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Manufacturers' views on outcome-based agreements

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ABSTRACT

Introduction: Outcome-based agreements (OBAs) are occasionally deployed to relieve the burden of high drug prices on healthcare budgets. However, it is not clear when manufacturers are willing to collaborate in establishing such agreements. Therefore, we explored the feasibility of OBAs from the manufacturer's point of view.

Methods: Dutch market-access experts from eight major pharmaceutical companies, globally active in the field of oncology, were interviewed. Opinions were compiled, and interviewees and their colleagues were then given the chance to review the manuscript for additional comments.

Results: Most interviewees believe that OBAs can be useful in providing access to off-label use of authorised medicines, especially when no alternative treatment is available for seriously ill patients. For the licenced indications, manufacturers seem to be more inclined to collaborate when there is a potential incentive to improve market-access (e.g., if the product is not used because of concerns regarding its effectiveness). However, manufacturers are less likely to collaborate when there are greater financial risks for the company. Further concerns were definition of outcome or performance, the impact of compliance on the effectiveness of a drug, administrative burden, uncertainty regarding revenue recognition and the challenges of reimbursing combination therapies.

Discussion: Market-access interviewees were generally positive about OBAs, however they were more reluctant towards OBAs for registered indications with low response-rate. The definition of performance or outcome and its clinical relevance and validity, the feasibility of OBAs and their administrative burden are relevant aspects that need to be addressed in advance. Ideally, countries should collaborate to share the outline of OBAs and create shared databases to accumulate evidence.

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Introduction

Increasingly, more expensive compounds are entering the market based on limited clinical evidence and with great uncertainty regarding their real-world effectiveness. Recent studies show that oncology drugs, which are registered based on single-arm studies are often not fully evaluated in subsequent randomised clinical trials or post-marketing studies [1–3]. In those cases when subsequent randomised clinical trials are carried out but the drugs fail to demonstrate clinical benefit, no refund or compensation is provided to the patients or payers. An example is olaratumab: thousands of sarcoma patients were treated globally with olaratumab between 2016 and 2019 [4], until the ANNOUNCE-trial data demonstrated that adding this compound to doxorubicin had no effect on overall-survival[5].

High prices of drugs are a burden to public and healthcare-systems. As a consequence, payers wish to reduce the financial risks associated with high-cost medicines, especially when there is uncertainty regarding their real-world effectiveness. This can be done by using performance-based schemes also known as outcome-based agreements (OBAs), in which payers can shift part of the financial risks to manufacturers. Needless to say, OBAs can only be rolled out when both payers and manufacturers are willing to share the financial risks. In order to find out manufacturers' views, we interviewed market-access experts of eight major multinational pharmaceutical companies active in the field of oncology.

Material and methods

We approached (by e-mail) market-access experts from eleven pharmaceutical companies, globally active in the

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field of oncology, to ask for their personal views on OBAs. All experts were based in the Netherlands, their participation was voluntary and unpaid, and their opinion was used anonymously. The experts were asked to: 1) propose what type of products or indications might be suitable for OBAs, 2) elaborate whether the available level of clinical evidence is of relevance for the willingness to reach an agreement, and 3) advise on potential objections to OBAs. The experts shared their personal opinion either by e-mail or by telephone interview, based on their own preferences. The opinions were then compiled into categories. The experts were allowed to consult with colleagues and share the manuscript for additional comments.

Results

Eight of the eleven experts were willing to share their opinion on OBAs. The results were then compiled in a draft manuscript and reviewed by the experts. In six cases, more than one person within the company reviewed the manuscript. In answering the questions regarding the types of product-indication pairs that are most suitable for OBAs and the relevance of the level of evidence, three major categories could be identified:

OBAs for approved indications based on limited data (e.g., phase II trials)

Most interviewees were positive about an outcome-based approach, provided that there is uncertainty about the effectiveness of the products in a certain subgroup or overall. For instance, if the product is not implemented in the clinic or guidelines or if it is not reimbursed because of uncertainty regarding the effectiveness or a negative assessment by health technology assessment (HTA) bodies, payers or clinical experts, OBAs may resolve concerns regarding effectiveness and help to spend the public funds responsibly. Other potential candidates are products for which traditional phase III trials are less feasible, e.g., drugs developed for tumour-agnostic indications or rare mutations. Precision medicine, combined with OBAs can potentially reduce waste in healthcare and contribute to the social affordability of effective but expensive treatments.

