Modelling of Lung Cancer Therapy; Modelled And Real-World Impact of Targeted Therapy And Immunotherapy In The Netherlands

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Abstract

Recent discoveries in molecular diagnostics and lung cancer drugs have improved the treatment of patients with advanced (inoperable) non-squamous NSCLC from solely platinum based chemotherapy to more personalized treatment including targeted therapies and immunotherapies. However, these improvements come at considerable costs, highlighting the need to assess cost-effectiveness for optimization of lung cancer care. Traditionally, cost-effectiveness models built to evaluate new lung cancer treatments were based on randomized control trial (RCT) findings. The strict RCT inclusion criteria make RCT patients not representative of real-world patients: Patients in RCT have better prognosis compared to real-world patients. Therefore, in this study we have developed and validated a diagnosis-treatment decision model for patients with advanced (inoperable) non-squamous NSCLC based on real-world data in the Netherlands. The model is a patient-level microsimulation model implemented as discrete event simulation with five health events. Patients are simulated from diagnosis to death, including at most three treatment lines. The base-model (non-personalized strategy) was populated using real-world data of patients treated with platinum-based chemotherapy between 2008 – 2014 in one of six Dutch's teaching hospitals. To allow simulation of personalized care, molecular tumor characteristics were incorporated in the model based on the literature. The impact of novel targeted treatments and immunotherapies was included based on published RCTs. To validate the model, we compared survival under a personalized treatment strategy against observed real-world survival. This model can be used for health-care evaluation of personalized treatment for patients with advanced (inoperable) NSCLC in the Netherlands.

1. Introduction

The treatment of patients with advanced (inoperable) non-small cell lung cancer (NSCLC) has changed drastically in the last decade. New treatments have widened the options for first line treatment from solely platinum based chemotherapy to also targeted therapies and immunotherapies [1]. Likewise, the diagnostic pathway had to be adapted to aid patient selection for optimal treatment decision making, which resulted in a personalized treatment scheme [1], [2].

These innovations have gone along with improved understanding of the biology and molecular subtypes of NSCLC. Such that, NSCLC has been defined as a heterogeneous disease consisting of molecular defined tumor subgroups that require personalized biomarker-guided treatment selection [3], [4]. For some NSCLC tumor subgroups, targeted treatment and immunotherapies have been shown to improve progression-free survival (PFS) and/or overall survival (OS) [4].

Although there are improvements in survival, they go together with a substantial increase in costs for both molecular diagnostics and drugs [5]. To support treatment decisions that optimize budget allocation such that health benefits are maximized, decision models are commonly recommended [6], [7]. Decision models simplify complex systems and allow integration of data from different sources as well as extrapolation of short-term effects to long-term outcomes [6]–[8]. Decision models are commonly used

for cost-effectiveness analyses and budget impact analyses to evaluate diagnostic and treatment decisions in different scenarios [9].

For personalized treatment of advanced lung cancer care, cost-effectiveness and budget impact evaluations have been carried out based on randomized controlled trials (RCTs) [10]–[15]. Holleman et al. [10], Chouaid et al. [11], Barbier et al. [12], and Westwood et al. [13] have taken a customary approach of modelling single drug(s) for a specific indication or a drug-diagnostic combination. To optimize the whole care pathway, diagnostic and treatment pathways have to be evaluated over multiple treatment lines. Thus, RCTs on single interventions are no longer sufficient. Simons et al. [14] and van Amerongen et al. [15] modelled the diagnostic and treatment pathways in multiple-lines based on data from several RCTs. However, RCTs represent highly selective populations that have in general better prognosis than patients not participating in RCTs. It has been shown that the real-world overall survival (OS) of patients with high PD-L1 expression who received first-line immunotherapy treatment is shorter than OS in RCTs [16]–[19]. It is unclear therefore whether the predictions of decision models simulating novel diagnostics and treatments based on an RCT setting translate well to the real-world clinical setting. To understand this, it is important to build decision models based on real-world data.

In the Netherlands, decision models based on real-world data have been developed for other tumor types. For example, an economic evaluation for advanced breast cancer treatment has been performed based on the Southeast Netherlands advanced breast cancer registry [20]. The study presented here aims to develop and validate a lung cancer diagnosis and treatment decision model for patients with advanced (inoperable) non-squamous NSCLC based on real-world data in the Netherlands that can be used for economic evaluations of personalized treatment and/or diagnostic in the Netherlands.

2. Materials And Methods

2.1 Overview of the microsimulation model

We developed a patient-level microsimulation model implemented as a discrete event simulation (DES). Patients with advanced (inoperable) non-squamous NSCLC are simulated from diagnosis to death, including at most three treatment lines (Fig 1). We adopted a patient-level simulation framework to capture the complexity of the disease by modelling patients' characteristics (attributes) and treatment history leading to outcome variation on a patient level [21]. In addition, DES allows time to events to vary by patient by directly sampling event times from parametric distributions [22].

The model incorporates three life prolonging treatment lines and five health events:

- DIAG, diagnosis of advanced (inoperable) non-squamous NSCLC.
- L1T, start of first-line systemic treatment.
- L2T, start of second-line systemic treatment.
- L3T, start of third-line systemic treatment.

- Death, death (absorption event).

All patients start at DIAG and reach the next event in a continuous time framework. From DIAG to L3T, a patient can start a subsequent treatment line or die. Not every patient passes all events; a patient may die before reaching the subsequent treatment line. A patient may die from the disease or from death due to other causes (DoC).

