Erasmus School of
Health Policy
& Management

Affordability and sustainability of innovative medicines

Carin Uyl-de Groot
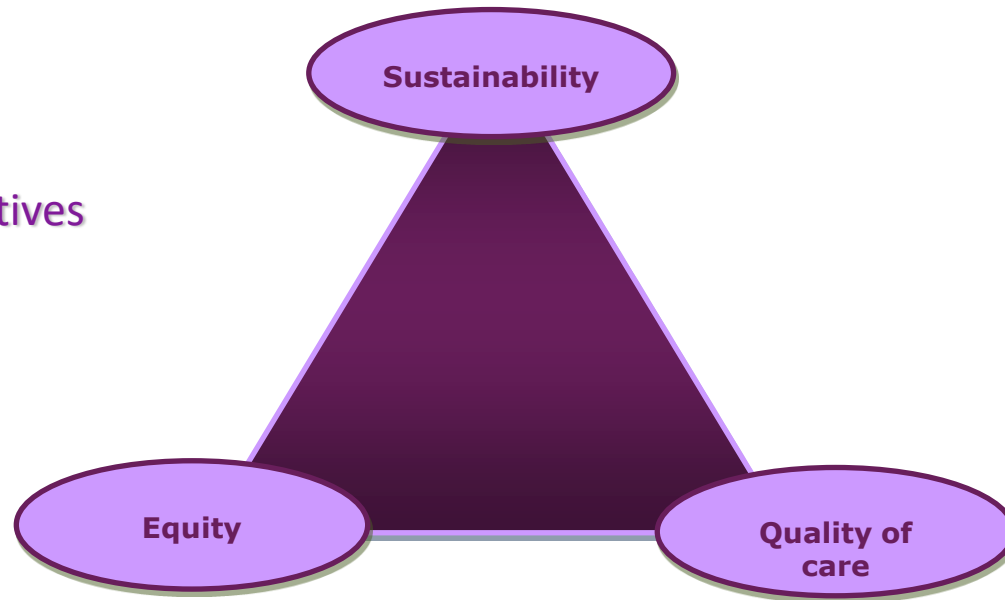
Inspire2Live Webinar September 7, 2020

Erasmus University Rotterdam

Policy goals in health care

System objectives

Goal:
Ensuring affordable and equitable access for (all) patients to effective therapies in a sustainable manner

The good news (1)…..

Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study

Roberta De Angelis, Milena Sant, Michel P Coleman, Silvia Francisci, Paolo Baili, Daniela Pierannunzio, Annalisa Trama, Otto Visser, Hermann Brenner, Eva Ardanaz, Magdalena Bielska-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 analysed data from 107 cancer registries for more than 10 million patients with cancer diagnosed up to 2007 and followed up to 2008. Uniform quality control procedures were applied to all datasets. For patients diagnosed 2000–07, 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 for 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] vs 81·7% [81·3–82·1]), non-Hodgkin lymphoma (53·8% [53·3–54·4] vs 60·4% [60·0–60·9]), and rectal cancer (52·1% [51·6–52·6] vs 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.

Findings: 5-year relative survival generally increased steadily over time for all European regions.

De Angelis et al. Lancet Oncology 2014;15:23-34

The good news (2):
Many innovative (cancer) drugs

The bad news (1):

Rise in health expenditures 2000-2015
as share Gross Domestic Product (GDP)

Country	2000	2005	2010	2015
Austria	9.2	9.6	10.1	10.4
Czech Republic	5.7	6.4	6.9	7.5
Denmark	8.1	9.1	10.4	10.6
France	9.5	10.2	10.7	11.0
Germany	9.8	10.2	11.0	11.1
Ireland	5.9	7.7	10.6	9.4
Netherlands	7.1	9.4	10.4	10.8
Norway	7.7	8.3	8.9	9.9
Poland	5.3	5.8	6.4	6.3
Spain	6.8	7.7	9.0	9.0
United Kingdom	6.3	7.4	8.5	9.8
Average EU	**7.3**	**8.2**	**8.9**	**9.0**

The bad news (2):
Huge differences within EU, unequal access

Costs of cancer treatment: € 102 per person in Europe
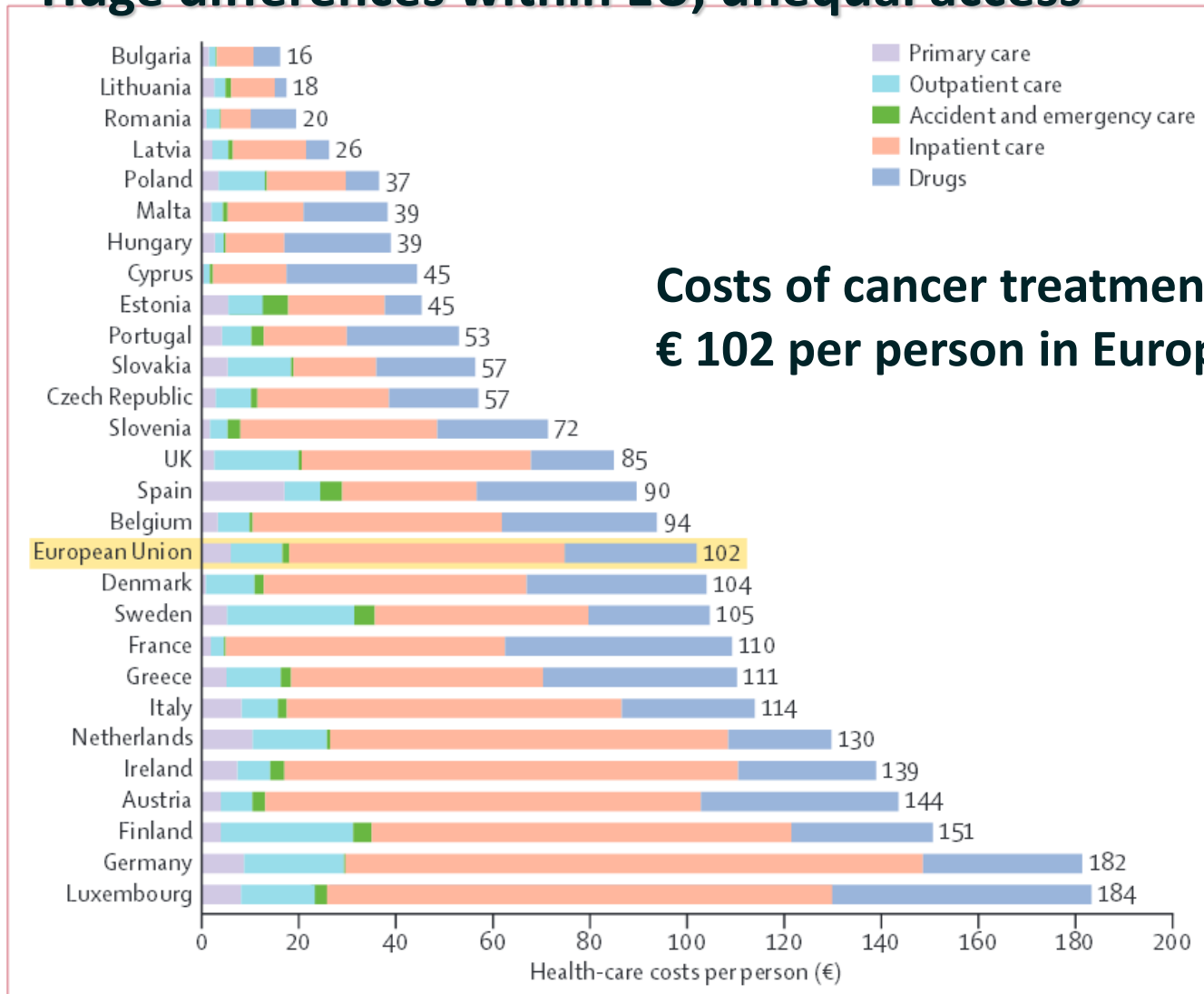
Figure 1: Health-care costs of cancer per person in European Union countries in 2009, by health-care service category

