Targeted Therapy: EGRF, ALK and ROS-1

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Disclosures

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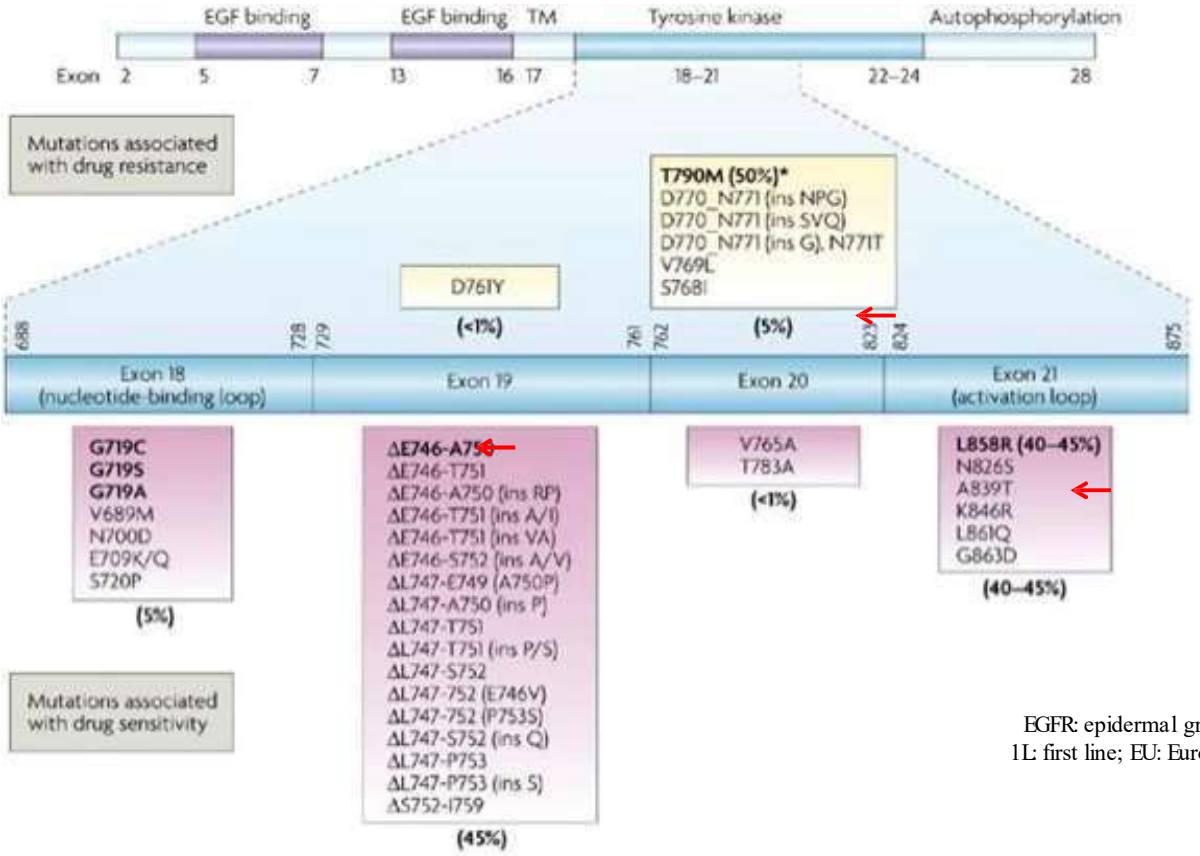
Syndax
Heat Biologics
Exosomes DX
Loxo Oncology

Speakers Bureau/Stocks: *None*

EGFR Tyrosine Kinase inhibitors (TKI)

- Gefitinib
- Afatinib
- Osimertinib*
- Erlotinib
- Dacomitinib
- Icotinib

EGFR Kinase Mutations (15-20%)



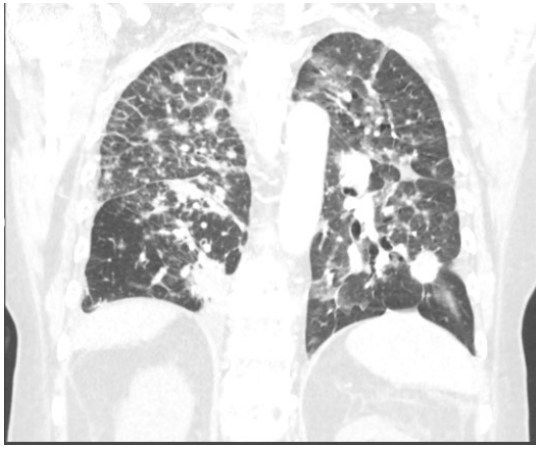
2003	Gefitinib conditionally approved
2004	EGFR TKD mutation described
2009	Erlotinib approved 1L EGFRmt; Gefitinib approved in EU
2013	Afatinib approved 1L EGFRmt
2015	Gefitinib approved 1L EGFRmt
2015	Osimertinib approved 2L T790M+
2018	Osimertinib approved 1L EGFRmt
2018	Afatinib approved in uncommon mutations G719X, L861Q, S768I
2018	Dacomitinib approved 1L EGFRmt

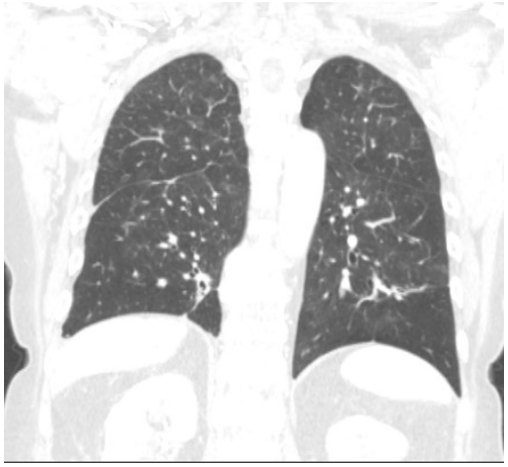
EGFR: epidermal growth factor receptor; TKD: tyrosine kinase domain; 1L: first line; EU: European Union; mt: mutation positive; 2L: second line

Sharma et al Nat Rev Cancer 2007

Clinical Case

62 year old with
Adenocarcinoma Stage IV
s/p carboplatin/pemetrexed
and bevacizumab
s/p nivolumab
Started on afatinib after EGFR-RAD51 was discovered by Foundation Medicine





2 years later patient still stable

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Letter to the Editor

EGFR-RAD51 Fusion: A Targetable Partnership Originated from the Tumor Evolution?

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- Basic and Translational Investigation Unit, Oncosalud-Auna, San Borja, Lima, Peru
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Available online 19 February 2018

CrossMark

Randomized Studies of First Line EGFR TKI in Patients with EGFR Mutations

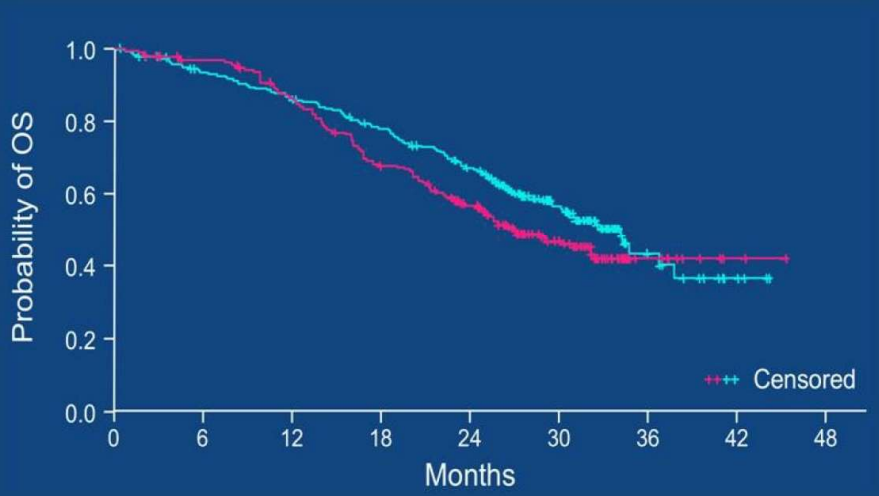
Author	Study	Agent	N (EGFRm+)	RR	Median PFS (months)	Median OS (months)
Mok et al.	IPASS	Gef	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Lee et al.	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al.	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al.	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al.	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al.	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al.	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
Wu et al.	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

