Terapia Sistemica in pazienti con metastasi cerebrali da NSCLC

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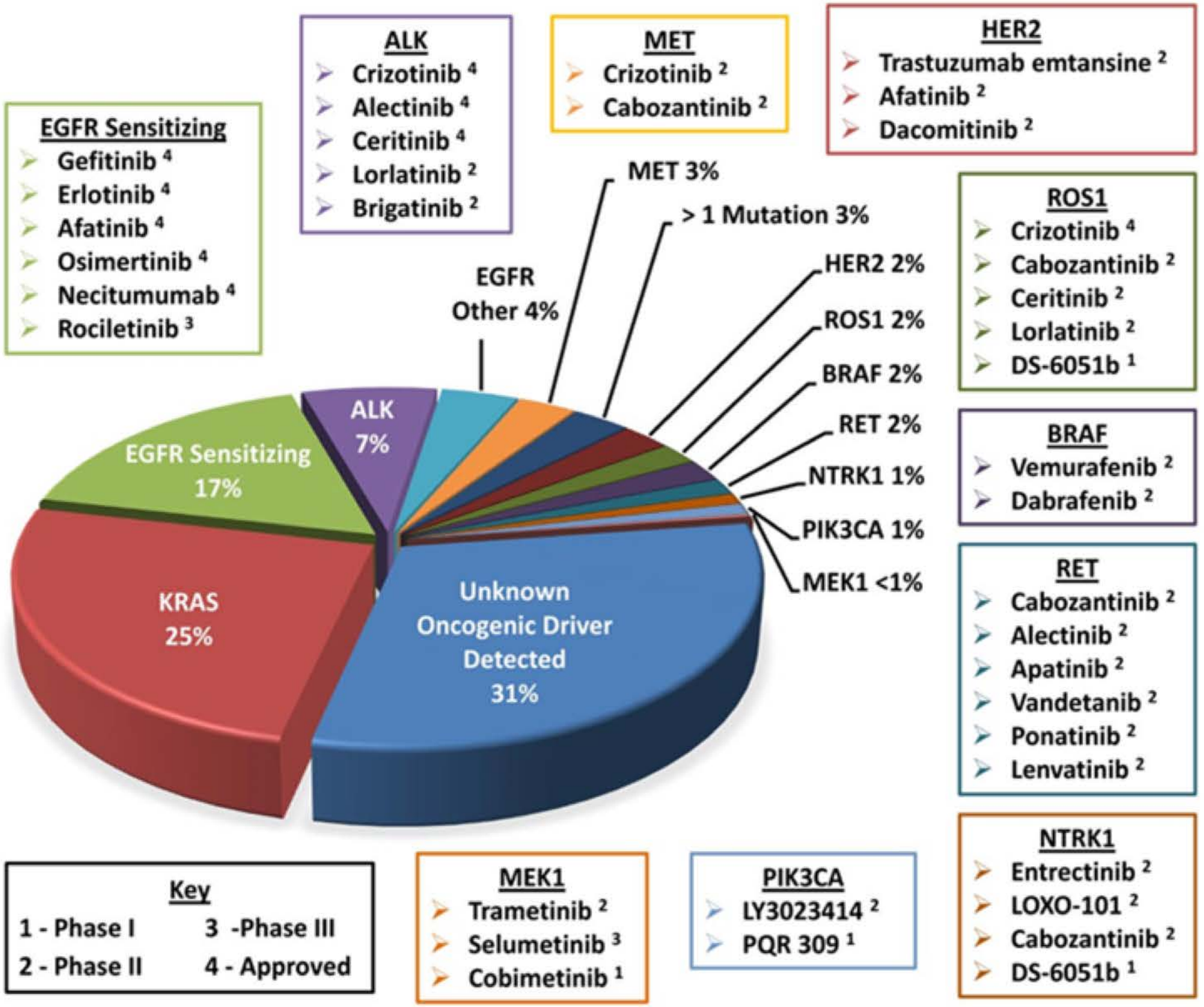
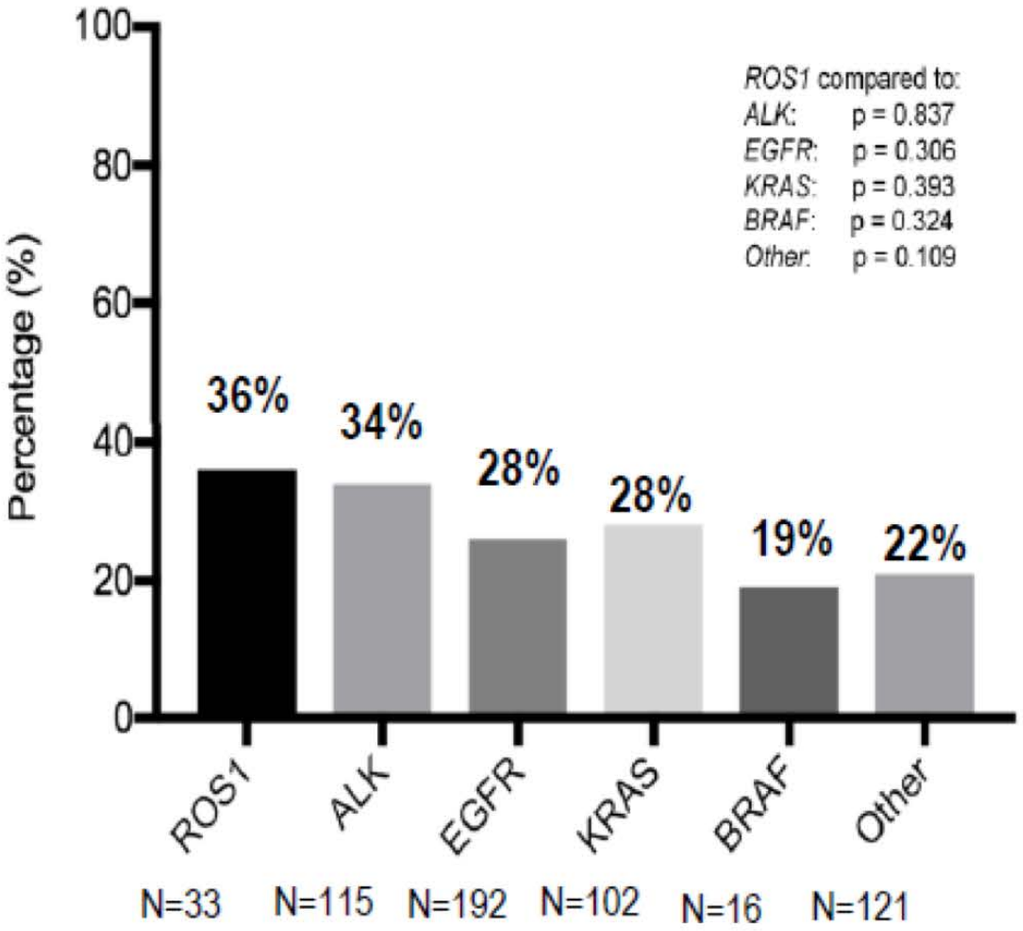
- **NSCLC seconda neoplasia più frequente**
- **Alta prevalenza di metastasi cerebrali**
- **Metastasi cerebrali impattano negativamente sulla sopravvivenza**
- **Sottogruppi particolari hanno tropismo spiccato su tessuto cerebrale**


EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET
Crizotinib 2
Cabozantinib 2
HER2
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
BRAF
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
EGFR Sensitizing 17%
ALK 7%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
PIK3CA
LY3023414 2
PQR 309 1

BMs incidence in mNSCLC

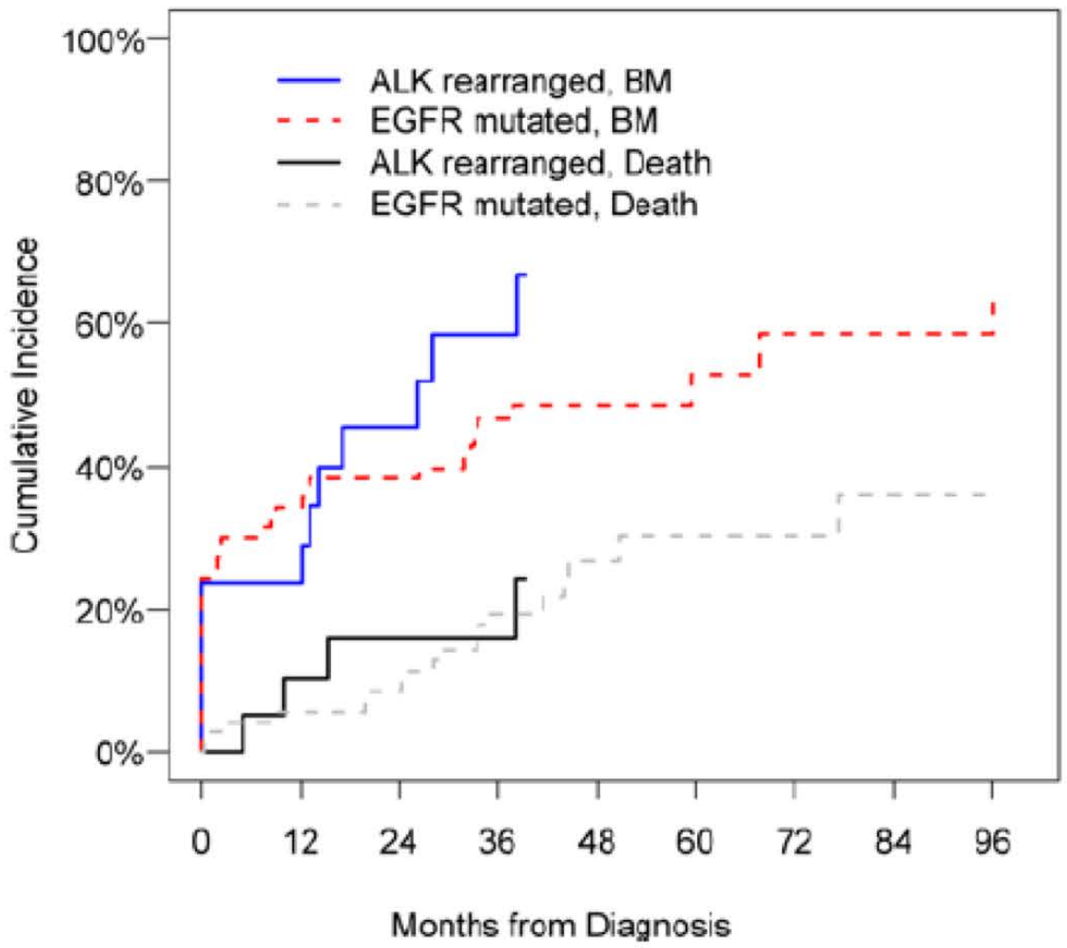
10-20% at diagnosis

Proto, *TLCR* 2016



Increased incidence overtime

At 1y ~34%, and at 5y: ~53%

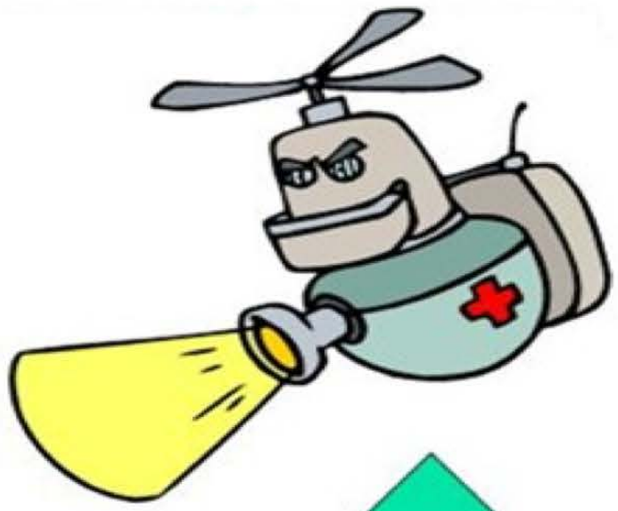


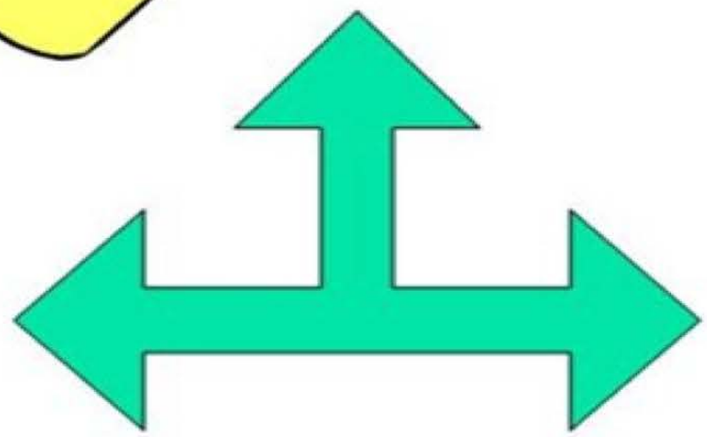
Patil – JTO 2018 * Gainor – JCO PO 2017; Rangachari –Lung Cancer 2014

How to select for treatment…and which treatment?

RADIOTERAPISTA

CHIRURGO



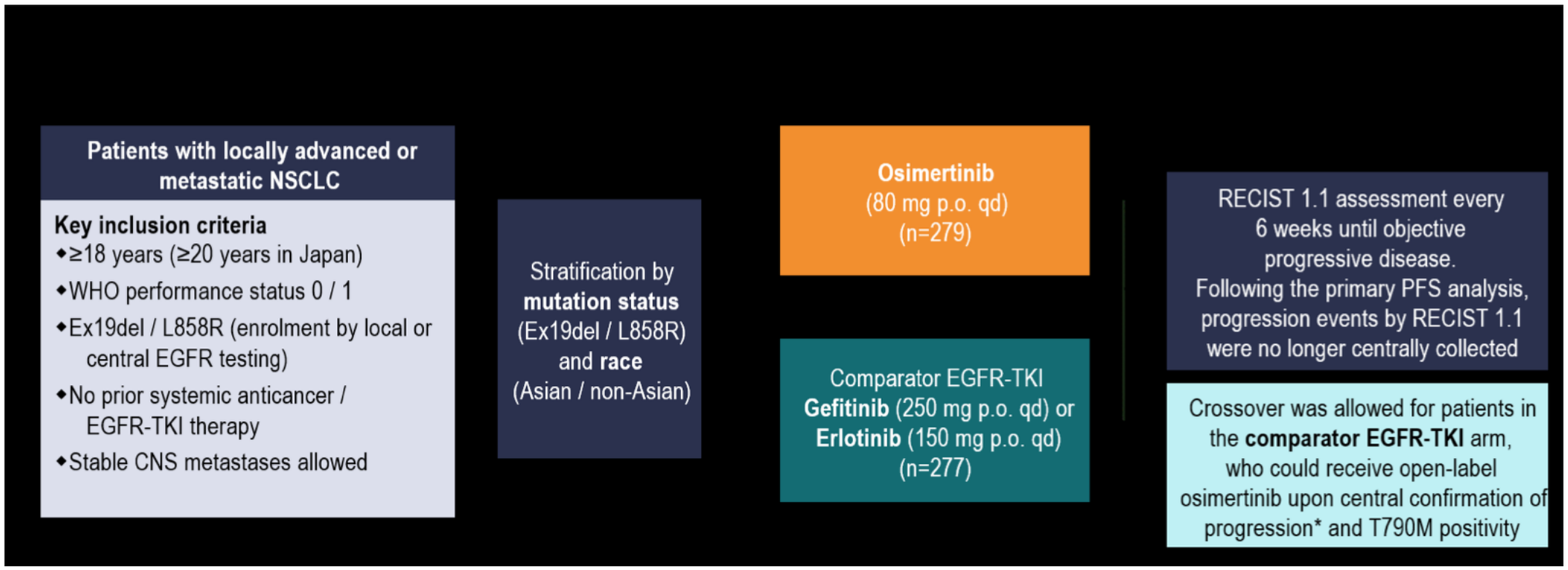


ONCOLOGO

AGENDA:

