Adverse event management costs associated with immune checkpoint inhibitors approved for various advanced or metastatic cancers in the United States

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Inizio Advisory

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Background and objective

- ICIs enhance the body's ability to combat tumour cells by targeting key regulatory pathways in the immune system. They have contributed to improved survival in various tumours, especially in patients with advanced and/or metastatic diseases. To date, a total of 9 ICIs have been approved by the US FDA for treatment of various cancers (1-3)
- Although ICIs have demonstrated improved clinical efficacy, their introduction in clinical practice has been accompanied by a range of AEs, which can vary in severity. These AEs not only pose significant clinical challenges and affect patients' quality of life but also result in a considerable economic burden on healthcare systems (4,5)
- The economic burden associated with AEs can vary widely, depending on the type and severity of the event, the specific ICI used, and the cancer type (6). An evaluation of these costs can inform decision-making in clinical practice and health policy
- This study aimed to evaluate costs associated with AE management in patients receiving ICIs approved for advanced/metastatic cancers in the United States

Methods

- The AE management cost for each ICI regimen was calculated by multiplying the frequency reported of each AE by its unit management cost and then aggregating it across all the AEs. Only grade 3-4 AEs were considered in the analysis, as these are associated with significant costs
- Frequencies of grade 3-4 AEs were obtained from the publications of the registrational clinical trials for the ICI regimens in the respective indication
- The analysis assumes that all grade 3-4 AEs require hospitalisation
- Unit costs of hospitalisation for the respective AE were sourced from the NIS in HCUP. Inpatient stays related to each AE of interest were identified as cases with a diagnosis of the respective AE at the primary diagnosis position (DX1) and diagnoses of any primary and secondary cancer (excluding basal cell carcinoma) at a secondary diagnosis position (DX2-DX40)
- Charges were converted into costs using the cost to charge ratios and weighted by the sample discharge weights available in the NIS data to arrive at the US national estimates of the unit costs
- All costs were adjusted to 2023 US dollar using the medical component of CPI (7)

Results

- The AE management costs associated with approved ICI regimens in advanced or metastatic cancers, and derived using the methods described above, are shown in Tables 1-5. The tables also include the 3 most frequent AEs reported for the regimen

Table 1. AE management costs (per patient, 2023 US$) associated with ICIs approved for melanoma

Treatment (LOT)	Trial name/ID	Three most frequent grade 3-4 AEs (frequency, %)	AE cost
Ipilimumab (1L)	CheckMate 067 (8)	Colitis (7.7%), diarrhoea (5.8%), lipase increased (3.9%)	$3191
Ipilimumab (1L+)	MDX010-20 (9)	Diarrhoea (9.9%), fatigue/asthenia (6.9%), colitis (5.3%)	$5,080
	KEYNOTE-006 (10)	Colitis (7.0%), diarrhoea (3.1%), fatigue/asthenia (2.0%)	$2,130
	NCT01515189 (11); 10 mg/kg	Diarrhoea (10.7%), colitis (6%), ALT increased (3.8%)	$3,536
	NCT01515189 (11); 3 mg/kg	Diarrhoea (5.8%), colitis (2.8%), hypophysitis (2.5%)	$2,870
Nivolumab (1L)	CheckMate 067 (8)	Lipase increased (5.8%), diarrhoea (2.9%), amylase increased (2.2%)	$1,629
	CheckMate 066 (12)	Diarrhoea (1%), rash/pruritus (1%), vomiting (0.5%)	$239
	RELATIVITY-047 (13)	Hepatitis (1.1%), rash/pruritus (1.1%), pneumonitis (0.6%)	$577
Nivolumab (1L+)	CheckMate 037 (14)	Anaemia (0.7%), fatigue/asthenia (0.7%), diarrhoea (0.3%)	$267
Pembrolizumab (1L+)	KEYNOTE-006 (10); Q2W	Diarrhoea (2.5%), colitis (1.4%), hepatitis (1.8%)	$746
	KEYNOTE-006 (10); Q3W	Colitis (2.5%), hepatitis (1.8%), diarrhoea (1.1%)	$991
Nivolumab + ipilimumab (1L)	CheckMate 067 (8)	Lipase increased (10.9%), diarrhoea (9.6%), ALT increased (8.6%)	$6,777
Ipilimumab + GP peptide vaccine (1L)	MDX010-20 (9)	Fatigue/asthenia (5%), diarrhoea (4.5%), dyspnoea (3.7%)	$3,720
Relatlimab + nivolumab (1L)	RELATIVITY-047 (13)	Hepatitis (3.9%), fatigue (1.1%), diarrhoea (0.8%)	$1,209
Atezolizumab + CT (1L)	IMspire150 (15)	Blood creatine phosphokinase increased (20.0%), lipase increased (20.0%)	$8,924

