Breakthroughs in Basic Research

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HARVARD MEDICAL SCHOOL

Breakthroughs in Basic Research

- Squamous Cell Lung Cancer
- New Oncogenes in adenocarcinoma
- Co-clinical trials to guide clinical drug development

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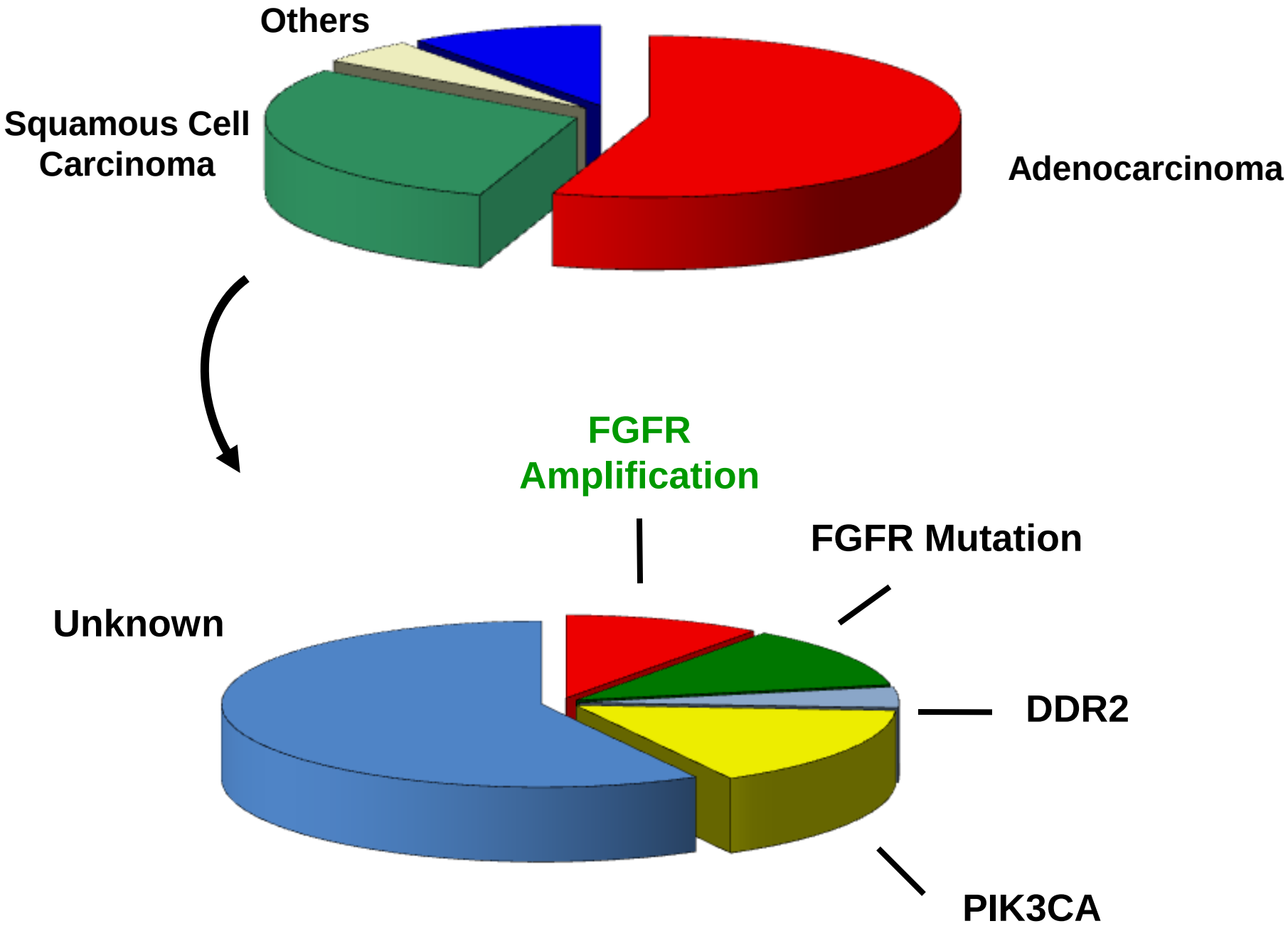
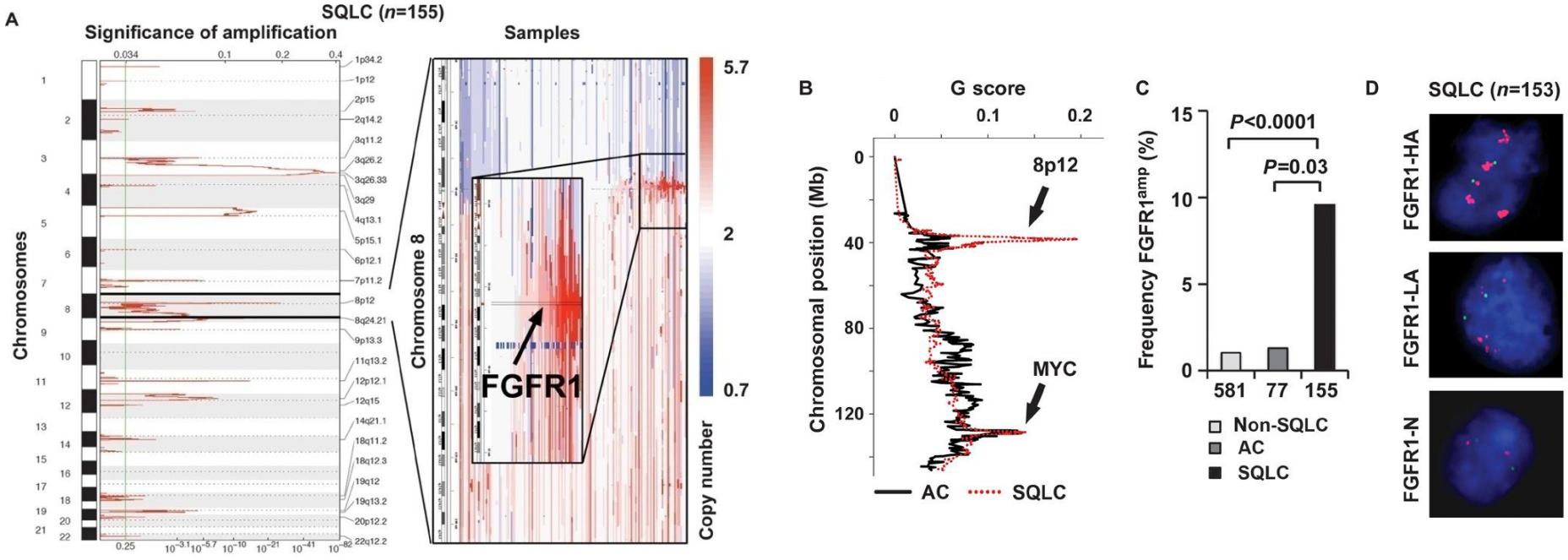
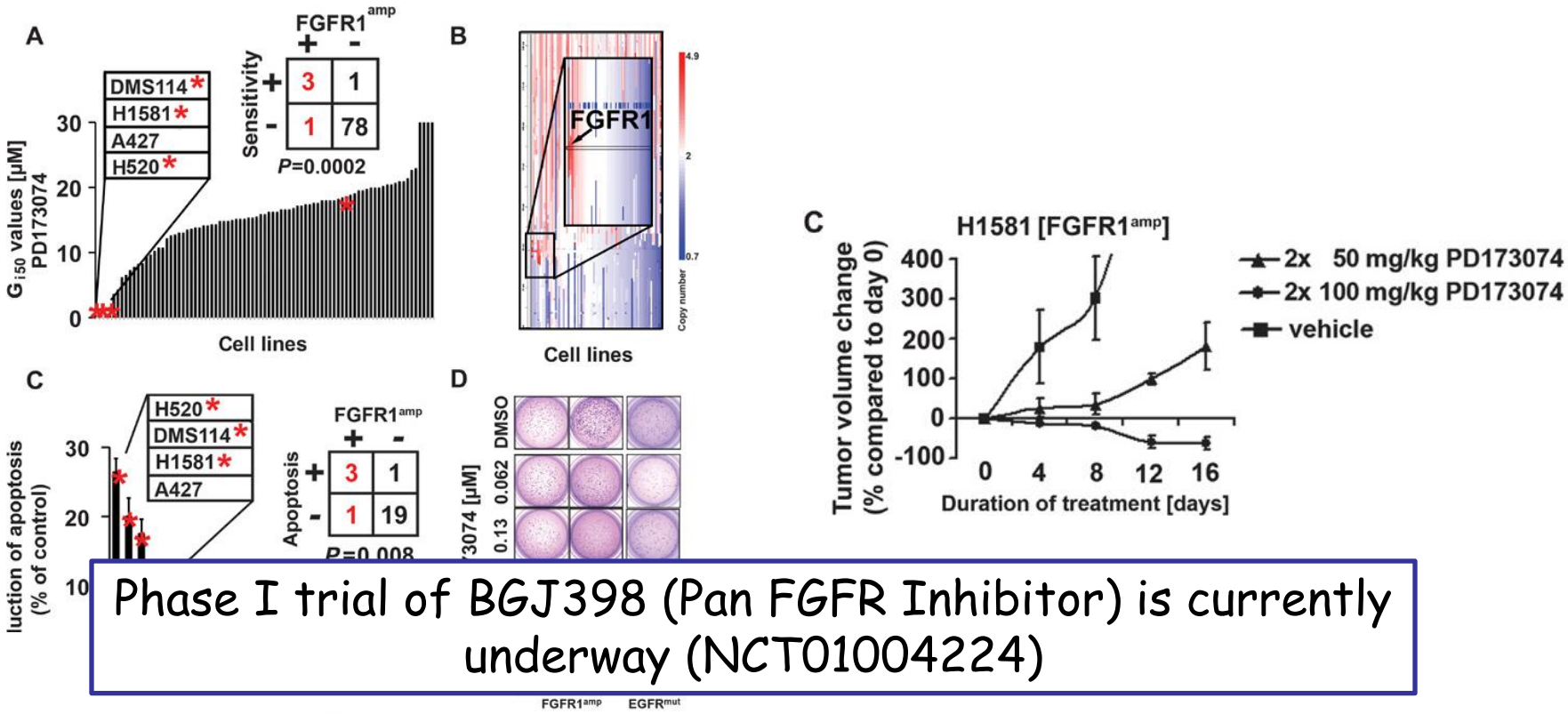

Others
Squamous Cell Carcinoma
Adenocarcinoma
FGFR Amplification
FGFR Mutation
Unknown
DDR2
PIK3CA

FGFR1 Amplification in a Subset of Squamous Cell Cancers



Weiss J et al. Sci Transl Med 2010

FGFR1 Inhibitor is Effective in FGFR1 Amplified Cells

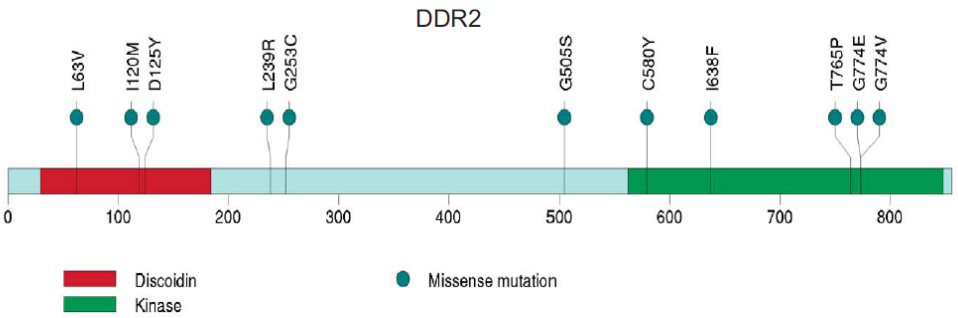


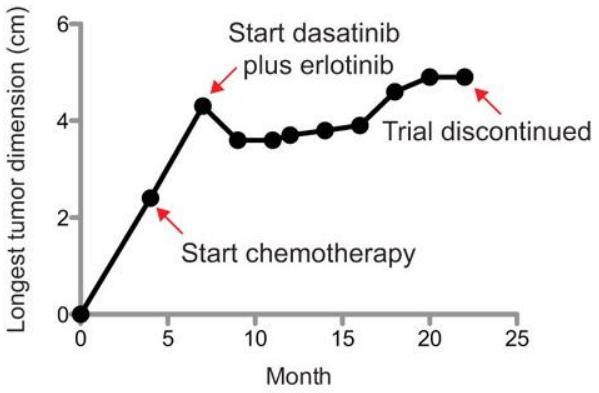
Phase I trial of BGJ398 (Pan FGFR Inhibitor) is currently underway (NCT01004224)

