Development of Rational Drug Combinations for Oncology Indications - An Industry Perspective

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Conventional Oncology Drug Development

- Identify a biological feature (*relatively*) unique to cancer cells versus normal cells
  - Ex. Constitutively activated growth factor signaling pathway
- Identify a drug-able target
- Generate clinical candidates with acceptable preclinical pharmacology and toxicology
- Assess human safety and PK
- Assess clinical activity either as a single agent or in combination with standard of care (SOC) therapy in tumor type of highest interest

Limitations of developing targeted drugs *"one target at a time"*

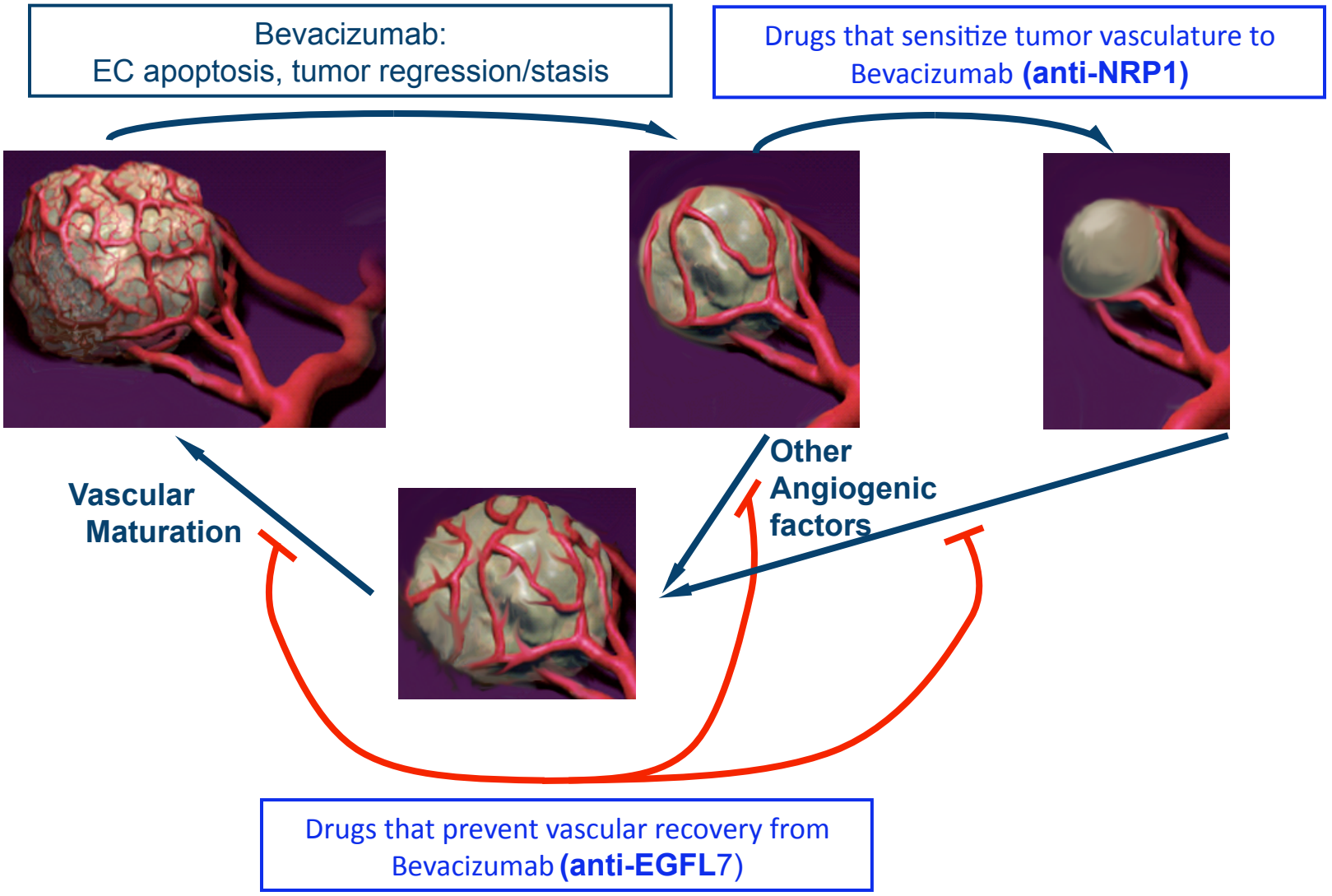
- High failure rate due to
  - Lack of clinically meaningful single agent activity
  - Inability to combine with SOC therapy (ie. chemotherapy)
- Approved drugs may have only modest benefit
  - Pathway not fully suppressed
  - Biological process not fully suppressed (Ex. tumor angiogenesis)
  - Resistance pathways either pre-exist or are induced
  - Disease heterogeneity
- Value of the drug to patients and sponsor not fully realized

Examples of Genentech Drug Combinations

Drug	MOA	Drug	MOA	Status
Tarceva®	EGFR inhibitor	Avastin®	Anti-angiogenesis	Phase III negative
Tarceva®	EGFR inhibitor	MetMAb	Met inhibitor	Phase III
Herceptin®	HER2 Signaling	Pertuzumab	HER2 Signaling	Phase III
Rituxan®	ADCC	Navitoclax[1]	BCL2 inhibitor	Phase II
Avastin®	Anti-angiogenesis	Anti-EGFL7	Anti-angiogenesis	Phase II
Avastin®	Anti-angiogenesis	Anti-NRP1	Anti-angiogenesis	Phase Ib terminated
Vemurafenib	RAF inhibitor	Yervoy®[2]	Immunotherapy	Phase Ib
Vemurafenib	RAF inhibitor	GDC-0973	MEK inhibitor	Phase Ib
GDC-0941	PI3K inhibitor	GDC-0973	MEK inhibitor	Phase Ib

