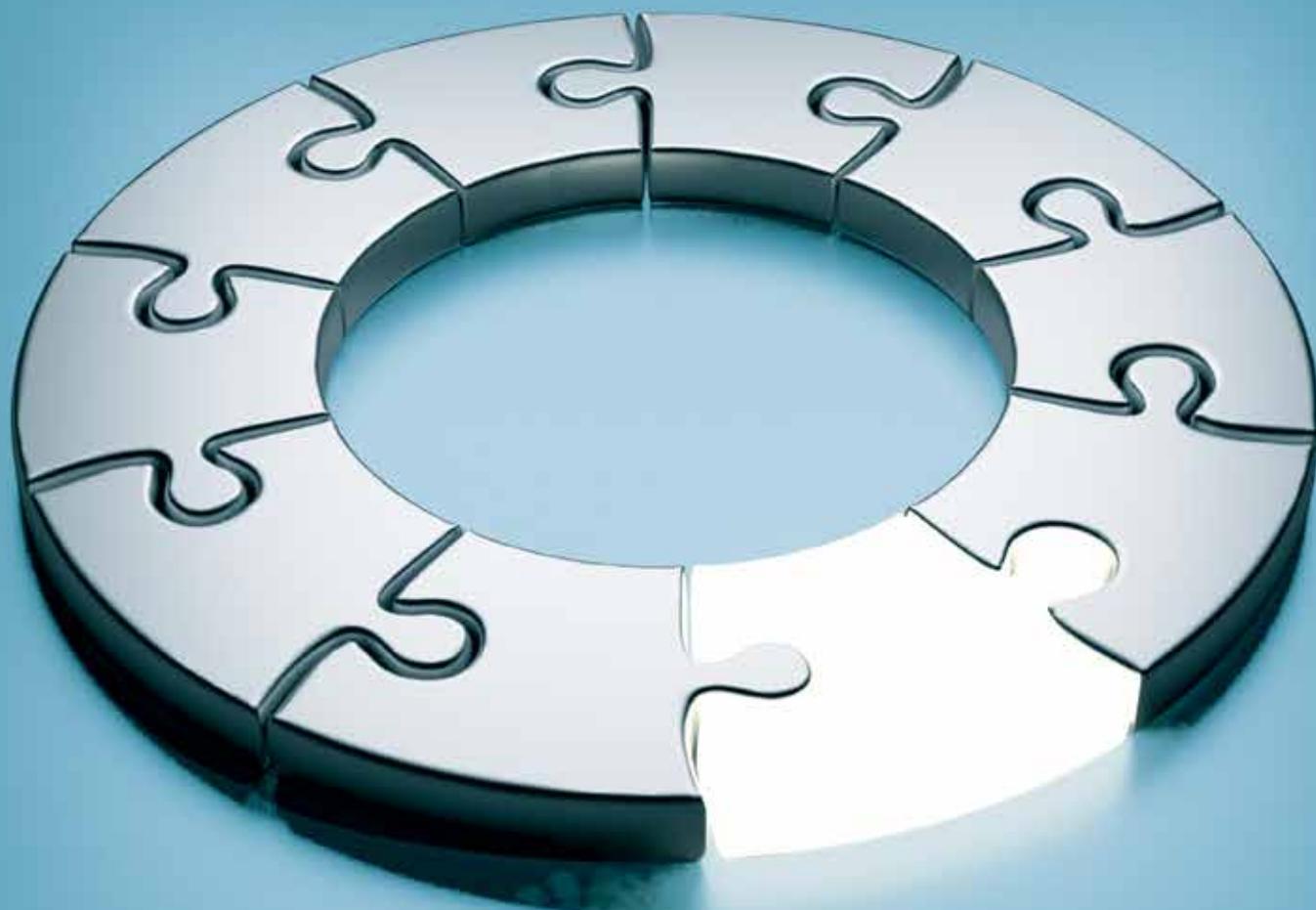


Immuno-oncology: a policy action framework

Creating enabling policies to provide patients
with an innovative cancer treatment modality



