The AZ-Merck Collaboration

Institute of Medicine
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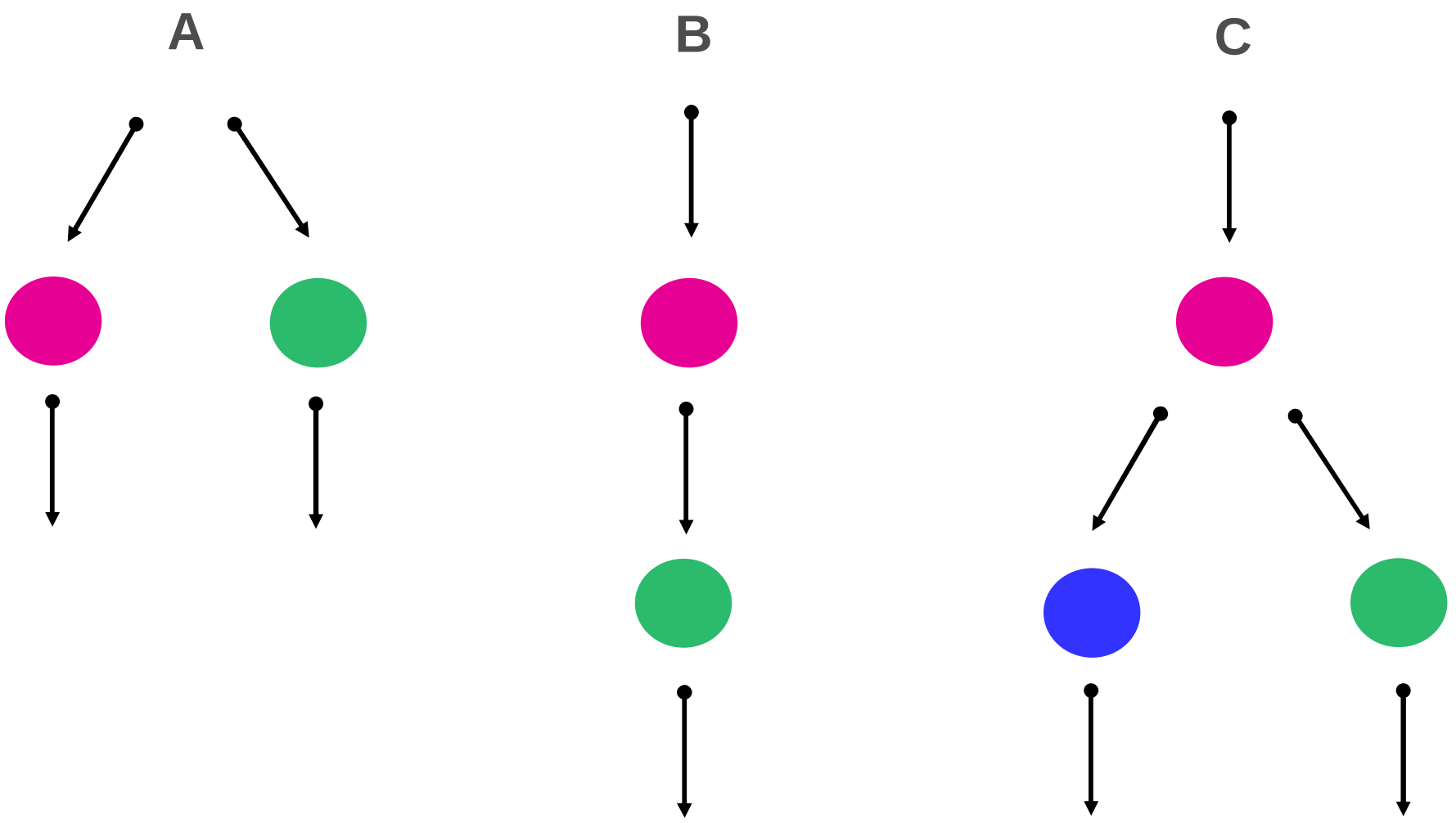
On behalf of the AZ/Merck Collaboration Team

Combination Therapy is Standard of Care in the Management of Multiple Diseases

- Combination therapy: simultaneous administration of multiple agents at fixed doses
- Improved therapeutic index
  - Greater efficacy
  - “Equivalent” or better safety and tolerability
- Combination therapy is a standard of care in multiple therapeutic areas: e.g., cancer, infectious disease, cardiovascular and metabolic diseases.

Three Molecular Targeting Strategies for Combination Therapy



Combination therapy is restricted by the pharmaceutical properties of the single agents

- Drug-drug interactions that do not interfere with desired pharmacokinetic properties
- Tolerable toxicities: complementary and overlapping
- Understanding of dosing and schedule to achieve optimal inhibition of targets and improved efficacy

- In Oncology, New Chemical Entities are commonly combined with SOC treatment for registration.

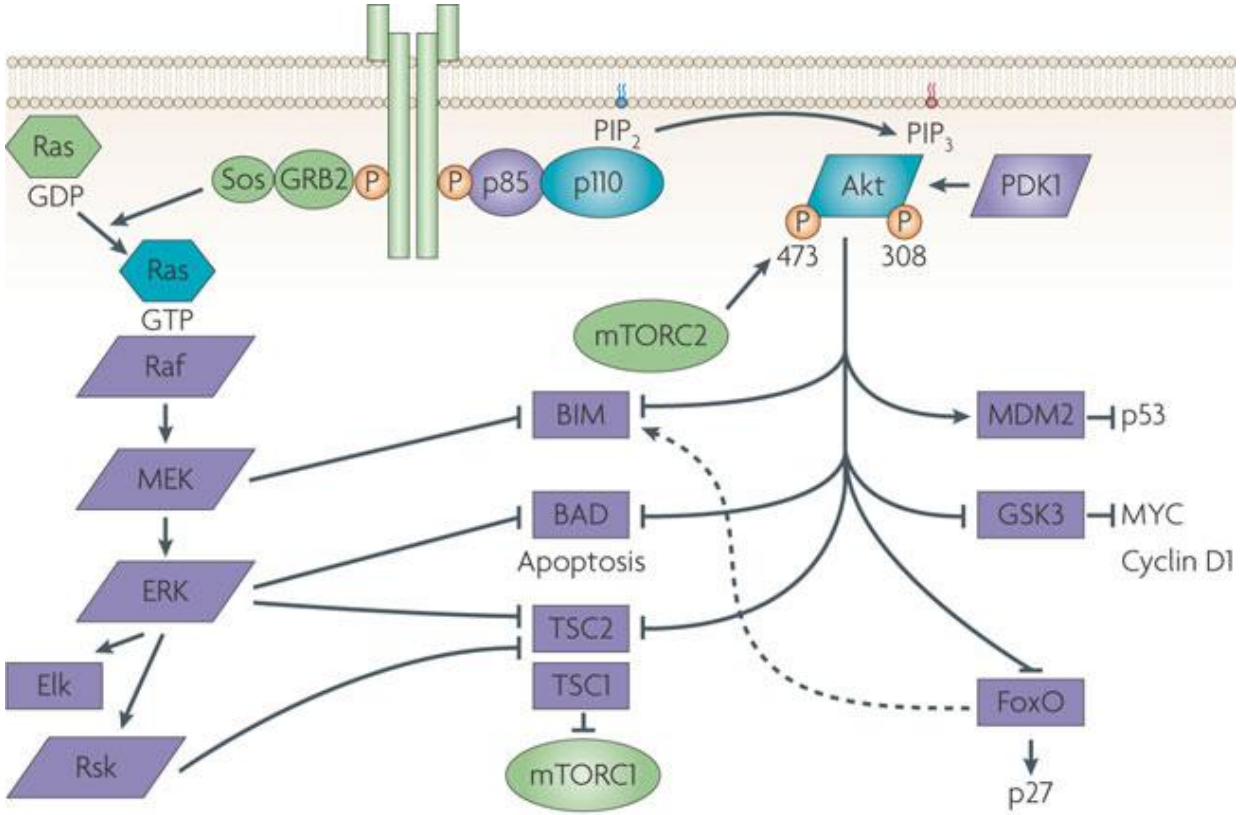
Phase III trials of targeted agents combined with standard cancer treatments

