NOVEL DRUG DEVELOPMENT FOR TUMOURS WITH NO MOLECULAR ABERRATIONS

Alex A. Adjei,

Roswell Park Cancer Institute,

Buffalo, New York, USA

The 3 Basic Tenets of Phase I Studies

Define a recommended dose:

- **SAFELY** (minimum number of serious toxicities)
- **EFFICIENTLY** (smallest possible number of patients)
- **RELIABLY** (high statistical confidence)
- **SAFETY TRUMPS EVERYTHING ELSE**

Preclinical toxicology

1. Typically, a rodent (mouse or rat) and non-rodent (dog or non-human primate) species
2. Very few animal organ-specific toxicities predict for human toxicity
    I. Bone marrow and GI toxicity more predictable
    II. Hepatic and renal toxicities – large false-positives
    III. Toxicological parameters
        - LD10 – lethal dose in 10% of animals
        - TDL (toxic dose low) – lowest dose that causes any toxicity in animals

Phase I trials: Starting dose

- 1/10th of the LD10 in rodents

Or

- 1/3rd of the TDL in large animals
- **Expressed as mg/m^2**
- These have historically been safe doses

Why mg/m^2 ?

- Physiological processes such as BMR across species correlated with BSA rather than weight
- Drug clearance scaled allometrically on the basis of BSA rather than weight.

Equivalent surface area dosage conversion factors

	Mouse 20 g	Rat 150 g	Monkey 3 kg	Dog 8 kg	Man 60 kg
Mouse	1	½	¼	1/6	1/12
Rat	2	1	½	¼	1/7
Donkey	4	2	1	3/5	1/3
Dog	6	4	5/3	1	½
Man	12	7	3	2	1

Freireich EJ, et al. *Cancer Chemother Rep* 1966;50:219–244.

Phase I study endpoints

1. Dose, toxicity, pharmacology (efficacy?)
2. Classical goals
   - Identify DLTs
   - Identify the MTD
   - Assess pharmacokinetics
3. **Evaluate target modulation**

Defining toxicities: NCI Common Terminology Criteria for Adverse Events (CTCAE)

- Grade 1 = mild
- Grade 2 = moderate
- Grade 3 = severe
- Grade 4 = life-threatening
- Grade 5 = fatal

Maximum tolerated dose

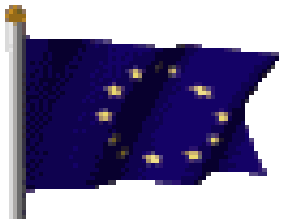
1. Inconsistently defined as either:
   - Dose at which ≥33% of patients experience unacceptable toxicity (DLT in ≥ 2 of 3 or ≥ 2 of 6)

   Or

   - 1 dose level below that
2. MTD = level @ DLT (in Europe or Japan)
3. MTD = level below DLT (in US)
4. 6–10 patients treated at the recommended Phase II dose (MTD or 1 dose level below)

Recap: Transatlantic differences in terminology

- Important to note that: “Maximum tolerated dose” (MTD):
  - Usually means “recommended phase 2 dose (RP2D)” in US
  - Usually means dose level above RP2D in Europe and some other countries



Dose-limiting toxicities

- Toxicities that are considered to be unacceptable, and limit further dose escalation
- Defined in advance of starting trial
- Classically based on cycle 1 toxicity
- Examples:
  - ANC <500 for ≥5 or 7 days
  - ANC <500 of any duration with fever
  - PLT <10,000 or 25,000
  - Grade 3 or greater non-hematological toxicity
  - Inability to re-treat patient within 2 weeks of scheduled treatment

Definition of DLT is dynamic

- Examples: DLTs in 2015
  - Diarrhea: ≥ Grade 3 in spite of adequate antidiarrheal therapy (loperamide)
  - Nausea and vomiting: ≥ Grade 3 in spite of adequate anti-emetic prophylaxis and therapy (steroids, 5HT3 antagonists)
  - Hypertension: ≥ Grade 3 in spite of adequate anti-hypertensive therapy
  - Hyperglycemia : Grade 3 in spite of adequate anti-hyperglycemic therapy
  - Inability to take at least 90% of drug doses in a cycle (continuous oral meds)
  - Grade 2 chronic unremitting toxicity

Phase I Trial Design : Dose Escalation

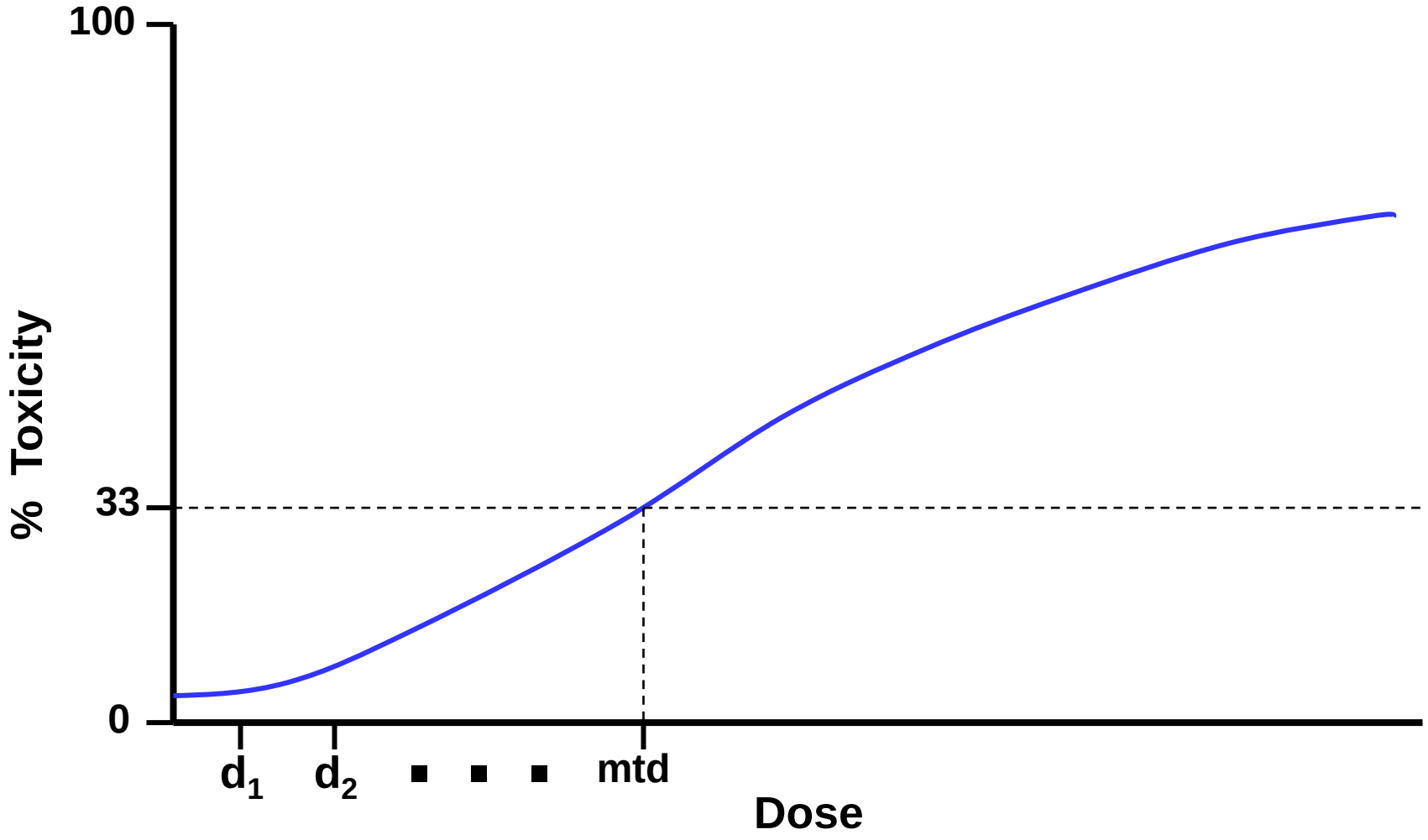
- “Escalation in decreasing steps”
- Attributed to a merchant from Pisa in the 13th century (Leonardo Bonacci, 1170-1240; aka Fibonacci)
- Outlined a number of problems including “how many pairs of rabbits can be produced from a single pair under specified conditions?” (1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144…..) in a book, “Liber abacus”

Phase I Dose escalation :

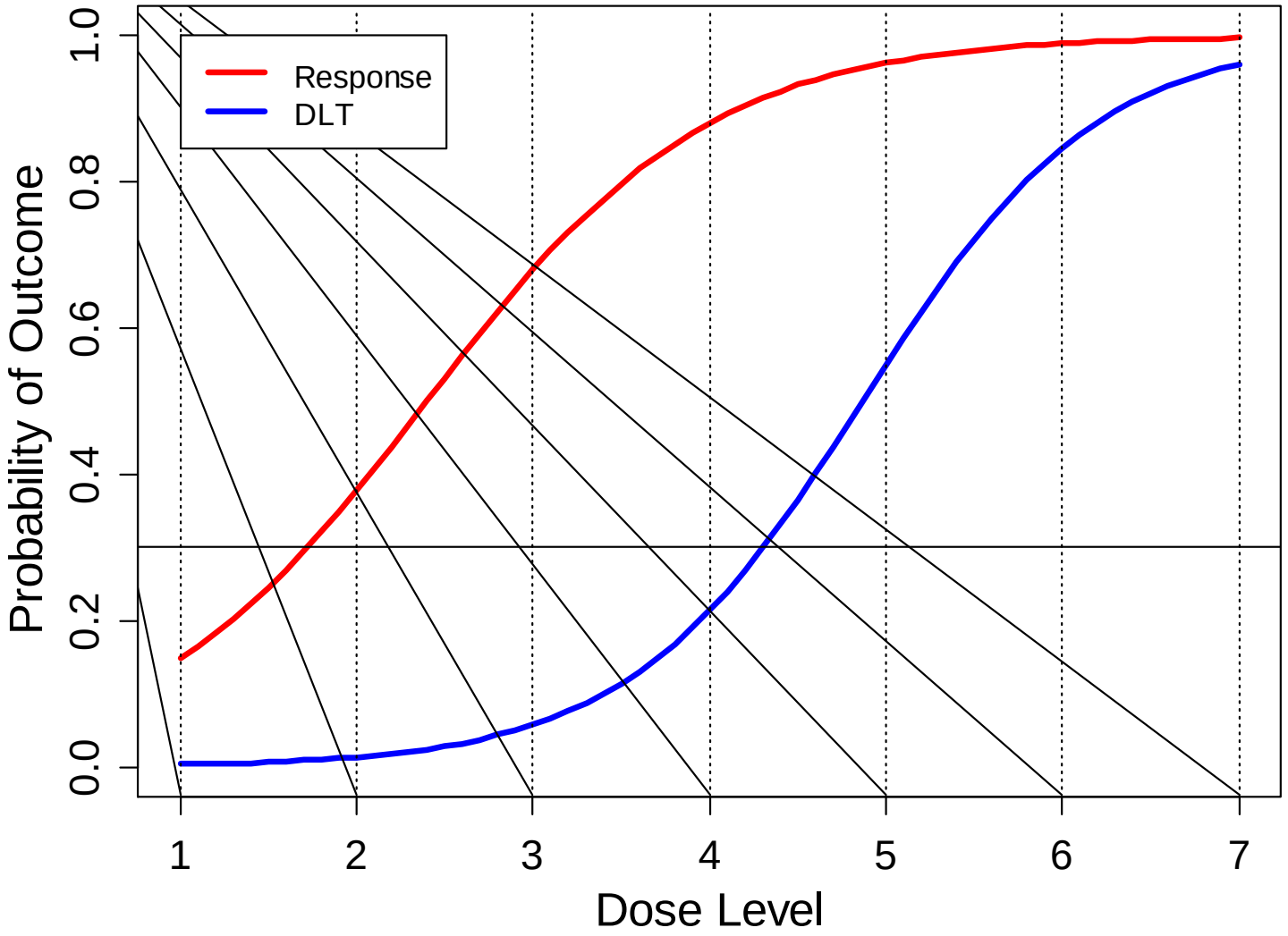
The modified Fibonacci schedule

Cohort	Dose	Escalation (%)
1	n	First dose
2	2 n	100%
3	3.3 n	67%
4	5 n	50%
5	7 n	40%
6 and higher		25–33%

