PERSONALIZED TARGETED THERAPY FOR NSCLC

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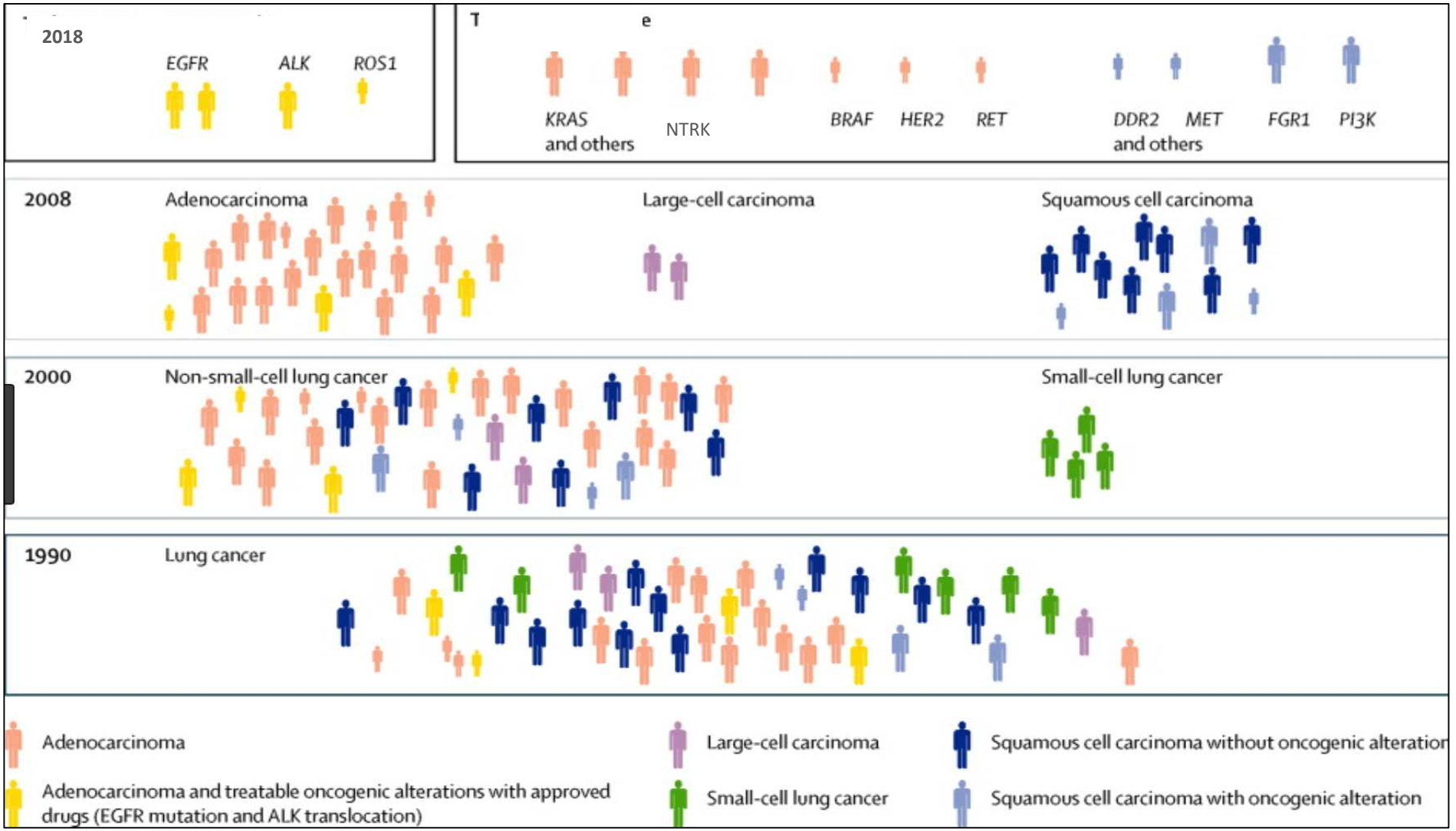
11th International Conference of Contemporary Oncology, Poznan, 15th March 2019

NON-SMALL CELL LUNG CANCER:

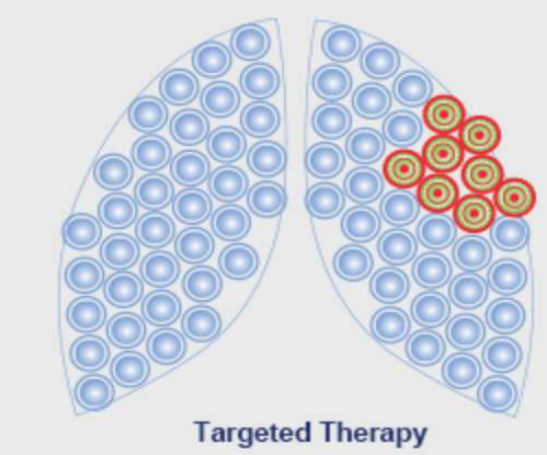
IS IT STILL ONE DISEASE?



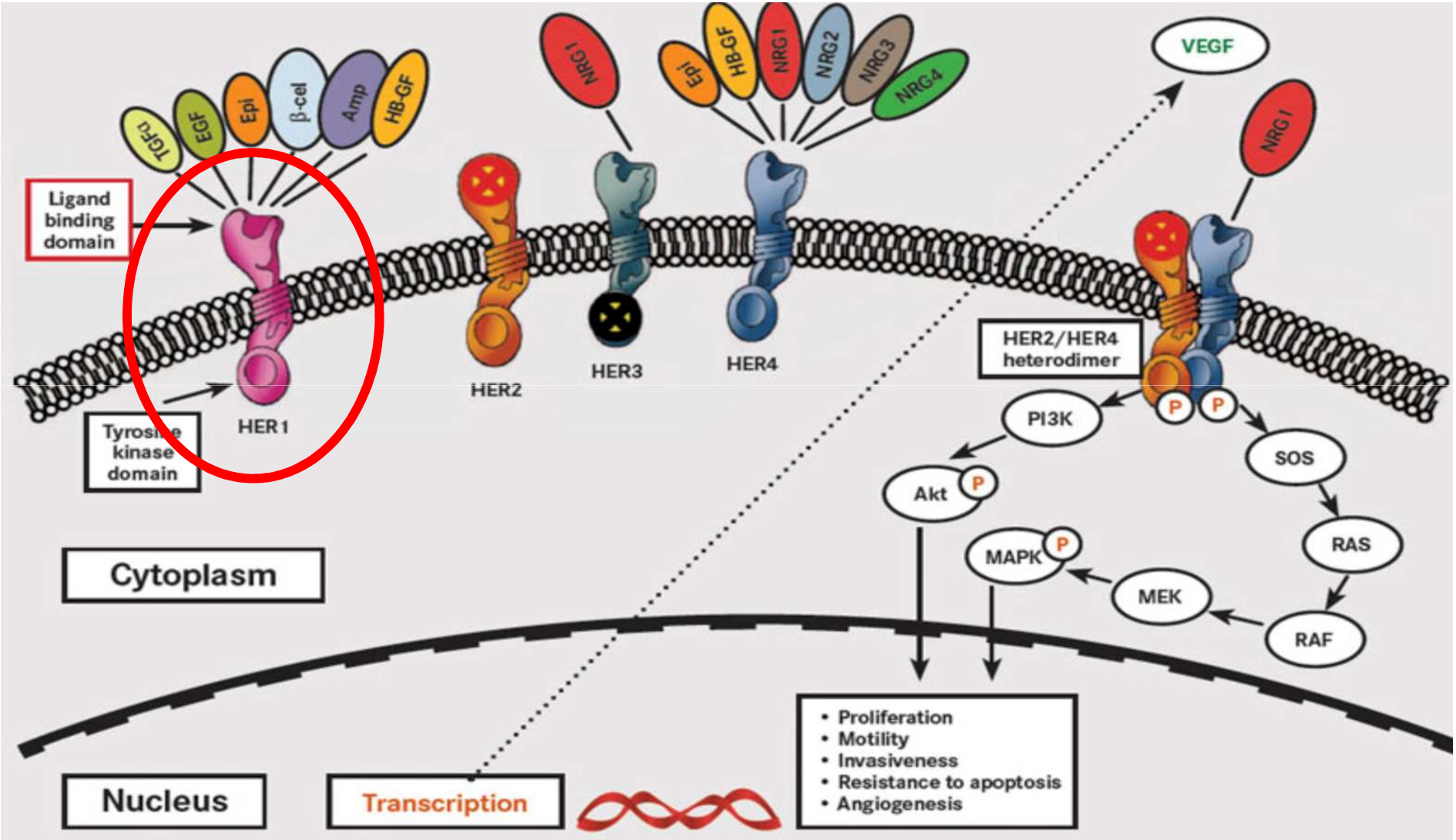
LET'S TALK ABOUT TREATMENT OPTIONS FOR….

- **EGFR**
- **ALK**
- **ROS1**
- **NTRK**
- **BRAF**

positive NSCLC



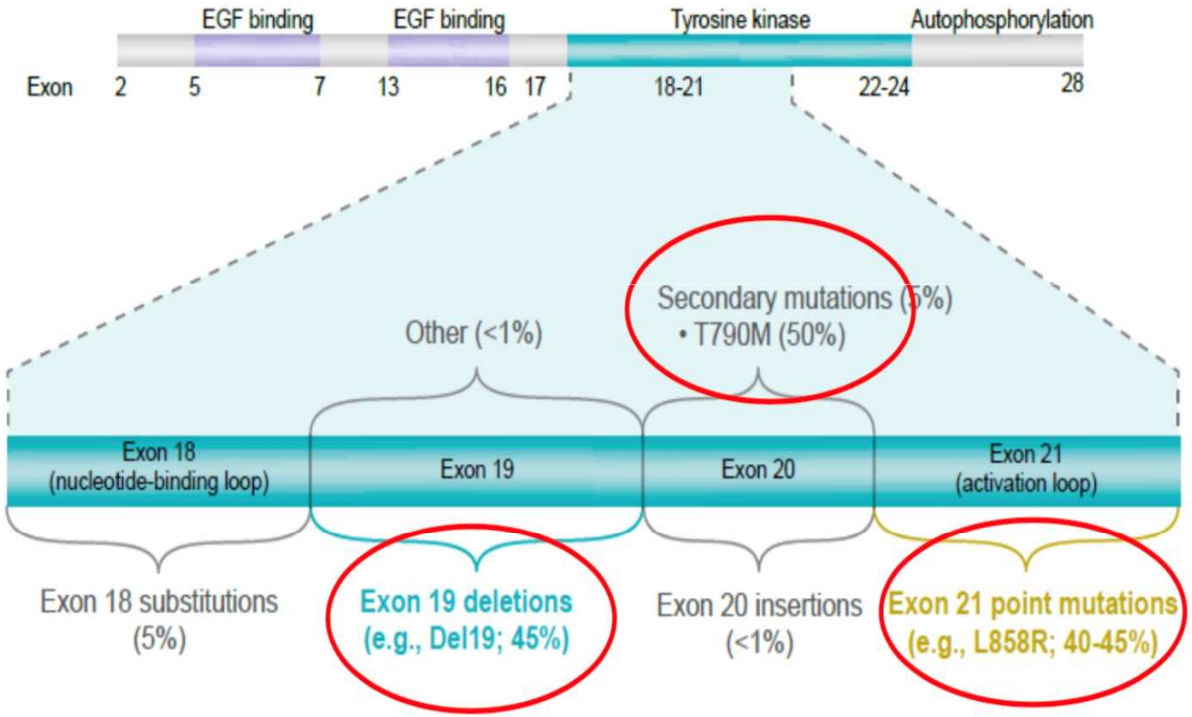
HER RECEPTORS FAMILY

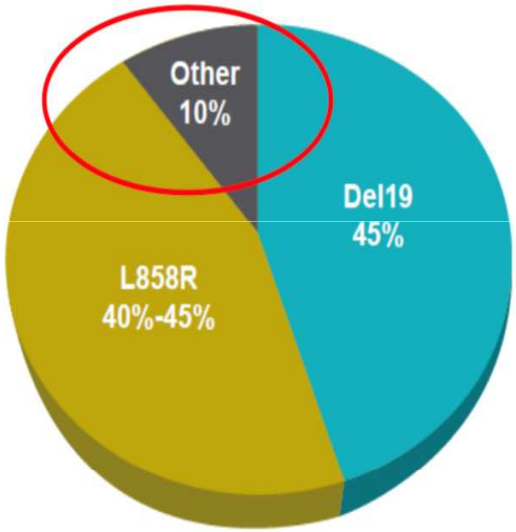


Ross J. et al. *The Oncologist*, 2009;14:320-366

EGFR GENE MUTATIONS

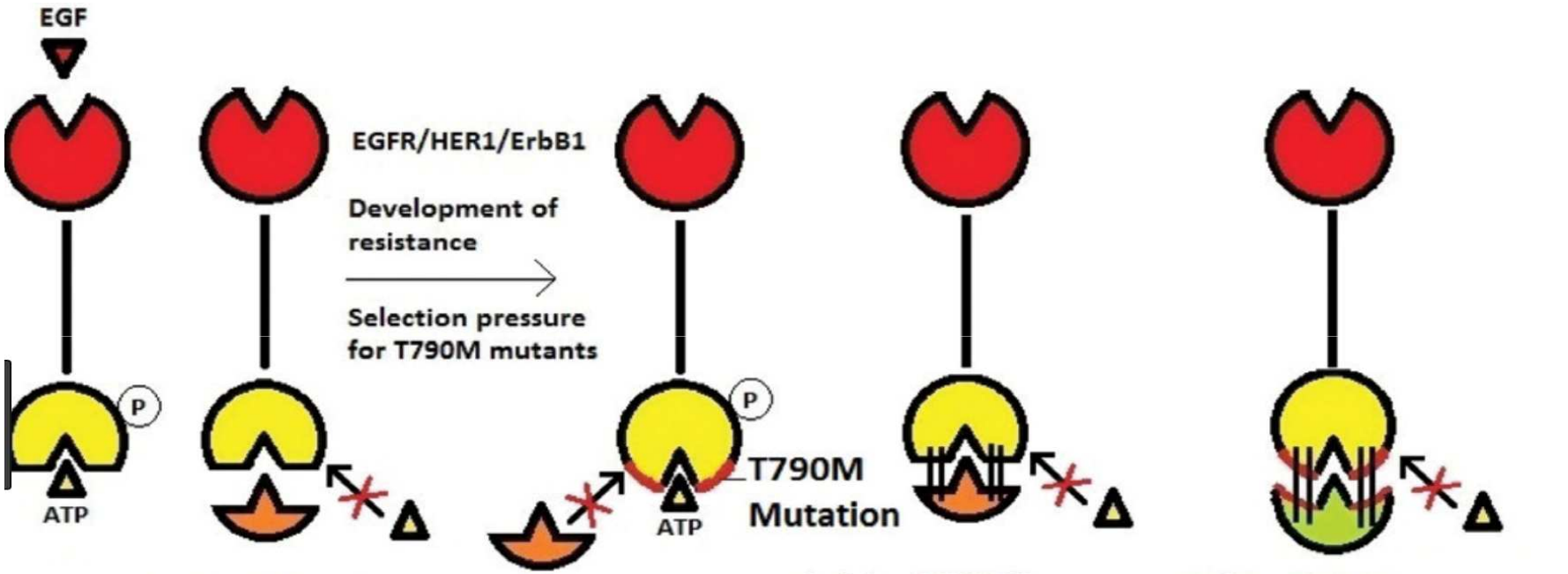
younger
women
adenocarcinomas
non-smokers





Sharma et al. *Nat Rev Canc*, 2007;7:169

TKI EGFR IN NSCLC



1st Gen EGFR TKI
- Reversible binding to EGFR
- Inhibits binding of ATP

erlotinib
gefitinib

2nd Gen EGFR TKI
- Irreversible covalent binding to EGFR
- Alters ATP affinity to EGFR
- Overcomes T790M driven resistance

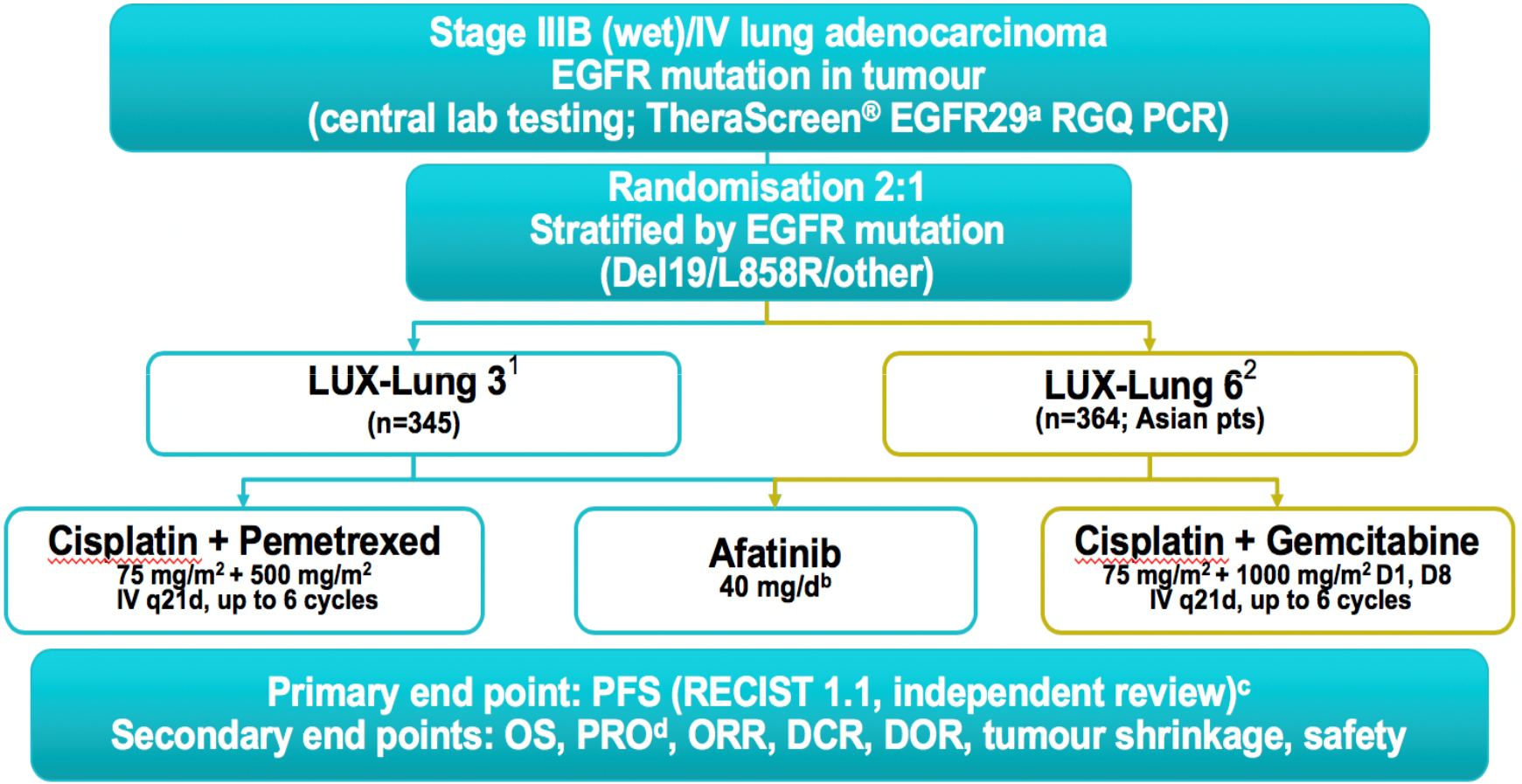
afatinib
dacomitinib

3rd Gen EGFR TKI
- Irreversible covalent binding to EGFR
- Specificity to T790M mutants

ozimertinib

Chua B. *Austr Med. Stud J*, 2015

AFATINIB: LUX-LUNG 3 AND LUX-LUNG 6

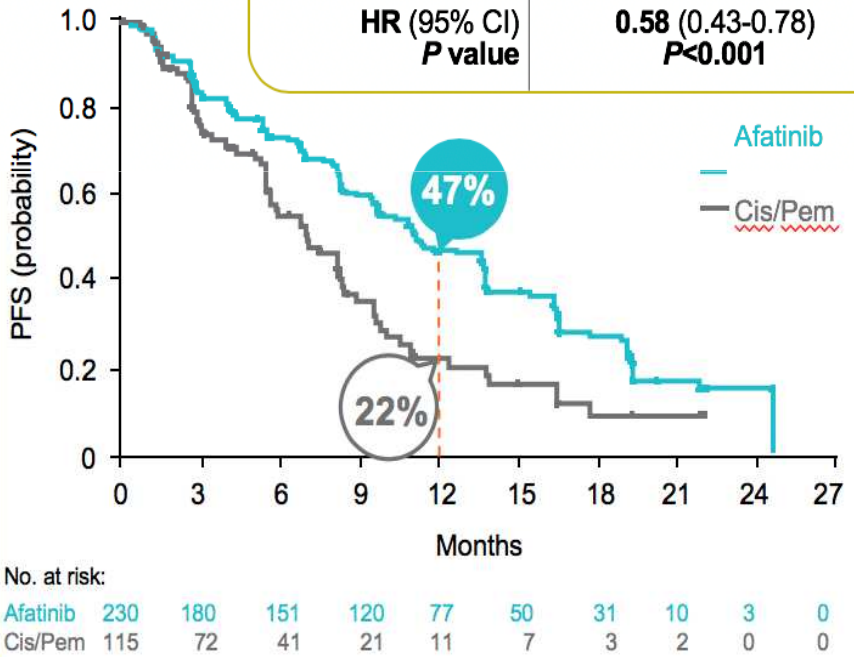


Sequist et al. *J Clin Oncol,* 2013:31(27):3327-34, Wu Y-L et al. *Lancet Oncology*, 2014;15:213-22