Data not adjusted for price differentials.

Result budget problems

The Netherlands (2014): € 530 million spent on new cancer drugs
Maximum growth budget per year: 1.2%

New cancer drugs 2016	Estimated costs per	ICER	Estimated budget impact
Nivolum**Opportunity cost**			200 mln
Pertuzumab	€ 78.000	€ 150.000	€ 40 mln
Ibrutinib	€ 70.000	Unknown	€ 100 mln
Palbociclib	Unknown	Unknown	€100 mln
CAR-T cells	€300-400.000	Unknown	Unknown

Affordable (expensive) therapies
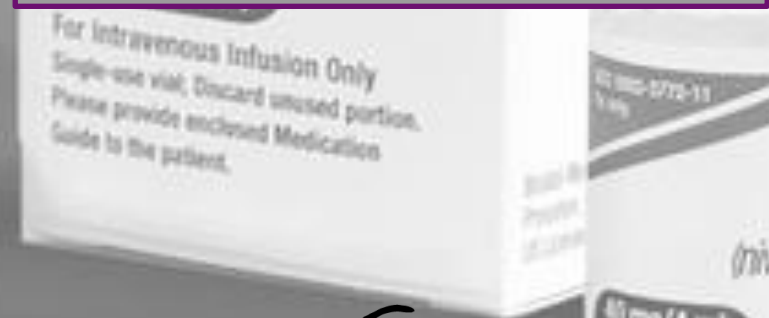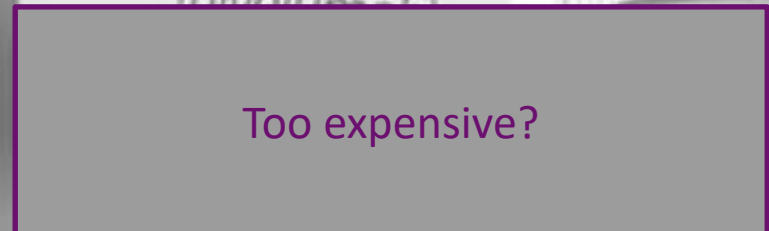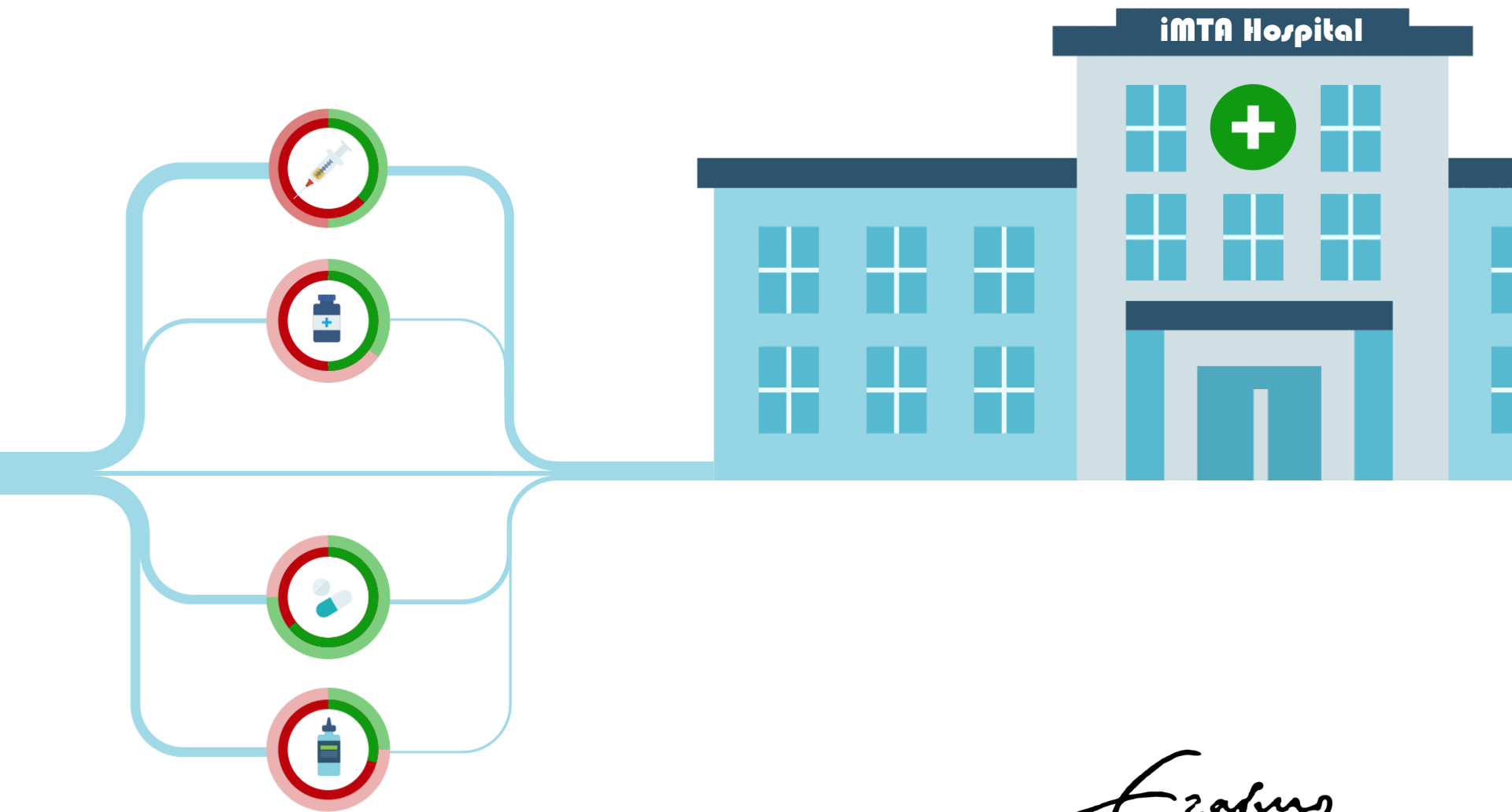
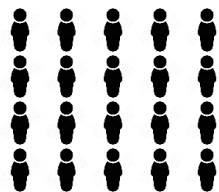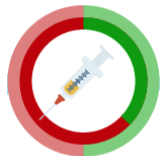Thanks to Matthijs Versteegh

