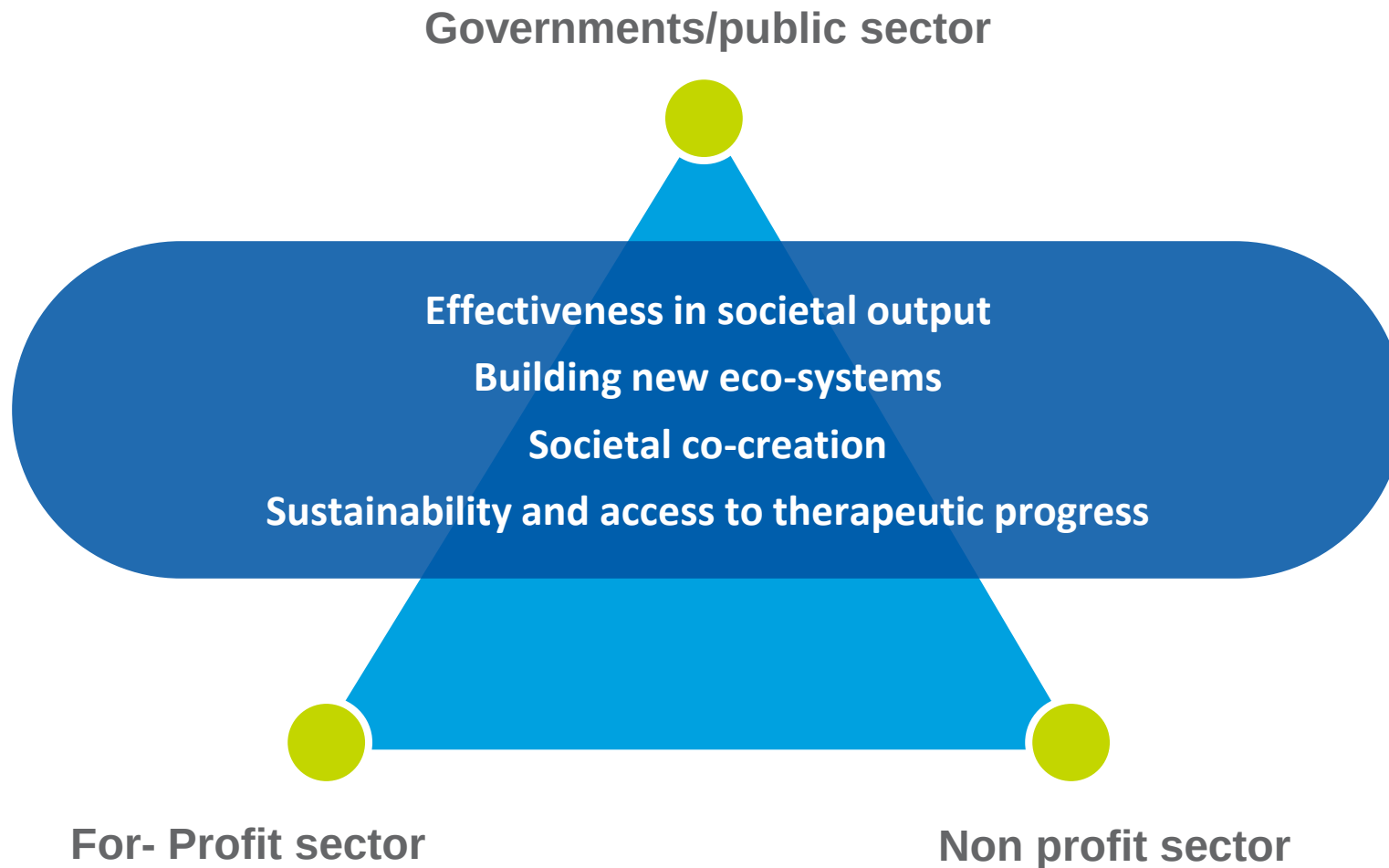


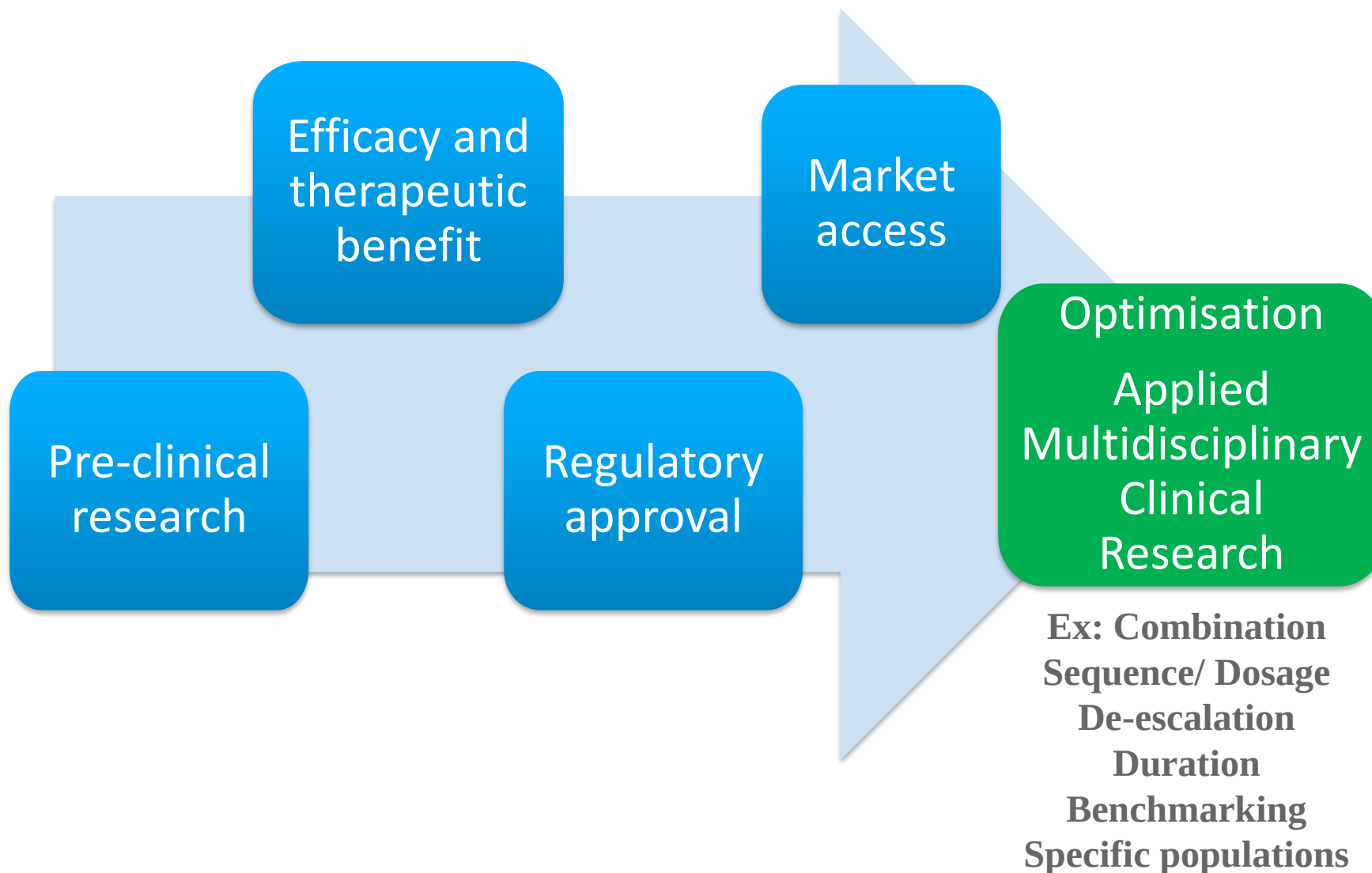
From treatment development to healthcare: Is the continuum becoming a reality?

