# Appendix 3 – Cost-effectiveness model

For the purpose of illustrating how applying QBA methods within the context of a CEM can reduce uncertainty in the model outputs, a stylised CEM was developed. This stylised example was based on a real case study of an immunotherapeutic agent in lung cancer, for which the CEM has been substantially simplified, and comparators were anonymised. In this section we report the methods and parameter values utilised to develop the CEM.

## Model structure

A three-state-PartSA was constructed in Microsoft Excel®, following a typical approach used in modelling of metastatic cancers. In this model, the number of patients in each health state at any time is determined directly from the underlying survival curves. An overview of the structure of the model is presented in Figure 1 below.

Graphical user interface, diagram

Description automatically generated

Figure 1. Model Structure

The model allows to capture the progressive nature of lung cancer for the relevant patient population and is in line with the clinical treatment paradigm in the population of interest – whereby patients receive therapy with the aim of preventing disease progression.

The model is described by three mutually exclusive health states: (i) pre-progression state; (ii) progressed disease (PD); and (iii) death (Figure 1). In this PartSM, survival functions are used to estimate the health state occupancy cycle-by-cycle by accounting for transitions of (i) patients moving from pre-progression to progressed disease, and (ii) from pre-progression or progressed disease to death. Transitions were assumed to occur on a monthly model cycle. The proportion of patients within each health state is estimated directly based on the PFS and OS survival curves, with the proportion of patients in the progressed-disease health state represented by the difference between PFS and OS curves.

All patients start in the pre-progression health state, and they remain in this state until their disease either progresses or they experience death. Following disease progression, patients remain in the PD health state until death, which is considered the absorbing state.

Patients within the pre-progressed state continue to be on treatment, until they move to the progressed state or the state of death.

## Population

The population of interest in this model based economic analysis consists of patients with a rare genetic subtype of lung cancer, who were refractory or relapsed following first line of treatment. Patients were assumed to have a starting age of 52.3 years.

## Intervention & comparator

The treatment assessed in this modelling application is a novel immunotherapeutic agent in lung cancer, compared with another pharmaceutical agent that constitutes standard of care (SoC) for the patient population of interest.

Within the model, treatment was assumed to be continued until disease progression, in line with both agents’ marketing authorisation. Following progression, termination of active treatment with no subsequent lines of pharmacological treatment was assumed.

## Time horizon

A time horizon of 10 years was used for this analysis. This time horizon was selected as most treated patients were expected to be dead by the end of this time period, and it therefore allowed all differences in costs and outcomes, between the intervention and the comparator, to be captured within the timeframe of the analysis.

## Perspective

The analysis focused on estimating the clinical and economic burden associated with the treatment of a specific genetic subtype of lung cancer, from the perspective of the UK National Health Service (NHS), comparing SoC to a scenario in which the novel pharmaceutical agent is reimbursed for the treatment of this patient population. Since the analysis took a UK NHS perspective, a cost-effectiveness threshold of £30,000/QALY was used as a decision rule.

## Discounting

A discount rate of 3.5% was applied to both costs and QALYs.

## Clinical effectiveness

Proportional hazards parametric survival curves were fitted to simulated time-to-event data so that information within the PFS and OS survival curves could be extrapolated for use within the CEM. The exponential, Weibull PH (proportional hazards parametrisation), and Gompertz distributions were fit to the data and the best fitting model was used in the CEM.

Baseline hazard functions for the PFS and OS were estimated for the comparator. These baseline hazard functions provided an ‘anchor’ for hazard ratios, which were used to model the relative effectiveness of the intervention arm. A Weibull distribution was used to model the baseline (comparator arm) PFS and the OS, as it provided the best fit for both outcomes. Parameter values of these distributions are presented in Table 1.

Table 1. Parameter value for baseline survival functions

|  |  |  |
| --- | --- | --- |
| **Input** | **Mean (Lower, Upper limit)** | **Covariance matrix** |
| PFS | Weibull shape: 0.2309  Weibull scale: 0.2774 | |  |  |  | | --- | --- | --- | |  | Shape | Scale | | Shape | 0.003437 | -0.000104 | | Scale | -0.000104 | 0.005851 | |
| OS | Weibull shape: 0.1757  Weibull scale: 0.1155 | |  |  |  | | --- | --- | --- | |  | Shape | Scale | | Shape | 0.003676 | -0.000482 | | Scale | -0.000482 | 0.006161 | |

All unmeasured confounding adjusted hazard ratios were generated and then input into the CEM. Firstly the ‘true’ (albeit unknown) hazard ratio was assumed using the entirety of the available retrospective data. Then analyses were conducted using a naïve unadjusted comparison of survival from the two data sources, and an additional comparison using the two methods [1, 2] to adjust for unmeasured confounding. Parameters for these estimates were produced for the 3 different scenarios reflecting different scenarios for the level of knowledge around the unmeasured confounding (Table 1 in main text).

