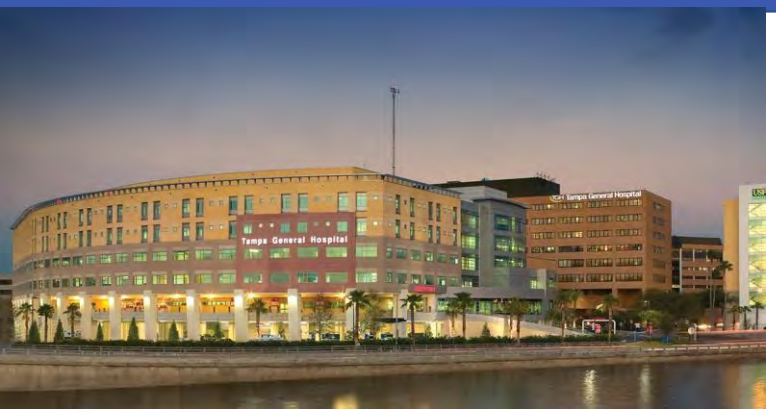


Targeted Therapy in Lung Cancer

(FLASCO May 2024)

Michelle Mintz APRN

Noman Ashraf MD

TGH Cancer Institute

Disclosures

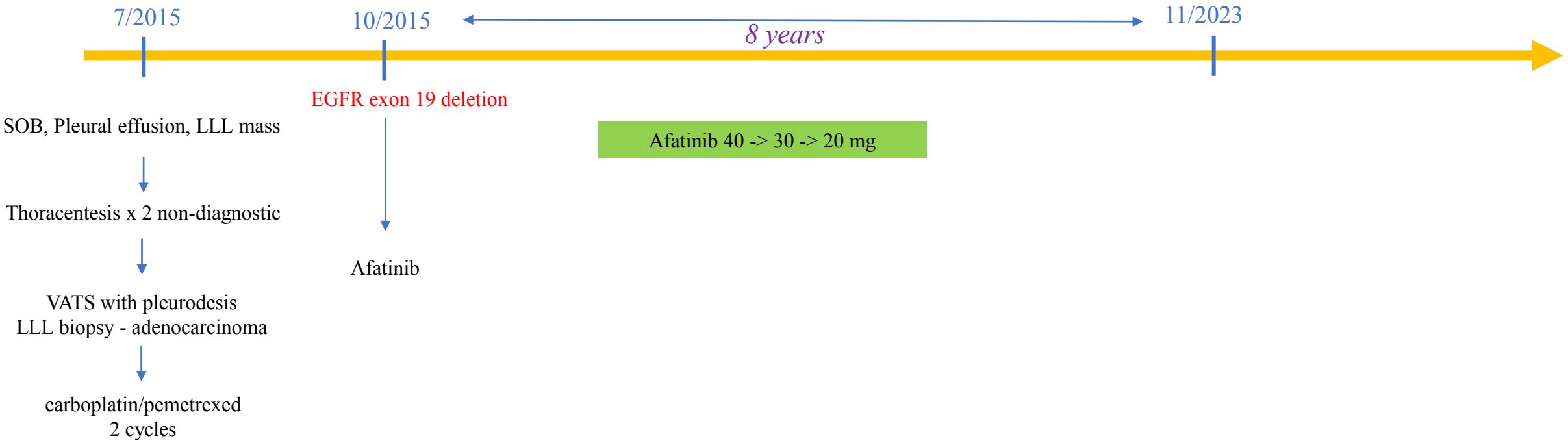
- Noman Ashraf, MD – Advisory Board with Astra Zeneca; relationship ended during the past 24 months

Outline

- Case presentation
- Targeted therapy for non-small cell lung cancer (NSCLC)
  - Advanced disease
  - Localized disease
- Summary

