Updates in Targeted Therapies for NSCLC

Jonathan Riess, M.D. M.S.
Associate Professor of Medicine
University of California Davis School of Medicine
UC Davis Comprehensive Cancer Center

UCDAVIS COMPREHENSIVE CANCER CENTER

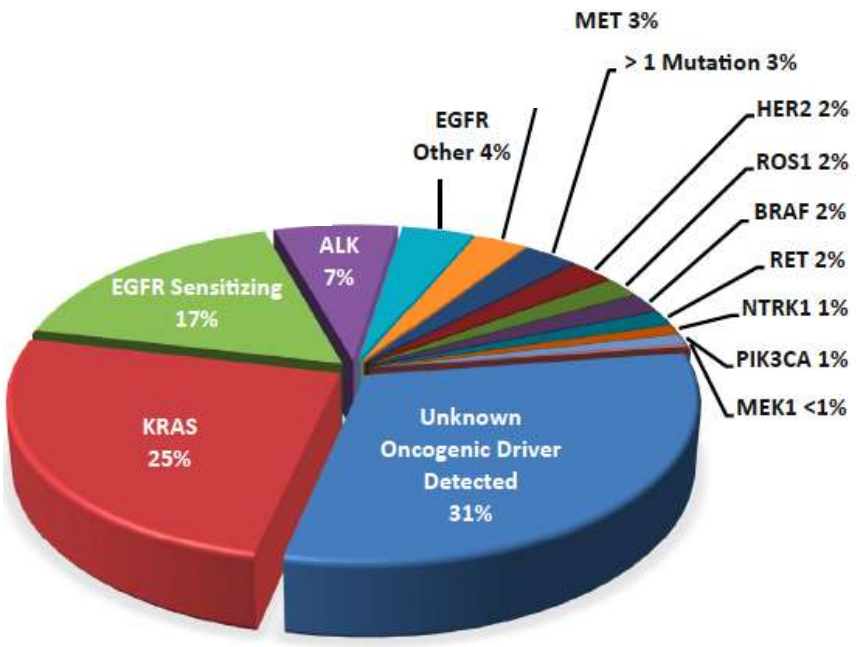
NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

- Grant/Research Support (To Institution): Merck, AstraZeneca, Novartis, Boehringer Ingelheim, Spectrum

- Consultant (Advisory Board): Spectrum, Loxo Oncology, Celgene, Heron Pharmaceuticals, Boehringer Ingelheim

Progress in Targeted Therapy for NSCLC-Adenocarcinoma



EGFR:
gefitinib, afatinib, erlotinib, osimertinib, dacomitinib

ALK:
Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib, entrectinib

ROS1:
Crizotinib, cabozatinib, ceritinib, brigatinib, lorlatinib, entrectinib, ropotrectinib

BRAF:
Dabrafenib/trametinib, vemurafenib, dabrafenib

FDA

MET:
Crizotinib, cabozatinib, capmatinib, tepotinib, savolitinib, merestinib, glesatinib

KRAS G12C
MTRX-849, AMG 510

HER2:
Transtuzumab emtansine, afatinib, dacomitinib, poziotinib, neratinib-temsirolimus, XMT-1522, TAK-788, DS-8201a

PI3K
LY3023414, PQR-309

RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, LOXO 292, BLU-667, RXDX-105

MEK
Trametinib, selumetinib, cobimetinib

NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

EGFR exon 20 insertions
TAK-788, poziotinib

Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

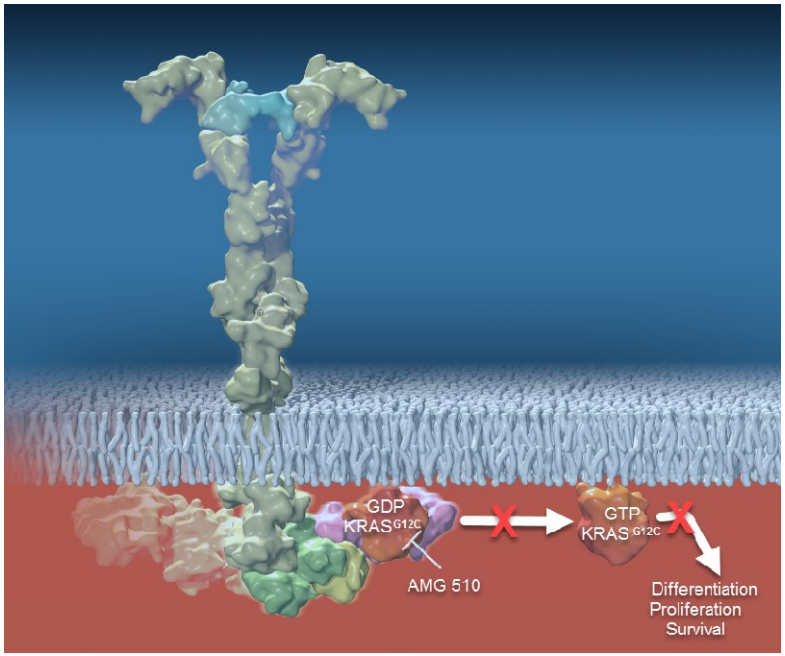
Approaches to Targeting KRAS in 2019

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling [1,2]
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival)[3]
- Direct RAS inhibitors – combinations
- Combinations with SHP2 inhibitors
- Blocking downstream effectors

1. Prior IA, et al. *Cancer Res.* 2012;72:2457-2467.
2. Ostrem JM, et al. *Nat Rev Drug Discov.* 2016;15:771-785.
3. Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720.

AMG 510 is a First in Class KRAS^{G12C} Inhibitor

- *KRAS^{G12C}* mutation has been identified as an oncogenic driver of tumorigenesis
- *KRAS^{G12C}* mutation is found in approximately 13% of lung cancer[1] 3% of colorectal (CRC)[2] and appendix cancer, and 1-3% of other solid tumors[3]
- Currently there is no approved therapy targeting this mutation
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS^{G12C} by locking it in an inactive GDP-bound state



GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog;
KRAS^{G12C}, KRAS protein with a G12C mutation at the protein level.

1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198.
2. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862
3. Zhou L et al. *Med Oncol.* 2016;33:32.

AMG 510 First in Human Study Design

This is a multicenter, open-label, phase 1, first in human study (NCT 03600883) in adult patients with locally advanced or metastatic *KRAS*^{G12C} mutant solid tumors

Key Eligibility Criteria

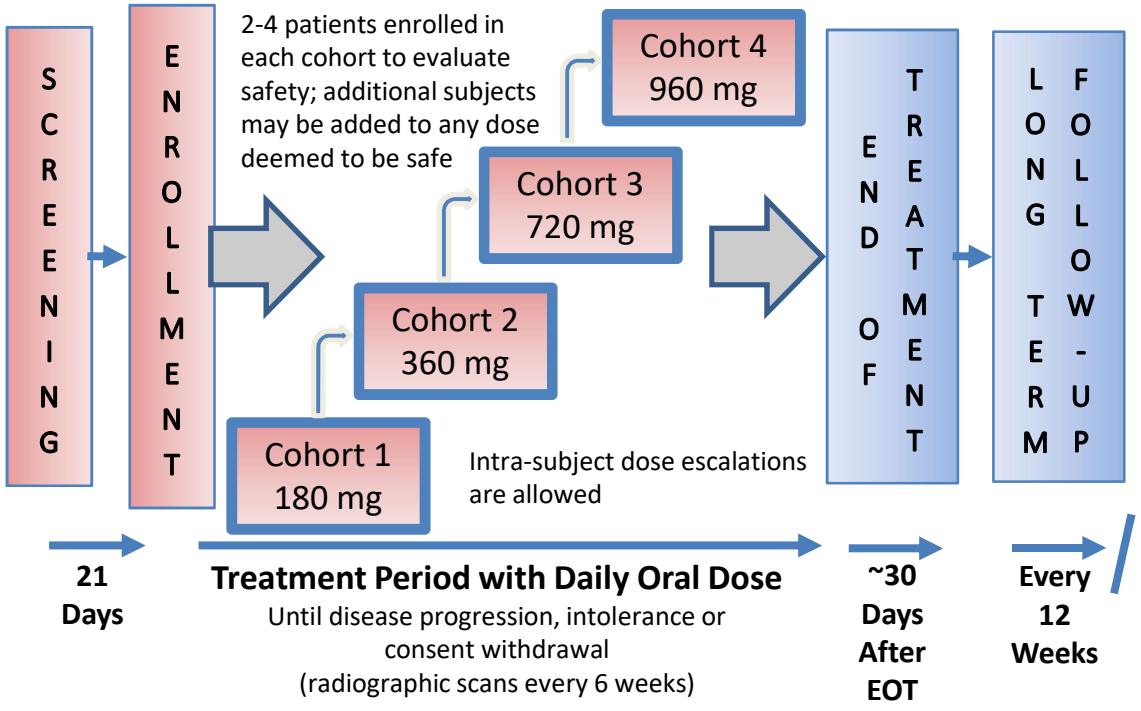
- Documented locally-advanced or metastatic *KRAS*^{G12C} measurable or evaluable solid tumors
- Received prior standard therapy appropriate for tumor type and stage of disease
- No active brain metastases

Primary Endpoints

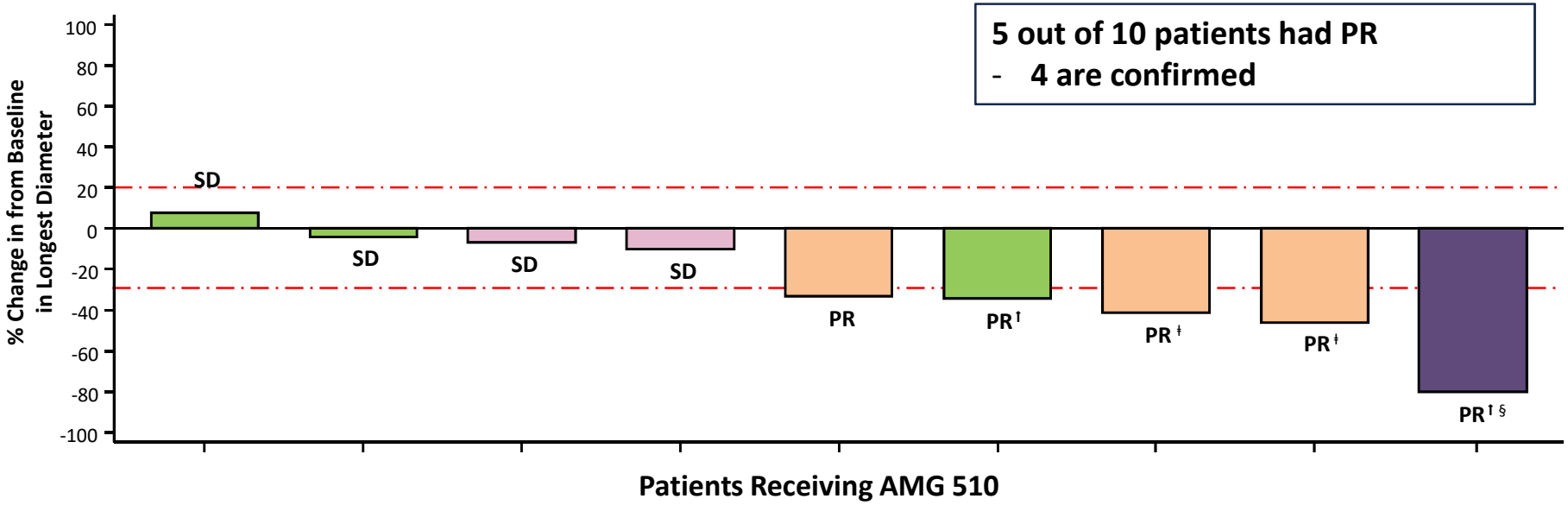
- Safety and tolerability including the incidence of AEs and DLTs

Key Secondary Endpoints

- PK, best response
- Objective response rate , duration of response and duration of stable disease and PFS

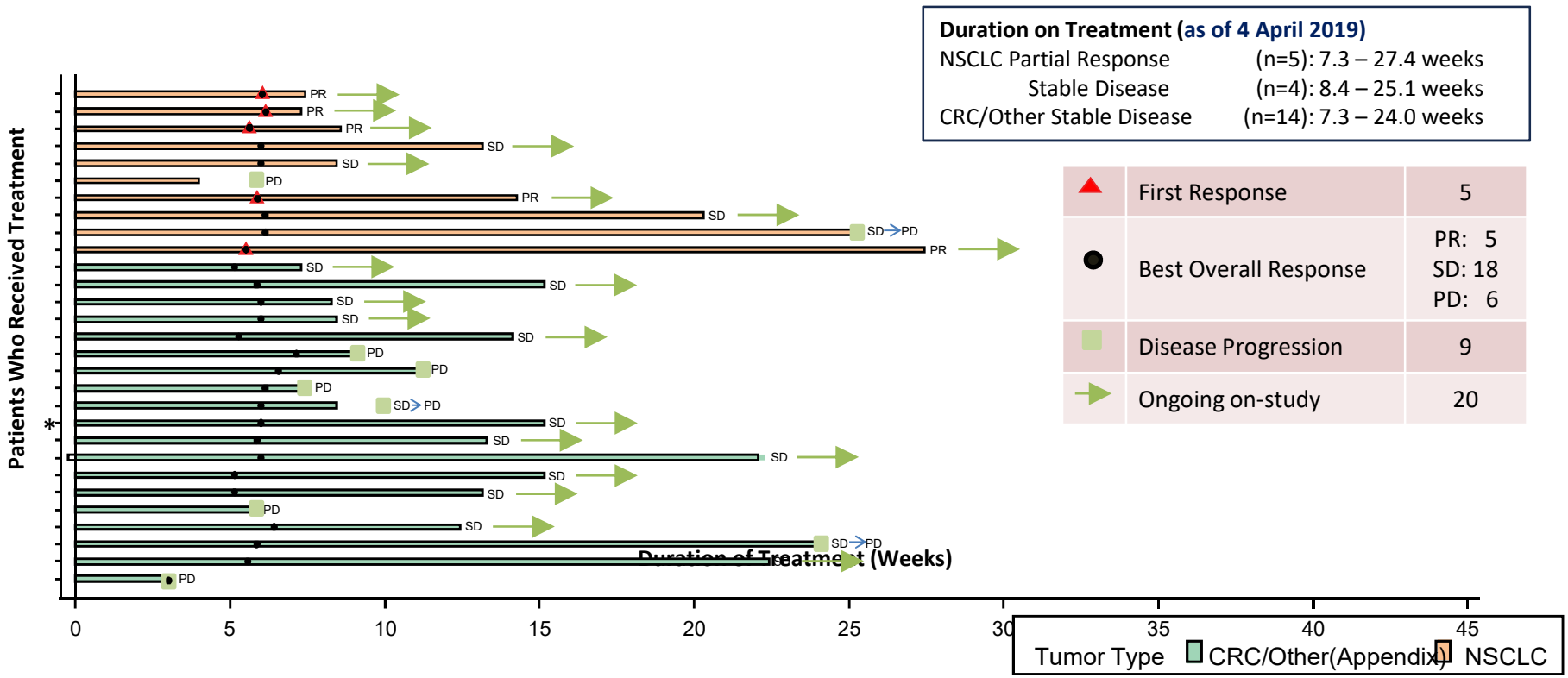


NSCLC: Best Tumor Response* (n=10; 35 pts total)



* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 patient had clinical progression prior to week 6 and is not on this graph
† Confirmed response
‡ 2 additional patients had confirmed PR post data cutoff
§Patient had a CR of the target lesions at week 18, post data cutoff

Duration of Treatment by Tumor Types and Responses (n=29)



* Appendix adenocarcinoma patient

SD → PD: Patient with best response of SD but who later progressed

EGFR Updates

FLAURA: Osimertinib vs Gefitinib/Erlotinib in EGFR-mutated NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- **≥18 years***
- **WHO performance status 0 / 1**
- **Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)**
- **No prior systemic anti-cancer / EGFR-TKI therapy**
- **Stable CNS metastases allowed**

Stratification by **mutation status** (Exon 19 deletion / L858R) and **race** (Asian / non-Asian)

Osimertinib (80 mg p.o. qd) (n=279)

Randomised 1:1

EGFR-TKI SoC§; **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

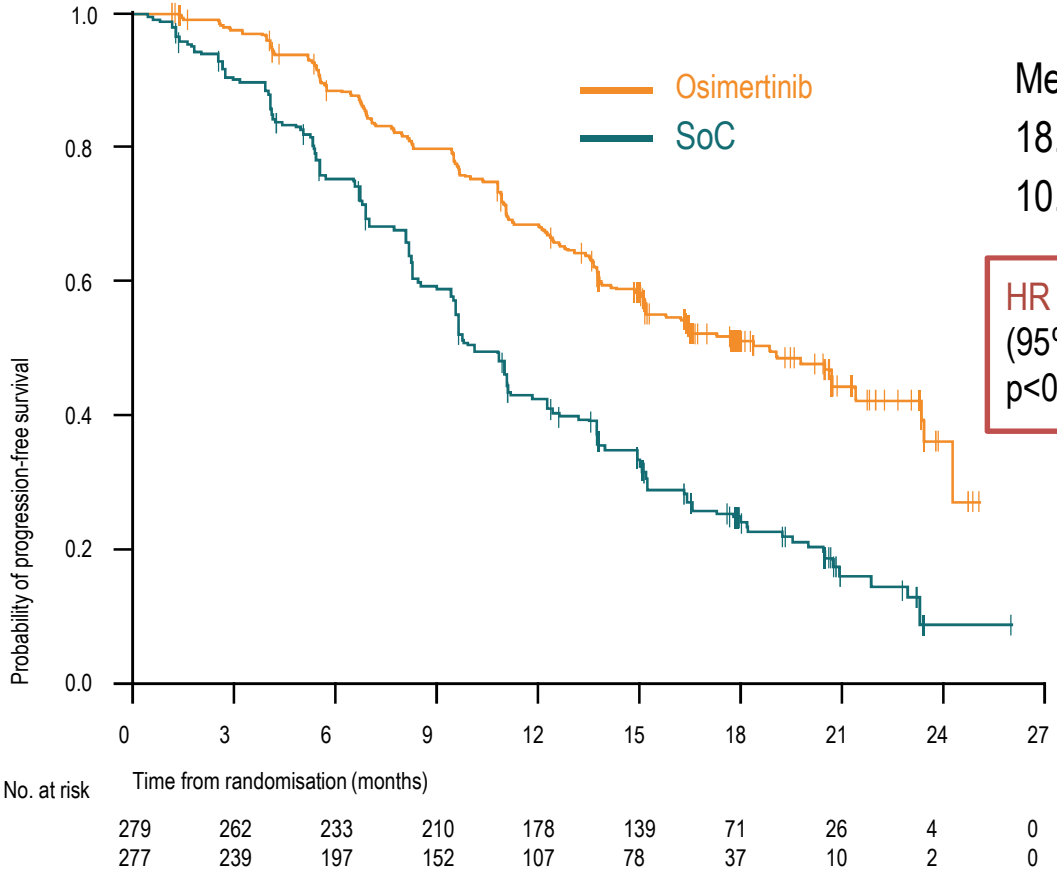
Endpoints
- **Primary endpoint: PFS** based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective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

FLAURA data cut-off: 12 June 2017; NCT02296125
*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care;
TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Ramalingam S, et al. ESMO 2017. Abstract LBA2_PR

FLAURA: Primary endpoint: PFS by investigator assessment

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



Median PFS, months (95% CI)
18.9 (15.2, 21.4)
10.2 (9.6, 11.1)

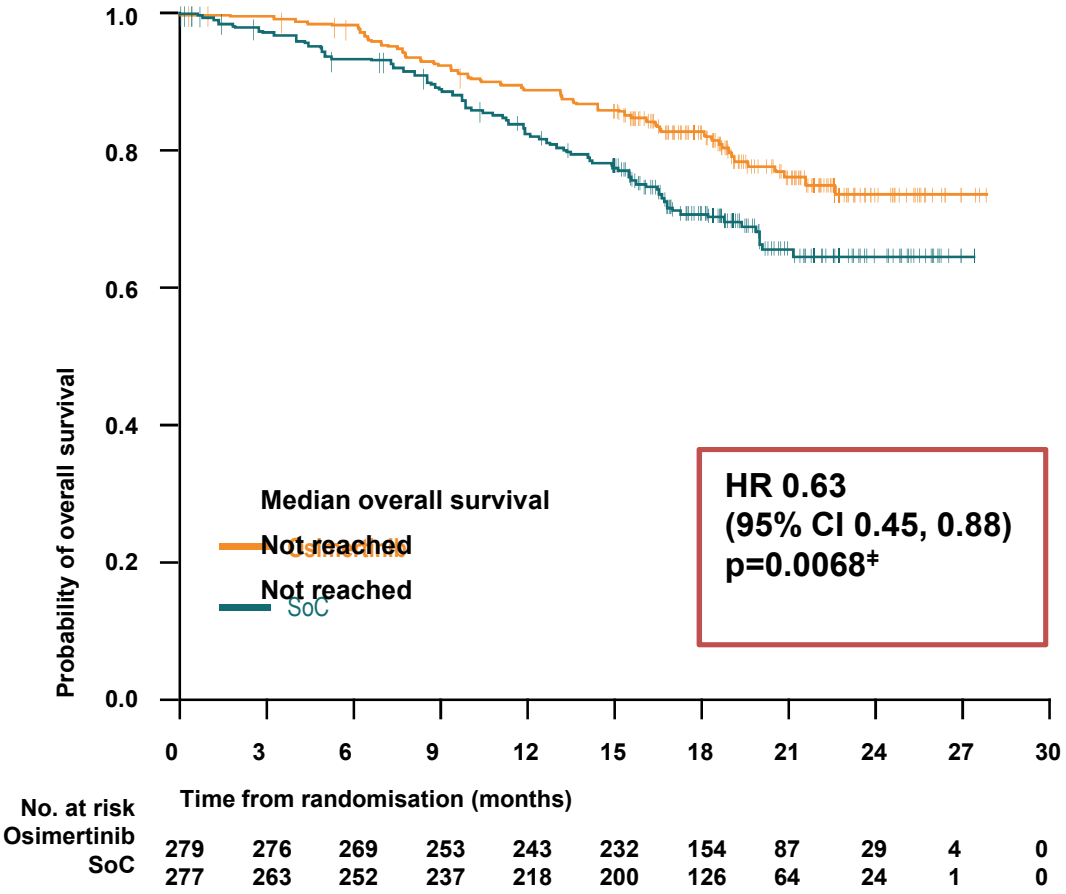
HR 0.46
(95% CI 0.37, 0.57)
p<0.0001

CNS progression
17 (6%) osi
vs 42 (15%) SoC

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data;
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care; PFS, progression-free survival

Ramalingam ESMO 2017

FLAURA: OVERALL SURVIVAL INTERIM ANALYSIS



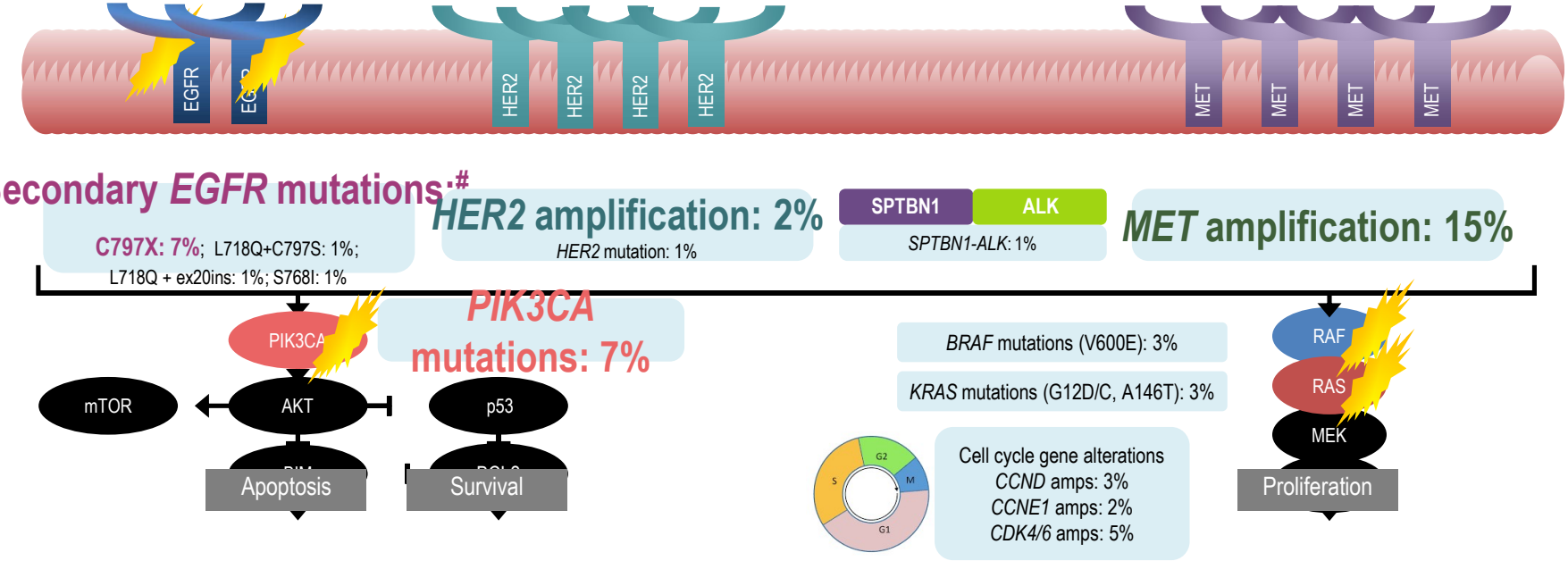
‡A p-value of <0.0015 was required for statistical significance at current maturity

Recent press release – "achieved statistical significance for a clinically meaningful OS benefit."

141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%) Ramalingam 2017

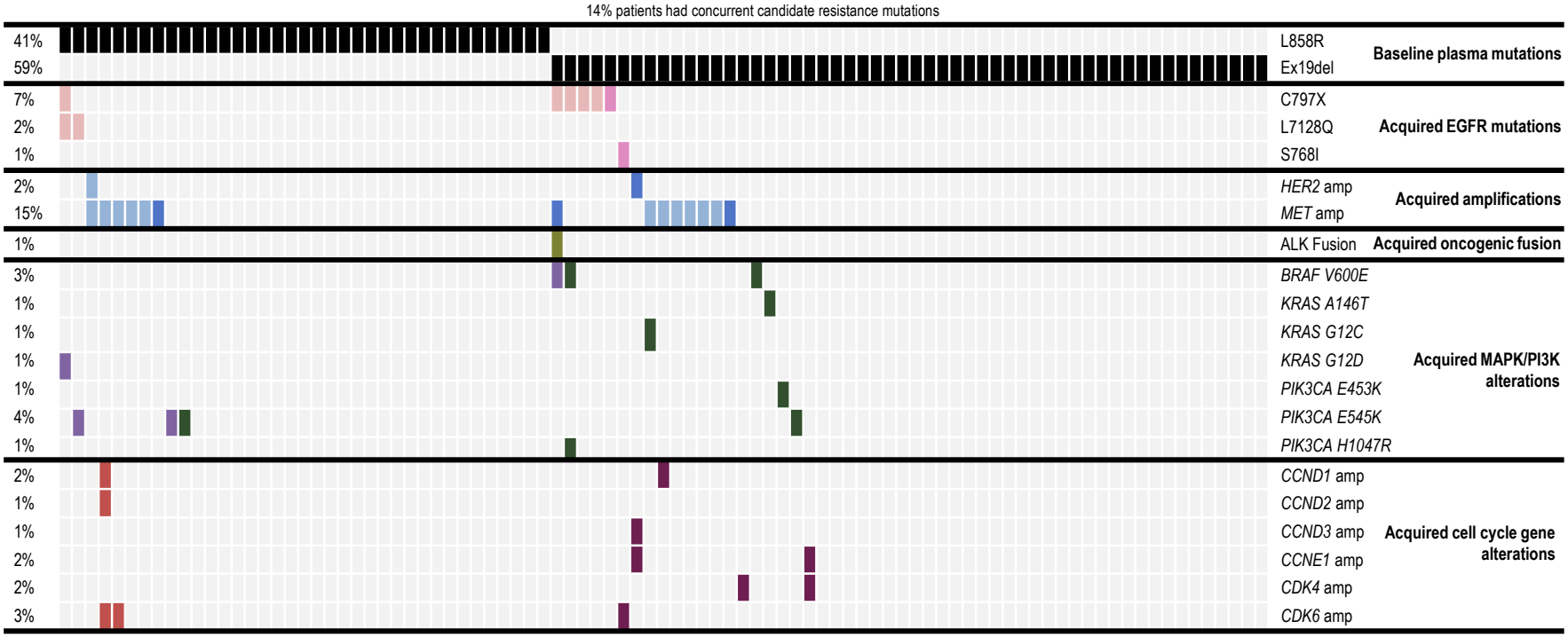
RESULTS of CURRENT STUDY: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- **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**



