ESMO ON AIR

EGFR-mutated Metastatic Non-small Cell Lung Cancer

ESMO GUIDELINES : REAL WORLD CASES

Lizza Hendriks, *Chair*

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Programme

26 March 2025

10 min	**Welcome and introduction** Lizza Hendriks
10 min	**Case Presentation** Elene Mariamidze
20 min	**Presentation of the ESMO Clinical Practice Guideline for Critical Analysis of the Case** Egbert Smit
10 min	**Considerations Related to Guideline Implementation in Everyday Clinical Practice and Discussion** Mila Petrova
10 min	**Live Q&A and Discussion** All speakers

Lizza Hendriks
Chair
Maastricht University Medical Center, Maastricht

Elene Mariamidze
Speaker
Research Institute of Clinical Medicine (Todua Clinic), Tblisi

Egbert Smit
Speaker
Netherlands Cancer Institute

Mila Petrova
Speaker
Nadezhda Hospital

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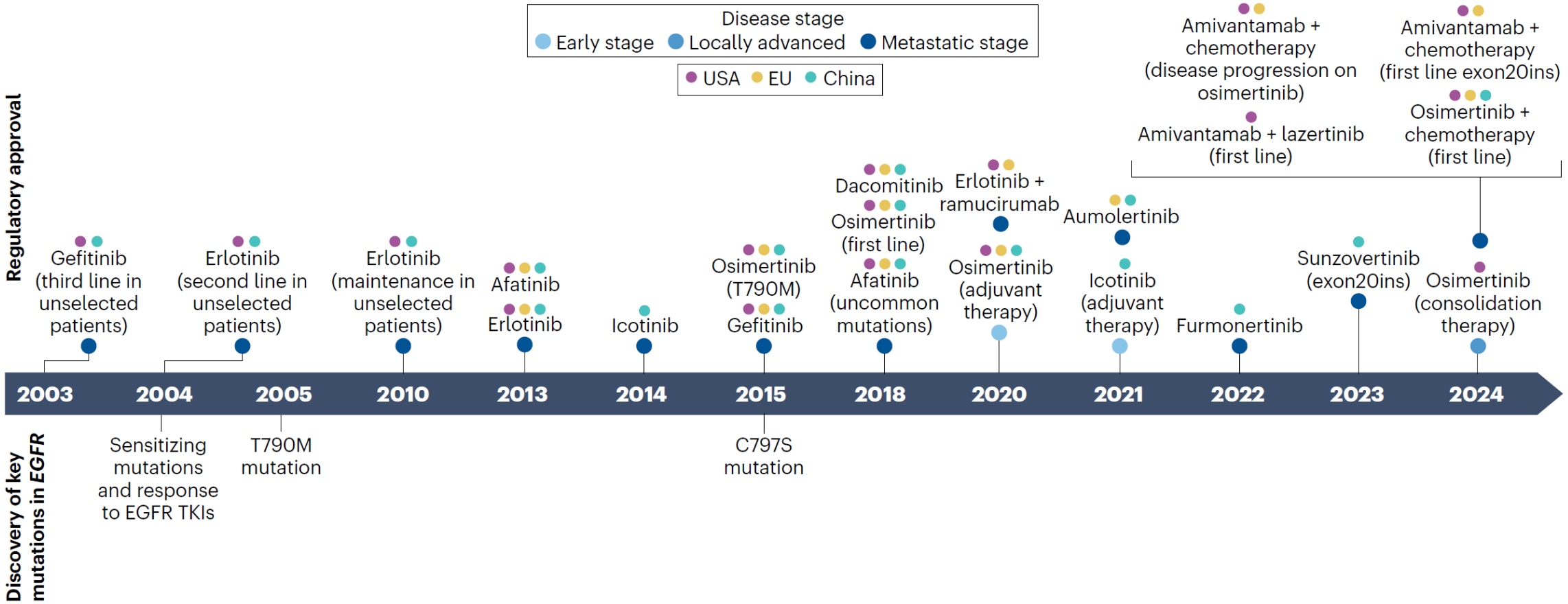
Learning objectives

