Determining Dose in the Era of Targeted Anticancer Therapies

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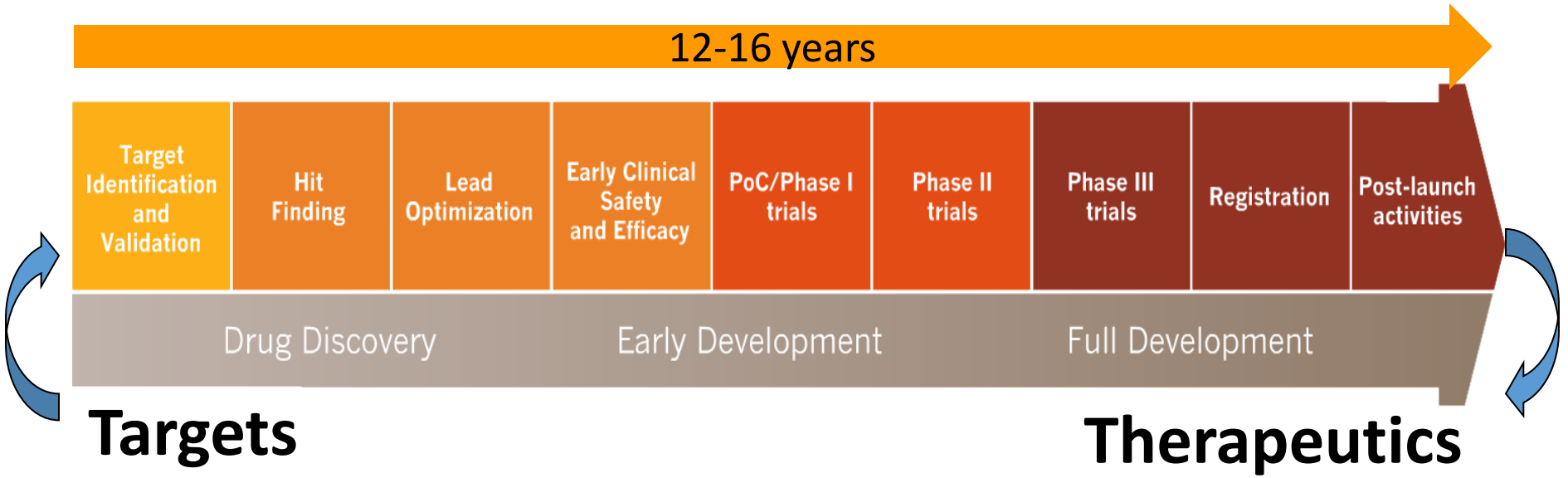
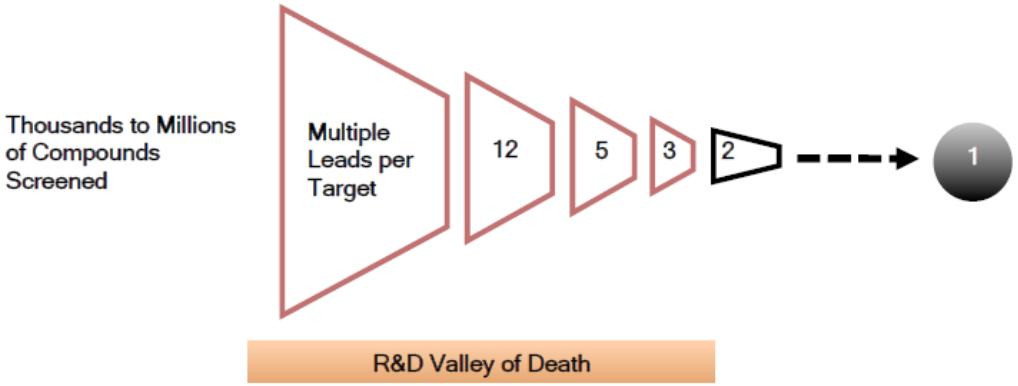
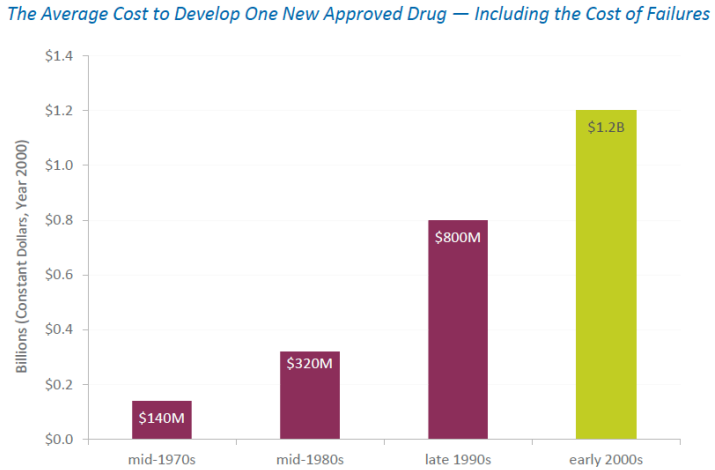
Clinical Trial Process

- 1906: **Pure Food and Drugs Act** -protect against misbranding and adulteration of foods, drinks, and drugs
- 1938: **Food, Drug and Cosmetic Act** –pre-market proof of safety (in response to elixir sulfanilamide, which contained a solvent analog of antifreeze, resulting in deaths)
- 1962: **Kefauver–Harris Amendment** to the 1938 Food, Drug, and Cosmetic Act (in response to birth defects arising from thalidomide) required that sponsors seeking approval of new drugs demonstrate the drug's efficacy, in addition to its safety, through a formal process that includes "adequate and well-controlled" clinical trials as the basis to support claims of effectiveness.
- 1970: first **package insert** required (information for patients on risk/benefits)
- 1997: **Regulatory Modernization Act**: Creates a law allowing FDA to “fast track” products
- 2012: **FDA Safety and Innovation Act (FDASIA)-**’breakthrough therapy designation’

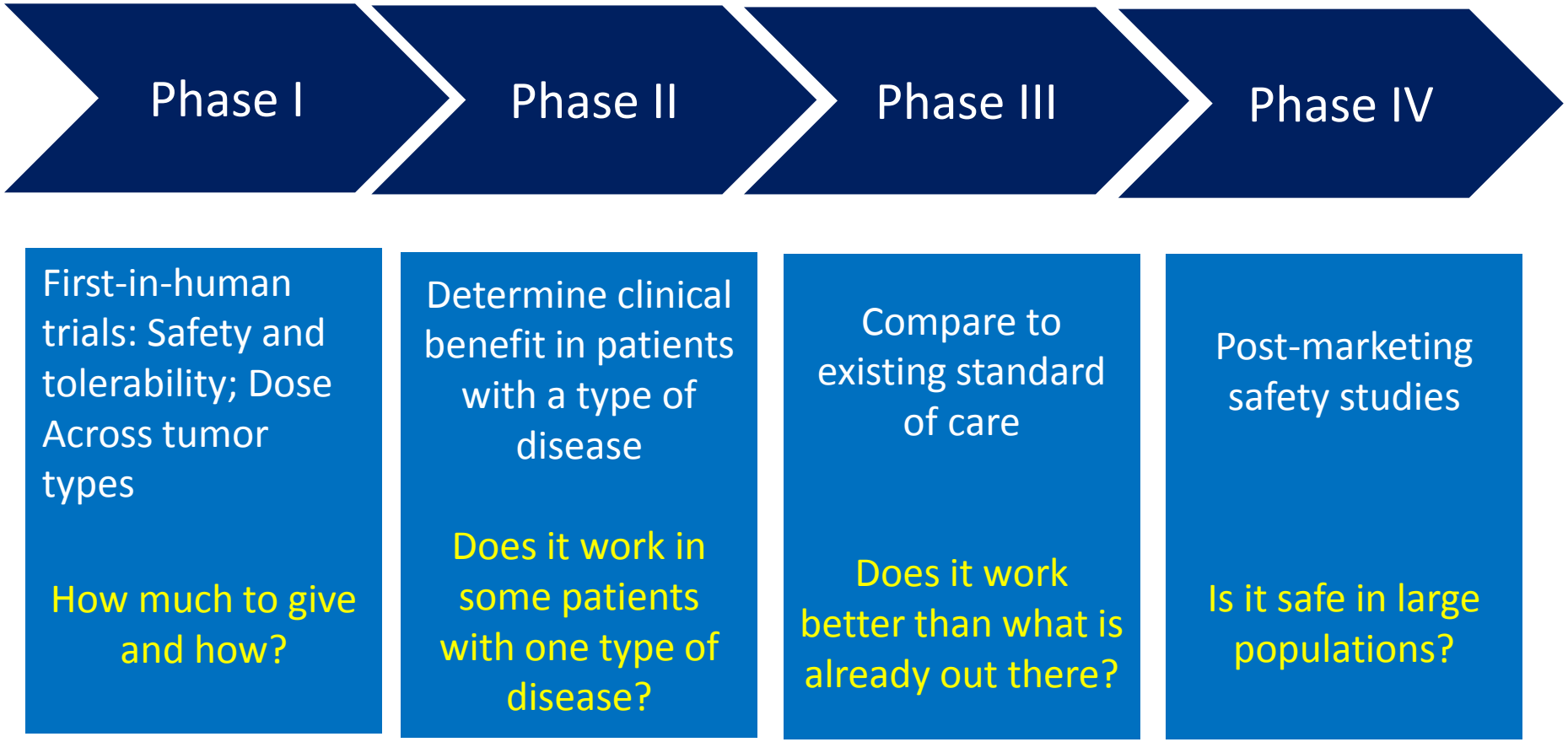
Drug Development Pipeline







Stages of Clinical Research



The Purpose of Toxicology Evaluation in Drug Development

Toxicology studies are **not** about proving the safety of a molecule.

They are intended to characterize the sequence and extent of adverse effects as they relate to dose/exposure.

Performed in two mammalian species, usually rat and dog. Have to be conducted in accordance with Good Laboratory Practices (21CFR 58)

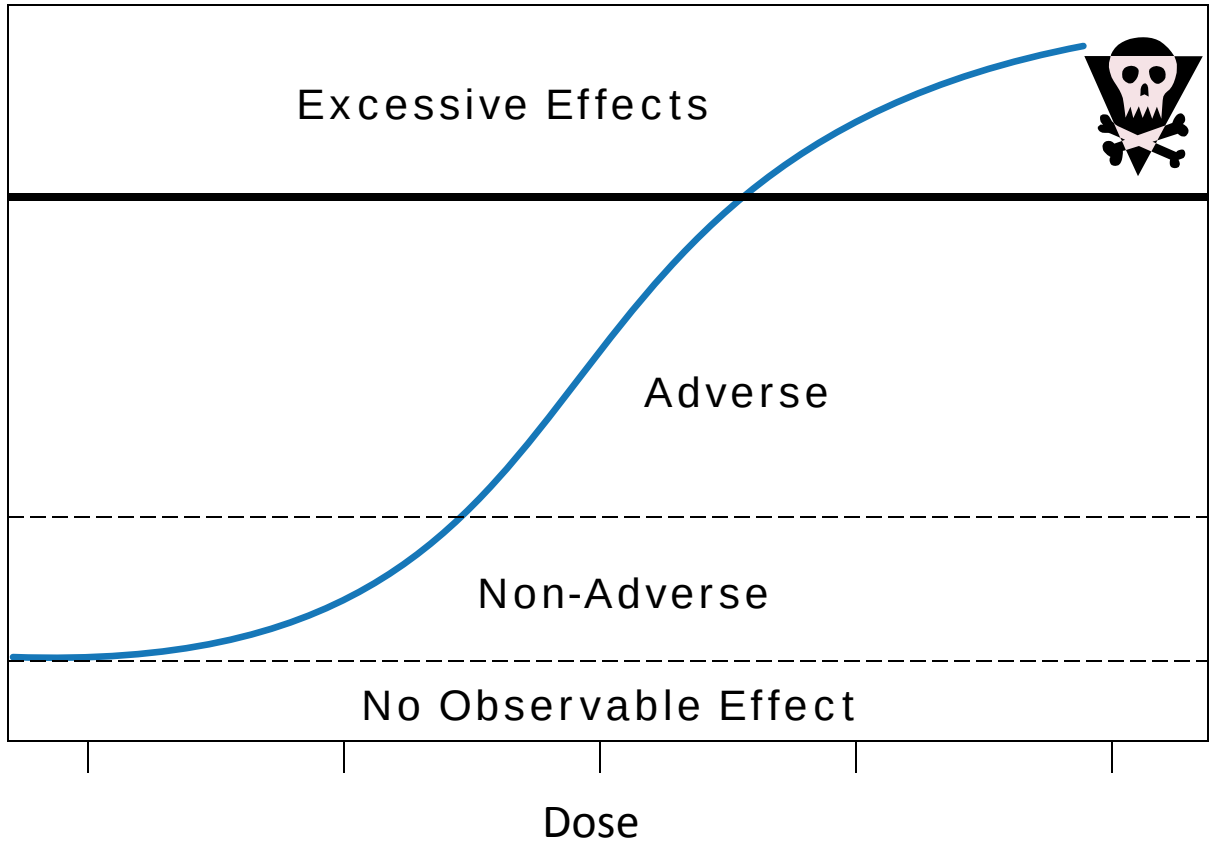
Recommended reading-The no-observed-adverse-effect-level in drug safety evaluations: Use, issues, and definition(s), Michael A. Doratoa and Jeffery A. Engelhardt
Regulatory Toxicology and Pharmacology Volume 42, Issue 3, August 2005, Pages 265-274

Courtesy: Myrtle Davis, DVM, PH.D.

The Concept of "*Margin of Safety*"

Highest Dose/Exposure Associated with No Toxicity (NOEL) or "Manageable" Toxicity (NOAEL)

Efficacious Dose/Exposure in Appropriate Test System

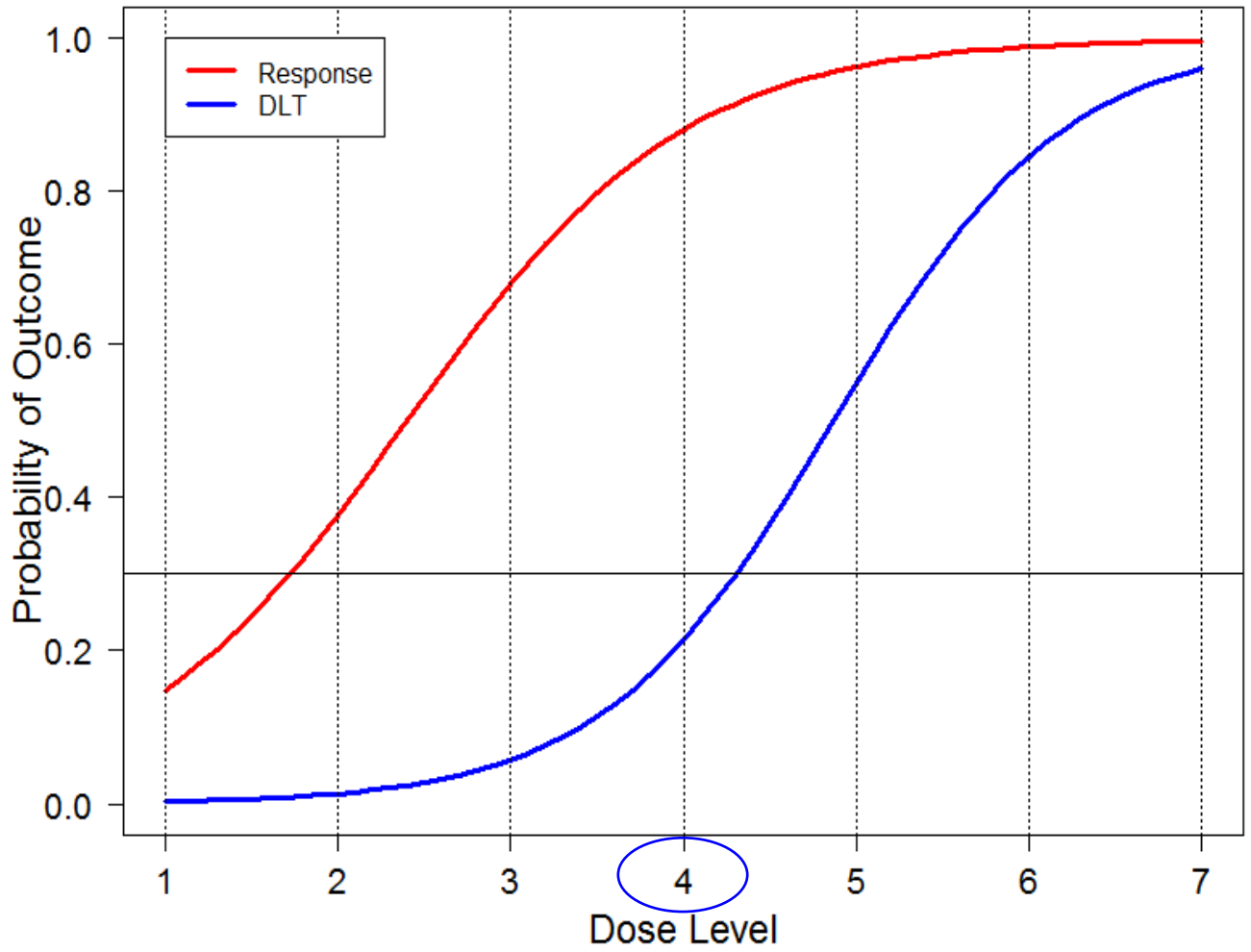


The NOAEL is the dose on the toxicology dose–response curve that is compared to the pharmacodynamic effective dose to establish the MOS.

