NATIONAL LUNG CANCER ROUNDTABLE

American Cancer Society

Project ECHO

Addressing Lung Cancer Biomarker Testing Through Project ECHO: 2022-2023 Expansion

Session 6: Updates on Targeted Therapy in NSCLC

An Era of Hope

ACS/NLCRT Lung Cancer Biomarker Testing Project ECHO

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PLEASE WELCOME TODAY'S FACILITATIVE PARTNER

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

TODAY'S SESSION WILL BE FACILITATED BY

DR. ESTELAMARI RODRIGUEZ

A HIGHLY RESPECTED THORACIC ONCOLOGIST

ASSOCIATE DIRECTOR OF COMMUNITY OUTREACH

Estelamari Rodriguez, MD, MPH

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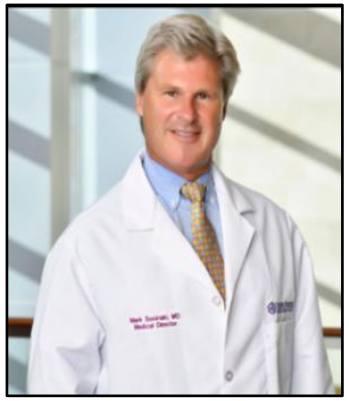
THANK YOU TO OUR FLORIDA FACULTY

Jhanelle E. Gray, MD

MOFFITT CANCER CENTER

*Facilitative Partner

Mark Socinski, MD



AdventHealth

Rami Manochakian, M.D

MAYO CLINIC

Luis Raez, MD

Memorial Healthcare System

Michael Diaz, MD

FLORIDA CANCER SPECIALISTS & Research Institute

Estelamari Rodriguez, MD

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

*Facilitative Partner

Today's Agenda

Agenda Preview & Introductions (10 min)

Didactic Presentation: Dr. Rami Manochakian (10 min)
Updates on Targeted Therapy in NSCLC. An Era of Hope.

Case Presentation: Dr. Correia (10 min)
Hematology/Oncology Fellowship Program, Mayo Clinic

Case Presentation Recommendations/Discussion (20 min)

Post-Session Poll & Wrap Up (5 min)

This ACS/NLCRT Lung Cancer Biomarker Testing ECHO series is made possible by funding provided by:

Additional thanks to Foundation Medicine

MEET OUR FLORIDA ACS ECHO TEAM

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DIDACTIC PRESENTATION

Updates on Targeted Therapy in NSCLC. An Era of Hope.

Rami Manochakian, MD
Thoracic Oncologist
Associate Professor of Medicine
Vice Chair-Education
Hem/Onc Division
Mayo Clinic, FL

Twitter @RManochakian

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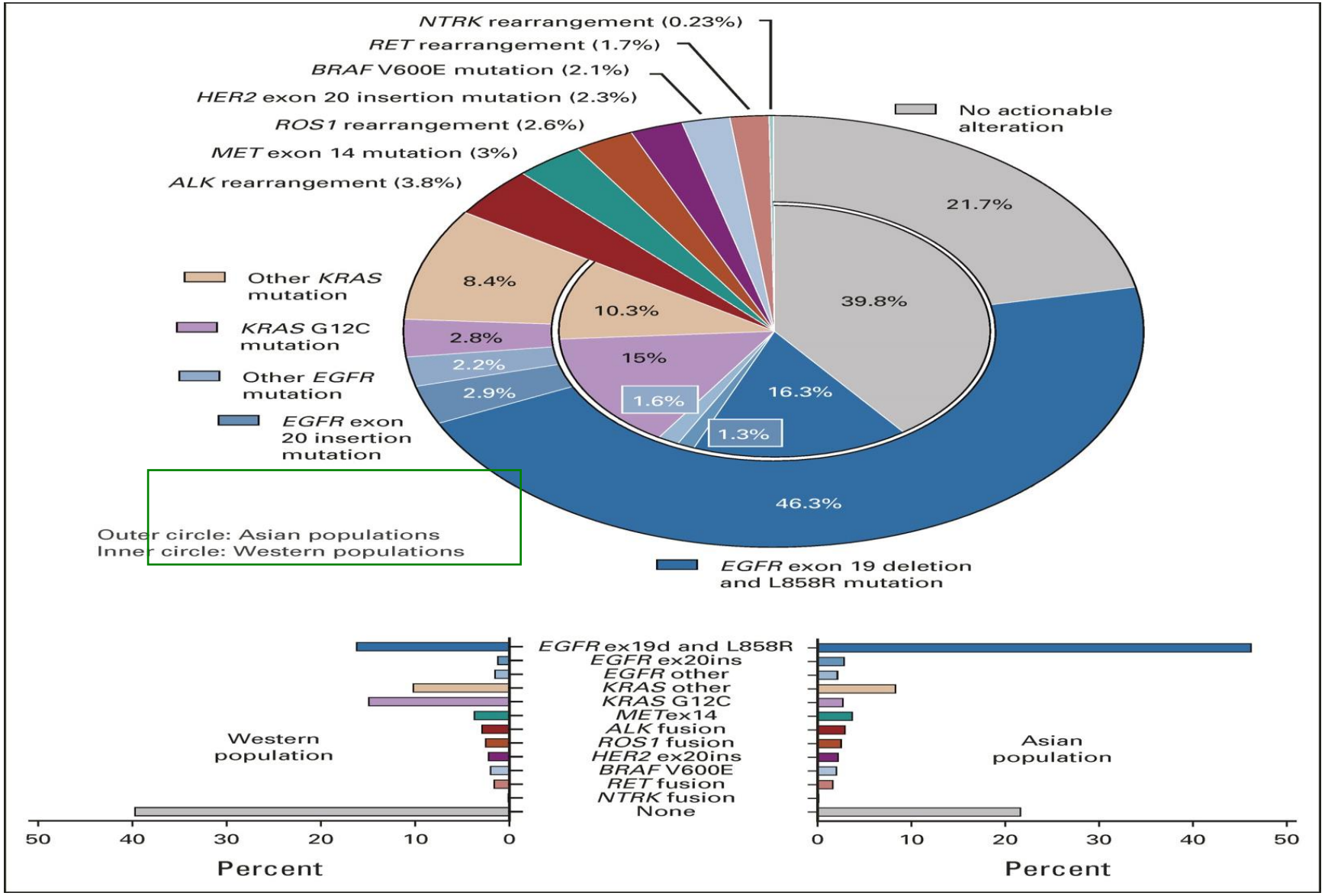
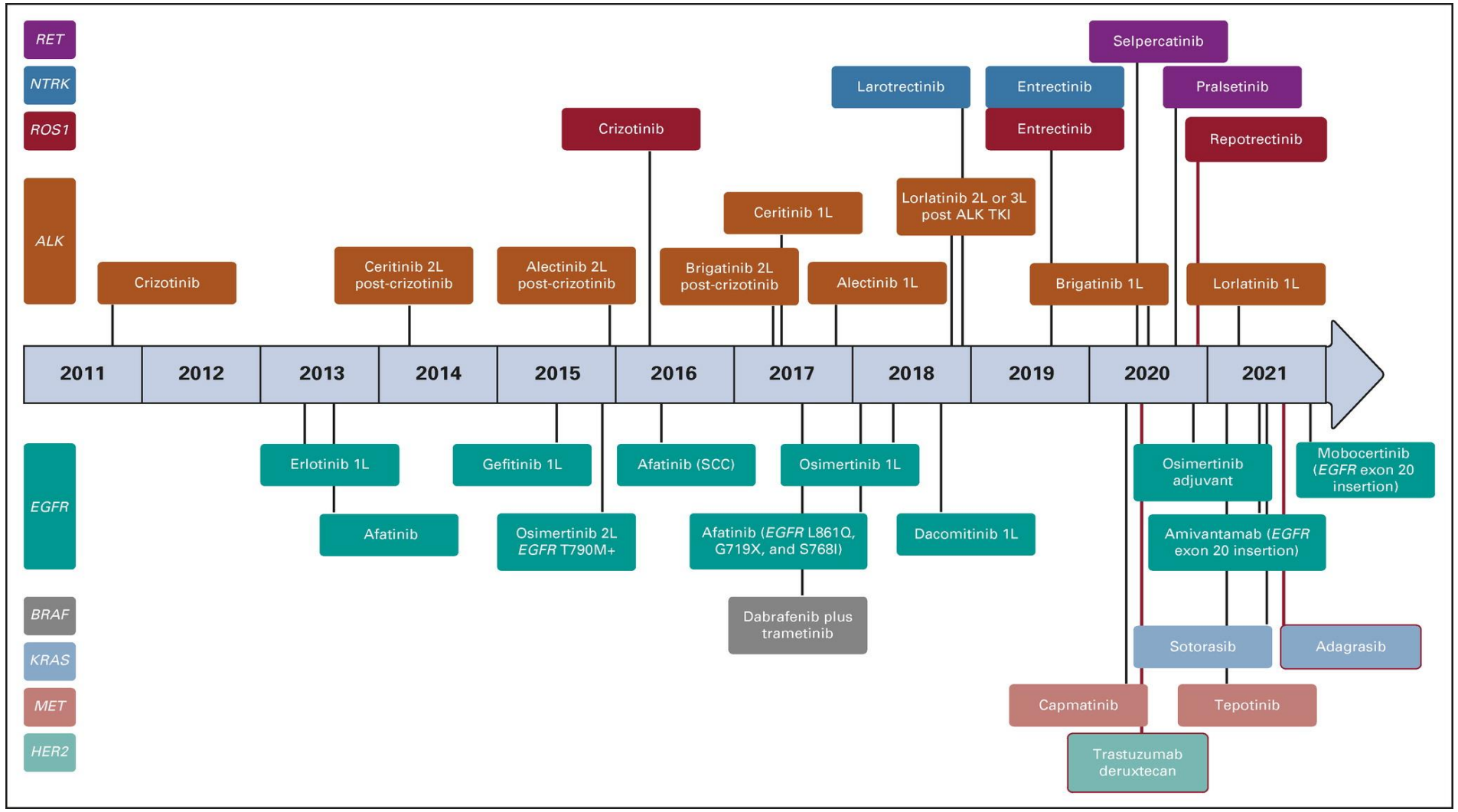
Molecular Profiling of Lung Adenocarcinoma