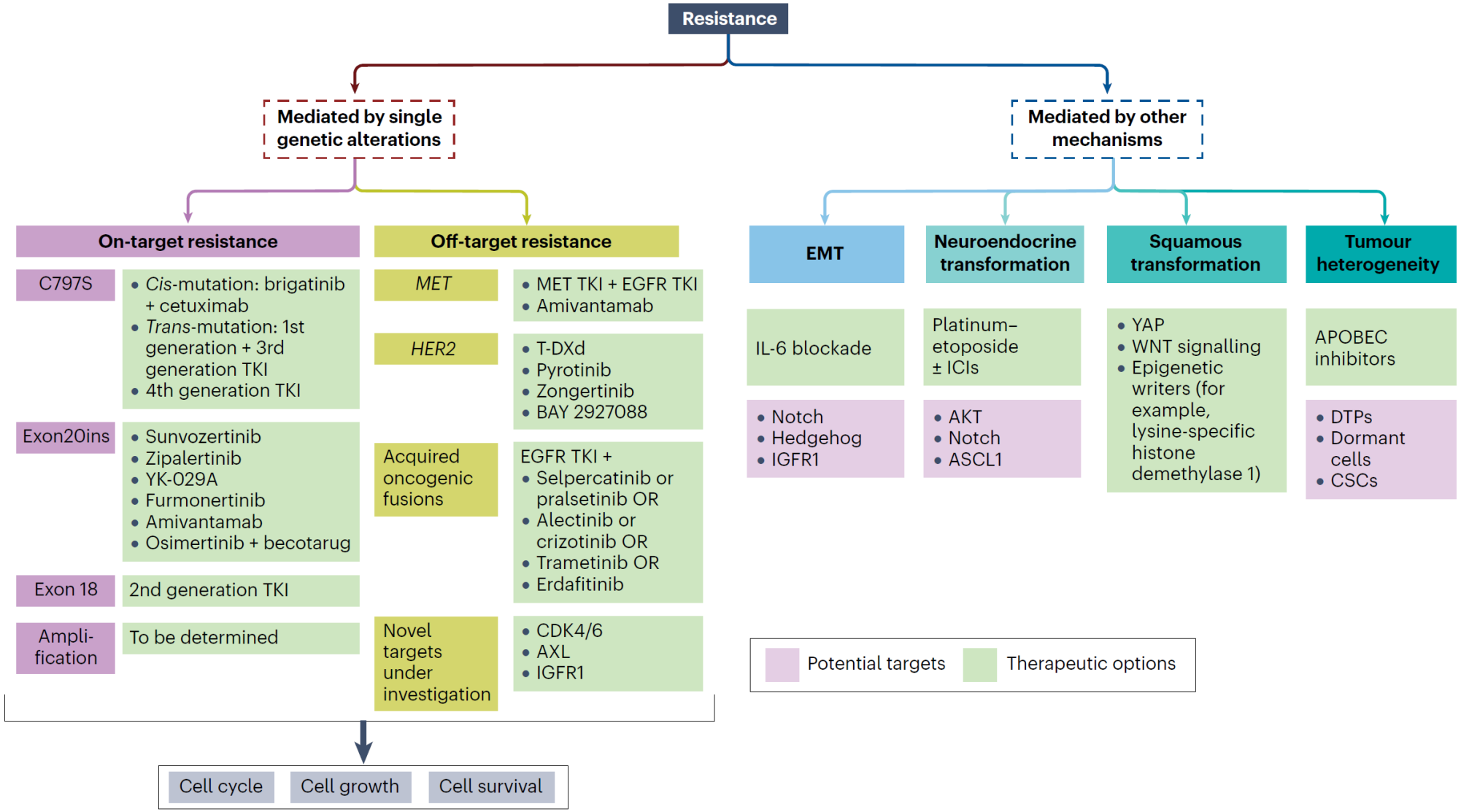
- Promote evidence-based quality cancer care by disseminating the ESMO Clinical Practice Guidelines (CPG) in the oncology community.
- Present a clinical case for each of the selected topics for discussion in the context of the ESMO CPG recommendations.
- Present and critically review the ESMO CPG recommendations for each selected cancer type.
- Discuss the case, the ESMO CPG recommendations, their impact on care and implementability in the daily practice setting under the guidance of a moderator senior expert, with participation of the guideline authors, practicing oncologists and young oncologists.
- Audit the fulfillment of the learning objectives and acceptability of the ESMO CPG recommendations by means of an online questionnaire.

