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Health Policy Analysis

Determining the Comparative Value of Pharmaceutical Risk-Sharing Policies in Non–Small Cell Lung Cancer Using Real-World Data

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ABSTRACT

Background: Risk-sharing arrangements (RSAs) can be used to mitigate uncertainty about the value of a drug by sharing the financial risk between payer and pharmaceutical company. We evaluated the projected impact of alternative RSAs for non–small cell lung cancer (NSCLC) therapies based on real-world data. **Methods:** Data on treatment patterns of Dutch NSCLC patients from four different hospitals were used to perform "what-if" analyses, evaluating the costs and benefits likely associated with various RSAs. In the scenarios, drug costs or refunds were based on response evaluation criteria in solid tumors (RECIST) response, survival compared to the pivotal trial, treatment duration, or a fixed cost per patient. Analyses were done for erlotinib, gemcitabine/cisplatin, and pemetrexed/platinum for metastatic NSCLC, and gemcitabine/cisplatin, pemetrexed/cisplatin, and vinorelbine/cisplatin for nonmetastatic NSCLC. **Results:** Money-back guarantees led to moderate cost reductions to the payer. For conditional treatment continuation schemes, costs and outcomes associated with the different treatments were dispersed. When price was linked to the outcome, the payer's drug costs reduced by 2.5% to 26.7%. Discounted treatment initiation schemes yielded large cost reductions. Utilization caps mainly reduced the costs of erlotinib treatment (by 16%). Given a fixed cost per patient based on projected average use of the drug, risk sharing was unfavorable to the payer because of the lower than projected use. The impact of RSAs on a national scale was dispersed. **Conclusions:** For erlotinib and pemetrexed/platinum, large cost reductions were observed with risk sharing. RSAs can mitigate uncertainty around the incremental cost-effectiveness or budget impact of drugs, but only when the type of arrangement matches the setting and type of uncertainty.

Introduction

At the time a reimbursement decision is made, the real value of a drug is often uncertain. Typically, there is efficacy evidence from a randomized controlled trial, but such trials are often conducted in highly selected patients and settings. In clinical practice a drug is likely to be used in a much broader range of patients and settings than in randomized controlled trials, and practices often change over time. This poses a risk for health care payers because the real-world effectiveness of a drug may be lower than predicted, the costs may be higher, or both.[1]

Several types of policies have been designed to mitigate this uncertainty by sharing the financial risk between the payer and the pharmaceutical company. An example is the use of a money-back guarantee, where the payer (i.e., the government or health insurer) is refunded if patients do not achieve specified targets (i.e., tumor remission). Such agreements may allow drugs to be accepted for reimbursement relatively early, while preventing the waste of public resources on drugs that are ineffective or do not live up to expectations.[2,3] Worldwide, hundreds of different risk-sharing arrangements (RSAs) have been implemented over the last few years.[3–5] However, little is known about the relative merits of each type.

The results of some individual policies have been analyzed,[4,5] but there has never been a study to quantify and compare the costs and benefits of alternative RSAs based on real-world data.

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There is little guidance for policy makers on when to use which type of risk-sharing policy, the feasibility of these schemes, and potential adverse effects. This has resulted in inconsistencies; for example, similar drugs may have completely different RSAs for certain indications or in different countries. There is often a lack of transparency regarding the details of RSAs. A potential reason for this is that pharmaceutical companies may wish to keep the details of an RSA secret, not to give competitors an advantage.

While RSAs may reduce the drug expenditures to the payer, they may also influence the benefits a drug can realize for patients. Therefore, this study aims to evaluate and quantify the costs (from a payer's perspective) and benefits of alternative, theoretical risk-sharing policies. A real-world non–small cell lung cancer (NSCLC) database[6] was used to determine the expected total costs and benefits associated with different types of risk-sharing.

Methods

Data

Retrospectively collected data from the Dutch lung cancer database were used to inform the resource use, costs, and clinical outcomes associated with the selected drugs in the absence of risk-sharing.[6] The database contained a random sample of unselected patients with NSCLC who were identified through hospital databases of four hospitals (two academic and two nonacademic hospitals). Data on 1067 randomly selected patients newly diagnosed with stage I–IV NSCLC between January 31, 2009, and January 31, 2011, were collected. An earlier study showed that the distributions of patient characteristics in the four selected hospitals are similar to the total Dutch NSCLC population, except for clinical stage.[7] For the purposes of this paper, patients who received the following drug regimens were included in the analyses: erlotinib, gemcitabine/cisplatin, and pemetrexed/platinum (either carboplatin or cisplatin) for metastasized NSCLC (M+) and gemcitabine/cisplatin, pemetrexed/cisplatin, and vinorelbine/cisplatin for patients with nonmetastasized disease (M0). These drugs were selected based on the high number of patients treated with these therapies in the database. The Dutch acquisition price of the included drugs is not based on risk-sharing or outcome-based pricing. Thus, the base case costs in this study are not inherently risk-sharing based.

Scenarios

Based on literature, a taxonomy of RSAs was determined and six different types of RSAs were included in the analyses[2,3] (Fig. 1). Risk-sharing policies can be health outcome based ("performance-based arrangements" in Fig. 1) and non–health outcome based ("cost-sharing arrangements" in Fig. 1). For each type of patient-level arrangement, one or multiple different scenarios were defined, based on existing RSAs and to illustrate potential effects in "what-if" analyses (Table 1). Selected scenarios did not include an "expenditure cap" or "price–volume agreement," because these arrangements require population-level utilization data, which were not available in our database.

