Targeted therapies for advanced non-small cell lung cancer

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Topics

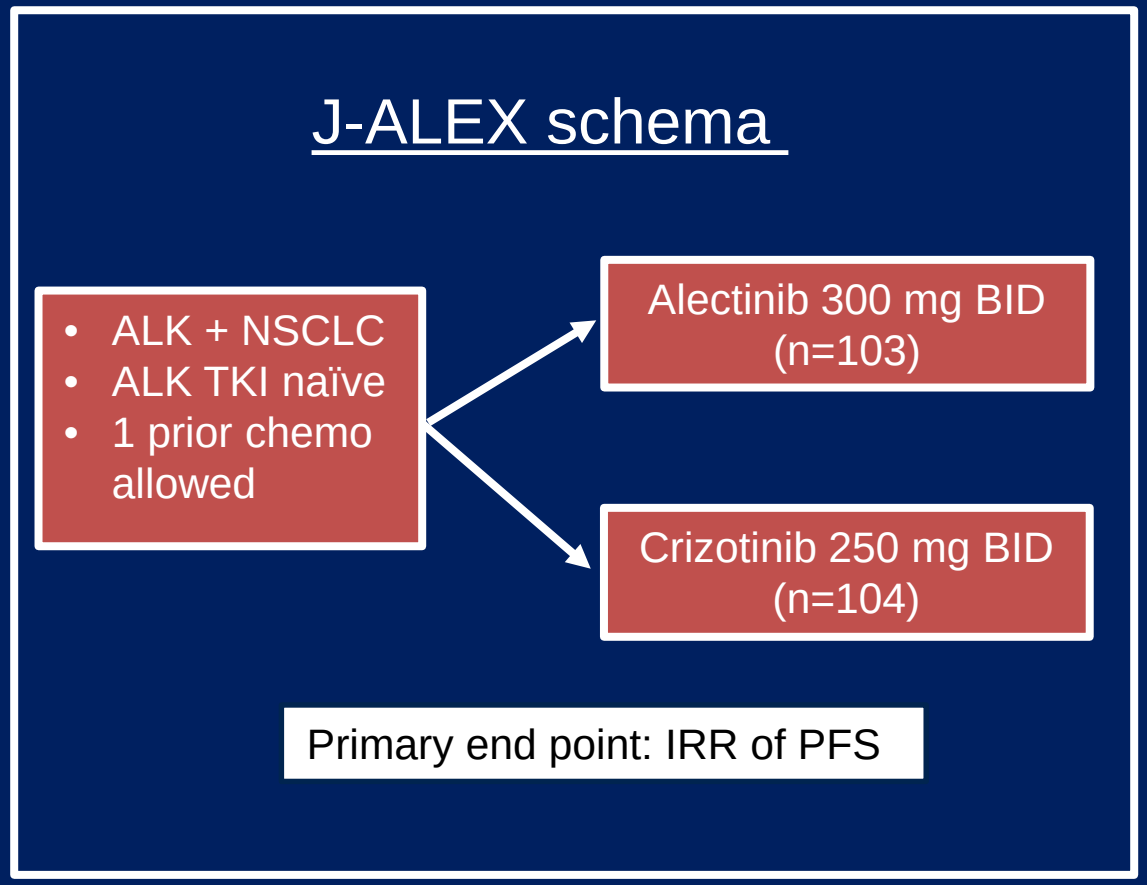
- *ALK* rearranged NSCLC
- *ROS1* rearranged NSCLC
- *EGFR* mutation: exon 19/exon 21 L858R and “uncommon” mutations
- *BRAF* V600E mutant NSCLC
- *MET* exon 14 and *MET* amplified
- *RET* rearranged NSCLC
- *HER2* mutant NSCLC

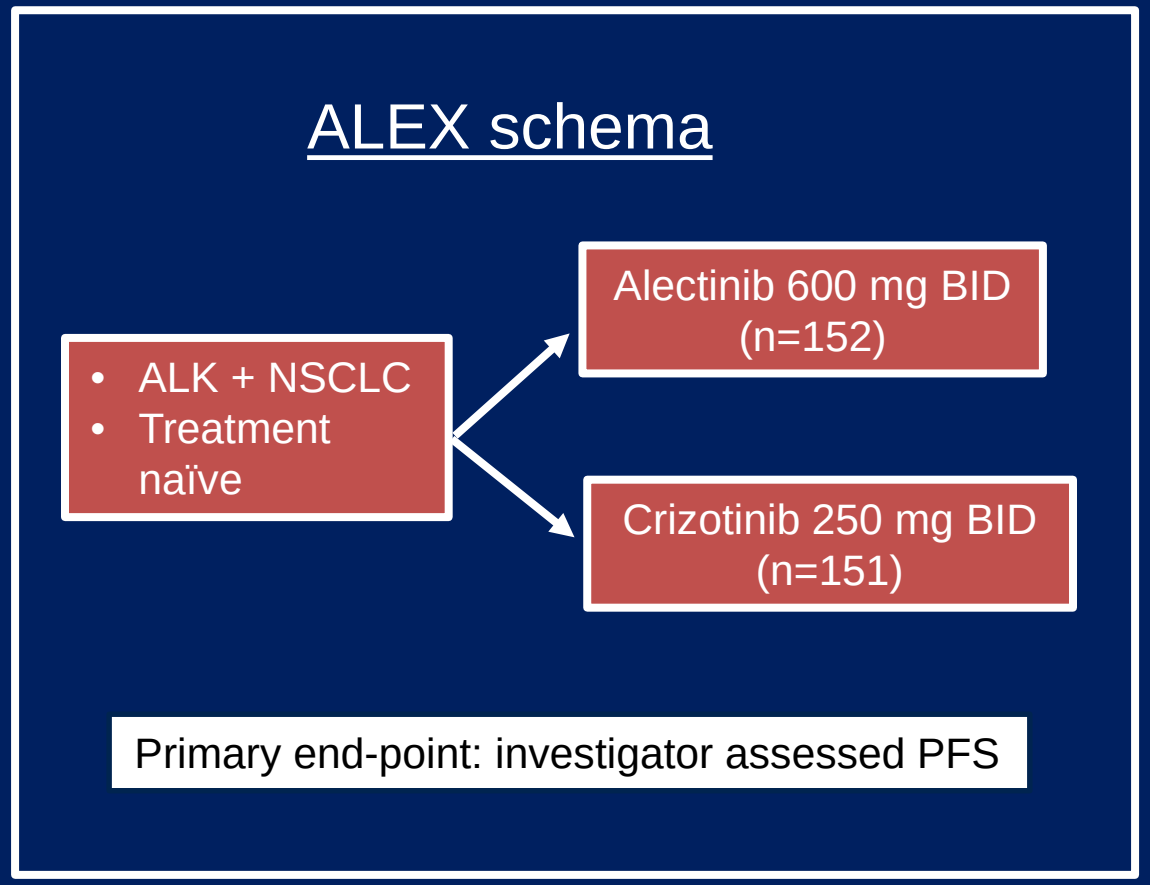
ALK + NSCLC background

- Prevalence of 5-8% in NSCLC with adenocarcinoma histology
- Crizotinib, ceritinib and alectinib available as first-line therapy
- Brigatinib, ceritinib and alectinib available as second-line agents
- Lorlatinib with breakthrough designation
- Optimal sequence and activity of agents after next generation ALK TKI's unknown
- Preclinical data available on impact on acquired resistance mutations on activity of next generation

