Clinical Drug Investigation
https://doi.org/10.1007/s40261-026-01567-7

ORIGINAL RESEARCH ARTICLE

Assessing the Impact on Health and Productivity Outcomes of Anti-PD-(L)1 Agents to Treat Early-Stage Cancers in Italy

Andrea Marcellusi[1] · Fabio Calabrò[2] · Anna Maria Di Giacomo[3] · Fabio Puglisi[4,5] · Alessio Cortellini[6,7,8] · Isobel Thornton[9] · Yan Zhi Tan[10] · Alessandro Catanzaro[10] · Catarina Neves[10] · Fabrizio Ascone[11] · Matilde Franceschini[11] · Mario Calandriello[11] · Raquel Aguiar-Ibáñez[12] · Yizhen Lai[13]

Received: 9 December 2025 / Accepted: 14 May 2026

Abstract

Background Anti-programmed cell death-(ligand) 1 (anti-PD-[L]1) agents are approved for advanced and early-stage cancers. While they may offer clinical and economic benefits in the neoadjuvant and/or adjuvant setting, their population-level impact in Italy has not been thoroughly evaluated.

Objective This study aims to estimate health and productivity outcomes of introducing anti-PD-(L)1 agents for neoadjuvant and/or adjuvant therapy in early-stage cancers in Italy (melanoma Stage IIB/C, melanoma Stage III, renal cell carcinoma, triple-negative breast cancer and resectable non-small-cell lung cancer) over a 10-year horizon.

Methods We developed a model synthesising outputs from five indication-specific Markov models comparing two worlds: one without anti-PD-(L)1 agents use in the neoadjuvant and/or adjuvant settings versus one with their use. Italian-specific population and incidence inputs were used, with clinical and quality-of-life data from individual trials, from a societal perspective with 3% annual discount. Outcomes included total life years (LYs), recurrence- free (RF)/event-free (EF)/disease-free (DF) LYs, quality-adjusted LYs (QALYs), number of recurrences/events, metastatic treatments, total deaths and deaths after first event/recurrence. Productivity gains were estimated using a human capital approach.

Results Between 2025 and 2034, 118,329 patients with early-stage cancer were estimated to be eligible for anti-PD-(L)1 agents in Italy. Compared with no early-stage use, neoadjuvant/adjuvant use was associated with increased total LYs (+20,458, +5%), RF/EF/DF LYs (+60,631, +19%), QALYs (+21,093, +6%) and fewer recurrences/events (−20,209, −33%), metastatic treatments (−25,220, −38%), total deaths (−7137, −24%) and deaths after first event/recurrence (−8021, −32%). Productive years gained were 35,897 (+30%).

Conclusions Our study suggests that the use of anti-PD-(L)1 agents in early-stage cancers is associated with substantial health and societal gains in Italy. Expanding their use across approved indications translates trial benefits into fewer recurrences, deaths and productivity losses, informing national planning and access decision.

1 Introduction

There has been a notable increase in the incidence and prevalence of cancer across the EU over the past three decades. In Italy, the annual number of newly diagnosed cancers has risen by approximately 60% since 1995 [1], with at least 400,000 cases diagnosed each year [2]. In 2022 alone, an estimated 407,240 new cancer cases were recorded, with breast, colorectal, lung and prostate cancers accounting for almost half of these [3]. Between 2010 and 2020, cancer prevalence in Italy increased by 27%, likely reflecting both rising incidence and longer life expectancy [1]. Despite this,

Key Points

Anti-programmed cell death-(ligand) 1 (anti-PD-[L]1) agents are used increasingly for advanced cancers, but its use in early-stage cancers is relatively understudied, despite demonstrating survival benefits.

In this analysis, introducing anti-PD(L)1 agents in the early-stage settings is associated with substantial health gains.

Additionally, the use of anti-PD(L)1 agents may lead to increased productivity for both patients and caregivers.

Extended author information available on the last page of the article

Published online: 06 June 2026

Italy's age-standardised cancer mortality was 6% lower than the EU average, largely due to medical advances [1]. With mortality falling but incidence and prevalence rising, the survivorship burden continues to grow in Italy, consistent with patterns reported across high-income nations [4]. Similar to other EU countries, cancer expenditure in Italy has steadily increased over the past decade, reaching an estimated €20 billion in 2022 with indirect costs included [5]. In January 2023, the National Oncology Plan 2023–2027 was adopted with a mission to identify and reduce known inequalities in cancer detection and care, and to improve patient outcomes and strengthen cancer prevention [6]. Among its objectives, the plan places an emphasis on the early detection of cancers.

Early detection enables treatment at earlier stages of disease, improving patient outcomes and reducing the overall cancer burden [7]. Anti-programmed cell death-(ligand) 1 (anti-PD-[L]1) agents are already established as the standard of care in advanced and metastatic settings in Europe [8–11]. More recently, substantial benefits have also been observed in earlier-stage settings across multiple tumour types. Clinical trials have shown improved overall survival (OS), progression-free survival (PFS) and recurrence-free survival (RFS) with the use of anti-PD-(L)1 agents versus standard of care in melanoma Stage IIB/C [12, 13], melanoma Stage III [14, 15], renal cell carcinoma (RCC) [16], triple-negative breast cancer (TNBC) [17, 18] and non-small-cell lung cancer (NSCLC) [19–22]. These findings highlight the potential of anti-PD-(L)1 agents to alter disease trajectories when used in earlier-stage settings, for which they have also received reimbursement approval by the Agenzia Italiana del Farmaco (AIFA) [23–26].

While better outcomes have been reported for individual indications, the potential health and productivity benefits from the use of anti-PD-(L)1 agents across multiple early-stage cancer indications on a population-level in Italy remain unknown. Understanding the broader implications of extensive uptake of anti-PD-(L)1 therapies in clinical practice is essential, as their use expands beyond metastatic disease into early-stage settings. To explore these implications, a model was developed to assess the impact of the wide-scale adoption of anti-PD-(L)1 agents for neoadjuvant and/or adjuvant treatment in five different early-stage cancer indications (melanoma Stage IIB/C, melanoma Stage III, RCC, TNBC and resectable NSCLC) over a 10-year period.

2 Methods

2.1 Model Overview

A model was developed to estimate the health and productivity outcomes of introducing anti-PD-(L)1 agents for neoadjuvant and/or adjuvant treatment settings for early-stage cancers in Italy over a 10-year period, from 2025 to 2034. The model examined and compared the outcomes in two worlds: World without anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings versus world with anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings (Fig. 1). A 10-year horizon was chosen to capture long-term clinical and societal benefits that require time to fully accrue in early-stage treatment settings [27].

All outcomes were discounted at 3.0%, in accordance with AIFA guidelines [28]. The difference in outcomes between the two worlds represent the impact of introducing anti-PD-(L)1 agents to neoadjuvant and/or adjuvant settings (Fig. 1). Results for individual indications were then aggregated to derive the total impact at a multi-indication level.

Five licensed indications—melanoma Stage IIB/C, melanoma Stage III, TNBC, RCC and resectable NSCLC—were selected and examined in this analysis. The model was informed by five indication-specific Markov models [29–40]. The models had the same structure with four mutually exclusive health states (Fig. 2) and weekly cycles. The model was harmonised with the same model time horizon, weekly cycle length and discounting rates across indications. New incident cohorts were assumed to enter the model in the recurrence-free (RF), event-free (EF) or disease-free (DF) state on a weekly basis, and were subjected to risk of three competing events: locoregional recurrence (LR), distant metastases (DM) or death, which comprises of all-cause mortality.

