Memorial Sloan Kettering Cancer Center

Year in Review in Non-Small Cell Lung Cancers

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Agenda: what's old is new, and what's new is old

- HER2 alterations
  - Pyrotinib
  - Trastuzumab deruxtecan
- NTRK Fusions
  - Larotrectinib
  - Entrectinib
- ROS1 fusions
  - Entrectinib
- KRAS G12C mutations
  - AMG510 (sotorasib)
- ALK Fusions
  - Lorlatinib
  - Brigatinib
  - Ensartinib

HER2 IHC as biomarker: 6 negative phase II lung cancer trials

TABLE 2. Studies with Trastuzumab-Containing Regimens Studies in NSCLC

Study Name	Study Design	Eligibility Criteria	Pts (*n*)	Treatment Arm (s)	Line (s) of Treatment	ORR (CR/PR)	PFS (months)	OS (months)
CALGB 39810[65]	Phase II, nonrandomized	HER2 IHC 2+/3+	24	Weekly T	Up to one prior CT regimen	5%	2.6	5.3
ECOG 2598[61]	Phase II, nonrandomized	HER2 IHC 1+/2+/3+	44	CP + weekly T	First line	24.5%	3.3	10.1
Gatzemeier et al.[62]	Phase II, randomized	HER2 IHC 2+/3+ or HER2 amplification or serum HER2 levels >15 ng/ml (ELISA)	103	CG + weekly T	First line	18% vs. 21%	6.1 vs. 7.0	12.2 vs. NR
Krug et al.[35]	Phase II, randomized	Stratification according HER2 IHC status	64	Weekly D + T vs. weekly P + T	First line	23% vs. 32%	NR	16 vs. 14
Lara et al.[64]	Phase II, randomized	HER2 IHC 2+/3+ or HER2 amplification	13	Induction with D or T weekly. After induction phase, all patients recived the combination of weekly D + T	<2 prior nonanthracycline-containing chemotherapy	8%	4.3	5.7
Zinner et al.[63]	Phase II, nonrandomized	HER2 IHC 1+/2+/3- or serum HER2 levels >15 ng/ml (ELISA)	21 (prematurely stopped)	CG + weekly T	First line	38%	TTP 8.5 months	One-year survival rate of 62%

CG, cisplatin–gemcitabine; CP, carboplatin–paclitaxel; D, Docetaxel; P, paclitaxel; T, trastuzumab; NSCLCs, non–small-cell lung cancer; ORR, overall response rate; PR, partial response; PFS, progression-free survival; OS, overall survival; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay; TTP, time to progression. CR, complete response; NR, not reported, CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group.

- All negative trials, including randomized phase II trial cisplatin/gemcitabine ± trastuzumab in HER2 IHC2+/3+ lung cancers (Gatzemeier Ann Oncol 2004)

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Courtesy of Paul K Paik, MD

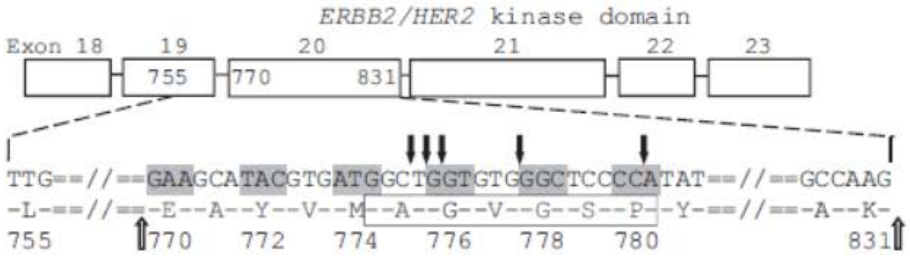
Ricciardi et al. J Thorac Oncol 2014

HER2 activating mutations in lung cancer

- **2-4% of lung cancers**
- **Most common *HER2* mutation is exon 20 insYVMA**
- **More common in women, never-smokers**

A

Schematic organization of *ERBB2* kinase domain



Wild-type sequence, exon 20

B

Spectrum of *ERBB2/HER2* mutations

Mut size	Total Cases (n = 25)	Nucleotide sequence*	CDS mutation (inserted sequence)	Amino acid mutation
12-bp ins	19 (76%)	TTG==//==GAAGCATACGTGATGGC**ATACGTGATGGC**TGGTGTGGGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**Y--V--M--A**--G--V--G--S--P--Y	c.2324_2325ins12 (ATACGTGATGGC duplication*)	p.Ala775_Gly776insTyrValMetAla

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Courtesy of Paul K Paik, MD

Stephens et al. Nature. 2004
Arcila et al. Clin Cancer Res. 2012

Refined biomarkers + better drugs = win

Biomarker	Afatinib ORR	T-DM1 ORR	T-DM1 Median PFS
HER 2 2+ IHC	~0%	0%	2.6mo

Courtesy of Paul K Paik, MD

Stinchcombe ASCO 2017
Li ASCO 2017

Refined biomarkers + better drugs = win

Biomarker	Afatinib ORR	T-DM1 ORR	T-DM1 Median PFS
HER 2 2+ IHC	~0%	0%	2.6mo
HER2 3+ IHC	5%	20%	2.7mo

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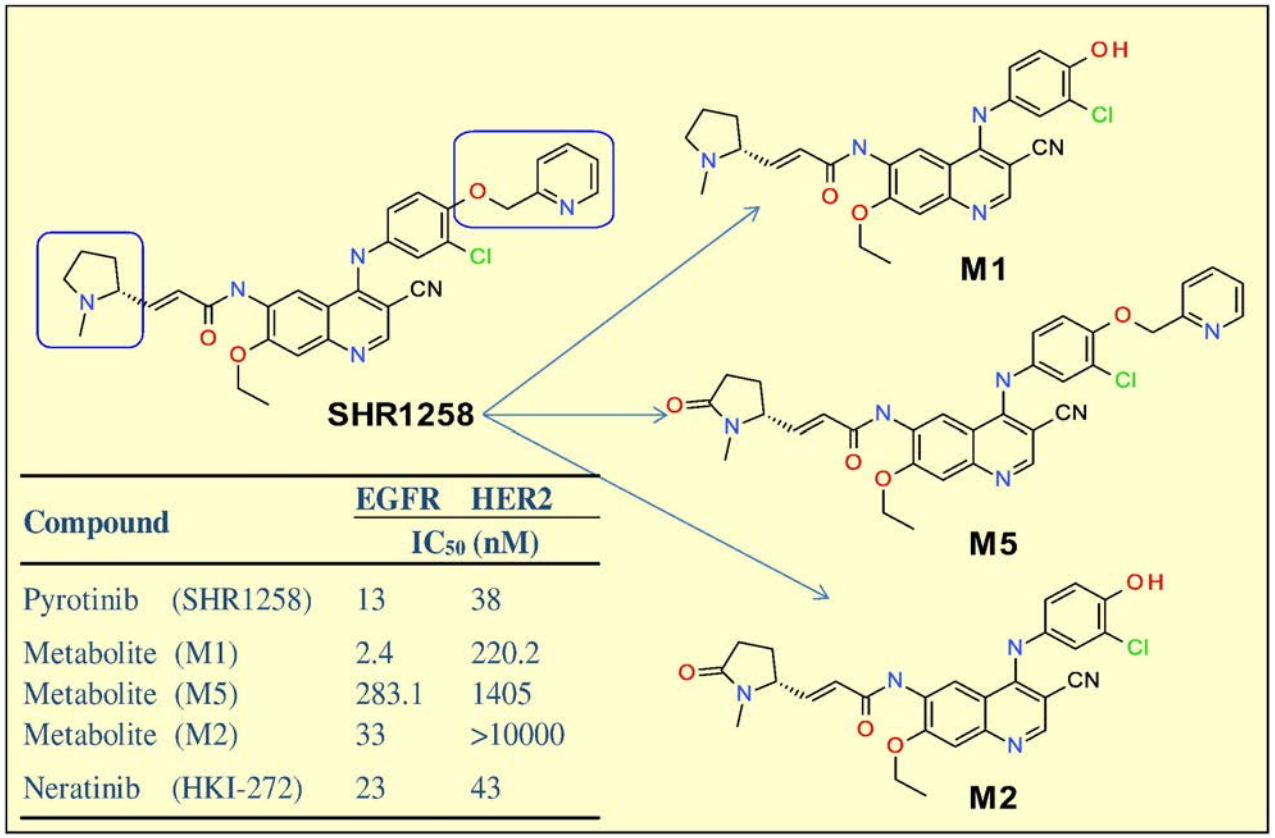
Refined biomarkers + better drugs = win

Biomarker	Afatinib ORR	T-DM1 ORR	T-DM1 Median PFS
HER 2 2+ IHC	~0%	0%	2.6mo
HER2 3+ IHC	5%	20%	2.7mo
HER2 exon 20 YVMA ins	NA	**56%**	**5.6mo**

Courtesy of Paul K Paik, MD

Stinchcombe ASCO 2017
Li ASCO 2017

Pyrotinib



Compound	EGFR	HER2
	IC_{50} (nM)	
Pyrotinib (SHR1258)	13	38
Metabolite (M1)	2.4	220.2
Metabolite (M5)	283.1	1405
Metabolite (M2)	33	>10000
Neratinib (HKI-272)	23	43

- EGFR/HER2 dual tyrosine kinase inhibitor
- Phase 1 study in 2017 identified an MTD of 400mg po qd
- Approved for HER2+ breast cancer in combination with capecitabine in China

Courtesy of Paul K Paik, MD

Li et al. Eur J Pharm Sci 2017

Pyrotinib in lung cancer

- Open-label single arm Phase 2 trial in China
- HER2 mutation required, centrally confirmed
- First-line refractory setting
- Pyrotinib 400mg po qd in an every 21-day cycle

Courtesy of Paul K Paik, MD

Zhou et al. J Clin Oncol 2020

Patient characteristics and adverse events

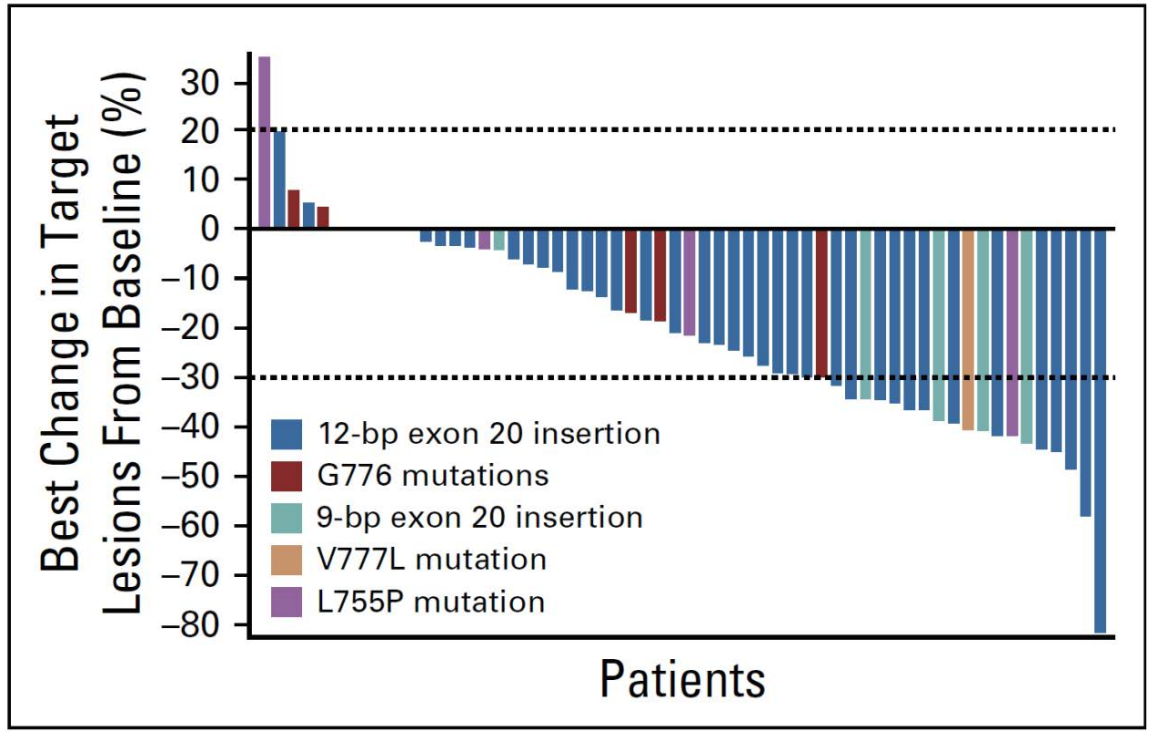
Characteristic	Pyrotinib (N = 60), No. (%)
Median age, years (range)	57 (40-72)
Sex	
Male	27 (45.0)
Female	33 (55.0)
Smoking history	
Never	43 (71.7)
Former	16 (26.7)
Current	1 (1.7)
HER2 mutation type	
12-bp exon 20 insertion	44 (73.3)
G776 mutations	6 (10.0)
9-bp exon 20 insertion	5 (8.3)
V777L mutation	1 (1.7)
L755P mutation	4 (6.7)

	Pyrotinib (N = 60), No. (%)	
Adverse Event	All Grades	Grade 3 or 4
Diarrhea	55 (91.7)	12 (20.0)
Blood creatinine increased	18 (30.0)	0
Vomiting	17 (28.3)	1 (1.7)
ALT increased	9 (15.0)	0
AST increased	9 (15.0)	1 (1.7)
Nausea	8 (13.3)	0
Weight decreased	8 (13.3)	0
Anemia	8 (13.3)	0
WBC decreased	7 (11.7)	0
Rash	7 (11.7)	0
Asthenia	6 (10.0)	0
Paronychia	6 (10.0)	0