- In patients with melanoma, the AE management cost ranged from $239 with nivolumab to $8,924 with atezolizumab + CT
- Monotherapy regimens, such as nivolumab and pembrolizumab, were associated with lower AE management costs compared with combination therapies. Ipilimumab was an exception among monotherapies, with substantially higher AE management costs compared with nivolumab and pembrolizumab monotherapies

Table 2. AE management costs (per patient, 2023 US$) associated with ICIs approved for lung cancer

Treatment (LOT)	Trial name/ID	Three most frequent grade 3-4 AEs (frequency, %)	AE cost
NSCLC			
Atezolizumab (1L)	IMpower110 (16)	Pneumonia (2.4%), hyponatraemia (2.1%), anaemia (1.7%)	$1,269
Pembrolizumab (1L)	KEYNOTE-042 (17)	Pneumonitis (3.1%), ALT increased (1.4%), fatigue/asthenia (0.9%)	$1,349
	KEYNOTE-024 (18)	Diarrhoea (3.9%), infusion-related reactions (3.9%), pneumonitis (2.6%)	$2,072
Durvalumab (1L+)	PACIFIC (19)	Pneumonia (4.4%), pneumonitis (3.4%), anaemia (2.9%)	$2,056
Atezolizumab (2L)	OAK (20)	Fatigue/asthenia (22.7%), nausea (8.7%), decreased appetite/anorexia (8.5%)	$5,525
Durvalumab (2L+)	ARCTIC (21)	Lymphocyte count decreased (1.7%), dyspnoea (1.12%); fatigue/asthenia (1.12%)	$1,235
Pembrolizumab (2L+)	KEYNOTE-010 (22)	Severe skin reactions/infusion-related reactions (3.9%), diarrhoea (3.9%), pneumonitis (2.6%)	$2,072
Tremelimumab (2L+)	ARCTIC (21)	Diarrhoea (13.3%), colitis (5%), AST/ALT increased (3.3%)	$3,732
Cemiplimab (1L)	EMPOWER-Lung 1 (25)	AST increased (1.4%), maculopapular rash/rash/pruritus (1.1%), pneumonia (1.1%)	$1,294
Durvalumab + tremelimumab (2L+)	ARCTIC (21)	Diarrhoea (2.9%), pneumonitis (2.9%), fatigue/asthenia (2.3%)	$2,910
Nivolumab + ipilimumab + CT (1L)	CHECKMATE-9LA (23)	Neutropenia (6.7%), lipase increased (6.1%), anaemia (5.1%)	$6,066
Cemiplimab + CT (1L)	EMPOWER-Lung 3 (24)	Anaemia (9.9%), neutropenia (5.8%), fatigue/asthenia (4.2%)	$3,733
Tremelimumab + durvalumab + CT(1L)	POSEIDON (26)	Anaemia (17.3%), neutropenia (16.1%), neutrophil count decreased (7.3%)	$7,675
Durvalumab + CT (1L)		Anaemia(15.3%), neutropenia (12.6%), neutrophil count decreased (7.2%)	$6,366
Squamous NSCLC			
Nivolumab (1L+)	Lung-MAP S1400I (27)	Fatigue/asthenia (5.7%), tuberculosis (4.9%), pneumonitis (4.9%)	$7,533
	CheckMate 017 (28)	Decreased appetite/anorexia (0.8%), fatigue/asthenia (0.8%), leukopenia (0.8%)	$290
Pembrolizumab + CT (1L)	KEYNOTE-407 (29)	Neutropenia (22.7%), anaemia (15.5%), thrombocytopenia (6.8%)	$7,985
Nivolumab + ipilimumab (1L+)	Lung-MAP S1400I (27)	Fatigue/asthenia (8.9%), pneumonitis (7.3%), hyponatraemia (5.6%)	$7,631
Non-squamous NSCLC			
Nivolumab (1L+)	CheckMate 057 (30)	Fatigue/asthenia (1.4%), diarrhoea (0.7%), nausea (0.7%)	$463
Nivolumab + ipilimumab (1L)	CheckMate 227 (34)	Diarrhoea (1.7%), fatigue/asthenia (1.7%), rash (1.6%)	$866
Atezolizumab + bevacizumab + CT (1L)	IMpower150 (31)	Neutropenia (13.7%), febrile neutropenia (9.2%), thrombocytopenia (9.2%)	$10,102
Pembrolizumab + CT (1L)	KEYNOTE-189 (32)	Anaemia (16.3%), neutropenia (15.8%), fatigue/asthenia (11.9%)	$9,054
Atezolizumab + CT (1L)	IMpower130 (33)	Neutropenia (32.1%), anaemia (29.2%), thrombocytopenia/platelets decreased (17.3%)	$15,197
SCLC			
Atezolizumab (1L)	IMpower133 (35)	Neutropenia (23.2%), anaemia (14.1%), neutrophil count decreased (14.1%)	$11,085
Nivolumab (1L+)	CheckMate 451 (36)	Fatigue/asthenia (2.2%), diarrhoea (1.1%); decreased appetite/anorexia (0.4%)	$503
Nivolumab + ipilimumab (1L+)	CheckMate 451 (36)	Diarrhoea (5.4%), fatigue/asthenia (2.9%), rash/pruritus (2.9%)	$1,493
Durvalumab + CT (1L)	CASPIAN (37)	Neutropenia (24.2%), anaemia (9.1%), leukopenia/WBCs decreased (7.9%)	$10,428
Durvalumab + tremelimumab + CT (1L)		Neutropenia (32.0%), anaemia (12.8%), thrombocytopenia/platelets decreased (10.2%)	$13,272

