Oncology's PoS Problem

May 2023

Lumanity Clarion | A LUMANITY BUSINESS

Presented for:
Emerging Frontiers in Oncology 2023

Presented by:
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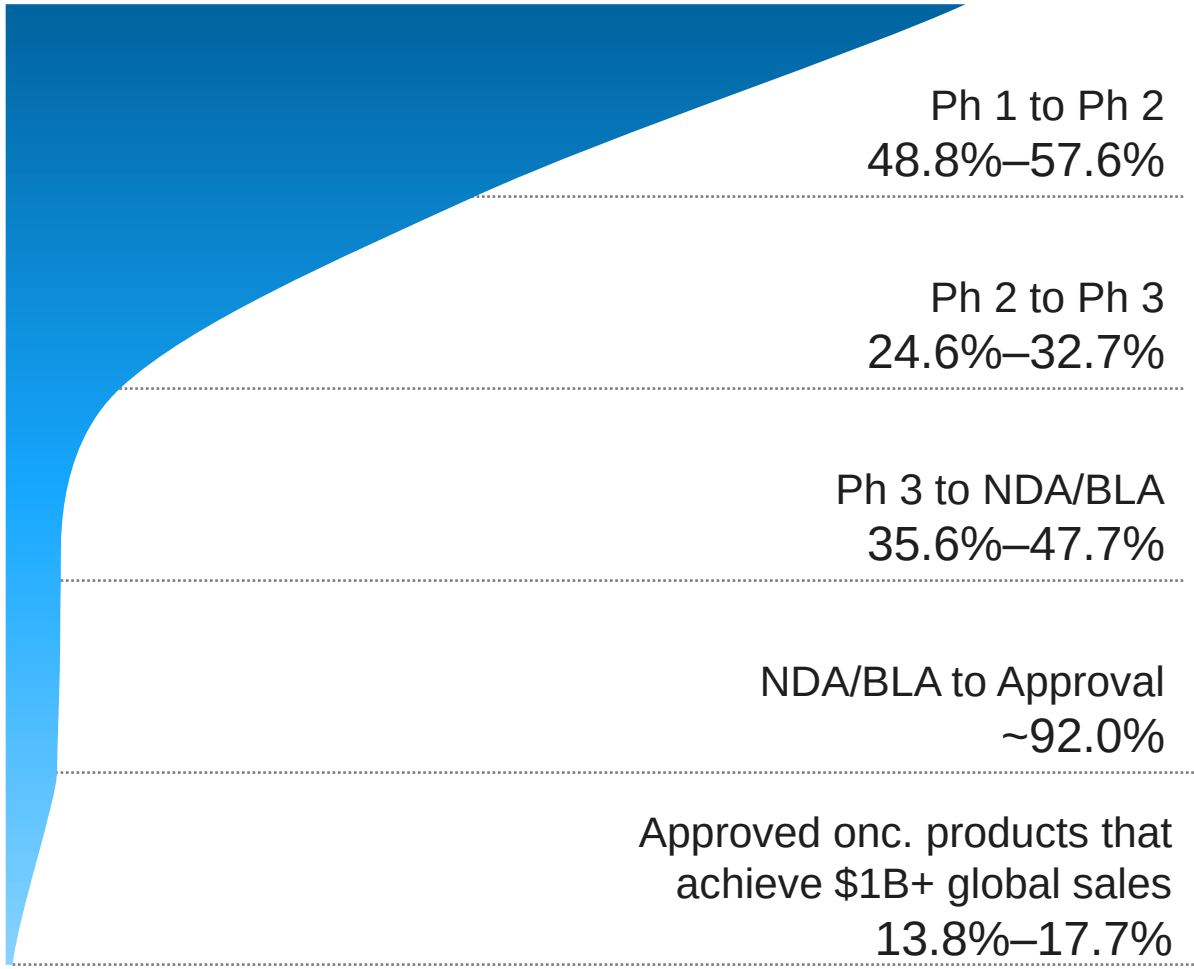
Oncology has one of the lowest PoS of any therapeutic area



Oncology product likelihood of approval from phase 1
~3.4–5.3%[2,3]

Oncology product likelihood of >$1B peak sales from phase 1
~0.5–0.9%[4,5]

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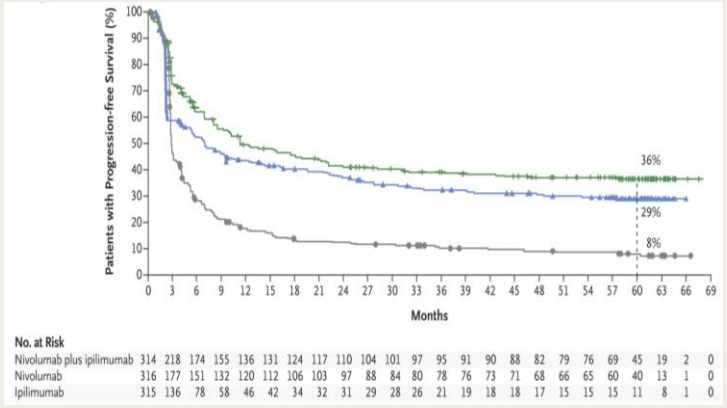
Sources: 1) Clarion analysis; 2) Wong & Siah 2019 Biostatistics 20(2):273–286; 3) BIO, QLS, Informa (Feb 2021) Clinical Development Success Rates and Contributing Factors 2011–2020; 4) McKinsey (Sep 2020) Delivering Innovation: 2020 Oncology Outlook; 5) Schuhmacher et al. (2022) Nat Rev Drug Discov

Oncology drug development does “work”

In the last 10 years, we have seen transformative successes including:

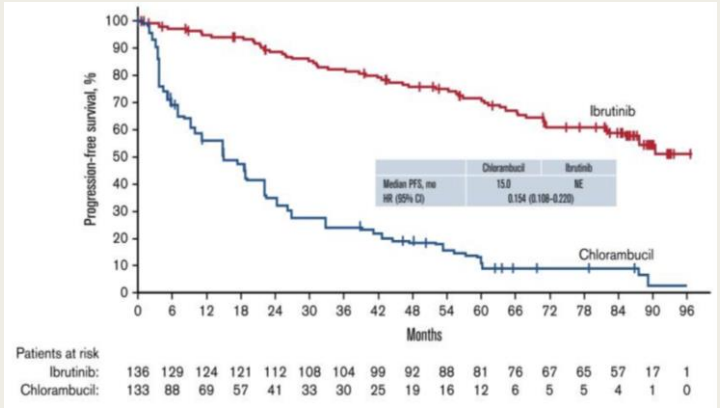
Curative Immunotherapies

- Nivo ± Ipi for metastatic melanoma
- Pembro + chemo for mNSCLC
- CD19 CAR-T for r/r B-ALL and B-NHL
- …



