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Comparative cost-effectiveness of three strategies for guiding second-line erlotinib initiation in non small-cell lung cancer: a French prospective multicenter study (ERMETIC Project Part 3)

Short title: Erlotinib cost-effectiveness analysis in second-line lung cancer therapy

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Abstract (229 words)

Rationale: Several clinical and biological parameters are known to influence the efficacy of second-line erlotinib therapy for non small-cell lung cancer (NSCLC), but their medico-economic impact has not been evaluated. The objective of this study was to compare the incremental cost-effectiveness ratios (ICERs) of strategies for second-line erlotinib initiation in NSCLC: clinically guided initiation (non smoker women with adenocarcinoma receive erlotinib, all other patients receive docetaxel) and biologically guided selection (patients with *EGFR* mutation receive erlotinib; patients with wild-type *EGFR* or unknown status receive docetaxel), compared to initiation with no patient selection (strategy reference).

Methods: A Markov model was constructed. Outcomes (overall and progression-free survival), transition probabilities, and direct medical costs (from the French third-party payer's perspective) were prospectively collected for individual patients treated with erlotinib or docetaxel, from treatment initiation to disease progression. Published data were used to estimate utilities and post-progression costs. Sensitivity analyses were performed.

Results: The biologically and clinically guided strategies were both more efficient (incremental QALY respectively equal to 0.080 and 0.081) and less expensive (cost decrease respectively equal to 5020 and 5815 €) than the no-selection strategy, and the biologically guided strategy was slightly less expensive than the clinically guided strategy. Sensitivity analyses confirmed the robustness of the results.

Conclusion: The cost-effectiveness of second-line NSCLC treatment is improved when patients are selected, on either clinical or biological grounds.

Key words: cost-utility, erlotinib, non small-cell lung cancer, EGFR mutation

Introduction

Lung cancer is the leading cause of cancer-related death and represents a considerable public health burden worldwide. Estimates from the United States indicate that per-patient lung cancer management costs rose by a factor of at least five between 1991 and 2002 (1, 2). These costs may increase further still with the introduction of novel targeted therapies. Non small-cell lung cancer (NSCLC) accounts for 85% of all primary lung cancers. First- and second-line chemotherapy is the standard of care for patients who have advanced NSCLC and good performance status, improving symptom control and survival compared with best supportive care (3-5). When disease progression occurs after initial treatment, second-line options include two chemotherapeutic agents (docetaxel and pemetrexed) and erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (6). Docetaxel improves overall survival (OS) relative to best supportive care (5). Pemetrexed showed similar efficacy but less toxicity when compared head-to-head with docetaxel in a phase III randomized trial involving previously treated patients with advanced NSCLC (4). In a landmark trial, erlotinib improved OS and quality of life when compared to best supportive care, with a median OS benefit of 2 months relative to the placebo arm (6). The rates of response to erlotinib were higher in some patient subgroups, including patients of Asian origin, women, never-smokers, and patients with adenocarcinoma (6-8). However, never-smoker status was the only clinical factor associated with improved OS in multivariable analysis. The influence of clinical factors on outcomes was recently evaluated in a retrospective study of 121 consecutive Caucasian patients treated with erlotinib in a routine clinical setting. Patients with adenocarcinoma had better progression-free survival (PFS) than other patients, but similar OS. Likewise, never-smokers had longer PFS (7 months) and OS (13 months) than smokers and ex-smokers. Gender had no noteworthy influence (7, 9). Molecular predictors of erlotinib efficacy were also evaluated when sufficient tumor tissue was available (10-13). Preliminary studies suggested that strong EGFR protein expression, measured with immunohistochemical methods, and high EGFR gene copy number, were associated with better

response and survival rates on erlotinib (14). However, these analyses were retrospective and limited by sample availability. It has since been established that EGFR mutation status influences the efficacy of EGFR tyrosine kinase inhibitors in both first-line and second-line settings (15-18).