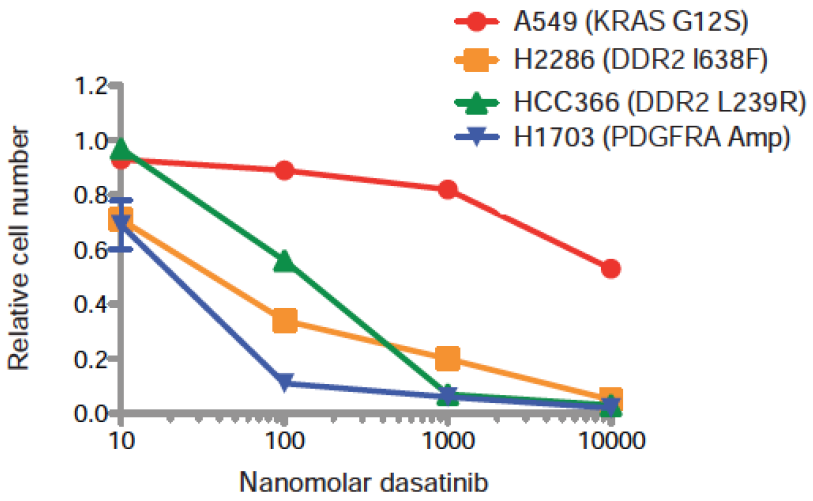
In Vitro **In Vivo**

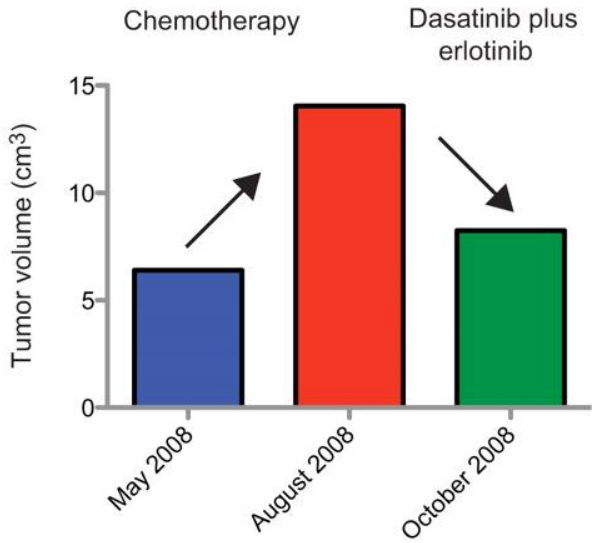
Weiss J et al. Sci Transl Med 2010

Sanger sequencing of the tyrosine kinome of lung SqCCs identifies recurrent mutations in *DDR2*



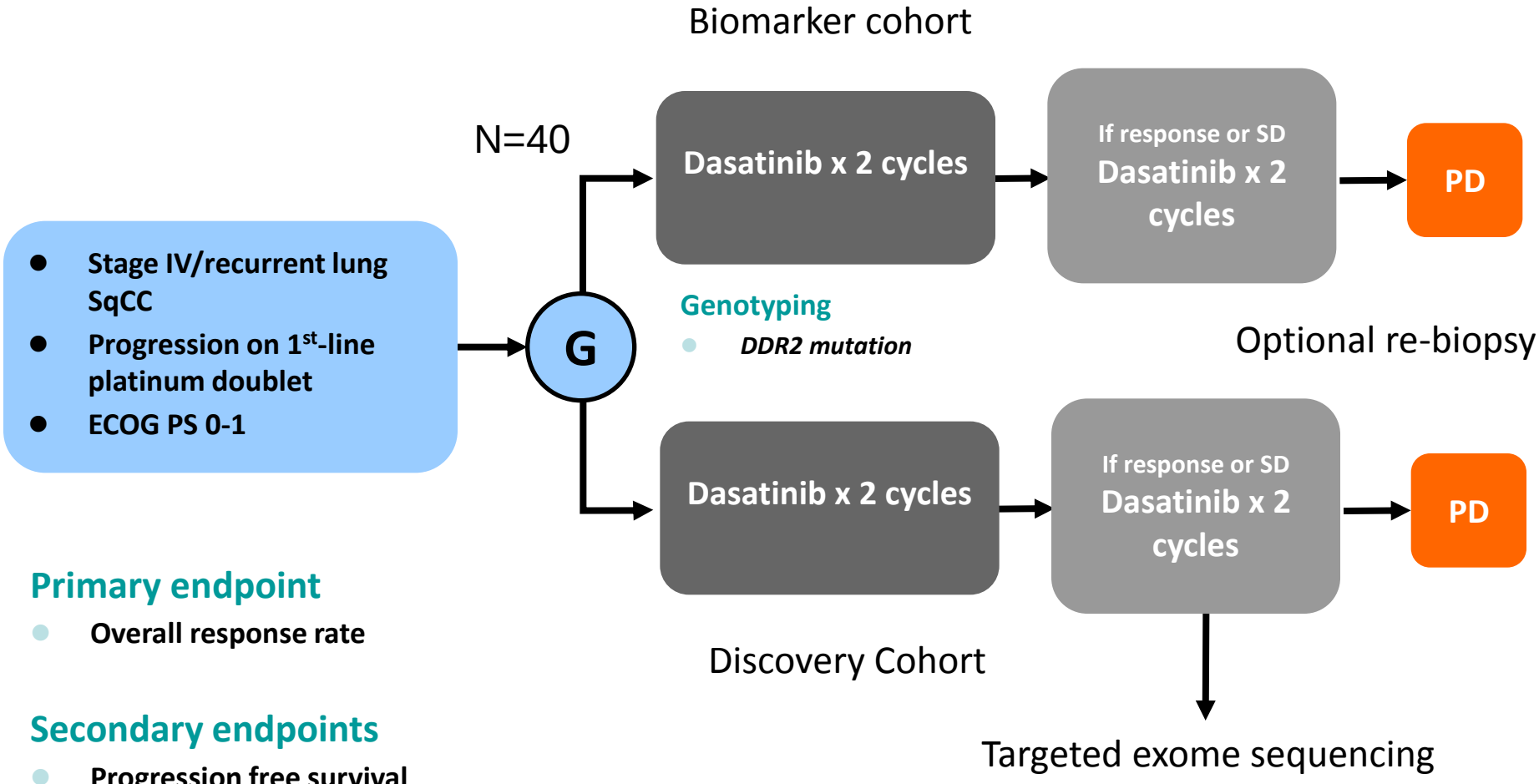






Hammerman et al. Cancer Discovery 2011

A phase II study of dasatinib in lung SqCC



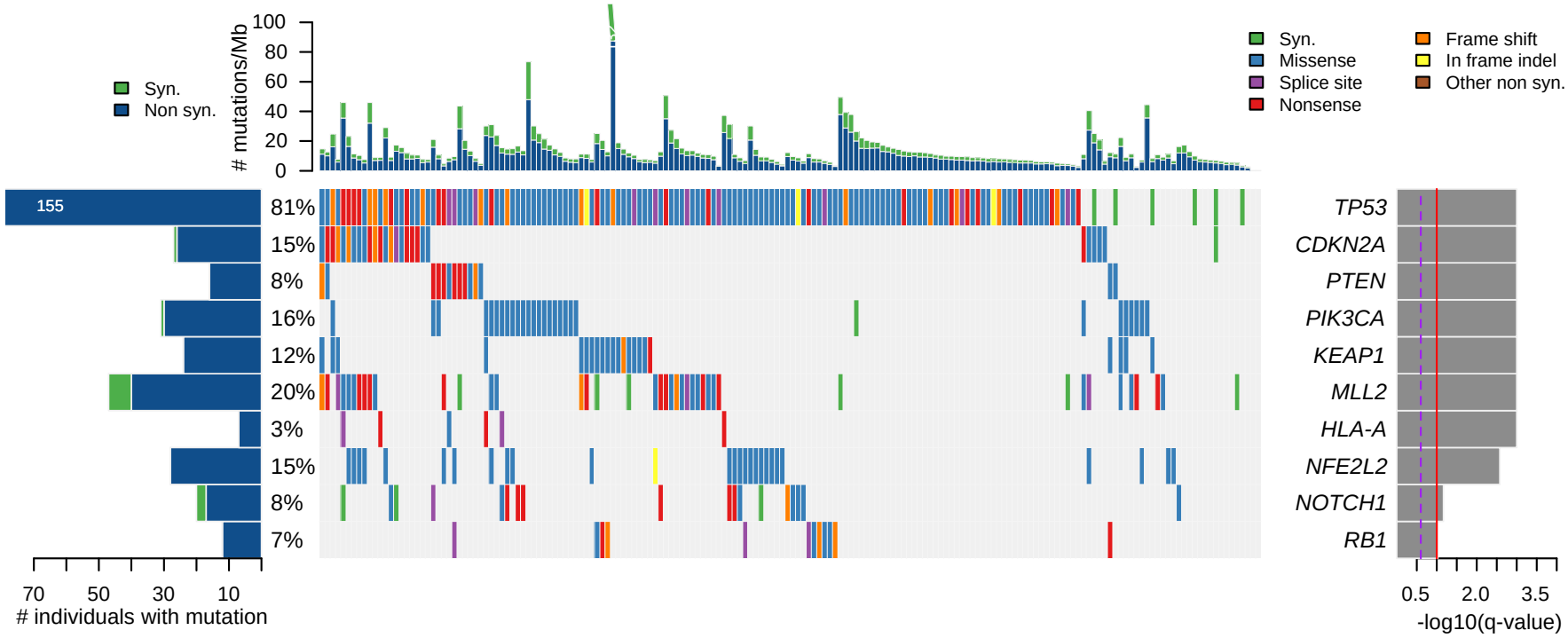
Primary endpoint

- Overall response rate

Secondary endpoints

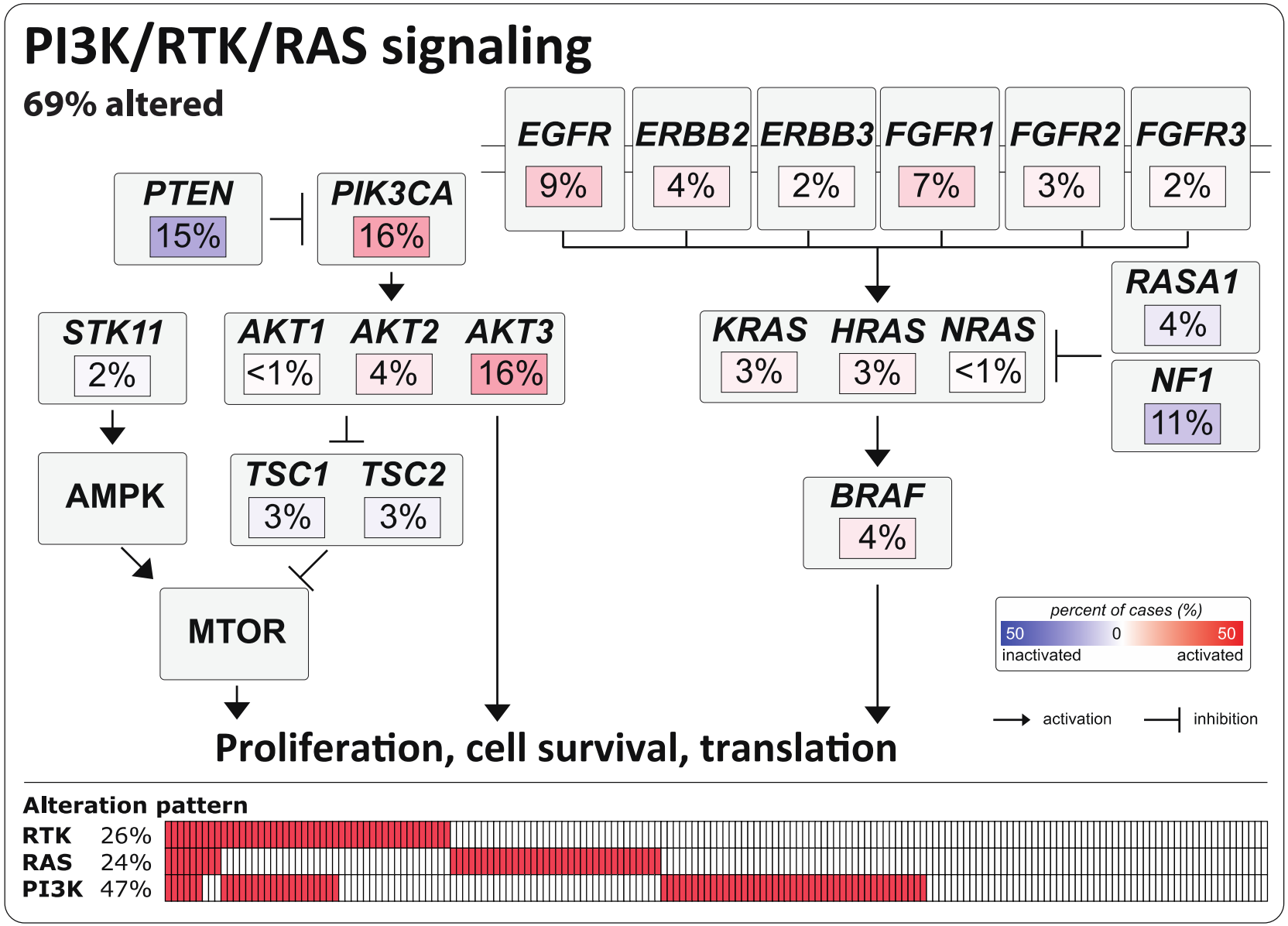
- Progression free survival
- Overall survival
- Safety
- DDR2 genotype subset analysis

Squamous Cell NSCLC – TCGA



TCGA (Hammerman) Nature. 2012 Sep 9.

