Inhibiting K-RAS in the Clinic – Are we There yet ?

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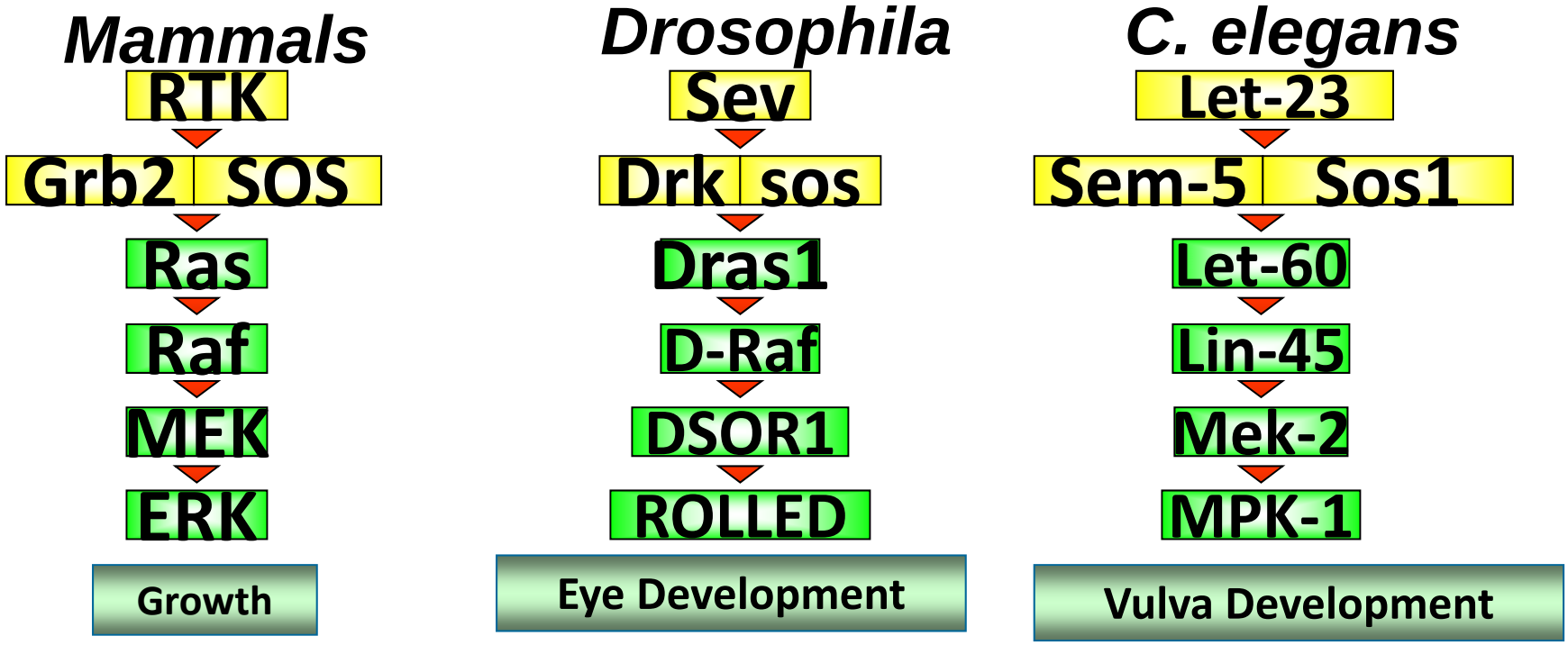
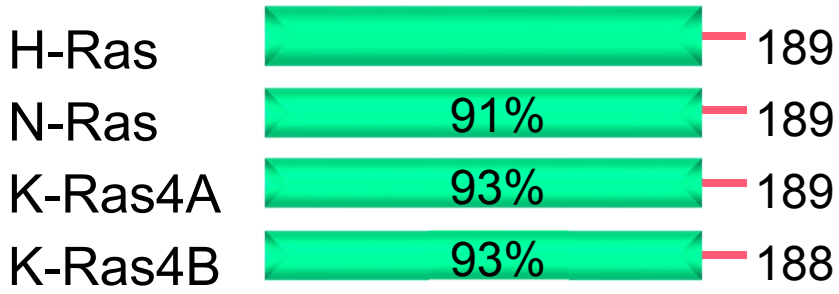
October 3, 2019
SWOG Translational Science Symposium
Chicago, IL

RAS signaling is evolutionally conserved across species

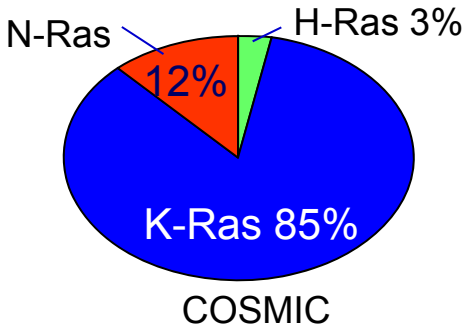


Ras is the most mutated oncogene in Cancer



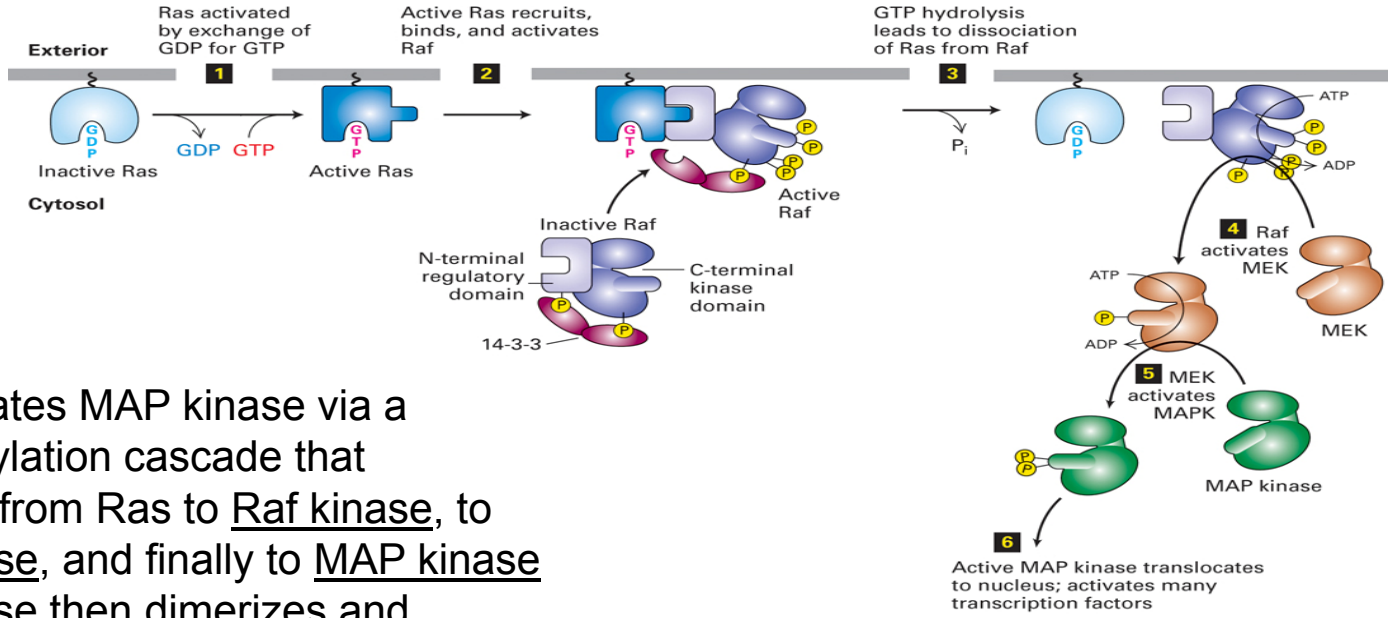
- 32% of all human cancers have Ras missense mutations

