Supplemental Online Content

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eFigure. Second Panel Impact Inventory

Sector	Type of Impact (list category within each sector with unit of measure if relevant)[a]	Included in This Reference Case Analysis From...Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	☒	☒	
	Health-related quality-of-life effects	☒	☒	
	Other health effects (eg, adverse events and secondary transmissions of infections)	☒	☒	
	Medical costs			
	Paid for by third-party payers	☒	☒	
	Paid for by patients out-of-pocket	☒	☒	
	Future related medical costs (payers and patients)	☒	☒	
	Future unrelated medical costs (payers and patients)	☒	☒	
Informal Health Care Sector				
Health	Patient-time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☒	
	Transportation costs	NA	☒	
Non−Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☒	
	Cost of unpaid lost productivity due to illness	NA	☒	
	Cost of uncompensated household production[b]	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal or Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	

eTable 1: Base case model second-line treatment costs. References below.

Treatment	Estimated Monthly Cost ($)	Reference
Bevacizumab	$2,679	Average Wholesale Price[1]
Carboplatin	$335	Average Wholesale Price[2]
Cemiplimab	$16,649	Average Wholesale Price[3]
Cisplatin	$170	Average Wholesale Price[4]
Docetaxel	$2,415	Average Wholesale Price[5]
Entrectinib	$24,052	Average Wholesale Price[6]
Fam-trastuzumab deruxtecan-nxk	$17,464	Average Wholesale Price[7]
Fluorouracil	$335	Average Wholesale Price[8]
Gemcitabine	$369	Average Wholesale Price[9]
Irinotecan	$177	Average Wholesale Price[10]
Larotrectinib	$46,782	Average Wholesale Price[11]
Nivolumab	$18,222	Average Wholesale Price[12]
Paclitaxel	$393	Average Wholesale Price[13]
Pembrolizumab	$16,990	Average Wholesale Price[14]
Pemetrexed	$12,956	Average Wholesale Price[15]
Selpercatinib	$27,118	Average Wholesale Price[16]
Tisotumab	$44,051	Average Wholesale Price[17]
Topotecan	$574	Average Wholesale Price[18]
Vinorelbine	$992	Average Wholesale Price[19]
Brachytherapy, 5 fractions/5 implants	$25,227	CMS Physician Fee Schedule[19]
Intensity Modulated Radiotherapy, 5 fractions	$9,994	CMS Physician Fee Schedule[19]
Pelvic Exenteration	$66,316	PelxEx Collaborative,[20] 2020
Best Supportive Care	$4,954	Shi et al,[21] 2022
Base Case Model Input[a,b]	***$13,759***	

[a]Drug costs were calculated as the sum of the drug's average wholesale price assuming a patient weight of 70 kg[22] and a body surface area of 1.86 m^2 [23]; costs of infusion[19]; a 7% reduction[24]; and converted to a monthly cost.

[b]Average of all 2024 National Comprehensive Cancer Network guideline-endorsed subsequent-line treatments[25].

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eTable 2. Associated costs of grade 3-4 treatment-related adverse events. References per main text.

Adverse Event[a]	No. of patients (%)[b]	Costs in 2024 USD[c]	Reference
Pembrolizumab			
White blood cell count decreased, leukopenia	174 (32.9%)	$21,552	Wong et al,[43] 2018
Anemia	122 (23.1%)	$14,432	Shi et al,[17] 2022
Neutrophil count decreased	83 (15.7%)	$1,138	Insinga et al,[44] 2019
Neutropenia	61 (11.6%)	$10,455	Shi et al,[17] 2022
Diarrhea	27 (5.1%)	$4,256	Shi et al,[17] 2022
Platelet count decreased	25 (4.7%)	$12,711	Insinga et al,[44] 2019
Nausea, vomiting	13 (2.5%)	$4,267	Shi et al,[17] 2022
Hypo/hyperthyroidism	5 (0.9%)	$25,625	Wong et al,[43] 2018
Weighted average[d]	-	*$13,499*	
Placebo			
White blood cell count decreased, leukopenia	172 (32.4%)	$21,552	Wong et al,[43] 2018
Anemia	117 (22.1%)	$14,432	Shi et al,[17] 2022
Neutrophil count decreased	81 (15.3%)	$1,138	Insinga et al,[44] 2019
Neutropenia	57 (10.8%)	$10,455	Shi et al,[17] 2022
Diarrhea	25 (4.7%)	$4,256	Shi et al,[17] 2022
Nausea, vomiting	17 (3.2%)	$4,267	Shi et al,[17] 2022
Platelet count decreased	15 (2.8%)	$12,711	Insinga et al,[44] 2019
Weighted average[d]	-	*$13,332*	

[a]Refers to treatment-related adverse events of any grade that occurred in ≥15% of total patients in the KEYNOTE-A18 trial. Our analysis only included and evaluated grade 3-4 treatment-related adverse events.