Analyses

First, for each treatment, base case costs and outcomes were calculated per patient in the absence of risk-sharing. Second, it was estimated how these costs and outcomes would change when different risk-sharing scenarios would be introduced, provided that all other things would remain equal (e.g., clinicians would not change their treatment decisions). Changes in costs were assessed from the payer's perspective only. Finally, differences in costs and differences in outcomes were determined for the risk-sharing scenarios compared to the base case. Risk-sharing–associated incremental cost-effectiveness ratios (RSA ICERs) were calculated for scenarios that had an impact on both the costs and the outcomes, compared to the base case without risk-sharing. These RSA ICERs reflect the incremental cost-effectiveness of the RSA, as opposed to the incremental cost-effectiveness of the drug regimen. RSA ICERs were not calculated for scenarios that did not have an impact on the outcomes, as a ratio cannot be calculated when the incremental effects are zero.

The results of the RSAs were extrapolated to estimate the expected impact of the RSAs on national scale. In addition, several sensitivity analyses were done to test the uncertainty around the effects of the RSAs.

All outcomes were expressed in quality-adjusted life-years gained (QALYs). Based on literature, the following utility values were used: first-line progression-free (PF) NSCLC 0.71, first-line progressive disease (PD) 0.67, second-line PF 0.74, second-line PD 0.59, third-line and further line PF 0.62, and third-line and further line PD 0.46. Definitive radiotherapy was assumed to be associated with the same utility value as the therapy from the previous

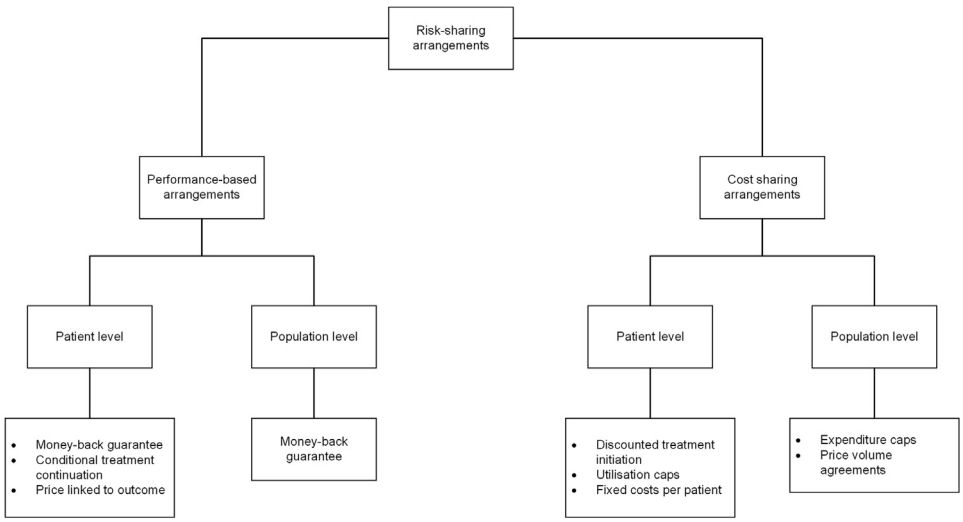

Fig. 1 – Taxonomy of included risk-sharing arrangements (based on Garrison et al.[3] and Walker et al.[2]).

Table 1 – Overview of the analyzed scenarios.

RSA type	Scenario
Money-back guarantee	1.1. Price of the drug to the payer was reduced to 0 for each patient with a recorded RECIST response to the drug that was never more favorable than "progressive disease." Full drug price was paid in all other cases. This is a patient-level RSA.
	1.2. Real-world median OS was compared to median OS in the pivotal trial. When the former was lower, the price of the drug (for all patients) was reduced proportionally.[14,15] This is a population-level RSA.
Conditional treatment continuation	2.1. Treatment was continued only in patients who had a complete or partial response after a maximum of three treatment cycles. Early treatment discontinuation was assumed not to have an effect on OS.
	2.2. Treatment was continued only in patients who had a complete or partial response after a maximum of three treatment cycles. Early treatment discontinuation was assumed to reduce OS, in line with the assumptions specified in Appendix A (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007).
	2.3. The health care payer paid for the drug for up to three cycles. Only patients who demonstrated an adequate response (complete or partial) to the therapy continued with treatment. The pharmaceutical company subsequently provided free-of-charge drugs for these patients.[16,17]
Price linked to outcome	3.1. Full drug costs were reimbursed by the pharmaceutical company for patients who did not show a partial or complete response within four cycles.[18]
Discounted treatment initiation	4.1. The first cycle of the drug was offered for free. Thereafter, full drug price was paid.
	4.2. A drug price discount of 50% was applied to the first 9 weeks of treatment.[5,19]
Utilization caps	5.1. The health care payer paid for the drug for up to three cycles. The pharmaceutical company subsequently provided free-of-charge drugs for those patients who received more than three cycles.[5,20]
Fixed cost per patient	6.1. The drug was available at a single fixed cost per patient, irrespective of the duration of treatment.[a]
	6.2. The drug was available at a single fixed cost per patient irrespective of the duration of treatment.[21,a] This single fixed cost is half of the cost used in RSA 6.1.
	6.3. The drug was available at a single fixed cost per patient per cycle.[a] Any excess (real-world cost per patient per cycle is higher than the fixed cost) led to proportional price reductions (real-world cost as percentage of the fixed cost) of the exceeded cost.[22]

OS, overall survival; RECIST, response evaluation criteria in solid tumors; RSA, risk-sharing arrangement.
[a] Fixed costs for each treatment were based on Dutch drug assessment reports.[23–26]

episode. Palliative radiotherapy, radiotherapy aimed at distance metastases, and all types of surgery were assumed to be associated with a utility value of 0.62 (for PF) and 0.52 (for PD).[8,9]

Costs were estimated from a hospital perspective, based on Dutch prices, and were converted to EUR 2017. Costs were reported as mean total costs per patient, including the costs of the drug treatment of interest and all subsequent treatments, diagnostics, follow-up visits, and hospitalizations. SPSS Statistics 23 was used for all analyses. More information on the assumptions underlying the risk-sharing scenarios can be found in Appendix A (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007).

