Health economic effects of introducing comprehensive genomic profiling in precision oncology: A case-study on non-small cell lung cancer therapy in Belgium.

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14-03-2021

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1. Introduction

1.1. Lung cancer

Lung cancer is the largest cause of cancer-related deaths worldwide (Bray et al., 2018). Incidence is highest in Europe, North America and parts of Asia; and quickly rising in developing nations (Bray et al., 2018). Smoking is by far the biggest risk-factor in lung cancer and creates familiar patterns in incidence and mortality across the world as tobacco companies successfully introduce their product and are subsequently reined in by tobacco control policies (de Groot et al., 2018; Malhotra et al., 2016). This pattern usually happens in men first, followed by women. The US were the first to reach a peak for lung cancer incidence in 2005 and it has been decreasing ever since (Barta et al., 2019). In Belgium, like in many European nations, the overall incidence continues to increase as the decreasing incidence in males is offset by a continued increase in females (Barta et al., 2019; *Belgian Cancer Registry*, 2018a). Countries in the developing world seem destined to repeat these patterns as tobacco companies shift their marketing and lobbying efforts to territories with less comprehensive tobacco control policies. The greater socio-economic inequality, inconsistent access to healthcare and greater environmental contamination in these regions will likely aggravate the issue. Apart from smoking, about a quarter of lung cancer diagnoses happen in people who have never smoked (Sun et al., 2007). Other risk-factors include radon and asbestos exposure, air pollution, ionising radiation, chronic obstructive pulmonary diseases (COPD) & genetic predisposition (Malhotra et al., 2016). The Belgian cancer registry has been collecting data on cancer diagnosis and follow-up since the mid 90s and registers 8.000 new lung cancer diagnoses every year (*Belgian Cancer Registry*, 2018a).

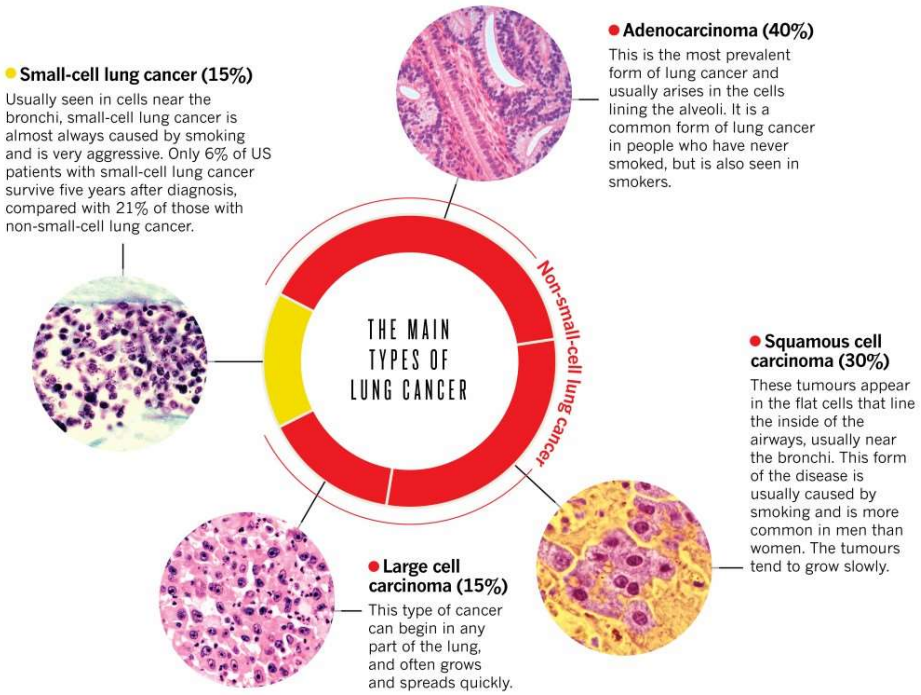


Figure 1: Histological subtypes of lung cancer (Bender, 2014)

Lung cancer can be divided in two main types: small-cell lung cancer (SLCL) and non-small cell lung cancer (NSCLC) (Bender, 2014). More than 80% of lung cancer diagnoses are non-small cell lung cancers (NSCLC). NSCLC, in turn, branches out in three subtypes based on the cancer's cellular origins. Adenocarcinoma (ADC) originates in mucus-secreting cells, squamous cell carcinomas start in the squamous cells that make up the inner lining of the lungs, while large cell carcinoma grows from undifferentiated cells in any part of the lungs (Figure 1) (Bender, 2014).

Early stage lung cancer can often successfully be treated with surgery and radiation therapy. Yet early screening programs for lung cancer are virtually non-existent and remain a hotly debated topic among health economists (Shojaee et al., 2017). Lung cancer symptoms, like coughing and chest pain, usually only appear when the cancer has progressed. As a result, more than 70% of all lung cancers are locally advanced (stage III) or metastatic (stage IV) at diagnosis (Belgian Cancer Registry, 2018b). For decades the only available therapy for these unresectable cancers was chemotherapy and expectations were grim (Lu et al., 2019). Advanced stage lung cancer inevitably progresses and five-year survival was less the 5%. The gradual introduction of precision medicine in the last decade has improved this outlook and patient subgroups receiving personalised treatment are exceedingly extending their overall survival and quality of life (Joshi et al., 2020).

1.2. Precision medicine & immunotherapy

Joshi et al. (2020) describe the advent of precision medicine and the promise it holds for improving the overall survival (OS) and health-related quality of life (HRQoL) of lung cancer patients. Precision medicine refers to the tailoring of treatments based on biomarkers in a subset of patients. In cancer, these biomarkers are usually specific oncogenic drivers. Two types of precision medicine exist. Targeted therapies are therapeutic agents aimed at stopping hyperactive cellular proliferation pathways caused by a mutation in a specific gene. They are usually gene- and tissue-specific although some have been successfully validated in tumours with the same mutation from different tissues or even in tumours with a different mutation. Immunotherapies are therapies that target the interaction between cancer cells and the immune system, they are often tissue-agnostic and have shown promising results in many cancer types. Unlike targeted therapy that can only be used in the minority of patients that presents with a actionable gene mutation, immunotherapy has the potential to complement or even replace chemotherapy as the standard first-line treatment in advanced cancer (Joshi et al., 2020).

Majeed et al. (2021) give an overview of the history and future perspectives of targeted therapy in lung cancer, which have only proven effective in non-squamous NSCLC. The first therapies were developed after the discovery of *EGFR*-activating mutations in subsets of patients. Currently, third generation EGFR Tyrosine Kinase inhibitors (TKIs) are being evaluated in early phase trials. Other activating mutations have been targeted with TKIs as well. ALK & ROS1 TKIs have become an indispensable element in the arsenal of non-squamous NSCLC treatment in the last decade, while more recently NTRK TKIs have also proven to increase survival in patients with *NTRK* fusions. Apart from TKIs, drugs with different mechanisms of disrupting oncogenic drivers have been launched for patients with specific *BRAF*, *MEK* and *RET* alterations. Although targeted therapies are very effective, only 20 to 30% percent of lung cancer patients have an actionable mutation (Majeed et al., 2021).

The current advances in immunotherapy-treated lung cancer were reviewed by Lim et al. (2020). Like targeted therapies, immunotherapies are a group of therapies with various different mechanisms of action. Immune checkpoint inhibitors (ICIs) are currently the most relevant for lung cancer and are effective in both squamous and non-squamous NSCLC. After discovering that many cancer cells disarm the immune system by over-expressing programmed death ligand 1 (PD-L1), drugs blocking PD-L1 from binding on host T-cells became interesting drug candidates. ICIs like pembrolizumab and nivolumab have become an effective treatment option for many different types of cancer, often drastically improving overall survival chances (Lim et al., 2020). The initial clinical trials for these drugs generated tremendous gains in overall and progression free survival in patients with a very dim survival rate, forcing many national health care payers to break the bank and reimburse these

therapies well above the cost-effectiveness threshold. In spite of this, the benefits from immunotherapy are far from guaranteed. The European Society of Medical Oncology (ESMO) advises first-line pembrolizumab for patients with tumours expressing PD-L1 in more than 50% of the cells, even though an objective response was achieved in less than half of the patients in clinical trials (Planchard et al., 2020; Reck et al., 2016). Tumours with a PD-L1 expression score of less than 50% are advised to receive first-line pembrolizumab and chemotherapy combination therapy to which even fewer respond (Cuppens et al., 2020; Gandhi et al., 2018; Planchard et al., 2020).

In 2005, 1.6% (roughly 50 million euros) of the Belgian healthcare budget for pharmaceutical specialties was spent on precision oncology drugs. In 2021, around 10% of the budget, or more than 800 million euros, will be spent on precision oncology drugs (Van Dyck et al., 2016). Though these therapies have increased the OS and HRQoL of cancer patients, the high costs and seemingly random distribution of benefits have raised concerns among decision makers and policy analysts (Annemans, 2018; Van Dyck et al., 2016). Effective diagnostics to better stratify patients, find actionable targets and/or response-predicting biomarkers are of crucial importance to the cost-effective use of these hyper expensive treatments, yet they are often treated as an afterthought (Govaerts et al., 2020). In NSCLC, as in oncology as a whole, better diagnostics can lead more people into potentially life-saving clinical trials and reduce the budget impact of immunotherapies.

1.3. Current diagnostic practices

Diagnostic cascades are often a complex combination of techniques to which newly discovered biomarkers are added in a modular fashion, leading to inefficient pathways and long turnaround times (Roelofsen-De Beer et al., 2020). For medical laboratories, especially those subject to ISO certification and national accreditation bodies, validating and implementing new biomarkers at the same pace as they are discovered presents a big challenge (Roelofsen-De Beer et al., 2020). Additionally, diagnostic tests are often reimbursed months, if not years, after their counterpart therapy (Govaerts et al., 2020). Leaving already underfinanced and understaffed labs at the grace of diagnostic manufacturers to prove the clinical and health economic value of tests that can improve patient outcomes in their hospital.

In NSCLC the standard of care cascade is a combination of histopathology, immunohistochemistry (IHC), fluorescent in situ hybridization (FISH) and molecular testing (Pauwels et al., 2016, 2018). Some biomarkers can be multiplexed in a single test, others need individual assessment. As a result, the sequential strategy used to assess NSCLC subtypes differs from one laboratory to another, leading to delays in time to treatment with potentially dramatic consequences (Neal et al., 2015; van de Ven et al., 2019). In an attempt to streamline the diagnostic cascade pathologists from the Belgian Society of Pathology (BSP) published the decision tree in Figure 2 (Pauwels et al., 2016, 2018). Samples with a clear squamous morphology are advised to be tested for PD-L1 expression to determine suitability for immunotherapy. Non-squamous samples require additional molecular testing. At a minimum, *EGFR* mutations, *ROS1* fusions and *ALK* fusions need to be assessed. In addition to the BSP guidelines, ESMO advises testing for *NTRK* fusions, *MET* exon 14 skipping and *BRAF*, *PIK3CA* and *ERRB2* mutations (Planchard et al., 2020). Mutations are commonly tested by next-generation DNA sequencing. Fusions genes can be visualized with IHC probes and confirmed with FISH. Due to the increasing amount and importance of clinically relevant fusion genes, the Belgian Commission for Personalized Medicine (ComPerMed) recently added RNA sequencing to the NSCLC workflow as an alternative to IHC + FISH testing (*ComPerMed*, 2021). Although effective, RNA sequencing requires some inhouse expertise in molecular biology and bio-informatics and turnaround times remain low even in advanced labs (UZ Ghent, 2021; UZ Leuven, 2021).

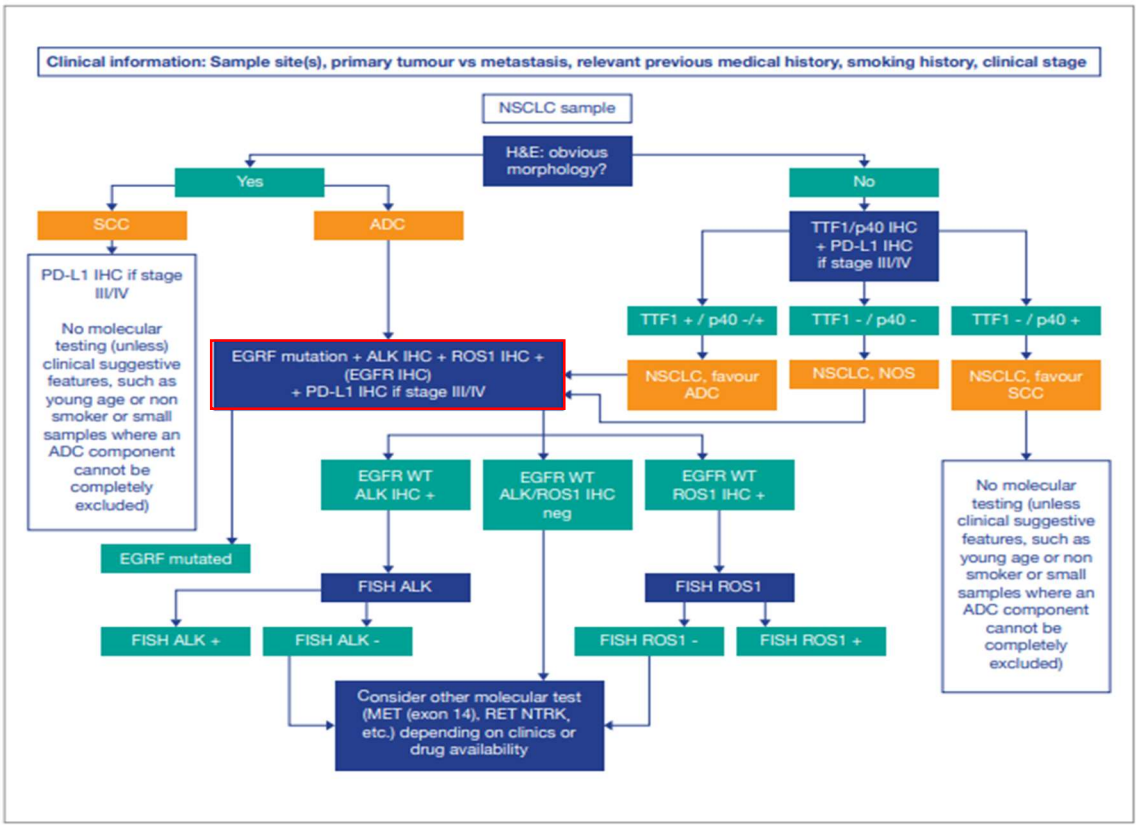


Figure 2: Sequential diagnostic cascade of NSCLC samples in Belgium as advised by Pauwels et al., (2018). Red box marks start of molecular testing, potential place of comprehensive genomic profiling.

Whole genome sequencing has long been thought to be the eventual endpoint of the continuous innovation in genomic technology. In WGS the entire genome of a normal and a tumour cell are sequenced and aligned, revealing all genomic differences between the two (Nakagawa & Fujita, 2018). In oncology diagnostics, it could replace all currently used targeted sequencing panels, detect DNA mutations and RNA fusions and future-proof the diagnostic cascade for yet-to-become actionable alterations (Nakagawa & Fujita, 2018). In 2016, the Dutch research organisation ZonMw assessed the potential of WGS in oncology in the TANGO project. Preliminary results presented at conferences at their annual symposium are freely available on the Zenodo platform. For now, the project concluded that WGS is not cost-effective in metastatic NSCLC (Tango project researchers, 2020).

