Uncommon Mutation of Lung Adenocarcinoma

台大胸腔科 吳尚俊

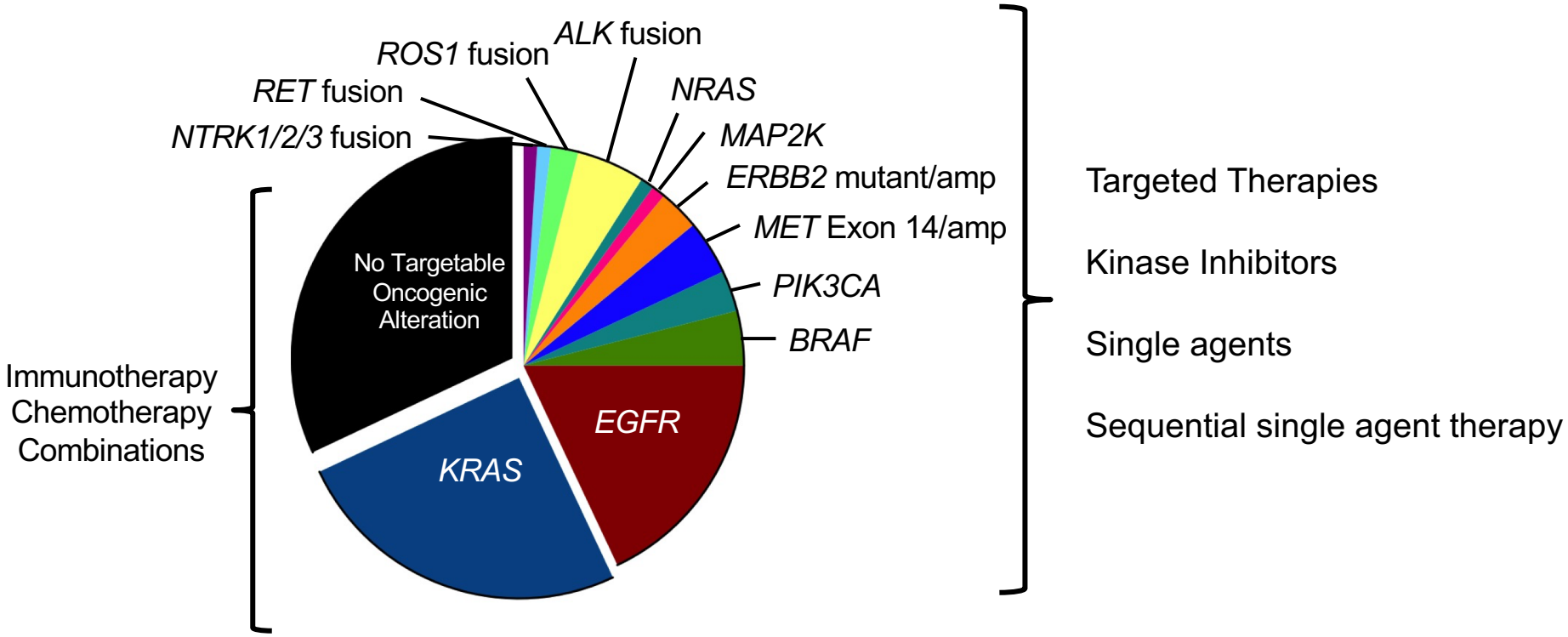
Disclosure

Speaking honoraria from Roche, AstraZeneca and Pfizer.

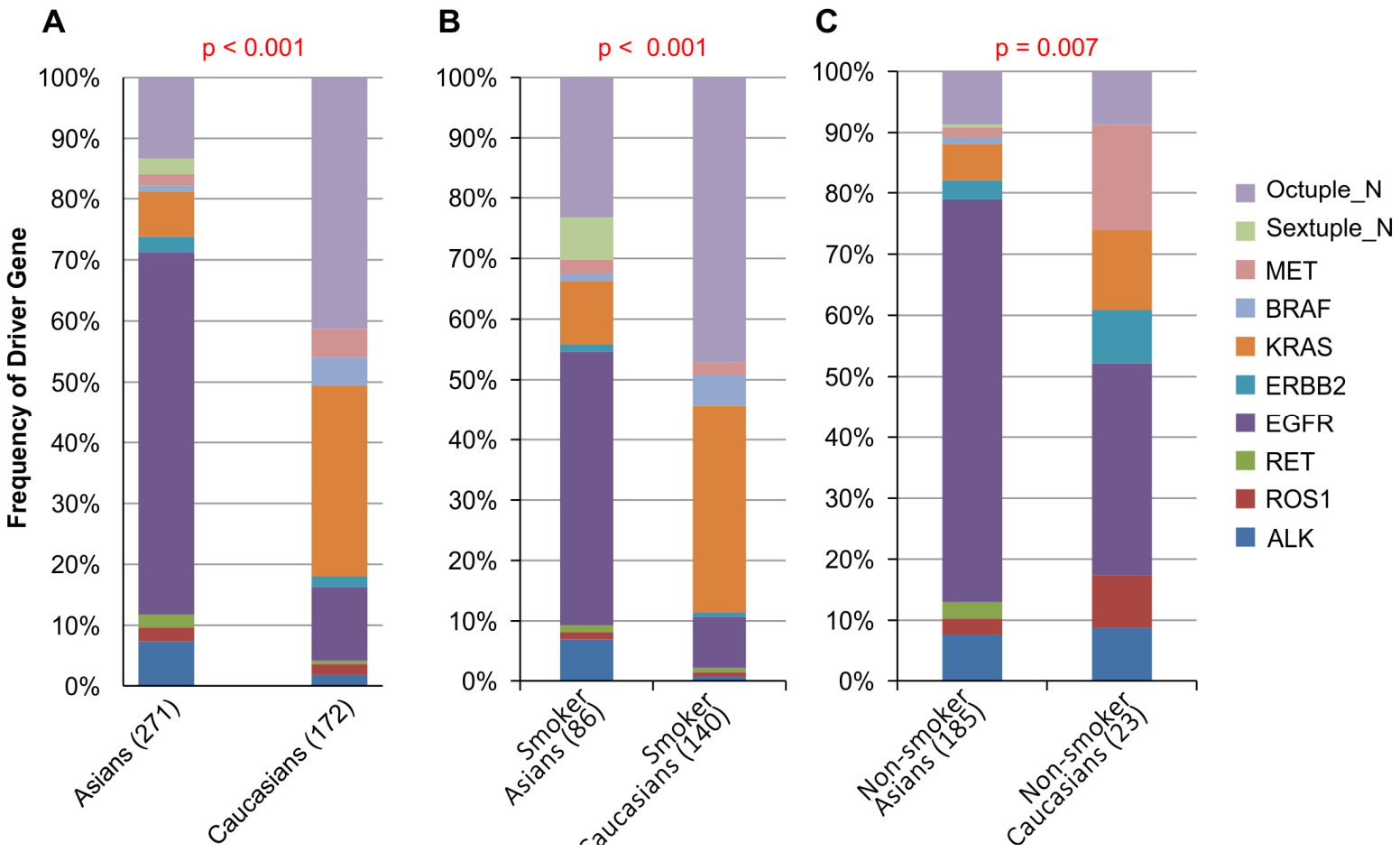
Outline

- Introduction
- ROS1
- NTRK
- KRAS

Precision Therapy for Lung Adenocarcinoma in 2019



Distribution of oncogene mutation frequencies in Asians compared with that in Caucasians



J Thorac Oncol. 2016 (12):2129-2140.

Outline

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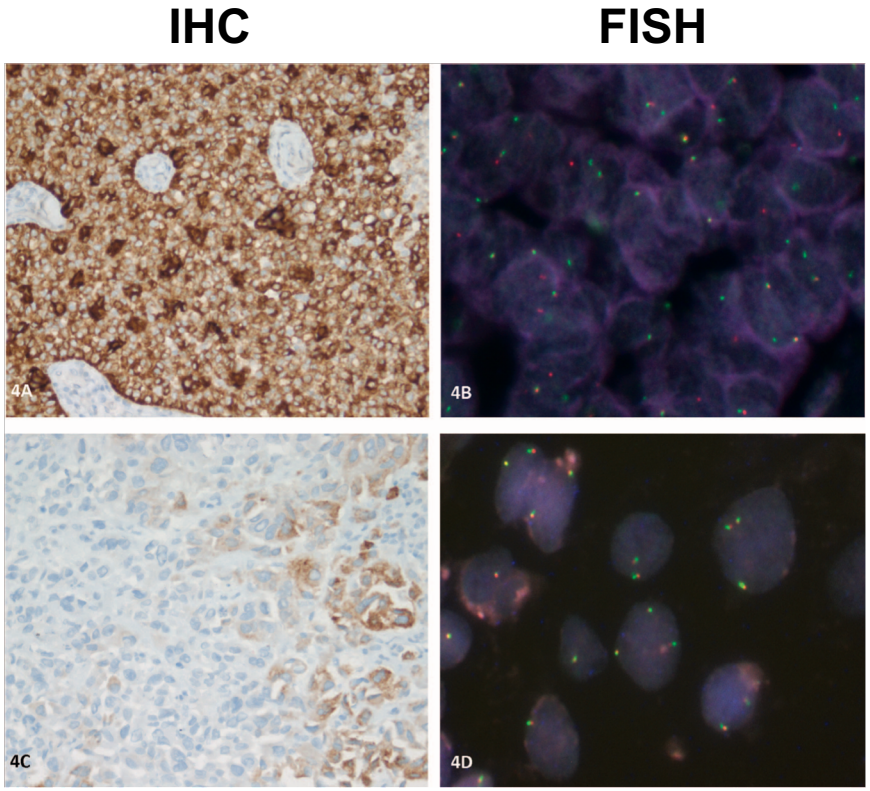
- ROS1
- NTRK
- KRAS

ROS1 Rearrangements in NSCLC

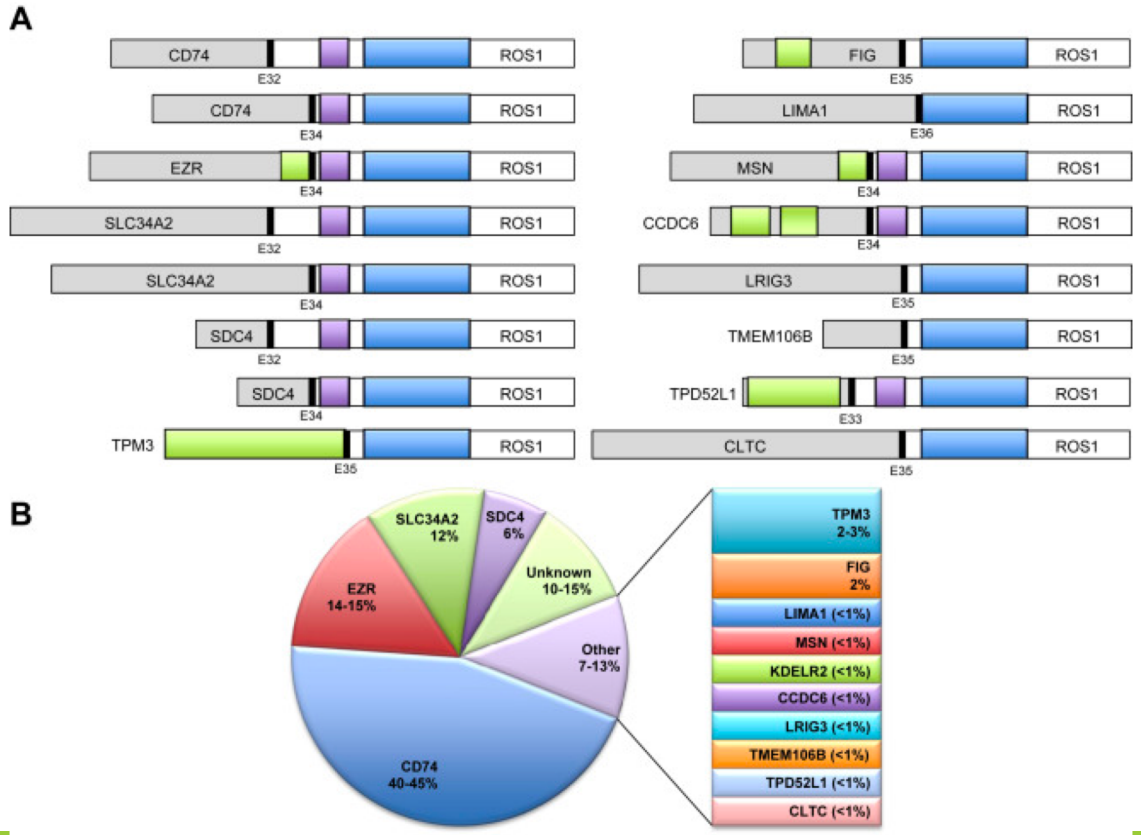
- **Frequency**: 1-2 % overall
- **Most common**:
  - ✓Younger pts
  - ✓Never-smokers
  - ✓Adenocarcinoma
  - ✓High-grade histology
- **Testing:**
  - ✓Vysis break apart FISH (> 15% cells with split signal in 50 nuclei scored)
  - ✓ROS1 NGS, PCR, IHC (not validated)



1. Bergethon. JCO. 2012;30:863. 2. Dugay. Oncotarget. 2017;8:53336. 3. Davies. Clin Cancer Res. 2013;19:4040.
4. Lin. J Thorac Oncol. 2017;12:1611. 5. Lin. J Thorac Oncol. 2017;12:1611.