The European Expert Group on Immuno-Oncology*

*The European Expert Group on Immuno-Oncology is an independent network composed of Francesco de Lorenzo (European Cancer Patient Coalition (ECPC)); Philippe de Backer, MEP; Cristian Silviu Busoi, MEP; Cedrik M. Britten (Association for Cancer Immunotherapy (CIMT)); Marc van den Bulcke (Institute of Public Health, Belgium); Szymon Chrostowski (Let's Win Health Foundation, Poland); Edith Frenoy, European Federation of Pharmaceutical Industries and Associations (EFPIA); Christoph Huber (CIMT); Burçak Karaca (Turkish Immuno-Oncology Society); James Larkin (Royal Marsden Hospital, UK); Cilia Linssen (Lung Cancer Europe (LUCE)); Olivier Michielin (European Society for Medical Oncology (ESMO)); Mihaela Militaru (ECPC); Ingrid van den Neucker (European CanCer Organisation (ECCO)); Francisco Ventura Ramos (Portuguese Institute of Oncology, Lisbon)



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Immüno-Onkoloji Derneği

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Executive summary

Cancer in the EU – still the unbeaten disease¹

2.45 million
new cases
per year

1.23 million
deaths
per year

126 billion
Euros in
direct
healthcare
costs

75 billion
Euros in
indirect
costs

1 in 3 people with cancer today will not survive more than 5 years²

Note: all figures above are for all types and stages of cancer

Immuno-oncology: a real innovation for cancer patients

Europe is experiencing an unprecedented cancer epidemic, driven by our ageing population. And despite important progress made in the prevention, screening and treatment of many cancers, finding a definitive cure for cancer still remains an elusive goal.

But recent findings with **therapies that use the body's immune system³ to fight cancer** (immuno-oncology therapies) have fuelled hope for the first time that long-term, quality survival may now be possible for patients with many forms of advanced cancer.

"Immuno-oncology therapies offer significant potential for cancer patients as they have already led to major treatment breakthroughs for a number of cancers."

Professor Francesco de Lorenzo, President of the European Cancer Patient Coalition (ECPC)

What does this mean for policymakers?

Immuno-oncology therapies are expected to become one of the cornerstones of cancer therapy in years to come, and policymakers will play an important role in ensuring that the safest and most effective of these important therapies are made available to cancer patients across Europe as quickly as possible.

In 2014, the **European Expert Group on Immuno-Oncology**, was set up as an independent network to propose a framework for action for European and national policymakers to encourage rapid and appropriate access for patients to immuno-oncology therapies across Europe.

As patients, oncology healthcare professionals, scientists, researchers, and politicians, we propose that a comprehensive policy response should be built around **five priority areas**:

^a The **immune system** is how the body recognises and defends itself against bacteria, viruses, and substances that appear foreign and harmful.

What can policymakers do?

- 1 Promote **greater understanding** of what is unique about immuno-oncology – amongst policymakers, regulatory agencies, health professionals and patients
- 2 Ensure that regulatory decisions on the value of immuno-oncology therapies are based on **what matters most to patients**: long-term quality survival
- 3 Ensure **flexibility in regulatory pathways** to provide patients early access to immuno-oncology therapies
- 4 Invest more in **research** to understand how immuno-oncology works in patients
- 5 **Include innovative therapies** in national cancer plans, treatment pathways and funding streams

“Bringing innovation and new therapies quickly and safely to the patient is crucial. Therefore, the EU should create a framework that stimulates excellent research and allows new therapies to come to the market without unnecessary delay. This can improve the lives of thousands of patients.”

Philippe de Backer, MEP



1 Understanding what is unique about immuno-oncology

Immuno-oncology therapies were heralded as 'breakthrough of the year' by Science magazine in 2013³ and have the potential to revolutionise the way we treat cancer patients.⁴



Researchers have been investigating ways to harness the immune system^b to fight cancer for several decades. However, it was only recently that this knowledge translated into effective therapies, known as immuno-oncology therapies.

What makes immuno-oncology therapies unique?^{5;6}

Immuno-oncology therapies work by enabling the body's immune system to fight cancer.

- They target the body's **immune system**, not the tumour itself
- They **selectively recognise and target cancer cells**, not healthy cells
- They give **long-lasting memory to the immune system**, so that it can continually adapt to the cancer over time and provide durable, long-term response to the cancer.

What's more, immuno-oncology therapies are **potentially effective in many types of cancer** because they work by activating the patient's own immune response as opposed to working directly on the tumour. Immuno-oncology therapies are now available to patients with advanced melanoma^{7,8} and prostate cancer⁹ and many more are being investigated, targeting some of the most common and difficult-to-treat cancers.⁶

^b The **immune system** is how the body recognises and defends itself against bacteria, viruses, and substances that appear foreign and harmful.