Mok et al. *N Engl J Med*. 2009;361:947-57
Lee et al. WCLC 2009
Mitsudomi et al. *Lancet Oncol*. 2010;11;121-8
Maemondo et al. *N Engl J Med*. 2010;262:2380-88
Zhou et al. ESMO 2010
Rosell et al. ASCO 2011
Yang et al. ASCO 2012, Sequist IASLC 2012
Wu et al. ASCO 2013

Cross-over to an EGFR TKI in the control groups felt to reduce detectability of any possible OS benefit (all mutations)

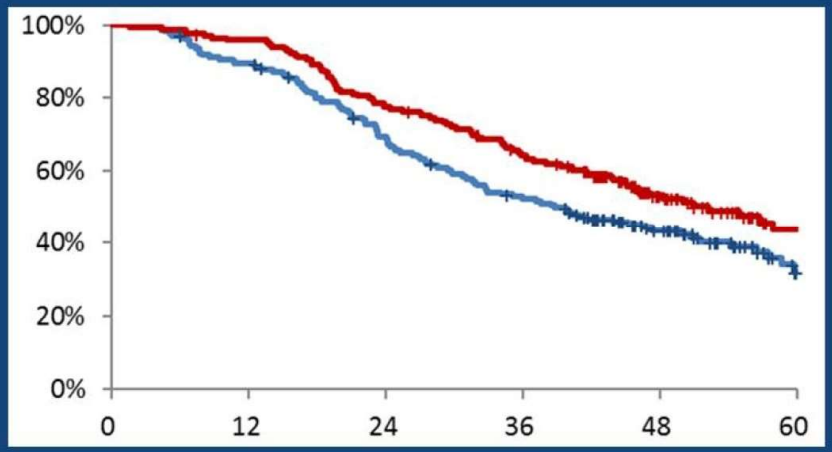
First phase III trials demonstrating OS benefit in EGFR M+ NSCLC
with an EGFR TKI control

ARCHER 1050 (n=452)
Median f/u 31.3 m



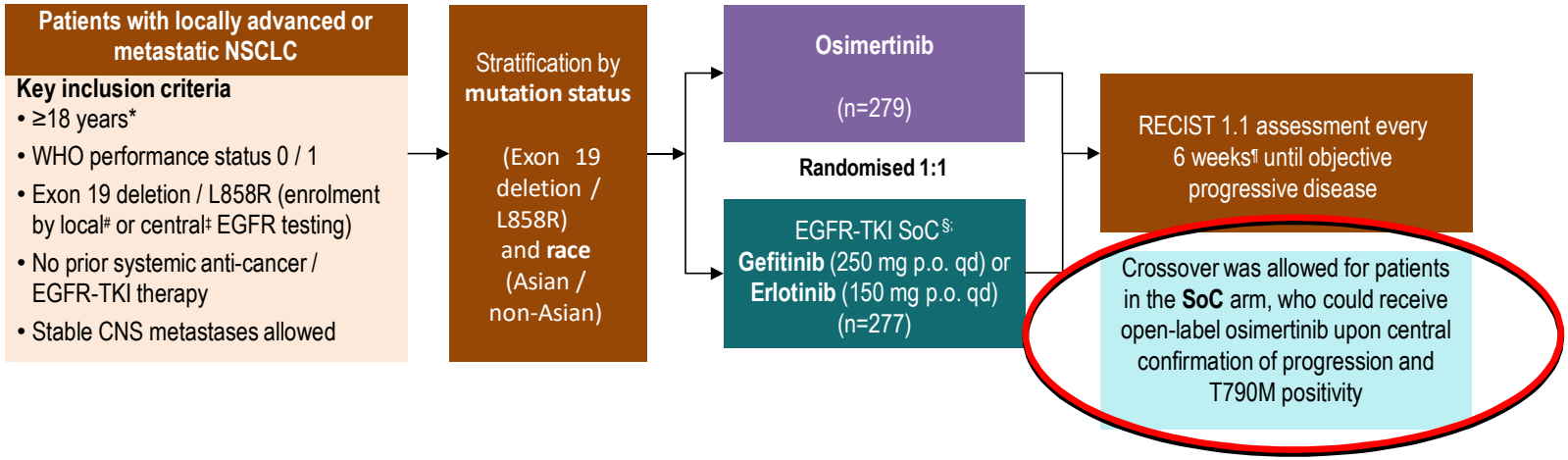
	Median OS	95% CI
gefitinib	26.8 m	23.7 - 32.1
Dacomitinb	34.1 m	29.5 - 37.7
	HR 0.76 (95%CI 0.582 - 0.993) p=0.0219	

NEJ009 (n=345)
Median f/u minimum 42 m



	Median OS	95% CI
Gefitinib	38.8 m	31.1 - 50.8
Gefitinib + PemCb	52.2 m	44.0 - NR
	HR 0.695 (95%CI 0.520 - 0.927) p=0.013	

FLAURA - Double-blind study design



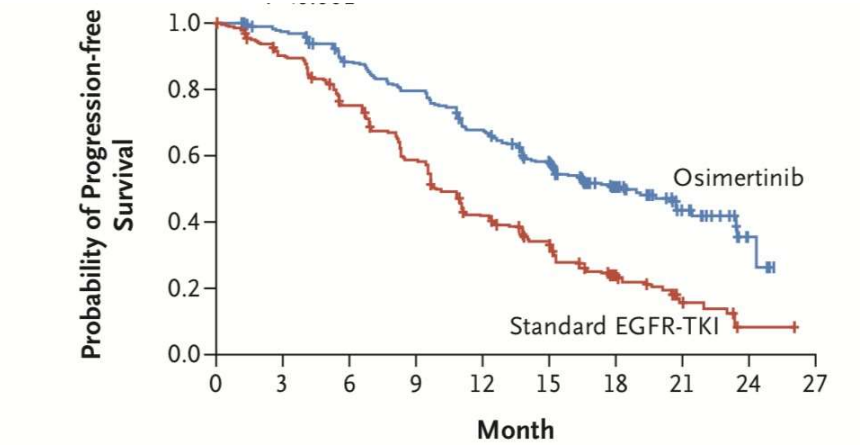
Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Ramalingam S. et al. ESMO 2017; Soria JC et al. N. Engl. J. Med. 2018;378:113-125

Outcomes of the FLAURA Study

- Improvement of PFS, primary endpoint, of 8.7 months favoring Osi (18.9 vs. 10.2, HR=0.46), benefit in all subgroups.



