The Future of Access to Innovative Medicines in Cancer Therapy: Towards Conditional Dialogue Fostering Affordable Therapeutic Innovation

September 2016

Walter Van Dyck
Jacques De Grève
Rik Schots
Ahmad Awada
Tine Geldof
The Future of Access to Innovative Medicines in Cancer Therapy: Towards Conditional Dialogue Fostering Affordable Therapeutic Innovation

Vlerick Policy Paper Series

September 2016

This paper is endorsed by:

the Belgian Society for Medical Oncology
the Belgian Haematological Society
the College of Oncology
Table of Content

Acronyms and Abbreviations .................................................................................................................. 5
Acknowledgements .................................................................................................................................... 7
Foreword .................................................................................................................................................. 8
Executive Summary ................................................................................................................................. 9
1. Introduction ........................................................................................................................................ 12
2. The Burden of Cancer in Belgium – Epidemiology ............................................................................ 14
   2.1 Incidence ....................................................................................................................................... 16
   2.2 Mortality ....................................................................................................................................... 18
   2.3 Evolution of Cancer Incidence, 2004-2013 .................................................................................... 19
   2.4 Evolution of Cancer Mortality, 2004-2012 ................................................................................... 20
   2.5 Projection 2025 ............................................................................................................................ 21
   2.6 Survival ........................................................................................................................................ 21
   2.7 The Belgian Cancer Registry ......................................................................................................... 23
   2.8 Epidemiological Conclusions ........................................................................................................ 25
   2.9 Recommendations ......................................................................................................................... 25
3. Future Developments in Oncological Medical Innovation ................................................................. 26
   3.1 Driving forces of oncological medical innovation ......................................................................... 26
   3.2 The evolutionary nature of anti-cancer drug development ........................................................... 28
   3.3 Cancer treatment R&D races too much in overlapping domains.................................................. 30
   3.4 Cancer research is expensive ........................................................................................................ 32
   3.5 The difficulty of assessing value in oncology .................................................................................. 33
   3.6 Towards precision medicine .......................................................................................................... 34
   3.7 Conclusions ................................................................................................................................... 35
4. Funding of Access to Therapeutic Innovation in Oncology .................................................................. 36
   4.1 A 2020 Oncology Horizon Scan ................................................................................................... 37
      Fit with the 2015 Minister’s Growth Pact .......................................................................................... 41
   4.2 A first role of competition in a Conditional Dialogue between Payers and Industry .................... 42
   4.3 Recommendations ......................................................................................................................... 43
5. The Need for Early Involvement in Adaptive Pathways-enabled Medicines Development .................. 44
   5.1 Stimulating research into areas of unmet need .............................................................................. 45
   5.2 Towards open collaborative Adaptive Pathways and Adaptive Licensing .................................... 46
5.3 Recommendations........................................................................................................... 47
6. Accelerating Access to Affordable Innovative Medicines in Oncology ...................... 49
   6.1 Dealing with unsustainable prices in oncology....................................................... 51
   6.2 Negotiating following value-based principles pricing ............................................. 54
   6.3 Pricing based on comparative effectiveness ......................................................... 56
       Superior comparable effectiveness...................................................................... 56
       Comparable comparative effectiveness.............................................................. 57
       Still insufficient comparable comparative effectiveness .................................... 58
   6.5 Multi-indication pricing ...................................................................................... 59
   6.6 Recommendations.............................................................................................. 60
7. Building a Learning Healthcare System in Oncology ................................................. 62
   7.1 Operating the Oncology Healthcare Learning System ........................................ 63
       Towards a conditional approval and pricing & reimbursement process .............. 63
       Registries-based or science-based research? ...................................................... 64
   7.2 Towards Dynamic Pricing ................................................................................. 65
   7.3 Towards an outcome-based healthcare learning system .................................... 66
       The need for cancer networks and a Trusted Third Party.................................... 68
   7.4 Recommendations.............................................................................................. 69
8. Conclusions and Recommendations.......................................................................... 70
   Summary Recommendations.................................................................................... 71
       Acting with foresight .......................................................................................... 71
       Early dialogue between manufacturer and payer .............................................. 71
       An integrated foresight, access & pricing system ............................................. 72
       Value-based and competition-based pricing ...................................................... 72
       Founded on an outcome-based disease-centric healthcare learning system ....... 73
References .................................................................................................................. 74
Appendix I: Assumptions for the 2020 Budget Projection ............................................. 80
Appendix II: Overview of Innovative Cancer Treatments reimbursed in Belgium in 2016 ...
................................................................................................................................. 85
# Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR</td>
<td>Belgian Cancer Registry</td>
</tr>
<tr>
<td>BIA</td>
<td>Budget Impact Analysis</td>
</tr>
<tr>
<td>CAGR</td>
<td>Compound Annual Growth Rate</td>
</tr>
<tr>
<td>CAR</td>
<td>Chimeric Antigen Receptor</td>
</tr>
<tr>
<td>CED</td>
<td>Coverage with Evidence Development</td>
</tr>
<tr>
<td>CIVARS</td>
<td>Chapter IV Agreement Requesting System</td>
</tr>
<tr>
<td>CRM/CTG</td>
<td>Commission Remboursement des Médicaments/Commissie Terugbetaling Geneesmiddelen</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-Adjusted Life Year</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>HER</td>
<td>Electronic Health Record</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EPD</td>
<td>Electronisch Patiënten Dossier</td>
</tr>
<tr>
<td>ETA/ETR</td>
<td>Early Temporary Access / Reimbursement</td>
</tr>
<tr>
<td>ERP</td>
<td>External Reference Pricing</td>
</tr>
<tr>
<td>ESMO-MCBS</td>
<td>European Society for Medical Oncology Magnitude of Clinical Benefit Scale</td>
</tr>
<tr>
<td>ESR</td>
<td>European Standard Rate</td>
</tr>
<tr>
<td>FAMP</td>
<td>Federal Agency for Medicines and Health Products</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>IMA-AIM</td>
<td>Intermutualistic Agency (Belgian association amongst sick funds)</td>
</tr>
<tr>
<td>ISPOR</td>
<td>International Society for Pharmacoeconomics and Outcomes research</td>
</tr>
<tr>
<td>MCDA</td>
<td>Multi Criterion Decision Analysis</td>
</tr>
<tr>
<td>MCDD</td>
<td>Multi Criterion Decision Deliberation</td>
</tr>
<tr>
<td>MEA</td>
<td>Market Entry Agreement</td>
</tr>
<tr>
<td>MOC</td>
<td>Multidisciplinary Oncological Consult</td>
</tr>
<tr>
<td>NHB</td>
<td>Net Health Benefit</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NIHDI</td>
<td>Belgian National Institute for Health and Disability Insurance (NIHDI/RIZIV/INAMI)</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PASS/PAES</td>
<td>Post-authorization Safety and Effectiveness Studies</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PFP</td>
<td>Pay For Performance</td>
</tr>
<tr>
<td>PMx</td>
<td>Personalized Medicines</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
</tr>
<tr>
<td>PASS/PAES</td>
<td>Post Authorization Safety and Effectiveness Studies</td>
</tr>
<tr>
<td>PBA</td>
<td>Performance Based Agreement</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Clinical Trial</td>
</tr>
<tr>
<td>RR</td>
<td>Response Rate</td>
</tr>
<tr>
<td>RSR</td>
<td>Relative Survival Rate</td>
</tr>
<tr>
<td>RWE</td>
<td>Real World Evidence</td>
</tr>
<tr>
<td>STAMP</td>
<td>Safe and Timely Access to Medicines</td>
</tr>
<tr>
<td>TTP</td>
<td>Trusted Third Party</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness To Pay</td>
</tr>
<tr>
<td>WSR</td>
<td>World Standardised Incidence Rates</td>
</tr>
</tbody>
</table>
Acknowledgements

Having been established in the field of financial services, this paper is the first issue of the Vlerick Policy Paper Series to appear in the domain of healthcare policy.

Chosen themes, scientific and technical data, expressed viewpoints and policy recommendations are under the full responsibility of the authors only. Only the authors are responsible for possible errors or omissions\(^1\).

The authors want to acknowledge and sincerely thank Dr. Liesbeth Van Eycken, Director of the Belgian Cancer Registry for her major contribution and recommendations related to disease epidemiology and data registration made in the second chapter of this report.

Furthermore, the author’s viewpoints did benefit greatly from the personal insights gathered from a distinguished list of experts, and also collected during the Vlerick HMC Workshop on Real World Evidence held in February 2016 in Brussels and the KCE-ZIN Drug Pricing Scenarios Project workshops held in April-May 2016 in Amsterdam.

In this respect, we are particularly grateful to:

Lieven Annemans (Health Economics, UGent), Francis Arickx (NIHDI, Brussel), Peter Bach (Memorial Sloan Kettering Cancer Centre, New York), Katelijne De Nys (CTG/KU Leuven), Ri De Ridder (NIHDI, Brussels), Joeri Guillaume (IMA-AIM, Brussels), Ansgar Hebborn (Roche, Basel Switzerland), Yves Horsmans (CTG, UCL Hepatology), Isabelle Huys (pharmaceutical faculty KU Leuven), Panos Kanavos (London School of Economics Health, London), Marc Peeters (UZA, Antwerpen), Steven Simoens (Pharmacoeconomics, KU Leuven), Françoise Stryckmans (pharma.be, Brussels), Mark Trusheim (MIT, Boston Massachusetts), Anouk Waeytens (NIHDI, Brussel), Entela Xoxi (AIFA, Milano).

\(^1\) The authors or the organisations they represent received no grants or payments related to this work. Vlerick Business School only was the recipient of an unconditional grant from Roche to logistically support its Healthcare Management Centre.
Foreword

Cancer as a therapeutic domain has been and still is largely underserved compared to other domains. This leaves many cancer patients ultimately with unresolved high medical needs. In recent years an acceleration in therapeutic innovation is creating high hopes. Especially (but not only) novel immunotherapies as a new modality in addition to chemotherapy, hormonal therapies and targeted agents are literally shaking up longstanding treatment algorithms and their promising broad applicability will create a tsunami effect of opportunities for patients but also a challenge for payers. In contrast to earlier innovations which were often directed at specific cancer (sub)populations, these treatments represent cancer-wide innovation. Not only the broad applicability, but also the high success rate of the ongoing clinical trials are changing variables in previously elaborated predictive budget models.

With prices listed there is a strong perception that budgetary impact for payers will be unprecedented and unaffordable in current prospects.

In the current work we have attempted to estimate these adapted budgetary prospects taking into account all major identifiable variables and secondly we have pondered on how the affordability could be realized at a societal level and without introducing any financial burden on the individual patient level.

We have done this work in collaboration between medical and economical expertise.

We believe that the coming innovations can be affordable pending recognition of an objective need for a (reasonable) budgetary increase for cancer medicines, the medicine domain with the greatest ongoing innovation wave and adaptations in the interaction between pharma and payers in letting market forces regulate prices more than today. We believe that contrary to current thinking, this can be implemented, maybe at the expense of me-too and futile developments but without jeopardizing true innovation.

The authors
Executive Summary

Cancer represents the second highest cause of disease burden on Belgian society for the foreseeable future. In the field of oncology, next to advances in molecular biology, bioinformatics or diagnostic imaging, surgical interventions, radiotherapy and drug-based therapies are the health technologies used to save or extend patient life or to improve its quality.

Belgium’s total healthcare spend as a percentage of GDP is commensurate with its economic productivity or societal wealth. Total drug spend and growth rates are in line with the other European developed health care markets (EU-18), all providing universal care and facing similar funding constraints of budgets under continued austerity. However, its proportional spend on drug-based therapeutic technology compared to disease burden in Oncology is below average and below other therapeutic areas. Still, Belgium is among the leading countries in survival rates for most prominent cancers.

Until 2013 this historical underspending was caused by the innovative drug-based cancer therapy pipeline essentially being flat due to late-stage development failure. Now, as evidenced in this study the last years the world is experiencing a surge in expensive innovative targeted therapies and in particular immunotherapies now rapidly becoming accessible. In contrast to earlier developments these latter therapies are characterised by a highly successful and accelerated clinical development. Following our horizon scanning results, by 2020 innovative drug-based cancer treatments will represent more than 70% of the total cancer drug budget in Belgium and all cancer drugs will consume a quarter of the total pharmaceutical specialties budget projected to be then around €4.6 billion. To fund the projected 2016 – 2020 oncology innovation pipeline, given the fixed pharmaceutical specialties budget annual growth rates agreed upon with industry in the Minister’s Summer 2015 Growth Pact, the agreed upon budget is in line with the needs for innovation until 2017. However, it will be exceeded in 2018 when then starting to be confronted with a significant raise in budgetary needs caused by a pipeline of innovative therapies becoming accessible to the patient.

As a result, given their high-cost nature and amplified by the more general applicability of immunotherapies across a broad range of indications this will severely stress the Belgian pharmaceutical specialties budget for the years to come. Hence, we believe that health care policy and the payer decision making process needs to be adapted to ensure that patients can have optimal access to the upcoming innovations without any social discrimination while at the same time the affordability of our healthcare system in the long run should be guaranteed.

To do so, we will argue that the future of access to innovative medicine-based therapies is about society engaging into a ‘conditional dialogue’ with the innovative biopharmaceutical industry, centred on competition and being rewarded for therapeutic innovation. Society engaging into a conditional dialogue acknowledges that industry has an obligation to satisfy shareholder expected return whilst engaging in high-risk research but also the corporate social responsibility to serve the public good to make people better on conditions society can afford.
In this paradigm, the dialogue between payer and manufacturer is initiated conditional on the acclaimed high potential level of therapeutic innovation and continued conditional on clinical and real-world outcome delivered fighting unmet medical need. Hence, lower levels of ‘me-too’ therapeutic innovation will face more competition in market access and reimbursement decision processes. Higher levels of therapeutic innovation, potentially offering ‘breakthrough’ medical benefits can be reviewed at an accelerated pace and be conditionally accepted on the market until real-world evidence gathered confirms up-front claimed performance, after which market access and a fixed price can be assumed for a set time period. For incumbent therapies being superseded by novel therapies delivering better real world outcome the dialogue is stopped and the product is eventually de-reimbursed.

The implementation of a conditional dialogue between society and the innovative medical industry hinges on five principles; (1) acting with foresight, (2) early dialogue between manufacturer and payer, (3) an integrated foresight, access & pricing system, (4) value-based and competition-based market access, and be (5) founded on an outcome-based disease-centric healthcare learning system.

Acting with foresight implies installing a longer-term agreement between the payer and industry to become an institutionalised part of a systematic horizon scanning system. The latter system, starting from the unmet patient needs is able to confront demand and supply of innovative medical technology over a sufficiently long time horizon. This will enable timely health budget prioritization and early identification of promising candidate therapies. Given that constrained health budgets call for making –often hard– budget allocation choices, this principle, together with the implementation of a disease-centric outcome-based healthcare learning system should be given the highest priority.

The first while providing the priority areas of unmet need on which to focus early dialogue between manufacturer and payer accelerating access to potentially promising innovation. And for being the foundation of a value-based and competition-based pricing system to be implemented that could curb excessive cost while still incentivising innovation. Value-based competitive pricing uses principles of competition between similar innovative drugs and dynamic outcome-based pricing to conditionally provide continued access and reimbursement for drug-based cancer therapies i.e. rewarding comparative effectiveness as shown in real life. Disease-centric registries allow for competitive comparison of cost-effectiveness of various treatment strategies.

The authors are convinced that moving towards a more competitive pricing system for market access even for innovative drugs will not endanger innovation, but rather foster the initiation of true innovation. More specifically, previous pharmaceconomic research shows that the use of price competition (in overcrowded on-patent areas) and R&D competition (in areas with high breakthrough potential) promoted respectively by payers and investors has a positive downward effect on novel therapy price, on the speed with which novel therapies are discovered in domains of high unmet medical need, and on avoiding monopolistic therapy markets.
In conclusion, sustainably providing patients with socially equitable access to the delivering drug-based cancer treatment pipeline in these times of austerity calls for health budget prioritization and competitive real outcome-based prices at a level society can afford. A conditional dialogue between society and the innovative biopharmaceutical industry is a prerequisite and a guarantee to make this happen.
1. Introduction

Cancer represents the second highest cause of disease burden on Belgian society for the foreseeable future. In the field of oncology, next to advances in molecular biology, bioinformatics or diagnostic imaging, surgical interventions, radiotherapy and drug-based therapies are the health technologies used to save or extend patient life or to improve its quality (Adams, Bessant, & Phelps, 2006).

Belgium’s total healthcare spend as a percentage of GDP is commensurate with its economic productivity or societal wealth. Its proportional spend on drug-based therapeutic technology compared to disease burden in Oncology is below average while keeping total drug spend and growth rates in line with the other European developed health care markets (EU-18), all providing universal care and facing similar funding constraints of budgets under continued austerity. Belgium is among the leading countries in survival rates for most prominent cancers.

While this provides apparent evidence for the cost-effectiveness of present Belgian healthcare policy governing the use of oncological medicines-based therapy, its robustness against future shocks caused by an extremely promising pipeline of breakthrough innovative but expensive drug-based targeted and immunotherapies now materializing and becoming accessible to the patient, remains to be proven.

In this Policy Paper we will argue that the future of access to innovative medicine-based therapies is about society engaging into a ‘conditional’ dialogue with the innovative biopharmaceutical industry, centred on therapeutic innovation and competition.

