- International Drug Development Institute (IDDI) is an expert center in biostatistical and integrated eClinical services for pharmaceutical and biotechnology companies in several disease areas, including oncology and ophthalmology.

- IDDI optimizes the clinical development of drugs, biologics and devices thanks to proven statistical expertise and operational excellence.

- Founded in 1991, IDDI is headquartered in Brussels, Belgium, with US operations in Raleigh (NC).

IDDI

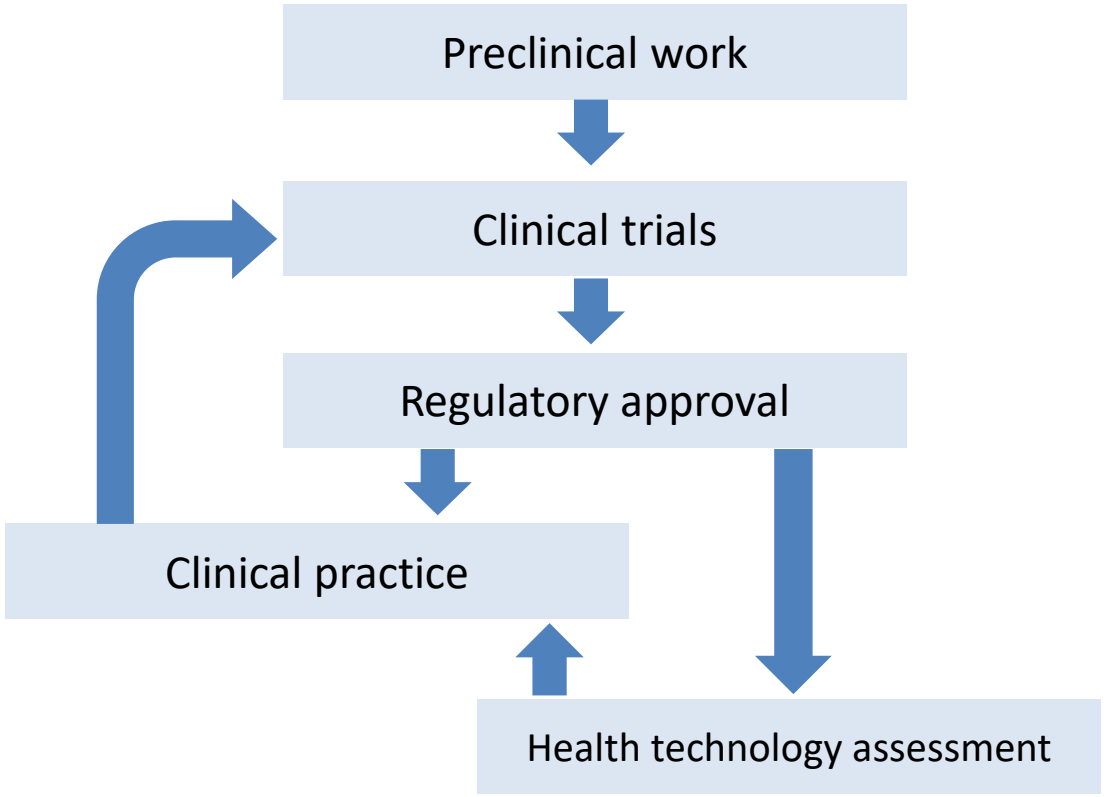
PASSION. SCIENCE. EXPERIENCE.

Randomization and the Limits of Precision Oncology

Everardo D. Saad
Medical Director, IDDI

Different (and complementary) settings, perspectives and implications

1. **Drug development**
   - **Early phases**
   - Late phases
2. Clinical practice
3. Policy making



What is a curmudgeon?

SOUNDING BOARD

Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.

"The concept of personalized medicine is so appealing that seemingly only curmudgeons could criticize it."

curmudgeon

/kəːˈmʌdʒ(ə)n/

noun

a bad-tempered person, especially an old one.

Tannock and Hickman, N Engl J Med 2016;375:1289-94

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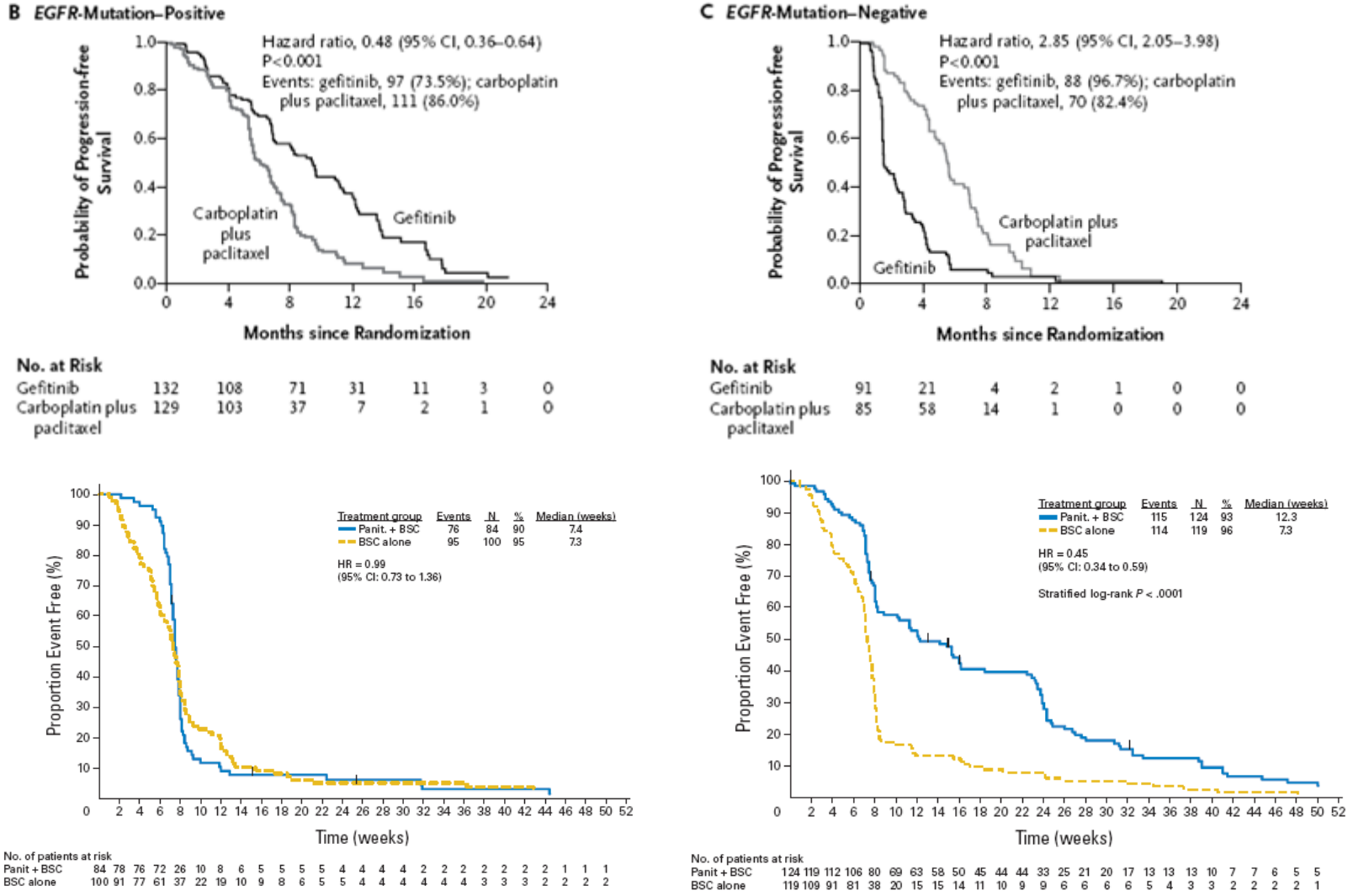
What is precision oncology?