Tan et al; *JCO* 2022

Timeline of FDA-approved targeted therapies for oncogene-driven NSCLC



Tan et al; *JCO* 2022

FDA approved Targeted therapeutic agents in Lung Adenocarcinoma *(as of April 12th, 2023)*

Gene	FDA approved Therapeutic Agents
ALK	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib
BRAF V600E	Dabrafenib plus Trametinib
EGFR (exon 19, 21)	Osimertinib, Erlotinib, Afatinib, Gefitinib, Dacomatinib, Erlotinib + Ramucirumab
EGFR Exon 20	Amivantamab, Mobocertinib *(in 2nd line)*
KRAS (G12C)	Sotorasib, Adagrasib *(in 2nd line)*
MET exon 14 skipping	Capmatinib, Tepotinib
NTRK	Larotrectinib, Entrectinib
RET	Selpercatinib, Pralsetinib
ROS-1	Crizotinib, Entrectinib
HER-2	Trastuzumab Deruxtecan *(in 2nd line)*

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Epidermal Growth Factor Receptor (EGFR) mutations

- Osimertinib

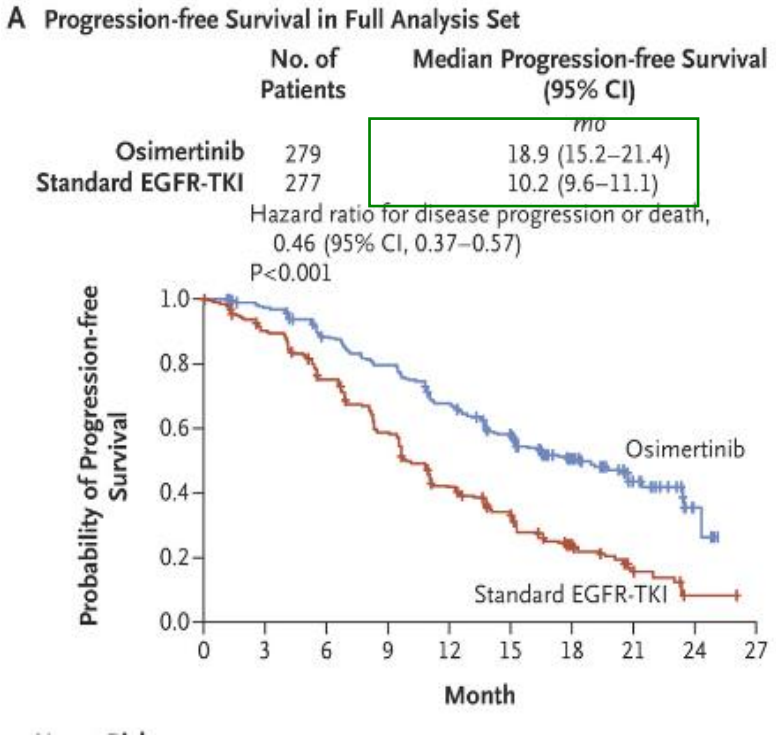
FLAURA (Osimertinib vs 1st generation TKI): Initial PFS results

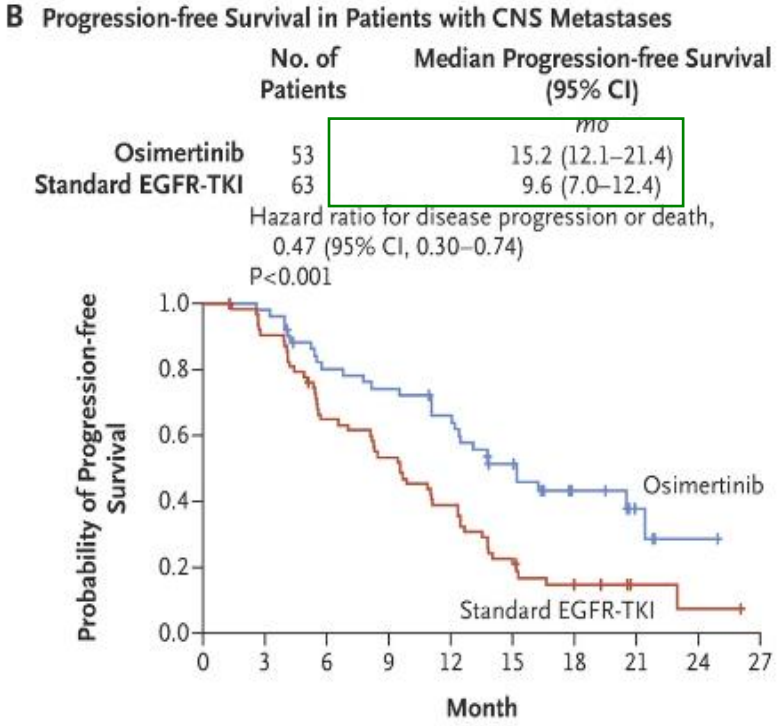
CNS progression occurred in

6% treated with Osimertinib

Vs

15%





Soria et al. N Engl J Med Jan 2018

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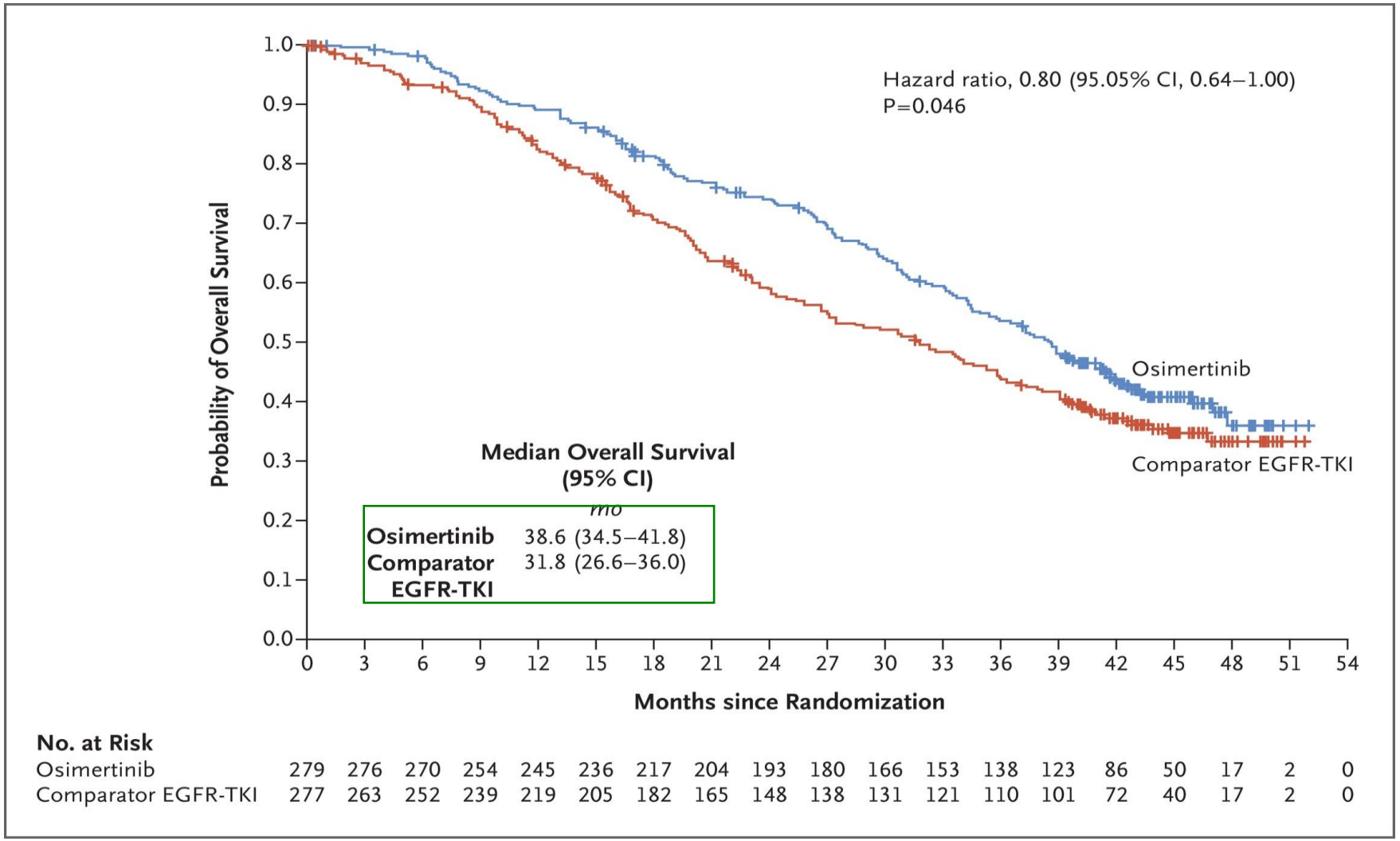
FLAURA (Osimertinib vs 1st generation TKI): Updated OS data

