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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of an Individualized First-Line Treatment Strategy Offering Erlotinib Based on *EGFR* Mutation Testing in Advanced Lung Adenocarcinoma Patients in Germany

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Abstract

Background Lung cancer is among the top causes of cancer-related deaths. Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors can increase progression-free survival compared with standard chemotherapy in patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC).

Objective The aim of the study was to evaluate the cost-effectiveness of *EGFR* mutation analysis and first-line therapy with erlotinib for mutation-positive patients compared with non-individualized standard chemotherapy from the perspective of German statutory health insurance.

Methods A state transition model was developed for a time horizon of 10 years (reference year 2014). Data sources were published data from the European Tarceva versus Chemotherapy (EURTAC) randomized trial for drug efficacy and safety and German cost data. We additionally performed deterministic, probabilistic and structural sensitivity analyses.

Results The individualized strategy incurred 0.013 additional quality-adjusted life-years (QALYs) and additional costs of €200, yielding an incremental cost-effectiveness ratio (ICER) of €15,577/QALY. Results were most sensitive to uncertainty in survival curves and changes in utility values. Cross-validating health utility estimates with recent German data increased the ICER to about €58,000/QALY. The probabilistic sensitivity analysis indicated that the individualized strategy is cost-effective, with a probability exceeding 50 % for a range of possible willingness-to-pay thresholds.

Limitations The uncertainty of the predicted survival curves is substantial, particularly for overall survival, which was not a primary endpoint in the EURTAC study. Also, there is limited data on quality of life in metastatic lung cancer patients.

Conclusions Individualized therapy based on *EGFR* mutation status has the potential to provide a cost-effective alternative to non-individualized care for patients with advanced adenocarcinoma. Further clinical research is needed to confirm these results.

Electronic supplementary material The online version of this article (doi:10.1007/s40273-015-0305-8) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

Individualized therapy selection based on patients' genetic characteristics, e.g., *EGFR* mutation status, has the potential to be cost-effective for the healthcare insurance system and can increase patients' quality of life.

A clear understanding of the impact of different clinically relevant metastatic lung cancer health states on patients' quality of life is important to reliably assess the benefits of new therapeutic approaches.

Adequately powered trials are needed to compare various targeted agents and chemotherapies between different patient populations and individual patient characteristics, as a basis for future cost-effectiveness studies.

1 Introduction

Lung cancer is currently the leading cause of cancer-related deaths among males and the second most important cause among females, with a total of 55,600 new cases estimated in Germany in the year 2014 [1]. Of these cases, non-small cell lung cancer (NSCLC) accounts for approximately 80–85 %, with about 50 % of patients found to be in advanced stage IV at the time of diagnosis [2]. Testing for certain mutations in the epidermal growth factor receptor (*EGFR*) gene is recommended for patients with adenocarcinoma at the point of diagnosis in order to choose the most appropriate therapeutic strategy [3–5]. Until now, several randomized phase III trials have shown a significantly prolonged progression-free survival (PFS) as well as better tolerability with EGFR-tyrosine kinase inhibitors (TKIs) (e.g., erlotinib, gefitinib and afatinib) when compared with conventional doublet chemotherapy in *EGFR*-mutant NSCLC patients [6, 7]. Most of these studies were conducted on East Asian populations [8]. As known from other studies, patients with East Asian ethnicity, adenocarcinoma histology, female sex, and never-smoker status have a higher probability of having an *EGFR* mutation than other groups [9, 10].

The question whether *EGFR* mutation testing and individualized first-line targeted therapy selection is more cost-effective in the German context still remains unclear, since, to our knowledge, there is no study examining this issue. Furthermore, various international cost-effectiveness studies have assessed the use of EGFR-TKI for individualized first-line or second-line therapy of advanced NSCLC [11, 12], with divergent results, ranging from dominant [13] to an incremental cost-effectiveness ratio (ICER) of over US$100,000/QALY [14, 15] for the testing strategy. Important causes of this variability may include cross-country differences and the perspective of evaluation. As Germany is among the top three countries with the highest healthcare cost expenditure for lung cancer in the EU [16], it is an important setting in which to investigate this question and provide reliable knowledge for clinical and political decision making in today's challenging health landscape.

In this context, the aim of this study was to develop a decision-analytic model for the population of advanced lung adenocarcinoma patients from the perspective of German statutory health insurance (SHI) in order to evaluate the cost-effectiveness of an *EGFR* mutation testing strategy comprising individualized first-line therapy with erlotinib for *EGFR* mutation-positive patients compared with a non-testing strategy with all patients receiving a standard chemotherapy.

2 Methods

This study was primarily based on published data from the European Tarceva versus Chemotherapy (EURTAC) clinical trial, which was undertaken at 42 institutions in Spain, France and Italy [17]. It is, to our knowledge, currently the only randomized clinical trial (RCT) targeting exclusively European patients whose tumors have *EGFR* mutations [8] and was therefore considered most suitable to apply in the context of Germany. All cost calculations in this study were based on German SHI prices. Model inputs are summarized in Table 1. We performed all analyses using R statistical software version 3.0.3 (R Foundation, Vienna, Austria).