FDA approved NDA submitted [1]co-development with Abbott [2]BMS

Strategies to enhance the anti-angiogenic activity of bevacizumab

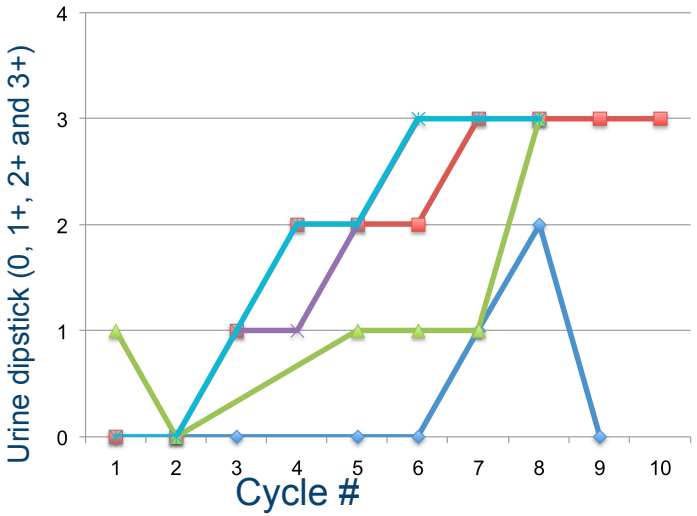


Anti-NRP1 Potentiates Bevacizumab-induced Proteinuria

- Proteinuria was not observed in the anti-NRP1 Phase I
- Phase Ib: Arm A - escalating doses anti-NRP1 with Bevacizumab
  Arm B – escalating doses of anti-NRP1 with Bevacizumab/Taxol

	Cohort (mg/kg)	n	Grades 1-2 (n)	Grades 3-4 (n)	All Grades (%)
Arm A	15	3	2	0	67
	24	7	2*	1	43
	Subtotal %	**14**	**29**	**7**	**36**
Arm B	12	5	2	1	60
	16	5	1	1**	40
	Subtotal %	**10**	**30**	**20**	**50**
	Total %		**29**	**13**	**42**

New ≥2+ urine dipstick (Grade ≥2) in 5/5 of patients on study for ≥6 cycles



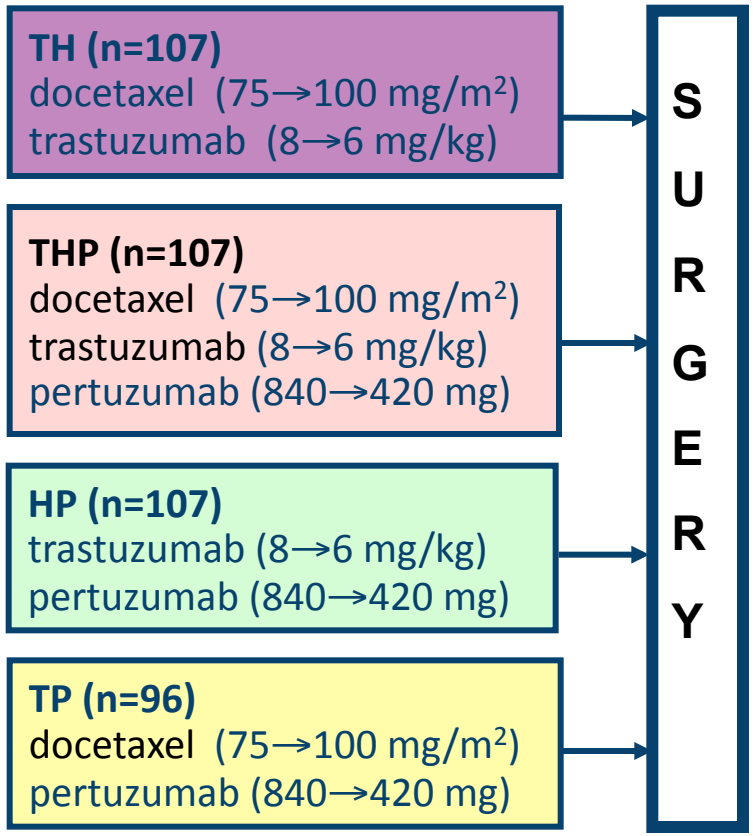
- **Anti-NRP1 development terminated**
- **Anti-EGFL7 found to be safe and tolerable in a similar Phase Ib and has moved into Phase II testing with chemo/Avastin®**

TAT, 2011 and Proc ASCO, 2011

NEOSPHERE – A randomized Phase II evaluating combination therapy targeting HER2

Patients with operable or locally advanced / inflammatory* HER2-positive BC

Chemo-naïve & primary tumors >2cm (N=417)