Maximum Recommended Starting Dose (MRSD) for First In Human Trials

- **Step 1: Determination of the No Observed Adverse Effect Level (NOAEL)**
- **Step 2: Conversion of NOAEL to Human Equivalent Dose (HED)**
- **Step 3: Selection of the most appropriate animal species**
- **Step 4: Application of a safety factor to determine MRSD**
- **Step 5: Compare MRSD with pharmacologically active dose (PAD)**
- **Selection of MRSD**

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



Dose Escalation

- 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)
- 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)

Phase I Trial Designs

- **Traditional 3+3 design:**
  - Treat 3 patients at dose D:
  - If 0 patients experience a DLT, escalate to dose D+1
  - If 2 or more patients experience DLT, de-escalate to level D-1
  - If 1 patient experiences DLT, treat 3 more patients at dose level D
    - If 1 of 6 experiences DLT, escalate to dose level D+1
    - If 2 or more of 6 experiences DLT, de-escalate to level D-1
  - The MTD is defined as the highest dose at which 0 or 1 patient out of 6 enrolled at the dose have a DLT.
- Modified Fibonacci sequence: the dose first increases by 100%, and then 67%, 50%, 40%, and 30%–35% of the preceding doses
- An excessive number of escalation steps, large proportion of patients e treated at low (i.e. potentially sub-therapeutic) doses
- Alternate rules proposed: “2+4,” “3+3+3,” and “3+1+1” (“best of five”) rules

Accelerated Titration Designs

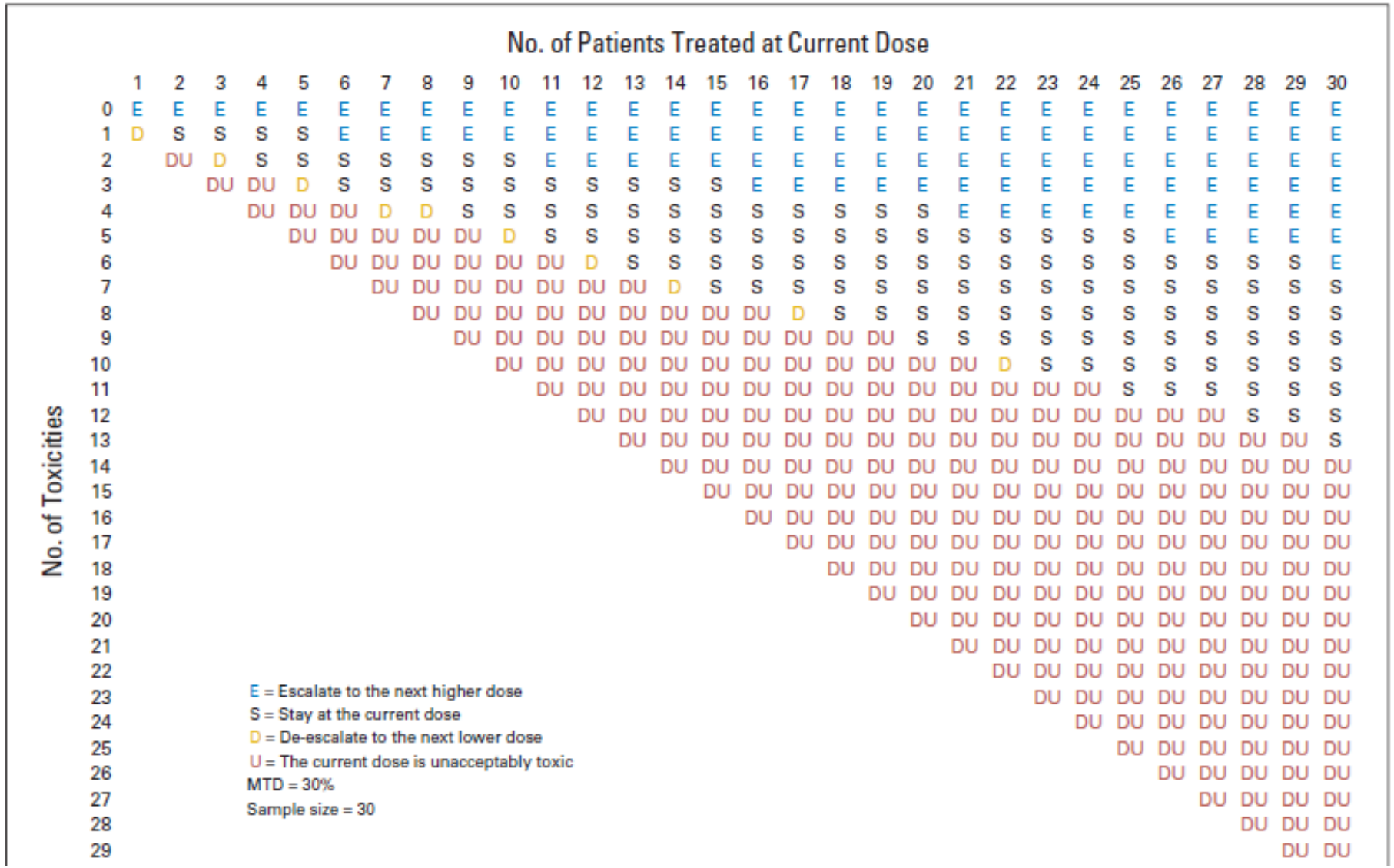
- 40% and 100% dose escalations
- Single patient cohorts until a dose-limiting toxicity or two moderate toxicities are observed during cycle 1 or any cycle; then revert to 3+3 design
- Reduces the number of patients who are treated at sub-therapeutic doses

Pharmacologically Guided Dose Escalation

- Assumes that dose-limiting toxicities can be predicted by plasma drug concentrations and that animal models can accurately reflect this relationship in humans
- As long as the pre-specified plasma exposure is not reached, dose escalation proceeds with one patient per dose level and typically at 100% dose increments
- Requires real time PK; difficulty in extrapolating from animal data, risk of toxicity if AUC was atypically low in the previous patient.

Continual Reassessment Method

- First Bayesian model–based method proposed in 1990
- Data from all toxicities observed during the trial are used to determine the MTD
- The occurrence of toxicity (or not) in patients enrolled at each dose level provides additional information for the statistical model and results in an adjustment of θ (which represents the slope of the dose–efficacy or dose-toxicity curve)
- Allows for rapid dose escalation
- Needs statistical support
- Concern for overdose if model incorrect
    - led to the Escalation with Overdose Control (EWOC) design



Dose-finding spreadsheet of the **modified Toxicity Probability Interval (mTPI)** method. The spreadsheet is generated based on a beta/binomial model and precalculated before a trial starts. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI. MTD, maximum-tolerated dose.

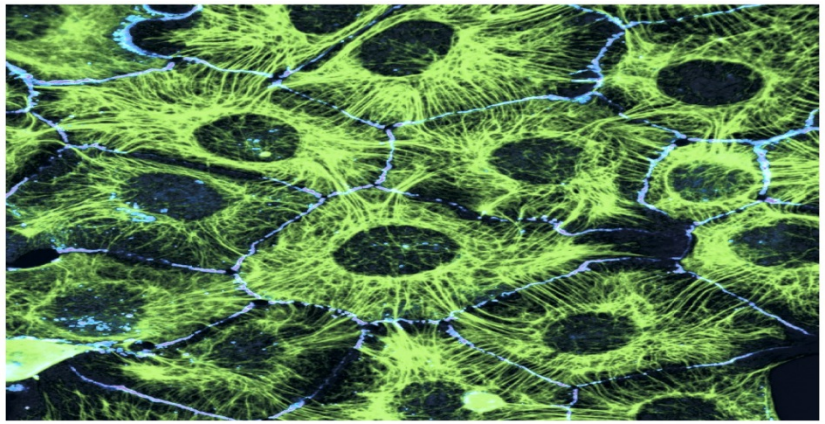
Translation of statistical designs into practice phase I trial designs

- Modeling of Bayesian adaptive designs demonstrates that more patients are treated at optimal doses compared with standard up-and down methods
- Abstract records of 1235 cancer clinical phase I trials from the Science Citation Index database between 1991 and 2006 were evaluated along with 90 statistical studies
- Only 1.6% of the phase I cancer trials (20 of 1,235 trials) followed a design proposed in one of the statistical studies.
- All the rest followed the standard up-and-down methods

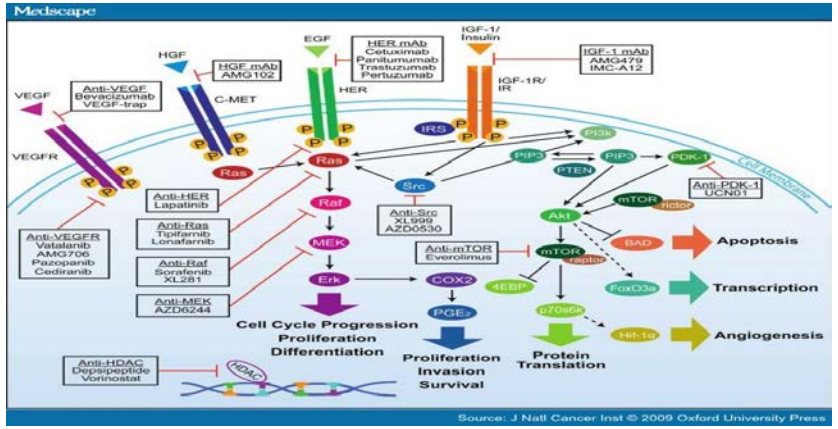
Rogatko A, et al. J Clin Oncol 2007; 25(31):4982

Changing Landscape of Drug Development

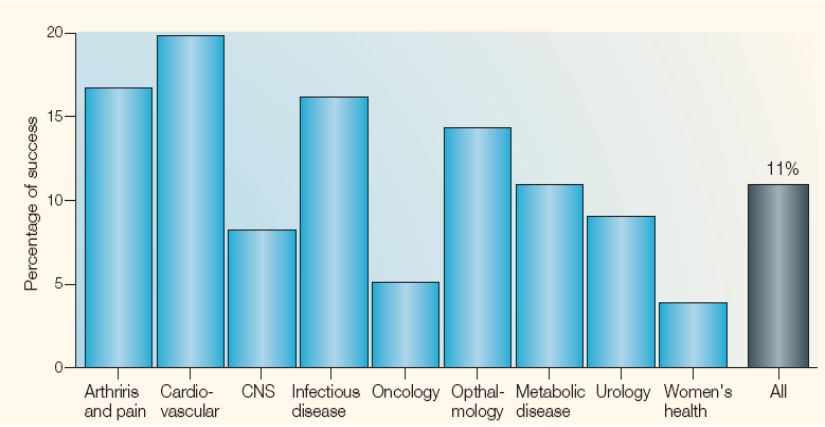
Increased Understanding of Cancer Biology



Advent of Targeted Therapies

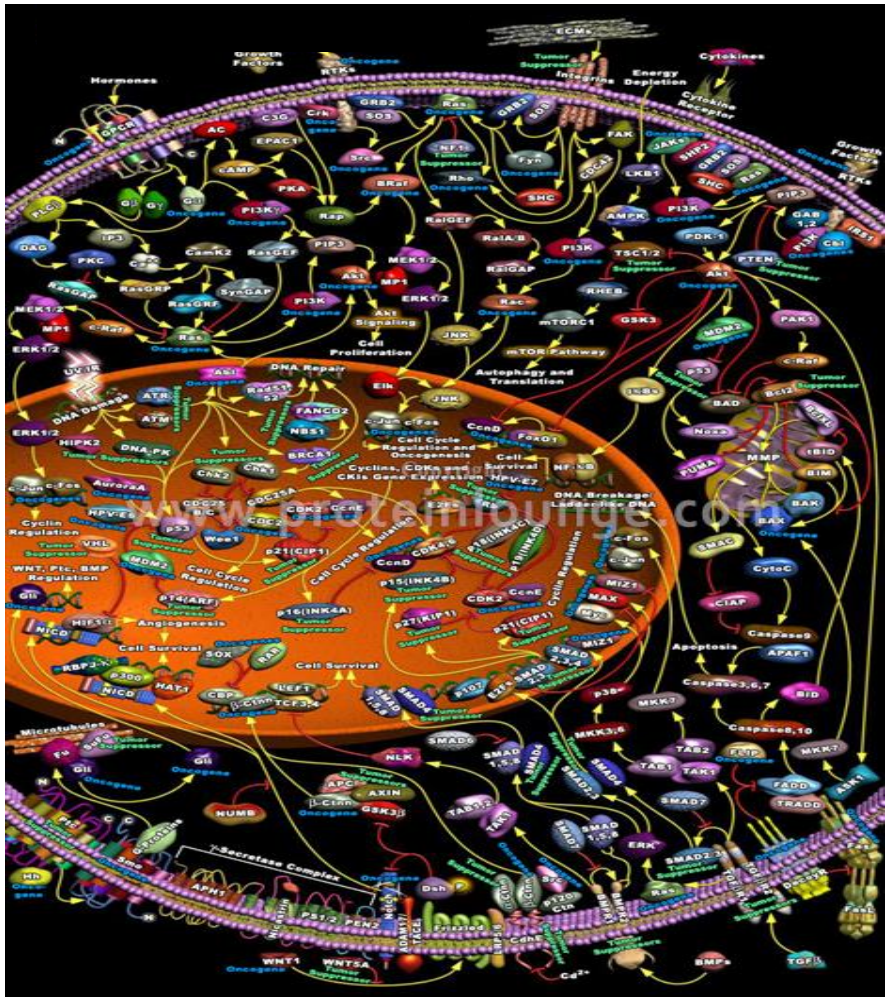


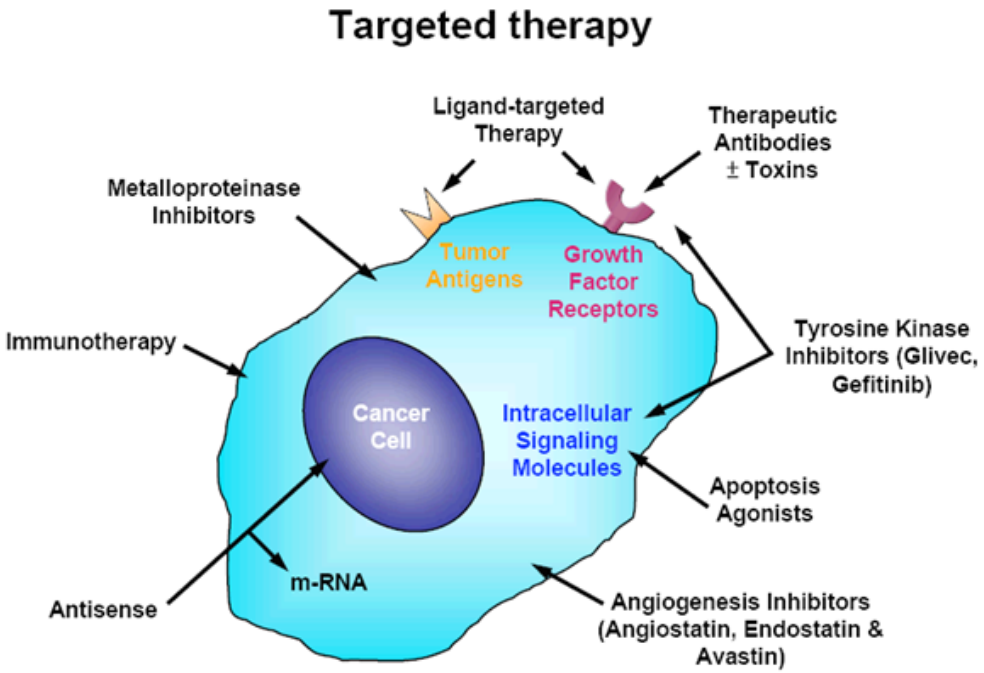
High Attrition Rates/High Costs



Personalized Medicine

Development of molecularly targeted therapies





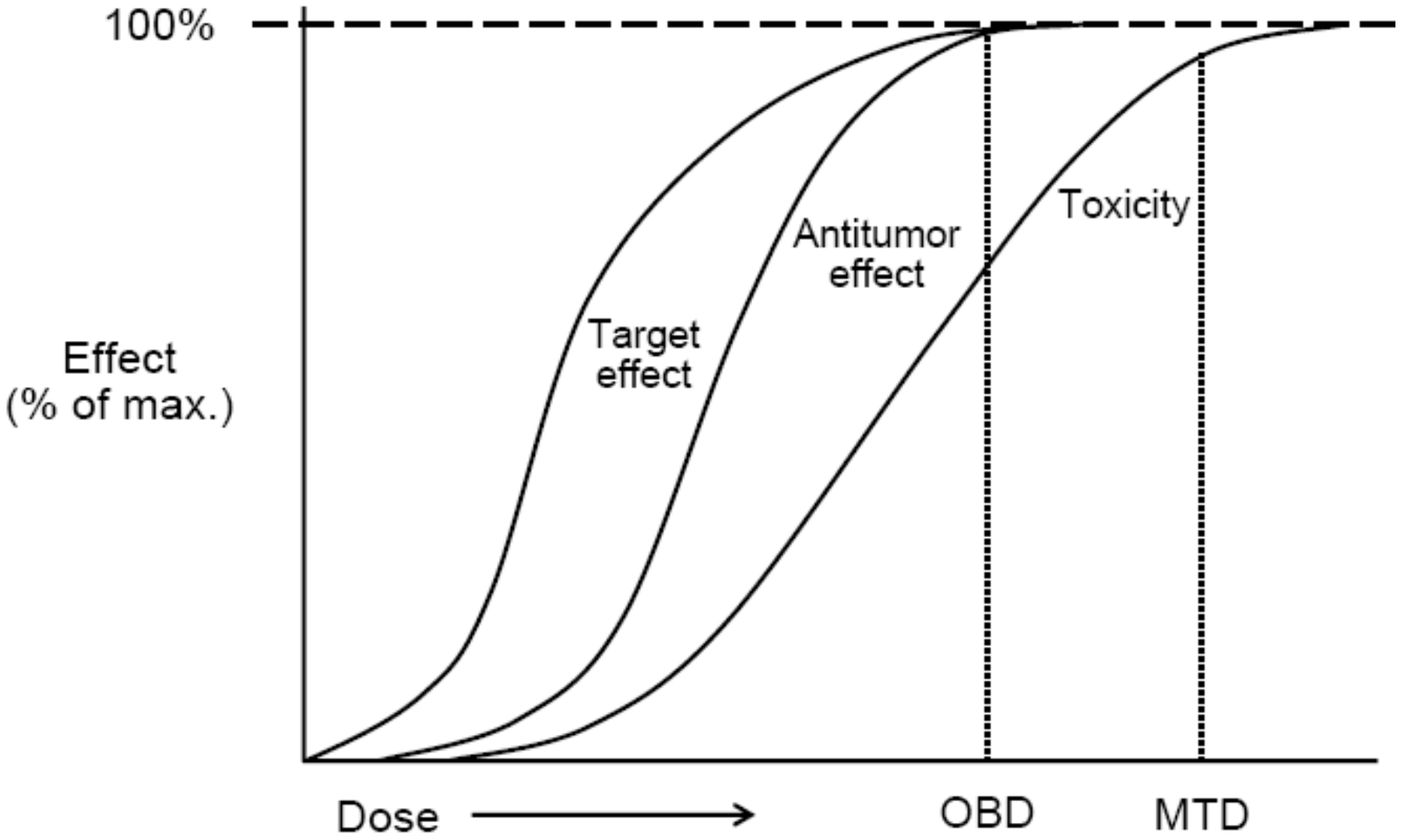
- Target is important for disease initiation or progression
- Agent modulates the target and this modulation is associated with a desired effect in preclinical models

Development of Cytotoxic Versus Molecularly Targeted Agents

	Conventional chemotherapy	Molecularly targeted agents
Cellular effects	Cytotoxic	May be cytostatic
Toxicity	Usually nonspecific multiple organ system; often bone marrow, gastrointestinal, hepatic	Presumably less toxic; target specific or off-target
Phase 1 primary end-points	Characterize toxicities; DLT, MTD; evaluate PK	Determine target inhibition, OBD; evaluate PK & toxicities
Patient selection	Disease histology	Molecular pathology or presence of target(s)
Phase 2 efficacy trial end-points	Objective tumor response (tumor shrinkage)	Objective tumor response or stabilization (progression-free survival)
Measures of efficacy	Anatomical imaging	Anatomical or functional imaging
Time to clinical response	Relatively short (e.g., 6–8 weeks)	Relatively late; may require prolonged dosing for therapeutic effect