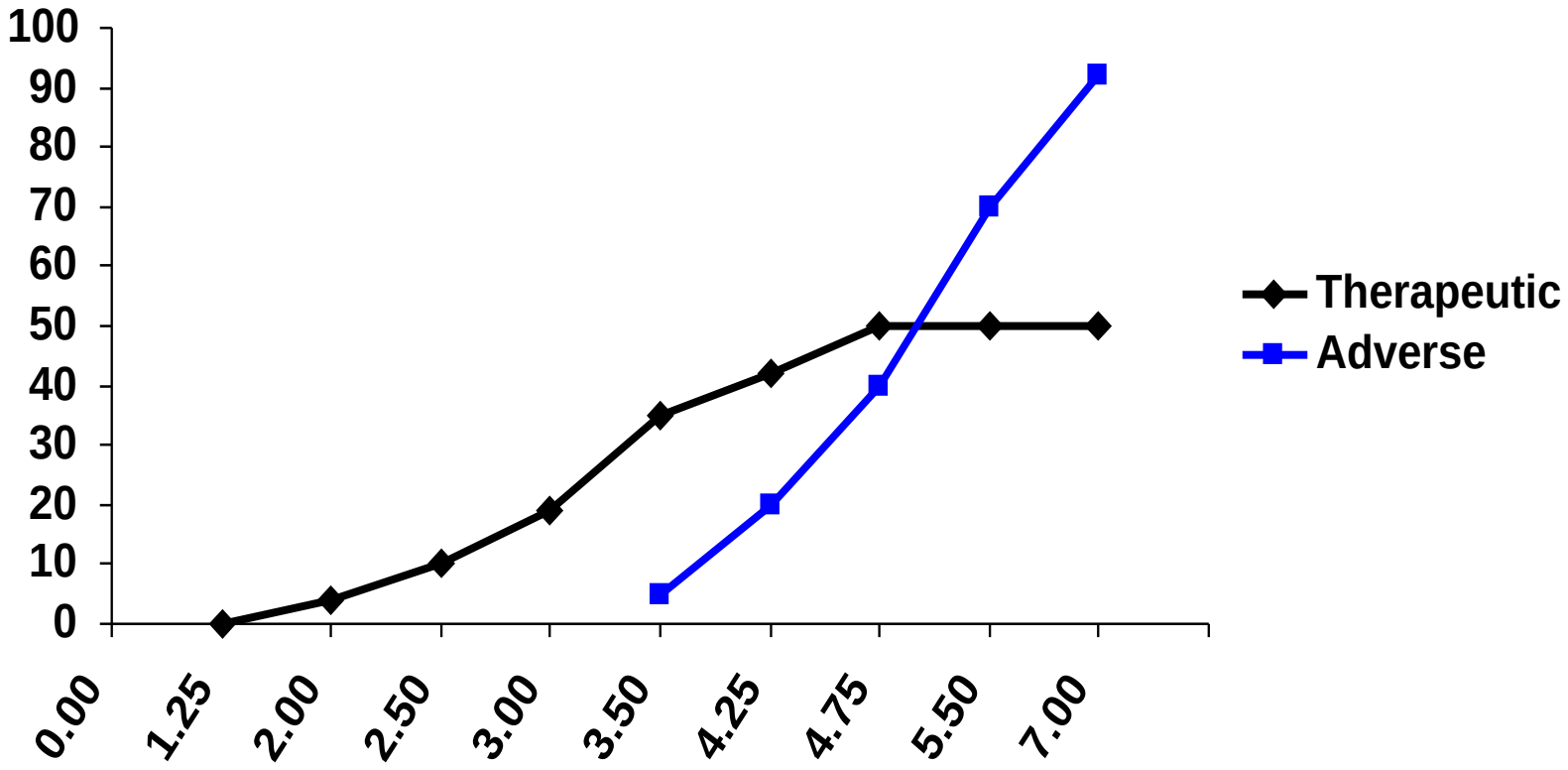
Schematic of Classic Phase I Trial



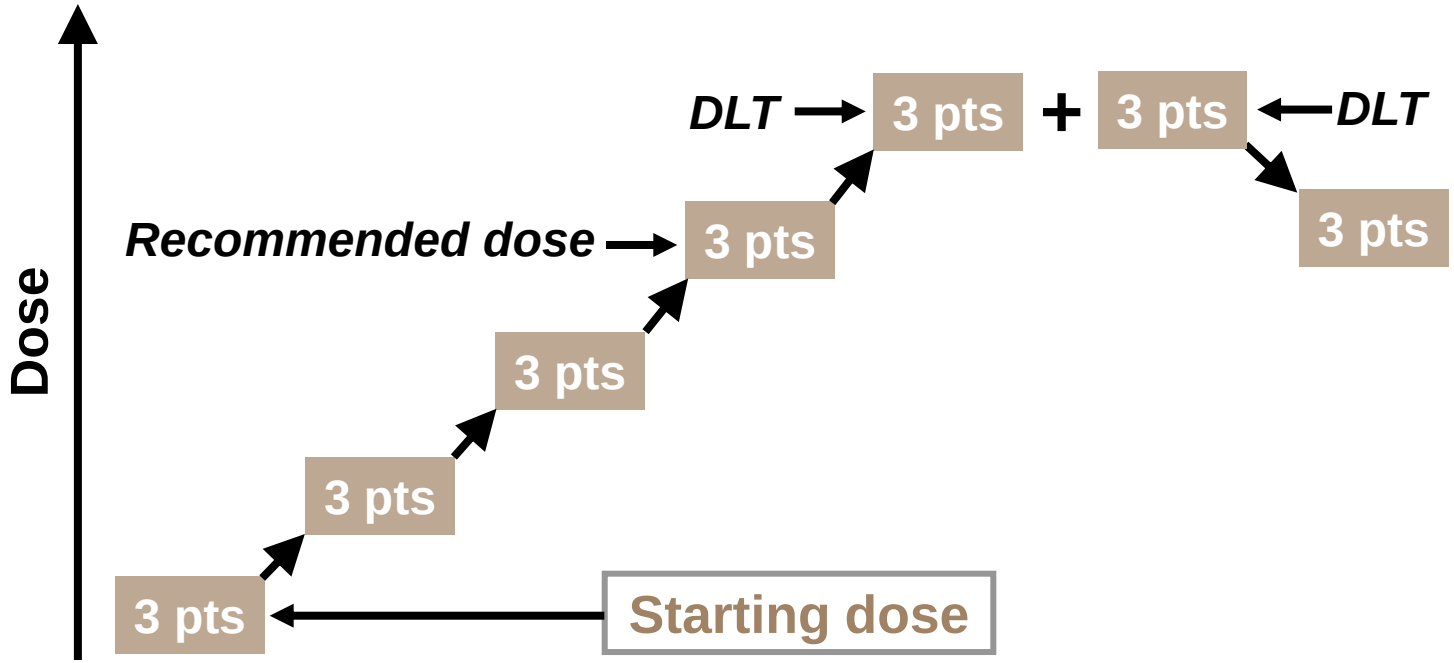
Based on Presumption: Efficacy and toxicity both increase with dose



Dose-response: Efficacy and Toxicity



Phase I standard 3 + 3 design



Eisenhauer EA, et al. *J Clin Oncol* 2000;18:684–692.

Classic Phase I trial design limitations

- Patients treated at ineffective doses in first cohorts
- High risk of severe toxicities at late cohorts
- Wide confidence intervals

Dose Level	Actual P(DLT)	Chance of being highest tried dose
1	0.10	9%
2	0.15	17%
3	0.20	21%
4	0.25	21%
5	0.30	32%

Even if dose level 5 corresponds exactly to a DLT rate of 0.30, the chance that this particular trial will ever reach it is only 32%.

The chance of correctly concluding dose level 5 is the MTD is 16%.

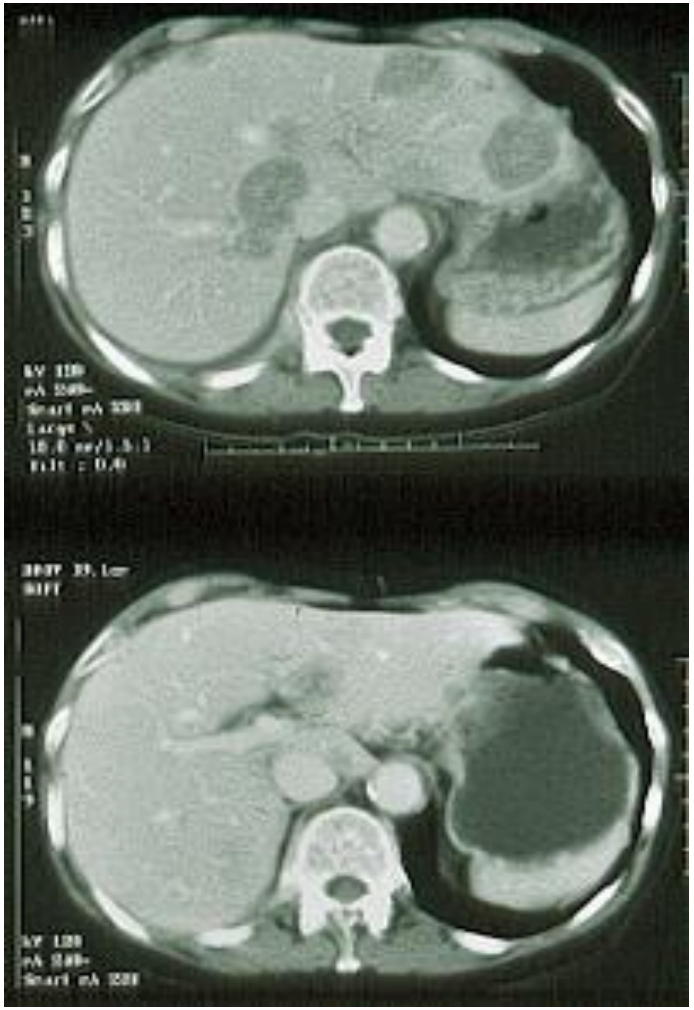
Intra-patient dose escalation

- Treat patients at dose level 1
- Dose level 2 is well tolerated and patients at dose level 1 have no toxicities
- Patients at level 1 are escalated to level 2