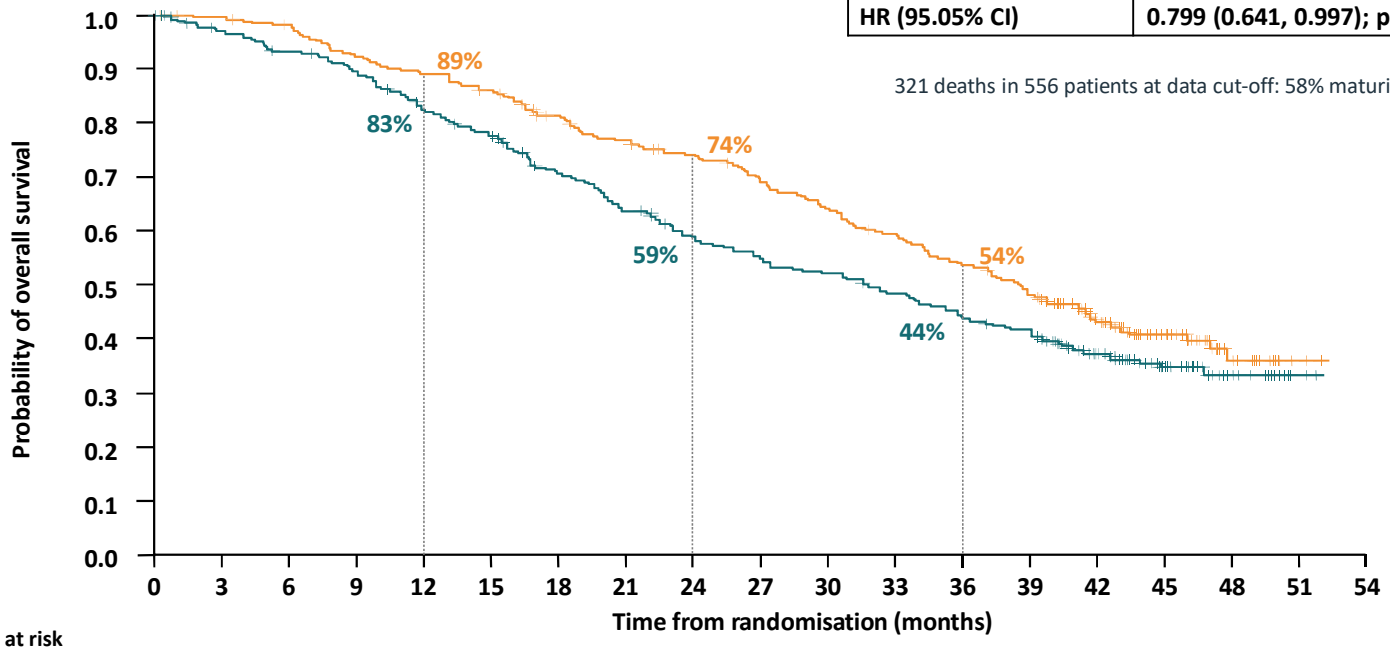
- PFS improvement seen and comparable in patients with and without brain mets at baseline
- Superior ORR and superior duration of response (49% vs. 19% at 18 months)
- Safety profile of Osi was comparable to SoC with lower rates of grade > 3 AEs and lower discontinuation rate

Ramalingam S. et al. ESMO 2017; Soria JC et al. N. Engl. J. Med. 2018;378:113-125

FLAURA: Final analysis—overall survival

	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); p=0.0462**

321 deaths in 556 patients at data cut-off: 58% maturity



No. at risk																		
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

Afatinib: Only FDA Approved Drug for Uncommon *EGFR* Mutations

	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

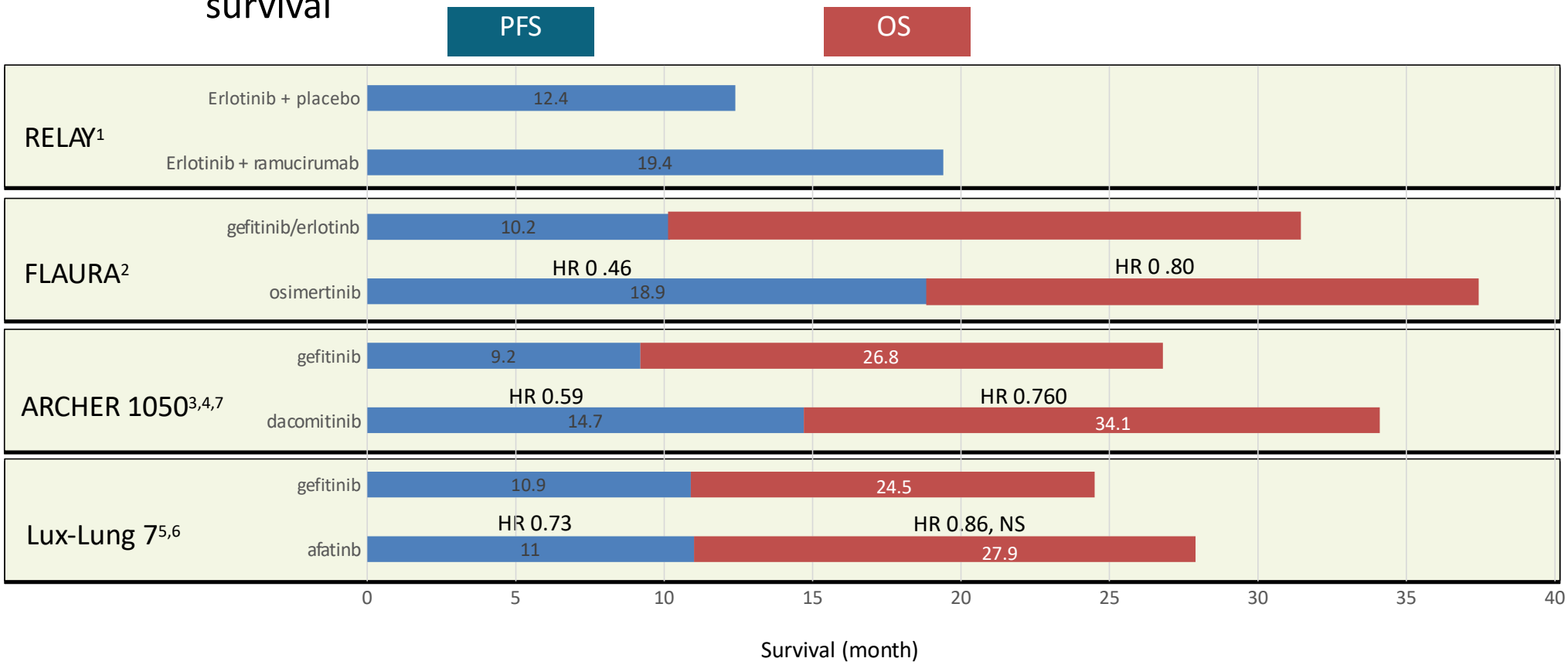
Data are n (%, 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

***Table 3*: Activity of afatinib in specific compound uncommon mutations**

Afatinib is active in NSCLC tumours that harboured certain types of uncommon EGFR mutations, especially G719X, L861G, and S768I, but less active in other mutations types. Clinical benefit is lower in patients with de-novo T790M and exon 20 insertion mutations.

James C-H Yang et al. Lancet Oncol 2015; 16:830-8.

Recent trials of the first line treatment for EGFR+ patients: Progression-free survival and overall survival



1. Nakagawa K, et al. ASCO 2019. Abstract 9000; 2. Soria JC, et al. N Engl J Med. 2018;378(2):113–125; 3. Wu YL, et al. Lancet Oncol. 2017;18(11):1454–1466;
4. Mok T, et al. ASCO 2018. Abstract 9004; 5. Paz-Ares L, et al. Ann Oncol. 2017;28(2):270–277; 6. Park K, et al. Lancet Oncol. 2016;17(5):577–89.;
7. Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

