15.5 (15.2-15.9)	17.9 (17.6-18.2)	13.3 (11.9-14.9)	11.1 (10.8-11.4)	9.0 (8.7-9.3)	10.4 (10.2-10.6)	10.5 (9.8-11.3)	12.6 (12.4-12.8)	14.7 (14.4-15.0)	13.2 (13.0-13.4)	6.0 (5.4-6.7)	7.4 (7.2-7.6)	8.6 (8.3-8.9)	7.7 (7.5-7.9)
5th to 95th percentile	9.0-40.4	8.3-35.0	7.3-27.2	7.9-33.4	2.9-31.9	3.0-26.6	2.6-21.0	2.9-24.8	4.0-19.1	5.6-22.4	7.0-25.4	5.9-23.8	1.3-14.5	2.0-17.1	2.6-19.6	2.1-18.1
1st to 99th percentile	5.6-52.0	5.6-41.4	4.6-30.4	4.9-40.3	1.3-40.9	1.5-32.9	1.2-24.3	1.3-32.3	2.6-23.5	3.4-26.4	4.4-30.0	3.5-28.2	0.6-18.7	0.9-21.1	1.2-24.0	0.9-22.4
Difference in geometric mean of 4 mg/kg Q6W versus reference doses, %																
200 mg Q3W	–	–	–	–	–	–	–	–	–	–	–	–	-74	-62	-45	-57
400 mg Q6W	–	–	–	–	–	–	–	–	–	–	–	–	-55	-34	-5	-26
2 mg/kg Q3W	–	–	–	–	–	–	–	–	–	–	–	–	-43	-42	-42	-42
AUC																
Geometric mean (95% CI), µg*day/mL	1473 (1421-1527)	1190 (1178-1202)	964 (953-975)	1112 (1102-1121)	1701 (1633-1771)	1377 (1361-1392)	1116 (1101-1130)	1287 (1275-1299)	668 (643-693)	785 (778-793)	913 (903-924)	824 (818-830)	771 (739-804)	909 (899-919)	1057 (1043-1071)	953 (945-962)
5th to 95th percentile	969-2042	772-1741	663-1330	719-1694	1038-2411	842-2084	727-1601	792-2015	421-948	527-1102	633-1256	540-1184	453-1131	575-1322	708-1505	594-1418
1st to 99th percentile	810-2423	656-1953	523-1453	575-1953	852-2939	694-2358	562-1763	625-2354	353-1104	433-1245	507-1424	431-1331	371-1347	465-1502	549-1717	464-1610

Difference in geometric mean of 4 mg/kg Q6W versus reference doses, %																
200 mg Q3W	–	–	–	–	–	–	–	–	–	–	–	–	-48	-24	+10	-14
400 mg Q6W	–	–	–	–	–	–	–	–	–	–	–	–	-55	-34	-5	-26
2 mg/kg Q3W	–	–	–	–	–	–	–	–	–	–	–	–	15	16	16	16

AUC, area under the curve; C_{trough}, trough concentration; Q3W, every 3 weeks; Q6W, every 6 weeks.

The body weight for each participant was collected at baseline.

Supplementary Table 4. Proportion of participants below the 5th and 1st percentile C_{trough} and AUC for 200 mg Q3W and 400 mg Q6W after initial dosing (first 6 weeks)

