Timely Access in Cancer Care: Defining Clinical Benefit and Value

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January 16, 2025

Conflicts of Interest

Support for attending meetings and/or travel: Daiichi Sankyo, Novartis.

Outline

- Price and economic impact
- Clinical benefit in oncology
- Value in cancer care
- Timely access in Cancer Care

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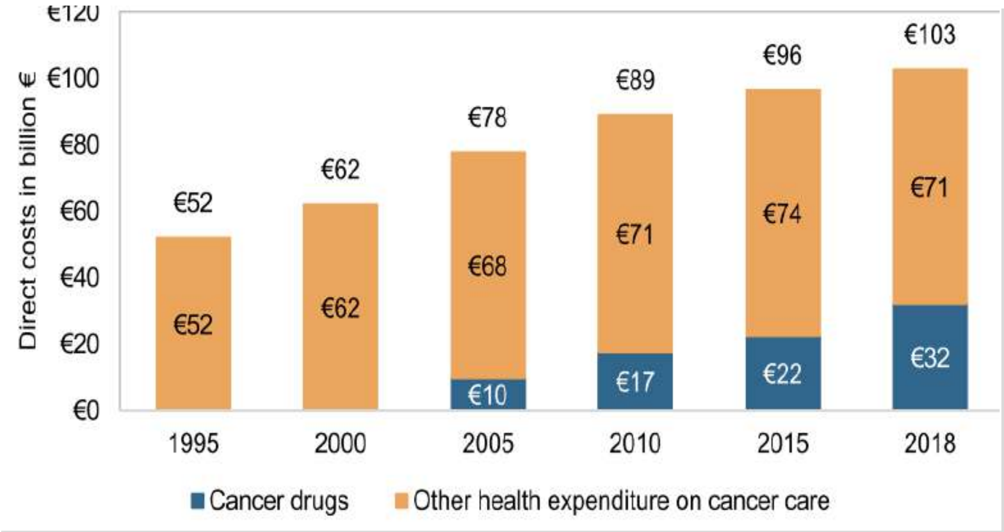
Nature of the problem: Cost of Cancer Care is Rising

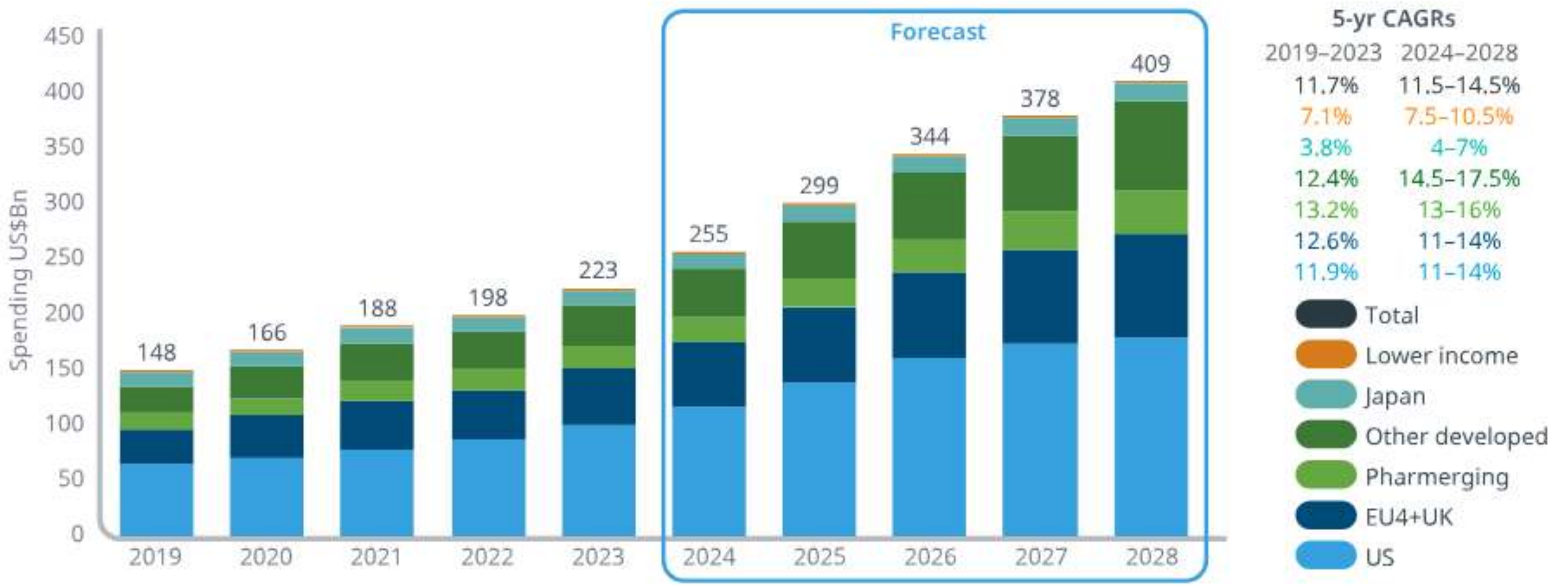
Oncology drug prices are a determinant of health disparities worldwide



Sisko AM, et al. Health Aff (Millwood), 2019.
Hofmarcher T, et al. European Journal of Cancer, 2020.

Nature of the problem: It is expected to keep increasing

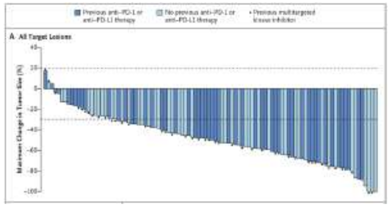
Emerging markets are growing rapidly, while developed markets remain the largest contributors



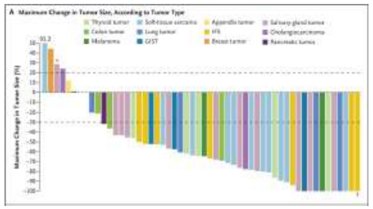
IQVIA Institute Report Dec 2023

The changing scenario in Drug Approval

Unprecedented Response Rates in Solid Tumors



Drilon A NEJM 2020



Drilon A NEJM 2018

RET fusions

ORR 85%-64% (lung)

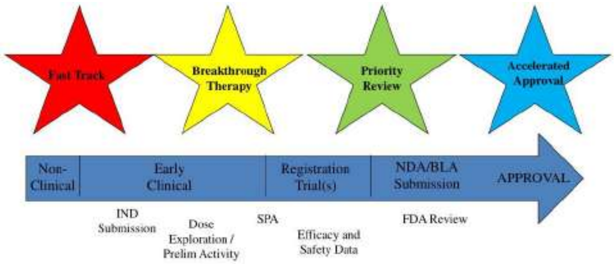
Selpercatinib
Phase I-II

NTRK fusions

ORR 75% (lung)

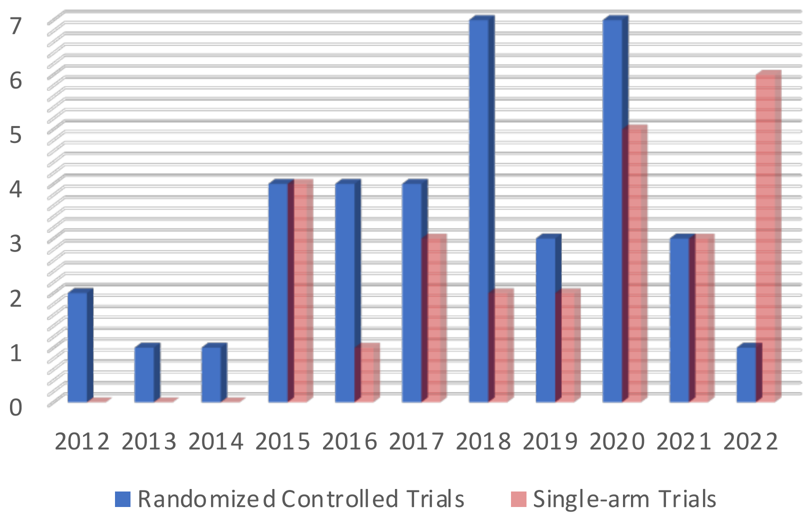
Larotrectinib
Phase I-II

Expedited Programs

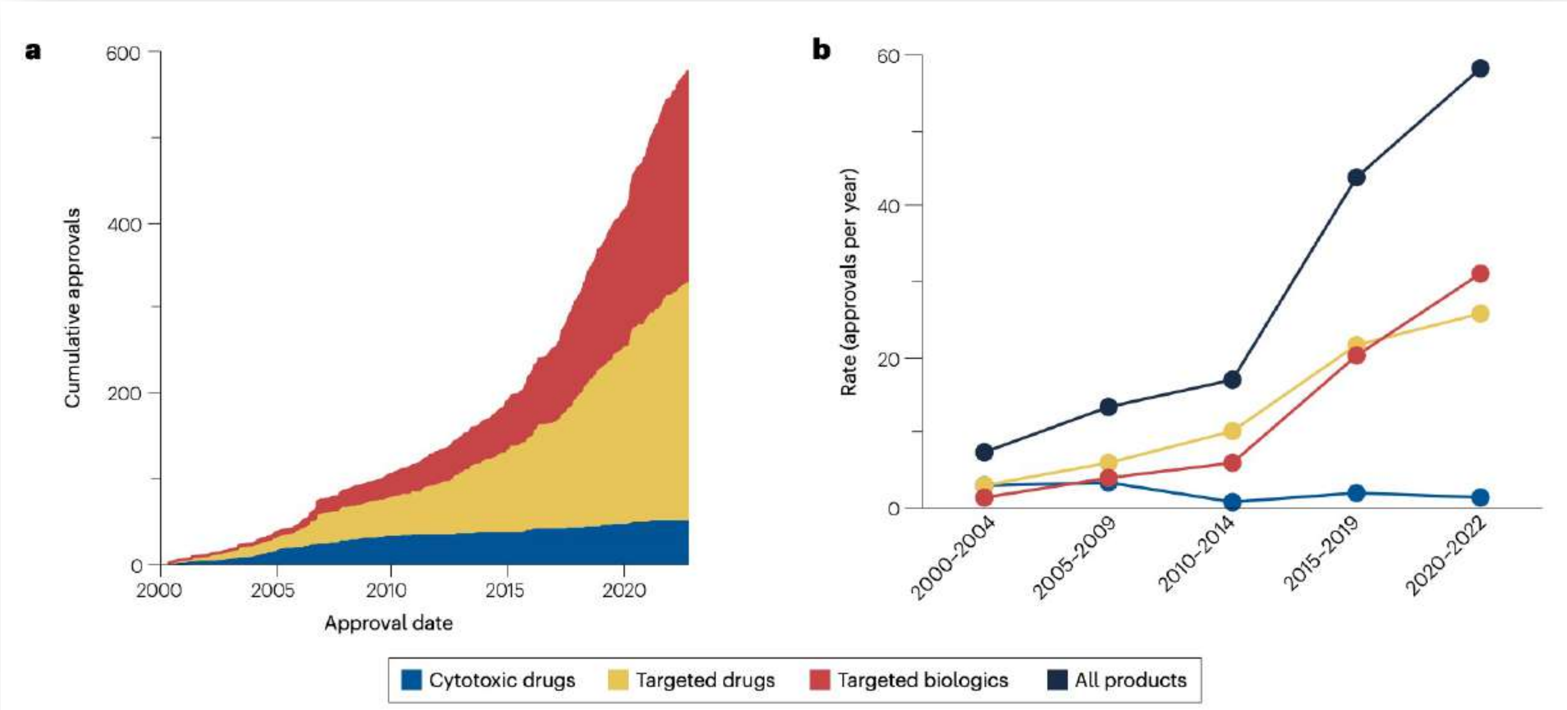


Increased use of SAT and surrogate endpoints as the basis for approval.