GENE	%*
HRAS	3
NRAS	8
KRAS	21

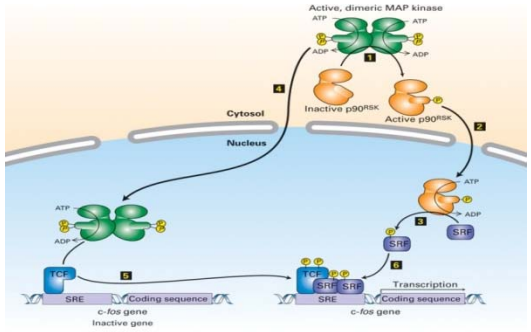


Pancreatic	90%	*KRAS*
Colorectal	50%	*KRAS*
Lung	30%	*KRAS*
Melanoma	25%	*NRAS*

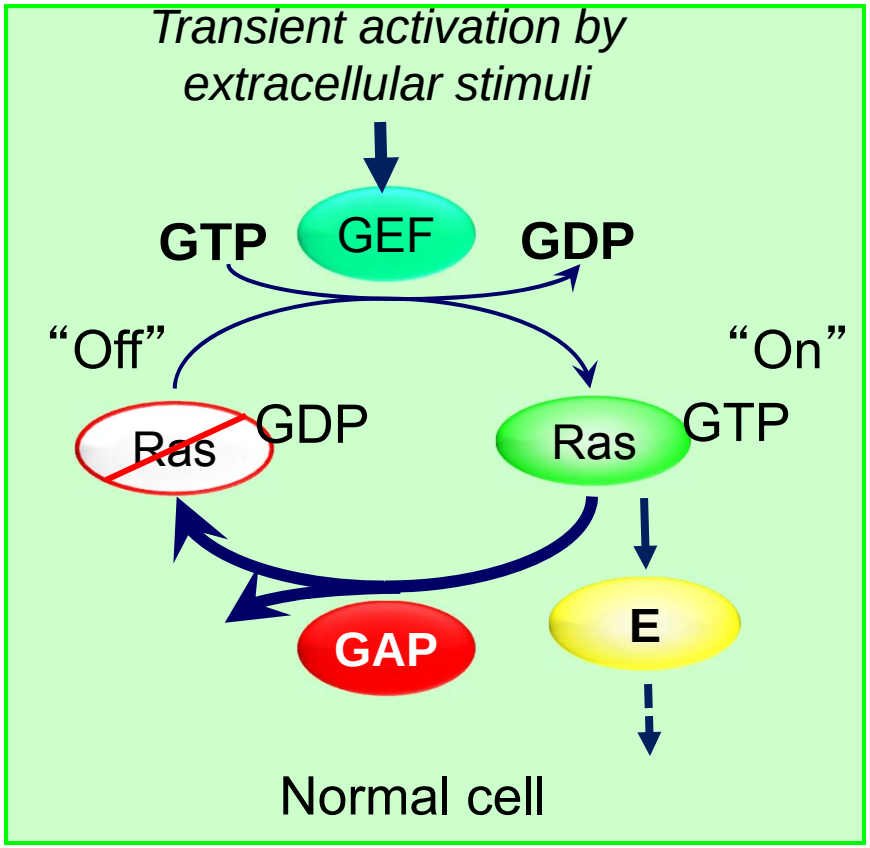
Ras Signaling

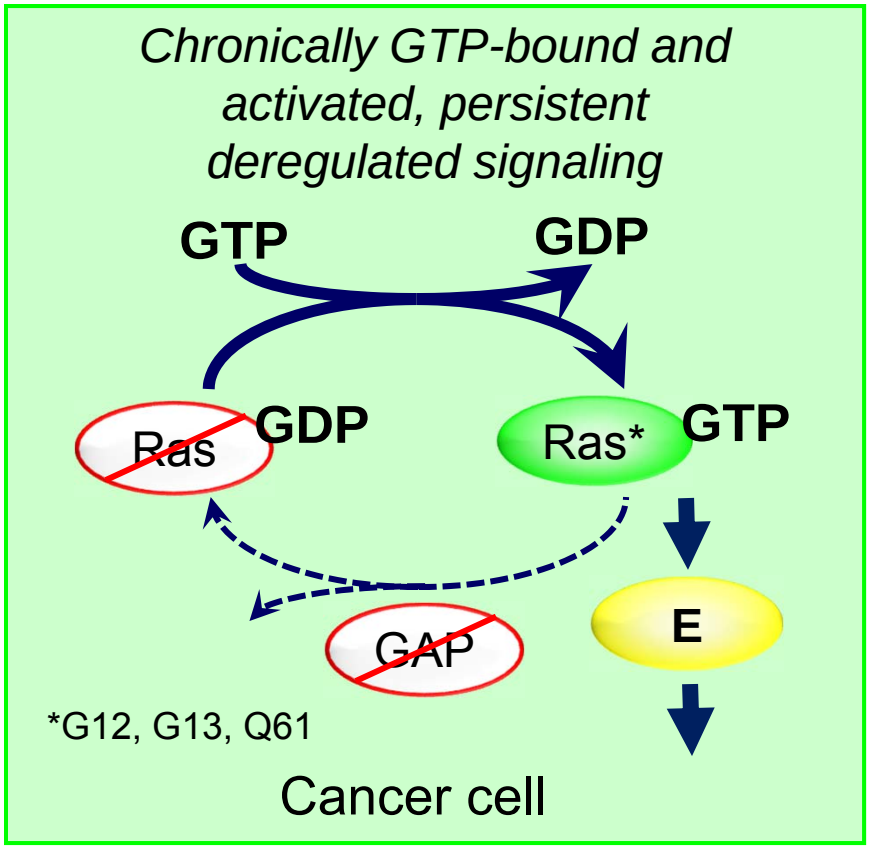


Ras activates MAP kinase via a phosphorylation cascade that proceeds from Ras to Raf kinase, to MEK kinase, and finally to MAP kinase MAP kinase then dimerizes and enters the nucleus.

