Other Driver Mutations:

cMET, B-RAF, RET, NTRK

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Memorial Cancer Institute
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Herbert Wertheim College of Medicine
Florida International University

Research Support: *BMS*

Genentech/Roche
Pfizer

Biodesix
MSD

Merck Serono
Lilly Oncology

Boheringer Ingelheim
Novartis
Astra-Zeneca

Liquid Genomics

Speakers Bureau/Stocks: *None*

NTRK TRANSLOCATIONS

NTRK (TRK1, TRK2 and TRK3) Targets in NSCLC Therapy

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Memorial Cancer Institute
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Florida International University (FIU)

NTRK 1-3 are protein coding genes contained within the DNA of a cell that provide instructions for synthesizing proteins.

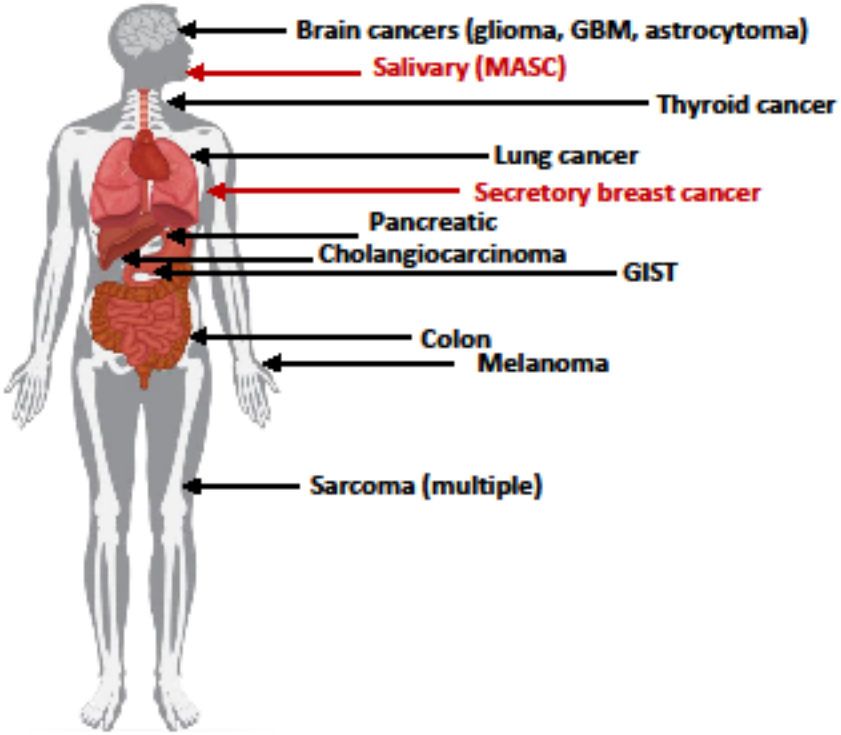
The NTRK 1-3 genes encode for the TRK (tropomyosin receptor kinase) family of receptor proteins that sit on the surface of cells, known as TrkA, TrkB, and TrkC.

TRK receptors are found primarily in neurons. The activating ligands are collectively referred to as neurotrophins (nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3 and NT-4). These signaling pathways help regulate how neurons function in the setting of pain, cognition, movement, memory, propioception and mood.

Translocations involving the TRK kinase domain, mutations involving the TRK ligand-binding site, amplifications of NTRK, TRK splice variants, and autocrine/paracrine signaling are described in lung cancer and other tumor types, and contribute to tumorigenesis (Vaishnavi, 2013).

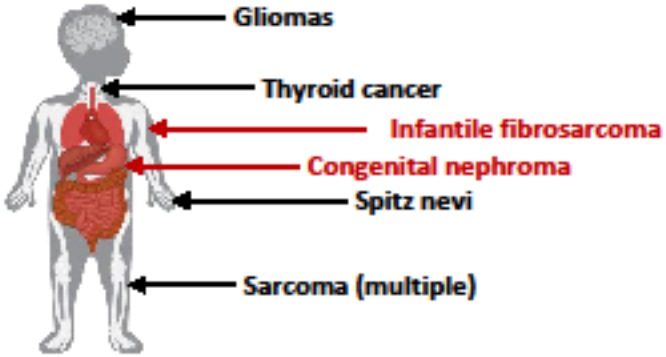
**TrkA is present 3.3% , TrkB in 1.39% and TrkC < 1% .

TRK fusions found in diverse cancer histologies



Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



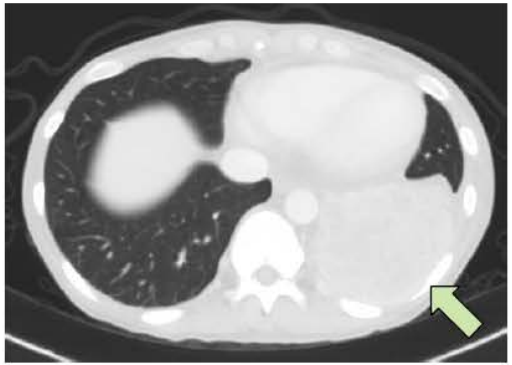
Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

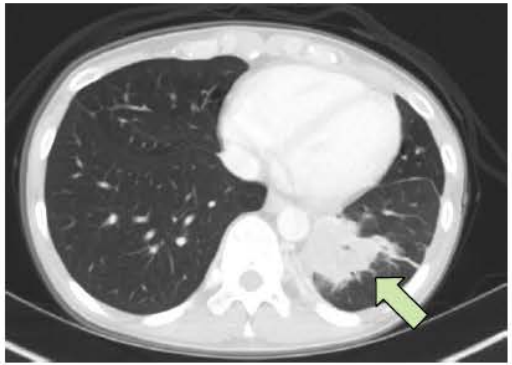
Clinical activity of larotrectinib in patients with TRK fusion cancers