FDA Single-Arm Trial Lung Cancer Drug Approvals 2012-22



Explosion of the New FDA Cancer Drug Approvals



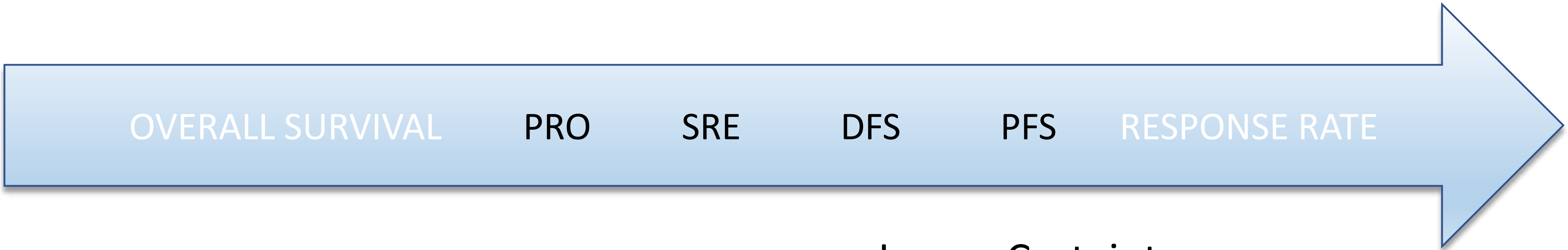
Years	Approvals / Year
2000–2004	7.4
2017-2022	56

△ **757%**

Scott EC Nat Rev Drug Discov. 2023 Aug;22(8):625-640.

Efficacy Endpoints and Approval Pathways

Certainty of Predicting Direct Clinical Benefit



- Higher Certainty
- Based on improvement in a *direct measure* of clinical benefit
- Traditional (Regular) Approval

- Lower Certainty
- Based on improvement in a surrogate endpoint *reasonably likely* to predict clinical benefit
- Accelerated Approval

Strengths and Limitations of Rapid Approval

- Strengths
  - Early patient access to novel therapeutic agents

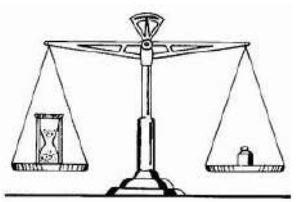
- Risks
  - Increased use of intermediate and surrogate endpoints
  - Under-recognition of adverse effects at the time of market entry
  - A more limited understanding of clinical benefit

Outline

- Price and economic impact
- Clinical benefit in oncology
- Value in cancer care
- Timely access in Cancer Care

Why is Clinical Benefit Important?

- The principal **goals** of any treatment are *to extend the patient's life and/or improve their quality of life.*

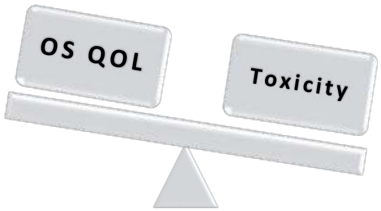


- **Key Requirements for Drug Approval**:
  - Demonstration of clinical benefit (efficacy)
  - Adequate and well-controlled trials
  - Evidence based on *life extension, improved quality of life or surrogate for these outcome*.

How do we define the clinical benefit of a treatment?

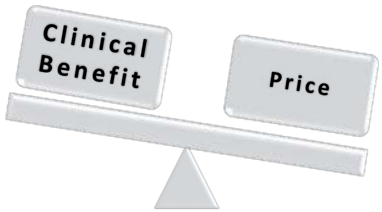
Emergence of "Clinical Benefit" and "Value" Criteria

Clinical benefit = (Improvement in *Overall Survival* + *QoL) / Toxicity*



Value = *Outcomes* achieved / *Cost*

To identify the optimal treatment for a given clinical scenario at the lowest cost.



Models to Establish Clinical Benefit in Oncology

Efforts to Increase Value in Cancer Care

	ASCO-VF v1. and v2	ESMO-MCBS v1.0 and v1.1	NCCN Evidence Blocks
Efficacy	HR (point estimate) for overall, progression-free, disease-free survival, response rate	HR (LL95%CI) for overall, progression-free, disease-free survival, response rate minimum absolute gain in months	End points vary, assessed by expert opinion
Safety	Grade 1-4 adverse events	Grade 3-4 adverse events	End points vary, assessed by expert opinion
Quality of Life	Cancer-related symptoms, treatment-free interval	Credits QoL gains and has a separate scale for QoL studies	Not considered
Scenarios evaluated	Hematologic or solid tumors	Hematologic or solid tumors	Hematologic or solid tumors
Sources of evidence	RCTs	RCTs and SAT	RCTs and SAT (aggregate)
Relies on expert judgment?	No	No	Expert based

- ASCO, American Society of Clinical Oncology Value Framework - Net Health Benefit Score (ASCO VF – NHB) version 1 and 2 [3]
- European Society for Medical Oncology - Magnitude of Clinical Benefit Scale version (ESMO-MCBS) 1.0 and 1.1[4]. American Society of Clinical Oncology Value Framework (ASCO-VF), European Society for Medical Oncology-Magnitude of Clinical Benefit Scale

[2]Ellis LM; J Clin Oncol. 2014;32(12):1277-1280
[3]Schnipper LE; J Clin Oncol. 2016;34(24):2925-2934
[4]Cherny NI; Ann Oncol. 2017;28(10):2340-2366

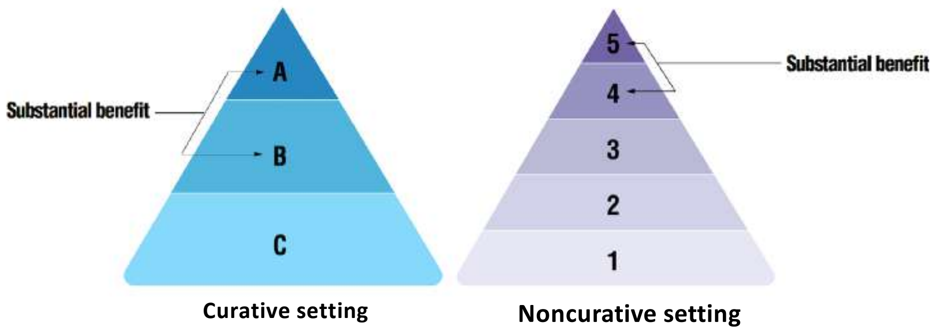
ESMO-MCBS (ESMO – Magnitude of Clinical Benefit Scale)

A composite measure of clinical benefit based on drug efficacy, safety, and QoL.

Calculate Aggregate Value (Formulation)	**Form 1 (ESMO-MCBS)** **Form 1 (1a, 1b ESMO-MCBS:H)**	**Form 2 (2a, 2b, 2c)**	**Form 3**
Scenarios evaluated	Treatments with curative intent	Treatments with non-curative intent	Treatments with non-curative intent in “orphan diseases” and in diseases with “high unmet need”
Sources of evidence	RCT SAT (ESMO-MCBS:H)	RCT	SAT
First step. Preliminary score described with the evaluated outcome (primary endpoint)	DFS or OS	OS (Form 2a) PFS (Form 2b) QoL, ORR, AE (Form 2c)	PFS or ORR
Second step. Positive (score upgrade) and negative (score downgrade) adjustments of the preliminary score	1. Acut transient and persistent toxicity (Form 1a and 1b).	1. QoL improved or worsened. 2. AE that impact daily well-being. 3. Incremental toxicities that result in hospitalization (Form 2b). 4. Plateau (Form 2a, 2b) 5. OS and PFS benefit (Form 2b) 6. Early crossover (Form 2b).	1. QoL improved or worsened. 2. Side effects that impact daily well being. 3. Phase 4 experience

Aims:

1. To assess the clinical benefit of new cancer drug therapies.
2. To guide physicians/patients/health technology assessment in selecting high-value treatments.



Scientific questions

1. Which is the clinical benefit of approved cancer drugs?

2. Which is the clinical benefit of cancer drugs assessed in single-arm trials as the basis for approval?

3. Which is the long-term clinical benefit of approved cancer drugs?

Clinical Benefit FDA Cancer Drugs

JNCI J Natl Cancer Inst (2018) 110(5): djx232

doi: 10.1093/jnci/djx232
First published online December 13, 2017
Article

OXFORD

ARTICLE

Magnitude of Clinical Benefit of Cancer Drugs Approved by the US Food and Drug Administration

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ESMO-MCBS v1.0

JAMA Oncology

RESEARCH LETTER

Magnitude of Clinical Benefit of Cancer Drugs Approved by the US Food and Drug Administration Based on Single-Arm Trials

For regulatory approval, the US Food and Drug Administration (FDA) requires evidence of safety and efficacy of new drugs from adequate and well-controlled trials.[1] Improved understanding of the molecular basis of cancer, has led to rapid development of new drugs. In combination with regulatory changes providing rapid review and approval of drugs for diseases with unmet need,[2] this acceleration has led the FDA to use overall response rates (ORRs) assessed in single-arm trials as the basis for approval.

ment. For each trial, ESMO-MCBS grades were applied by 2 of us (C.M. and M.B.). Disagreement was resolved by consensus with a third author (A.T.). Substantial clinical benefit was defined as grade A or B for trials of curative intent and grade 5 or 4 for those of noncurative intent. Data were reported descriptively as proportions, medians, and ranges. Comparisons between groups were assessed using the Mann-Whitney and χ^2 tests for continuous and categorical variables, respectively. Data analyses were conducted using SPSS version 21 (IBM Corp). Statistical significance was defined as a 2-sided $P < .05$. Per the Government of Canada, Panel on Research Ethics, this study was exempt from the requirement for ethical approval in view of its use exclusively of publicly available data.

