Supplementary Material
Table S1. Patient Disposition for Total Population and Expansion Cohort of Patients With Advanced Solid Tumors

	Total Population		Expansion Cohort (melanoma only)[c]	
Status for Study Medication	**Monotherapy Arm[a] *n* = 48**	**Combination Therapy Arm[b] *n* = 65**	**ICI Naive *n* = 13**	**ICI Treated *n* = 7**
Completed	13 (27.1)	2 (3.1)	0	0
Discontinued	35 (72.9)	63 (96.9)	13 (100)	7 (100)
Adverse event	2 (4.2)	8 (12.3)	3 (23.1)	0
Disease progression[d]	29 (60.4)	41 (63.1)	4 (30.8)	6 (85.7)
Physician decision	1 (2.1)	6 (9.2)	2 (15.4)	1 (14.3)
Study terminated by	0	4 (6.2)	4 (30.8)	0

sponsor[e]				
Withdrawal by patient	3 (6.3)	4 (6.2)	0	0

Abbreviation: ICI, immune checkpoint inhibitor.

[a]Includes all patients from the dose acceleration, dose escalation, and dose confirmation phases.

[b]Includes all patients from the dose escalation/confirmation cohort and the expansion cohort.

[c]Subset of the 65 patients in the combination arm.

[d]Defined as clinical progression or progressive disease.

[e]Patients were transferred to the follow-up study with the option to complete therapy with pembrolizumab according to the protocol.

Table S2. Geometric Mean Serum Pharmacokinetic Parameters of MK-4166 in Cycle 1 When Administered Alone (Monotherapy Arm) or in Combination With Pembrolizumab (Combination Therapy Arm) in Patients With Advanced Solid Tumors

Geometric Mean, %GCV[a]							
MK-4166 Dose, mg	***n***	**C_{max}, ng/mL**	**T_{max},[b] days**	**$t_{1/2}$, days**	**AUC_{0-21}, days·ng/mL**	**Clearance, L/day**	**Volume, L**
MK-4166 Monotherapy[c,d]							
0.0015	1	0.536	0.96 (0.96–0.96)	2.61	1.08	1.38	5.19
0.0045	1	5.18	0.03 (0.03–0.03)	2.74	3.91	1.15	4.55
0.014	1	17.3	0.03 (0.03–0.03)	2.68	24.7	0.565	2.18
0.04	1	21.1	0.03 (0.03–0.03)	3.48	39.0	1.02	5.11
0.12	1	34.3	0.03 (0.03–0.03)	2.73	69.4	1.73	6.80
0.37	1	205	0.03 (0.03–0.03)	2.10	672	0.550	1.67
1.1	1	585	0.08 (0.08–0.08)	3.39	3140	0.344	1.68
3.3	1	1,580	0.02 (0.02–0.02)	3.30	8300	0.392	1.87
10	1	3,550	0.08 (0.08–0.08)	7.62	19,100	0.341	3.74