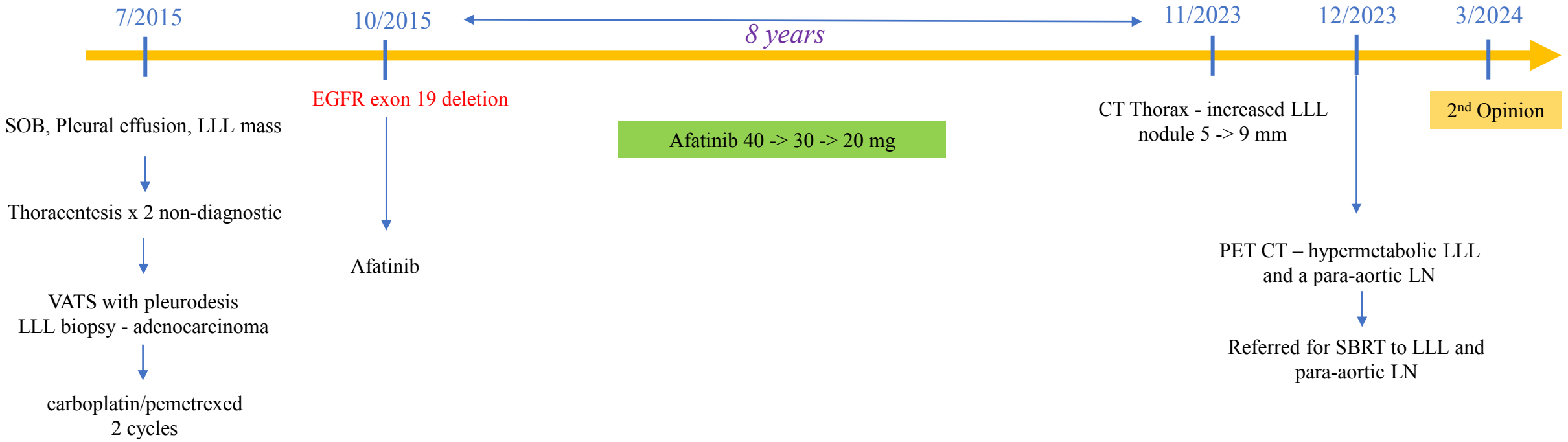
Case

- 68yo Hispanic male – lifetime nonsmoker

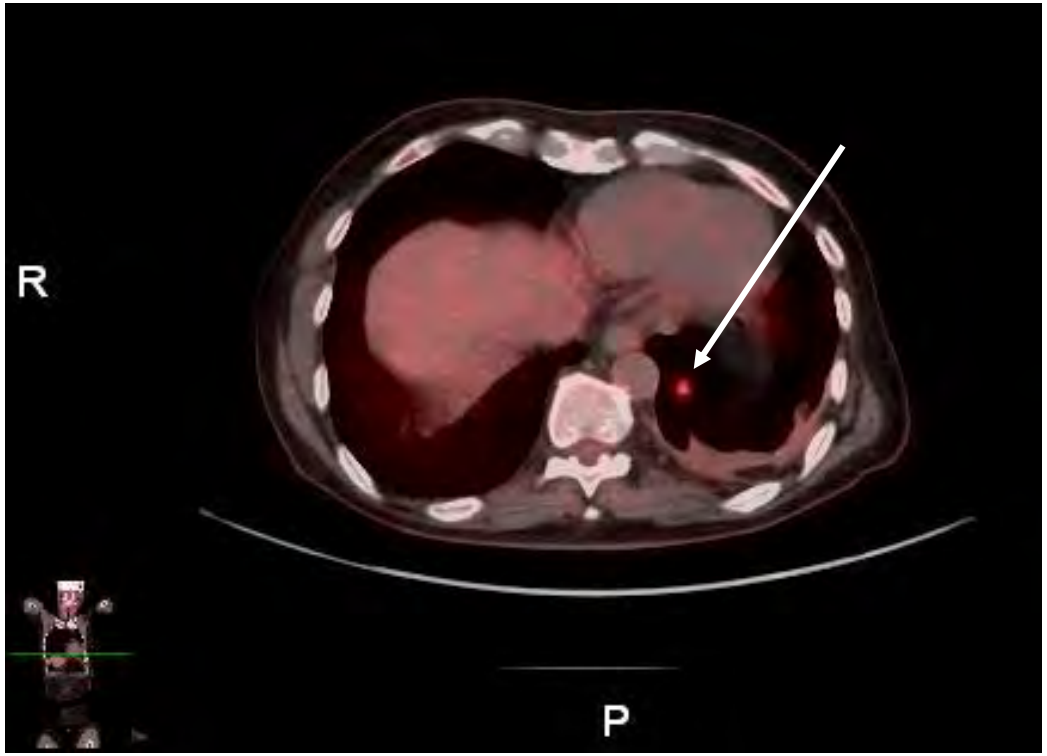


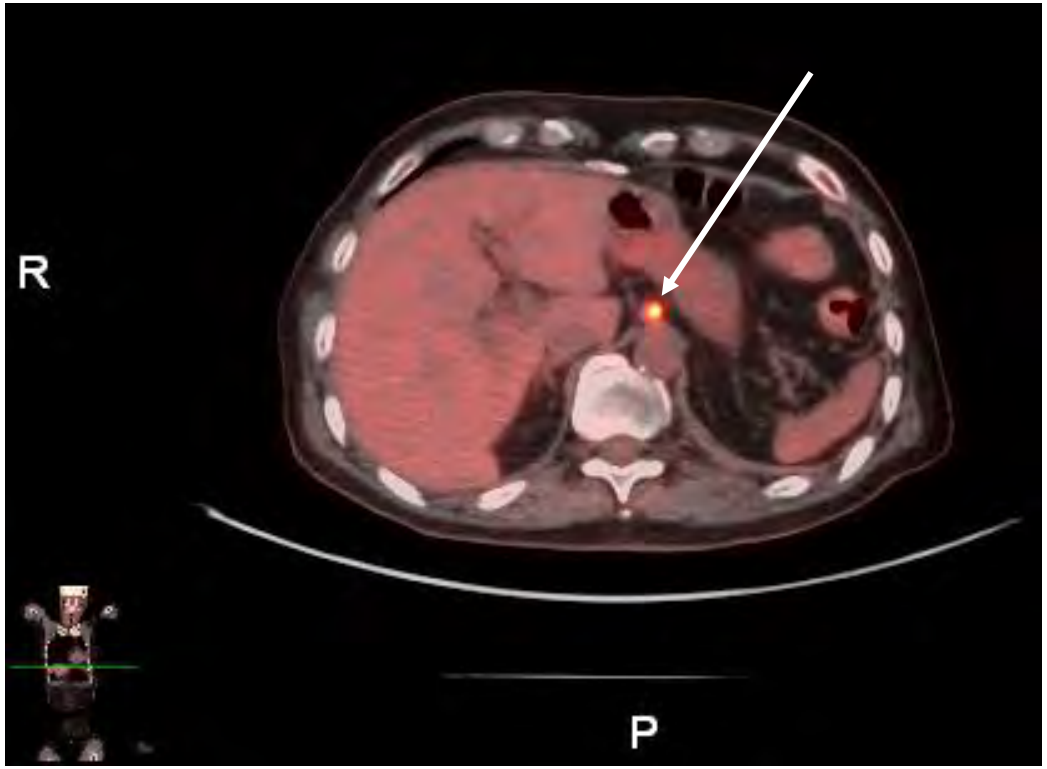
Case - continued

- 68yo Hispanic male – lifetime nonsmoker

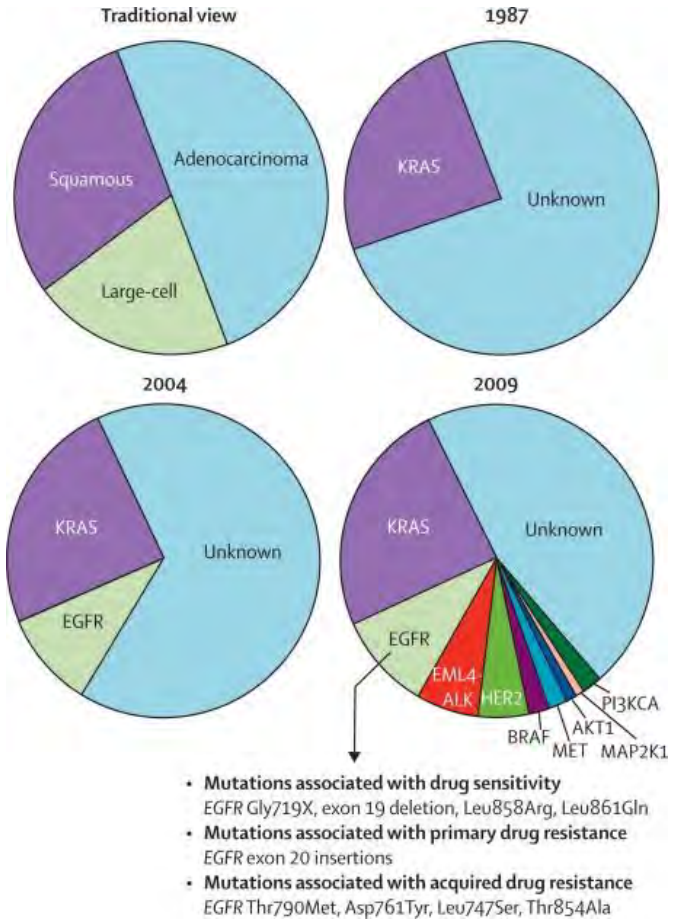


Case - continued





Targeted Therapy for NSCLC – Advanced



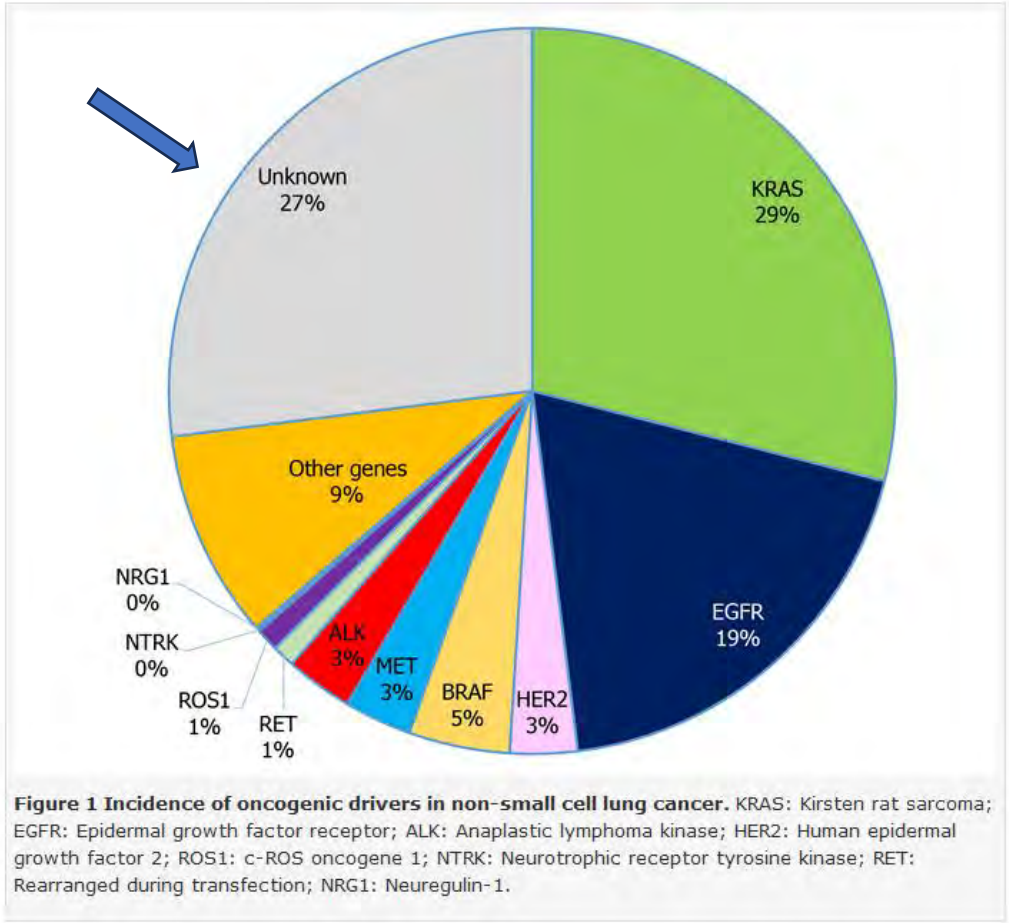


Figure 1 Incidence of oncogenic drivers in non-small cell lung cancer. KRAS: Kirsten rat sarcoma; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; HER2: Human epidermal growth factor 2; ROS1: c-ROS oncogene 1; NTRK: Neurotrophic receptor tyrosine kinase; RET: Rearranged during transfection; NRG1: Neuregulin-1.

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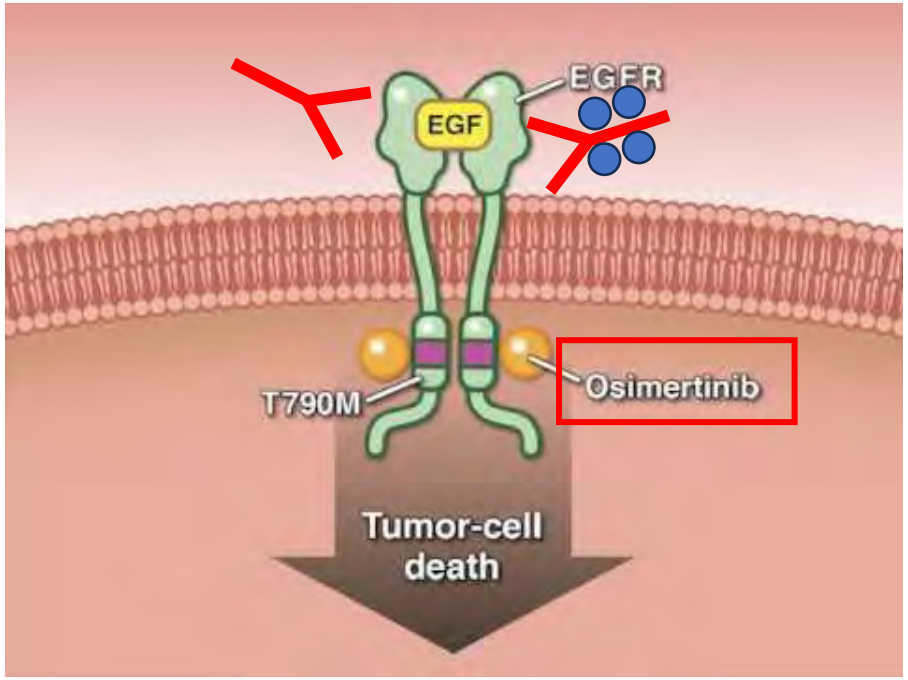
* *Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011 Feb;12(2):175-80.*
* *Chevallier et al. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future . World J Clin Oncol 2021; 12(4): 217-237*

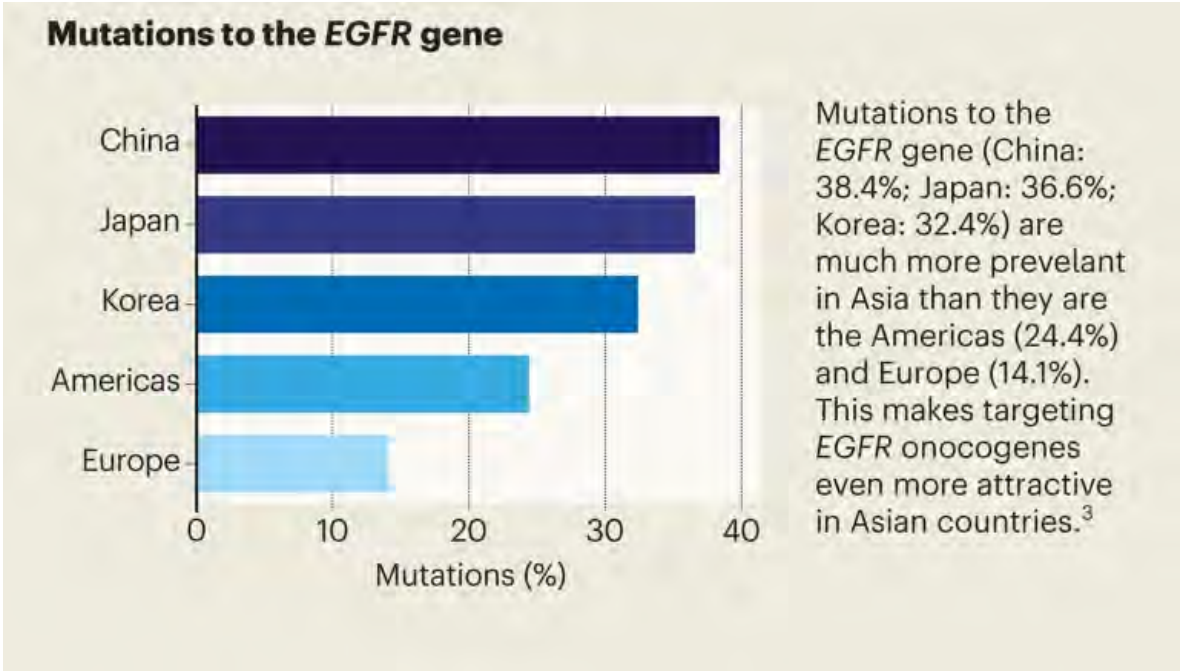
Targeted Therapy

- *"type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread"*
- Targeted therapy
  a) Tyrosine kinase inhibitors
  b) Antibodies
  c) Antibody drug conjugate (ADC)



Targeted Therapy for NSCLC

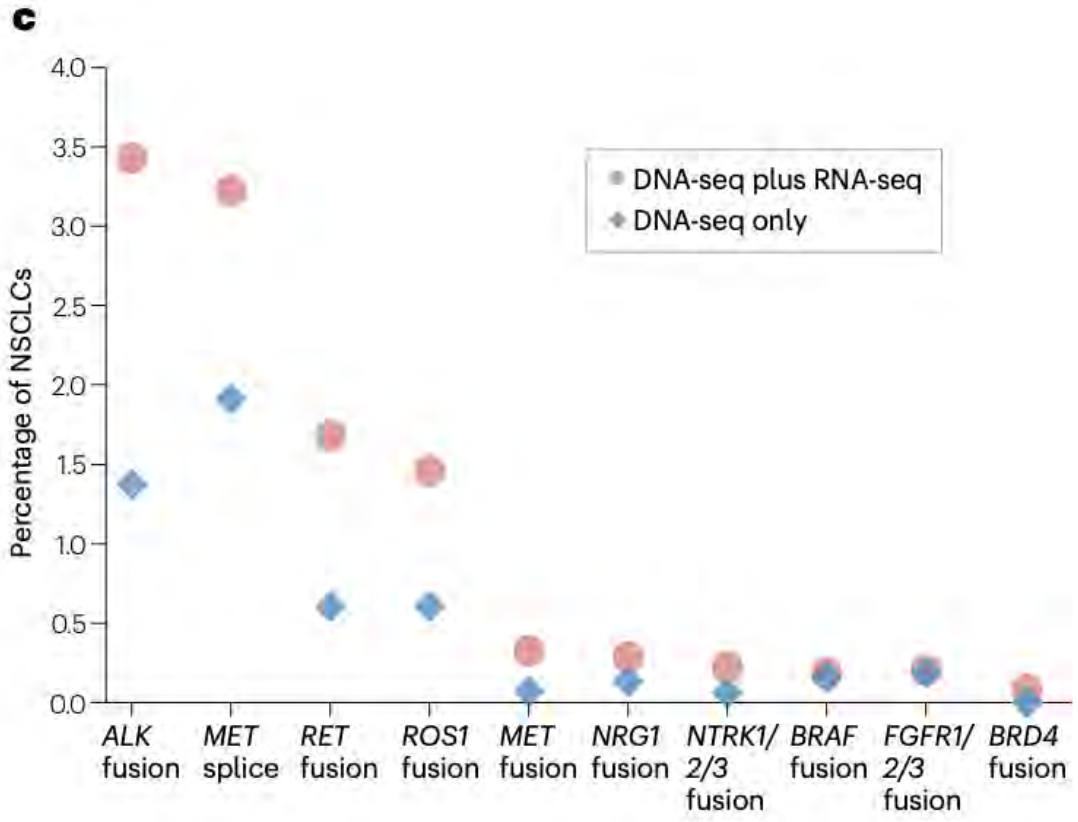
- Misconceptions
  - Non-smokers
  - Asians
  - Females
  - Non-squamous
- Testing
  - IHC
  - FISH
  - PCR
  - NGS
    - Tissue
    - Peripheral blood



* *Chevallier et al. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future . World J Clin Oncol 2021; 12(4): 217-237*

Molecular Testing for NSCLC

- DNA vs. DNA + RNA



* *Nat Rev Clin Oncol. 2023 Apr;20(4):229-249*

Molecular Testing for NSCLC

- US Oncology

MYLUNG Consortium

Test Types	Overall (N = 3,474)	Nonsquamous (n = 2,820)
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

Study Period: April 2018 to March 2020

* *https://doi.org/10.1200/JCO.2021.39.15_suppl.900*

Treatment of NSCLC – Targeted therapy

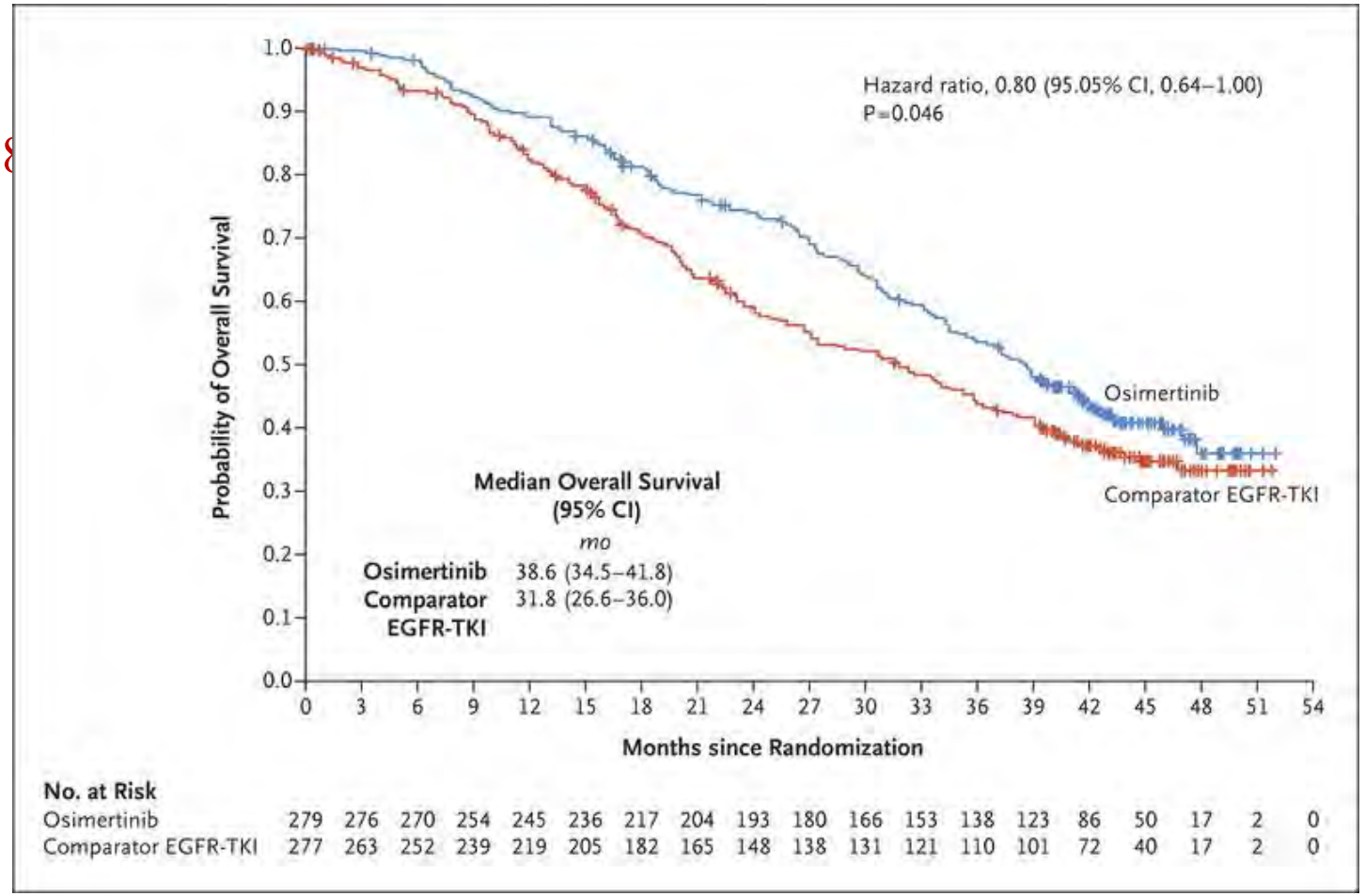
- FDA approved
  - 9 genes
  - 27 drugs

Mutation	Drugs approved by the FDA		
	1st Generation	2nd Generation	3rd Generation
1. EGFR *A. Del 19, L858R*	Erlotinib, Gefitinib	Dacomitinib, Afatinib	Osimertinib
B. Exon 20 insertion	Mobocertinib, Amivantamab		
2. ALK	Crizotinib, Ceritinib	Brigatinib, Alectinib	Lorlatinib
3. ROS1	Crizotinib	Entrectinib	Repotrectinib
4. RET fusion*	Pralsetinib, Selpercatinib		
5. MET exon 14 skipping mutation	Capmatinib, Tepotinib		
6. KRAS G12C	Sotorasib, Adagrasib		
7. BRAF V600E*	Dabrafenib/Trametinib, Encorafenib/Binimetinib		
8. Her2 Mutation	Trastuzumab Dxd		
9. NTRK*	Entrectinib, Larotrectinib		