Kris et al JAMA 2014, Barlesi et al Lancet 2016

Phase 3 trials of alectinib versus crizotinib

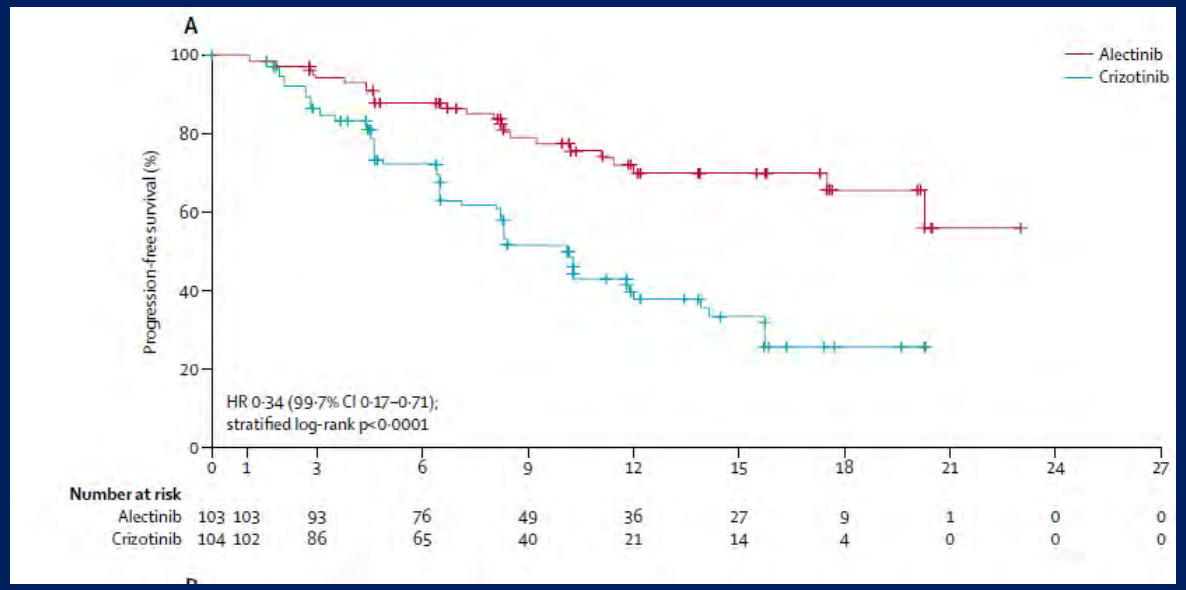




Hida et al Lancet Oncology 2017, Peters et al NEJM 2017

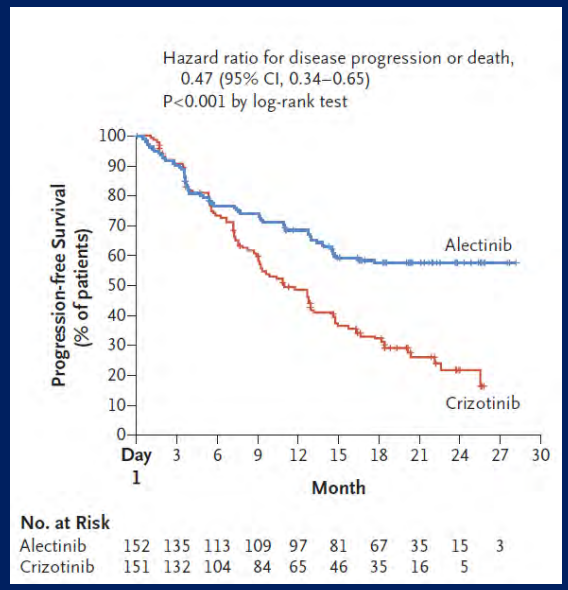
Current standard therapy for advanced NSCLC with ALK rearrangement

