Optimizing the Design of Breast Cancer Trials

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Optimizing the Design of Breast Cancer Trials

Oleg Gluz

West German Study Group/Breast Center Niederrhein

University Clinics Cologne

Challenge of clinical trials

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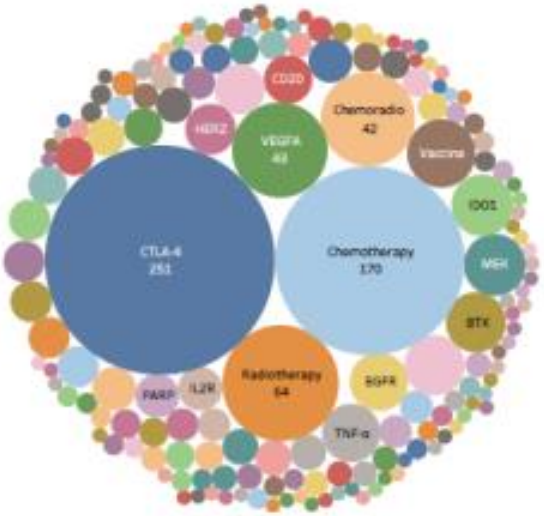
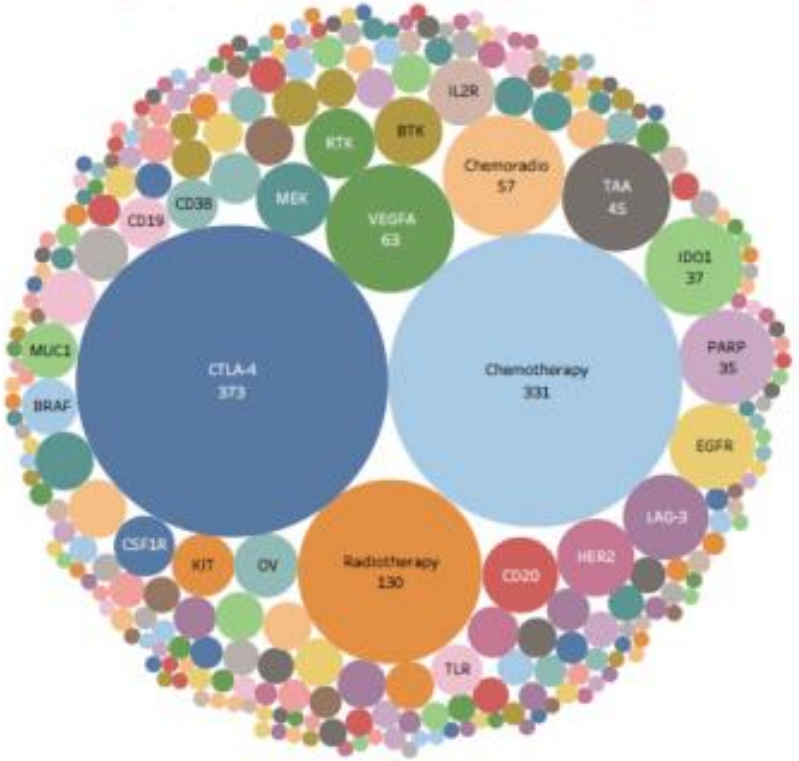
835 more combo trials and 100 more targets in 17 months

In 2017, **1,102** active trials testing **165** targets



Currently, **1,937** active trials testing **275** targets



Tang et al, *Ann Oncol*, 2018; CRI update in Feb 2019

Development cycle of drugs

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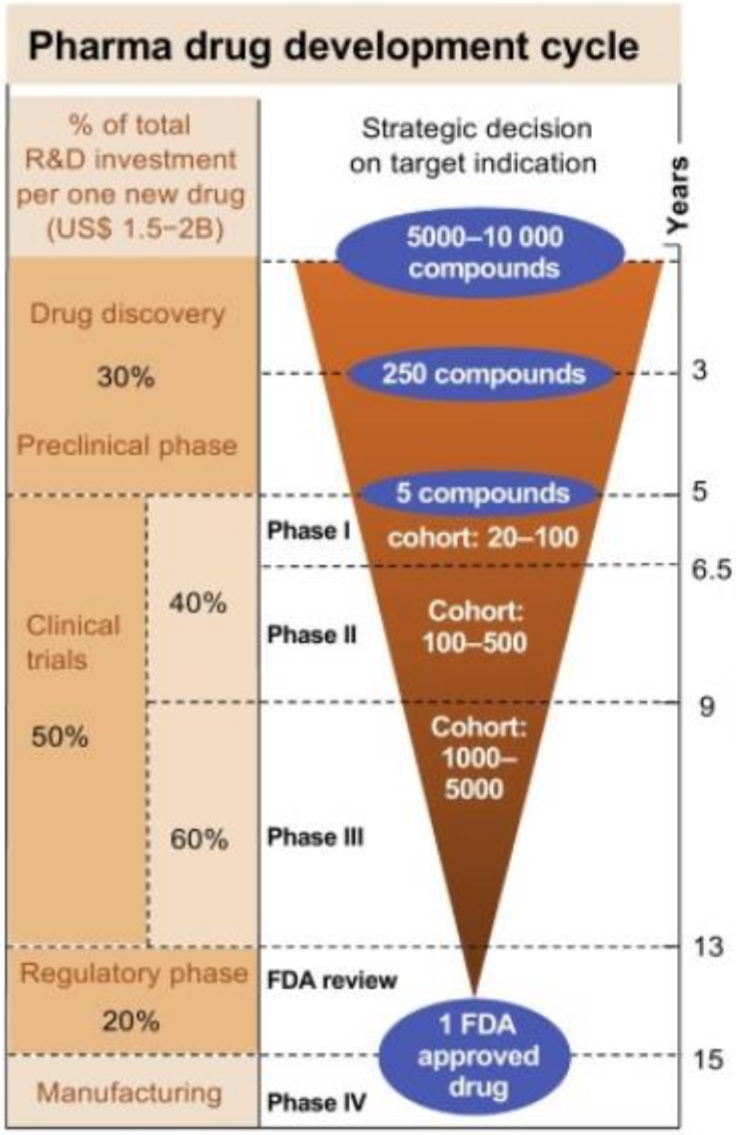
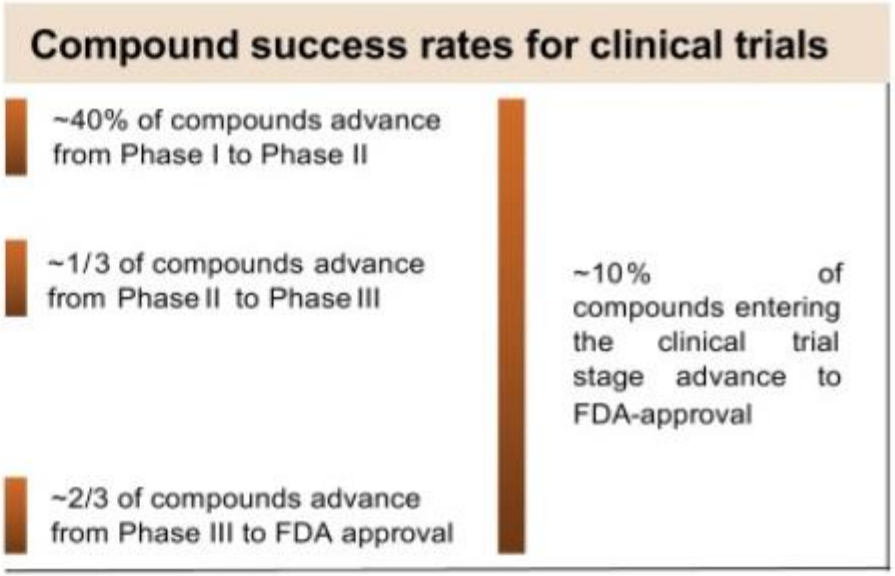
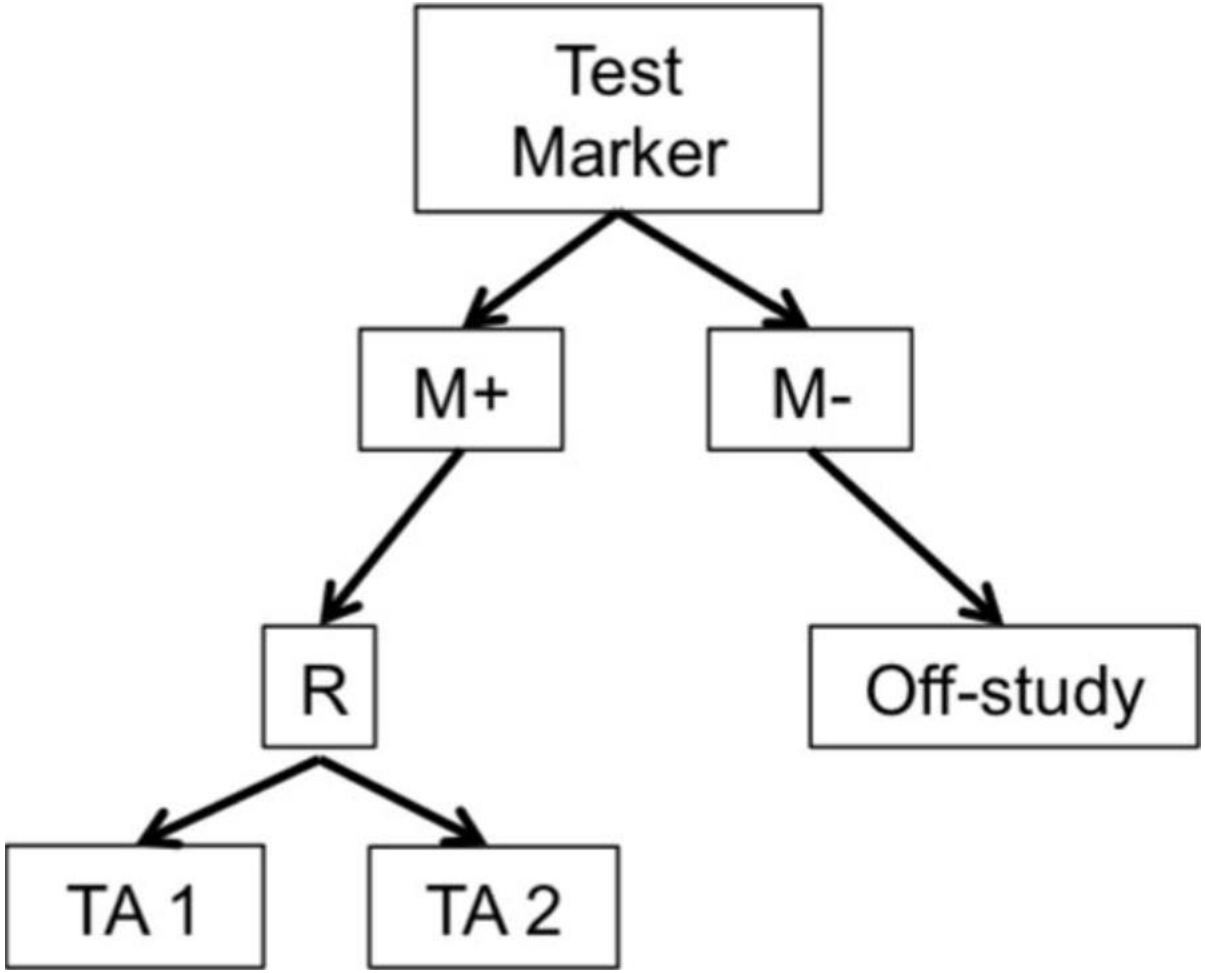