- EGFR mutati
- ALK traslocati

The FLAURA trial

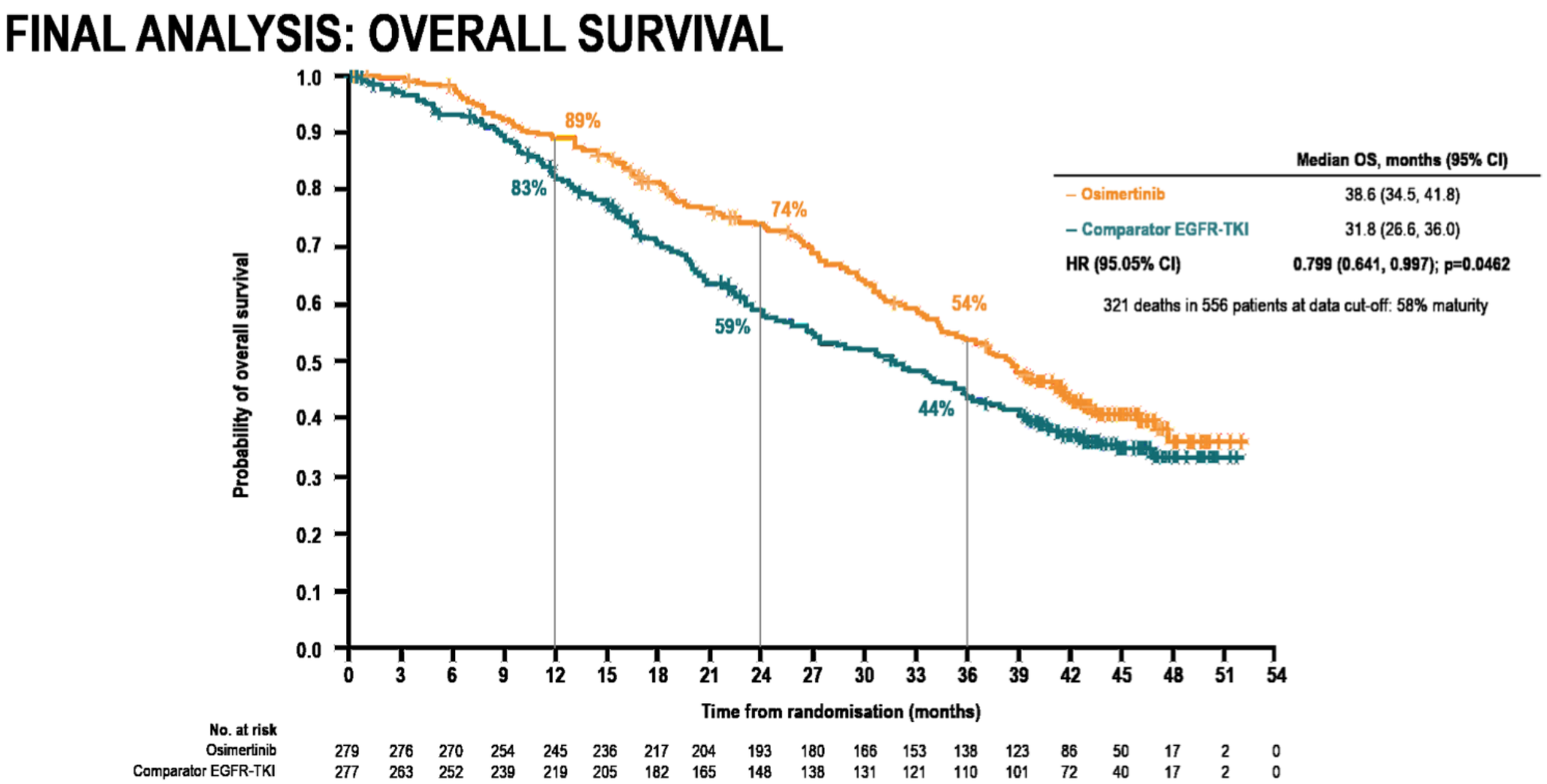


Primary end-point: PFS

Secondary end-points: OS, ORR, DOR, DCR, depht of response, safety

Soria JC, NEJM 2018

Outcome 2: OS



Ramalingam S, ESMO 2019

CNS Effects of 1st/2nd Generation EGFR TKIs

Gefitinib

CNS penetration of 1%[a]

Efficacy in 41 *EGFR+* patients without prior RT[b]

RR: 87.8%

mOS: 21.9 mo

mPFS: 14.5 mo

Erlotinib

- CNS penetration of 3-5%[c]
- Efficacy in 17 *EGFR+* patients[d]
  - mOS: 19.1 mo vs 9.3 mo for *EGFR* WT (P = .534)
- Efficacy with pulse dosing[e]

Patients, n	19 (8 with brain lesions)
ORR, %	74
mPFS, mo	10
CNS progression, n	3

Afatinib

- Low CNS penetration[f]
- Efficacy from pooled analysis of LUX-Lung trials[g]

	Afatinib	Chemo	P value
Patients, n	57	34	
mPFS, mo	8.2	5.4	.0297
Prior WBRT (n = 24)	13.8	4.7	.0767
No WBRT (n = 57)	6.9	5.4	.2222
mOS, mo	22.4	25.0	.6412

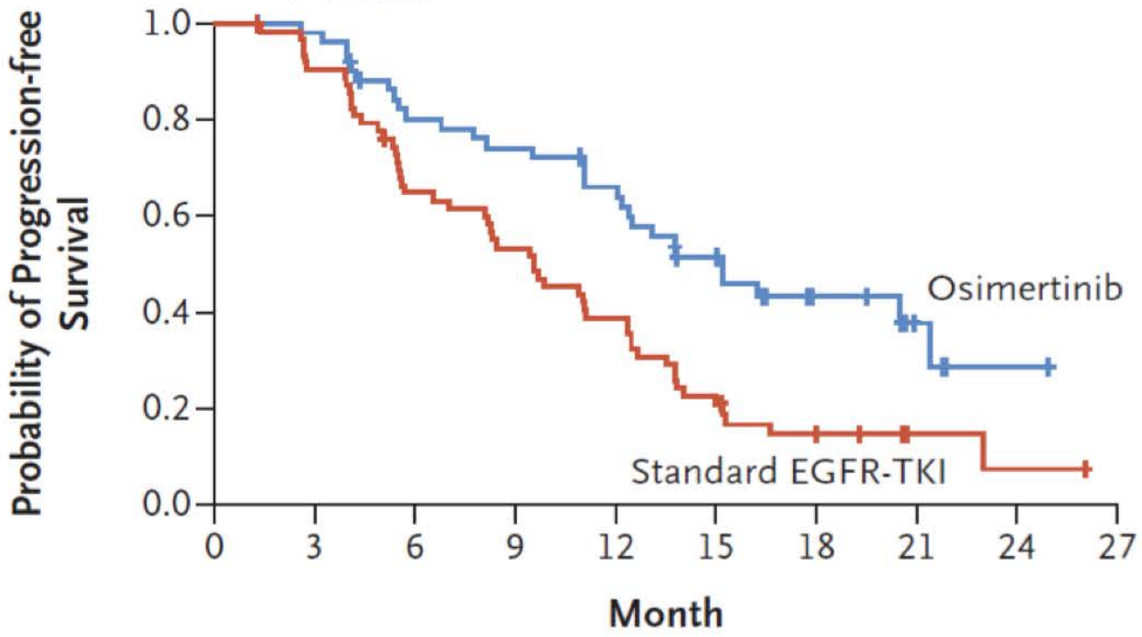
a. Zeng YD, et al. *Oncotarget*. 2015;6:8366-8376; b. Iuchi T, et al. *Lung Cancer*. 2013;82:282-287; c. Deng Y, et al. *Mol Clin Oncol*. 2014;2:116-120; d. Welsh JW, et al. *J Clin Oncol*. 2013;31:895-902; e. Arbour KC, et al. *Cancer*. 2017 f. Hoffknecht P, et al. *J Thorac Oncol*. 2015;10:156-163; g. Schuler M, et al. *J Thorac Oncol*. 2016;11:380-390.

