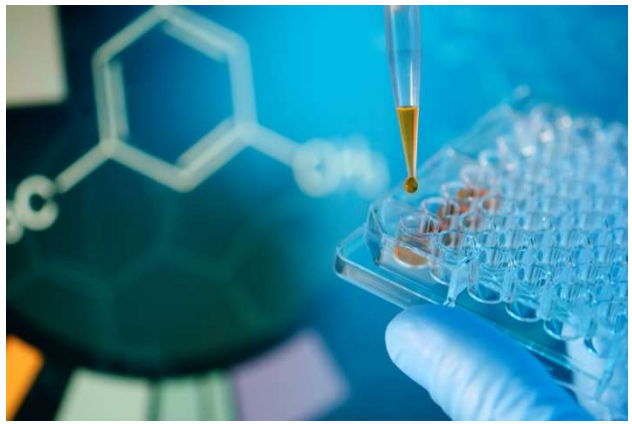
Innovative Early Phase Clinical Trial Designs



Shivaani Kummar, MD, FACP
Professor of Medicine
Director, Phase I Clinical Research Program-Oncology
Co-Director, Translational Oncology Program
Director, Clinical and Translational Unit
Stanford University

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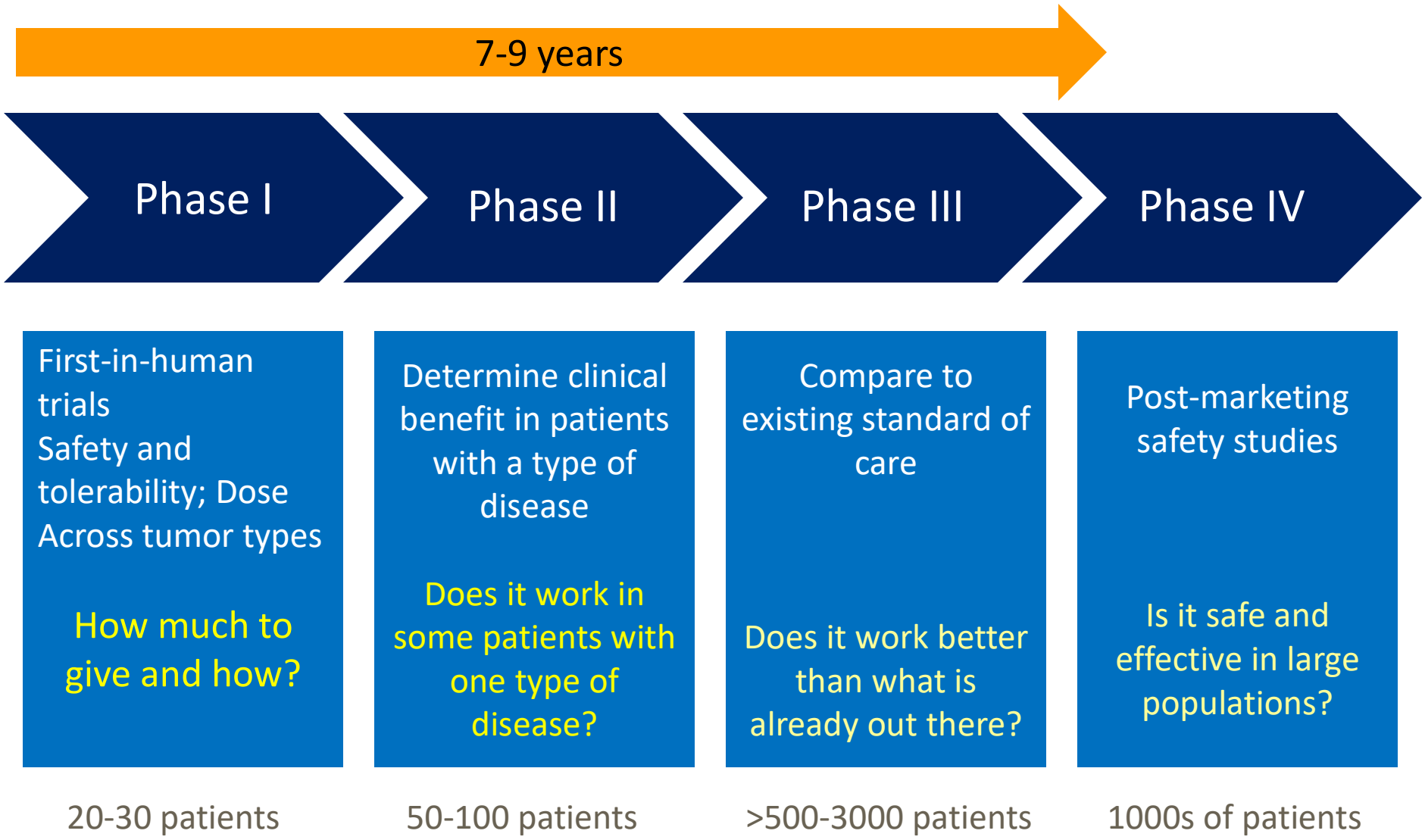
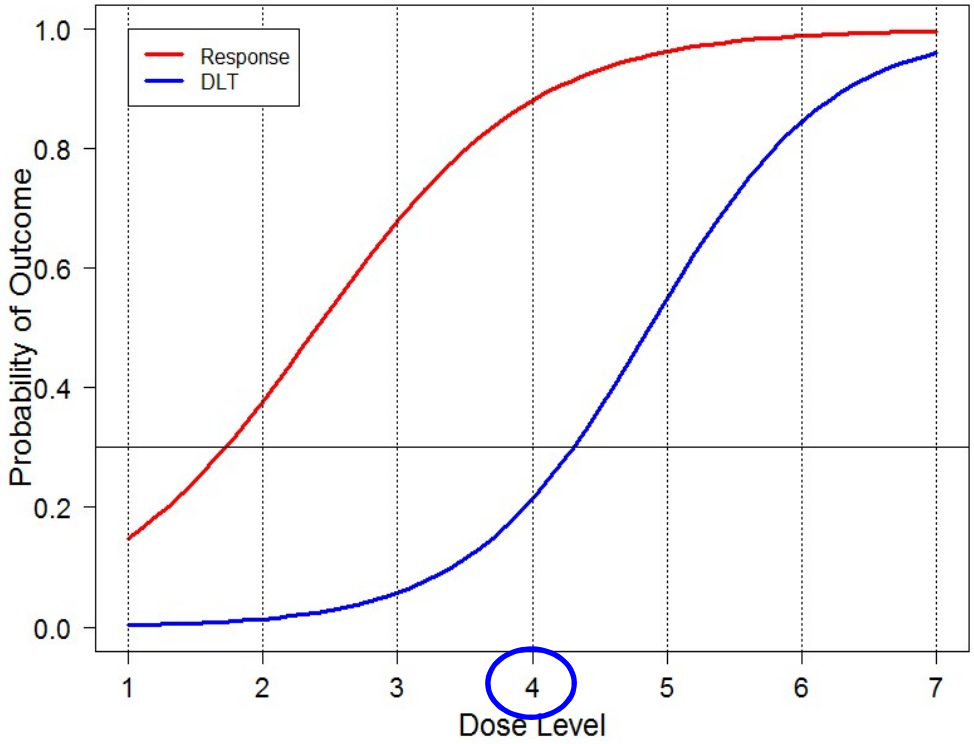
Stages of Clinical Research-Traditional



Toxicity driven dosing : Hypothetical dose-response and dose-toxicity (DLT) curves



