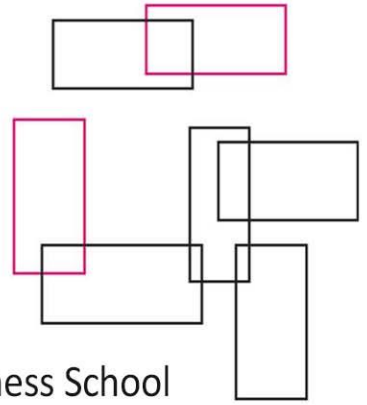
ACTA Summit 2018

Building a self-improving healthcare system



29-30 November 2018 I The University of Sydney Business School

Novel Trial Designs in Oncology

Mustafa Khasraw

Medical Oncologist Royal North Shore Hospital

Clinical Lead, NHMRC Clinical Trials Centre, The University of Sydney

MRFF *Next Generation Clinical Trials* Fellow

Why New Designs

- Rapid advances in biology
- Explosion of number of new treatments to be tested
- Increasing number of rare subsets
- Rising costs and shrinking funding +++
- Many large trial with inconclusive results
- Molecular heterogeneity challenges design
- Inter-patient heterogeneity of low frequency biological events
- Intra-patient heterogeneity through space and time
  - Serial molecular profiling.

- ✧ Next-Gen trial designs aimed to address heterogeneity.
- ✧ Novel ‘Exploratory’ and ‘Expansion’ Platform clinical trial designs.

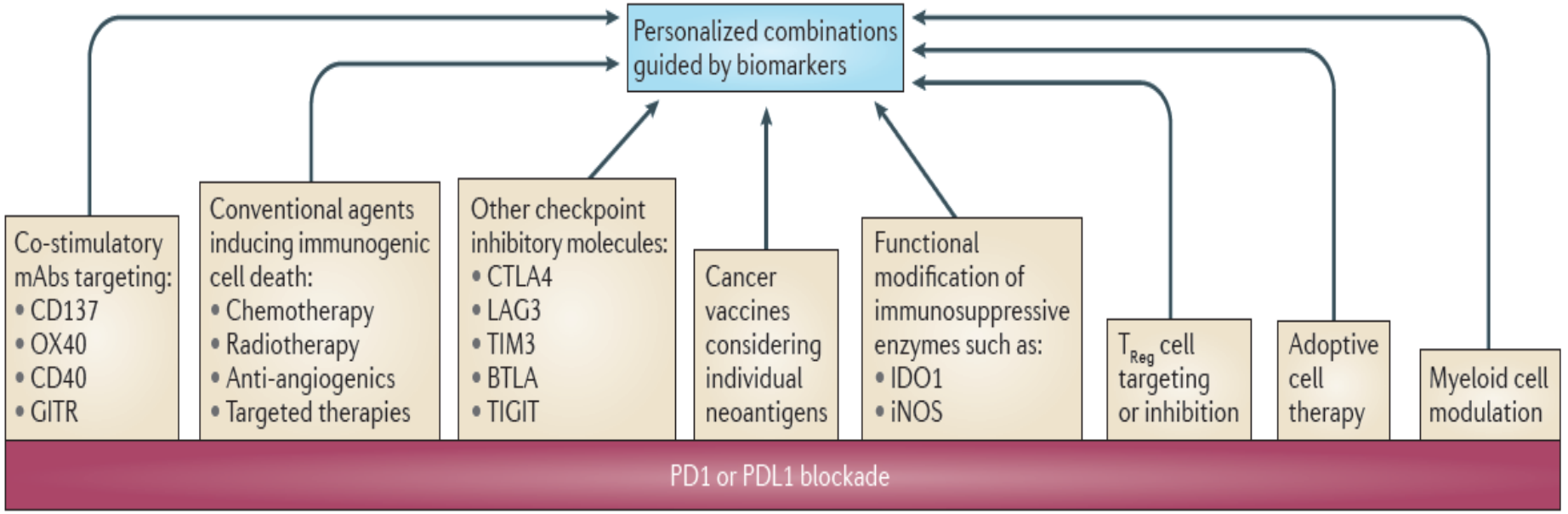
Common reasons for failed trials

- ✓ Selecting the wrong patients
  - ✓ Selecting the wrong dosing
  - ✓ Selecting the wrong endpoint.
- ✓ Biological activity but wrong indication.
- ✓ Right indication but wrong subpopulations
- ✓ Wrong dose or dose interval
- ✓ Trial Design Not Giving Clear Answers

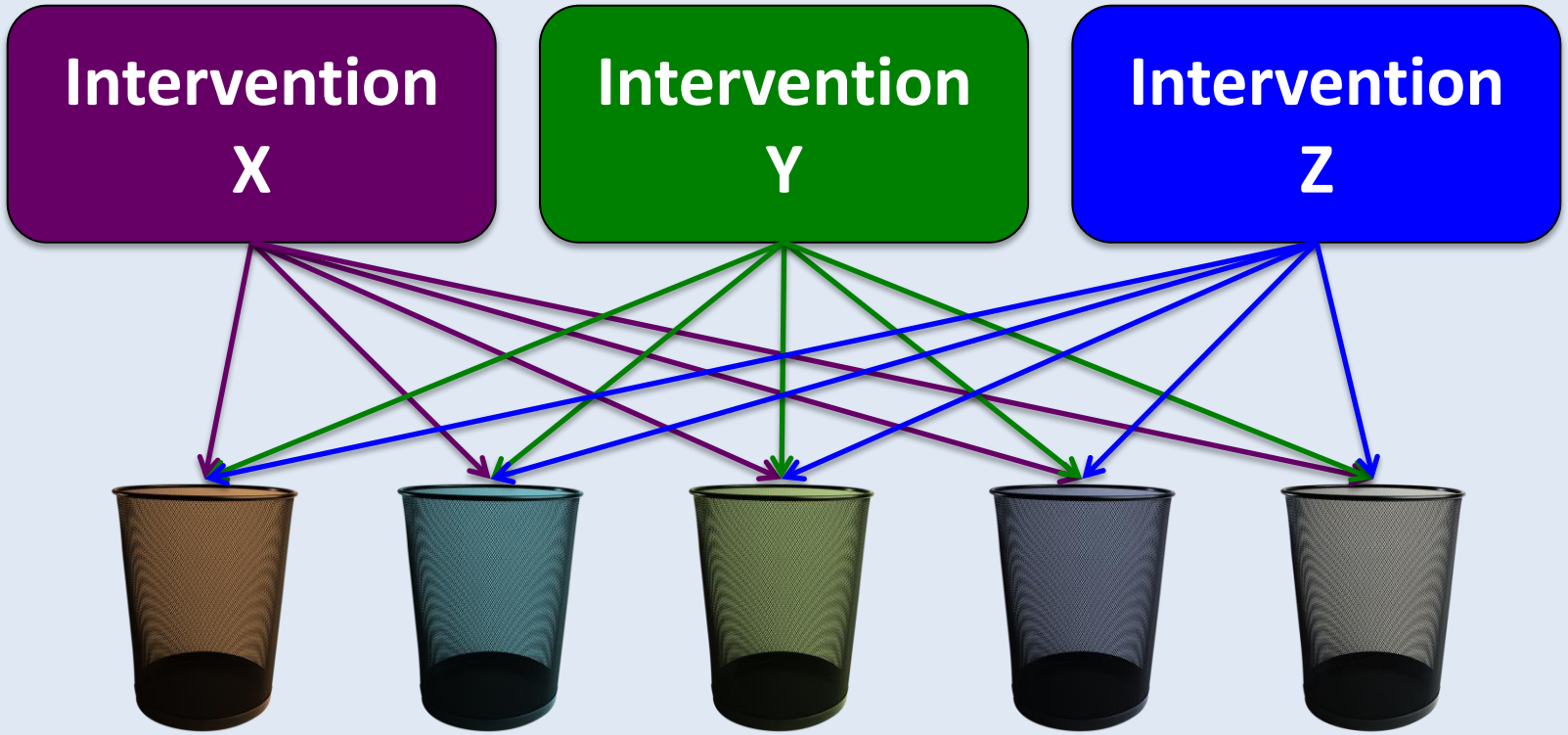
Principles and Practice of Clinical Trial
Medicine and Global Clinical Trials Playbook.

Evolving synergistic combinations of targeted immunotherapies to combat cancer

Ignacio Melero[1], David M. Berman[2], M. Angela Aznar[1], Alan J. Korman[3], José Luis Pérez Gracia[1] and John Haanen[4]



Multiple hypotheses = need for a platform trial



Basket Trials*

- Targeted drug
- Restrict to tumors expressing target
- Simultaneously develop across organ-specific tumors
- Sample sizes tiny, borrow; may be “pool”
- Formalizes “Gleevec phenomenon”

*Berry DA. The Brave New World of clinical cancer research: Adaptive biomarker-driven trials integrating clinical practice with clinical research. *Molecular Oncology* 9(2015):951-959.

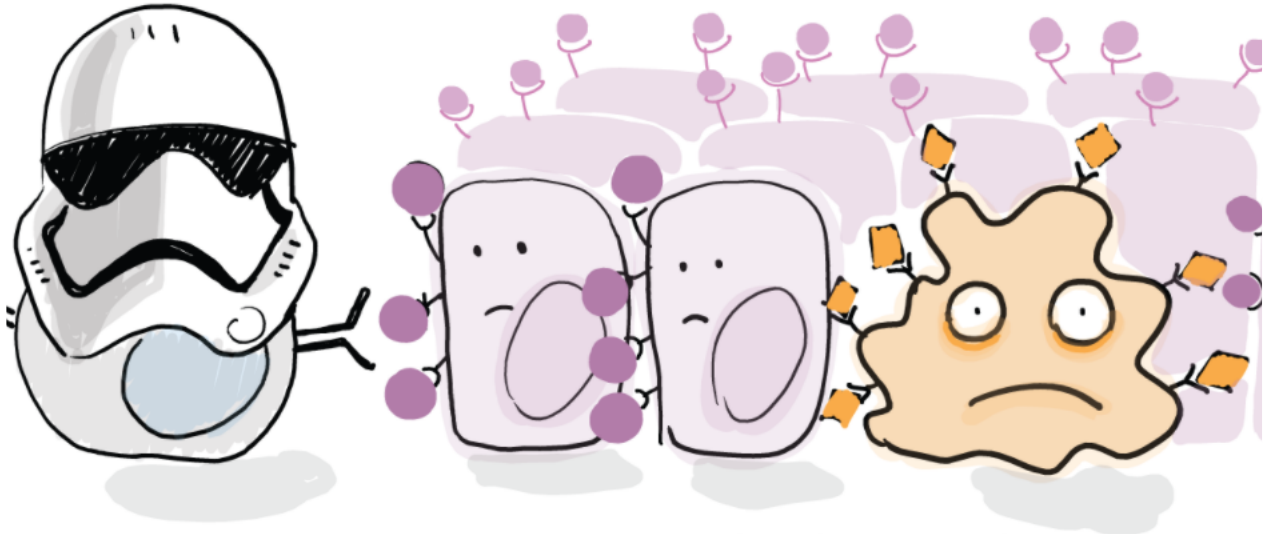
*Berry DA. Emerging innovations in clinical trial design. *Clinical Pharmacology & Therapeutics* 98(2015). doi:10.1002/cpt.285.

