

Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain

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Background: The purpose of this study was to investigate the savings accrued using bevacizumab-based treatment for non-small-cell lung cancer from the societal perspective, taking only public costs into account, in France, Germany, Italy, and Spain.

Methods: Societal costs were estimated by collecting and analyzing labor costs, carer costs, sickness benefits, disability benefits, and home care benefits. Cost inputs were derived from publicly available databases or from the published literature. Expert opinion was only used if no other source was available. Efficacy data from two randomized clinical trials were used. The time horizon in the health economic model was lifetime. Efficacy and costs were discounted by 3.5%. All main model parameters were tested in deterministic and probabilistic sensitivity analyses.

Results: Mean incremental savings to society per patient ranged from €2277 in Italy to €4461 in Germany. The results were most sensitive to the change in proportion of patients working full-time and the proportion of patients who were able to return to work.

Conclusion: This analysis shows that bevacizumab-based treatment in non-small-cell lung cancer is associated with more savings to society compared to standard chemotherapy in terms of increased productivity and decreased social benefits paid to patients who are able to work in France, Germany, Italy, and Spain.

Keywords: non-small-cell lung cancer, bevacizumab, chemotherapy, economic model, France, Germany, Italy, Spain

Introduction

There are about 200,000 new cases of lung cancer and 140,000 lung cancer deaths each year in the European Union.¹ Patients with lung cancer have a poor prognosis. The disease accounts for approximately 20% of all cancer-related deaths in Europe, and accounts for more deaths than any other malignancy.² The majority of lung cancer cases are diagnosed when the disease is at an advanced stage.³ The age-adjusted 5-year survival rate for lung cancer is only around 10%.¹ Non-small-cell lung cancer (NSCLC) accounts for around 80% of lung cancer cases.³

Patients with advanced lung cancer experience a high symptom burden.⁴⁻¹² The significant burden on lung cancer patients is due to the large number of symptoms experienced and their severity, which increase as the disease progresses, and health-related quality of life decreases accordingly.¹³ In addition to improving overall survival of advanced NSCLC patients, extending progression-free survival is a clinically

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meaningful treatment goal for patients. Prolonging the time before symptoms worsen (disease progression) can delay the negative physical and emotional consequences associated with disease progression.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor and indicated for first-line treatment of unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC in combination with platinum-based chemotherapy in Europe.¹⁴ It has been shown to delay tumor progression significantly compared with standard platinum chemotherapy alone (Table 1).^{15,16} The efficacy of the various chemotherapies available has been shown to be similar.^{17,18} It has been reported that the efficacy of bevacizumab is generally consistent across chemotherapies, including carboplatin and cisplatin doublets.¹⁹

Research has demonstrated that improvements in health care have considerable value to society.²⁰ The value is created by investments in medical research and through the experiences using these technologies in clinical practice. Increasingly, questions are being asked about the value of new health technologies in respect to their costs. Although benefits are commonly considered in their widest possible sense; costs in economic evaluations are typically limited to the “payer” perspective.^{21,22} Some health technology assessment and reimbursement agencies recommend considering the societal perspective.²³ The societal perspective is defined as incorporating all costs and benefits, no matter who pays the costs and who receives the benefits.²⁴ It has been argued that abandoning the societal perspective may lead to suboptimal decisions about allocation of resources.²⁵ In this analysis, the societal perspective is defined as public health service and government.

Governments face high costs related to the treatment of lung cancer. Treatment of advanced lung cancer is associated with frequent hospital visits, surgery, radiation therapy, chemotherapy, and targeted therapies. There are further losses

arising from lost productivity due to sick leave, disability, and premature deaths linked to lung cancer. Patients with advanced NSCLC who can no longer work do not pay into social contribution schemes like health insurance funds, pension funds, or nursing care funds. Depending on the country, these payments will be made on behalf of the patient by the health insurance fund or out of tax funds. The productivity losses double when an employed family member becomes a carer for the patient with lung cancer. Additionally, patients who are no longer able to look after themselves will require formal care.

An observational cost-of-illness study, ie, ALCEA (Advanced Lung Cancer Economic Assessment), reports on considerable societal burden associated with the disease in patients with advanced NSCLC. A high level of health care resource utilization and a significant productivity loss were observed.²⁶ Another study found that bevacizumab-based treatment can result in substantial cost savings in patients with advanced NSCLC who are progression-free.²⁷ The aim of this study was to explore the incremental societal savings attributable to bevacizumab-based treatment compared with chemotherapy in France, Germany, Italy, and Spain.

