Novel Drug Combinations: Challenges from a Clinician's Perspective

Patricia Mucci LoRusso, D.O.
Director – Experimental Medicine
Karmanos Cancer Institute
Detroit, MI

Novel drug combinations will become a pivotal tool in cancer drug therapy

Novel Combinations

- Based on our current knowledge database, are we moving forward too fast into the clinic?
- Do we possess the necessary translational tools that will help us identify the right drug combinations, ratios and schedules thereof, with the right patient?

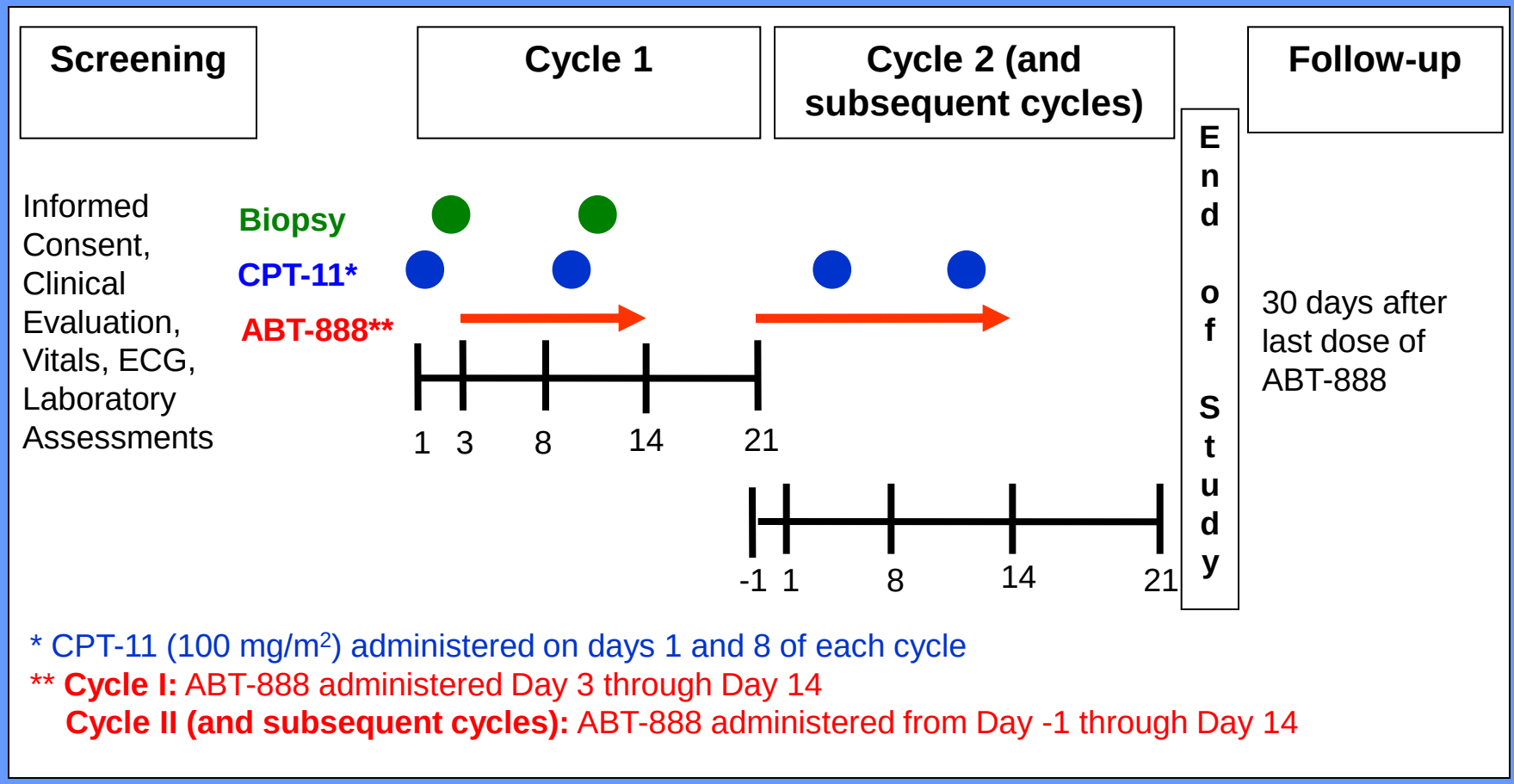
Where will Novel Combinations Have the Greatest Impact?

- Most appropriate stage of combination development
  - Metastatic disease vs
  - adjuvant or neoadjuvant setting
- What are the risks involved in studying combinations at the wrong clinical stage?

Phase I Combination Studies

- Expectations different than traditional monotherapy studies
  - Demands for direct PD evaluation
  - Tolerable combination with minimal response?
- Lack of appropriate tools/assays and interrogation even when tools are available
  - Just as important to know why agent isn't working
- Rely too heavily on surrogate
  - Most imaging tools do not help us define tumor effects

NCI #7977: Trial Schema

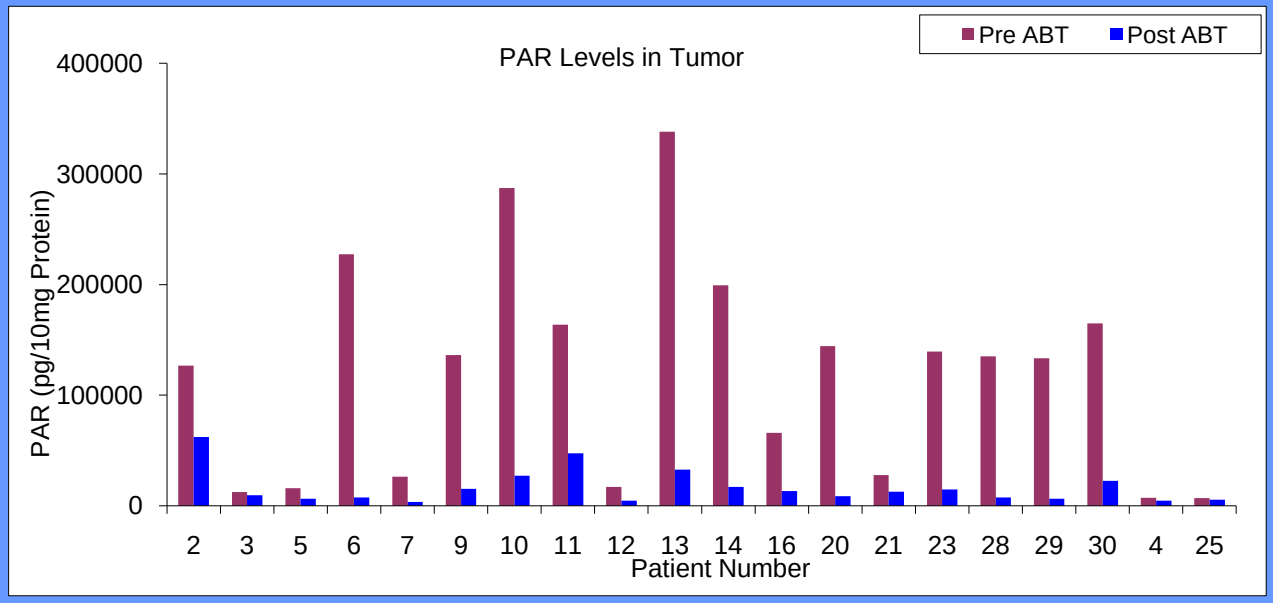


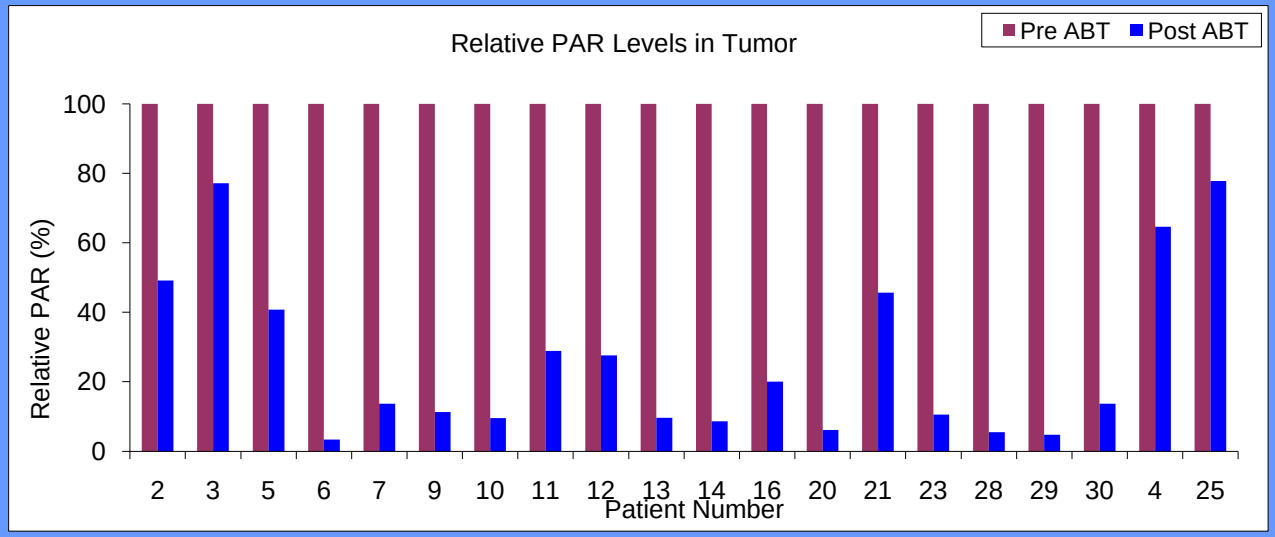
Tumor Collections: **D2: 28h** **D9: 28h**