Master Protocol

- An overarching protocol that includes one or more of
  - Multiple diseases
  - Multiple treatmnets
  - Multiple molecular markers
- Other names
  - Umbrella trials
  - Cloud trials
  - Basket trials

AWAKEN THE FORCE WITHIN

Immunotherapy brings a new hope to cancer treatment



Immunotherapy Approaches

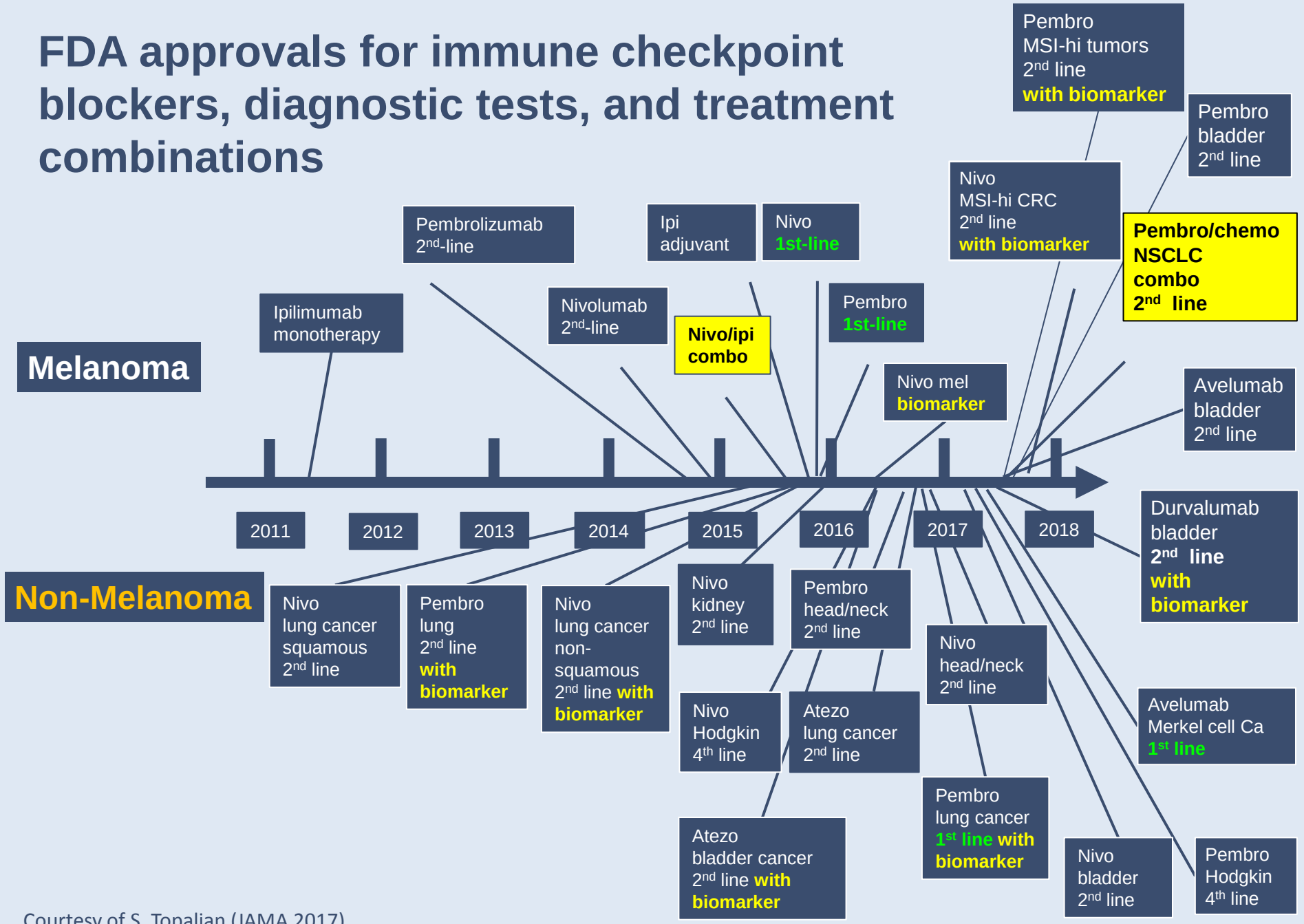
Immunotherapy is NOT one thing.

- Checkpoint Inhibitors ✔
- Oncolytic Viruses ✔
- Bi-specific Antibodies ✔
- Cancer Vaccines ✔
- CAR-T ✔
- Natural Killer Cell
- T-cell Receptors

- DART
- STING
- Cytotoxic T-cells
- Tumor Infiltrating Lymphocytes
- More…

✔ = FDA Approved

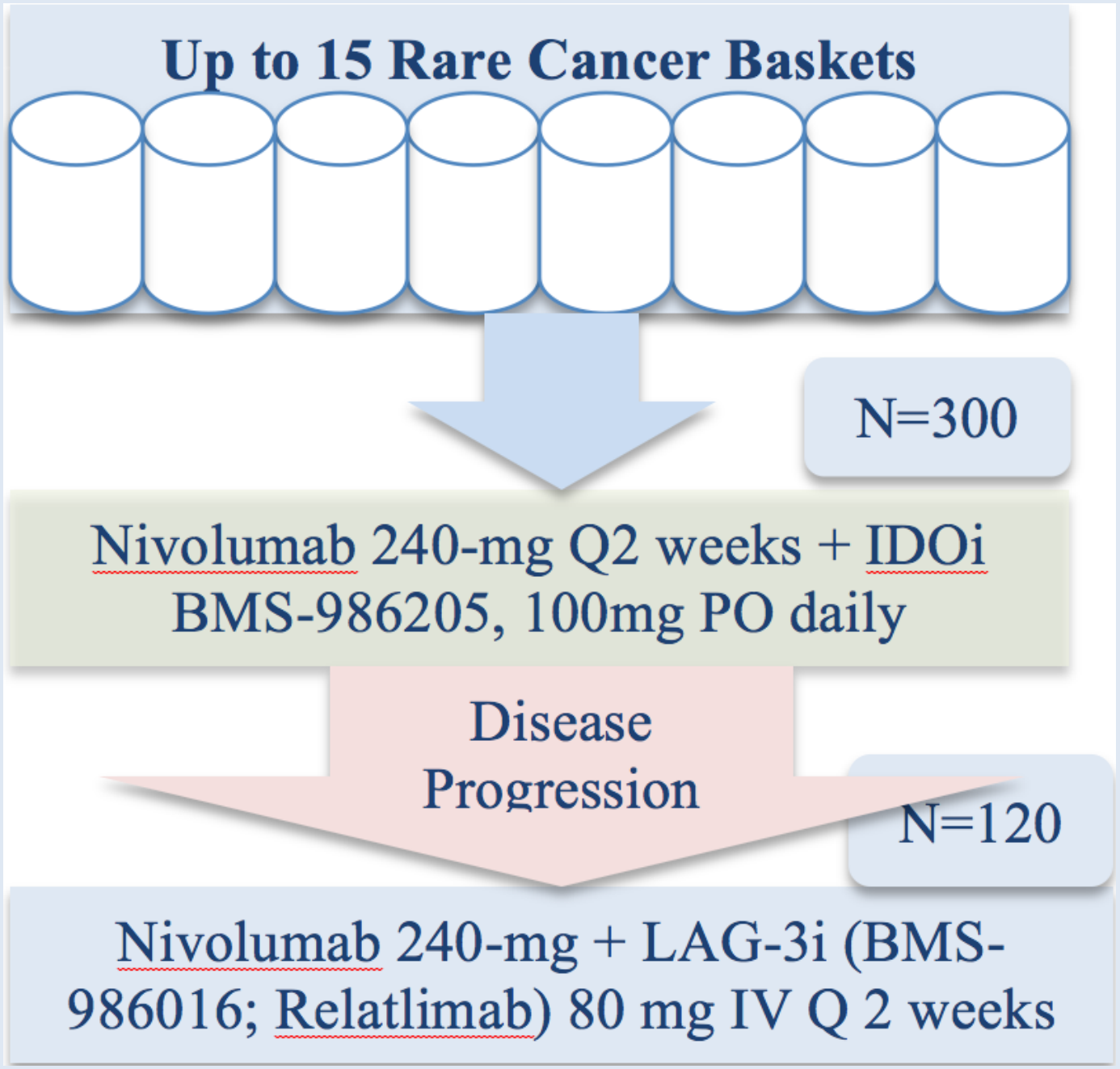
FDA approvals for immune checkpoint blockers, diagnostic tests, and treatment combinations



Courtesy of S. Topalian (JAMA 2017)

SEQUential ImmunoTherapy in Underserved Rare cancers (SEQUITUR)

Tumour Type and historical Response Rates		
1	Adrenocortical cancer	7%[11]
2	Carcinoma of the small bowel	20%[12]
3	Anal Cancer	24%[13]
4	Biliary Tract Cancer	7.7%[14]
5	NECs	29%[15,16]
6	NETs	29%[17]
7	Uterine Sarcoma	20%[18]
8	Vulvar Cancer	20%[19]
9	SCC of the Cervix or Vagina	17%[20,21]
10	Endometrial Cancer	27%[22]
11	Rare Ovarian Cancers†	15%[23]
12	Rare breast Cancers‡	18%[24,25]
13	IDH mutated glioma	6%[26,27]
14	IDH wild-type glioma	21%[28,29]
15	Rare glial tumours§	20%[30]
16	Thymic carcinoma	22%[31]


Up to 15 Rare Cancer Baskets
N=300
Nivolumab 240-mg Q2 weeks + IDOi BMS-986205, 100mg PO daily
Disease Progression
N=120
Nivolumab 240-mg + LAG-3i (BMS-986016; Relatlimab) 80 mg IV Q 2 weeks

SPECIFIC AIMS of SEQUITUR

- Conduct simulation studies to evaluate the performance of the analysis under various assumptions for the distribution of true underlying RR across the tumour types and assess operating characteristics including power and type I error

- A model will be developed prospectively by evaluating its performance from simulated trials allowing for the controlling of the false positive rate assessment of statistical power.

