Targeted therapies in NSCLC: MET, BRAF, RET & NTRK

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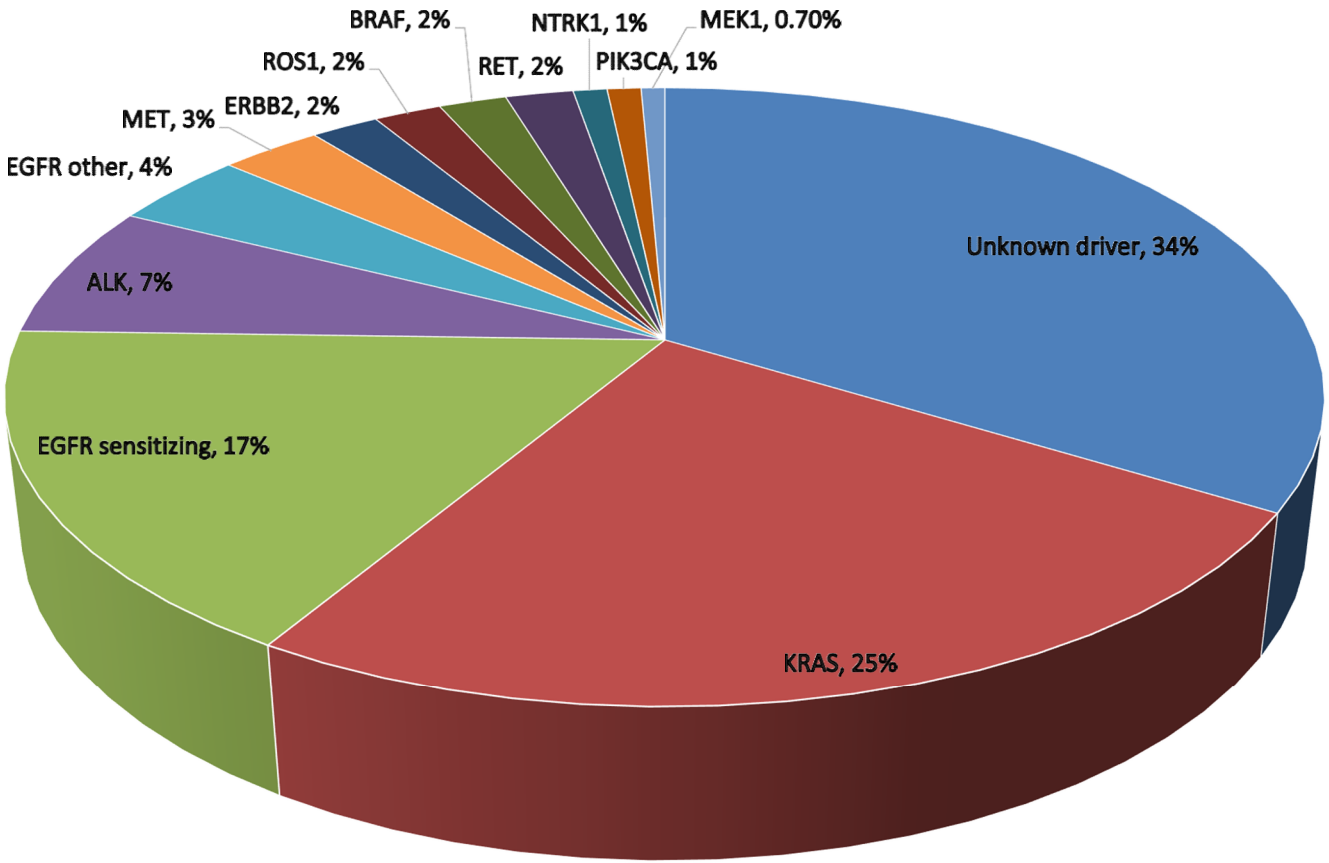
Saint Luke's
HEALTH SYSTEM

Disclosures

- Research funding: Novartis, Merck, CanStem, Helsinn, Biocept, Incyte, Genetech & Paradigm
- Advisory role: Astra Zeneca, Boehringer Ingelheim, Novartis, Eli Lilly & Pfizer
- Speakers bureau: Astra Zeneca & Boehringer Ingelheim

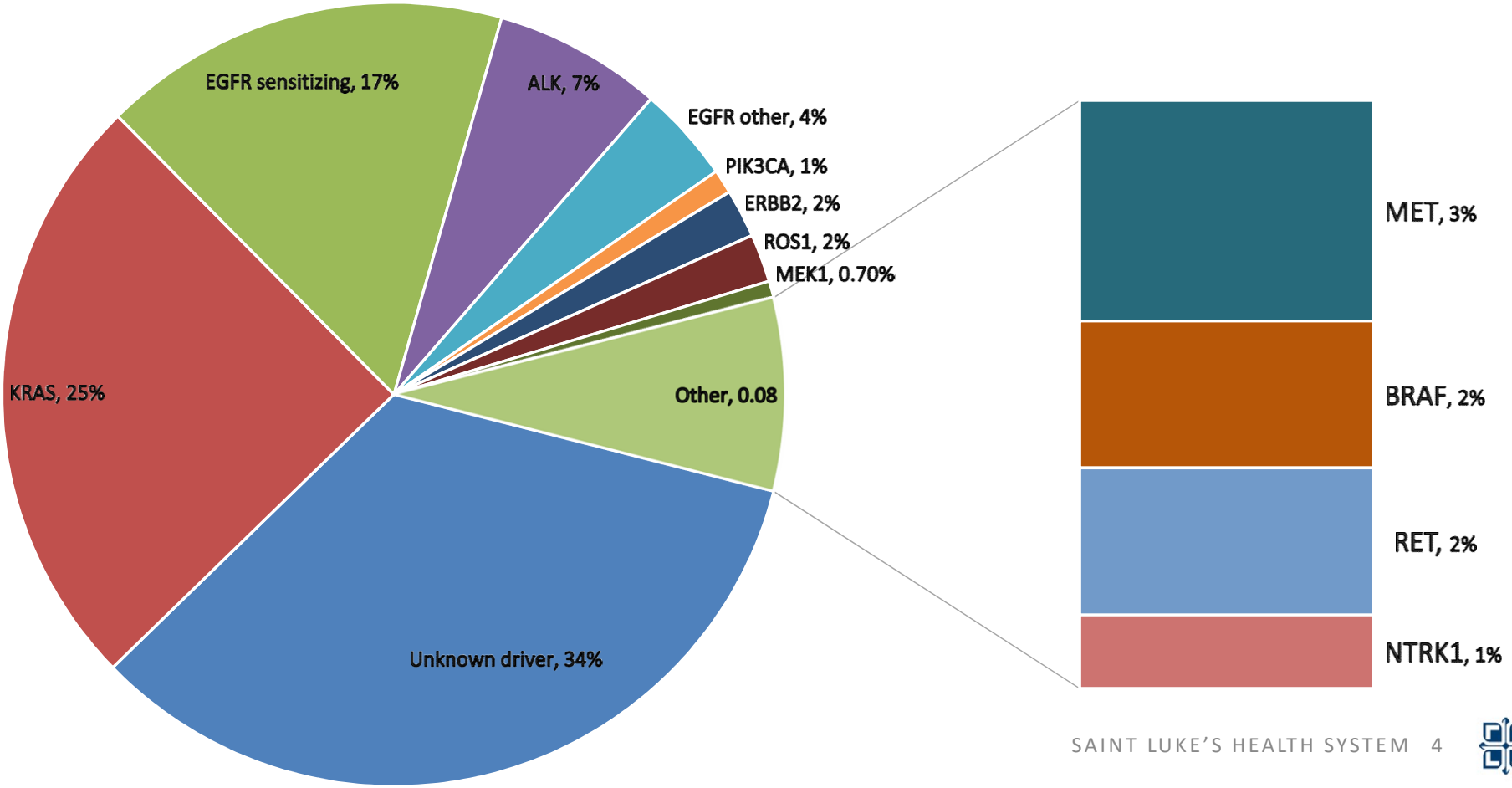
Hanahan D & Weinberg RA et al. Cell 2000