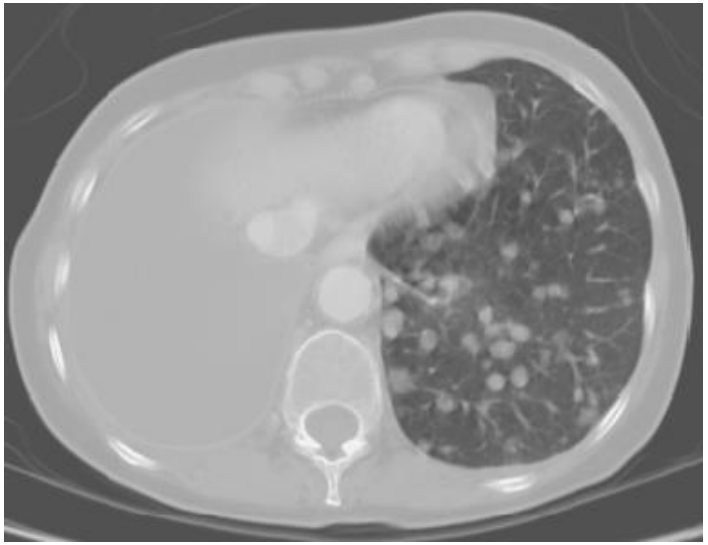
WHY NOT ALWAYS DO THIS?

- Makes evaluation of chronic toxicities difficult
- The proverbial 1 responder at dose level 1

Response to lonarfarnib and EKB569

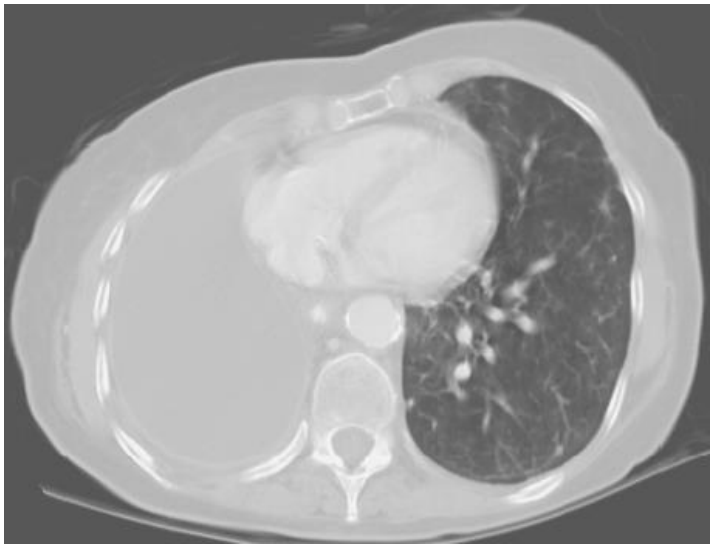


Pre-FTI



March 29, 2001

3 Months



September 19, 2001

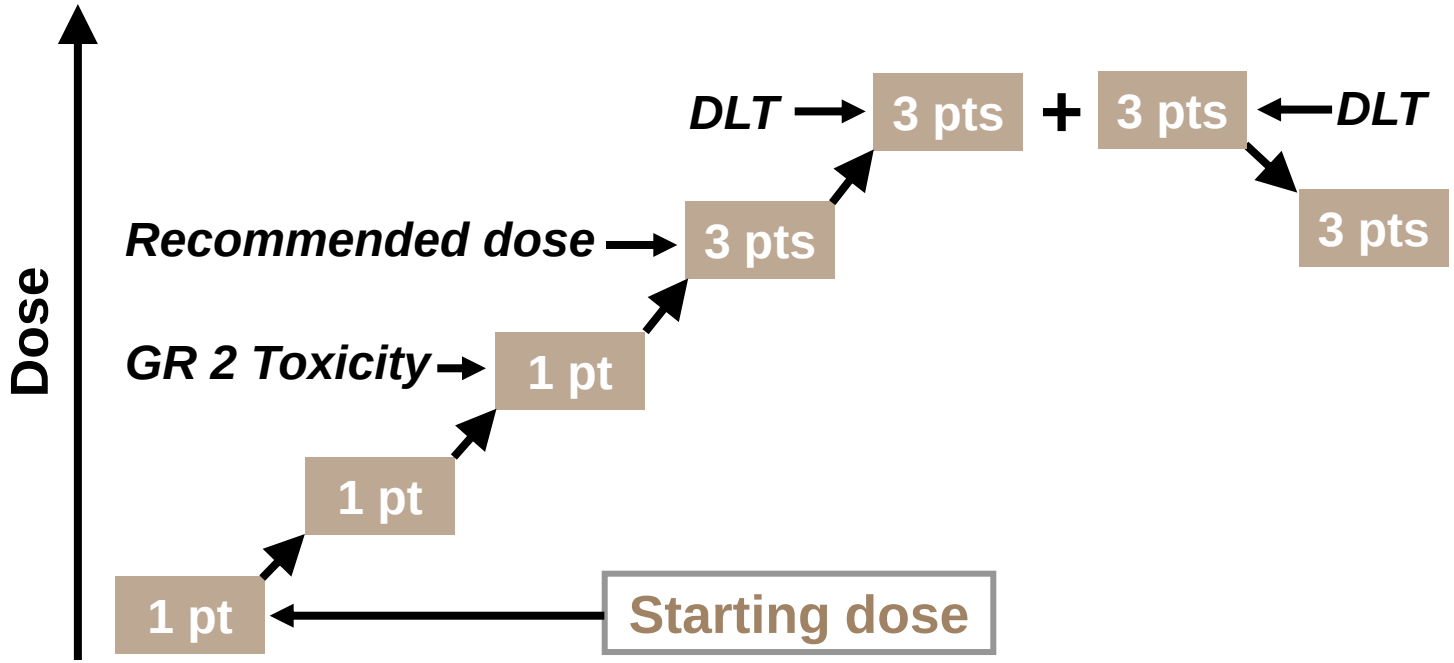
Novel designs – wish list

- Maximiize safety
  - ↓ patients exposed to DLT
  - Safe RP2D
- Maximize chance benefit
  - ↓ patients exposed to likely sub-therapeutic doses of drugs
- Efficiency (↓ N patients , ↑ speed)
- Reduce time trial is on hold

Frequentist
Rule-based

Bayesian
Model-based

Accelerated Titrated Design



Eisenhauer EA, et al. *J Clin Oncol* 2000;18:684–692.

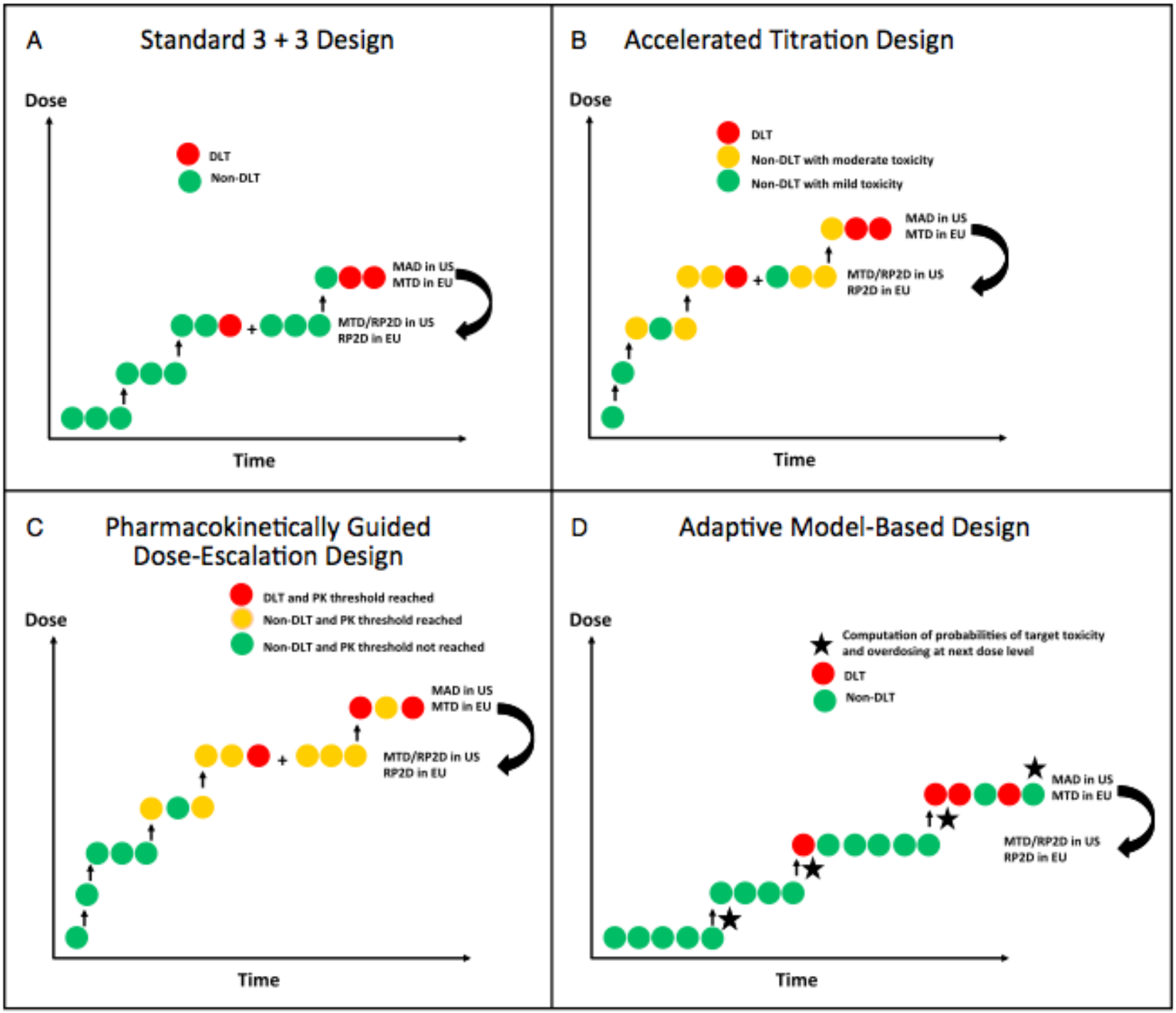
Bayesian designs

Escalation Scheme	Description
Modified continual reassessment method (mCRM)	Preset estimated MTD and dose levels. Update MTD statistically on basis of each pt's data. http://www.cancerbiostats.onc.jhmi.edu/software.cfm
TriCRM	incorporates both toxicity and efficacy data into the estimation of the biologically optimal dose – but OR takes time to mature… (phase I/II better?)
Ewoc (escalation with overdose control)	Uses real time toxicity data to make decisions http://sisyphus.emory.edu/software_ewoc.php

