The Health Impact of Using Anti-PD-1 Agents to Treat Early-Stage Cancer in Belgium

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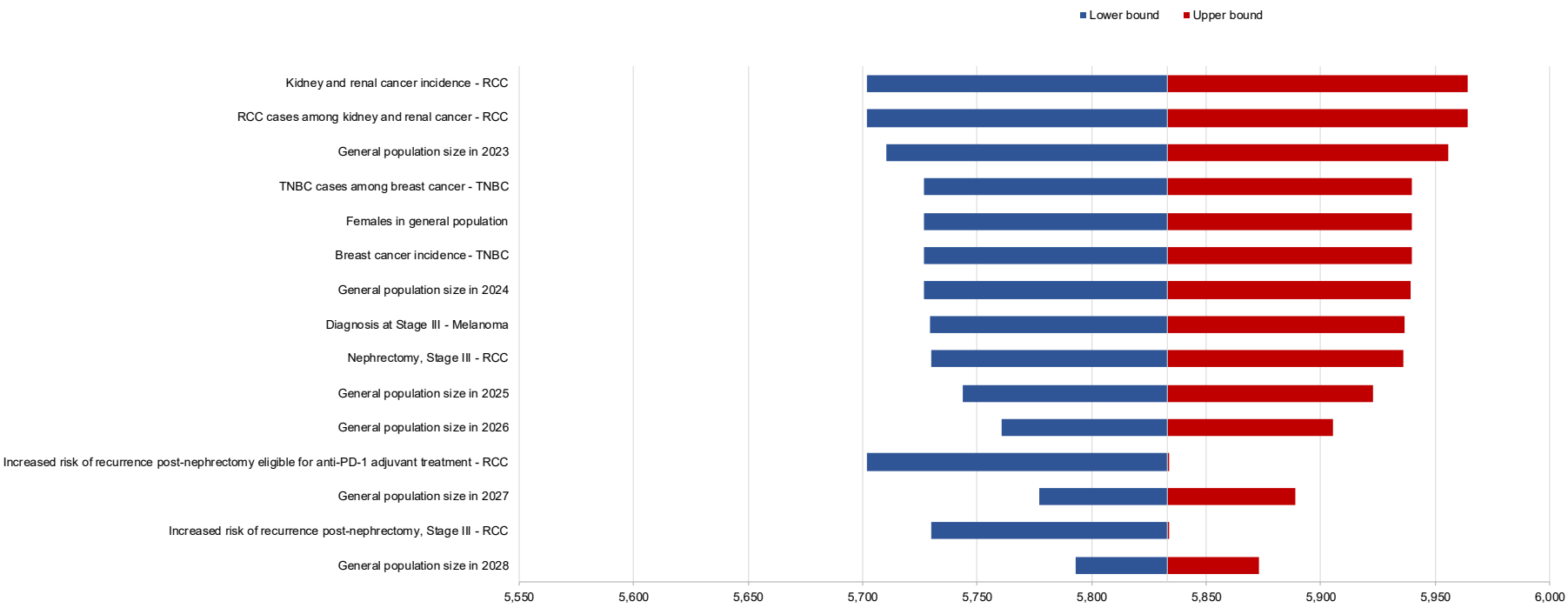
Running head: Impact of anti-PD-1 agents on early-stage cancer

SUPPLEMENTARY MATERIAL

Supplemental Figure 1. One-way sensitivity analysis



Abbreviations: RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; PD-1, programmed cell death protein 1

One-way sensitivity analysis identified the fifteen most influential parameters on recurrence-/event-/disease-free LYs over ten years. The central axis is the base case value of recurrence-/event-/disease-free LYs (5,833).

Supplemental Table 1. Values for sensitivity analysis

Parameter description	Input base value	Input lower bound	Input upper bound
Kidney and renal cancer incidence - RCC	17.27 per 100,000	15.55 per 100,000	19.00 per 100,000
RCC cases among kidney and renal cancer - RCC	83.20%	74.88%	91.52%
General population size in 2023	11,646,562	10,481,905	12,811,218
TNBC cases among breast cancer - TNBC	8.59%	7.73%	9.45%
Female in general population	50.72%	45.65%	55.79%
Breast cancer incidence - TNBC	198.30 per 100,000	178.47 per 100,000	218.13 per 100,000
General population size in 2024	11,709,453	10,538,508	12,880,398
Diagnosis at Stage III - Melanoma	5.63%	5.07%	6.19%
Nephrectomy, Stage III - RCC	87.50%	78.75%	96.25%
General population size in 2025	11,772,684	10,595,416	12,949,953
General population size in 2026	11,836,257	10,652,631	13,019,882
Increased risk of recurrence post-nephrectomy eligible for anti-PD-1 adjuvant treatment - RCC	100.00%	90.00%	100.00%
General population size in 2027	11,900,172	10,710,155	13,090,190
Increased risk of recurrence post-nephrectomy, Stage III - RCC	100.00%	90.00%	100.00%
General population size in 2028	11,964,433	10,767,990	13,160,877