Blood Collections: **D1: 0; 3.5; 5.5; 8.5; 28; 48 h**

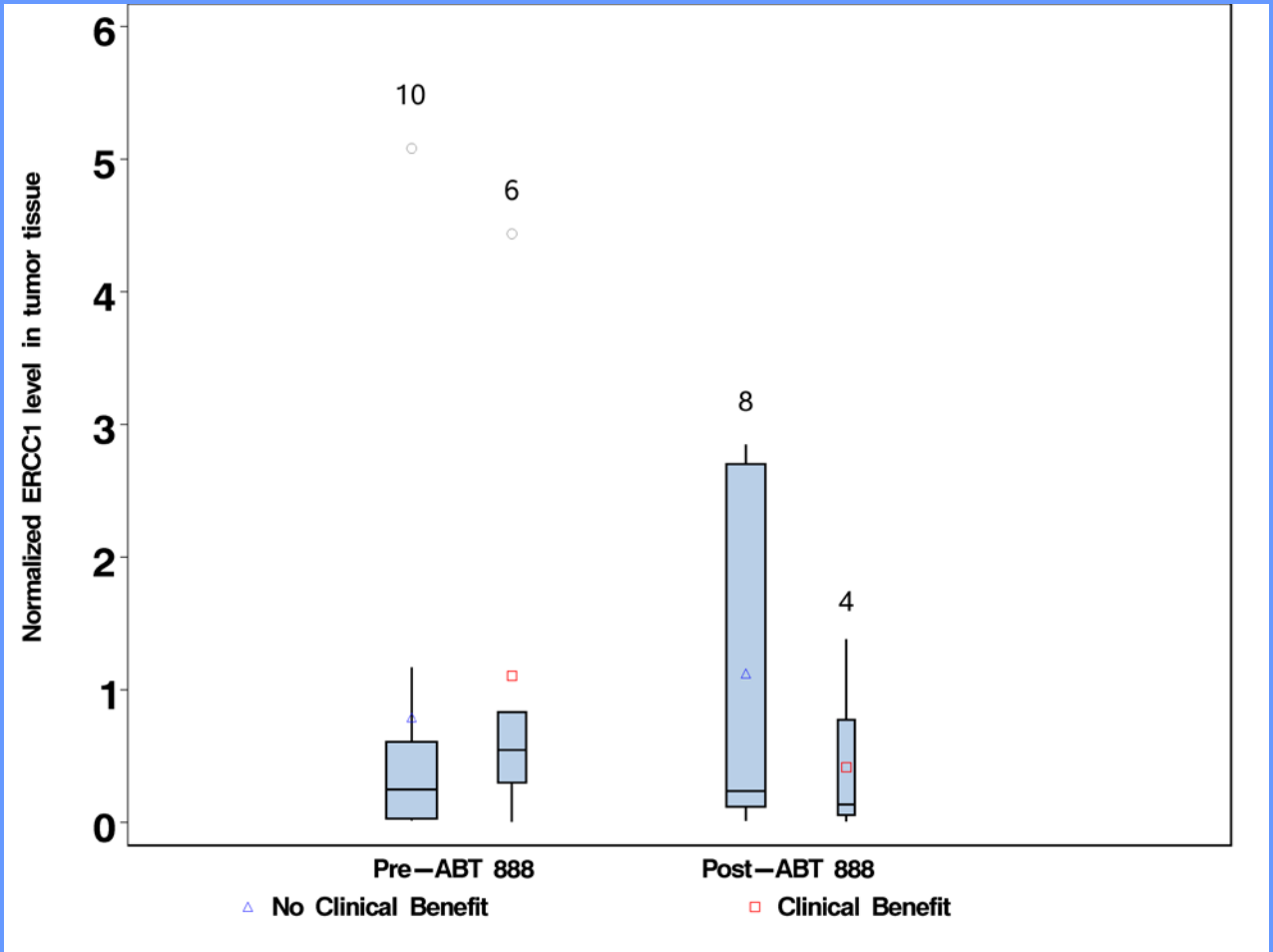
D8: 0, 3.5; 5.5; 8.5; 28; 48 h

PAR Levels in Tumors: Predose vs. Postdose





ERCC1 Levels in Tissue



Clinician's Challenges

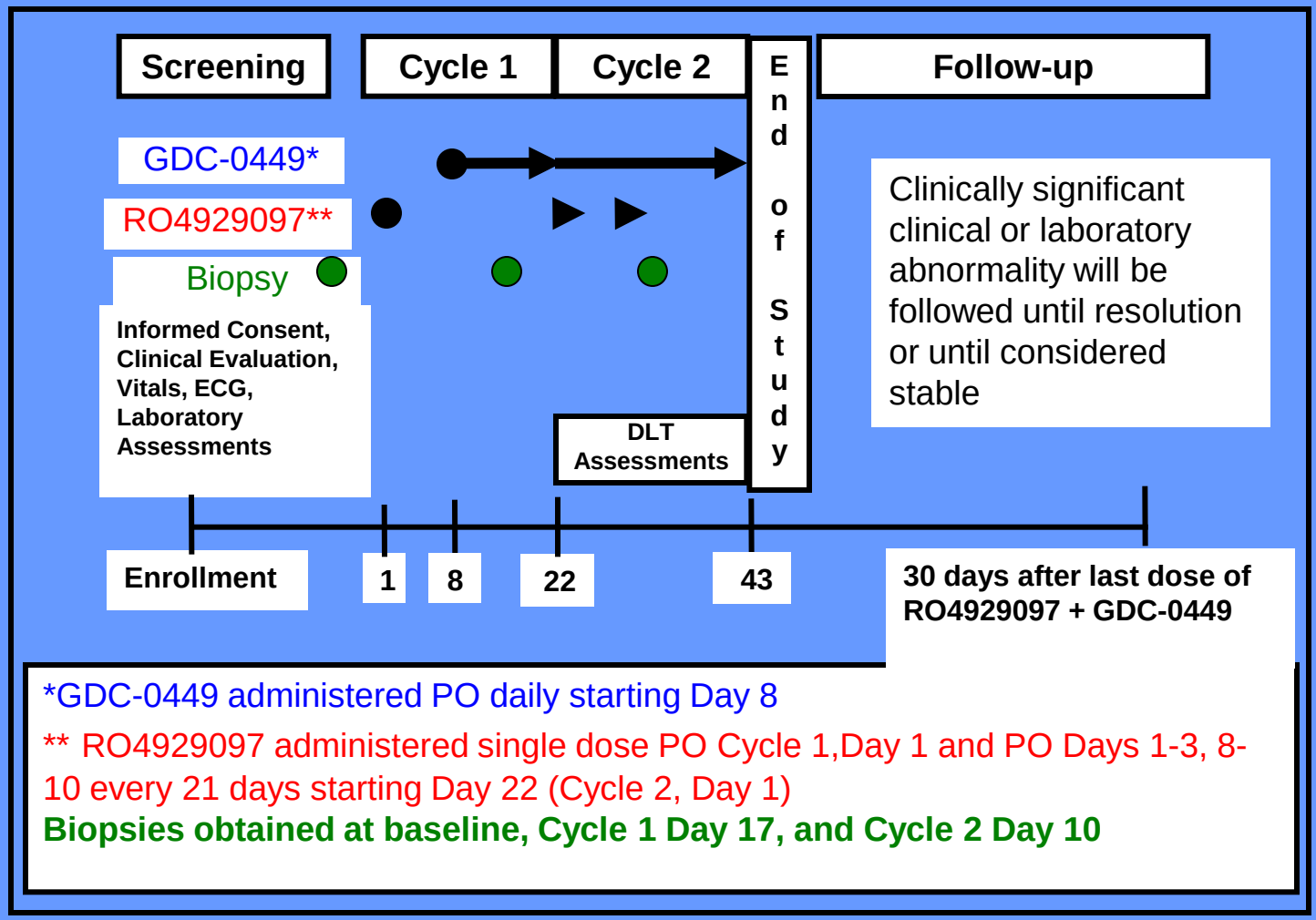
- How do we get the best drugs to use in combination?
  - How do we partner with different companies?
  - How do we get LOI approval from the NCI?
  - What are our moral and ethical obligations?
    - What if agents not best in class?
  - How many novel/novel combinations of similar targets are needed?
- Do we need the best drugs or should we just begin with proof of concept?

NCI#8420: Phase I clinical trial

- A Phase I Dose-Escalation Study of the Sonic Hedgehog Smoothened Antagonist GDC-0449 (NSC # 747691) Plus Pan-Notch Inhibitor RO4929097 (NSC # 749225) Administered in Patients with Advanced Breast Cancer
  - Karmanos Cancer Institute (Pat LoRusso, D.O. PI)
  - University of Michigan (Max Wicha, M.D./David Smith, M.D.)
  - Baylor College of Medicine (Jenny Chang, M.D.)
  - University of Mississippi (Lucio Miele, M.D., Ph.D.)
  - Johns Hopkins University (Vered Stearns, M.D./William Matsui, M.D.)

NCI# 8420: Study Schema

SCHEDULE A:



Clinical Challenges

- So what if you are working with agents that ARE NOT best in class and the combination does not prove effective?
  - Does this limit advancing similar targeted combinations forward?
  - What if you are not preselecting tumor types with appropriate targets?
  - Is it fair to use these drugs as proof of concept?
  - Does it slow down, rather than advance, clinical development?