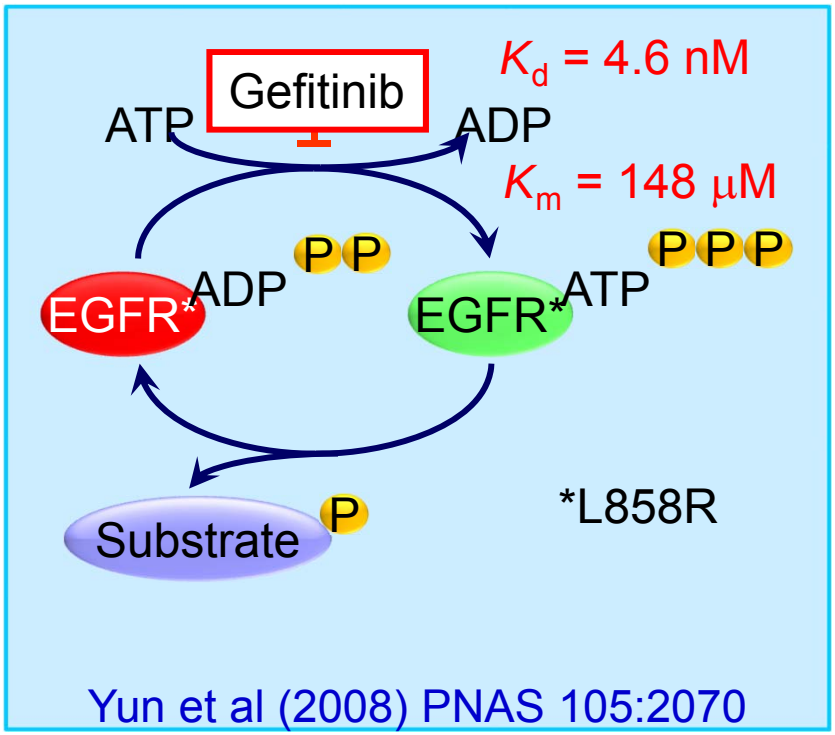


Mutant Ras is GAP-insensitive and persistently GTP-bound

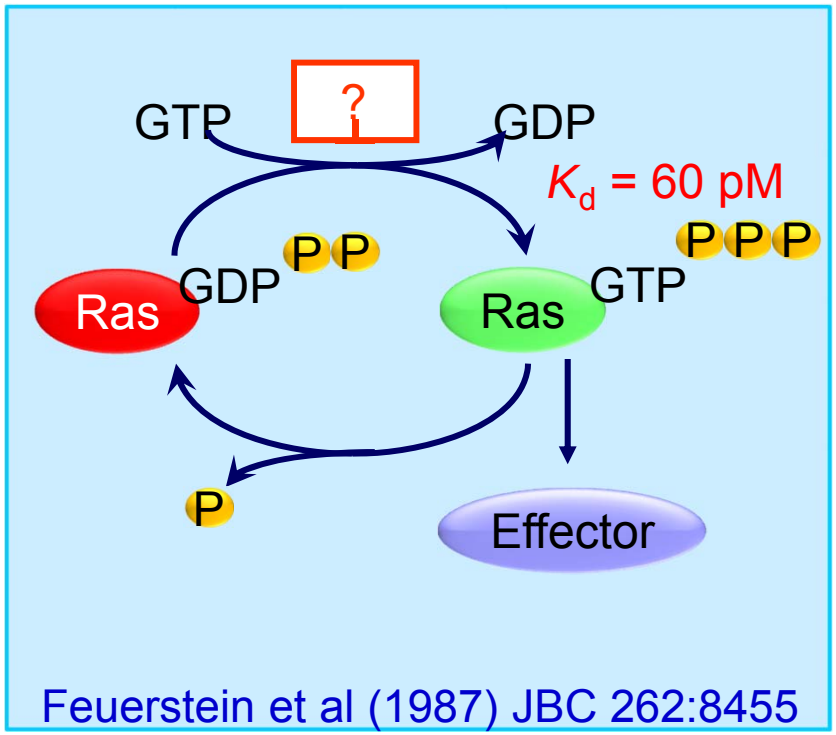




Ras binds GTP with pM affinity: Difficult to disrupt

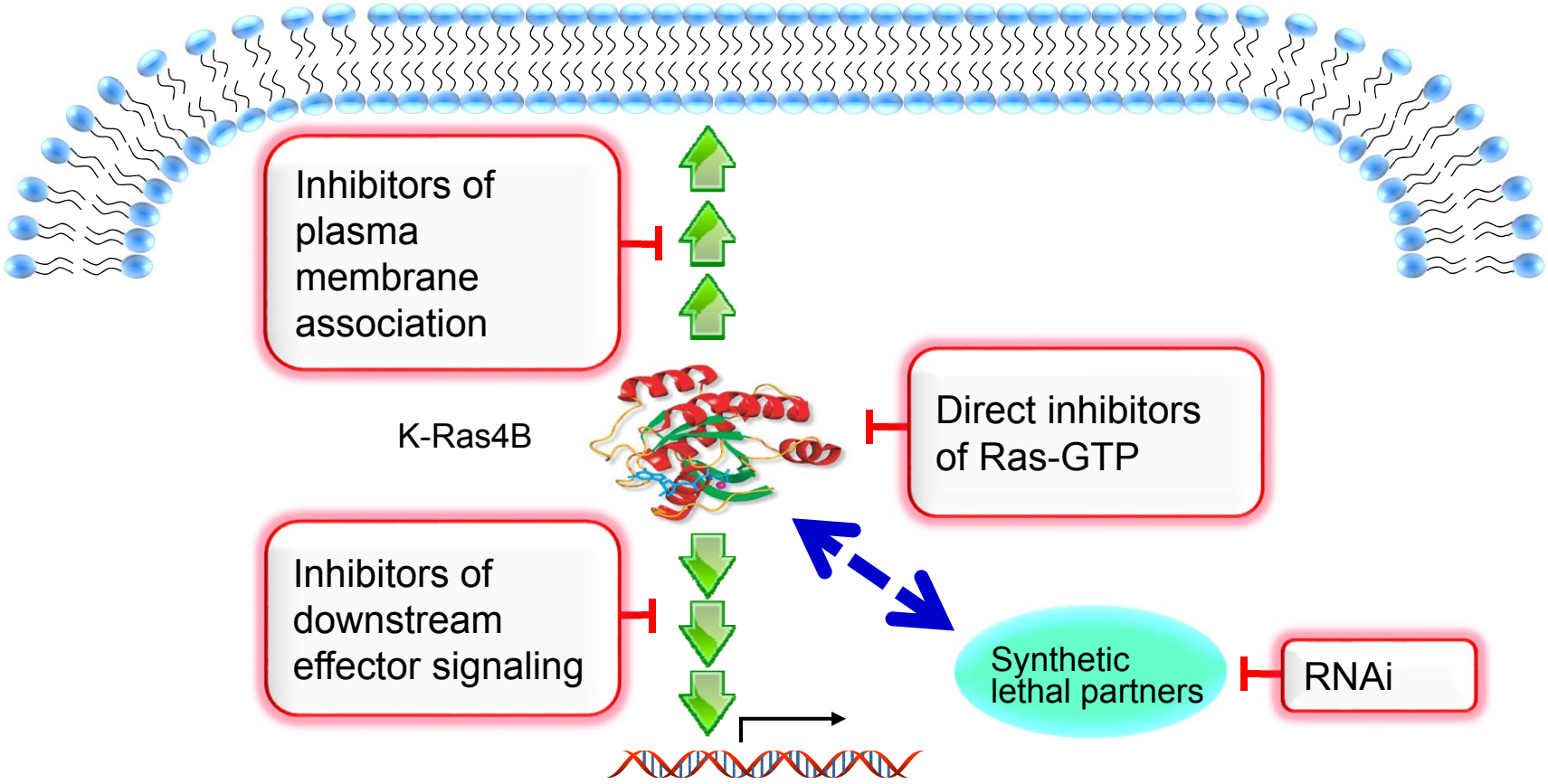


Yun et al (2008) PNAS 105:2070

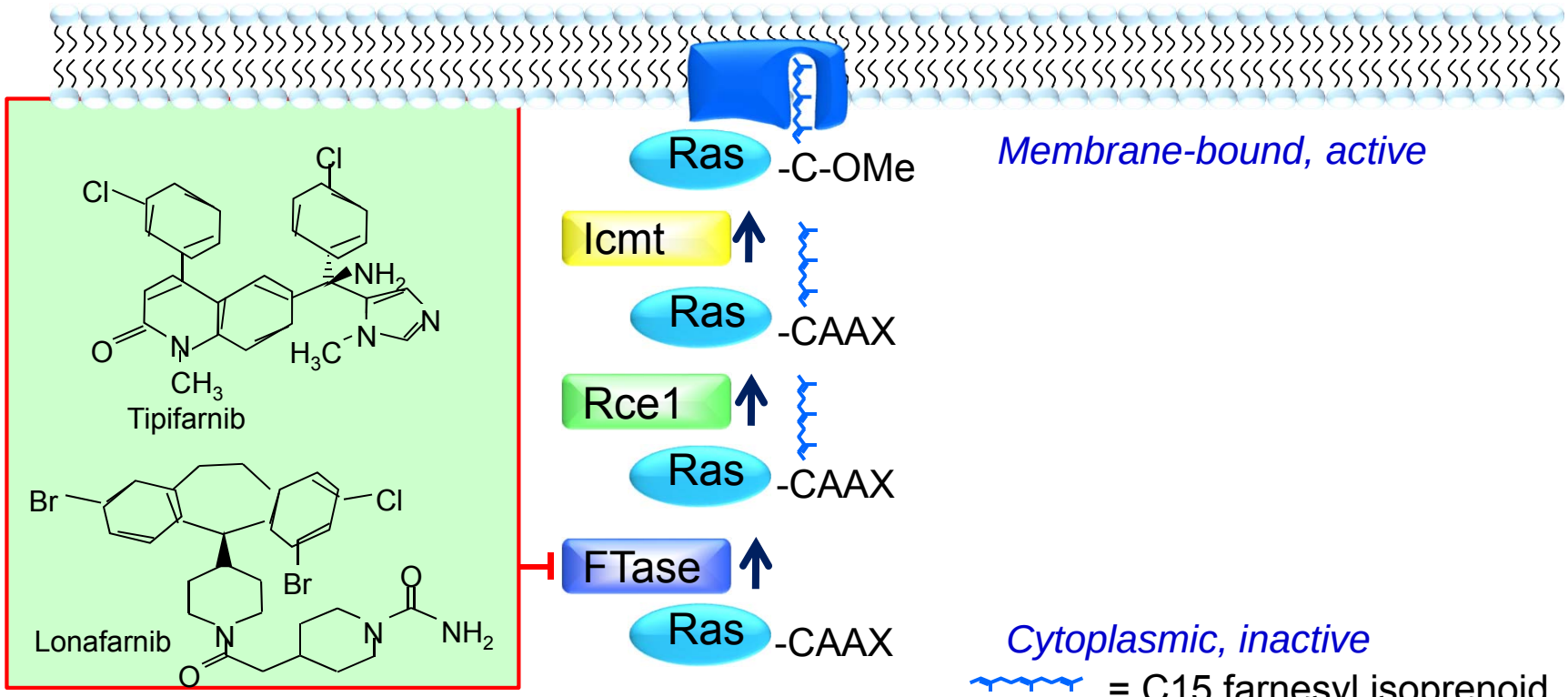


Feuerstein et al (1987) JBC 262:8455

Anti-K-Ras strategies

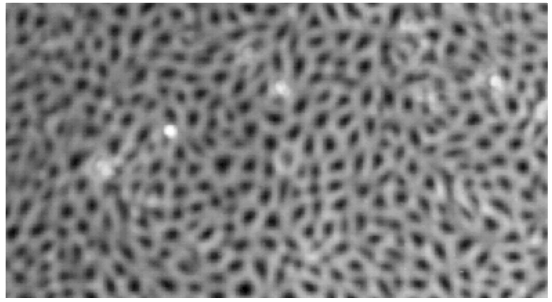


Inhibitors of Ras membrane association:
the farnesyltransferase inhibitors (FTIs)

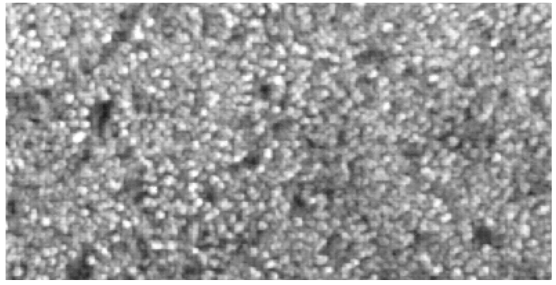


FTIs Reverse the Malignant Phenotype

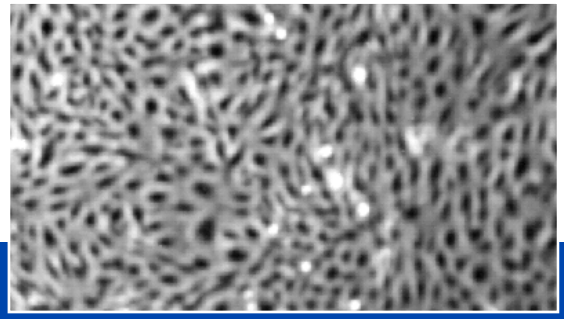
Control



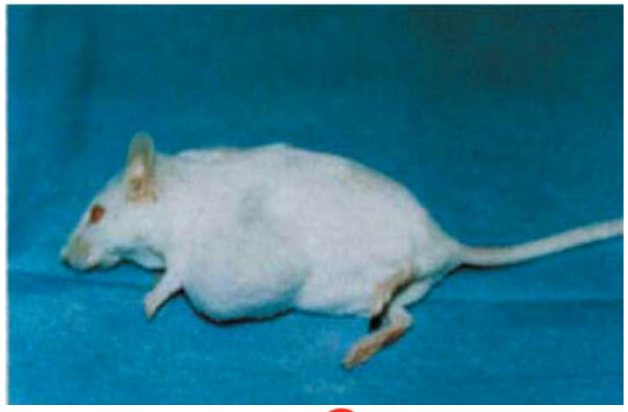
H-Ras Tranformed



H-Ras Transformed + FTI



FTIs Cure H-*ras* mutant Tumor-Bearing Mice



ARTICLES

Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in *ras* transgenic mice

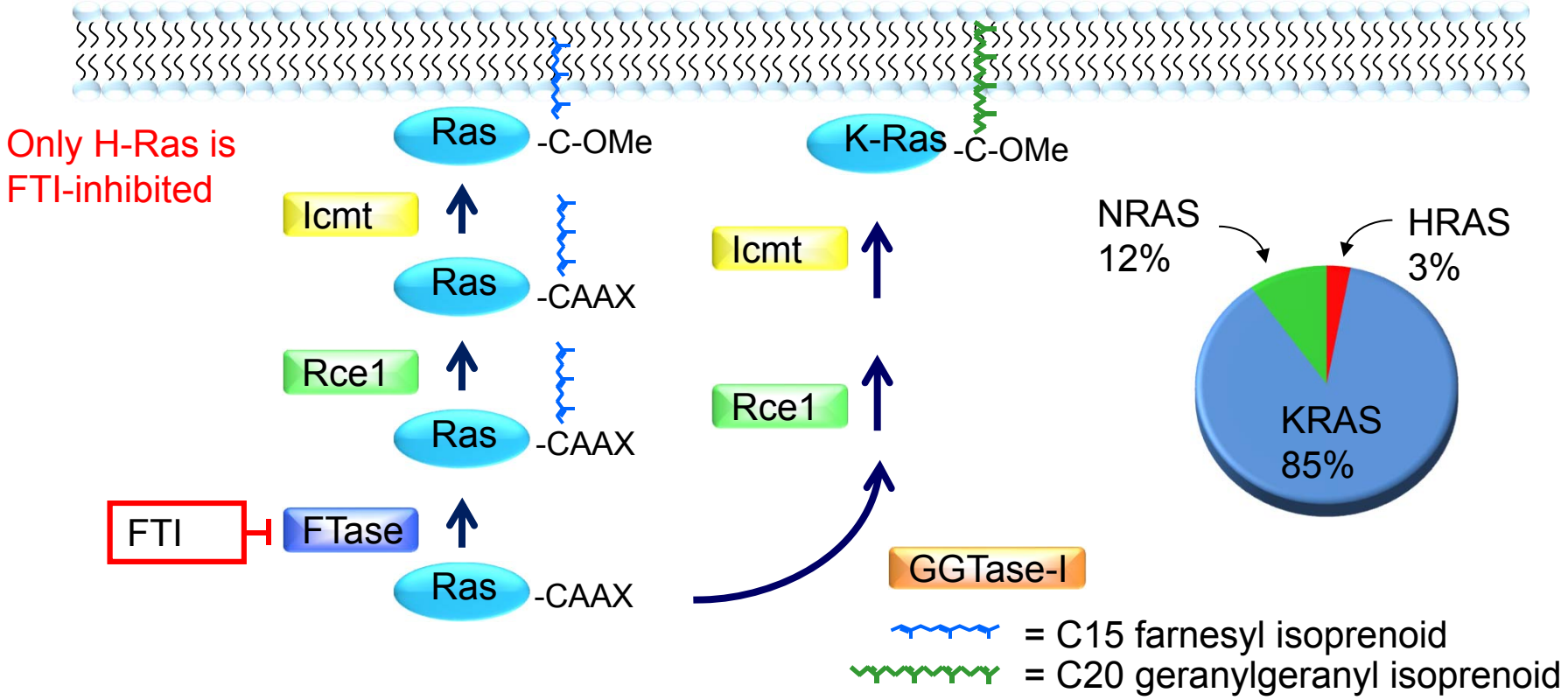
Nancy E. Kohl[1], Charles A. Omer[1], Michael W. Conner[2], Neville J. Anthony[3], Joseph P. Davide[1], S. Jane deSolms[3], Elizabeth A. Giuliani[3], Robert P. Gomez[3], Samuel L. Graham[3], Kelly Hamilton[1], Laurence K. Handt[4], George D. Hartman[3], Kenneth S. Koblan[1], Astrid M. Kral[1], Patricia J. Miller[1], Scott D. Mosser[1], Timothy J. O'Neill[1], Elaine Rands[1], Michael D. Schaber[1],