Results

For metastasized NSCLC, patients treated with erlotinib (n = 47), gemcitabine/cisplatin (n = 21), and pemetrexed/platinum (either carboplatin or cisplatin) (n = 98) were included in the analyses. For nonmetastasized NSCLC, patients treated with gemcitabine/cisplatin (n = 69), pemetrexed/cisplatin (n = 58), and vinorelbine/cisplatin (n = 24) were included in the analyses. As a result, data from 317 patients were included. Table B2 in Appendix B (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007) shows the baseline characteristics of included patients.

Table 2 presents, among other things, the base case results as obtained by analyzing the real-world data. Nonmetastasized NSCLC treated with pemetrexed/cisplatin was associated with the highest mean total costs per patient. Erlotinib treatment for metastasized disease was associated with the lowest mean costs of all included regimens. The mean number of QALYs accrued by patients was highest in patients with nonmetastasized disease treated with vinorelbine/cisplatin.

Money-Back Guarantee (Scenarios 1.1 and 1.2)

Two different outcome-based money-back scenarios were tested (Table 2). If RSA 1.1 would have been implemented, savings for the payer would have been largest for pemetrexed/platinum and erlotinib for patients with metastasized disease, which showed the highest proportion of patients with PD. For the vinorelbine/cisplatin combination treatment, all patients with nonmetastasized disease responded or remained stable with treatment, and thus the costs were the same as the base case costs. In scenario 1.2, only the median OS of patients with metastasized NSCLC treated with gemcitabine/cisplatin was lower compared to the median OS in the pivotal trial (see Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007).[10] As a result, this scenario yielded a small reduction of costs for patients treated with gemcitabine/cisplatin, *ceteris paribus*.

Conditional Treatment Continuation (Scenarios 2.1, 2.2, and 2.3)

The accrued number of QALYs was lower in scenario 2.2 than in scenario 2.1 because of the assumed impact of treatment discontinuation on survival times. As a result, the RSA ICERs of scenario 2.1 compared to the base case ranged from €1457 to €319,600, and the RSA ICERs of scenario 2.2 ranged from €1150 to €106,533 per QALY gained. The RSA ICERs associated with scenario 2.3 ranged from €1729 to €146,400 per QALY gained.

Table 2 – Results base case and all analyzed scenarios.

	Mean total costs[a]	Δ Mean total costs (%)[b]	Mean QALYs[b]	Δ Mean QALYs	RSA ICER
Base case					
Erlotinib M+	27,463	N/A	0.46	0	N/A
Gemcitabine/cisplatin M+	31,401	N/A	0.65	0	N/A
Pemetrexed/platinum M+	40,636	N/A	0.62	0	N/A
Gemcitabine/cisplatin M0	30,220	N/A	0.93	0	N/A
Pemetrexed/cisplatin M0	43,707	N/A	0.98	0	N/A
Vinorelbine/cisplatin M0	30,519	N/A	1.11	0	N/A
Scenario 1.1					
Erlotinib M+	26,318	−1,145 (4.2)	0.46	0	N/A
Gemcitabine/cisplatin M+	31,172	−229 (0.7)	0.65	0	N/A
Pemetrexed/platinum M+	36,021	−4,615 (11.4)	0.62	0	N/A
Gemcitabine/cisplatin M0	30,116	−104 (0.3)	0.93	0	N/A
Pemetrexed/cisplatin M0	42,860	−847 (1.9)	0.98	0	N/A
Vinorelbine/cisplatin M0	30,519	0 (0)	1.11	0	N/A
Scenario 1.2					
Erlotinib M+	27,463	0 (0)	0.46	0	N/A
Gemcitabine/cisplatin M+	31,304	−97 (0.3)	0.65	0	N/A
Pemetrexed/platinum M+	40,636	0 (0)	0.62	0	N/A
Gemcitabine/cisplatin M0	30,220	0 (0)	0.93	0	N/A
Pemetrexed/cisplatin M0	43,707	0 (0)	0.98	0	N/A
Vinorelbine/cisplatin M0	30,519	0 (0)	1.11	0	N/A
Scenario 2.1					
Erlotinib M+	24,267	−3,196 (11.6)	0.45	−0.01	319,600
Gemcitabine/cisplatin M+	31,216	−185 (0.6)	0.64	−0.01	18,500
Pemetrexed/platinum M+	38,285	−2,351 (5.8)	0.59	−0.03	78,367
Gemcitabine/cisplatin M0	30,151	−69 (0.2)	0.89	−0.04	1,725
Pemetrexed/cisplatin M0	42,500	−1,207 (2.8)	0.92	−0.06	20,167
Vinorelbine/cisplatin M0	30,417	−102 (0.3)	1.04	−0.07	1,457
Scenario 2.2					
Erlotinib M+	24,267	−3,196 (11.6)	0.43	−0.03	106,533
Gemcitabine/cisplatin M+	31,216	−185 (0.6)	0.61	−0.04	4,625
Pemetrexed/platinum M+	38,285	−2,351 (5.8)	0.56	−0.06	39,183
Gemcitabine/cisplatin M0	30,151	−69 (0.2)	0.87	−0.06	1,150
Pemetrexed/cisplatin M0	42,500	−1,207 (2.8)	0.89	−0.09	13,411
Vinorelbine/cisplatin M0	30,417	−102 (0.3)	1.04	−0.07	1,457
Scenario 2.3					
Erlotinib M+	23,071	−4,392 (16)	0.43	−0.03	146,400
Gemcitabine/cisplatin M+	30,967	−434 (1.4)	0.61	−0.04	10,850
Pemetrexed/platinum M+	35,911	−4,725 (11.6)	0.56	−0.06	78,750
Gemcitabine/cisplatin M0	30,115	−105 (0.3)	0.87	−0.06	1,750
Pemetrexed/cisplatin M0	42,323	−1,384 (3.2)	0.89	−0.09	15,378
Vinorelbine/cisplatin M0	30,398	−121 (0.4)	1.04	−0.07	1,729
Scenario 3.1					
Erlotinib M+	20,837	−6,626 (24.1)	0.46	0	N/A
Gemcitabine/cisplatin M+	30,086	−1,315 (4.2)	0.65	0	N/A
Pemetrexed/platinum M+	29,775	−10,861 (26.7)	0.62	0	N/A
Gemcitabine/cisplatin M0	28,930	−1,290 (4.3)	0.93	0	N/A
Pemetrexed/cisplatin M0	35,110	−8,597 (19.7)	0.98	0	N/A
Vinorelbine/cisplatin M0	29,762	−757 (2.5)	1.11	0	N/A
Scenario 4.1					
Erlotinib M+	21,869	−5,594 (20.4)	0.46	0	N/A
Gemcitabine/cisplatin M+	30,797	−604 (1.9)	0.65	0	N/A
Pemetrexed/platinum M+	36,283	−4,353 (10.7)	0.62	0	N/A
Gemcitabine/cisplatin M0	29,518	−702 (2.3)	0.93	0	N/A
Pemetrexed/cisplatin M0	39,708	−3,999 (9.1)	0.98	0	N/A
Vinorelbine/cisplatin M0	29,918	−601 (2.0)	1.11	0	N/A
Scenario 4.2					
Erlotinib M+	25,923	−1,540 (5.6)	0.46	0	N/A
Gemcitabine/cisplatin M+	30,594	−807 (2.6)	0.65	0	N/A
Pemetrexed/platinum M+	33,585	−7,051 (17.4)	0.62	0	N/A
Gemcitabine/cisplatin M0	29,480	−740 (2.4)	0.93	0	N/A
Pemetrexed/cisplatin M0	40,832	−2,875 (6.6)	0.98	0	N/A
Vinorelbine/cisplatin M0	29,984	−535 (1.8)	1.11	0	N/A