3,000 patients

€80,000 per patient

Survival gain of 3 months (median)

Too expensive?

iMTA Hospital
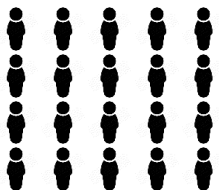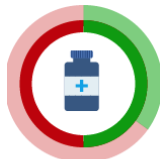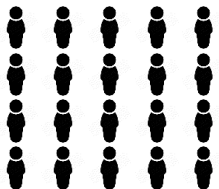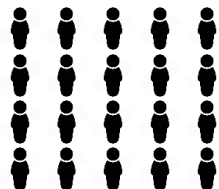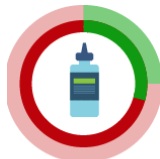
"The invisible patient"

Opportunity costs

What we give to patient A, we cannot give to patient B.

Given a **limited health care budget** (or a limited willing to pay a higher premium) it is **unethical** not to make a societal decision.

Why is it expensive?
Development phase: a long and winding road to registration
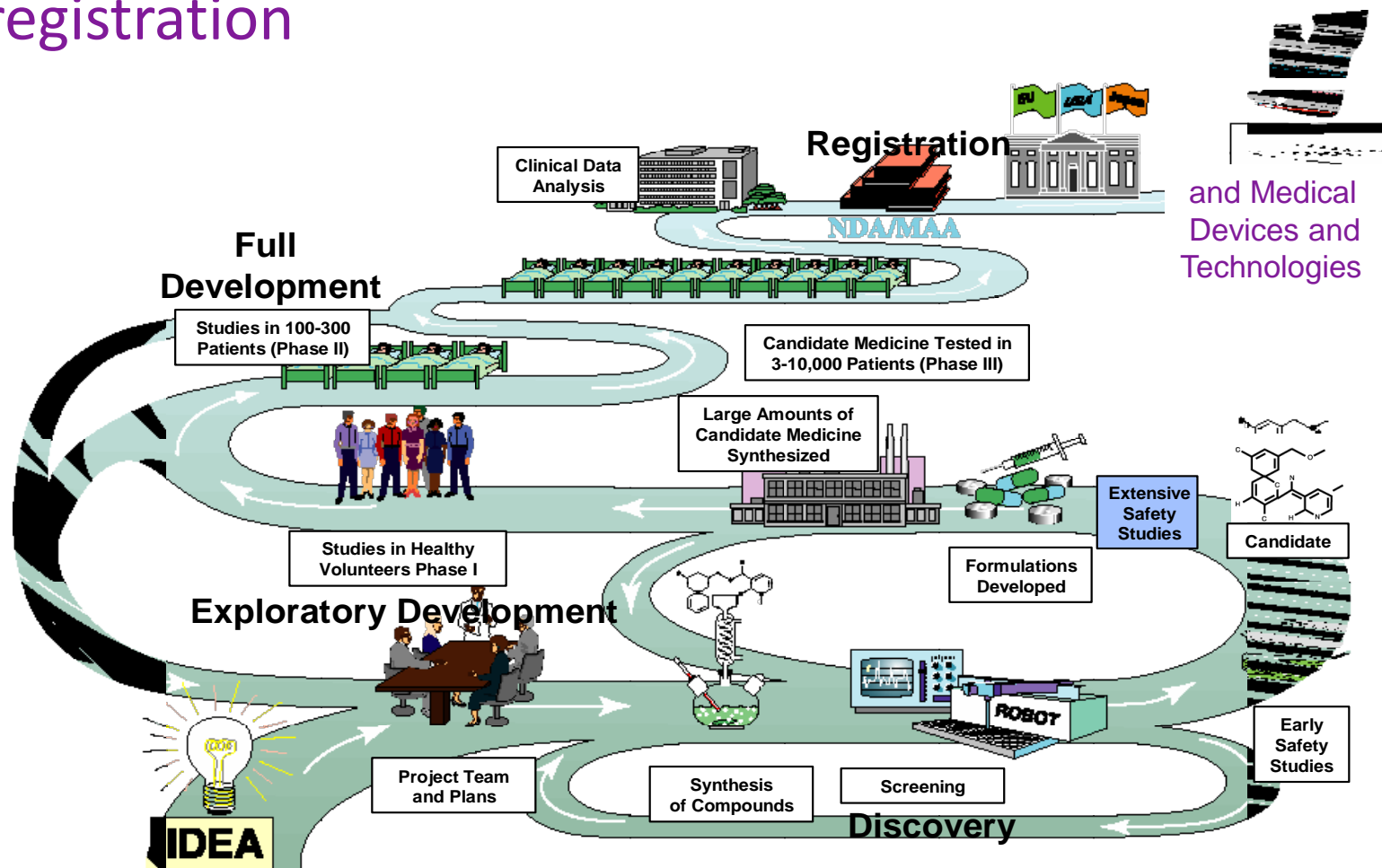
and Medical Devices and Technologies

