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Immuno-oncology (IO) Rechallenge Approach and Its Impact on The Cost-Effectiveness of IO in Early-Stage Cancer

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List of Acronyms

ACT	Adoptive Cell Therapy
ADCs	Antibody-drug conjugates
AEs	Adverse events
CAR-T	Chimeric antigenic receptor - T
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DFS	Disease-free survival
DM	Distant metastatic
EF	Event-free
EFS	Event-free survival
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-to-effectiveness ratio
ICI	Immune checkpoint inhibitors
IO	Immuno-oncology
LR	Locoregional
mAbs	Monoclonal antibodies
NACT	Neoadjuvant chemotherapy
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
OS	Overall survival
OV	Oncolytic virus
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
QALY	Quality adjusted life years
SoC	Standard of care
TNBC	Triple-negative breast cancer
TP	Transition probabilities

Abstract

Immuno-oncology (IO) Rechallenge Approach and Its Impact on The Cost-Effectiveness of IO in Early-Stage Cancer

Introduction: Immuno-oncology (IO) rechallenges in the metastatic setting, after usage in earlier stages, is challenging. The lack of rationale of IO rechallenge approaches complicates the development of pharmacoeconomic models. This study aims to review the different assumptions of IO rechallenge used in health technology assessment (HTA) submissions for early-stage cancer, and test their impact on the cost-effectiveness result.

Methods: This study consisted of two steps. First, a literature review on HTA submissions for IO in early-stage cancer was performed. The HTAs were assessed for the IO rechallenge approach and related criticisms. Then, a cost-effectiveness model was to test different IO rechallenge scenarios. The model was built to reflect NICE TA851. The input parameters were obtained from KEYNOTE-522 and KEYNOTE-355 trials, relevant HTAs, and data for the UK population. The IO rechallenge was applied first in the distant metastatic state (DM) and then in both locoregional recurrence (LR) state and DM state. The resulting incremental cost-to-effectiveness ratios (ICER) were compared. The analysis was performed using R and Excel.

Result: The literature review found that mostly IO rechallenge was permitted either in the DM and/or the LR state, under variable assumptions. Many of them assumed a minimum time interval between IO retreatment and previous treatment (6, 12, 18, or 24 months). Although the models were generally accepted, many criticisms arose, especially regarding the uncertainty of IO restriction and the lack of real-world evidence. Then, the cost-effectiveness model found that different IO restriction scenarios in the DM state only slightly altered the ICER (0-2.4%) but produced more prominent changes if applied in both DM and LR states (21.8-45.8%).

Conclusion: This study indicates that different IO rechallenge approaches could change the ICER significantly, and its impact could be augmented if applied in multiple post-progression states. Studies are needed to suggest the optimal IO rechallenge approach.

Keywords: Immuno-oncology, Immuno-oncology rechallenge, cost-effectiveness model

[Abstract in French]

Approches de réintroduction de l'immuno-oncologie (IO) et son impact sur le coût-efficacité de l'IO dans le cancer au stade précoce

Introduction : La réintroduction de l'immuno-oncologie (IO) dans le contexte métastatique, après son utilisation dans des stades précoces, présente un défi majeur. Le manque de rationalité des approches de réutilisation de l'IO complique le développement de modèles pharmaco-économiques. Cette étude vise à examiner les différentes hypothèses de réutilisation de l'IO utilisées dans les soumissions d'évaluation des technologies de la santé (ETS) pour le cancer à un stade précoce, et à évaluer leur impact sur la coût-efficacité.

Méthodes : Cette étude s'est déroulée en deux étapes. Tout d'abord, une revue de la littérature sur les soumissions d'ETS pour l'IO dans le cancer à un stade précoce a été effectuée. Les ETS ont été évaluées pour l'approche de réutilisation de l'IO et les critiques associées. Ensuite, un modèle de rentabilité a été utilisé pour tester différents scénarios de réutilisation de l'IO. Le modèle a été construit pour refléter le NICE TA851. Les paramètres d'entrée ont été obtenus à partir des essais KEYNOTE-522 et KEYNOTE-355, des ETS pertinentes et des données pour la population britannique. La réutilisation de l'IO a d'abord été appliquée à l'état métastatique à distance (DM), puis à la fois à l'état de récurrence locorégionale (LR) et à l'état DM. Les ratios coût-efficacité différentiels (RCED) résultants ont été comparés. L'analyse a été réalisée à l'aide de R et Excel.

Résultats : La revue de la littérature a révélé que la réutilisation de l'IO était principalement autorisée soit dans l'état de DM et/ou l'état de LR, selon des hypothèses variables. Beaucoup d'entre elles supposent un intervalle de temps minimum entre la réadministration de l'IO et le traitement précédent (6, 12, 18 ou 24 mois). Bien que les modèles aient été généralement acceptés, de nombreuses critiques sont apparues, en particulier concernant l'incertitude de la restriction de l'IO et le manque de preuves du monde réel. Ensuite, le modèle de coût-efficacité a montré que différents scénarios de restriction de l'IO dans l'état de DM n'ont que légèrement modifié l'ICER (0-2,4%), mais ont produit des changements plus importants s'ils étaient appliqués à la fois dans les états de DM et de LR (21,8-45,8%).

Conclusion : Cette étude indique que différentes approches de réutilisation de l'IO pourraient modifier de manière significative le RCDR, et que son impact pourrait être augmenté s'il était appliqué dans plusieurs états de post-progression. Des études sont nécessaires pour suggérer l'approche optimale de réutilisation de l'IO.

Mots-clés: Immuno-oncologie, réintroduction de l'immuno-oncologie, modèle de coût-efficacité

Introduction

1.1 Immuno-oncology

Immuno-oncology (IO) has become a transformative approach in cancer treatment. IO is a type of cancer treatment that uses the body's own immune system to prevent, control, and eliminate cancer.[1] Immunotherapy works by modulating tumour immunity to shift the ongoing immune response from tumour-promoting to tumour-rejecting, hence providing durable and adaptable cancer control.[2]

1.1.1 Types of Immuno-oncology

Immune-oncology involves the stimulation of the immune system to effectively target and eliminate cancer cells. It includes a variety of therapies, each with distinct mechanism of action:

1. Monoclonal Antibodies (mAbs): Monoclonal antibodies are engineered antibodies designed to target specific antigens on cancer cells, facilitating their destruction by the immune system. Recent advances include the development of bispecific antibodies and antibody-drug conjugates (ADCs).[3]
2. Immune Checkpoint Inhibitors (ICI): These drugs inhibit the checkpoints that cancer cells use to protect themselves from being attacked by the immune system. Among these drugs, pembrolizumab and nivolumab, which target the PD-1 receptor on T cells, have shown efficacy in melanoma, lung cancer, and other cancers.[4]
3. Cancer Vaccines: They are therapeutic vaccines designed to elicit an immune response against cancer-specific antigens. Cancer vaccines that have been approved for clinical use by the FDA include Bacillus Galmette-Guerin (BCG, bacterial-based) for urothelial carcinoma, Talimogene laherparepvec (TVEC, virus-based) for melanoma, and Provenge (Sipuleucel T, Dendritic cell-based) for prostate cancer.[5]
4. Adoptive Cell Therapy (ACT): This therapy involves the collection and use of patients' own immune cells to treat their cancer. CAR T-cell therapy, a form of ACT, has been particularly successful in treating certain types of leukemia and lymphoma.[6]
5. Oncolytic Virus (OV) Therapy: This therapy uses genetically modified viruses that selectively infect and kill cancer cells. Two OVs, Talimogene laherparepvec (T-VEC) and Oncorine, have been approved by FDA in the treatment of advanced melanoma and advanced nasopharyngeal carcinoma.[7]

1.1.2 Role of Immuno-oncology in Cancer Treatment

The integration of IO therapies into the oncology landscape has significantly altered the treatment paradigm for several cancers. To date, most of the advances in IO therapy have been shown in patients with late-stage and metastatic cancer, offering better clinical value or added value to standard treatment.[8] Among the pioneering IO treatments, mAbs are now considered to be a main component of cancer therapy, alongside surgery, radiation, and chemotherapy. For example, trastuzumab offers a targeted therapy that significantly improves survival rates of HER2-positive breast cancer.[9] Moreover, ICI have revolutionized the treatment of advanced melanoma and non-small cell lung cancer, diseases that were previously associated with poor prognosis. For example, pembrolizumab and nivolumab which target the PD-1/PD-L1 pathway, have shown remarkable efficacy in treating a range of cancers, including melanoma and non-small cell lung cancer (NSCLC).[10] Similarly, CTLA-4 inhibitors like ipilimumab have proven effective in advanced melanoma, marking the first class of immune checkpoint inhibitors to demonstrate a survival benefit in this challenging disease.[11]

The integration of IO into cancer treatment protocols has not only expanded therapeutic options but also shifted the focus towards more personalized and less invasive strategies.[12] Cancer vaccines, although still in the early stages of clinical use, hold promise for both the prevention and treatment of cancer. Sipuleucel-T is the first therapeutic vaccine indicated for metastatic prostate cancer.[5] Moreover, adoptive cell therapy, particularly CAR T-cell therapy, represents a breakthrough in treating hematologic malignancies. Tisagenlecleucel, approved for certain types of leukemia, has achieved unprecedented success rates in relapsed or refractory cases.[6]

1.2 Immuno-oncology Use in Early-Stage Cancer

Thanks to its success, IO has started to be studied for earlier stage cancer in recent decades. In early-stage cancer, the goal is not only to treat but also to prevent recurrence. IO therapies have been proven successful as a part of treatment in non-metastatic cancer, such as breast cancer, melanoma, and other solid tumors.[13]

1.2.1 Breast Cancer

In early-stage breast cancer, the integration of IO therapies, particularly immune checkpoint inhibitors, has begun to change the treatment paradigm. Trials such as the IMpassion130 have demonstrated the efficacy of atezolizumab, a PD-L1 inhibitor, in combination with nab-paclitaxel in triple-negative breast cancer (TNBC), a subtype that previously had limited treatment options. Moreover, combination neoadjuvant chemotherapy (NACT) with pembrolizumab then continued in the adjuvant setting also demonstrated efficacy

in early TNBC. These combinations have shown a significant improvement in progression-free survival in patients with PD-L1-positive tumors, marking a significant step forward in the management of early-stage TNBC.[14]

1.2.2 Melanoma

Melanoma has been at the forefront of IO research, with early-stage patients benefiting significantly from checkpoint inhibitor therapies. The CheckMate 238 trial, for example, highlighted the role of nivolumab, a PD-1 inhibitor, in reducing the risk of recurrence in patients with resected advanced melanoma compared to ipilimumab, a CTLA-4 inhibitor. This finding highlights the potential of IO therapies to not only treat but also prevent the recurrence of melanoma in the early stages, offering a durable response and potentially improving long-term outcomes.[15]

1.2.3 Other cancers

Beyond breast cancer and melanoma, IO therapies are making strides in other cancer types in the non-metastatic setting. For instance, in non-small cell lung cancer (NSCLC), the PACIFIC trial demonstrated the efficacy of durvalumab, a PD-L1 inhibitor, as consolidation therapy in patients with stage III, unresectable NSCLC who did not progress after chemoradiotherapy.[16] Another example is recent outcome from KEYNOTE-564 showed that the addition of pembrolizumab in the adjuvant setting increased disease-free survival (DFS) resulting to its approval in the adjuvant setting for RCC for patients at high risk of recurrence.[17] In conclusion, IO therapies approach has led to a significant improvement in both progression-free and overall survival, illustrating the versatility and potential of IO therapies across different cancer types.