Progress in treatment of EGFR-mutated NSCLC



Ramalingam NRCO 2025

Potential resistance mechanisms



Ramalingam NRCO 2025

ESMO living guidelines

ESMO Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guideline

To cite this living guideline, please include the original Clinical Practice Guideline citation "Ann Oncol. 2023;34(4):339-357" and this online publication, including date and version number: "ESMO Oncogene-A Metastatic Non-Small-Cell Lung Cancer Living Guideline, v1.2 January 2025"

This living guideline was prepared by L Hendriks, F Cortiula, E Mariamidze, D Martins-Branco, G Pentherc and M Reck, on behalf of the Clinical Practice Guideline author group.

Version:
v1.2 - January 2025

"Hello? I need help choosing a helpline."

Aims of treatment

- Improve not only PFS, but also OS
- Control CNS
- Maintain / improve QoL
- Limit patient burden (toxicity, cost, time)

Consensus

3G TKI ± chemotherapy is preferred for common *EGFR* mutations

How to choose?

Monotherapy or combination?
If combination, which one?
Role of co-mutations?
Type of *EGFR* mutation?
ctDNA?
Costs and toxicity

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EGFR mutated metastatic non-small-cell lung cancer

Clinical Case

Elene Mariamidze , MD

Todua Clinic

Department of Oncology and Hematology

Tbilisi,Georgia

ESMO YOC

Georgian School of Oncology

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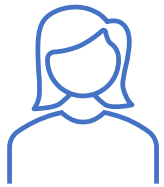
DECLARATION OF INTERESTS

Elene Mariamidze

For this case nothing to declare

Financial interest	Company/organisation
Expert Testimony	Astra-Zeneca, MSD, Novartis
Sponsoring Georgian young oncologists' conference	Astra-Zeneca, Roche, Sanofi
Research Funding	ICF
Non-financial interest	
Membership	ASCO, ESO, ESCO, GSO, GSGO

November 2024



Initial presentation

- 71 yo Female
- No Major Comorbidities
- No FHC
- Never Smoker .Spouse is an active smoker -40 PACK Years
- Admitted with Persistent Dry Cough
- ECOG 1

November 2024

Primary Investigations

- CT scan -91x53x67 mm mass encompassing nearly whole upper lobe of the segment 2 of Right Lung. The 2nd and 3rd segmental bronchi are obstructed. Ipsilateral Mediastinal, Contralateral Hilar LN +
- Bronchoscopy -Endoscopic findings correlate with a peripheral lung cancer in the right upper lobe.
- Morphology , IHC –Lung Adenocarcinoma , G3

Primary Investigations

- PET –CT –Abnormal mass in the upper lobe of the right lung 89*59 mm with cavitation in the center-SUV max 10 , Ipsilateral Mediastinal, Contralateral Hilar LN +

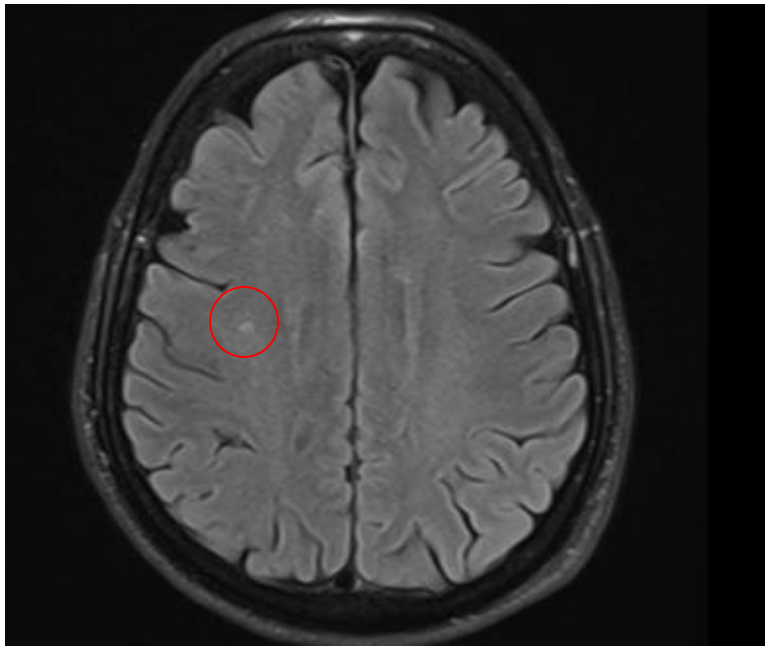
- Brain MRI-Single suspicious metastatic lesion identified in the semioval center, measuring 3–4 mm

