Which endpoints
are clinically relevant
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The development of new cancer medicines is a long and complex journey, from research to effective treatment for patients.

A crucial step in this process is the reimbursement procedure for a new medicine. Since April 2025, patient organizations in Belgium have a voice in this decision-making process, allowing their perspectives to play a full role in the evaluation of new treatments. This also means patient organizations need insight into how the efficacy and safety of oncology medicines are assessed in clinical trials. This publication focuses on efficacy.

The goal of a new medicine is to deliver added value for patients compared with the current standard treatment. For this reason, most oncology studies emphasize demonstrating longer survival—also called overall survival (OS)—with maintained or improved quality of life compared with the current standard treatment. However, demonstrating an extension in overall survival can be difficult in practice for various reasons.

To give patients faster access to innovative therapies, it is therefore valuable to also consider other clinically relevant endpoints that can be measured sooner.

During an advisory board, supported by AstraZeneca, representatives of various Belgian oncology patient and peer organizations discussed how endpoints such as disease-free survival, absence of disease progression, or a complete tumor response can provide hope and reassurance, and how much importance they attach to these in decisions about the reimbursement of new treatments. The various intermediate endpoints were explained by Prof. Sandrine Aspeslagh, medical oncologist at UZ Brussel.

These patient organizations were unable to attend the advisory board but provided input afterwards.

1. The pathway of a new oncology medicine and reimbursement in Belgium

The route from research to effective access to treatment is long and complex.

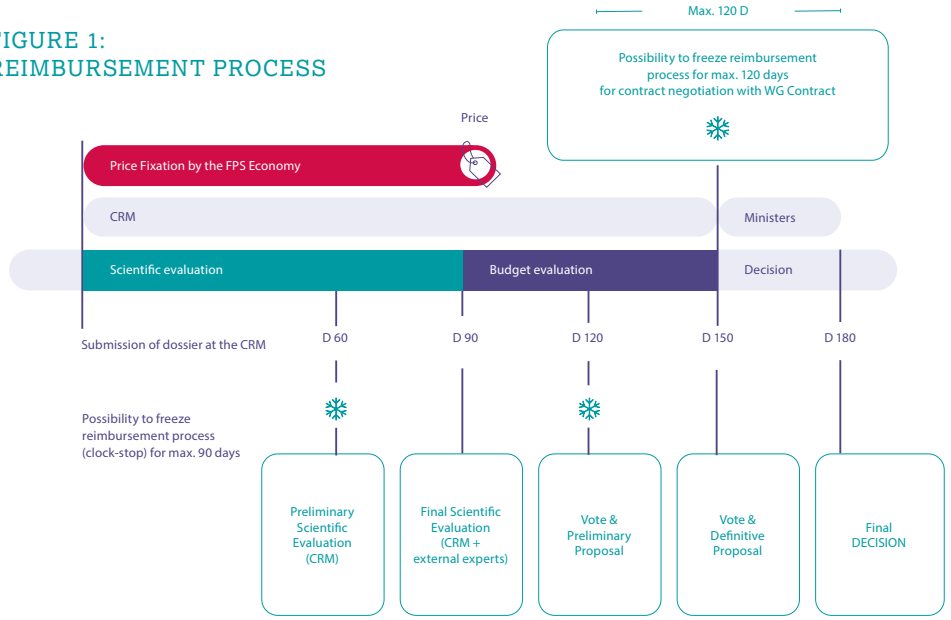
After years of research and clinical trials, the European Medicines Agency (EMA) first assesses whether the medicine is safe and effective. If this leads to a marketing authorization, it is then up to the individual European member states, such as Belgium, to decide whether they will reimburse the medicine.

In Belgium, this decision is guided by the Commission for Reimbursement of Medicines (CRM) of the National Institute for Health and Disability Insurance (RIZIV/INAMI) and ultimately determined by the Minister of Social Affairs.

Since April 2025, with the participation of patient organizations in the CRM, patient-specific insights are now included in medicine evaluation.

The patient perspective is represented at all CRM meetings by VPP (Vlaams Patiëntenplatform) and la LUSS (Ligue des Usagers des Services de Santé). Because these permanent representatives need substantial input from various patient organizations, it is essential to collect disease-specific experiential knowledge in a structured way via a questionnaire.