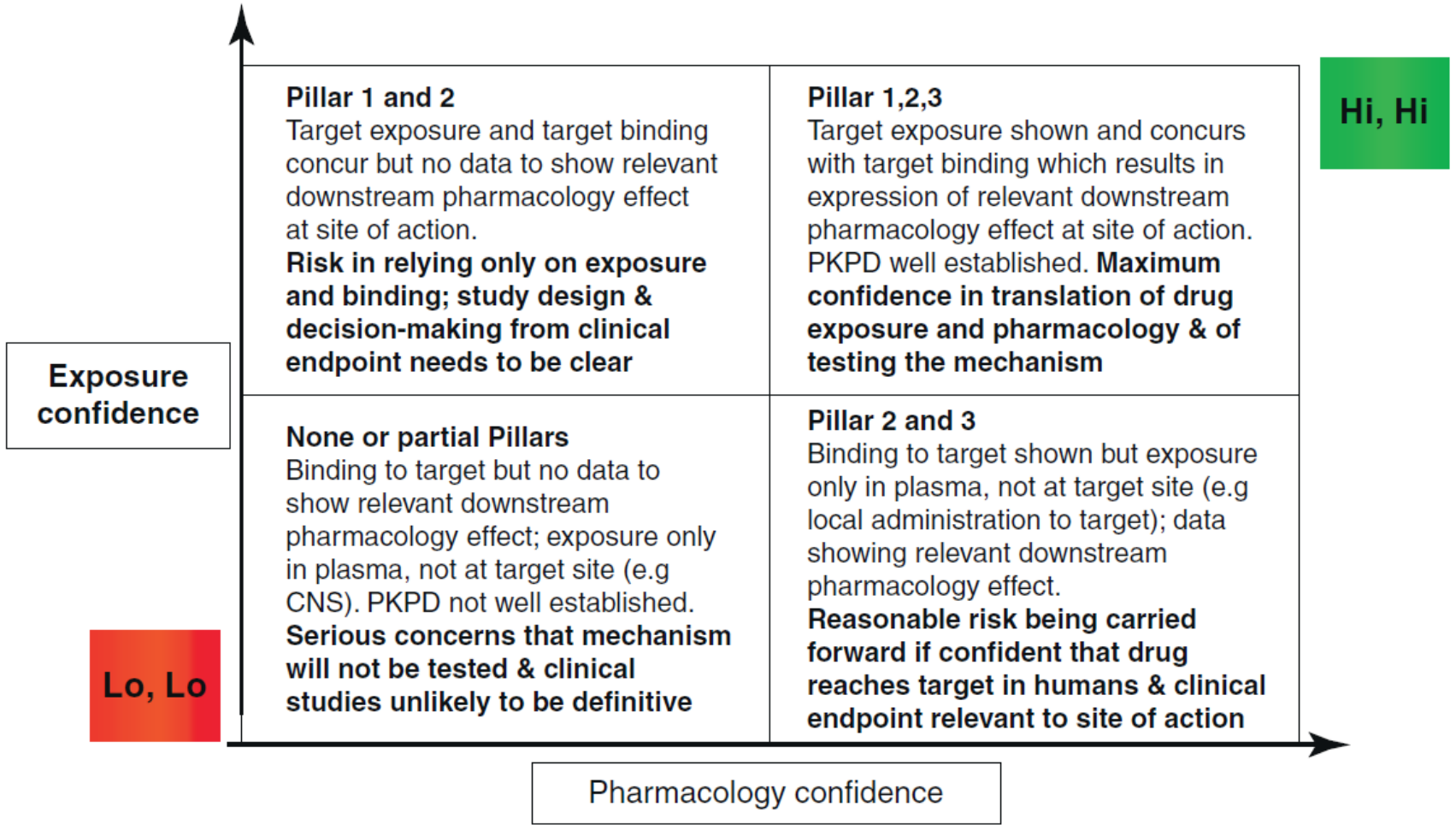
Kummar S, et al. *Br J Clin Pharmacol*. 2006;62:15-26

Dose-effect curves for the antitumor and toxic effects of a MTA



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 s expected for its mode of action
Functional modulation of target

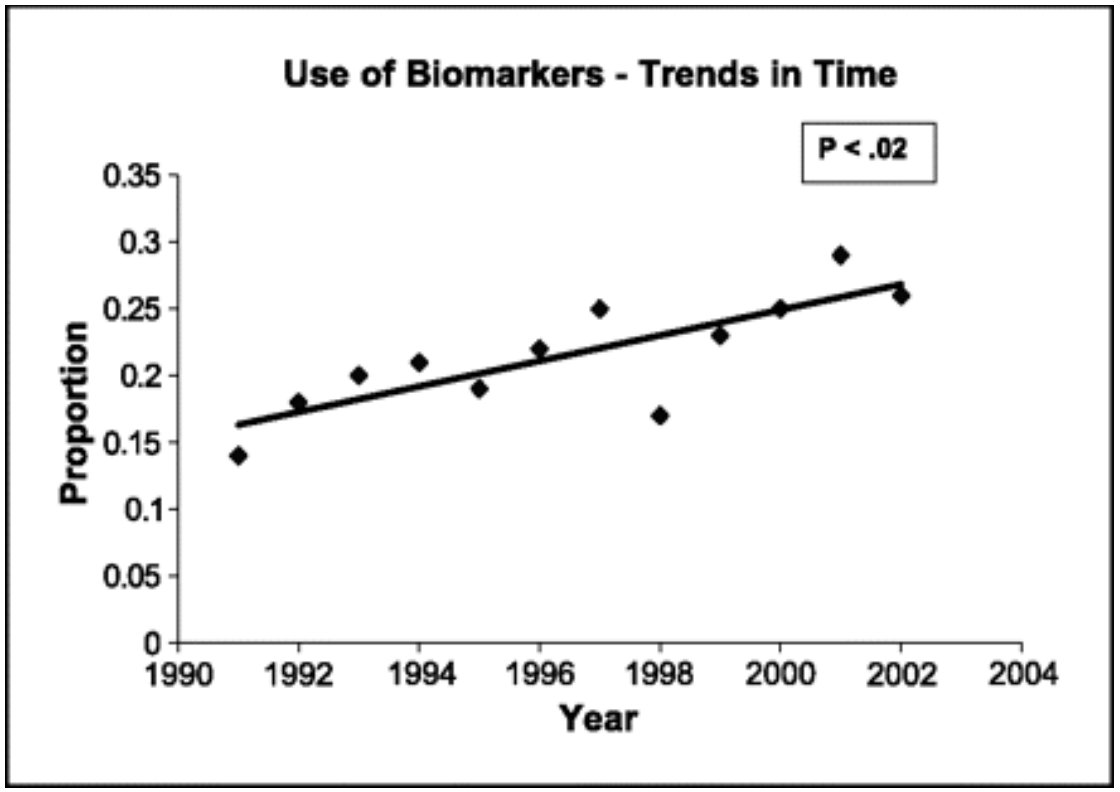


Morgan P, Van der Graaf P. Drug Discovery Today, Numbers 9/10 May 2012

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

Trends in Biomarker Utilization



ASCO abstracts between 1991 to 2002 that included biomarkers went up from 14% to 26%, 1 out of 87 trials used biomarker as the basis for phase II dose selection.

Goulart, et al. Clin Cancer Res 2007

Biomarker:
A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or a pharmacologic response to a therapeutic intervention

Why are successful biomarker studies uncommon?

- **Biological heterogeneity**
  - Cellular, tumor, patient
  - Target; Tissue of interest
  - Stability
  - Day to Day variability within patient
  - Other medical conditions affecting target

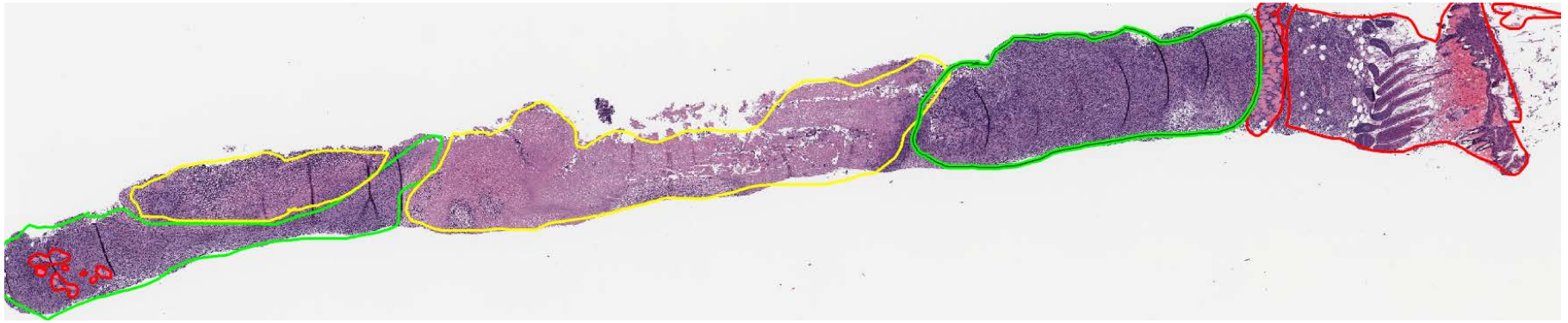
- **Assay variability**
  - Within assay, between assays

- **Specimen variability**
  - Specimen handling and processing
  - Sampling procedures and amount of sample

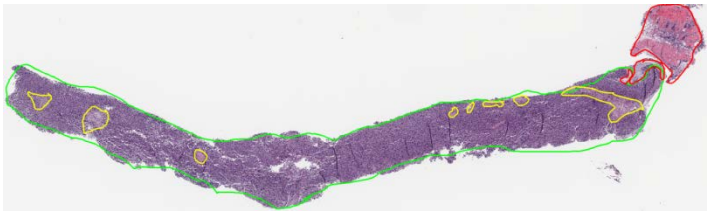
- **Logistical and resource considerations:** Lab tests whose results are used for patient management must be validated, performed and reported by a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments, Centers for Medicare & Medicaid Services (CMS)

What should be the tumor content of the biopsy?

Tumor content (%) = Tumor area / (Viable Tumor + Necrotic Tumor + Stroma area)



Green – Tumor tissues
Yellow – Necrotic tissues
Red – Stroma Tissue



Tumor content in the biopsies: amount of minimal necrosis and stromal tissue; tumor enrichment using macrodissection.

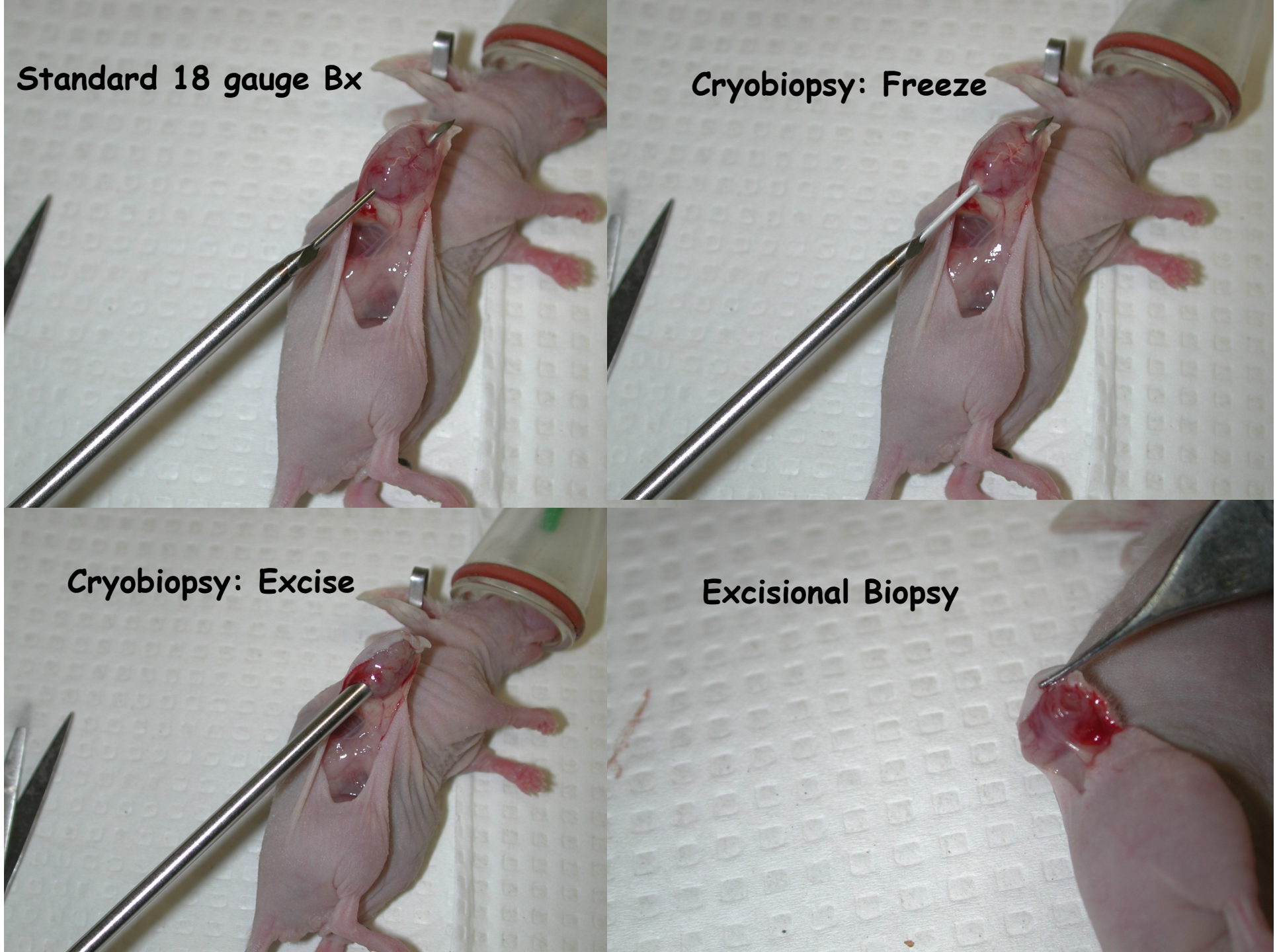
Reason for indeterminate results from tumor biopsies

Cause of Insufficiency Based on One Image Minimum	Number of Biopsies	Percentage
Damaged After Collection	3/23	13%
No Tumor	4/23	17%
Low Tumor Content	16/23	70%

- Main reason for insufficiency is no or low tumor content, 87% (20/23) of failures and 27% (20/73) overall.
- ~45% of all liver biopsies were insufficient due to no or low tumor content (32% insufficiency for all tissues combined).
- Two trials sample sets evaluated showed a trend in decreased tumor content in the post dose biopsy (Post dose time points were Day 6 or Day 8).

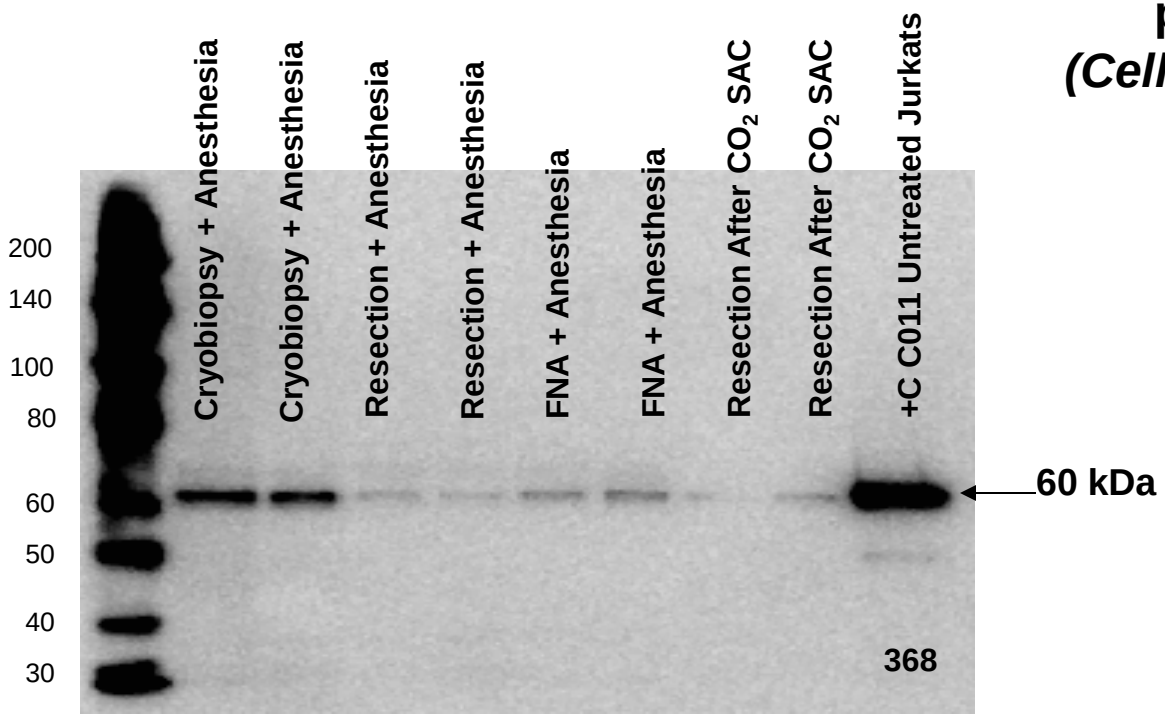
Tissue of Origin	Insufficient Biopsies
Liver	9
Pleural	1
Axilla Node	1
Periumbilical Node	2
Cervical Mass	3
Supraclavicular Node	4

Courtesy: J Doroshow, NCI


Standard 18 gauge Bx
Cryobiopsy: Freeze
Cryobiopsy: Excise
Excisional Biopsy

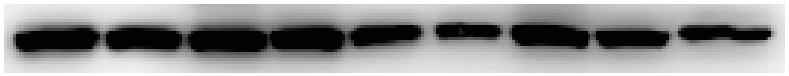
Comparing Effect of 4 Tumor Harvest Methods on pAKT Levels

phospho-AKT
(Cell Signaling #9271)



pAKT Settings
Min 20.0
Max 75.0
1 min exp.

b-Actin



Actin Settings
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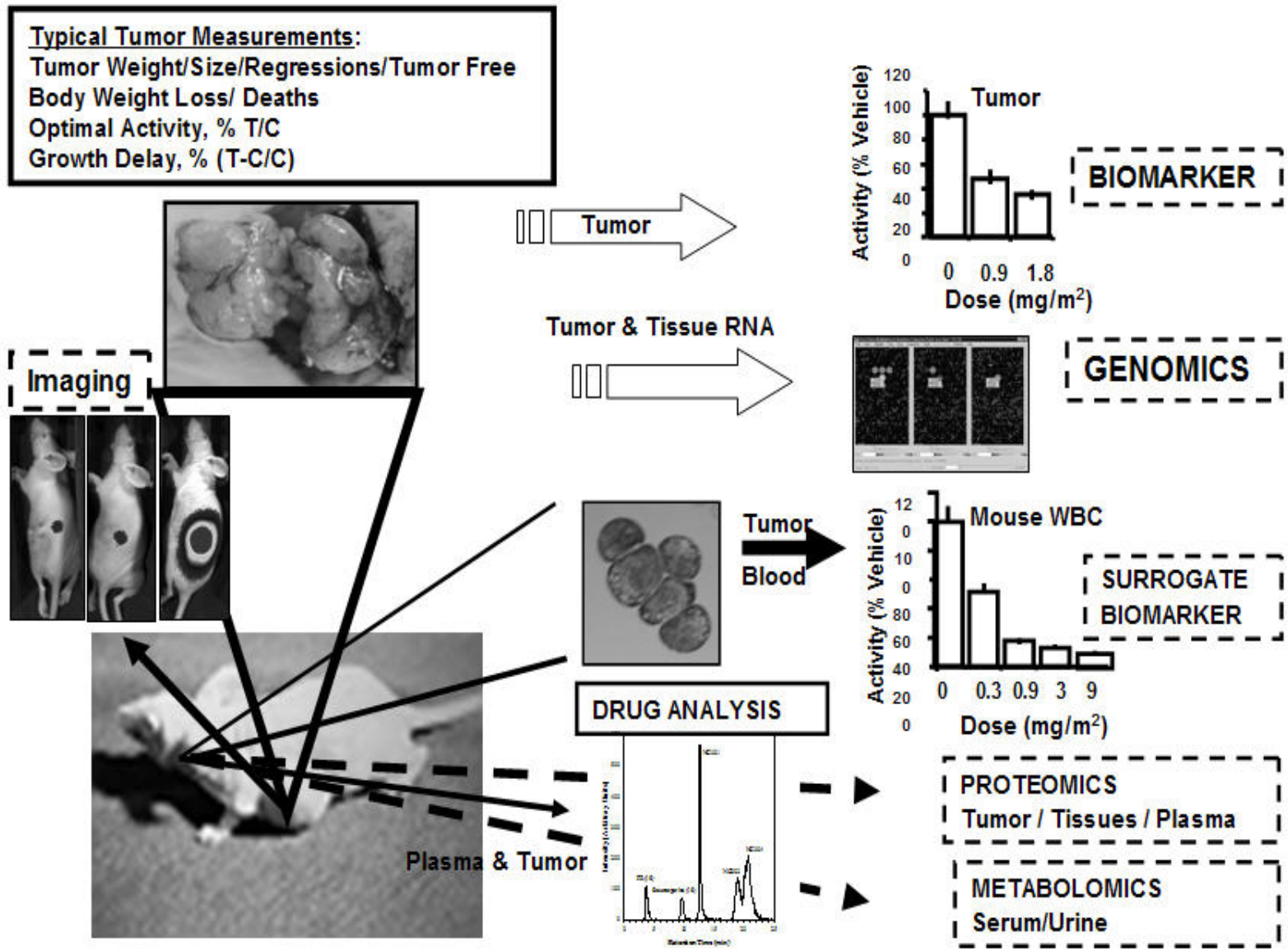
30 sec exp.