“Functional cures” in hematology

- BTK inhibitors for 1L CLL/SLL
- Daratumumab combos for 1L MM
- …



Precision medicines for new patient populations

- KRAS G12C inhibitors
- PARPi for BRCAm/HRD cancers
- T-DXd for HER2-low breast cancer
- MET inhibitors for MET-mut NSCLC
- BRAFi + MEKi for BRAF V600E
- NTRKi for NTRK fusions
- RETi for RET fusions
- …

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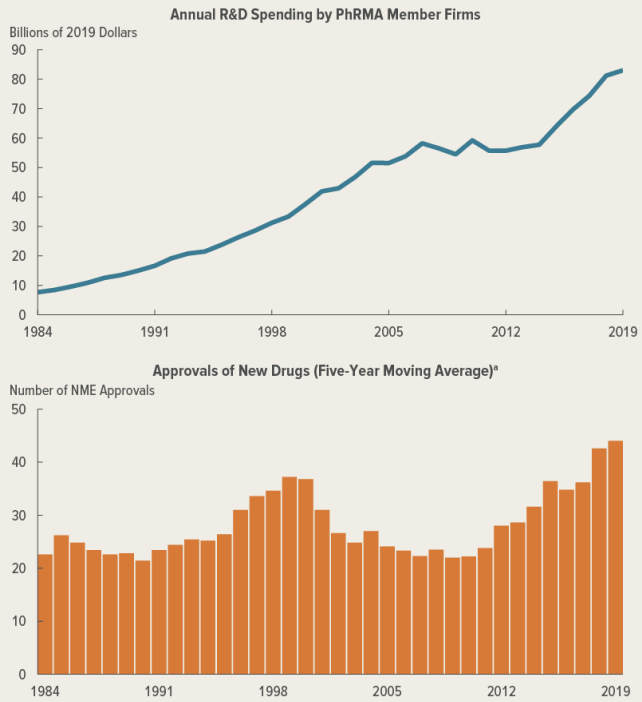
Sources: Larkin 2019 NEJM 381:1535; Novello 2023 JCO 41:1999; Garassino 2023 JCO 41:1992; Cappell & Kochenderfer 2023 Nat Rev Clin Oncol; Barr 2022 Blood Adv 6:3440; ASH 2022 #4561; FDA

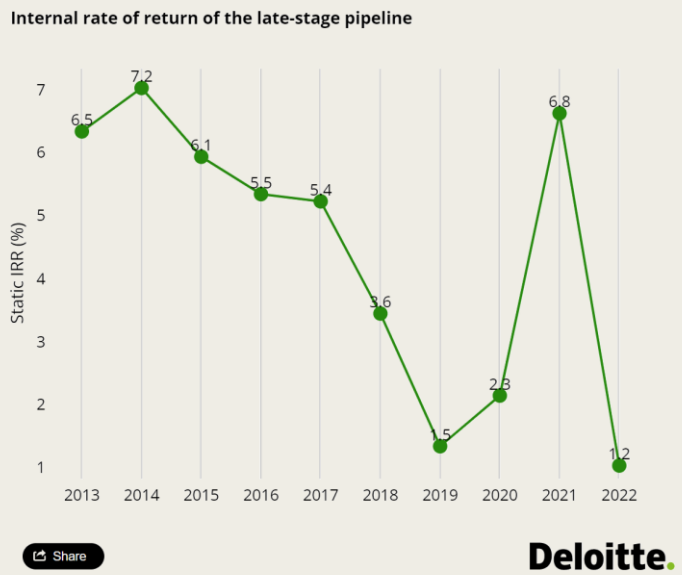
…but the investment needed is not viable

Across the pharma industry (not only oncology):

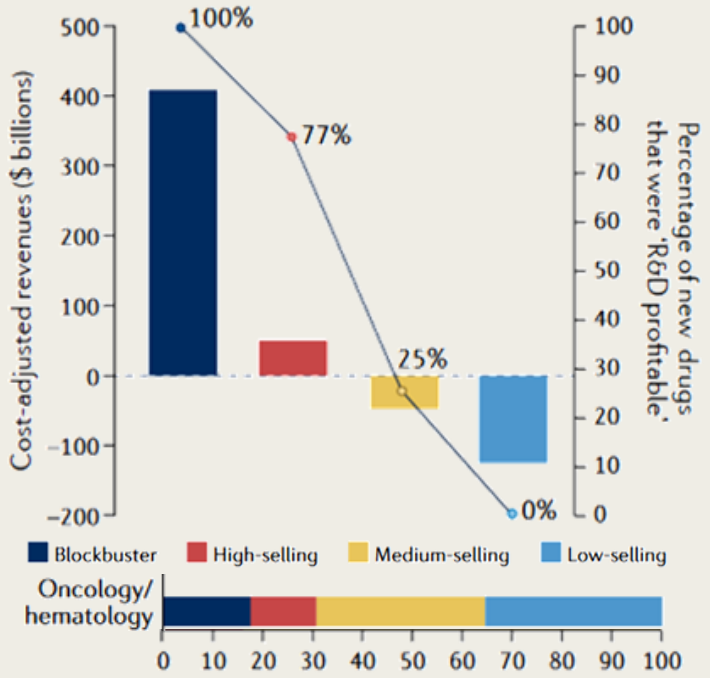
R&D spending has increased faster than drug approvals



The ROI of R&D is at an all-time low



Most drugs are not 'R&D profitable'