In 2005, the French National Cancer Institute (INCa) funded a nationwide 2-year multicenter prospective study to address the standardization of mutation analysis. The study, entitled Evaluation of EGFR mutation status for EGFR-TKI administration in non small-cell lung carcinoma (ERMETIC), involves 16 French clinical centers, pathology laboratories and medical laboratories. The project had 3 successive objectives: i) to validate routine sequencing-based screening for EGFR and KRAS mutations on fixed paraffin-embedded tissues (19); ii) to select and rank clinical, pathological and biological predictors of the response to EGFR-TKI and the resulting clinical benefit in a large prospective patient cohort (8); and iii) to determine the most cost-effective strategy for prescribing EGFR-TKIs, with or without the use of EGFR biomarkers. The present study focuses on part 3 of the ERMETIC project.

There are currently no published clinical trials directly comparing EGFR mutation screening with no screening prior to second-line erlotinib initiation for NSCLC. Then we conducted an indirect comparison of the cost-utility of EGFR mutation screening, based on data from two prospective studies, namely the ERMETIC prospective multicenter cohort (8) and a prospective, randomized multicenter trial (the GFPC0506 study) comparing docetaxel and pemetrexed in the second-line setting (20). The objective was to compare, using a Markov model, the cost-effectiveness ratios (CERs) of three hypothetical strategies for second-line erlotinib initiation for NSCLC: initiation with no patient selection, clinically guided initiation (non smoker women with adenocarcinoma receive erlotinib; other patients receive docetaxel) and initiation based on EGFR mutation status (erlotinib for EGFR-mutated patients and docetaxel for all other patients).

Patients and methods

Study population

The study population consisted of patients with advanced NSCLC in whom at least one platinum-based chemotherapy regimen had failed and who were eligible for erlotinib or chemotherapy.

Strategies compared

The three hypothetical strategies for second-line erlotinib initiation are shown in figure 1. In the no-selection strategy, all patients were assumed to receive erlotinib. In the clinically guided strategy, patients with favorable clinical features (women never smokers with adenocarcinoma) were assumed to receive erlotinib, while all other patients were assumed to receive docetaxel. In the biologically guided strategy, patients with known EGFR mutations were assumed to receive erlotinib, while patients with no EGFR mutations or unknown status were assumed to receive docetaxel. Docetaxel was chosen as the alternative to erlotinib as it is routinely used for second-line NSCLC therapy (3) and is more cost-effective than pemetrexed (20, 21). It was assumed that docetaxel has the same efficacy in a clinically selected population as in an EGFR wild-type population (17).

We used a Markov model, i.e. a multistate transitory model in which patients make transitions through various health states, at different rates, over extended periods (22). The structure of the model was similar for the 3 strategies. The first node determined the nature of the treatment administered (erlotinib or docetaxel). The probability of receiving erlotinib was 1 in the no-selection strategy (all patients received erlotinib), while it corresponded to the proportion, in the Ermetic cohort, of never smoker women with adenocarcinoma for the clinically guided strategy and to the proportion of EGFR-mutated patients for the biologically guided strategy. Then,

whatever the treatment received, the course of NSCLC after treatment initiation was described using three exclusive health states, as follows: a progression-free state, a disease progression state, and death (an absorbent state). The length of the Markov cycle was one month, meaning that patients made transitions among health states each month until death or until the end of a 30-month period (corresponding to the maximal follow-up period in the ERMETIC cohort). Patients who progressed were assumed to receive palliative care until death. In this model, using partition survival methods, the overall effectiveness of the strategies was derived by summing the mean time spent in the “progression-free” and “disease progression” health states, adjusted for quality of life, yielding quality-adjusted life years (QALY) and associated direct costs.

Clinical inputs

Clinical inputs were derived from individual patient data in the ERMETIC study (8) and the GFPC0506 study (20) (Table 1). ERMETIC (8) was a prospective observational multicenter cohort involving 522 consecutive patients with advanced NSCLC treated with second-line erlotinib between March 2007 and April 2008 in 16 French centers. In this study, outcomes (PFS and OS) and costs were prospectively recorded from erlotinib initiation until progression. The characteristics of the patients in this cohort are described in detail elsewhere (8). Briefly, median age was 63 years, 32% of patients were female, 87% were Caucasian, 18% had never smoked, 65% had adenocarcinoma and 8.4% had EGFR mutations (Table 1). The patients’ EGFR status was systematically sought: testing was done by sequencing in each center, after a national quality assurance program (19). The GFPC0506 study was a phase III, randomized, multicenter trial comparing the CERs of docetaxel and pemetrexed as second-line treatments for NSCLC. Outcomes and costs were prospectively assessed and 75 patients were enrolled in each arm between February 2006 and June 2008 by 27 French centers. The characteristics of the patients treated with docetaxel were the following: median age was 59 years, 15% of patients were

female, 93% of patients had a PS of 0 or 1, 9% had never smoked, and 74% had adenocarcinoma. The EGFR status of these patients was unknown (20).

