Uncommon Oncogenic Drivers in NSCLC

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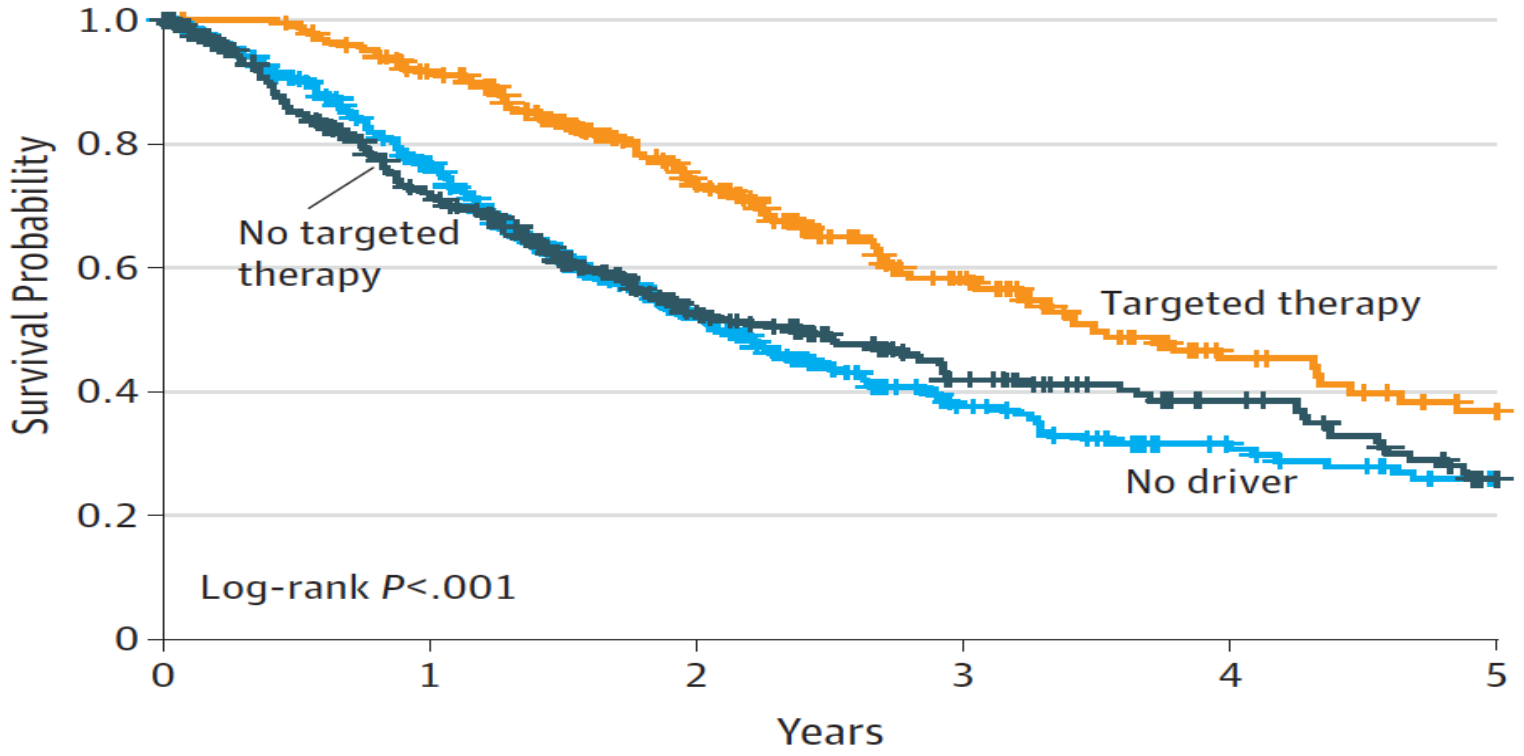
Oncogene mutations and therapeutic options

Oncogene	Mutation prevalence	Therapy	Predicted response rate
EGFR	Asians 30-40%/ Caucasian 10-20%	EGFR TKIs (most mutations)/pan-HER inhibitors	Erlotinib 60-80% Gefitinib 70% Afatinib 60% Osimertinib 50-60% (T790M)
ALK	1-7%	ALK inhibit…s	Crizotinib 50-60% Ceritinib 60% Alectinib 60% Brigatinib 60% Lorlatinib 48%
ROS1	1.7%, higher in…	…itors	Crizotinib 60-70% Ceritinib 60%
BRAF	2%	BRAF/MEK inhibitors	Dabrafenib 30% Dabraf/trametinib 60%
NTRK	<1%	Crizotinib/Larotrectinib/ NTRK inhibitors	Larotrectinib 76%
RET	1.7% (15% in EGFR/ALK/KRAS-)	RET inhibitors	Cabozantinib 40% Vandetinib 20%
MET	10%	Crizotinib/MET inhibitors	Crizotinib 25%
HER2	2%	Trastuzumab; pan-HER inhibitors	Dacomitinib 12% Ado-trastuzumab 20%; TDM-1 44%

Approved

Why Does Testing Matter?
Survival by Use of Targeted Therapy

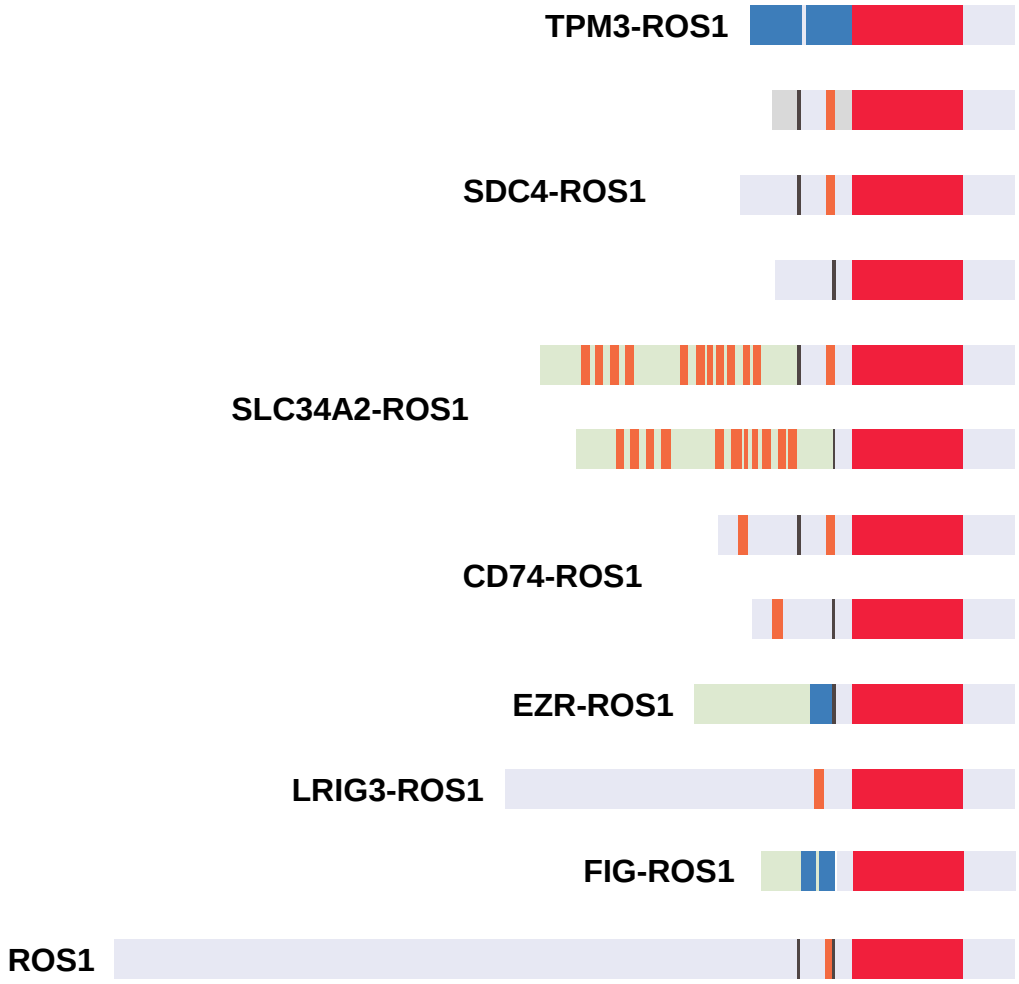


Genotype/Therapy	Median OS, y	95% CI
Oncologic driver + targeted therapy	3.49	3.02-4.33
Oncologic driver + no targeted therapy	2.38	1.81-2.93
No targeted therapy	2.08	1.84-2.46

The ultimate goal of genomic testing is to use the information generated to select therapies and improve outcomes

Kris et al, 2014.

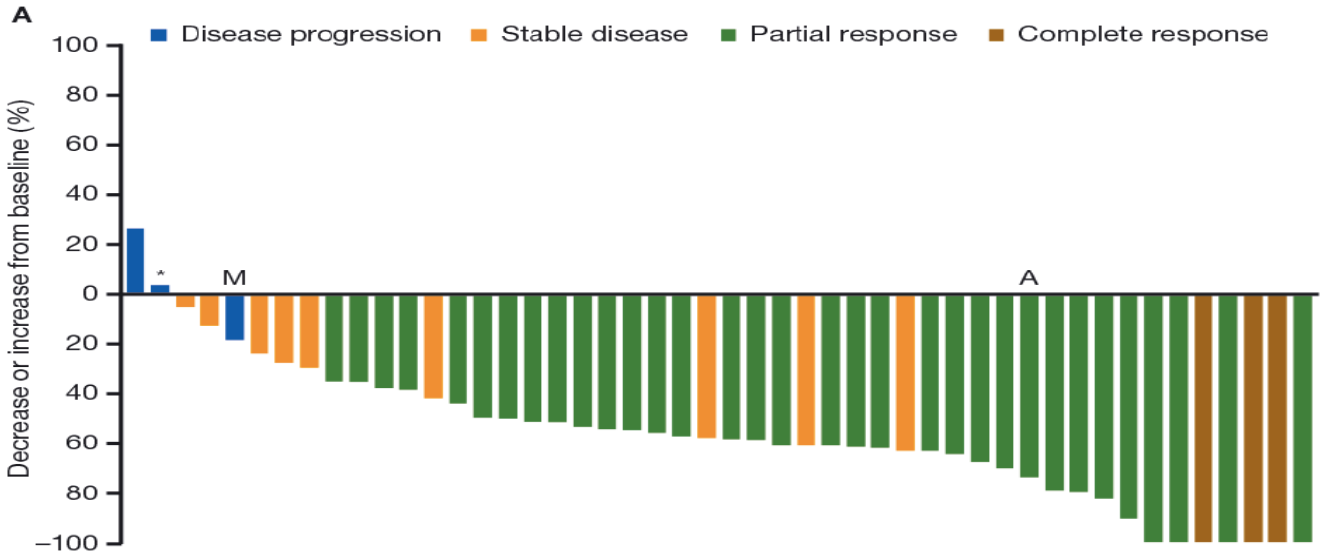
ROS1 Rearrangements in NSCLC (1% NSCLC)



- First discovered in NSCLC in 2007
- Also found in some GBMs, cholangiocarcinomas, gastric, ovarian & other tumor types
- Activated by chromosomal rearrangement, leading to constitute kinase activation and oncogene addiction
- No overlap with ALK

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012; Rimkunas et al., CCR 18(16): 4449-57, 2012

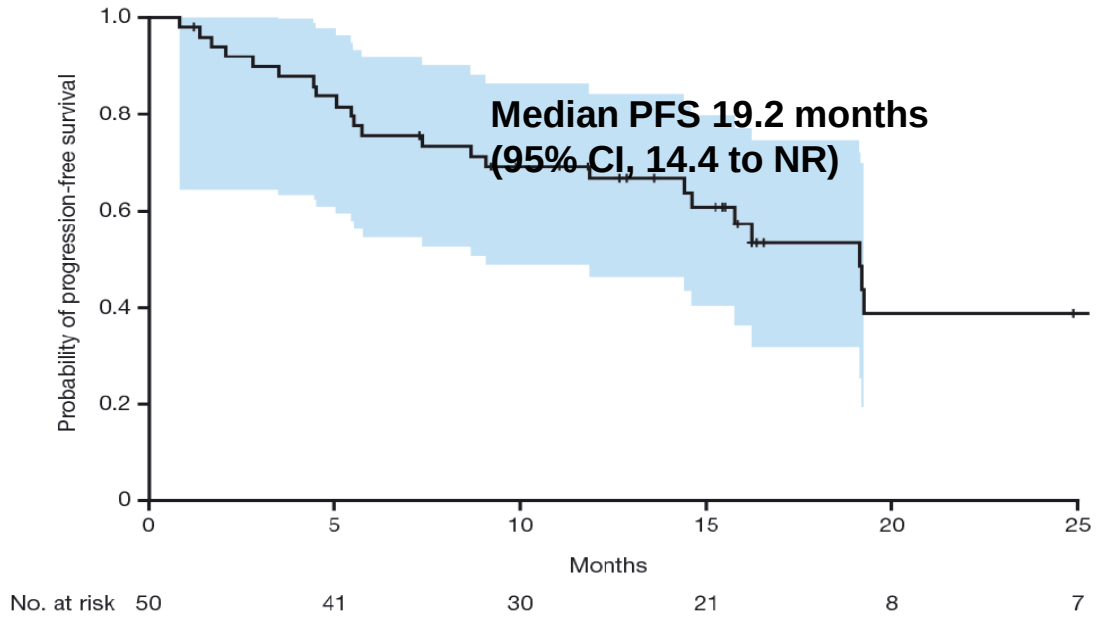
Summary of *ROS1* Anti-Tumor Efficacy with Crizotinib in PROFILE 1001 Study



50 patients; Crizotinib 250 mg BID,

RR –72%; mPFS -19.3 m;

mDOR – 24.7m; **mOS – 51.4 m**



Treatment –related AE's – were mainly grade 1-2; no grade≥4 TRAE's and no permanent discontinuation.