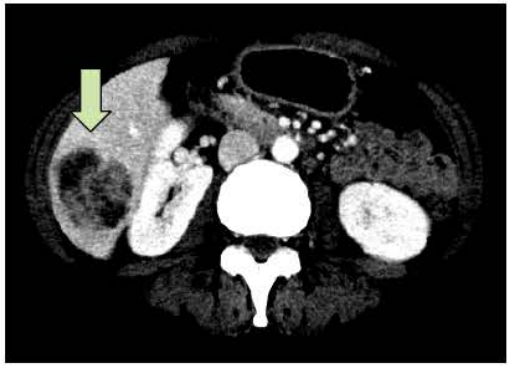
	Enrolled patients with confirmatory response data available (n=50)	All enrolled patients (n=55)*
Objective response rate (95% CI)	**76%** (62–87%)	**78%** (65–88%)
Partial response	**64%**	**65%***
Complete response	**12%**	**13%***
Stable disease	12%	11%
Progressive disease	12%	11%

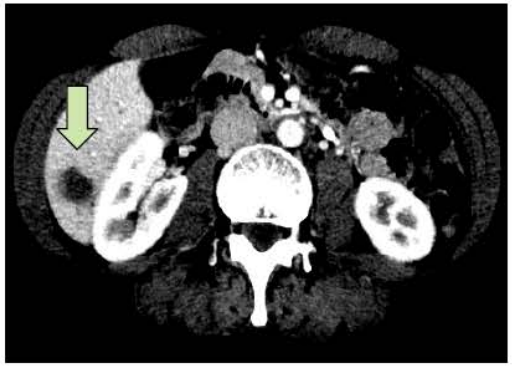
*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.

SQSTM1-NTRK1 lung cancer patient









Baseline

Cycle 4

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms

LOXO-101 : TRK-A, TRK-B, TRK-C INHIBITOR

(Bouhana et al. 2014 EORTC-NCI-AACR SYMPOSIUM NOV 20, 2014)

Phase I of LOXO-101: 15 patients evaluated across 3 dose cohorts
Orally administered and generally well tolerated.
Most common AEs: Gr1 and 2 fatigue, dizziness and anemia. No SAEs.
MTD not reached. PK showed good systemic exposure of LOXO-101 after oral dosing

(Burris et al. 2015 AACR APR 21, 2015).

7 SAEs were reported in 4 patients (unrelated)
At the 100-mg BID dose level, one DLT occurred, delirium (Grade 3, unrelated)
Tumors: CRC, head&neck, sarcoma, NSCLC, mesothelioma, peritoneal carcinomatosis, Anal, Thyroid, Thymus, Pancreatic, Melanoma.

Current: Oral TRK Inhibitor LOXO-101 for Treatment of Advanced Adult Solid Tumors. NCT02122913

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

N Engl J Med 2018;378:731-9.

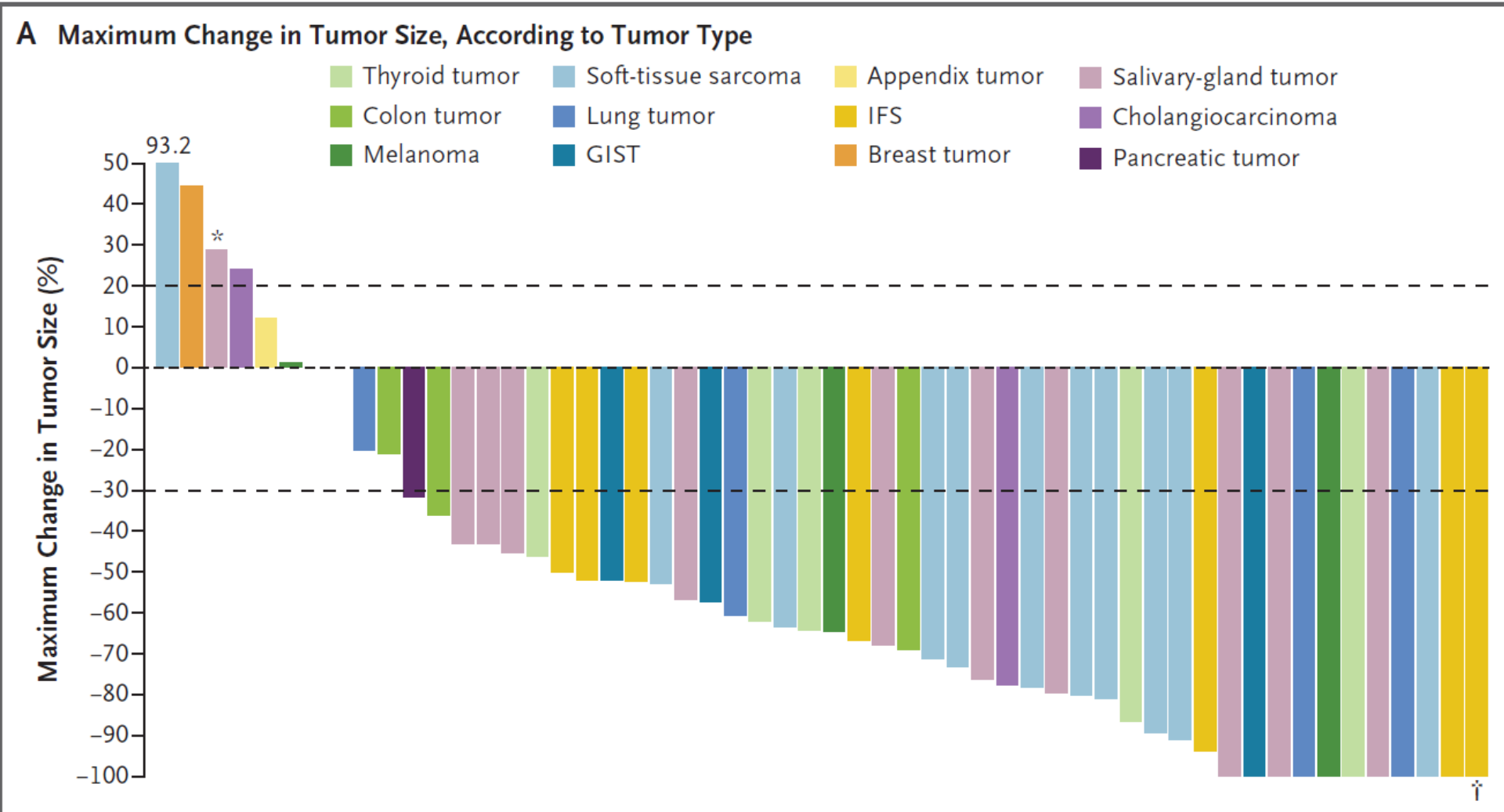

A Maximum Change in Tumor Size, According to Tumor Type
Thyroid tumor
Soft-tissue sarcoma
Appendix tumor
Salivary-gland tumor
Colon tumor
Lung tumor
IFS
Cholangiocarcinoma
Melanoma
GIST
Breast tumor
Pancreatic tumor
93.2
*
Maximum Change in Tumor Size (%)
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
†