Denis Lacombe, MD, MSc
EORTC, Director General
Brussels, Belgium

Looking at the societal balance



Steps of drug development



Estimation of Distant Metastasis-free Survival in Trials of Adjuvant Therapy for Melanoma

TO THE EDITOR: Recently, trials of adjuvant therapy for melanoma in which therapies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), or BRAF and MEK are assessed have reported positive results in terms of relapse-free survival and distant metastasis-free survival.¹⁻⁴ The European Organization for Research and Treatment of Cancer (EORTC) 18071 trial¹ compared ipilimumab with placebo in patients with resected stage III melanoma; the

CheckMate 238 trial² compared nivolumab with ipilimumab in patients with resected stage IIIB, IIIC, or IV melanoma; and the COMBI-AD trial (Nov. 9, 2017, issue)^{3,4} compared dabrafenib plus trametinib with placebo in patients with stage III melanoma with BRAF mutations.

The trials defined relapse-free survival as the time from randomization until first recurrence (local, regional, or distant metastasis) or death (or second primary cancer in the COMBI-AD

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Original Research

Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial



Alexander M.M. Eggermont ^{a,*}, Vanna Chiarion-Sileni ^b, Jean-Jacques Grob ^c, Reinhard Dummer ^d, Jedd D. Wolchok ^e, Henrik Schmidt ^f, Omid Hamid ^g, Caroline Robert ^h, Paolo Antonio Ascierto ⁱ, Jon M. Richards ^j, Celeste Lebbe ^k, Virginia Ferraresi ^l, Michael Smylie ^m, Jeffrey S. Weber ⁿ, Michele Maio ^o, Fareeda Hosein ^p, Veerle de Pril ^q, Michal Kicinski ^r, Stefan Suciu ^{s,1}, Alessandro Testori ^{s,1}

THE LANCET
Oncology

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FAST TRACK — ARTICLES | VOLUME 6, ISSUE 12, P937-944, DECEMBER 01, 2005

Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Dr Martin JB Taphoorn, MD ^a, Roger Stupp, MD ^a, Corneel Coens, MSC ^a, David Osoba, MD ^a, Rolf Kortmann, MD ^a, Martin J van den Bent, MD ^a, et al. Show all authors

Published: November 17, 2005 • DOI: [https://doi.org/10.1016/S1470-2045\(05\)70432-0](https://doi.org/10.1016/S1470-2045(05)70432-0)

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial



Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Lu A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuw Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Ma Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Boga

Summary

Background If tr axillary lymph n regional control, comparable regi

original reports

Standard Anthracycline Based Versus Docetaxel-Capecitabine in Early High Clinical and/or Genomic Risk Breast Cancer in the EORTC 10041/BIG 3-04 MINDACT Phase III Trial

Suzette Delaloge, MD, MSc^{1,2}; Martine Piccart, PhD³; Emiel Rutgers, PD, PHD⁴; Saskia Litière, PhD⁵; Laura J. van 't Veer, PhD⁶; Franchette van den Berkmoortel, MD, PhD⁷; Etienne Brain, MD, PhD⁸; Aleksandra Dudek-Peric, PhD⁹; Miguel Gil-Gil, MD¹⁰; Patricia Gomez, MD¹¹; Florentine S. Hilbers, MSc¹²; Zaman Khalil, MD¹³; Susan Knox, MA¹⁴; Sherko Kuemmel, PhD¹⁵; Georg Kunz, MD¹⁶; Anne Lesur, MD¹⁶; Jean-Yves Pierga, MD¹⁷; Peter Ravdin, MD, PhD¹⁸; Isabel T. Rubio, MD, PhD¹⁹; Mahasti Saghatelyan, MD²⁰; Tineke J. Smilde, MD, PhD²⁰; Alastair M. Thompson, MBChB, MD²¹; Giuseppe Viale, MD²²; Gabriele Zoppoli, MD, PhD²³; Peter Vuylsteke, MD²⁴; Konstantinos Tryfonidis, MD²⁵; Coralie Poncet, MSc²⁶; Jan Bogaerts, ScD²⁷; and Fatima Cardoso, MD²⁸; on behalf of MINDACT investigators and the TRANSBIG Consortium

VOLUME 35 • NUMBER 15 • MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirmanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

Paolo G. Casali, John Zalberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Lars H. Lindner, Ian R. Judson, Patrick Schöffski, Serge Leyvraz, Antoine Italiano, Viktor Grünwald, Antonio Lopez Pousa, Dusan Kotasek, Stefan Sleijfer, Jan M. Kerst, Piotr Rutkowski, Elena Fumagalli, Pancras Hogendoorn, Saskia Litière, Sandrine Marreard, Winette van der Graaf, Alessandro Gronchi, and Jaap Verweij on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group

Challenge Statement

Many new treatments are
developed based on their MoA

New regulatory science
based on early access

Innovation:
how do we measure efficacy
& give access to patients

Integration in multidisciplinary
strategies

Where can we find answers?