J-ALEX trial: alcetinib vs crizotinib PFS



ORR: 92% vs 79%,
Median PFS: NR vs 10.2 months

ALEX: alectinib vs crizotinib PFS

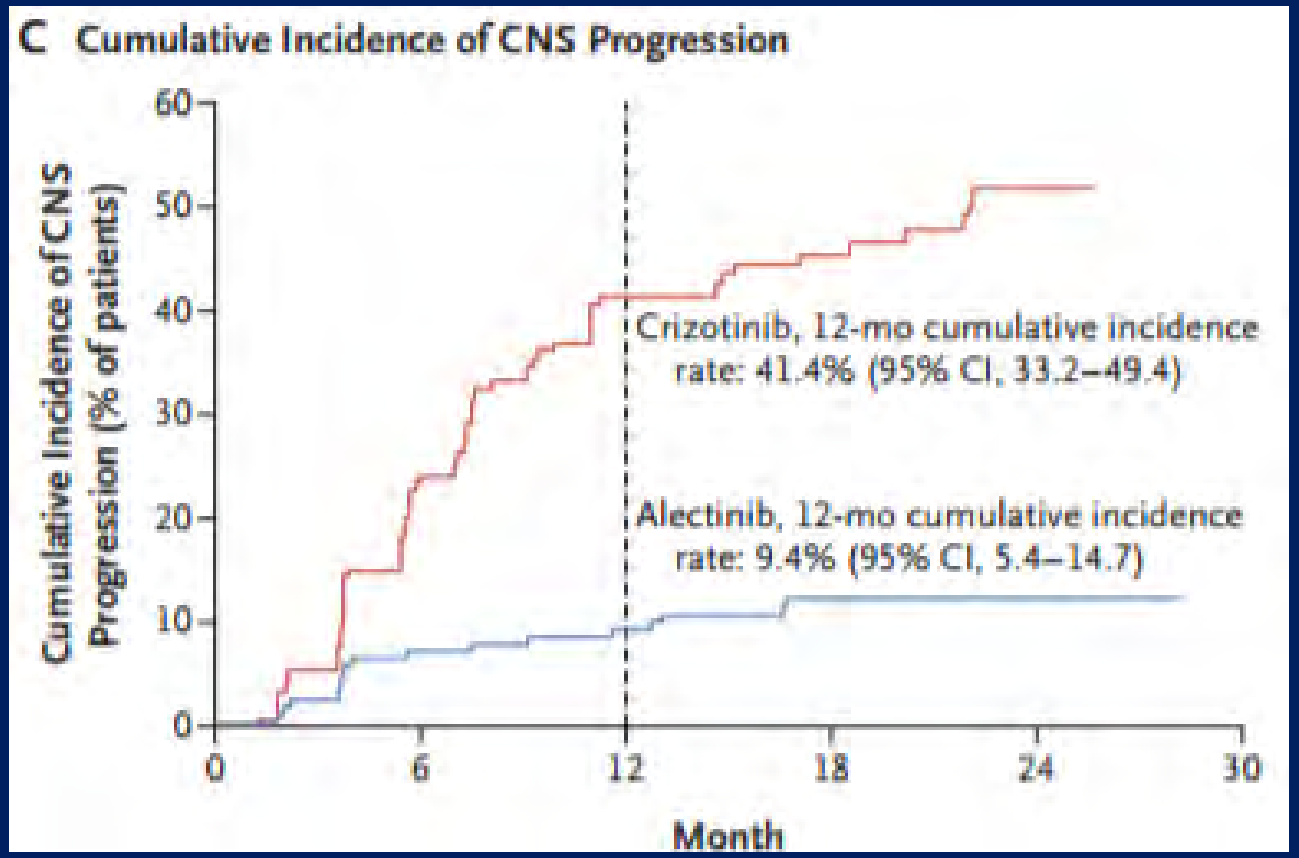


ORR: 83% vs 75.5%
Median PFS: 25.7 vs 10.4 months by IRC

Alectinib preferred first-line therapy per NCCN guidelines

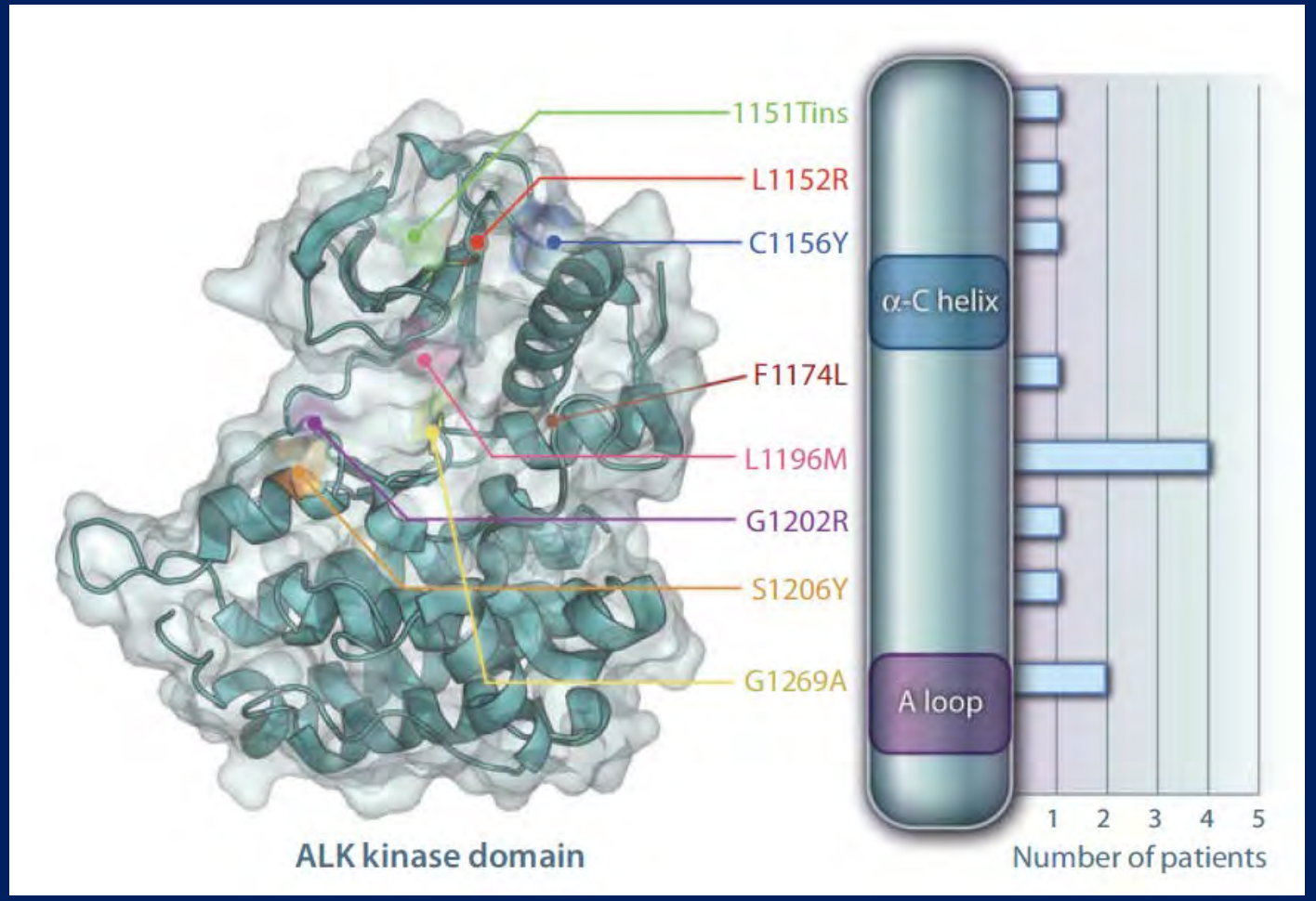
Hida et al Lancet Oncology 2017, Peters et al NEJM 2017,
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

CNS activity: preventing brain metastases



Peters et al NEJM 2017

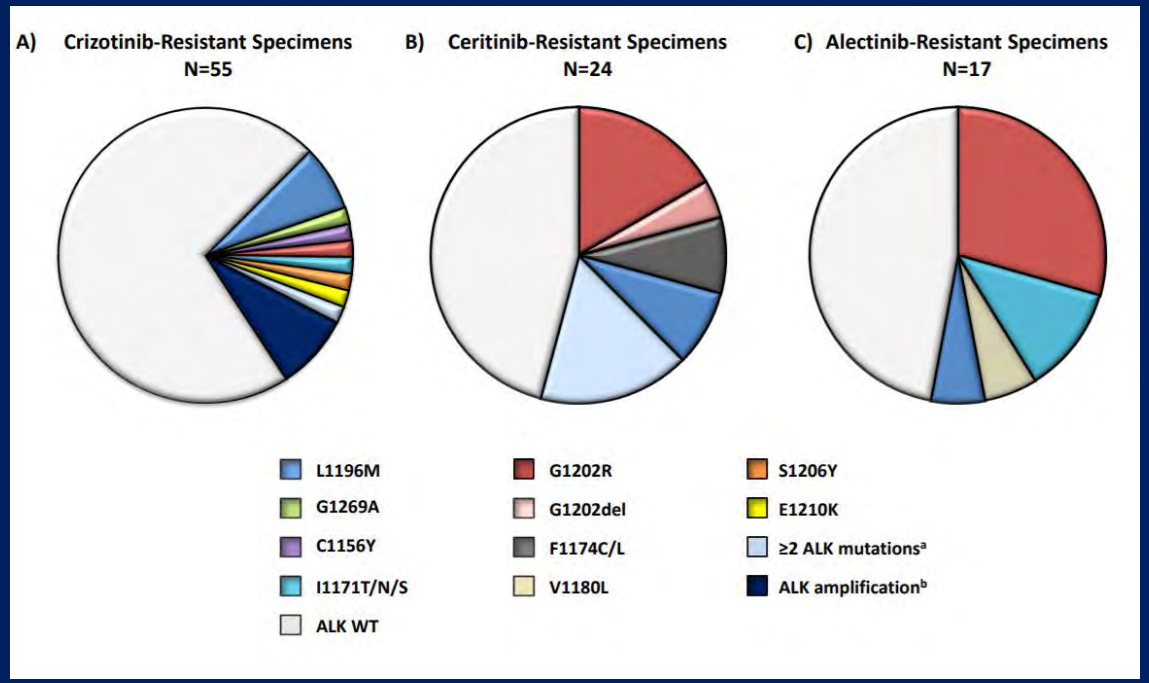
Many Different ALK Resistance Mutations



Lovly and Pao, Sci Transl Med 2012;4(120):120ps2

Rate of resistance mutations and potential impact on therapy

Rate of mutations after 1st and 2nd generation ALK TKI's



Sensitivity and resistance related to specific mutations

Cellular ALK Phosphorylation Mean IC50 (nM)

