YOU HAVEN'T SEEN ANYTHING YET

Apr Marc Dooms







The speed of innovation brings new technologies, more personalized care…..but greater costs

The Problem



1900 — *Surgical treatment as only therapeutic solution*

Radiotherapy
Treat tumors using X-rays

1940

Single agent chemotherapy
Antitumor drugs for hematological and solid tumors

1970

Combination chemotherapy

1980

Combination chemo-radiation therapy

1990

Oral chemotherapy

2000

Targeted therapies including biologicals
Tyrosine kinase inhibitors & monoclonal antibodies, directed to tumors and molecular alteration

2010

Checkpoint inhibitors
Monoclonal antibodies able to stimulate the immune system against cancer

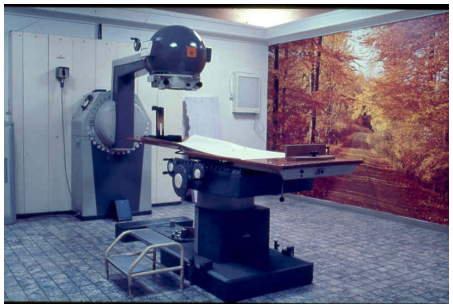
2015

First immuno-therapy (Ipilimumab)

2019

CAR-T and ATMPs

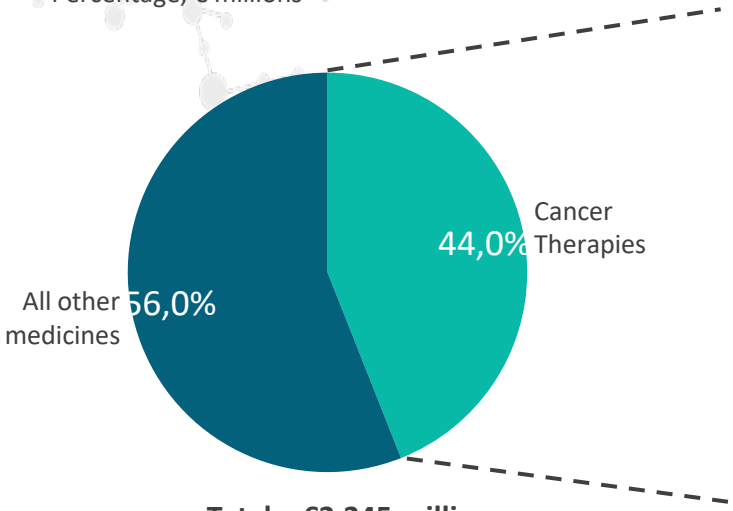
more personalized care for each individual patient



The Problem

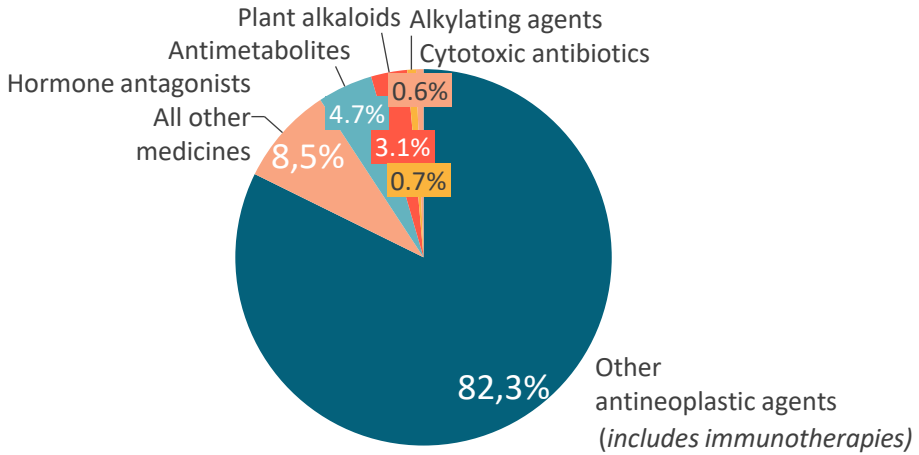
44% of the Belgian medicines budget is spent on cancer therapies, the majority of which are other antineoplastic agents