...s/treatment
...hold up their promises

Clinically relevant questions
unaddressed / missing datasets

Impact on access

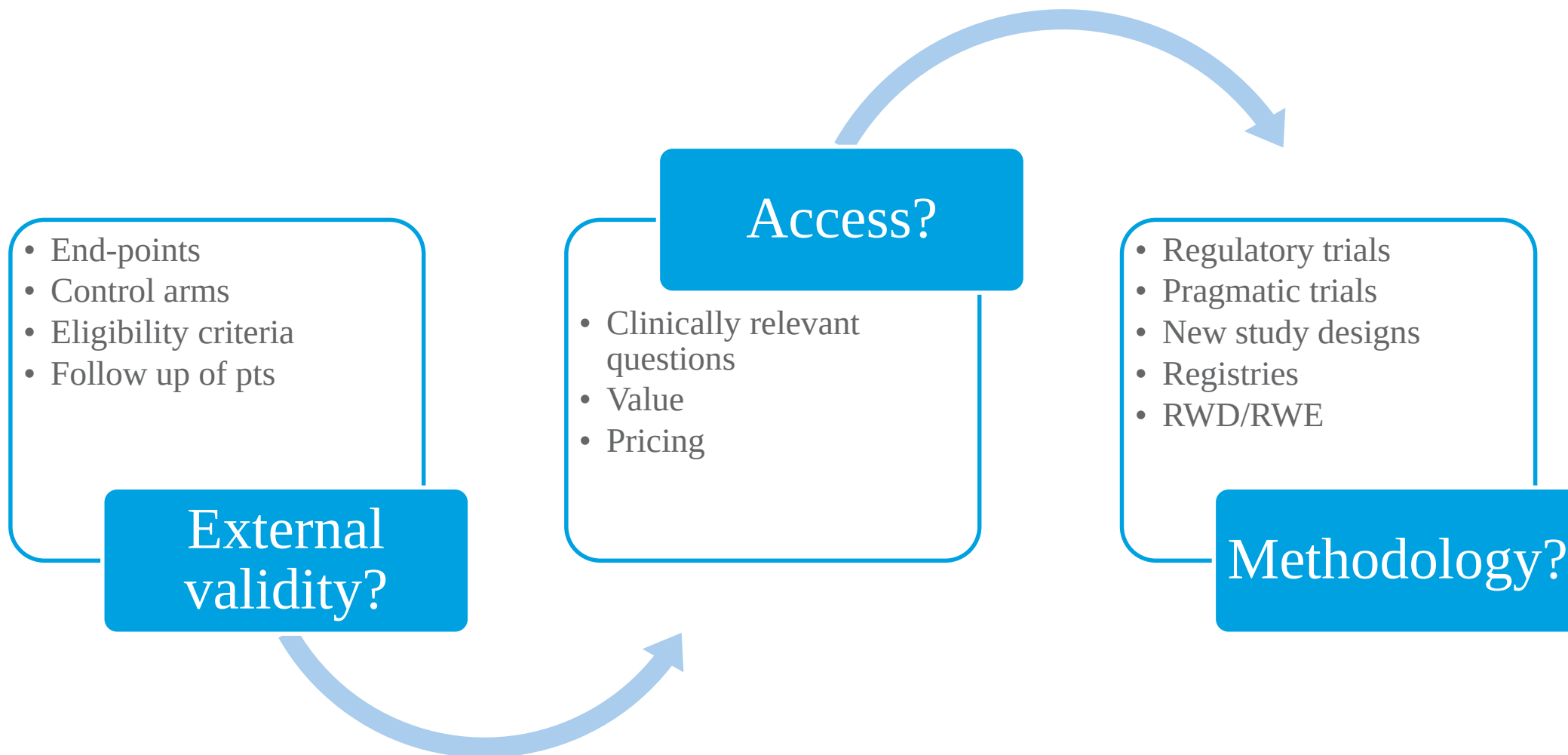
Many challenges ahead..

- Understanding the complexity
- Tumor and micro-environment
- Fragmentation of diseases
- Heterogeneity of the disease
- Patterns of relapse