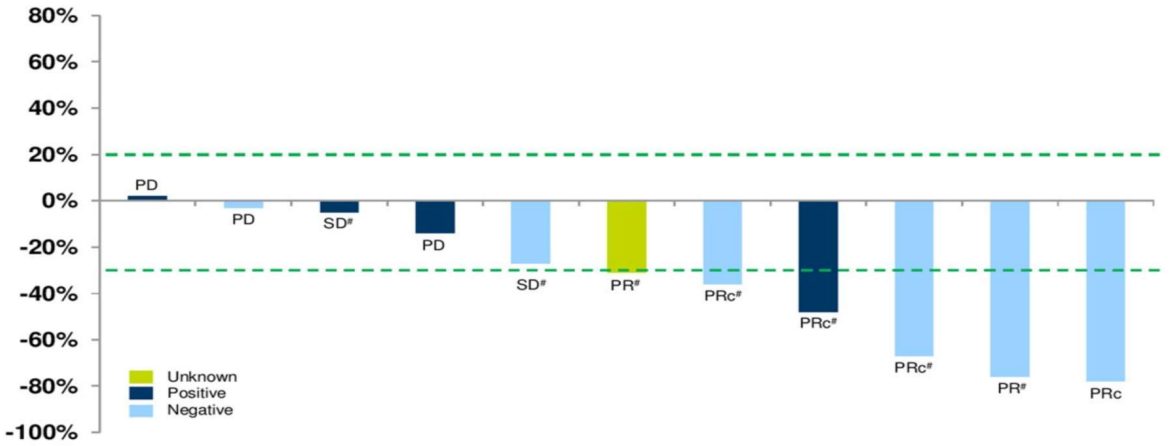
*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

CANDIDATE ACQUIRED ALTERATIONS WITH OSIMERTINIB

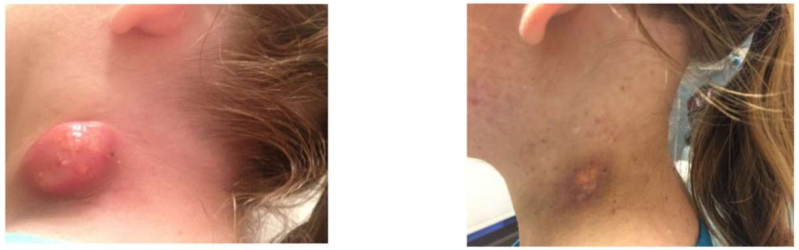


- No Osimertinib-treated patients showed evidence of T790M-mediated acquired resistance
- The most frequent resistance mechanisms were *MET* amplification (15%) & *EGFR* C797S mutation (7%)
- No new mechanisms of resistance identified
- Caveat: Plasma ctDNA (not tissue); Multiple aberrations in same patient

Osimertinib and Savolitinib in *EGFR*+ NSCLC



*Population: all patients dosed who had a baseline and 6-week RECIST assessment
#Patients ongoing treatment at data cut-off
PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

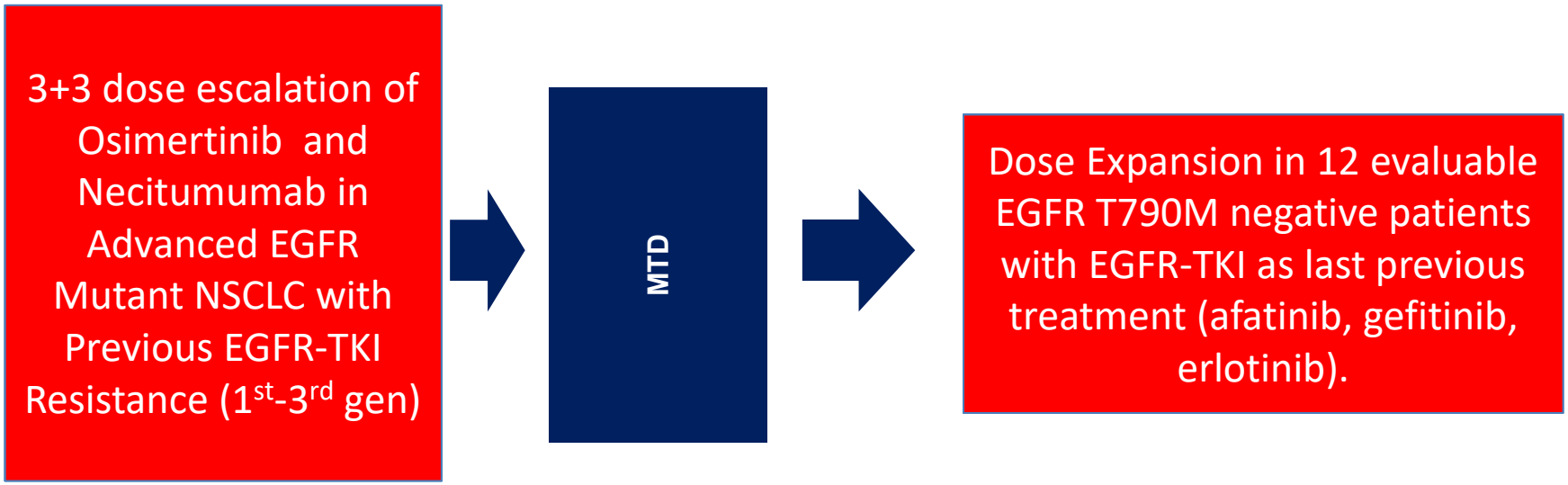


Pre-treatment **4 weeks**

32-year-old female with a tumor harboring exon 19 deletion and high MET amplification responds to AZD9291/savolitinib 800 mg.

Oxnard et al J Clin Oncol 2015; abstract 2509

A Phase I Trial of Osimertinib and Necitumumab in EGFR Mutant NSCLC with Previous EGFR-TKI Resistance



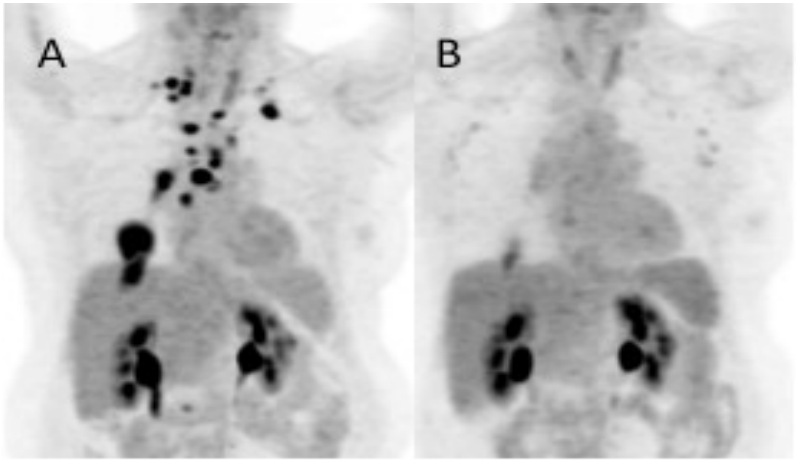
Primary Endpoint: Safety and Tolerability
Main Secondary Endpoint:
ORR is T790M negative population (3≥12 responses)

Molecular Studies
Biopsy – Pre-treatment and post progression for EGFR T790M, EGFR FISH and NGS
Plasma cfDNA for EGFR-TKI resistance mechanisms
Creation of EGFR-TKI resistant PDX
Single Cell NGS for Intratumoral Heterogeneity

Clinical and Radiographic Responses in Unmet EGFR-mutant Patient Populations: EGFR T790M negative after erlotinib and in C797S positive lung cancer after osimertinib

