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How to design trials to meet the perspectives of personalized cancer medicine

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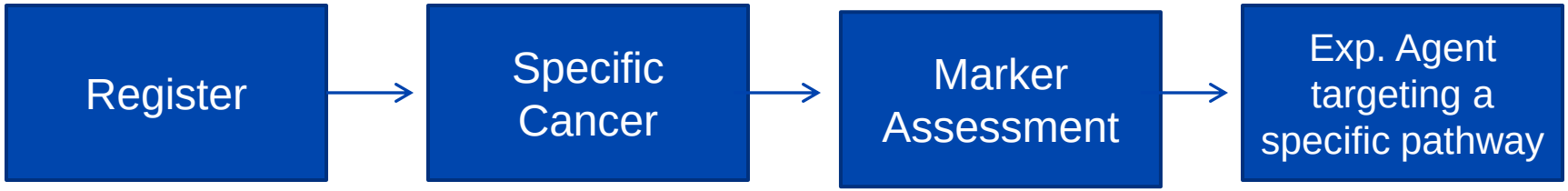
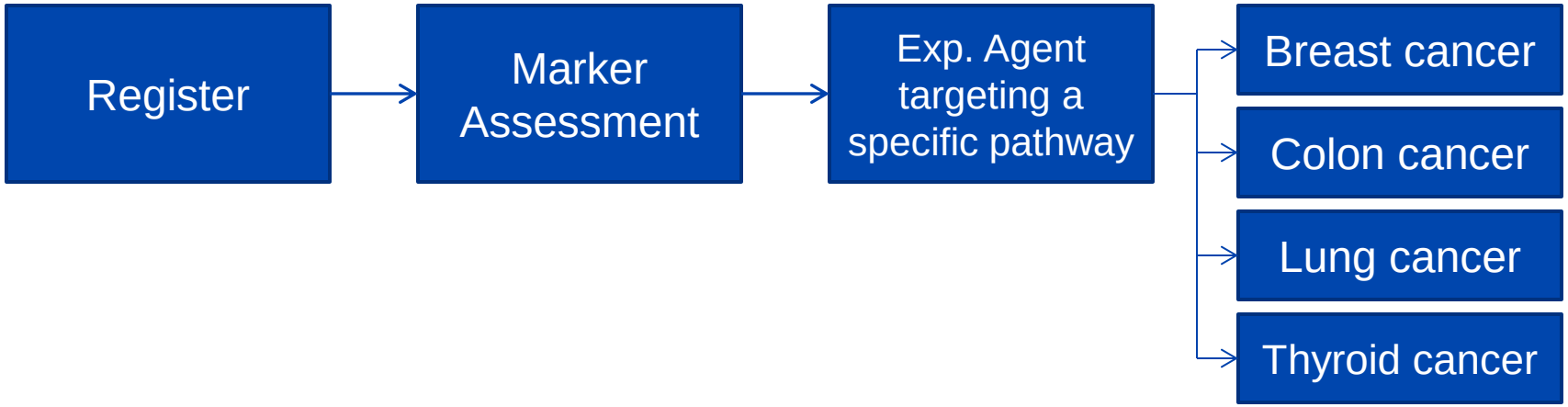
Molecular Profiling: Challenges and Perspectives
Special Symposium
ESMO Congress, September 28, 2014

Disease-based Trials

Disease-based and Marker-based Trials



Marker-based Trials



Early Phase Design Considerations

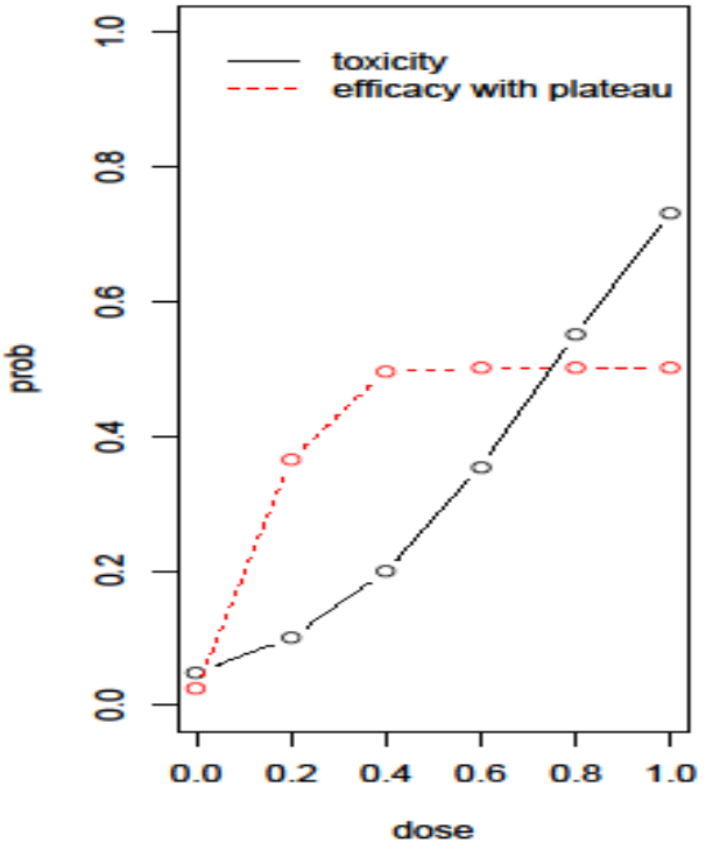
- Establish preliminary efficacy signal, in addition to understanding safety
  - Choice of endpoints
  - Model-based design algorithms

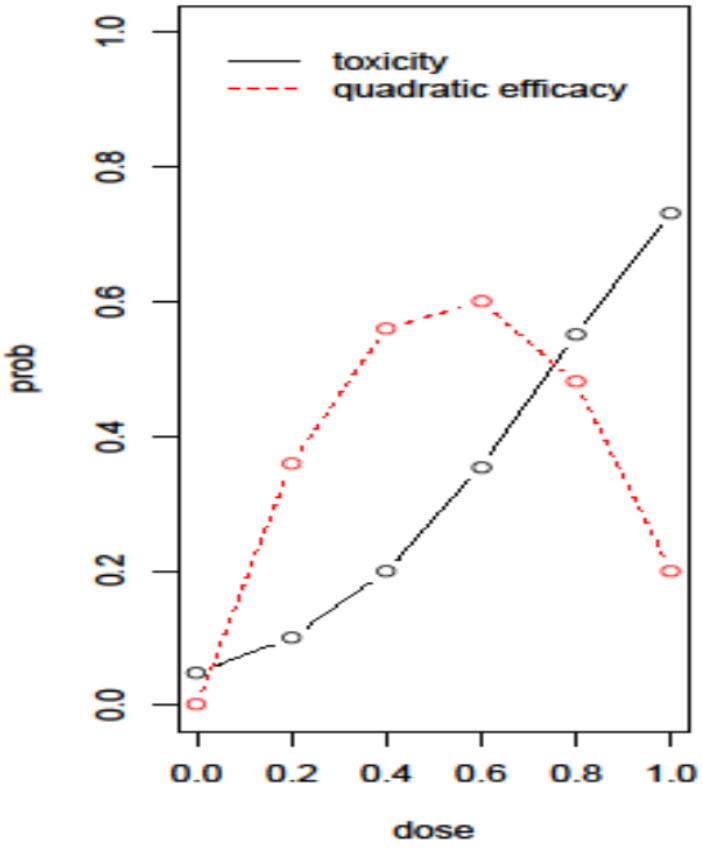
- Identify subsets of patients most likely to benefit from the new treatment
  - Enrichment strategies
  - Expansion cohorts

Choice of Endpoints

- **M**aximum **T**olerated **D**ose
  - Highest safe dose is the most efficacious dose?
- **M**aximum **E**ffective **D**ose
  - Incorporate a measure of efficacy in addition to safety assessment – Dual Endpoints.
    - Toxicity; and Biomarker or clinical response
- Challenges with biomarker assessments:
  - Correlation between biomarker and clinical outcome established?
  - Assay characteristics and performance?
  - Assessment time points?

Model Based Designs
Dynamic estimation of the dose-toxicity and dose-efficacy curves





Patient Selection

- Enrichment strategies: pros
  - Identify subsets who benefit most from treatment
  - Increase feasibility of trials in rare genotypes
  - Examples:
    - Crizotonib for ALK positive NSCLC
    - Vemurafenib for BRAF mutation melanoma
- Enrichment strategies: caution!
  - Valid assays?
  - Real time assessment?
  - Complete understanding of tumor biology?
  - Complete understanding of drug metabolism pathway?