Many more variations, some including pk

Cumulative Cohort Design

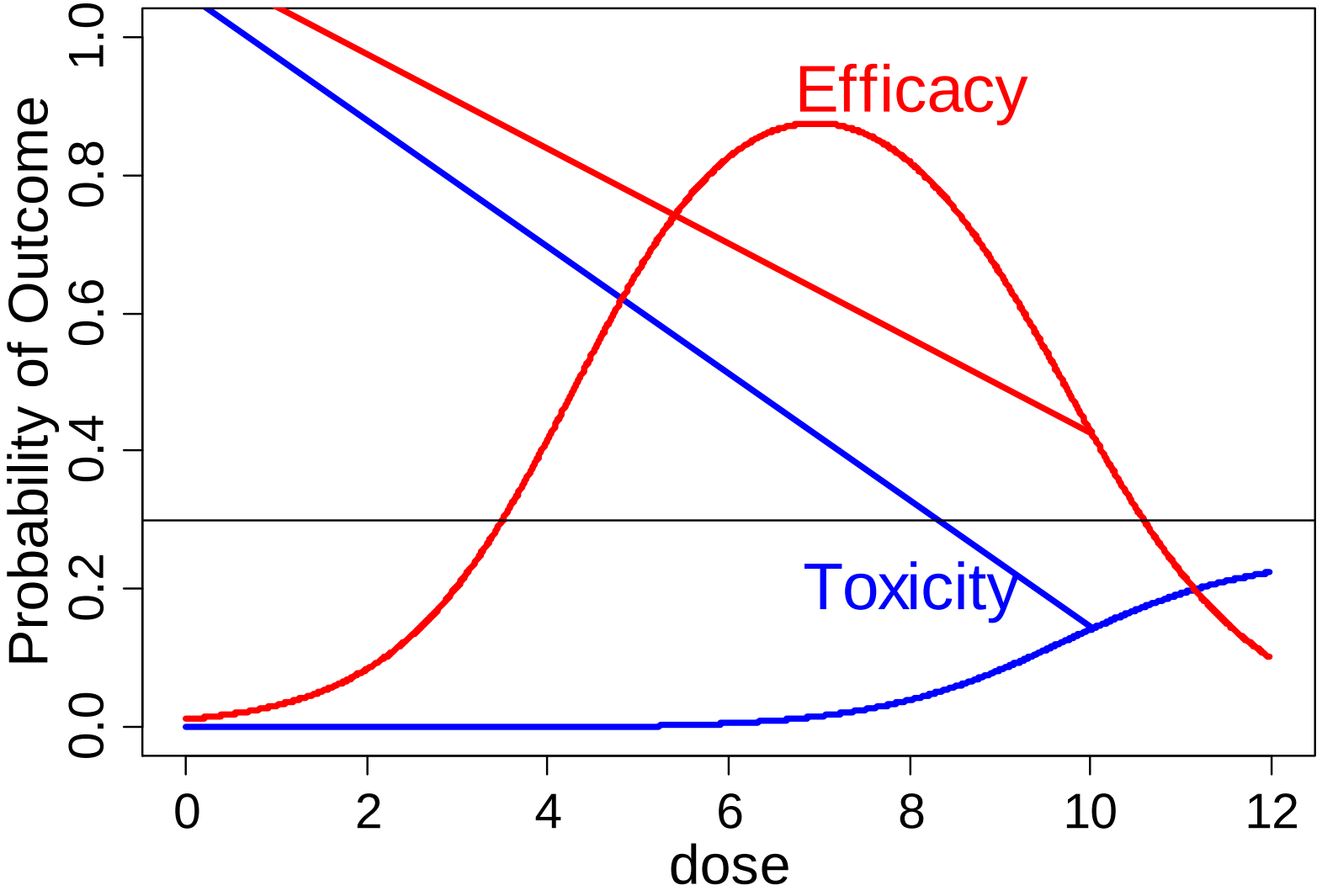
At the current dose level						
n (number of evaluable pts)	**x (number of patients with DLTs)**					
	0	**1**	**2**	**3**	**4**	**≥5**
1	stay	down				
2	stay	down	down			
3	up‡	stay	down	***down***†		
4	up‡	stay	down	***down***†	***down***†	
5	up‡	stay	down	***down***†	***down***†	***down***†
6	up‡	stay	stay	down	***down***†	***down***†
7	up‡	up‡	stay	down	***down***†	***down***†
8	up‡	up‡	stay	down	down	***down***†
9	up‡	up‡	stay	stay	down	***down***†


A
Standard 3 + 3 Design
Dose
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
B
Accelerated Titration Design
Dose
DLT
Non-DLT with moderate toxicity
Non-DLT with mild toxicity
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
C
Pharmacokinetically Guided
Dose-Escalation Design
Dose
DLT and PK threshold reached
Non-DLT and PK threshold reached
Non-DLT and PK threshold not reached
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time
D
Adaptive Model-Based Design
Dose
Computation of probabilities of target toxicity
and overdosing at next dose level
DLT
Non-DLT
MAD in US
MTD in EU
MTD/RP2D in US
RP2D in EU
Time

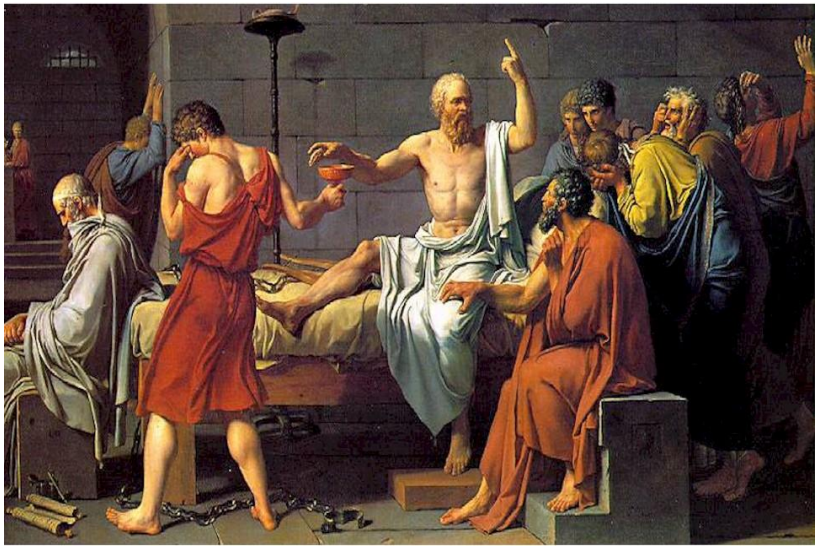
Phase I trial design:Targeted agents

- MTD may *not* be the goal of Phase I as specificity of effect may be lost at MTD
- Pharmacological effect may not equal biological effect
- Goal: Identify Optimal Biologic Dose (OBD)
- Biomarkers can guide dose escalation and dose selection

Possible Dose-Toxicity & Dose-Efficacy Relationships for Targeted Agent



Biomarker



Biomarker - “a characteristic that is objectively measured and evaluated as an indicator of biologic processes, pathogenic processes or pharmacologic responses to therapeutic intervention”

Holy Grail : The Surrogate Endpoint

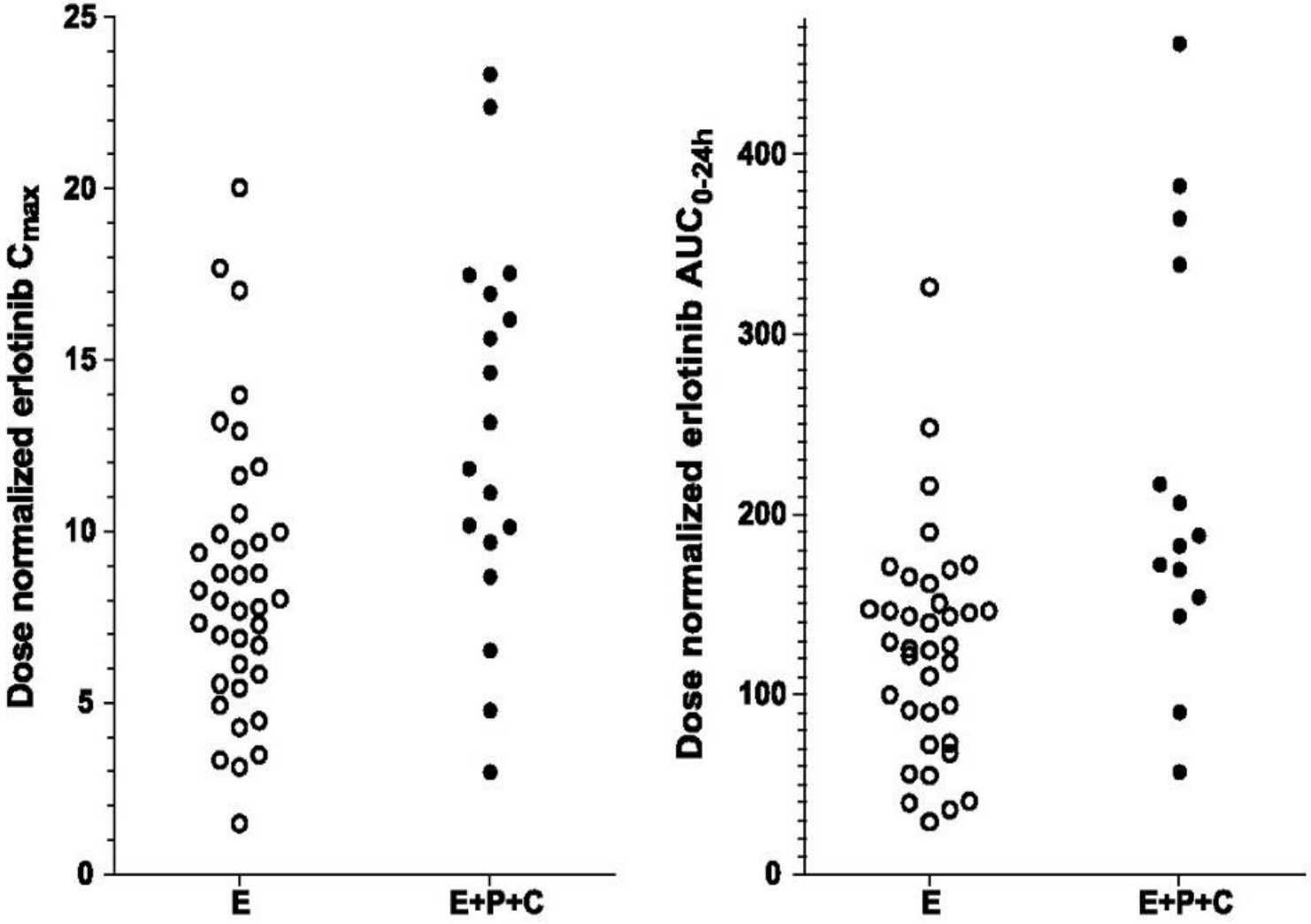
- A biomarker intended to substitute for a clinical endpoint.
- A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence