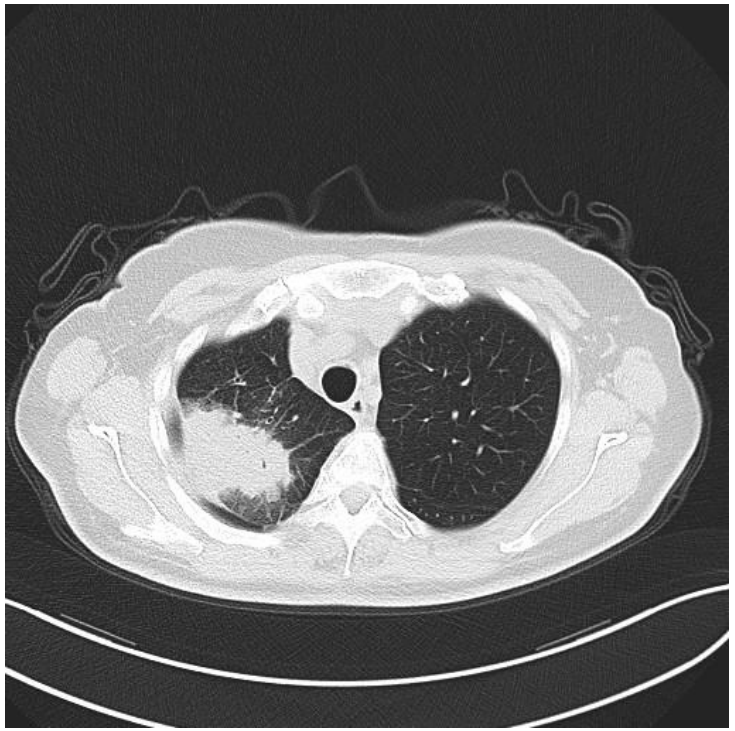
- Molecular Profile -EGFR, ALK, ROS, RET , MET mutations were not found by PCR . PD-L1 -TPS -30%, Her2 –

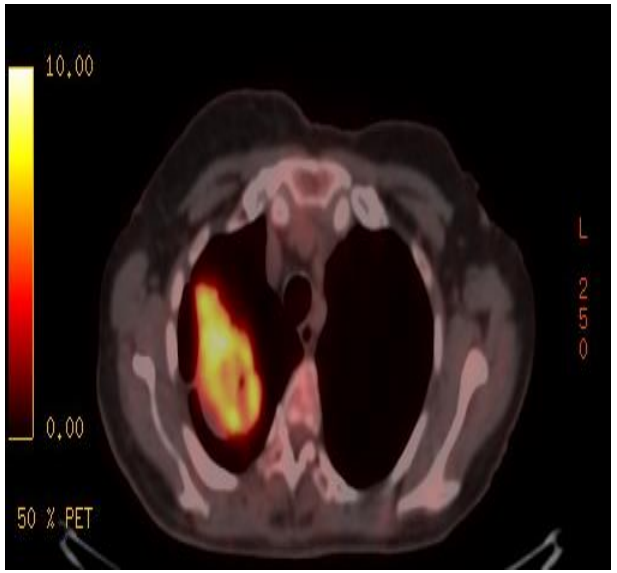
- NGS Pending

Final Diagnosis

Right Lung Oligometastatic Adenocarcinoma , G3
Non Oncogene addicted cT4N3M1b IVa stage