Comprehensive Genomic Profiling (CGP) is a compelling alternative to WGS in oncology diagnosis. Since it doesn't sequence two whole genomes it is more feasible in sequencing costs and data analytics. Yet its scope is wide enough to enable the detection of all mutations and fusions currently known to be relevant in oncology, meaning it could be a first-line molecular test across all cancer types and lead patients without currently actionable biomarkers to ongoing clinical trials. CGP has been shown to perform to the same standard as WGS for the scoring of aggregate markers such as tumour mutational burden (TMB), Human Leukocyte Antigen (HLA) diversity and microsatellite instability (MSI) (Szustakowski et al., 2018), as such it could lead to more effective use of immunotherapy. In lung cancer, CGP offers the additional benefit of easing the pressure to get a high tumour yield from the biopsy and reducing the chance of needing a re-biopsy (Kim & Tsao, 2014; Planchard et al., 2020).

Research on CGP's clinical value and applicability was previously published by researchers at RadboudUMC (Kroeze et al., 2020). Earlier this year the Belgian Society of Medical Oncology (BSMO)

partnered with several companies with the intention to study the clinical value of CGP using Illumina's TSO500 panel in the BALLETT study (*Press Release*, 2021). With research to CGP's clinical value ongoing, very little evidence exists regarding the health economic value of CGP. The introduction of a new, more expensive diagnostics will require will require proof of cost-effectiveness before it can become part of the standard of care (SoC).

1.4. Health economic modelling

Health technology assessment in diagnostics and genomics is subject to much debate and methodologies developed for drugs or medical devices are not necessarily adequate for sequencing-based tests (Wordsworth & Buchanan, 2019). Establishing an adequate comparator can be difficult as the standard of care might differ from one lab to another (Buchanan & Fermont, 2016). Generating average costs and outcomes over a lifetime horizon is near impossible since patients are usually not followed up longitudinally and the analytical context might change with different samples (Buchanan & Fermont, 2016). Moreover, the great ethnical and regional variability in the genetics of a population affects the efficacy of a genomic diagnostic. As a result, many diagnostic tests enter the market under a Research Use Only (RUO) label.

Capturing the value of CGP as a first-line diagnostic in precision oncology is beyond the scope of this work. The framework for many facets of its value is still being developed and real-world data to support definitive conclusions is missing. Instead, this report uses two early models to simulate the health economic effects of introducing CGP. First, the value of finding more genomic alterations and sending more patients into potentially life-saving clinical trials is assessed. Second, the cost-savings that can be generated by having more adequate predictors of durable response to immunotherapy are estimated. Though these benefits apply to all cancer types that can be treated with targeted and immunotherapy, this case study focusses on NSCLC, a cancer with a complex diagnostic cascade and a correspondingly complicated arsenal of treatments.

1.5. Objective and Research Questions

This evaluation neatly fits in the ongoing assessments of comprehensive genomic profiling as a standard first-line diagnostic test in oncology. Research on the clinical value of CGP for NSCLC is ongoing, but reimbursement agencies will require proof of cost-effectiveness before it can become part of the standard of care (SoC). This work can provide more information for the decision makers deciding on reimbursement for diagnostic practices.

Main research question: *What is the health economic value of CGP in the diagnosis of metastatic, non-squamous NSCLC?*

1) *What is the value of finding more gene alterations in metastatic, non-squamous NSCLC patients and entering more patients to clinical trials?*
2) *What savings can be made by stratifying patients for immunotherapy using biomarkers resulting from CGP rather than just PD-L1 expression?*

2. Research Methods

2.1. Overview

This report aims to determine the value of CGP as a standard first-line diagnostic in patients with metastatic, non-squamous NSCLC in Belgium. Two effects of introducing CGP on the use of therapy are analysed.

Firstly, the value of finding additional gene alteration and sending more patients to clinical trials is determined using a decision model comparing CGP with the SoC cascade in the Belgian health care setting. CGP has a much broader scope than the SoC in terms of genomic biomarkers and is assumed to have a positive impact on the fraction (%) of patients being identified with a gene alteration. If more gene alterations are identified, more patients with metastatic, non-squamous NSCLC are expected to be treated with targeted therapies, which will result in positive health effects. Within the decision model, a partitioned survival model was build to allow modelling of the costs and effects for patients with and without an identified gene alteration. Model inputs for this partitioned survival model were taken from the BIOMARKERs study, an observational study conducted between April 2012 and July 2014 in 17,664 patients, that compared patients with and without an identified gene alteration (Barlesi et al., 2016). In the decision model the outputs from the partitioned survival models are weighted against the distribution of the patients across both groups (gene alteration identified and unidentified) by the diagnostic cascade. Finally, the costs of the diagnostics (GCP and SoC cascades) are taken into account to result in average costs and effects of CGP versus SoC resulting in an ICER/LY (Figure 3a).

In a second part of this report the more efficient stratification of patients for immunotherapy and chemotherapy by CGP is analysed. Again, a decision model comparing CGP with the SoC cascade in the Belgian health care setting is developed. Currently, stratification for immunotherapy or immunotherapy + chemotherapy is done solely based on PD-L1 expression levels and only in a minority of patients an objective response is achieved. Using a combination of biomarkers from CGP is expected to lead to better prediction of susceptibility and resistance to immunotherapy. Certain patient subgroups, in which no response could have been achieved with immunotherapy, can immediately be treated with much cheaper chemotherapy. Partitioned survival models are created to generate average costs and outcomes for each patient subgroup as well as for non-responders. Model inputs are taken from the KEYNOTE-024 and -189 trials, comparing the effects of immunotherapy and/or chemotherapy in patients with different levels of PD-L1 expression (Gandhi et al., 2018; Reck et al., 2016). The decision model then weights the outputs from the partitioned survival model against the distribution of patients in each subgroups. Again, the final step is to take the costs of diagnostics into account to result in average cost savings per patient (Figure 3b).

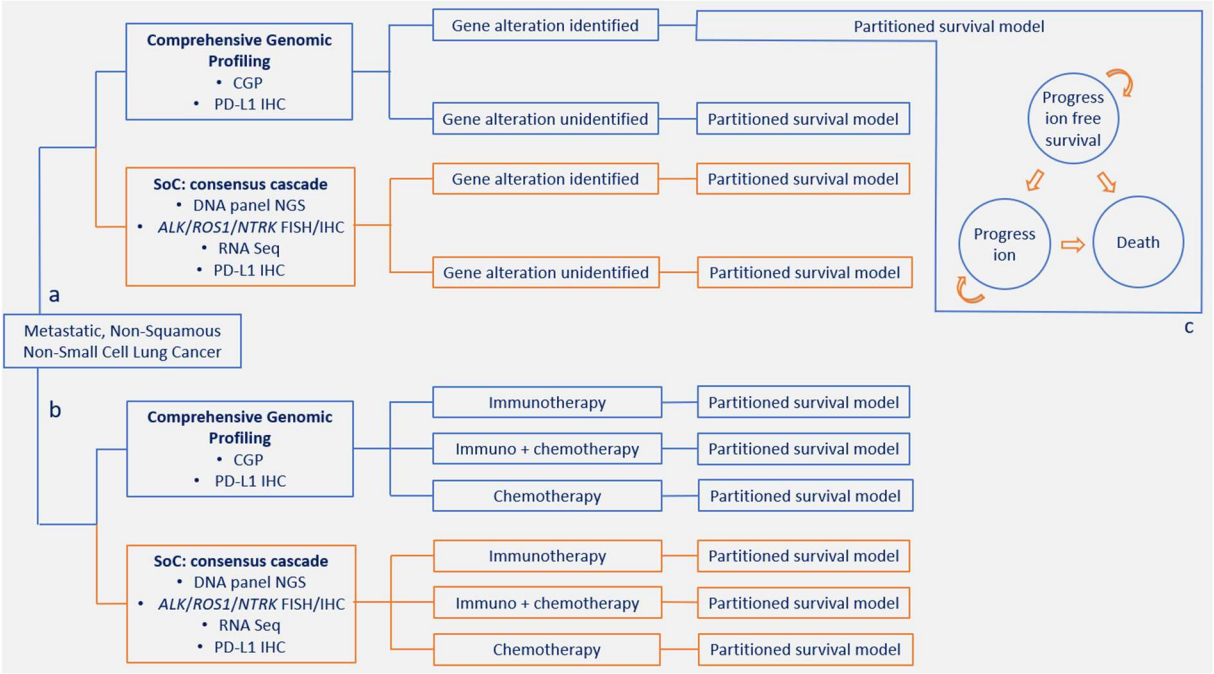


Figure 3: Overview of the analyses in this report. (a) Cost-effectiveness analysis of identifying genomic markers using CGP or the SoC cascade. (b) Cost-savings model by using CGP or SoC cascade to stratify patients for immunotherapy. (c) Partitioned survival model used to determine average costs and outcomes for each patient subgroup.

2.2. Partitioned survival models

2.2.1. Model characteristics

All models are constructed following the guidelines of the Belgian Healthcare Knowledge Centre (KCE) (Swartenbroeckx et al., 2012). All costs are sourced with a healthcare payer perspective as required, but no evidence exists about the HRQoL of targeted therapies or immunotherapies as a whole. Therefor Life Years (LYs) gained, rather than Quality-Adjusted Life Years (QALYs) gained, are used as a primary outcome. The introduction of CGP is assumed to result in more patients having access to targeted therapies and more efficient use of immunotherapy. Since targeted therapies are generally accepted to be associated with higher HRQoL compared to conventional chemotherapy, and non-responders to immunotherapy do not lose any utility from not getting ineffective treatment, using LYs rather than QALYs is a warranted and conservative approach.

The KCE requires a time horizon that catches all relevant costs and outcomes associated with patients in each group. Traditionally, cost-effectiveness studies on metastatic NSCLC have used 10-year horizons since 5-year survival rate has been lower than 5% for decades. However, both targeted therapies and immunotherapies have significantly increased that number, some patient subgroups even reaching 20-30% 5-year survival rates (EB et al., 2019; Lin et al., 2016). Unfortunately, most of these therapies have only been launched in the last 5 to 10 years and no long-term survival data exists. All partitioned survival models will therefore use a 20-year horizon. Cycle length is set at 3 weeks. All future costs and outcomes are half-cycle corrected when appropriate and discounted to account for time preference. As required by the KCE the discount rate is set at 3% for costs and 1.5% for outcomes. The discount rate is used to generate a discount factor (D_n) for every year of the horizon using the following formula:

$$\mathbf{D_n = 1 / (1+r)^n}$$

D_n= discount factor

r = discount rate

n = number of years ahead

2.2.2. Gene alteration identified vs unidentified – clinical input

The partitioned survival model for patients with and without an identified gene alteration is based on the BIOMARKERs study by the French Cooperative Thoracic Intergroup (IFCT) (Barlesi et al., 2016). The researchers compared 17,774 non-squamous NSCLC patients and determined PFS and OS for patients with an identified gene alteration in *EGFR, ERBB2*, *KRAS*, *BRAF*, *PIK3CA* and *ALK* and for patients without a gene alteration in these genes. Patients got treatment based on decisions by the treating physician who either adapted treatment based on the available genomic information or prescribed a chemotherapy regimen. Patients could also be entered into clinical trials or receive best supportive care only. Three third generation platinum-based chemotherapy doublets were available, with cisplatin/pemetrexed the favoured option. Targeted therapies consisted of first-generation *EGFR* TKIs and crizotinib, an *ALK* TKI.

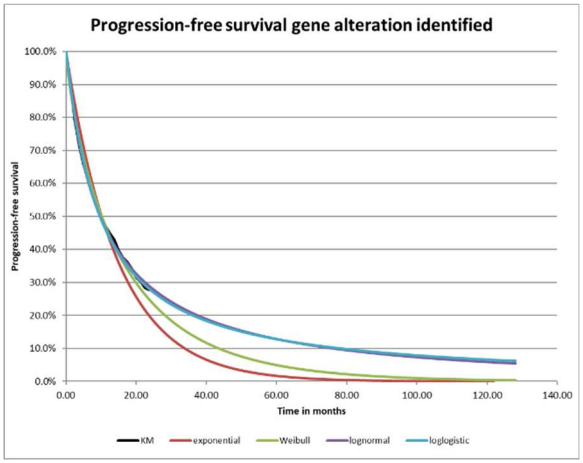
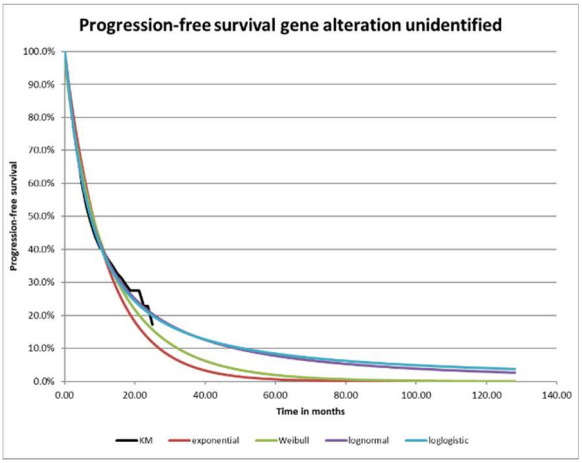
The average distribution across the therapy options for the group with and without an identified gene alteration can be found in table 1. The full distribution of first- and second-line therapies in the BIOMARKER study can be seen in supplementary table 1. Patients were assumed to receive first line treatment until progression and an average of 6 cycles of second line therapy after progression.

Distribution				
	First line		**Second line**	
	Gene alteration identified	**Gene alteration unidentified**	**Gene alteration identified**	**Gene alteration unidentified**
Targeted therapy	31%	1%	21%	12%
Chemotherapy	46%	55%	25%	25%
Trial	3%	3%	2%	3%
BSC only	27%	30%	47%	50%

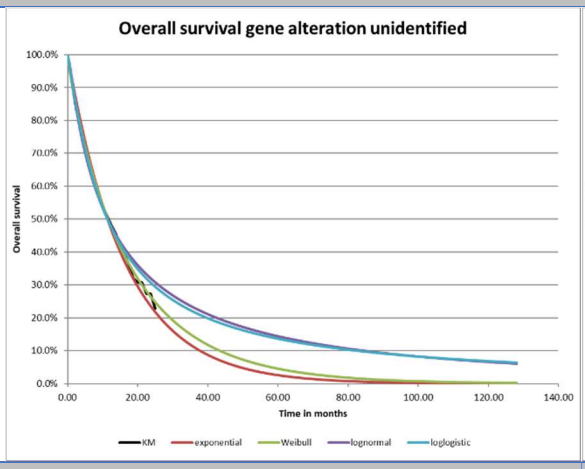
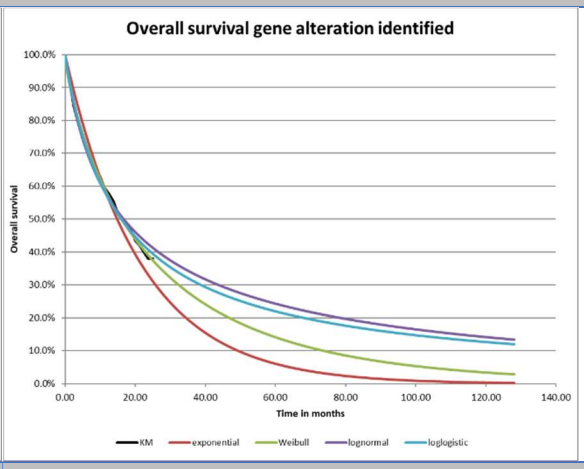
Table 1: Treatment distribution for different patient groups in the BIOMARKERS study. Adapted from Barlesi et al., (2016).

The Kaplan-Meier (KM) PFS and OS curves from the BIOMARKERs study presented by Barlesi et al. (2016) are used to estimate the underlying individual patient data (IPD) using the methods described by Hoyle & Henley (2011). The IPD are fit and extrapolated to the lifetime horizon along four distinct parametric distributions (exponential, Weibull, lognormal and loglogistic). All OS and PFS KM curves and corresponding parametric distributions are presented in table 2. The fit between each parametric curve and the actual KM data is evaluated visually and by calculating the Akaike Information Criteria with the R script also provided by Hoyle & Henley (2011).