Attività encefalica

B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



No. at Risk

Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

CNS Effects of III Generation EGFR TKI

Pre-specified subgroup analysis assessing CNS response from the pooled AURA extension and AURA2 Phase II studies

Patients evaluable for CNS response (n=50)	
CNS ORR,* %	54 (95% CI: 39, 68)
Complete response, n (%)	6 (12)
Partial response, n (%)	21 (42)
Stable disease ≥6 weeks, n (%)	19 (38)
Progressive disease, n (%)	3 (6)
Not evaluable, n (%)	1 (2)
CNS DCR, %	92 (95% CI: 81, 98)

CNS response based on prior brain RT status*	
Prior RT ≤6 months before first dose, n	19 / 50
CNS ORR, %	32 (95% CI: 13, 57)
Complete response / partial response, %	11 / 21
No prior RT or RT >6 months before first dose, n	31 / 50
CNS ORR, %	68 (95% CI: 48, 83)
Complete response / partial response, %	13 / 55

CNS PFS by BICR	Total (n=50)
Median follow-up for CNS PFS*	11.2 months
CNS progression or death#	19 / 50
Maturity	38%
Median CNS PFS,# months	NC (95% CI 7, NC)
Progression-free	
at 6 months§	72% (95% CI 57, 83)
at 12 months§	56% (95% CI 40, 70)

- At 9 months, 75% (95% CI 53, 88) of patients were estimated to remain in CNS response without progression or death

DCR is calculated from the percentage of patients with a best overall CNS response of complete response, partial response, or stable disease at ≥6 weeks, prior to CNS progression; no objective response includes stable disease, non-evaluable and disease progression. *Responses required confirmation after 4 weeks.

Goss et al *Ann Oncol* 2018

CNS Effects of III Generation EGFR TKI

Practice Changing Data

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

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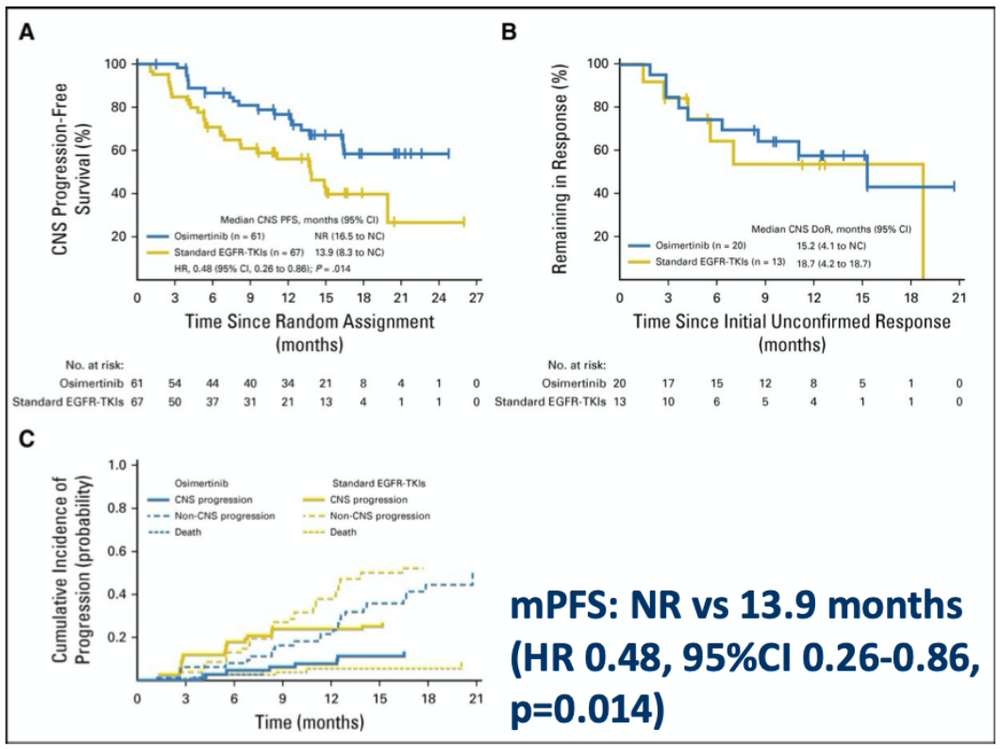