Drivers in Lung Adenocarcinoma

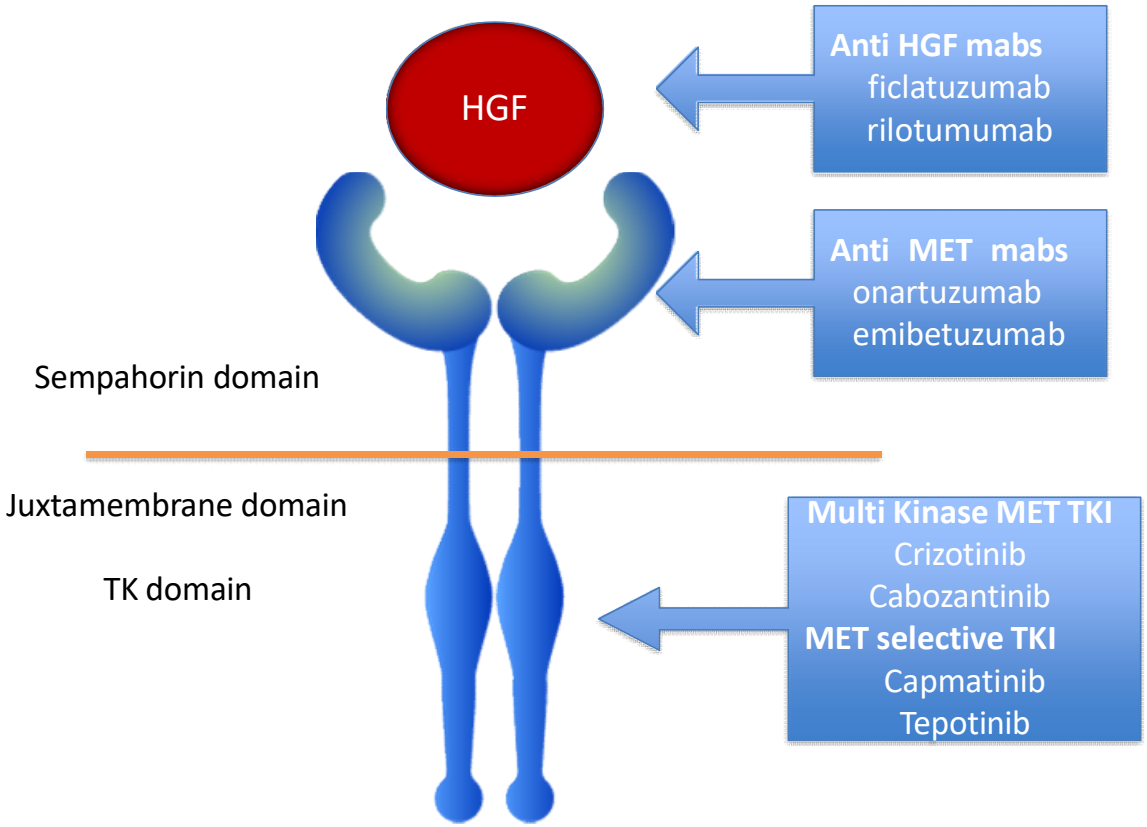


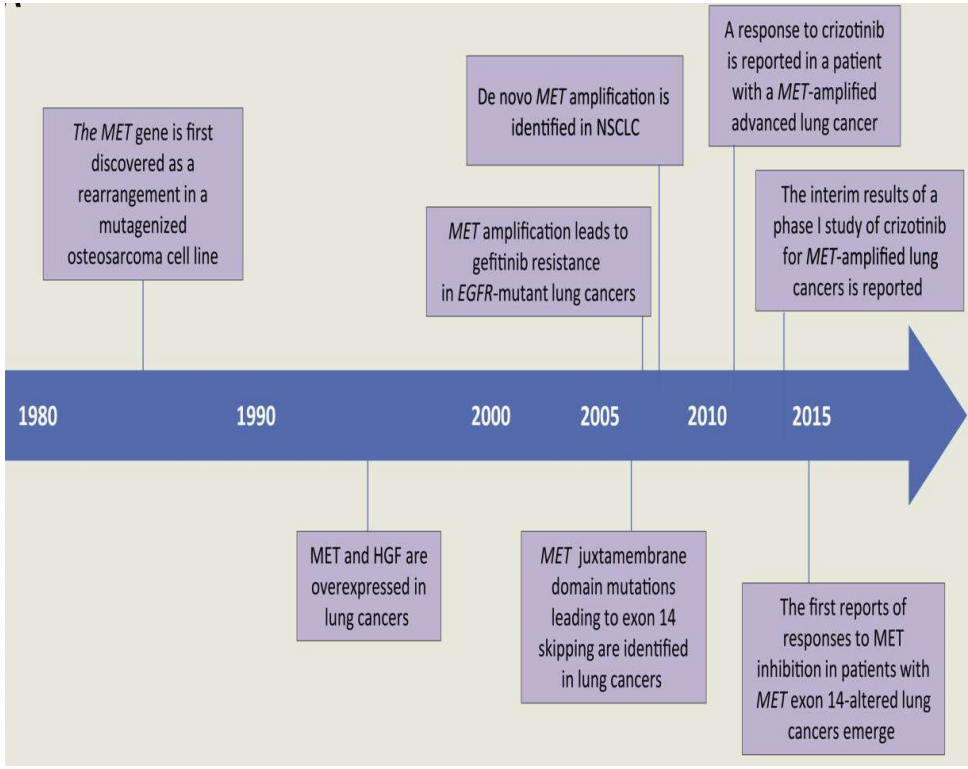
Adapted from https://mycancergenome.org

BRAF, MET, RET & NTRK in Lung Adenocarcinoma



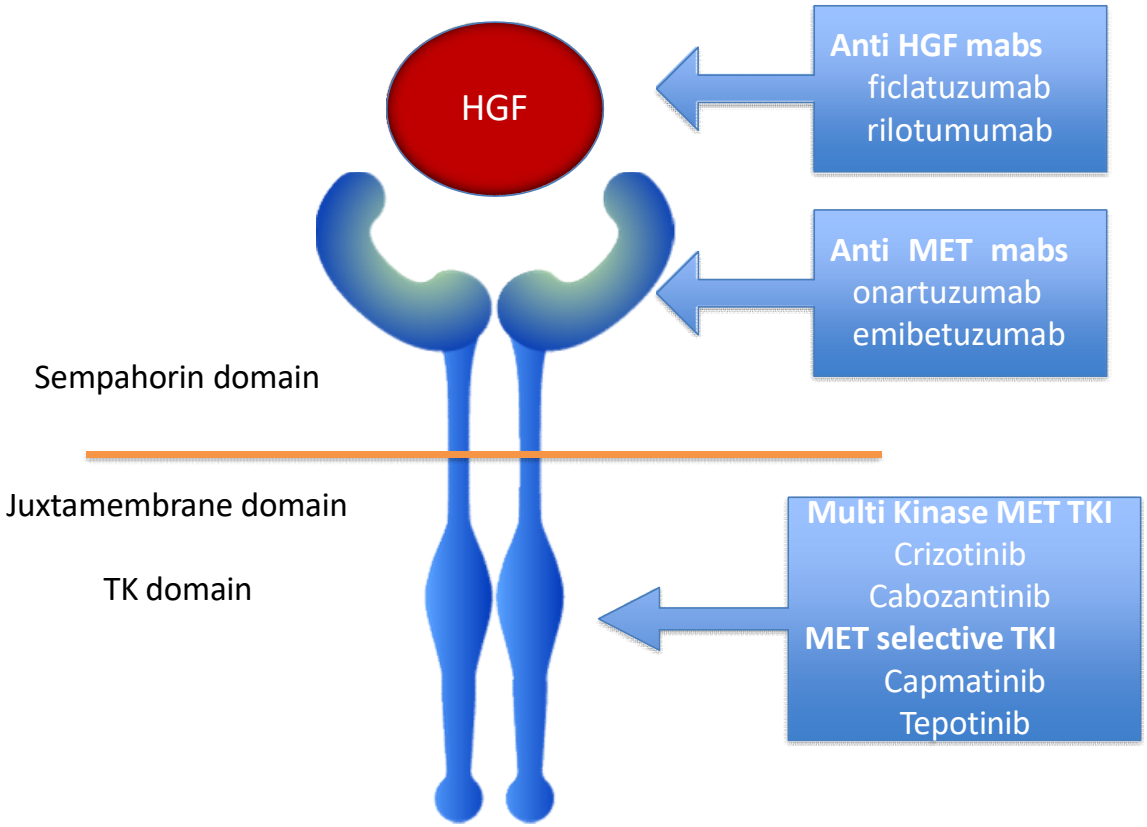
MET alterations in NSCLC



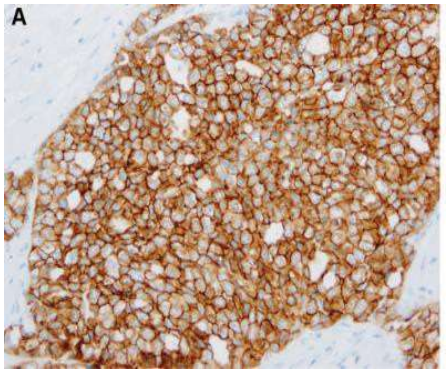


Drilon JTO 2017

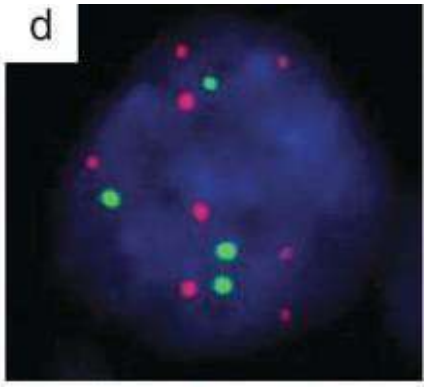
MET alterations in NSCLC



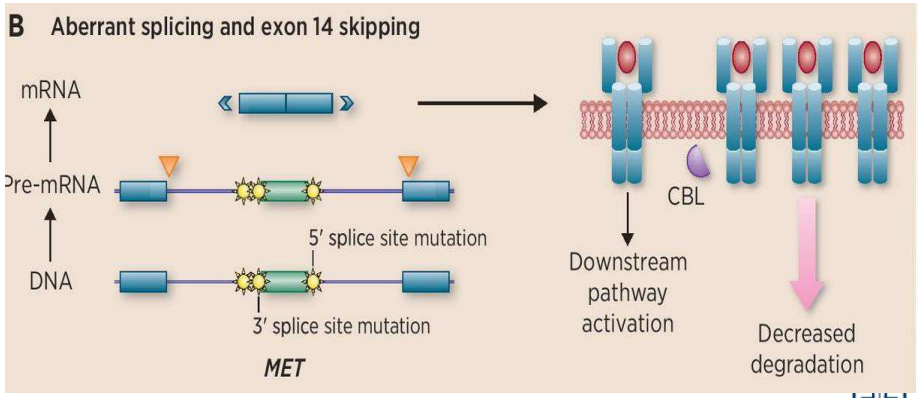
MET Over-expression
25%-75%



MET Amplification
5%-25%



MET Exon 14 skipping
3%



Drilon JTO 2017, Tong Clin Cancer Rsrch 2016, Drilon Clin Cancer Rsrch 2016

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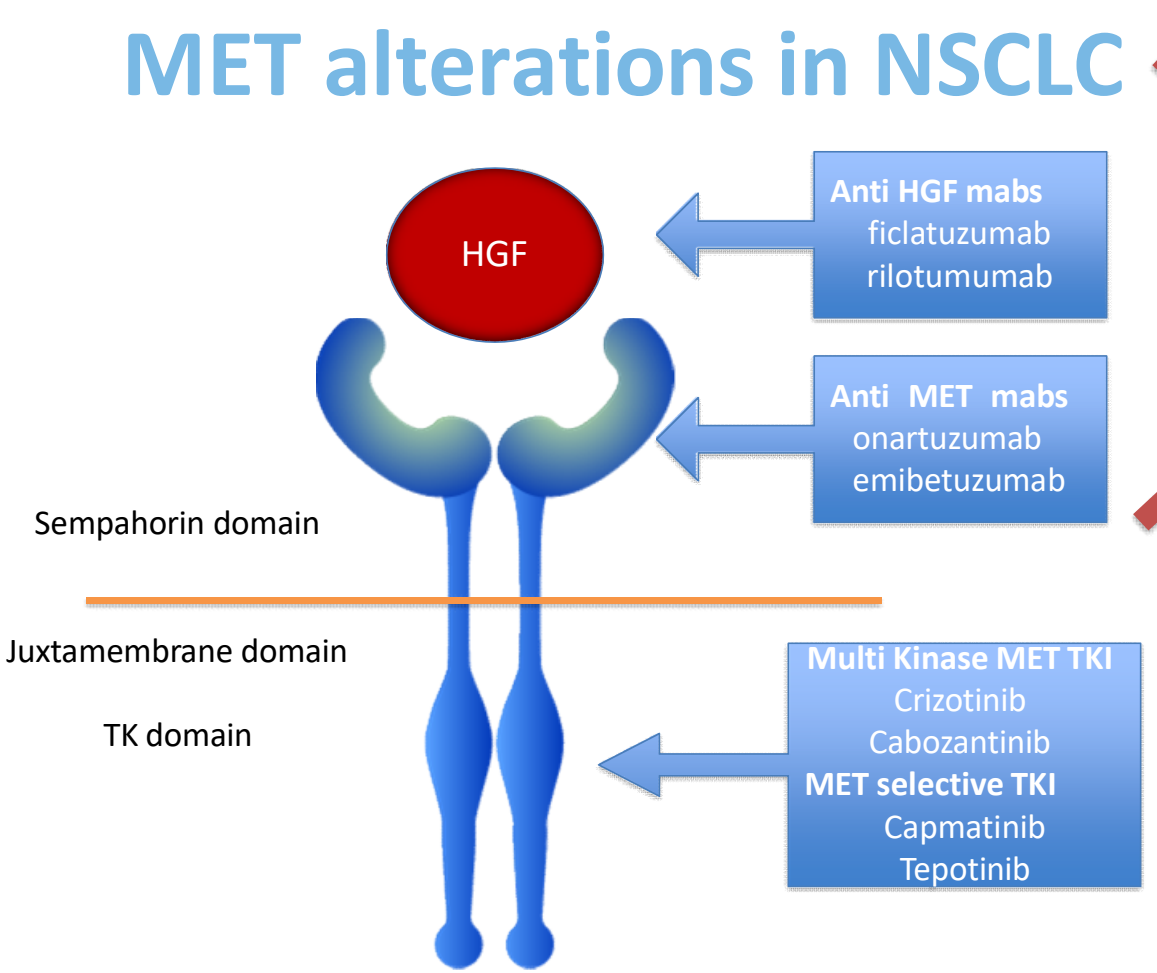

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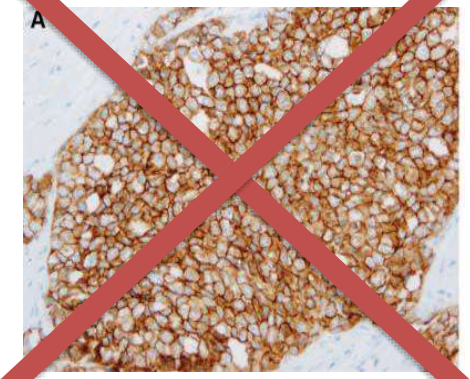

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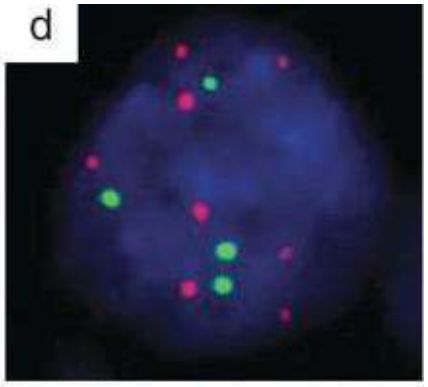

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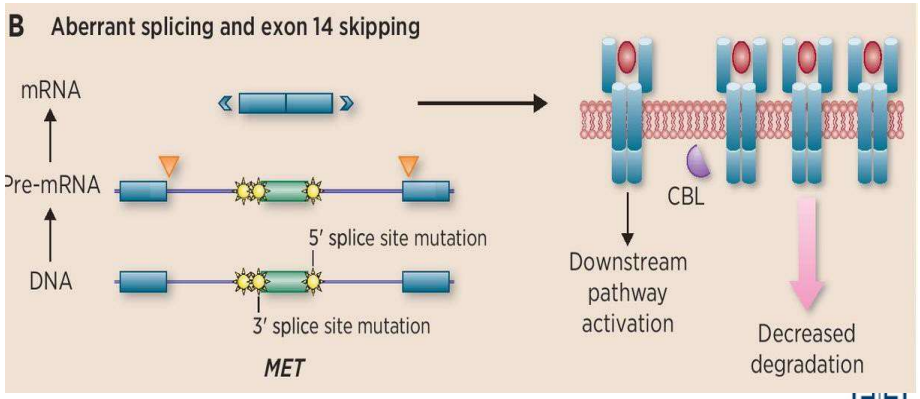
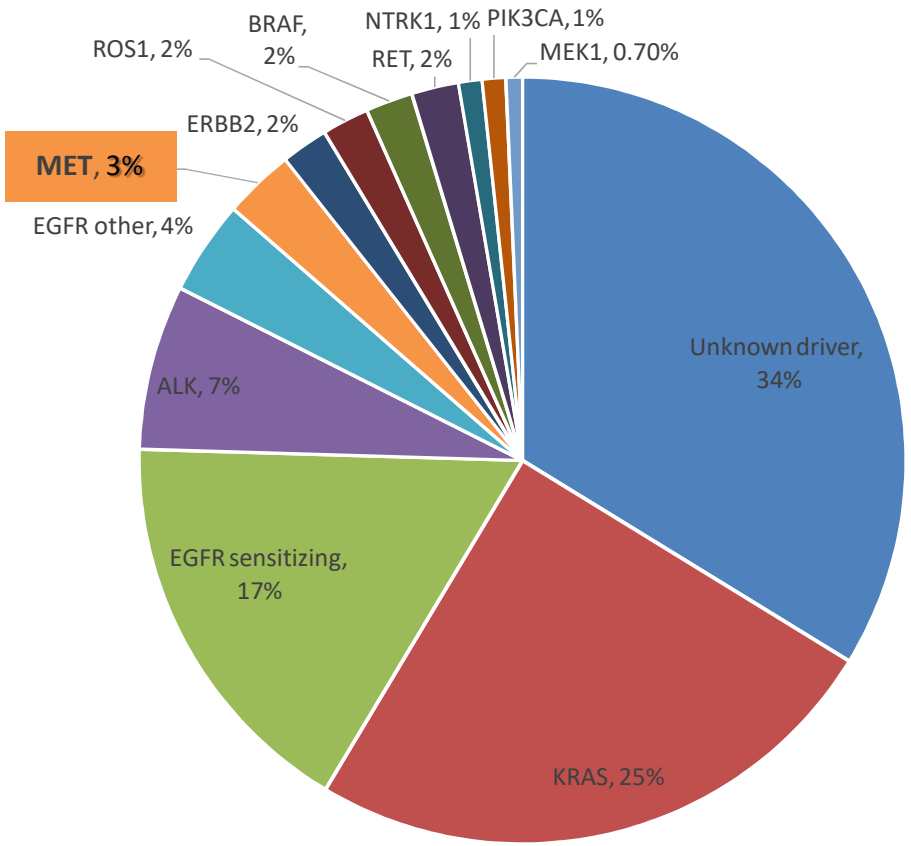


Drilon JTO 2017, Tong Clin Cancer Rsrch 2016, Drilon Clin Cancer Rsrch 2016

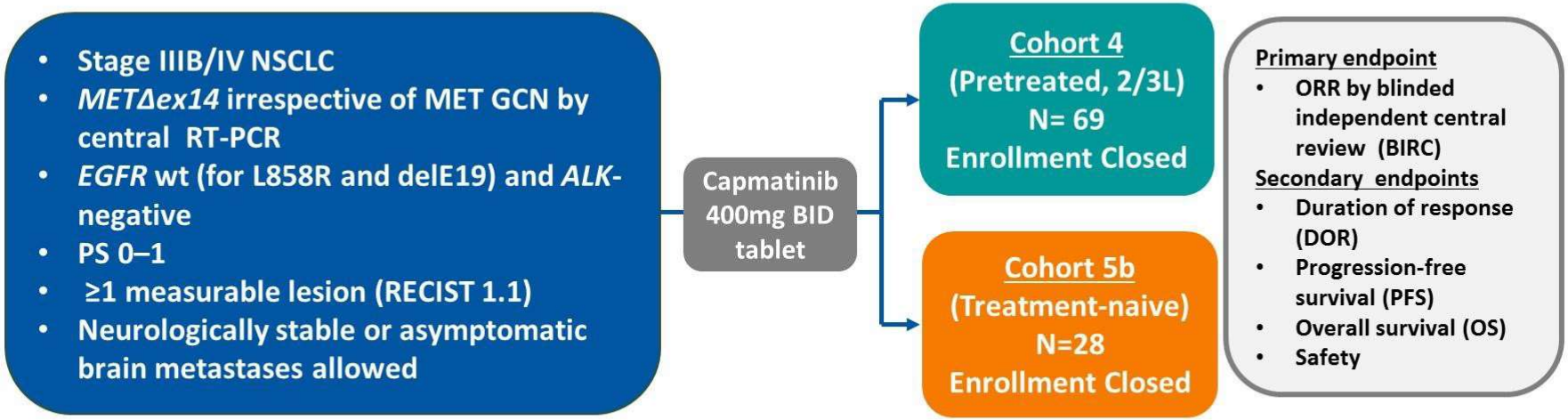
MET Exon 14 Skipping mutation



Awad JCO 2016

- Older patients, median age > 70 yrs
- > 60% were tobacco smokers
- Predominantly adenocarcinoma
- Sarcomatoid pleomorphic type
- Mutually exclusive with KRAS and EGFR activating mutations
- Concurrent MET amplification in 20%.