Although the lower AIC suggests the lognormal curve is a better fit for both targeted therapy and chemo PFS, the Weibull curve is a more clinically plausible option. The heavy tail of the lognormal curve is unlikely to fit the real world as a small percentage of patients would have to survive progression-free for more than a decade. Moreover, given that Weibull is the best fit for the OS curve, choosing a lognormal distribution for PFS would mean the proportion of patients surviving progression free is higher than the overall survival could allow. Once more, the lack of long-term survival data on targeted therapies creates considerable uncertainty, as the lognormal curve might be a better fit for the higher overall survival rates of targeted therapies. This is explored in sensitivity analysis.

PFS	
	

Gene alteration identified				Gene alteration unidentified			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
12249.83	12172.58	12120.88	12139.9	3878.486	3863.541	3834.025	3836.769

OS	
	

Gene alteration identified				Gene alteration unidentified			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
10654.88	10564.59	10569.72	10581.41	3555.22	3551.243	3563.00	3557.80

Table 2: PFS and OS KM curves and parametric distributions to extrapolate the data. Corresponding AIC for the fit of each parametric distribution to the KM data.

2.2.3. Immunotherapy models – clinical input

The KEYNOTE trials are a series of randomized controlled trials (RCTs) sponsored by Merck Sharp & Dohme (MSD) to test the effectiveness of their immunotherapy pembrolizumab in different patient populations and against different comparators. In KEYNOTE-024, patients with advanced NSCLC, a PD-L1 score ≥ 50% and no actionable alterations in *EGFR* and *ALK* received 35 cycles of pembrolizumab or a platinum-based chemotherapy doublet (Reck et al., 2016). In KEYNOTE-189, patients with advanced NSCLC and no actionable alterations in *EGFR* and *ALK* received 35 cycles of pembrolizumab + a platinum-based chemotherapy doublet or a platinum-based chemotherapy doublet + placebo (Gandhi et al., 2018). The KEYNOTE-189 researchers presented results stratified by PD-L1 expression level (Gandhi et al., 2018).

Both clinical trials showed a significant increase in PFS and OS in the pembrolizumab-treated patient group. An objective response rate was reached in 44.8%, 48.4% and 32.3% of PD-L1 ≥ 50%, 50% > PD-L1 ≥ 1 % and PD-L1 < 1 % patients, respectively (Gandhi et al., 2018; Reck et al., 2016). As a result, ESMO guidelines were updated to make pembrolizumab the first-line therapy for advanced NSCLC patients with PD-L1 score ≥ 50%; and pembrolizumab + chemotherapy the first-line therapy for advanced NSCLC patients with a 1% ≤ PD-L1 score < 50% and PD-L1 negative patients (PD-L1 < 1%) (Planchard et al., 2020).

Using the data from KEYNOTE-024 and -189, three separate partitioned survival models are constructed to quantify average costs and outcomes for populations with PD-L1 ≥ 50%, 50% > PD-L1 ≥ 1 % and PD-L1 < 1 %. PFS and OS KM curves from the trials are extrapolated and fit to parametric distributions using the same method as before (section 2.2.2.). All KM curves and AIC scores can be found in the supplementary table 2-4 in the appendix. Similar to the previous model, the Weibull distribution is the best choice to model PFS and OS in all models regardless of AIC scores, since the heavy tails of the lognormal and loglogistic distributions make them clinically implausible.

2.2.4. Cost inputs

2.2.4.1. Drug acquisition costs

A targeted therapy proxy was created based on the average cost per day of all patent protected targeted therapies for NSCLC currently reimbursed by the Belgian healthcare payer (table 3). This proxy will be used to model costs for targeted therapy. Given that this is an average, the uncertainty this creates will be investigated in sensitivity analysis.

Name	**Price/tablet**	**Daily/dosage**	**Cost per day**	**Target**
Ceritinib	€ 31.20	3	€ 93.60	*ALK*
Afatinib	€ 71.85	1	€ 71.85	*EGFR*
Osimertinib	€ 215.33	1	€ 215.33	*EGFR*
Crizotinib	€ 82.15	4	€ 328.60	*ALK + ROS1*
Alectinib	€ 25.87	8	€ 206.93	*ALK*
Lorlatinib	€ 184.59	1	€ 184.59	*ALK + ROS1*
Dabrafenib	€ 60.41	4	€ 241.64	*BRAF*
Trametinib	€ 227.25	1	€ 227.25	*BRAF + MEK*
Larotrectinib	€ 130.00	2	€ 260.00	*NTRK*
Source	Riziv – *Geneesmiddelen* (web application)	Package inserts		Cancer.org
		Average	**€ 203.31**	

Table 3: A targeted therapy proxy to be used in the gene alteration identified vs unidentified model. The proxy is based on the average cost per day of all targeted therapies patent-protected and currently reimbursed in Belgium.

Costs for patients on chemotherapy are based on the most commonly used platinum-based chemotherapy doublet regimen in advanced NSCLC, three weekly intravenous injections of 500 mg/m2 pemetrexed and 75 mg/m2 cisplatin for 6 cycles followed by three weekly 500 mg/m2 pemetrexed maintenance therapy. Costs for pembrolizumab are calculated for 200 mg once per cycle intravenously.

Dose per cycle and dosage are taken from package inserts. Unit price are sourced from RIZIV/INAMI's *Geneesmiddelen* web application on which drug acquisition costs for the Belgian health care payer

are published (RIZIV/INAMI, 2021). When more than one option was available cheapest price was taken. Unit prices are multiplied with units per cycle to obtain costs per cycle (Table 4).

	Targeted therapy (proxy)	Pembroli-zumab	Platinum doublet chemotherapy		Pemetrexed mainten-ance therapy	Source
			Peme-trexed	Cisplatin		
Admin method	Oral	IV	IV	IV	IV	Package insert
Doses per cycle	21	1	1	1	1	
Dosage	1	200 mg	500 mg/m^2	75 mg/m^2	500 mg/m^2	
IV min/admin	/	30	10	120	10	
Treatment duration	TDP	TDP	6 weeks	6 weeks	After 6 weeks	BIOMARKER & KEYNOTE
Formulation	/	100 mg/4ml	500 mg 100 mg	100 mg 50 mg	500 mg 100 mg	Package insert
Unit Price (€)	203.31	3460.26	422,23 84,47	40.80 22.99	422,23 84,47	Riziv – *Genees-middelen* (web application)
BSA (m^2)	1.79	1.79	1.79	1.79	1.79	(Sacco et al., 2010)
Required units per cycle	21	2	1+4	1+1	1+4	
Costs/cycle	**€ 4,269.51**	**€ 6,920.52**	**€ 760.21**	**€ 63.79**	**€ 760.21**	

Table 4: Calculation of drug acquisition costs per cycle using information from clinical trial regimens, package inserts and prices published by RIZIV.

2.2.4.2. Premedication and concomitant medication costs

Patients receiving platinum-based chemotherapy doublets receive pre- and concomitant medication to manage side effects and avert allergic reactions. Dose per cycle and dosage is sourced from package inserts, unit prices from *Geneesmiddelen* web application. Unit price is multiplied by units per cycle to obtain costs per cycle.

	Dexamethasone	Folic acid	Vitamin b12	Source
Admin method	IM	Oral	IM	Package insert
Doses per cycle	3	31	1/3	
Dosage	5 mg	1 mg	1000 mg	
Unit Price (€)	1.52	1.50	120.00	Riziv – *Geneesmiddelen*
Required units per cycle	3	21	1/3	
Costs/cycle	**€ 4.56**	**€ 31.50**	**€ 40**	

Table 5: Calculation of premedication and concomitant costs per cycle for patients on chemotherapy regimens.

2.2.4.3. Drug administration costs

Intravenous therapy administration (chemotherapy and pembrolizumab) requires supervision from a trained oncologist and the infusion is prepared by a pharmacist. Sources for the costs per hour of these healthcare professionals come from the KCE manual for costing and are indexed using the Belgian Health Index as described in section 2.2.4.8.

Medical specialist	Hourly costs	Source/comment
Oncologist	€ 100.45	1/4 * half a day costs from KCE Report (Cleemput et al., 2012), indexed from 2012 using Be-HI
Pneumologist	€ 98.45	1/4 * half a day costs from KCE Report (Cleemput et al., 2012), indexed from 2012 using Be-HI
Radiologist	€ 173,41	1/4 * half a day costs from KCE Report (Cleemput et al., 2012), indexed from 2012 using Be-HI
Pharmacist	€ 61.70	Hourly costs from KCE Report (Cleemput et al., 2012), indexed from 2012 using Be-HI

Table 6: Hourly costs for healthcare professionals in Belgium.

	Pembrolizumab	Chemotherapy	Source
Oncologist supervision	30 min	30 min	KOL interview
Pharmacist preparation	1 hr	1 hr	
Costs/cycle	**€ 111.93**	**€ 111.93**	

Table 7: Calculation of drug administration costs per cycle for patients receiving intravenous therapy.

2.2.4.4. Disease management

Costs for healthcare resources used in disease management were based on the RIZIV/INAMI Nomensoft web application. Frequency of use was taken from a KOL interview. Radiologists were assumed to need 30 min for an MRI/CT scan. Forfaits for consultations/day visits in the oncology ward were separated by therapy (basic for oral tablets/targeted therapy, maxi forfait monotherapy for pembrolizumab, maxiforfait combitherapy for pemetrexed/cisplatin).

	Costs	Source/comment
Outpatient consultation	€ 50.28	Forfait oncologische basiszorg – Riziv Nomensoft (web application)
Outpatient day visit monotherapy	€ 127.47	Maxiforfait monotherapy oncologisch dagziekenhuis – Riziv Nomensoft (web application)
Outpatient day visit combitherapy	€ 171.02	Maxiforfait combitherapie oncologisch dagziekenhuis – Riziv Nomensoft (web application)
Lab tests	€ 72.88	Sum of costs for hematological, renal & hepatic tests from Riziv – Nomensoft (web application)
Tumour response assessment (MRI/CT)	€ 132.66	Tomography – Riziv Nomensoft (web application)

Table 8: Costs of healthcare resources used in disease management.

	Targeted therapy proxy		Pembrolizumab		Chemotherapy	
	SD	PD	SD	PD	SD	PD
Outpatient consultation	1	1	0	0	0	0
Outpatient day visit monotherapy	0	0	1	1	0	0
Outpatient day visit combitherapy	0	0	0	0	1	1
Oncologist consultation	1	0	1	0	1	0
Lab tests	1	0	1	0	1	0
Tumour response assessment (MRI/CT)	0,4	0	0,4	0	0,4	0
Radiologist consultation	0,2	0	0,2	0	0,2	0
Costs/cycle	**€ 294.01**	**€ 50.28**			**€ 414.75**	**€ 171.02**
Source	KOL interview					

Table 9: Calculation of disease management costs per cycle for all therapy groups before and after progression.

2.2.4.5. Re-biopsy

Costs for re-biopsy depend on the medical personnel and technique used for the intervention. Whether or not a re-biopsy is done depends on the advice of the tumour board. One third of the gene alteration known patients is assumed to need re-biopsy at progression. No re-biopsies are considered for patients with gene alteration unidentified or patients in the immunotherapy models.

	Costs	Frequency		Source/comment
		Gene alteration identified	Gene alteration unidentified, immunotherapy, chemotherapy	
Re-biopsy	€ 350,00	0.33	0	KOL Interview

Table 10: Costs of re-biopsy for patients with a gene alteration identified who progress.

2.2.4.6. Best supportive care & end-of-life

Best supportive care costs for NSCLC patients were taken from a Dutch cost-effectiveness analysis of EGFR TKIs and indexed accordingly. End of life costs were taken from an international study of terminal care costs specific for lung cancer, converted and indexed. BSC and EoL are considered constant across therapy groups.

	Costs	Source/comment
Best supportive care	€ 1.895,98	BSC costs in the Netherlands from (Holleman et al., 2020) indexed from 2016 using Be-HI
End of life costs	€ 5.215,47	Cancer patients end of life costs for Belgium from (Bekelman et al., 2016), converted to euro and indexed from 2010 using Be-HI

Table 11: Costs per cycle for best supportive care and end of life costs per death.

2.2.4.7. Adverse events

Adverse events for the targeted medicine proxy and the associated costs are sourced from a dutch cost-effectiveness study on first generation EGFR-TKIs (Holleman et al., 2020). Incidence of AE of Pembrolizumab and chemotherapy is taken from KEYNOTE-024, associated costs are taken from a French cost-effectiveness study based on the same trial.

AE	Costs	Source/Comment
ALT/AST increase	€ 478.22	(Holleman et al., 2020)
Anemia	€ 2,012.85	
Anorexia	€ 821.43	
Asthenia	€ 837.92	
Colitis	€ 3,625.77	(Chouaid, Loirat, et al., 2017)
Decreased appetite	€ 851.31	(Holleman et al., 2020)
Diarrhoea	€ 2,431.30	
Dyspnea	€ 481.31	
Fatigue	€ 837.92	
Nausea	€ 750.31	
Neutropenia/Decreased neutrophil count	€ 1,448.06	(Chouaid, Loirat, et al., 2017)
Paronychia	€ 2,431.30	(Holleman et al., 2020)
Pneumonitis	€ 6,060.08	(Chouaid, Loirat, et al., 2017)
Rash/Skin reaction	€ 2,431.30	(Holleman et al., 2020)
Stomatitis	€ 4,435.46	
Thrombocytopenia/decreased platelet count	€ 217.11	(Chouaid, Loirat, et al., 2017)
Type I Diabetes Mel.	€ 8,119.96	
Vomiting	€ 750.31	(Holleman et al., 2020)

Table 12: Costs of treating adverse events sourced from cost-effectiveness studies of similar patient groups and treatments.

AE	Incidence targeted therapy	Incidence Pembrolizumab	Incidence chemotherapy
ALT/AST increase	0,02575	0	0
Anemia	0	0,019	0,193
Anorexia	0,0055	0	0
Asthenia	0	0	0
Colitis	0	0,013	0
Decreased appetite	0,01075	0	0,027
Diarrhoea	0,03825	0,039	0,013
Dyspnea	0	0	0
Fatigue	0,00925	0,013	0,033
Nausea	0	0	0,02
Neutropenia/Decreased neutrophil count	0,0045	0	0,173
Paronychia	0,0115	0	0
Pneumonitis	0	0,026	0,007
Rash/Skin reaction	0,06425	0,039	0,015
Stomatitis	0,016	0	0,013
Thrombocytopenia/decreased platelet count	0	0	0,113
Type I Diabetes Mel.	0	0,006	0
Vomiting	0	0,006	0,007
Average cost per patient	**€ 388.39**		**€ 905.48**
Source	(Holleman et al., 2020)	KEYNOTE-024	KEYNOTE-024

Table 13: Costs for treatment of adverse events per therapy group. Frequency taken from clinical trials and/or literature.

2.2.4.8. Indexes & conversion rates

The Belgian Bureau of Statistics (STATBEL) maintains monthly and yearly records on the Belgian Health Index (B-HI). This index is used to index costs whenever necessary using the following formula.

$$C_{2021} = C_n * (B\text{-}HI_{2021}/B\text{-}HI_n)$$

C_n= Original costs from year n

Year	Health Index (base 2013)	Source/Comment
2010	93,36	(*Health Index | Statbel*, 2021)
2011	96,22	
2012	98,77	
2013	100	
2014	100,4	
2015	101,45	
2016	103,58	
2017	105,49	
2018	107,35	
2019	108,92	
2020	110	
2021	110,64	
Euro to dollar conversion rate (avg. 2010)	1.327	(*Euro to US Dollar Spot Exchange Rates for 2010*, 2021)

Table 14: Belgian health index and conversion rate US dollar to Euro for 2010.