ESMO-MCBS v1.1

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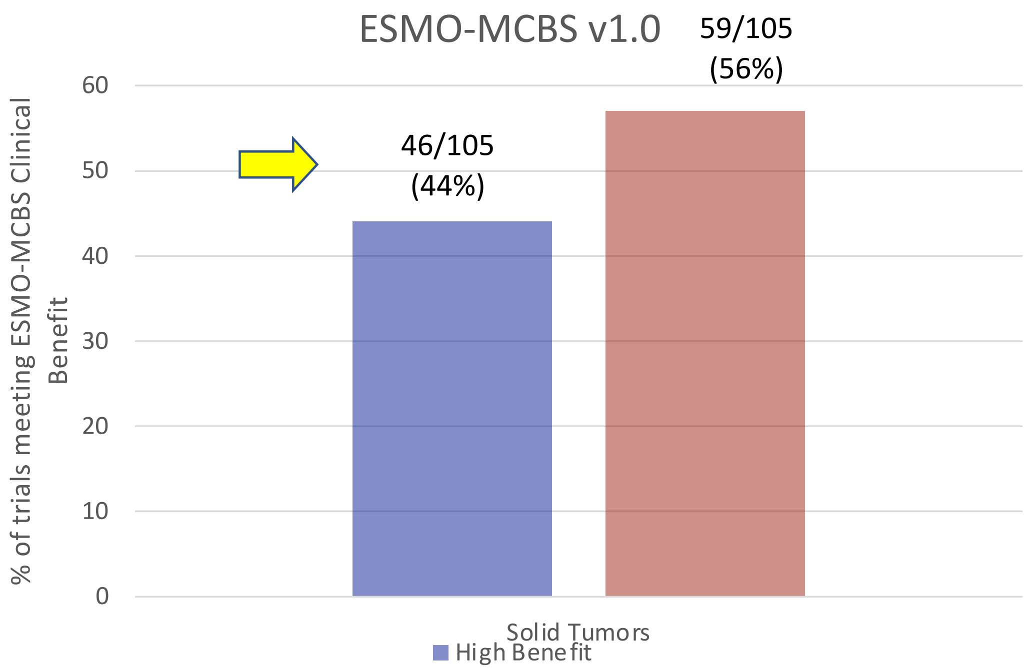
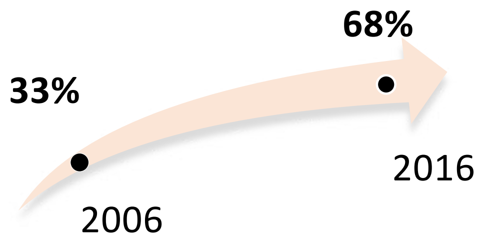
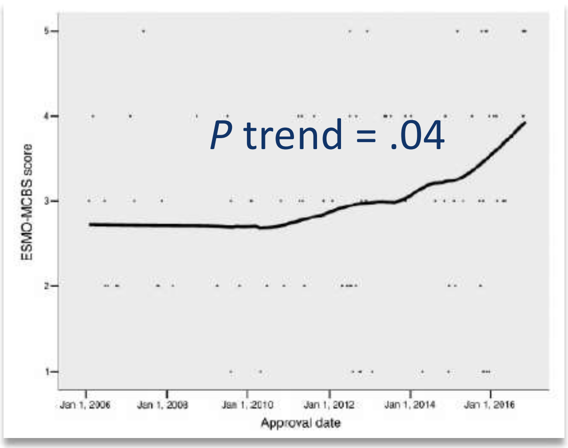
Tibau A et al. J Natl Cancer Inst. 2018 May 1;110(5):486-492.
Tibau A et al. JAMA Oncol. 2018 Nov 1;4(11):1610-1611.

Clinical Benefit FDA Cancer Drugs 2006-2016

44% trials met the ESMO-MCBS threshold for substantial clinical benefit for solid tumors



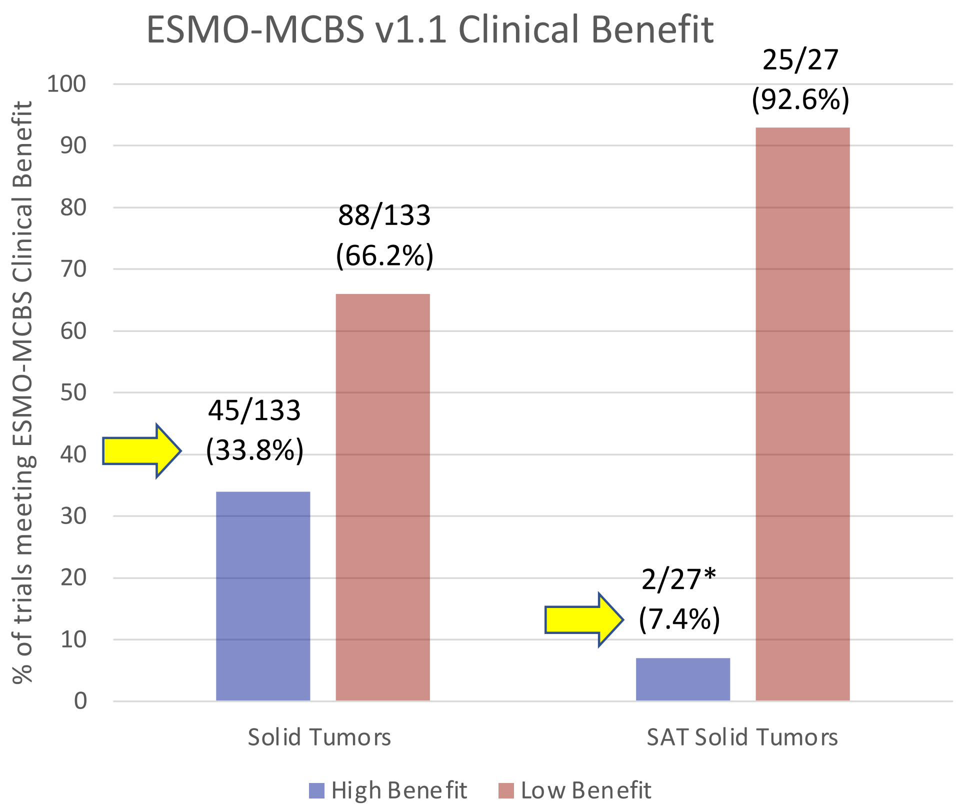




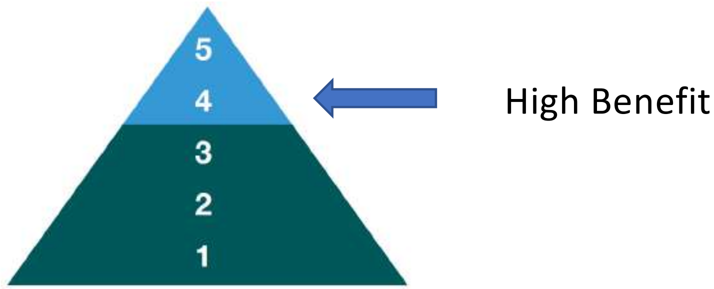
Tibau A et al. J Natl Cancer Inst. 2018 May 1;110(5):486-492.

Clinical Benefit SAT FDA Cancer Drugs 2006-2016

33% trials met the ESMO-MCBS threshold for substantial clinical benefit
7% SAT met the ESMO-MCBS threshold for substantial clinical benefit



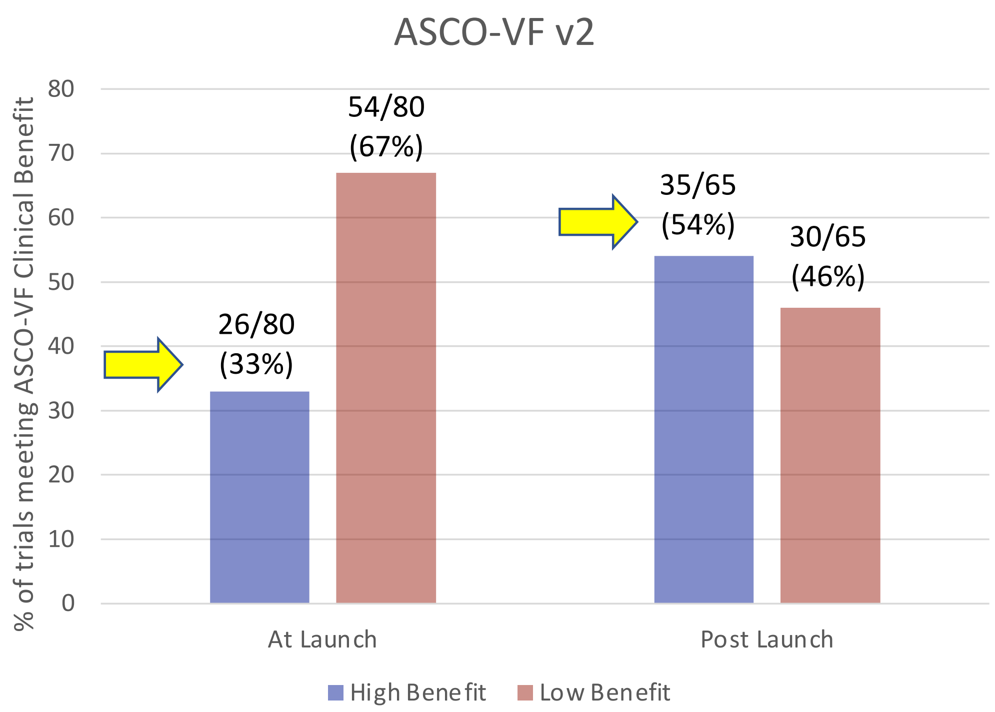
- Osimertinib for T790M-mutated NSCLC
- Crizotinib for ALK-rearranged NSCLC

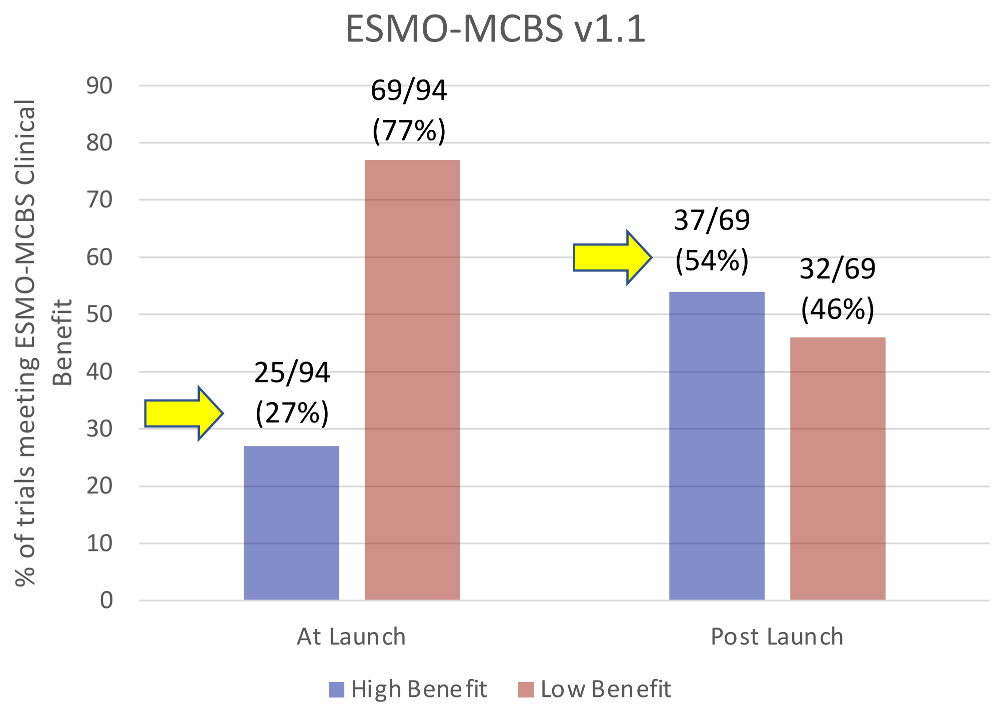


Tibau A et al. JAMA Oncol. 2018 Nov 1;4(11):1610-1611.