- "Giving the right treatment to the right patient at the right time"
- This entails using targeted therapy and biomarkers

- At least three meanings, with considerable overlap:

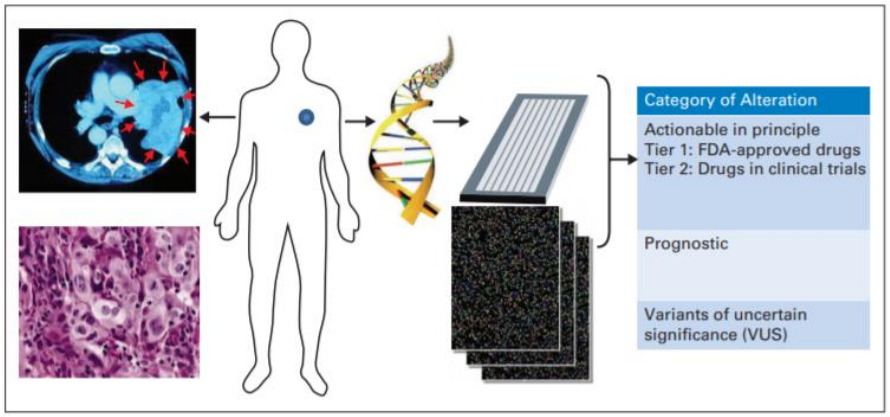
1. Choosing treatment based on predictive biomarkers
2. Interrogating tumor genomes to select among existing therapies
3. Using molecular features to select evidence-based treatment

Choosing treatment based on predictive biomarkers



Mok et al, N Engl J Med 2009; 361:947; Amado et al, J Clin Oncol 2008; 26:1626

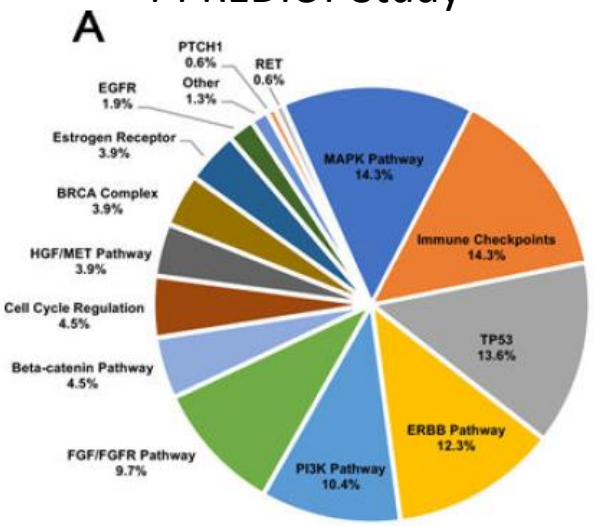
Interrogating genomes to select among existing therapies

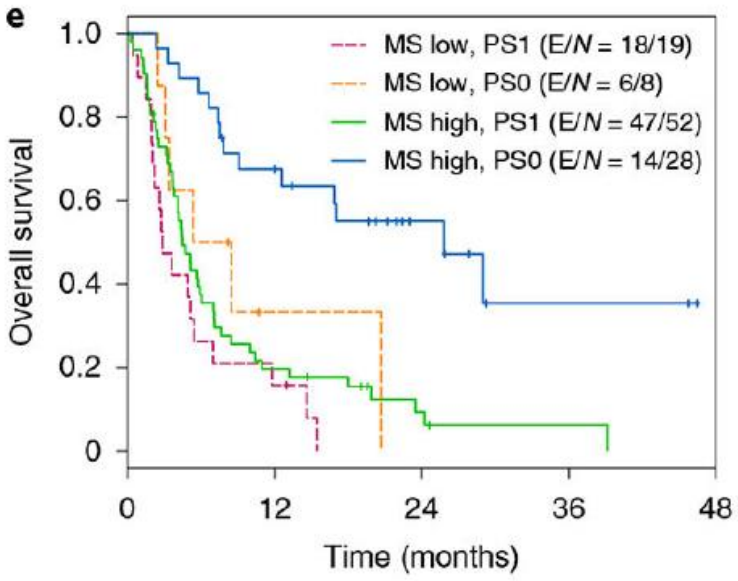


WINTHER Trial

$$S_i = 100 \cdot \sum_{g \in M_i} \frac{F_{g,i}^{x} \cdot I_g}{|M_i|}$$

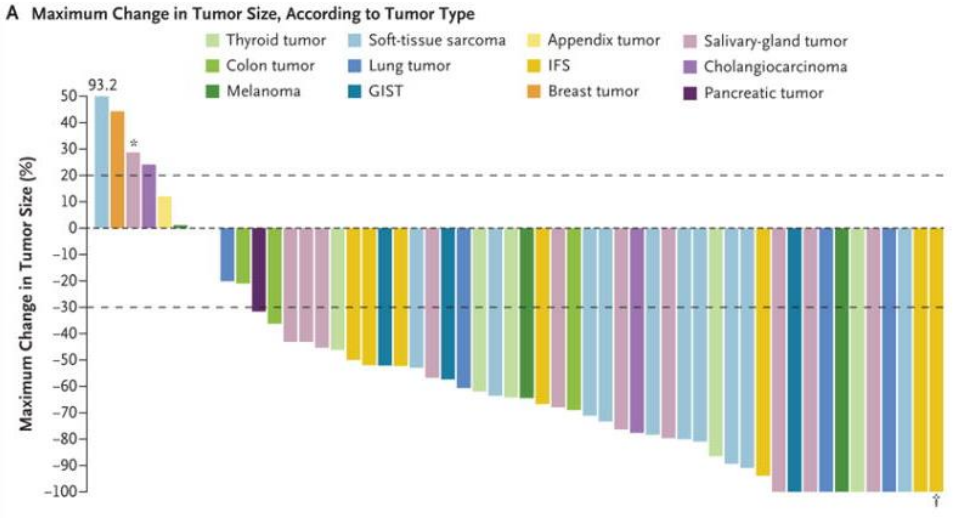
I-PREDICT Study

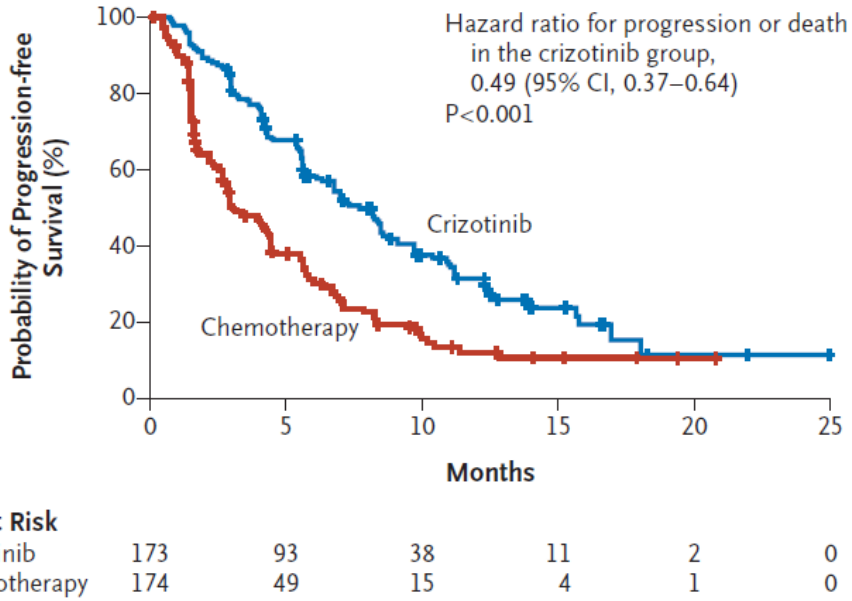




Garraway et al, J Clin Oncol 2013;31:1803-5; Sicklick et al, Nat Med 2019;25:744–50; Rodon et al, Nat Med 2019; 25: 751-8