GEOMETRY mono-1: A phase II trial of capmatinib in patients with advanced NSCLC harboring *MET exon14 skipping* mutation



Study methodology:

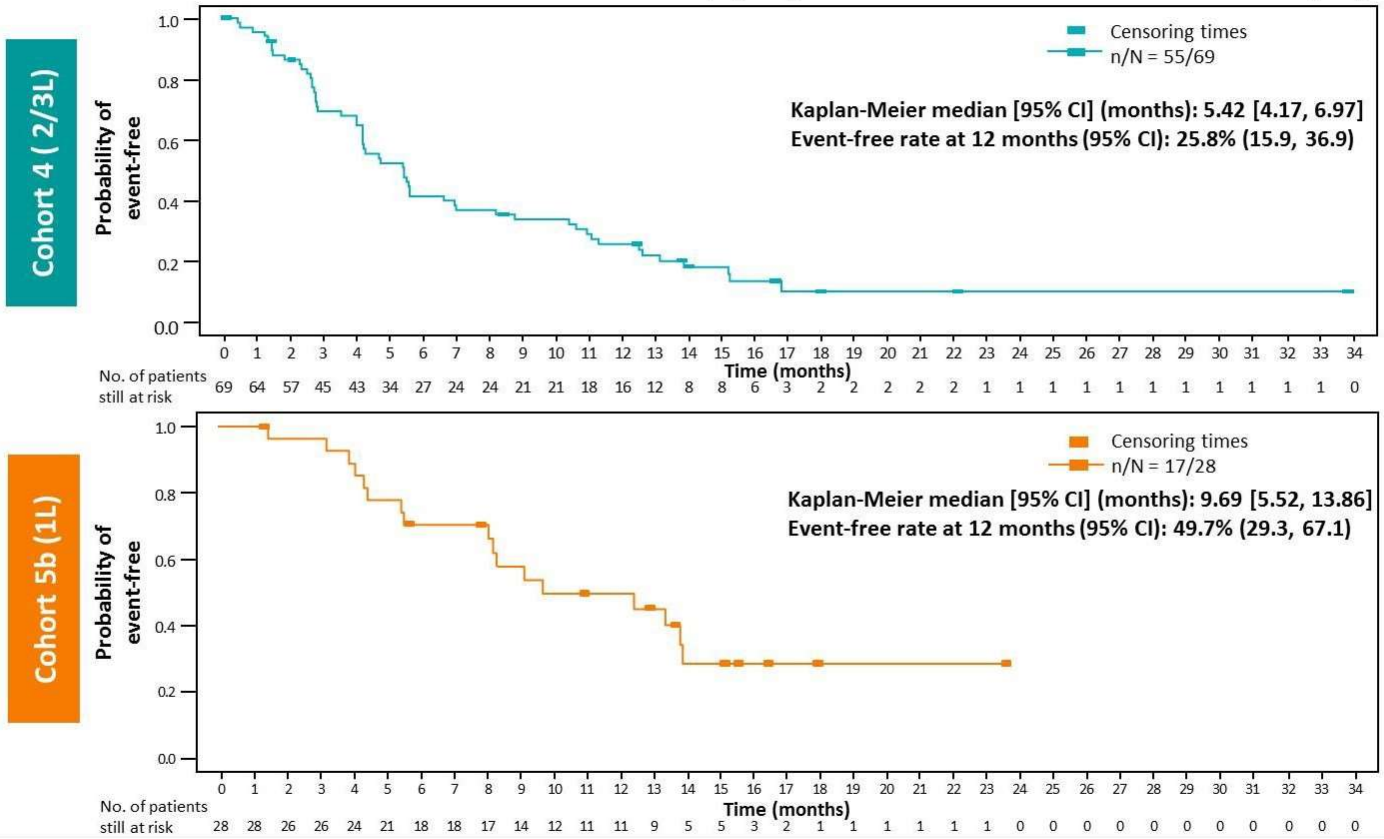
- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~30) and Cohort 7 (1L; N~27)

Wolf ASCO 2019

Progression-free survival per BIRC

Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)



Median PFS per investigator was 4.80 months (95% CI: 4.11, 7.75) in Cohort 4 and 11.14 months (95% CI: 5.52, 15.24) in Cohort 5b 11

n is the number of events, N is the number of patients

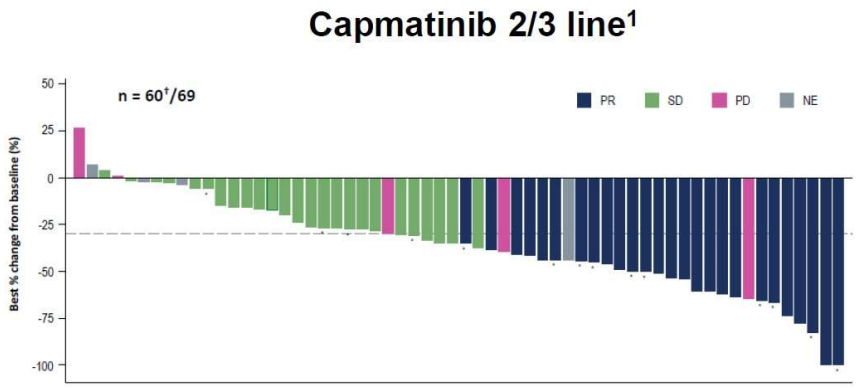
Wolf ASCO 2019

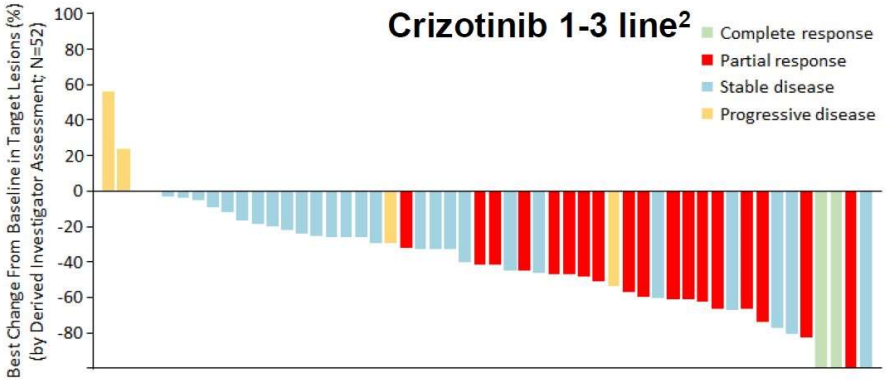
MET TKI – Clinical Trials

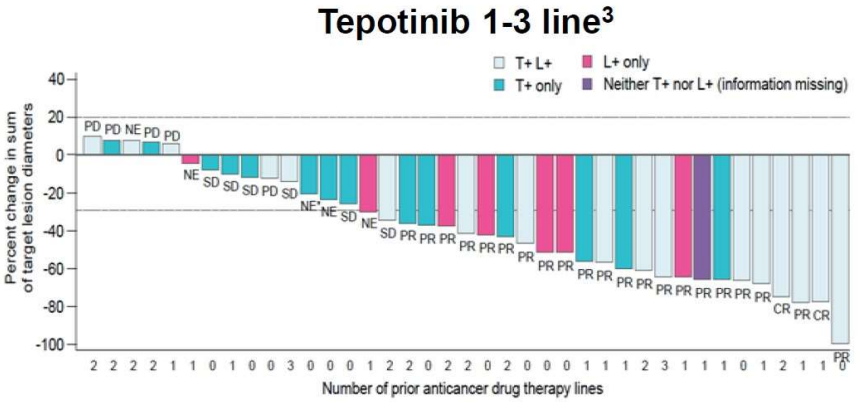
Agent	Line	Testing	N	ORR (95% CI)	DOR (months)	PFS (months)
Crizotinib	1-3	Tumor/ ctDNA	65	32% (21-45)	9.1	7.3
Capmatinib	1	Tumor	28	67.9% (47.6-84.1)	11.1	9.7
	2/3	Tumor	69	40.6% (28.9-53.1)	9.7	5.4
Tepotinib	1-3	Tumor/ ctDNA	32 Tumor 24 ctDNA	45% (31.1-59.7) 50% (35.2-64.8)	15.7 12.7	10.8 9.5
Savolitinib	1-3	Tumor	31	54.8%	NA	NA

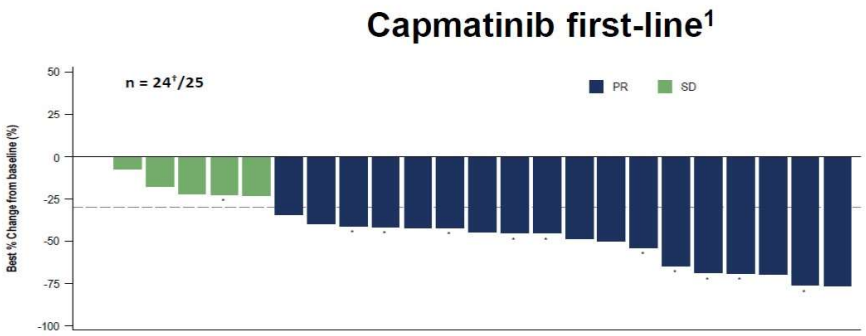
Drilon et al WCLC 2018, Wolf et al ASCO 2019, Paik et al ASCO 2019, Lu et al ASCO 2019

Is One Better Than The Other?









Drilon et al WCLC 2018, Wolf et al ASCO 2019, Paik et al ASCO 2019, Lu et al ASCO 2019

Adverse Events

All Grade (Grade ≥ 3) %	Crizotinib	Capmatinib	Tepotinib	Savolitinib
Edema	47 (3)	58.7 (4.3)	40.4 (6.3)	36.6 (4.9)
Vision disorder	40 (0)	-	-	-
Nausea	33 (0)	21.7 (0)	32.8 (1.7)	41.5 (0)
Diarrhea	30 (0)	37 (2.2)	11.6 (0)	-
Vomiting	23 (0)	-	19.2 (2.0)	24.4 (0)
Constipation	10 (0)	15.2 (0)	-	7 (0)
Bradycardia	23 (1)	-	-	-
Fatigue	13 (0)	17.4 (2.2)	13.2 (3.3)	23 (2)
Elevated Cr	-	21.7 (0)	19.2 (0)	
Elevated transaminases	10 (3)	10.9 (4.3)	-	26.8 (7.3)

Drilon et al WCLC 2018, Wolf et al ASCO 2019, Paik et al ASCO 2019, Lu et al ASCO 2019

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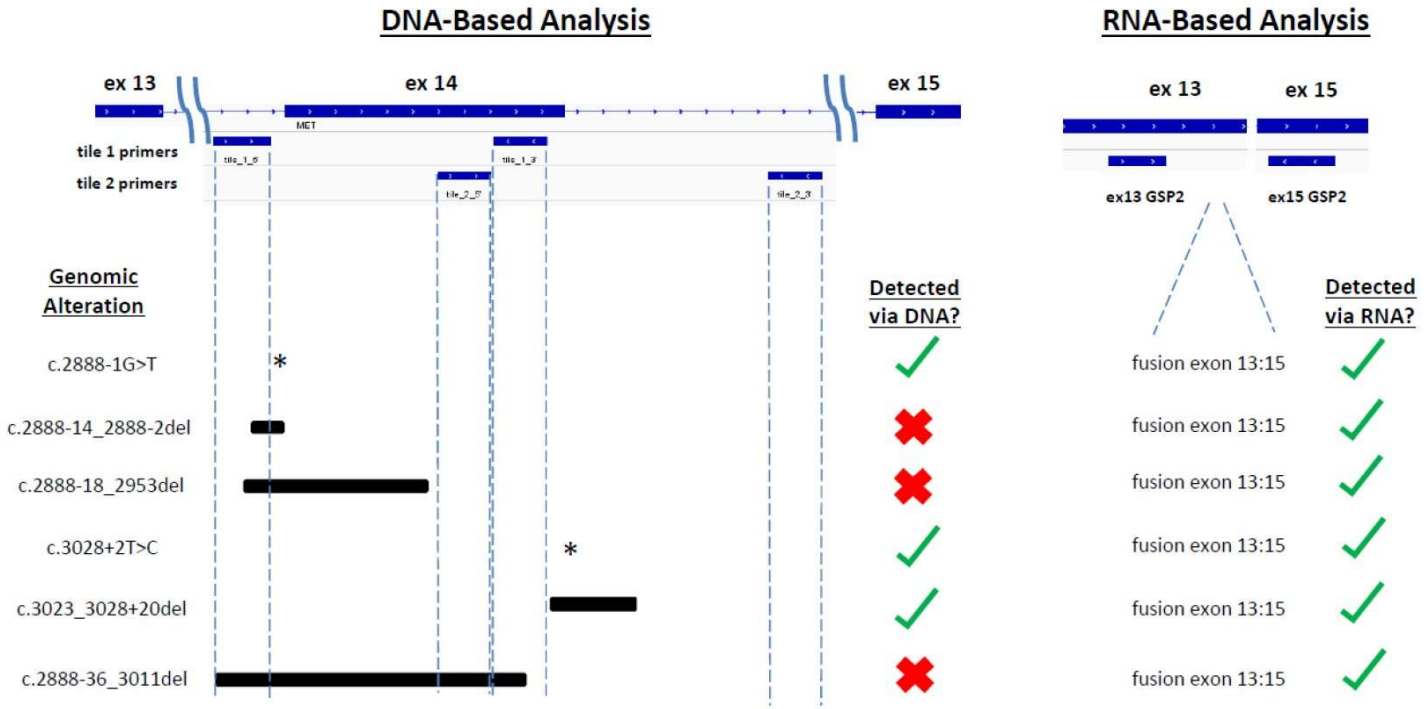
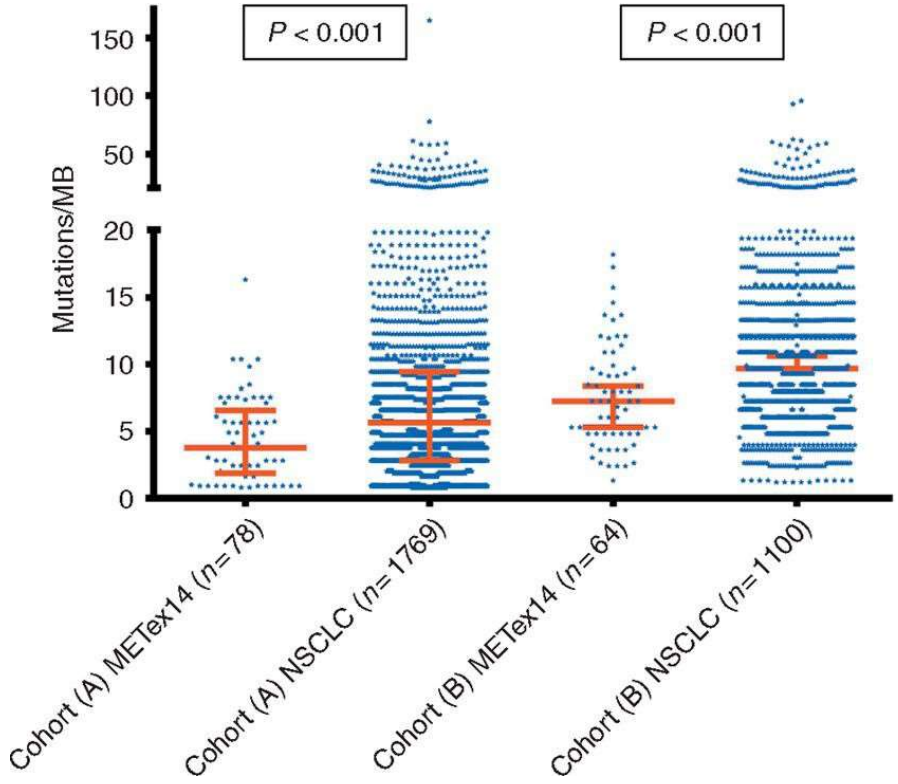
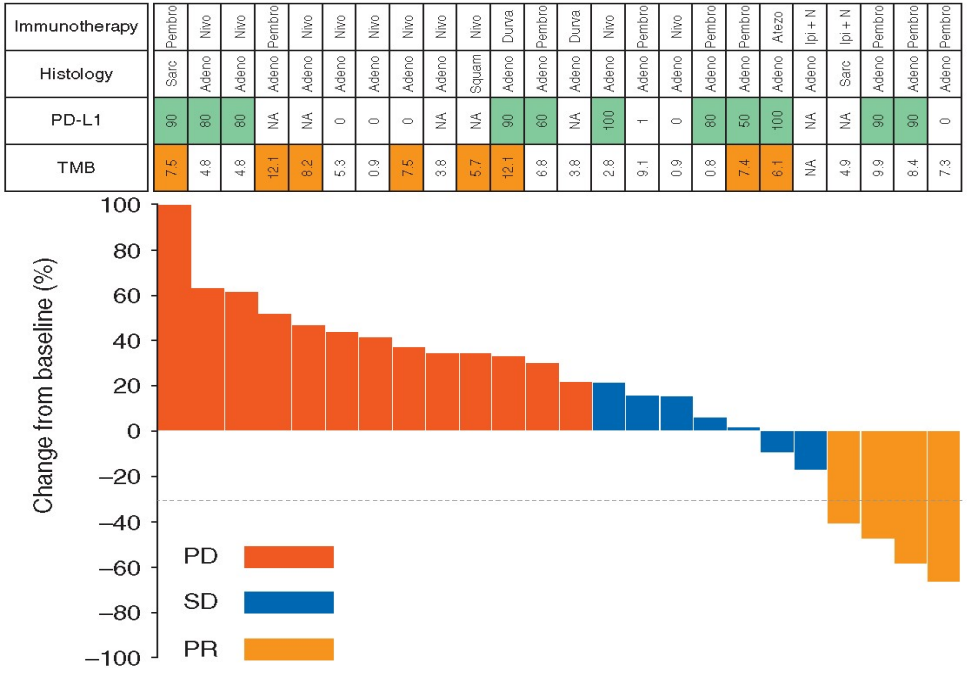
NGS Testing is Key to Detection of *MET* Ex14 (Both DNA & RNA seq)