SPECIFIC AIMS of SEQUITUR

- Answer economic questions about the cost-effectiveness of the research from the perspective of research funders (government, funders, industry, and charity)

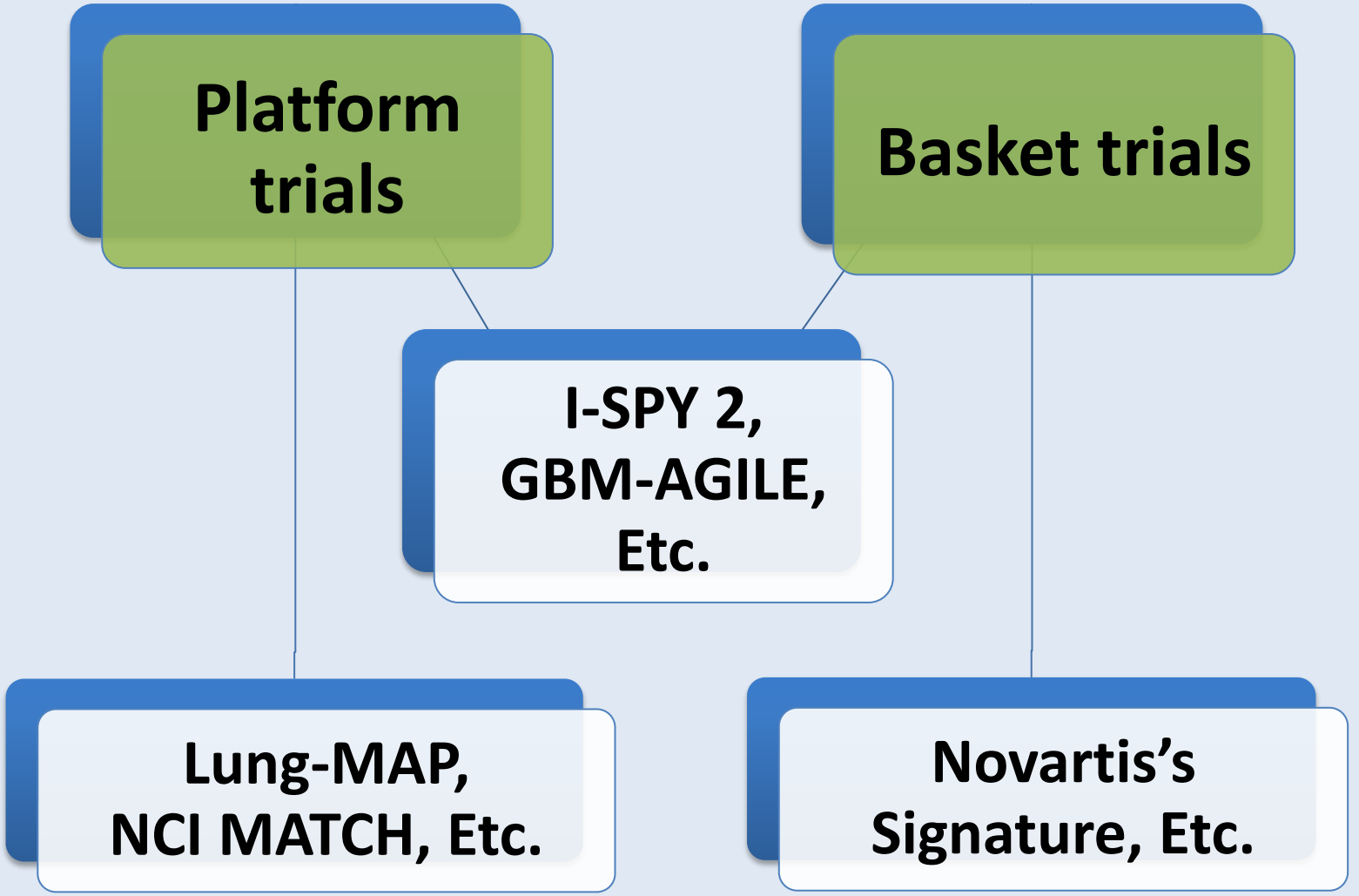
  - What are the costs and benefits of a basket trial approach for adults with rare cancers versus a standard trial approach?
  - Are expected resource efficiencies realised?

Bayesian response adaptive randomization (BRAR) designs

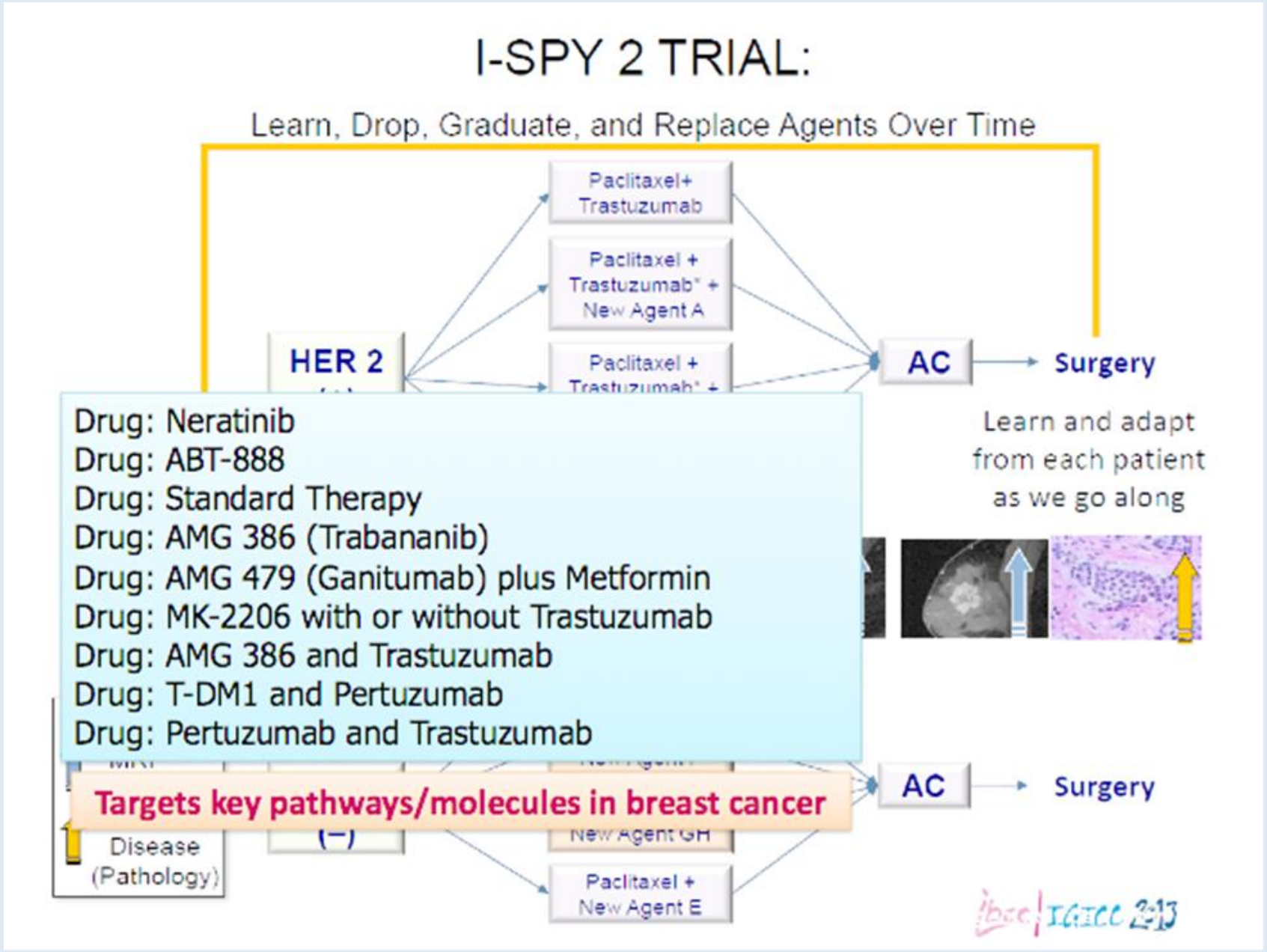
- Increase patient allocation to treatment arms that are performing well during the course of the trial. In this paper,
- BRAR and flexible MAMS designs have comparable power and type 1 error rate under varying
- Simulated scenarios, allowing for addition of flexible treatment selection. BRAR outperforms flexible MAMS
- When there is a single effective treatment, flexible MAMS designs are more efficient compared to BRAR when there are no effective treatments.
- BRAR performance increases as the probability of a treatment arm being dropped increases.