Surrogate Endpoints in Drug Development

- **Blood pressure**
- **Intraocular pressure (glaucoma)**
- **HgbA1c**
- **Psychometric testing**
- **AFP/HCG (Testicular Cancer)**
- **Serum cholesterol**

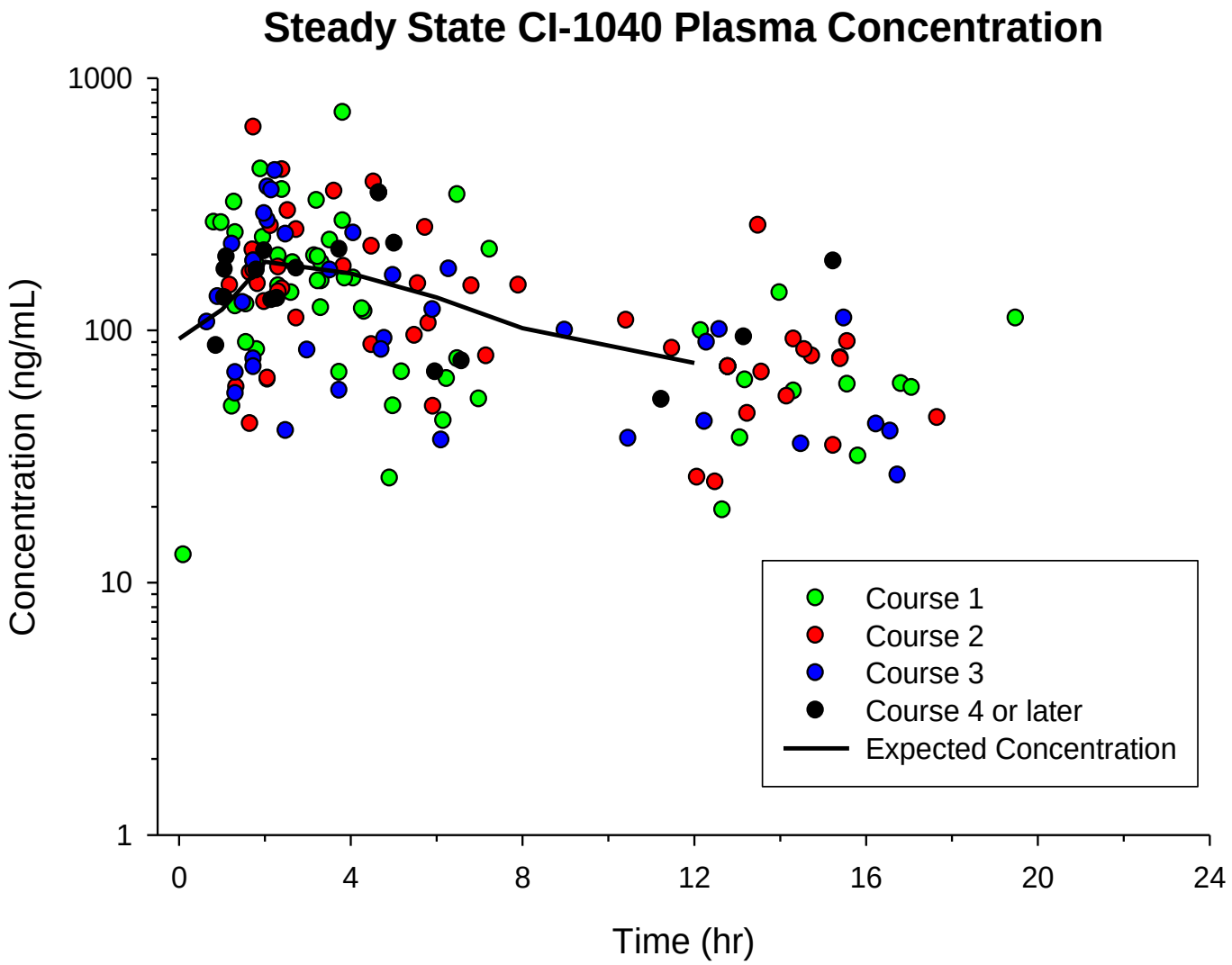
Erlotinib PK

Clinical Cancer Research



Patnaik A, et al. *Clin Cancer Res* 2006;12:7406–7413.

Phase II study of the MEK inhibitor, CI-1040



Rinehart et al. *J Clin Oncol.* 2004;22:456-62.

What's the target?

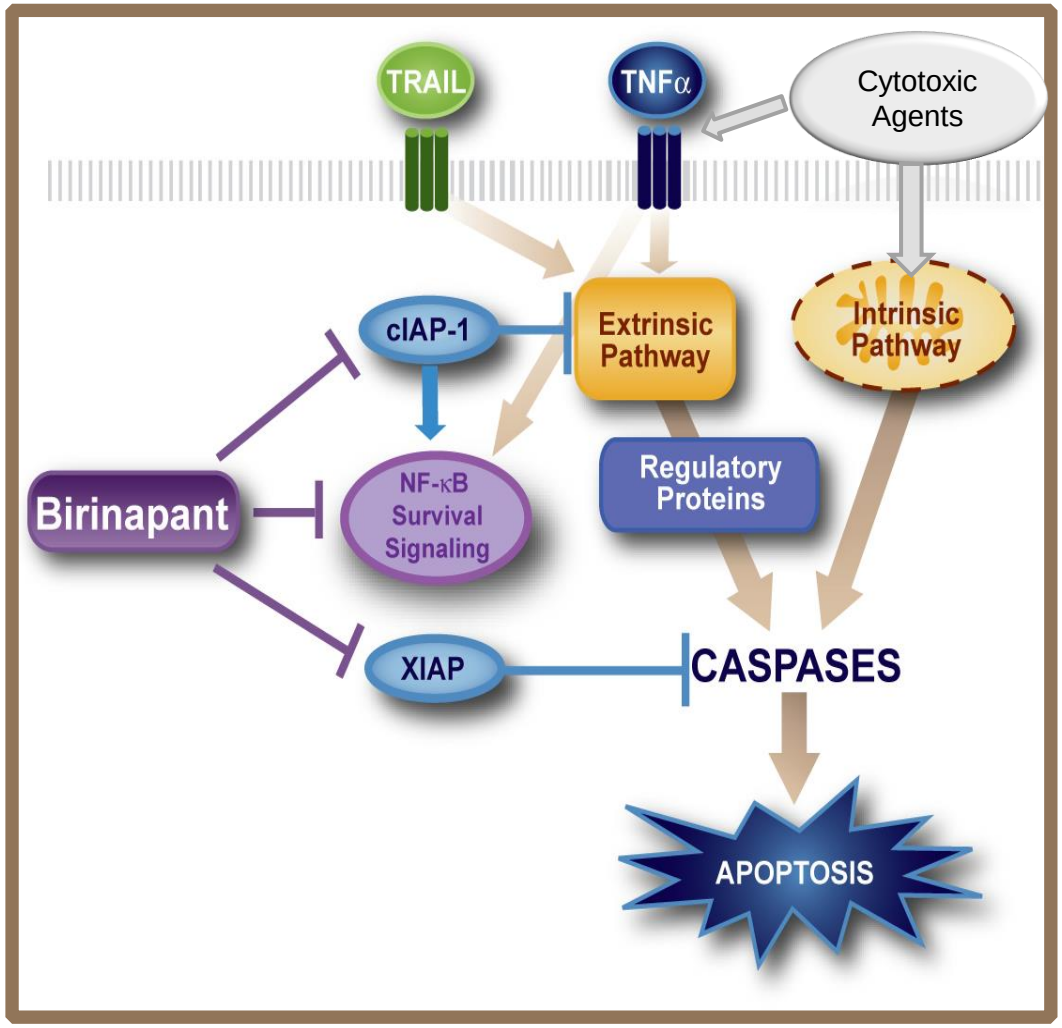
- Sorafenib (Raf kinase inhibitor) VEGFR1–3
- 5-Azacytidine (antimetabolite) methylation
- Imatinib (PDGFR) bcr-abl, kit
- Crizotinib (MET) EML4/ALK
- Iniparib (PARP) ??? alkylating agent forming adducts with cysteine rich proteins
- Tivantinib (MET) anti-tubulin

Solution?

- Randomized dose-ranging studies
  - –Temsorilimus
  - –Gefitinib
- Therapeutic drug monitoring

Birinapant (TL32711), a Novel Smac Mimetic

Targeting Critical Blockades in the Apoptosis/TNF Signaling Pathways



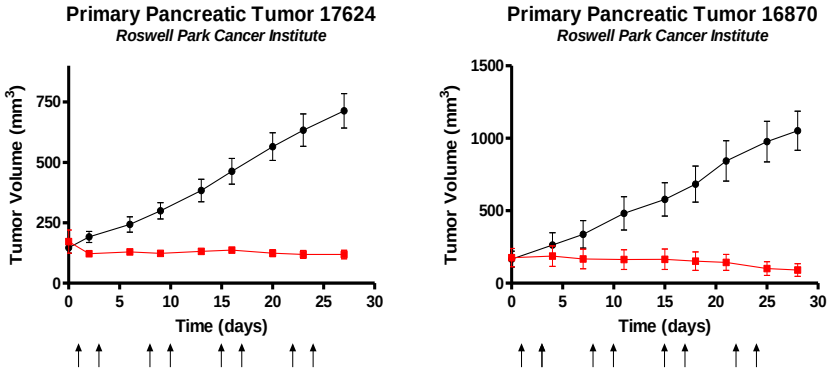
- **Bivalent Smac* Mimetic that unblocks apoptosis**
  - Differentially antagonizes the IAPs (Inhibitor of Apoptosis Proteins cIAP-1, cIAP-2, ML-IAP, XIAP)
- **Enables death receptor activation** (i.e. TNFα or TRAIL)
- **Suppresses canonical NF-κB activation**
- **Synergy with multiple therapies**

***Smac – Second Mitochondrial-derived Activator of Caspases**

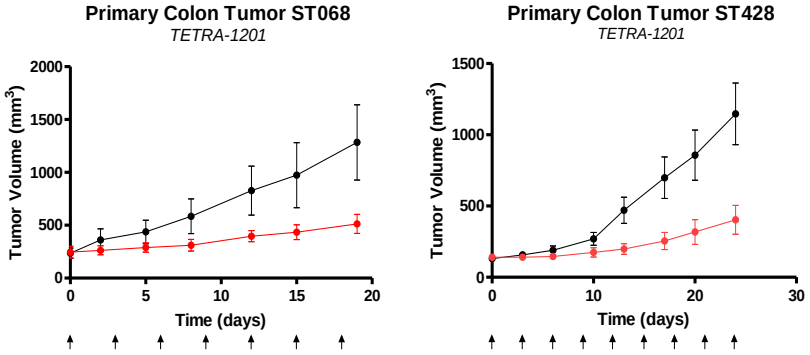
Birinapant is Potent in Patient-Derived Xenografts and Demonstrates Synergy with Multiple Chemotherapies