AEs:
Grade ≥3
AE
42% with
Osimertinib
vs
47% with
erlotinib/gefitinib



Ramalingam SS et al. N Engl J Med Jan 2020

EGFR Exon 20 insertion

Two drugs FDA approved in 2nd line:

Amivantamab (IV):

RR: 40%, clinical benefit rate: 74%
mDOR: 11.1 months mPFS: 8.3 months mOS: 23 months

Mobocertinib (PO):

RR: 28% mDOR: 17.5 months

mPFS: 7.3 months. mOS: 24 months

Park et al, JCO Oct 2021
Zhou et al, JAMA Onc Oct 2021

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ALK Rearrangements

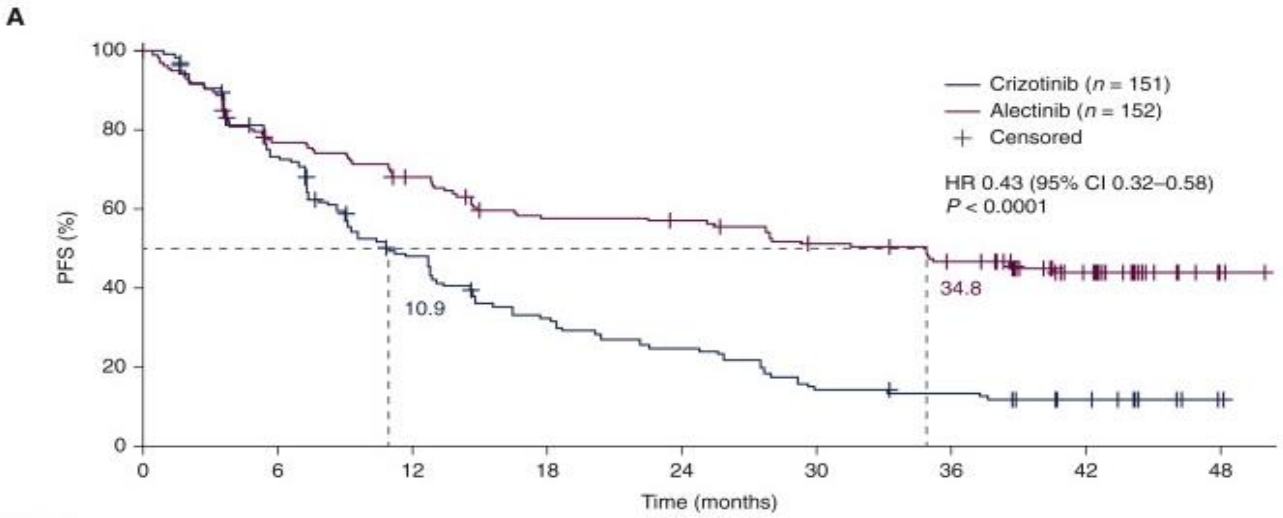
- **1st line:**

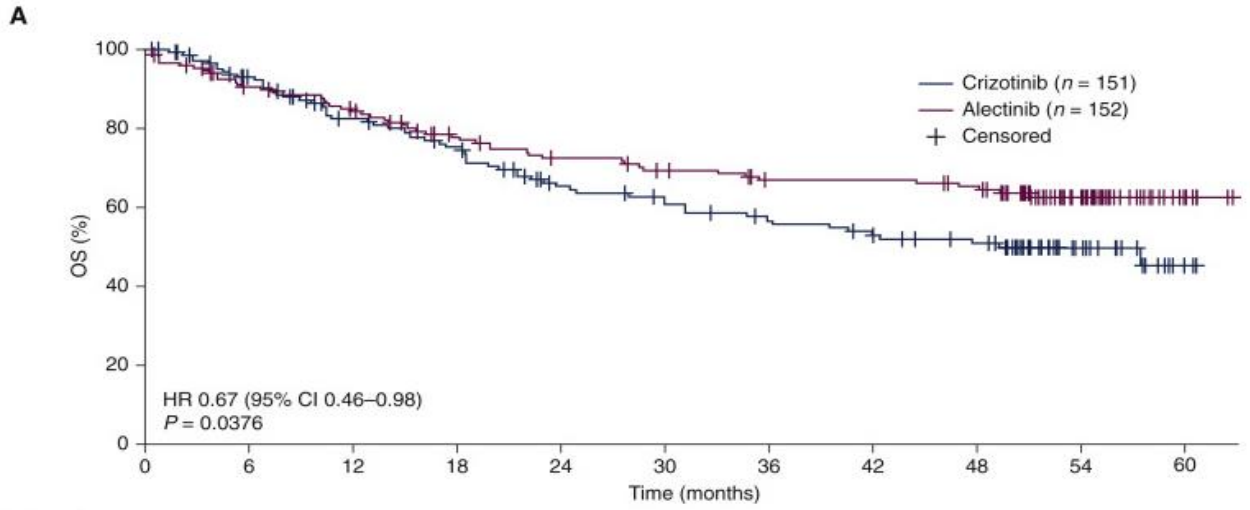
- Alectinib
- *Brigatinib*
- *Lorlatinib*
- *Ceritinib*

- **After progression**

Based on limited data, and depending on 1st line, can try to sequence Alectinib, Brigatinib, Ceritinib and Lorlatinib

Alectinib vs Crizotinib (ALEX study)





5 Y OS rates:

62.5%

vs

45%

Mok et al, Annals of Oncology 2020

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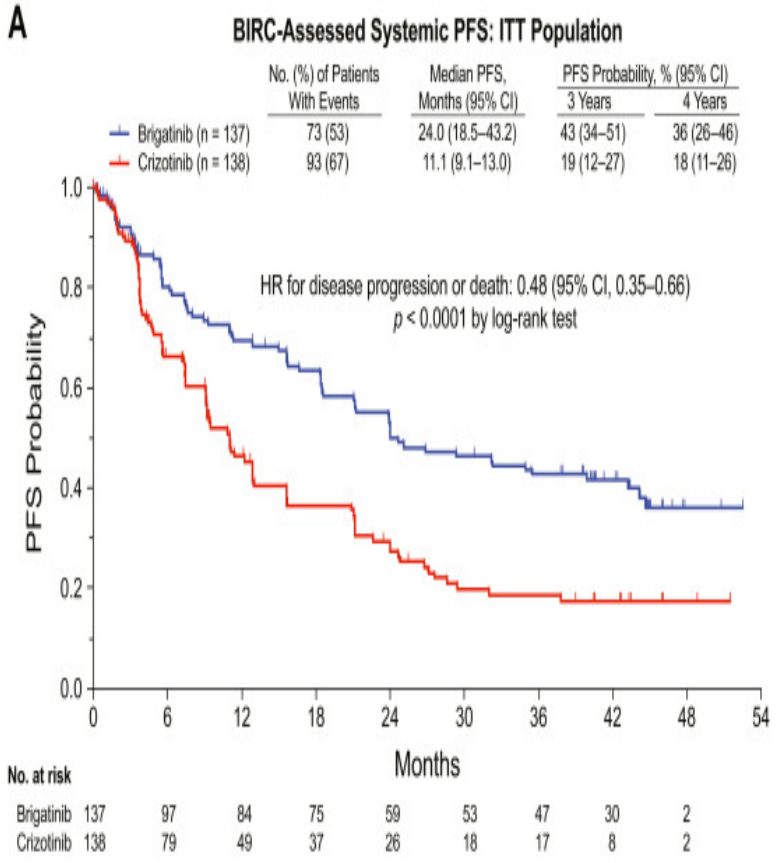
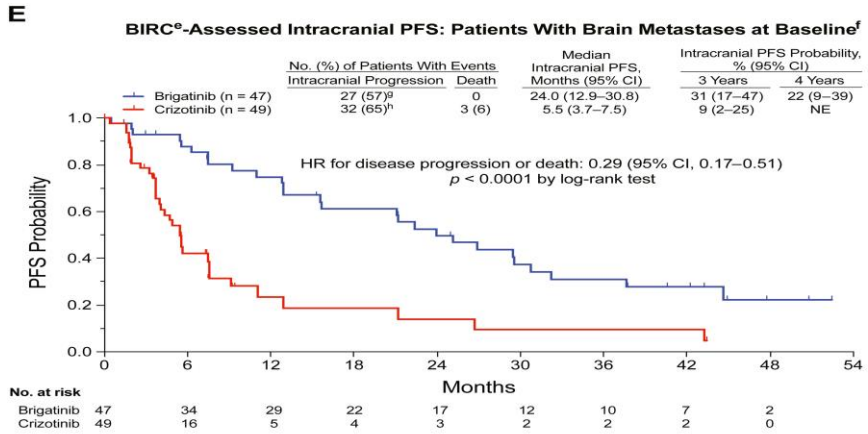
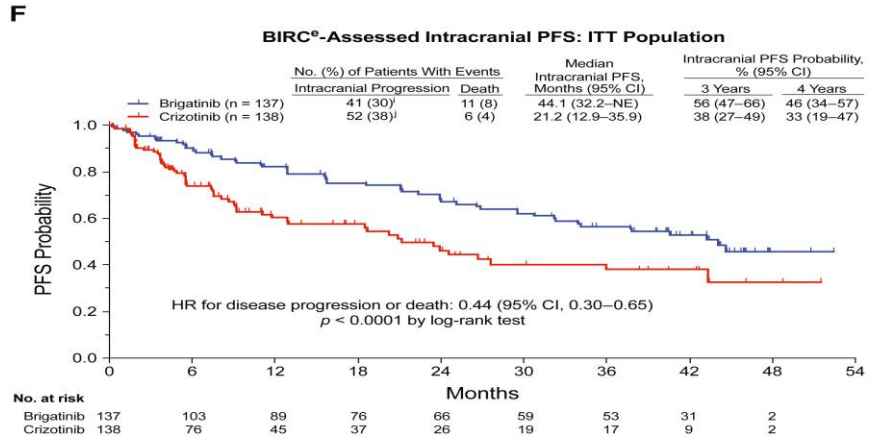
Brigatinib vs Crizotinib (ALTA)