Dose Escalation to Establish MTD

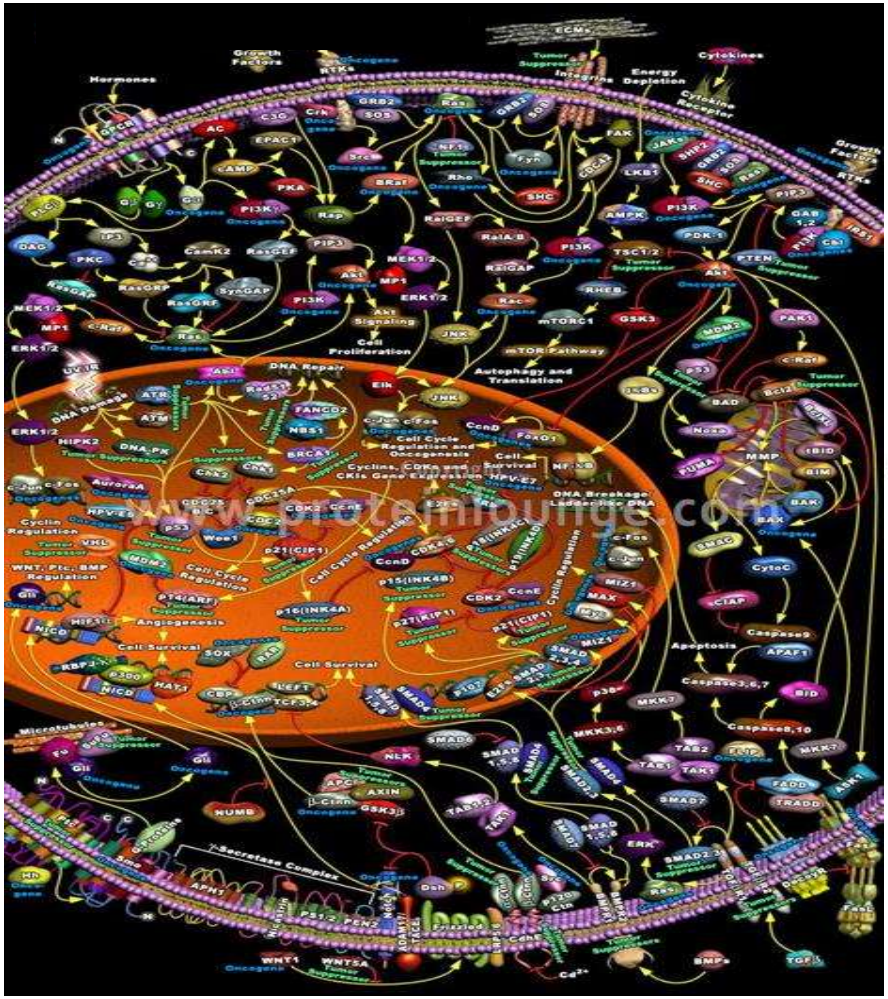
Rule-based designs:

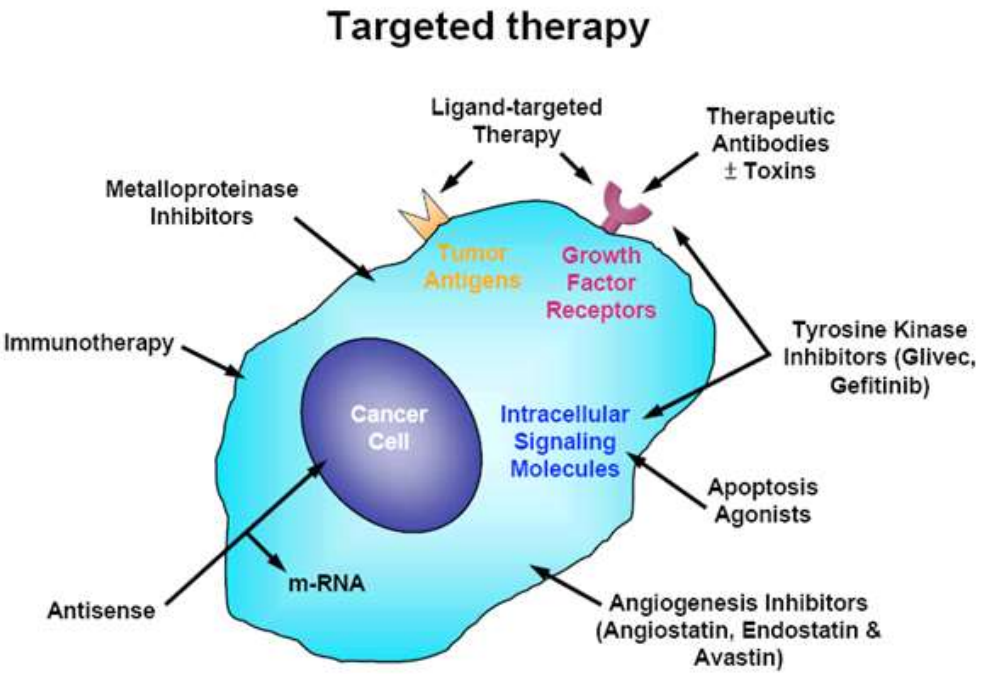
Assign patients to dose levels according to pre-specified rules based on actual observations of target events (e.g., the dose-limiting toxicity) from the clinical data. (3+3 design; accelerated titration design)

Model-based designs:

Assign patients to dose levels and define the MTD for phase II trials based on the estimation of the target toxicity level by a model depicting the dose–toxicity relationship. (Continuous reassessment method)

Development of molecularly targeted therapies





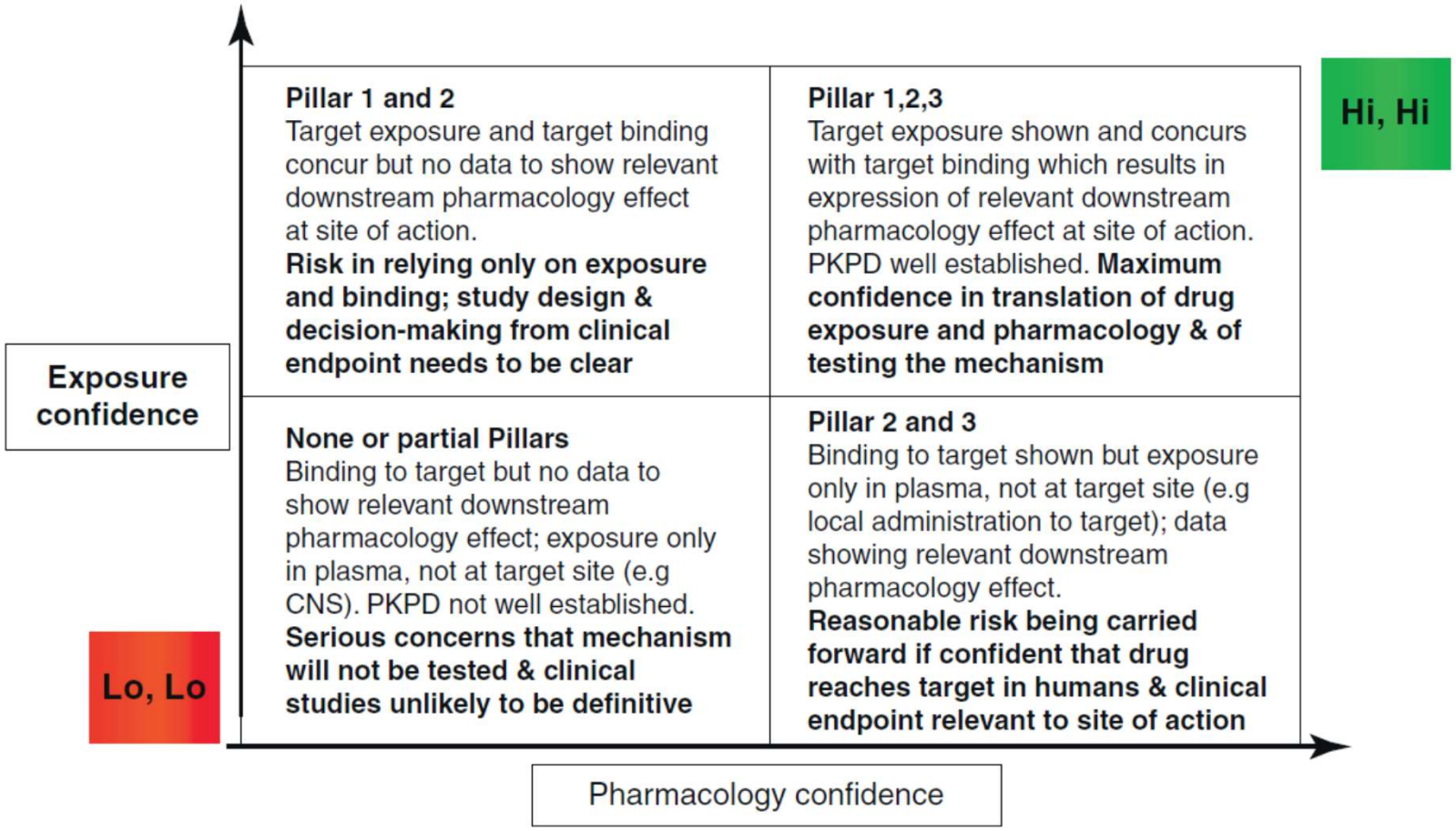
- Target is important for disease initiation or progression
- Agent modulates the target and this modulation is associated with a desired effect in preclinical models