Abbreviations: RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; PD-1, programmed cell death protein 1

Supplemental Table 2. Melanoma stage IIB-C adjuvant treatment market shares

Adjuvant treatment	All years
Reference scenario	
Pembrolizumab	0.00%
Nivolumab	0.00%
Watchful waiting	100.00%
ESD scenario	
Pembrolizumab	39.29%
Nivolumab	39.29%
Watchful waiting	21.43%

Abbreviations: ESD; early-stage disease

Supplemental Table 3. Melanoma stage IIB-C, 1L metastatic treatment market shares

	Adjuvant treatment			
	Anti-PD-1 agent [A]			Observation
1L treatment	Rechallenge eligible [B]	Eligible for retreatment with anti-PD-1 agent [C]	Ineligible for retreatment with anti-PD-1 agent [C]	
Pembrolizumab	100.0%	16.9%	0.0%	27.8%
Ipilimumab	0.0%	4.7%	38.7%	0.0%
Nivolumab	0.0%	11.0%	0.0%	22.3%
Nivolumab + ipilimumab	0.0%	35.8%	0.0%	22.3%
Vemurafenib	0.0%	0.0%	0.0%	0.0%
Dabrafenib	0.0%	0.0%	0.0%	0.0%
Dabrafenib + trametinib	0.0%	24.4%	54.1%	20.0%
Clinical trials	0.0%	3.6%	3.6%	3.6%
No active treatment	0.0%	3.6%	3.6%	3.6%
Total	100.0%	100.0%	100.0%	100.0%

Abbreviations: PD-1, programmed death-1; 1L, first-line

[A] The anti-PD-1 agents included in this model were pembrolizumab and nivolumab.

[B] Individuals were eligible for rechallenge if a recurrence occurred more than 18 months after the start of adjuvant treatment.

[C] Individuals were eligible for retreatment if a recurrence occurred less than 18 months after adjuvant treatment.

Supplemental Table 4. Melanoma stage IIB-C, 2L metastatic treatment market shares

	Adjuvant treatment			
	Anti-PD-1 agent [A]			Observation
2L treatment	**Rechallenge eligible [B]**	**Eligible for retreatment with anti-PD-1 agent [C]**	**Ineligible for retreatment with anti-PD-1 agent [C]**	
Pembrolizumab	16.8%	16.8%	0.0%	8.4%
Ipilimumab	25.2%	25.2%	37.8%	51.5%
Nivolumab	16.8%	16.8%	0.0%	8.4%
Nivolumab + ipilimumab	6.7%	6.7%	0.0%	9.8%
Vemurafenib	0.0%	0.0%	2.0%	0.0%
Dabrafenib	0.0%	0.0%	0.0%	0.0%
Dabrafenib + trametinib	18.5%	18.5%	12.0%	14.8%
No active treatment	16.0%	16.0%	48.3%	7.0%
Total	100.0%	100.0%	100.0%	100.0%

Abbreviations: PD-1, programmed death-1; 2L, second-line

[A] The anti-PD-1 agents included in this model were pembrolizumab and nivolumab.

[B] Individuals were eligible for rechallenge if a recurrence occurred more than 18 months after the start of adjuvant treatment.

[C] Individuals were eligible for retreatment if a recurrence occurred less than 18 months after the start of adjuvant treatment.