Materials and methods

This study estimates the potential savings from the societal perspective resulting from reduced productivity losses in patients with advanced NSCLC in Germany, France, Italy and Spain.

A health economic model was developed to assess the societal savings associated with bevacizumab-based treatment when compared with chemotherapy. A Markov model was selected because it allows assessment of patient transition between different health states separately in both treatment arms. Patient level data from two randomized, controlled, double-blind Phase III trials of first-line therapy for advanced NSCLC were used to derive Markov model cycle-specific numbers of progression-free patients as well

Table 1 Efficacy of randomized clinical trials

| | Description | Chemotherapy | Bevacizumab-based therapy |
|---------|---|--------------|---------------------------|
| BO17704 | Median time in progression-free survival (months) | 6.1 | 6.7 |
| | 95% confidence interval (months) | 5.6–6.4 | 6.3–6.9 |
| | Hazard ratio | 0.75 | |
| | 95% confidence interval | 0.62–0.91 | |
| | P value | 0.0026 | |
| E4599 | Median time in progression-free survival (months) | 4.8 | 6.4 |
| | 95% confidence interval (months) | 4.40–5.39 | 6.11–6.87 |
| | Hazard ratio | 0.65 | |
| | 95% confidence interval | 0.56–0.76 | |
| | P value | <0.0001 | |

as those patients whose disease progressed, who died, or who were censored.^{15,16,28} These data were fitted into Weibull distributions that were used to estimate the numbers of patients in each health state for the duration of the model. Health outcomes as well as associated costs were modeled in monthly cycles. The analysis time horizon was lifetime. The model has two states, ie, progression-free survival and disease progression or death. The progression-free survival state is divided into proportions of patients who can work after induction therapy and those who cannot do so. Each patient has a probability of having an informal carer, a formal carer, or not having a carer. Patients were given bevacizumab + standard chemotherapy or only standard chemotherapy. The chemotherapy was either cisplatin-gemcitabine or carboplatin-paclitaxel. More details of the studies and treatment regimes have been described elsewhere.^{15,16,28} Clinical outcomes and costs were discounted at a rate of 3.5%.

All patients were assumed to be off work during the treatment induction phase, when bevacizumab + chemotherapy or chemotherapy is administered for six cycles. Each treatment cycle lasts 21 days for both therapies. The proportion of patients assumed to return to work after initial induction therapy was 32% for the bevacizumab-based treatment arm and 19% for the chemotherapy arm.²⁹

Incident lung cancer patients in the working age population were estimated from the Globocan database.² The working age was defined as 15–55 years at the time of diagnosis. A normal distribution was assumed around the mean age to derive the cohort of patients who would be aged 55 years or under at diagnosis. Of these patients, clinical experts estimated that 36% were patients with advanced and/or metastatic NSCLC. The proportion of patients treated with various therapies was assumed to be equally split, eg, 25% each treated with bevacizumab + cisplatin-gemcitabine, bevacizumab + carboplatin-paclitaxel, cisplatin-gemcitabine, or carboplatin-paclitaxel.

Only patients who were employed prior to their diagnosis are considered in the study. The employment rates for France, Germany, Italy, and Spain are 64%, 71%,

57%, and 59%, respectively.³⁰ The proportions of patients assumed to be working full-time and part-time are shown in Table 2. These proportions were applied to both patients and informal carers. For simplicity, it was assumed that patients who worked full-time prior to their diagnosis would return to work full-time. The same assumption was made for part-time workers, ie, if they were part-time workers they returned to work part-time. The informal carer's return to work was not dependent on their working status prior to diagnosis, but on whether the patient returned to work, and whether it was full-time or part-time. Thirteen percent of the patients were assumed to have informal carers.²⁹

The patients who were estimated to return to work continued to work until disease progression or death, whichever occurred first. Only patients who were aged 55 years or under at the time of diagnosis were assumed to return to work. This estimate is based on expert opinion because no published evidence was identified.

The labor costs applied are shown in Table 2. The cost of sick leave and a possible disability pension were also taken into consideration. The details of the figures included are shown in Table 2. Informal carers were assumed to be on unpaid leave during the time that they were unable to work. No long-term benefits were considered in this study due to the complexity of including them. No home care benefits were assumed for Italy, because there was no home care benefit scheme in place during the study period.