AFATINIB: LUX-LUNG 3

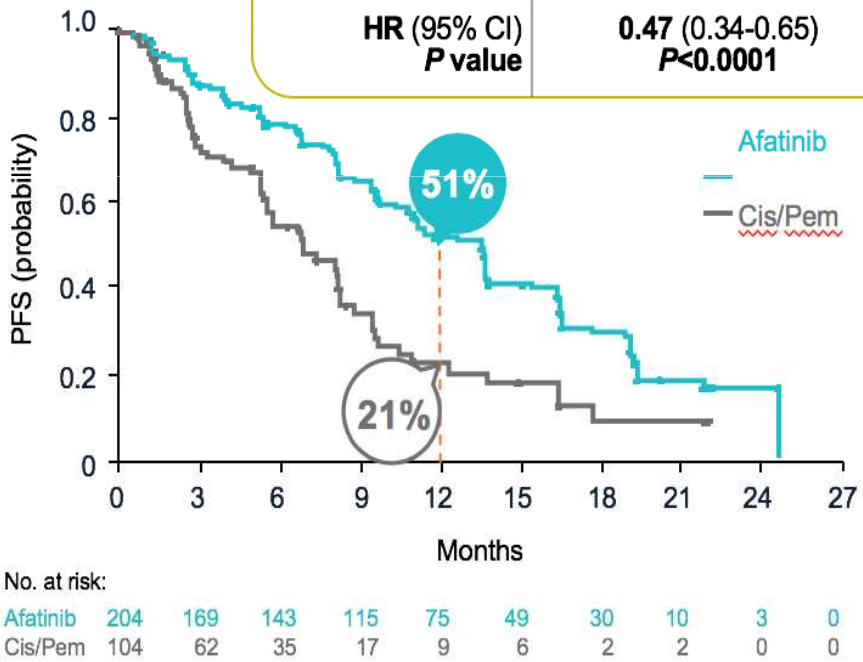
PFS in overall population

	Afatinib (n=230)	Cis/Pem (n=115)
PFS event, n (%)	152 (66)	69 (60)
Median PFS (mo)	**11.1**	**6.9**
HR (95% CI) ***P* value**	**0.58** (0.43-0.78) ***P*<0.001**	



PFS in patients with common mutations

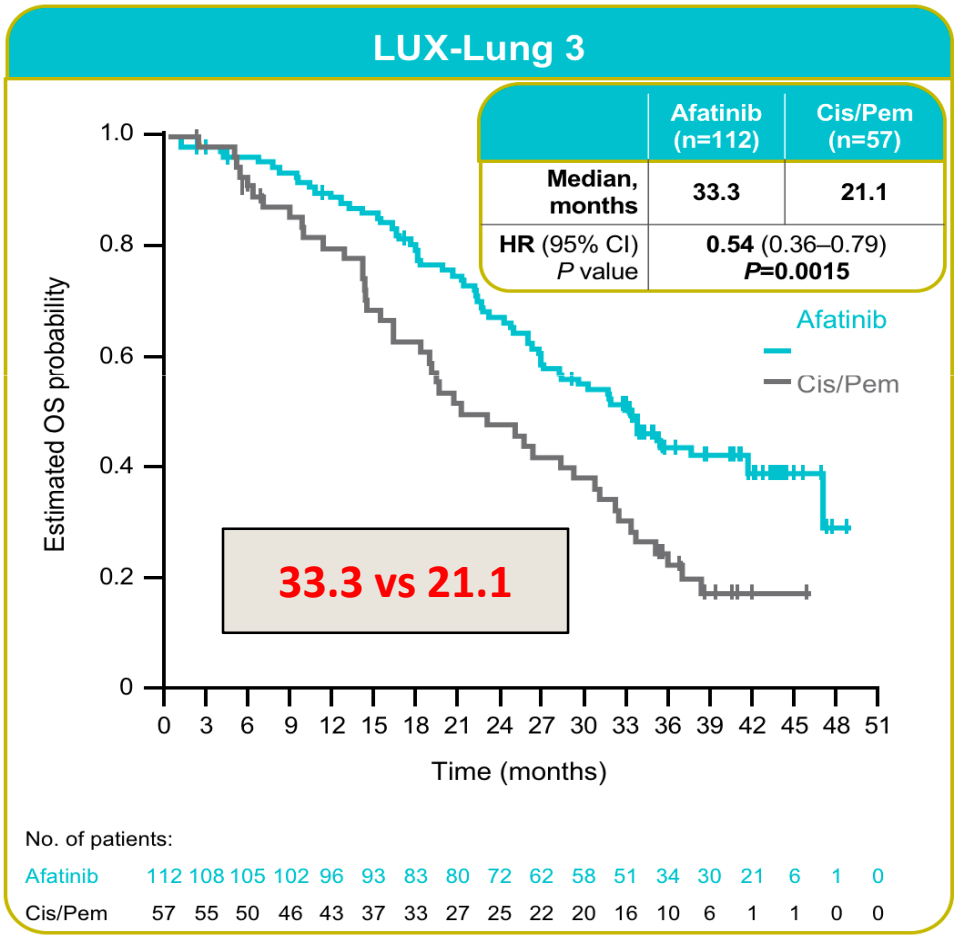
	Afatinib (n=204)	Cis/Pem (n=104)
PFS event, n (%)	130 (64)	61 (59)
Median PFS (mo)	**13.6**	**6.9**
HR (95% CI) ***P* value**	**0.47** (0.34-0.65) ***P*<0.0001**	

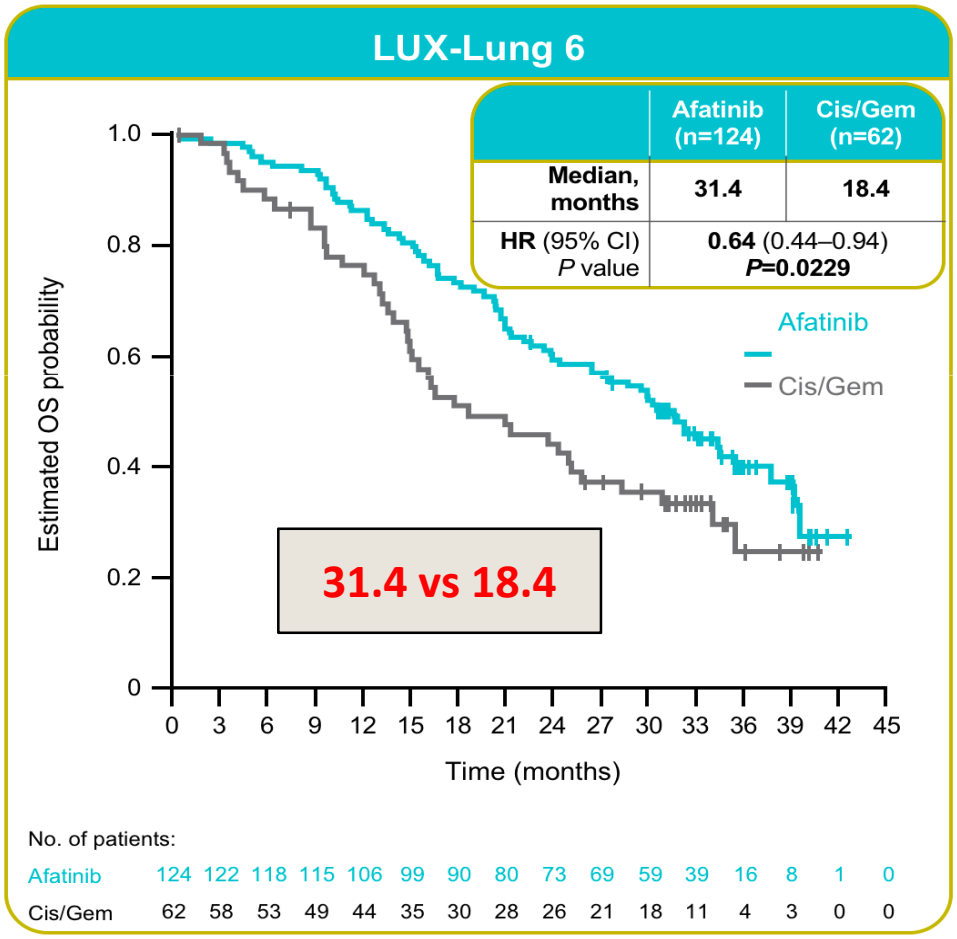


Sequist et al. *J Clin Oncol,* 2013:31(27):3327-34

AFATINIB: LUX-LUNG 3 AND LUX-LUNG 6

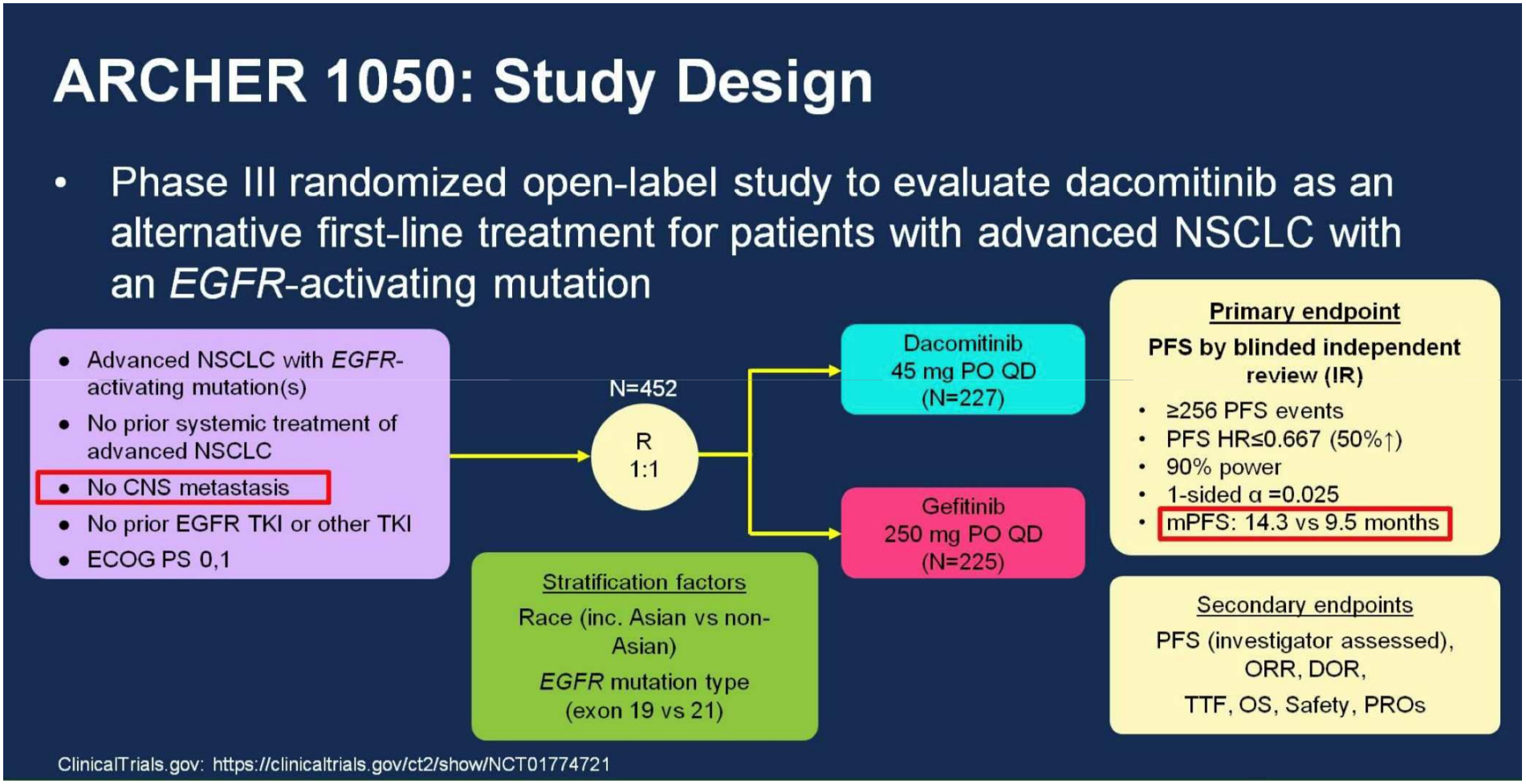
del19





Yang et al. *Lancet Oncology,* 2015;16:141-151

DACOMITINIB: ARCHER 1050

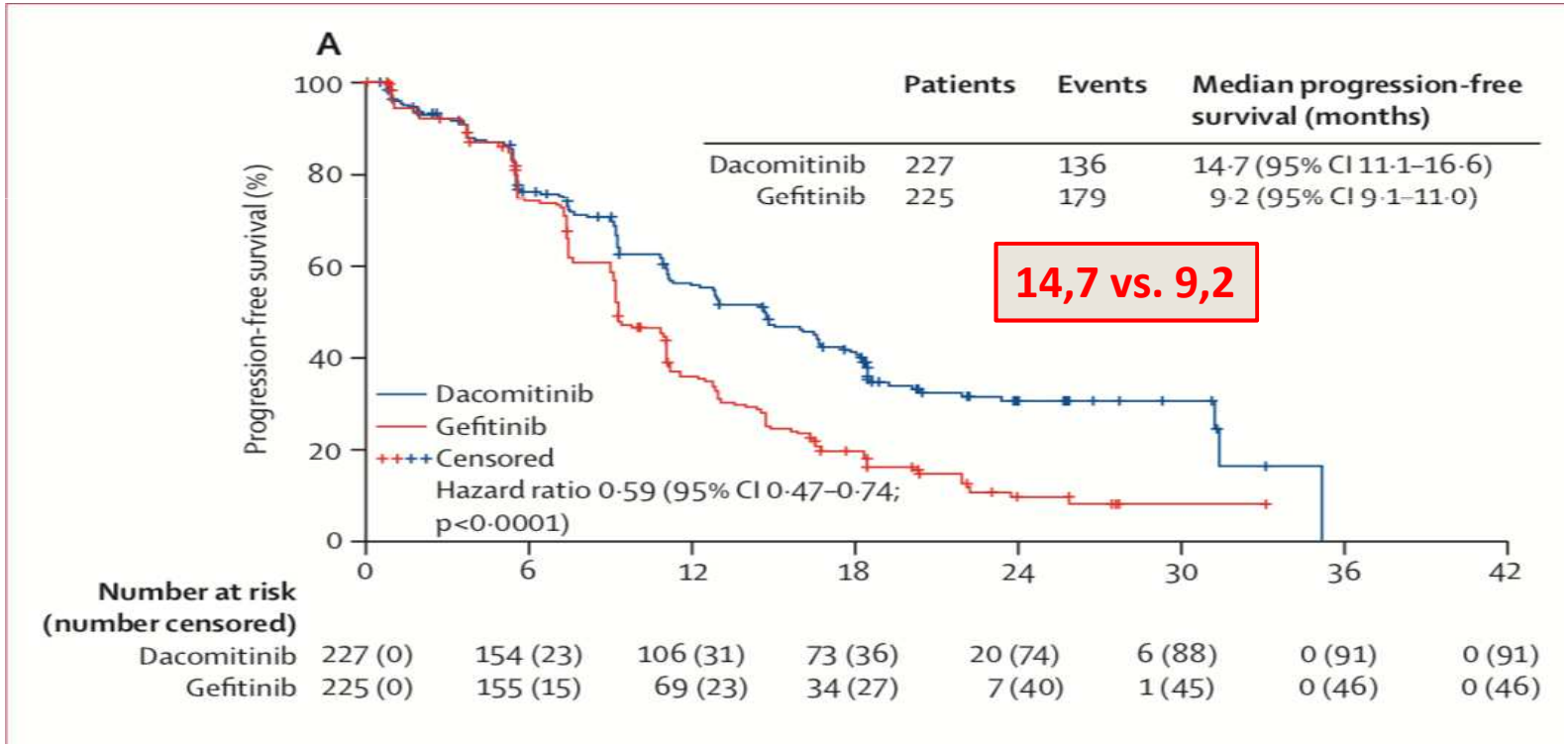


Mok T. et al. *ASCO2018*

DACOMITINIB: ARCHER 1050

Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

Yi-Long Wu, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Fumito Tsuji, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I Sbar, Tao Wang, Jane Liang White, Sashi Nadanaciva, Rickard Sandin, Tony S Mok