Chapman et al., NEJM 2011; Shaw et al., NEJM 2013

Expansion Cohorts

- Studying safety profile
- Exploring neighboring dose levels for BOD/MED
- Performing PK/PD studies
- Assessing efficacy in enriched subgroups

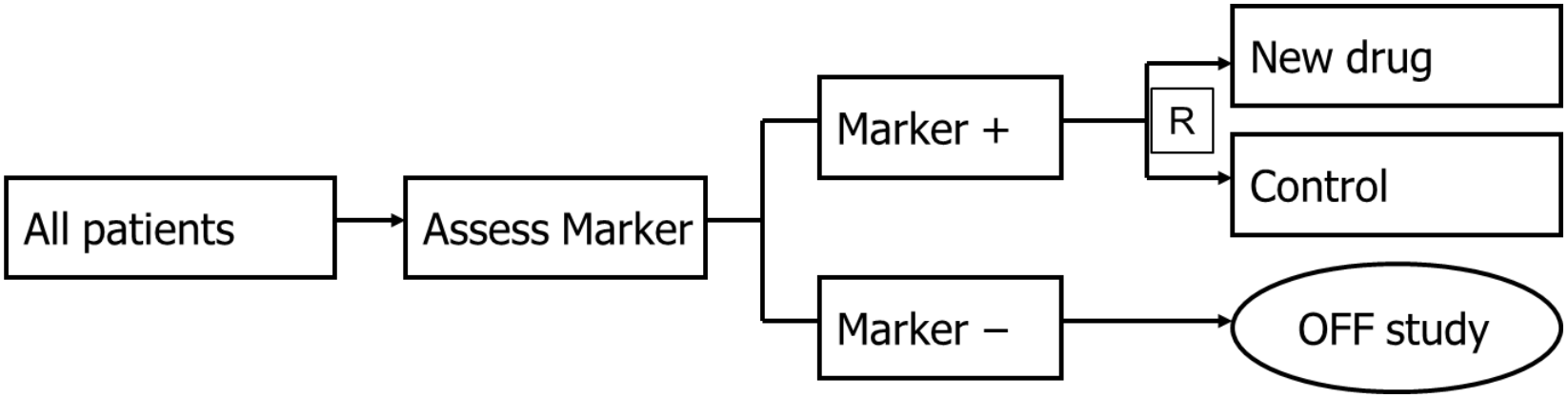
- Design of expansion cohorts:
  - Rigorous: pre-defined hypotheses etc.

  OR
  - Exploratory – refine assay, cut points, patient subset identification

Manji et al., JCO 2013

Phase II and III Design Considerations
Single marker case

Enrichment or targeted trial design



- Randomize marker positive patients only

Enrichment Design example: Vemurafenib in Melanoma with BRAF V600E Mutation

- Compelling evidence: Prior phase I and phase II trials demonstrated response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.
  - 5 patients with WT did not respond in Phase I to therapeutic doses of Vemurafenib
- Phase III trial: Patients with BRAF V600E mutation were randomized 1:1 to vemurafenib with dacarbazine
- Central testing: At one of five central laboratories in the United States, Germany, and Australia.
- Vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine ($P<0.001$ for both comparisons).

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Chapman et al., NEJM 2011

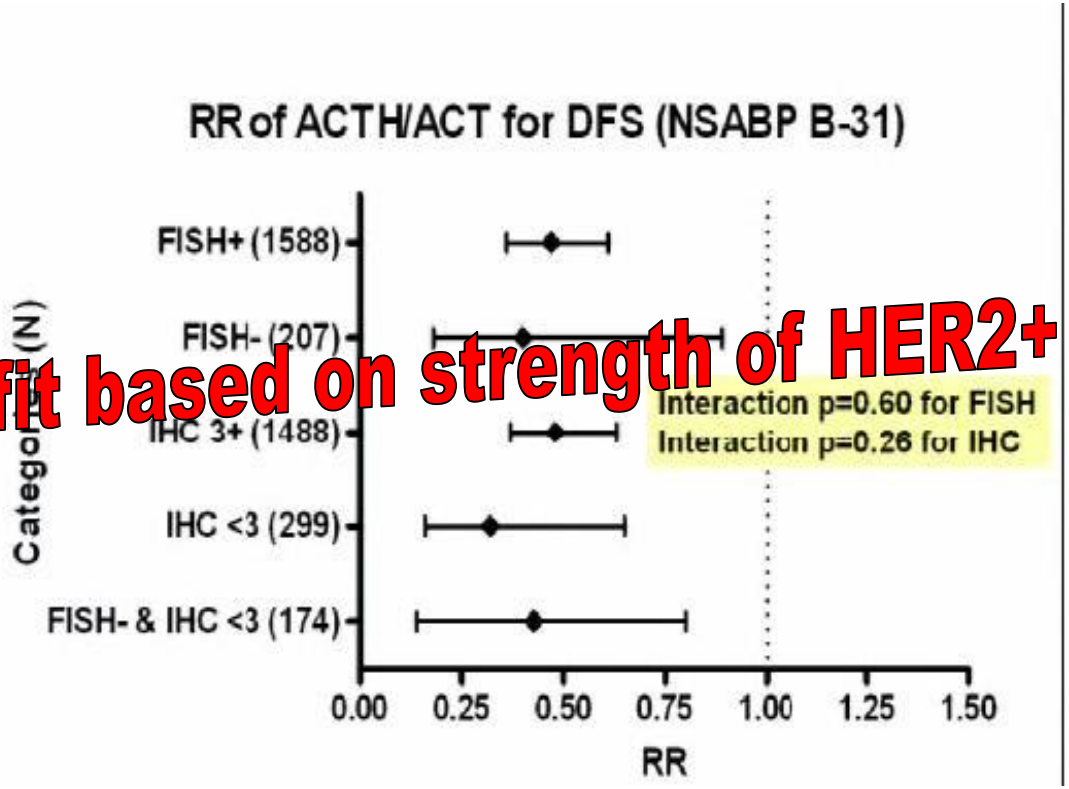
Using markers to restrict trial eligibility: beware

Table 1. Relative Risks of Disease Progression and Death among Patients in the ACT with the ACT Group.*

End Point and Central HER2 Assay†	ACT	ACTH	Relative Risk (95% CI)
	no. of events/total no. of events		
Disease progression			
HER2-positive	163/875	85/804	0.47 (0.37–0.62)
HER2-negative	20/92	7/82	0.34 (0.14–0.80)
Death			
HER2-positive	55/875	38/804	0.66 (0.43–0.99)
HER2-negative	10/92	1/82	0.08 (0.01–0.64)

* The 95% confidence intervals (CI) and P values were adjusted according to the numl gen-receptor status from the univariate Cox proportional-hazards model for each subg Adjuvant Breast and Bowel Project B-31 trial. ACT denotes doxorubicin, cyclophospha ACT plus trastuzumab.

† Central HER2 assay results were defined as negative if they were negative by both flu (PathVysion, Vysis) and immunohistochemical analysis (Herceptest, Dako) and were