Designing the first-in-human trial

1. Assess target modulation
   - Directly or measure effect on a disease process
     - Possess validated PK and PD assays that accurately and reproducibly measure drug levels and allow evaluation of drug effect
2. Dose and schedule
   - Starting dose and schedule based on preclinical data
   - Incrementally increase dose-MTD or OBD?
   - Degree and duration of inhibition
3. Patient Selection-select based on presence of target

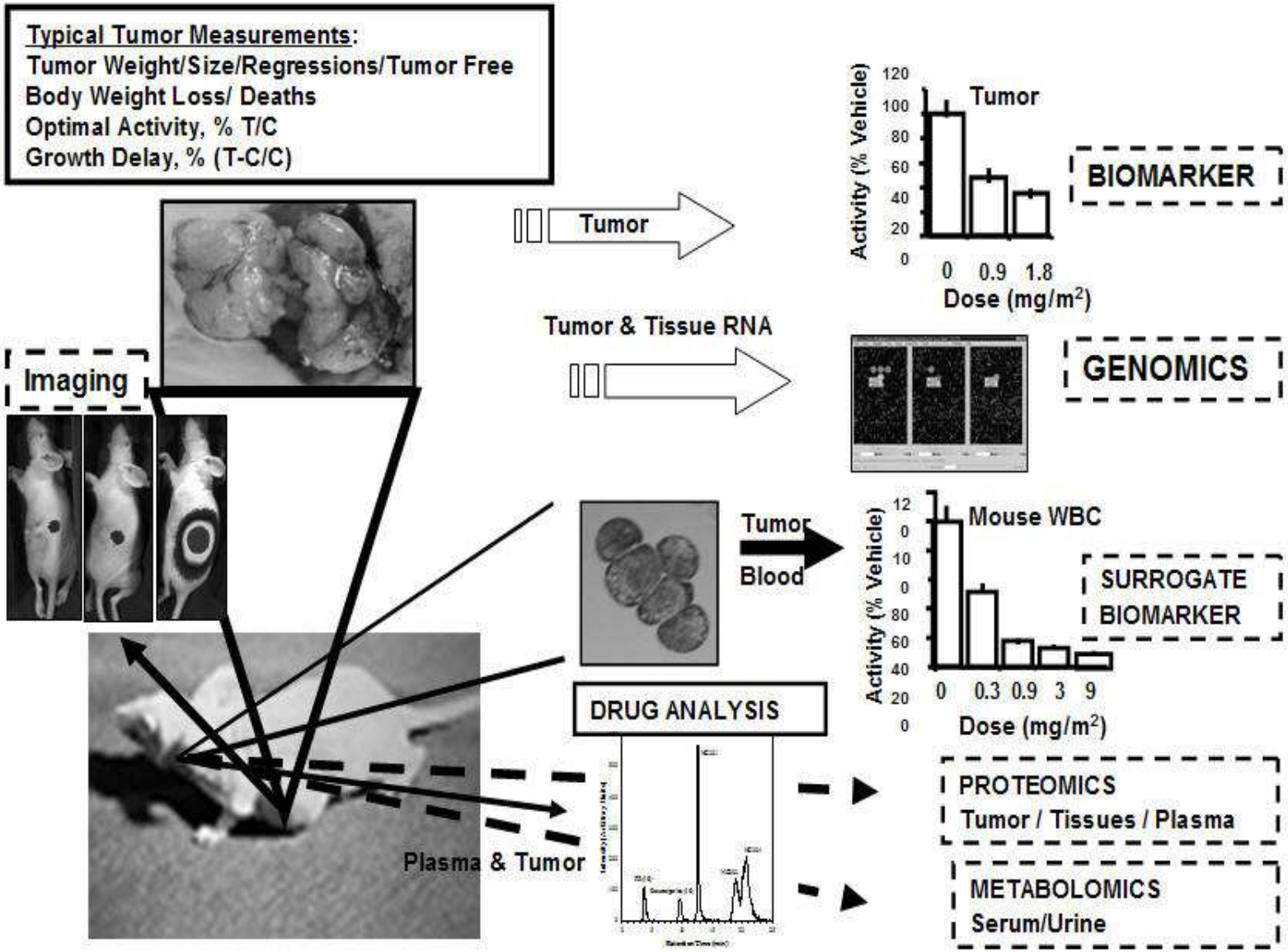
Three pillars for successful transition from early phase to late phase

Exposure at the target site of action over a desired period of time
Target occupancy/binding as expected for its mode of action
Functional modulation of target