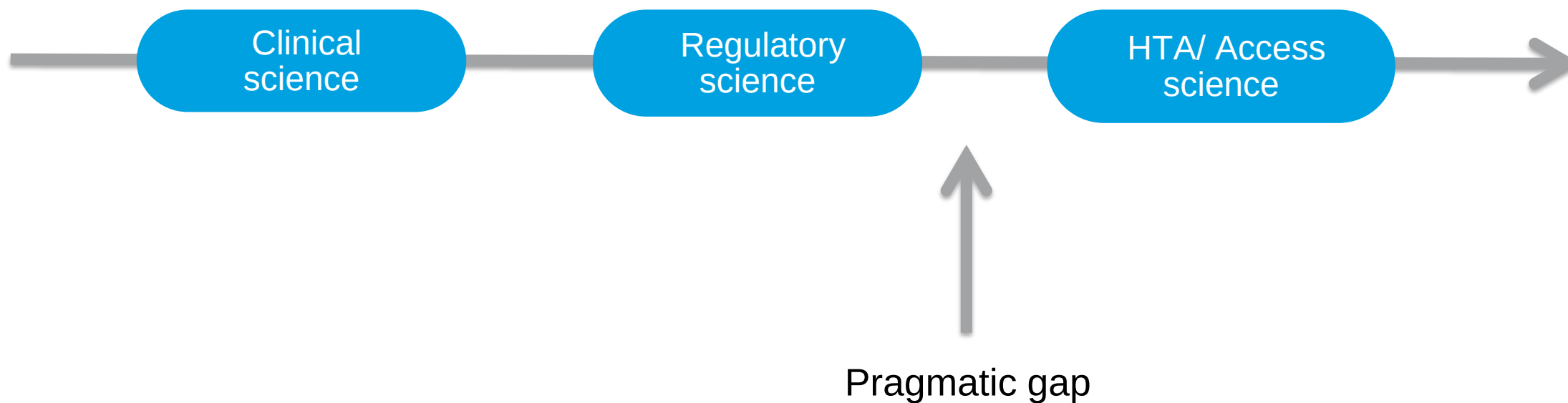


**Complex evolutive
multidimensional data sets
informing patients and society**

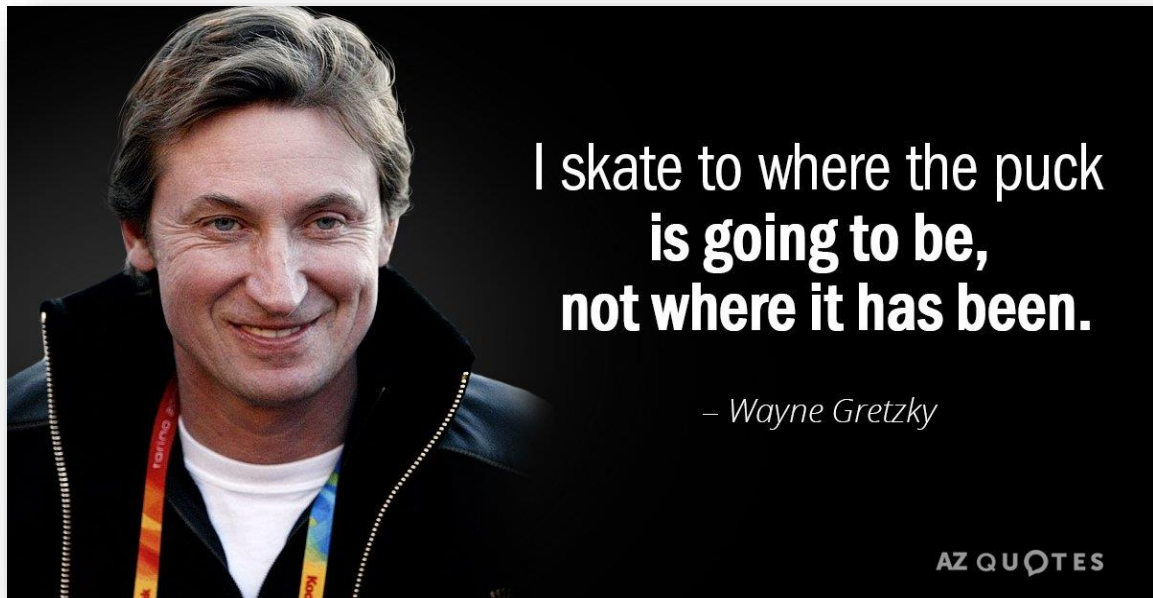
A multidimensional complex landscape



A new continuum to be set upRe-engineer....



A transformative society..



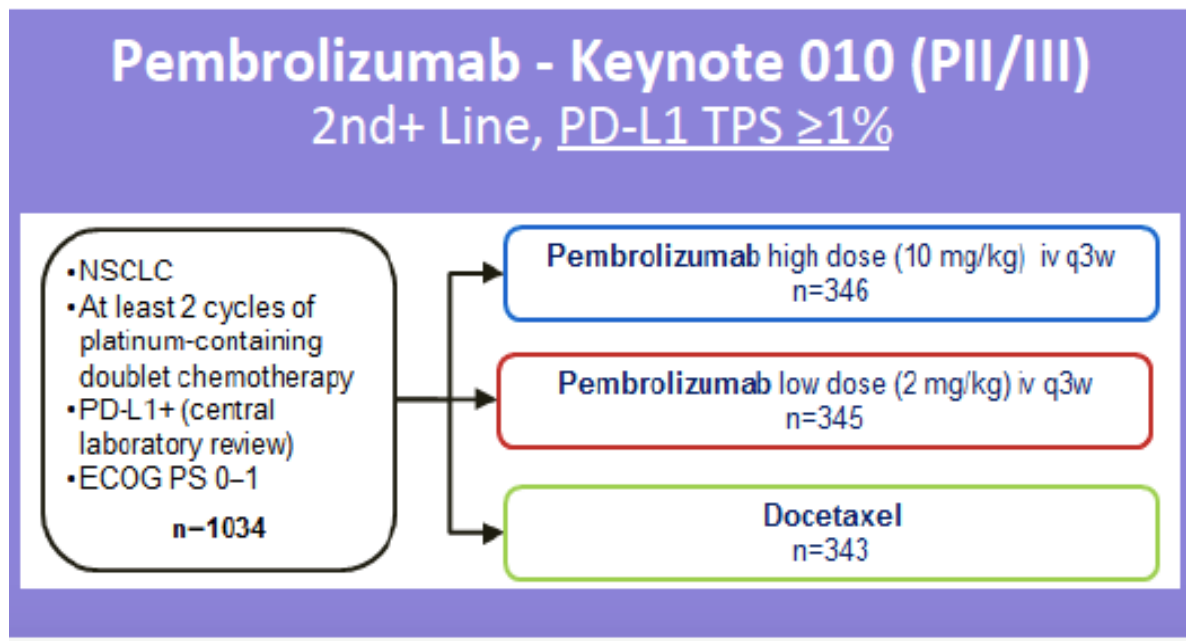
- More patient oriented science and more disruptive ideas to change treatment access
- Build based on the ultimate goal and adapt the means to get there.

Any accelerated approach has the potential to bring innovation faster to the clinic but the potential for negative consequences is real.

