CO26

Impact in health outcomes of anti-PD-(L)1 inhibitors to treat early-stage cancers in Belgium

Raquel Aguiar-Ibáñez[1]; Catarina Neves[2]; Tyler Mantaian[3]; André Bento Abreu[4]; Demet Sönmez[5]; Arthur Sillah[6]; Gursel Aktan[6]

[1]Merck Canada, Inc., Kirkland, QC, Canada; [2]Lumanity, Utrecht, Netherlands; [3]Lumanity, Bethesda, MD, USA; [4]MSD Belgium, Brussels, Belgium; [5]MSD Sweden, Stockholm, Sweden; [6]Merck & Co., Inc., Rahway, NJ, USA

Background

- In 2020, there were approximately 19.3 million new cancer cases worldwide, projected to rise to 28.4 million by 2040.[1] In Belgium, between 2004 and 2018, the number of annual cancer diagnoses increased by 21%.[2] Early detection and appropriate treatment can reduce the cancer burden, given the higher chance of cure if diagnosed early and treated appropriately[3]
- Anti-programmed cell death 1/anti-programmed death-ligand 1 (anti-PD-(L)1) inhibitors are mainstay treatments for several advanced/metastatic cancers, and their expansion into the early-stage settings is further changing the treatment paradigm
- Treatment of early-stage tumors with anti-PD-(L)1 inhibitors is linked to significantly better outcomes (eg, improved recurrence-free survival after surgery[4,5]) and has expanded rapidly
- As part of informing the sustainability of cancer treatment in general, it is crucial to recognize the value of anti-PD-(L)1 inhibitors and to integrate them into health planning as adjuvant/neoadjuvant treatment options

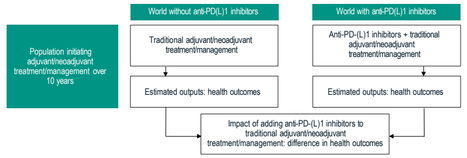
Objectives

- We developed a health outcomes projection tool to assess the health benefits of adopting anti-PD- (L)1 inhibitors in multiple early-stage cancers in Belgium across 5- and 10-year time horizons. More specifically, the tool compares the health outcomes between two scenarios: one where anti-PD-(L)1 inhibitors can be used for patients with early-stage disease (world with anti-PD-(L)1 inhibitors) vs a second scenario where anti-PD(L)1 inhibitors are reserved for patients who develop advanced/ metastatic disease (world without anti-PD-(L)1 inhibitors)

Methods

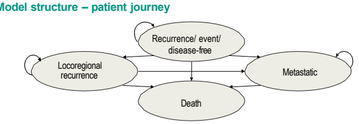
- The health outcomes projection tool focuses on 3 high-incidence cancers: melanoma, renal cell carcinoma (RCC), and triple-negative breast cancer (TNBC)
- The tool tracks clinical outcomes throughout the average patient journey in weekly cycles from when they initiate adjuvant/neoadjuvant treatment. The model structure and input data are primarily based on the cost-effectiveness and budget impact models used for health technology assessments[6-9]
- Clinical outcomes estimated include life-years (LY) without event or recurrence and in total, quality-adjusted life-years (QALY), events or recurrences, active treatments for metastatic disease, adverse events (AE), and deaths (total and after first event or recurrence)

Figure 1. Model structure – calculations



Key: PD-(L)1, programmed cell death 1/programmed death-ligand 1.

Figure 2. Model structure – patient journey



Note: The direction of the arrows indicates how patients transition between health states after entering the model.