Using molecular features to select evidence-based treatment





Drilon et al, N Engl J Med 2018;378:731-739; Shaw et al, N Engl J Med 2013;368:2385-94

Biomarkers

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. Categories of biomarkers:
  - susceptibility/risk biomarker
  - diagnostic biomarker
  - monitoring biomarker
  - prognostic biomarker
  - **predictive biomarker**
  - pharmacodynamic/response biomarker
  - safety biomarker

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

FDA-NIH Biomarker Working Group, 2018

Companion diagnostics

- 46 companion diagnostics
- 45 are in oncology (1 in thalassemia)
- 11 dedicated to HER-2 (plus some including HER-2)

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Indication(s) Trade Name (Generic) - NDA/BLA
***PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome / Myeloproliferative Disease (MDS/MPD)**	H140005	ARUP Laboratories, Inc.	Myelodysplastic syndrome/myeloproliferative disease • Gleevec (imatinib mesylate) – NDA 021335
cobas KRAS Mutation Test	P140023	Roche Molecular Systems, Inc.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
therascreen KRAS RGQ PCR Kit	P110030 P110027	Qiagen Manchester, Ltd.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
Dako EGFR pharmDx Kit	P030044/S002	Dako North America, Inc.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
FerriScan	DEN130012/K124065	Resonance Health Analysis Services Pty Ltd	Non-transfusion-dependent thalassemia • Exjade (deferasirox) – NDA 021882
Dako c-KIT pharmDx	P040011	Dako North America, Inc.	Gastrointestinal stromal tumors • Gleevec (imatinib mesylate) – NDA 021335 • Glivec (imatinib mesylate) – NDA 021588
INFORM HER-2/neu	P940004	Ventana Medical Systems, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
PathVysion HER-2 DNA Probe Kit	P980024	Abbott Molecular Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	P990081/S001-S028 P990081/S039	Ventana Medical Systems, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792 • Kadcyla (ado-trastuzumab emtansine) - BLA 125427

https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Current predictive or "enrichment" biomarkers in oncology

1. HER-2 and trastuzumab/lapatinib/pertuzumab/T-DM1
2. BCR-Abl and imatinib/dasatinib/nilotinib
3. EGFR and erlotinib/gefitinib/afatinib/osimertinib/amivantamab-vmjw
4. FGFR and erdafitinib
5. KRAS and cetuximab/panitumumab/sotorasib
6. ALK-EML or ROS-1 and crizotinib/ceritinib/alectinib
7. BRAF V600E and vemurafenib/dabrafenib/encorafenib/trametinib
8. BRCA-1/2 and olaparib/veliparib/niraparib/rucaparib
9. PIK3CA and alpelisib
10. PD-L1 and pembrolizumab/nivolumab/atezolizumab
11. CD20 and rituximab/obinotuzumab
12. IDH1 and ivosidenib
13. IDH2 and enasidenib
14. FLT3 and midostaurin
15. MMR and dostarlimab-gxly
16. EZH2 and tazemetostat

Conclusion. We found that the requirement of a predictive biomarker testing before prescription of an anti-cancer drug is often the result of drug development conducted in only biomarker-positive patients and seldom relies on a statistically significant treatment-by-biomarker interaction. Even though drug development in oncology will increasingly face ethical and scientific challenges, clinicians and patients should be aware of these limitations.

Vivot et al, Sci Rep 2017;7:6882

Precision oncology is compelling

Early Accelerated Approval for Highly Targeted Cancer Drugs

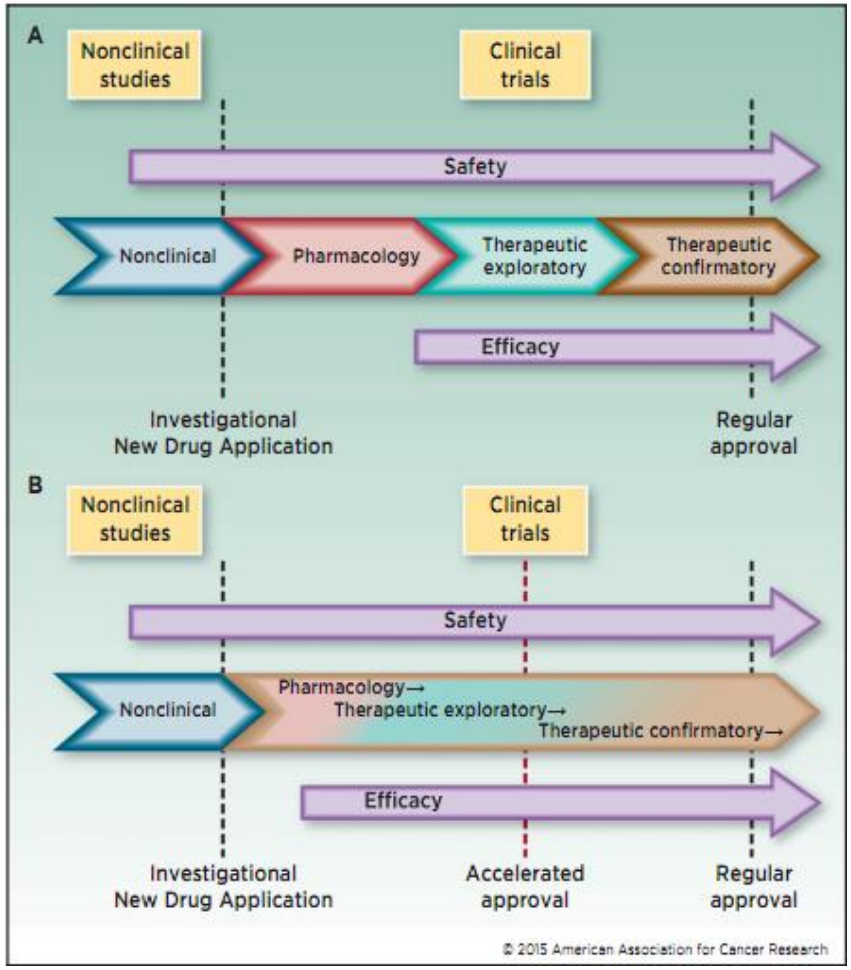
Because we can now define patient subgroups with high response rates in phase 1 trials, performance of phase 3 trials for these drugs raises important issues. If patients with incurable disease who have the right biomarker for response are informed of these impressive early results, they will want and perhaps deserve access to the new drug and may not accept random assignment to a modestly effective and toxic standard agent. The phase 3 trial may lack equipoise in the eyes of both physicians and patients.

Given trialists' ability to define patient subgroups with responsive tumors in phase 1 trials, I propose that for diseases lacking therapies that meaningfully extend survival, the FDA should set flexible standards permitting accelerated approval of new drugs after phase 1.