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

IC50 ≤ 50 nM
IC50 > 50 <200 nM
IC50 ≥ 200 nM

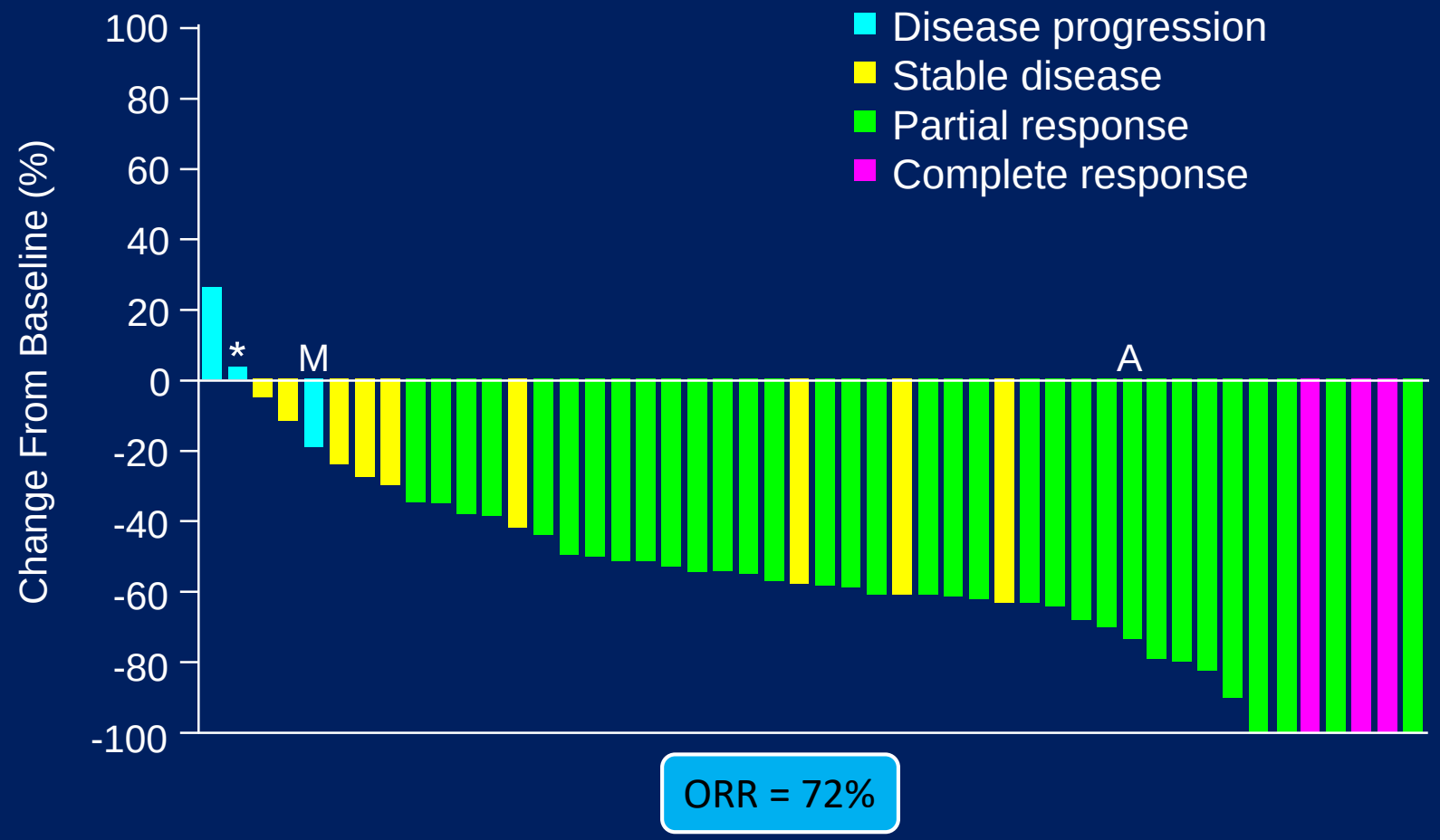
Gainor et al Cancer Discovery 2017

American Society of Clinical Oncology guidelines

"There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for patients with lung adenocarcinoma with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted TKI"

Kalemkerain et al JCO 2018

Crizotinib in Advanced ROS1+ NSCLC



*Patient later determined to not have *ALK* rearrangement.
A, FISH positive, NGS negative for ROS; *ALK*+ on both.
M, Also MET amplification positive.

Shaw AT, et al. *N Engl J Med.* 2014;371(21):1963-1971.

Efficacy of Entrectinib in ROS1+ NSCLC

Best Response by BICR, n (%)	Total (N=32)
Objective Response Rate (BICR-ORR)* (95% CI)	68.8% (50.0, 83.9)
▪ Complete Response, n (%)	2 (6.3)
▪ Partial Response, n (%)	20 (62.5)
▪ Stable Disease, n (%)	4 (12.5)
Intracranial BICR-ORR (patients with measurable disease) (95% CI)	83.3% (35.9, 99.6)
Median Duration of Response (BICR-mDOR) (95% CI)	28.6 months (6.8, 34.8)
Median Progression-Free Survival (BICR-mPFS) (95% CI)	29.6 months (7.7, 36.6)

*** Investigator-Assessed ORR (95% CI) = 78.1% (60.0, 90.7)**

Ahn et al WCLC 2017

BICR = blinded independent central review

Data cutoff date: 13 September 2017

Lorlatinib: phase 2

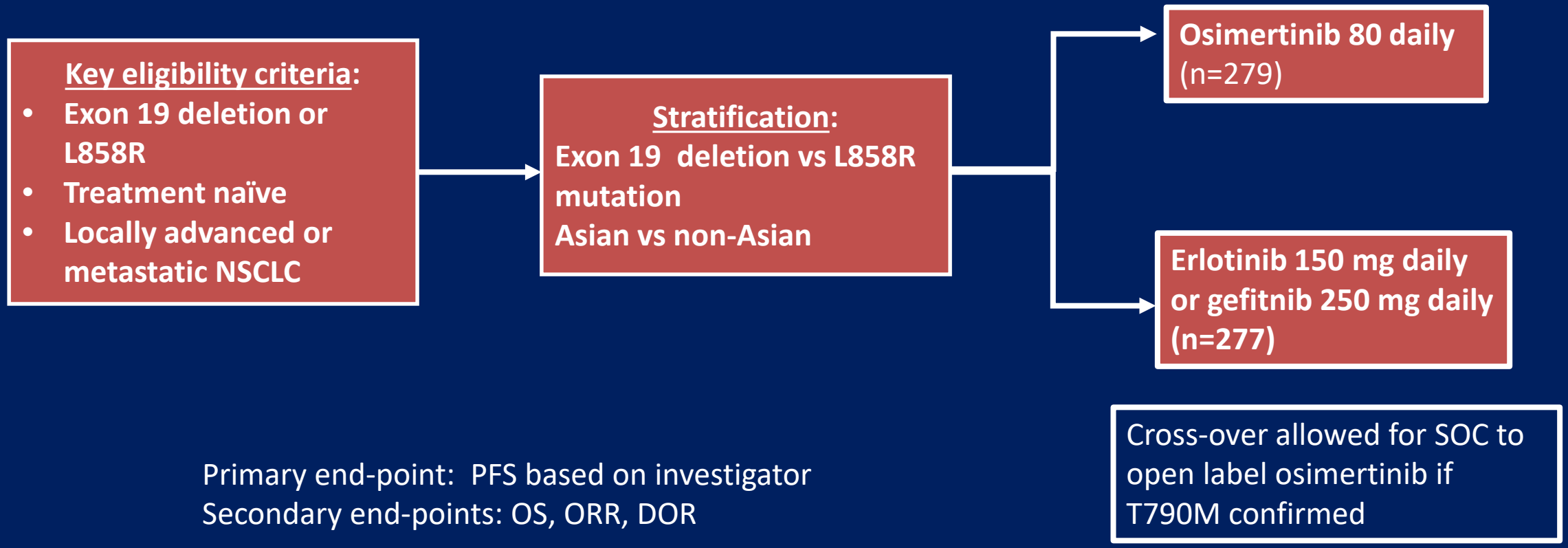
Efficacy end-point	Treatment naïve	Post-crizotinib	ALK TKI treated (non-crizotinib)	2 or 3 ALK TKI treated	ROS1
ORR	90% (27/30)	69% (41/59)	33% (9/27)	39% (43/111)	36% (17/47)
Intra-cranial ORR	75% (6/8)	68% (25/37)	42% (5/12)	48% (40/83)	56% (14/25)
Median PFS (months)	Not reached	Not reached	5.5	6.9	9.6

G1202R mutation: ORR 11/19 (58%)

Most common adverse events (≥10%): hypercholesterolemia (81%), hypertriglyceridemia (60%), edema (43%) peripheral neuropathy (30%), weight increase (18%), cognitive effects (18%), mood effects (15%), fatigue (13%), diarrhea (11%), arthralgia (10%), increased AST (10%)

Solomon et al WCLC 2018 (abstract OA 05.06)

Phase 3 trial: Osimertinib compared to erlotinib or gefitinib in patients with *EGFR* mutant NSCLC (FLAURA)