Table 1. General base-case settings and input assumptions

Input	Value
Perspective	Belgian healthcare system
Time horizon	5 and 10 years
Discounting for clinical outcomes	1.50%
Tumor sites	• Stage III melanoma • RCC at increased risk of recurrence following nephrectomy +/- resection of metastatic lesions • Locally advanced or early-stage TNBC at high risk of recurrence
Population	• The annual target population is distributed evenly throughout the year (assuming new cohorts of patients initiate adjuvant/neoadjuvant treatment each week) • 2022 population: 11,584,008[10] • Growth rate of 0.54% applied to Year 2023 and onwards[10] • Females: 50.72%[10]
Health state transitions	Transitions from recurrence-/event-/disease-free state and from locoregional disease are specific to the treatments received in the adjuvant/neoadjuvant setting. Transitions from the metastatic disease state are specific to the metastatic treatment received
Treatment duration	Treatment duration is specific to the treatment options received either in the adjuvant/neoadjuvant setting or in 1L and 2L metastatic disease setting
Market shares	Market shares for all treatment options in the adjuvant/neoadjuvant setting and 1L and 2L metastatic treatments (conditional on adjuvant/neoadjuvant treatment received) are based on expert opinion
Retreatment with anti-PD-(L)1 agents	• Retreatment with any or the same anti-PD-(L)1 inhibitor is possible immediately after adjuvant treatment completion for melanoma and RCC • Retreatment with the same anti-PD-(L)1 inhibitor is possible 1 year after neoadjuvant/adjuvant treatment completion for TNBC
AEs	• Mostly, AEs included are drug-related, Grade 3+ with ≥5% incidence in any treatment arm for multiple treatment settings/lines of therapy • AEs and corresponding disutilities are accounted for as one-off events at treatment initiation
Health state utilities	Health state utilities from relevant clinical trials[11-13] are mapped to local values using Belgian and European algorithms. Age- and sex-related disutilities[14] are also considered

Key: 1L, first-line; 2L, second-line; AE, adverse event; PD-(L)1, programmed cell death 1/programmed death-ligand 1; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Results

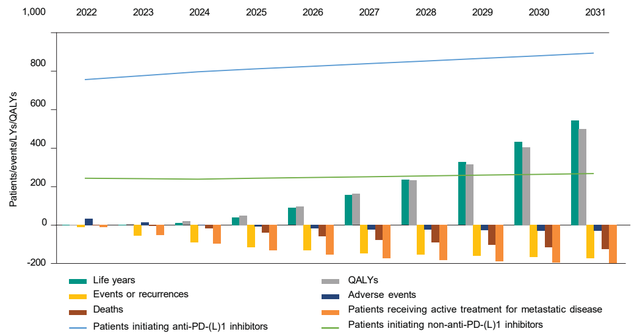
- Of the 10,798 eligible patients over 10 years (2022-2031), 8,295 are estimated to initiate adjuvant/neoadjuvant treatment with anti-PD-(L)1 inhibitors for melanoma, RCC, and TNBC
  - Of the 5,174 patients eligible over 5 years (2022-2026), 3,965 are estimated to initiate adjuvant/neoadjuvant treatment with anti-PD-(L)1 inhibitors
- Introducing anti-PD-(L)1 inhibitors in the adjuvant/neoadjuvant setting for melanoma, RCC, and TNBC is anticipated to:
  - Increase by 645 (7%) and 4,154 (13%) the LYs without recurrence over 5 and 10 years, respectively
  - Avoid 404 (25%) and 1,199 recurrences (25%) over 5 and 10 years, respectively
  - Prevent 448 (29%) and 1,384 (29%) active treatments in the metastatic setting over 5 and 10 years, respectively
  - Avoid 126 (26%) and 663 (29%) post-recurrence deaths over 5 and 10 years, respectively

Table 2. Patients eligible for adjuvant/neoadjuvant treatment with anti-PD-(L)1 inhibitors in Belgium, as estimated by the health outcomes projection tool

Treatment received	2022	2023	2024	2025	2026	2027–2031	Cumulative
Anti-PD-(L)1 inhibitors*	756	776	796	812	825	4,330	8,295
Non-anti-PD-(L)1 inhibitors*	243	240	238	242	246	1,294	2,503
Total	**999**	**1,016**	**1,034**	**1,054**	**1,071**	**5,624**	**10,798**

Key: PD-(L)1, programmed cell death 1/programmed death-ligand 1.
Note: *, in world with anti-PD-(L)1 inhibitors

Figure 3. Patients eligible for adjuvant/neoadjuvant treatment with anti-PD-(L)1 inhibitors and Δ clinical outcomes



Key: LY, life-year; PD-(L)1, programmed cell death 1/programmed death-ligand 1; QALY, quality-adjusted life-year.