Davies et al J Thorac Oncol 2019

IO in *MET* Ex 14 positive patients





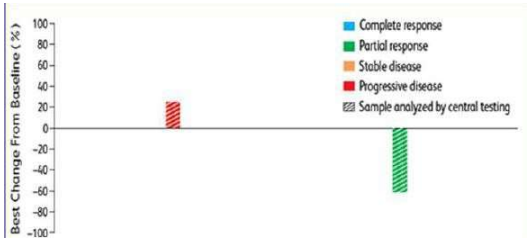
ORR = 17%
Median PFS = 1.9 months

Sabari JK et al Ann Oncol 2018

What about *MET* copy amplified tumors?

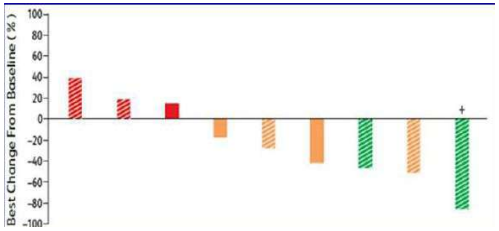
Crizotinib

Low MET (1.8-2.2), n = 3



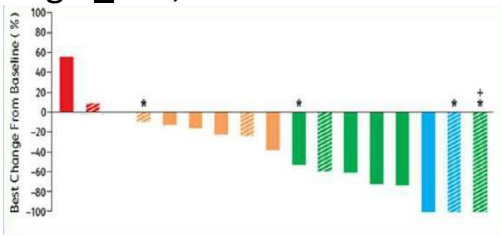
ORR 33.3% (0.8-90.6) PFS 1.8 (0.8-14)

Intermediate (>2.2-<4.0), n = 14



ORR 14.3% (1.8-42.8) PFS 1.9 (1.3-5.5)

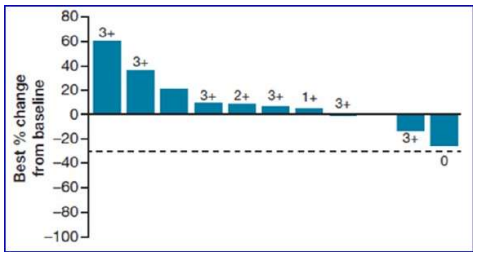
High ≥ 4.0, n = 20



ORR 40% (19.1-63.9) PFS 6.7 (3.4-7.4)

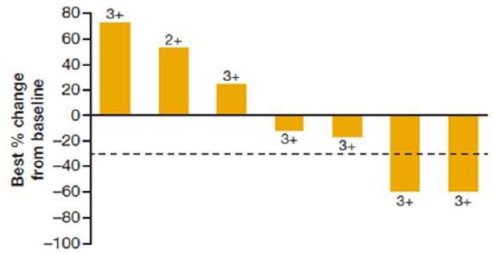
Capmatinib

GCN < 4, n = 17



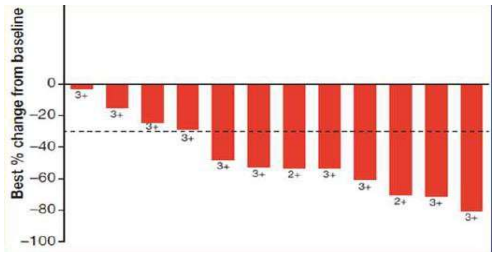
ORR 0% (0.8-90.6) PFS 1.8 (0.8-14)

GCN ≥ 4 & < 6. n = 12



ORR 17.0% (2.1-48.4)

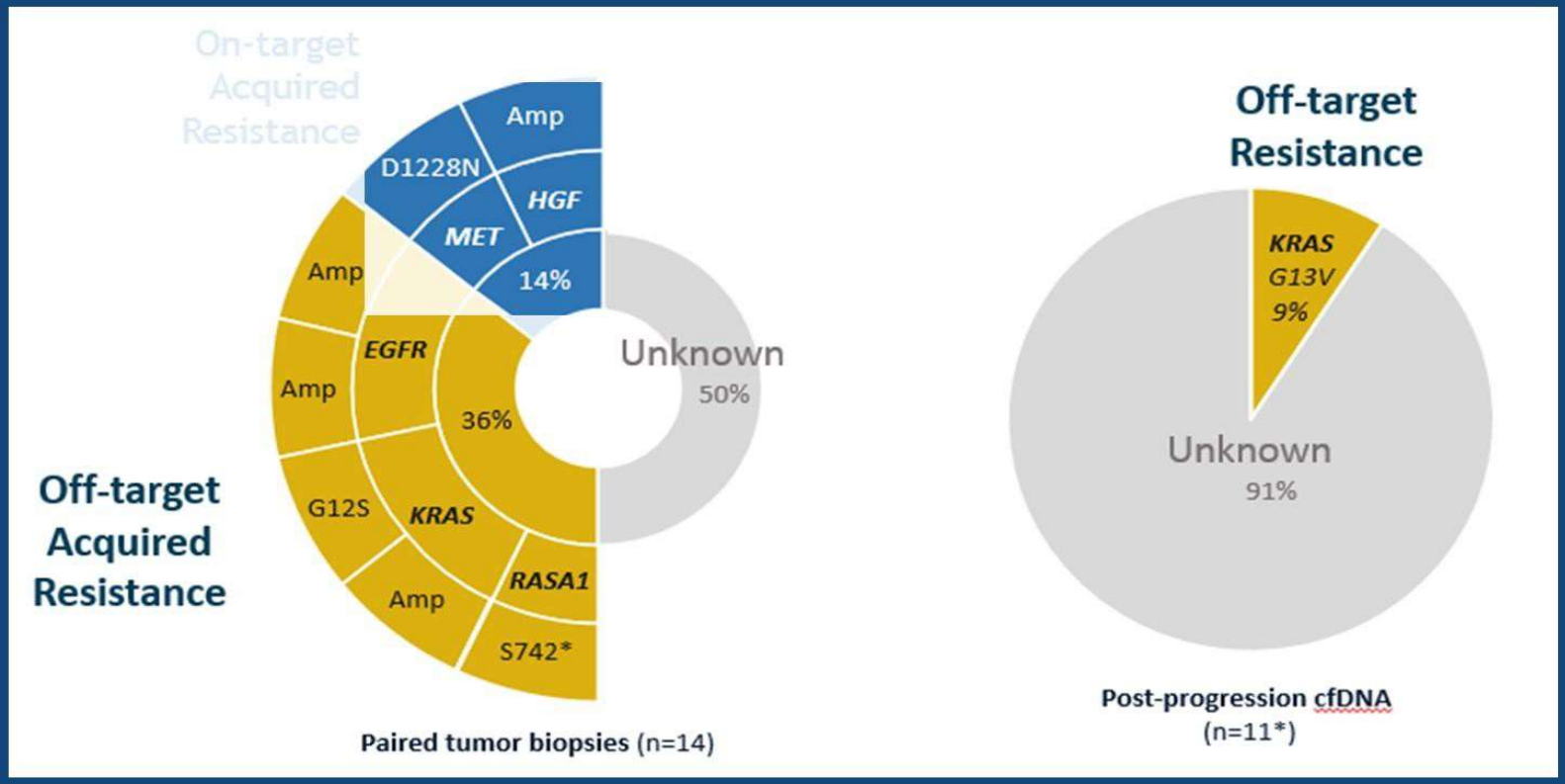
GCN ≥ 6 n = 15



ORR 70% (21.3-73.4) PFS 1.8 (0.8-14)

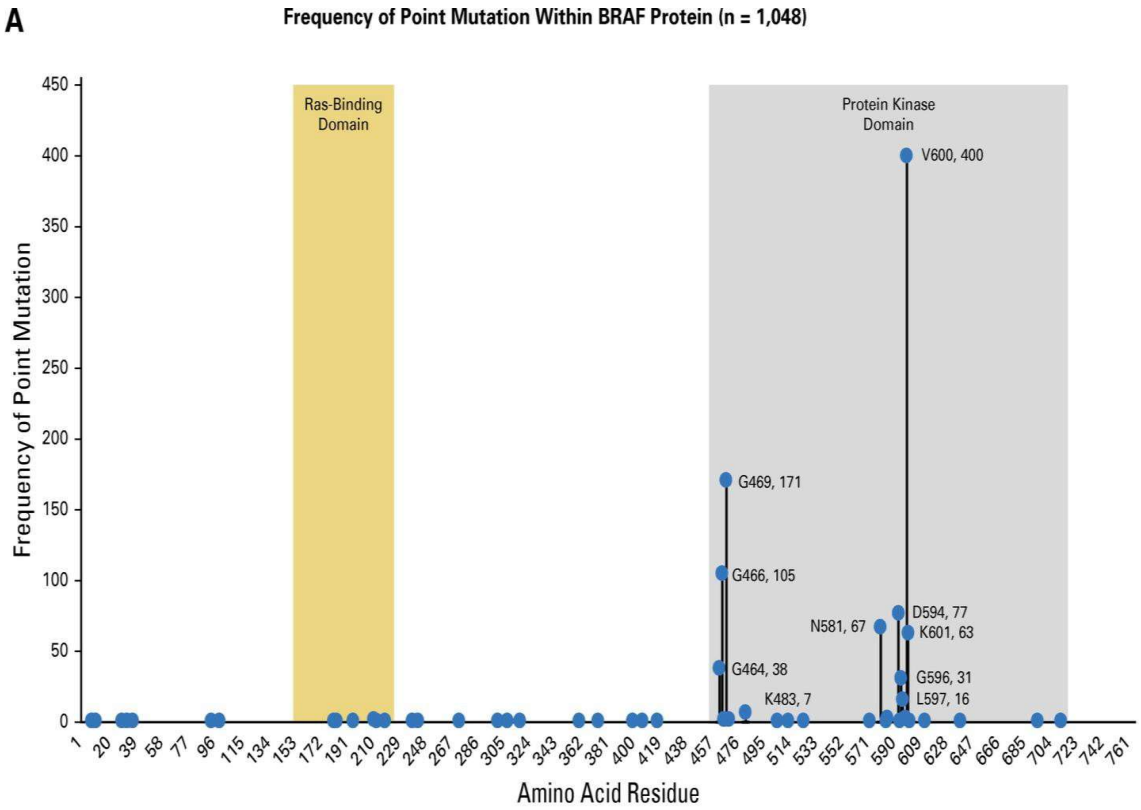
Camidge ASCO 2018, Schuler ASCO 2016

Acquired resistance involves on target and bypass pathways



Guo et al ASCO 2019

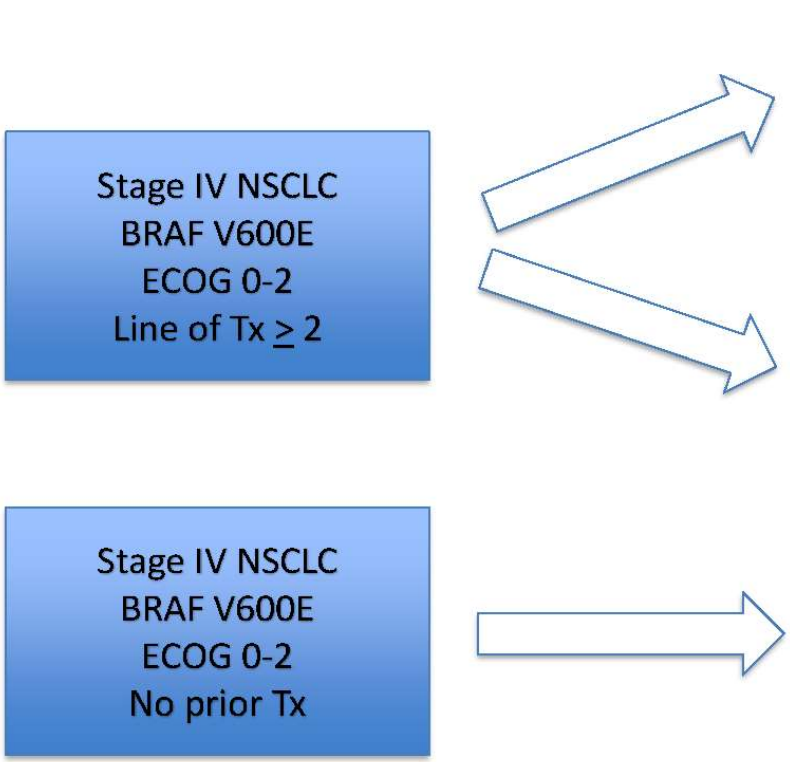
BRAF V600 mutations



Sheikine et al J Clin Oncol 2019

- Serine-threonine kinase linking RAS GTPase to downstream MEK/ERK pathway.
- BRAF alterations incidence at 4.4%.
- BRAF V600E ~ 40% - Class I
- Median age 64 & predominantly adenocarcinoma (65%)
- Non V600* or Class II & III generally considered to be non-actionable and ~60%.