2.1 Model Structure and Strategies

For our target population of patients with advanced (predominantly stage IV) adenocarcinoma of the lung, we developed a state transition model with three mutually exclusive health states: PFS, progressive disease (PD) and death (Fig. 1). The cycle length of the state transition model corresponds to 3 weeks (equal to one chemotherapy cycle). A time horizon of 10 years was chosen to reflect a patient's lifetime, given the mortality of metastatic patients in Germany [18]. At the starting point of the model, all of the patients were in a progression-free state and were assumed to follow one of the two treatment strategies:

1. Without prior testing for *EGFR* gene mutations, all patients were assumed to be treated with first-line

Table 1 Model inputs for base case analysis

Model input	Base case (mean)	Standard error	References
Survival regression parameters			
Weibull model of PFS for erlotinib			
Scale	15.24	1.55	[17]
Shape	1.18	0.07	
Weibull model of PFS for chemotherapy			
Scale	6.86	0.65	[17]
Shape	1.18	0.07	
Exponential model of OS for erlotinib (lamda)	0.033	0.005	[17]
Exponential model of OS for chemotherapy (lamda)	0.032	0.006	[17]
Probabilities			
EGFR mutation prevalence in patients with adeno-NSCLC in Germany	0.128	0.007	[49]
Not enough tissue for *EGFR* mutation testing	0.184	0.02	[19]
No rebiopsy	0.10	0.01	Thoracic Hospital of Heidelberg
Non-informative rebiopsy	0.175	0.013	Thoracic Hospital of Heidelberg
Complications of biopsy procedures			
Pneumothorax (percutaneous needle aspiration biopsy)	0.066	0.002	[50]
Pneumothorax (bronchoscopic biopsy)	0.002	0.001	[15, 51]
Severe hemorrhage (percutaneous needle aspiration biopsy)	0.01	0.001	[50]
Severe hemorrhage (bronchoscopic biopsy)	0.005	0.001	[15, 51]
Proportion of patients receiving chemotherapy in inpatient settings	0.4	0.06	University Hospital of Munich
Proportion of patients receiving different chemotherapeutic regimens			
Cisplatin plus docetaxel	0.061	0.017	[27]
Cisplatin plus gemcitabine	0.281	0.031	[27]
Carboplatin plus docetaxel	0.492	0.036	[27]
Carboplatin plus gemcitabine	0.183	0.027	[27]
Grade 3/4 adverse event probabilities (total reported)			
Erlotinib ($n = 84$)			
Diarrhea	0.048	0.023	[17]
Fatigue	0.06	0.026	[17]
Rash	0.131	0.037	[17]
Anemia	0.012	0.012	[17]
Aminotransferase rise	0.024	0.017	[17]
Platinum-based chemotherapy ($n = 82$)			
Anemia	0.037	0.021	[17]
Fatigue	0.195	0.044	[17]
Neutropenia	0.22	0.045	[17]
Febrile neutropenia	0.037	0.021	[17]
Alopecia	0.024	0.017	[17]
Thrombocytopenia	0.146	0.039	[17]
Appetite loss	0.024	0.017	[17]
Proportion of patients receiving second-line chemotherapy within first-line chemotherapy group	0.195	0.044	[17]

Table 1 continued

Model input	Base case (mean)	Standard error	References
Proportion of patients receiving second-line chemotherapy within first-line erlotinib group	0.627	0.067	[17]
Health state utilities			
Stable disease while receiving oral therapy	0.672	0.023	[14, 23]
Stable disease while receiving IV chemotherapy	0.653	0.022	[23]
Progressive disease	0.473	0.031	[23]
Disutilities related to adverse events			
Diarrhea	0.047	0.015	[23]
Fatigue	0.073	0.019	[23]
Rash	0.032	0.012	[23]
Neutropenia	0.09	0.015	[23]
Febrile neutropenia	0.09	0.016	[23]
Thrombocytopenia	0.053	0.005	[15]
Pneumothorax	0.023	0.002	[15]
Hemorrhage	0.023	0.002	[15]
Hair loss	0.045	0.015	[23]
Anemia	0.07	0.007	[24]

Model input	Unit costs 2014	Description of unit[a]	Standard error	References
Costs				
Drug acquisition[b]				
Erlotinib	€1839	Per cycle	€92	[32]
Cisplatin plus docetaxel	€1529	Per cycle	€76	[32]
Cisplatin plus gemcitabine	€978	Per cycle	€49	[32]
Carboplatin plus docetaxel	€1710	Per cycle	€86	[32]
Carboplatin plus gemcitabine	€984	Per cycle	€49	[32]
1 tube of Cleocin T gel (60 g 1 % cream)	€43	Per rash episode	€2	[52]
Neupogen (480 µg), 10 vials	€1616	Per neutropenia episode (19.2 %)	€81	[14, 32]
Loperamide (2 mg), 30 tablets	€6	Per diarrhea episode	€0.3	[32]
Medical services (outpatient)				
Bronchoscopic biopsy of pulmonary nodules, performed outpatient (EBM codes 13662, 13642)	€121	Per test	€6.07	[31]
EGFR mutation testing using DNA sequencing of exons 19–21 (EBM 11212, EBM 11322)	€323	Per test	€16.14	[31]
Outpatient management of oral therapy (EBM codes 13492, 13500, 13502, 86512)	€100	Per quarter	€5	[31]
Outpatient management of IV chemotherapy (EBM codes 13492, 13500, 13502, GOP 86512, 86516)	€268	Per quarter	€13	[31]
Chemotherapy infusion, 4 h (EBM code 01511)	€97	Per session	€4.84	[31]
Chemotherapy infusion, 30 min (EBM code 02100)	€6	Per session	0.3	[31]
Outpatient visit (dermatology)	€19	Per consultation	€2	[33]
Outpatient visit (internal medicine)	€65	Per consultation	€7	[33]
Red blood cell transfusion (incl. EBM codes 02110, 02111, 32540, 32545, 32556)	€155	Per anemia episode	€8	[31]