Enrichement design: the only way to make a randomized study to be focused



The New England Journal of Medicine

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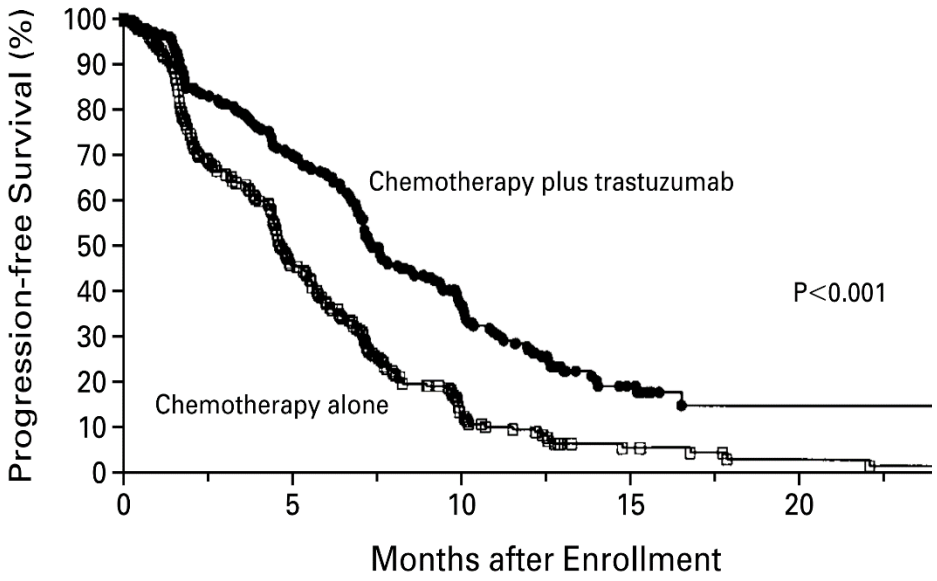
VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

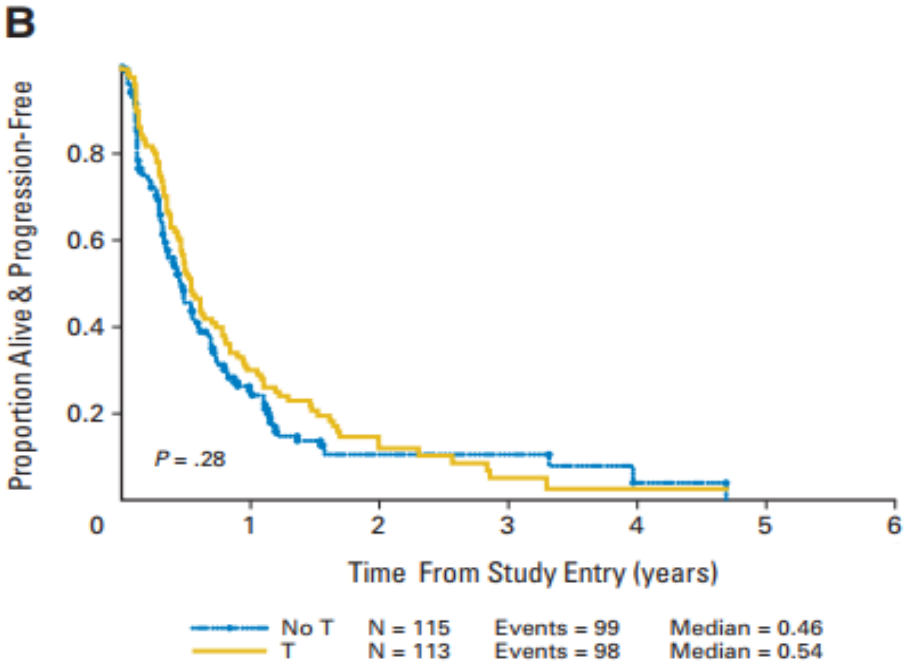


VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840

Andrew D. Seidman, Donald Berry, Constance Cirrincione, Lyndsay Harris, Hyman Muss, P. Kelly Marcom, Grandella Gipson, Harold Burstein, Diana Lake, Charles L. Shapiro, Peter Ungaro, Larry Norton, Eric Winer, and Clifford Hudis



Study in an unselected population would be negative

Multistage-Arm trial

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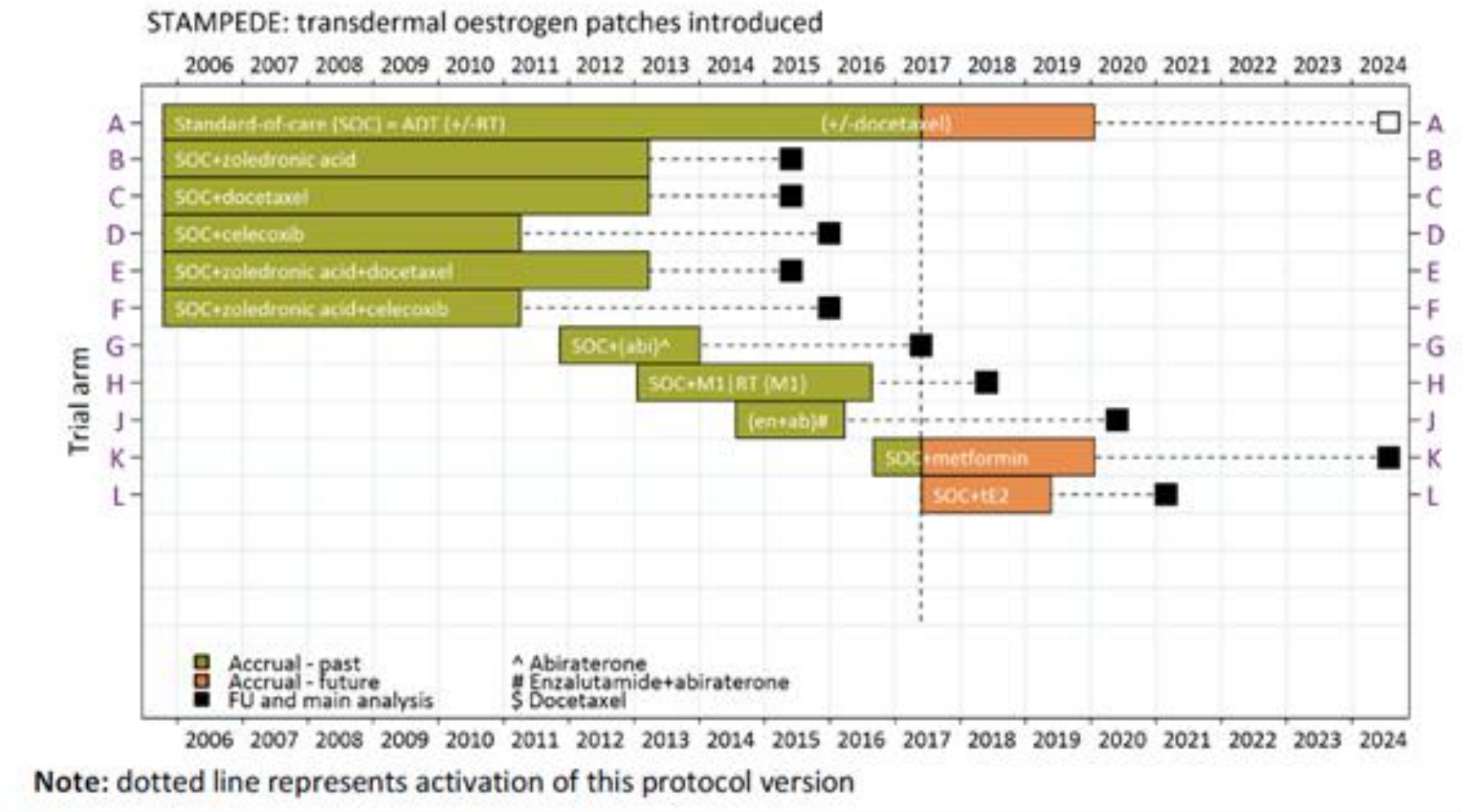
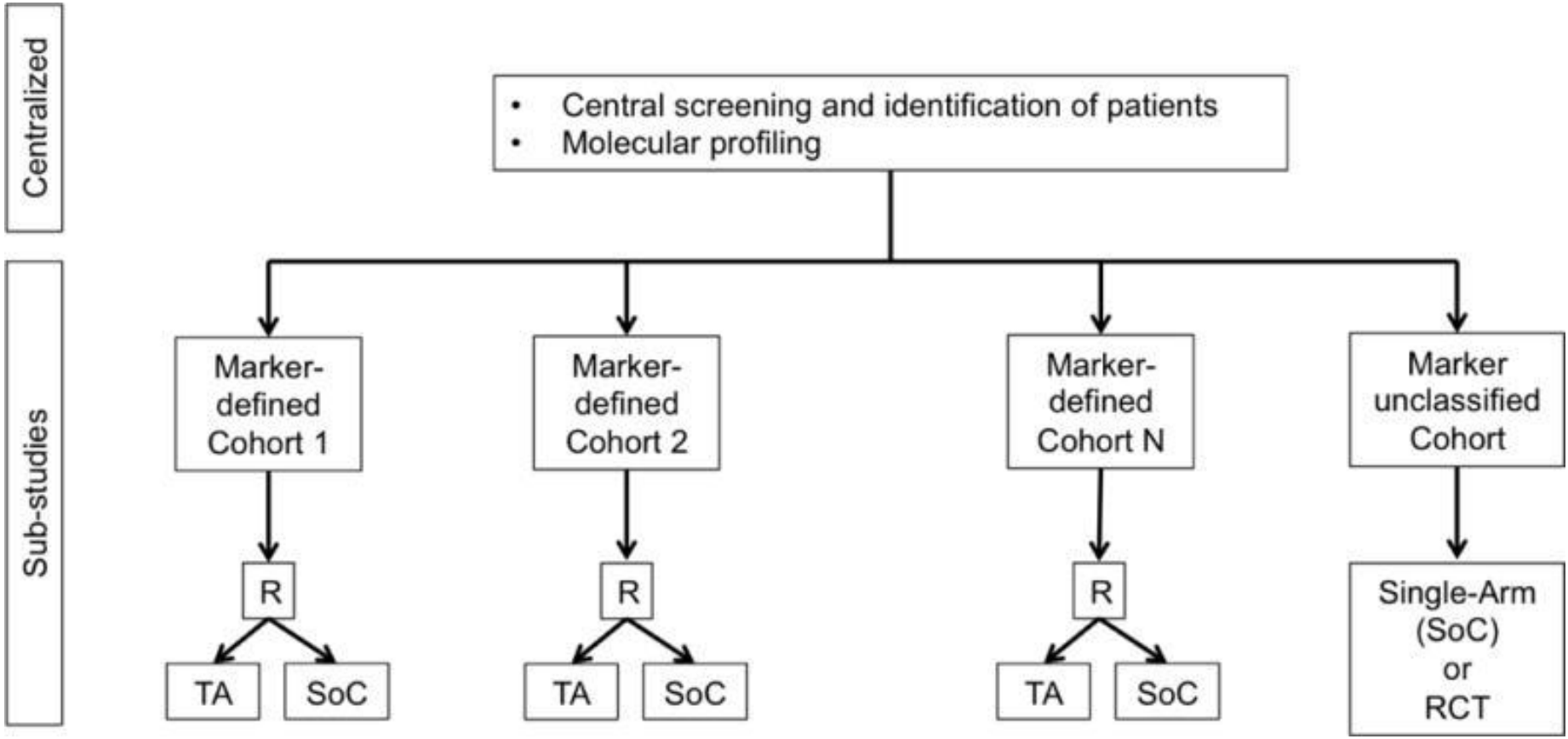
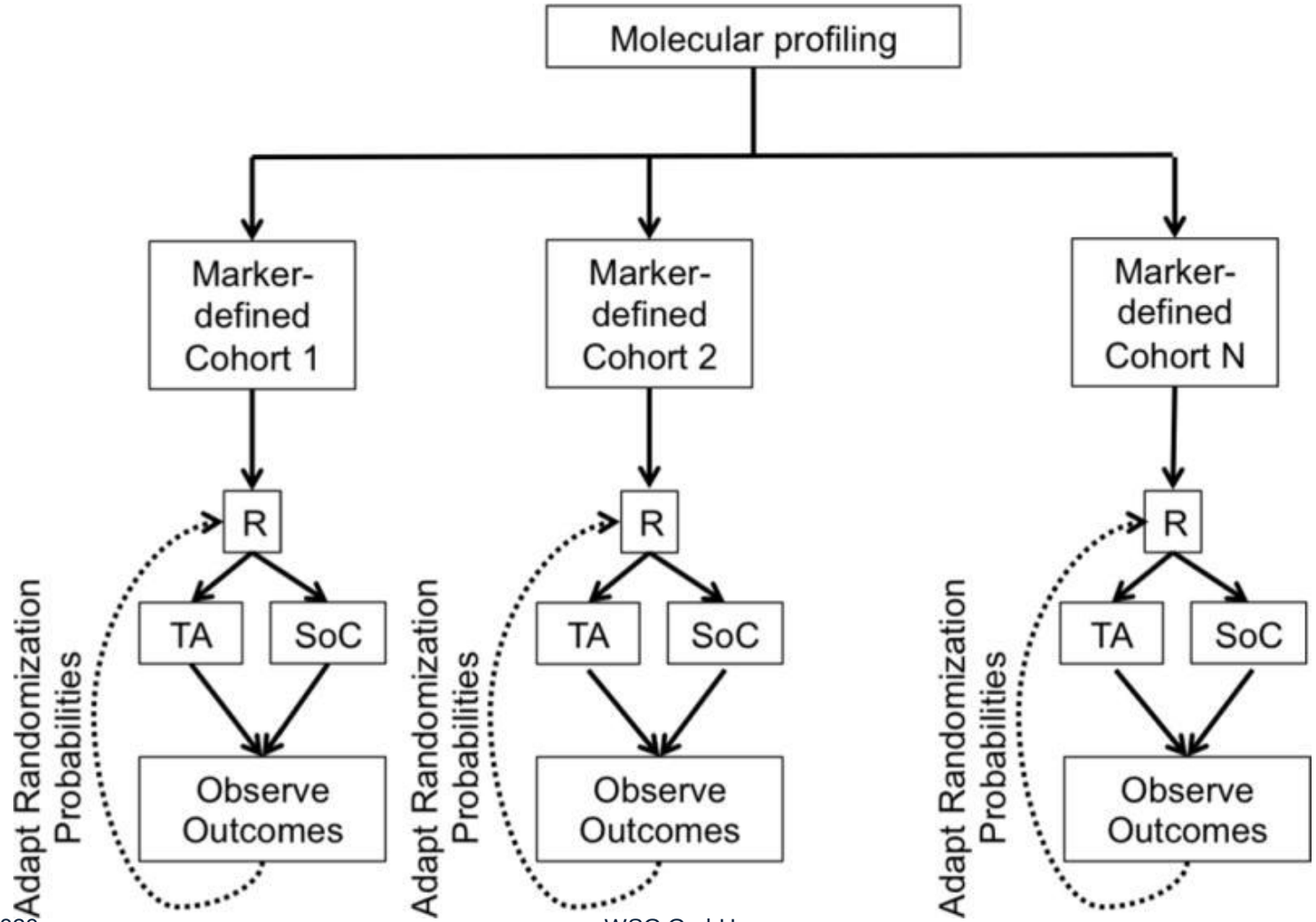