J. Lin, V. Bunn / Contemporary Clinical Trials 54 (2017) 48–59

Cancer Trial Landscape



I-SPY 2 TRIAL:


Learn, Drop, Graduate, and Replace Agents Over Time
Paclitaxel+ Trastuzumab
Paclitaxel + Trastuzumab* + New Agent A
Paclitaxel + Trastuzumab* +
HER 2
AC
Surgery
Learn and adapt from each patient as we go along
Drug: Neratinib
Drug: ABT-888
Drug: Standard Therapy
Drug: AMG 386 (Trabananib)
Drug: AMG 479 (Ganitumab) plus Metformin
Drug: MK-2206 with or without Trastuzumab
Drug: AMG 386 and Trastuzumab
Drug: T-DM1 and Pertuzumab
Drug: Pertuzumab and Trastuzumab
Targets key pathways/molecules in breast cancer
AC
Surgery
(−)
New Agent GH
Disease (Pathology)
Paclitaxel + New Agent E

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2016 VOL. 375 NO. 1

Adaptive Randomization of Neratinib in Early Breast Cancer

J.W. Park, M.C. Liu, D. Yee, C. Yau, L.J. van 't Veer, W.F. Symmans, M. Paoloni, J. Perlmutter, N.M. Hylton, M. Hogarth, A. DeMichele, M.B. Buxton, A.J. Chien, A.M. Wallace, J.C. Boughey, T.C. Haddad, S.Y. Chui, K.A. Kemmer, H.G. Kaplan, C. Isaacs, R. Nanda, D. Tripathy, K.S. Albain, K.K. Edmiston, A.D. Elias, D.W. Northfelt, L. Pusztai, S.L. Moulder, J.E. Lang, R.K. Viscusi, D.M. Euhus, B.B. Haley, Q.J. Khan, W.C. Wood, M. Melisko, R. Schwab, T. Helsten, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, L.J. Esserman, and D.A. Berry, for the I-SPY 2 Investigators*

ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

I-SPY 2 — Toward More Rapid Progress in Breast Cancer Treatment

Lisa A. Carey, M.D., and Eric P. Winer, M.D.

PERSPECTIVE

STATISTICS IN MEDICINE

I-SPY 2 — A Glimpse of the Future of Phase 2 Drug Development?

David Harrington, Ph.D., and Giovanni Parmigiani, Ph.D.

The articles by Rugo et al. (pages 23–34) and Park et al. (pages 11–22) in this issue of the

ing in larger, phase 3 trials. The value of I-SPY 2, however, may well go beyond the clinical re-

good responses and, equally important, may be useful in allowing patients to avoid treatments

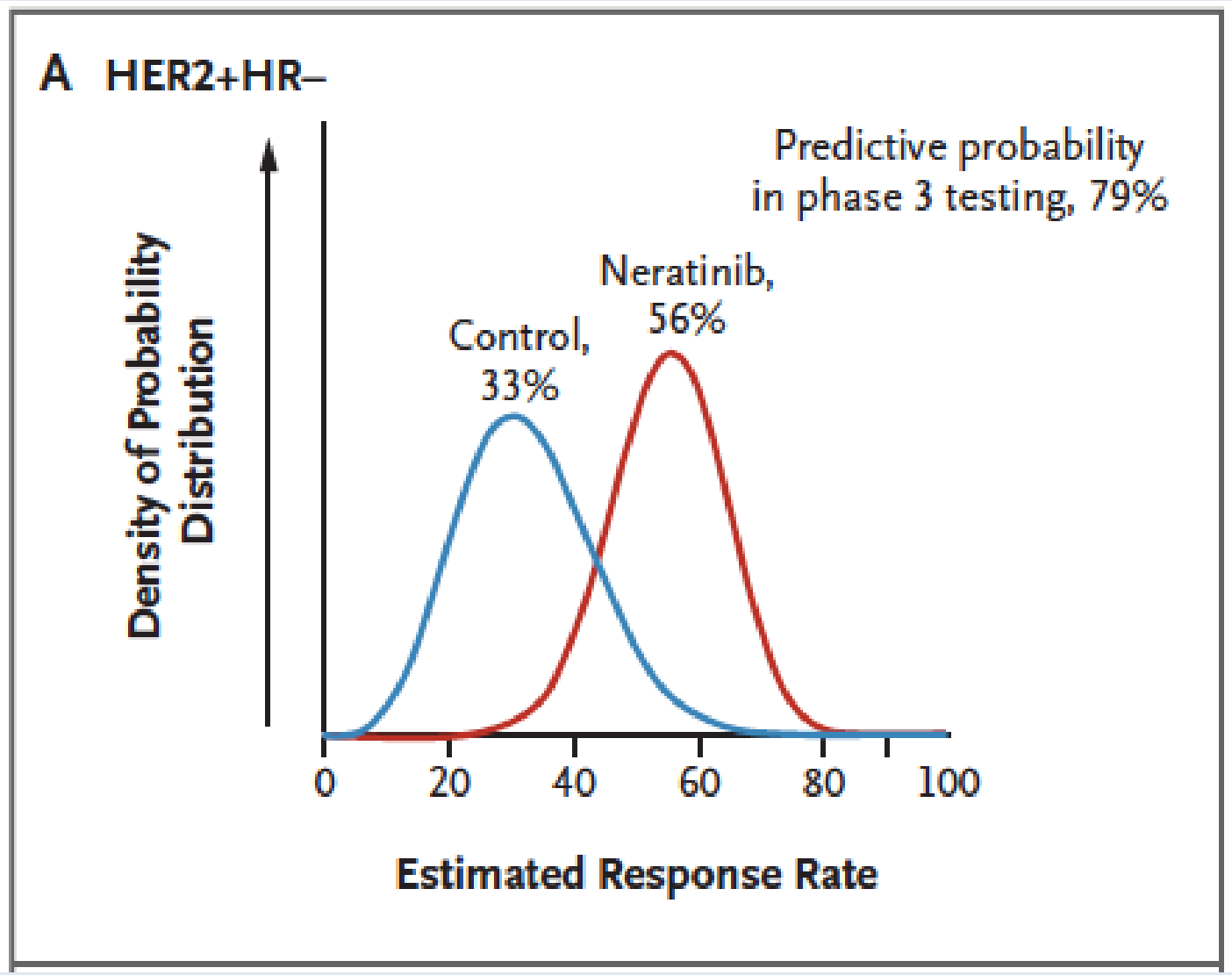
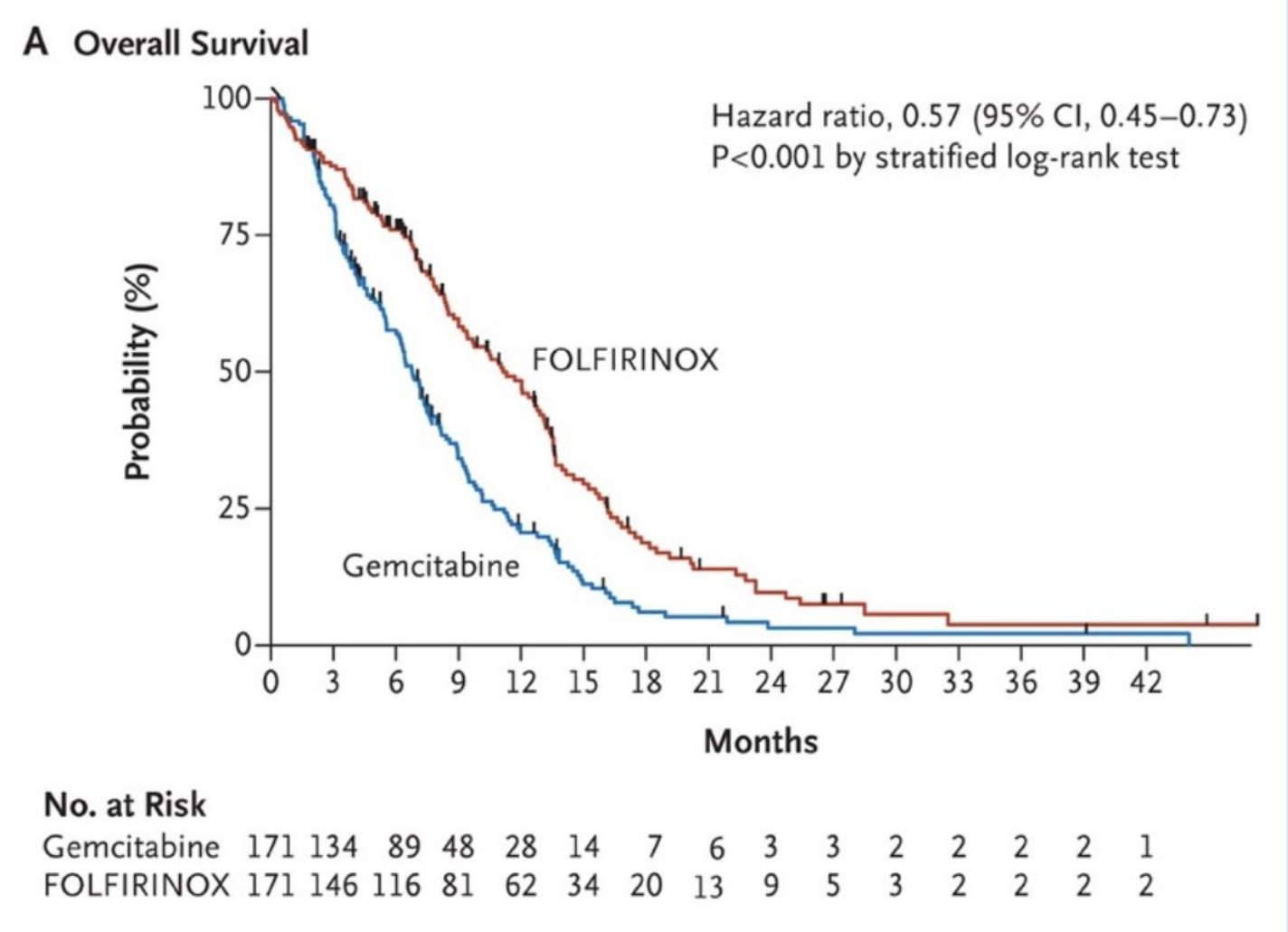

A HER2+HR–
Predictive probability in phase 3 testing, 79%
Neratinib, 56%
Control, 33%
Density of Probability Distribution
0
20
40
60
80
100
Estimated Response Rate

Table 2. Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to 10 Biomarker Signatures.