First, we provide an overview of the epidemiological trends in the field of cancer and discuss the present and suggested future role of the Belgian Cancer Registry in understanding and managing cancer. Then, we present an overview of the evolutions in drug-based therapeutic innovation, which is essential to understand the regulatory innovation and health policy changes needed to manage for affordable access to these innovative medicines in a sustainable way i.e. preserving the biopharmaceutical industry’s potential for future innovation.

Second, taking as a basis the budgetary needs following from the pipeline of emerging innovative targeted therapies and immunotherapies we confront this with the Minister of Health and Wellbeing’s Pact for Growth convened with the biopharmaceutical industry in Summer 2015. Here, it will be argued that such a dialogue with industry will have to be institutionalized into a future horizon scanning system incorporating a transversal budgeting system for health budgets.

Then, in the following chapters we take the medicinal innovation and access process as the basis to discuss how the conditional dialogue between institutional parties and innovative biopharmaceutical industry could be shaped to ultimately bring safe and affordable medicines that respond to patient’s unmet needs and respect the current social equality of access to anticancer drugs in Belgium.

The implementation of a conditional dialogue between society and the innovative medical industry hinges on five principles; (1) acting with foresight, (2) early dialogue between
manufacturer and payer, (3) an integrated foresight, access & pricing system, (4) value-based and competition-based market access, and be (5) founded on an outcome-based disease-centric healthcare learning system.

Doing so, the conditional dialogue will ensure expedited affordable access to and foster future therapeutic innovation while guaranteeing value-based prices for new pharmaceuticals.

We conclude each Chapter of this Policy Paper with a set of recommendations for health policy makers, healthcare providers and health services, and industry alike.

For summary conclusions and an overview of all recommendations made by this study to implement a conditional dialogue paradigm between society and industry the reader is referred to the last Chapter.
2. The Burden of Cancer in Belgium – Epidemiology

In Belgium, cancer is the second highest cause of disease burden on society for the foreseeable future. Its share of disease burden due to cancer is above European benchmark average. As can be verified on Figure 1 its share of overall DALY\(^2\) is 19.6% compared to an international 18.8% average.

![Oncology Share of Disease Burden in Belgium compared to European benchmark](Source: WHO and BCG Analysis presented November 2015)\(^3\)

Belgium has the second highest overall cancer incidence rate across the benchmark and the highest for breast and bladder cancer. The age-adjusted incidence of the “top 4” cancers in Belgium is above average European benchmark level (Figure 2). However, the high disease burden is not driven by adverse age demographics.

Standardized mortality of cancers in Belgium is above European benchmark average for breast, lung and bladder cancer (Figure 3).

---

\(^2\) DALY: Disability Adjusted Life Years.


Note: NHL = Non-Hodgkin Lymphoma.
Source: Lancet, "Global surveillance of cancer survival 1995-2009: analysis of individual data for 25'676'887 patients from 279 population-based registries in 67 countries" (CONCORD 2); Survival of Cancer Patients in Europe, the EUROCare-5 Study.
Figure 2: Age-adjusted incidence of cancer types in comparison to other European countries (Source: Globoscan and BCG Analysis, 2012). 

Figure 3: Age-standardized mortality rates of cancer types in comparison to other European countries (Source: Globoscan and BCG Analysis, 2012).

Notes:
4 All data from 2012; NHL = Non-Hodgkin Lymphoma.
5 See Note 3.
However, on a comparative basis, as can be verified on Figure 4, Belgium has very high cancer 5-year relative survival rates (RSR) in comparison to other European countries.

![Relative 5 year survival (%)](image)

**Figure 4: Age-standardized relative 5 year survival (%) of cancer types in comparison to other European countries (Source⁶: Lancet, Data from 2005-2009).**

### 2.1 Incidence

In 2013, the Belgian Cancer Registry has registered 65,487 new cancers (excluding non-melanoma skin cancer) 34,542 in males, 30,945 in females. This means that one in three males and one in four females will get the disease before their 75th anniversary.

The incidence data are equivalent to an average annual crude incidence of 634 new cases per 100,000 person years in men and 547 per 100,000 in women. Age-standardised incidence (using the European Standard Population) is 493/100,000 in men and 403/100,000 in women. This is equivalent to a male predominance of 22%, whereas in other European countries, this predominance has already decreased e.g. to 17% (the Netherlands and Finland), 16% (Norway), owing to a more early increased incidence of lung cancer in women and a more rapid decrease in men.

Combining the data from men and women reveals that breast and prostate cancer are the most frequent tumours (10,695 and 7,909 cases, respectively), followed by colorectal cancer (8,670) and lung cancer (8,196). These four tumour localisations together cover

---

more than 54% of all the cancers. Figure 5 shows an overview of the incidence of the ten most frequently occurring cancers per sex.

![Figure 5: Overview of the ten most frequently occurring tumours in Belgium, 2013](source: Belgian Cancer Registry [www.belgiancancerregistry.org/cancerfigures])

The incidence of cancer is closely associated with age. Figure 6 shows the age-specific incidence data for the year 2013. About two thirds of the women and three quarters of the men are 60 years of age or older at the time of diagnosis. In men, the incidence increases mainly from the age of 55 and reaches 3,000 per 100,000 person years at the age of 75 years. In women, the increase in cancer incidence starts at a younger age (from 40 years on) and reaches 1,500 per 100,000 person years at the age of over 75 years. The higher age-specific incidence in the age group 25 to 55 years in women is mainly caused by breast cancer, melanoma and gynaecological cancers. From the age of 55 years, the age-specific incidence is higher in men than in women, but from the age of 65 years, the risk of developing cancer in men is more than twice as high as the risk in women.
2.2 Mortality

In 2012, a total number of 26,923 persons died of cancer, i.e. 15,146 males (56%) and 11,777 females (44%). Cancer is the second leading cause of death (26%) in Belgium after cardiovascular diseases which are responsible for 29% of all deaths\(^7\). The fifteen most frequent causes of death due to cancer are presented in Figure 7. Mortality-Incidence ratios of close to 1 are typically found in cancer types that are fatal in the short-term, such as lung, liver, oesophageal and pancreas carcinoma. Other types of cancer such as breast, colon, skin, uterine cervix and testis with a better prognosis, have a mortality-incidence ratio of less than 1.

\(^7\) Algemene Directie Statistiek België (Statistics Belgium www.statel.fgov.be/).
2.3 Evolution of Cancer Incidence, 2004-2013

In Belgium, the annual number of new invasive tumours increased by 12% between 2004 and 2013, i.e. from 58,465 to 65,487. This is mainly due to the ageing and growth of the population. Other causes can be found in changes in lifestyle and risk factors (UV exposure, tobacco and alcohol consumption, obesity, HPV infection, ...), early detection by population based screening programs (such as the breast, colorectal and cervical cancer screening program), opportunistic screening activities (e.g. PSA assay) and early diagnosis due to more advanced imaging techniques. Each type of cancer has its specific evolution over time (increase, decrease, stable).

Comparisons of absolute numbers and crude incidence rates can lead to inaccurate conclusions due to differences in the age structure of the populations. This can be solved by comparing age standardised incidence rates using the European standard population (ESR).

Age standardised incidence rates (ESR) are decreasing in males (0.6% annually) while the risk for females is increasing with 1% annually, mostly due to the opposite incidence trends for smoking related cancers (see Figure 4). In males, mainly the rapid decline in prostate cancer incidence since 2006 (-3.5% per year) and a continuous decline in head and neck cancer (-1.4% per year) and lung cancer (-1.2% per year) explain the decrease of risk.
over time. Cancer incidence in females increases by 1% per year due to the growing incidence rate of tobacco related cancers (especially lung cancer and head and neck cancer). Women started smoking later than men and its impact is now being felt in the figures. The average latency between cigarette smoking and lung cancer is about 30 years (Weiss, 1997).

2.4 Evolution of Cancer Mortality, 2004-2012

Although the absolute number of cancer deaths is increasing over time, the age standardised mortality rate (or the risk of dying from cancer) is decreasing (see Figure 8). The mortality rate is decreasing three times faster in males (-1.6% annually) than in females (-0.5% annually). The decline in men is largely due to a reduction of the lung cancer incidence, which has an immediate, significant and beneficial effect on mortality. The improvement in both sexes is due to better diagnostic tools, more sensitive medical imaging techniques and to screening programs which allow a (more) early diagnosis with more effective treatment and better prognosis. Improved treatment strategies at various levels such as for example advanced and less invasive surgical techniques, optimized radiation techniques, new chemotherapeutic agents, targeted therapies, immunotherapy and combinations of therapies also explain these results. In addition, the evolving knowledge of the tumour characteristics enables to administer targeted and more personalized treatments.

![Figure 8: Invasive tumours (excluding non-melanoma skin cancer): Trends in age-standardised incidence and mortality rate (ESR) by sex, 2004-2013](image-url)
2.5 Projection 2025

By 2025, the number of patients diagnosed with cancer is expected to increase to almost 78,000. This represents an increase of 19% when compared to 2013 (see Figure 9). In males, this is mainly due to the ageing and growth of the population. On the other hand, an additional increase is expected in females since the risk in females is more increasing over time when compared to males. The male-female ratio will be close to 1.0 in 2025 meaning that the number of cancers will be divided equally among men and women. Due to the latency time, it is expected that women will continue their strong catch up with males for tobacco-related tumours (lung cancer, head and neck tumours), while for men a lasting downward trend is expected for these cancers as well as for prostate cancer.

Figure 9 (left): Invasive tumours (excl. non-melanoma skin cancer): Observed and projected number of new diagnoses (N) by sex, Belgium 2004-2025, and Figure 9 (right): Invasive tumours (excl. non-melanoma skin cancer): Observed and projected incidence (WSR) by sex, Belgium 2004-2025

2.6 Survival

The estimated 5-year relative survival rates are 59% in males and 69% in females. Figure 10 and 11 give an overview of the tumours with the highest and lowest 5-year relative survival rates.
An increase of 4% in the relative survival proportion for solid tumours is observed over time in the Flemish Region (1999-2013). The prognosis for haematological malignancies has substantially improved mostly due to therapeutic advances: the 5-year relative survival has increased from 56% in the period 1999-2003 to 67% in the period 2008-2012 (see Figure 12).
2.7 The Belgian Cancer Registry

The previous overview of key epidemiologic data on cancer incidence and mortality was prepared by the Belgian Cancer Registry (BCR).

Since 2005, the Belgian Cancer Registry (BCR) produces and monitors the Belgian descriptive statistics on cancer incidence including spatiotemporal trends, prevalence and survival.

The Law of December 2006 provides a legal basis for the activities of the Cancer Registry and describes the clinical and pathological anatomy pathway for data collection. Data are routinely gathered in these two settings allowing first-way missed cases to be notified by the other one. The law also provides the authorisation to use the national number (social security number INSZ-NISS) for the patient identification. The use of this unique patient ID offers a very interesting perspective on linkage with other available medical and/or administrative data (e.g. nomenclature, hospital discharge and pharmacological data) and hence longitudinal research. Such a linkage not only requires the authorization of the Privacy Commission but also implies severe measures and rules for privacy protection and confidentiality.

The Flemish region achieved a full coverage and completeness since the year of incidence 1999. The data were published in ‘Cancer Incidence in Five Continents’, volume VIII and IX (Curado, Edwards, Shin, & al., 2007). From 2004 on, data are also complete for the whole country: they were more recently published in ‘Cancer Incidence in Five Continents’, volume X (Forman, Bray, Brewster, & al.). Data are now available for Belgium and Flanders.

---

Figure 12: Evolution of the 5-year relative survival in the Flemish Region for solid and haematological malignancies

---

for 10 (2004-2013), respectively 15 consecutive incidence years. Cancer incidence data 2014 will be made available as from October 2016.

A first survival report (diagnoses 2004-2008) for Belgium and the three regions was published in December 2012, followed by a specific booklet in 2013 on incidence and survival of Childhood Cancer (period 2004-2009) and haematological malignancies in 2015 (period 2004-2012). In June 2014, a prevalence report (1, 5, 10, 15 and 20 years) was made available for the first time.

In a European and International context, the Belgian Cancer Registry participates in the European network of Cancer Registries, Eurocare, RareCarenet, Cancer Incidence in Five Continents (IARC) and the Concord study.

The progress made during the last years, is clearly related to the legislation activities, new initiatives on clinical registration in the Flemish, Brussels and Walloon hospitals, and the sustained registration efforts of the data managers, physicians, oncologists and pathologists from the oncological care programs.

Although the figures represent a very important output of a cancer registry, this achievement can only be considered as a first deliverable in a multi-step process. Cancer registries indeed see their role more and more extended in cancer control (Armstrong, 1992). The creation of a Belgian comprehensive information data base does not only aim to produce the classic descriptive epidemiologic parameters (such as incidence, prevalence, survival and mortality) but also to evaluate the real world outcome and quality of life of cancer patients through the systematic analysis of evidence-based interventions in prevention, early diagnosis, (new) treatment (strategies), and palliative care. Quality of care studies indeed should result in optimizing treatment strategies, reducing variability in treatment and ultimately improving the prognosis and quality of life of cancer patients. These studies frequently focus on process, structure and outcome parameters.

The BCR is increasingly involved in these studies through data obtained by linkage of the cancer registry with administrative data bases. The availability of these data led to participation in a number of KCE reports on quality indicators in oncology (breast, oesophageal, stomach and lung cancer), the Vlaams Indicatoren Project (VIP). These collaborations resulted in individual feedback reports from the BCR to all Belgian hospitals involved in cancer diagnosis and treatment.

Sometimes, more detailed and clinically up to date information on prognostic and predictive variables, diagnostic procedures, biomarkers, treatment patterns and follow up is necessary in order to analyse, evaluate and monitor real world (and population based) medical practice and outcome (e.g. evaluation of new reimbursement strategies for new drugs). Possible solutions would be prospective cancer registration through extension of the Multidisciplinary Team Meeting form with a well-defined, relevant set of supplementary

---

13 Vlaams Indicatorenproject: breast, rectum and prostate cancer and the Walloon and Brussels Hospital Quality Indicators initiative (BCR-Stichting tegen Kanker/Fondation contre le Cancer: breast, rectum and prostate cancer).
variables. There is also a clear need for a standardized synoptic reporting system for the pathology protocols to make relevant pathologic and genetic characteristics of the tumour more available for research.

It remains an important challenge to make use of information technology as much as possible and to avoid overlapping registration efforts.

2.8 Epidemiological Conclusions

One man in three and one woman in four will develop cancer before their 75th anniversary. Every year, there are more than 65,400 new cancer diagnoses in Belgium.

Breast and prostate cancer are the most frequent tumours, followed by colorectal cancer and lung cancer. These four tumour localisations together cover more than 54% of all the cancers.

In 2012, a total number of 26,923 persons died of cancer in Belgium, i.e. 15,146 males (56%) and 11,777 females (44%). Cancer is the second leading cause of death (26%) after cardiovascular diseases.

The 5-year estimated relative survival rates are 59% in males and 69% in females (period 2009-2013).

An increase of 4% in the relative survival proportion for solid tumours is observed over time in the Flemish Region (1999-2013). The prognosis for haematological malignancies has substantially improved: the 5-year relative survival has increased from 56% in the period 1999-2003 to 67% in the period 2008-2012.

By 2025, the number of patients diagnosed with cancer is expected to increase to almost 78,000. This represents an increase of 19% when compared to 2013.

By 2025, the male-female ratio will be close to 1.0 in 2025 meaning that the number of cancers will be divided equally among men and women.

2.9 Recommendations

- The BCR should be involved in prospective cancer registration through extension of the Multidisciplinary Oncology Team Meeting form with a well-defined, relevant set of supplementary variables.
- A standardized synoptic reporting system should be set up for the pathology protocols to make relevant pathologic and genetic characteristics of the tumour more available for research.
- Information technology should be used to a maximal extent and to avoid overlapping registration efforts.
3. Future Developments in Oncological Medical Innovation

Cancer often remains an incurable disease and survival is to a large extent determined by the cancer type. The 5-year age-adjusted relative survival rate (RSR) for all cancers taken together is around 60% with less than 5% improvement over the past decade. Some cancers such as prostate cancer, breast cancer and lymphomas are highly curable because they are often detected in a localized stage and cured by surgery and/or radiotherapy and adjuvant systemic treatments or because of effective systemic treatment of more advanced disease. On the other hand, figures remain most dramatic for lung cancer where the 5-year RSR is between 15 and 25% depending on age category. It is clear that in many cancers an unmet medical need persists either for the primary treatment (e.g. lung cancer, pancreatic cancer) or for more advanced stages of the disease (metastatic cancer).

Future improvement in fighting cancer will depend on progress at several levels of care: prevention, screening programs for early detection and drug development.