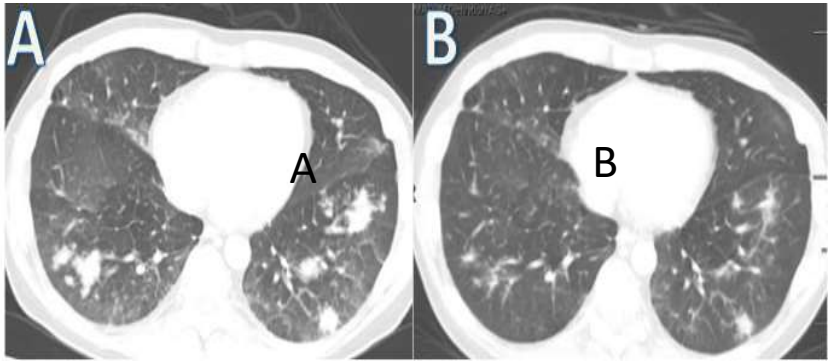
E19del/T790M^{neg}

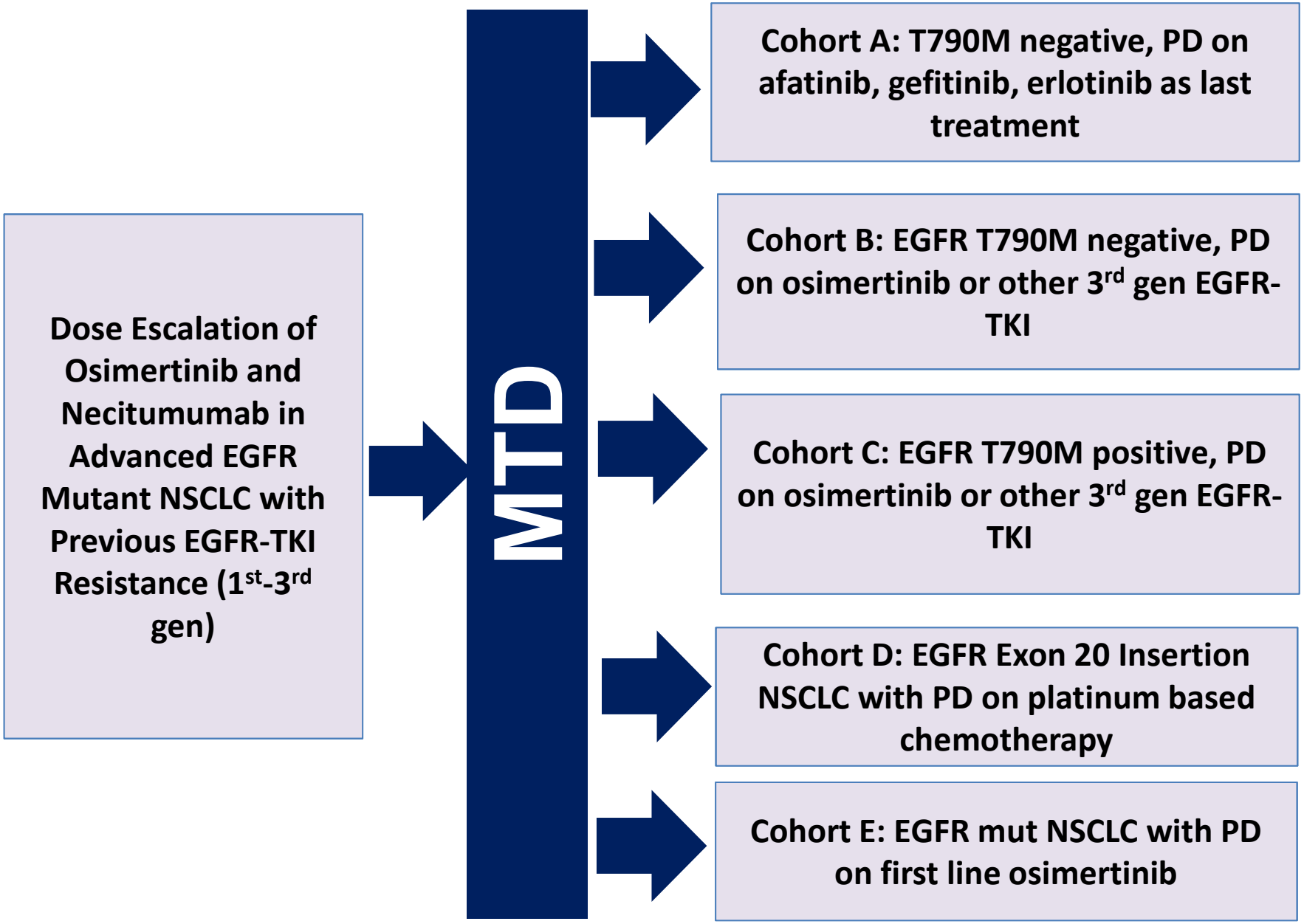
PD on erlotinib



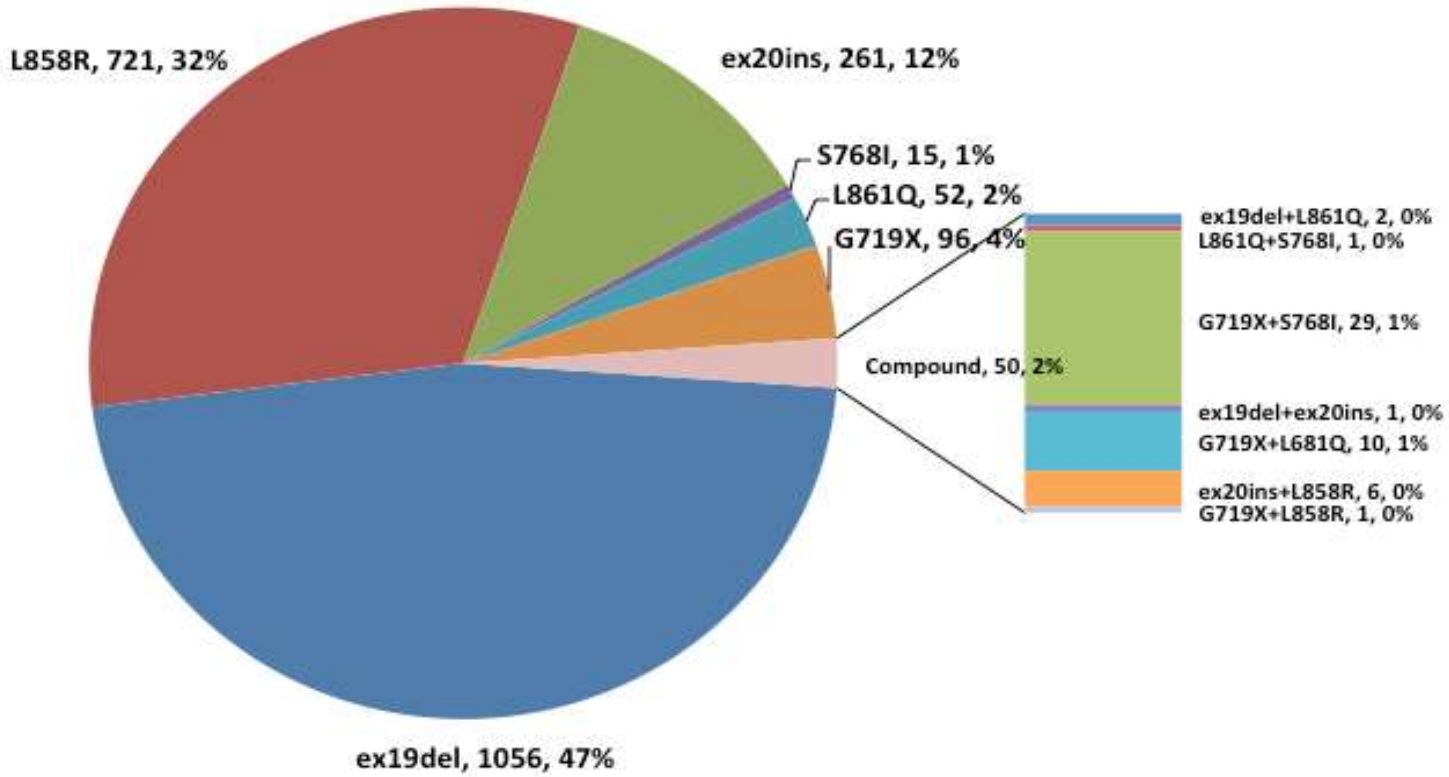
E19del/T790M^{pos}/C797S^{pos}

PD on osimertinib



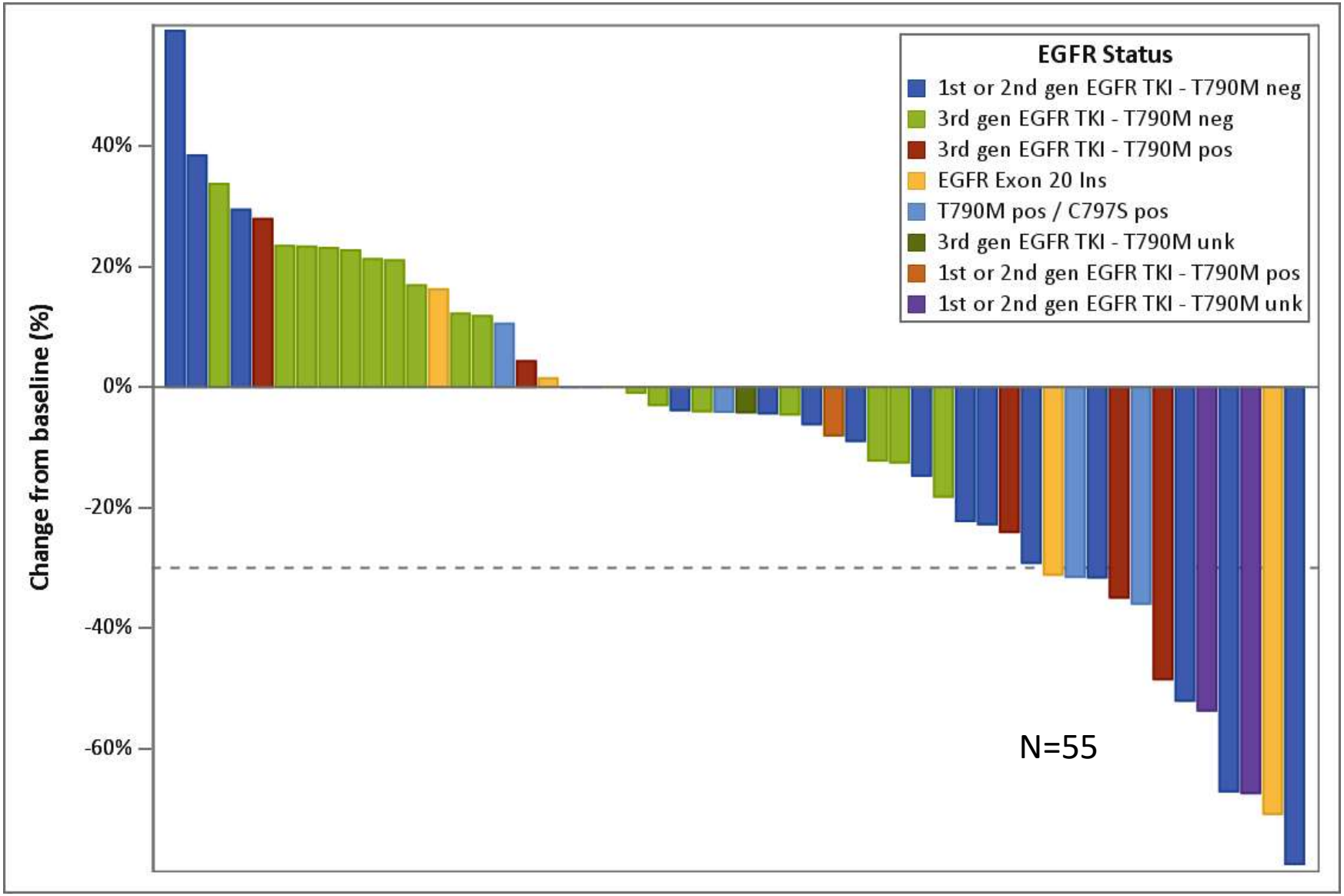

Dose Escalation of Osimertinib and Necitumumab in Advanced EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (1st-3rd gen)
MTD
Cohort A: T790M negative, PD on afatinib, gefitinib, erlotinib as last treatment
Cohort B: EGFR T790M negative, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort C: EGFR T790M positive, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort D: EGFR Exon 20 Insertion NSCLC with PD on platinum based chemotherapy
Cohort E: EGFR mut NSCLC with PD on first line osimertinib

Frequency and Distribution of 2,251 *EGFR* mutations in NSCLC Detected by Broad Genomic Profiling.



JW Riess et al. Journal of Thoracic Oncology 2018.

Waterfall Plot of Best Response by Molecular Status

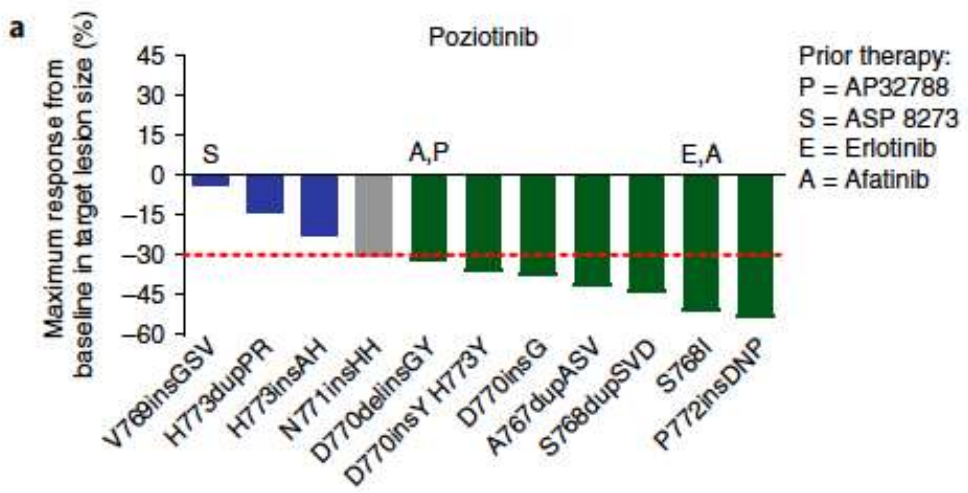


JW Riess et al. ASCO 2019

Poziotinib in EGFR Exon20 Ins NSCLC induces partial responses in EGFR Exon 20 mutations

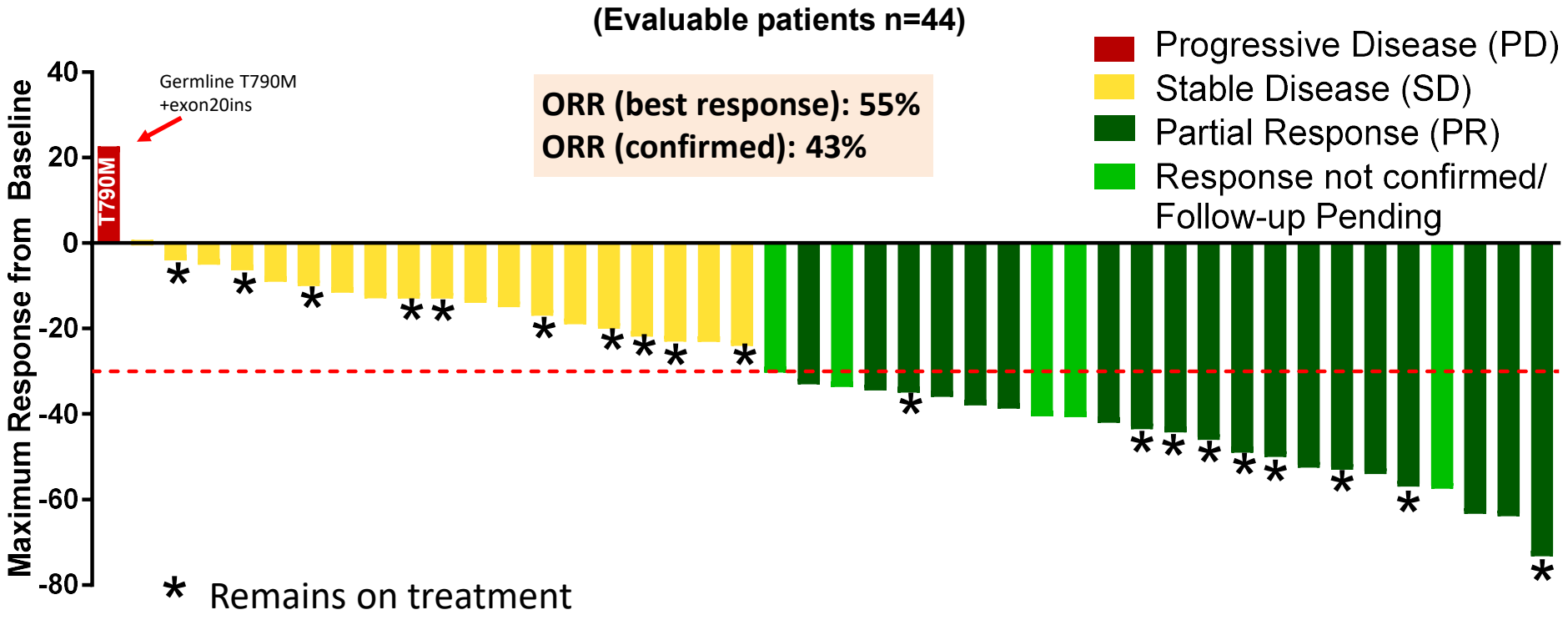
-11 EGFR exon 20 patients with baseline and follow up scans at 2 m (longest on treatment=6 months).
-**Activity**: 8/11 PR observed; 2 patients have had additional follow up scans confirming PR.
-duration of response not yet evaluable; only one patient with PD thus far.
-Evidence of CNS activity in patient with CNS metastasis and another with LMD
-additional patient treated on compassionate use IN (CIND) also had PR

-**Toxicities**: significant EGFR-related toxicities include rash, diarrhea, paronychia, mucositis consistent with those previously described.
-55% underwent dose reduction to 12mg thus far



Robichaux et al. Nature Medicine 2018

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

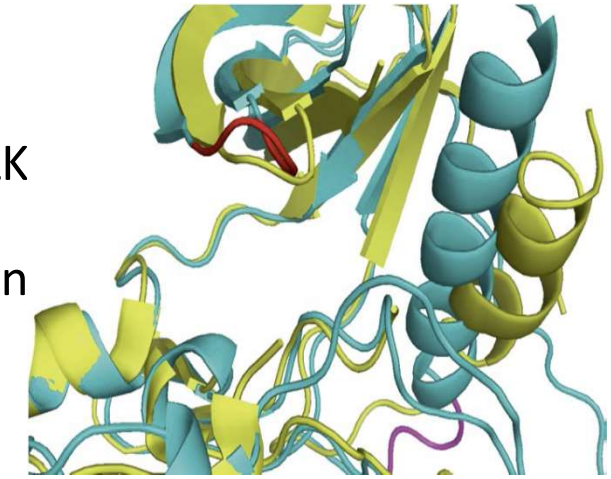


JV Heymach, University of Texas MD Anderson Cancer Center, USA. WCLC 2018

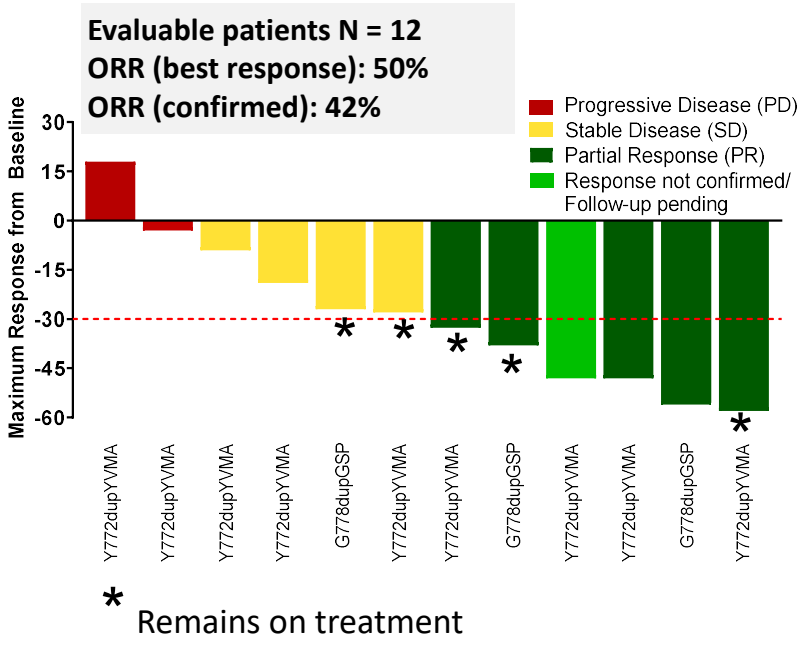
Median PFS 5.5 months

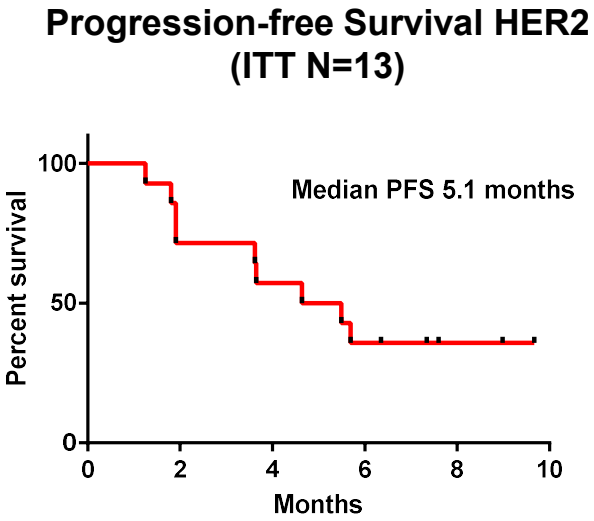
HER2 (ERBB2, *neu*) in NSCLC

- HER2 mutations are seen in 2-4% NSCLC patients, usually mutually exclusive with EGFR, KRAS, and ALK gene alterations
- HER2 mutation incidence up to 6% in EGFR/KRAS/ALK negative pts
- HER2 mutations usually seen with adenocarcinoma in never smokers and women
- HER2 mutations occur in exons 18 to 21 of the tyrosine kinase domain, altering the ATP-binding pocket of the HER2 receptor
- 90% HER2 mutations are exon 20 mutations