Utilities

Utilities were derived from community population-based studies of advanced NSCLC performed in the UK (23, 24) and using the standard gamble interview and a visual analog scale to assess quality of life (Table 2).

Costs

Costs were estimated from the French health payer's perspective, during the period extending from second-line chemotherapy initiation until death. All resources consumed from second-line treatment initiation until disease progression were prospectively collected for each patient, in both the ERMETIC cohort (8) and the GFPC0506 study (20). Resources consumed were chemotherapy drugs, erlotinib, supportive treatments (including recombinant human erythropoietin, antiemetics, colony-stimulating factors, antibiotics, management of adverse effects, etc), transfusion, and hospitalization for any reason. The specific unit costs are listed in Table 2. Costs incurred after disease progression were derived from a representative French nationwide sample of 428 patients, using chart review to assess the mean direct monthly cost of the first 18 months of NSCLC patient management (25). Specifically, the costs included outpatient and inpatient services, care provision at skilled nursing facilities, outpatient and inpatient drugs and other medications, nursing care organization, home health visits and durable medical equipment. Assuming a yearly increment of 3.5%, one month of palliative care cost 2324 euros (2010 value) (Table 2). The cost of EGFR mutation screening was taken as the sum reimbursed to French hospitals. Discounting was applied at a rate of 3% for year 2 and 3 of the analysis.

Cost-utility analysis

Incremental CERs (ICERs) were calculated. These ratios correspond to the difference in costs divided by the difference in effectiveness based on QALY between two strategies. The cost-utility analysis conformed to the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine (26).

Statistical analysis

PFS was defined as the time between second-line treatment initiation and the first subsequent event (progression or death from any cause). Patients who were alive and progression-free were censored at their date of their last follow-up visit. OS was defined as the time from second-line treatment initiation to death from any cause. Living patients were censored at the date of their last follow-up visit. For the ERMETIC study, the cut-off date was 1 October 2009, 18 months after enrolment of the last patient. The median follow-up period was 24 months. For the GFPC 0506 study the cutoff date was 31 August 2009, 14 months after enrolment of the last patient. The median follow-up period was 28 months. PFS and OS were estimated with a monthly actuarial method to obtain the exact distribution of PFS and OS per Markov cycle, during a 30-month horizon time. This time horizon, which corresponded to the maximal follow-up period in the ERMETIC cohort, was chosen in order to avoid the need to extrapolate PFS and OS beyond the 30-month period.

Assessing uncertainty

The uncertainty in the model was evaluated by means of one-way sensitivity analysis. The estimate for a given model parameter was varied, while keeping the other parameters constant, within a range of likely values derived from confidence intervals or reasonable ranges in published sources. In addition, a multivariate probabilistic sensitivity analysis was implemented

in a second-order Monte Carlo simulation in which the model inputs (PFS, OS, costs and transition probabilities) were drawn from individual data extracted from both the ERMETIC cohort and the GFPC0506 study. Specific distributions were assigned to utility data by using published means and standard deviations to derive a normal distribution. A simulation with 10,000 replications of the model was used to obtain the non parametric 95% confidence intervals for the cost and effectiveness parameters, and to determine the proportion of replications in each quadrant of the cost-effectiveness plane. The multiway sensitivity analysis was presented in a radar screen format, where the X-axis shows the difference in effectiveness and the Y-axis shows the difference in costs between two strategies. Dots represent the 10,000 replications. SAS software version 9 (SAS INC Cary NC) and Data TreeAge Pro Health Care were respectively used for statistical analyses and modeling.

