The truth, the whole truth, and nothing but the truth about cancer drug prices

Prof. Carin A. Uyl-de Groot, PhD
(uyl@bmgeur.nl)

Institute for Medical Technology Assessment (iMTA)
Institute of Health Policy and Management (iBMG)
Erasmus University Rotterdam

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Outline

- INTRODUCTION HEALTH TECHNOLOGY ASSESSMENT (HTA)
- PROBLEM DEFINITION
- REASONS OF HIGH PRICES
- POSSIBLE SOLUTIONS AT SEVERAL LEVELS OF DECISION MAKING
Cancer survival in Europe 1999–2007 by country and age: results of EUROCare-5—a population-based study

Roberta De Angelis, Milena Sant, Michiel P Coleman, Silvia Frangiea, Paolo Balli, Daniela Pierannunzio, Annalisa Trama, Otto Visser, Hermann Brenner, Eva Ardanaz, Magdalena Bród ska-Lasota, Gerda Engholm, Alice Nennecke, Sabine Siesling, Franco Berrino, Riccardo Capocaccia, and the EUROCare-5 Working Group

Summary
Background Cancer survival is a key measure of the effectiveness of health-care systems. EUROCare—the largest cooperative study of population-based cancer survival in Europe—has shown persistent differences between countries for cancer survival, although in general, cancer survival is improving. Major changes in cancer diagnosis, treatment, and rehabilitation occurred in the early 2000s. EUROCare-5 assesses their effect on cancer survival in 29 European countries.

Methods In this retrospective observational study we used SEER data from 107 cancer registries for more than 10 million patients with cancer diagnosed up to 2007, and followed up to 2014. Linkage with control procedures were applied to all datasets. For patients diagnosed 2001–07, we calculated 5-year relative survival for 46 cancers weighted by age and country. We also calculated country-specific and age-specific survival for ten common cancers, together with survival differences between time periods (1999–2001, 2002–04, and 2005–07).

Findings 5-year relative survival generally increased steadily over time for all European regions. The largest increases from 1999–2001 to 2005–07 were for prostate cancer (73.4% [95% CI 72.9–73.9] versus 81.7% [81.3–82.1]), non-Hodgkin lymphoma (53.8% [53.3–54.4] versus 60.4% [60.0–60.9]), and rectal cancer (52.1% [51.6–52.6] versus 57.6% [57.1–58.1]). Survival in eastern Europe was generally low and below the European mean, particularly for cancers with good or intermediate prognosis. Survival was highest for northern, central, and southern Europe. Survival in the UK and Ireland was intermediate for rectal cancer, breast cancer, prostate cancer, skin melanoma, and non-Hodgkin lymphoma, but low for kidney, stomach, ovarian, colon, and lung cancers. Survival for lung cancer in the UK and Ireland was much lower than for other regions for all periods, although results for lung cancer in some regions (central and eastern Europe) might be affected by overestimation. Survival usually decreased with age, although to different degrees depending on region and cancer type.


The good news.....
The bad news: rise in costs

Costs of cancer treatment: € 102 per person in Europe (i.e. 3% of total health care expenses in The Netherlands)

Figure 1: Health-care costs of cancer per person in European Union countries in 2009, by health-care service category
Data not adjusted for price differentials.
Growth in real per capita pharmaceutical expenditure, 2000-09 (or nearest year)

Development two value frameworks

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)


American Society of Clinical Oncology Statement: A conceptual framework to assess the value of cancer treatment options.

Good grading scales, however........

No incorporation of cost-effectiveness and budget impact.

Result: no solution for the problem the frameworks aimed for.
Budget problem

In the Netherlands in 2014: 530 million Euros spent on new cancer drugs
Maximum growth budget per year: 1.2%

<table>
<thead>
<tr>
<th>New cancer drugs 2016</th>
<th>Estimated costs per patient</th>
<th>ICER</th>
<th>Estimated budget impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>€ 80.000</td>
<td>€ 134.000</td>
<td>€ 200 mln</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>€ 78.000</td>
<td>€ 150.000</td>
<td>€ 40 mln</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>€ 70.000</td>
<td>Unknown</td>
<td>€ 100 mln</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Unknown</td>
<td>Unknown</td>
<td>€100 mln</td>
</tr>
</tbody>
</table>
Question: Why are the prices of new drugs high?
Development phase: a long and winding road to registration