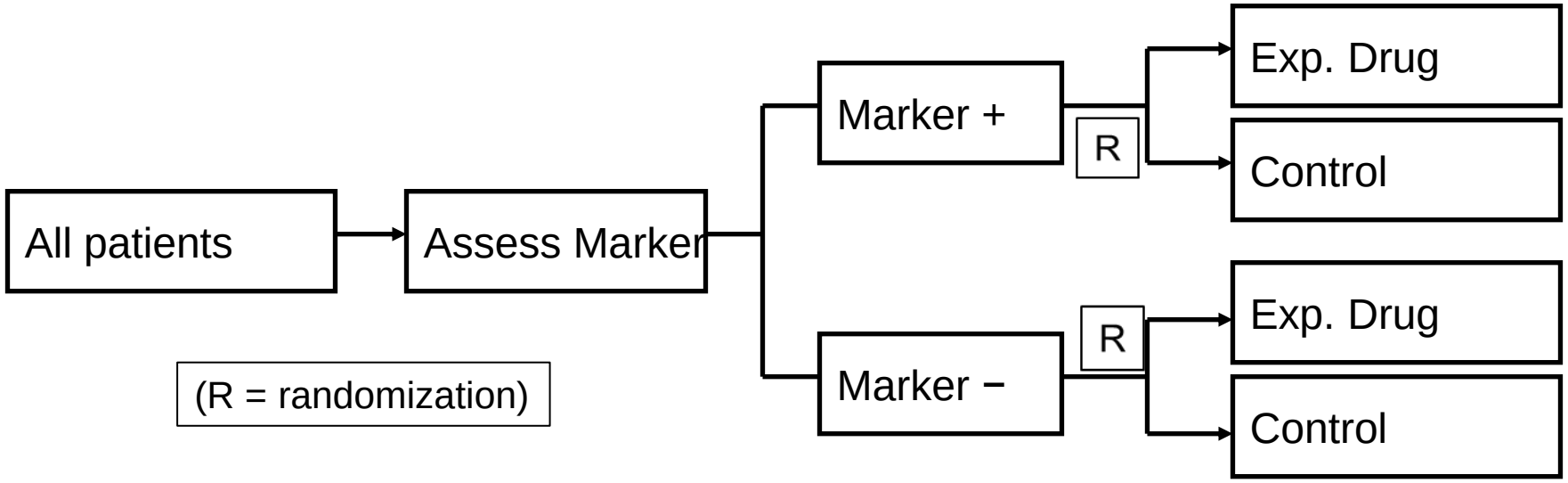


No difference in benefit based on strength of HER2+

Ongoing study of Herceptin in patients with low (1+ or 2+) HER2-positive BC.

Paik et al, NEJM 2008
Hayes et al., NEJM 2011

Marker by treatment interaction Design, AKA Biomarker Stratified Design



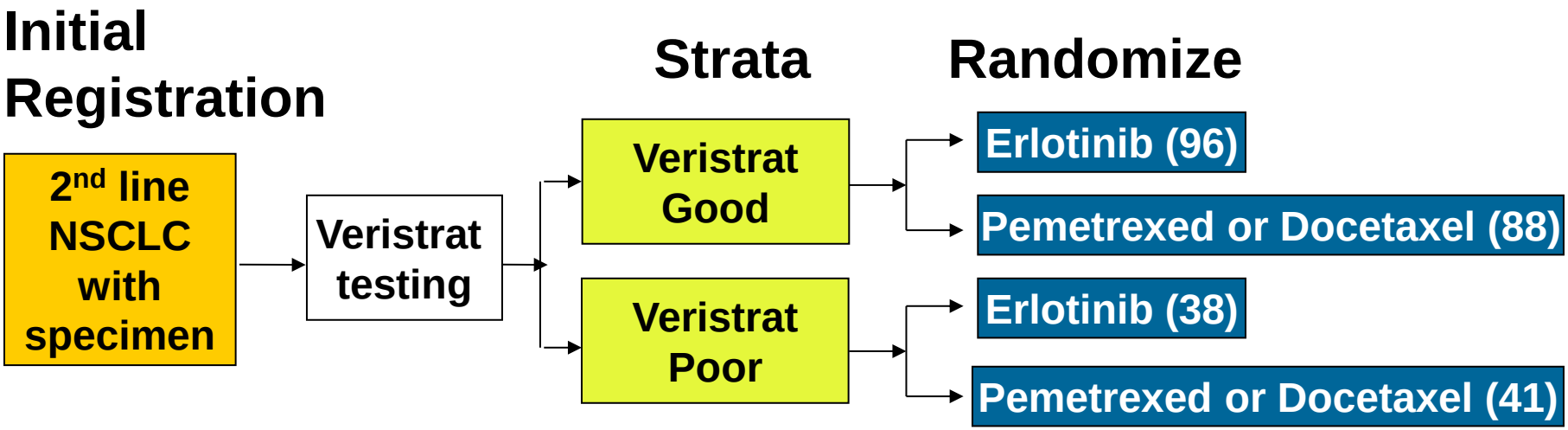
Randomize all patients, stratified by marker status.

Mostly used in settings with two approved regimens.

Sargent et al., JCO 2005; Mandrekar et al. JCO 2009

Randomized Proteomic Stratified Study of Second-Line Erlotinib versus Chemotherapy in Patients with Inoperable Non-Small Cell Lung Cancer
PROSE Trial

VeriStrat is a serum based protein assay.

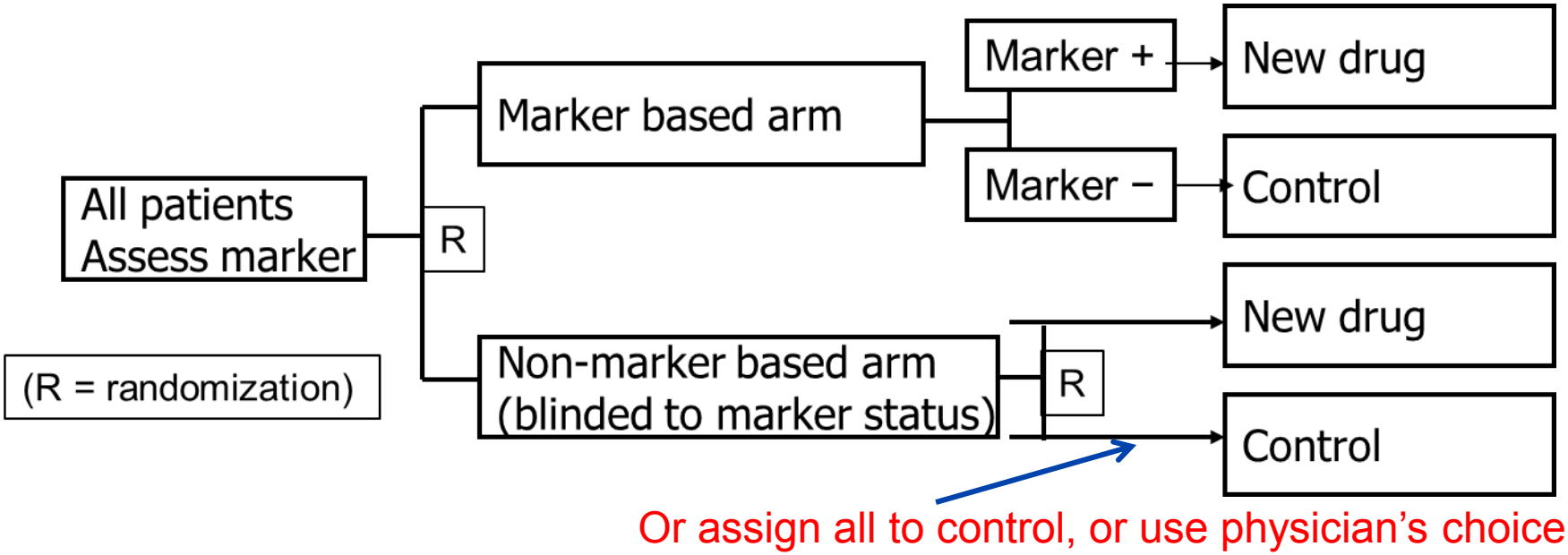


Primary Endpoint: Overall Survival; Secondary: PFS, RR

Good group: No difference in OS; Poor Group: Chemo better than Erlotinib
Significant interaction between treatment and veristrat classification (p=0.037)