Results

The results of the model are shown in table 3. The median PFS and OS in the entire Ermetic cohort (n=522 patients) were 2.4 and 5.6 months, respectively. In the subgroup of non smoker women with adenocarcinoma (n=114 patients), the median PFS and OS were 2.9 and 9.4 months, respectively. The median PFS and OS for the 44 EGFR-mutated patients were respectively 8.4 and 14.4 months. In the GFPC0506 study the median PFS and OS for the 75 patients treated with docetaxel were 2.8 and 8.0 months, respectively. The model yielded mean life expectancies of 9.9, 11.6 and 11.7 months, respectively, for the strategies with no selection, clinical selection and biological selection. QALY estimates were 0.478, 0.558, and 0.559 QALYs, respectively. The no-selection strategy was therefore the least effective, while the clinically and biologically guided strategies had equivalent efficacy. The incremental efficacy of the clinical and the biological-guided strategies were respectively 0.080 and 0.081 QALY, as compared to the no-selection strategy. Cost estimates were 21 025 €, 16 005 €, and 15 210 €, respectively, for the strategies with no selection and clinical and biological selection (Table 3). The clinical and the biological-guided strategies were then less expensive of 5020 € and 5815 € respectively, as compared to the no-selection strategy (Table 3). The no-selection strategy was both the least effective and the most expensive. The biological and clinically guided strategies were dominant, but the biological strategy was slightly less expensive than the clinical strategy.

The results of the one-way sensitivity analysis are shown in Table 4. Whatever the parameter that was varied, the no-selection strategy was systematically less effective and more expensive than the other two strategies. Assuming a low prevalence of EGFR mutation (i.e. 1%), the clinically guided strategy was more effective but more expensive than the biologically guided strategy, with an ICER of 96 354 €/QALY. Conversely, the biologically guided strategy was more effective but more expensive than the clinically guided strategy when the EGFR mutation

prevalence was 30%, with an ICER of 40 147 €/QALY. Variations of cost parameters never challenged the conclusions drawn from the base case.

Figure 2 shows the results of multivariate probabilistic sensitivity analyses. The no-selection strategy was dominated by the clinical and biological strategies in 61% and 64% of cases, respectively. Comparison of the latter two strategies showed an equal distribution of replications among the four quadrants of the cost-effectiveness plan, demonstrating the equivalent cost-effectiveness of the two strategies.

Discussion

This cost-effectiveness study shows that three strategies of second-line erlotinib initiation for NSCLC, namely no patient selection, and patient selection on clinical or biological grounds, had respective cost-effectiveness ratios of 43°985, 28°683 and 27°209 €/QALY. The no-selection strategy was inferior to the other two strategies not only in the base case scenario but also in all the scenarios tested by sensitivity analysis. Multivariate probabilistic sensitivity analysis showed the equivalence of the clinical and biological strategies in terms of the CER.

Few economic studies of second-line treatments for advanced NSCLC have been published (21, 27, 28) and most are based on models using clinical trial data. The ICER of second-line erlotinib versus placebo in patients with previously treated advanced-stage NSCLC has recently been published (29). Resource utilization was determined from individual patient data in the BR21 trial database. The ICER was $94°638 (in 2007 Canadian dollars; 95%CI = $52°359 to $429°148) per life-year gained. The main drivers of cost-effectiveness included the magnitude of the survival benefit and the cost of erlotinib. Subgroup analyses showed that the ICER was better in never-smokers but not in women; likewise, a high EGFR gene copy number, contrary to EGFR mutations, was associated with a favorable ICER. The authors concluded that the patient population most likely to benefit from this drug needed to be better defined. In this study, efficacy was measured in terms of years of life gained, with no weighting for quality of life. However, the latest guidelines recommend that quality of life be taken into account when considering second-line treatment for NSCLC (30). Regarding the burden of NSCLC in terms of health-related quality of life, little information is available on the preferences of patients or society with respect to disease states. We used data from Nafees et al. (24), who adapted existing health-state descriptions in metastatic breast cancer to evaluate the utilities of patients receiving second-line treatment for NSCLC. Each health state describes the symptom burden of a disease and its functional impact. More recently, Lewis (23) used the same method to establish health utilities

for erlotinib therapy, based on data for 154 members of the UK general population, using the EuroQol EQ-5D instrument. We used the results of both studies to test the robustness of our model with varying utility values.