30	6	10,900 (37.1)	0.05 (0.02–0.08)	7.77 (67.2)	84,700 (36.5)	0.286 (54.0)	3.20 (32.6)
42	3	12,300 (21.8)	0.03 (0.02–0.08)	7.49 (107.2)	111,000 (32.9)	0.299 (55.5)	3.23 (48.9)
59	3	21,800 (13.3)	0.02 (0.02–0.03)	2.93 (85.2)	142,000 (31.1)	0.400 (37.7)	1.69 (49.7)
82	3	23,300 (40.7)	0.02 (0.02–0.03)	12.8 (27.6)	226,000 (46.3)	0.246 (59.5)	4.56 (35.4)
120	3	38,100 (28.5)	0.03 (0.02–0.07)	6.37 (87.7)	291,000 (39.6)	0.348 (54.4)	3.19 (69.7)
170	3	58,600 (16.2)	0.03 (0.02–0.03)	7.66 (31.4)	457,000 (23.3)	0.305 (31.1)	3.37 (19.3)
240	5	68,600 (25.1)	0.03 (0.02–1.10)	5.17 (126.5)	426,000 (30.4)	0.479 (51.5)	3.57 (79.9)
340	4	96,500 (25.8)	0.02 (0.02–1.11)	12.0 (69.2)	770,000 (59.0)	0.304 (67.1)	5.27 (67.9)
480	3	149,000 (16.6)	0.03 (0.02–0.08)	11.3 (22.7)	1,110,000 (21.4)	0.320 (17.2)	5.21 (34.4)
670	3	195,000 (44.4)	0.02 (0.02–0.08)	13.1 (37.2)	1,730,000 (28.7)	0.259 (9.9)	4.92 (48.4)
900	3	301,000 (18.8)	0.08 (0.02–1.06)	12.3 (4.5)	3,110,000 (17.5)	0.199 (19.2)	3.54 (17.1)
MK-4166 + Pembrolizumab[c,d]							
1.1	3	1790 (16.6)	0.03 (0.03–0.08)	2.86 (9.63)	7700 (32.6)	0.142 (32.8)	0.587 (30.2)
3.3	4	3670 (72.9)	0.03 (0.03–0.08)	3.64 (27.7)	19,900 (87.1)	0.161 (89.4)	0.844 (55.6)
10	3	5010 (39.7)	0.08 (0.03–0.09)	6.15 (78.5)	33,800 (89.1)	0.249 (122)	2.21 (33.9)
30	3	16,300 (32.2)	0.08 (0.03–0.09)	12.0 (60.9)	137,000 (41.4)	0.150 (74.4)	2.61 (10.8)

42	3	16,900 (51.1)	0.02 (0.02–0.08)	7.31 (48.9)	119,000 (71.4)	0.296 (90.1)	3.12 (46.6)
59	3	20,400 (5.75)	0.03 (0.02–0.08)	8.60 (66.6)	147,000 (25.9)	0.315 (46.0)	3.91 (22.6)
82	4	26,300 (32.1)	0.04 (0.02–0.08)	8.84 (14.3)[e]	271,000 (25.0)[e]	0.244 (23.4)[e]	3.11 (28.8)[e]
120	3	28,300 (44.5)	0.03 (0.02–0.09)	10.9 (28.8)	248,000 (57.6)	0.302 (51.3)	4.73 (21.2)
170	3	552,00 (17.2)	0.08 (0.02–0.08)	11.9 (12.0)	516,000 (21.1)	0.233 (15.9)	4.01 (27.1)
240	3	859,00 (12.7)	0.04 (0.03–0.08)	13.0 (10.6)	832,000 (11.4)	0.193 (12.4)	3.62 (14.0)
340	3	109,000 (8.9)	0.03 (0.02–0.09)	7.81 (120.0)	986,000 (26.2)	0.262 (52.3)	2.95 (48.8)
480	3	144,000 (2.8)	0.08 (0.02–0.09)	13.4 (37.4)[f]	1,370,000 (7.7)[f]	0.230 (26.2)[f]	4.44 (10.4)[f]
670	4	210,000 (11.8)	0.05 (0.02–0.13)	9.03 (77.4)	1,740,000 (50.3)	0.287 (77.0)	3.74 (1.0)
900	23	234,000 (22.7)	0.08 (0.02–0.13)	12.0 (70.1)	2,130,000 (27.5)	0.279 (40.9)	4.85 (38.1)

Abbreviations: $AUC_{0\text{-}21}$, area under the curve from time 0 to 21 hours; $\mathbf{C_{max}}$, maximum serum concentration; GCV, geometric coefficient of variation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

[a]%GCV values were not reported when $n < 2$.

[b]Median (min–max).

[c]Hemolyzed samples were demonstrated to have an impact on the quantitation of MK-4166 levels in human serum using an ultra-sensitive Singulex platform in a method validation study. Therefore, the patients with hemolyzed samples analyzed using this method are removed from the analysis.

[d]A few samples were analyzed outside of stability. Therefore, these samples were excluded from the analysis.

[e]$n = 3$.

[f]$n = 2$.