Conceivably, non-targeted agents could also satisfy criteria for approval after phase 1. High response rates (>50%), high disease-control rates (>75%), and an acceptable toxicity profile in a biomarker-defined population of 75 to 100 subjects should be sufficient for accelerated approval if there's a clear unmet need. Randomized comparisons with minimally effective treatments or placebo should not be required.

Chabner, N Engl J Med 2011;364:1087-9

Changing regulatory landscape



Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

Pembrolizumab Response Rate by Tumor Type.*

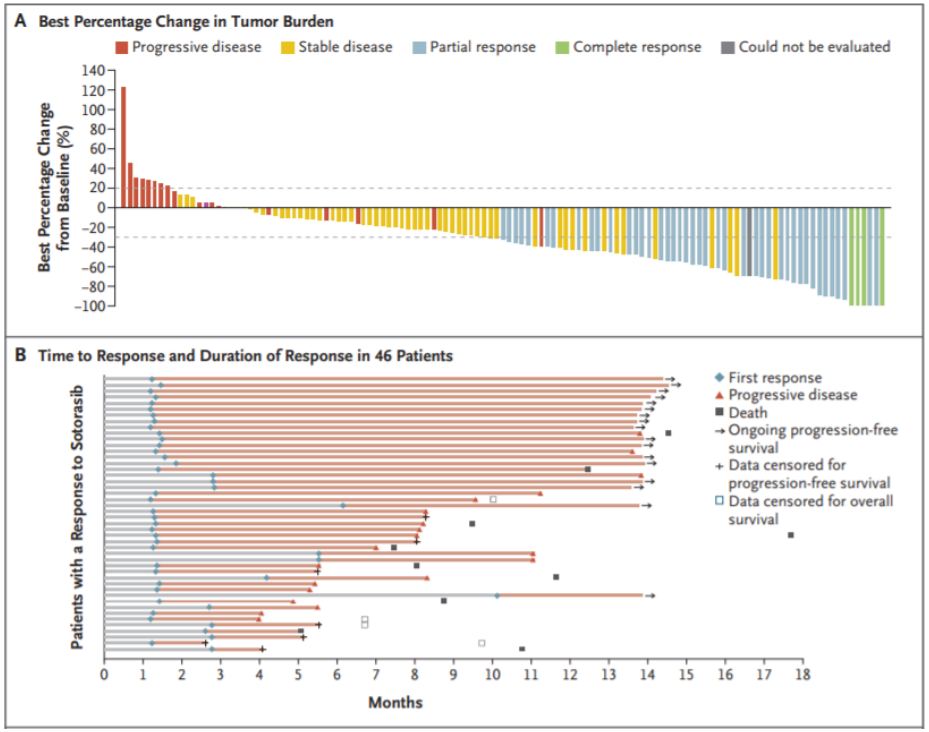
Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

Theoret et al, Clin Cancer Res 2015;21:4545-51; Lemery et al, N Engl J Med 2017; 377:1409-1412
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm616325.pdf

A recent approval

Sotorasib in advanced NSCLC with the KRAS G12C mutation



N=126

57% in second or third line

ORR, 37%

Median PFS, 6.8 months

Median OS, 12.5 months

All Patients (N = 126)

	Any Grade	Grade 1 or 2	Grade 3	Grade 4	Fatal
	number of patients (percent)				
Adverse event	125 (99.2)	48 (38.1)	53 (42.1)	4 (3.2)	20 (15.9)
Treatment-related adverse event	88 (69.8)	62 (49.2)	25 (19.8)	1 (0.8)	0

Skoulidis et al, N Engl J Med 2021;384:2371-81

Approval* based on non-randomized evidence – 1

Review of Oncology and Hematology Drug Product Approvals at the US Food and Drug Administration Between July 2005 and December 2007

Rajeshwari Sridhara, John R. Johnson, Robert Justice, Patricia Keegan, Aloka Chakravarty, Richard Pazdur

Thirty-seven of the 53 indications were based on data from randomized studies. These randomized studies included 17 "add-on" studies in which the investigational drug plus standard chemotherapy was compared with the standard chemotherapy alone, four studies in which placebo was the comparator, and four studies in which best supportive care was the comparator (Table 1). The study sample sizes in the randomized studies ranged from 87 patients for the use of eculizumab in paroxysmal nocturnal hemoglobinuria to 19747 patients for the use of raloxifene for the reduction in risk of invasive breast cancer. The remaining 16 indications were based on data from single-arm studies with no comparison group. In these studies, the sample sizes ranged from 18 patients for the use of imatinib mesylate in dermatofibrosarcoma protuberans to 232 patients for the use of nilotinib hydrochloride monohydrate in chronic-phase chronic myeloid leukemia (Table 1). Forty-four of the 53 indications were based on results from a single study.

*Whether accelerated or conventional

Sridhara et al, J Natl Cancer Inst 2010;102:230-43

Approval* based on non-randomized evidence – 2

Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999–2014

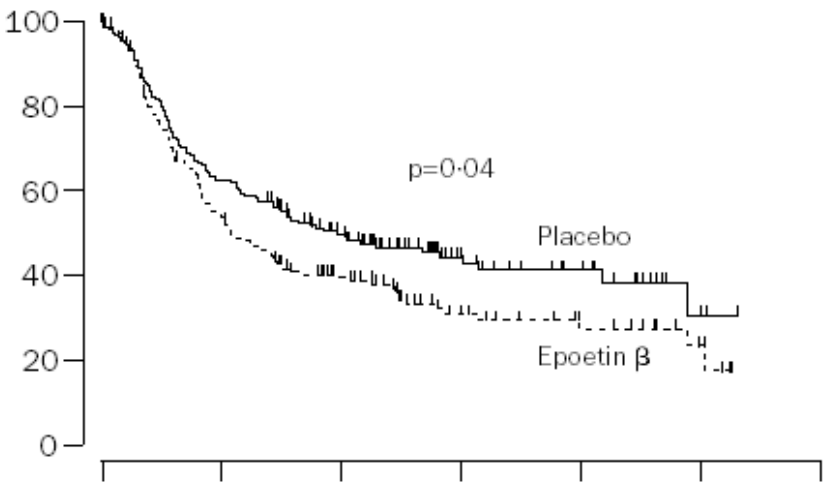
*Whether accelerated or conventional

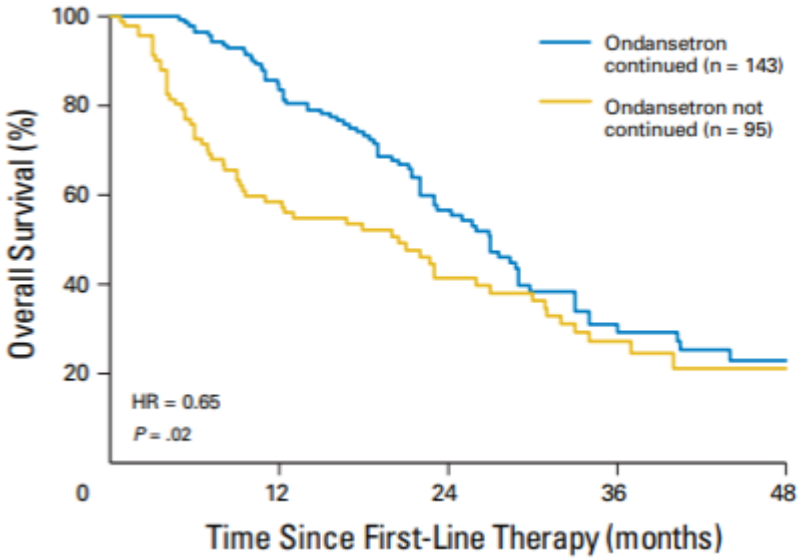
Table 2 Drugs submitted to the EMA and the FDA containing only uncontrolled clinical studies

