

**Indirect Treatment Comparison of Nivolumab Versus Observation or Ipilimumab as Adjuvant
Therapy in Resected Melanoma Using Pooled Clinical Trial Data**

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SUPPLEMENTAL APPENDICES

Supplementary Table S1 Drug and medical unit costs (2018 USD) inputs

Costs input		Unit costs, \$
Drug acquisition costs per mg^a		
Nivolumab		25.83
Ipilimumab		141.35
Observation		0.00
Drug administration costs^b		
<i>HCPCS Code</i>	<i>Description</i>	
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug	144.72
96415	Chemotherapy administration, IV infusion; each additional hour	31.68
Medical costs^c		
Hospitalization day		1710.18
Emergency department visit		342.40
Outpatient visit ^d		403.19
Hospital outpatient visit		548.86
Physician office visit		219.10
Home healthcare		268.44

HCPCS Healthcare Common Procedure Coding System, *USD* United States dollars

^a Drug acquisition unit costs were based on wholesale acquisition costs [24] as of January 5, 2018

^b Drug administration unit costs were based on the average of the facility and nonfacility prices for chemotherapy IV infusion (2018 USD) from the Centers for Medicare & Medicaid Services Physician

Fee Schedule [25]. Per the protocols for CheckMate 238 and EORTC 18071, nivolumab was considered as administered in 1-hour infusions, and ipilimumab and observation in 90-minute infusions

^c Medical costs for each visit type were obtained from [26]. Unit costs for hospitalization is per day of hospitalization (all-cause); all other unit costs are per visit. Costs are listed in 2013 USD, but were inflated to 2018 USD for costs per life-month analyses

^d Outpatient visit unit costs were calculated as the weighted average of hospital outpatient and physician office unit costs, weighted by the frequency of each visit type in the CheckMate 238 trial. Outpatient visit unit costs were used to calculate costs associated with visits for EORTC 18071 patients only; unit costs for hospital outpatient visit and physician office visit were used to calculate costs associated with visits for CheckMate 238 patients

Supplementary Table S2 Mean duration of recurrence-free life-month, recurrence rates, drug costs, and medical costs

Outcome measures	Nivolumab 3 mg/kg <i>n</i> = 278	Observation <i>n</i> = 365	Ipilimumab 10 mg/kg <i>n</i> = 644
Through month 12			
Mean duration of recurrence-free life-months^a	10.1	8.1	9.3
Recurrence-free survival rate, %^b	74.1	48.7	61.6
Total costs per patient, 2018 USD	140,937	5493	503,155
Mean drug costs	136,388	0	488,958
Mean drug acquisition costs ^{c,d}	133,486	0	488,227
Mean drug administration costs ^e	2902	0	731
Mean medical costs ^{c,f}	4550	5493	14,198
Hospitalization costs ^g	4007	5061	13,336
Emergency room visit costs ^h	14	3	25
Outpatient visit costs ⁱ	523	427	827
Home healthcare costs	6	2	9
Through month 16			
Mean duration of recurrence-free life-months^a	13.2	10.1	11.8
Recurrence-free survival rate, %^b	70.2	44.3	57.0

Total costs per patient, 2018 USD	141,420	8147	519,524
Mean drug costs	136,388	0	504,047
Mean drug acquisition costs ^{c,d}	133,486	0	503,294
Mean drug administration costs ^e	2902	0	753
Mean medical costs ^{c,f}	5033	8147	15,477
Hospitalization costs ^g	4430	7658	14,541
Emergency room visit costs ^h	16	3	26
Outpatient visit costs ⁱ	581	484	900
Home healthcare costs	6	2	9
Through month 18^j			
Mean duration of recurrence-free life-months^a	14.4	10.8	12.7
Recurrence-free survival rate, %^b	70.0	41.8	54.5
Total drug costs per patient, 2018 USD	136,388	0	516,154
Mean drug acquisition costs ^{c,d}	133,486	0	515,383
Mean drug administration costs ^e	2902	0	771
Through month 24^j			
Mean duration of recurrence-free life-months^a	18.5	13.2	15.9
Recurrence-free survival rate, %^b	66.8	37.6	51.3