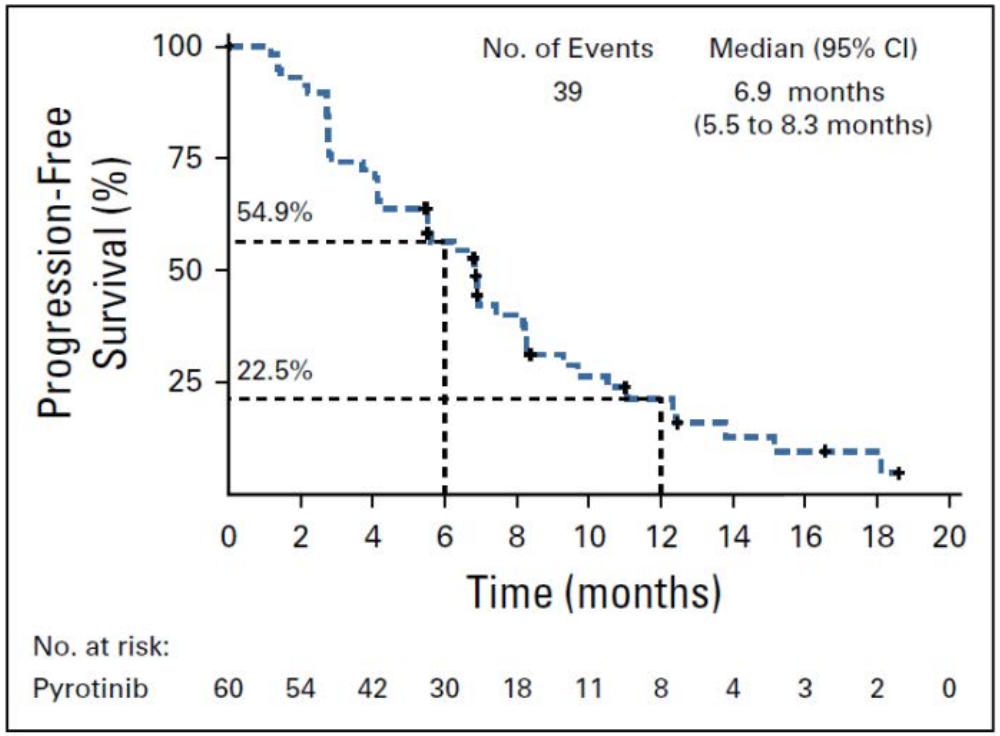
Courtesy of Paul K Paik, MD

Zhou et al. J Clin Oncol 2020

Pyrotinib efficacy



ORR = 30% (19-43%)



Median PFS = 6.9 months

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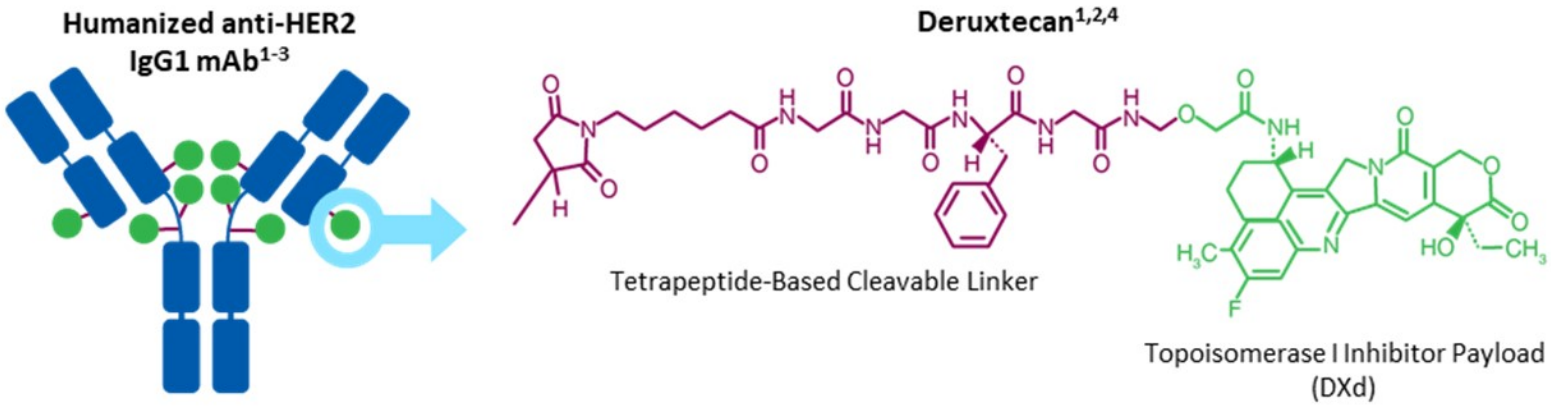
Courtesy of Paul K Paik, MD

Zhou et al. J Clin Oncol 2020

Trastuzumab deruxtecan

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

DESTINY-1 trial

DESTINY-Lung01 Study Design

An open-label, multicenter, phase 2 study (NCT03505710)

Patients

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- HER2-expressing *or* HER2-activating mutation[a]
- No prior HER2-targeted therapy, except pan-HER TKIs

Cohort 1 (n = 42)
HER2 expressing (IHC 3+ or IHC 2+)

Cohort 2 (n = 42)
HER2 mutated

T-DXd 6.4 mg/kg q3w

Primary endpoint

- Confirmed ORR by independent central review

Data cutoff: November 25, 2019

- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

[a] Based on local assessment of archival tissue.

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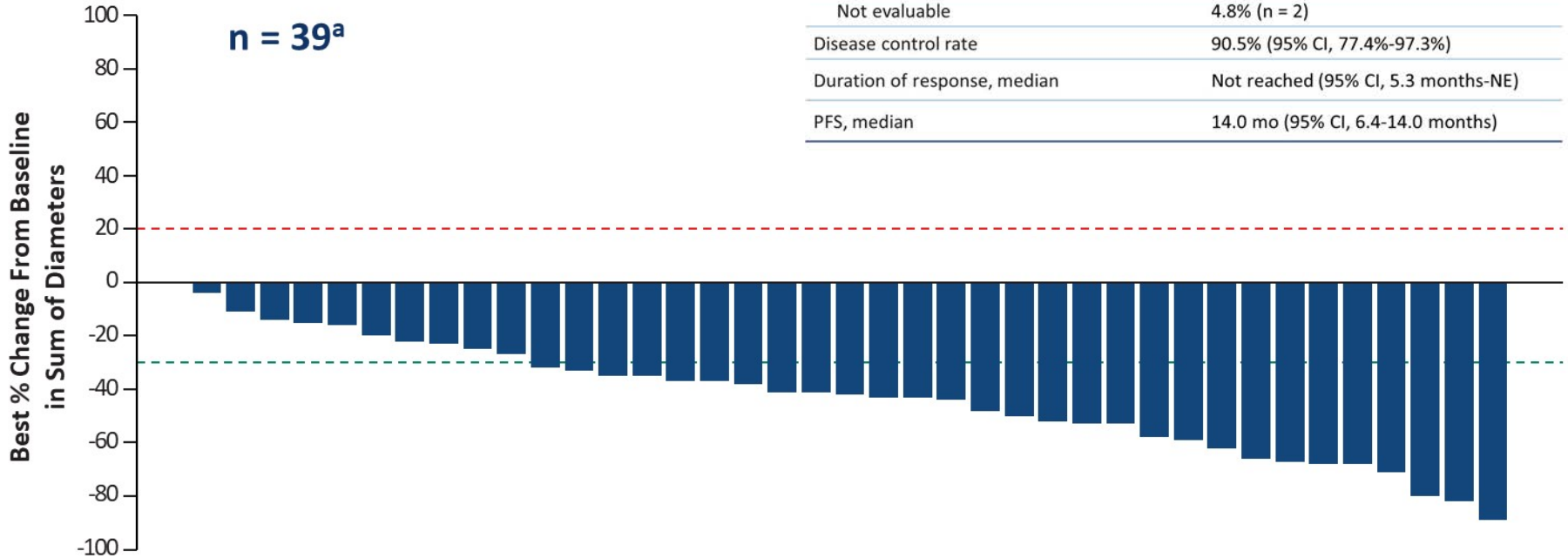
Courtesy of Paul K Paik, MD

Smit EF et al. ASCO 2020

DESTINY-1 efficacy

Best Change in Tumor Size

	Patients (N = 42)
Confirmed ORR by ICR	**61.9% (n = 26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)



Based on independent central review. Baseline is last measurement taken before enrollment. Shown is best (minimum) percent change from baseline in the sum of diameters for all target lesions.

[a] One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.

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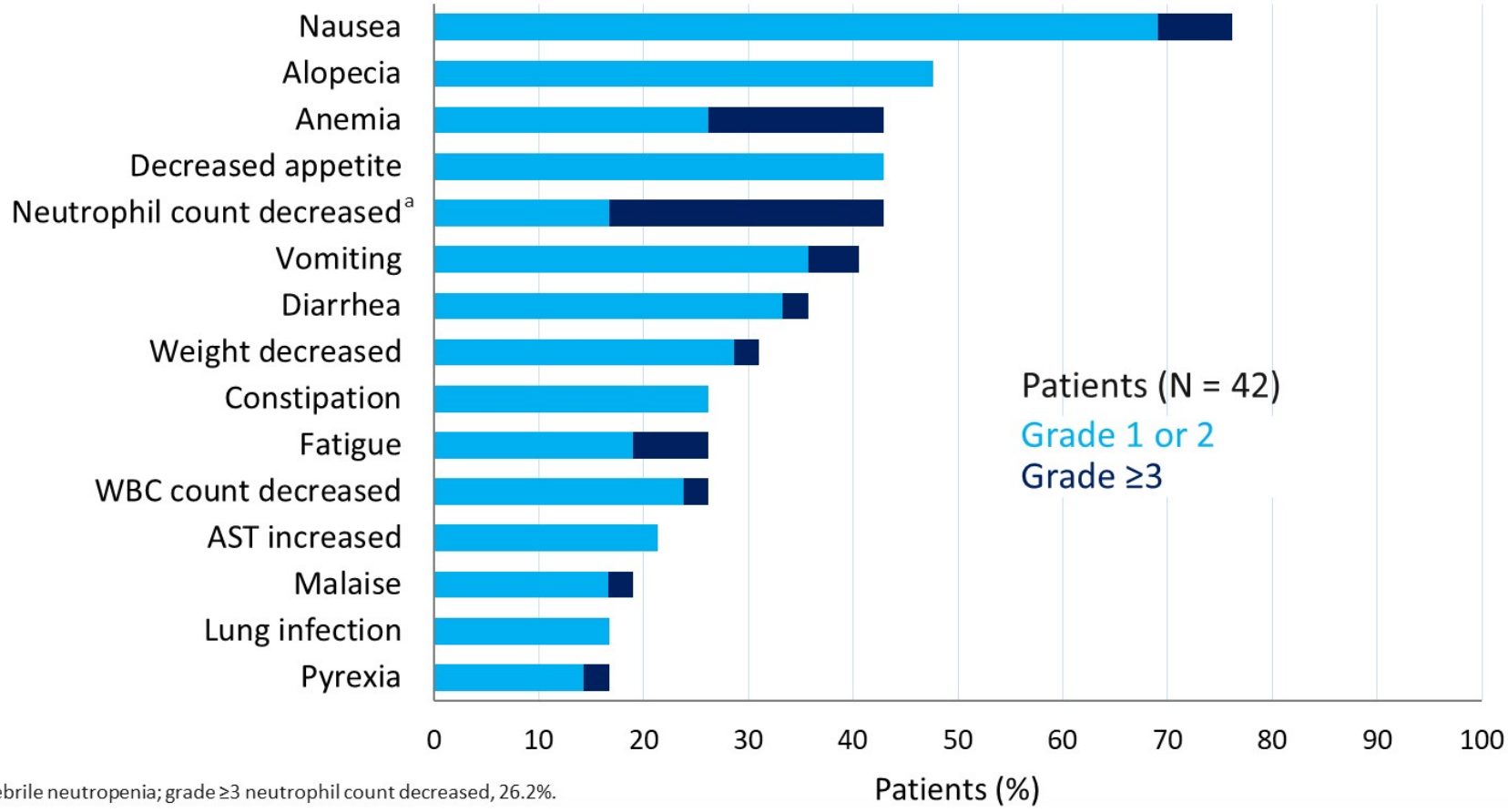
Smit EF et al. ASCO 2020

Trastuzumab deruxtecan side effects

Treatment-Emergent Adverse Events in >15% of Patients



[a] 2 patients had febrile neutropenia; grade ≥3 neutrophil count decreased, 26.2%.