Table 2. HR values used in the model for different scenarios and methods

|  |  |  |  |
| --- | --- | --- | --- |
| **Input** | **Mean - Good Knowledge**  **(Lower, Upper limit)** | **Mean – Poor knowledge**  **(Lower, Upper limit)** | **Mean – Incorrect knowledge**  **(Lower, Upper limit)** |
| OS HR (unadjusted) | 0.691 (0.528-0.904) | 0.691 (0.528-0.904) | 0.691 (0.528-0.904) |
| OS HR (True) | 0.534 (0.405-0.704) | 0.534 (0.405-0.704) | 0.534 (0.405-0.704) |
| OS HR (Huang) | 0.481 (0.017-0.868) | 0.594 (0.217-0.930) | 0.712 (0.387-1.051) |
| OS HR (Ding) | 0.498 (0.346-0.718) | 0.618 (0.453-0.841) | 0.731 (0.528-1.098) |
| PFS HR (unadjusted) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) |
| PFS HR (True) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) |
| PFS HR (Huang) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) |
| PFS HR (Ding) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) | 0.741 (0.575-0.954) |

## Health-related quality of life

Utility weights were attached to the time spent in each of the health states to reflect the health-related quality of life (HRQoL) of patients residing in each state. A distinct utility value by treatment arm was applied to the pre-progression health state to account for the different tolerability profiles of the two pharmacological agents.

For progression-free survival, utility values were estimated by mapping values from the EORTC QLQ-C30 questionnaire to the EuroQoL EQ-5D-3L based on patient-level data from a single-arm trial of the intervention [3]. The tariff scoring algorithm was used to derive utility values using a value set from England [4].

For patients with progressed disease, evidence from published literature was used to inform their utility values [5].

Disutility values associated with adverse events were not considered explicitly in the model as values used to inform utility parameters of the pre-progression health state were derived from the clinical trial of each of the two treatments.

Table 3. Summary of utility values used in the CEM

|  |  |  |
| --- | --- | --- |
| **Health state** | **Utility value**  **Mean (SE)** | **Reference** |
| PFS health state - intervention | 0.787 (0.121) | Intervention trial data |
| PFS health state - comparator | 0.730 (0.121) | Comparator HTA submission |
| Progressed disease | 0.460 (0.121) | Chouaid, Agulnik [5] |

## Costs

The cost items included in the model reflected the most significant costs bared by the NHS and social care services in England. These included costs associated with pharmacological treatment, supportive care, healthcare professional time, and lab and procedure costs. All costs were inflated to reflect 2020 prices (Table 4).

Treatment costs were estimated by applying the unit costs of the two pharmacological agents to their dose as recommended by the treatment protocol. Because of the mode of treatment administration, the administration costs were assumed to be 0.

Costs associated with the pre-progression state included healthcare provider’s visit costs (i.e., cancer nurse visits, outpatient visits, general practitioner [GP] visits), and laboratory test and procedure costs (i.e., complete blood count, computerized tomography [CT] scan, X-ray, and serum chemistry).

Costs associated with post-progression state included healthcare provider’s visit costs (i.e., cancer nurse visits, outpatient visits, and GP visits), medications (i.e., steroids, nonsteroidal anti- inflammatory drugs (NSAIDs), morphine, bisphosphonate, and dietary supplements), and laboratory tests and procedure costs (i.e., complete blood count, serum chemistry, CT scan, home oxygen, and X-ray).

Table 4. Summary of cost values used in the CEM

|  |  |
| --- | --- |
| **Costs** | **Cost**  **Mean** |
| Intervention treatment cost (monthly) | £3,418 |
| Comparator treatment cost (monthly) | £3,418 |
| Pre-progression | £198 |
| Progressed disease | £343 |

## Sensitivity analyses

To study the impact of different levels of unmeasured confounding on the uncertainty around the model outputs in isolation, only uncertainty around the baseline PFS, OS, and effectiveness parameters was explored in the CEM.

A univariate sensitivity analysis was conducted to explore the impact on the outputs by applying the low and upper limit of each HR (Table 2), while other parameters remained constant. The lower and upper values of HR parameters was determined by the corresponding 95% CI of each HR. For the Huang and Ding methods, due to the multiple number of HRs produced under various assumptions, the lower 95% CI of the lowest mean HR, and the upper 95% CI of the highest mean HR were used to define the lower and upper values of the HR parameters in the univariate sensitivity analysis.

A probabilistic sensitivity analysis (PSA) was also conducted to describe how uncertainty around the HRs and the baseline PFS and OS function is translated into uncertainty around the estimated model outputs. Suitable probability distributions were assigned to these model parameters to characterise uncertainty around their mean values. Specifically, a Cholesky decomposition was applied to the OS and PFS curve-fitting parameters, while a log-normal distribution was applied to parameters of comparative effectiveness. Values were sampled from these distributions in an iterative process of 30,000 Monte Carlo simulations, in order to determine the joint distribution of incremental costs and incremental QALYs between the intervention and the comparator.

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