Agent	Cancer	Chemotherapy		Outcome
		Concurrent administration	Preclinical support for combination?	
Gefitinib	Lung (two trials)	Y	Y	Failed (no difference in RR and OS)[9]
Erlotinib	Lung (two trials)	Y	Y	Failed (no difference in RR and OS)[10]
	Pancreas	Y	Y	Improved survival[8]
Trastuzumab	Breast/HER2+	Y	Y	Improved survival[4]
Bevacizumab	Colon (2 trials)	Y	Y	Improved survival[5]
	Breast: first line	Y	Y	Improved survival with paclitaxel[3]
	Breast: second/third line	Y	Y	Failed (improved RR but no difference in PFS)[9]
	Lung	Y	Y	Improved survival[1]
Oblimersen	Melanoma	Y	?	Failed to improve OS[6]
Cetuximab	Head and neck	Y	Y	Failed (improved RR but no statistically significant difference in PFS)[7]
	Head and neck	Radiation	Y	Improved survival[2]

OS, overall survival; PFS, progression-free survival; RR, response rate

From Dancy and Chen, Nature Reviews Drug Discovery 2006: 5:651-659

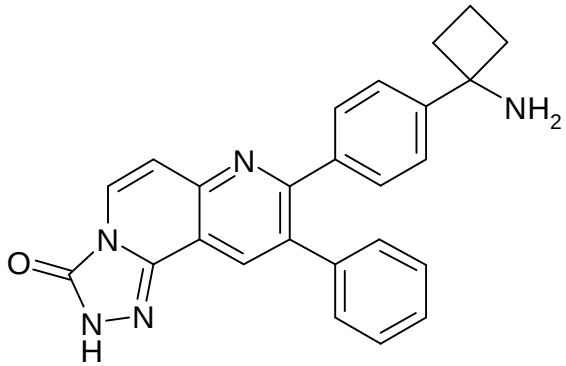
Growth Factor Signalling Pathways



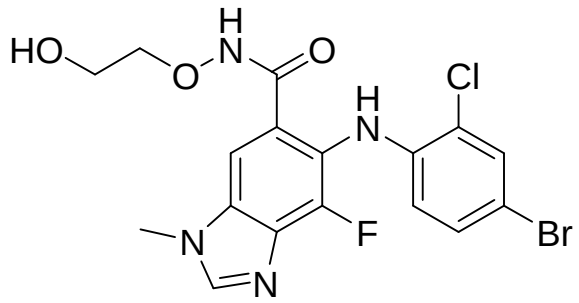
Nature Reviews | Cancer

Two allosteric kinase inhibitors

MK-2206

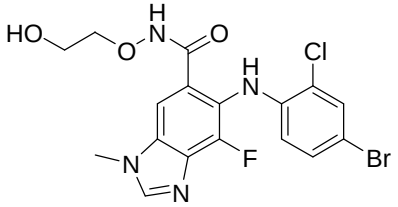


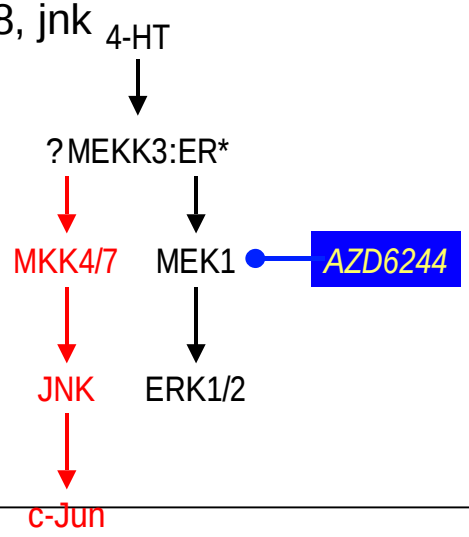
AZD-6244

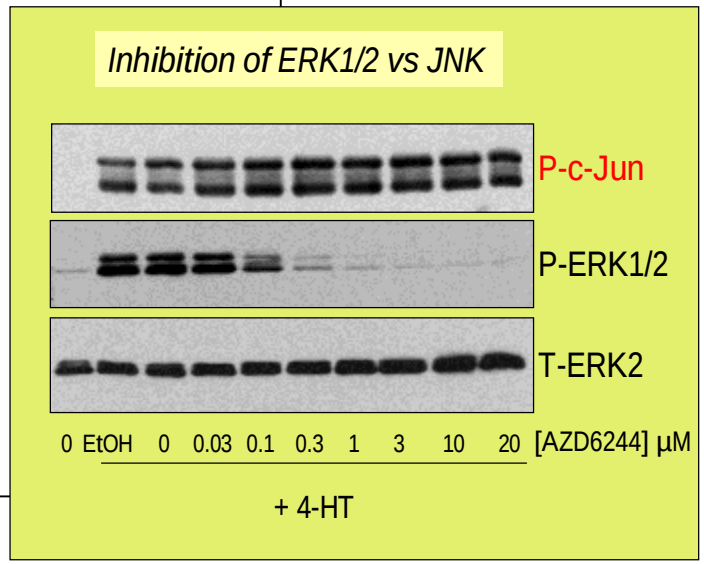


AZD6244*
Potency and Selectivity

- Tight binding uncompetitive inhibitor of MEK1/2
  - binds to an allosteric binding pocket adjacent to MgATP binding site
  - 10 – 14nM IC_{50}
- Highly selective for the MEK/ERK pathway
  - Cellular selectivity demonstrated over other pathways
    - MEK5, p38, jnk