Grade 1-2 – visual, GI, peripheral edema, elevated LFT's, fatigue, dysgeusia, neutropenia, sinus bradycardia, hypophosphatemia,

Crizotinib (preferred NCCN)

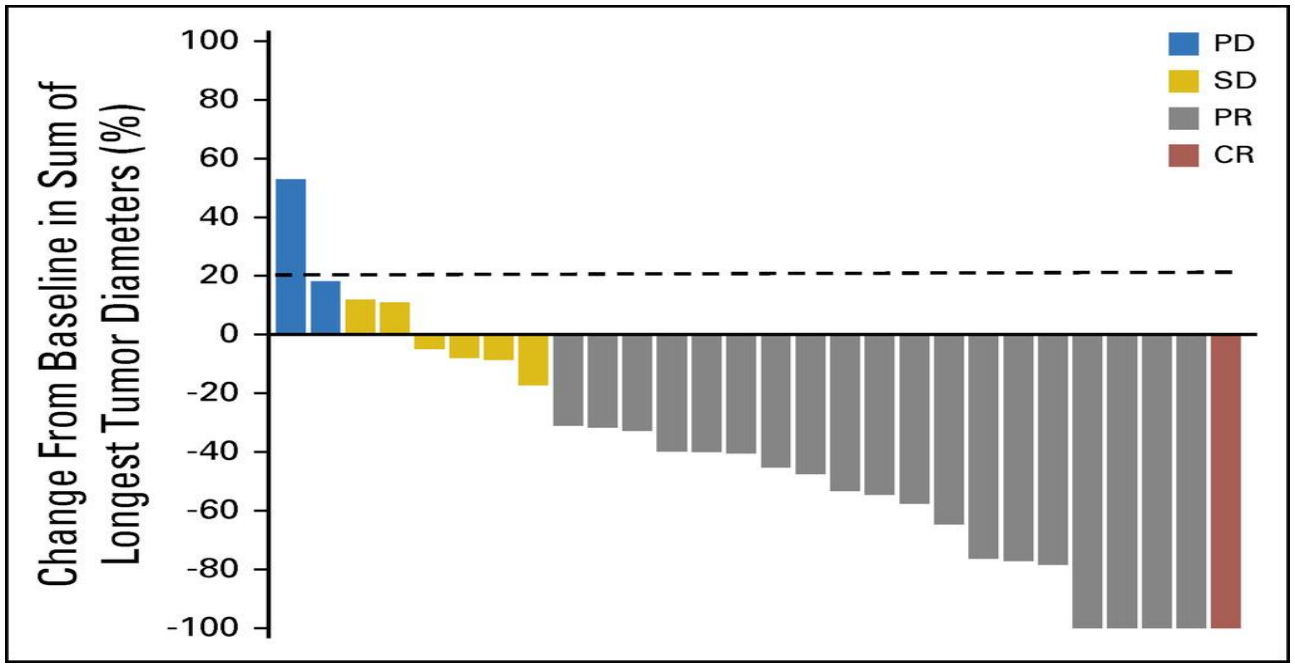
Shaw et al. NEJM 371(21): 1963-71, 2014; updated at European Cancer Congress April 11,2019

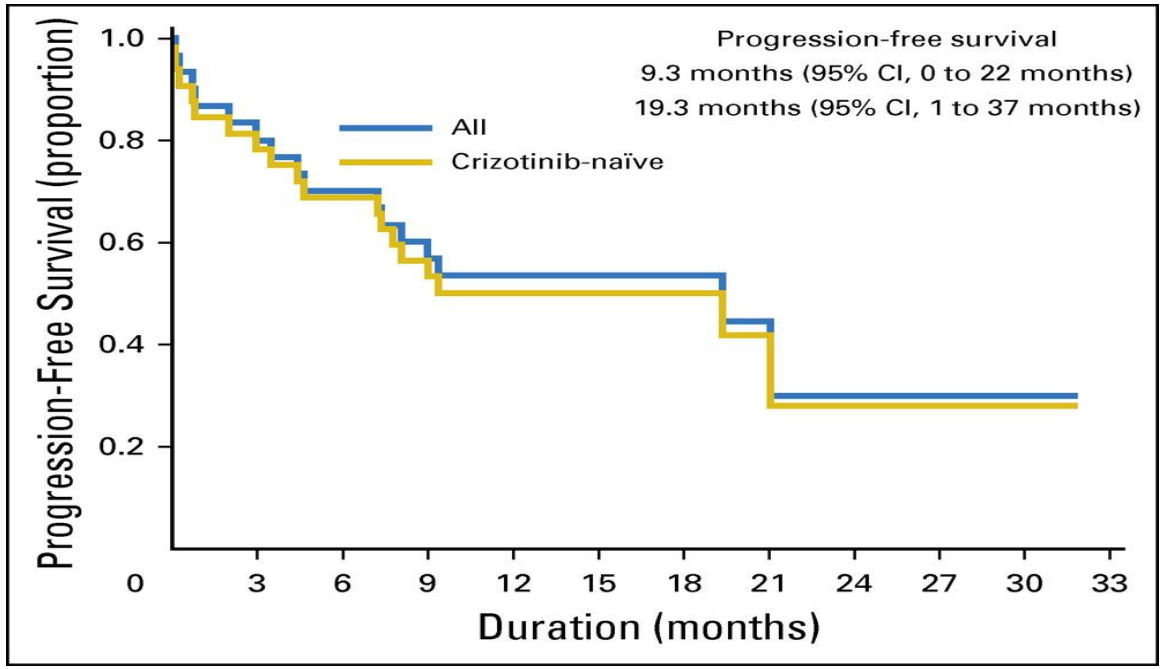
Efficacy of ceritinib in NSCLC harboring ROS1 Rearrangement

32 patients; Ceritinib 750 mg QD, **ORR –62% (Crizotinib naïve 67%; 2 patients with prior crizotinib – no response)**

mPFS -19.3 m (in Crizotinib naïve), 9.3 m for all patients;

mDOR – 21 m; **mOS – 24 m**





Treatment –related AE's – (majority grade 1-2 were diarrhea, nausea, anorexia; most common grade 3-4 fatigue, increased LFT's); only 1 pt discontinued Tx due to generalized weakness and anorexia);

Lim et al J Clin Oncol VOLUME 35 • NUMBER 23 • AUGUST 10, 2017

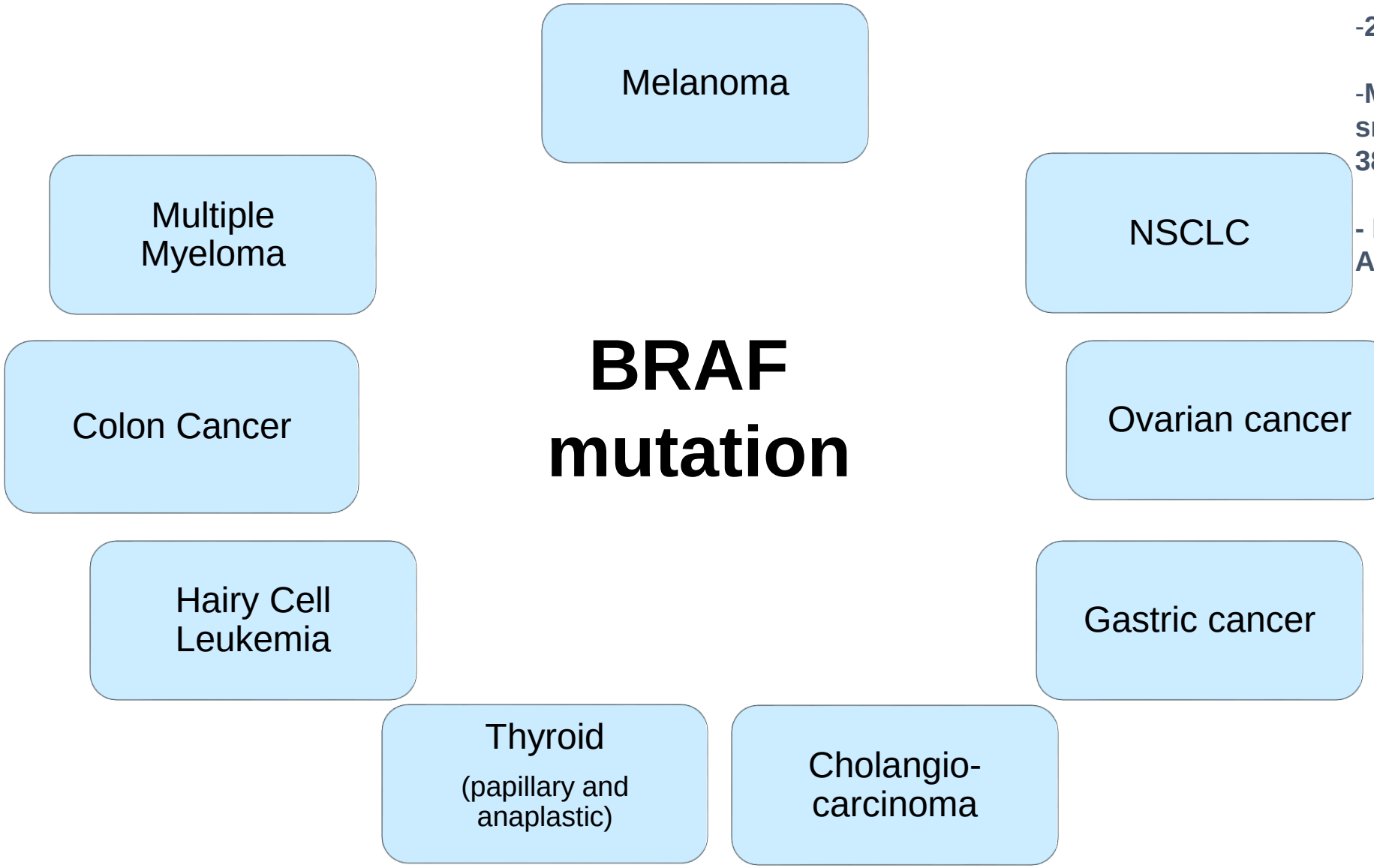
Lorlatinib in ROS1 positive NSCLC

- 47 pts, 13 crizotinib naïve, 34 crizotinib treated.
- ORR 36.2% in all cohorts ; RR in crizotinib naïve 61.5% and crizotinib treated 26.5%.
- Responses lasted as long as 10 months – 5 crizotinib naïve and 5 crizotinib pretreated.
- RR in brain mets 56% with duration lasting at least 12 months for 5 patients (4 of whom were previously exposed to crizotinib).

- Common adverse events: hypercholesterolemia 83% and hypertriglyceridemia 60%, neurocognitive and mood effects triggered by the drug can be managed by dose interruption and reduction

Al.Shaw Lancet Oncol 2017;18:1590; update - WALC 2018

BRAF mutations occur in multiple tumor types



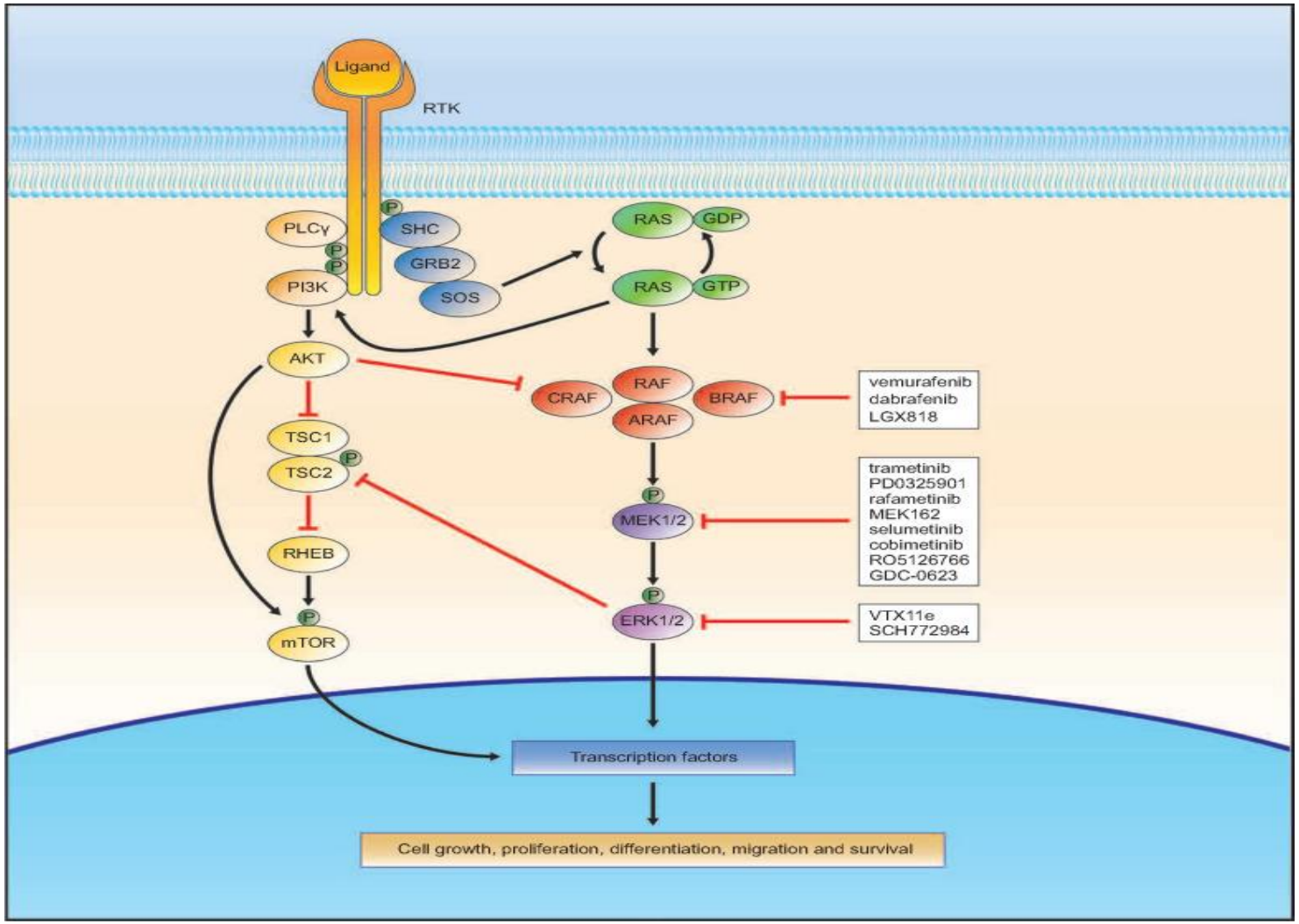
-2 - 4 % NSCLC (adenocarcinoma)

-More often current or former smokers with median smoking hx of 38 pack years

- Majority white (majority nonwhite – Asian)

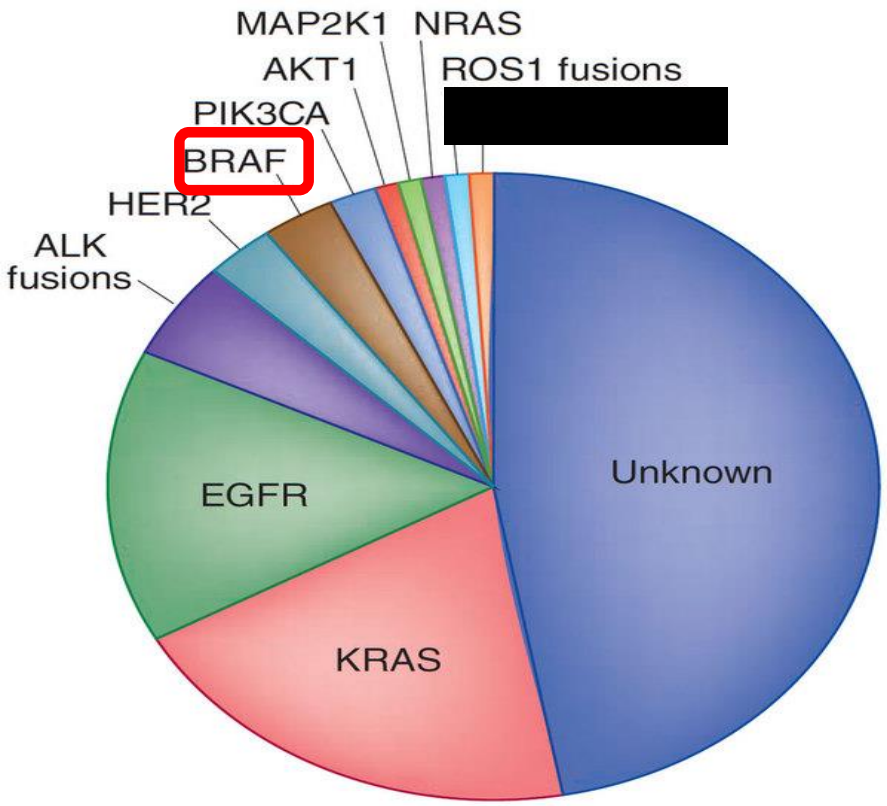
Paik et al J Clin Oncol 2011 VOLUME 29:2046-2051

Illustration of RAS–RAF–MEK–ERK MAP kinase signaling pathway.



- As a member of the Ras/mitogen-activated protein kinase signalling pathway, BRAF lies downstream of KRAS, and directly phosphorylates ERK.
- The pathway culminates in the transcription of genes favouring proliferation and survival.