Gregorc et al., ASCO 2013; WCLC 2013

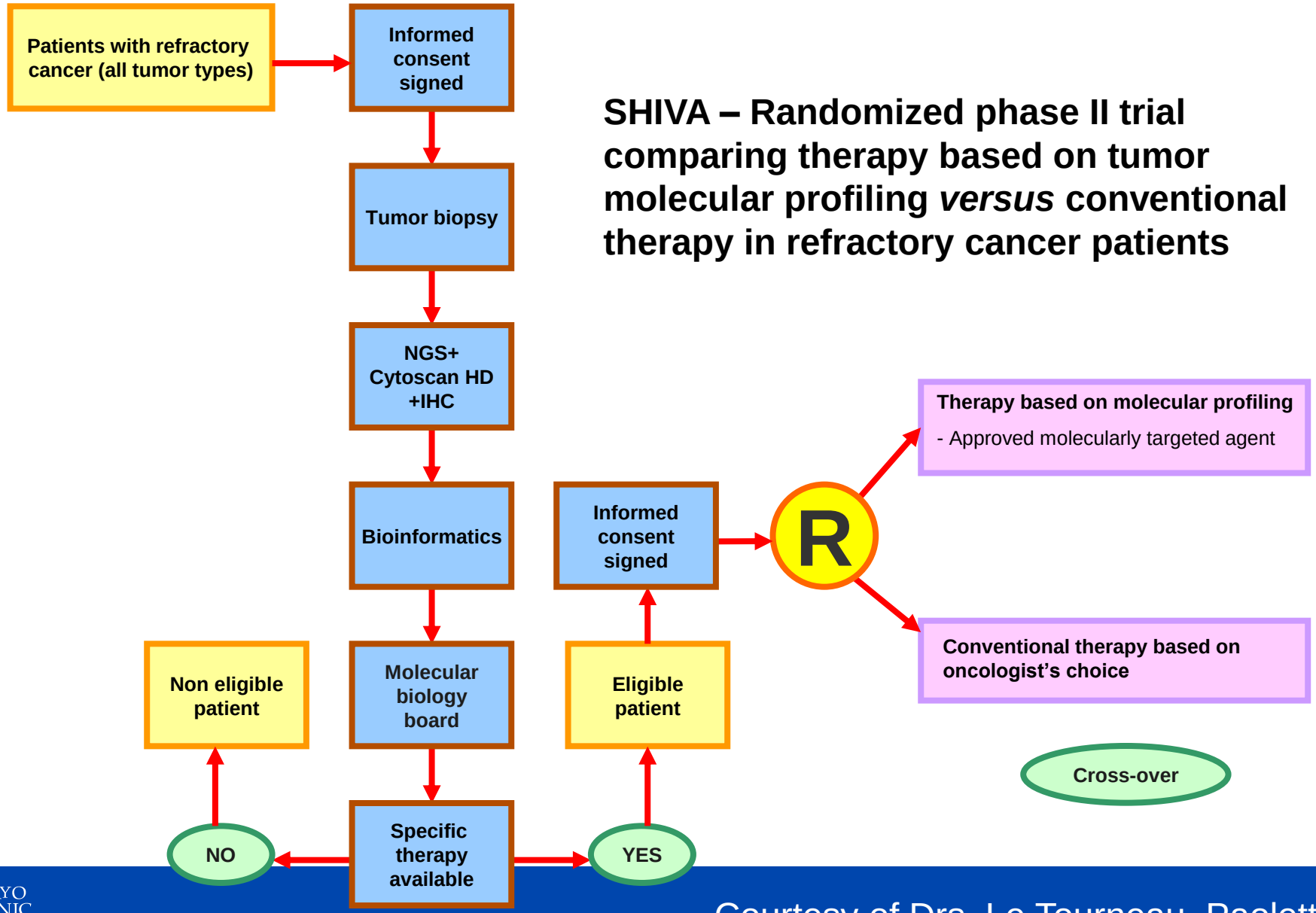
Marker Strategy design



- %Overlap in treatments on both arms – dilutes the ability to distinguish treatment from marker effect!
- Special considerations needed for the randomization ratio to marker prevalence in the non-marker based arm

Sargent et al., JCO 2005; Mandrekar et al. JCO 2009

Enrichment followed by “modified” marker strategy design



SHIVA – Randomized phase II trial comparing therapy based on tumor molecular profiling *versus* conventional therapy in refractory cancer patients

Courtesy of Drs. Le Tourneau, Paoletti

SHIVA Design Details

- Endpoint: 6 months PFS rate

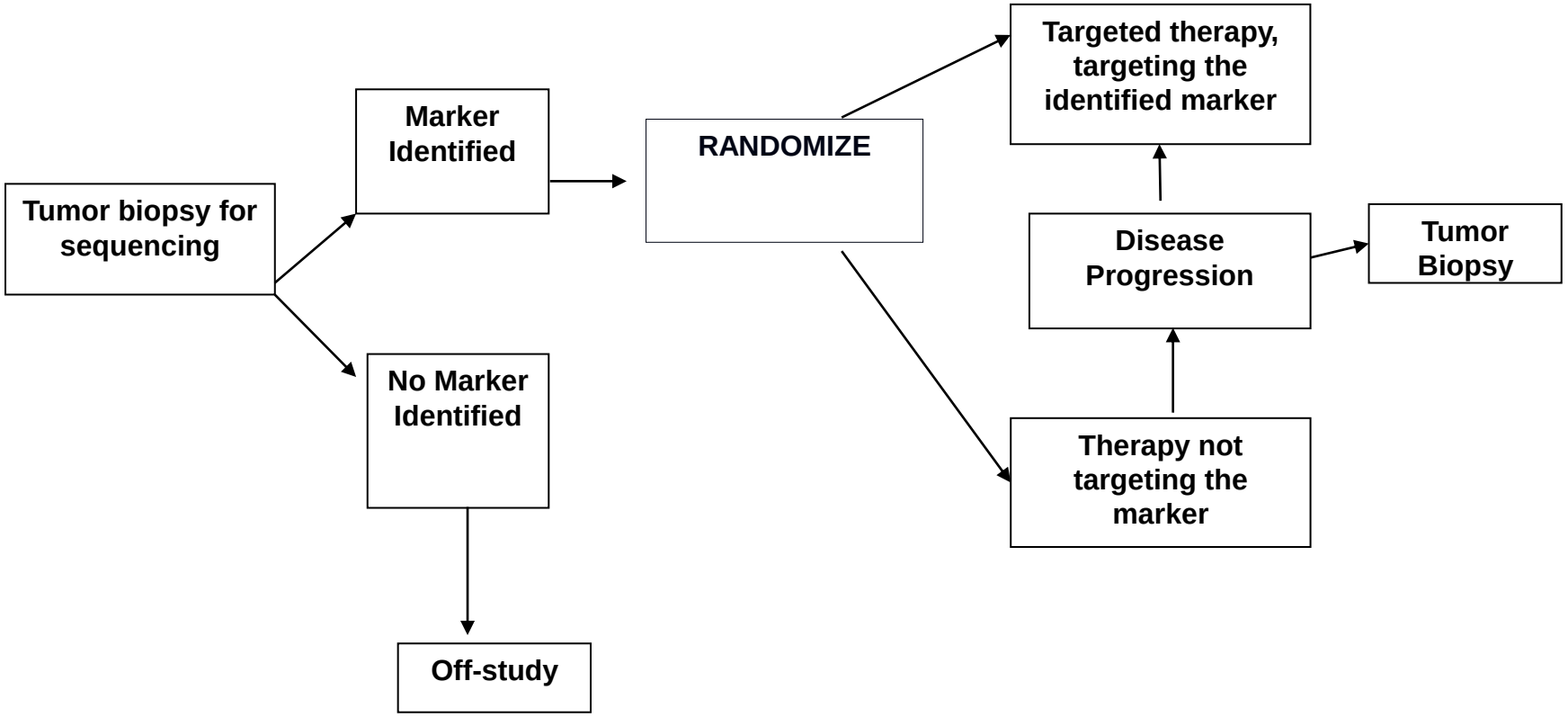
- Hypothesis: 15% for cytotoxic agents versus 30% in the experimental arm (HR = 1.6)

- → 142 events; 2-sided type 1 error of 5%, power of 80%
- → 200 patients to be randomized (~1000 screened)