ROS1 Fusion

- Several variants identified; clinical significance unknown
  - FIG-, CD74-, SCL34A2-, TPM3-, SDC4-, EZR-, LRIG3, KDELR2-, and CCDC6-



Journal of Thoracic Oncology Vol. 12 No. 11: 1611-1625

ROS1 Inhibitors

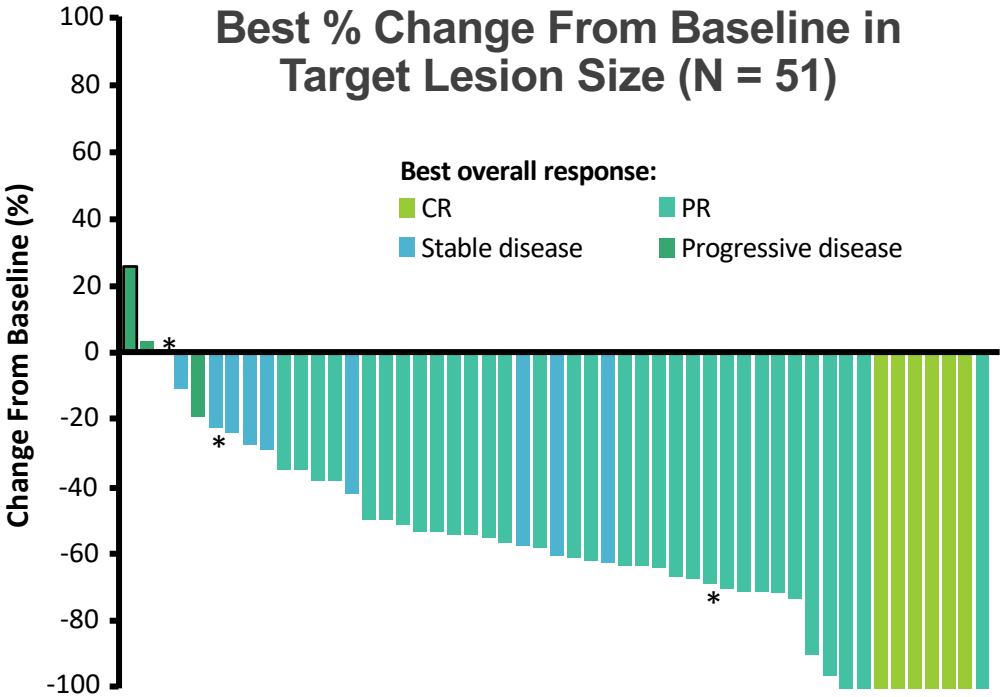
- **Crizotinib:** ***ROS1*** **rearrangement–positive (FDA: 2016/04) or** ***ALK*** **fusion–positive metastatic NSCLC**

- **Entrectinib:** ***ROS1*** **rearrangement–positive NSCLC (FDA: 2019/08) or** ***NTRK*** **fusion–positive solid tumors**

- **Lorlatinib**: metastatic ***ALK*** **fusion–positive NSCLC (2018/11) patients** who have progressed on crizotinib and at least one other ALK inhibitor, alectinib, or ceritinib.

1. Demetri. ESMO 2018. Abstr LBA17. 2. Crizotinib PI. 2018. 3. Lorlatinib PI. 2018.

Crizotinib in *ROS1* Rearrangement–Positive NSCLC



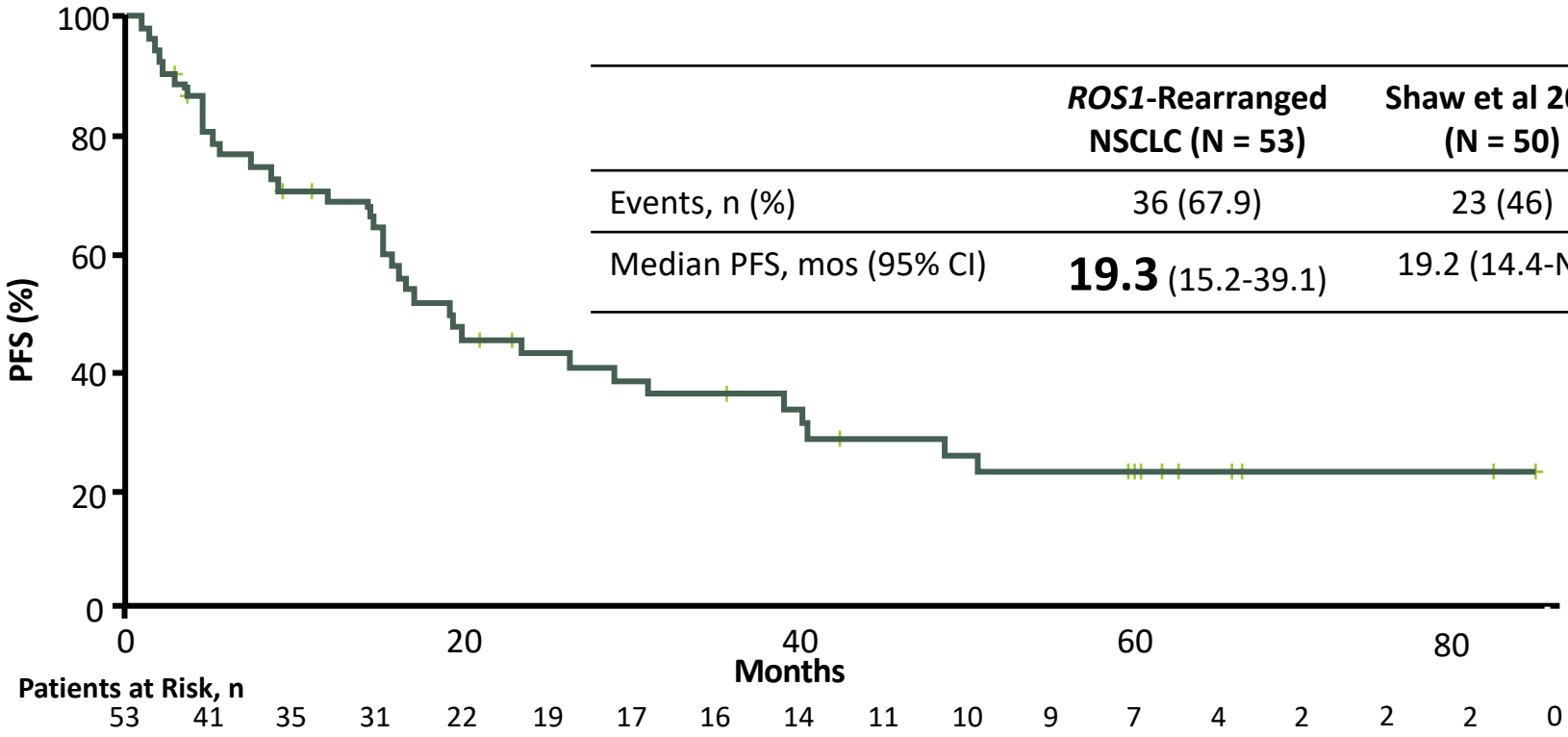
*Indicates tumor assessment by RECIST v1.1.
[a]Excludes 2 patients: one with early death and one with indeterminate response.

ROS1-Rearranged NSCLC 2019 (N = 53)		Shaw et al 2014 (N = 50)
BOR, n (%)		
CR	6 (11.3)	3 (6)
PR	32 (60.4)	33 (66)
SD	10 (18.9)	9 (18)
PD	3 (5.7)	3 (6)
NE[a]	2 (3.8)	2 (4)
ORR, %	71.7	72.0
95% CI	57.7-83.2	58-84
Median TTR, wks	7.9	7.9
(range)	4.3-103.6	4.3-32.0

Responses could not be evaluated in 2 patients because of early death or indeterminate response.

Shaw. NEJM. 2014;371:1963.
Ann Oncol. 2019;30(7):1121-1126.

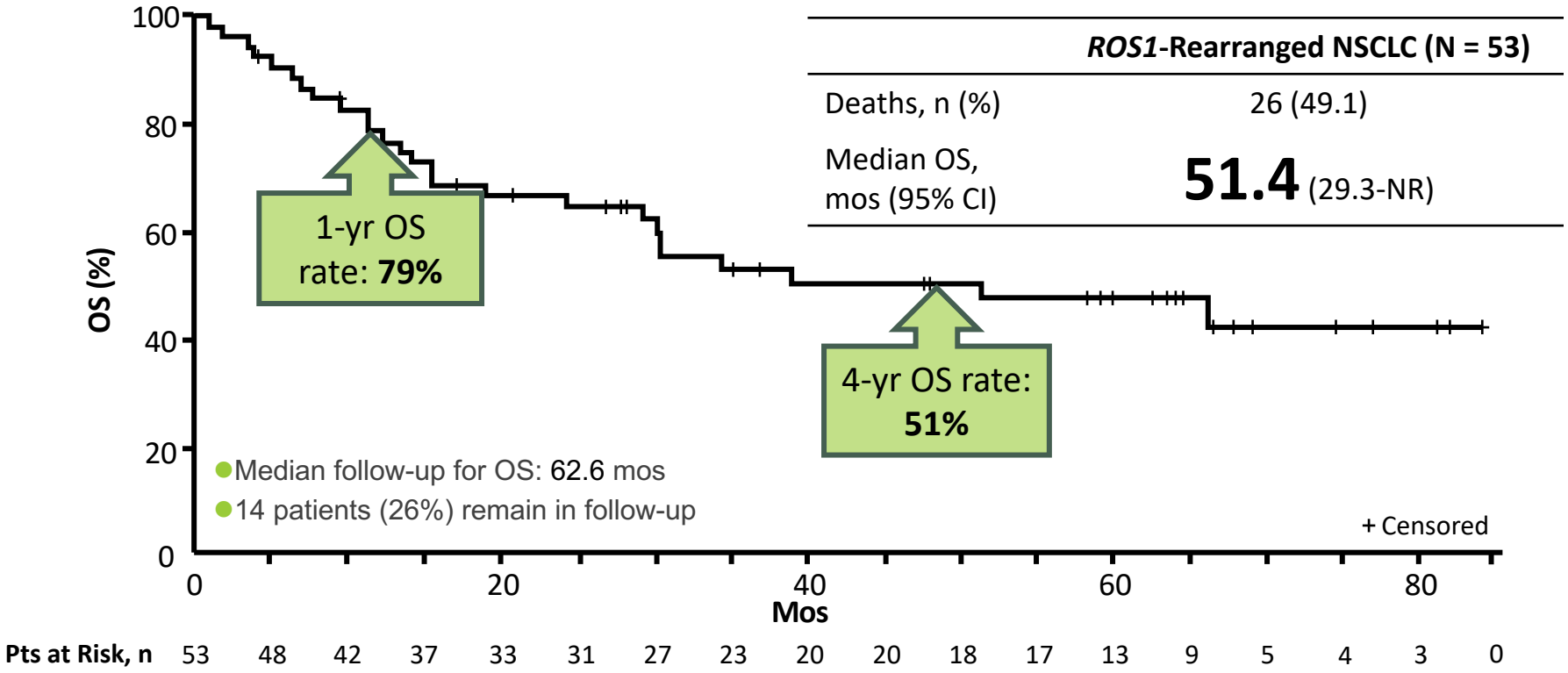
Crizotinib in *ROS1* Rearrangement–Positive NSCLC



	ROS1-Rearranged NSCLC (N = 53)	Shaw et al 2014 (N = 50)
Events, n (%)	36 (67.9)	23 (46)
Median PFS, mos (95% CI)	**19.3** (15.2-39.1)	19.2 (14.4-NR)