FTIs (Tipifarnib, Lonafarnib) Negative Pivotal trials

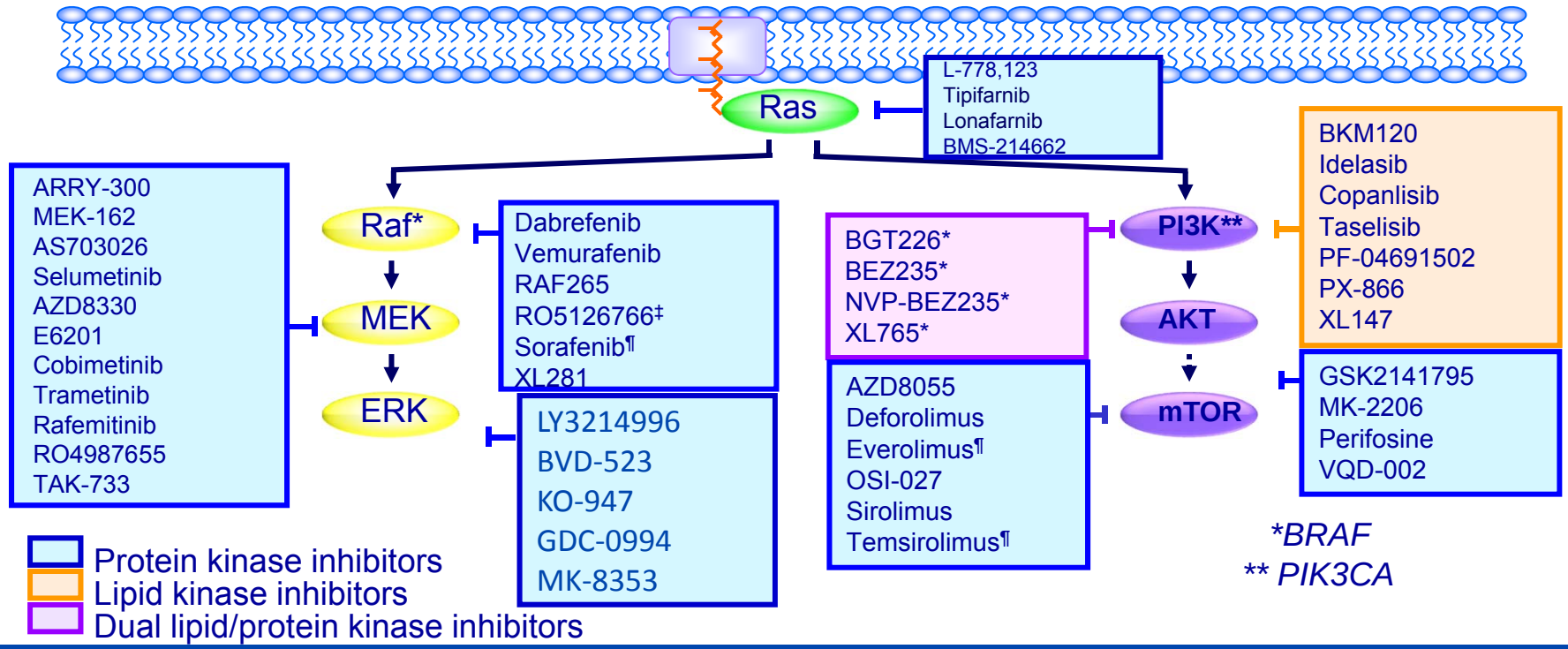
- Pancreatic Cancer
- Non-small Cell Lung Cancer
- Colorectal Cancer
- Acute Myelogenous Leukemia

Admit it .... you feel like doing this to someone everyday.

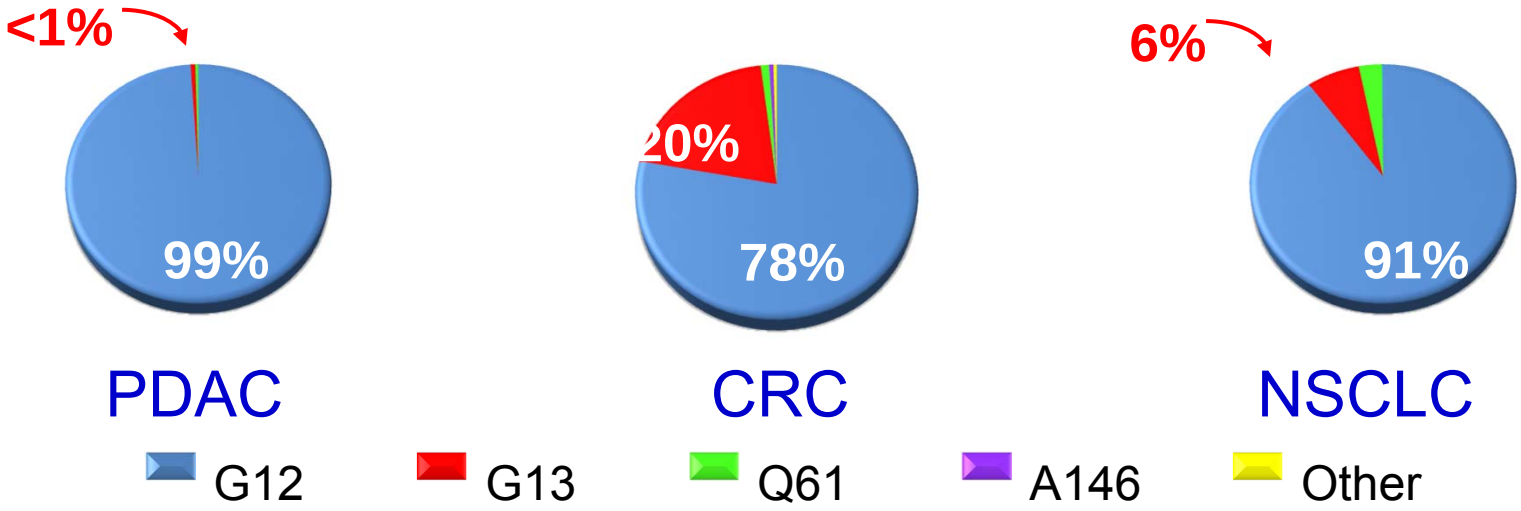
K-Ras and N-Ras undergo FTI-induced alternative prenylation



Efforts have focused on “indirect” inhibition of Ras Downstream Signaling

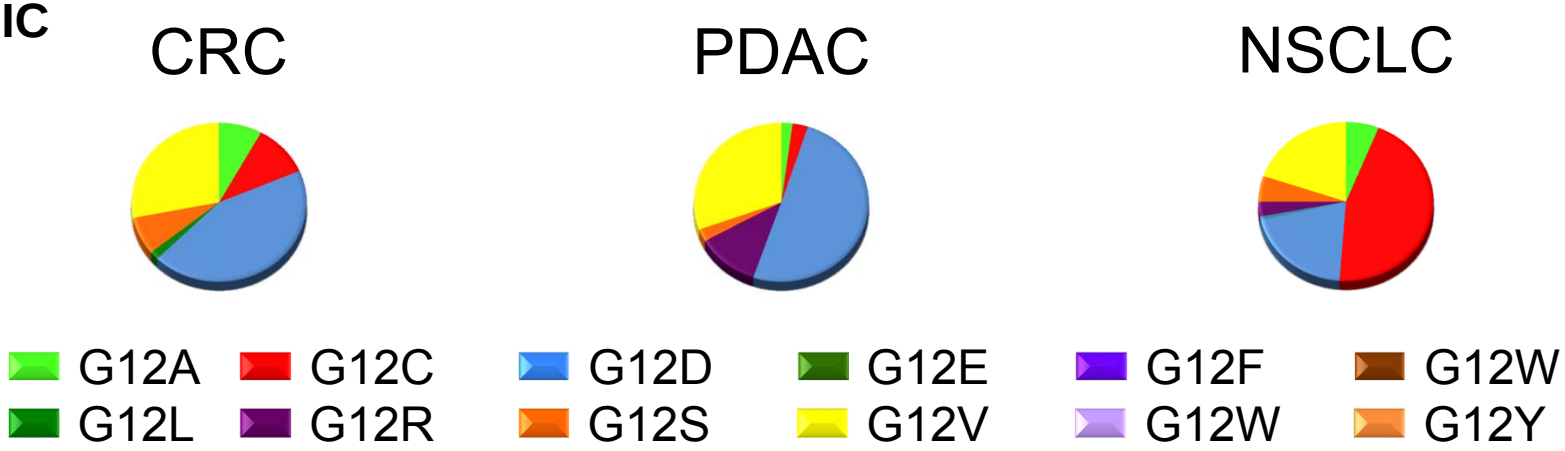


KRAS G12 mutations are the most frequent in different cancers



KRAS G12 mutation frequencies in different cancers may provide a role for mutation-specific therapies

COSMIC

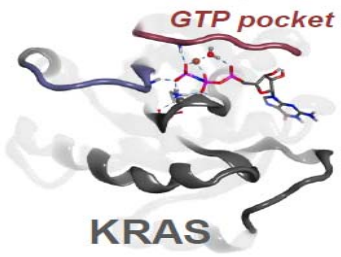


RAS mutations and oncogenesis: Miller & Miller (2011) Front Genet 2:100

Approach to inhibiting KRAS G12C

The KRAS Binding Problem

The KRAS GTP pocket is inaccessible due to high affinity for GTP

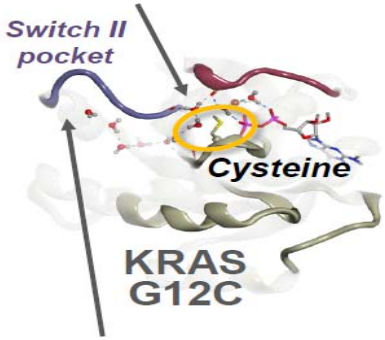


GTP binds and activates KRAS

KRAS tumor survival signaling

The KRAS G12C Opportunity

1. KRAS G12C has a **cysteine** present in its inactive form



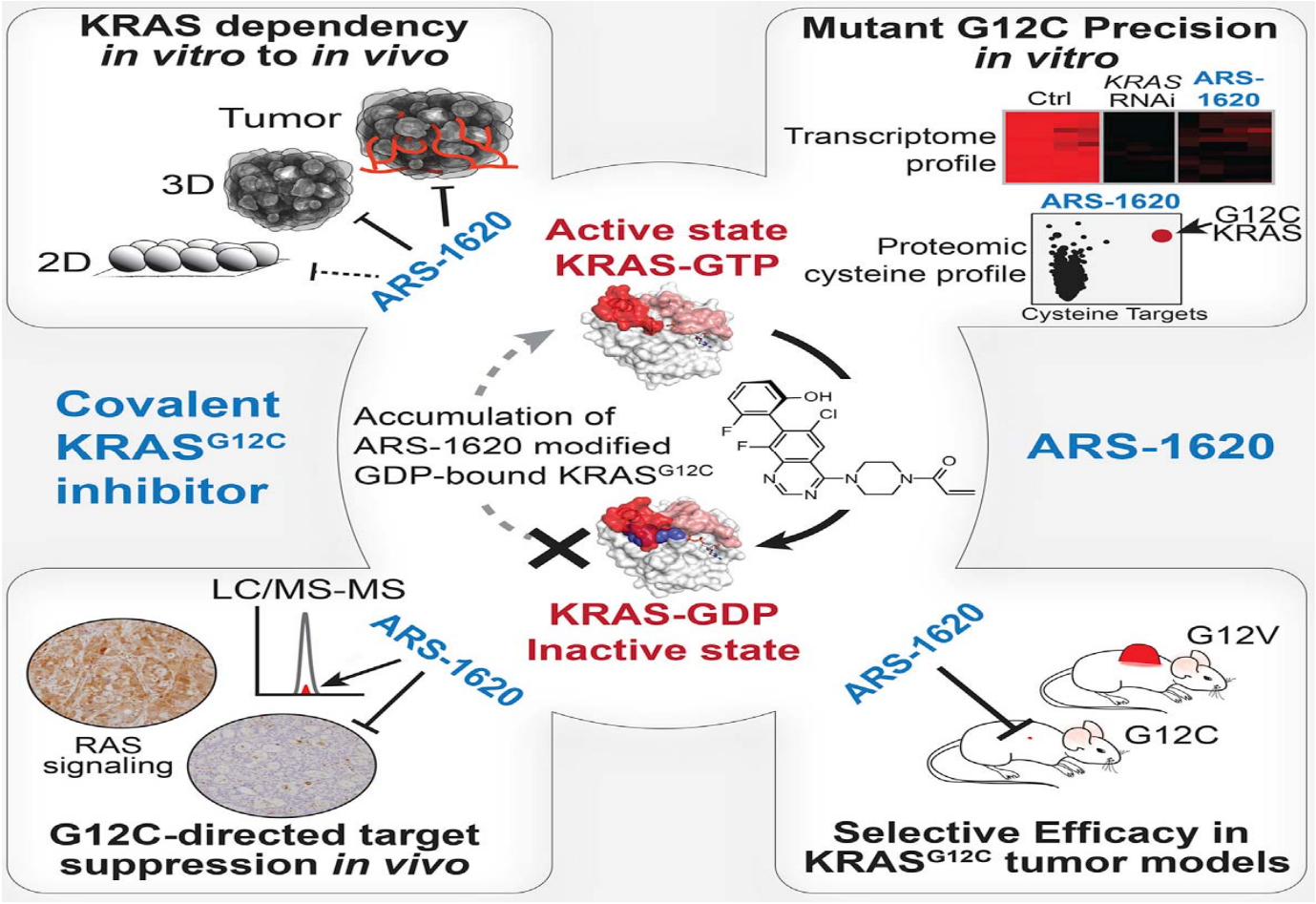
2. Binding to the cysteine opens an adjacent Switch II pocket