Yi-Long W. et al. *Lancet Oncology*, 2017;18:1454-66

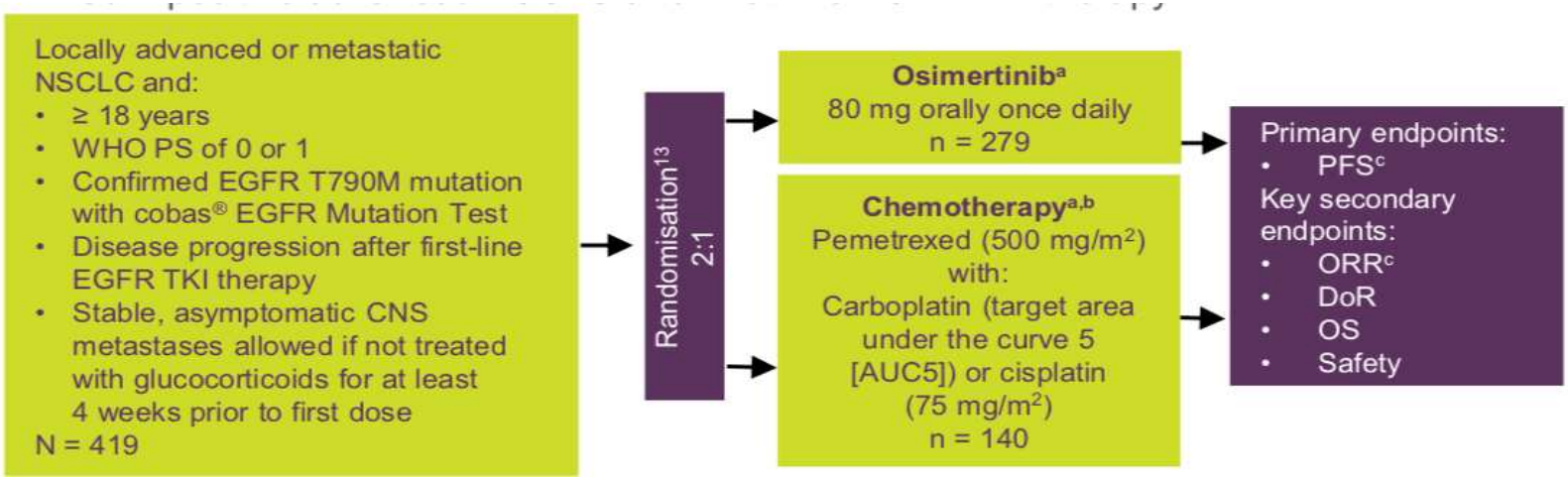
OSIMERTINIB: AURA 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

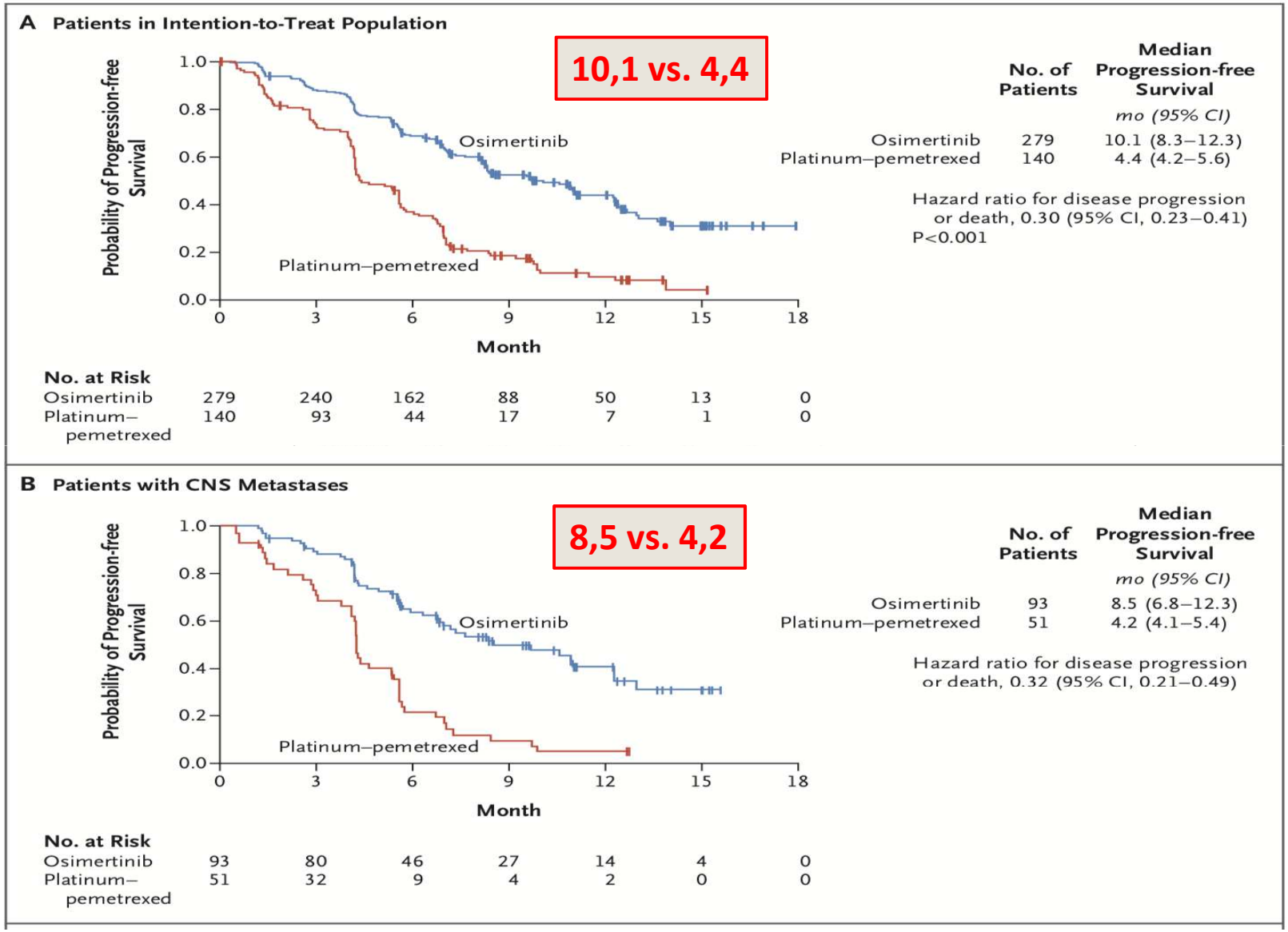
Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*



Mok T. et al. *NEJM*, 2017;376:629-40

OSIMERTINIB: AURA 3



Mok T. et al. *NEJM*, 2017;376:629-40

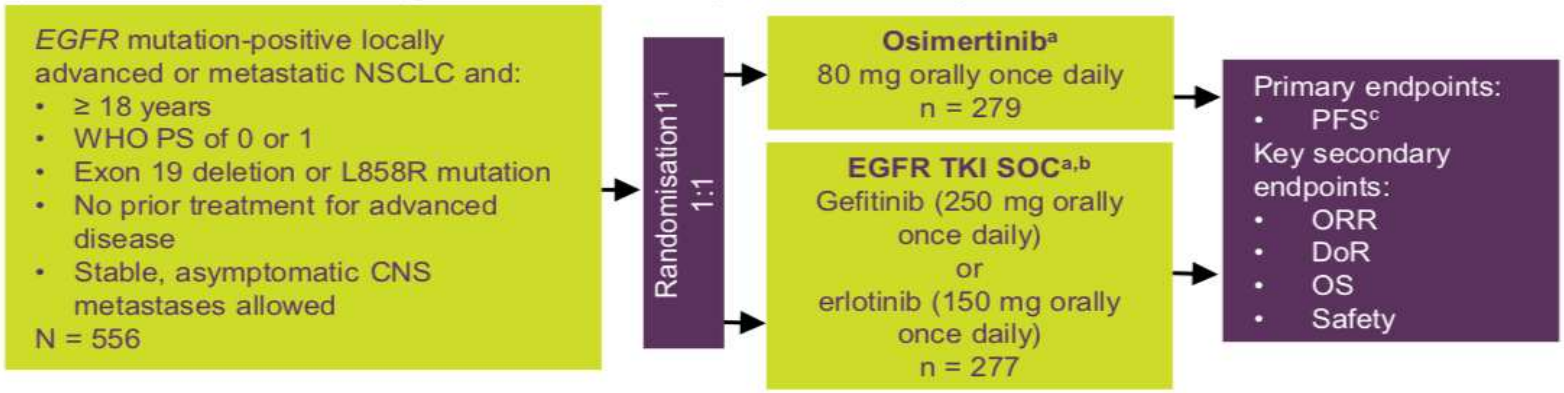
OSIMERTINIB: FLAURA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

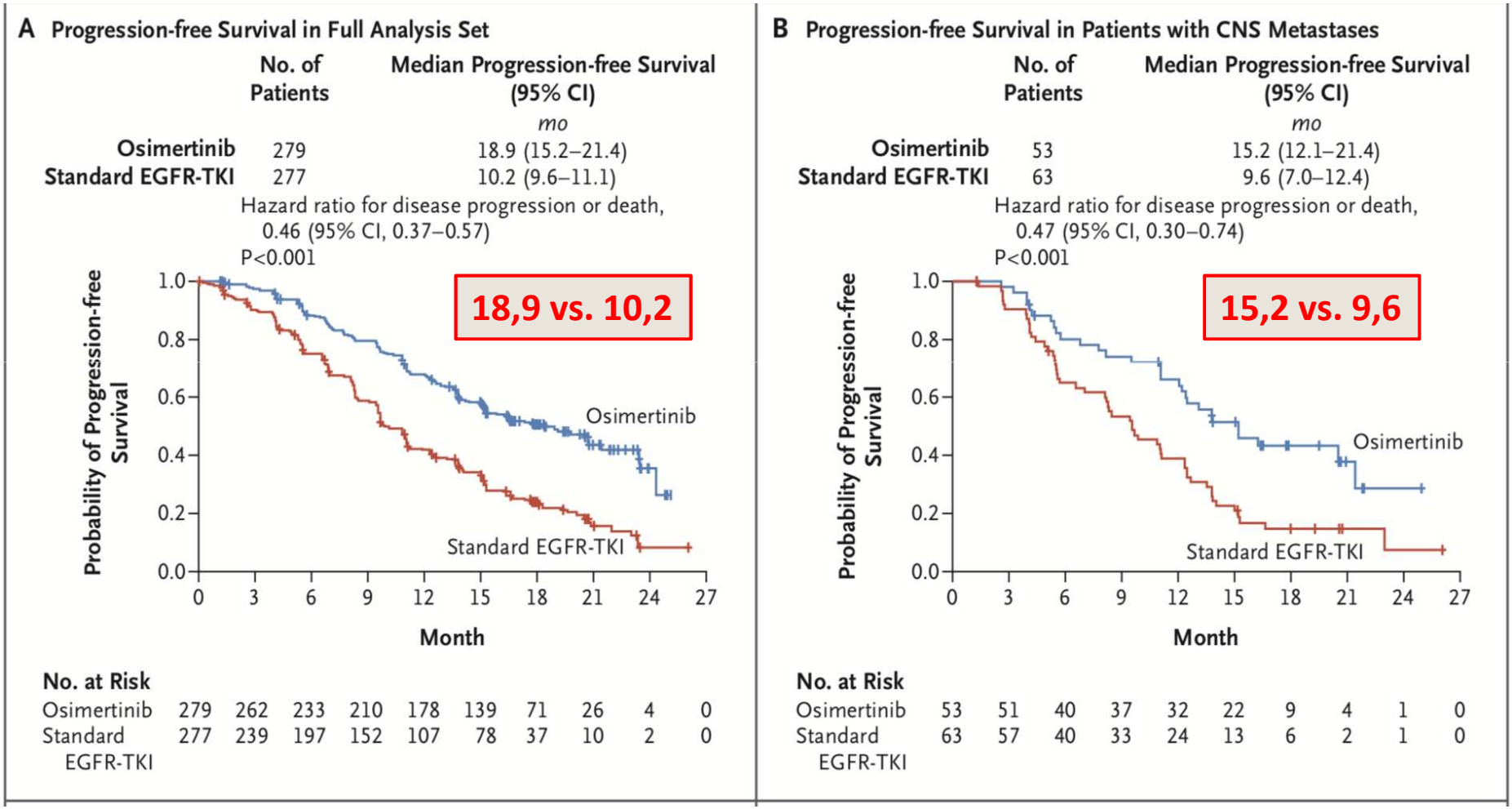
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*



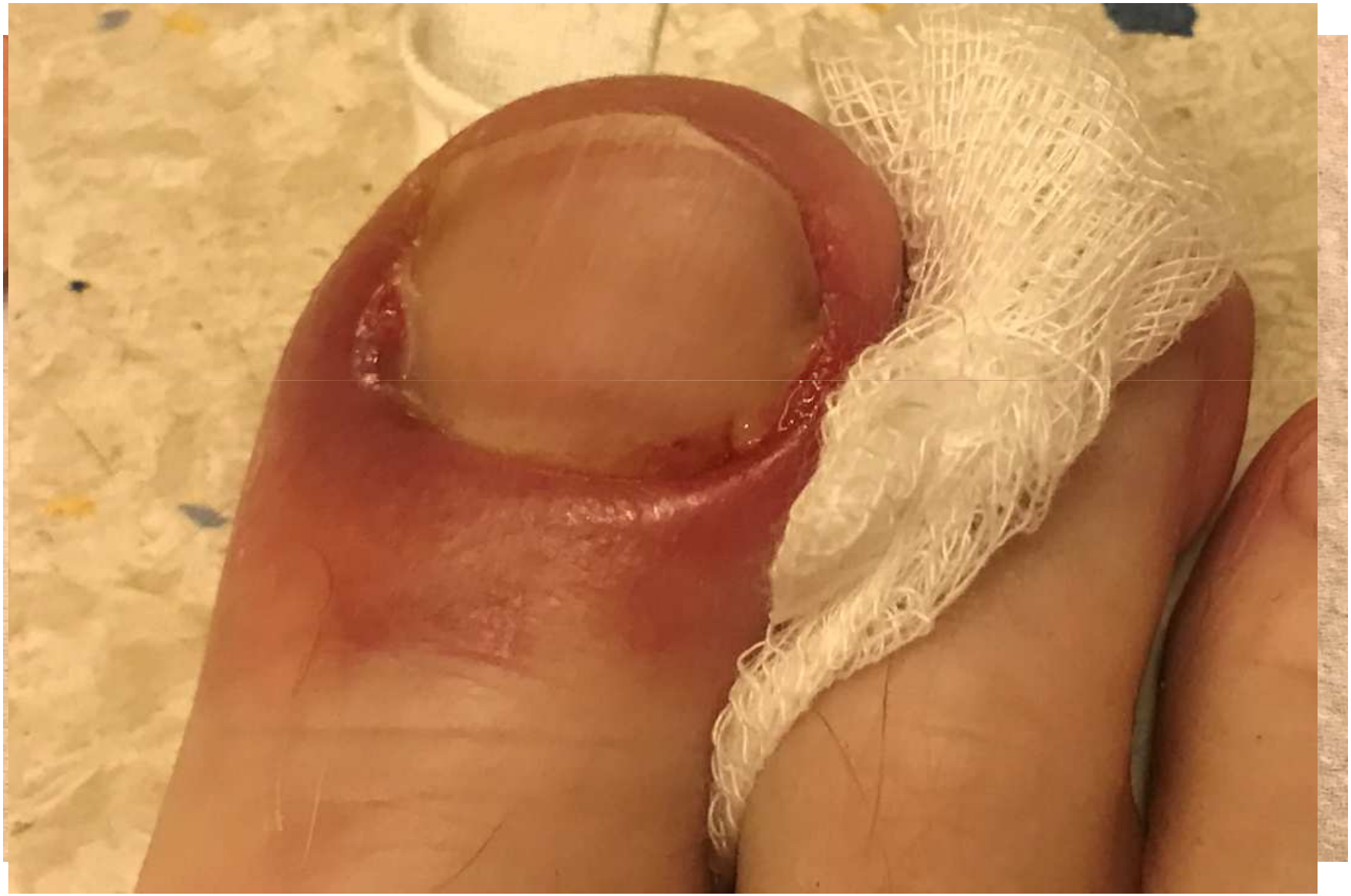
Soria J. i wsp. *NEJM*, 2018;11:378(2):113-125

OSIMERTINIB: FLAURA



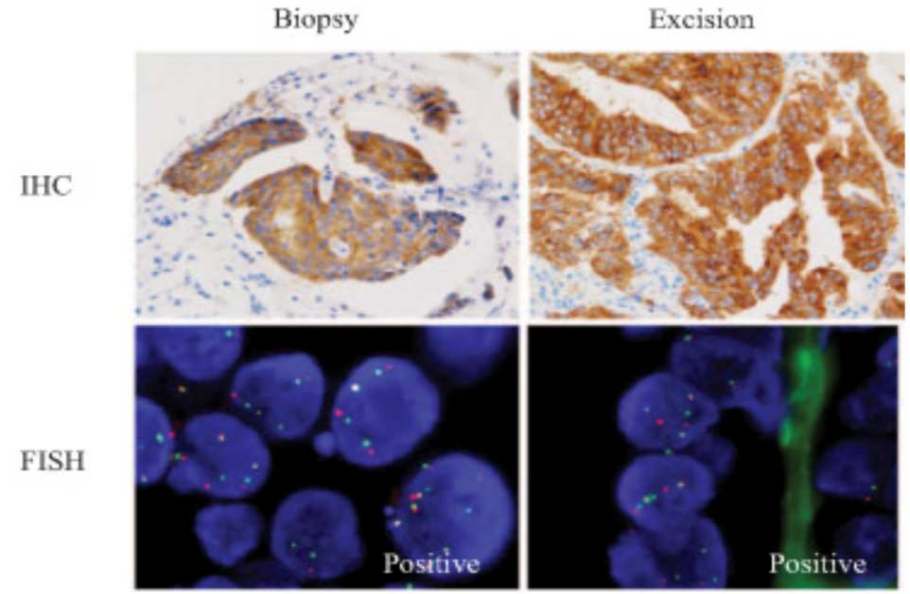
Soria J. et al. *NEJM*, 2018;11:378(2):113-125

TKI EGFR: SIDE EFFECTS



ALK REARRANGEMENT IN NSCLC

- Incidence in NSCLC: 3-5%
- Mainly: adenocarcinoma, *signet ring* subtype,
- More common: younger, women, non-smokers or former smokers
- Excluding with *EGRF* gene or *KRAS* gene mutation
- Clinical presentation of pleural effusion and lymph nodes involvement
- CNS metastases present in 40% ALK+ patients