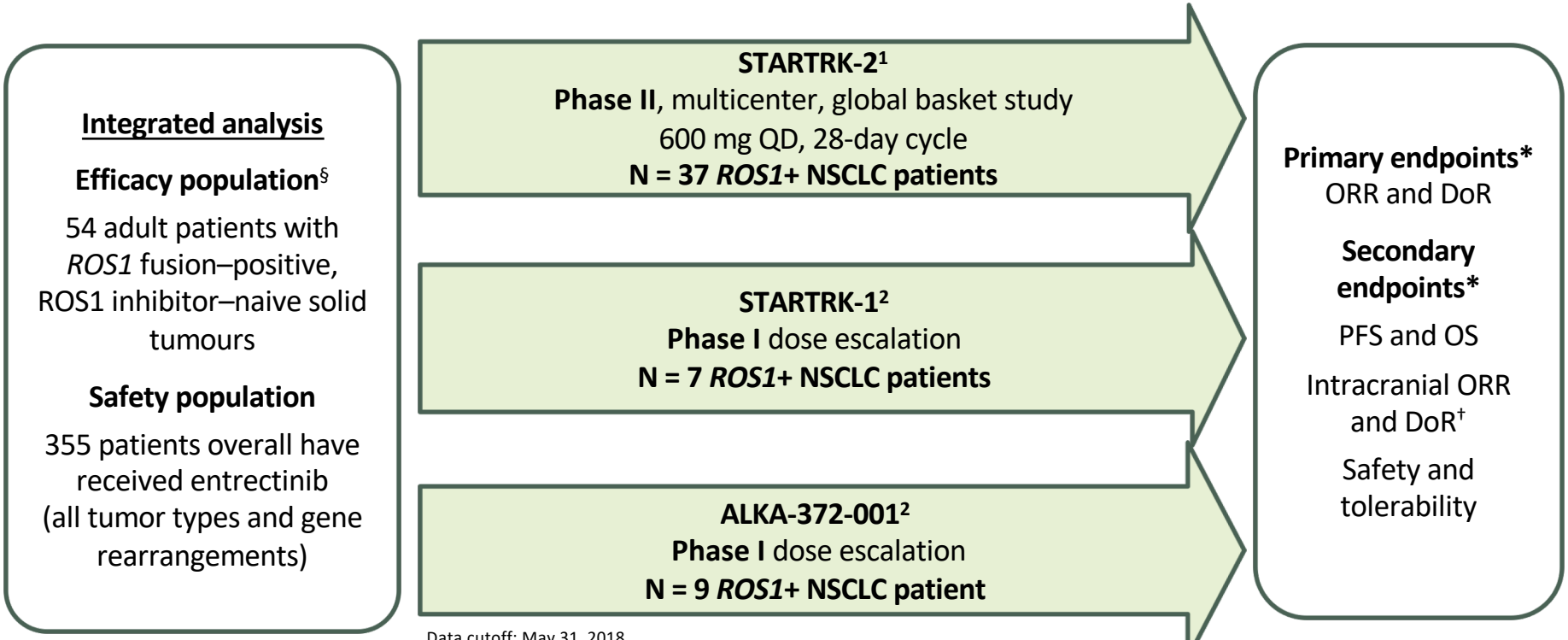
Shaw. NEJM. 2014;371:1963.
Ann Oncol. 2019;30(7):1121-1126.

Crizotinib in *ROS1* Rearrangement–Positive NSCLC



Ann Oncol. 2019 Jul 1;30(7):1121-1126.

Integrated Efficacy and Safety Analysis of Entrectinib: *ROS1* Fusion–Positive NSCLC



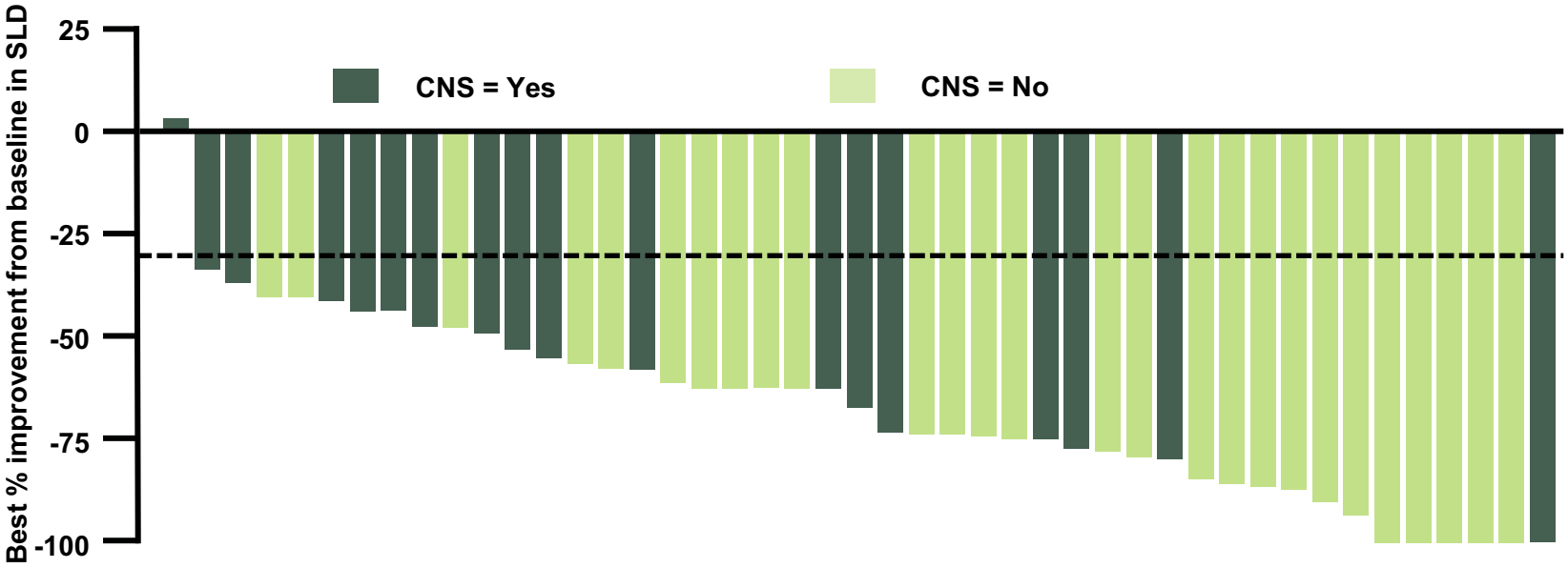
Data cutoff: May 31, 2018

§Patients with at least 6 mos of follow-up

*Per blinded independent central review measured by RECIST v1.1

†Patients with measurable and non-measurable CNS lesions at baseline

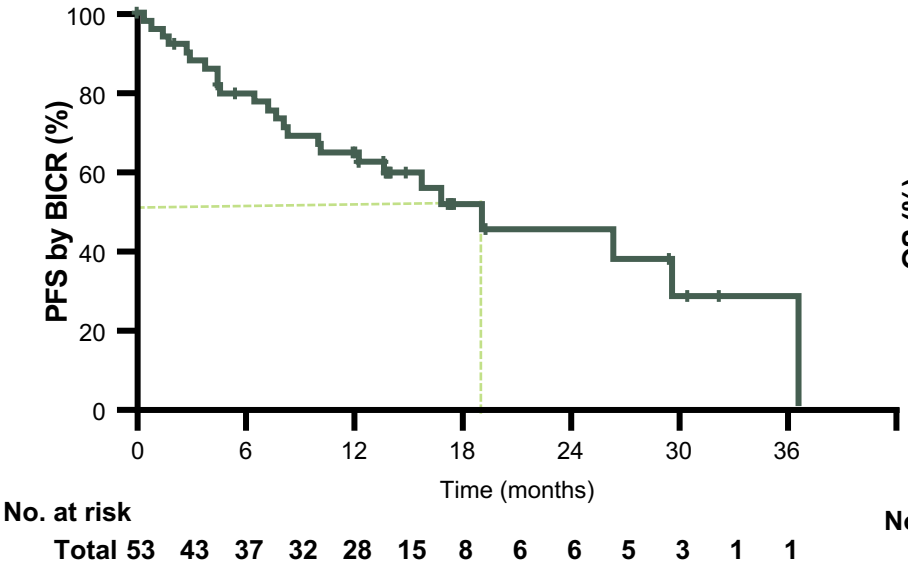
Systemic Efficacy of Entrectinbib



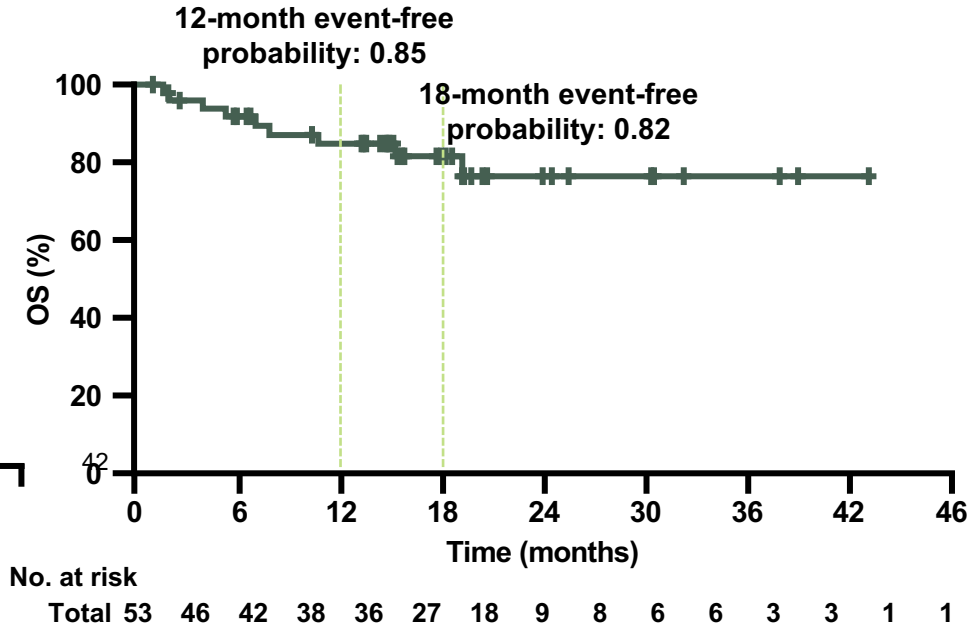
n (%)	Total (n=53)	CNS disease present at baseline† (n=23)	CNS disease absent at baseline† (n=30)
ORR	**41 (77.4)**	**17 (73.9)**	**24 (80.0)**
CR	3 (5.7)	0	3 (10.0)

PFS & OS OF ENTRECTINIB

PFS: 19.0 months



OS: NE months



CNS(-): 26.3 mo.
CNS(+): 13.6 mo.

Safety Profile of Entrectinib

- In patients who received at least one dose of entrectinib (N=355), entrectinib was well tolerated with a manageable safety profile[1]
- Most treatment-related AEs were grade 1/2
- Treatment-related AEs leading to:
  - dose reduction: 27.3%
  - discontinuation from treatment: 3.9%
- No grade 5 treatment-related AEs were reported

Most common (≥10%) treatment-related AEs, n (%)	Safety evaluable population (N=355)
Dysgeusia	147 (41.4)
Fatigue	99 (27.9)
Dizziness	90 (25.4)
Constipation	84 (23.7)
Diarrhea	81 (22.8)
Nausea	74 (20.8)
Weight increased	69 (19.4)
Paresthesia	67 (18.9)
Blood creatinine increased	54 (15.2)
Myalgia	54 (15.2)
Edema peripheral	50 (14.1)
Vomiting	48 (13.5)
Arthralgia	44 (12.4)
Anemia	43 (12.1)
AST	39 (11.0)

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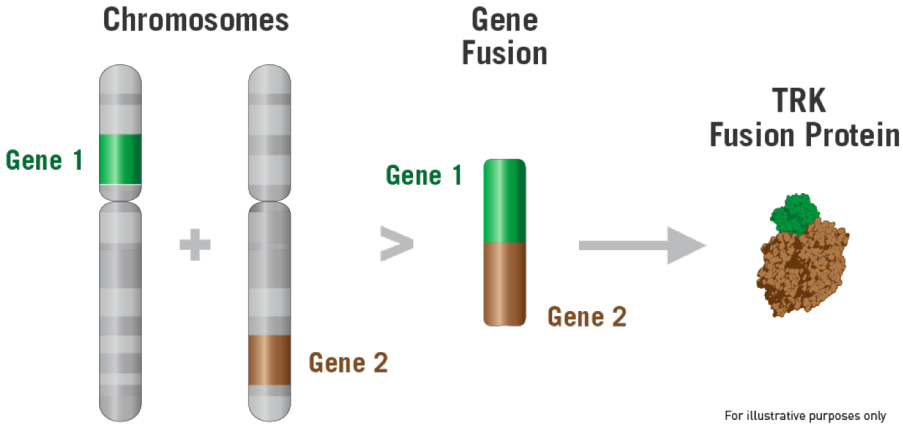
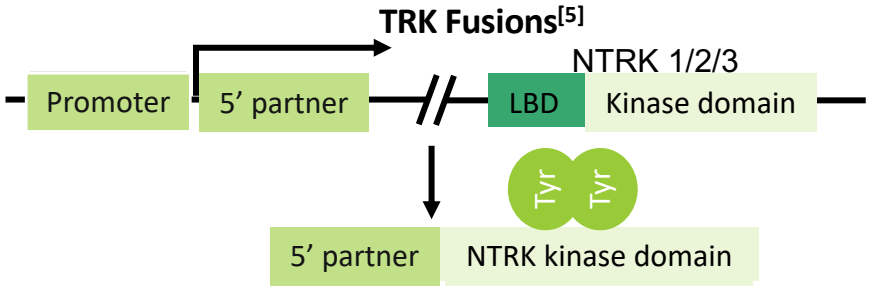
TRK: Role in Normal Biology and Cancer

- **NTRK: The neurotrophic tyrosine receptor kinases**
- **TRK receptors:**
  - Adult nervous system
  - Embryonal development
  - Rarely expressed in normal nonneuronal or cancerous tissues