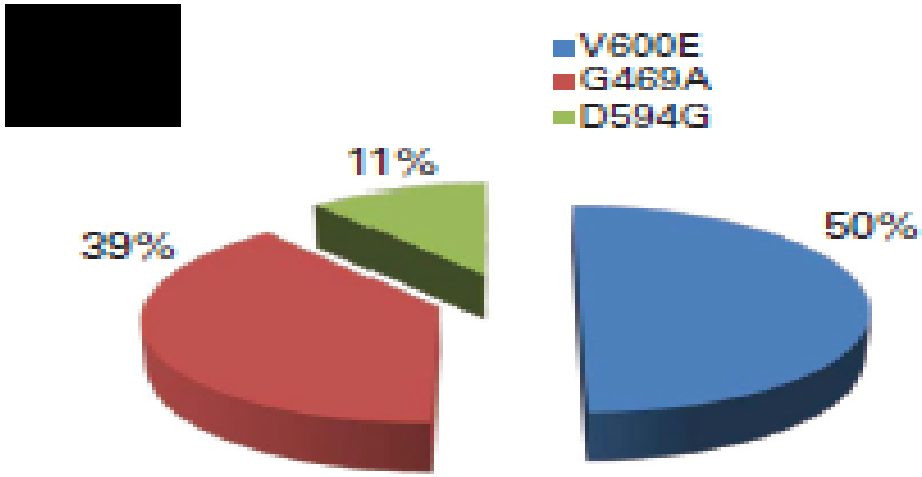
BRAF mutations in NSCLC



Relative distribution of 'driver' mutations in lung adenocarcinoma

BRAF – 2-4% and 50% are BRAF-V600E

Pao and Hutchinson Nature Medicine Vol 18(3), 2012

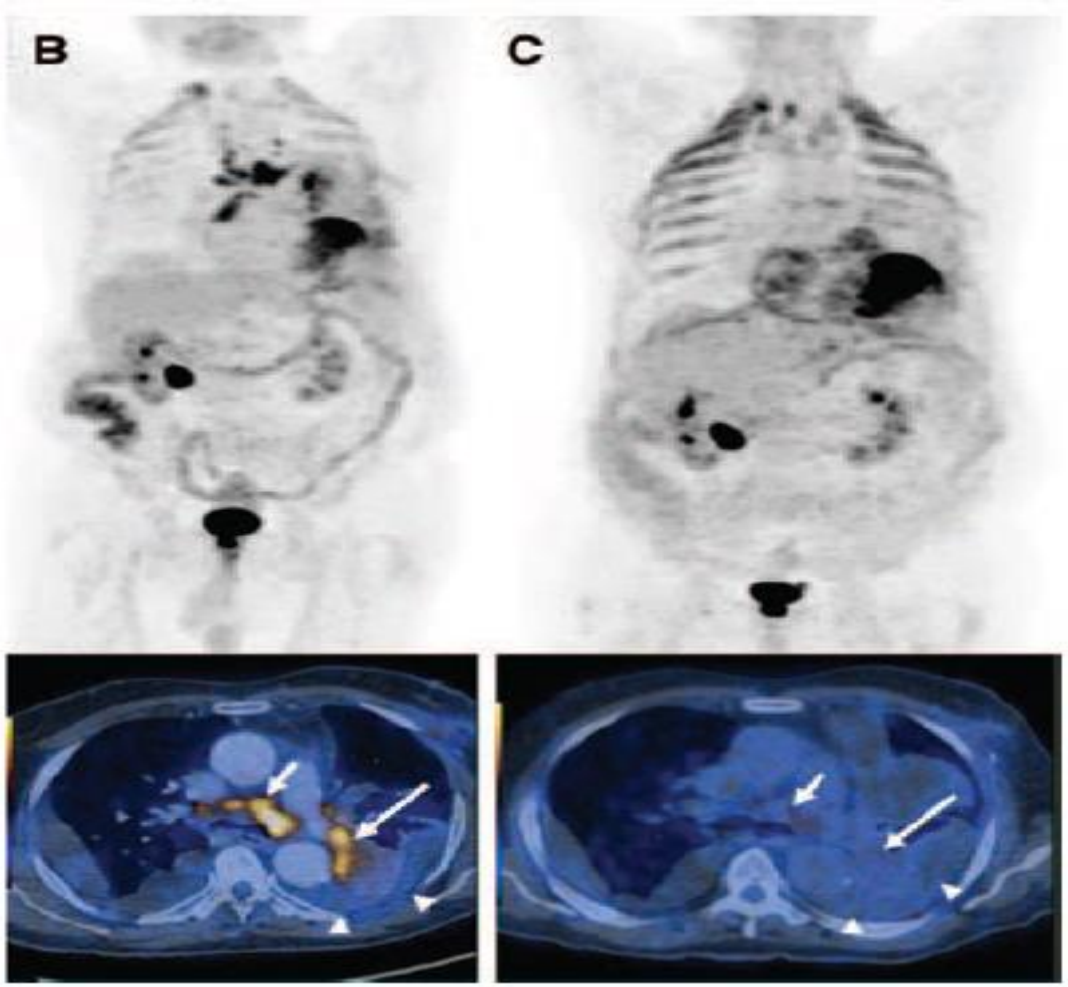


Relative distribution of BRAF mutations in NSCLC.

BRAF mutations more commonly found in current or former smokers.

Paik P et al JCO 2011

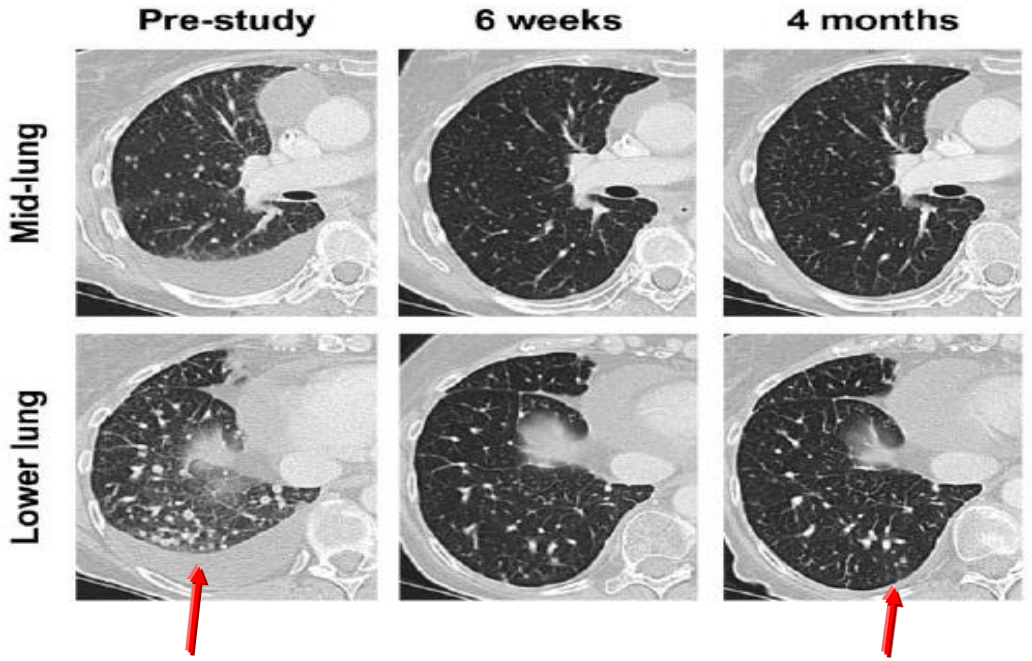
Response of *BRAF* V600E mutant NSCLC to vemurafenib/ dabrafenib therapy



Pre vemurafenib

2 weeks post vemurafenib (960mg po bid)

Gautschi et al JTO 2012



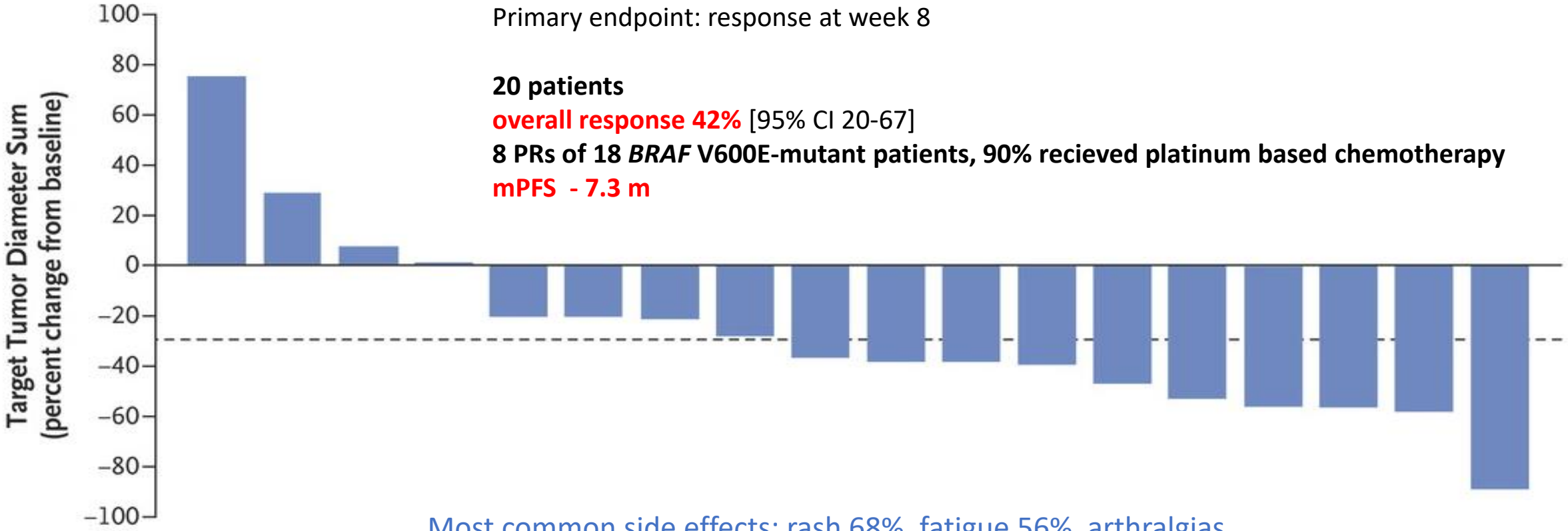
Response to dabrafenib in patient with BRAF V600E mutant NSCLC.

Rudin et al JTO 2013

Vemurafenib in *BRAF* V600E-Mutant Lung Cancer (20 patients)

Multicenter phase 2 basket study
Vemurafenib 960 mg twice daily
Primary endpoint: response at week 8

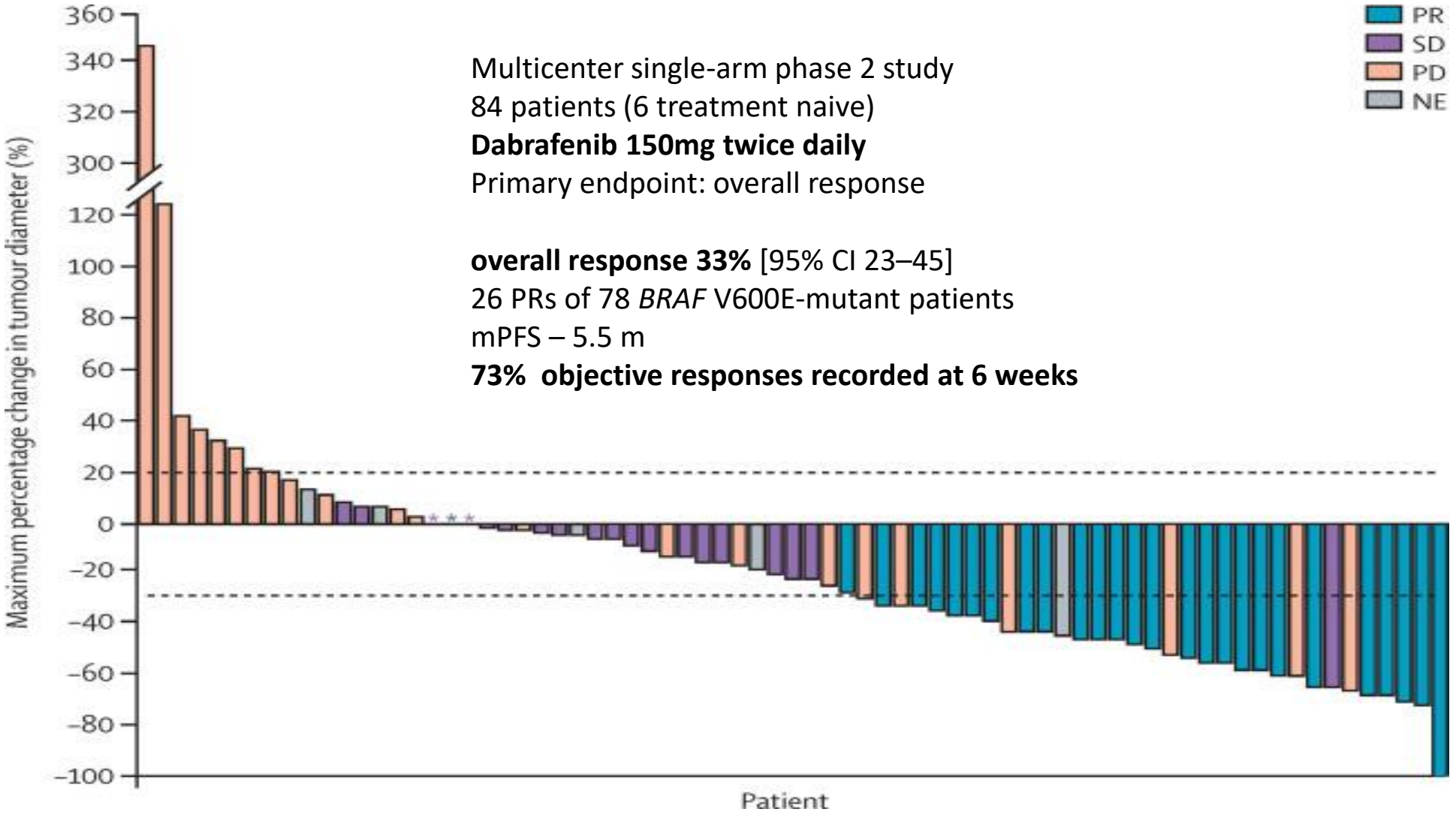
20 patients
overall response 42% [95% CI 20-67]
8 PRs of 18 *BRAF* V600E-mutant patients, 90% recieved platinum based chemotherapy
mPFS - 7.3 m



Most common side effects: rash 68%, fatigue 56%, arthralgias 40%

Hyman et al. NEJM 2015;573:726-36

Dabrafenib in *BRAF* V600E-Mutant Lung Cancer



Multicenter single-arm phase 2 study
84 patients (6 treatment naive)
Dabrafenib 150mg twice daily
Primary endpoint: overall response

overall response 33% [95% CI 23–45]
26 PRs of 78 *BRAF* V600E-mutant patients
mPFS – 5.5 m
73% objective responses recorded at 6 weeks

Planchard et al. Lancet Oncol 2016;17:642-50

Dabrafenib +Trametinib 1st Line in *BRAF* V600E-Mutant Lung Cancer

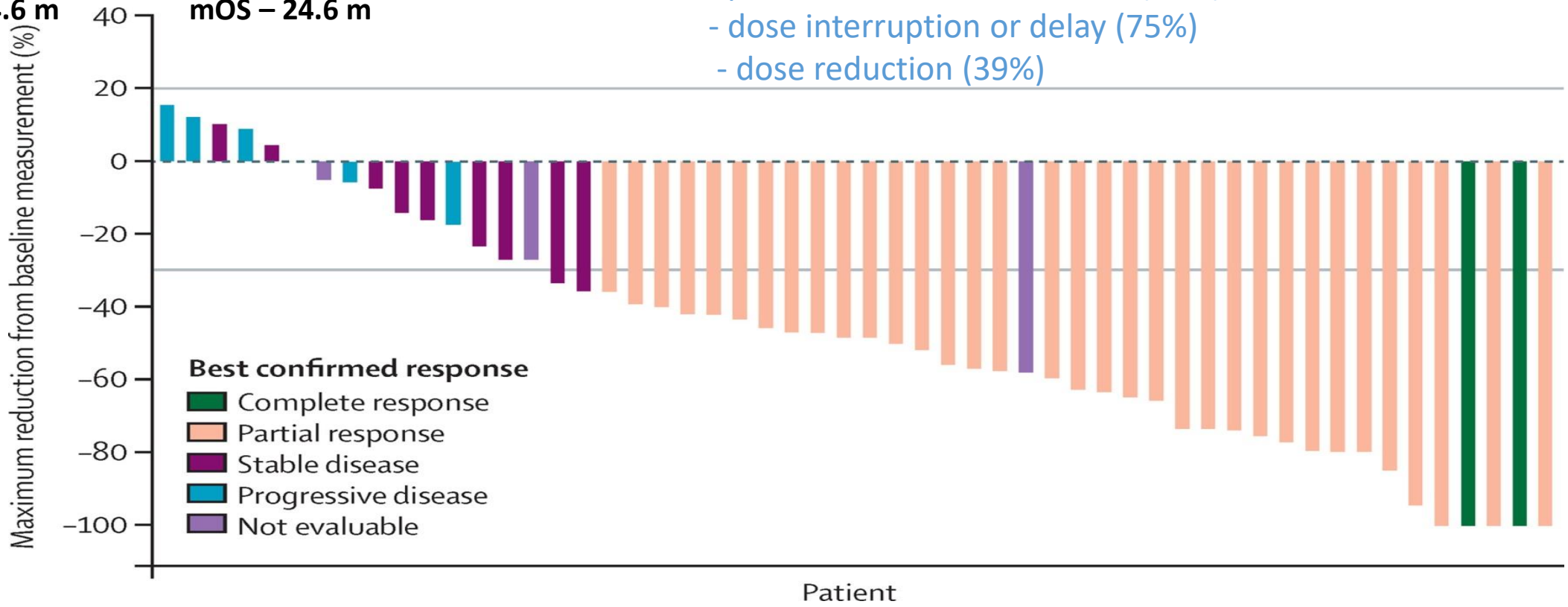
Multicenter single-arm phase 2 study
Dabrafenib 150 mg twice daily + Trametinib 2 mg daily
Primary endpoint: overall response