-Synergy with Irinotecan by chemo-induced TNFα induction

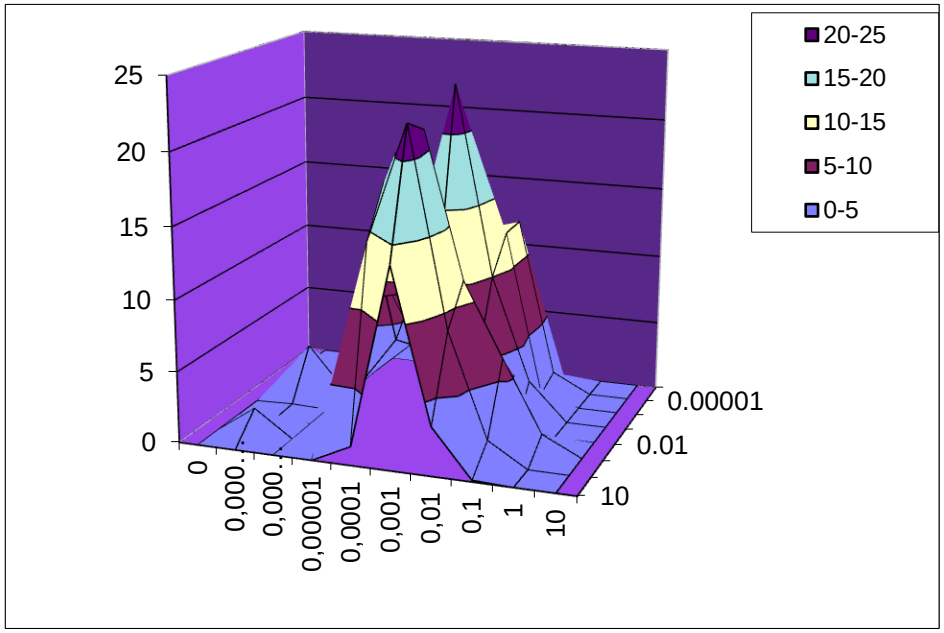
Pancreatic PDX



CRC PDX



TNFα-based Synergy with SN38 (irinotecan)

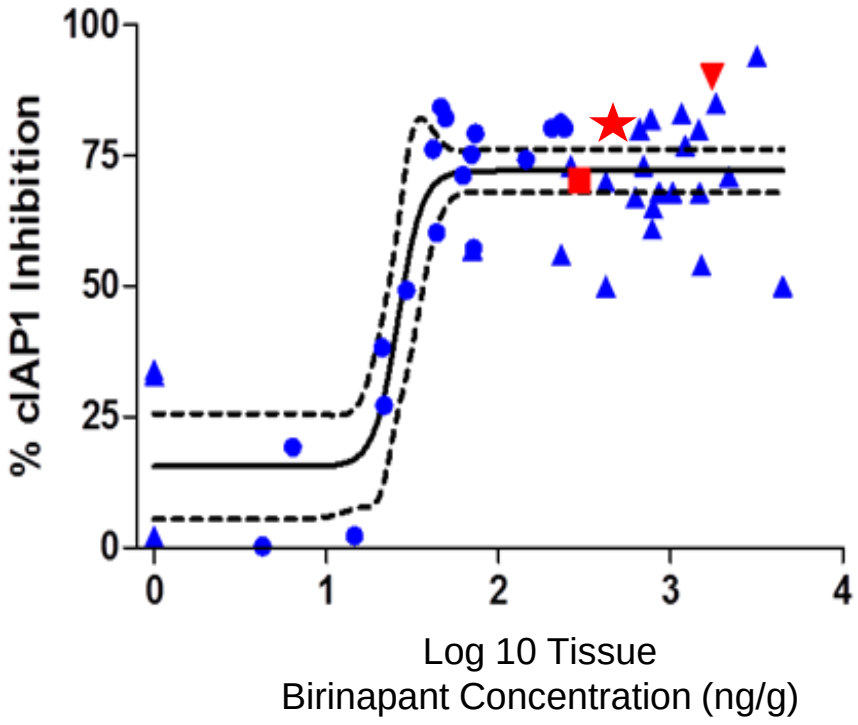


MacSynergy Volume = 278

Volume >100 deemed significant;
>200 deemed biologically relevant

Viability measured by MTT assay following 72 hrs incubation with combination treatments

Birinapant Inhibits cIAP1 at Well-Tolerated Drug Exposure Levels



- Melanoma Xenograft (ST019
- Breast Xenograft (MD-MB-231)
- Clinical PBMC (2.8mg/m^2) at (Cycle1 Day2)
- Clinical Melanoma Biopsy (11.5mg/m^2) at Cmax (D1)
- Clinical Colorectal Biopsy (17mg/m^2) at Cmin (D7)

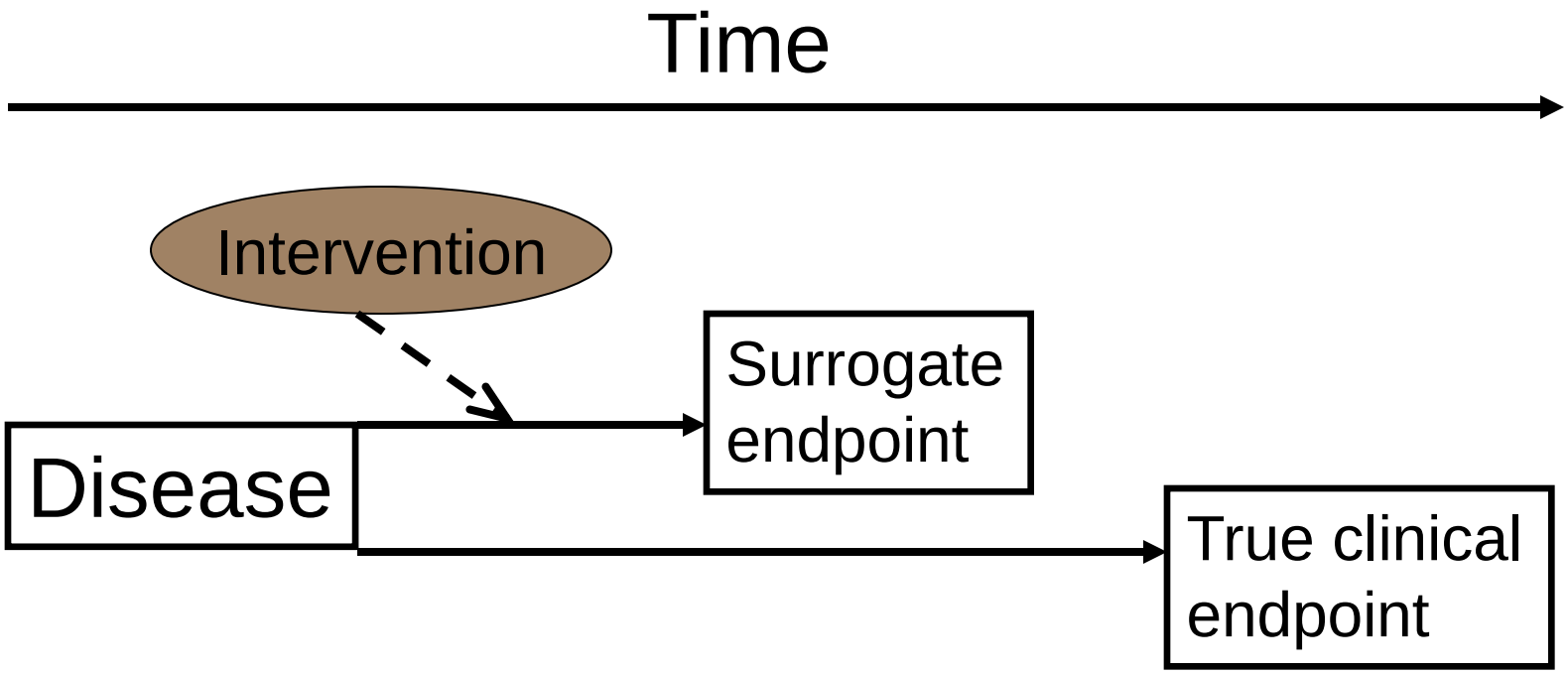
R^2 = 0.7634
EC_{50}- 26ng/g
(95% CI 21-32)

%cIAP1 inhibition – Western Blot Comparison to Baseline cIAP1 Levels

Graham et al. AACR-NCI-EORTC 2011

Paradigm for Failure of Surrogate Endpoint

(Surrogate is not in causal pathway)



Fleming & DeMets, 1996

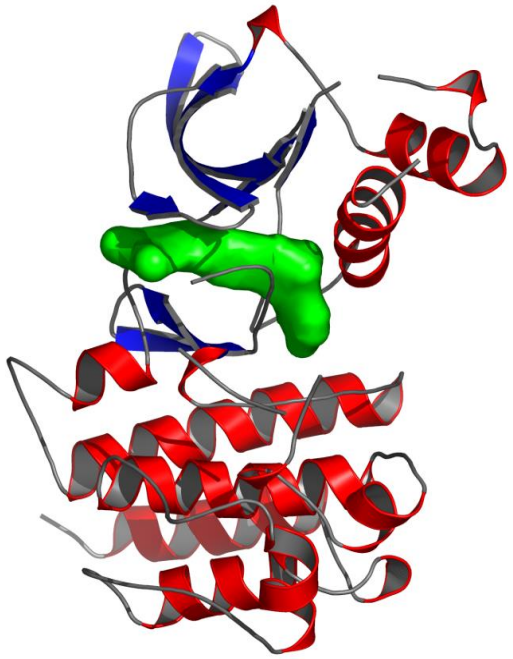
Alternate Design
When Unsure of Biomarker