Table 2. Overall Response Rate, According to Investigator and Central Assessment.*

Response	Investigator Assessment (N = 55)	Central Assessment (N = 55)
	percent	
Overall response rate (95% CI)†	80 (67–90)	75 (61–85)
Best response		
Partial response	64‡	62
Complete response	16	13
Stable disease	9	13
Progressive disease	11	9
Could not be evaluated	0	4

Entrectinib (RXDX 101 or NMS-E628)

TRKA, TRKB, TRKC, ALK and ROS-1 (FDA orphan drug 2/2015)

400mg/m2 day

7-8 more potent than crizotinib (CNS and mutants: L1196M and C1156Y)

Two Phase I studies: *De Braud et al. (ASCO 2014 and 2015) and Manish et al (ASCO 2015)*

67 patients in both trials (NTRkA/B/C, ALK and ROS-1).

17 pts reported: 58% ORR and 70% SD

DLT: G3 cognitive impairment and G3 fatigue.

AE: Paresthesias, nausea, myalgia, asthenia, fatigue, dysgeusia, vomiting.

Current:

A Phase 1/2a Study of Oral RXDX-101 in Adult Patients With Locally Advanced or Metastatic Cancer; Study Targeting ALK, ROS-1 or TRK A/B/C

NCT02097810

Impact of MET inhibitors on survival among patients with *MET* exon 14 mutant non-small cell lung cancer

Mark M. Awad,[1] Giulia C. Leonardi,[1] Sasha Kravets,[1] Suzanne E. Dahlberg,[1] Alexander Drilon,[2] Sinead A. Noonan,[3] D. Ross Camidge,[3] Sai-Hong Ignatius Ou,[4] Daniel B. Costa,[5] Shirish M. Gadgeel,[6] Conor E. Steuer,[7] Patrick M. Forde,[8] Viola W. Zhu,[9] Yoko Fukuda,[10] Jeffrey W. Clark,[11] Pasi A. Jänne,[1] Tony Mok,[12] Lynette M. Sholl,[13] Rebecca S. Heist[11]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]University of Colorado, Aurora, CO; [4]University of California Irvine School of Medicine, Orange, CA; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Karmanos Cancer Institute, Detroit, MI; [7]Winship Cancer Institute, Atlanta, GA; [8]Johns Hopkins Kimmel Cancer Center, Baltimore, MD; [9]University of California San Francisco, Fresno, CA; [10]Frisbie Memorial Hospital, Rochester, NH; [11]Massachusetts General Hospital Cancer Center, Boston, MA; [12]Chinese University of Hong Kong, Hong Kong, China; [13]Brigham and Women's Hospital, Boston, MA.

Clinical Science Symposium: Old Targets, New Drugs: HER2 and MET, June 4, 2017, 8:36 AM, Abstract #8511

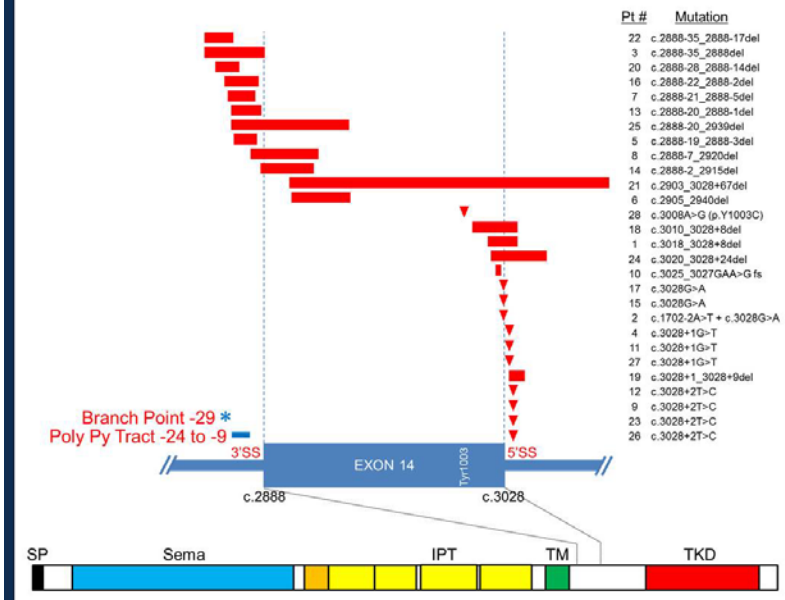
DANA-FARBER CANCER INSTITUTE

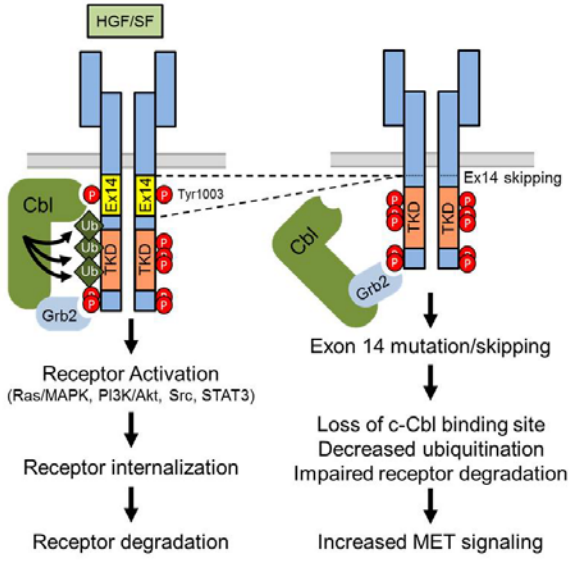
Presented by: Mark M. Awad, MD, PhD

HARVARD MEDICAL SCHOOL

Background

3% of NSCLCs harbor *MET* exon 14 mutations





TCGA, *Nature*. 2014 Jul 31;511(7511):543-50.

Awad MM, et al, *J Clin Oncol*. 2016 Mar 1;34(7):721-30.