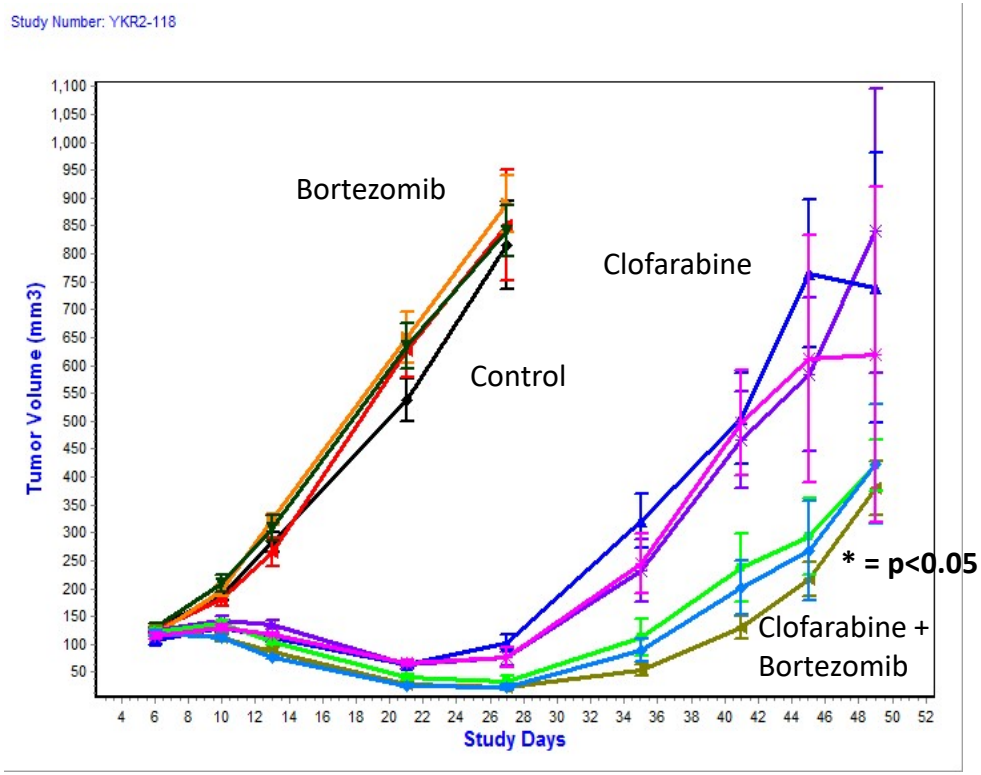


Morgan P, Van der Graaf P. Drug Discovery Today, Numbers 9/10 May 2012

Developing the 'Right' Assay Tools for Early Stage Proof of Mechanism Studies



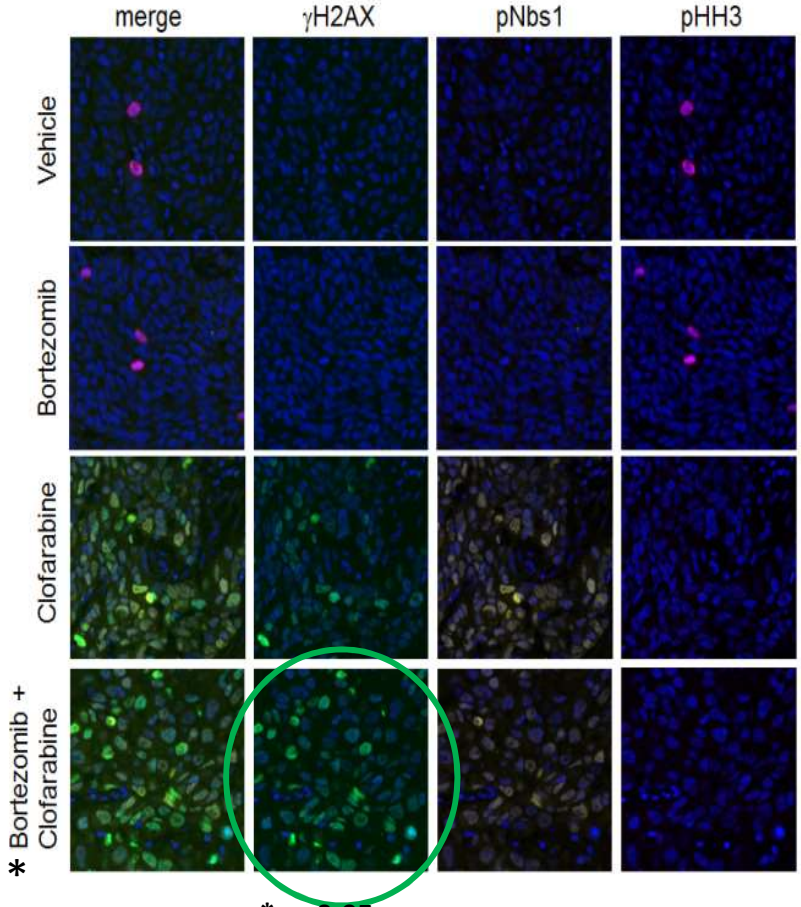
Multiplex Assays: Correlating Efficacy with MOA



HCT-116 Colon Xenograft

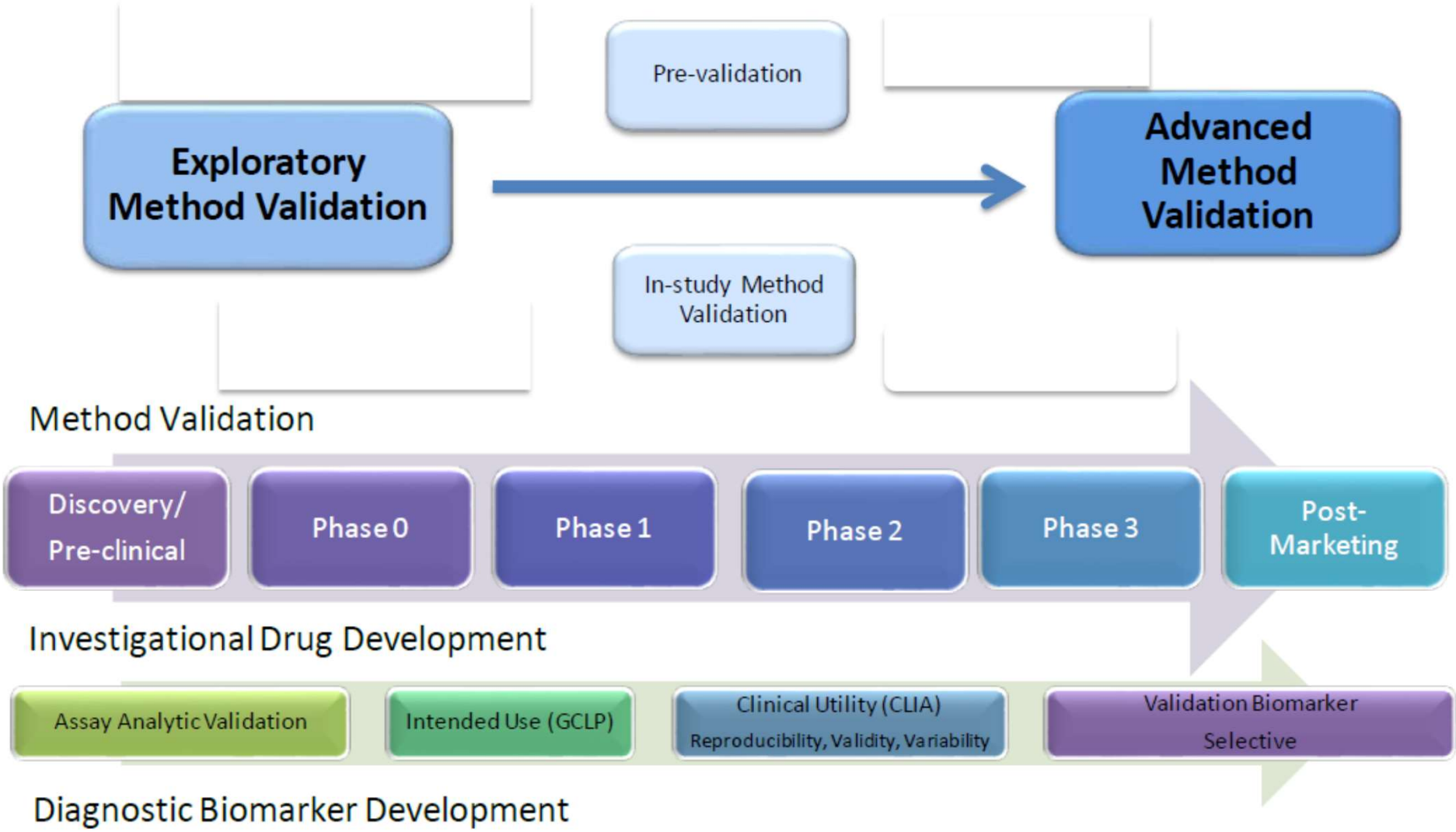
Similar results in HT-29 (colon) and NCI-H522 (lung) xenografts