A targeted validation exercise was conducted to test key model assumptions and inputs. Clinical validation comprised of 1:1 discussions with Italian domain experts for each cancer site, and included inputs on patient funnel and epidemiology, treatment mix, plausibility of survival extrapolations, utilities and productivity inputs. Validation with an Italian health economist was also conducted to assess overall model structure, analysis schema, utility estimation and approach to productivity loss. Outcomes from the exercise informed refinements to selected inputs and documentation.

2.2 Model Inputs

2.2.1 Population

The analysis was conducted from an anti-PD-(L)1 agent class perspective; accordingly, the target population comprised of patients eligible to receive anti-PD-(L)1 therapy in the perioperative/adjuvant setting. Baseline patient characteristics in the model were informed by the inclusion criteria and baseline profiles from pivotal pembrolizumab trials in early stage-cancers (Table 1). These trials were used because patient-level data were available to parameterise the model,

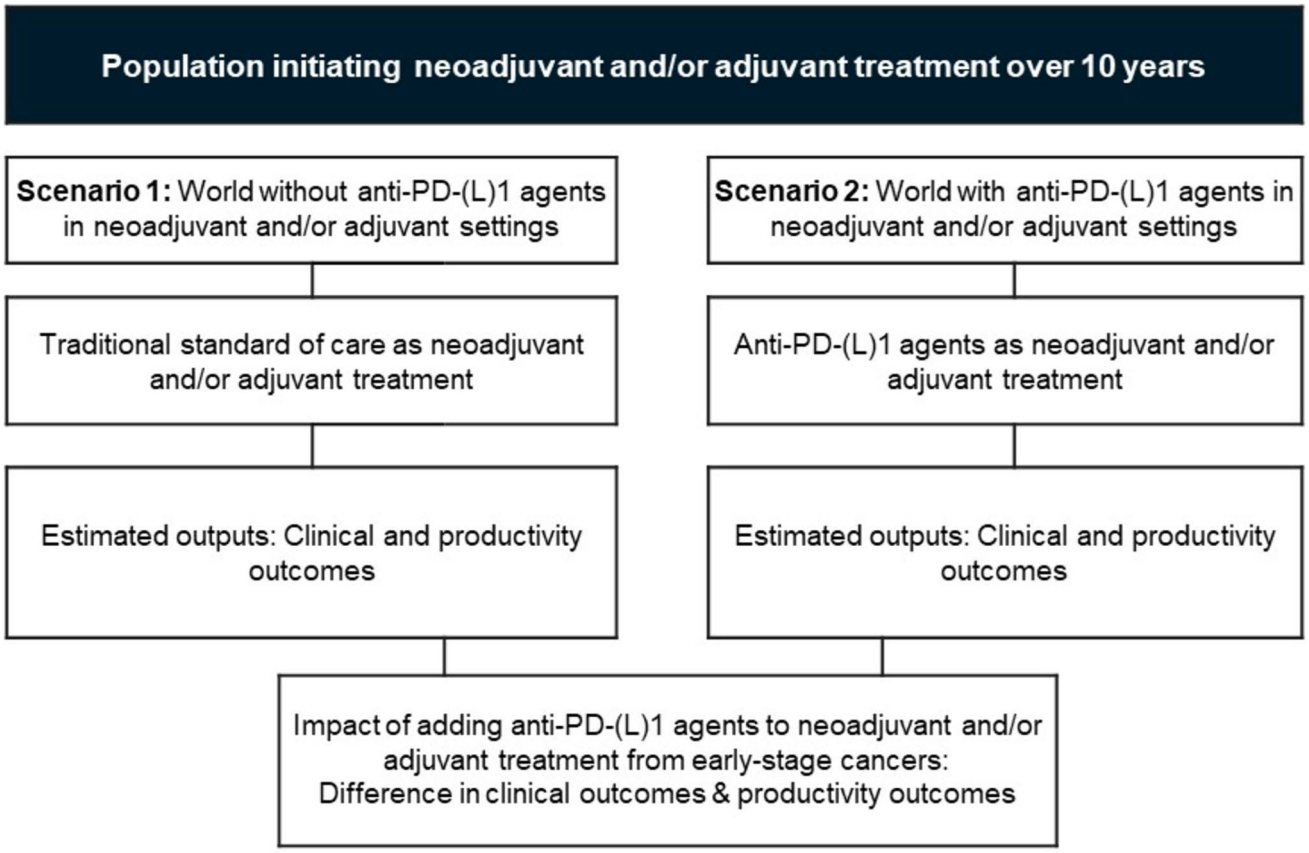

Fig. 1 Analysis overview. The analysis examines the differences in outcomes in a world without anti-PD-(L)1 agents used in neoadjuvant and/or adjuvant settings versus a world with anti-PD-(L)1 agents available. Each world is modelled separately, based on a population that is anticipated to be eligible for neoadjuvant and/or adjuvant treatment over a 10-year period. Anti-PD-(L)1, anti-programmed cell death-(ligand) 1

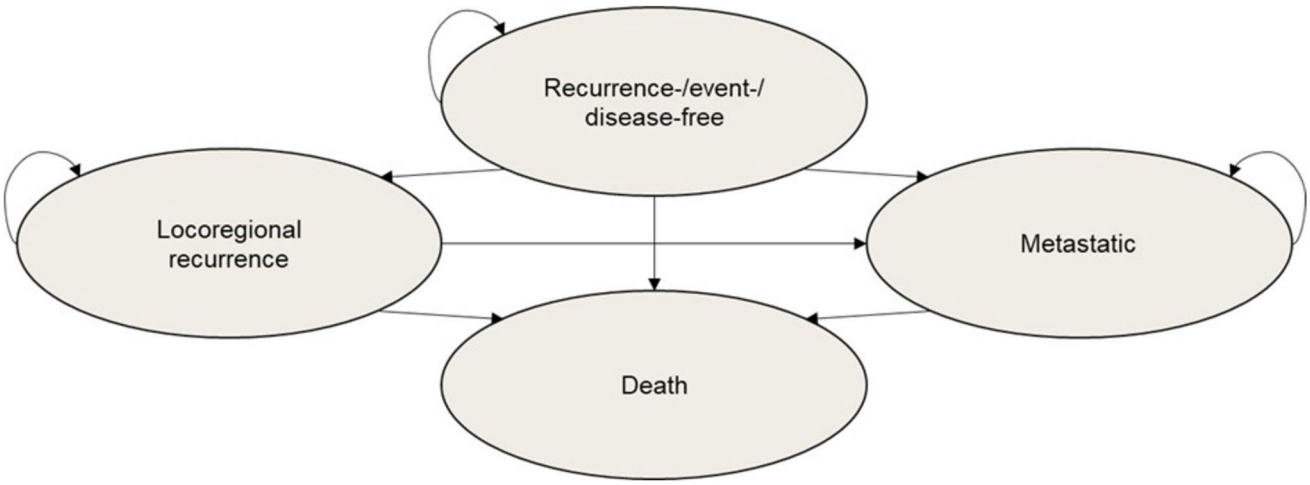

Fig. 2 Model structure. All indications were modelled separately, following the same four-state Markov model. All patients enter the model in the recurrence-/event-/disease-free state and can move to locoregional recurrence or metastatic states. Death is the absorbing state

whereas comparable data from other early-stage anti-PD-(L)1 trials were not available.

The population size for each cancer was derived from Italian sources and the proportion of patients who are eligible for treatment with anti-PD(L)1 agents in each indication was subsequently estimated using a combination of epidemiology data and clinical expert consultations (Supplementary Fig. S1, in Supplementary Materials) [2, 41].

2.2.2 Treatment Patterns

The treatment mix, defined as the distribution of patients across different neoadjuvant and/or adjuvant treatments, was informed by market research and expert opinion (Table 2). In the world without anti-PD-(L)1 agents, all individuals with melanoma Stage IIB/C or RCC were managed through watchful waiting, while all patients with TNBC and resectable NSCLC Stage II–IIIB were assumed to receive neoadjuvant chemotherapy. Individuals with melanoma Stage III were managed through watchful waiting (56%) or adjuvant dabrafenib and trametinib (44%).