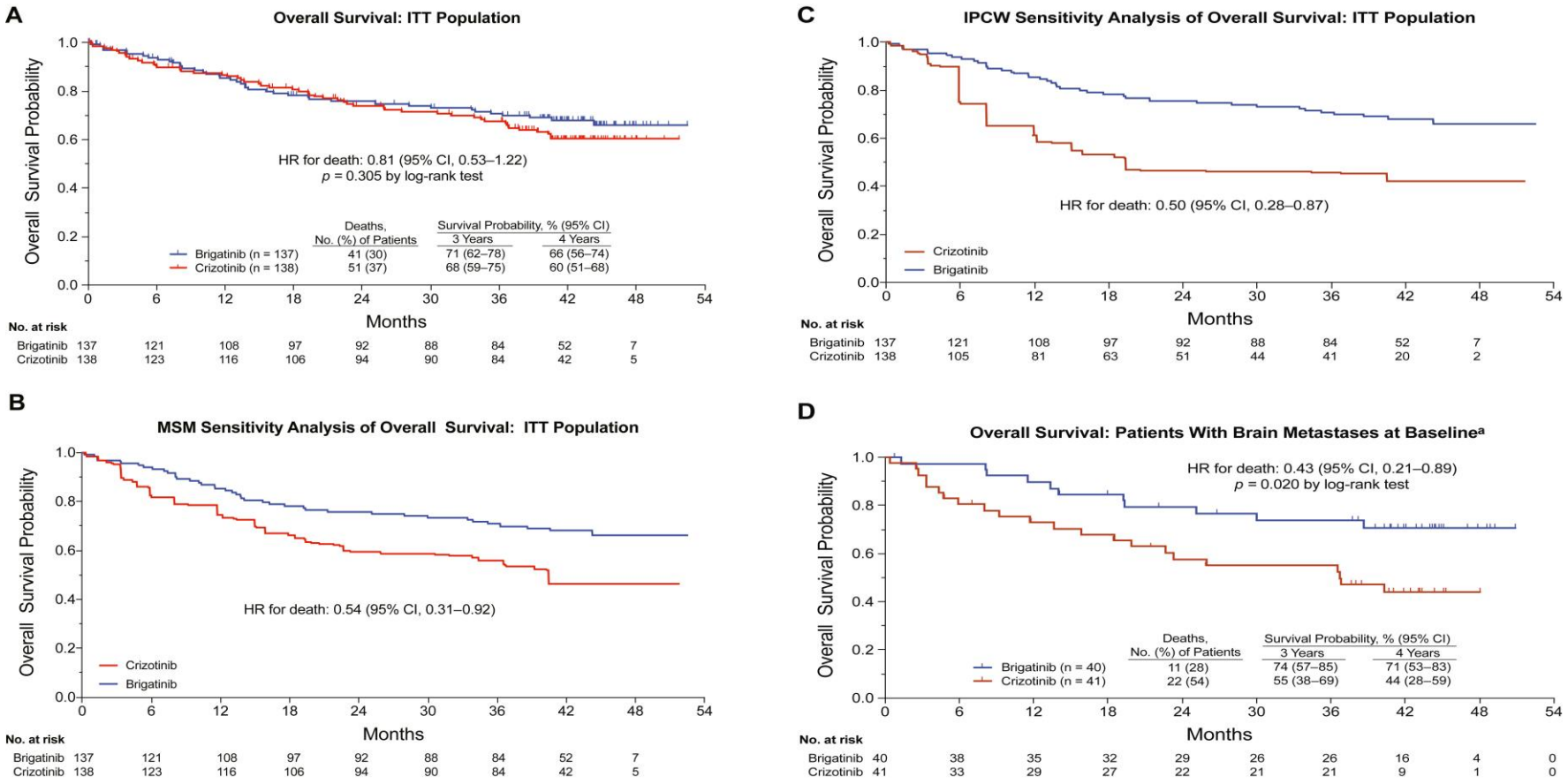






Camidge et al, Journal of Thoracic Oncology 2021

Brigatinib vs Crizotinib (ALTA)



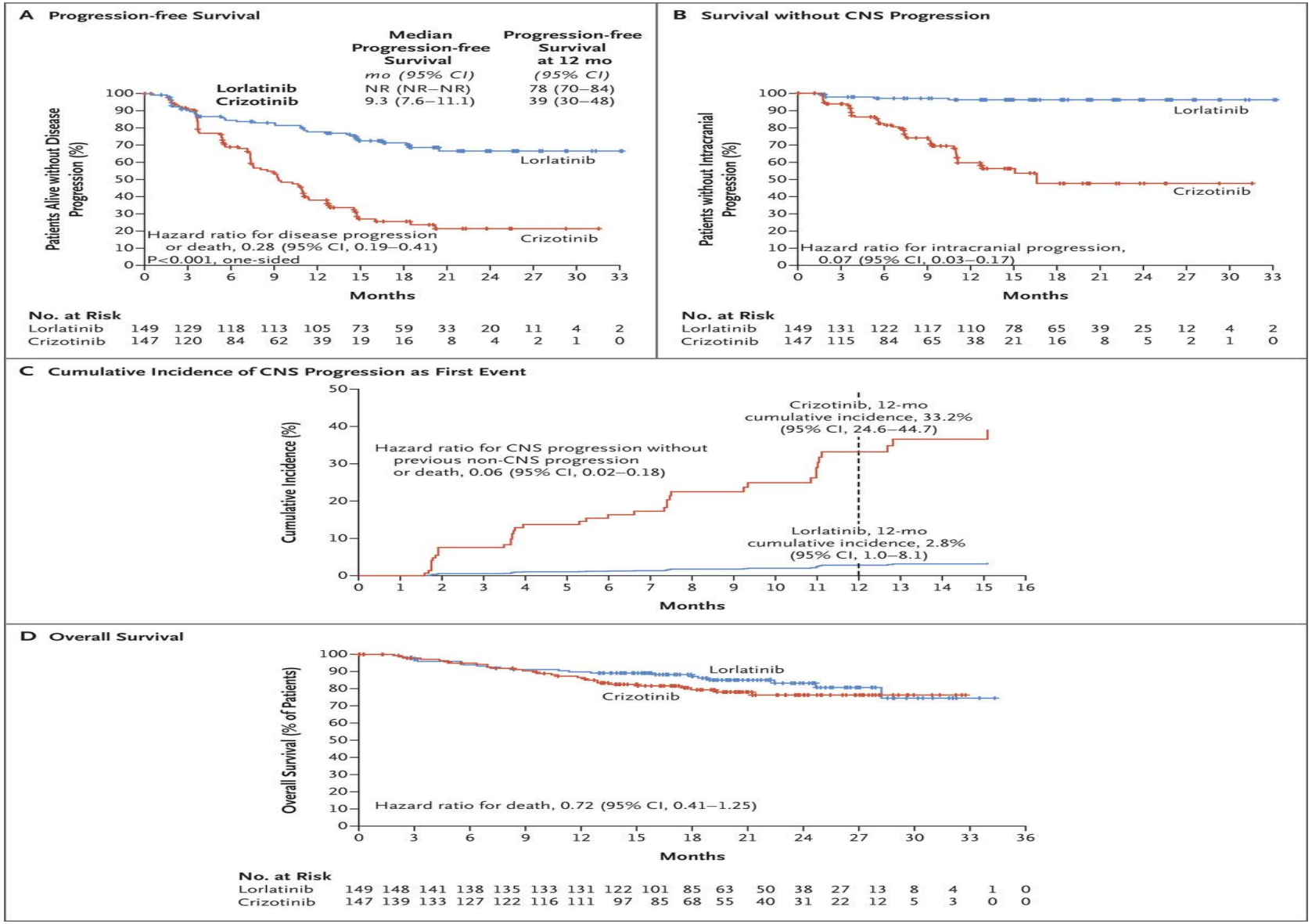
Camidge et al, Journal of Thoracic Oncology 2021

Lorlatinib vs Crizotinib (CROWN)