Revisiting the kinome by exome sequencing

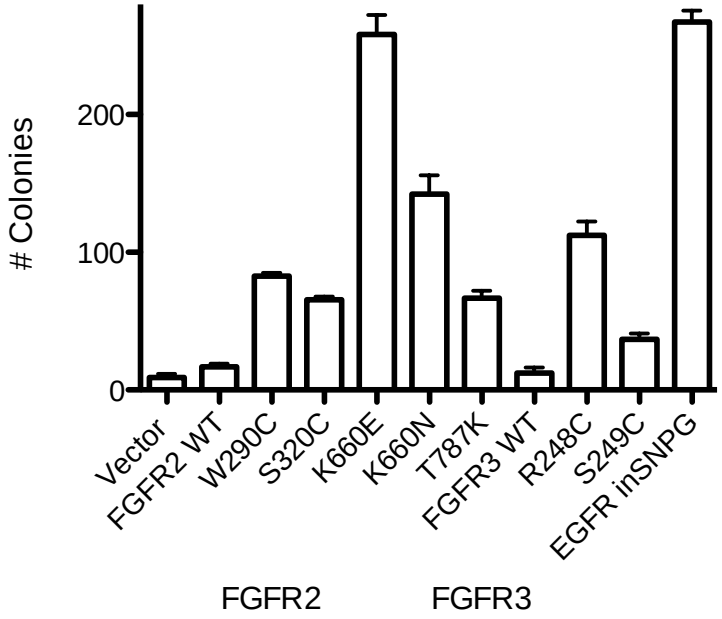


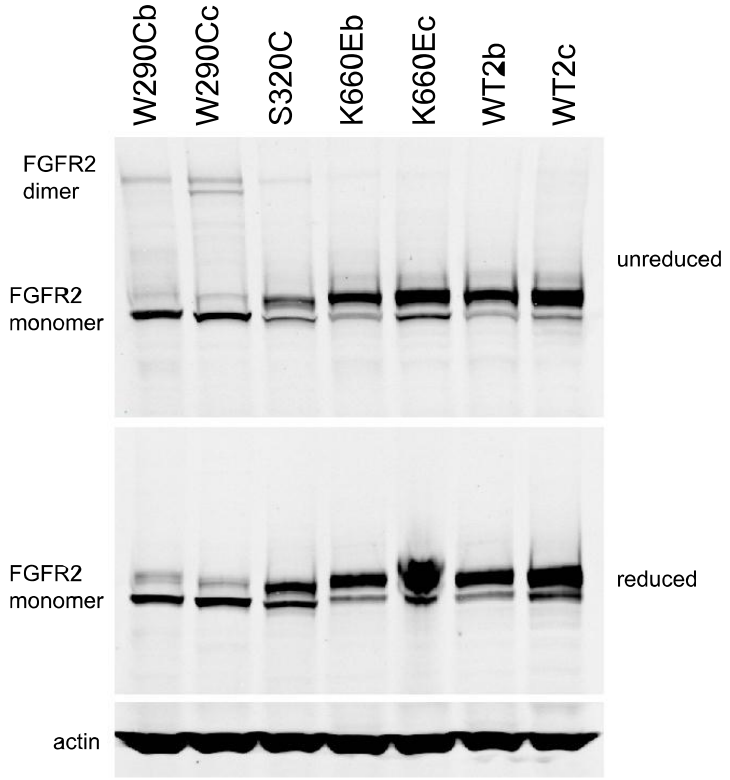
FGFR Mutations in TCGA lung squamous cancer

FGFR1	P25Q	FGFR3	R248C	FGFR2	K660E	FGFR1	S789C
FGFR1	W471L	FGFR3	S249C	FGFR2	K660N	FGFR3	R623S
FGFR1	R445W	FGFR3	S249C	FGFR2	G584W	FGFR2	T787K
FGFR2	R190G	FGFR3	S249C	FGFR3	K717M	FGFR2	R738K
FGFR2	W290C			FGFR4	Q738K		
FGFR2	G302W	FGFR4	Q144E				
FGFR2	S320C						
FGFR3	S435C						
FGFR2	E471Q	FGFR4	R434Q				

Note: Recurrent mutations at FGFR2 K660 (kinase domain) and FGFR3 aa 248-249 (extracellular domain).

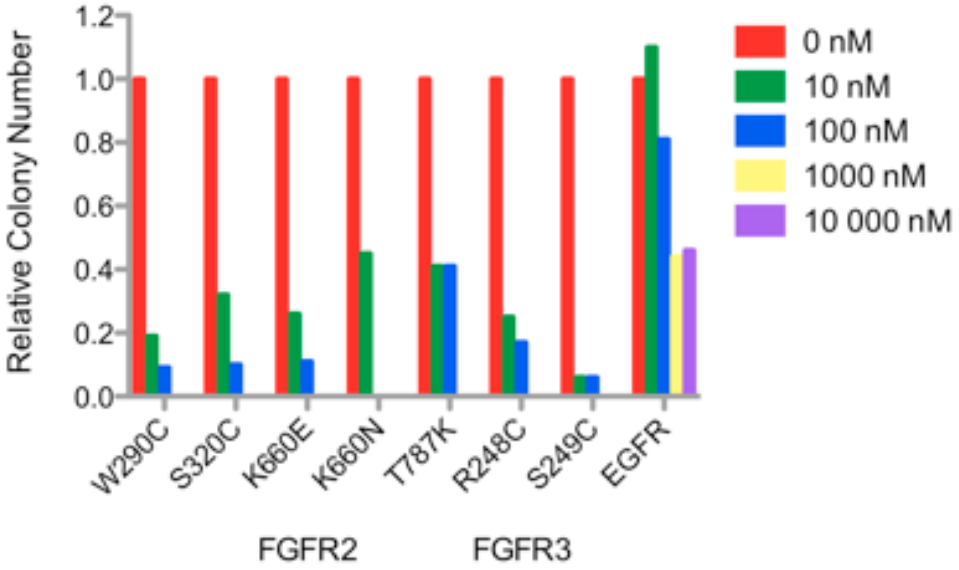
FGFR mutations are oncogenic



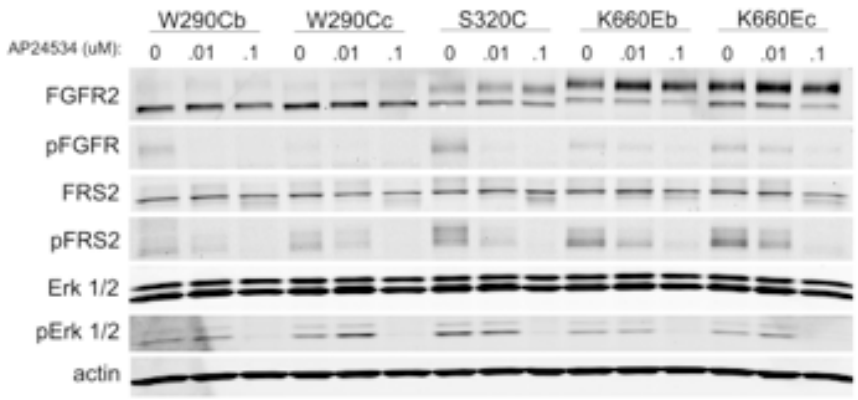


Peter Hammerman

FGFR-driven transformation is blocked by multiple FGFR kinase inhibitors



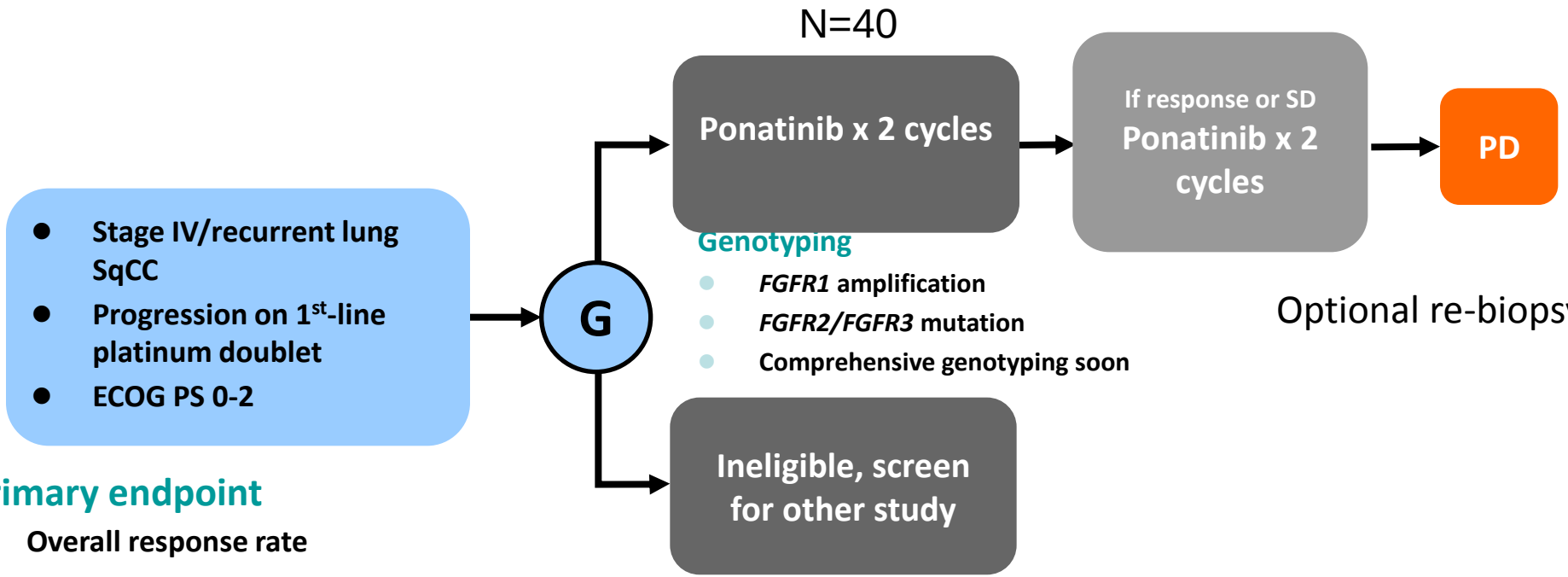
BGJ398



Ponatinib

Peter Hammerman

Trial Design: Ponatinib in Lung SqCC



Primary endpoint

- Overall response rate

Secondary endpoints

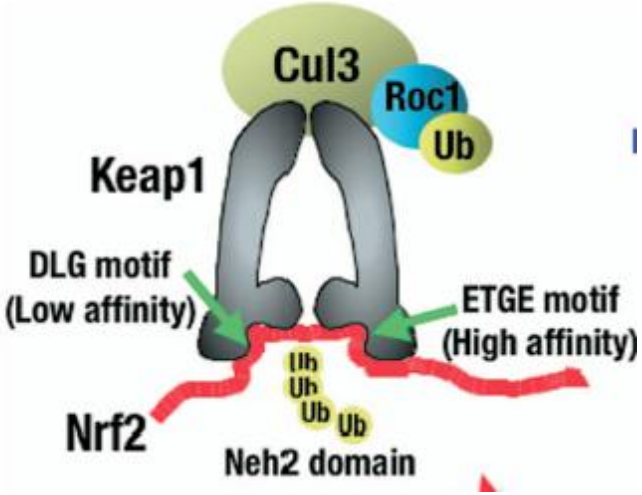
- Progression free survival
- Overall survival
- Safety
- FGFR genotype subset analysis

