FLASCO SPRING SESSION 2019
Case presentation

LUNG CANCER SESSION

Sonam Puri M.D
Fellow, Hematology and Oncology
H. Lee Moffitt Cancer Center

Case Presentation

60 year old male, life time never smoker presented to an outside hospital with 2 week history of cough and chest discomfort

- CT Angiogram to rule out PE showed a RUL mass, mediastinal LAD (right paratracheal and subcarinal) and 2 lesions in the 5^{th} and 6^{th} anterior ribs concerning for metastatic disease.

Pathology

ANATOMICAL PATHOLOGY

- EBUS of the subcarinal LN showed adenocarcinoma from lung primary

MOLECULAR PATHOLOGY

- Tumor Pyrosequencing showed a EGFR exon 19 E746-A750 mutation
- The specimen was tested negative for KRAS , BRAF , ROS1, RET, ALK ,MET or NTRK mutations
- PD-L1 IHC TPS was 50%

Initial Staging

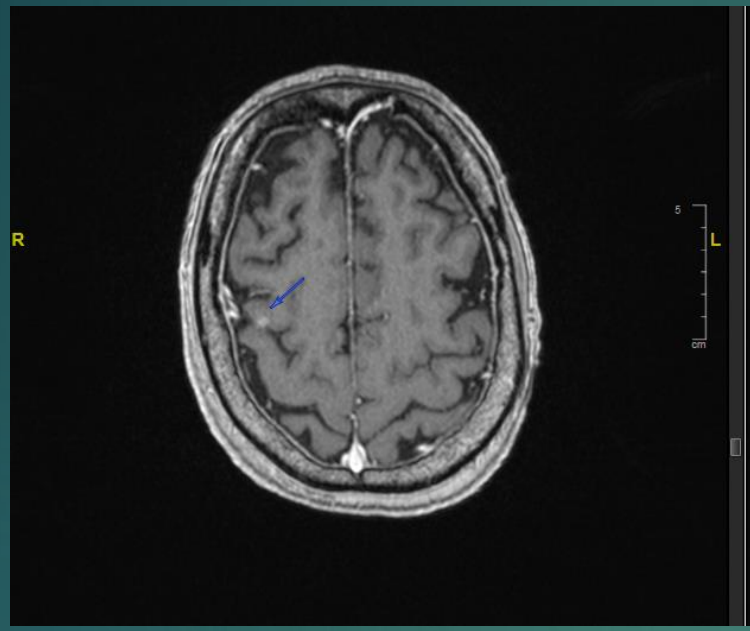
- **PET CT** : Metabolically active RUL mass, right hilar and mediastinal (precarinal, subcarinal, right azygo-esophageal LAP), right thoracic pleural metastases with involvement of the right posterolateral fifth and sixth rib, and metabolic activity in the left superior acetabulum
- **MRI brain**: Negative for intracranial metastasis

Treatment course on Afatinib

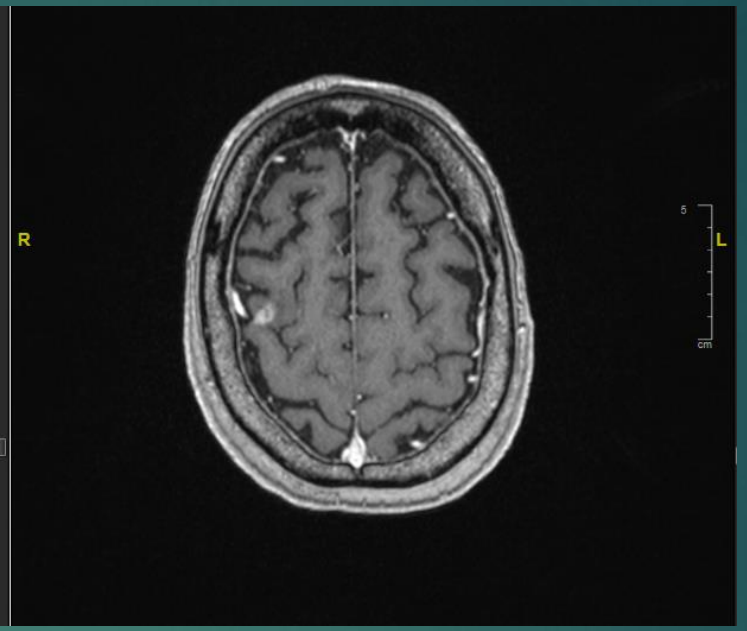
- Patient was started on first line therapy with EGFR TKI afatinib in January 2017
- Restaging scans on afatinib showed PR
- Approximately 10 months after starting afatinib, he developed persistent headache and gait imbalance.
- Restaging imaging in October 2017 showed new brain lesions (right frontal lobe and cerebellum) and systemic progression of disease
- Plasma Guardant$_{360}$ testing revealed a new EGFR T790M mutation and persistent EGFR exon 19 del.
- Patient was started on osimertinib at 80mg/day for progressive disease in early November 2017.