Total drug costs per patient, 2018 USD	136,388	0	539,188
Mean drug acquisition costs ^{c,d}	133,486	0	538,382
Mean drug administration costs ^e	2902	0	806

USD United States dollars

^a The mean duration of recurrence-free life-months within 12 months, 16 months, 18 months, and 24 months were calculated as the area under the weighted Kaplan-Meier curve of recurrence-free survival within 12 months, 16 months, 18 months, and 24 months, respectively, among all randomized patients ($n = 278$ for nivolumab, $n = 365$ for observation, and $n = 644$ for ipilimumab). The maximum duration of recurrence-free life-months among the pooled population was 31.4 for nivolumab, 83.3 for observation, and 88.5 for ipilimumab

^b Recurrence-free survival rates for treatments and comparators were extracted from the Kaplan-Meier analysis of recurrence-free survival

^c The mean drug and medical costs were calculated using the patient-level data pooled from the safety population of the EORTC 18071 and CheckMate 238 clinical trials. The safety population of EORTC 18071 included all patients who received at least one dose of the relevant treatment ($n = 474$ for observation and $n = 471$ for ipilimumab). The safety population of CheckMate 238 included all patients who received at least one dose of the relevant treatment ($n = 452$ for nivolumab and $n = 453$ for ipilimumab). This analysis accounts for drug wastage based on the 40-mg and 100-mg vials for nivolumab and 50-mg and 200-mg vials for ipilimumab

^d Drug acquisition unit costs were based on the wholesale acquisition costs [24] as of January 5, 2018

^e Intravenous (IV) administration schedules for nivolumab, ipilimumab, and observation were based on the clinical protocols of EORTC 18071 and CheckMate 238. Patients received 90 minutes IV infusion of ipilimumab or observation in EORTC 18071. The infusion duration was 60 minutes for nivolumab and 90 minutes for ipilimumab in CheckMate 238. Drug administration costs for patients in the observation group were set

to \$0 so the results could be better generalized into real-world population. Drug administration unit costs were based on the average of the facility and nonfacility prices for chemotherapy IV infusion (2018 USD) from the Centers for Medicare & Medicaid Services Physician Fee Schedule Search [25]

^f Medical costs inputs, as well as groupings for individual visits, were obtained from [26]. Costs inputs were inflated from 2013 USD to 2018 USD using an inflation factor of 1.136 based on the Consumer Price Index for all urban consumers in medical care service. Medical costs were estimated based on nonprotocol-specified visits and hospitalizations. Per the CheckMate 238 clinical trial protocol, healthcare resource utilization data were collected up until 128 days from either the last dose or treatment discontinuation date

^g Length of stay was calculated based on the start and end date for each hospitalization. For hospitalizations with missing dates of service, length of stay was imputed based on the average length of stay for each treatment group within 24 months

^h To be consistent with the groupings for CheckMate 238, emergency department visits resulting in hospitalizations were not considered in the calculation of emergency department costs for EORTC 18071. All patients with emergency department visits resulting in hospitalization had an observation for a corresponding hospitalization beginning on the same day; thus, costs associated with emergency department visits resulting in hospitalizations are included in the calculation of hospitalization costs for these patients

ⁱ Outpatient visit costs included both hospital outpatient visit costs and physician office visit costs. Outpatient visit unit cost was calculated as the weighted average of hospital outpatient and physician office unit costs, weighted by the frequency of each visit type in the CheckMate 238 trial

^j Healthcare resource utilization in the CheckMate 238 trial was captured only until 128 days after last dose or treatment discontinuation date. For EORTC 18071, the median number of days after last dose when healthcare resource utilization data were collected was 168 days. To be consistent with the time periods for CheckMate 238, the calculation of medical costs at 16 months included costs until day 493 (treatment period of 365 days