Cabozantinib (XL184) Target Profile

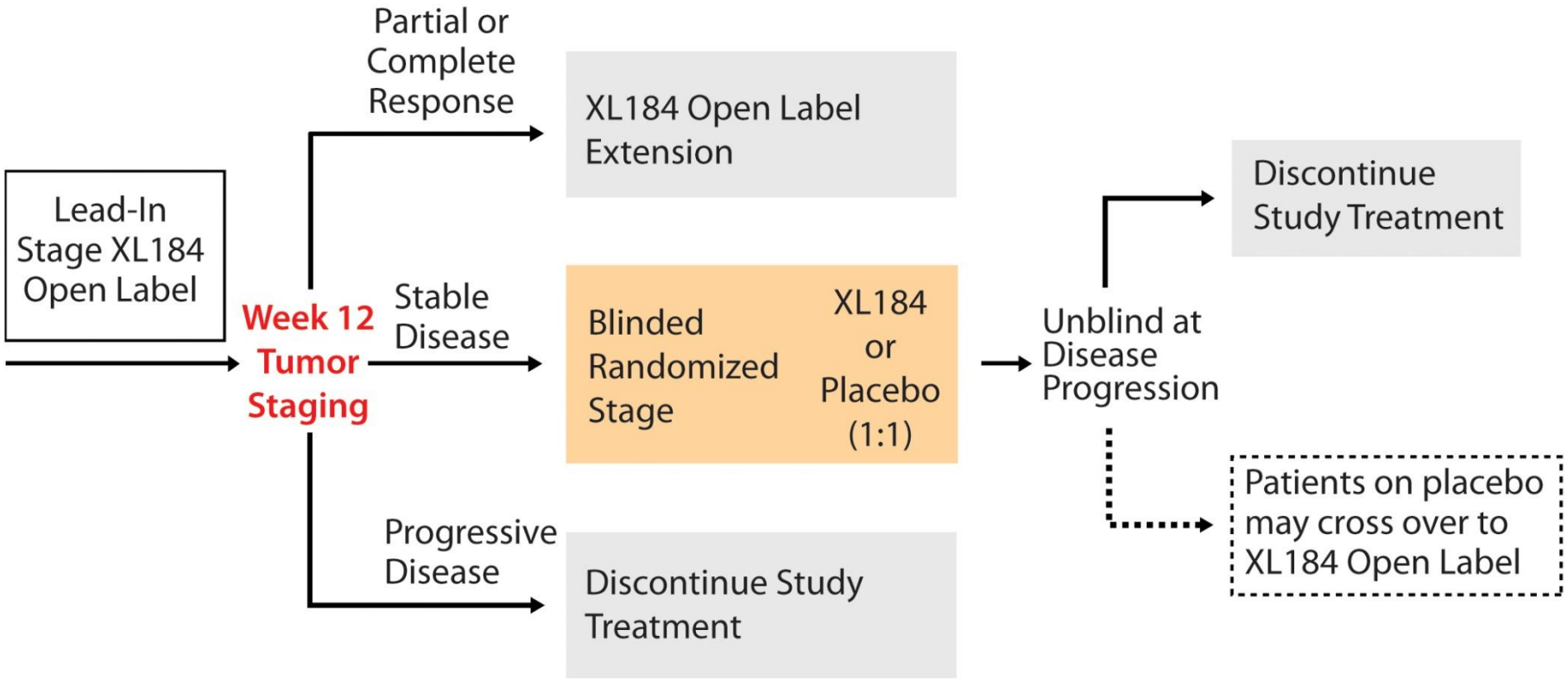
Kinase	IC_{50} (nM)
MET	1.8
VEGFR2	0.035
RET	5.2
KIT	4.6
AXL	7.0
TIE2	14
FLT3	14
S/T Ks (47)	>200

ATP competitive, reversible

RTK	Cellular IC_{50} (nM) autophosphorylation
MET	8
VEGFR2	4



Randomized Discontinuation Study Design

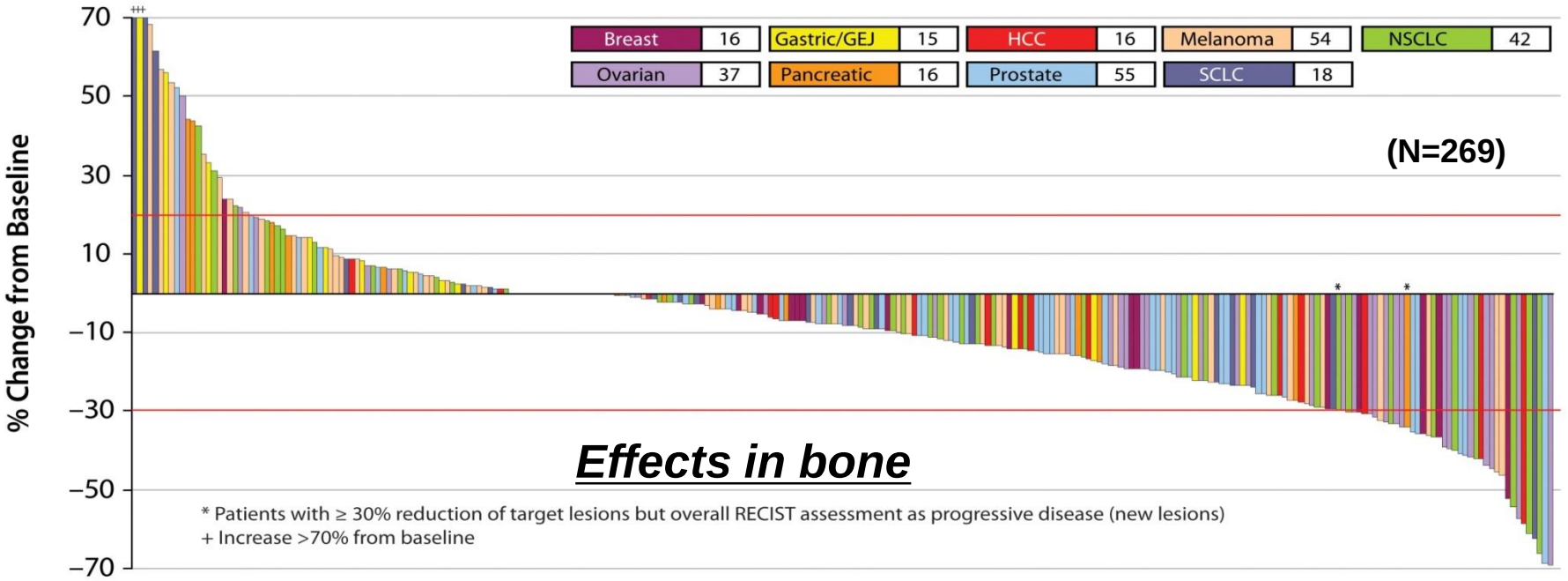


Cabozantinib (XL184) given orally QD at 100 mg (125 mg salt equivalent)

Tumor Types

Breast cancer	Gastric/GEJ cancer	HCC	Melanoma	NSCLC	Ovarian cancer	Pancreatic cancer	Prostate cancer	SCLC

Broad Anti-tumor Activity Across Multiple Tumor Types



39 PARTIAL RESPONSES IN 269 PATIENTS WITH ≥1 POST-BASELINE ASSESSMENT

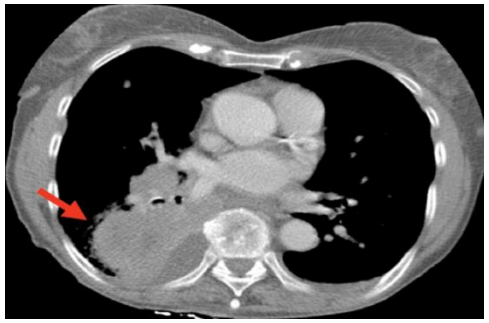
Interim RDT data presented at 2010 EORTC-NCI-AACR Symposium

NSCLC: Dramatic Response in Tumor with Cabozantinib (XL184)

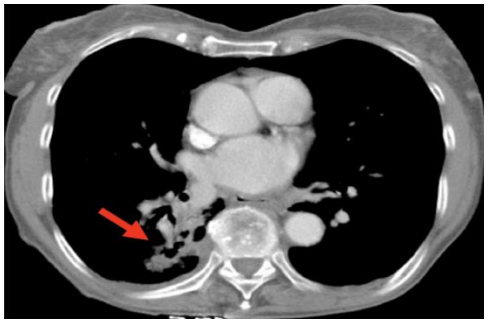
Radiographic Images from a 88-Year-Old Female with Metastatic NSCLC

PATIENT WITH ADENOCARCINOMA WITH A 61% REDUCTION IN THE SUM OF TARGET LESIONS

PRIOR ANTICANCER TREATMENT: SUNITINIB (SD AS BEST RESPONSE)



Screening

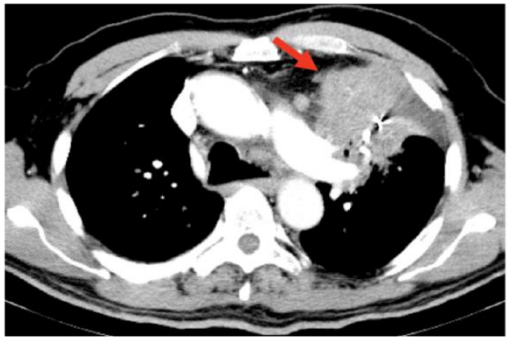


Week 12

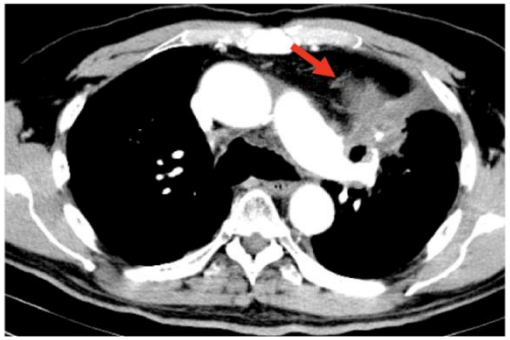
Radiographic Images from a 72-Year-Old Male with Metastatic NSCLC

PATIENT WITH ADENOCARCINOMA WITH A 36% REDUCTION IN THE SUM OF TARGET LESIONS

PRIOR ANTICANCER TREATMENT: PACLITAXEL/CARBOPLATIN, ERLOTINIB, INVESTIGATIONAL AGENT (SD AS BEST RESPONSE)