2.3. Diagnostic decision models

2.3.1. The diagnostic cascade

Diagnostic decision models are used to compare the CGP cascade with the SoC diagnostic cascade. The CGP cascade consist of CGP and PD-L1 IHC (table 15d). The SoC cascade is based on the BSP and ESMO guidelines and the workflow published by ComPerMed (table 15a). Consulting a KOL revealed that RNA sequencing is an optional addition to the SoC and depends on the lab's technical expertise and the willingness of the treating physician to wait for the longer turnaround time of RNA sequencing. Whether or not RNA sequencing is done affects both the costs of the diagnostic cascade and the biomarkers that are detected (*RET* fusions and *MET* exon 14 skipping can only be detected using RNA sequencing). For our base case analysis we assume that half the samples follow an SoC cascade without RNA sequencing as seen in table 15b, while the other half follows an SoC cascade with immediate DNA and RNA sequencing as seen in table 15c.

(a) BIOMARKERS	**Method**					**Use**
	FISH	**IHC**	**DNA seq**	**RNA seq**	**CGP**	
EGFR mutations			V		V	*EGFR* TKI therapy
ALK fusions	V	V		V	V	*ALK* TKI therapy
ROS1 fusions				V	V	*ROS1* TKI therapy
BRAF mutation			V		V	*BRAF* inhibitor therapy
NTRK fusions	V	V		V	V	*NTRK* TKI therapy
*RET f*usions				V		*RET* inhibitor therapy
MET ex. 14 skip				V		*MET* inhibitor therapy
PD-L1 expression	V	V				ICIs
SOURCE	(ComPerMed, 2021; Pauwels et al., 2018; Planchard et al., 2020)					
(b) Standard of care cascade – Option A						
Phase I: Simultaneous targeted DNA NGS Panel + *IHC* ALK + *IHC* ROS1 + *IHC* PD-L1 Phase II: Confirmation FISH *ALK* & *ROS1* Phase II: *TRK* – IHC						
(c) Standard of care cascade – Option B						
Phase I: Simultaneous targeted DNA + RNA sequencing + PD-L1						
(d) Comprehensive Genomic Profiling						
Phase I: Simultaneous CGP + IHC PD-L1						

Table 15: Biomarkers imperative in NSCLC diagnosis; consensus standard of care cascade and comprehensive genomic profiling according to ESMO, BSP and Compermed (Planchard et al., 2020; Pauwels et al. 2018; ComPerMed, 2021).

2.3.2. Biomarker prevalence

The diagnostic decision models weight the outputs from the partitioned survival model against the distribution of patients by each diagnostic cascade. This distribution is dependent on the prevalence of the biomarkers within the population.

In the first decision model, the diagnostic cascade determines the proportion of patients on targeted therapy. The base case analysis is done with the biomarker prevalence reported in the BIOMARKERs study used to develop the corresponding partitioned survival model, an additional source from literature is added to use in scenario analysis (table 16a). The SoC cascade can detect all biomarkers in table 15a if it includes RNA sequencing, the SoC cascade without RNA sequencing does not detect *RET* fusions and *MET* exon 14 skipping. CGP can detect all biomarkers and will identify a gene alteration in the proportion of patients reported as unknown or wild type (WT). In how big a proportion of this group CGP will detect an alteration is impossible to predict. ICERs/LY resulting from the diagnostic model will therefore be presented with an additional 5, 10 and 15% genomic alterations identified as compared to the SoC cascade with RNA sequencing.

The second decision model compares the stratification of patients for immunotherapy by both diagnostic cascades. In addition to PD-L1 expression (used to stratify patients after the SoC cascade), CGP uses HLA diversity scores and TMB status to determine immunotherapy susceptibility. Several literature sources are consulted to generate three sets of distributions for these biomarkers, all biomarkers are considered independent. The results from Cuppens et al. (2021) are used for the base case. Two additional sets of distributions of PD-L1 expression and TMB status are used in scenario analyses (table 16b). Because of the lack of standardization in HLA diversity scoring, no other sources could be used for the purpose of scenario analyses

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(a) Biomarkers for targeted therapy		
	Prevalence	Prevalence
EGFR	0.11	0.19
KRAS	0.29	0.29
BRAF	0.02	0.05
ERRB2	0.01	0.03
PIK3CA	0.02	0.02
ALK	0.05	0.03
ROS1	0.02	0.01
NTRK1-3	0.0023	0.001
MET (exon 14 skipping)*	0.02*	0.03
*RET**	0.01*	0.01
SUM	**0.5523**	**0.661**
Unknown alterations and WT	**0.4477**	**0.339**
SOURCE	(Barlesi et al., 2016)	(Chevallier et al., 2021)

(b) Biomarkers for immunotherapy			
	Set 1	**Set 2**	**Set 3**
PD-L1 ≥ 50%	0.50	0.30	0.22
50% ≥ PD-L1 ≥ 1%	0.28	0.44	0.30
PD-L1 ≤ 1%	0.22	0.26	0.48
Source	(Cuppens et al., 2020)	(Holmes et al., 2019)	(Dietel et al., 2019)
TMB-H	0.56	0.40	0.46
TMB-L	0.44	0.60	0.54
Source	(Cuppens et al., 2020)	(Yarchoan et al., 2019)	(Zehir et al., 2017)
Low HLA-I diversity	0.64	0.64	0.64
High HLA-I diversity	0.36	0.36	0.36
Source	(Cuppens et al., 2020)		
Detected by SoC cascade and CGP			
Detected by CGP			

Table 16: (a)Two sets of biomarker prevalence relevant for targeted therapy in NSCLC patient populations sourced from literature.(*) RET fusions and MET exon 14 skipping mutations can only be found if the consensus cascade includes RNA sequencing (see section 2.3.2.). (b) Three sets of biomarker prevalence relevant for immunotherapy stratification of NSCLC patients sourced from literature.

2.3.3. Costs of the diagnostic cascade

The reimbursement paid by the healthcare payer per test type is published in the RIZIV/INAMI Nomensoft web application (table 17). Prices per test are used to calculate the average price per patient of each cascade after taking the incidence of each biomarker into account (table 18). The average cost of both SoC cascade options is calculated and used in both decision models.

Test	Costs		Source
IHC	€	92.42	RIZIV - Nomensoft (web application)
FISH	€	191.66	
DNA seq (panel)	€	360.43	
RNA seq (panel)	€	555.56	
CGP (DNA+RNA)	€	915.99	

Table 17: Costs by the healthcare payer per test type from RIZIV/INAMI Nomensoft.

Standard of care – Option A			
		End of testing for:	Percentage of total patients
Phase I: Simultaneous test DNA seq + IHC ALK + IHC ROS1 + IHC PD-L1	€ 637.69	*EGFR, KRAS, BRAF, ERBB2, PIK3CA*	45%
Phase II: Confirmation FISH ALK & ROS1	€ 91.66	*ALK, ROS1*	7%
Phase II: TRK - IHC	€ 92.42	*NTRK1-3*	0.23%
Average cost per patient	**€ 345.02**		
Standard of care – Option B			
		End of testing for:	Percentage of total patients
Phase I: Simultaneous test DNA seq + RNA seq + IHC PD-L1	€ 1,008.41	All	100%
Average cost per patient	**€ 1,008.41**		
Consensus Standard of care (50% A – 50% B)			
Average cost per patient	**€ 676.71**		
Comprehensive Genomic Profiling			
Phase I: Simultaneous CGP panel + PD-L1 IHC	€ 1,008.41	End of testing for:	Percentage of total patients
		All	100%
Average cost per patient	€ **1,008.41**		

Table 18: Calculation of the costs of the diagnostic cascade combining prevalence of biomarkers (table 15) with cost per test (table 17)

2.3.4. Proportion of patients with identified gene alterations

The first decision models weights the average costs and outcomes for patients with and without an identified gene alteration against the proportion of patients in each group. This proportion is determined by the diagnostic cascade used and the prevalence of biomarkers in the population. Using the prevalence in table 16 the percentage of patients with an identified gene alteration is determined (table 19).

Cascade	Gene alterations identified	Percentage of total patients
Standard of care – Option A	*EGFR, KRAS, BRAF, ERBB2, PIK3CA, ALK, ROS1, NTRK1-3*	52.23%
Standard of care – Option B	*EGFR, KRAS, BRAF, ERBB2, PIK3CA, ALK, ROS1, NTRK1-3, RET, MET exon 14 skipping*	55.23%
Consensus Standard of care		**53.73%**
Comprehensive genomic profiling	*EGFR, KRAS, BRAF, ERBB2, PIK3CA, ALK, ROS1, NTRK1-3, RET, MET exon 14 skipping + …*	**55.23 % + 5/10/15%**

Table 19: Proportion of patient with an identified gene aklteration for each cascade.

2.3.5. Stratification of patients for immunotherapy

The second decision model weights the outputs of the immunotherapy partitioned survival models with the proportion of patients in each subgroup created by the diagnostic cascades. The SoC cascade stratifies patients in three subgroups based on PD-L1 expression level from table 16. Based on their response to immunotherapy, sourced from corresponding KEYNOTE trials, all subgroups are split into responders and non-responders resulting in six final subgroups with different costs and outcomes.

Standard of care	Proportion of Patients	First line therapy	Response rates	Responders	Non-responders
PD-L1 ≥ 50%	500.00	Immuno-therapy	0.448	**224.00**	**276.00**
50% ≥ PD-L1 ≥ 1%	280.00	Immuno + Chemotherapy	0.484	**135.52**	**144.48**
PD-L1 ≤ 1%	220.00	Immuno + Chemotherapy	0.323	**71.06**	**148.94**
SOURCE	Table 16		KEYNOTE-024 & -189		

Table 20: Subgroups of patients created by the SoC cascade.

Using CGP + PD-L1 leads to three biomarkers stratifying patients in 12 subgroups (table 21a). For all but two subgroups, response rates are assumed the same as determined by PD-L1 status alone. Response rates for triple positive patients (PD-L1 ≥ 50%, TMB-H & HLA diversity high) and triple negative patients (PD-L1 ≤ 1%, TMB-L & HLA Diversity low) are taken from recent evidence published by Cuppens et al. (2020) (table 21b). Triple positives patients have a response rate of 64% while triple negative patients have a response rate of 0% and therefore do not receive immunotherapy. Based on these response rates the 12 subgroups are split into responders and non-responders, resulting in 23 subgroups with different costs and outcomes and one empty group (table 21c).

(a) Proportion of patients	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	0.17920	0.10035	0.7885	
TMH-L	0.14080	0.7885	0.6195	
Proportion of patients	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	0.10080	0.5645	0.4435	
TMH-L	0.7920	0.4435	0.3485	
(b) Response rates per group	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	0.448	0.484	0.323	
TMH-L	0.448	0.484	**0***	
Response rates per group	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	**0.64****	0.484	0.323	
TMH-L	0.448	0.484	0.323	
(c) Responders and non-responders	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	0.08028	0.04857	0.02547	
	0.09892	0.05178	0.05338	
TMH-L	0.06308	0.03816	**0.00**	
	0.07772	0.04069	**0.06195**	
Responders and non-responders	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	**0.06451**	0.02732	0.01433	
	0.03629	0.02913	0.03003	
TMH-L	0.03548	0.02147	0.01126	
	0.04372	0.02289	0.02359	
First-Line Therapy	**Immuno-therapy**	**Immunotherapy + chemotherapy (*): first line chemotherapy**		

Table 21: Stratification of patients by CGP cascade. (/**) different response rates of triple positives and negatives.*

3. Results

3.1. Finding more gene alterations and sending more patients to clinical trials

3.1.1. Base case analysis

Treatment	Gene alteration identified	Gene alteration unidentified
Drug acquisition costs - SD	€ 41,418	€ 8,883
Chemo admin costs - SD	€ 1,840	€ 1,685
Premed & concomitant costs SD	€ 863	€ 790
Disease management costs - SD	€ 6,953	€ 5,070
BSC costs - SD	€ 12,625	€ 10,746
AE costs SD	€ 329	€ 253
Drug acquisition costs - PD	€ 5,153	€ 1,104
Chemo admin costs - PD	€ 233	€ 157
Premed & concomitant costs PD	€ 109	€ 74
Re-biopsy costs PD	€ 111	€ 0
Disease management costs - PD	€ 725	€ 331
BSC costs	€ 5,122	€ 5,505
End of life costs	€ 4,860	€ 5,215
TOTAL	**€ 80,340**	**€ 39,812**
LYs accrued in SD state	1.43	1.08
LYs accrued in PD state	0.89	0.39
TOTAL	**2.32**	**1.48**

Table 22: Disaggregated results of the partitioned survival model for patients with and without an identified gene alteration.

The average costs and outcomes from the partitioned survival model of patients with and without an identified gene alteration are shown in table 22. Average costs for patients with an identified gene alteration are € 80,340 versus € 39,812 for patients without an identified gene alteration. Average outcome is 2.32 LYs gained for patient with an identified gene alteration versus 1.48 LYs gained for those without. These differences are largely driven by a proportion of patients within the gene alteration identified group receiving expensive but effective targeted therapy.

The first diagnostic decision model weights these output against the proportion of patients in each group to determine the ICER/LY of the diagnostic (table 23). This second step also takes the costs of diagnostic cascade into account. Since it is impossible to predict the additional percentage patients in which CGP will find a genomic alteration, results are presented as a triple ICER/LY with 5, 10 and 15% more patients in the gene alteration identified group (+1.5% for RET and MET fusions missed by the SoC consensus cascade; see section 2.3.1).

Regardless of the additional gene alterations identified by CGP, the average incremental cost for diagnostics is €331.70. Depending on the additional gene alterations identified, CGP results in an incremental average cost of therapy of € 3,297.68 - € 7,350.42 and 0.055 - 0.140 LYs gained. CGP's ICERs/LY for an additional 5, 10 and 15% gene alterations identified are € 59,920.64, € 54,679.66 and € 52,615.04, respectively.

Standard of care cascade vs. Comprehensive genomic profiling						
	Costs of diagnostics	Proportion gene alteration identified	Proportion gene alteration unidentified	Average cost per patient	Average LY	ICER/LY
SoC cascade	€ 676.71	0.5373	0.4627	€ 61,932.52	1.930	
CGP	€ 1,008.41	0.6023	0.3977	€ 65,230.20	1.985	
Δ	€ 331.70	0.065	-0.065	€ 3,297.68	0.055	**€ 59,920.64**
SoC cascade	€ 676.71	0.5373	0.4627	€ 61,932.52	1.930	
CGP	€ 1,008.41	0.6523	0.3477	€ 67,256.57	2.027	
Δ	€ 331.70	0.115	-0.115	€ 5,324.05	0.097	**€ 54,679.66**
SoC cascade	€ 676.71	0.5373	0.4627	€ 61,932.52	1.930	
CGP	€ 1,008.41	0.7023	0.2977	€ 69,282.95	2.070	
Δ	€ 331.70	0.165	-0.165	€ 7,350.43	0.140	**€ 52,615.04**

Table 23: ICER/LY for three scenarios in which CGP identifies 5, 10 and 15% more patients with a gene alterations based on average costs and outcomes from partitioned survival model in table 18.

3.1.2. Scenario analyses

3.1.2.1. Scenario I: Different distribution of biomarkers

Treatment	Gene alteration identified	Gene alteration unidentified
Average costs	€ 80,340	€ 39,812
Average outcomes	2.32	1.48

Standard of care cascade vs. Comprehensive genomic profiling						
	Costs of diagnostics	Proportion gene alteration identified	Proportion gene alteration unidentified	Average cost per patient	Average LY	ICER/LY
SoC cascade	€ 705.72	0.641	0.359	€ 66,193.24	2.018	
CGP	€ 1,008.41	0.711	0.289	€ 69,635.53	2.077	
Δ	€ 302.69	0.07	-0.07	€ 3,442.30	0.059	**€ 58,080.69**
SoC cascade	€ 705.72	0.641	0.359	€ 66,193.24	2.018	
CGP	€ 1,008.41	0.761	0.239	€ 71,661.91	2.119	
Δ	€ 302.69	0.12	-0.12	€ 5,468.67	0.102	**€ 53,824.73**
SoC cascade	€ 705.72	0.641	0.359	€ 66,193.24	2.018	
CGP	€ 1,008.41	0.811	0.189	€ 73,688.28	2.162	
Δ	€ 302.69	0.17	-0.17	€ 7,495.04	0.144	**€ 52,072.28**

Table 24: Average costs and outcomes and resulting ICERs/LY using a different biomarker distribution.