Registration

Clinical Data Analysis

NDA/MAA

Full Development

Studies in 100-300 Patients (Phase II)

Candidate Medicine Tested in 3-10,000 Patients (Phase III)

Large Amounts of Candidate Medicine Synthesized

Extensive Safety Studies

Candidate

Studies in Healthy Volunteers Phase I

Formulations Developed

Exploratory Development

Early Safety Studies

IDEA

Project Team and Plans

Synthesis of Compounds

Screening

Discovery

14

Development phase
From discovery to patient

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

1 medicinal product

0   5 years   10 years   15 years   20 years
Patent expiry

10 years of research

2 to 3 years of administrative procedures

15   Source: *"Recherche & Vie", LIM (AGIM)*
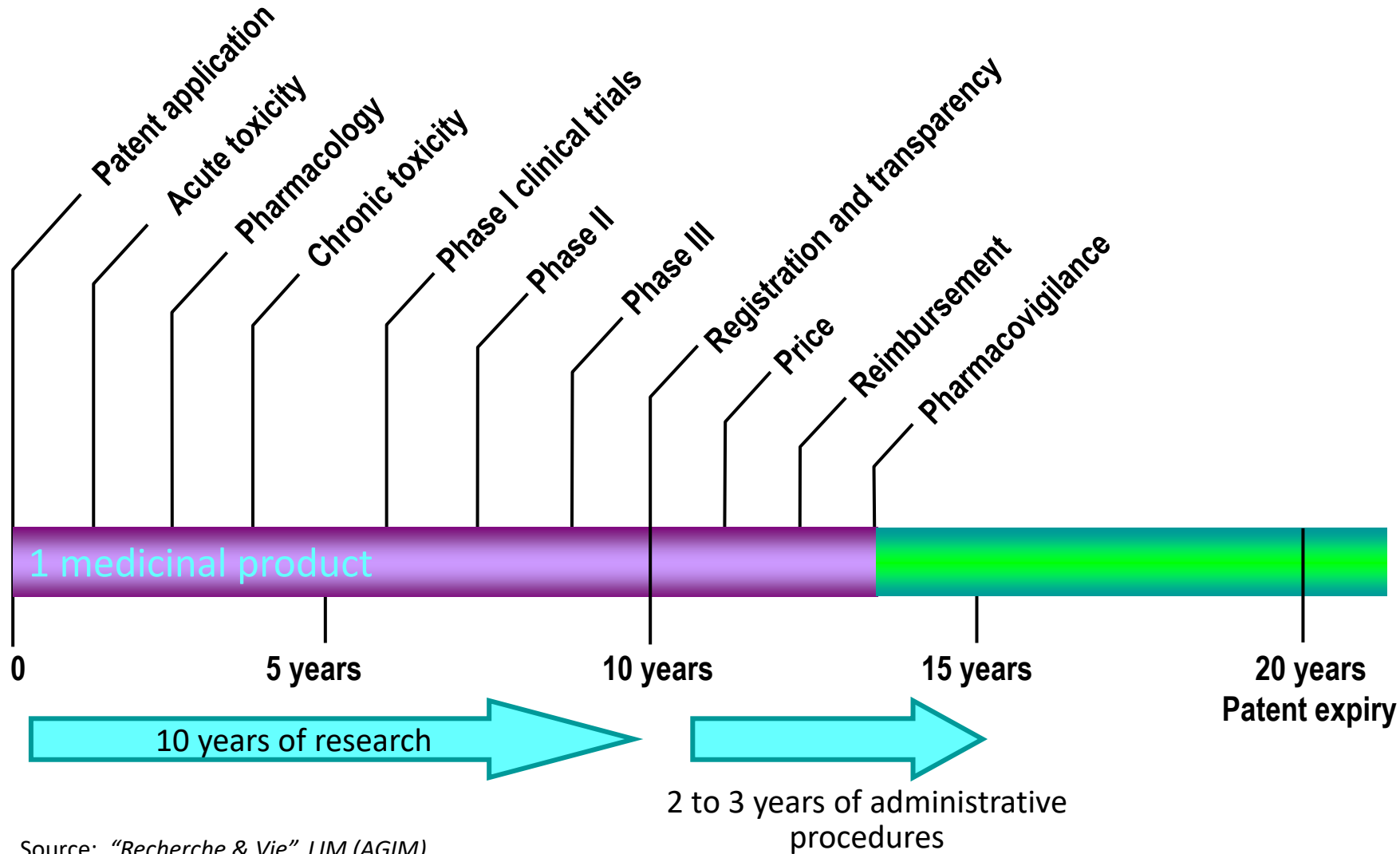
Costs of development new drug

Cost factors:

- R&D (including failures)
- Manufacturing
- Marketing and promotion

- Estimation: 300 million -2.6 billion dollars

Life cycle of a technology

development   introduction   growth   maturity   decline

↑
Sales

Time →

Ellery and Hansen, Pharmaceutical Lifecycle management, Wiley 2012

Worldwide total revenues of leading pharmaceutical companies in 2014 (in billion dollars)