Biomarker Signature	Estimated Rate of Pathological Complete Response (95% Probability Interval)		Probability of Neratinib Being Superior to Control	Predictive Probability of Success in Phase 3 Trial
	Neratinib	Control		
		percent		
Any	33 (24–40)	23 (14–33)	93	48
Hormone-receptor positive	23 (13–33)	16 (6–28)	81	40
Hormone-receptor negative	44 (30–55)	31 (17–45)	92	58
HER2 positive	39 (28–51)	23 (8–38)	95	73
HER2 negative	28 (15–37)	24 (13–35)	69	25
High-risk category 2 on 70-gene profile*	48 (30–60)	29 (11–48)	93	72
HER2 positive, hormone-receptor positive	30 (18–44)	17 (3–32)	91	65
HER2 positive, hormone-receptor negative	56 (37–73)	33 (11–54)	95	79
HER2 negative, hormone-receptor positive	14 (3–25)	16 (5–27)	42	14
HER2 negative, hormone-receptor negative	38 (22–50)	31 (15–46)	77	40

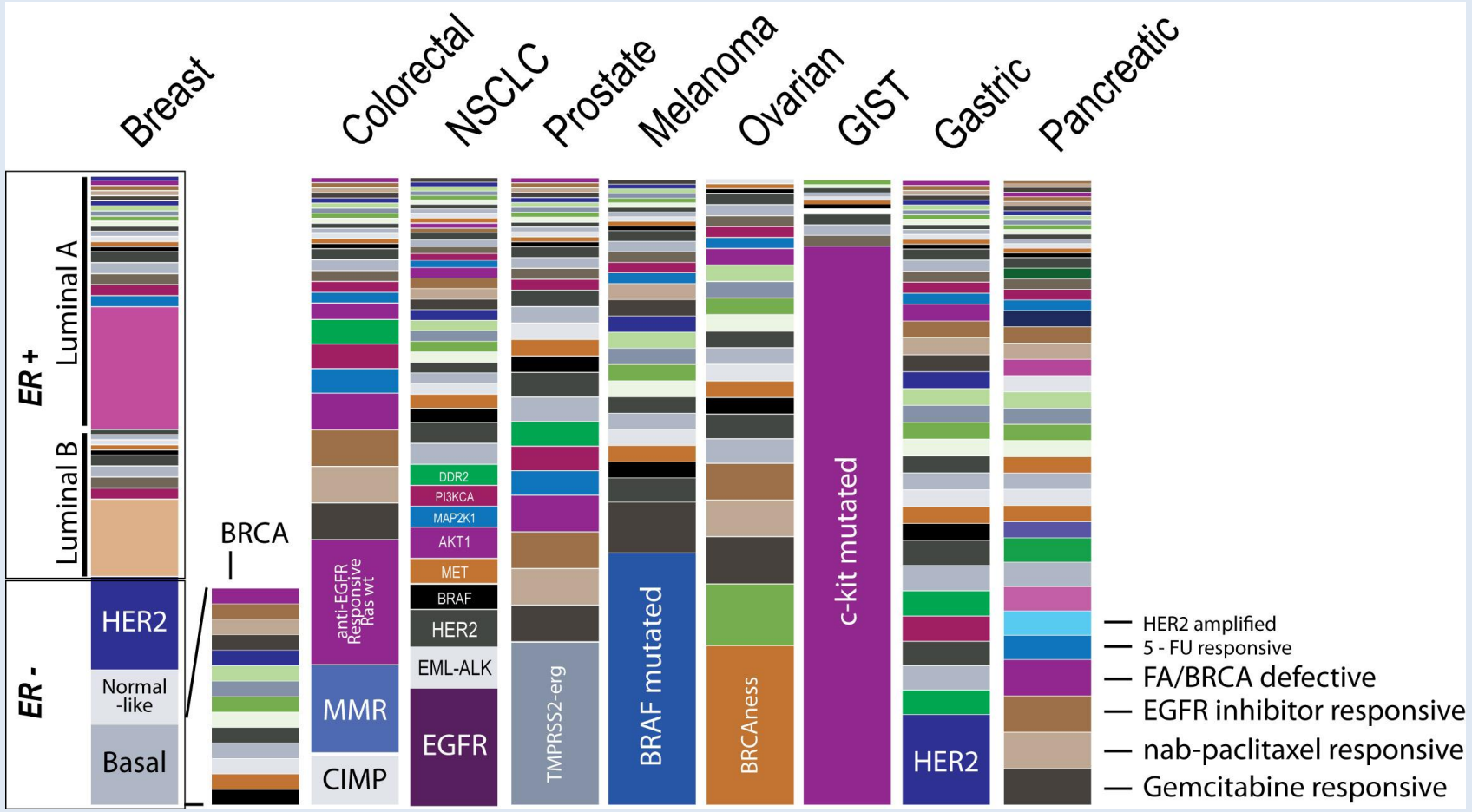
Pancreatic Cancer



Conroy *et al NEJM 2011;* Goldstein *et al* JNCI 2015

Emerging Molecular Taxonomy

Prevalence of Phenotypes



Courtesy Lorraine Chantril and Andrew Biankin

The precision-oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

Precision oncology promises to pair individuals with cancer with drugs that target the specific mutations in their tumour, in the hope of producing long-lasting remission and extending their survival. The basic idea is to use genetic testing to link patients with the drugs that will work best for them, irrespective of the tissue of origin of their tumour. Enthusiasm has been fuelled by reports of exceptional or super responders — individuals for whom experimental therapies seem to work spectacularly well.

In one such example, an individual with metastatic bladder cancer showed a dramatic response to the drug everolimus[1]. Sequencing later revealed that the patient had a mutation that affects the mTOR pathway, which is the mechanism of action of everolimus. Yet despite the hype surrounding rare cases such as these, most people with cancer do not benefit from the precision strategy, nor has this approach been shown to improve outcomes in controlled studies. Precision oncology remains a hypothesis in need of verification.

Few patients benefit from precision oncology. Data from some 2,600 people enrolled in a sequencing programme at the MD Anderson Cancer Center in Houston, Texas, showed that just 6.4% were paired with a targeted drug for identified mutations[2]. Similarly, the Molecular Analysis for Therapy Choice (NCI-MATCH) trial at the US National Cancer Institute has enrolled 795 people who have relapsed solid tumours and lymphoma, but as of May 2016 it had only been able to pair 2% of patients with a targeted therapy[3].

NOT SO EXCEPTIONAL

But being assigned such a therapy is not proof before their supposedly miraculous response to precision oncology[5]. It is hard to avoid the unsettling conclusion that such cases do not reflect the success of precision oncology, but rather the selective reporting of individuals who were always likely to do well.

When considered objectively, the prospects and potential of precision oncology are sobering. At best, we may expect short-lived responses in a tiny fraction of patients, with the inevitable toxicity of targeted therapies and inflated cost that this approach guarantees.

PRECISION ONCOLOGY ON TRIAL

In medical science, the ultimate judge of a therapeutic strategy is the randomized controlled trial. So far, precision oncology has been tested in only one such published study[6]. The SHIVA trial assigned 99 patients with cancer to therapies based on an identified mutation or mutations, and 96 patients to the treatment selected by their physicians. Median progression-free survival, the primary endpoint, was almost equally poor in both cases (2.3 and 2.0 months, respectively).

No single trial can prove that a therapy does not work in any circumstances, and SHIVA is no exception. It paired patients with drugs for 'pathway' mutations, not just for mutations that can be targeted with drugs, allowing those running the trial to enrol more than a quarter of screened patients. But further randomized controlled trials are needed to test alternative hypotheses, and the use of different medications and alternative pathways. These trials will have to balance applicability and generalizability (the percentage of screened patients that can be enrolled) against the strength of the biological rationale. Several

WHEN CONSIDERED **OBJECTIVELY,** THE PROSPECTS AND POTENTIAL OF PRECISION ONCOLOGY ARE **SOBERING.**

Precision and The Person

- Precision Medicine
- Personalized Medicine

The Premise, The Promise and The Hype!

Precision Promise

- Pancreatic cancer is an area of great need
- Two standard chemo regimens available but the outcome is still very dismal
- PanCAN is sponsoring Precision Promise and providing funding to support its goal to change patient outcomes for those suffering from pancreatic cancer
- The statistical design of Precision Promise is based on the I-SPY breast cancer trial, in collaboration with PanCAN and with guidance from the U.S. Food and Drug Administration (FDA)

The Precision Promise's design

- Adaptive Phase II/III platform of first- and second-line pancreatic cancer
  Primary end point is OS
- Adaptive randomization
- Re-randomization for second-line if they progress on first-line treatment
- Two control arms (mFOLFIRINOX and gemcitabine/nab-paclitaxel)