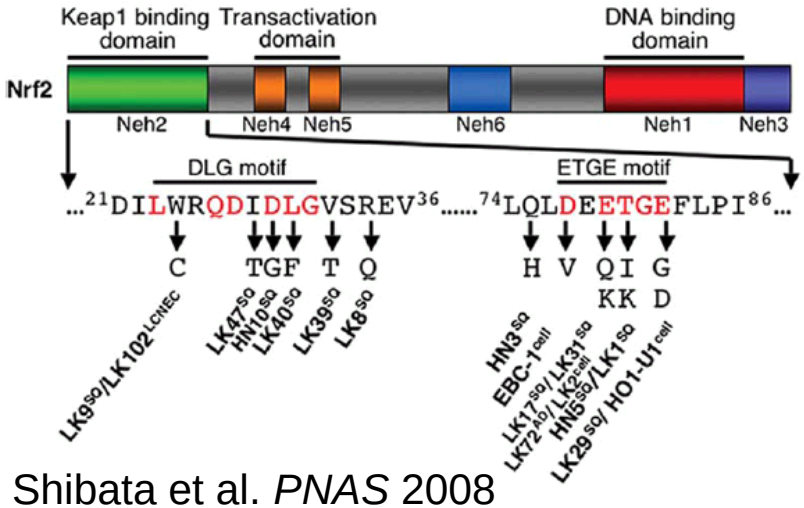
Correlatives

- Primary xenografts for shRNA and inhibitor profiling
- Tumor IHC (p-FRS2, p-FGFR), *FGFR1* expression
- Comprehensive genomics for resistance

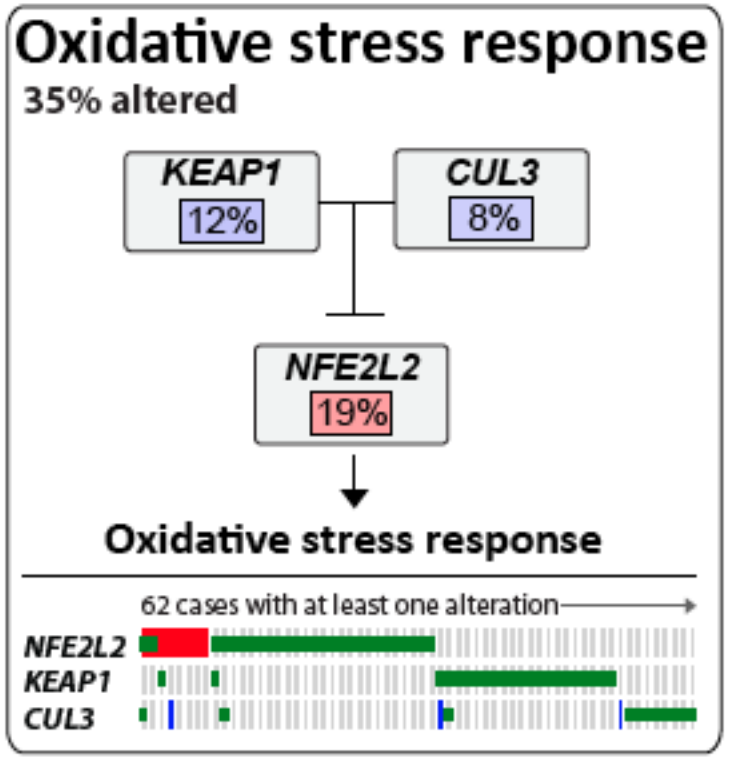
NFE2L2/KEAP1/CUL3

- Mutations in KEAP1 are lof (frequent LOH of second allele)
- Mutations in NRF2 cluster in DLG and ETGE motif -> prevent KEAP1 interaction -> results in NRF2 stabilization and nuclear entry



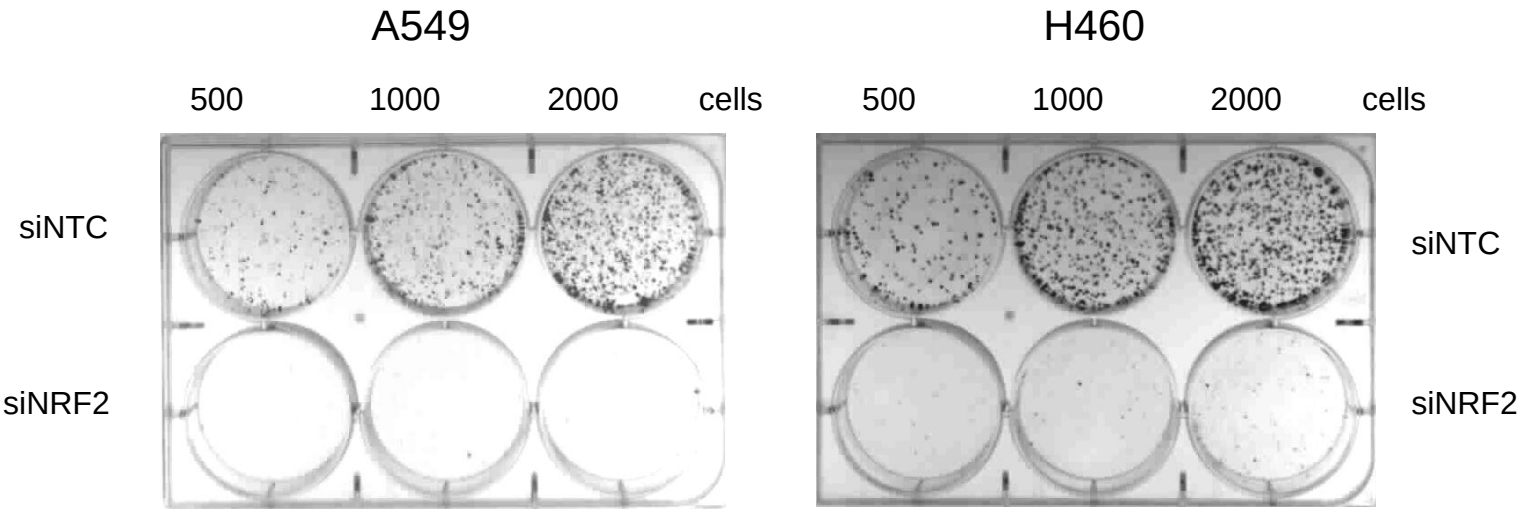


Shibata et al. *PNAS* 2008

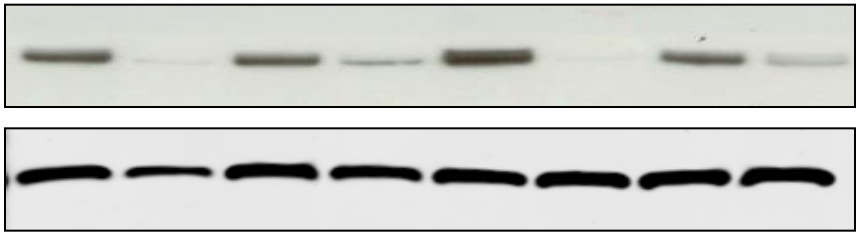


In head and neck cancer mutations in *NFE2L2/KEAP1/CUL3* are mutually exclusive with HPV+ ($p<0.02$); *TP53* ($p=0$), *CDKN2A* ($p<0.001$)

2 KEAP1 mutant lung cancer lines are sensitive to siRNA targeting NFE2L2



A549				H460			
siNTC-D3	siNRF2-D3	siNTC-D7	siNRF2-D7	siNTC-D3	siNRF2-D3	siNTC-D7	siNRF2-D7



Mohamed Abazeed

Breakthroughs in Basic Research

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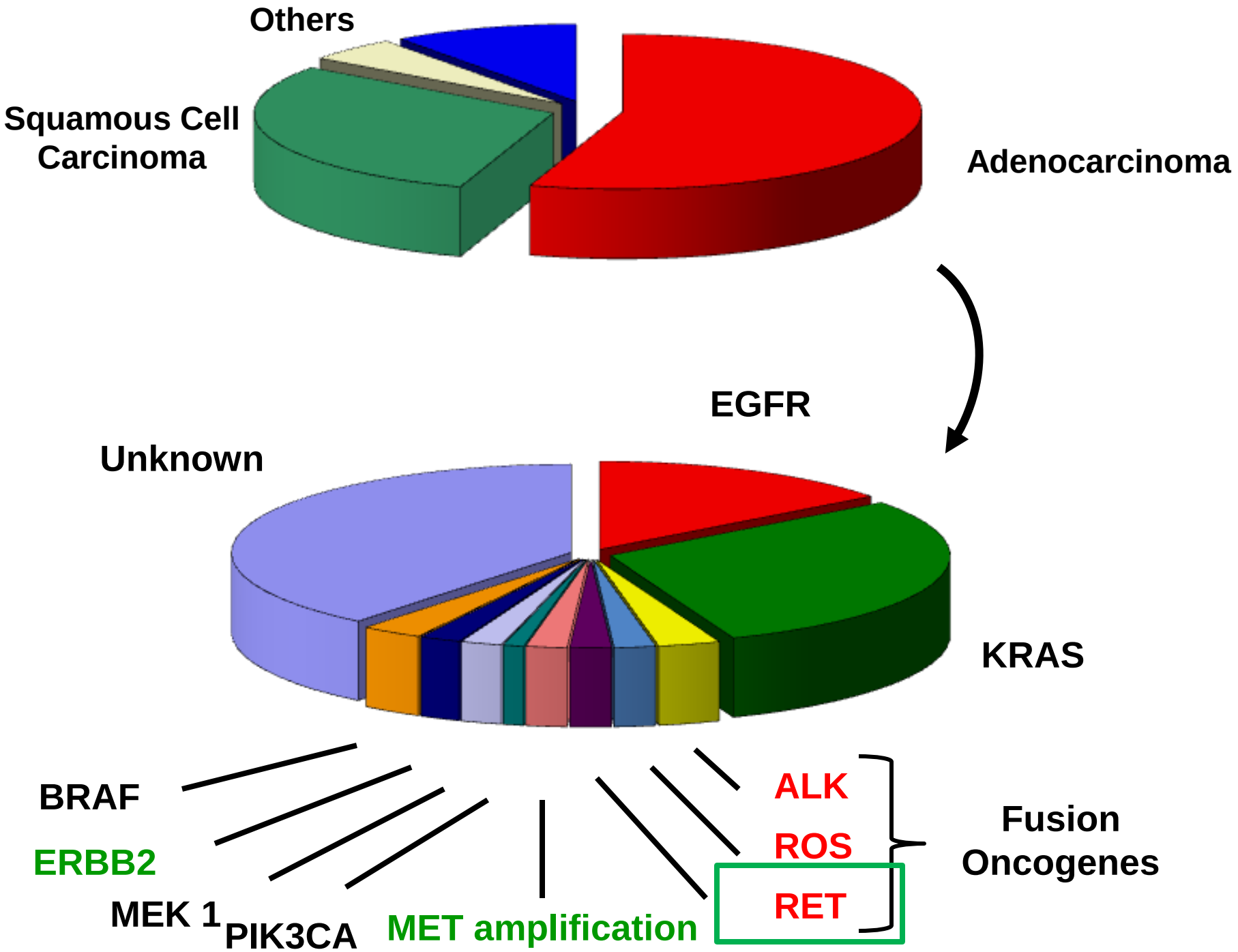
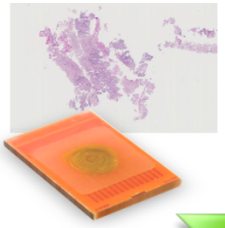
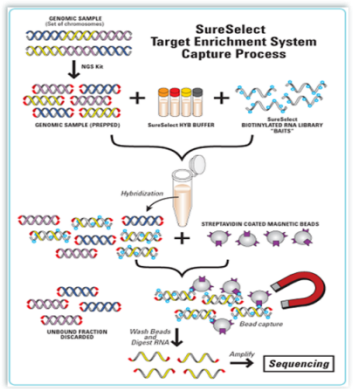
- New Oncogenes in adenocarcinoma
- Co-clinical trials to guide clinical drug development