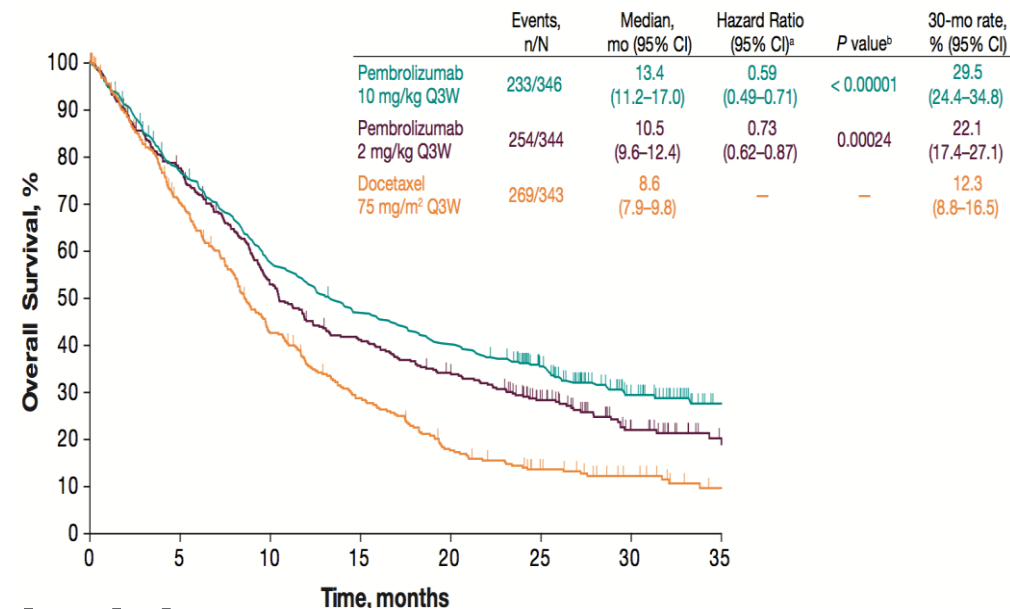
How do we control uncertainty for the patient? for society?
Which policy actions could be proposed?

Pembrolizumab doses evolved with time

- Initially approved at 2 mg / kg every 3 weeks



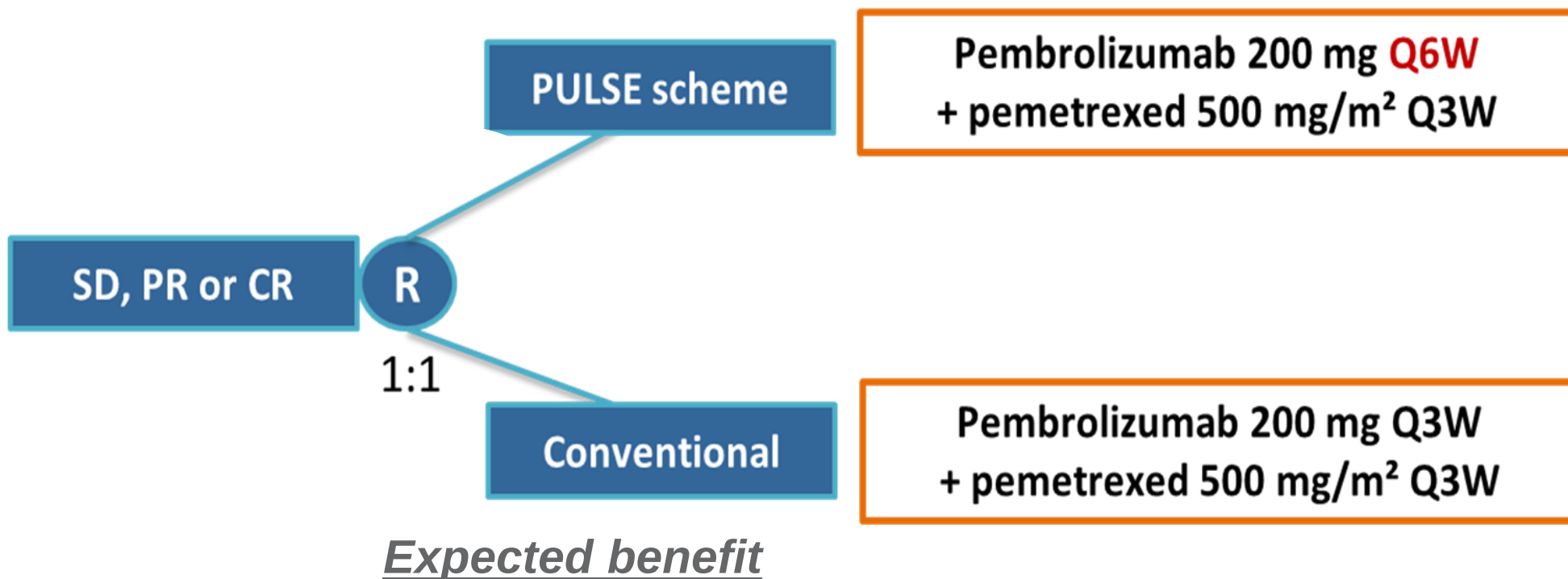
- Then flat dose 200 mg every 3 weeks (PK analysis)
- Then 400 mg every 6 weeks (PK modelization)