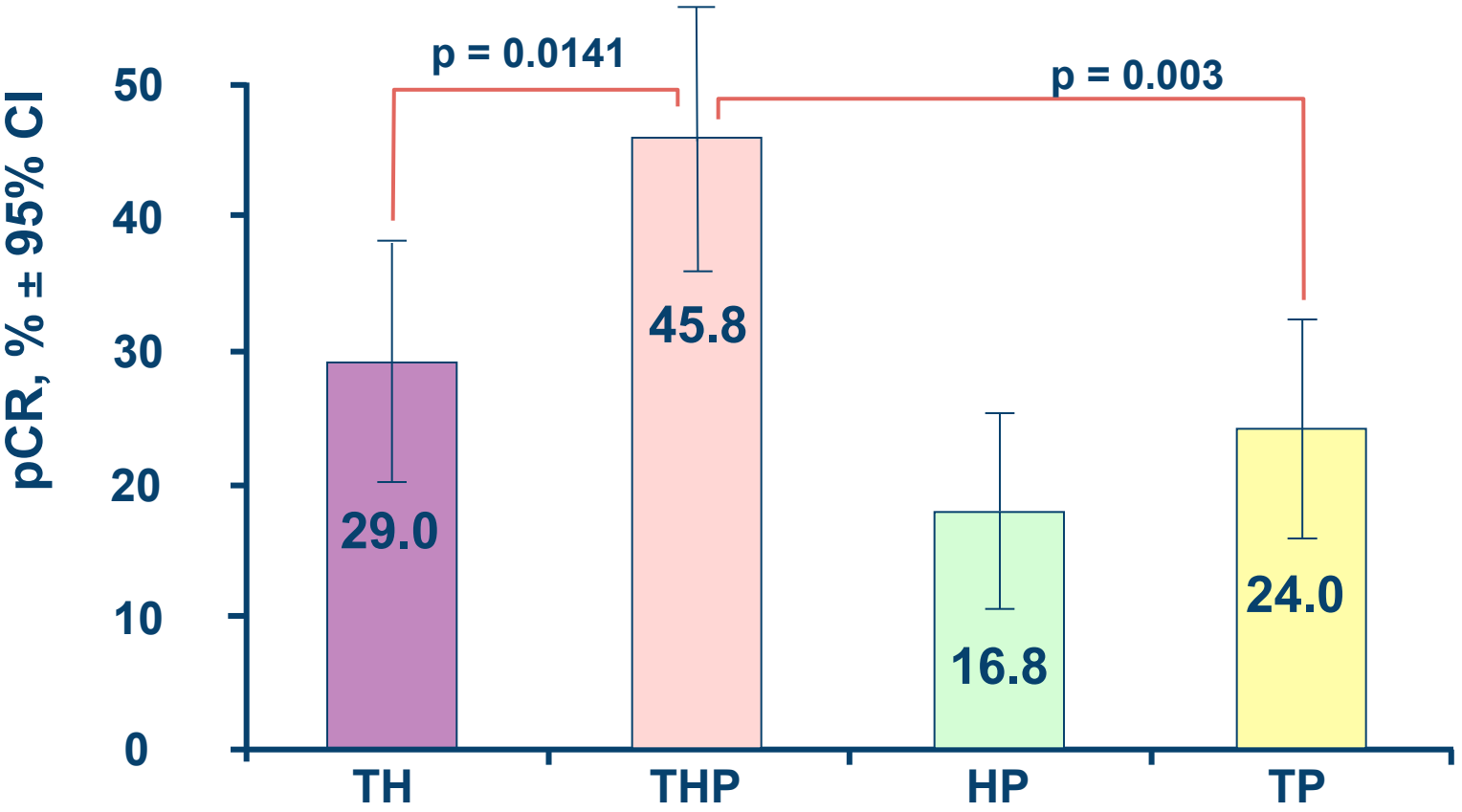


Study dosing: q3w x 4

- Primary endpoint:
  - comparison of pCR rates
    - TH vs THP
    - TH vs HP
    - THP vs TP
- Secondary endpoints:
  - Clinical response
  - DFS
  - Breast conservation rate
  - Biomarker evaluation

Proc SABCS, 2010

Pertuzumab increased pCR when added to trastuzumab/docetaxel



Proc SABCS, 2010

H, trastuzumab; P, pertuzumab; T, docetaxel

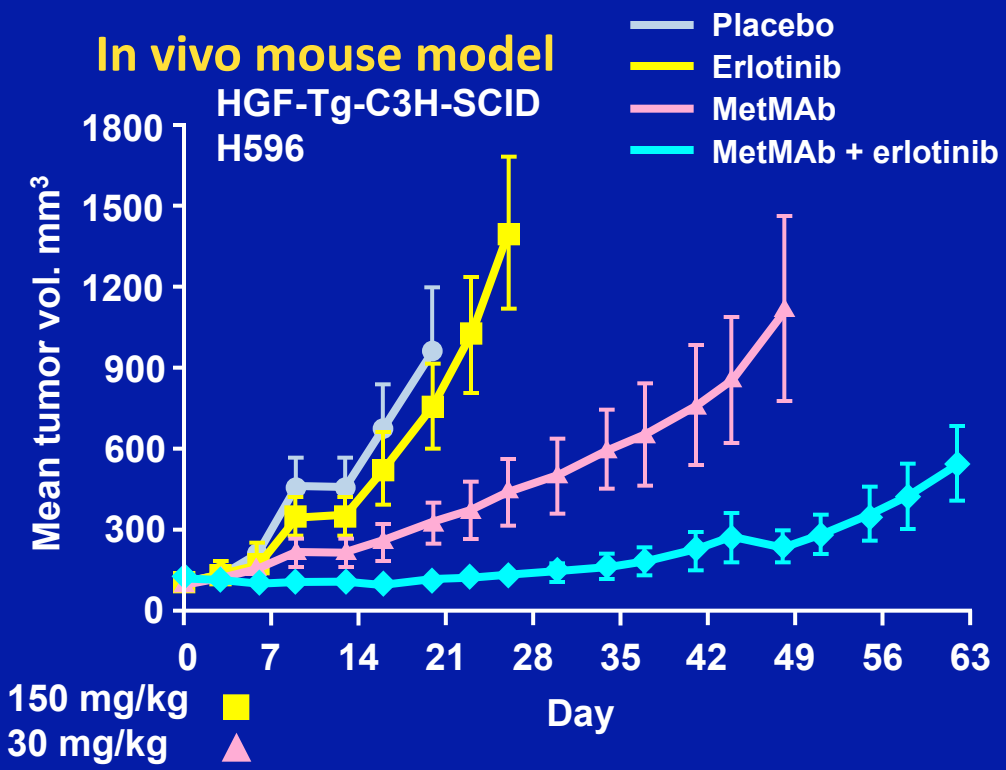
Data supporting an erlotinib plus anti-MET Ab (MetMAb) combination in NSCLC