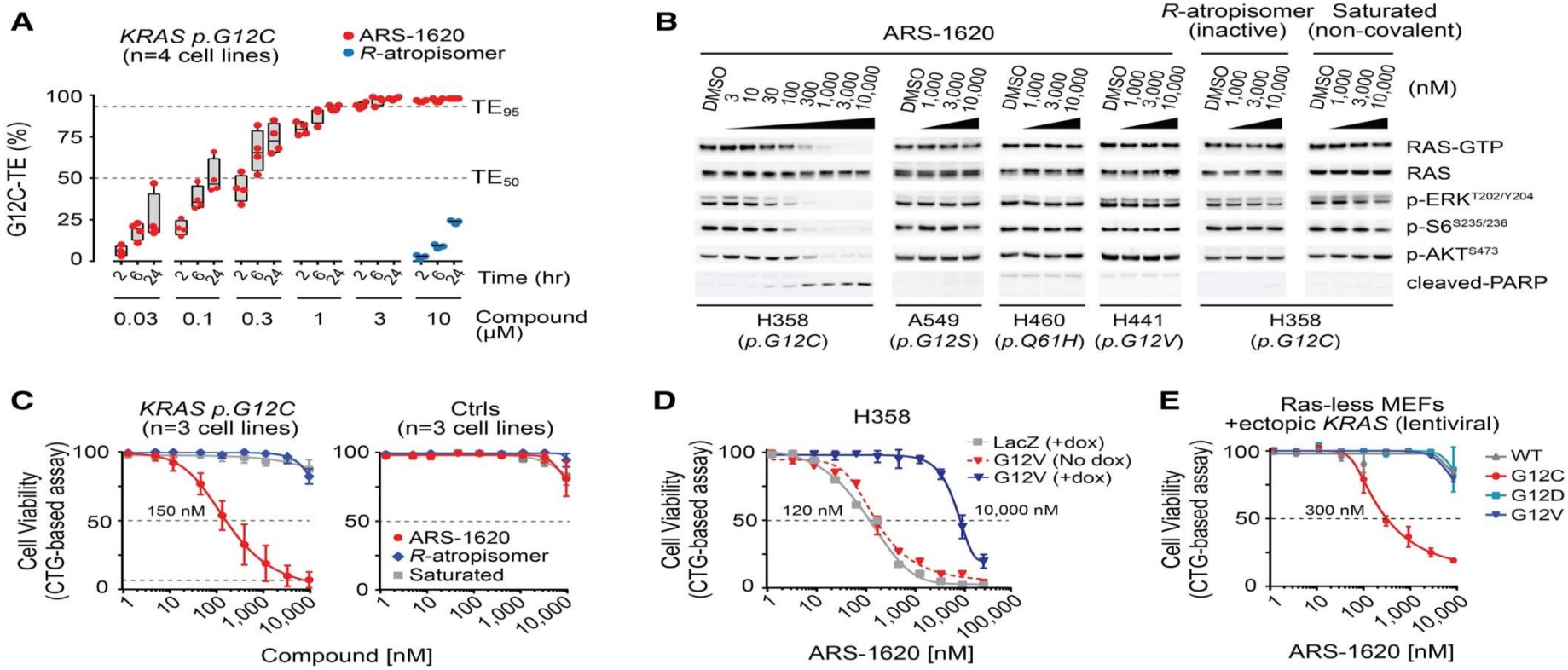
3. Inhibitor covalently binds to the **cysteine** and the induced **Switch II pocket**

4. KRAS G12C is irreversibly **locked** in the **inactive state**

KRAS tumor survival signaling is halted

Janes et al., 2018, Cell 172, 578–589


KRAS dependency
in vitro to in vivo
Tumor
3D
2D
ARS-1620
Mutant G12C Precision
in vitro
Ctrl
KRAS RNAi
ARS-1620
Transcriptome profile
ARS-1620
G12C KRAS
Proteomic cysteine profile
Cysteine Targets
Active state
KRAS-GTP
Covalent
KRAS G12C
inhibitor
Accumulation of
ARS-1620 modified
GDP-bound KRAS G12C
ARS-1620
KRAS-GDP
Inactive state
LC/MS-MS
ARS-1620
RAS signaling
G12C-directed target
suppression in vivo
ARS-1620
G12V
G12C
Selective Efficacy in
KRAS G12C tumor models



Janes et al., 2018, Cell 172, 578–589

Covalent Inhibitors of KRAS G12C in the clinic

- AMG 510 (NCT03600883)
- MRTX 849 (NCT03785249)
- JNJ-74699157 (NCT04006301)

Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics (PK) and Efficacy of AMG 510, a Novel Small Molecule KRAS^{G12C} Inhibitor, in Advanced Solid Tumors

Marwan G Fakih, MD;[1] Bert Howard O'Neil, MD;[2] Timothy J Price, MBBS, FRACP;[3] Gerald S Falchook, MD;[5] Jayesh Desai, MBBS, FRACP;[6] James Kuo, MBBS, FRACP;[7] Ramaswamy Govindan, MD;[8] Erik Rasmussen, MS;[4] Phuong Khanh Morrow, MD;[4] Jude Ngang, PharmD;[4] Haby Henary, MD;[4] David Hong, MD[9]

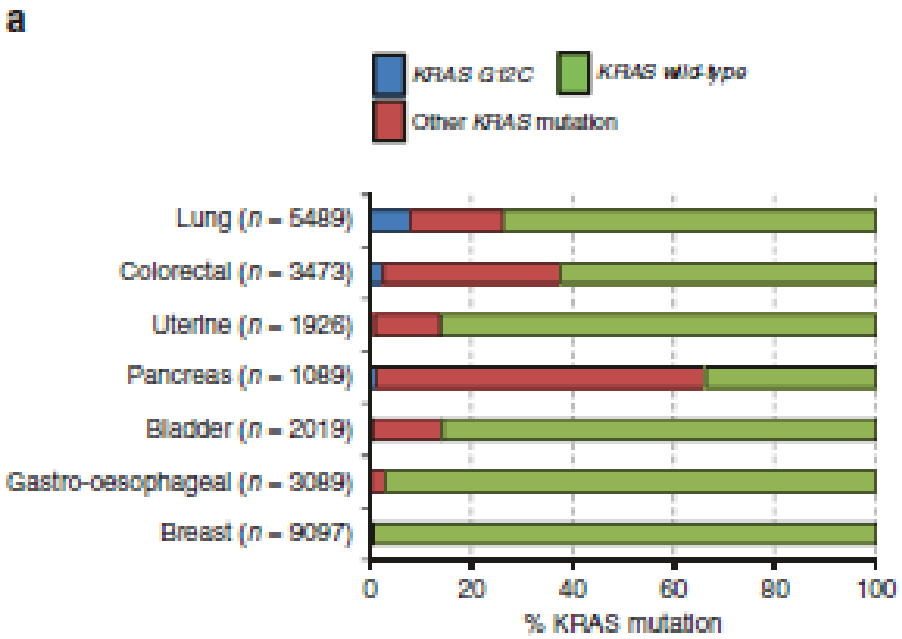
[1]City of Hope, Duarte, CA, USA; [2]Indiana University, Simon Cancer Center, Indianapolis, IN, USA; [3]The Queen Elizabeth Hospital, Woodville South, AU; [4]Amgen Inc, Thousand Oaks, CA, USA; [5]Sarah Cannon Research Institute, Denver, CO, USA; [6]Peter MacCallum Cancer Centre, Melbourne, AU; [7]Scientia Clinical Research, Randwick, AU, [8]Washington University, St Louis, MO, USA; [9]MD Anderson Cancer Center, Houston, TX, USA

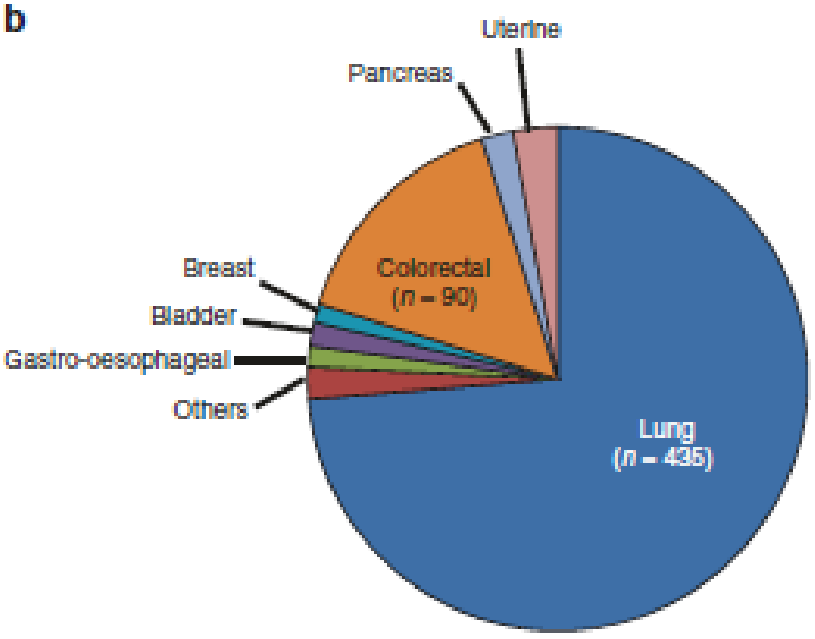
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Marwan G. Fakih, MD