OBAs for approved indications based on phase III trials but for which number needed to treat (NNT) is considered high

Most interviewees thought that OBAs would not be plausible when a relatively high number of patients need to be treated in order to avoid an event, as it would be too costly for the manufacturer. Only in certain circumstances such agreement might be considered, for instance if there is a competitive landscape. However, even in such cases it might be easier to provide discounts instead of setting up complicated OBAs. Some interviewees emphasised that their companies are dedicated to biomarker research to further identify predictive factors of tumour response. In the future, it is expected that machine-learning algorithms can predict response and improve outcomes.

OBAs for off-label indications

The interviewees were familiar with the recently implemented pilot OBA, which provides access to nivolumab for MSI-H tumours in the Netherlands[6]. In this OBA, which concerns an off-label indication, manufacturers provide drugs free-of-charge for the first 16 weeks of treatment. After 16 weeks and two radiological response assessments based on Response Evaluation Criteria in Solid Tumors (RECIST)[7], the clinical benefit will be determined. If there is clinical benefit (stable disease, partial or complete response), the costs of continued treatment will be reimbursed by the health-insurance. Generally, the interviewees were positive about OBAs, especially when market-access is needed for patients with serious illness, for whom no alternative treatment is available. This is a practical way to provide access when a manufacturer has no intention to further develop the product in that indication. However, if the manufacturer eventually decides to submit a dossier to the regulatory authorities at a later stage, it would be helpful if the data can be used for the adaptive pathways approach.

One expert indicated that OBAs can be useful in making drugs available to the paediatric population. Most interviewees believed that there should be an acceptable level of clinical evidence (minimally a phase II trial), before making structural arrangements for an off-label indication.

Finally, the responders were asked to express their concerns and objections. One of the concerns was the definition of performance. Overall-survival gain is an important outcome, but mostly not feasible because of the effects of subsequent treatments. Therefore, surrogate endpoints can be used. In fact, some interviewees argued that an OBA is only feasible if the performance can be measured after a short period of time, for instance by using surrogate endpoints. It would be important to involve all stakeholders, to develop a common ground for defining (surrogate) outcome-measure and their clinical relevance.

According to interviewees, the medical society remains the most relevant stakeholder in determining the outcome. In addition, it is important to have a uniform evaluation of the response between centres, which is applicable to various tumours.

One expert emphasised that OBAs should be considered as instruments for providing access to innovative treatments, especially when routine reimbursement pathways do not provide satisfactory solutions. In order to provide a structural solution, nation-wide registries and OBAs need to be embedded in the national reimbursement system. Another expert argued that HTAs should be benchmarked with similar assessments in other countries to be able to arrange feasible agreements.

Two interviewees believed that OBAs should be flexible; and it should be possible to adapt the inclusion-criteria or stop-criteria based on new insights. Therefore, it is important to build regular evaluation points in OBAs. Several interviewees expressed their concern regarding the impact of treatment non-compliance on the effectiveness of the drug. They proposed that adherence, co-medication and comorbidities should be monitored.

Another concern was administrative burden: collecting patient data can be costly and a broad implementation is complex. Besides, companies may face great uncertainty regarding revenue recognition, which makes administration complex, for both the accounting and commercial aspects.

One expert argued that pay-for-benefit is a more practical approach to OBAs. With pay-for-benefit, no clinical outcome is measured, as the agreement is simply based on treatment duration. Eventually, all events leading to treatment-discontinuation (progression, side-effects or death) are reflected in pay-for-benefit. Pay-for-benefit is scalable and has a low administrative burden as data can be extracted from the insurance claim-records. In addition, no consensus is needed regarding the definition of performance or outcome. Pay-for-benefit or fee per treatment may also offer a solution for combination therapies (e.g., by splitting the fee between companies either equally or based on the estimated value of their products).