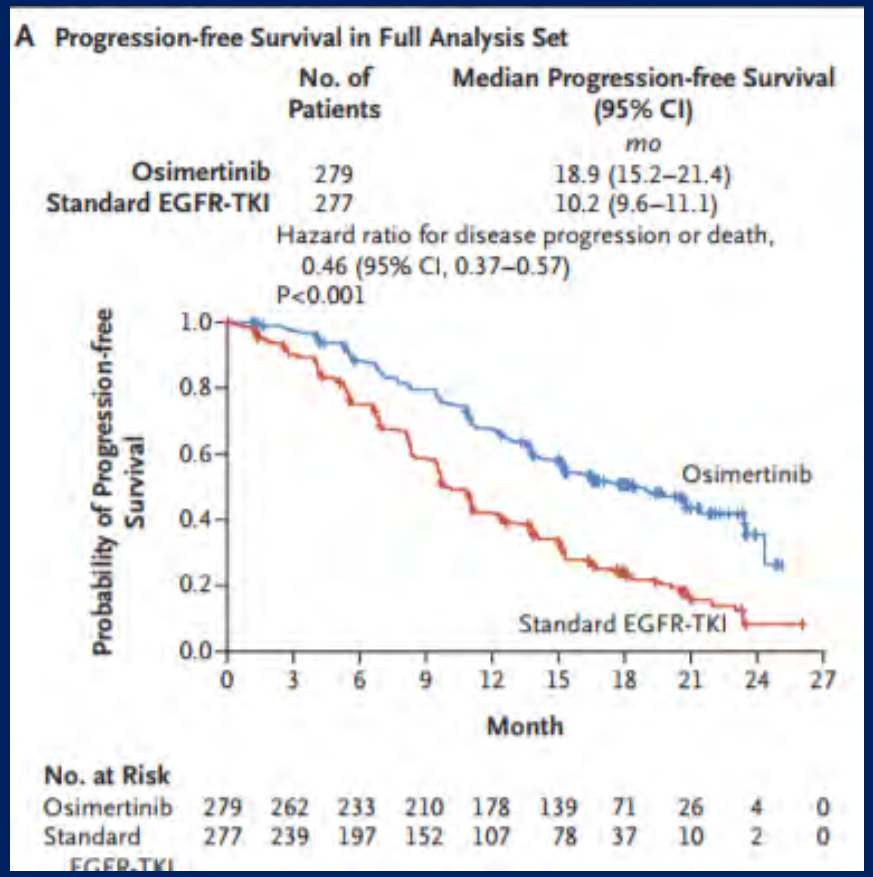


Primary end-point: PFS based on investigator
Secondary end-points: OS, ORR, DOR

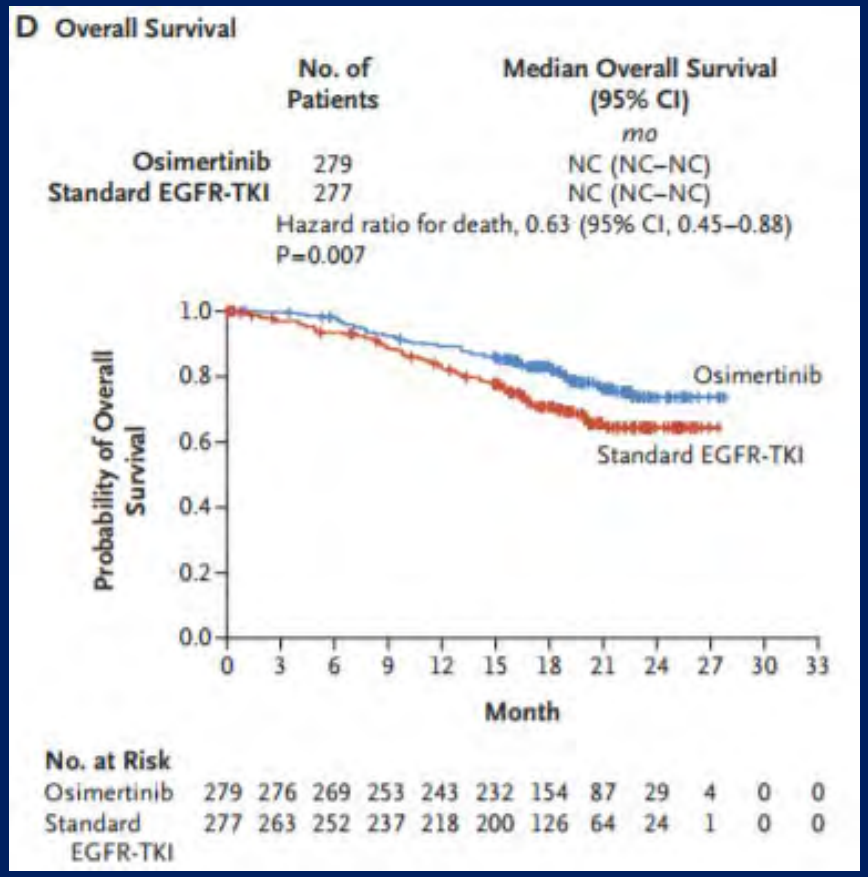
Soria et al NEJM 2017

Efficacy results

Progression-free survival



Overall survival

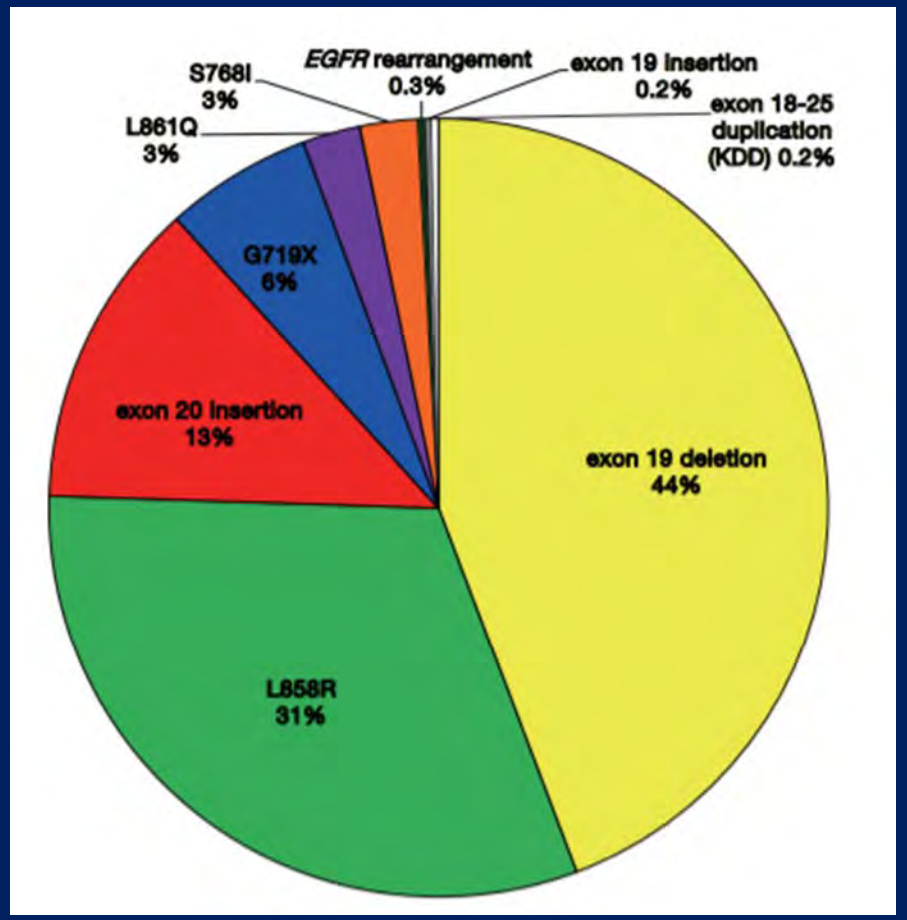


ORR: 80% vs 76%, OR: 1.27; p=0.24
DOR: 17.2 vs 8.5 months

Soria et al NEJM 2017

Uncommon EGFR mutations

- Exon 18 G719X, exon 20 S768I, exon 21 L861Q represent 10-15% of EGFR mutations
- Have lower affinity for EGFR TKI than exon 19 and L858R
- Greater sensitivity to EGFR TKI than *EGFR* wild-type
- In cell line models mutation subtype impacts sensitivity to specific EGFR TKI