Table S3. Baseline Characteristics of the Expansion Cohort of Patients With Advanced Melanoma

Characteristic	ICI naive *n* = 13	ICI treated *n* = 7
Age, median (range), years	63.0 (42-81)	74.0 (48-82)
Male, n (%)	10 (76.9)	5 (71.4)
ECOG PS, *n* (%)		
0	11 (84.6)	5 (71.4)
1	2 (15.4)	2 (28.6)
Elevated baseline lactate dehydrogenase, *n* (%)	3 (23.1)	4 (57.1)
Baseline tumor size, median (min, max), mm*	23 (10, 184)	80 (11, 211)
Prior lines of therapy, *n* (%)		
0	10 (76.9)	0
1	3 (23.1)	3 (42.9)
≥2	0	4 (57.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

*Baseline tumor size was based on RECIST v1.1 and was available for 12 patients in the ICI-naive group and seven patients in the ICI-treated group.

Table S4. GEP[a] Analysis of Baseline Tumor Samples in the Expansion Cohort of ICI-Naive Patients With Advanced Melanoma

GEP Level	MK-4166 PN001 MK 4166 + Pembrolizumab Combination Therapy in ICI-Naive Patients			MK-3475-KEYNOTE-006 Study Pembrolizumab Monotherapy in IPI-Naive Patients[1] (for comparison)		
		Response Rate			Response Rate	
	N	*n* (%)	95% CI	*N*	*n* (%)	95% CI
Overall	12[b]	9 (75)	43-95	306	127 (42)	36-47
GEP low (GEP <–0.318)	4	3 (75)	19-99	89	20 (22)	14-33
GEP-non-low (GEP ≥–0.318)	8	6 (75)	35-97	217	107 (49)	43-56

Abbreviations: GEP, gene expression profile; ICI, immune checkpoint inhibitor; IPI, ipilimumab.

[a]The 18-gene T-cell–inflamed GEP was developed to evaluate the combined expression pattern of IFN-γ responsive genes linked to antigen presentation, chemokine expression, cytotoxicity, and adaptive immune resistance in the tumor microenvironment.[2]

[b]A sample from one patient in the expansion cohort was unavailable for this analysis because it did not meet quality control standards.

Data from IPI-naive patients treated with pembrolizumab monotherapy are provided for comparison.

Figure S1. Study design. A pretreatment tumor biopsy (archival or newly obtained) was required for enrollment. An additional biopsy was requested, but not required, in Cycle 1 between day 8 and day 15. *Patients received the maximum-tolerated dose of MK-4166. Abbreviation: TPI, toxicity probability interval.

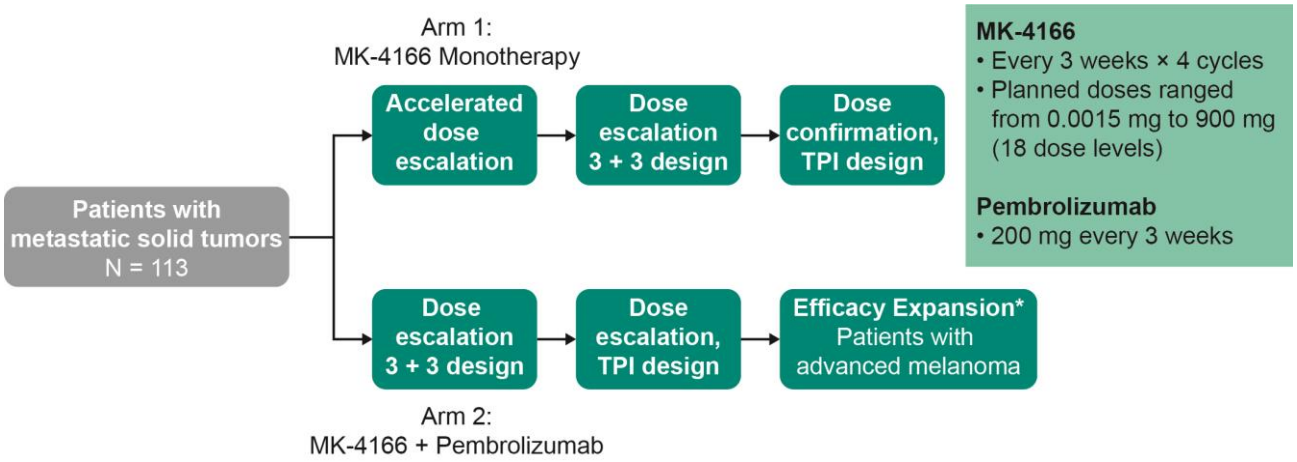


Figure S2. Best change in baseline tumor size in the expansion cohort in patients with advanced melanoma.