The distribution of biomarkers is highly dependent on the region of testing and the ethnical and genetic characteristics of the population. The BIOMARKER researchers themselves reported that the biomarker distribution they reported was likely an underestimation of the real world prevalence of actionable alterations (Mazières et al., 2016). In a first scenario analysis we used the distribution from a recent review by Chevallier et al. (2021) and verify the effect on the results (table 16).

Using a different prevalence for the biomarkers affects the cost of the SoC cascade as more patients will require additional phases of testing. Since the costs for the CGP cascade remain the same the incremental costs for diagnostics are slightly lower. There is a slight increase in additional gene alterations identified by CGP because of a higher prevalence of *MET* exon 14 skipping mutations. As a result average costs and outcomes per patient for the entire population are slightly higher. Because the relative increase in LYs is higher, the corresponding ICERs/LY are slightly lower than the base case analysis.

3.1.2.2. Scenario II: Overall survival gene alteration identified follows lognormal distribution

Treatment	**Gene alteration identified**	**Gene alteration unidentified**
Average costs	€ 81,014	€ 39,812
Average outcomes	3.74	1.48

Standard of care cascade vs. Comprehensive genomic profiling						
	Costs of diagnostics	**Proportion gene alteration identified**	**Proportion gene alteration unidentified**	**Average cost per patient**	**Average LY**	**ICER/LY**
SoC cascade	€ 676.71	0.5373	0.4627	€ 62,294.89	2.693	
CGP	€ 1,008.41	0.6023	0.3977	€ 65,636.40	2.841	
Δ	€ 331.70	0.065	-0.065	€ 3,341.52	0.147	**€ 22,670.35**
SoC cascade	€ 676.71	0.5373	0.4627	€ 62,294.89	2.693	
CGP	€ 1,008.41	0.6523	0.3477	€ 67,696.50	2.954	
Δ	€ 331.70	0.115	-0.115	€ 5,401.61	0.261	**€ 20,713.50**
SoC cascade	€ 676.71	0.5373	0.4627	€ 62,294.89	2.693	
CGP	€ 1,008.41	0.7023	0.2977	€ 69,756.59	3.068	
Δ	€ 331.70	0.165	-0.165	€ 7,461.70	0.374	**€ 19,942.61**

Table 25: Average costs and outcomes and resulting ICERs/LY using a lognormal distribution to model gene alteration identified OS.

Long-term survival rates in NSCLC are historically low, as a result all four KM curves were conservatively extrapolated using a Weibull distribution in the base case analysis. Early long-term survival data for targeted therapies show that a proportion of patients may survive beyond the five-year mark (Lin et al., 2016; Rennert et al., 2021). In the second scenario analysis this long-term survival is accounted for by changing the extrapolation of the OS data in the gene alteration identified group to a lognormal distribution (table 25).

Changing the parametric distribution greatly affects the average outcomes of patient in the gene alteration identified group who gain 3.74 LYs as compared to 2.32 LYs before. As a result, the additional gene alterations identified by CGP generate additional average LYs for the entire population and the incremental LYs gained increase from 0.055-0.014 to 0.147-0.374. The resulting ICERs/LY decrease to € 22,670.35 - € 19,942.61. It is important to remark that though the lognormal curve might be a better fit for targeted therapies, most additional LYs gained are generated after progression. The partitioned survival model accounts for a constant average of six therapy cycles per progressed patient based on data from the BIOMARKERs study. If overall survival increases, average number of therapy cycles, associated costs and ICERs/LY would likely increase as well.

3.1.2.3. Scenario III: Average price of targeted therapy equals costs of crizotinib

Treatment	Gene alteration identified	Gene alteration unidentified
Average costs	€ 103,631	€ 40,309
Average outcomes	2.32	1.48

Standard of care cascade vs. Comprehensive genomic profiling						
	Costs of diagnostics	Proportion gene alteration identified	Proportion gene alteration unidentified	Average cost per patient	Average LY	ICER/LY
SoC cascade	€ 676.71	0.5373	0.4627	€ 74,676.93	1.930	
CGP	€ 1,008.41	0.6023	0.3977	€ 79,456.23	1.985	
Δ	€ 331.70	0.065	-0.065	€ 4,779.30	0.055	**€ 86,842.55**
SoC cascade	€ 676.71	0.5373	0.4627	€ 74,676.93	1.930	
CGP	€ 1,008.41	0.6523	0.3477	€ 82,622.32	2.027	
Δ	€ 331.70	0.115	-0.115	€ 7,945.39	0.097	**€ 81,601.58**
SoC cascade	€ 676.71	0.5373	0.4627	€ 74,676.93	1.930	
CGP	€ 1,008.41	0.7023	0.2977	€ 85,788.40	2.070	
Δ	€ 331.70	0.165	-0.165	€ 11,111.47	0.140	**€ 79,536.95**

Table 26: Average costs and outcomes and resulting ICERs/LY using a higher cost per day for targeted therapy.

A targeted therapy proxy was created based on the average cost per day of all patent protected and reimbursed targeted therapies in Belgium. In a final scenario analysis this average is changed with the costs per day of the most expensive therapy, crizotinib (table 26).

Costs for targeted therapy change from € 203.31 to € 328.60. As a result, the average costs per patient of both the gene alteration identified and unidentified groups increase. The larger increase of the patient group with an identified gene alteration results in an increase of incremental average costs of € 3,297.68 - € 7,350.42 to € 4,779.30 - € 11,111.47. This greatly increases the ICERs/LY to € 86,842.55, € 81,601.58 and € 79,536.95.

3.2. Cost-savings from more effective use of immunotherapy

3.2.1. Average costs and outcomes for patient subgroups

PD-L1 ≥ 50%	**Immunotherapy**	**Chemotherapy**	**Non-responders immuno**
Average costs	€ 213,688	€ 36,915	€ 65,319
Average outcomes	3.102	1.906	1.906
50% > PD-L1 ≥ 1%	**Immunotherapy + chemotherapy**	**Chemotherapy**	**Non-responders immuno + CT**
Average costs	€ 239,150	€ 38,248	€ 75,689
Average outcomes	2.310	1.354	1.354
PD-L1 < 1%	**Immunotherapy + chemotherapy**	**Chemotherapy**	**Non-responders immuno + CT**
Average costs	€ 172,156	€ 35,148	€ 69,876
Average outcomes	2.380	1.616	1.616

Table 27: Average costs and outcomes from partitioned survival models of patients receiving immunotherapy and/or chemotherapy as well as non-responders.

Partitioned survival models were created to generate average costs and outcomes for patients receiving first-line immunotherapy, immunotherapy + chemotherapy or chemotherapy alone based on their PD-L1 expression levels (table 27). Additionally, patients that did not respond to immunotherapy were modelled to account for costs and outcomes of ineffective use of immunotherapy.

Patients with PD-L1 ≥ 50% receive first-line immunotherapy. Average costs of this therapy is € 213,688 for which an average of 3.102 LYs are gained. Non-responsive patients cost € 65,319 on average while patients receiving first-line chemotherapy cost € 36,915, both gain an average of 1.906 LYs.

Patients with 50% > PD-L1 ≥ 1% or PD-L1 < 1% receive first-line immunotherapy + chemotherapy. Average costs of this combination therapy are € 239,150 or € 172,156 for which an average of 2.310 LYs or 2.380 LYs are gained. Non-responsive patients cost € 75,689 or €69,876 on average while patients receiving first-line chemotherapy cost € 38,248 or € 35,148 both gain an average of 1.354 or 1.616 LYs.

The complete disaggregated costs and outcomes per patient group can be found in supplementary table 5-8 of the appendix.

3.2.2. Average costs and LYs using the standard of care diagnostic cascade

Standard of care	Pro-portion of patients	First line therapy	Response rates	Pro-portion respond ers	Pro-portion non-respond ers	**Proportional costs**	**Pro-portio nal LYs**
PD-L1 ≥ 50%	0.50	Immuno-therapy	0.448	0.224	0.276	€ 65,894.27	1.221
50% ≥ PD-L1 ≥ 1%	0.28	Immuno + Chemotherapy	0.484	0.136	0.144	€ 43,345.11	0.509
PD-L1 ≤ 1%	0.22	Immuno + Chemotherapy	0.323	0.071	0.149	€ 22,640.74	0.410
					Average costs and outcomes per patient	**€ 131,880.12**	**2.139**

Table 28: Average costs and outcome per patient are calculated by combining the distributional effects of the SoC cascade and the response rates per subgroup and therapy (table 20) with the average costs and outcomes per subgroup (table 27).

The second decision model weights the average costs and outcomes per patient subgroup against the proportional distribution by the diagnostic cascade. The SoC cascade stratifies patients for immunotherapy in three subgroups based on PD-L1 expression, 50%, 28% and 22% of patients respectively. Each subgroups is subsequently split in responders and non-responders based on response rates from literature, 44.8%, 48.4% and 32.3% respectively. Taken together, the proportional costs and outcomes per subgroup result in an average cost of € 131,880.12 per patient and an average of 2.139 LYs gained per patient (table 28).

3.2.3. Average costs and LYs using Comprehensive Genomic Profiling

Responders and non responders	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	0.08028	0.04857	0.02547	
	0.09892	0.05178	0.05338	
TMH-L	0.06308	0.03816	**0.00**	
	0.07772	0.04069	**0.06195***	

Responders and non responders	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	**0.06451**	0.02732	0.01433	
	0.03629	0.02913	0.03003	
TMH-L	0.03548	0.02147	0.01126	
	0.04372	0.02289	0.02359	

Proportional costs	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	€ 17,155.22	€ 11,615.60	€ 4,384.45	
	€ 6,461.29	€ 3,919.29	€ 3,729.99	
TMH-L	€ 13,479.10	€ 9,126.54	**€ -**	
	€ 5,076.73	€ 3,079.44	**€ 2,177.50***	

Proportional costs	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	**€ 13,785.44**	€ 6,533.77	€ 2,466.25	
	€ 2,370.31	€ 2,204.60	€ 2,098.12	
TMH-L	€ 7,581.99	€ 5,133.68	€ 1,937.77	
	€ 2,855.66	€ 1,732.19	€ 829.22	

Proportional LYs	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 diversity Low
TMB-H	0.249	0.112	0.061	
	0.189	0.070	0.086	
TMH-L	0.196	0.088	**0.000**	
	0.148	0.055	**0.100***	

Proportional LYs	PD-L1 ≥ 50%	50% ≥ PD-L1 ≥ 1%	PD-L1 ≤ 1%	HLA-1 Diversity high
TMB-H	**0.200**	0.063	0.034	
	0.069	0.039	0.049	
TMH-L	0.110	0.050	0.027	
	0.083	0.031	0.038	
First-Line Therapy	**Immuno-therapy**	**Immunotherapy + chemotherapy (*): first line chemotherapy**		

Table 29: Proportional costs and outcome per patient are calculated by combining the distributional effects of the CGP cascade and the response rate per subgroup and therapy (table 21) with the average costs and outcomes per subgroup (table 27).

The additional biomarkers from the CGP cascade result in an extensive stratification of subgroups as shown earlier (table 21). For 21 out of 23 subgroups, response rates are assumed the same as they would be based on PD-L1 expression alone (table 29). Based on recent research by Cuppens et al. (2020) triple positive patients (PD-L1 high, TMB-H and HLA Diversity High) are assumed to have a higher response rate of 64%. Based on the same research it's assumed that no durable response rate can be achieved in triple negative patients (PD-L1 Low, TMB-L and HLA Diversity low), who are therefore given first-line chemotherapy. As a consequence, proportional costs and LYs are slightly different than they would have been based on PD-L1-only response rates. Taking all proportional costs and LYs together then results in an average cost per patient of € 129,734.15 and an average of 2.147 LYs gained per patient (table 30).

Comprehensive genomic profiling	Costs	LYs
Average per patient	**€ 129,734.15**	**2.147**

Table 30: Proportional costs and outcomes are taken together to get average costs and outcomes per patient.

3.2.4. Cost savings using Comprehensive Genomic Profiling

Treatment	**Cost of diagnostics**	**Average proportion responders**	**Average proportion non-responders**	**Average costs + costs of diagnostics**	**Average LY**
SoC cascade	€ 676.71	0.4306	0.5694	€ 132,557.83	2.139
CGP	€ 1,008.41	0.5821	0.4179	€ 130,742.56	2.147
Δ	€ 331.70	0.1515	-0.1515	**€ -1,815.27**	**0.008**

Table 31: Cost savings are calculated by combining the costs of the diagnostic cascade with the average costs and outcomes per patient after each diagnostic cascade (tables 28 & 30).

In the final step the decision model takes the costs of each diagnostic cascade (section 2.3.3 – table 18) into account. This is combined with the average costs and outcomes after stratification by each diagnostic (tables 28 and 30). Total average costs after stratification with the SoC cascade are € 132,557.83 for an average 2.139 LYs gained. Stratification with the additional biomarkers from CGP leads to € 130,742.56 average costs and 2.147 average LYs gained. Using CGP thus leads to cost-savings of € 1,815.27 per patient and a negligible increase in LYs gained (0.008 LYs).

3.2.5. Scenario analyses

Biomarker distribution – Set 2					
Diagnostic cascade				Average Costs	Average LYs
Standard of Care				€ 110,691.45	1.972
Comprehensive genomic profiling				€ 129,734.15	2.147
Treatment	Cost of diagnostics	Average proportion responders	Average proportion non-responders	Average costs + costs of diagnostics	Average LY
SoC cascade	€ 676.71	0.3986	0.6014	€ 124,878.50	2.007
CGP	€ 1,008.41	0.6582	0.3418	€ 111,699.86	1.972
Δ	€ 331.70	0.2596	-0.2596	**€ -13,178.65**	**-0.036**

Table 32: Scenario analysis using a different set of biomarker distributions (set 2 - Table 16).

Biomarker distribution – Set 3					
Diagnostic cascade				Average Costs	Average LYs
Standard of Care				€ 133,748.60	2.004
Comprehensive genomic profiling				€ 127,862.88	1.993
Treatment	Cost of diagnostics	Average proportion responders	Average proportion non-responders	Average costs + costs of diagnostics	Average LY
SoC cascade	€ 676.71	0.4341	0.5659	€ 134,426.32	2.004
CGP	€ 1,008.41	0.6143	0.3857	€ 128,871.29	1.993
Δ	€ 331.70	0.1802	-0.1802	**€ -5,555.02**	**-0.011**

Table 33: Scenario analysis using a different set of biomarker distributions (set 3 - Table 16).

The research by Cuppens et al. (2020) on the use of additional biomarkers from CGP and their distribution in the population was done on a relatively small sample size (N = 126). To account for the uncertainty resulting from this sample size we sourced additional distributions of biomarkers from large international studies (N > 1000) to use in scenario analysis. Two sets of biomarkers (table 16) were entered into the model and resulted in increased cost savings of € -13,178.65 and € -5,555.02. The extremely small gain in LYs of the base case model turns into a loss of LYs of 0.036 and 0.011 LYs. Both sets of biomarkers have an increased amount of patients in the PD-L1 ≤ 1% group that drives the increased savings and diminished LYs in these scenarios.