In the world with anti-PD-(L)1 use in the neoadjuvant and/or adjuvant settings, we assumed 100% uptake among eligible patients to estimate the potential impact of full access to this therapeutic class. The specific anti-PD-(L)1 agent represented in each indication was determined by evidence availability; pembrolizumab was used as the proxy where robust comparative evidence across agents was not available. For resectable NSCLC Stage I–IIIB, where evidence was available to parameterise more than one agent, uptake was split 50/50 between pembrolizumab and nivolumab. For melanoma Stage IIB–C and Stage III, nivolumab was not explicitly modelled because its relative efficacy versus other treatments could not be robustly estimated in the absence of a network meta-analysis (NMA) at the time of analysis. Therefore, pembrolizumab was used to represent the overall impact of perioperative/adjuvant anti-PD-(L)1 therapy. The treatment mix was held constant over the model time horizon for all indications.

Patients who transitioned to the DM state were assumed to initiate first-line (1L) metastatic treatment. Treatment at this stage was contingent on two factors: (a) which

Table 1 Pivotal trials informing baseline patient characteristics in the model

Indication	Melanoma, Stage IIB/C	Melanoma, Stage III	RCC, postnephrectomy	TNBC, high-risk early-stage	NSCLC resectable Stage II–IIIB
Key phase III trial	KEYNOTE-716 [12]	KEYNOTE-054 [14]	KEYNOTE-564 [16]	KEYNOTE-522 [17]	KEYNOTE-671 [19]
Age (years)	59.3	54.0	58.9	49.0	63.1
Male (%)	60.4%	61.6%	73.3%	N/A	70.6%
Trial intervention	Pembrolizumab	Pembrolizumab	Pembrolizumab	Pembrolizumab + chemotherapy	Pembrolizumab + chemotherapy
Trial comparator	Watchful waiting	Watchful waiting	Watchful waiting	Chemotherapy	Chemotherapy

N/A not available, *NSCLC* non-small-cell lung cancer, *RCC* renal cell carcinoma, *TNBC* triple-negative breast cancer

Table 2 Treatments used in neoadjuvant and/or adjuvant treatment settings for each indication

	Melanoma, Stage IIB/C	Melanoma, Stage III	RCC	TNBC	NSCLC resectable Stage II–IIIB
World without anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings					
Anti-PD-(L)1 agents	0%	0%	0%	0%	0%
Watchful waiting	100%	56%	100%	N/A	N/A
Chemotherapy	N/A	N/A	N/A	100%	100%
Dabrafenib + trametinib	N/A	44%	N/A	N/A	N/A
World with anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings					
Anti-PD-(L)1 agents	100%	100%	100%	100%	100%
Watchful waiting	0%	0%	0%	N/A	N/A
Chemotherapy	N/A	N/A	N/A	0%	0%
Dabrafenib + trametinib	N/A	0%	N/A	N/A	N/A

N/A not applicable, *NSCLC* non-small-cell lung cancer, *PD-(L)1* programmed cell death-(ligand) 1, *RCC* renal cell carcinoma, *TNBC* triple-negative breast cancer

treatment had been previously received in the neoadjuvant and/or adjuvant setting and (b) whether re-treatment with anti-PD-(L)1 agents in the advanced or metastatic setting was permitted. The allowance and timing of re-treatment were based on clinical expert input and varied by indication. In the advanced or metastatic setting, the treatment mix was informed by market research and expert opinion and assumed to remain constant over the model time horizon.

2.2.3 Efficacy

To model disease progression, patient movement across the four health states (Fig. 2) was informed by weekly transition probabilities derived from the cost-effectiveness models developed in line with published AIFA guidance [28–40]. Parametric survival curves were fitted to patient-level data (PLD) for the interventions (i.e. pembrolizumab-containing therapies) and comparators (i.e. watchful waiting or chemotherapy) included in the KEYNOTE trials across the five indications; these curves were used to estimate the probability of transitioning from the RF/EF/DF states to LR, DM, or death [12, 14, 16, 17, 19]. All survival extrapolations followed standard modelling practices [42], with transitions to death adjusted for background mortality [43]. The best fits were selected on the basis of visual fit to observed Kaplan–Meier curves during the trial observation period, statistical fit using Akaike information criteria, Bayesian information criteria and mean squared error, as well as validation with Italian clinicians to assess clinical plausibility (Supplementary Table S1). For the comparator not included in the KEYNOTE trials (dabrafenib + trametinib in melanoma Stage III), hazard ratios (HRs) from a published NMA study of the adjuvant treatment of Stage III melanoma were used to estimate transitions from the RF state to other states [44]. NMA-based HRs were also used to estimate EF transitions for nivolumab in resectable NSCLC, based on an NMA conducted on the basis of trials in perioperative, resectable NSCLC [45].

From the DM state to death, several methods were used to estimate transitions for the different 1L treatments, including parametric models based on PLD or the observed median survival, and HRs derived from NMAs when available. Transitions for each 1L metastatic treatment were then weighted on the basis of the treatment mix and subsequently aggregated to derive overall transitions.

2.2.4 Utilities

Health-related quality of life (HRQoL) was incorporated into the model by assigning distinct utility values to each health state, reflecting differences based on cancer progression and recurrence status. Utility values were derived from the respective pivotal clinical trials using the European Quality of Life Five-Dimension, Five-Level Version (EQ-5D) questionnaire and, when available, mapped to country-specific value sets using either EU or Italian algorithms, with adjustments for age and sex [46]. The impact of treatment-related adverse events (AEs) on HRQoL was accounted for by applying a one-time reduction in utility (i.e. a disutility) at treatment initiation. These disutilities were based on data for Grade 3+ AEs with an incidence of 5% or more in the respective clinical trials.

2.2.5 Productivity Losses

To assess the broader societal impact of adopting anti-PD-(L)1 agents, the model accounted for productivity losses of both patients and caregivers using a human capital approach. The human-capital approach was used, as it was judged to be the most relevant and interpretable approach within the Italian context based on expert validation. In contrast, friction-cost approach, while considered, could not be implemented due to a lack of detailed labour-market parameters (e.g. friction period) for Italy. Productivity was measured in terms of productive years lost due to illness or caregiving responsibilities, including both absenteeism (time off work) and presenteeism (reduced productivity while at work). Both patients and caregivers could experience either absenteeism or presenteeism across states. Model inputs for absenteeism and presenteeism were first informed by a US published survey on the human and economic burden of recurrences among patients diagnosed with early-stage cancers and thereafter confirmed with Italian clinical experts through 1:1 interviews. Productivity losses were greater for recurrences or events corresponding to metastatic disease rather than event-free or locoregional disease, reflecting the severity of late-stage disease [47]. Labour market parameters were based on Italian data, with average weekly working hours set to 36.2 [48], a retirement age of 67 years [49] and an employment rate of 62.4% [50].

2.2.6 Outcomes

The modelled outcomes included total life years (LYs), RF/EF/DF LYs, quality-adjusted LYs (QALYs), number of recurrences, active metastatic treatments, total deaths, deaths after first event/recurrence and productivity losses for each world. The impact of introducing anti-PD-(L)1 agents in the early-stage setting was estimated by comparing outcomes between the two worlds. Results were first generated for each individual indication and then aggregated to estimate the overall clinical, humanistic and societal impact of adopting anti-PD-(L)1 agents in early-stage treatment pathways.