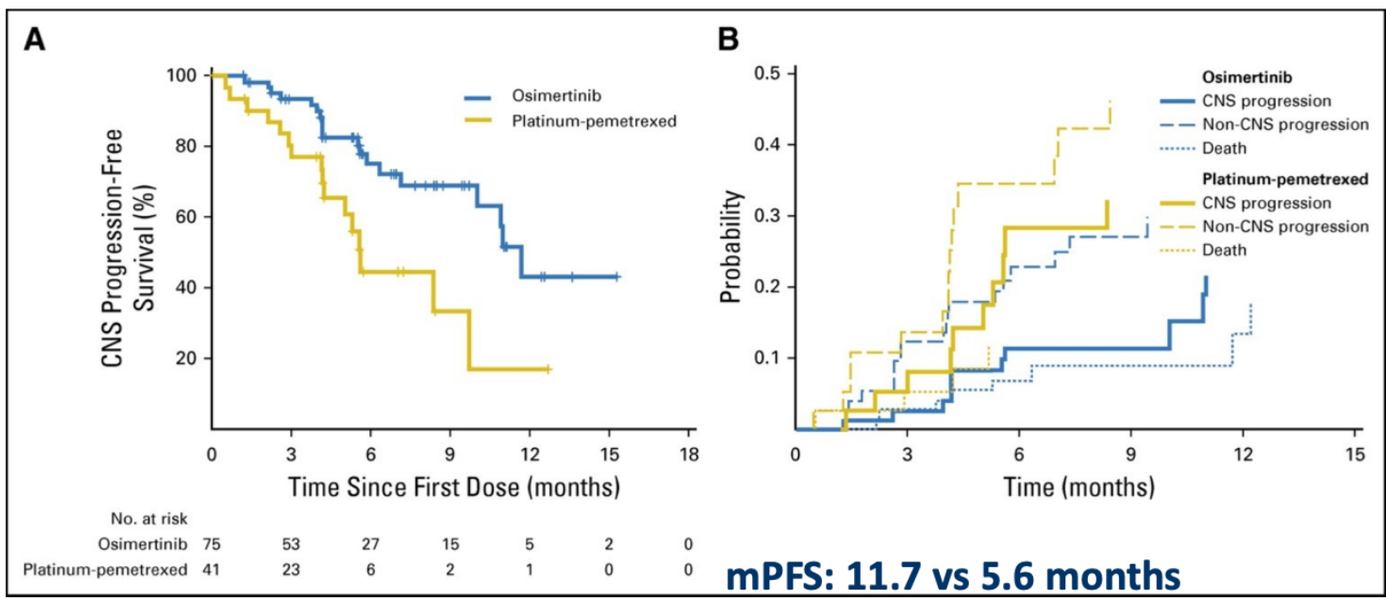
mPFS: NR vs 13.9 months (HR 0.48, 95%CI 0.26-0.86, p=0.014)

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

Yi-Long Wu, Myung-Ju Ahn, Marina Chiara Garassino, Ji-Youn Han, Nobuyuki Katakami, Hye Ryun Kim, Rachel Hodge, Paramjit Kaur, Andrew P. Brown, Dana Ghiorghiu, Vassiliki A. Papadimitrakopoulou, and Tony S.K. Mok



mPFS: 11.7 vs 5.6 months (HR 0.32, 95%CI 0.15-0.69, p=0.004)