Combination studies: Design Attributes

- Determination of Starting Dose
  - Knowledge of single agent dosing and minimal “effective” doses
    - Is this enough to help define starting doses?
  - Justification of starting doses of drugs:
    - If standard therapy part of combo, is there justification for lowering standard doses?
  - Combination toxicity
  - Drug-drug interactions
  - Clear definitions of endpoints to limit dosing
  - Markers to follow target effects (if applicable)

Preclinical studies Directing Clinical Trials

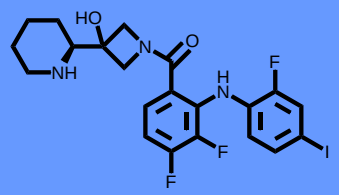
Clinical combination of the MEK inhibitor GDC-0973 and the pan-PI3K inhibitor GDC-0941: A first-in-human phase Ib study testing daily and intermittent dosing schedules in patients with advanced solid tumors

G. Shapiro, P. LoRusso, E. L. Kwak, J.M. Cleary, L. Musib, C. Jones, A. de Crespigny, M. Belvin, M. McKenzie, M. Gates, I.T. Chan, J. Bendell

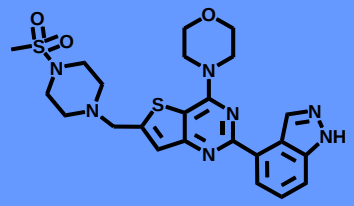
ASCO 2011 Annual Meeting
Abstract #3005

GDC-0973 and GDC-0941 are potent, selective inhibitors

GDC-0973
MEKi

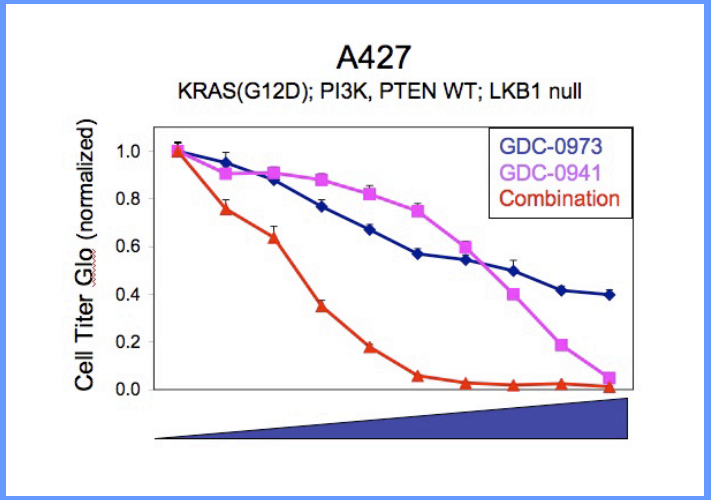


GDC-0941
pan-PI3Ki

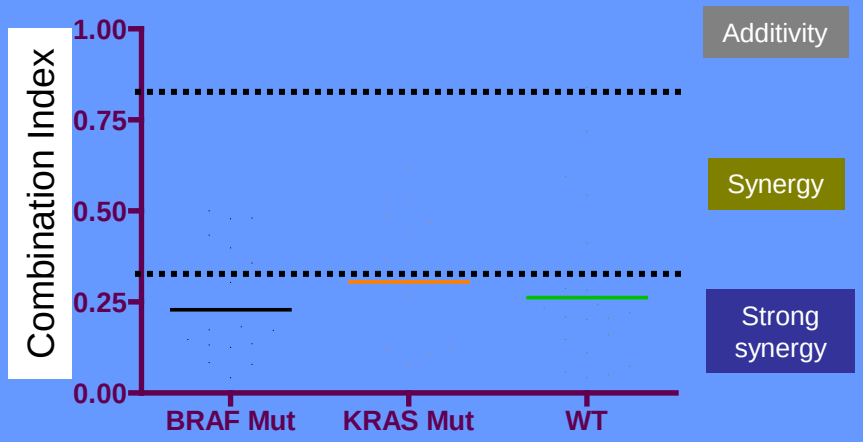


	GDC-0973	GDC-0941
Biochemical potency	MEK1: 4.2 nM	p110α: 3 nM p110β: 33 nM p110δ: 3 nM p110γ: 75 nM
Selectivity	>100x selectivity against 100 kinases	>100x selectivity against 288 kinases

In vitro combination activity



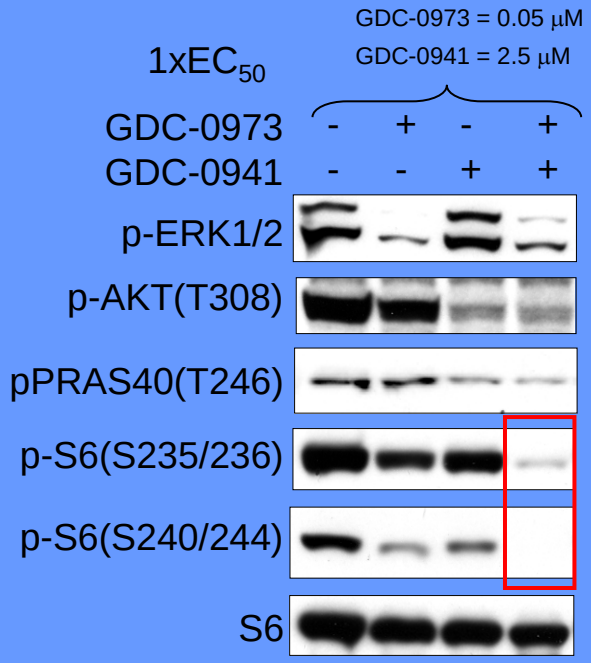
GDC-0973 + GDC-0941



Chou and Talalay method of calculating in vitro combination synergy

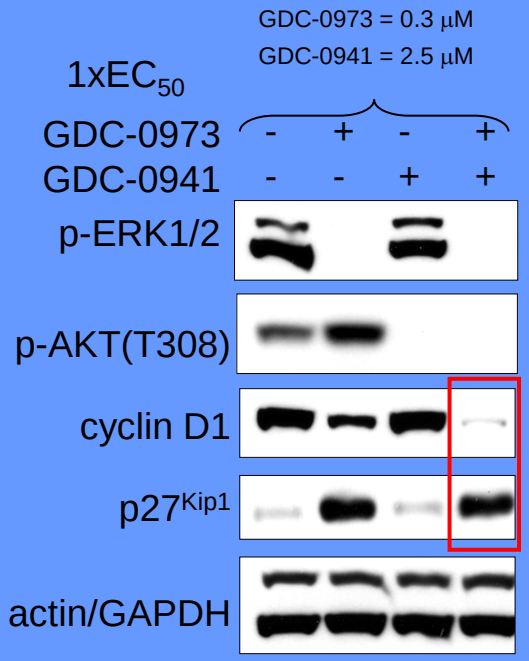
Combined effects on markers of pathway signaling, cell cycle, and apoptosis

Pathway Inhibition



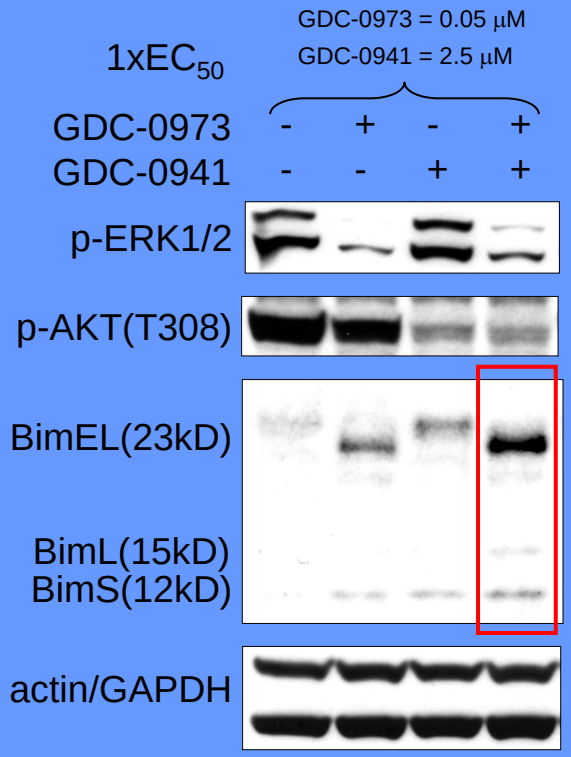
888MEL
BRAFV600E

Cell cycle



624MEL
BRAFV600E

Apoptosis



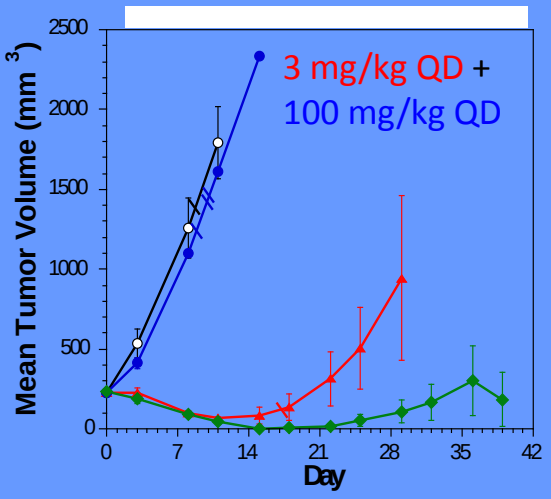
888MEL
BRAFV600E

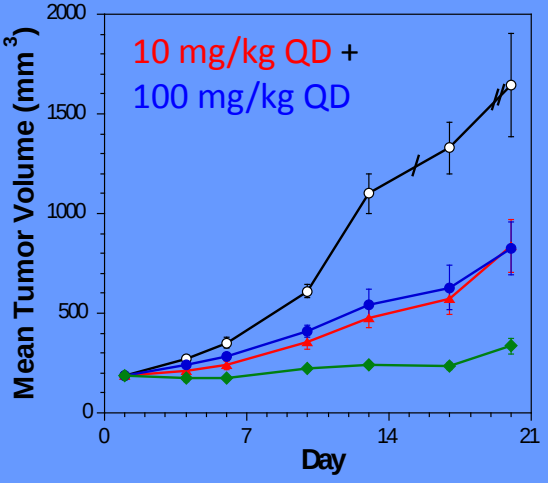
Daily dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenograft models