**Tumor agnostic*

Treatment of Advanced NSCLC - EGFR

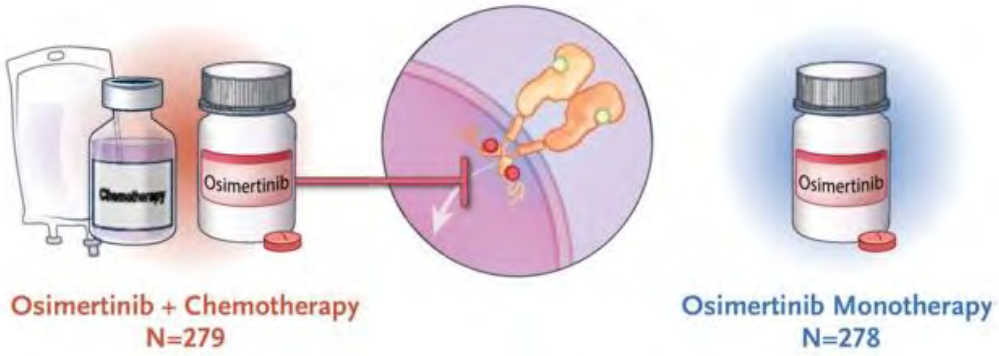
1. EGFR (Exon 19 del, L858
   - First generation TKIs
     a. Erlotinib
     b. Gefitinib
   - Second generation
     a. Afatinib
     b. Dacomitinib
   - Third generation
     a. Osimertinib

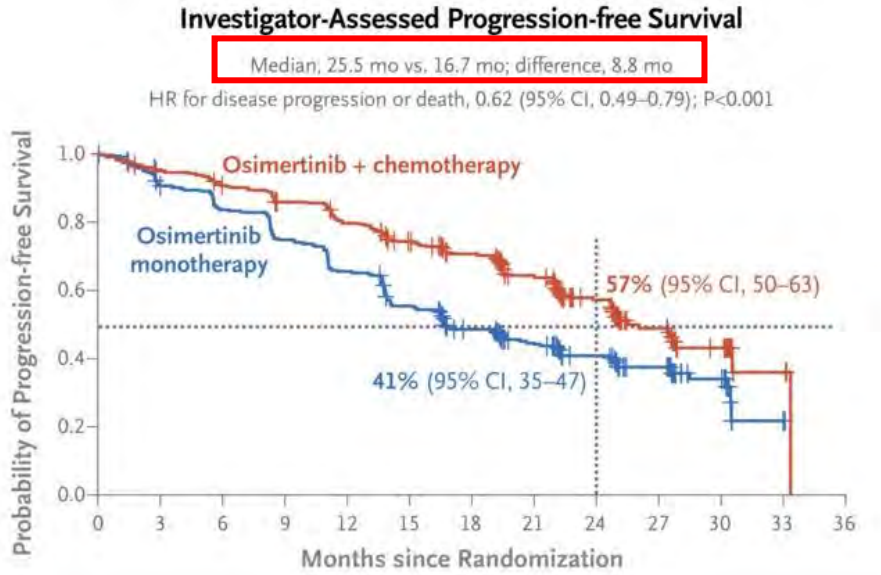


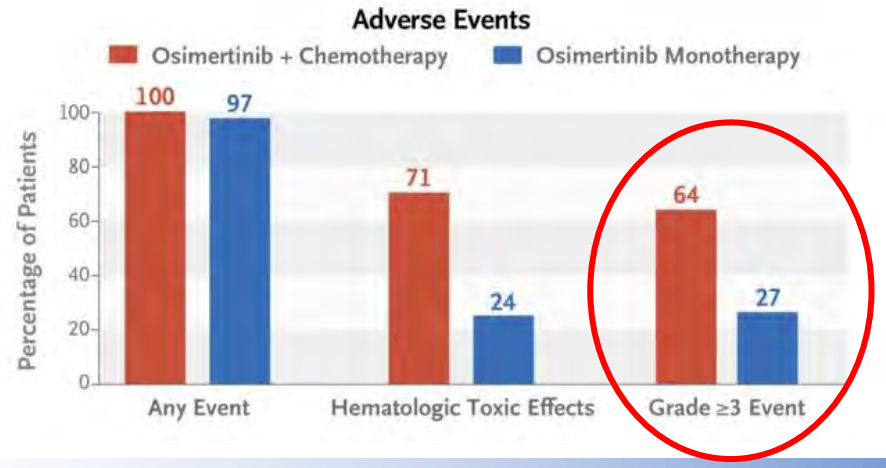
*N Engl J Med 2018; 378:113-125
*N Engl J Med 2020; 382:41-50

EGFR – Updates

1. FLAURA 2







N Engl J Med 2023;389:1935-1948

EGFR – Updates

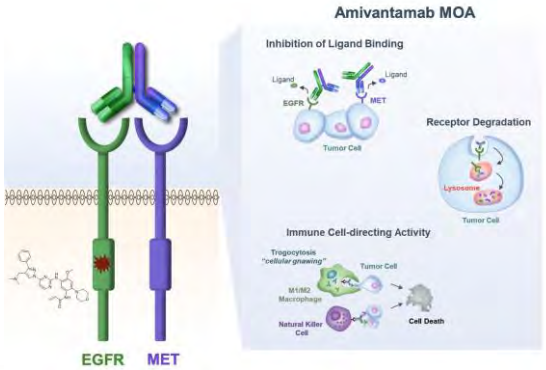
1. FLAURA 2

Feb 19, 2024

*N Engl J Med 2023;389:1935-1948

EGFR – Recent updates

2. MARIPOSA



Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- Amivantamab + lazertinib vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

**Presented at Madrid, ESMO 2023*

EGFR – MARIPOSA

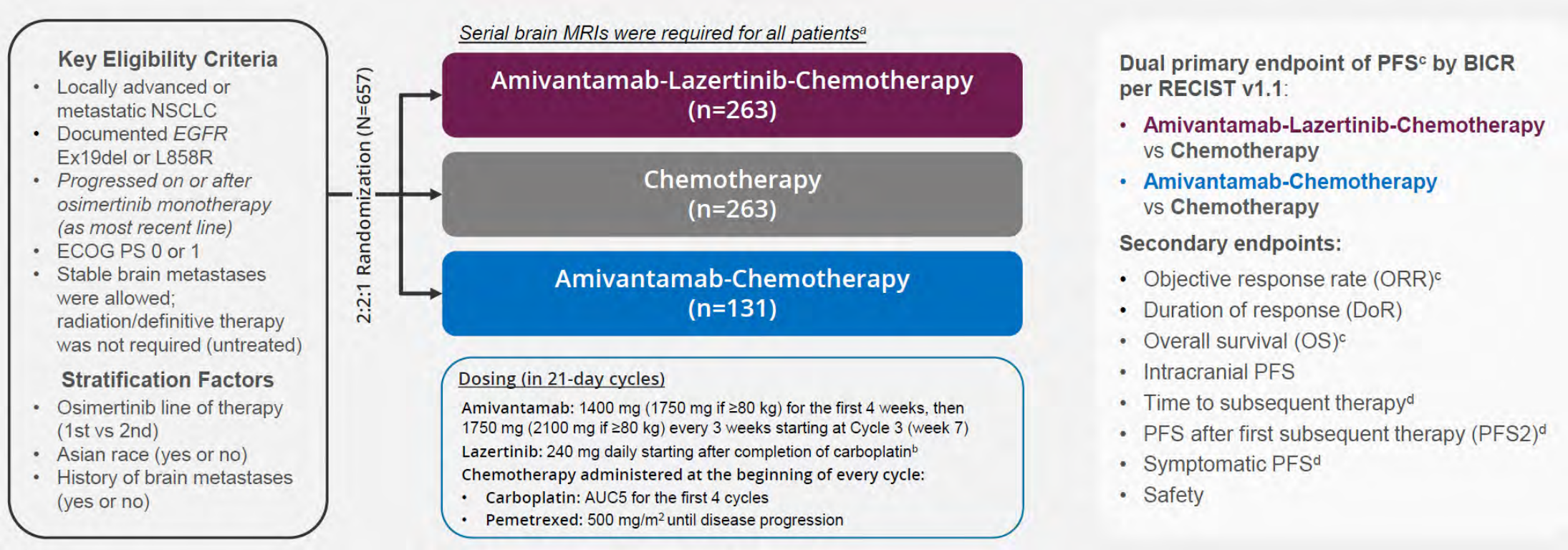
TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

*Presented at Madrid, ESMO 2023

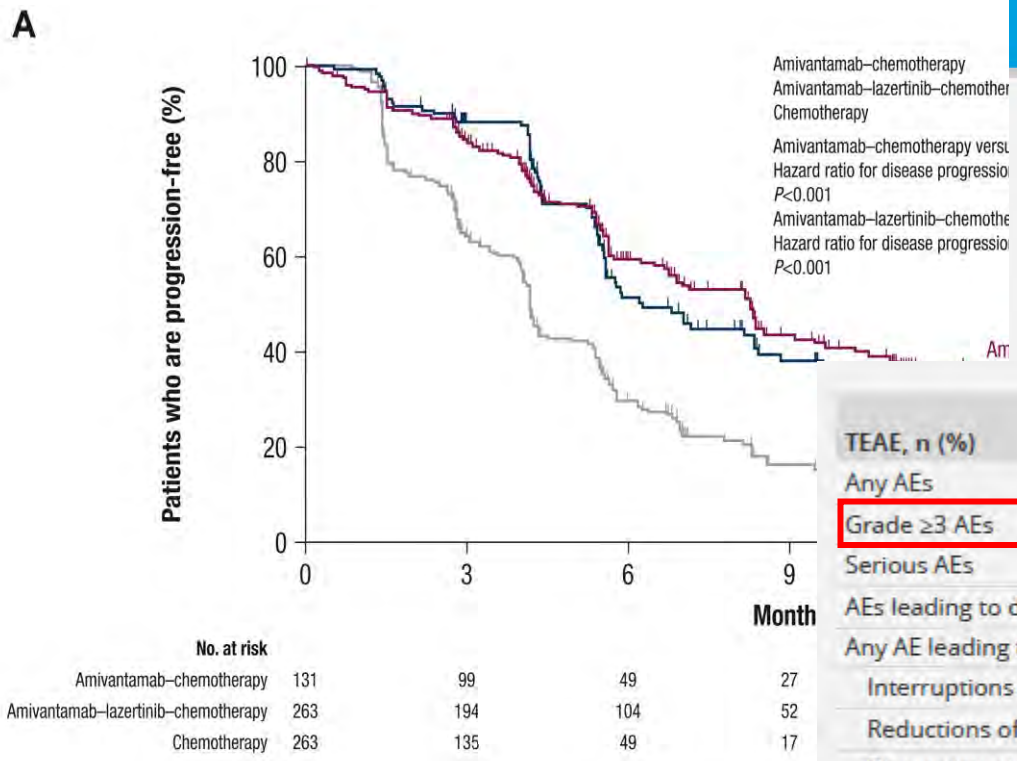
EGFR – Beyond first line

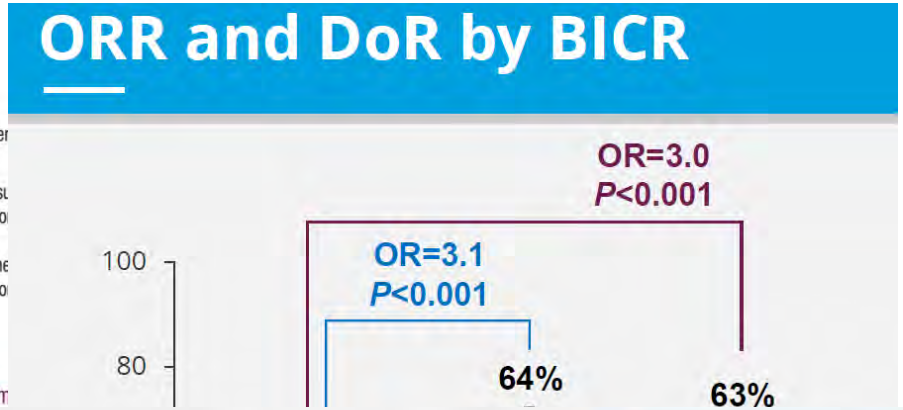
1. MARIPOSA-2



*Annals of Oncology 2024 3577-90DOI: (10.1016/j.annonc.2023.10.117)