1.3 Challenges of Immuno-oncology Rechallenge

The landscape of IO rechallenge in the metastatic setting, following its initial use in earlier stages, presents a complex array of challenges. There are two primary concerns: the uncertainty of efficacy and the intricacies involved in HTA submission and health economics evaluation.[18,19]

1.3.1 Efficacy Issue

The efficacy of IO rechallenge in the metastatic setting remains a subject of considerable debate. Initial treatment with IO therapies in early-stage cancer has shown promising results, yet the subsequent rechallenge in the event of disease progression or recurrence, especially in a metastatic context, is filled with uncertainties. To date, there is

limited evidence on the efficacy and safety of IO rechallenge in metastatic settings.[18] Factors such as the development of resistance mechanisms, changes in the tumor microenvironment, and alterations in the immune landscape post-initial treatment contribute to the complexity of predicting rechallenge outcomes.[20,21] Hu et al. (2023) conducted a systematic review of the current findings of IO rechallenge that found that the rechallenge efficacy could be affected by patients' characteristics, therapeutic strategy selection, and the timing of treatment.[18]

1.3.2 HTA Issue

The high cost of IO treatments, coupled with the uncertainty surrounding their efficacy upon rechallenge, complicates the economic evaluation and reimbursement decision-making processes. To date, there is no guidance regarding the IO rechallenge approach for HTA.[19] Different IO rechallenge assumptions may affect the cost-effectiveness result and this hasn't been studied well. Previous HTA submissions often resorted to rely on a relatively subjective basis such as clinical expert opinion to determine the IO rechallenge approach in pharmacoeconomic models. From the HTA agency perspective, it is often difficult to assess and validate these models due to the subjective nature of reference and the lack of real-world study studying the respective disease. Therefore, a study that evaluates the different assumptions of IO rechallenge used in HTA submissions and compares their impact on the cost-effectiveness result, will reveal the current gap among HTA submissions and provide additional evidence in considering the IO rechallenge approach in pharmacoeconomic models.

1.4 Aims and Objectives

This study aims to evaluate the different assumptions of IO rechallenge used in HTA submissions for early-stage cancer, and test their impact on the cost-effectiveness result.

1.4.1 Primary Objectives

The primary objectives of this study are:

1. Review HTA submissions assessing IO therapies in early-stage cancer and identify methods used to model the IO rechallenge assumptions post progression and any criticism associated with them.
2. Evaluate the impact on the final incremental cost-effectiveness ratio (ICER) results under several IO rechallenge scenarios in the distant metastasis (DM) stage:
    - Only rechallenge of different IO is allowed in metastatic setting
    - IO rechallenge is fully restricted
    - IO rechallenge is allowed without restriction

- IO rechallenge is permitted if DM occurs 2 years after the initiation of adjuvant therapy.

1.4.1 Secondary Objectives

The secondary objective of this study is evaluating the ICER under different methods of modelling IO efficacy in the locoregional (LR) recurrence stage:

- Only rechallenge of different IO is allowed in metastatic setting
- IO rechallenge is fully restricted
- IO rechallenge is allowed without restriction
- IO rechallenge is permitted if LR recurrence occurs 2 years after the initiation of adjuvant therapy.

Methods

2.1 Study Design

2.1.1 Targeted Literature Review

This study consists of two steps. Firstly, a targeted literature review of HTA submissions for IO in non-metastatic settings was conducted. Literature search was performed in three main HTA databases: NICE (The National Institute for Health and Care Excellence), HAS (*Haute Autorité de Santé*), and CADTH (Canadian Agency for Drugs and Technologies in Health). HTAs were included if indicated for non-metastatic cancer. Database search was performed for the following interventions:

Table 1. List of interventions included in the literature search.

Drug class	Drug name
Checkpoint Inhibitors	Pembrolizumab (Keytruda) Nivolumab (Opdivo) Ipilimumab (Yervoy) Atezolizumab (Tecentriq) Durvalumab (Imfinzi)
CAR T-Cell Therapy	Axicabtagene ciloleucel (Yescarta) Tisagenlecleucel (Kymriah) Lisocabtagene maraleucel (Breyanzi)
Cytokines	Interferon-alpha Interleukin-2 (aldesleukin)
Monoclonal Antibodies	Rituximab (Rituxan) Trastuzumab (Herceptin) Cetuximab (Erbitux) Bevacizumab (Avastin) Blinatumomab (Blincyto) Catumaxomab (Removab)
Cancer Vaccines	Sipuleucel-T (Provenge) Bacillus Calmette-Guérin (BCG) vaccine
Oncolytic Virus Therapy	Talimogene laherparepvec (T-VEC)
Adoptive Cell Transfer	Tumor-infiltrating lymphocyte (TIL) therapy

HTAs were then reviewed in four main aspects:

1. The approach to model subsequent treatments (in which health states IO is used, and whether there are differences between treatments).
2. The assumption or restriction on using IOs as subsequent treatment and the basis of assumption.
3. The approach of modelling efficacy (how subsequent treatment affects efficacy).
4. How subsequent treatment affects costs.

The findings from literature reviews, especially the assumptions of IO rechallenge, were used to determine scenarios to be tested in the next step.

2.1.2 Cost-Effectiveness Model

In the next step, a cost-effectiveness model was built to test different IO rechallenge assumptions based on findings from literature review. To simplify the implementation, the model was built to reflect the NICE TA851 "Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of early and locally advanced non-metastatic triple-negative breast cancer".[22] Breast cancer was selected because it has the most relevant HTA submissions. Additionally, breast cancer has relatively good survival compared to other diseases, in the hope that it could reflect more impacts of IO scenarios on the survival in the metastatic stage. The model was built using data of the United Kingdom (UK) population.

1. **Patient Population**

   The patient population included in this model consisted of adults diagnosed with early stage triple negative breast cancer (TNBC) at high risk of recurrence. It is in line with patient characteristics based on the KEYNOTE-522 trial (Appendix A. Table 1). KEYNOTE-522 is a phase 3 trial evaluating the immune checkpoint inhibitor pembrolizumab plus neoadjuvant chemotherapy as compared with neoadjuvant chemotherapy alone, followed by the receipt of adjuvant pembrolizumab or placebo, respectively, in patients with early triple-negative breast cancer (KEYNOTE-522). Patients are included if they have previously untreated locally advanced non-metastatic TNBC according to AJCC staging criteria (T1c, N1-2 to T4T4a-d, N0-N2).[23]

2. **Model Structure**

   A 4-state semi-Markov (state-transition) cohort model was developed to reflect health outcomes and costs in the early-stage TNBC setting using Microsoft Excel® for Microsoft 365. This model uses a monthly cycle for simplifying purposes, and a time horizon of 51 years with half-cycle correction following the NICE TA851. Discount rate of 3.5% is applied on costs and utility. The model uses health-care perspective.[22] The health states and transitions in the model are illustrated in Figure 1 below. The model consists of four mutually exclusive health states; event-free (EF), locoregional recurrence (LR), distant metastasis (DM), and death. In the Markov and semi-Markov model, health statuses are represented as Markov states, and the movement of patients between health states are quantified by transition probabilities between states. While the transition probabilities in the Markov model are constant, in Semi-Markov

models, the transition probabilities change based on the amount of time that has passed.[25] This model was adopted because it can explicitly capture disease pathways of patients with early-stage TNBC as well as the functionality to model metastatic outcomes.

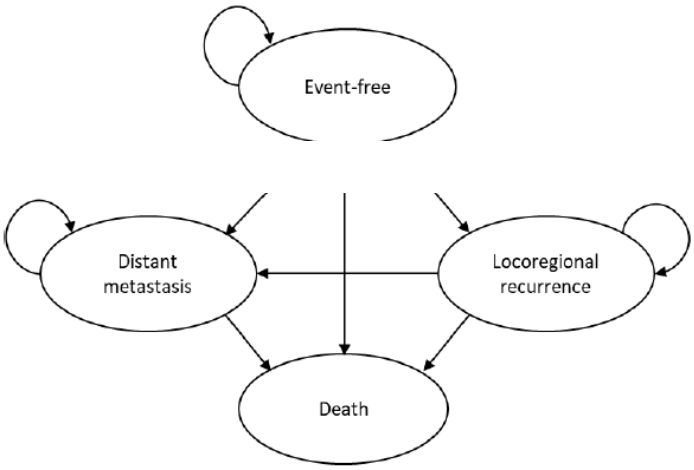

Figure 1. Cost-effectiveness model structure.

Patients begin in the “EF” health state. At the end of each cycle, patients from the “EF” state could stay in “EF”, transition to the “LR” state, transition to the “DM” state or die. Patients in the “LR” state could stay in the “LR” state, transition to the “DM” state, or die, but could not transition back to the “EF” state. Similarly, patients who are in the “DM” state could stay in the “DM” state or die but could not transition back to the “EF” or “LR” state. The “death” state is an absorbing health state in which no costs or benefits are accrued.

3. Intervention technology and comparators

The intervention for this model is pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab as a single regimen based on KEYNOTE-522. The standard neoadjuvant chemotherapy used in the KEYNOTE-522 was divided into two treatments. The first treatment was carboplatin in combination with paclitaxel, followed by the second treatment of either doxorubicin or epirubicin in combination with cyclophosphamide. Following surgery, adjuvant pembrolizumab monotherapy was administered.[22]

The pembrolizumab component was applied in the model based on the licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]) in the neoadjuvant and adjuvant phases. The neoadjuvant chemotherapy component was applied based on KEYNOTE-522:

carboplatin (AUC 5 Q3W on days 1, 8 and 15) and paclitaxel (80mg/m^2 weekly on days 1, 8 and 15) followed by doxorubicin (60mg/m^2 Q3W) or epirubicin (90mg/m^2 Q3W) and cyclophosphamide (600mg/m^2 Q3W).[22]

The comparators in this model are standard neoadjuvant and adjuvant therapy without pembrolizumab based on the placebo arm in the KEYNOTE-522 trial. The standard neoadjuvant chemotherapy regimen is the same as in the intervention arm. Placebo was administered for adjuvant regimen.[22]

2.2 Data Sources

The input parameters used in the model, including clinical parameters, utilities, and costs are obtained from the NICE TA851. However, since several data are not published, another TA with the same indication from HAS along with other sources are also used to complement the data.[26]

2.2.1 Clinical parameters and variables

1. Modelling transitions from event-free health state

Transition probabilities starting from the EF state were calculated based on survival analysis of individual patient-level data (IPD) of event-free survival (EFS) curve from the KEYNOTE-522 trial. IPD data was generated using the Graph Digitizer software. The EFS curve is then extrapolated until the end of the time horizon following the best fit distribution. Three transition probabilities were estimated from this survival function: EF to LR, EF to DM and EF to death. Then, the transition probability of each event occurring is estimated based on the extrapolated EFS data and the probabilities of experiencing LR, DM, or death as the first EFS event in each treatment arm derived from the KEYNOTE-522 clinical trial.[22] Because the data for the probability of experiencing LR, DM, or death as the first EFS event is not available in NICE TA851, it is taken from a similar TA submitted to HAS (Appendix A. Table 2).[26]

The cost-effectiveness model further assumed that the probability of the EFS event was constrained by the all-cause natural mortality. Therefore, the transition probabilities of EF → LR, EF → DM, and EF → death were calculated as follows:

- $TP_{EF \rightarrow LR}$ = TP_{EFS} event * probability of the first EFS event being LR
- $TP_{EF \rightarrow DM}$ = TP_{EFS} event * probability of the first EFS event being DM
- $TP_{EF \rightarrow death}$ = max(TP_{EFS} event * probability of the first EFS event being death, probability of death among the general population – $TP_{EF \rightarrow LR}$ – $TP_{EF \rightarrow DM}$).[22]

2. Modelling transitions from locoregional recurrence health state

The transition probabilities of LR→DM and LR→death were assumed to be constant based on the NICE TA851. The transition probabilities of LR→DM, and LR→death were calculated based on the transition probabilities of LR→DM or death, and the proportions of DM and death respectively. The transition probability of LR→DM or death is assumed to be independent from the treatment received in the locoregional setting. It was estimated based on exponential extrapolation of time from LR to DM or death.[22] Because the data of transition probability of LR→DM or death, as well as the proportions of patients experiencing DM or death from LR state is not available in NICE TA851, it is taken from a similar TA from HAS submission (Appendix A. Table 3).[26] Furthermore, the model constrained the transition probability of LR to DM or death by the all-cause natural mortality.[22] The all-cause mortality data according to sex and age was obtained from ONS UK database 2020 data.[27]

Therefore, the transition probabilities of LR → DM, and LR → death were calculated as follows:

- $TP_{LR \rightarrow DM} = TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of patients progressed from LR to DM
- $TP_{LR \rightarrow death} = \max(TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of death from LR, probability of death among the general population – TPLR→DM).