4. Discussion

4.1. Results

Diagnostic decision models were developed to analyse the health economic effects of introducing Comprehensive Genomic Profiling in the diagnosis of metastatic, non-squamous NSCLC, as a case study for the broader value of CGP in precision oncology. The decision models used average costs and outcomes generated by partitioned survival models. One model was used to estimate the cost-effectiveness of identifying more gene alterations in patients and increase the use of targeted therapies. Another was used to determine the cost savings that could be achieved by more efficient stratification of immunotherapies.

The base case analysis of the first decision model used average costs and outcomes from a partitioned survival model generated with inputs from the BIOMARKERs study, an observational trial that followed nearly 18.000 non-squamous NSCLC patients as they were diagnosed for the presence of a genetic alteration and treated accordingly by the French healthcare system. Unsurprisingly, average costs and outcomes were higher for patients with an identified gene alteration (€ 80,340 for 2.32 LYs) gained than in those without (€ 39,812 for 1.48 LYs gained). Disaggregation of the costs showed that higher costs are driven by a third of the patients with known gene alterations receiving expensive targeted therapy. It is assumed that these therapies are also the driver of the higher average outcomes in patients with an identified gene alteration. However, since the BIOMARKERs study was an observational study and not a designed clinical trial this can't be concluded with absolute certainty. Several other limitations arising from the layout of the BIOMARKERs study are discussed later.

The decision model combined the output of the partitioned survival model with the diagnostic cascade. To do so the costs and distributional effects of each cascade were assessed and the effect of the prevalence of the biomarkers in the population was taken into account. It is impossible to predict how big the fraction of unknown gene alteration that CGP can additionally identify is. Consequently, the results generated by the model were shown in triple ICERs/LY, representing three possible scenarios in which CGP identifies 5, 10 and 15% more gene alteration than the SoC cascade. This resulted in three ICERs/LY of € 59,920.64, € 54,679.66 and € 52,615.04, respectively.

Very little real world data exist on the costs and effects of large scope sequencing diagnostics such as CGP. In the construction of the early model several assumptions were made to compensate for this lack of data. Scenario analysis was performed to account for some of the uncertainty created the assumptions. It showed that CGP's ICERs/LY was not sensitive to changes in biomarker distribution in the population, but could be heavily impacted by better outcomes or higher prices of targeted therapies. Although this is not an unexpected result, more long-term survival data could help later modelling efforts generate more robust ICERs.

The Belgian healthcare payer has no formal ICER or Willingness-To-Pay (WTP) threshold on which potential reimbursement hinges, rather reimbursement decisions are made on a case-by-case basis using broad assessment criteria (Cleemput et al., 2011). Consequently, the results generated by the first model cannot conclusively determine whether CGP is considered a cost-effective use of healthcare resources according to the Belgian healthcare payer's standards. Nevertheless, the ICERs/LY are an interesting result as they are not solely the result of the incremental costs of the diagnostic cascade divided by the incremental outcome. They are, in large part, determined by the increased use of more expensive targeted therapy that is already reimbursed. Broken down, the increased cost of CGP as compared to the SoC cascade makes up 5 to 10% of the total incremental

costs. As such, the question is not as much whether these ICERs/LY show cost-effective or not. Rather, is it worth paying 331.70 euro more per patient to identify more gene alterations and increase the use of targeted therapies at an ICER/LY of €52,615.04 to € 59,920.64 to unlock better outcomes for patients currently receiving ineffective chemotherapy? Because the Belgian healthcare payer does not publish ICERs to protect the confidentiality, it is impossible to compare this ICER to those of reimbursed precision oncology drugs. However, given that our costs (and presumably outcomes) were generated using an average of the prices of those same targeted therapies, it's hard to imagine their respective ICERs would be of a completely different scale.

Taken together, the results from the first diagnostic model suggest that the Belgian healthcare payer should at least consider introducing conditional reimbursement for CGP for the remainder of its clinical evaluation. That way the detection of genetic alterations and use of targeted therapy in current metastatic non-squamous NSCLC patients could increase while more data is gathered to confirm or deny the assumptions made in this early model, specifically regarding the increased detection of gene alterations and the effectiveness of targeted therapy. Once finished, the data from these studies should be followed by a more mature model of cost-effectiveness for which this report can be the basis. This could then be used to make a final decision on reimbursement of CGP.

A second diagnostic decision model was developed to determine cost-savings that could be achieved by better stratifying metastatic, non-squamous NSCLC patients for immunotherapy regimens. Following research by Cuppens et al. (2020), the additional biomarkers from CGP could lead to the early exclusion of patient groups in which no durable response can be achieved, while in other patient groups higher response rates can be achieved. The decision model used average costs and outcomes of partitioned survival models based on input from the KEYNOTE trials that determined the effectiveness of immunotherapy and immuno + chemotherapy in patients with different PD-L1 expression levels. The decision model took into account the costs of the diagnostic, the distribution in patient subgroups with different first-line therapies by the diagnostic and the response rate of each subgroup. Resulting in an average cost per patient of € 132,557.83 for an average of 2.139 LYs gained by using the SoC cascade to stratify patient. Using CGP-based stratification led to an average cost per patient of € 130,742.56 for an average of 2.147 LYs gained. The second decision model thus suggest that using CGP to stratify patients for immunotherapy regimens can lead to an average decrease of € 1,815.27 per patient and a negligible gain in LYs.

Scenario analyses was used to account for the small sample size on which the biomarker distributions taken from Cuppens et al. (2020) were based. This showed that the cost-savings from the base case analysis is likely a conservative estimate and savings could be as high as € 13,178.65, though a different biomarker distribution could also lead to small amounts of LYs lost.

It is advisable to wait for the results of the ongoing clinical valuation of CGP and the effects of an increased sample size on the stratification proposed by Cuppens et al.(2020). Of particular interest are the response rates of triple positive and triple negative patients as these drive the cost savings. If the stratification proposed by Cuppens et al. (2020) holds in a larger patient group, than the results from this second early decision model generate strong arguments for the reimbursement of CGP in the diagnosis of metastatic, non-squamous NSCLC.

4.2. Limitations & future research

The early models used in this report were made with historical data that does not necessarily reflect the current situation. The assumptions made to compensate for the lack of appropriate data limit the conclusions that can be drawn from this report and its results.

The BIOMARKERs study, used to create the partitioned survival model for patients with identified gene alteration, followed NSCLC patients between 2012 and 2014. *EGFR, ERBB2*, *KRAS*, *BRAF*, *PIK3CA* and *ALK* were considered the only relevant genes for NSCLC diagnosis and the only available targeted therapies were EGFR TKI's and crizotinib. In 2021, a study of the same nature would certainly assess more genomic alterations and more targeted therapies would be available for the alterations found. It is also more common to enter patients into clinical trials due to the spread of genomic data-analytics. The ongoing BALLETT study presents an ideal opportunity to gather more real-world evidence on the identification of genetic alterations and the consequences thereof. A greater focus on data collection and evidence generation is urgently needed to increase the adoption of innovative In Vitro Diagnostics.

The cost savings generated by the second model are driven by the stratification proposed by Cuppens et al. (2020). Although impressive, their research was done on a relative small group of patients and should be confirmed in a larger scale study. Again, the ongoing BALLETT study provides a great opportunity to gather this data and make more definitive conclusions.

Collecting data during the BALLETT study could also take away the need to have two diagnostic decision models with and partitioned survival models embedded within. Data could be collected from a single study allowing the comparison of the effects of immunotherapy, targeted therapy and chemotherapy in a single patient population.

5. Conclusion

Early decision models suggest the introduction of comprehensive genomic profiling could have beneficial effects on the health economics of therapy options for metastatic, non-squamous NSCLC patients in Belgium. The results suggest that CGP could unlock better outcomes for patients with very dim survival rates by detecting more genetic alterations than the current standard of care diagnostic cascade, allowing for increased use of targeted therapies. Moreover, in patients without gene alterations, biomarkers from the CGP cascade can lead to cost savings by more efficiently stratifying patients for immunotherapy regimens. Taken together these results make a strong case for the health economic benefits of CGP. Although the assumptions made in the construction of the early models need to be confirmed in a real world setting. The BALLETT study provides a unique opportunity to do so and decision makers should consider conditionally reimbursing CGP for the duration of the study.

6. References

Annemans, L. (2018). *Precision Medicine. A Health Economic perspective Ghent University*. http://medicalfuturist.com

Barlesi, F., Mazieres, J., Merlio, J. P., Debieuvre, D., Mosser, J., Lena, H., Ouafik, L., Besse, B., Rouquette, I., Westeel, V., Escande, F., Monnet, I., Lemoine, A., Veillon, R., Blons, H., Audigier-Valette, C., Bringuier, P. P., Lamy, R., Beau-Faller, M., … Zalcman, G. (2016). Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *The Lancet*, *387*(10026), 1415–1426. https://doi.org/10.1016/S0140-6736(16)00004-0

Barta, J. A., Powell, C. A., & Wisnivesky, J. P. (2019). Global Epidemiology of Lung Cancer. *Annals of Global Health*, *85*(1). https://doi.org/10.5334/AOGH.2419

Bekelman, J. E., Halpern, S. D., Blankart, C. R., Bynum, J. P., Cohen, J., Fowler, R., Kaasa, S., Kwietniewski, L., Melberg, H. O., Onwuteaka-Philipsen, B., Oosterveld-Vlug, M., Pring, A., Schreyögg, J., Ulrich, C. M., Verne, J., Wunsch, H., & Emanuel, E. J. (2016). Comparison of site of death, health care utilization, and hospital expenditures for patients dying With cancer in 7 developed countries. *JAMA - Journal of the American Medical Association*, *315*(3), 272–283. https://doi.org/10.1001/jama.2015.18603

Belgian Cancer Registry. (2018a). https://kankerregister.org/Statistieken_tabellen_jaarbasis (C34)

Belgian Cancer Registry. (2018b). *Cancer Fact Sheet Lung Cancer*. https://kankerregister.org/media/docs/CancerFactSheets/2018/Cancer_Fact_Sheet_LungCancer_2018.pdf

Bender, E. (2014). Epidemiology: The dominant malignancy. *Nature 2014 513:7517*, *513*(7517), S2–S3. https://doi.org/10.1038/513s2a

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Buchanan, J., & Fermont, J. (2016). *Personalised Medicine & Resource Allocation, Oxford - YouTube*. https://www.youtube.com/watch?v=QihAuBSTCcU

Chevallier, M., Borgeaud, M., Addeo, A., & Friedlaender, A. (2021). Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. *World Journal of Clinical Oncology*, *12*(4), 217. https://doi.org/10.5306/WJCO.V12.I4.217

Chouaid, C., Loirat, D., Clay, E., Millier, A., Godard, C., Fannan, A., Lévy-Bachelot, L., & Angevin, E. (2017). ClinicoEconomics and Outcomes Research Dovepress Cost analysis of adverse events associated with non-small cell lung cancer management in France. *ClinicoEconomics and Outcomes Research*, *2017*, 9–443. https://doi.org/10.2147/CEOR.S138963

Chouaid, C., Pouvourville, G. De, & Laura, L. (2017). Cost-effectiveness analysis of afatinib vs gefitinib in EGFR-Mutated population with advanced non-small-cell lung cancer. *European Respiratory Journal*, *50*(suppl 61), PA2794. https://doi.org/10.1183/1393003.CONGRESS-2017.PA2794

Cleemput, I., Neyt, M., Thiry, N., & De Laet, C. (2011). Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions Mark Leys. *International Journal of Technology Assessment in Health Care*, *27*, 71–76. https://doi.org/10.1017/S0266462310001194

Cleemput, I., Neyt, M., Van de Sande, S., & Thiry, N. (2012). *BELGISCHE RICHTLIJNEN VOOR ECONOMISCHE EVALUATIES EN BUDGET IMPACT ANALYSES: TWEEDE EDITIE*. http://www.kce.fgov.be

ComPerMed. (2021). https://www.compermed.be/en

Cuppens, K., Froyen, G., Cruys, B., Geerdens, E., Zhang, S., Zhang, B., Decoster, L., Thomeer, M., & Maes, B. (2020). 1037P Tumour mutational burden and HLA diversity by TruSight oncology 500 (TSO500) next generation sequencing panel and clinical outcome in non-small cell lung cancer. *Annals of Oncology*, *31*, S713–S714. https://doi.org/10.1016/J.ANNONC.2020.08.1157

de Groot, P. M., Wu, C. C., Carter, B. W., & Munden, R. F. (2018). The epidemiology of lung cancer. *Translational Lung Cancer Research*, *7*(3), 220–233. https://doi.org/10.21037/TLCR.2018.05.06

EB, G., MD, H., NA, R., E, C., NB, L., MJ, A., JP, E., AS, B., C, A., L, H., A, P., M, G., SS, R., E, F., JW, G., C, S., E, J., DA, K., & R, H. (2019). Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *37*(28), 2518–2527. https://doi.org/10.1200/JCO.19.00934

Euro to US Dollar Spot Exchange Rates for 2010. (2021). https://www.exchangerates.org.uk/EUR-USD-spot-exchange-rates-history-2010.html

Gandhi, L., Rodríguez-Abreu, D., Gadgeel, S., Esteban, E., Felip, E., Angelis, F. De, Domine, M., Clingan, P., Hochmair, M. J., Powell, S. F., Cheng, S. Y.-S., Bischoff, H. G., Peled, N., Grossi, F., Jennens, R. R., Reck, M., Hui, R., Garon, E. B., Boyer, M., … Garassino, M. C. (2018). Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *Https://Doi-Org.Eur.Idm.Oclc.Org/10.1056/NEJMoa1801005*, *378*(22), 2078–2092. https://doi.org/10.1056/NEJMOA1801005

Govaerts, L., Simoens, S., Van Dyck, W., & Huys, I. (2020). Shedding Light on Reimbursement Policies of Companion Diagnostics in European Countries. *Value in Health*, *23*(5), 606–615. https://doi.org/10.1016/J.JVAL.2020.01.013

Health index | Statbel. (2021). https://statbel.fgov.be/en/themes/consumer-prices/health-index

Holleman, M. S., Al, M. J., Zaim, R., Groen, H. J. M., & Uyl-de Groot, C. A. (2020). Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with non-small cell lung cancer harbouring EGFR mutations. *European Journal of Health Economics*, *21*(1), 153–164. https://doi.org/10.1007/s10198-019-01117-3

Holmes, M., Mahar, A., Lum, T., Boyer, M., Kao, S., & Cooper, W. (2019). P1.09-26 Prevalence of PD-L1 Expression Rates in Different NSCLC Specimens. *Journal of Thoracic Oncology*, *14*(10), S506. https://doi.org/10.1016/J.JTHO.2019.08.1055

Hoyle, M. W., & Henley, W. (2011). Improved curve fits to summary survival data: Application to economic evaluation of health technologies. *BMC Medical Research Methodology*, *11*(1), 139. https://doi.org/10.1186/1471-2288-11-139

Joshi, E., Nanayakkara, B., Barnes, D. J., Troy, L. K., & Michie, C. (2020). Precision Medicine in Lung Cancer. *Citation: EMJ Oncol*. https://doi.org/10.33590/emjoncol/19-00145

Kim, L., & Tsao, M. S. (2014). Tumour tissue sampling for lung cancer management in the era of personalized therapy: What is good enough for molecular testing? *European Respiratory Journal*, *44*(4), 1011–1022. https://doi.org/10.1183/09031936.00197013

Kroeze, L. I., de Voer, R. M., Kamping, E. J., von Rhein, D., Jansen, E. A. M., Hermsen, M. J. W.,

Barberis, M. C. P., Botling, J., Garrido-Martin, E. M., Haller, F., Lacroix, L., Maes, B., Merkelbach-Bruse, S., Pestinger, V., Pfarr, N., Stenzinger, A., van den Heuvel, M. M., Grünberg, K., & Ligtenberg, M. J. L. (2020). Evaluation of a Hybrid Capture–Based Pan-Cancer Panel for Analysis of Treatment Stratifying Oncogenic Aberrations and Processes. *Journal of Molecular Diagnostics*. https://doi.org/10.1016/j.jmoldx.2020.02.009