Vehicle, GDC-0973, GDC-0941, Combination

A375
BRAF^{V600E}
Melanoma

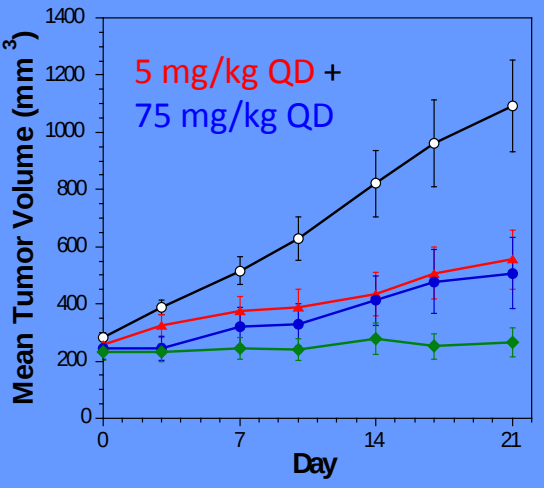
6 CR (n=10/grp)
2 PRs, 8 CRs

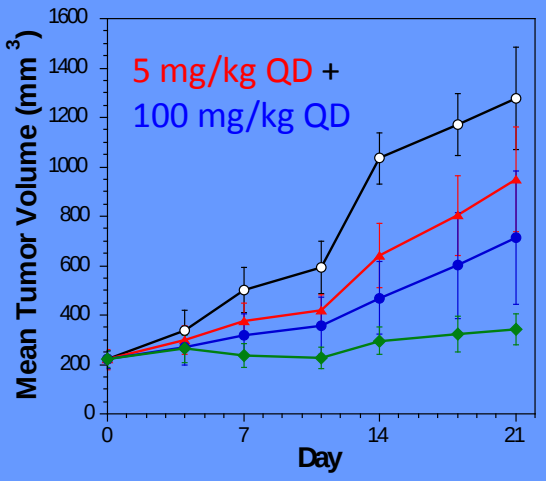




A2058
BRAF^{V600E}
PTEN^{null}
Melanoma

NCI-H2122
KRAS^{G12C}
NSCLC



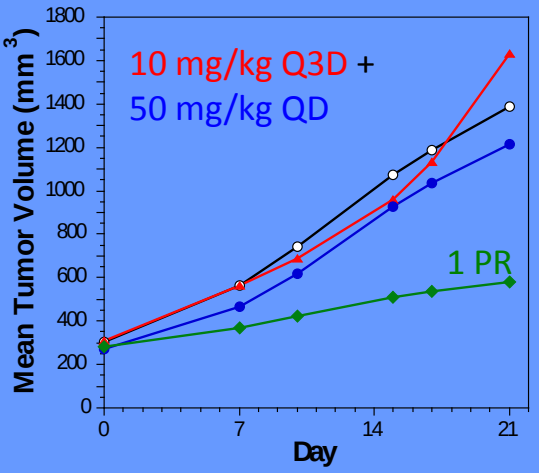


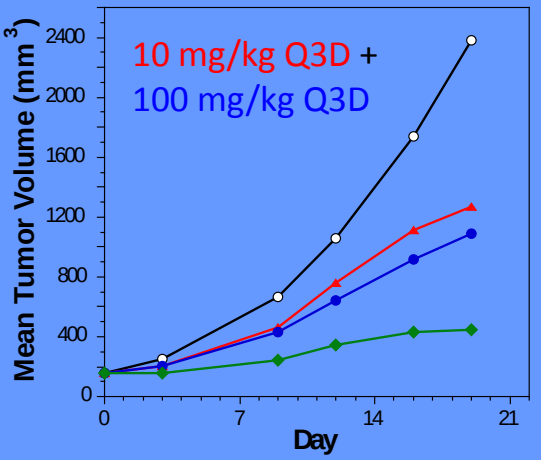
DLD-1
KRAS^{G13D}
PIK3CA^{E545K}
CRC

Intermittent dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenograft models

Vehicle, GDC-0973, GDC-0941, Combination

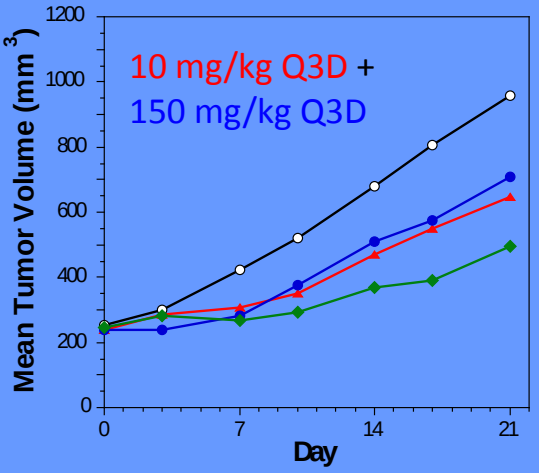
A375
BRAF^{V600E}
Melanoma

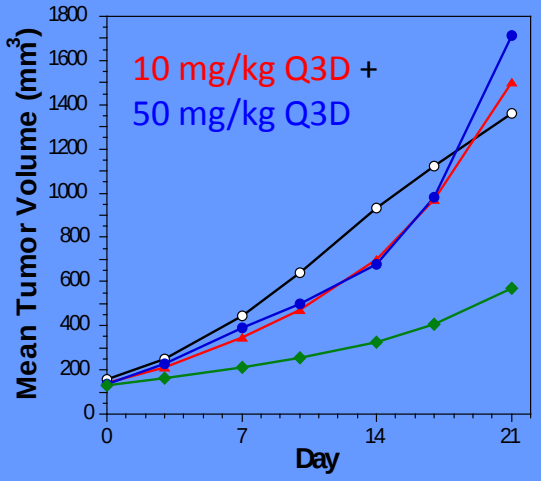




A2058
BRAF^{V600E}
PTEN^{null}
Melanoma

NCI-H2122
KRAS^{G12C}
NSCLC

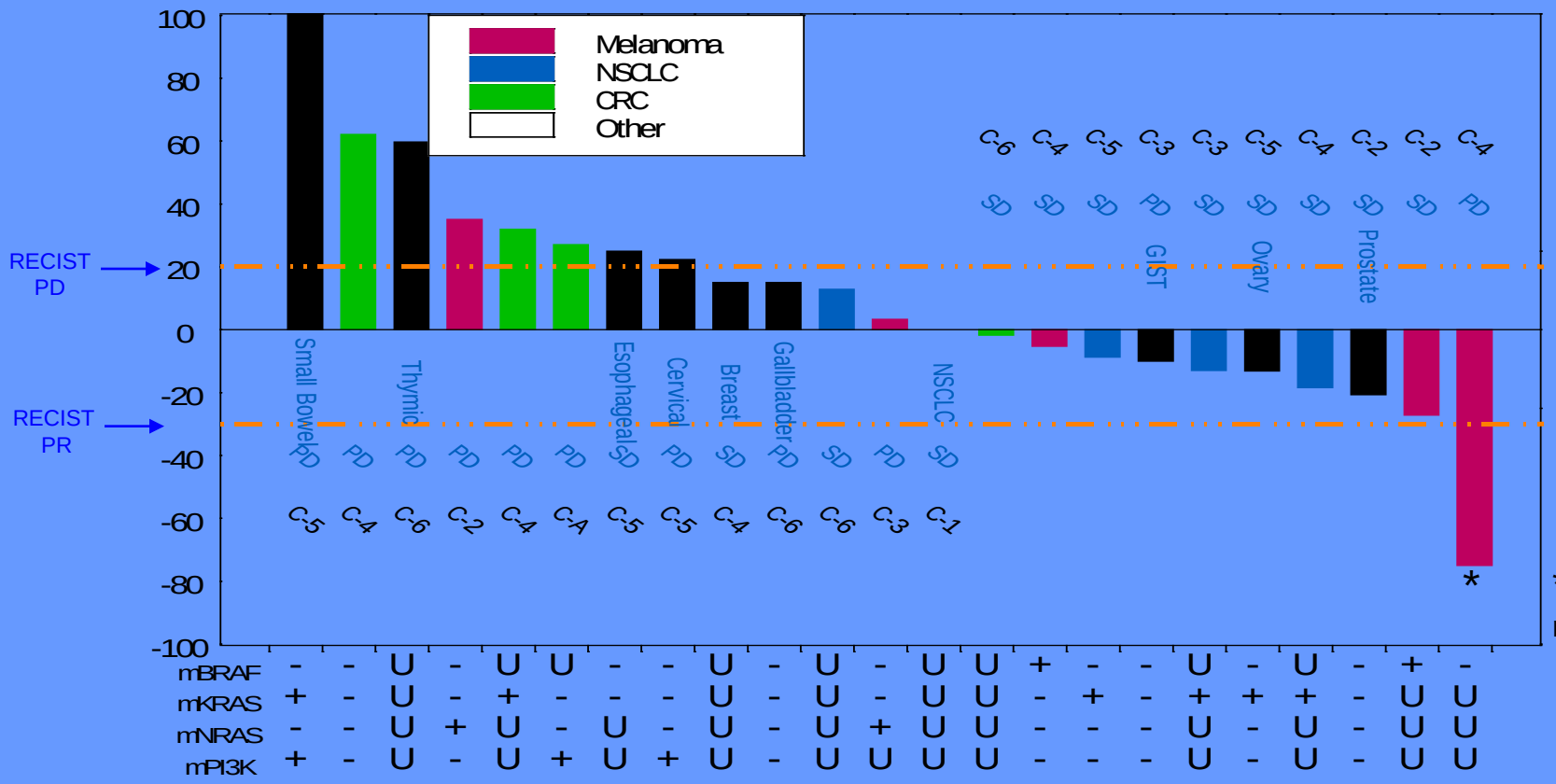




DLD-1
KRAS^{G13D}
PIK3CA^{E545K}
CRC

Did the Preclinical Data Help Us?