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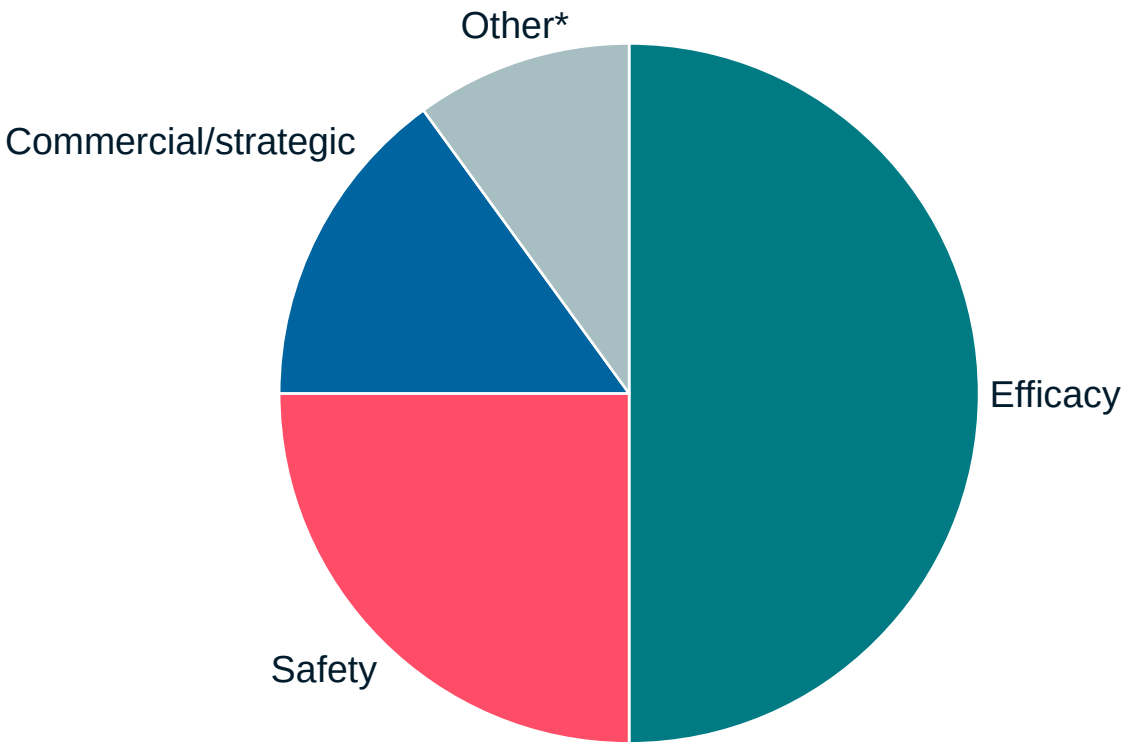
Sources: US Congressional Budget Office (Apr 2021) "Research and Development in the Pharmaceutical Industry"; Deloitte (2022) "Seize the digital momentum: Measuring the return from pharmaceutical innovation 2022"; HIT Consultant report (Feb 2023) "Pharma R&D ROI Falls to Lowest Level in 13 Years"; Schumacher et al. (2022) Nat Rev Drug Discov

Why do drugs fail?

Commonly cited reasons for clinical trial failures

(All therapeutic areas, 2010–2017)



* “Other” may include operational reasons or poor drug-like properties

What are the root causes?

- **Misapplication of the science**
  - Insufficient vetting of the **biological hypothesis**
  - Poorly predictive **preclinical models**
- **Insufficient product optimization**
  - Poor target/compound **selectivity**
  - Suboptimal PK/PD or **target engagement**
  - Suboptimal **dose schedule/exposure**
- **Overreliance on old trial paradigms**
  - Signal finding in **late lines of therapy**
  - Suboptimal **patient selection**
- **Challenging market dynamics**
  - Unprecedented **competitive intensity**
  - Constrained **funding/resources**

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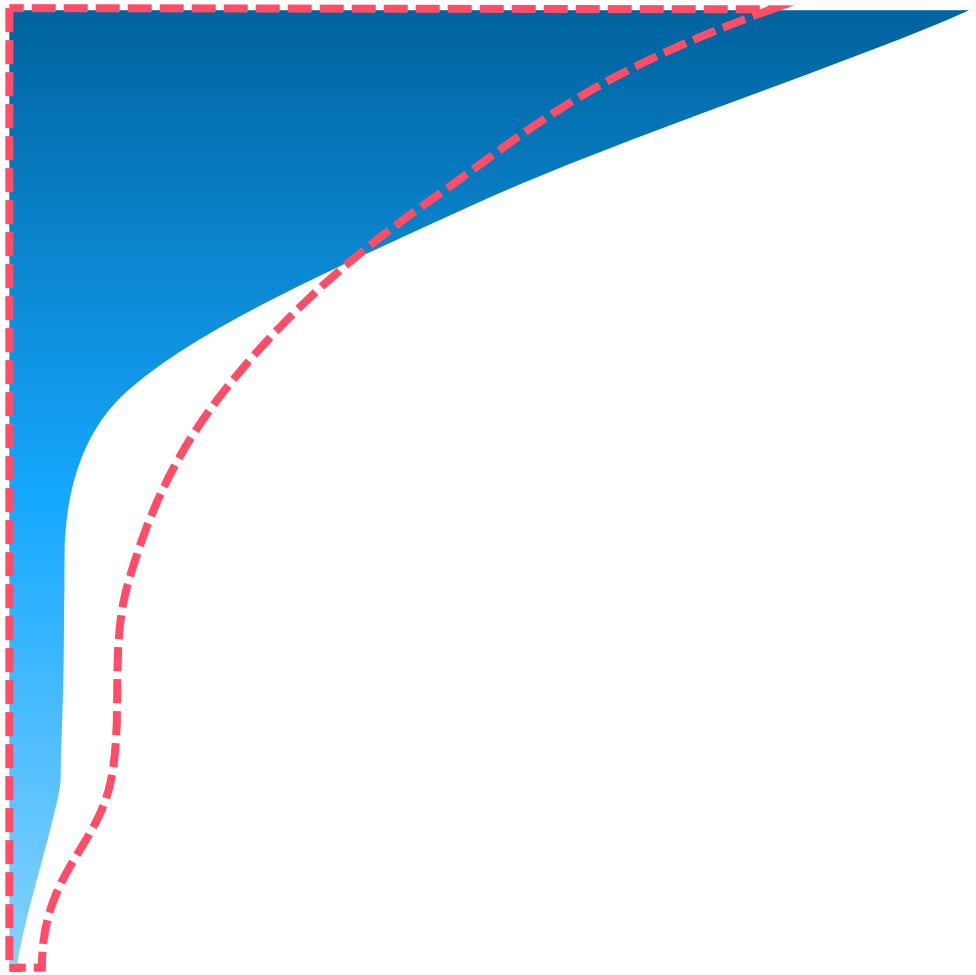
Sources: Sun et al. 2022 Acta Pharmaceutica Sinica B 12:3049; Harrison 2016 Nat Rev Drug Discov 15:817

What are the solutions?



Better Innovation

Improving the quality of candidates at the top of the funnel

- Targeting new/stronger biology
- Leveraging new modalities
- Developing better preclinical models
- More robust preclinical vetting of candidates

Better Implementation

Improving the efficiency and effectiveness of the funnel itself

- Rigorous optimization of the product/regimen
- Improving patient selection
- “Smarter” clinical trial designs
- “Failing fast”

Targeting new/stronger biology (1 of 2)

The pipeline is crowded with follow-on products

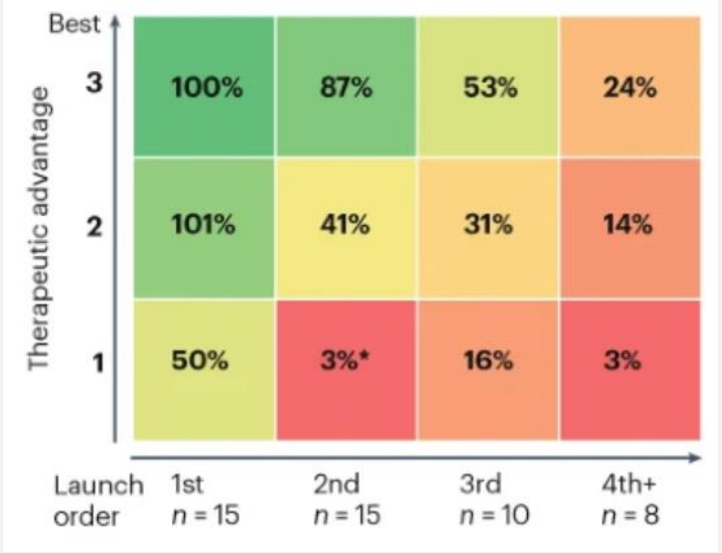
- Herd mentality: Hundreds of products for the same 20 targets
- Exchanging technical risk for commercial risk
- Flawed vision of ROI

Top 20 Therapeutic Targets in US Oncology Pipeline (N=2079 agents)

Commercial value diminishes with later order of entry

- Differentiation is paramount
- How many “best in class” drugs can there be?