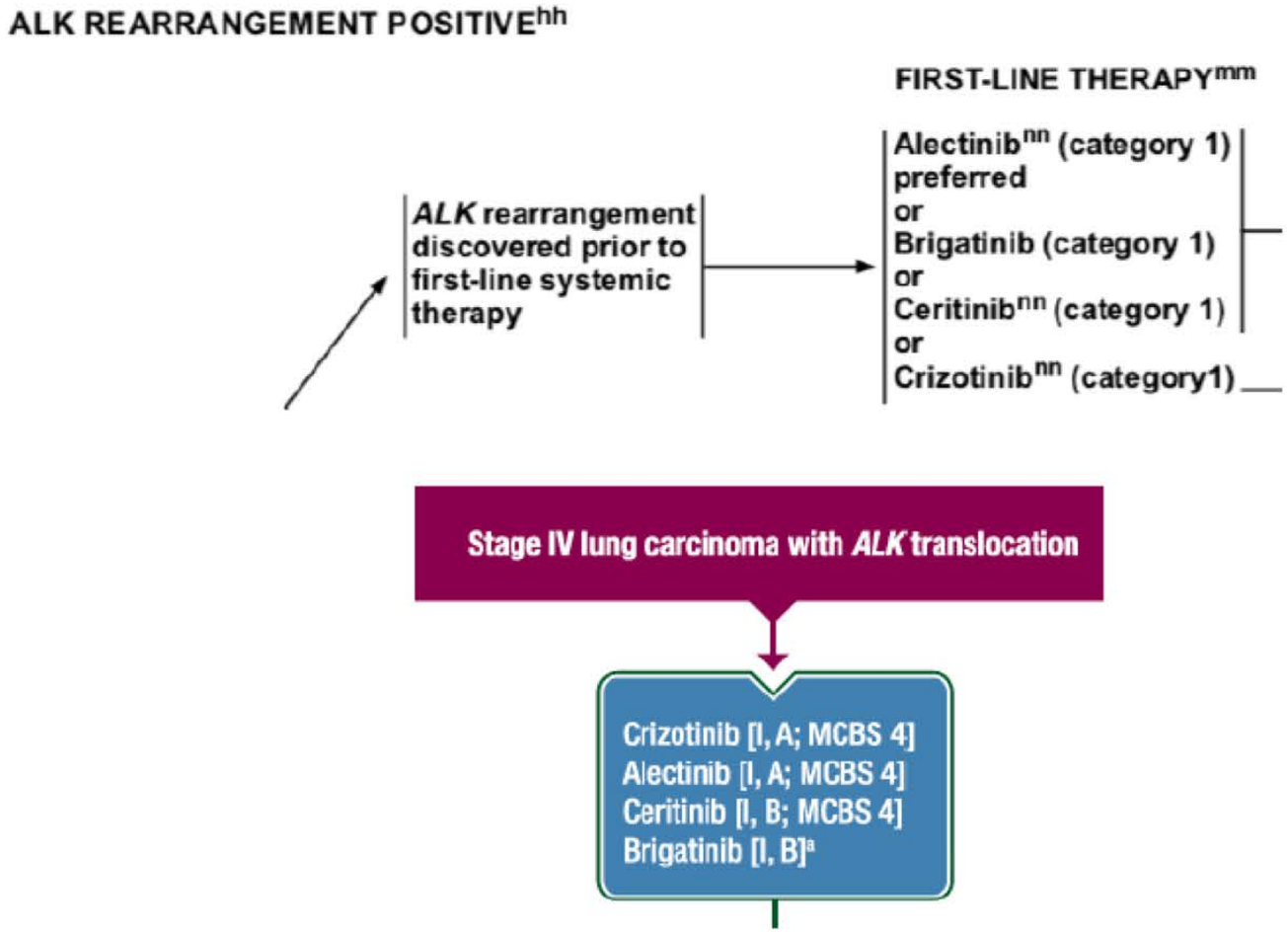
BMs in ALK+ NSCLC

3-5% of patients

High incidence of BMs: 30-40% at diagnosis, 60% during course of disease

Long survival time (>4 years)

Many effective targeted agents



Griesinger et al. Oncotarget 2018; NCCN guidelines 2018v3; Planchard et al. Ann Oncol 2018

Poor CNS Penetrance by Crizotinib

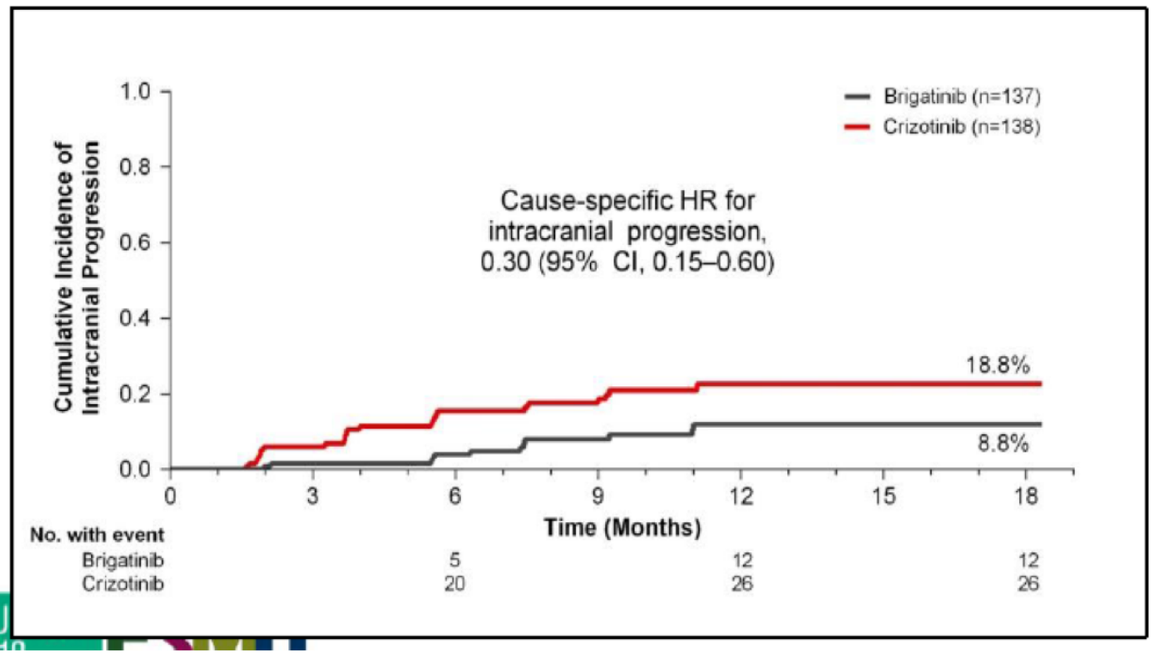
