Rethinking the reimbursement of innovative medicines in oncology: Looking beyond overall survival

M. Piccart, MD, PhD[1], J. Vansteenkiste, MD, PhD[2], H. Prenen, MD, PhD[3], F. Duhoux, MD, PhD[4], A. Janssens, MD, PhD[2], M. Delforge, MD, PhD[2], A. Awada, MD, PhD[1], P. Neven, MD, PhD[2], A. Sibille, MD[5], B. Neyns, MD, PhD[6]

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ABSTRACT

The oncological treatment landscape is evolving at a very rapid pace with a continuous stream of novel treatment options. To fully leverage these therapeutic advances in clinical practice it is important to facilitate a rapid access to innovative anticancer drugs for patients. Specifically for Belgium, the delay from EMA approval to reimbursement for anticancer drugs is very long, with an average of almost 600 days, and a substantial proportion of innovative drugs never make it to the patient. The stringent focus of the Belgian Commission for Reimbursement of Medicines (CRM) on OS data in reimbursement decisions is believed to be an important contributor to this situation. However, the ever-increasing pace at which new anticancer therapies are being developed in combination with an earlier detection of cancer will make it increasingly difficult to present mature OS data at the time of regulatory approval in the years to come. As such, there is an urgent need for a debate with the regulators to consider more readily available endpoints in their reimbursement assessments. In fact, when a strong treatment effect is seen on an intermediate endpoint such as disease-free or progression-free survival, a benefit in OS is quite likely. As such, our reimbursement system needs to be adapted to better align with the scientific progress in oncology. In this, a temporary reimbursement decision based on intermediate endpoints could give Belgian patients earlier access to promising life-saving medicines. In this, we as oncologists, including specialists in haematology, respiratory oncology, and gastrointestinal cancer, strongly encourage the CRM to use the grading provided by the ESMO magnitude of clinical benefit scale to evaluate the clinical added value of future cancer treatments. This will not only facilitate a faster patient access to innovative therapies, but will also help policy-makers in advancing 'accountability for reasonableness' in their resource allocation deliberations.

INTRODUCTION

The management of cancer is evolving at an ever-accelerating speed, leading to an earlier cancer detection and an increasing treatment personalisation ultimately resulting in a better prognosis for patients.[1] However, in order to allow patients to benefit from this scientific evolution, they need to have access

[1]Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium, [2]Respiratory Oncology Unit, University Hospitals Leuven, Leuven, Belgium, [3]Department of Oncology, University Hospital Antwerp (UZA), Antwerp, Belgium, [4]Department of Medical Oncology, Cliniques Universitaires St-Luc, Brussels, Belgium, [5]Pneumology - Allergology Department, CHU de Liège, Liège, Belgium, [6]Medical Oncology Department, University Hospital Brussels, Brussels, Belgium.

Please send all correspondence to: J. Vansteenkiste, MD, PhD, Kortrijkstraat 27, 3210 Linden, Belgium, email: johan.vansteenkiste@uzleuven.be.