36 pts - overall response 64 % [95% CI 49·3-75·6]
6% CR's and 58% PRs of 36 *BRAF* V600E-mutant patients

mPFS- 14.6 m **mOS – 24.6 m**

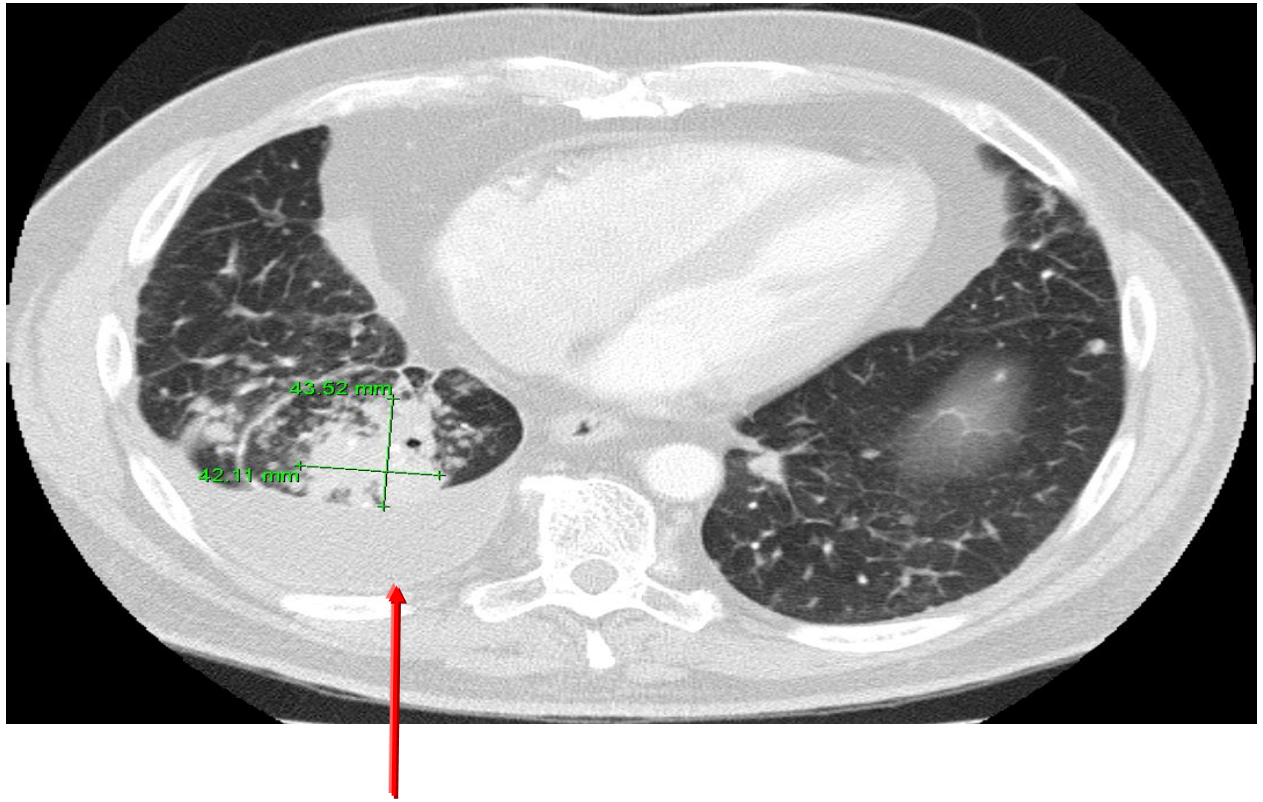
AE's : pyrexia, anorexia, N/V, diarrhea, increased LFT's, fatigue, peripheral edema, decrease in LVEF, HTN, dry skin.

Adverse events led to:
- permanent discontinuation (22%),
- dose interruption or delay (75%)
- dose reduction (39%)

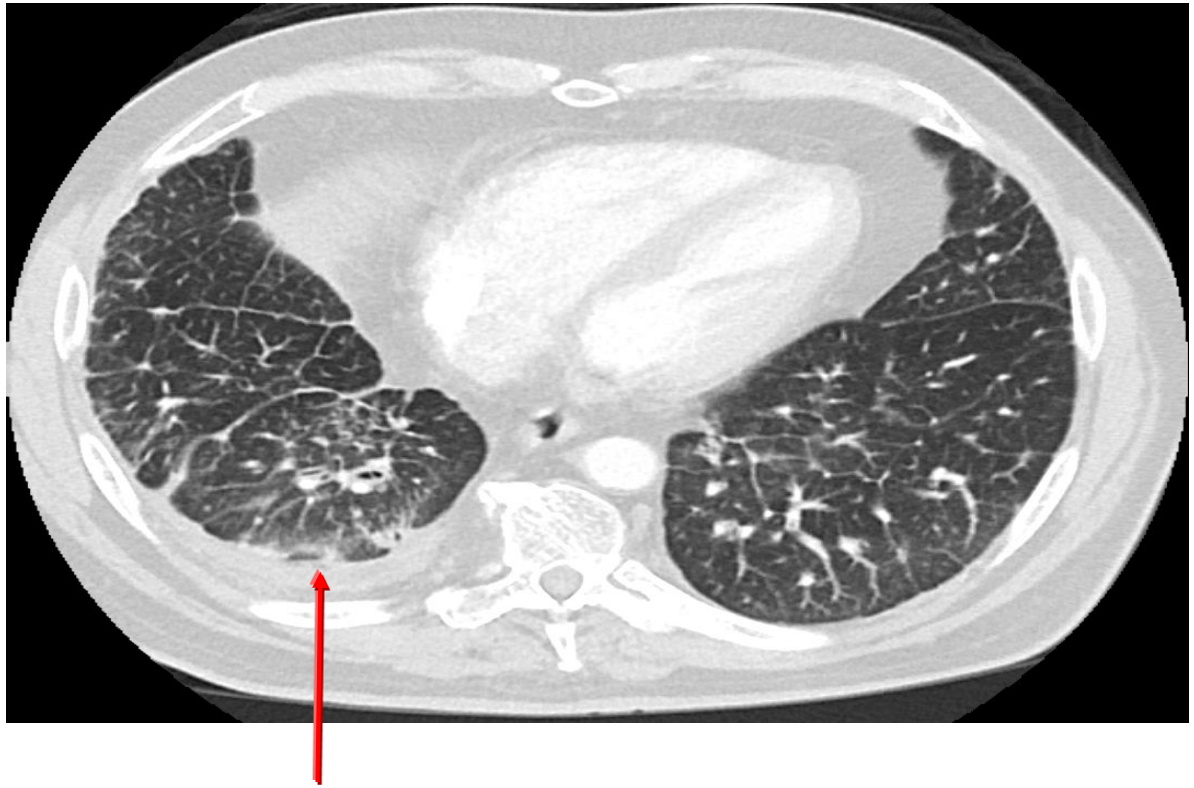


Planchard et al. Lancet Oncol 2017 Vol 18(10):1307-16

BRAF V600E NSCLC Treated with Dabrafenib and Trametinib



August 2012



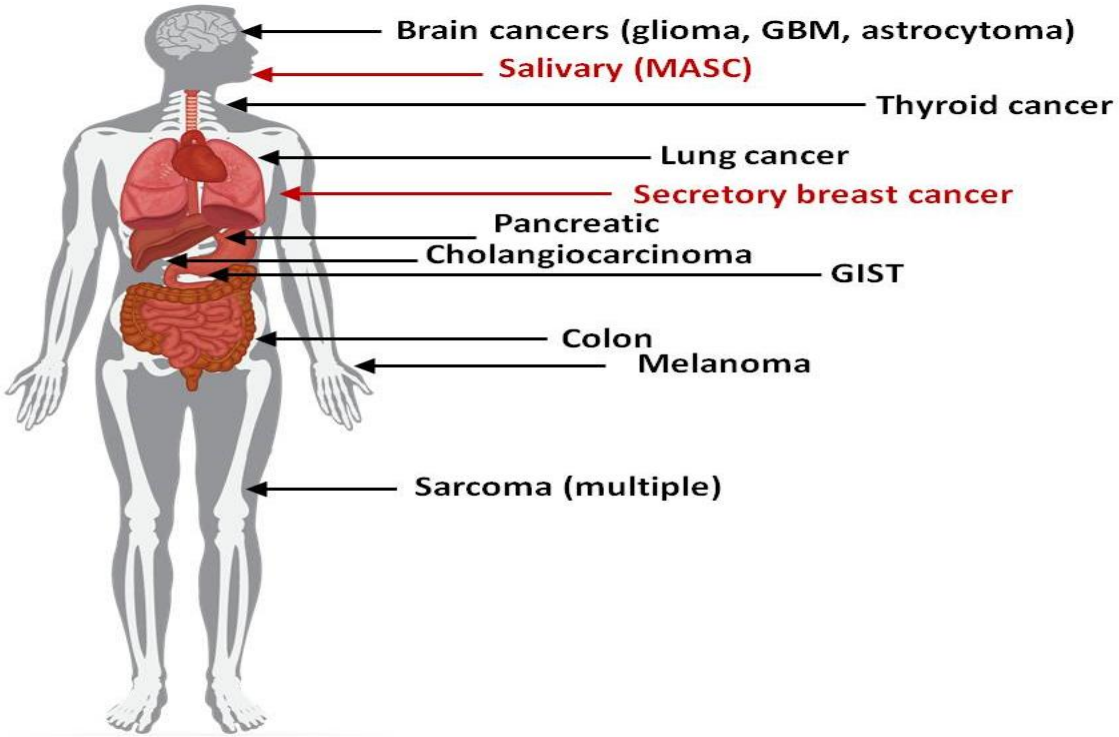
June 2014

Courtesy of B. Johnson

NTRK Gene Fusions are Oncogenic and Signal Through Canonical Downstream Pathways

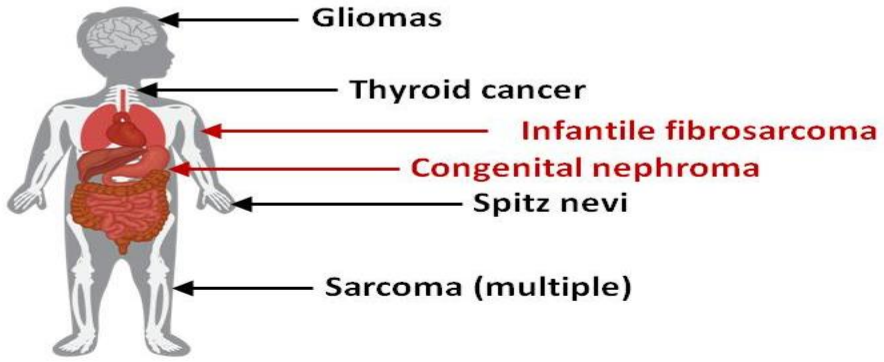
- The neurotrophic receptor tyrosine kinase genes *NTRK1, NTRK2, and NTRK3* encode the tropomyosin receptor kinase (***TRK***) proteins *TRKA, TRKB,* and *TRKC*, respectively.
- After embryogenesis, TRK expression is limited primarily to the nervous system, where these kinases help regulate pain, proprioception, appetite, and memory.
- Recurrent chromosomal fusion events involving the carboxy-terminal kinase domain of TRK and various upstream amino-terminal partners have been identified across diverse cancers that occur in children and adults.
- *TRK fusions lead to overexpression of the chimeric protein, resulting in constitutively active, ligand-independent downstream signaling.*
- *Biologic models and early clinical evidence suggest that these fusions lead to oncogene addiction regardless of tissue of origin and, in aggregate, may be implicated in up to 1% of all solid tumors*

TRK Fusions Found in Diverse Cancer Histologies



Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



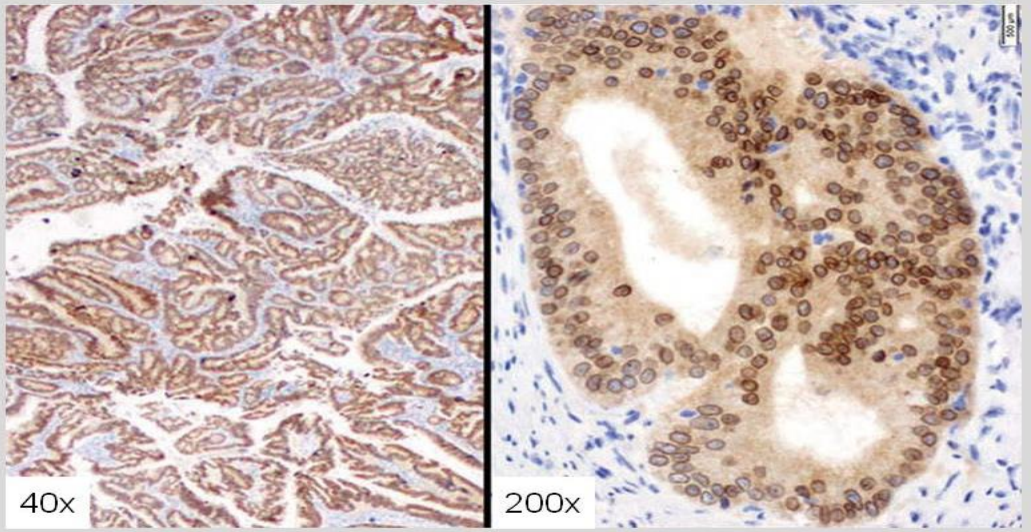
Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Hyman et al ASCO 2017 #LBA 2501; Drilon et al NEJM 2018

Methods to detect *TRK* Fusions

- Several modalities:
  - DNA & RNA NGS, FISH, IHC
- Large NTRK introns (compared to ALK, ROS1, RET) make DNA-based detection challenging
- Loxo/Ventana developing Pan-TRK IHC companion diagnostic (CDx)
- NGS "universal" CDx tests under FDA review include TRK fusion detection*