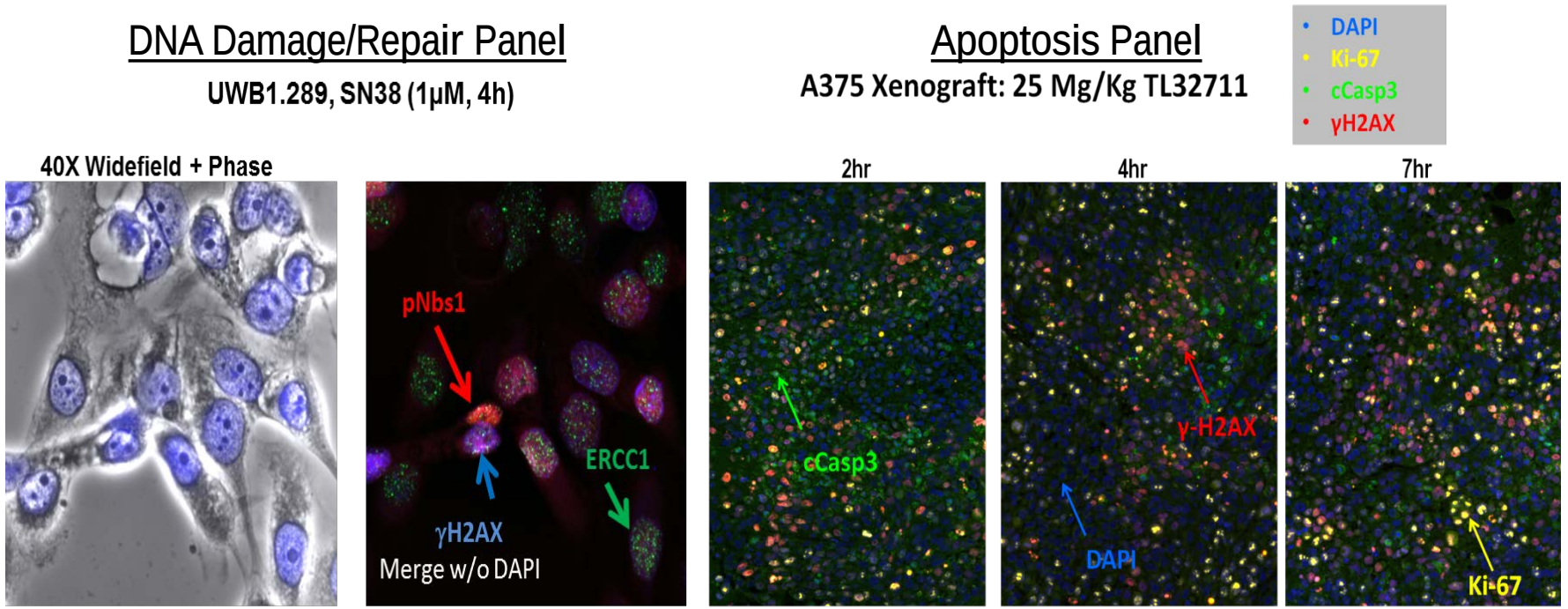
Separated on an 8% Tris-Gly Gel

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



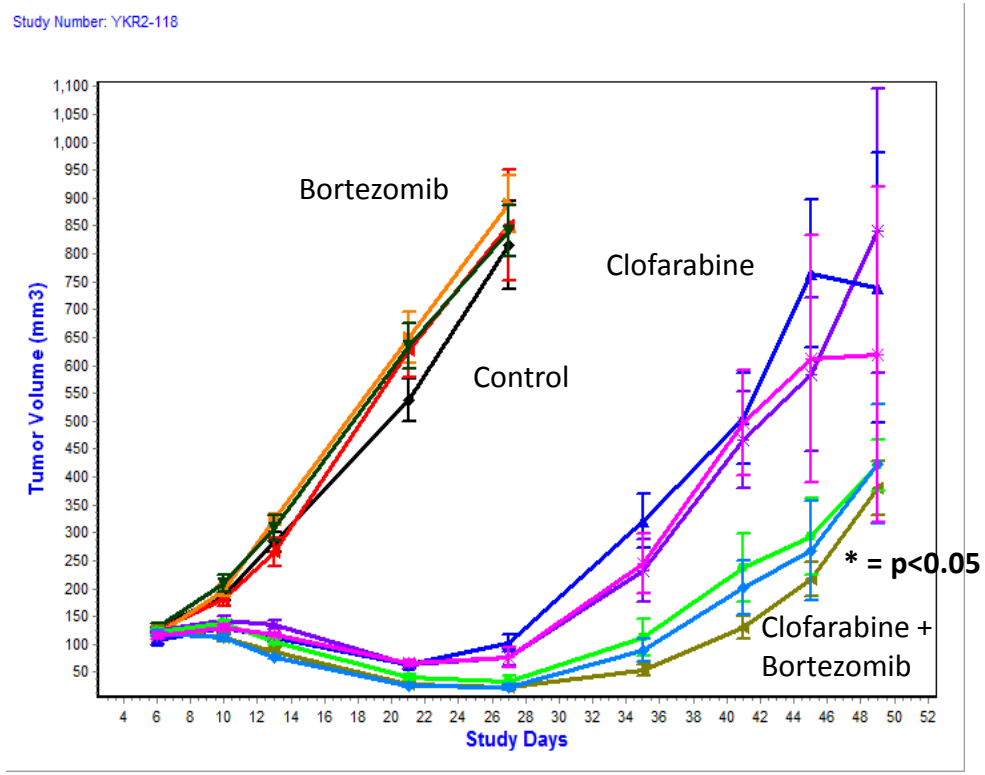
Developing Multiplex Assays

- Require PD assays prior to clinical trials: Establish Proof-of-Mechanism
- Multiplex platforms
  - Evaluate multiple targets and downstream effectors
  - Build on successful γH2AX quantitative IFA
  - Focus on DNA damage/repair & apoptosis
- Define tissue handling, background levels, time course, calibrators
- High priority agents for NCI trials: PARPi; ATRi; XIAP inhibitors



Courtesy: Robert Kinders, PhD, Leidos-NCI

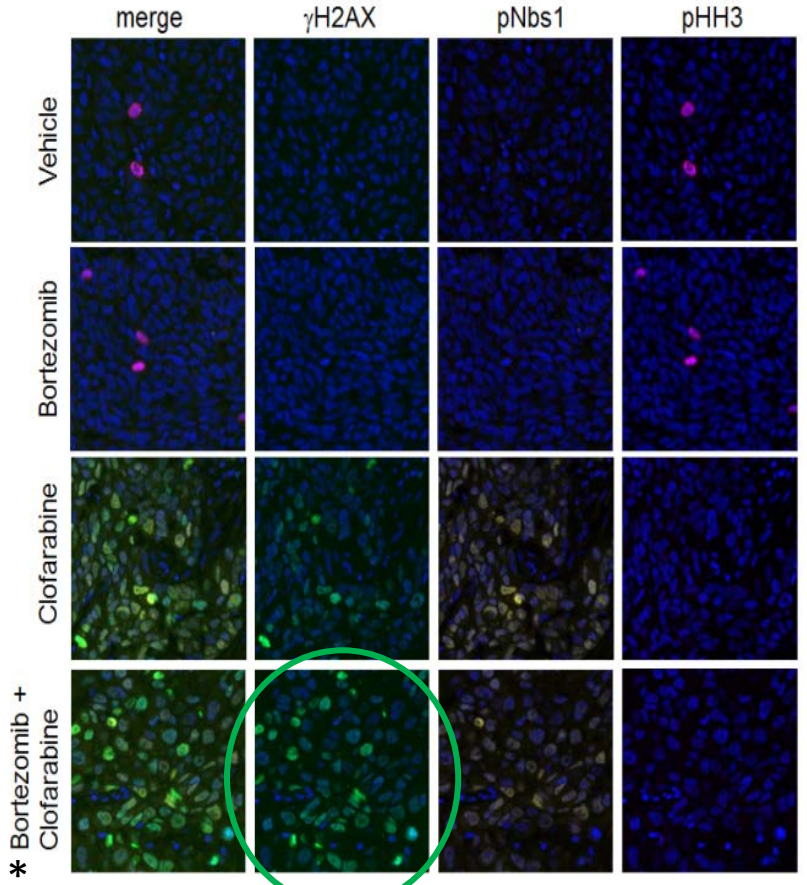
Multiplex Assays: Correlating Efficacy with MOA



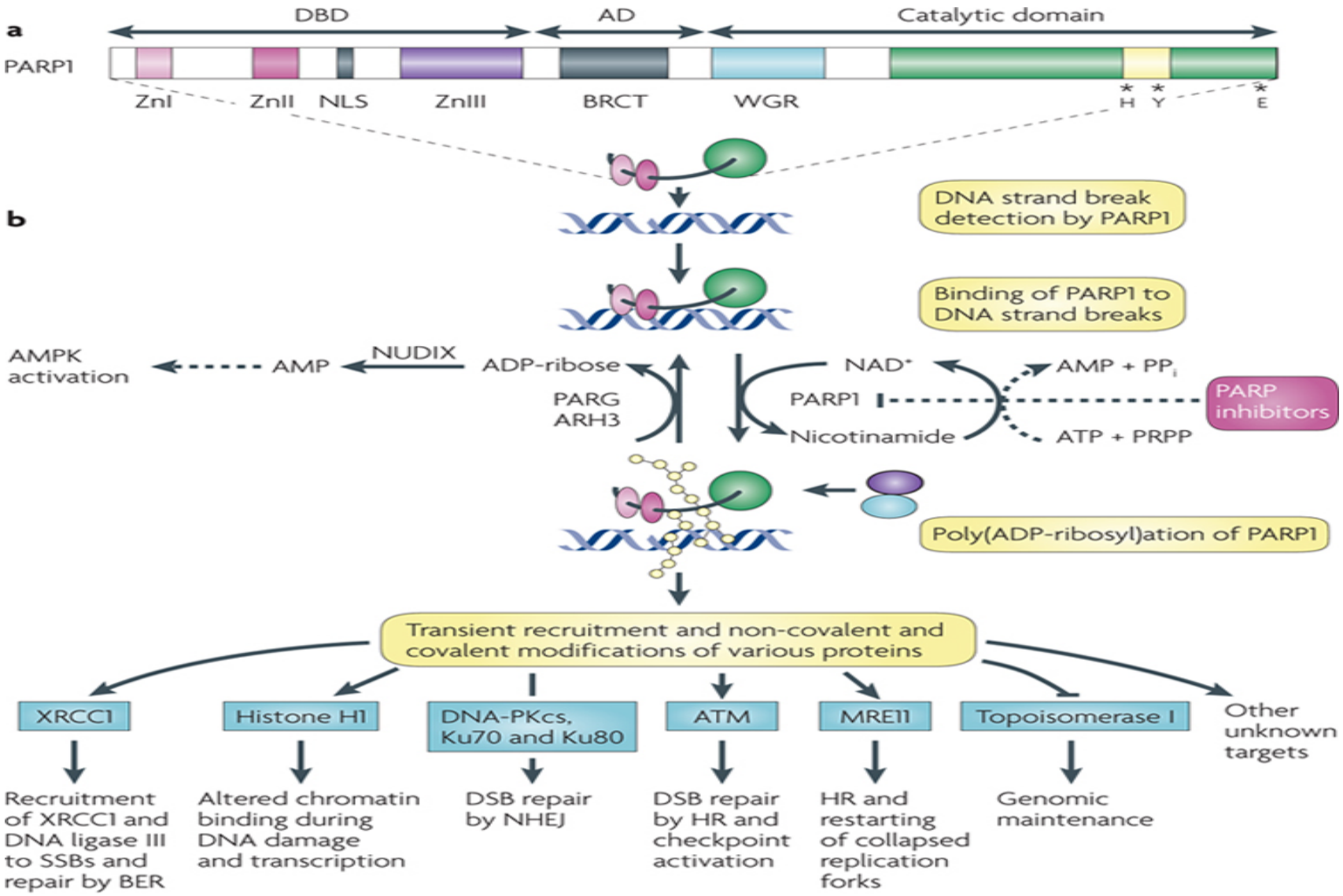
HCT-116 Colon Xenograft

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

DNA Damage Panel



Poly (ADP-ribose) Polymerase [PARP 1]



Nature Reviews | Cancer
2010;10:293-301

Temporal Effects of Single-Dose ABT-888 on PAR Levels in Colo829 Xenografts

				ABT-888* + 2 hours			
	Vehicle	**1.56**	**3.13**	**6.25**	**12.5**	**25**	**TPT 15***
Mean	18029 ± 6711	1361 ± 874	454 ± 786	293 ± 457	159 ± 319	143 ± 299	32701 ± 19583
95% CI	10986–25072	444–2278	LLQ–1279	LLQ–773	LLQ–666	LLQ–393	12150–53252
				ABT-888* + 5 hours			
	Vehicle	**1.56**	**3.13**	**6.25**	**12.5**	**25**	**TPT 15***
Mean	20002 ± 6076	11392 ± 6375	13274 ± 10913	10606 ± 9062	7907 ± 3899	4023 ± 2332	19904 ± 12658
95% CI	13626–26378	3477–19307	1822–24726	LLQ–21858	3066–12748	1128–6918	6620–33188
				ABT-888* + 24 hours			
	Vehicle	**1.56**	**3.13**	**6.25**	**12.5**	**25**	**TPT 15***
Mean	18866 ± 5185	33927 ± 17651	11353 ± 3358	10404 ± 4173	8342 ± 7753	8794 ± 4957	1917 ± 2332
95% CI	6070–31662	12010–55844	4062–18644	37–20771	LLQ–17969	LLQ–21108	LLQ–4365

*All doses are mg/kg. n = 6 animals per group; whole xenografts were surgically excised and half of the excised specimen was measured in the PAR immunoassay at protein loads of 10 to 20 µg per well.

Single-dose topotecan was administered by intraperitneal injection as an additional control.
Collection time points were selected to mimic the time points in the clinical trial.
All units are pg PAR/mL per 100 µg protein.

TPT = topotecan; LLQ = lower limit of quantitation of the assay.

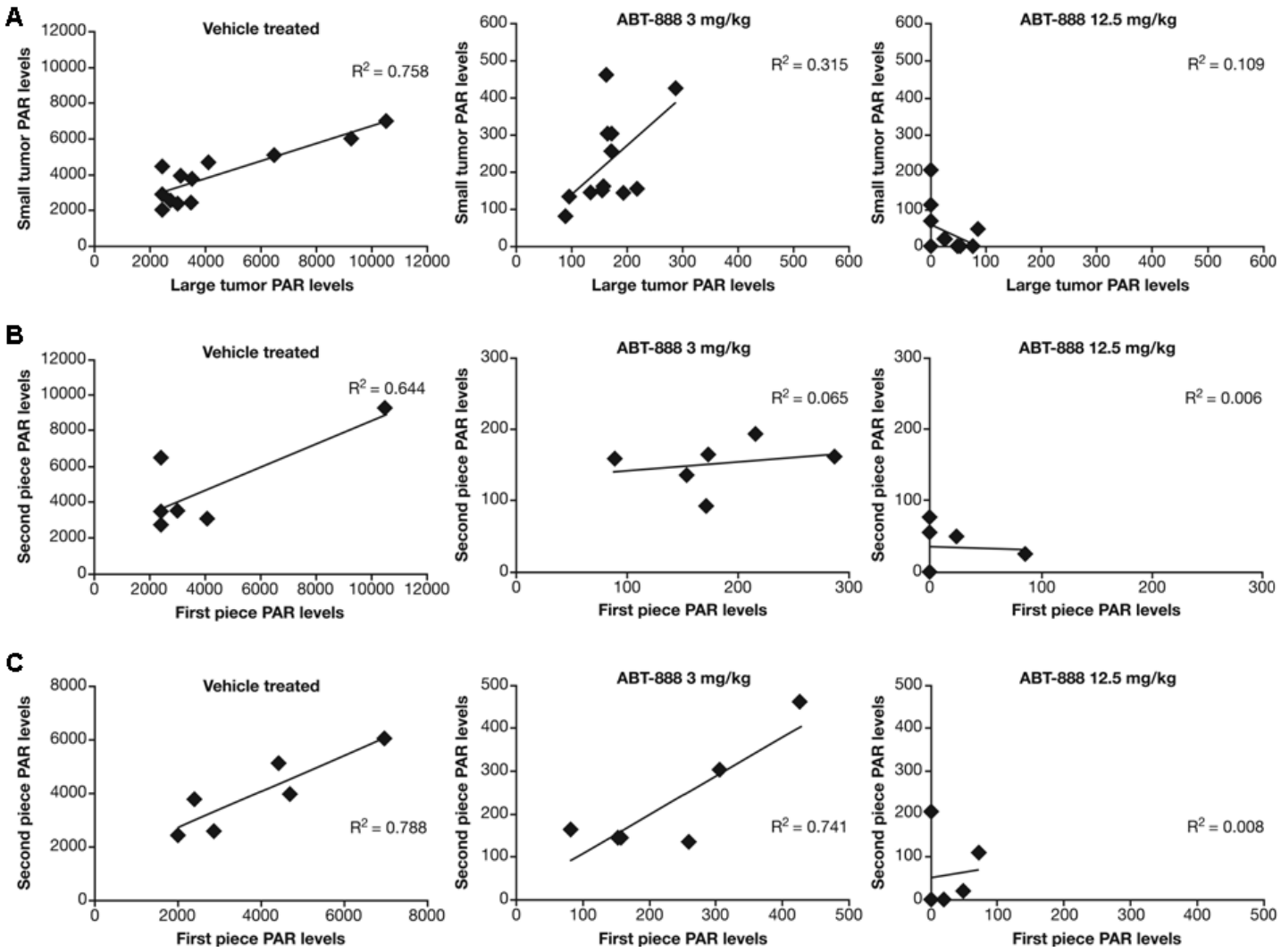
Kinders R, et al. *Clin Cancer Res*. 2008;14:6877-85.