Secondary Analysis

To evaluate the impact of IO rechallenge assumption in the LR stage, secondary analysis was performed where treatment with IOs was assumed to be possible. In secondary analysis, the transition probability from the LR state is assumed to be time-independent. Similar to the approach considered in the primary analysis, the transition probabilities were calculated based on the relative efficacy and market shares of each subsequent treatment received in the LR state (Table 2). Not all patients were assumed to receive LR treatment, and the transition probability from the LR state to DM or death in patients who didn't receive treatment, as well as the proportion of TP from LR—> DM and LR—> death is assumed equal to the main scenario. To calculate TP in other treatments, the transition rate of patients receiving no treatments is multiplied with the HR of each LR treatment against placebo (Appendix A. Table 4). The HRs were taken from NICE TA837 Pembrolizumab for adjuvant treatment of resected stage 2 melanoma with high risk of recurrence.[28] It is noted that assuming similar efficacy of LR treatments for melanoma and TNBC is not clinically plausible, the assumption is made for simplifying purpose and aims to assess the impact of a hypothetical scenario where IO re-challenge is allowed earlier in the treatment pathway. As such, it was deemed acceptable for the purpose of this study.

Table 2. List of market shares of LR treatments under each IO rechallenge scenario.

1L treatment	Pembrolizumab arm			Chemo-therapy arm
	Pembrolizumab rechallenge is not allowed	IO rechallenge is fully restricted*	No IO restriction	
Pembrolizumab	0%	0%	24.0%	24.0%
Nivolumab	24.0%	0%	24.0%	24.0%
Dabrafenib + trametinib	32.0%	32.00%	32.0%	32.0%
No treatment	44.0%	68.00%	20.00%	20.0%

*In the scenario where IO rechallenge is allowed after 24 months from the start of adjuvant therapy, the market shares are the same as IO rechallenge is fully restricted when metastasis occurs within 24 months or the same as no IO restriction when metastasis occurs after 24 months.

3. Modelling transitions from distant metastasis health state

In the DM state, the model assumed that a proportion of patients would receive the 1L treatment for metastatic disease (62.5% in pembrolizumab arm and 70.3%in placebo arm), which were obtained from the KEYNOTE-522 trial.[26] The model used OS data from KEYNOTE-355 to estimate transition probabilities from DM to death.[22] The phase 3 KEYNOTE-355 trial examined the efficacy of pembrolizumab in enhancing the antitumor activity of chemotherapy, in patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer.[29] KEYNOTE-355 overall survival (OS) data is used due to the current immaturity of the KEYNOTE-522 OS data.

The mean OS in the DM state was estimated as a weighted average of mean OS of patients who received 1L treatments based on market share estimates, and patients who did not receive the 1L treatments. The average mean OS then extrapolated assuming exponential distribution to calculate the transition probability from DT to death. The list of 1L treatments followed the 1L treatments in the TA851.[22] While the mean OS for pembrolizumab was obtained from KEYNOTE-355, the mean OS for other treatments were calculated based on hazard ratio from network meta-analysis (NMA) by Haiderali et al (2024). This NMA assessed eight phase II/III clinical trial data and compared the efficacy of each treatment in metastatic TNBC to KEYNOTE-355.[30] The hazard ratios (HRs) were applied to the OS. Time of treatment in the metastatic setting was estimated based on the PFS data of KEYNOTE-355 for pembrolizumab, PFS data of IMpassion130 trial for atezolizumab, and time of treatment used in TA851 for chemotherapy.[24,31] IMpassion130 trial is a phase-III clinical trial assessing the efficacy of first-line atezolizumab plus nab-paclitaxel, as compared with placebo plus nab-paclitaxel, in patients with locally advanced or

metastatic TNBC.[31] The mean OS and time of treatment of each 1L treatment is presented in Appendix A. Table 5.

The market share of 1L treatments were estimated based on IO rechallenge assumption scenario and market shares of 1L treatments used in NICE TA886 Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893], as it is not provided in TA851.[32] The market share of anti PD-L1 followed the positive testing rate of PD-L1 38% reported in TA851.[22] Some assumptions need to be made for the market shares of treatments that are not available. Since the market shares distribution differs under different IO rechallenge scenarios, the average mean OS and transition probability also differs under different scenarios. There are four scenarios tested: Pembrolizumab rechallenge is not allowed, IO rechallenge is fully restricted, No IO restriction, and IO rechallenge allowed after 24 months from the start of adjuvant therapy. The list of 1L treatments and market shares of each treatment under three IO rechallenge assumptions scenarios are presented in Table 3.

Table 3. List of market shares of 1L treatments under each IO rechallenge scenario.

1L treatment	**Pembrolizumab arm**			**Chemotherapy arm**
	Pembrolizumab rechallenge is not allowed	**IO rechallenge is fully restricted**	**No IO restriction**	
Pembrolizumab + taxanes	0%	0%	19.00%	19.00%
Paclitaxel	13.00%	21.00%	13.00%	13.00%
Carboplatin	17.00%	26.00%	17.00%	17.00%
Carboplatin + paclitaxel	5.00%	11.00%	5.00%	5.00%
Gemcitabine + carboplatin	5.00%	11.00%	5.00%	5.00%
Atezolizumab + Nab-paclitaxel	38.00%	0%	19.00%	19.00%
Capecitabine	22.00%	31%	22.00%	22.00%

*In the scenario where IO rechallenge is allowed after 24 months from the start of adjuvant therapy, the market shares are the same as IO rechallenge is fully restricted when metastasis occurs within 24 months or the same as no IO restriction when metastasis occurs after 24 months.

4. Adverse events

Adverse events (AEs) experienced by patients were taken into account in the model to factor in the extra costs incurred. The incidence of AEs was obtained from

the KEYNOTE-522. The model only included all-cause Grade 3+ AEs (incidence rate ≥ 5%).22 The list of AEs included in the model along with their incidences are presented in Appendix A. Table 6.

2.2.2 Measurement and valuation of health effects

1. Utility

The utility value in each health state was taken from NICE TA886 Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893], as it is not provided in TA851.[32] It is presented in Appendix A. Table 7. The QALY gains in each health state were calculated as follows:

- $QALY_{EF}$ = Utility EF * EFSe
- AE-related QALY decrement = one-time grade 3+ AE utility decrement
- $QALY_{LR}$ = Utility LR * time spent in the LR state
- $QALY_{DM}$ = Utility DM * time spent in the DM state.[22]

2. Adverse reactions

The grade 3+ AE disutility was also included in the model. The disutility value of AE in EF state was taken from TA submitted to HAS with the same indication as TA851 NICE. It is estimated to be 0.021. The AE disutility is applied at the first cycle of the model.[26]

3. Age-related disutility

The TA851 adopted adjustment to the utility values based on age, age-squared, and gender, according to Ara et al.[22] The coefficients of linear regression used for adjustment are presented in Appendix A. Table 8.

2.2.3 Cost and healthcare resource use identification, measurement and valuation

1. Intervention and comparator drug acquisition costs

The unit costs and dosing of intervention and comparators in the model were taken from TA851. The drug acquisition costs were sourced from the British National Formulary, the Monthly Index of Medical Specialities and the electronic Market Information Tool (eMIT). The dosing and schedule followed the KEYNOTE-522 protocol.[22] The details of doses of intervention and comparators, as well as the drug acquisition costs are presented at table Appendix A. Table 9 and 10, respectively.

2. Subsequent treatment drug acquisition costs

Drug acquisition and administration costs of metastatic TNBC therapies were applied as one-time costs upon entry into the DM state.[22] The proportion of patients entering the DM state who receive an active 1L metastatic treatment was obtained from TA submitted to HAS for the same indication as TA851, as it is not presented in TA851. It is based on observation in KEYNOTE-522. The proportion is 62.5% in the pembrolizumab arm and 70.3% in the chemotherapy arm.[26] The total costs for each 1L metastatic treatment regimen were calculated as a function of the monthly drug acquisition costs (Appendix A. Table 10), mean treatment duration (Appendix A. Table 11) and administration costs (Appendix A. Table 12). Drug unit cost and dosing schedule were obtained from TA851.[22] For the LR treatments in secondary analysis, the drug acquisition costs and dosing schedule were taken from TA837.[28] Dosing schedule is presented at Appendix A. Table 9.

All patients who receive 1L treatments were also assumed to receive subsequent lines (2L, 3L and 4L) of treatments for the metastasis as a lump sum cost. They were obtained from NICE TA Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522]. The monthly cost of subsequent treatment lines is £1200. The total cost of subsequent treatment lines is obtained by multiplying the monthly cost and duration of treatment of each treatment (Appendix A. Table 13.)

3. Drug administrations costs

Administration costs included in the model depend on the type of treatment and its complexity (Appendix A. Table 12). Administration costs are taken from TA851.[22] For the LR treatments in secondary analysis, the drug acquisition costs and dosing schedule were taken from TA837.[28]

4. Health-state unit costs and resource use (HSRU)

HSRU components and unit costs were taken from TA851. It consists of disease management costs, terminal care and end-of-life costs. Recurring disease management costs were accrued to the event-free, locoregional recurrence and distant metastasis states. The event-free state was divided into 4 stages: year 1-3, year 4-5, year 6-10, year 11+ to reflect the decreased resource use with the length of time spent in the event-free state. The frequency of resource use per health state is multiplied by the respective medical unit cost to calculate the total cost applied in each

model cycle per health state. The list of the disease management resource use costs used is presented at Appendix A. Table 14. The frequency of recurring resource use is shown in Appendix A. Table 15. Additional health care resource use for the first year in the event-free state is also added to reflect the resource use during treatment (Appendix A. Table 15). Additional one-off cost of £474.76 is applied for the locoregional recurrence and distant metastasis states in the first model cycle to reflect the resource use related to disease diagnosis. To reflect the additional costs associated with terminal and palliative care, a lump-sum cost of £8,347.03 is also added at the time of death.[22]

5. **Adverse reaction unit costs**

Unit costs related to the management of AEs are taken from TA851 and are presented at Appendix A. Table 17. They were obtained from the NHS Reference Costs 2019/20. The AE management cost is applied one time at the first model cycle for simplicity in each of the treatment arms.[22]

6. **Procedure costs**

Procedure cost consists of surgery and radiotherapy. Surgery costs were applied within the model as a one-time cost before the start of adjuvant therapy, and were calculated based on the unit costs of surgery and the proportion of patients receiving surgery in each treatment arm. The unit cost of surgery and the proportion of patients undergoing surgery were taken from TA851. Similarly, radiotherapy costs were applied one time during adjuvant treatment and were calculated based on the unit costs of radiotherapy and the proportion of patients receiving it in each treatment arm. The unit cost of radiotherapy was taken from TA866, and the proportion of patients receiving radiotherapy were taken from TA submission for HAS with the same indication as TA851. The unit cost of procedures and the proportion of recipients are presented at Appendix A. Table 1.

2.3 Statistical Analysis

2.3.1 Survival Extrapolation of PFS from KEYNOTE-522

The survival curve fitting was conducted following the NICE DSU guidelines. To extrapolate the endpoints from the trial until the end of time horizon, standard parametric

models were fitted to the IPD EFS data of the pembrolizumab arm and placebo arm in the KEYNOTE-522 trial. The analysis was performed in R using *survival, flexsurv* and *survreg* packages. The following steps were performed for curve fitting:

- The assumption of proportional hazard (PH) was tested using cumulative hazard plots.
- If the PH assumption was proven correct, the data from both treatment arms were going to be fitted in the same model. All standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma) were considered and compared. If the PH assumption was wrong, independent separate survival models were explored, in which models were separately fitted to each treatment arm.
- Visual inspection was used to assess the fit of the fitted curves to the observed clinical trial data among various parametric survival models. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to help identify the most appropriate survival models.

After the best parametric survival model was chosen, extrapolation of the survival curve was conducted following the chosen parametric distribution. The extrapolation was performed using "*predict*" function in R.

2.3.2 Mean OS Calculation from KEYNOTE-355

Mean OS data of the pembrolizumab arm from KEYNOTE-355 was used to calculate the transition probability in the metastatic setting. Firstly, the IPD data was constructed to obtain the Kaplan Meier curve. Then, it is extrapolated assuming exponential distribution. The area under the OS curve (restricted mean survival time) was then estimated using integration. The analysis was performed in R.

Results

3.1 Targeted Literature Review

A total of 27 HTAs fulfilling the inclusion criteria were found on NICE, HAS, and CADTH databases. The summary of disease areas and sources is presented below (Table 4). The details of data extractions from each TA were provided in Appendix B. Table 1.