*FoundationOne, Oncomine Universal Dx



Pan-TRK IHC detects expression, shared among TRK fusions

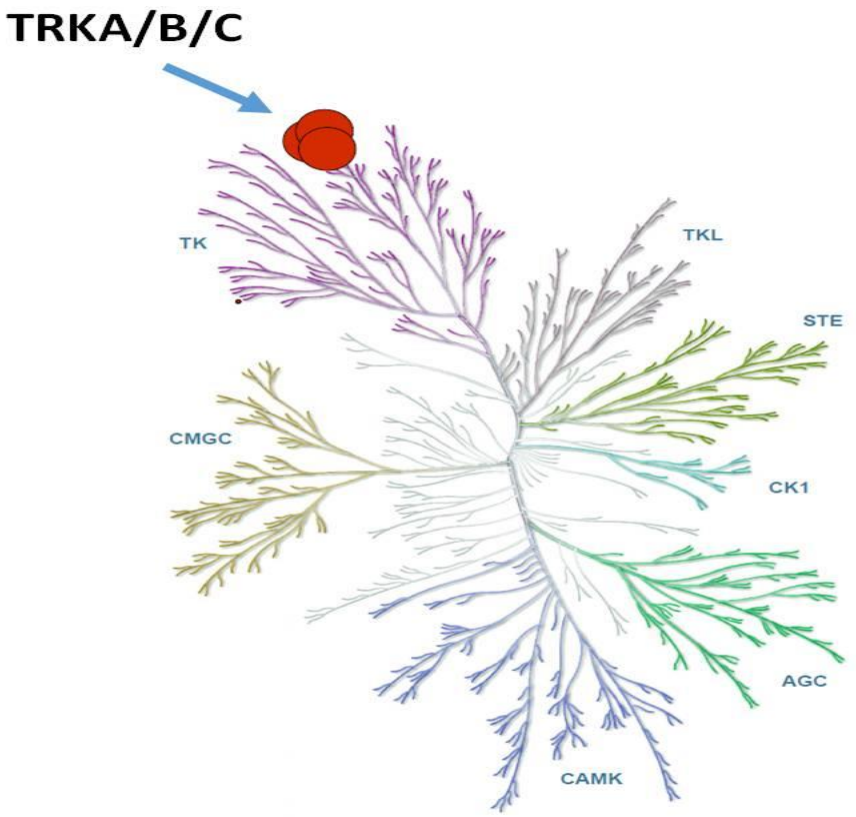
More info: www.TRKtesting.com

Hyman et al ASCO 2017 #LBA 2501; Drilon et al NEJM 2018

Larotrectinib: A Selective TRK Inhibitor

Larotrectinib

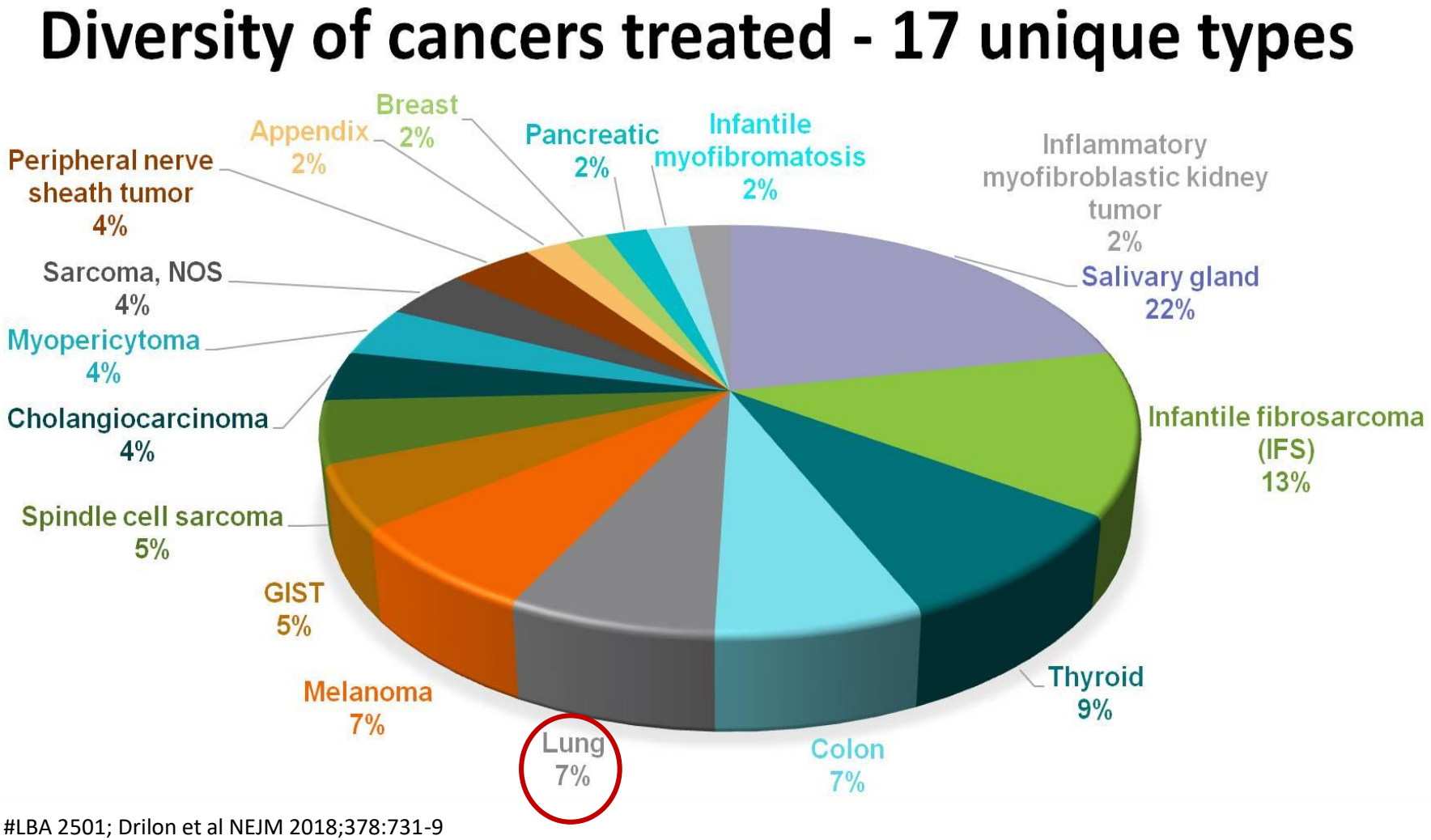
- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC
  - 5–11 nM IC_{50} in cellular assays
- Highly selective
- Development timeline
  - March 2015: 1st TRK-fusion patient treated
  - July 2016: breakthrough therapy designation
  - February 2017: pivotal enrollment complete



Hyman et al ASCO 2017 #LBA 2501; Drilon et al NEJM 2018

Efficacy of Larotrectinib: In TRK-Fusion Positive Cancers in Adults and Children

TRK fusions were identified by NGS or by FISH

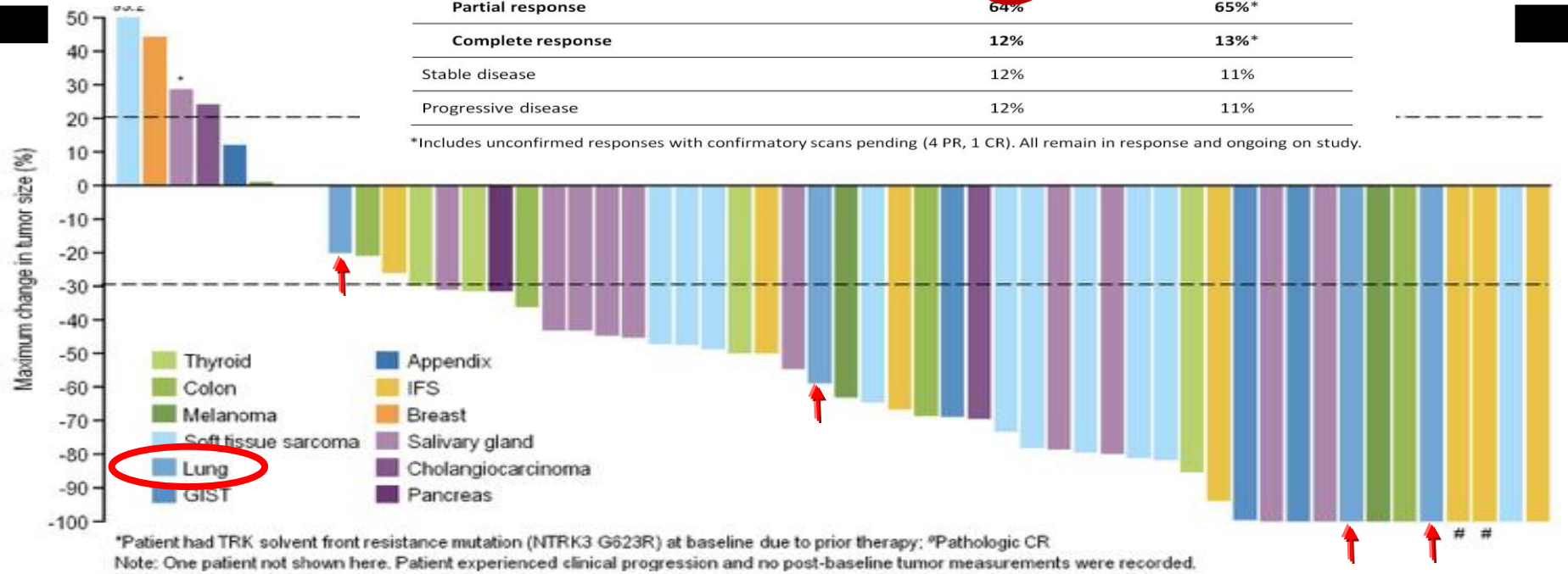


Hyman et al ASCO 2017 #LBA 2501; Drilon et al NEJM 2018;378:731-9

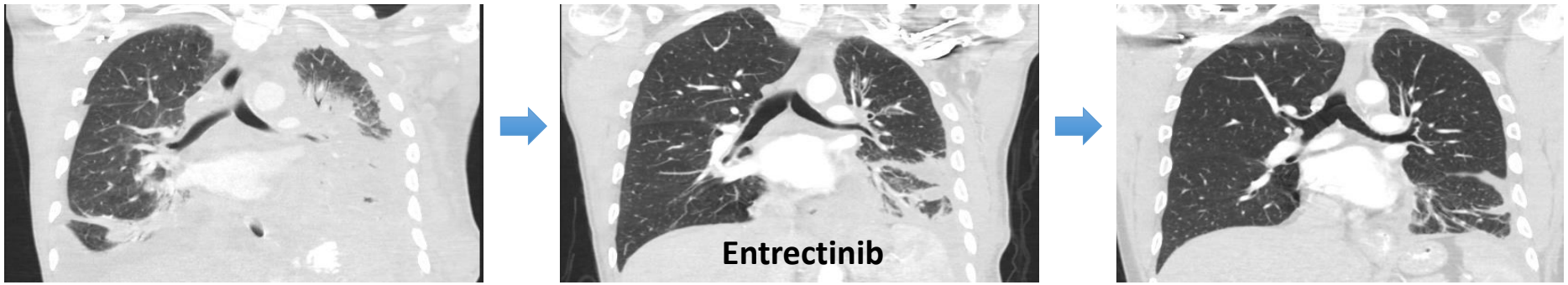
TRK Inhibition in *NTRK*-Rearranged Tumors

	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.

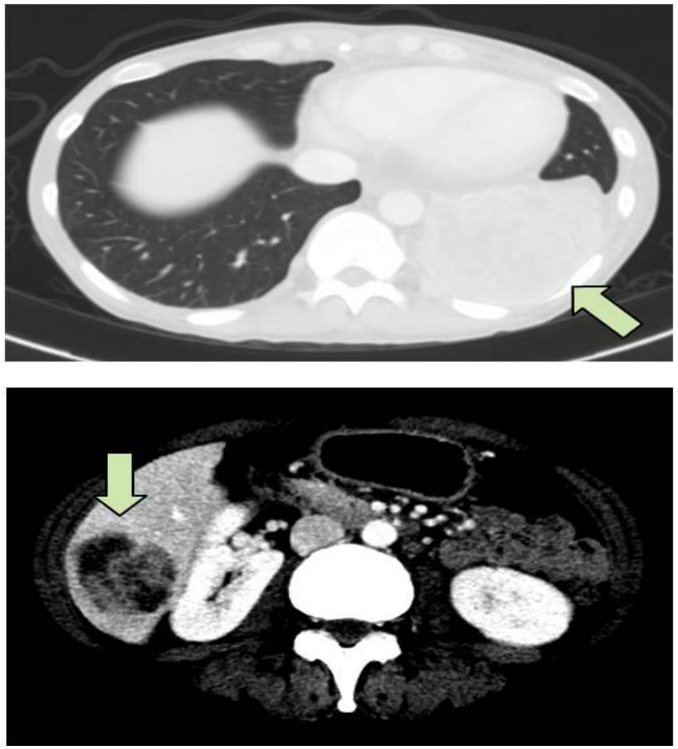


*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

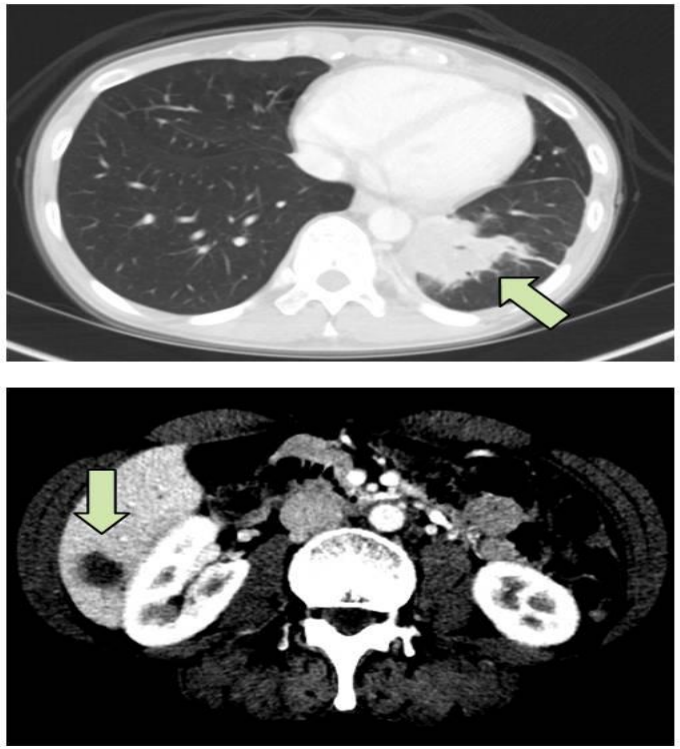


Drilon et al, Cancer Discovery 2017; Hyman ASCO 2017; Farago et al, JTO 2016; Drilon et al NEJM 2018

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

Hyman et al ASCO 2017 #LBA 2501

Larotrectinib—AEs

	Treatment-emergent AEs (%)*					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Fatigue	15	18	5	–	38	1	–	18
Dizziness	22	4	2	–	27	1	–	20
Nausea	20	5	2	–	26	2	–	18
Anemia	8	9	9	–	26	3	–	10
Vomiting	18	6	–	–	24	–	–	13
Increased AST	16	4	3	–	23	1	–	18
Constipation	20	2	1	–	22	–	–	12
Cough	18	2	–	–	21	–	–	2
Increased ALT	14	2	4	–	20	4	–	17
Diarrhea	14	5	1	–	20	–	–	6
Dyspnea	10	6	2	–	18	–	–	–

7 (13%) patients required dose reductions – all maintained tumor regression (1 CR, 5 PR, 1 SD) on reduced dose. No discontinuations for adverse events.

Hyman et al ASCO 2017 #LBA 2501; Drilon et al NEJM 2018

Emerging targets

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib[1-5]
RET rearrangements	Cabozantinib[6,7] Vandetanib[8]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

[1]Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.
[2]Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32(Suppl 5): Abstract 8001.
[3]Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015;5:850-859.
[4]Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov 2015;5:842-849.
[5]Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpresion. J Clin Oncol 2016;34:721-730.
[6]Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.
[7]Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016;17:1653-1660.
[8]Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol 2017;28:292-297.
[9]Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncol 2018;36:2532-2537.
[10]Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378:2093-2104.
[11]Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–2426.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MET in NSCLC

- *MET* is a proto-oncogene that encodes for the transmembrane *MET* tyrosine receptor kinase
- Through ligand binding to HGF(hepatocyte growth factor), signaling pathways such as PI3K/AKT, MAPK, NF-kB, and STATs (signal transducer and activator of transcription proteins) are activated, which leads to cell proliferation and invasion
- Protein over-expression and phosphorylation are the most common forms of *MET*-positive NSCLC, but responses to therapy have been varied
- *MET* amplification occurs in less than 5% of lung adenocarcinoma; *MET* exon 14 alterations are found in 4 % of lung adenoca and predominantly associated with older age(median 73) and smoking history. *MET* gene rearrangement is uncommon, but the kinase fusion KIF5B-MET has been reported in adenoca.
- Multitargeted TKIs have been used to target MET in lung cancer (e.g., cobazantinib, crizotinib, merestinib) and a variety of TKIs with increased sensitivity are also under investigation (e.g., salvolitinib, tepotinib, capmatinib, sitravatinib, AMG337, tivantinib)
- A phase II study of tepotinib in patients with ***MET*** exon 14 skipping mutations is ongoing – preliminary data 60% RR.