Pfizer -- http://www.pfizer.co.uk/pfizer_uk/navigation/research_frame.htm
Development phase
From discovery to patient

1 medicinal product

0 5 years 10 years 15 years 20 years

Patent application
Acute toxicity
Pharmacology
Chronic toxicity
Phase I clinical trials
Phase II
Phase III
Registration and transparency
Price
Reimbursement
Pharmacovigilance

10 years of research
2 to 3 years of administrative procedures

Source: “Recherche & Vie”, LIM (AGIM)
Costs of development new medical entity (NME)

- Estimation: 800 million dollars  
  (range: 60 million - 2.6 billion)

Main cost factors:
- R&D (including failures)
- Manufacturing
- Marketing and promotion

Note that in this case return on investment for nivolumab will already be reached in 4 years in The Netherlands.
## Costs per clinical phase in percentage of total R&D, period 2000-2007

<table>
<thead>
<tr>
<th>Phase</th>
<th>Percentage of total R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical (incl. Basic research)</td>
<td>8%</td>
</tr>
<tr>
<td>Phase I</td>
<td>12%</td>
</tr>
<tr>
<td>Phase II</td>
<td>20%</td>
</tr>
<tr>
<td>Phase III</td>
<td>60%</td>
</tr>
</tbody>
</table>
Life cycle of a drug

development → introduction → growth → maturity → decline

↑ Sales

Time →

Ellery and Hansen, Pharmaceutical Lifecycle management, Wiley 2012
Introduction phase
Differences in the uptake of innovation

Sales of innovative products (launched 2005-2009) per 100,000 inhabitants in 2009 per country

*SOURCE: IMS MiDAS, analysis for iNAMI*
Pharmaceutical companies envisage tougher environment for pricing, reimbursement and listing.

- **Regulatory**
  - Quality
  - Efficacy
  - Safety

- **Pricing, Reimbursement**
  - Comparative effectiveness in real world
  - Cost-effectiveness (trial-based and model-based)

- **Purchase, listing**
  - Budget impact analyses
But they still have a poor image

- Profitability far above average other manufacturing industries (20 vs 10%)
- Innovation is flagging, less new medical entities
- Little sensitivity to equity considerations: poorer countries and weaker citizens should have same access to drugs as richer countries and better-of citizens
- More is spent on marketing than on R&D
- Safety issues
What is our “Product”? - Product Positioning

• A molecule is not a product.....for price estimation purposes they must define its “positioning”

• “Positioning” (here) = place in the treatment regimen

Positioning variables

- Line of therapy?
- Target Patients?
- Prevention or treatment?
- Monotherapy or combination?

...different implications for.....

D

R

Positve
Differentiation
Value

Reference
Price

Negative
Differentiation
Value

Perceived
Value

V
But system is not sustainable so:

How to reduce spending on drugs?

- Shift from expensive to cheap drugs within the same class
- Make patients or the insurance pay a larger part
- Reduce the prices of drugs
- Reduce the total use of drugs
- Focus on reduction of prices
Possibilities for price reductions

- Reference pricing
- Value based pricing
- Global tiered framework
- Price ceilings
- Profit limitation
- Etc.
International Reference Pricing (IRP) is used in some form in most European countries