Paik PK, et al, *Cancer Discov*. 2015 Aug;5(8):842-9.

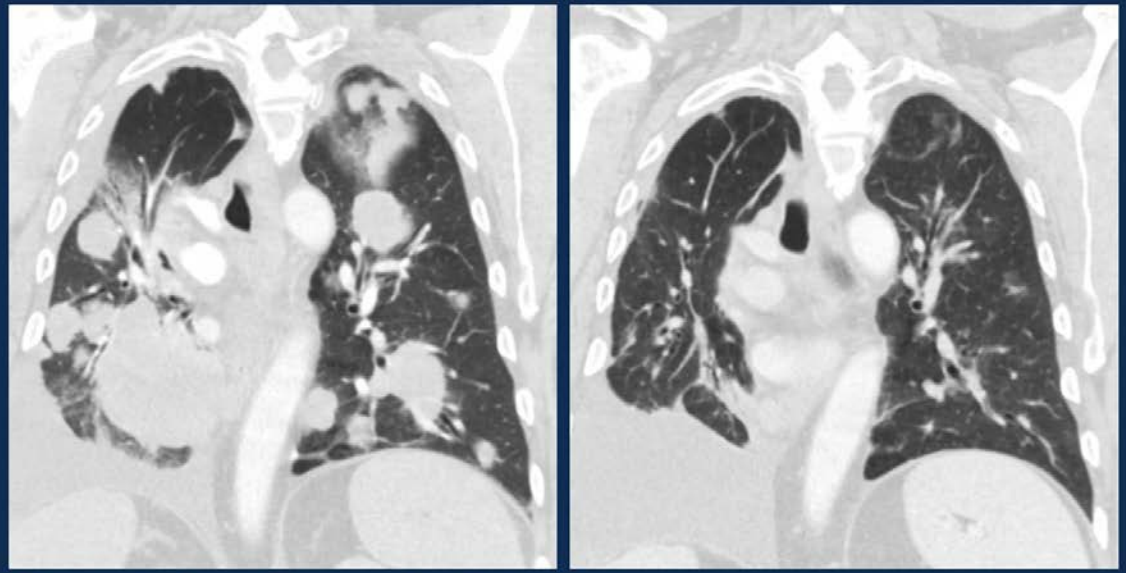
Frampton GM, et al, *Cancer Discov*. 2015 Aug;5(8):850-9.

Awad MM, et al, *J Clin Oncol*. 2016 Mar 10;34(8):879-81.

Background

73yoM never smoker
MET c.3028+1G>T

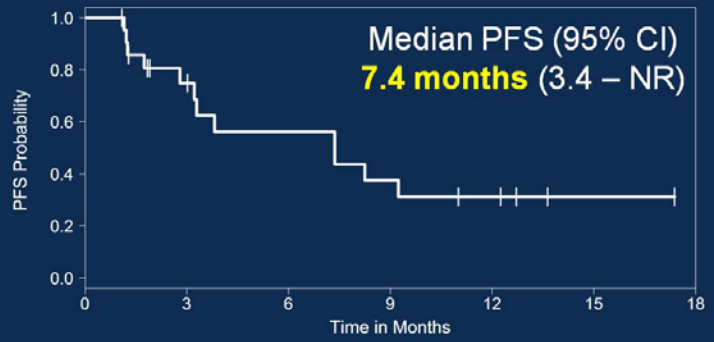
After 2 months
on crizotinib



Dana-Farber Cancer Institute

Outcomes on Crizotinib

Progression-free survival
on crizotinib
(and no prior MET TKI)
N = 22



Overall survival
on crizotinib
(and no other MET TKI)