BRAF inhibition in Lung Cancer



Cohort A
Dabrafenib 150mg BID
N = 84

Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

David Planchard, Tae Min Kim, Julien Mazieres, Elisabeth Quoix, Gregory Riely, Fabrice Barlesi, Pierre-Jean Souquet, Egbert F Smit, Harry J M Groen, Ronan J Kelly, B C Cho, Mark A Socinski, Lini Pandya, Christine Nase, Bo Ma, Anthony D'Amelio Jr, Bijoyesh Mookerjee, C Martin Curtis Jr, Bruce E Johnson

Cohort B
Dabrafenib 150mg BID+
Trametinib 2mg QD
N = 59

Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

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BRAF inhibition in Lung Cancer

Stage IV NSCLC
BRAF V600E
ECOG 0-2
Line of Tx ≥ 2

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ORR 33%, mPFS 5.5 months
(Lancet Oncol 2016)

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Stage IV NSCLC
BRAF V600E
ECOG 0-2
No prior Tx

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ORR 63%, mPFS 9.7 months
(Lancet Oncol 2016)

Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, TaeMin Kim, Julien Mazieres, Silvia Novello, James E Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

ORR 64%, mPFS 10.9 months
(Lancet Oncol 2017)

Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

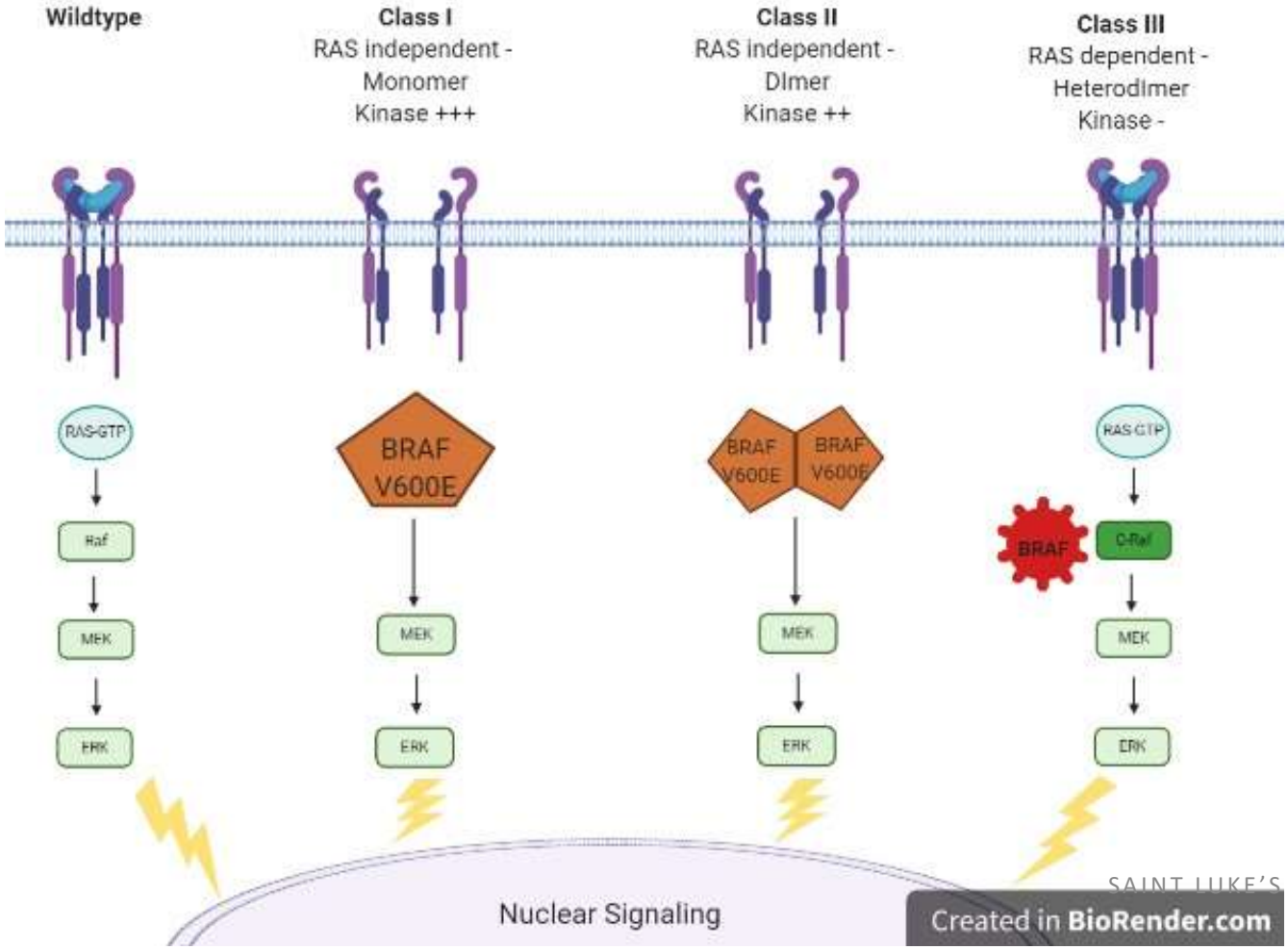
Non V600* BRAF Kinase mutations

Class II Kinase Active	Class III Kinase Dead/Inactive
G464A, G464E, G464V	G466E, G466R, G466V
G466A	G469E
F468C	D594A, D594E, D594G, D594H, D594N, D594V, D594Y
G469A, G469R, G469S, G469V	G596R
N581S	T599I
E586K	
F595L	
L597Q, L597R, L597S, L597V	
K601E	

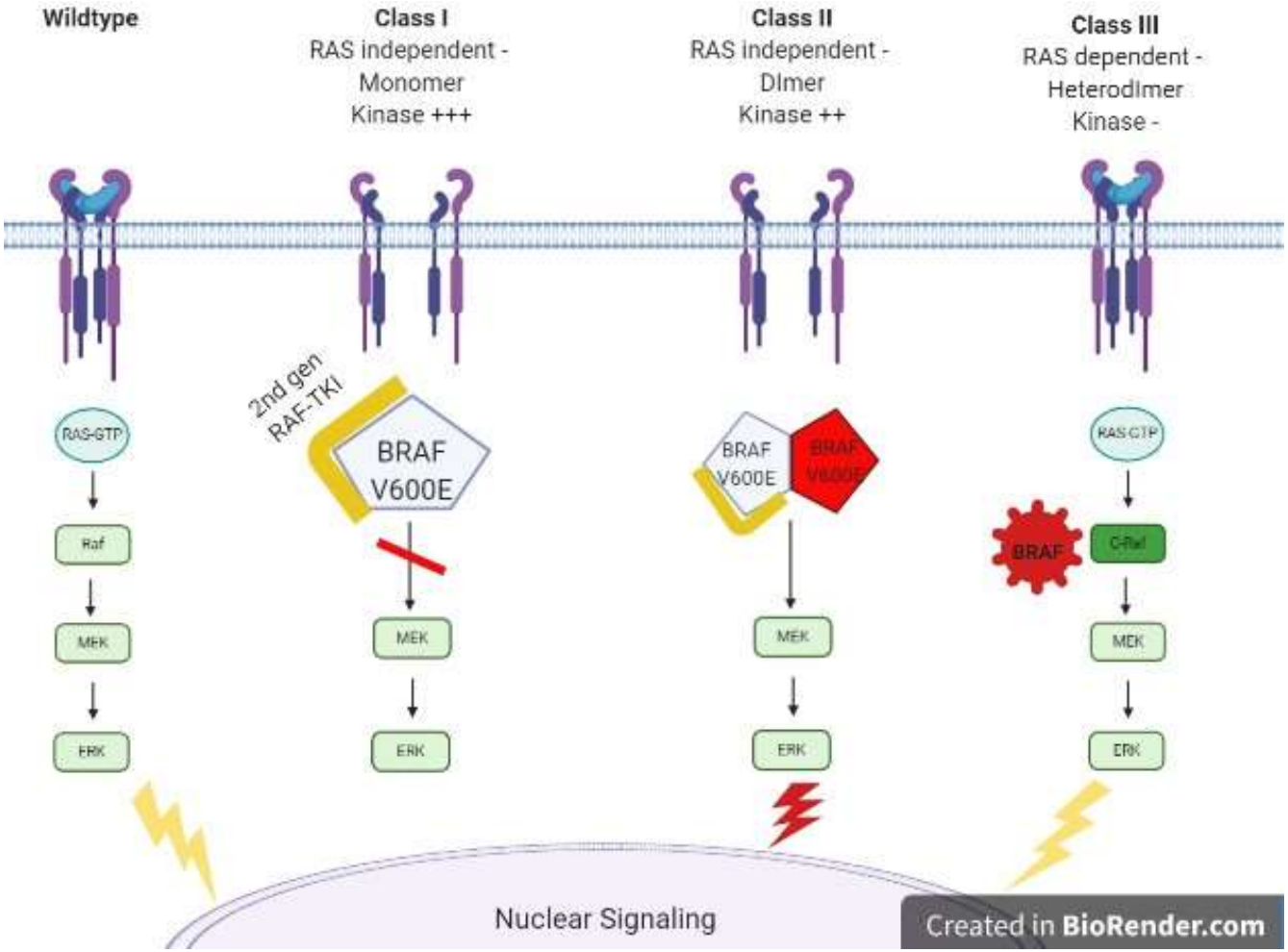
- Class II and III mutations constitute more than half of all patients with BRAF mutations.
- 2nd generation RAF kinase inhibitors are ineffective against both class II and III BRAF mutations.

Sheikine et al J Clin Oncol 2019, Yao et al Cancer Cell 2015, Gautschi et al JTO 2015, Mazieres et al JTO 2019

BRAF Kinase Inhibition



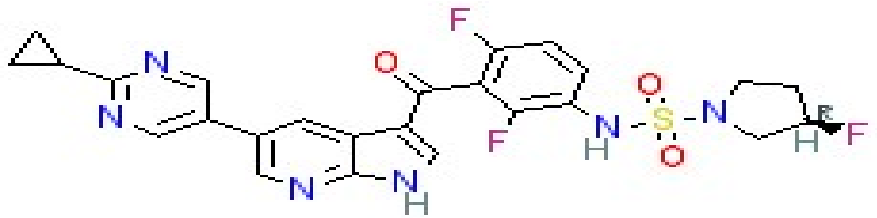
BRAF Kinase Inhibition

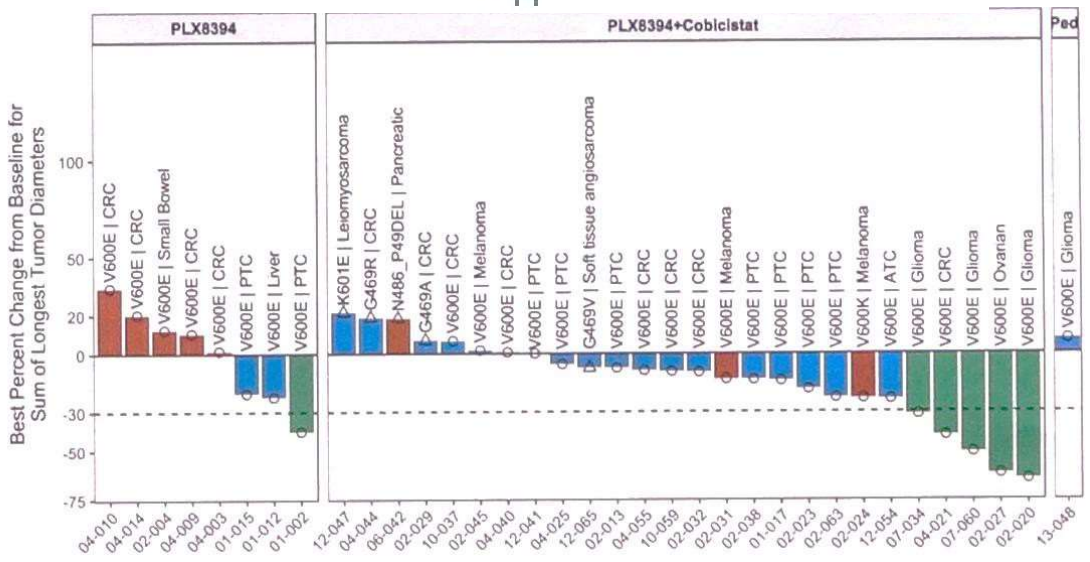


Targeting non-V600 mutations, 3rd gen RAF TKI

- 2nd gen RAF TKIs ineffective against BRAF homo & heterodimers.
- Plus risk for paradoxic ERK activation
- 3rd gen RAF TKIs avoid paradoxic activation and active against BRAF dimers.

PLX8394





Janku ASCO 2018

Way Forward in V600* population – Triple therapy?

nature medicine
LETTERS
https://doi.org/10.1038/s41591-019-0448-9

Dabrafenib, trametinib and pembrolizumab or placebo in *BRAF*-mutant melanoma

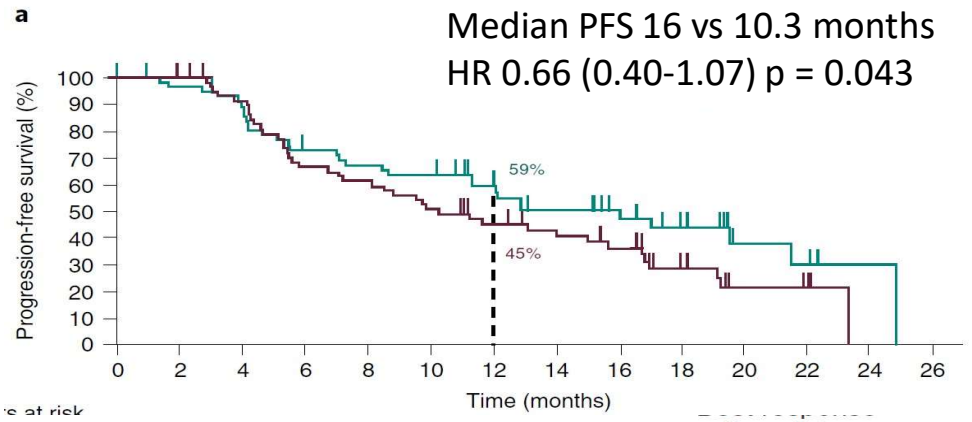
Paolo Antonio Ascierto[1,18*], Pier Francesco Ferrucci[2,18*], Rosalie Fisher[3], Michele Del Vecchio[4],

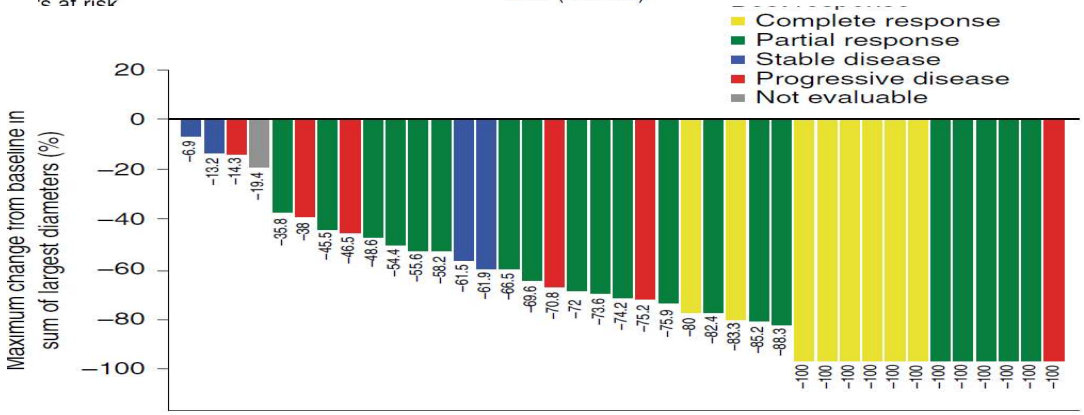
nature medicine
LETTERS
https://doi.org/10.1038/s41591-019-0474-7