The model was developed in two steps. First, we developed the model simulating a non-personalized treatment strategy, that reflects a real-world disease trajectory under standard systemic chemotherapy regimens commonly used before 2014 and best supportive care (BSC). Second, the model parameters were adjusted to simulate a personalized strategy. Adjustment includes adding a molecular diagnosis-treatment decision tree (Fig. 2). The molecular diagnosis-treatment decision tree simulates patient's molecular biomarkers used to inform first-line treatment choice. In personalized strategy patients can receive targeted therapies and immunotherapies as treatment options depends on patient's molecular biomarker.

Below, the data used for model quantification, the model development and the internal and external validation is described in detail.

2.2 Data used for parameter estimation

2.2.1 Santeon registry 2008-2014 for model development (non-personalized strategy)

Data from six Dutch teaching hospitals working under the Santeon group [23] was used. This dataset includes patients with advanced (inoperable) NSCLC diagnosed and treated between 2008 and 2014 (Santeon registry 2008 – 2014). Patients were followed until January 31, 2017 [24]. Between 2008 and 2014 platinum-based chemotherapies were standard of care. At that time, first-line immunotherapy was not among the treatment options while targeted therapy was introduced in the last phase of 2008 – 2014 [25], [26].

For model development, we used the subset of 2196 patients with non-squamous histology. The median (range) follow-up time to end-date of follow-up was 59 months (0 - 106). At the end-date of follow-up 98 percent of 2196 patients had died.

We used the following patients' characteristics as model attributes; year of diagnosis (year), age at diagnosis (age), sex, histology, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and Charlson comorbidity Index (CCI). Patients received either best supportive care (BSC) or one or more lines of systemic chemotherapy. Patients were excluded if they had squamous cell carcinoma (527), were treated with targeted or unspecified therapy in any of the treatment lines (258), or had inconsistency in the event times (1). The descriptive statistics of the 2196 patients and the bivariate associations among covariates are given in electronic supplementary materials (ESM) Tables A1 and A2. Throughout this manuscript, we will refer to this dataset as "*template dataset*".

2.2.2 Molecular characteristics and novel treatment effects

The prevalence of molecular biomarkers used to aid personalized treatment decisions was taken from the scientific literature [27]–[31]. See ESM Table A3. Molecular biomarkers included were activating mutation of epidermal growth factor receptor (EGFR) gene, anaplastic lymphoma kinase (ALK) gene rearrangements, genetic aberrations of ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF), MET proto-oncogene (MET), RET proto-oncogene (RET), neurotrophic receptor tyrosine kinase 1 (NTRK_(1, 2, 3)) and Kirsten rat sarcoma viral oncogene homolog (KRAS). Additionally, PD-L1 protein expression [3] was included. For EGFR mutation, a distinction was made between classic activating EGFR mutations (exon 19 deletions and exon 21 L858R point mutations, i.e., EGFR_{classic}) and non-classic activating EGFR mutations, resistance mutations, and other mutations (EGFR_{non-classic}) [28].

The impact of novel treatments in terms of reducing the hazard rate to progression compared to standard chemotherapy per molecular subgroup and per treatment line was taken from randomized controlled trials (RCT) (i.e., direct treatment comparisons [32]–[36], from a network meta-analysis (NMA) [37] and a systematic review providing pooled estimates [38]. See ESM Table A4 and A5.

2.2.3 Validation datasets

The strategy simulating personalized treatment was externally validated using PFS and OS curves for different therapies from the Santeon registry 2015 – 2018 [16]. Data from Cramer-van der Welle et al. (2021) were reconstructed using the method described by Hoyle & Henley [39]. Reconstructed data were 1) OS of 147 patients with EGFR_{classic} subgroup treated with first-line EGFR tyrosine kinase inhibitor (EGFR-TKI i.e., gefitinib or erlotinib). 2) PFS and OS of 83 patients with PD-L1 $\geq$ 50% subgroup treated with first-line pembrolizumab monotherapy. Patient characteristics are provided in Cramer-van der Welle et al. In addition, we used the patient level data of 52 patients with known EGFR_{classic} mutation treated with first-line EGFR-TKI (gefitinib or erlotinib) in Santeon registry 2008 – 2014 [40]. Their Characteristics are given in [40]. Lastly, published data from the United States (US) [18], [19], were used to validate the subgroup of patients treated with a combination of pembrolizumab plus chemotherapy for patients with PD-L1 $\geq$ 50% or PD-L1 1 – 49%.

2.3 Parametrization of the non-personalized strategy

Parameters for the non-personalized strategy were directly estimated from *the template dataset*. We used Chi-square test, t-test, and one-way Anova to assess the bivariate association between baseline patients' characteristics and treatment decision after diagnosis. Logistic and linear regression models were used to sample a treatment decision based on the influential patient characteristics (ESM Table A6).

Parameters for sampling a patients' time to event were estimated by fitting parametric survival models. First, from DIAG to L1T and to Death (*Fig1, dotted cycle and lines*), two independent parametric distributions were used to describe time to L1T, for the patients receiving a life prolonging systemic treatment (first-line treatment) and time to Death for the BSC group as a function of baseline attributes.

This means that first-line treatment and BSC were not considered competing events. The following survival functions were considered; Exponential, Weibull, Gompertz, Log-logistics, Log-normal, and generalized gamma. Based on visual inspection [41], [42], log-logistic and log-normal distributions had the best fit from DIAG to L1T and DIAG to Death, respectively.