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Table 2 – *continued*

	Mean total costs[a]	Δ Mean total costs (%)[b]	Mean QALYs[b]	Δ Mean QALYs	RSA ICER
Scenario 5.1					
Erlotinib M+	23,071	−4,392 (16)	0.46	0	N/A
Gemcitabine/cisplatin M+	30,967	−434 (1.4)	0.65	0	N/A
Pemetrexed/platinum M+	35,911	−4,725 (11.6)	0.62	0	N/A
Gemcitabine/cisplatin M0	30,115	−105 (0.3)	0.93	0	N/A
Pemetrexed/cisplatin M0	42,323	−1,384 (3.2)	0.98	0	N/A
Vinorelbine/cisplatin M0	30,398	−121 (0.4)	1.11	0	N/A
Scenario 6.1					
Erlotinib M+	27,545	+82 (100.3)	0.46	0	N/A
Gemcitabine/cisplatin M+	32,971	+1,570 (105)	0.65	0	N/A
Pemetrexed/platinum M+	40,779	+143 (100.4)	0.62	0	N/A
Gemcitabine/cisplatin M0	32,263	+2,043 (106.8)	0.93	0	N/A
Pemetrexed/cisplatin M0	48,447	+4,740 (110.8)	0.98	0	N/A
Vinorelbine/cisplatin M0	31,854	+1,335 (104.4)	1.11	0	N/A
Scenario 6.2					
Erlotinib M+	23,865	−3,598 (13.1)	0.46	0	N/A
Gemcitabine/cisplatin M+	31,134	−267 (0.9)	0.65	0	N/A
Pemetrexed/platinum M+	33,433	−7,203 (17.7)	0.62	0	N/A
Gemcitabine/cisplatin M0	30,427	+207 (100.7)	0.93	0	N/A
Pemetrexed/cisplatin M0	41,102	−2,605 (6.0)	0.98	0	N/A
Vinorelbine/cisplatin M0	30,577	+58 (100.2)	1.11	0	N/A
Scenario 6.3					
Erlotinib M+	26,425	−1,038 (3.8)	0.46	0	N/A
Gemcitabine/cisplatin M+	31,381	−20 (0.1)	0.65	0	N/A
Pemetrexed/platinum M+	36,998	−3,638 (9.0)	0.62	0	N/A
Gemcitabine/cisplatin M0	30,160	−60 (0.2)	0.93	0	N/A
Pemetrexed/cisplatin M0	42,824	−883 (2.0)	0.98	0	N/A
Vinorelbine/cisplatin M0	30,429	−90 (0.3)	1.11	0	N/A

M+, metastatic NSCLC; M0, nonmetastatic NSCLC; RSA ICER, risk-sharing associated incremental cost-effectiveness ratio.
[a] Costs in euros.
[b] Difference between the base case costs/outcomes and the costs/outcomes after applying the risk-sharing scenarios.