In vitro

NSCLC cell line	Treatment	Erlotinib IC_{50} (μM)	
		TGFα	TGFα +HGF
H596	–	0.508	>10
	MetMAb		0.997

H596: Met-Exon14Δ, EGFR WT cell line

In vivo mouse model



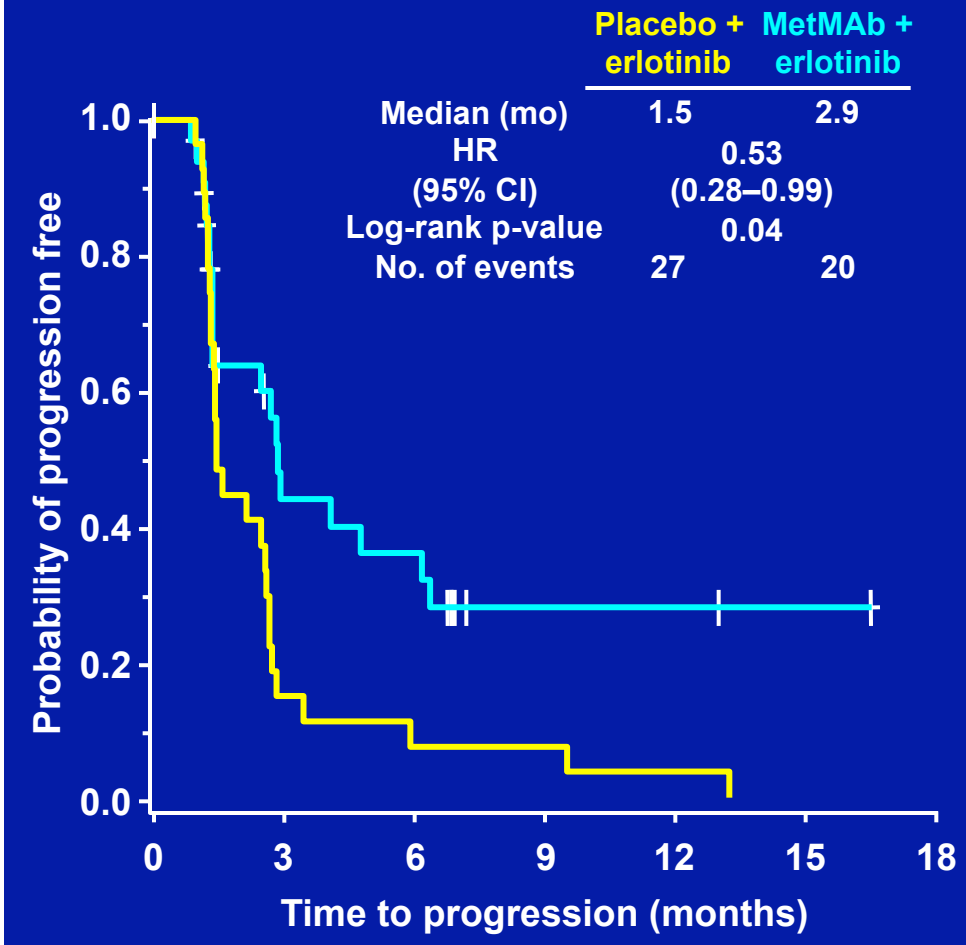
Clinical

MET gene amplification is associated with EGFR-TKI resistance in EGFR mutant NSCLC *(Engelman et al., Science 2007)*