Supplemental Table 5. Melanoma stage III adjuvant treatment market shares

Adjuvant treatment	All years
Reference scenario	
Pembrolizumab	0.00%
Nivolumab	0.00%
Watchful waiting	56.25%
Dabrafenib + trametinib	43.75%
ESD scenario	
Pembrolizumab	39.29%
Nivolumab	39.29%
Watchful waiting	7.14%
Dabrafenib + trametinib	14.29%

Abbreviations: ESD, early-stage disease

Supplemental Table 6. Melanoma stage III, 1L metastatic treatment market shares

	Adjuvant treatment		
	Anti-PD-1 agent [A]		Observation
1L treatment	**Eligible for retreatment with anti-PD-1 agent [B]**	**Ineligible for retreatment with anti-PD-1 agent [B]**	
Pembrolizumab	15.0%	0.0%	24.8%
Ipilimumab	5.0%	40.2%	0.0%
Nivolumab	23.0%	0.0%	32.7%
Nivolumab + ipilimumab	18.0%	0.0%	11.9%
Vemurafenib	2.0%	2.4%	3.0%
Dabrafenib	0.0%	0.0%	0.0%
Dabrafenib + trametinib	37.0%	57.3%	27.7%
Total	100.0%	100.0%	100.0%

Abbreviations: PD-1, programmed death-1; 1L, first-line

[A] The anti-PD-1 agents included in this model were pembrolizumab and nivolumab.

[B] Individuals were eligible for retreatment if a recurrence occurred more than 12 months after the start of adjuvant treatment.

Supplemental Table 7. Melanoma stage III, 2L metastatic treatment market shares

	Adjuvant treatment		
	Anti-PD-1 agent [A]		Observation
2L treatment	**Eligible for retreatment with anti-PD-1 agent [B]**	**Ineligible for retreatment with anti-PD-1 agent [B]**	
Pembrolizumab	16.8%	0.0%	8.4%
Ipilimumab	25.2%	37.8%	51.5%
Nivolumab	16.8%	0.0%	8.4%
Nivolumab + ipilimumab	6.7%	0.0%	9.8%
Vemurafenib	0.0%	2.0%	0.0%
Dabrafenib	0.0%	0.0%	0.0%
Dabrafenib + trametinib	18.5%	12.0%	14.8%
No treatment	16.0%	48.3%	7.0%
Total	100.0%	100.0%	100.0%

Abbreviations: PD-1, programmed death-1; 2L, second-line

[A] The anti-PD-1 agents included in this model were pembrolizumab and nivolumab.

[B] Individuals were eligible for retreatment if a recurrence occurred more than 12 months after the start of adjuvant treatment.

Supplemental Table 8. Renal cell carcinoma adjuvant treatment market shares

Treatment	All years
Reference scenario	
Pembrolizumab	0.00%
Watchful waiting	100.00%
ESD scenario	
Pembrolizumab	81.82%
Watchful waiting	18.18%

Abbreviations: ESD, early-stage disease

Supplemental Table 9. Renal cell carcinoma, 1L metastatic treatment market shares

	Adjuvant treatment	
1L treatment		
Pembrolizumab + axitinib	48.70%	60.15%
Nivolumab + ipilimumab	24.17%	19.48%
Avelumab + axitinib	4.35%	3.23%
Nivolumab + cabozantinib	17.39%	12.90%
No treatment	5.39%	4.23%
Total	100.0%	100.0%

Abbreviations: PD-1, programmed death-1; 1L, first-line

[A] The anti-PD-1 agent included in this indication was pembrolizumab.

Supplemental Table 10. Renal cell carcinoma 2L metastatic treatment market shares

	Adjuvant treatment	
2L treatment		
Axitinib	25.45%	25.45%
Cabozantinib	9.09%	9.09%
Pazopanib	9.09%	9.09%
Sunitinib	9.09%	9.09%
No treatment	47.27%	47.27%
Total	100.00%	100.00%

Abbreviations: PD-1, programmed death-1; 2L, second-line

[A] The anti-PD-1 agent included in this indication was pembrolizumab.

Supplemental Table 11. Triple-negative breast cancer neoadjuvant/adjuvant treatment market shares

Neoadjuvant/adjuvant treatment	All years
Reference scenario	
Pembrolizumab + chemotherapy	0.00%
Chemotherapy	100.00%
ESD scenario	
Pembrolizumab + chemotherapy	69.56%
Chemotherapy	30.44%

Abbreviations: ESD, early-stage disease

Supplemental Table 12. Triple-negative breast cancer 1L metastatic treatment market shares

	Neoadjuvant/adjuvant treatment		
	Anti-PD-1 agent [A]		
1L treatment	**Eligible for retreatment with anti-PD-1 agent [C]**	**Rechallenge eligible [B]**	**Chemotherapy**
Pembrolizumab + paclitaxel	12.01%	62.50%	13.51%
Pembrolizumab + gemcitabine + carboplatin	7.78%	0.00%	8.75%
Paclitaxel	16.33%	0.00%	18.36%
Gemcitabine + carboplatin	13.42%	0.00%	15.09%
Atezolizumab + nab-paclitaxel	3.70%	0.00%	4.16%
Capecitabine	3.00%	0.00%	3.37%
Clinical trials	6.26%	0.00%	7.04%
No treatment	37.50%	37.50%	29.70%
Total	100.00%	100.00%	100.00%

Abbreviations: PD-1, programmed death-1; 1L, first-line

[A] The anti-PD-1 agent included in this indication was pembrolizumab.