- ORR 76% vs 58%
- CNS RR: 66% (61 % with complete CNS response)

  vs

  20 %



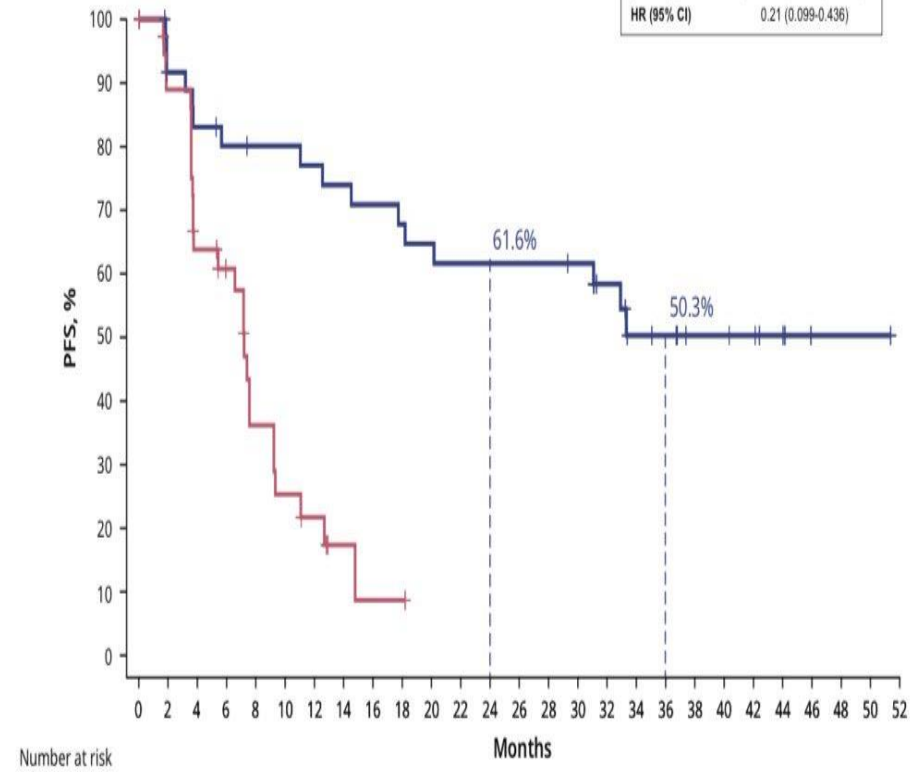
Shaw et al. NEJM 2020

Lorlatinib vs Crizotinib (CROWN)

Figure 2: PFS by BICR

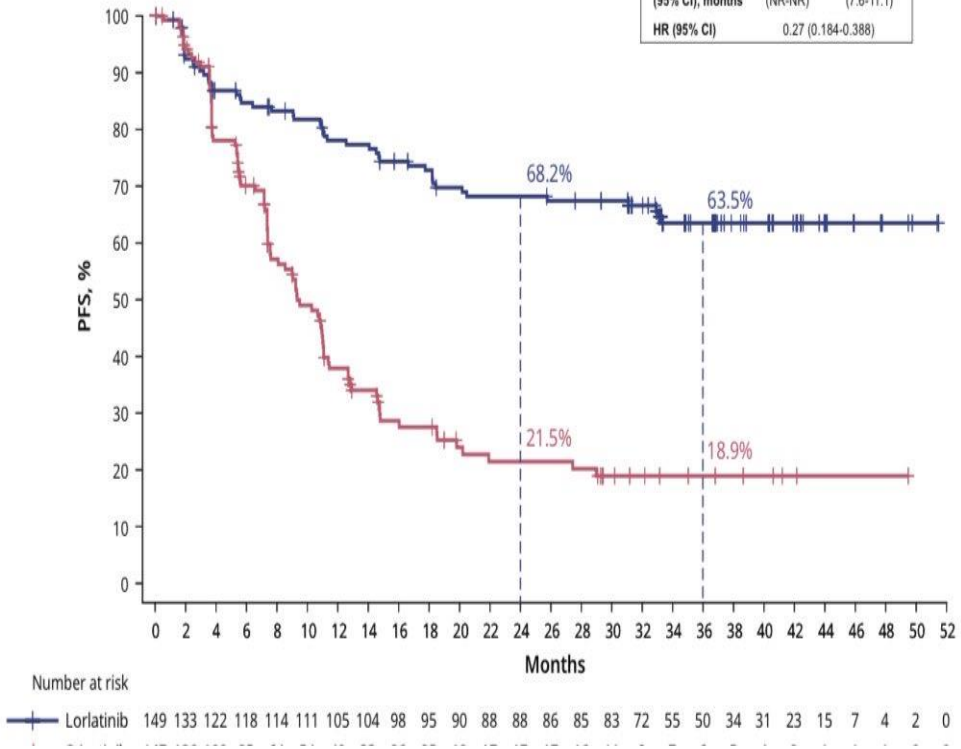
B. Patients with baseline brain metastases

	Lorlatinib (n=37)	Crizotinib (n=39)
Events	16	27
PFS, median (95% CI), months	NR (18.2-NR)	7.2 (3.7-9.2)
HR (95% CI)	0.21 (0.099-0.436)	



A. ITT population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
PFS, median (95% CI), months	NR (NR-NR)	9.3 (7.6-11.1)
HR (95% CI)	0.27 (0.184-0.388)	



Updated Data presented at AACR 2022

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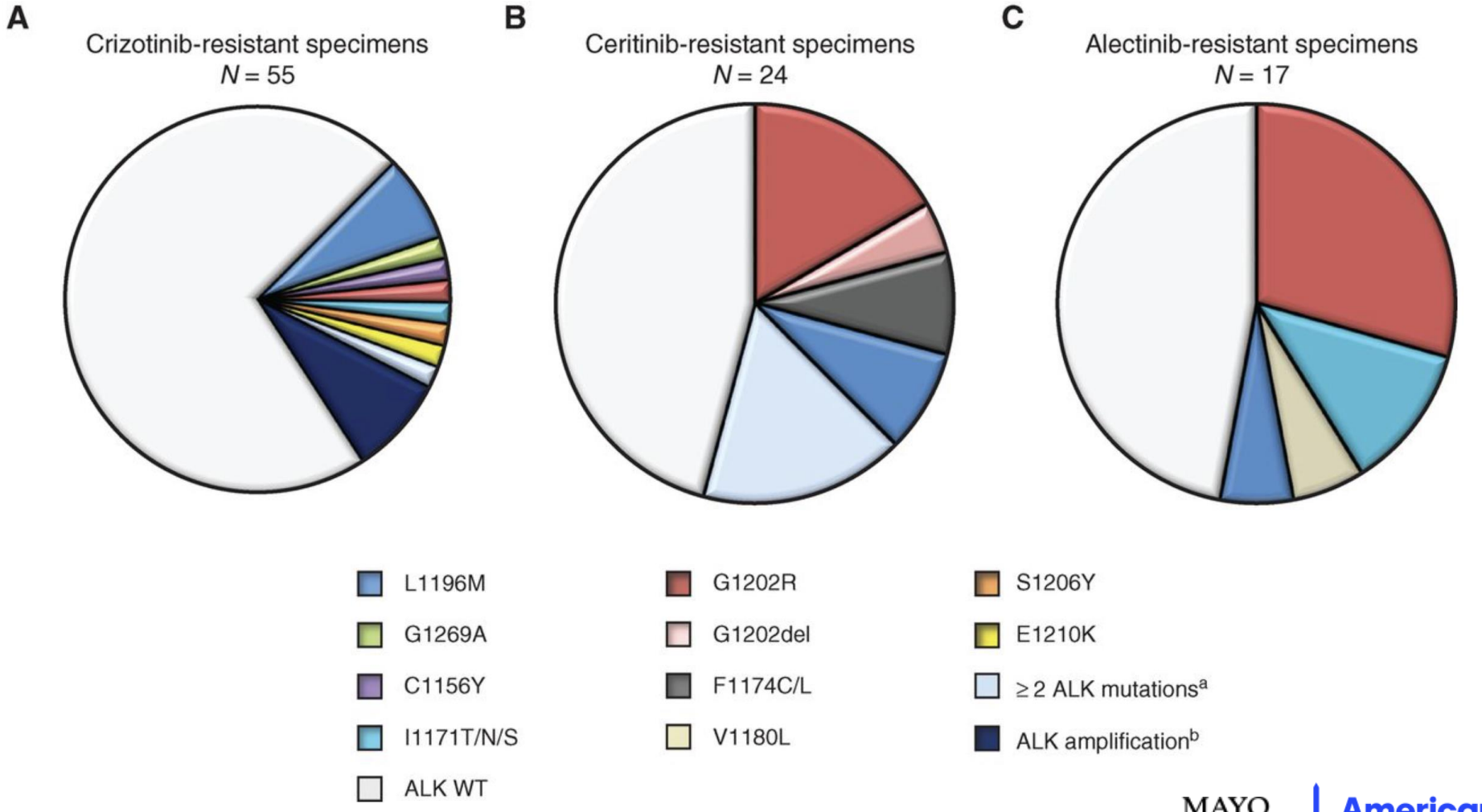
Resistance to ALK TKI inhibitors



Gainor et al, Cancer Discovery Oct 2016

ROS 1+ (rearrangement)

Crizotinib

Phase 1 PROFILE 001:

ORR: 72% mPFS: 19.3 months, mOS: 51.4 months

4-year survival: 51%

Shaw et al, ANN Onc 2019

Entrectinib

Two phase 1 studies (ALKA-372-001/STARTRK-1) & phase 2 global basket study (STARTRK-2):