Anti-tumor Activity: Best Radiographic Response GDC0941 + GDC0973



- 6 patients had > 10% decrease in RECIST measurable target lesions
  - 2 melanoma (BRAF WT and BRAF mutant)
  - 1 prostate cancer
  - 2 KRAS mutant NSCLC
  - 1 KRAS mutant ovarian cancer
- After the database cutoff, one uPR observed in a Cohort C KRAS mutant endometrioid cancer patient

Database cutoff April 28, 2011

Phase I Response

- Although efficacy is not an endpoint, at what point do we begin more rigorous patient selection, especially when we are bringing novel agents forward in combination?
- Best way to define tumor “effect”
- Determination of response driver: monotherapy vs combination

Patient Selection

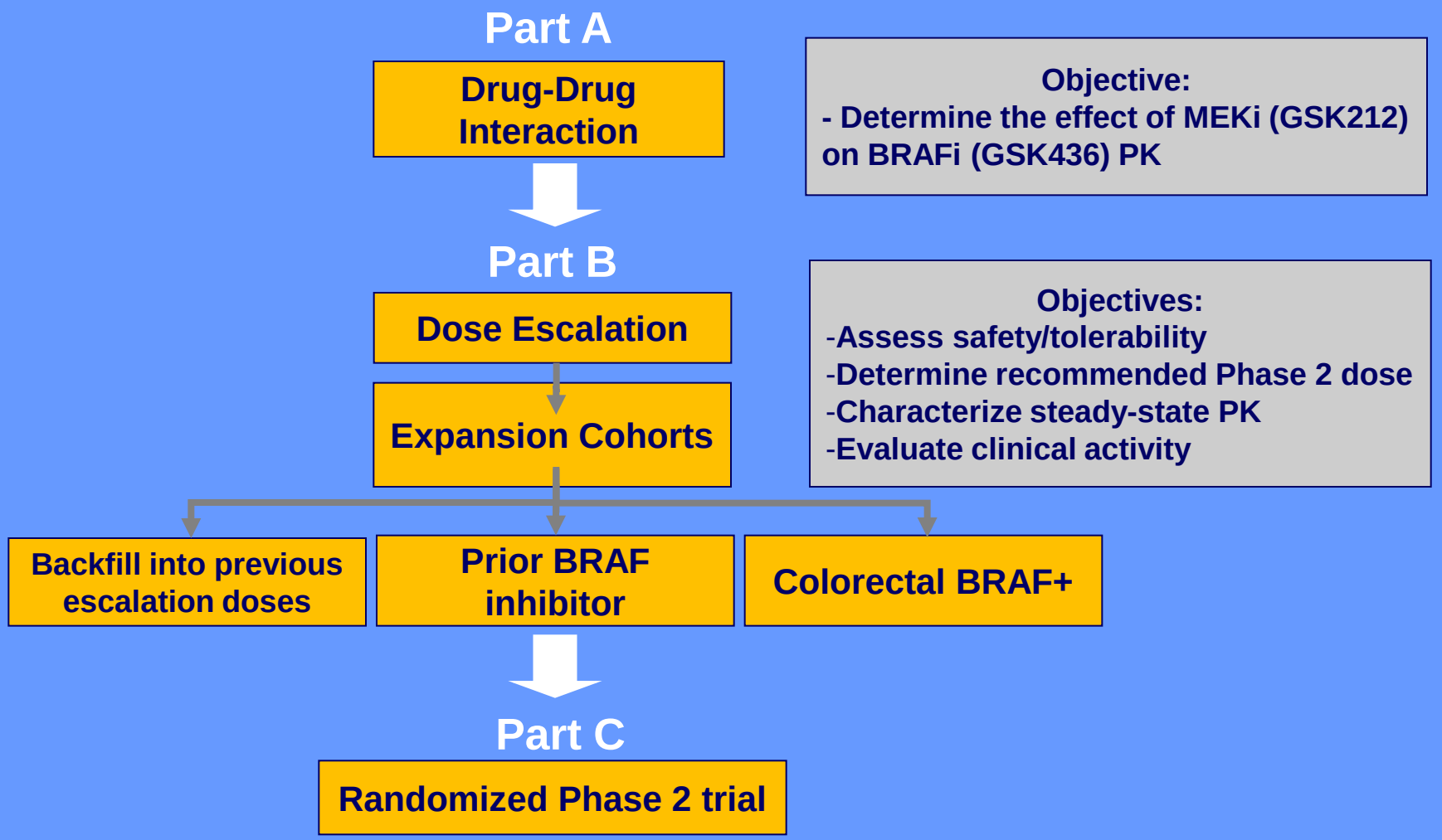
- Could potentially slow down recruitment
- Success = speed
- Currently lack effective tools
  - Limited markers available
  - Tissue acquisition & processing
  - Assay development
  - Cost
  - Availability
- Is this a good enough starting point?
- Profiling for patient selection
  - Site selection for biopsy

Phase I/II Study of the Oral MEK 1/2 Inhibitor GSK1120212 Dosed in Combination with the Oral BRAF Inhibitor GSK2118436

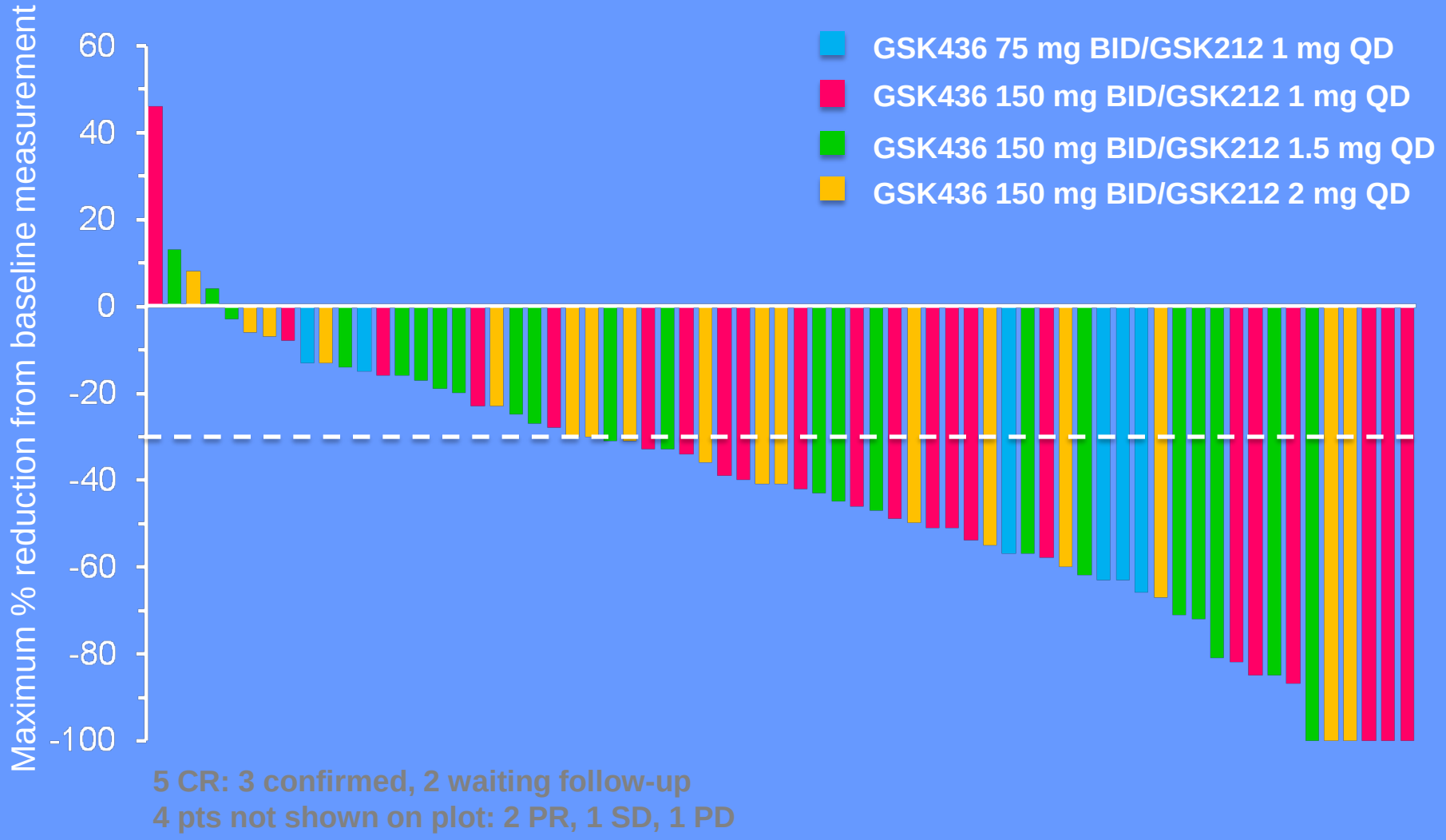
Jeffrey Infante[1], Gerald Falchook[2], Donald Lawrence[3], Jeff Weber[4], Richard Kefford[5] , Johanna Bendell[1], Razelle Kurzrock[2], Geoffrey Shapiro[3], Ragini Kudchadkar[4], Georgina Long[5], Howard Burris[1], Kevin Kim[2], Arthur Clements[5], Peng Sun[6], Bingming Yi[6], Alicia Allred[6], Daniele Ouellet[6], Kiran Patel[6], Peter Lebowitz[6], Keith Flaherty[3]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]MGH/DFCI, Boston, MA, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5] Melanoma Institute of Australia and Westmead Hospital, University of Sydney, Australia; [6]GlaxoSmithKline Research and Development, Philadelphia, PA and RTP, NC, USA