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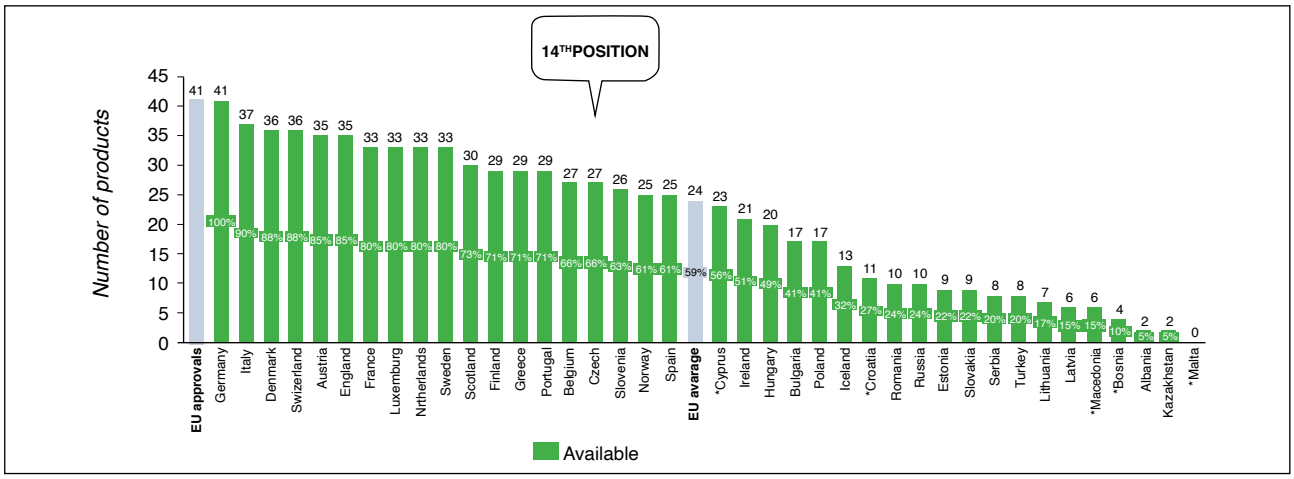

FIGURE 1 . Rate of availability, measured by the number of medicines available to patients in European countries as of 1st January 2022, based on a total of 41 EMA approvals between 2017 and 2020.[7]

to the most effective treatment option for their particular tumour type. Before patients can receive a new treatment, it first has to be approved by regulators such as the European Medicines Agency (EMA). In this, the EMA carries out a thorough assessment of the clinical data obtained with the treatment in question to decide whether or not the medicine is safe, effective and of good quality, and is therefore suitable for use in patients. In their assessment reports, each team summarises the data from the application, presents its judgments of the medicine's effects and its views on any uncertainties and limitations of the data. They also identify questions that will have to be answered by the applicant. After EMA approval is being granted, governmental bodies ('payers') of the individual European member states have to assess whether they consider this new treatment option eligible for reimbursement. Whereas regulatory agencies largely base their decisions on a trade-off between the clinical added value of a novel therapy compared to the current standard of care and judge on any uncertainties and limitations of the data, the payers focus on allocating a set healthcare budget to those treatments that will likely yield the best outcome in terms of mortality, morbidity, and quality of life (QoL). As a result, payers and regulators use different parameters in their evaluation of novel treatment modalities. For payer-decisions, overall survival (OS) data remain the gold standard. Notwithstanding the fact that OS is a crucial endpoint in the oncological setting, a stringent focus on OS data can stand in the way of a rapid access to new medicines that can improve the outcome of patients with cancer. For example, in early disease stages it can take a (very) long time for OS data to mature. In both the early and advanced cancer setting, the use of subsequent lines of therapy can make it challenging to prove the true OS effect of a given treatment.[2,3] This raises the ethical dilemma of waiting until there is clarity on the OS impact of a novel treatment, a process that may take several years, and giving patients rapid access to innovative treatment options. To overcome this dilemma, regulatory agencies also base their decisions on alternative oncology-related endpoints, such as progression-free or disease-free survival when evaluating a new treatment option.[4] This is however far less the case for payers. As a result, the focus of payers on OS data leads to a delayed access to regulatory-approved treatments, which may lead to treatment-eligible patients missing out on effective treatment options.[5]

The ever-increasing pace at which new anticancer therapies are being developed in combination with an earlier detection of cancer will make it even more difficult to present mature OS data at the time of regulatory approval in the years to come. As such, there is an urgent need for a debate with the regulators to consider more readily available endpoints in their reimbursement assessments. This will allow for a faster access to new medicines, without lowering the safety and efficacy thresholds of the evaluations.