3.1 Driving forces of oncological medical innovation

Medical innovation in cancer treatment has evolved from classical chemotherapy to so called “targeted therapy” using drugs able to target the tumour cell specifically or its microenvironment. Examples are targeting oncogene products such as the BCR-ABL kinase by tyrosine kinase inhibitors, targeting intracellular pathways involved in oncogenesis such as the NFKappa-B pathway by proteasome inhibitors, or HER signalling pathways in breast and lung cancer. The tumour microenvironment (cancer cell niche, cytokine pathways, vascularisation) can be targeted by immunomodulatory drugs or angiogenesis inhibitors. Medical innovation is based on the expanding knowledge and understanding of cancer biology. The basic concept is to identify biological, often molecular, biomarkers involved in the oncogenic process and then to target these markers by more or less specific drugs. Precision medicine and personalized therapy based on targeting mutations of tumours in individual patients are increasingly introduced. Also, immunotherapy has emerged as an almost universal approach in cancer treatment including the use of monoclonal antibodies targeting cancer cells and checkpoint inhibitors allowing to reverse cancer-induced cellular immune paresis. Targeted therapy including immunotherapy is likely to change therapeutic paradigms in oncology as illustrated by progress in some cancers but somewhat more pronounced in haematological malignancies. Hematologic malignancies represent 10% of all malignancies in the Western world and over the past decade an almost 10% improvement of the RSR, from 57 to 66%, has been observed. This is to a large extent the result of medical innovation: tyrosine kinase inhibitors (chronic myeloid leukaemia), anti-CD20 antibodies (B cell lymphoma and leukaemia), proteasome inhibitors (myeloma) and immunomodulating agents (myeloma, lymphoma).

There are currently 18 targeted treatments accessible in Belgium. A very promising clinical development pipeline is becoming accessible in the 2016 – 2020 horizon (Figure11). Also, whilst advances in genomics and cell biology have led to ever more selective therapeutics,
for some pathologies combinations have been shown to be beneficial in tumour treatment. Therefore, targeted therapies are now or will be given in combination with other drugs, addressing multiple pathways in tumours hence potentially leading to substantial increases in overall survival. As an example, the addition of pertuzumab to trastuzumab and docetaxel in HER2-positive metastatic breast cancer led to a significant increase of 15.7 months in median overall survival as compared with addition of placebo (56.5 months versus 40.8 months) (Swain et al., 2015). This survival improvement is unprecedented among studies of metastatic breast cancer. However, these combinations also lead to increased total prices and to potentially higher side effects.

Immunotherapies are the latest cancer treatments now becoming accessible to patients holding the promise of improved survival. They make highly effective use of the patient's own anticancer immune response enabling effective cell killing. What makes many of the recent immune-oncology therapies wanted is their demonstrated anti-tumour effects potentially translating into long-term survival. A total of 45 indications are presently in the pipeline, with non-small cell lung cancer and melanoma the most competitively crowded indications. Two immunotherapies are currently accessible to patients in Belgium (Figures 13-14).

Although immunotherapies (light-shaded area in Figure 13) account for only one third of the agents in the innovative oncology therapy pipeline, they account for half of the prospective total budget impact, due to the broad range of indications they will be able to target and the comparatively high probability of ultimate success in clinical development.
Finally, much later gene therapies are expected to become accessible. Editing genes and correcting inherited mutations by introducing genetic material into cells this technology and chimeric antigen receptor (CAR) technology allows for effective individualized exploitation of immune responses to fight cancer. While targeting currently very limited numbers of patients and tailored to the individual patient some expect prices in the range of €1million. This extremely high price might be the strongest access-inhibiting factor pleading for future flexible platform- and outcome-based approval and registration strategies (Brennan & Wilson, 2014; Naldini, 2015).

3.2 The evolutionary nature of anti-cancer drug development

The innovation path from initial fundamental scientific discovery (most often in academic context) to an approved drug is usually long, spanning one or more decades. While all elements are important and essential, the potential impact of the decisions taken along that path gradually decreases as drug development progresses. For example not making the scientific discovery or missing discoverable effectiveness biomarkers will have a much larger impact than post-marketing corrective measures and studies. However, in late clinical development and market access there can still be incremental aspects to be handled.

Cancer treatments typically become available in one sub-population but sometimes evolve and expand value into subsequent paths of new indications or lines of therapy, often in combination with other drugs. For example, treatments might start off fighting metastatic cancer and evolve into an adjuvant curative scenario, following a signal of treatment benefit and better disease biology understanding (Cook, Golec, Vernon, & Pink, 2011) or start in a specific mutated target in a specific cancer type and then expand to other cancer types bearing the same mutation. Trastuzumab, a drug used in about 20% of women with breast cancer is a case in point illustrating the evolutionary nature of fighting cancer.
Granted US market approval in 1998 for metastatic breast cancer it was granted access for adjuvant treatment of early breast cancer in 2006. Initial projections showed that by 2016 the annual volume of patients receiving adjuvant treatment would be more than three times higher than the volume of metastatic cancer patients, which in turn and over time would also lower the incidence of these latter patients (Garrison, 2010). Trastuzumab also expanded to a subtype of gastric cancer. Another example is lenalidomide in multiple myeloma. It was developed around 2005 initially as the successor of thalidomide in relapsed and refractory multiple myeloma leading to 11 months progression-free survival in this relatively small subset of patients. Today it has become established as first-line treatment in more than two-thirds of the newly diagnosed myeloma population leading to a time to next treatment of 39 months. In the meantime, lenalidomide has maintained its position in combinations for the relapsed and refractory myeloma setting. These examples show that the clinical and economic value of cancer treatment can expand dramatically over time following an evolutionary pathway. For example, Precision Belgium is a BSMO initiative that aims at expanding genotype-based targeted cancer treatments beyond the strict registered disease associated contexts. An example is afatinib, a pan-HER inhibitor approved for EGFR mutated lung cancer that will be explored in EGFR, HER and HER3 mutant cancers of any type.

Pathways will include newer combinations of targeted treatments and immunotherapies. Taking the trastuzumab example further, in 2013 it was combined with pertuzumab in addition to taxanes for treating HER2-positive metastatic or locally recurrent unresectable breast cancer (Swain et al., 2015; Swain et al., 2013). Adding to the complexity, combinations can and will be produced by several manufacturers leading to co-opetition with manufacturers possibly jointly developing and marketing combinations in one indication whilst competing in other indications.

Typically, medical and economic value expansion beyond an initial approved indication sets out in six possible paths; use in different disease stages, use in different treatment lines or stage, use in different treatment regimen, orphan designations, move into patient sub-populations for whom the drug works better, and use in new administration routes (Réjon-Parrilla et al., 2014).

Each step made represents progress in cancer treatment and in oncology researchers’ disease understanding with successes and failures in clinical trials providing clues for the best next steps. The addition of all these small steps potentially leads to substantial gains in survival (Paddock et al., 2015).

From a pharmacoeconomic point of view, this evolutionary nature of cancer treatment development pleads for a dynamic model of net economic value estimation. In this model, net economic value is estimated using cumulative numbers for the medical and economical value generated over the whole product life cycle. This instead of the presently widely used static method evaluating one new product for one specific indication at the time (Garrison, 2010; Garrison & Veenstra, 2009).

---

14 Co-opetition is the combined and simultaneous use of competition and strategic collaboration of two companies with each other.
3.3 Cancer treatment R&D races too much in overlapping domains

Research and development of innovative cancer therapies is conducted by competing biopharmaceutical companies being engaged in so-called R&D races. In such a race, the first in class is referred to as the breakthrough drug followed by ‘me-too’ follow-on drugs, the latter being defined as new drugs with a similar chemical structure or the same mechanism of action or both as that of the breakthrough drug defining the new class. Industry critics condemn research on these follow-on drugs to be duplicative, wasteful and showing limited progress against major cancers. Too many me-too drug development portfolios are claimed to result in duplication of efforts and redundant pharmaceutical pipelines (Jena, Calfee, Mansley, & Philipson, 2009; Light & Lexchin, 2012), leading to potentially huge amounts of needless development costs and thus contributing to high prices.

Figure 15: Comparison of Cancer Therapies in the Pipelines of Pharmaceutical Companies According to Their Putative Mechanisms of Action (Source: Fojo et al, 2014)

As such a recent study depicted in Figure 15 above found that 124 oncology agents (74%) in the pipelines of nine top companies active in oncology examined had an overlapping mechanism of action\textsuperscript{15}, while only 41 (24%) had a non-overlapping mechanism of action (Fojo, Mailankody, & Lo, 2014).

\textsuperscript{15} Non-overlapping was defined as a pharmaceutical agent whose mechanism of action is not similar to that of an FDA-approved drug and also not similar to that of a drug in the pipeline of another top-10 company. However,
Another recent mapping of 100 phase II and phase III clinical trials shows that increased competition from biopharmaceutical companies that are new in the field can be expected in multiple indications (Figure 16).

![Figure 16: Pipelines of Pharmaceutical Companies by Numbers and Selected Pathways (Source: IMS Health Global Oncology Trend Report 2015)](image)

However, it should be noted that while being the result of research conducted in parallel, so-called ‘me-too’ developments cannot always be seen as sheer imitations of the breakthrough drug, hence purely as the result of wasted R&D effort. Instead, while some of them provide therapeutic options they do inject possible use of price competition by payers (DiMasi & Paquette, 2004, 2005; Hollis, 2005), avoiding monopolistic winner-takes-all scenarios.

While it may seem plausible for a pharmaceutical company to drop research in riskier therapeutic areas given the uncertain return on investments it does make itself vulnerable to the resulting fierce price competition in these ‘easy’ over-crowded ‘me-too’ areas. Also, investors show their appreciation for more firms being active in R&D races in innovative therapeutic areas featuring high unmet need and with high breakthrough innovation potential by lowering the risk premium they commonly demand.

Taken together, the use of price competition (in on-patent overcrowded areas) and R&D competition (in areas with high breakthrough potential) promoted respectively by payers and investors has a positive downward effect on novel therapy price, on the speed with

---

this does not exclude the possibility that the mechanism is similar to that of a drug in the pipeline of a company that is not in this list (Fojo et al., 2014, legend description).
which novel therapies are discovered in domains of high unmet medical need, and on avoiding monopolistic therapy markets (Pammolli, 2011).

3.4 Cancer research is expensive

Progress in the field of cancer research has its price. Cancer drugs tend to be more expensive than those in many other therapeutic areas. This is due to the high complexity of the science involved, which ultimately leads to longer clinical development times and lower success rates, especially in the most expensive Phase III trials characterised by a high rate of late failure (Burock, Meunier, & Lacombe, 2013; DiMasi & Grabowski, 2007; Lacombe et al., 2014).

Cancer treatment development costs being already amongst the highest across disease areas, given the by definition smaller sub-populations targeted than the ones targeted by conventional therapies, they are even more expensive than non-targeted treatments (Figure17).

![Price comparison on targeted therapies vs. non-targeted therapies per cycle in NSCLC treatment](image)

*Figure 17: Source: Drummond, Presentation at ISPOR Conference Milan, Nov 2015.*

These considerations however are different for the new immunotherapies that have both a variably high success rate in clinical development and a broad applicability in cancer.

For individualized gene therapies in the future high development risk and extremely individual applicability might become a challenge again.
Although a higher payer willingness to pay is observed as compared to other therapeutic areas (Seabury, Goldman, Maclean, Penrod, & Lakdawalla, 2012), health technology assessment organizations faced with—often far too—high incremental cost effectiveness ratios (ICER)\textsuperscript{16} are ‘struggling with cancer’s “exceptionalism”’ (Neumann, Bliss, & Chambers, 2012).

The effectiveness of the most recent immunotherapies and their high subjective tolerability, which in contrast to small sub-population targeted therapies and even most chemotherapies are potentially applicable to a wide range of patient (sub)-populations, together with an ageing population is worrying payers worldwide faced with a too high burden on healthcare budgets.

3.5 The difficulty of assessing value in oncology

Questions can be raised about the reliability of surrogate endpoints that are predominantly used in cancer research. How predictive are they for the primary clinical outcome i.e. overall survival (OS), Progression-free survival (PFS), being used the most for gaining market access (Table 1) is also relevant due to its impact on patient experience. However, it should be validated in a real world setting.

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Definition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>Time from randomisation until death from any cause, measured in the intent-to-treat population</td>
<td>18</td>
</tr>
<tr>
<td>Progression-free survival (PFS)</td>
<td>Time from randomisation until objective tumour progression or death</td>
<td>28</td>
</tr>
<tr>
<td>Event-free survival (EFS)</td>
<td>Time after primary treatment in which the patient remains free of certain complications or events that the treatment was intended to prevent or delay</td>
<td>1</td>
</tr>
<tr>
<td>Overall response rate (ORR)</td>
<td>Proportion of patients with a tumour size reduction of a predefined amount and for a minimum time period</td>
<td>5</td>
</tr>
<tr>
<td>PFS/OS (co-primary)</td>
<td>Both PFS and OS are evaluated as primary endpoints</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>e.g., Major Cytogenic Response (MCR), change in SEGA volume, Complete Responses (CR/Cbu)</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 1: Primary endpoints of pivotal studies available in EU HTA agencies for the period of 2011-2015 (Drummond, ISPOR Conference, Nov 2015)

\textsuperscript{16} The ICER measures the economic value of a new health technology as a ratio—the incremental cost $\Delta$C of a new intervention versus the standard of care (the numerator) over the incremental health benefits $\Delta$QALY (the denominator). The latter is summarized in a common metric that aims to convert all health outcomes to an equivalent number of healthy life-years, by adjusting expected life-years gained for changes in the quality of life: this is called the “quality-adjusted” life-year (QALY) or “utility.” The ICER is typically used in a Cost Effectiveness analysis (CEA) and measured as ICER = $\Delta$C/$\Delta$QALY.
Given the poor results of FDA-approved results in the real clinical world, in a recent study analysing 5 years (2011 – 2015) of drug approvals on the basis of surrogate end points and their subsequent overall survival, the authors argued for a timeline for drugs approved on the basis of a surrogate endpoint to prove their effectiveness. Based on a median follow-up of 4.4 years of 36 drugs, of which 19 were approved based on response rates (RR) and 17 based on progression-free survival (PFS), 18 failed to show any improvement on OS and 13 had no result, only 5 demonstrated improvement in OS in randomized clinical trials (Kim & Prasad, 2015). In the future additional surrogate endpoints such as pCR after neoadjuvant therapy in breast cancer should be further considered (Wang-Lopez et al., 2015).

Overall survival as a decision endpoint is acceptable in cancers or cancer stages or specific cancer lines of treatment that currently have a bad prognosis. In other cancers such as early breast cancers this endpoint is so distant that awaiting this evidence will delay access of patients to innovative treatments for many years.

However considering the above, decisions based on surrogate endpoint should be temporary until the final endpoint, overall survival, can be assessed.

The inherent conflict between a need for early access to medicines that are likely (by a strong surrogate endpoint) to improve outcome and the long interval needed to assess survival impact could in some cases be solved by granting temporary and reversible market access conditioned on subsequent demonstration of survival benefit. Reimbursement authorities could even invoke the uncertainties to negotiate significantly lower pricing.

3.6 Towards precision medicine

Following Jameson and Longo (2015) we define precision medicine as ‘treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations’. This with the goal to improve clinical outcomes for individual patients whilst minimizing exposure to potentially toxic and costly therapies for those less likely to have a response to a particular treatment (Jameson & Longo, 2015).

In the treatment of cancer, testing for genomic abnormalities (germline or somatic) has truly transformed the field. As an example, in lung cancer, traditional anatomic and histological criteria-based classification is being augmented by molecular testing of genetic markers like EGFR, MET, ROS, and ALK done by specific diagnostic tests leading to more specific use and fewer side effects of targeted treatments. Also, these diagnostic technologies are not only used for properly targeting personalized medicine usage, but also more and more for screening, monitoring and treatment optimization (Schneider et al., 2012).

The convergence of biomedical technologies like genetics, epigenetics, proteomics and metabolomics and diagnostic and imaging technology turns medical science more and
more into an information science. Now, precision medicine can be exercised based on patient data captured in the precision medicine ecosystem built on biobanks and the patient’s unique electronic health record (EHR) to which patients, clinicians, researchers and clinical laboratories have portal-based access to design and implement actionable treatment strategies (Aronson & Rehm, 2015; Jameson & Longo, 2015).

3.7 Conclusions

Therapeutic innovation in cancer treatment is an evolutionary process where each – predominantly incremental, not radical– novel therapy builds on previous discoveries to gradually close the gap to a full cure. Therefore, access and pricing discussed later should be seen in this light; a drug candidate offering marginal improvement in a metastatic setting might later offer real breakthrough survival or enhanced quality of life potential in adjuvant settings. So, for each access and pricing decision made after the initial decision health payers need to take into account the additional value created by a therapy over its entire life cycle.

Cancer treatments are developed in a step-wise process targeting predominantly overcrowded but also high medical need therapeutic areas with a therapeutic void. Health policy should stimulate industry conducting research into the latter high-risk areas representing highest unmet medical need for society, whilst discouraging research into overcrowded areas. One of the tools at the payers’ disposal is the reimbursement decision.

To have this high impact a European or global cooperation is needed as it is unlikely that measures taken at the Belgian level could have repercussions on early development choices.

Given the difficulty assessing medical added value of cancer treatments, access pathways should be made flexible and conditional upon proven performance in clinical studies, but also modulated by results obtained in the real world. Regulatory access and reimbursement procedures should be adapted to this latter thinking.

Regulatory access and reimbursement processes for cancer treatments should cater for the trend towards combination therapies and drug-diagnostic solutions used to enable personalized medicine.

Innovative pricing approaches are certainly to be recommended for combinations of targeted therapies and certainly for future gene therapies to eventually become broadly accessible.
4. Funding of Access to Therapeutic Innovation in Oncology

Belgium’s total healthcare spend is in line with its economic productivity and in line with the other EU countries. Its oncology share of drug spend is slightly-below average but generally in line and growing at the same pace as the other EU countries. However, relative to its share of overall disease burden in all countries a general underspending is observed on oncological drug spending (Figure 18).