Total Spend on All hospital Medicines in Belgium, 2018
Percentage, € millions



Total = €2,245 million

Total Spend* on Cancer Therapies in Belgium, 2018
Percentage, €millions



Total = €994.7 million

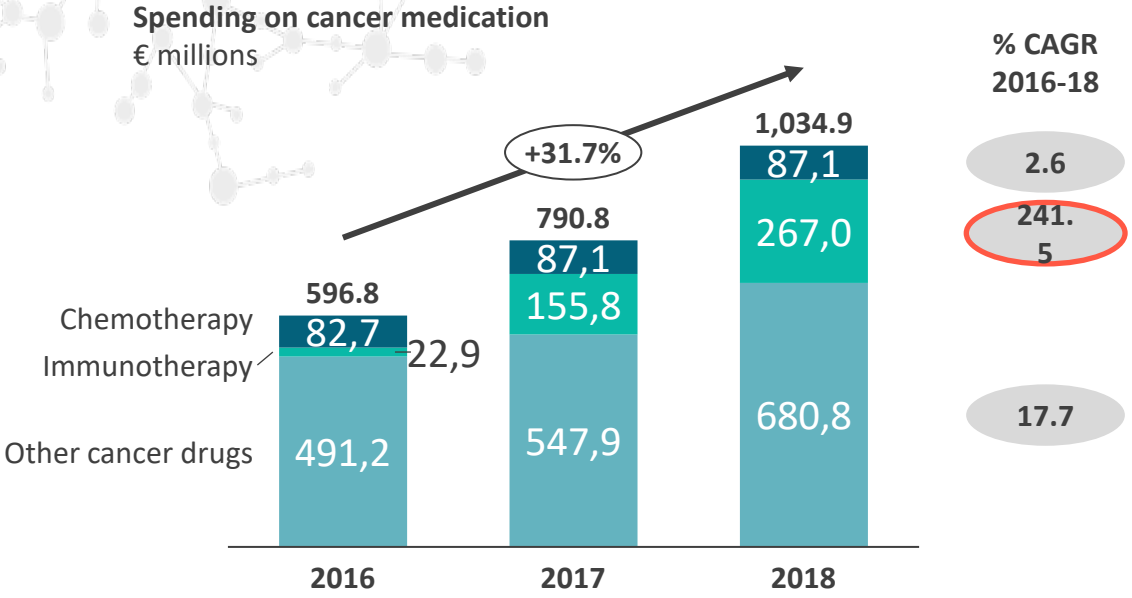
*Includes outpatient, inpatient, and pharmacy spend
Source: RIZIV Cancer Therapeutics Spending Data



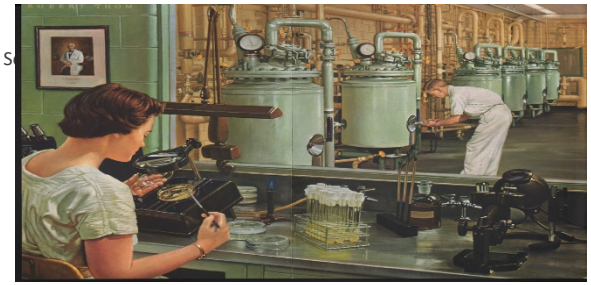
Houston, we have a problem: spending on cancer therapies has increased nearly 32% since 2016