REIMBURSEMENT OF ONCOLOGY DRUGS IN BELGIUM: ROOM FOR IMPROVEMENT

According to European regulations, the decision on the reimbursement of a novel EMA approved drug in the different member states needs to be taken within 180 days. However, during this period, the producer of the drug has the chance to issue a clock stop allowing them to provide more information to the decision makers. The advice whether to reimburse a new drug in Belgium has to come from the Belgian Commission for Reimbursement of Medicines (CRM), which is composed of representatives of the different health insurers, academics, physicians, and pharmacists. After its evaluation,

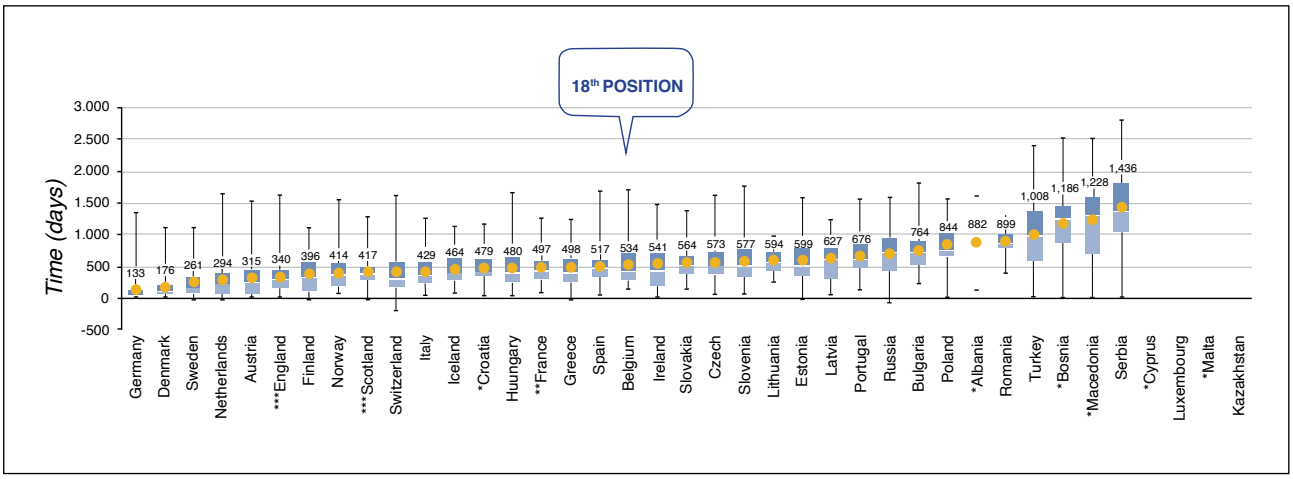

FIGURE 2 . Time from central approval to availability, in days between marketing authorisation by EMA and the date of availability to patients in European countries.[7]

the CRM can advise for a definitive or temporary reimbursement, advice not to give a proposal, or advise not to reimburse the medicine in question. In case of a temporary reimbursement, the reimbursement process is transferred to a working group convention for further negotiation on the solidity of the scientific data and the potential budget impact. This procedure (managed entry agreement, MEA) has the advantage that patients are allowed access to the drug in question and gives the applicant the time to provide extra information if requested. Reimbursement through an MEA also has the advantage that the government can reduce the financial risk associated with the reimbursement of drugs that are associated with a certain level of uncertainty (clinical and/or financial). The applicant company can be asked to give refunds and/or to collect additional evidence. On the other hand, the increasing refunds in MEA also put increasing pressure on the pharmaceutical industry, which in turn may affect the willingness to invest in oncological research, including the set-up of future clinical trials in Belgium.[6]

According to data from the European Federation of the Pharmaceutical Industry, 41 oncological drugs received an EMA marketing authorisation between 2017 and 2020.7 In January 2021, only 27 of these drugs (66%) were reimbursed in Belgium. While this 66% exceeds the average of 59% across the entire European Union, Belgium is lagging behind most other Western European countries in this ranking (*Figure 1*). The Belgian situation is even more complex when looking at the time between EMA marketing authorisation and reimbursement. In fact, in Belgium this process takes 534 days on average, referring Belgium to the 18th place in the European ranking (*Figure 2*).[7]

In contrast, Belgium ranks among the top European countries when it comes to participation in clinical trials. This leads to the paradox that Belgian cancer patients often have better access to new treatment options prior to marketing authorisation than afterwards.