Value captured in a drug class by order of entry and therapeutic advantage (oncology)

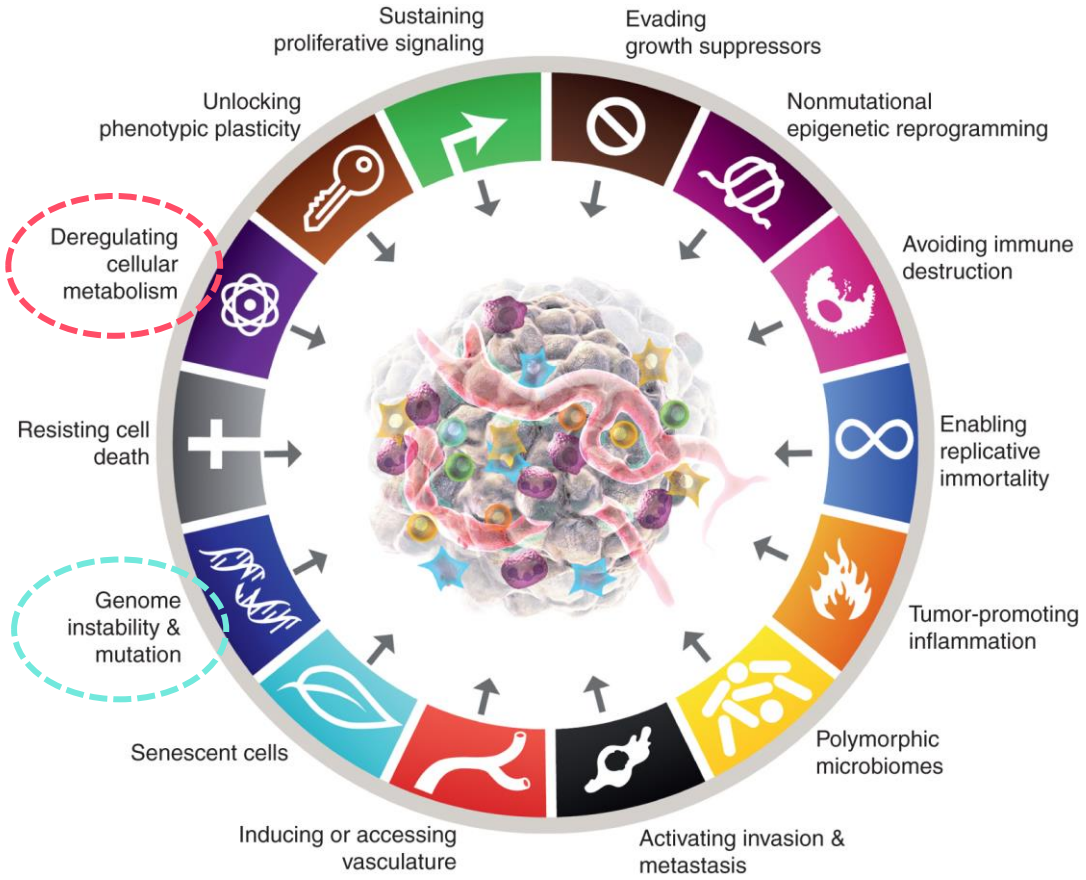


Source: Lumanity BioConsulting analysis; Adis R&D Insight, Cortellis/Clarivate; BCG analysis: Spring et al. (2023) Nat Rev Drug Discov

Targeting new/stronger biology (2 of 2)

Some mechanisms cause amplifying effects such that the cancer cell is **“pushed off a cliff”**.

E.g., PARP inhibition



Some mechanisms are mitigated by feedback inhibition or compensatory pathways making it an **“uphill battle”**.

E.g., glutaminase inhibition

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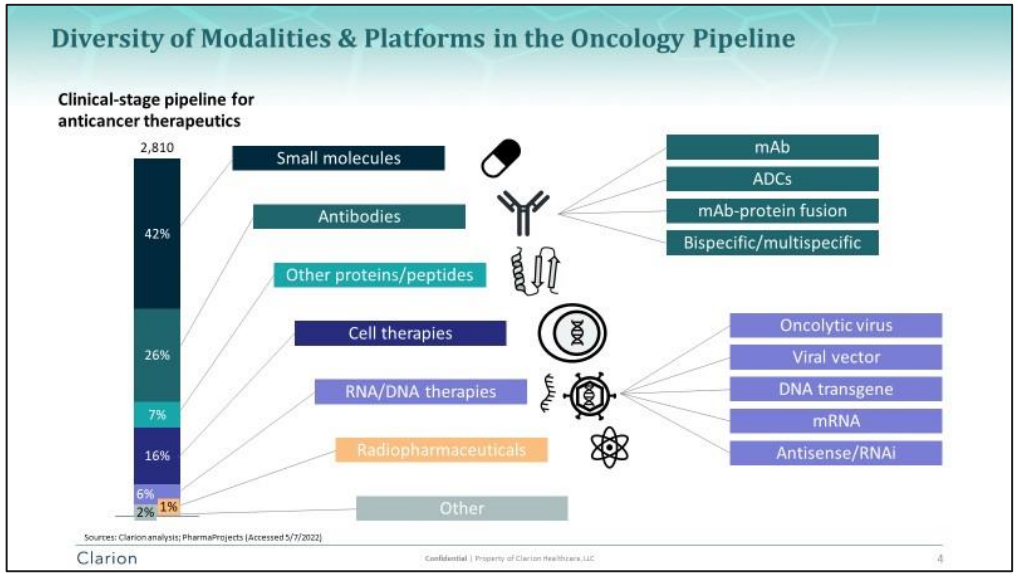
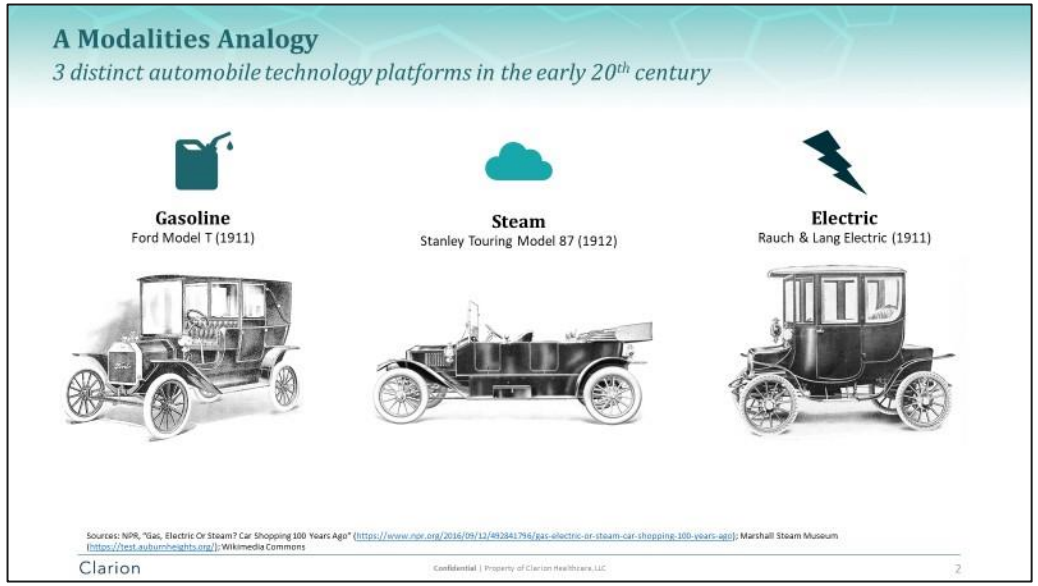
Source: Hanahan 2022 Cancer Discov 12(1):31–46.