We conducted sensitivity and scenario analyses to test uncertainty around key inputs and assumptions, respectively. One-way sensitivity analyses (OWSA) were conducted to

examine likely influence of parameters pertaining to epidemiology, baseline characteristics, utility decrements and measures of relative effectiveness on outcomes. For scenario analysis, alternative assumptions were explored. The first scenario considered a 6-month delay in access to anti-PD-(L)1 agents in the early-stage setting, reflecting potential delays in patient access despite regulatory approval. The second scenario applied increasing annual incidence, recognising that real-world incidence may rise over time, in contrast to the static incident cases assumed in the base case. Annual growth was derived from the Global Burden of Disease Study 2021 [51], with increases of approximately 0.71% for melanoma, 2.25% for RCC, 2.95% for TNBC and 2.36% for NSCLC. We also investigated the likely effect of a 20% lower anti-PD-(L) 1 uptake (i.e. 80% anti-PD-(L) 1 uptake).

3 Results

From 2025 to 2034, 118,329 eligible patients are estimated to initiate neoadjuvant and/or adjuvant therapy with anti-PD-(L)1 agents across five indications in the world where anti-PD(L)1 agents are used (Table 3).

The 10-year cumulative impact of early treatment with anti-PD-(L)1 agents was calculated for each health outcome, with results presented for both worlds alongside the directional difference and percentage change (Table 4). Across the time horizon, the use of anti-PD-(L)1 agents is associated with overall health gains across all five indications in the analysis, including increases in total LYs (+20,458, +5%), RF/EF/DF LYs (+60,631, +19%) and QALYs (+21,093, +6%). The use of anti-PD-(L)1 agents was also projected to reduce the number of recurrences or disease progression events (−20,209, −33%) and to lower the number of active treatments required for metastatic disease (−25,220, −38%). Fewer total deaths (−7137, −24%) and fewer deaths following first recurrence or disease progression event (−8021, −32%) were also observed over the modelled period. As a result of increased survival and time spent in the RF/EF/DF health states, anti-PD-(L)1 use was associated with reduced absenteeism and presenteeism among both patients and caregivers, leading to a reduction in productive years lost (−35,897, −30%) (Table 4). The increases in total LYs, EF/DF/RF LYs and QALYs, together with the reduction in productive years lost, accumulated consistently over the 10-year period, reflecting the long-term clinical benefits of fewer progression events or recurrences (Fig. 3). Similar trends were also observed for each indication (Supplementary Table S2).

The OWSA indicated that the most influential parameters were disease-specific incidences (driving RF/EF/DF LY gains), treatment effects of subsequent therapies (driving reductions in post-recurrence deaths and LY gains) and utility values (driving QALY gains). Tornado diagrams for selected outcomes are presented in Supplementary Fig. S1.

The 10-year cumulative impact of early treatment with anti-PD-(L)1 agents was also calculated under each scenario and compared against that of the main analysis (Table 5). Outcomes followed expected patterns: a 6-month delay in access to anti-PD-(L)1 agents resulted in fewer LYs gained (−10% for RF/EF/DF LYs, −13% for total LYs), fewer QALYs gained (−13%) and fewer productive years gained (−10%), but higher numbers of events/recurrences (+6%) and deaths (+8%). Conversely, higher incidence was associated with increased absolute gains in LYs (+5% for RF/EF/DF, +4% for total) and QALYs (+4%), as the result of a greater number of affected individuals that directly drives larger overall gains. Additionally, a 20% lower anti-PD-(L)1 uptake (80% versus 100%) resulted in a proportional reduction of approximately 20% across all estimated benefits and impacts.

Table 3 Estimated number of individuals for the world with anti-PD-(L)1s used in the early-stage setting

Patients initiating early-stage treatment	2025	2026	2027	2028	2029	2030–2034	Cumulative
All indications	*11,107*	*11,625*	*11,625*	*11,625*	*11,971*	*60,375*	*118,329*
Melanoma Stage IIB/C	1535	1535	1535	1535	1535	7675	15,350
Melanoma Stage III	2235	2235	2235	2235	2235	11,174	22,349
RCC	4565	4565	4565	4565	4565	22,824	45,649
TNBC	1561	1561	1561	1561	1561	7805	15,610
NSCLC resectable Stage II–IIIB	1211	1730	1730	1730	2076	10,896	19,371

Numbers may differ marginally due to rounding-up

NSCLC non-small-cell lung cancer, *PD-(L)1* programmed cell death protein (ligand) 1, *RCC* renal cell carcinoma, *TNBC* triple-negative breast cancer

Italics refers to the sum of the values of the individual indications in the rows below

Table 4 Health and productivity outcomes with anti-PD-(L)1 agents in neoadjuvant and/or adjuvant settings

Outcome	World without anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings	World with anti-PD-(L)1 agents used in the neoadjuvant and/or adjuvant settings	Difference (%)
LYs—recurrence-/event-/disease-free	323,677	384,308	+60,631 (+19%)
LYs—total	441,040	461,498	+20,458 (+5%)
QALYs	360,221	381,314	+21,093 (+6%)
Events or recurrences	61,755	41,546	−20,209 (−33%)
Active treatments for metastatic disease	67,204	41,984	−25,220 (−38%)
Deaths—total	29,164	22,028	−7137 (−24%)
Deaths after first event or recurrence	25,378	17,357	−8021 (−32%)
Productive years lost	119,039	83,142	−35,897 (−30%)

A reduction in productive years lost as a result of the introduction of anti-PD(L)1 agents can be interpreted as a gain in productive years

LYs life years, *PD-(L)1* programmed cell death protein (ligand) 1, *QALYs* quality-adjusted life years

4 Discussion

This analysis, which focuses on the Italian population, reinforces the growing body of evidence on the clinical benefits of anti-PD-(L)1 agents in the treatment of early-stage cancers. Pivotal trials across multiple tumour types have demonstrated the efficacy of anti-PD-(L)1 therapies in reducing recurrence risk and improving long-term outcomes [12, 14, 16, 17, 19]. Our findings suggest that, over a 10-year period, the introduction of anti-PD-(L)1 agents in Italy could generate substantial health gains, including increases in LYs, RF/EF/DF LYs and QALYs, and a reduction in mortality. These benefits are accompanied by reductions in cancer recurrence events and the need for active metastatic treatment, which may also translate into lower healthcare resource use for advanced disease management. Additionally, an increase in productive years of around 30% were estimated, suggesting that the value of early intervention with anti-PD-(L)1 agents extends beyond direct clinical outcomes to include broader economic and societal impacts.

The results of this study mirror that of previous analyses in Belgium [52], Switzerland [53] and the UK [54], whereby introducing anti-PD-(L)1 agents in early-stage cancers has also demonstrated favourable patient and societal outcomes. To our knowledge, no prior studies have been conducted to quantify the collective, population-level impact of introducing anti-PD-(L)1 agents across multiple early-stage cancers in the Italian setting. In addition to clinical outcomes, it also captures productivity impacts at the societal level in Italy, aligning to the overarching goals of the National Oncology Plan 2023–2027 [6]. Productivity outcomes remain an important and often overlooked component of economic evaluations, particularly given the substantial and persistent burden of cancer-related productivity losses projected across Europe in the coming decades [55]. By examining the population-level effects across five tumour types, this analysis offers a broader perspective on the clinical and societal value of early anti-PD-(L)1 treatment, addressing a gap in the existing Italian literature where such aggregation has not previously been undertaken.