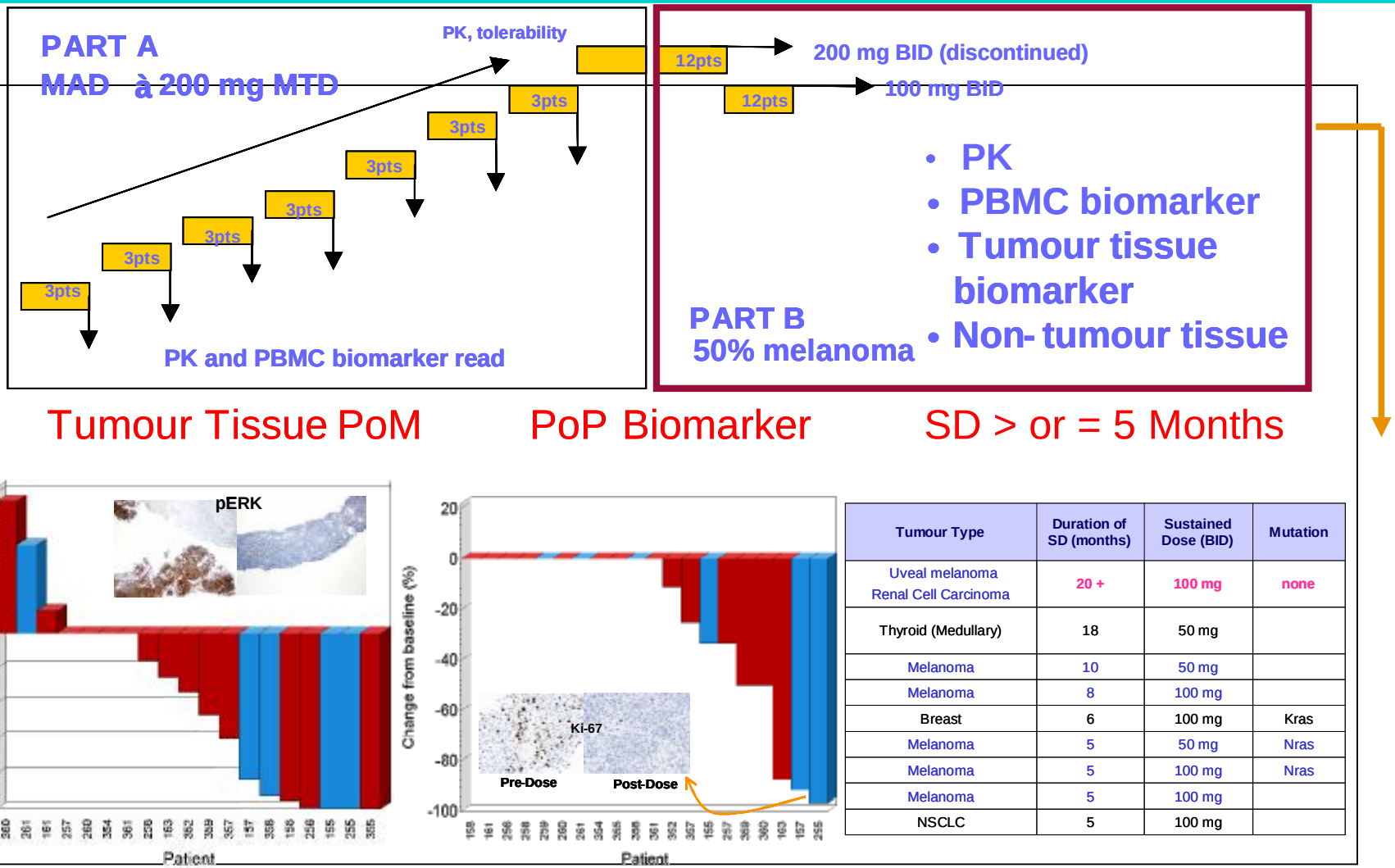






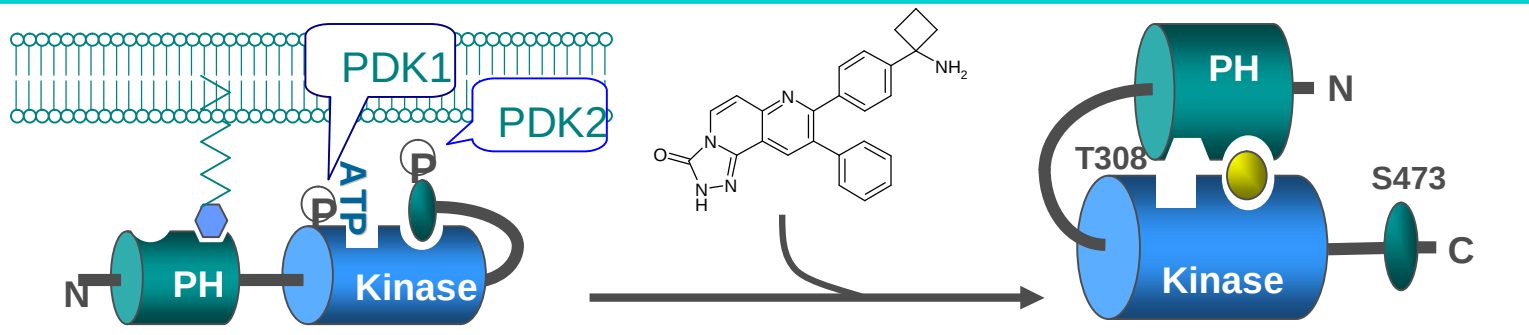
* ARRY-142886

AZD6244 Phase I Clinical Trial



Tumour Type	Duration of SD (months)	Sustained Dose (BID)	Mutation
Uveal melanoma Renal Cell Carcinoma	20 +	100 mg	none
Thyroid (Medullary)	18	50 mg	
Melanoma	10	50 mg	
Melanoma	8	100 mg	
Breast	6	100 mg	Kras
Melanoma	5	50 mg	Nras
Melanoma	5	100 mg	Nras
Melanoma	5	100 mg	
NSCLC	5	100 mg	