NCI Precision Medicine Initiatives

Enrichment followed by modified marker strategy design

M-PACT Trial



Endpoints: response rate and 4-month progression-free survival

Single marker case: Prevalence Considerations

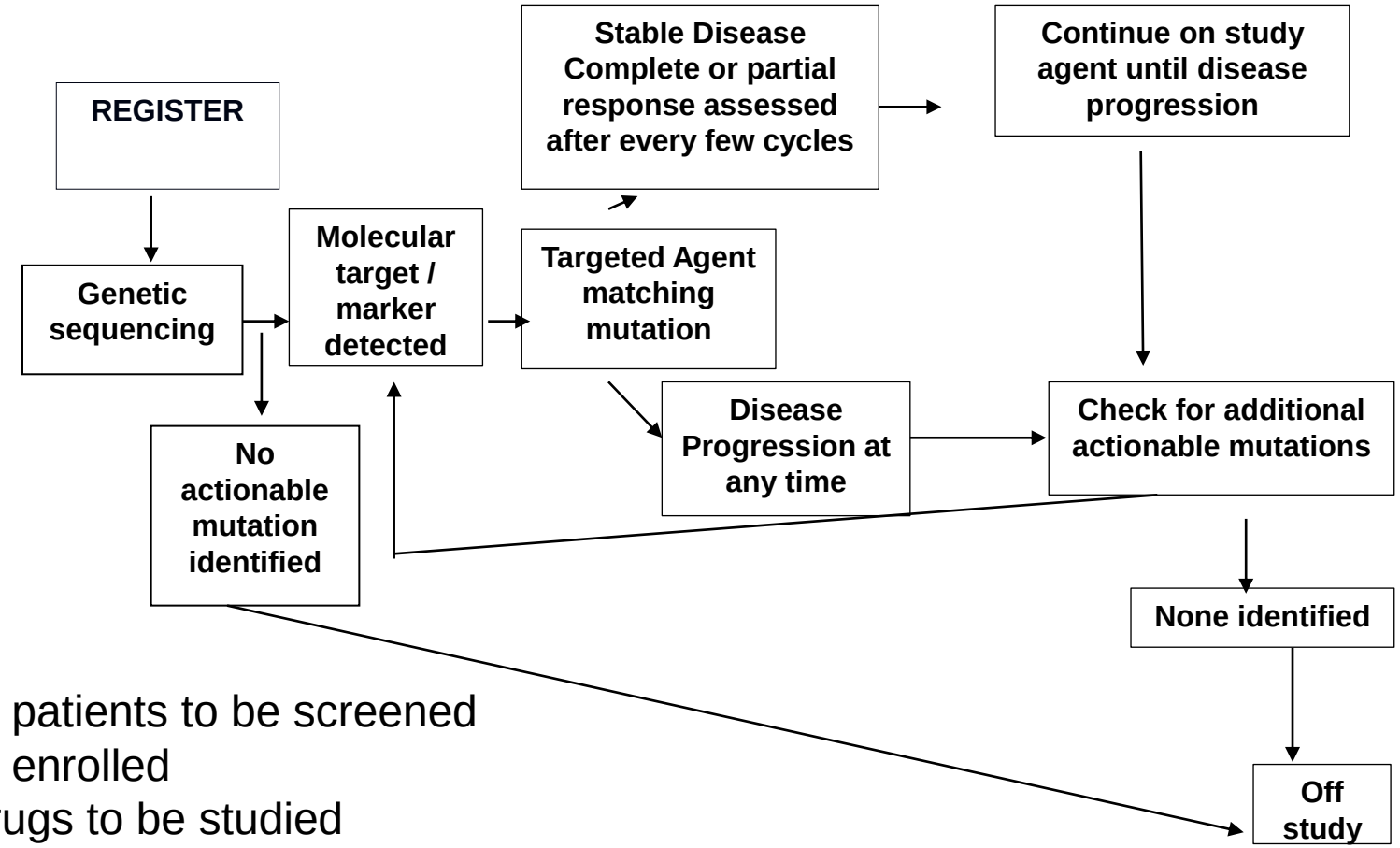
- Low (< 20%): Consider enrichment designs
- High (>50%): All-comers with retrospective marker subgroup assessments or adaptive designs
- Moderate (20%-50%):
  - Stratified by marker, primary hypothesis in one marker subset; but enroll all to confirm no benefit in the other subgroup

Rare populations: N of 1?

- Enroll and treat few subjects
- Examine genomic profiles
  - Match treatment to genomic profile?
- Assess safety and efficacy within:
    - Certain tumor types, and/or
    - Certain genomic profiles
- Basket Trial Designs
  - 1st phase: unselected population -- Identify patients who benefit using genomic profiling, NGS etc.
  - 2nd phase: prospectively screen patients with that profile, parallel phase 2 studies

NCI Precision Medicine Initiatives

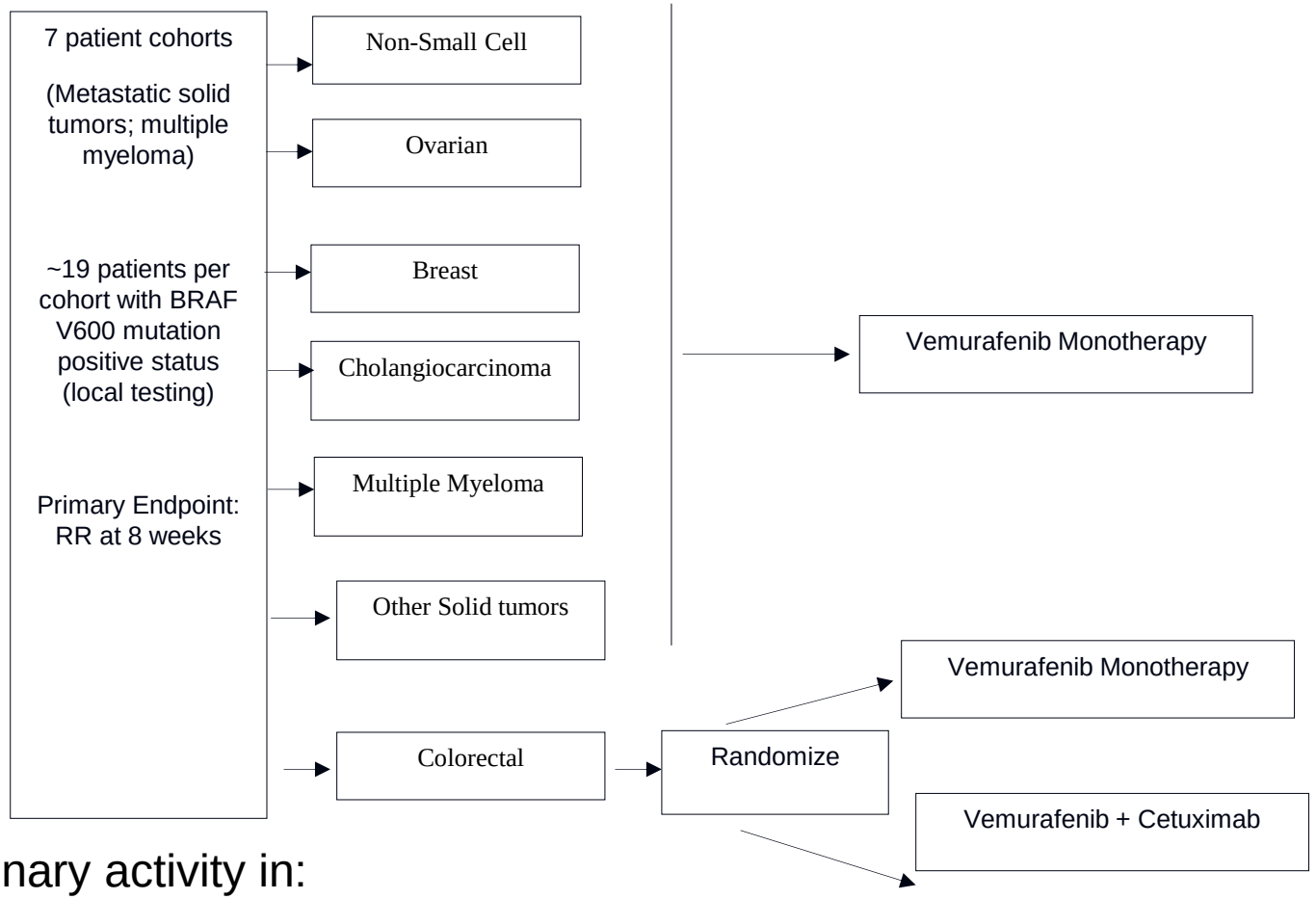
MATCH Trial (ECOG-ACRIN)



~3000 patients to be screened
~1000 enrolled
~15 drugs to be studied

Endpoints: Response Rate and 6-month Progression-free Survival Rate
Success: > 25% RR, and/or > 35% 6-month PFS rate