In our view, this general underspending in oncology relative to its overall disease burden demonstrates that it is essentially the technology supply side, or the pipeline of innovative medicines becoming accessible that determines the budget needed to fund innovation. While until 2013 the innovative drug-based therapeutic pipeline was essentially flat due to major late-stage clinical development failure (Burock et al., 2013; Lacombe et al., 2014), the last years it is actually raising thanks to a range of novel targeted therapies and immunotherapies now rapidly becoming accessible. As a result and as discussed before, given their high-cost nature and the more general applicability of immunotherapies across a broad range of indications this will severely stress the Belgian pharmaceutical specialties budget for the years to come.

Figure 18: Oncology Share of Drug Spend (%) Relative to its Share of Overall Disease Burden (DALYs)(%); Source BCG Analysis, November 2015
Better prevention and prediction, the latter enabled by population stratification initiated at General Practitioner level potentially modulating treatment for high- and low-risk cases could, later in the more costly phases of the disease pathway lead to easing the pressure on several health budgets provided the necessary investments in point-of-care diagnostics at primary care level are made (Van Dyck et al., 2012). Also, national screening programs (e.g., breast cancer and colon cancer) in collaboration with the GP level can be very successful for early detection and lead to substantial cost-savings on the long term. In addition genetic testing for high risk genes could also avoid costly diseases.

However, next to prevention, prediction and early detection other health policy and budgetary measures will have to be taken to fund the emerging innovative oncological treatment pipeline and to keep the pharmaceutical specialties budget under control.

4.1 A 2020 Oncology Horizon Scan

The present Belgian budgeting system provides a systematic one-year forecast of pharmaceutical specialties expenditure. Although budget projection accuracy is rather high we do consider a one year-only planning horizon to be too short-sighted to detect longer term surges (or drops) in drug-based therapeutic innovation as seen now in the present day case of oncology. Also, budgeting for innovation in diagnostics is not covered at present.

Instead, to increase horizon scanning robustness and reliability, a pharmaceutical specialties and diagnostics pipeline should be constructed on an international, possibly European level. Also, the horizon scan time laps should be fixed at 5 year instead of shorter periods. This is caused by the fact that in the pharmaceutical industry the time to get certainty about projected probability of access is too long. Especially now in the oncology case we described here before where the majority of the pipeline is now in Phase II and hence still featuring low access probability and being separated 3 to 5 years from market access.

The 2020 Oncology Horizon scan in Figure 19 below plots projected budget need from the therapeutic innovation pipeline, defined here as all targeted therapies and immunotherapies accessible to the Belgian healthcare system, as described in further detail in Appendix 2.

Over the full 5-year horizon the budget needed for oncology will more than double from the present €491M to over one billion Euros in 2020 (Table 2). By 2020, the budget needed for innovative targeted and immunotherapies (see Appendix 2 for definition) will amount to €825 M, then representing 72% instead of the present 50% of the total oncology drug budget.
Figure 19: (a) 2020 projection of innovative cancer therapies defined as targeted therapies and immunotherapies as part of the overall Belgian pharmaceutical specialties budget for oncology; (b) 2020 Projection of development and access phase contribution to innovative cancer therapies budget (Source: Vlerick HMC Analysis)
By 2020, the budget for oncology will have risen to about 24% of the total projected Belgian pharmaceutical specialties budget, representing a significant raise from the present (Figure 20).

This projection of net budgetary needs based already on net prices before negotiation\textsuperscript{17}, takes into consideration the product lifecycle perspective of the present budgeting system and its ensuing fixed and automatic price reductions (Figure 21; green area) foreseen for funding innovation (Figure 21; red area). Notice that these price reductions gradually increase the access bar for novel competitive therapies while the lower cost comparator makes it more difficult for a new drug to show a beneficial cost-effectiveness level (Camejo, McGrath, & Herings, 2011).

Doing the horizon scan one can observe in Figure 21 that taking a three-year planning horizon the mechanistic price reductions from innovative cancer therapies available on the

\textsuperscript{17} Prices negotiated between payer and manufacturer are held confidential
market can only fund 35% of innovation. Taking a five year perspective this drops to only 24% indicating the need for urgent further budgetary measures, potentially including budget increase, to fund the emerging therapeutic innovation pipeline. In our analysis we did not take into account the cannibalisation effects of new drugs on existing drugs, nor did we take into account the effect of cost sharing market entry agreements.

Furthermore, disinvesting from low-benefit use of established medicines (Henshall, Schuller, & Mardhani-Bane, 2012), de-reimbursements (Lepage-Nefkens et al., 2013) will have to be considered to better balance the budget needed for therapeutic innovation in oncology. As recently suggested as a measure to increase competition in the US healthcare system (Shepherd, 2016), also in the Belgian context, providing equal access to the market to “cheap” originals, generics and biosimilars is a way to free up means for therapeutic innovation.

![Figure 21: 2020 projection of funding released through expected mechanistic price cuts in Belgium and the expected sales from novel targeted therapies and immunotherapies. The total price reductions over these 5 years can fund 24% of the projected therapeutic innovation. (Source: Vlerick HMC Analysis)](image)

Clearly, systematically doing this scan on a sufficiently long horizon is needed to reveal early enough whether we do have a problem funding innovation if not changing health budgetary policy now. As a result of this horizon scanning one can conclude that to fund innovation in cancer treatment, if no further measures are taken the pharmaceutical specialties budget will need to be raised notwithstanding optimal price control measures proposed further. Needless to say that in the present conditions of austerity this is not an obvious choice, but might be justified taking into account the gradual filling of therapeutic voids in cancer treatment.
Fit with the 2015 Minister’s Growth Pact

The agreement concluded by the Minister of Health and the pharmaceutical industry should be applauded as a first attempt to formulate policy starting from a horizon scan. This effort now needs to be embedded in the management of the healthcare system.

To fund the projected 2016 – 2020 oncology innovation pipeline, given the fixed pharmaceutical specialties budget annual growth rates agreed upon with industry in the Minister’s Summer 2015 Growth Pact, it can be verified in Table 3 below that the agreed upon budget is in line with the needs for innovation. Only, it will be exceeded near its end in 2018 when then starting to be confronted with a significant raise in budgetary needs caused by a Phase III and pre-market access pipeline becoming gradually more accessible (Figure19(b)).

It does mean in the long run that the Minister’s 2015 Growth Pact should not be seen as a one-off exercise. Instead, a longer-term agreement between the payer and industry should become an institutionalised part of a systematic horizon scanning system that, starting from the unmet patient needs is able to confront demand and supply of innovative medical technology over a sufficiently long horizon enabling action with foresight.

The future horizon scanning system should evaluate the maturity and time to access of novel technologies, allocate budgets and set priorities in a holistic way. Instead of treating various health budgets in isolation they should be handled in relation to each other, also called transversal budgeting. As an example, if a new drug-based therapeutic innovation can be shown in real world to reduce the need for hospitalization then this should be reckoned for in the various related budgets.

Horizon scanning should not be a seen as a stand-alone exercise, conducted in splendid isolation. Instead, it should be the basis for priority setting, which will be much needed in conditions of austerity.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIHDI TOTAL</strong></td>
<td>4.057M</td>
<td>4.074M</td>
<td>4.134M</td>
<td>4.209M</td>
<td>4.365M</td>
<td>4.522M</td>
<td>4.635M</td>
</tr>
<tr>
<td><strong>Of which PMx</strong></td>
<td>203M</td>
<td>220M</td>
<td>262M</td>
<td>294M</td>
<td>362M</td>
<td>430M</td>
<td>481M</td>
</tr>
<tr>
<td><strong>Of which IO</strong></td>
<td>16M</td>
<td>25M</td>
<td>46M</td>
<td>94M</td>
<td>184M</td>
<td>279M</td>
<td>343M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIHDI TOTAL</strong></td>
<td>4.057M</td>
<td>4.074M</td>
<td>4.127M</td>
<td>4.130M</td>
<td>4.135M</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Realised Savings</strong></td>
<td>-</td>
<td>60</td>
<td>96</td>
<td>126</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Comparison projection of Minister’s Pact and our projected needs caused by the total targeted therapies and immunotherapies innovative pipeline.
(Source: Vlerick HMC Analysis)
4.2 A first role of competition in a Conditional Dialogue between Payers and Industry

From the future developments in oncological medical innovation described in the previous Chapter followed by the budgetary discussion above we conclude so far that health policy innovation is needed to match the supply and demand of technological innovation with constrained pharmaceutical specialties budgets and that competition can play a defining role in managing this matching process.

As discussed before, health policy innovation should be geared to avoid biopharmaceutical me-too innovation behaviour and stimulate R&D races for breakthrough innovation in domains of high unmet medical need by making use of respectively price and R&D competition. This has been shown to have a downward pressure on me-too prices whilst still having a positive effect on the speed with which new therapies at a price premium are discovered. Hence, making use of price and R&D competition a better match is made between supply and demand for innovative medical technology.

From this Chapter it should have become clear that acting with sufficient foresight is essential to capture potential future needs for innovative medical technology, which should be funded to maximum extent by savings from increased competition amongst and from generics and biosimilars. Also, de-reimbursements resulting from novel therapeutics successfully competing with and hence replacing less cost-effective incumbent therapies should free up resources for medical innovation.

These are the first elements of a paradigm, a way of working between society and the innovative pharmaceutical industry we would define as a 'Conditional Dialogue', centred on competition and rewarding true therapeutic innovation. Society engaging into a conditional dialogue acknowledges that industry has an obligation to satisfy shareholder expected return whilst engaging in high-risk research but also the corporate social responsibility to serve the public good to make people better on conditions society can afford. This aims for a win-win outcome with a positive return on investment for pharma at prices society considers to be fair and affordable.

From a health budget perspective the conditional dialogue can be defined to be successful to the extent it can avoid a budget raise needed to match supply and demand of innovative medical technology.

In the following Chapters we will discuss subsequent elements constituting the conditional dialogue between society and industry.
4.3 Recommendations

To sustainably match the demand and need for innovative medicines a pharmaceutical specialties budgeting system should be based on resolving unmet needs and responding to societal preferences, specifying societal urgency.

- To capture the scientific evolution of the oncology treatment pipeline a 5-year rolling (i.e. updated every year) forecast should be conducted by NHIDI in collaboration with the pharmaceutical industry. Ideally this is conducted on an international or European level.

- Conducted at national level only, a horizon scanning transversal budgeting system is used as input to a 5-year rolling (i.e. yearly-adjusted) budget forecast exercise.

- Savings considered within a transversal budgeting system take into account product life cycle-based adaptations to prices and de-reimbursement of actual medications.

- The use of cheap medicines should be promoted to release means for funding innovation.

- Implementation of strategies to obtain the lowest price possible also for innovative treatments, with an emphasis on me-too innovation.

- Budget spill-overs, calculated from budget impact analysis (BIA), are taken into account releasing cross-budget lines means for innovation, leading to better use of scarce resources. The transversal system takes into consideration spill-overs from surgery, radiotherapy, and hospitalisation.

- Transparency on budget allocation should be well managed toward public opinion and societal expectations. However, it should not be the basis for setting expectations towards patient populations.
5. The Need for Early Involvement in Adaptive Pathways-enabled Medicines Development

Payers and regulators should foster industry research into novel oncological therapies responding to areas of unmet medical need and simultaneously raise the bar for me-too innovation. Unmet medical need means a ‘condition for which there exists no satisfactory methods of diagnosis, prevention or treatment in the Community or, even if such a method exists, that the medicinal product concerned will be of major therapeutic advantage to those affected’¹⁸. An example of unmet medical need is pancreatic cancer for which a solution is lacking. Or, one can have an innovative solution available like an immunotherapy but access is lacking if the regulatory system is too stringent.

It should be noted that in the present access system initiative to introduce new therapies is heavily tilted towards industry. In our view, it is society’s duty to restore that balance and indicate to industry which medical, therapeutic and societal needs are most wanted. A horizon scanning system matching unmet need with the present status of the scientific pipeline can serve such a purpose but needs to be built. This way the health priorities and long-term goals of the country are matched with the potential offered by the cancer treatment pipeline.

It is important that the perspectives of all health stakeholders are taken into account to perform this horizon scan. Collection of evidence-based information from medical oncologists, industrial and academic clinicians, patients and payers should be the foundation for the system. In practice this could be a task of the Cancer Centre involving all stakeholders and in cooperation with a European level to carry enough weight.

One could for example lead to commissioning academia/industry in developing novel therapies in a particular high need situation such as pancreatic cancer. An historic example is the path that led to the development of paclitaxel in the 1980-90’s (DeFuria & Horovitz, 1993), still a very valuable drug in an array of cancers that even expanded further in recent years.

Second, there is growing patient demand for timely access to novel therapies while “the safest drug that no one can afford or that arrives too late is of no benefit to a patient” (Eichler et al., 2015). Although met by some with scepticism stating that fast market access has led to an estimated 35% increase in safety warnings and substantial numbers of black-box warnings and even market withdrawals (Cassie et al., 2014; Naci, Carter, & Mossialos, 2015), an adaptive development and licensing paradigm seems to be the way forward for payers and regulators to improve access to promising therapies (Eichler et al., 2015; Eichler et al., 2012). Care should be taken that further trial commitments are effectively complied with which has been problematic in the past.

Third, both national and international publicly funded pragmatic and practice-oriented clinical trials could be the answer for research questions that are unlikely to be answered by medical manufacturers. This could be research into older often cheap medicines outside the innovative cancer treatment field, that no longer can be patented but that may be

instrumental fighting its causes such as alcohol abuse (FlemishCancerLeague, 2013). Therefore, the recommendations of the related KCE Report 246Cs (Neyt, Christiaens, Demotes, & Hulstaert, 2015) are supported. The questions put in such trials and the trial methodology should be carefully picked as the past has shown that academia is often unable to complete phase III trials in a reasonable timespan, so answers might come late or not at all.

Finally, acknowledging the need to concentrate expertise there should be less treatment centres with more patients or adequate supported networking to expose patients to the highest expertise possible and enhance recruitment in clinical trials. The nodes in these networks should be able to follow easier procedures, make use of simplified recruitment facilitated by interconnected patient registers and databases.

There’s a need for clarification of the standard of care cost as compared to the extra hospital cost for patients recruited in a RCT (Randomized Clinical Trial). There’s a need for a standard contract and fee structure.

As a general rule, to ensure efficient data collection whilst managing data and analysis quality it is recommended to decentralize screening in peripheral hospitals and GP practices but to centralize experimental treatments. In this respect, MOCs between institutions are part of network creation.

5.1 Stimulating research into areas of unmet need

Stimulating research into areas of unmet need starts with horizon scanning serving as an early warning system to policy makers identifying the pipeline of promising health technologies becoming available. On the other hand, capturing domains of unmet need using more inclusive processes involving patient communities and a broad range of health stakeholders seems to be the best way forward to prioritize attention for appropriate decision making and resource allocation supporting promising industry research (Mattison, 2013; Murphy, Packer, Stevens, & Simpson, 2007). Involving the patient in the decision-making process increases transparency and societal buy-in to health policy. Also, it provides insight in their driving rationales, ethical considerations and fundamental trade-offs made (Cleemput et al., 2014). The conceptual framework to assess the value of cancer treatment recently developed by ASCO and ESMO was designed to also be used to facilitate physician – patient discussion on the personalized treatment to be followed (Cherny et al., 2015; Schnipper et al., 2015). It needs to be further evaluated but should be applauded as an initiative while promoting patient engagement in her/his treatment process.

In 2014, in an effort to align this supply and demand for innovative medical technology the unmet medical need (UMN) process was implemented in Belgium providing early temporary access (ETA) and reimbursement (ETR) to promising medicines that however are not accessible yet following the normal regulatory pathway. This program is not very successful for oncology and should be amended.

At this moment, to be implementable in practice a prioritization system for unmet need should be worked out in detail. Disease burden might be a good starting point. As such cancer would feature higher on the priority list than diabetes. However, in our view this
should not be confounded with quality of treatment. As an example, we do not believe that a PFS-only oncology treatment should be compared with enhanced glycaemia control in diabetes. Both treatments should be compared with other candidate therapies in their own domains for prioritization.

Finally, based upon this prioritization and starting from Phase I early scientific advice on development plans, regulatory support and early health technology assessment (HTA) advice should be provided to promising medicines in development in industry, providing them with an ‘early access’ label. In this sense the Safe and Timely Access to Medicines (STAMP) PRIME project conducted by the Federal Agency for Medicines and Health Products (FAMP) is supported. It can be used by industry innovators for early market assessment and economic evaluation and for investigating pricing and reimbursement scenarios connected to clinical development (IJzerman & Steuten, 2011). The goal of such scientific advice process should be to collaboratively (payer/regulator – manufacturer) getting agreement on what constitutes innovation and getting clear on which target to aim for; which value expansion to be expected, which could lead to more positive HTA decisions.

Finally, for payers, being involved early in clinical development also prepares them well for subsequent price negotiations preceding market access (Pham et al., 2014).

Concluding, early dialogue between innovating manufacturers, regulators, and HTA/payers integrating scientific and HTA advice avoids being involved only in late, hence marginal therapy development. This would lead to more positive market authorization decisions in areas of high unmet medical need.