Cancer & Clinical Benefit at Launch and Post-Launch

33% trials & 54% met the ASCO-VF threshold for substantial clinical benefit at launch and post-launch
27% trials & 54% met the ESMO-MCBS threshold for substantial clinical benefit at launch and post-launch



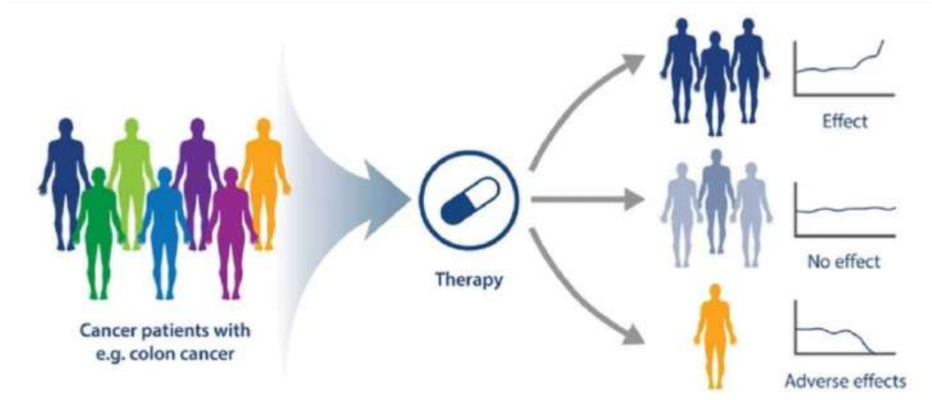


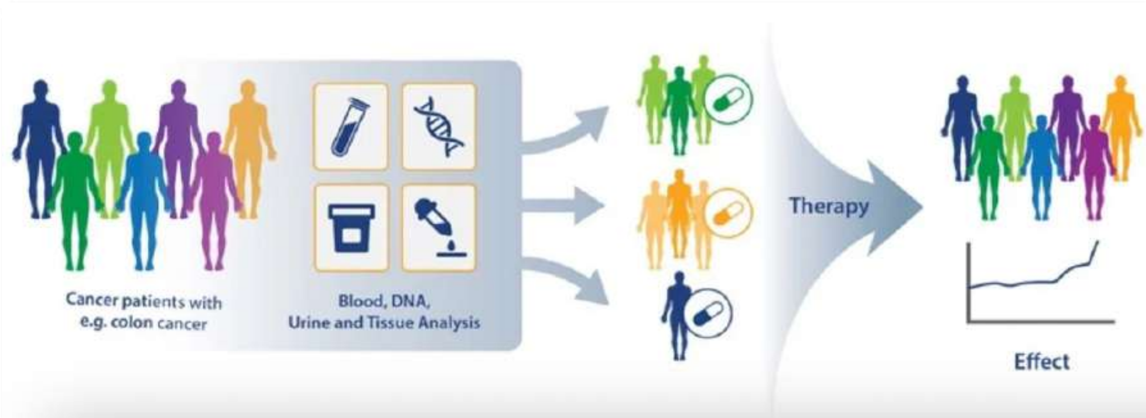
Bujosa A et al. J Natl Compr Canc Netw. 2021.

Toward Precision Oncology

One treatment fits all → More Personalized Diagnostics and Treatments

(40% of FDA Cancer Drug Approvals)





Cytotoxic chemotherapies
Non-genome targeted agents

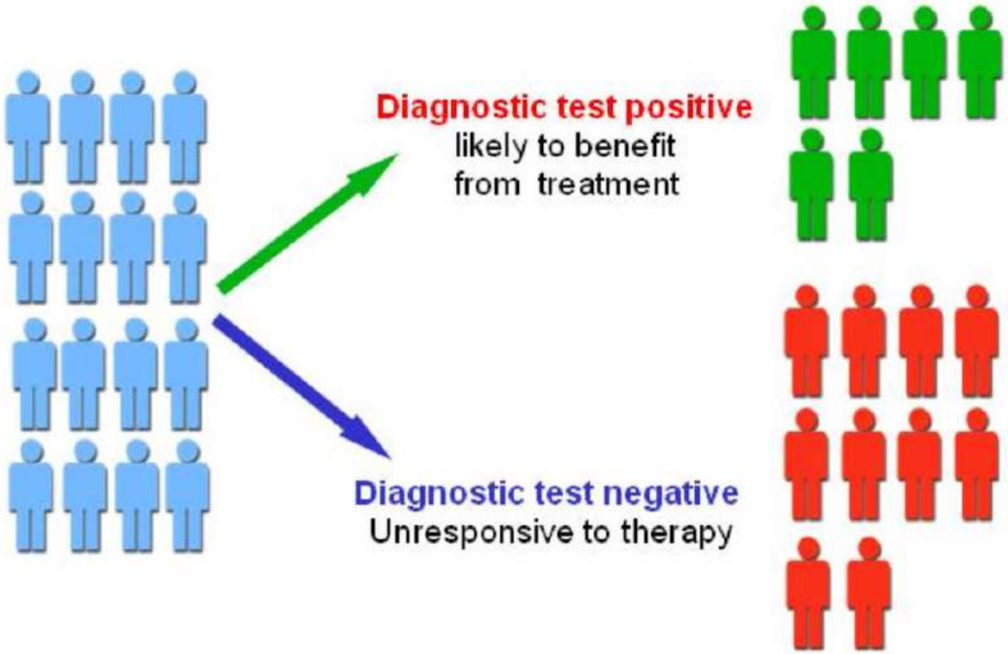
Genome-targeted therapies

Drugs approved based on a genomic test in which the drug targeted a given genomic alteration.

A Tibau, et al. JAMA Oncol.

Personalized Cancer Therapy Aims

Maximizing Effectiveness, Minimizing Adverse Effects



Increase efficacy

Avoid unnecessary toxicities

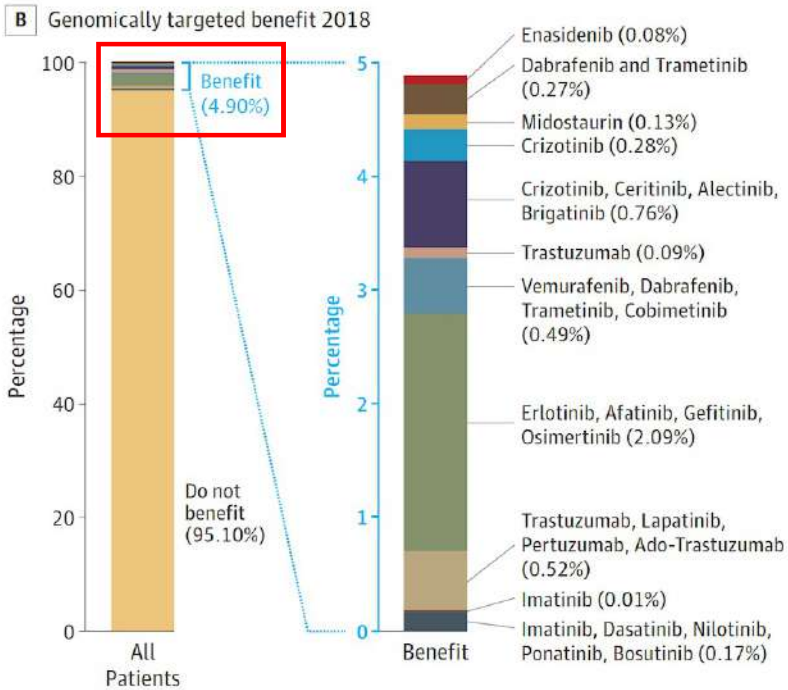
Groundbreaking treatments:

- Trastuzumab-pertuzumab for HER2-expressing breast cancer *Swain SM, et al. Lancet Oncol. 2020. PMID: 32171426.*
- Osimertinib for EGFR-mutated non-small cell lung cancer *Ramalingam SS, et al. N Engl J Med. 2020. PMID: 31751012.*

Challenges of Personalized Cancer Therapy

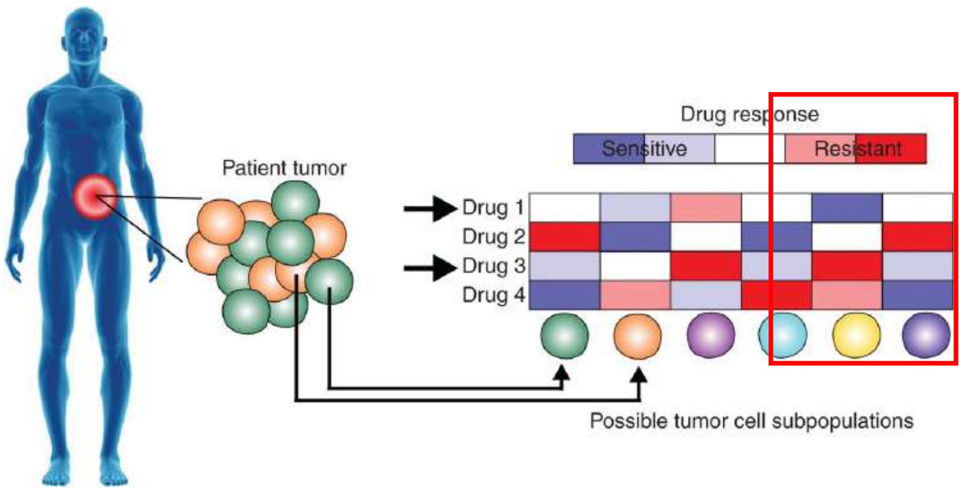
Limited benefits for most patients with metastatic cancer

due to limited number of potential responders…



Estimated percentage of US patients with cancer benefiting from genome-targeted therapy by year in 2018.