Table 4. Summary of HTAs sources.

Disease area	NICE	CADTH	HAS	Total TAs
Breast cancer	4	5	2	11
Lung cancer	3	3	1	7
Melanoma	1	1	1	3
Urothelial carcinoma	1	1	1	3
Renal cancer	1	1	0	2
Gastrointestinal cancer	1	0	0	1

3.3.1 Subsequent treatment approach and IO rechallenge assumptions

Summary of the results from literature review is reported in Table 5. Out of 27 TAs, 13 (48%) allows IO rechallenge only in metastatic setting while 7 (26%) allows IO rechallenge in both locoregional and metastatic setting. Three TAs (NICE TA817[33], HAS 2022[34], CADTH PC0253[35]) don't allow IO rechallenge at all while one TA allows only in locoregional settings (CADTH PC0050[36]). Among those that allows IO rechallenge, 9 TAs allows rechallenge with time restrictions in regards to previous treatment initiation: at least 18 months after previous treatment initiation (4 TAs), 24 months (3 TAs), 36 months (1 TA) and 6 months after the last treatment (2 TAs). Two breast cancer TAs allow rechallenge only in the PD-L1 positive population (Table 5).

In general, assumptions regarding subsequent treatment are accepted by the reviewer. Indeed, 7 TAs were criticized because of the uncertainty of subsequent treatment distribution (Table 5). Three TAs were criticized because of limited evidence of retreatment restriction while 7 TAs were criticized for their choice of Io rechallenge assumption (Table 5). For example, reviewers criticized the lack of explanation whether trastuzumab emtansine use in early stage could modify the treatment sequences at the metastatic stage (HAS, 2020)[37], the assumption of using atezolizumab instead of pembrolizumab in IO-eligible population (NICE TA851[22]), and the prohibition of atezolizumab rechallenge in LR setting (CADTH PC0269[38]). Reviewer also stated in one TA that treatment eligibility should also depend on time of recurrence in the LR state, not only in the metastatic stage (CADTH PC0286[39]).

IO rechallenge is also tested in scenario analysis. In general, prohibiting IO rechallenge or extending restriction decreased the ICER while allowing IO rechallenge increased the ICER.

For example, a significant change is observed in NICE TA876, in which the extension of IO rechallenge restriction from 6 to 12 months decreased the ICER by 42% while the removal of IO rechallenge restriction increased the ICER by 72%.[40] However, an exception is reported in NICE TA837, in which prohibiting pembrolizumab rechallenge in the metastatic stage increased the ICER by 40%.[28] Changing the type of IO also influences the ICER. In NICE TA851, changing 50% of IO from atezolizumab to pembrolizumab increased ICER by 42%.[22]

3.3.2 Approach to model efficacy and cost of subsequent treatments

The summary of approach to model efficacy and cost subsequent treatments is detailed at Table 5. Generally, the method to model efficacy corresponds to the method in modelling costs of subsequent treatments. However, one TA was criticized due to inconsistency of the method in estimating cost and modelling of post-progression state (HAS, 2019[41]).

In modelling efficacy in the metastatic stage, the majority of TAs relied on OS per subsequent treatment or its surrogate while some TAs didn't differentiate efficacy based on subsequent treatment received. Most TAs used mean OS (12 TAs) or median OS (2 TAs) per subsequent treatment. Similarly, two TAs adopted PFS and post-progression survival (PPS) as surrogate of OS while one TA used time spent in distant-metastasis free survival (DMFS) as surrogate of OS. In contrast, three TAs applied mean OS without being affected by treatment distribution (Table 5).

Only a few TAs explained the methods to model efficacy in the LR recurrence state. Two TAs used survival probabilities directly from clinical trial data while other two TAs adopted HRs of DMFS failure for each adjuvant treatment. Meanwhile, two TAs didn't rely on efficacy per treatment to calculate TP (Table 5).

In calculating the cost of subsequent treatment, the majority of TAs (13) used weighted average costs based on market shares of each 1L metastatic treatment while four TAs used treatment proportion from clinical trials. To estimate duration of treatment, six TAs reported using mean PFS per subsequent treatment in cost calculation (Table 5).

The external validation of survival extrapolation is well accepted by reviewers in most TAs. However, several TAs were criticized for poor survival validation. For example, four TAs were found lacking external validity. Moreover, two TAs were criticized for their assumption and methods of extrapolation which lead to overestimation of survival. Reviewers also commented about the difficulty in validating survival data. For instance, they criticized data immaturity in one TA, and the lack of literature as an external source in three TAs (Table 5).

Table 5. Summary of results from literature review.

Characteristics	HTAs
Subsequent treatment approach	
IO rechallenge in both LR and metastatic setting	NICE TA424, NICE TA569, NICE TA632, HAS Trastuzumab-emtansine as adjuvant for HER2-positive breast cancer, NICE TA837, NICE TA837, CADTH PC0286, HAS Pembrolizumab as adjuvant for melanoma
IO rechallenge only in metastatic setting	NICE TA851, HAS Pembrolizumab as neoadjuvant for TNBC, CADTH PC0241, CADTH PC0127, CADTH PC0182, CADTH PC0269, CADTH PC0131, HAS Durvalumab as monotherapy for unresectable NSCLC, NICE TA876 , CADTH PC0303, NICE TA830, CADTH PC0237, CADTH PC0272
IO rechallenge only in locoregional settings	CADTH PC0050
IO rechallenge fully prohibited	NICE TA817, HAS Nivolumab as adjuvant for urothelial carcinoma, CADTH PC0253
IO rechallenge assumption	
At least 18 months after treatment initiation	CADTH PC0241, CADTH PC0286, HAS Pembrolizumab as adjuvant for melanoma, CADTH PC0237
At least 24 months after treatment initiation	NICE TA851, HAS Pembrolizumab as neoadjuvant for TNBC, NICE TA837
At least 6 months after treatment initiation	NICE TA830
Only in the PD-L1+ population	NICE TA876, CADTH PC0303
Criticisms related to IO rechallenge and subsequent treatment	
Uncertainty of subsequent treatment distribution	HAS Pembrolizumab as neoadjuvant for TNBC, CADTH PC0127, NICE TA876, HAS Pembrolizumab as adjuvant for melanoma, CADTH PC0286, NICE TA830, CADTH PC0272
Limited evidence of retreatment restriction	CADTH PC0131, NICE TA876, NICE TA830
IO rechallenge assumption	CADTH PC0127, CADTH PC0182, HAS Trastuzumab emtasine as adjuvant for HER2-positive, NICE TA851, CADTH PC0269, CADTH PC0286
Inconsistency of methods	HAS Durvalumab as monotherapy for unresectable NSCLC without progression after chemotherapy
Efficacy approach in DM state	
Use of mean OS per subsequent treatments	NICE TA851, HAS Pembrolizumab as neoadjuvant for TNBC, NICE TA424, CADTH PC0241, NICE TA569, CADTH PC0127, NICE TA823, NICE TA837, CADTH PC0286, HAS Pembrolizumab as adjuvant for melanoma, NICE TA817
Use of median OS per subsequent treatments	NICE TA830, CADTH PC0237
Use of OS surrogate	NICE TA632, HAS Trastuzumab emtasine as adjuvant for HER2-positive breast cancer, CADTH PC0272
Use of mean OS without treatment distribution	CADTH PC0131, CADTH PC0303, HAS Nivolumab as adjuvant for urothelial carcinoma
Efficacy approach in LR state	
Use survival probabilities from clinical trial	NICE TA424, NICE TA569
Used HRs of DMFS failure	NICE TA837, CADTH PC0286
Didn't use efficacy per treatment	HAS Trastuzumab-emtasine as adjuvant for HER2-positive breast cancer, HAS Pembrolizumab as adjuvant for melanoma
Costing approach in DM state	
Use weighted average costs based on market shares	NICE TA851, HAS Pembrolizumab as neoadjuvant for TNBC, NICE TA569, CADTH PC0127, NICE TA632, HAS Trastuzumab emtasine as adjuvant for HER2-positive breast cancer, NICE TA876 , NICE TA837, CADTH PC0286, HAS Pembrolizumab as adjuvant for melanoma , NICE TA830, CADTH PC0237
Use treatment proportion from clinical trials	NICE TA424, CADTH PC0131, HAS Durvalumab as monotherapy for unresectable NSCLC without progression after chemotherapy, CADTH PC0272
Criticism to survival extrapolation	
Lacking external validity	CADTH PC0279, HAS Nivolumab as adjuvant for urothelial carcinoma, CADTH PC0286, CADTH PC0237
Incorrect assumption and methods of extrapolation	NICE TA823, CADTH PC0131
Data immaturity	NICE TA798
Lack of external source	HAS Pembrolizumab as neoadjuvant for TNBC, NICE TA632, NICE TA823

3.2 Cost-Effectiveness Modelling

3.2.1 Extrapolation of PFS Keynote-522

Since the assumption of proportional hazard was not met, the PFS curves of Pembrolizumab and Chemotherapy were fitted separately. The result of survival curve fitting of the PFS for Pembrolizumab and Chemotherapy arm from KEYNOTE-522 is presented at figure 2A and 2B, respectively. The corresponding AIC and BIC values of each parametric distribution were detailed in Table 6. Based on AIC and BIC value, generalized gamma was chosen as the best fit for both treatment arms. Visual inspection of survival curve fitting showed that the fitted curve reflected the original curve pretty well.

Figure 2A (left) and 2B (right). Curve Fitting of PFS from KEYNOTE-522 for Pembrolizumab (2A).

Table 6. AIC and BIC of curve fitting of PFS KEYNOTE-522.

Distribution	Pembrolizumab		Chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	1576	1580	1113	1117
Weibull	1578	1587	1113	1121
Gompertz	1574	1583	1114	1122
Lognormal	1564	1573	1103	1111
Log logistic	1575	1584	1110	1118
Generalised Gamma	**1554**	**1568**	**1100**	**1112**
Gamma	1577	1587	1112	1120

The extrapolation of the PFS curve for pembrolizumab and Chemotherapy arm from KEYNOTE-522 is presented at Figure 2A and 2B, respectively. Both curves were extrapolated using generalized gamma distribution.

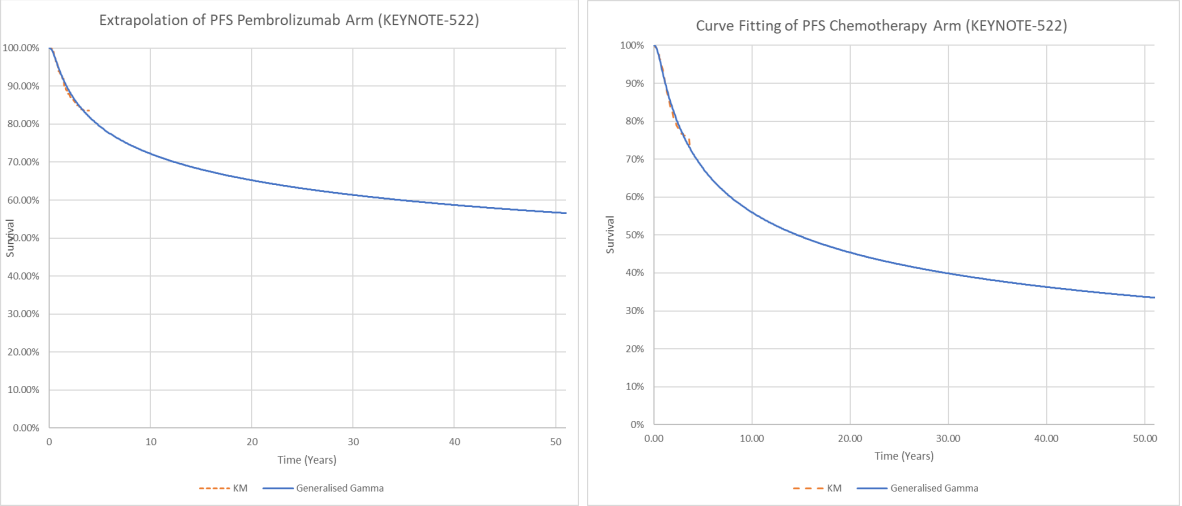

Figure 2A (left) and 2B (right). Extrapolation of PFS KEYNOTE-522 Pembrolizumab (2A) and Chemotherapy (2B) arm.