Over the years, several initiatives have been launched to improve and speed up the access to innovative drugs in Belgium (e.g., unmet medical need procedures). However, in order to provide a universal framework the Belgian Ministry of Health is currently working on a novel reimbursement procedure. This initiative could create a momentum to argue in for a bigger acceptance of non-OS data in the reimbursement evaluation of novel anticancer agents.

SUPPORTING DECISION MAKING IN THE ABSENCE OF OS DATA

As indicated before, certain clinical situations make it difficult to demonstrate an OS benefit for a novel anticancer agent at the time of the reimbursement negotiation. In these situations, it is clear that endpoints that measure disease status and/or the impact of the disease on patients can have an intrinsic value in assessing the efficacy and safety of the treatment at hand. In fact, it has been demonstrated that certain intermediate endpoints can be used as a surrogate for OS in specific situations. For example, disease-free survival (DFS) or relapse-free survival (RFS) were shown to be good surrogates for OS in the adjuvant treatment of colon cancer, gastric cancer, melanoma, and HER2-positive breast cancer.[8] Similarly, in patients with HER2-positive metastatic breast cancer, a significant correlation was demonstrated between progression-free survival (PFS) and OS.[9] In hematological malignancies, minimal residual disease (MRD) has been identified as a strong surrogate marker for both OS and PFS.[10,11]

In recent years, regulatory agencies (e.g., EMA, FDA) are increasingly accepting these endpoints as a basis to approve

a novel treatment in the absence of OS data. For example, more than 70% of the FDA-approvals for adult cancer drugs approved between 2006 and 2017 were based on PFS or RFS data.[12] Similarly, 39% of all the EMA approvals of oncology drugs between 2014 and 2017 were granted at the time of immature OS data.[13]

In contrast, these non-OS endpoints remain to be questioned during reimbursement negotiations. In this respect, a recent position paper by *Lux et al.* argues that the fact that OS data are not available or are limited at the time of the reimbursement decision should not itself prevent patient access, provided that other clinically-meaningful and patient-centred benefits that were pre-specified in the trial design have been demonstrated.[14] A similar claim was made by a global expert group in a report from the Boston Consulting Group on the value assessment of novel cancer therapies.[4] In this report, the experts urge to consider oncology-relevant endpoints other than OS in this value assessment and underscore the importance of building up further evidence on the use of non-OS endpoints that provide an earlier indication of treatment efficacy.[4]

In recent years, several tools have been developed that can help to mitigate the uncertainties that come with reimbursement of an agent in the absence of mature OS data.[4] The most relevant of these tools for the European situation consists of the magnitude of clinical benefit scale developed by the European Society of Medical Oncology (ESMO-MCBS).[15,16] The objective of the ESMO-MCBS is to present a clear and unbiased statement regarding the magnitude of clinical benefit from new therapeutic approaches based on the results of high-quality clinical trials. By using a rational, structured, and consistent approach, new oncological therapies are ranked with a score reflecting the magnitude of clinically meaningful benefit that can be expected.[15] The tool is developed as a generic instrument, applicable to all types of cancer. Importantly, apart from OS data, the ESMO-MCBS scale also uses threshold hazard ratios for PFS and DFS, response rate, QoL and toxicity data, and takes the prognosis of the condition in which the new treatment is being evaluated into consideration.[15] In doing so, the scale aims to distinguish treatments that substantially improve the duration of survival and/or the QoL of patients from trials demonstrating more limited or sometimes even marginal benefits.[10] The scoring system of the ESMO-MCBS is based on the following premises:

1) Cure takes precedent over deferral or death.
2) Direct endpoints such as OS or QoL take precedent over 'surrogates' such as PFS or response rate.
3) DFS in a curative setting is a more valid surrogate than PFS in a non-curative setting.
4) The interpretation of the evidence for a benefit derived from surrogate outcomes (such as PFS, or response rate) may be influenced by secondary outcome data.
5) The tail of the curve data may sometimes indicate an im portant gain for a minority of responders, and finally,
6) Data from randomised controlled trials are more credible than data coming from single arm studies.