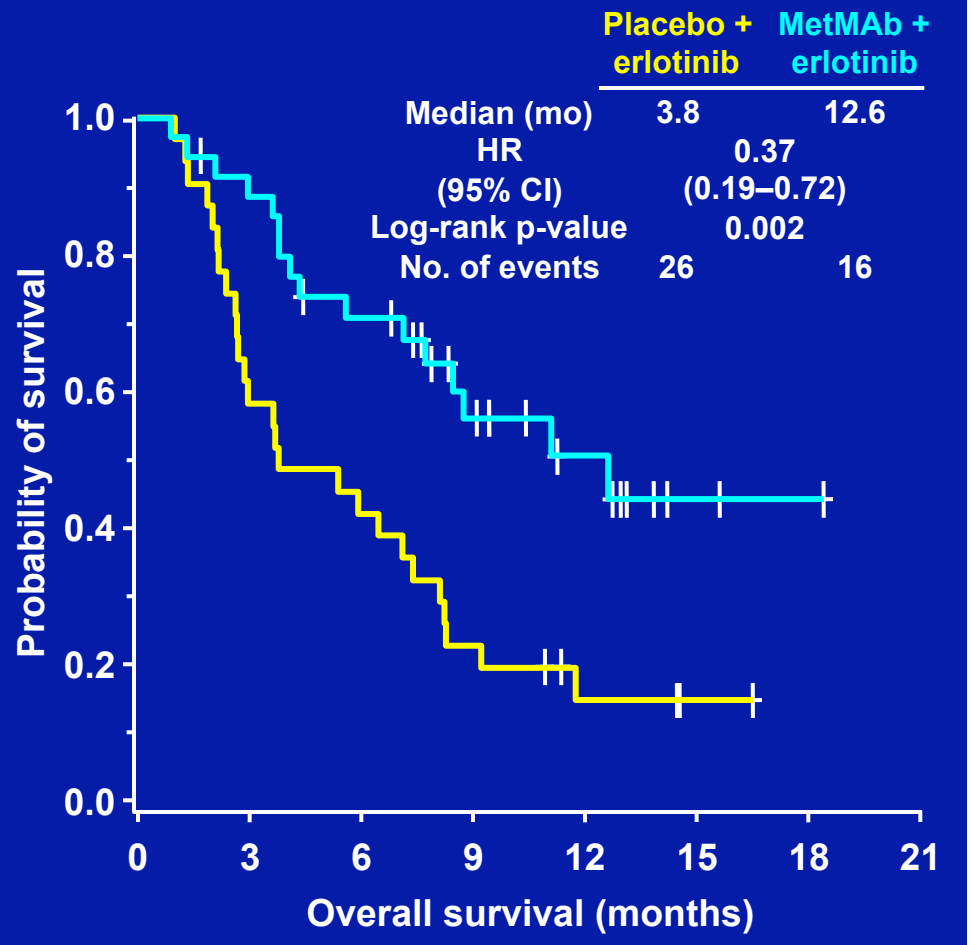
Proc ASCO, 2011

MetMAb plus erlotinib in Met Dx+ patients

PFS: HR=0.53



OS: HR=0.37



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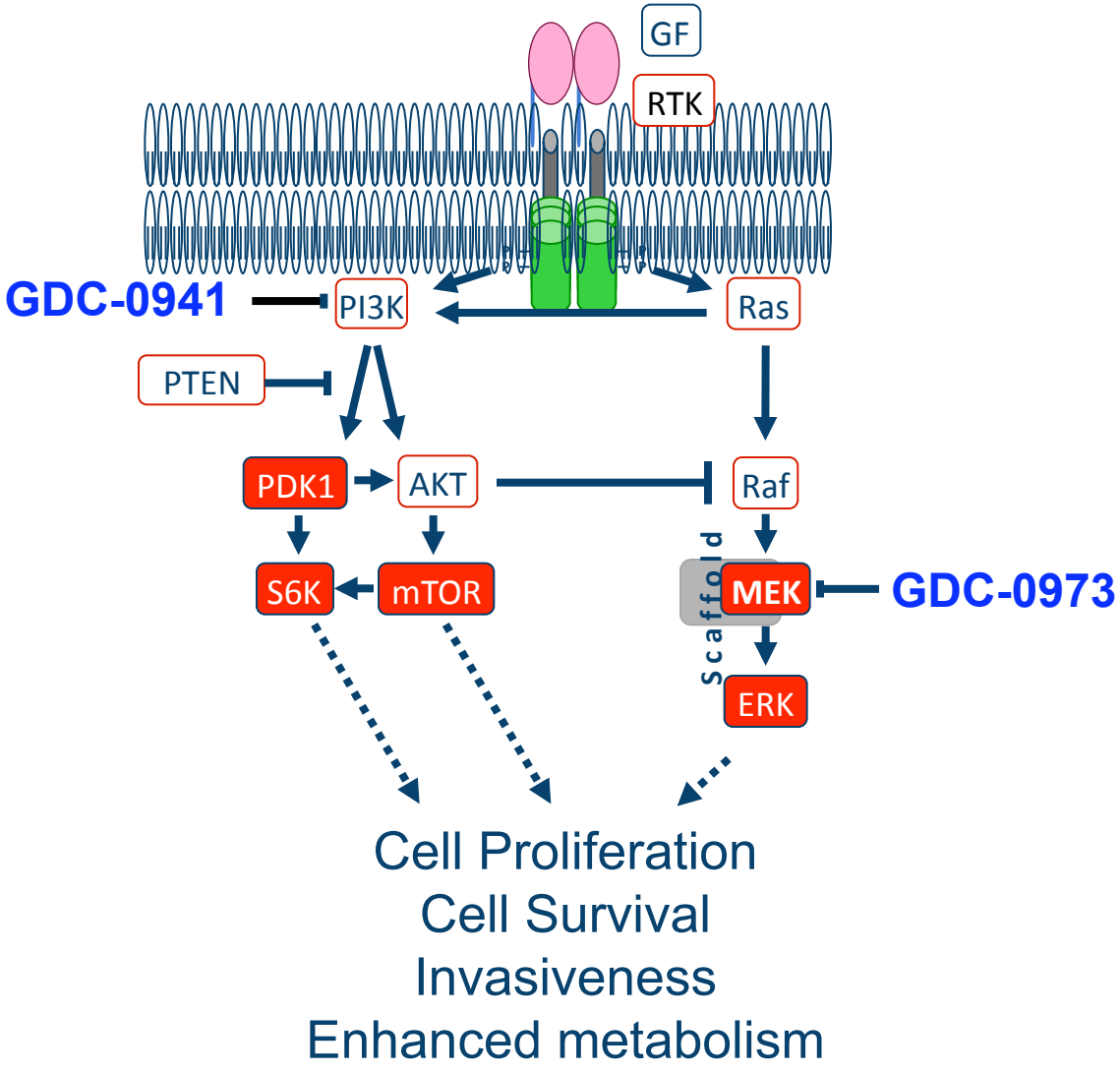
Targeting PI3K-AKT-mTOR and RAS-RAF-MEK Pathways