Costa Translational Lung Cancer Research 2016, Yun et al Cancer Cell 2007, Banno et al Cancer Science 2016, Kobayashi et al CCR 2016

Clinical data with EGFR TKI in uncommon mutations

First author	Agent	# of pts	ORR	PFS (months)	OS (months0
Yang G719X L861Q S768I	Afatinib	38 14 9 8	71% 77.8% 56.3% 100%	10.7 13.8 8.2 14.7	19.4 26.9 17.1 NE
Chiu	Gefitnib or erlotinib	154	41.6%	7.7	17.3
Baek	Gefitinib or erlotinib	50	20.6%	2.6	12.7
Arrieta	Gefitinib, erlotinib, or afatinib	38	39.3%	3.9	17.4

Afatinib approved at 40 mg daily based on blinded radiological review (n=32):

- ORR: 66% (95% CI, 47-81)
- 21 responders with response duration ≥ 12 months

Yang et al Lancet Oncology 2015, Chiu et al JTO 2015, Baek et al Lung Cancer 2015
Arrieta et al Lung Cancer 2015, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm592558.htm

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Ahn et al WCLC 2017

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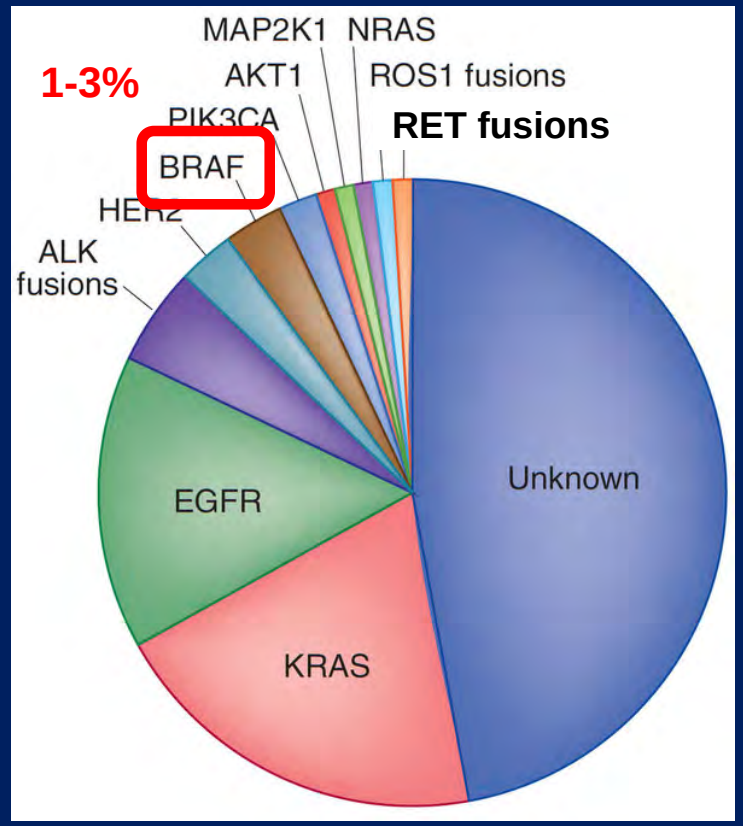
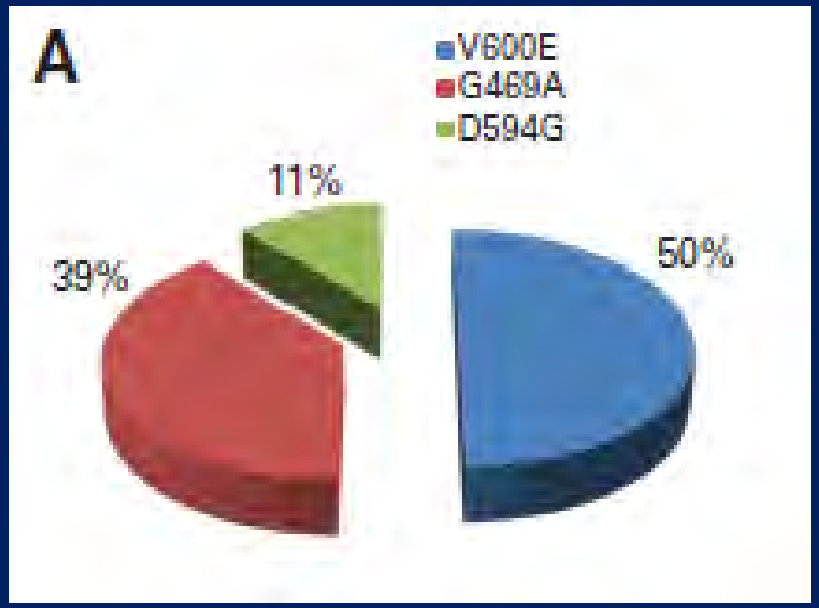
BRAF mutation in NSCLC



Relative distribution of 'driver' mutations in lung adenocarcinoma.

Pao and Hutchinson 2012



Relative distribution of BRAF mutations in NSCLC.

Paik P et al JCO 2011

BRAF V600E-directed therapy

	ORR	Median DOR (months)	Median PFS (months)	Median OS (months)
Dabrafenib (n=78)	**33%**	**9.6**	**5.5**	**12.7**
Dabrafenib/Trametinib (n=59)	**63.2%**	**9.0**	**9.7**	**NR**
Dabrafenib/Trametinib (n=36)	**64%**	**10.4**	**10.2**	**24.6 months**