Discussion

As increasingly more oncology drugs are entering the market based on non-randomised studies, OBAs can become more prevalent, replacing part of the current standard of 'paying for pills'. Our results show that manufacturers are more inclined to collaborate, when there is a potential incentive to improve market-access for a licenced indication, for instance, if a product is not used or reimbursed because of concerns regarding its effectiveness. Evidently, manufacturers are less likely to collaborate when there are greater financial risks for the company (e.g., high NNT).

Measuring performance or outcome is a key step for an OBA. OBAs are therefore more complicated than regular price discounts. Some market-access experts believe that it is crucial to be able to measure performance rapidly and therefore surrogate endpoints should be used. However, this can complicate negotiations, as surrogate endpoints may not closely correlate with clinical outcomes and therefore be of less value to payers. Ideally, the validity of surrogates for each indication needs to be assessed in advance using the guidelines of the relevant HTA-agency. The outcome should be specified in quantitative terms, can be measured timely and objectively and should be relevant to the patient's health and survival. In some cases, it is relevant to monitor patients' adherence, so that the outcome is not affected by lack of compliance. Another concern was the administrative burden. Pay-for-benefit was discussed as a less complex alternative, as the required data can be extracted from the insurance claim-records. However, there seems to be no one-size-fits-all formula for designing and implementing OBAs.

The general belief is that OBAs can be useful in providing access to off-label use of authorised medicines, especially when no alternative treatment is available for seriously ill patients. Experts also agreed that at least a minimum level of clinical evidence (e.g. a phase II trial) is required for willingness to reach such an agreement. Recently, we implemented a pilot OBA in the Netherlands for the off-label use of nivolumab for MSI-H tumours[6]. Nevertheless, we believe that agreements on off-label indications with limited evidence should be considered with utmost care.

The government in the Netherlands has introduced a conditional reimbursement policy for medicines that are registered based on low-level of evidence (e.g., medicines with conditional-marketing authorisation and approvals under exceptional-circumstances or orphan-designations) and do not meet the HTA-requirements. The manufacturer has to submit a research proposal and provide relevant data at a later stage. The proposal should be prepared in collaboration with healthcare professionals, patient-advocacy group and an independent research institute. This allows controlled-access to medicines and the collected data can support final decision-making at a later stage[8].

Recently, Eichler et al.[9] explored the feasibility of OBAs by interviewing reviewers from seven competent

authorities for pricing and reimbursement. The type of product that can be considered as an OBA is described as a novel treatment with easily measurable outcomes for an unmet medical need but with uncertainty regarding its budget-impact or clinical value. Nonetheless, in situations where the price and budget-impact are the main issues, other financial agreements can be used such as discounts, budget-caps or price-volume agreements. In general, OBAs were not often the preferred option for payers due to practical hurdles including manufacturers' unwillingness to collaborate, differences in perception of value and administrative workload[9].

One shortcoming of this paper is that we only focused on major international companies. Views of companies can differ according to their size and their ability to take greater financial risks. In addition, the findings should be treated with caution, given the small sample size and the fact that the ideas presented are the personal views of Dutch market-access experts and not the official standpoints of their companies. In most cases, however, the aggregated results were reviewed by more than one person within each company. In addition, the umbrella organisation for pharmaceutical companies in the Netherlands (VIG) also reviewed the manuscript. Therefore, we assume that we have obtained representative opinions, which provide valuable insights in manufacturers' perspective.

Ideally, payers and HTA-bodies of different countries should collaborate to share the outline of OBAs and create shared databases to accumulate evidence. A close collaboration with regulatory agencies can help to address the uncertainties regarding the effectiveness and safety of each drug when setting up national or cross-border databases. Whether the OBAs eventually offer a sustainable solution for the high prices of novel therapies remains to be explored.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Précis

Outcome-based agreements are likely to become more prevalent in the future.

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