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Courtesy of Paul K Paik, MD

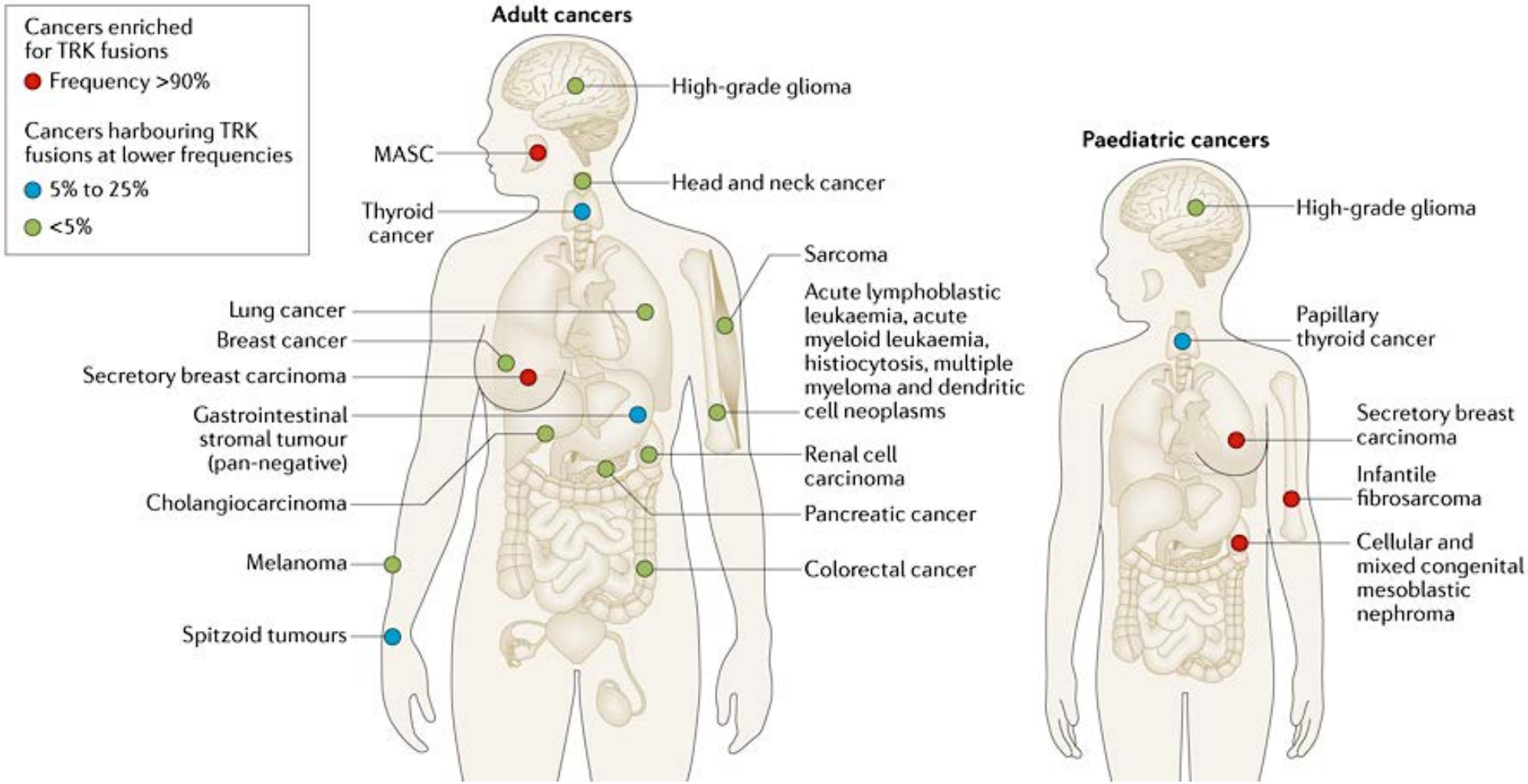
Smit EF et al. ASCO 2020

Conclusion

- Clinical implications
  - Trastuzumab-deruxtecan has, preliminarily, best in class efficacy against lung cancers harboring HER2 mutations (predominantly exon 20 alterations)
  - ORR and PFS appear to be better than other antibody and TKI-based approaches
  - Will become a standard treatment for this subset once regulatory approval is received

- Future directions
  - May 2020: trastuzumab deruxtecan granted breakthrough designation
  - Await final results, FDA approval, including overall survival and HER2/3 expression cohort, of DESTINY-Lung01 trial

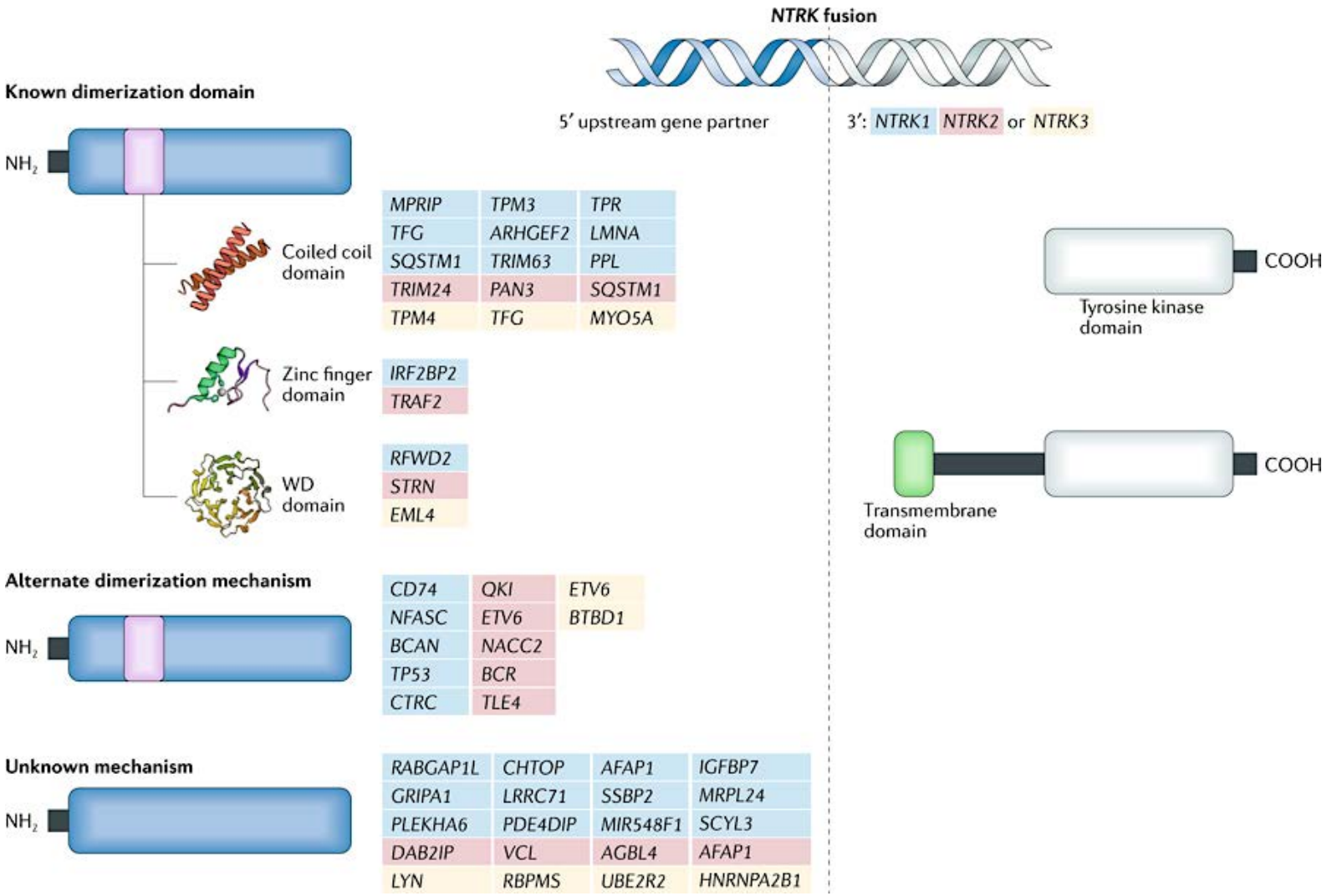
TRK fusions occur in multiple cancer types …



Courtesy of Paul K Paik, MD

Cocco et al, Nat Rev Clin Oncol 2018

… and have multiple partners leading to constitutive dimerization



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Courtesy of Paul K Paik, MD

Cocco et al, Nat Rev Clin Oncol 2018

First generation TRK inhibitors are highly effective

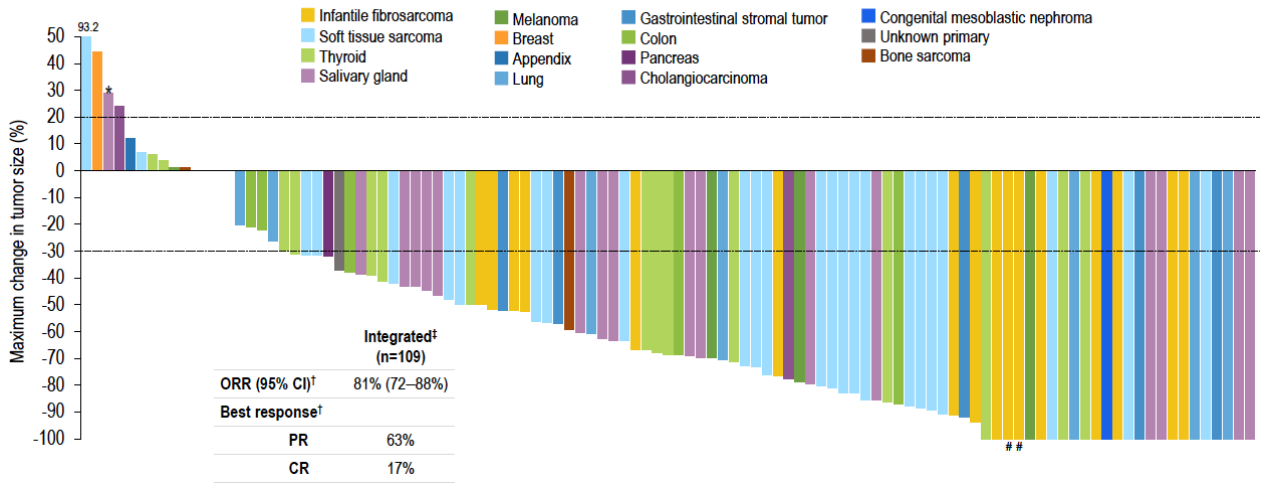
Larotrectinib

ORR 81%

(95% CI 72-88%, n=109)

Median DoR not reached

Median PFS not reached



FDA approved for NTRK fusion+ cancers November 2019

Entrectinib

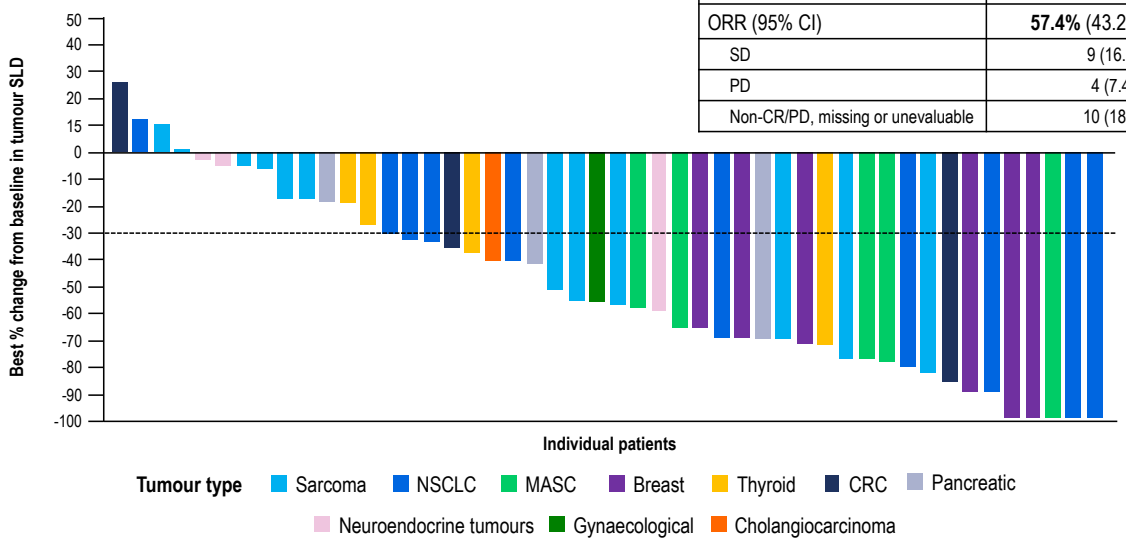
ORR 57%

(95% CI 43-71%, n=54)

Median DoR 10 mos

Median PFS 11 mos

	NTRK+ all patients (n=54)
ORR (95% CI)	**57.4%** (43.21–70.77)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)