Making an impact on some of the deadliest cancers: the example of lung cancer

Lung cancer is the leading cause of cancer-related death worldwide in men, and the second leading cause in women. Eighty percent of patients with advanced lung cancer die within one year of diagnosis.¹⁰ A patient diagnosed with lung cancer today has the same chance of dying as 40 years ago.^{11;12} Lung cancer also incurs the highest economic cost of all cancers in Europe,¹ and bears a huge burden on caregivers.¹³

A number of immuno-oncology therapies are being investigated in Phase III trials for lung cancer^{14,15} and these therapies are eagerly awaited by patients.

“Lung cancer patients have very limited treatment options and any new treatment can mean a great step forward. Speed is of the essence here, because our patients tend not to have much time. Speed in getting the drug to the market, but also in getting structures in place to test patients for suitability of the treatment. Speed to ensure quick and full access whenever a new safe and effective drug becomes available that could help our patients.”

Cilia Linssen, Vice-president of Lung Cancer Europe



Key recommendations:

What is needed

Better understanding by policymakers, regulatory authorities, professionals and patients of what immuno-oncology is and its potential role in cancer treatment.

What policymakers can do

- Ensure that immuno-oncology therapies are integrated into **cancer plans and policies**, for example via the Joint Action on Comprehensive Cancer Control (CANCON)
- Encourage **open scientific discussion** about novel developments in immuno-oncology with experts from regulatory, Health Technology Assessment (HTA) and reimbursement agencies
- Provide dedicated funds to make **professional training** on immuno-oncology part of the standard oncology curriculum across Europe
- Provide support and funding to patient organisations to provide **clear and up-to-date information to cancer patients** about immuno-oncology

2 Measuring what matters to patients: long-term quality survival

“ESMO and other professional societies have long recognised that long-term, quality survival is what matters most to cancer patients – the challenge is to adapt the way we measure benefit in clinical trials to be sure that we are capturing these benefits fully for new cancer therapies.”

Professor Rolf Stahel, President of the European Society for Medical Oncology (ESMO)



Immuno-oncology therapies offer the potential for long-term quality survival

Long-term quality survival has long been recognised as the ultimate goal of cancer therapy.¹⁶ What is exciting about immuno-oncology therapies is that evidence from clinical trials suggests they may offer the potential for long-term quality survival to a number of patients for whom treatment options were previously very limited.^{6;7;9} The impact of this survival on patients is bound to be considerable – in terms of their ability to return to work, and lead healthy, productive and engaged lives for many years. (see patient stories on www.theanswertocancer.org)

Validated intermediate endpoints that are predictive of long-term survival

Obtaining evidence of long-term survival may take several years, therefore it is important to identify validated intermediary endpoints that are predictive of long-term survival with immuno-oncology therapies.¹⁷ These endpoints may help facilitate expedited review or accelerated approval for immuno-oncology therapies that show early evidence of clinical benefit, ultimately making them available faster to patients with high unmet needs.⁵

Unfortunately, the clinical development frameworks (clinical trials^c) traditionally used in oncology are typically based on short-term measures which are not necessarily predictive of long-term survival. These frameworks were developed for conventional therapies such as chemotherapy and need to be adapted to reflect effects seen with immuno-oncology therapies.¹⁸

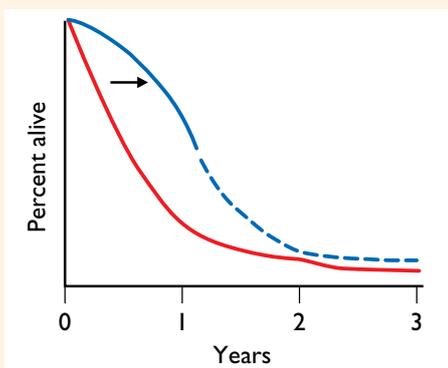
^c **Clinical trials** are research studies that test how well new medical approaches work in people.

Long-term survival: shifting the curve

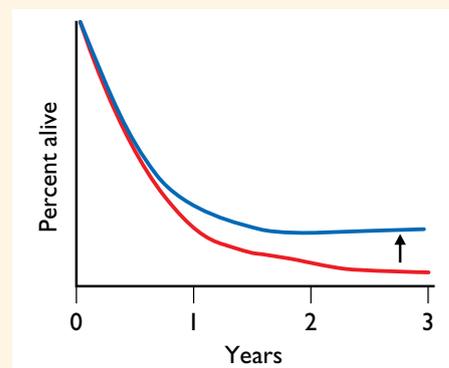
The figures below provide an illustration of the difference in treatment effects between immuno-oncology therapies and conventional therapies. Figure A shows the percentage of patients alive over time for conventional therapies, and Figure B, for immuno-oncology therapies. The red curve in both graphs represents patients receiving 'control' therapy (placebo or standard therapy).