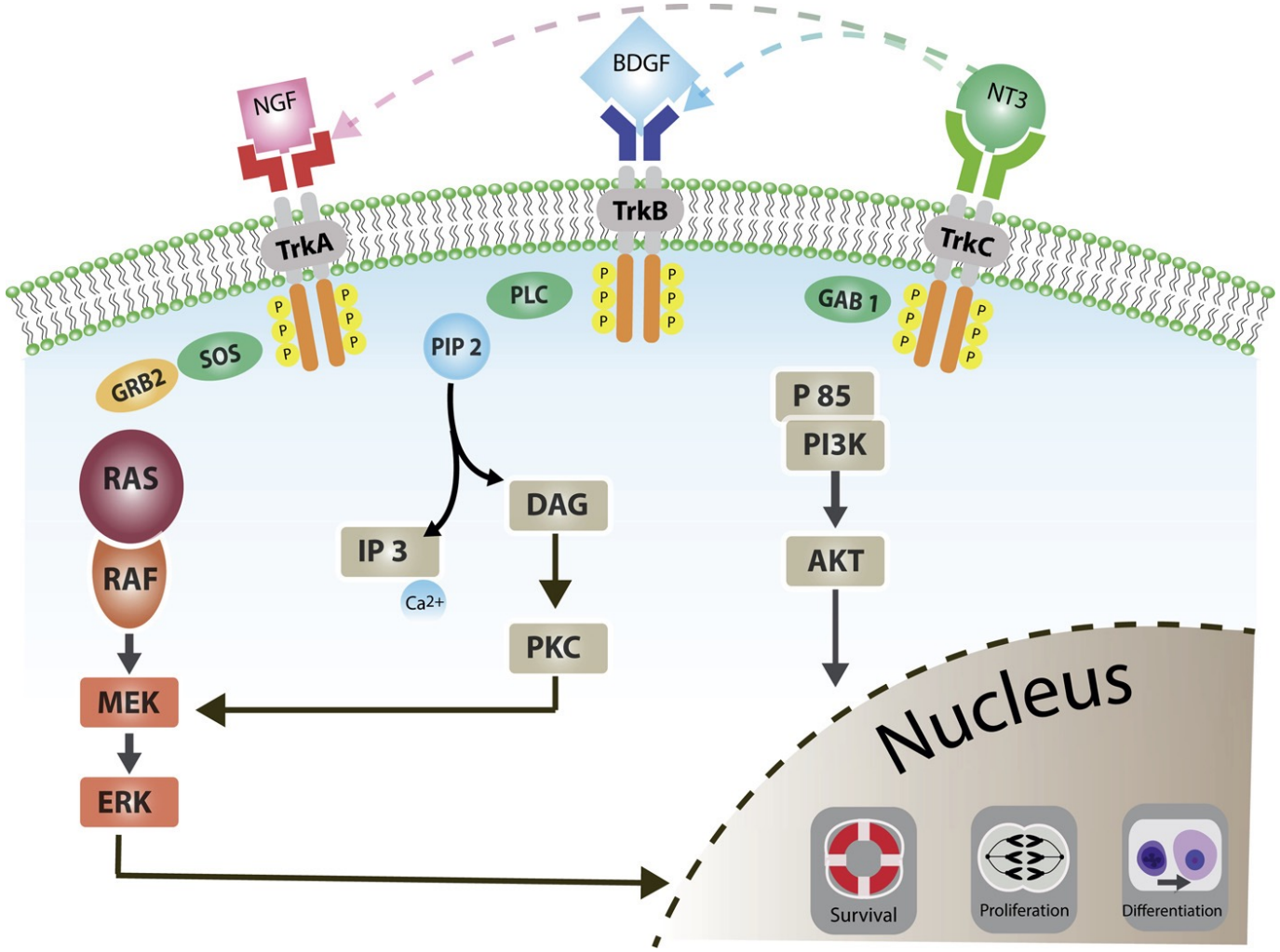
NT Receptor	Gene	Normal Function in Adults
TRKA	*NTRK1*	Pain, thermoregulation
TRKB	*NTRK2*	Movement, memory, mood, appetite, body weight
TRKC	*NTRK3*	Proprioception



Fusions of any *NTRK* genes (*NTRK1/2/3*) are powerful oncogenic drivers

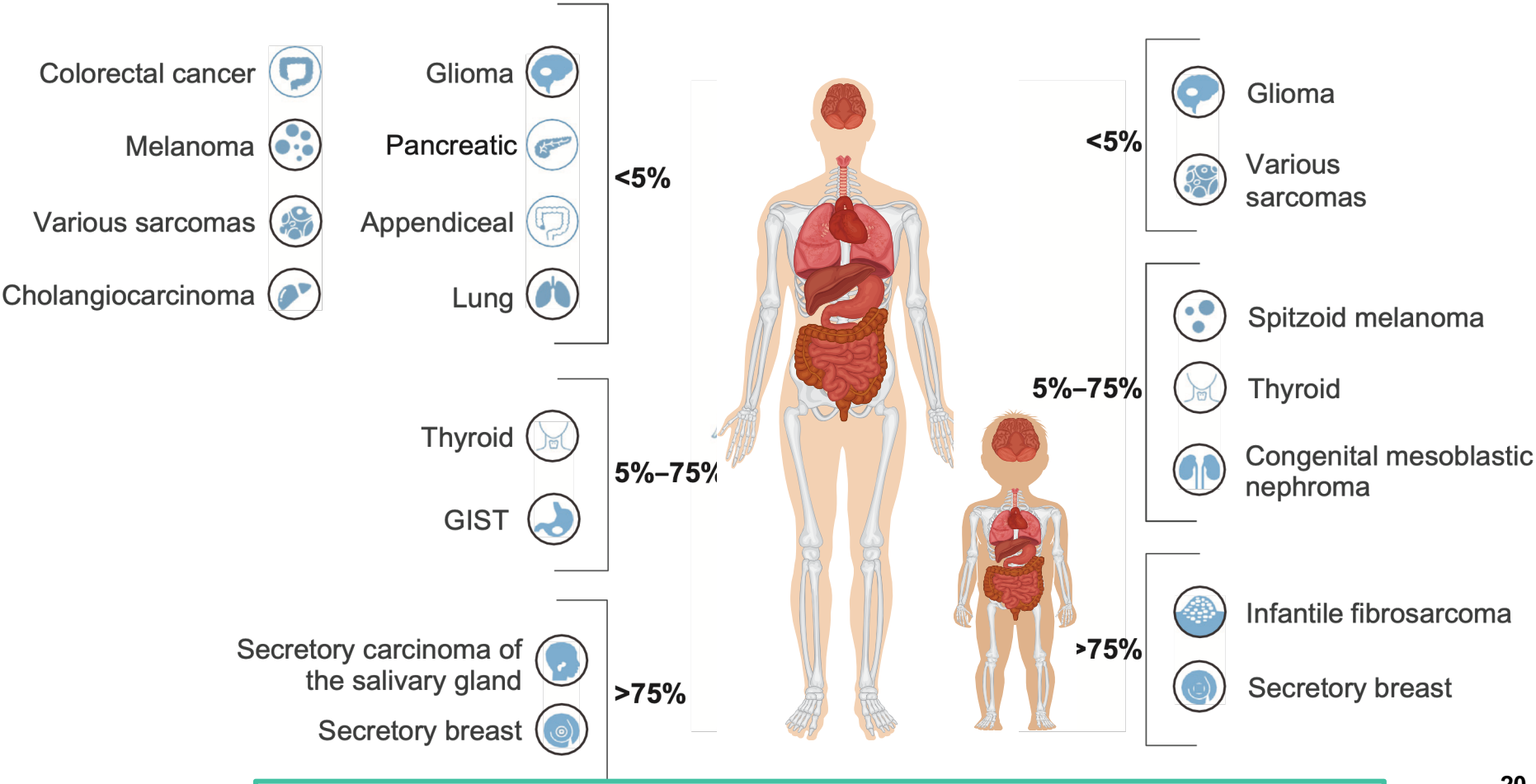
1. Amatu. ESMO Open. 2016;1:e000023. 2. Loewenthal. Pediatr Res. 2005;57:587. 3 . Razzoli. Genes Brain Behav. 2011;10:424. 4. Inoue. Blood Cells Mol Dis. 2003;30:157. 5. Hyman. ASCO 2017. Abstr LBA2501

TRK Signaling Pathway



Pathology - Research and Practice 215 (2019) 152572

TRK Fusions Observed Across Diverse Cancer Types in Both Adults and Children



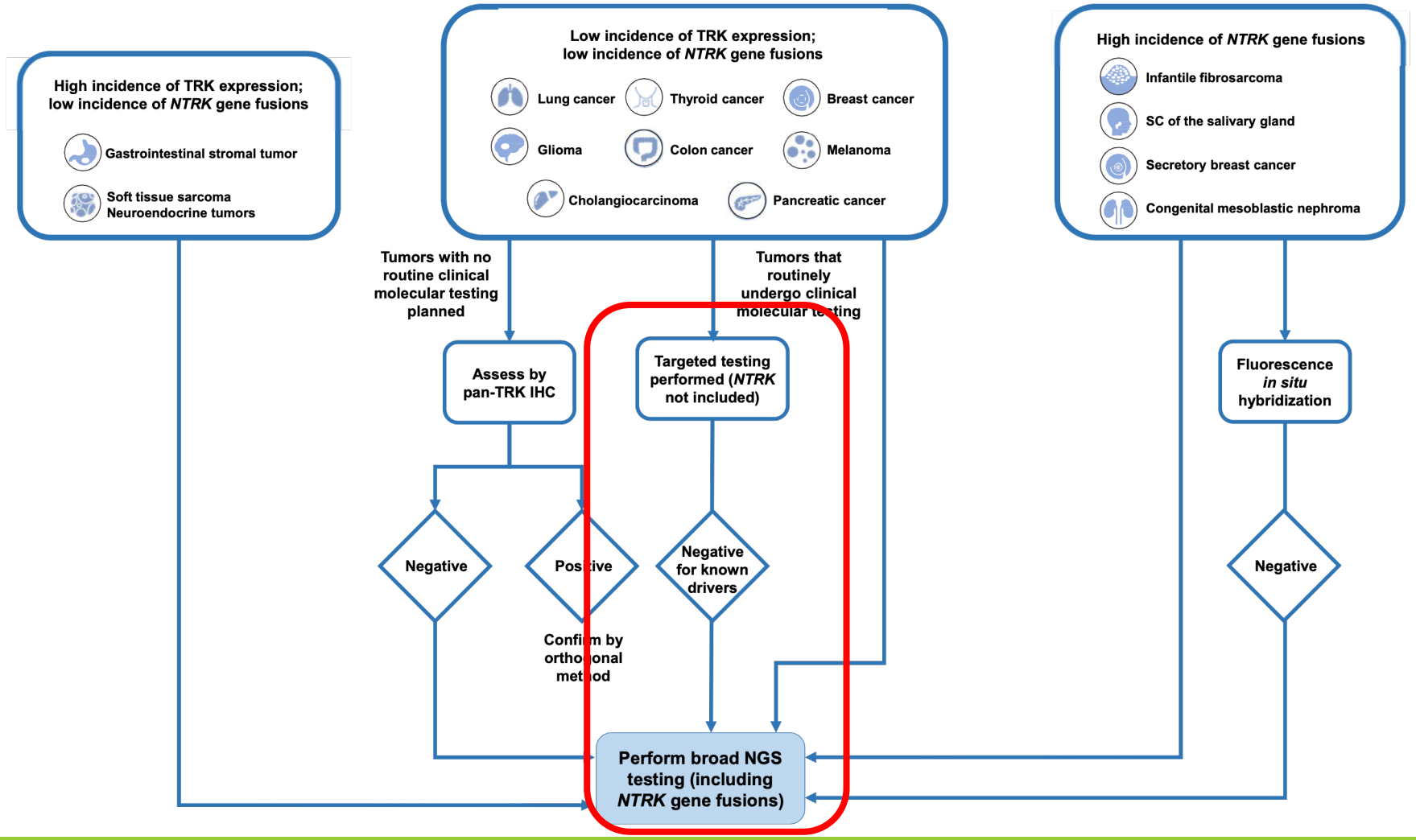
Estimated 1500-5000 patients with *NTRK* fusion–positive cancers in the US annually

J Mol Diagn 2019, 21: 553e571

Diagnosis TRK Fusion

	IHC	FISH	NGS
Advantages	✓ Rapid results ✓ Detects transcribed and translated events only ✓ Low cost as single test	✓ Rapid results	✓ Potential for multiplexed testing ✓ Less depletion of tissue ✓ Fusion partner and position are defined
Disadvantages	– Depletion of tissue – Fusion partner and position unknown – Less well-validated currently	– Depletion of tissue – Fusion partner and position unknown – Can be difficult to interpret	– Longer wait time for results – Cost

DIAGNOSIS OF TRK FUSIONS



J Mol Diagn 2019, 21: 553e571

TRK Inhibitors

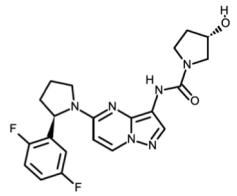
- **Larotrectinib**: solid tumors with a *NTRK* gene fusion (FDA: 2018/12)