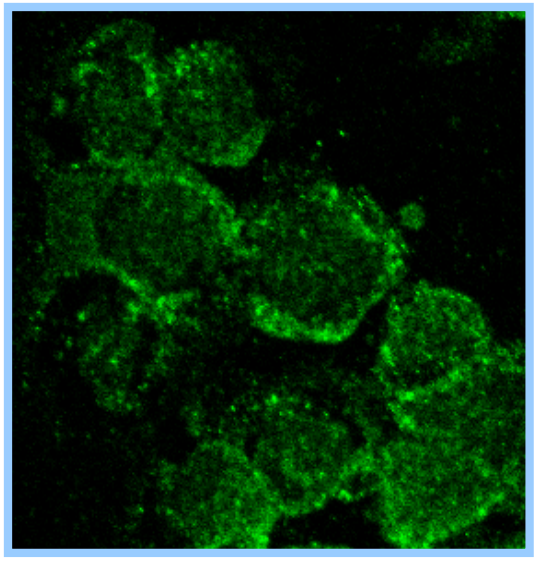
MK-2206: an Allosteric and Selective AKT inhibitor



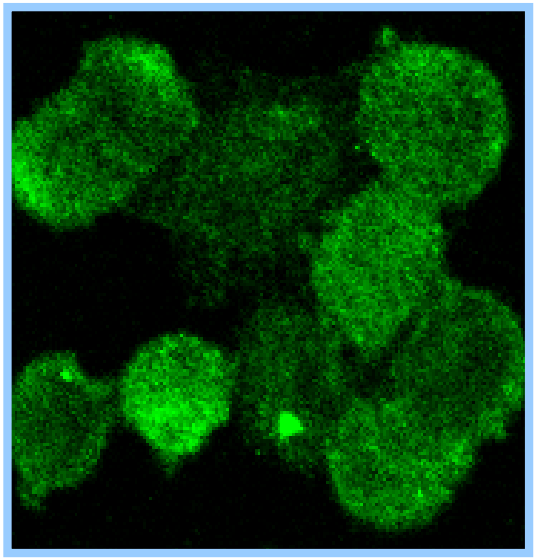
Active AKT

MK-2206

Inhibited AKT
(Incapable of membrane localization)