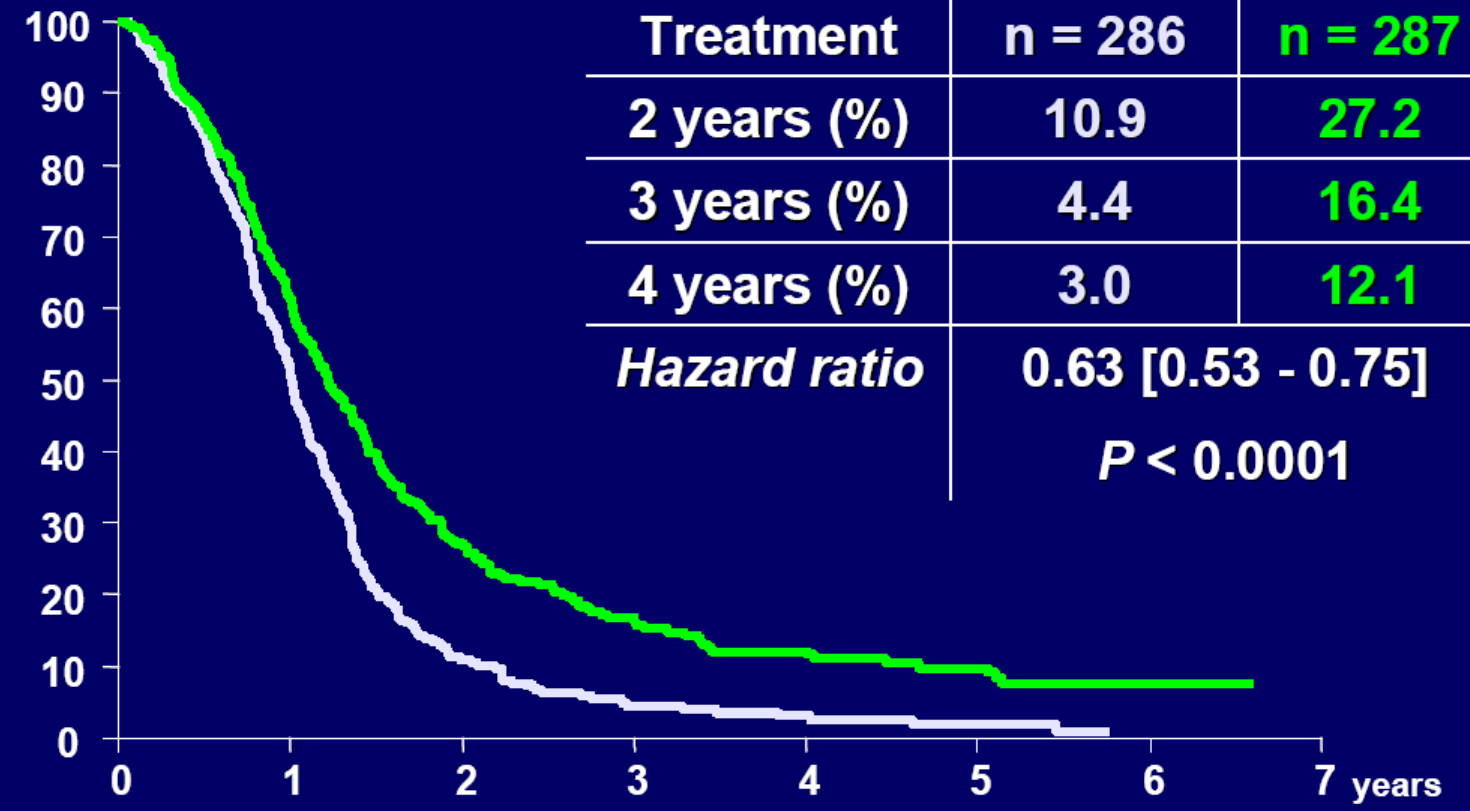
- Minimizes numbers needed to achieve statistically significant data

- Expected to launch 2019 at 14 high-volume pancreatic cancer centers (US)

Glioblastoma
GBM

Overall survival

Treatment	RT n = 286	RT+TMZ n = 287
2 years (%)	10.9	27.2
3 years (%)	4.4	16.4
4 years (%)	3.0	12.1
Hazard ratio	0.63 [0.53 - 0.75]	
	P < 0.0001	



O	N	Patients *at risk*:					
278	286	144	31	11	6	3	0
254	287	175	76	39	23	14	6

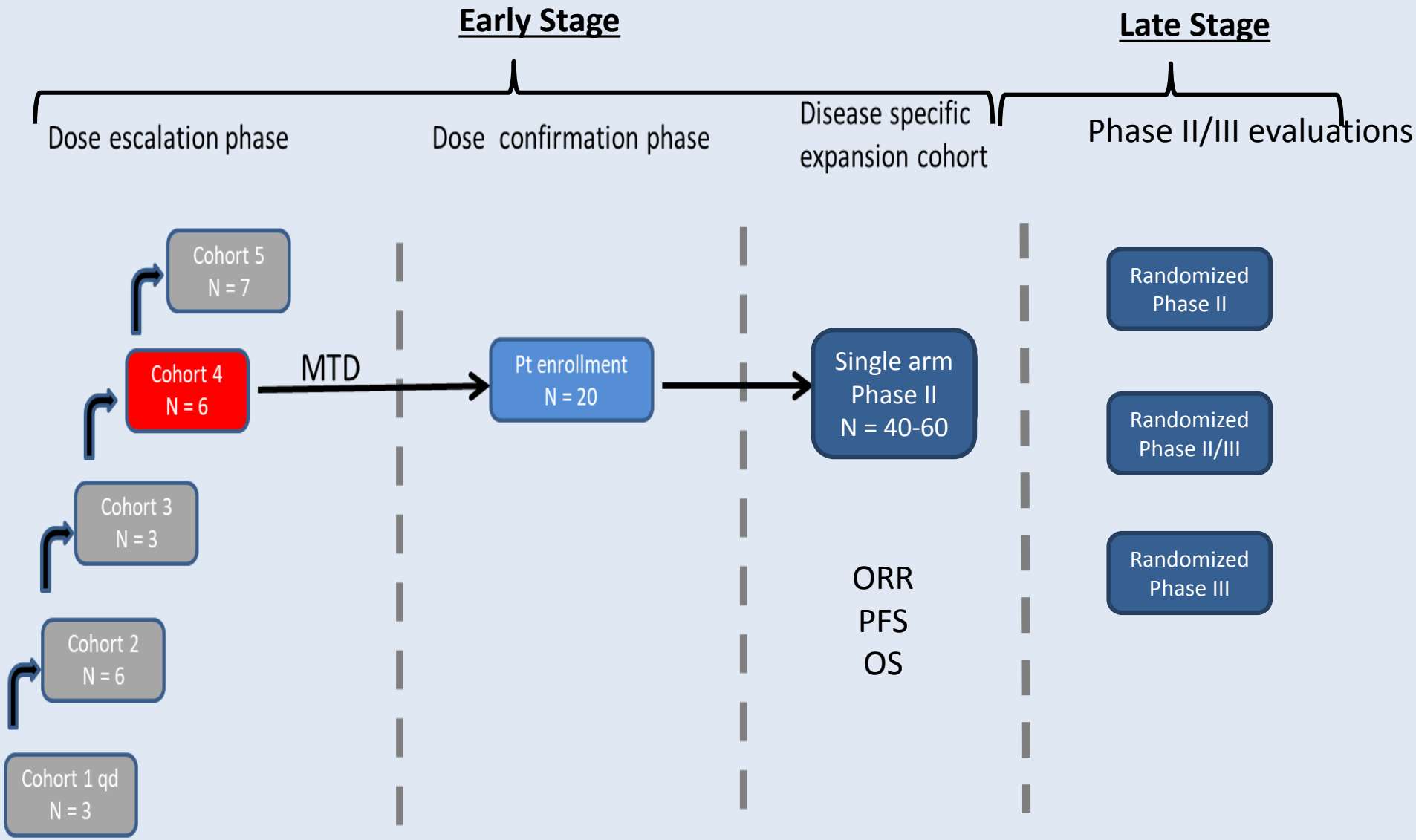
RT
RT+TMZ

The Study of Glioblastoma in *an*

Adaptive, Global, Innovative Learning Environment
GBM – AGILE

Alexander BM, …Khasraw M…; Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE; Clin Cancer Res. 2017 Aug 16. pii: clincanres.0764.2017.

Clinical Development: Standard Early to Late Stage Development in Neuro-Oncology



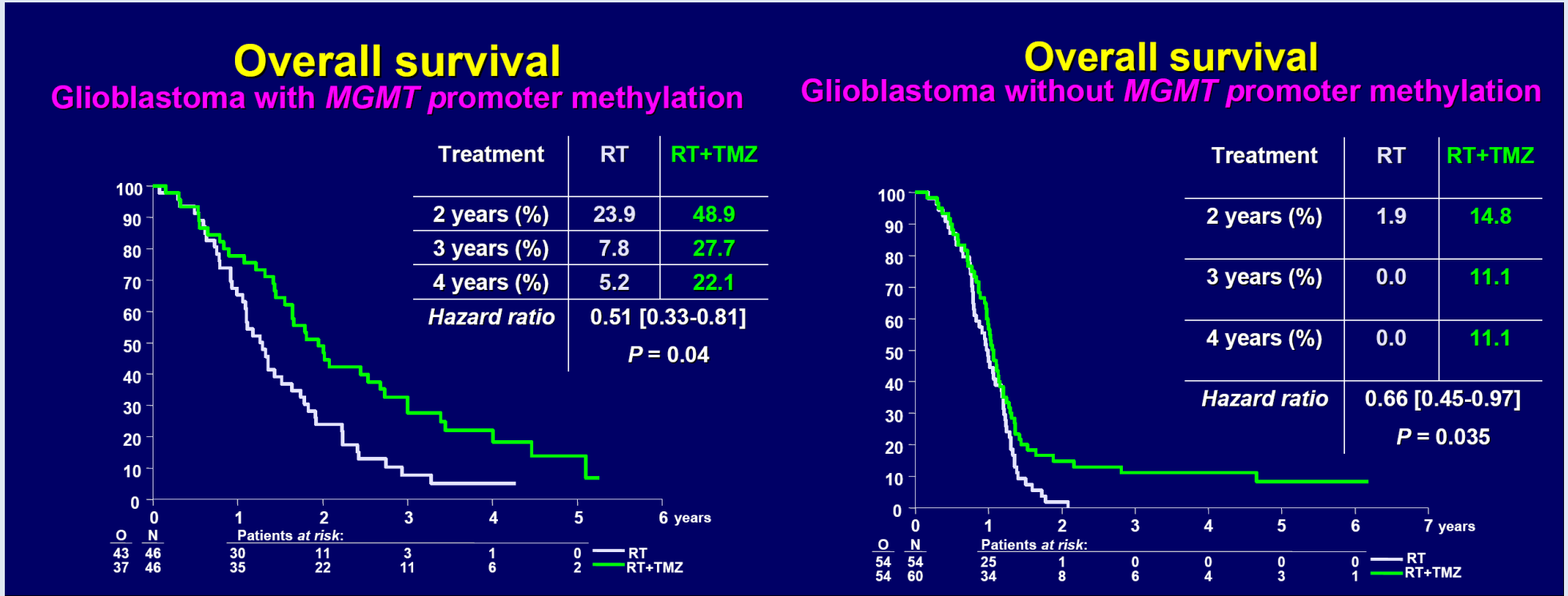
GBM Development has many lengthy, costly (knowable?) failures