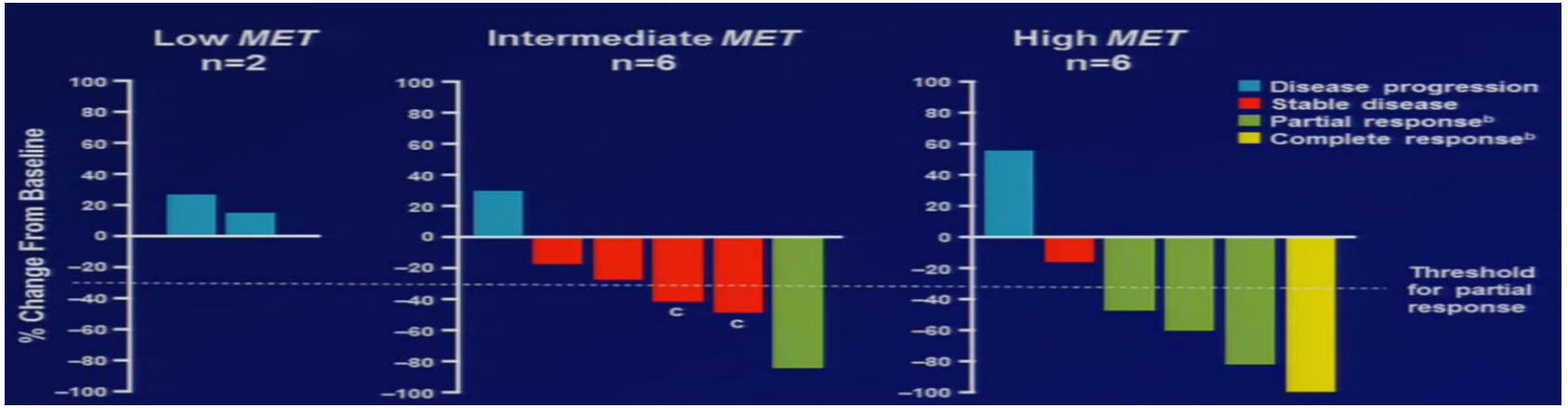
Crizotinib in *MET*-amplified lung cancers

Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

2018	Low *MET* (*MET/CEP7* 1.8-2.2) n=3	Intermediate *MET* (*MET/CEP7* >2.2-<4.0) n=14	High *MET* (*MET/CEP7* ≥4.0) n=20
Overall response	33.3 % (95%CI 0-84)	14.3 % (95%CI 0-64)	**40 %** (95%CI 22-96)
Medan DoR m Median PFS m	12.1 1.8	3.7 1.9	5.5 **6.7**

***MET* amplification determined by FISH**

2014

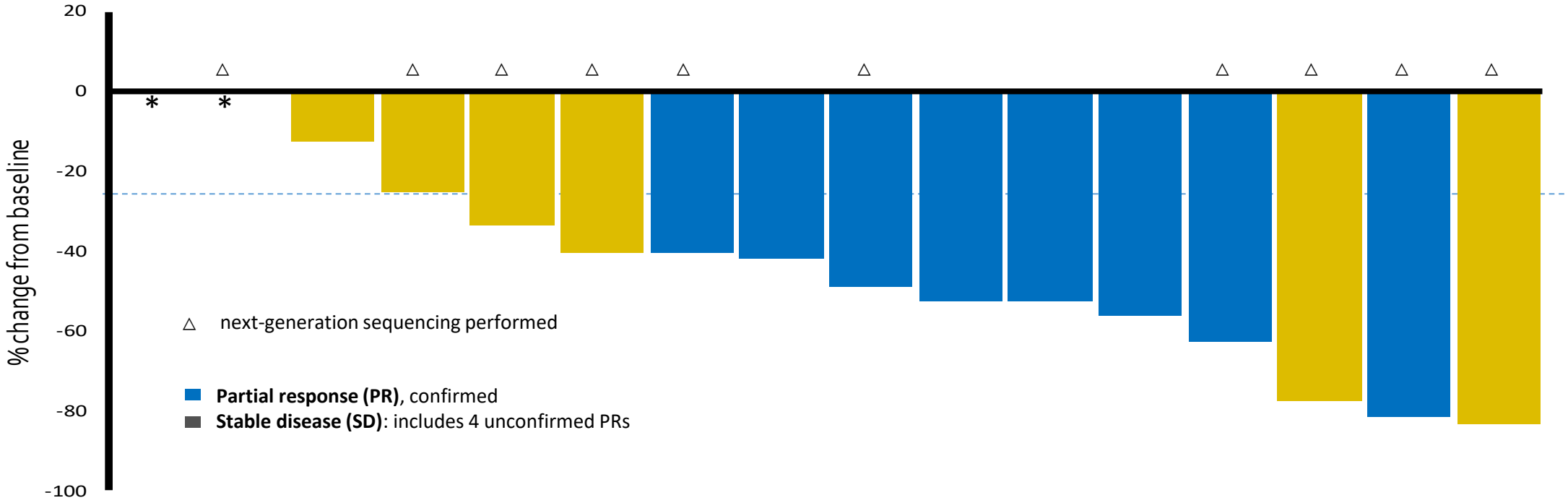


Camidge et al, ASCO Annual Meeting 2014, updated ASCO 2018

Crizotinib in *MET*ex14-altered lung cancers

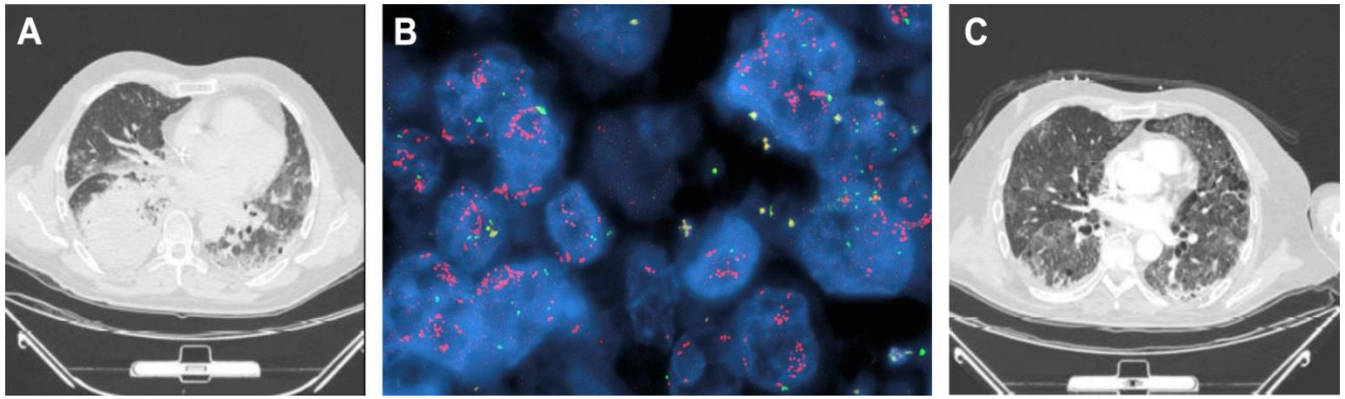
Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

69 patients,
Overall response rate (ORR)
32% (95% CI: 22–69), 3 – CR, 18 –PRs
mPFS – 7.3m, m TTR – 7.6 weeks



Drilon et al, ASCO Annual Meeting 2016; updated JTO Volume 13 (10) October 2018 pS348

Responses to Crizotinib Can Occur in High-Level *MET*-Amplified Non–Small Cell Lung Cancer Independent of *MET* Exon 14 Alterations



before crizotinib.

2 months on crizotinib.

B) **FISH analysis** on a central nervous system resection specimen with MNNG HOS Transforming gene (*MET*) (SpectrumRed) and chromosome centromere 7 (*CEP7*) (SpectrumGreen) **showing *MET* gene amplification** (mean *MET* copies per cell = 20.53; mean *CEP7* copies per cell = 2.07; *MET/CEP7* ratio = 9.94).

Caparica R et al. January 2017 Volume 12, Issue 1, Pages 141–144

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

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Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

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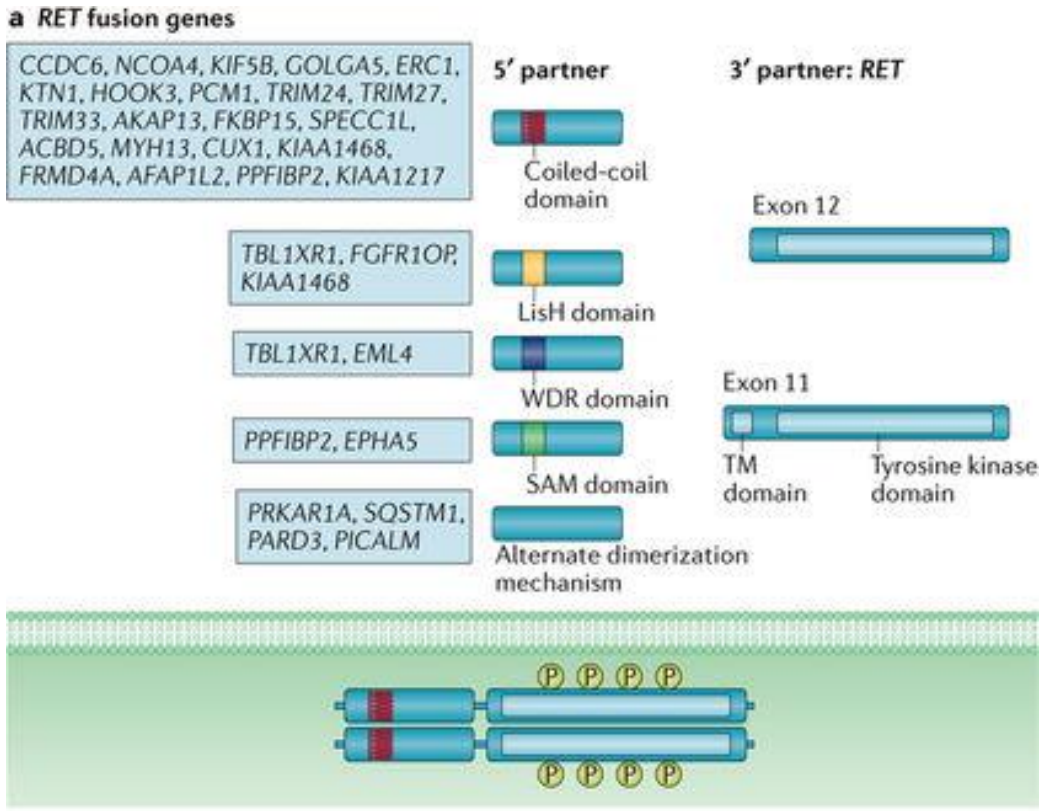
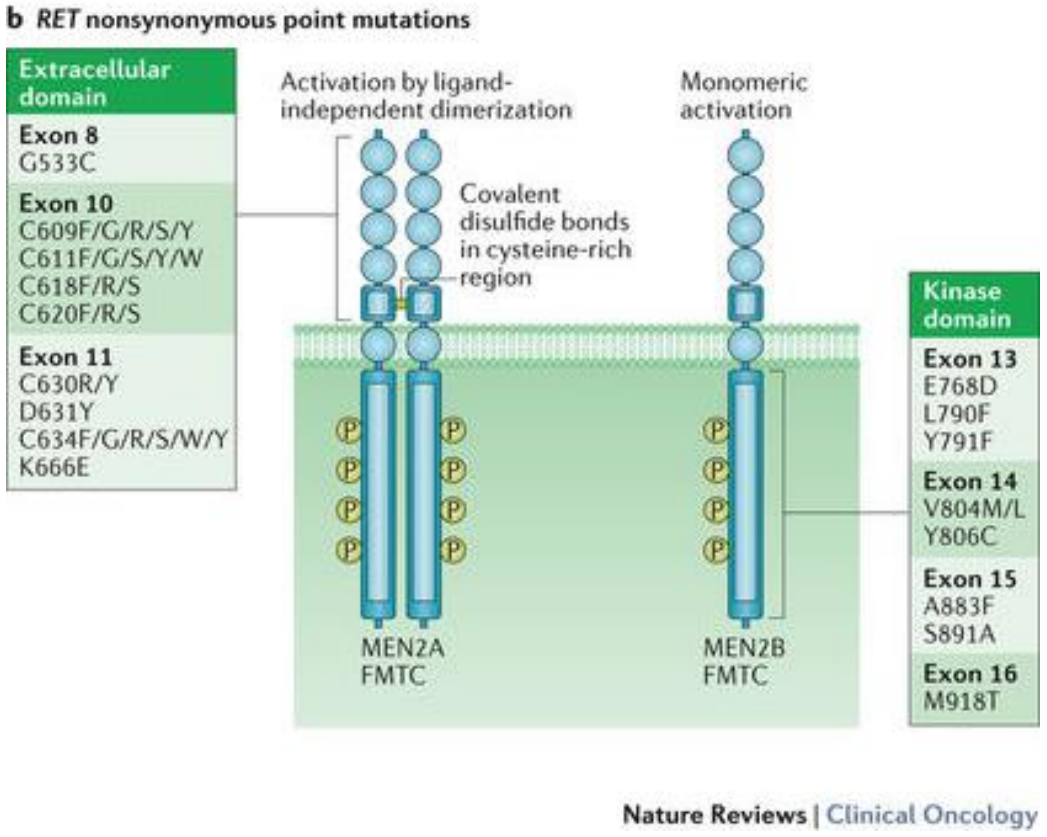
Several genomic alterations activate RET in cancer

RET Fusions



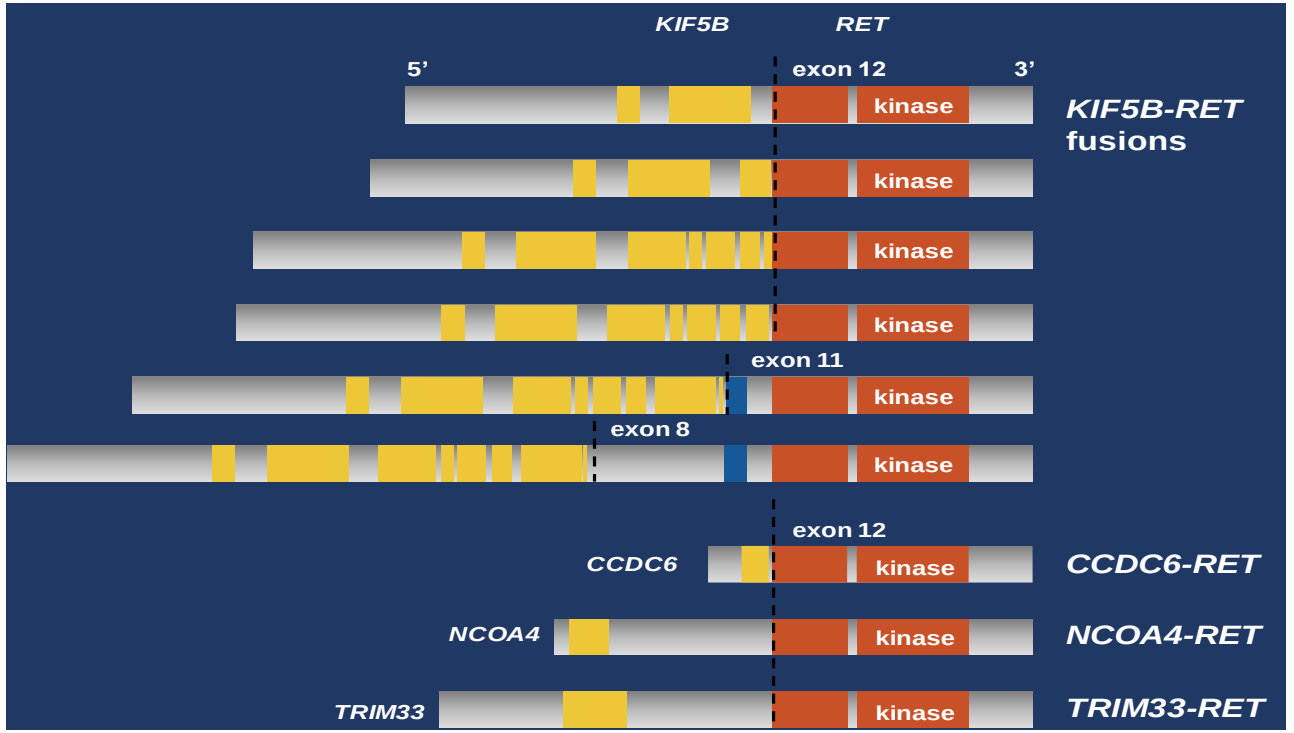
RET Mutations



Drilon, A. et al. (2017) Nat. Rev. Clin. Oncol

RET Rearrangements

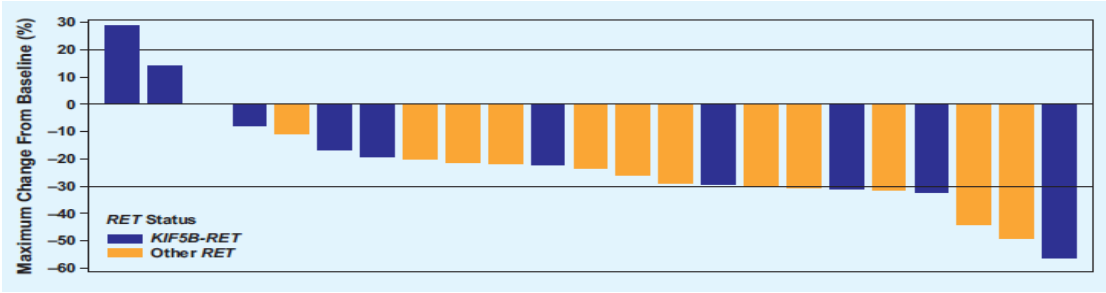
- intact tyrosine kinase domain fused to an upstream gene partner
  - **most common: *KIF5B***
  - others: *CCDC6, NCOA4, TRIM33, KIAA1468*
- result in ligand-independent dimerization and downstream growth pathway activation
- oncogenic *in vitro* and *in vivo*
- **1-2% NSCLC, more likely to be present in younger, never-smokers with adenocarcinoma**