A French clinical trial : the PULSE regimen

Induction phase

Pemetrexed
Cisplatin or
carboplatin
pembrolizumab
4 cycles

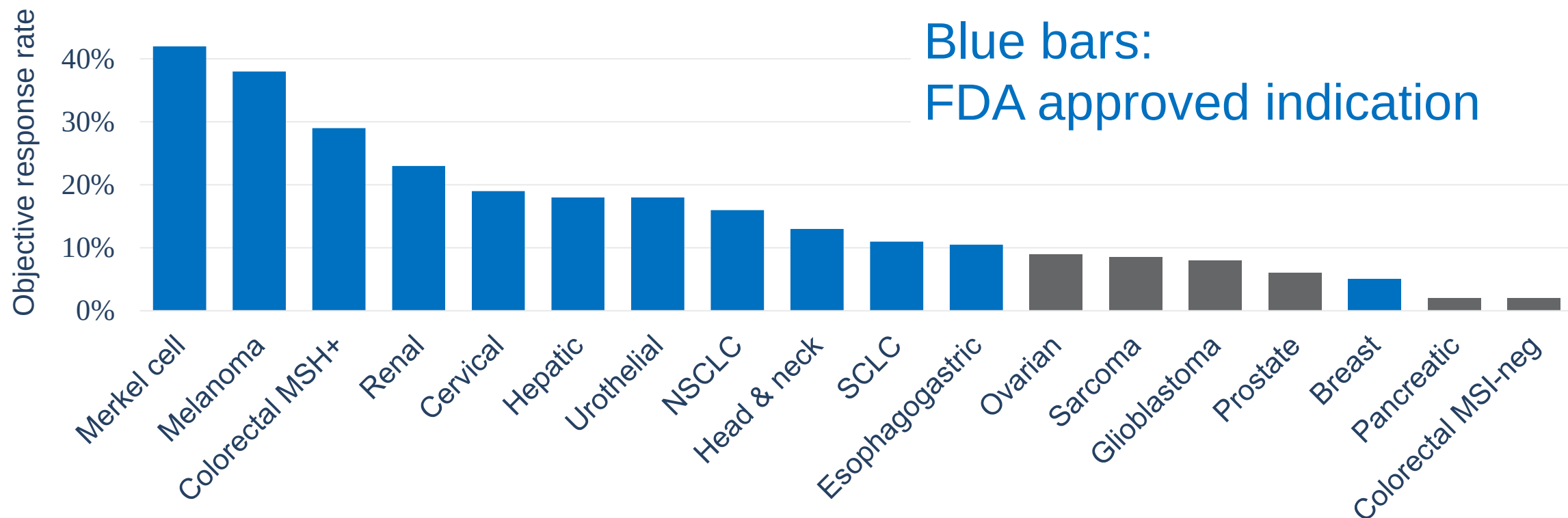


Expected benefit

- Less toxicity ?
- The pulse regimen would lead to save 57 760 euros per patient
- **At the country level, the PULSE regimen may save around 1 billion / 3 yrs**
- **Current funding by the French grant PHRC : 1 692 435 euros**

Poor immunotherapy response rates

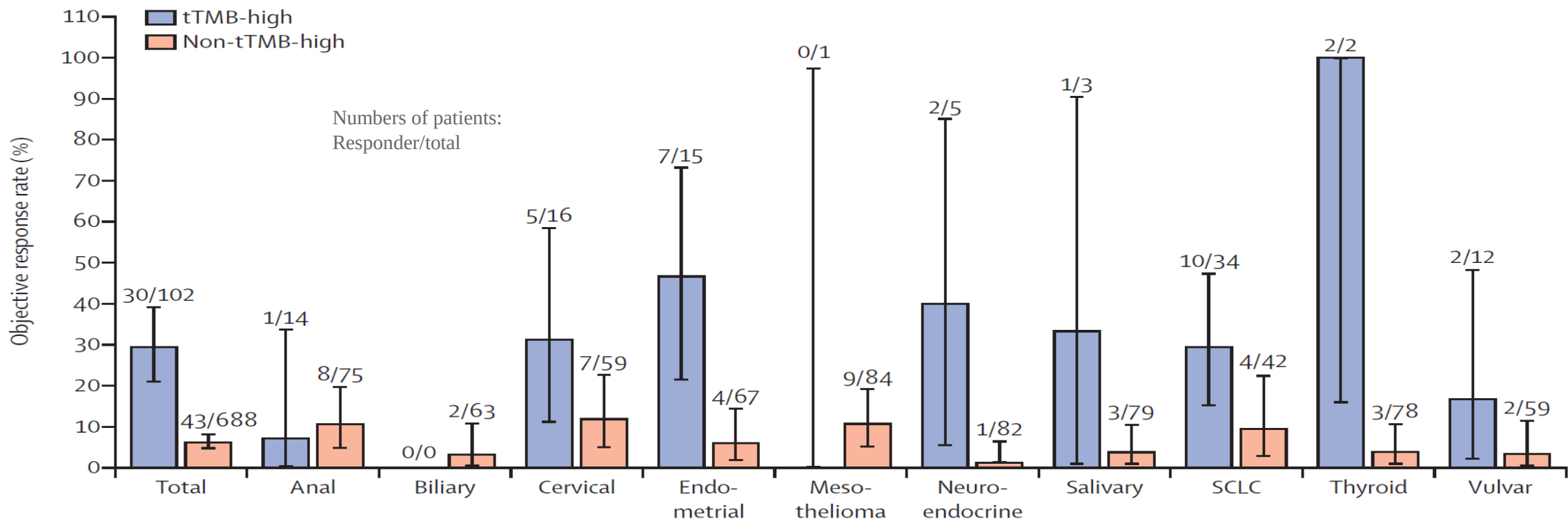
- Response rates to immunotherapy are low in most tumour types
- There is a need for better biomarkers of response