Price Linked to Outcome (Scenario 3.1)

The price linked to outcome RSA resulted in large cost reductions, particularly for pemetrexed/platinum (€10,861 for M+ and €8597 for M0 NSCLC). The reduction in payer costs was also substantial for erlotinib (€6626), as a function of its high drug costs and relatively large proportion of nonresponders.

Discounted Treatment Initiation (Scenarios 4.1 and 4.2)

Offering the drug for free during the first 30 days substantially affected the costs associated with erlotinib treatment for patients with metastasized lung cancer. The effect of a drug price discount of 50% for the first 9 weeks of treatment was relatively moderate for most treatment combinations, except for pemetrexed/platinum, which showed a cost reduction of €7051 in patients with metastasized disease.

Utilization Caps (Scenario 5.1)

When the pharmaceutical company provided free-of-charge drugs for patients who received more than three treatment cycles, the effect on the reduction of the costs was dispersed, ranging from a 0.3% to a 16% reduction in mean costs. This was due to different proportions of patients treated with chemotherapy who did not receive more than three treatment cycles (Table 2).

Fixed Costs Per Patient (Scenarios 6.1, 6.2, and 6.3)

In the scenarios where drug costs were based on the projected use before reimbursement, this resulted in an increase in the total costs per patient for all drugs compared to the base case results. This reflects the fact that real-world use for each of the drug regimens in daily practice was lower than projected. When projected drug costs were halved (scenario 6.2), the fixed price resulted in a cost reduction for four out of six treatments (Table 2). In scenario 6.3, a fixed cost per patient per cycle was applied. This RSA resulted in slight reductions in the cost per patient for all treatments (Table 2).

Figure 2 shows the results of all scenarios for all treatments. Scenarios 3.1 and 4.1 led to the largest cost reduction for erlotinib and pemetrexed/platinum treatment in patients with metastasized NSCLC. Overall, large cost reductions were mainly observed for erlotinib and pemetrexed/platinum treatment (M+). However, for gemcitabine/cisplatin in patients with metastasized or nonmetastasized disease and for vinorelbine/cisplatin (M0), the changes in costs were relatively small. In general, most RSAs resulted in a cost reduction, and some scenarios resulted in a loss of QALYs compared with a situation without RSA.

Table 3 provides an overview of the different types of RSA's, including their potential effects on costs, outcomes, and managing uncertainty.

Extrapolation of the Results

We estimated the expected impact of RSAs on a national scale by multiplying the proportion of patients receiving one of the six selected treatments with the total Dutch population diagnosed with NSCLC between 2009 and 2011, which was based on previous study. Also based on this earlier study, it was assumed that 45% of all patients with NSCLC received systemic treatment.[7] Moreover,

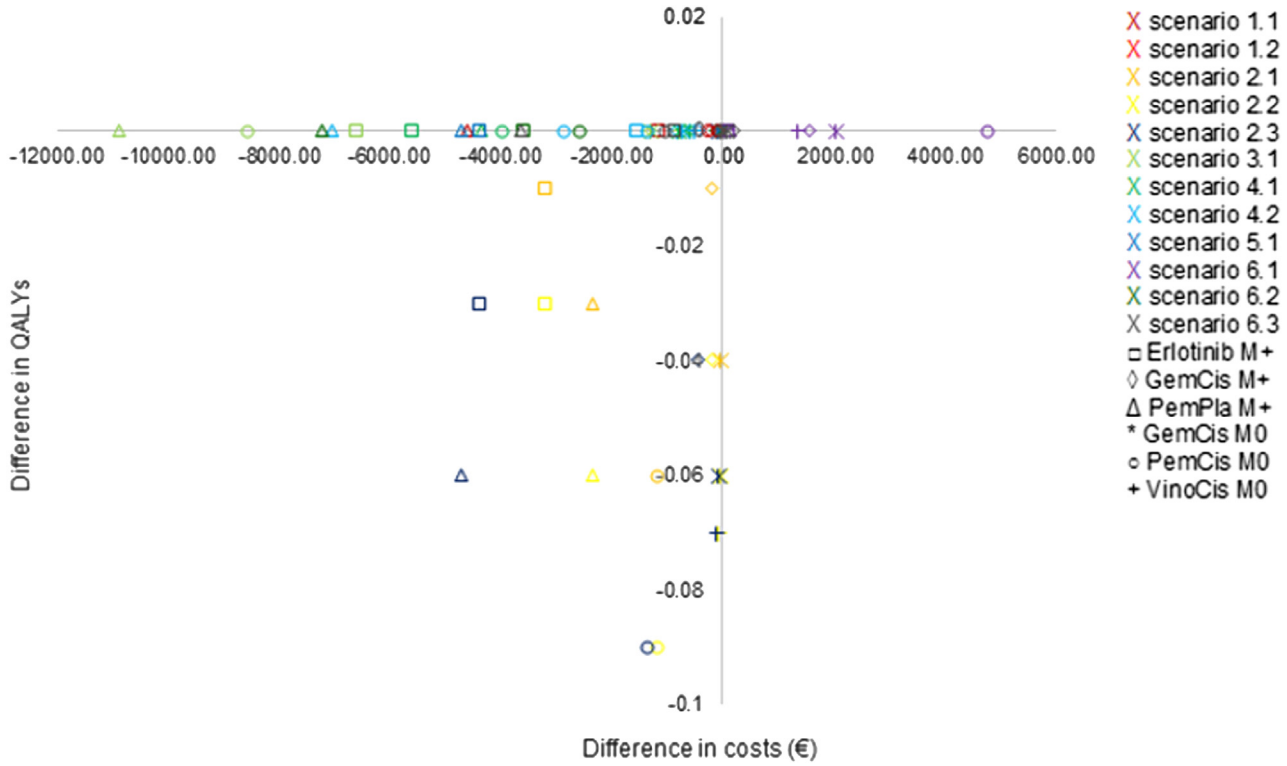

Fig. 2 – Overview of the results of all scenarios for all treatments. Erlotinib M+, erlotinib for metastatic NSCLC; GemCis M+, gemcitabine/cisplatin for metastatic NSCLC; GemCis M0, gemcitabine/cisplatin for nonmetastatic NSCLC; PemCis M0, pemetrexed/cisplatin for nonmetastatic NSCLC; PemPla M+, pemetrexed/platinum for metastatic NSCLC; QALYs, quality-adjusted life-years; VinoCis M0, vinorelbine/cisplatin for nonmetastatic NSCLC.