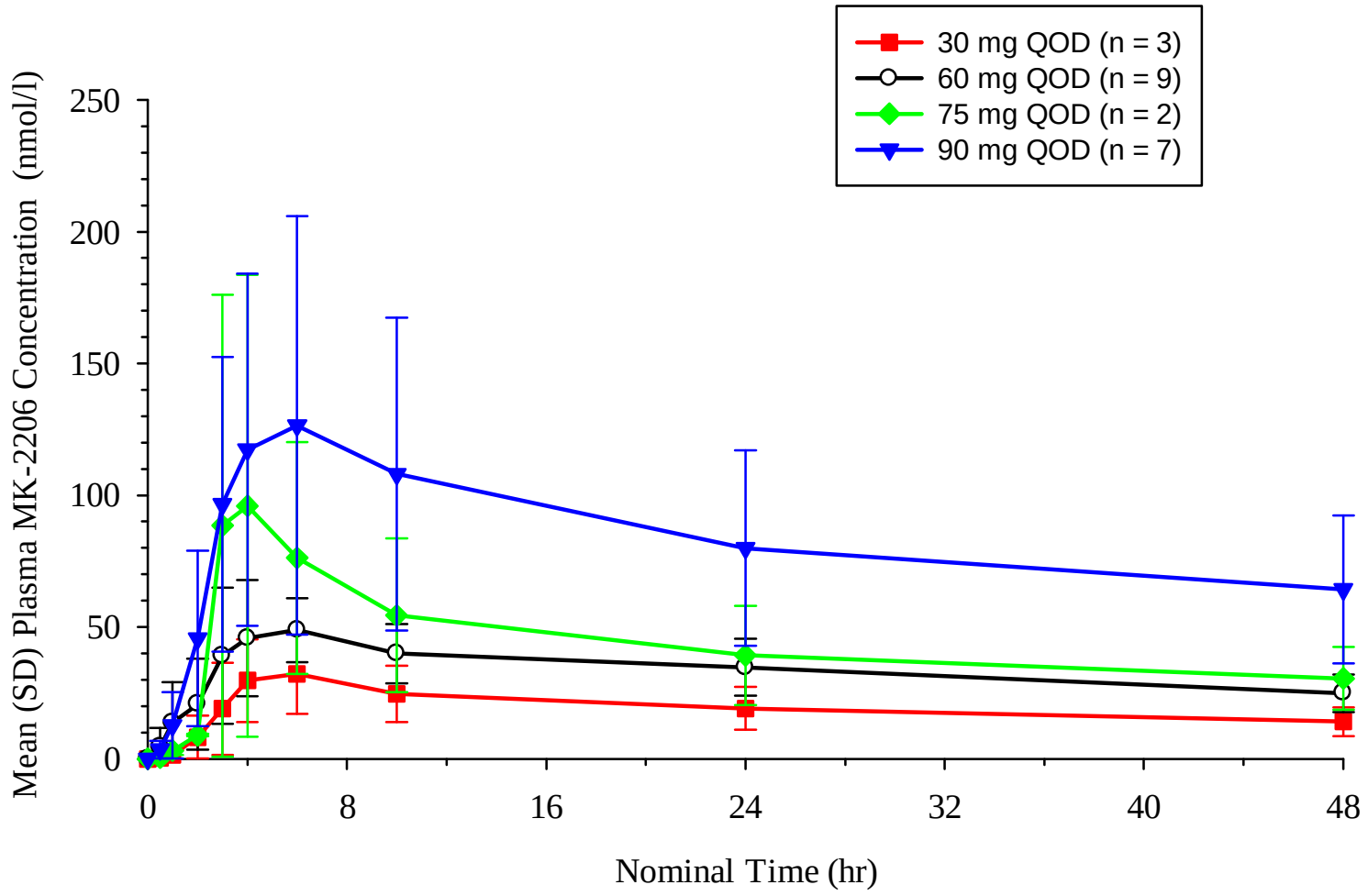


Vehicle



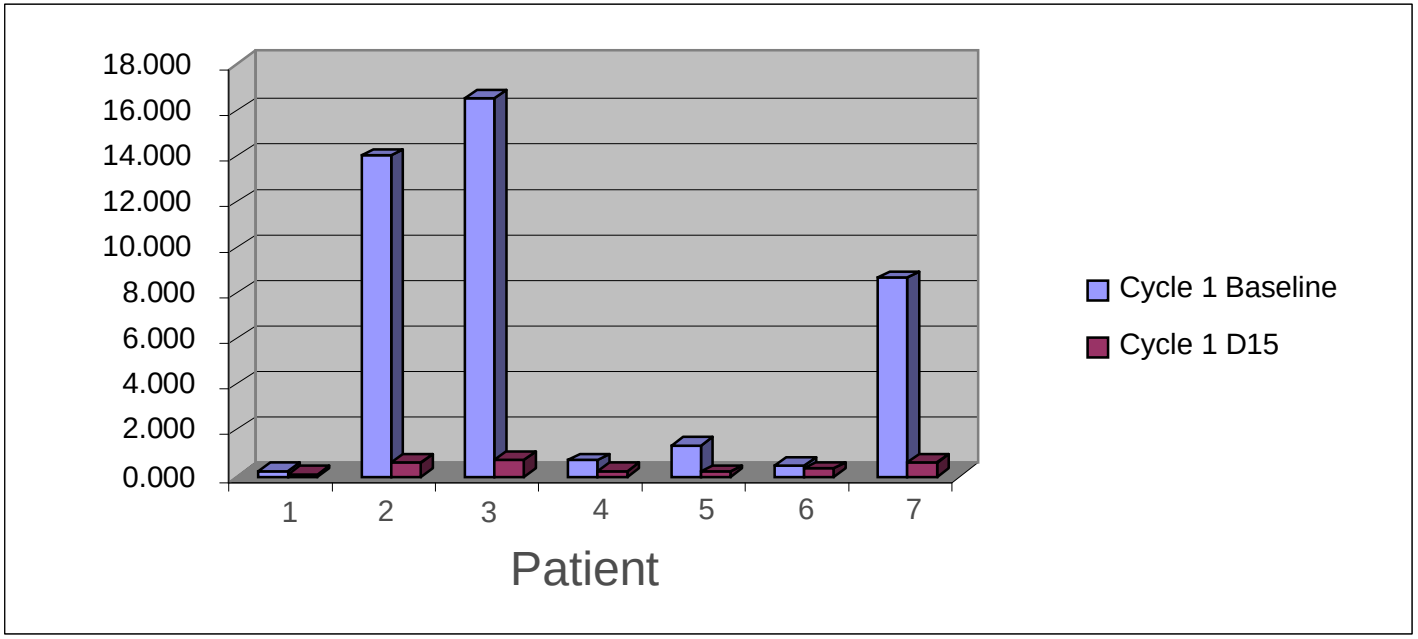
AKTi-1/2C
tool compound

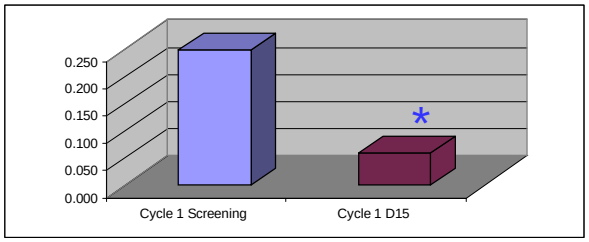
Single Dose Human PK of MK-2206



PD Summary of MK-2206
60 mg QOD – Tumor

~ 90% tumor pAkt inhibition in 5 out of 7 patients





* C1D15 pAKT value was below LLOD

Pt 1 – Kaposi sarcoma
Pt 2 – DSRCT sarcoma
Pt 3 – Pheochromocytoma
Pt 4 – Breast
Pt 5 – Breast
Pt 6 – Melanoma
Pt 7 – Breast

Collaboration Announced

THE WALL STREET JOURNAL.

MONDAY, JUNE 1, 2009

AstraZeneca, Merck to Test Cancer Drugs in 'Cocktail'

By Ron Winslow

ORLANDO, Fla. -- Merck & Co. and AstraZeneca PLC plan to announce Monday an unusual agreement to test a potential new cancer regimen composed of two experimental agents that are still in early human trials and several years away from reaching the market.

The collaboration, sparked by an encounter between scientists from the companies in an airport security line in Dublin, is based on laboratory evidence that the two compounds given in combination could have a much more potent effect against tumors than each may have as separate treatments. Merck and AstraZeneca scientists say the treatment could prove effective against several types of cancer.

The drugs -- MK-2206 from Merck and AZD6244 from AstraZeneca -- are candidates for the burgeoning arsenal of so-called targeted treatments that is transforming cancer care by disrupting whether combining the drugs will improve survival over Nexavar alone in patients with advanced liver cancer.