The Problem



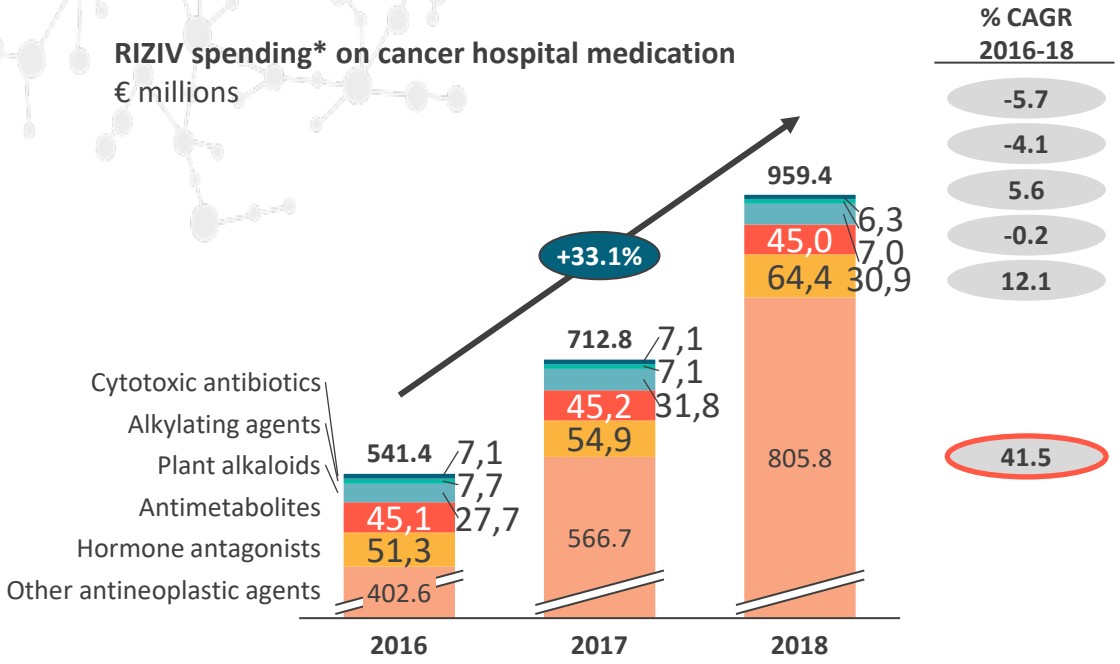


- In 2018, oncology therapeutic expenditure was **over €1 billion**, up from €596.8 million in 2016
- The greatest increase in spend has been on immunotherapy, growing over 240% from €22.9 million in 2016 to €267 million in 2018



The Problem

In 2018, spend on other antineoplastic agents--which includes immunotherapies--was €805m, growing over 40% since 2016



*Includes outpatient and inpatient spend only (not pharmacies)
Source: RIZIV Cancer Therapeutics Spending Data



- While overall cancer spending has grown **just over 33%,** the **greatest increase has come from other antineoplastic agents**, from €403m in 2016 to over €800m in 2018
- The other antineoplastic agents category includes therapies such as **monoclonal antibodies and immunotherapies**
- Spending on three categories has declined from 2016-2018: cytotoxic antibiotics, alkylating agents, and antimetabolites

ATMP regulation 1394/2007

- ATMP
  - products in gen therapy (GTMP)
  - products in somatic cell therapy (sCTMP)
  - products in tissue engineering (TEP)
  - combined products (Combined)
  - 'Manipulated': minimum 1 of the 2 criteria



"substantial manipulation" :
NOT: cut, centrifuge, sterilise, freeze,… (Annex I)
BUT: cell expansion, ex vivo cell activation or –differentiation, …

not the same essential function in receiver and donor

Gene Therapy



Biological medicinal product with the following characteristics:

a) it contains an active substance which contains or consists of a **recombinant nucleic acid** used in or administered to human beings **with a view to regulating, repairing, replacing, adding or deleting a genetic sequence**;

b) its therapeutic, prophylactic or diagnostic effect **relates directly to the recombinant nucleic** acid sequence it contains, or to the product of genetic expression of this sequence. Not include vaccines against infectious diseases.



Cell Based Medicinal Products

- **Somatic cell therapy** medicinal products:
- -**substantially manipulation** cells or tissues **or not intended** to be used for **the same essential function**(s);
- -administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action.
- **Tissue engineered** product:
- -**engineered (substantially manipulated)** cells or tissues, and
- -administered to human beings with a view to re repairing or replacing a human tissue.