Leveraging new modalities



As discussed last year:

- The oncology pipeline has a broad and growing diversity of technology platforms



Link to Clarion blog post and video presentation

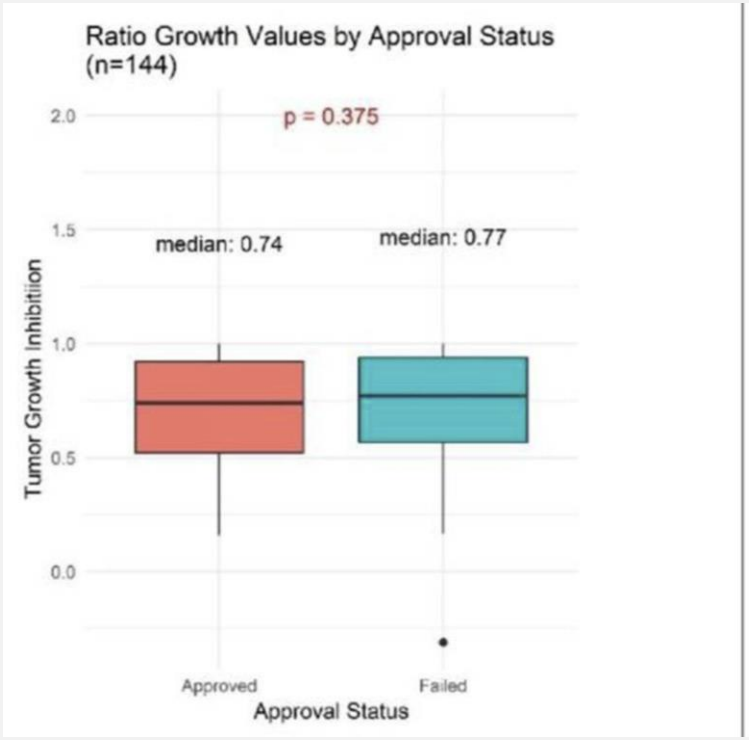
However, not all modalities are destined to transform oncology treatment. Some technologies will prove to be "dead ends"; others may be "ahead of their time" and will only become relevant in future generations

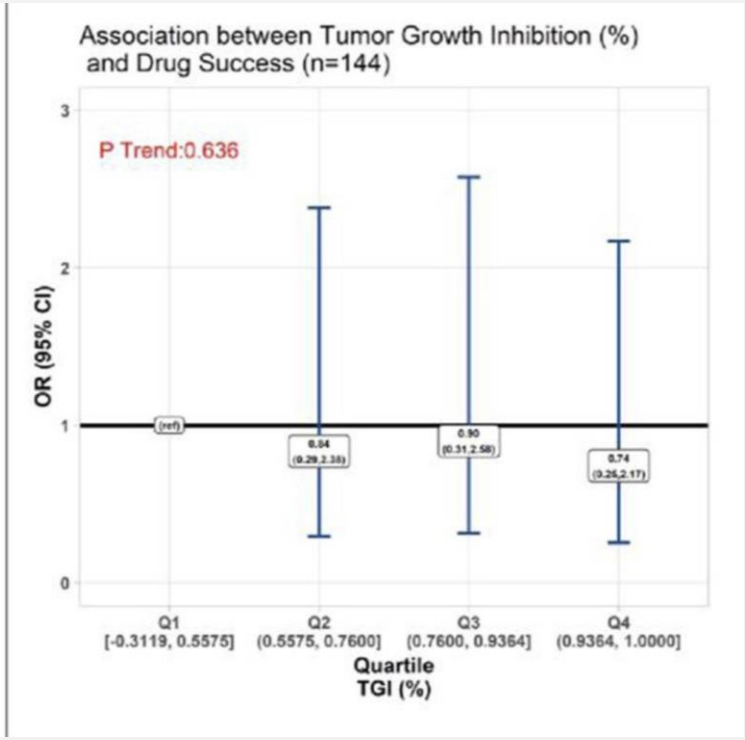
Source: Clarion (2022) "New Modalities at the Crossroads" presented at the 4th annual Emerging Frontiers in Oncology

Activity in preclinical models does not correlate with clinical success

Tumor growth inhibition (TGI) in murine models vs. approval/failure of lung cancer drugs

(1996–2014)





How to develop better preclinical models?

- Better mouse “avatars” of human patients
- Better non-mouse models
- Better patient-derived organoids
- Better in silico models

How to make better use of models we already have?

- Use a mix of models with complementary attributes
- Analyze model data more rigorously (e.g., focus on regression, not TGI)
- Move more quickly to clinical trials as a more definitive test?