Given the expected rise in cancer incidence in Italy [3], the growing economic and humanistic burden highlights the need for comprehensive strategies to address and mitigate these impacts. The Italian National Oncology Plan 2023–2027, in alignment with the EU's Beating Cancer Plan, emphasises the importance of measures such as widespread screening, early disease detection and improved access to effective treatments to enhance cancer care in Italy [6]. Initiatives such as early detection and screening have been shown to positively impact patient outcomes [3] by enabling earlier access to therapies that have a greater likelihood of halting progression. In this context, anti-PD(L)1 agents have demonstrated significant benefits in early stage-cancers, including reductions in recurrence rates and improvements in OS [12, 14, 16, 17, 19]. Encouraging full adoption of anti-PD-(L)1 agents will help ensure that the benefits of early detection and screening translate into more substantial health gains for patients.

Expanding the use of anti-PD-(L)1 agents represents an investment in advancing population health and achieving optimal outcomes for those who are clinically eligible. Our analysis suggests that long-term savings are likely, driven by the anticipated reductions in recurrences and metastatic treatments needed with the adoption of anti-PD-(L)1 agents in early-stage settings. This finding is consistent with evidence from another Italian study, which reported €121 million in indirect cost savings following the introduction of immune checkpoint inhibitors for late-stage cancers, largely attributable to reduced premature mortality [56]. In addition, as clinical experience with anti-PD-(L)1 agents grows—and given their generally favourable safety profile and ease of administration [57, 58]—transitioning their administration

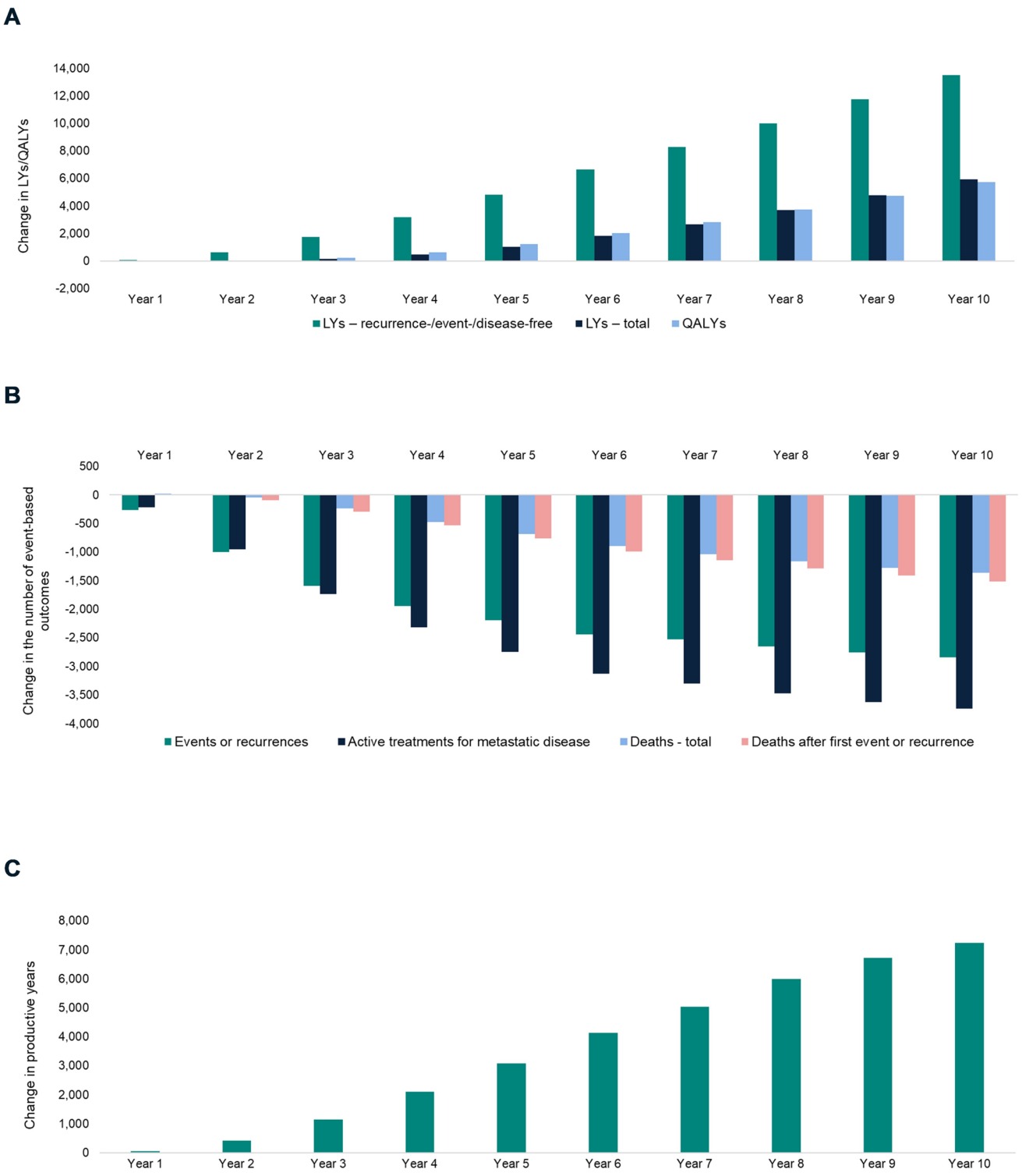

Fig. 3 Annual impact when anti-PD-(L)1 agents are used in neoadjuvant and/or adjuvant settings on **A** LYs/QALYs, **B** event-based outcomes and **C** productivity. For **C**, a reduction in productive years lost as a result of the introduction of anti-PD(L)1 agents (Table 4) can be interpreted as a gain in productive years. *LY* life year, *PD-(L)1* programmed cell death protein (ligand) 1, *QALY*, quality-adjusted life year

Table 5 Scenario-based sensitivity analysis presenting health and productivity outcomes with anti-PD-(L)1 agents in neoadjuvant and/or adjuvant settings

Outcome	Difference from main analysis (%)[a]
Scenario: 6-month delay in access to anti-PD-(L)1 agents	
LYs—recurrence-/event-/disease-free	−6267 (−10%)
LYs—total	−2731 (−13%)
QALYs	−2632 (−13%)
Events or recurrences	+1221 (+6%)
Active treatments for metastatic disease	+1682 (+7%)
Deaths—total	+594 (+8%)
Deaths after first event or recurrence	+647 (+8%)
Productive years gained[b]	−3400 (−10%)
Scenario: Assume annual increase in incidence for all indications	
LYs—recurrence-/event-/disease-free	+2807 (+5%)
LYs—total	+717 (+4%)
QALYs	+762 (+4%)
Events or recurrences	−1459 (−7%)
Active treatments for metastatic disease	−1474 (−6%)
Deaths—total	−364 (−5%)
Deaths after first event or recurrence	−455 (−6%)
Productive years gained[b]	+1680 (+5%)
Scenario: Assume 20% lower anti-PD-(L)1 uptake	
LYs—recurrence-/event-/disease-free	−12,126 (−20%)
LYs—total	−4092 (−20%)
QALYs	−4219 (−20%)
Events or recurrences	+4042 (+20%)
Active treatments for metastatic disease	+5044 (+20%)
Deaths—total	+1427 (+20%)
Deaths after first event or recurrence	+1604 (+20%)
Productive years gained[b]	−7179 (−20%)

LY life year, *PD-(L)1* programmed cell death protein (ligand) 1, *QALY* quality-adjusted life year

[a]Difference shows the change relative to the main analysis (Table 4), with positive and negative values indicating increases or reductions, respectively

[b]Reduction in productive years lost represents a net gain in productive years

to outpatient settings, as recommended in the National Oncology Plan 2023–2027 [6], could help relieve capacity constraints in hospitals and tertiary centres, thereby expanding patient access.