DNA Damage Panel

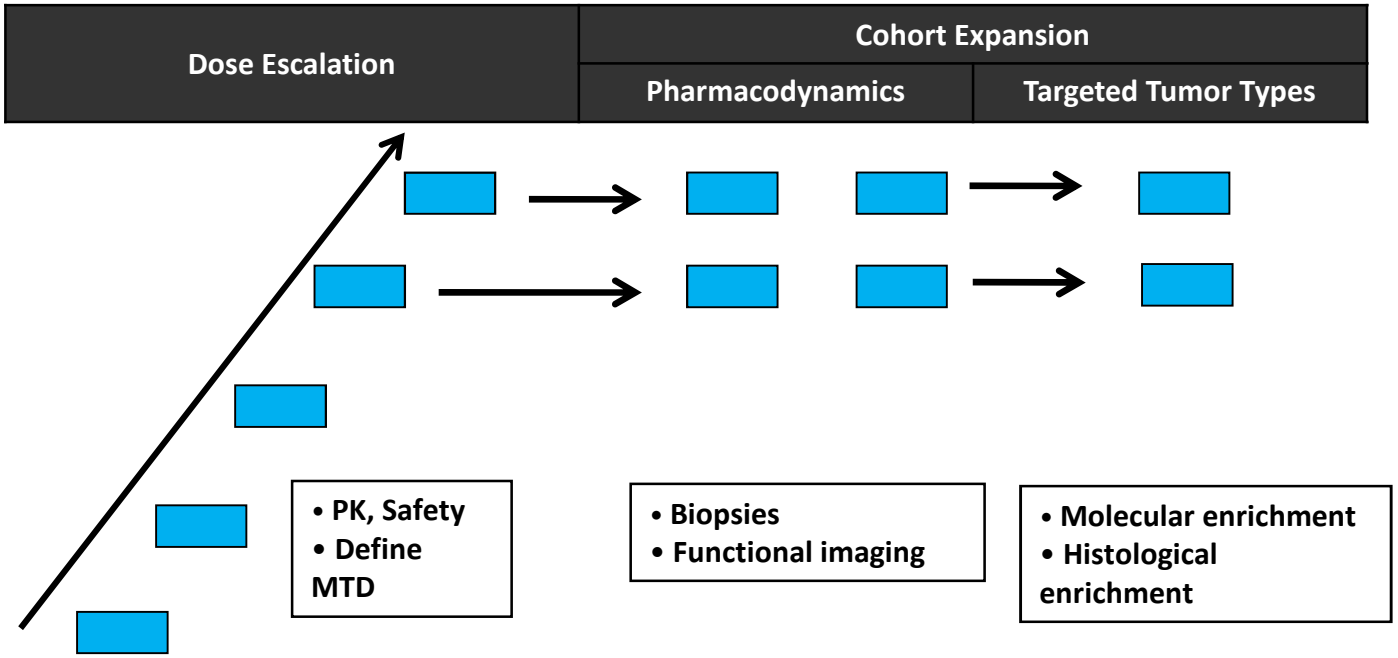


Courtesy: JH Doroshow, MD, NCI

Fit-for-Purpose:
Parallel Drug and Biomarker Development

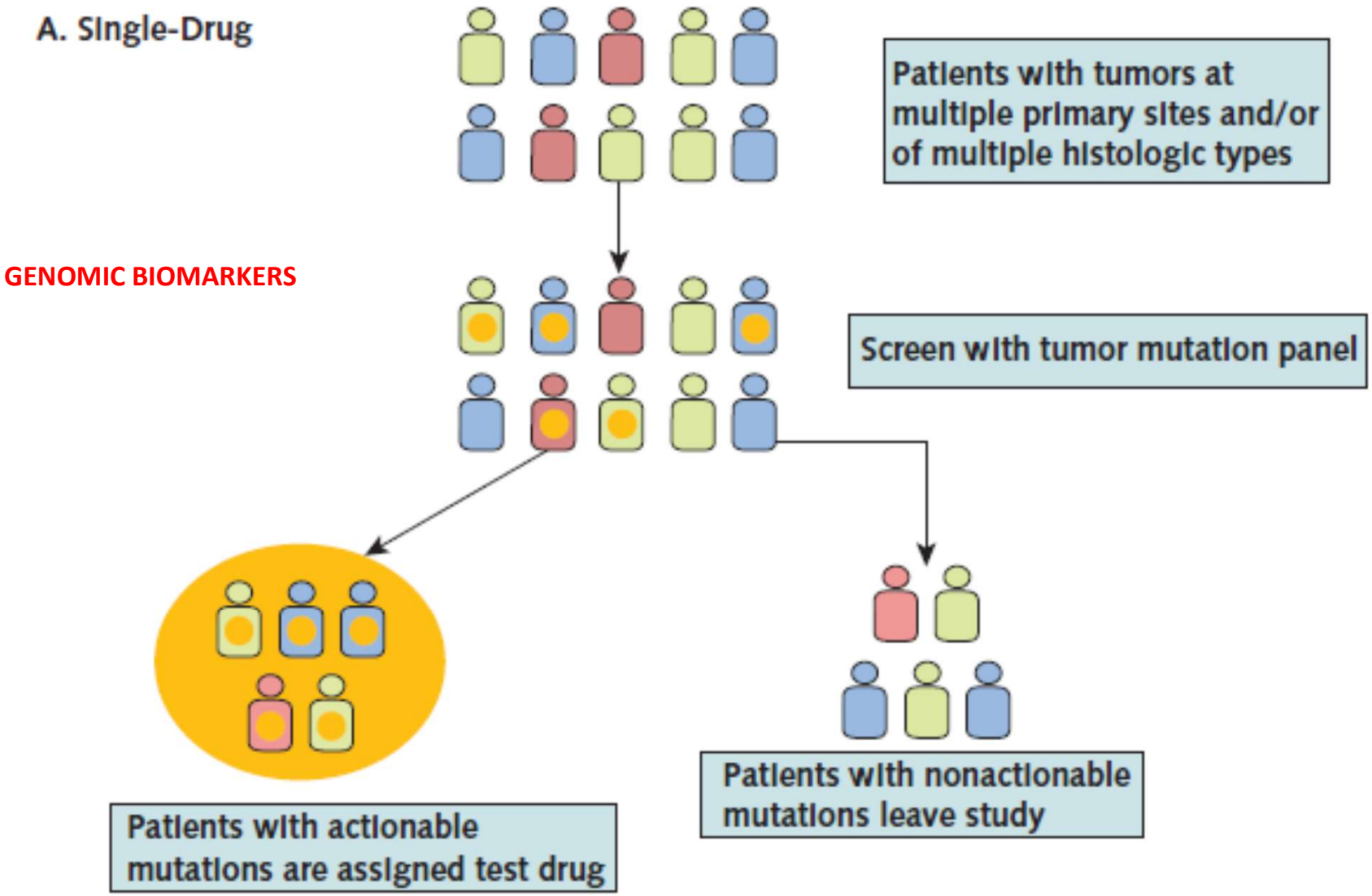


Phase I Study Design – Unselected Patients (or molecularly enriched population) in Dose Escalation followed by Specific Expansion Cohorts

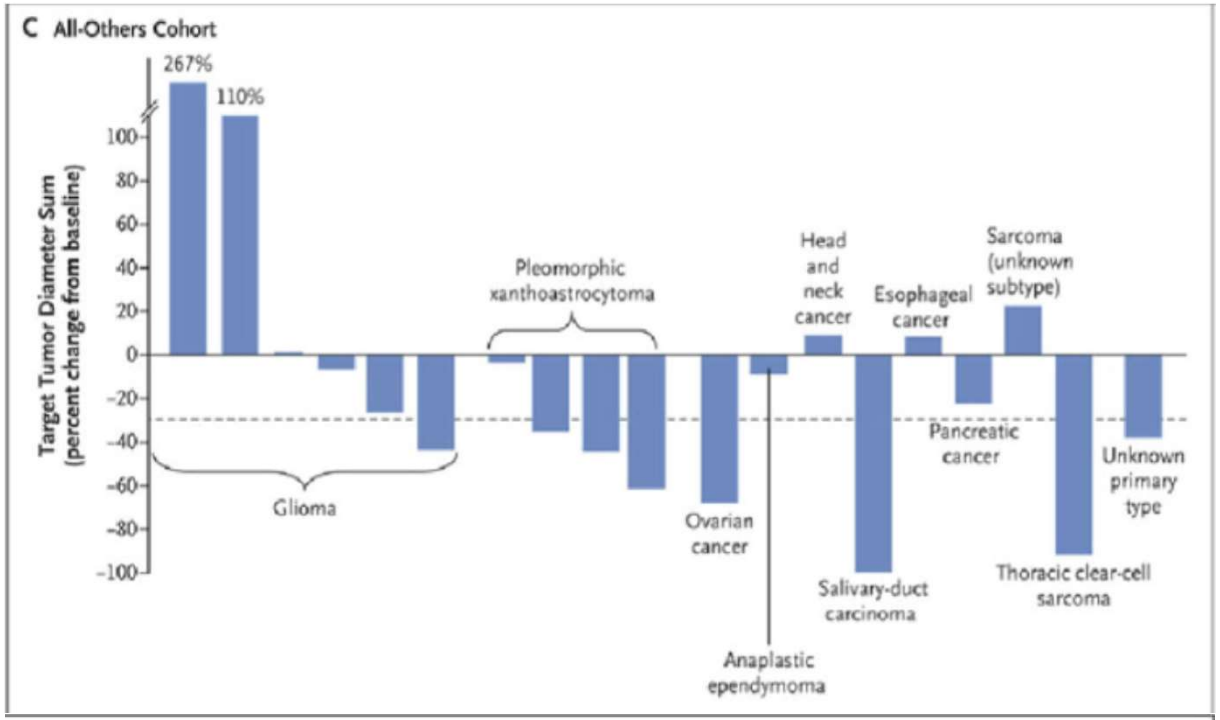


Define the degree and duration of target inhibition to establish optimal biologic dose and schedule
Dose-PK-PD relationship-important to inform dose and schedule of drug combinations