Source: R. Salgado

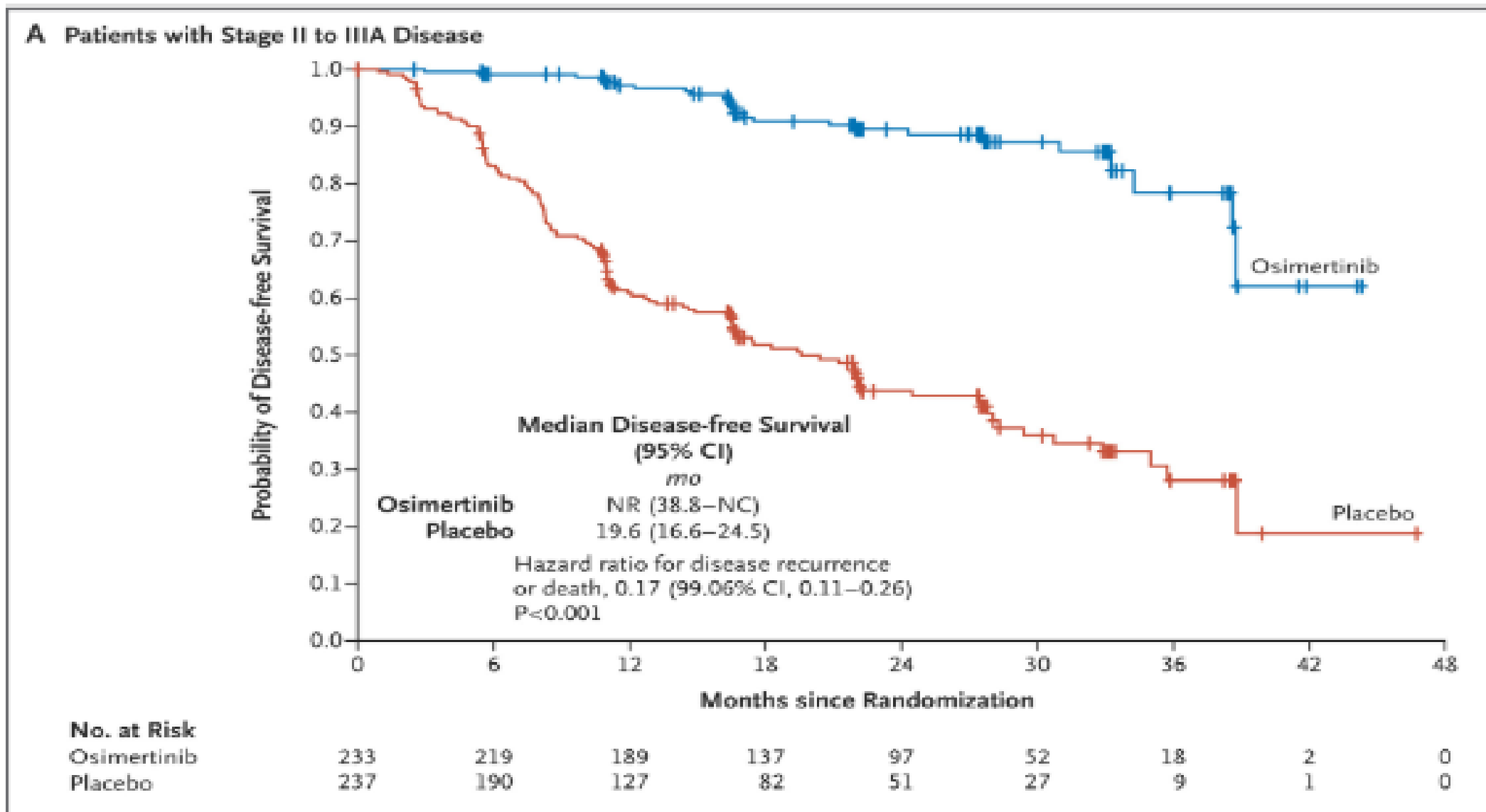
TMB recommendations & approvals

- Data from the Keynote-158 (below) has led to:
- Pan-cancer approval for pembrolizumab
- In some cancer types, there are more responders in the Non-tTMB-high segment



Source: R. Salgado

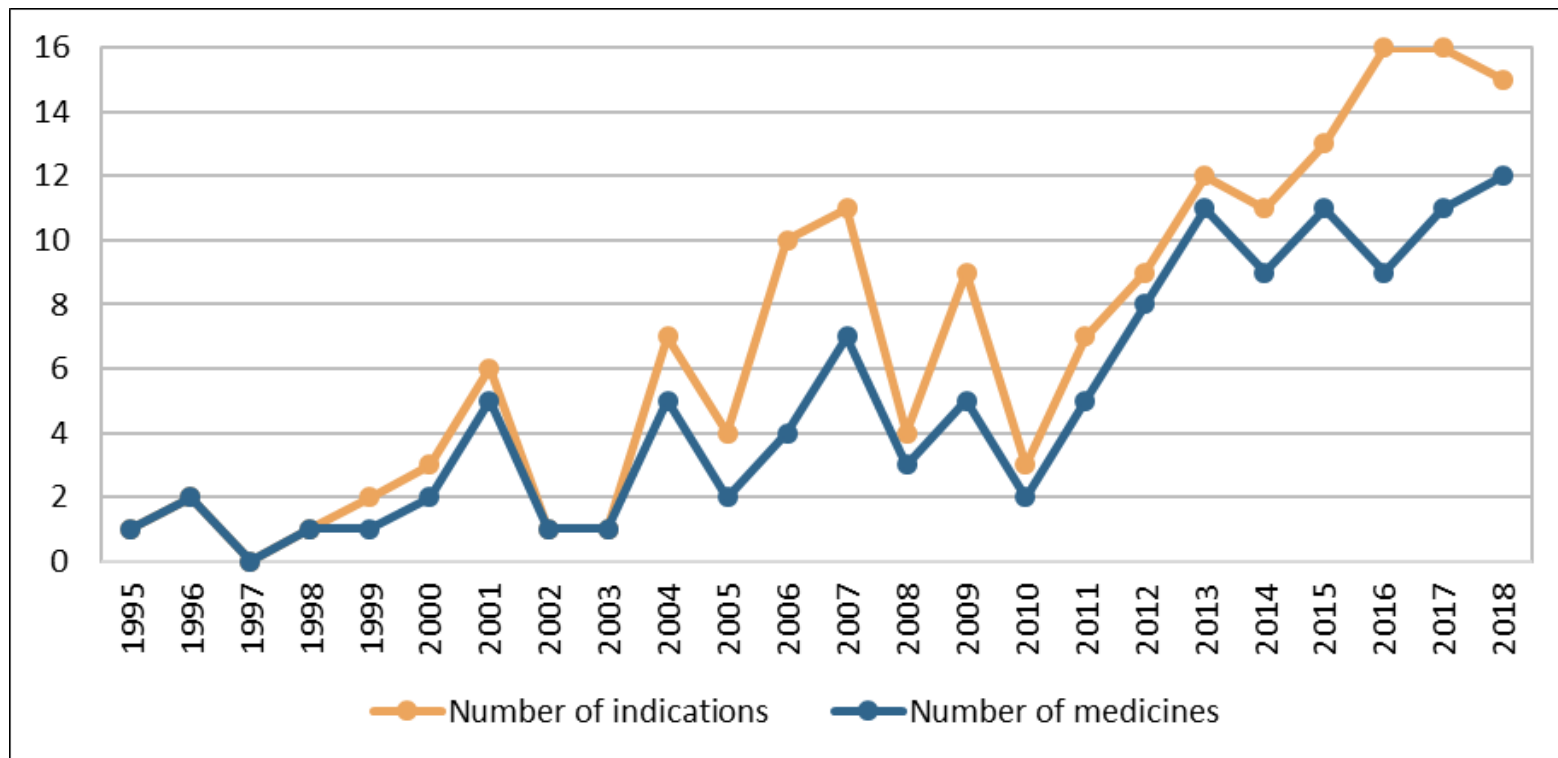
ADAURA: adjuvant treatment Osimertinib in resected EGFRm+ NSCLC