5.2 Towards open collaborative Adaptive Pathways and Adaptive Licensing

The core paradigm in oncology drug development needs to be changed to be built on early patient stratification (Blankin, Piantadosi, & Hollingworth, 2015). To do so, open (i.e. across organisations and companies) registries-based patient recruitment for clinical studies should be stimulated to answer the recruitment challenges in stratified medicine. An appropriate legal framework is needed for bio-banking to stimulate research and innovation in advanced medicinal products.

Also, to cater for the high uncertainty the process should follow an adaptive pathway making therapy development and market authorization an iterative process that progressively provides access to patients integrated with adaptive pricing.

Furthermore, Belgium should be further seen as a Reference Member State for clinical trials oncology and be recognized as “preferential reporter member state” as from 2016. It should maintain its position for Phase I Clinical Trials.

Science-industry involvement should be organised on an international level. Belgium should participate more in these international collaborations. HOVON and EORTC academic trials are a good example of this.
Finally, all clinical results (RCT and RWE (Real World Evidence)) should be published on a centralised portal reporting in advance conflicts of interest following the ‘only once’ principle and connected in a EU context. In this respect, the national clinical trial site that facilitates the access to such information could be a major help (e.g. cancertrials.be organized by the BSMO) (Awada et al., 2013).

The more recent Precision Belgium initiative for off-label genotype-matched treatments also works in that direction including a centralized database.

5.3 Recommendations

Oncological research needs fast-track approvals for potential breakthrough medicines, more pre-competitive collaboration, patient pooling of data and an adaptive medicinal development process that seamlessly transits from clinical studies showing efficacy to real world evidence-based studies testing for (cost-)effectiveness in the real world. More specifically;

- Open registries-based patient recruitment for clinical studies should be stimulated to answer the recruitment challenges in stratified oncological medicine.
- An appropriate legal framework is needed for biobanking to stimulate research and innovation in advanced medicinal products.
- To cater for the high uncertainty therapy development and market authorization should be made an iterative ‘adaptive’ process that progressively provides access to patients conditional upon performance and integrated with adaptive pricing reflecting the real-time level of evidence.
- Initiatives increasing early payer and HTA advice involvement in clinical development decision making should be stimulated. Early advice is scientific in nature and hence dealing with concerns on comparators and endpoints (binding advice), pragmatic (i.e. better attuned to real-life evidence) trials not being too selective in study populations.
- Current Art 81, 81bis and ETA/ETR unmet need initiatives should be improved providing early access and early visibility on the most value-adding medical technology innovation.
- Early dialogue should also be clear on the unmet clinical need and its implications for further development and on the link to post-marketing evidence generation.
- To accelerate medical progress, incentives should be created to allow research institutions to access data and samples to identify better biomarkers for better patient selection. It is crucial therefore that tissue banks and data collected in pharma sponsored studies be opened to academic investigators.
- Need for clarification of the standard of care cost as compared to the extra hospital cost for patients recruited in a RCT. There’s a need for a standard contract and fee structure.
• Fund both national and international publicly funded pragmatic and practice-oriented clinical trials to answer specific clinical effectiveness and cost-effectiveness questions that are unlikely to be answered by medical manufacturers. The recommendations of the related KCE Report 246Cs (Neyt et al., 2015) are supported.

• Science-industry involvement should be organised on international level. Belgium should participate more in these international collaborations and should be promoted as a preferred state for conducting Phase I clinical trials.

• Acknowledging the need for less experimental treatment centres with more patients; easier procedures, simplification of recruitment (connections registers and database).

• Recommendation to decentralize screening but centralize experimental treatment. Proposition for MOCs between institutions (part of network creation).
6. Accelerating Access to Affordable Innovative Medicines in Oncology

A pharmaceutical company willing to release its medicine-based therapies on the European market seeks market authorization at either EMA (European Medicines Agency) via the centralized or decentralized authorisation procedure or via the national Belgian FAGG (Federal Agency for Medicines and Health Products) procedure. Approval of oncology drugs is mostly performed by a request at EMA level where the quality, safety and efficacy of the drug under ideal conditions i.e. following clinical –not real-life– studies, is evaluated against an active comparator or against placebo if the drug has no direct substitutes.

Then, at Belgian national level a file is submitted by the applicant to the Commission for Reimbursement of Medicines (CRM/CTG) that will provide advice on reimbursement. In parallel, a price proposal is sent to the Ministry of Economic Affairs. The applicant assigns a class claim to its drugs. “Class 1 is restricted to drugs with added therapeutic value, Class 2 for drugs with similar or analogous therapeutic value and Class 3 includes generics and copies” (Le Polain, Franken, Koopmanschap, & Cleemput, 2010).

Belgium is seen to have one of the slowest market access systems for innovative medicines or new indications in Europe with average time between market authorization and reimbursement for Class I medicines exceeding 350 days on average (Figure 22). However, this is not only the result of the decision process. It is also caused by applicant-initiated “clock stops” meant to collect additional data requested by the CRM/CTG. In general, these delays could have a negative impact on patient outcomes. In cancer treatment it results in reduced survival. However this often is accommodated by pharma providing free early drug access when a reimbursement file is likely to ultimately succeed.

---

Figure 22: Average time between EU Approval and local accessibility, 2008 – 2010 (in days)
(Source: European Federation of Pharmaceutical Industries and Associations)

---


20 Notes Figure 22: 1. for 66 new medicines obtaining marketing authorization by EMA between 2008 and 2010. No data for Bulgaria, Croatia, Germany, Hungary, Iceland, Latvia, Lithuania, Luxembourg, Poland 2. Data up and until end of 2009 3. Average for 29 new medicines; Note: W.A.I.T. = Waiting to Access Innovative Therapies.
The decision taken to establish in Belgium the specialised CRM/CTG committee for the assessment and appraisal of new drug proposals was and still is well received by all health players involved. Although the drug pricing and reimbursement procedure followed is clear to all parties, with enforced deadlines –Belgium having to accept the company-stated price if not handled within 180 days– it still has one of the longest real observed timelines in Europe. We and many others would want to see that Belgian national access to therapeutic innovation should be granted at the same time as market approval at EMA level. This could be on conditional and reversible terms pending a definitive decision.

In its novel therapy appraisal the CRM/CTG, as in other European countries has the added therapeutic value i.e. efficacy, effectiveness, safety and side-effects, ease of use and comfort prevailing in its evaluation made. Next to these criteria, pricing, budget impact, cost-effectiveness and therapeutic importance in the light of unmet medical need are also taken into consideration. As in most of the other European countries (Le Polain et al., 2010), all of these criteria are used to formulate a binary access decision (Class 1-3 granted) in a multiple criterion decision deliberation (MCDD) based on a holistic consideration of the criteria, rather than being the result of an explicit hierarchy or formal weighing of the criteria in a multiple criterion decision analysis (MCDA).

Although having cost-effectiveness as one of the appraisal criteria, as in most other European countries, with the exception of the UK and Sweden, it is not formally used as a threshold in the pricing decision (Caro et al., 2010). So novel therapy added value, although influencing the price negotiated, is actually decoupled from pricing.

Belgium applies elements of value-based pricing but does not have it integrated in its pricing & reimbursement system where for all medicines external reference pricing (ERP), widely used in Europe, is used as supportive information, calculating a benchmark price as the average of a basket of 24 countries, (Bouvy & Vogler, 2013), more specifically for Belgium 6 countries. This ERP system also implies that Belgium, as a small country referenced by countries with larger markets it is especially vulnerable to launch sequence strategies used by pharmaceutical companies to delay or avoid launching new drugs in markets with potential lower prices. For example, following Rémuzat (2015) ‘there is evidence that pharmaceutical companies systematically delayed dossier submission in Belgium in order to avoid the Belgian price, usually not in the highest EU range’. Industry analysis conducted by pharma.be contradicts this.

Finally, a critique of the current reimbursement system is that patients are not systematically involved in CRM/CTG decision-making. It is claimed that, although not necessarily being versed in medicinal science patients can and should have a voice related to the ethics of decision-making (Cleemput et al., 2014; FlemishCancerLeague, 2013). Also, further research in close collaboration with patients should be conducted to better understand the behavioural and societal aspects of the patient in her/his caregiver environment. However, being the first stakeholder most intimately involved in the ultimate decision, in our opinion they should not be consulted related to individual therapy access files. Still, during the treatment process patients should be actively involved to understand to a maximum extent the most relevant treatment benefits, and the trade-offs between
benefits and harms. They could also be involved in post-marketing real-world studies including patient preference measurements.

Concluding, although the Belgian pricing & reimbursement decision-making process was innovative at its creation it is in need now of an overhaul following three proposed key principles. First, actions should be taken to improve access timing in line with EMA market authorization. In this context and given the evolution towards a drug-diagnostic nature of targeted therapy solutions the market access and pricing & reimbursement process should be organised for simultaneous evaluation of diagnostic and targeted drug so that a belated access decision of one component of a solution cannot stall the other one, as suggested in Van Dyck & Geldof (2015). Second, in an effort to enhance transparency of pricing decision making, a shift is needed from the presently used external reference pricing system towards a value-based pricing policy as the basis for value-for-money competitive payer-manufacturer negotiations. Value-based prices for innovative agents should reward therapeutic innovation. But also, if properly designed a value-based pricing system can be used by the payer to tilt the negotiation power balance into its favour when being confronted with prices set by global biopharmaceutical manufacturers. Finally, third, pricing and access decisions for novel therapeutics should be made flexible and contingent upon the risk they represent to society and their outcome proven in the real world. Therefore, access and pricing decisions taken in the CRM/CTG should be made less rigid and revisable in the light of new evidence at the initiative of any of the stakeholders represented in the CTG/CRM. For example this could be competition-based pricing when innovative me-too drugs are subsequently becoming available (next section). Doing so, as further explained in the next Chapter, they should evolve following novel therapy real world evidence built up in a coverage with evidence development (CED) or a pay-for-performance (PFP) scheme.

6.1 Dealing with unsustainable prices in oncology

The trend of unaffordable oncological drug prices are source of controversy world-wide bringing in the question of fairness of cancer drug pricing, particularly in the US where there’s a feeling that drug pricing has become more to do with ‘what the market can bear’ (Kantarjian & Rajkumar, 2015) rather than being oriented on the value therapeutic innovation brings to the healthcare system and the patient in particular.
As can be verified in Figure 23 above, in a recent longitudinal study of oncology treatment prices in the US they have shown to have risen in a number steps. However, what is more to be worrying about is that there’s a growing general feeling that cancer treatment prices have grown completely out of proportion and their prices do not reflect their worth any more (ExpertsInChronicMyeloidLeukemia, 2013; Howard, Bach, Berndt, & Conti, 2015). As summarized in The Lancet: “The cost of the new generation of drugs is getting out of all proportion to the added benefit” (Cavalli, 2013). Although newer drugs are associated with greater survival benefits (Howard et al., 2015), at least in some cases drug prices are felt to be rising faster than the accumulated health benefits associated with them.

How do the prices of new cancer drugs get decided? A group of more than 100 experts in chronic myeloid leukaemia (CML) argue that price increases “follow a simple formula: start with the price for the most recent similar drug on the market and price the new one within 10% to 20% of that price (usually higher)”. Further, they provide the example of imatinib, a targeted therapy that was priced at $30.000 at initial launch in the US in 2001 and for which the price has more than tripled since then in 2012 despite R&D already being accounted for, new FDA-approved indications and a dramatically increasing prevalence, which gave raise to questions about the morally justifiable price for a cancer drug. They conclude stating their belief “that drug prices should reflect objective measures of benefit,
but also should not exceed values that harm our patients and societies” (ExpertsInChronicMyeloidLeukemia, 2013). They further propose a dialogue involving all parties to curb the situation.

Now, the problem of disproportional rising of drug prices is not confined to the US, but initial undisputed price setting in the US seems often to be at the root of the global problem. Drug pricing being a global process (Danzon, Towe, & Mestre-Ferrandiz, 2015) delivering affordable cancer care in high-income countries like in Europe has also become seen to be a burden stressing health budgets. While in the US the non-ability of payers to negotiate is probably one of the main drivers of high prices, in particular in Europe with its public payer systems more and more interacting with industry there’s a feeling that value-based approaches, having suitable clinical research and integrated early health economic studies, not accepting substandard evidence and an informed transparent regulatory system can bend the cost curve and deliver fair prices for real value offered by therapeutic innovation (Sullivan et al., 2011).

Therefore, inspired by thirty years of health payers documented efforts to get drug prices under control (Leopold, Chambers, & Wagner, 2016; Sullivan et al., 2011), a range of market access agreements used across Europe (Jaroslawski & Toumi, 2011), and the nature of anti-cancer drug innovation as specified in Chapter 3 above, we propose a conditional dialogue to be arranged between health payers and the innovative biopharmaceutical industry. This should allow pharmaceutical innovators to formulate a basis of reimbursement that leads to a positive return on investment whilst being mindful of physicians’, patients’ and payers’ norms of fairness in pricing.

Now, medicines pricing conducted by pharmaceutical companies is a global approach that follows Ramsey optimal pricing. Following this logic ‘charging different prices in different markets based on willingness and ability to pay is economically rational and efficient in the sense of minimizing welfare loss resulting from monopoly’ (Danzon & Towe, 2003). This way richer countries contribute more to finance global R&D than poorer countries that are given access to the novel medicine but at an affordable price.

In Belgium, shaped in the CRM/CTG and taking maximal patient value for money as a decision criterion this conditional dialogue could operate following a set of pricing methods that fill in the key principles of the conditional dialogue proposed before as the basis for a redesigned reimbursement system that is centred on competition and rewarding true innovation.

The high prices of cancer treatment should more and more lead to negotiations based on value-based principles. The evolutionary nature of cancer drug development pleads for the use of dynamic lifecycle pricing and multi-indication pricing. The difficulty of assessing value in oncology using overall survival (OS) has led to the use of surrogate endpoints like progression-free survival (PFS) being used instead. However, both clinicians and regulators are concerned about real world effectiveness and cost-effectiveness of these PFS-based market approvals. This will necessarily lead to therapy pricing being in the future more and more outcome-based, based on comparative effectiveness –rather than on efficacy alone–, and leading to risk-based payment models and coverage with evidence development.
We discuss each in turn below. Dynamic lifecycle pricing, outcome-based, risk-based payment models, and coverage with evidence development will be dealt with in the next Chapter.

Excluded from the following is the use of insurance-based models to pay for high-cost therapies, making continued payment contingent upon improved patient health as measured using biomarkers (Brennan & Wilson, 2014; Naldini, 2015). Also, platform-based approval and registration strategies for individual patient-targeted gene and cell therapies 'as is the case for the transfer of T-cell antigen receptor genes that target tumour neoantigens into autologous T cells of people with cancer' (Naldini, 2015), will not be further elaborated here but could be the subject of further work.

6.2 Negotiating following value-based principles pricing

Instead of or in addition to external reference pricing (ERP) widely used in Europe today, pricing following value-based principles should be the basis for negotiations between payer and manufacturer. The major argument against ERP is that it does not reflect the willingness to pay of a country. Instead, it merely aligns its prices to a basket of prices which lead to convergence but not necessarily to price a country can afford or is willing to pay (Bouvy & Vogler, 2013). It limits a country’s freedom to accept a price that is commensurate its national health system.

Negotiating following value-based principles represents an approach to pricing that takes the basic principle of value-based pricing but which is more in line with the reality of present decision-making and the potential of the decision-making methods used today. Similar to the latter value-based pricing concept the quoted price in the negotiation should be based on an evidence-based scientific assessment of cost and clinically-proven benefits of the new technology (Claxton, Sculpher, & Carroll, 2011; Danzon et al., 2015). However, the disputable nature of the explicit or implicit ICER threshold used in the method (Cleemput, Neyt, Thiry, De Laet, & Leys, 2011; Ubel, Hirth, & Chernew, 2003) lead us to only use the evidence-base principle of the approach. Also, with ICERs frequently exceeding the £20-£30K threshold the introduction of the Cancer Drug Fund in the UK shows that appraisals using a CE threshold might ‘not always be appropriate for oncology treatments’ (Réjon-Parrilla et al., 2014). And finally, from a recent review QALYs were reported to be limited in their ability to capture the value of health gains (Garau et al., 2011).

Instead, pricing following value-based principles leads to a commercial agreement between payer and manufacturer for a health solution –the latter while potentially a combination of drugs or a targeted treatment-diagnostic combination (Van Den Bulcke et al., 2015) – rewarding effect on patient population outcome and health system efficiency.

21 The ICER measures the economic value of a new health technology as a ratio—the incremental cost ∆C of a new intervention versus the standard of care (the numerator) over the incremental health benefits ∆QALY (the denominator). The latter is summarized in a common metric that aims to convert all health outcomes to an equivalent number of healthy life-years, by adjusting expected life-years gained for changes in the quality of
This in contrast to pricing based on manufacturer input-related factors such as out-of-pocket development costs, costs of failure and required shareholder returns, which only lead to controversy on methodology and assumptions used (DiMasi, Hansen, & Grabowski, 2005; Light & Warburton, 2005a; Light & Warburton, 2005b; Paul et al., 2010).

So, in this method, value is accounted for but it is not immediately tied to what a health payer is willing to pay for an incremental health benefit through the upfront defined threshold. It requires value judgment from the CRM/CTG experts on the clinical benefits and healthcare system costs realized as compared to the best present standard of care.