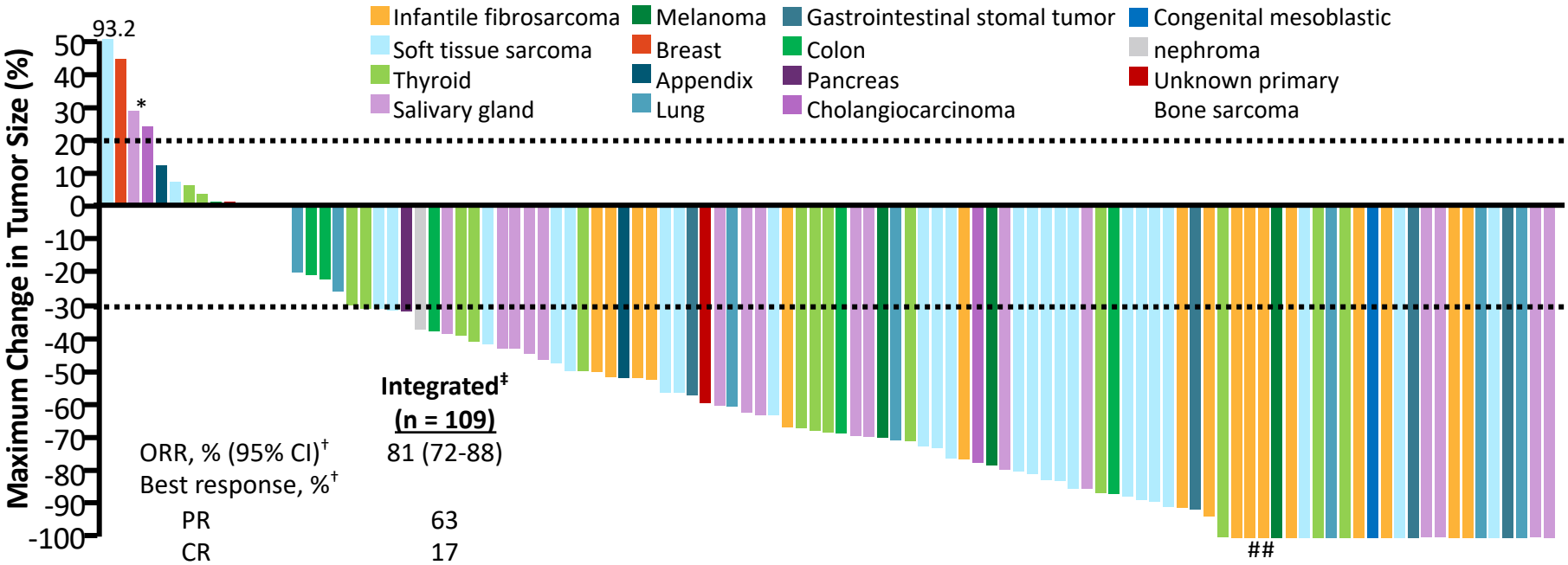
- **Entrectinib**: *NTRK* fusion–positive solid tumors and metastatic *ROS1*+ NSCLC (FDA: 2019/08)

- **LOXO-195**: second-generation TKI with activity against multiple TRK kinase domain mutations in patients with solid tumors with a *TRK* gene fusion

1. Larotrectinib PI. 2018. 2. Demetri. ESMO 2018. Abstr LBA17. 3. Hyman. AACR 2019. Abstr CT127.

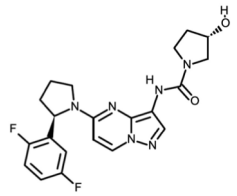
Larotrectinib: Antitumor Activity Across Tumor Types

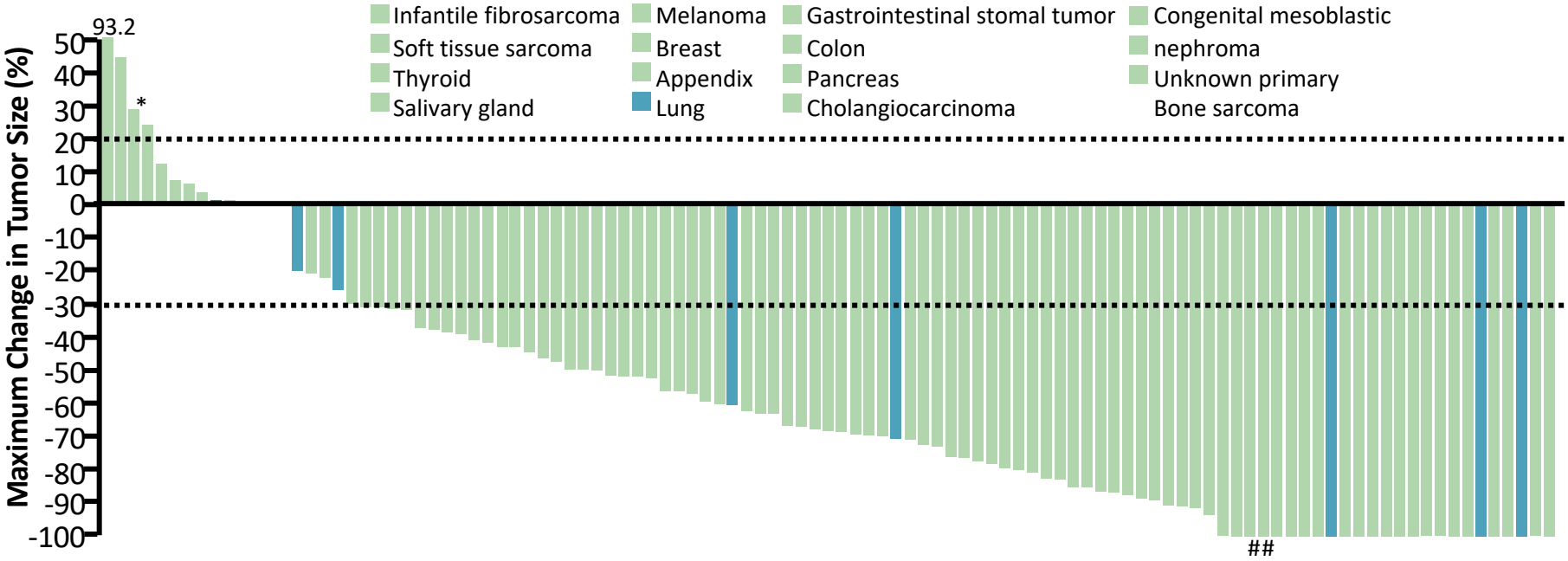




Lassen. ESMO 2018. Abstr 279.

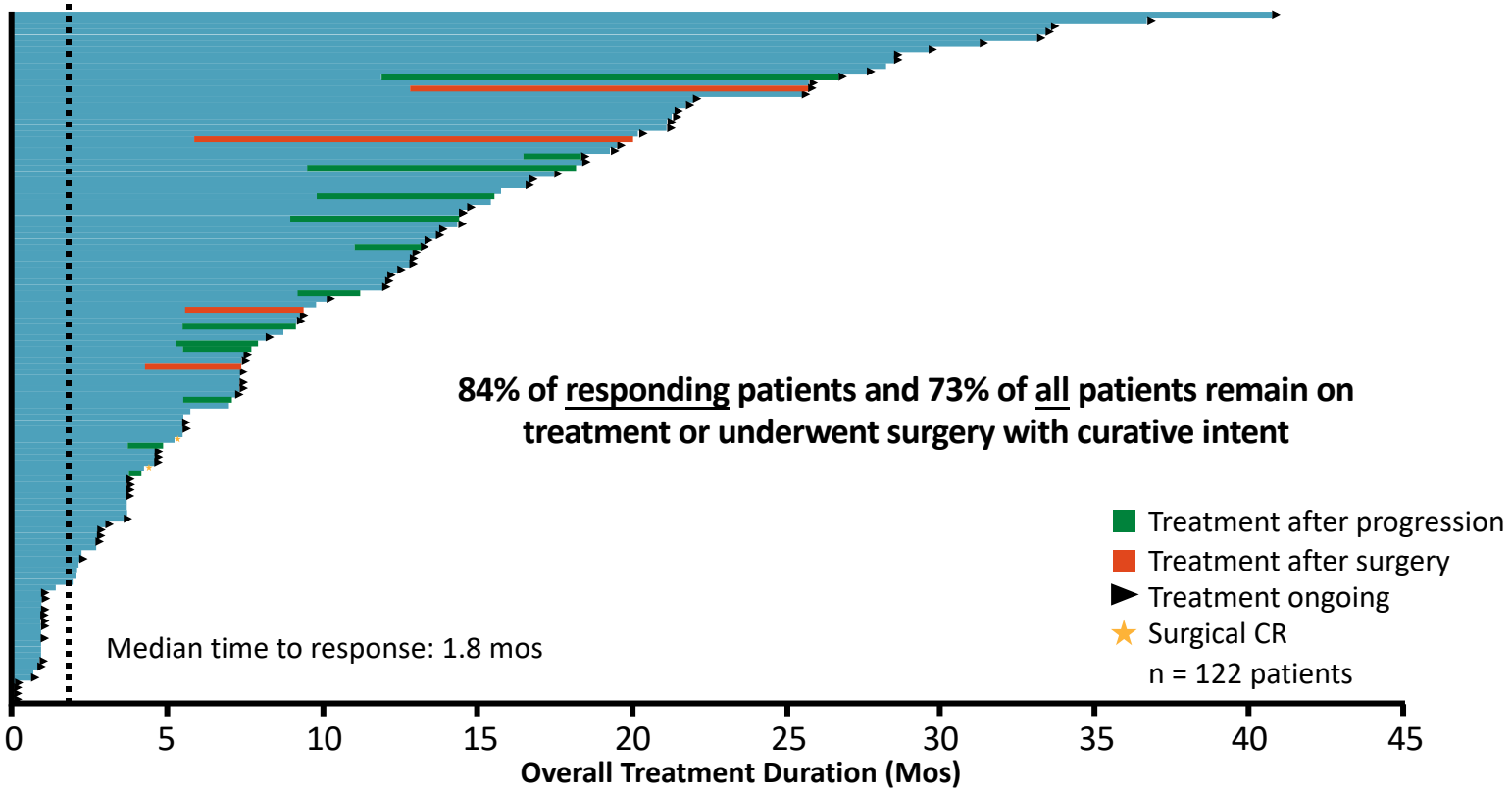
Larotrectinib: Antitumor Activity in Lung Cancer





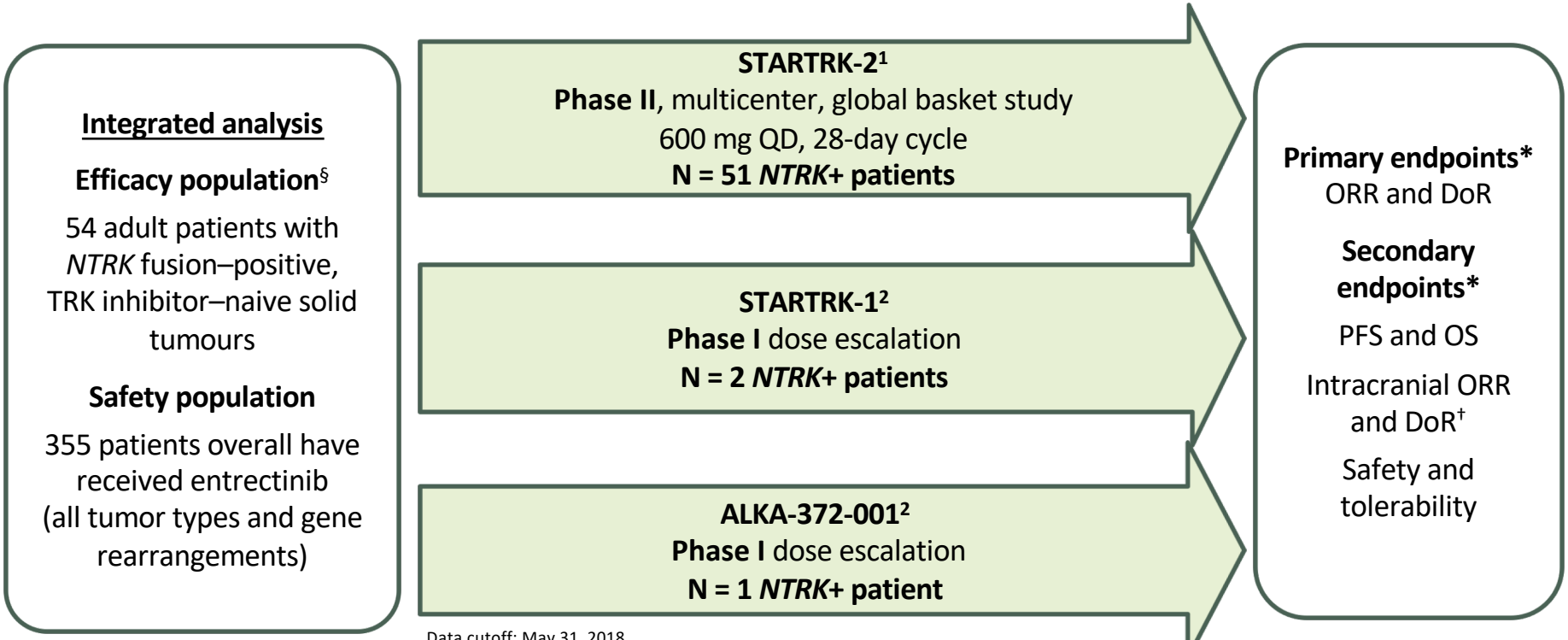
Lassen. ESMO 2018. Abstr 279.