Secondly, after start of first line treatment (from L1T to L2T and to Death; from L2T to L3T and to Death; and from L3T to Death, *Fig 1, solid cycles and lines*), the patients' disease trajectory was estimated by a *parametric multistate statistical model* (par MSSM) adjusted for patients' attributes [43], [44]. In this study we evaluated three proportional hazard (PH) distribution functions (Exponential, Weibull, and Gompertz). The optimal distribution was chosen based on visual inspection. The Gompertz distribution had the best fit for time from L1T to L2T and L1T to Death while the exponential distribution was optimal for time from L2T to L3T and L2T to Death. Because of the limited number of patients, an exponential distribution was selected for time from L3T to Death. The patient characteristics influencing the time to event were selected based on backward selection (cutoff p-value < 0.05).

Time to Death was corrected for background mortality (DoC), described by age and sex specific life table of the general Dutch population adjusted for smoking [45].

Data analysis as well as the construction of the microsimulation model was performed using statistical software R, version 4.0.2 [46]. For time to event data analysis, the dataset was managed using "msprep" function of mstate package [47] and analyzed using "phreg" function of the eha package [48] and "flexreg" of flexsurv package [49].

For details of parameter estimation and microsimulation model development see ESM.

2.4 Adjustment of the non-personalize strategy to simulate the personalized strategy

To simulate the personalized strategy, we adjusted the non-personalized strategy by adding information on molecular biomarkers currently used to aid treatment decisions as shown in Fig 2. In the model, we assumed that molecular biomarkers are independent of clinical and pathological characteristics. Molecular biomarkers included were described in section 2.2.2 and their prevalence are given in ESM Table A3.

Consequently, for treated patients, first-line systemic as well as second-line treatment were adapted to project outcomes under the personalized strategy according to the decision tree shown in Fig 2 [1]. The Decision tree can flexibly be specified in the model, detailing the type of treatment as a function of the presence of molecular biomarkers in the individual patient.

Currently we assumed that patients with a targetable mutation ($EGFR_{\text{classic}}$, $EGFR_{\text{non-classic}}$, ALK, ROS1, BRAF, and NTRK) receive corresponding first-line targeted therapy otherwise patients are treated according to PD-L1 expression [1]. See ESM Table A4.

Second-line treatment in the personalized strategy depends on first-line treatment. For example, patients with an ALK mutation, treated with alectinib in the first-line, are treated with lorlatinib in the second-line; and patients with a BRAF mutation and treated with first-line combination of dabrafenib plus trametinib, are treated based on PD-L1 expression in the second-line. In all other patient subgroups, chemotherapy is given as second-line treatment (ESM Table A5).

To simulate a patient's disease trajectory under the personalized strategy, the survival models were adjusted to reflect the PFS and OS benefit of receiving targeted therapy or immunotherapy compared to chemotherapy. For patients treated with first-line or second-line targeted therapy, hazard rate (HR) ratios for PF survival derived from RCTs (described in section 2.2.2) are straightforwardly incorporated in the time to event functions from L1T to L2T and to Death, and in the time to event functions from L2T to L3T and to Death. No treatment adaptations for third-line treatment are currently included in the model. It is known that the long-term benefit of EGFR-TKIs is limited [50], thus two approaches were explored for adaptation of first-line EGFR-TKI treatment. First, assuming treatment benefit is long-lasting until progression to subsequent treatment-line or death and second, assuming limited treatment benefit. Limiting treatment benefit was achieved by assuming that from time point "t" the patients' time to event function to progression will be identical to the time to event function fitted under the non-personalized strategy. Time point "t" was calibrated against the validation dataset. "t" was calibrated by comparing the modelled progression free estimate with long-lasting treatment benefit against progression free estimate of validation dataset. Then, "t" was the point at which modelled progression free K-M estimate start to deviate from the validation K-M estimates. Furthermore, the prognostic value of the EGFR_{classic} [51] and ALK mutation [52] were incorporated in time to event from L1T to L2T and to Death.

2.4.1 Simulating time to event for immunotherapy

Evidence suggest that patients treated with immunotherapy are divided into two subgroups: a subgroup of patients that have long-term benefit and a subgroup of patients with moderate benefit [53]–[55]. Standard time to event distributions may fail to capture these differences and in turn under-estimate long-term survival outcome. To account for that, we have assumed that the time to event from start of first-line immunotherapy (i.e., from L1T to L2T and to Death) follows a mixture cure time to event distribution [56]–[58]. The mixture cure time to event was implemented by assuming that 23 percent of patients were long-term survivors (we referred to the cured fraction as long-term survivor fraction). The long-term survivor fraction was based on the published five-year survival probability from the keynote-001 trial [54]. We randomly assigning a subgroup of patients to the long-term survivors who are no longer at risk for lung cancer death after treatment but die from background mortality instead. Patients not pertaining to the group of long-term survivors (moderate survivor) are subjected to the event-specific hazards of the par MSSM with adjusted HR. The input HR (inHR) for immunotherapy in the subgroup of moderate survivor patients required calibration to ensure that the overall HR of all patients receiving immunotherapy (outHR) was equal to what was observed in RCTs (ESM Table A4).

In addition, a deterministic sensitivity analysis (DSA) was performed to assess the impact of the mixture cure time to event assumption as well as the value of long-term survivor fraction. DSA was done by assuming different value of long-term survivor fraction. Assuming 0 percent long-term survivor fraction is equivalent to the standard time to event distribution (here, Gompertz distribution) assumption. Under the mixture cure time to event distribution, a different value of long-term survivor fraction was used in the range of 14 percent to 34 percent (a 95% confidence intervals [95% CI] of five-years survival rate of Keynote 001 [54]) in steps of 5 percent.