FDA approved for NTRK fusion+ cancers August 2019

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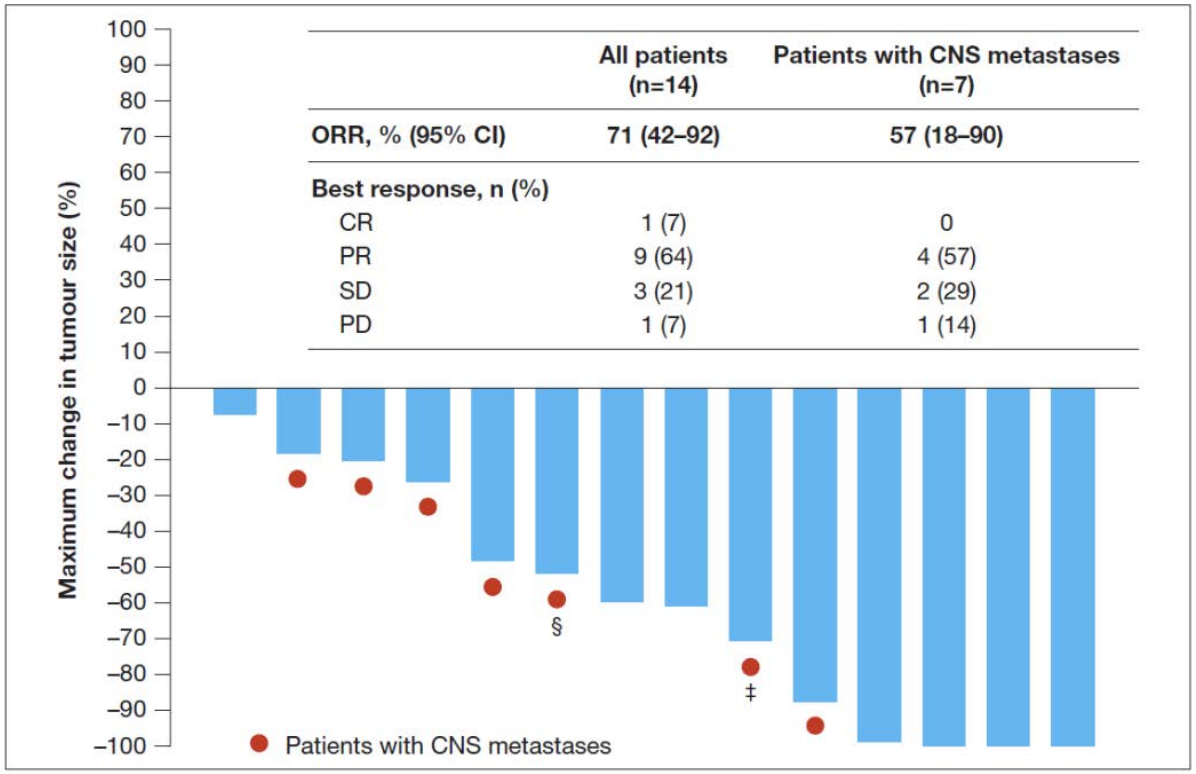
Courtesy of Paul K Paik, MD

Drilon et al. NEJM 2018

Doebele et al. Lancet Oncol 2020

Larotrectinib in lung cancer



	All patients (n=14)	Patients with CNS metastases (n=7)
ORR, % (95% CI)	71 (42–92)	57 (18–90)
Best response, n (%)		
CR	1 (7)	0
PR	9 (64)	4 (57)
SD	3 (21)	2 (29)
PD	1 (7)	1 (14)

ORR = 71%

PFS, DOR, OS not yet reached

Preferred term	All AEs n (%)			Treatment-related AEs n (%)	
	Grade 1 or 2	Grade 3	Any grade	Grade 3	Any grade
Myalgia	7 (50)	1 (7)	8 (57)	1 (7)	5 (36)
Cough	7 (50)	0	7 (50)	–	–
Dizziness	7 (50)	0	7 (50)	0	4 (29)
Arthralgia	6 (43)	0	6 (43)	0	1 (7)
AST increased	5 (36)	0	5 (36)	0	3 (21)
Diarrhoea	5 (36)	0	5 (36)	–	–
ALT increased	4 (29)	0	4 (29)	0	4 (29)
Constipation	4 (29)	0	4 (29)	–	–
Fatigue	4 (29)	0	4 (29)	0	1 (7)
Pyrexia	4 (29)	0	4 (29)	0	1 (7)
Anaemia	2 (14)	1 (7)	3 (21)	–	–
Back pain	3 (21)	0	3 (21)	–	–
Dry skin	3 (21)	0	3 (21)	0	1 (7)
Hypotension	2 (14)	1 (7)	3 (21)	0	1 (7)
Leukocyte count decreased	3 (21)	0	3 (21)	0	2 (14)
Muscular weakness	3 (21)	0	3 (21)	–	–
Nausea	3 (21)	0	3 (21)	0	1 (7)
Peripheral oedema	3 (21)	0	3 (21)	0	1 (7)
Pain in extremity	3 (21)	0	3 (21)	–	–
Pruritus	3 (21)	0	3 (21)	–	–
Rash	3 (21)	0	3 (21)	0	2 (14)
Vomiting	3 (21)	0	3 (21)	0	1 (7)
Weight increased	3 (21)	0	3 (21)	0	2 (14)

Courtesy of Paul K Paik, MD

Drilon et al. ESMO 2020

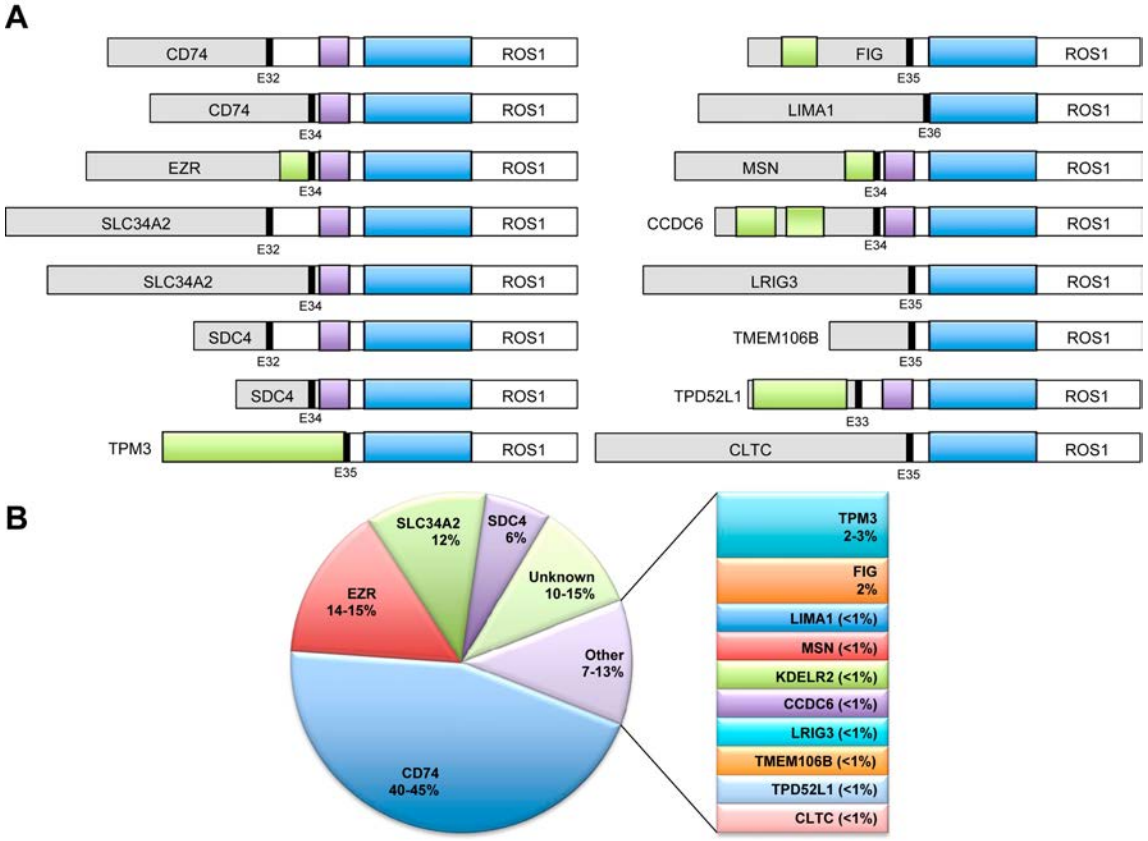
Farago et al. IASLC 2020

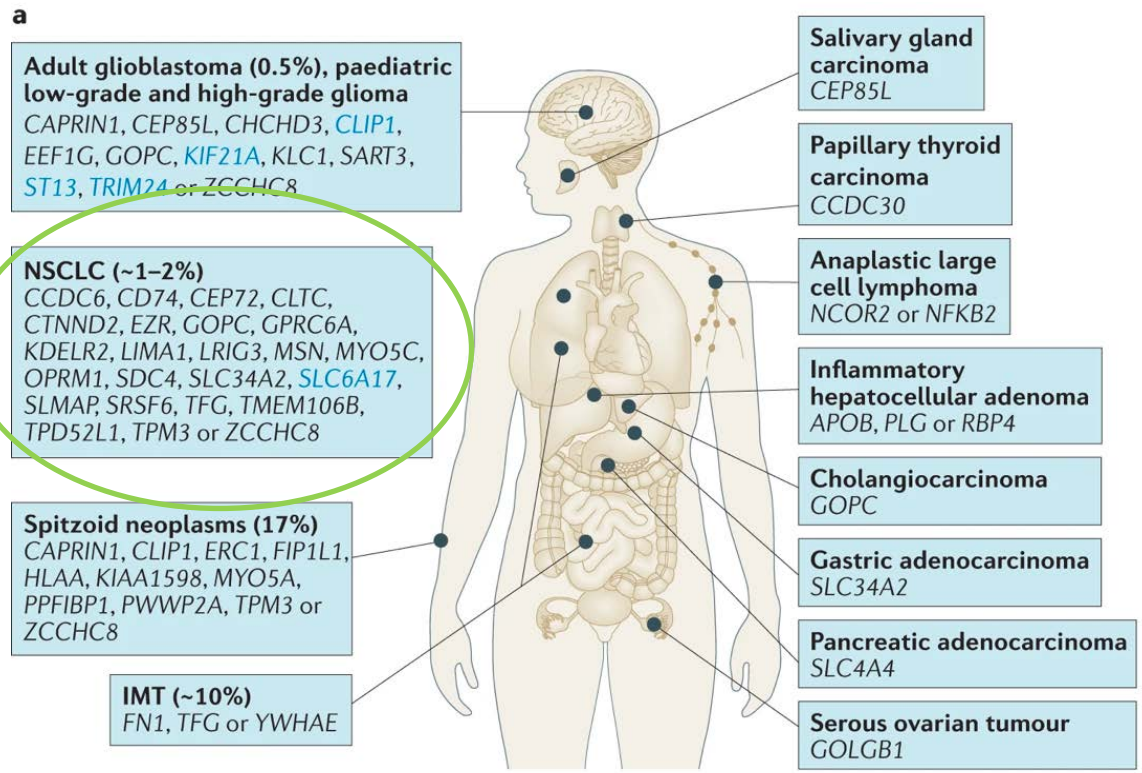
Conclusion

- Clinical implications
  - Larotrectinib and entrectinib are FDA-approved for TRK fusion positive lung cancers with high overall efficacy and durable responses
  - Routine molecular testing should be done to detect these alterations at the time of diagnosis
  - These agents should be given first-line if a TRK fusion is detected in time

- Future directions
  - Acquired resistance work is ongoing
  - Solvent front secondary mutations have been detected that can be overcome with next-generation TRK inhibitors (repotrectinib, LOXO-195)

ROS1 fusion partners are varied, and occur in many cancer types





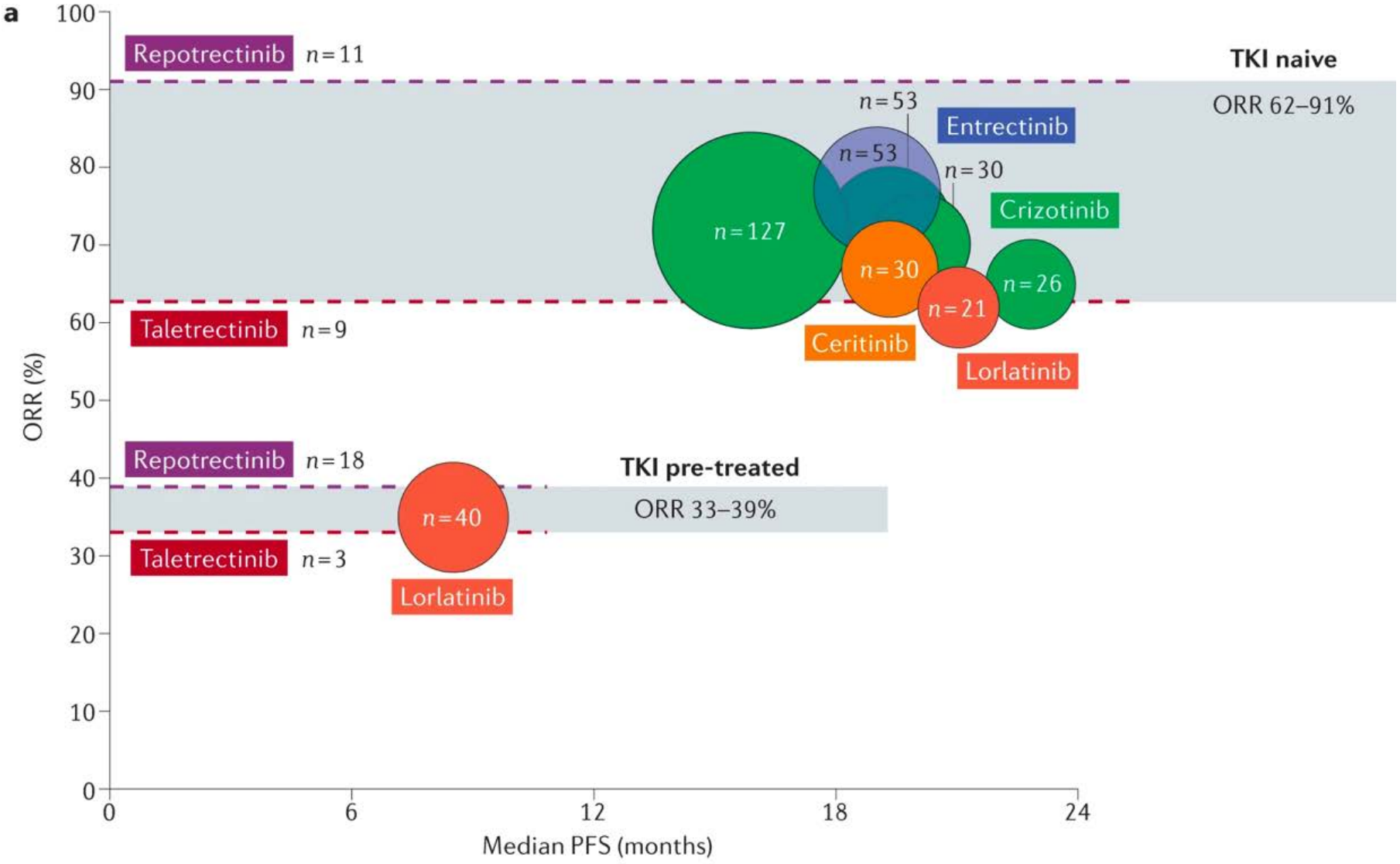
ROS1 inhibitors are highly effective across drugs in TKI-naïve patients