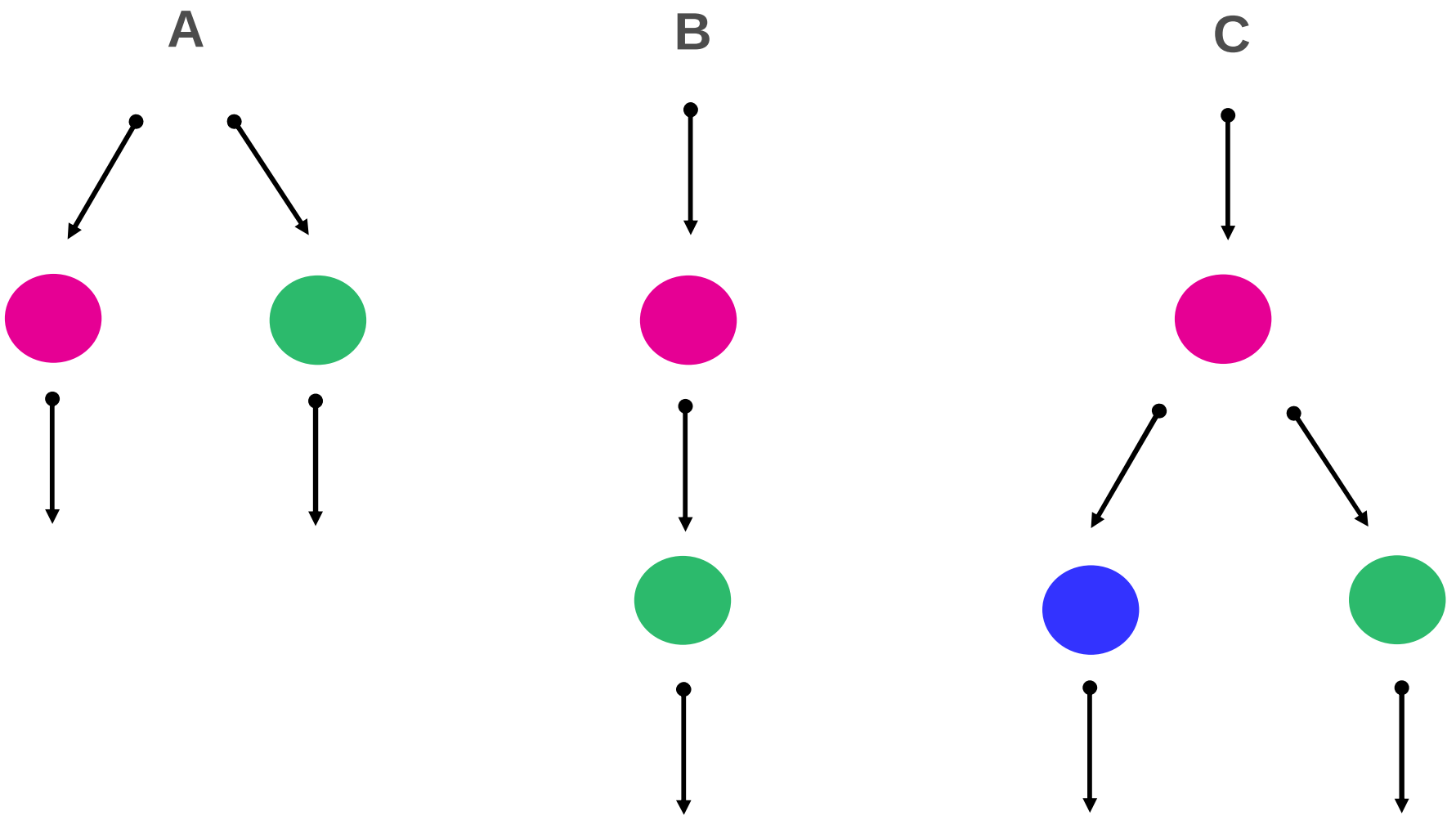
Merck, Whitehouse Station, N.J., and AstraZeneca are announcing the collaboration during the annual scientific meeting of the American Society of Clinical Oncology in Orlando. They say they are the first large pharmaceutical companies to join forces to test a combination treatment with compounds so early in development. AZD6244, which blocks a pathway known as MEK, has been tested in early-to-midstage trials in patients with skin, colorectal and lung cancers. Merck's drug, which inhibits a pathway called Akt, has been shown to have activity against tumors in a handful of patients in an early-stage test.

MEK and Akt "are two critical pathways in oncogene signaling," said Gary Gilliland, senior vice president and franchise head for oncology at Merck Research Laboratories. "If we shut down compounds together, he seemed "bewildered," she recalls. It wasn't public knowledge that Merck was developing an Akt inhibitor. But by the end of the conversation, they both agreed to take the idea to their respective companies. "We immediately clicked," she says. In an email message, Dr. Smith said he recalls thinking that being hailed as "the MEK guy" was an unusual greeting in a public place.

Even though AstraZeneca was working on its own Akt blocker and Merck was developing an MEK inhibitor, the companies say they determined that joining forces would offer a chance to get a treatment to market quicker.

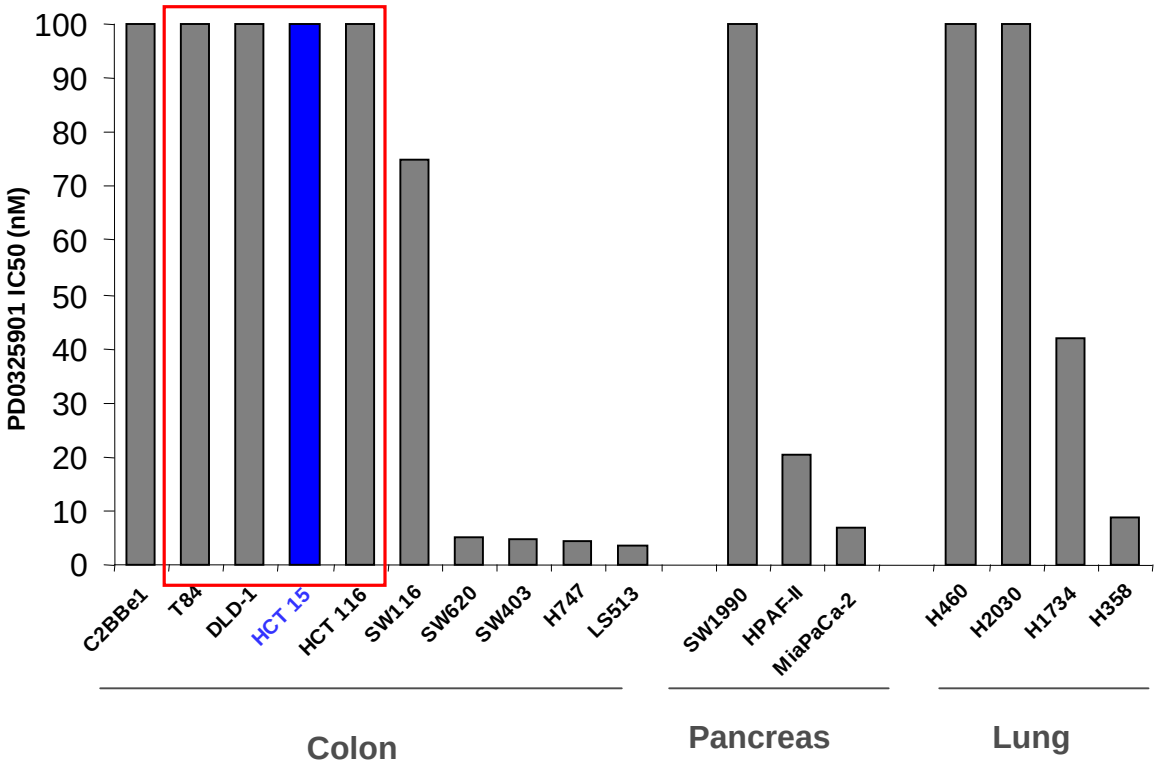
The companies initially crafted an agreement to do lab studies to see if the science supported moving ahead with human tests of the combination. They cleared that hurdle. The new pact calls for the companies to share costs of testing the compounds in an early-stage

Dosing, Sequence, Context?