Lim, S. M., Hong, M. H., & Kim, H. R. (2020). Immunotherapy for Non-small Cell Lung Cancer: Current Landscape and Future Perspectives. *Immune Network*, *20*(1). https://doi.org/10.4110/IN.2020.20.E10

Lin, J. J., Cardarella, S., Lydon, C. A., Dahlberg, S. E., Jackman, D. M., Jänne, P. A., & Johnson, B. E. (2016). Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*, *11*(4), 556. https://doi.org/10.1016/J.JTHO.2015.12.103

Lu, T., Yang, X., Huang, Y., Zhao, M., Li, M., Ma, K., Yin, J., Zhan, C., & Wang, Q. (2019). Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Management and Research*, *11*, 943. https://doi.org/10.2147/CMAR.S187317

Majeed, U., Manochakian, R., Zhao, Y., & Lou, Y. (2021). Targeted therapy in advanced non-small cell lung cancer: current advances and future trends. *Journal of Hematology & Oncology 2021 14:1*, *14*(1), 1–20. https://doi.org/10.1186/S13045-021-01121-2

Malhotra, J., Malvezzi, M., Negri, E., Vecchia, C. La, & Boffetta, P. (2016). Risk factors for lung cancer worldwide SERIES THORACIC ONCOLOGY. *Eur Respir J*, *48*, 889–902. https://doi.org/10.1183/13993003.00359-2016

Mazières, J., Merlio, J.-P., Missy, P., Moro-Sibilot, D., & Barlesi, F. (2016). Routine molecular profiling of patients with NSCLC – Authors' reply. *The Lancet*, *388*(10049), 1054–1055. https://doi.org/10.1016/S0140-6736(16)31136-9

Nakagawa, H., & Fujita, M. (2018). Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Science*, *109*(3), 513–522. https://doi.org/10.1111/CAS.13505

Neal, R. D., Tharmanathan, P., France, B., Din, N. U., Cotton, S., Fallon-Ferguson, J., Hamilton, W., Hendry, A., Hendry, M., Lewis, R., Macleod, U., Mitchell, E. D., Pickett, M., Rai, T., Shaw, K., Stuart, N., Tørring, M. L., Wilkinson, C., Williams, B., … Emery, J. (2015). Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. In *British Journal of Cancer* (Vol. 112, Issue 1, pp. S92–S107). Springer Nature. https://doi.org/10.1038/bjc.2015.48

Pauwels, P., Hoton, D., Van Dorpe, J., Dhaene, K., Dome, F., Jouret-Mourin, A., Weynand, B., & D'Haene, N. (2016). Pathological diagnosis and molecular testing in non-small cell lung cancer: Belgian guidelines. *Belgian Journal of Medical Oncology*, *10*(4), 123–131.

Pauwels, P., Remmelink, M., Hoton, D., Van Dorpe, J., Dhaene, K., Dome, F., Jouret-Mourin, A., Weynand, B., & D'Haene, N. (2018). PD-L1 Testing for Non-Small Cell Lung Cancer: Belgian Guidelines - BJMO. *Belgian Journal of Medical Oncology*, *12*(5), 233–238.

Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., Mok, T. S., Reck, M., Van Schil, P. E., Hellmann, M. D., Peters, S., & ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. (2020). *Clinical Practice Living Guidelines – Metastatic Non-Small-Cell Lung Cancer | ESMO*. https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer

Press Release. (2021). Illumina.Com. https://emea.illumina.com/company/news-center/press-

releases/press-release-details.html?newsid=208d1c9f-3f6e-489b-8a88-7205d012f356

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., Gottfried, M., Peled, N., Tafreshi, A., Cuffe, S., O'Brien, M., Rao, S., Hotta, K., Leiby, M. A., Lubiniecki, G. M., Shentu, Y., Rangwala, R., & Brahmer, J. R. (2016). Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *Https://Doi-Org.Eur.Idm.Oclc.Org/10.1056/NEJMoa1606774*, *375*(19), 1823–1833. https://doi.org/10.1056/NEJMOA1606774

Rennert, G., Gottfried, M., Rennert, H. S., Lejbkowicz, F., Frank, M., Cohen, I., Kelt, S., Agbarya, A., Dudnik, E., Dudnik, J., Katznelson, R., Mishali, M., Rabinovich, N. M., Nechushtan, H., Onn, A., Rosenberg, S. K., Wollner, M., Zer, A., Bar, J., & Gronich, N. (2021). Long term follow-up of EGFR mutated NSCLC cases. *Translational Oncology*, *14*(1). https://doi.org/10.1016/J.TRANON.2020.100934

RIZIV/INAMI. (2021). *Geneesmiddelen*. https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch

Roelofsen-De Beer, R., Wielders, J., Boursier, G., Vodnik, T., Vanstapel, F., Huisman, W., Vukasović, I., Vaubourdolle, M., Sönmez, Ç., Linko, S., Brugnoni, D., Kroupis, C., Lohmander, M., Šprongl, L., Bernabeu-Andreu, F., Meško Brguljan, P., & Thelen, M. (2020). Validation and verification of examination procedures in medical laboratories: Opinion of the EFLM Working Group Accreditation and ISO/CEN standards (WG-A/ISO) on dealing with ISO 15189:2012 demands for method verification and validation. *Clinical Chemistry and Laboratory Medicine*, *58*(3), 361–367. https://doi.org/10.1515/cclm-2019-1053

Sacco, J. J., Botten, J., Macbeth, F., Bagust, A., & Clark, P. (2010). The average body surface area of adult cancer patients in the UK: A multicentre retrospective study. *PLoS ONE*, *5*(1), 8933. https://doi.org/10.1371/journal.pone.0008933

Shojaee, S., Vachani, A., & Nana-Sinkam, P. (2017). The Financial Implications of Lung Cancer Screening: Is It Worth It? *Journal of Thoracic Oncology*, *12*, 1177–1179. https://doi.org/10.1016/j.jtho.2017.06.016

Sun, S., Schiller, J. H., & Gazdar, A. F. (2007). Lung cancer in never smokers - A different disease. In *Nature Reviews Cancer* (Vol. 7, Issue 10, pp. 778–790). Nature Publishing Group. https://doi.org/10.1038/nrc2190

Swartenbroeckx, N., Obyn, C., Guillaume, P., Lona, M., & Cleemput, I. (2012). *KCE Report 178C - MANUAL FOR COST-BASED PRICING OF HOSPITAL INTERVENTIONS*. http://www.kce.fgov.be

Szustakowski, J. D., Green, G., Geese, W. J., Zerba, K., & Chang, H. (2018). Abstract 5528: Evaluation of tumor mutation burden as a biomarker for immune checkpoint inhibitor efficacy: A calibration study of whole exome sequencing with FoundationOne®. *Cancer Research*, *78*(13 Supplement), 5528–5528. https://doi.org/10.1158/1538-7445.AM2018-5528

Tango project researchers. (2020). *Technology Assessment of Next Generation Sequencing in Personalized Oncology - TANGO Project | Zenodo*. https://zenodo.org/communities/tango-wgs/?page=1&size=20

UZ Ghent. (2021). *Platform Moleculaire Diagnostiek UZ Gent (MDG) - Centrum Medische Genetica*. https://www.cmgg.be/nl/zorgverlener/labguide/platform-moleculaire-diagnostiek-uz-gent-mdg

UZ Leuven. (2021). *Staal afnemen en TAT | UZ Leuven*. https://www.uzleuven.be/nl/pathologische-ontleedkunde/staalafnames

van de Ven, M., Retèl, V. P., Koffijberg, H., van Harten, W. H., & IJzerman, M. J. (2019). Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the

Netherlands. *Lung Cancer*, *134*, 34–41. https://doi.org/10.1016/j.lungcan.2019.05.023

Van Dyck, W., De Grève, J., Schots, R., Awada, A., & Geldof, T. (2016). *Vlerick Policy Paper Series The Future of Access to Innovative Medicines in Cancer Therapy: Towards Conditional Dialogue Fostering Affordable Therapeutic Innovation The Future of Access to Innovative Medicines in Cancer Therapy: Towards Conditional Dialog*.

Wordsworth, S., & Buchanan, J. (2019). *Translating Genomic Tests into Clinical Practice in the UK NHS - YouTube*. https://www.youtube.com/watch?v=tDojZcKxvco

Yarchoan, M., Albacker, L. A., Hopkins, A. C., Montesion, M., Murugesan, K., Vithayathil, T. T., Zaidi, N., Azad, N. S., Laheru, D. A., Frampton, G. M., & Jaffee, E. M. (2019). PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. *JCI Insight*, *4*(6). https://doi.org/10.1172/JCI.INSIGHT.126908

Zehir, A., Benayed, R., Shah, R. H., Syed, A., Middha, S., Kim, H. R., Srinivasan, P., Gao, J., Chakravarty, D., Devlin, S. M., Hellmann, M. D., Barron, D. A., Schram, A. M., Hameed, M., Dogan, S., Ross, D. S., Hechtman, J. F., DeLair, D. F., Yao, J., … Berger, M. F. (2017). Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Medicine 2017 23:6*, *23*(6), 703–713. https://doi.org/10.1038/NM.4333

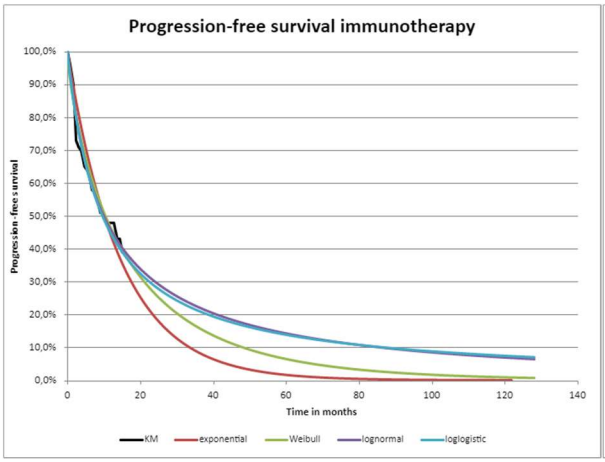
7. Appendix

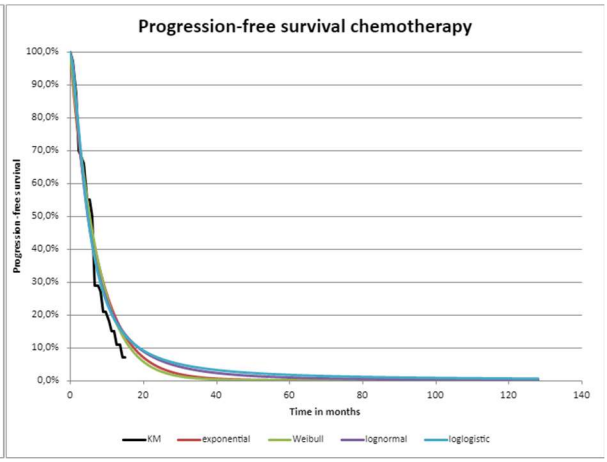
Table S1: Full distribution of therapy options in the BIOMARKER study.

N	Overall population 17664	*EGFR* mutation 1787		*KRAS* mutation 4588		*BRAF* mutation 230		*ERBB2* mutation 92		*PIK3CA* mutation 157		*ALK* rearrangement 340		Average for mutation-positive and treatment adapted group	Full WT 2769
		All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All	All
First-line treatment															
Number with data	8448	1128	662	2085	979	146	64	62	28	73	29	236	120		1214
Number with data (%)	0.48	0.63	0.37	0.45	0.21	0.63	0.28	0.67	0.30	0.46	0.18	0.69	0.35		0.44
Weight			0.35		0.52		0.03		0.01		0.02		0.06		
Pemetrexed-based regimen	0.33	0.17	0.09	0.38	0.54	0.35	0.53	0.5	0.64	0.23	0.38	0.47	0.46	0.31	0.33
Vinorelbine-based regimen	0.06	0.03	0.01	0.06	0.07	0.03	0.03	0	0	0.1	0.1	0.06	0.08	0.05	0.07
Taxane-based regimen	0.13	0.05	0.03	0.13	0.17	0.14	0.19	0.13	0.14	0.15	0.24	0.07	0.09	0.10	0.15
First line chemo	**0.52**	**0.25**	**0.13**	**0.57**	**0.78**	**0.52**	**0.75**	**0.63**	**0.78**	**0.48**	**0.72**	**0.6**	**0.63**	**0.46**	**0.55**
EGFR-TKI	0.08	0.48	0.79	0.01	0.01	0.02	0.03	0	0	0.01	0.03	0.02	0.02	0.18	0.01
Crizotinib	0.001	0	0	0	0	0	0	0	0	0	0	0.08	0.15	0.01	0
First line PM	**0.11**	**0.51**	**0.84**	**0.04**	**0.06**	**0.07**	**0.11**	**0.05**	**0.04**	**0.01**	**0.03**	**0.17**	**0.27**	**0.31**	**0.01**
Trial‡	**0.03**	**0.03**	**0.05**	**0.03**	**0.05**	**0.05**	**0.08**	**0.05**	**0.04**	**0**	**0**	**0.07**	**0.1**	**0.03**	**0.03**
Other§	0.08	0.02	0.01	0.08	0.08	0.08	0.05	0.08	0.11	0.14	0.17	0.03	0.03	0.06	0.11
BSC only	**0.29**	**0.21**	**0.03**	**0.31**	**0.09**	**0.33**	**0.09**	**0.24**	**0.07**	**0.37**	**0.07**	**0.22**	**0.08**	**0.27**	**0.3**
Second-line treatment															
Number with data	5518	698	381	1358	566	106	37	43	22	48	12	157	102		797
Number with data (%)	0.31	0.39	0.21	0.30	0.12	0.46	0.16	0.47	0.24	0.31	0.08	0.46	0.30		0.29
Weight			0.34		0.51		0.03		0.02		0.01		0.09		
Taxane	0.14	0.07	0.09	0.17	0.36	0.15	0.22	0.14	0.18	0.1	0.17	0.03	0.04	0.12	0.15
Pemetrexed	0.11	0.18	0.25	0.1	0.19	0.08	0.16	0.12	0.18	0.08	0.17	0.08	0.1	0.12	0.1
Second line chemo	**0.25**	**0.25**	**0.34**	**0.27**	**0.55**	**0.23**	**0.38**	**0.26**	**0.36**	**0.18**	**0.34**	**0.11**	**0.14**	**0.25**	**0.25**
Erlotinib	0.14	0.33	0.57	0.09	0.17	0.08	0.11	0.12	0.18	0.04	0.17	0.06	0.06	0.17	0.12
Crizotinib	0.01	0	0	0	0	0	0	0	0	0	0	0.46	0.72	0.04	0
Second line PM	**0.15**	**0.33**	**0.57**	**0.09**	**0.17**	**0.08**	**0.11**	**0.12**	**0.18**	**0.04**	**0.17**	**0.52**	**0.78**	**0.21**	**0.12**
Trial‡	**0.02**	**0.01**	**0.02**	**0.02**	**0.05**	**0.05**	**0.14**	**0.07**	**0.09**	**0.04**	**0.08**	**0.03**	**0.04**	**0.02**	**0.03**
Other§	0.08	0.01	0.02	0.07	0.11	0.08	0.19	0.19	0.36	0.04	0.17	0.03	0.03	0.05	0.1
BSC only	**0.49**	**0.39**	**0.04**	**0.54**	**0.14**	**0.57**	**0.19**	**0.37**	**0**	**0.69**	**0.25**	**0.3**	**0.02**	**0.47**	**0.5**

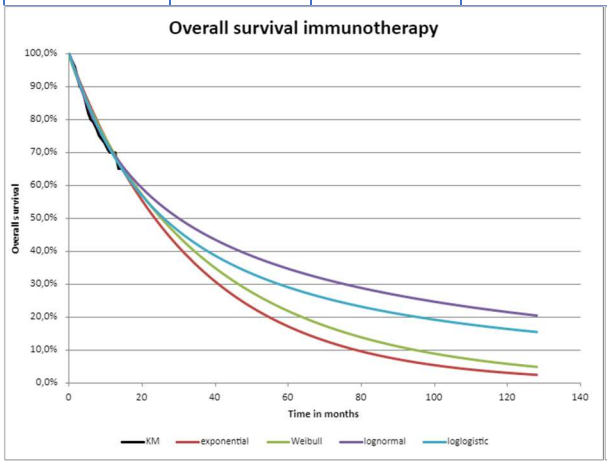
Table S2-S4: Kaplan Meier curves and corresponding parametric distributions and AIC scores for the partitioned survival models of immunotherapy patients.