There are few published cost-effectiveness studies directly comparing erlotinib with other agents (docetaxel and pemetrexed). In a model-based analysis (31), the economic value of docetaxel, pemetrexed and erlotinib was compared in a cohort of no clinically or EGFR mutated selected patients with refractory advanced-stage NSCLC. The authors developed a decision analysis model to evaluate, from the US payer's perspective, the incremental costs and QALY of these three drugs, based on efficacy and adverse event rates observed in published clinical trials. The authors used Nafees' work for the utilities and public available cost sources. They found that treatment with erlotinib, docetaxel and pemetrexed yielded 0.42, 0.41, and 0.41 QALY, respectively, compared to 0.478, 0.558 and 0.559 in our no-selection, clinically guided selection and biologically guided selection strategies. Total costs were US$ 37°000, 39°100 and 43°800 for erlotinib, docetaxel and pemetrexed, respectively, compared to 21°025, 16°005 and 15°210 € in our study. A more recent cost-utility analysis compared erlotinib and docetaxel for second-line management of advanced NSCLC in the UK National Health Service (23). The authors used a health-state transition model, based on the two pivotal phase III studies of erlotinib versus best supportive care and docetaxel versus best supportive care, to estimate direct costs, QALY, and the subsequent net monetary benefit. Erlotinib was associated with a reduction in total costs (£13 730 versus £13 956) and a gain in QALY. The comparison of our results with those of these studies confirms the importance of patient selection (on clinical or biological grounds) for cost-effective erlotinib therapy.

An advantage of our study was the prospective cost collection of data, and at least in the ERMETIC study, a cohort of patients representative of those receiving second-line treatment in the routine clinical setting. However, our study has certain limitations. First, costs were identified

prospectively only during the active treatment periods. Management costs after the end of active treatments were derived from a 2004 national database. Some patients may have received third-line chemotherapy but the cost of these chemotherapies would be the same for the 3 strategies and would not impact on the final results. Second, our analysis was limited to direct lung cancer-related medical costs: indirect costs such as lost productivity and caregiver salaries were not included. Third, the way in which we expressed utilities reflects the value from the point of view of society rather than that of the patients concerned. As this study is based on an indirect comparison, we have no information on the clinical efficacy, safety, and resource utilization for the interventions in the same population. We also assumed the same OS benefit of docetaxel in a general population and in non mutated and clinically selected populations. However, the use of sensitivity analyses overcomes these limitations: the conclusions based on the base-case scenario were not modified when we varied the different model parameters. Uncertainty on costs and effectiveness may be still present, however. Ultimately, head-to-head comparative trials will be needed to determine whether there are significant differences between the treatment strategies in terms of OS or PFS.

In conclusion, the cost-effectiveness ratios of the three strategies tested here for second-line erlotinib initiation in patients with advanced-stage NSCLC are within the limits considered acceptable for society, although patient selection based on clinical grounds or EFGR mutation status appears to improve cost-effectiveness.