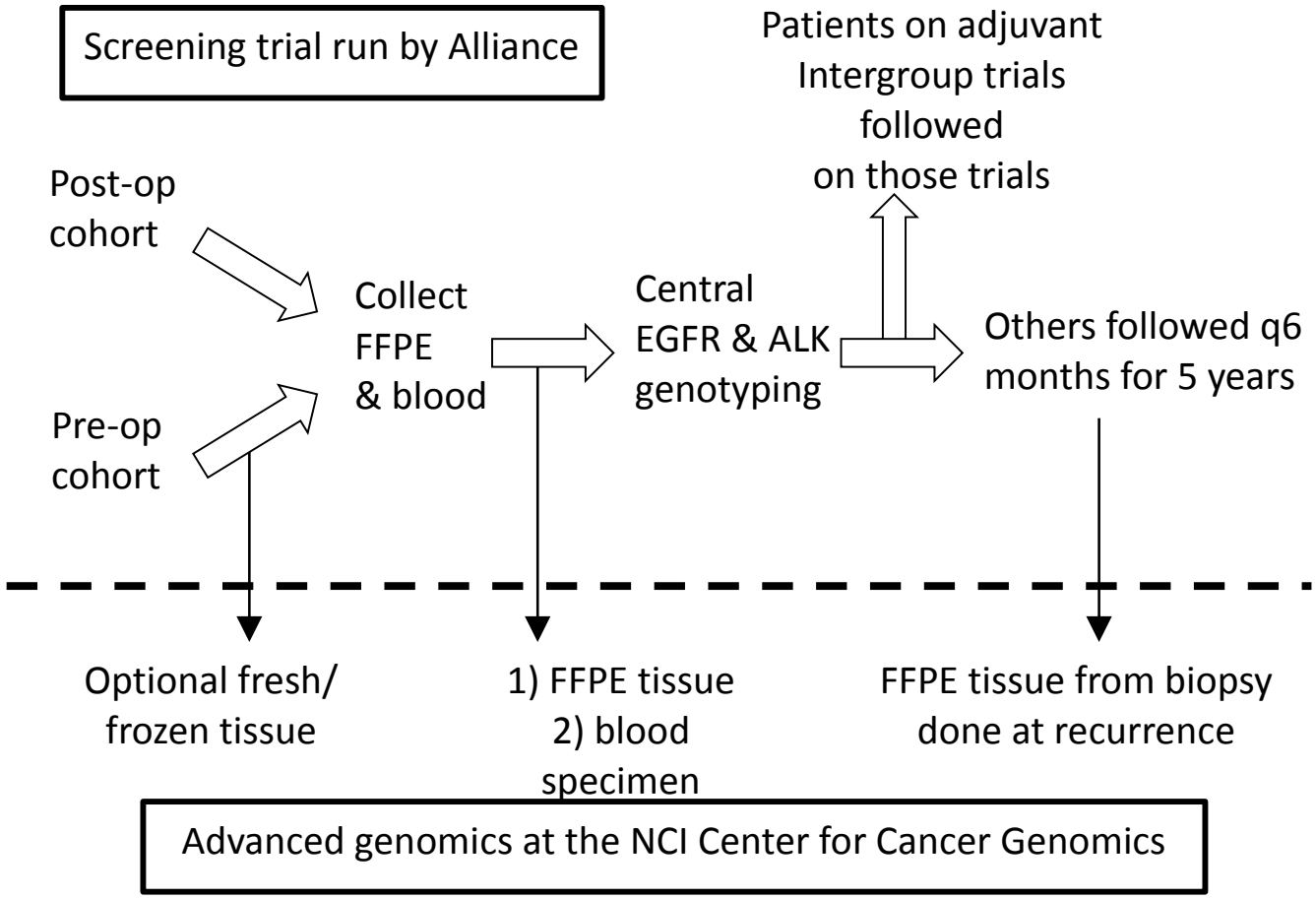
Vemurafenib Basket trial (VE-BASKET): Non-Melanoma BRAF V600-mutation positive tumors



Preliminary activity in:
NSCLC, Orphan tumors, Cholangiocarcinoma

Hyman et al., ASCO, 2014

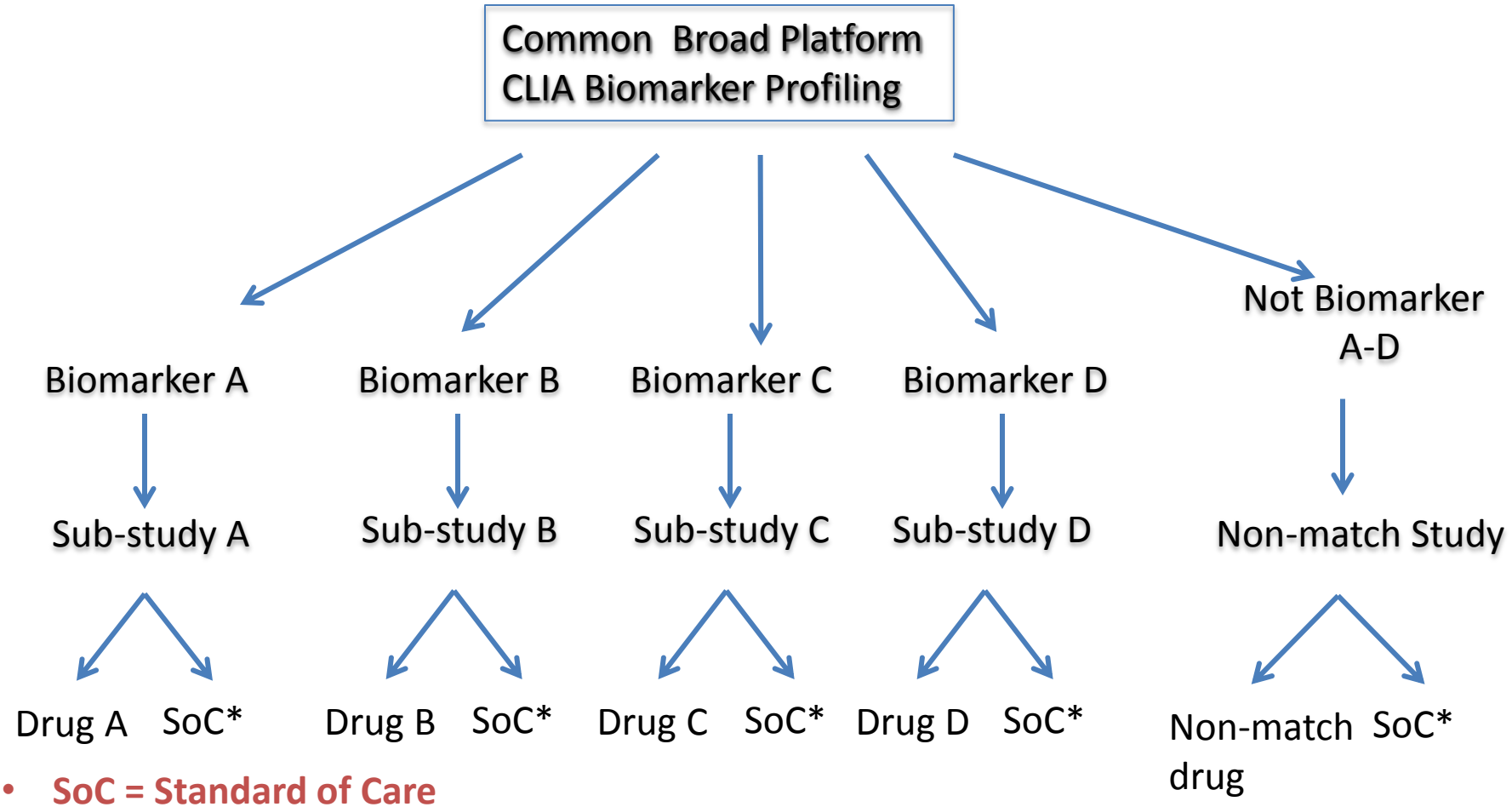
Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)