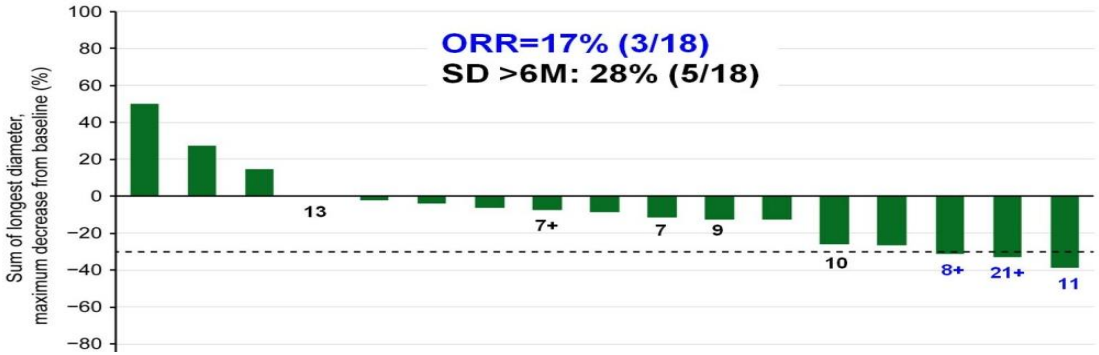
Drilon AD, Cancer Discov 2013;3:630-5, Kohno T, Nat Med 2012;18:375-7, Saito M, Carcinogenesis 2014;35:2452-6
Suehara Y, Nat Med 2012;18;6599-608, Lipson D, Nat Med 2012;18:382-40, Takeuchi K, Nat Med 2012;18:378-81

Multikinase inhibitors in *RET*-rearranged lung cancers

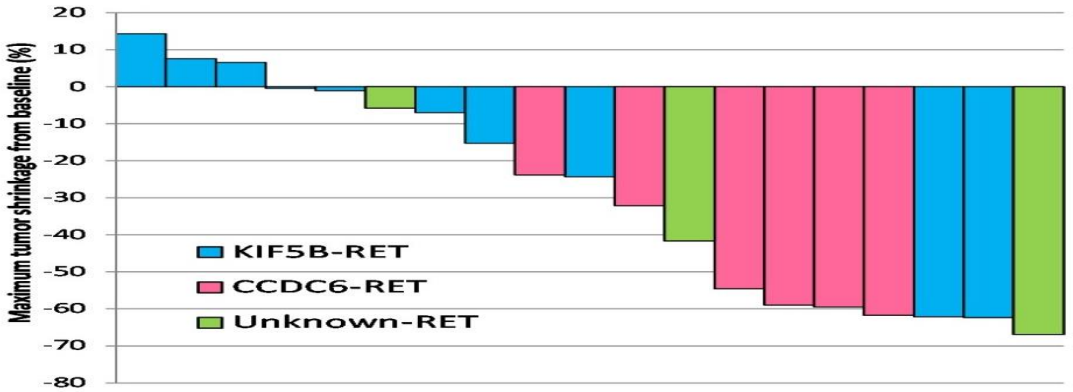
Multicenter phase 2 trial
Primary endpoint: response
Lenvatinib ORR 16%, mPFS– 7.3m



Korean phase 2 trial
Primary endpoint: response
Vandetanib ORR 18%, mPFS – 4.5 m



Japanese phase 2 trial (**LURET**)
Primary endpoint: response
Vandetanib ORR 53%, mPFS – 4.7m



Velcheti et al ESMO 2016, Lee et al Annals Oncol 2017, Yoh et al ASCO 2016

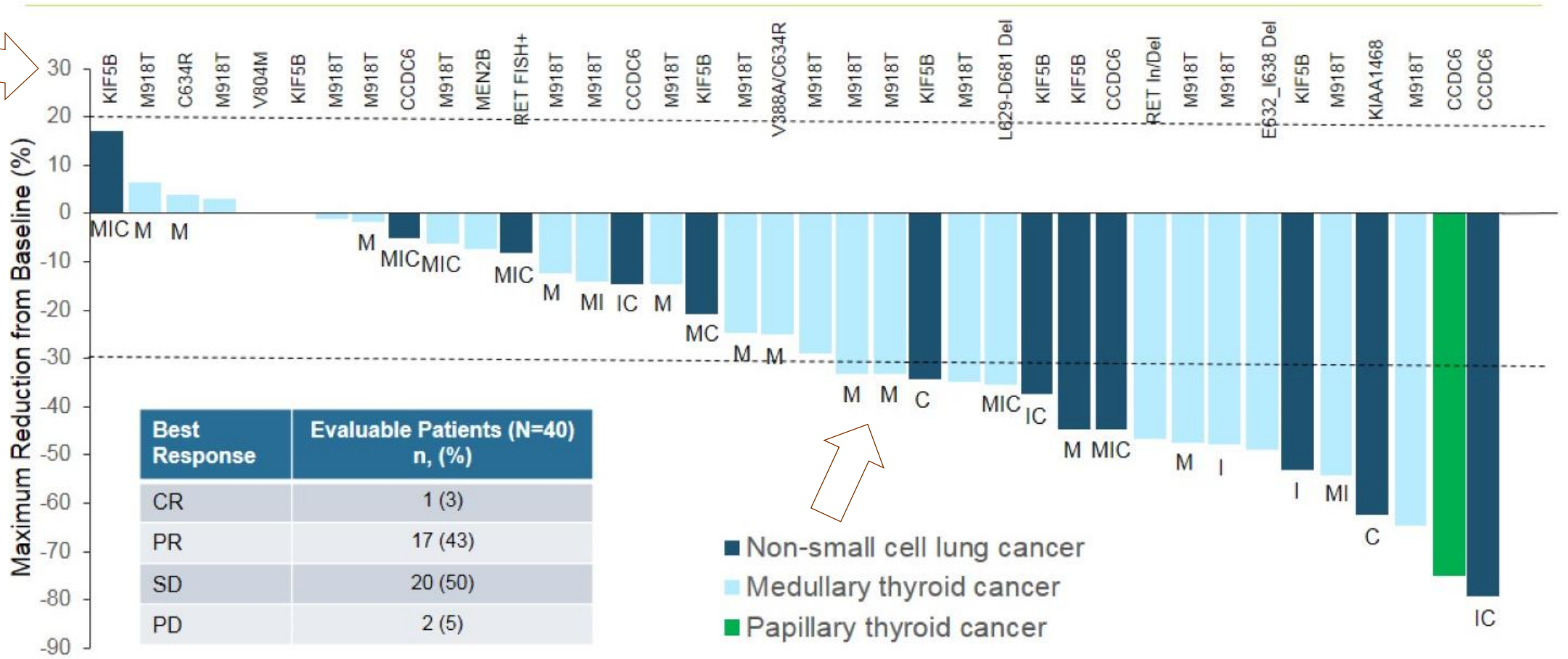
RET Inhibitors—Efficacy Summary

Agent	*RET* testing	n	ORR (%)	PFS (months)	OS (months)
Cabozantinib (Drilon, ASCO 2015)	FISH/NGS	Stage I, 16	38	7	10
Cabozantinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	13	31	3.6	4.9
Vandetanib (Sato, ASCO 2016)	FISH/RT-PCR	19/17	47/53	4.7	47% 1-year
Vandetanib (Lee, ASCO 2016)	FISH confirmed	18	17	4.5	11.6
Vandetanib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	11	18	2.9	10.2
Sunitinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	9	22	2.2	6.8
Lenvatinib (Velcheti, ESMO 2016)	NGS	25	16	7.3	NR
Any RET inhibitor (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	41	23	2.9	6.8

More selective RET inhibition is active in *RET*-altered cancers—BLU 667

Many tumors were molecularly well-characterized.

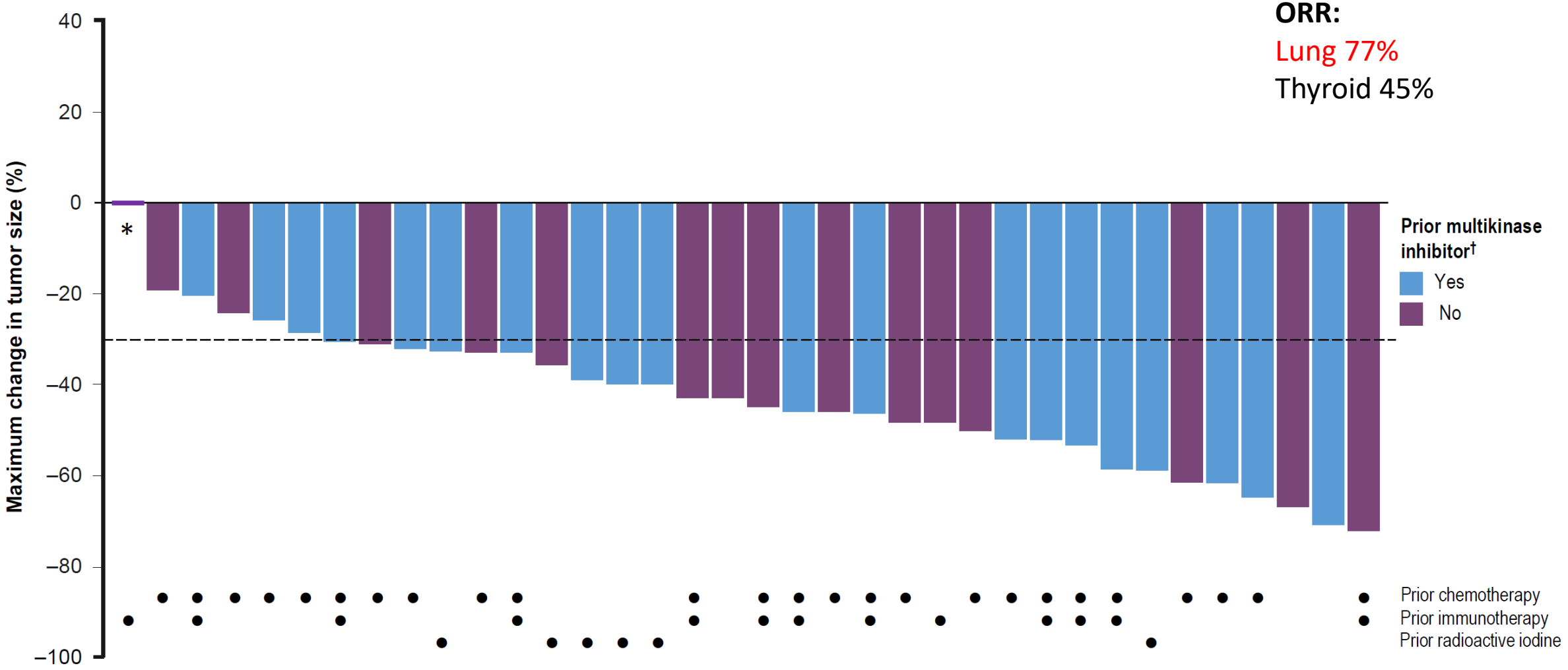
ORR:
Lung 36%
Thyroid 24%



Best Response	Evaluable Patients (N=40) n, (%)
CR	1 (3)
PR	17 (43)
SD	20 (50)
PD	2 (5)

Responses were seen both in multikinase inhibitor pre-treated and TKI-naïve lung and thyroid cancer patients.

Efficacy of LOXO-292 regardless of prior therapy



Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size; †Includes alectinib, cabozantinib, lenvatinib, pazopanib, ponatinib, RXDX-105, sitravatinib, sorafenib, and vandetanib; April 2, 2018 cut-off date

Drilon et al ASCO 2018

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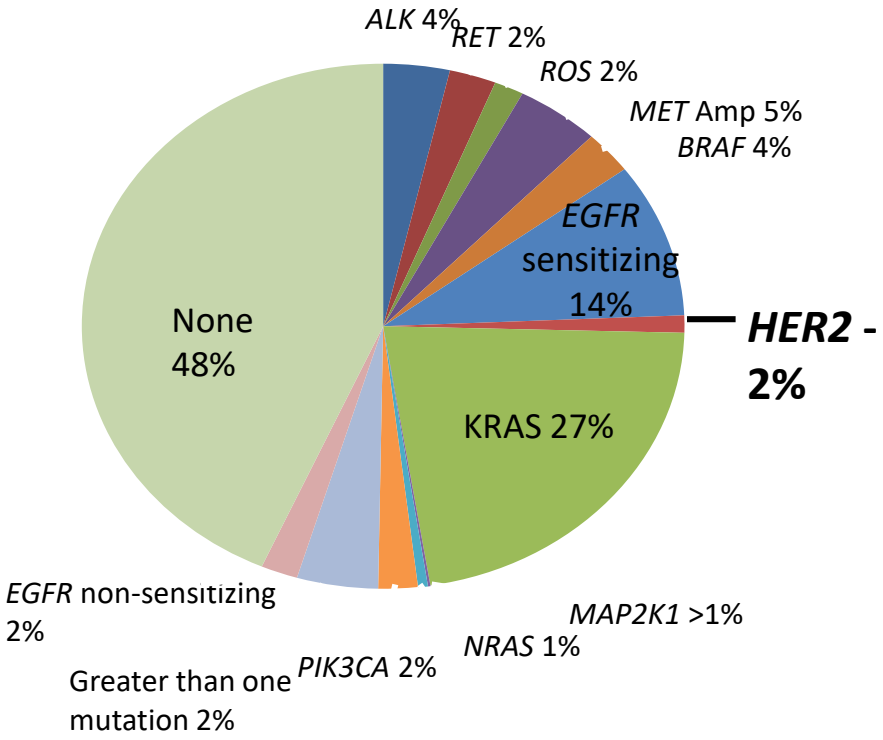
Oncogenic alterations: *HER2* mutations