[b]Number within each treatment arm: pembrolizumab (N=528), placebo (N=530).

[c]Cost per one-month cycle.

[d]Calculated as an average cost of toxicity using the weighted frequency of occurrence. This value was used in the base-case model.

eTable 3. Disutility from grade 3-4 treatment-related adverse events. References per main text.

Adverse Event[a]	No. of patients (%)[b]	Disutility[c]	Reference
Pembrolizumab			
White blood cell count decreased, leukopenia	174 (32.9%)	0.20	Li et al,[49] 2022
Anemia	122 (23.1%)	0.38	Zheng et al,[18] 2023
Neutrophil count decreased	83 (15.7%)	0.20	Zheng et al,[18] 2023
Neutropenia	61 (11.6%)	0.20	Zheng et al,[18] 2023
Platelet count decreased	27 (5.1%)	0.27	Zheng et al,[18] 2023
Diarrhea	25 (4.7%)	0.018	Nafees et al,[47] 2008;
Nausea, vomiting	13 (2.5%)	0.017	Nafees et al,[47] 2008;
Hypo/hyperthyroidism	5 (0.9%)	0.042	Houten et al,[48] 2021
Weighted average[d]	-	*0.231*	
Placebo			
White blood cell count decreased, leukopenia	172 (32.4%)	0.20	Li et al,[49] 2022
Anemia	117 (22.1%)	0.38	Zheng et al,[18] 2023
Neutrophil count decreased	81 (15.3%)	0.20	Zheng et al,[18] 2023
Neutropenia	57 (10.8%)	0.20	Zheng et al,[18] 2023
Diarrhea	25 (4.7%)	0.018	Nafees et al,[47] 2008;
Nausea, vomiting	17 (3.2%)	0.017	Nafees et al,[47] 2008;
Platelet count decreased	15 (2.8%)	0.27	Zheng et al,[18] 2023
Weighted average[d]	-	*0.230*	

[a]Refers to treatment-related adverse events of any grade that occurred in ≥15% of total patients in the KEYNOTE-A18 trial. Our analysis only included and evaluated grade 3-4 treatment-related adverse events.

[b]Number within each treatment arm: pembrolizumab (N=528), placebo (N=530).

[c]Disutility per one-month cycle.

[d]Calculated as an average disutility of toxicity using the weighted frequency of occurrence. This value was used in the base-case model.

eTable 4: Unknown standard deviation sensitivity analysis.

Unknown Standard Deviation	Probability of Pembrolizumab Being Cost-Effective at $100,000/QALY	Probability of Pembrolizumab Being Cost-Effective at $150,000/QALY
10%	35.3%	56.1%
20%[a]	37.3%	53.9%
30%	38.9%	52.8%
40%	40.6%	51.9%

[a]This value was used in the base-case model.

eTable 5: Three-way sensitivity analysis of disease response to pembrolizumab.

Probability of complete response with pembrolizumab	Probability of partial response with pembrolizumab	Probability of stable disease with pembrolizumab	ICER ($/QALY)
10%	10%	80%	-12967145.98
0%	20%	80%	-2924603.86
10%	0%	90%	-1452430.32
0%	10%	90%	-1048976.87
0%	0%	100%	-639102.97
100%	0%	0%	138942.42
90%	10%	0%	144249.83
80%	20%	0%	149978.81
70%	30%	0%	156181.68
90%	0%	10%	158201.97
60%	40%	0%	162919.75
80%	10%	10%	165119.35
50%	50%	0%	170265.44
70%	20%	10%	172669.33
40%	60%	0%	178304.81
60%	30%	10%	180942.82
80%	0%	20%	183660.06
30%	70%	0%	187140.98
50%	40%	10%	190049.06
70%	10%	20%	193048.95
20%	80%	0%	196898.59
40%	50%	10%	200120.45
60%	20%	20%	203449.50
10%	90%	0%	207729.72
30%	60%	10%	211319.01
50%	30%	20%	215034.52
70%	0%	30%	218883.03
0%	100%	0%	219821.81
20%	70%	10%	223845.19
40%	40%	20%	228018.59
60%	10%	30%	232350.56
10%	80%	10%	237949.95
30%	50%	20%	242671.40
50%	20%	30%	247584.03
0%	90%	10%	253951.75
20%	60%	20%	259336.77