Inter- and Intra-Tumor Variability of PAR Levels in Colo829 Xenografts in Vehicle- and ABT-888-Treated Mice

Correlation of PAR levels between resected **small and large tumors**. The difference in scale of PAR values in vehicle compared with ABT-888 treatment groups is due to significant drug suppression of PAR.

Correlation of PAR levels between first and second quadrants dissected from resected **large tumors**.

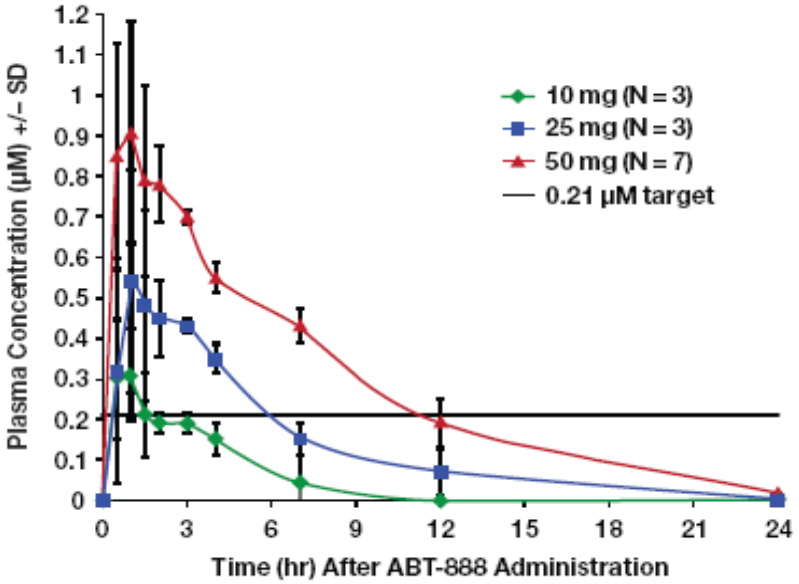
Correlation of PAR levels between first and second quadrants dissected from resected **small tumors**.

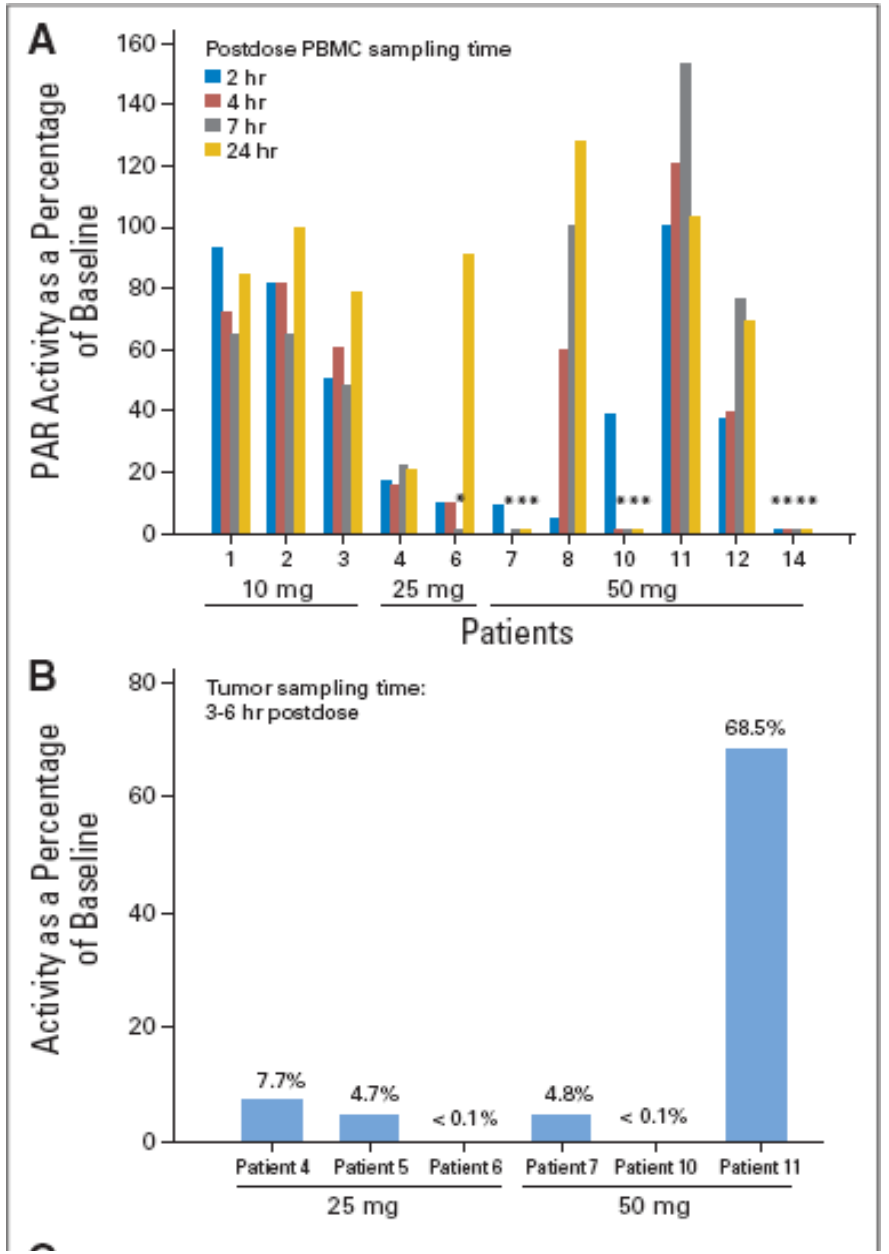


PAR levels were measured 4 h following ABT-888 administration at doses of 3 or 12.5 mg/kg as indicated (n = 6 animals/group).
Values are pg PAR/mL, normalized to 100 µg protein.
Solid diamond, measured point; line, linear regression fit.

Kinders R, et al. *Clin Cancer Res*. 2008;14:6877-85

First-in-human trial of ABT-888 in Solid Tumors





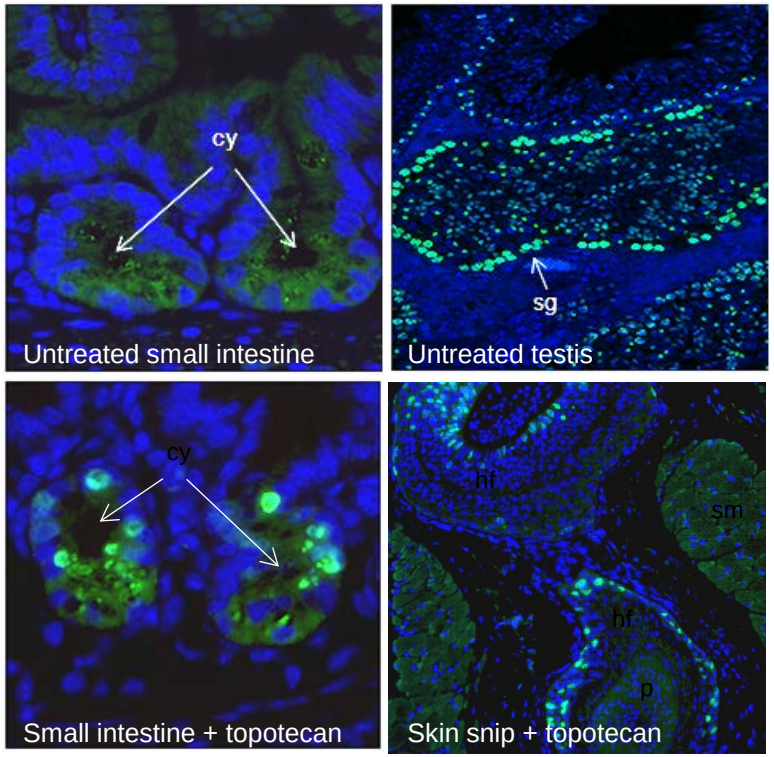
Kummar et al. J Clin Oncol 27(16); 2009

γH2AX

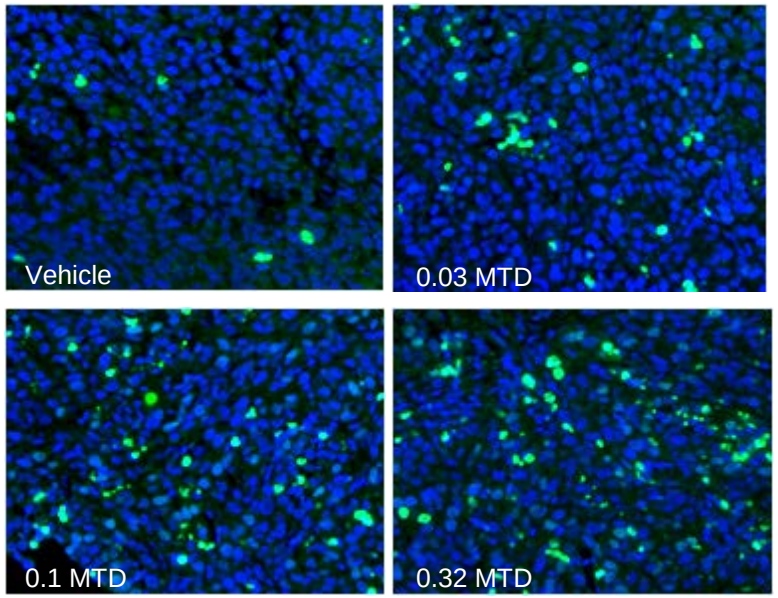
H2AX is a major effector of the ATM kinase pathway

Serine 139 phosphorylation of Histone H2AX occurs in response to double strand DNA breaks

A



B



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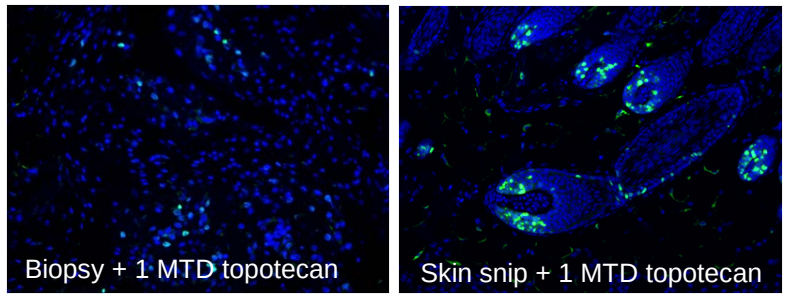

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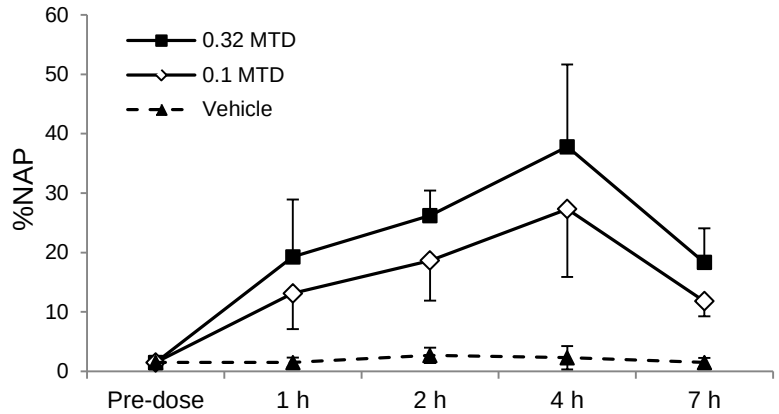
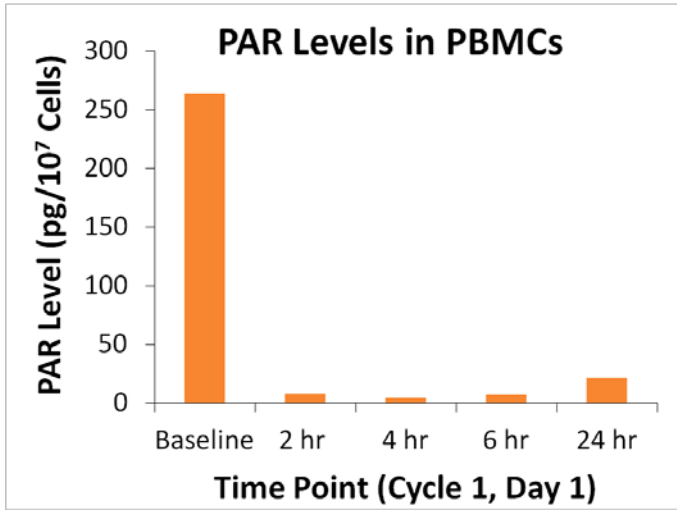
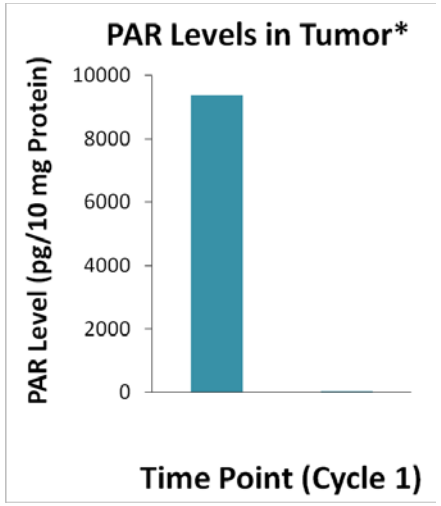
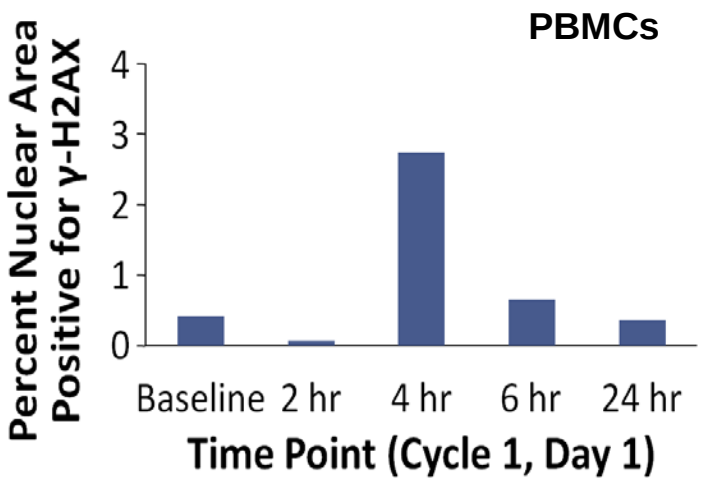


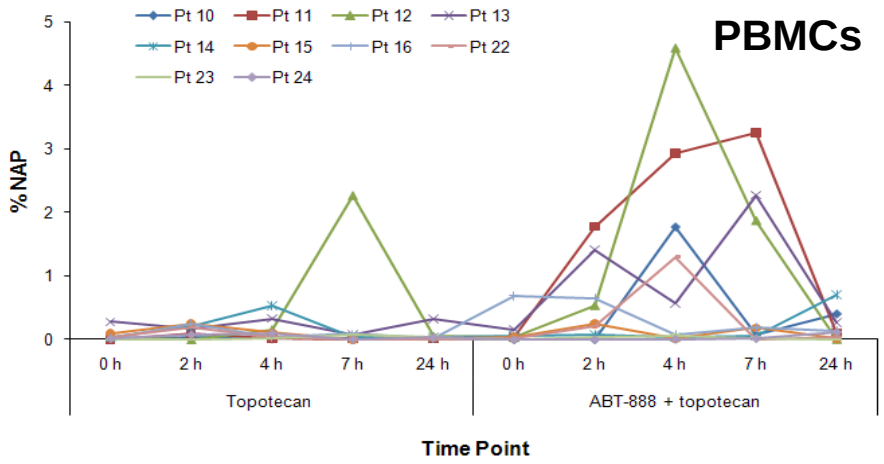
Clin. Cancer Res. 16:5447, 2010

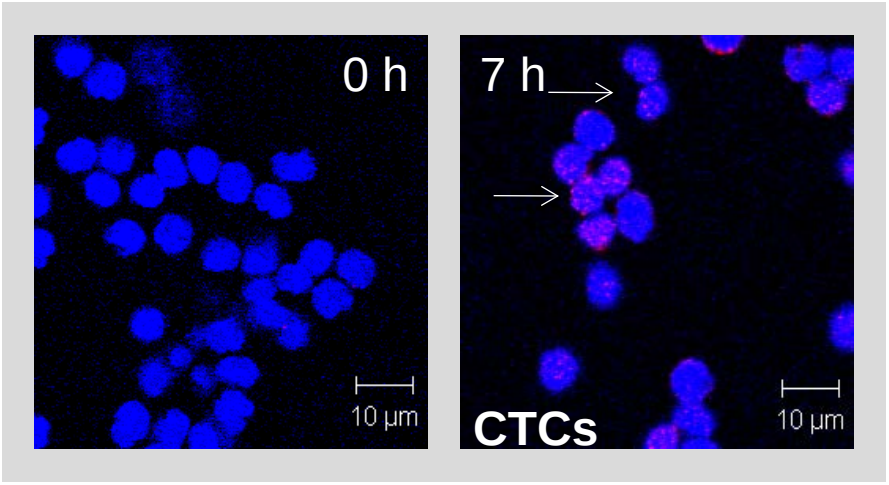
Veliparib in combination with cytotoxic chemotherapy: Assessing drug target effect