1st Line Treatment of *EGFR* NSCLC

Strategy	Trial	Treatment	Median PFS, months	PFS HR (95%CI)	Median OS, months	OS HR (95%CI)
2nd *or* 1st generation EGFR TKI	**CTONG 091**	Erlotinib *vs*. gefitinib	**13.0 *vs.*** 10.4	0.81 (0.62-1.05)	-	-
	LUX-Lung 7	Afatinib *vs*. gefitinib	**11.0 *vs.*** 10.9	**0.73 (0.57-0.95)**	27.9 *vs*. 24.5	0.86 (0.66-1.12)
	Archer 1050	Dacomitinib *vs*. gefitinib	**14.7 *vs*.** 9.2	**0.59 (0.47-0.74)**	**34.1** *vs*. 26.8	**0.76 (0.58-0.99)**
1st generation EGFR TKI + Antiangiogenic agents	**JO25567**	Erlotinib + bevacizumab *vs*. erlotinib	**16.0** *vs*. 9.7	**0.54 (0.36-0.79)**	47.0 vs. 47.4	0.81 (0.53-1.23)
	NEJ026	Erlotinib + bevacizumab *vs*. erlotinib	**16.9** *vs*. 13.3	**0.61 (0.42-0.88)**	-	-
	RELAY	Erlotinib + ramucirumab *vs*. erlotinib + placebo	**19.4** *vs*. 12.4	**0.59 (0.46-0.76)**	NR *vs*. NR	0.83 (0.53-1.30) Not mature
EGFR TKI + EGFR MAb	**IFCT 1503**	Afatinib + cetuximab *vs*. afatinib	Stopped for futility (ASCO 2019 #9079)			
1st generation EGFR TKI + chemotherapy	**NEJ009**	Gefitinib + carbo-pemetrexed *vs*. gefitinib	**20.9** *vs*. 11.2	**0.49 (0.39-0.63)**	**52.2** *vs*. 38.8	**0.60 (0.52-0.93)**
	Noronha	Gefitinib + carbo-pemetrexed *vs*. gefitinib	**16** *vs*. 8	**0.51 (0.39, 0.66)**	**NR** *vs*. 17	**0.45 (0.31-0.65)**
3rd generation EGFR TKI	**FLAURA**	Osimertinib *vs*. gefitinib or erlotinib	**18.9 *vs*.** 10.2	**0.46 (0.37-0.57)**	NR *vs*. NR	0.63 (0.45-0.88) Not mature (ESMO)

Yang JC et al., BJC 2017; Paz-Ares et al., Ann Oncol 2017; Mok et al., JCO 2018; Seto et al., ASCO 2018; Saito et al., Lancet Oncol 2019; Nakagawa et al., ASCO 2019; Nakamura et al., ASCO 2018; Noronha et al., ASCO 2019; Soria et al., NEJM 2018; Cortot, ASCO 2019

From Perol, M. ASCO 2019

ARTIMUS: Phase 3 study of 1L bevacizumab +/- erlotinib in Chinese patients with advanced EGFR-mutated NSCLC

	PFS benefit over 1st gen TKI	Overall survival benefit	Nationality
Gefitinib + chemo (Noronha et al ASCO 2019)	16 vs 8 months	Not reached vs 17 months	India
Gefitinib + chemo (NEJ 009)	20.9 vs 11.2 months	52.2 vs 38.8 months	Japan
Erlotinib + Bevacizumab (NEJ 026)	16.9 vs 13.3 months	Not available	Japan
Erlotinib + Ramucirumab (RELAY study)	19.4 vs 12.4 months	Not available	Multinational
Erlotinib + Bevacizumab (ARTIMUS)	18.0 vs 11.3 months	Not available	China

- This is the third study confirming the improvement of PFS by adding bevacizumab
- Incidence of T790M mutation at progression are similar
- Added toxicity

Zhou Q, et al. ESMO 2019. Abstract 1480O.

Conclusions—*EGFR* NSCLC Front-line

- Combination therapy for *EGFR* NSCLC may be beneficial to prolong PFS and OS if osimertinib is not available
- Osimertinib remains the SOC for front-line *EGFR* NSCLC
- Combination treatment increased toxicities including hypertension and bleeding (erl-ram); and cytopenias/renal toxicity (CPG)
- Impact to patients' convenience
- Combination therapy using osimertinib as the control arm will be investigated

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Osimertinib plus platinum/pemetrexed in newly-diagnosed advanced *EGFR*m-positive NSCLC; the phase 3 FLAURA2 study

Pasi A Jänne,[1] David Planchard,[2] Paul Howarth,[3] Alexander Todd,[3] Kunihiko Kobayashi[4]

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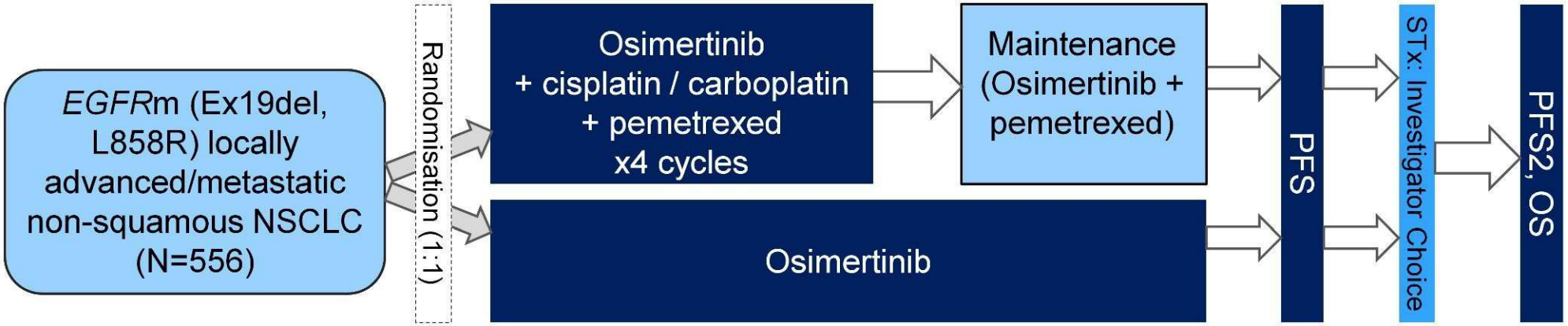
2. Dept of Cancer Medicine, Gustave Roussy, Department of Medical Oncology, Thoracic Group, Villejuif, France
3. AstraZeneca, Cambridge, UK
4. Department of Respiratory Medicine, International Medical Center, Saitama Medical University, Hidaka City, Japan.

Study design: randomised phase

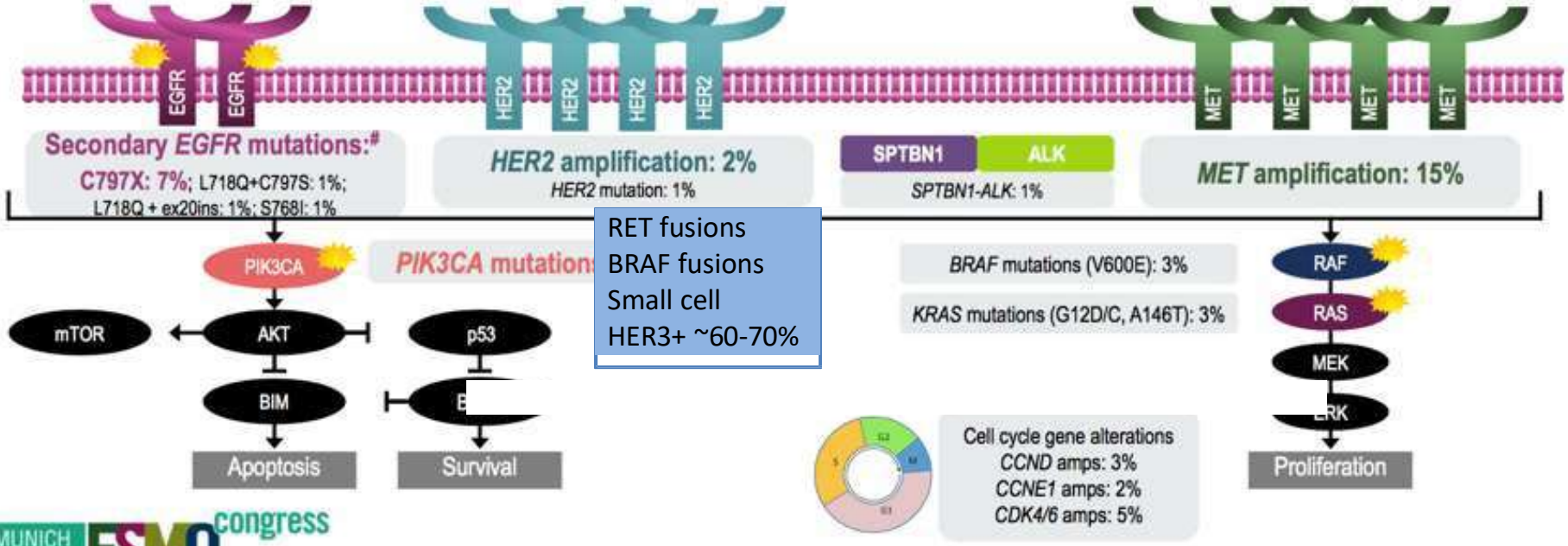


- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death on a subsequent treatment; QD, once daily; STx, subsequent treatment; vs, versus; WHO, World Health Organization

RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



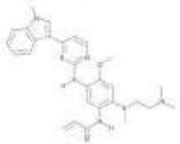
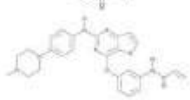
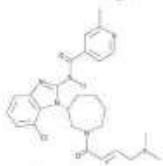
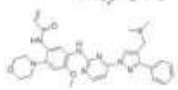
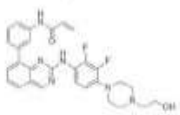
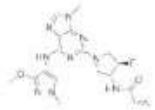
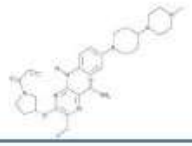
RET fusions
BRAF fusions
Small cell
HER3+ ~60-70%

MUNICH 2018 ESMO congress

*Patients may have had mutations reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

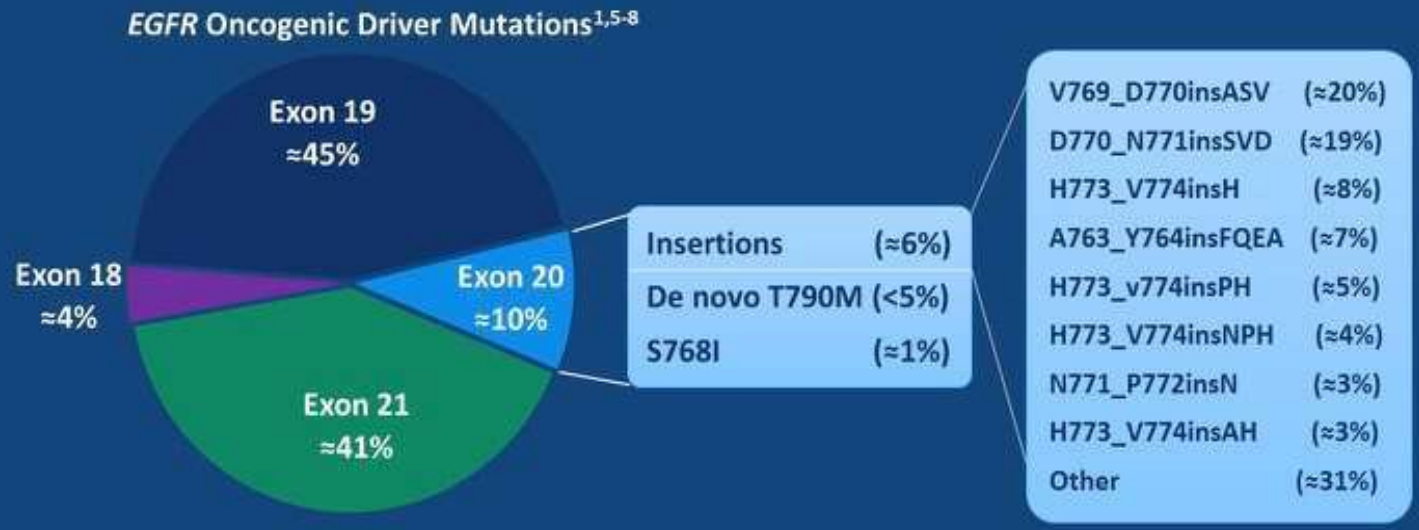
Ramalingam ESMO, J Clin Oncol 2018; Piotrowska Cancer Disc 2018; Jamie ASCO 2019

Third generation EGFR TKI landscape for metastatic EGFR mutant NSCLC

Drug	Structure	RP2D	Status of development	Off target kinase inhibition
Osimertinib (AZD9291)		80mg OD	Approved for first-line use in EGFR exon 19 deletion/L858R mutations Approved for post-EGFR TKI T790M mutation	ACK1, ALK, BLK, BRK, BTK, ERBB2/4 MLK1, MNK2
Olmutinib (HM61713)		800mg OD	Production halted	Unknown
Nazartinib (EGF816)		150mg OD	Phase 2, Phase 3 trial withdrawn	ALK, ABL1, BRAF, FGFR3, FLT3, KIT, LRRK2, MET, PIK3CA, RET
Lazertinib (YH25448)		To be determined	Phase 1/2	AXL, FER, MLK1, MER, RET
CK-101 (RX518)		To be determined	Phase 1/2 Planned for Phase 3 (2019)	Unknown
Maverlertinib (PF06747775)		200mg OD	Phase 1/2, development terminated	Unknown
Naquotinib (ASP8273)		300mg OD	Phase 1, development terminated	Unknown

Tan AC et al Exp Rev Anticancer Ther 2019; 19:431-435

EGFR Exon 20 Insertions in NSCLC



- Approximately 6% of *EGFR*-mutated NSCLC tumors have *EGFR* exon 20 insertion mutations, and there are no approved targeted treatment options for patients with these mutations[1]
- Currently approved EGFR TKIs have shown efficacy in NSCLC patients with common activating *EGFR* mutations, but are largely ineffective in patients with *EGFR* exon 20 insertions, with poor response rates and median PFS of approximately 2 months[2,4]

EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor. 1. Kobayashi Y, Mitsudomi T. *Cancer Sci* 2016;107:1179–1186; 2. Wu J-Y et al. *Clin Cancer Res* 2008;14:4877–4882; 3. Naidoo J et al. *Cancer* 2015;121:3212-3220; 4. Yasuda H et al. *Sci Transl Med*. 2013;5:1-23; 5. Arcila ME et al. *Mol Cancer Ther* 2013;12:220–229; 6. Oxnard GR et al. *J Thorac Oncol* 2013;8:179–184; 7. Inukai M et al. *Cancer Res*. 2006;66:7854-7858; 8. Yasuda H et al. *Lancet Oncol*. 2012;13:e23-31.

TAK-788 Antitumor Activity in Patients With *EGFR* Exon 20 Insertions

Exon 20 Insertion Variant	No. of Patients	No. of Confirmed Responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown	4	2	50%
Other	15	6	40%

- Median (range) best percent change: -32.5% (-100%, 26.3%)
- Three patients were excluded from the waterfall plot: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans

IO, immuno-oncology therapy; PD, progressive disease.

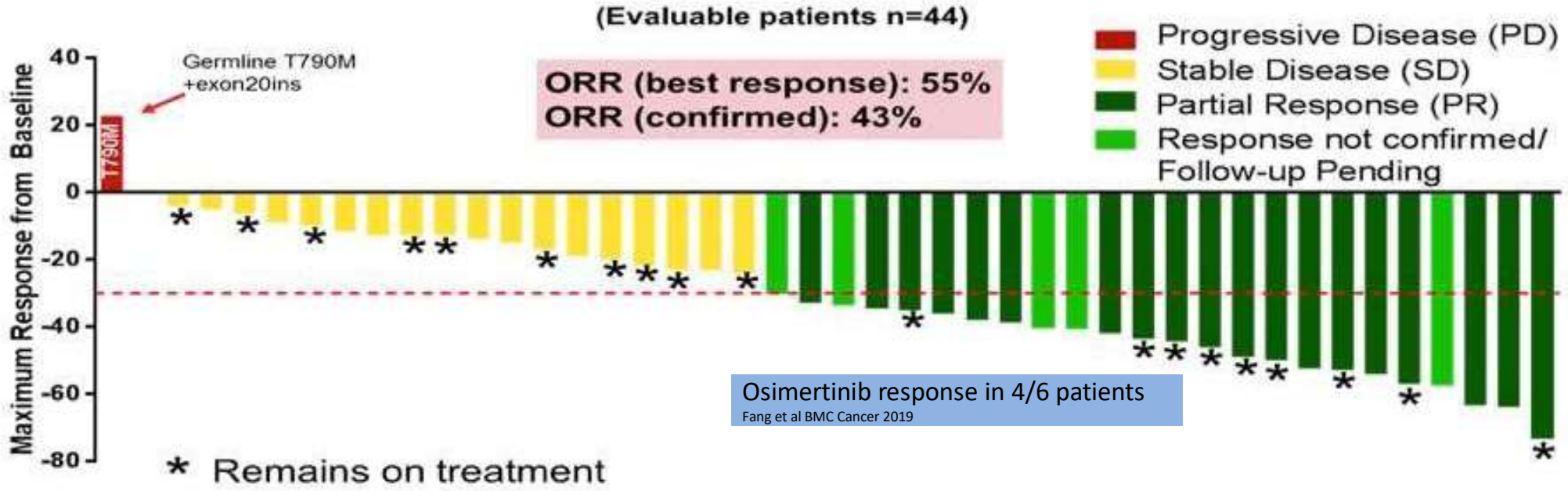
Treatment-Related AEs in Patients Treated With TAK-788