Study Design and Objectives

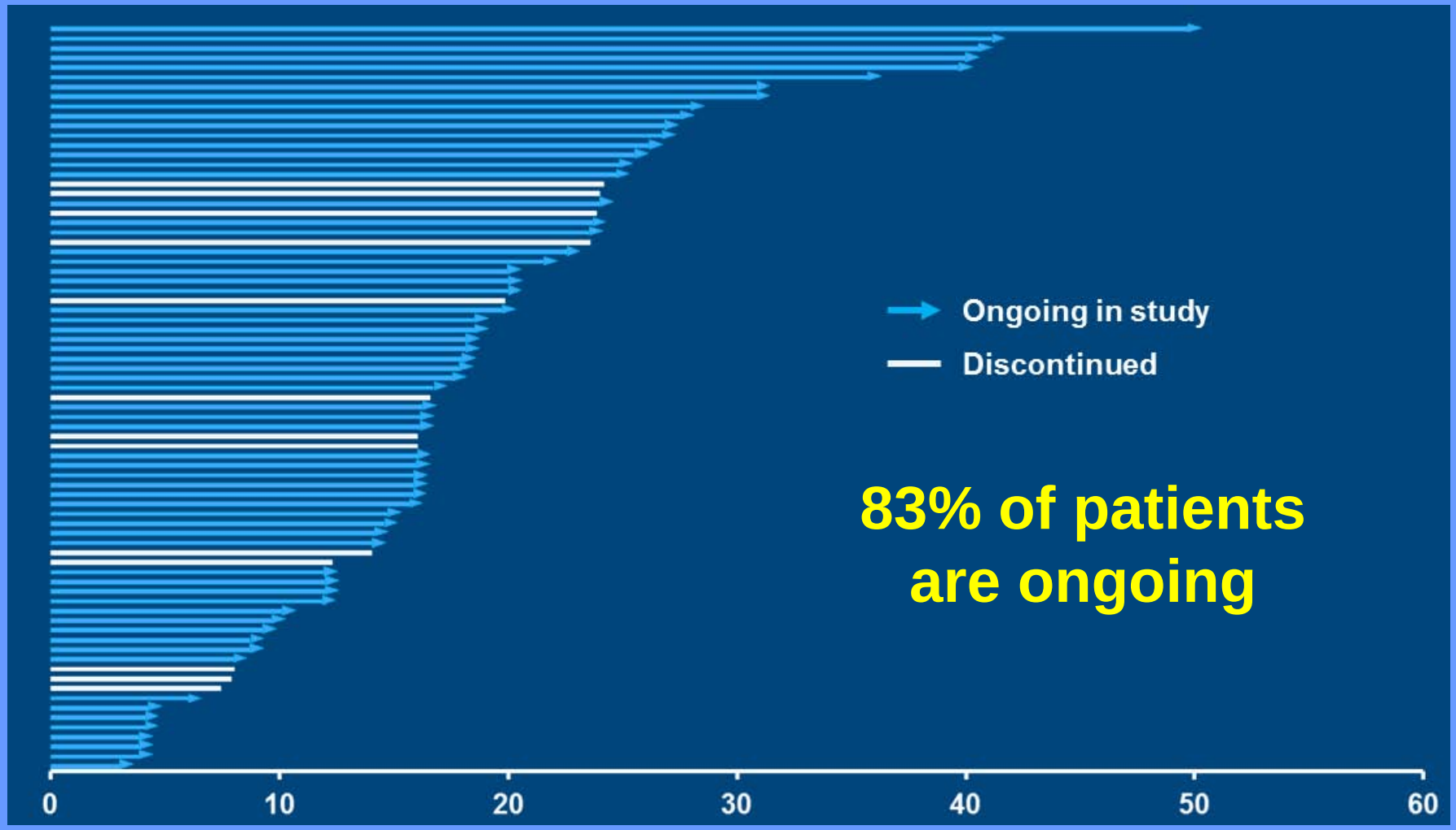


Waterfall Plot for Melanoma Patients without Prior BRAFi (n=71)

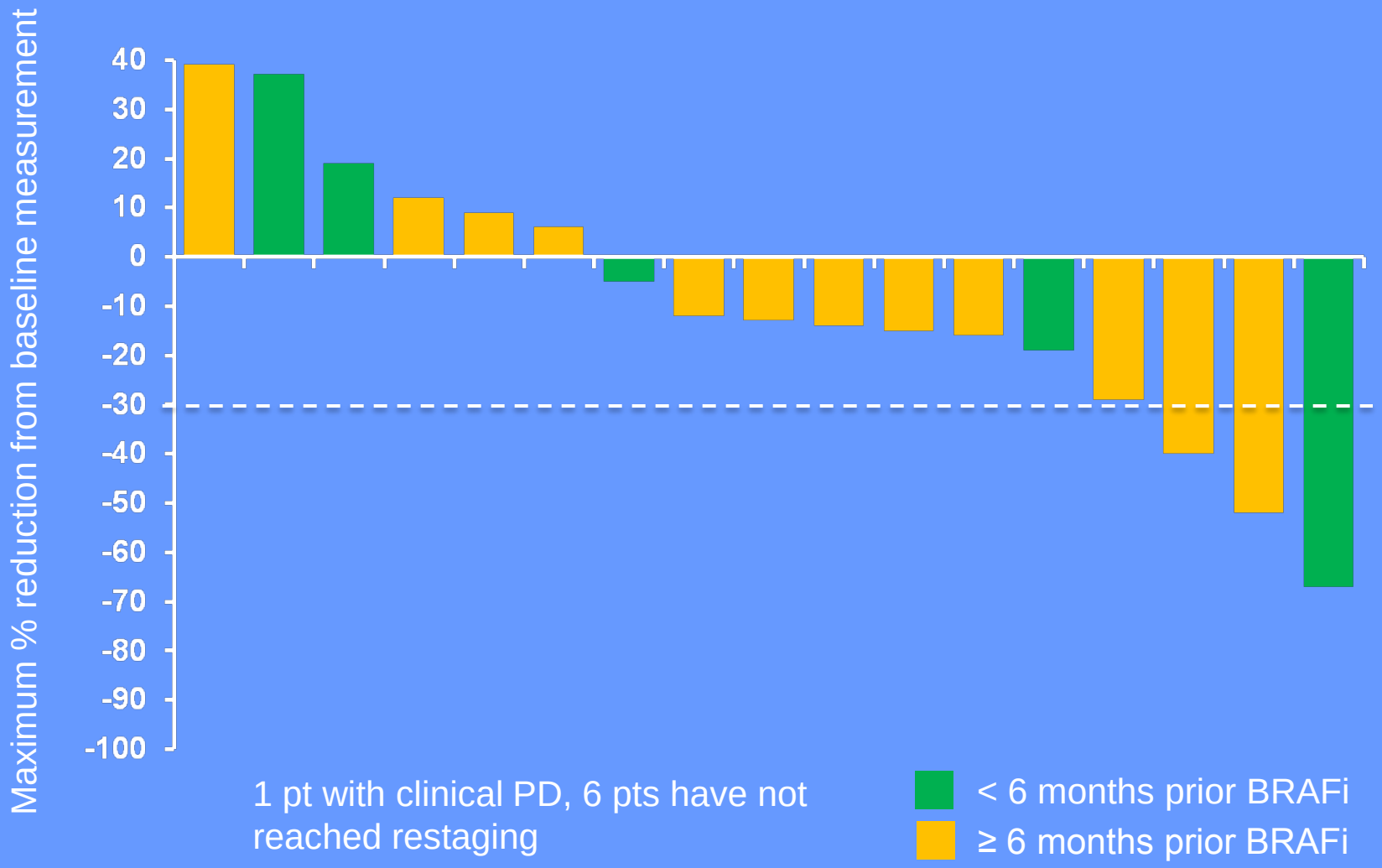


5 CR: 3 confirmed, 2 waiting follow-up
4 pts not shown on plot: 2 PR, 1 SD, 1 PD

Treatment Duration for Melanoma Patients without Prior BRAFi (n=77)



Waterfall Plot for Melanoma Patients with Prior BRAFi (n=24)



Patient Preselection

- Infante selection easy
- Trial designs focusing on patient preselection
  - One arm/one trial vs multiple arms one trial
  - Novel trial designs are pivotal
    - Multi-arm phase I drugs in a phase I trial
    - Multi-arm phase I combinations
    - Challenges
      - Site selection
      - Study availability
      - Careful oversite

How does escalation scheme impact on results?