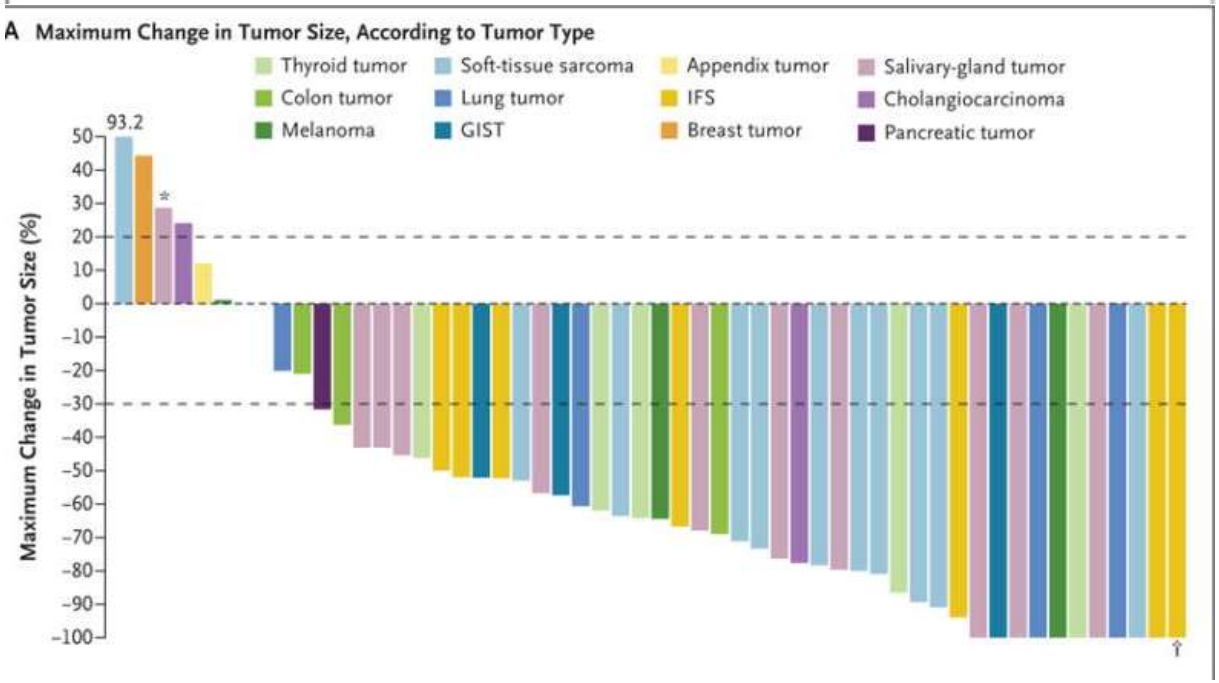
BASKET Trials



Simon R. Ann Int Med 2016; 165:270



Vemurafenib approved for certain tumor types carrying the BRAF V600 mutation



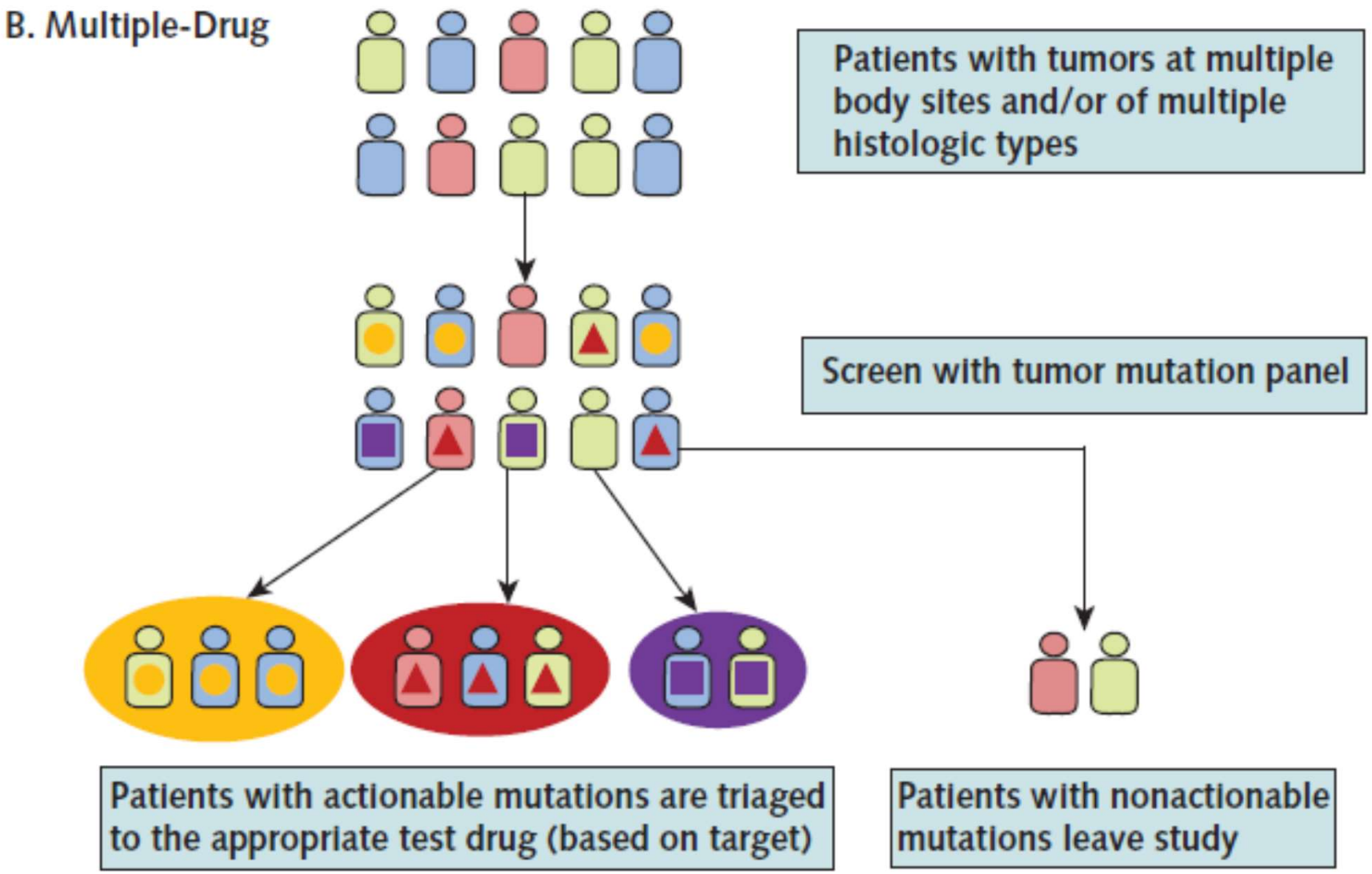
Larotrectinib is FDA approved for Patients with Advanced Solid Tumors Harboring an NTRK Gene Fusion (tissue-agnostic indication)

Is tumor histology important?

- Treatment decisions: target driven or histology driven?
- Importance of target may be disease context dependent
- Vemurafenib in BRAF V600E melanoma vs colorectal cancer): BRAF(V600E) inhibition caused feedback activation of EGFR in colon cancer [Prahallad A, et al. Nature 2012; 483(7387):100]
- Depends on the target and agent- larotrectinib versus vemurafenib

- *BASKET trials need to have independent cohorts based on histology; data can be pooled depending on clinical observations*

Umbrella Trials



Copenhagen Prospective Personalized Oncology (**CoPPO**) trial:
Clinical Utility of Using Molecular Profiling to Select Patients to Phase I Trials

- 591 enrolled→500 underwent fresh biopsy for WES & RNA sequencing →460 were analyzed→ potentially actionable target identified in 352 (70%)→101 (20%) received matched treatment
- 15 patients achieved a PR {*BRAF* (*n* = 7), *FGFR1/2* (*n* = 1), *NOTCH* (*n* = 1), *BRCA1* (*n* = 1), *ERBB2* (*n* = 1), *ALK* (*n* = 1), *PTEN* (*n* = 1), and *CCND1* amplification(*n* = 1).
- Biopsy related complications in 15 patients (hematoma (*n* = 6), pneumothorax (*n* = 3), and others (*n* = 6).
- No patients allocated to treatment based on RNA expression obtained response according to RECIST1.1.