Table 3. Clinical outcomes by year

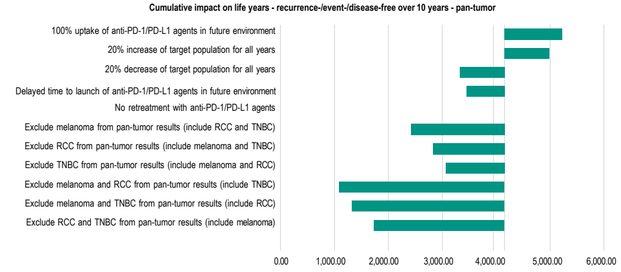
Outcome	2022	2023	2024	2025	2026	2027–2031	Cumulative	Difference (cumulative)
Impact –world with anti-PD-(L)1 inhibitors world vs without anti-PD-(L)1 inhibitors								
LYs – recurrence-/ event-/disease-free	2.89	33.08	102.79	197.89	308.83	3,508.51	4,153.99	13%
LYs – total	-0.20	0.34	11.14	39.52	86.96	1,691.18	1,828.95	4%
QALYs	-0.39	2.92	18.03	49.39	96.75	1,611.91	1,778.62	5%
Events or recurrences	-11.08	-54.89	-91.48	-114.95	-131.27	-795.61	-1,199.27	-25%
Active treatments for metastatic disease	-10.59	-53.63	-98.18	-131.24	-154.48	-935.88	-1,384.00	-29%
Adverse events	32.40	14.46	-0.13	-9.79	-16.81	-138.57	-118.44	-2%
Deaths – total	0.62	-3.73	-18.99	-38.54	-57.88	-511.69	-630.19	-25%
Deaths after first event or recurrence	-0.12	-5.52	-20.58	-40.26	-60.01	-536.45	-662.94	-29%

Key: LY, life-year; PD-(L)1, programmed cell death 1/programmed death-ligand 1; QALY, quality-adjusted life-year.

Sensitivity analyses

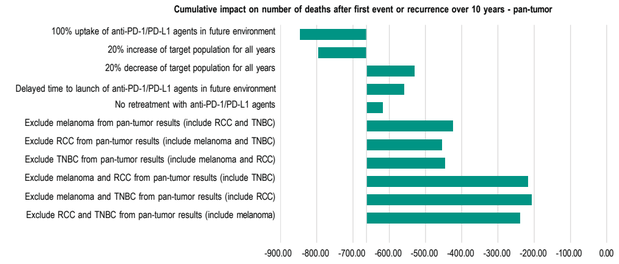
- We conducted sensitivity and scenario analyses to test uncertainty around key inputs in the model. A benefit in terms of LYs free of recurrences/events/disease, recurrences or events, and deaths after recurrence continued to be observed across the tested scenarios and input variations

Figure 4. Scenario analysis – impact on LYs in recurrence-/event-/disease-free health state



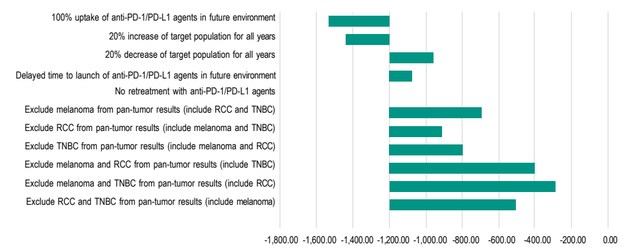
Key: LY, life-years; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Figure 5. Scenario analysis – impact on deaths after first event or recurrence



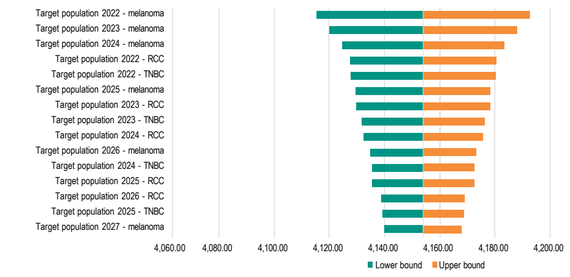
Key: PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Figure 6. Scenario analysis – impact on number of events/recurrences



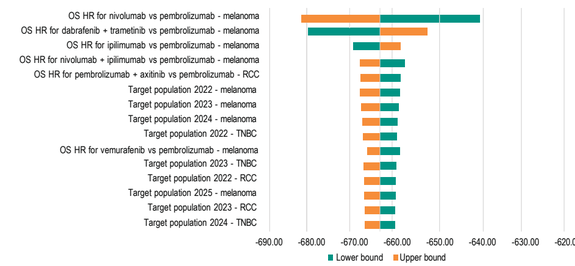
Key: PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Figure 7. OWSA – impact on LYs in recurrence-/event-/disease-free health state