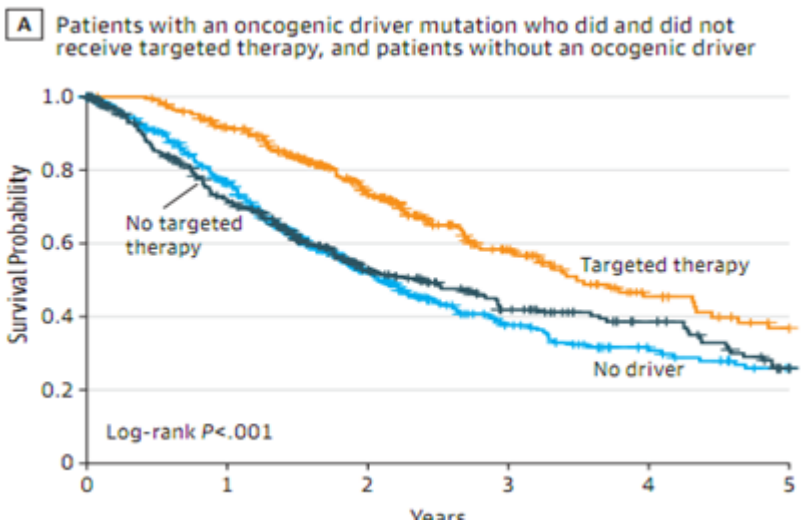
Generic name	Condition
Abarelix	Prostate cancer
Alemtuzumab	Chronic lymphocytic leukaemia (CLL)
Alglucosidase alfa	Pompe disease
Alipogene tiparvovec	Familial lipoprotein lipase deficiency
Anagrelide	Essential thrombocytopenia
Argatroban	Heparin-induced thrombocytopenia
Arsenic trioxide	Acute promyelocytic leukaemia
Asparaginase Erwinia chrysanthemi	Acute lymphoblastic leukaemia (ALL)
Bendamustine hydrochloride	Non-Hodgkin's lymphoma
Betaine anhydrous	Homocystinuria
Bexarotene	Cutaneous T-cell lymphoma (CTCL)
Bortezomib	Multiple myeloma (MM)
Bortezomib	Mantle cell lymphoma (MCL)
Bosutinib	Chronic myeloid leukaemia (CML)
Brentuximab vedotin	Hodgkin's lymphoma (HL)
Brentuximab vedotin	Systemic anaplastic large cell lymphoma (sALCL)
Busulfan	Haematopoietic progenitor cell transplantation (HPCT)
Carfilzomib	MM
Carglumic acid	Chronic hyperammonaemia
Ceritinib	Non-small cell lung cancer
Cetuximab	Colorectal cancer
Cholic acid (Kolbam)	Inborn errors in primary bile acid synthesis
Cholic acid (Orphacol)	Inborn errors in primary bile acid synthesis
Cladribine	Hairy cell leukaemia
Clofarabine	ALL
Crizotinib	Non-small-cell lung cancer

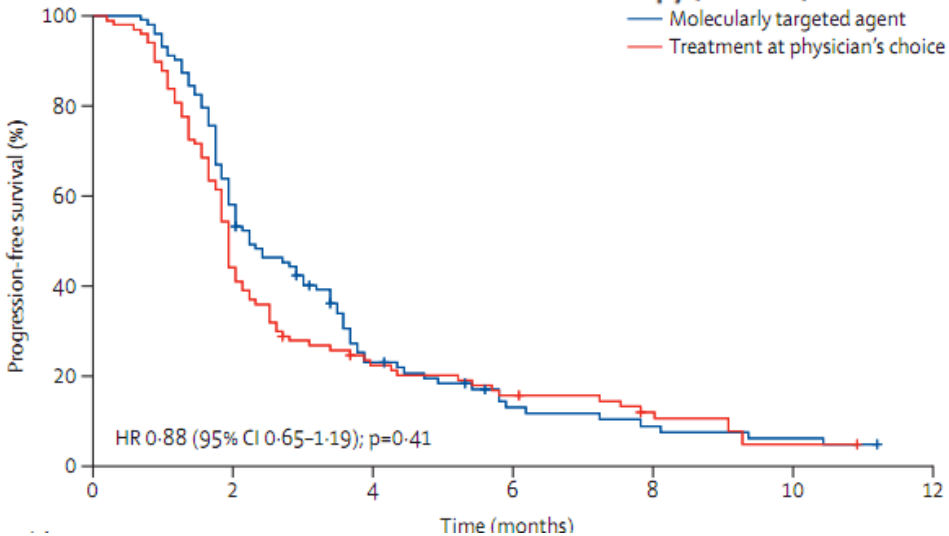
Hatswell et al, BMJ Open 2016;6(6):e011666

Observation vs randomization









Henke et al, Lancet 2003;362:1255-60; Kopetz et al, J Clin Oncol 2009;27:1732-3; Kris et al, JAMA 2014;311:1998-2006; Le Tourneau et al, Lancet Oncol 2015;16:1324-34

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Why do we randomize?

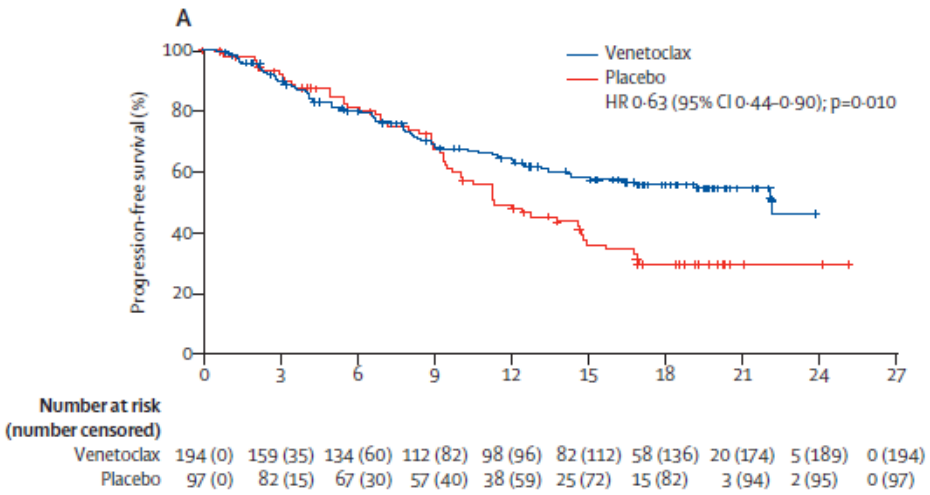
- To control for selection bias in known and unknown prognostic factors
- To avoid the effects of stage migration and improved supportive care
- To have reliable conclusions about time-to-event endpoints
- To disentangle the prognostic and the predictive impact of molecular alterations
- To validate predictive biomarkers
- To allow future validation of surrogate endpoints
- To allow more informative health economics