based on the data, it was assumed that the six systemic treatments that were included in this study accounted for approximately 40% of all prescribed systemic treatments in the Netherlands. The costs, effects, and impact of the RSAs in the study population were assumed to be generalizable to the national scale. The results of the extrapolation to the total Dutch population can be found in Table B3 in Appendix B (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007). On a national scale, the differences in costs of one of the RSAs ranged from €2,178,680 (increased costs) to −€8,479,765 (cost savings).

Sensitivity Analyses

To test the robustness of the effects of the RSAs, various sensitivity analyses were conducted (Table B4 in Appendix B; see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.007). Scenarios 2.1a and 2.1b showed cost savings and decreased QALYs for most treatments, which was in accordance with the main results, but for some treatments, the effects in terms of QALYs were similar to the base case. For scenario 2.2a, the impact of the RSAs followed the same pattern as in the main results with RSA ICERs, ranging from €1957 to €82,325. However, in scenario 2.2b, incremental mean total costs were much lower than in scenario 2.2 (−€617 vs. −€3196 per patient). In scenarios 2.3a and 2.3b, the impact on costs and effects had the same direction as in the main results of scenario 2.3 with RSA ICERs ranging from €457 to €122,925. The impact of RSAs in scenario 3.1a and 3.1b had a similar pattern as in scenario 3.1 with cost savings ranging between −€817 and −€11,795 per patient. When the first two cycles were offered for free (scenario 4.1a), the cost savings were larger than when only the first treatment cycle was offered for free (scenario 4.1). Larger cost savings were also seen when a 75% discount was applied to the first 9 weeks of treatment (scenario 4.2a) instead of a 50% discount (scenario 4.2). For scenario 5.1a and 5.1b, the cost savings followed the same pattern as in scenario 5.1. However, when we assumed that treatment was discontinued when the patient did not show an adequate response within a maximum four instead of three cycles, a few treatments in scenarios 2.1, 2.1, 2.3, and 5.1 showed no differences compared to the base case costs. This was due to the fact that most patients did not receive more than four treatment cycles, and thus these patients discontinued treatment after four cycles anyway.

Discussion

This research shows the expected impact of a range of theoretical RSAs. It illustrates that the impact on mean total cost per patient can differ substantially between RSAs as well as between drug regimens within the same RSA. Furthermore, it illustrates that one type of RSA (a conditional treatment continuation scheme) can adversely affect patient outcomes, when treatment is discontinued prematurely and this results in reduced patient survival. The effect of early treatment discontinuation for nonresponders may differ between drugs, depending on the probability of delayed response with continued treatment.

Looking at our results, RSAs show a larger cost impact in metastasized NSCLC than in nonmetastasized NSCLC, despite shorter survival times in the metastasized setting. This is partially due to higher costs of some regimens in the metastasized setting and partially due to lower proportions of responders with metastasized NSCLC, for example, because patients were more

Table 3 – Effects of different types of risk-sharing arrangements, from the perspective of the payer.

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilization caps	Fixed cost per patient
Δ Total costs for the payer	Increase?	No	Yes, when the costs of the design, implementation, and execution of the RSA are higher than the cost savings because of the RSA.	Yes, when the costs of the design, implementation, and execution of the RSA are higher than the cost savings because of the guarantee.	No	No	Yes, depending on the level of the fixed cost that is agreed upon. In the drugs discussed in this study, cost per patient were generally lower than originally projected, which results in potential losses to the payer if fixed costs are based on prelisting projections.
	Equal?	Yes, when the savings equal the cost of the RSA.	Yes, when the savings equal the cost of the RSA.	Yes, when the savings equal the cost of the RSA.	No	No	Yes, depending on the level of the fixed cost that is agreed upon.
	Decrease?	Yes, when the prespecified endpoint was not reached, either by (a proportion) of patients (e.g., nonresponders, scenario 1.1), or by the population (e.g., median OS, scenario 1.2), and this results in savings that exceed the cost of the RSA. Increase: when the costs of the design, implementation, and execution of the RSA are higher than the cost savings because of the guarantee.	Yes, when the condition was not met for a proportion of patients (e.g., nonresponders) and the resulting savings exceed the cost of the RSA.	Yes, when the prespecified endpoint was not reached, and this results in savings that exceed the cost of the RSA.	Yes, it is likely that this RSA reduces costs for the payer, since the initial part of a treatment is discounted. The cost of the RSA is likely limited, since it does not require real-world data collection.	Yes, it is likely that this RSA reduces costs for the payer, since only the initial part of a treatment must be paid for. The cost of the RSA is likely limited, since it does not require real-world data collection. It may be most valuable in oncology, since treatment duration is highly variable in this area (e.g., patients are treated until disease progression).[4]	Yes, depending on the level of the fixed cost that is agreed upon.
Δ Total outcomes for patients	Increase?	No	No	No	No	No	No
	Equal?	Yes, patient outcomes are not affected.	Yes, when the condition is met for all patients, or when early treatment discontinuation does not reduce patient outcomes.	Yes, patient outcomes are not affected.	Yes, patient outcomes are not affected.	Yes, patient outcomes are not affected, provided that patients can continue treatment beyond the utilization cap (i.e., sponsored by the pharmaceutical company).	Yes, patient outcomes are not affected.
	Decrease?	No.	Yes, when the condition is not met for all patients, and early treatment discontinuation reduces patient outcomes.	No	No	No	No
Type of uncertainty it manages		Uncertainty around the benefits of a treatment, for example, response rates, PFS, or OS. The less evidence available at the time a reimbursement decision is made, the higher the money-back value.[27] Hereby, it manages uncertainty around the incremental	Uncertainty around certain (intermediate) benefits of a treatment that can be measured during treatment, for example, response rates. Hereby, it manages uncertainty around the incremental cost-effectiveness of the treatment.	Uncertainty around the benefits of a treatment, for example, response rates, PFS, or OS. Hereby, it manages uncertainty around the incremental cost-effectiveness of the treatment.	Uncertainty around the benefits of a treatment, and especially when the benefits are expected to be highest for patients who continue treatment beyond an initial, prespecified period. It is also a way to reduce costs and therefore budget impact.	Uncertainty around the average duration of treatment: especially when the payer wants to facilitate that all patients can try the treatment, but wants to limit the costs associated with extended treatment durations. This RSA may be most beneficial in case there is limited	Uncertainty around the average duration of treatment or the dosages patients will receive. It reduces uncertainty about the budget impact of a treatment.