ALK-prevalence ~ 5%; EGFR mutation prevalence ~10-15%

Phase II and III Design Considerations
Multi marker scenario

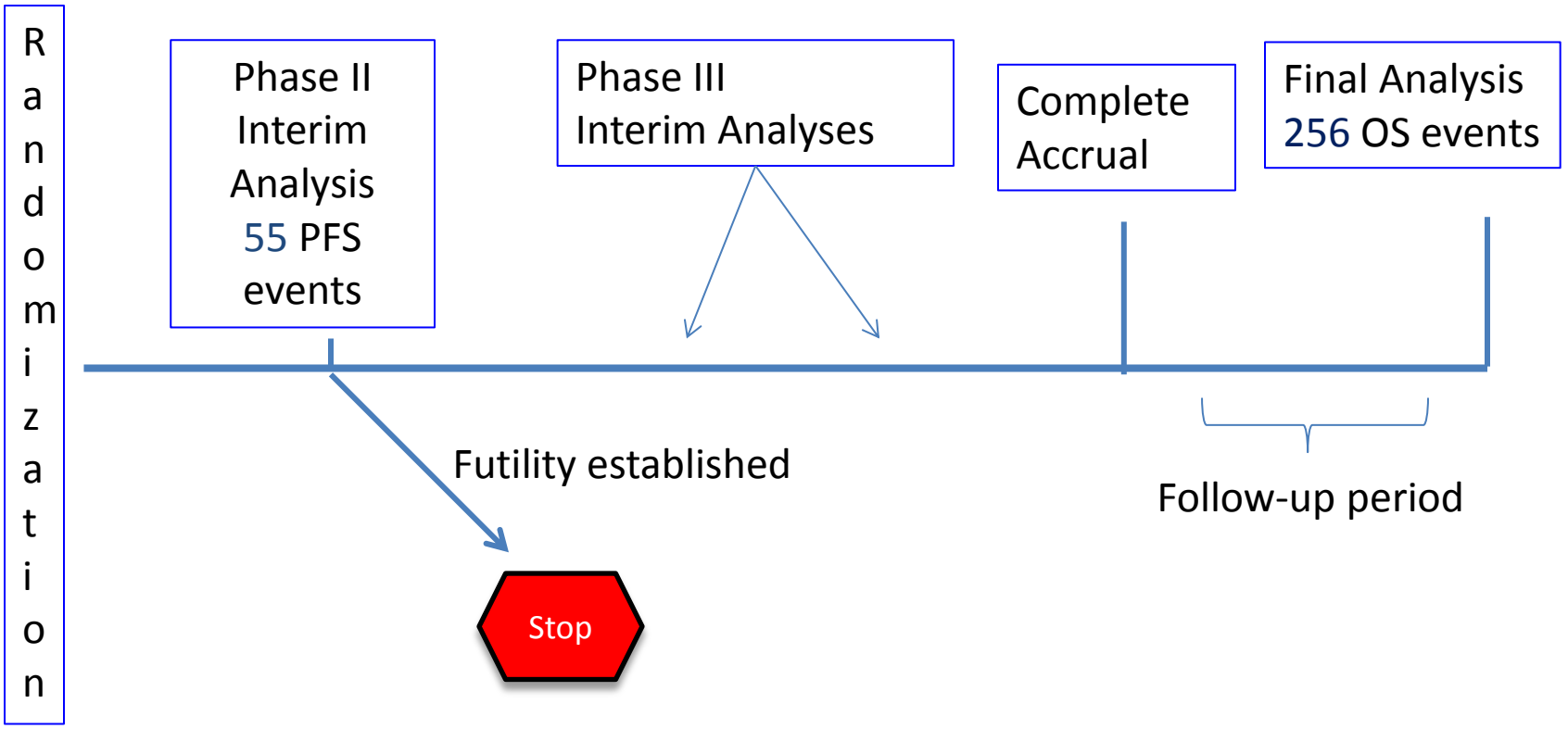
SWOG S1400 Master Lung Protocol Design: Lung-MAP



- SoC = Standard of Care
- Experimental drug could be single agent or a combination; SoC can vary by biomarker.
- Patients with multiple markers assigned randomly to a sub study: randomization ratio matching marker prevalence

Courtesy of Dr. Redman, SCT, 2014

Phase II/III Design: SWOG S1400



PFS: Primary endpoint for Phase II
OS: Primary endpoint for Phase III

Courtesy of Dr. Redman, SCT, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

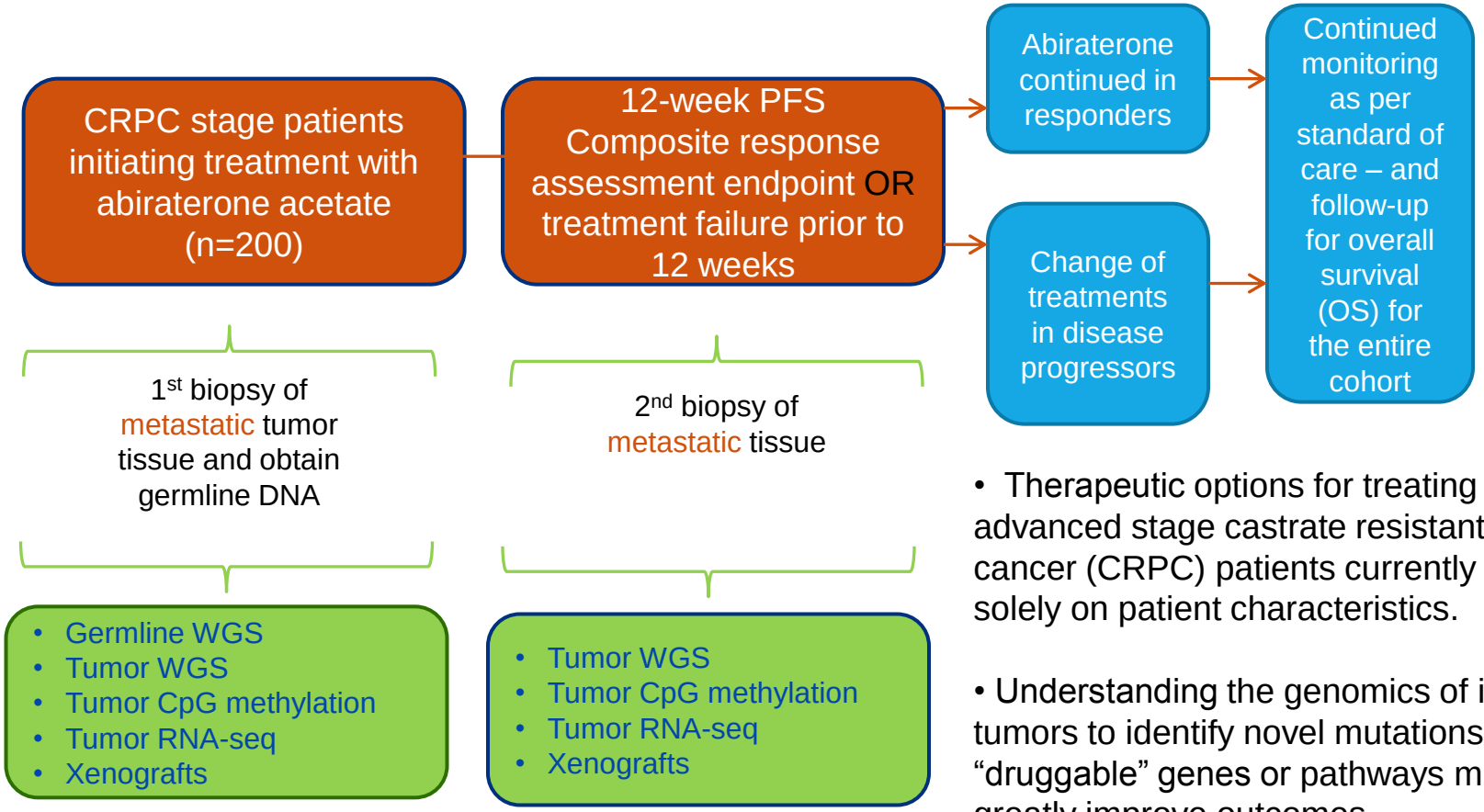
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.

Once you start studying medicine you never get through with it
--Dr. Charles H. Mayo

PROstate cancer Medically Optimized genome enhanced ThErapy – I (PROMOTE)
PI: Dr. Kohli



- Therapeutic options for treating advanced stage castrate resistant prostate cancer (CRPC) patients currently based solely on patient characteristics.

- Understanding the genomics of individual tumors to identify novel mutations in “druggable” genes or pathways might greatly improve outcomes.

PROMOTE-II Design based on PROMOTE-I

- Compelling evidence: Enrichment design
- Fairly strong, but not compelling evidence: Biomarker Stratified design
- Evidence preliminary and exploratory: adaptive design

Treatment of Platinum resistant Ovarian Cancer (PI: Dr. Haluska)

- Avatars generated at the time of surgery.
- Upon engraftment, the avatars would be expanded in platinum-chemotherapy to develop platinum resistant disease.
- Upon regrowth (typically 4-8 weeks), randomized to one of 4 salvage regimens.