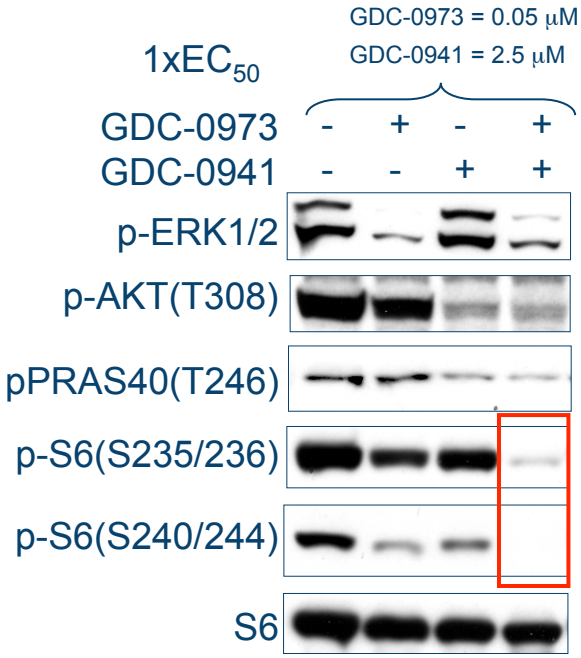


Scientific Rationale

- Pathways downstream of validated oncology drug targets (HER2, EGFR, KIT)
- Prominent mutational activation in multiple tumor types
- Extensive pathway cross-talk leading to primary or acquired resistance to single agent/single pathway therapy

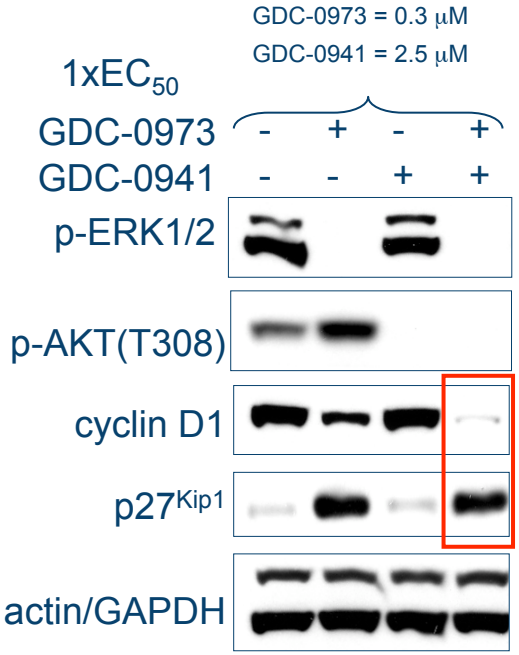
Combined effects of PI3Ki and MEKi on markers of pathway signaling, cell cycle, and apoptosis