Larotrectinib: Duration of Treatment



Lassen. ESMO 2018. Abstr 279.

Integrated Efficacy and Safety Analysis of Entrectinib: *NTRK* Fusion–Positive Solid Tumors



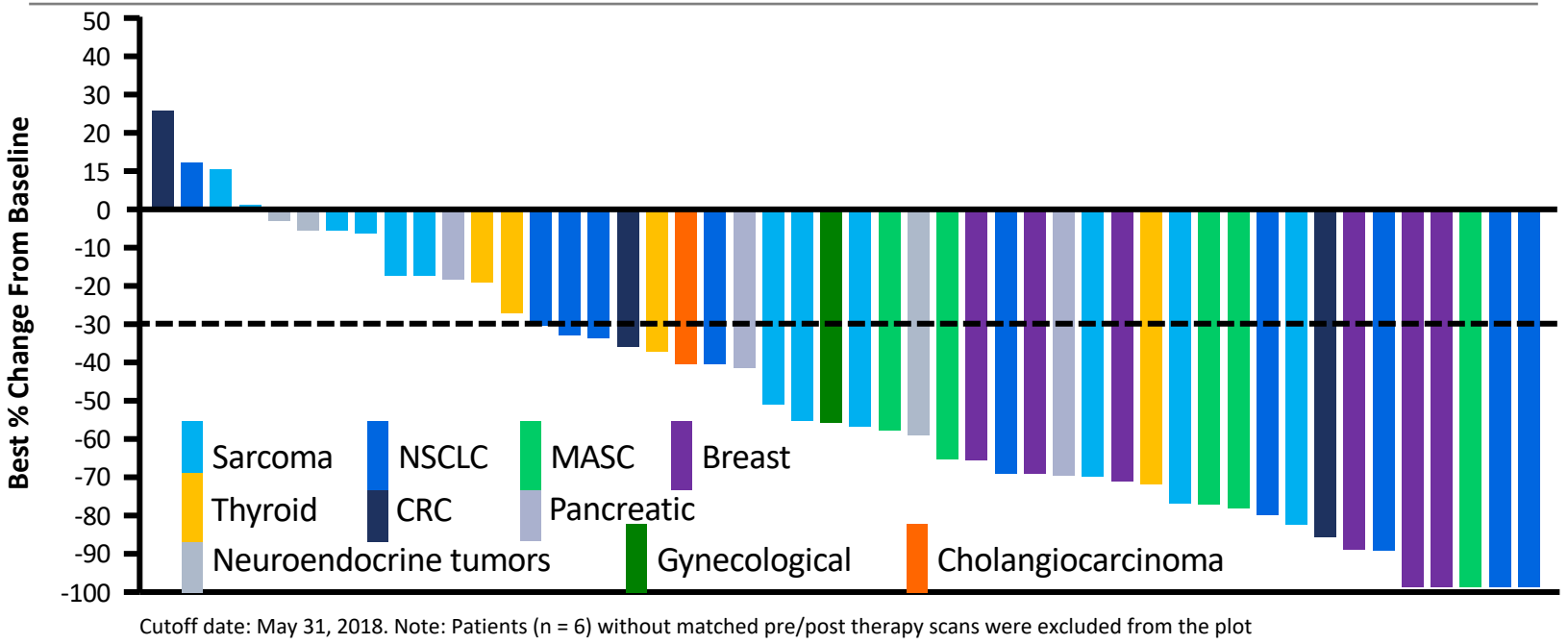
Data cutoff: May 31, 2018

§Patients with at least 6 mos of follow-up

*Per blinded independent central review measured by RECIST v1.1

†Patients with measurable and non-measurable CNS lesions at baseline

Entrectinib in *NTRK* Fusion–Positive Solid Tumors: Individual Patient Responses by Tumor Type

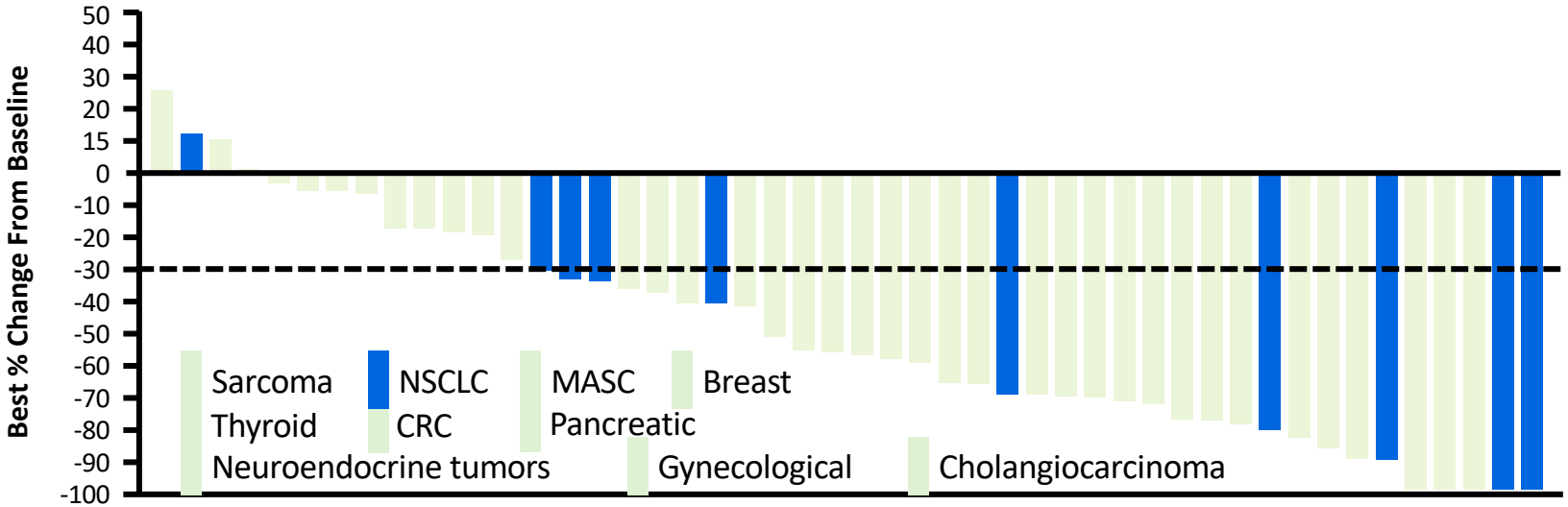


Cutoff date: May 31, 2018. Note: Patients (n = 6) without matched pre/post therapy scans were excluded from the plot

Results per blinded independent central review (BICR)

	***NTRK*+ Patients (n = 54)**
ORR, % (95% CI)	**57.4** (43.2-70.8)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)

Entrectinib in *NTRK* Fusion–Positive NSCLC

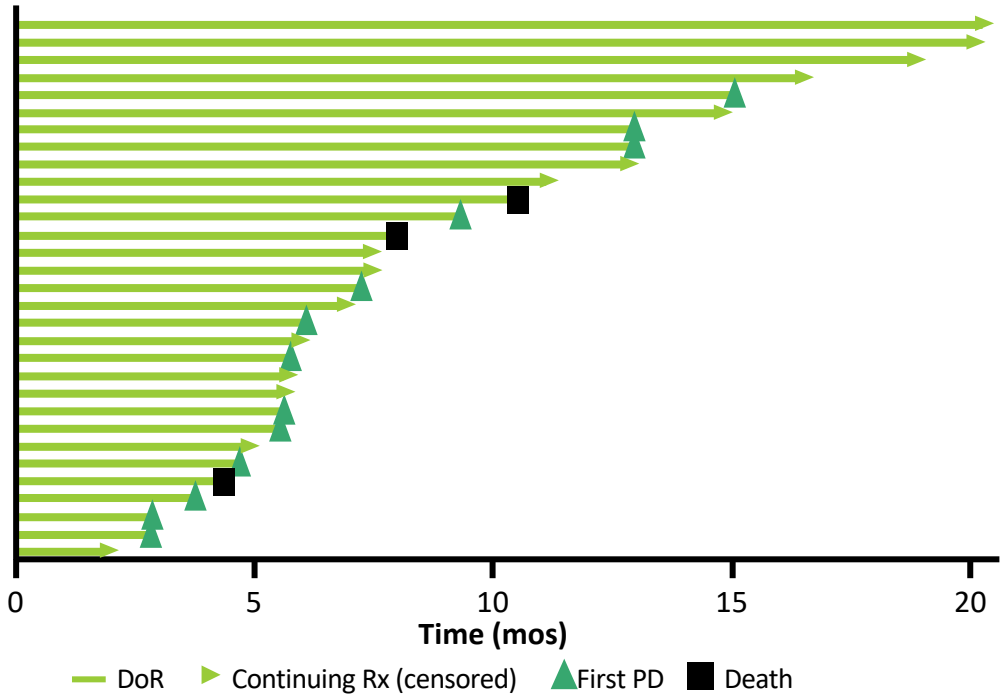


Cutoff date: May 31, 2018. Note: Patients (n = 6) without matched pre/post therapy scans were excluded from the plot

Results per blinded independent central review (BICR)

	***NTRK*+ NSCLC (n = 10)**
ORR, % (95% CI)	70.0 (34.8-93.3)
CR	1
PR	6
SD	1
PD	0
Missing or unevaluable	2

Entrectinib Activity in *NTRK* Fusion–Positive Solid Tumors: Duration of Response, PFS and OS



	DoR	PFS	OS
Patients included in analysis, n	31	54	54
Patients with event, n (%)	16 (51.6)	29 (53.7)	16 (29.6)
PD, n Death, n	13 3	20 9	-- 16
Median , mos	**10.4**	**11.2**	**20.9**
95% CI for median	7.1-NE	8.0-14.9	14.9-NE

Median duration of survival follow-up (PFS, OS): 12.9 mos
Median duration of response follow-up (DoR): 13.1 mos

Entrectinib Activity in *NTRK* Fusion + Solid Tumors: Intracranial ORR in Patients With CNS Mets at Baseline

	Patients With CNS Mets at Baseline (n = 11) per BICR
Intracranial ORR, n (%) (95% CI)	**6 (54.5)** (23.4-83.3)
CR	**3 (27.3)**
PR	3 (27.3)
SD	1 (9.1)
PD	1 (9.1)
Non CR/PD, Missing or unevaluable	3 (27.3)
Intracranial median DoR, mos (95% CI)	NE (5.0-NE)
Intracranial median PFS, mos (95% CI)	**14.3** (5.1-NE)

Demetri. ESMO 2018. Abstr LBA17.

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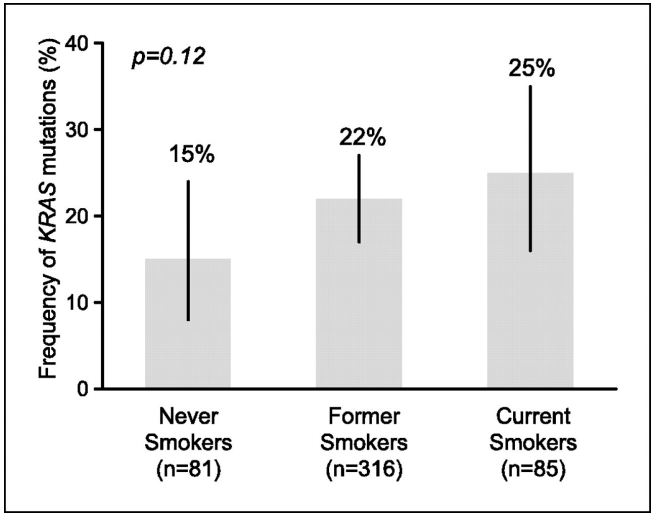
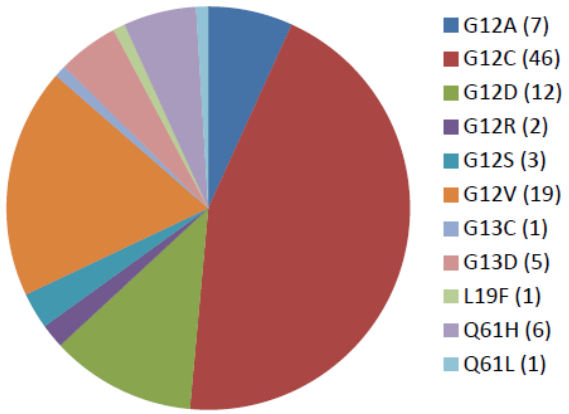
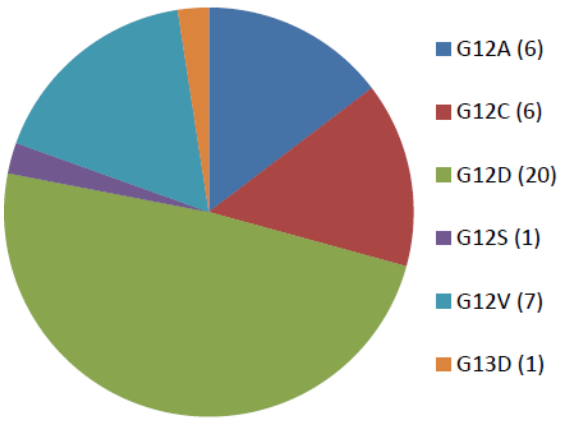
Prevalence and type of KRAS mutation in Lung adenocarcinoma