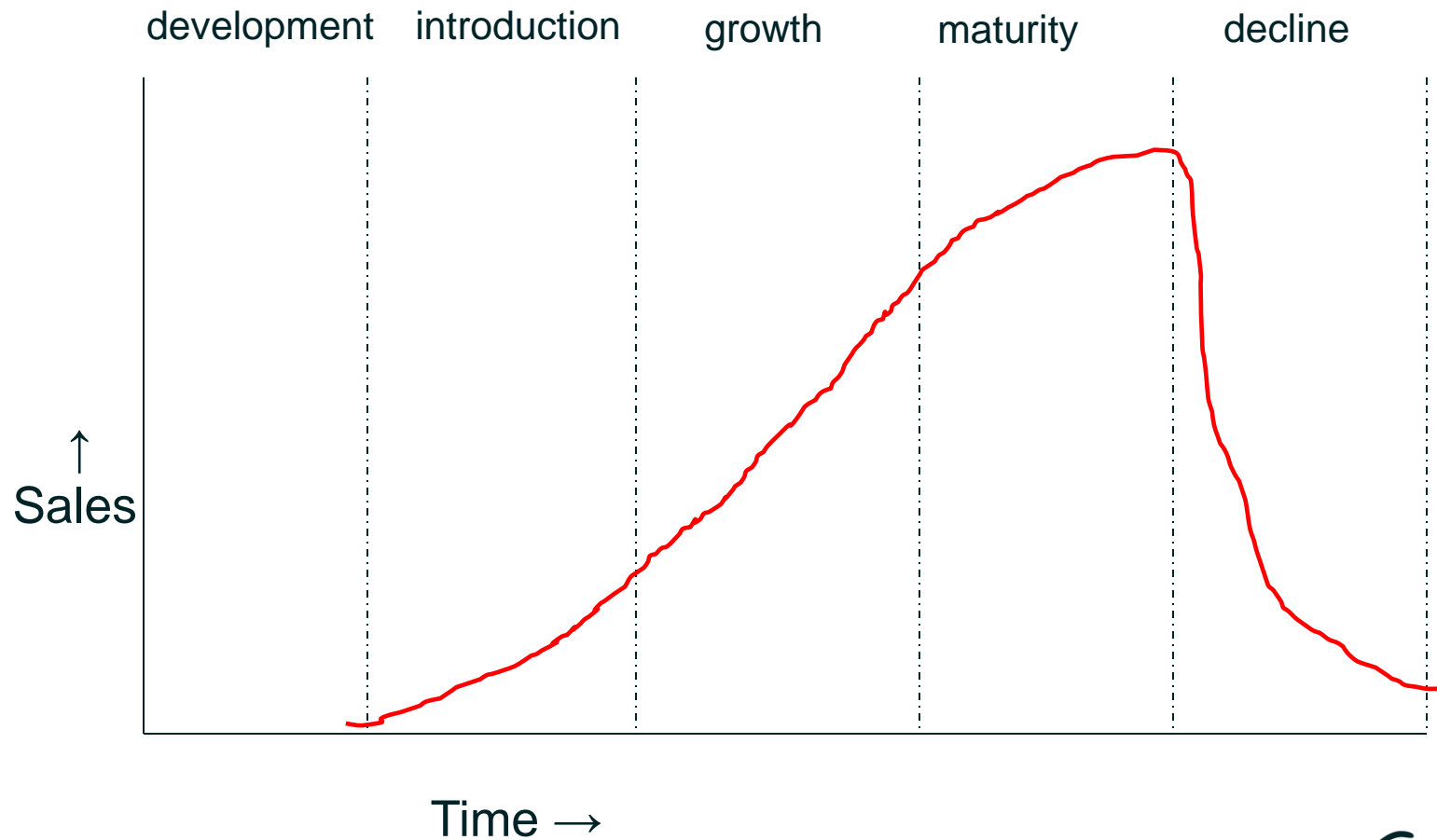| Company	Total revenue ($)	R&D costs ($)	Sales and Marketing costs ($)	Other activities costs* ($)	Profit ($)	Profit Margin (%)
1. Johnson & Johnson	71.3	8.2	17.5	31.8	13.8	19
2. Novartis	58.8	9.9	14.6	25.1	9.2	16
3.			11.4	11.6		3
4.						4
5.						1
6.						0
7. GSK	41.4	5.3	9.9	17.7	8.5	21
8. AstraZeneca	25.7	4.3	7.3	11.5	2.6	10
9. Eli Lilly	23.1	5.5	5.7	7.2	4.7	20
10. AbbVie	18.8	2.9	4.3	7.5	4.1	22
Total Top 10 global companies Percentage of total revenue – profit	429.4	65.8 (19%)	98.3 (29%)	175.5 (52%)	89.8	20.9

Pharma highest profit: 20%, followed by banks 10%

*Other activities' costs = Total revenue – R&D costs – Sales and marketing costs. Overhead costs are included in R&D, sales and marketing and other activities.

# Poor image

- Profitability far above average other manufacturing industries (20 vs 10%)
- Innovation is flagging
- Little sensitivity to equity considerations: poorer countries and weaker citizens should have same access to drugs as richer countries and better-of citizens
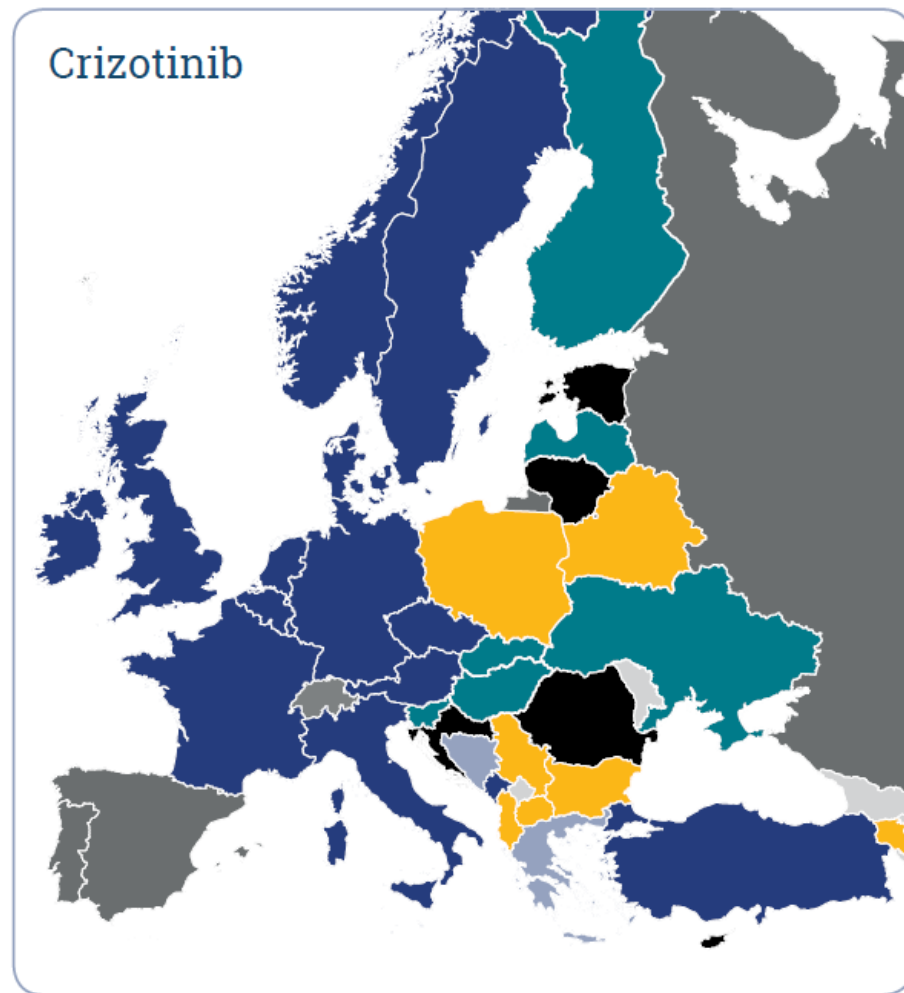- More is spent on marketing than on R&D
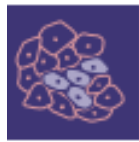- Safety issues