Results

Our analysis shows that gains in productivity and associated reductions in societal expenditure are higher in the bevacizumab treatment arm (€5216, €6739, €3455, and €4046 per person in France, Germany, Italy, and Spain, respectively) than in the chemotherapy arm (€1774, €2278, €1178, and €1377, respectively). These societal gains are due to the time spent in progression-free survival by patients who were estimated to be able to return to work in each treatment arm. A comparison of the two treatments arms is shown in Figure 1.

Table 2 Model input data

| Description | France | Germany | Italy | Spain |
|-------------------------------------|----------|----------|----------|-----------|
| Employment rate | 64.00% | 71.10% | 56.90% | 58.60% |
| Employment at diagnosis (full-time) | 87.72% | 78.98% | 84.61% | 88.73% |
| Employment at diagnosis (part-time) | 12.28% | 21.02% | 15.39% | 11.27% |
| Labor cost (inflated) (€) | 2798 | 3449 | 2215 | 2031 |
| Sick leave benefit (amount, €) | 1399 | 2414 | 1475 | 1523 |
| Sick leave benefit (duration) | 360 days | 78 weeks | 160 days | 12 months |
| Disability pension (€) | 738 | 684 | 680 | 936 |

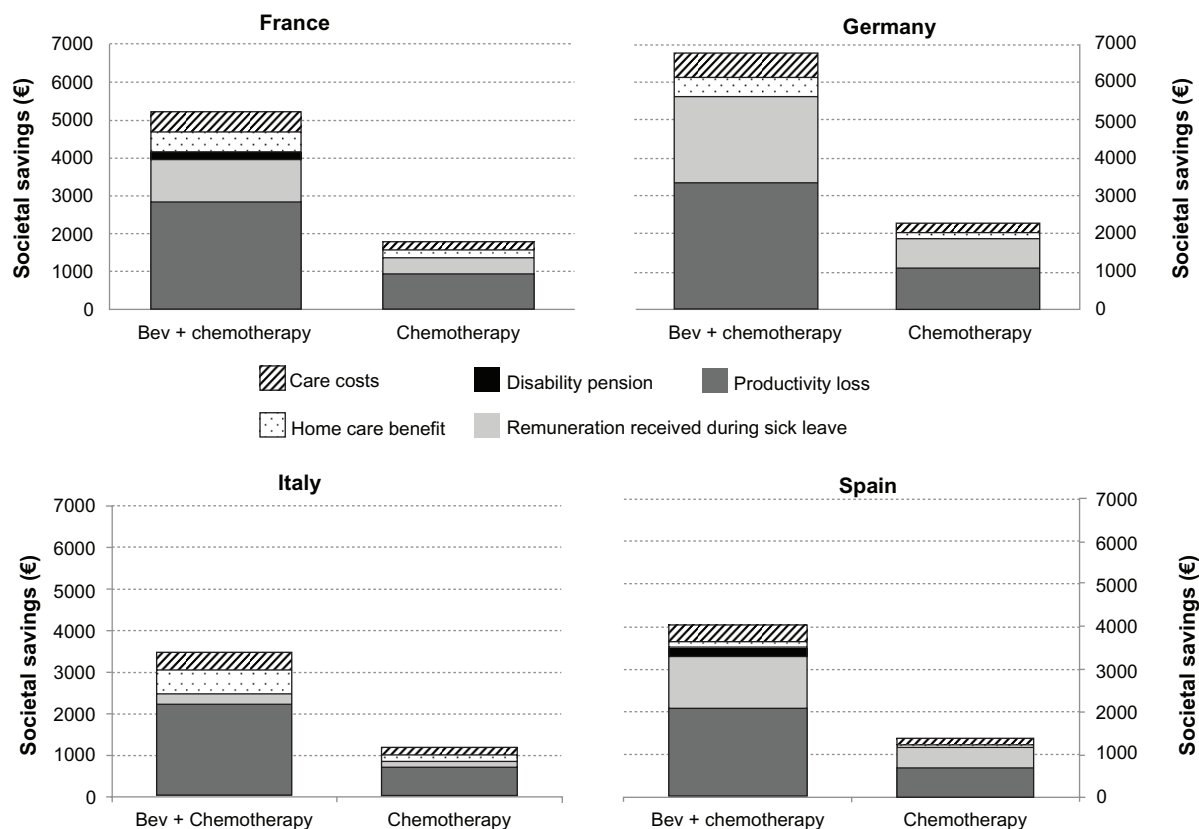


Figure 1 Comparison of Bevacizumab plus chemotherapy treatment and chemotherapy treatment savings (5 year cumulative savings).