[B] Individuals were eligible for rechallenge if a recurrence occurred more than 24 months after the start of neoadjuvant/adjuvant treatment.

Supplemental Table 13. Utilities for health states, by cancer

Cancer	Melanoma Stage IIB-C	Melanoma Stage III	Renal cell carcinoma	Triple-negative breast cancer
Recurrence-/event-/disease-free	0.89	0.89	0.88	0.83
Locoregional recurrence	0.87	0.87	0.87	0.83
Metastatic, pre-progression	0.84	0.84	0.82	0.77
Metastatic, post-progression	0.84	0.84	0.82	0.67
Source	[29]	[29]	[27]	[28]

Supplemental Table 14. Cumulative health impact of early-stage disease treatment with anti-PD-1 agents in Belgium from 2023-2032 by cancer type

	Health outcome						
	LYs, recurrence-/event-/disease-free	LYs, total	QALYs	Events or recurrences	Active treatments for metastatic disease	Deaths after first event or recurrence	Deaths, total
Reference scenario							
Multi-cancer	43,425	56,672	47,760	6,848	7,425	3,148	3,530
TNBC	16,343	18,164	14,612	1,315	666	682	762
Melanoma stage III	8,850	13,807	11,912	2,638	3,626	1,252	1,312
Melanoma stage IIB-C	9,214	12,484	10,828	1,673	1,934	679	756
RCC	9,018	12,217	10,408	1,221	1,199	535	700
ESD scenario							
Multi-cancer	49,258	59,175	50,102	5,167	5,303	2,265	2,689
TNBC	17,408	18,754	15,158	928	441	471	556
Melanoma stage III	11,059	14,670	12,736	2,001	2,460	951	1,012
Melanoma stage IIB-C	10,462	12,984	11,302	1,299	1,419	512	598
RCC	10,329	12,767	10,907	939	983	330	523
Health impact (% change)							
Multi-cancer	5833 (13.4%)	2503 (4.4%)	2342 (4.9%)	-1682 (-24.6%)	-2122 (-28.6%)	-883 (-28.0%)	-842 (-23.8%)
TNBC	1065 (6.5%)	589 (3.2%)	546 (3.7%)	-387 (-29.5%)	-225 (-33.8%)	-210 (-30.8%)	-206 (-27.0%)
Melanoma stage III	2209 (25.0%)	863 (6.3%)	823 (6.9%)	-638 (-24.2%)	-1167 (-32.2%)	-301 (-24.1%)	-301 (-22.9%)
Melanoma stage IIB-C	1247 (13.5%)	500 (4.0%)	474 (4.4%)	-375 (-22.4%)	-515 (-26.6%)	-167 (-24.6%)	-158 (-20.9%)
RCC	1311 (14.5%)	550 (4.5%)	499 (4.8%)	-282 (-23.1%)	-215 (-18.0%)	-205 (-38.3%)	-178 (-25.4%)

Abbreviations: ESD, early-stage disease; LY, life-year; PD-1, programmed cell death protein 1; QALY, quality-adjusted life-year; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer

The cumulative health impact of ESD treatment is the difference between the ESD and reference scenario values for each of the health outcomes after ten years (2023-2032). A positive percent change indicates LYs and QALYs gained by ESD treatment, while a negative percent change indicates events/recurrences, metastatic treatments, and deaths

avoided with the ESD treatment. Multi-cancer are the combined results for individuals with RCC, melanoma (stage IIB-C and III), or triple-negative breast cancer who are eligible for ESD treatment.