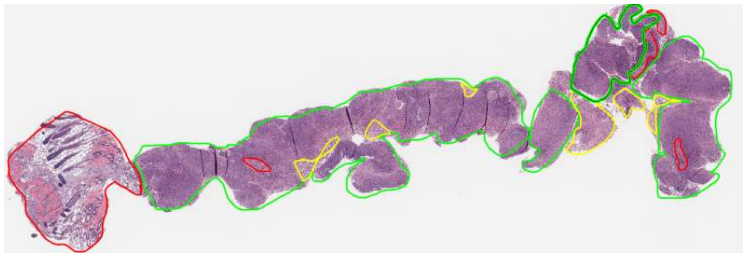
[Tuxen IV, et al. Clin Can Res 2019:25(4)]

Defining Actionability

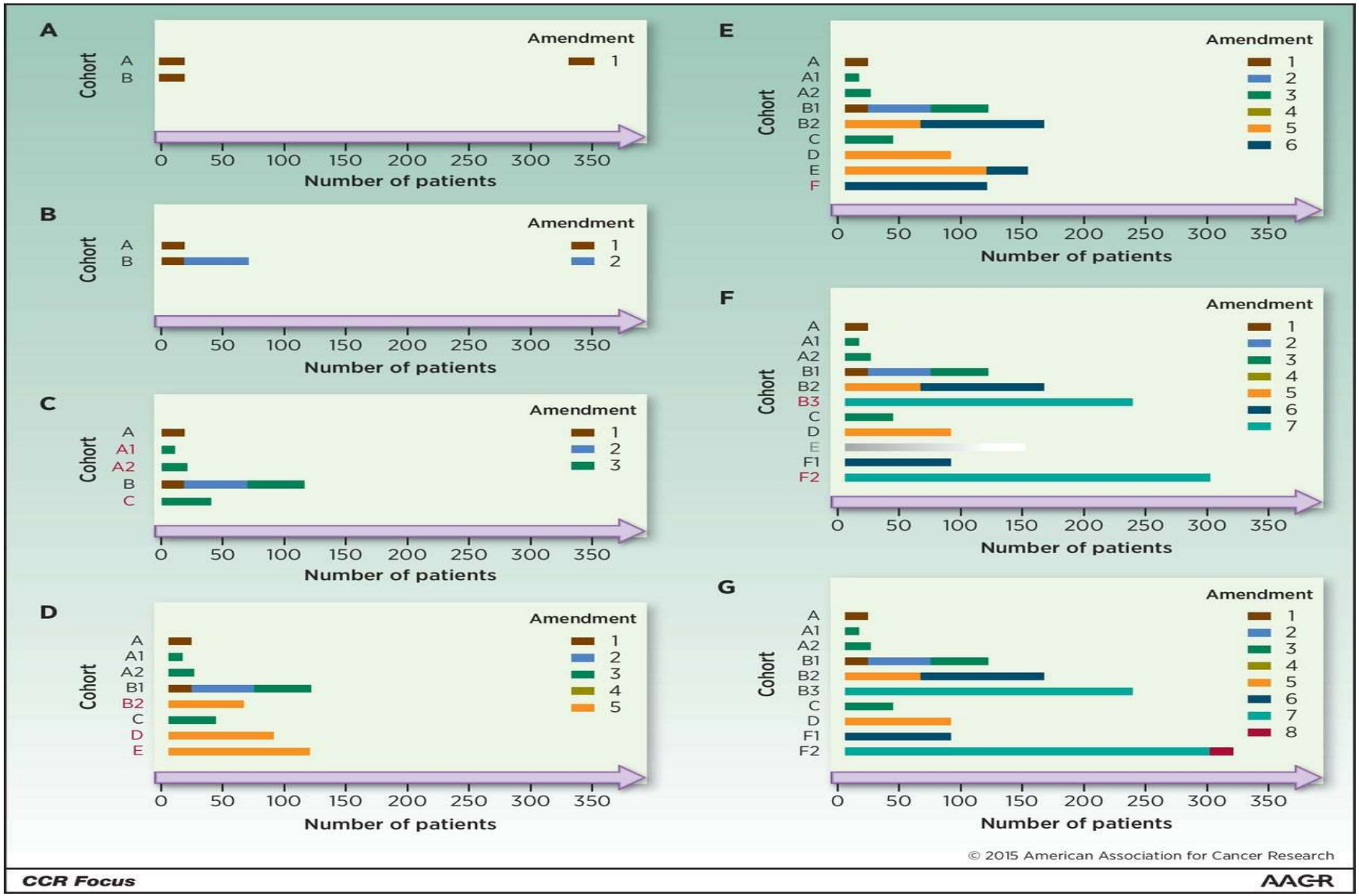
A genetic aberration or mutation is considered actionable if it is oncogenic and/or differentially expressed in tumor cells, and there is an agent/drug that putatively works against it."

Considerations in designing MP driven trials

- Is the molecular aberration a ‘driver’? Does it have a functional consequence?
- What should be the tumor content of the biopsy? How many biopsies need to be analyzed?
- How many cells need to carry the mutation of interest?
- Single vs multiple aberrations?
- Efficacy of the agent-direct t-inhibitor or downstream?



Seamless Drug Development: FIH protocol for pembrolizumab



Marc R. Theoret et al. Clin Cancer Res 2015;21:4545-4551

Clinical Cancer Research
AACR American Association for Cancer Research

Design of Large First-in-Human Cancer Trials

- Is there a compelling rationale for including multiple expansion cohorts?
- Is the sample-size range consistent with the stated objectives and end points?
- Is there an appropriate statistical analysis plan for all the stated end points?
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

Prowell T, et al. N Engl J Med 2016;374(21):2001

Shift in the Clinical Trial Paradigm: Seamless Drug Development

- Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry
- *…….the first time a new medicine is tested in humans – that compresses the traditional three phases of trials into one continuous trial, called an expansion cohort trial"-Scott Gottlieb, FDA Commissioner*
- FIH multiple expansion cohort trial:
  - a single protocol with an initial dose-escalation phase
  - also contains three or more cohorts with cohort-specific objectives:
    - assessment of anti-tumor activity in a specific disease-,
    - safe dose in specific populations
    - alternative doses or schedules,
    - combinations, or
    - establishing predictive value of a potential biomarker.
  - Comparison of activity between cohorts is not planned except where a prespecified randomization and analysis plan are part of the protocol design.

What do we want to achieve at the end of an early phase trial?

- Determine safety, tolerability and define a dose
- Look for antitumor activity (hints of activity to guide agent development; proof of concept)

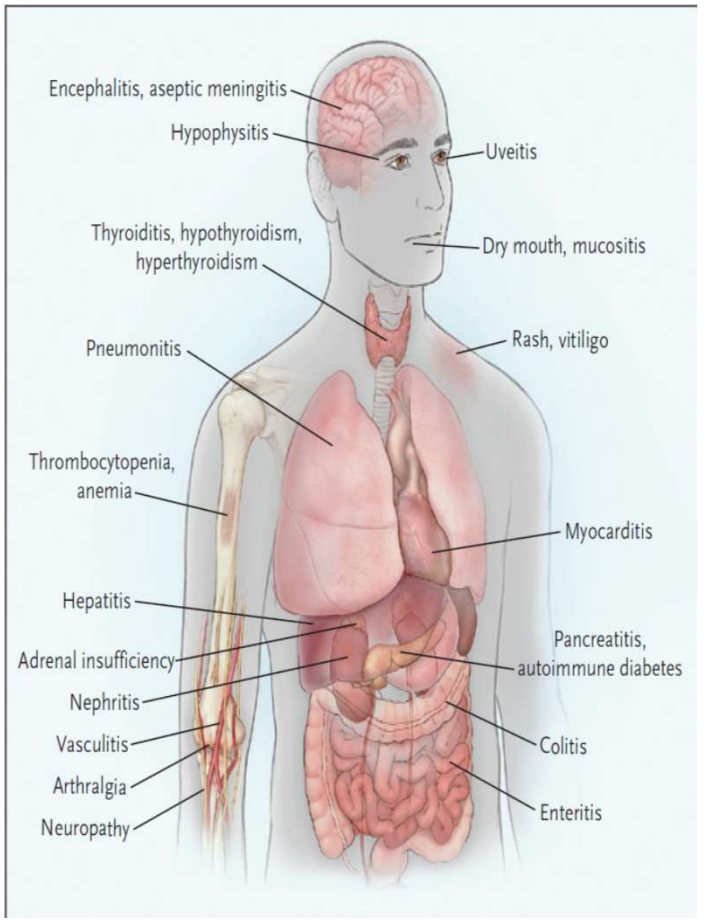
What do we want to achieve at the end of an early phase trial?

– Determine Dose

- Defining DLTs: Used to be first cycle and then toxicities had to recover to grade 1/baseline prior to re-initiating treatment at the next lower dose
- For immunotherapies:
  - May not occur in the first cycle
  - Take weeks to resolve
  - Not dose related
  - Can we safely continue the patient on

  treatment following resolution of toxicity?