Intracranial disease control on osimertinib

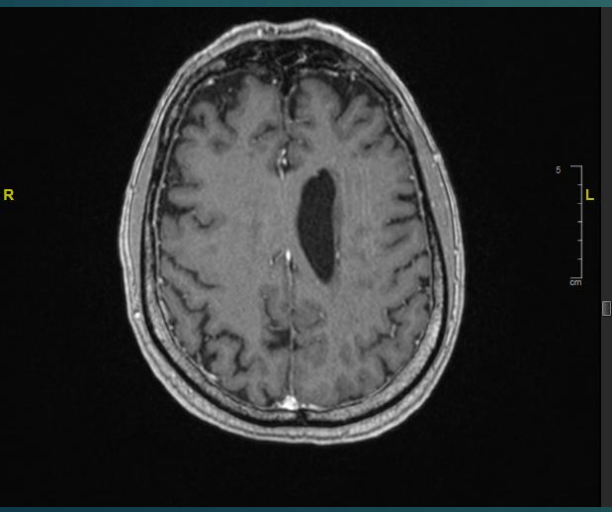
February 2018



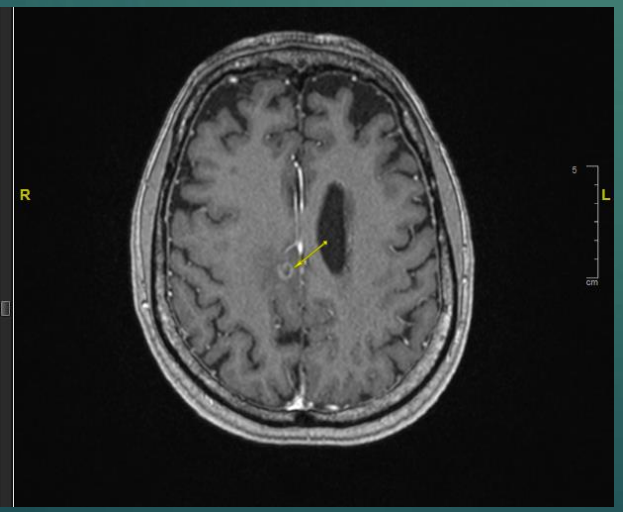
October 2017



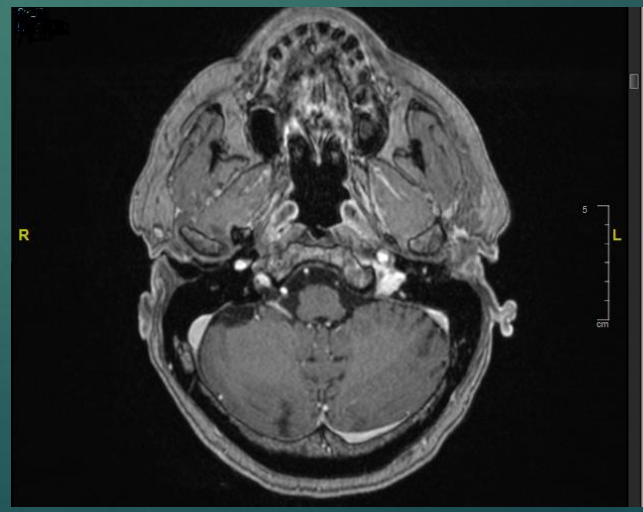
February 2018



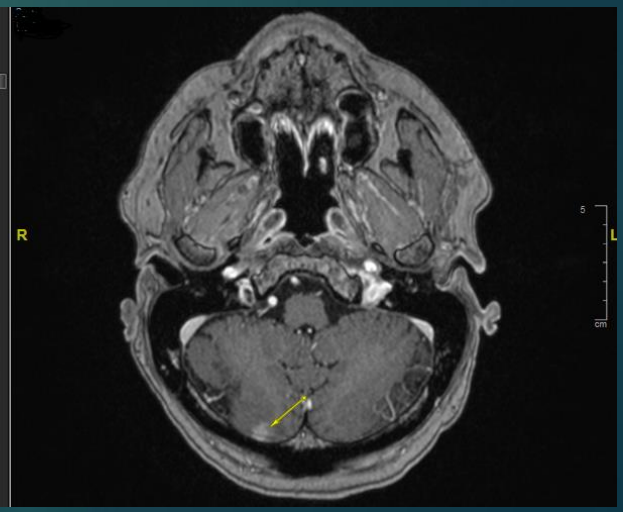
October 2017



February 2018



October 2017



MRI brain with and without contrast , Left side images are prior to initiation of osimertinib , Right side images show response to treatment with osimertinib