ORR: 77% mPFS: 19 months

Dillon et al, Lancet Onc 2020

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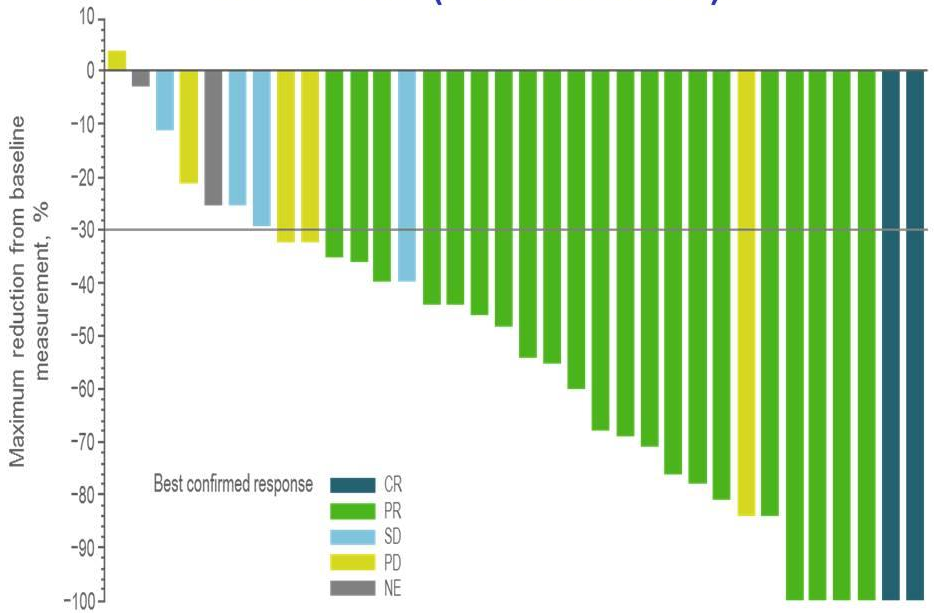
BRAF+ (V600E) mutations

Clinical benefit with dabrafenib + trametinib

2ND LINE

ORR: 64% (95% CI 46-79)



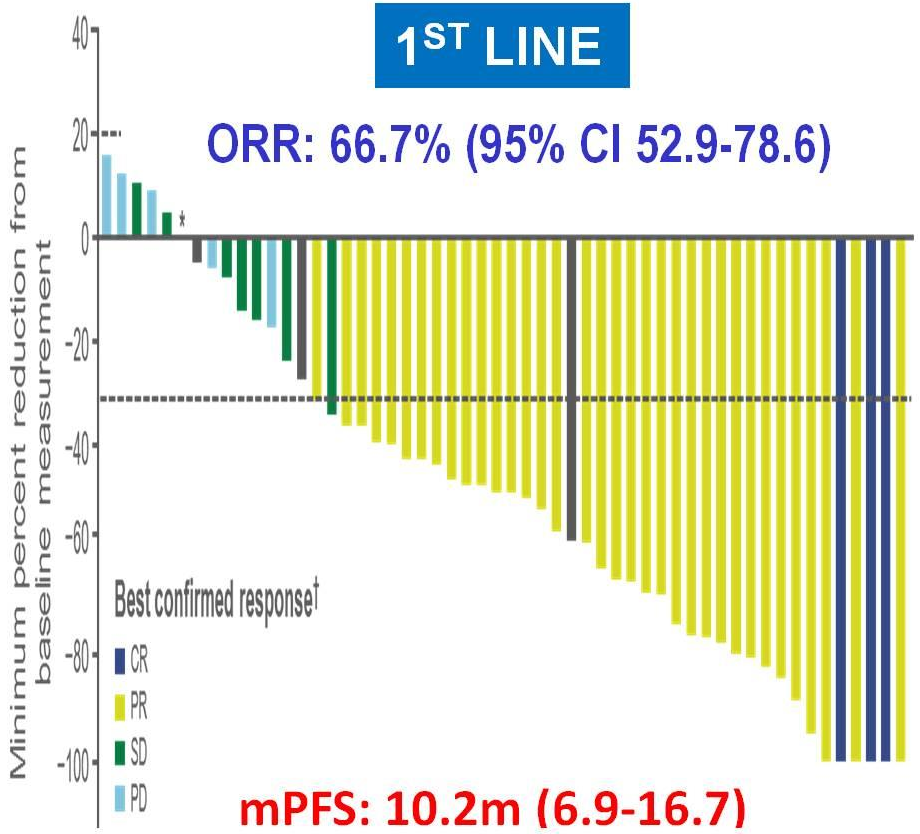
mPFS: 10.9m (7.0-16.6)

PRESENTED AT: 2018 ASCO ANNUAL MEETING

Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

1ST LINE

ORR: 66.7% (95% CI 52.9-78.6)



mPFS: 10.2m (6.9-16.7)

Planchard D *et al. Lancet Oncol* 2016;17:984–993;
Planchard D *et al. J Clin Oncol* 2017;35(Suppl):Abst 9075

Presented By David Planchard at 2018 ASCO Annual Meeting

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MET exon 14 Skipping Mutation

Capmatinib

RR: 40% in previously treated. 67% in 1st L

mDOR: 11.1 months in previously treated. 12 months in 1st L

Tepotinib

RR: 46%

mDOR: 11.1 months

Wolf et al, NEJM Sep 2020

Paik et al, NEJM Sep 2020

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RET+ mutations

Selperctatinib

RR in 1st line : 85%

RR in 2nd line: 64%

mDOR: 17.5 months

91% CNS response

Pralsetinib

RR in 1st line : 70%. CR: 11%

RR in 2nd line: 53%. CR: 6%

Drilon et al, NEJM Aug 2020
Gainor et Al, Lancet Onc June 2021

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KRAS mutation (G12C)

Sotorasib (in 2nd line):

CodeBreak 100: Phase 2 study:

RR: 37% CR: 3% mDOR: 11.1 months Disease control: 80%

mPFS: 6.8 months mOS: 12.5 months

Skoulidis et al, NEJM June 2021

2 Y F/U Updated data from AACR 2022:

RR: 41% mDOR: 12.3 months Disease control: 84%

mOS: 12.5 months 2Y OS: 32%

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KRAS mutation (G12C)

Adagrasib (in 2nd line):

Krystal-1 study:

RR: 44% mDOR: 8.5 months

mPFS: 6.5 months mOS: 12.6 months

Janne et al, NEJM July 2021

NTRK fusion

Larotrectinib

RR (in NSCLC): 75%

mPFS: 28.3 months mOS: 44.4 months

Entrectinib

RR (in NSCLC): 70%

mPFS: 14.9 months

Haratake et al, Clini Lung CA Jan 21

HER 2 mutation

The NEW ENGLAND JOURNAL of MEDICINE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

MULTICENTER, INTERNATIONAL, PHASE 2 STUDY

91

Adults with metastatic *HER2*-mutant NSCLC refractory to standard treatment (median follow-up, 13 mo)

Confirmed objective response (assessed by independent central review)	55% (95% CI, 44–65)
Duration of response	9.3 mo
Progression-free survival	8.2 mo
Overall survival	17.8 mo

Grade 3 or higher drug-related adverse events occurred in 46% of patients.

Trastuzumab deruxtecan showed durable anticancer activity.

B.T. Li et al. 10.1056/NEJMoa2112431

Li et al, NEJM Jan 2022

The FUTURE of targeted Therapy in NSCLC

- Integrating Targeted therapy in early-stage cancers
- Assessing response through serial NGS testing
- Overcoming the resistance to current targeted therapies (identify and target new resistant mutations)
- New discovered actionable mutations are actively being studied

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Thank You

Acknowledgment: Patients and their families

“The human spirit is much stronger than anything that could happen to it”

George Scott

Twitter: @RMAnochakian

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CASE PRESENTATION

A case of NSCLC with *ALK* rearrangement

Guilherme Sacchi de Camargo Correia, MD

Hematology & Oncology Fellow

Mayo Clinic

Jacksonville, Florida

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History of Present Illness

- 55-year-old female with a painless lump in the supraclavicular area in November 2017, without other associated symptoms.

- Initial concern for infection, treated with antibiotics without improvement.

- Subsequent CT of the neck and chest in December 2017 showed:
  - 1.3 cm right lower lobe lesion
  - Mediastinal lymphadenopathy
  - 3.5 cm right supraclavicular lymph node

History of Present Illness

- US-guided biopsy of the supraclavicular lymph node:
  - **Adenocarcinoma**

- PET-CT:
  - Right lower lesion, supraclavicular lymph node, mediastinal, right hilar, and infrahilar lymph nodes were hypermetabolic.

- MRI brain without metastatic lesions.

Clinical Staging

- **Stage IIIB** (cT1b N3 M0).

Previous Medical History

- Hypertension and seizure disorder.

Family History

- Brother with history of ALL.
- Grandmother with history of pancreatic cancer.