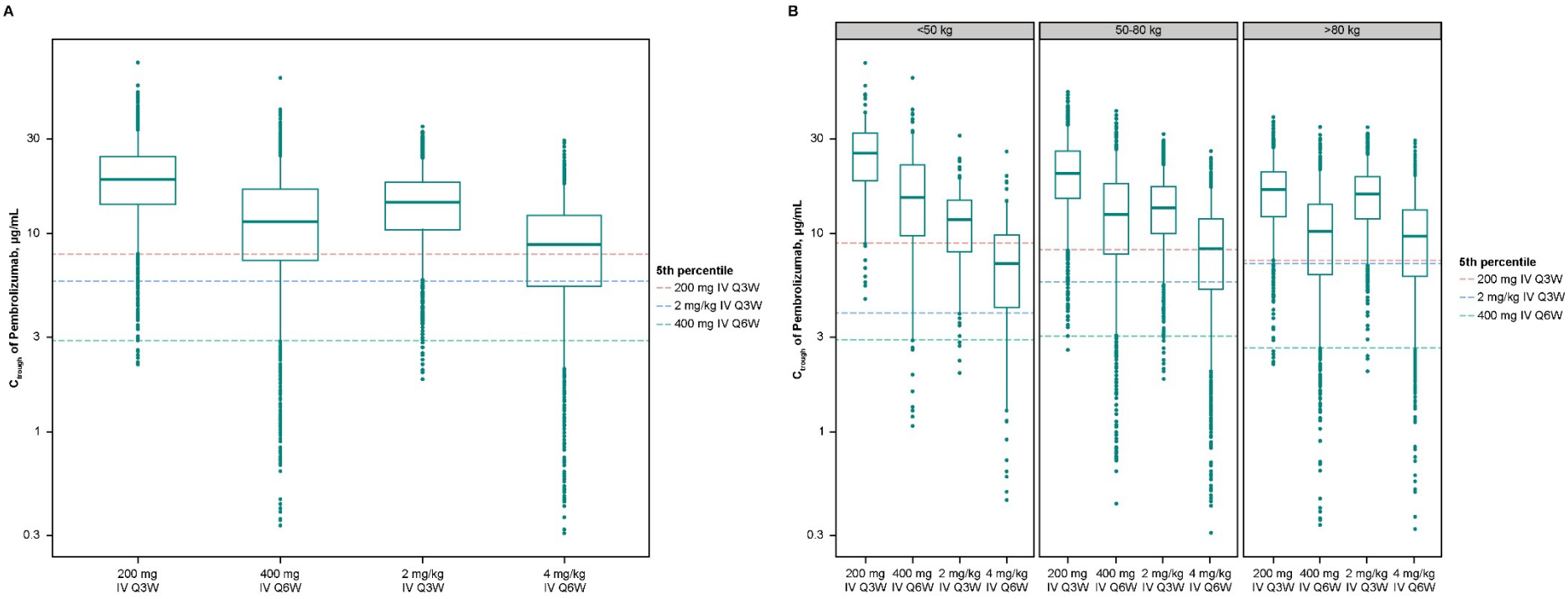
	4 mg/kg Q6W			
	<50 kg n = 169	**50-80 kg n = 2109**	**>80 kg n = 1329**	**Overall N = 3607**
C_{trough}				
Participants falling below the 5th percentile of the reference dose in overall population, n (%)				
200 mg Q3W	98 (58)	969 (46)	482 (36)	1549 (43)
400 mg Q6W	21 (12)	198 (9)	80 (6)	299 (8)
2 mg/kg Q3W	66 (39)	644 (31)	322 (24)	1032 (28)
Participants falling below the 5th percentile of the reference dose within body weight group, n (%)				
200 mg Q3W	115 (68)	1035 (49)	438 (33)	-
400 mg Q6W	21 (12)	213 (10)	70 (5)	-
2 mg/kg Q3W	38 (22)	592 (28)	422 (32)	-
Participants falling below the 1st percentile of the reference dose within body weight group, n (%)				
200 mg Q3W	64 (38)	585 (28)	206 (15)	754 (21)
400 mg Q6W	8 (5)	61 (3)	15 (1)	73 (2)
2 mg/kg Q3W	21 (12)	262 (12)	193 (15)	415 (12)
AUC				
Participants falling below the 5th percentile of the reference dose in overall population, n (%)				
200 mg Q3W	59 (35)	385 (18)	76 (6)	520 (14)
400 mg Q6W	80 (47)	574 (27)	160 (12)	814 (23)
2 mg/kg Q3W	20 (12)	71 (3)	13 (1)	104 (3)
Participants falling below the 5th percentile of the reference dose within body weight group, n (%)				
200 mg Q3W	134 (79)	526 (25)	47 (4)	-
400 mg Q6W	152 (90)	738 (35)	83 (6)	-
2 mg/kg Q3W	4 (2)	60 (3)	34 (3)	-
Participants falling below the 1st percentile of the reference dose within body weight group, n (%)				
200 mg Q3W	85 (50)	237 (11)	10 (1)	145 (4)

400 mg Q6W	103 (61)	325 (15)	17 (1)	246 (7)
2 mg/kg Q3W	1 (1)	15 (1)	8 (1)	23 (1)

AUC, area under the curve; C_{trough}, trough concentration; Q3W, every 3 weeks; Q6W, every 6 weeks.

The body weight for each participant was collected at baseline.

Supplementary Figure 1. C_{trough} after initial dosing (first 6 weeks) by dose (A) and by body weight group (B). Percentiles of the predicted C_{trough} distribution among 3607 participants are represented by the line (50th), box (25th-75th) and whiskers (5th-95th). Dots show individuals at both extremes of the distribution; i.e. <5th and >95th percentiles. The horizontal dashed lines represent the 5th percentile values of 2 mg/kg Q3W, 200 mg Q3W, and 400 mg Q6W doses in the overall population in panel A and within each body weight group in panel B. The number of participants with exposures below these 5th percentile values are reported in Supplementary Table 4. C_{trough}, trough concentration; Q3W, dose every 3 weeks; Q6W, dose every 6 weeks.



Supplementary Figure 2. AUC after initial dosing (first 6 weeks) by dose (A) and body weight group (B). Percentiles of the predicted AUC distribution among 3607 participants are represented by the line (50th), box (25th-75th) and whiskers (5th-95th). Dots show individuals at both extremes of the distribution; i.e. <5th and >95th percentiles. The horizontal dashed lines represent the 5th percentile values of 2 mg/kg Q3W, 200 mg Q3W, and 400 mg Q6W doses in the overall population in panel A and within each body weight group in panel B. The number of participants with exposures below these 5th percentile values are reported in Supplementary table 4. AUC, area under the curve; Q3W, dose every 3 weeks; Q6W, dose every 6 weeks.