… and drug resistance and cancer progression



Marquart J et al. JAMA Oncol. PMID: 29710180

NGS: Next-generation sequencing

NGS allows sequencing of a high number of nucleotides in a short time frame.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Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.
N Engl J Med 2016; 375:1289-1294 | September 29, 2016 | DOI: 10.1056/NEJMsb1607705

Comments open through October 19, 2016

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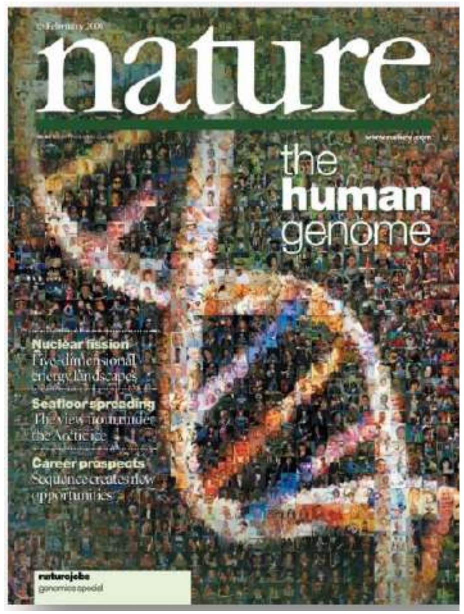
Rapid advances in the molecular characterization of tumors, including complete gene sequencing of multiple cancers in the Cancer Genome Project, have led to an increased understanding of the molecular pathways that underlie cancer. These genomic changes differentiate tumors from normal tissues, permitting targeted treatments for several types of tumor and thereby extending survival



Key point

To date, most genomic alterations are of unknown clinical relevance

Tannock IF, et al. N Engl J Med. 2016. PMID: 27682039

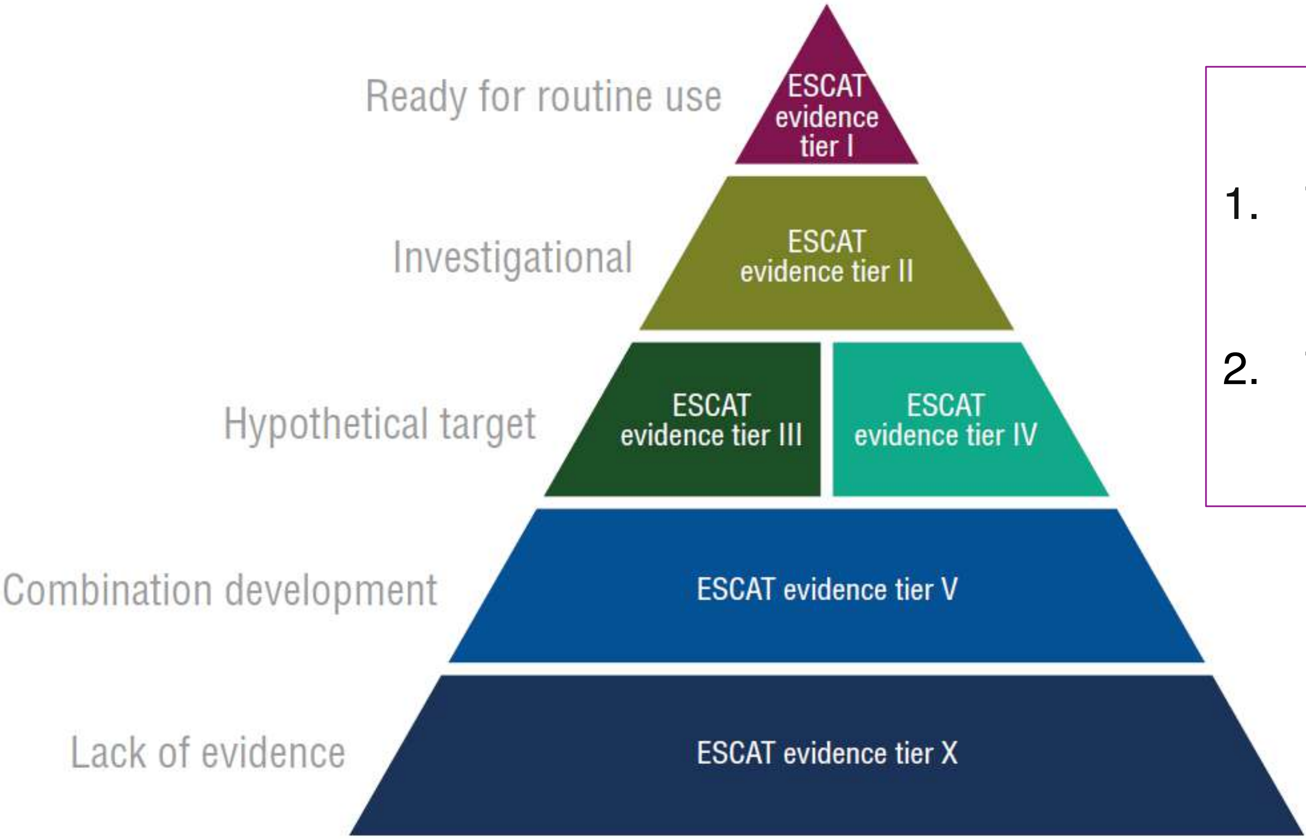
Scientific questions

1. What was the validity of the targets and the clinical benefit of *FDA-approved* genome-targeted cancer drugs?

2. What was the validity of the targets and the clinical benefit of genome-targeted cancer drugs recommended in *clinical practice*?

ESCAT (ESMO Scale for Clinical Actionability of Molecular Targets)

A framework to rank genomic alterations as targets for molecular-targeted cancer therapies



Aims:

1. To identify actionable genomic alterations in cancer patients.
2. To facilitate decision-making for molecular targeted therapies.

Mateo J et al. Ann Oncol, 2018. PMID: 30137196.

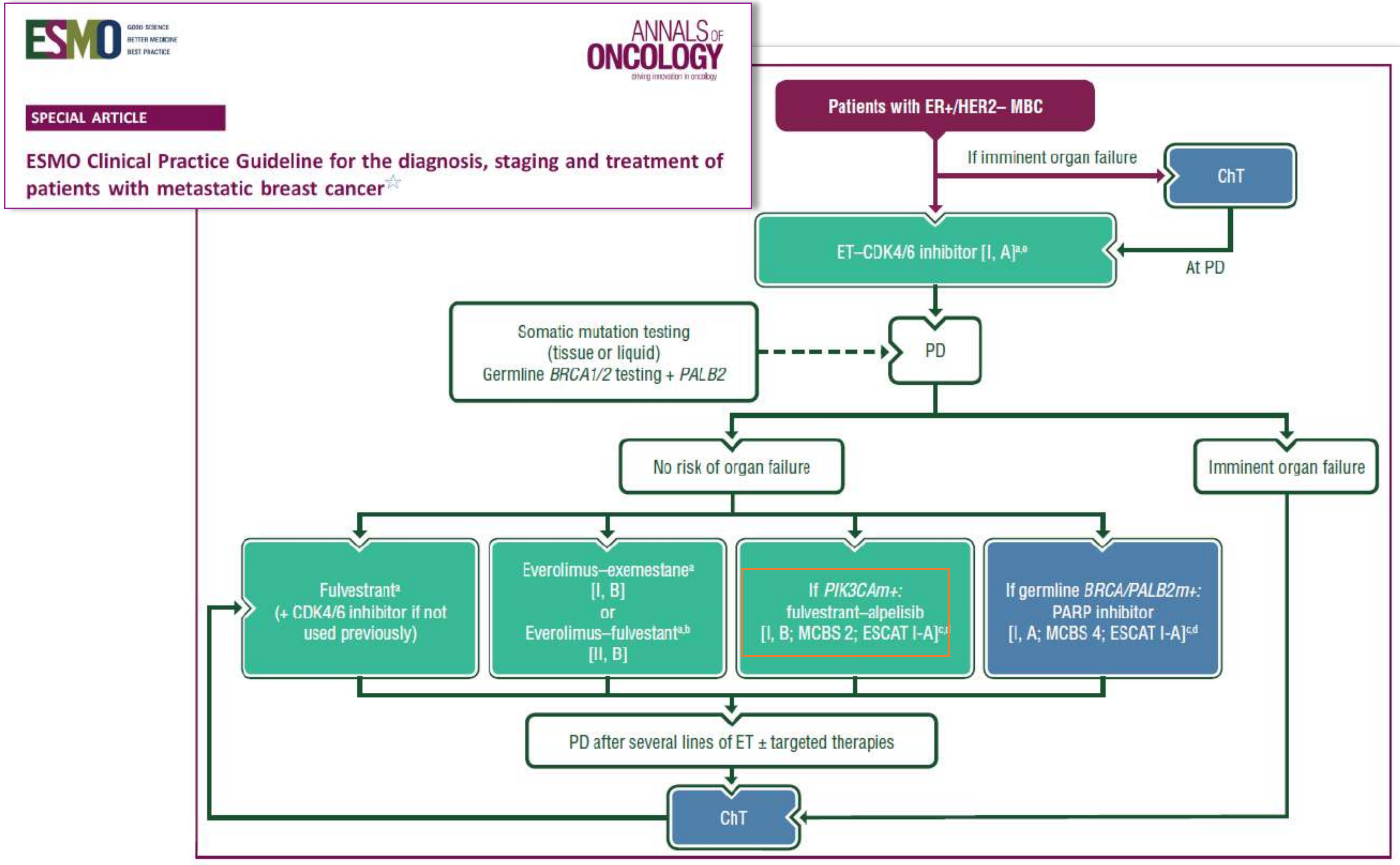
ESCAT Tiers		Clinical implications	Level of evidence	Examples
Tier -I	Clinically relevant	Ready for routine use Access to the treatment should be considered standard of care	A: survival benefit in prospective, randomised trials	BRCA1/BRCA2 mutations-rucaparib in ovarian cancer.
			B: clinical benefit in prospective, single-arm trials	BRCA1/BRCA2 mutations-rucaparib in prostate cancer.
			C: clinical benefit in basket trials	NTRK1 fusion (agnostic-tumors)
Tier -II	Potentially clinically relevant	Investigational Treatment to be considered “preferable”	A: clinical benefit in retrospective trials	PIK3CA mutation in prostate
			B: increased responsiveness and outcome in prospective trials	BRCA1/BRCA2 mutations-rucaparib in pancreatic cancer
Tier -III	Potentially clinically relevant	Hypotetical target Clinical trials to be discussed with patients	A: clinical benefit in other tumor entities	BRCA1/BRCA2 mutations-rucaparib in lung cancer
			B: biomarker is located in the same gene/pathway as Tier I-IIIA targets	ERBB3 mutation in breast cancer
Tier -IV	Evidence from preclinical studies	Hypotetical target Treatment should “only be considered” in the context of early clinical trials.	A: improved drug sensitivity in in-vitro or in-vivo models	IGF1R, MYC, SF3B1 in breast cancer
			B: actionability shown in insilico models	CCND1 and FGFR1 amplifications in breast cancer

ESCAT – Originally a clinical benefit-centered system

ESCAT ranked genomic alterations ready for routine use as targets associated with a meaningful improvement as defined by the ESMO-MCBS v1.1

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care

Mateo J et al. Ann Oncol, 2018. PMID: 30137196.