2.5 Validation of microsimulation model

The microsimulation model was validated according to the ISPOR-SMDM guideline [59].

2.5.1 Internal validity of the microsimulation model

We compared the simulated patient attributes and survival time under the non-personalized strategy with those observed (template dataset). Model output was based on simulating 1000 runs, each with the same sample size as the template dataset (*of 2196 patients*). The comparison was done visually and quantitatively. For baseline attributes, we visualize the distribution of patients' attributes and parameters of their regression models. For association among baseline attributes, we computed the percentage of simulated runs having a bivariate testing p-values less than 0.05 and compared to observed p-value in the template dataset.

For survival times, we visualized the distribution of simulated survival probabilities at 1 to 60 months for first-line, second-line, third-line PFS and OS and compared with the survival probabilities from the template dataset. Finally, we evaluated the proportion of simulated medians and means of times to event, and first-line PFS and OS contained within the respective 95% CI of the observed means and medians in template dataset.

2.5.2 External validity of the microsimulation model

The adapted model for simulation of the personalized strategy was externally validated. To perform external validation, we simulated the personalized strategy with 300,000 patients and compared the modelled PFS and OS curves or rates with that of real-world PFS and OS curves or rate. Validated subgroups were described in section 2.2.3.

It should be noted that, model validation and model building was an iterative process. When validation indicated that the model results were undesirable, the model was adjusted and re-validated again. When appropriate we have reported model results of pre- and post-validation adjustment.

2.6 Ethical statement

All methods were carried out in accordance with relevant guidelines and regulations. The original data collection (Santeon registry 2008-2014) was approved by the Santeon institutional review board and

informed consent was waived (SDB219-008). Data were provided to the authors in a de-identified fashion. The study was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

3.1 Time to event estimates

For treated patients in the template data, the median time from DIAG to L1T was 1.00 month (95% CI 0.92 – 1.05) and it was significantly shorter for females compared to males. For BSC patients, the median time from DIAG to Death was 2.27 months (95% CI 2.14 – 2.46) and it was significantly shorter for patients with bad or unknown PS compared to good PS, and for females compared to males.

The hazard from L1T to L2T was significantly lower for females and decreased with increasing age at diagnosis, while the hazard from L1T to Death was significantly higher for bad PS compared to good PS. For patients in L2T, their hazard to L3T was significantly lower for females compared to males, and decreased with increasing age at diagnosis, while the hazard to Death was significantly higher for patients treated with carboplatin doublets in first-line compared to patients received cisplatin doublets, and was lower for females compared to males. The results of the parametric survival analyses for all time to event models are given in ESM Table A7.

3.2 Modelled progression-free and overall survival time

The results of the microsimulation model for the non-personalized and personalized strategies are given in Table I. Out of 300,000 simulated patients, 65 percent received BSC and had mean OS of 5.0 months irrespective of modelling strategy. For treated patients (35 percent), the mean OS was 11.2 months and 58.0 months for non-personalized strategy and personalized strategy, respectively.

For treated patients in the personalized strategy, 14 percent received first-line targeted therapy while 86 percent had immunotherapy. The mean OS was 34.9 months and 61.9 months, for targeted therapy and immunotherapy, respectively. The molecular subgroups with the highest mean OS were patients with the ALK mutation who were treated with alectinib (mean OS of 91.4 months, i.e., 7.6 years). This was followed by patients with the PD-L1 $\geq 50\%$ who were treated with a combination of pembrolizumab plus chemotherapy (mean OS of 66.5 months i.e., 5.5 years).

3.3 Internal validation

Patients' baseline attributes as well as the parameters of the baseline regression models from 1000 runs of the microsimulation model were distributed well around corresponding values from the template dataset (ESM Figures A1 and A2). Likewise, the modelled bivariate associations were in agreement with the results from the template dataset (ESM Table A2 and Figure A1).

The distribution of the PFS and OS probabilities at specific time points of 1000 simulation runs of the non-personalized strategy are given in Fig 3 a – e. Except in the tails of the distributions, simulated PFS and OS probabilities from first-line, second-line and third line were distributed around the observed values close to their respective 95% CI. Likewise, simulated medians, restricted means and proportion of patients who progressed to L2T and L3T match acceptably well with observed 95% CI (ESM Figure A3).

Table I. Modelled median and mean PFS and OS in month (n=300,000)

Biomarker	1L Treat	n (%)	PFS		OS	
			Median	Mean	Median	Mean
Best-supportive care ^a						
N/A	BSC	195700 (65.2)	-	-	2.2	5.0
Non-personalized strategy						
ALL Treated	PDCT	104300 (34.8)	5.4	9.4	6.8	11.2
Personalized strategy						
ALL Treated	-	104300 (34.8)	11.2	56.3	13.5	58.0
Targeted therapy (TT)						
ALL TT	-	14860 (14.3) ^c	14.7	31.4	17.8	34.9
EGFR _{classic} ^b	EGFR-TKI	7380 (7.1)	14.4	15.9	16.2	20.3
EGFR _{non-classic} ^b	Afatinib	1060 (1.0)	14.9	16.4	16.2	18.2
ALK	Alectinib	2100 (2.0)	40.6	88.7	44.0	91.4
ROS1 ^b	Crizotinib	1970 (1.9)	13.3	14.9	14.8	16.6
BRAF ^b	Dabraf & Tramet	2190 (2.1)	8.5	12.2	10.9	15.1
NTRK _(1,2,3) ^b	Larotrectinib	160 (0.2)	7.6	10.2	8.8	11.7
Immunotherapy (IT)						
23% long-term survivor fraction						
ALL IT	-	89430 (85.7)	10.5	60.5	12.8	61.9
PD-L1 ≥ 50%	Pembrolizumab	5670 (5.4)	10.9	62.4	13.1	63.8
	<i>Long-term</i>	<i>1310</i>	<i>218</i>	<i>227</i>	<i>218</i>	<i>227</i>
	<i>Moderate</i>	<i>4360</i>	<i>7.0</i>	<i>12.7</i>	<i>8.6</i>	<i>14.4</i>
PD-L1 ≥ 50%	Pembro & PDCT	17000 (16.3)	17.1	65.1	19.3	66.5
	<i>Long-term</i>	<i>3940</i>	<i>209</i>	<i>219</i>	<i>209</i>	<i>219</i>