Table 1 continued

Model input	Unit costs 2014	Description of unit[a]	Standard error	References
Medical services (inpatient)				[30]
Bronchoscopic biopsy of pulmonary nodules, with 1-day hospital stay (or mean length of stay) (G-DRG E71B)	€796 (€1992)	per test	€40 (€100)	[30]
Percutaneous needle aspiration biopsy of pulmonary nodules, with 1-day hospital stay (or mean length of stay) (G-DRG E71A)	€1645 (€4328)	per test	€82 (€216)	[30]
Biopsy of metastatic sites, with 1-day hospital stay (or mean length of stay) (G-DRG E02C)	€2065 (€4338)	per test	€103 (€217)	[30]
Hospitalization for pneumothorax (G-DRG E76C)	€3005	per stay	€150	[30]
Hospitalization for hemorrhage, with 1-day hospital stay (G-DRG X62Z)	€695	per stay	€35	[30]
IV chemotherapy admission with 1-day hospital stay (G-DRG E71B)	€796	per stay	€40	[30]
Oncology day fee	€150	per stay	€8	University Hospital of Munich
1-day hospital stay for rash (G-DRG J68B)	€612	per stay	€31	[30]
Hospitalization for diarrhea (G-DRG G67C)	€1402	per stay	€70	[30]
Hospitalization for fatigue (G-DRG Z65Z)	€1610	per stay	€81	[30]
1-day hospital stay for anemia (Q61D)	€944	per stay	€47	[30]
1-day hospital stay for aminotransferase rise (G-DRG Z65Z)	€701	per stay	€35	[30]
1-day hospital stay for non-febrile neutropenia (G-DRG Q60C)	€811	per stay	€41	[30]
Hospitalization for febrile neutropenia (G-DRG T64B)	€3289	per stay	€165	[30]
1-day hospital stay for thrombocytopenia (G-DRG Q60C)	€811	per stay	€41	[30]
Hospitalization for anorexia (G-DRG K62B)	€1957	per stay	€98	[30]

Adeno adenocarcinoma, *EBM* ambulatory physicians' fee schedule ("Einheitlicher Bewertungsmaßstab"), *EGFR* epidermal growth factor receptor, *G-DRG* German Diagnosis Related Groups, *IV* intravenous, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PFS* progression-free survival, *GOP* fee schedule position ("Gebührenordnungsposition"), *incl.* including

[a] One cycle of the state transition model is equal to 3 weeks. One-quarter corresponds approximately to four cycles

[b] Pharmacy sales prices (including legally mandated discounts, excluding individual contractual rebates)

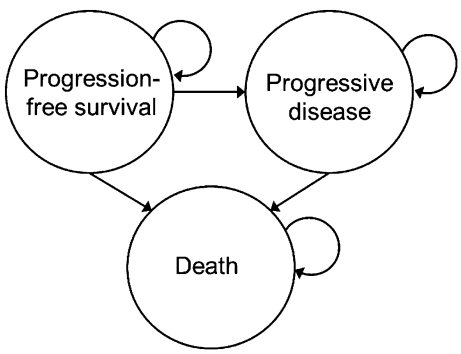
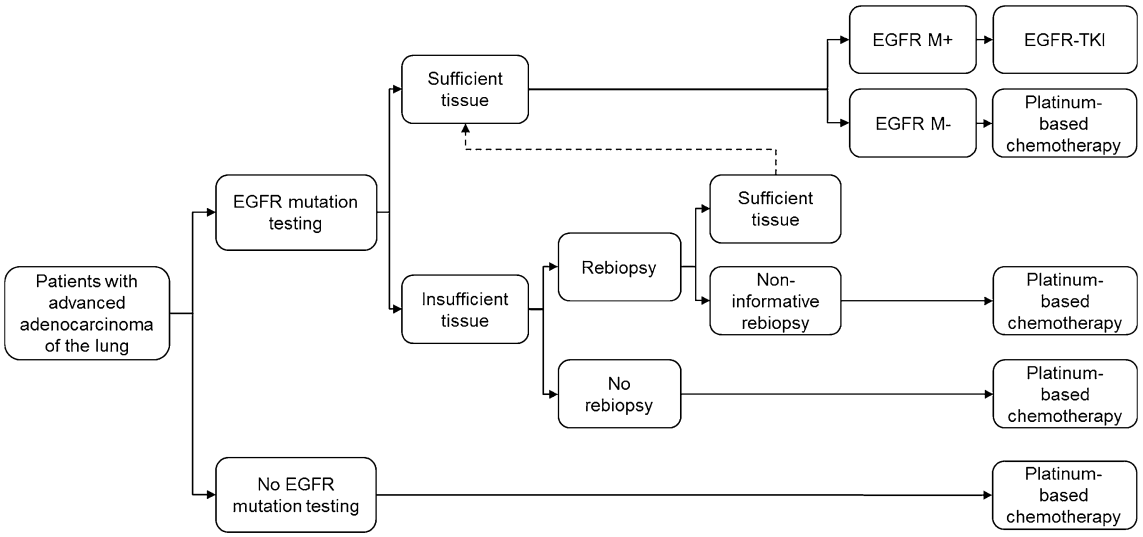


Fig. 1 Representation of the underlying state transition model

intravenous combination chemotherapy, consisting of a platinum (cisplatin or carboplatin) and docetaxel or gemcitabine (non-individualized treatment strategy) [17].

2. Molecular testing of the *EGFR* gene was assumed to be conducted using DNA sequencing of exons 18–21 to guide the individualized first-line therapy [3] such that *EGFR*-mutant patients received *EGFR*-targeted therapy with erlotinib, while all others were treated with chemotherapy (individualized treatment strategy).

Figure 2 summarizes the diagnosis and treatment algorithm, which was oriented at a previous study by Handorf



EGFR, epidermal growth factor receptor; M+, mutation-positive; M-, mutation-negative; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

Fig. 2 Patient flow chart for the diagnosis and treatment algorithm used in both strategies. *EGFR* epidermal growth factor receptor, *M+* mutation-positive, *M−* mutation-negative, *NSCLC* non-small cell lung cancer, *TKI* tyrosine kinase inhibitor

et al. [15]. Based on clinical expert knowledge (SAR), we assumed that 90 % of biopsy samples would be obtained by bronchoscopy, 5 % by transthoracic needle aspiration and 5 % by biopsy of metastases in lung cancer patients. As rebiopsies may be recommended in cases where insufficient tumor tissue is available, we thus integrated the possibility of repeat biopsy in the testing strategy, as seen in the literature [15, 19]. We assumed that over 80 % of all NSCLC biopsy specimens can reliably be analyzed for *EGFR* gene mutations [19] and that less than 20 % of repeat biopsies would be uninformative. All patients who tested true negative or had insufficient tissue available for mutation identification (false negative) were assumed to receive conventional platinum-based chemotherapy.