+ 128 days). In addition, the calculation of medical costs at 18 months and 24 months may not capture visits or hospitalizations that occurred after data collection

Supplementary Table S3 NNT per additional recurrence-free survivor among patients with stage IIIB, IIIC and IV Melanoma (sensitivity analysis)

Data source	Treatment vs. comparator	Time horizon (months)	RFS rate of treatment^a, %	RFS rate of comparator^a, %	Absolute risk reduction, %	NNT of treatment vs. comparator (95% CI)
CheckMate 238 (Stage IIIB, IIIC, IV) ^b	Nivolumab vs. ipilimumab	12	70.4	60.0	10.4	9.65 (6.06, 23.66)
		18	65.8	53.0	12.8	7.79 (5.22, 15.38)
		24	62.6	50.2	12.5	8.03 (5.30, 16.59)

CI confidence interval, *NNT* number needed to treat, *RFS* recurrence-free survival

^aSurvival rates for treatments and comparators were extracted from the Kaplan-Meier analysis of recurrence-free survival

^bIn the CheckMate 238 trial, there were 453 patients at risk at 0 months for both the nivolumab and ipilimumab group. The number of patients at risk at 12 months was 311 and 251 for nivolumab and ipilimumab, respectively. The number of patients at risk at 18 months was 280 and 216 for nivolumab and ipilimumab, respectively. The number of patients at risk at 24 months was 205 and 149 for nivolumab and ipilimumab, respectively

Supplementary Table S4 Costs per recurrence-free survivor (sensitivity analysis)

Outcome measures	Nivolumab 3 mg/kg <i>n</i> = 453	Ipilimumab 10 mg/kg <i>n</i> = 453
Through month 12		
Mean total costs per recurrence-free survivor, 2018 USD^a	194,286	831,137
Mean drug costs per recurrence-free survivor	186,836	810,341
Mean medical costs per recurrence-free survivor	7450	20,796
Through month 16		
Mean total costs per recurrence-free survivor, 2018 USD^a	207,874	905,303
Mean drug costs per recurrence-free survivor	199,073	881,208
Mean medical costs per recurrence-free survivor	8801	24,095
Through month 18		
Mean drug costs per recurrence-free survivor, 2018 USD ^a	199,779	917,814
Through month 24		
Mean drug costs per recurrence-free survivor, 2018 USD ^a	209,897	968,941

USD United States dollars

^aMean costs per recurrence-free survivor were calculated as mean costs divided by recurrence-free survival rate

Supplementary Table S5 Mean duration of recurrence-free life-month, recurrence rates, drug costs, and medical costs among patients with stage IIIB, IIIC, and IV melanoma (sensitivity analysis)

Outcome measures	Nivolumab 3 mg/kg <i>n</i> = 453	Ipilimumab 10 mg/kg <i>n</i> = 453
Through month 12		
Mean duration of recurrence-free life-months^a	10.0	9.2
Recurrence-free survival rate^b, %	70.4	60.0
Total costs per patient, 2018 USD	136,738	498,803
Mean drug costs	131,495	486,322
Mean drug acquisition costs ^{c,d}	128,660	485,596
Mean drug administration costs ^e	2835	725
Mean medical costs ^{c,f}	5243	12,481
Hospitalization costs ^g	4587	11,550
Emergency room visit costs ^h	19	34
Outpatient visit costs ⁹	629	881
Home healthcare costs	8	15
Through month 16		
Mean duration of recurrence-free life-months¹	12.8	11.6

Recurrence-free survival rate², %	66.1	55.2
Total costs per patient, 2018 USD	137,308	499,619
Mean drug costs	131,495	486,322
Mean drug acquisition costs ^{3,4}	128,660	485,596
Mean drug administration costs ⁵	2835	725
Mean medical costs ^{3,6}	5813	13,297
Hospitalization costs ^g	5081	12,334
Emergency department visit costs ^h	20	34
Outpatient visit costs ⁱ	703	914
Home healthcare costs	9	15
Through month 18^j		
Mean duration of recurrence-free life-months^a	14.0	12.6
Recurrence-free survival rate^b, %	65.8	53.0
Total drug costs per patient, 2018 USD	131,495	486,322
Mean drug acquisition costs ^{c,d}	128,660	485,596
Mean drug administration costs ^e	2835	725
Through month 24^j		
Mean duration of recurrence-free life-months^a	17.8	15.6