EGFR – MARIPOSA-2





TEAE, n (%)	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=130)	Amivantamab-Lazertinib-Chemotherapy[a] (n=263)
Any AEs	227 (93)	130 (100)	263 (100)
Grade ≥3 AEs	117 (48)	94 (72)	242 (92)
Serious AEs	49 (20)	42 (32)	137 (52)
AEs leading to death	3 (1)	3 (2)	14 (5)
Any AE leading to treatment:			
Interruptions of any agent	81 (33)	84 (65)	202 (77)
Reductions of any agent	37 (15)	53 (41)	171 (65)
Discontinuations of any agent	9 (4)	24 (18)	90 (34)
Discontinuations of all agents due to AE	10 (4)	14 (11)	38 (14)

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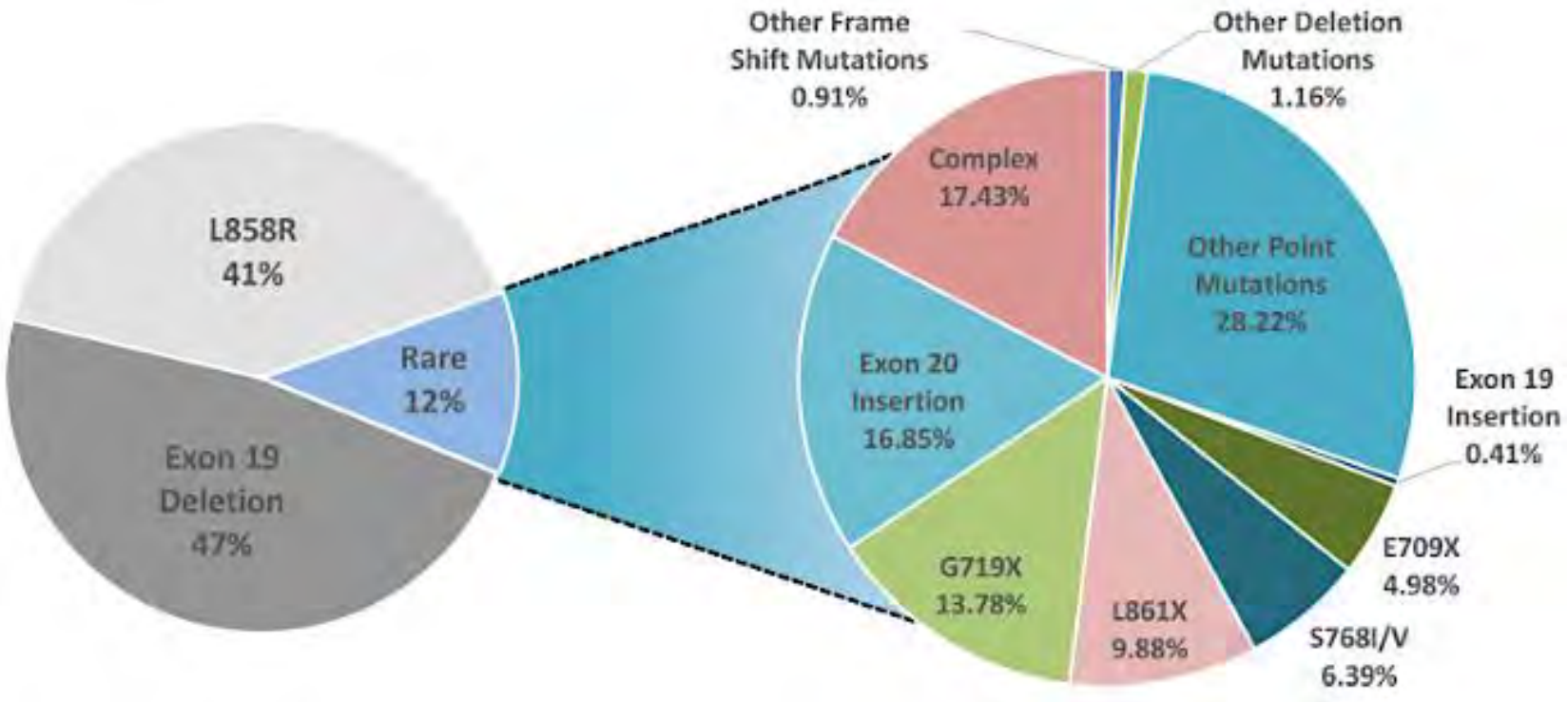
*Annals of Oncology 2024 3577-90DOI: (10.1016/j.annonc.2023.10.117)

Treatment of NSCLC – EGFR

1. EGFR (Exon 20 insertions)
   - *Only in second-line*
     a. Mobocertinib
     b. Amivantamab



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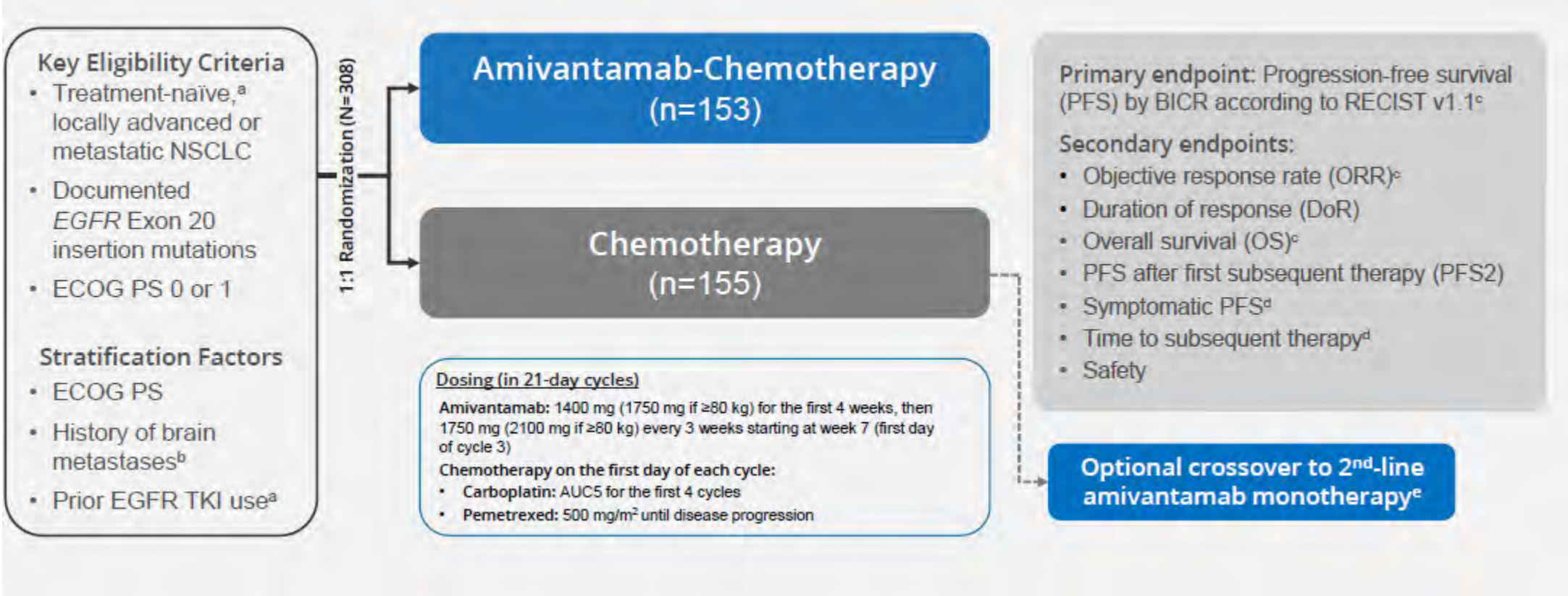
*Zhou et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial. JAMA Oncol. 2021 Dec 1;7(12):e214761.
*Park et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021 Oct 20;39(30):3391-3402

Treatment of NSCLC – EGFR Exon 20 insertion
PAPILLON Trial



N Engl J Med. 2023 Nov 30;389(22):2039-2051.

Treatment of NSCLC – EGFR Exon 20 insertion

PAPILLON Trial

*N Engl J Med. 2023 Nov 30;389(22):2039-2051.

Treatment of NSCLC – Targeted therapy

2. ALK rearrangements

- First generation TKIs
  a. Crizotinib
  b. Ceritinib

- Second generation
  a. Alectinib
  b. Brigatinib
  c. Ensartinib

- Third generation
  a. Lorlatinib

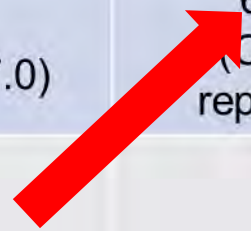
	Most frequent serious adverse events reported
Crizotinib	Dyspnoea, pulmonary embolism
Ceritinib	Pneumonia, pleural effusion, vomiting, nausea, dyspnoea, hyperglycaemia, increased aspartate aminotransferase, lung infection, pericardial effusion
Brigatinib	Pneumonia, interstitial lung disease/pneumonitis, pyrexia, dyspnoea, pulmonary embolism, asthenia
Alectinib	Pneumonia, renal impairment (reported in ≥2% patients)

Figure 3: Efficacy and safety of anaplastic lymphoma kinase inhibitors in the first-line setting.[30-35,40-43]
Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.
CI: confidence interval; HR: hazard ratio; IRC: Independent Review Committee; NR: not reached.

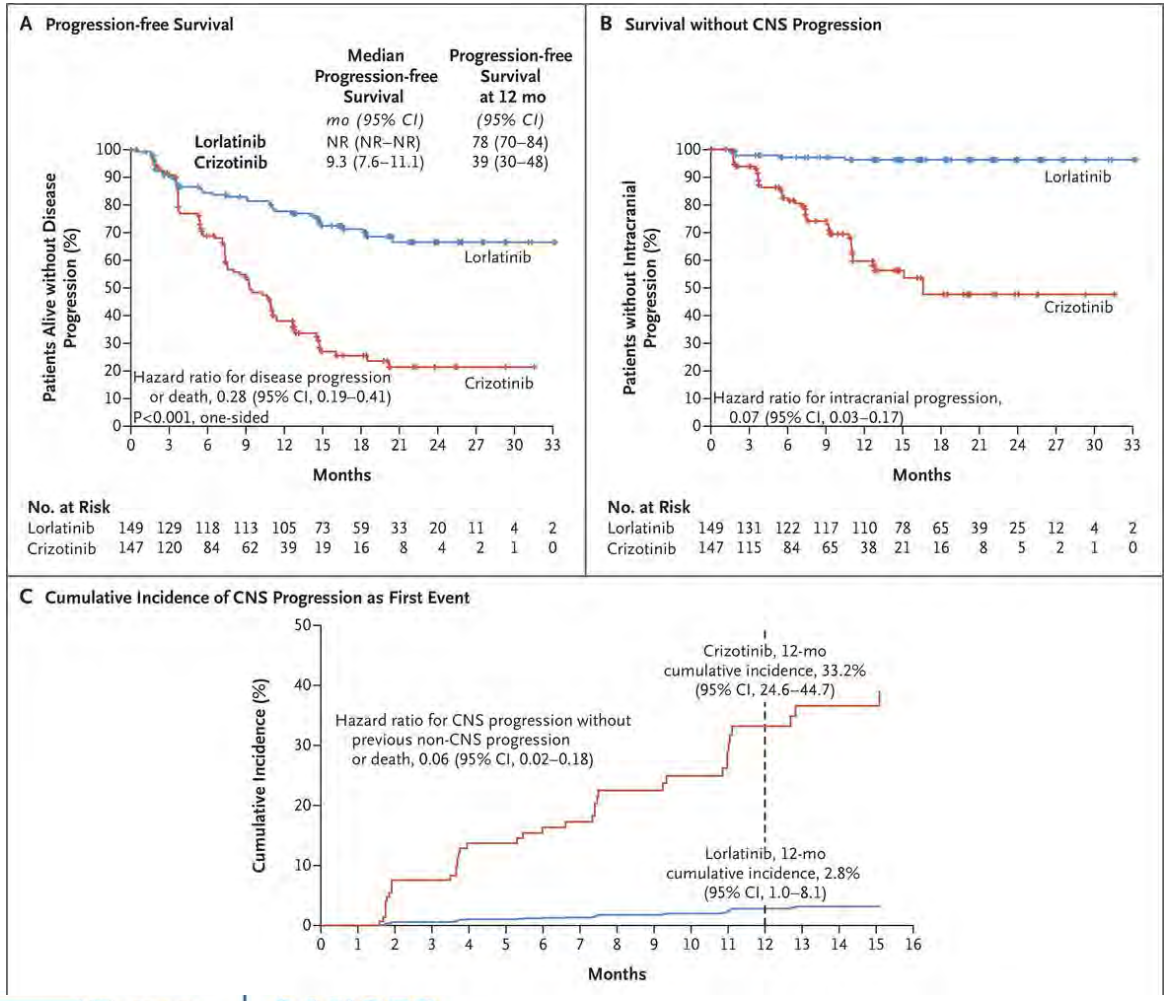
EMJ Oncol. 2020;8[1]:33-42.