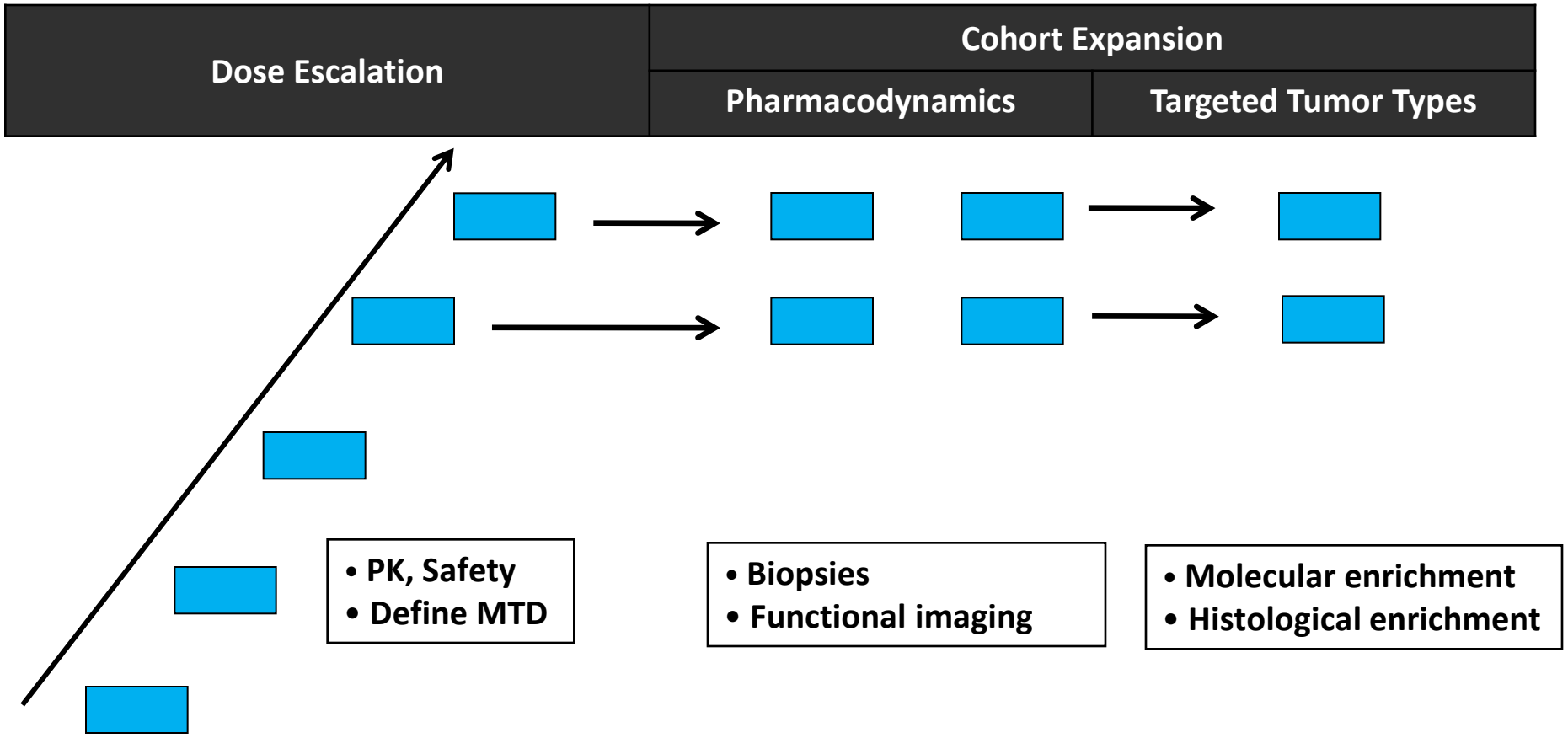




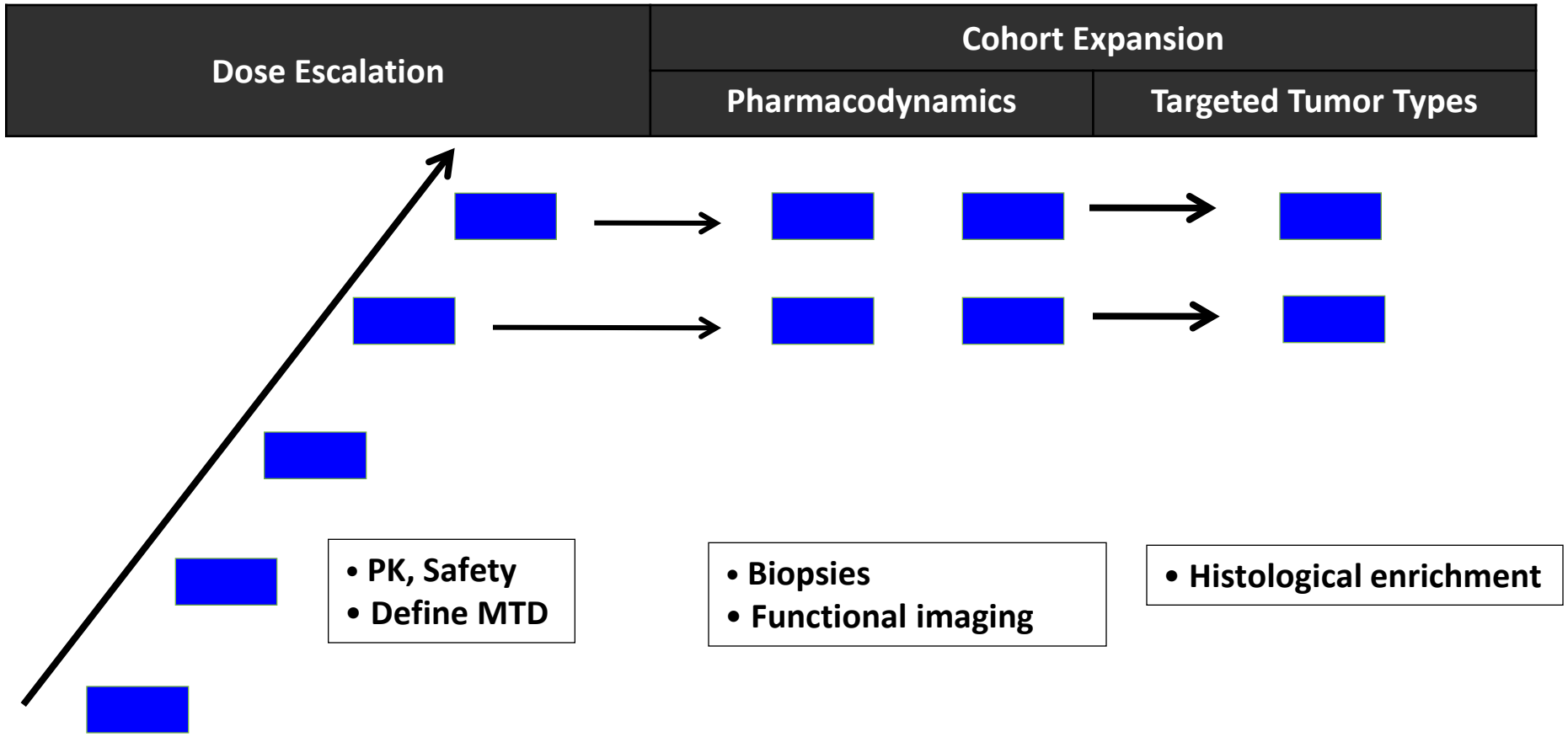


Kummar S, et al. J Clin Oncol 2009; Clin Cancer Res 2012

Phase I Study Design – Unselected Patients in Dose Escalation followed by Specific Expansion Cohorts



Phase I Study Design – Only Molecularly Enriched Patients



Biomarkers: regulatory definitions

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.

Integral

- Used for patient selection
- Used to determine patient treatment
- Performed in CLIA environment
- e.g. mutBRaf(V600) with BRaf inhibitor (dabrafinib, vemurafinib)

Integrated

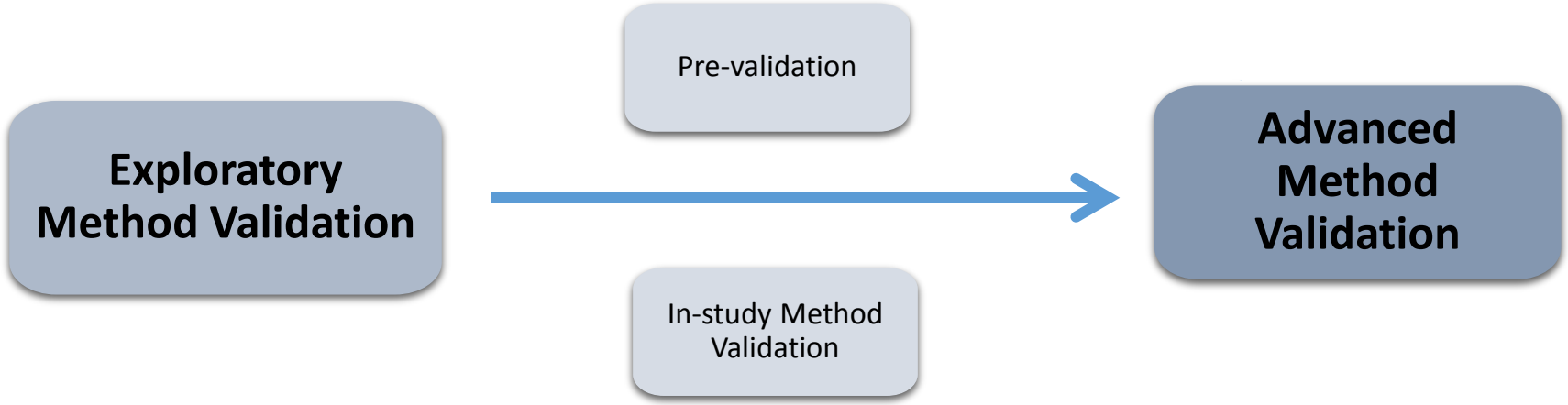
- Used for patient description
- Provide evidence of pathway activation
- Pharmacodynamic
- CLIA ready
- e.g. study of biomarkers for Ras/Raf/MEK signaling

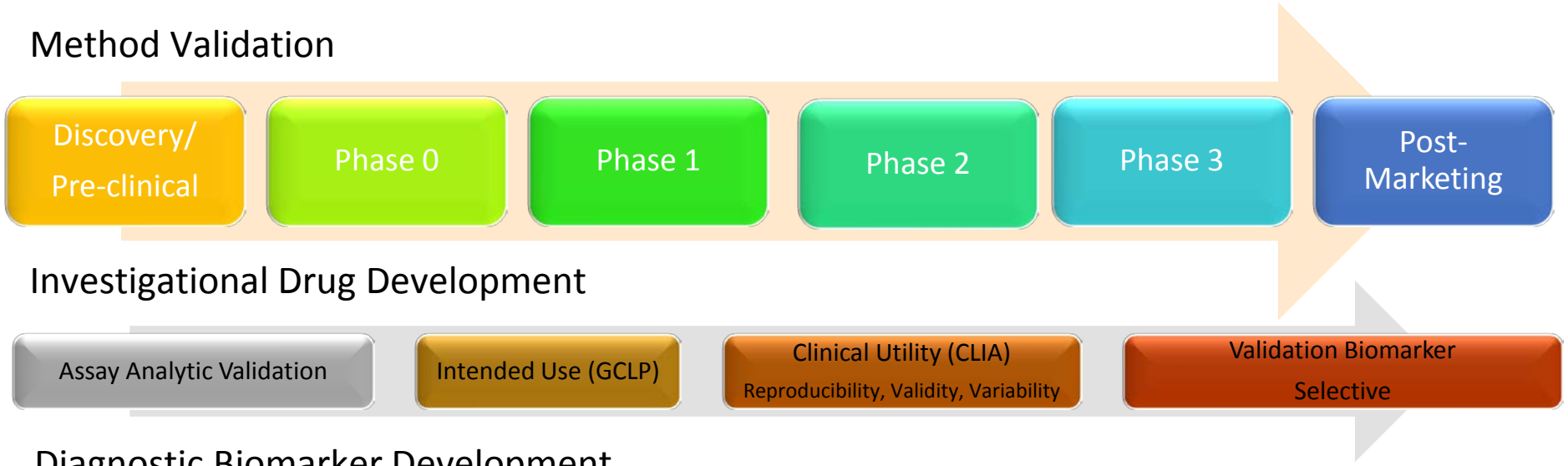
Exploratory

- Descriptive
- Not validated or fit-for-purpose
- e.g. study of cross talk between Ras/Raf/MEK and PI3K signaling cascades

BEST (Biomarkers, EndpointS, and other Tools) Resource

Fit-for-Purpose:
Parallel Drug and Biomarker Development



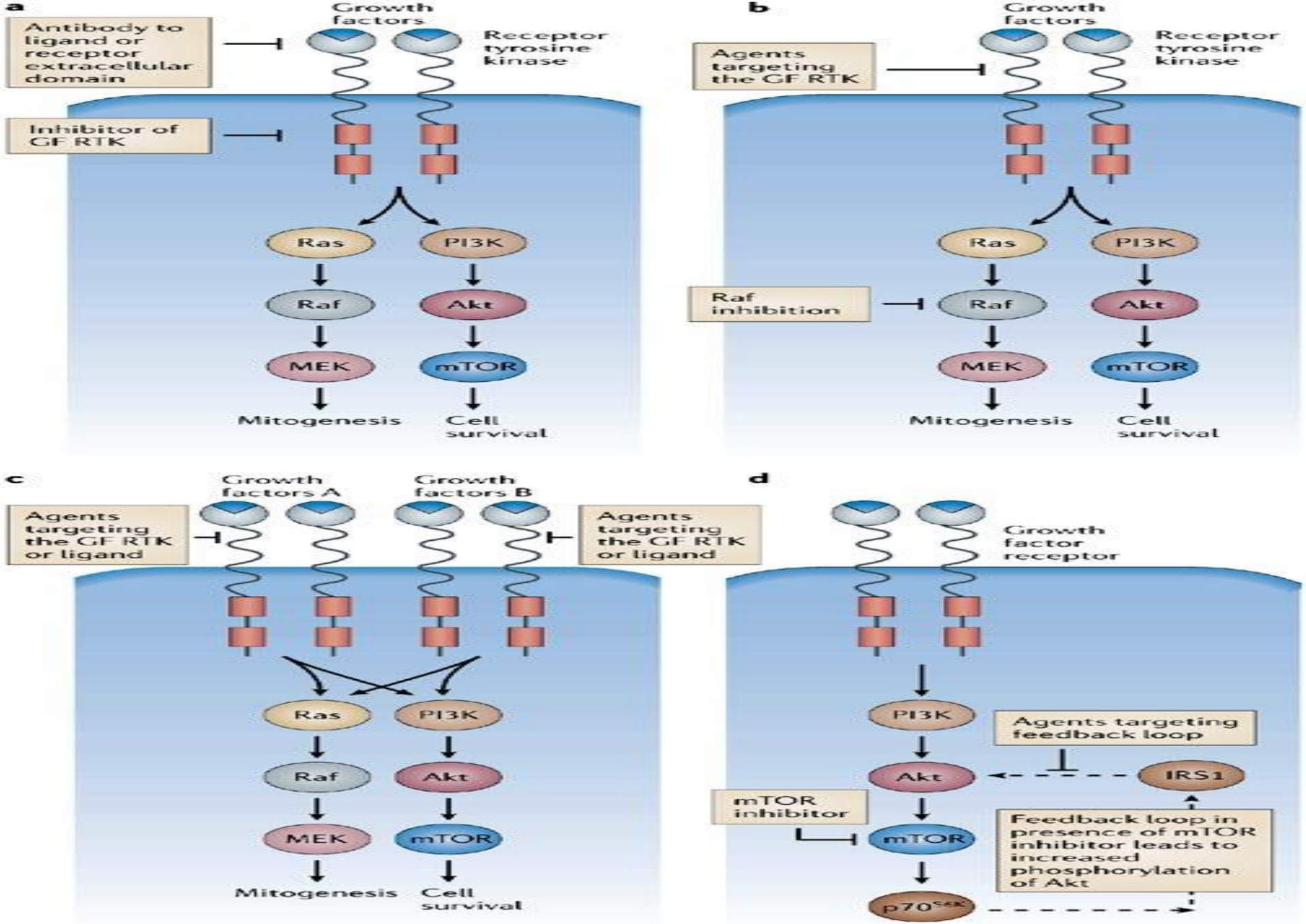


Definitions

- ***Analytical performance (analytical validity):*** how accurately the test detects the analyte(s) of interest

- ***Clinical Validity***: How well does the assay result correlate with outcome?

- ***Clinical Utility***: How does use of the assay improve outcome?

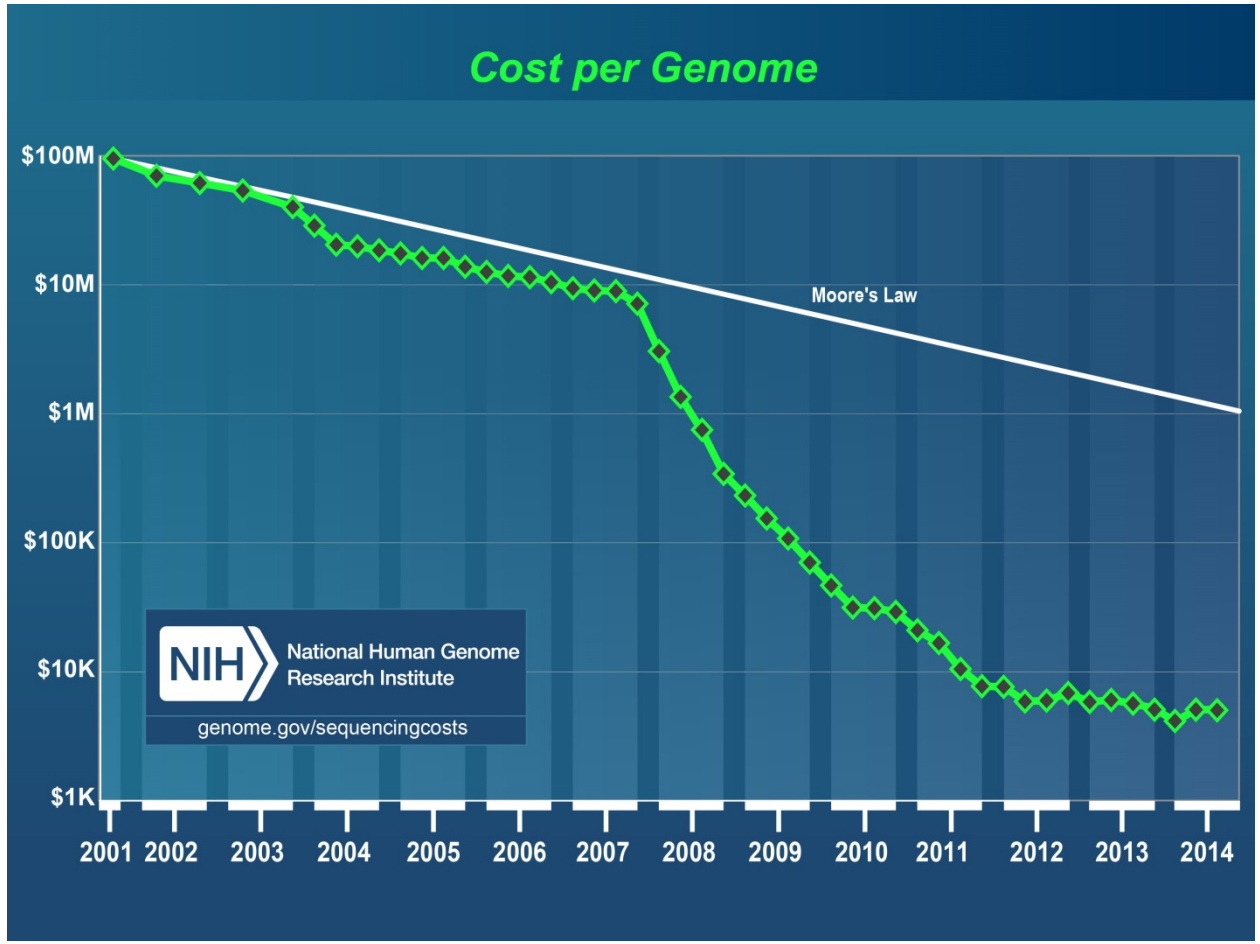

a
Antibody to ligand or receptor extracellular domain
Growth factors
Receptor tyrosine kinase
Inhibitor of GF RTK
Ras
PI3K
Raf
Akt
MEK
mTOR
Mitogenesis
Cell survival
b
Growth factors
Receptor tyrosine kinase
Agents targeting the GF RTK
Ras
PI3K
Raf inhibition
Raf
Akt
MEK
mTOR
Mitogenesis
Cell survival
c
Growth factors A
Growth factors B
Agents targeting the GF RTK or ligand
Agents targeting the GF RTK or ligand
Ras
PI3K
Raf
Akt
MEK
mTOR
Mitogenesis
Cell survival
d
Growth factor receptor
PI3K
Agents targeting feedback loop
Akt
IRS1
mTOR inhibitor
mTOR
Feedback loop in presence of mTOR inhibitor leads to increased phosphorylation of Akt
p70S6K