More recently, the magnitude of benefit is not specifically considered to reach a level of evidence I-A or I-B

Research

JAMA Oncology | Original Investigation

Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies

Ariadna Tibau, MD, PhD; Thomas J. Hwang, MD; Consolacion Molto, MD, PhD; Jerry Avorn, MD; Aaron S. Kesselheim, MD, JD, MPH

Aim

- To assess the validity of molecular targets and therapeutic benefits of US Food and Drug Administration–approved genome-targeted cancer drugs based on the outcomes of their corresponding pivotal clinical trials.

Methods

- Cohort study
- Genome-targeted cancer drugs that were FDA-approved between January 1, 2015, and December 31, 2022
- From FDA drug labels and trial reports, key characteristics of pivotal trials were extracted, including the outcomes assessed.
- Data Synthesis:
  - ESCAT: to assess the strength of evidence supporting molecular targetability
  - ESMO-MCBS: to evaluate the clinical benefit for approved indications.
- **High-benefit genomic-based cancer therapies: Molecular targets associated with substantial clinical benefit by ESMO-MCBS (grade of A or B for curative intent and 4 or 5 for noncurative intent) and qualifying for ESCAT category level I-A and I-B.**

Tibau A. JAMA Oncol. 2024 PMID: 38573645

Research

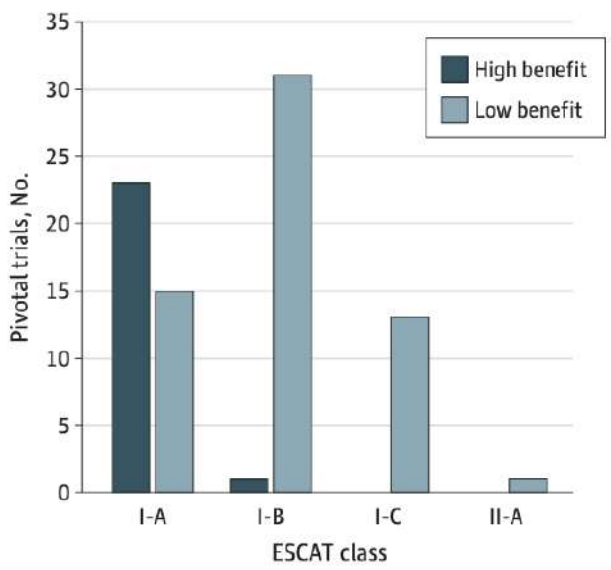
JAMA Oncology | Original Investigation

Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies

Ariadna Tibau, MD, PhD; Thomas J. Hwang, MD; Consolacion Molto, MD, PhD; Jerry Avorn, MD;
Aaron S. Kesselheim, MD, JD, MPH

Results

ESCAT Class Distribution of Molecular Targets by High Benefit vs Low Benefit



- 50 molecular-targeted drugs covering 84 indications were identified.
- 24 indications (29%) supported high-benefit genomic-based cancer treatments.

Tibau A. JAMA Oncol. 2024 PMID: 38573645 thebmj

Clinical value of guideline recommended molecular targets and genome targeted cancer therapies: cross sectional study

Ariadna Tibau,[1,2] Thomas J Hwang,[1,3,4] Jerry Avorn,[1] Aaron S Kesselheim[1]

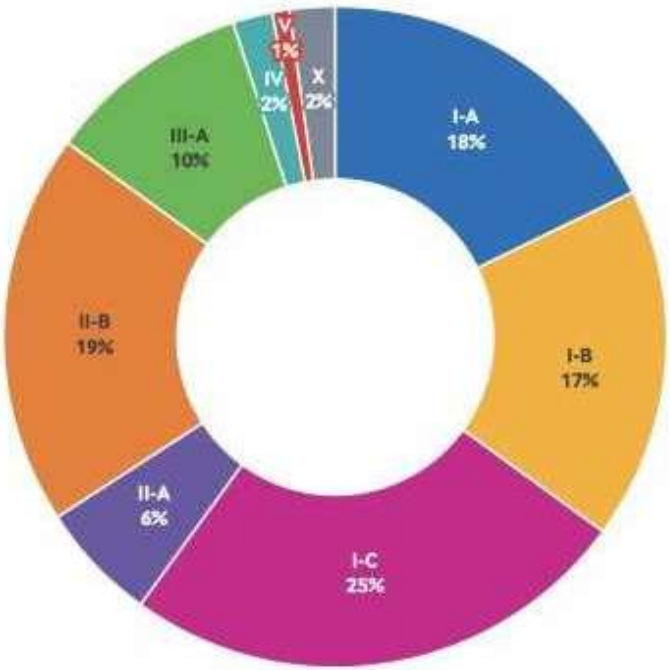


Fig 2 | European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) levels of evidence for molecular targets. Figure shows proportions of molecular targets falling into different ESCAT levels of evidence among genome targeted drugs recommended by National Comprehensive Cancer Network guidelines

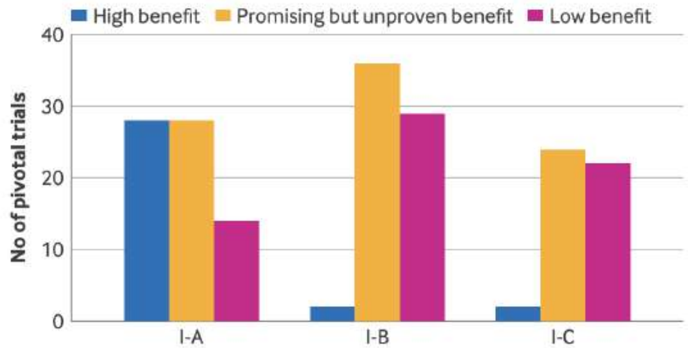


Fig 3 | Value of molecular targets recommended by National Comprehensive Cancer Network (NCCN) guidelines. Molecular targets associated with substantial clinical benefit by European Society for Medical Oncology - Magnitude of Clinical Benefit Scale (ESMO-MCBS) (grade 4 or 5 for those of non-curative intent) and qualifying for ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) tiers I-A, I-B, and I-C, were rated as high benefit genome based cancer treatments. Molecular targets achieving a grade 3 on ESMO-MCBS and qualifying for ESCAT tiers I-A, I-B, and I-C were classified as being of promising but unproven benefit

- 411 recommendations 74 genome targeted drugs targeting 50 driver alterations

- 12% (32/267 scorable drugs) of trials supported a determination of high-benefit genomic-based cancer treatments.

Tibau A. The BMJ. 2024 PMID: 39164034

Key Findings and policy Implications (1)

1. The number of trials meeting the ESMO-MCBS threshold for clinical benefit has improved over time.

2. Less than half of RCTs supporting FDA approval meet the threshold for meaningful benefit.

3. Approvals based on single-arm studies are less likely to show substantial benefit with ESMO-MCBS
   - likely due to the high thresholds used for calibration.

4. New evidence of benefit rarely emerges after regulatory approval.

5. ESMO-MCBS and ESCAT can guide cancer therapy selection
   -prescribers must communicate to patients the variability in evidence supporting drug approvals.

Tibau A et al. J Natl Cancer Inst. 2018.
Tibau A et al. JAMA Oncol. 2018.
Bujosa A et al. J Natl Compr Canc Netw. 2021.
Tibau A. JAMA Oncol. 2024 PMID: 38573645
Tibau A. The BMJ. 2024 PMID: 39164034

Outline

- Price and economic impact
- Clinical benefit in oncology
- Value in cancer care
- Timely access in Cancer Care

Scientific questions

1. Was there an association between clinical benefit and prices for cancer drugs?

2. Was there an association between clinical benefit, launch prices and postlaunch price changes for cancer drugs?

Value in Cancer Care

There were no significant associations between monthly treatment costs for solid tumors and clinical benefit.

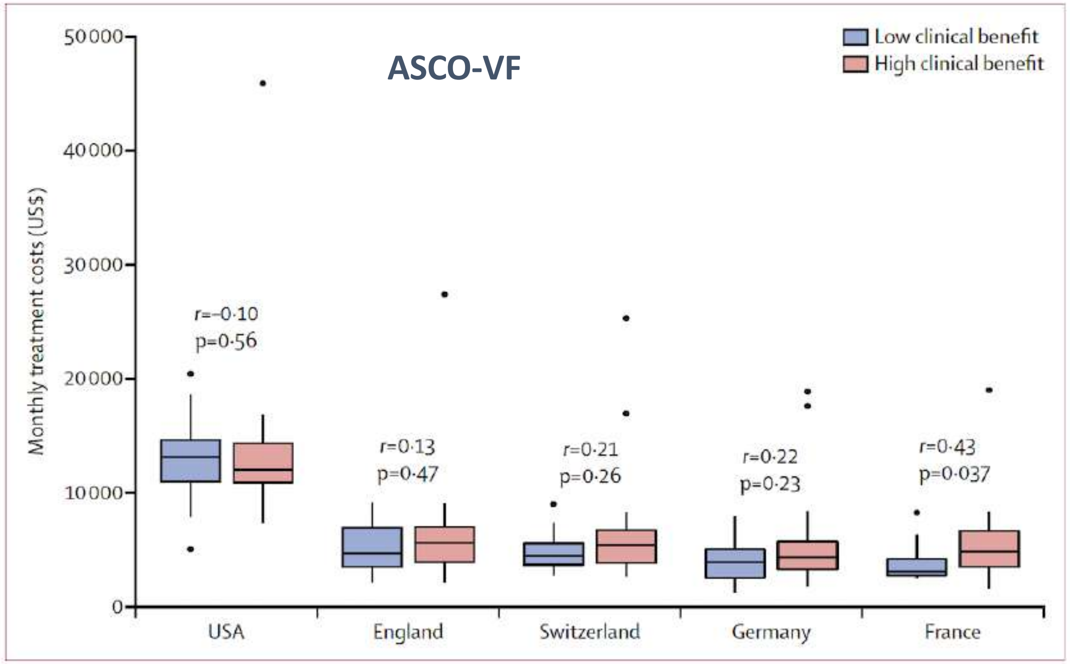


Figure 2: Monthly drug treatment costs stratified by clinical benefit using the ASCO-VF