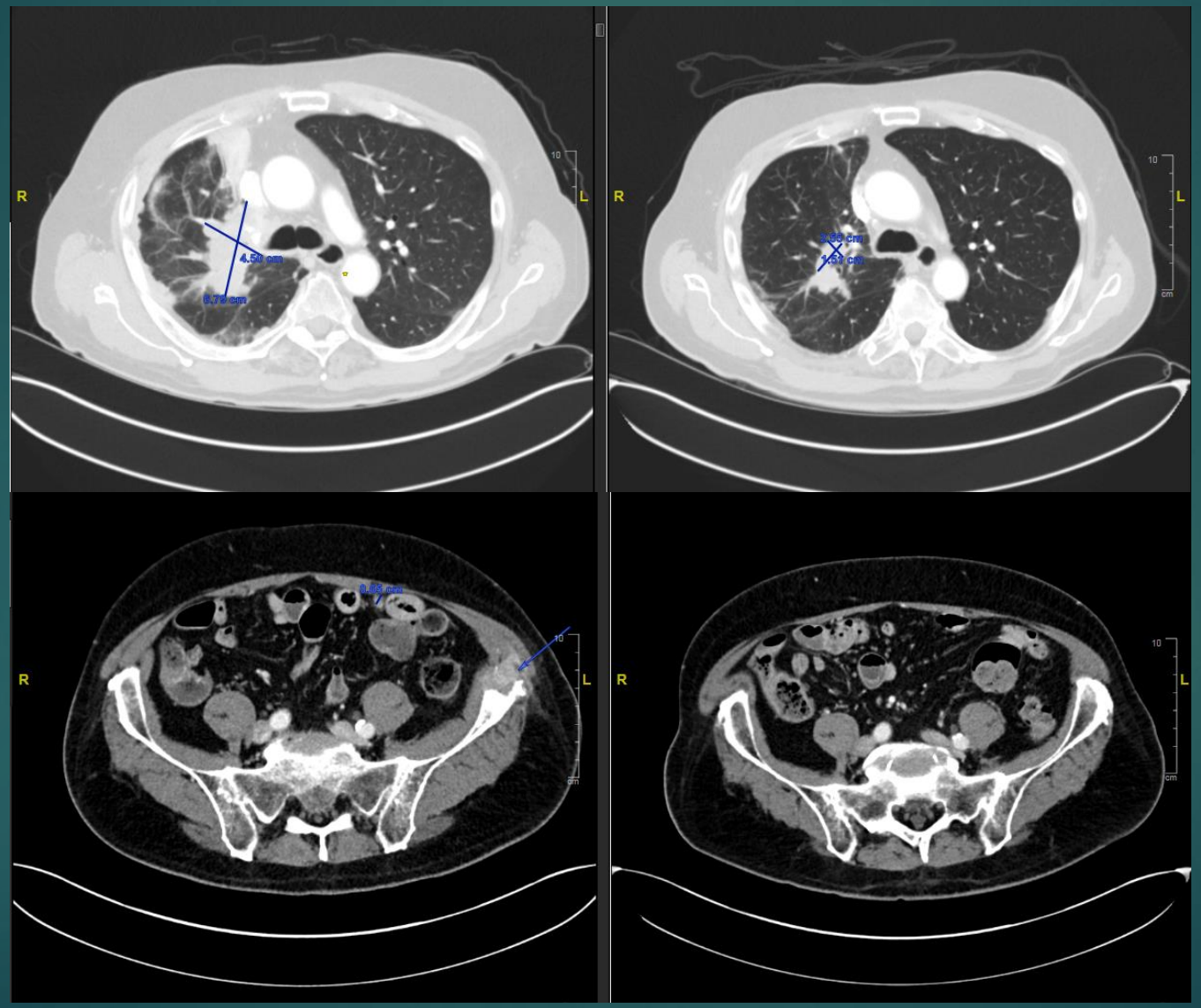
Treatment course on Osimertinib

- Restaging CT scans after 10 months of therapy with Osimertinib, in September 2018 showed systemic progression of disease.
- CT guided biopsy of a new left iliac soft tissue mass was TTF-1, synaptophysin, chromogranin and CD56 positive, Napsin A and P40 negative, concerning for **small cell carcinoma.**
- Molecular testing: Plasma Guardant $_{360}$ testing showed that the EGFR T790M mutation was not detectable and there was new MYC, PIK3CA and BRAF amplification and new TP53 V218L and G226S mutation.

Progression of disease on osimertinib

September 2018

June 2018



CT chest/Abdomen/pelvis with contrast , Left side images are on osimertinib with response to therapy , Right side images show progression of disease on osimertinib

DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.
- Mechanisms of resistance to osimertinib
- Treatment after progression on osimertinib

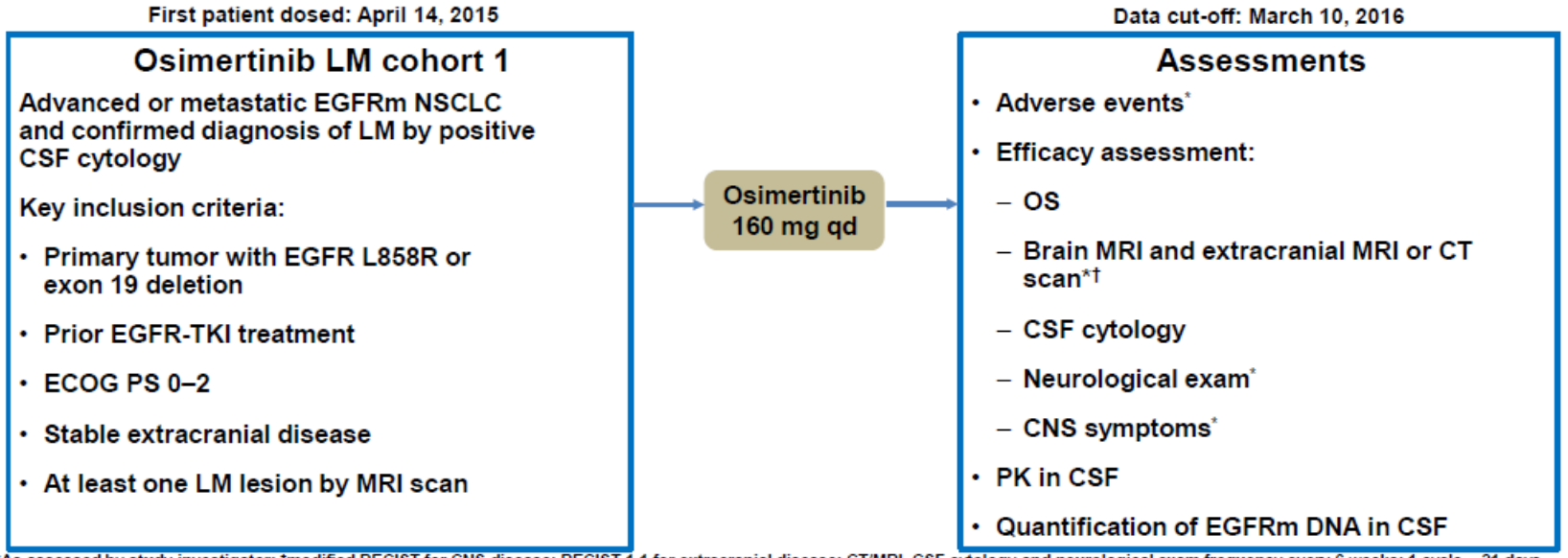
DISCUSSION

- **Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.**
- Mechanisms of resistance to osimertinib
- Treatment after progression on osimertinib

Intracranial activity of Osimertinib at 160mg/ day dose

BLOOM Study Design: Osimertinib LM Cohort 1

Study objectives, cohort 1—EGFRm NSCLC and LM:
To assess the safety and tolerability of osimertinib in patients with LM



*As assessed by study investigator; †modified RECIST for CNS disease; RECIST 1.1 for extracranial disease; CT/MRI, CSF cytology and neurological exam frequency every 6 weeks; 1 cycle = 21 days of continuous dosing.

CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors

National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02228369. Accessed on June 8, 2016.

Yang JC, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 9002.

Adapted from https:// www.prime oncology.org

Intracranial activity of Osimertinib 160mg/ day dose

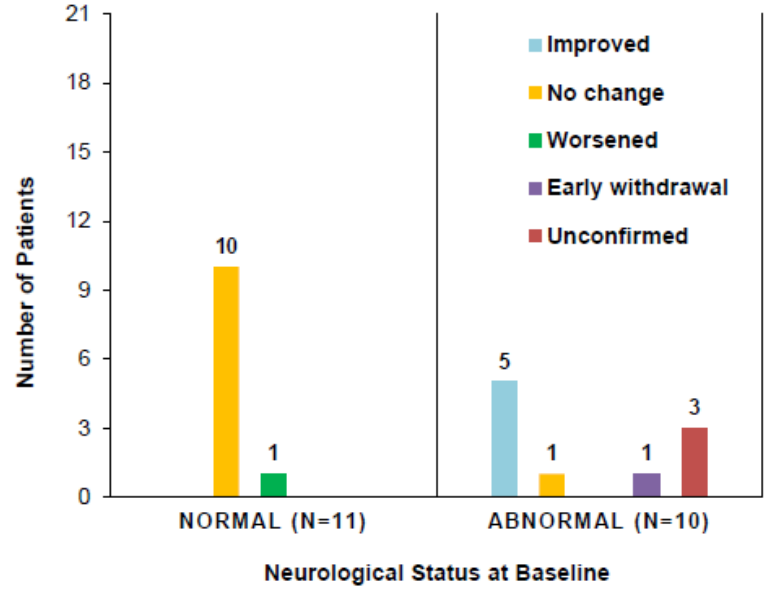
Osimertinib Activity Across LM Assessments

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

Best MRI Imaging Intracranial Response, n (%)	N = 21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	

Best Confirmed Neurological Status†



Population: efficacy, n = 21.*Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

Yang JC, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 9002.