2.2 Clinical Inputs

As clinical inputs, the efficacy and safety data were derived from the EURTAC trial [17]. In the EURTAC trial, patients with advanced, *EGFR*-mutated NSCLC, most of whom had adenocarcinoma (90–95 %), were assigned to erlotinib (86 patients) or chemotherapy (87 patients). The study showed a significantly prolonged PFS in the erlotinib arm; however, overall survival (OS) did not differ between treatment groups.

2.2.1 Statistical Methods

The distribution of patients across the health states over time was not based on transition probabilities, but was directly calculated on the basis of published Kaplan–Meier curves [17]. Patient-level data corresponding to these Kaplan–Meier curves were reconstructed using a published algorithm with the help of the DigitizeIt software version 2.0 [20]. According to the smallest values of Akaike's information criterion (AIC) (see online resource 1, electronic supplementary material, WebTable 1), the best model fit was chosen on the basis of common survival distributions, namely the exponential, Weibull, log-logistic, log-normal and Gompertz [21]. Parametric Weibull and exponential regression curves were then fitted to the reconstructed patient-level time-to-event data, respectively, to extrapolate beyond the follow-up period (Webfig. 1).

2.2.2 Adverse Events

We included all grade 3 and 4 drug-related adverse events (AEs) with a frequency of ≥1 % in our model that showed a difference between both treatment groups in the EURTAC study [17] (Table 1). These differences in severe or life-threatening events were considered to be both clinically and economically relevant irrespective of the level of statistical significance. For all AEs, it was assumed that they were treated in the same cycle in which they appeared and the utility decrement was related to only one cycle length [22]. A constant incidence rate was assumed over time for all AEs in patients in PFS or PD disease states. Detailed information on the assumed resource use for the treatment of these events can be found in WebTable 2.

2.3 Health Utility Inputs

The utility values representing patients' health-related quality of life (HRQoL) were obtained from published literature [14, 23–25]. We primarily used comprehensive data from Nafees et al. [23], a study that is widely used in health economic evaluations of lung cancer therapies and which provided a community-based utility model for metastatic NSCLC patients in the UK, using the standard gamble interview and taking different treatment-related toxicities and disease states into account. On this basis, the state of PFS was assigned a utility value of 0.67 with erlotinib and 0.65 with chemotherapy in the base case analysis [14, 23]. The utility value for the PD state corresponded to 0.47 in both of the groups, as seen in the literature [14, 15, 26]. Additionally, treatment-related AEs were assumed to further reduce a patient's HRQoL. Quality-adjusted life-years (QALYs) were then calculated for each strategy.

2.4 Cost Inputs

As this analysis was conducted from the perspective of German SHI, only direct costs were included, with resource utilization and unit costs estimated as described below.

2.4.1 Drug Utilization

Patients were treated with assigned first-line therapy until disease progression or unacceptable AEs occurred. We assumed that all chemotherapies would be administered for up to six cycles [5], with the estimated distribution of these chemotherapies based on observed rates in Germany [27].

Dosing regimens were extracted from Rosell et al. [17], and detailed information can be found in the referenced data. It was assumed that 40 % of patients would receive chemotherapy in inpatient settings, while the remaining 60 % would be treated as outpatients.

The chemotherapy dose was calculated using the patient's body surface area. Calculations were carried out separately for males and females, assuming the average weight and height of a population aged 65 and older in Germany, while accounting for weight loss during chemotherapy of lung cancer patients (8 %) [28, 29]. A weighted average of chemotherapy costs was obtained using the relative proportions of estimated incident lung cancer cases in Germany in 2014 (65 % males, 35 % females) [1]. Erlotinib was given daily as a 150-mg tablet and can be administered in an outpatient setting.

Following a conservative approach, we assumed that after regular completion of chemotherapy, costs would be equal in both strategies in the progression-free state. If the disease progressed or unacceptable AEs occurred, we assumed that a second-line treatment was initiated, thereby allowing patients to have cross-over therapy, with proportions estimated from Rosell et al. [17]. In particular, we assumed that around 60 % of patients with first-line erlotinib treatment receive second-line platinum-doublet chemotherapy for up to six cycles and that the remaining patients stay on an EGFR-TKI therapy. For the patients with first-line chemotherapy, we assumed that around 80 % of patients receive an EGFR-TKI as second-line treatment and that the remaining patients stay on the platinum-doublet chemotherapy for an additional six cycles. For the cost calculation of subsequent treatments, we assumed that unit costs would be comparable to those of first-line medications. No cost differences were assumed in the third-line setting.

2.4.2 Unit Costs

All unit costs are reported from the perspective of German SHI and were estimated from multiple sources. We used the 2014 version of the German Diagnosis Related Groups (G-DRG) system for inpatient costs [30], the Uniform Value Scale ("Einheitlicher Bewertungsmaßstab") for outpatient costs [31] and the Lauer-Taxe (official pharmacists' price schedule) for drug costs [32]. For AEs requiring an outpatient visit, we estimated unit costs on the basis of recent literature, when no other information was available [33].

As the ICER depends upon incremental costs and effects, it was considered reasonable in the case of limited resources to make simplifying assumptions that have no effect on the ICER between the two strategies. Therefore, the modeled wild-type population is based on the same effectiveness data for patients undergoing first-line chemotherapy in the EURTAC trial. This was considered appropriate, as we assume a mutation test with a specificity of 100 % [34] and the same chemotherapy regimens in both treatment strategies. All costs and benefits were discounted at an annual rate of 3 % in this study. The costs were expressed in euros and the price year was 2014.