50% of HER2 exon 20 mutant NSCLC patients had a partial response with poziotinib treatment

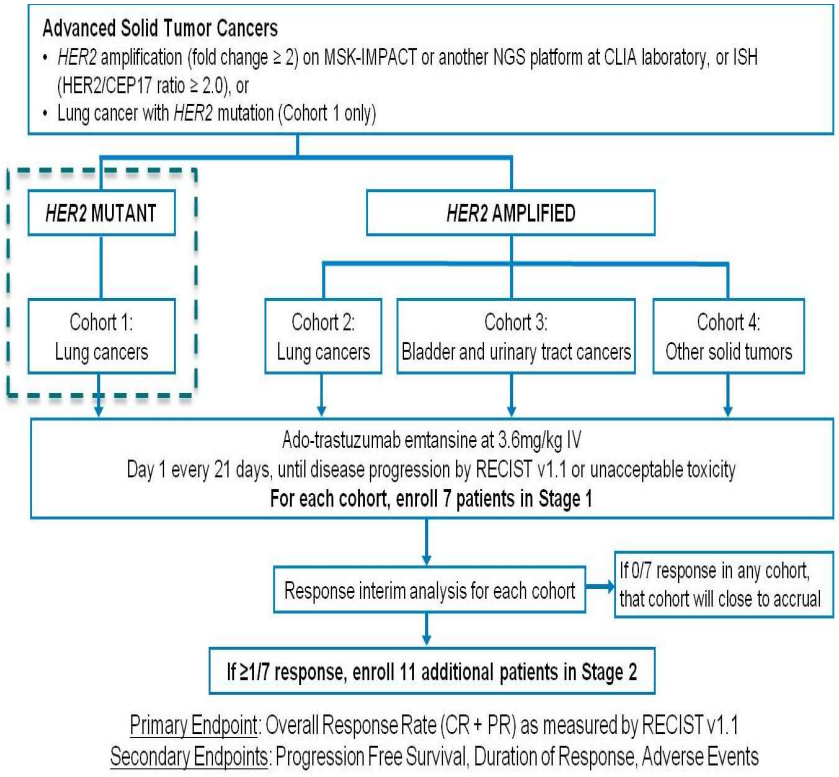




Heymach WCLC 2018

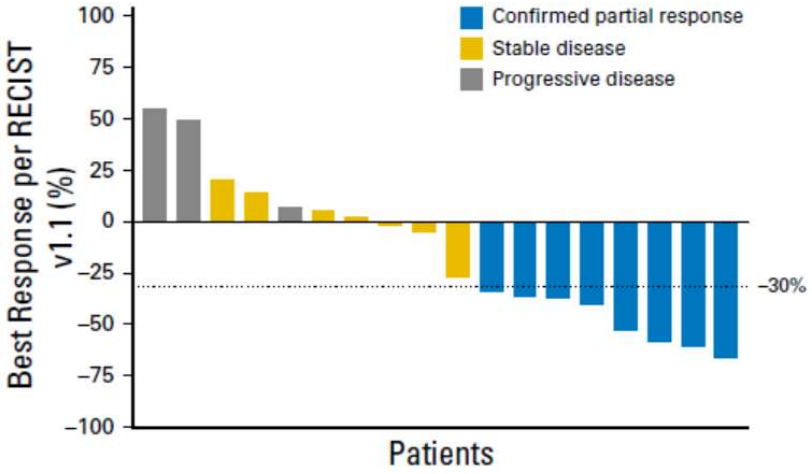
Ado-trastuzumab emtansine (T-DM1)

- Phase II basket trial in 18 HER2-mutant NSCLC patients
- N=18, mostly women (72%) and nonsmokers
- RR 44%
- Median PFS 5 months
- Minor toxicities (grade 1-2) included infusion reactions, thrombocytopenia, transaminitis

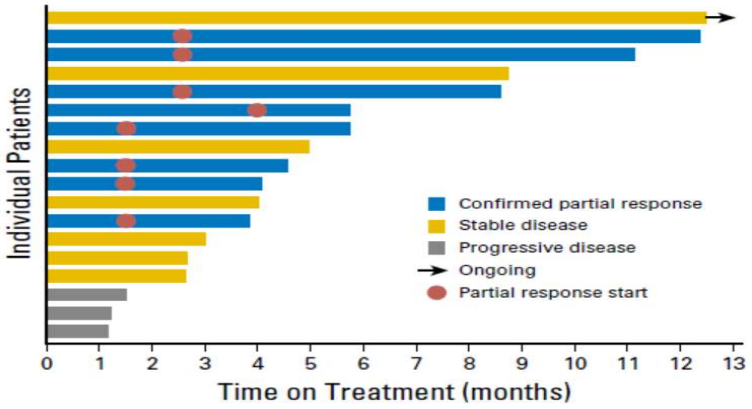


Li BT, et al. JCO. 2018;36:2532–7.

Activity of ado-trastuzumab emtansine (T-DM1) in *HER2*-mutant lung cancers



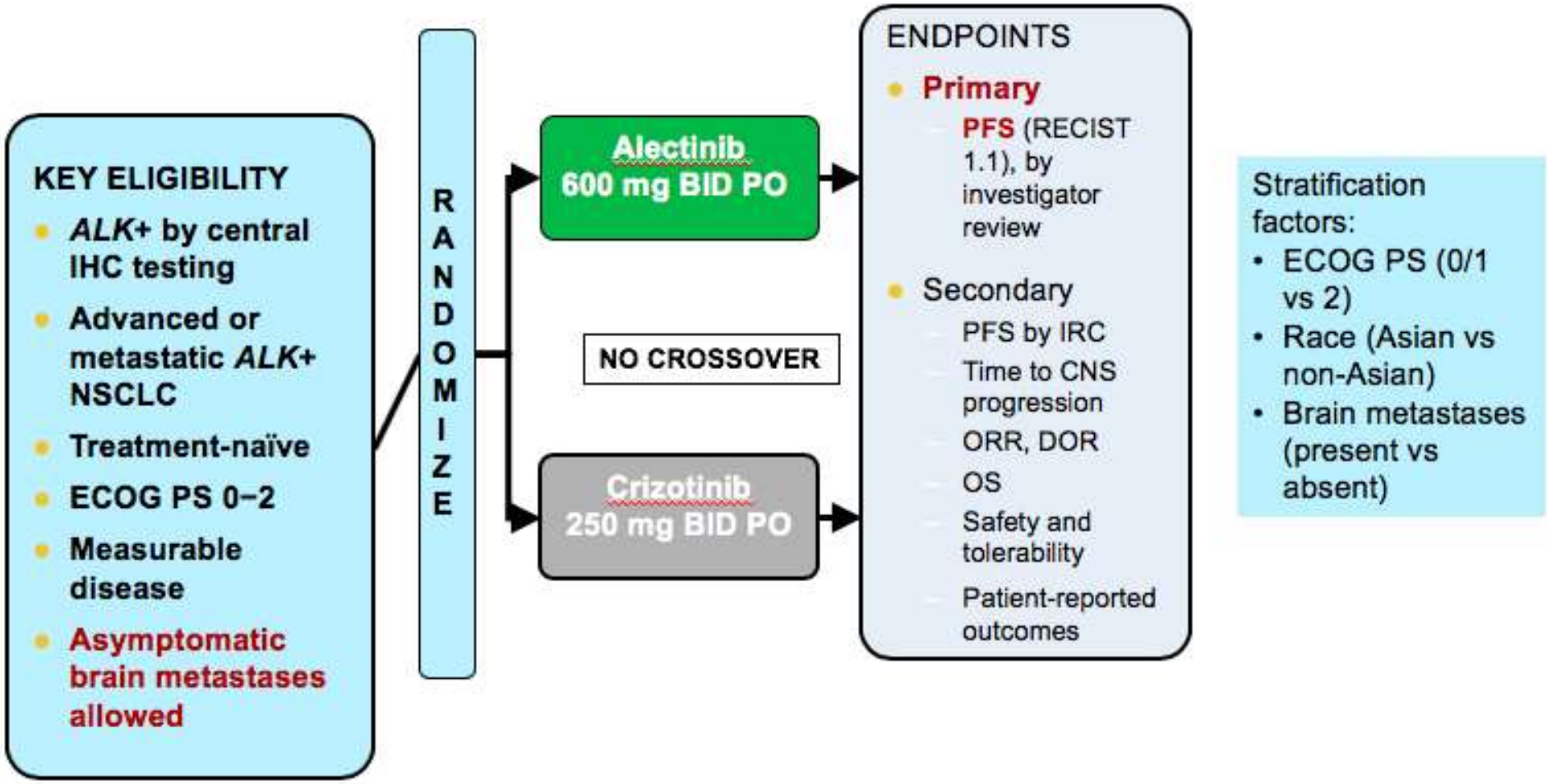
ORR 44% (95% CI: 22-69%)
Median PFS 5 months