Cancer diagnoses generally result in reduced quality of life (QoL) for both patients [59] and caregivers [60]. Later-stage diagnoses typically require more aggressive treatment regimens and are associated with poorer prognoses, which can exacerbate the burden on patients and caregivers [61]. The National Oncology Plan 2023–2027, noting that around one third of patients are of working age at diagnosis, highlights the importance of maintaining QoL throughout the entire care pathway [6]. Our findings suggest that adopting anti-PD-(L)1 agents in early-stage cancers could help prevent disease progression and reduce recurrences, thereby potentially mitigating some of the QoL declines and caregiver burden associated with late-stage disease. Timely and effective interventions during early-stage disease may therefore play a key role in preserving QoL. Such benefits are also likely to extend to immediate family members and caregivers, helping avert potential negative health and mental health implications [47, 62]. Adoption of effective treatments in early-stage settings should therefore be encouraged to meet the overarching aims of the National Oncology Plan 2023–2027.

There are some limitations in this study. The 10-year time horizon used in this model may not fully capture the long-term benefits of early anti-PD-(L)1 treatment, particularly for patients who remain recurrence-free and continue to experience survival gains beyond this period. Longer horizon

results will be useful to confirm the sustained benefits but would introduce greater uncertainty due to extrapolation. In addition, the model used trial data cuts available at the time of model development and adopted the best-fitting parametric survival extrapolations from the underlying indication-specific cost effectiveness publications. While more mature data from later data cuts can be used to validate these extrapolations, uncertainty in long-term survival remains and may affect the magnitude of the estimated outcomes. For all indications except resectable NSCLC, health utilities were not derived from Italy-specific value sets and were instead based on the broader EU algorithm, which may not fully reflect national preferences. While this may improve the accuracy of the impact on HRQoL, the overwhelming improvements in quality of life are likely similar regardless of mapping algorithms used. Furthermore, estimation of productivity gains was conducted based on findings from a US study combined with Italian employment inputs. We acknowledge potential cross-country differences in productivity impact of early-stage cancers for both patients and carers. Collecting Italian-specific productivity data would therefore reinforce and contextualise our results and provide stronger evidence. Lastly, this analysis is limited to a predefined set of early-stage indications, reflecting the study focus on perioperative/adjuvant settings and data availability. The model also does not account for future treatments, including anti-PD-(L)1 agents or other novel therapies that may become available over the modelled time horizon. Uncertainty in treatment uptake assumptions could influence long-term outcomes.

5 Conclusions

This analysis illustrates the potential health and societal benefits of introducing anti-PD-(L)1 agents in the neoadjuvant and/or adjuvant settings in Italy, rather than deferring their use to the metastatic setting. By reducing recurrences, prolonging recurrence-/event-/disease-free life years and lowering the need for metastatic treatment, early intervention can improve health outcomes while also increasing productivity among patients and caregivers.

As national strategies continue to focus on earlier detection and improved outcomes, these findings can support future planning and the appropriate allocation of oncology-related health care resources. Incorporating the broader value of early-stage treatment, both clinical and societal, will be key to shaping more effective and sustainable cancer care in Italy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-026-01567-7.

Funding The study was funded by MSD, whose role in this research includes interpretation of results and manuscript writing.

Declarations

Conflict of Interest Andrea Marcellusi has received honoraria as a speaker and adviser for MSD, Astra Zeneca, Eli Lilly and other pharma companies. He is an Editorial Board member of *Clinical Drug Investigation*, but was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Fabio Calabrò has received honoraria as speaker for MSD, Astra Zeneca, Pfizer, Novartis, Bayer, Ipsen, Johnson and Johnson, Recordati and Astellas. Anna Maria Di Giacomo has served as an advisor or board member for MSD, Bristol Myers Squibb, Incyte, Pierre Fabre, Sanofi, GSK, Novartis, SunPharma and Immunocore. She has also received honoraria for MSD, Roche, Bristol Myers Squibb, Sanofi, Pierre Fabre, GSP and Vyvamed. Fabio Puglisi has received honoraria for advisory boards, activities as a speaker, travel grants and research grants from Amgen, Astra Zeneca, Bayer, Daiichi Sankyo, Celgene, Eisai, Eli Lilly, Exact Sciences, Gilead, Ipsen, Italfarmaco, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Takeda and Viatris. He has also received research funding from Astra Zeneca, Eisai and Roche. Alessio Cortellini received grants for consultancies/advisory boards: MSD, OncoC4, Roche, Regeneron, Bristol Myers Squibb, Amgen, Daiichi Sankyo, Astra Zeneca, Access Infinity, Ardelis Health, Alpha Sight, Capvision, Techspert, Alira Health, Atheneum, Lightening Health. He also received speaker fees from Astra Zeneca, Roche, Pierre-Fabre, MSD, Sanofi/Regeneron and Yuhan corporation, compensation for writing/editorial activity from Bristol Myers Squibb, MSD and travel support from Sanofi, MSD, Roche and funding (to institution) from the International Association for the Study of Lung Cancer. Isobel Thornton, Yan Zhi Tan, Alessandro Catanzaro and Catarina Neves are employees of Lumanity, which have been contracted by MSD for this study, and do not have any further financial or nonfinancial interests to disclose. Fabrizio Ascone, Matilde Franceschini and Mario Calandriello are employees of MSD, Italy. Raquel Aguiar-Ibáñez is an employee of Merck Canada Inc., Kirkland, QC, Canada. Yizhen Lai is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Availability of Data and Material The data used in this study can be made available from the corresponding author on reasonable request.

Code Availability Not applicable; no coding was used for this study.

Ethical Approval All data used in this study were fully de-identified; ethics approval was not required and was not sought.

Consent to Participate Not applicable; this modelling study is exempt from informed consent.

Consent to Publication Not applicable.

Author Contributions Study conceptualisation and design: all authors; study conduct: I.T., Y.Z.T., A.C., C.N. and Y.L.; analysis and interpretation of results: I.T., Y.Z.T., C.N. and Y.L.; draft manuscript preparation: I.T., Y.Z.T., C.N., R.A., M.F. and Y.L. All authors read and approved the final version and agree to be accountable for the research.