2.5 Assessing Uncertainty

2.5.1 Univariate Deterministic Sensitivity Analysis

To address uncertainty around mean incremental costs and effectiveness, we conducted deterministic one-way sensitivity analyses, where we varied one variable at a time while keeping all other variables constant at their base case value. We ran analyses using the upper and lower limit of the 95 % confidence intervals (CIs) (WebTable 3). For variables for which we did not have information on the 95 % CI, we varied parameters by ±20 % of the mean [15]. Furthermore, a two-way sensitivity analysis of *EGFR*

mutation prevalence and mutation test costs was performed in order to assess a wider range of uncertainty in the parameters considered to be particularly relevant.

2.5.2 Probabilistic Sensitivity Analysis

In the performed multivariate probabilistic sensitivity analysis, cost data were assumed to follow a gamma distribution; beta distributions were chosen for utility values and probabilities, with parameters estimated on the basis of the expected value and on the standard error (Table 1). In the case that the standard error could not be calculated from the source, it was set according to our estimations of the true parameter uncertainty. Thus we chose 5 % of the mean in the case of costs based on publicly available prices and 10 % in the case of expert opinions. The discount rate and proportions of patients hospitalized for AEs were fixed in the probabilistic sensitivity analysis. To incorporate survival uncertainty, we adopted a bootstrap approach and therefore used the reconstructed patient-level data with linked PFS and OS data of the given Kaplan–Meier estimates. It was ensured for the fitted parametric models that PFS estimates do not exceed the OS estimates, as this would imply negative results for the time of post-progression survival. The distribution of incremental costs and effects was evaluated on the basis of 10,000 bootstrap samples, and the results were expressed as a scatter plot and a cost-effectiveness acceptability curve (CEAC).

2.5.3 Structural Sensitivity Analysis

We additionally examined the influence of important sources of structural uncertainty in the following scenarios: We considered the assumption that the time-to-event curves can be fitted by flexible regression models [21] (Webfig. 2) (Scenario 1). We also altered the assumptions regarding health state utility estimates, supposing equal PFS utility values of chemotherapy (0.65) for both treatment groups (Scenario 2) and all health states (Scenario 3). In Scenario 4, we cross-validated our estimates for health state utilities with recent German data [35]. On the basis of this study, the PFS disease state was assumed to have a utility value of 0.63 and the PD disease state a utility value of 0.53 in both of the treatment groups. In Scenario 5, we assessed the assumption that all biopsy samples can reliably be analyzed, so that mutation tests do not need to be repeated. In Scenario 6, we considered the assumption that patients would receive cisplatin plus pemetrexed, a highly effective but cost-intensive combination chemotherapy, instead of a regimen based on gemcitabine or docetaxel. The hazard ratios (HRs) of PFS for platinum plus gemcitabine or docetaxel chemotherapy compared with pemetrexed were estimated at 0.90 and 0.83, respectively [36]. The HRs of OS were furthermore estimated at 0.85 and 0.94, respectively. The cost of pemetrexed therapy was estimated at €3826 per cycle [32]. We made the simplifying assumption that AE rates do not differ between different chemotherapies.

Table 2 Incremental cost analysis and cost components

Strategy	Biopsy and *EGFR* mutation testing (as appropriate)	Drug cost		Adverse event cost (treatment related)	Drug administration cost		Overall cost
		First-line	Subsequent lines		Outpatient care	Inpatient care	
Individualized treatment strategy	€1378	€8431	€64,615	€447	€1604	€1428	€77,902
Non-individualized treatment strategy	€860[a]	€7933	€65,251	€493	€1707	€1458	€77,702
Incremental cost (individualized vs. non-individualized)	€518	€498	€−637	€−46	€−103	€−30	€200

All costs associated with the entire time horizon of 10 years are presented in year 2014. Annual discount rate was 3 %

EGFR epidermal growth factor receptor

[a] We assumed that all patients, regardless of the treatment strategy, will receive at least one lung biopsy for diagnostic purposes

Table 3 Results of base case analysis

Strategy	Cost	Incremental cost	Effect (QALYs)	Incremental effect (QALYs)	ICER (€/QALY)
Non-individualized treatment strategy	€77,702		1.2298		
Individualized treatment strategy	€77,902	€200	1.2426	0.0129	€15,577

All costs are in 2014 euros. Annual discount rate was 3 %

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

3 Results

3.1 Base Case Analysis

Details on incremental cost analysis and cost components can be found in Table 2. The obtained results of the base case analysis are then summarized in Table 3. Overall, it can be seen that the cost estimates were higher in the individualized treatment group, with a difference of €200. Total QALYs were also slightly higher in the individualized strategy than in the non-individualized strategy, with a difference of 0.013 QALYs. Therefore, an ICER of €15,577/QALY was obtained, when comparing both strategies in terms of cost-effectiveness.

3.2 Sensitivity Analysis

3.2.1 Deterministic Sensitivity Analysis

The results of the one-way sensitivity analysis are presented in the form of two tornado diagrams, with most influential parameters on incremental costs and effects displayed in descending order (Fig. 3). Incremental cost results were most sensitive to variations in mutation test costs, resulting