Others
Squamous Cell Carcinoma
Adenocarcinoma
EGFR
Unknown
KRAS
BRAF
ERBB2
MEK 1
PIK3CA
MET amplification
ALK
ROS
RET
Fusion Oncogenes

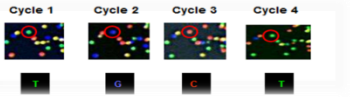
Foundation Medicine Cancer Genotyping Platform



Fixed sample slides



DNA extraction, Library construction, Hybrid capture



Sequencing (Illumina HiSeq™ 2000)

ANALYSIS PIPELINE

Point Mutations
Bayesian algorithm

Short Insertions/deletions
Local assembly

Copy Number Alterations
Comparison with process-matched normal control

Rearrangements
Analysis of chimeric pairs

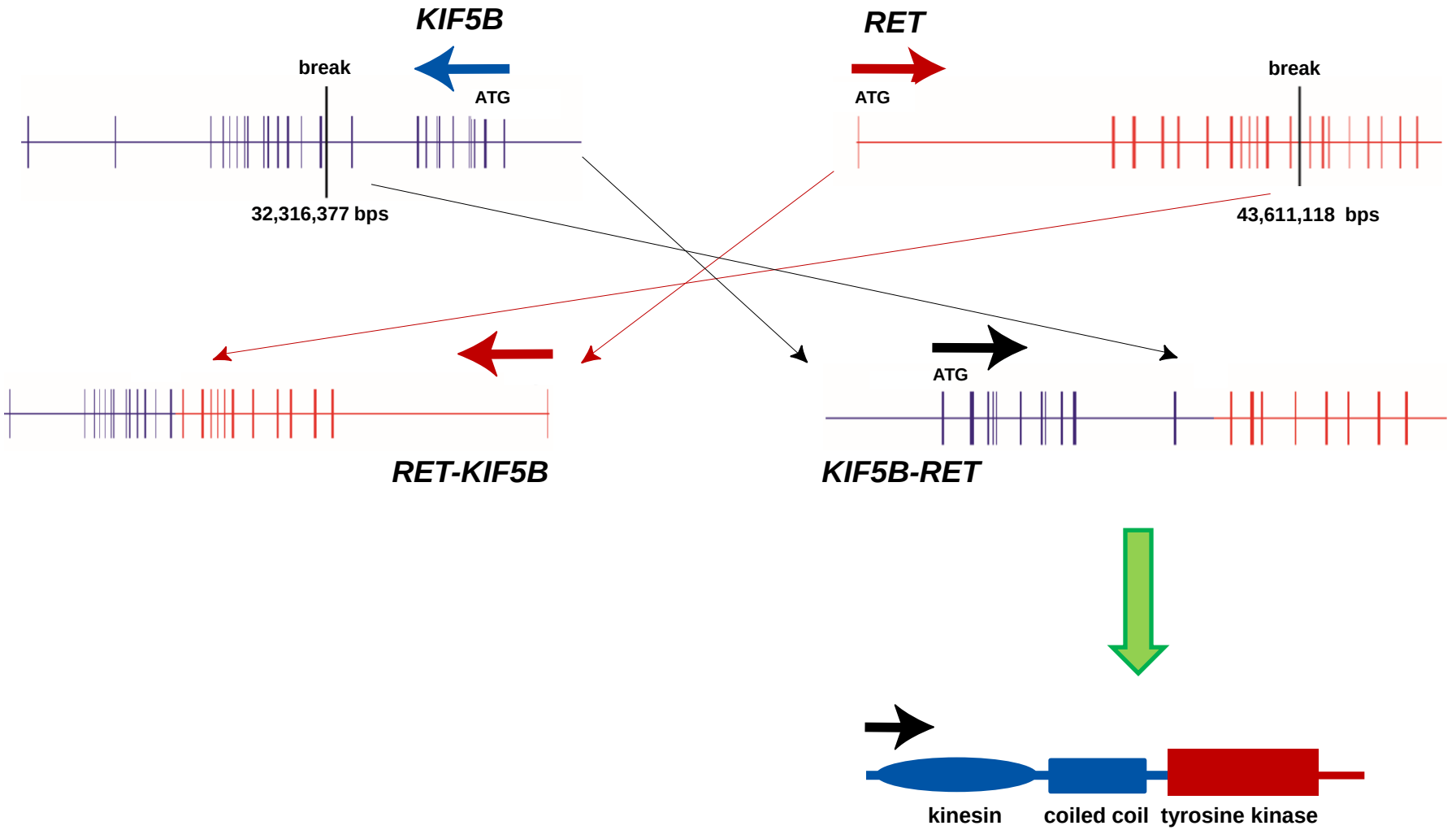
Annotation & Interpretation

dbSNP
COSMIC
Med. Literature

Clinical Report

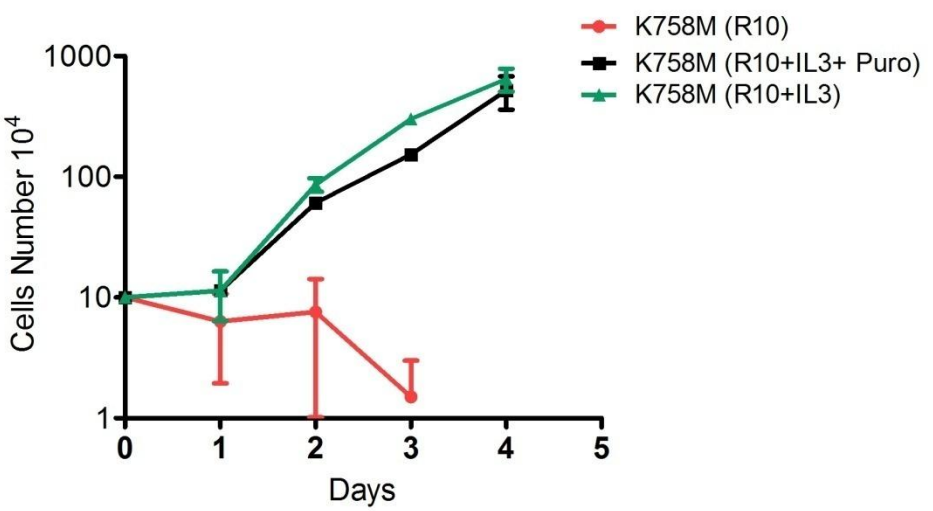
< 21 days

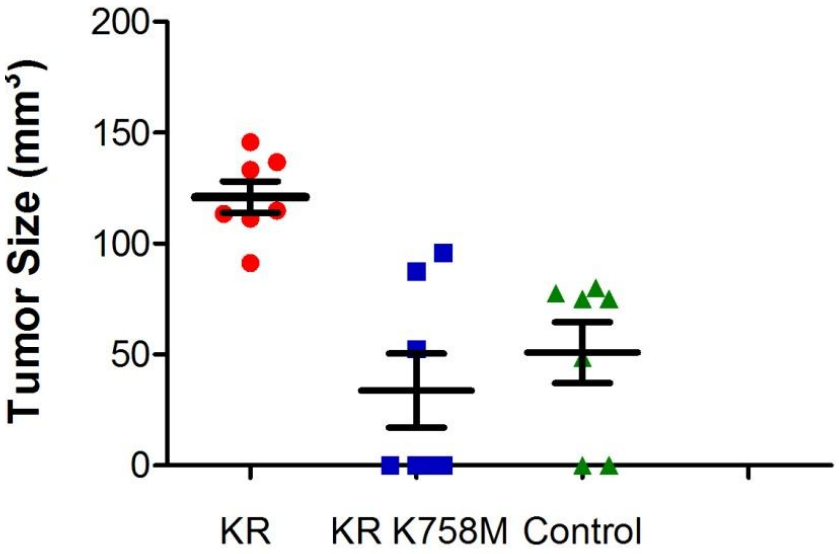
Identification of a pericentric inversion on chromosome 10 leading to KIF5B-RET



Lipson, Capelletti et al. Nature Medicine 2012

KIF5B-RET is oncogenic in vitro and in vivo and requires kinase activity





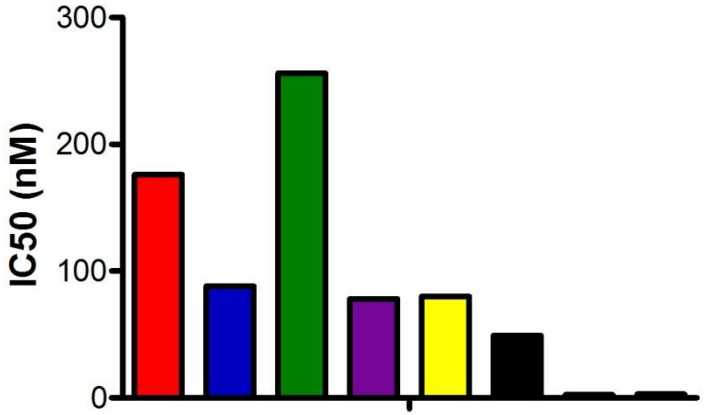
Ba/F3 cells

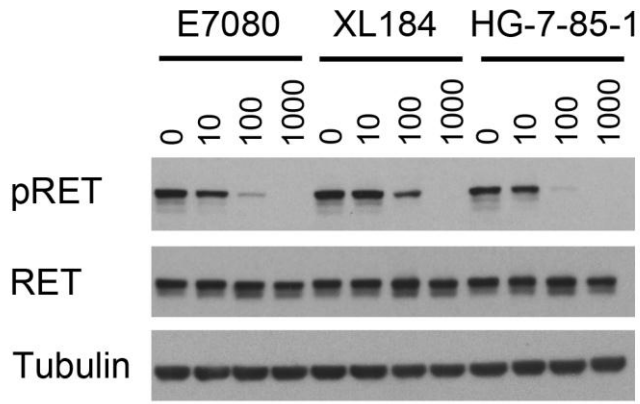
BEAS2B cells

Marzia Capelletti

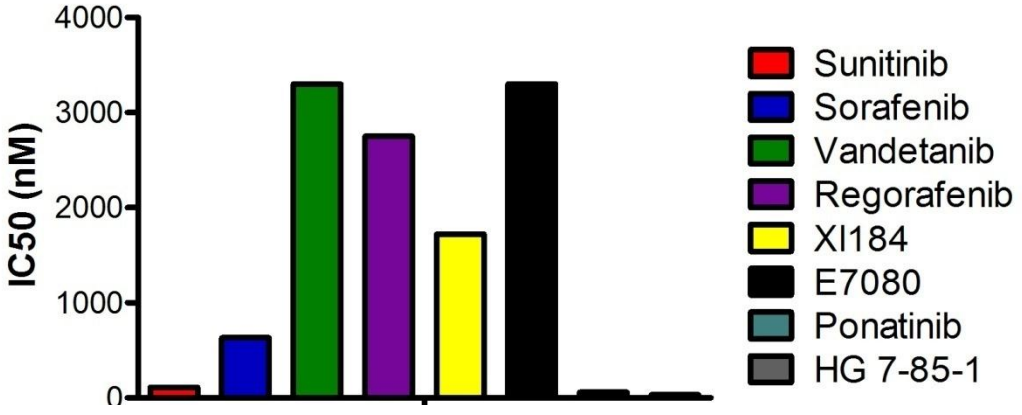
Efficacy of kinase inhibitors against KIF5B-RET and KIF5B-RET V804M Ba/F3 cells

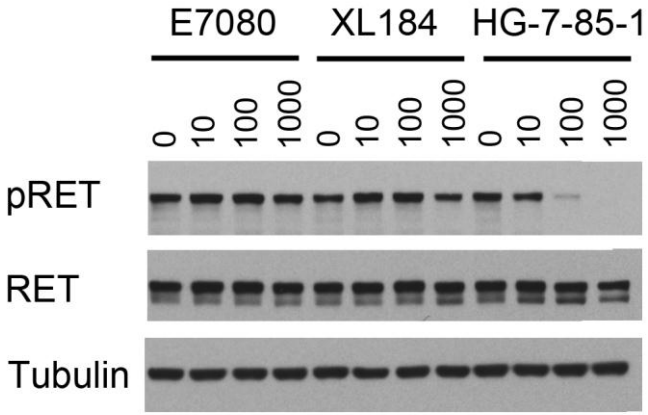
KIF5B-RET





KIF5B-RET V804M





Marzia Capelletti

Sunitinib in Never-Smokers with NSCLC

- Advanced NSCLC
- ≥ 1 prior chemotherapy
- "Triple negative" for EGFR, KRAS, ALK
- Never smoker or known RET rearrangement