Availability of 2 cancer drugs

Source: ECL report, October 2018
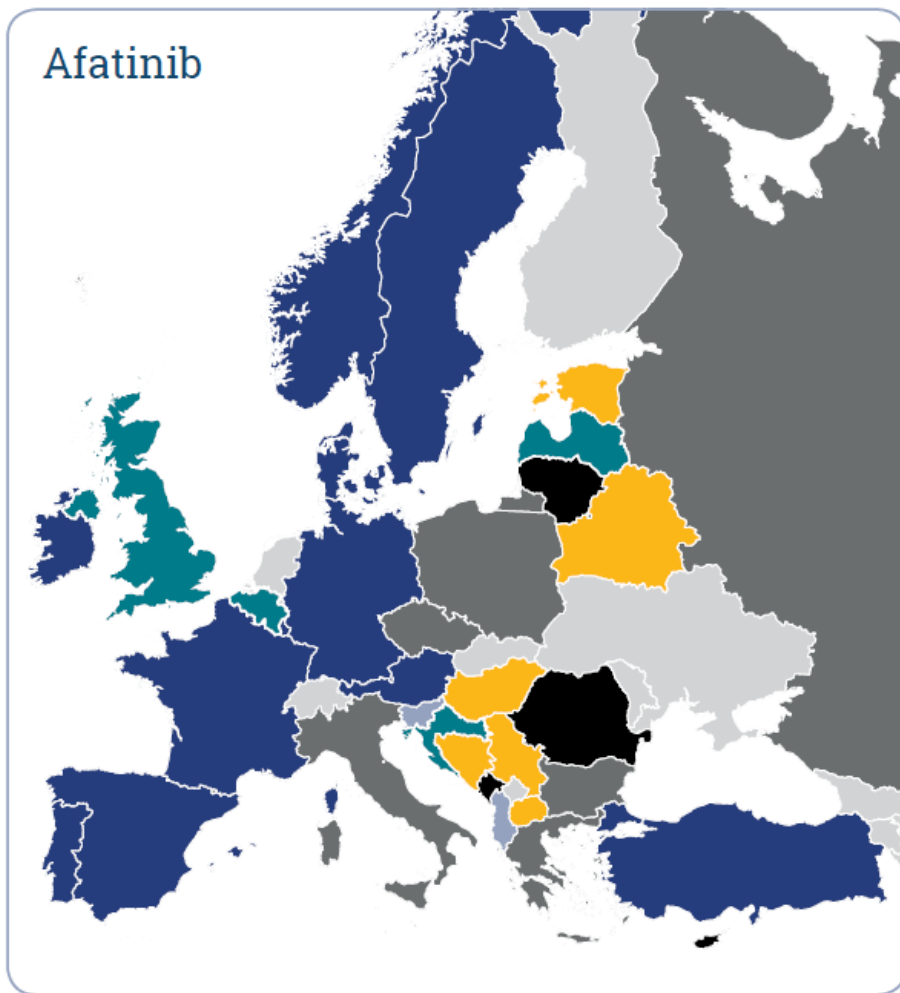
Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe

Carin A. Uyl-de Groot [1,*], Renaud Heine [1] , Marieke Krol [2] and Jaap Verweij [3]