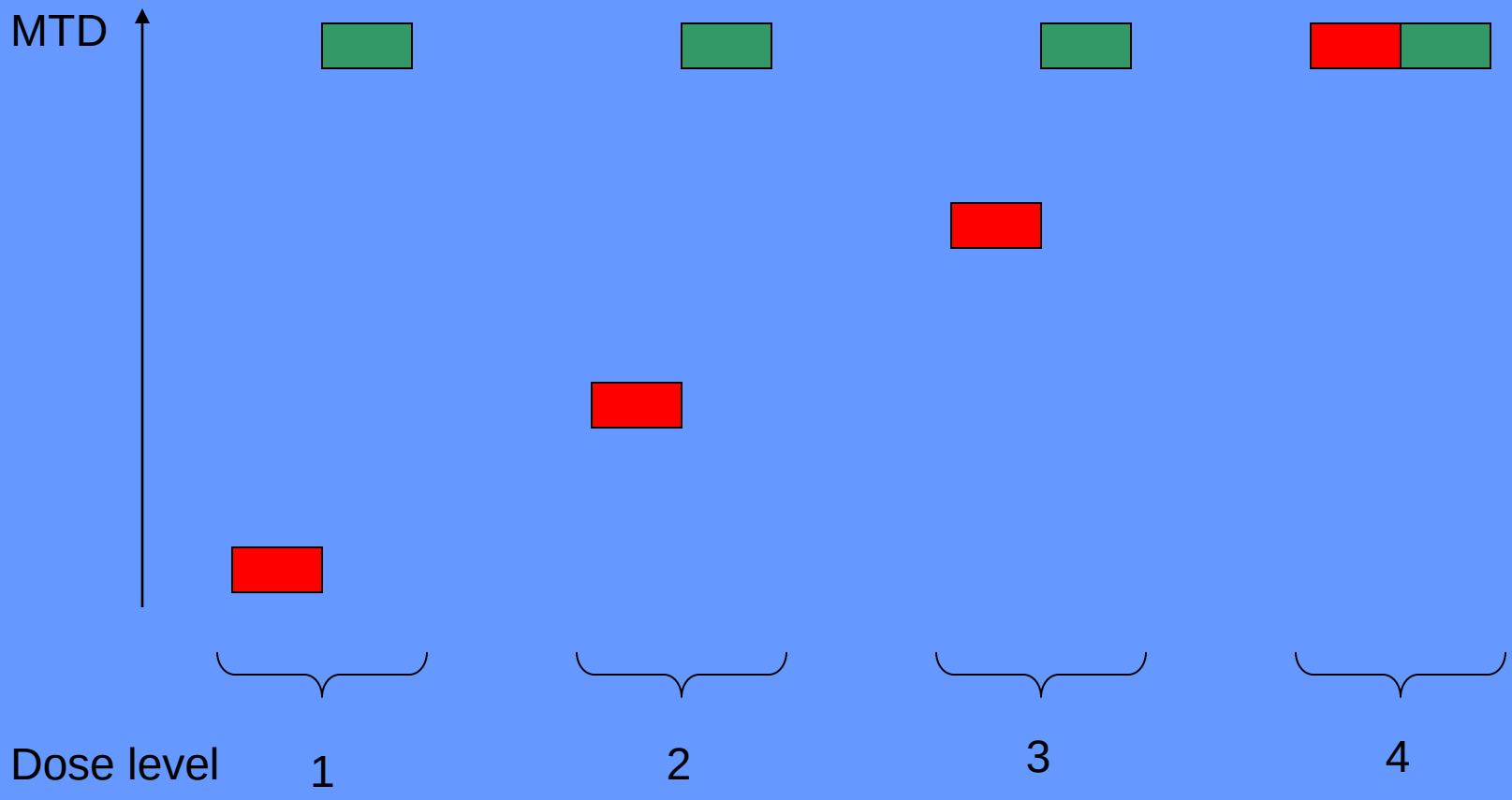
Definition of MTD of drug combination

Toxicities of drug combination

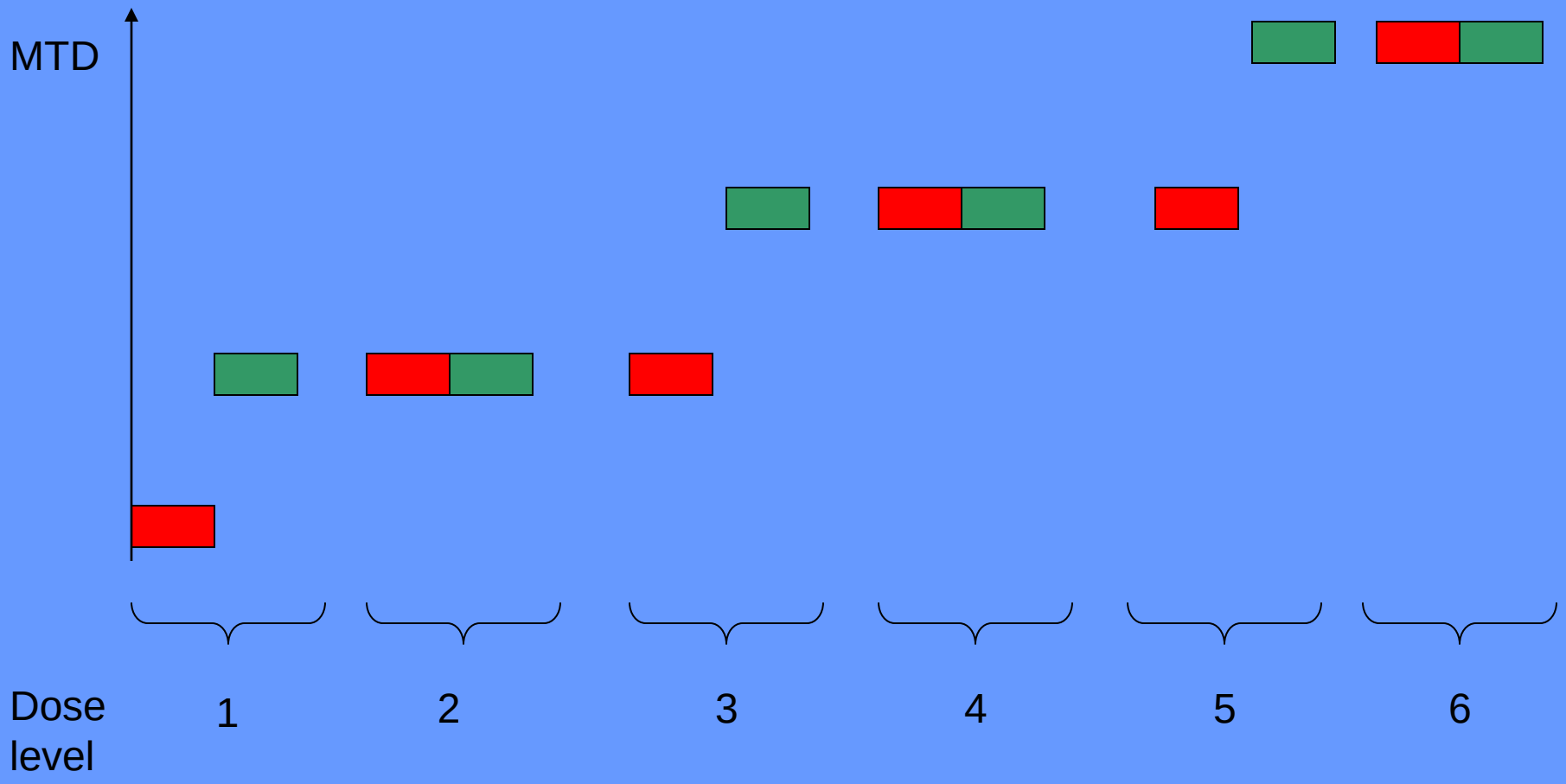
Ultimately – tumor response

Dose Level Options:
No single “right” way!

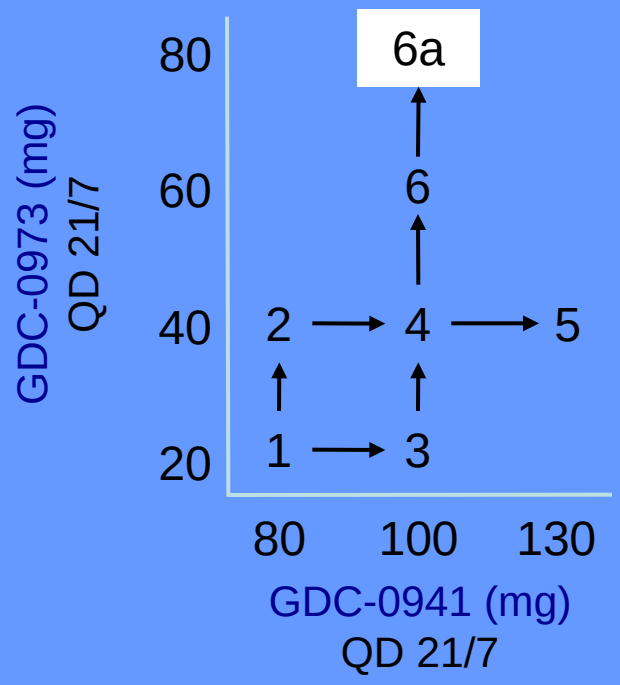
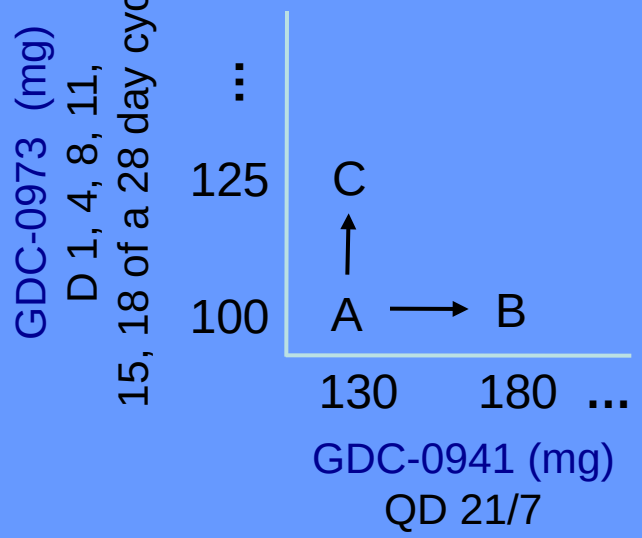
Base on best conceptual and actual data



Dose Level Options:
No single "right" way!
Base on best conceptual and actual data



Dose Escalation and Study Design (GDC 0941 + GDC 0973)

	21/7 Dosing	Intermittent MEK Dosing
Dose Escalation Schema		

3+3 study design
PK sample collection
Serial FDG-PET scans
Tumor assessments q8 weeks
Archival tumor tissue collection

Combination Drug Toxicity Issues

- Obviously main concern
- Often difficult when overlap in toxicity
- Makes sense to have experienced investigators
  - who know either drug(s) or drug class
- Can trial design help you?
  - Simultaneous/sequential/intermittent/pulse
    - Impact on combination effect
  - Lack appropriate models to help determine best schedule

Combination MTA Toxicity Issues

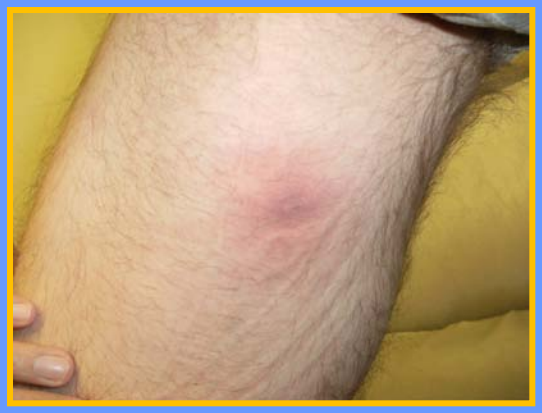
- Controversies of combination toxicity
  - Asymptomatic biochemical toxicities
  - Toxicities of mono vs combination therapy
  - Onset of toxicity
  - CTCAE toxicity criteria
- Can newly discovered toxicities of drug(s) in combination affect drug approval?