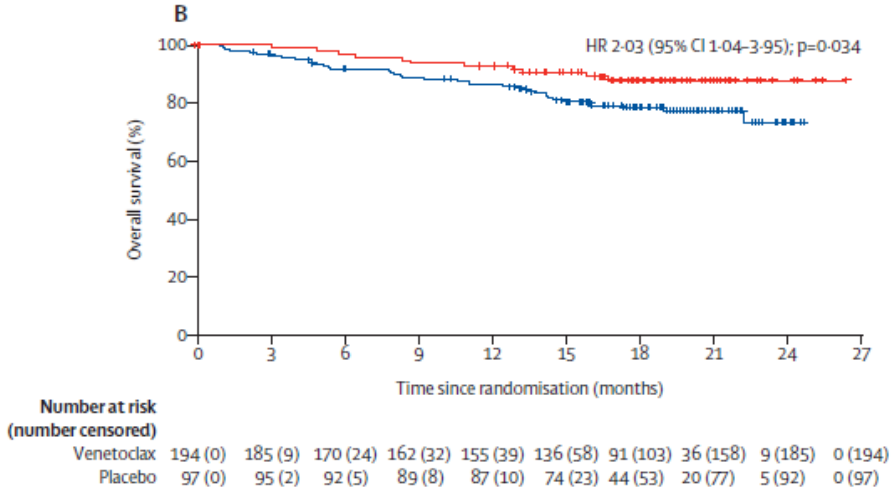
Toxicity may be an issue

SHIVA Trial

	Patients who received molecularly targeted agents (n=100*)			Patients who received cytotoxic chemotherapy (n=91†)		
	Grade 2 necessitating drug interruption or delay‡	Grade 3	Grade 4	Grade 2 necessitating drug interruption or delay	Grade 3	Grade 4
Any event§	12 (12%)	36 (36%)	7 (7%)	9 (10%)	28 (31%)	4 (4%)

BELLINI Trial





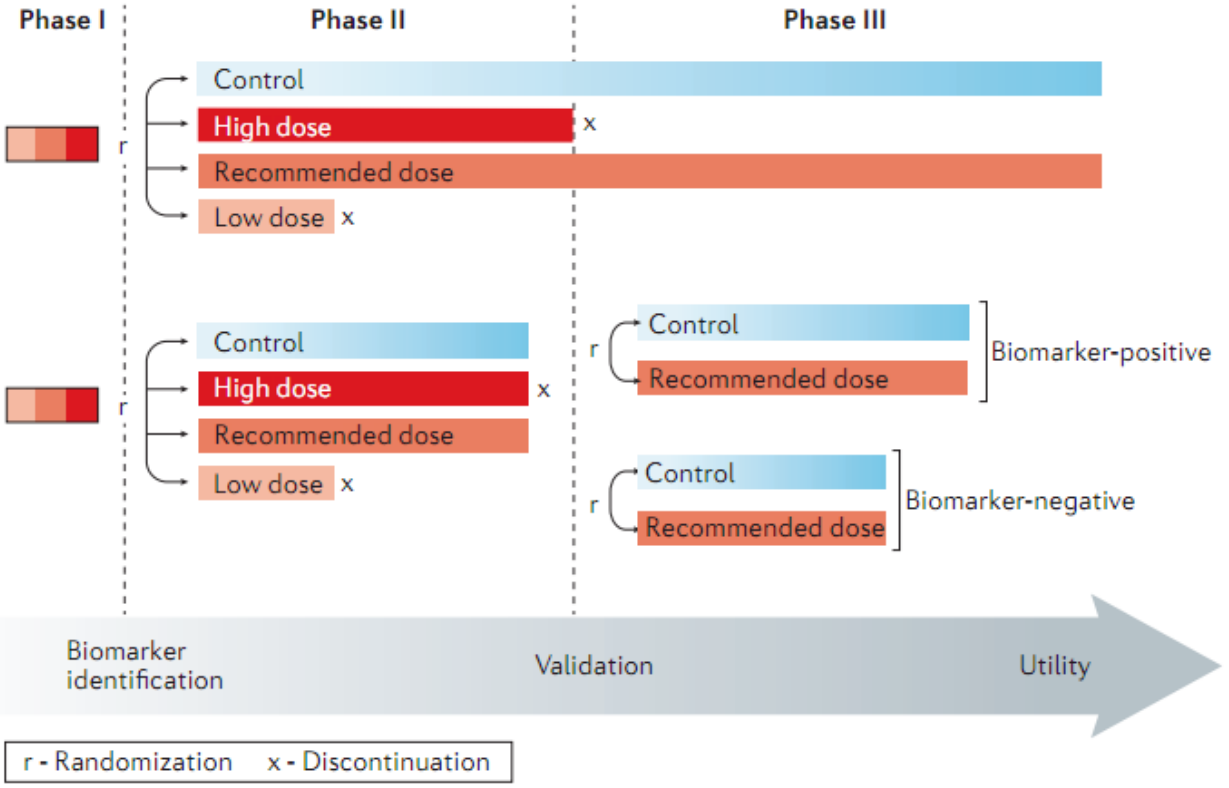
Le Tourneau et al, Lancet Oncol 2015;16:1324-34; Kumar et al, Lancet Oncol 2020;21:1630-1642

If possible, randomize

OPINION

Precision medicine needs randomized clinical trials

Everardo D. Saad, Xavier Paoletti, Tomasz Burzykowski and Marc Buyse



Saad et al, Nat Rev Clin Oncol 2017;14:317-23

The usual arguments against

- The ethical
  - It can go both ways
- The biological
  - Beware the tautology
  - N-of-1
- The practical
  - Yes, but…

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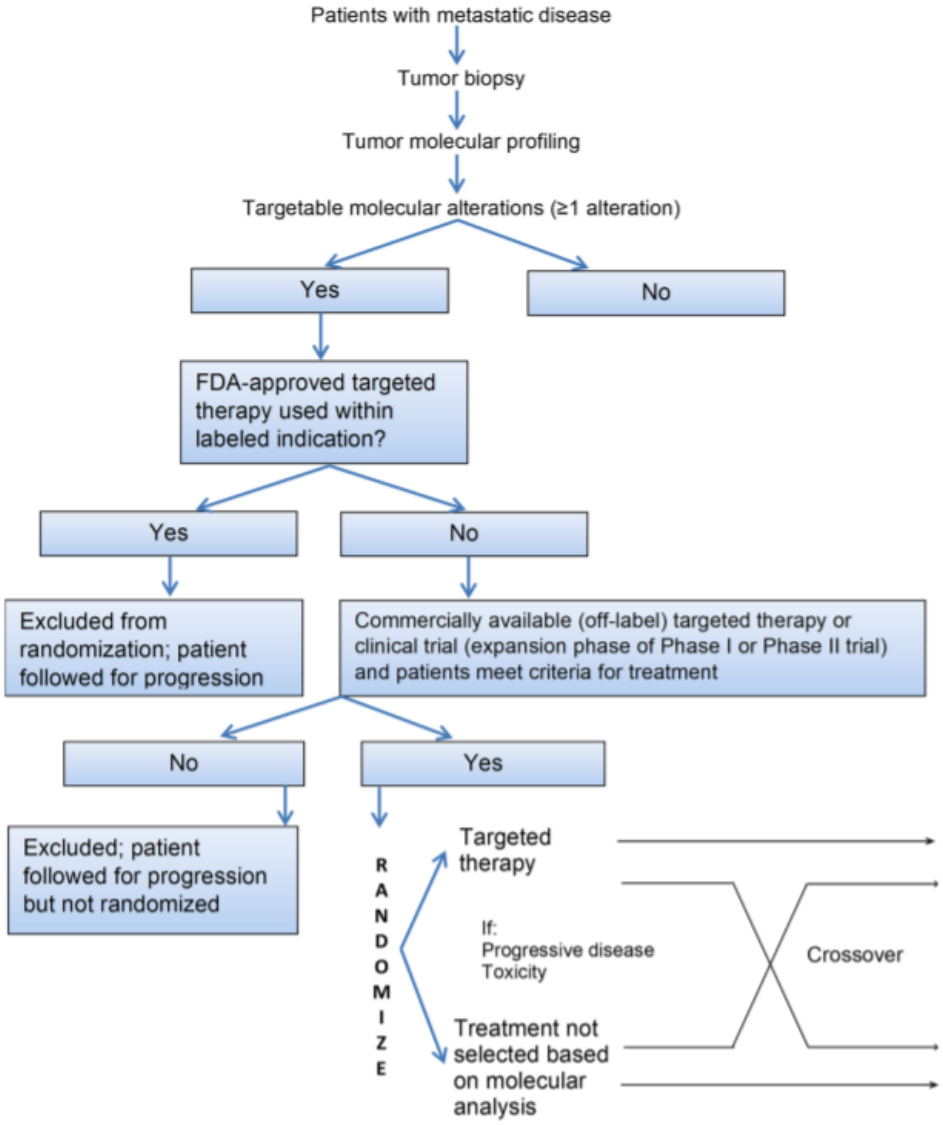
Control arms