LCMC

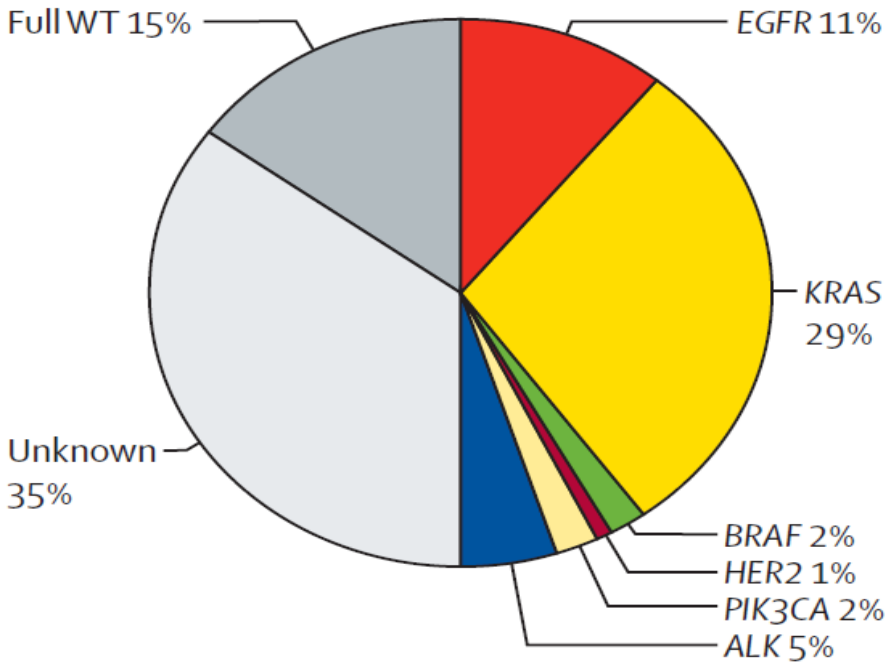
***HER2:* 18/810 – 2%**
(95% CI 1.3 to 3.5 %)



Kris M JAMA 2014

IFCT

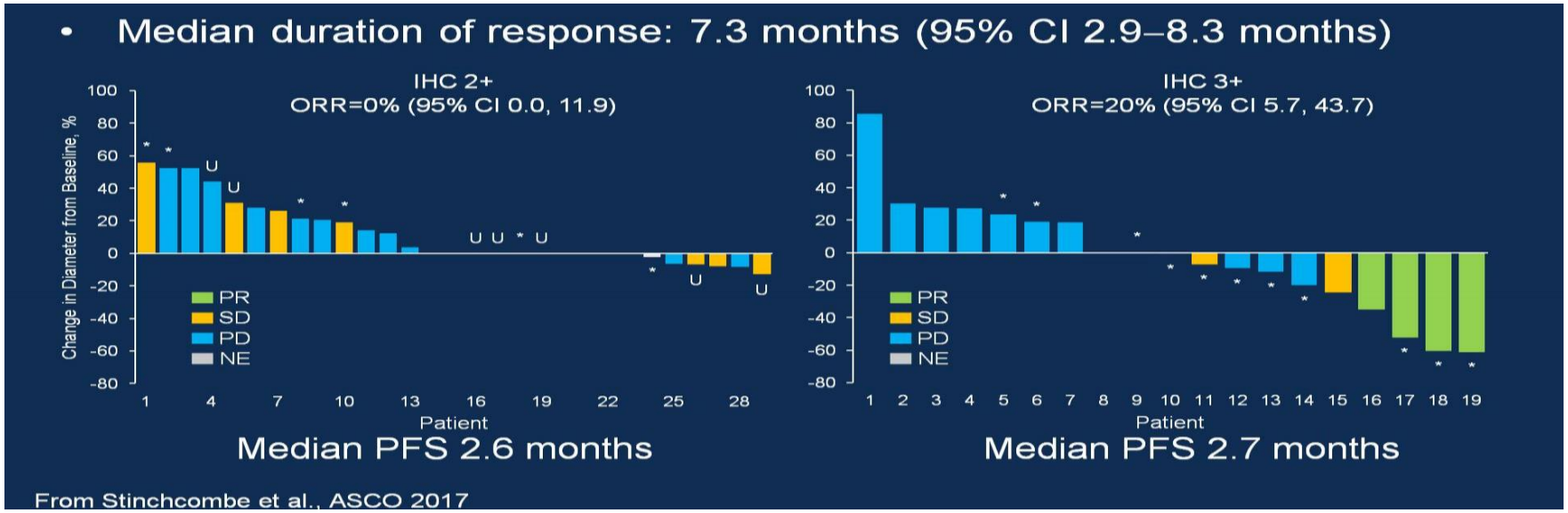
***HER2*: 98/11,723 – 1%**
(95% CI 0.8 to 1.2 %)



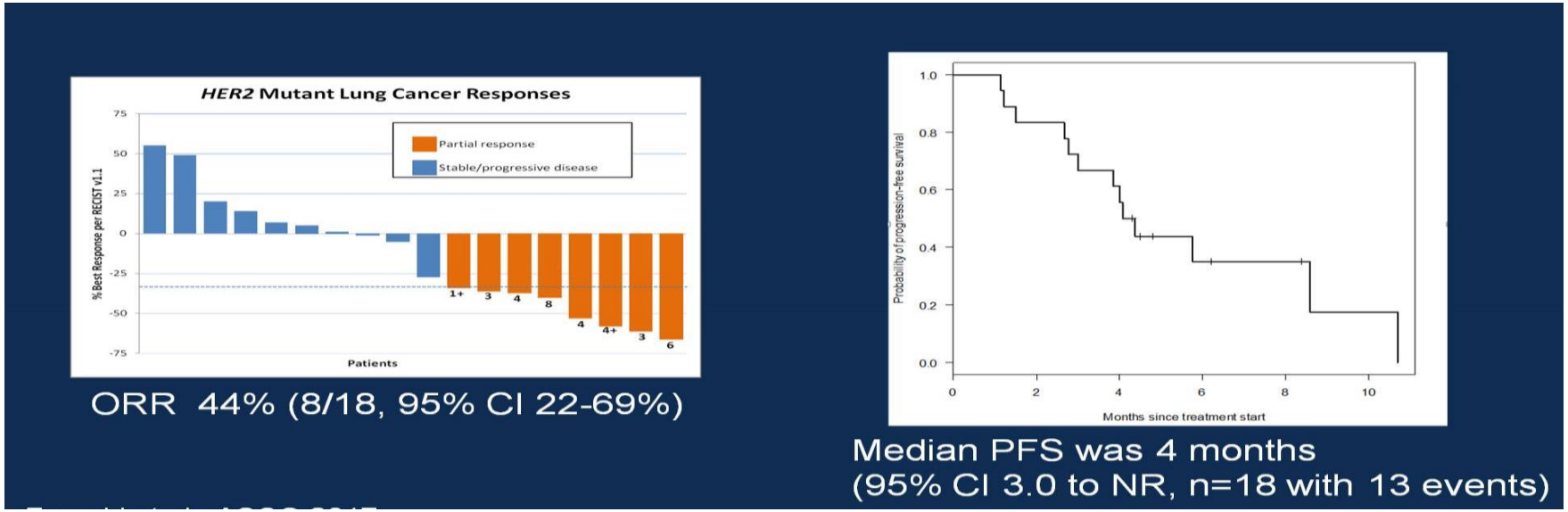
Barlesi Lancet 2016
IFCT – French Cooperative Thoracic Intergroup

TDM-1 (Ado-trastuzumab) in *HER2*- Mutant NSCLC

HER2 expression

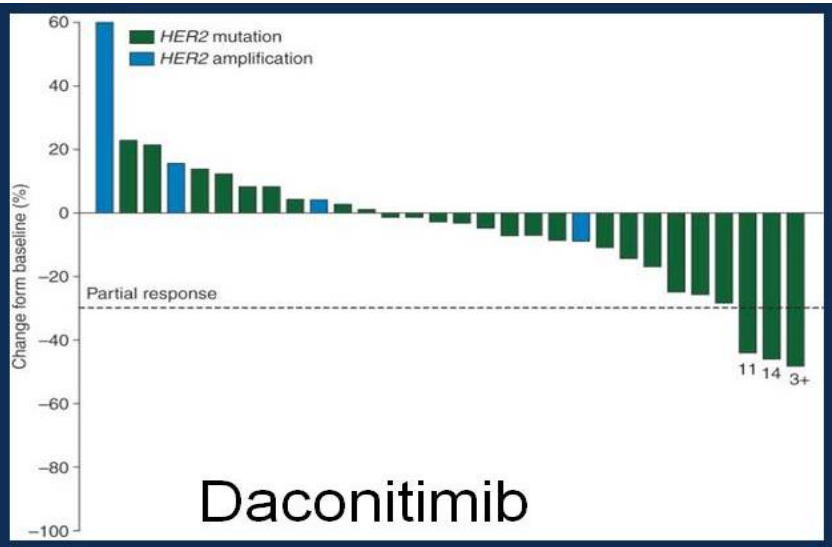


HER2 mutation



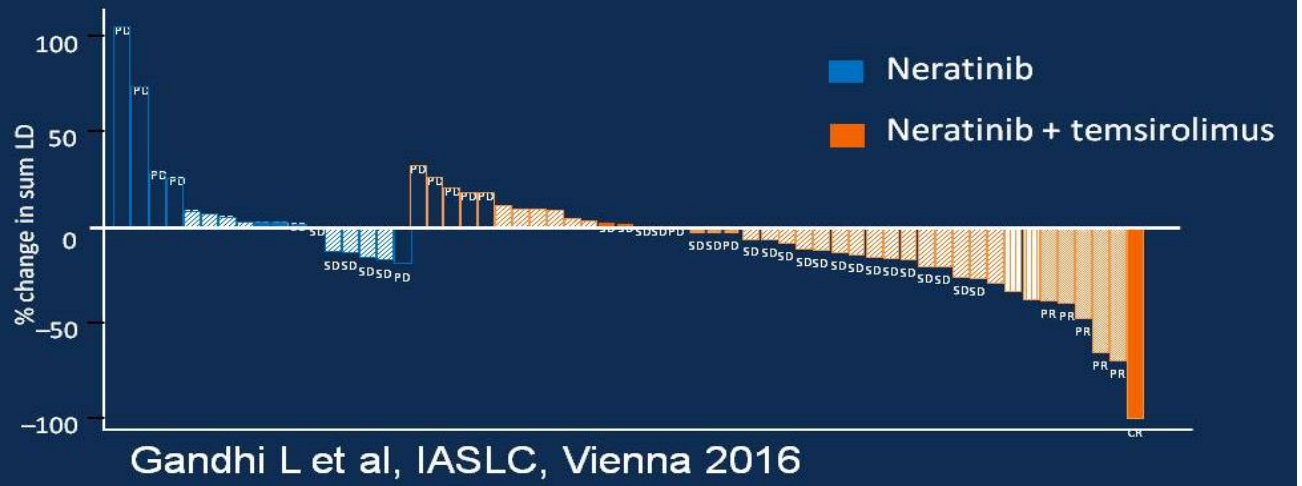
Li J Clin Oncol 2018

HER2 TKIs in *HER2*-activated lung cancers



Kris M et al., Ann Oncol 2015 Jul; 26 (7): 1421-27

Median PFS 3 months



Gandhi L et al, IASLC, Vienna 2016

Median PFS neratinib 2.9 months

Median PFS neratinib + temsirolimus 4 months

AFATINIB:

0/13 responses in prospective trial/PFS 3 months (Smit el al. ASCO 2017 Abstract #9070)

3/22 responses in retrospective series (Lai et al. ASCO 2017 Abstract #9071)

HER2 mutant NSCLC treated with chemotherapy and *HER2*-targeted drugs retrospective cohort study.

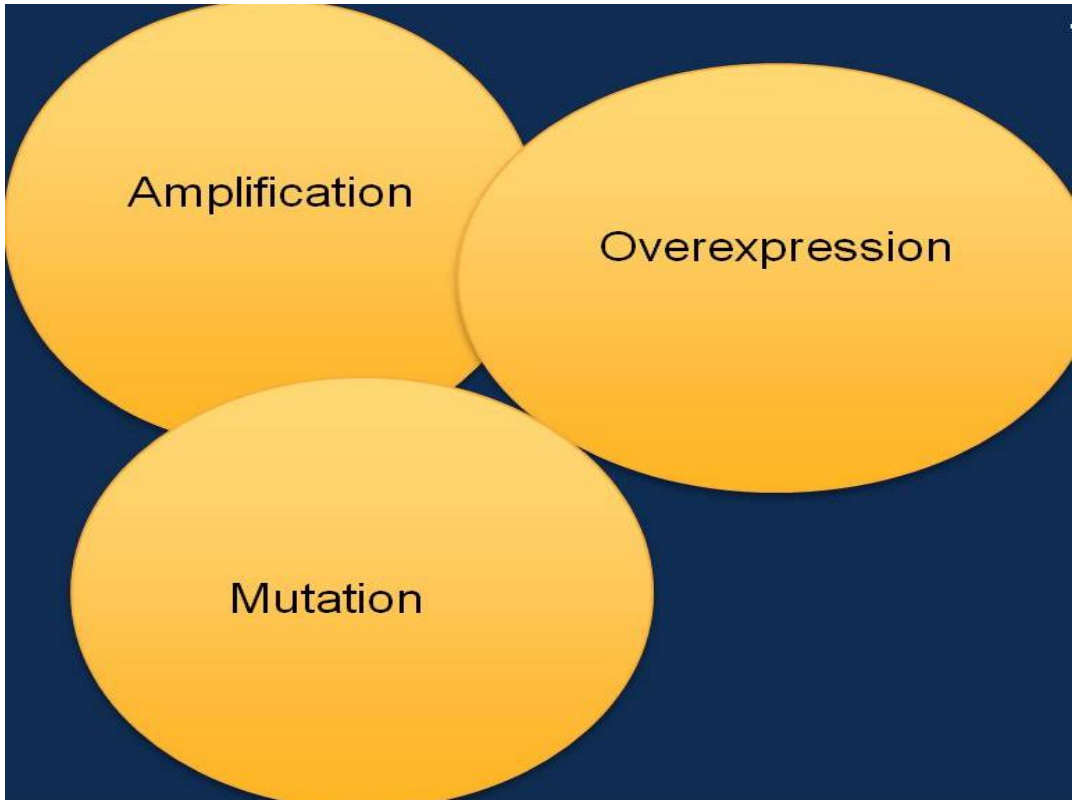
European EUHER2 cohort

Treatment	n	ORR	DC	PFS median	OS median
First-line: without HER2-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line: without HER2-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DM1	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)

Mazières J et al. Ann Oncol 2016

HER2-directed agent	*HER2* alteration	n	ORR (%)	PFS (months)	OS (months)
Dacomitinib (Kris MG et al. Ann Oncol 2015)	mutation or amplification	30 (26 mut/ 4 amp)	12 mut/ 0 amp	3 mut	9
Afatinib (De Grève, 2012; Mazières, 2013; De Grève, 2015; Li,2015)	mutation	17 case reports	NA	1.8-10	NA
Lapatinib (Lopez-Chavez A et al. J Clin Oncol 2015)	mutation or amplification	6	0	NA	NA
Neratinib + temsirolimus (Besse B et al. ESMO 2014)	mutation	14	21	4	NA
Any therapy (Mazières J et al. Ann Oncol 2016)	mutation	101	23	6	23.4
Trastuzumab combination, T-DM1 (Mazières J et al. Ann Oncol 2016)	mutation	58	50.9%	4.8	13.3
Any HER2 therapy (Mazières J et al. Ann Oncol 2016)	mutation	65	50	5.1	NA

Identifying the target in HER2-activated lung cancers



- Significant heterogeneity exists in the molecular aberrations in *HER2* in lung cancers
- Variable effectiveness of HER2 kinase inhibitors reflects the diversity in alterations
- Define important characteristics
  - Type of mutation
  - presence and degree of *HER2* amplification
  - HER2 protein expression, and
  - concurrent pathway activation
- SUMMIT study (neratinib), importance of concurrent pathway activation[1]

[1]Hyman et al. Nature 2018

Conclusions—Emerging targeted therapy

- *MET* exon14 is a promising alteration with multiple MET inhibitors in clinical development
- *RET* alterations have had responses to multitargeted TKIs and more specific RET-targeted agents are in ongoing trials
- *HER2* demonstrates heterogeneous mutations with variable responses to current targeted therapies
- Greatest barrier to treatment and enrollment in trials is testing—liquid biopsies more common eligibility in trials

Thank you!

Questions?