MAYO CLINIC

Proportion of G12C and non G12C mutations in selected cancers

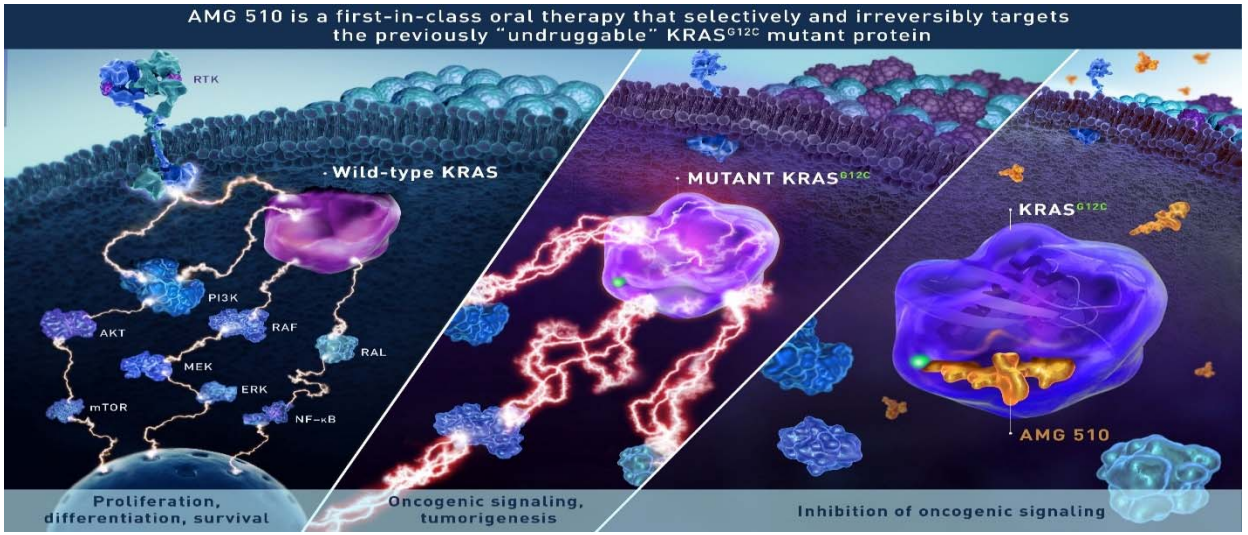




- **13% of NSCLC**, **3% of CRC** & appendix cancer, and **1%–3% of other solid tumors**

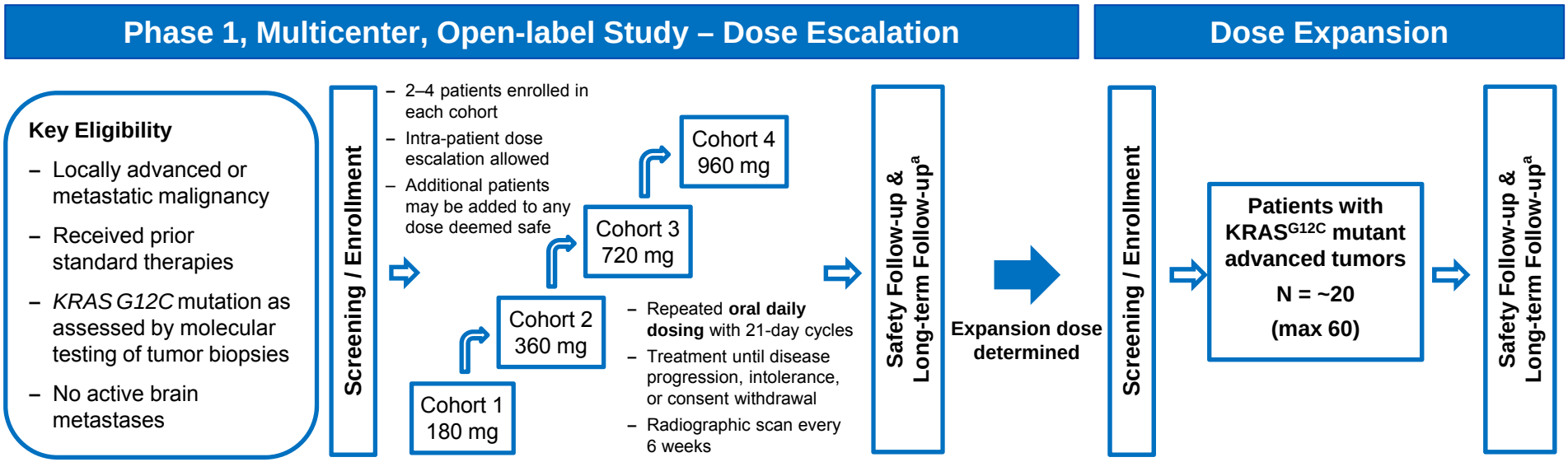
AMG 510 is a First-in-Class KRAS^{G12C} Inhibitor

- AMG 510 specifically and irreversibly inhibits KRAS^{G12C} by permanently locking it in an inactive GDP-bound state



1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198.
2. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862.
3. Zhou L, et al. *Med Oncol.* 2016;33:32.

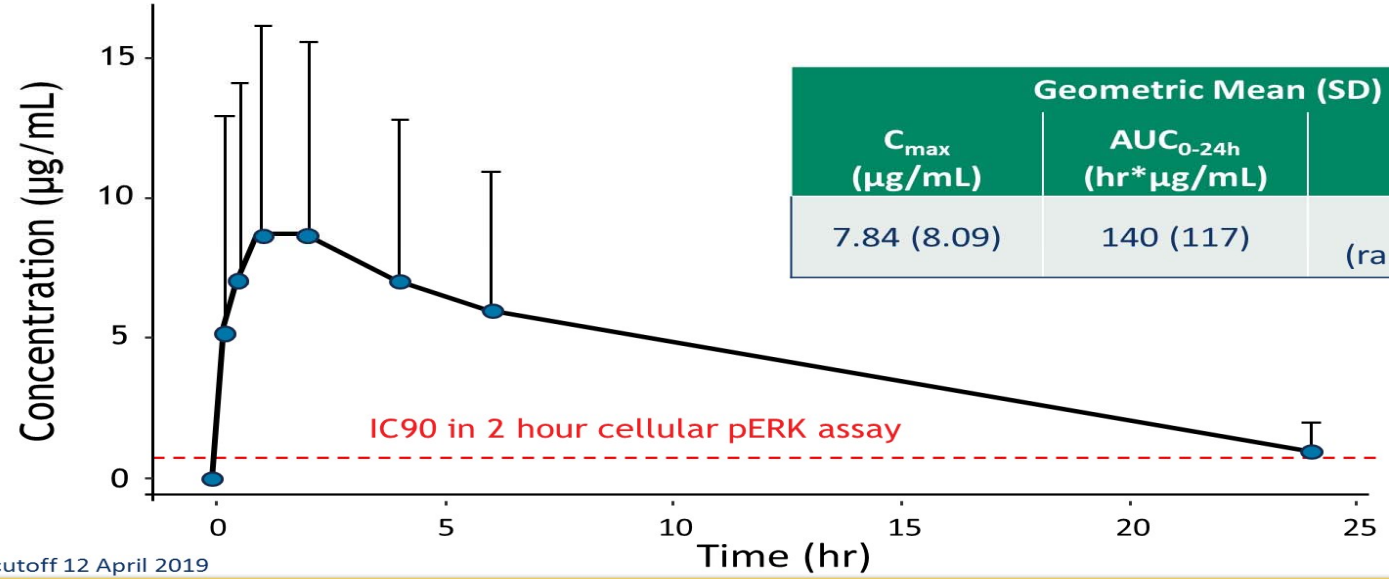
AMG 510 First-in-Human Study Design



Primary endpoints: dose-limiting toxicities; safety
Key secondary endpoints: PK; objective response rate; duration of response; disease control rate; PFS; duration of stable disease

[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

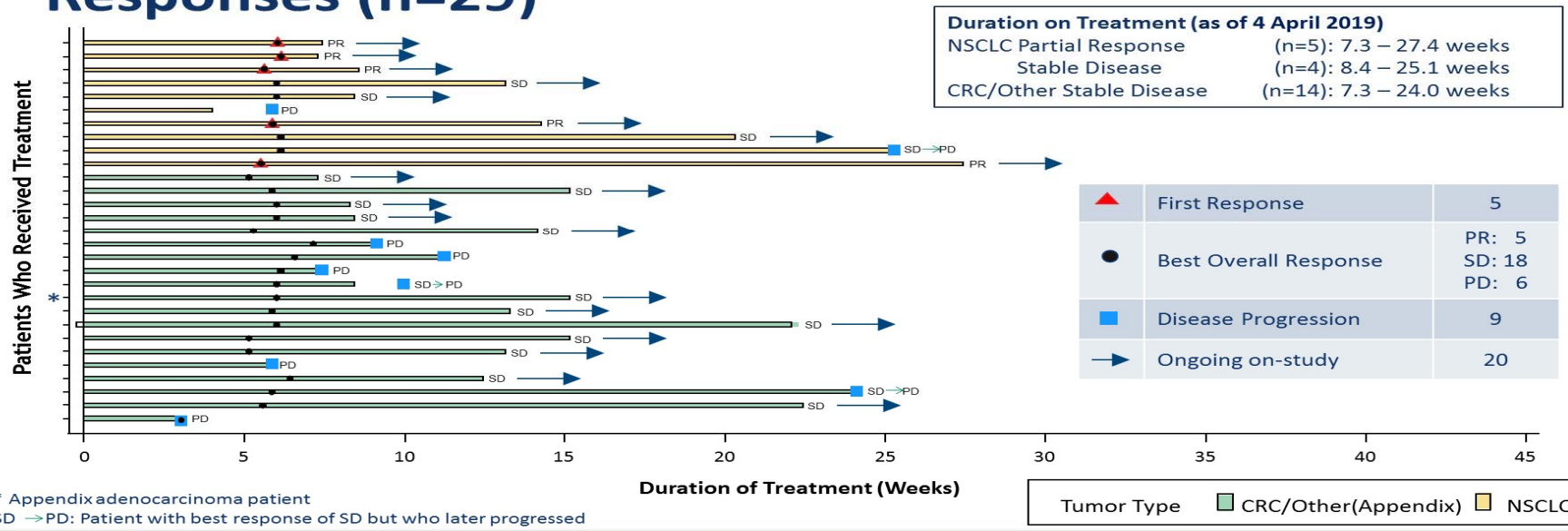
AMG 510 Pharmacokinetic Profile - 960 mg PO Dose (n=9*)



Geometric Mean (SD)		
C_{max} (µg/mL)	AUC_{0-24h} (hr*µg/mL)	$t_{1/2,z}$ (hr)
7.84 (8.09)	140 (117)	6.5 (range: 4.2-8.0)

*PK data cutoff 12 April 2019

Duration of Treatment by Tumor Types and Responses (n=29)



Duration on Treatment (as of 4 April 2019)

NSCLC Partial Response	(n=5): 7.3 – 27.4 weeks
Stable Disease	(n=4): 8.4 – 25.1 weeks
CRC/Other Stable Disease	(n=14): 7.3 – 24.0 weeks

First Response	5
Best Overall Response	PR: 5 SD: 18 PD: 6
Disease Progression	9
Ongoing on-study	20