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Figure: Time to first uptake for 12 newly registered oncological drugs across Europe (in days)
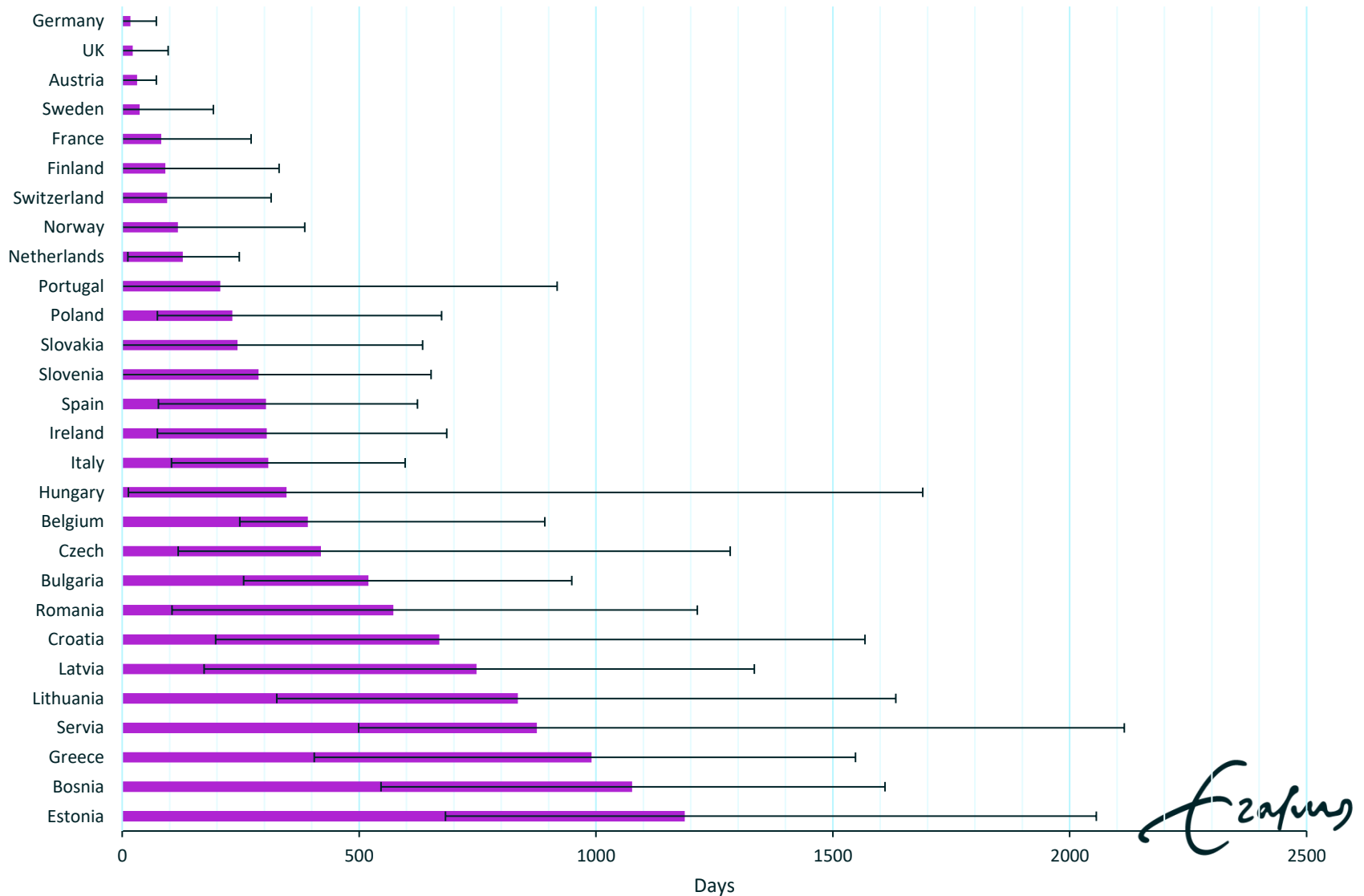
Figure: Speed of drug uptake for 12 newly registered oncological drugs in first two years across Europe
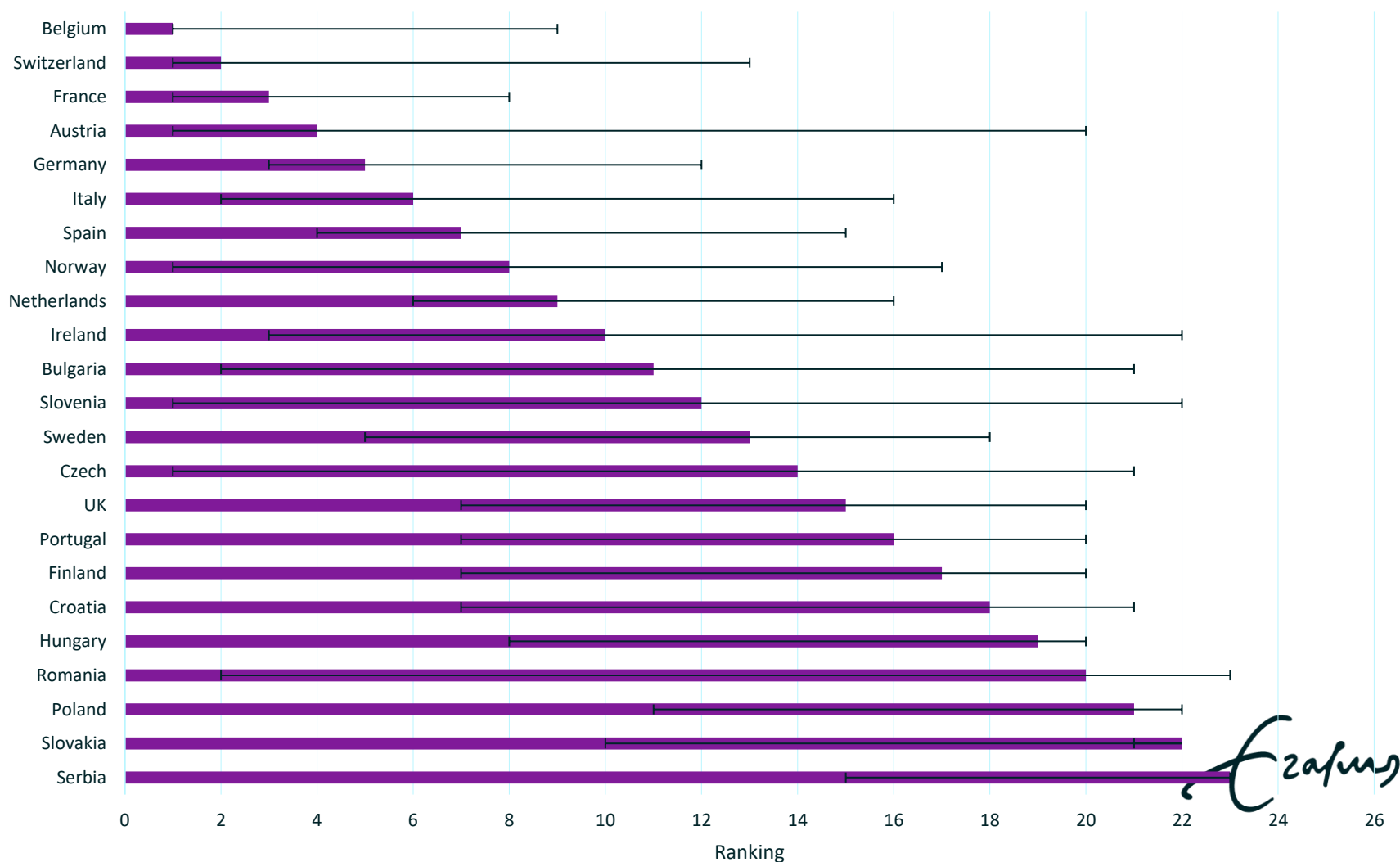
Systems are not sustainable so:

How to reduce spending?