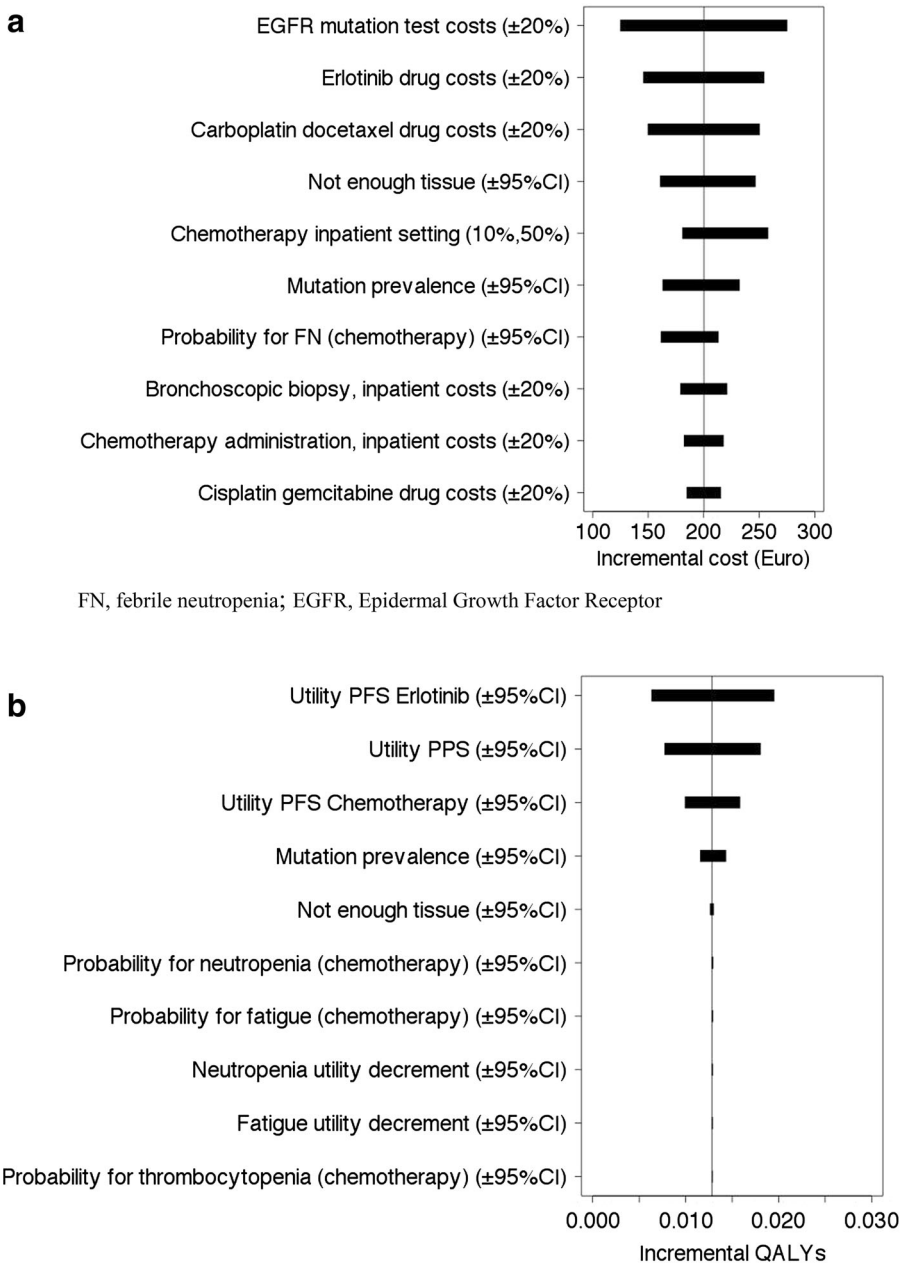


Fig. 3 Tornado diagram of univariate sensitivity analysis. The effect of changes in selected variables on **a** incremental cost and **b** incremental QALYs are shown on the *x-axis*. The *y-axis* shows the top ten most influential variables in descending order. The *vertical line* indicates the base case result. Full details on upper and lower bound estimations for the parameters varied can be found in Webtable 3. *CI* confidence interval, *EGFR* epidermal growth factor receptor, *FN* febrile neutropenia, *PFS* progression-free survival, *PPS* post-progression survival, *QALY* quality-adjusted life-year

FN, febrile neutropenia; EGFR, Epidermal Growth Factor Receptor

in incremental costs ranging from €125 to €275 compared with the base case of €200 because of the lower and upper limits of the parameter's range (Webtable 3). Further incremental cost drivers were drug cost estimates of provided therapies (€150–€251 for erlotinib and €145–€255 for carboplatin plus docetaxel, respectively), the probability of insufficient tissue for mutational analysis (€161–€247), changes in the proportion of patients treated in inpatient settings (€181–€258) and mutation prevalence (€163–€232).

On the other hand, the effectiveness results were most sensitive to uncertainties in the utility values of the health states. Variation in PFS utility value for patients treated with erlotinib influenced the estimates of total QALYs gained the most (0.006–0.02), followed by variation in PD utility value (0.008–0.018) and PFS utility value for patients treated with chemotherapy (0.01–0.016).

The results of the two-way sensitivity analysis of *EGFR* mutation prevalence and mutation test costs (Webfig. 3) show that higher prices are still cost-effective (and in many cases dominant) if a higher mutation prevalence is present.

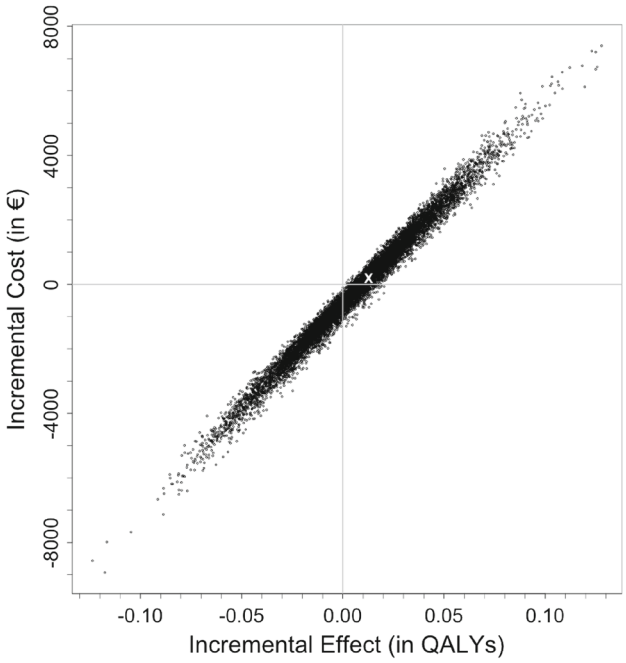


Fig. 4 Probabilistic sensitivity analysis of individualized strategy versus non-individualized strategy (scatter plot). *Oblique cross* (X) corresponds to the base case result. Scatter plot based on 10,000 bootstrap replicates. Base case ICER was €15,577/QALY compared with non-individualized strategy. The 95 % confidence interval ranges from €−4558 to €4010 (mean €200) for incremental costs and from −0.061 to 0.073 (mean 0.013) for incremental effects. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