Pathway Inhibition



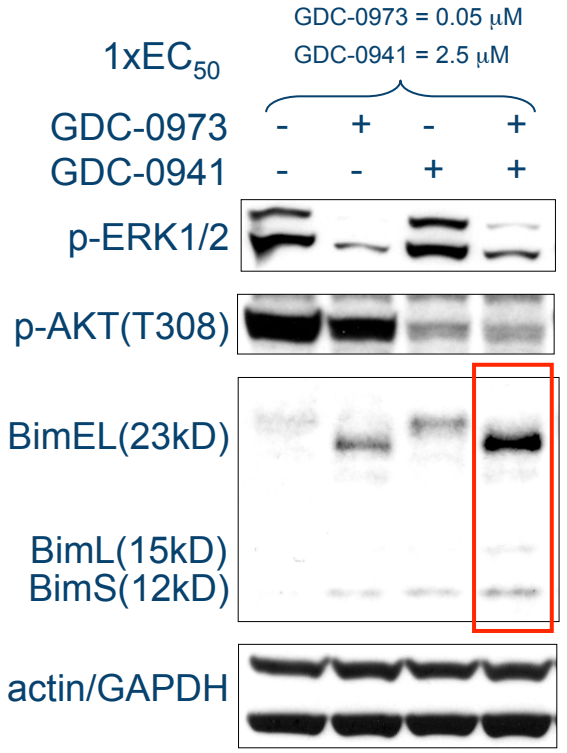
888MEL BRAFV600E

Cell cycle



624MEL BRAFV600E

Apoptosis



888MEL BRAFV600E

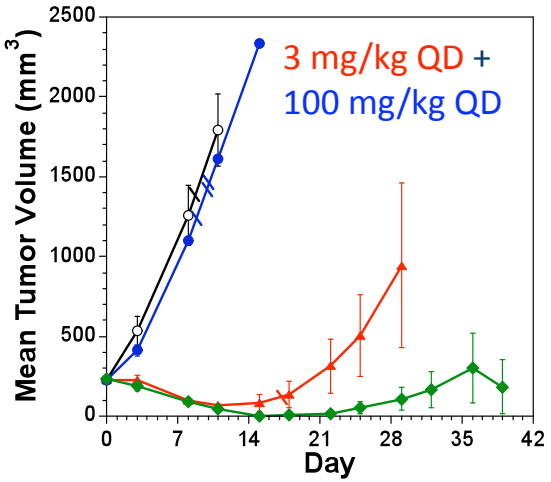
Proc ASCO, 2011

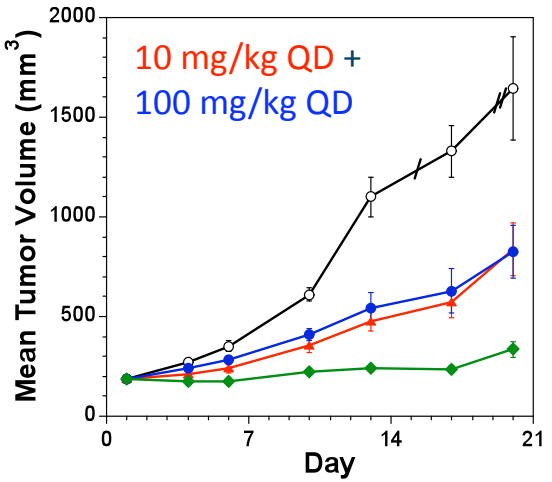
Daily (and intermittent) dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenografts

Vehicle, GDC-0973, GDC-0941, Combination

A375
$BRAF^{V600E}$
Melanoma

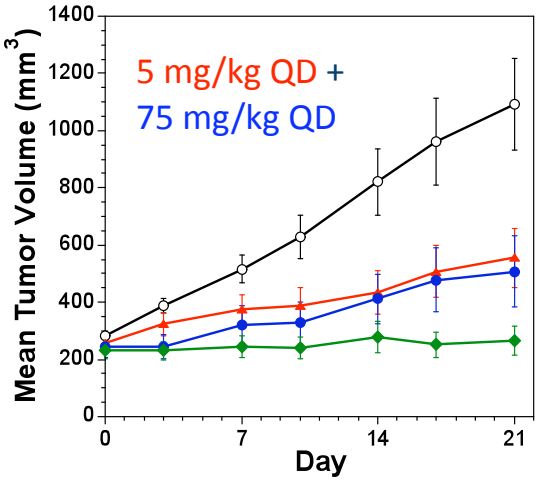
6 CR (n=10/grp)
2 PRs, 8 CRs

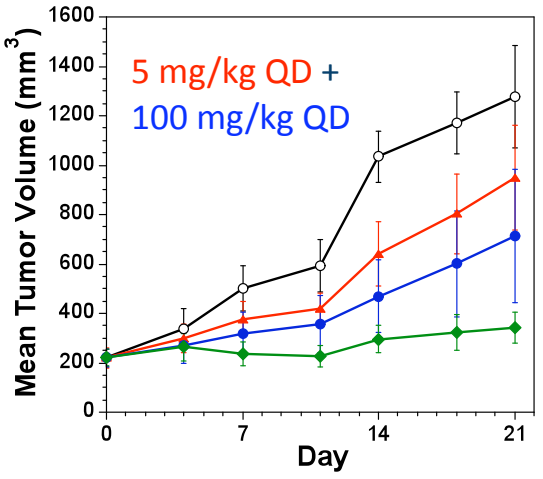




A2058
$BRAF^{V600E}$
$PTEN^{null}$
Melanoma

NCI-H2122
$KRAS^{G12C}$
NSCLC





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

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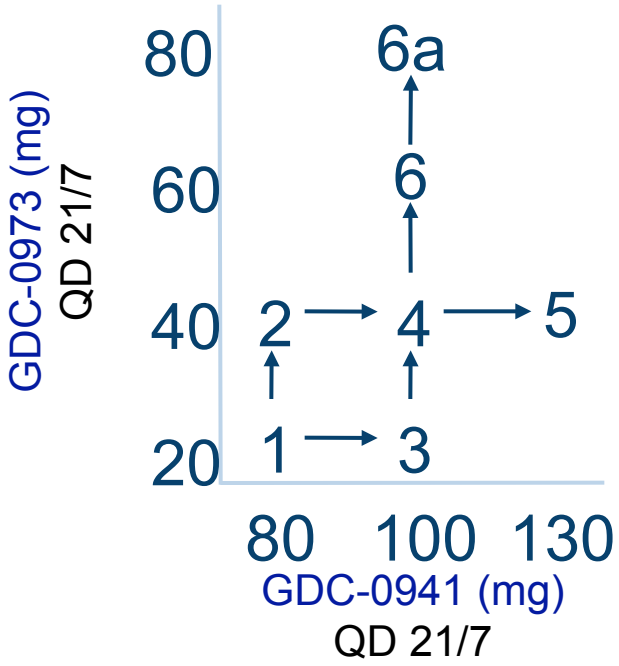
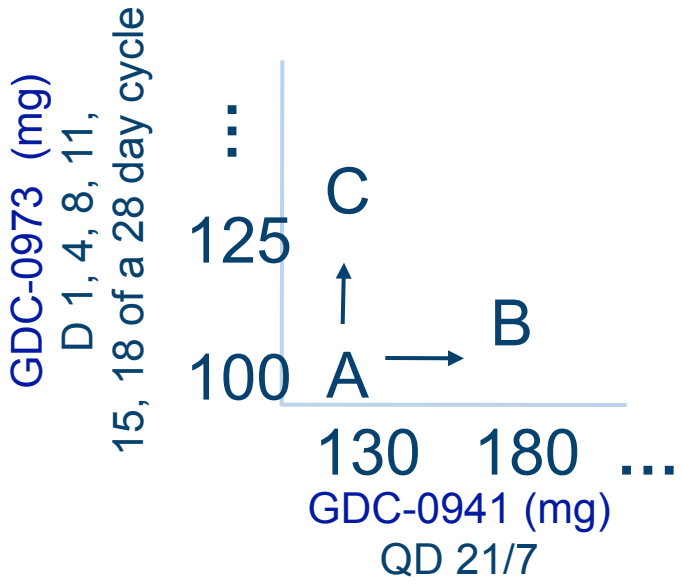
Phase Ib Study of GDC-0973 and GDC-0941 - Dose Escalation Cohorts