Concentration of TKI in the cerebrospinal fluid and plasma

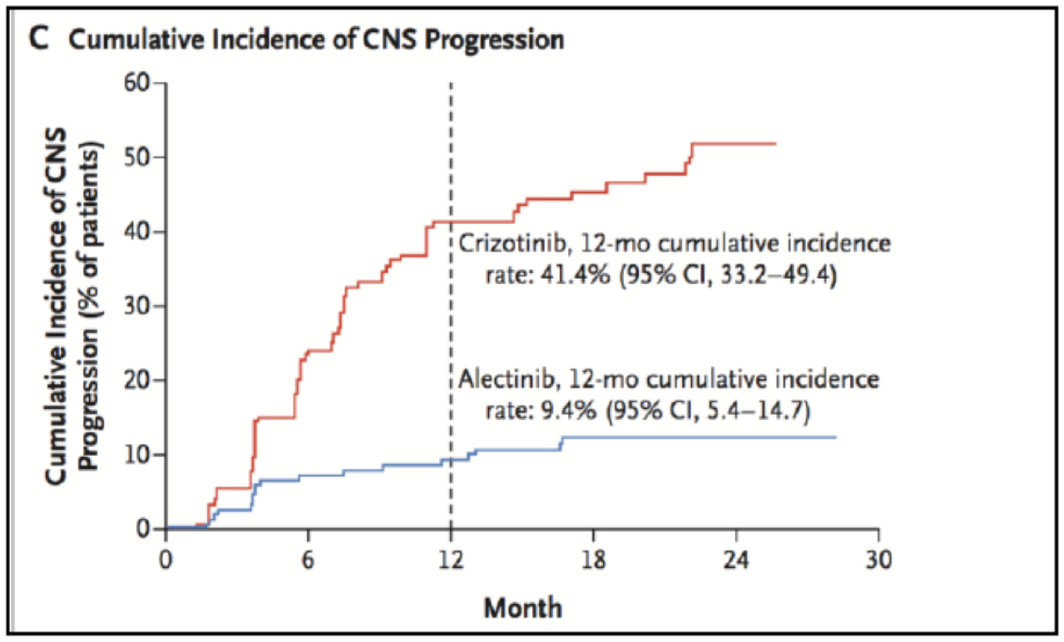
Compound	Plasma concentration	Cerebrospinal fluid concentration	Cerebrospinal fluid penetration rate
Crizotinib	237 ng/mL	0.616 ng/mL	0.26%
Alectinib	3.12 nM	2.69 nM	86%
Ceritinib	Not reported	Not reported	15%
Lorlatinib	Not reported	Not reported	20–30%