Drug	Target	Line	NCT #	N	ORR	PFS
Crizotinib[1] FDA approved 2016	ROS1	1-3	NCT00585195 (PROFILE 1001)	50	72%	19.2 months PFS (14.4,NR) 18.3 months DOR (12.7,NR)
Lorlatinib[2]	ROS1	1	NCT01970865	13	61.5% (31.6,86.1)	21 months (4.2,26.7)
		>1	NCT01970865	34	26.5% (12.9, 44.4)	8.5 months (4.4, 18.0)
Ceritinib[3]	ROS1	1	-	30	67% (48-81)	19.3 months (1, 37)
Entrectinib[4] FDA approved 2019	ROS1	1	NCT02097810 (STARTRK-1) NCT02568267 (STARTRK-2) EudraCT 2012-000148-88 (ALK)	53	77.4% (63.8,87.7)	19.0 months PFS (12.2,36.6) 24.6 months DOR (11.4,34.8)

Courtesy of Paul K Paik, MD

1. Shaw et al. NEJM 2014; 2.Ou et al. IASLC WCLC 2018; 3. Lim et al. JCO 2017; 4. Drilon et al. Lancet Oncol 2019

Next gen ROS1 inhibitors: similar efficacy to older drugs



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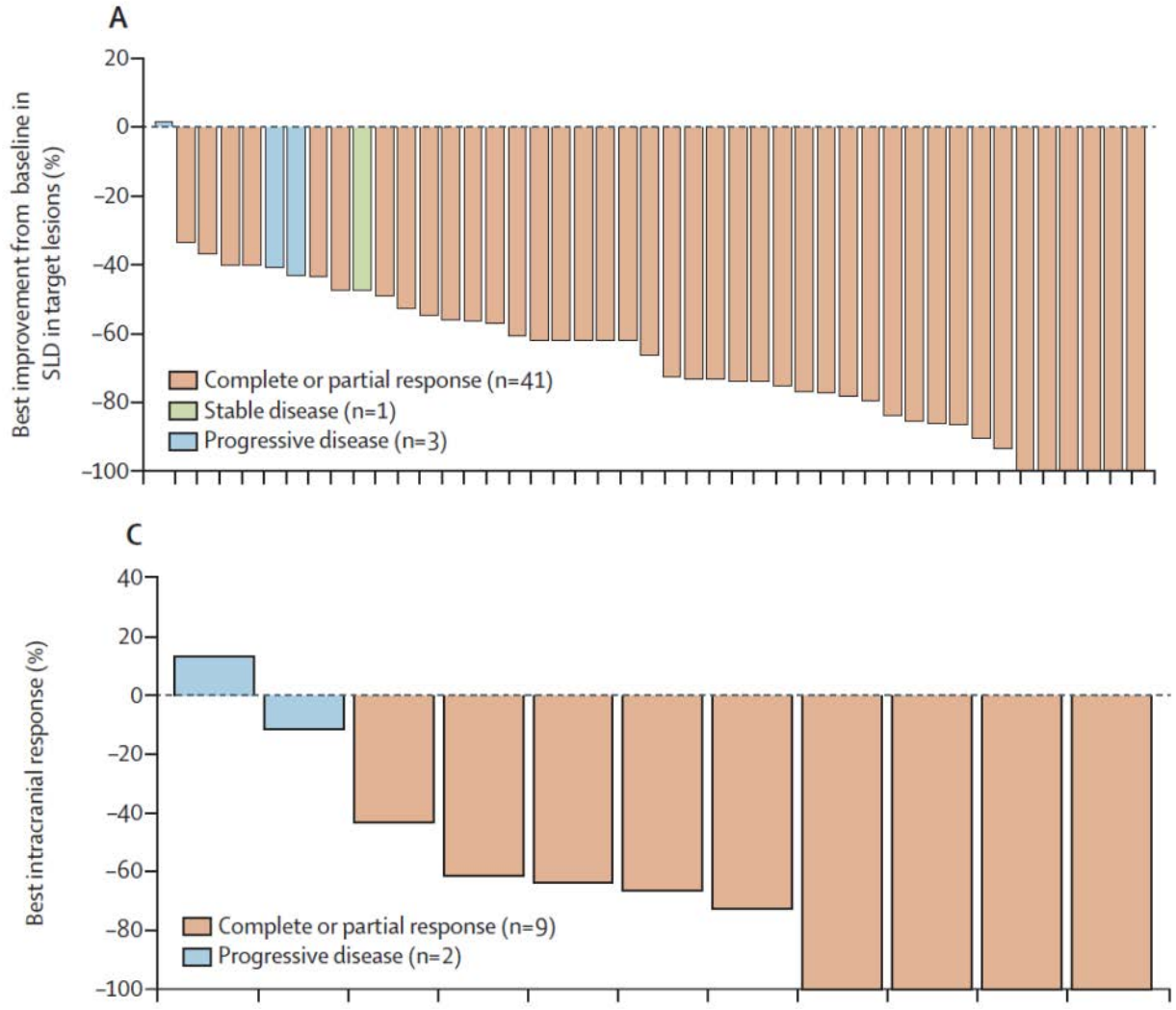
Drilon et al. Nat Rev Clin Oncol 2017

Entrectinib in ROS1+ lung cancer update



- ORR = 77% (64-88%)
- Median DOR = 24.6 months (11.4-34.8)
- Median PFS = 19 months (12.2-36.6)
- Intracranial ORR = 55% (32-77%)

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Courtesy of Paul K Paik, MD

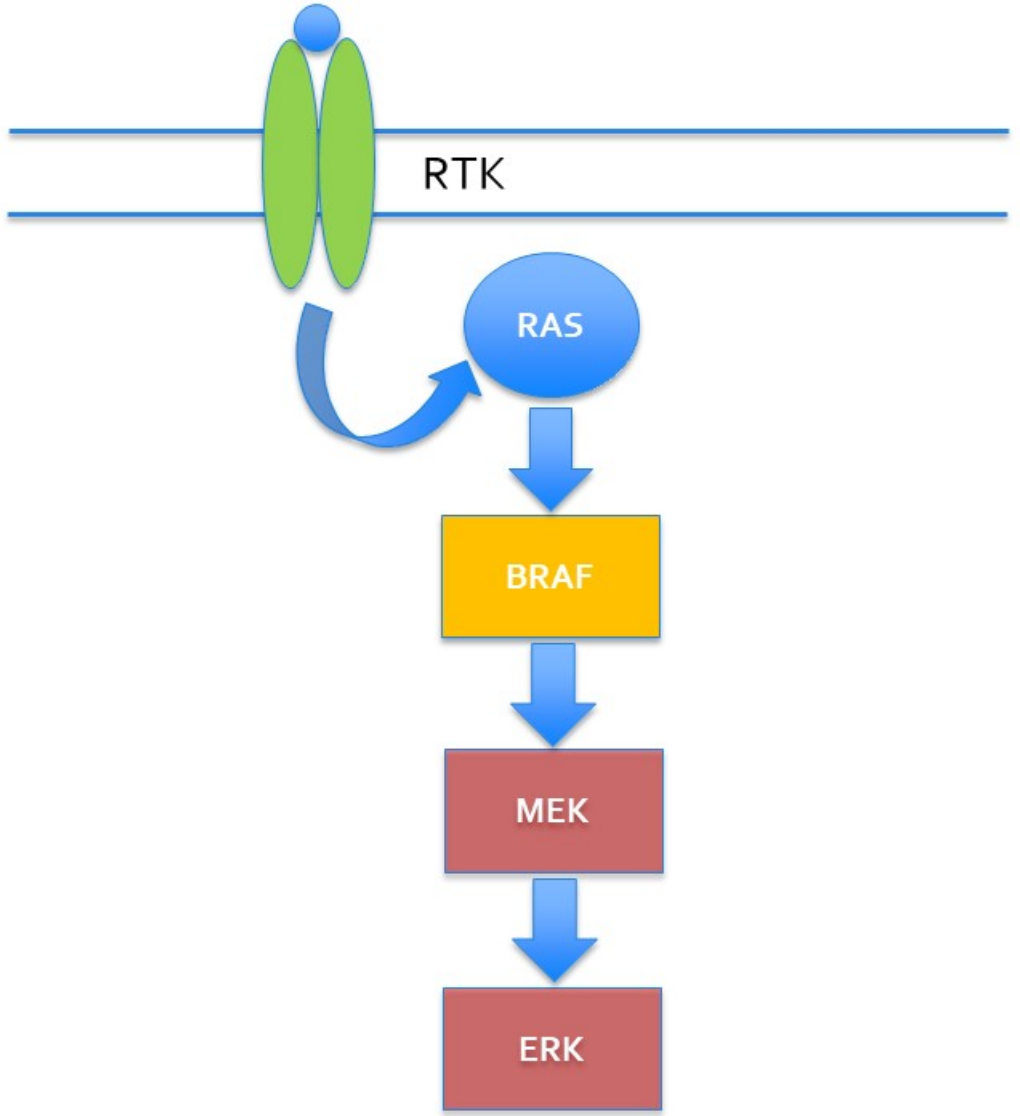
Drilon et al. Lancet Oncol 2020

Conclusion

- Clinical implications
  - Crizotinib, lorlatinib, and entrectinib are all FDA-approved for use in ROS1+ lung cancers
  - Efficacy and durability of response are high across all drugs
  - Selective ROS1 inhibitors appear to be modestly better than crizotinib
  - Routine testing for ROS1 fusions should occur at the time of diagnosis, and ROS1 inhibitors given first-line if found

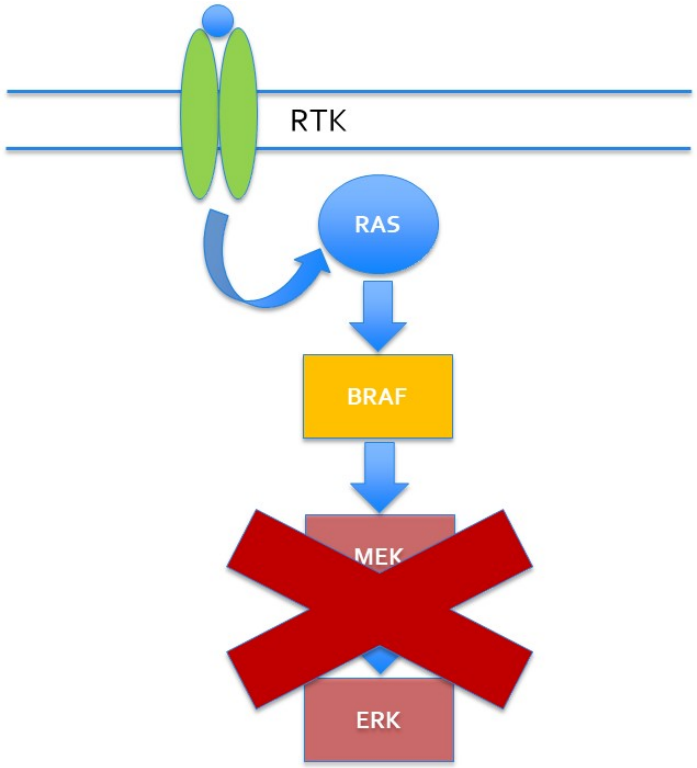
- Future directions
  - Acquired resistance work is ongoing
  - Solvent front secondary mutations have been identified