- A. **Conventional therapy:** While many conventional therapies to date have shown promising anti-tumour effects in patients, in most cases these effects do not last and therefore do not result in increased long-term survival. This is illustrated below: there is an early improvement of the survival curve (at the arrow) but the curves gradually come together at the tail of the curve, suggesting no long-term survival benefit over control therapy.
- B. **Immuno-oncology therapy:** What is different about many of the recent immuno-oncology therapies is that they have demonstrated durable anti-tumour effects, which may translate into long-term survival. The survival curves show a delayed separation but a plateau at the tail, suggesting that a higher proportion of patients are still alive several years after the beginning of treatment (at the arrow).⁷

A. Conventional therapy



B. Immuno-oncology therapy



Adapted from:
Ribas et al 2012⁹

Key recommendations:

What is needed

Quality long-term survival or intermediate endpoints predictive of long-term survival as the basis for all decisions to make immuno-oncology therapies available to patients

What policymakers can do

- Ensure **alignment between regulatory and reimbursement authorities** on how the benefits of immuno-oncology therapies are measured
- Encourage health technology assessment (HTA) and similar agencies to consider the **full societal value of long-term quality survival** in their assessment of cancer therapies, in terms of impact on quality of life, productivity and caregiver time

3 Flexible regulatory frameworks

“What we need is a flexible, but safe, approach to the way we approve cancer therapies. Bureaucratic hurdles and budgetary constraints should not cause unnecessary delays in making the most promising drugs available to patients who need them most.”

Marc van den Bulcke, Belgium

Expensive and lengthy developmental pathways

Regulatory frameworks need to have very strict data requirements for new therapies, however these requirements often make for lengthy and expensive development pathways. The cost per patient in a clinical trial has risen from an estimated \$25,000 per patient in 2000 to as much as \$100,000 in 2012.²⁰ Varying data requirements between national reimbursement and HTA agencies have also added to costs both for developers and regulators due to multiple assessments of the same data.

Balancing the need for increasing safety data and access to innovation

Increasing regulatory requirements, particularly for safety data, may also result in delaying, or restricting, patients' access to potentially beneficial innovations.²¹ As a result, patients, researchers and industry have called for more flexible approaches to regulatory decisions. One possible solution would be to allow **regulatory decisions for conditional and facilitated access to the market to be made based on an evolving set of data.**

Flexibility for early clinical testing as well as for conditional and facilitated entry into the market may help ensure that an appropriate balance is made between the need for adequate safety and efficacy data and the need to provide access to breakthrough innovations to patients; and that regulatory frameworks evolve based on lessons learnt from the clinical development of recently approved therapies.^{18;22}

A promising example of such a flexible approach is that of 'adaptive pathways' being piloted by the European Medicines Agency (see box overleaf).

Adaptive pathways: ensuring timely access to new technologies^{23;24}

In adaptive pathways, approval decisions are not a one-off, but instead decisions to make therapies available to patients are based on an evolving set of evidence, and data gathering and regulatory evaluation are both done in an iterative way.

By allowing for continuing evidence generation, adaptive pathways aim to provide patients and professionals with up-to-date information to enable them to make the best-informed individual treatment decisions in light of evolving evidence.²⁴

Early collaboration between drug developers, regulatory agencies (EMA), HTA agencies and payers is key, as they need to agree to a comprehensive development and licensing plan early on (adaptive licensing), matched with adaptive frameworks for reimbursement and HTA decisions as well.



Key recommendations:

What is needed

Flexibility in regulatory frameworks to allow for rapid development and patient access to immuno-oncology therapies that show early evidence of meaningful clinical benefit

What policymakers can do

- Promote **early dialogue** between regulatory authorities and immuno-oncology developers to further explore the development of **flexible pathways**
- Ensure that **regulatory guidance** finds an appropriate balance between the need for safety and efficacy data and access to innovation
- Promote collaboration between Member States to ensure **consistency in application of guidance across Europe**

4 More investment in research

“Europe needs to do more to incentivise research and development efforts to bring to patients the most innovative therapies that will make a real difference to them. A better understanding of how these therapies work in patients in ‘real world’ settings will allow to select the right treatment for a given patient and to identify the right patient for a given treatment.”