→

Sunitinib
50 mg daily
4 weeks on,
2 weeks off

35 patients total

→

Molecular comparison of responders & non-responders

PRIMARY ENDPOINT:

Overall response rate

SECONDARY ENDPOINT:

Activity in subset with RET rearrangements

PI: Geoff Oxnard

Breakthroughs in Basic Research

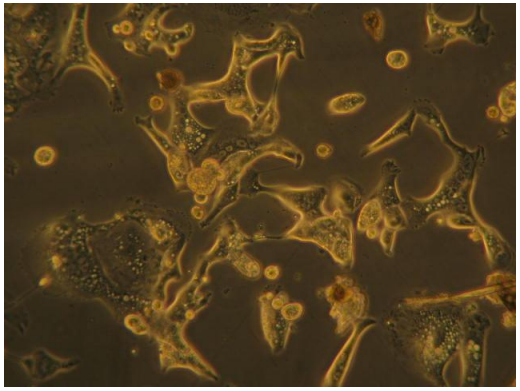
- Squamous Cell Lung Cancer
- New Oncogenes in adenocarcinoma
- Co-clinical trials to guide clinical drug development

Co-Clinical Trial

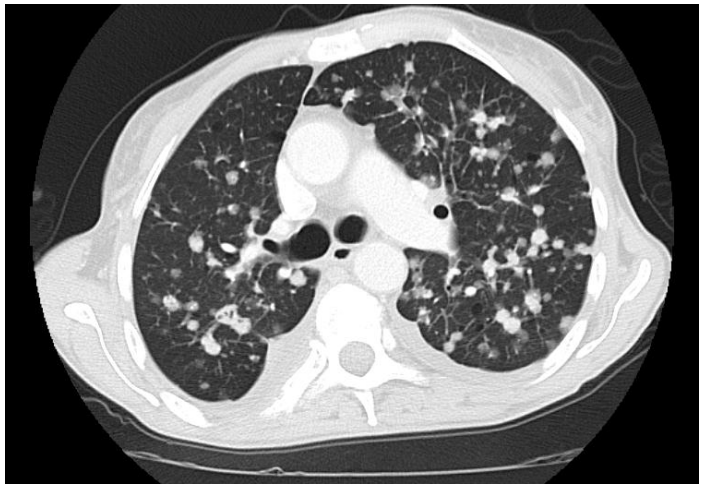
- Perform analogous study in model system at the same time as human clinical trial
  - Genetically engineered mouse models that can recapitulate human cancer
- Findings can inform development and/or interpretation of findings from human trial

Preclinical model systems

NSCLC patients



Guide clinical drug development



Inform preclinical studies

- Prioritize clinical therapies
- Identify resistance mechanisms
- Test novel combination therapies

- Evaluate targeted therapies
- Determine biomarker modulation
- Study clinical drug resistance

Co-clinical trials: mouse studies to mimic ongoing human clinical studies

KRAS mutant lung cancer

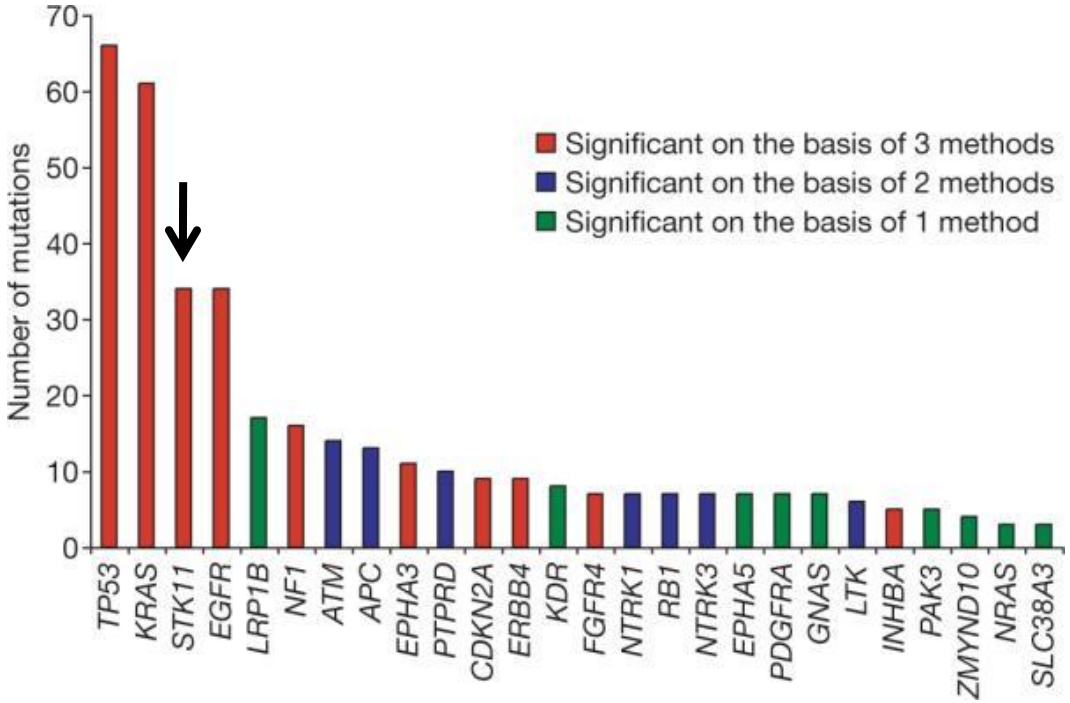
- Docetaxel
- Docetaxel & Selumetinib

Kras K12D lung cancer

- Docetaxel
- Docetaxel & Selumetinib

LKB1 in NSCLC

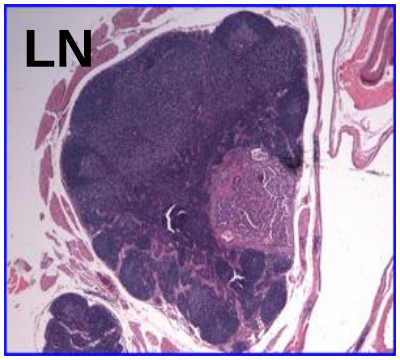
Common in NSCLC
Associated with *KRAS* (~ 30%) mutations; not with EGFR mutations

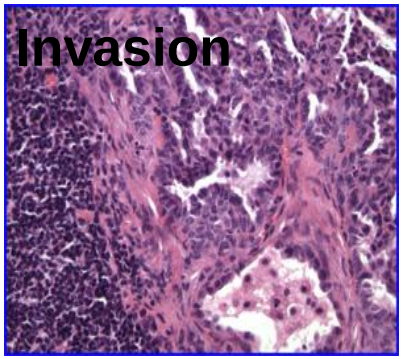


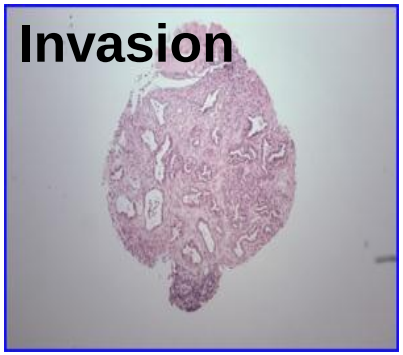
Ding et al. Nature 2008

Kras G12D/Lkb1$^{-/-}$ mice have a more aggressive phenotype than *Kras* G12D alone

Genotype	Survival	Histology	Metastases
Kras G12D	24 weeks	100% Adeno ca	0% (0/19)
LKb1$^{-/-}$	> 40 weeks	No tumors	N/A
Kras G12D/*Lkb1*$^{-/-}$	9 weeks	56% mixed	61% (27/44)
Kras G12D/*p53*$^{-/-}$	14 weeks	100% Adeno ca	44% (4/9)