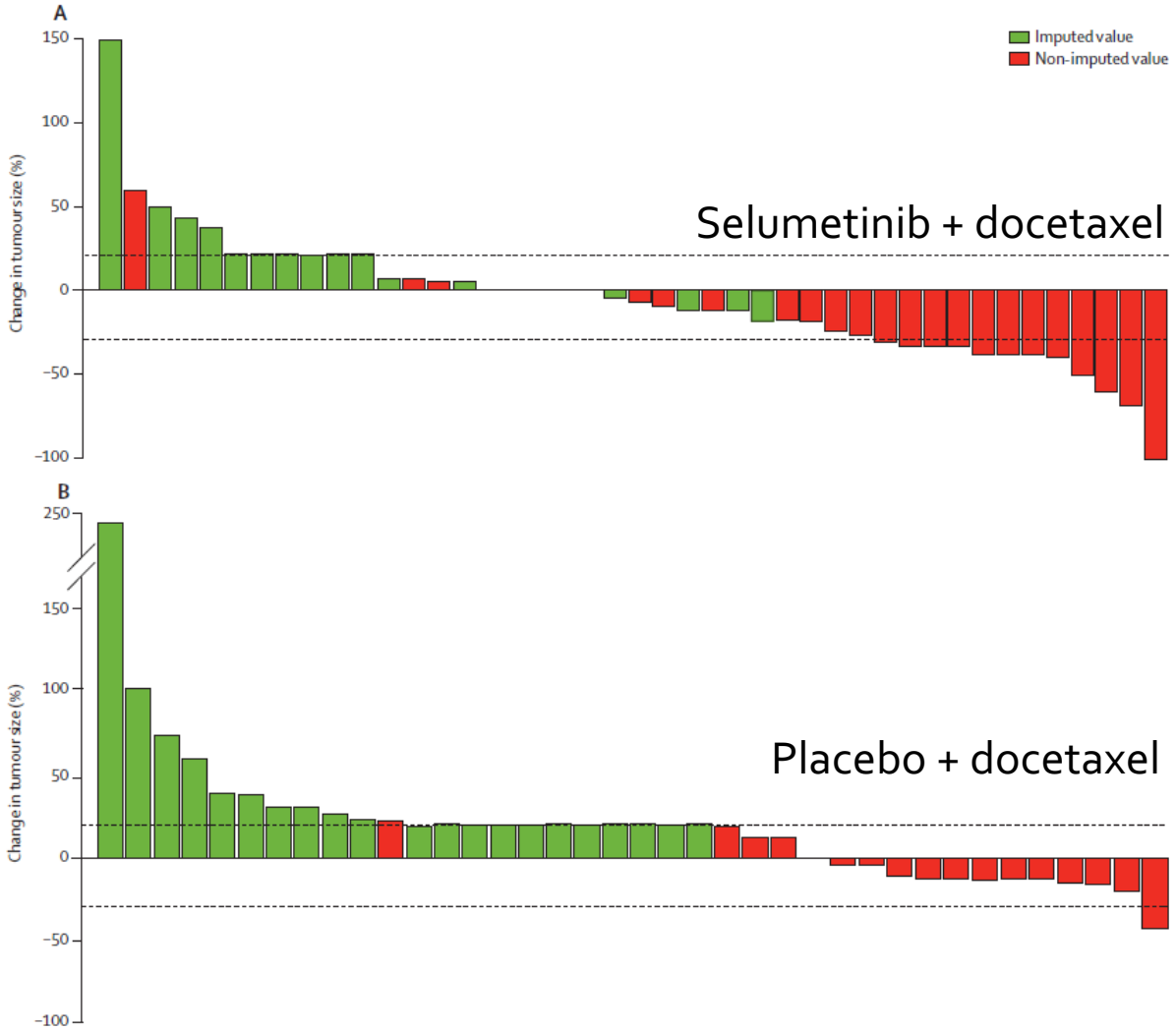
RAS signaling 101



Courtesy of Paul K Paik, MD

RAS signaling inhibition: MEK inhibition failures





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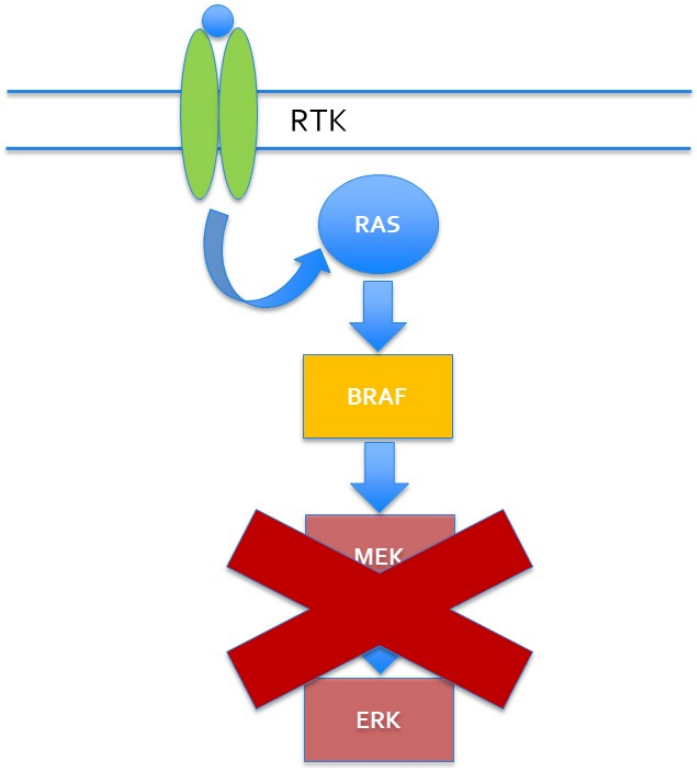
Courtesy of Paul K Paik, MD

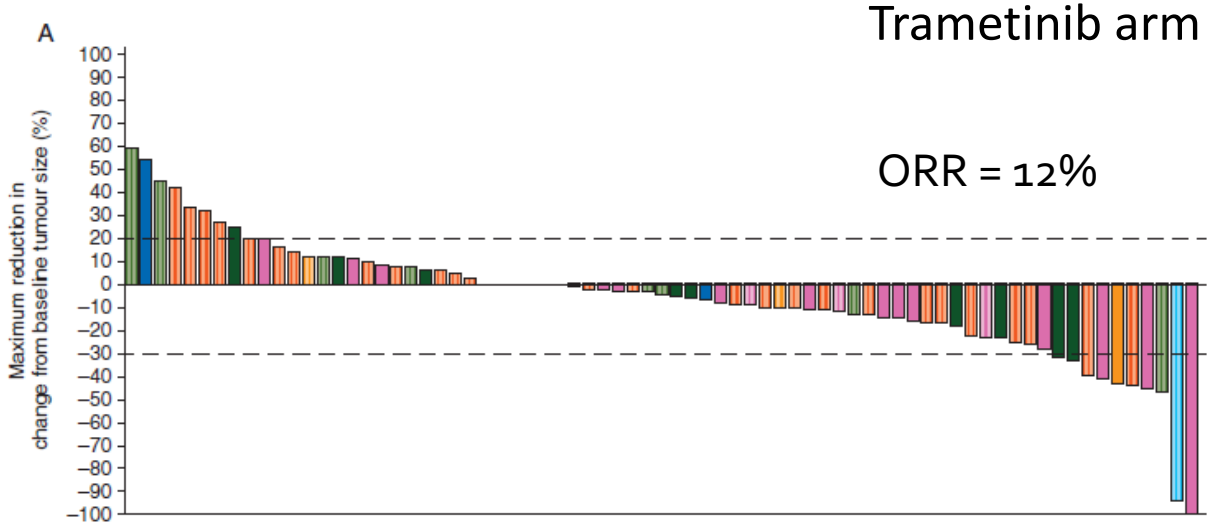
Janne et al. Lancet Oncol 2013

RAS signaling inhibition: MEK inhibition



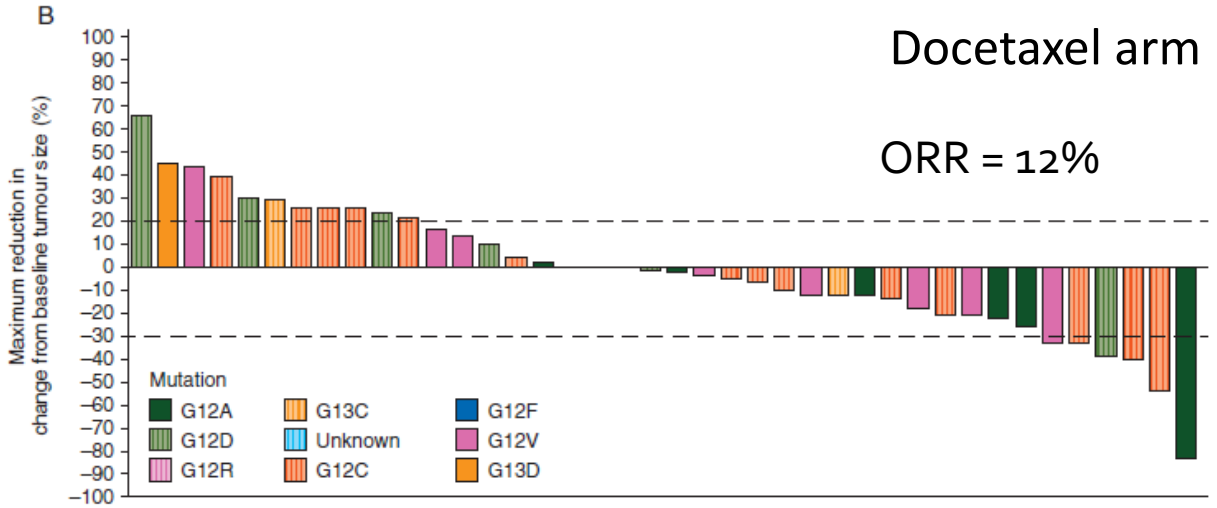
Trametinib arm

ORR = 12%



Docetaxel arm

ORR = 12%



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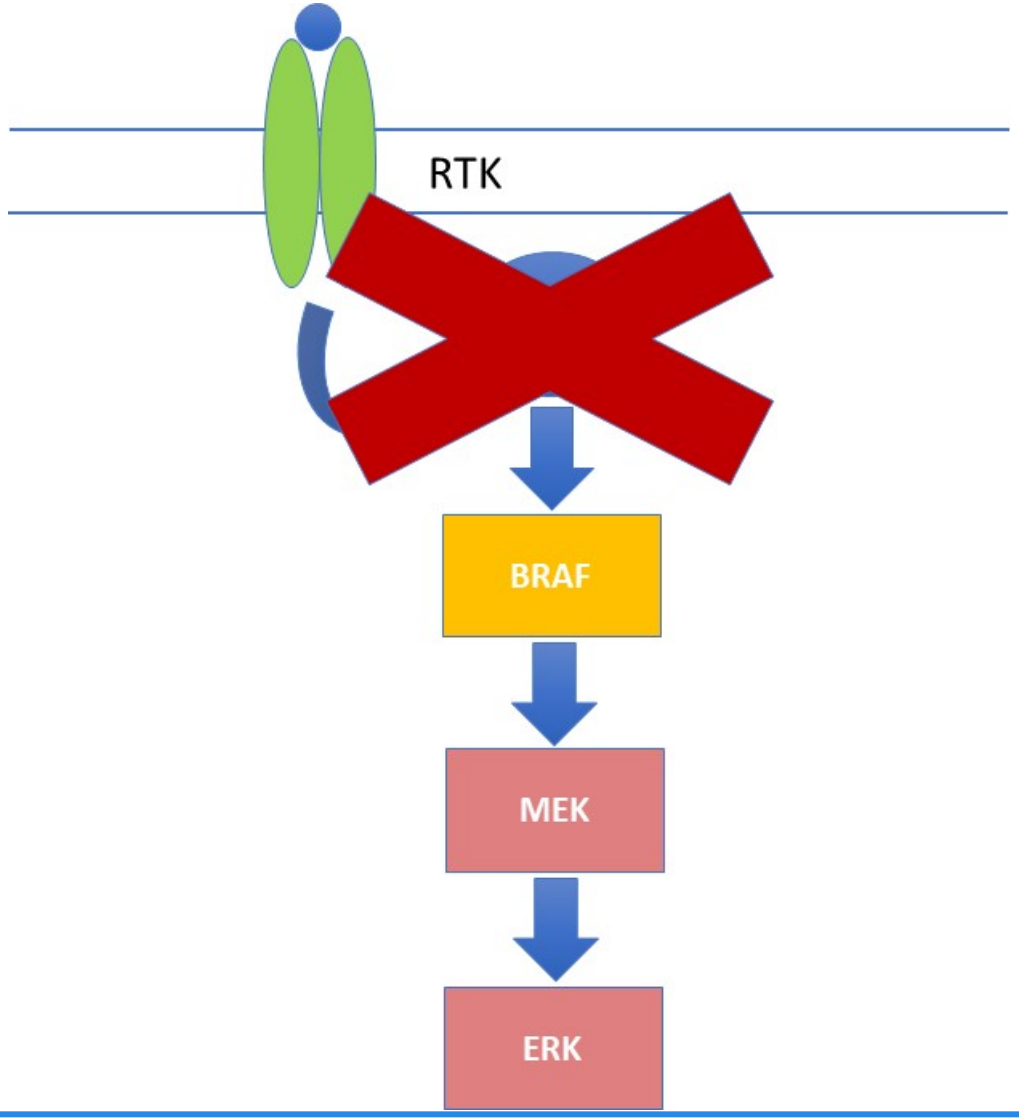
Courtesy of Paul K Paik, MD