- The AE management cost ranged from $1,235 with durvalumab to $7,675 with tremelimumab + durvalumab + CT in patients with NSCLC, and from $503 with nivolumab to $13,272 with tremelimumab + durvalumab + CT in patients with SCLC
- The AE management cost ranged from $290 with nivolumab to $7,985 with pembrolizumab + CT in patients with squamous NSCLC, and from $463 with nivolumab to $15,197 with atezolizumab + CT in patients with non-squamous NSCLC
- Understandably, the combination of ICIs and chemotherapy was associated with substantially higher AE management costs compared with other treatments

Table 3. AE management costs (per patient, 2023 US$) associated with ICIs approved for RCC

Treatment (LOT)	Trial name/ID	Three most frequent grade 3-4 AEs (frequency, %)	AE cost
Nivolumab (1L+)	CHECKMATE 025 (38)	Fatigue/asthenia (2.5%), anaemia (1.7%), pneumonitis (1.5%)	$1,190
Avelumab + axitinib (1L)	JAVELIN Renal 101 (39)	Hypertension (25.6%), diarrhoea (6.7%), ALT increased (6.0%)	$8,609
Nivolumab + cabozantinib (1L)	CHECKMATE-9ER (40)	Hypertension (12.5%), hyponatraemia (9.4%), fatigue/asthenia (7.8%)	$9,720
Nivolumab + ipilimumab (1L)	CHECKMATE 214 (41)	ALT increased (5.1%), diarrhoea (3.8%), maculopapular rash/rash/pruritus (3.7%)	$2,717
Pembrolizumab + axitinib (1L)	KEYNOTE-426 (42)	Hypertension (22.1%), ALT increased (13.3%), diarrhoea (9.1%)	$8,493
Pembrolizumab + lenvatinib (1L)	KEYNOTE-581 (43)	Hypertension (27.6%), diarrhoea (9.7%), proteinuria (7.7%)	$8,548

- The AE management cost in patients with RCC ranged from $1,190 with nivolumab to $9720 with nivolumab + cabozantinib. The AE management cost associated with the combination of ICI and TKI was estimated to be more than $8,000 per patient with RCC

Table 4. AE management costs (per patient, 2023 US$) associated with ICIs approved for GI cancers