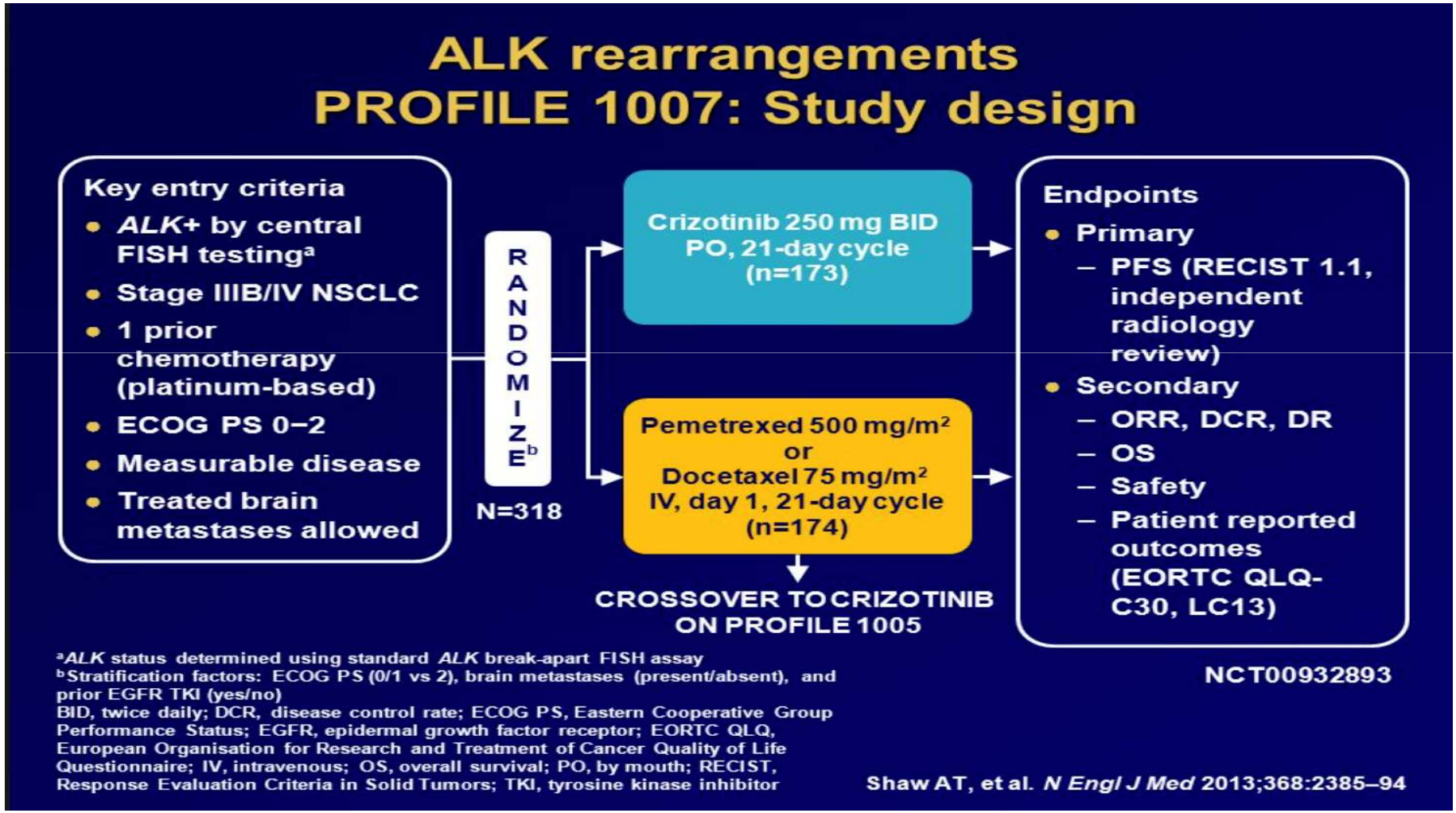


Abe H. et al, *J Thor Oncol*, 2015

AVAILABLE ALK-TKI AND THEIR PIVOTAL TRIALS

		1st line	mPFS (mths)	Following crizotinib	mPFS (mths)
1st generation	Crizotinib 2x250mg	**PROFILE 1014**	10.9	--	--
2nd generation	Alectinib 2x600mg	**JALEX**	25.9	**ALUR**	9.6
		ALEX	34.8		
	Ceritinib 1x750mg	**ASCEND 4**	16.6	**ASCEND 5**	5.4
	Brigatynib 90mg x 7 days → 180 mg/d	**ALTA 1L (ongoing)**	NR	**ALTA**	15.6
3rd generation	Lorlatynib 150mg/d	**NCT03052628 (ongoing)**	NA	**NCT01970865**	13.5

CRIZOTINIB in ALK+ NSCLC: PROFILE 1007
2nd LINE



Shaw A. et al, *NEJM*, 2013

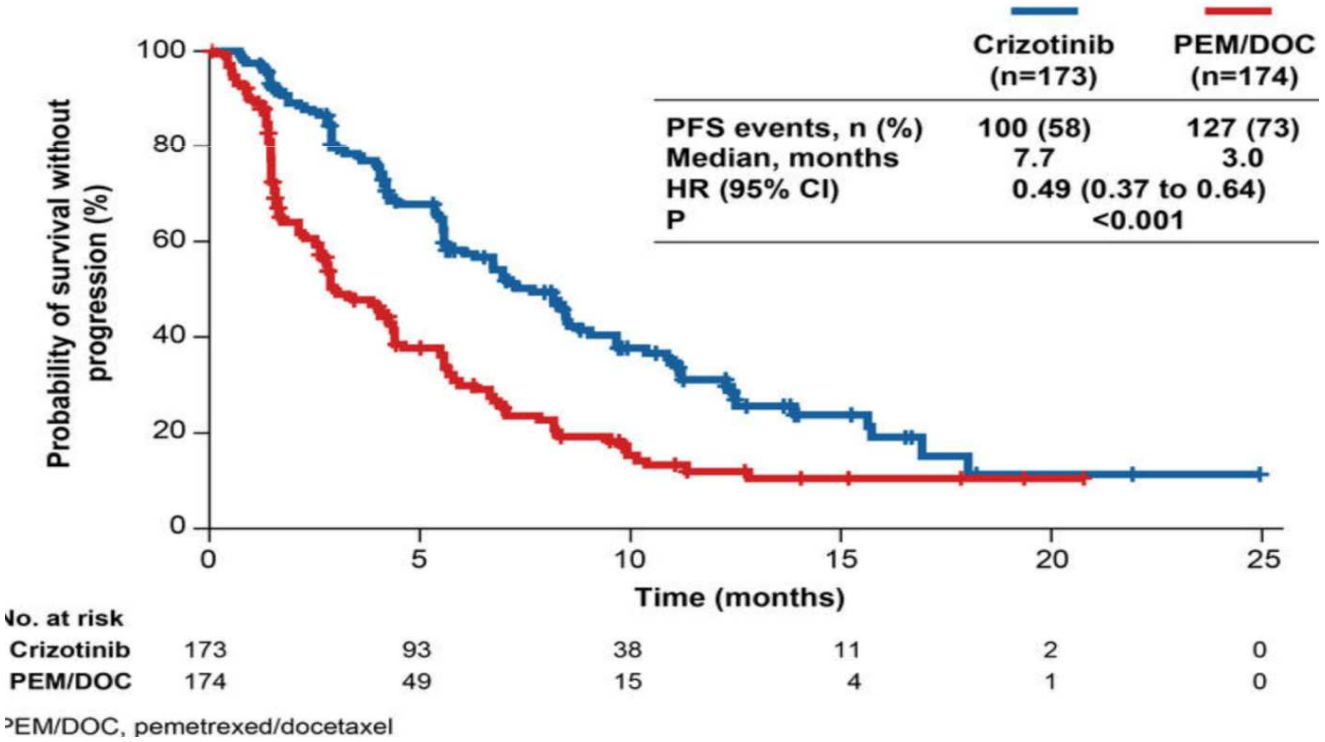
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., et al.

PROFILE 1007 Primary Endpoint: PFS by Independent Radiologic Review



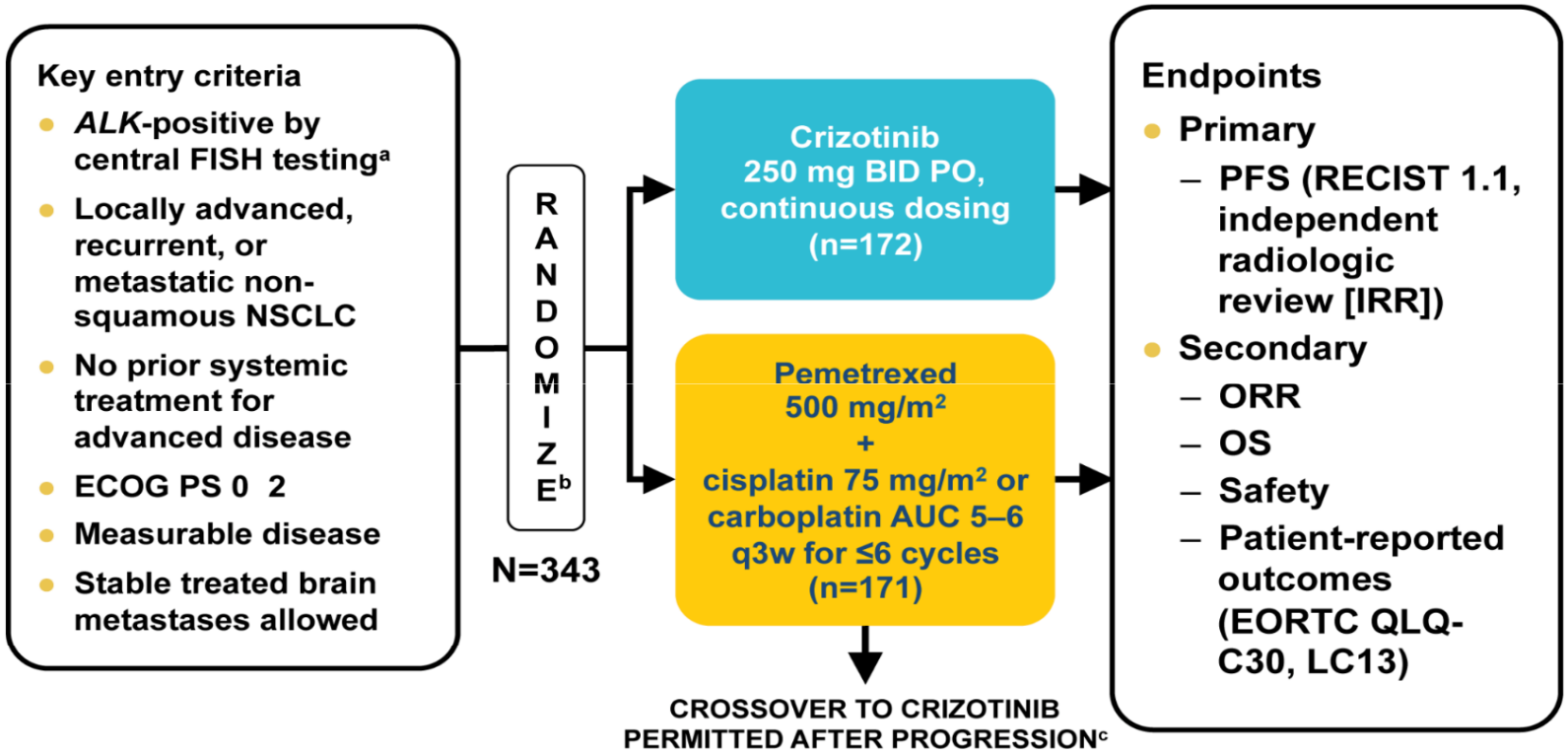
PEM/DOC, pemetrexed/docetaxel

7,7 vs 3,0 months

Shaw A. et al., *NEJM*, 2013

CRIZOTINIB IN ALK+ NSCLC: PROFILE 1014

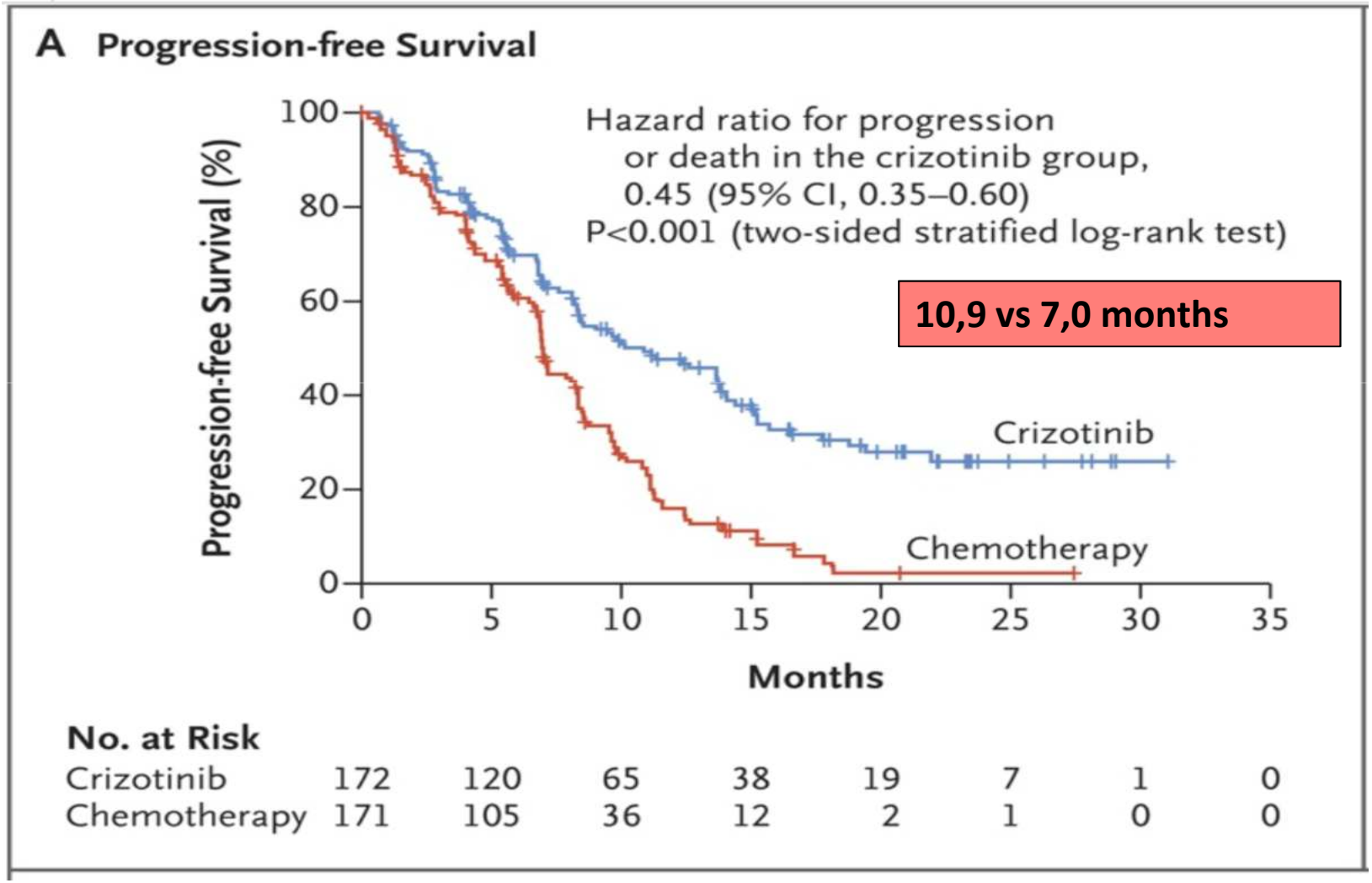
1st LINE



PROFILE 1014: NCT01154140

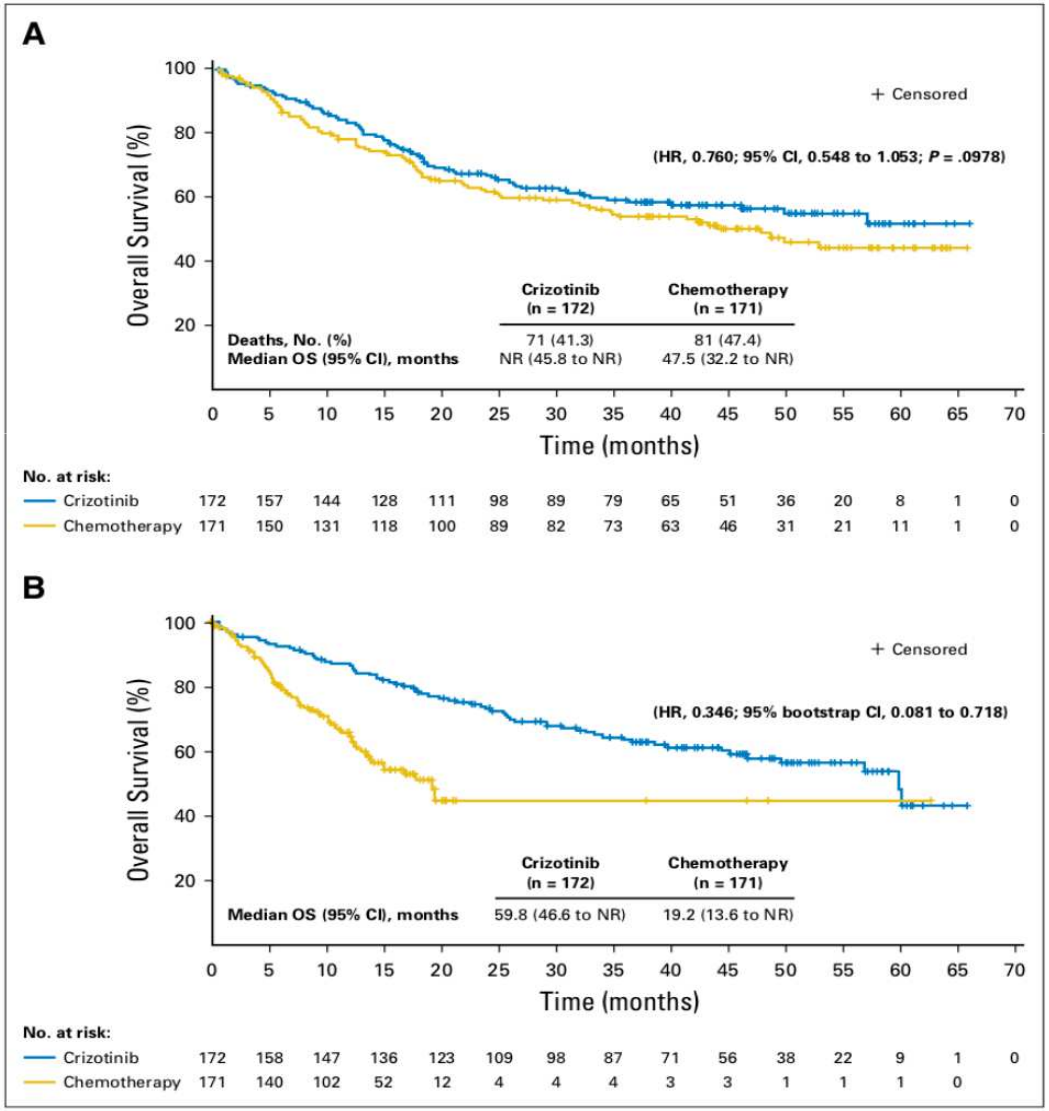
www.clinicaltrials.gov

CRIZOTINIB IN ALK+ NSCLC: PROFILE 1014



Solomon B. et al., *NEJM*, 2014

CRIZOTINIB IN ALK+ NSCLC: PROFILE 1014: IMPACT ON OS?