In total, ESMO-MCBS uses five different scoring cards depending on the disease setting (curative *vs.* non-curative) and the information available in the peer reviewed publication of the clinical trial that led to the licensed indication of the treatment. Evaluation form 1 is used to classify novel adjuvant or potentially curative therapies as grade A, B or C, with grades A and B being approaches providing a substantial benefit.[15,16] The idea behind this rating is that reimbursement of therapies with an A or B rating is the best way to strive for equality in cancer care across all countries of the European Union. In the non-curative setting, separate evaluation forms have been developed for trials with OS (form 2a), PFS (form 2b), or another measure (form 2c) as primary endpoint. In this, forms 2a and 2b use separate sheets in function of the median OS or PFS that can be achieved with the existing standard of care. Finally, form 3 was developed for the evaluation of single-arm studies in "orphan diseases" and for diseases with "high unmet need" in which the primary outcome is PFS or response rate. When using form 2a, a treatment modality can get a grade of 1 to 5, whereas studies that require forms 2b, 2c or 3 can only get a grade of 1 to 4. In the non-curative setting, grades 4 and 5 indicate a substantial magnitude of clinical benefit.[10,11] and thus similarly should get reimbursement to provide equality in cancer care across all countries of the European Union.

On June 1st 2023, the ESMO-MCBS had been used on 322 studies in the non-curative setting of which 20 were classified as grade 5 (6.2%) and 105 as grade 4 (32.6%). In the curative setting, 43 studies were evaluated with 41 studies receiving a grade A classification (95.3%).[17] Recently, a variation on the ESMO MCBS has been developed in collaboration with the European Hematology Association (EHA) to allow scoring of drugs that are used in the treatment of hematological malignancies (ESMO-MCBS:H).[18]

CONCLUSIONS

The oncological treatment landscape is evolving at a very rapid pace with a continuous stream of novel treatment options. To fully leverage these therapeutic advances in clinical practice it is important to facilitate a rapid access to innovative anticancer drugs for patients. Specifically for Belgium, the delay from EMA approval to reimbursement for anticancer drugs is very long with an average of almost 600 days, and

a substantial proportion of innovative drugs never making it to the patient. The stringent focus of the Belgian CRM on OS data in reimbursement decisions is believed to be an important contributor to this situation. To improve and speed up the access to innovative anticancer drugs it seems therefore reasonable to also consider oncology-relevant endpoints other than OS in the value assessment of novel treatment modalities. In fact, when a strong treatment effect is seen on an intermediate endpoint such as DFS or PFS, a benefit in OS is quite likely. In situations where the hazard ratio for such an intermediate endpoint is much better than the thresholds used in ESMO-MCBS, one could even argue that withholding access to this drug based on OS immaturity is unethical. As such, our reimbursement system needs to be adapted to better align with the scientific progress in oncology. In this, a temporary reimbursement decision based on intermediate endpoints could give patients living in Belgium earlier access to new promising life-saving medicines. Awaiting final reimbursement, more mature data can be gathered to confirm and solidify the earlier results on intermediate endpoints and better assess the tolerability of the treatment at hand in a real-world setting. In this, we as oncologists, including specialists in haematology, respiratory oncology, and gastrointestinal cancer, strongly encourage the CRM to use the grading provided by the ESMO-MCBS to evaluate the clinical benefit of future cancer treatments. This will not only facilitate a faster patient access to innovative therapies, but will also help policy-makers in advancing 'accountability for reasonableness' in their resource allocation deliberations.

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