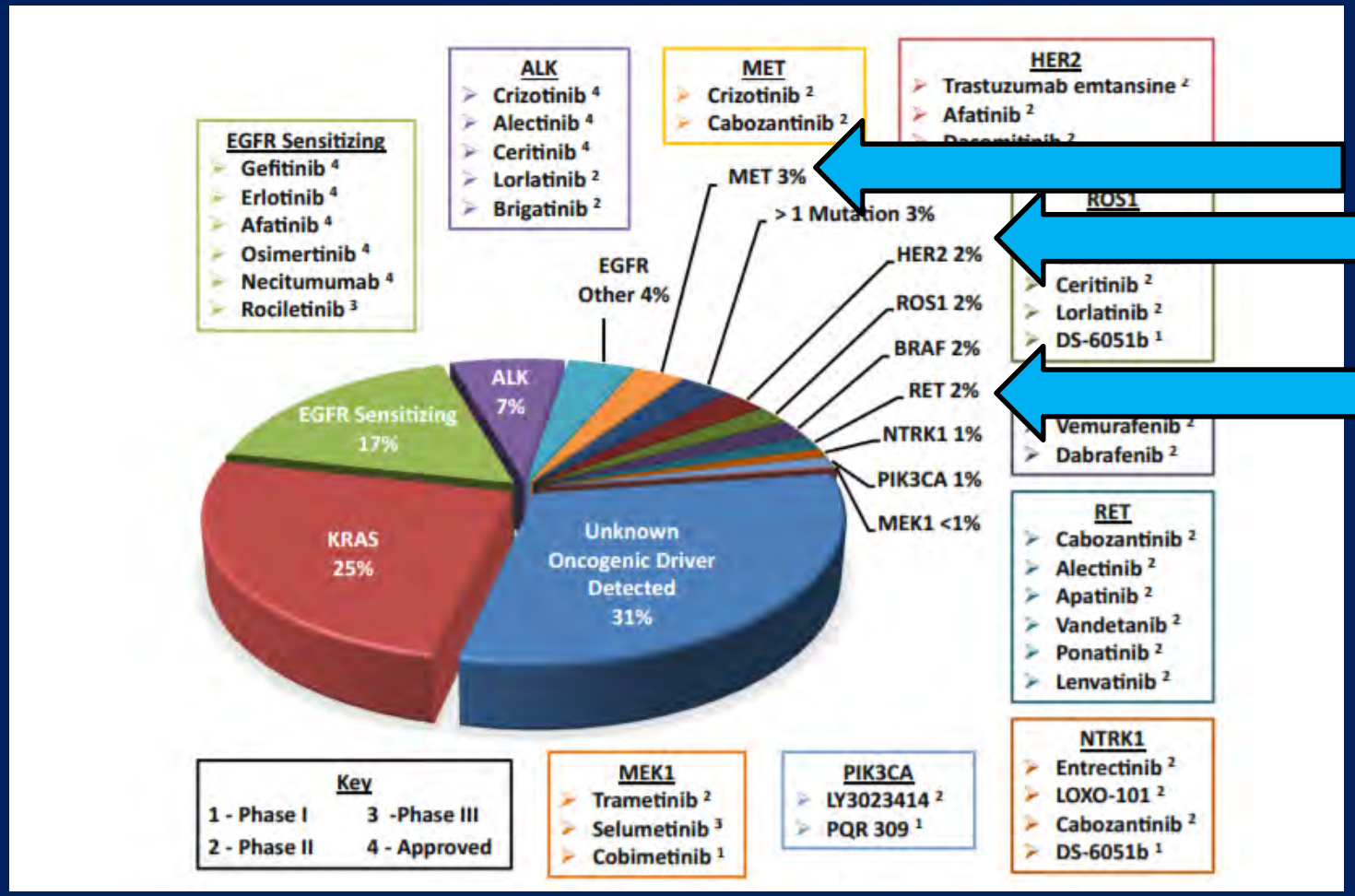
Planchard et al Lancet Oncology May 2016, Planchard et al Lancet Oncology July 2016, Planchard et al Lancet Oncology 2017

Dabrafenib alone and with trametinib in *BRAF* V600E NSCLC: Adverse events

Treatment	Grade 3 AE's ≥ 5%	Treatment delivery
Dabrafenib	Squamous cell carcinoma (12%) Asthenia (5%) basal cell carcinoma (5%),	6% discontinued due AE 43% required dose interruption 18% required dose reduction
Dabrafenib/trametinib (previously treated)	Neutropenia (9%) Hyyponatremia (7%) Anemia (6%)	12% discontinued due AE 61% required dose interruption or delay 58% of patients received 80% of planned dabrafenib 75% of patients received 80% planned trametinib
Dabrefenib/trametinib (first-line)	Pyrexia (11%) ALT increase (11%) HTN (11%) Vomiting (8%)	AE's leading to treatment discontinuation (22%), dose interruption (75%), and dose reduction (39%) Dose reduction dabrafenib: 47%, Dose reduction trametinib 28%

Planchard et al Lancet Oncology 2016, Planchard et al Lancet Oncology 2016, Planchard Lancet Oncology 2017

Emerging molecular subsets



Tsao et al Journal of Thoracic Oncology 2015

MET exon 14 alterations

- Introns flanking *MET* exon 14 in pre-mRNA are spliced out resulting MET mRNA which is translated into functional MET receptor
- *MET* exon 14 encodes the ubiquitin ligase binding site which is used in receptor degradation
- Mutations that disrupt splice sites result in *MET* exon 14 skipping producing a MET receptor that lacks ubiquitin binding site → reduced degradation of MET protein → sustained MET activation
- Next generation sequencing the preferred testing method
- *MET* exon 14 skipping mutations in 20-30% of pulmonary sarcomatoid carcinoma, and cab be seen in squamous histology
- Median age 73 years,

Drilon et al JTO 2017, Liu et al JCO 2016

Crizotinib in MET exon 14 and amplified NSCLC

MET exon 14

Response	Number
CR	0
PR	8 (44%)
SD	9 (50%)
Unconfirmed PR/CR	5 (28%)
ORR	44% (95% CI: 22-69)

- MET amplification present in 15-20% of samples

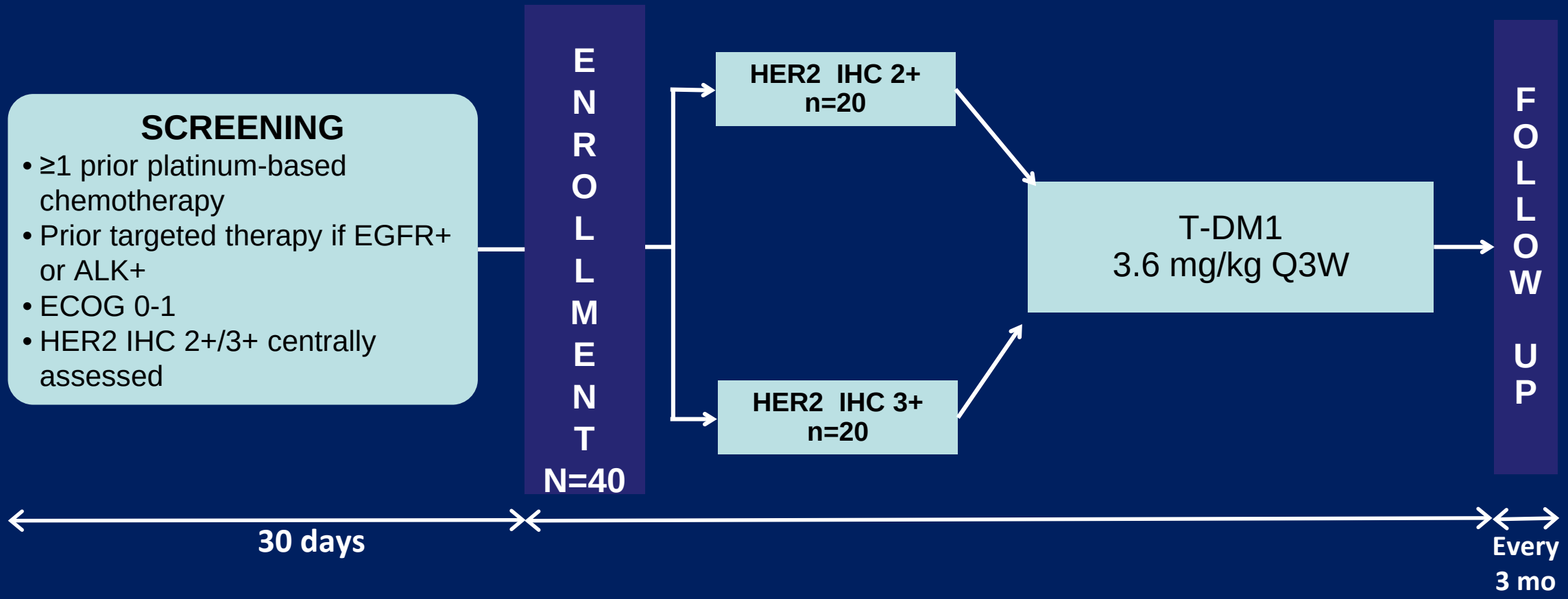
MET amplified

MET/CEP7 ratio	% of total	ORR
<1.8	92.6	
≥1.8 to ≤ 2.2	3.6	
> 2.2 to < 5.0	3.0	16.7% (1 of 6)
≥ 5.0	0.8	50% (3 of 6)

MET amplified defined by copy number as well. Copy number cut-off vary depending on testing

Drilon et al JTO 2017, Drilon et al ASCO 2016, Camidge et al ASCO 2014, Schrock et al JTO 2016