Genetic Background of Tumor Cells determines response to MEK/MAPK Inhibition

Cell Line	Colon	
C2BBe1	WT	WT
T84	K-Ras (G13D)	PI3K (E545K)
DLD-1	K-Ras (G13D)	PI3K (E545K)
HCT-15	K-Ras (G13D)	PI3K (E545K)
HCT 116	K-Ras (G13D)	PI3K (H1047R)
SW1116	K-Ras (G12A)	
SW 620	K-Ras (G12V)	
SW403	K-Ras (G12V)	
H747	K-Ras (G13D)	
LS513	K-Ras (G12D)	
	Pancreas	
SW 1990	K-Ras (G12D)	
HPAF-II	K-Ras (G12D)	
Mia PaCa-2	K-Ras (G12C)	
	NSCLC	
H460	K-Ras (Q61K)	PI3K (E545K)
H2030	K-Ras (G12C)	
H1734	K-Ras (G13C)	
H358	K-Ras (G12C)	



Data from Neal Rosen, MSKCC

Cell Biomarker Discovery: multiple tumor cell types respond to dual inhibition by a MEKi and an AKTi

Lung	CI at: ED50	ED75	ED90
A427	0.07	0.04	0.04
A549	0.06	0.05	0.06
CAL12T	0.23	0.11	0.09
CALU1*	0.93		
CORL23	0.23	0.18	0.14
DV90	0.22	0.13	0.11
EBC-1	0.15	0.12	0.12
H1155	0.37	0.36	0.37
H1593			
H1650	1.3		
H1975	0.04	0.004	0.008
H1993	0.04	0.01	0.004
H2030	0.19	0.22	0.26
H2009	0.05	0.03	0.02
H2122	0.23	0.16	0.12
H23	0.26	0.26	0.35
H28	0.16	0.12	0.09
H460	0.02	0.06	0.16
H596	0.29	0.18	0.12
KNS62*	0.15	0.15	0.19

Colon	CI at: ED50	ED75	ED90
CACO2	0.29	0.31	0.34
COLO201	1.6	0.87	0.47
COLO205	0.43	0.23	0.13
DLD1	0.19	0.13	0.09
DKO3	0.04	0.03	0.03
H-630	0.89		
H-716	0.058	0.018	0.006
HCT8	0.1	0.1	0.13
HCT15	0.15	0.22	0.33
HCT116	0.49	0.91	
HKH2	0.17	0.17	0.18
HT29	0.52	0.27	0.17
LOVO	0.12	0.59	
RKO	0.21	0.13	0.08
SKCO1	0.23	0.22	0.2
SW48	0.11	0.07	0.05
SW837	0.1	0.04	0.03
SW948	0.13	0.11	0.1
T84	0.61	0.88	1.3

Melanoma	CI at: ED50	ED75	ED90
A2058	0.17	0.15	0.14
A375	0.51	0.44	1.03
SKMEL-28	0.19	0.37	0.72
SKMEL-5	0.16	0.096	0.19
UACC-62	0.31	0.08	0.02
A7	0.61	0.41	0.5
HMCB	0.52	0.48	0.45
HT-144	0.53	0.28	0.15

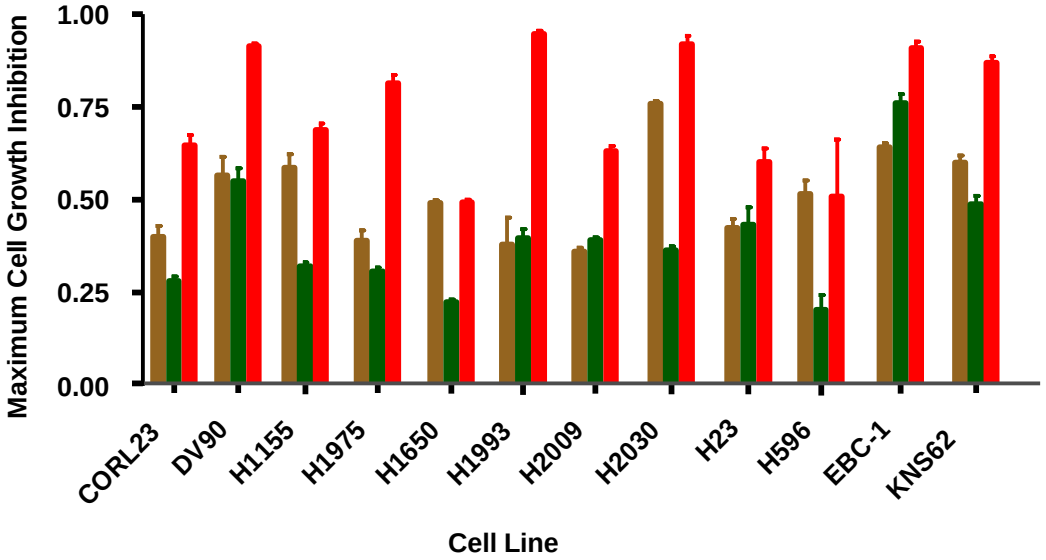
Pancreatic	CI at: ED50	ED75	ED90
ASPC-1	0.13	0.17	0.26
BX-PC3	0.14	0.2	0.55
CAPAN2			
HPAF-II	0.07	0.06	0.061
KP-3	0.6		
MIA-PACA	0.25	0.48	1.4
PANC1	0.12	0.09	0.06
PL-45	0.04	0.03	0.02

Breast	CI at: ED50	ED75	ED90
BT20	0.54	0.58	0.64
BT549	0.71	0.68	0.7
Cal51	0.73	0.85	0.98
CAL85	0.3	0.31	0.34
CAL120	0.32	0.92	
FR2	1.1		
HS578T	0.42	0.67	1.1
MT3			
SVCT	0.12	0.23	0.44
HCC38			
HCC70	0.26	0.1	0.04
MDA231	1.2	0.99	0.82
MDA468	0.71	0.46	0.3

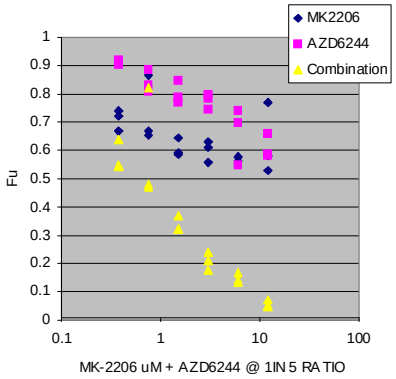
<0.1	very strong synergism
0.1-0.3	strong synergism
0.3-0.7	synergism
0.7-0.9	moderate to slight synergism
0.9-1.1	nearly additive
1.1-1.45	slight to moderate antagonism
1.45-3.3	antagonism
>3.3	strong antagonism