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Liste of tables

Liste of figures

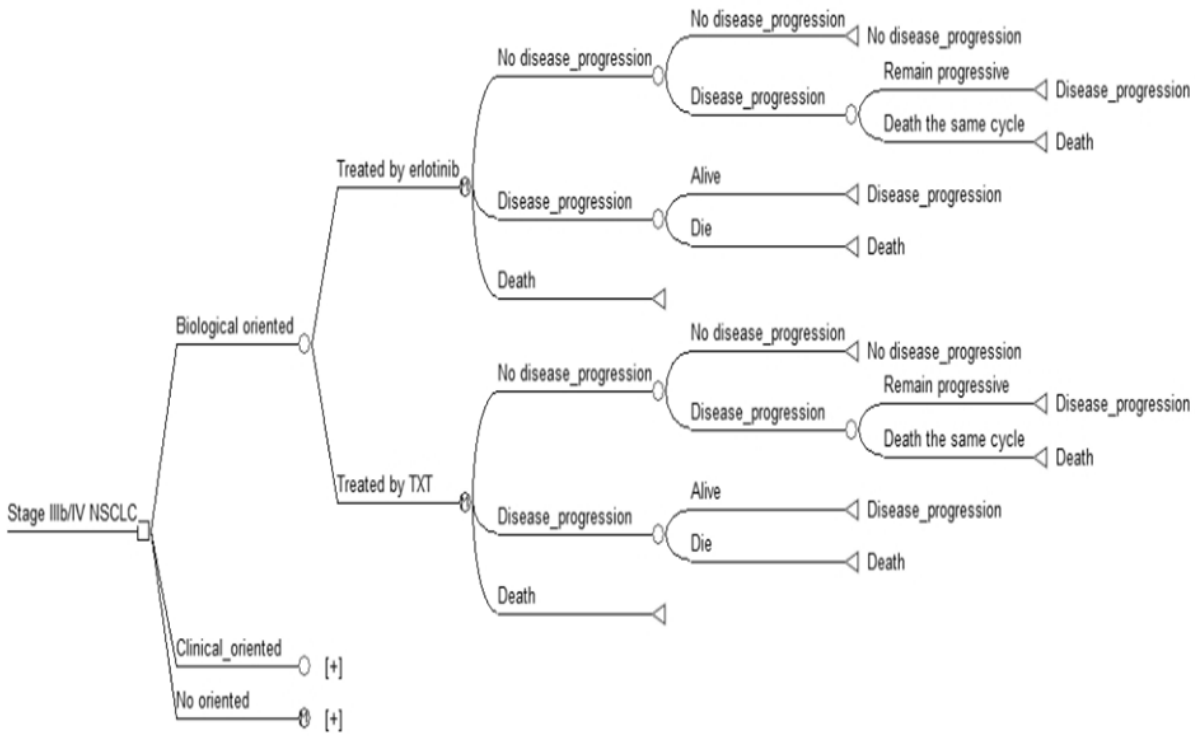


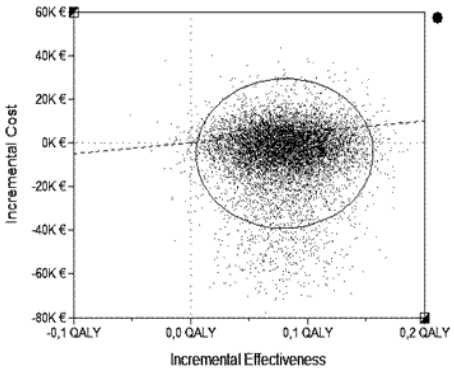
Figure 2: Multivariate probabilistic sensitivity analysis (results of a 10 000-replication simulation).

Each figure represents a cost-effectiveness plane of the comparison of two strategies.

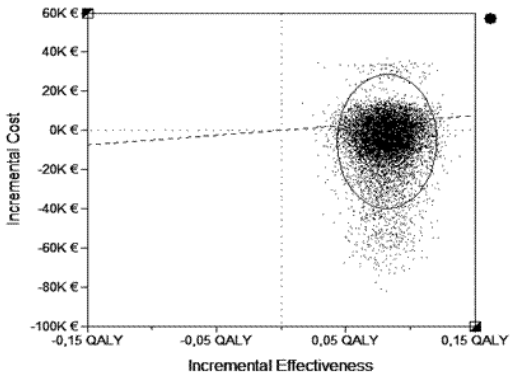
a. Clinically guided strategy versus no-selection strategy

b. Biologically guided strategy versus no-selection strategy

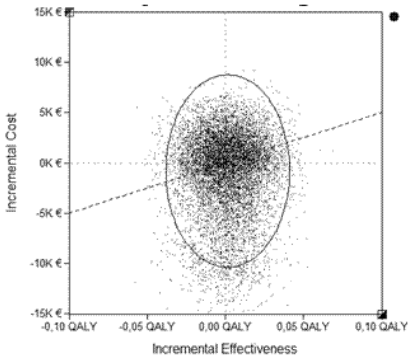
c. Clinically guided strategy versus biologically guided strategy



A- Clinically guided strategy versus no-selection strategy



B- Biologically guided strategy versus no-selection strategy



C- Clinically guided strategy versus biologically guided strategy

d.