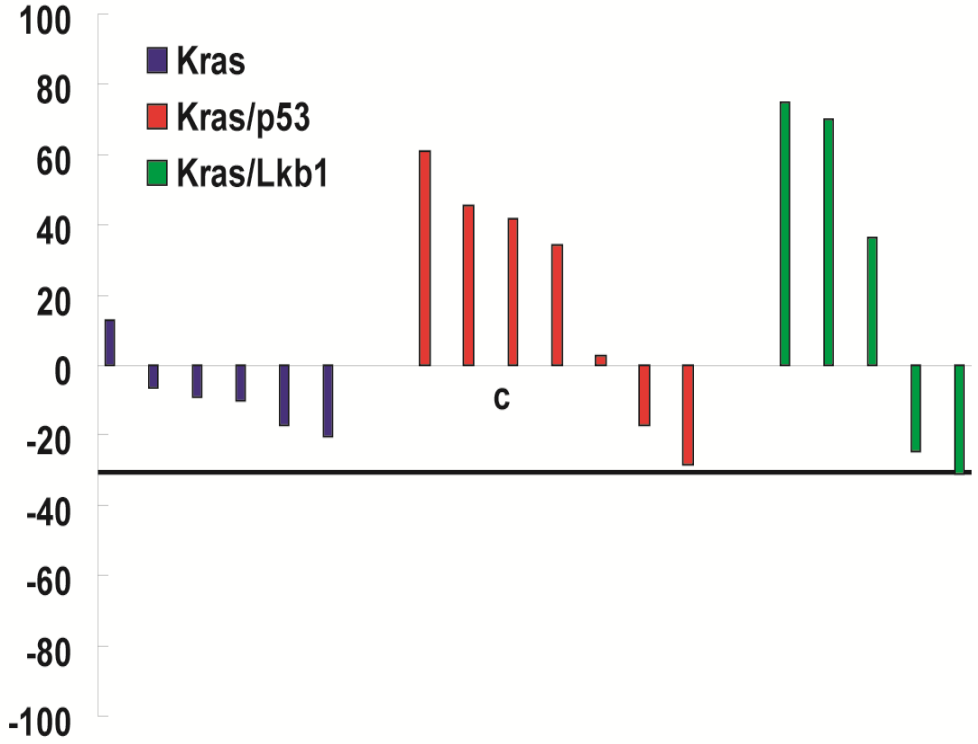
Li et al. Nature 2007

Impact of genotype on treatment with selumetinib

Kras G12D

Kras G12D : $p53^{-/-}$

Kras G12D : $Lkb^{-/-}$



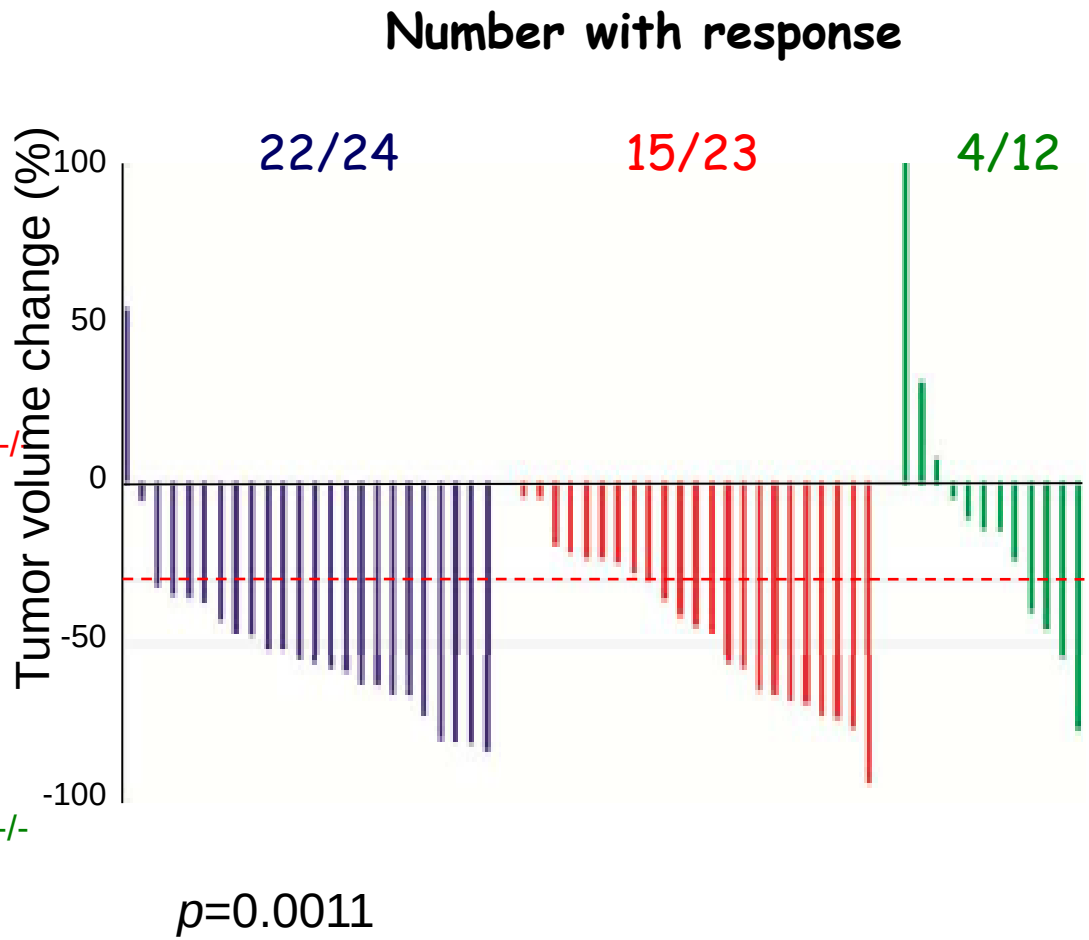
Chen et al. Nature 2012

Impact of genotype on treatment with selumetinib/docetaxel

Kras G12D

Kras G12D : $p53^{-/-}$

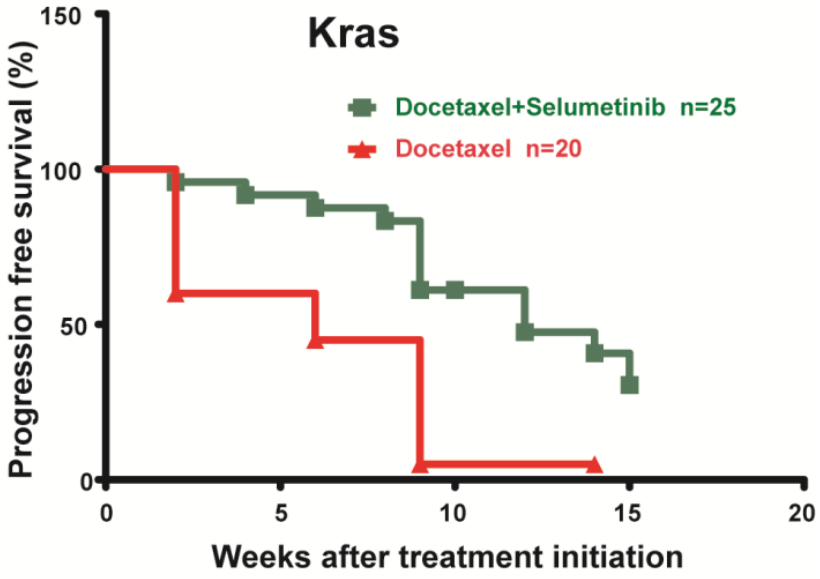
Kras G12D : $Lkb^{-/-}$

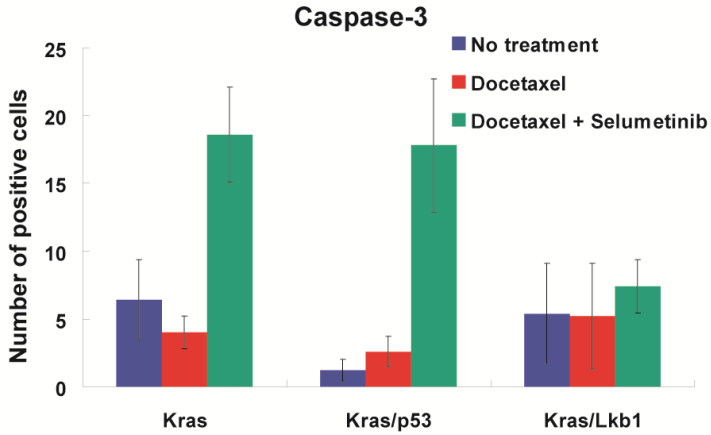


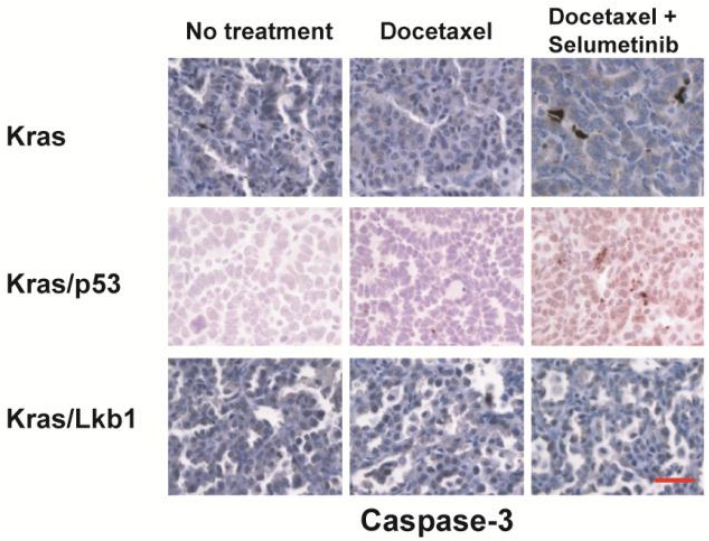
p=0.0011

Chen et al. Nature 2012

Improved PFS with Docetaxel/Selumetinib compared with docetaxel in *Kras* G12D murine model of NSCLC

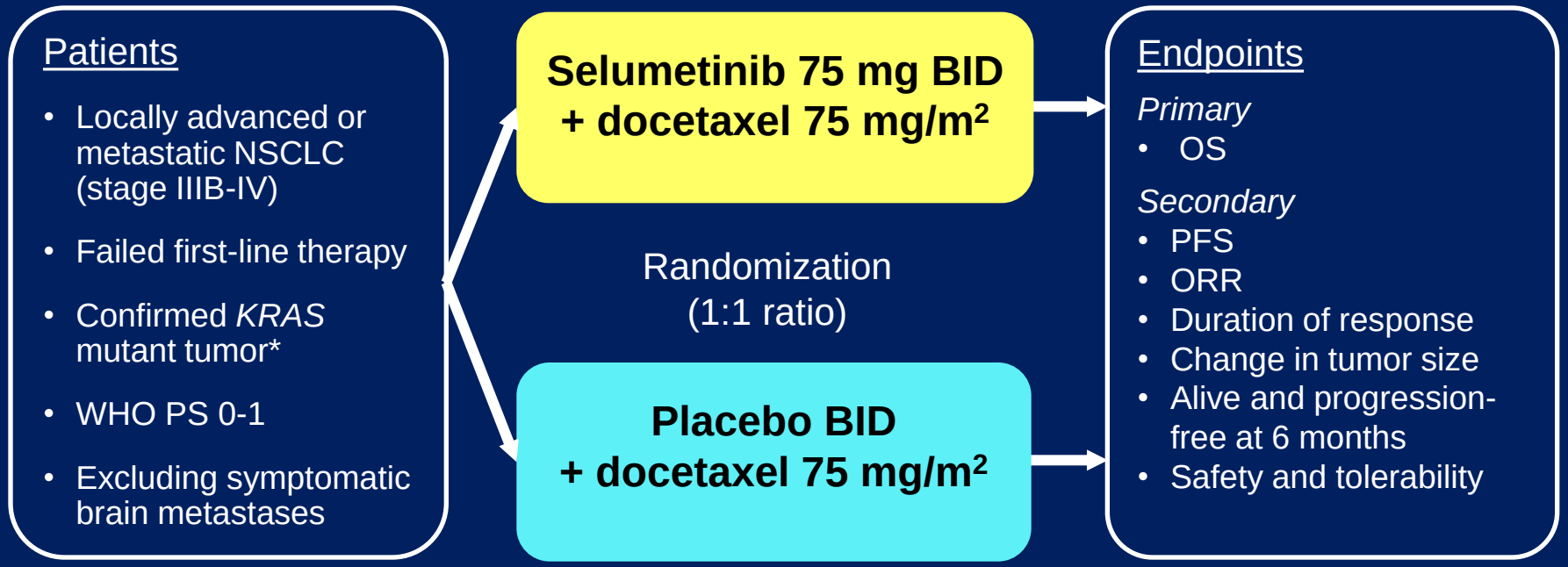






Chen et al. Nature 2012

Phase II, double-blind, randomised, placebo-controlled, multi-centre trial; NCT00890825

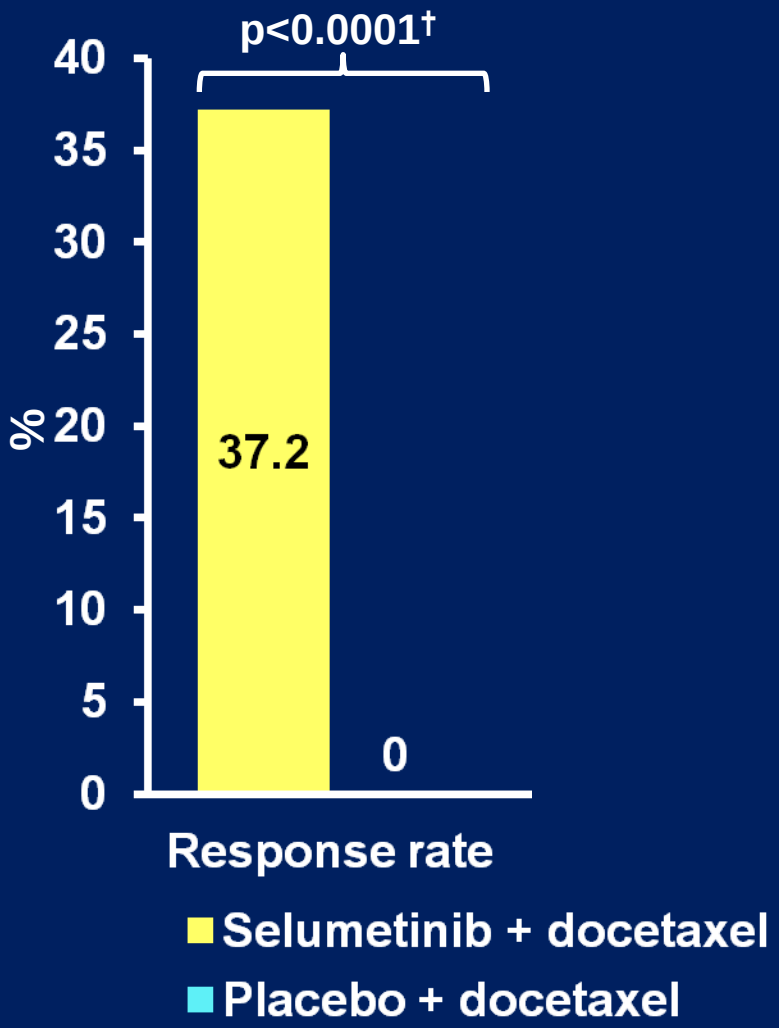


- Docetaxel was administered every 21 days for a maximum of 6 cycles followed by SEL/PBO
- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size‡
  - OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level

*Mutation status determined either by central laboratory (Esoterix, ARMS) or an approved local laboratory
‡To allow decisions to be made based on OS data without breaking study blinding at the earlier endpoint of PFS