Recurrence-free survival rate^b, %	62.6	50.2
Total drug costs per patient, 2018 USD	131,495	486,322
Mean drug acquisition costs ^{c,d}	128,660	485,596
Mean drug administration costs ^e	2835	725

USD United States dollars

^a The mean duration of recurrence-free life-months within 12 months, 16 months, 18 months, and 24 months was calculated as the area under the Kaplan-Meier curve of recurrence-free survival within 12 months, 16 months, 18 months, and 24 months, respectively, among all randomized patients ($n = 453$ for nivolumab and $n = 453$ for ipilimumab). The maximum duration of recurrence-free life-months was 31.4 for nivolumab and 31.1 for ipilimumab

^b Recurrence-free survival rates for treatments and comparators were extracted from the Kaplan-Meier analysis of recurrence-free survival

^c The mean drug and medical costs were calculated using the patient-level data of the CheckMate 238 clinical trial among the safety population. The safety population included all patients who received at least one dose of the relevant treatment ($n = 452$ for nivolumab and $n = 453$ for ipilimumab). This analysis accounts for drug wastage based on the 40-mg and 100-mg vials for nivolumab and 50-mg and 200-mg vials for ipilimumab

^d Drug acquisition unit costs were based on the wholesale acquisition costs [24] as of January 5, 2018

^e Intravenous (IV) administration schedules for nivolumab and ipilimumab were based on the clinical protocol of CheckMate 238. The infusion duration was 60 minutes for nivolumab and 90 minutes for ipilimumab. Drug administration unit costs were based on the average of the facility and nonfacility prices (2018 USD) for chemotherapy IV infusion from the Centers for Medicare & Medicaid Services Physician Fee Schedule [25]

^f Medical costs inputs as well as groupings for individual visits were obtained from [26]. Costs inputs were inflated from 2013 USD to 2018 USD using an inflation factor of 1.136 based on the Consumer Price Index for all urban consumers in medical care service. Medical costs were estimated based on nonprotocol-specified visits and hospitalizations. Per the CheckMate 238 clinical trial protocol, healthcare resource utilization data were collected up until 128 days from either the last dose or treatment discontinuation date

^g Length of stay was calculated based on the start and end date for each hospitalization. For hospitalizations with missing dates of service, length of stay was imputed based on the average length of stay for each treatment group within 24 months

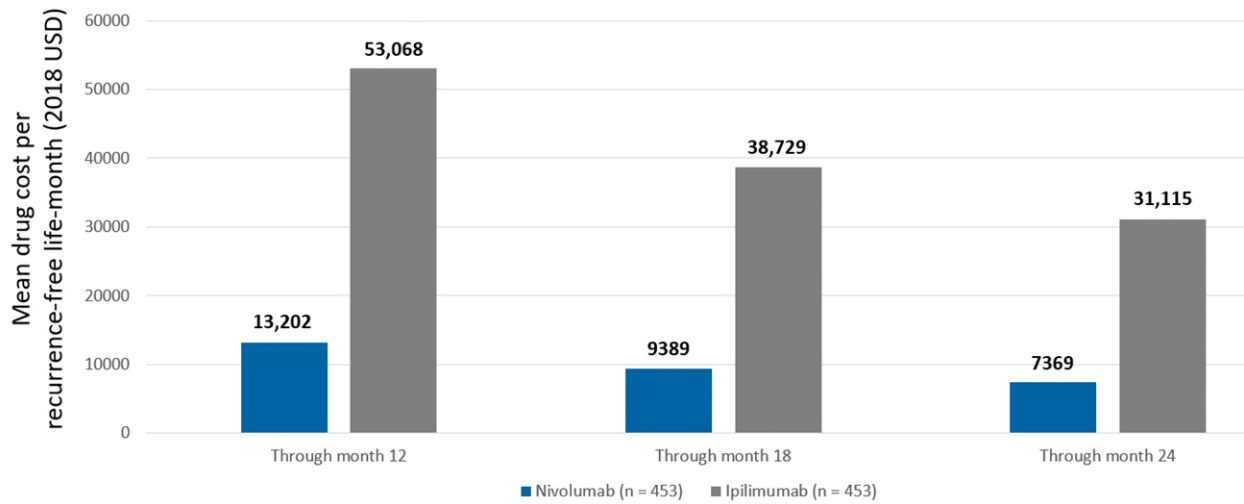
^h Emergency department visit costs include costs only for emergency department visits that did not result in hospital admission