Treatment of NSCLC – ALK

Efficacy Data	ALEX[1]		ALTA-1L[2]		CROWN[3]	
	Alectinib (n = 152)	Crizotinib (n = 151)	Brigatinib (n = 137)	Crizotinib (n = 138)	Lorlatinib (n = 147)	Crizotinib (n = 149)
Median PFS, months	34.8	10.9	24.0	11.1	Not reached	9.3
HR (95% CI)	0.47 (0.32–0.58)		0.49 (0.35–0.66)		0.27 (0.18–0.39)	
PFS rate at 36 months, % (95% CI)	46.4 (CI not reported)	13.5 (CI not reported)	43.0 (34.0–51.0)	19.0 (12.0–27.0)	63.5 (CI not reported)	18.9 (CI not reported)
Median duration of follow-up, months	37.8		40.4		36.7	



Treatment of NSCLC – ALK - Lorlatinib



Updated analysis of CROWN with approximately 3 years of follow-up

- **3-year PFS rate with lorlatinib: 63.5%**

*Lancet Respir Med. 2023 Apr;11(4):354-366

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Treatment of NSCLC – Targeted therapy

3. RET fusion
   - Selpercatinib
   - Pralsetinib

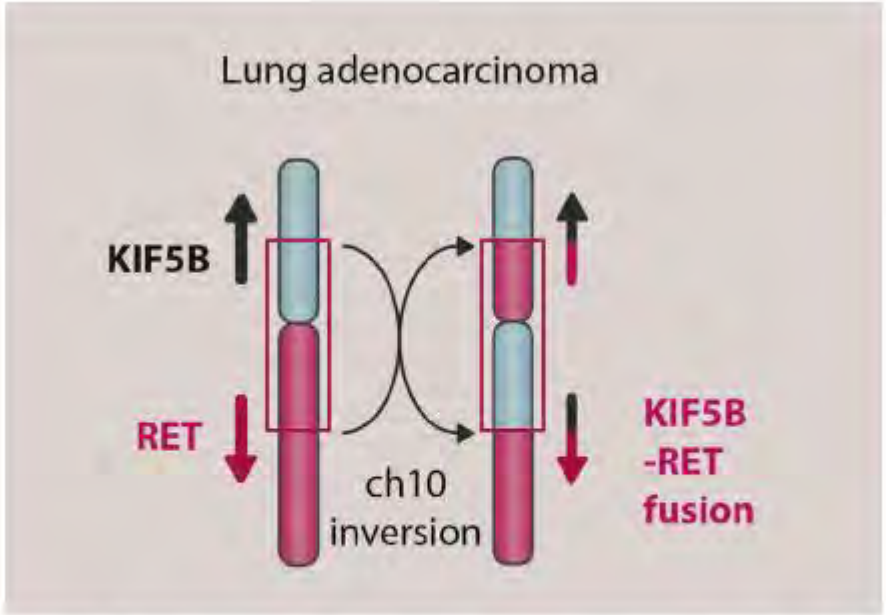


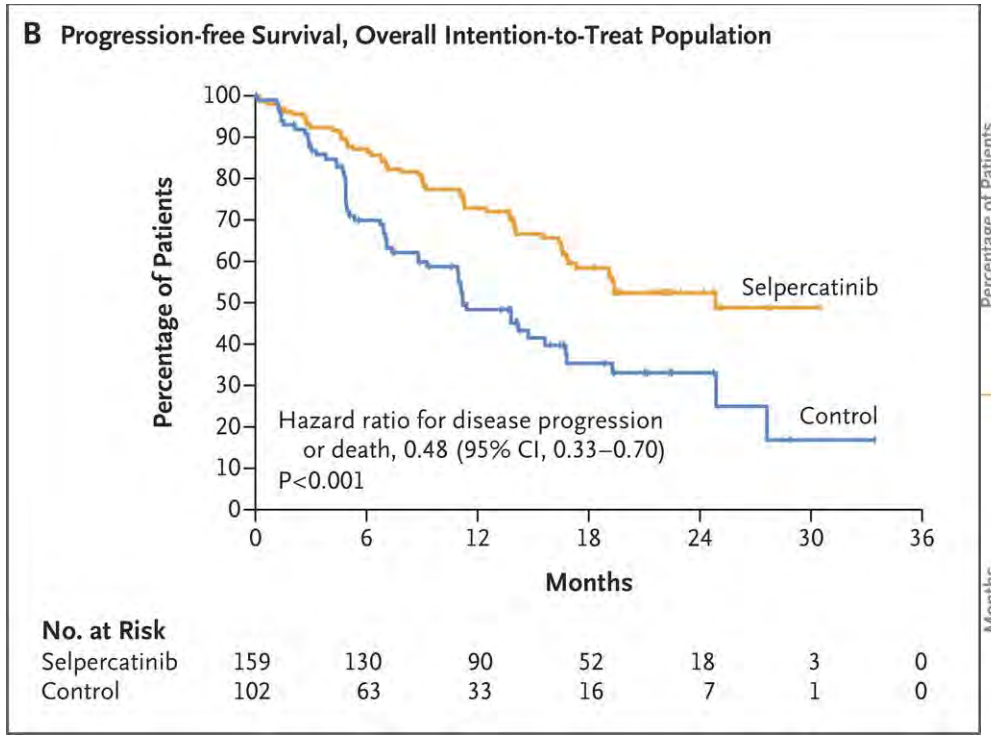
Figure 3. Pericentric inversion chromosome 10 (kinesin family member 5B gene [*KIF5B*]- rearranged during transfection proto-oncogene gene [*RET*]) in lung adenocarcinoma.

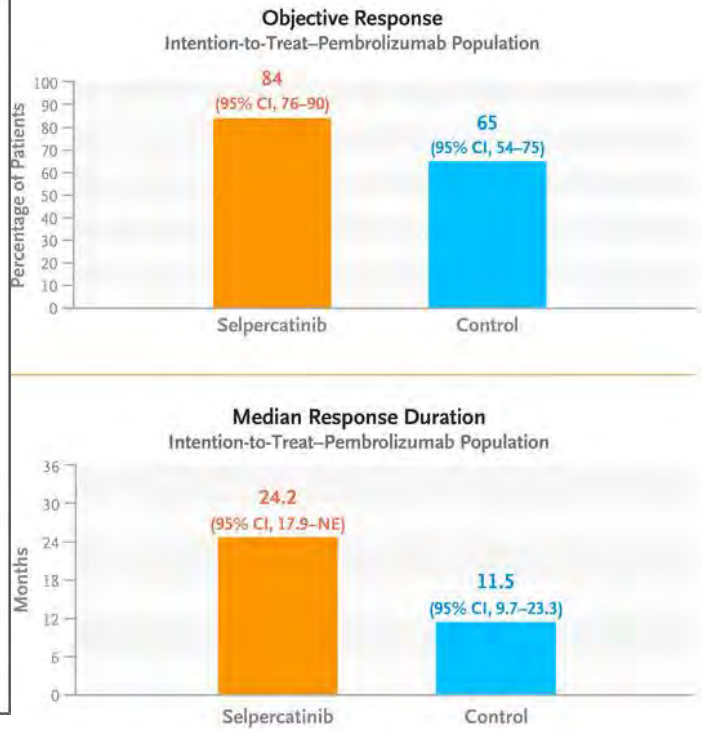
* *J Thorac Oncol. 2018 Jan;13(1):27-45.*