- Shift from expensive to cheap technologies
- 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
- However, we have to deal with the unequal access issue across Europe

Value based pricing

Incremental cost-effectiveness ratios: Cost per QALY gained
Thresholds
- NICE: £ 30.000, US: US$ 50-100.000
- WHO threshold: depend on WHO region and Gross Domestic Product (GDP)

Still budget impact problem.

Pay for performance (P4)
- Reimbursement dependent on treatment success

Volume-price arrangements
- sales < Y price P1; sales > Y lower price P2

Rationale for adapting the business model of (cancer) drug pricing

Issues:

1. A free market does not work for innovative (cancer) drugs
   - *Informational imbalance*
   - *Failure of competition*
2. Current cancer drug prices not justified by Research and Development (R&D)
3. Country specific solutions did not solve the problem
   - EUNeHTA
4. Restricted access to innovative drugs

New pricing model innovative (cancer) drugs:

https://www.youtube.com/watch?v=znTgYPRWyrA

Sustainability and affordability of cancer drugs: a novel pricing model

Carin A. Uyl-de Groot & Bob Löwenberg

The algorithm

$$\text{Fair Cost of New Medicine} = \left[\frac{\text{R\&D costs}}{\text{nr. of patients} \times \text{years of patent left}} + \text{production costs per patient per year} \right] \times (1 + \text{profit margin})$$

Carin A. Uyl-de Groot and Bob Löwenberg, Sustainability and affordability of cancer drugs: a novel pricing model. *Nature Reviews,* July 2018. [link]

Some assumptions examples in algorithm

Costs R&D
- Enzalutamide: US$473.3 million
- Ruxolitinib: US$1,097.8 million
- Maximum reported: US$2.588 billion, including abandoned drugs

Number remaining patent years
- Average all drugs: appr. 10 years
- Enzalutamide: 13 years
- Ruxolitinib: 12.2 years

Profit margin depend on clinical benefit (MCBS score)

Table 1 Calculation of cost price of average treatment of one patient with a new drug

	Estimation number of patients	Costs R&D* (US$)	Costs Drug (US$)	Costs without profit (US$)	Profit margin 20% (US$)	Profit margin 30% (US$)	Profit margin 40% (US$)
Base case 1	100,000	2,558	650	3,208	3,850	4,170	4,491
Base case 2	10,000	25,580	650	26,230	31,476	34,099	36,722
Enzalutamide	140,000	260	1,950	2,210	2,652	2,873	3,094
Enzalutamide	300,000	121	1,950	2,071	2,486	2,693	2,900
Ruxolitinib	7,600	11,840	1,430	13,270	15,924	17,251	18,578
Ruxolitinib	76,000	1,184	1,430	2,614	3,137	3,398	3,660

Outline adapted business model of (cancer) drug pricing

Registration of new drug for certain indication (FDA, EMA, other)

Central level (US, EU, other)

Calculation of maximum price of new cancer drug

Calculation maximum price of new cancer drug based on algorithm

Algorithm includes:

- Research & development (R&D) cost including abandoned drugs
- New drug (manufacturing, sales, marketing, overheads) costs
- Profit margin linked to clinical benefit
- Number of patent years after registration
- Number of patients worldwide

Establishment of proposed price for new cancer drug by e.g. an EU or USA agency (subject to adjustment to national circumstances)

Ongoing debate and progress

Meetings with the European Parliament
- Resolution: transparency R&D costs, discounts (2017)
- White paper access to medicines (October 2018)

Dutch Ministry of Health: BeNeLuxAI
ESMO: access to medicine hot topic
EHA: task force fair prices

Patient organizations: e.g. Inspire2Live

Pharmaceutical companies (improving access/uptake)

Collaboration with other organizations:
- Fair Medicine

Joint pricing between countries

- Netherlands
- BeNeLuxAI
- And next……

	Number of inhabitants (in millions)	Perc. Europe (cumulative)	Western Europe
NL	17	2%	4%
BeNELux	29	4%	7%
BeNELuxA	38	5%	9%
BeNeLuxAI	42	6%	10%
UK	66	15%	16%
Italy and Spain	107	29%	25%
Western Europe	421	57%	100%

Example: niraparib (Zejula)

For the maintenance treatment of ovarian, fallopian tube, or primary peritoneal cancer.

$$\text{Fair Cost} = \left[\frac{\text{R\&D costs}}{\text{nr. of patients} \times \text{yrs of patent}} + \text{production} \right] \times (1 + \text{profit margin})$$

Input:
- R&D costs of Tesaro from 2010 to 2017 = €1,882,000,000
- Estimated number of patients = 50,000
  [Source: Globocan 2012. Assumption: 30% eligible patients worldwide]
- Years of patent left = 11.5 years
- Production cost (per patient, per year) = [€5 (per caps) x 3 (caps. per day) x 365]
  = € 5,475

- Profit margin factor = 40%

Fair price vs. actual price

Fair price of niraparib (Zejula) per patient per year = **€14,547**

Price of niraparib (Zejula) per patient per year **in The Netherlands** = **€ 126469**

Calculated revenue with fair price per year

- **With fair price based on all eligible** = 50,000 patients x €14,547 = **€ 727,338,043**

                                                                ($ 833,859,609)

Fair price vs. actual price

Fair price of niraparib (Zejula) per patient per year = **€14,547**

Price of niraparib (Zejula) per patient per year **in The Netherlands** = **€ 126,469**

Actual revenue vs. calculated revenue with fair price

- **Net sales 2017** **(extrapolated) = $145,333,333**
- **With fair price based on all eligible** = 50,000 patients x €14,547 = **€ 727,338,043 =**

$ 833,859,609

Measures needed at different levels (national, European), but barriers and limitations

Access issue is broader than discussion about drug prices

Change health systems/legislation: will take years

- Patient's right to health – right to have access to optimal quality of cancer care

- Collaboration between all stakeholders, including pharmaceutical companies

- Encourage joint negotiations

Health systems:

Take home message

- Faster access to new (cancer) therapies

- Better access to new (cancer) therapies

- Lower prices for new (cancer) therapies

It is not a utopia.

"IT ALWAYS SEEMS IMPOSSIBLE UNTIL IT IS DONE."
-NELSON MANDELA

THANK YOU