Note: dotted line represents activation of this protocol version

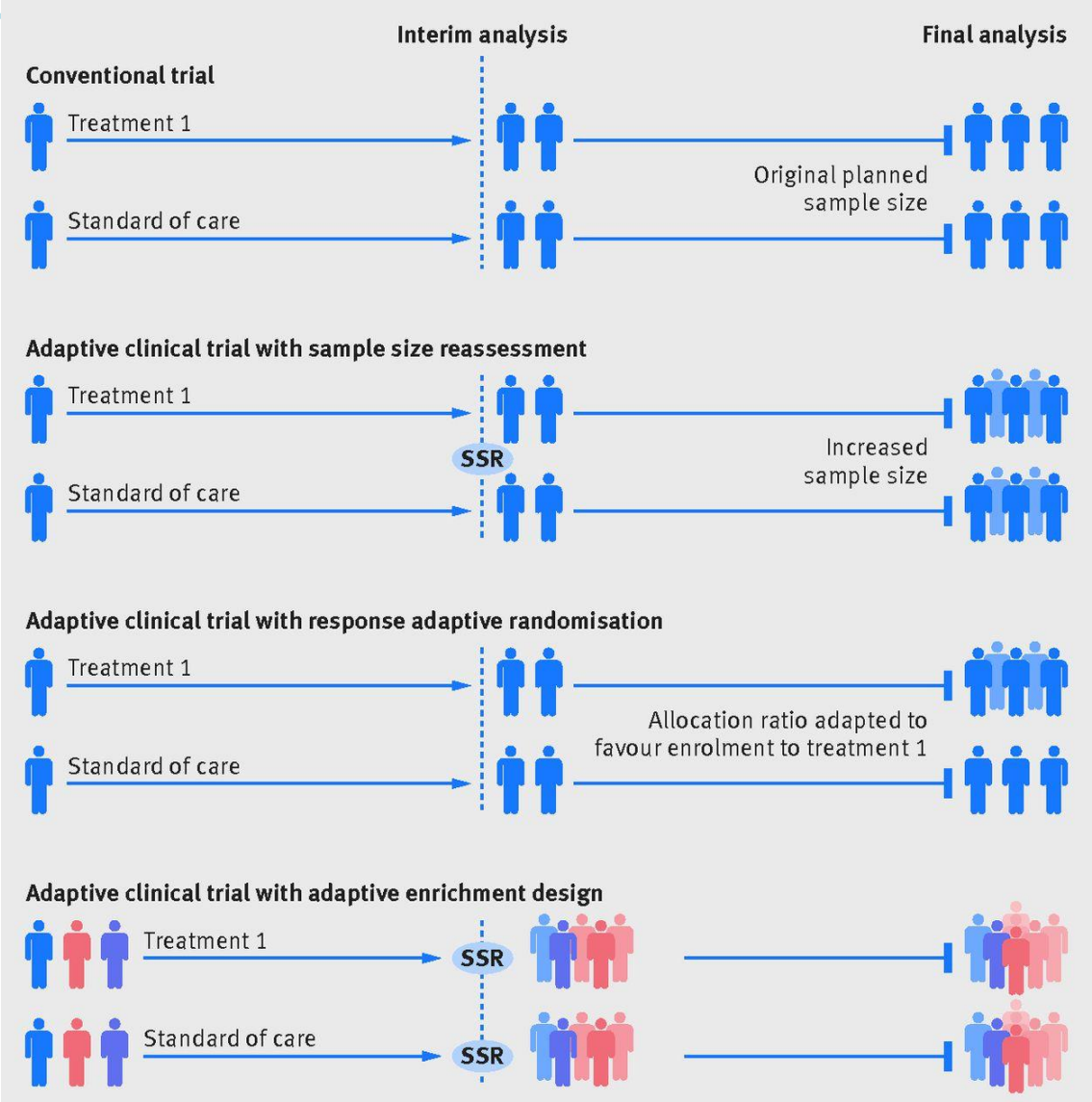
Umbrella Protokoll



Adaptive Design

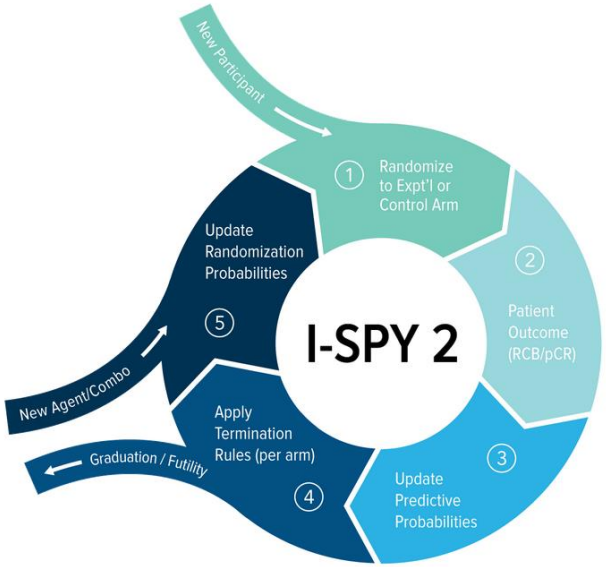


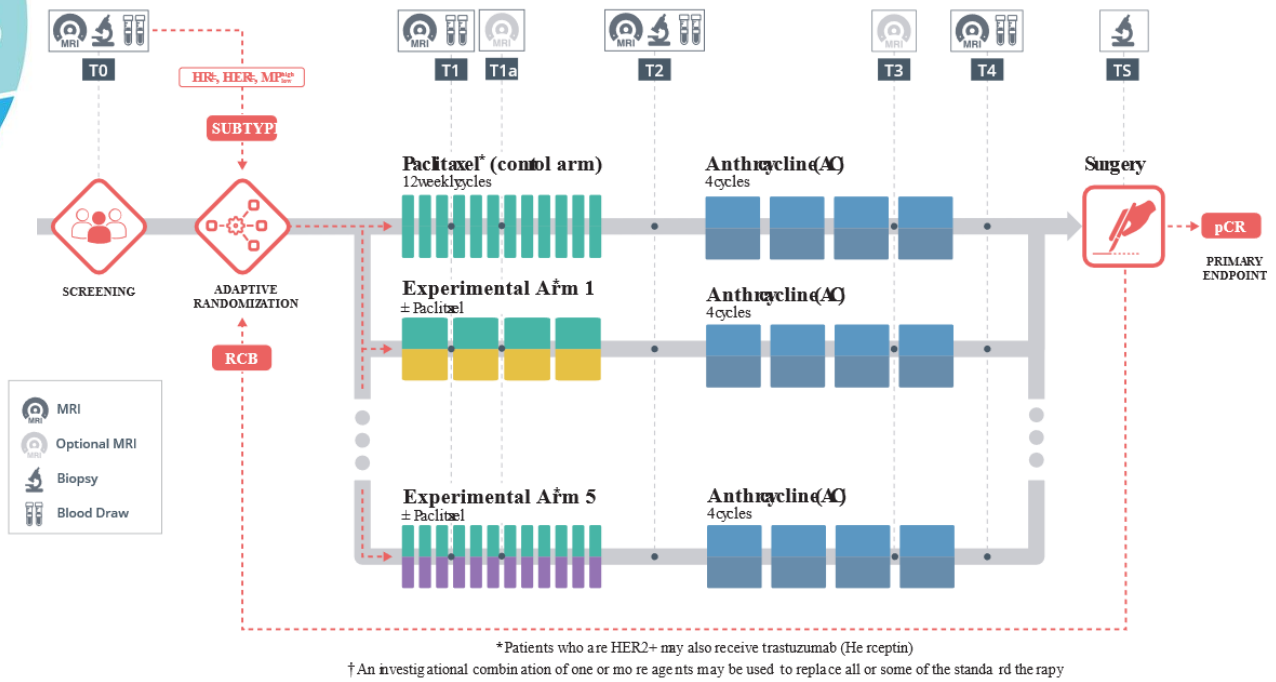
Adaptive vs. enriched design



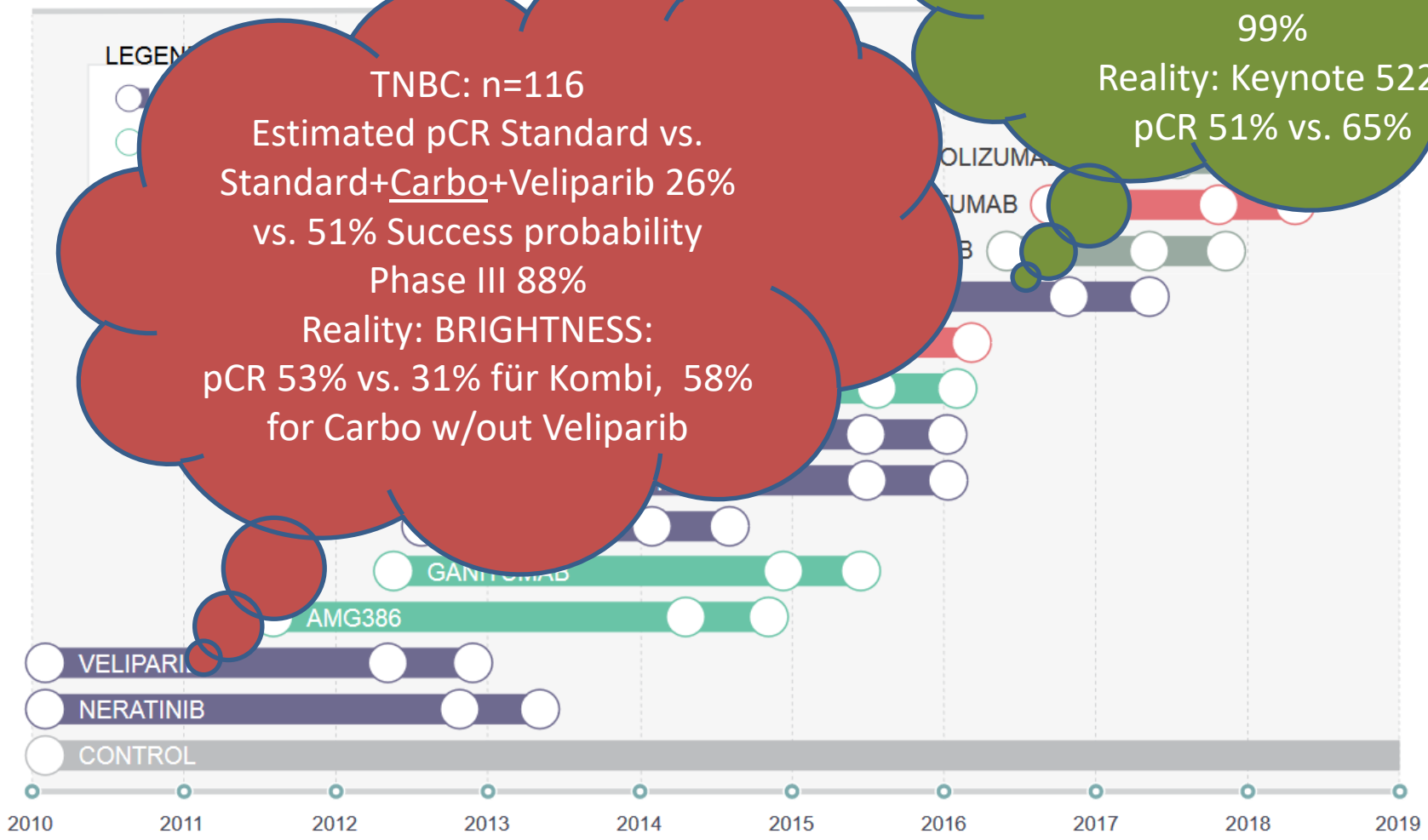
Thorlund et al. BMJ 2018

I-SPY

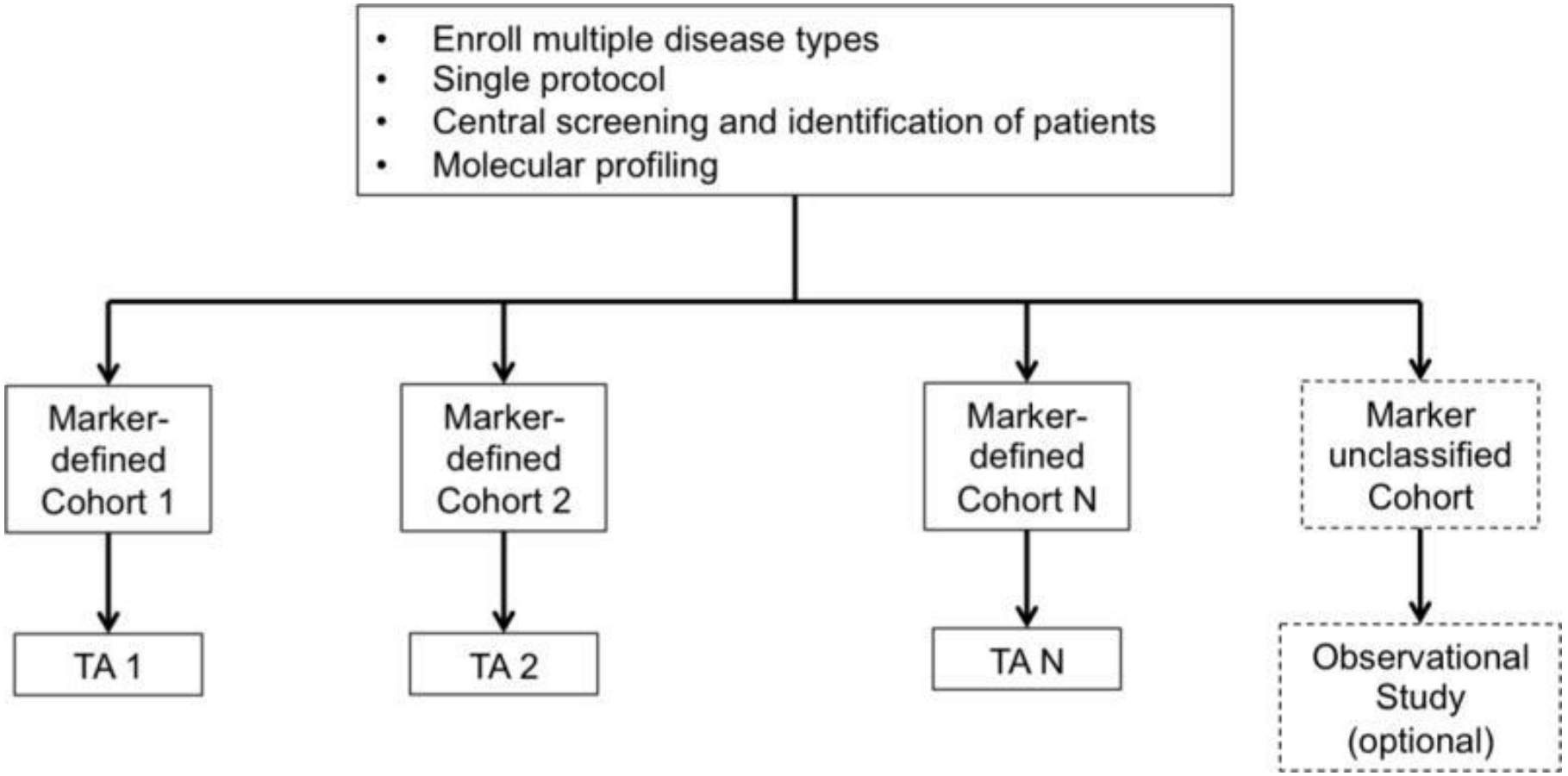

New Participant
1 Randomize to Expt'l or Control Arm
2 Patient Outcome (RCB/pCR)
3 Update Predictive Probabilities
4 Apply Termination Rules (per arm)
5 Update Randomization Probabilities
New Agent/Combo
Graduation / Futility
I-SPY 2


T0
T1
T1a
T2
T3
T4
TS
SUBTYPE
SCREENING
ADAPTIVE RANDOMIZATION
RCB
Paclitaxel* (control arm)
12 weekly cycles
Anthracycline (AC)
4 cycles
Experimental Arm 1
± Paclitaxel
Experimental Arm 5
± Paclitaxel
Surgery
pCR
PRIMARY ENDPOINT
MRI
Optional MRI
Biopsy
Blood Draw
*Patients who are HER2+ may also receive trastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

I-SPY


TNBC: n=116
Estimated pCR Standard vs. Standard+Carbo+Veliparib 26% vs. 51% Success probability Phase III 88%
Reality: BRIGHTNESS: pCR 53% vs. 31% für Kombi, 58% for Carbo w/out Veliparib
TNBC: n=103
Estimated pCR Standard vs
Standard+Pembro 22% vs
62%
Success probability Phase I
99%
Reality: Keynote 522:
pCR 51% vs. 65%
AMG386
NERATINIB
CONTROL
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019