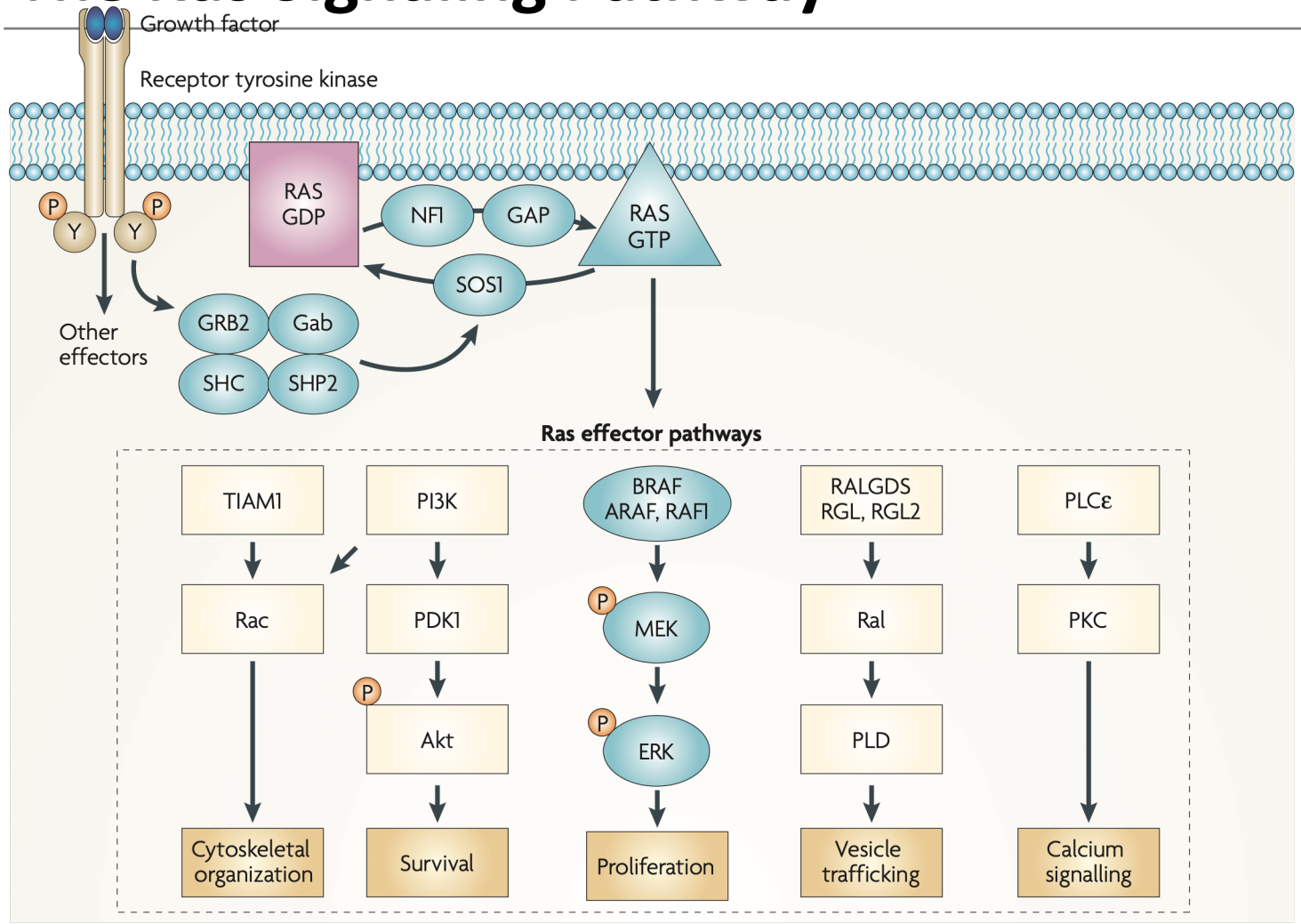
Current/Former Smokers



Never Smokers

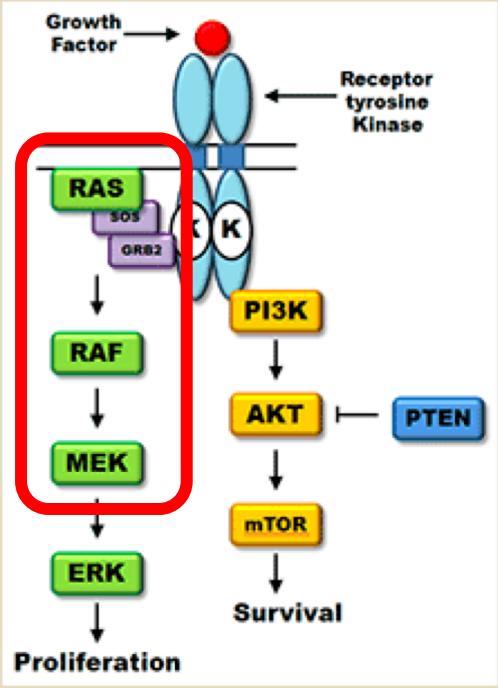
Riely et al. CCR 2008; Redig et al. ASCO 2016

The Ras Signaling Pathway



Schubbert *Nature Reviews Cancer* 7:295-308

MEK inhibitors +/- Docetaxel in KRAS mutant NSCLC

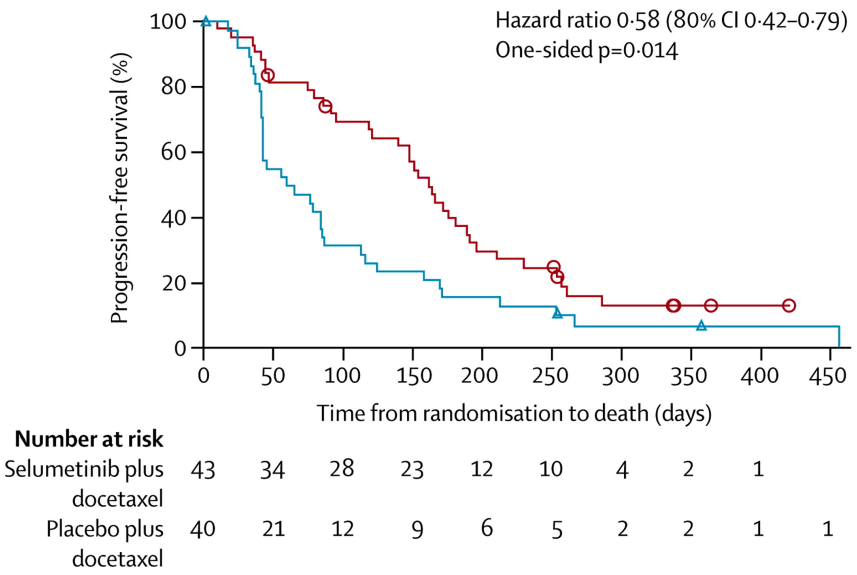


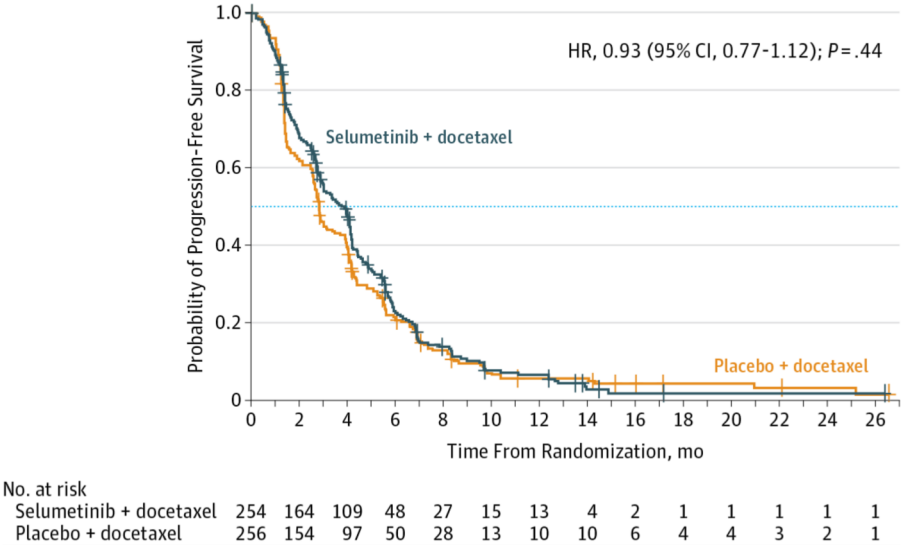
Study	Mutation	RR	TTP/PFS	OS
Selumetinib[1]	No selection n=42	5%	2.2 mo	N/A
Selumetinib[2]	*KRAS* mutant n=11	0%	4.0 mo	10.5 mo
Trametinib[3]	*KRAS* mutant n=86	12%	2.7 mo	8.0 mo

Study	Mutation	RR	TTP/PFS	OS
Selumetinib/doc[4]	*KRAS* mutant n=44	37%	5.3 mo	9.4 mo
Trametinib/doc[5]	*KRAS* mutant n=25	28%	N/A	N/A

1. Hainsworth J et al. J Thorac Oncol 2010;5:1630-6; 2. Carter et al. Ann Oncol 2016;; 3. Blumenschein et al. ASCO 2013 ; 4 Jänne et al. Lancet Oncol 2013; 5 Gandara et al. ASCO 2013