Pricing following value-based principles can evolve to become value-based differential pricing if one is prepared to assign a willingness-to-pay level to an incremental health benefit. An example in which this could be applied is the new immunotherapies having high upfront likelihood of benefit in melanoma and low in breast cancer. The recent introduction of mandatory baseline e-health registration of high-priced treatments makes such an organ-based categorization of drug use possible. Now, for solid cancers the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) could be used as a standardized approach to derive a relative categorization of the clinically meaningful benefit to be expected from an oncological curative or non-curative treatment, as derived from comparative outcome studies, most commonly Phase III RCTs. Its use is recommended because not consistently using such a standardized approach might lead to overstating benefits potentially causing harm to the credibility of cancer research and, most importantly, to the patient who might become the victim of inappropriate hype or disproportionate expectations (Cherny et al., 2015).

However, the ESMO-MCBS although claimed to be an unbiased tool it is uniquely based on randomized clinical trial data, hence on clinical efficacy data excluding real-world effectiveness evidence. When the full benefit of a treatment can only be seen by looking beyond the period of trial, as in immuno-oncological treatments where a significant portion of the patients remain alive at the end of the trial, the tool in its present form will not rightly assess therapy benefits. Second, in its current form it cannot distinguish between a given clinical benefit in two different cancers affecting different populations. And finally, while not evaluating economic benefits or costs, in its current form it cannot be used directly to evaluate the impact on economic value or pricing. However, it could be used as basis though for such a system. But this would need to be further researched.

As depicted in Figure 24, following ESMO-MCBS a medicine that would fall into the A or B categories for curative treatments and the 4 or 5 categories for non-curative treatments are marked following this method to show substantial improvement in clinical benefit. However, this does not automatically mean they are also of high value, which depends on the price one needs to pay for them. In value-based principles pricing it can be one of the most important criteria used in the judgment when determining the price one is willing to pay.
A method to do so could be seen as an integrated component of a horizon scanning system to be designed where ICER thresholds are varied by health conditions or severity, social or altruistic preferences, potentially using an approach that integrates a range of value elements and integrates them into one transparent decision system informed by the societal values and choices made (Towse & Barnsley, 2013). As an example, in such a system willingness to pay (WTP) could increase with disease severity (Danzon et al., 2015) or when treatments forestall death more immediately i.e. paying more when life expectancy is shorter (Bach, 2015).

6.3 Pricing based on comparative effectiveness

Pricing based on comparative effectiveness allows for rewarding innovation whilst playing out competition when appropriate. Building upon the previous point made related to value-based pricing it does not link pricing to the underlying therapy cost but, instead, it links payment rates to comparative effectiveness information. Following this pricing model a drug therapy candidate can show evidence of superior, comparable or still insufficient comparative clinical effectiveness (Pearson & Bach, 2010).

**Superior comparable effectiveness**

A drug-based therapy candidate can be proposed as showing health technology assessment (HTA)-backed superior comparable effectiveness. In the present Belgian system this would be a Class 1 health solution. To make a positive access decision and determine a price comparative effectiveness –does the candidate differentiate from the present best alternative? – and pharmaceutical specialties budget impact through disease
prevalence should be considered, not a marginal measure such as cost-effectiveness. If the therapy is judged to be superior on effect and its required budget fits the budget constraints foreseen for this type of technology as derived from horizon scanning, then a positive decision should be taken, regardless of cost-effectiveness levels. Budget impact can be limited by price negotiation with the manufacturer and by restricting use.

As an example, pertuzumab, trastuzumab, docetaxel (THP) combination therapy targeting overexpression of the human epidermal growth factor receptor 2 (HER2/neu) occurring in 20-25% of breast cancer patients, is showing low probability of cost-effectiveness, even at willingness to pay (WTP) levels well above commonly accepted thresholds (Durkee et al., 2016).

However, clinical evidence showed high improved progression free survival and significant improvement of overall survival in a metastatic setting. With ICERs varying between $47K per QALY gained when almost given for free and nearing $500K per QALY gained when paid for, the probability of getting access could rightfully be judged to be extremely low if only judged on this criterion. Considering budget impact, widespread use of this regimen in the US population with metastatic disease would cost $3.71 billion. Also considering indirect costs this would rise to $5.14 billion. However, this should be seen in the context of a US cancer-related budget of $207 billion by 2020. So, here we have a case of a therapy being highly effective, not cost-effective but affordable provided upfront a societal choice has been made to tackle this disease with priority, presenting an opportunity cost to other treatment candidates if a budget is constrained, within the context of horizon scanning.

Moreover, a Canadian CEA showed that the addition of pertuzumab was cost-effective in the neoadjuvant (=before definitive surgery) treatment of HER2-positive early breast cancer (Attard et al., 2015), while no impact on survival has been shown (yet). This again shows the limitations of the ICER and demonstrates that a broad perspective, which goes beyond the application of an ICER-only determined threshold, should be used when evaluating drugs for advanced cancer (see section 3.4).

Therefore, access and pricing & reimbursement decision-making should be connected to each other and not be seen in isolation, as currently in use. Doing so, the ICER can be used as the connector, as a basis for (1) price setting following value-based differential pricing principles (Danzon et al., 2015) and possibly corrected as specified in section 6.2 above, and (2) to determine health budget as a result of a systematic horizon scanning exercise, modulated by unmet need and budget impact.

Comparable comparative effectiveness

If the drug solution candidate is judged by oncological experts of the CRM/CTG to be comparable to the first-in-line therapy then therapeutic competition can be used to set a price. This would apply to the Belgian Class 2 candidates. Instead of demanding HTA, a therapeutic reference price would be given that maximally equals the present standard of care solution within the therapeutic cluster.
Given the R&D race character novel therapies become sequentially accessible in a therapeutic class. Downward pressure exerted on prices can be maximized by allowing prices for newcomers to be maximally equal to the lowest price of all presently available alternatives within the therapeutic class. Then, at regular intervals, based on real world evidence built up in disease registries, NIHDI could stimulate voluntarist behaviour of physicians by providing scientific advice informing them about the –then– best cost-effective therapies. This way, manufacturers choosing to be active in ‘me-too’ zones are incentivized to capture more market share by being motivated to lower their price. For a me-too drug moreover a maximum price could be set that is systematically lower by a certain percentage than the first-in class drug.

Oncologists would then still preserve freedom of prescription if a particular drug would be more suitable for a particular patient, but counting on their social education and conscience for choosing in general the cheaper drug.

However, the R&D race character of cancer research signals the importance of estimating likeliness of new and established drugs in the cluster and the difficulty for CRM/CTG experts to judge the comparative difference of the likely sequence of drugs becoming accessible. Taking lung cancer as an example, there are several drug candidates targeting the same cancer causing mechanism, called the ALK rearrangement. Key first line indications are occupied by Pfizer's Xalkori and second line by Novartis’ Zykadia. Of course only 3 to 8% are driven by this ALK mechanism and the high number of candidates in human trials is probably explained by the high price potential of this domain, even knowing that in the US only a few thousand patients will suffer from it. So what would happen with the new candidates? In the negotiation the manufacturer will rightfully try to find unoccupied therapeutic space by proposing a Class 1 innovative agent proposed to be more effective or better tolerated than the present best in the cluster. In any case the patient/society wins by the competition. Or by getting access to a better treatment option if judged to be a Class 1 compound. Or by having access to a potentially cheaper alternative to best in class if judged to be Class 2.

Still insufficient comparable comparative effectiveness

Candidate compounds fit this category if the evidence presented to the CRM/CTG does not allow the innovative therapy to be classified as being comparable, superior or even inferior to the present treatments in the therapeutic cluster. In this case ‘dynamic pricing’ would be used where for a period of three years real world evidence would be collected and a price would be agreed upon which, while still showing uncertain performance, is substantially lower than the actual price that could be received after this initial ‘learning’ period. To accelerate access this period could already start one year before EMA approval.

In the present Belgian system this description would fit the Art. 81 and ETA/ETR regulation. Products that are qualified for this categorization are orphan medicines, Class 1 drugs or products for which reimbursement for a new indication (with a therapeutic or social need) is asked, and for products for which the reference product is reimbursed under “T”, which means after a contract is signed between the pharmaceutical company and the social security. According to Art. 81 (February 2010) and Art. 81bis (July 2014) of the Belgian law, the Minister may allow the negotiation of a reimbursement contract for drugs, which possibly can fulfil the criteria of being an ‘unmet medical need’, for which there was no
definitive motivated proposal formulated by the CRM within the fixed deadline of 150 days due to clinical or budgetary uncertainty. This contract can be proposed on the initiative of the company itself (Art. 81) or by the CRM/CTG (Art. 81bis). The timings of the negotiations for reimbursement are prolonged with a maximum of 120 days. The agreement is formed between the pharmaceutical company and NIHDI, with consent of the Minister of Social Affairs and the Minister of Budget, and results in the possibility of a temporary (maximum three years) reimbursement of the product. The agreement determines the price and reimbursement level of the product under contract and might obligate the pharmaceutical company to make a financial commitment for limiting the NIHDI expenses (e.g. repaying part of the expenses of the product, lowering the reimbursement level of other products of the company, etc.). Data are usually collected during this temporary period to re-evaluate the therapeutic efficiency, the cost-efficiency and the budget impact.

6.5 Multi-indication pricing

As stipulated before and depicted in Figure 25 below, many medicines currently available in oncology and many more in the pipeline will be effective in multiple indications (Aitken, Blansett, & Mawrie, 2015). Medical value delivered is likely to be different across these indications. However, in the present uniform pricing system this does not correctly reflect value which might hamper access or stifle innovation. Knowing that more than 50 per cent of major cancer medicines marketed in 2014 were for multiple indications and that by 2020 this share is estimated at 75 per cent (Mestre-Ferrandiz, Towse, Dellamano, & Pistollato, 2015) this is a problem to be dealt with.

Multi-indication differential pricing is preferred to the use of a single uniform price across indications while if a single price is based on a higher value indication it would be too high for lower value uses/indications potentially leading to restricted access while judged cost-effective. If a single price is based on a lower value indication it could discourage manufacturers to conduct research into areas that then might lead to insufficient return on investment, which would stifle innovation in areas of high unmet need (Chapman & Karlsberg Schaffer, 2015; Mestre-Ferrandiz et al., 2015; Pearson, Dreitlein, & Henshall, 2016).
Figure 25: Anticipated number of oncological products featuring multi-indications  
(Source: Aitken, Blansett and Mawrie, 2015)

In Belgium, by coupling CIVARS (explain) with IMA (explain)sick fund data, both being operational, an integrated information architecture is in place to make indication-specific pricing possible.

6.6 Recommendations

To promote access to therapeutic innovation in areas of high unmet need under conditions of healthcare budget austerity it is recommended to;

- Reform CRM/CTG access and pricing & reimbursement decision-making to make it an integral part of a horizon scanning-based budgeting definition and execution system.
- Reform access and pricing & reimbursement decision-making to be connected to each other. Doing so, the ICER can be used as the connector, as a basis for (1) price setting following value-based differential pricing principles, and (2) to determine health budget as a result of a systematic horizon scanning exercise, modulated by unmet need and health budget impact.
- Implement value-based differential pricing to replace or supplement external reference pricing for Class 1 drugs. It represents a clear evolution from the presently implicitly conducted ‘judgment-based’ decision-making based on value-based principles.
- Implement pricing based on comparative effectiveness allowing for Class 2 competitive pricing when comparative effectiveness is comparable to the most cost-effective present alternative in the therapeutic class.
• Implement for all Classes dynamic pricing conditional upon comparative effectiveness to replace ‘one-off’ pricing at launch.

• Organize for real world evidence collection to support outcome-based and multi-indication pricing

• Start a longitudinal study evaluating cost containment policy effectiveness. In other words: whether the proposed competitive pricing mechanism is strong enough to have a downward effect on drug-based therapy prices.

• Start a study to see how the ESMO-MCBS can be used to evaluate clinical value of novel medicines and to inform health policy decisions as in which early development to stimulate.
7. Building a Learning Healthcare System in Oncology

Today, in most European drug-based therapy development and patient access pathways an essentially linear process of discovery and clinical development is followed by the manufacturer, culminating in a dossier submission to the regulators and payers. It is concluded by a binary approval/no-approval Market Authorization decision being granted at one moment in time after which the actual usage starts.

Pressurized by patients and physicians demanding early this linear process is gradually being replaced by a flexible, evolutionary version. The need for the new adaptive model is exacerbated by the arrival of targeted therapies and immunotherapies typically delivered in domains of high unmet medical need and small-size patient groups.

It should be understood that while randomized clinical trials are considered the gold standard, they may not always be possible as in areas where no or few treatment options exist. Also, RCTs might be challenged given the highly selective nature of included patients, excluding the ‘average’ patient seen in practice. Lung cancer trials might provide an example for this where ‘heavier’ patients might be seen in practice than in trials. Then, additional evidence collected in Phase IV and non-interventional studies in the real-world environment is a necessity.

In this now called ‘adaptive pathway’ process (Eichler et al., 2015; Eichler et al., 2012) the drug candidate progresses in the pathway from lab to patient conditional upon observed sufficient level and reduction of uncertainty on clinical effectiveness and cost-effectiveness. In essence, novel drug evaluation and progression to market access and usage becomes an ‘end-to-end’ continuum where clinical efficacy, safety and side-effects and preliminary healthcare system cost knowledge of the drug candidate accumulated in clinical development is gradually converted into real-world effectiveness, cost-effectiveness and value-in-use knowledge in a set of ‘adaptive licensing’ steps, which are granted conditionally upon delivery of ever deeper scientific evidence of ‘real-world’ drug therapy performance i.e. in standard clinical practice.

Adaptive licensing pushes the initial market license upstream right after phase II. Then, real world evidence (RWE) is gathered and monitored in a patient registry under a risk-based market entry agreement (MEA) concluded with the manufacturer aiming to show positive benefit-risk and added value in a specified patient sub-population, probably the one with the highest unmet medical need. Subsequently, in a longitudinal approach RWE can be further gathered to confirm, review, reject or extend initial authorization and gradually expanding into other subpopulations, further reducing uncertainty. Clearly, this flexible early access approach can only be initiated in domains of unmet need where society judges the immediate availability of the drug to outweigh the inherent residual risk of an expedited approval. It should be noted though that some would still call this approach ‘regulatory enthusiasm for faster market access’ only to the benefit of industry (Naci et al., 2015).

Eventually, the gathering of real world evidence will result in healthcare evolving to become a continuously learning system built on clinical care and real world patient evidence feeding back into research (Aronson & Rehm, 2015; Biankin et al., 2015). As an
example, if patient registry-based information can be aggregated to disease registries they could inform future pharmaceutical discovery of high risk population profiles, in advance of any symptoms and predict disease onset or generate research questions leading to novel therapies based on real world insights.

As a general rule, real world evidence collection systems should be disease-centric rather than being drug product-centric. This will enable comprehensive views of patient’s disease journeys but also inform and facilitate therapeutic reference pricing and competitive price negotiations as specified before.

7.1 Operating the Oncology Healthcare Learning System

The following would be mostly applicable to new treatments that have an indication of a high therapeutic impact in a high medical need area and concern rarer indications in which large-scale evidence gathering is either impossible in a reasonable timeframe. To make the adaptive pathway approach work in practice a learning system should be built and operated requiring (1) a conditional approval and pricing & reimbursement process, (2) patient registries or observational studies collecting information on patient experiences and routine clinical practice, and (3) a set of RCT-based post-authorization safety and effectiveness studies (PASS/PAES) conducted by manufacturers to monitor the life cycle of their innovative therapies brought to the patient.

Towards a conditional approval and pricing & reimbursement process

Following an adaptive licensing process the innovating manufacturer would initially conduct some small (while often orphan designations) conventional RCTs. If successful and based upon this succinct information an initial market approval may be granted (A1 in Figure 26). Subsequent uncontrolled observational studies then aim to show treatment outcome based on real world evidence (e.g. mortality, time to event) and safety (e.g. incidence of life-threatening adverse effects) collected in a patient registry to remain above a pre-agreed threshold, which is a point estimate and interval obtained from the initial RCTs, and prior obtained outcome knowledge of best supportive care. Conditional upon positive results subsequent approval could be granted (A2 in Figure 26) providing the conditions to a full license (Eichler et al., 2012).
To ensure swift and qualitative evidence collection meeting the demands of regulators and HTA bodies an appropriate and facilitative infrastructure needs to be set up, as well as a legal structure to accommodate this secondary use of data (Cole, Garrison, Mestre-Ferrandiz, & Towse, 2015). In Belgium, such an adaptive process making use of patient registries can already now be made possible making use of the CIVARS system provided it is connected with the IMA payment data as captured by the sick funds.

Registries-based or science-based research?

It should be noted that the mentioned registry-based observational studies are uncontrolled meaning that unlike clinical controlled clinical trials, in which patient inclusion and exclusion criteria are stipulated in the trial protocol to minimize bias and promote internal validity, here this is not the case. Instead, real world registries typically have heterogeneous patient enrolment aiming to reduce uncertainty about efficacy or effectiveness in the tested population as compared to the standard of care, whether the initial patient sub-population is the right one and does not need to be adapted following real world evidence gathered (Garrison Jr. et al., 2013). This results in registries to be used more to complement prior clinical knowledge focussing on comorbidities and the use of concomitant medications, rather than to confirm prior results. By definition registries are not protocol-driven, which distinguishes them from Phase IIIb to Phase IV studies, which can be conducted as protocol-driven RCT. This means that, to support continued market access decision-making post-marketing protocol-driven science is still seen to be needed to correct earlier access. As an example in lung cancer EGFR inhibitors are shown not to work or even to be detrimental in EGFRwt (Kelly et al., 2008). Still being reimbursed in 2016 shows post-reimbursement evidence could have been used to correct (revoke) access.