Atezolizumab plus cobimetinib and vemurafenib in *BRAF*-mutated melanoma patients

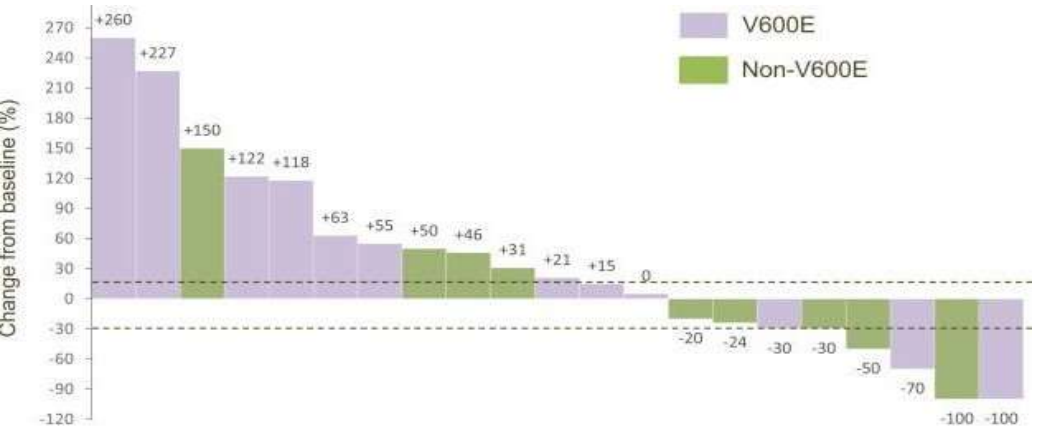
Ryan J. Sullivan[1*], Omid Hamid[2], Rene Gonzalez[3], Jeffrey R. Infante[4],

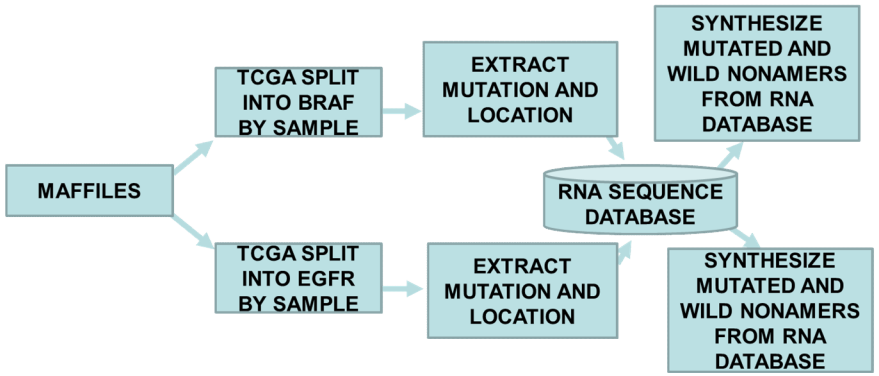
Median PFS 16 vs 10.3 months
HR 0.66 (0.40-1.07) p = 0.043

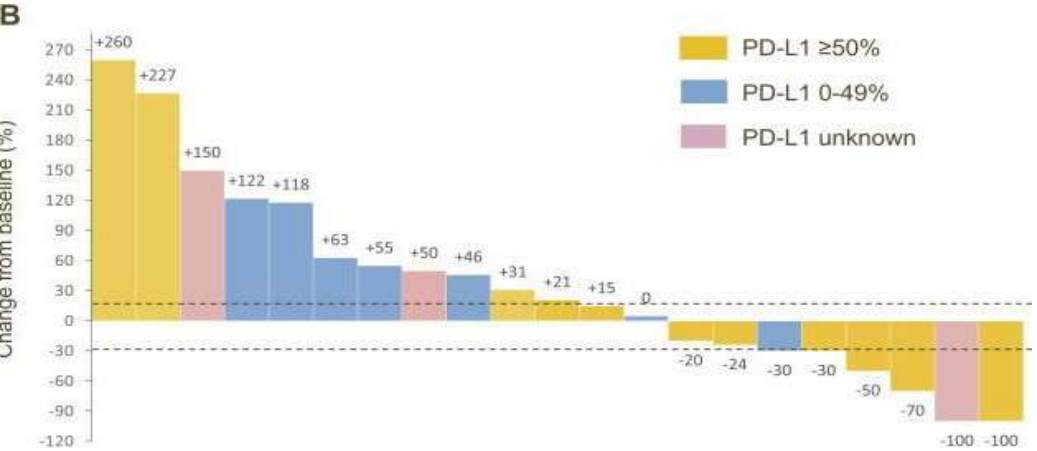




IO in BRAF V600* lung cancer



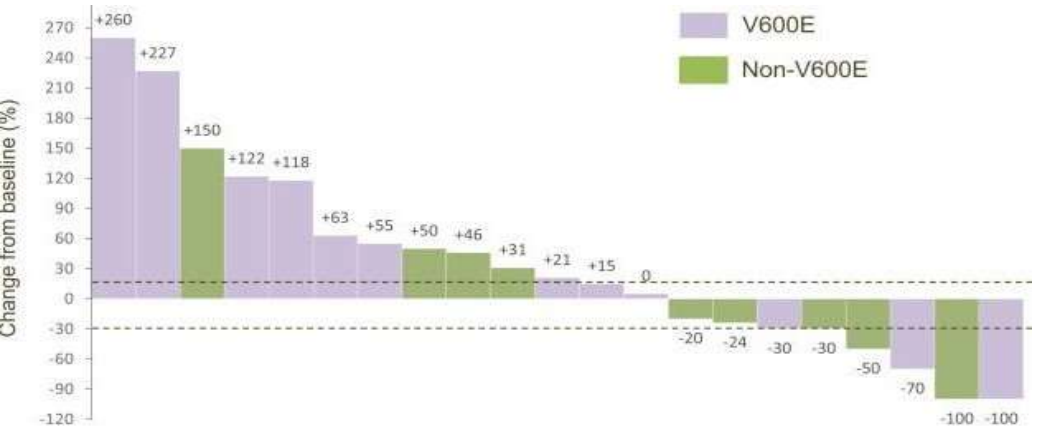


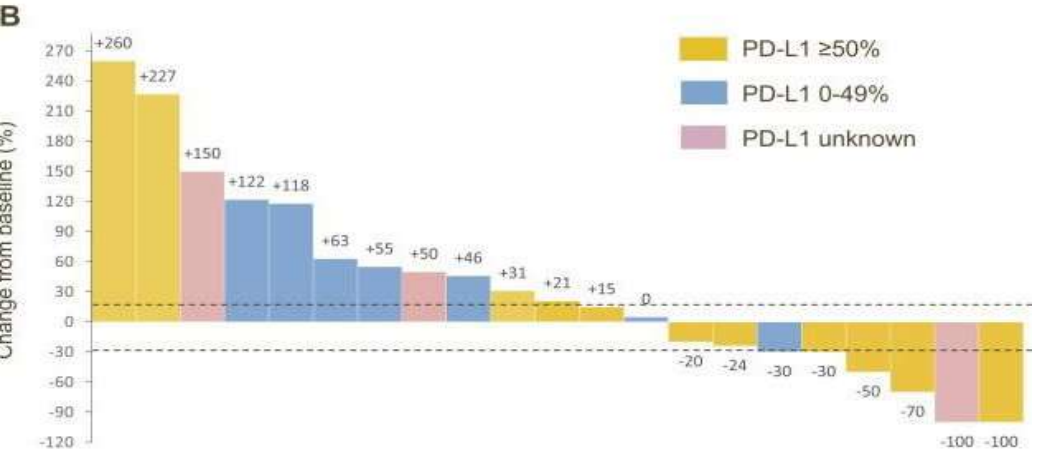


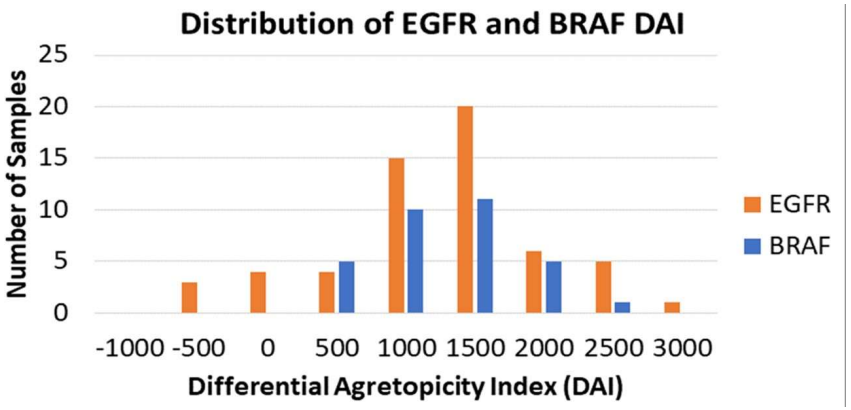
	Total	group		p-Value	Std Diff (%)
	n = 103	braf n = 35	egfr n = 68		
Mutation Burden	158.0 (75.0, 488.0)	445.0 (165.0, 776.0)	90.5 (60.5, 219.5)	0.001	64.7
Number Affinities	3173.5 (1531.0, 9914.5)	9536.5 (3839.5, 14626.0)	1895.5 (1148.5, 4766.5)	< 0.001	75.3

Dudnik et al JTO 2018, Case et al ESMO 2019

IO in BRAF V600* lung cancer







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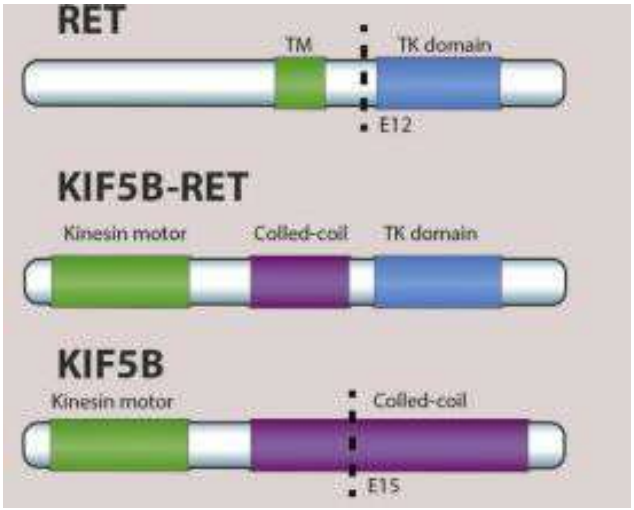
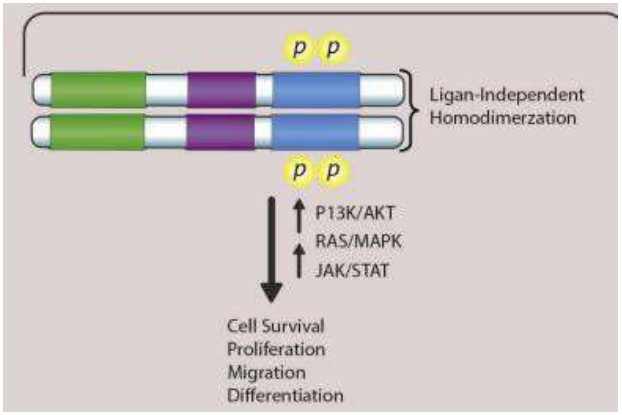
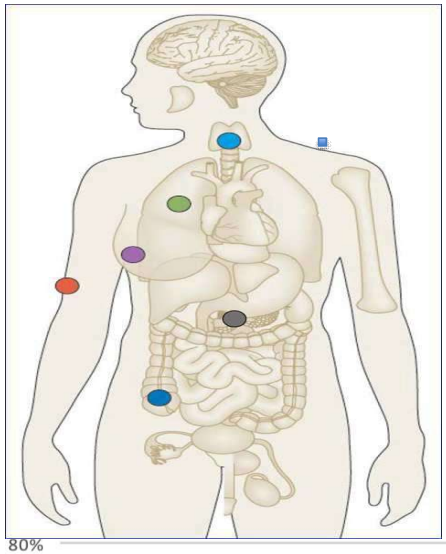
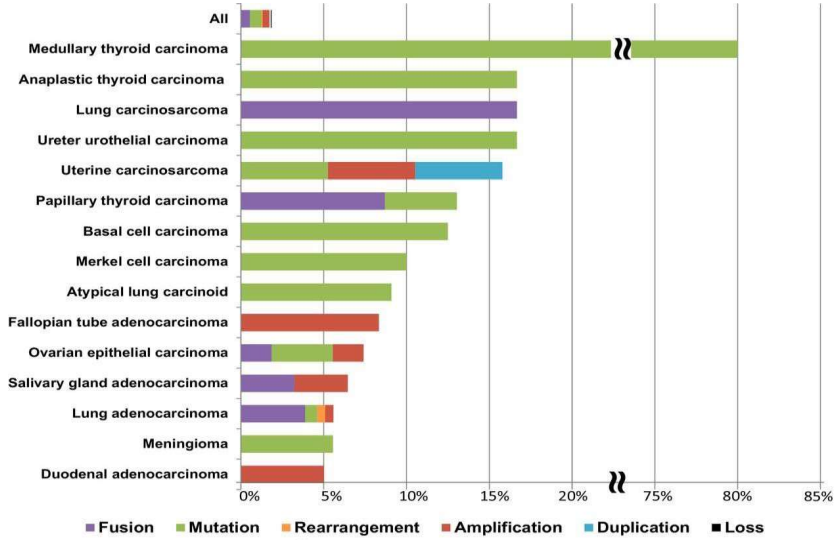
Dudnik et al JTO 2018, Case et al ESMO 2019