Figure 3: Acceptability curve showing the probability for each strategy of being cost-effective.

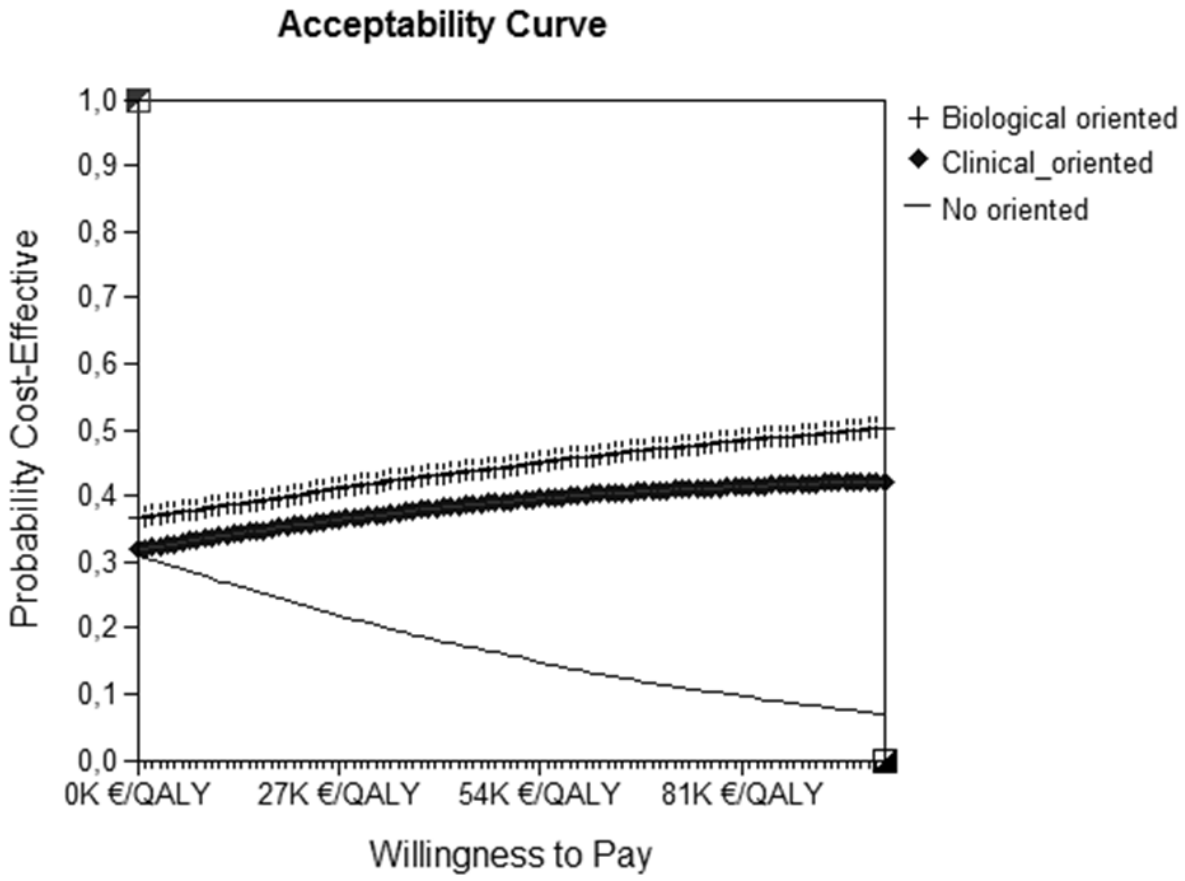

Acceptability Curve
Probability Cost-Effective
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0K €/QALY
27K €/QALY
54K €/QALY
81K €/QALY
Willingness to Pay
Biological oriented
Clinical_oriented
No oriented