Dr Cedrik M. Britten and
Professor Christoph Huber, CIMT



The need for more translational research

A critical barrier to the development of immuno-oncology therapies in Europe is the limited amount of funds available to translate science into patient care.²⁵ More targeted funds are needed to improve our understanding of how immuno-oncology therapies work in patients (‘from bench to bedside’) – and to bring these findings back to the lab to help the future development of immuno-oncology therapies (‘from bedside to bench’).

Research in this field is critical, as at the moment we lack a clear understanding of what biological factors make a given immuno-oncology therapy work in a particular patient. Without this understanding, we leave patients more dependent on rules of chance rather than on biological facts.²⁶

Public Private Partnerships

To make best use of available resources, it is highly desirable to be able to select patients for immuno-oncology therapies with the highest likelihood of responding. Collaborative research efforts involving basic scientists, drug developers and research institutes may allow to combine findings from immuno-oncology clinical trials into large databases to help identify which patient characteristics make individuals more likely to respond to different therapies. This knowledge may be used to help identify reliable tools – such as biomarkers – to select patients who are most likely to benefit from these therapies and to define the most effective patient treatment pathways.

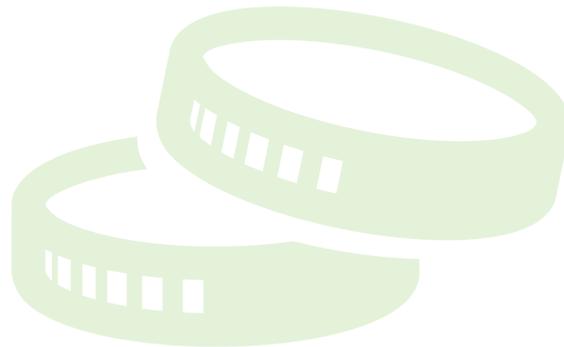
Key recommendations:

What is needed

Collaborative, multidisciplinary research platforms to help improve our understanding of which patients are most likely to benefit (ie. finding the right treatment for a given patient)

What policymakers can do

- Support the development of **Public Private Partnerships** (PPIs) focused on how immuno-oncology therapies work in patients
- Provide **targeted funds** for translational research on immuno-oncology, e.g. through the European Commission's Directorate General on Research and Innovation, Horizon 2020 and national research grants



5 Comprehensive pathways and funding for innovative cancer therapies

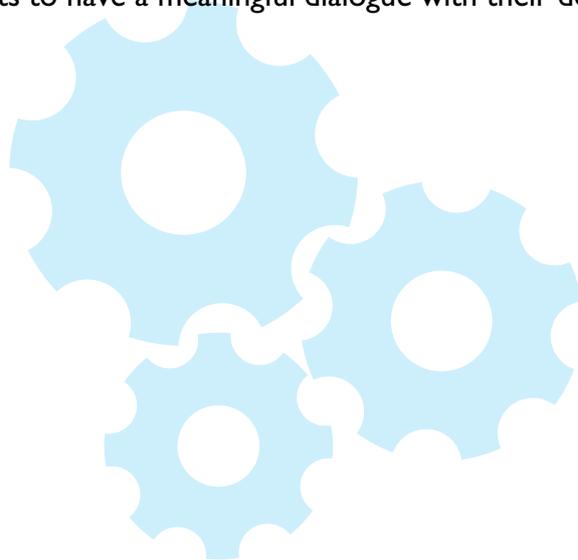
Securing local access to innovation in cancer care

For any new therapy to be made available to patients, it needs to be integrated into national cancer plans, as well as built into local care pathways and funding streams. A first step to securing funding is to include all available, effective new therapies into clinical pathways and recommendations, as was done in the UK for melanoma (see box opposite).

Yet financial pressures on health care systems across Europe have created a challenging environment for new therapies. Professional societies such as the American Society for Clinical Oncology have called for a 'total cost of care' approach to the economic evaluation of new cancer therapies – i.e. the full economic impact of a new therapy should be considered, as opposed to making decisions on drug costs alone (so-called 'siloed funding'^d).

Dedicated professional education across the whole multidisciplinary team

Finally, it is important to note that immuno-oncology is an evolving science, therefore dedicated professional education on immuno-oncology across the whole multidisciplinary team will be critical to ensure that immuno-oncology therapies are used as appropriately as possible in patients who are most likely to benefit. In addition, **continuous support and information to patients must be built into all care pathways** to enable patients to have a meaningful dialogue with their doctors about what to expect from therapy.