continued on next page

Table 3 – *continued*

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilization caps	Fixed cost per patient
		cost-effectiveness of the treatment.				evidence on whether longer treatment durations result in additional benefits.	
	Potential adverse effects	• May substantially increase registration burden, since it is dependent on real-world outcomes. • Is dependent on the widespread acceptance of a definition of the outcome of interest (e.g., response), the reproducibility of this endpoint, and the independence of adjudicators.[4,28] Moreover, the method of measuring outcomes should ideally be simple and outcomes should be clearly defined. • May not result in cost savings even when the drug performs worse than expected. For example, if the money-back guarantee was based on improving median OS and the drug of interest did not improve median OS, this might not actually be obvious from real-world data. For example, OS might have been improved by another, later-line drug becoming available since the introduction of the RSA. • May not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high.	• May reduce patient outcomes when treatment is discontinued in patients who would have benefitted later. • May lead to undesirable effects, especially when an effective alternative treatment is not available for non-responders who must discontinue the treatment. • May substantially increase registration burden, since it is dependent on real-world outcomes. • Is dependent on the widespread acceptance of a definition of the outcome of interest (e.g., response), the reproducibility of this endpoint, and the independence of adjudicators.[4,28,29] Any misclassification of responders may lead to unjust discontinuation of treatment. • May not be possible in certain disease areas where there are no universally accepted short-term response or benefit measures. • May not be acceptable to clinicians and patients, as it forces clinicians to treat their patients in a predefined way (i.e., stop treatment while there might still be benefit to gain from it). • May not result in cost savings even when the drug performs worse than expected, for example, when other improvements in care processes (e.g., better supportive care) improve the intermediate outcome of interest.	• May substantially increase registration burden, since it is dependent on real-world outcomes. • Is dependent on the widespread acceptance of a definition of the outcome of interest (e.g., response), the reproducibility of this endpoint, and the independence of adjudicators.[4,28] Moreover, the method of measuring outcomes should ideally be simple and outcomes should be clearly defined. • May not result in cost savings even when the drug performs worse than expected, similar to the example for the money-back guarantees. • May not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high.	• May not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high.	• May not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high. • Is dependent on the availability of health outcomes data, since an agreed upon utilization threshold should be established.[4]	• May result in higher costs for the payer than in a situation without an RSA. • May not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low.

OS, overall survival; PFS, progression-free survival.

heavily pretreated. If the aim of RSAs is to reduce the risk to the payer, they are most favorable in clinical settings with considerable uncertainty regarding response rates, survival, patient numbers, or any other characteristics that affect budget impact. When these uncertainties do not exist, RSAs lose their value.

Based on the results of this study, the choice of whether and which type of RSA to use should depend on a careful analysis of the type of outcomes expected, and the type of uncertainty one aims to manage, reduce, or share. This is also reflected in the RSA ICERs, which differ substantially for different drug regimens within the same RSA scenario.

Health care payers generally will not be able to force a pharmaceutical company into an RSA that the company considers unacceptable. Negotiations will be dependent on the perceived value of the drug, the willingness of the payer to reject the drug for reimbursement in case the company is not willing to accept the RSA, and the viable price range for the company.[11] Even when a performance-based RSA is agreed upon and drug performance turns out to be limited, difficulties with the clinical evidence may cause discussions and delays in effectuating refunds or price cuts. In such instances, negotiating power from the payer may be limited because patients are already receiving the drug and it is difficult to remove from the market.

Interpretation of clinical evidence can be difficult and there is a lack of guidance for decision makers on how to quantify performance of drugs in the context of performance-based RSAs. Many pharmaceuticals are not prescribed as monotherapy (e.g., chemotherapy plus immunotherapy), which means that improved clinical outcomes can be attributed to multiple compounds. Furthermore, patients may receive treatment sequences that may change over time and may hamper the interpretation of clinical evidence. For example, in the context of an Australian managed entry scheme for ipilimumab in melanoma, it was found that the availability of postipilimumab treatments (e.g., dabrafenib, trametinib, pembrolizumab, and nivolumab) via compassionate access programs might have affected survival rates. Survival was higher than in the pivotal trial and refunds to government were not required.[12]

It is important to note that the success of RSAs should not (solely) be measured by their impact on reducing costs to the payer. Even when an RSA does not result in effective price reductions compared to a situation without RSA, it may result in reduced uncertainty for a payer who aims to maximize value for money.