Li et al. *J Clin Oncol*. 2018

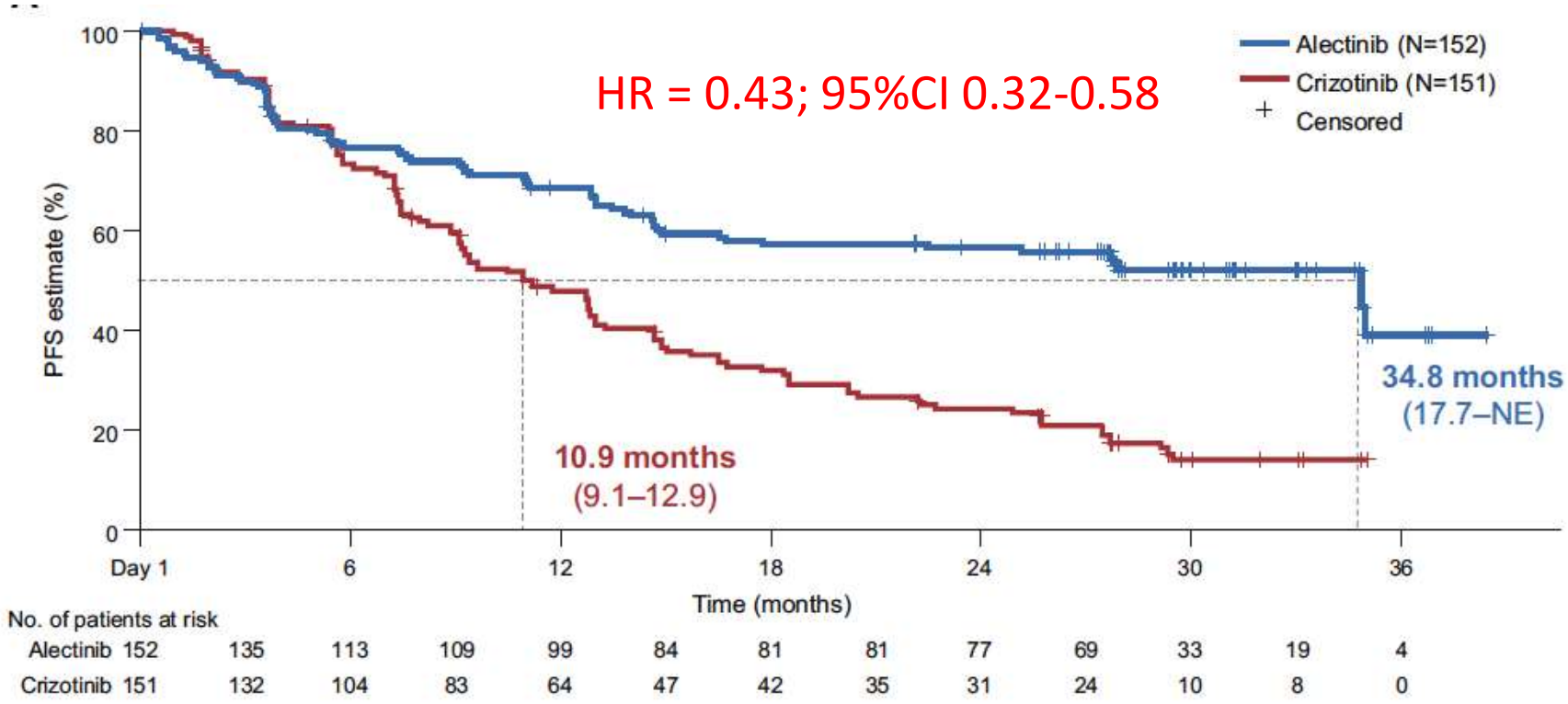
ALK Updates

ALEX Study: Alectinib vs Crizotinib in ALK+ NSCLC



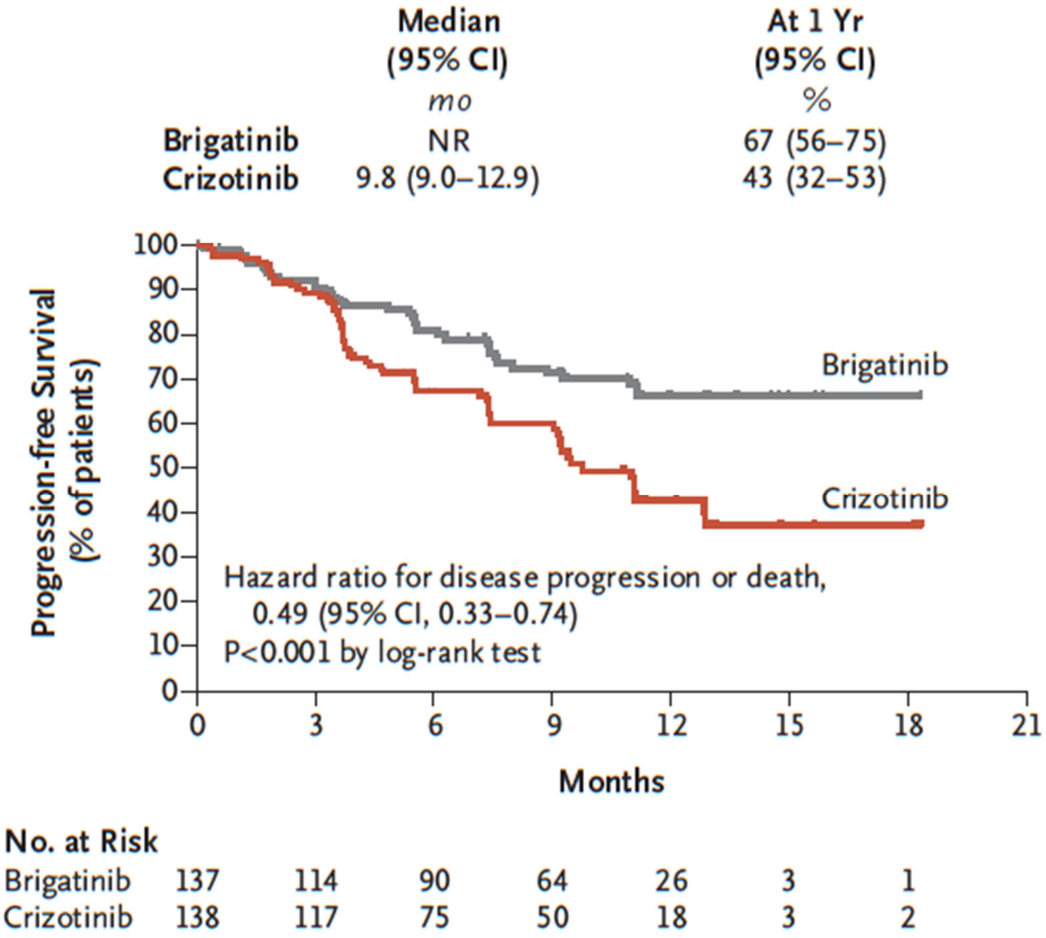
Shaw A et al. Proc. ASCO 2017

Updated ALEX PFS



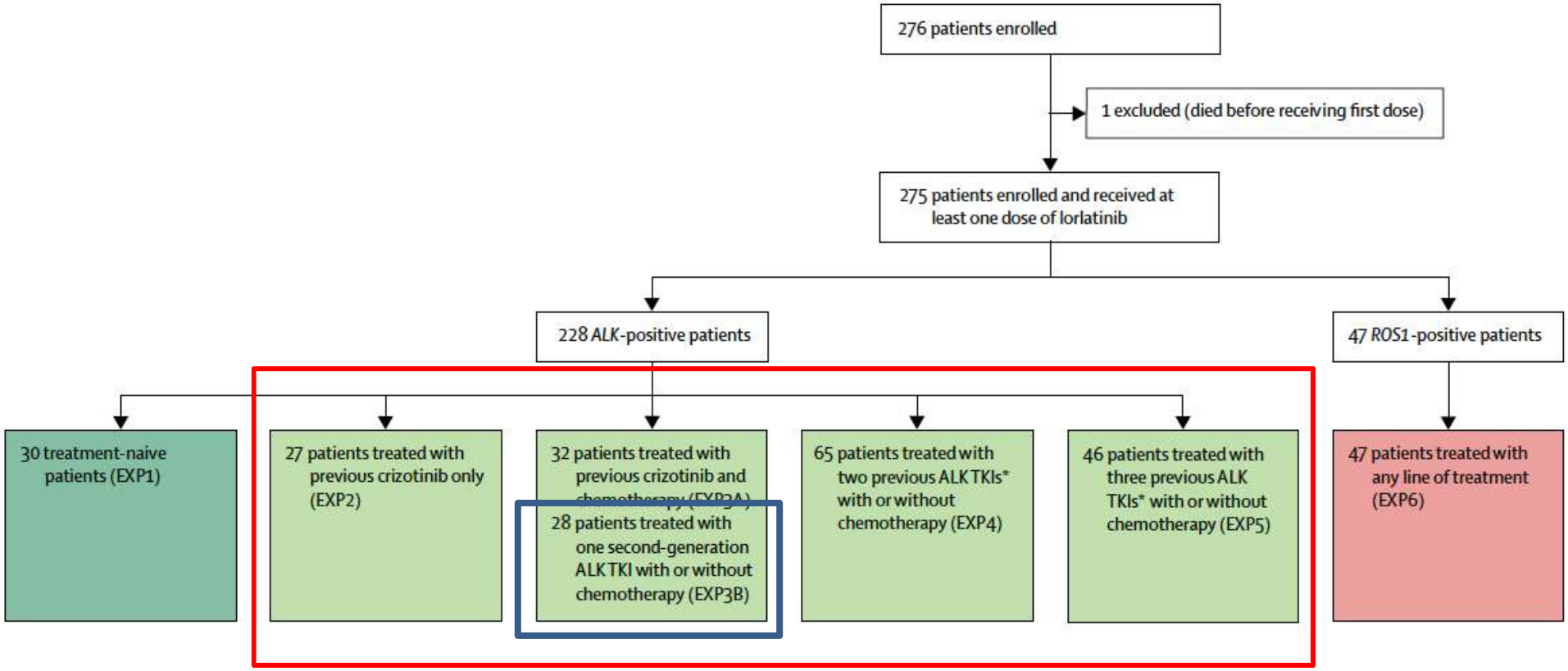
Camidge JTO 2019

Brigatinib as 1L Treatment of Advanced ALK+ NSCLC (ALTA-1)



Camidge et al, *NEJM* 2018;379: 2027-2039

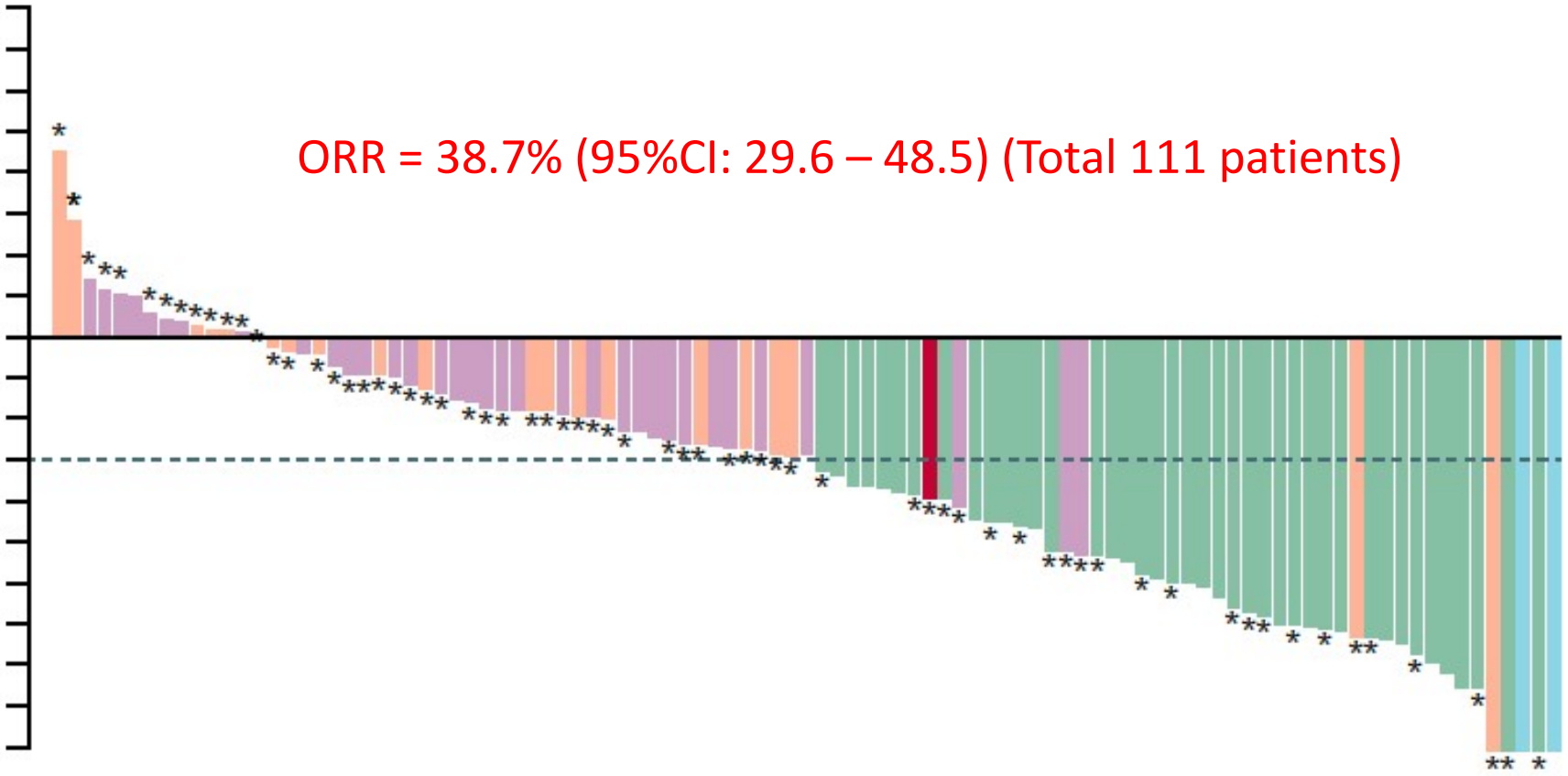
Lorlatinib (3rd gen ALK TKI) Phase 2 schema



Solomon et al, Lancet Oncology 2018

Lorlatinib Phase 2 EXP4-5 ORR (>= 2 ALK TKIs)

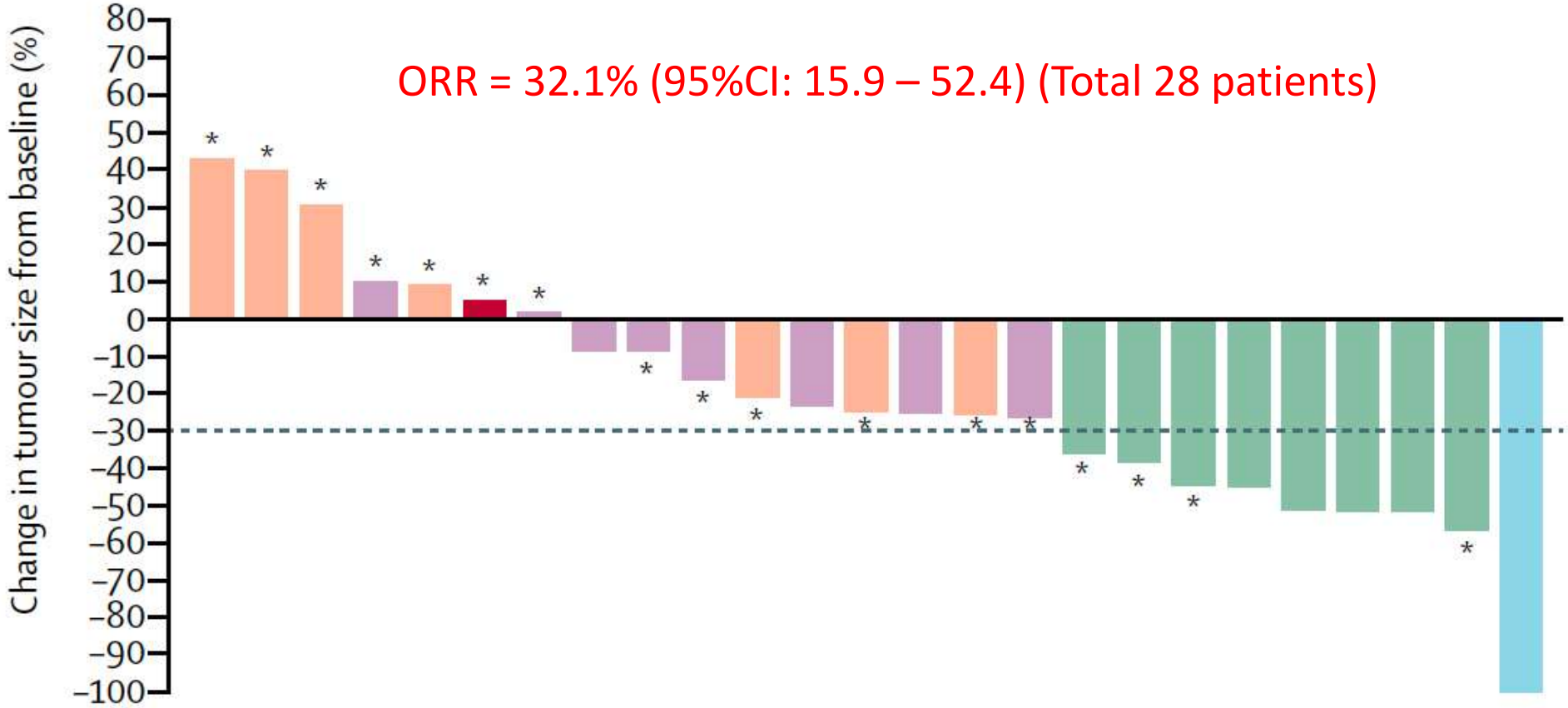
ORR = 38.7% (95%CI: 29.6 – 48.5) (Total 111 patients)



Solomon et al, Lancet Oncology 2018

Lorlatinib Phase 2 EXP3B (post-only one 2G ALK TKI (ceritinib. alectinib)

ORR = 32.1% (95%CI: 15.9 – 52.4) (Total 28 patients)



Solomon et al, Lancet Oncology 2018

Heatmap of all 6 ALK inhibitors against ALK mutations

Variant	Crizotinib	Ceritinib	Alectinib	Brigatinib	Ensartinib	Lorlatinib	
WT	205.62	124.27	49.72	23.02	27.75	5.31	
G1123S	57.62	759.16	4.60	20.91	1.79	4.29	
1151Tins	583.55	293.45	>10000	26.92	109.39	37.04	
L1152P	162.7	214.1	3.77	1.37	16.12	4.98	
L1152R	376.2	348.8	8.21	1.48	29.03	9.75	
C1156T	281.9	118.9	45.67	13.73	30.75	9.02	
C1156Y	154.50	127.15	8.24	4.39	16.39	3.63	
I1171N	287.2	182.7	341.7	21.63	21.5	34.8	
I1171T	168.58	56.21	18.11	4.04	13.63	8.82	
F1174C	400.06	344.63	238.92	50.72	70.9	15.51	
F1174L	224.95	207.9	28.355	26.85	40.92	7.95	
F1174V	612.4	578.23	221.83	70.70	82.51	23.09	
V1180L	160.68	44.53	1375.85	10.49	15.434	5.34	
L1196M	803.5	142.42	297.24	20.80	75.58	53.53	
L1198F	41.95	1636.33	1122.25	108.28	3.072	68.66	
G1202del	281.23	645.13	697.1	118.88	424.62	21.78	
G1202R	420.36	441.6	>10000	85.07	453.43	33.59	
D1203N	617.75	681.95	277.4	257.06	59.88	90.22	
S1206C	299.3	236.25	215.6	59.2	41.81	6.67	
S1206Y	156.59	74.65	8.477	17.66	45.25	3.67	
E1210K	609.8	470.5	926.6	219.8	644	16.59	
F1245C	377.16	316.23	262.58	58.94	70.46	19.5	
G1269A	670.06	108.25	1549.78	13.65	170.50	58.85	
G1269S	919.7	195.5	148.6	17.71	328	156.7	