Most of the societal savings were accrued from reduced losses in labor costs. These savings represented 55%, 50%, 64%, and 52% of all savings in France, Germany, Italy, and Spain, respectively. The rest of the societal savings were due to not having to file a claim sickness benefit, disability benefit, or home care benefit, and having reduced formal care costs. Additionally, if the patient had an informal carer, savings were increased because the carer was able to return to work. The breakdown of these savings can be seen in Figure 1.

To assess for uncertainty in the model structure and inputs, two types of sensitivity analysis techniques were used, ie, one-way and probabilistic. In one-way sensitivity analysis, the varied inputs were discounting rate (0% and 5%), time horizon (one year and 3 years), labor cost ($\pm 10\%$), proportion of patients in full-time employment (of those who are employed) prior to diagnosis (0% and 100%), and proportion able to return to work ($\pm 10\%$). The results of the one-way sensitivity analyses are shown in Figure 2.

Probabilistic sensitivity analyses are often used to assess how uncertainty in model outputs can be apportioned to imperfect knowledge of the parameter input values. In our probabilistic sensitivity analysis, we used a cohort simulation technique to assess for parameter uncertainty.

Cohort simulation is often used to test the robustness of the results of random variation in the values of the key parameters. The number of iterations run was 1000. Table 3 shows the results.

Discussion

For most patients, a diagnosis with advanced cancer is a terminal prognosis. The impact of advanced NSCLC extends beyond the individual, affecting both the emotional and financial well-being of patients and their families.

There are only a few studies published on the cost of illness in lung cancer, especially ones taking a societal perspective. Country cancer registries have been used to assess the overall morbidity from lung cancer.^{31,32} A study by Stanisc et al assessed the economic burden of metastatic NSCLC from a societal perspective,²⁷ and found that the mean cost savings after one year were €21,667, €21,171, €17,578, and €12,401 in France, Germany, Italy, and Spain, respectively. The study results suggest that there are reduced productivity losses due to improved progression-free survival in patients treated with bevacizumab-based therapy compared with patients treated with chemotherapy alone. Another study found that the productivity losses associated with advanced

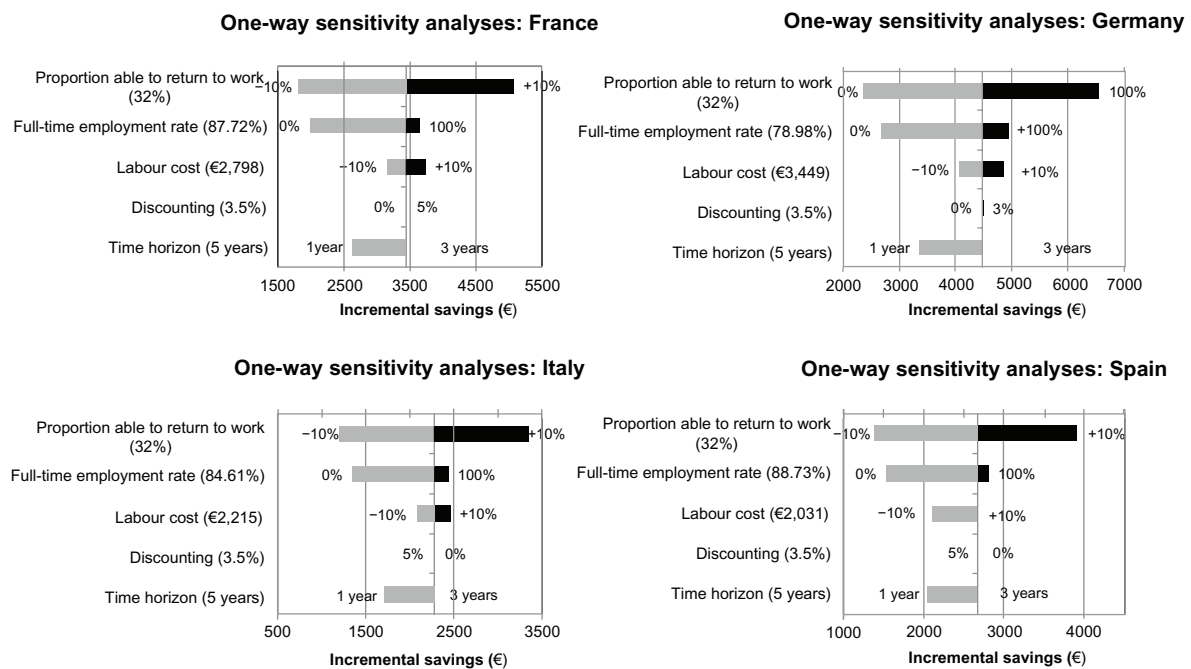


Figure 2 One-way sensitivity analyses: impact of one parameter changing at the time.