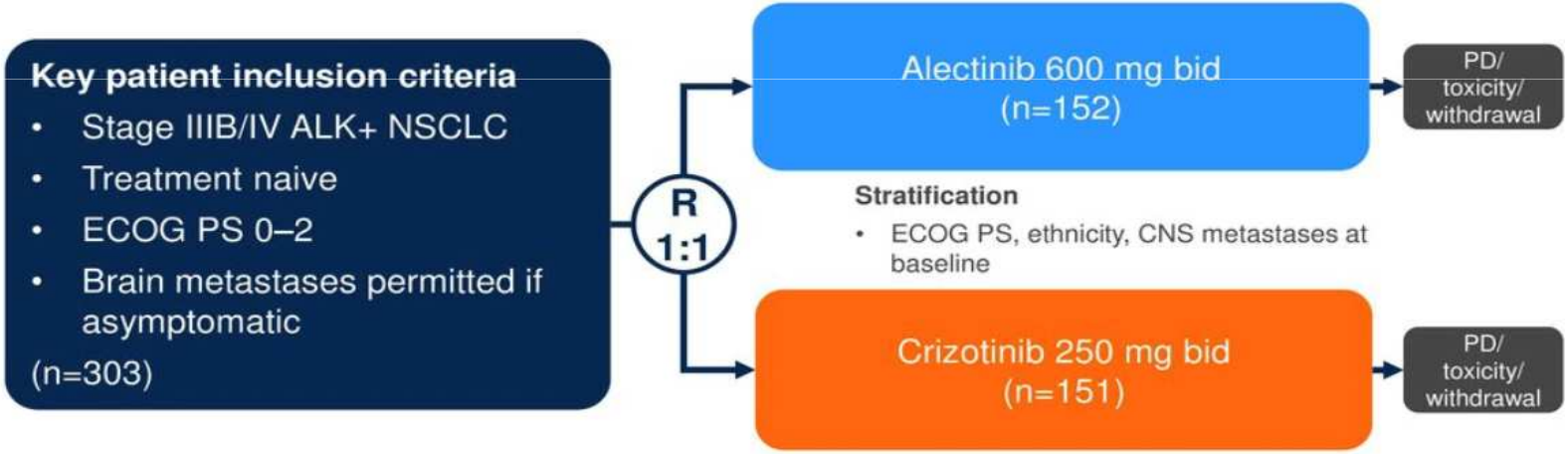
59,8 vs 19,2 months

Solomon B. et al., *JCO*, 2018

ALECTINIB IN 1st LINE TREATMENT FOR ALK+ NSCLC:
ALEX (BO28984)

1298O_PR: Alectinib vs crizotinib in treatment-naïve ALK+ NSCLC: CNS efficacy results from the ALEX study – Gadgeel S, et al

- **Study objective**
  - To assess the systematic and CNS efficacy of alectinib vs. crizotinib as 1L therapy in patients with advanced/metastatic ALK+ NSCLC



Primary endpoint

- PFS (investigator assessed)

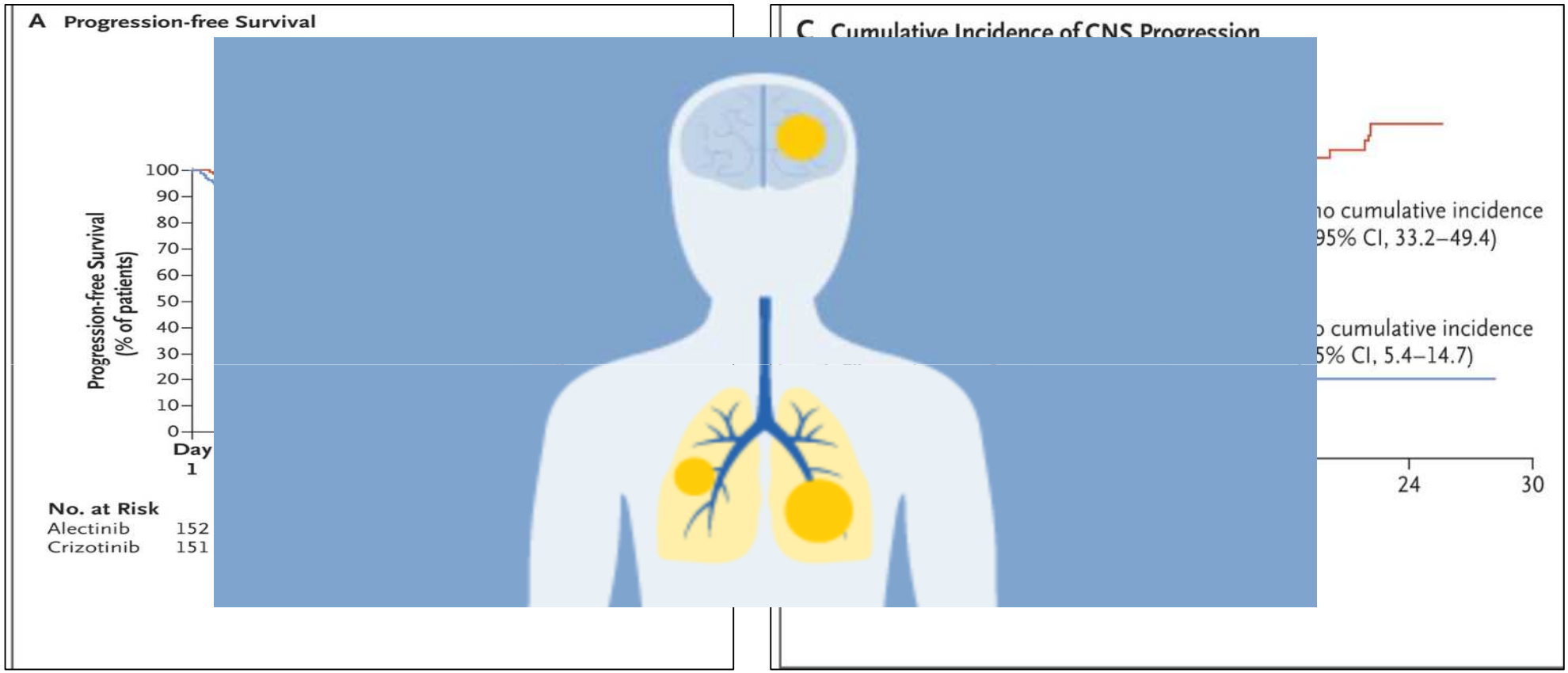
Secondary endpoints

- Time to CNS progression, CNS ORR, CNS DoR

1024 × 768

Gadgeel S et al. Ann Oncol 2017;28(suppl 5):Abstr 1298O_PR

ALECTINIB IN 1st LINE TREATMENT FOR ALK+ NSCLC:
ALEX (BO28984)



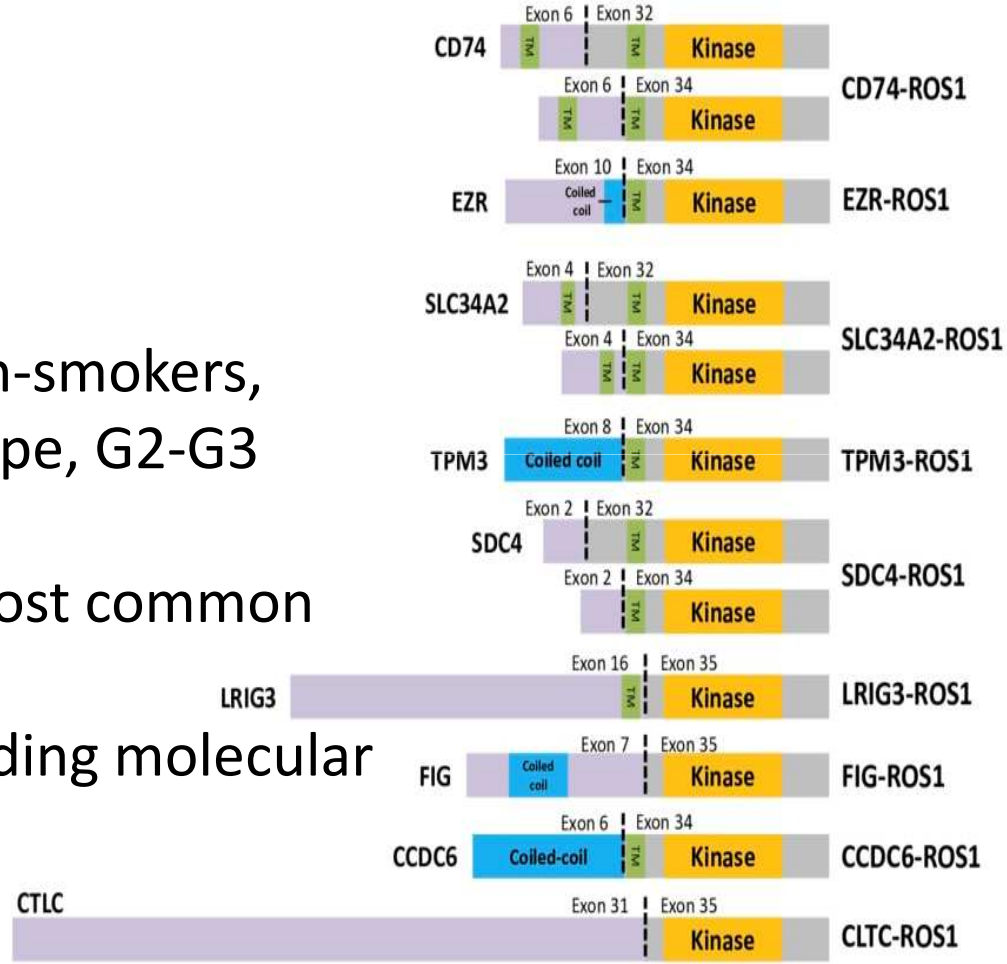
34,8 vs 10,9 months

9,4% vs 41,4%

Peters et al., *NEJM*, 2017, Camidge et al., *ASCO* 2018

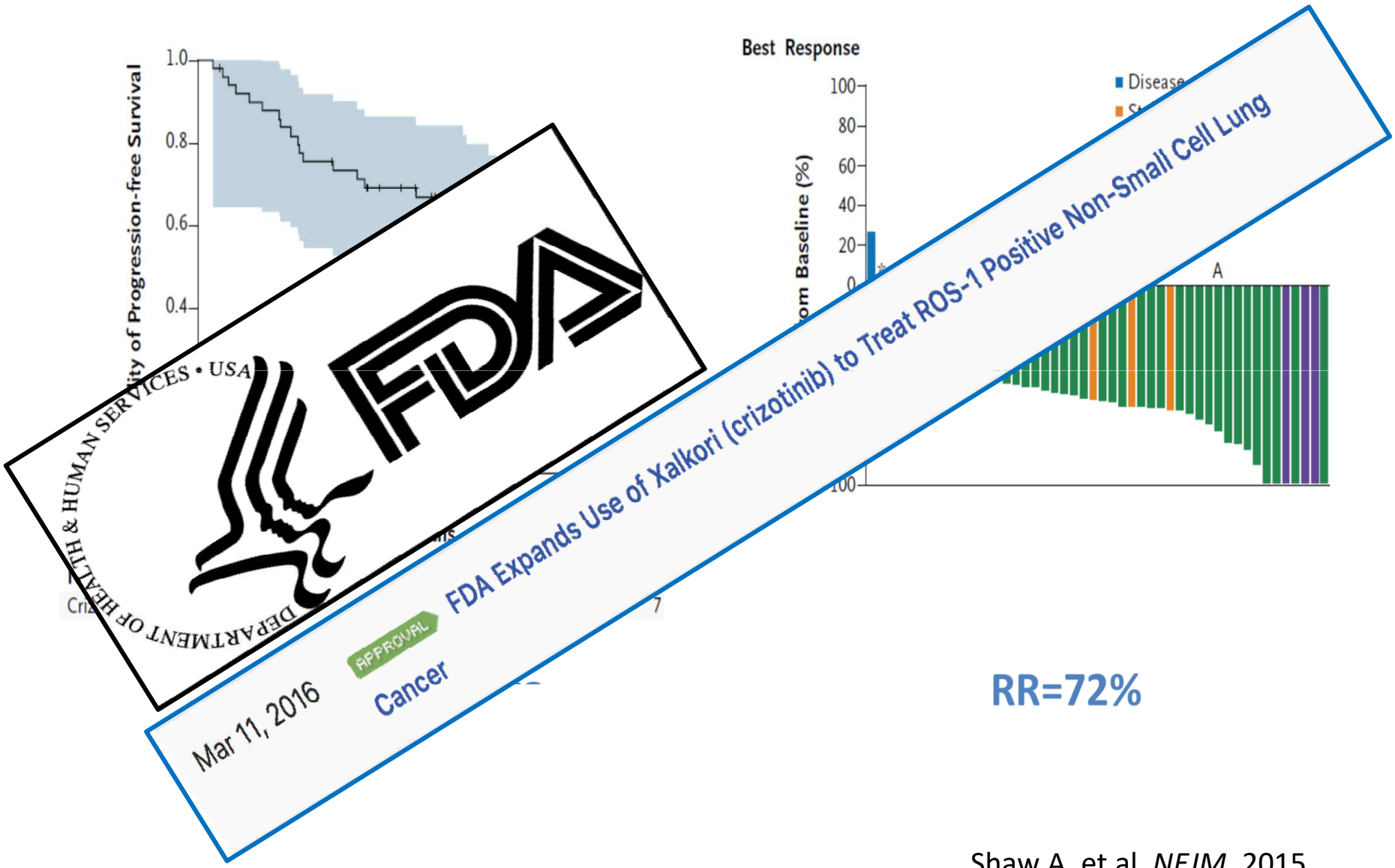
ROS1 rearrangement in NSCLC

- Incidence in NSCLC: 1-2%
  (Asian race: 2-3%)
- More common: younger, non-smokers, adenocarcinoma, solid subtype, G2-G3
- Fusion: 12 partners, CD74 most common
- Not observed with other leading molecular driver alterations
- Diagnostics: NGS



Kohno T. et al., *Trans Lung Cancer Res*, 2015

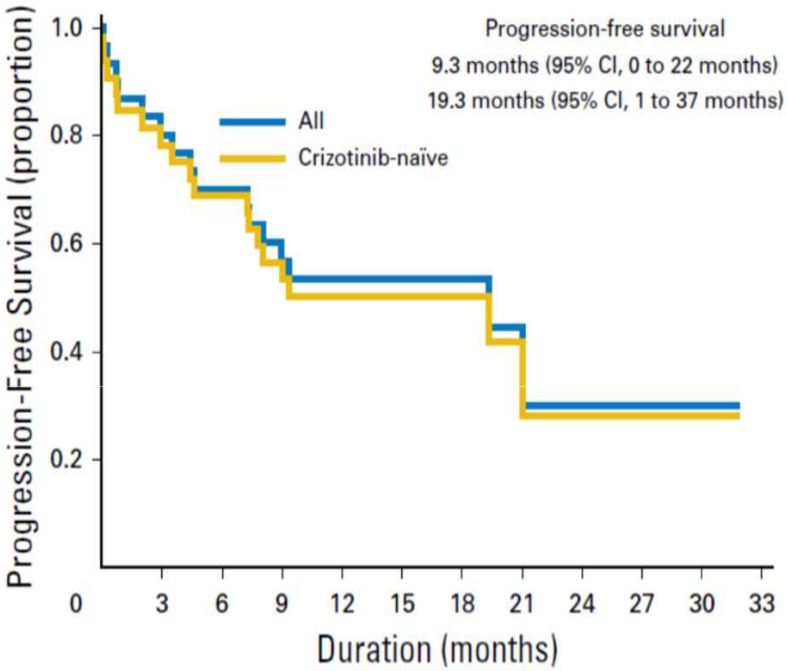
Crizotinib in *ROS1*+ NSCLC: PROFILE 1001