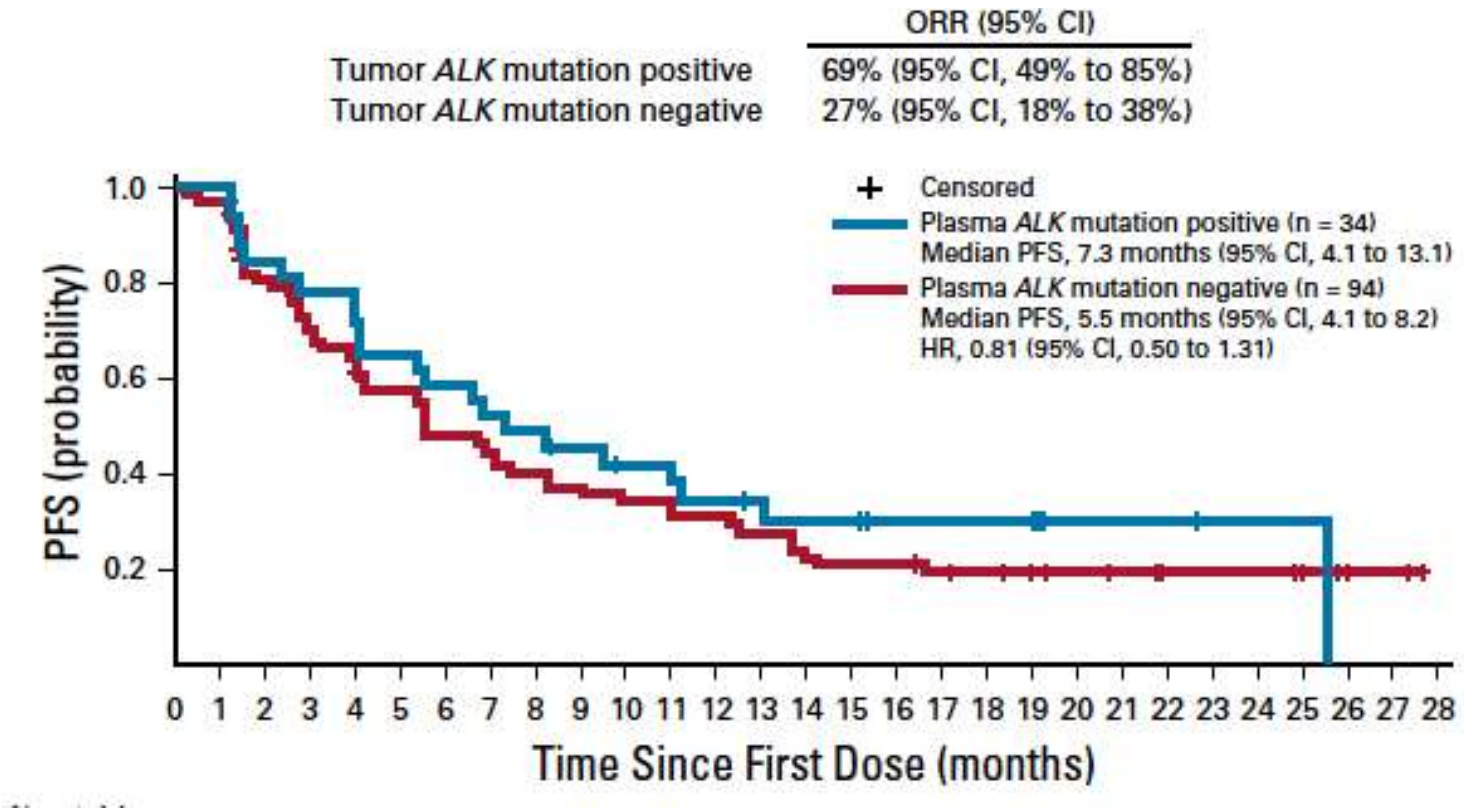
EML4-ALK V3 Average IC50 (nM)

IC50<50nM	50nM<IC50<200nM	IC50>200nM

- The spectrum of ALK resistance mutations varies according to ALK inhibitor
- Majority are resistant to crizotinib

Slide courtesy of : Huan Qiao, MD, PhD, Vincent Huang and Christine Lovly MD, PhD

Importance of understanding resistance mutations post 2G ALK TKIs Regarding Efficacy of Lorlatinib



Shaw et al, JCO 2019

The Oncologist®

Lung Cancer

Clinical Management of Adverse Events Associated with Lorlatinib

Todd M. Bauer,[a] Enriqueta Felip,[b] Benjamin J. Solomon,[c] Holger Thurm,[d] Gerson Peltz,[e] Marc D. Chioda,[f] Alice T. Shaw[g]

[a]Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, Tennessee, USA; [b]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [c]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [d]Pfizer Oncology, La Jolla, California, USA; [e]Pfizer Oncology, Groton, Connecticut, USA; [f]Pfizer Oncology, New York, New York, USA; [g]Massachusetts General Hospital, Boston, Massachusetts, USA

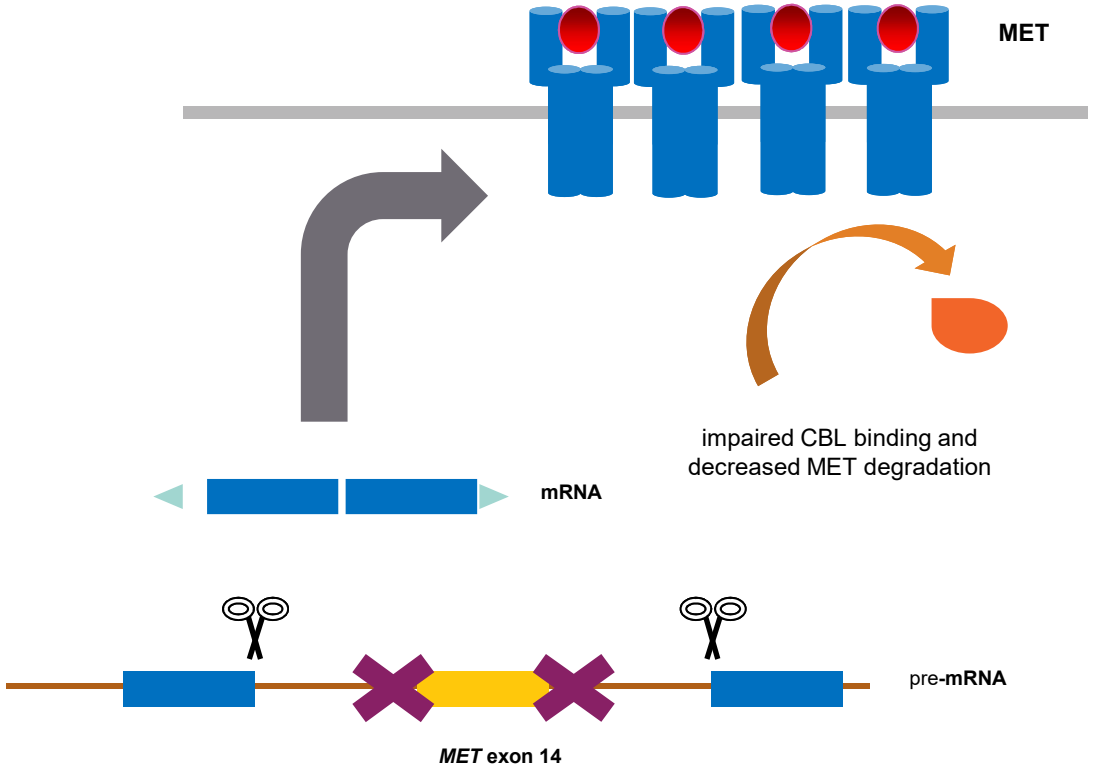
Disclosures of potential conflicts of interest may be found at the end of this article.

- **Hypertriglyceridemia**
- **Hyperlipidemia**
- **Mood Effects**

Oncologist 2019

MET ex14 alterations in NSCLC

- *MET* mutations can lead to decreased MET degradation
  - – deletions, insertions, or base substitutions
  - – disrupt splice sites flanking *MET* exon 14 → exon 14 skipping
  - – absence of JM domain, Cbl ubiquitination process inhibited
  - – increased MET receptor on the tumor cell surface



Adapted from Drilon et al J Thorac Oncol 2016

Drilon et al Clin Cancer Res 2016; Kong-Beltran M et al. Cancer Res 2006;66. Ma et al. Cancer Res 2003;63. Frampton GM et al. Cancer Discov 2015; Drilon et al J Thorac Oncol 2016.

MET TKI preliminary efficacy in *MET* ex14 NSCLC

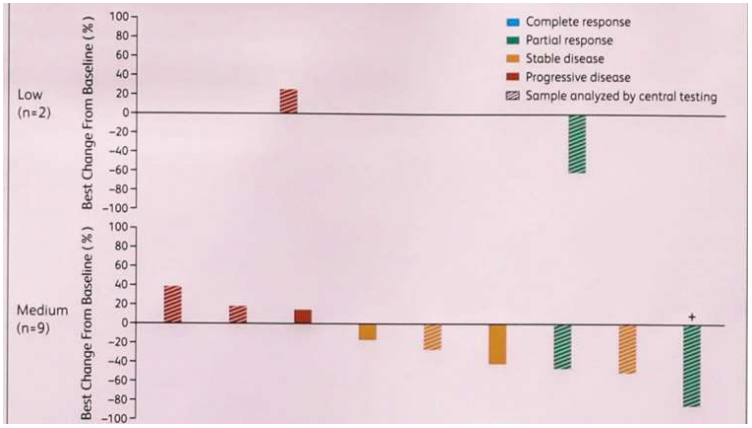
Agent	*MET* testing	n	Brain metastases (n)	ORR % (95% CI)	DOR (months)	PFS (months)
Capmatinib (Wolf J et al ASCO 2019; abstract 9004)	Tissue RT-PCR	97 **1L**—28 **2/3L**—69	**1L**—3 **2/3L**—11	**1L**—67.9(47.6, 84.1) **2/3L**—40.6 (28.9, 53.1)	**1L**—11.1 (5.55, NE) **2/3L**—9.7 (5.55, 12.98)	**1L**—9.7 (5.5, 13.86) **2/3L**—5.4 (4.2, 6.97)
Tepotinib (Paik et al ASCO 2019; abstract 9005)	Liquid (DNA based NGS) Tissue (RNA based NGS)	73 **Liquid**—48 **Tissue**—51	8	**Liquid**—50 (35.2, 64.8) **1L**—58.8 (32.9, 81.6) **2L**—53.3 (26.6, 78.7) **≥3L**—37.5 (15.2, 64.6) **Tissue**—45 (31.1, 59.7) **1L**—44.4 (21.5, 69.2) **2L**—50 (26, 74) **≥3L**—40 (16.3, 67.7)	**Liquid**—12.4 (5.8, NE) **Tissue**—15.7 (9.0, NE)	**Liquid**—9.5 (6.7, NE) **Tissue**—10.8 (6.9, NE)
Crizotinib (Drilon A et al WCLC 2018)	Tissue-local Prospective central tissue & liquid ctDNA	65	na	32 (21-45)	9.1 (6.4, 12.7)	7.3 (5.4, 9.1)
Savolitinib (Lu S et al AACR 2019)	Tissue	29	5	54.8	na	na

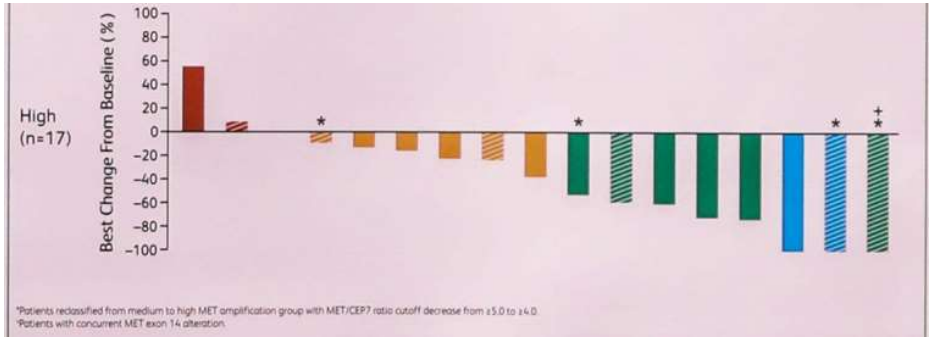
Crizotinib in *MET*-amplified lung cancers

Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

MET amplification determined by FISH

	Low *MET* (*MET/CEP7* 1.8-2.2) n=3	Intermediate *MET* (*MET/CEP7* >2.2-<5.0) n=14	High *MET* (*MET/CEP7* ≥5.0) n=20
Overall response, n (%)	1 (33%) (95%CI 0.8-90.6)	2 (14.3%) (95%CI 1.8-42.8)	8 (40%) (95%CI 19.1-63.9)
Medan DoR (mo)	12.1	3.7	5.5
PFS (mo)	1.8 (0.8, 14.0)	1.9 (1.3, 5.5)	6.7 (3.4, 7.4)