Population	Treatment (LOT)	Trial name/ID	Three most frequent grade 3-4 AEs (frequency, %)	AE cost
HCC	Pembrolizumab (2L)	KEYNOTE-240 (44)	AST increased (13.3%), blood bilirubin increased (7.5%), ALT increased (6.1%)	$4,825
	Atezolizumab + bevacizumab (1L)	IMbrave150 (45)	Hypertension (15.2%), AST increased (7%), ALT increased (3.6%)	$5,094
	Nivolumab + ipilimumab (1L+)	CHECKMATE 040 (46)	Hepatitis (20.4%), AST increased (16.3%), lipase increased (12.2%)	$9,932
	Durvalumab (1L)	HIMALAYA (47)	AST increased (6.7%), lipase increased (4.1%), ALT increased (3.1%)	$2,547
	Tremelimumab + durvalumab (1L)		Lipase increased (6.2%), AST increased (5.2%), diarrhoea (4.4%)	$3,794
Colorectal cancer	Pembrolizumab (1L)	KEYNOTE-177 (48)	Hypertension (7.2%), abdominal pain (6.5%), fatigue/asthenia (5.9%)	$4,888
Adv./met. oesophageal cancer or GEJC	Pembrolizumab + CT (1L)	KEYNOTE-590 (54)	Neutropenia (37%), anaemia (12.4%), leukopenia/lymphocytopenia/WBCs decreased (12.2%)	$15,036
	Pembrolizumab (2L)	KEYNOTE-181 (55)	Fatigue/asthenia (1.9%), anaemia (1.3%)	$596
HER2+ adv. GC or GEJC	Pembrolizumab + trastuzumab + CT (1L)	KEYNOTE-811 (56)	Thrombocytopenia/platelet count decreased (11.1%), anaemia (8.8%), diarrhoea (7.4%)	$9,752
Adv. GC/GEJC/EAC	Nivolumab + CT (1L)	CheckMate 649 (57)	Neutropenia (15.1%), neutrophil count decreased (10.6%), anaemia (6%)	$8,902
Adv. R/M ESCC	Nivolumab (1L+)	ATTRACTION-3 (58)	Anaemia (1.9%), diarrhoea (1%), decreased appetite/anorexia (1%)	$733
Adv. ESCC	Nivolumab + CT (1L)	CheckMate 648 (59)	Anaemia (9.7%); neutrophil count decreased (8.1%), stomatitis (6.5%)	$5,828
Adv. ESCC	Nivolumab + ipilimumab (1L)		Rash/pruritus (3.1%), decreased appetite (1.6%), fatigue (1.2%)	$973
Adv. biliary tract cancer	Durvalumab + CT (1L)	TOPAZ-1 (60)	Anaemia (23.7%), neutrophil count decreased (21%), neutropenia (20.1%)	$14,554

- In patients with GI cancer indications, the AE management cost ranged from $2,547 with durvalumab to $9,932 with nivolumab + ipilimumab (HCC), from $596 with pembrolizumab to $15,036 with pembrolizumab + CT (GI tract cancers), and from $733 with nivolumab to $5,828 with nivolumab + CT (ESCC)
- In patients with colorectal and biliary tract cancers (indications with only 1 approved ICI), the AE management cost was $4,888 with pembrolizumab and $14,554 with durvalumab + CT, respectively

Table 5. AE management costs (per patient, 2023 US$) associated with ICIs approved for other cancers