Dose Escalation Schema

21/7 MEKi Dosing



Intermittent MEKi Dosing



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

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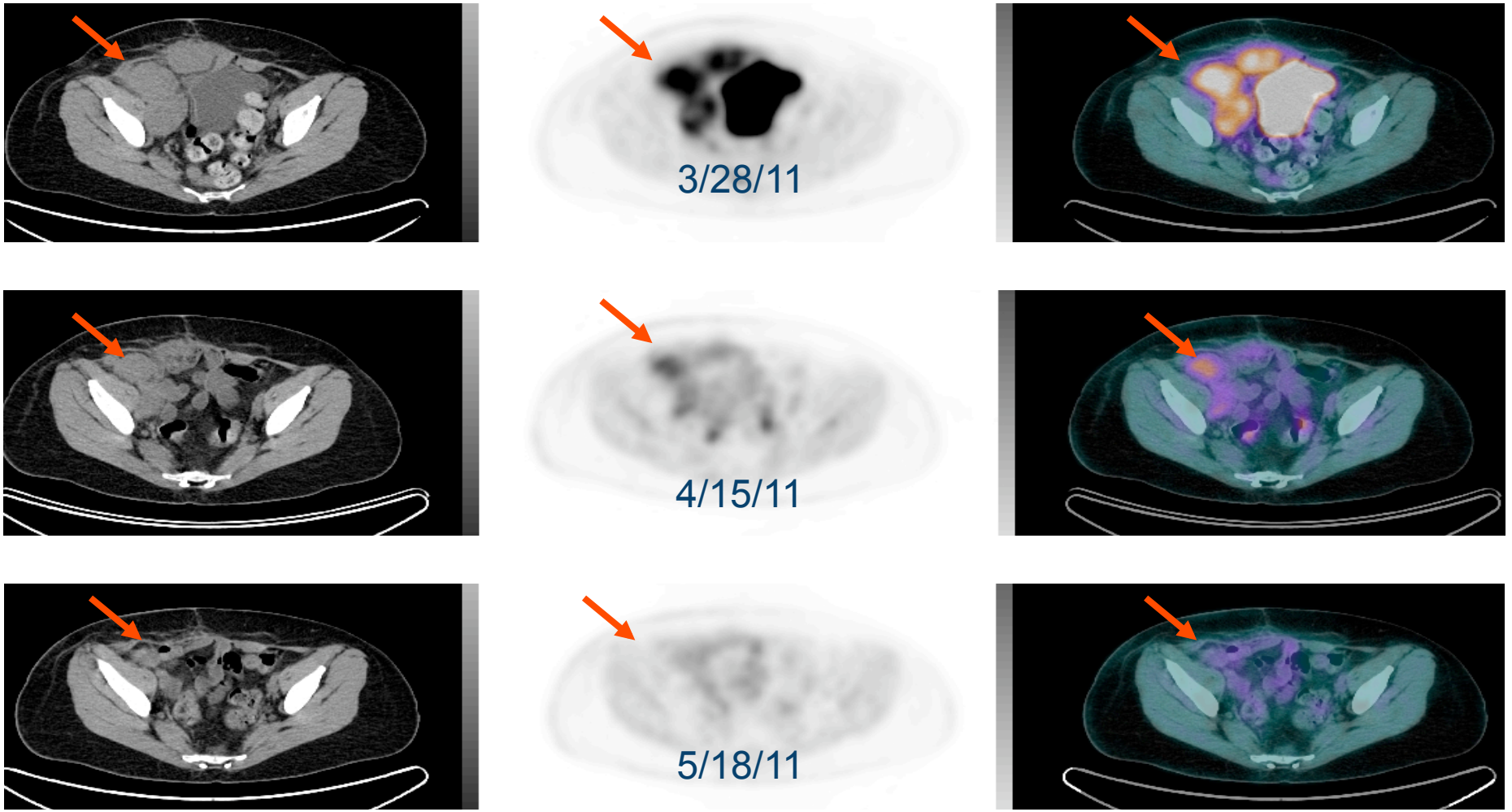
Example of anti-tumor activity in K-RAS mutant endometrial cancer

125 mg GDC-0973 intermittent + 130 mg GDC-0941 21/7



Proc ASCO, 2011

Summary and Conclusions

- Rational combination strategies have started to yield promising results in the clinic
- Success requires a strong scientific rationale and pharmacologically compatible molecules
- Early Phase Ib testing of combinations is feasible and recommended
- Efficiently identifying an optimal dose and schedule for combinations of small molecules is challenging
- Biomarkers (predictive and pharmacodynamic) for the combination should be strongly considered
- Enhanced toxicity (either additive or synergistic) will derail some combinations
- Direct collaboration between sponsors is happening at early stages of drug development to rapidly evaluate promising drug combinations