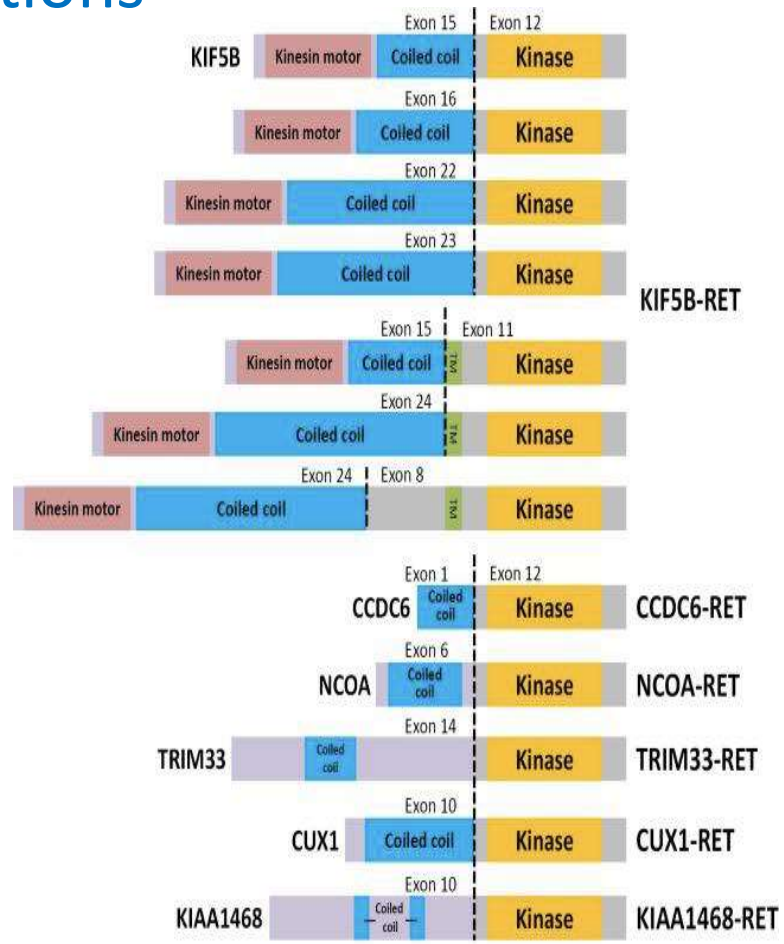


Camidge et al, ASCO Annual Meeting 2018; abstract 9062

RET Alterations

- RET (REarranged during Transfection) can be altered in two distinct ways
  - point mutations found predominantly in MTC
  - fusions seen in papillary thyroid cancer and NSCLC
    - 12 known fusion partners
    - Intact thyrosine kinase domain fused with upstream partner.
    - KIF5B is the most common fusion partner in lung cancer

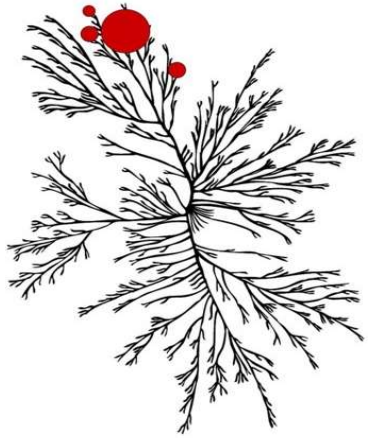
- Frequency in lung caner: 1-2 % overall
- Testing
  - Immunohistochemistry (IHC) ?
  - Fluorescent in situ hybridization (FISH)
  - Next generation sequencing (NGS)
  - RT-PCR



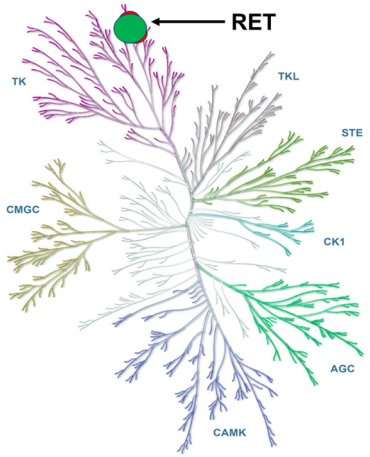
Ju YS, et al. Genome Res. 2012;22:436-445.; Drilon A, et al. Cancer Discov. 2013;3:630-635.
Wang R, et al. J Clin Oncol. 2012;30:4352-4359; Kohno T, et al. Cancer Sci. 2013;104:1396-1400.

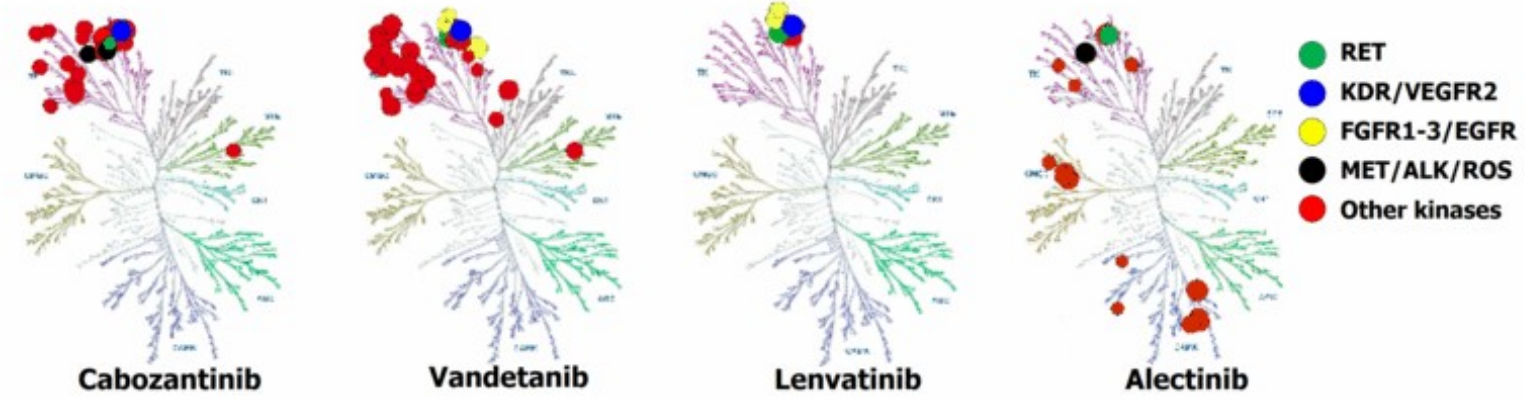
Selective RET vs multikinase RET inhibitors

BLU-667

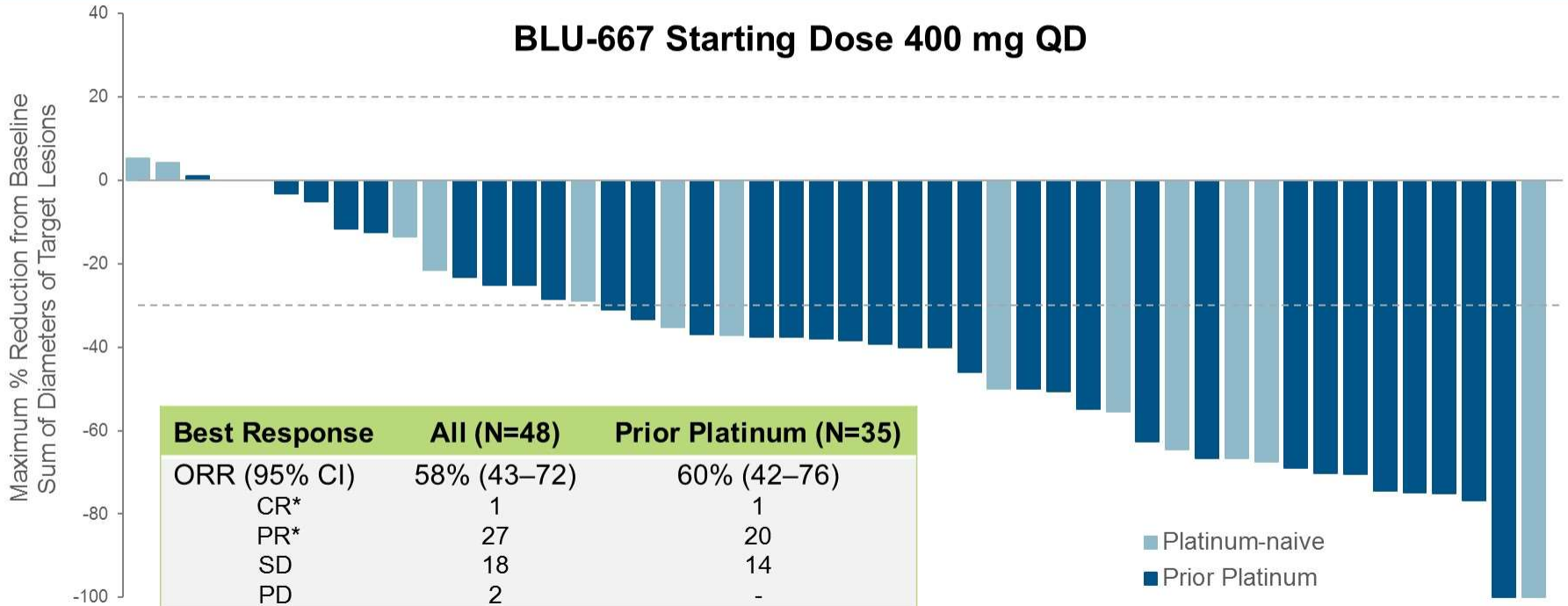


LOXO-292





BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC



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

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

Presented By Justin Gainor at 2019 ASCO Annual Meeting

BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

	RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)			
	Treatment-Emergent (≥15% overall)		Treatment-Related	
Adverse Events	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia[a]	26%	13%	26%	13%
AST increased	24%	5%	20%	2%
Fatigue	21%	3%	13%	3%
Hypertension	20%	13%	13%	10%
Anemia	18%	7%	11%	4%
Diarrhea	18%	2%	9%	-
Pyrexia	18%	-	2%	-
ALT increased	17%	3%	13%	2%
Cough	17%	-	3%	-
Dry mouth	17%	-	12%	-

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia[b] (3%).

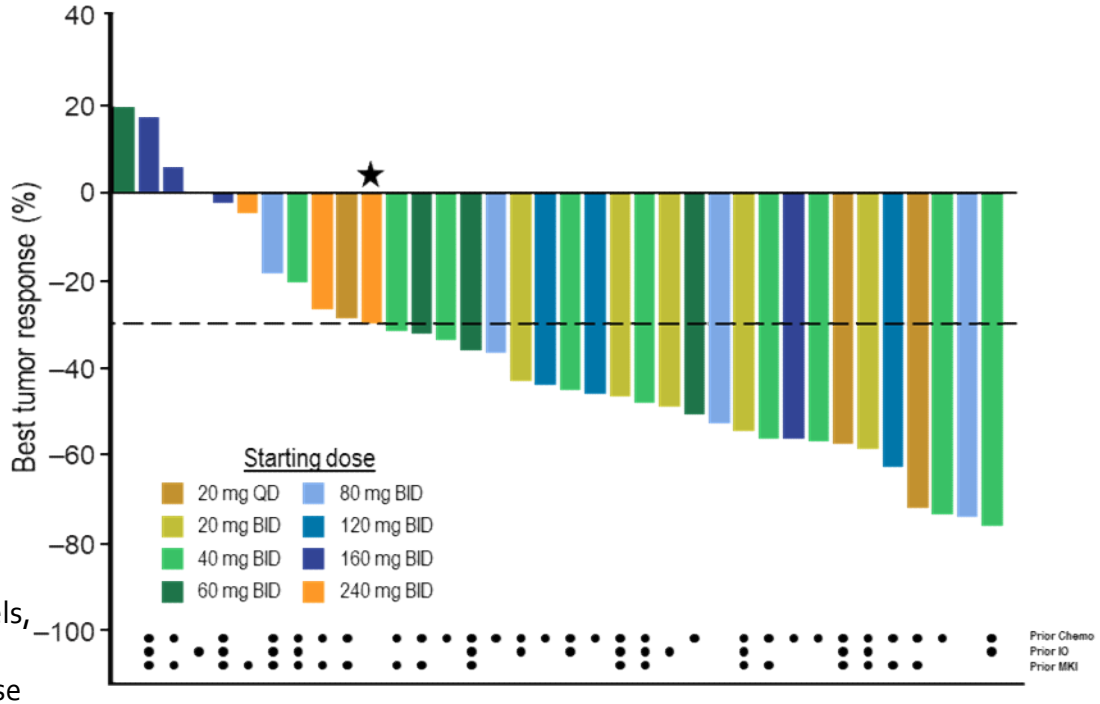
Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

- Treatment-related toxicity is generally low-grade and reversible
- 7% discontinued BLU-667 due to treatment-related toxicity*
  - Pneumonitis, respiratory distress/ hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia

** Across the entire study (n=276), rate of discontinuation due to treatment-related toxicity is 4%.*

Efficacy of LOXO-292 in *RET* fusion-positive NSCLC (RECIST 1.1)

ORR (95% CI)	**68% (n=26/38) (51–83%)**
Confirmed ORR* (95% CI)	**68% (n=25/37) (50–82%)**
CR	–
PR**	26
SD	8
PD	2
NE	2



- RECIST 1.1 responses were seen at all starting dose levels, prior to any intrapatient dose escalation, and in 18/26 (69%) responding patients at each patient's starting dose
- Activity independent of prior therapy
- 4/4 confirmed intracranial responses (1 CR, 3 PR) in patients with measurable CNS lesions

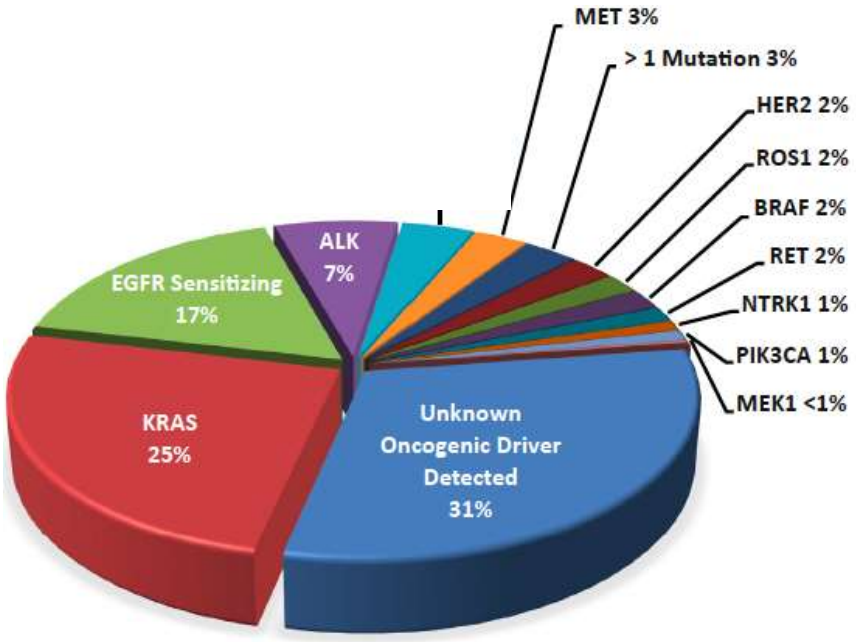
1% G3 diarrhea, 1% G3 headache

★pending confirmation; * Excludes one patient with unconfirmed PR pending confirmation at time of data cut-off; ** 25 confirmed PR, 1 unconfirmed PR pending confirmation

NSCLC patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Presented at WCLC 2018

Summary – More and Better Pieces of Pie



> 50%