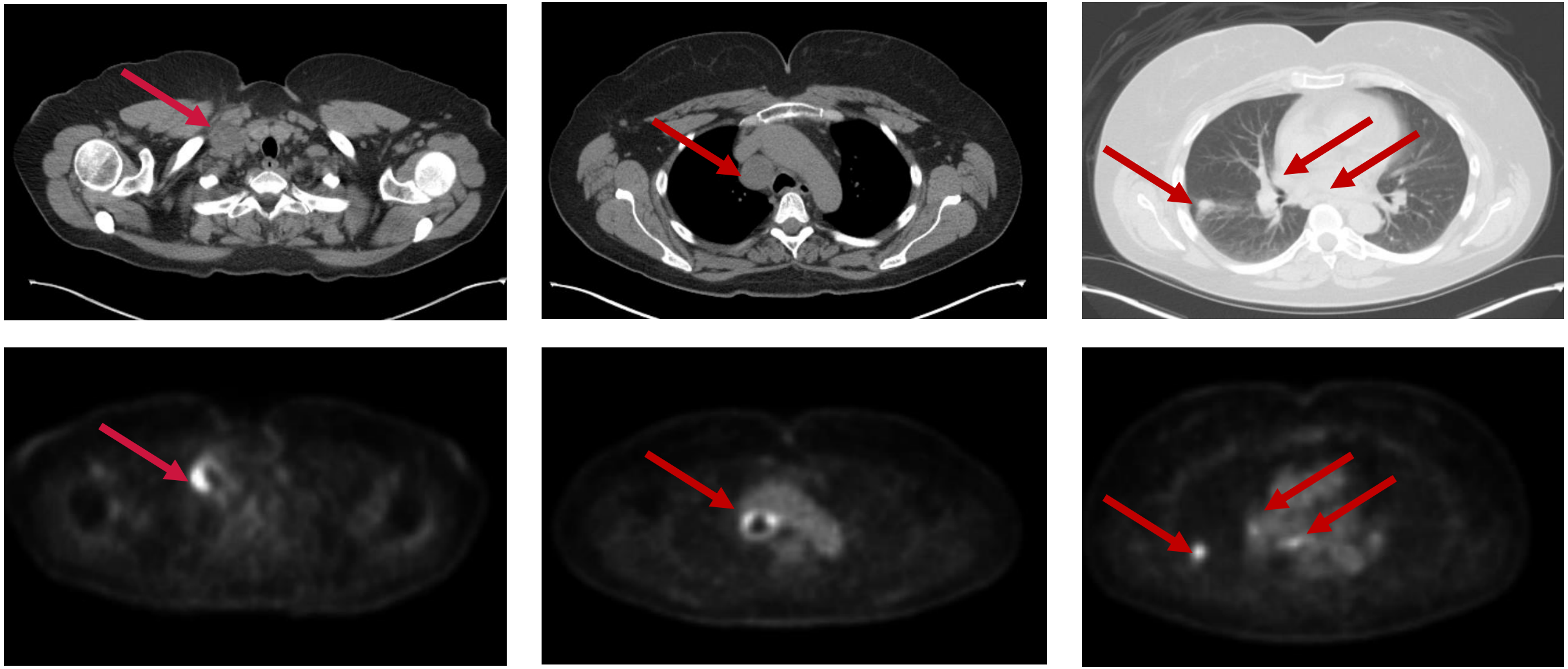
Social History

- Former smoker (approximately 5 pack-years, quit 30 years prior).

Physical Exam

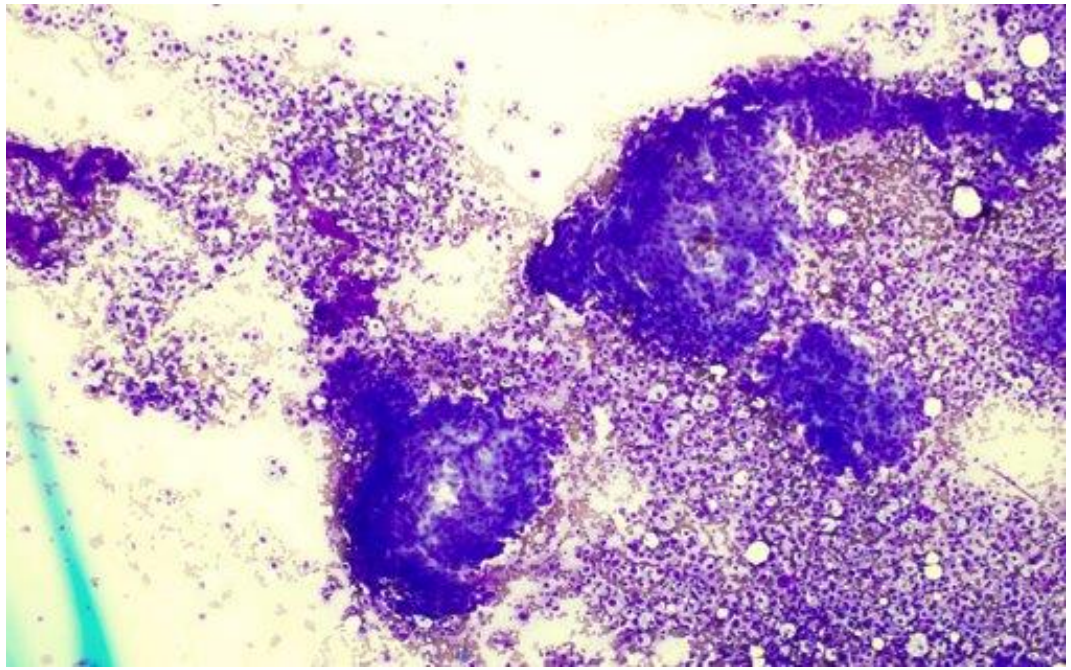
- Remarkable only for **enlarged right-sided supraclavicular lymph node, non-tender**

Imaging Studies



Pathology

- Right supraclavicular lymph node FNA:
  - **Adenocarcinoma** with extensive necrosis.
  - IHC: **CK7, TTF-1, Napsin A positive**. CK20, CK5/6, and p63 negative;
  - PD-L1 expression assay (22C3): low expression, <10%.



Next-Generation Sequencing

- **Liquid Biopsy** (ctDNA):
  - No actionable mutations
  - CDKN2A and CTNNB1

- **Tissue NGS**:
  - Not enough tissue to be performed

Clinical Course

- Initial treatment with concurrent chemo-radiation:
  - **Cisplatin** 75 mg/m² IV
  - **Pemetrexed** 500 mg/m² IV
  - **RT** 60 Gy in 30 fractions

  } Every 3 weeks for 3 cycles

- Partial response to therapy

- Consolidation immunotherapy:
  - **Durvalumab** 10 mg/kg IV every 2 weeks;
  - 19 cycles administered between March 2018 and December 2018.

Clinical Course

- Re-staging scan in December 2018:
  - **Progression of cancer with interval increase in size of several mediastinal lymph nodes** (right upper paratracheal, subcarinal, left inferior hilar, right lower periesophageal).

- Bronchoscopy/EBUS-guided biopsy:
  - Station 2R Lymph node: **positive for malignancy, non-small cell carcinoma**;
  - Stations 4R and 10R: atypical and negative for malignancy, respectively.

Clinical Course

- Salvage therapy:
  - **Carboplatin** AUC 6 IV;
  - **Paclitaxel** 200 mg/m² IV;
  - **Atezolizumab** 1200 mg IV;
  - **Bevacizumab** 15 mg/kg IV;

  } Every 3 weeks for 2 cycles

- Next-generation sequencing (FoundationOne) was in process at this time.

Clinical Course

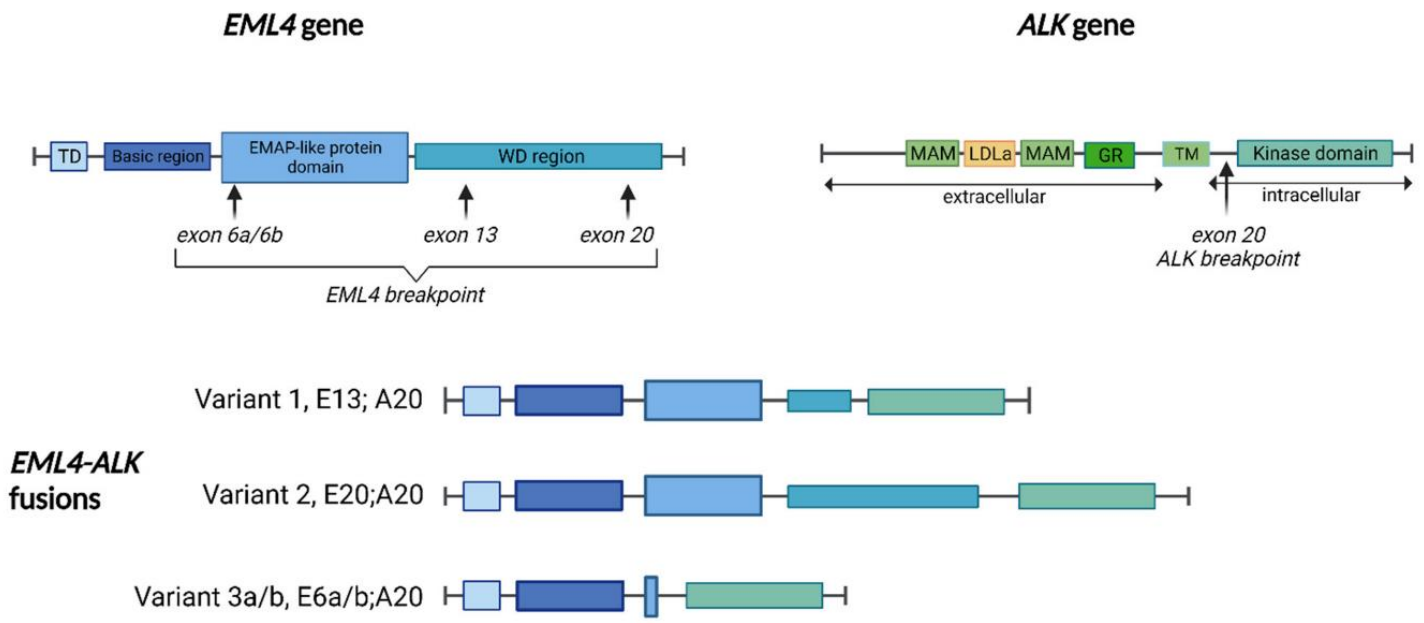
- Re-staging scan in February 2019 (after 2 cycles of salvage therapy) :

  Partial Response with:

  - Decrease in size of mediastinal and subcarinal lymph nodes
  - Decrease in the number of left lower lobe pulmonary micronodules
  - Stable left upper lobe ground-glass nodule
  - No evidence of new lesions in the thorax, abdomen, or pelvis

Clinical Course

- Tissue NGS results:
  - ***ALK***:
    - EML4-ALK fusion (Variant 3a/b);
    - ALK-EML4 rearrangement.