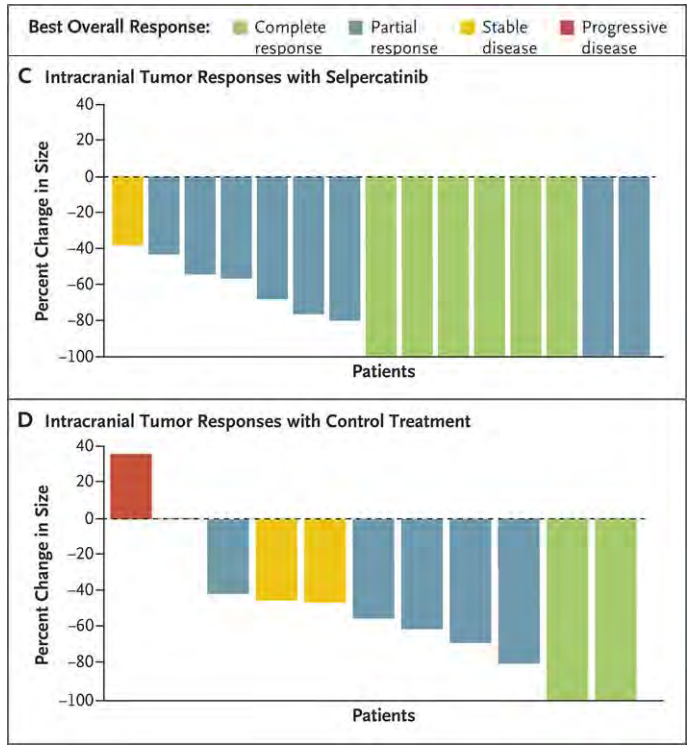
Treatment of NSCLC – RET fusion

LIBRETTO-431 Trial

Selpercatinib





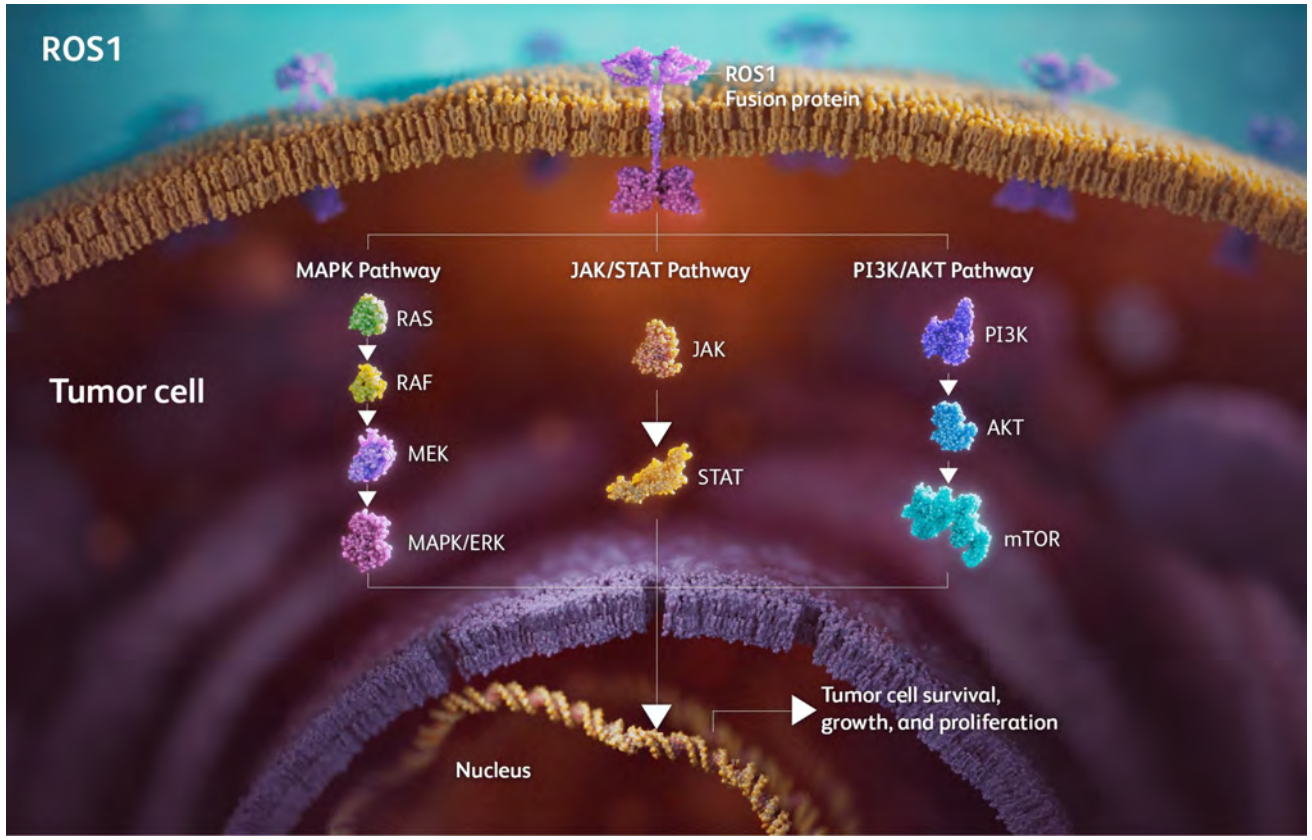


* *N Engl J Med. 2023 Nov 16;389(20):1839-1850*

Treatment of NSCLC – Targeted therapy

4. ROS1
    - Crizotinib
    - Entrectinib

- Second generation
    - Repotrectinib



**www.fda.gov – accessed 3/29/2024, BMS Science*

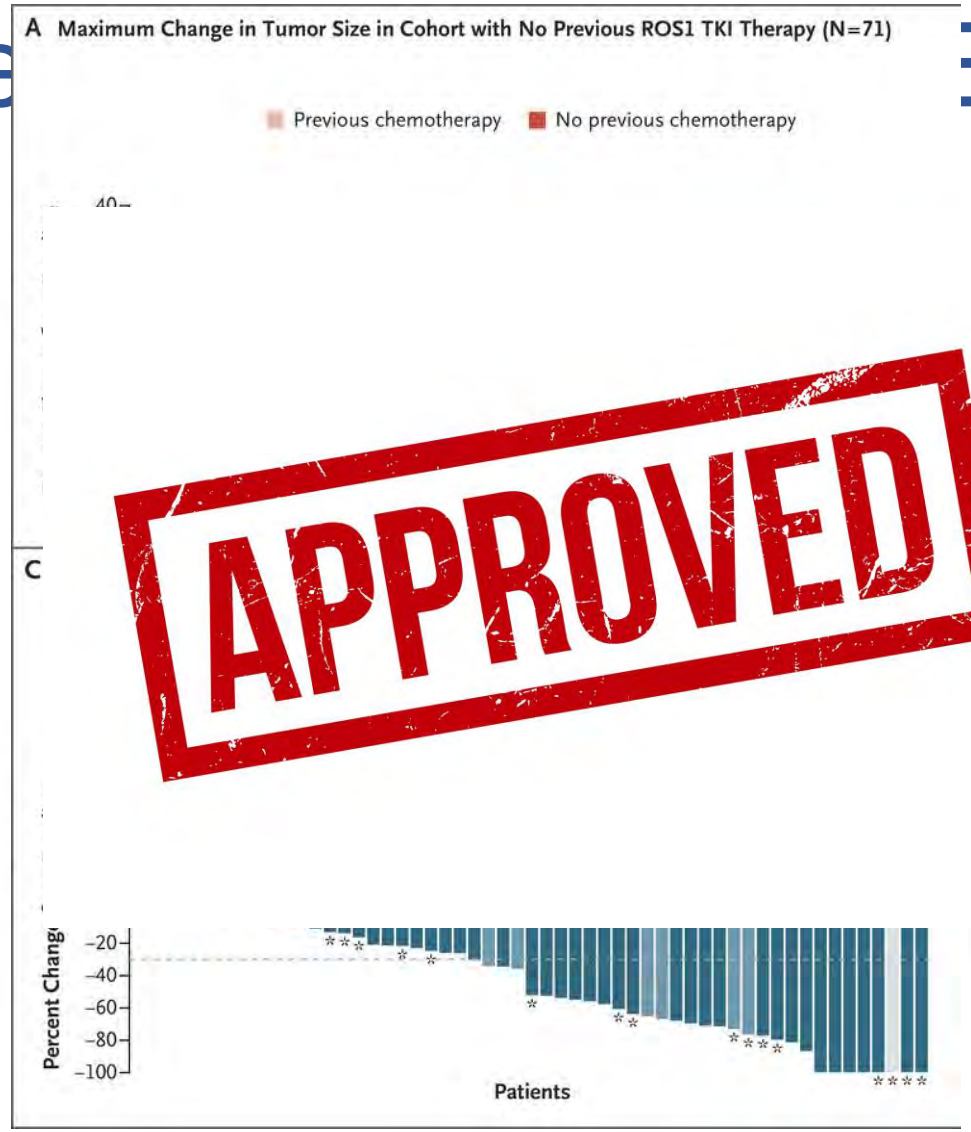
Treatme :T fusion

TRIDENT-1

Repotrectinib

103 + 416

Nov 15, 2023



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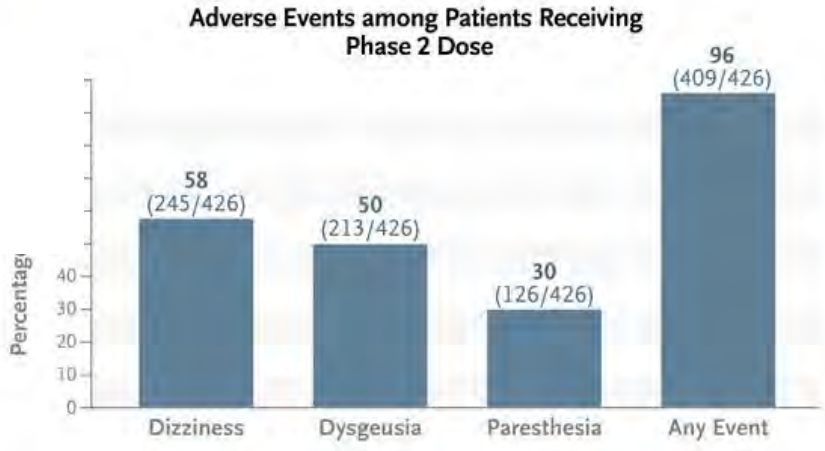

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* *N Engl J Med. 2024 Jan 11;390(2):118-131*

Treatment of NSCLC – Targeted therapy

5. BRAF V600E
   - Dabrafenib/Trametinib
   - Encorafenib/Binimetinib

6. MET exon14 skipping
   - Capmatinib
   - Tepotinib

7. NTRK 1/2/3 fusion
   - Larotrectinib
   - Entrectinib

8. Her2 mutations*
   - Fam-Trastuzumab deruxtecan

9. KRAS G12C*
   - Sotorasib
   - Adagrasib

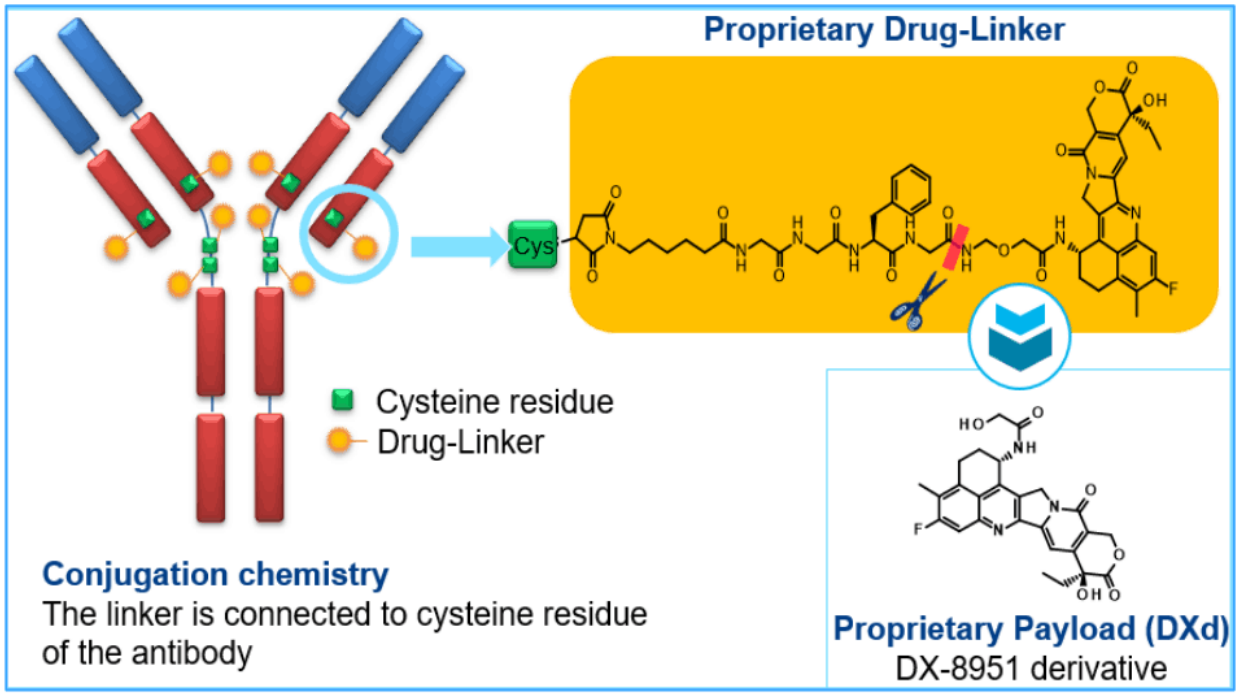
* Second-line

*www.fda.gov – accessed 11/29/22

Treatment of NSCLC – Her2 Mutations

8. Her2 Mutations

- Trastuzumab deruxtecan



*Janne P, WCLC 2023, Abstract MA13.20

Treatment of NSCLC – Her2 Mutations

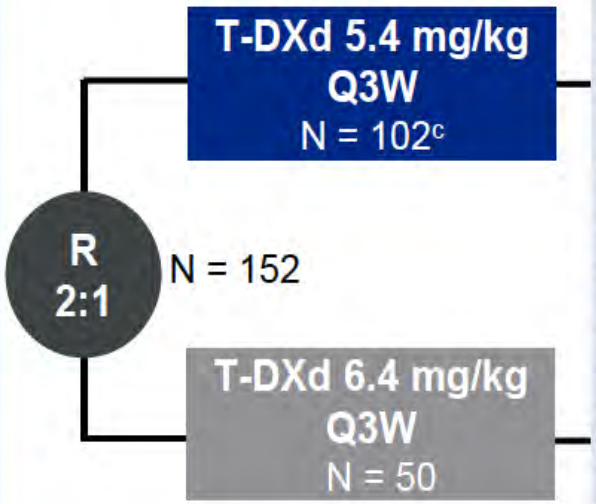
8. Her2 Mutations

- Trastuzumab deruxtecan

DESTINY-Lung02:
Study Design

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment



Primary Endpoint
- Confirmed ORR by BICR

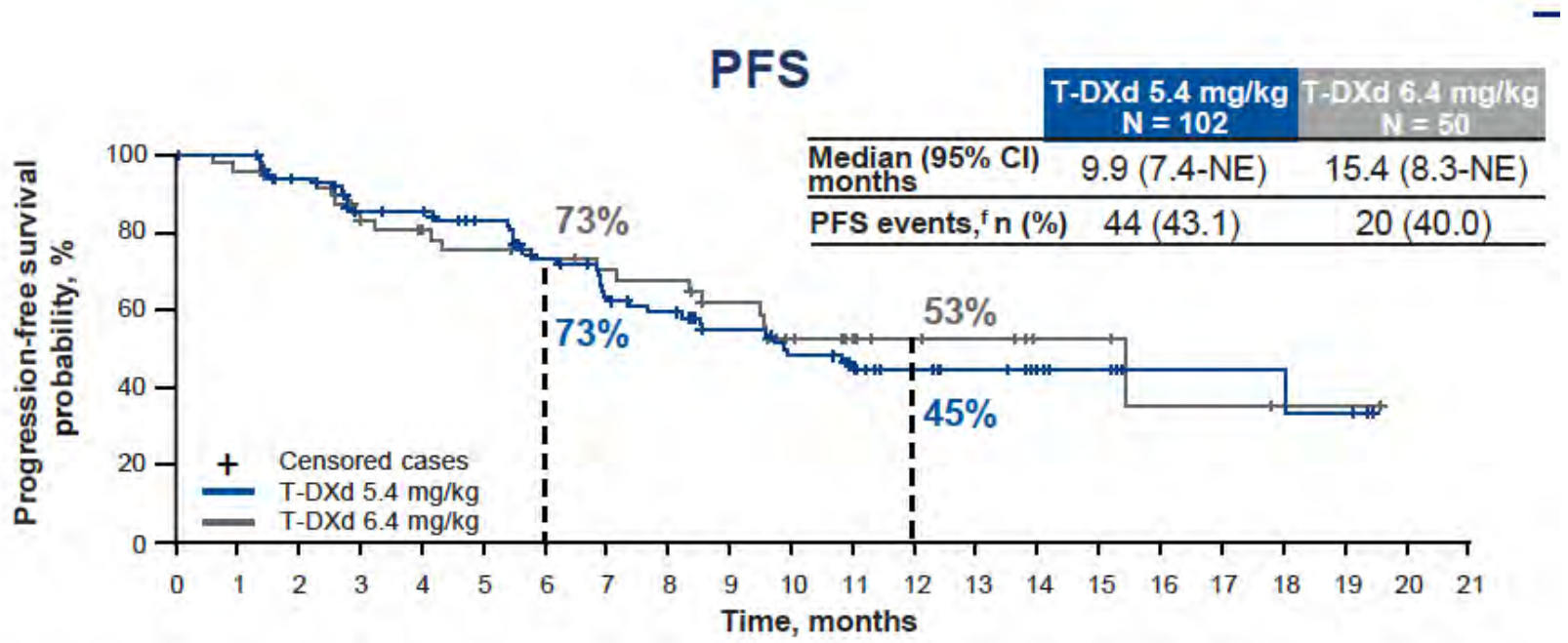
Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff:
23 December 2022