Basket trial



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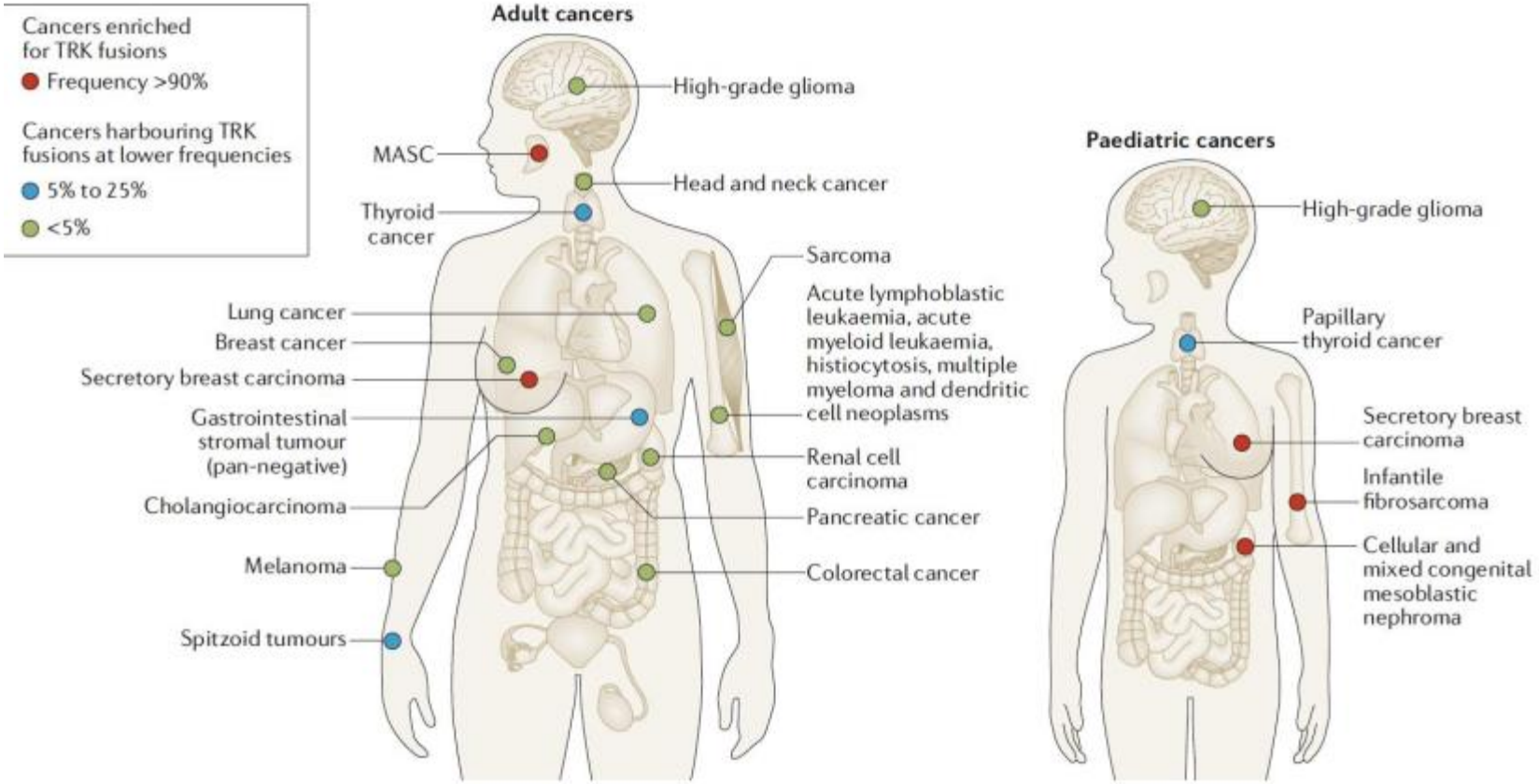
NTRK fusion

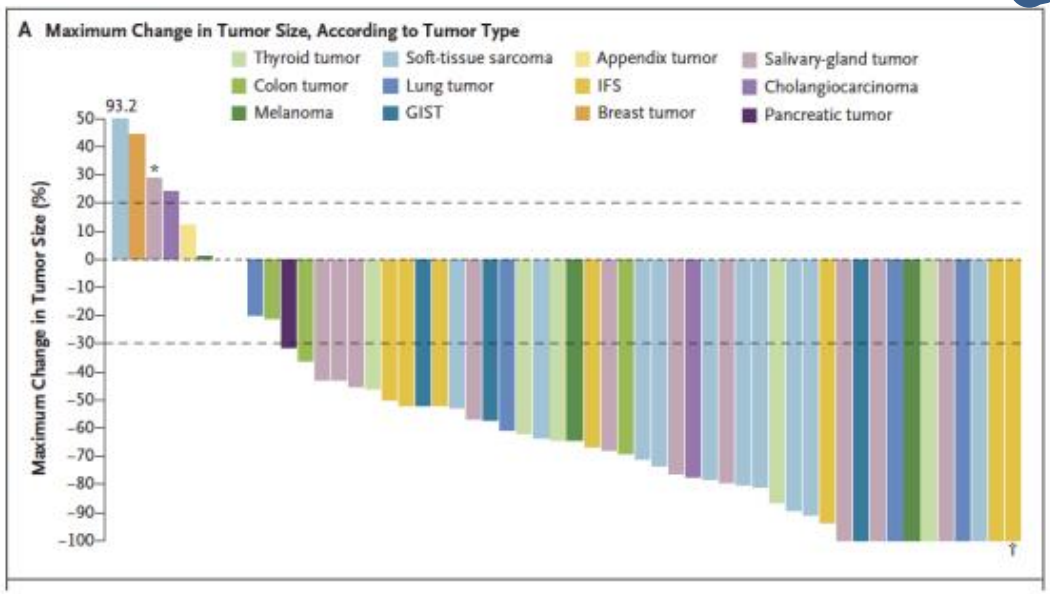


No phase III possible

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion-Positive Cancers in Adults and Childre

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Dem
M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati,
M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik,
J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski,
F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed,
M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox,
D.S. Hawkins, D.S. Hong, and D.M. Hyman



Pembrolizumab
1. Agnostic approval

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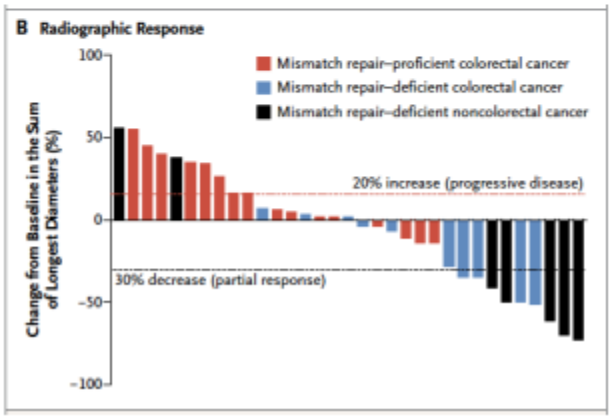
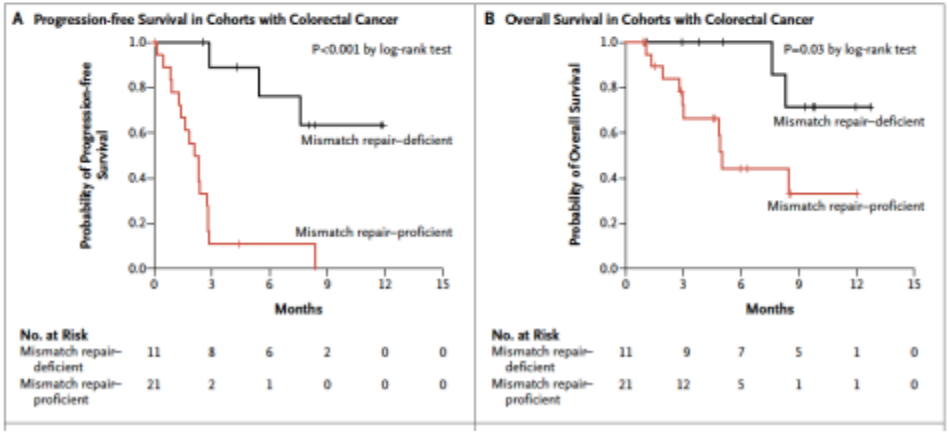
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.





ESCAT criteria

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Table 2. The ESCAT

	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
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	III-A: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types III-B: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved	Clinical trials to be discussed with patients
	IV: pre-clinical evidence of actionability	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models IV-B: actionability predicted *in silico*	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

- ✓ **Molecular classification:**

Based on Clinical evidence for molecular targets ESCAT (*Mateo, Ann Oncol 2019*)

- ✓ I: targets ready for implementation in routine clinical decisions
- ✓ II: investigational targets that likely define a patient population that benefits from a targeted drug, but additional data are needed
- ✓ III: clinical benefit previously demonstrated in other tumors types or for similar molecular targets
- ✓ IV: preclinial evidence of actionability
- ✓ V: evidence supporting co-targeting approaches
- ✓ X: lack of evidence for actionability

Mateo, Ann Oncol 2019

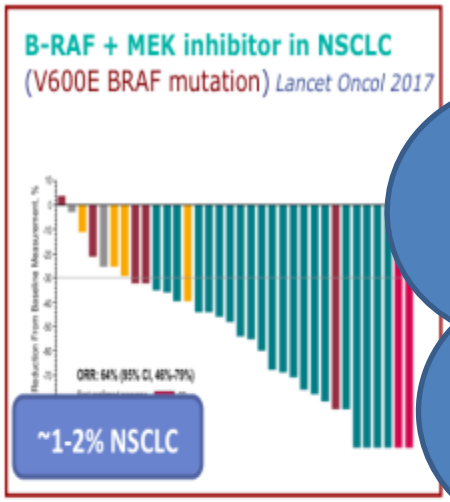
Table 2. The ESCAT

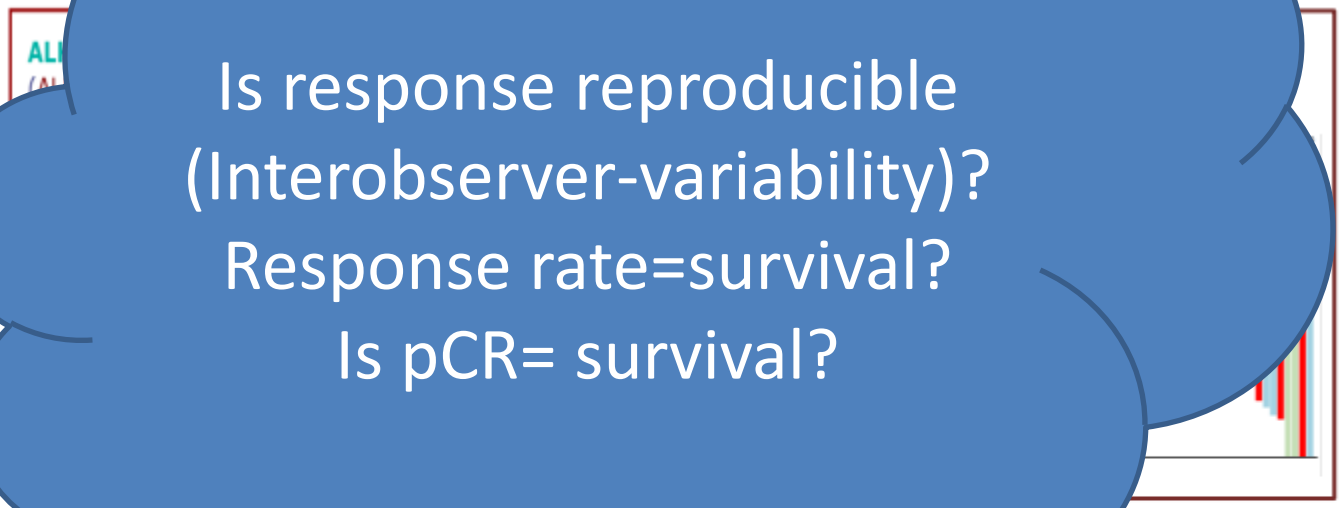
	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results 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