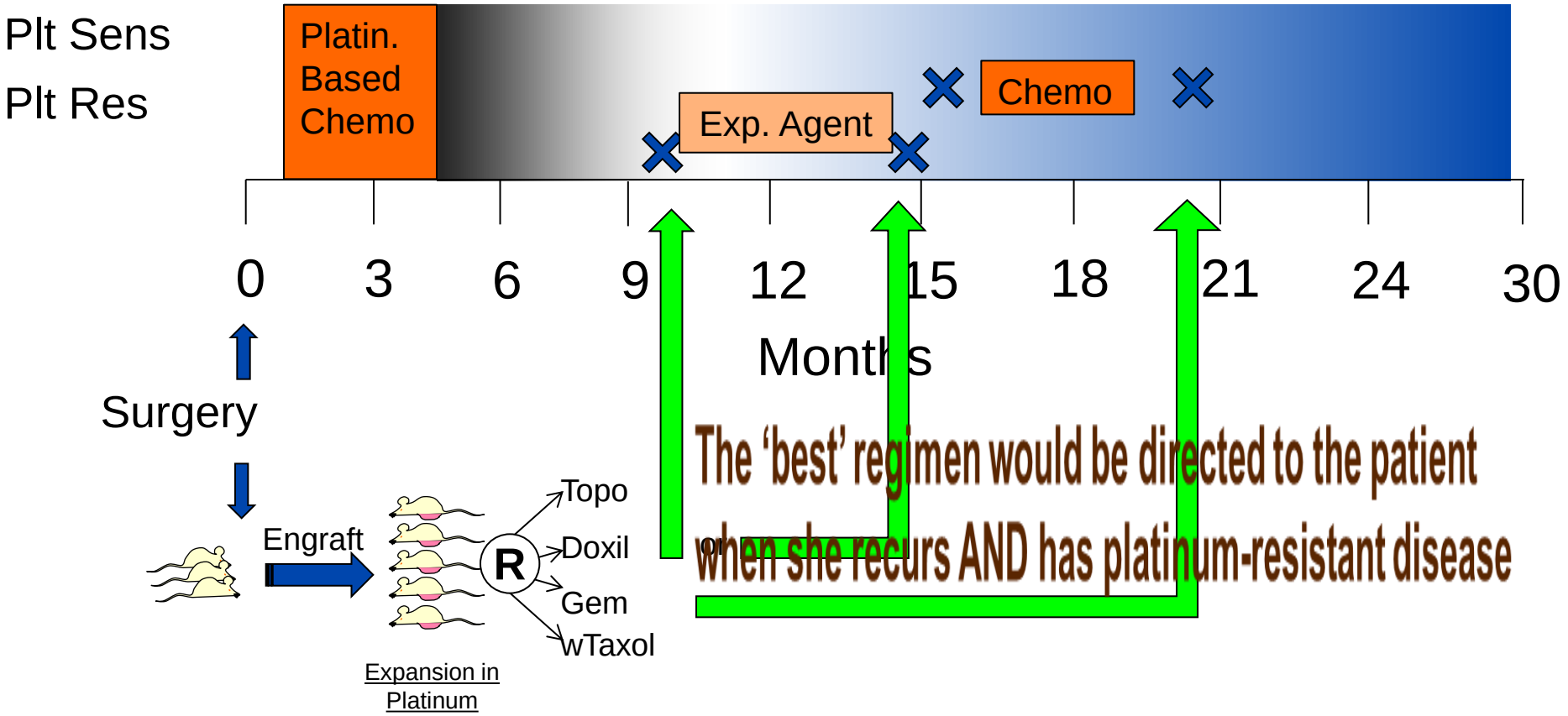
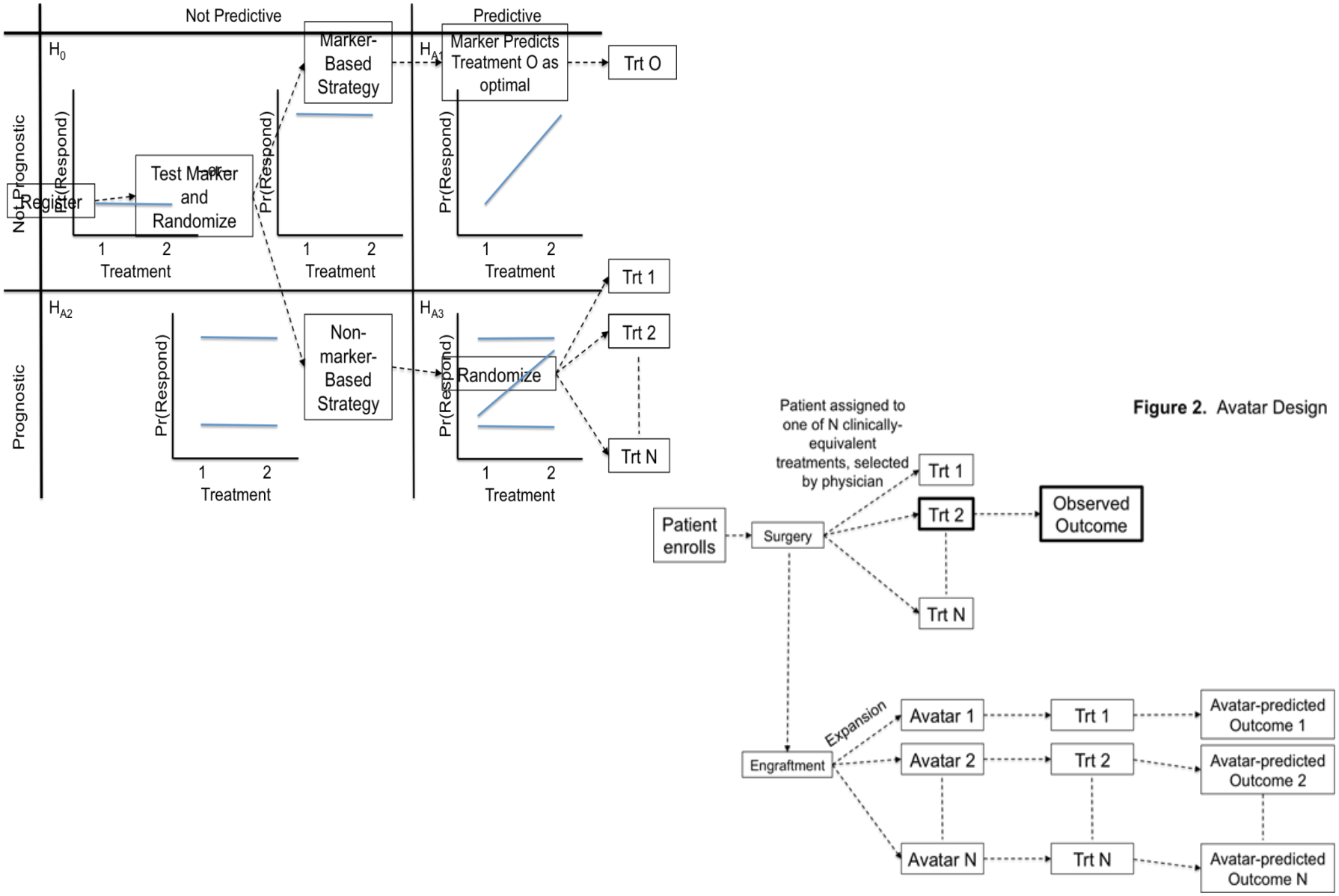


Figure 1. Marker Strategy Design

Figure 2. Avatar Design



Overall Design Strategy Recommendations

- Phase I: No restrictions
  - Use expansion cohorts to further understand marker-subgroup effects, endpoints etc.
- Phase IIa (optional): Single arm, enriched
  - Proof of concept
- Phase IIb: Randomized phase II unselected
  - Primary comparison: Marker (+)
  - Randomize enough Marker (-) to demonstrate lack of benefit
  - Consider adaptive designs
- Phase III: Based on randomized phase II
  - Enrichment, all-comers, marker-stratified, marker-strategy, adaptive

Important Considerations Integral Biomarker Studies

- Strength of pre-clinical evidence of the marker
  - Restrict patients based on marker status or enroll all patients regardless of the marker status?
- Reproducibility and validity of assays
  - Local versus Central Testing
- Prevalence of the marker
  - Low versus moderate
  - Threshold for cut offs; detection limits?
- Feasibility and timing of biomarker assessments
  - Multiple biopsies: pre and post treatment
- Key Message: You cannot have many moving parts or unknowns in the design of a trial

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THANK YOU FOR YOUR ATTENTION

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