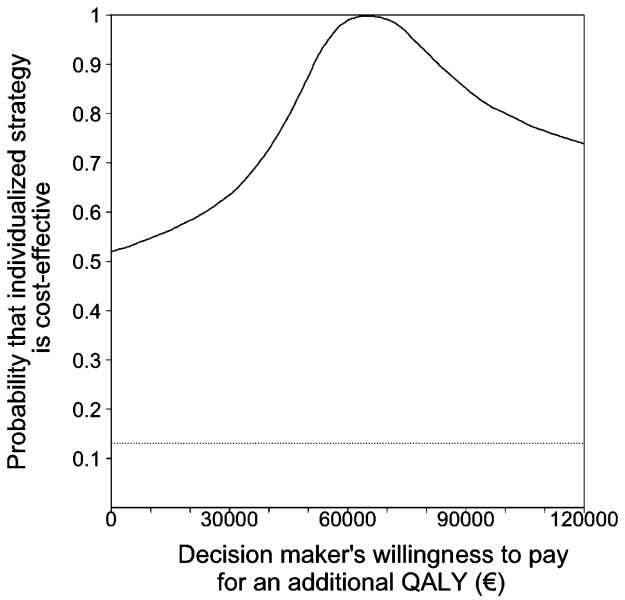


Fig. 5 Cost-effectiveness acceptability curve of individualized strategy. *Dotted horizontal line* corresponds to the share of points falling into the dominant quadrant of the scatter plot (*southeast quadrant*). *QALY* quality-adjusted life-year

3.2.2 Probabilistic Sensitivity Analysis

The results of the multivariate probabilistic sensitivity analysis are provided as a CEAC (Fig. 5), derived from the obtained scatter plot (Fig. 4). As the scatter plot shows, there is a high uncertainty regarding incremental cost and incremental effectiveness. Compared with a setting in which survival uncertainty is not included in the model (Webfig. 4 and 5), it is noticeable that the main uncertainty stems from the PFS and OS curves that influence both additional cost and gained QALYs. Despite this uncertainty, the CEAC shows that, although the probability of the individualized treatment strategy being more cost-effective is declining beyond €60,000/QALY, the probability remains above 50 % for a broad range of potential willingness-to-pay values for an additional QALY [15].

3.2.3 Structural Sensitivity Analysis

The results of the structural sensitivity analyses are summarized in Table 4. In Scenario 1, using a flexible regression model, the ICER increased from €15,577/QALY to €16,232/QALY by roughly 4 %. In Scenario 2, the ICER increased by 27 % to €19,837 due to equivalent PFS utility values in both treatment groups. When extending the assumption on PD (Scenario 3), the individualized strategy is dominated by the non-individualized strategy, which is plausibly attributable to the absence of an OS benefit in the erlotinib group. Scenario 4 resulted in an increased ICER of €58,144. In Scenario 5, when assuming that all biopsy

Table 4 Results of structural sensitivity analysis. Individualized strategy compared with non-individualized strategy

Scenario	Incremental cost	Incremental effect (QALYs)	ICER (€/QALY)
Scenario 1: Flexible survival regression model for PFS and OS	€244	0.0151	€16,232
Scenario 2: Equivalent PFS utility values (i.e., 0.653 for both treatments)	€200	0.0101	€19,837
Scenario 3: Equivalent PFS and PD utility values (i.e., 0.653 for all health states in both treatment groups)	€200	−0.0053	Dominated (more costly, less effective)
Scenario 4: Health state utilities estimated on the basis of German data (i.e., 0.63 for PFS and 0.53 for PD health state)	€200	0.0034	€58,144
Scenario 5: Probability of insufficient tissue set to 0 %	€−12	0.0135	Dominant (less costly, more effective)
Scenario 6: Cisplatin plus pemetrexed as standard chemotherapy	€−1449	−0.0017	€864,595 (less costly, less effective)

Base case ICER was €15,577/QALY compared with non-individualized strategy. All costs are in 2014 euros. Annual discount rate was 3 %

ICER incremental cost-effectiveness ratio, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *QALY* quality-adjusted life-year

samples could reliably be analyzed, the individualized strategy appears to be dominant. In Scenario 6, assuming that patients would receive first-line treatment with cisplatin and pemetrexed, non-individualized strategy resulted in a gain of 0.002 QALYs at higher costs of over €800,000/QALY.

4 Discussion

According to the results of our study, an individualized treatment strategy for patients with advanced adenocarcinoma of the lung incurs incremental costs of €15,577 per additional QALY compared with a non-individualized treatment strategy from the German SHI perspective. Deterministic one-way and two-way sensitivity analyses suggest that a higher probability of *EGFR* mutation can increase the impact and cost-effectiveness of *EGFR* mutation testing. Conversely, when considering that the EURTAC trial also included small subgroups of NSCLC patients with lower mutation prevalence (9.8 %, all histologies including squamous cell and large cell lung cancer [10]), the base case ICER may increase to around €28,000/QALY. Probabilistic sensitivity analysis showed that there is substantial uncertainty surrounding the incremental costs and effects. Since the EURTAC trial included relatively small numbers of participants, uncertainty particularly arises from the estimated survival curves, and especially OS, which was not a primary endpoint. Due to a lack of individual patient data, the uncertainty may additionally be overestimated by the bootstrap approach. Furthermore, survival estimates can have both an influence on additional costs and gained QALYs, which results in a positive correlation on the scatter plot. Nevertheless, the interpretation of the probability of cost-effectiveness did not change substantially when comparing the results with and without bootstrap-based implementation of the survival uncertainty.