3.2.2 Mean OS of Metastatic Treatments

Using the area under the OS curve of pembrolizumab from KEYNOTE-355, the mean OS of pembrolizumab was estimated at 28.4 months. Mean OS of other 1L metastatic treatments were calculated using HR and were presented at Table 7. Pembrolizumab + taxanes had the longest OS followed by Atezolizumab + nab-paclitaxel, while carboplatin monotherapy had the shortest OS.

Table 7. Mean OS of 1L metastatic treatments.

1L treatment	Mean OS (months)
Pembrolizumab + taxanes	28.4
Paclitaxel	15.4
Carboplatin	10.1
Carboplatin + paclitaxel	12.3
Gemcitabine + carboplatin	12.3
Atezolizumab + Nab-paclitaxel	20.0
Capecitabine	15.4
No treatment	5.1

3.2.3 Survival Comparison

The survival result of the economic model was presented. Each of the IO rechallenge scenarios were treated as separate comparators. They differ only in OS result due to the difference in metastatic treatment efficacy. It is shown that pembrolizumab has better PFS than chemotherapy alone (Figure 3). The median PFS of pembrolizumab and chemotherapy is 336 months and 165 months, respectively. The mean time spent in the EF state is 296 months in the pembrolizumab group and 223 months in the placebo group. In the LR

recurrence state, the mean time spent is 15 months vs 9 months pembrolizumab and chemotherapy group, respectively.

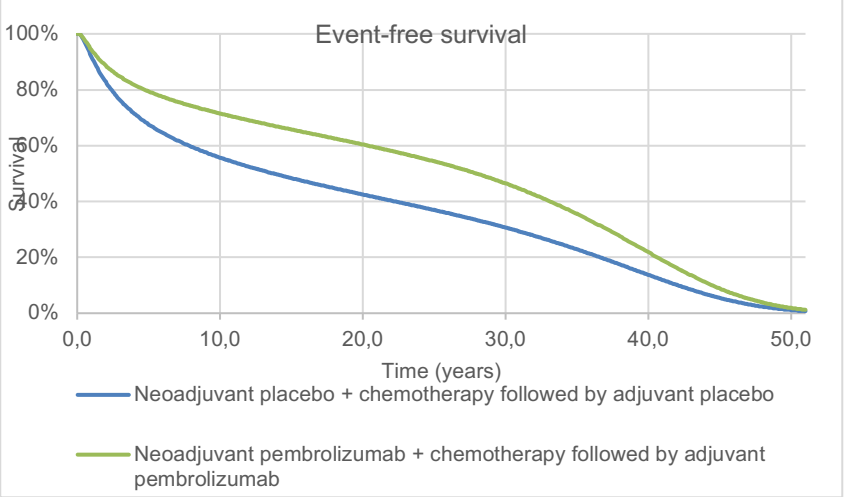

Figure 3. State occupancy of event-free health state of Pembrolizumab and Chemotherapy from economic modelling.

The OS and mean time spent in DM state of all comparators are presented below (Table 8). Overall, the OS of chemotherapy was lower than pembrolizumab in all IO rechallenge scenarios while the mean time spent in DM state is longer. The OS and mean time spent in DM state only differs slightly between all scenarios.

Table 8. Overall survival of all comparators from economic modelling.

Year	Pembrolizumab rechallenge is not allowed	IO rechallenge is fully restricted	No IO restriction	IO rechallenge permitted after 2 years	Chemo-therapy
1	98.43%	98.38%	98.44%	98.38%	98.62%
5	86.96%	86.47%	87.16%	86.54%	80.76%
10	76.69%	76.29%	76.91%	76.47%	64.76%
15	69.21%	68.96%	69.38%	69.09%	54.24%
20	62.73%	62.57%	62.85%	62.65%	46.39%
Median OS	345 months	344 months	345 months	345 months	211 months
Mean time in DM state	6 months	5 months	7 months	6 months	10 months

3.2.4 Utility, Cost, and Cost-Effectiveness Comparison

The details of discounted QALY value in each health state and comparators were provided in Appendix B. Table 2. Overall, pembrolizumab resulted in higher QALY than chemotherapy in all IO rechallenge scenarios. The QALY difference is not significant between

all IO scenarios. No IO restriction produced the highest QALY while full restriction produced the lowest.

On the other hand, chemotherapy was associated with the lowest cost, mainly due to far lower drug acquisition cost in the neoadjuvant and adjuvant settings. Among all IO scenarios, not allowing only pembrolizumab rechallenge had the highest cost, while fully restricting IO rechallenge had the lowest. The differences in cost among all IO scenarios were contributed mainly from the drug acquisition cost in the metastatic setting, followed by HCRU costs in the metastatic stage. The breakdowns of cost components in each comparator are reported in Appendix B. Table 3.

Table 9. Comparison of ICER between all scenarios.

Comparator	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	ICER change
Chemotherapy	79,110	10.331	-	-	-	NA
IO rechallenge is fully restricted	168,806	12.598	89,696	2.27	39,563	-2.35%
IO rechallenge permitted after 2 years	171,426	12.610	92,315	2.28	40,517	-
No IO restriction	173,244	12.651	94,134	2.32	40,580	0.15%
Pembrolizumab rechallenge is not allowed	173,449	12.633	94,338	2.30	40,986	1.04%

The comparison of ICER among all comparators is shown at Table 9. Among all IO scenarios, full restriction of IO rechallenge was the most cost-effective. On the contrary, restriction of only pembrolizumab rechallenge resulted in the highest ICER. The difference of ICER between the highest and the lowest is £1,423.20 or 3.6% difference compared to the lowest ICER.

3.2.4 Secondary Analysis

For secondary analysis, the results of discounted QALY are presented at Appendix B. Table 4. Overall, pembrolizumab resulted in higher QALY than chemotherapy in all IO rechallenge scenarios. The QALY difference is not significant between all IO scenarios. No IO restriction produced the highest QALY while full restriction produced the lowest.

On the other hand, chemotherapy was associated with the lowest cost. Among all IO scenarios, no IO restriction had the highest cost, while fully restricting IO rechallenge had the lowest. Compared to the main analysis, the cost difference in secondary analysis is lower. This is because even though treatment cost in neoadjuvant and adjuvant settings is higher in the pembrolizumab arm, the cost of LR treatment is larger in the chemotherapy arm, due to

higher LR recurrence in the chemotherapy arm. The differences in cost among all IO scenarios were contributed mainly from the drug acquisition cost in the LR and metastatic setting. The breakdowns of cost components in each comparator are reported in Appendix B. Table 5.

The comparison of ICER in all scenarios are shown at Table 10. Among all IO scenarios, full restriction of IO rechallenge was the most cost-effective. On the contrary, no IO restriction resulted in the highest ICER. In comparison to the main analysis, the ICER change is significantly larger. Compared to restricting only pembrolizumab rechallenge, no IO restriction increased the ICER by 46% while full restriction reduced the ICER by 45%.

Table 10. Comparison of ICER between all scenarios.

Comparator	**Total costs (£)**	**Total QALYs**	**Incremental cost (£)**	**Incremental QALYs**	**ICER (£)**	**ICER change**
Chemotherapy	£174,291	10.426	-	-	-	NA
IO rechallenge is fully restricted	£193,189	12.662	£18,897	2.24	£8,451	-45.2%
Pembrolizumab rechallenge is not allowed	£209,945	12.736	£35,653	2.31	£15,437	-
IO rechallenge permitted after 2 years	£217,044	12.702	£42,752	2.28	£18,786	21.7%
No IO restriction	£227,555	12.793	£53,263	2.37	£22,502	45.8%

Discussion

4.1 Importance of Shifting IOs Earlier in the Treatment Pathway

IO has become part of the standard of care (SoC) in the treatment pathways of cancer in the metastatic stage thanks to its high effectiveness. Because of its success, IO then started to be studied to use in earlier cancer stages. In 2016, pertuzumab was the first IO approved for early-stage cancer that was approved by NICE as neoadjuvant treatment for HER2-positive breast cancer.[42] Today, many IOs have proven successful for use in non-metastatic cancer. As more IOs are expected to be approved for earlier cancer stages, questions about re-treatment of patients in the later settings where IOs are now SoC remains unanswered.

There is a lack of clinical evidence to suggest how re-treatment will be handled. Moreover, there is limited evidence of the overall impact of re-treatment on patients. A review by Hu et al. (2023) indicated that ICI rechallenge using the original regimens of CTLA-4 or PD-1/PD-L1 inhibitors is advantageous for patients. Furthermore, other studies found that it was safe and effective to switch to different PD-1/PD-L1 inhibitors. However, outcomes were inconsistent.[18] Watanabe et al. reported that switching to different PD-1/PD-L1 inhibitors did not demonstrate clinical benefits.[43] Additionally, it's still questionable whether the efficacy of IO in the metastatic stage is comparable among IO-naive patients and rechallenged patients. A study by Eggermont et al (2021) found that in patients initially treated with pembrolizumab or placebo for stage III melanoma, the efficacy in the pembrolizumab rechallenged group is lower compared to crossover group, with median PFS 8.5 months vs 4.1 months, respectively.[44] More studies are needed to compare the efficacy of IO in these settings.

Question remains on the ideal time interval between two IO courses. In the real-world clinical setting, there should be a time-interval between the initial treatment and rechallenge. For example with ICIs, the drug from the initial treatment could still be present in the patients' blood circulation if the rechallenge is given too early, because some ICIs have long half-lives.[18] To date, the evidence on this topic is sparse. Cybulska et al. studied patients with advanced melanoma who were rechallenged with ipilimumab after the initial anti-PD-1 antibody treatment with median time interval 4 weeks. They did not find a correlation between the length of rechallenge intervals with median PFS, median OS, or immune-related adverse events (irAEs), in patients with advanced melanoma who were rechallenged with ipilimumab after the initial anti-PD-1 antibody treatment.[45] In contrast, NiKi et al. found that among patients with advanced NSCLC who received ICI rechallenge with the same drug, those who responded to rechallenge had a shorter treatment interval than those who did not (1.6 vs. 4.7 months), suggesting that the immunological memory from the initial treatments could persist after the treatment ends.[46]

Moreover, early IO treatment may also mean cure for some patients. Consequently, the clinical profile of patients who end up with late-stage disease may also change. This could alter the survival and efficacy of treatment in the later stage, and remains as an important clinical point to be assessed.

4.2 Summary of Findings from Literature Review

Overall, IO rechallenge is allowed in the majority of TAs submitted for early-stage cancer. However, the approaches and assumptions used vary widely across TAs. In most TAs, rechallenge is applied only in the metastatic setting and restricted at least 18 months or 24 months after the initiation of IO in the previous stage. Most TAs based their approach of retreatment restriction on clinical expert opinion because there is limited clinical evidence to rely on. Overall, this assumption is accepted by the reviewer. Nevertheless, it's important to note that several criticisms arose regarding limited evidence of retreatment restriction. Retreatment restriction affects the subsequent treatment distributions. Majority of TAs estimated subsequent treatment distribution according to market research and clinical expert opinion. This subjectivity led to high uncertainties and also received a number of criticisms.

Similar to the IO rechallenge approach, the methods adopted to calculate the TP and costs in the post-progression states varied across TAs. To calculate TP in the metastatic stage, most of the TAs used mean OS or median OS per subsequent treatment, or its surrogate, weighted according to distribution of 1L metastatic treatment. To estimate the cost of subsequent treatment, the majority of TAs calculated weighted average costs based on market shares of each 1L metastatic treatment while some TAs used treatment proportion directly from clinical trials. On the other hand, some TAs didn’t incorporate information of subsequent treatments to calculate TP, notably in LR recurrence state, but then calculated the costs based on market shares of subsequent treatments. Indeed, this inconsistency in the method to estimate cost and to model the post-progression state was criticized. As there are large uncertainties on the components of TP calculation, external validation of the resulting survival and state occupancy becomes critical. Although there is no large deviation in the external validation in the majority of TAs, some TAs were criticized due to poor comparison of their survival with external study. Moreover, reviewers highlighted the difficulty in assessing the validity of some TAs due to lack of external study available.