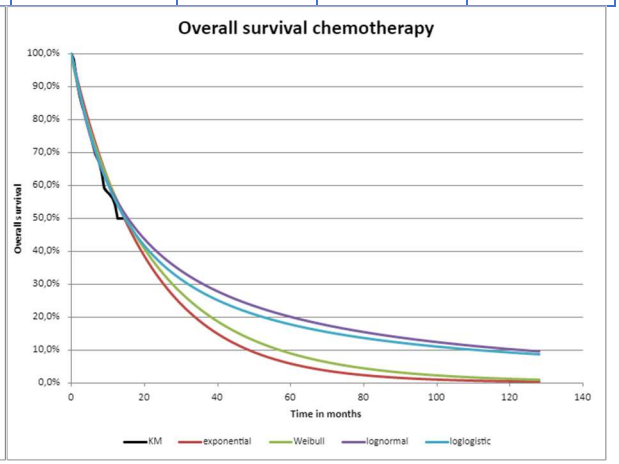
Immunotherapy I – KEYNOTE-024





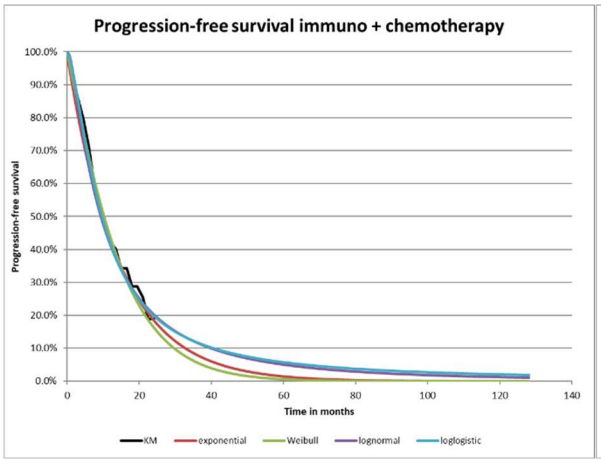
PFS							
Immunotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
588.9915	585.0808	575.0603	579.1243	769.3036	770.2073	756.5085	756.0489

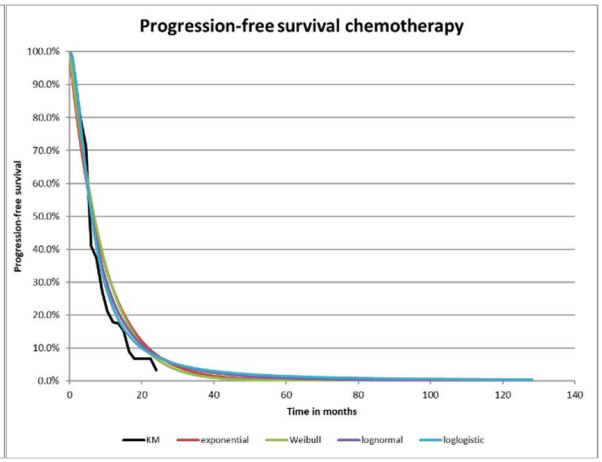




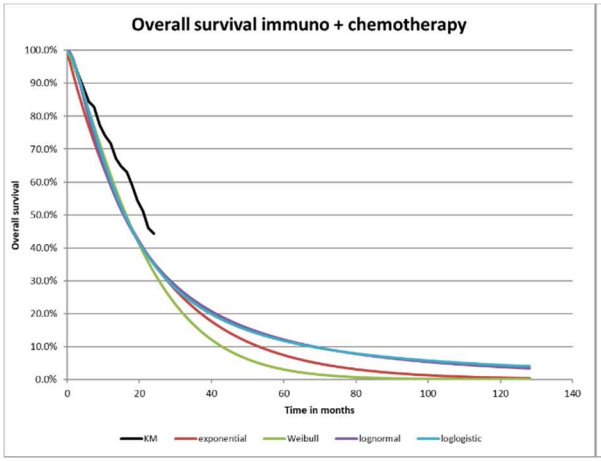
OS							
Immunotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
415.7498	417.3362	415.1901	416.5377	547.6024	548.8006	543.5672	545.6462

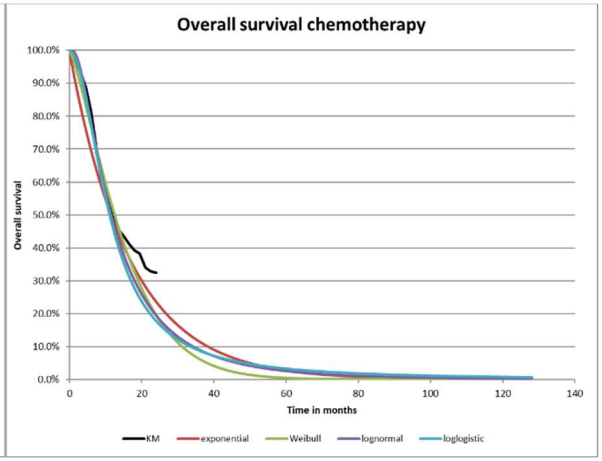
Immunotherapy II – KEYNOTE-189





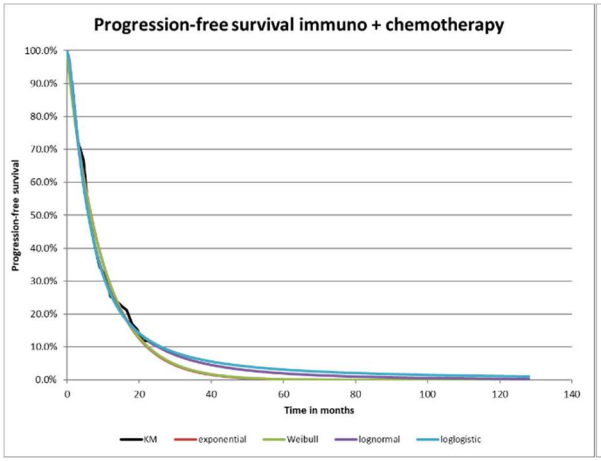
PFS							
Immuno + chemotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
613.7898	613.9813	618.7834	615.8768	286.5851	288.0318	279.8964	277.7273

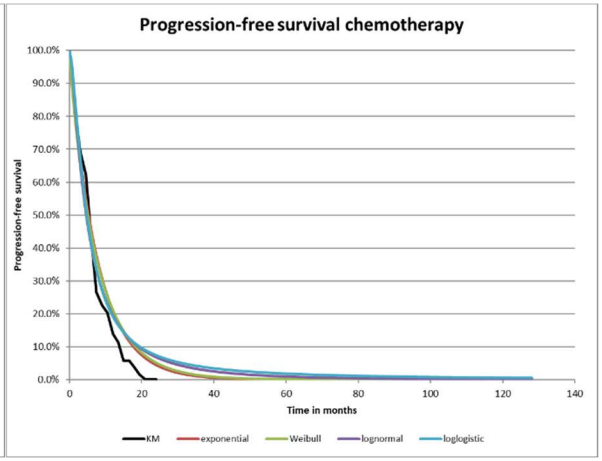




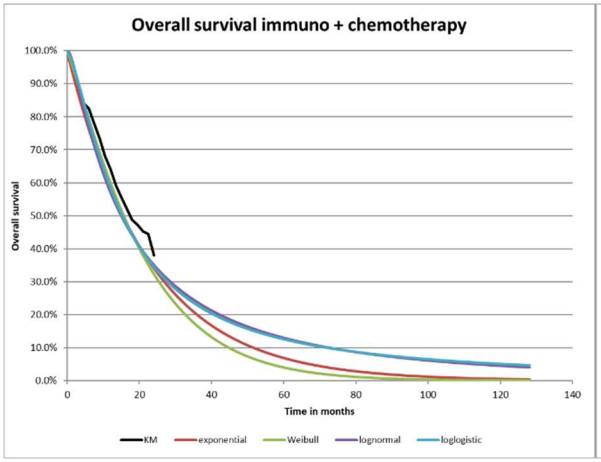
OS							
Immuno + chemotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
487.5107	486.0291	489.6381	488.1634	251.9553	250.3661	241.9534	242.6173

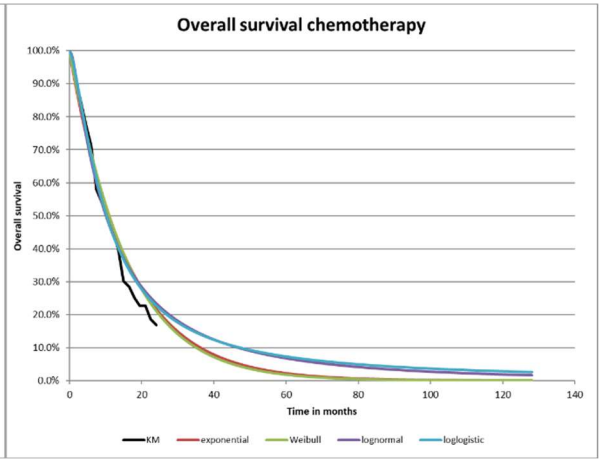
Immunotherapy III – KEYNOTE-189





PFS							
Immuno + chemotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
621.4821	623.4212	617.6984	617.0643	308.0606	309.7599	307.7	306.0196





OS							
Immuno + chemotherapy				Chemotherapy			
exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
535.1314	535.6156	539.3703	537.3294	337.2915	339.189	338.7867	337.3319

Table S5-S8: Disaggregated costs and outcomes from partitioned survival models of immunotherapy patients.

IMMUNOTHERAPY I – PD-L1 ≥ 50%

Treatment	Pembrolizumab	Chemotherapy	Increment	Non durable resp	Increment
Drug acquisition costs - SD	€ 184,725	€ 8,681	€ 176,043	€ 38,689	€ 146,036
Chemo admin costs - SD	€ 2,659	€ 4,293	-€ 1,633	€ 3,957	-€ 1,298
Premed & concomitant costs SD	€ 0	€ 2,014	-€ 2,014	€ 1,624	-€ 1,624
Disease management costs - SD	€ 9,368	€ 4,350	€ 5,018	€ 3,880	€ 5,488
BSC costs - SD	€ 0	€ 0	€ 0	€ 0	€ 0
AE costs SD	€ 497	€ 905	-€ 409	€ 497	€ 0
Sum	**€ 197,248**	**€ 20,242**	**€ 177,006**	**€ 48,647**	**€ 148,602**
Drug acquisition costs - PD	€ 2,360	€ 2,238	€ 122	€ 2,238	€ 122
Chemo admin costs - PD	€ 464	€ 159	€ 305	€ 159	€ 305
Premed & concomitant costs PD	€ 218	€ 75	€ 143	€ 75	€ 143
Disease management costs - PD	€ 3,224	€ 3,693	-€ 469	€ 3,693	-€ 469
BSC costs	€ 5,430	€ 5,582	-€ 151	€ 5,582	-€ 151
Sum	**€ 11,697**	**€ 11,747**	**-€ 50**	**€ 11,747**	**-€ 50**
End of life costs	€ 4,743	€ 4,926	-€ 183	€ 4,926	-€ 183
Total costs	**€ 213,688**	**€ 36,915**	**€ 176,772**	**€ 65,319**	**€ 148,368**
LYs accrued in SD state	1.54	0.61	0.935022851	0.61	0.9350229
LYs accrued in PD state	1.56	1.30	0.261292242	1.30	0.2612922

IMMUNOTHERAPY II – 1% ≤ PD-L1 < 50%

Treatment	Pembrolizumab	Chemotherapy	Increment	Non durable resp	Increment
Drug acquisition costs - SD	€ 188,232	€ 11,289	€ 176,943	€ 48,345	€ 139,887
Chemo admin costs - SD	€ 6,373	€ 3,935	€ 2,438	€ 4,450	€ 1,923
Premed & concomitant costs SD	€ 1,846	€ 1,846	€ 0	€ 1,835	€ 11
Disease management costs - SD	€ 8,587	€ 5,687	€ 2,901	€ 5,071	€ 3,517
BSC costs - SD	€ 0	€ 0	€ 0	€ 0	€ 0
AE costs SD	€ 1,402	€ 905	€ 497	€ 1,402	€ 0
Sum	**€ 206,440**	**€ 23,662**	**€ 182,778**	**€ 61,102**	**€ 145,338**
Drug acquisition costs - PD	€ 19,880	€ 2,225	€ 17,655	€ 2,225	€ 17,655
Chemo admin costs - PD	€ 466	€ 158	€ 308	€ 158	€ 308
Premed & concomitant costs PD	€ 218	€ 74	€ 144	€ 74	€ 144
Disease management costs - PD	€ 1,853	€ 1,574	€ 279	€ 1,574	€ 279
BSC costs	€ 5,446	€ 5,549	-€ 103	€ 5,549	-€ 103
Sum	**€ 27,864**	**€ 9,580**	**€ 18,284**	**€ 9,580**	**€ 18,284**
End of life costs	€ 4,845	€ 5,006	-€ 161	€ 5,006	-€ 161
Total costs	**€ 239,150**	**€ 38,248**	**€ 200,901**	**€ 75,689**	**€ 163,461**
LYs accrued in SD state	1.41	0.81	0.605102688	0.81	0.6051027
LYs accrued in PD state	0.90	0.55	0.351513912	0.55	0.3515139

IMMUNOTHERAPY II –PD-L1 < 1%

Treatment	Pembrolizumab	Chemotherapy	Increment	Non durable resp	Increment
Drug acquisition costs - SD	€ 124,660	€ 9,884	€ 114,776	€ 43,671	€ 80,988
Chemo admin costs - SD	€ 4,221	€ 2,607	€ 1,615	€ 3,060	€ 1,161
Premed & concomitant costs SD	€ 1,223	€ 1,223	€ 0	€ 1,205	€ 18
Disease management costs - SD	€ 6,388	€ 4,973	€ 1,415	€ 4,980	€ 1,408
BSC costs - SD	€ 0	€ 0	€ 0	€ 0	€ 0
AE costs SD	€ 1,402	€ 905	€ 497	€ 1,402	€ 0
Sum	€ 137,894	€ 19,592	€ 118,303	€ 54,319	€ 83,575
Drug acquisition costs - PD	€ 20,187	€ 2,232	€ 17,955	€ 2,232	€ 17,955
Chemo admin costs - PD	€ 473	€ 159	€ 314	€ 159	€ 314
Premed & concomitant costs PD	€ 222	€ 74	€ 147	€ 74	€ 147
Disease management costs - PD	€ 3,023	€ 2,566	€ 456	€ 2,566	€ 456
BSC costs	€ 5,530	€ 5,566	-€ 36	€ 5,566	-€ 36
Sum	€ 29,435	€ 10,597	€ 18,837	€ 10,597	€ 18,837
End of life costs	€ 4,827	€ 4,959	-€ 133	€ 4,959	-€ 133
Total costs	€ 172,155	€ 35,148	€ 137,007	€ 69,876	€ 102,279
LYs accrued in SD state	0.92	0.70	0.213434267	0.70	0.2134343
LYs accrued in PD state	1.46	0.91	0.550362124	0.91	0.5503621