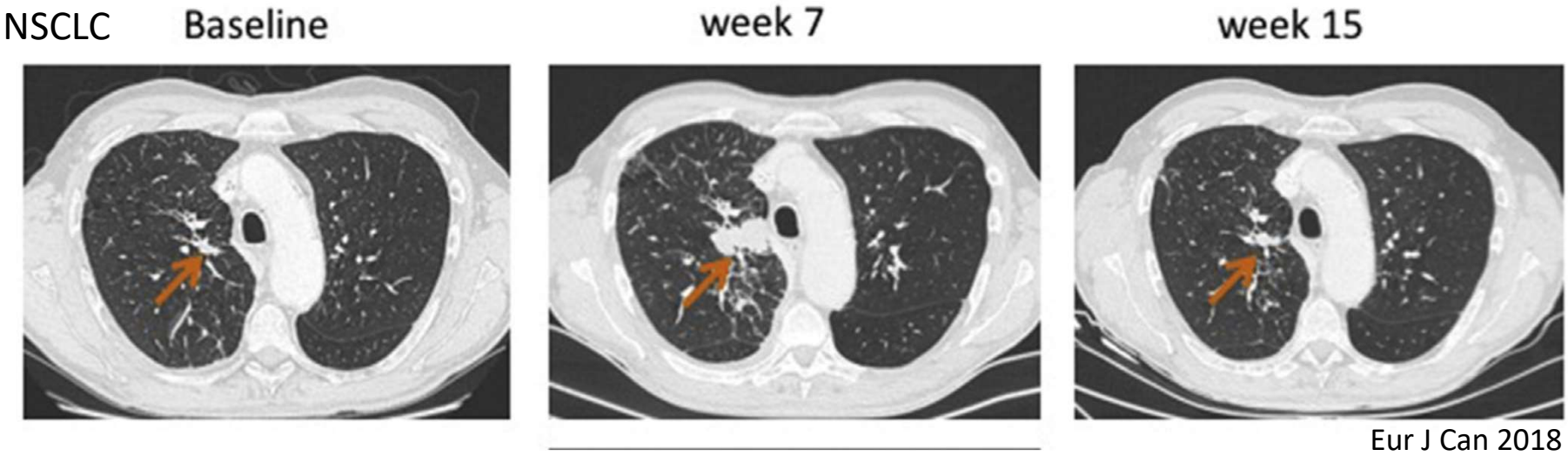
– Antitumor activity (hint of activity)



Adverse events associated with IO agents
N Engl J Med 378;2 (2018)

Determining Antitumor Activity

- RECIST 1.1, iRECIST, irRECIST, imRECIST
- Pseudoprogression (PP) as an increase in the size of lesions, or the visualization of new lesions, followed by a response, which might be durable. Need for confirmatory scans



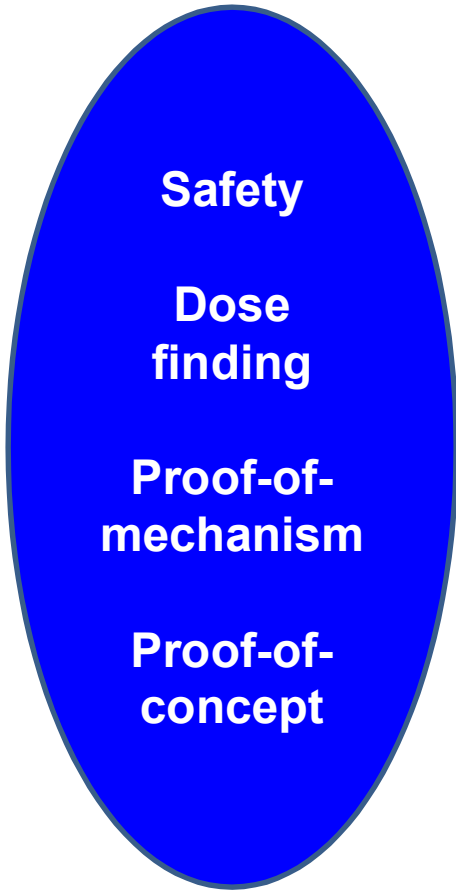
Eur J Can 2018

24/655 (7%) pts in KEYNOTE-001 melanoma trial of pembrolizumab (*J Clin Oncol 2016 (34)*

Other solid tumors: PP 2%. *J Clin Oncol* 34 (15)suppl (May 2016) 6580

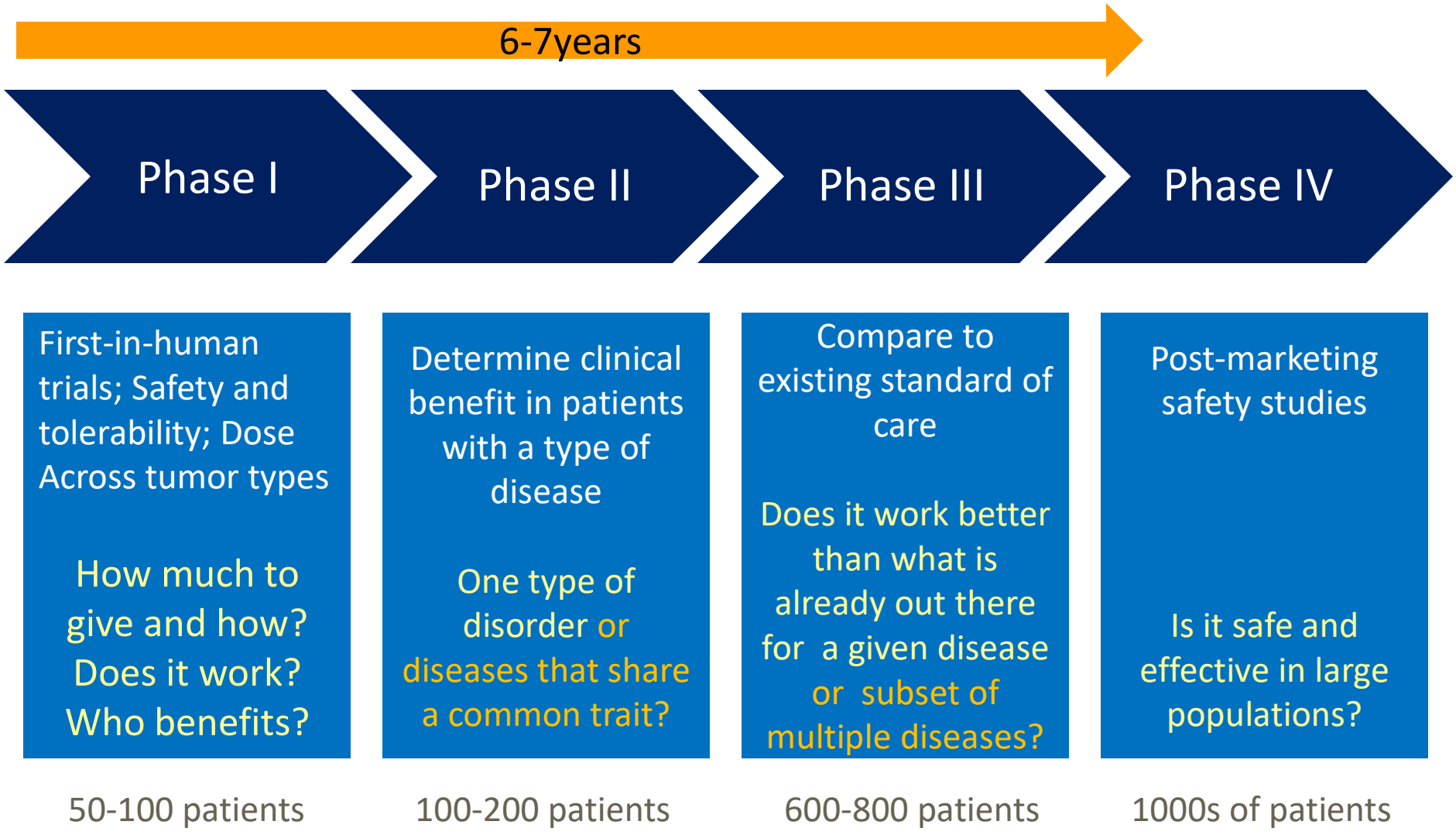
Evolution of early phase trials

- Establishment of MTD- Cytotoxic Chemotherapies
- Target modulation; Establishing the 'Optimal Biologic Dose'- Targeted Agents
- "Concept of driver mutations"-Basket/umbrella trials
- "Seamless drug development"- Early phase trials with multiple expansion cohorts: Immunotherapies
- Intersection of target modulation, molecular profiling, immunotherapy in early phase trials



Stages of Clinical Research-Reinvented

Phase I trials sit at the interface of laboratory advances and later stage clinical care; **expedite development of new treatments** ; **basis to prioritize resource allocation**



Stanford University, Palo Alto, CA, USA

Phase I group