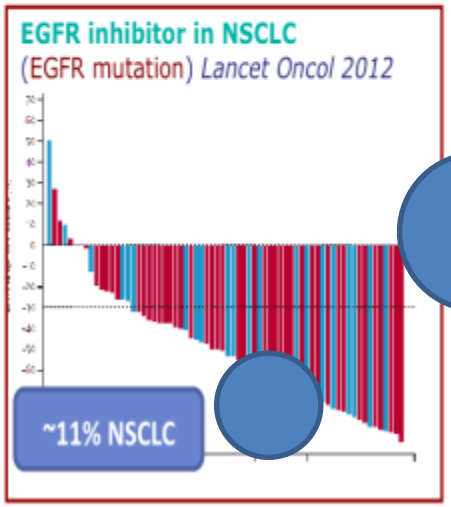
Examples: *EGFRm lung, T790M lung, ALKr lung, ROS1 lung, BRAFm lung/melan, HER2amp breast, METm lung, etc.*

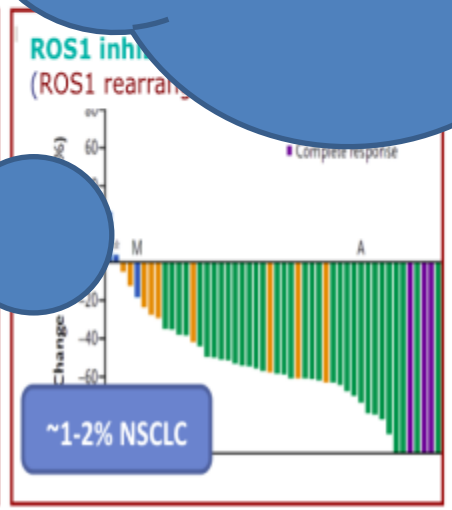
Mateo, Ann Oncol 2019

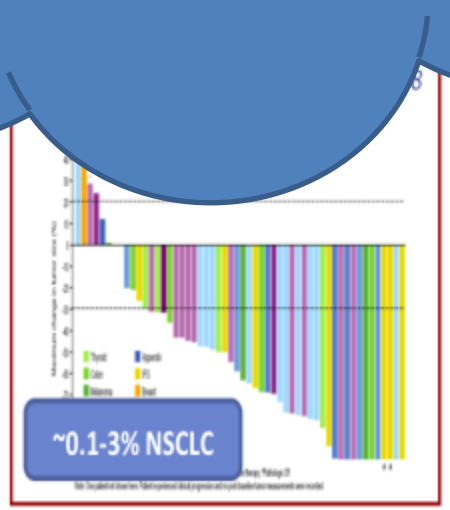
Response rates

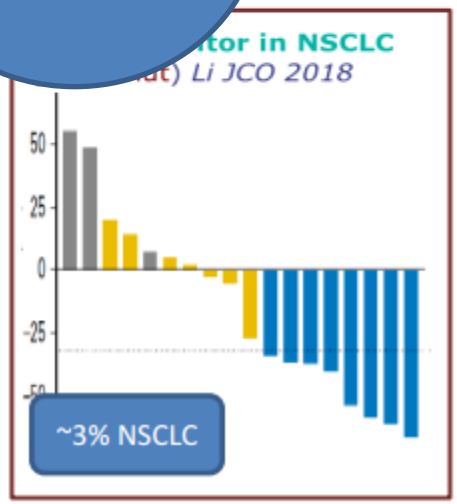










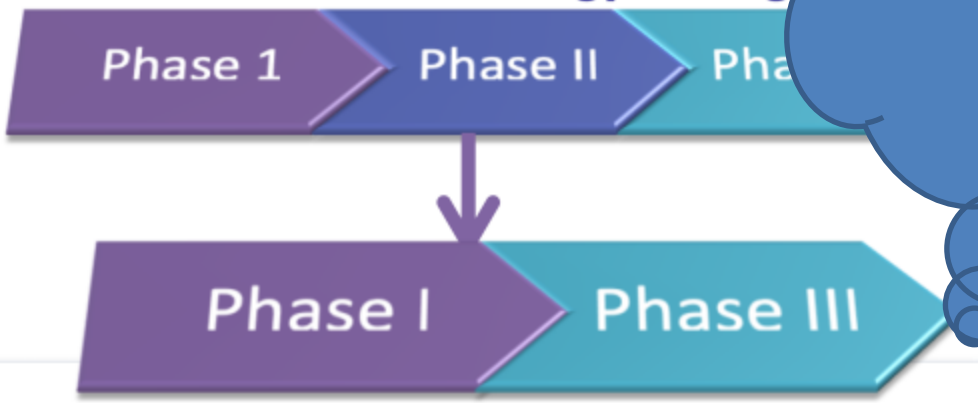


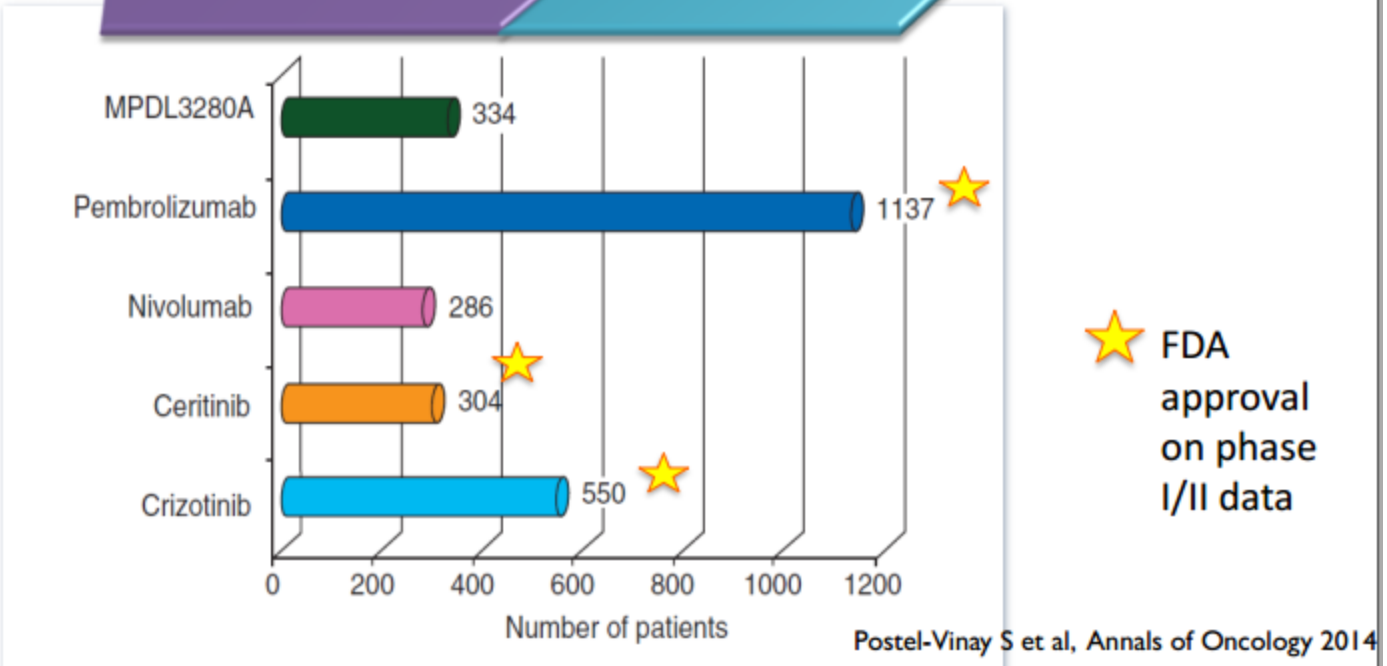
Is response reproducible (Interobserver-variability)?
Response rate=survival?
Is pCR= survival?

Rapid development

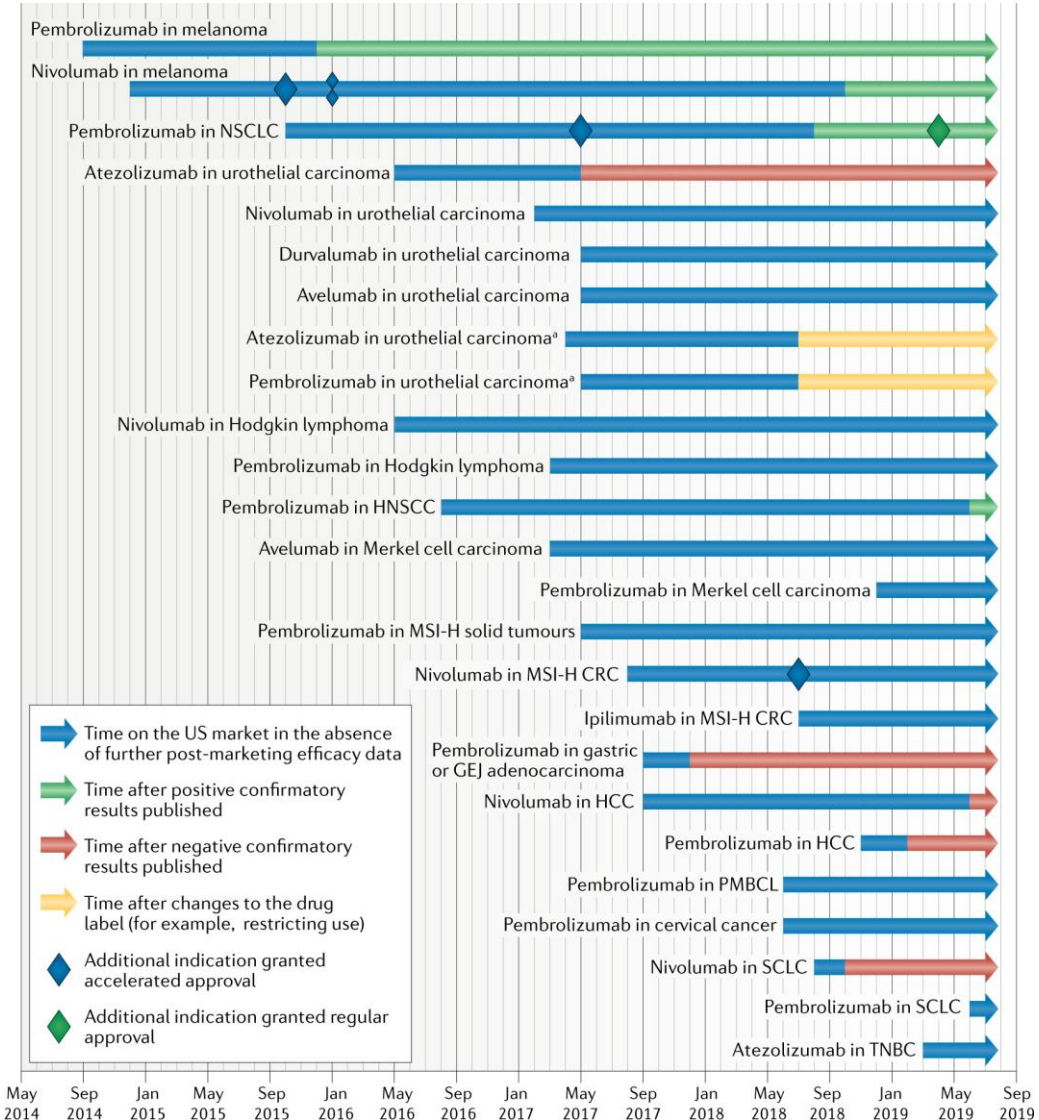
Would Real-World Evidenz be a better alternative?