Due to their patient heterogeneity, uniqueness, prospective and non-interventional design exploring patient reported outcomes, disease resource utilization, outcome or safety and risk assessments, observational studies are more seen as ‘learning vehicles’ whose results
are seen by many not to weigh up against protocol-steered prospective post-marketing trials. Leading to additional expenses on the manufacturer and an unwarranted burden on oncologists and sometimes even patients they are not generally seen to add value.

With European regulators following the FDA Breakthrough Designation logic, hence becoming more ‘AL in thinking’ and HTA/payers moving in the opposite direction becoming ever more rigid on evidence expectations, challenges are raised for manufacturers and treating physicians alike. All too often expectations for post-launch value assessments are unrealistic, often based on misconceptions about clinical research methodology. Also, multiple single registries capturing data for one company, one product, and one payer are costly to implement from a financial and workload perspective and do not contribute efficiently to public health knowledge. It is rather seen as a post-launch industry investment dominated by the needs of disconnected payer and regulator requests rather than by a programme to increase value of using new medicines.

### 7.2 Towards Dynamic Pricing

Payer – regulator interaction following this adaptive process should be brought in line with pricing. This can be organised around the concept of dynamic pricing in which pricing is synchronized with the conditional approval process thus mimicking its adaptive nature. As depicted in Figure 27 below the value-based price can be modulated by the life cycle phase.

Dynamic pricing could also bring more sophistication in HTA studies looking when it is desirable to publicly fund or reimburse a drug. As mentioned before, the relative therapeutic value of a cancer treatment is likely to change over time. Being brought first to patients suffering from advanced-stage disease, their net health benefit may be marginal or low as compared to the standard of care. However, considering the evolutionary nature of drug development the NHB (Net Health Benefit) can be considerably higher when introduced later in an adjuvant or curative setting, or in when limited to a biomarker-specified patient sub-population.

For this to happen the price of the drug along its life cycle should not be static as defined at launch. Instead, from pre-launch to discontinuation it should be made dynamic following its evolving cost-effectiveness profile, adapted to new medical information coming in including competitive newcomers, and following a potentially new place in the medication-based treatment spectrum (Pistollato, 2015; Schnipper et al., 2015). But more importantly, it would bring more fairness to pricing, both from a payer and from a manufacturer point of view.

As an example depicted in Figure 26 above, entering the first experimental phase of the process entails a drug being conditionally used. As long as its value is under assessment it seems fair that the price is substantially lower than the one eventually obtained at market approval.
While path (1) in Figure 27 above represents the present price-volume arrangement pricing evolution following market authorization, it should move more into the overall pattern above where an initial price is convened with the manufacturer which is lower than the eventual value-based price while being adjusted for the risk it still represents. Then, for each subsequent indication price should not be automatically dropping following ‘automatic’ volume-price considerations. Instead, to promote innovation in oncology, for each subsequent indication the manufacturer or the payer should be allowed to propose an indication-specific price (Ex: Path (2)) based on the comparative value which can be higher or lower than the first indication. The ICER used in this value-based price could build upon the history of the innovative agent (Garrison, 2010; Garrison & Veenstra, 2009).

7.3 Towards an outcome-based healthcare learning system

Outcome-based pricing involves reimbursement for a drug by the payer only when the drug works in real life (Bach, 2009). Outcome-based deals between manufacturers and payers take the form of a Market Entry Agreement (MEA) maximally entailing manufacturer rebates in cases of treatment failure (Ferrario & Kanavos, 2013, 2015).

Summarized in Figure 28 below, real world evidence can be used to manage drug utilization in the real world, giving raise to performance-based agreements (PBA), or to provide evidence regarding the remaining uncertainty in a MEA type called Coverage with Evidence Development (CED). While in the latter CED case real life evidence is used to reassess reimbursement status at the end of the agreement, in the former PBA case depending on the performance results of the drug the manufacturer may be asked to fully or partially rebate in case of treatment failure.
Figure 28: Health-based and Financial-based Market Entry Agreements and their effect on final target variables (Kanavos 2015, Presentation at Vlerick HMC Health Conference)

An example of a ‘Payment for result’ outcome-based MEA scheme can be provided for a hypothetical low impact drug. This being defined as a drug for which the overall size of the benefit is small, where there’s uncertainty on who benefits while lacking a biomarker, and where there’s uncertainty pertaining to the useful duration of therapy. In this case the MEA could entail measuring treatment duration and having the manufacturer pay the first x months of treatment (with x being derived from Phase III clinical trials), subsequently the responder patients fraction is paid by the payer. Alternatively, the drug could be reimbursed if treatment duration is longer than x, and not if less. Such an outcome-based agreement would discourage futile treatments, optimize drug use according to utility, and no assessment of RR (explain) or PFS would be needed. Also, to cater for the uncertainty on useful duration the manufacturer could pay for continuation beyond certain treatment duration.

A recent result of a PBA is provided by an Italian study on the use of bevacizumab in various indications. Here, payment by results including manufacturer payback in case of non-response led to the net effect of list prices being reduced to 80% of its value for breast cancer, lung cancer and renal cell carcinoma, and to slightly above 60% for ovarian cancer.

Finally, these examples show that next to financial-based MEAs, risk-sharing based schemes such as CED or PBA are valid measures to control budget impact. But also, it should be seen by industry as a stimulus for innovation where early access is granted on the condition that real world evidence on performance is collected. In this respect outcome-based MEAs should be seen as enablers and the ‘closing piece’ for personalized care.

Xoxi, E. (Feb 2016) Presentation at Vlerick HMC RWE Workshop, Brussels, Belgium.

22
medicine; the more measurable the results of a candidate treatment, the higher its market potential and stronger the incentive to do research (Jameson & Longo, 2015).

**The need for cancer networks and a Trusted Third Party**

To make the outcome-based learning healthcare system work in oncology implies that a number of important components need to be developed. Among these are a more detailed registration of cancer cases, not only at diagnosis but also at later stages of the disease, at times of relapse or when a treatment line is abandoned or changed. In fact the clinical course of cancer patients should be mapped from the start until cure or treatment failure and death. This will require more elaborated e-communication between healthcare providers and authorities, within the framework of e-health for example. These components are required to evaluate the clinical efficacy of potentially innovative therapies. In view of the diversity of the oncology field, many parameters are needed to be registered and are dependent on the specific cancer subtype. The scientific organisations such as the Belgian Haematology Society and the Belgian Society of Medical Oncology and others should be involved in the design of the specific cancer tracks to be followed. Before such a comprehensive scheme could be implemented it would be necessary to align hospital EPD’s so that automatic data capture by e-health would be possible. Otherwise the additional burden on already heavily challenged oncologists would be unacceptable.

A trusted third party (TTP) such as the Belgian Cancer Registry should be involved to collect, analyse and report the data. Advantages of such an approach include its objectivity and representativeness – as compared to RWE collection being organised by manufacturers –, and potential for national standardisation leading to higher data quality, speed of analysis and centralized build-up of expertise. However, the TTP should be given the legal means to stimulate filling of the registries by all contributing parties like physicians and manufacturers.

On the other hand, the oncology field needs to better organize in order to efficiently capture all the data. Centralizing treatment will only be acceptable for rare/complex cancers. Centralizing diagnosis and therapeutic strategy will be more practicable and should be organized in well-designed cancer networks between hospitals. High-quality registration, comprehensive follow-up and data reporting to the Cancer Registry could be functions related to these cancer networks. These networks can be submitted to quality control mechanisms for conditioned governmental financial support. The Italian experience having implemented an integrated monitoring process and exchange of data between pharmacist, clinician and patients under control of the regulatory authority governed by law may serve as inspiration in this matter (Xoxi, Tomino, de Nigro, & Pani, 2012).
7.4 Recommendations

Main points:

• Real world evidence collection systems should be disease-centric rather than being drug product-centric. This will enable comprehensive views of patient’s disease journeys but also inform and facilitate therapeutic reference pricing and competitive price negotiations as specified before.

• A more detailed registration of cancer cases is needed, not only at diagnosis but also at later stages of the disease, at times of relapse or when a treatment line is abandoned or changed. In fact the clinical course of cancer patients should be mapped from the start until cure or treatment failure and death.

• Promote use of drug monitoring registries supporting capture of drug utilisation data, dynamic pricing and outcome-based market entry agreements (MEA) for innovative medicines in areas of high unmet need.

• Set up patient registries that account for the evolution in patient population and treatment strategies over their lifetime this way enabling cost-effectiveness calculations of medicines relative to alternative treatments.

• Centralize diagnosis and therapeutic strategy setting organized in well-designed cancer networks between hospitals.

• Stimulate the use of coverage with evidence development (CED) by assigning a role of trusted third party (TTP). The Belgian Cancer Registry could take up such a role assuring anonymised capture of real world evidence as opposed to clinical evidence.

• Ensure minimal or preferably no additional administrative burden for healthcare professionals to promote uptake and ensure sustainability of CED systems by automatic capturing of data from aligned hospital EPD’s.

• Have a standardized e-approach for automatic data capturing across the Belgian healthcare landscape, which is currently highly fragmented.
8. Conclusions and Recommendations

The conclusion of this White Paper is that a conditional dialogue is needed between society and the pharmaceutical industry. This should aim for a win-win outcome – positive return on investment for pharma and prices society considers to be fair and affordable. This dialogue is not a one/off conducted when submitting a dossier to get market access. Instead, it runs throughout the entire life cycle of a medicine, from the R&D phase through to launch and during actual market usage.

Success of this conditional dialogue hinges on a performant horizon scanning system. Scientific research drives the supply of technologies and medicines. If policy makers and payers want to determine a realistic budget, they need to know what therapies will become available in the pipeline and confront this with the unmet medical need. To be robust, this horizon scanning should be done on an international or European level and involving payer, patient and industry insights.

A successful conditional dialogue also requires early scientific advice to steer and stimulate R&D and innovation in areas of unmet needs, e.g. lung cancer for which the 5-year age-adjusted relative survival rate is only between 15% and 25%, depending on age category. A horizon scanning system that matches the pipeline of promising therapies with the identified unmet needs should form the basis for priority-setting. All health system stakeholders, including patients should be involved in this process.

For the conditional dialogue to work, the present pricing system should evolve to become a value-based transparent and integrated approval and pricing system that actually rewards innovation in areas of unmet needs. A medicine’s pricing should reflect whether it meets an unmet need, in which case it can be higher, or whether it’s essentially just a me-too product, in which case competitive pricing should be used. Oncologists should be more educated about the societal budgetary constraints and accept that affordability should be prioritized over minor not essential differences between similar drugs. Value-based pricing that rewards innovation also gives more negotiating power to the payer and to society. The question is how much do we as a society want to pay for an improved health benefit? This willingness to pay should be higher for an unmet need.

Finally, this conditional dialogue should be supported by performant post-launch systems to collect real-world evidence in order to set up a learning healthcare system. A system is needed to gather real-world evidence to monitor the performance of a drug after its launch and to intervene if necessary. Gathering evidence in the real world is far from obvious, though, because it’s an uncontrolled environment, with lots of confounding factors. But it’s a must. It also allows pharmaceutical companies to learn and adapt their products to patients’ most pressing needs. And logically, a medicine’s reimbursement should be made conditional on its performance, built up over its life-cycle.

Sustainably providing patients with access to the delivering drug-based cancer treatment pipeline in these times of austerity calls for health budget prioritization and competitive real outcome-based price setting at a level society can afford. A conditional dialogue between society and the innovative biopharmaceutical industry is a prerequisite and a guarantee to make this happen.
Summary Recommendations

The conditional dialogue between society and the innovative medical industry should be based on five principles; (1) acting with foresight, (2) early dialogue between manufacturer and payer, (3) an integrated foresight, access & pricing system, (4) value-based and competition-based pricing, and be (5) founded on an outcome-based disease-centric healthcare learning system.

Acting with foresight

- To capture the scientific evolution of the oncology treatment pipeline a 5-year rolling (i.e. updated every year) forecast should be conducted by NHIDI in collaboration with the pharmaceutical industry. Ideally this is conducted on an international or European level.
- Conducted at national level only, a horizon scanning transversal budgeting system is used as input to a 5-year rolling (i.e. yearly-adjusted) budget forecast exercise.
- Savings considered within a transversal budgeting system take into account product life cycle-based adaptations to prices and de-reimbursement of actual medications.
- The use of cheap medicines should be promoted to release means for funding innovation.
- Implementation of strategies to obtain the lowest price possible also for innovative treatments, with an emphasis on me-too innovation.
- Budget spill-overs, calculated from budget impact analysis (BIA), are taken into account releasing cross-budget lines means for innovation, leading to better use of scarce resources. The transversal system takes into consideration spill-overs from surgery, radiotherapy, and hospitalisation.
- Transparency on budget allocation should be well managed toward public opinion and societal expectations. However, it should not be the basis for setting expectations towards patient populations.

Early dialogue between manufacturer and payer

- Open registries-based patient recruitment for clinical studies should be stimulated to answer the recruitment challenges in stratified oncological medicine.
- An appropriate legal framework is needed for biobanking to stimulate research and innovation in advanced medicinal products.
- To cater for the high uncertainty therapy development and market authorization should be made an iterative ‘adaptive’ process that progressively provides access to patients conditional upon performance and integrated with adaptive pricing.
- Initiatives increasing early payer and HTA advice involvement in clinical development decision making should be stimulated. Early advice is scientific in nature and hence
dealing with concerns on comparators and end points, pragmatic (i.e. better attuned to real-life evidence) trials not being too selective in study populations.

• Current Art 81, 81bis and ETA/ETR unmet need initiatives should be improved providing early access and early visibility on the most value-adding medical technology innovation.

• Early dialogue should also be clear on the unmet clinical need and its implications for further development and on the link to post-marketing evidence generation.

• To accelerate medical progress, incentives should be created to allow research institutions to access data and samples to identify better biomarkers for better patient selection.

• Need for clarification of the standard of care cost as compared to the extra hospital cost for patients recruited in a RCT. There’s a need for a standard contract and fee structure.

• Fund both national and international publicly funded pragmatic and practice-oriented clinical trials to answer specific clinical effectiveness and cost-effectiveness questions that are unlikely to be answered by medical manufacturers. The recommendations of the related KCE Report 246Cs (Neyt et al., 2015) are supported.

• Science-industry involvement should be organised on international level. Belgium should participate more in these international collaborations and should be promoted as a preferred state for conducting Phase I clinical trials.

• Acknowledging the need for less experimental centres with more patients; easier procedures, simplification of recruitment (connections registers and database).

• Recommendation to decentralize screening but centralize experimental treatment. Proposition for MOCs between institutions (part of network creation).

An integrated foresight, access & pricing system

• Reform CRM/CTG access and pricing & reimbursement decision-making to make it an integral part of a horizon scanning-based budgeting definition and execution system.

• Reform access and pricing & reimbursement decision-making to be connected to each other. Doing so, the ICER can be used as the connector, as a basis for (1) price setting following value-based differential pricing principles, and (2) to determine health budget as a result of a systematic horizon scanning exercise, modulated by unmet need and health budget impact.

Value-based and competition-based pricing

• Implement value-based differential pricing to replace or supplement external reference pricing for Class 1 drugs. It represents a clear evolution from the presently implicitly conducted ‘judgment-based’ decision-making based on value-based principles.
• Implement pricing based on comparative effectiveness allowing for Class 2 competitive pricing when comparative effectiveness is comparable to the most cost-effective present alternative in the therapeutic class.

• Implement for all Classes dynamic pricing conditional upon comparative effectiveness to replace ‘one-off’ pricing at launch.

• Organize for real world evidence collection to support outcome-based and multi-indication pricing

• Start a longitudinal study evaluating cost containment policy effectiveness. In other words; whether the proposed competitive pricing mechanism is strong enough to have a downward effect on drug-based therapy prices.

• Start a study to see how the ESMO-MCBS can be used to evaluate clinical value of novel medicines and to inform health policy decisions as in which early development to stimulate.

**Founded on an outcome-based disease-centric healthcare learning system**

• Real world evidence collection systems should be disease-centric rather than being drug product-centric. This will enable comprehensive views of patient’s disease journeys but also inform and facilitate therapeutic reference pricing and competitive price negotiations as specified before.

• A more detailed registration of cancer cases is needed, not only at diagnosis but also at later stages of the disease, at times of relapse or when a treatment line is abandoned or changed. In fact the clinical course of cancer patients should be mapped from the start until cure or treatment failure and death.

• Promote use of drug monitoring registries supporting automatic capture of drug utilisation data, dynamic pricing and outcome-based market entry agreements (MEA) for innovative medicines in areas of high unmet need.

• Set up patient registries that account for the evolution in patient population and treatment strategies over their lifetime this way enabling cost-effectiveness calculations of medicines relative to alternative treatments.

• Centralize diagnosis and therapeutic strategy setting organized in well-designed cancer networks between hospitals.