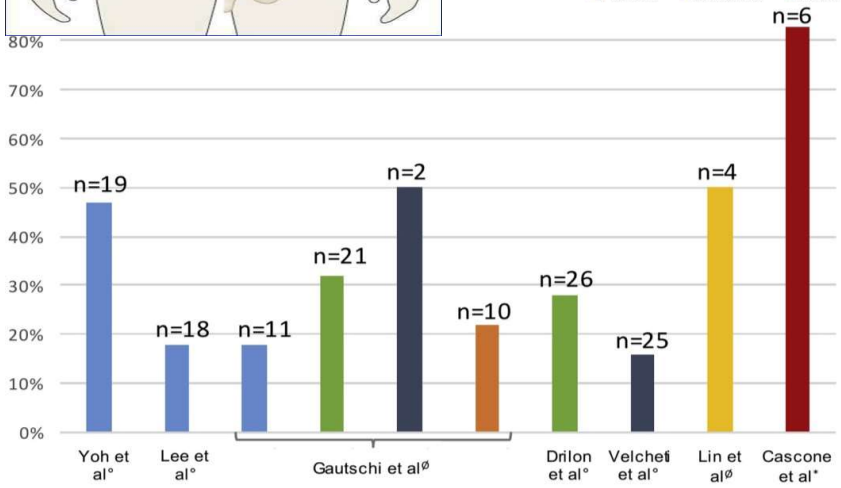
RET fusions

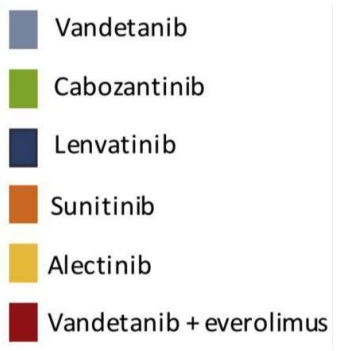






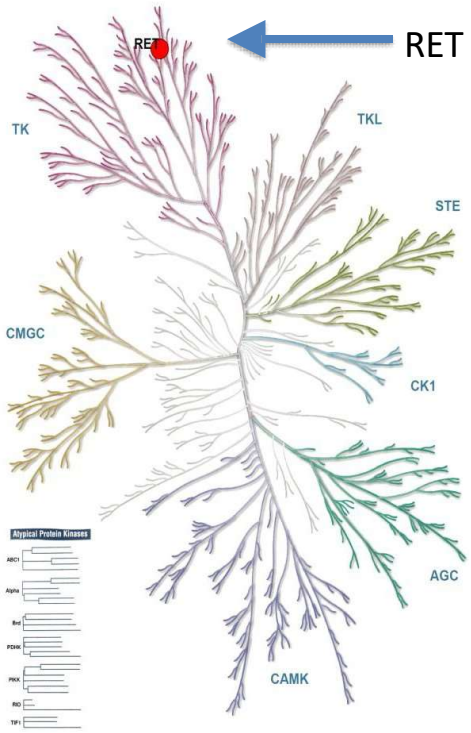




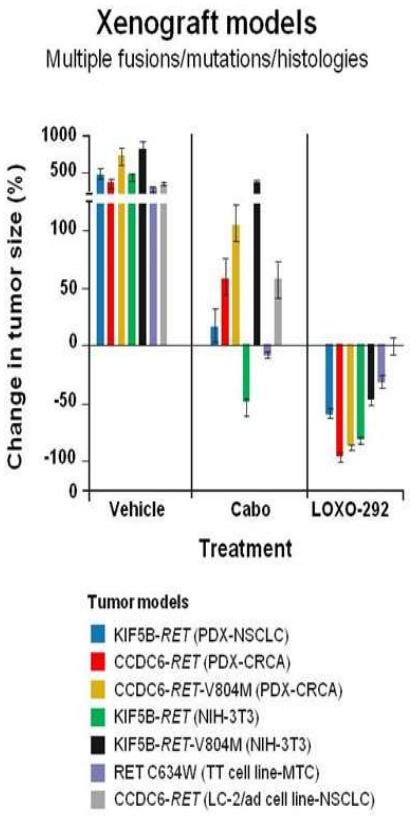


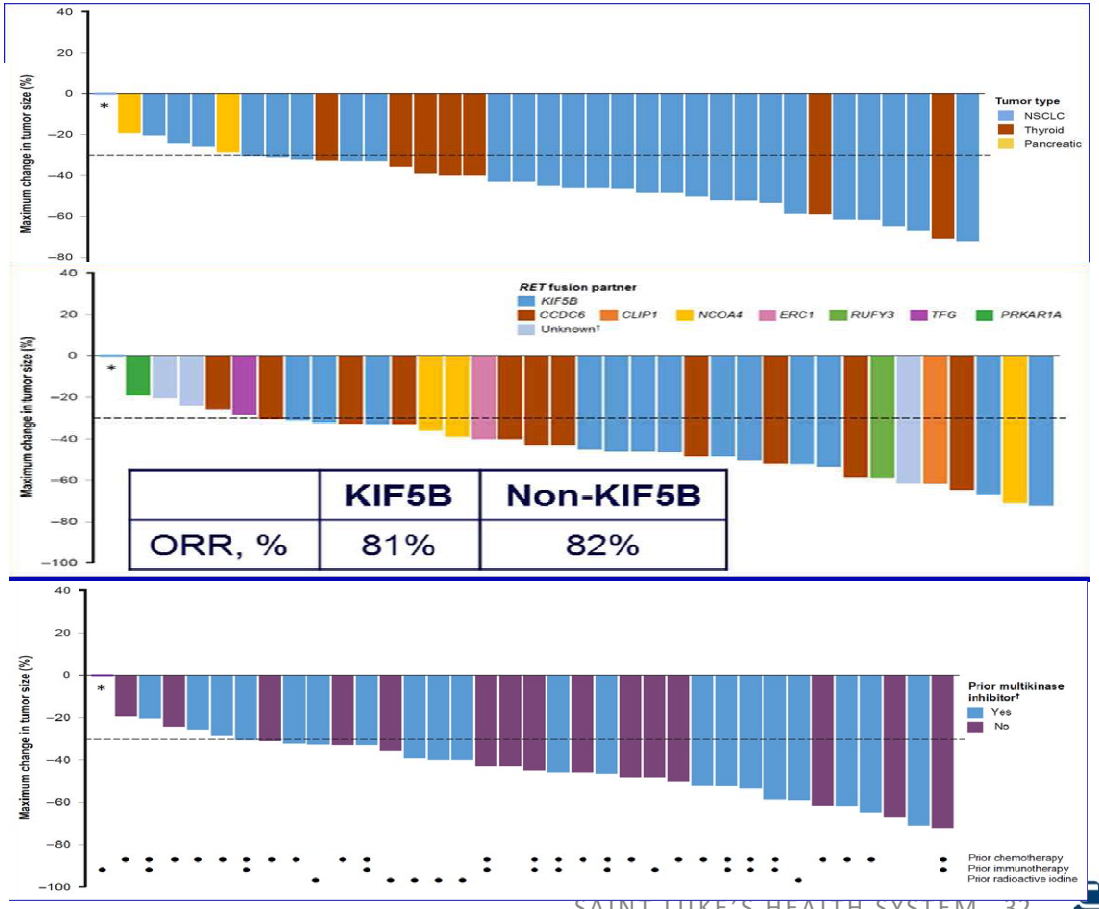
Ferrara JTO 2017, Kato Clin Cancer Res 2017

LOXO-292 (Selpercatinib)



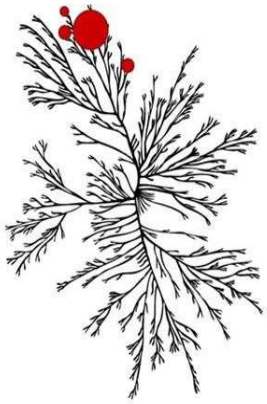
Drilon ASCO 2018





BLU-667

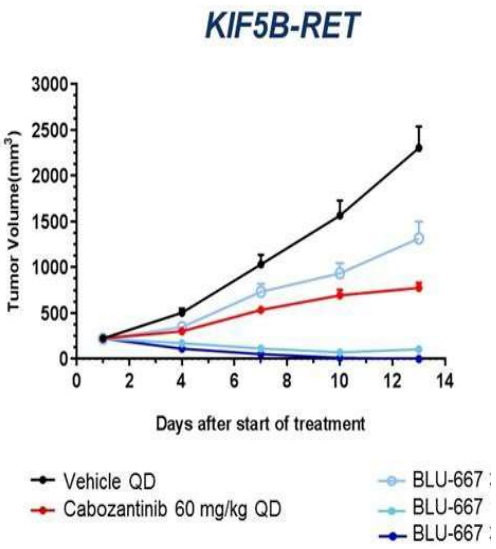
BLU-667: High kinome selectivity for RET[a]



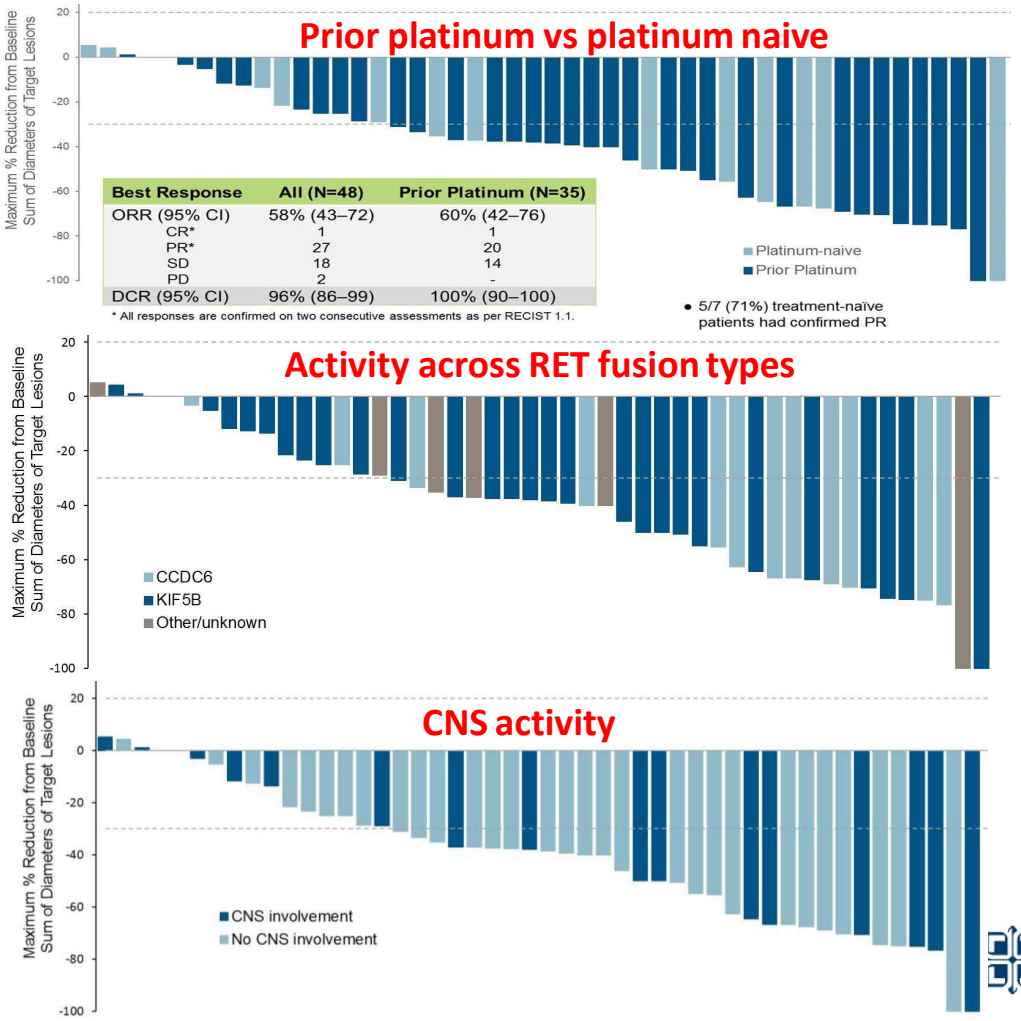
BLU-667 vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

Gainor et al ASCO 2019



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

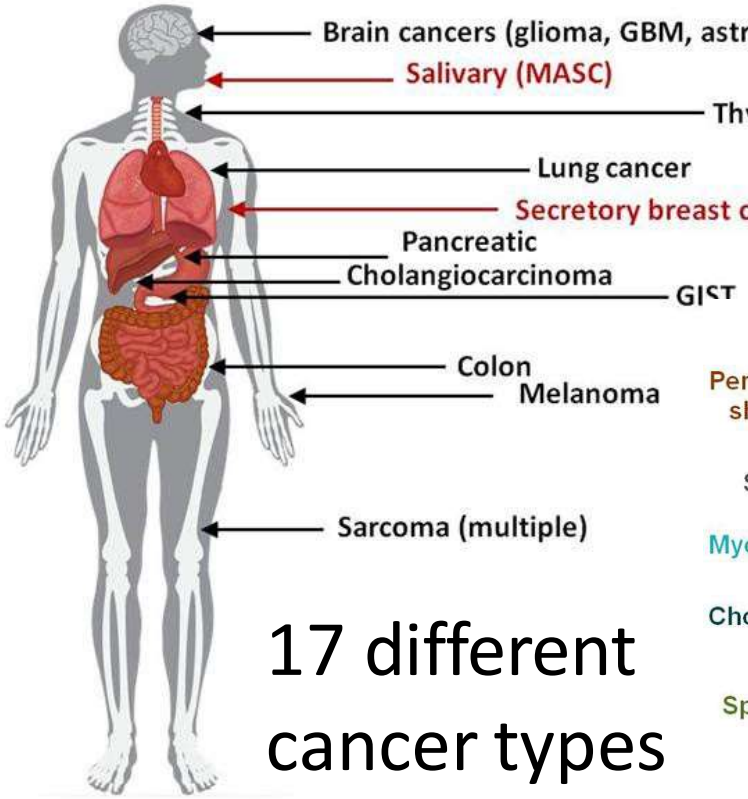


Safety Profile LOXO-292 & BLU-667

All Grade (Grade ≥ 3) %	Treatment emergent		Treatment related	
	LOXO-292 (≥ 10%) N = 82	BLU-667 (≥ 15%) N = 120	LOXO-292	BLU-667
Constipation		30 (2)	2 (-)	17 (2)
Fatigue	20 (-)	21 (3)	13 (-)	13 (3)
Diarrhea	16 (-)	18 (2)	2 (-)	9 (-)
Dry mouth	12 (-)	17 (-)	6 (-)	12 (-)
Nausea	12 (-)	-	5 (-)	-
Dyspnea	11 (1)	-	-	-
Neutropenia	-	26 (3)	-	26 (13)
Anemia	-	18 (7)	-	11 (4)
AST increased	-	24 (5)	-	20 (2)
Hypertension	-	20 (13)	-	13 (10)
ALT increased	-	17%	-	13 (2)

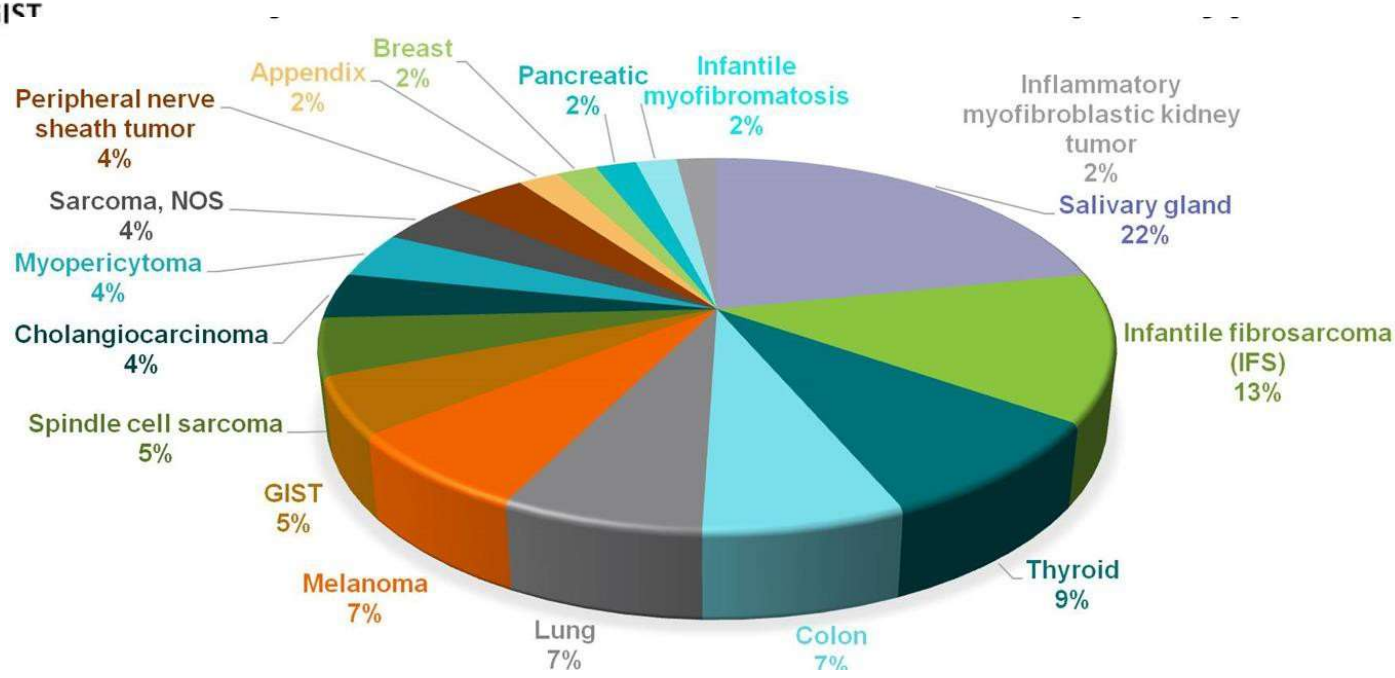
Gainor et al ASCO 2019, Drilon ASCO 2018