Population	Treatment (LOT)	Trial name/ID	Three most frequent grade 3-4 AEs (frequency, %)	AE cost
Urothelial cancer	Pembrolizumab (1L)	KEYNOTE-361 (49)	Anaemia (10.3%), urinary tract infection (9.3%), fatigue/asthenia (5%)	$4,767
	Pembrolizumab (2L)	KEYNOTE-045 (50)	Pneumonitis (2.3%), fatigue/asthenia (1.5%), diarrhoea (1.1%)	$1,101
	Avelumab + BSC (1L+)	JAVELIN Bladder100 (51)	Urinary tract infection (4.4%); anaemia (3.8%), fatigue/asthenia (1.7%)	$1,529
	Pembrolizumab + CT (1L)	KEYNOTE-361 (49)	Anaemia (34.7%), neutropenia (23.2%), thrombocytopenia/platelets decreased (14%)	$14,480
R/M HNSCC	Pembrolizumab (1L)	KEYNOTE-048 (61)	Anaemia (4.7%), fatigue/asthenia (4%), hypokalaemia (2%)	$1,935
	Nivolumab (1L+)	CHECKMATE 141 (62)	Fatigue/asthenia (2.5%), AST increased (1.3%), stomatitis (0.4%)	$591
	Pembrolizumab + cetuximab (1L)	KEYNOTE-048 (61)	Anaemia (25.4%), neutropenia (17.8%), thrombocytopenia/platelets decreased (14.5%)	$17,035
Loc. adv. cSCC	Cemiplimab (1L+)	NCT02760498 (63, 64)	Hypertension (7.7%), pneumonia (6.4%), pneumonitis (3.8%)	$5,040
Met. cSCC			Anaemia (6.1%), fatigue/asthenia (3.5%), pneumonitis (2.6%)	$2,068
R/M LR MCC	Pembrolizumab (1L)	KEYNOTE-017 (65)	AST increased (12%), ALT increased (7.7%), hyponatraemia (7.7%)	$2,947
R/R cHL	Nivolumab (2L+)	CHECKMATE 205 (66)	Lipase increased (4.5%), ALT increased (3.3%), neutropenia (3.3%)	$2,165
Adv./met. cHL	Nivolumab (1L)	CHECKMATE 205 (67)	Febrile neutropenia (9.8%), neutropenia (49%), anaemia (3.9%)	$9,990
	Pembrolizumab (1L+)	KEYNOTE-204 (68)	Pneumonitis (4.1%), pneumonia (2%), neutropenia (2%)	$1,866
R/R PMBCL	Pembrolizumab (2L+)	KEYNOTE-170 (69)	Neutropenia (13.2%), AST increased (1.9%), fatigue/asthenia (1.9%)	$2,214
R/M cervical cancer	Pembrolizumab (1L+)	KEYNOTE-826 (52)	Anaemia (30.3%), neutropenia (12.4%), hypertension (9.4%)	$11,225
Endometrial cancer	Pembrolizumab + lenvatinib (1L)	CHECKMATE-775 (53)	Hypertension (37.9%), decreased appetite (7.9%), diarrhoea (7.6%)	$10,505
Adv./met. TNBC	Pembrolizumab + CT (1L)	KEYNOTE-355 (70)	Neutropenia (29.7%), neutrophil count decreased (17.4%), anaemia (16.5%)	$9,641
Unresec. MPM	Nivolumab + ipilimumab (1L)	CHECKMATE-743 (71)	Lipase increased (3.7%), diarrhoea (3.3%), colitis (2.3%)	$1,587

- In patients with HNSCC, the AE management cost was substantially lower with monotherapy regimens, like nivolumab and pembrolizumab, compared with combination therapies
- In patients with cHL, the AE management cost was found to be substantially higher with nivolumab compared with pembrolizumab ($9,990 vs $1,886)
- In patients with MCC, PMBCL, cervical cancer, endometrial cancer, TNBC, and MPM—indications with only 1 approved ICI-based treatment—the AE management cost ranged from $1,587 with nivolumab + ipilimumab (unresectable MPM) to $10,505 with pembrolizumab + lenvatinib (endometrial cancer)

Conclusions

- AE management costs associated with ICI treatments varied according to the specific ICI regimen and type of cancer
- Monotherapy regimens were generally associated with lower AE management costs. However, there were differences in costs between specific ICIs—at the lower end of the AE burden scale were nivolumab and pembrolizumab, and at the higher end were atezolizumab and ipilimumab
- Combination treatments—especially those with TKIs or CTs or those including ICIs that were at the higher end of the AE burden scale—were found to be associated with significant AE management costs compared with ICI monotherapies
- These results underscore the pertinence of AE management costs when choosing between various ICI regimens for treating patients with cancer in the United States

Abbreviations: 1L, first line; 2L, second line; adv., advanced; AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; BSC, best supportive care; cHL, classic Hodgkin lymphoma; cSCC, cutaneous squamous cell carcinoma; CPI, consumer price index; CT, chemotherapy; EAC: oesophageal adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; FDA, Food and Drug Administration; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; GI, gastrointestinal; GP, glycoprotein; HER2, human epidermal growth factor receptor 2; HCC, hepatocellular carcinoma; HCUP, Healthcare Cost and Utilization Project; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; loc., locally; LOT, line of therapy; LR, locoregional; met., metastatic; MCC, Merkel cell carcinoma; MPM, malignant pleural mesothelioma; NIS, national (nationwide) inpatient sample; NSCLC, non-small cell lung cancer; PMBCL, primary mediastinal large B-cell lymphoma; Q2W, twice a week; Q3W, 3 times a week; recur., recurrent; RCC, renal cell carcinoma; R/M, recurrent or metastatic; R/R, relapsed or refractory; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; TNBC, triple negative breast cancer; unresec., unresectable; US, United States; WBC, white blood cell

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