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>IRP used?</th>
<th>Formal/ Informal</th>
<th>Calculation used</th>
<th>Price referenced</th>
<th>Drugs</th>
<th>Frequency of re-referencing (months)</th>
<th>No. of Reference Countries</th>
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<tr>
<td>Austria</td>
<td>Y</td>
<td>F</td>
<td>AVERAGE</td>
<td>MNF</td>
<td>Reimbursed</td>
<td>-</td>
<td>25</td>
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<td>I</td>
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<td>18</td>
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<tr>
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<td>LOWEST</td>
<td>MNF</td>
<td>POM</td>
<td>6</td>
<td>15</td>
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<td>Cyprus</td>
<td>Y</td>
<td>F</td>
<td>AVG. OF LOWEST 4</td>
<td>TRD</td>
<td>Imported medicines</td>
<td>24</td>
<td>4</td>
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<td>MNF</td>
<td>All</td>
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<td>8</td>
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<tr>
<td>Denmark</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>3</td>
<td>3</td>
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<td>I</td>
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<td>TRD</td>
<td>Reimbursed</td>
<td>60</td>
<td>26</td>
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<td>France</td>
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<td>1/F</td>
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<td>MNF</td>
<td>Innovative medicines</td>
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<td>Germany</td>
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<td>I</td>
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<td>MNF</td>
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<td>TRD</td>
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<td>F</td>
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<td>MNF</td>
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<td>MNF</td>
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<td><strong>Netherlands</strong></td>
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<td>TRD</td>
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<td>AVG. OF LOWEST 3</td>
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<td>Portugal</td>
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<td>MNF</td>
<td>POM</td>
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<td>F</td>
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<td>Slovenia</td>
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<td>F</td>
<td>95% OF AVG OF 3</td>
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<tr>
<td>Sweden</td>
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<td>-</td>
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<tr>
<td>UK</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>
International price referencing is a common global tool for benchmarking pharmaceutical prices. Many of these referencing laws were instated in the last 5 years.
Value based pricing (I)  
Incorporating thresholds

- NICE: £ 30.000
- US: US$ 50.000
- The Netherlands: € 80.000
- WHO threshold: depend on WHO region and Gross Domestic Product (GDP)
  - 1x GDP very cost-effective
  - 1-3x GDP cost-effective
  - > 3x GDP not cost-effective

Still budget impact problem.
<table>
<thead>
<tr>
<th>Negotiations</th>
<th>Threshold ICER ( \geq \€ 52.000 )</th>
<th>Threshold ICER ( &lt; \€ 52.000 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always, unless topics below are applicable</td>
<td>• High budget impact</td>
<td>• High budget impact</td>
</tr>
<tr>
<td></td>
<td>• Low burden of disease</td>
<td>• Low burden of disease</td>
</tr>
<tr>
<td></td>
<td>• Risk at more indications</td>
<td>• Risk at more indications</td>
</tr>
<tr>
<td>No negotiations</td>
<td>• High burden of disease</td>
<td>Always, unless topics above are the case</td>
</tr>
<tr>
<td></td>
<td>• Very rare disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lack of treatment alternative</td>
<td></td>
</tr>
</tbody>
</table>

* Uyl-de Groot&Huijgens. Niet mensenleven maar geneesmiddel waarderen. Medisch Contact 2015
Value based pricing (II)
Pay for Performance (P4P)

• Contract: reimbursement dependent on treatment success (e.g. pomoladomide)

• Advantages:
  – “no cure, no pay” => value for money
  – application on best patient groups
  – after contract new decision possible

• Disadvantages:
  – transaction costs contract
  – clear outcome indicator crucial
  – cost of monitoring/registration
Volume-price arrangements

• Volume-price agreements (E.g. France)
• sales < Y price P1; sales > Y lower price P2

Advantages:
• less uncertainty on budget impact
• industry can cover R & D costs (P1*V1)

Disadvantages:
• does not address value for money
• negotiations not transparent
• more strategic (gaming) conduct
Policy goals in health care

System objectives

Sustainability

Equity

Quality of care

Goal:
Ensuring affordable and equitable access for (all) patients to effective medicines in a sustainable manner
Measures needed at several levels

National/local level:
• E.g. Drugs in a ‘lock’, negotiations based on cost-effectiveness.
• However: Results not transparent, benefits to health insurer and not to hospital

European level:
• Negotiations/thresholds per region
• Proposed responsibility: European Commission or EMA

Pan-European:
• Division thresholds in WHO regions
• Proposed responsibility: WHO
Conclusion:

The truth

• Drug prices are too high: 20 fold increase compared to early 90’s
• No relation with value

The whole truth

• Frameworks ESMO and ASCO valuable, but value for money should be included.
• Cost-effectiveness and budget impact analyses useful tools, but also exceptions should be possible
• More transparency about prices

Nothing but the truth

• Negotiations should be done at several levels: not only focus on The Netherlands as we are a small country