	<i>Moderate</i>	<i>13060</i>	<i>10.9</i>	<i>18.7</i>	<i>12.8</i>	<i>20.6</i>
PD-L1 1-49%	Pembro & PDCT	66760 (64.0)	9.3	59.1	11.5	60.5
	<i>Long-term</i>	<i>15350</i>	<i>209</i>	<i>222</i>	<i>209</i>	<i>222</i>
	<i>Moderate</i>	<i>51410</i>	<i>6.0</i>	<i>10.6</i>	<i>7.5</i>	<i>12.4</i>
DSA of the mixture cure event time distribution of IT						
0% long-term survivor fraction						
ALL IT	-	89430 (85.7)	11.4	19.5	13.3	21.4
PD-L1 $\geq$ 50%	Pembrolizumab	5670 (5.4)	11.2	19.2	13.6	21.1
PD-L1 $\geq$ 50%	Pembro & PDCT	17000 (16.3)	16.6	26.0	18.9	27.9
PD-L1 1-49%	Pembro & PDCT	66760 (64.0)	10.4	17.9	12.3	19.8

Biomarker, molecular biomarker; 1L treat, first-line systemic treatment; n, number of simulated patients; PFS, progression-free survival; OS, overall survival; BSC, best-supportive care; PDCT, platinum-based doublet chemotherapy, here assumed, Cisplatin and pemetrexed; Dabraf & Tramet, dabrafenib plus trametinib; Pembro, pembrolizumab; EGFR_{classic}, epidermal growth factor receptor (exon 19 deletions and exon 21 L858R point mutation); EGFR_{non-classic}, epidermal growth factor receptor (non-classic activating EGFR mutations, resistance mutations, and other mutations); ALK, anaplastic lymphoma kinase gene rearrangements; ROS1, genetic aberrations of ROS proto-oncogene 1; BRAF, B-Raf proto-oncogene; NTRK_(1,2,3), neurotrophic receptor tyrosine kinase 1; PD-L1, high programmed death ligand 1 expression; Long-term, long-term survivors who their time to death from first-line treatment described by background mortality (DoC); DSA, deterministic sensitivity analysis.

^a Best-supportive care group was kept constant in both strategies.

^b It is assumed the first-line treatment benefits wear-out after 15 months.

^c Percentage withing subgroups of personalized strategy were calculated out of total number of treated patients (denominator 104300).

External validation

The validation results for the EGFR_{classic} subgroup who were treated with first-line TKI (gefitinib or erlotinib) are given in Fig 4 below. When first-line TKI benefit was restricted to 15 months, the modelled PFS and OS curves matched well to the real-world curves of the Santeon registry 2008-2014 and 2015-2018 cohorts. Modelled median PFS of 14.4 months was contained within the 95% CI of Santeon 2008 – 2014 median PFS (i.e., 12.5, 95% CI 9.8 – 18.3 months). Similarly, the modelled median OS of 16.2

months was contained with 95% C.I of Santeon 2008 – 2014 and 2015 – 2018 medians OS, that is 17 months (95% CI 10.3 – 22.2) and 15.5 months (95% CI 11.6 – 19.1), respectively. It should be noted that, when first-line TKI benefit assumed to last until progression, the modelled median PFS and OS were not affected but the long-term PFS as well as OS were over-estimated compared to what was observed (ESM Figure A4).

Fig 5 and ESM Table A8 show the validation results of PD-L1 $\geq$ 50% subgroup who were treated with first-line pembrolizumab monotherapy. Fig 5 shows that the modelled PFS and OS curves match well with the real-world curve of Santeon 2015 - 2018 (blue) with their median within 95% C.I of Santeon 2015 – 2018. Beyond 12 months, model seems a bit optimistic on PFS but match well the OS. Furthermore, the modelled 24 month and 36 month OS rates were closer to the US real-world survival rates [19] (ESM Table A8). The 60 month (5 year) survival rate was the same as that of Keynote-001 [54] that is 23 percent (green lines).

The results of DSA of the mixture cure time to event assumption and value of the long-term survivor fraction are given in Table I and Figure A6 (ESM). Figure A6 shows that, the impact of long-term survivor fraction is on long-term PF and OS with minor impact on earlier time. OS rate at five-year ranged from 16 percent to 31 percent for curve of the long-term survivor fraction of 14 percent and 34 percent, respectively. When the standard time to event distribution was assumed (i.e., 0 percent long-term survivor fraction) in patients with PD-L1 $\geq$ 50% who were treated with pembrolizumab, the median OS was increased by 0.5 month while the mean OS decreased by 42.7 months (3.6 years, Table I). The huge change in the mean OS was due to the longer survival time in the long-term survivor subgroup, which had mean OS of 222 months (18.5 years), while the moderate survivor subgroup had mean OS of 14.4 months (1.2 years) (Table I).