Critical Analysis

- DFS, relevance of the end-point? Potentially cured patient population, objective should be long term survival (secondary end-point, not mature)
- Surrogacy of DFS demonstrated in CT trials. Surrogacy expected to be under question with now efficient treatments at relapse
- CT to provide a survival benefit in this pt population: but only 60% of pts in trial received it. Risk to switch to a new drug which has not demonstrated survival benefit yet
- Even if limited, still side effects expected for a cure patient population
- For 3 years, treatment at 200K/year
- Control arm pts will received the drug at recurrence: impact on on OS?
- Pts who received treatment in the adjuvant setting: risks of early acquired resistance?
- **Optimal design: immediate vs delayed access with primary OS ?**

Growing stream of cancer medicines and indications



EMA approvals of 118 new medicines and 164 indications in oncology 1995-2018

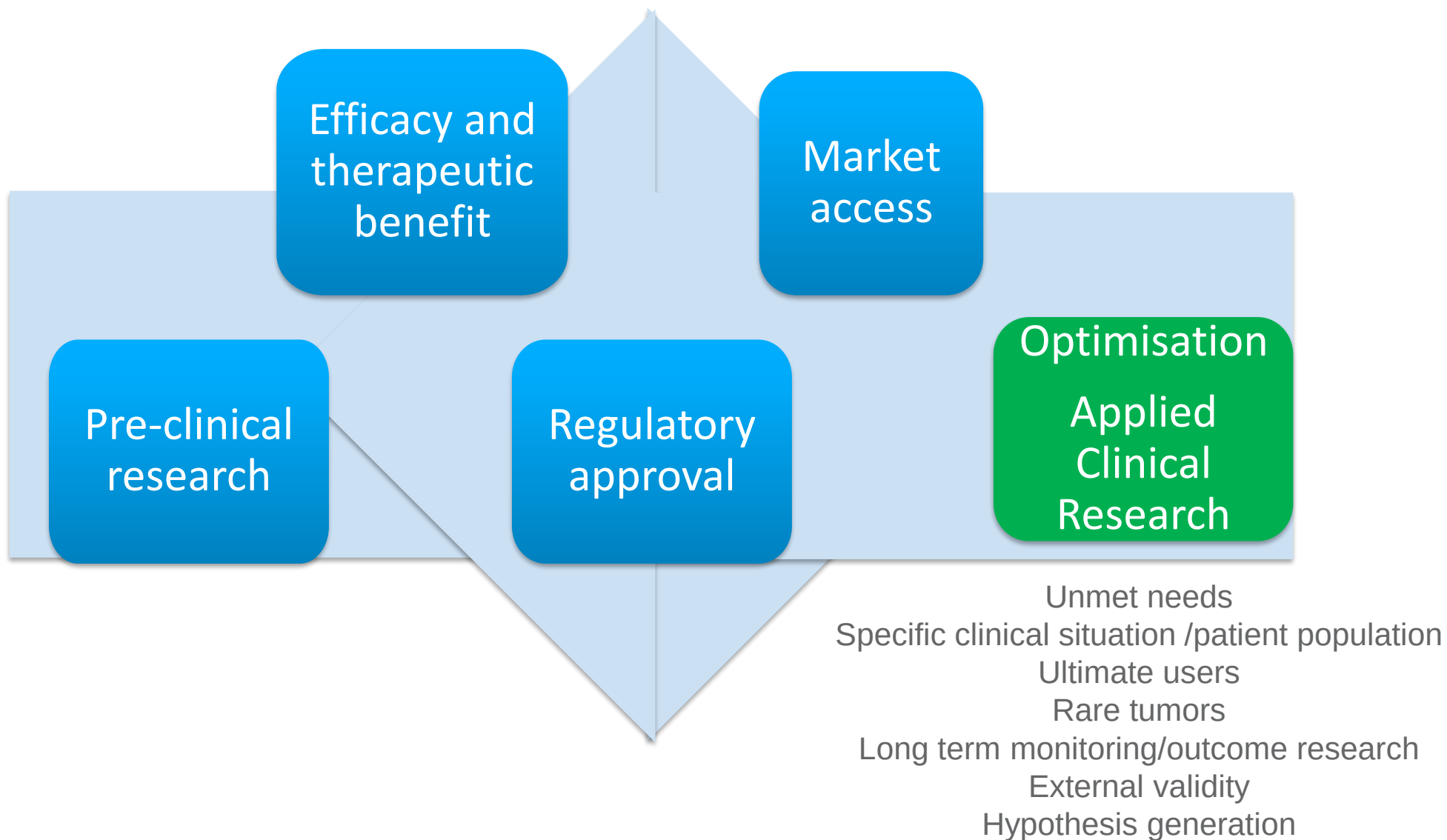
Total of 40 cancer medicines introduced until 1995

Number of EMA-approved cancer medicines and indications, 1995–2018

Notes: Indications refer to label extensions to cancer types in addition to the initially approved cancer type

Source: EMA

The reverse continuum...



Some conceptual changes

- The identification of candidate therapies and the assessment of key clinical questions to be taken forward in healthcare systems based on a multinational, independently-driven access system.
- The development of therapeutic strategies based on a scientific rationale that is complementary to the remit of commercial pipelines. Regulatory trials do not inform on outcome
- **Three scientific pillars to define future directions:**
 - Clinical research
 - Epidemiology
 - Health economics



Generate datasets informative to clinicians and HTAs

Conclusions

- Society must develop the means to generate datasets such as comparative evidence aiming at documenting the optimal treatment for cancer patients through the integration of clinical research, free of commercial interest in the process of access to treatments, and inform healthcare systems.
- Society must re-engineer new models of partnership commercial/ non-commercial research in the continuum of clinical science, regulatory science, into Health Technology Assessment.
- Public health priorities need to command up stream research, to focus innovation where needed and avoid multiplication of redundant agents of the same class.
- Society must support independent multidisciplinary clinical research through new mechanisms, and include health economic assumptions in assessing public savings based on optimized therapeutic strategy trials into healthcare.

In a transformative society, we, actors in the field should “unlearn” what we have done, so that we can learn how to do things differently and create completely new concepts

Reach a process to perform efficiently widely applicable clinical research in the best interest of therapeutic progress while preserving patient interests and rights



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The future of cancer therapy