FIGURE 1:
REIMBURSEMENT PROCESS



The CRM focuses on determining the therapeutic added value of a new medicine compared with existing treatments, based on efficacy (mortality, morbidity, and quality of life), safety, effectiveness, ease of use, and applicability, but it primarily concentrates on overall survival (OS)[1].

Demonstrating a clear survival benefit is important,
but it is becoming increasingly difficult for several reasons:

Long follow-up times: Earlier detection and treatment of cancer mean patients live longer, so it takes longer to obtain survival data. For some cancers, such as hormone-sensitive breast cancer, it can take up to 10 years before sufficient survival data is available [2].

Crossover effects: In some clinical trials, patients in the control group are allowed to switch to the new treatment if their disease worsens, this is called crossover. As a result, the groups become more similar, making the difference in overall survival appear smaller, even if the new treatment truly provides a benefit.

The rarity of certain cancers or mutations makes it difficult to enroll enough patients in a clinical trial to achieve statistically significant differences in survival[1].

People with cancer often receive **multiple therapies in sequence**. This makes it difficult to isolate the effect of one specific treatment on survival benefits.

While the EMA more consistently considers such "intermediate endpoints" in its authorization assessments, this is less the case at the CRM. Given that patient organizations now also have a voice within the CRM, it is crucial to understand patients' perspectives on these intermediate endpoints.

2. Clinical endpoints in oncological research

Clinical endpoints are essential for assessing treatment effects in studies of new medicines.

Their selection depends on the study design and clinical setting (e.g., localized versus metastatic disease).

Below, several clinical endpoints are highlighted, though this list is not exhaustive.

Quality of life is not discussed here, as there is broad agreement that it is an important endpoint.

Overall Survival (OS)

Definition:
The time a person with a cancer diagnosis remains alive after starting treatment.

Importance:
It is a hard outcome; therefore, OS is considered the most convincing measure of treatment effect.

Intermediate endpoints

In addition to overall survival, there are endpoints that show effects sooner and can be indicative of a long-term survival benefit[3].

FOR LOCALLY LIMITED, OPERABLE CANCER (NEOADJUVANT/ADJUVANT TREATMENT)

Neoadjuvant treatment (before surgery/radiation): Aims to shrink the tumor for a less invasive operation or better organ function.

- Pathologic Complete Response (**pCR**): No cancer cells found in the removed tissue after neoadjuvant treatment.
- Event-Free Survival (**EFS**): Time from the start of treatment to the occurrence of an unfavorable "event" (such as cancer returning, progression, stopping treatment due to unfavorable side effects, or the patient's death).

Adjuvant treatment (after surgery/radiation): Aims to destroy any remaining cancer cells to reduce the chance of the disease returning.

- Disease-Free Survival (DFS): The time during which the patient remains alive without experiencing a disease relapse.

FOR METASTATIC CANCER

- Progression-Free Survival (**PFS**): Time after the start of treatment during which a patient remains alive without experiencing disease progression.

3. The value of intermediate endpoints in oncological research

Although demonstrating a survival benefit remains the goal, several factors make this difficult.

That is why intermediate endpoints are crucial:

Faster results:
It often takes years to show differences in OS. Intermediate endpoints provide earlier signals, allowing promising medicines to be identified sooner.

Faster patient access:
If the CRM also considers these endpoints, new innovative treatments can be assessed and made available more quickly

Potential for better long-term outcomes:
A good intermediate endpoint has predictive value: if it improves, the likelihood that survival will ultimately be better is higher.

Healthcare cost savings:
Treatment at an early stage and early access to effective therapies not only improve patients' lives but also reduce societal costs (for example, through fewer hospitalizations or a quicker return to work).

It is important that these intermediate endpoints are clinically validated, relevant to patients, accurately reflect the treatment objective, and ideally show a clear association with a long-term survival benefit.

4. Intermediate endpoints through the eyes of patients

Patient organizations unanimously agree that survival is very important, but they emphasize a crucial nuance: longer survival is only valuable when it is accompanied by an acceptable quality of life.

This perspective highlights several important points:

Quality of life (QoL) is decisive: Patients emphasize that survival is only valuable if it is accompanied by an acceptable quality of life. Chronic side effects (such as pain, fatigue, or diarrhea) can have a major impact on daily life and should not be underestimated.

Logistical burden is important:
Patients value treatments that disrupt their daily lives as little as possible. For example, oral medication that can be taken at home is preferred by some patients over intravenous treatments that require regular hospital visits, even if the survival benefits are slightly less favorable.