Presented By Mark Awad at 2017 ASCO Annual Meeting

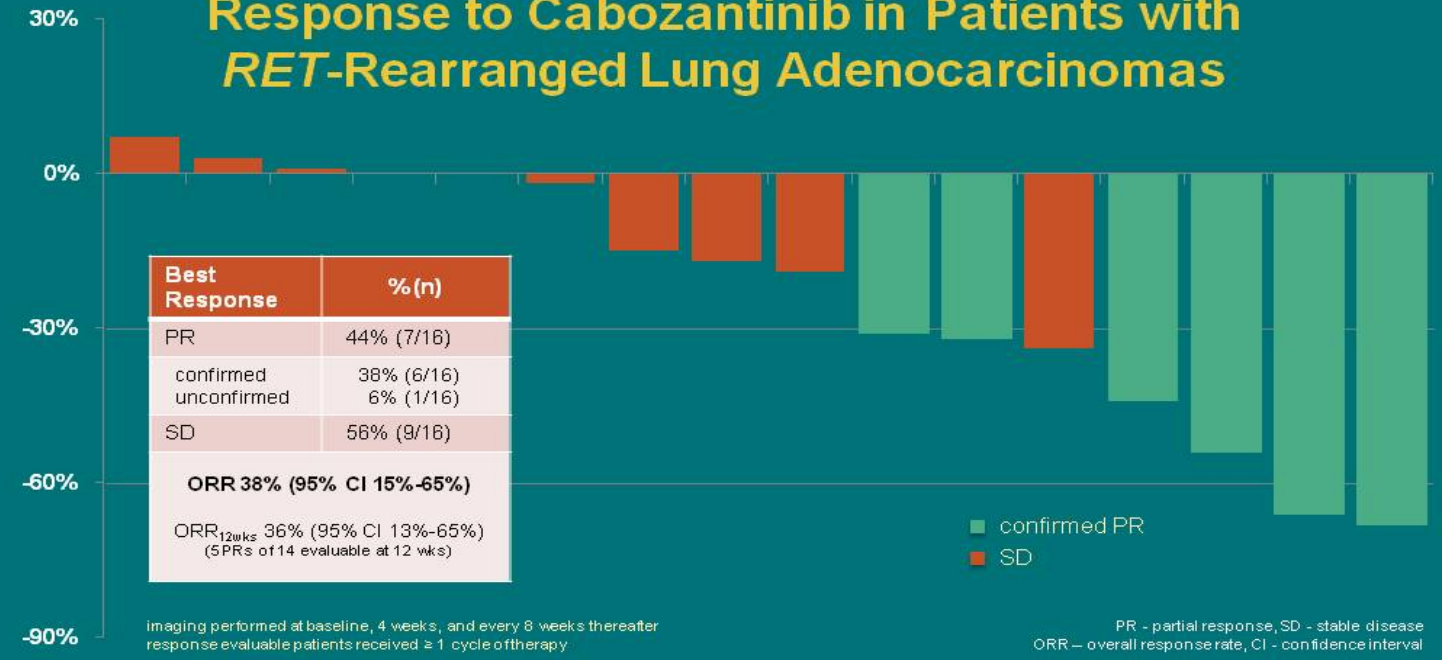
RET FUSION

RET Fusion

- Patients: AdenoCA and adenoSCC carcinoma, never or former smokers, poor differentiation ?, earlier LN metastases
- Frequency:
  - 1.4% in all,
  - 5.6 % in “triple negative”(EGFR, ALK, KRAS)
  - 6.3% in non smokers negative for EGFR, KRAS, ALK, HER2, BRAF, and ROS1
  - 16% in non smokers negative for EGFR, KRAS, ALK, ROS1, NRAS, BRAF, HER2, PIK3CA, MEK1, and AKT
- Biology: Several variants have been identified in NSCLC so far
  - Clinical significance is unknown.
  - KIF5B-, CCDC6-, NCOA4-. TRIM33

Ju YS, Genome Res, 2012
Wang R, J Clin Oncol 30: 2012
Drilon, Cancer Discover March 2013
Kohno, Cancer Science Aug 2013

Response to Cabozantinib in Patients with *RET*-Rearranged Lung Adenocarcinomas



Best Response	%(n)
PR	44% (7/16)
confirmed	38% (6/16)
unconfirmed	6% (1/16)
SD	56% (9/16)

ORR 38% (95% CI 15%-65%)

ORR_{12wks} 36% (95% CI 13%-65%)
(5 PRs of 14 evaluable at 12 wks)

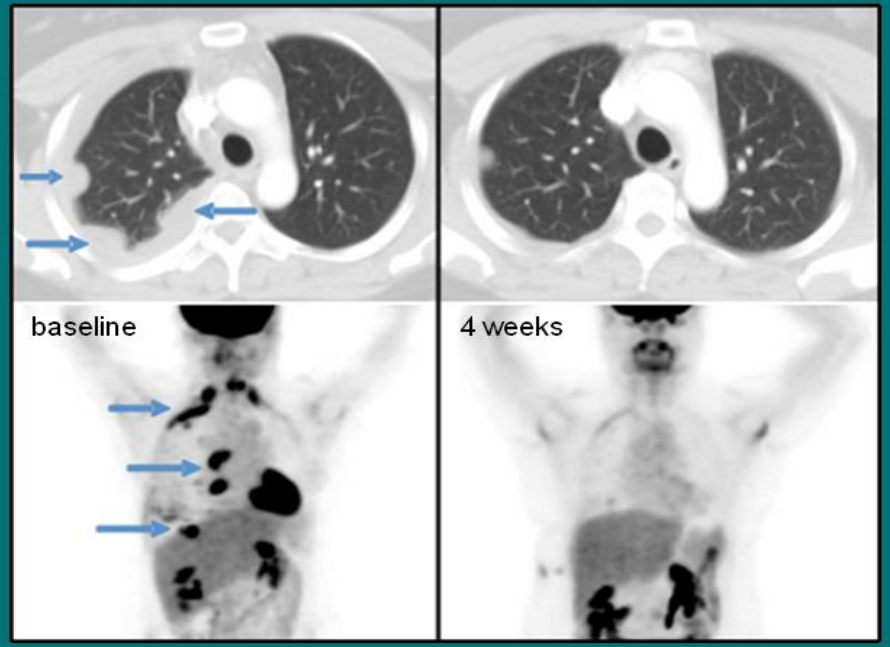
imaging performed at baseline, 4 weeks, and every 8 weeks thereafter
response evaluable patients received ≥ 1 cycle of therapy

PR - partial response, SD - stable disease
ORR – overall response rate, CI - confidence interval

PRESENTED AT: ASCO Annual '15 Meeting

Response to Cabozantinib

- 46-year-old female never smoker with *CLIP1-RET*-rearranged lung adenocarcinoma
- received cabozantinib as first-line therapy
- confirmed partial response lasting 19 months



Overall Survival (OS)

OS calculated from date of initiation of cabozantinib to death, NA – not applicable