Adapted from https:// www.prime oncology.org

Intracranial activity of Osimertinib at 80mg/day dose

Osimertinib for patients (pts) with leptomeningeal metastases (LM) associated with EGFRm advanced NSCLC

- EGFR T790M-positive advanced NSCLC with asymptomatic, stable CNS metastases, including leptomeningeal disease across AURA studies
- 22 pts with leptomeningeal disease(LM).
- ORR was 55% (95% CI 32, 76),
  - Complete LM response and partial LM response reported in 6 pts (27%) each.
- Median LM DoR for confirmed responders was not calculable (range 1.3–11.1 mo).
- Median LM PFS was 11.1 mo (95% CI 4.6, NC).
- Median OS was 18.8 mo (95% CI 6.3, NC).

Presented by Ahn et al. European Society of Medical Oncology, Asia 2018 Congress

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste

Table 3. CNS Response to Osimertinib Versus Standard EGFR-TKIs

Response	cFAS (n = 128)		cEFR (n = 41)	
	Osimertinib (n = 61)	Standard EGFR-TKIs (n = 67)	Osimertinib (n = 22)	Standard EGFR-TKIs (n = 19)
CNS ORR, No. (%)*	40 (66)	29 (43)	20 (91)	13 (68)
CR	25 (41)	16 (24)	5 (23)	0
PR	15 (25)	13 (19)	15 (68)	13 (68)
SD ≥ 6 weeks†	15 (25)	27 (40)	1 (5)	4 (21)
PD	0	5 (7)	0	2 (11)
Not evaluable	6 (10)	6 (9)	1 (5)	0
CNS DCR, No. (%)	55 (90)	56 (84)	21 (95)	17 (89)
95% CI‡	80 to 96	73 to 92	77 to 100	67 to 99
OR§	1.8		2.5	
95% CI	0.6 to 5.5		0.2 to 55.8	
P¶	.269		.462	
Median time to response, weeks (interquartile range)	6 (6-12)	12 (6-18)	6 (6-6)	6 (6-12)
Median CNS DoR, months (95% CI)	NR (11.9 to NC)	14.4 (7.0 to 18.7)	15.2 (4.1 to NC)	18.7 (4.2 to 18.7)
Estimated % remaining in response (95% CI)*‖				
At 3 months	92 (77 to 97)	89 (71 to 97)	85 (60 to 95)	85 (51 to 96)
At 6 months	86 (70 to 94)	76 (55 to 89)	75 (50 to 89)	65 (30 to 85)
At 9 months	80 (63 to 90)	67 (43 to 82)	65 (40 to 81)	54 (21 to 78)
At 12 months	65 (46 to 79)	67 (43 to 82)	58 (33 to 77)	54 (21 to 78)

Abbreviations: cEFR, CNS evaluable-for-response set; cFAS, CNS full-analysis set; CR, complete response; DCR, disease control rate; DoR, duration of response; *EGFR*, epidermal growth factor receptor; NC, not calculable; NR, not reached; OR, odds ratio; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease; TKI, tyrosine kinase inhibitor.

*Responses did not require confirmation, per RECIST 1.1 guidance on randomized studies.

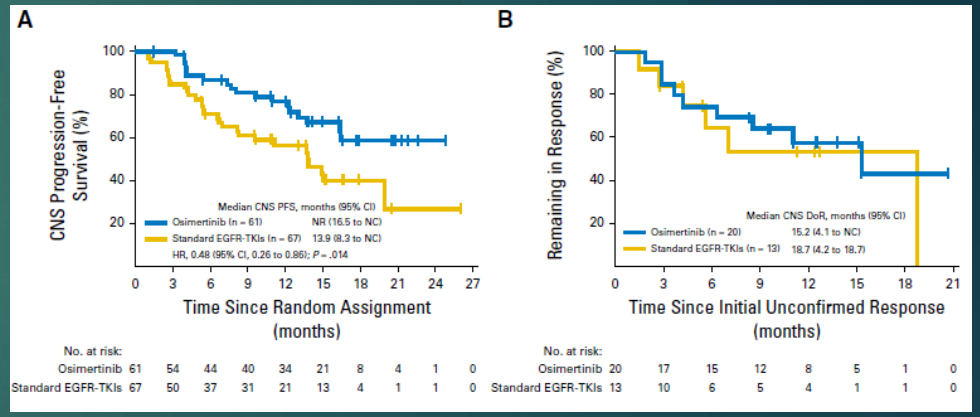
†Includes non-CR, non-PD in patients with nontarget lesions only.

‡Calculated using Clopper-Pearson exact method for binomial proportions.

§This analysis was performed using logistic regression with a factor for treatment; CI was calculated using profile likelihood. An OR > 1 favors osimertinib.

¶The *P* value was calculated based on the likelihood ratio test, which compared two models (one model with the intercept only and a second model including the treatment factor).

‖Calculated using Kaplan-Meier technique.