4.1 Comparison with Other Studies

To our knowledge, there are five studies assessing the cost-effectiveness of individualized EGFR-TKI therapy either in the context of first-line [13, 15], maintenance [37] or second-line therapy [14, 26]. In the study by de Lima Lopes et al. [13], an individualized strategy with gefitinib was found to be dominant compared with a non-individualized strategy from the perspective of three Singapore cancer centers. In a more recent study by Handorf et al. [15], conducted from a US payer's perspective, cost-effectiveness estimates of US$110,644/QALY (without rebiopsy) and US$122,219/QALY (including rebiopsy) were reported for the individualized treatment strategy with erlotinib compared with a non-individualized strategy. Compared with these previous cost-effectiveness studies, one major strength of this study is that a time-dependent state-transition model was used instead of a decision-tree model [13, 15]. Besides other methodological aspects, such as the absence of discounting, further differences to prior studies exist, including comparator treatments, probability of carrying and identifying mutations, and dealing with further line treatments. Despite these limits of comparability, our findings can be interpreted in line with the referred studies examining individualized first-line therapy, supporting the strategy of testing for *EGFR* mutations in patients with metastatic lung cancer prior to first-line medical decision making.

4.2 Limitations

Along with the strengths of this study there are several limitations which may affect the results and should therefore be taken into consideration when interpreting the data. First, research evidence from RCTs, generalizable to the German context, was found to be limited. The reason is that the majority of studies carried out to compare EGFR-TKIs with chemotherapy in patients with *EGFR* mutations exclusively or predominately included East Asian patients [38–44]. Our clinical model input data therefore primarily relied on one European trial (EURTAC), conducted in the Caucasian population. Second, we had to make assumptions about the survival after the end of follow-up by extrapolating through regression analysis. However, using another more flexible regression model did not change the ICER substantially. Another caveat of this study is that the included comparator treatments may not fully represent the state-of-the-art clinical practice in Germany; however, as a systematic review pointed out, there is a lack of evidence for all chemotherapeutic drug comparisons such that finding the optimal chemotherapeutic strategy remains a field of active research [36]. A further limitation is that we were unable to model second and further therapy lines separately, as no randomized trial was found to examine both issues and provide sufficient information. As treatment cross-over was part of the EURTAC trial and is also recommended as an option in clinical guidelines [4, 5], we estimated second-line costs on the basis of the unit costs of first-line therapy. In addition, we assume that any grade 3/4 drug-related AE is an unacceptable toxicity and led to discontinuation of the assigned treatment; however, this might not always be necessary. Therefore, the validity of the findings depends on the accuracy of the assumptions made. It was also considered appropriate in light of the research question to not model the EGFR wild-type population separately; however, this implies that absolute costs and effects should be interpreted with caution. Because of the perspective of the analysis, we did not include indirect costs; however, considering this aspect has the potential to further increase cost-effectiveness, as patients treated with erlotinib showed significantly prolonged PFS, which may turn into increased productive contribution to society.

4.3 Implications of this Study

The question of whether a cost-effectiveness threshold value can exist in Germany and what its value should be is a matter of ongoing scientific and political debate. Germany's Institute for Quality and Efficiency in Health Care recommends extrapolating the efficiency frontier [45], which is not applicable here because of a lack of comparators. Alternative concepts include the threshold area of £20,000–£30,000/QALY used by the English and Welsh National Institute of Clinical Excellence (NICE) [46] or the World Health Organization definition of the cost-effectiveness threshold (less than threefold of the nation's gross domestic product per capita, €70,500–€106,000 in Germany) [47, 48]. Given the lack of an explicit threshold for Germany, these results can only serve as input for the decision makers' deliberations. The recommendation by international and German clinical guidelines that *EGFR* mutation testing should be conducted prior to the initiation of first-line therapy in patients with adenocarcinoma of the lung is consistent with the observation that this intervention is cost-effective if compared with the mentioned benchmarks.

Furthermore, an important key factor that can influence the cost-effectiveness is the probability of carrying and identifying *EGFR* mutations. In this context, it is conceivable that younger women and never-smokers, who have a higher *EGFR* mutation prevalence, may benefit most from the analysis of mutation status, although it is not recommended to exclude patients from mutation analysis on the basis of clinical criteria [3, 10]. Nevertheless, at a big picture level, it is the task of further clinical and economic research to evaluate the impact of other histological and molecular aspects in a broader context. Especially, there is a need for more research on the wider cost-effectiveness across the whole patient pathway, also including the possibility to test for alterations in other genes (e.g., anaplastic lymphoma kinase gene) or repeat biopsy after progression of patients with previously insufficient tissue.

One area in need of further research is the drug's effectiveness in terms of OS and HRQoL in patients with stable or PD.

5 Conclusions

The results of our model indicate that *EGFR*-targeted treatment incurs costs of €15,577/QALY compared with non-individualized care of metastatic lung cancer patients in Germany. These results remain to be confirmed in future well-powered clinical trials including the systematic assessment of health state-specific quality of life. One next step should be to extend this model to other targeted lung cancer drugs and other mutation types.

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Author contributions KS, BS and WR are responsible for the conception and design of the study. Continuing clinical advice and expertise was provided by AT, RH and SAR. Model implementation and analysis was conducted by KS. Methodological advice was provided by a statistician (BS). The manuscript was drafted and improved by KS, BS and WR. The English editing was done by a native English speaker (AT). The overall guarantor for the content of this paper is KS.

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