Supplemental Table 15. Health impact of early-stage disease treatment with anti-PD-1 agents from 2023-2032, by year

	Health outcome						
	LYs, recurrence-/event-/disease-free	LYs, total	QALYs	Events or recurrences	Active treatments for metastatic disease	Deaths after first event or recurrence	Deaths, total
2023							
Reference scenario	666.9	702.4	606.2	115.9	81.1	6.4	10.7
ESD scenario	671.1	702.3	606.0	99.3	65.1	5.9	11.0
Health impact (% change) [A]	4 (0.6%)	0 (0.0%)	0 (0.0%)	-17 (-14.3%)	-16 (-19.7%)	0 (-6.7%)	0 (2.0%)
2024							
Reference scenario	1809.1	2044.5	1756.4	353.2	289.2	47.1	61.3
ESD scenario	1858.8	2046.5	1761.3	272.5	207.3	38.4	54.2
Health impact (% change) [A]	50 (2.7%)	2 (0.1%)	5 (0.3%)	-81 (-22.8%)	-82 (-28.3%)	-9 (-18.4%)	-7 (-11.5%)
2025							
Reference scenario	2752.2	3305.4	2823.2	527.0	491.5	121.8	144.8
ESD scenario	2904.0	3324.2	2848.2	393.7	341.0	92.4	116.9
Health impact (% change) [A]	152 (5.5%)	19 (0.6%)	25 (0.9%)	-133 (-25.3%)	-150 (-30.6%)	-29 (-24.1%)	-28 (-19.3%)
2026							
Reference scenario	3565.4	4466.3	3797.1	645.4	655.5	207.3	237.7
ESD scenario	3854.3	4525.5	3863.0	479.3	453.9	151.6	183.8
Health impact (% change) [A]	289 (8.1%)	59 (1.3%)	66 (1.7%)	-166 (-25.7%)	-202 (-30.8%)	-56 (-26.8%)	-54 (-22.7%)
2027							
Reference scenario	4288.3	5526.4	4680.4	732.7	785.2	291.2	328.2
ESD scenario	4734.3	5651.1	4808.3	544.9	547.6	209.4	248.9
Health impact (% change) [A]	446 (10.4%)	125 (2.3%)	128 (2.7%)	-188 (-25.6%)	-238 (-30.3%)	-82 (-28.1%)	-79 (-24.2%)
2028							
Reference scenario	5030.2	6611.8	5581.0	814.3	903.8	376.5	420.5
ESD scenario	5659.0	6829.9	5794.1	607.8	636.5	268.8	316.4
Health impact (% change) [A]	629 (12.5%)	218 (3.3%)	213 (3.8%)	-207 (-25.4%)	-267 (-29.6%)	-108 (-28.6%)	-104 (-24.8%)
2029							
Reference scenario	5530.5	7362.1	6196.2	851.7	966.4	439.2	488.1
ESD scenario	6324.9	7685.0	6502.1	639.2	688.1	312.9	366.7
Health impact (% change) [A]	794 (14.4%)	323 (4.4%)	306 (4.9%)	-212 (-24.9%)	-278 (-28.8%)	-126 (-28.8%)	-121 (-24.9%)
2030							

Reference scenario	6087.9	8166.5	6855.6	898.3	1032.3	500.4	555.0
ESD scenario	7061.9	8613.0	7269.4	677.8	742.8	356.8	417.8
Health impact (% change) [A]	974 (16.0%)	447 (5.5%)	414 (6.0%)	-220 (-24.5%)	-289 (-28.0%)	-144 (-28.7%)	-137 (-24.7%)
2031							
Reference scenario	6605.5	8904.1	7456.9	937.9	1087.1	554.9	615.1
ESD scenario	7761.5	9486.6	7987.9	711.3	789.9	396.4	464.8
Health impact (% change) [A]	1156 (17.5%)	583 (6.5%)	531 (7.1%)	-227 (-24.2%)	-297 (-27.3%)	-158 (-28.6%)	-150 (-24.4%)
2032							
Reference scenario	7089.2	9582.6	8007.0	971.9	1133.1	603.0	668.7
ESD scenario	8427.9	10310.6	8662.0	740.7	830.8	432.0	508.0
Health impact (% change) [A]	1339 (18.9%)	728 (7.6%)	655 (8.2%)	-231 (-23.8%)	-302 (-26.7%)	-171 (-28.4%)	-161 (-24.0%)

Abbreviations: ESD, early-stage disease; PD-1, programmed cell death protein 1; QALY, quality-adjusted life-year

[A] The health impact is the difference between the ESD and reference scenarios for each health outcome. A positive percent change indicates LYs and QALYs gained by ESD treatment, while a negative percent change indicates events/recurrences, metastatic treatments, and deaths avoided with the ESD treatment. These are the combined yearly results for individuals in Belgium with renal cell carcinoma, melanoma (stage IIB-C and III), or TNBC who are eligible for ESD treatment.