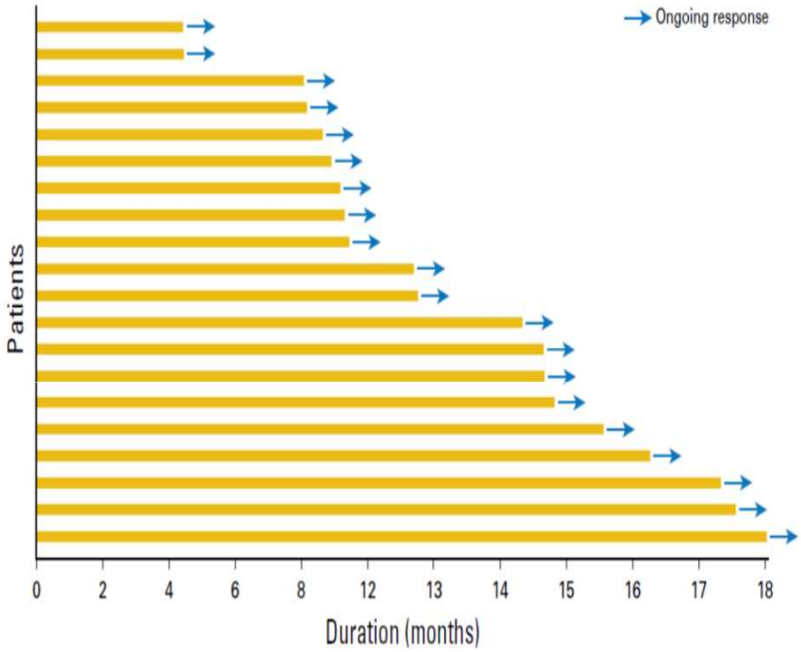


RR=72%

Shaw A. et al, *NEJM*, 2015

Ceritinib in *ROS1* (+) NSCLC



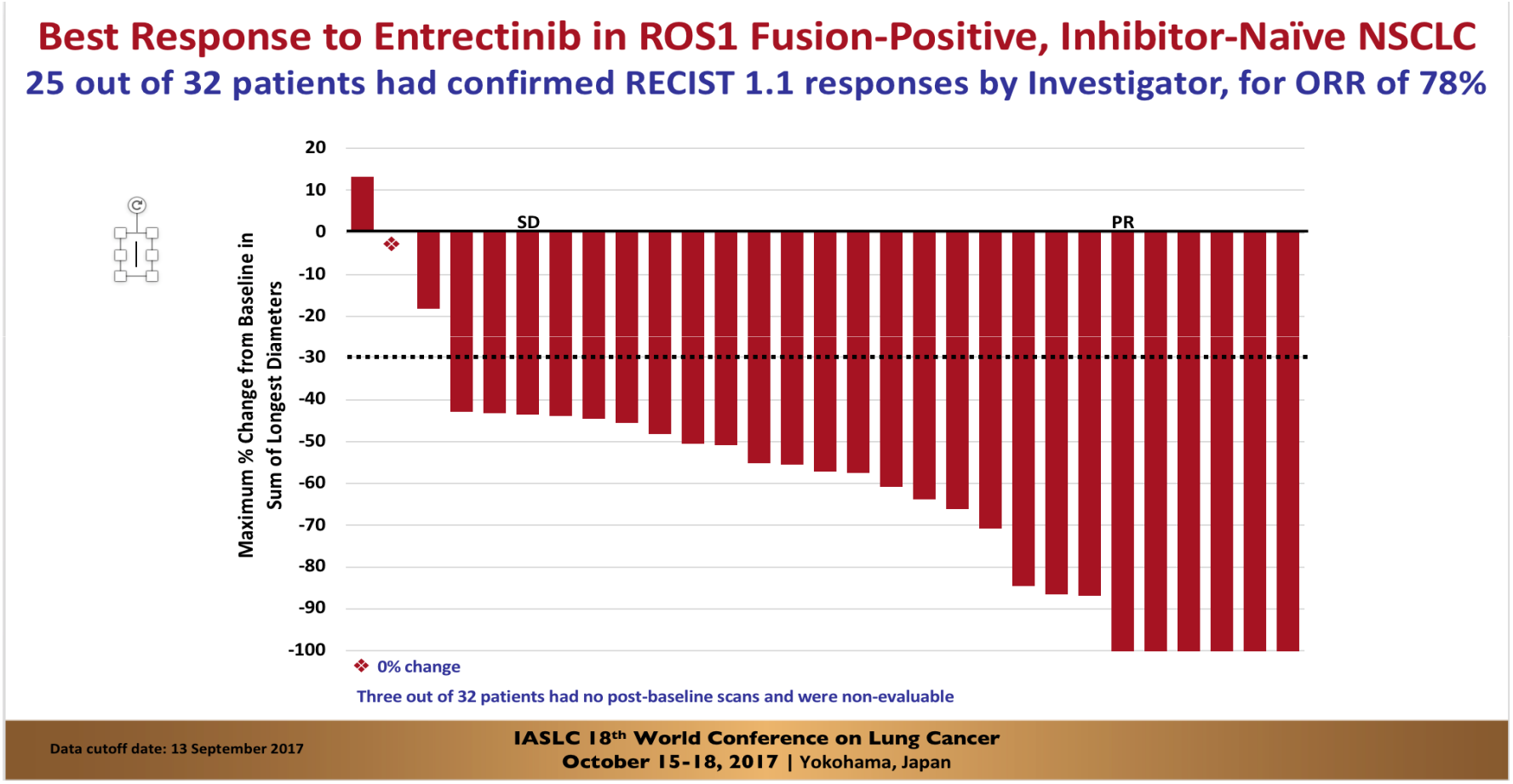


– ORR = 62% (67% in not previously treated with crizotinib)
– mPFS = 9,3 months (19,3 months in not previously treated with crizotinib)
– mOS = 24 months
– most common reported AEs in >50% patients: diarrhoea (78%), nausea (59%), anorexia (56%) i vomiting (53%), AE mostly G1 or G2

Sun Min Lin et al, *JCO*, 2017

Entrectinib in *ROS1+* NSCLC:

ALKA-372-001, STARTRK-1, STARTRAK-2



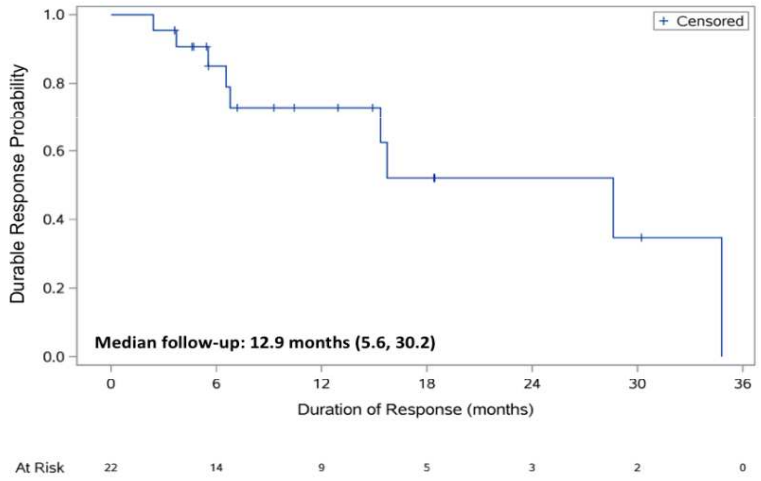
Myung-Ju Ahn et al., WCLC, 2017

Entrectinib in *ROS1+* NSCLC:

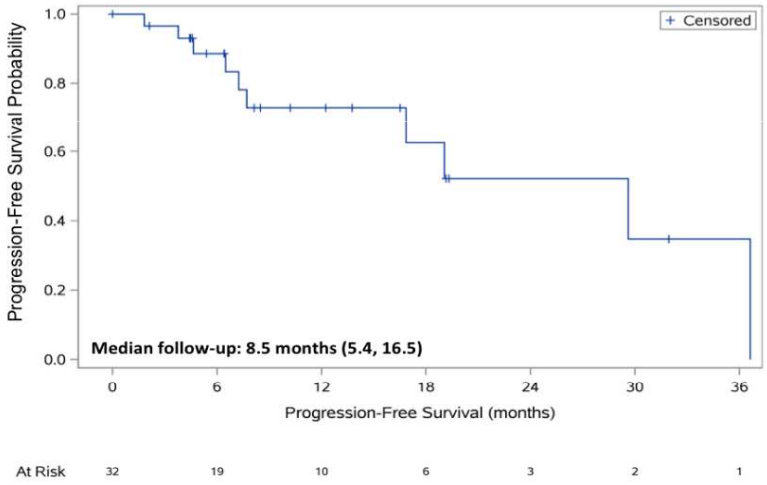
ALKA-372-001, STARTRK-1, STARTRAK-2

Durability of Entrectinib Treatment in ROS1+ NSCLC Patients (by BICR)

Median DOR of 28.6 months (95% CI: 6.8, 34.8)



Median PFS of 29.6 months (95% CI: 7.7, 36.6)

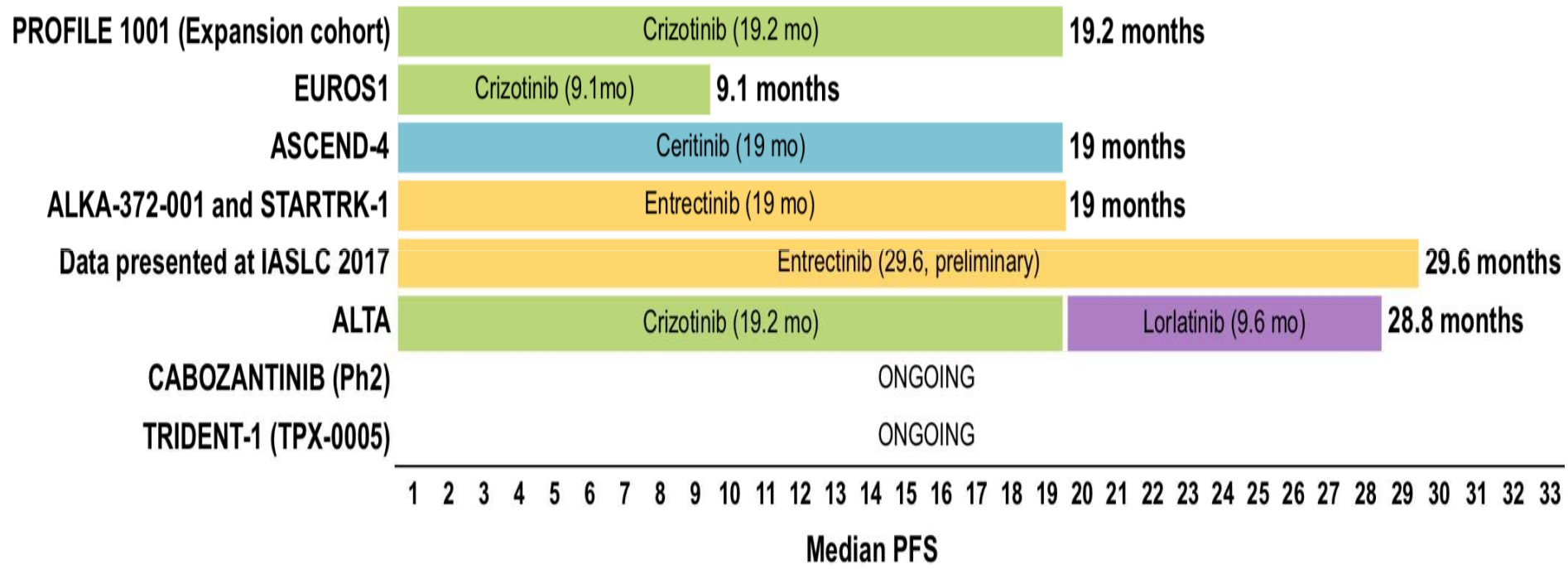


Data cutoff date: 13 September 2017
BICR = blinded independent central review

IASLC 18th World Conference on Lung Cancer
October 15-18, 2017 | Yokohama, Japan

Myung-Ju Ahn et al., WCLC, 2017

Treatment options in *ROS1*+ NSCLC



Shaw A et al., *NEJM*, 2014, Mazières et al., *JCO*, 2015, Soria JC et al, *Lancet*, 2017, Solomon et al. *IASLC*, 2017. Drillon et al, *Cancer Discovery* 2017. Lin JJ, Shaw AT, *JTO*, 2017, Ortiz-Cuaran S, *WCLC* 2017

Activity of *ROS1* inhibitors in crizotinib refractory NSCLC

Preclinical data (not all validated in patients)

	Gatekeeper	αC helix		Solvent front	
	L2026M	S1986Y/F	G2032R	D2033N	L1951R
Crizotinib	No	No	No	No	No
Ceritinib	Yes	No	No	No	No
Brigatinib	Yes	Unknown	No	No	No
Lorlatinib	Yes	Yes	Yes/No	Yes	Unknown
Entrectinib	No	Unknown	No	Unknown	Unknown
TPX-0005	Yes	Unknown	Yes	Yes	Unknown
Cabozantinib	Yes	Unknown	Yes	Yes	Yes

Lin J, Shaw A, *JTO*, 2017

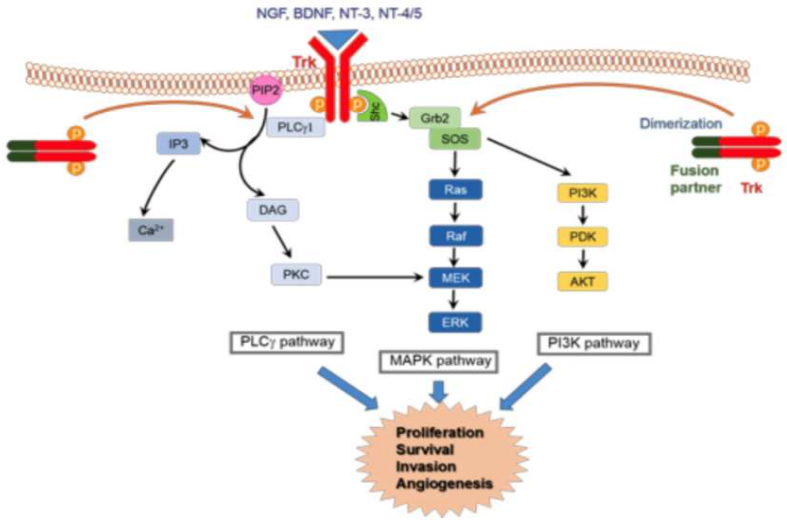
TRK receptors family

- TRK – receptor of tyrosine kinase associated with tropomiosin
- Activated by neurotrophins
- *NTRK1* (NTRKA), *NTRK2* (NTRKB), *NTRK3* (NTRKC)
- Incidence of fusion in NSCLC: < 1%
- Fusion incidence