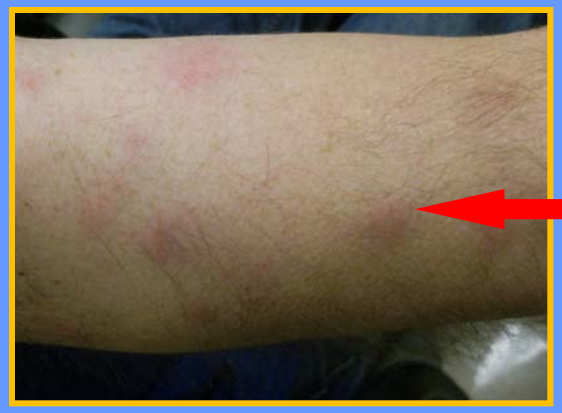
Phase I/II Study of the Oral MEK 1/2 Inhibitor GSK1120212 Dosed in Combination with the Oral BRAF Inhibitor GSK2118436

Jeffrey Infante[1], Gerald Falchook[2], Donald Lawrence[3], Jeff Weber[4], Richard Kefford[5] , Johanna Bendell[1], Razelle Kurzrock[2], Geoffrey Shapiro[3], Ragini Kudchadkar[4], Georgina Long[5], Howard Burris[1], Kevin Kim[2], Arthur Clements[5], Peng Sun[6], Bingming Yi[6], Alicia Allred[6], Daniele Ouellet[6], Kiran Patel[6], Peter Lebowitz[6], Keith Flaherty[3]

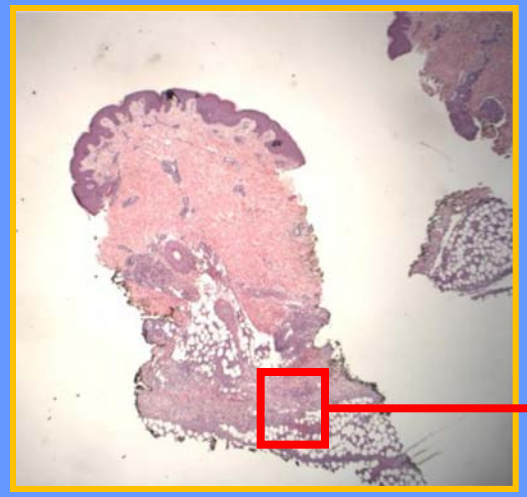
[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]MGH/DFCI, Boston, MA, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5] Melanoma Institute of Australia and Westmead Hospital, University of Sydney, Australia; [6]GlaxoSmithKline Research and Development, Philadelphia, PA and RTP, NC, USA

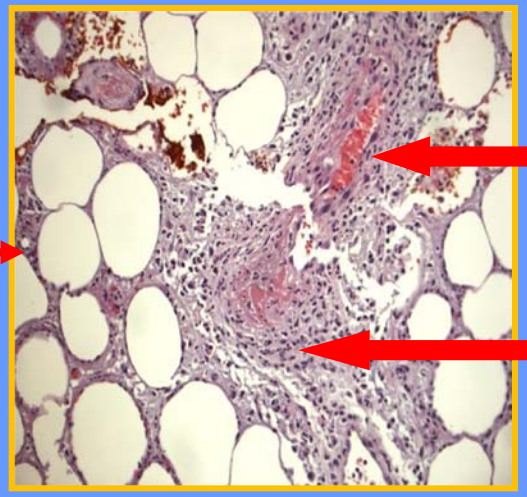
DLT: Recurrent Grade 2 Neutrophilic Panniculitis with Small/Medium Vessel Vasculitis





Painful, red, nodular lesions associated with fevers and chills





Fibrinoid necrosis with a destroyed vessel

Predominant neutrophilic inflammatory response in fatty layer of skin

Deep skin punch BX

Infante, et al., ASCO 2011

Treatment-Related AEs Occurring in ≥10% of Patients

	Dose level (BRAFi GSK436/ MEKi GSK212)				
Preferred Term	**75/1 (n=6)**	**150/1 (n=23)**	**150/1.5 (n=27)**	**150/2 (n=53)**	**Total (n=109)**
Any event, n (%)	**5 (83%)**	**21 (91%)**	**23 (85%)**	**37 (70%)**	**86 (79%)**
Pyrexia	2 (33%)	6 (26%)	8 (30%)	18 (34%)	34 (31%)
Rash	2 (33%)	9 (39%)	5 (19%)	11 (21%)	27 (25%)
Chills	2 (33%)	7 (30%)	7 (26%)	8 (15%)	24 (22%)
Nausea	1 (17%)	5 (22%)	6 (22%)	10 (19%)	22 (20%)
Diarrhea	0	5 (22%)	5 (19%)	9 (17%)	19 (17%)
Fatigue	2 (33%)	1 (4%)	6 (22%)	8 (15%)	17 (16%)
Vomiting	1 (17%)	1 (4%)	3 (11%)	6 (11%)	11 (10%)

Treatment-related AEs ≥ Grade 3 occurred in 19% of all patients; events occurring in more than 1 patient: neutropenia (3), leukopenia (2), diarrhea (2), pyrexia (2).

Infante, et al., ASCO 2011

Dose Escalation Enrollment

Dose level (GSK436/GSK212)	Dose escalation enrollment	Expansion cohort enrollment	Dose-limiting toxicity
75 mg BID/1 mg QD	4	2	–
150 mg BID/1 mg QD	4	19	–
150 mg BID/1.5 mg QD	4	23	–
150 mg BID/2 mg QD	6	47	Recurrent Grade 2 neutrophilic panniculitis

Full monotherapy doses were administered in combination

Conclusions

- **Significant Challenges exist**
  - Lack of preclinical and translational data for combinations
  - Multiple drugs with same target – best in class?
  - Trial designs for scheduling, ratios and dosing
  - Need to define and realize true endpoints
  - "Personalized Medicine" - patient selection
  - Cost – is it more cost effective to do it better?

THE GREATEST AND MOST LIMITED RESOURCE
THE PATIENT

Ultimate Participation Goal – THEY WANT TO LIVE!


Thank You!!!

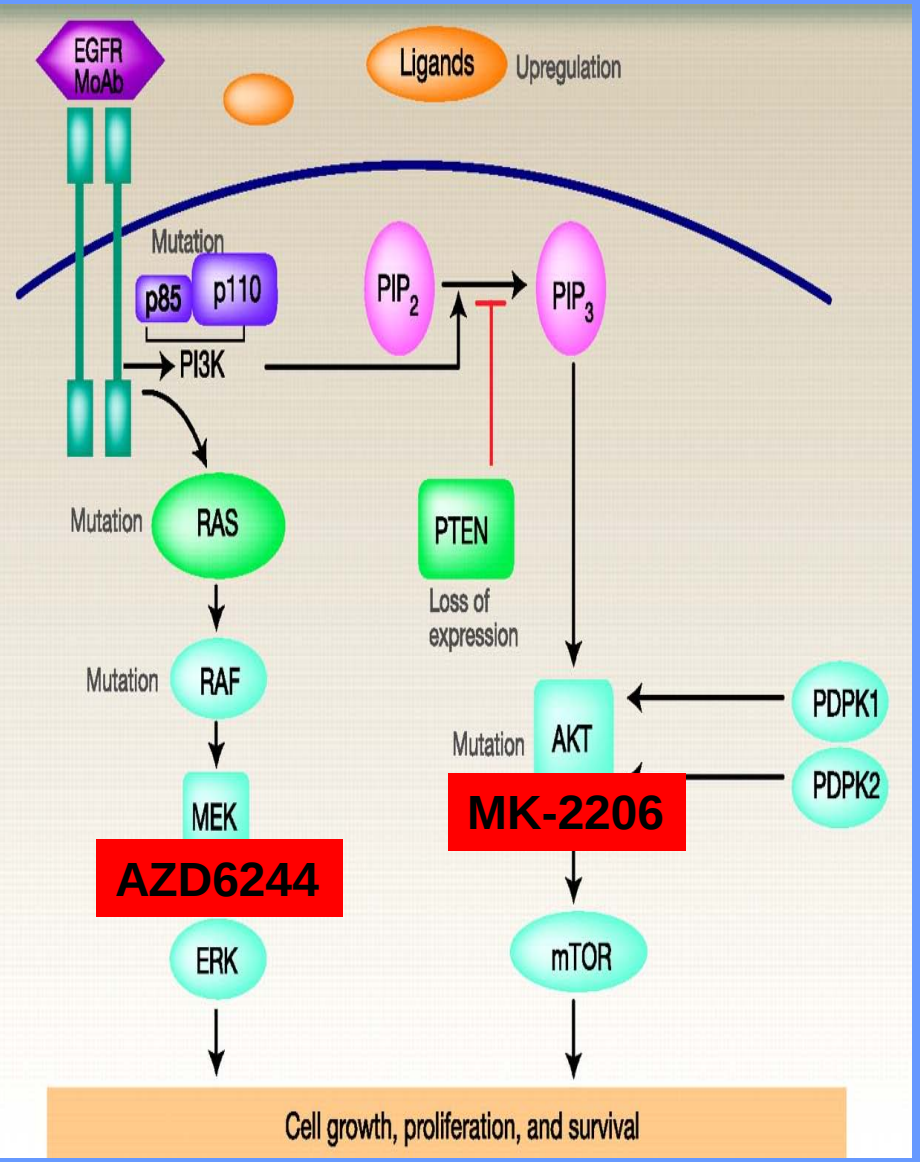
Novel-Novel drug combination development is very challenging, and with the appropriate background information and right conditions, is a worthwhile endeavor to develop better anti-cancer therapies for patients

Topics

- Tox – how do you dissect out, define what to do
- Where are we going with combo's?
- Fear of targeted agents
  - Wipe out what we need
    - Stewart's stuff
- When do you add the 2 drugs – simultaneously – add one when other begins to fail??
- How do we sequence the agents for max response
- How does PK and/or PD factor in to the equation
- What do we do with all our initial failures
- How does added toxicity impact on drug approval?
- Can bringing 2 of the not best agents together significantly enhance secondary to pathway effects?
  - AZD6244
- What guides us? How to help us? How much preclinical is enough?
- Concern – haste can make waste – if we don't look we may not ever know and the enthusiasm of targeted therapeutic combinations may vanish
  - Not looking may hurt more than help us if we aren't getting ravishing results
  - Not only for efficacy but exposure levels – how much exposure is going to be needed and the ratio of the combo therapies
- When not working with the best agents in combination – does it matter if we can now inhibit different targets and different pathways?

- Mistakes in design leading to erroneous recommendations can have serious consequences
- Best approaches consider: ***what will be done next with this combination?***
  - Will all scenarios need same ratios/doses of the agents in combination?

Background



The RAS/RAF/MEK and PI3K/AKT/mTOR signaling pathways are frequently co-activated in malignancies

Preclinical antitumor activity by AKT inhibition was abrogated by activating Ras mutations

Similarly, activation of the PI3K & AKT decreases activity of inhibitors of the RAS/RAF/MEK pathway

Hypothesis that combined inhibition will enhance antitumor activity

Challenges of Novel Combinations

- Dose(s) and schedule selection
  - Suited for all scenarios and tumor types?
  - Better preclinical guides
  - Preliminary clinical trials
- Scheduling to circumvent toxicity
  - sequencing vs pulsing vs continuous
    - Toxicity vs Efficacy

Defining response

- Patient &/o Tumor selection