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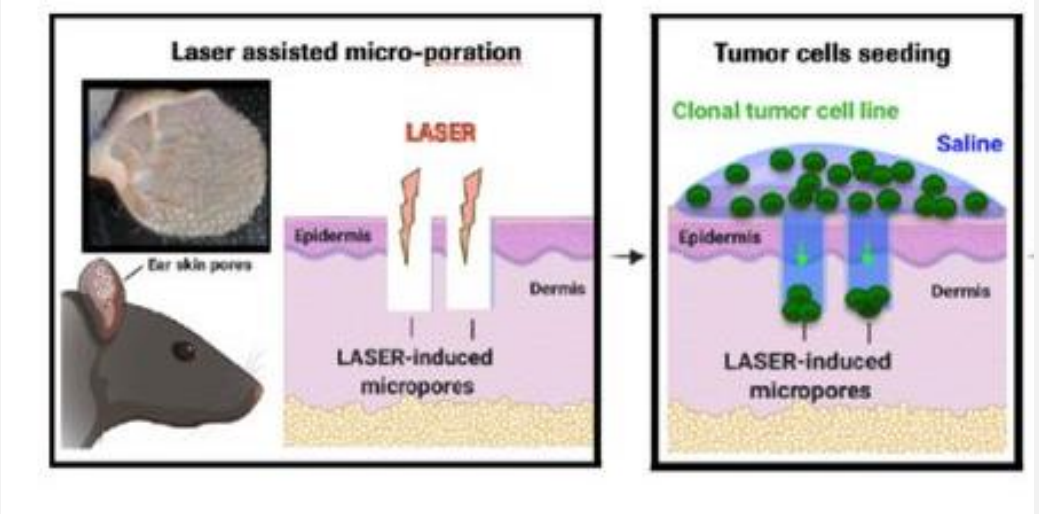
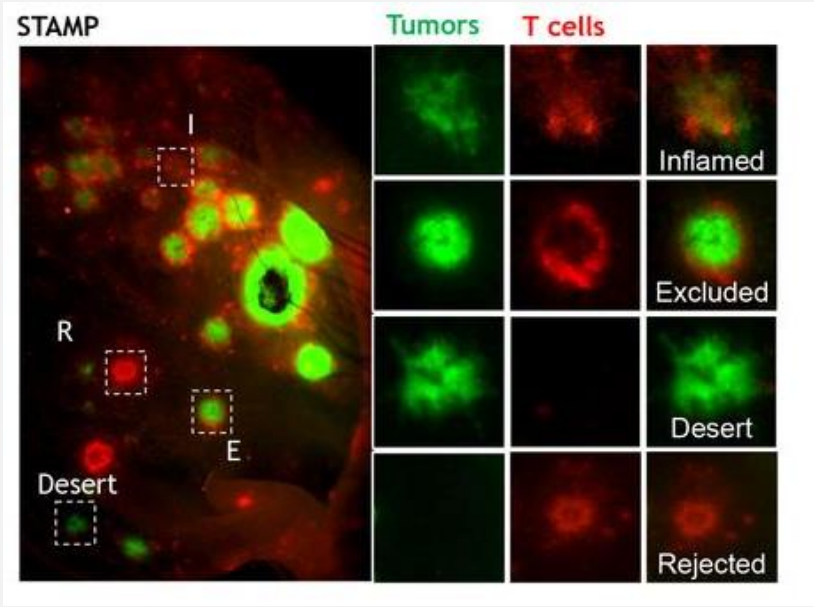
Source: Pan et al. 2020 Front Oncol 10:591

Can preclinical models ever work well for immuno-oncology?

STAMP (skin tumor array by micro-poration) experiments underscore the challenges in modeling immune phenotype in animals



The STAMP method entails seeding a mouse ear with tumor cells in an array to enable many replicate experiments to be done in one animal.



Diverse immune phenotypes were seen in any single array.

Immune phenotypes cannot be reliably reproduced even when placing the same tumor cells in the same mouse millimeters apart.

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Source: Ortiz-Muñoz et al., bioRxiv (posted 2021) https://www.biorxiv.org/content/10.1101/2021.05.27.445482v1.full

Optimization of the product/regimen

Many drugs fail clinical trials despite well validated targets.

Examples:

AR	orteronel	**ER**	amcenestrant
BTK	spebrutinib	**PI3Kα**	taselisib
EGFR	canertinib, zalutumumab	**VEGFR**	brivanib, motesanib

While others are approved but uptake is limited by poor "drug-like properties."

- Significant toxicity / monitoring requirements
- High pill burden
- Inconvenient dosing schedule
- …

Do "good" drugs fail due to insufficient optimization?

How do we prevent that from happening?

Example recommendations:

- **Set a high enough bar** for drug properties
- **Use/develop PD biomarkers** to validate target engagement
- **Go beyond plasma exposure** for PK assessment
- **Customize resource allocation:** Identify situations where extra effort is required on formulation & dose optimization (e.g., pan-essential targets)

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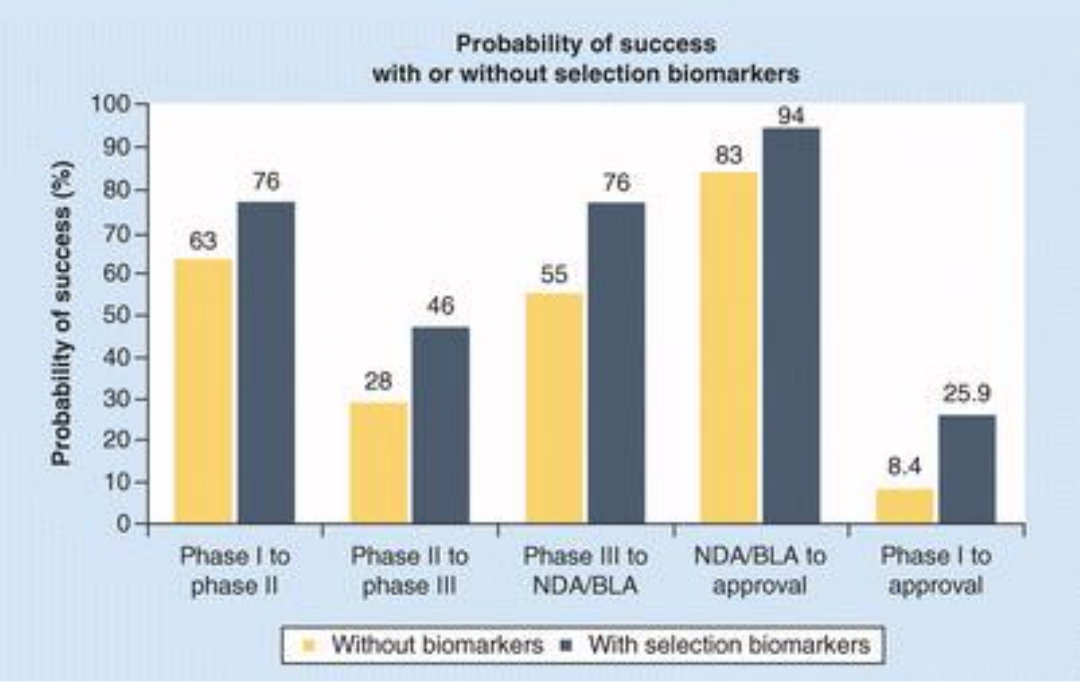
Source: Sun et al. (2022) Why 90% of clinical drug development fails and how to improve it? Acta Pharm Sin B 12:3049; Chang et al. (2021) Cancer Cell 39:466

Improving patient selection

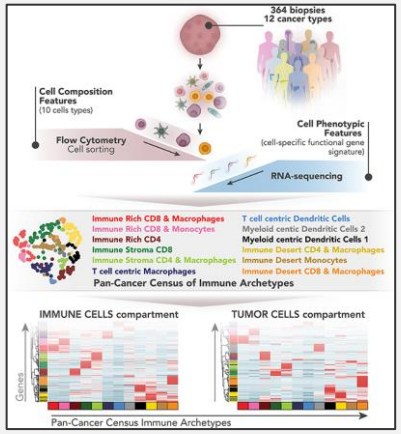
Precision medicine has higher PoS than all-comers approaches



How do we develop better biomarkers?