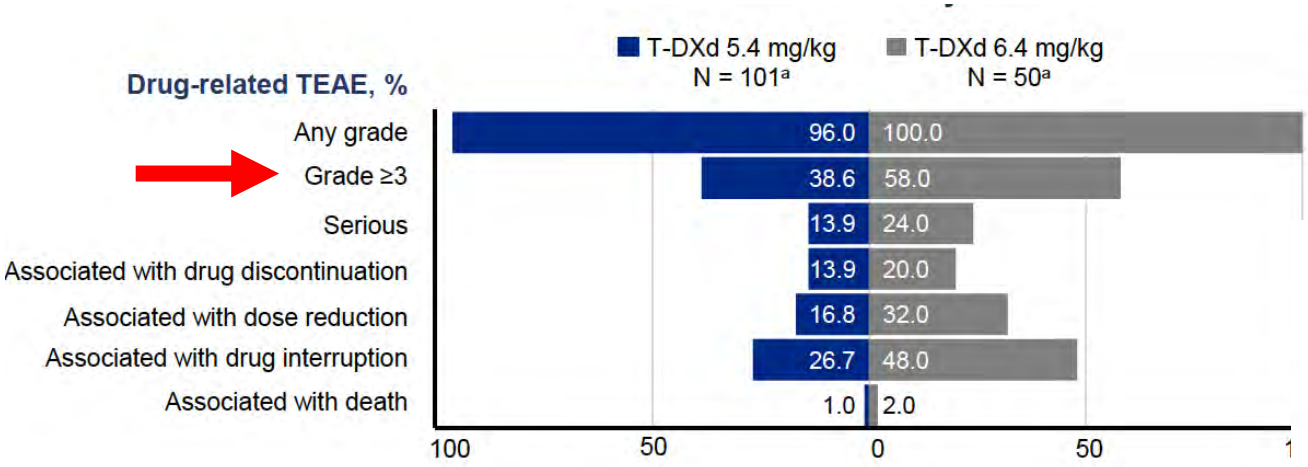
**Janne P, WCLC 2023, Abstract MA13.20*

Treatment of NSCLC – Her2 Mutations



*Janne P, WCLC 2023, Abstract MA13.20

Treatment of NSCLC – DESTINY Lung02



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

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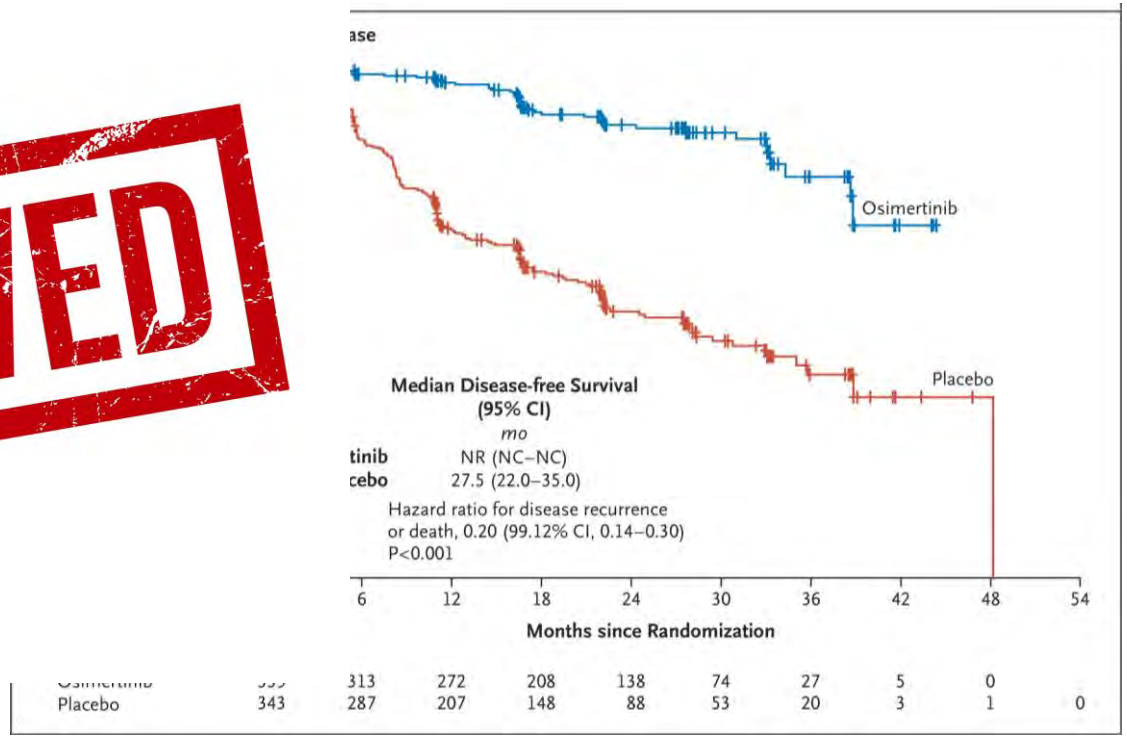
**Janne P, WCLC 2023, Abstract MA13.20*

Treatment of NSCLC – Localized - EGFR

1. EGFR muta
   - Adjuvant O
     - EGFR mu
     - Resected
     - Chemothe

APPROVED



December 18, 2020

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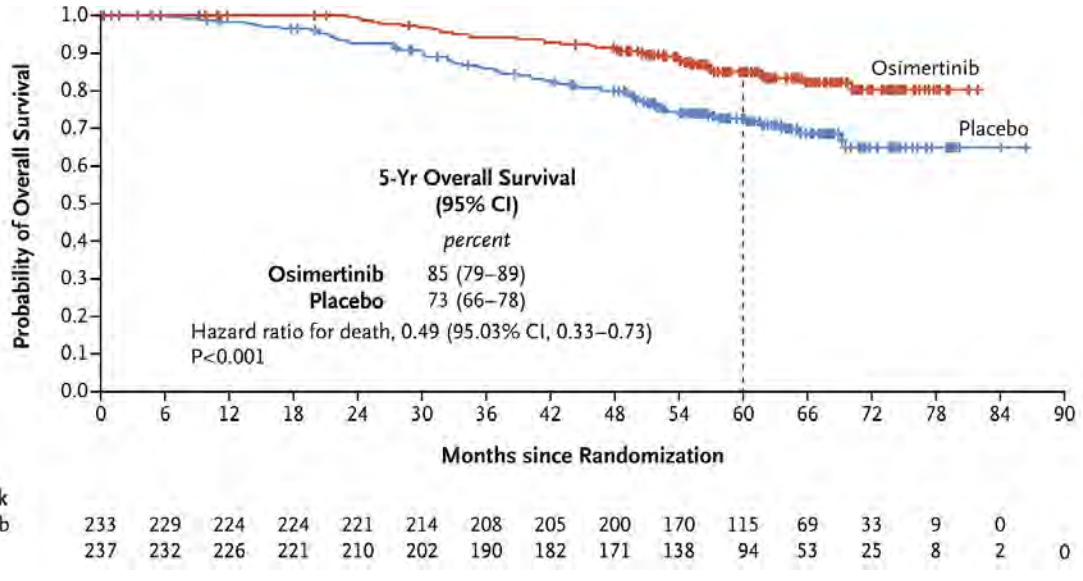
** Wu et l; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723.*

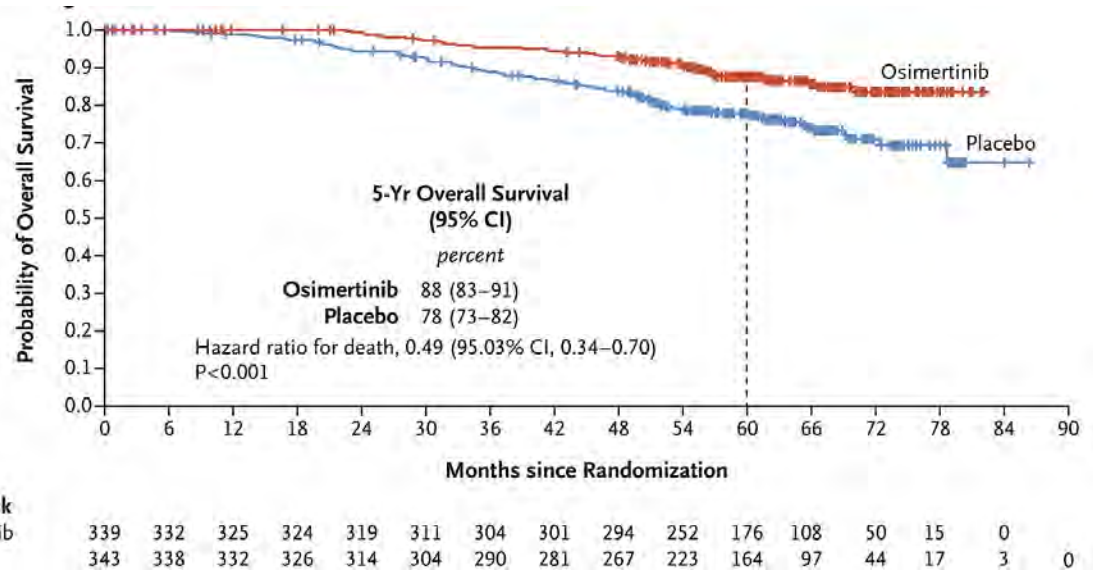
Treatment of NSCLC – ADAURA Updates

Stage II-IIIA (primary endpoint)
OS HR 0.49 (95.03%% CI, 0.33-.73)
P<.001



No. at Risk															
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

Stage IB-IIIA (overall population)
HR 0.49 (95.03% CI, 0.34-.70)
P<.001



No. at Risk															
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

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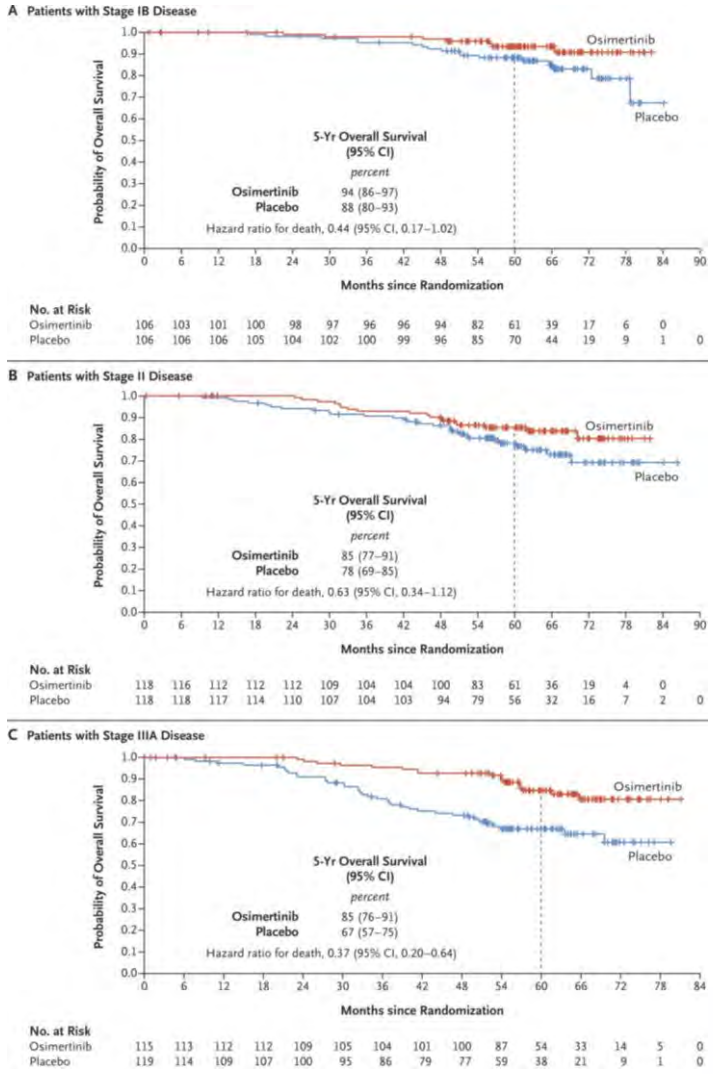
*Tsuboi M et al. N Engl J Med 2023;389:137-147

Treatment of NSCLC – ADAURA Updates



Stage IB
HR 0.44 (95% CI, 0.17-1.02)

Stage II
HR 0.63 (95% CI, 0.34-1.12)

Stage IIIA
HR 0.37 (95% CI, 0.20-.64)

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*Tsuboi M et al. N Engl J Med 2023;389:137-147

Treatment of NSCLC – Localized - ALK

2. ALK

- Adjuvant Alectinib *(ALINA)*

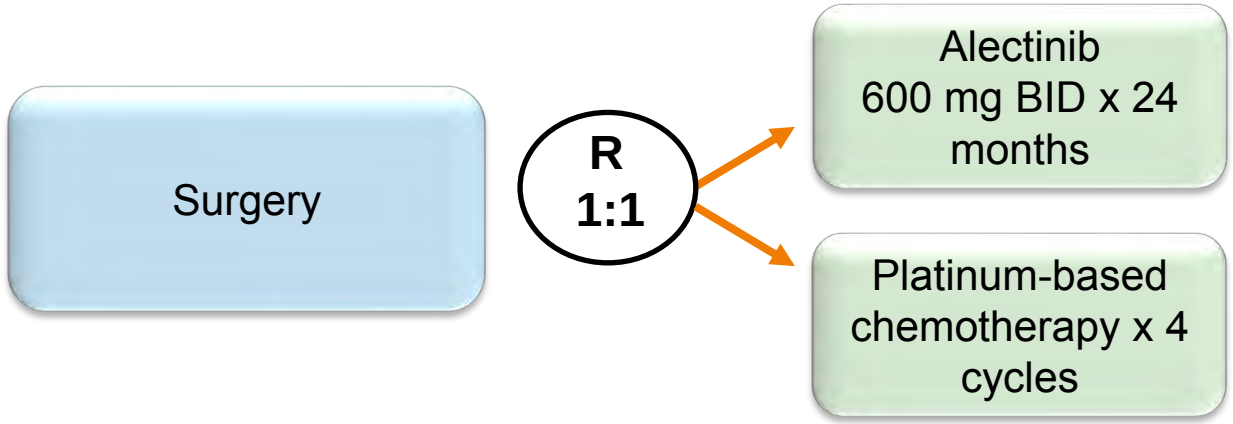
N=257

Key eligibility

- Stage IB-IIIA (>4cm)
- ALK fusion
- Complete resection with negative margins

Stratification:

- Stage (IB vs II vs IIIA)
- race (Asian vs non-Asian)



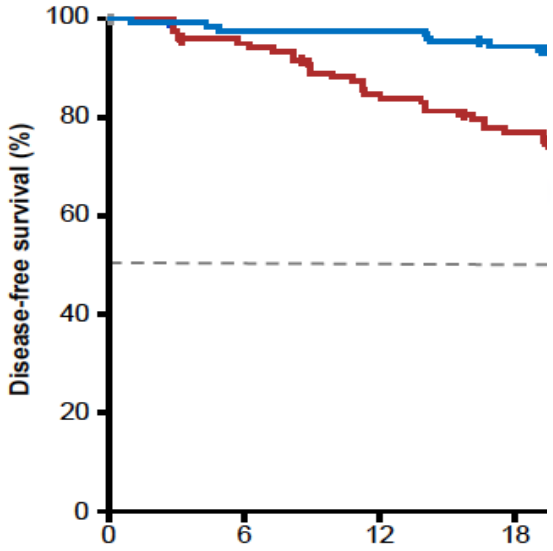
Primary endpoint : DFS, by investigator assessment

Secondary endpoints include: OS; safety; PK

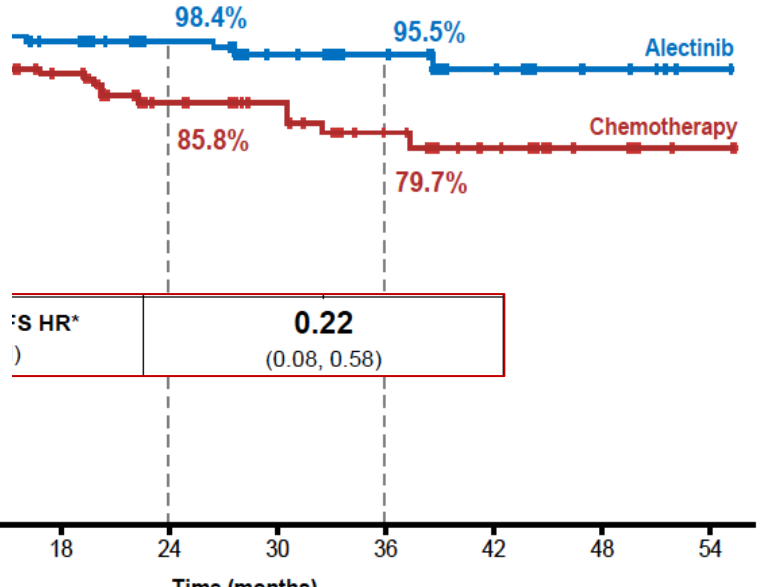
*Solomon et al. ESMO 2023

Treatment of NSCLC –ALK - ALINA

Disease-free



APPROVED



No. at risk										
Alectinib	130	123	123	118	74	55	39	22		
Chemo	127	112	98	89	55	41	27	18		