EMA Marketting Authorization

YESCARTA®
(axicabtagene ciloleucel)

zynteglo™
(autologous CD34+ cells
encoding $\beta^{A\text{-}T87Q}$-globin gene)

ALOFISEL



IMLYGIC
alimogene laherparepve
SUSPENSION FOR INJECTION
PFU/mL and 10^8 PFU/mL single-use vi

Strimvelis®
EMA APPROVED

zolgensma®
(onasemnogene
abeparvovec-xic
suspension for intravenous infusi

LIBMELDY

ZALMOXIS

HOLOCLAR

PROVENGE®
(sipuleucel-T)

TECARTUS™
(brexucabtagene autoleucel)

CHONDROCELECT™
When evidence makes a difference
cartilage lesions of femoral condyle ICRS III-IV
TIGENIX
Living Medicines

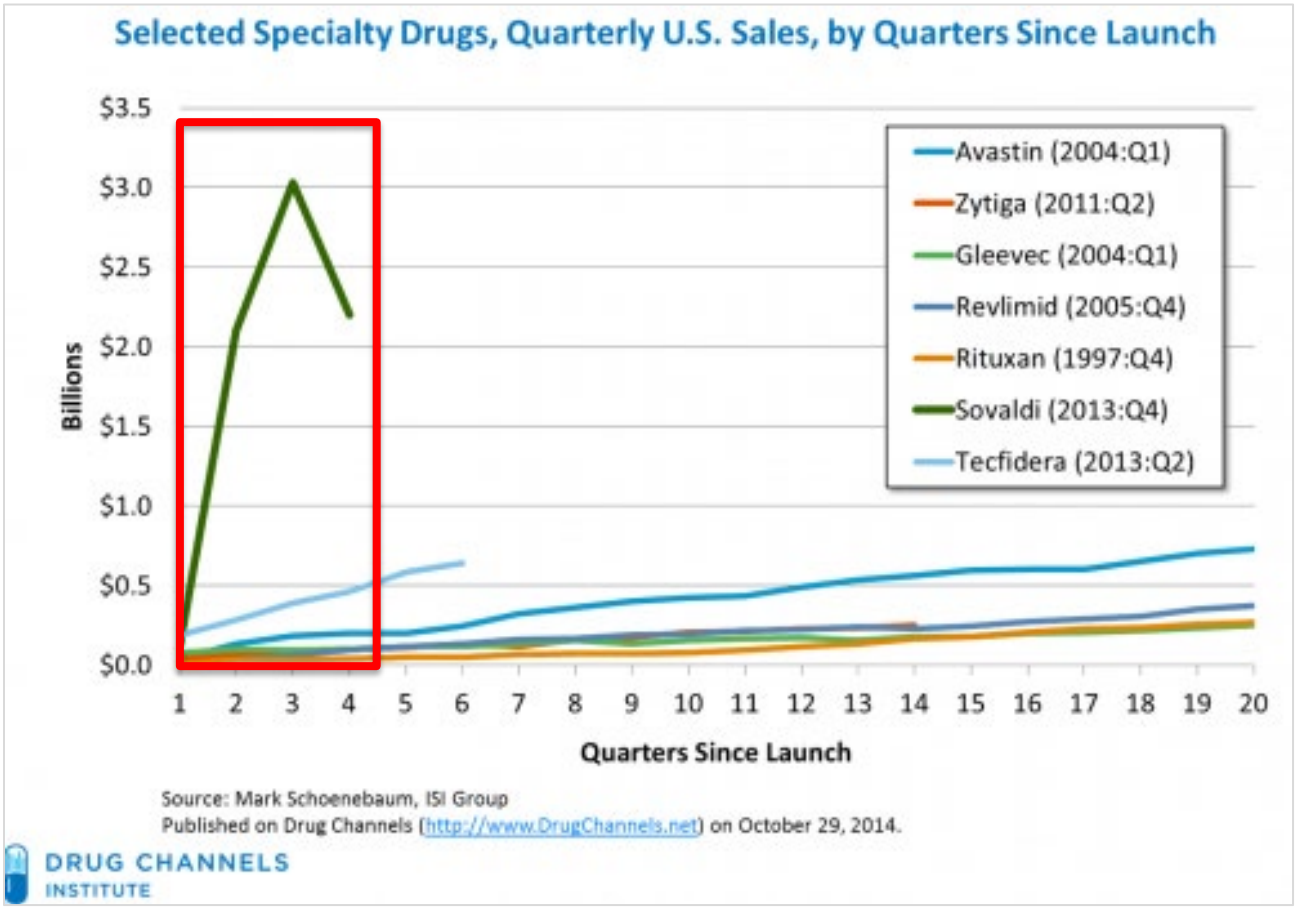
KYMRIAH™
(tisagenlecleucel) Suspe
for IV