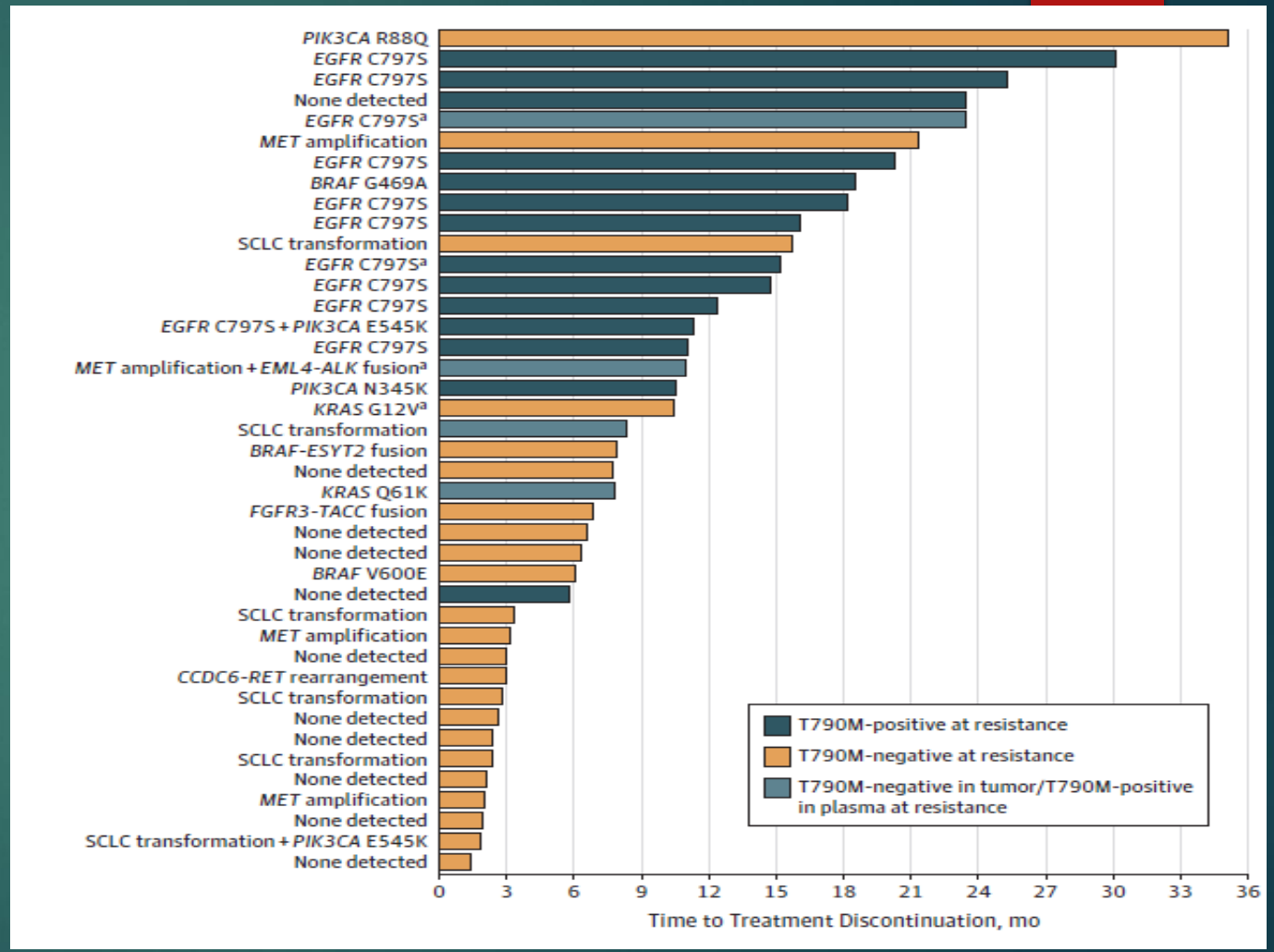


DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.
- **Mechanisms of resistance to osimertinib**
- Treatment after progression on Osimertinib

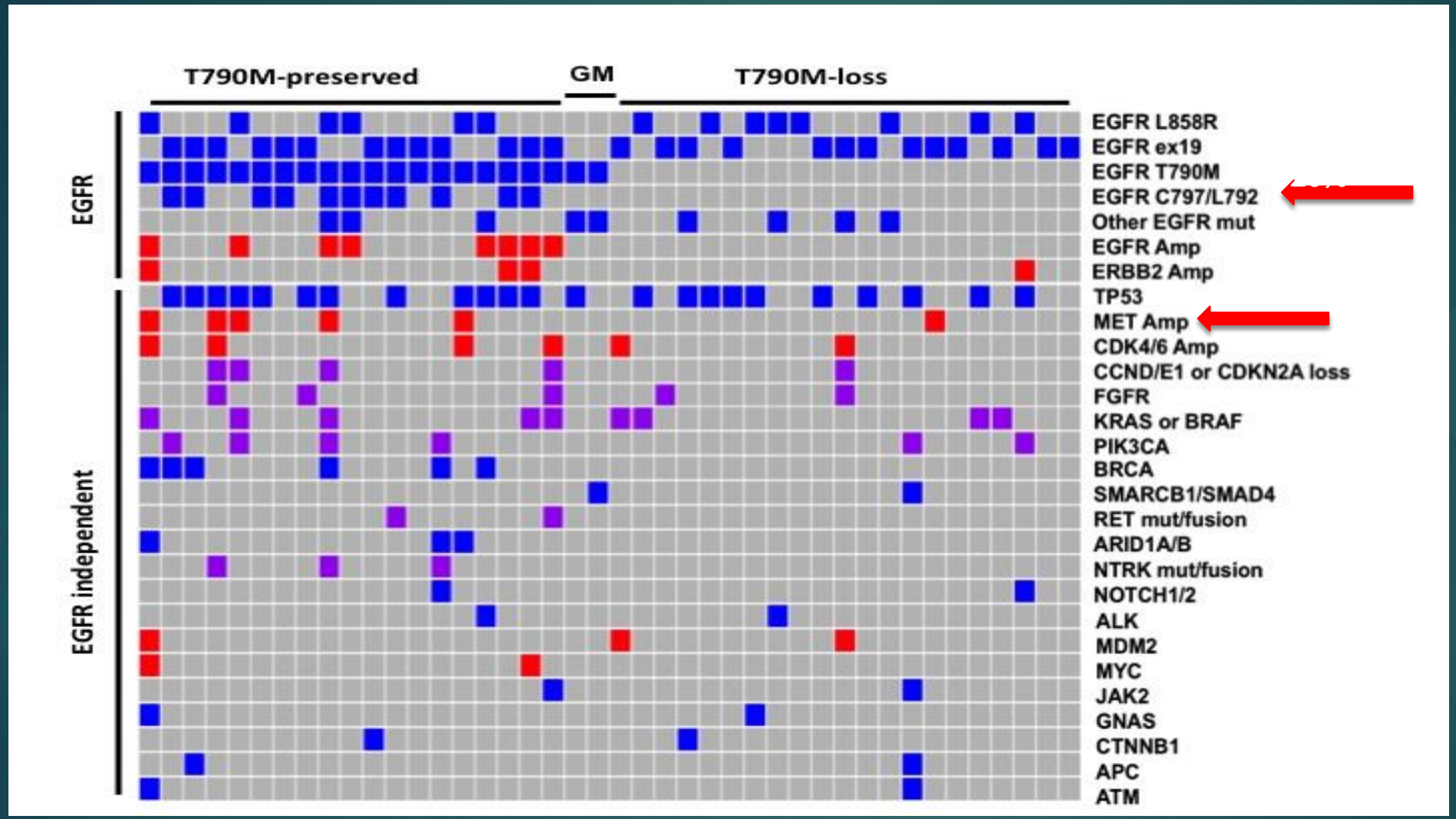
RESISTANCE TO OSIMERTINIB IN PATIENTS WITH EGFR T790M MUTATION MULTI-INSTITUTION COHORT, N= 41