NTRK fusions in cancer



17 different cancer types

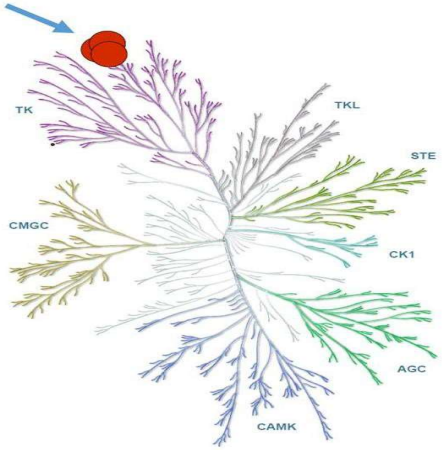
Estimated 1500 – 5000 patients with cancer harbor TRK fusions annually in the United States



Hyman ASCO 2017

Larotrectinib (LOXO-101), highly selective TRK inhibitor

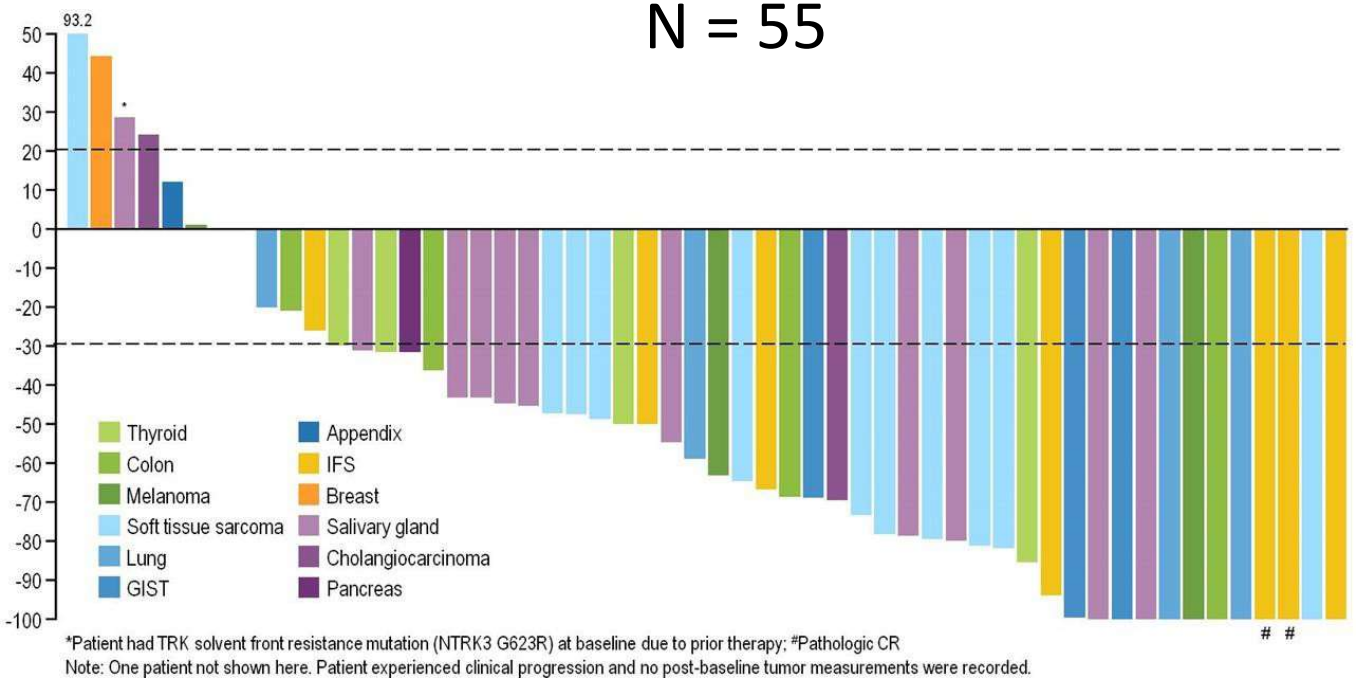
TRKA/B/C



- Highly selective NTRK inhibitor
- Development program (n = 55)
  - Adult phase I (n = 8)
  - SCOUT pediatric phase II
  - (n =12)
  - NAVIGATE adult/adolescent phase II basket trial
  - (n = 35)

Effective irrespective of tumor type

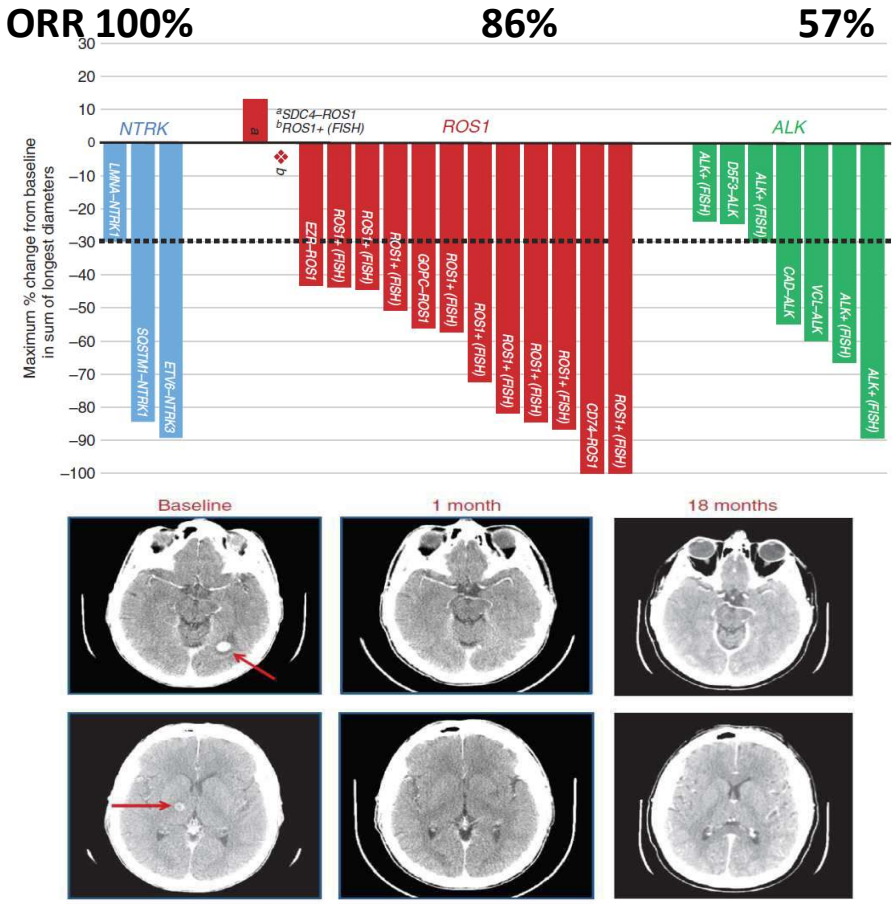
N = 55

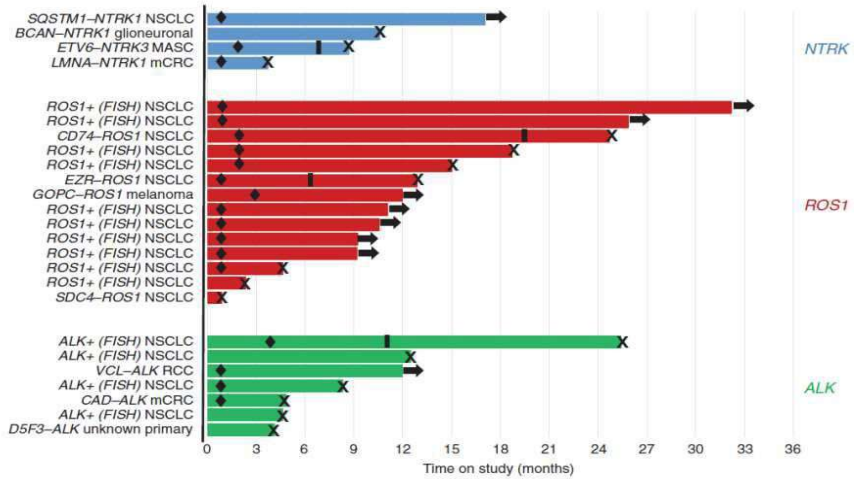


*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Drilon NEJM 2018

Entrectinib (RXDX-101), Pan-TRK, ALK & ROS1 inhibitor

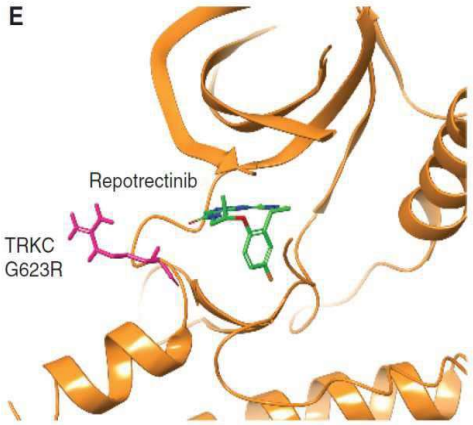


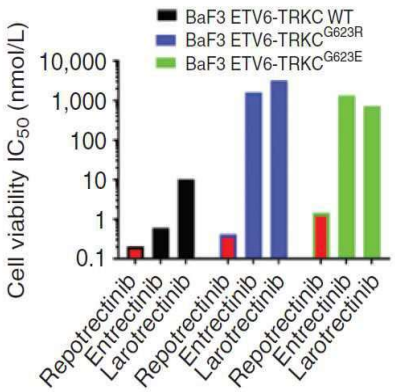


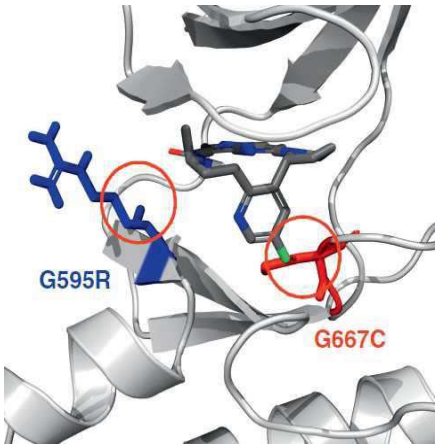
- N = 25, ALKA-372-001 & STARTRK-1 trials
- TKI naïve
- Intracranial response rate 63%

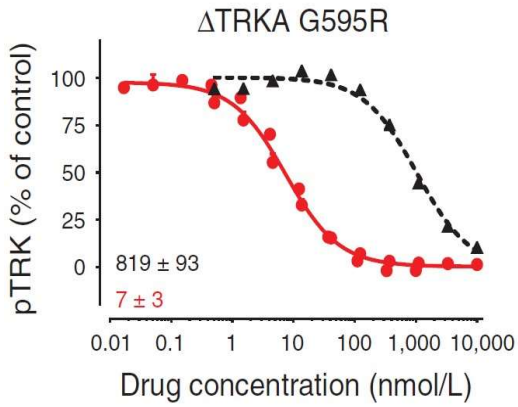
Drilon Cancer Discov 2017

Resistance and potential 2nd line options



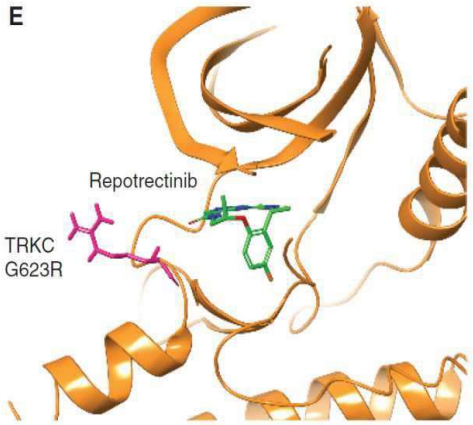


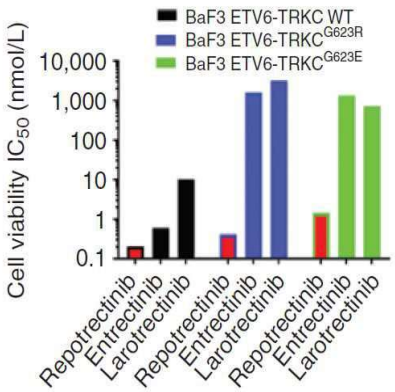


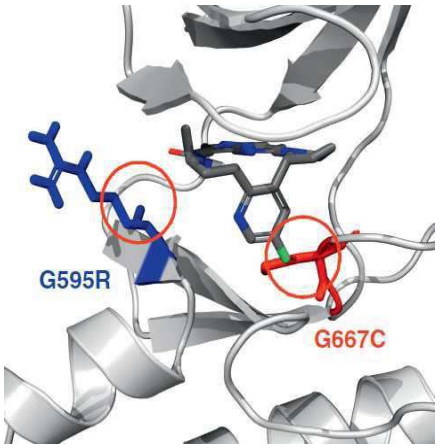


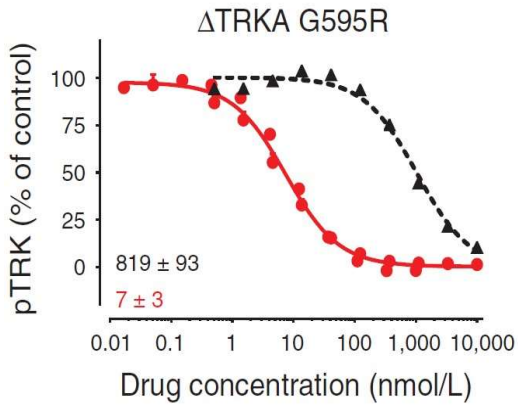
- Kinase domain mutations
  - Solvent front
    - TRKA G595R, TRKC G623R
  - Gatekeeper
    - TRKA F589L
  - Activation loop
    - TRKA G667S, TRKC G696A

Resistance and potential 2nd line options









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Current Landscape & the Way Forward

- MET
  - Specific TKIs to target MET ex14 are expected to be approved in the near future (capmatinib & tepotinib).
  - NGS testing key to detectiong MET ex14.
  - Is MET amplification a target?
  - Met protein expression by IHC not a therapeutic biomarker.
- RET
  - LOXO-292 & BLU-667 highly selective and effective RET inhibitors.
  - Is LOXO-292 (selpercatinib) better tolerated?

Current Landscape & the Way Forward

- BRAF
  - Established target- need to build on existing treatment paradigms
    - Rational combinations with IO and other small molecule inhibitors ? ERK.
  - 3rd generation RAF TKIs needed to target non V600 BRAF and limit effects of paradoxic activation.
- NTRK
  - Tumor and age agnostic target.
  - Highly effective inhibitors available (Larotrectinib & Entrectinib).

Thank You

- Questions?