References

1. Manzano ASC, Hofmarcher T, Wilking N. Comparator report on cancer in Europe 2025—disease burden, costs and access to medicines and molecular diagnostics. 2025. https://www.efpia.eu/media/nbbbsbhp/ihe-comparator-report-on-cancer-in-europe-2025.pdf.
2. Associazione Italiana Registri Tumori (AIRTUM). I numeri del cancro in Italia 2023. 2023. https://www.registri-tumori.it/cms/sites/default/files/pubblicazioni/I%20numeri%20del%20cancro%20in%20Italia%20-%20versione%20per%20operatori_1.pdf.
3. OECD/European Commission. EU country cancer profile: Italy 2025. Paris: OECD Publishing; 2025.
4. Force LM, Kocarnik JM, May ML, Bhangdia K, Crist A, Penberthy L, et al. The global, regional, and national burden of cancer, 1990–2023, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025;406(10512):1565–86. https://doi.org/10.1016/S0140-6736(25)01635-6.
5. A A. Tumori: spesi 20 miliardi nel 2022 per le cure, un quarto a carico dei pazienti. Il Sole 24 ORE 2023. https://www.ilsole24ore.com/art/tumori-spesi-20-miliardi-2022-le-cure-quarto-carico-pazienti-AFJWBK4B.
6. Ministero della Salute. Piano Oncologico Nazionale: documento di pianificazione e indirizzo per la prevenzione e il contrasto del cancro 2023-2027. 2023. https://www.salute.gov.it/new/sites/default/files/imported/C_17_pubblicazioni_3291_allegato.pdf.
7. Crosby D, Bhatia S, Brindle KM, Coussens LM, Dive C, Emberton M, et al. Early detection of cancer. Science. 2022;375(6586):eaay9040. https://doi.org/10.1126/science.aay9040.
8. Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, et al. Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(3):244–58. https://doi.org/10.1016/j.annonc.2021.11.012.
9. Amaral T, Ottaviano M, Arance A, Blank C, Chiarion-Sileni V, Donia M, et al. Cutaneous melanoma: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025;36(1):10–30. https://doi.org/10.1016/j.annonc.2024.11.006.
10. Zer A, Ahn MJ, Barlesi F, Bubendorf L, De Ruysscher D, Garrido P, et al. Early and locally advanced non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025. https://doi.org/10.1016/j.annonc.2025.08.003.
11. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860–77. https://doi.org/10.1016/j.annonc.2022.05.009.
12. Luke JJ, Rutkowski P, Queirolo P, Del Vecchio M, Mackiewicz J, Chiarion-Sileni V, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected Stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet. 2022;399(10336):1718–29. https://doi.org/10.1016/S0140-6736(22)00562-1.
13. Kirkwood JM, Del Vecchio M, Weber J, Hoeller C, Grob JJ, Mohr P, et al. Adjuvant nivolumab in resected Stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nat Med. 2023;29(11):2835–43. https://doi.org/10.1038/s41591-023-02583-2.
14. Eggermont AMM, Blank CU, Mandalà M, Long GV, Atkinson VG, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected Stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(5):643–54. https://doi.org/10.1016/s1470-2045(21)00065-6.
15. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected Stage III or IV melanoma. N Engl J Med. 2017;377(19):1824–35. https://doi.org/10.1056/NEJMoa1709030.
16. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang Y-H, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med. 2021;385(8):683–94. https://doi.org/10.1056/NEJMoa2106391.
17. Schmid P, Cortes J, Dent R, McArthur H, Pusztai L, Kümmel S, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. N Engl J Med. 2024;391(21):1981–91. https://doi.org/10.1056/NEJMoa2409932.
18. Harbeck N, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. LBA11 IMpassion031: results from a phase III study of neoadjuvant (neoadj) atezolizumab + chemotherapy in early triple-negative breast cancer (TNBC). Ann Oncol. 2020;31:S1144. https://doi.org/10.1016/j.annonc.2020.08.2239.
19. Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;404(10459):1240–52. https://doi.org/10.1016/S0140-6736(24)01756-2.
20. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected Stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398(10308):1344–57. https://doi.org/10.1016/s0140-6736(21)02098-5.
21. Mitsudomi T, Ito H, Okada M, Sugawara S, Shio Y, Tomii K, et al. Neoadjuvant nivolumab plus chemotherapy in resectable non-small-cell lung cancer in Japanese patients from CheckMate 816. Cancer Sci. 2024;115(2):540–54. https://doi.org/10.1111/cas.16030.
22. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. N Engl J Med. 2023;389(18):1672–84. https://doi.org/10.1056/NEJMoa2304875.
23. Agenzia Italiana del Farmaco (AIFA). Regime di rimborsabilita' e prezzo a seguito di nuove indicazioni terapeutiche del medicinale per uso umano «Keytruda». (Determina n. 240/2025). 2025. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2025-03-03&atto.codiceRedazionale=25A01307.
24. Agenzia Italiana del Farmaco (AIFA). Regime di rimborsabilita' e prezzo a seguito di nuove indicazioni terapeutiche del medicinale per uso umano «Keytruda». (Determina n. 1762/2019). 2019. https://www.gazzettaufficiale.it/eli/id/2019/12/10/19A07733/sg.
25. Agenzia Italiana del Farmaco (AIFA). Regime di rimborsabilita' e prezzo, a seguito di nuove indicazioni terapeutiche, del medicinale per uso umano «Keytruda». (Determina n. 476/2023). 2023. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2023-07-18&atto.codiceRedazionale=23A04031.
26. Agenzia Italiana del Farmaco (AIFA). Regime di rimborsabilita' e prezzo, a seguito di nuove indicazioni terapeutiche, del medicinale

per uso umano «Opdivo». (Determina n. 267/2025). 2025. https://www.gazzettaufficiale.it/eli/id/2025/03/24/25A01679/SG.
27. Williamson M, Press DJ, Hansen SA, Tomar A, Jhuti GS, Revil C, et al. Population-level impact of adjuvant trastuzumab emtansine on the incidence of metastatic breast cancer: an epidemiological prediction model of women with HER2-positive early breast cancer and residual disease following neoadjuvant therapy. Breast Cancer. 2024;31(1):84–95. https://doi.org/10.1007/s12282-023-01514-w.
28. Agenzia Italiana del Farmaco (AIFA). Linee guida per la compilazione del dossier a supporto della domanda di rimborsabilità e prezzo di un medicinale. 2019. https://www.aifa.gov.it/documents/20142/1283800/Linee_guida_dossier_domanda_rimborsabilita.pdf/8249e3d6-b2fc-915d-a211-02abafb8aa6d.
29. Bensimon AG, Zhou Z-Y, Jenkins M, Song Y, Gao W, Signorovitch J, et al. An economic evaluation of pembrolizumab versus other adjuvant treatment strategies for resected high-risk Stage III melanoma in the USA. Clin Drug Investig. 2020;40(7):629–43. https://doi.org/10.1007/s40261-020-00922-6.
30. Huang M, Fasching AP, Haiderali A, Xue W, Yang C, Pan W, et al. Cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant single-agent pembrolizumab for high-risk early-stage triple-negative breast cancer in the United States. Adv Ther. 2023;40(3):1153–70. https://doi.org/10.1007/s12325-022-02365-1.
31. Lai Y, Bensimon AG, Gao E, Bhattacharya R, Xu R, Chevure J, et al. Cost-effectiveness analysis of pembrolizumab as an adjuvant treatment of renal cell carcinoma post-nephrectomy in the United States. Clin Genitourin Cancer. 2023;21(5):612.e1-.e11. https://doi.org/10.1016/j.clgc.2023.03.016.
32. National Institute for Health and Care Excellence. TA837: Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma. 2022 [cited 12 August 2025]. https://www.nice.org.uk/guidance/ta837.
33. National Institute for Health and Care Excellence. TA766: Pembrolizumab for adjuvant treatment of completely resected Stage 3 melanoma. 2022 [cited 12 August 2025]. https://www.nice.org.uk/guidance/ta766.
34. National Institute for Health and Care Excellence. TA830: Pembrolizumab for adjuvant treatment of renal cell carcinoma. 2022 [cited 12 August 2025]. https://www.nice.org.uk/guidance/ta830.
35. National Institute for Health and Care Excellence. TA851: pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer. 2022 [cited 12 August 2025]. https://www.nice.org.uk/guidance/ta851.
36. National Institute for Health and Care Excellence. TA1017: pembrolizumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer. 2024 [cited 12 August 2025]. https://www.nice.org.uk/guidance/ta1017/evidence/committee-papers-pdf-13604993245.
37. Zhang S, Bensimon AG, Xu R, Jiang R, Greatsinger A, Zhang A, et al. Cost-effectiveness analysis of pembrolizumab as an adjuvant treatment of resected Stage IIB or IIC melanoma in the United States. Adv Ther. 2023;40(7):3038–55. https://doi.org/10.1007/s12325-023-02525-x.
38. Fan H, Feng H, Gridelli C, Rai P, Riccaboni M. Cost-effectiveness of perioperative pembrolizumab for resectable nsclc: a lifetime evaluation in the Italian healthcare system SIFO Congress; 2025.
39. Silvola S, Restelli U, Croce D, Lai Y, Iacovelli R. Analisi di costo-utilità dell'utilizzo di pembrolizumab per il trattamento adiuvante del carcinoma delle cellule renali post nefrectomia nel contesto italiano. Clinicoecon Outcomes Res. 2024;19:85–98.
40. Valentini I, Basile M, Rumi F, Di Brino E, Haideral A, Jamotte A. Cost-effectiveness analysis of pembrolizumab in combination with chemotherapy in the treatment of high-risk triple-negative breast cancer: evidence from DALY indicator integration ISPOR Rome Chapter 2025; 2025.
41. Associazione Italiana di Oncologia Medica (AIOM). I numeri del cancro in Italia 2022. 2022. https://www.aiom.it/wp-content/uploads/2022/12/2022_AIOM_NDC-web.pdf.
42. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices – overview: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Med Decis Making. 2012;32(5):667–77. https://doi.org/10.1177/0272989x12454577.
43. Statbel. Tables de mortalité et espérance de vie. 2022. https://statbel.fgov.be/fr/themes/population/mortalite-et-esperance-de-vie/tables-de-mortalite-et-esperance-de-vie#documents.
44. Lorenzi M, Arndorfer S, Aguiar-Ibañez R, Scherrer E, Liu FX, Krepler C. An indirect treatment comparison of the efficacy of pembrolizumab versus competing regimens for the adjuvant treatment of Stage III melanoma. J Drug Assess. 2019;8(1):135–45. https://doi.org/10.1080/21556660.2019.1649266.
45. MSD. KEYNOTE-671 neoadjuvant/adjuvant NSCLC: SLR and NMA. 2024.
46. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509–18. https://doi.org/10.1111/j.1524-4733.2010.00700.x.
47. Aguiar-Ibáñez R, McQuarrie K, Jayade S, Penton H, DiGiovanni L, Raina R, et al. Impact of recurrence on employment, finances, and productivity for early-stage cancer patients and caregivers: US survey. Future Oncol. 2025;21(3):349–65. https://doi.org/10.1080/14796694.2024.2436342.
48. OECD. Average usual weekly hours worked on the main job. 2025. https://data-explorer.oecd.org/vis?tm=working%20hours%20per%20week&pg=0&snb=16&vw=tb&df[ds]=dsDisseminateFinalDMZ&df[id]=DSD_HW%40DF_AVG_USL_WK_WKD&df[ag]=OECD.ELS.SAE&df[vs]=1.0&dq=ITA..._T._T....ICSE93_1._T...&pd=2010%2C&to[TIME_PERIOD]=false.
49. ISTAT. Gross hourly wage per hour paid of employee jobs in euros (median). 2025 [cited 25 July 2025]. https://esploradati.istat.it/databrowser/#/en/dw/categories/IT1,Z0500LAB,1.0/LAB_EMPLWAGE/DCSC_RACLI/IT1,533_957_DF_DCSC_RACLI_1,1.0.
50. Istituto Nazionale di Statistica. Occupati e disoccupati (dati provvisori) – Febbraio 2026. 2026 [cited 01 April 2026]. https://www.istat.it/comunicato-stampa/occupati-e-disoccupati-dati-provvisori-febbraio-2026/.
51. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133–61. https://doi.org/10.1016/s0140-6736(24)00757-8.
52. Bento-Abreu A, Vandekeere S, Sönmez D, Neves C, Mantaian T, Ethgen O, et al. The health impact of using anti-PD-1 agents to treat early-stage cancer in Belgium. Oncol Ther. 2025. https://doi.org/10.1007/s40487-025-00357-z.
53. Favre-Bulle A, Stankovic M, Mantaian T, Frei C, Schaefer S, Gabriel SS, et al. Health impact of using anti-PD-(L)1 agents to treat early-stage cancers in Switzerland: a modeling study. Front Immunol. 2025;16:1601377. https://doi.org/10.3389/fimmu.2025.1601377.
54. Burton H, Greenall S, Tan YZ, Neves C, Macdonald N, Aguiar-Ibáñez R. Impact on health outcomes and productive work of adding anti-PD-1 agents to treat early-stage cancers in the United