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

BUDGET Impact Gene Therapies

Indication	Product	Regulatory approval	Market price[a]	Estimated number of eligible patients (US + Europe)
ADA-SCID[b]	Strimvelis (Orchard Therapeutics)	EMA-2016	€594,000	30–40
Leber amaurosis	Luxturna (Sparks Therapeutics)	FDA-2017 EMA-2018	$850,000	>2,000
SMA[c]	Zolgensma (Novartis)	FDA-2019	$2.1 million	>1,500
B-ALL[d]	Kymriah (Novartis)	FDA-2017 EMA-2018	$475,000	1,000
DLBCL[e]	Kymriah (Novartis)	FDA-2017 EMA-2018	$373,000	1,200
	Yescarta (Gilead)	FDA-2017 EMA-2018	$375,000	
β-thalassemia[f]	Zynteglo (Bluebird)	EMA-2019	€1.58 million	>10,000

THE PROBLEM OF CURING: IMMEDIATE FUNDING FOR UNCERTAIN LONG-TERM VALUE DELIVERED



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Contracting can accommodate payer and manufacturer concerns when covering innovative gene therapies

Alternative contracting

Elements of alternative contracting agreements

Classes		Elements	Description
Alternative contracting agreements	Coverage with evidence development	RWE collection – registry data	Coverage or reimbursement based on product or research outcomes determined using RWE
		Trial data updates	Coverage or reimbursement based on product or research outcomes determined using post marketing studies and pivotal trials updates
	Financial-based agreements	Capitation	Refers to an agreed upon cap on total spending irrespective volume/dose/duration (it can be per patient or at population level)
		Risk-sharing to manage bleeding episodes	Manufacturer to cover the costs of bleeding episodes by reimbursing the cost of FIX replacement therapy
		Installment based agreements	The cost of the drug is covered in periodic payments
	Performance-based risk share	Outcomes based rebates	Refers to the type of agreements wherein further rebates are granted to payers in case desired clinical outcomes are not met
		Payment on results	Payment is based upon attaining positive results within agreed upon performance parameters (e.g. intermediate or clinical endpoints)

Note: *elements can be combined into broader contracting 'concepts' e.g. coverage with evidence development with registry data and outcomes based rebates based on performance tracked through registry data*

MEA with Annuity /Spread Payment

- Shortcutting hospital not possible yet due to internal local accounting rules
- Possible mechanism:
  - Hospital pays company initially 100% of price
  - RIZIV reimburses hospital for 100%
  - Company refunds X % of initial hospital payment back to RIZIV
  - RIZIV pays total price to company over a spread period according to agreed timetable
- First payment should cover fixed “activation” costs



Available ATMP's

Cell Therapies: Alofisel

Gene therapies: Imlygic, **Kymriah**, Libmeldy, Luxturna, Strimvelis, Yescarta, Zolgensma, Zynteglo

Tissue Engeneering: **Holoclar**, Spherox

Kymriah Chapter IV



Evaluations based on:

- Cheson criteria 2014 (vital functions, ECOG, blood test, PET scan,...) for DLBCL
- NCCN criteria (RC, RCi, no response or progression) for ALL
- Overall Survival
- Treatments post infusion



r/r DLBCL

Timeline: reimbursement requests through e-health, with recording of patient assessments

Cell Chain

Product request form

Cells accepted on site

E-Health §100

Electronic reimbursement request

E-Health §200

Notify response and patient situation at month 6 & 12 *

E-Health §300

Notify response and patient situation at month 18 & 20 *

Patient selected	Delivery day	Perfusion day 0	+6 months	+12 months	+18 months	+20 months
Patient assessments			Clinical evaluation and PET scan	Clinical evaluation	Clinical evaluation and PET scan	Clinical evaluation
Invoice/reimbursement request		**X**		**X**		**X**
		280.000€		20.000€		20.000€