PRESENTED AT: ASCO Annual '15 Meeting

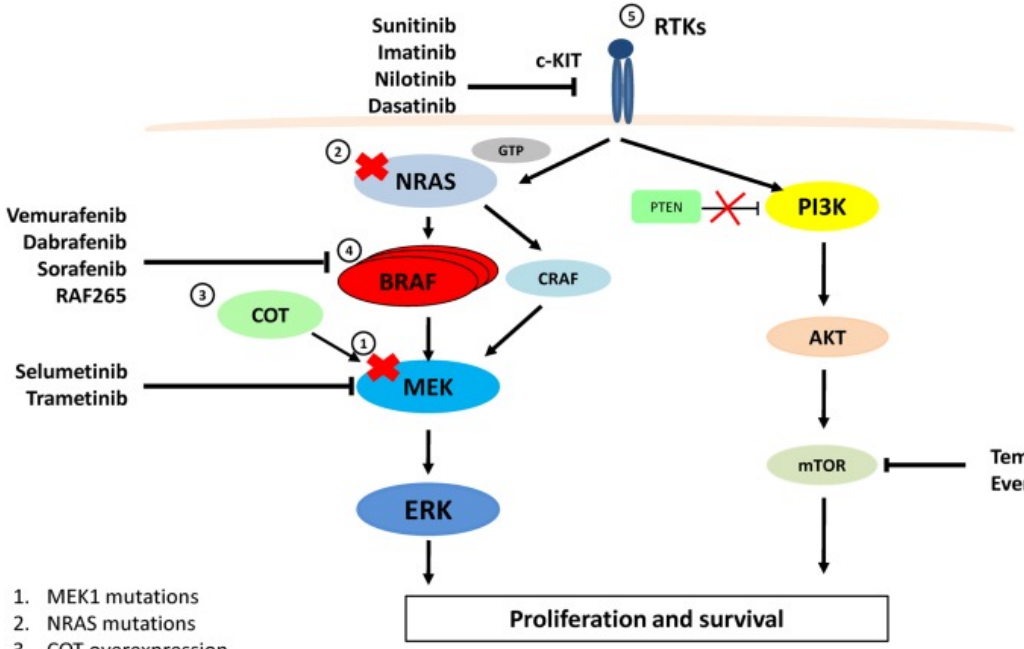
Summary

- Cabozantinib is active in patients with *RET*-rearranged lung adenocarcinomas.
  - stage 1 completed
    - ORR 38% (95% CI 15%-65%)
    - Median PFS 7 months (95% CI 5-NA months)
    - Median OS 10 months (95% CI 8-NA months)
  - stage 2 currently accruing
- Drug-related adverse events were mostly grade 1 or 2 but were frequent.
  - at a starting dose of 60 mg daily, most patients required a dose reduction
  - clinical benefit can be maintained despite dose reduction
- This phase II trial has met its primary endpoint.
  - sufficient total responses (minimum of 5 at any stage surpassed) to meet primary endpoint
  - a larger, confirmatory trial is warranted

RET Fusion Gene Agents

- Sunitinib, Sorafenib, Vandetanib, Carbozatinib, Ponatinib, and Lenvatinib all have potential for activity
- All active in KIF5B-RET–transformed cell lines
- Last 4 are in formal clinical trials

BRAF V600 MUTATIONS


Sunitinib
Imatinib
Nilotinib
Dasatinib
c-KIT
5 RTKs
GTP
2 NRAS
PTEN
PI3K
Vemurafenib
Dabrafenib
Sorafenib
RAF265
4 BRAF
CRAF
3 COT
AKT
1
Selumetinib
Trametinib
MEK
mTOR
Temsirolimus
Everolimus
ERK
Proliferation and survival
1. MEK1 mutations
2. NRAS mutations
3. COT overexpression
4. BRAF amplification/ splicing
5. RTKs overexpression/activation (PDGFRβ, IGR1F)

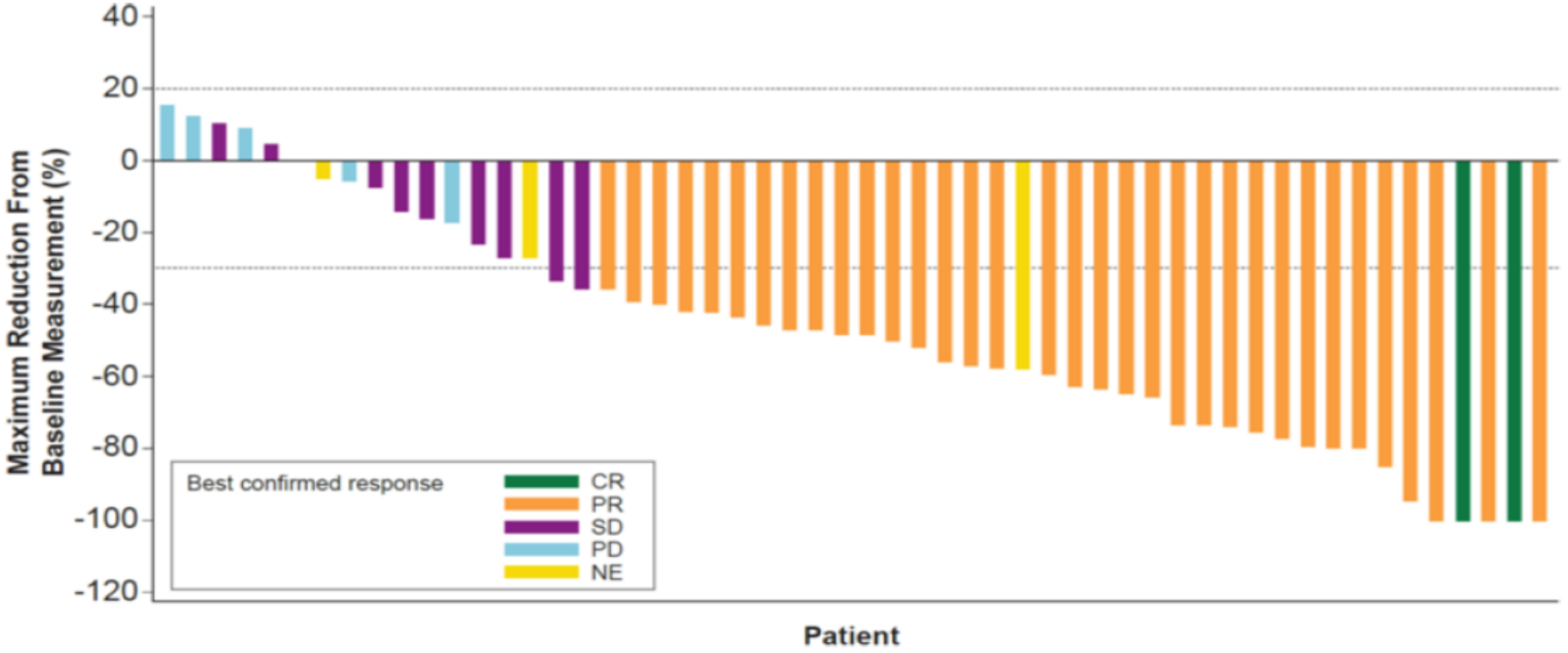


Figure 2. Tumor responses to dabrafenib + trametinib in *BRAF* V600E–mutant non-small cell lung cancer

Maximum reduction from baseline sum of lesion diameters by best investigator-assessed confirmed response in ≥ second-line patients (n=57). CR=complete response. NE=not evaluable. PD=progressive disease. SD=stable disease.