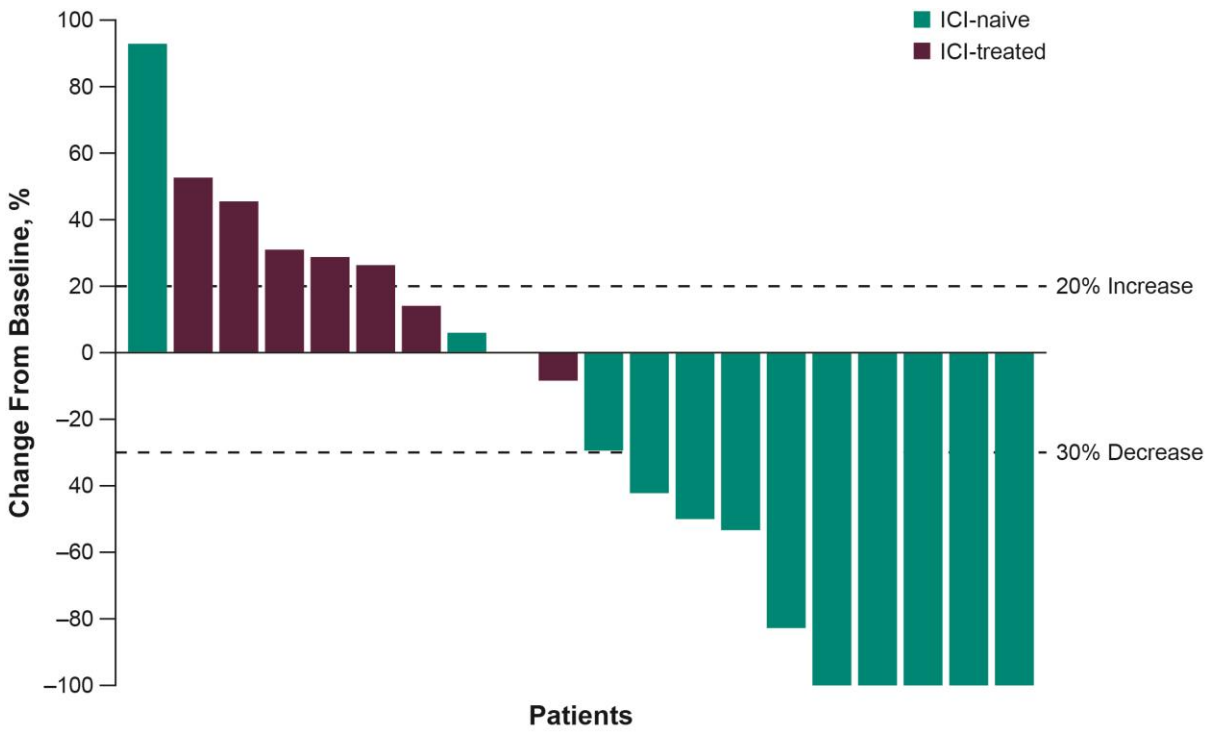
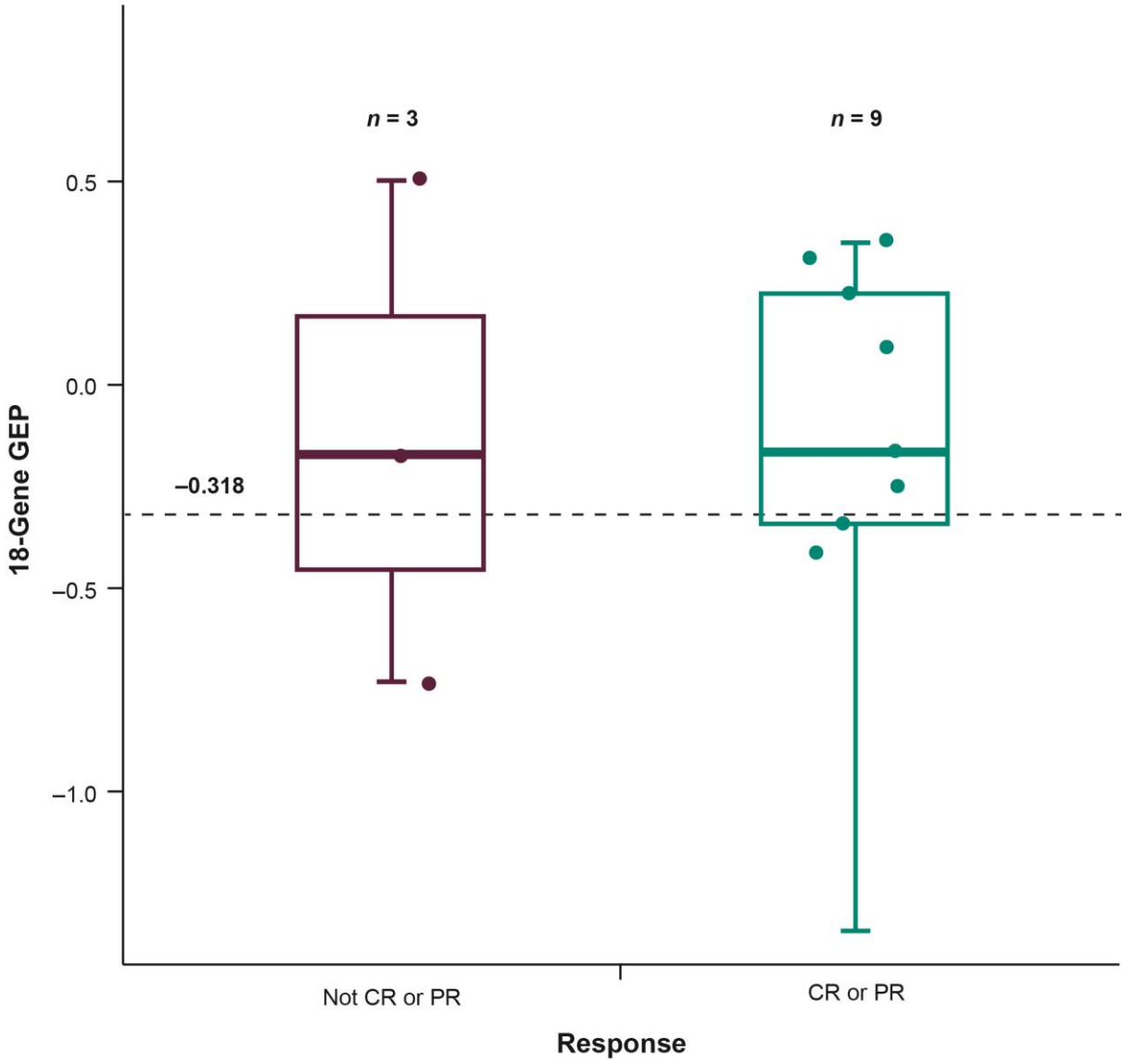


Figure S3. Association between GEP* status (high *v* low cutoff = –0.318) and tumor response in the efficacy expansion cohort of ICI-naive patients with advanced melanoma. The 18-gene T-cell–inflamed GEP was developed to evaluate the combined expression pattern of IFN-γ responsive genes linked to antigen presentation, chemokine expression, cytotoxicity, and adaptive immune resistance in the tumor microenvironment.[2]

Abbreviations: CR, complete response; GEP, gene expression profile; ICI, immune checkpoint inhibitor; PR, partial response.



Supplementary Reference

1. Ribas A, Robert C, Schacter K, Long GV, Arance A, Carlino MS, et al. Tumor mutational burden (TMB), T cell-inflamed gene expression profile (GEP) and PD-L1 are independently associated with response to pembrolizumab (Pembro) in patients with advanced melanoma in the KEYNOTE (KN)-006 study [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 4217.
2. Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest 2017;127:2930–40.