Similar findings were obtained for validation of the group of patients who were treated with a combination of pembrolizumab plus chemotherapy and had either PD-L1 $\geq$ 50% or PD-L1 1-49%. For validation of these two subgroups we used published US real-world estimates (Velcheti, Hu, Piperdi, & Burke, 2021; Waterhouse et al., 2021). See ESM Table A8.

4 Discussion

We developed a patient-level microsimulation model to simulate treatment trajectories for patients with advanced (inoperable) non-squamous NSCLC in the Netherlands. All patients are simulated from diagnosis to death, and undergo at most three treatment lines. The model has been designed to address various HTA questions (such as health-economic, budget impact, or evaluation of clinical guidelines) for treatment decisions for patient with advanced (inoperable) non-squamous NSCLC in the Netherlands. It is urged that multi-use models will improve efficiency and consistence in decision making [60]. In the near future, we plan to use the model to perform *an early CEA of using whole-genome sequencing in treatment decision of NSCLC patients treated with immunotherapy in the Netherlands*.

Internal validation as well as external validation for specific subgroup was demonstrated. External validation was demonstrated for subgroup of EGFR_{classic} treated with first-line TKI and PD-L1 $\geq 50\%$ treated with immunotherapy. External validation was performed comparing the results of personalized strategy against the real-world PFS and OS.

For the EGFR_{classic} subgroup who treated with first-line EGFR-TKI; when first-line EGFR-TKI benefit assumed to last until progression, the model overestimated the long-term PFS and OS compared to the real-world data. When we restricted first-line EGFR-TKI benefit to last up to 15 months, the modelled PFS and OS matched well with the real-world data. Because treatment resistance is known for earlier generation targeted therapies [50], we have extended the assumption of limited first-line targeted therapy's benefit (up to 15 months) to all patients who received first-line targeted therapies. Exception was made for patients with ALK subgroup who received second-generation ALK-inhibitor (alectinib), for durability of first-line treatment benefit of alectinib has been demonstrated in updated results of the ALEX study [61].

The Immunotherapy treated group is known to have delayed treatment effects and/or a subgroup of patient who have better treatment response [56], [62]–[64]. The mixture cure time to event distribution (mixture cure model) have been proposed and used as a modelling solution to improve long-term projection in the immunotherapy treated subgroup [56]–[58], [65], [66]. We have shown that under the standard time to event distribution, the model results a lower long-term OS estimate compared to the real-world OS estimates. On the contrary, when the mixture cure time to event distribution was used, the modelled long-term OS estimates was comparable to the real-world OS estimates. The mixture cure assumption had almost no impact on the median OS and PFS, but affected the mean OS and PFS. The mean OS simulated with the mixture cure time to event distribution was 40 months higher compared to the OS of the standard time to event distribution. This increase was caused by the fact that subgroup of long-term survivor fraction was assumed to have the same mortality rate as the general Dutch population. The assumption whether the mortality rate of long-term survivors is the same as that of the general Dutch population remains to be validated. Nevertheless, recent updated RCT literature have shown, the subgroup of patients (20 to 30 percent) who completed 35 cycle of pembrolizumab had most treatment benefit with more than 80 percent three-year or five-year overall survival rate [53], [55].

HTA decision models for advanced (inoperable) non-squamous NSCLC have been developed before [10], [11], [14]. These studies were mainly based on RCTs. We compared the findings of the base-case analysis of these three studies against the results of the personalized strategy of our proposed model. These studies were selected because they are similar to the proposed model in term of modelling a Dutch perspective and/or used similar sources to incorporate benefits of novel treatment.

The mean life years (mean OS) of the currently proposed model for EGFR-TKI subgroup is four month lower compared to the mean life years reported by Holleman et al. [10] that is, 20.3 months in proposed model compared to 24 (25) months for gefitinib (erlotinib) treatment in Holleman et al. The difference can partly be explained by limiting the benefit of gefitinib (erlotinib) to 15 months to correct for treatment

resistance as also demonstrated in the real-world data. Meanwhile, for the ALK subgroup treated with alectinib, a durable treatment benefit was assumed resulting a mean life years that were twice as high in the proposed model compared to the mean life years reported by Simons et al. [14] (Strategy A, online supplementary) that is, 91.4 months versus 45.6 months. Durability of treatment benefit of alectinib in patients with ALK mutation was supported by updated results of the ALEX study [61].

For patients with PD-L1 $\geq$ 50% who were treated with pembrolizumab monotherapy, the proposed model with 23 percent long-term survivor fraction [54] had twice the mean life years (63.8 months) compared to the reported results by Chouaid et al. [11] (34 months) as well as by Simons et al. [14] (29 months). But when the 0 percent long-term survivor fraction was assumed, the proposed model had lower mean life years (21.1 months) compared to Chouaid et al. and Simons et al. Similarly, for patients with PD-L1 $\geq$ 50% treated with a combination of pembrolizumab and chemotherapy, the mean life years were three times higher compared to Simons et al. when the long-term survivor fraction was assumed (66.5 months vs 23 months), and about 4 months higher when long-term survivor fraction was not assumed (27.9 months vs 23 months).