Table 1: Characteristic of the patients

	No selection	Clinically guided strategy		Biologically guided strategy	
	Erlotinib	Erlotinib	Docetaxel	Erlotinib	Docetaxel
Number of patients	522	114	408	44	478
Gender (male, %)	354 (68%)	0	354 (87%)	27 (61%)	327 (68%)
Median age (years)	63	63	63	67	63
Performance Status					
0-1	331 (65%)	79 (69%)	252 (69%)	29 (66%)	302 (69%)
2-3	146 (28%)	32 (28%)	114 (31%)	15 (34%)	135 (31%)
Histology					
Squamous	94 (18%)	0	94 (23%)	4 (9%)	90 (19%)
Adenocarcinoma	335 (65%)	114 (100%)	221 (55%)	32 (74%)	303 (64%)
Other	88 (17%)	0	88 (22%)	7 (16%)	81 (17%)
Smoking status					
Current smoker	75 (14%)	0	75 (19%)	4 (9%)	71 (15%)
Former smoker	349 (67%)	53 (47%)	296 (73%)	19 (43%)	330 (70%)
Never smoker	94 (19%)	61 (53%)	33 (8%)	21 (48%)	73 (15%)

Table 2: Model inputs

	Base case	Low	High	Source
Median OS (months)				
No selection (n=522)	5.6	4.6	7.0	(8)
Clinical selection				
Clinical + (n=114)	9.4	5.5	12.7	(8)
Clinical – (n=408)	8.0	5.1	10.4	(8)
EGFR-based selection				
EGFR+ (n=44)	14.4	8.0	20.6	(8)
EGFR- (n=478)	8.0	5.1	10.4	(8)
Median PFS (months)				
No selection (n=522)	2.4	2.3	2.6	(8)
Clinical selection				
Clinical + (n=114)	2.9	2.5	3.8	(8)
Clinical - (n=408)	2.8	2.2	4.2	(8)
EGFR-based selection				
EGFR+ (n=478)	8.4	3.0	15.3	(8)
EGFR- (n=75)	2.8	2.2	4.2	(20)
Health state utilities				(23, 24)
Stable disease on oral therapy	0.670	0.27	0.80	
Stable disease on IV therapy	0.653	0.26	0.78	
Progressive disease	0.473	0.19	0.56	
Death	0			
Prevalence of *EGFR* mutation	0.08	0.01	0.15	(8)
Cost of medical services and drugs (€)				
Erlotinib 30-day supply (150 mg)	2174.7			
Mean duration of erlotinib treatment (months)	2.5	0.1	26.0	
Docetaxel	10.7/mg			
Mean number of docetaxel cycles	3.7 ± 1.9			
Cost of hospitalization for docetaxel administration	368			
Frequency of hospitalization for adverse events*	0.44 ± 0.84			(25)
G-CSF injection (per cycle)	557.4	1627	3021	
Erythropoietin (per cycle)	199.1	91	400	
Palliative care after progression (per month)	2324			
EGFR test	130			

Table 3: Mean cost and effectiveness per patient by strategy

Strategy	No selection	Clinically guided	Biological guided
QALY (mean)	0.478 ± 0.098	0.558 ± 0.082	0.559 ± 0.092
Incremental QALY as compared to the no selection strategy (QALY)	-	0.080	0.081
Cost (mean, euros)	21 025 ± 12 175	16 005 ± 6 758	15 210 ± 6 860
Incremental cost as compared to the no selection strategy (euros)	-	- 5 020	- 5 815
CER (euros/QALY)	43 985	28 683	27 209

QALY: quality-adjusted life-years

CER= cost-effectiveness ratio

Table 4: Sensitivity analysis

	No selection	Clinical guided selection	Biological guided selection
Base case	43 985	28 682	27 209
Clinical parameters of selection of the clinical-guided selection			
No smokers with adenocarcinoma	43 985 [#]	26 682	27 209 [#]
No smoker women	43 985 [#]	30 671	27 209 [#]
Women with adenocarcinoma	43 985 [#]	29 109	27 209 [#]
Prevalence of EGFR mutation			
1%	43 985 [#]	28 682 [#]	25 927
30%	43 985 [#]	28 682 [#]	29 802
Biological testing cost			
91 €	43 985 [#]	28 682 [#]	27 071
400 €	43 985 [#]	28 682 [#]	27 504
Post-progression cost			
1627 €	38 033	27 589	26 776
3021 €	49 939	29 634	27 477
Erlotinib tariff			
-30%	38 311	27 096	26 193
+ 30%	49 661	30 129	28 060

[#] Same estimates as for the base case.