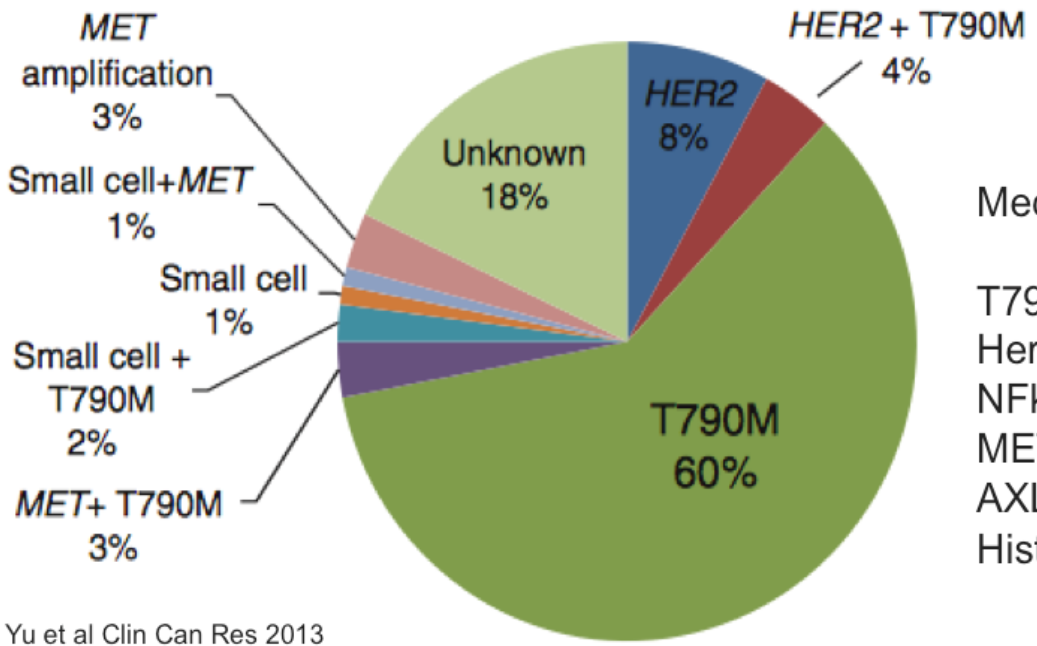
Antitumor activity in ≥ second-line patients

	Investigator Assessment (N=57)	Independent Assessment (N=57)
Best response, n (%)		
Complete response (CR)	2 (3·5)	0
Partial response (PR)	34 (59·6)	36 (63·2)
Stable disease (SD)	9 (15·8)	4 (7·0)
Progressive disease (PD)	7 (12·3)	8 (14·0)
Non-CR/non-PD	0	3 (5·3)
Not evaluable	5 (8·8)	6 (10·5)
Overall response (CR + PR), n (%) [95% CI]	36 (63·2) [49·3–75·6]	36 (63·2) [49·3–75·6]
Disease control rate (CR + PR + SD), n (%) [95% CI]	45 (78·9) [66·1–88·6]	43 (75·4) [62·2–85·9]
Progression-free survival, median (95% CI), months	9·7 (6·9–19·6)	8·6 (5·2–19·1)
Duration of response, median (95% CI), months	9·0 (6·9–18·3)	9·0 (5·8–17·6)

HER-2 GENETIC ABERRATIONS

HER 2 Insertions

- **Patients*:*** Adenocarcinomas, never smokers
- **Frequency:** Incidence 2.8-4.2%
- **Biology:**
  - In-frame insertions into exon 20. Transgenic mouse models confirm oncogenicity
- **Therapy:**
  - Drugs of interest: neratinib, afatinib, dacomitinib
    - Preclinical models show synergy with mTOR inhibitors.
    - Clinical trial of neratinib + temsirolimus ongoing, several PR are reported
    - Both afatinib and dacomitinib have case reports of responses



Yu et al Clin Can Res 2013

Mechanisms of Resistance:

T790M 60%
Her2 Amplification
NFkB Upregulation
MET Amplification
AXL Upregulation
Histologic Transformation

HER2 in Lung Cancers

Agents Targeting HER2
Amplification and Protein Expression

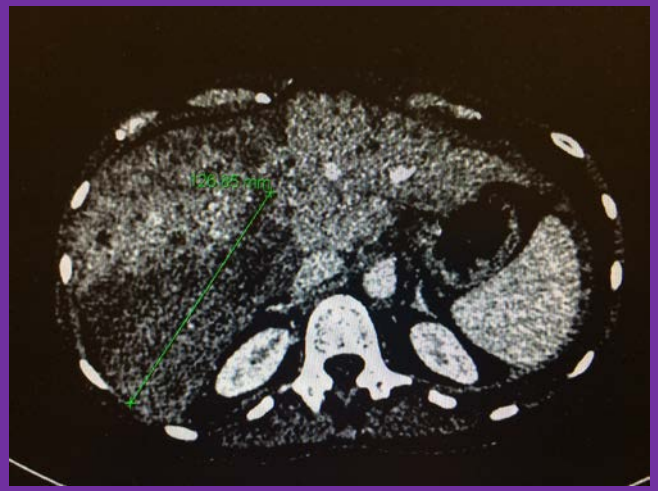
- Trastuzumab
- Pertuzumab
- Lapatinib
- Ado-Trastuzumab Emtansine

Trials of Investigational Agents
Targeting HER2 Mutations

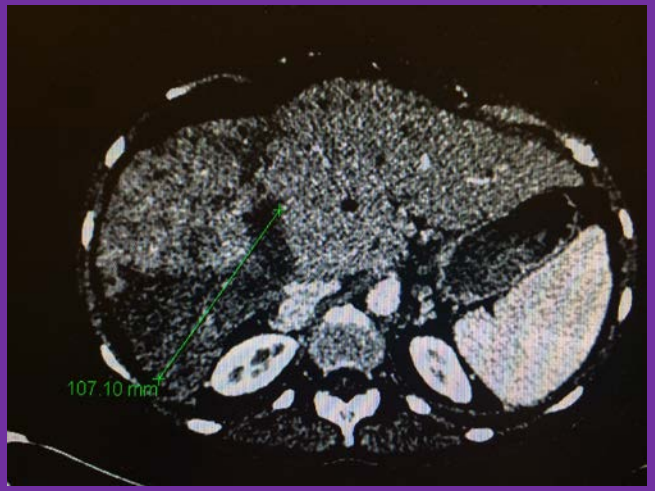
- Dacomitinib
- Afatinib
- Neratinib
- Neratinib + Temsirolimus