Experimental	Indication	Phase II-phase III time	Phase III N	Phase II N	Phase II endpoint	Phase II RCT?
Cilengitide	Newly Diagnosed	7.6	545	112	OS	No
Intraoperative RT	Newly Diagnosed	6.3	314	12	MTD	No
ICT-107	Newly Diagnosed	8.9	414	124	OS	Yes
NovoTTF	Newly Diagnosed		700			
Bevacizumab	Newly Diagnosed	5.8	921	70	OS	No
Bevacizumab	Newly Diagnosed	6.8	637	70	OS	No
Rindopepimut	Newly Diagnosed	9.3	745	82	PFS	No
ddTMZ	Newly Diagnosed		1173			
Nivolumab	Newly Diagnosed		550			
DCVax	Newly Diagnosed	9.9	348	240	PFS	Yes
VB-111	Recurrent	7.0	252	75	OS	No
Enzastaurin	Recurrent	4.8	397	120	Activity	No
Cediranib	Recurrent	4.3	423	31	PFS	No
Nivolumab	Recurrent		626			
NovoTTF	Recurrent		236			
AP 12009	Recurrent	8.8	27 (term)	141	ORR	Yes

Courtesy of Brian Alexander

MGMT methylation

Prospective marker for patients who would benefit from chemo



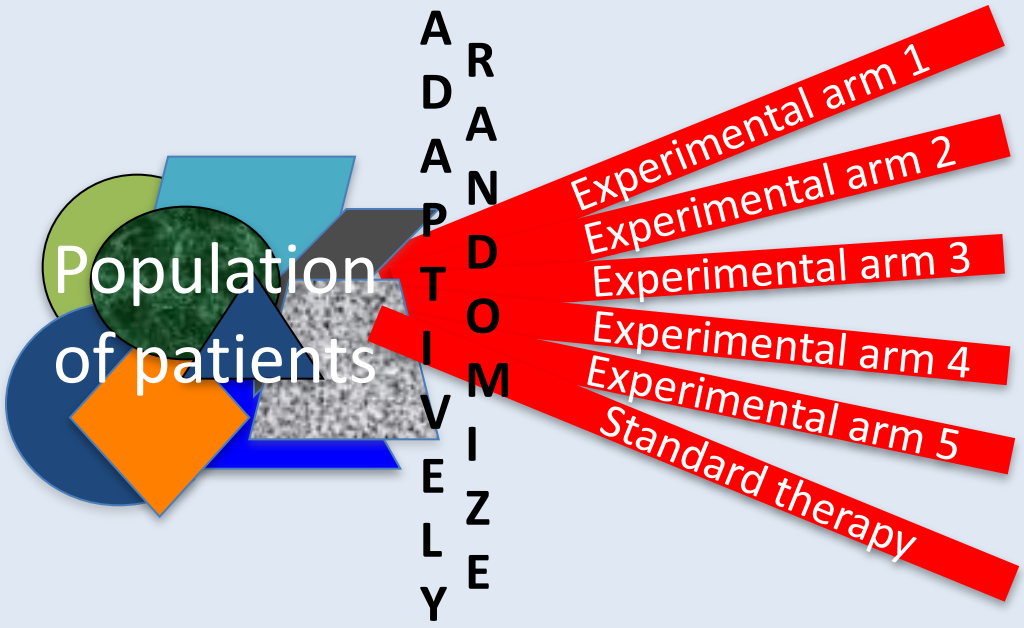
2 × 2 Biomarkers → 3 Signatures

Newly diagnosed MGMT-unmethylated	Newly diagnosed MGMT-methylated
Recurrent GBM MGMT-unmethylated	Recurrent GBM MGMT-methylated

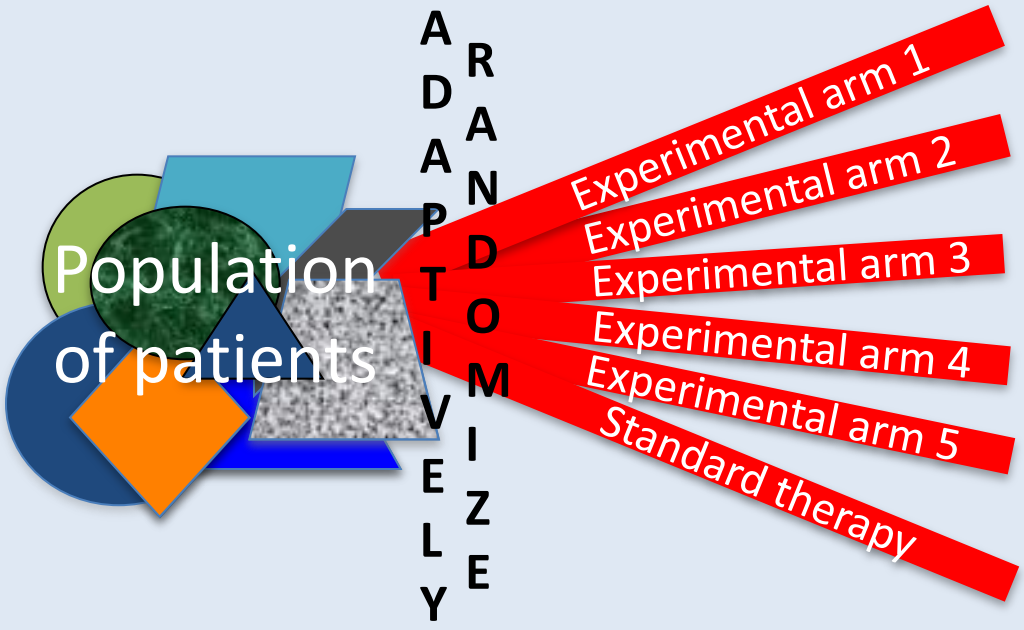
Drug Signature

- Combination of biomarker subsets
- Examples:
  - All GBM
  - Target A
  - Target B
  - A + B
  - Etc.
- Each drug is continuously evaluated within each candidate signature

GBM AGILE

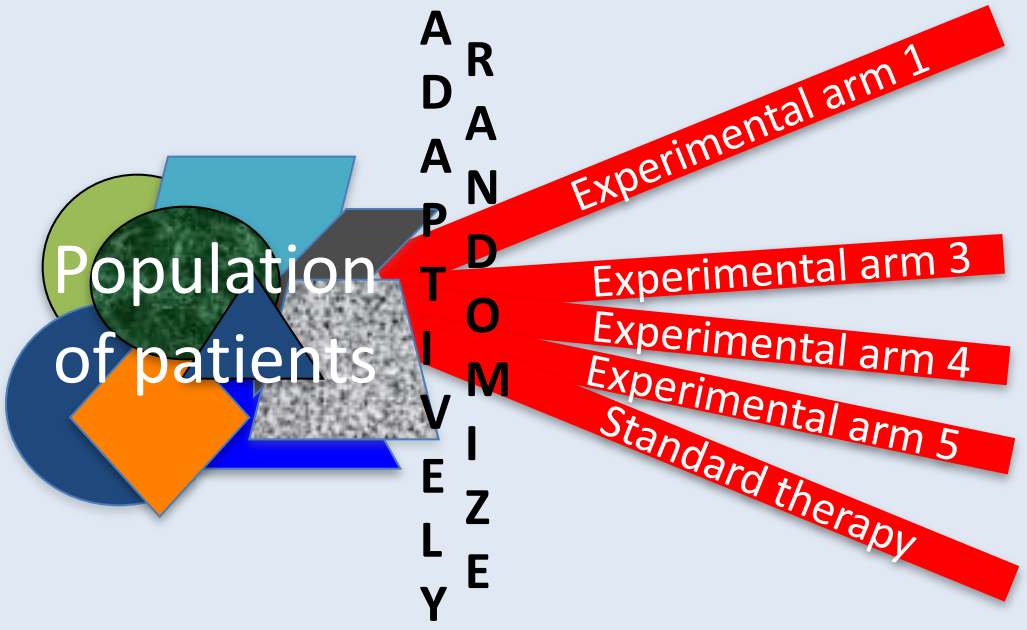

Population of patients
ADAPTIVELY RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy

GBM AGILE



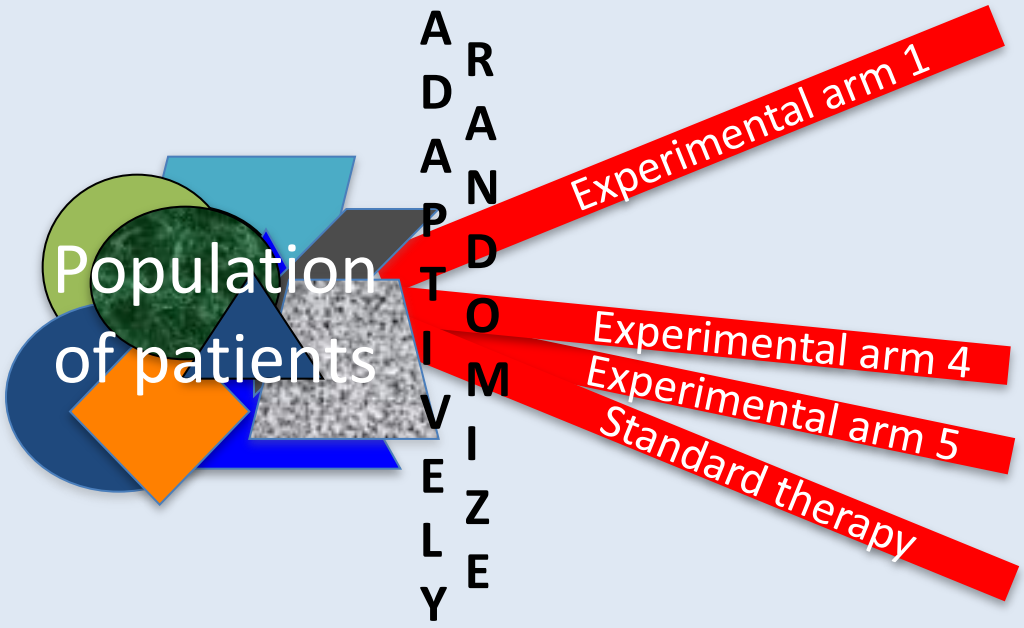
Arm 2 graduates to small focused Phase 3 trial