Supplemental Table 16. Sensitivity analysis

Scenario analysis	Change in health impact from base case analysis (% change)						
	LYs, recurrence-/event-/disease-free	LYs, total	QALYs	Events or recurrences	Active treatments for metastatic disease	Deaths after first event or recurrence	Deaths, total
100% uptake of anti-PD-1 agents							
Multi-cancer	1502 (25.8%)	668 (26.7%)	626 (26.7%)	-456 (-27.1%)	-557 (-26.3%)	-240 (-27.1%)	-233 (-27.7%)
TNBC	466 (43.8%)	258 (43.8%)	239 (43.8%)	-170 (-43.8%)	-99 (-43.8%)	-92 (-43.8%)	-90 (-43.8%)
Melanoma stage III	464 (21.0%)	174 (20.1%)	167 (20.3%)	-137 (-21.5%)	-282 (-24.2%)	-66 (-22.0%)	-69 (-23.1%)
Melanoma stage IIB-C	340 (27.3%)	136 (27.3%)	129 (27.3%)	-102 (-27.3%)	-140 (-27.3%)	-46 (-27.3%)	-43 (-27.3%)
RCC	232 (17.7%)	100 (18.2%)	90 (18.1%)	-47 (-16.8%)	-36 (-16.6%)	-36 (-17.5%)	-31 (-17.4%)
Delayed time to launch of anti-PD-1 agents							
Multi-cancer	-1568 (-26.9%)	-850 (-33.9%)	-764 (-32.6%)	272 (16.2%)	358 (16.9%)	202 (22.9%)	191 (22.7%)
TNBC	-318 (-29.9%)	-210 (-35.7%)	-185 (-33.9%)	74 (19.2%)	43 (19.2%)	48 (22.9%)	50 (24.1%)
Melanoma stage III	-594 (-26.9%)	-298 (-34.6%)	-274 (-33.3%)	101 (15.8%)	203 (17.4%)	71 (23.6%)	70 (23.2%)
Melanoma stage IIB-C	-327 (-26.2%)	-164 (-32.8%)	-150 (-31.6%)	60 (15.9%)	92 (17.8%)	37 (22.1%)	34 (21.5%)
RCC	-328 (-25.0%)	-176 (-32.0%)	-155 (-31.1%)	36 (12.7%)	20 (9.5%)	46 (22.3%)	38 (21.1%)
No retreatment with anti-PD-1 agents							
Multi-cancer	0 (0.0%)	-283 (-11.3%)	-223 (-9.5%)	7 (0.4%)	-303 (-14.3%)	86 (9.7%)	86 (10.2%)
TNBC	0 (0.0%)	-48 (-8.2%)	-31 (-5.7%)	0 (0.0%)	0 (0.0%)	15 (6.9%)	15 (7.1%)
Melanoma stage III	0 (0.0%)	-122 (-14.1%)	-97 (-11.8%)	0 (0.0%)	-153 (-13.1%)	37 (12.2%)	37 (12.2%)
Melanoma stage IIB-C	0 (0.0%)	-113 (-22.7%)	-95 (-20.0%)	7 (1.8%)	-150 (-29.2%)	35 (20.8%)	35 (21.9%)
RCC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: LY, life-year; PD-1, programmed cell death protein 1; QALY, quality-adjusted life-year; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer

The following changes were made separately to the ESD scenario for the sensitivity analysis: 100% update of anti-PD-1 agents, delayed time to launch of anti-PD-1 agents by 15 months, no retreatment with anti-PD-1 agents. The values are the difference between the new ESD scenario health impact results minus the base case health impact results. A positive percent change for LYs and QALYs indicates an increase in LYs and QALYs gained, while a positive percent change for events/recurrences, metastatic treatments, and

deaths indicates an increase in these outcomes with the alternative ESD scenario. A negative percent change for LYs and QALYs indicate a decrease in these health outcomes, while a negative percent change for events/recurrences, metastatic treatments, and deaths indicates a greater avoidance of these outcomes with the alternative ESD scenario. Multi-cancer are the combined results for individuals with renal cell carcinoma, melanoma (stage IIB-C and III), or triple-negative breast cancer who are eligible for ESD treatment.