Cognigni V. et al, Cancers 2022

Clinical Course

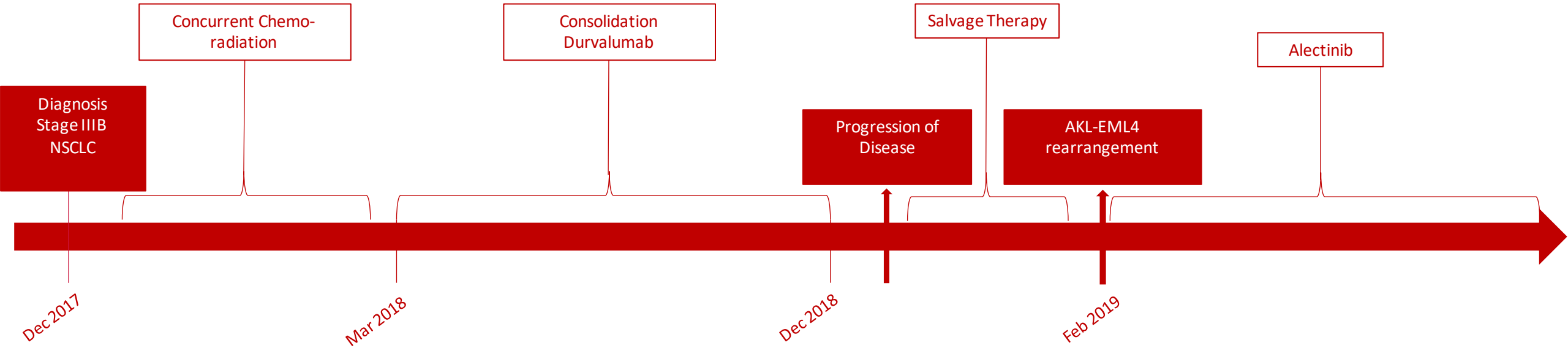
- Partial response to 2 cycles of salvage therapy (carboplatin/ paclitaxel/ atezolizumab/ bevacizumab) and newly found *ALK* rearrangement on NGS.
- Discussed with patient and opted to proceed with targeted therapy.
- Alectinib 600 mg PO BID initiated on 02/20/2019.

Clinical Course

- Since Alectinib has been initiated, disease remained stable (minimal), with no evidence of disease progression.

- Undergoing re-staging scans every 3-4 months.

Summary of Clinical Course



Questions and Discussion

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Discussion

- Whenever possible, wait for NGS results prior to initiating therapy for advanced/recurrent NSCLC.

- If Tx needs to be started prior to NGS results, consider starting chemo alone.

- IO may lead to increased toxicities in patients with some actionable mutations (eg, EGFR and others) when they are started subsequently on targeted therapy.

- In general IO is not effective in patients with +EGFR and +ALK NSCLC. However, one Tx combination showed possible benefit of IO in +ALK or +EGFR NSCLC: **IMpower 150** (carboplatin/ paclitaxel/ atezolizumab/ bevacizumab). *Ironically, We chose it here for different reason though (patient received pemetrexed before).*

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Discussion

- An ongoing debate:

-Should patients with stage III +ALK NSCLC who received concurrent chemoradiation offered consolidation durvalumab.

PS: The PACIFIC trial included patients with ALK rearrangement.

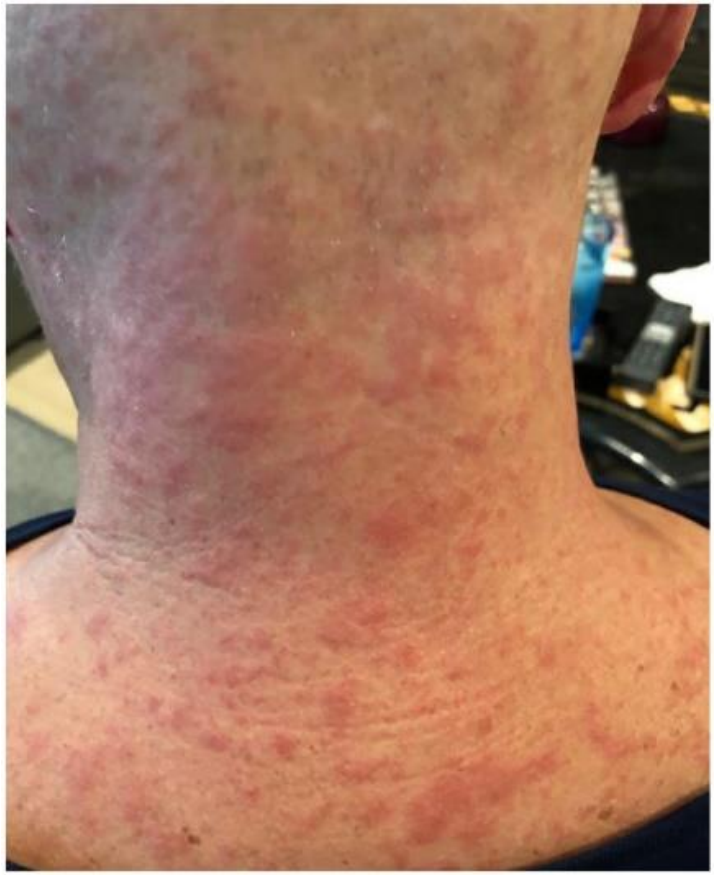
-Would have we offered this patient consolidation durvalumab if we knew she had ALK rearrangement from the beginning ?

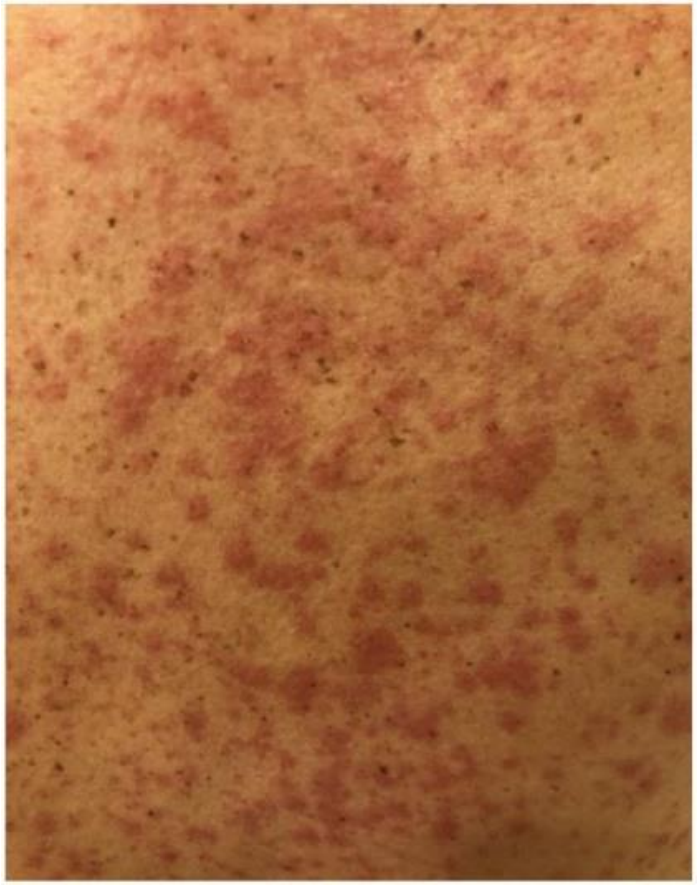
- Similar debate already ongoing regarding +EGFR NSCLC

- Role of targeted therapy in early-stage NSCLC is evolving (ongoing trials)

One more thing…

- 11 days after initiation of Alectinib, she presented with grade 3 maculopapular rash over the neck, back, and face:





Seegobin K, Manochakian R et al., SAGE Open Med Case Rep. 2020

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One more thing…

- Alectinib was held one day after rash's onset
- Treatment with Medrol Dosepak, with resolution of the rash in 6 days
- Alectinib was resumed 8 days after onset, following a *desensitization* protocol:
  - Alectinib 150 mg PO BID for 2 days;
  - Alectinib 300 mg PO BID for 5 days;
  - Alectinib 450 mg PO BID for 8 days;
  - Alectinib 450 mg PO in the AM and 600 mg PO in the PM for 8 days;
  - Alectinib 600 mg PO BID.

Seegobin K, Manochakian R et al., SAGE Open Med Case Rep. 2020

One more thing…

- Skin rash is a known adverse event from alectinib.
- In this case, it is unclear whether prior exposure to IO (last dose of atezolizumab was 27 days prior to initiation of alectinib) may have contributed to the adverse event.
- Immunotherapy-related adverse events after targeted therapy initiation have been reported mostly with other TKIs, such as osimertinib.

Q & A

Wrap-Up & Post-Session Poll Questions

A Few Reminders:

Next ECHO Session: **May 25th @9am EST**

Next **Didactic** Presenter: Dr. Estelamari Rodriguez
Next **Case Presentation**: Dr. Samuel Kareff

Materials and Resources will be made available via the ACS ECHO Website

Faculty: All future case presentations will be shared with you at least 24-hours in advance

Additional Feedback on Today's Session? Tell us in the Post Session Feedback Forum
(URL in chat box)

Questions: Contact korey.hofmann@cancer.org or Leah.Mitchem@cancer.org

THANK YOU!

PLEASE JOIN US AGAIN

THURSDAY, MAY 25TH @9AM EST

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