Jänne et al. ASCO 2012

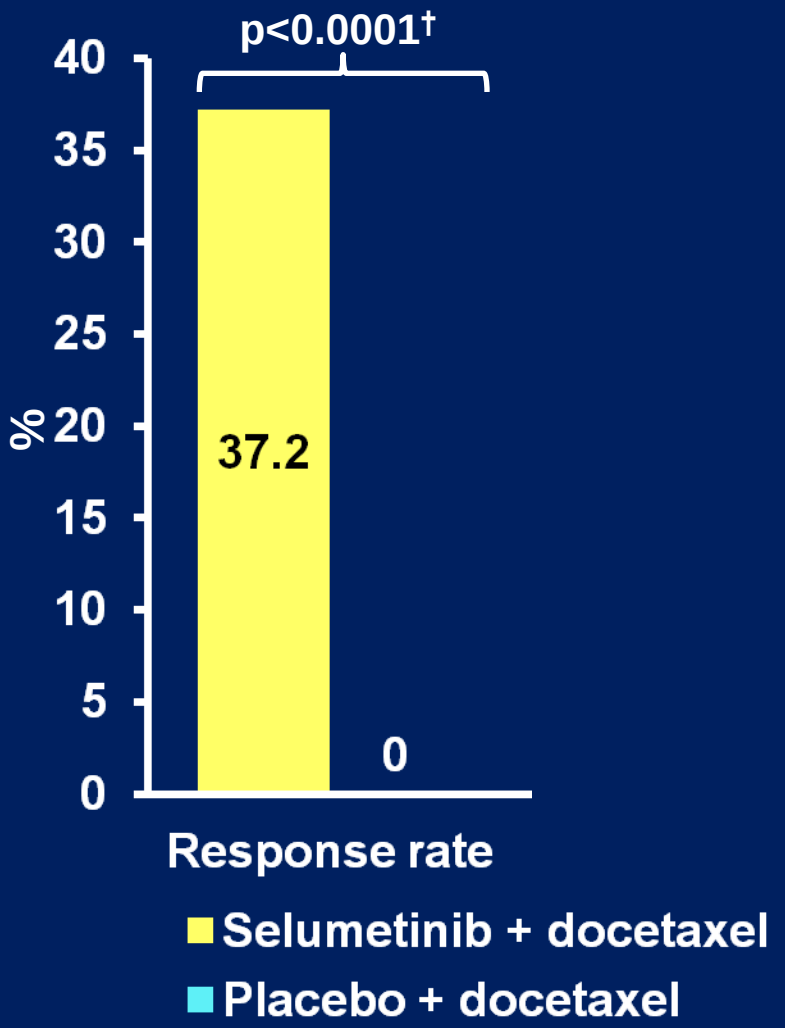
Response Rate and Alive and Progression Free at 6 months



†Fisher's exact 2-sided mid p value
‡1-sided p value

CR, complete response; PR, partial response; SD, stable disease
PD, progressive disease; DoR, duration of response;
APF6, alive and progression-free at 6 months

Response Rate and Alive and Progression Free at 6 months



	Selumetinib + docetaxel N=44	Placebo + docetaxel N=43
Best objective response (RECIST 1.0), number (%)		
CR	0	0
PR	16 (37.2)*	0§
SD ≥6 weeks	19 (44.2)	20 (50.0)
PD	8 (18.6)	18 (45.0)
Not evaluable	0	2 (5.0)
Median DoR, days	182	-

CR, complete response; PR, partial response; SD, stable disease
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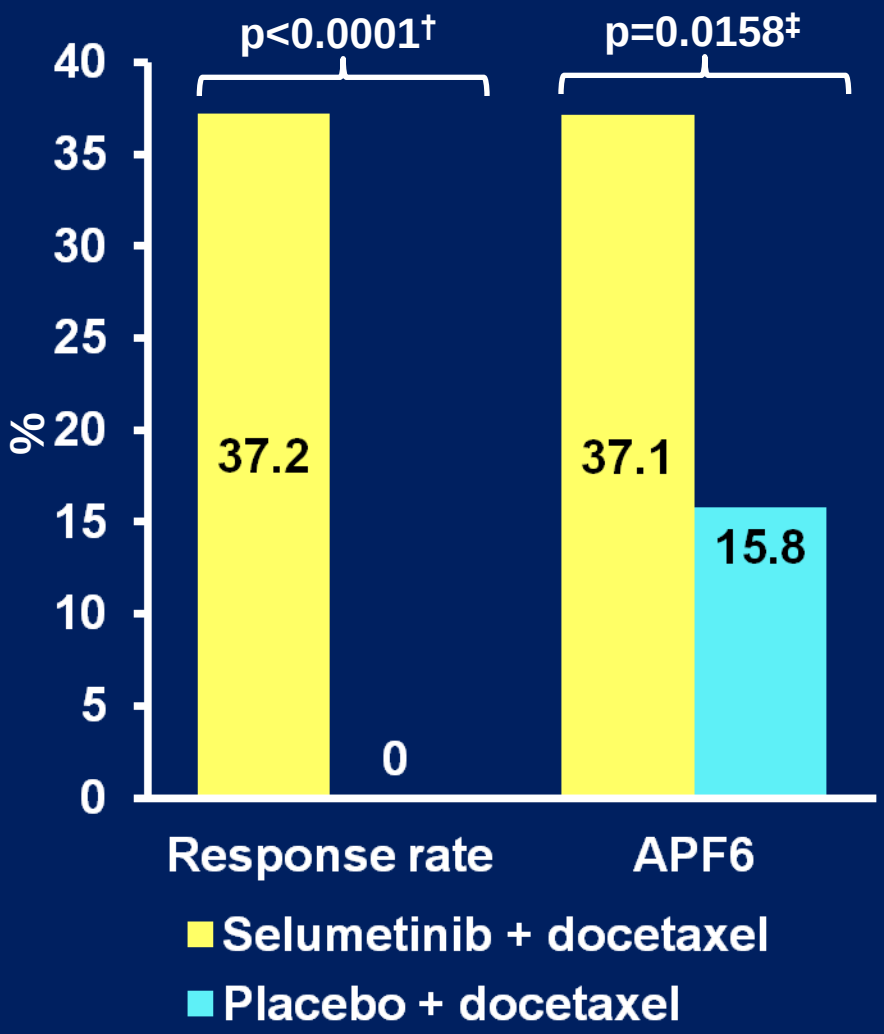
†Fisher's exact 2-sided mid p value
‡1-sided p value
*11 confirmed, 5 unconfirmed
§One patient was classed as non-evaluable due to non-evaluable non-target lesions and would have had a partial response according to RECIST 1.1 criteria

Response Rate and Alive and Progression Free at 6 months



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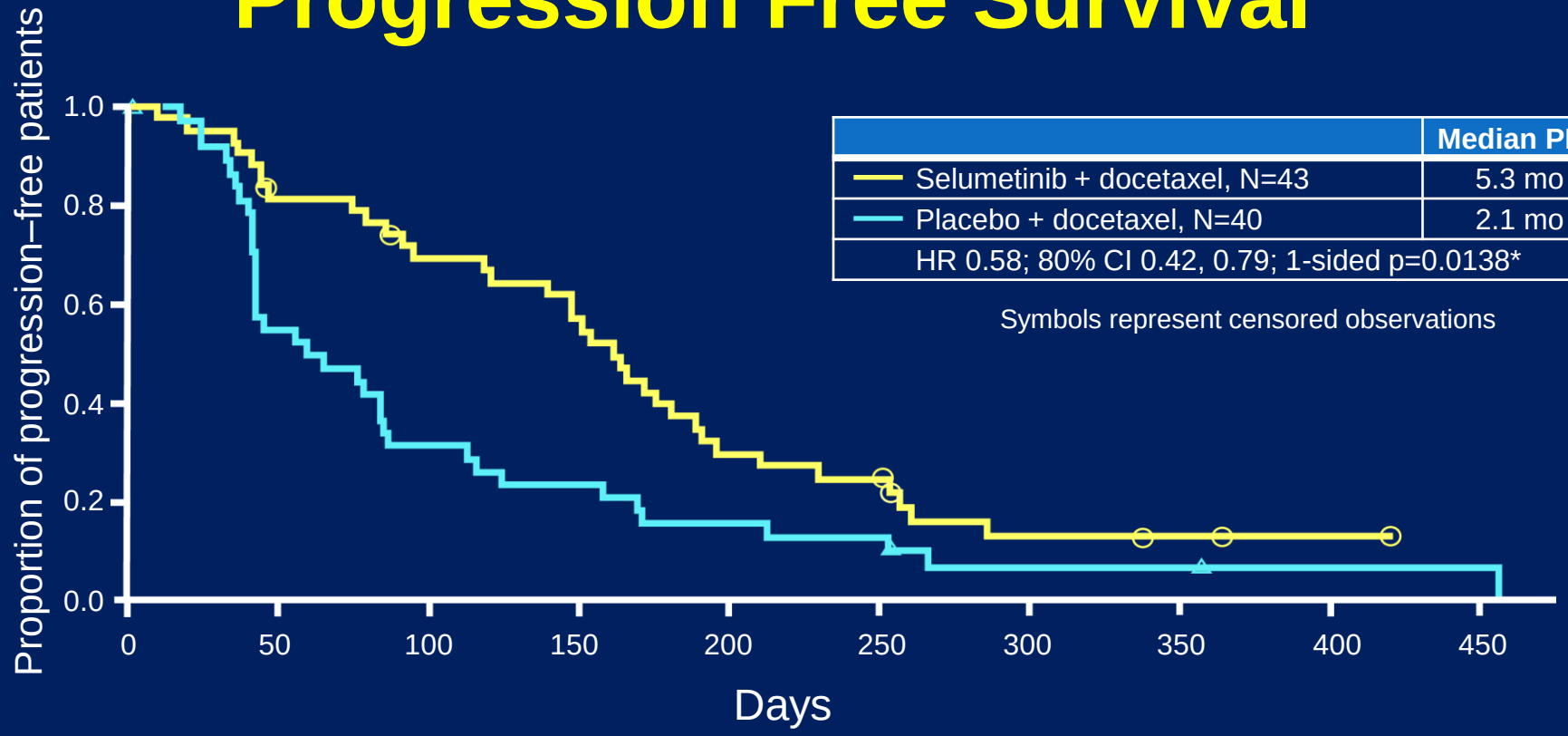
Progression Free Survival



	Median PFS
Selumetinib + docetaxel, N=43	5.3 mo
Placebo + docetaxel, N=40	2.1 mo
HR 0.58; 80% CI 0.42, 0.79; 1-sided p=0.0138*	

Symbols represent censored observations

Number at risk

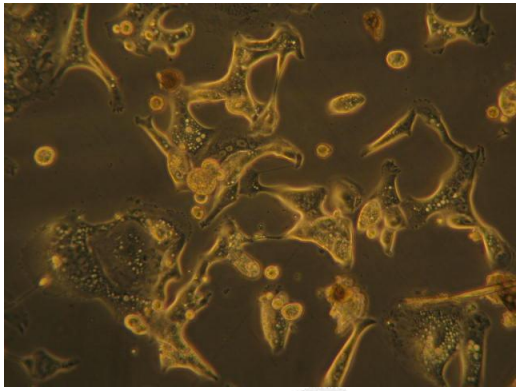
43	34	28	23	12	10	4	2	1	
40	21	12	9	6	5	2	2	1	1

- There was a statistically and clinically significant improvement in PFS
  - 71/83 events (85.5%): selumetinib + docetaxel 35/43, placebo + docetaxel 36/40

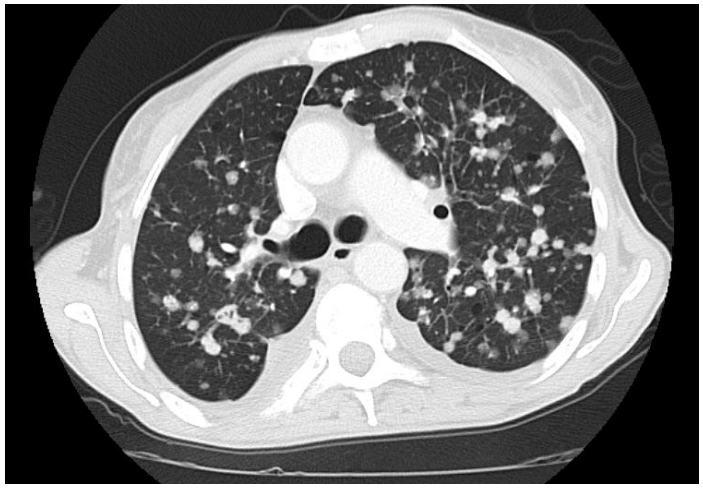
*Analysis was performed using a Cox proportional hazards model; The model allows for the effect of treatment and included terms for WHO PS, gender, histology and smoking status.

Preclinical model systems

NSCLC patients



Guide clinical drug development



Inform preclinical studies

- Efficacy of docetaxel/selumetinib
- Impact of *Lkb1*$^{-/-}$ on drug treatment

- Efficacy of docetaxel/selumetinib
- ? Impact of *LKB1*$^{-/-}$

Develop strategies to evaluate *LKB*$^{-/-}$ from human tumors
Evaluate retrospectively or prospectively

Co-Clinical Trial

- Perform analogous study in model system at the same time as human clinical trial

- Findings can inform development and/or interpretation of findings from human trial
  - Predict outcome of human trials
    - Use model to prioritize most effective therapeutic strategy to study in humans
  - Biomarker discovery
    - Validate biomarker in human clinical trials

Breakthroughs in Basic Research

- Squamous Cell Lung Cancer
- New Oncogenes in adenocarcinoma
- Co-clinical trials to guide clinical drug development