Kingdom: a modelling study. Front Pharmacol. 2025;16:1613120. https://doi.org/10.3389/fphar.2025.1613120.
55. Ortega-Ortega M, Hanly P, Pearce A, Soerjomataram I, Sharp L. Projected impact on labour productivity costs of cancer-related premature mortality in Europe 2018-2040. Appl Health Econ Health Policy. 2023;21(6):877–89. https://doi.org/10.1007/s40258-023-00824-6.
56. Canali B, Apolone G, Ascierto PA, De Braud F, Grossi F, Perrone F, et al. Effect of immuno-oncology on clinical and economic outcomes for a selection of cancers in Italy. Expert Rev Pharmacoecon Outcomes Res. 2025;25(6):905–15. https://doi.org/10.1080/14737167.2025.2493130.
57. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget. 2017;8(5):8910–20. https://doi.org/10.18632/oncotarget.13315.
58. Felip E, Rojas CI, Schenker M, Kowalski DM, Casarini IA, Csöszi T, et al. Subcutaneous versus intravenous pembrolizumab, in combination with chemotherapy, for treatment of metastatic non-small-cell lung cancer: the phase III 3475A-D77 trial. Ann Oncol. 2025;36(7):775–85. https://doi.org/10.1016/j.annonc.2025.03.012.
59. Nayak MG, George A, Vidyasagar MS, Mathew S, Nayak S, Nayak BS, et al. Quality of life among cancer patients. Indian J Palliat Care. 2017;23(4):445–50. https://doi.org/10.4103/ijpc.Ijpc_82_17.
60. Guerra-Martín MD, Casado-Espinosa MDR, Gavira-López Y, Holgado-Castro C, López-Latorre I, Borrallo-Riego Á. Quality of life in caregivers of cancer patients: a literature review. Int J Environ Res Public Health. 2023. https://doi.org/10.3390/ijerph20021570.
61. Chung KC, Muthutantri A, Goldsmith GG, Watts MR, Brown AE, Patrick DL. Symptom impact and health-related quality of life (HRQoL) assessment by cancer stage: a narrative literature review. BMC Cancer. 2024;24(1):884. https://doi.org/10.1186/s12885-024-12612-z.
62. Aguiar-Ibanez R, McQuarrie K, Martinez A, Penton H, DiGiovanni L, Raina R, et al. A US survey across seven early-stage cancers assessing the humanistic burden of recurrence on patients and caregivers. Oncol Ther. 2025;13(2):339–61. https://doi.org/10.1007/s40487-025-00328-4.

Authors and Affiliations

Andrea Marcellusi[1] · Fabio Calabrò[2] · Anna Maria Di Giacomo[3] · Fabio Puglisi[4,5] · Alessio Cortellini[6,7,8] · Isobel Thornton[9] · Yan Zhi Tan[10] · Alessandro Catanzaro[10] · Catarina Neves[10] · Fabrizio Ascone[11] · Matilde Franceschini[11] · Mario Calandriello[11] · Raquel Aguiar-Ibáñez[12] · Yizhen Lai[13]

✉ Yizhen Lai
joyce.lai2@merck.com

1 Department of Pharmaceutical Sciences-DISFARM, University of Milan, Milan, Italy

2 Department of Medical Oncology 1, National Cancer Institute Regina Elena, IRCCS, Rome, Italy

3 Center for Immuno-Oncology, University Hospital of Siena, University of Siena, Siena, Italy

4 Department of Medical Oncology, National Cancer Institute, Centro di Riferimento Oncologico RCCS, Aviano, Italy

5 Department of Medicine, University of Udine, Udine, Italy

6 Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy

7 Operative Research Unit of Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy

8 Department of Surgery and Cancer, Imperial College of London, Hammersmith Hospital Campus, Du Cane Road, London, UK

9 Lumanity, London, UK

10 Lumanity, Utrecht, The Netherlands

11 MSD Ltd, Rome, Italy

12 Merck Canada Inc., Kirkland, QC, Canada

13 Merck & Co., Inc., Rahway, NJ, USA