Any grade: ≥20% of all patients Grade ≥3: ≥3% of all patients	All Patients Treated at 160 mg qd[a] (n=72)		All Patients Treated at Any Dose[b] (N=137)	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Diarrhea	85	18	74	12
Nausea	43	6	33	4
Rash	36	1	26	1
Vomiting	29	3	22	2
Decreased appetite	25	1	22	1
Stomatitis	18	4	14	3
Increased lipase	10	6	8	3
Increased amylase	8	4	8	3

[a] Patients who received at least 1 dose of TAK-788 at 160 mg qd (initial dose) during dose escalation or expansion cohorts 1 to 7. [b] Patients who received at least 1 dose of TAK -788 (5–180 mg total daily dose) during the escalation or expansion phase. Data cutoff: 1 Mar 2019.

- Most treatment-related AEs were grade 1–2 and reversible
- Per protocol, no primary prophylaxis plan for AEs was in place
- Food instructions have been updated in this ongoing study with the potential to improve gastrointestinal tolerability based on emerging data in healthy subjects that suggest lack of low-fat meal effect on PK of TAK-788

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC



Presented By John Heymach at 2019 ASCO Annual Meeting

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

JV Heymach, WCLC Toronto 2018

Summary

- Key to precision medicine is molecular testing... and targeted treatment
- EGFR TKI remains our standard 1st line in EGFR mt lung cancer patients
  - Osimertinib, dacomitinib/afatinib, erlotinib/gefitinib
  - Adding chemotherapy and VEGF inhibition may improve outcomes with 1st genTKIs
  - No data with better EGFR inhibitors /ongoing trials
- EGFR resistance mutations (exon 20 excluding T790M)
  - 1st line standard is chemotherapy
  - Exciting options in clinical trials: poziotinib, TAK788, osimertinib, JNJ-372

ALK Inhibitors

Crizotinib

Ceritinib

Alectinib

Brigatinib

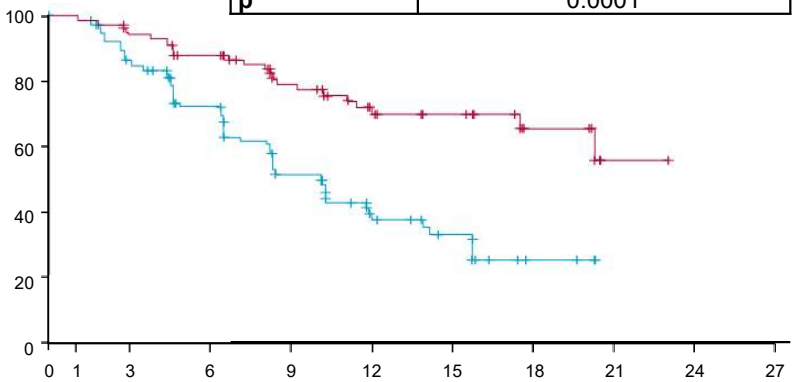
Lorlatinib

Ensartinib

Entrectenib

Alectinib as First Line

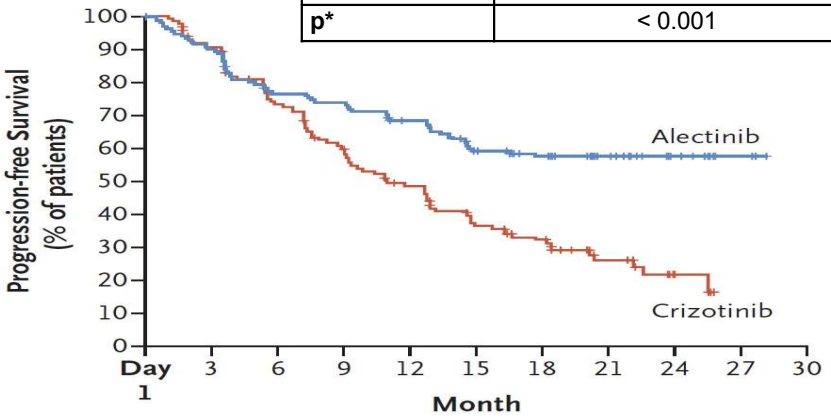
	Alectinib (n = 103)	Crizotinib (n = 104)
Events, n (%)	25 (24.3)	58 (55.8)
Median, mo	25.9	10.2
HR (99.7% CI)	0.38 (0.26–0.55)	
p*	0.0001	



J-ALEX: PFS

Hida Lancet 17 (updated ASCO 17)

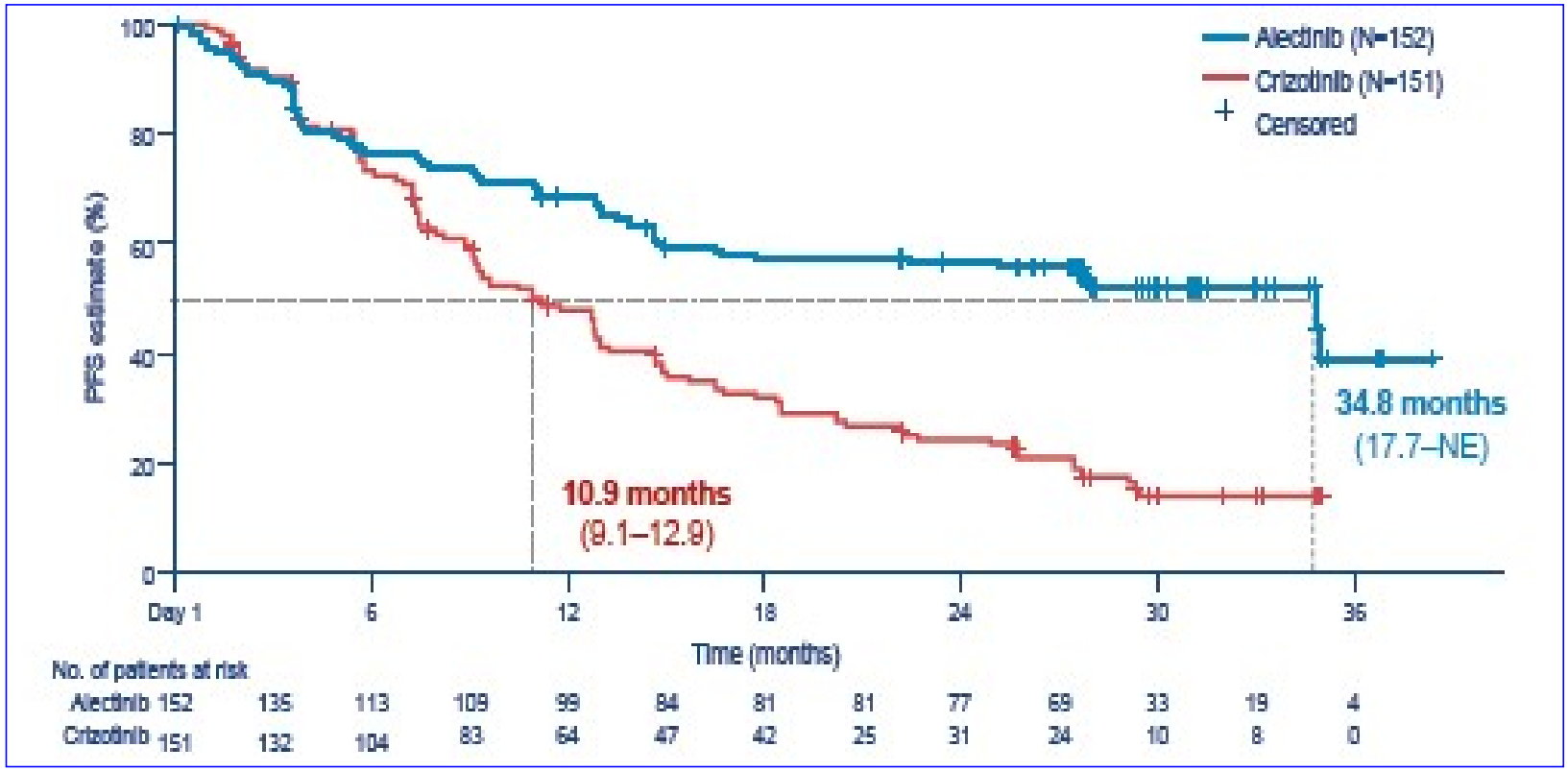
	Crizotinib (n = 151)	Alectinib (n = 152)
Events, n (%)	102 (68)	62 (41)
Median, mo	11.1	NR
HR (95% CI)	0.47 (0.34–0.65)	
p*	< 0.001	