Challenges in developing drug combinations

- **Dose adjustments required for overlapping toxicities: is the dose still resulting in adequate exposure?**
- Lack of preclinical models of combination therapy
  - No standard, combinatorial high-throughput screening models to examine combinations in vitro;
  - no in vivo models standardized for use with targeted combinations;
  - and lack of approved or investigational agents available for preclinical evaluation
- Inability to assess target effects clinically. That is, lack of assays or imaging tools, and lack of assay standardization
- Inadequate clinical trials methodology for combination studies
  - Need to screen large numbers of patients for specific mutations?
  - Need for tumor biopsies? Relevance of histological versus genetic homogeneity?
  - Pharmacokinetic interactions? Relevant end points for trials — response versus lack of disease progression?
- Intellectual property challenges to combining agents from competing sponsors
- Regulatory framework for the commercialization of targeted combinations

Dose is context dependent: Patient Selection

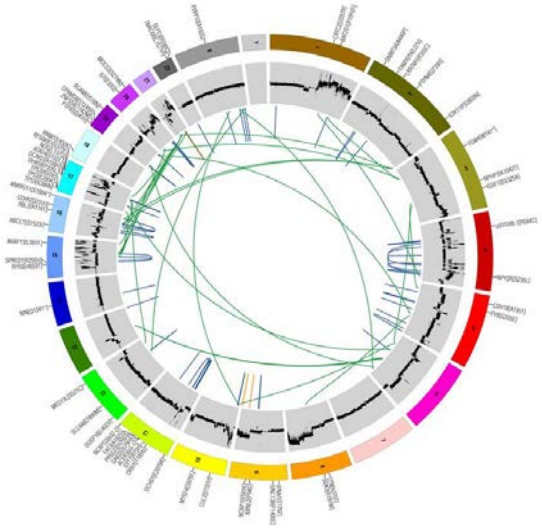
Declining costs of sequencing: massively parallel next-generation sequencing and subsequent computational analysis



Date	Cost per Mb	Cost per Genome
Sep-01	$5,292.39	$95,263,072
Mar-02	$3,898.64	$70,175,437
Sep-02	$3,413.80	$61,448,422
Mar-03	$2,986.20	$53,751,684
Oct-03	$2,230.98	$40,157,554
Jan-04	$1,598.91	$28,780,376
Apr-04	$1,135.70	$20,442,576
Jul-04	$1,107.46	$19,934,346
Oct-04	$1,028.85	$18,519,312
Jan-05	$974.16	$17,534,970
Apr-05	$897.76	$16,159,699
Jul-05	$898.90	$16,180,224
Oct-05	$766.73	$13,801,124
Jan-06	$699.20	$12,585,659
Apr-06	$651.81	$11,732,535
Jul-06	$636.41	$11,455,315
Oct-06	$581.92	$10,474,556
Jan-07	$522.71	$9,408,739
Oct-07	$397.09	$7,147,571
Jan-08	$102.13	$3,063,820
Oct-08	$3.81	$342,502
Jan-09	$2.59	$232,735
Oct-09	$0.78	$70,333
Jan-10	$0.52	$46,774
Oct-10	$0.32	$29,092
Jan-11	$0.23	$20,963
Apr-11	$0.19	$16,712
Jul-11	$0.12	$10,497
Oct-11	$0.09	$7,743
Jan-12	$0.09	$7,666
Apr-12	$0.07	$5,901
Jul-12	$0.07	$5,985
Oct-12	$0.07	$6,618
Jan-13	$0.06	$5,671
Oct-13	$0.06	$5,096
Jan-14	$0.04	$4,008
Apr-14	$0.05	$4,920
Jul-14	$0.05	$4,905

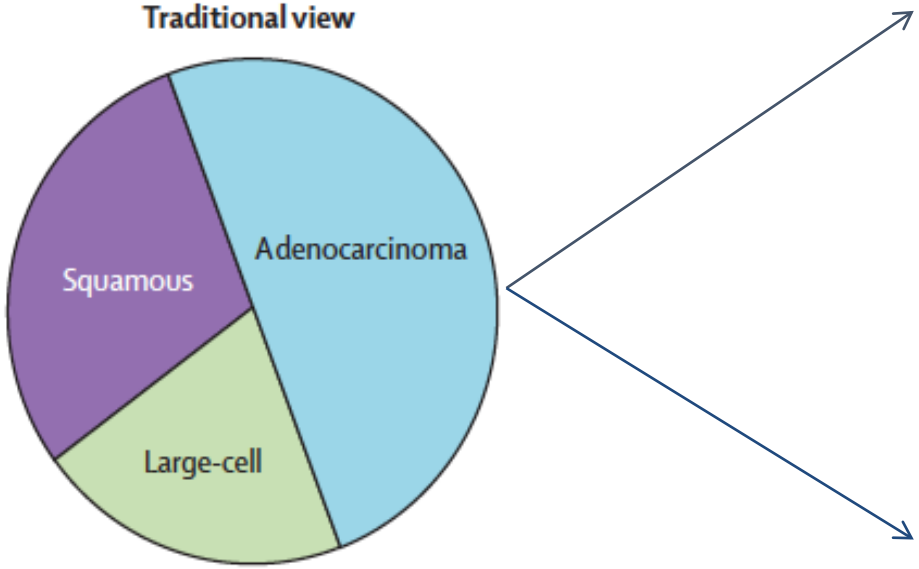
COSMIC: Catalog of Somatic Mutations in Cancer

- COSMIC launched in 2004, detailed 4 cancer genes
- 2014: world's largest and most comprehensive resource
  - 2, 002, 811 coding point mutations in over one million tumor samples
  - 6 million noncoding mutations,
  - 10, 534 gene fusions,
  - 61 299 genome rearrangements
  - 695, 504 abnormal copy number
  - segments and
  - 60,119,787 abnormal
  - expression variants

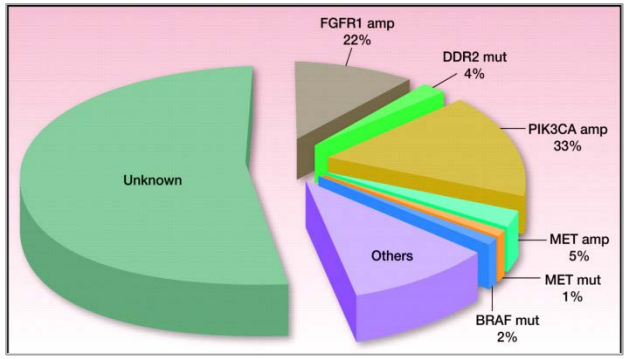


Forbes SA, et al. *Nucl. Acids Res. 2015; 43 (D1): D805*

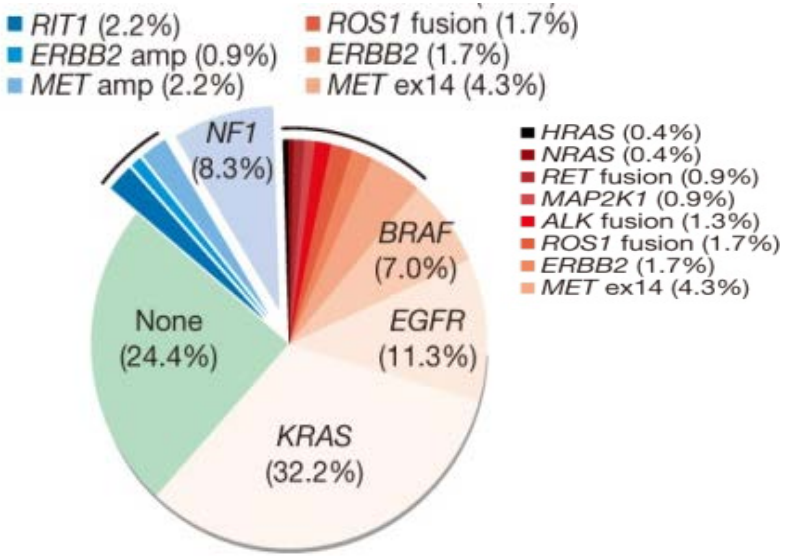
Transition From Histology → Genomic Driver Mutations



SQUAMOUS



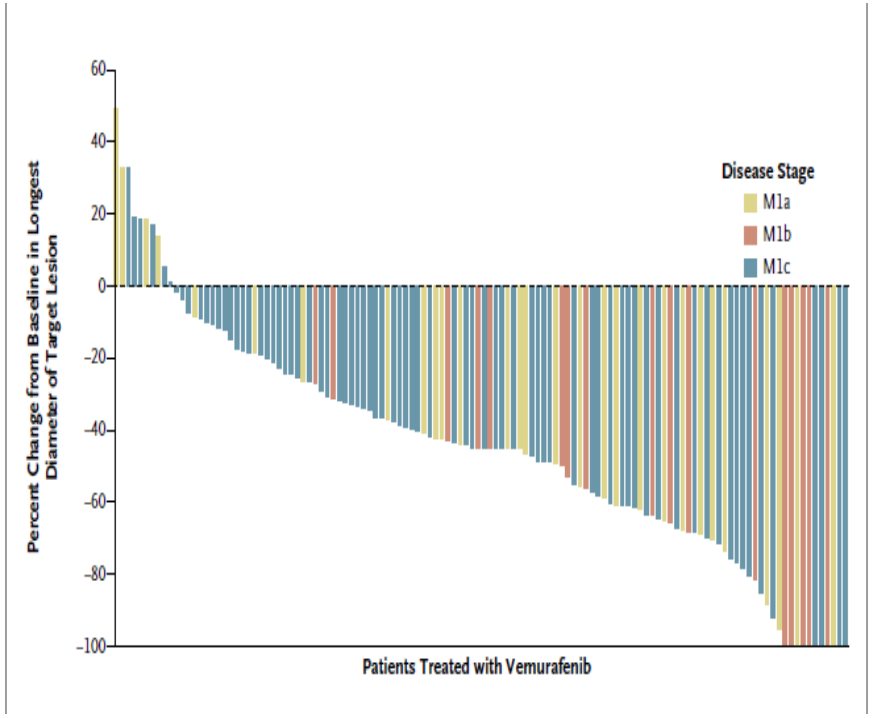
ADENOCARCINOMA



Pao W, Girard N. *Lancet Oncol*. 2011;12:175-180;
Perez-Moreno P, et al. *Clin Cancer Res*. 2012;18:2443-2451;
Cancer Genome Atlas Research Network. *Nature*. 2012;489:519-525;
Cancer Genome Atlas Research Network. *Nature*. 2014;511:543-550.

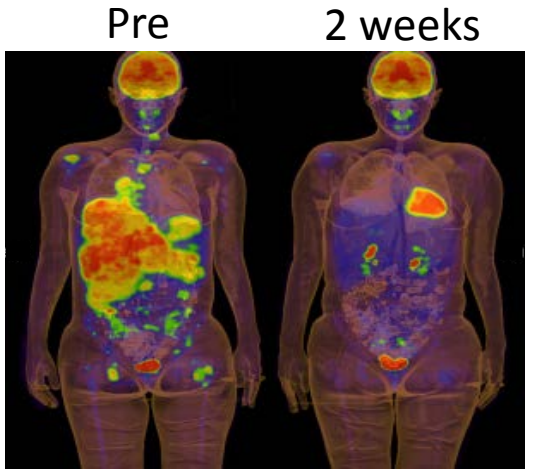
Targeting mutations works!!

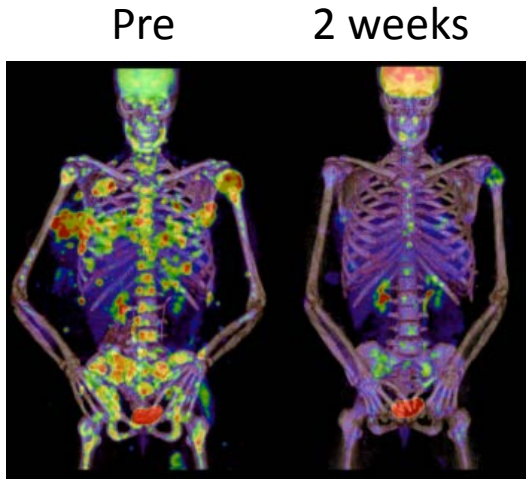
Vemurafenib in melanoma harboring activating mutations (T→A transversion at position 1799)in B-RAF (V600)

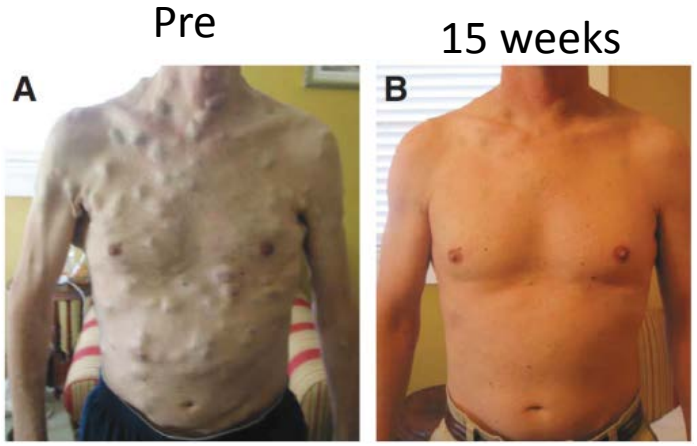


RR (6%CR, 47% PR); PFS 6.8 mos

Sosman J, et al. NEJM 2012;366:8

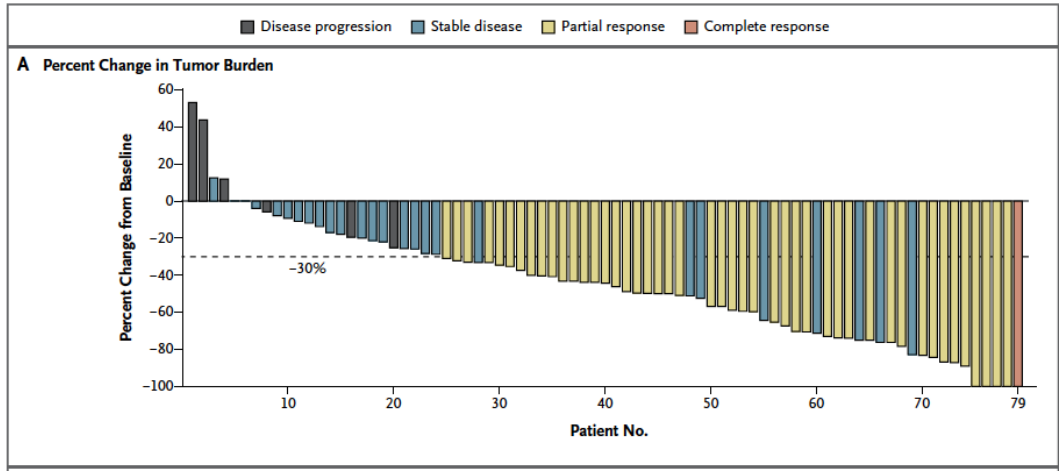






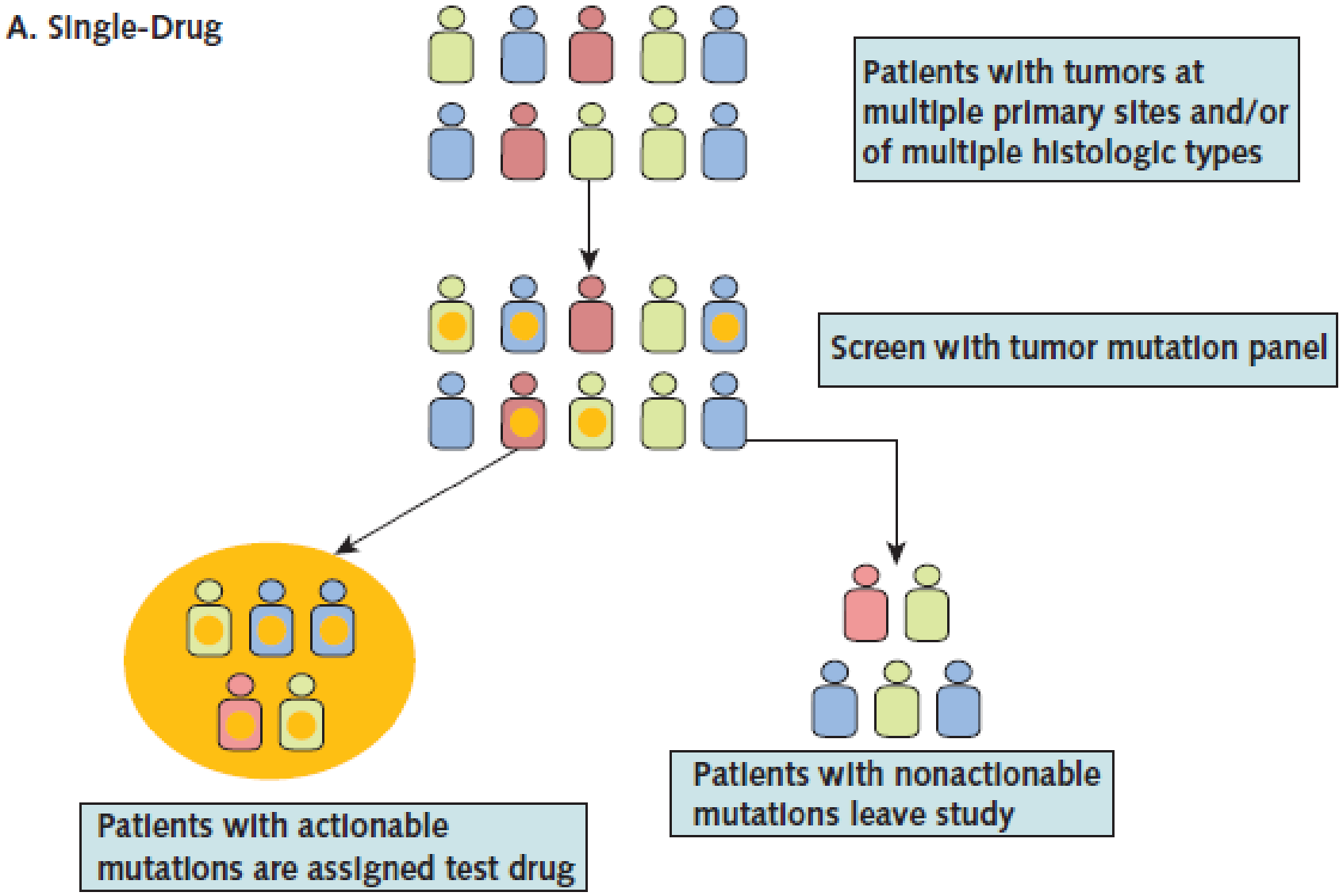
Incorporating Molecular Profiling into Early Phase Trials