No. at risk										
Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

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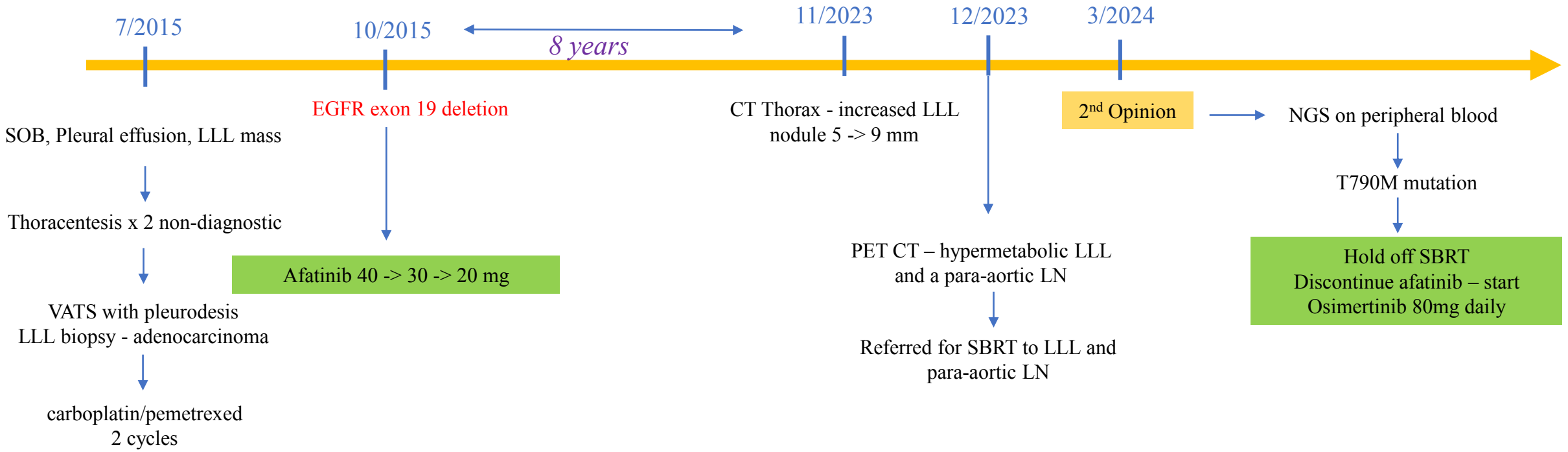
*Solomon et al. ESMO 2023

Targeted Therapy for NSCLC – Future

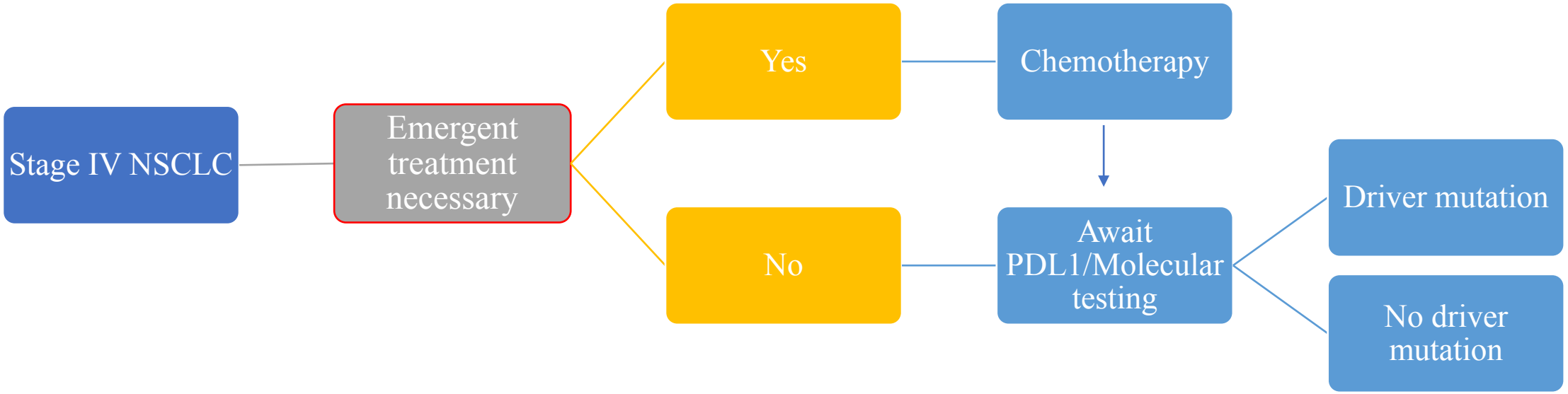
- Her3 Directed ADCs
- TROP2 ADCs
- CEACAM5 ADCs
- Combining chemotherapy or immunotherapy with targeted therapy

* *Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011 Feb;12(2):175-80.*
* *Chevallier et al. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future . World J Clin Oncol 2021; 12(4): 217-237*

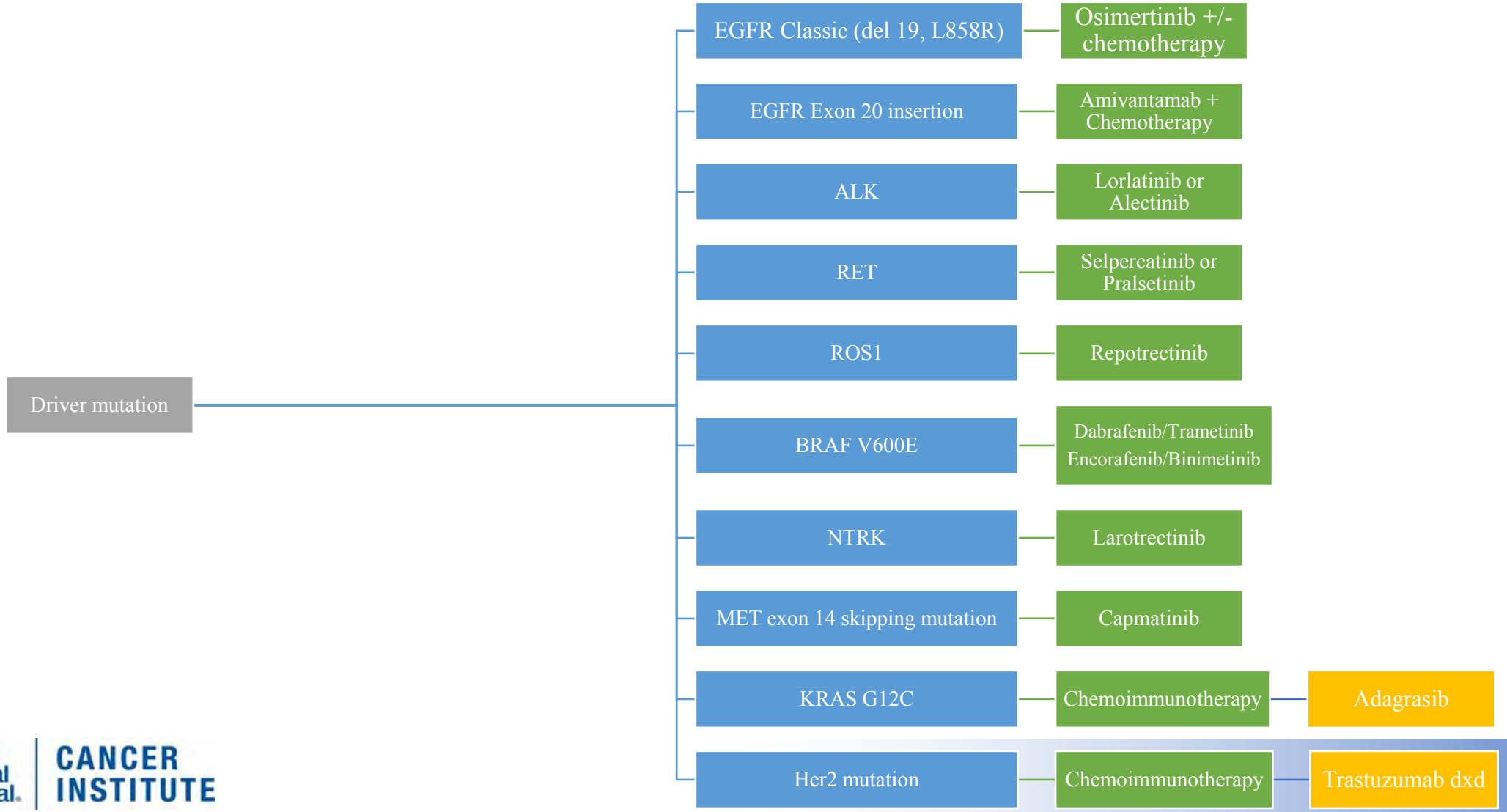
Case - continued



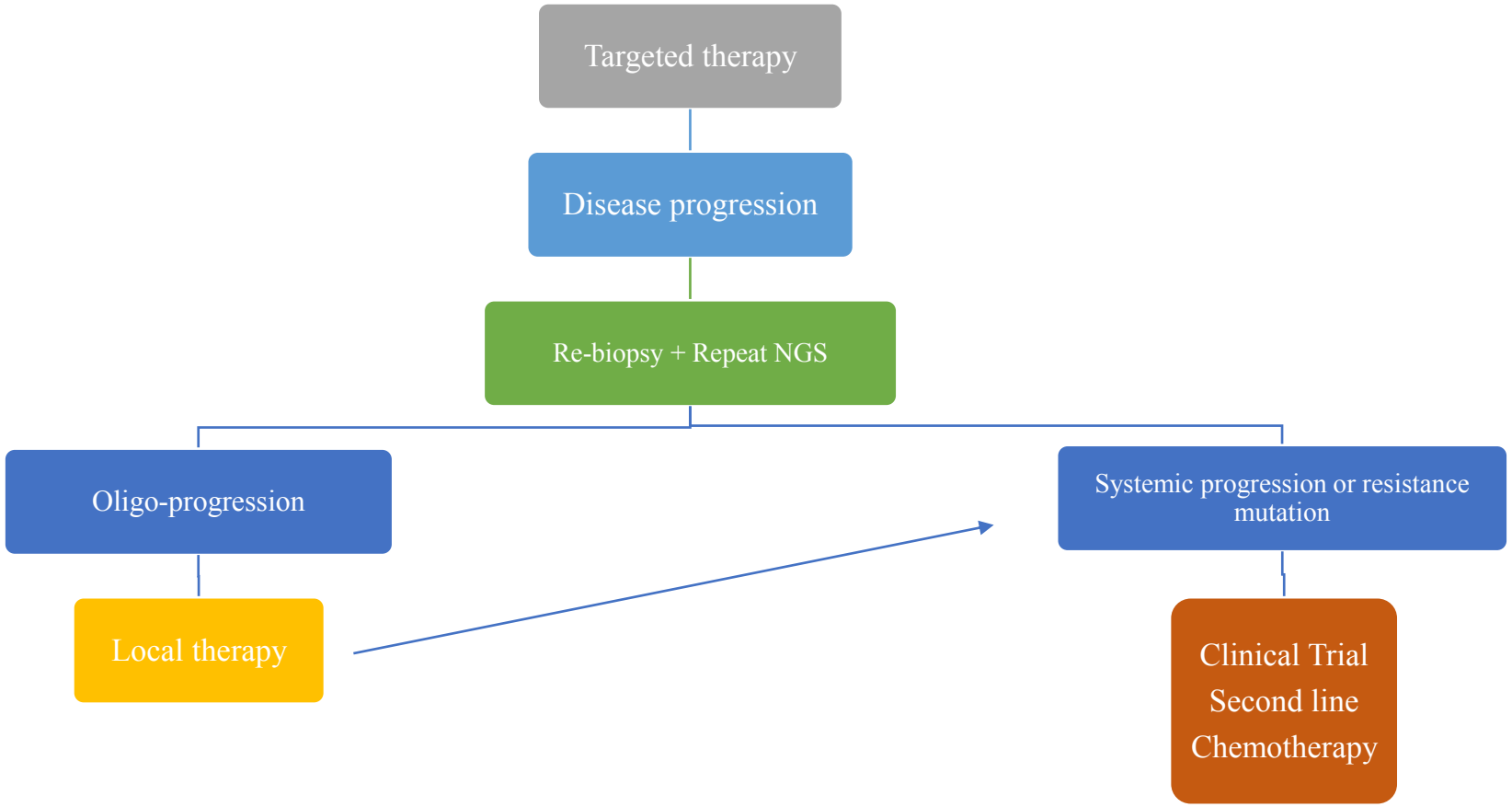
My approach to advanced NSCLC



My approach to advanced NSCLC – with driver mutation



My approach to advanced NSCLC (with driver mutation) at progression



Summary

A. Non-small cell lung cancer
   - Broad-based molecular testing by NGS and PD-L1 for *all patients before starting therapy*
   - With driver mutation
     - Resectable – surgery -> adj chemo, osimertinib or alectinib
     - Stage IV
       a. Driver mutation – targeted therapy in first-line (except Her2 mutation, KRAS G12C)
          a. Repeat NGS at progression
          b. Local therapy for oligo-progression

Thank you!