Tumor Type: CRC/Other(Appendix) NSCLC

* Appendix adenocarcinoma patient

SD →PD: Patient with best response of SD but who later progressed

CRC: Individual Patient Radiologic Response and Biomarkers

Demographics:

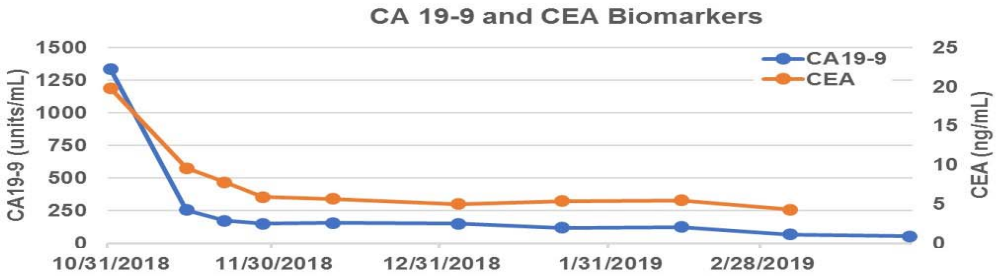
34 y.o. Female, diagnosed with metastatic colon adenocarcinoma April 2014

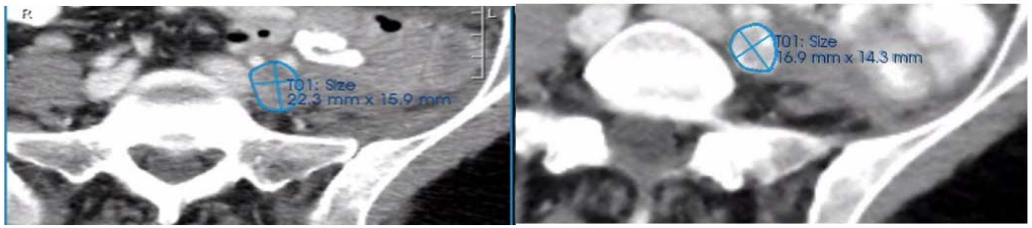
Treatment history:

- FOLFOX and HIPEC in Aug 2015, followed by FOLFOX until Dec 2015
- FOLFIRI with PD in Aug 2016
- HIPEC Oct 2016
- Capecitabine + bevacizumab Aug 2017
- Phase I clinical trial March-June 2018
- AMG 510 - 360 mg since Oct 2018

Response:

- Biochemical response (normal CEA)
- SD (-18% local read), still on treatment (22.3 weeks as of data cutoff)

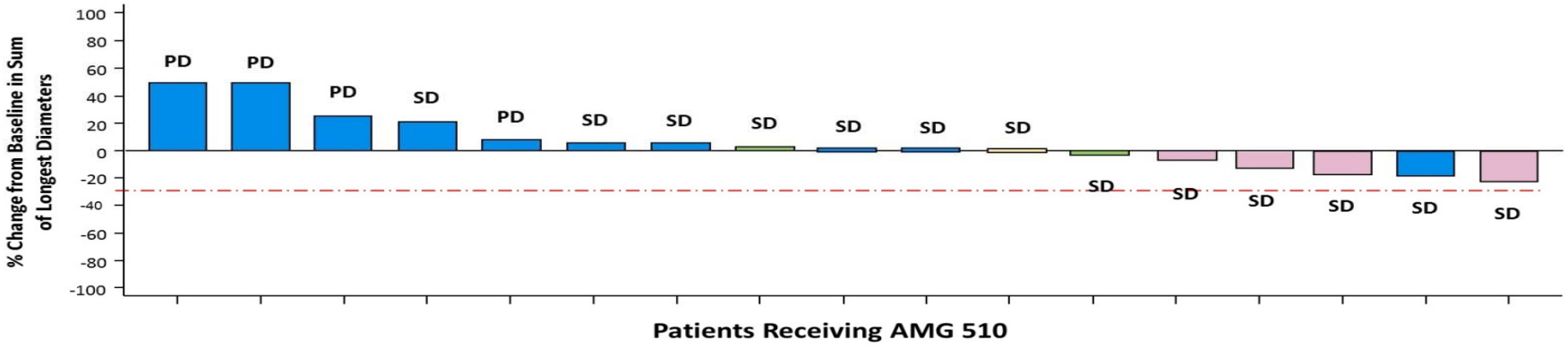




Baseline

Week 24 Follow-up

CRC and Other Solid Tumors: Best Tumor Response* (n=19)



* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 CRC patient progressed prior to week 6 and is not on this graph
1 appendix patient had clinically stable disease but is not shown on this graph

Planned Dose 180 mg 360 mg 720 mg 960 mg

CRC Cohort : Update at ESMO

- 12 pts treated at RP2D
- 1 PR (8%)
- 10 SD
- DCR (92%)

Phase 1 Study of Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510, a Novel KRAS^{G12C} Inhibitor, in Non-Small Cell Lung Cancer

Ramaswamy Govindan, MD;[1] Marwan G Fakih, MD;[2] Timothy J Price, MBBS, DHlthSci, FRACP;[3] Gerald S Falchook, MD;[4] Jayesh Desai, MBBS, FRACP;[5] James C Kuo, MBBS, FRACP;[6] John H Strickler, MD;[7] John C Krauss, MD;[8] Bob T Li, MD;[9] Crystal S Denlinger, MD;[10] Greg Durm, MD;[11] Jude Ngang, PharmD;[12] Haby Henary, MD;[12] Gataree Ngarmchamnanrith, MD;[12] June Kim, PhD;[12] Phuong Khanh Morrow, MD;[12] David S Hong, MD[13]

[1]Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, MO, USA; [2]City of Hope, Duarte, CA, USA; [3]The Queen Elizabeth Hospital, Woodville South, Australia; [4]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]Scientia Clinical Research, Randwick, Australia; [7]Duke University Medical Center, Durham, NC, USA; [8]University of Michigan, Ann Arbor, MI, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Fox Chase Cancer Center, Philadelphia, PA, USA; [11]Indiana University, Simon Cancer Center, Indianapolis, IN, USA; [12]Amgen Inc., Thousand Oaks, CA, USA; [13]MD Anderson Cancer Center, Houston, TX, USA

Patient Disposition

Overall Trial Accrual

N = 76
Total patients enrolled
- NSCLC, N = 34
- CRC, N = 36
- SCLC, N = 1[a]
- Appendiceal cancer, N = 3
- Endometrial cancer, N = 1
- Small bowel cancer, N = 1

N = 34
NSCLC patients enrolled

N = 19, escalation cohort
- 180 mg: N = 3
- 360 mg: N = 2
- 720 mg: N = 6
- 960 mg: N = 8

N = 15, expansion cohort
- 960 mg: N = 15

N = 23, evaluable
- Patients who had the first 6-week scan or early progressive disease

N = 30
Remained on study

N = 4
Discontinued study[b]
- None was related to treatment

First patient enrolled: 27 August 2018

Data cutoff: 17 July 2019

Baseline Characteristics

Baseline Characteristics	N = 34
Median age (range) – years	67.5 (49.0–77.0)
Female – n (%)	18 (52.9)
ECOG performance status score – n (%) 0 1 2	 5 (14.7) 26 (76.5) 3 (8.8)
Prior lines of systemic anticancer therapy – n (%) 1 2 > 2	 2 (5.9) 3 (8.8) 29 (85.3)
No. of prior systemic anticancer therapy – median (range)	3.5 (1–8)

Patient Incidence of Adverse Events (AEs): Summary

	All AEs N = 34 n (%)	All treatment-related AEs N = 34 n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	26 (76.5) 20 (58.8) 11 (32.4) 5 (14.7)	**12 (35.3)** **8 (23.5)** **3 (8.8)** **0 (0)**
Dose-limiting toxicity	0 (0)	**0 (0)**
Serious AEs	8 (23.5)	**0 (0)**[b]
Fatal AEs	4 (11.8)[a]	**0 (0)**
AEs leading to treatment discontinuation	0 (0)	**0 (0)**

- No dose-limiting toxicities were reported
- No treatment-related serious or fatal AEs were reported
- There were no AEs leading to treatment discontinuation

- **960 mg oral daily dose** was identified as the expansion dose and recommended phase 2 dose

Patient Incidence of Treatment-Related Adverse Events (AEs)

All Treatment-Related AEs	Any Grade N = 34, n (%)	Grade 3 N = 34, n (%)
Any treatment-related AEs	12 (35.3)	3 (8.8)
Diarrhea	4 (11.8)	2 (5.9)
Nausea	2 (5.9)	0 (0)
Dry mouth	1 (2.9)	0 (0)
Vomiting	1 (2.9)	0 (0)
ALT increased	2 (5.9)	0 (0)
AST increased	2 (5.9)	0 (0)
Blood alkaline phosphate increased	1 (2.9)	0 (0)
Lymphocyte count decreased	1 (2.9)	0 (0)
White blood cell count decreased	1 (2.9)	0 (0)

Cont.

All Treatment-Related AEs	Any Grade N = 34, n (%)	Grade 3 N = 34, n (%)
Decreased appetite	1 (2.9)	0 (0)
Hyperkalemia	1 (2.9)	0 (0)
Hypokalemia	1 (2.9)	0 (0)
Anemia	1 (2.9)	1 (2.9)
Leukopenia	1 (2.9)	0 (0)
Dysgeusia	1 (2.9)	0 (0)
Neuropathy peripheral	1 (2.9)	0 (0)
Proteinuria	1 (2.9)	0 (0)

- 12 of 34 patients **(35.3%)** reported treatment-related AEs; most were grade 1 or 2
- 3 of 34 patients **(8.8%)** reported two grade 3 treatment-related AEs: diarrhea and anemia
- There were no grade 4 or higher treatment-related AEs.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AE: adverse event.