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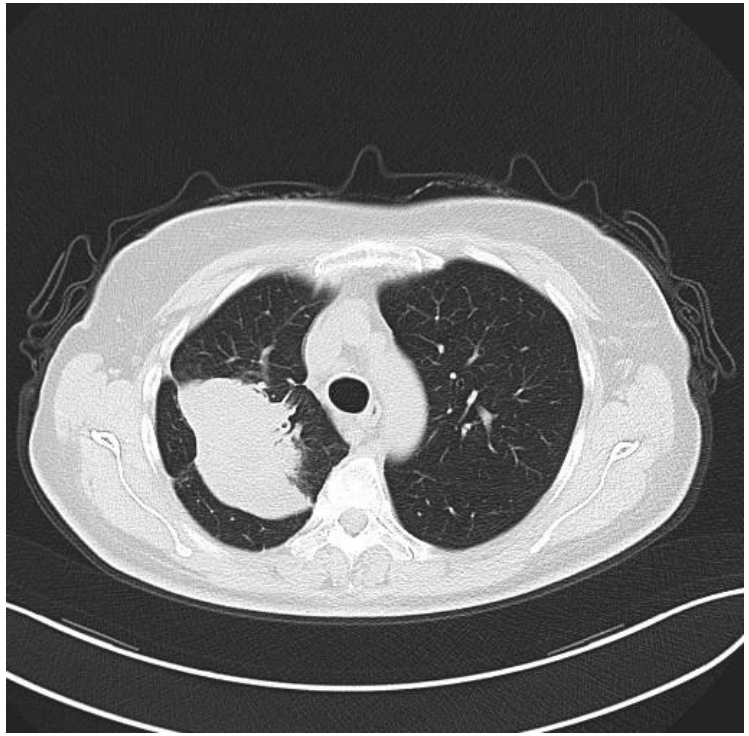
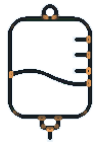
50 % PET



December 2024

09.12.2024

MDT



- `Pseudoneoadjuvant` chemo+immunotherapy using CHECKMATE 816 protocol (Nivolumab + chemotherapy - 3 cycles for Oligometastatic NSCLC

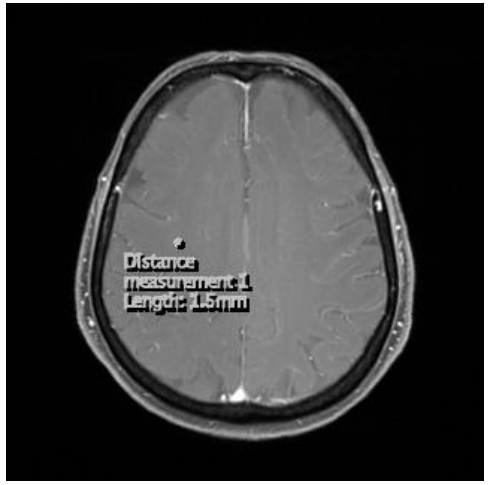
- 1st round of chemo – Nivolumab + Pemetrexed + Carboplatin
- NGS results came in – pathologic mutations were detected in EGFR and TP53 genes - c.2252_2277delinsAT (p.T751_I759delinsN) and c.991C>T (p.Q331*)

EGFR gene 19 exon “in-frame” deletion. TP53 Loss-of-function mutation

30.12.2024 - 2nd round of chemo – Osimertinib+Pemetrexed+Carboplatin

20.01.2025 - 3rd round of chemo- Osimertinib+Pemetrexed+Carboplatin

10.02.2025 – 4th round of chemo - Osimertinib+Pemetrexed+Carboplatin



Integral investigations

- Pet CT February 2025 – Abnormal mass in the upper lobe of the right lung 50*23mm in size (was 89*59),. Hypermetabolic uptake is only visible in its peripheral part SUV max 6 (was fully hypermetabolic, SUV max 10). Most of it is consolidated without metabolic activity. Hypermetabolic lymph nodes are not detectable anymore

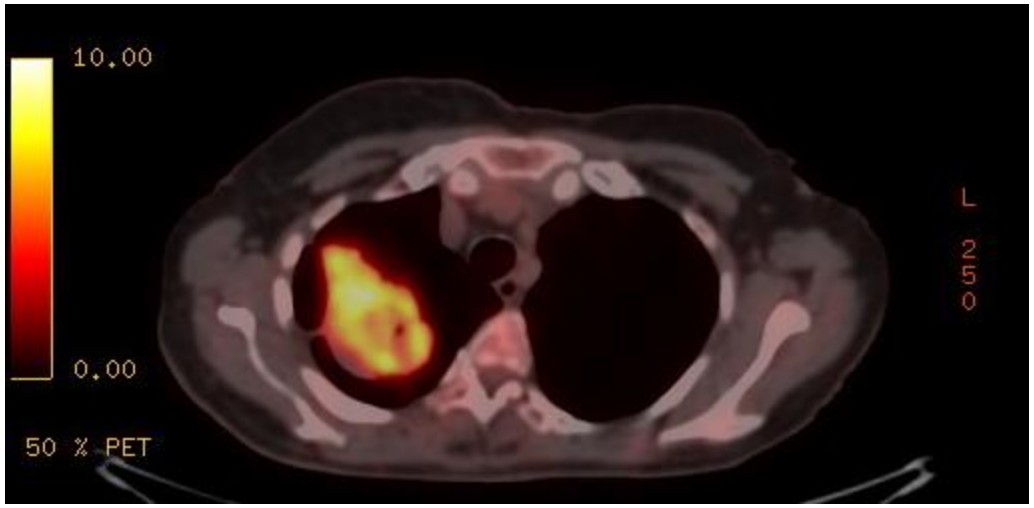
- Brain MRI February 2025 – previously detected MTS lesion is now 1,5mm in size (Was 4,5mm), no new growth or abnormal lesions