4.3 Summary of Findings from Cost-Effectiveness Model

This study conducted a cost-effectiveness model taking NICE TA851 as a reference. Breast cancer was selected among other indications because it has the most relevant TAs submission. Additionally, breast cancer has relatively good survival among other cancers so

it is expected that a significant proportion of patients would transition to the metastatic stage. Consequently, it is hoped that the impact of different IO restriction scenarios on survival and costs would be better captured. TA851 was specifically selected because it used a relatively simpler model compared to other breast cancer TAs.

In the main analysis, IO restrictions were only applied in the distant metastasis state. The results showed that the different IO restrictions approach didn't affect the ICER significantly. Fully restricting IO only decreased the ICER slightly while removing IO restrictions completely almost didn't affect the ICER. The ICER difference is mainly driven by the changes in the costs in the metastatic stage, in which full IO restriction costs the least. The cost difference is contributed primarily by the absence of IO's high cost, and its shorter duration of treatment thanks to shorter PFS in patients receiving subsequent chemotherapy compared to subsequent IO. This result is somewhat aligned with the findings in the literature review which found that generally IO restrictions decreased the ICER.

In contrast, the secondary analysis showed that IO restriction approaches impacted the ICER more significantly. Compared to restricting only pembrolizumab rechallenge, no IO restriction increased the ICER by 46% while full restriction reduced the ICER by 45%. The ICER difference is primarily contributed by higher costs in the LR recurrence state when allowing IO rechallenge, added by the higher costs in DM state. The cost difference in the LR recurrence state is more than the cost changes in the DM state because the state occupancy in the LR recurrence state is larger than in the DM state.

Interestingly, the IO restriction approach almost didn't impact the result in survival or utility, both in main analysis or secondary analysis. Possibly, this is because the overall survival is mainly influenced by the survival in the EF state rather than the survival in the LR recurrence and DM state. In this study, patients in the pembrolizumab arm, in all IO rechallenge scenarios, had a median PFS of 336 months and median OS 345-346 months. Hence, the difference in the survival in the LR recurrence or DM state became negligible compared to OS. The resulting changes in survival and utility could be different with diseases with shorter PFS. For comparison, a real-world study by Samlowski et al. (2022) reported that in stage IIB-IIC melanoma patients who are completely resected, the median PFS was 49.8 months and the median OS was 117.6 months.[47] The result could even be more notable in diseases with poorer survival. Provencio et al. reported the median PFS and OS of stage IIIA NSCLC patients to be 37 months and 10 months, based on a nationwide cohort study in Spain.[48]

It is difficult to perform external validation of the EFS and OS due to the lack of long-term real-world study of early TNBC patients. One real-world study by Lucas et al. (2024) conducted a retrospective study of early TNBC patients (stage I-III) in the UK with median

follow-up 6.5 years, and reported an OS of 79% (95%CI: 77-80%) at 5 years. The 5-year EFS was 89%, 81% and 51% for stages I, II, and III, respectively.[49] The OS at 5 years of the chemotherapy group (81%) in this study corresponds pretty well with Lucas et al. study. The PFS at 5 years in the chemotherapy group (68%) could not be validated because there is no study that reported aggregated PFS data.

The findings in this study indicate that the impact of IO restriction approaches on ICER could be significant and may potentially change the reimbursement decision. Furthermore, the impact on the ICER is influenced by several factors. Firstly, the impact will be augmented if IO rechallenges are applied in both DM state and LR recurrence state compared to only in the DM state, as the differences in costs and utility would be accumulated. Secondly, the changes on ICER will theoretically be larger if IO rechallenge is applied in the earlier stage of progression where patients spend longer time, rather than in the end stage of disease where only a small number of patients remains and little time is spent in the state. Thirdly, the natural progression of disease also influences the outcome. The impact of IO restriction would be more prominent in diseases with shorter PFS as more patients would transition to the later stage of disease. Hence, the amount of time spent in later stages would matter more to the overall survival. Consequently, the differences in utility and costs would also become more significant.

4.4 Strengths, Limitations

This is a first study that conducted a comprehensive review on HTA submissions assessing IO therapies in early-stage cancer and identify methods used to model the IO rechallenge assumptions post progression and any related criticism. The findings on this review is important to suggest future pharmacoeconomic models on determining IO retreatment approaches. The findings from literature review is then complemented by a cost-effectiveness model dedicated to test the impact of IO rechallenge scenarios in different stages of diseases, on the ICER.

The limitation of this study is the limited data available for some input parameters, especially the subsequent treatment distributions. Moreover, the treatment in the LR recurrence stage is mainly based on assumption and didn't reflect the actual treatment pathway. Other assumptions were also made for other parameters. The utility is taken from another TA with a different indication, and based on a study of the general breast cancer population instead of TNCB. This is because there is no open-access data on utility from the KEYNOTE-522 trial and TA851. Additionally, the cost data were taken directly from the respective TAs without adjusting to inflation. Therefore, the ICER generated in this study doesn't accurately reflect the actual value of the respective indication. Nevertheless, the

assumptions made in this model are still deemed acceptable because the purpose of this study is not to evaluate accurately the ICER of an intervention but to compare the differences in ICER as a result of IO rechallenge approaches.

4.5 Recommendations for Future Research and HTA Agencies

As this study proves that IO rechallenge approaches could impact the ICER significantly, it suggests that more attention needs to be given in considering the IO rechallenge approaches in a pharmacoeconomic model. Further studies to test the impact of IO rechallenge approach in other diseases are recommended to explore the outcome in different survival profiles. Additionally, this study highlights the need for more studies evaluating the efficacy of IO rechallenge and related aspects, such as the ideal time interval of rechallenge, and compatibility of efficacy when rechallenge is performed with different IO agents. Therefore, it is hoped that the approach of IO rechallenge in pharmacoeconomic models could be determined more objectively. Furthermore, more real-world studies that evaluate the natural history of cancers, for which IOs are indicated in the early stage, are needed to provide the reference for external validation of models. These are important to reduce the amount of uncertainty in models. Additionally, it is suggested that the HTA agency publishes recommendations on this issue to promote more conformity and comparability in future HTA submissions.

Conclusion

This study provides a review of the IO rechallenge approach in HTAs submitted for early-stage cancer, as well as evaluates the impact of different IO rechallenge scenarios in the LR recurrence and DM state, on the cost-effectiveness result. From the literature review, it is found that IO rechallenge is generally applied in the previous HTAs and is accepted by HTA agencies. However, the approach used varies widely in terms of IO restrictions, and the approach to model efficacy and cost in post-progression states. A number of criticisms were given, especially regarding uncertainty in subsequent treatment distribution, IO restrictions, and limited evidence of IO restrictions.

The impact of the IO rechallenge approach on the ICER was then evaluated in the cost-effectiveness model. It is proven that different IO restriction scenarios in the LR recurrence setting significantly alter the ICER while its impact in the DM setting is not significant. In line with findings from the literature review, stricter IO restrictions decreased the ICER. These findings indicate that the IO rechallenge approach is an important factor in pharmacoeconomic models. Furthermore, its impact is augmented if it is applied in both the LR recurrence state and DM state. Possibly, a similar pattern may potentially be observed if applied at an earlier stage of disease or in a disease with high metastatic recurrence rate.

Further research to test similar impact on other diseases with different survival profiles is recommended. Given the lack of clinical evidence, more studies evaluating the efficacy of IO rechallenge and the ideal rechallenge interval are warranted to provide an objective basis in determining the correct IO rechallenge approach. Moreover, more real-world studies assessing the clinical outcome of patients in this indication are needed as a source for external validation. Finally, HTA agencies are suggested to publish recommendations leading to more conformity and comparability in future HTA submissions.

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Appendix

Appendix A. Data Sources.

Table 1. Baseline characteristics of the population in the cost-effectiveness model.

Patient characteristics	Value	Source
Age (years), median (min-max)	49.0 (22 - 80)	KEYNOTE-522[24]
Weight (kg), mean (SD)	69.67 (16;28)	
BSA (m^2), mean (SD)	1.76 (0.21)	
Proportion of female* (%)	100	

*Even though a male subject was enrolled in the trial, it is assumed that all patients are female for simplicity.

Table 2. Probability of the first EFS event.[26]

Treatment arm	Year 1			Year 2+		
	%LR	%DM	%Death	%LR	%DM	%Death
Pembrolizumab	36.5%	48.1%	15.4%	26.8%	63.4%	9.9%
Placebo	44.8%	51.7%	3.4%	28.1%	64.1%	7.8%

Table 3. Transition probability and proportions of transitions from LR state.[26]

Treatment arm	Proportion		Transition probability
	LR—> DM	LR—> death	LR—> DM or death
Pembrolizumab	90%	10%	0.0133
Placebo			

Table 4. List of LR treatments and HR.

1L treatment	**HR**	**Reference**
No treatment	-	-
Pembrolizumab	0.60	No treatment
Nivolumab	0.60	No treatment
Dabrafenib + trametinib	0.55	No treatment

Table 5. List of 1L treatments, HR and time of treatment.

1L treatment	**HR**	**Reference**	**Duration of treatment (months)**
Pembrolizumab + taxanes	-	-	7.5
Paclitaxel	1.85	Pembrolizumab	5.6
Carboplatin	1.52	Taxanes	5.6
Carboplatin + paclitaxel	1.25	Assumed the same as gemcitabine +carboplatin	5.6
Gemcitabine + carboplatin	1.25	Taxanes	5.6
Atezolizumab + Nab-paclitaxel	1.42	Pembrolizumab	7.2
Capecitabine	1.85	Assumed the same as paclitaxel	7.1

Table 6. List of adverse events and their incidences.[24]

AE	Proportion in the Pembrolizumab arm	Proportion in the Chemotherapy arm
Neutropenia	35%	34%
Neutrophil count decreased	19%	24%
Anaemia	20%	16%
Febrile neutropenia	18%	16%
White blood cell count decreased	8%	5%
Alpha-1 antitrypsin (AAT) increased	6%	3%

Table 7. Utility values in each health state.[32]

Health state	Utility
Event-free	0.869
Locoregional recurrence	0.869
Distant metastasis	0.685

Table 8. Coefficients of utility adjustment.[22]

Parameter	Coefficient
Age (years)	-0.0002587
Age2	-0.0000332
Male	0.0212126
Intercept	0.9508566

Table 9. Dosing schedule of intervention and comparators used in the model.

Treatment arm	Component	Dosing schedule
Pembrolizumab (neoadjuvant)	Pembrolizumab (200mg Q3W)	Pembrolizumab (200mg Q3W) 200mg Q3W on day 1 of cycles 1-8
	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W on day 1 of cycles 1-4
	Paclitaxel	80mg/m2 weekly on days 1, 8, 15 of cycles 1-4
	Cyclophosphamide	600 mg/m2 Q3W on day 1 of cycles 5-8
	Doxorubicin	60 mg/m2 Q3W on day 1 of cycles 5-8
	Epirubicin	90 mg/m2 Q3W on day 1 of cycles 5-8
Pembrolizumab (adjuvant)	Pembrolizumab (200mg Q3W)	200 mg Q3W on day 1 of cycles 1-9
Placebo (neoadjuvant)	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W on day 1 of cycles 1-4
	Paclitaxel	80mg/m2 weekly on days 1, 8, 15 of cycles 1-4
	Cyclophosphamide	600 mg/m2 Q3W on day 1 of cycles 5-8
	Doxorubicin	60 mg/m2 Q3W on day 1 of cycles 5-8
	Epirubicin	90 mg/m2 Q3W on day 1 of cycles 5-8

Table 10. Drug acquisition costs.

Drug	Vial concentration	Cost per vial
Pembrolizumab	100mg/4ml	£2,630.00
Carboplatin	50mg /5ml	£3.18
	150mg / 15ml	£6.08
	450mg /45ml	£13.51
Paclitaxel	30mg / 5ml	£4.15
	100mg /16.7ml	£8.06
	150mg / 25ml	£10.15
	300mg/50ml	£15.97
Doxorubicin	10mg / 5ml	£2.83
	50mg / 25ml	£7.09
	200mg / 100ml	£20.02
Epirubicin	10 mg / 5ml	£5.06
	50mg /25ml	£23.23
	200mg / 100ml	£35.42
Cyclophosphamide	500mg/ vial	£8.23
	1000mg/ vial	£13.55
	2000mg/ vial	£27.50
Nab-paclitaxel	100mg	£246.00
Gemcitabine	200mg / 2ml	£3.18
	1000mg / 10ml	£6.08
	2000mg / 20ml	£13.51
Atezolizumab	840 mg / 14ml	£2,665.38
Capecitabine	150mg (60 tablets pack)	£4.43
	300mg (60 tablets pack)	£7.77
	500mg (120 tablets pack)	£26.30
Nivolumab	40 mg/vial	£439.00
	100 mg/vial	£1,097.00
Dabrafenib	75 mg (28 tablets pack)	£1,400.00
Trametinib	2 mg (30 tablets pack)	£ 4,800.00

Table 11. Mean treatment duration (months) of distant metastatic treatments.