Blumenschein Ann Oncol 2015

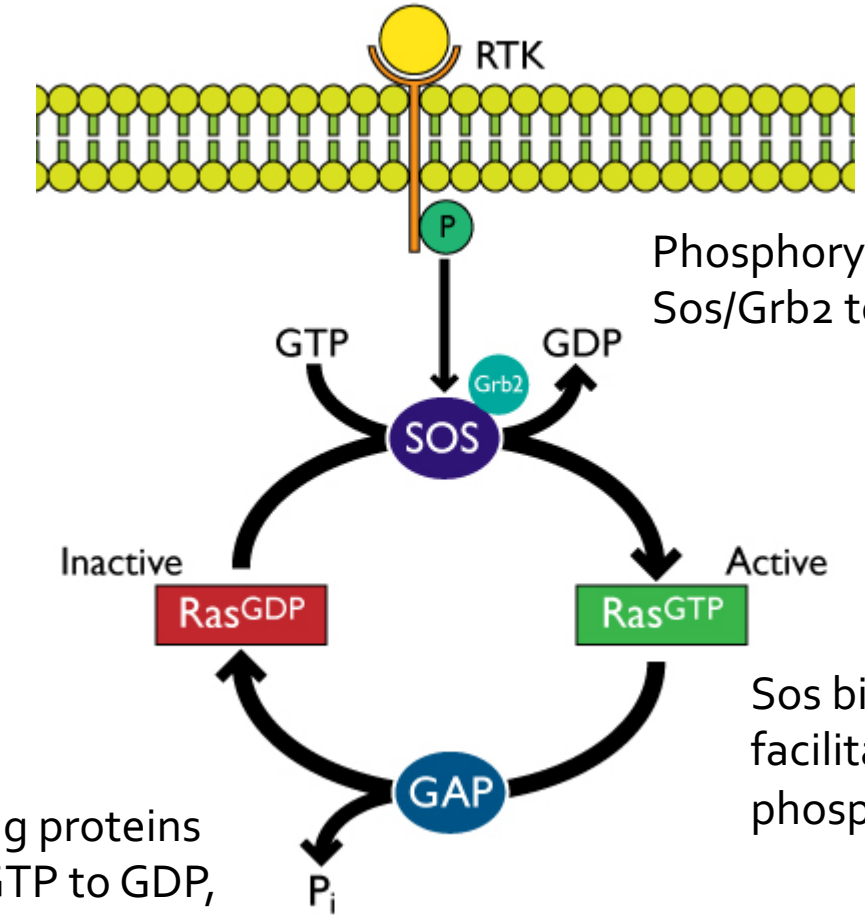
RAS signaling 101: inhibition of KRAS

- Inhibition of RAS activation
  - Allosteric kinase pocket inhibition



Courtesy of Paul K Paik, MD

KRAS activation is mediated by GEFs and GAPs



Phosphorylated RTK recruits Sos/Grb2 to receptor

Sos binds Ras-GDP and facilitates GDP phosphorylation to GTP

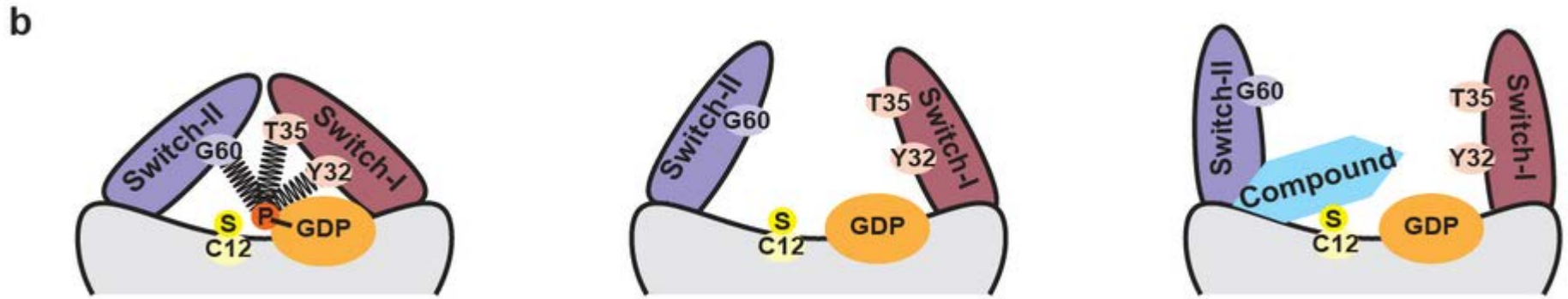
GTPase activating proteins (GAPs) convert GTP to GDP, inactivating RAS

Courtesy of Paul K Paik, MD

Image from cytoskeleton.com

KRAS G12C allosteric inhibitors: how they work

- RAS has picomolar affinity for GTP/GDP making competitive inhibition difficult
- RAS mutations impair GTP hydrolysis to GDP, causing constitutive activation
- Novel compound irreversibly binds GTP pocket through cysteine affinity at G12C
- Sos-mediated nucleotide exchange impairment leading to inhibition of KRAS



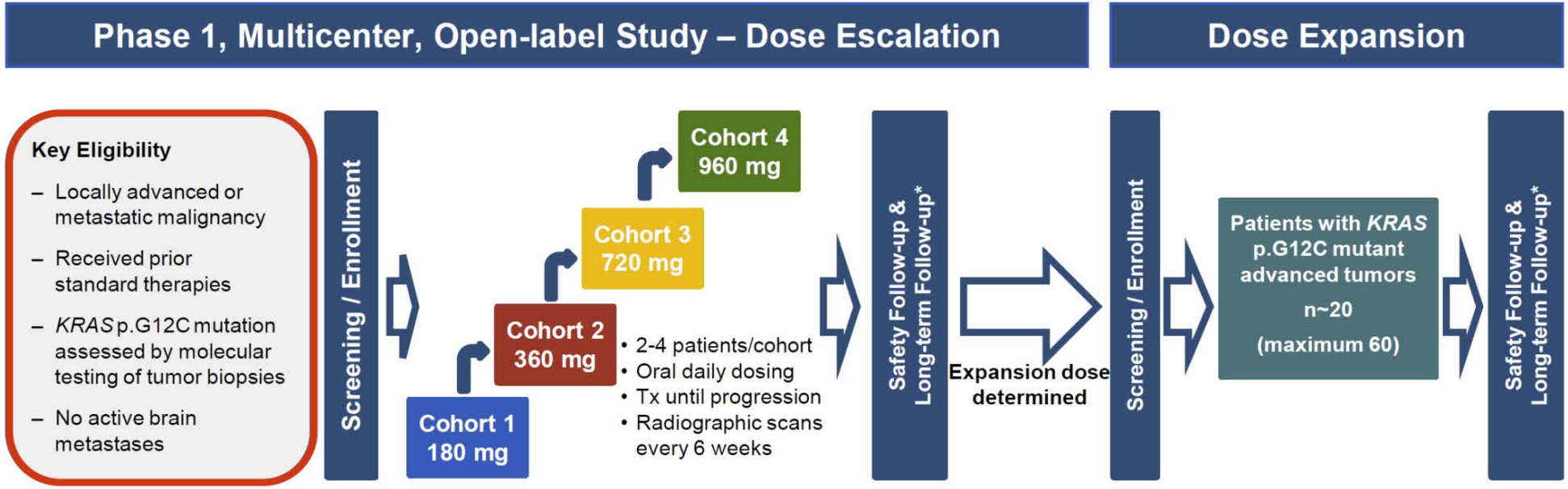
Courtesy of Paul K Paik, MD

Ostrem Nature 2013

AMG510 (sotorasib): CodeBreaK100

VIRTUAL 2020 ESMO congress

Phase 1 study design (CodeBreaK100: NCT03600883)



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AMG510 (sotorasib) adverse events

Treatment-related Adverse Events	All Patients (N = 59) n (%)		
	Any Grade	Grade ≥3	Grade ≥4
Any	39 (66.1)	11 (18.6)	1 (1.7)
Diarrhea	15 (25.4)	3 (5.1)	0 (0.0)
ALT increased	12 (20.3)	6 (10.2)	1 (1.7)*
AST increased	12 (20.3)	3 (5.1)	0 (0.0)
Fatigue	6 (10.2)	0 (0.0)	0 (0.0)
Nausea	6 (10.2)	0 (0.0)	0 (0.0)
Alkaline phosphatase increased	5 (8.5)	2 (3.4)	0 (0.0)
Decreased appetite	4 (6.8)	0 (0.0)	0 (0.0)

Treatment-related Adverse Events	All Patients (N = 59) n (%)		
	Any Grade	Grade ≥3	Grade ≥4
Vomiting	4 (6.8)	0 (0.0)	0 (0.0)
Abdominal distension	3 (5.1)	0 (0.0)	0 (0.0)
Abdominal pain	3 (5.1)	0 (0.0)	0 (0.0)
Anemia	2 (3.4)	2 (3.4)	0 (0.0)
Lymphocyte count decreased	2 (3.4)	1 (1.7)	0 (0.0)
GGT increased	1 (1.7)	1 (1.7)	0 (0.0)
Hepatitis	1 (1.7)	1 (1.7)	0 (0.0)
Hyponatremia	1 (1.7)	1 (1.7)	0 (0.0)

Courtesy of Paul K Paik, MD

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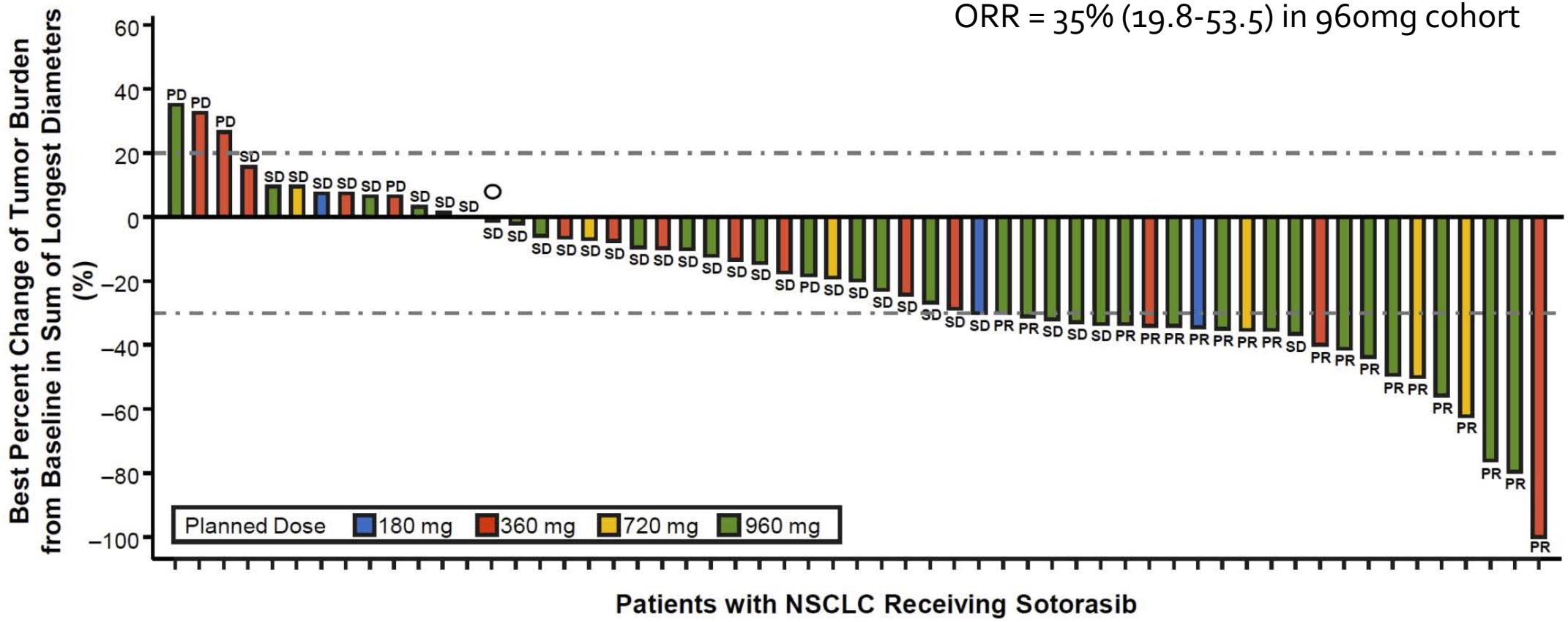
AMG510 (sotorasib) efficacy

ORR = 35% (19.8-53.5) in 960mg cohort



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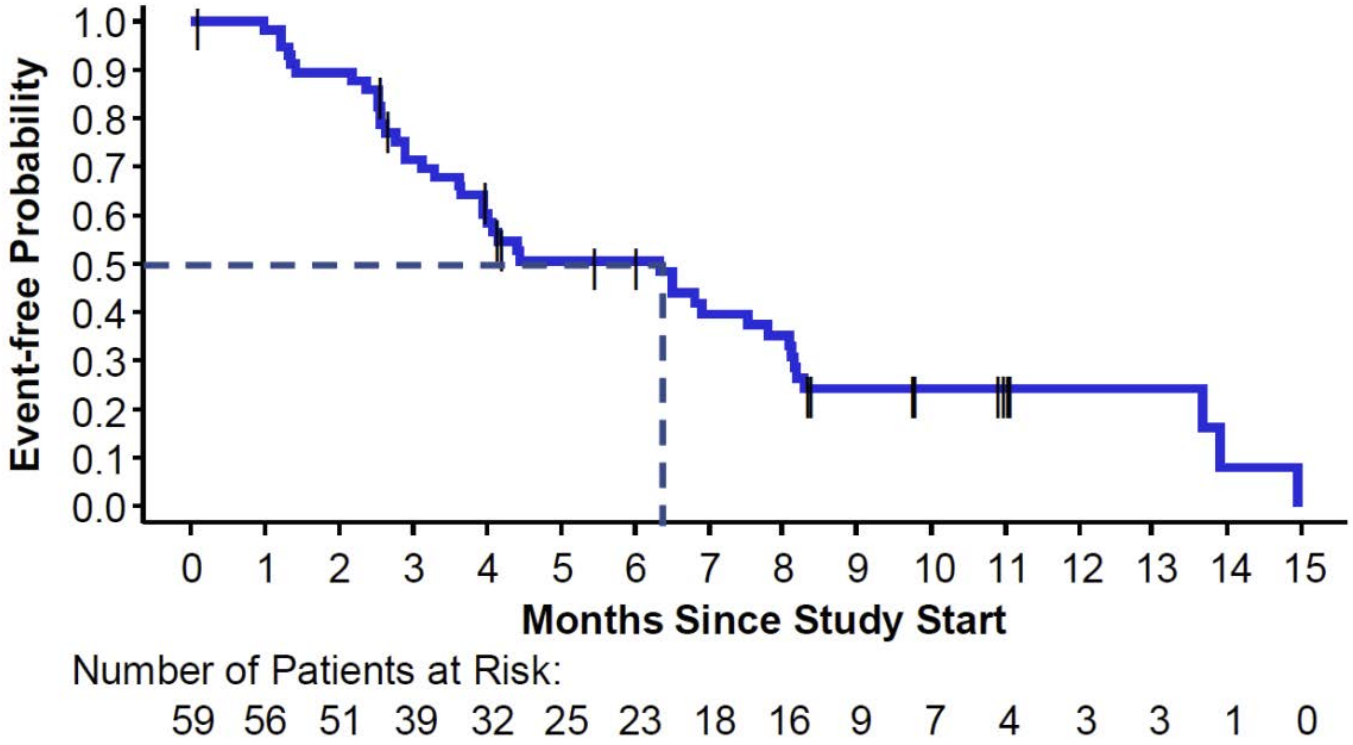
AMG510 (sotorasib) efficacy