Study Design



Primary Efficacy Endpoint: *ORR by Investigator (RECIST v1.1)*
Secondary Endpoints: *PFS by Investigator, DoR, OS, safety*
Exploratory biomarker analysis

Presented by Stinchcombe ASCO 2017

Phase 2 trial of T-DM1 in patients with advanced NSCLC with HER2 over-expression by IHC

Efficacy parameter	IHC cohort 2+ (n=29)	IHC cohort 3+ (n=20)
ORR	0	20% (95% CI: 6-44%)
CBR	7% (95% CI: 1-23%)	30% (95% CI: 12-54%)
PFS	2.6 months	2.7 months
OS	12.2 months	15.3 months

CBR: response or stable disease for at least 6 months

Stinchcombe et al ASCO 2017

A phase 2 trial of ado-trastuzumab emtansine for patients with *HER2* amplified or mutant cancers (NCT02675829)

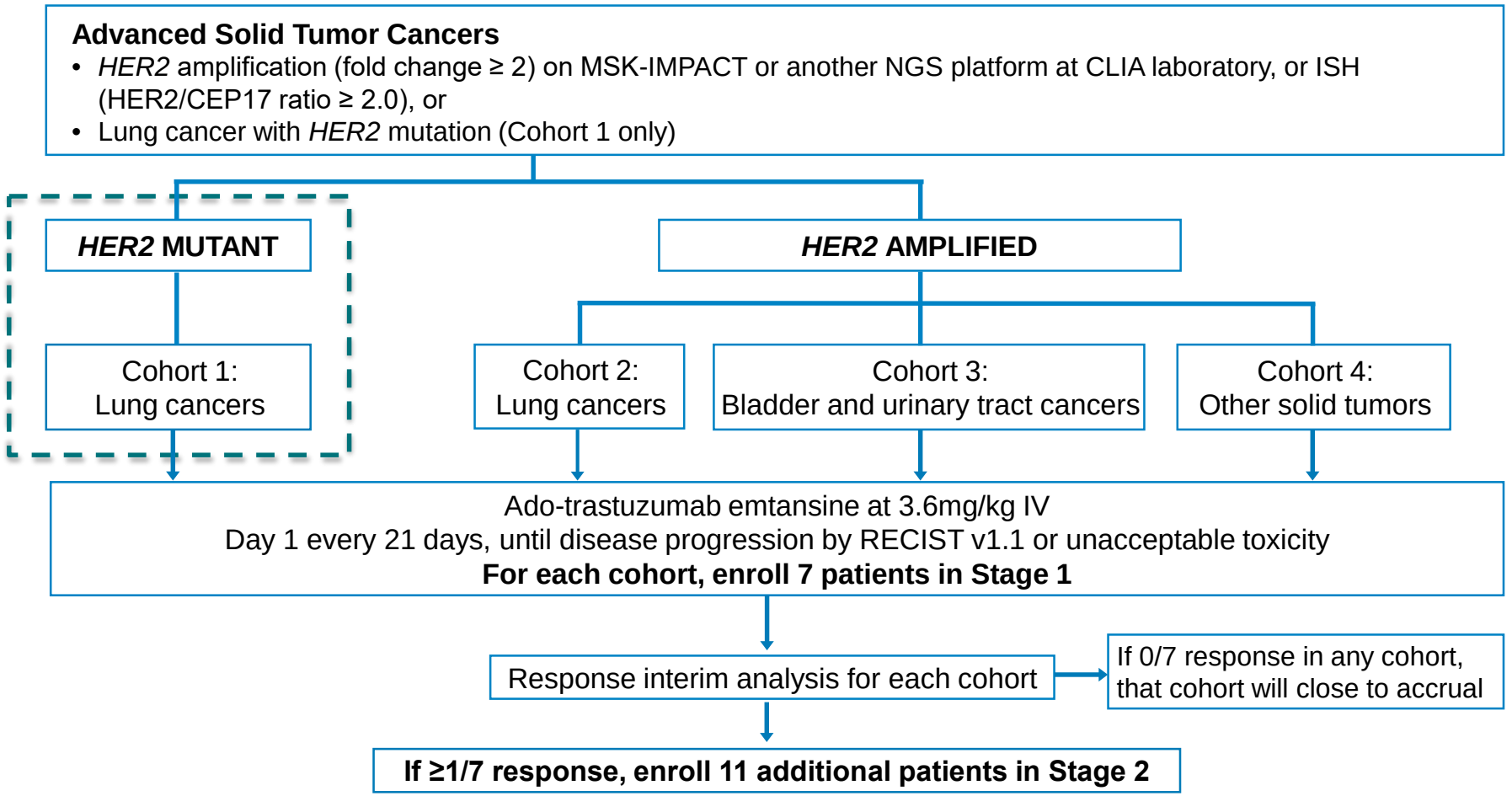
CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology
YOUNG INVESTIGATOR AWARD RECIPIENT

Null hypothesis:
ORR≤10%

Alternate hypothesis:
ORR ≥40%

Family-wise α<10%
Power 89%

At least 5/18 responses



Primary Endpoint: Overall Response Rate (CR + PR) as measured by RECIST v1.1
Secondary Endpoints: Progression Free Survival, Duration of Response, Adverse Events

Phase 2 trial of T-DM1 in patients with advanced NSCLC with HER2 mutation

Efficacy parameter	HER2 mutant (n=18)	HER2 amplified NSCLC (n=6)
ORR	44% (95% CI: 22-69%)	50% (3/6)
PFS	5.0 months (95% CI: 3.0-NR)	6 months (95% CI: 6 to NR)
OS	11 months (95% CI: 8-NR)	12 months (95% CI: 12 to NR)

Li et al ASCO 2017, Li et al WCLC 2017

RET rearranged NSCLC

- *RET* rearrangements are detected in 1-2% of adenocarcinomas, 8% among patients who are *EGFR* and *ALK* negative
- *RET* proto-oncogene is rearranged with partner gene: *KIF5B* most common but others are *CCDC6*, *NCOA4, or TRIM33*
- Multi-targeted TKI's investigated in prospective phase 2 studies
- Frequent dose reductions for "off target" toxicities were observed, often related to VEGF and/or EGFR activity
- Best response to platinum-doublet 51%, median PFS of 7.8 months, and overall survival 24.8 months (n=84)

Gautschi et al JCO 2017, Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

Phase 2 trials of RET inhibitors

Agent	# of patients	ORR	PFS	Dose reduction
Vandetanib	17	47% (n=9) 95% CI: 24-71%	4.7 months 95% CI: 2.8-8.5	53% of patients
Vandetanib	18	18% (n=3)	4.5 months	22% of patients
Cabozantinib	26	28% (n=7) 95% CI: 12-49%	5.5 months 95% CI: 3.8-8.4	73% of patients

Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

Emerging targeted agents for patients with genetic alterations

Genetic Alteration (i.e. driver event)	Available targeted agent
High level MET amplification or MET exon 14 skipping mutation	Crizotinib
RET rearrangements	Cabozantinib, vandetanib
HER2 mutations	Ado-trastuzumab emtansine

Note: All recommendations are category 2A unless otherwise indicated
Clinical trials: NCCN believes that the best management of any patient with cancer is a clinical trial. Participation in clinical trials is especially encouraged.

https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf-accessed 2/19/2018
Version 2.2018

Take home messages

- Osimertinib the standard of care for patients with an *EGFR* mutation, and afatinib approved for uncommon *EGFR* mutations
- Alectinib the preferred first-line therapy for *ALK* rearranged NSCLC
- Dabrafenib/trametinib approved for *BRAF* V600E NSCLC
- Crizotinib for ROS1 rearrangements
- Targeted therapies in development for NSCLC with *MET* exon 14 alterations and MET amplified, *RET* rearrangements, and HER2 mutations