- Standard of care (SOC)
- Treatment of physician's choice (TPC)
- Immediate vs. delayed administration (e.g., crossover)
- SOC + experimental
- TPC + experimental
- Single agent vs. combination
- Different doses
- Different schedules
- Different durations (including randomized discontinuation)

IMPACT2 Trial

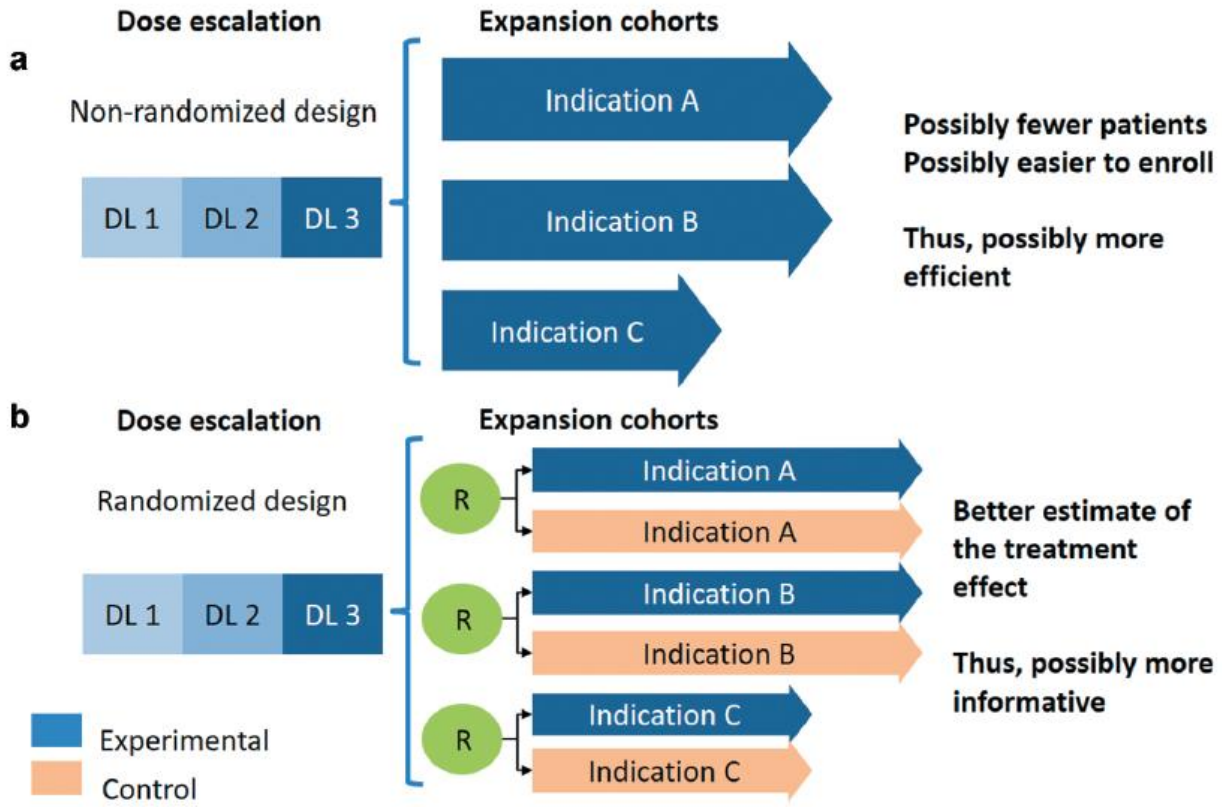


Tsimberidou et al, NPJ Precis Oncol 2021;5:21

Randomizing in expansion cohorts

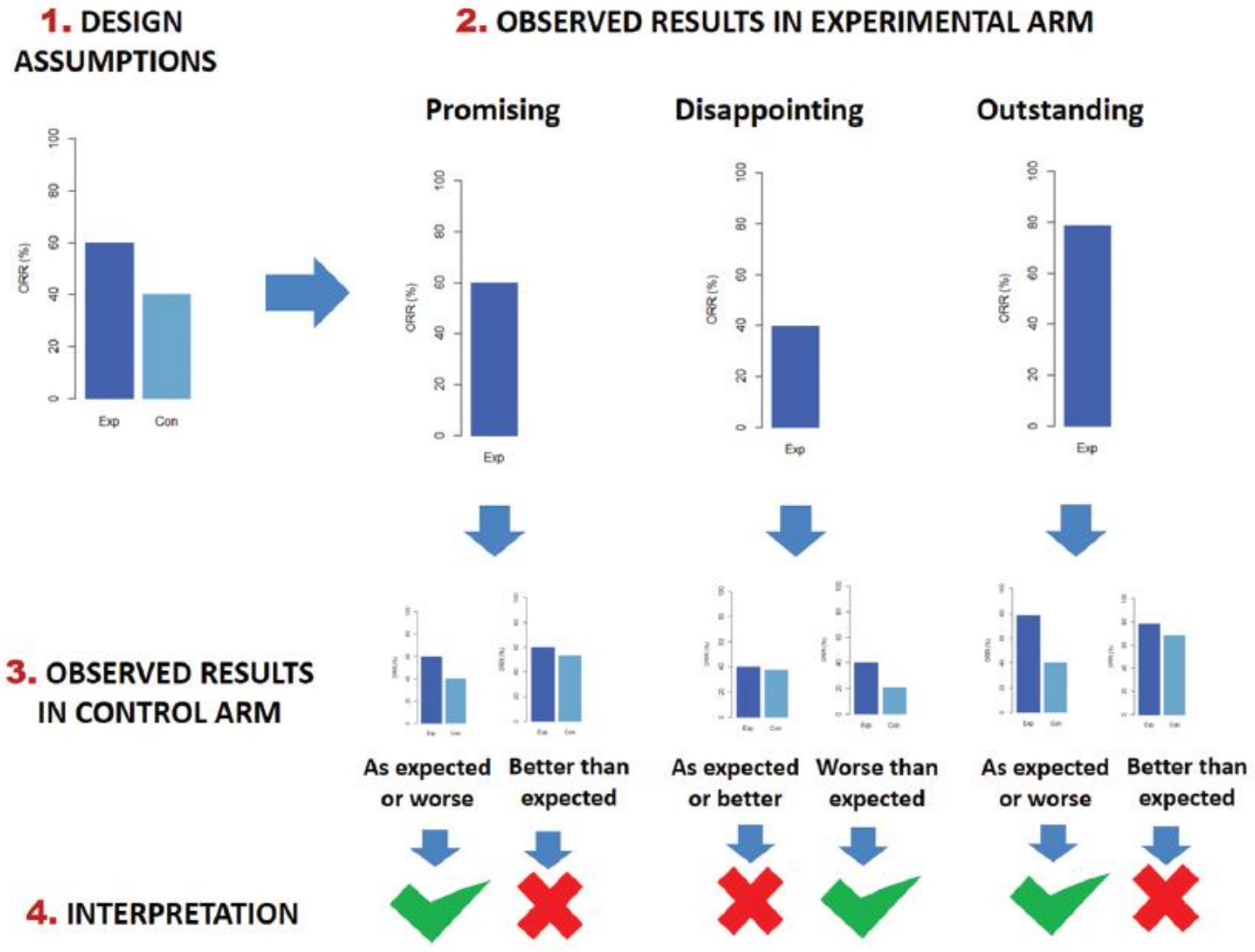
REVIEW

Considerations on the mechanics and sample sizes for early trials of targeted agents and immunotherapy in oncology



Coart and Saad, https://doi.org/10.1080/23808993.2021.1915693

Control arm for calibration



Coart and Saad, https://doi.org/10.1080/23808993.2021.1915693

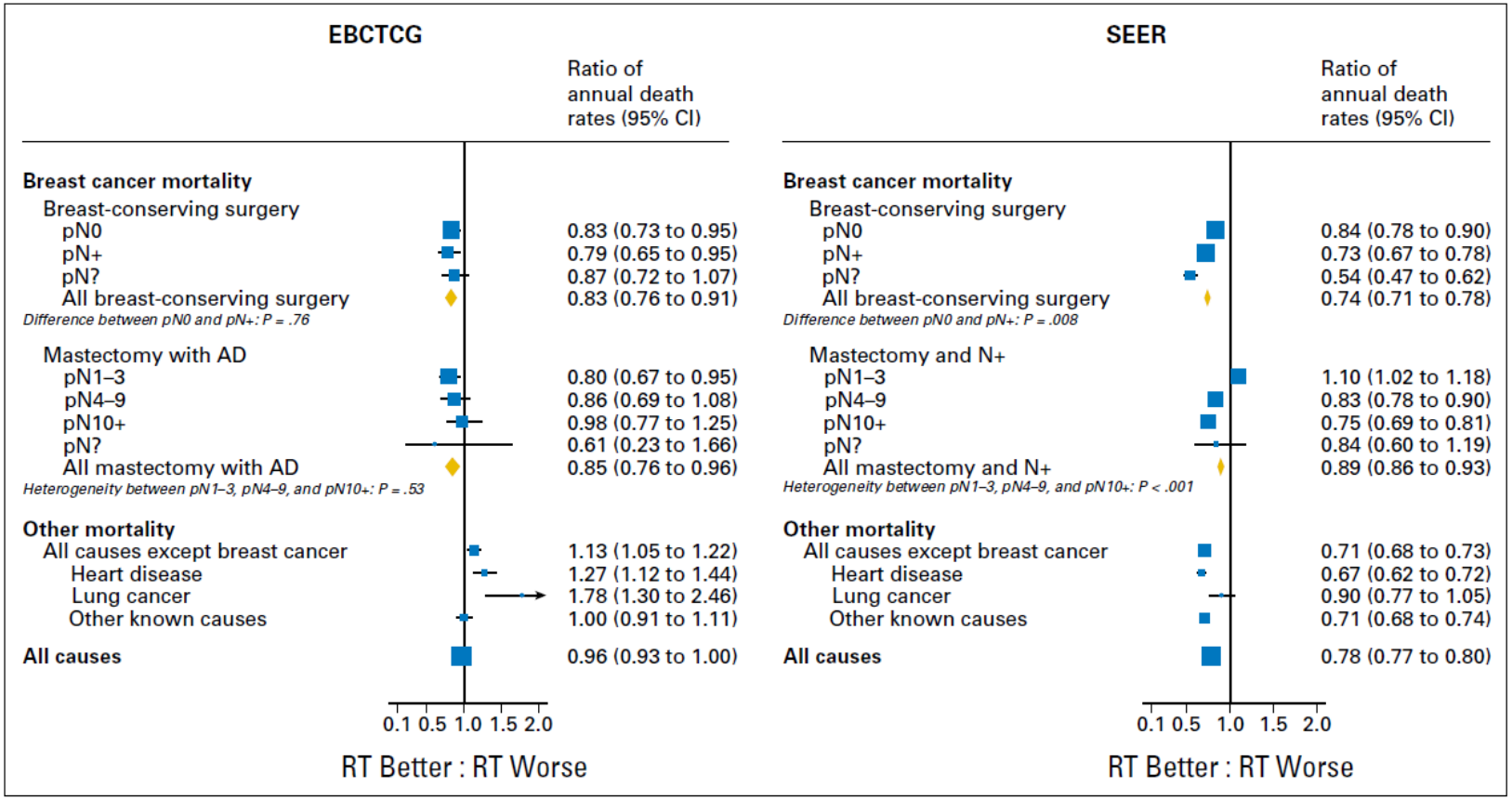
Big and real-world data

https://blogs.bmj.com/bjsm/2021/05/27/hop-distance-the-elephant-in-the-room/

RCTs vs observational data

The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.



Collins et al, N Engl J Med 2020;382:674-8; McGale et al, J Clin Oncol 2016;34:3355-7

When can we forgo randomization?

Role of randomized phase III trials in an era of effective targeted therapies

Manish R. Sharma and Richard L. Schilsky

Box 1 | Six criteria for targeted therapies to be approved without a phase III trial

- Preclinical studies should confirm that the drug targets a driver of the malignant phenotype
- An analytically validated assay should be available to identify which tumors have the intended target
- The drug should be studied in a population of patients that are selected on the basis of having the target
- The response rate and average response duration should indicate a clinically meaningful improvement over that which would be expected based on historical data for the existing standard of care in the same subset of selected patients
- These two outcome measures (response rate and response duration) must be interpreted in the context of the disease setting
- There should be no life-threatening safety concerns about the drug based on the total body of available data

Sharma and Schilsky, Nat Rev Clin Oncol 2012;9:208

Conclusion – 1

- We will continue do have RCTs:
  - How about the next NTRK or KRAS G12C inhibitor?
    - Don’t we have dozens of RCTs for anti-HER2, EGFR and ALK therapies?
  - How about biomarker and surrogate validation?
- We will continue to rely on some evidence from non-RCTs, but we need to consider:
  - The magnitude of the unmet need
  - The strength of the biological rationale
  - The rarity of the indication
  - The reliability of new methodology to minimize bias

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Conclusion – 2

- Questions for the near future:
  - Is the seduction of improved technology sufficient to relinquish on methodology?
  - Can we safely replace RCTs by synthetic controls, *in-silico* trials, causal inference methods?
  - Can we realistically and reliably develop criteria to forgo randomization?
  - What is more acceptable: randomize early or late?
  - Can we safely reverse the title of this talk?

"Precision Oncology and the Limits of Randomization"