Docetaxel +/- Selumetinib in KRAS mutant NSCLC



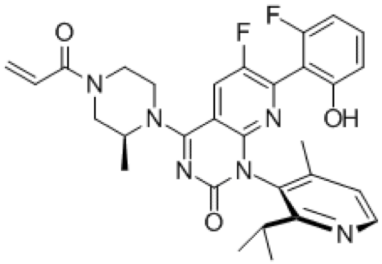


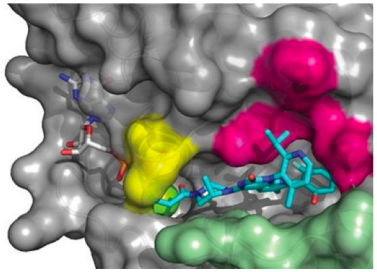
Randomized phase II study

Phase III Study

Jänne et al. Lancet Oncol 2013 and Jänne et al. JAMA 2017

AMG 510 Phase I trial





Overall Trial Accrual

N = 76

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

N = 34
NSCLC patients enrolled

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

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

N = 23, evaluable
- Patients who have been followed up for at least 6 weeks

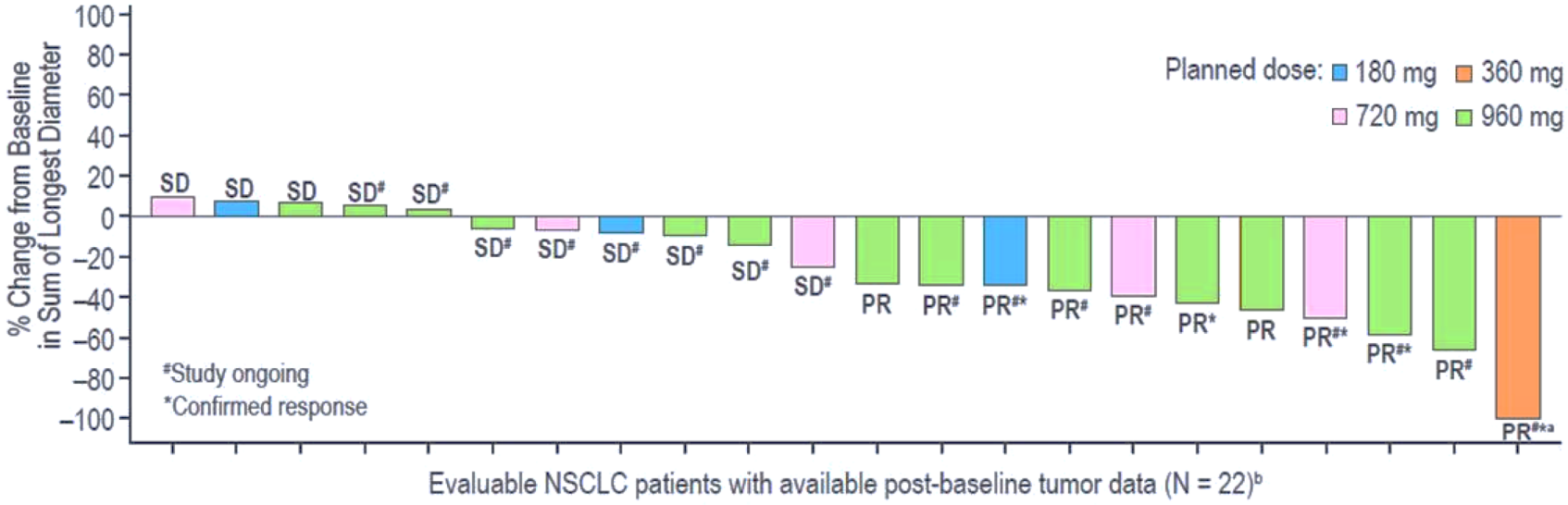
N = 30
Remained on study

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

First patient enrolled: 27 August 2018

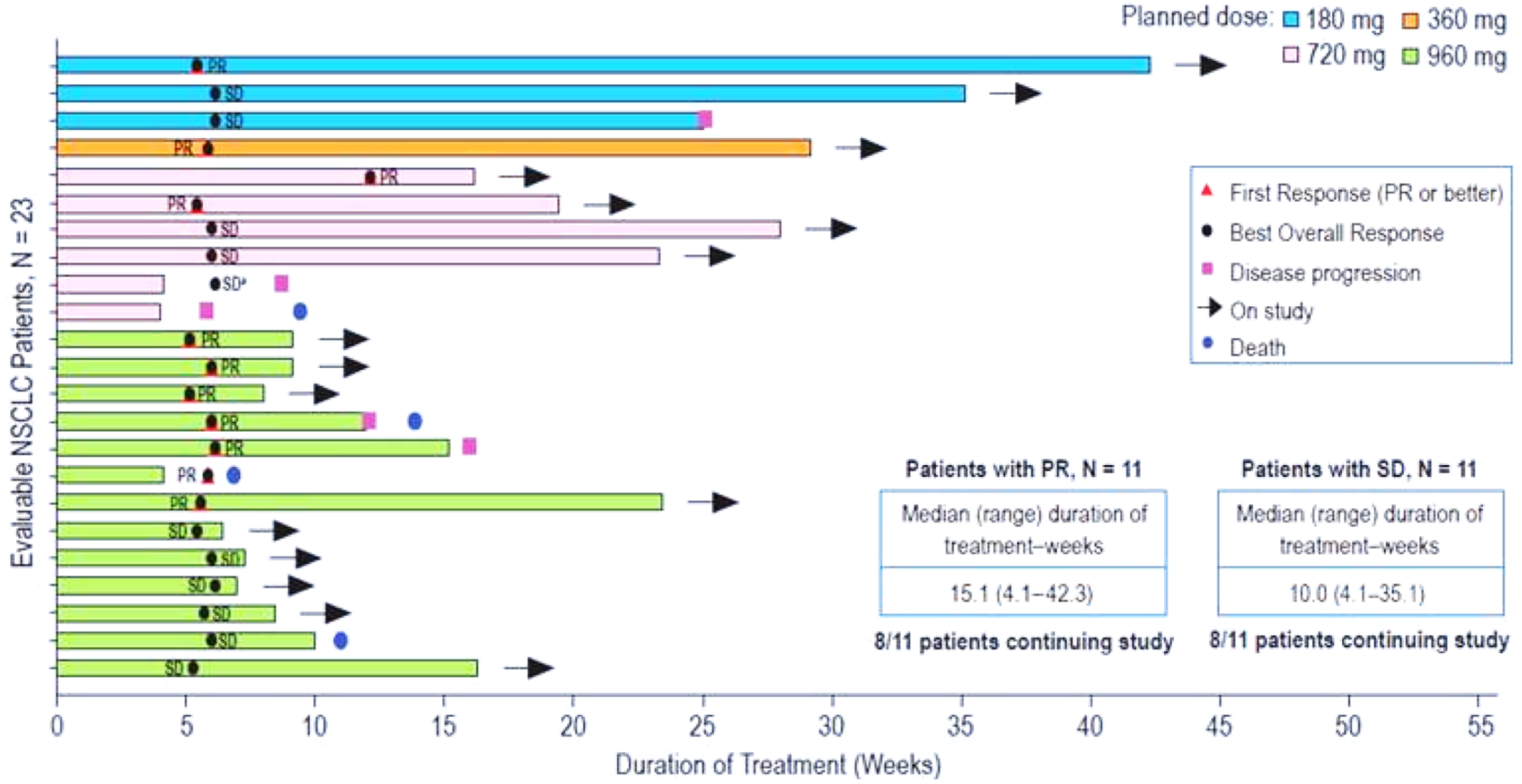
Data cutoff: 17 July 2019

Efficacy in NSCLC

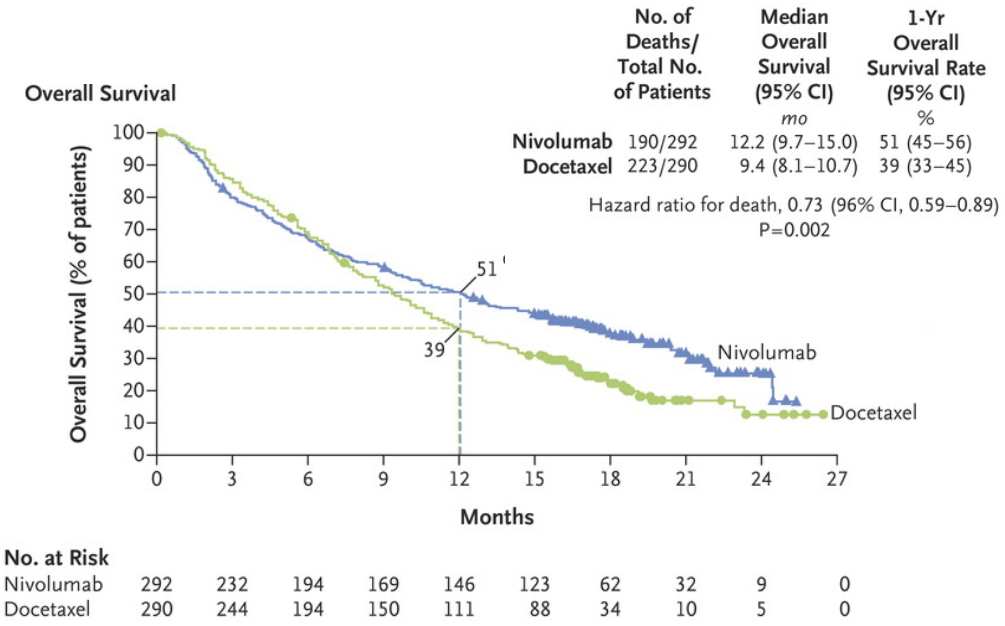


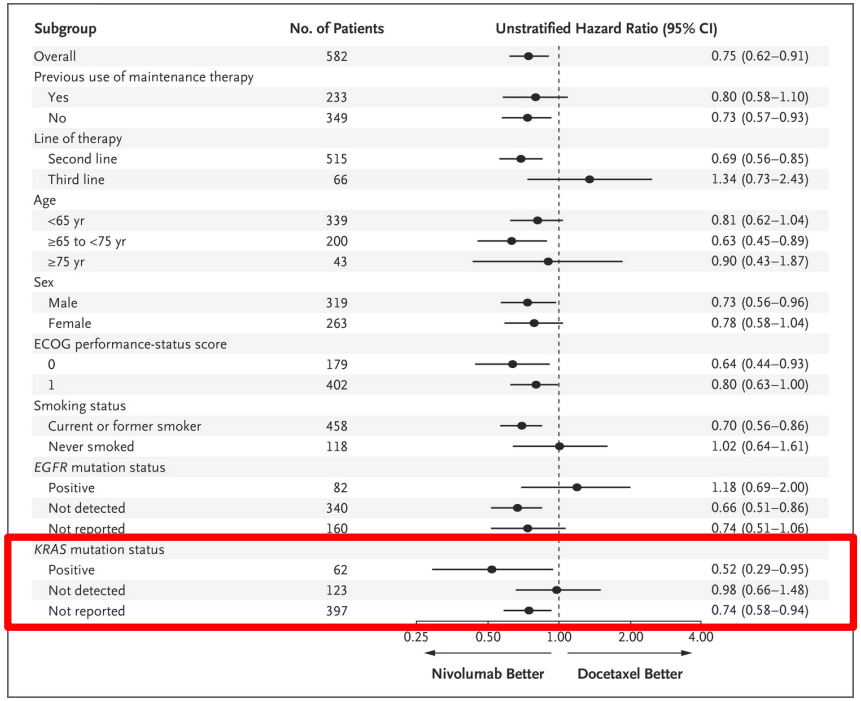
	Kras ^{G12C} NSCLC (n = 23)
PR	11 (48%)
SD	11 (48%)
PD	1 (4%)
ORR, %	**48%**
DCR, %	**96%**

Time to Response and Duration of Treatment



Efficacy of Nivolumab in Advanced NSCLC: CheckMate 057





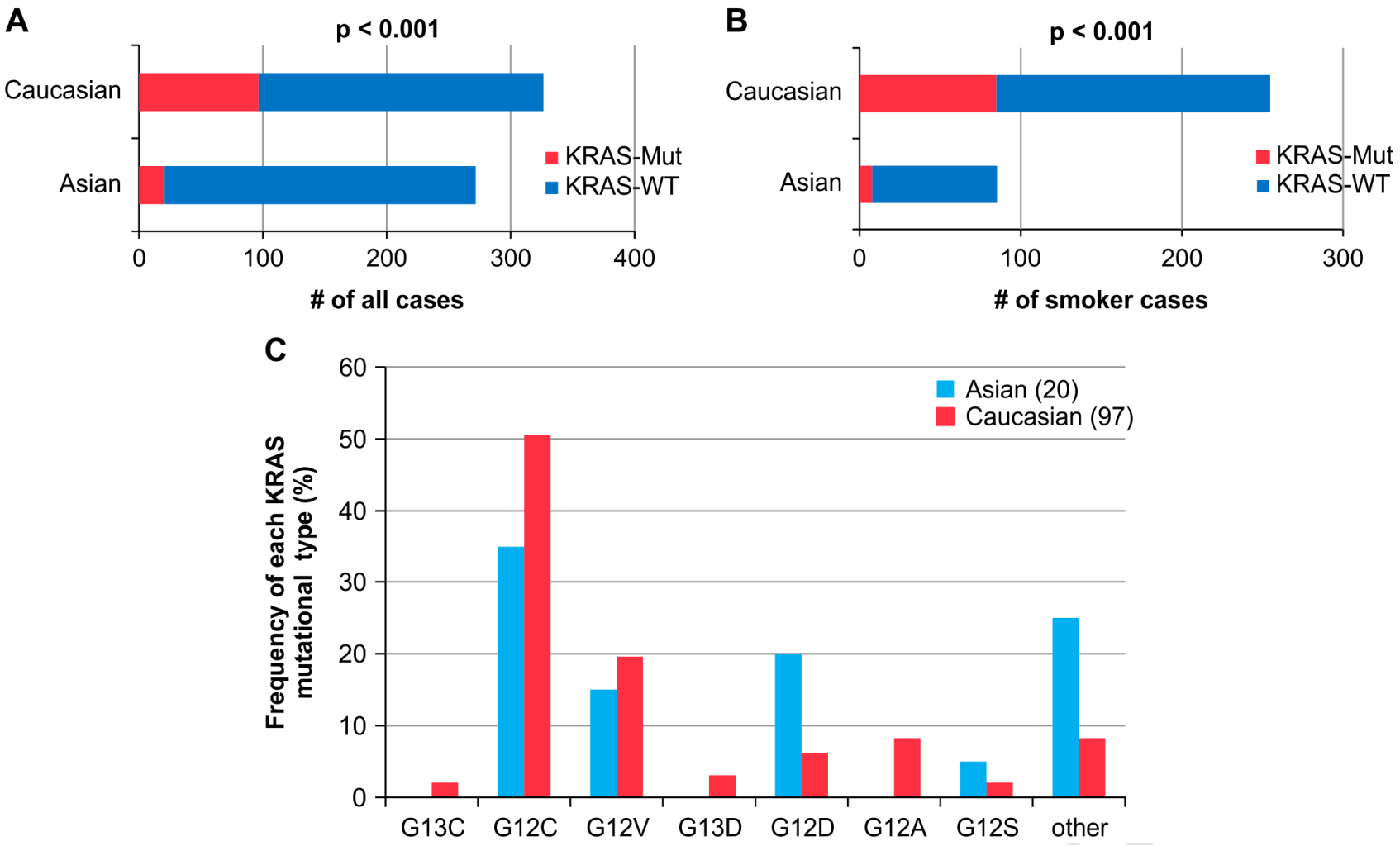
Borghaei et al. N Engl J Med 2015

Take Home Message

- All nonsquamous NSCLC should be tested for *ROS1*, *NTRK* and *KRAS* mutations
- Crizotinib is highly active in patients with *ROS1*-positive NSCLC
  - ORR of approximately 70%
  - Prolonged PFS (19.3) OS(51.4)
- Entrectinib demonstrated activity with durable responses in *ROS1*+ and *NTRK*+ NSCLC with and without CNS metastases
- AMG 510 demonstrated early promising antitumor activity in patients with advanced solid tumors harboring *KRAS* G12C mutation
- Immunotherapy may has effective in patients with *KRAS* mutant lung cancer.

Thank you for your attention !!

Distribution of KRAS mutation types



J Thorac Oncol. 2016 (12):2129-2140