^d **Siloed funding** refers to making funding decisions based solely on their impact on one category of costs – for example, only looking at the cost of a given drug and its impact on the drugs budget, instead of looking at the broader impact on all types of costs (hospital stays, doctor visits, etc).

Encouraging rapid and equitable access to immuno-oncology therapies: the example of the Melanoma Taskforce commissioning toolkit in the UK²⁷

The Melanoma Taskforce is a panel of British MPs, leading clinicians, experts and patient representatives in skin cancer. The aim of the taskforce was to help local commissioners responsible for funding care ensure equitable, timely and appropriate access to the full range of approved treatments for people with advanced melanoma.

The toolkit offers a comprehensive and system-wide approach, incorporating for example at the service level the importance of rapid referral and connectivity between specialist and local skin cancer multi-disciplinary teams. At the strategic level, the Taskforce has also highlighted the need for greater connectivity between those making funding decisions about care (commissioners) and regional specialist clinical networks tasked with innovation adoption. The Taskforce also published a report which outlines best practice pathways for melanoma in the UK.²⁸

The Taskforce guidelines are voluntary, however they are likely to play an important role in encouraging a comprehensive approach to improving the quality of care for melanoma patients, through multidisciplinary care pathways, exchange of information, clarification on funding and commissioning streams and integration of all available treatment options (including immuno-oncology) into care pathways.



Key recommendations:

What is needed

Integration of immuno-oncology therapies into multidisciplinary care pathways, supported by comprehensive cancer plans and appropriate funding streams

What policymakers can do

- Ensure that cancer patients across Europe have **equitable access to innovative therapies**, without undue delays and geographic disparities
- Promote funding strategies that take into consideration the **total cost of cancer to society** and discourage 'siloed funding' that may inadvertently limit access to meaningful new therapies

6 Conclusions

Immuno-oncology therapies hold considerable promise for cancer patients, but it is necessary that policymakers take action. Existing policies and frameworks need to be adapted to ensure that the most effective of these innovative therapies are made available to patients across Europe.

Key recommendations – what policymakers can do:

1 Promote greater understanding of what is unique about immuno-oncology

- Ensure that immuno-oncology therapies are integrated into **cancer plans and policies**, for example via the Joint Action on Comprehensive Cancer Control (CANCON)
- Encourage open scientific discussion about novel developments in immuno-oncology with experts from **regulatory, Health Technology Assessment (HTA) and reimbursement agencies**
- Provide dedicated funds to make **professional training** on immuno-oncology part of the standard oncology curriculum across Europe
- Provide support and funding to patient organisations to provide **clear and up-to-date information to cancer patients** about immuno-oncology

2 Measure what matters most to patients: long-term quality survival

- Ensure **alignment between regulatory and reimbursement agencies** on how the benefits of immuno-oncology therapies are measured
- Encourage HTA and similar agencies to consider the **full societal value of long-term quality survival** in their assessment of cancer therapies, in terms of impact on quality of life, productivity and caregiver time

3 Create flexible regulatory pathways to provide patients early access to immuno-oncology therapies

- Promote **early dialogue** between regulatory authorities and immuno-oncology developers to further explore the development of flexible pathways
- Ensure that **regulatory guidance** finds an appropriate balance between the need for safety and efficacy data and access to innovation
- Promote collaboration between Member States to ensure **consistency in application of guidance across Europe** innovative cancer therapies are made available to patients as quickly as possible

4 Invest more in research to understand how immuno-oncology works in patients

- Support **research** to help identify which patients are most likely to benefit (ie. finding the right treatment for a given patient)
- Provide **targeted funds**, e.g. through the European Commission's Directorate General on Research and Innovation, Horizon 2020 and national research grants, for translational research in immuno-oncology

5 Include innovative therapies in national cancer plans, treatment pathways and funding streams

- Ensure that cancer patients across Europe have **equitable access to innovative therapies**, without undue delays and geographic disparities
- Promote **funding strategies** that take into consideration the total cost of cancer to society and discourage 'siloed funding' that may inadvertently limit access to meaningful new therapies

"Bringing innovation and new therapies quickly and safely to the patient is crucial. Therefore, the EU should create a framework that stimulates excellent research and allows new therapies to come to the market without unnecessary delay. This can improve the lives of thousands of patients."

Philippe de Backer, MEP

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