Wrona *Cancer/Radiotherapie* 2019

Intracranial Efficacy

Intracranial Efficacy	ALTA-1L		ALEX	
	Brigatinib	Crizotinib	Alectinib	Crizotinib
Measurable Brain Metastases (N)	**18**	**21**	**21**	**22**
ORR % (95% CI)	**78** (52,94)	29 (11,52)	**81** (58,95)	50 (28,72)
Any brain metastases (N)	43	47	64	58
HR (95%CI) for PFS with BM	**0.27 (0.13-0.54) <0.0001**		**0.40 (0.25-0.64)**	





Popat S, et al. ESMO 2018. Abstract LBA58; Camidge DR, et al. *N Engl J Med*. 2018;379:2027-2039; Peters S, et al. *N Engl J Med*. 2017;377:829-838.

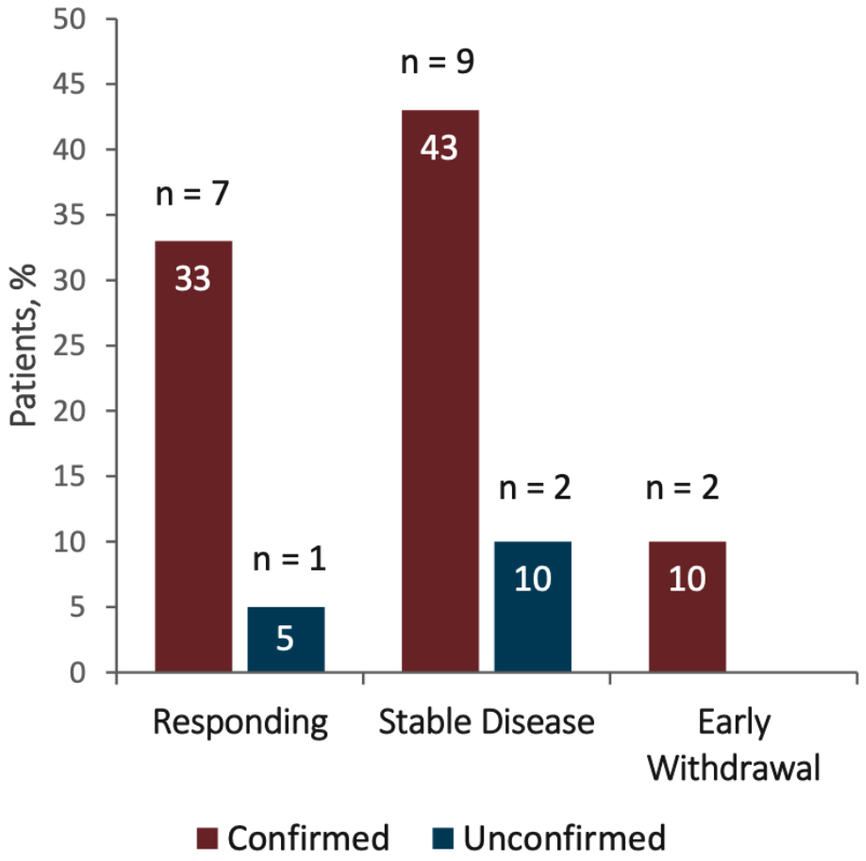
…and Leptomeningeal Metastases?

- **Very poor prognosis (mOS 1-3 mos with WBRT and IT CT)**
- **About 10% in all cancers and 5% in ALK+ NSCLC**

Gainor JF, *JTO* 2013; Lee SJ, *JTO* 2013

- BLOOM[a]

Best MRI Intracranial Response (n = 21)



Yang JC-H, ASCO 2017

4 out of 5 pts with suspected LM by BIRC achieved CR

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Table 4. Responses in Patients With Suspected LMs*

Treatment Arm	Highest Response: LMs	Highest Response: TL	Best Objective Response: CNS	Best Objective Response: Systemic
Osimertinib	CR	PR	PR	PR
Osimertinib	Non-CR, non-PD	No TL	SD	PR
Osimertinib	CR	No TL	CR	PR
Osimertinib	CR	No TL	SD	PR
Osimertinib	CR	CR	CR	PR
Standard EGFR-TKIs	Non-CR, non-PD	No TL	SD	PR
Standard EGFR-TKIs	Baseline only	No TL	NE	PR

Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; LMs, leptomeningeal metastases; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesion; TKI, tyrosine kinase inhibitor.

*LMs, TL and CNS responses were assessed by CNS BICR; systemic response was assessed by study BICR.

Reungwettwana T, *JCO* 2018

BMs in driver mutated NSCLC
NCCN and ESMO Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Limited Brain Metastases

"..Systemic therapy with good CNS penetration (ie for patients with ALK+ or EGFR+ NSCLC). Try to delay RT. Close MRI surveillance. No data from prospective clinical trials comparing the two strategies"

Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

"In patients with an actionable oncogenic driver (e.g. EGFR, ALK) and clinically asymptomatic brain metastases, next-generation TKIs may restore control of brain disease and delay cranial RT [II, A]"

"Patients with actionable oncogenic drivers and LMD can be treated with CNS-penetrant next-generation TKIs [III, B]"

NCCN.org; Planchard D. *Ann Oncol* 2018