Median PFS: 6.3 (range 0.0+ to 14.9) months

Courtesy of Paul K Paik, MD

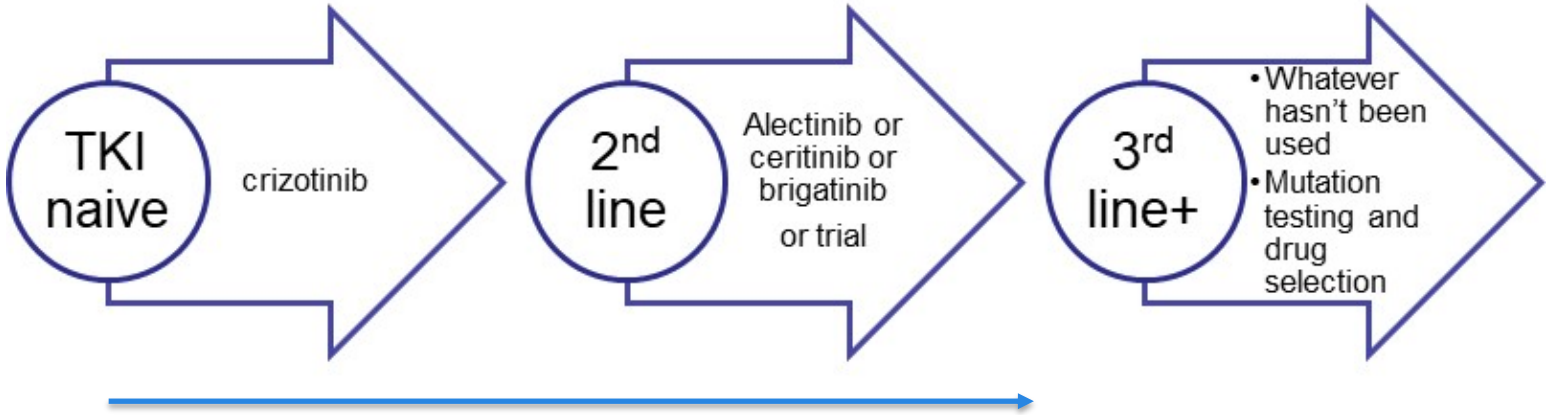
Hong et al. ESMO 2020

Conclusion

- Clinical implications
  - KRAS G12C covalent inhibitors are a new therapeutic approach in the treatment of KRAS G12C mutant cancers
  - Preliminary efficacy in KRAS G12C mutant lung cancer is promising

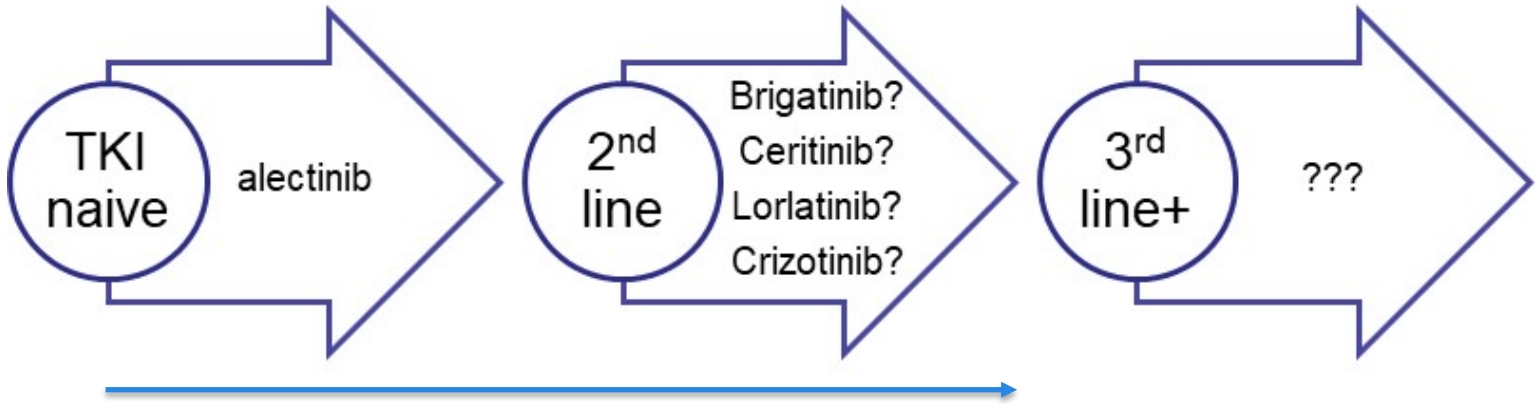
- Future directions
  - Combinatorial targeted strategies are being pursued to boost efficacy
  - Mechanisms of resistance to be further defined

ALK+ lung cancer: sequencing c. 2016

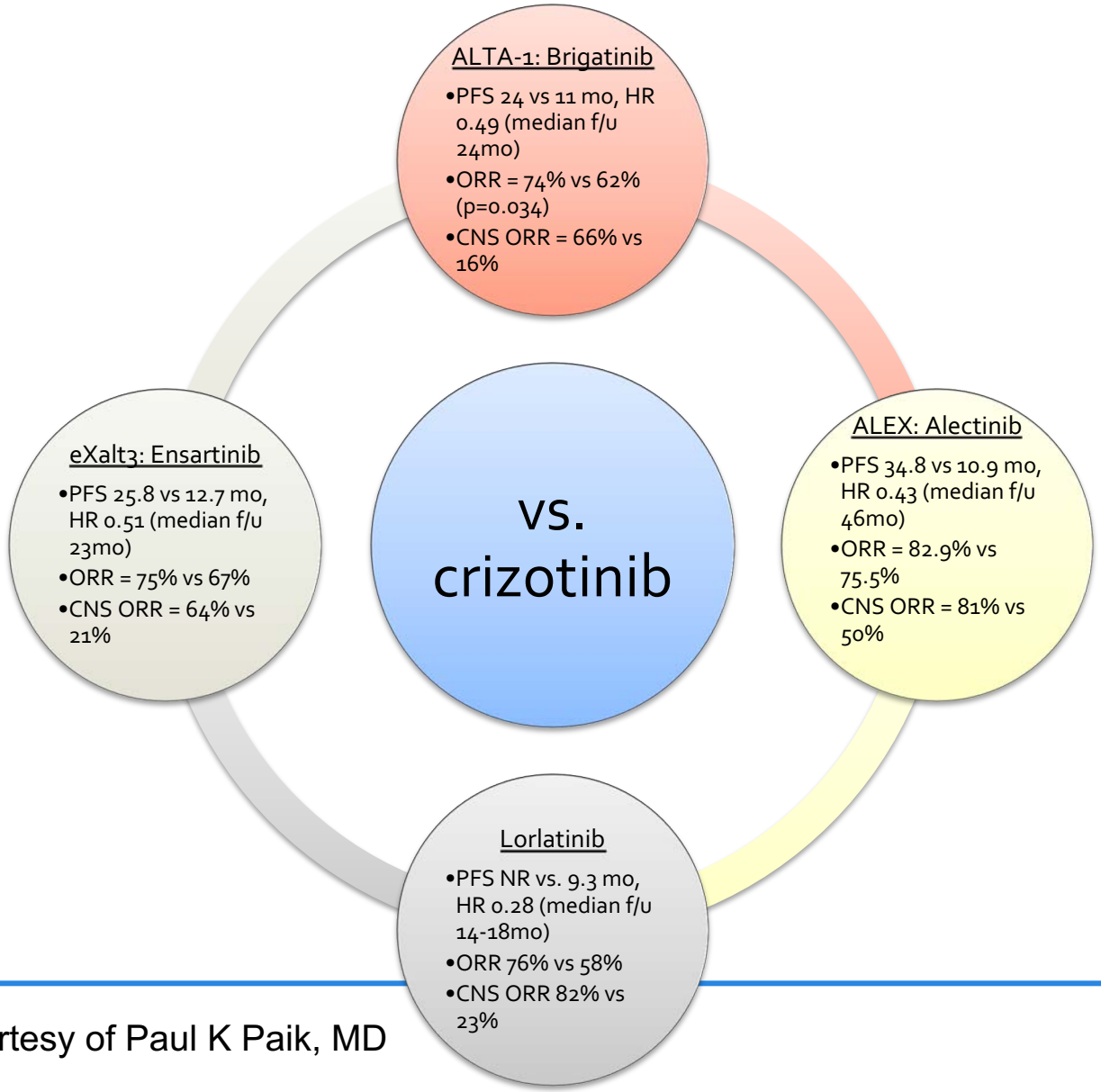


PFS ~ 15-18 mo

ALK+ lung cancer: sequencing c. 2019



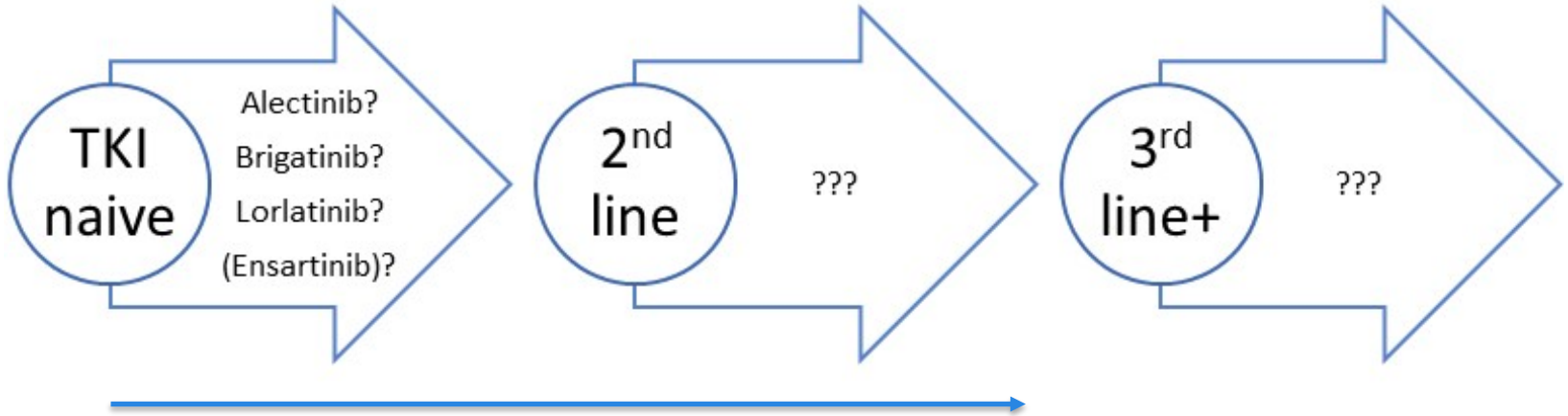
First-line ALK inhibitor trial readouts in 2020- are things clearer?



Courtesy of Paul K Paik, MD

Camidge et al. J Clin Oncol 2020
Mok et al. Ann Oncol 2020
Shaw NEJM 2020
Horn IASLC 2020

ALK+ lung cancer sequencing c. 2021



PFS ~ 30+ mo

Courtesy of Paul K Paik, MD

ALK+ lung cancer sequencing: one rational approach

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Memorial Sloan Kettering Cancer Center

Courtesy of Paul K Paik, MD

Gainor Cancer Disc 2016

Conclusion

- Clinical implications
  - First-line selective ALK TKIs are associated with high ORR, CNS activity, and durable responses
  - Sequencing of ALK drugs remains a question, head to head trials unlikely
  - Side effect profiles differ between drugs
    - Brigatinib: respiratory/pulmonary early events (3-6%)
    - Lorlatinib: elevated lipids, edema, neuropathy, cognitive effects
    - Ensartinib: rash
- Future directions
  - IO-refractory nature of ALK+ lung cancer and ways to overcome
  - Phase 3 crizotinib-refractory brigatinib vs. alectinib trial might provide some insight into how selective ALK inhibitors perform head to head