Screening

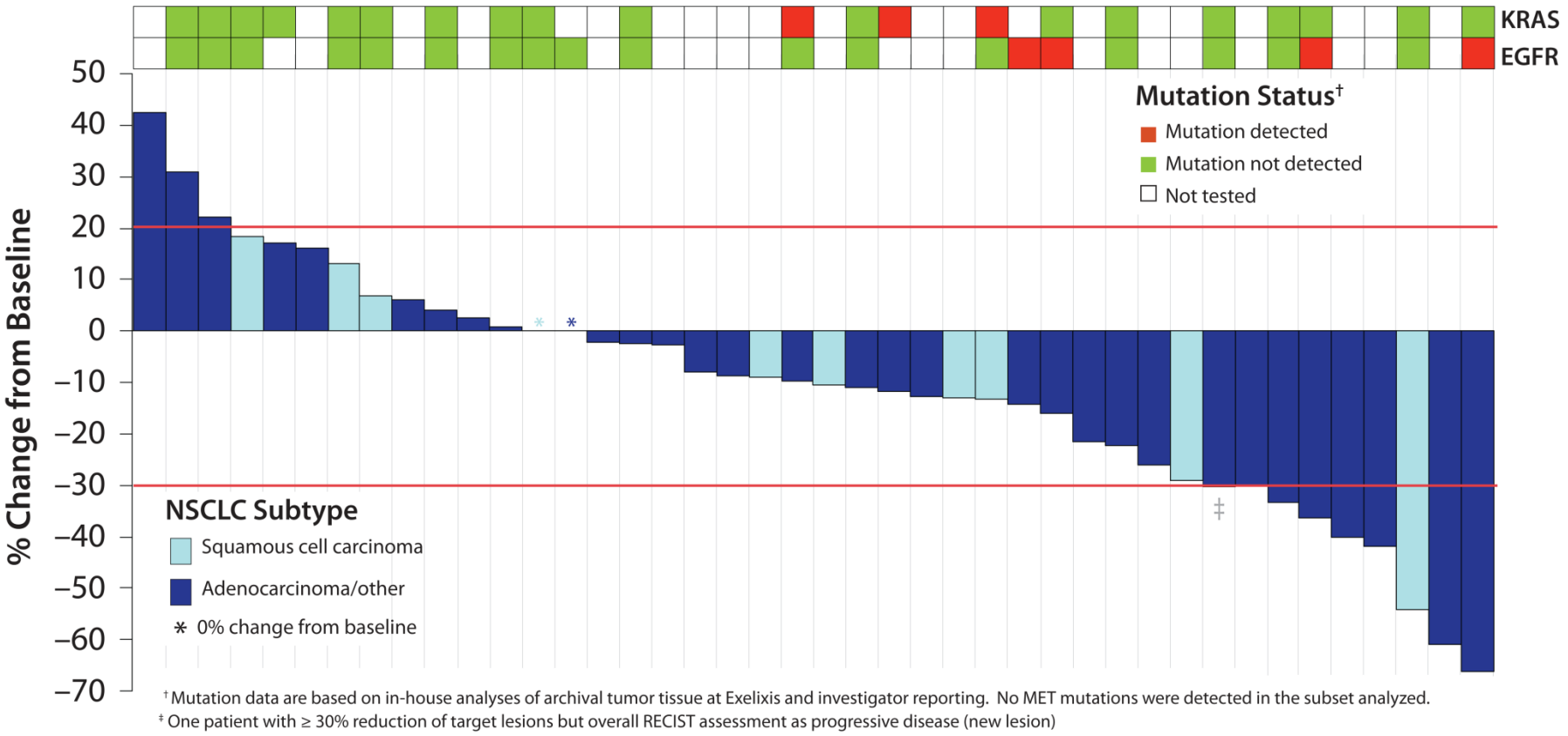


Week 12

Interim RDT data presented at 2010 EORTC-NCI-AACR Symposium

Cabozantinib (XL184) Shows Promising Activity in Previously Treated NSCLC Patients

Best Radiologic Time Point Response of Patients with ≥1 Post-baseline Tumor Assessment

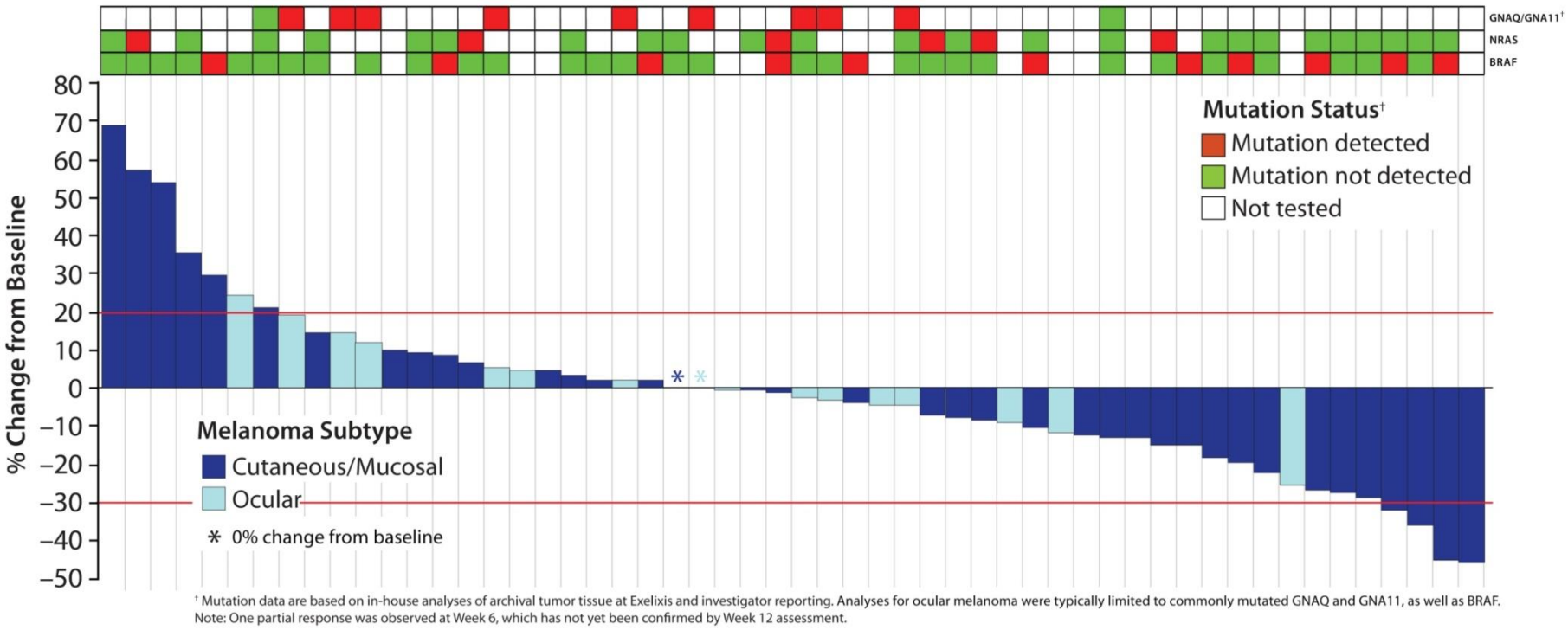


† Mutation data are based on in-house analyses of archival tumor tissue at Exelixis and investigator reporting. No MET mutations were detected in the subset analyzed.

‡ One patient with ≥ 30% reduction of target lesions but overall RECIST assessment as progressive disease (new lesion)

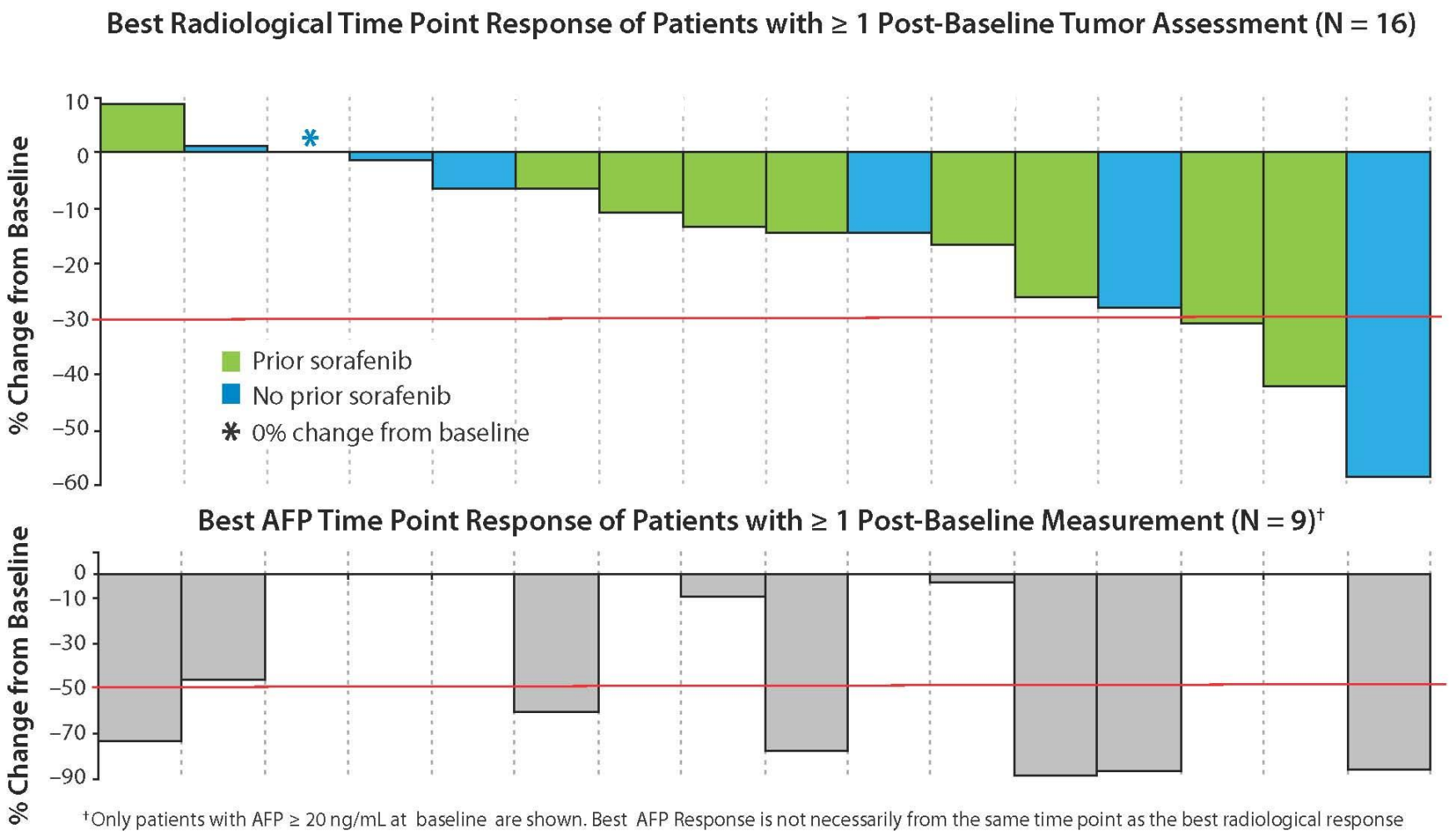
Interim RDT data presented at 2010 EORTC-NCI-AACR Symposium

Melanoma Cohort: Tumor Shrinkage Observed Regardless of BRAF Status



† Mutation data are based on in-house analyses of archival tumor tissue at Exelixis and investigator reporting. Analyses for ocular melanoma were typically limited to commonly mutated GNAQ and GNA11, as well as BRAF.
Note: One partial response was observed at Week 6, which has not yet been confirmed by Week 12 assessment.

Hepatoma Cohort: Effects on Tumor and AFP



†Only patients with AFP ≥ 20 ng/mL at baseline are shown. Best AFP Response is not necessarily from the same time point as the best radiological response

Conclusions

- Drugs targeting actionable mutations are finite
- We need to continue to develop other agents not targeting actionable mutations
  - For most drugs, an MTD can be defined
  - It may be chronic toxicity rather than classical cycle 1 DLTs
  - Evaluate intermediate doses
  - The optimal biologic dose in phase I is a flawed concept
  - The optimal dose could be identified by randomized dose-ranging studies or therapeutic drug monitoring
  - Biomarker endpoints are necessary for the few agents, such as antibodies, with no dose-dependent toxicities