The new trend in oncology drug





Confirmatory trials?



Gil/Pasad Nat Rev 2019

Flatiron Plattform

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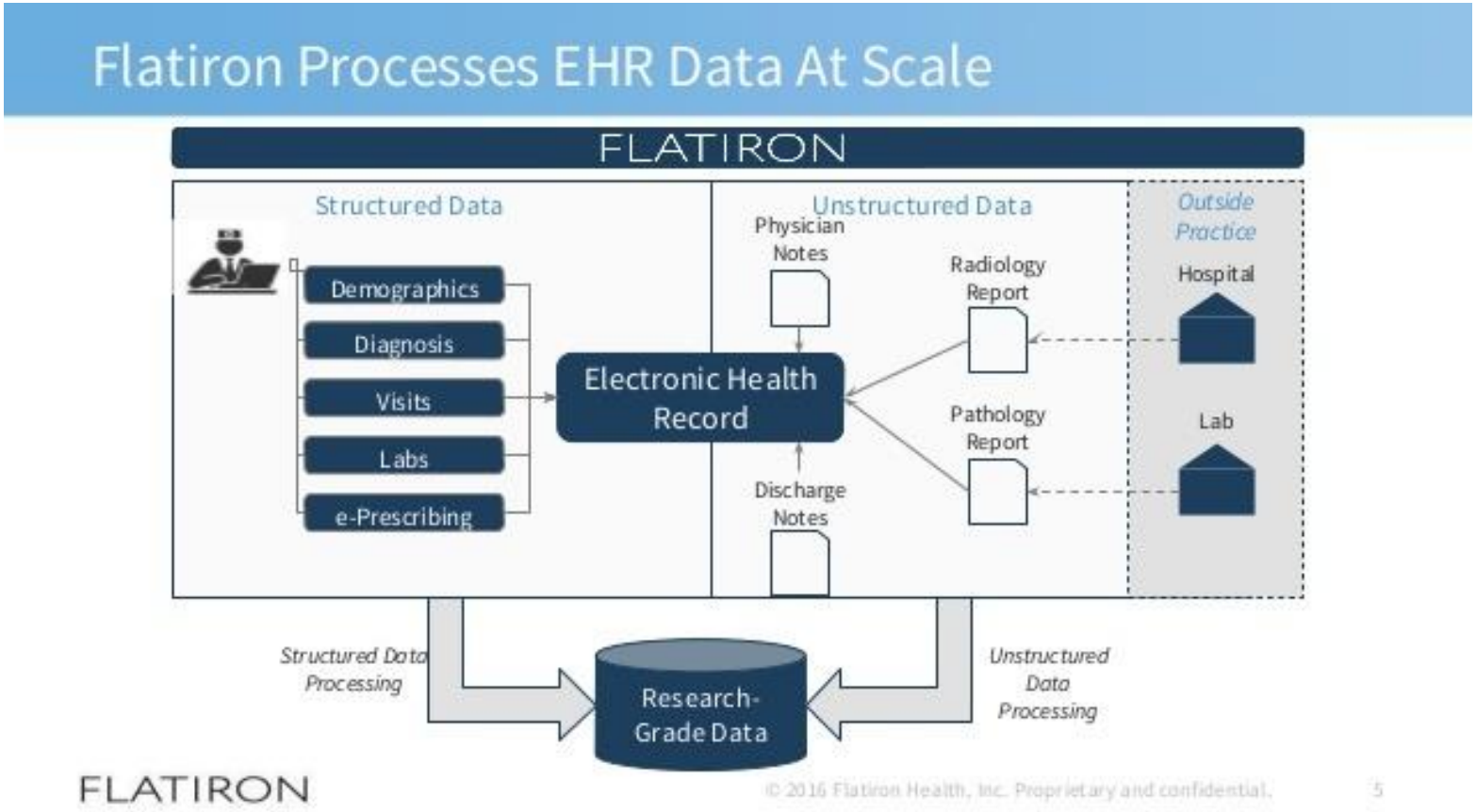


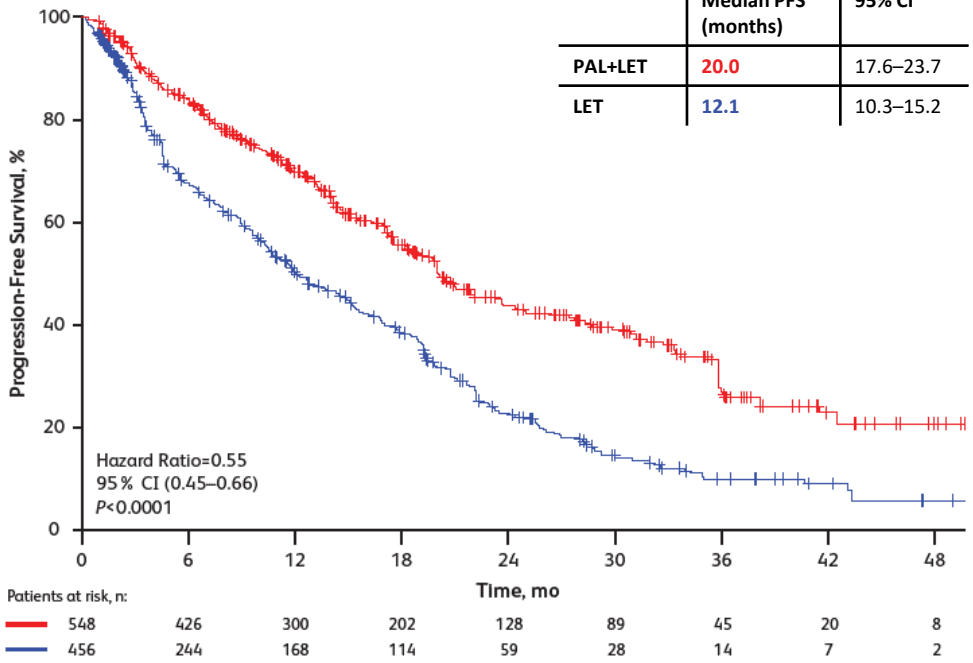
Overall Survival for First-Line Palbociclib Plus Letrozole vs Letrozole Alone for HR+/HER2– Metastatic Breast Cancer Patients in US Real-World Clinical Practice

Angela DeMichele, MD,[1] Massimo Cristofanilli, MD,[2] Adam Brufsky, MD, PhD,[3] Xianchen Liu, MD, PhD,[4] Jack Mardekian, PhD,[4] Lynn McRoy, MD,[4] Rachel M. Layman, MD,[5] Hope S. Rugo, MD,[6] Richard S. Finn, MD[7]

[1]University of Pennsylvania, College of Medicine, Philadelphia, PA, USA; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [3]University of Pittsburgh, College of Medicine, Pittsburgh, PA, USA; [4]Pfizer Inc, New York, NY, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [7]David Geffen School of Medicine at University of California Los Angeles, Santa Monica, CA, USA

After PSM*

	Median PFS (months)	95% CI
PAL+LET	20.0	17.6–23.7
LET	12.1	10.3–15.2



Presented at the San Antonio Breast Cancer Symposium 2019; P1-19-02

* PSM stabilized weight adjusted numbers of patients at risk are shown

LET=letrozole; PAL=palbociclib; PFS=progression-free survival; PSM=propensity score matching

1. Problem: Infrastructure!!!

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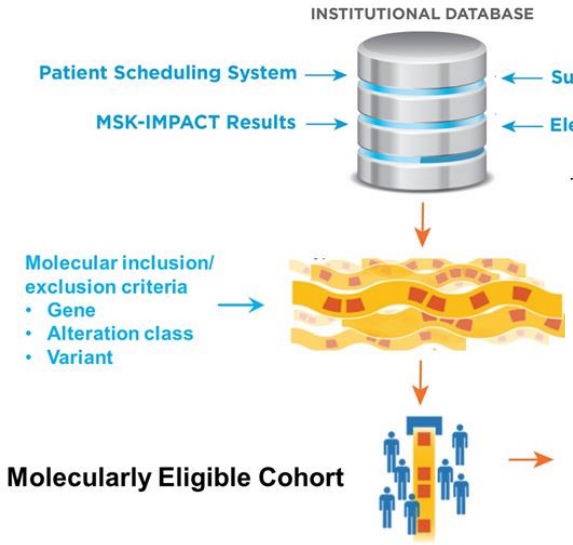
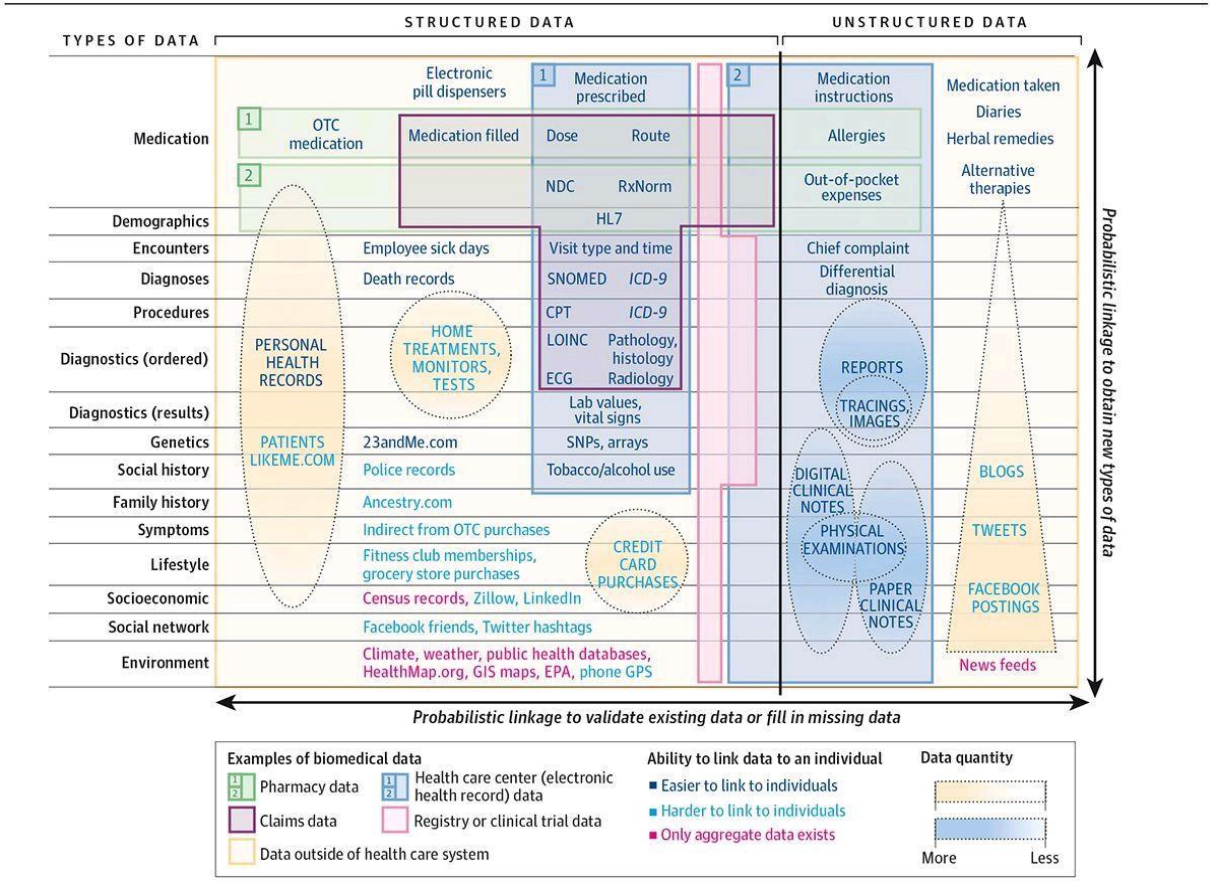
First lesson: These studies require unique support infrastructure