Pre- and Post-vinorelbine and trastuzumab treatment

Prior to treatment

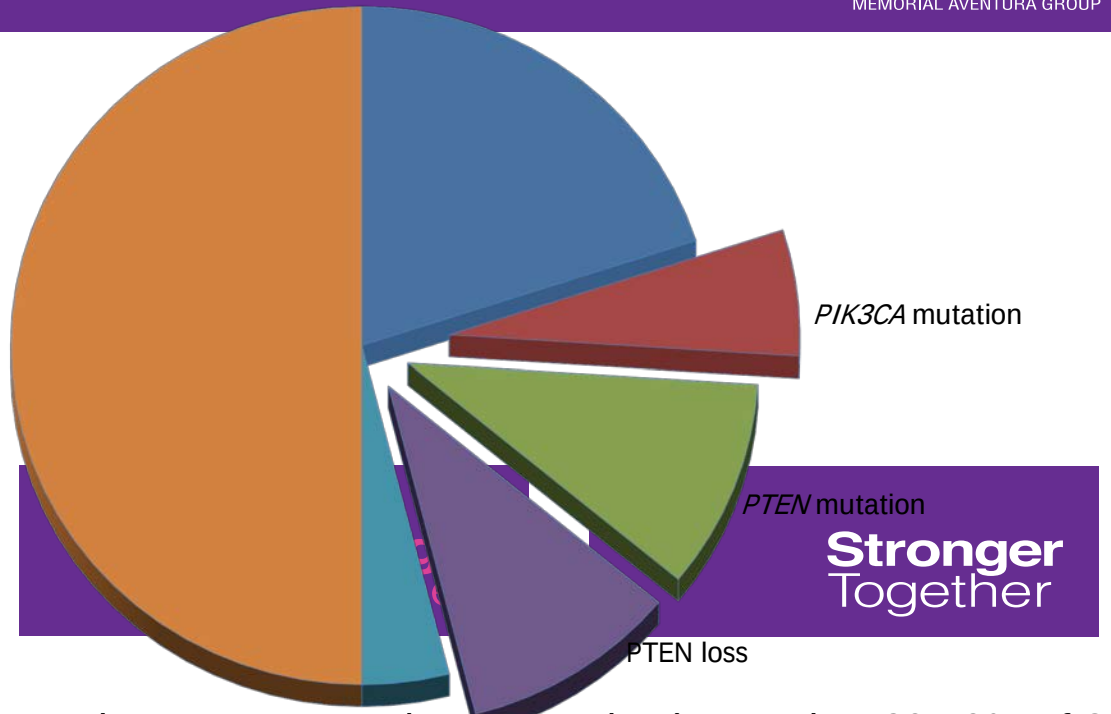


Post treatment



PI3K PATHWAY

Oncogenic PI3K pathway changes are common in SQCLC



- PI3K alterations (PIK3CA mutations, PTEN mutations, PTEN loss) occur in ~30-50% of SQCLCs
- PIK3CA amplification occurs in another 20-30%

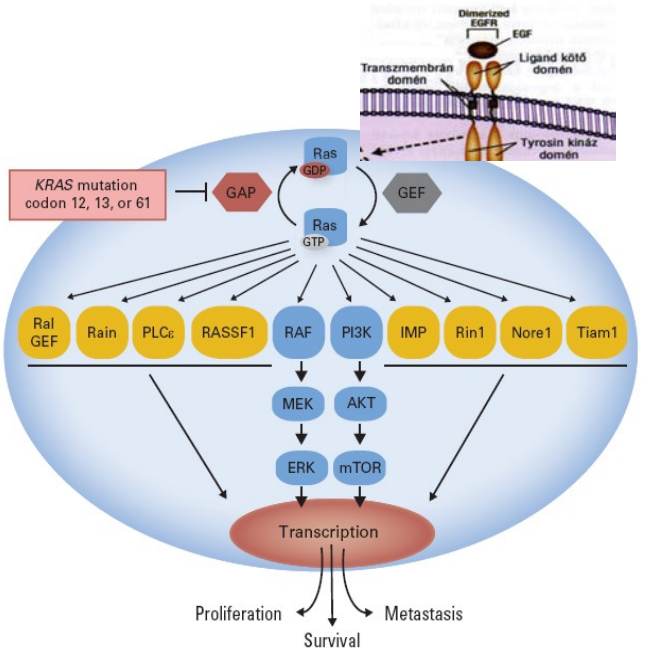
TCGA *Nature* 2012

KRAS GENETIC ABERRATIONS

Oncogenic KRAS mutations

- The KRAS oncogene in certain malignant tumors is present in one third of cases
- KRAS mutations in codon 12, 13 or 61
- KRAS mutation in CRC is a negative prognostic factor
- Prognostic and predictive role in lung adenocarcinoma is the most intensively studied question

	EGFR	KRAS
Lung adenocarcinoma	8-20%	15-25%
Colorectal cancer	~40% (amplif.)	35-45%



Roberts, Stinchcombe JCO 2013

Incidence of KRAS mutation/smoking habits

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Incidence of KRAS mutation in smokers and in non-smokers					
Study	No. of smokers	No. of non-smokers	KRAS mutation in smokers	KRAS mutation in non-smokers	P-value
Nelson	180	16	44 (24%)	0	0,028
Marchetti	35	35	12 (34%)	0	0,00016
De Gregorio	160	23	47 (29%)	0	0,0013
Gealy	32	23	8 (25%)	2 (9%)	0,18
Westra	84	27	36 (31%)	2 (7%)	0,017
Ahrendt	92	14	40 (43%)	0	0,0014
All	583	138	177 (30%)	4 (2,9%)	<0,001

Incidence of KRAS mutation in smoker adenocarcinoma patients: 24-43% Strong correlation with number of cigarettes during lifetime and with pack-year

Ahrendt et al. Cancer 2001 Mitzudomi t al. Int J Clin Oncol 2006 Kosaka at al. Cancer Res 2004

No response to EGFR-TKI treatment in KRAS mutant lung adenocarcinoma

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	Agent	n	Responses
Pao 2005	Gefitinib/Erlotinib	9	0
Tsao 2006	Erlotinib	20	1
Fujimoto 2006	Gefitinib	6	0
van Zandwijk 2006	Gefitinib	3	0
Han 2006	Gefitinib	9	0
Hirsch 2006	Gefitinib	6	0
Miller 2006	Erlotinib	19	0
Giaccone 2006	Erlotinib	10	0
Jackman 2007	Erlotinib	6	0
Douillard 2007	Gefitinib	20	0
Total		108	1 (< 1%)

Courtesy of G. Ostoros

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