The life stage and social context of a patient partly determine which endpoints are prioritized.

For example, a person in their thirties with young children will value different outcomes than a ninety-year-old with multiple comorbidities. What matters varies by person: for one, it's about time and energy for the family; for another, it's about comfort, independence, and as little medical burden as possible.

> *"Most people confronted with cancer start with one wish: to stay alive. At the same time, for most, living without a good quality of life is not desirable."*

Although survival and quality of life are of paramount importance, patient representatives certainly see value in intermediate endpoints when survival data are not yet available, especially if this leads to faster access to innovative treatments.

Specific viewpoints on intermediate endpoints

PATHOLOGICAL COMPLETE RESPONSE (**PCR**)

In the neoadjuvant setting, pCR is an intermediate endpoint that particularly resonates with patients. The message that all cancer cells are gone after treatment feels to many patients like a form of cure, which has a strong psychological and motivating effect.

Relevance for reimbursement: A clearly higher pCR rate is an important signal and should be explicitly considered in reimbursement decisions.

Need for context: Reimbursement based on pCR benefit should be interpreted within a broader framework that also takes into account any survival benefit and patients' quality of life.

Transparent communication: Treating physicians must clearly communicate whether pCR automatically leads to longer survival.

"A life without complications, even if it is not necessarily longer, is also valuable."

EVENT-FREE SURVIVAL (**EFS**) & DISEASE-FREE SURVIVAL (**DFS**)

Abstract concept: Patients find "time to an event" or "time without relapse" harder to interpret than survival. Although everyone agrees that relapse or having to stop due to side effects is better prevented or delayed, it is not immediately clear what this means for life expectancy and quality of life.

Clinical value: Patients acknowledge the importance of avoiding or delaying relapse as long as possible and not having to stop treatment due to toxicity.

Reduces anxiety: Having access to a treatment that lowers the risk of relapse can noticeably reduce anxiety and restlessness and provide greater peace of mind.

Facilitates access: EFS and DFS are valued as early indicators of treatment effect, which facilitates faster access when survival data are not yet available.

Long-term validation: If reimbursement is granted based on EFS/DFS, patients expect that this benefit will translate into longer survival in the long term and, moreover, will not have a negative impact on quality of life.

PROGRESSION-FREE SURVIVAL (**PFS**)

Concrete and tangible: For patients with metastatic cancer, the risk of progression is experienced as concrete and tangible. This is also reflected in discussions about intermediate endpoints with patient organizations, in which PFS is attributed to great clinical relevance. It shows how long the disease remains under control.

Source of hope: Being free from disease progression is an important source of hope for patients and their families.

It means **gaining precious time** with loved ones, especially when treatment side effects are acceptable.

"Every month without progression is a month of hope, a month longer with family. Moreover, it also buys time to potentially benefit from 'future' innovative treatments."

"As a patient, you also don't know whether a next line of treatment will work, or whether at the time of progression or relapse you will still be eligible for certain treatments."

Chance of future therapies:
Provides a crucial opportunity to qualify over time for future therapeutic innovations.

Importance of first-line treatment:
It underscores how important it is to remain without relapse or progression for as long as possible after starting first-line treatment—providing the side effects are acceptable.

Transparent communication:
Doctors should carefully frame expectations around PFS; patients or their families sometimes mistakenly view the absence of progression as synonymous with cure.

"If intermediate endpoints enable faster access, we as patients are certainly in favor, but only with good follow-up and ongoing dialogue."

5. Conclusion

Patient organizations emphasize that **survival and quality of life** should be the top priorities in decisions about the reimbursement of innovative treatments.

At the same time, they recognize the **practical and emotional relevance** of intermediate endpoints, especially when survival data will take a long time to become available.

They support the use of **intermediate endpoints** in reimbursement discussions if this can help ensure faster access to new, effective, and safe treatments.

HOWEVER, THIS REQUIRES A BALANCED APPROACH:

Robust validation:
Intermediate endpoints must be scientifically substantiated and validated.

Data collection after reimbursement:
Ongoing data collection after reimbursement is essential.

Ongoing dialogue:
A sustained conversation with patient organizations, with sufficient attention to the impact of treatment on patients' quality of life, is vital for sound, broadly supported decisions. Their input is crucial to understand patients' needs and priorities.

References

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PATIENT ORGANIZATIONS

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