• Stimulate the use of coverage with evidence development (CED) by assigning a role of trusted third party (TTP). The Belgian Cancer Registry could take up such a role assuring anonymised capture of real world evidence as opposed to clinical evidence.

• Have a standardized e-approach to collecting data across the Belgian healthcare landscape, which is currently highly fragmented.

• Ensure minimal or preferably no additional administrative burden for healthcare professionals to promote uptake and ensure sustainability of CED systems by automatic capturing of data from aligned hospital EPD’s.
References


Henshall, C., Schuller, T., & Mardhani-Bane, L. 2012. Using health technology assessment to support optimal use of technologies in current practice: The callenge of


Appendix I: Assumptions for the 2020 Budget Projection

Assumptions made during the budget projection were sequentially checked with experts from the field and are explained in this Appendix. As innovative therapies, we considered the budget impact of Personalized Medicines (PMx), as was described in the 2015 Horizon Scanning report (Van Dyck & Geldof, 2015), and added to this the budget impact of immunomodulating therapies in oncology.

A detailed overview of innovative products that are currently (April 2016) on the market in Belgium and received NIHDI reimbursement are depicted in Appendix II.

Step 1: Extrapolation of current reimbursed innovative products

Historical data was received from NIHDI for each product authorized and reimbursed in Belgium, ranging from 2005 to 2014 for PMx and immunotheapies (see Figure A1) and contained information regarding the net expenses per year for each product and the Defined Daily Dose (DDD) for the PMx products.

![Figure A1: Innovative products and their first entry dates, reimbursed before 2014, defined as targeted therapies (dark blue) and immunomodulating therapies (light blue). Data points are represented in correspondence with their cost/DDD (vertical axis) and DDDs (area) at that time (an estimation was made for the immunotherapies for the sole purpose of representation).](image)

23 The net NIHDI expenditures are the prices of each product (which is reimbursed in Belgium for 100% in oncology) after payer negotiations.

24 The assumed average maintenance dose per day for a drug used for its main indication in adults. Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use (WHO).
The corresponding (DDD) information is solely available for the PMx, wherefrom uptake profiles were calculated to estimate how fast a product increased in usage within the first year(s) of reimbursement and how the maximum potential of usage is achieved after several years (flattening out the uptake profile curve). In this way the product life cycle was retrieved for 11 years of being reimbursed. The results of the mean uptake profile $U$ is represented in Table A1, and given by $\bar{U} = \frac{\text{year}_{t+1}}{\text{year}_t}$

<table>
<thead>
<tr>
<th>Years Reimbursed</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DDD Uptake</td>
<td>4.28</td>
<td>1.28</td>
<td>1.20</td>
<td>1.49</td>
<td>1.26</td>
<td>1.10</td>
<td>1.03</td>
<td>1.10</td>
<td>1.09</td>
<td>1.11</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Mean C/DDD Uptake</td>
<td>0.99</td>
<td>1.00</td>
<td>0.98</td>
<td>0.91</td>
<td>0.87</td>
<td>1.00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

Table A1: Uptake profiles of the existing portfolio (reimbursed PMx) in Belgium and the mean uptake profile. Outliners by dying products or other exceptional events were excluded from the calculation of the mean.

The mean uptake profiles could only be estimated until 11 years of reimbursement (thanks to Herceptin, Glivex and Mabthera who are on the Belgian market since more than 12 years). No information was available to forecast values after 11 years. Hence, for those products which would start their 12th year of reimbursement in 2014, a linear extrapolation was performed using their most constant expense trend of the last years (in earlier years several events can and have changed the trends of the expenses due to, e.g. patent expiries, new reimbursed entries targeting the same indications, etc.)

Step 2: Expenditure estimation of the pipeline

The product pipeline can be divided into 4 phases; the Pre-Registration phase (products being under evaluation for market access by EMA or for reimbursement by NIHDI), clinical phase III, II and I, each with their own transition probability which needs to be taken into account as weight factors for the budget estimations (see Fig. A2). For example, a phase III drug with an estimated budget impact of 100€ and with a probability of 63.5% of reaching the market will have an expected budget impact equal to 63.5€.

---

25 Take for example Herceptin, where the rising expenditures changed to a somewhat less steep trend after 2008 due to the reimbursement of Tyverb in 2009, a new breast cancer therapy targeting HER2 amplifications.

26 The probability that a product in one clinical phase will, after success, transition to the next clinical phase. To obtain the probability that the product will reach the market, the product of the probabilities should be taken; e.g. for a phase II product the probability that the molecule will be launched is equal to 21%.
Products in this pipeline and different clinical phases are obtained by informing the NIHDI, EMA\textsuperscript{27} and clinicaltrials.gov website. Products in their first phase are not included into the calculations, whilst products in phase II are expected to be submitted for early approval. Five PMx products were already approved for market access by EMA and for reimbursement in Belgium before 2015, but not yet included into the NIHDI data due to a time lack.

![Development phases and transition probabilities for oncology drugs. (Source: Paul et al., 2010)](image)

**Reimbursement and market entry date**

For the phases shown in FigureA2 different time lengths were considered, shown in table A2. Mark that in this case, an extra phase was considered for products who were submitted to the CTG (NIHDI) for reimbursement assessment. Estimated phase completion dates for Phase II and Phase III products are retrieved from clinicaltrials.gov.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Years until reimbursement</th>
<th>Years starting after</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG evaluation</td>
<td>1 year</td>
<td>file submission date</td>
</tr>
<tr>
<td>Pre-Reg</td>
<td>1 + 0.5 years</td>
<td>EMA submission date</td>
</tr>
<tr>
<td>Phase III</td>
<td>1 + 0.5 years</td>
<td>estimated phase completion date</td>
</tr>
<tr>
<td>Phase II</td>
<td>2.5 + 1 + 0.5 years</td>
<td>estimated phase completion date</td>
</tr>
</tbody>
</table>

*Table A2: Estimated years until reimbursement.*

For estimating the budget impact of every new innovative entry, we make a distinction between calculations for PMx and for immunotherapies due to a difference in information availability. The assessment for both are explained below.

**Targeted therapies**

For each new product in the pipeline, a reference PMx is chosen, which targets at least the same indication and/or biomarker. For example, a new entry targeting HER2 overexpression in breast cancer was hence compared to the reference product Tyverb. On the

\textsuperscript{27} Contacting the list of approved drugs at the EMA website and the list of drugs under evaluation by EMA.
other hand, when new entries target breast cancers with no HER2 gene over-expression, we assumed the DDDs would be three times the DDDs of Tyverb, as 25% of breast cancers show HER2 gene amplification while the other 75% do not (Hamermesh, Selby, & Andrews, 2013). When the indication was an orphan disease (for which no current targeted treatment is available) other orphan products were used as reference (i.e. Sprycel and Tasigna). New entries targeting two or more products were compared to a corresponding amount of reference PMx.

The cost per DDD of a new product reimbursed in year \( t \) was set equal to the cost per DDD of its reference PMX in year \( t \), while the DDD of the new product follows a similar uptake as the reference PMX:

\[
(B_{\text{new entry}})_t = \left( \frac{B_{\text{PMX}}}{DDD_{\text{PMX}}} \right)_t \times (DDD_{\text{PMX}})_{t-t_0}
\]

With \( t \) equal to the year in which we want to estimate the expenditure of the new product and \( t_0 \) equal to the year of its first reimbursement. The index \( t- t_0 \) hence reflects the amount of years the new product will be reimbursed and on the Belgian market in year \( t \).

**Immunotherapies**

As no data was available regarding the DDDs of the immunomodulating products, the budget impact for new indications in year \( t \) were estimated to be equal to the mean expenditure of Yervoy and Imnovid in year \( t_0 \) corrected with the interest rate \( r \) equal to 1.5%:

\[
(B_{\text{new entry}})_t = \frac{(B_{\text{Yervoy}})_{t_0} \times (1 + r)^{t-t_0} + (B_{\text{Imnovid}})_{t_0+2} \times (1 + r)^{t-t_0-2}}{2}
\]

In the equation above, \( t \) represents the year for which the budget impact of the new entry has to be estimated, while \( t_0 \) represents the corresponding year of the reference product (which is in our case Yervoy).

Mark that not all patient will be treated with the new therapy (by means of combination therapy, next line therapy, etc.). Hence the above analysis is an overestimation of reality.

### Step 3: Estimation of savings

Savings due to events that reduce the reimbursement level should be taken into account during the horizon scanning. Different events that were considered could be classified in two leverage mechanisms\(^{28}\): automatic reductions and systematic reductions.

These are characterised by:

\(^{28}\) Other mechanisms exist, such as international reference pricing (IRP). This was not taken into account in our analysis.
<table>
<thead>
<tr>
<th>Event</th>
<th>Level of reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic reduction</td>
<td>Patent expiries</td>
</tr>
<tr>
<td>Systematic reduction</td>
<td>Price cut after 12 y</td>
</tr>
<tr>
<td></td>
<td>Price cut after 15 y</td>
</tr>
<tr>
<td></td>
<td>Price cut after 18 y</td>
</tr>
</tbody>
</table>

Source: (BCG, 2014) since 1/3/2016, patent cliff meaning higher automatic reduction at patent expiration

Targeted therapies losing patent protection by 2020 are summarized in Table A3. Glivec and Mabthera already lost patent before 2013, their decrease in budget impact is already included in the linear extrapolations of their trends above.

The systematic reductions result in a total of 19% (or 26.5% for biologicals) decrease in NIHDI expenses for “old drugs”. Nine reimbursed PMx qualify to be labelled as “old drugs” between 2014 and 2020.

In calculating the savings, no competition between therapies is taken into account.

<table>
<thead>
<tr>
<th>PMx losing</th>
<th>Expiry date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin</td>
<td>2014</td>
</tr>
<tr>
<td>Glivec</td>
<td>Expired</td>
</tr>
<tr>
<td>Mabthera</td>
<td>Expired</td>
</tr>
<tr>
<td>Erbitux</td>
<td>2016</td>
</tr>
</tbody>
</table>

Table A3: Products losing patent protection by 2020. (Source: IMS Health)

Step 4: Extrapolation of non-innovative products

Non-innovative products are those therapies that are considered as ‘pharmaceutical specialties’ who are not considered as targeted or immunomodulating therapies. While a detailed analysis of these products was not part of this study, an estimation of their total net expenses was needed to calculate the Compact Annual Growth Rate (CAGR) required over the planning horizon to fund the oncology innovation pipeline. We considered two scenarios:

- **Scenario 1**: The non-innovative products’ budget does not grow from its 2015 position.
- **Scenario 2**: The non-PMx budget keeps on growing at the yearly rate at which it grew between 2014 and 2015 – based on the average of the pharma.be and NIHDI projections.

Using both scenarios as upper and lower bound, we were able to estimate the expected total net NIHDI expenses of the non-innovative therapies to be €3.810M ± €20M

---

29 This reduction level depends on the drug reimbursement class. Innovative products are assumed to be class I reimbursed products. Entry of reference reimbursement results in a price reduction of 41% in this case.
30 This is only applicable for biological products.
Appendix II: Overview of Innovative Cancer Treatments reimbursed in Belgium in 2016

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Brand name</th>
<th>Indication</th>
<th>Biomarker</th>
<th>1st EMA registration</th>
<th>Reimbursed in Belgium since</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>HERCEPTIN</td>
<td>Breast Cancer</td>
<td>HER2 positive</td>
<td>28-08-2000</td>
<td>01-05-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastric Cancer</td>
<td>HER2 positive</td>
<td>19-01-2010</td>
<td>01-10-2010</td>
</tr>
<tr>
<td></td>
<td>HERCEPTIN SC</td>
<td>Breast Cancer</td>
<td>HER2 positive</td>
<td></td>
<td>01-07-2014</td>
</tr>
<tr>
<td>Imatinib</td>
<td>GLIVEC</td>
<td>CML</td>
<td>Bcr/Abl (Philadelphia chromosome)</td>
<td>07-11-2001</td>
<td>01-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GIST</td>
<td>Kit (CD117) positive, PDGFRA D842V negative</td>
<td>24-05-2002</td>
<td>01-07-2003</td>
</tr>
<tr>
<td>Rituximab</td>
<td>MABTHERA</td>
<td>Non-Hodgkin Lymphoma</td>
<td>CD20</td>
<td>21-03-2002</td>
<td>01-12-2002</td>
</tr>
<tr>
<td>Ibritumomab</td>
<td>ZEVALIN</td>
<td>Follicular Lymphoma</td>
<td>CD20</td>
<td>16-01-2004</td>
<td>01-09-2006</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>ERBITUX</td>
<td>Colorectal Cancer</td>
<td>RAS wild type</td>
<td>29-06-2004</td>
<td>01-07-2006</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>TARCEVA*</td>
<td>NSCLC</td>
<td>EGFR positive of EGFR-TK activating mutation</td>
<td>19-09-2005</td>
<td>01-07-2006</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>SPRYCEL</td>
<td>CML; ALL</td>
<td>Bcr/Abl (Philadelphia chromosome)</td>
<td>20-11-2006</td>
<td>01-09-2007</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>TASIGNA</td>
<td>CML</td>
<td>Bcr/Abl (Philadelphia chromosome)</td>
<td>19-11-2007</td>
<td>01-09-2008</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>VECTIBIX</td>
<td>Colorectal Cancer</td>
<td>RAS wild type</td>
<td>03-12-2007</td>
<td>01-09-2008</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>TYVERB</td>
<td>Breast Cancer</td>
<td>HER2 positive</td>
<td>10-06-2008</td>
<td>01-09-2009</td>
</tr>
<tr>
<td>Catumaxomab</td>
<td>REMOVAB</td>
<td>Malign Ascites</td>
<td>EpCam positive</td>
<td>20-04-2009</td>
<td>01-10-2011</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>IRESSA</td>
<td>NSCLC</td>
<td>EGFR-TK activating mutation</td>
<td>24-06-2009</td>
<td>01-07-2010</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>ZELBORAF*</td>
<td>Malign Melanoma</td>
<td>BRAF V600 mutation</td>
<td>17-02-2012</td>
<td>01-04-2013</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>XALKORI</td>
<td>NSCLC</td>
<td>ALK positive</td>
<td>23-10-2012</td>
<td>01-08-2013</td>
</tr>
<tr>
<td>Bozutinib</td>
<td>BOSULIF</td>
<td>CML</td>
<td>Bcr/Abl (Philadelphia chromosome); no T315I or V299L mutation</td>
<td>27-03-2013</td>
<td>01-04-2014</td>
</tr>
<tr>
<td>Active substance</td>
<td>Brand name</td>
<td>Indication</td>
<td>1st EMA registration</td>
<td>Reimbursed in Belgium since</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>TAFINLAR*</td>
<td>Malign Melanoma</td>
<td>BRAF V600 mutation</td>
<td>26-08-2013 01-05-2014</td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>PERJETA*</td>
<td>Breast Cancer</td>
<td>HER2 positive</td>
<td>04-03-2013 01-06-2014</td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>GIOTRIF</td>
<td>NSCLC</td>
<td>EGFR-TK activating mutation</td>
<td>25-09-2013 01-07-2014</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab-ermtansine</td>
<td>KADCYLA</td>
<td>Breast Cancer</td>
<td>HER2 positive</td>
<td>15-11-2013 01-12-2014</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>IMBRUVICA</td>
<td>CLL</td>
<td>17p deletion or TP53-mutation</td>
<td>21-10-2014 01-08-2015</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>LYNPARZA</td>
<td>EOC</td>
<td>BRCA1/2 mutation</td>
<td>16-12-2014 01-12-2015</td>
<td></td>
</tr>
<tr>
<td>Idelalisib</td>
<td>ZYDELIG</td>
<td>CLL</td>
<td>17p deletion or TP53-mutation</td>
<td>18-09-2014 01-12-2015</td>
<td></td>
</tr>
<tr>
<td>Ponatinib</td>
<td>ICLUSIG</td>
<td>CML</td>
<td>Bcr/Abl (Philadelphia chromosome) or T315I mutation</td>
<td>01-07-2013 01-03-2016</td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEKINIST</td>
<td>Malign Melanoma</td>
<td>BRAF V600 mutation</td>
<td>30-06-2014 File submitted</td>
<td></td>
</tr>
<tr>
<td>Certinib</td>
<td>ZYKADIA</td>
<td>NSCLC</td>
<td>ALK positive</td>
<td>06-05-2015 File submitted</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>IMATINIB TEVA31</td>
<td>CML</td>
<td>Bcr/Abl (Philadelphia chromosome)</td>
<td>08-01-2013 File submitted</td>
<td></td>
</tr>
</tbody>
</table>

*Products with an Art.81 or Art.81bis agreement. These products are reimbursed in Belgium under restricted market authorization, negotiated between the company and the CTG. A budgetary compensation scheme is agreed upon, meaning that the company will reimburse NIHDI the agreed percentage of the turnover of that product. (Van Dyck & Geldof, 2015)

Table A4: Chronological overview of reimbursed targeted therapies in Belgium with cancer indications

---

Table A5: Chronological overview of reimbursed immunomodulating therapies in Belgium with cancer indications Reimbursement of Keytruda since 1/5/2016

---

31 Imatinib Teva is a ‘generic medicine’. This means that Imatinib Teva is similar to a ‘reference medicine’ already authorized in the European Union (EU) called Glivec. The product is accepted for reimbursement due to patent expiry of Glivec.