IO example recommendations

- **Study samples across timepoints, locations, clinical response**
- **Profile diverse cell types**
- **Assess multiple analytes**



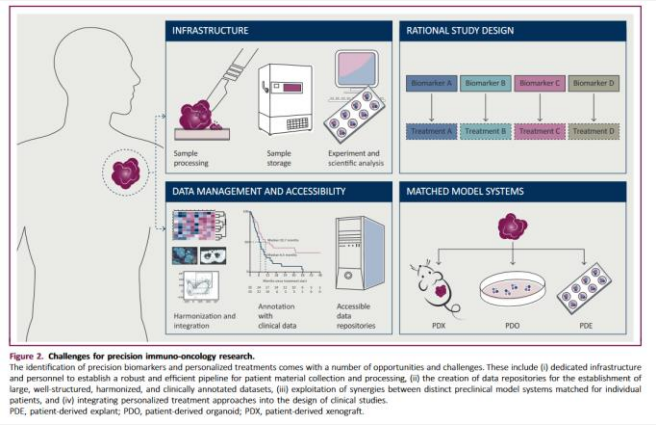


Figure 2. Challenges for precision immuno-oncology research.
The identification of precision biomarkers and personalized treatments comes with a number of opportunities and challenges. These include (i) dedicated infrastructure and personnel to establish a robust and efficient pipeline for patient material collection and processing, (ii) the creation of data repositories for the establishment of large, well-structured, harmonized, and clinically annotated datasets, (iii) exploitation of synergies between distinct preclinical model systems matched for individual patients, and (iv) integrating personalized treatment approaches into the design of clinical studies.
PDE, patient-derived explant; PDO, patient-derived organoid; PDX, patient-derived xenograft.

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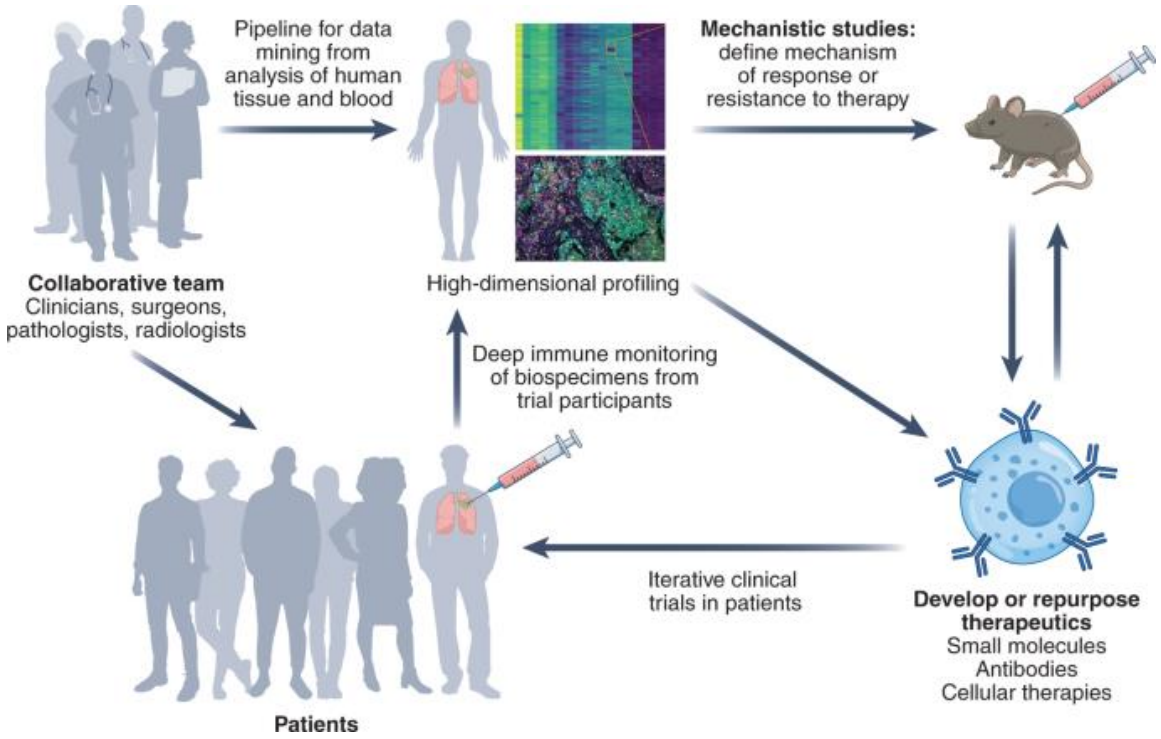
Source: Carroll (2016) Biomarkers Med 10:939; Chen & Mellman 2017 Nature 541:321; Combes et al. 2022 Cell 185:184; Roelofsen et al. 2022 Immunooncol Technol 14:100071

Neoadjuvant translation / Window-of-opportunity studies



Key Advantages:

- **Treatment-naïve setting** with less heterogeneous tumors and more intact immune systems vs conventional phase 1 trials
- **Large tissue specimens** for in-depth cellular & molecular analyses
- **Fast, small studies** with potentially lower cost

Key Requirements:

- **Multidisciplinary teams**
- **Maximum (fresh) tissue access**
- **Definition of clinically meaningful response** based on tissue pathology (may be different for IO vs neoadjuvant chemo)
- **Adaptive clinical trial** designs to maximize insight and accelerate iteration using small cohorts
- **Novel statistical methods** to account for unconventional tissue-based endpoints and adaptive designs