- Retrospective study
- Sample: Tissue from EGFR T790Mm+ NSCLC patients on commercially available osimertinib and plasma samples from Phase 1 AURA trial validation cohort.
- Genomic profiling analysis of post osimertinib progression tumor tissue by NGS and plasma by digital PCR
- Time to treatment discontinuation was significantly lower in the T790M loss vs T790M preserved group (6.1 vs. 15.2 months, p value = 0.01)



Oxnard et et al. JAMA Oncology 2018

RESISTANCE TO OSIMERTINIB IN PATIENTS WITH EGFR T790M MUTATION MOFFITT AND MD ANDERSON EXPERIENCE, N=118



- Blue box: Mutations
- Red box: Amplification
- Purple box: Mutation and/or amplification GM: Denovo (Suspected germline) EGFR T790M mutation with VAF ~50%

Le, Puri et al . Clinical Cancer Research December 2018

rapid communication

EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes

Nicolas Marcoux, MD[1,12]; Scott N. Gettinger, MD[2]; Grainne O'Kane, MD[3]; Kathryn C. Arbour, MD[4]; Joel W. Neal, MD[5]; Hatim Husain, MD[6]; Tracey L. Evans, MD[7,13]; Julie R. Brahmer, MD[8]; Alona Muzikansky, MA[1]; Philip D. Bonomi, MD[9]; Salvatore del Prete, MD[10]; Anna Wurtz, BS[2]; Anna F. Farago, MD, PhD[1]; Dora Dias-Santagata, PhD[1]; Mari Mino-Kenudson, MD[1]; Karen L. Reckamp, MD[11]; Helena A. Yu, MD[4]; Heather A. Wakelee, MD[5]; Frances A. Shepherd, MD[3]; Zofia Piotrowska, MD[1]; and Lecia V. Sequist, MD, MPH[1]

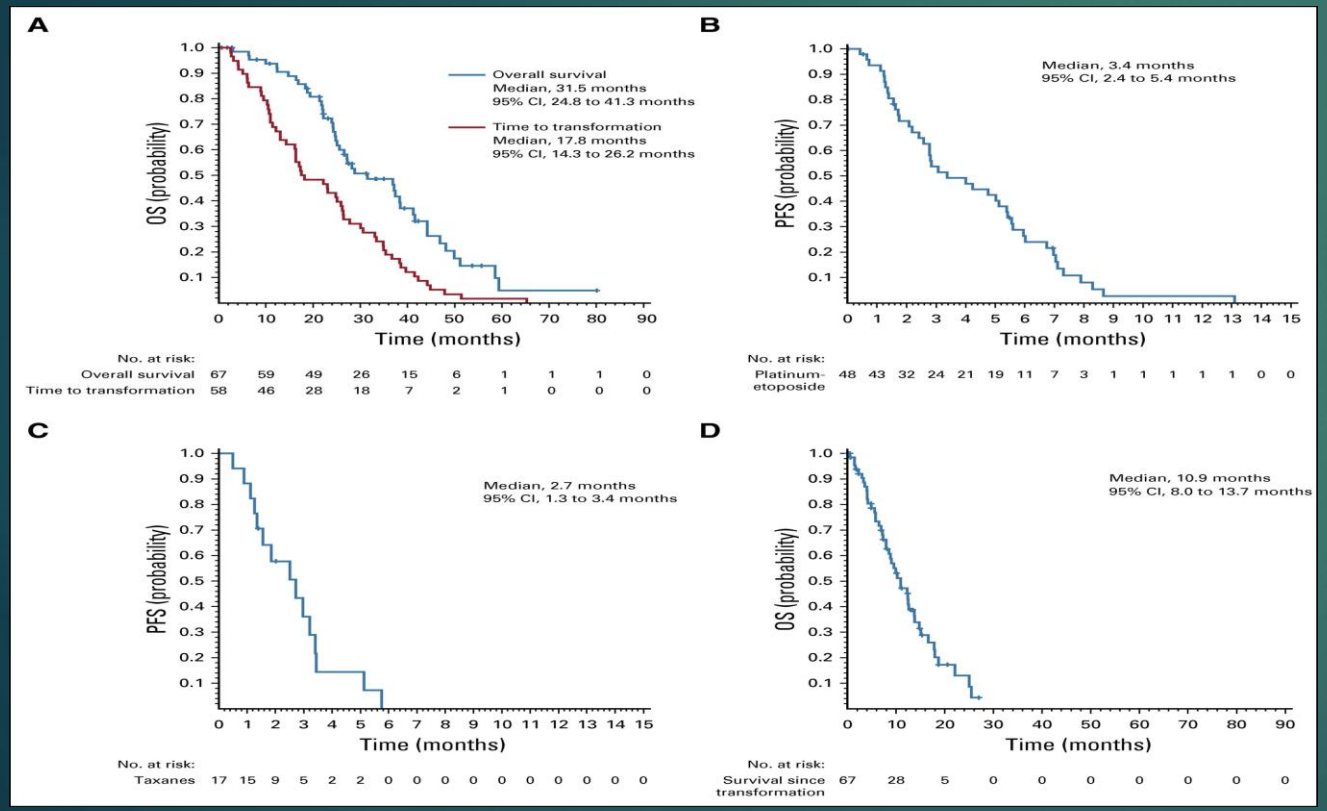


TABLE 3. Frequency of Common Mutations Within Small-Cell Lung Cancer Cases, by Testing Method