GBM AGILE



Arm 3 drops for futility

GBM AGILE



Arm 5 graduates to small focused Phase 3 trial

GBM AGILE:
Value to Drug Makers

- De-Risk (faster, cheaper)
  - Create a Master protocol with shared control and shared infrastructure
  - Infrastructure designed to shorten timelines
  - Use Bayesian statistics to right size trial (Fail early, Win Early)
  - Used for variety of development opportunities (1st to market, expanding indications)
  - Cost savings encourages involvement in orphan disease
- Innovate
  - Regulatory interest in these endeavors: seen as the future of clinical trials
  - Borrow across multiple signatures (possible indications) to increase power
  - Empower ability to ask biomarker questions (CDx)
  - For significant effect size allow for NDA with regulators
- Capitalize on a Win
  - Evaluate Multiple possible indications
  - Evaluate in multiple countries simultaneously
  - Establishing New controls
  - Opportunity for Rational Combinations
- International regulatory alignment

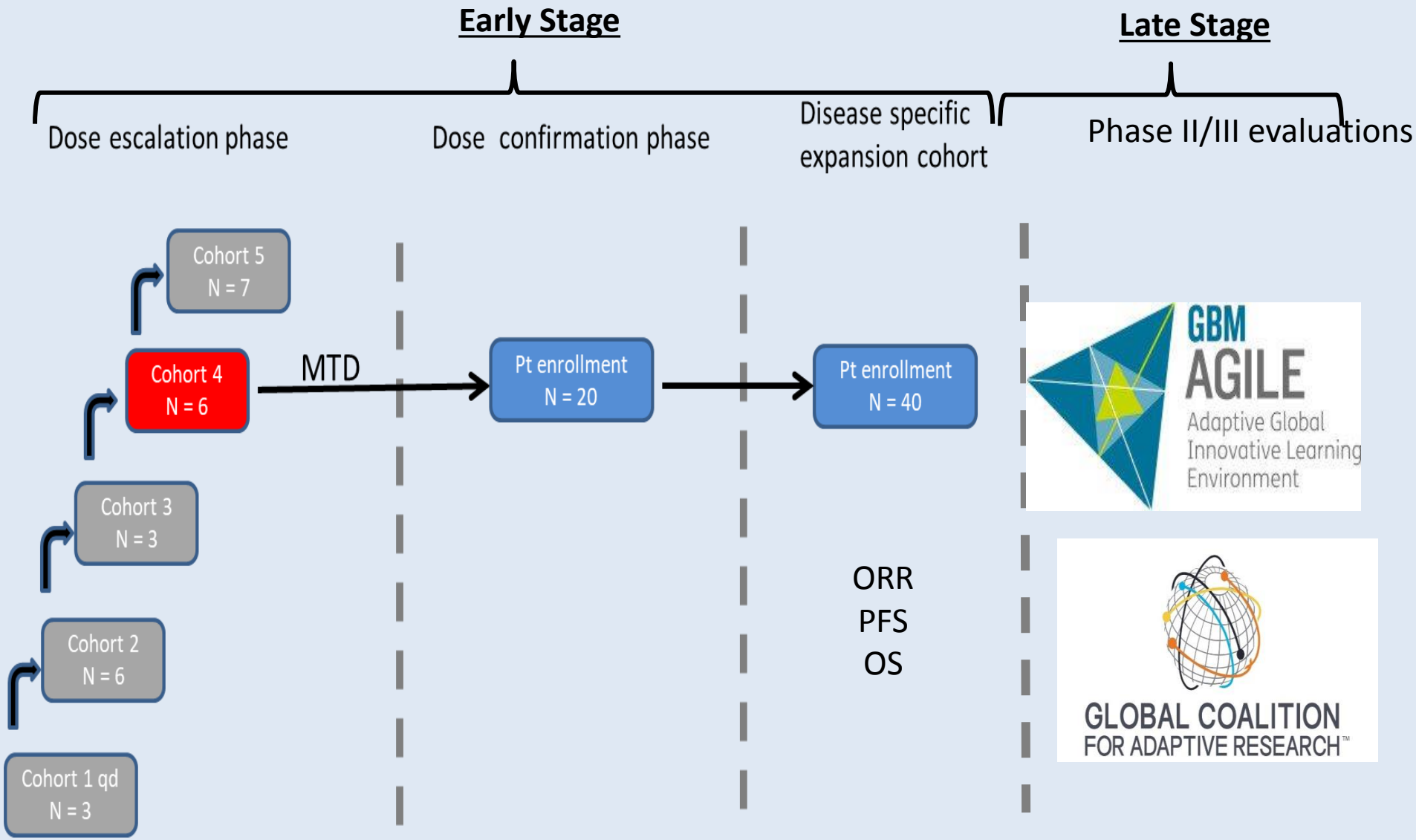
GBM AGILE: Value to Patients and Advocates

- Access
  - Multiple therapies available
  - Offered at many sites, potentially reducing travel distance
- Opportunity for continuous improvement
  - Trial becomes Standard of Care
- Precision Medicine
  - More likely to get most beneficial treatment for patient subtype today
- Design informed by patients and advocates
  - Disease centric not drug centric
  - Patient-centric trial design informed by patient and caregiver input
  - Shared control group
  - Faster to fail and faster to market

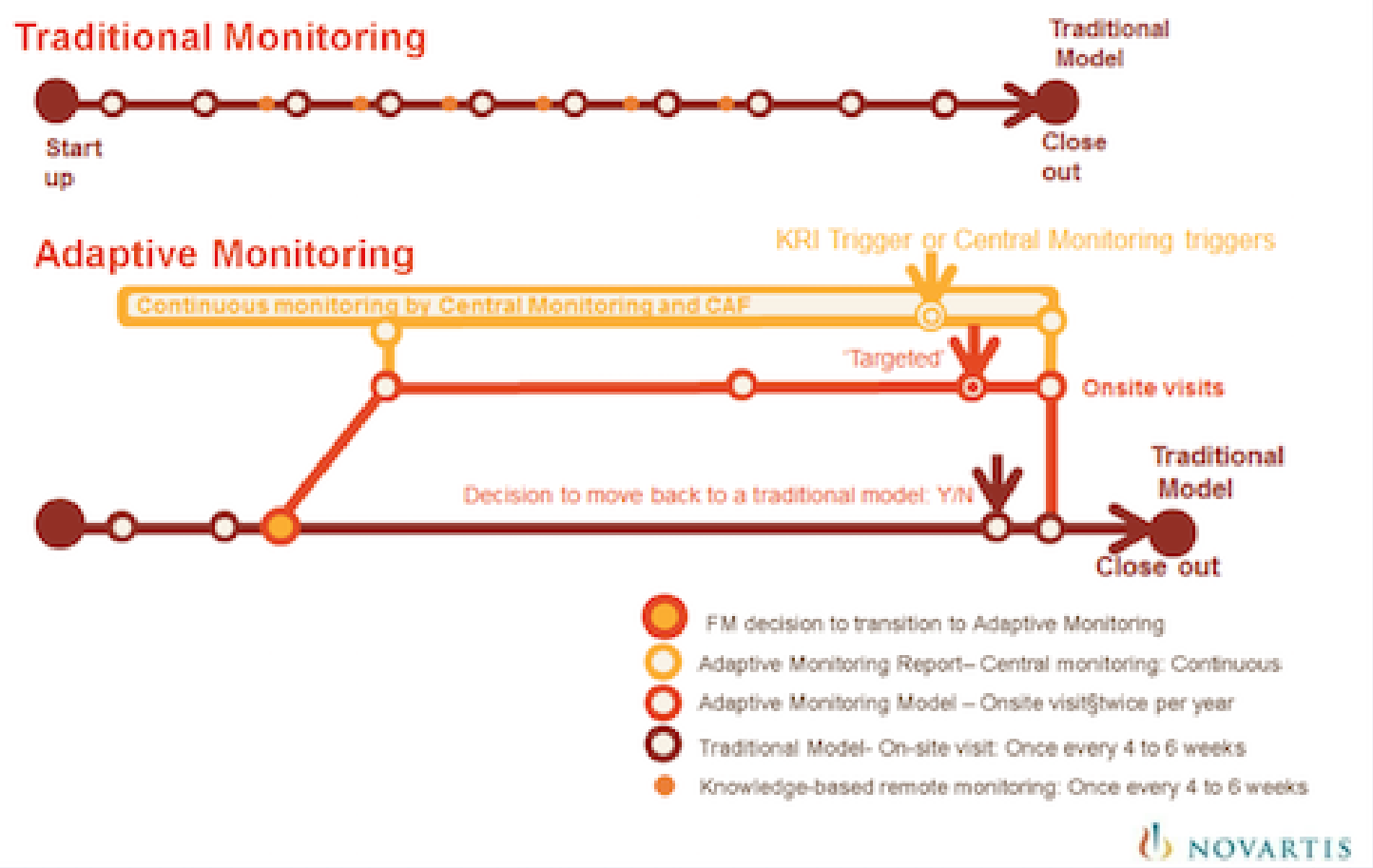
GBM AGILE: Value to Academics and Physicians

- Provides Late Stage Clinical Trial Portfolio
  - Less bias toward what is thought to be better drug
- Leadership Opportunities
  - lead late stage development of therapy
  - Broader international community interactions/engagement
- Opportunities for Continuous learning
  - Massive, longitudinal, highly annotated data set (imaging, outcomes, biomarkers) available to community of investigators

Clinical Development: Early to Late Stage Development in Neuro-Oncology



Complexity


Traditional Monitoring
Traditional Model
Start up
Close out
Adaptive Monitoring
KRI Trigger or Central Monitoring triggers
Continuous monitoring by Central Monitoring and CAF
"Targeted"
Onsite visits
Traditional Model
Decision to move back to a traditional model: Y/N
Close out
FM decision to transition to Adaptive Monitoring
Adaptive Monitoring Report– Central monitoring: Continuous
Adaptive Monitoring Model – Onsite visit§twice per year
Traditional Model- On-site visit: Once every 4 to 6 weeks
Knowledge-based remote monitoring: Once every 4 to 6 weeks
NOVARTIS

Challenges & Opportunities

Questions?