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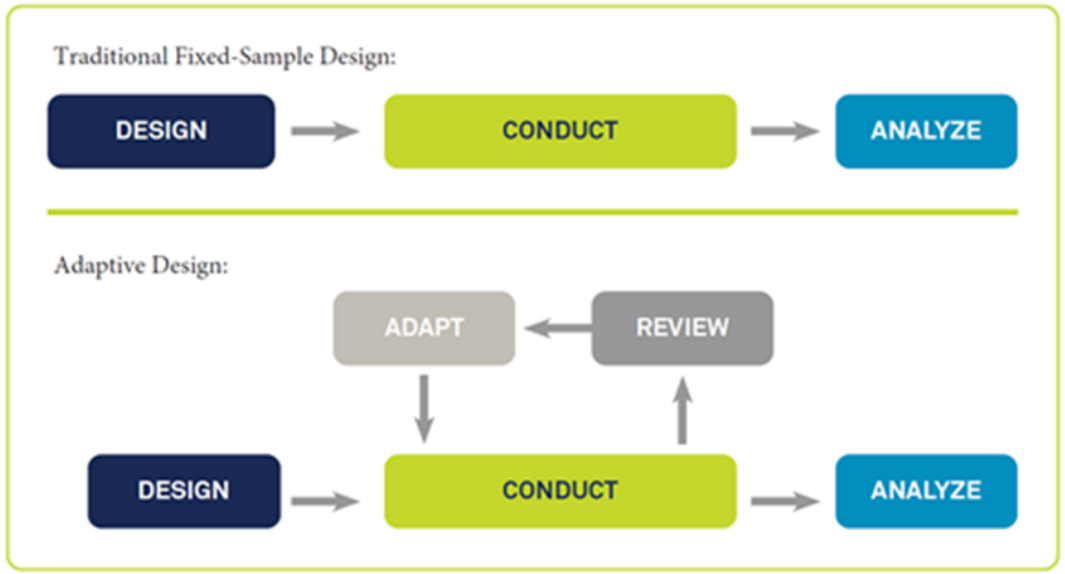
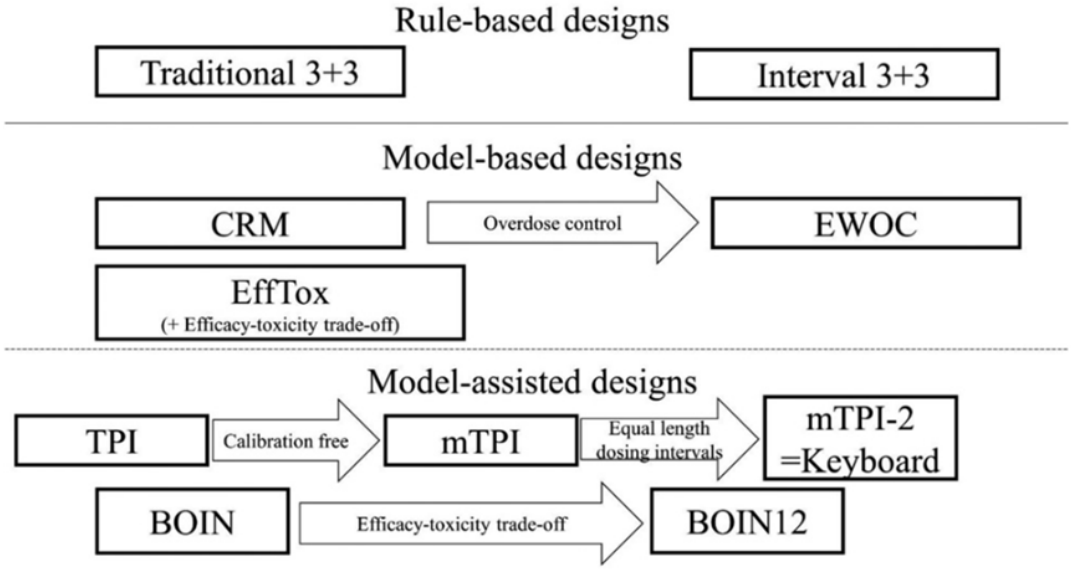
Source: Marron (2022) Nat Med 28:626

Other “Smart” clinical trial approaches

Adaptive Trials



Model-assisted Designs

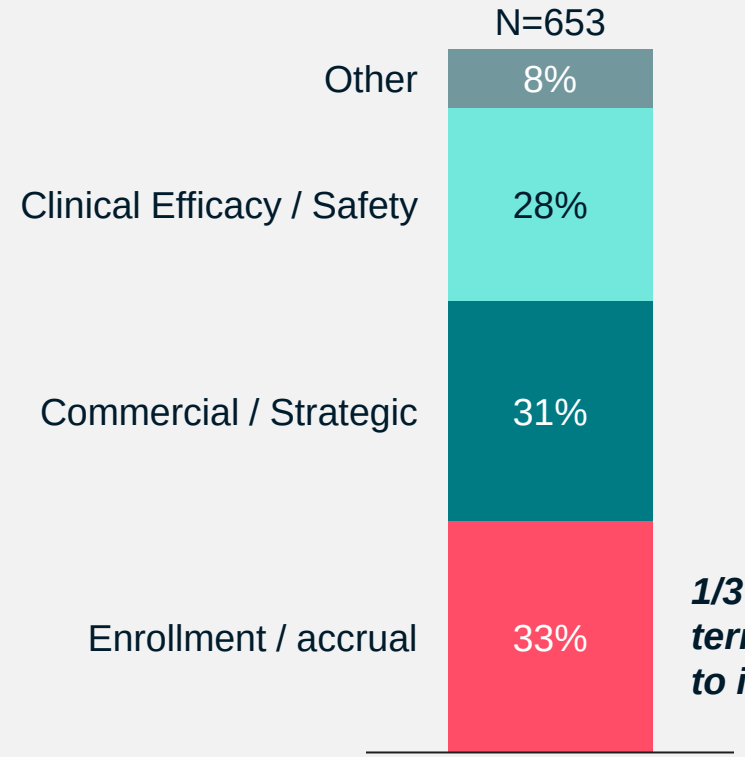


Source:

Improving clinical trial accrual

Reasons for Oncology Clinical Trial Terminations

Terminated industry-sponsored oncology trials (phases 1/2, 2, 3) with start dates in 2010+, with a reported reason for discontinuation



1/3 of oncology trial terminations are due to insufficient accrual

How do we improve trial accrual?

Key considerations

- **Inclusion/exclusion criteria** should not be excessively narrow
- **Patient concerns** including quality of care, understanding/education, emotional needs, remuneration, travel, time requirements
- **Investigator enthusiasm**
- **Complexity/burden** of trial measures
- **Clinical operations** effectiveness and resource allocation
- **Overall patient participation** in trials is still low; especially among minority groups

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Sources: Clarion analysis; Evaluate Pharma (accessed May 5 2023); Fogel (2018) Contemp Clin Trials Commun 11:156

Where should we prioritize effort/resource allocation?

Better Innovation

The right **targets**

The right **modalities**

The right **models**

The right **assays**

Improving the quality of candidates at the top of the funnel

Better Implementation

The right **formulation/dose**

The right **patient population**

The right **trial design**

The right **trial execution**

Improving the efficiency and effectiveness of the funnel itself

Thank You

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