Genotyping Platform	*TP53*	*RB1*	*PIK3CA*
All assays	38/48 (79)	18/31 (58)	14/52 (27)
Allele-specific PCR	2/8 (25)	—	3/8 (38)
NGS	32/35 (91)	15/26 (58)	11/39 (28)
Whole-exome sequencing	3/4 (75)	3/4 (75)	0/4 (0)
Unknown	1/1 (100)	0/1 (0)	0/1 (0)

NOTE. Data are given as No. (%). One case genotyped only by plasma cell-free DNA analysis is not included in this table (patient 53; Appendix Table A1).

Abbreviations: NGS, next-generation sequencing; PCR, polymerase chain reaction.

FIG 1. Time to event analyses. (A) Time since diagnosis to transformation to small-cell lung cancer (SCLC) and overall survival (OS) since the time of diagnosis. (B) Progression-free survival (PFS) of SCLC-transformed patients treated with platinum-etoposide. (C) PFS of SCLC-transformed patients treated with taxanes. (D) OS since the time of SCLC transformation.

Marcoux et al Journal of Clinical Oncology 2019 37278-285.DOI: 10.1200/JCO.18.01585

DISCUSSION

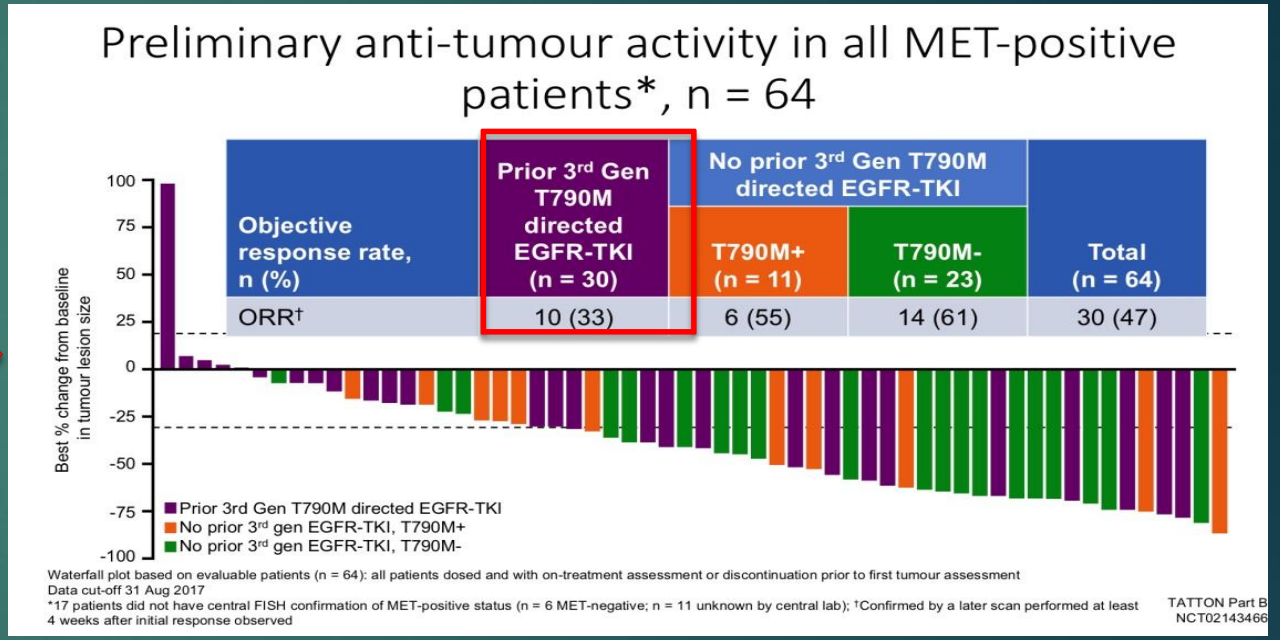
- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.
- Mechanisms of resistance to osimertinib
- **Treatment after progression on osimertinib**

FUTURE DIRECTIONS: TATTON TRIAL

- Multicenter, Multi arm phase I trial in patients with progression prior EGFR TKI.
- Osimertinib with ascending doses of
  - Savolitinib (AZD6094): cMET inhibitor or,
  - Selumitinib (MEK1/2 inhibitor) or,
  - Durvalumab (MEDI4736): PD-L1 inhibitor
- Phase IB dose expansion cohort

  (osimertinib + savolitinib) in osimertinib naïve or pretreated EGFRm+ and cMET +

  patients*
  - ORR was 33% in cohort of patients with prior T790M directed therapy
  - AE ≥ Grade 3 in 50% (33/66) pts, AE leading to death 6%(4/66), 40% (27/66) drug discontinuation due to AEs
- PD-L1 combination therapy arm on hold due higher incidence of interstitial lung disease



Ahn M-J et al . WCLC 2017 , Ahn M-J. ELCC 2016

TATTON: A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety,Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI

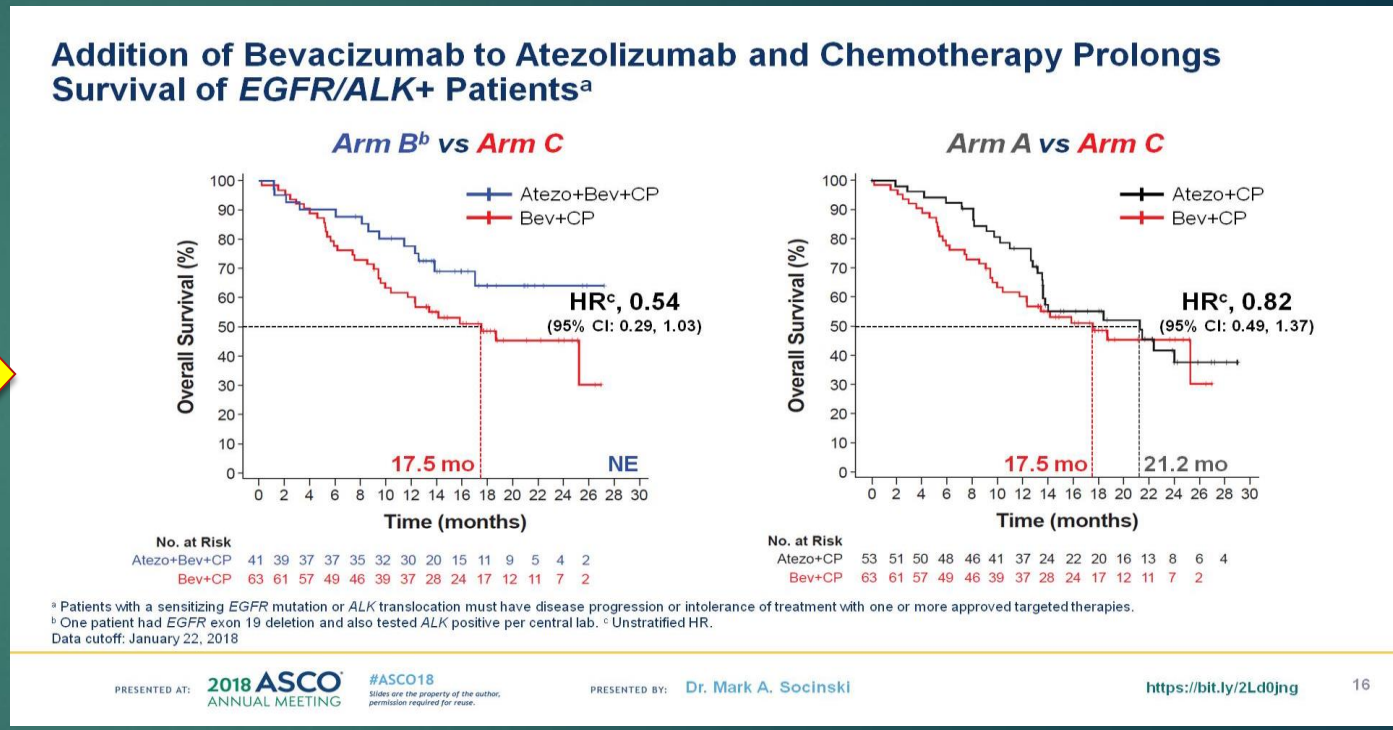
*MET-positive status was to be confirmed centrally by fluorescence in-situ hybridisation (FISH; MET gene copy ≥5 or MET/CEP7 ratio ≥2). Patients were allowed to be enrolled based on local FISH, immunohistochemistry (IHC; +3 in ≥50% of tumour cells), or NGS

FUTURE DIRECTIONS: CHEMO -IMMUNOTHERAPY

- Monotherapy with immune checkpoint inhibitors in the 2nd line setting does not improve survival in patients with EGFRm+ NSCLC.

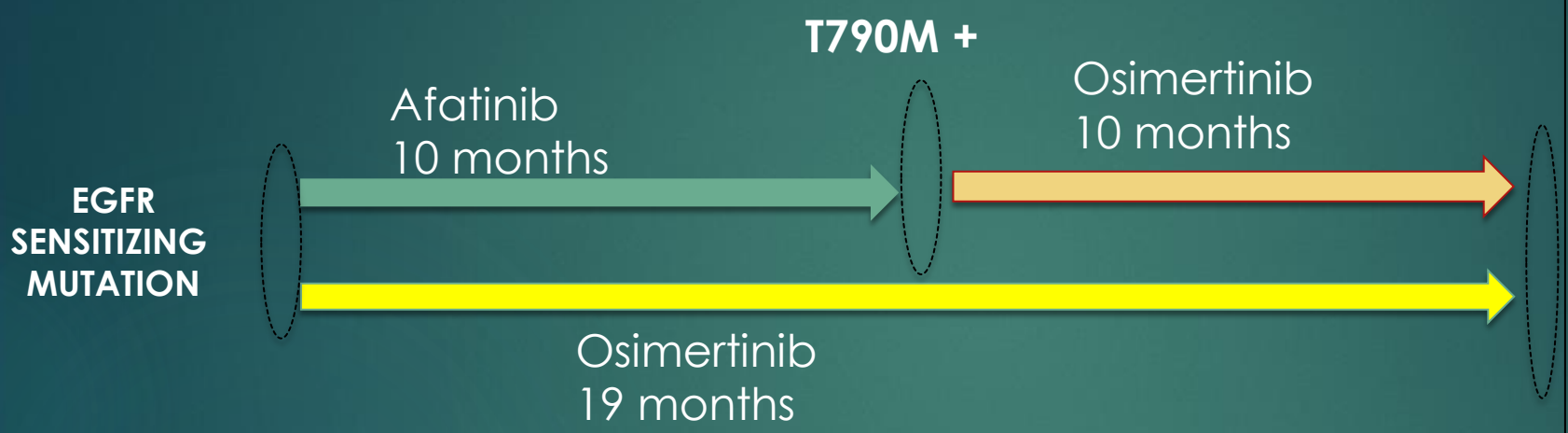
- IMPOWER150
  - Phase III trial
  - Atezolizumab in combination with carboplatin+paclitaxel +/- bevacizumab (ACP +/-B) compared to carboplatin + paclitaxel +bevacizumab (BCP) in patients with non squamous NSCLC
  - Subgroup of chemotherapy naïve patients with EGFR/ALK mutations have significantly higher PFS withABCP compared to BCP.

- Future chemo-immunotherapy trial
  - Carboplatin/Cisplatin plus pemetrexed with or without pembrolizumab in TKI resistant EGFR non squamous NSCLC (NCT03515837)
  - Includes Osi naïve or pre treated patients with or without T790M mutation



Lee et al. JAMA oncology. February 2018
Socinski et al. ASCO 2018

TREATMENT AFTER PROGRESSION ON OSIMERTINIB WHAT' NEXT??



- Clinical trials with EGFR TKIs combinations
- Clinical trails with IO +/- chemotherapy combinations
- Chemotherapy
+ VEGF
+ Immunotherapy
(IMPOWER150) trial
- Chemotherapy alone.

QUESTIONS??