ALEX: PFS

Peters NEJM 2017

ALEX trial Updated PFS… 34.8 months median PFS with firstline alectinib!



Camidge et. al. ASCO 2018

IASLC

Efficacy of ALK TKIs in the First-Line Setting

	PROFILE 1014[1] (N=172)	ASCEND-4[2] (N=189)	Global ALEX[3,4] (N=152)	ALTA-1L[5] (N=137)
ALK TKI	crizotinib 250 mg bid	ceritinib 750 mg qd	alectinib 600 mg bid	brigatinib 90->180 mg qd
Comparator	platinum/pem	platinum/pem	crizotinib	crizotinib
Median f/u	17.4 mos	19.7 mos	27.8 mos	11.0 mos
PFS, median	10.9 mos	16.6 mos	34.8 mos (HR 0.43)	NR (HR 0.49)
ORR	74%	73%	83%	71%
Intracranial ORR	NA	73% (n=22)	81% (n=21)	78% (n=18)

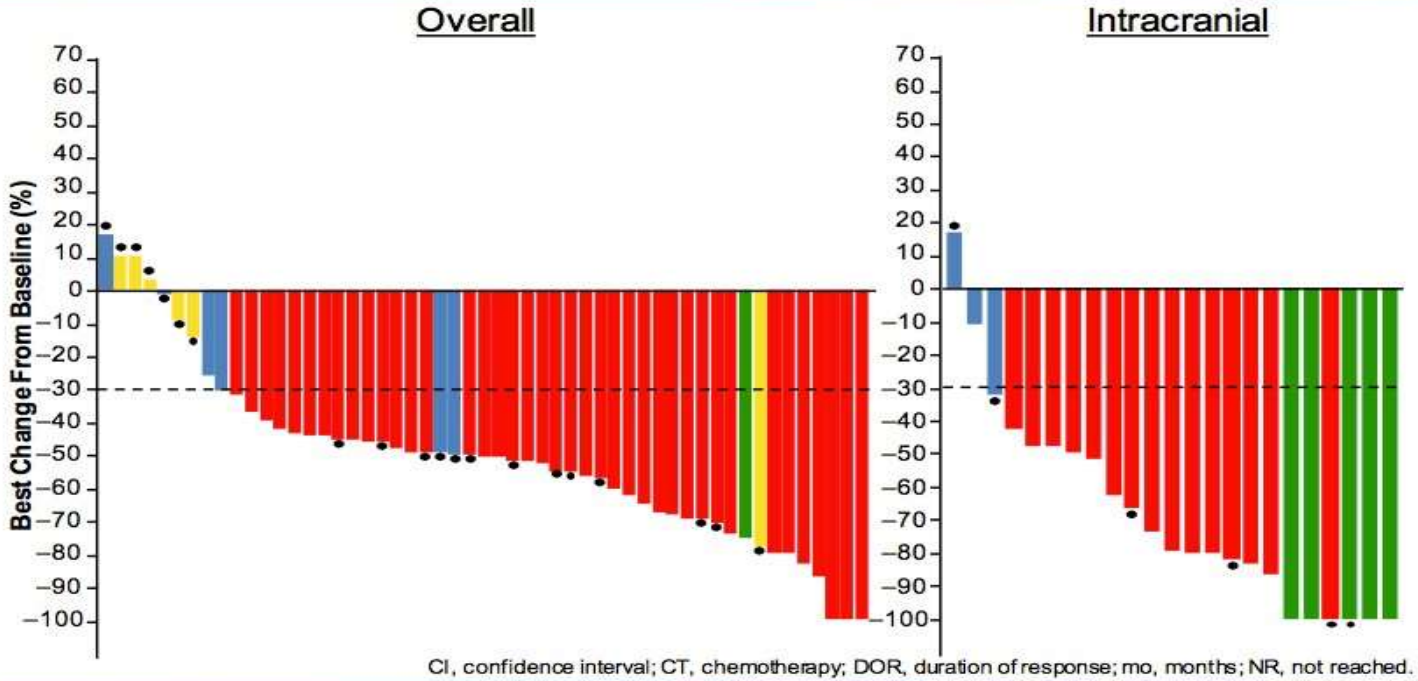
[1]Solomon et al., NEJM 371(23): 2167-77, 2014; [2]Soria et al., Lancet 389(10072): 917-29, 2017; [3]Peters et al., NEJM 377(9): 829-38, 2017; [4]Camidge et al., ASCO 2018; [5]Camidge et al., NEJM 379: 2027-39, 2018.

Lorlatinib Phase I/II Study: Crizotinib-Pretreated Patients

Efficacy in EXP2 (ALK+, Crizotinib Only) and EXP3A (ALK+, Crizotinib + CT)

	EXP2+3A (n=59)
ORR, n/N (%) (95% CI)	41/59 (69) (56, 81)
IC ORR, n/N (%) (95% CI)	25/37 (68) (50, 82)
Median DOR, mo (95% CI)	NR (11.1, NR)
DOR ≥6 mo, n°/n (%)	20/41 (49)
Median PFS, mo (95% CI)	NR (12.5, NR)

- 37 patients (63%) had brain metastases at baseline.



CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

Solomon et al. World Conference on Lung Cancer; Yokohama, Japan, 2017

ALK tumors evolve and develop resistant mutations

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

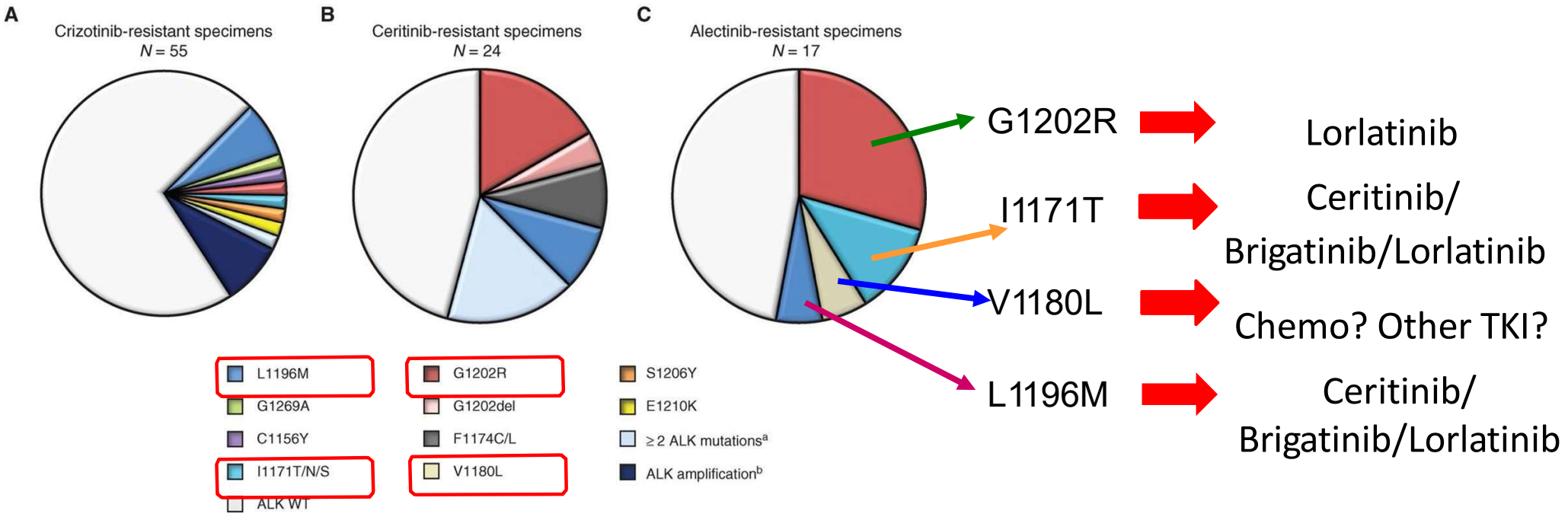
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	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

Will the Choice of 1st Line ALKi TKI Impact on Patterns of Progression & Mechanism of Resistance?



Justin F. Gainor et al. Cancer Discov 2016;6:1118-1133

ROS1 inhibitors

Crizotinib

Ceritinib

Entrectenib

Lorlatinib

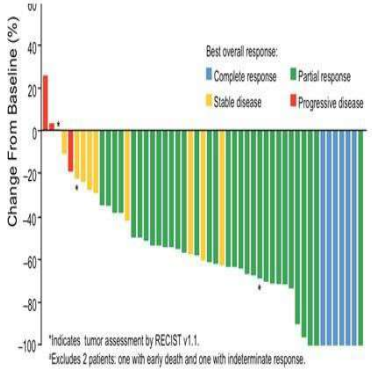
Characteristics of ROS-1 altered NSCLC

- 1-2% of all NSCLC
- Mainly adenocarcinoma, but also has been reported in pleomorphic carcinoma
- Solid pattern adenocarcinoma
- Signet ring
- Mainly non-smokers (~80%)
- Mainly female patients (~70%)
- IHC screening with FISH confirmation or rt-PCR

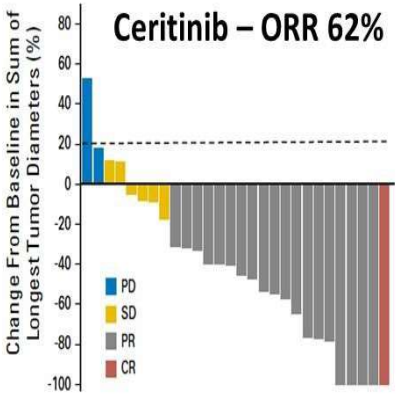
Park et al. Path Res Pract, 2019

ROS1 inhibitors—front line

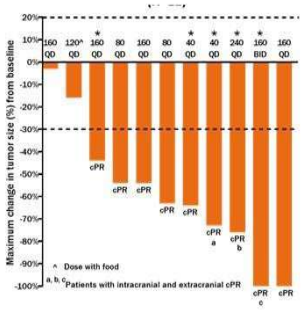
Crizotinib – ORR 72%



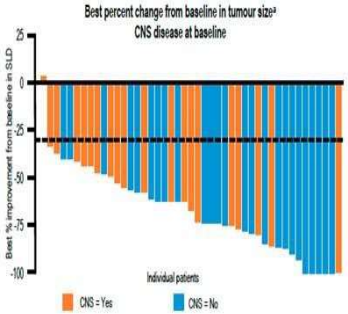
Ceritinib – ORR 62%



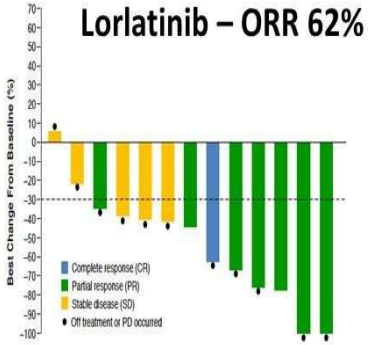
Repotrectinib – ORR 82%



Entrectinib – ORR 77%



Lorlatinib – ORR 62%



- ✓ High ORR but small n
- ✓ Dose doen't impact ORR
- ✓ PFS not available
- ✓ Efficacy vs. ROS1 fusion partner unknown

Besse – ESMO 2017 *Ou – WCLC 2018 * Solomon – ESMO 2018

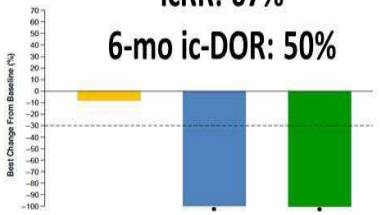
ROS1 inhibitors—CNS activity

Lorlatinib

TKI naive

icRR: 67%

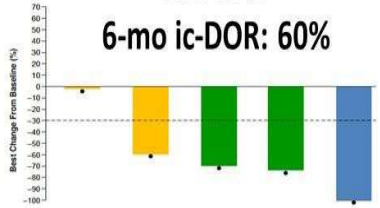
6-mo ic-DOR: 50%



Pretreated

RR: 53%

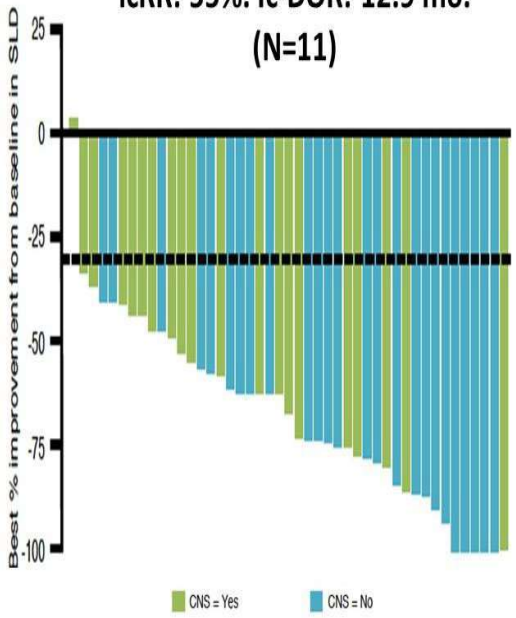
6-mo ic-DOR: 60%



Entrectinib

icRR: 55%. Ic-DOR: 12.9 mo.

(N=11)



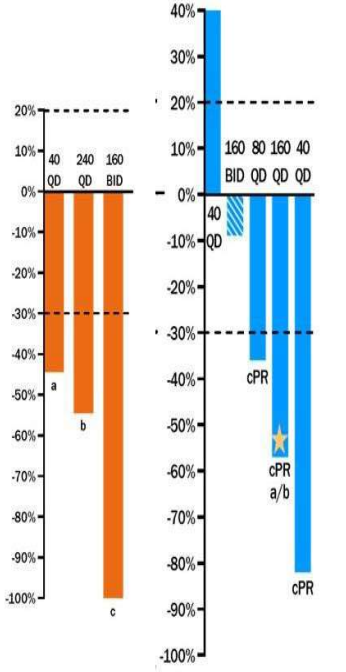
Repotrectinib

TKI naïve

icRR: 100%

Pretreated

icRR: 75%



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Memorial Hospital West | Memorial Hospital Miramar |Memorial Hospital Pembroke