lung cancer were around €11,390,000 in Italy, making the average loss per patient approximately €60,263.²⁶ The study by Perrone et al is a cost-of-illness study in Italy, assessing the direct and indirect costs associated with patients having lung cancer in Italy. Although these studies are not directly comparable with our analysis, our findings are in line with these studies. The previous work by Stanisic et al only took labor costs into consideration, whereas this analysis has taken a wider perspective by including productivity losses associated with informal carers, cost of formal carers, sick leave remuneration, disability pension, and home care benefits.²⁷ The outcomes from the Phase III trials used in our analysis are consistent with outcomes from the Phase IV trial.¹⁹

Our approach only took into account public expenditure, but excluded any similar private expenditure. For example, in Germany, the employer pays part of the sick leave remuneration, and after that it is paid by health insurance. The remuneration paid by the employer has not been included in our analysis. Including this expenditure would have increased the societal savings from bevacizumab-based therapy. Taking a wider societal perspective would have enabled inclusion

of all changes in resources as measured by changes in service production, changes in resources used by patients and their carers, and changes in the gross domestic product,³³ but would have resulted in a less conservative estimate of societal savings.

A real-life study was used to assess the proportion of patients who return to work after induction therapy.³⁴ The study reported that 32% of bevacizumab-based and 19% of chemotherapy patients returned to work. Other studies in various countries report that the proportion of NSCLC patients returning to work was between 13% and 40%.^{29,35–38} Hence, the real-life study results can be considered to be in line with previous findings.

Standard average OECD tax and contribution rates have been used in this study, and the average income has been used from the same source. However, this average income is available for single households only. There are reasons why this average might be considered an overestimation or underestimation. There is an inverse association between the highest level of education and lung cancer.^{39,40} On the other hand, patients with lung cancer tend to be older and there is a

Table 3 Probabilistic sensitivity analysis results

| Description | France | Germany | Italy | Spain |
|---|------------|------------|------------|------------|
| Societal savings, bevacizumab-based treatment (±SD) | 5216 ± 691 | 6702 ± 948 | 3429 ± 475 | 4060 ± 586 |
| Societal savings, chemotherapy (±SD) | 1770 ± 260 | 2272 ± 348 | 1173 ± 164 | 1380 ± 198 |
| Incremental savings | 3446 | 4431 | 2256 | 2680 |

Abbreviation: SD, standard deviation.

higher proportion of males than in the general population, and hence they have a higher income than the general population. Rather than trying to adjust for these variables, we opted to use simply the average income to maintain transparency in our analysis.

As with any analysis, some assumptions had to be made due to no published data being available. In this analysis, only patients who were employed prior to their diagnosis were considered. It was also assumed that patients who worked full-time prior to their diagnosis would return to work full-time. The same assumption was made for part-time workers, ie, if they were part-time workers they returned to work part-time. These assumptions applied equally to the bevacizumab-based treatment arm and chemotherapy arm. Nevertheless, they could overestimate the savings.

Deterministic sensitivity analyses showed that changes in time horizon had very little impact on overall societal savings. Full-time employment and the proportion able to return to work seemed to have the most impact on savings in all other countries, except France. In France, the labor costs represented the most influential impact, followed by the proportion working full-time. The results of the probabilistic sensitivity analysis are in line with the deterministic findings.

Currently, there are not many studies assessing savings related to treatments in advanced NSCLC from the societal perspective. This study has adopted the societal perspective because this is the classic approach to assessing the profitability of societal investments. Using a perspective other than the societal increases the risk that maximal health is not produced due to inefficiencies in the use of resources for health.²⁵ To allow for a more realistic estimate of the benefit to society, bevacizumab-based combination therapy should be examined from a wider societal perspective as well.

This study suggests that societal savings can be made in France, Germany, Italy, and Spain in patients who are treated with bevacizumab-based therapies when compared with standard chemotherapy alone. By extending the progression-free survival in patients with advanced NSCLC, bevacizumab-based therapy is favorable from the perspective of society by reducing the societal losses associated with this devastating disease.

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design, methods, analysis, and interpretation of data as well as having independence over the decision to submit the manuscript.

Disclosure

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