*Cheson et al. 2014 criteria

r/r ALL

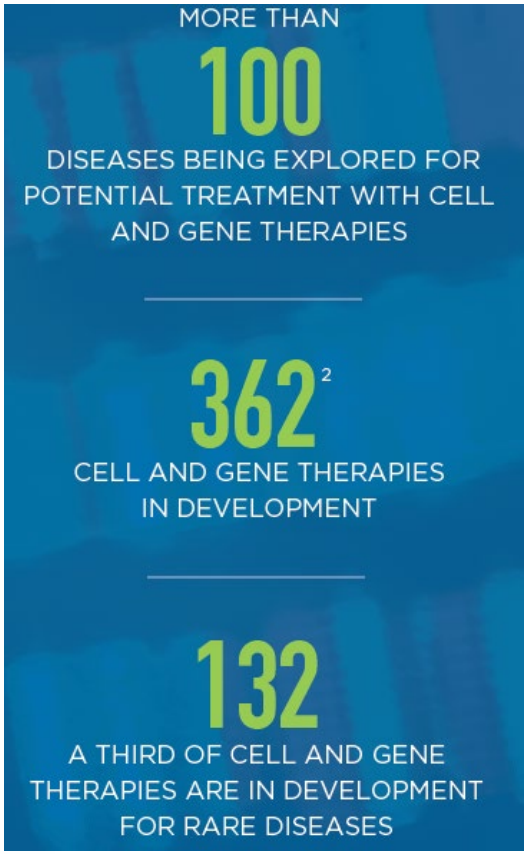
Timeline: reimbursement requests through e-health, with recording of patient assessments

Cell Chain		E-Health §100	E-Health §200	E-Health §300
Product request	Cells accepted on site	Electronic reimbursement request	Notify response and patient situation (NCCN criteria)	Notify response and patient situation (NCCN criteria)

Patient selected → Delivery day → Perfusion day → + 6 months → + 12 months

Patient assessments			Blood/ Bone marrow examination	Blood/ Bone marrow examination
Invoice/reimbursement request		**X**	**X**	**X**
		280.000€	20.000€	20.000€