40%	30%	30%	264955.12
60%	0%	40%	270822.29
10%	70%	20%	278459.90
30%	40%	30%	284947.74
50%	10%	40%	291745.11
0%	80%	20%	300627.77
20%	50%	30%	308203.76
40%	20%	40%	316171.45
10%	60%	30%	335593.21
30%	30%	40%	345061.72
50%	0%	50%	355080.05
0%	70%	30%	368325.56
20%	40%	40%	379762.67
40%	10%	50%	391932.82
10%	50%	40%	422223.32
30%	20%	50%	437321.16
0%	60%	40%	475374.14
20%	30%	50%	494598.89
40%	0%	60%	515444.13
10%	40%	50%	569141.70
30%	10%	60%	596920.20
0%	50%	50%	670141.13
20%	20%	60%	708990.00
10%	30%	60%	872868.11
30%	0%	70%	939953.34
0%	40%	60%	1135280.25
20%	10%	70%	1251448.68
10%	20%	70%	1871729.47
0%	30%	70%	3711173.27
20%	0%	80%	5327914.34

eTable 6: Three-way sensitivity analysis of disease response to placebo.

Probability of complete response with placebo	Probability of partial response with placebo	Probability of stable disease with placebo	ICER ($/QALY)
0%	0%	100%	88298.20836
0%	10%	90%	92742.41742
10%	0%	90%	94809.28261
0%	20%	80%	97657.70704
10%	10%	80%	99952.17312
20%	0%	80%	102357.0502
0%	30%	70%	103123.17
10%	20%	70%	105685.0132
20%	10%	70%	108377.3844
0%	40%	60%	109236.6546
30%	0%	70%	111210.5204
10%	30%	60%	112115.4904
20%	20%	60%	115150.1717
0%	50%	50%	116120.6745
30%	10%	60%	118353.7056
10%	40%	50%	119379.1998
40%	0%	60%	121740.5881
20%	30%	50%	122825.8835
0%	60%	40%	123930.7034
30%	20%	50%	126477.5077
10%	50%	40%	127649.3103
40%	10%	50%	130352.9111
20%	40%	40%	131597.9778
0%	70%	30%	132867.0584
50%	0%	50%	134473.3143
30%	30%	40%	135798.7374
10%	60%	30%	137150.5483
40%	20%	40%	140276.5262
20%	50%	30%	141719.429
0%	80%	20%	143192.3241
50%	10%	40%	145059.6829
30%	40%	30%	146603.205
10%	70%	20%	148179.9284
60%	0%	40%	150180.5474
40%	30%	30%	151835.5929
20%	60%	20%	153527.5234
0%	90%	10%	155257.5857

50%	20%	30%	157455.301
30%	50%	20%	159275.5426
10%	80%	10%	161138.3619
60%	10%	30%	163506.9883
40%	40%	20%	165470.7109
20%	70%	10%	167482.1755
0%	100%	0%	169543.1447
70%	0%	30%	170042.4544
50%	30%	20%	172167.3165
30%	60%	10%	174345.9554
10%	90%	0%	176580.4388
60%	20%	20%	179428.8067
40%	50%	10%	181796.3614
20%	80%	0%	184227.2311
70%	10%	20%	187329.8042
50%	40%	10%	189911.9566
30%	70%	0%	192566.2885
80%	0%	20%	195958.681
60%	30%	10%	198785.9878
40%	60%	0%	201696.0742
70%	20%	10%	208529.9852
50%	50%	0%	211734.6538
80%	10%	10%	219278.4736
60%	40%	0%	222824.8289
90%	0%	10%	231195.2209
70%	30%	0%	235140.9733
80%	20%	0%	248898.2688
90%	10%	0%	264365.3849
100%	0%	0%	281882.1989