1L treatment regimen	Duration of 1L treatment	Source	Duration of 2L+ treatment	Source
Pembrolizumab	7.5	PFS of Pembrolizumab arm Keynote-355[24]	6.9	Assumed the same as Atezolizumab
Paclitaxel	5.6	PFS of Chemotherapy arm Keynote-355[24]	2.5	Celik et al. (2023)[50]
Carboplatin	5.6			
Carboplatin + paclitaxel	5.6			
Gemcitabine + carboplatin	5.6			
Atezolizumab + nab-paclitaxel	7.2	PFS of IMpassion130[31]	6.9	Fabi et al. (2023)[51]
Capecitabine	7.0	NICE TA866[32]	2.5	Celik et al. (2023)[50]

Table 12. Administration costs.

Drug	Type of administration	NHS code	Setting	Unit cost
Neoadjuvant and Adjuvant				
Pembrolizumab	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Carboplatin	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Paclitaxel	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Cyclophosphamide	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Doxorubicin	Subsequent Chemotherapy	SB15Z	Outpatient	£253.77
Epirubicin	Subsequent Chemotherapy	SB15Z	Outpatient	£253.77
Subsequent treatments (distant metastatic stage)				
Pembrolizumab + taxanes	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Paclitaxel	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Carboplatin	Simple Chemotherapy	SB12Z	Outpatient	£221.35
Carboplatin + paclitaxel	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Gemcitabine + carboplatin	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Atezolizumab + Nab-paclitaxel	Complex Chemotherapy	SB14Z	Outpatient	£352.24
Capecitabine	Oral	NA	Outpatient	£10.00
Subsequent treatments (LR stage)				
Pembrolizumab	Simple Chemotherapy	SB12Z	Outpatient	£281.28
Nivolumab	Simple Chemotherapy	SB12Z	Outpatient	£281.28
Dabrafenib + trametinib	Oral	NA	Outpatient	£9.6

Table 13. Dosing schedule of subsequent treatments.

Treatment regimen	Component	Dosing schedule
Subsequent treatments (distant metastatic stage)		
Pembrolizumab	Pembrolizumab	200mg Q3W
	Paclitaxel	90 mg/m2 weekly on days 1, 8, 15 of cycles 1-4
	Nab-paclitaxel	100 mg/m2 on days 1, 8, 15 of every 28-day cycle
Paclitaxel	Paclitaxel	90 mg/m2 weekly on days 1, 8, 15 of cycles 1-4
Carboplatin	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle
Carboplatin + paclitaxel	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle
	Paclitaxel	90 mg/m2 weekly on days 1, 8, 15 of cycles 1-4
Gemcitabine + carboplatin	Gemcitabine	1000mg/m2 on days 1 and 8 of every 21-day cycle
	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle
Atezolizumab + nab-paclitaxel	Atezolizumab	840mg Q2W
	Nab-paclitaxel	100mg/m2 on days 1, 8, 15 of
Capecitabine	Capecitabine	1250mg/m2 twice daily days 1-14 of every 21-day cycle
Subsequent treatments (LR stage)		
Pembrolizumab	Pembrolizumab	400 mg Q6W
Nivolumab	Nivolumab	480 mg Q4W
Dabrafenib + trametinib	Dabrafenib	150 mg BID
	trametinib	2 mg every day

Table 14. Disease management resource use costs.[22]

Resource	Cost (£)	Reference
Health care professionals		
Oncologist visit	£151.03	NHS reference costs 2019-20
GP visit	£39.23	PSSRU 2020
Clinical nurse specialist	£91.24	NHS reference costs 2019-2020
Community nurse	£41.04	NHS reference costs 2019-2020
Imaging		
Mammogram	£12.25	TA424 (2016) - NHS BSP (inflated to 2020)
CT scan	£118.64	NHS reference costs 2019-2020
MRI scan	£202.52	NHS reference costs 2019-2020
Laboratory monitoring		
Full blood count	£2.58	NHS reference costs 2019-2020

Table 15. Annual frequency of recurring disease management resource use by health state.[22]

Disease state	Oncologist visit	GP visit	Mammogram	CT scan	Clinical nurse specialist	Community nurse	FBC	MRI
Event-free (Year 1-3)	2	2	1	-	-	-	-	-
Event-free (Year 4-5)	1	1	1	-	-	-	-	-
Event-free (Year 6-10)	-	1	-	-	-	-	-	-
Locoregional recurrence	2	-	1	2	-	-	-	1
Distant metastasis	12	1	-	4	12	3	17	-

Table 16. Additional disease management costs for the event free state.[22]

Disease state	Cost per week (£)	Source
Event-free (Year 0-1) – pembrolizumab arm	£81.99	TA851
Event-free (Year 0-1) – placebo arm	£38.06	

Table 17. Unit costs of AE management.

Grade 3+ AE	AE cost
Neutropenia	£635.68
Neutrophil count decreased	£635.68
Anaemia	£762.54
Febrile neutropenia	£3,580.80
White blood cell count decreased	£635.68
AAT increased	-

Table 18. Unit cost of procedures and the proportion of recipients.

Resource use	Weighted average cost (£)	% patients received surgery	
		Pembrolizumab arm	Placebo arm
Surgery	£5,823.04	98.0%	97.7%
Radiotherapy	£3,115.03	67%	67%

Appendix B. Results.

Table 1. Extraction table of literature review.

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
Pembrolizumab as neoadjuvant for triple-negative breast cancer (3 HTAs)	NICE TA851[22]	Included IO only in metastatic setting	• Allowed IO-rechallenge at least 2 years after pembrolizumab initiation. • Pembrolizumab rechallenge is allowed only in PD-L1 positive • IO rechallenge assumption is based on expert opinion and current availability of Atezolizumab + nab-paclitaxel in the metastatic setting	Administered atezolizumab instead of pembrolizumab to all patients who were IO-eligible in the base case company model. The ERG criticized this to be an error in the model and corrected for this in its base case	Used mean OS per subsequent treatment and calculated weighted mean OS based on market share of 1L treatment in metastatic setting	• Survival estimates redacted · • Choice of parametric distribution for DFS was criticized as DFS was mostly observed in the extrapolated period, and because the rate of survival was higher in the post-extrapolation period vs. the pre-extrapolation period.	• Used mean PFS per subsequent treatment • Calculated weighted average costs of patients who received 1L treatments based on the total treatment costs by 1L treatment and the market shares of each 1L metastatic treatment from the trial. Patients who receive 1L treatments were also assumed to receive subsequent lines (2L+) of treatments	Changing 50% of IO from atezolizumab to pembrolizumab increased ICER by 42%
	HAS[26]		• Allowed IO-rechallenge at least 2 years after pembrolizumab initiation. • Pembrolizumab rechallenge is allowed only in PD-L1 positive (TA851), or patients with CPS≥10 (HAS)	There is persistent uncertainty regarding the distribution and effectiveness of treatments received after MS recurrence as the KN-355 trial overestimated OS. Hence, it is recommended that efficacy results need to be corroborated by real-life data		External validity could not be validated due to lack of literature		Changing distribution of metastatic treatments to other market research (IO rechallenge didn't change) only changed the ICER by 1%
	CADTH PC0279 [52]	No information on subsequent treatment	No information on IO rechallenge assumption	No comments	No information on efficacy approach	OS estimates lacks external validity compared to real-world data	No information on the approach of subsequent treatment cost	One HTA didn't reported scenario analysis related to IO rechallenge

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
Pertuzumab as neoadjuvant for HER2-positive breast cancer (3 HTAs)	NICE TA424[42]	Included IO in non-metastatic recurrence and metastatic setting	No information on IO rechallenge assumption	No comments	• Used mean OS per subsequent treatment and calculated weighted mean OS based on market share of subsequent treatments • For LR stage, TP were based on data from the clniical trial (NICE TA424)	Survival estimates not reported in HTAs (not eligible for disclosure)	Calculated costs based on subsequent treatment proportions on the clinical trial	Not reported .
	CADTH PC0241 [53]	Included IO only in metastatic setting, and differentiated subsequent treatment options based on treatment arm and response to treatment in early-stage.	Allowed IO rechallenge 18 months after pertuzumab initiation				No information on the approach of subsequent treatment cost	Reported testing different treatment mix for metastatic stage but didn't report the ICER
	CADTH PC0050 [36]	Included IO only in non-metastatic recurrence setting	No information on IO rechallenge assumption		No information on efficacy approach			Not reported .
Pertuzumab as adjuvant for HER2-positive breast cancer (2 HTAs)	NICE TA569[54]	Included IO in non-metastatic recurrence and metastatic setting	No HTAs explained further the assumption they use to justify IO rechallenge	No comments	• All used mean OS per subsequent treatment and calculated weighted mean OS based on market share of 1L metastatic treatment treatments • Post-progression survival probabilities have been derived from the trial data (NICE TA569).	No comments	• Used mean PFS per subsequent treatment • Calculated cost based on treatment distributions from market research or expert opinion	No HTAs reported scenario analysis related to IO rechallenge
	CADTH PC0127 [55]	Included IO only in metastatic setting		• Rechallenging with pertuzumab-trastuzumab is considered more relevant for patients beyond 18 months and would be available to those patients that had a long disease-free interval. • Treatment mix from the APHINITY trial was considered more appropriate.			Calculated cost based on treatment distributions from market research or expert opinion	

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
Trastuzumab emtasine as adjuvant for HER2-positive breast cancer (3 HTAs)	NICE TA632[56]	Included IO in non-metastatic recurrence and metastatic setting	No HTAs explained further the assumption they use to justify IO rechallenge	No comments	Used extrapolation of the PFS and PPS curves as surrogate of OS and then weighted according to metastatic treatment distribution Didn't use efficacy data to calculate TP in the non-metastatic recurrence state (HAS)	Extrapolations validated by long terms studies of "trastuzumab"	• Cost in metastatic state based on treatment distributions from market research, internal study or assumption • Cost in non-metastatic recurrence state assumed that market shared between treatments is equal to Herceptin arm in the IDFS state (NICE TA632)	No HTAs reported scenario analysis related to IO rechallenge
	HAS[37]			The manufacturer did not discuss whether the early use of the drug in the treatment could modify the sequences of treatment at the DM stage		Choice of parametric distribution for extrapolation of IDFS criticised		
	CADTH PC0182[57]	Included IO only in metastatic setting		• pERC agreed with clinicians that Ado-trastuzumab (T-DM1) retreatment is only beneficial if DM recurred 6 months after adjuvant treatment. • T-DM1 would be used in DM setting after L1 with a HER2-directed therapy	No information on efficacy approach	Survival estimates not reported in CADTH submissions (not eligible for disclosure)	No information on the approach of subsequent treatment cost	
Atezolizumab as adjuvant for (Stage II to IIIa) NSCLC with no progression after chemotherapy with tumour expression of PD-L1	NICE TA823[58]	Included IO in the metastatic setting only in comparator arm	Only had chemotherapy as an option for 1L metastatic treatment in atezolizumab arm as UK clinical oncologists didn't think that re-challenge with immunotherapy would be reimbursed	The company's 1st metastatic recurrence treatment choice assumptions are insensitive to the NHS treatment pathway. The ERG prefers the ERG expert and NHS algorithm-informed approach to metastatic treatment availability and uptake assumptions instead of the company expert-informed approach.	• Used mean OS per treatment • Used clinical trial data to calculate the monthly tumour proportion for 1L and 2L. TP are the same for patients treated for MR with IO irrespective of specific IO which also applies to chemotherapy.	Limited published data identified for validation of DFS extrapolations, and the post-hoc adjustment of the atezolizumab arm criticized as being poorly justified, resulting in inflation of the absolute and relative risk of lifetime DFS.	Calculated the average monthly treatment costs via market shares (estimated by UK clinical oncologists)	Allowed IO rechallenge in scenario analysis but didn't report the ICER.