ⁱ Outpatient visits were defined as either hospital outpatient visits or physician office visits to be consistent with the categorization of healthcare resource utilization data in EORTC 18071

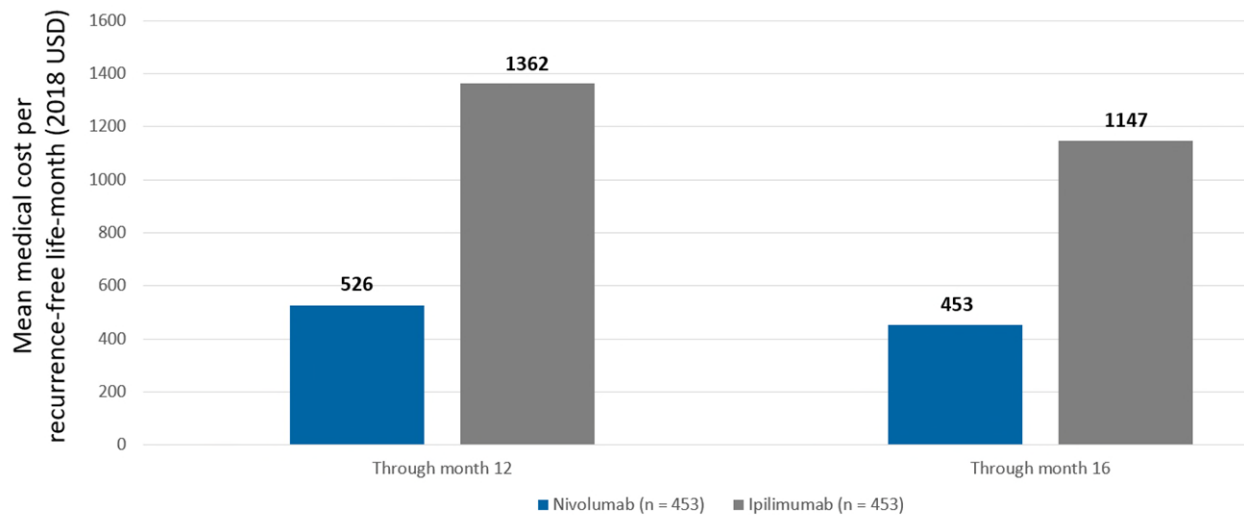
^j Healthcare resource utilization in the CheckMate 238 trial was captured only until 128 days after last dose or treatment discontinuation date.

Thus, the calculation of medical costs at 16 months included costs until day 493 (treatment period of 365 days + 128 days)

a



b



Supplementary Fig. S1 **Mean drug cost (a) and mean medical cost (b) per recurrence-free life-month (sensitivity analysis). USD United States dollars**

Mean costs per recurrence-free life-month was calculated as the division of mean costs by mean duration of recurrence-free life-months. Healthcare resource utilization in the CheckMate 238 trial was captured

only until 128 days after the last dose or treatment discontinuation date. Thus, the calculation of medical costs at 16 months included costs until day 493 (treatment period of 365 days + 128 days)