2. Problem: Different biology

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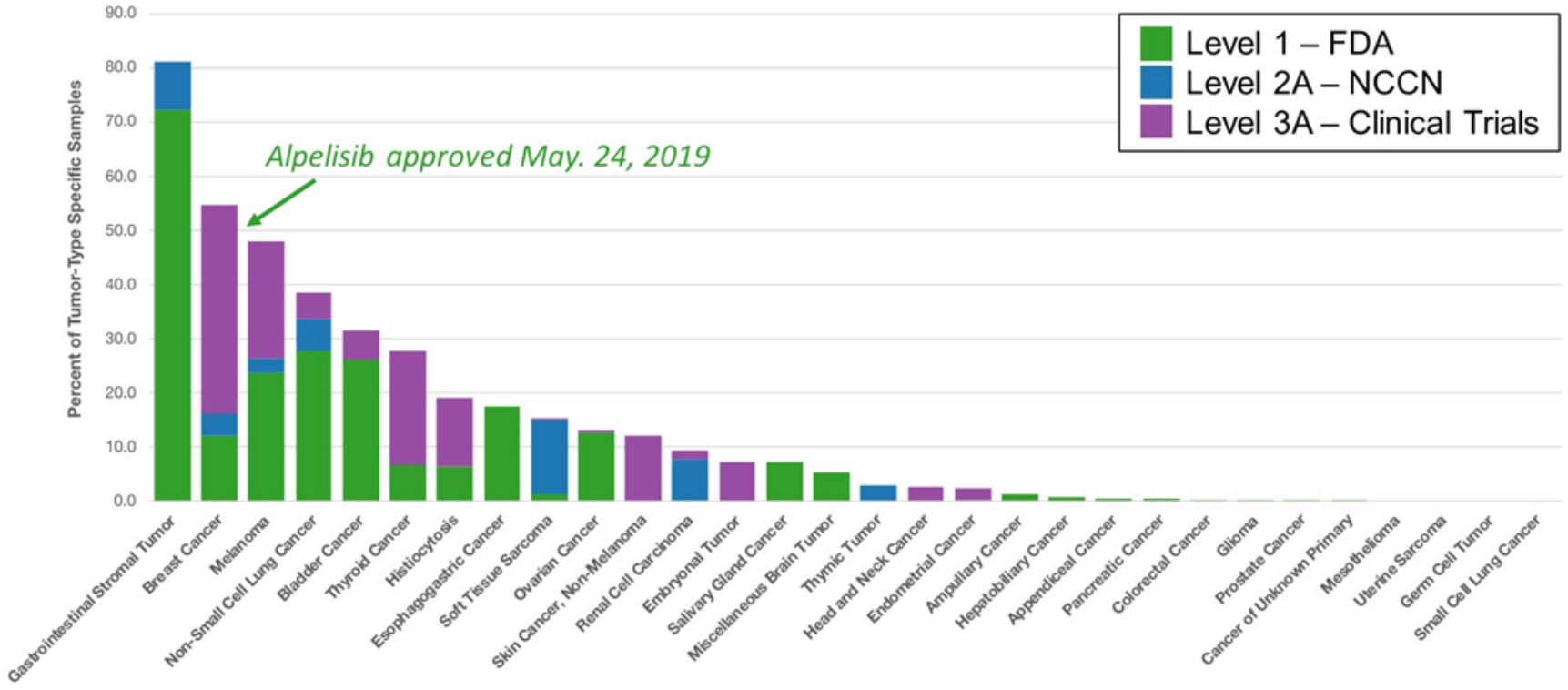
Rate of actionability varies markedly by cancer type



coKb.org, Chakravarty, Gao, Schultz, JCO PO, 2017, DOI: 10.1200/PO.17.00011

Memorial Sloan Kettering Cancer Center

Response rate according to mutation and tumor types

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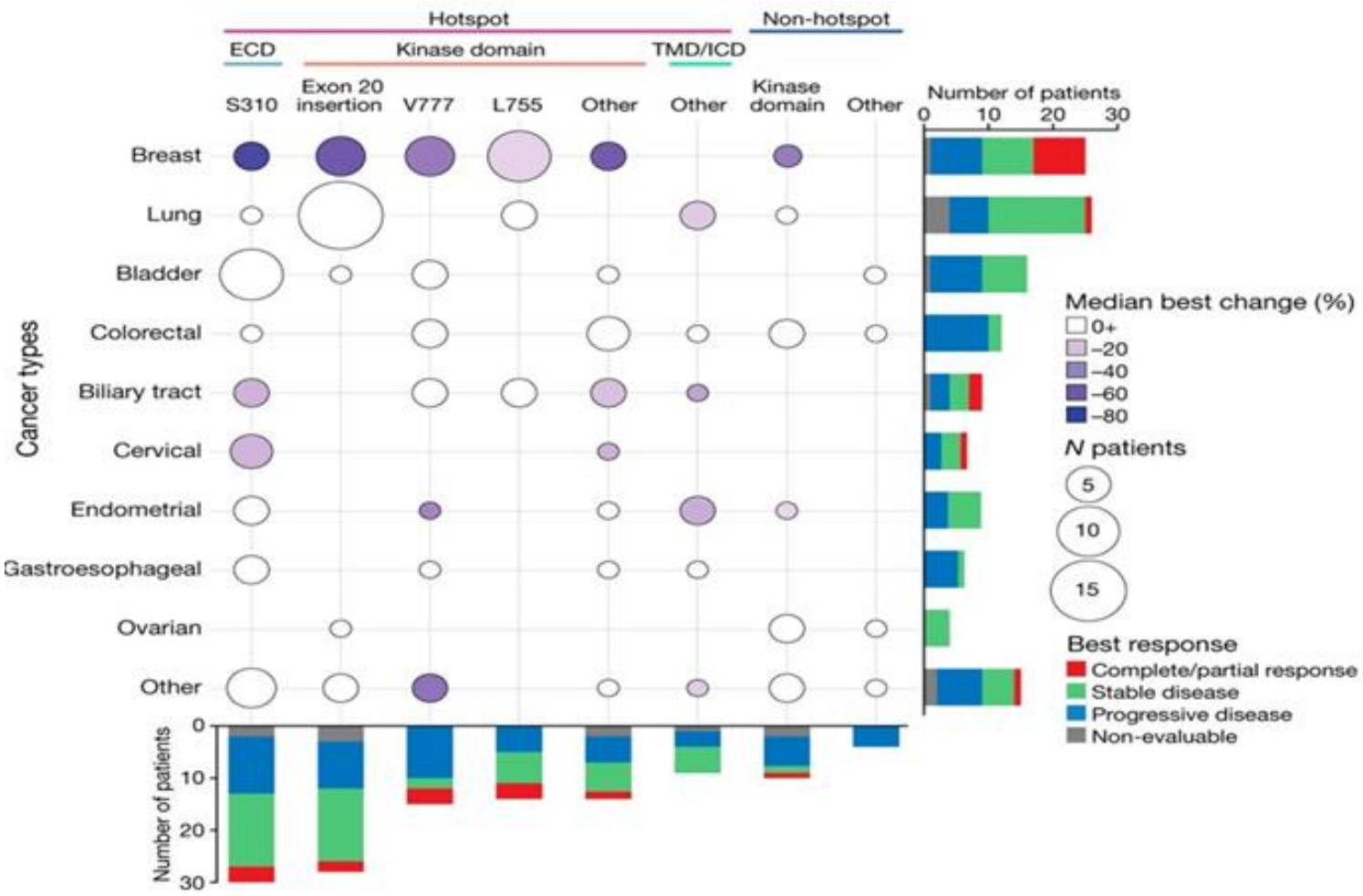

Randomized trials

- Gold standard in most (but not all) indications

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.

- Duration
- Costs!!!!

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Randomization Provides Evidence about Treatment Effects That Can Be Trusted

Randomization results in groups of patients that are balanced (give or take the play of chance) with respect to their risks of all types of health outcomes. Consequently, in sufficiently large randomized trials, the effects of a treatment can be reliably assessed.

Nonrandomized observational studies may be able to detect large treatment effects. However, the potential biases can be appreciable, so such studies cannot be trusted when the benefits or harms of a treatment are actually null or only moderate.

Obstacles to Randomized Trials Should be Removed to Protect Patients

Increased focus on adherence to rules rather than on the scientific principles that underlie randomized trials has substantially increased the complexity and cost of trials.

Promotion of nonrandomized analyses of databases as a rapid source of "real-world evidence" about the effects of treatments is a false solution to the problems caused by the bureaucratic burdens imposed on randomized trials.

Instead, obstacles to randomized trials should be removed to allow more new treatments to become available and to facilitate the reliable assessment of existing treatments.

Recommendations 2020

- Appropriate trial guidelines based on scientific principles
- Developed in partnership
- Enhanced recruitment faster and more predictable due to use of EHR
- Broader and more generalizable: Avoid unduly restrictive inclusion and exclusion criteria
- Improve quality (monitoring, FU, PRO's)