The differences between the currently proposed model and the three models mentioned above are partly due to different modeling strategies, that is, microsimulation DES model versus Markov cohort models [10], [14] and Partition Survival model [11]; as well as different modelling assumptions adopted in the proposed model such as assuming the mixture cure time to event distribution for immunotherapy. But also, partly due to different underlying population. For proposed model, the real-world population was used instead of RCT. To reproduce the real-world PFS and OS curves under personalized strategy, some model assumptions had to be made that were not implemented in the other models.

Our model has a number of strengths. First, the proposed model accounted for baseline patient heterogeneity by including patients' characteristics such as performance status, gender, and age.

Furthermore, in our model, we included patients who received best-supportive care (BSC) after diagnosis. It is uncommon for HTA studies to include the BSC subgroup, nevertheless BSC remains a largest subgroup of advanced (inoperable) non-squamous NSCLC. In the Netherlands, about 50 percent of patients with advanced NSCLC do not start a first-treatment line [16]. Ignoring this subgroup when making projections of the long-term benefits, costs, and budget impact of personalized care for NSCLC in a specific setting may leads to a distorted result. In addition to that, the proportion of patients undergoing a systemic treatment with life-prolonging intent may change over time as a result of improved toxicity profiles for certain personalized treatments such as immunotherapies. The potential impact of including versus ignoring BSC in the Netherlands can indirectly be identified from [16], [24]. In Cramer-van der Welle et al. [24] the proportion of patients receiving BSC after diagnosis was 59 percent (out of 2989 patients diagnosed between 2008 – 2014), while in Cramer-van der Welle et al. [16], the proportion of patients with BSC dropped to 48 percent (out of 1950 patients diagnosed between 2015 – 2018).

Secondly, the proposed model has flexibility to allow different modelling assumptions to be evaluated using the same model by simply changing model's arguments. Example, the proposed model allows to

model both limited and durable treatment benefit assumptions for targeted therapies. Likewise for immunotherapy, both the standard time to event distribution and the mixture cure time to event can be assumed by specify model arguments. Thus, the impact of such assumption in life years and cost can be evaluated using one model.

Furthermore, the model is syntax based, programmed in R computing language [46]. A syntax based model increase transparency, reproducibility [44] and flexibility. Thus, it can easily be adapted or extended to future data or future developments, if needed.

4.1 Limitations:

Our model has a number of limitations.

Firstly, we have assumed no post-progression survival benefit of treatment. This means that a patient's survival after first-line progression is independent of treatment regimens received during the first-line treatment. This assumption may under or over-estimate estimate long-term survival benefit of novel treatments such as EGFR-TKI and pembrolizumab. Nevertheless, there is limited evidence for the potential magnitude and direction of such benefit. In addition to that, we only accounted for a prognostic impact of the presence of the EGFR_{classic} [51] mutation and presence of an ALK gene rearrangements [52]. For the remaining molecular subgroups, we did not have any evidence on their prognostic significance. However, as the model is flexibly programmed, such prognostic impact can be included when evidence becomes available and this also holds for a post-progression treatment benefit.

Secondly, currently there are no phase III RCTs of crizotinib when used in patients with a ROS1 mutation, the combination of dabrafenib and trametinib used in patients with BRAF_{v600E} mutation, and larotrectinib when used patients with NTRK_(1,2,3) mutation. In simulating the personalized strategy for subgroups ROS1, BRAF_{v600E}, and NTRK_(1,2,3), it was assumed that crizotinib in ROS1 has the similar effectiveness as crizotinib in the ALK subgroup [33], dabrafenib and trametinib was equally effective in NSCLC BRAF_{v600E} as in melanoma BRAF_{val600} [67], and for larotrectinib in NTRK_(1,2,3) was assumed to have PF HR as that of prognostic value of EGFR_{classic} [38]. There was no data to validate the model outputs of these subgroup. In the future application of the model, a sensitivity analysis surrounding the treatment effectiveness on mentioned subgroups will be necessary.

Thirdly, we have assumed that 23 percent of patients treated with first-line immunotherapy (pembrolizumab monotherapy or in combination with chemotherapy) were long-term survivors with survival matching the survival of the general population given age and sex (background mortality). Patients in the long-term survival group were not eligible for second line treatment, they will die from other cause after first-line treatment. The long-term survivor fraction of 23 percent was based on patients attaining five years survival in keynote-001 [54] and it is supported by long-term follow up of keynote-024 [55]. Pembrolizumab treatment is relatively new in clinical care, therefore we had no real-world data

to validate the fraction of long-term survivor nor their survival profile beyond 36 months. Through sensitivity analysis, the impact of long-term survivor fraction was demonstrated.

Fourthly, the real-world template dataset (Santeon registry 2008 - 2014) that formed the basis of our model had a cohort of patients diagnosed and treated prior to the era of personalized treatment. Thus, the template data set did unfortunately not contain molecular characteristics nor the currently used novel treatments. To simulate personalized strategy, we incorporated molecular information from the literature, as well as the impact of novel treatment compared to standard chemotherapy based on published RCTs. This constrained us to the use parametric PH distributions (Exponential, Weibull, and Gompertz) to describe the transitions from the start of first line treatment to death, and necessitated the assumption that novel treatment has the same effects on competing transitions (i.e., time to subsequent treatment line or to death).

Lastly, in the presence of competing events, we have used cause-specific hazard functions to sample time of each competing event separately, and subsequently select the event that occurred first (in HTA literature this method is termed as event specific distribution (ESD) [22]. This choice was a deviation from the standard recommendation to jointly estimate the event time and select the event in a second step by using (multinomial) logistic regression [22], [68]. In this situation, we preferred ESD because of its convenience in estimation in presence of censoring. Also, if a novel treatment is believed to have a different impact on the hazard rate of two competing events, ESD can accommodate this by appropriately adjusting the HRs of particular transitions.