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
	CADTH PC0269 [38]	Included IO in metastatic setting only at 1L	No comments	● Therapeutic options for LR were misaligned with current Canadian clinical practice and that patients being treated with curative or palliative intent would receive IO as L1 option after LR. ● Assumption of limiting MR treatment until 2L may lead to underestimation of overall cost of treatment for MR ● Not allowing IO rechallenge in LR setting favoured the drug under review.	No efficacy measures were provided in the post-progression state	Cure analysis is criticized and adjusted, resulting in agreement that a non-negligible proportion of people are cured.	Calculated costs based on subsequent treatment option (atezolizumab or active surveillance) (in the metastatic setting)	Didn't report scenario analysis related to IO rechallenge.
Durvalumab as monotherapy for unresectable NSCLC without progression after chemotherapy (3 HTAs)	NICE TA798[59]	No information of IO as subsequent treatment	No comments	No comments	No information on efficacy approach	Noted data immaturity as well as few patiens at the end of the KM curve for PFS indicates uncertainty in the extrapolation	No information	No HTAs reported scenario analysis related to IO rechallenge
	CADTH PC0131 [60]	IO only used in the metastatic setting		There is insufficient evidence to support retreatment with durvalumab upon disease progression and that there was currently no clinical trial evidence to inform the optimal sequencing of durvalumab and subsequent therapies if disease progression occurred	Treatment distribution doesn't affect OS (taken directly from PACIFIC trial)	CADTH deemed the survival analysis not eligible for disclosure but noted that the assumption of 10 years of treatment benefit may be too optimistic and overestimated.	The distribution of treatment is based on PACIFIC trial and expert opinion	
	HAS, 2019[41]			It was noted that the method of estimating the costs of subsequent treatment was not consistent with the modeling of post- progression costs, and that the method to evaluate the costs of second-line treatments was not consistent with the modeling of the post-progression state.	No information on efficacy approach	HAS deemed the analysis to be compliant		

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
Nivolumab as neoadjuvant for resectable NSCLC (2 HTAs)	NICE TA876[40]	IO only included in metastatic setting	Patients who progressed within 6 months after last dose of nivolumab were not eligible for further IO treatment	• The distributions of treatment in the DM health state were not based on optimal evidence and are therefore subject to uncertainty • Additional uncertainty regarding the retreatment restrictions for patients receiving IO treatment	DM was an absorbing state with explicit transition to death. Instead of explicitly modelling the outcomes for post-DM treatments, one-off LYs, QALYs, and costs were applied upon entry into the DM state	No comments	Costs were calculated based on market share, collected by manufacturers and expert opinion	Extending IO rechallenge restriction from 6 to 12 months decreased the ICER by 42% while removing IO rechallenge restriction increased the ICER by 72%
	CADTH PC0303 [61]				Treatment distribution did not affect survival		• Treatment costs for patients in the LR health state were estimated using a basket approach. • Fixed-payoff approach to determine costs for patients with distant metastatic recurrence. Discounted outcomes were selected and weighted according to Canadian market shares.	IO rechallenge is fully prohibited in the scenario analysis but ICER not reported
Pembrolizumab as adjuvant for melanoma (3 HTAs)	NICE TA837[28]	Included IO in both non-metastatic recurrence and metastatic recurrence setting, differentiate treatment options in LR stage based on treatment arm	Allows pembrolizumab rechallenge only in metastatic setting after 24 months of adjuvant initiation.	No comments	• For metastatic recurrence, used mean OS per subsequent treatment and calculated weighted mean OS based on market share of 1L treatment in metastatic setting	• Survival estimates at different time points redacted	• For the metastatic stage, two TAs (CADTH PC0286 and HAS) calculated costs based on market shares obtained from market research and expert opinion while one TA (NICE TA837) used real-world data Systemic Anti-Cancer Treatment (SACT)	Prohibiting pembrolizumab rechallenge in metastatic stage increased the ICER by 40%

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
	CADTH PC0286 [39]	Included IO in both non-metastatic recurrence and metastatic recurrence setting	Allows pembrolizumab rechallenge in non-metastatic recurrence setting after 18 months of adjuvant initiation	• It was criticized that market shares of subsequent treatments in the LR and DM states did not reflect Canadian clinical practice • Treatment eligibility with anti-PD1 was modelled dependent only on treatment received in the RF state. However in clinical practice, treatment eligibility also depends on time of LR recurrence • Pembrolizumab's effectiveness when used across multiple lines of therapy is uncertain.	• For the non-metastatic recurrence stage, used trial-based HRs of DMFS failure per subsequent treatment and calculated a weighted average based on market shares	CADTH criticized the long term extrapolations of patients experiencing DM	report and market research • For the non-metastatic recurrence stage, costs were calculated according to market shares obtained from market research and expert opinion • All assumed patients to receive 2L+ metastatic treatments • Used mean PFS per subsequent treatment (NICE TA837 and HAS)	Tested prohibiting IO use in LR or DM states but didn't report the ICER
	HAS[62]			There is uncertainty regarding the proportion of patients who will actually be retreated in routine clinical practice. Since the retreatment of patients at stage III will increase the total cost for patients receiving pembrolizumab at stage II, the chosen approach is conservative.	For metastatic recurrence, used mean OS per subsequent treatment and calculated weighted mean OS based on market share of 1L treatment in metastatic setting • For the non-metastatic recurrence, didn't use efficacy to calculate TP	US Oncology Network study (providing 10 year data) deemed relevant and acceptable for the assessing external validity		• Prohibiting pembrolizumab rechallenge in LR stage decreased the ICER by 23% • Restricting pembrolizumab rechallenge in DM stage at least 18 months after treatment initiation in the LR stage (dominant)

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
Pembrolizumab as adjuvant for renal cell carcinoma (2 HTAs)	NICE TA830[63]	Included IO only in metastatic setting	Allows pembrolizumab rechallenge only as 2L treatment in base case, and as 1L treatment after 36 months of adjuvant initiation in scenario analysis	• Estimated cost of subsequent treatments was highly uncertain given reliance on market share assumptions as well as PFS and OS extrapolation • Company assumed an exponential survival model for all subsequent line treatments, without assessing quality of fit to KM data • Clinical experts considered that second-line market shares did not reflect current clinical practice • ERG's clinical experts advised that there is limited evidence available for treating patients who have received immunotherapy with a subsequent immunotherapy.	Used median OS per subsequent treatment.	Approach in which independent parametric models are fitted to each treatment arm was preferred by the ERG over the company's approach of jointly fitted time-varying treatment effects	• Calculated costs based on market shares obtained from country- specific market research and expert opinion • Used mean PFS per subsequent treatment	Allowing IO rechallenge from only in the 2L to 1L, at least 36 months after treatment initiation, decreased the ICER by 2%
	CADTH PC0237 [52]		Allows pembrolizumab rechallenge after 18 months of adjuvant initiation	No comments		Concerns about the model over the long-term survival of patients experiencing DM		No scenario analysis regarding IO rechallenge
Nivolumab as adjuvant for urothelial carcinoma (3 HTAs)	NICE TA817[33]	IO not included as subsequent treatments	Didn't explain the assumption of IO rechallenge	Drug was assumed to be administered until death however ERG noted that patients are likely to experience toxicity related to tolerability issues	Used the OS per subsequent treatment	No comments	• No information on the approach of subsequent treatment costs • No HTA used PFS per subsequent treatment	Didn't report scenario analysis related to IO rechallenge
	[34]HAS		Allowed IO rechallenge only in scenario analysis	No comments	TP is independent from subsequent treatments	Limitation in external validity noted and has been attributed to differences in clinical trials and real-life studies		Allowing IO rechallenge among patients treated with chemotherapy who are eligible, decreased the ICER by 2%

Indication	Source	Subsequent treatment approach	IO rechallenge assumption	Criticism on subsequent treatment and IO rechallenge	Efficacy approach	Criticism on survival extrapolation validation	Subsequent treatment costing approach	Scenario analysis related to IO rechallenge
	CADTH PC0272 [64]	Included IO only in metastatic setting, and cisplatin ineligible population	Not mentioned	• Sponsor assumed that 100% of patients experiencing disease recurrence would receive subsequent chemotherapy. According to the clinical experts consulted by CADTH, fewer patients are likely to be eligible for subsequent chemotherapy • Based on feedback from clinical experts consulted by CADTH, the list of metastatic treatments was outdated as patients may also be eligible for avelumab or enfortumab after disease recurrence • Distribution of subsequent chemotherapy was inappropriate	OS is estimated in the model via time spent in the DFS and post-recurrence health states	No comments	• Calculated costs based on proportion of treatments received, obtained from clinical trial and Canadian sources. Didn't used PFS per subsequent treatment	Didn't report scenario analysis related to IO rechallenge
Nivolumab as adjuvant for gastrointestinal cancer (1 HTA)	CADTH PC0253 [35]	IO not included as subsequent treatments	Not mentioned	No comments	TP is independent from subsequent treatments	No comments	No information on the approach of subsequent treatment costs	Didn't report scenario analysis related to IO rechallenge

Table 2. Breakdowns on discounted QALY in each health state in main analysis.

Comparator	EF state	LR state	Metastatic recurrence	Total
Pembrolizumab rechallenge is not allowed	11.992	0.401	0.240	12.633
IO rechallenge is fully restricted	11.992	0.401	0.206	12.598
No IO restriction	11.992	0.401	0.258	12.651
IO rechallenge permitted after 2 years	11.992	0.401	0.217	12.610
Chemotherapy	9.531	0.401	0.400	10.331

Table 3. Breakdowns on discounted costs components in each health state (£) in main analysis.

Comparator	Drug acquisition			Procedure costs	AE costs	Drug administration			HCRU			Terminal care			
	Neo-adjuvant stage	Adjuvant stage	Metastatic recurrence			Neo-adjuvant stage	Adjuvant stage	Metastatic recurrence	EF	LR	MR	EF	LR	MR	Total
Pembrolizumab rechallenge is not allowed	41991	46829	4876	7599	1202	9016	3136	946	46570	4653	2659	1900	74	1998	173449
IO rechallenge is fully restricted	41991	46829	563	7599	1202	9016	3136	970	46570	4653	2290	1900	74	2014	168807
No IO restriction	41991	46829	4538	7599	1202	9016	3136	894	46570	4653	2853	1900	74	1990	173245
IO rechallenge permitted after 2 years	41991	46829	3114	7599	1202	9016	3136	921	46570	4653	2413	1900	74	2009	171426
Chemotherapy	168	0	6800	7553	1103	6202	0	1313	38715	8140	4416	1274	127	3299	79111

Table 4. Breakdowns on discounted QALY in each health state in secondary analysis.

Comparator	**EF state**	**LR state**	**Metastatic recurrence**	**Total**
Pembrolizumab rechallenge is not allowed	11.992	0.509	0.235	12.736
IO rechallenge is fully restricted	11.992	0.468	0.203	12.662
No IO restriction	11.992	0.552	0.250	12.793
IO rechallenge permitted after 2 years	11.992	0.498	0.213	12.702
Chemotherapy	9.531	0.509	0.386	10.426

Table 5. Breakdowns on discounted costs components in each health state (£) in secondary analysis.

Comparator	Drug acquisition				Procedure costs	AE costs	Drug administration				HCRU			Terminal care			
	Neo-adjuvant stage	Adjuvant stage	LR recurrence	Metastatic recurrence			Neo-adjuvant stage	Adjuvant stage	LR recurrence	Metastatic recurrence	EF	LR	MR	EF	LR	MR	Total
Pembrolizumab rechallenge is not allowed	41991	46829	34880	4771	7599	1202	9016	3136	545	926	46570	5944	2601	1900	80	1955	209946
IO rechallenge is fully restricted	41991	46829	23640	555	7599	1202	9016	3136	21	957	46570	5448	2259	1900	78	1987	193189
No IO restriction	41991	46829	51882	4402	7599	1202	9016	3136	937	867	46570	6446	2767	1900	83	1930	227556
IO rechallenge permitted after 2 years	41991	46829	43883	3059	7599	1202	9016	3136	735	903	46570	5807	2366	1900	79	1970	217044
Chemotherapy	168	0	90876	6586	7553	1103	6202	0	1640	1271	38715	11290	4277	1274	141	3195	174292