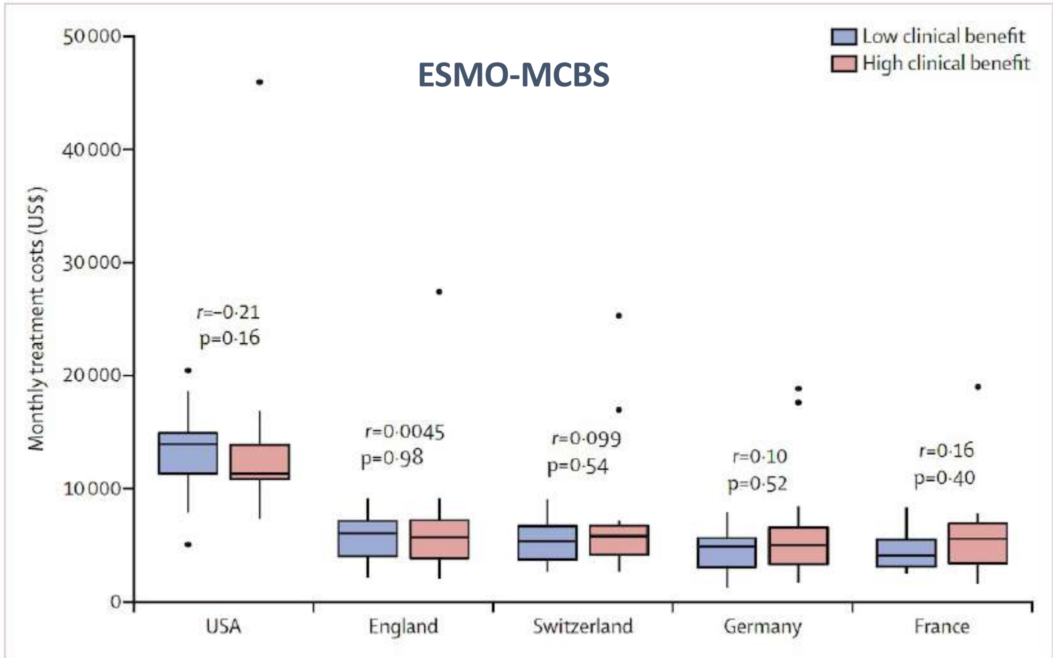
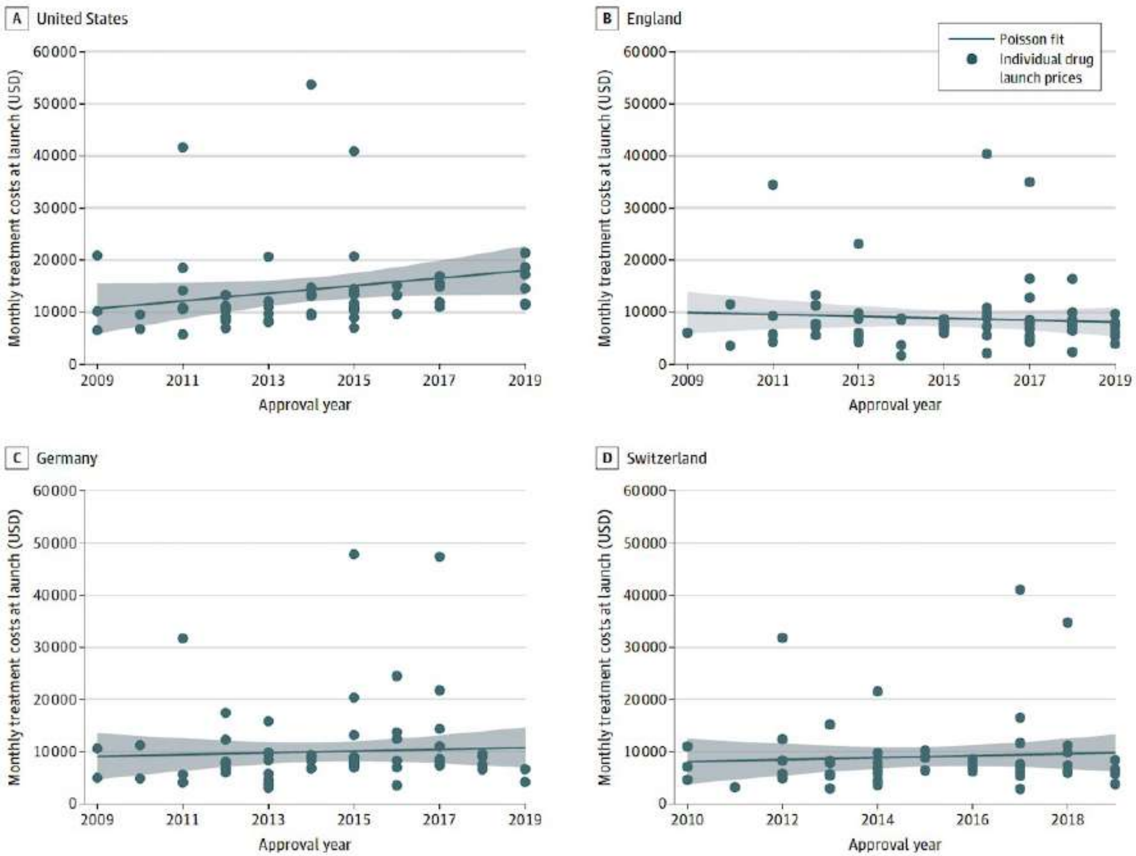


Figure 3: Monthly drug treatment costs stratified by clinical benefit using the ESMO-MCBS

Vokinger KN et al. Lancet Oncol. 2020 May;21(5):664-670.

Launch prices in the US compared with Europe

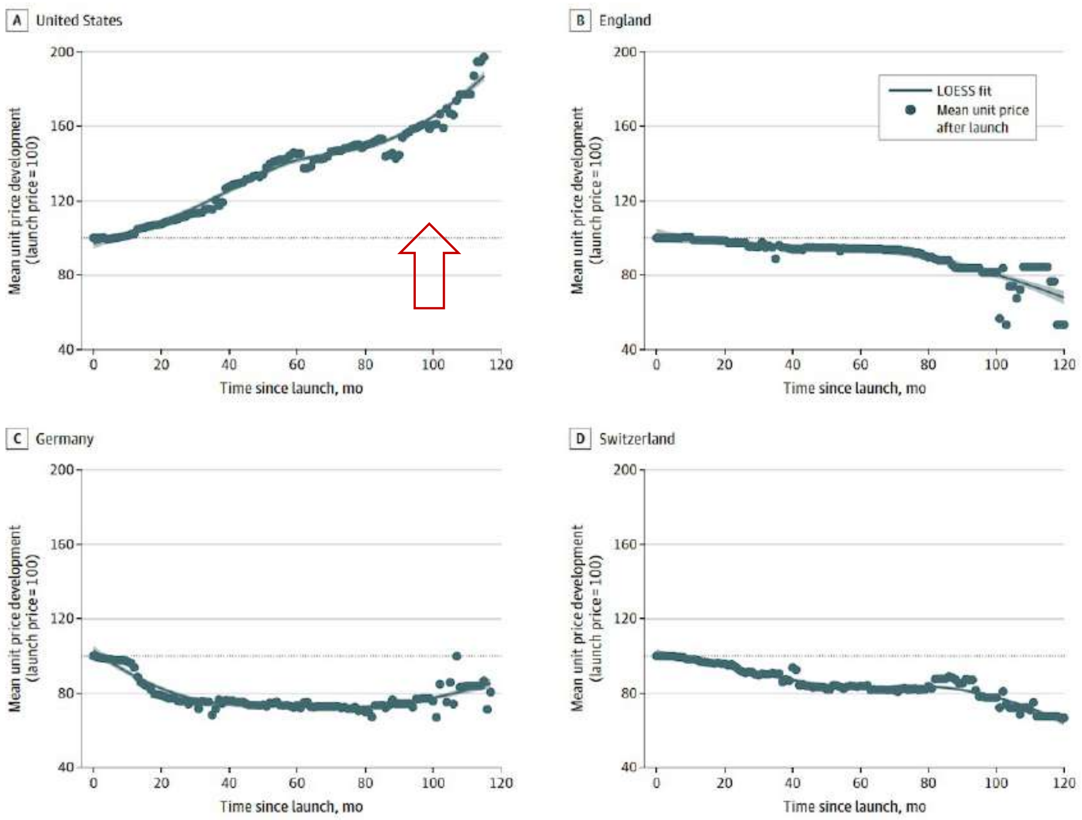
Launch prices of cancer drugs were higher in the US than in Europe.

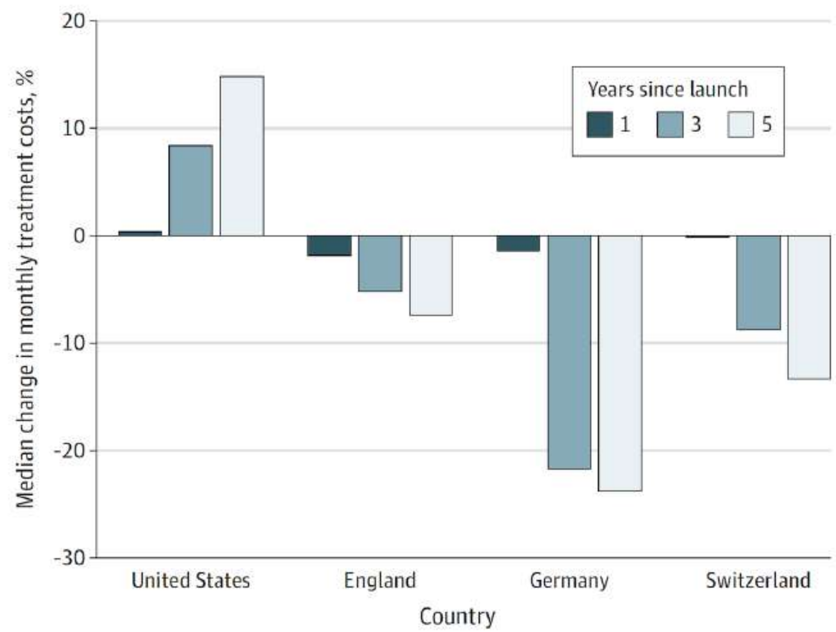


Vokinger KN et al. JAMA Oncol. 2021 PMID: 34196656

Inflation-Adjusted Price Changes After Launch

Cancer drug prices frequently increased faster than inflation in the US but decreased on inflation-adjusted terms in Europe.