- Targeting driver mutations; enrichment strategies
  - Phase I for Crizotinib –standard dose escalation in solid tumors, 2 pts responded→ profiling showed ALK rearrangement→protocol amended to include an expansion cohort→1500 patients screened from August 2008 through February 2010 to enroll 82 patients with FISH+ ALK rearrangement→57% objective confirmed partial/complete response
  - No statistically predetermined enrollment goal for *ALK*-positive patients was established.
  - August 26, 2011: Crizotinib received accelerated approval by the FDA along with a companion diagnostic (Vysis ALK Break Apart FISH Probe Kit)



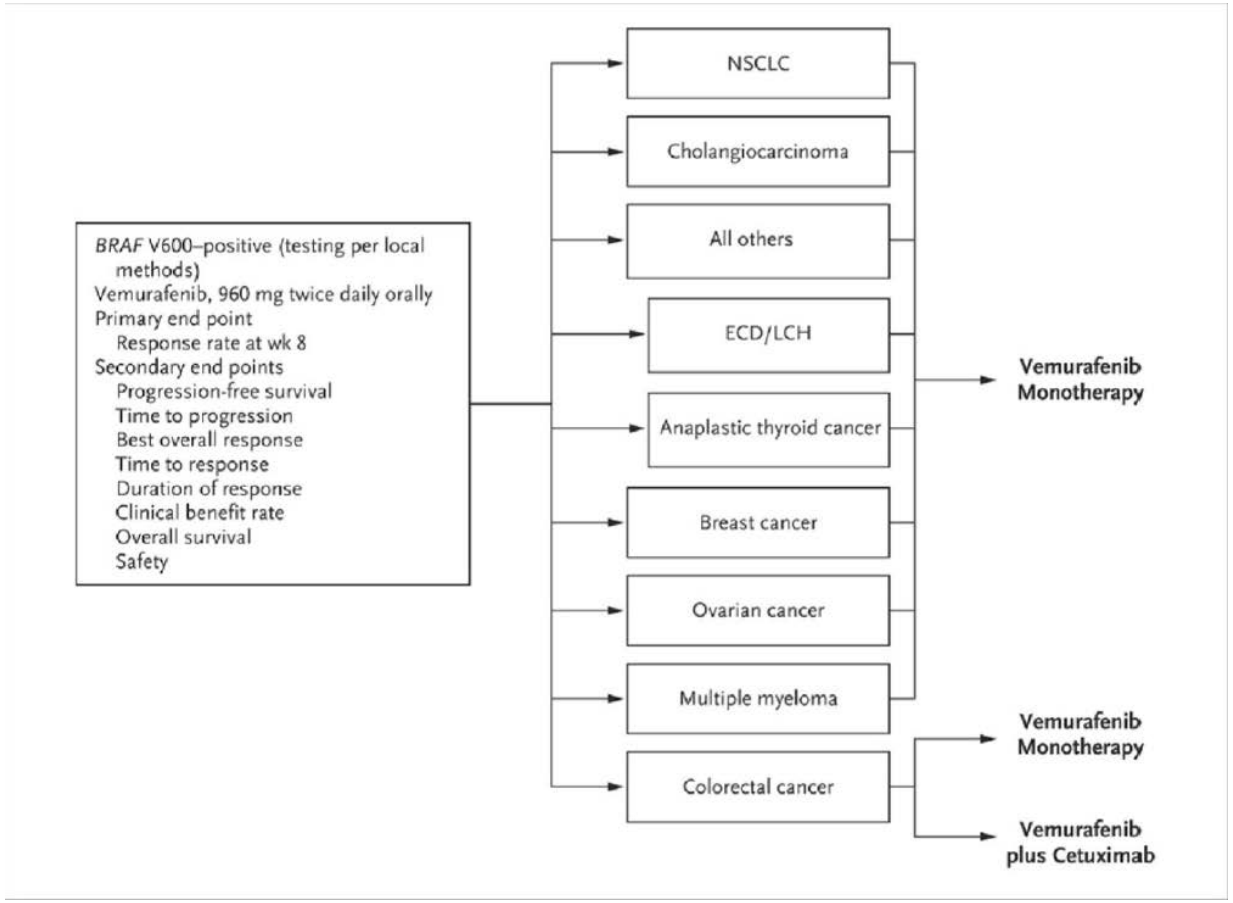
Kwak et al. N Engl J Med 2010;363:1693

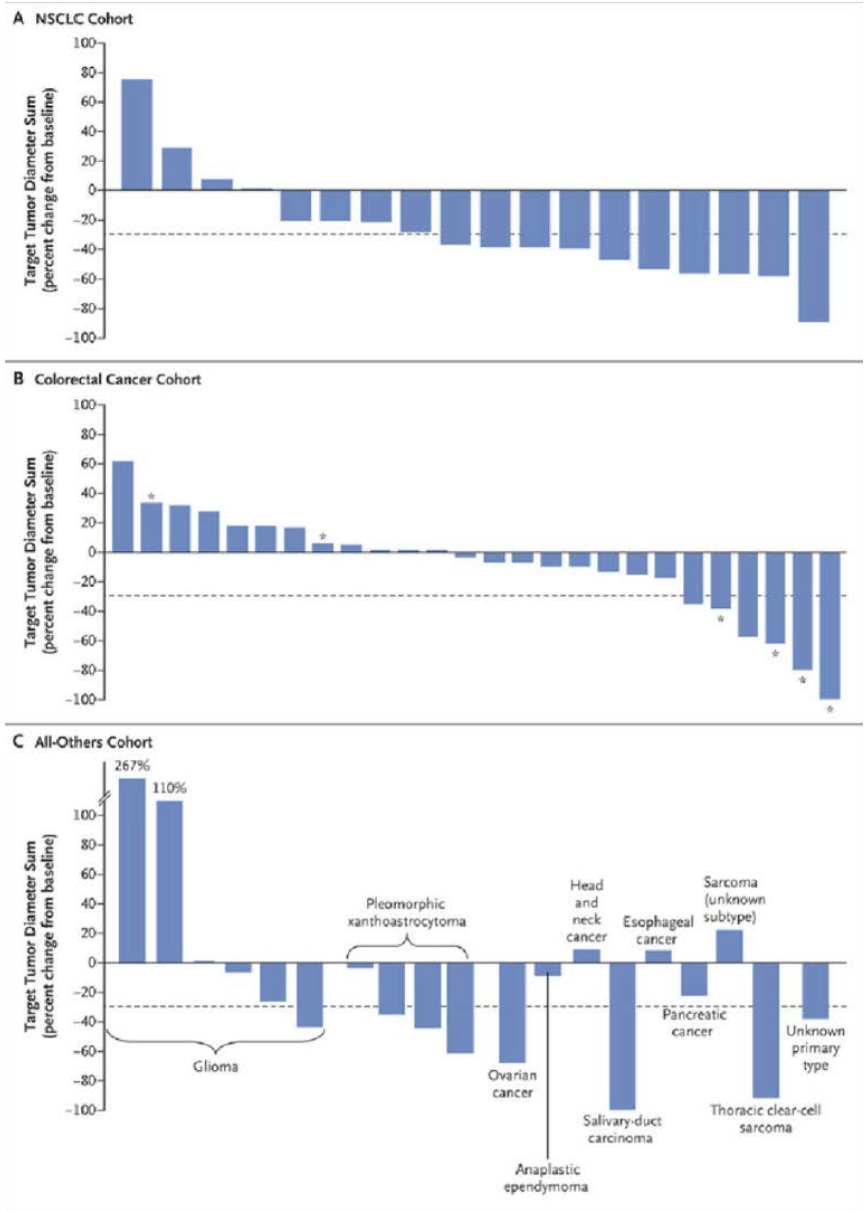
BASKET Trials



Simon R. Ann Int Med 2016; 165:270

Vemurafenib Basket Trial

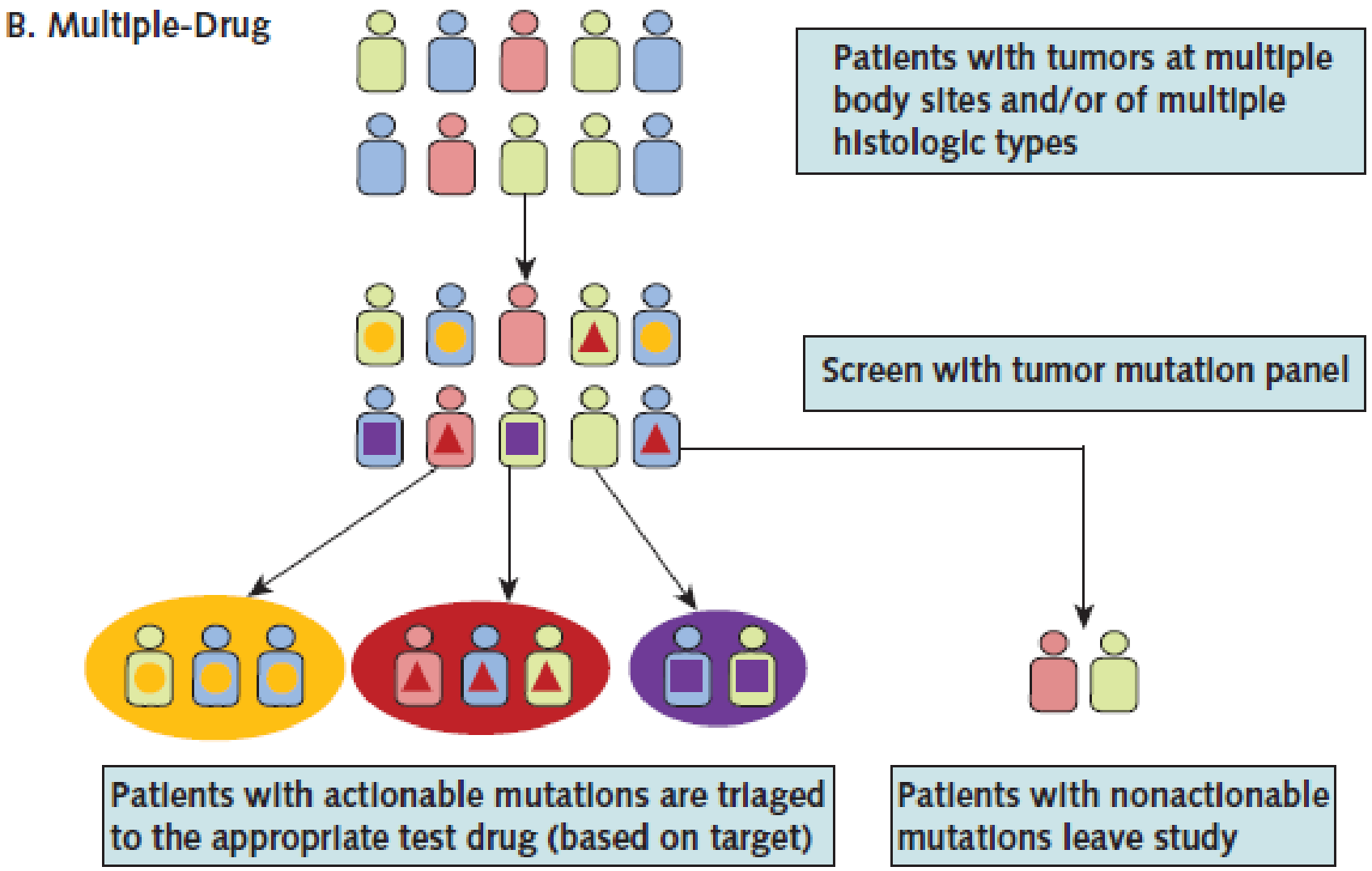




NSCLC RR 42%
LCH RR 43%

Hyman D, et al. N Engl J Med 2015; 373(8):726

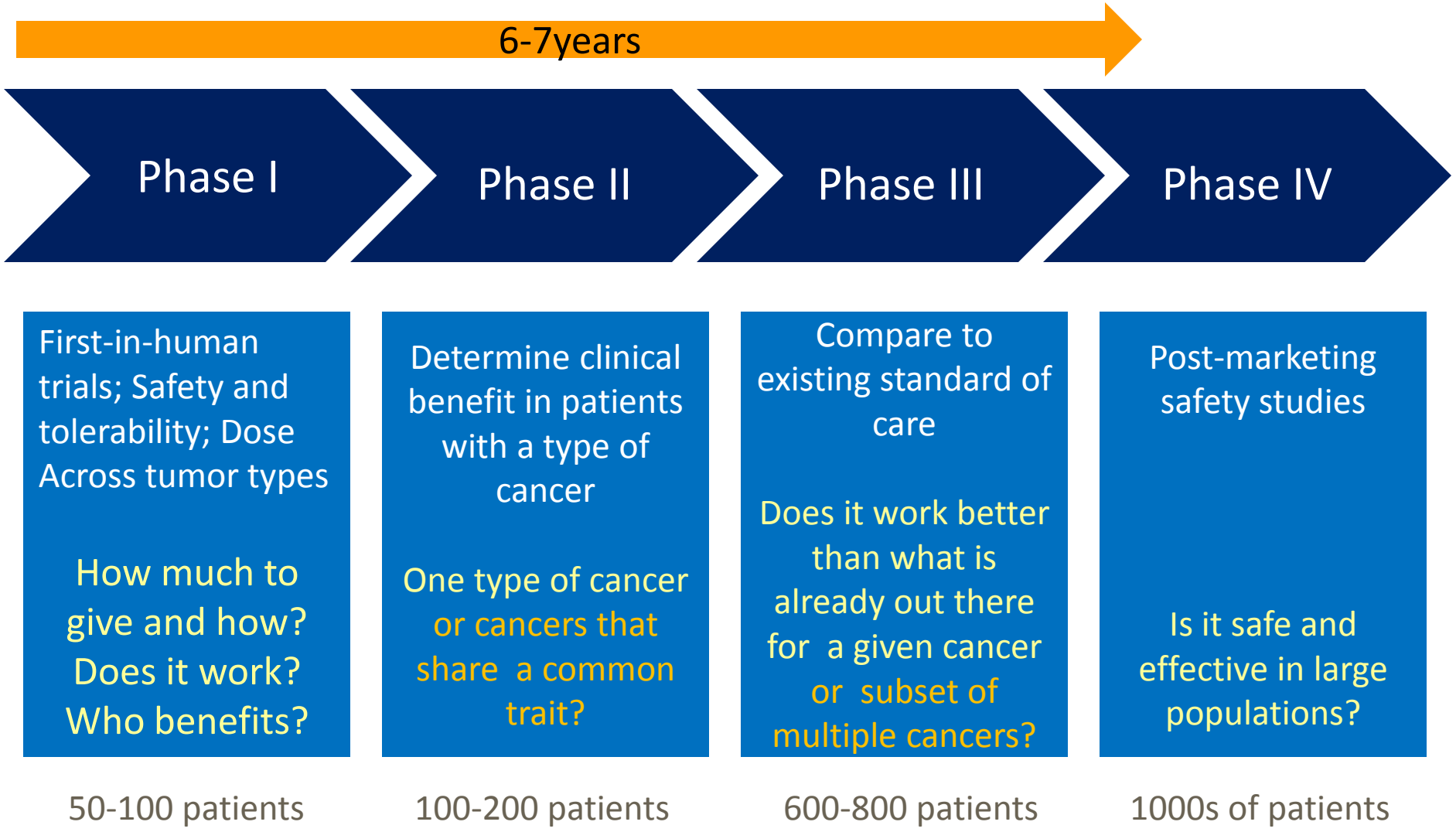
Umbrella Trials



Simon R. Ann Int Med 2016; 165:270

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



Future Considerations

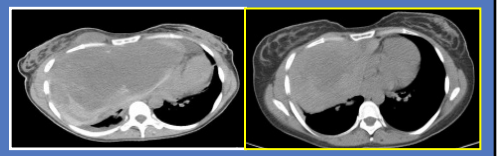
- **Early phase trials** (including FIH) will need to be designed to address key questions
  - Target modulation; PK/PD relationships
  - Duration and degree of modulation
  - Sequencing of drugs in combination

- **Establish RP2D**
  - Safe and Tolerable
    - ‘good’ normal tissue tolerability
    - Cumulative toxicities should be tolerable, not just first cycle DLTs
  - Has optimal antitumor effect
    - How does this correlate with target inhibition?
    - Need to define the desired level of target inhibition needed to achieve the antitumor effect
- **Proof-of-mechanism** (did you hit the target?) and **proof-of-concept** (did hitting the target affect growth-controlling pathways?)
- Understanding relationship between dose, schedule, target inhibition, and efficacy: essential for developing combinations

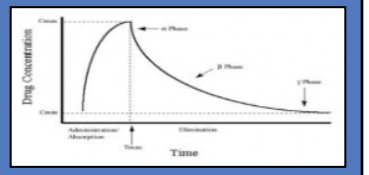
Clinical Translational Research and Cancer Biology: Bedside to Bench and Back

*Clinical observations:

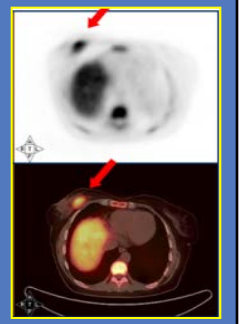
- Clinical response



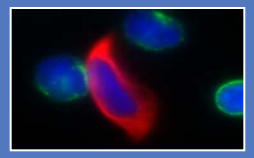
- PK



- Functional imaging



- Tumor and normal tissue PD markers
- CTCs, CECs



- Tumor-initiating cells

Patients eligible for early phase clinical trials

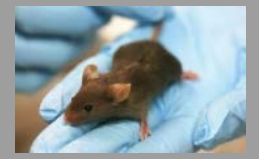
Analysis of tumor and Other tissues for pathway activation or biomarker *

Patient assigned to trial Based on molecular characterization of tumor

Patient monitoring *

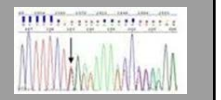
Patient monitoring: Post-treatment molecular re-analysis for response/ resistance *

Non-clinical models for targets

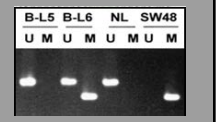


Translational research with clinical models

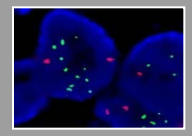
- Sequencing



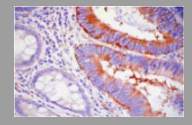
- Methylation



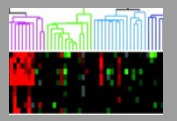
- FISH



- IHC



- Expression array



Standard Drug Development Pipeline: Re-envisioned