Lung=Pancreatic>Colon>Melanoma>Breast

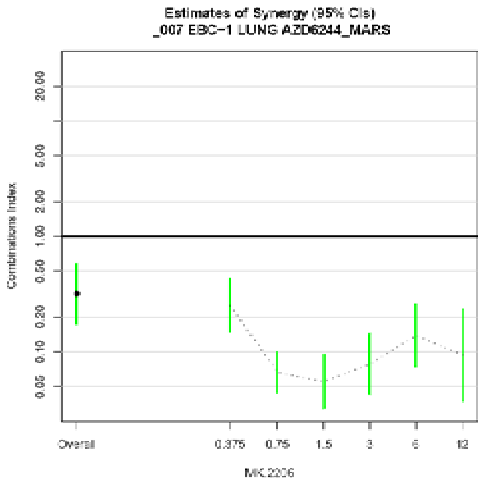
A Combination Effect from Dual Inhibition can be observed across the dose range



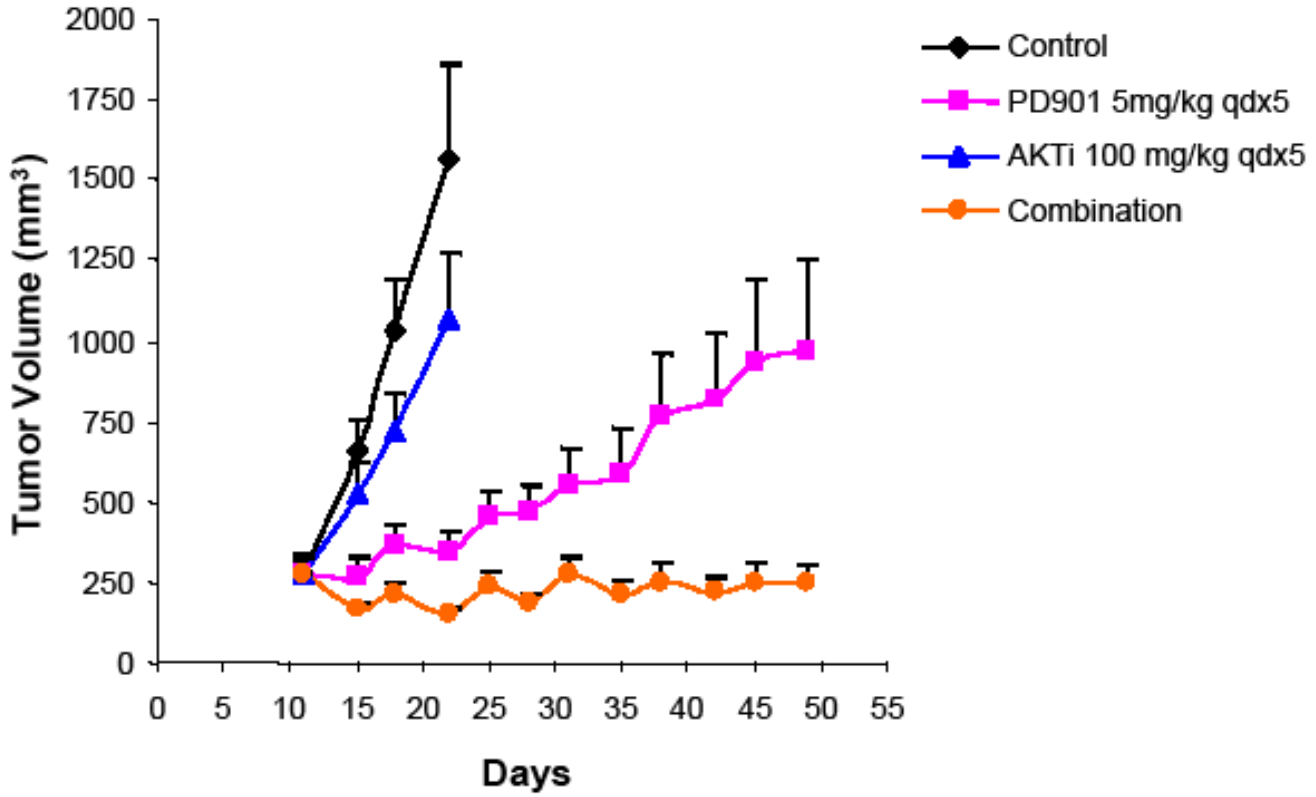
Combination effect can be observed in cells that exhibit montherapy resistance



Synergy Detected across the Dose range



AKTi in combination with MEK inhibitor synergistically suppresses SKMel-11 (PTEN mut, B-Raf mut) melanoma xenograft growth in vivo



Neal Rosen

Phase I Study Initiated

SAN ANTONIO BUSINESS JOURNAL
THE ESSENTIAL BUSINESS TOOL

Tuesday, January 5, 2010

Merck, AstraZeneca pick START to test anticancer compound

South Texas Accelerated Research Therapeutics **(START) has enrolled its first patient in a phase 1 clinical trial of a combination anticancer regimen made up of two investigational compounds.**

The two drugs are being developed by Merck & Co. Inc. **and** AstraZeneca**. The two pharmaceutical companies announced in June 2009 that they would collaborate on this project.**

The START Center for Cancer Care in San Antonio was chosen as the first phase 1 center to test the drug combination. START specializes in conducting Phase 1 clinical trials for oncology drugs.

Preclinical evidence showed that the two compounds (MK-2206 and AZD6244) could enhance their anticancer properties.

The agreement between Merck and AstraZeneca is significant, say START officials, because it involves two major pharmaceutical companies collaborating at an early stage of drug development.

Usually, combinations of anticancer agents would only be studied in clinical trials when one component is at a late stage of development or when one compound has already received marketing approval, officials say.

“This one-of-a-kind study, with two separate pharmaceutical companies sharing their novel agents for this one clinical trial performed at START, represents an exciting step forward for the betterment of cancer research, and most of all, patient care,” says Anthony Tolcher, clinical director of START and principal investigator for this trial.

Features of the Collaboration Agreement

- Staged agreement: preclinical and clinical.
- Joint governance, decision rights and shared costs.
- Freedom of operation for both parties: multiple combination studies with similar agents can occur independently and in parallel.
- Intellectual Property shared by inventors.

Opportunities and Challenges

- Recent advances in disease understanding and the availability of selective, novel targeted therapies can enable early testing of drug combinations for the treatment of specific cancers.

- To date, co-registration of two unapproved agents for the treatment of cancer is unprecedented.

Thanks to

- The AZ/Merck JSC and JDC

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- Paul Smith
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- Li Yan
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- Jay Gibbs
- David Harrison
- YuCynthia Jean-Louis
- Joan LaSota

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- The AZ MEK Team

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  - Kristopher Frese
  - Natalie Cook
  - David Tuveson

- MSKCC
  - Neal Rosen

- D. Gary Gilliland
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