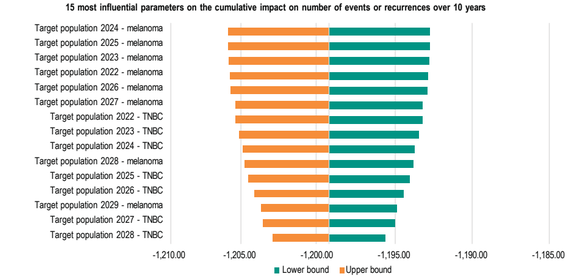
Key: LY, life-year; OWSA, one-way sensitivity analysis; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Figure 8. OWSA – impact on deaths after first event or recurrence



Key: HR, hazard ratio; OS, overall survival; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Figure 9. OWSA – impact on number of events/recurrences



Key: RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

Conclusions

- Early-stage treatment with anti-PD-(L)1inhibitors is linked with better outcomes by reducing the number of recurrences and deaths (in total and post-recurrence/event/disease), extending the time patients spend free of recurrences/events/disease, and reducing the number of treatments for metastatic disease
  - Continued reimbursement for anti-PD-(L)1 inhibitors for early-stage melanoma, RCC, and TNBC is crucial to ensure patients and society realize these benefits
- This health outcomes projection tool can support discussions around investment in anti-PD-(L)1 inhibitors in the adjuvant/ neoadjuvant settings (in both upcoming and already approved uses) and generally inform planning around investment in innovative treatments for early-stage cancers
  - Importantly, a long time horizon is needed to fully capture the range of health benefits experienced by patients using anti-PD-(L)1 inhibitors. The results generated by the tool considering 5- and 10-year time horizons are anticipated to be an underestimate of these health benefits

References

1. Sung H, et al. CA *Cancer J Clin*. 2021;71(3):209-249.
2. Belgian Cancer Registry. Cancer figures. Available at: https://kankerregister.org/Cancer%20Figures. Accessed April 7, 2023.
3. World Health Organization. Cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed May 17, 2022.
4. European Medicines Agency. OPDIVO: Procedural steps taken and scientific information after the authorisation. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/opdivo-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed May 24, 2022.
5. European Medicines Agency. KEYTRUDA: Procedural steps taken and scientific information after the authorisation. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/keytruda-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed May 24, 2022.
6. National Institute for Health and Care Excellence (NICE). Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma [TA766]. Available at: https://www.nice.org.uk/guidance/ta766. Accessed February 9, 2023.
7. National Institute for Health and Care Excellence (NICE). Pembrolizumab for adjuvant treatment of renal cell carcinoma [TA830]. Available at: https://www.nice.org.uk/guidance/ta830. Accessed February 9, 2023.
8. National Institute for Health and Care Excellence (NICE). Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer [TA851]. Available at: https://www.nice.org.uk/guidance/ta851. Accessed February 9, 2023.
9. Institut national d'assurance maladie-invalidité. Pembrolizumab, Arret Royal 01.02.2018 – IV 8090000. Available at: https://webappsa.riziv-inami.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch. Accessed March 21, 2023.
10. Statbel. Structure de la population. Available at: https://statbel.fgov.be/fr/themes/population/structure-de-la-population#news. Accessed November 23, 2022.
11. Merck & Co., Inc., Rahway, NJ, USA. Adjuvant immunotherapy with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC melanoma group (KEYNOTE-054). Data on file.
12. Merck & Co., Inc., Rahway, NJ, USA. A Phase 3, randomized, double-blind, placebo-controlled clinical trial of pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post nephrectomy (KEYNOTE-564). Data on file.
13. Merck & Co., Inc., Rahway, NJ, USA. A Phase III, randomized, double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for triple negative breast cancer (TNBC) (KEYNOTE-522). Data on file.
14. Ara R, et al. *Value Health*. 2010;13(5):509-518.

Presented at ISPOR 2023; Boston, MA, USA; May 7-10, 2023.