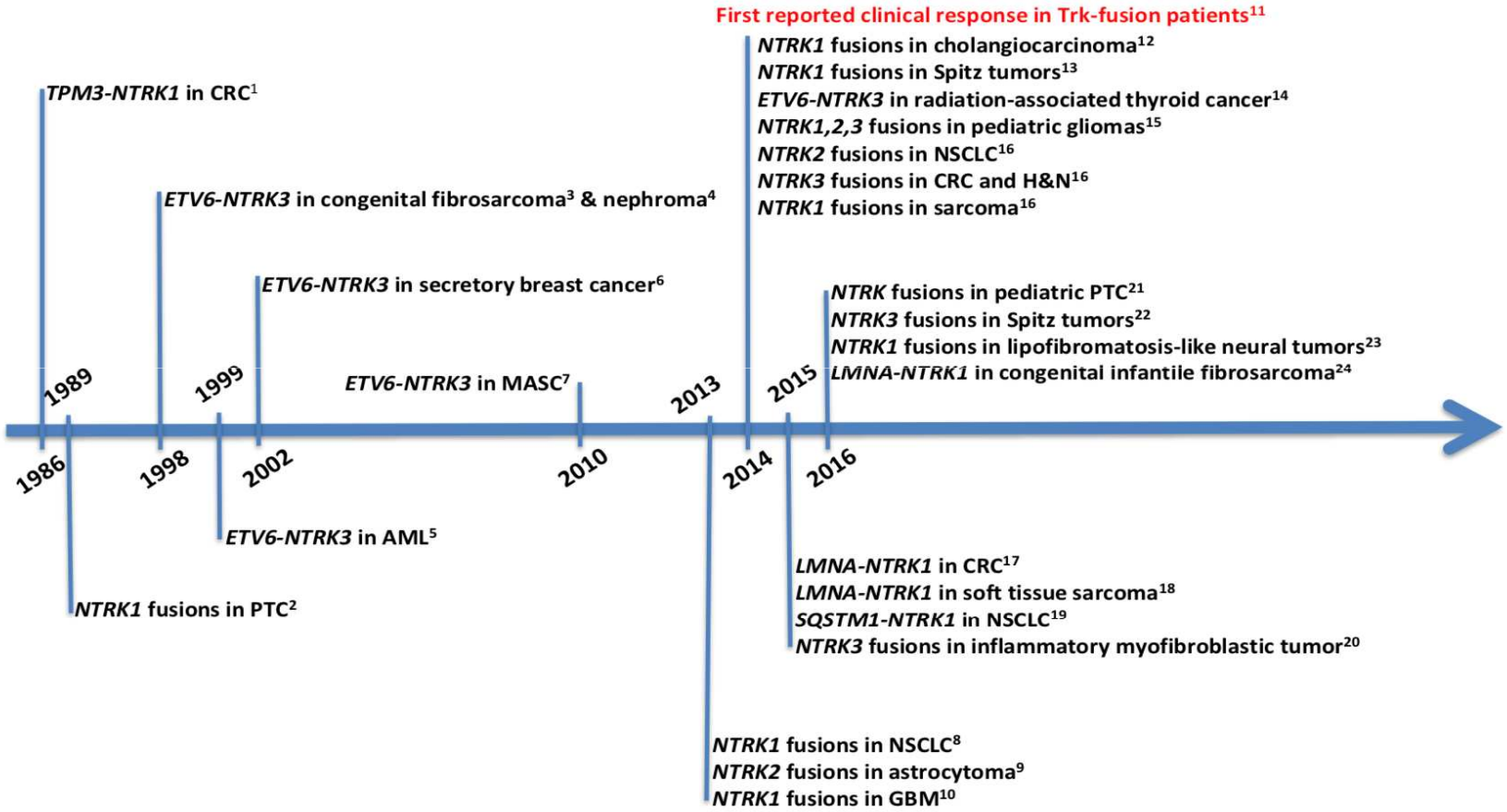
  is not associated with

  etnicity, sex, age or other

  features

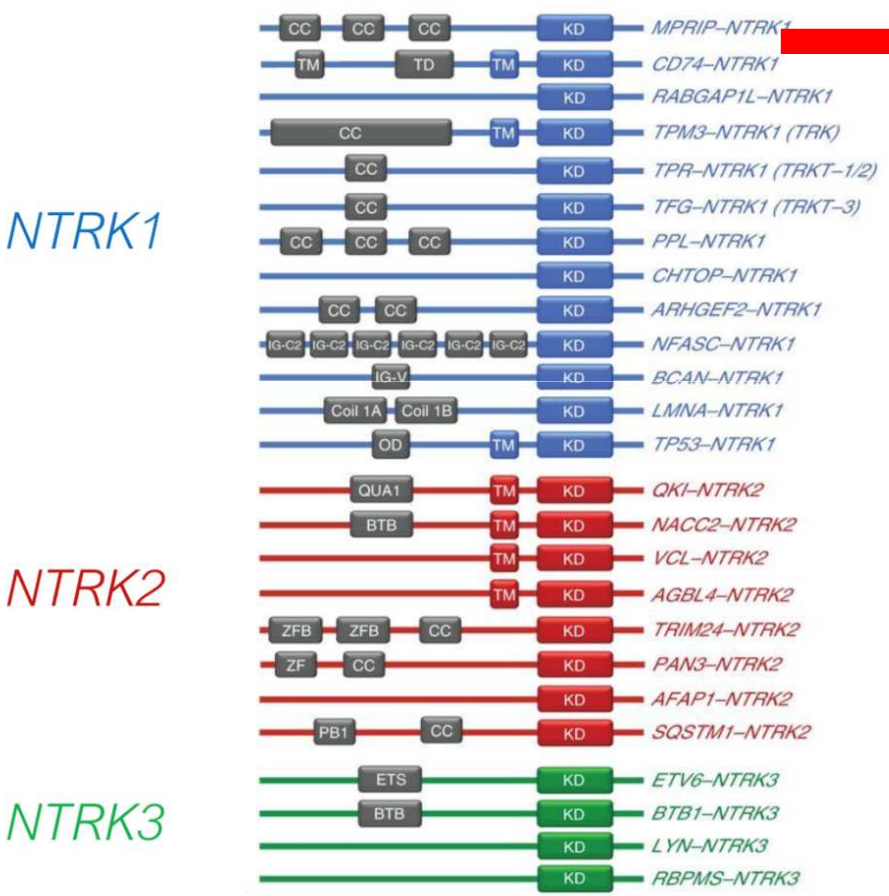


NTRK rearrangements in solid tumors



IGNYTA data on file

NTRK fusions in solid tumors



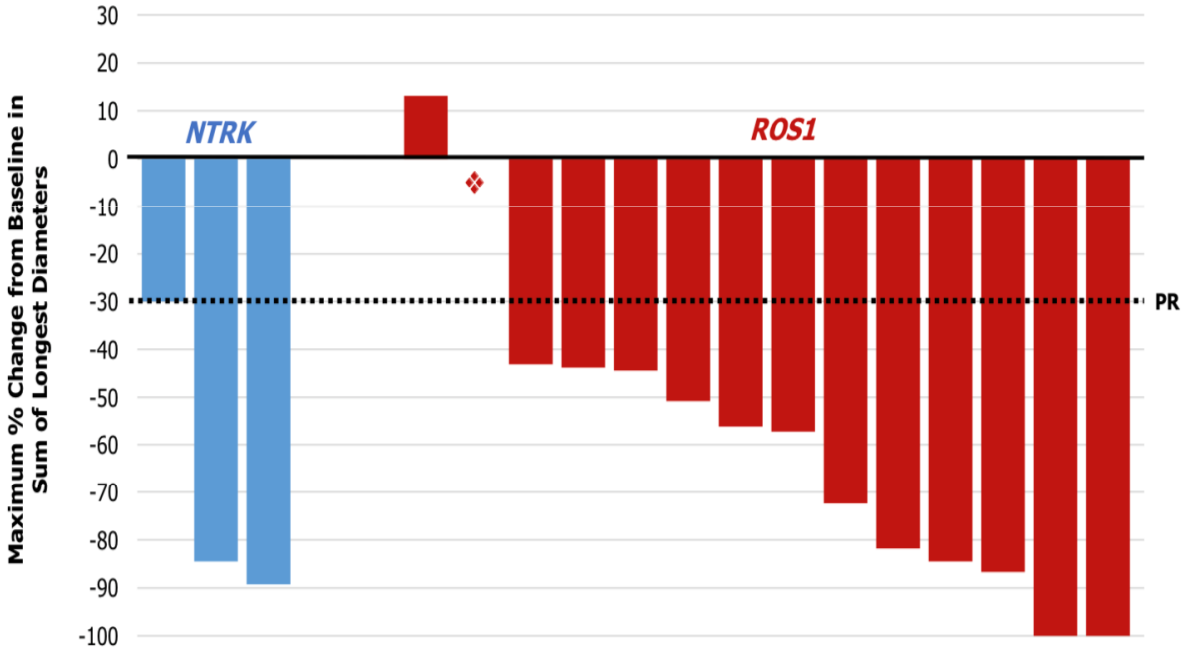
Gene fusion	Cancer	Frequency
NTRK1	Lung adenocarcinoma	3/91 (3.3%)
NTRK1	Intrahepatic cholangiocarcinoma	1/28 (3.6%)
NTRK1	Colorectal cancer	3 Isolated reports 1/66 (1.5%)
NTRK1	Papillary thyroid cancer	28/228 (12.3%)
NTRK1	Spitzoid neoplasms	23/140 (16.4%)
NTRK1	Glioblastoma	2/185 (1.1%) 4/162 (2.5%) 1/157
NTRK1	Sarcoma (TCGA)	1/103 (1%)
NTRK2	Astrocytoma	3/96 (3.1%)
NTRK2	Lung adenocarcinoma (TCGA)	1/513 (0.2%)
NTRK2	Head and neck squamous cell carcinoma (TCGA)	1/411 (0.2%)
NTRK2	Brain lower grade glioma (TCGA)	2/461 (0.4%)
NTRK3	Secretory breast carcinoma	12/13 (92%)
NTRK3	Mammary analogue secretory carcinoma	15/15 (100%)
NTRK3	Papillary thyroid cancer	9/62 (14.5%)[a] 7/243 (2.9%)[b]
NTRK3	Acute myeloid leukemia	2 Case reports
NTRK3	Congenital mesoblastic nephroma	5/6 (83%)
NTRK3	Congenital fibrosarcomas	10/11 (91%) 5/5 (100%)
NTRK3	Ph-like acute lymphoblastic leukemia	1/154 (0.7%)
NTRK3	Colon adenocarcinoma (TCGA)	2/286 (0.7%)
NTRK3	Thyroid carcinoma (TCGA)	7/498 (1.5%)
NTRK3	Skin cutaneous melanoma (TCGA)	1/374 (0.3%)
NTRK3	Head and neck squamous cell carcinoma (TCGA)	1/411 (0.2%)
NTRK1/NTRK2/NTRK3	Pediatric gliomas	8/112 (7.1%)

Vaishnavi et al., *Cancer Discovery*, 2015

Entrectinib activity in patients with solid tumors and *NTRK1/2/3* or *ROS1 fusion*:

STARTRK-1 and ALKA-372-001

Best Response in TKI Treatment-Naïve *NTRK*- and *ROS1*-fusion Tumors (n=17)



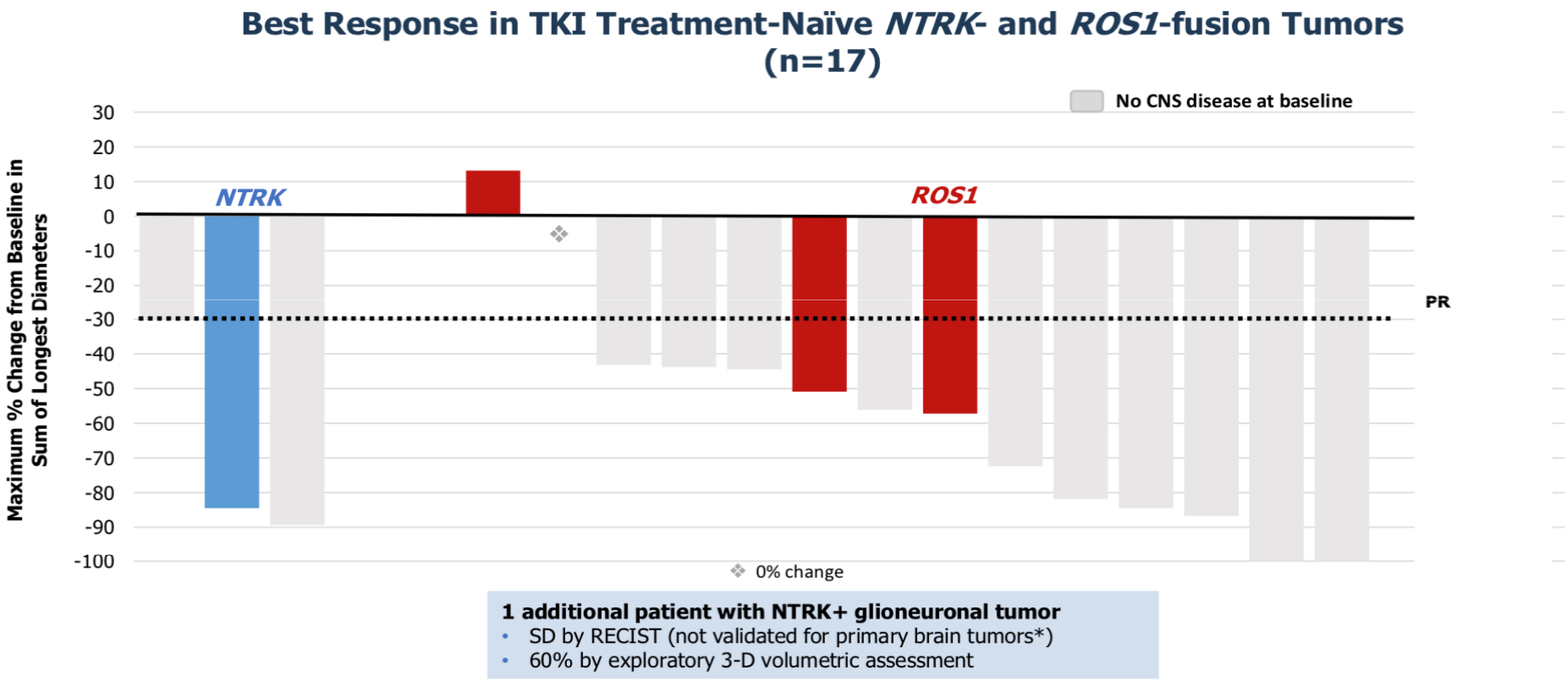
Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%

1 additional patient with NTRK+ glioneuronal tumor

- SD by RECIST (not validated for primary brain tumors*)
- 60% by exploratory 3-D volumetric assessment

Drilon A. et al., *Cancer Discov*, 2017

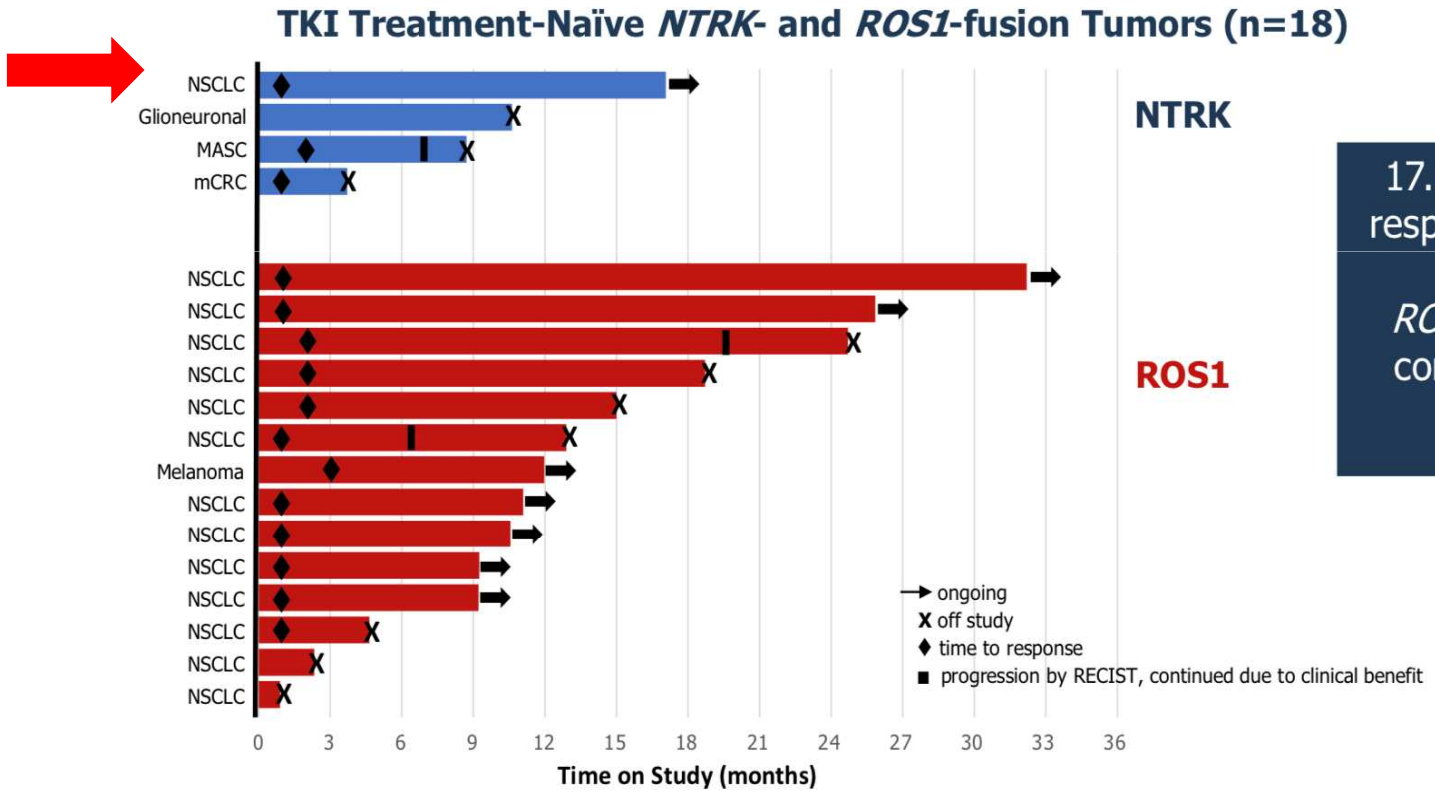
Entrectinib activity in patients with solid tumors and brain metastases and *NTRK1/2/3* or *ROS1 fusion*:



RECIST responses were noted across TRK and ROS1 in 60% of patients (3 out of 5) with primary or metastatic disease involving the brain

Drilon A. et al., *Cancer Discov*, 2017

Entrectinib treatment duration in patients with solid tumors and NTRK1/2/3 or ROS1 fusion: STARTRK-1 i ALKA-372-001

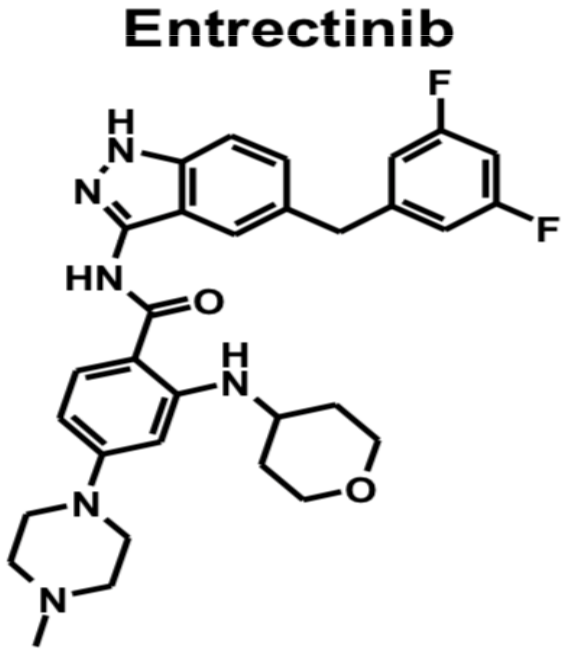


17.3 month median duration of response (95% CI: 12.7 months, NR) observed in *ROS1*-fusion positive NSCLC is comparable to DOR seen with crizotinib

Drilon A. et al., *Cancer Discov*, 2017

Safety of entrectinib treatment

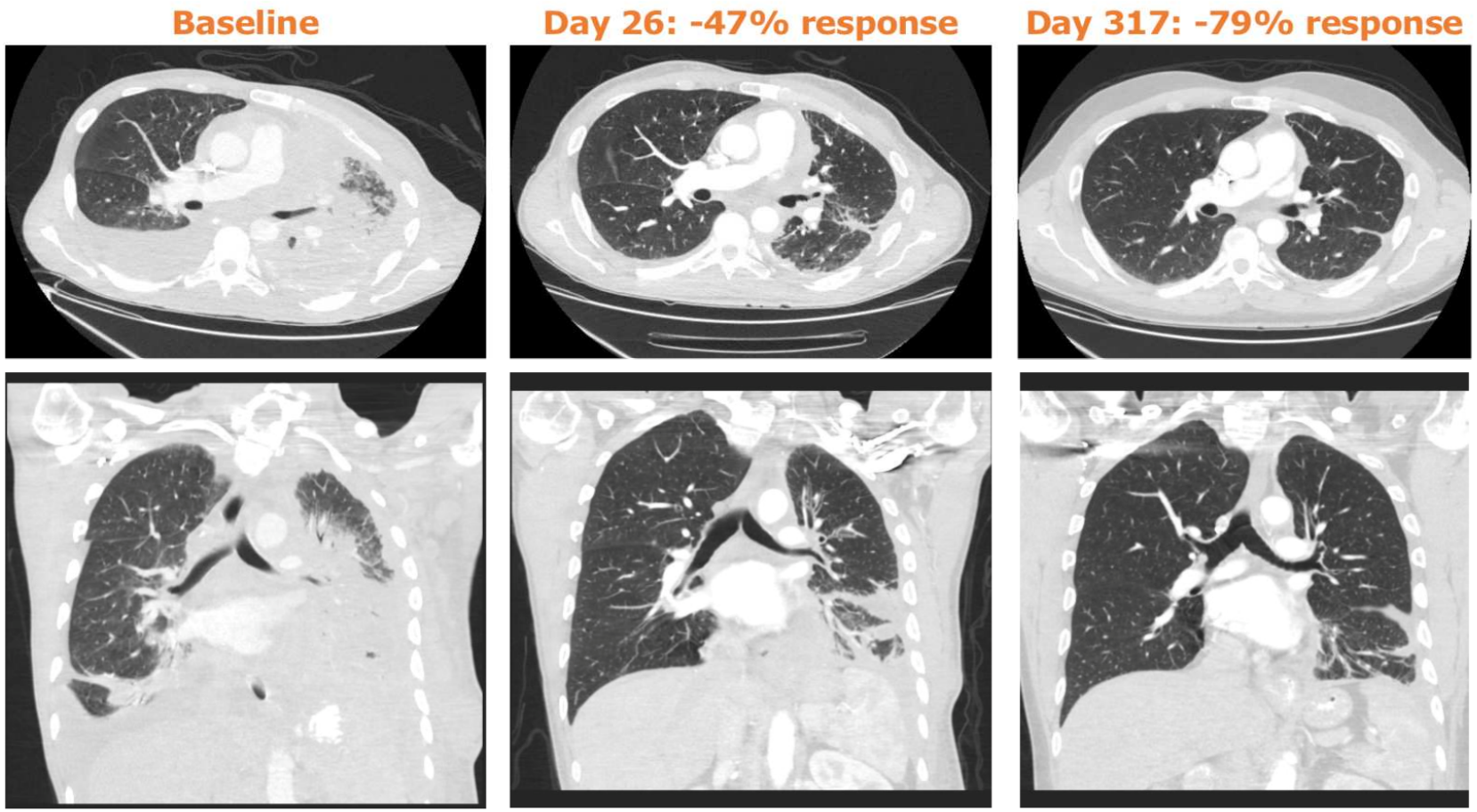
- 203 treated patients
- AE mostly G 1-2 and reversible
- AEs leading to treatment interruptions: 32%
- AEs leading to dose reductions: 19%
- Aes leading to treatment discontinuation: 3%
- SAE: 9%



Most Common (≥10%) Treatment-Related Adverse Events, n (%)	Patients treated at the RP2D (N=203)		
	All Grades	Grade 3	Grade 4*
Dysgeusia	78 (38)	1 (1)	--
Fatigue	59 (29)	6 (3)	--
Constipation	47 (23)	1 (1)	--
Dizziness	46 (23)	1 (1)	--
Weight increased	39 (19)	10 (5)	--
Diarrhea	35 (17)	1 (1)	--
Nausea	33 (16)	--	--
Paresthesia	32 (16)	--	--
Myalgia	27 (13)	1 (1)	--
Peripheral edema	25 (12)	--	--
Anemia	23 (11)	9 (4)	--
Blood creatinine increased	22 (11)	1 (1)	--
Vomiting	22 (11)	--	--
Arthralgia	21 (10)	1 (1)	--