An additional benefit of RSAs is that when an RSA results in a reduction of the effective price of drugs without reducing the list price, this may prevent companies from having to offer a similarly low price in other countries that adopt less stringent cost-effectiveness requirements. Even though confidential price reductions are common independent of RSAs, RSAs may provide payers and companies with another tool to reduce effective prices without impacting the list price.

Limitations

It should be recognized that shifting part of the cost away from payers to pharmaceutical companies may reduce incentives for (potentially risky) investment decisions by pharmaceutical companies. The potential impact on investments in research & development was not considered in this study. Also, the study did not consider the costs of designing, implementing, executing, and reviewing RSAs, or who would bear these costs. These costs may be substantial, especially in case real-world, patient-level data collection is required; however, these costs are highly context dependent and have not been published for the various types of RSAs.

Because we used a retrospectively collected dataset subtracted from medical records, data quality was determined by the information registered in the hospitals. Although chemotherapy treatment information is generally carefully registered, sometimes information was missing in the medical record (e.g., dosage) and had to be estimated (e.g., based on body weight). Moreover, because some patients were treated in multiple hospitals and data of these patients could only be obtained for the study hospitals, patients were censored from the moment they were referred to a nonstudy hospital. Despite these limitations, the dataset was highly suitable to perform these analyses. As opposed to most real-world datasets (such as administrative datasets), our data were specifically collected for pharmacoeconomic purposes and contained detailed information on resource use, costs, and also a large number of clinical outcomes, including type and date of tumor response/progression. These data enabled us to do the "what-if" analyses.

The study population could be considered as representative of the Dutch NSCLC population with regard to the distributions of age, gender, and tumor histology, but a relatively high proportion of patients was classified with clinical stage I–III (61% vs. 47%). Therefore, the representativeness of the study population is not guaranteed. Depending on a hospital's patient population, the impact of RSAs may differ substantially. Among others, RSAs may have a larger impact in academic/specialized hospitals as expensive drugs are more often prescribed in these centers.

Results in this study were not corrected for censoring, and therefore costs, QALYs, and RSA ICERs represent the study period only. Correction for censoring would increase the costs and QALYs because it would incorporate (an estimate of) the costs and QALYs that were accrued after the study by patients who were still alive at the end of the study period. It is unknown whether this would have an effect on the perceived relative benefits of RSAs.

The current analyses calculated the costs and outcomes associated with theoretical RSAs, assuming that all other things would remain equal. It is not an experimental study, but a study based on a retrospective patient registry. Therefore, it does not consider potential changes in prescribing behavior by clinicians in response to the RSA or potential changes in price setting by pharmaceutical companies. However, the study does not claim to predict what would happen in case of implementing these RSAs for these selected drugs, but instead provides insight into the range of different effects RSAs might have on costs and outcomes of a drug. Potential "adverse effects" of RSAs were discussed in Table 3. The drugs that were chosen are merely used as case studies, and it is not suggested that any type of RSA should have been implemented for any of these drugs.

Note that the results presented in this study (Table 2) do not include the acceptability of a certain RSA for patients or their doctors. For example, in certain treatment areas it may be considered unethical to implement a conditional treatment continuation scheme that declines nonresponders the option to continue a drug that might work for them in the future. Although drug restrictions can result in similar situations without RSAs, RSAs may be more controversial in case of potential detrimental effects on the quality of life or survival of patients.

"Expenditure caps" and "price–volume agreements" were excluded from analyses in this study, because these types of RSA require population-level utilization data. These RSAs aim to mitigate uncertainty around the budget impact and could be considered when there is uncertainty surrounding the average treatment duration or expected patient numbers.

This article did not discuss the option of implementing an RSA that combines aspects of different types of RSAs, such as a utilization cap combined with discounted treatment initiation.[13] Furthermore, the article did not discuss the practical aspects of how RSAs are implemented, which can determine their benefit.

For example, an RSA may be implemented as a cap on total budget impact, when there is uncertainty in the length of treatment, number of patients, or both. However, this could result in a situation where fewer patients receive the drug than predicted, but they take it for longer than expected. In this case the budget impact cap may not be reached, but the extended use per patient may render the drug cost-ineffective. As a result, RSAs that are implemented based on budget impact thresholds may form an incentive for drug companies to overestimate initial budget impact forecasts in reimbursement submissions, so that subsequently determined budget impact thresholds will not reduce their expected sales.

Lastly, the scope of this study was limited to the impact of RSAs on NSCLC treatments. However, the principles of RSAs are similar for other treatments within and beyond oncology. The value of RSAs in other populations depends on the uncertainty of the value of treatments in populations, the costs of these treatments, and the extent to which clearly defined outcomes (like tumor response and death) can be identified.[4]

Further Research

Further research regarding the costs of designing, implementing, and executing RSAs (e.g., transaction costs, administrative burden, and data collection) is recommended. Also, attitudes of clinicians, pharmaceutical companies, and payers to different types of risk-sharing should be studied, to inform acceptable RSAs that are beneficial to society without being detrimental to patient health and care.

Conclusions

RSAs can mitigate uncertainty around the incremental cost-effectiveness or budget impact of drugs. However, the choice of whether and which type of RSA to use should depend on a careful analysis of the type of outcomes expected and the type of uncertainty one aims to reduce.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.08.007.

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