4.2 Conclusion

We developed a multi-application microsimulation model for advanced (inoperable) non-squamous NSCLC in the Netherlands using real-world data. The model was populated with real-world data from six large teaching hospitals in the Netherlands. The model was internally validated, and also externally for the EGFR subgroup of NSCLC patients and for patients with PD-L1 expression receiving immunotherapy. We can argue that, being based on real-world data, the presented model is suitable to project long-term outcomes and cost-effectiveness of novel diagnostics-treatment combinations in the Dutch setting, and consequently to inform Dutch policy makers. In the near future, the model will be used to perform an early CEA of using whole-genome sequencing in treatment decision of NSCLC patients treated with immunotherapy in the Netherlands.

Statements And Declarations

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Authors' Contributions

Z.A.M: model conceptualization, methodology, design, model construction, performed analysis, data interpretation, writing main manuscript, review and editing. J.A.W and V.M.H.C: model conceptualization, methodology, design, model construction, performed analysis, data interpretation, writing main manuscript, review, editing, and study supervision. M.J.H.G.S, B.R, V.R, and M.J: model conceptualization, methodology, design, data interpretation, writing review and editing. C.M.C.v.d.W was responsible for acquisition of dataset, data interpretation, validation, writing review and editing. F.M.N.H.S, and E.M.W.v.d.G: data interpretation, validation, writing review and editing. All authors reviewed the manuscript.

Conflict of Interest

Valesca Retèl has received grants from Agendia B.V. and Intuitive Surgical outside the submitted work. Zakile A. Mfumbilwa, Janneke A. Wilschut, Martijn J.H.G. Simons, Bram Ramaekers, Manuela Joore, Christine M. Cramer-van der Welle, Franz M.N.H. Schramel, Ewoudt M.W. van de Garde, and Veerle M.H. Coupé declare no potential conflict of interest.

Data Availability

Correspondence and requests for data and materials should be addressed to Veerle M.H. Coupé.

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Figures

Figure 1

Microsimulation diagnosis-treatment model.

Arrows indicate the possible movement from an event to either start of a next treatment line or Death; DIAG, diagnosis; L1T, L2T, and L3T are start of first-, second-, and third-line treatment, respectively; BSC, best supportive care i.e., patients who are ineligible for L1T; Treated, patients who started at least one line of systemic treatment; Gray dotted cycle and lines, denote the treatment model and trajectory from DIAG, time from DIAG to L1T and time from DIAG to Death were modelled independently; Black complete cycles and lines denote the disease model and trajectory after treatment initiation, corresponding time to events (time to start of next treatment or death) from one event to another were modelled as parametric multistate statistical model (par MSSM).

SoC, standard of care; * EGFR includes classic activating EGFR mutation (exon 19 deletions/ 21 L858R, i.e., EGFR_{classic}), and non-classic activating EGFR mutation, resistance mutation and other mutations (i.e., EGFR_{non-classic}); (+), with; x, randomly assign to Immunotherapy or Immunotherapy with PDCT; PDCT, platinum doublets chemotherapy.

Figure 2

Molecular diagnosis-treatment decision tree.

Figure 3

Jitter plot comparing modelled and observed progression-free survival (PFS) probabilities and overall survival (OS) probabilities.

(a) and (b), OS and PFS from start of first-line treatment (1L); (c) and (d), OS and PFS from start of second-line treatment (2L); (e), OS from start of third-line treatment (3L); Vertical black dot and lines indicate point estimate and 95% confidence interval of observed probabilities from template data.

Figure 4

Comparison of modelled and real-world survivals curves for patients with the epidermal growth factor receptor (EGFR) mutation who had first-line EGFR tyrosine kinase inhibitor (EGFR-TKI).

EGFR-TKI were gefitinib or erlotinib;

Real-world included 52 Santeon patients' level data diagnosed and treated between 2008 – 2014 (blue) [40], and the digitized OS curve of 147 overall survival curve of Santeon patients diagnosed and treated between 2015 – 2018 (Orange) [16].

1L, first-line systemic treatment;

Modelled (black curve) was simulated such that, outHR for gefitinib was 0.43, erlotinib is 0.36 (NMA, Holleman et al., 2019), and prognostic value of EGFR was 0.82 (pooled, Simons et al., 2020); outHR was estimated by censoring simulated time at 20 months; inHR was 0.38, 0.25, and 0.80 for gefitinib, erlotinib, and prognostic value of EGFR, respectively; EGFR-TKI benefit was assumed to wear out after 15 months.

Figure 5

Comparison of modelled and real-world survival curves for patients with PD-L1 $\geq 50\%$ who were treated with pembrolizumab monotherapy.

PD-L1, programmed death ligand 1.

The real-world curves were fitted from digitized Santeon progression-free and overall survival curve of 83 patients diagnosed and treated between 2015 – 2018 [16]; Modelled (black curve) was simulated such outHR was 0.5 (RCT, [36]). Assuming a long-term survivor fraction of 23 percent and inHR of 0.75.

outHR was estimated with censoring of simulated time at 20 months. U.C.I, upper confidence interval; L.C.I, lower confidence interval; 5 yrs OS RCT, five-year overall survival from randomize control trial taken from Five-year update of Keynote – 001 [54].

Supplementary Files

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