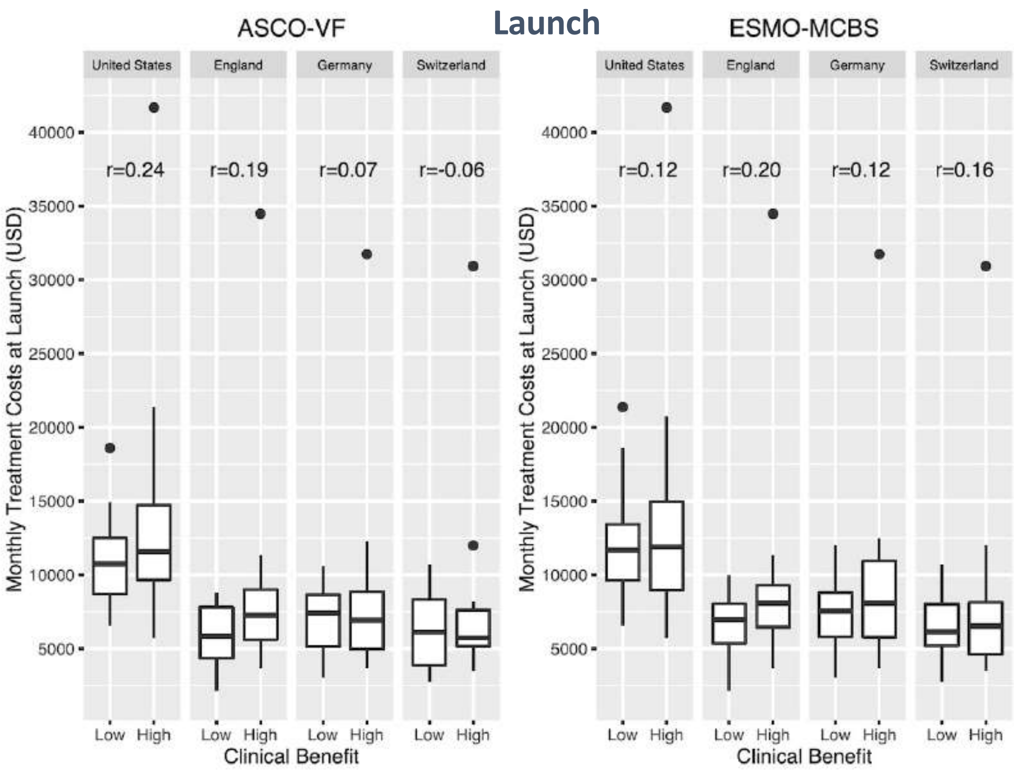


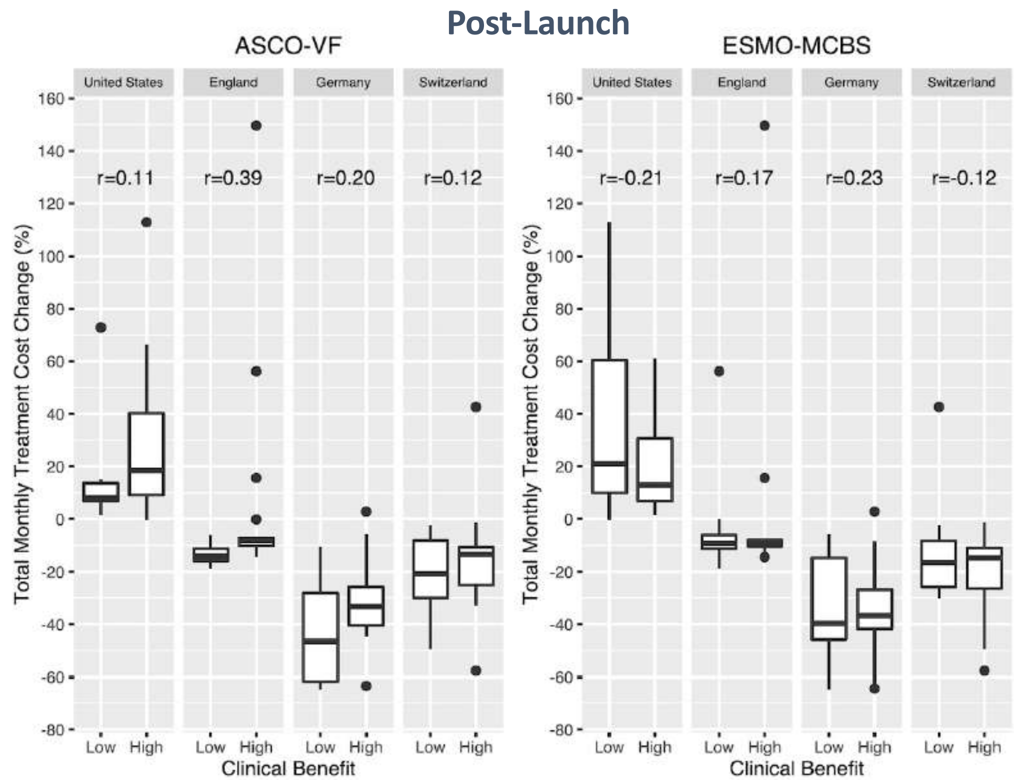


Vokinger KN et al. JAMA Oncol. 2021 PMID: 34196656

Value at Launch and Post-Launch

Launch price and postlaunch price increases were not associated with clinical benefit in any country





Vokinger KN et al. JAMA Oncol. 2021 PMID: 34196656

Key Findings and policy Implications (2)

1. There were no significant associations between monthly treatment costs for solid tumors and clinical benefit.

Cancer drugs with high clinical benefit might be prioritized for price negotiations. FRAMEWORKS can help!

2. Cancer drug prices frequently increased faster than inflation in the US but decreased on inflation-adjusted terms in Europe.

Although the US would need to take the most substantial steps to address the high costs of cancer drugs, Europe could also reexamine their pricing regulations to ensure better alignment with the clinical value.

Vokinger KN et al. Lancet Oncol. 2020 May;21(5):664-670.
Vokinger KN et al. JAMA Oncol. 2021 PMID: 34196656.

Outline

-
-
-
- Timely access in Cancer Care

Use of the ESMO-Magnitude of Clinical Benefit Scale to guide HTA recommendations on coverage and reimbursement for cancer medicines: a retrospective analysis

Panos Kanavos, Erica Visintin, Aris Angelis

- HTA reports and related sources from six country settings (Australia, Canada, England, France, the Canadian province of Quebec, and Scotland).
- New cancer medicines for treating solid tumours in a non-curative setting.

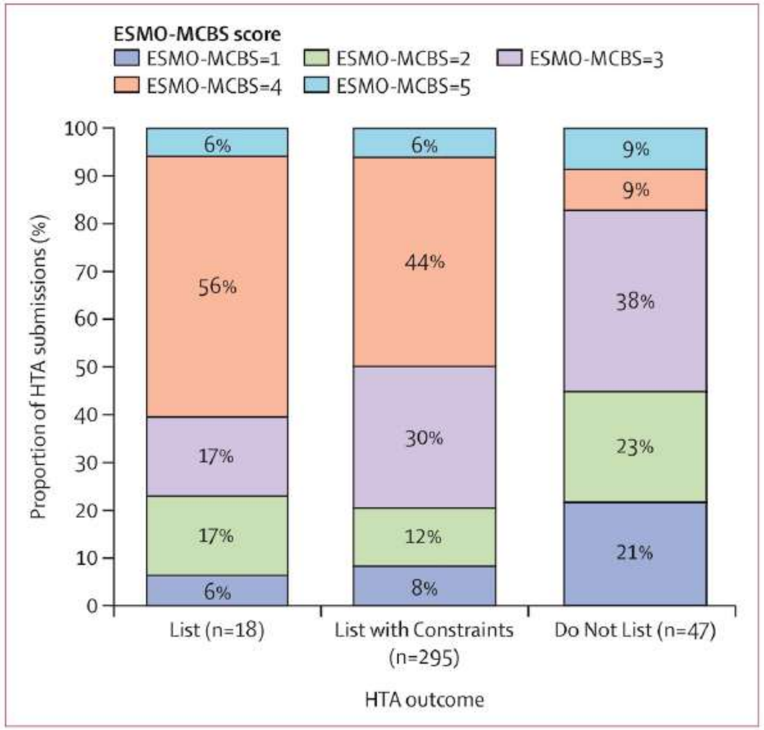


Figure 1: **Relationship between ESMO-MCBS score and HTA outcomes**

	HR (95% CI)	p value
Marketing authorisation process		
Accelerated (vs standard)	0·70 (0·51–0·95)	0·024
Parallel review (vs standard)	1·69 (1·13–2·54)	0·011
Product characteristics		
Orphan designation (vs non-orphan)	1·33 (0·88–1·99)	0·17
Funding mechanism		
Risk-sharing agreement (vs no funding agreement)	4·62 (2·51–8·51)	<0·0001
Special funding (vs no funding agreement)	4·16 (2·03–8·50)	0·0001
Clinical evidence		
High ESMO-MCBS score (vs low or average ESMO-MCBS score)†	1·42 (1·11–1·81)	0·0055
Time effect‡		
Year of HTA recommendation (per 1 calendar year increment)	0·96 (0·91–1·01)	0·11
Country-relevant (fixed) effects‡		
Canada, pCODR (vs England, NICE)	2·82 (1·68–4·75)	0·0001
France, HAS (vs England, NICE)	5·70 (2·87–11·33)	<0·0001
Quebec, INESSS (vs England, NICE)	1·30 (0·84–2·01)	0·23
Australia, PBAC (vs England, NICE)	1·39 (0·83–2·33)	0·22
Scotland, SMC (vs England, NICE)	1·43 (0·99–2·08)	0·057

Table 2: **Analysis of factors associated with time to a positive HTA outcome (List or List with Constraints) in stratified Cox proportional hazards regression***

Kanavos P et al. Lancet Oncol. 2024 PMID: 39637889.

Future Directions

- The goal of drug development is to demonstrate substantial evidence that a product provides meaningful clinical benefit to patients.

- Value frameworks could help identify therapies providing high clinical benefit that should be made rapidly available across countries.

- Natural extensions of these studies include:

  - the analysis of haematological malignancies,

  - cancer medicines designed for curative treatment,

  - HTA decision making for cancer medicines in upper-middle income countries.

  - Incorporate patient perspective and symptomatic improvements in drug development and approval should be a priority.

Acknowledgments

PORTAL
Program on Regulation, Therapeutics, And Law

- Agustí Barnadas
- Consolación Molto
- Aida Bujosa
- Thomas Hwang
- Kerstin Vokinger
- Eitan Amir
- Aaron Kesselheim

Thank you!

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