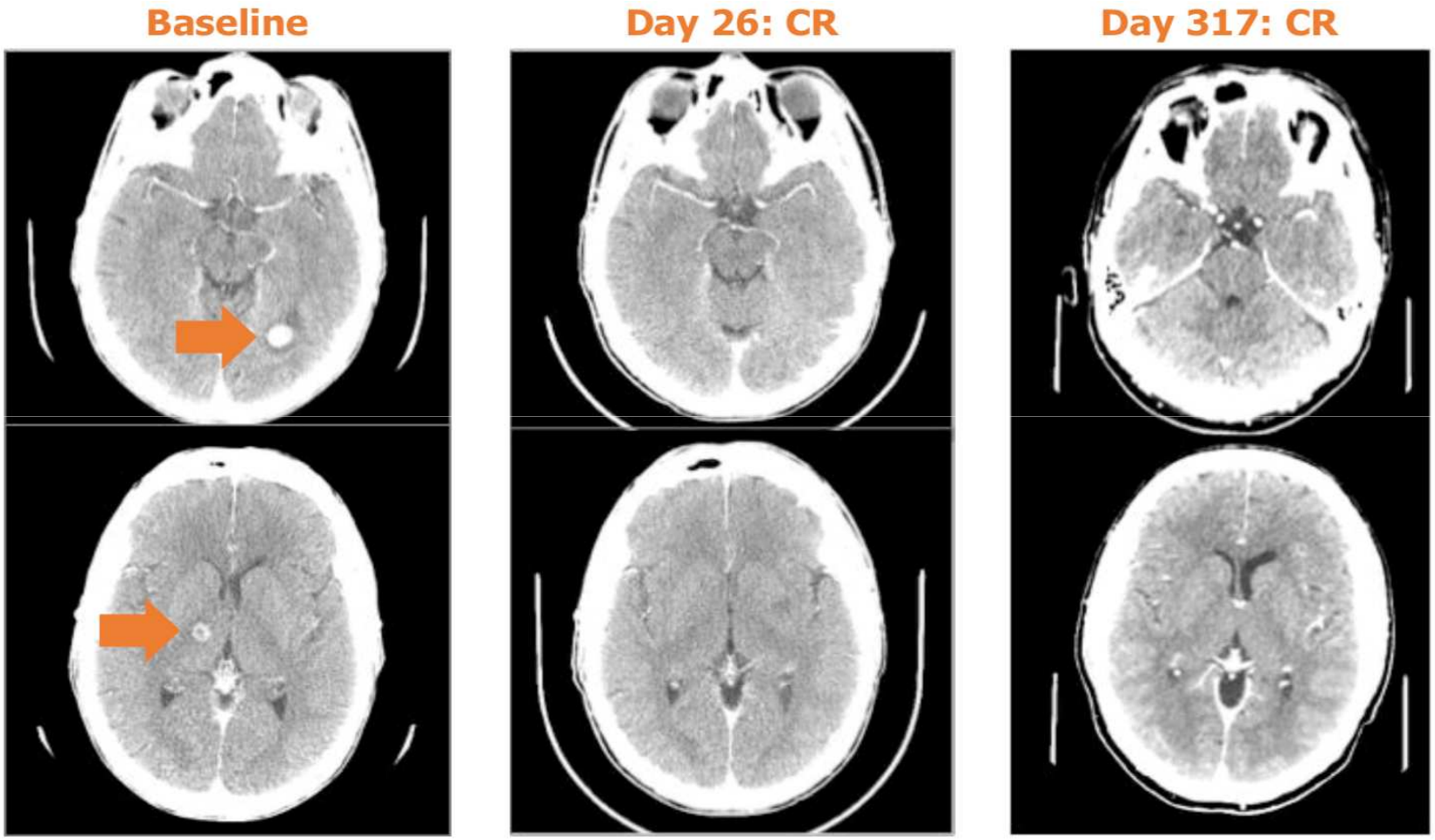
IGNYTA data on file

Entrectinib in patient with NTRK-rearranged NSCLC



Shaw A. et al., *J Thor Oncol*, 2015

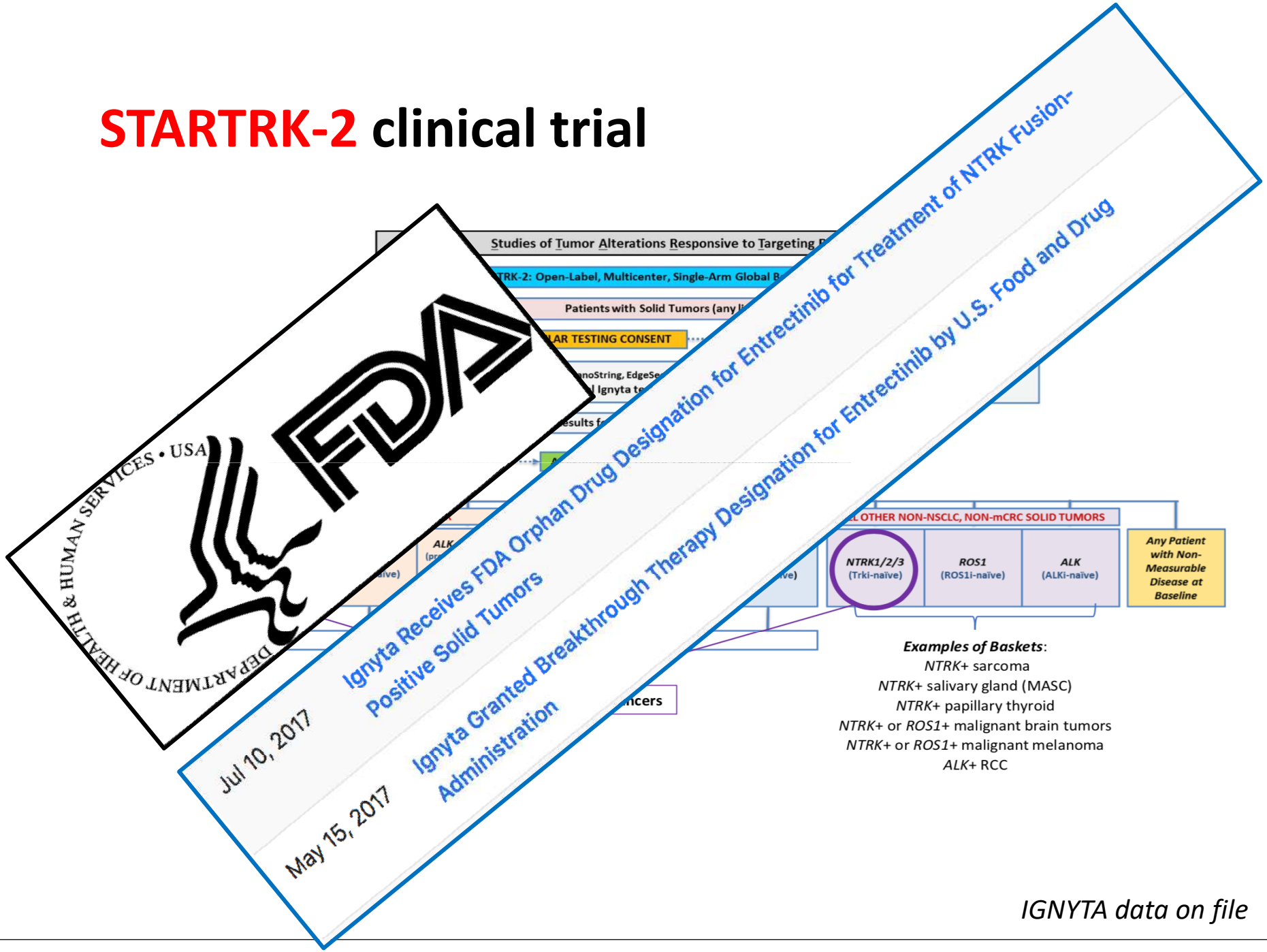
Entrectinib in patient with NTRK-rearranged NSCLC



Patient clinically progression-free >12 months

Shaw A. et al., *J Thor Oncol*, 2015

STARTRK-2 clinical trial



IGNYTA data on file

Larotrectinib (LOXO-101)

ASCO Meeting Library

Sign In

The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers.

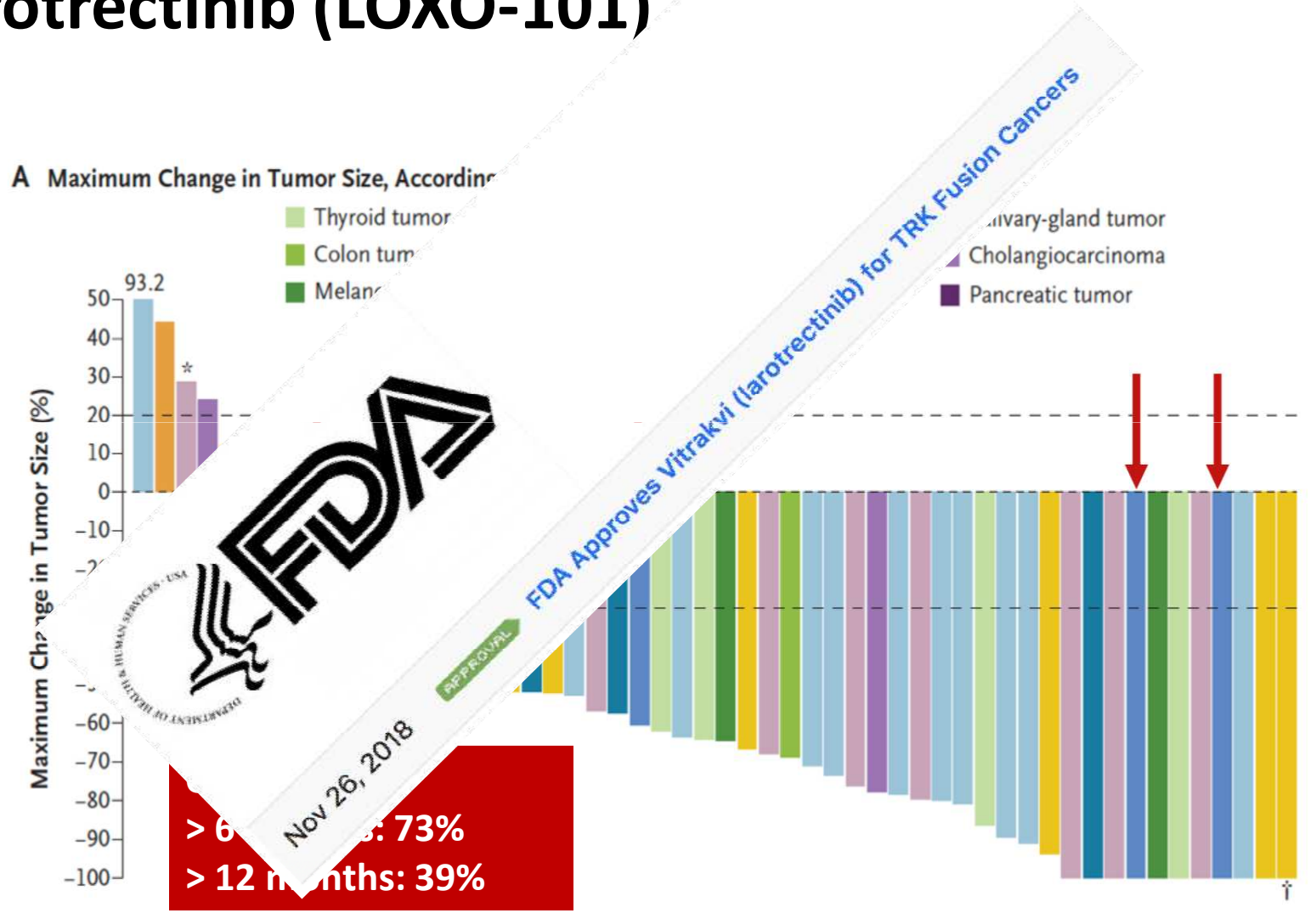
Add to Collection

Presented Saturday, June 3, 2017

Conclusions:

Larotrectinib has demonstrated consistent and durable antitumor activity in TRK fusion cancers, across a wide range of ages and tumor types, and was well-tolerated. Larotrectinib could be the first targeted therapy developed in a tissue type-agnostic manner, and the first developed simultaneously in adults and pediatrics. Clinical trial information: NCT02576431, NCT02122913, NCT02637687

Larotrectinib (LOXO-101)



Drilon et al., *NEJM*, 2018

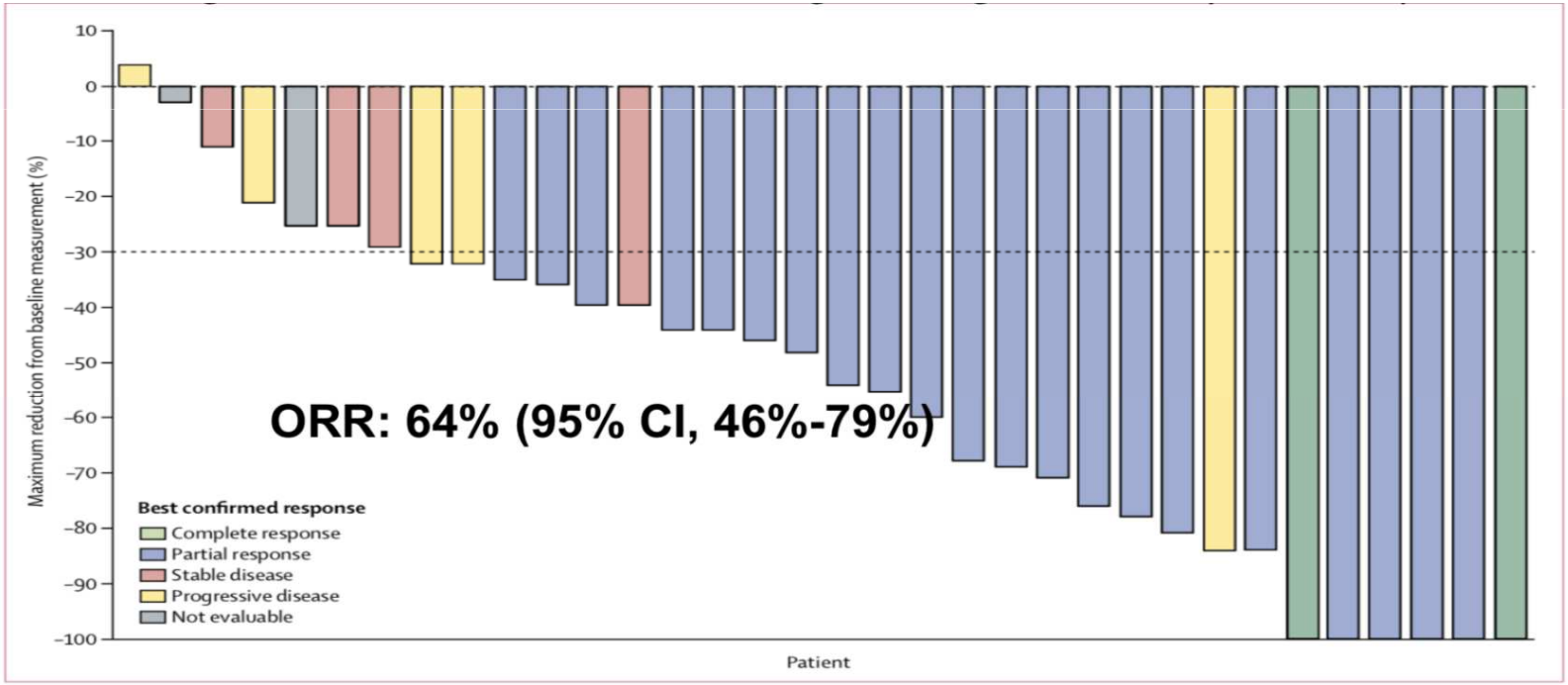
BRAF mutations in NSCLC

- Incidence: 2-4%
- Mostly adenocarcinoma, uncommon in other histological subtypes of NSCLC
- Mainly in women and oraz current and former smokers
- V600E BRAF mutation represents about 50% of BRAF mutations

BRAF mutated NSCLC*:* BRF 113928

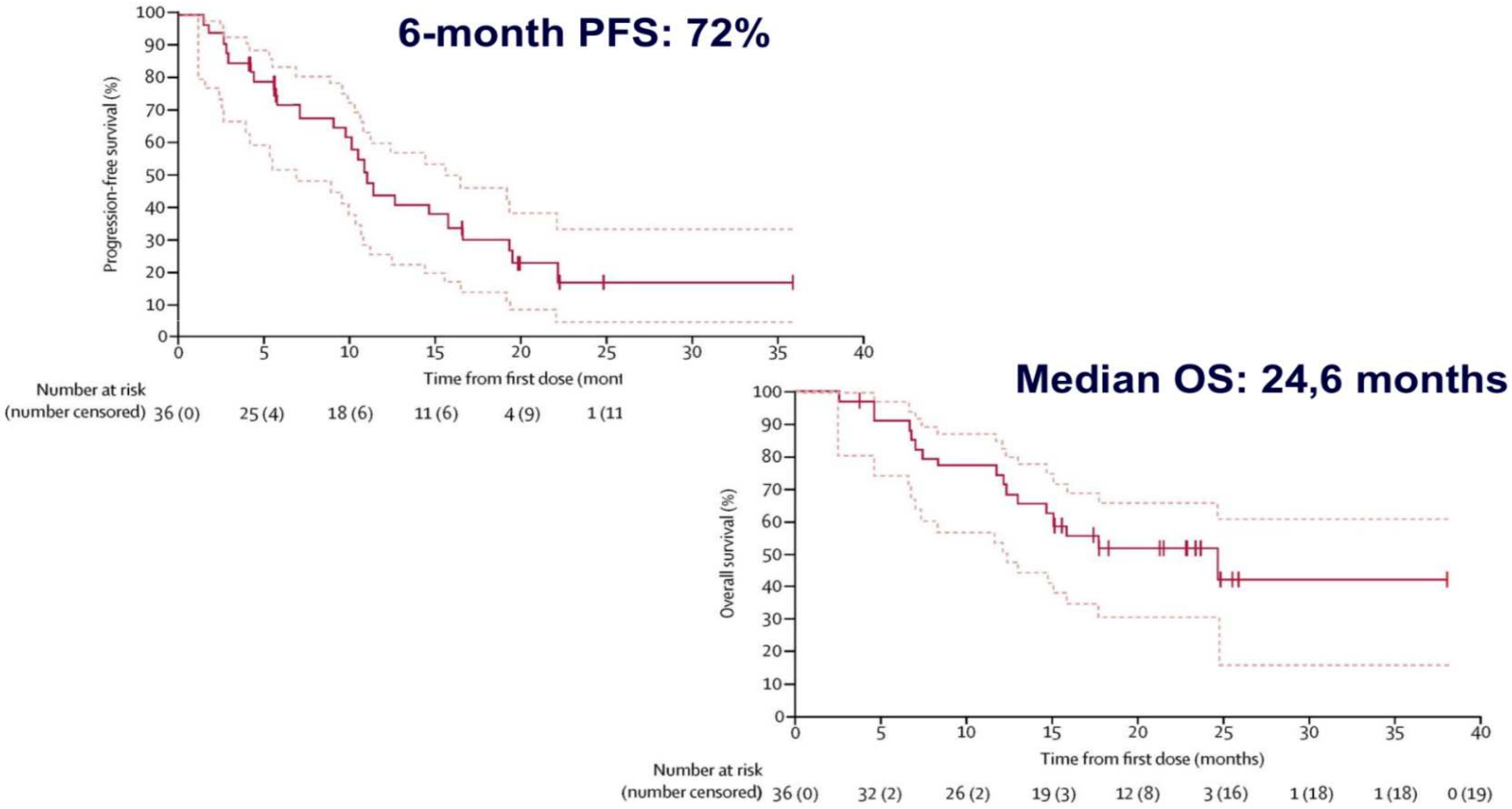
Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

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



Planchard D. et al., *Lancet Oncology*, 2017

BRAF mutated NSCLC*:* BRF 113928



Planchard D. et al., *Lancet Oncology*, 2017

CONTEMPORARY ONCOLOGY?

FASCINATING JOURNEY HAS JUST BEGUN…..