Cell and Gene therapies



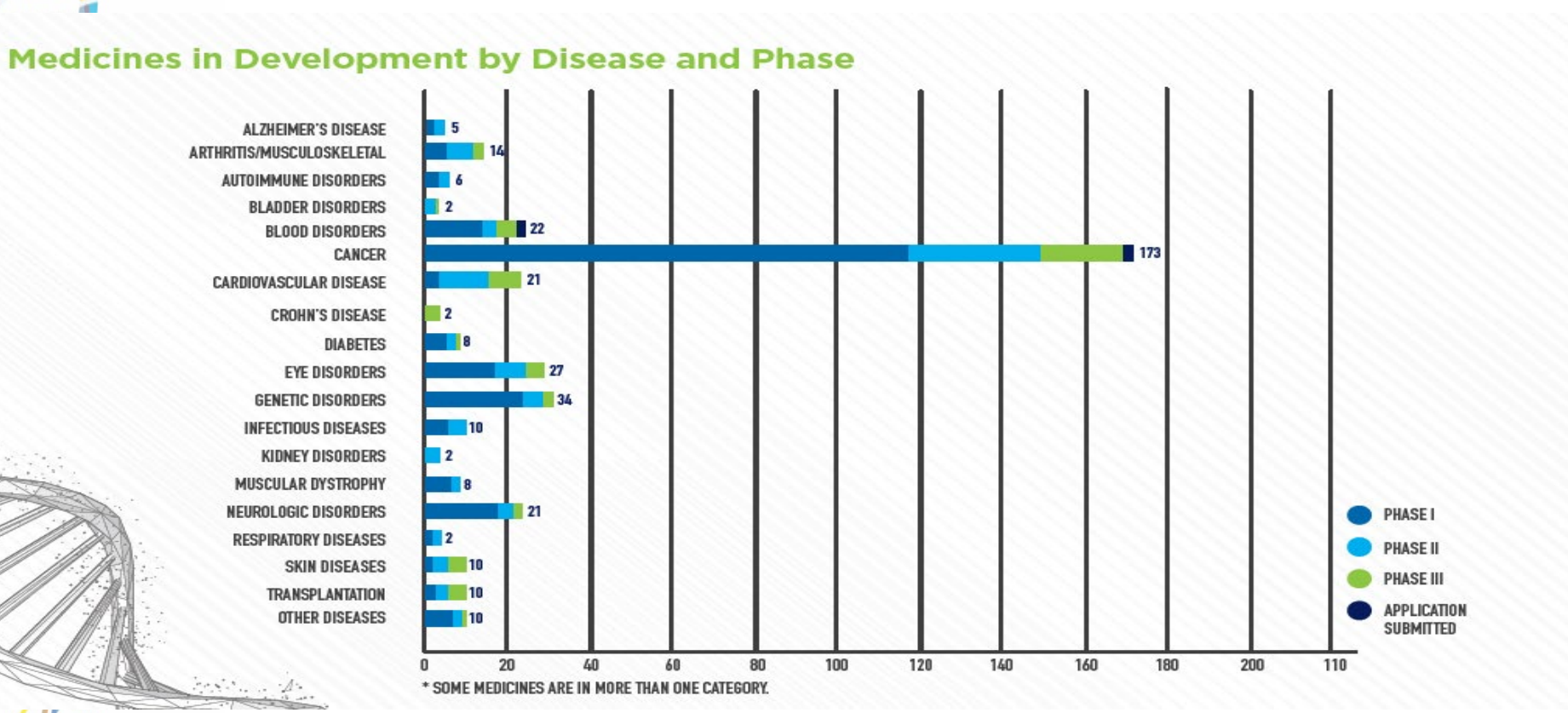
MEDICINES IN DEVELOPMENT | 2020 UPDATE

CELL AND GENE THERAPY

Nearly **400** Cell and Gene Therapies in Development Target a Broad Range of Diseases

Source: American BioPharmaceutical Medecines in Development report

Pipeline by disease and phase

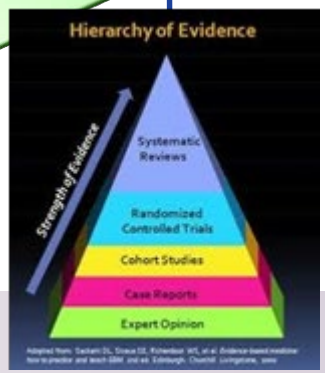


Woodcock: “Drug development can be described as the progressive reduction of uncertainty about the effects of a molecule in people”

Degree of certainty →→

100% ?

Time →→→



Perspectives

> Parent of a child with rapidly progressing rare disease

> Manufacturer
- -R&D
- -Marketing

> Regulator

FUTURE DEVELOPMENTS

Alliance for Regenerative Medicine

FDA

10 to 20 new ATMP's /year for the next 5 years

PaVe-GT Platform Vector Gene Therapy



Hospital Exemption (KB 8/01/17)

"ATMP's die volledig op individuele (non-routine) basis volgens specifieke kwaliteitsnormen in dezelfde lidstaat in een ziekenhuis worden gebruikt onder de exclusieve beroepsverantwoordelijkheid van een beoefenaar van een medisch beroep, om te voldoen aan een bepaald medisch recept voor een speciaal bereid geneesmiddel voor een bepaalde patiënt, moeten van het toepassingsgebied van deze Verordening zijn uitgesloten terwijl er tevens voor gezorgd wordt dat relevante communautaire voorschriften met betrekking tot de kwaliteit en de veiligheid niet worden ondergraven."



Hospital exemption in Belgium

Royal Decree (AR/KB 8-01-17)

⇨ An ATMP can be prepared and administered in a hospital when an exemption has been obtained: procedure!

⇨ Conditions:
- prepared in Belgium
- non-routine (annex 2)
- custom-made for an individual patient
- prepared according to volume 4 of "The rules governing medicinal products in the European Union"

⇨ Ethics committee / informed consent


I BELIEVE THIS IS
NOT THE END BUT
THE BEGINNING.
Gao Feng
QUOTEHD.COM


TIME
LOTT'S IMPEACHMENT PLAN
SPECIAL ISSUE
THE FUTURE OF
MEDICINE
How genetic engineering will change us in the next century


IN
ORDER
TO BE
IRREPLACEABLE
ONE
MUST
ALWAYS BE
DIFFERENT