NSCLC: Individual Patient Radiologic Responses

Demographics:

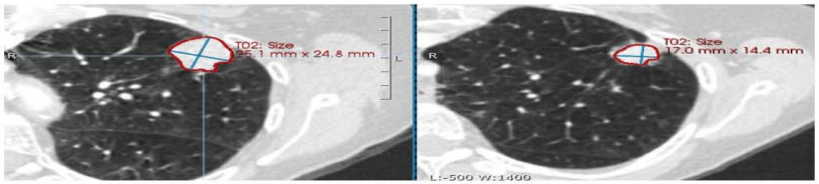
61 y.o. Female, diagnosed with KRAS^{G12C} metastatic NSCLC August 2010

Treatment history:

- Radiation + Carboplatin/Taxol from Aug 2010 until Oct 2010
- Carboplatin/Pemetrexed from Oct 2016 until Jun 2017
- Nivolumab from Aug 2017 until Apr 2018
- AMG 510 – 180 mg since Sept 2018

Best Response:

- PR (-34% central read) Still on treatment (27.4 weeks as of data cutoff)



Demographics:

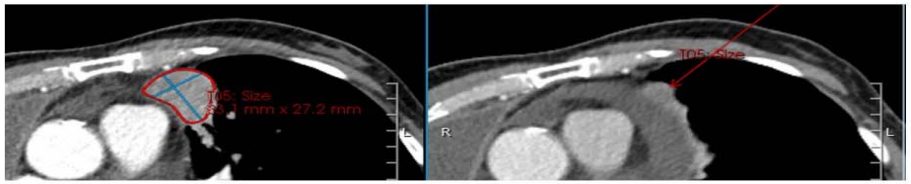
59 y.o. Male, with KRAS^{G12C} metastatic NSCLC, December 2013

Treatment history:

- Carboplatin/Pemetrexed Feb 2014 until Feb 2015
- Erlotinib from April 2015 until Jun 2015
- Nivolumab Aug 2015 until Aug 2017
- Dasatinib from Jul 2016 until Aug 2017
- M3541 (Targeted biologic) from Oct 2017 until Nov2017
- AMG 510 - 360 mg since Dec 2018

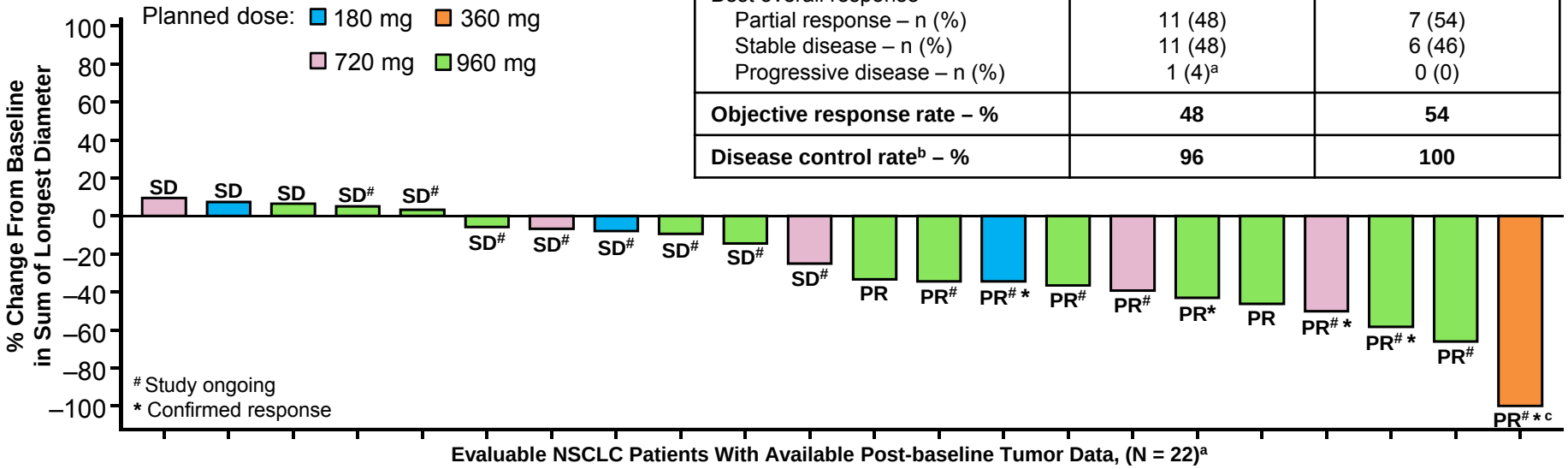
Best Response:

- PR (-67% central read) Still on treatment (14.3 weeks as of data cutoff)
- CR to the targeted lesions were reported at week 18 (post data cutoff)



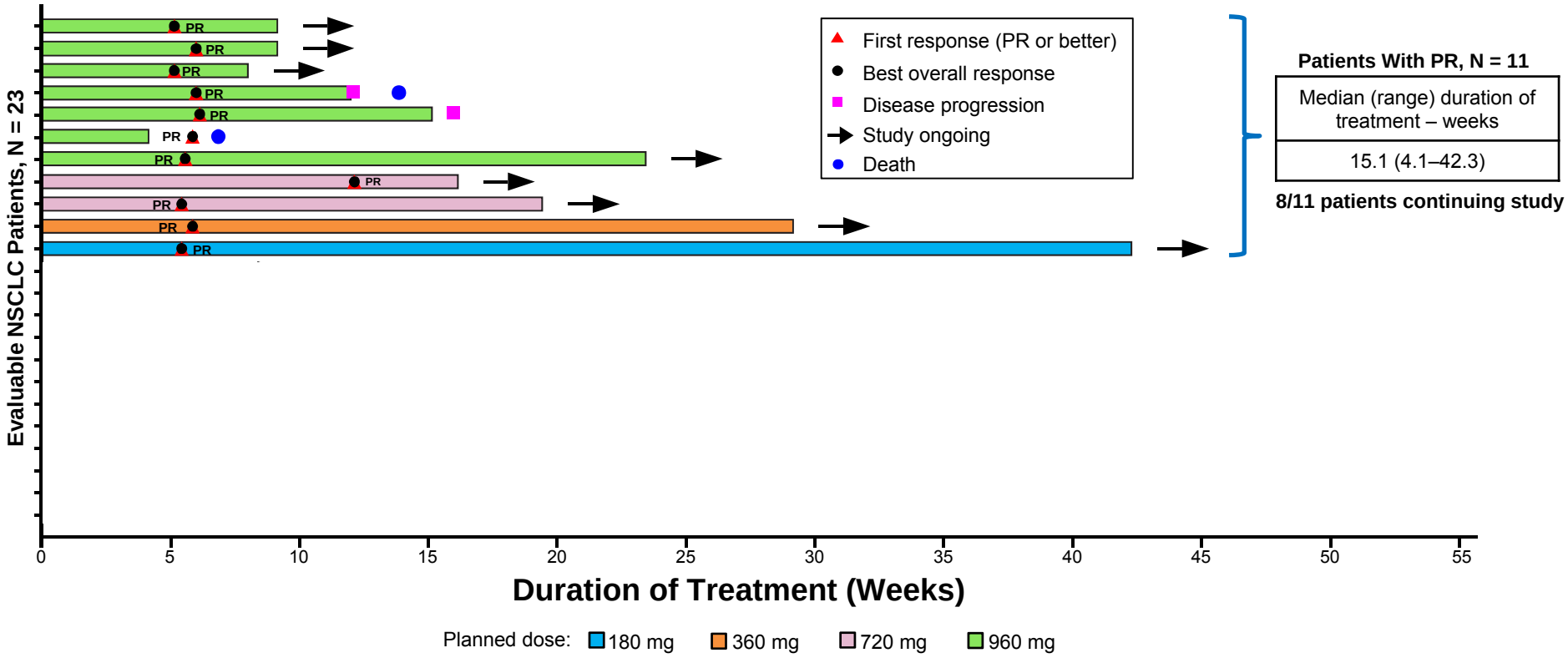
Best Tumor Response and Change in Tumor Burden From Baseline

Efficacy outcomes	All evaluable patients N = 23	Evaluable patients treated with 960mg N = 13
Best overall response		
Partial response – n (%)	11 (48)	7 (54)
Stable disease – n (%)	11 (48)	6 (46)
Progressive disease – n (%)	1 (4)[a]	0 (0)
Objective response rate – %	**48**	**54**
Disease control rate[b] – %	**96**	**100**

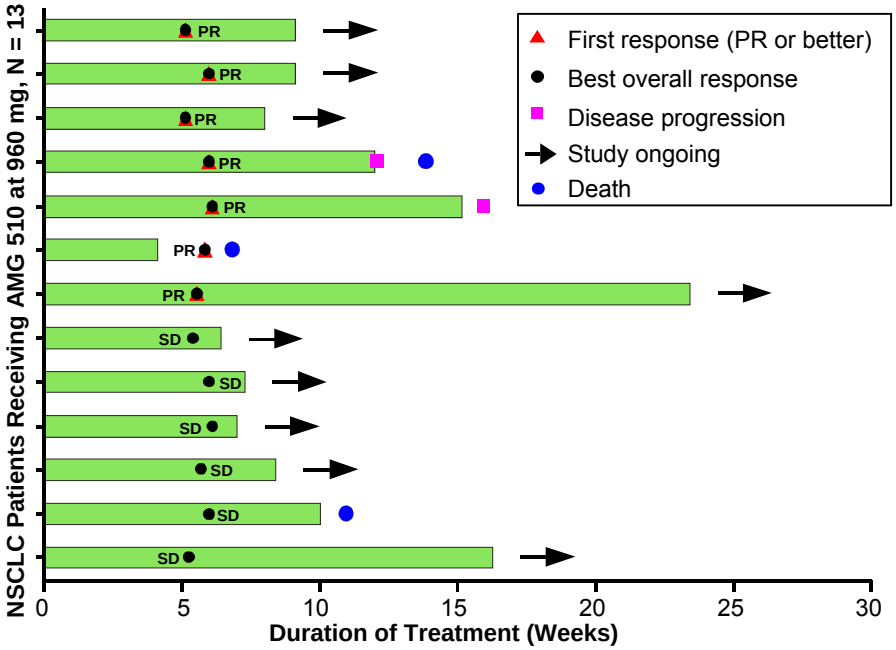


[a]One patient discontinued study due to PD prior to the 1st assessment, and the post-baseline tumor burden data are missing. [b]PR or SD at week 6. [c]Patient had complete response to the target lesions. Evaluable patients: patients who had the first 6-week scan or early PD; NSCLC: non-small cell lung cancer; PR: partial response; SD: stable disease; PD: progressive disease.

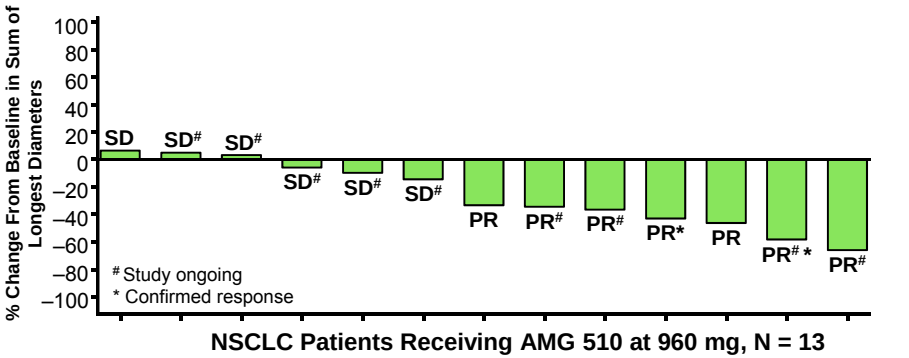
Time to Response and Duration of Treatment for All Dose Levels



Efficacy of AMG 510 Administered at 960 mg, the Recommended Phase 2 Dose



Efficacy with 960 mg	Evaluable NSCLC patients receiving 960 mg, N = 13
Best overall response Partial response – n (%) Stable disease – n (%) Progressive disease – n (%)	 7 (54) 6 (46) 0 (0)
Objective response rate – %	**54**
Disease control rate[a] – %	**100**



[a]PR or SD at week 6. Evaluable patients: patients who had the first 6-week scan or early progressive disease; PR: partial response; SD: stable disease.

AMG 510 Updates

- Expansion cohorts ongoing
- Combination with Trametinib
- Combination with AMG 404
- Other Combinations
- *Ongoing preclinical studies aimed at inhibiting G12D tumors*

Inhibiting Kras in the Clinic

We are almost there…….

MAYO CLINIC

THANKS!

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