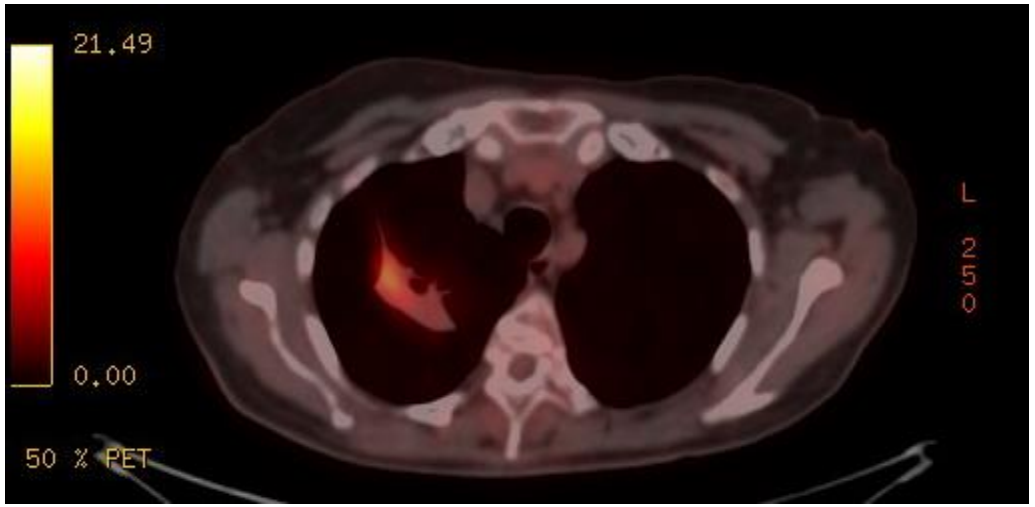
Questions to the Faculty

1. Stop chemo after 4 cycles and continue with Osimertinib without any local treatment?

2. Stop Osimertinib temporarily and continue with radical chemo+RT continue Osimertinib after RT?

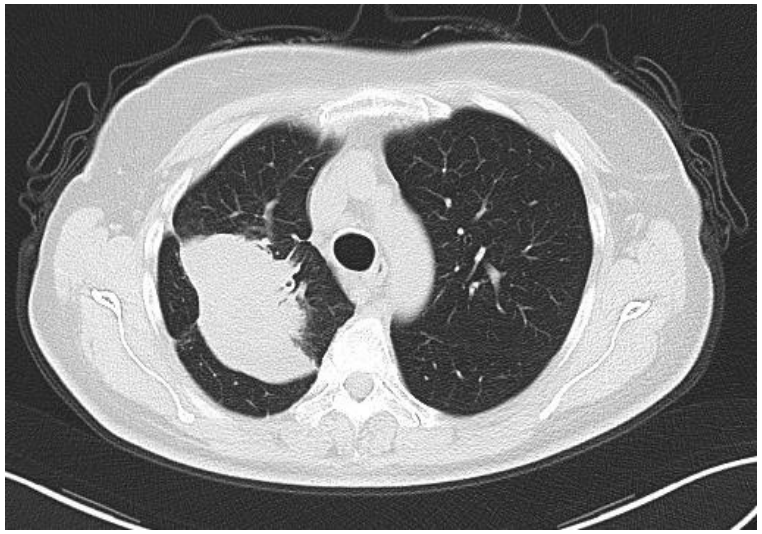
3. Stop chemo after 4 cycles , Perform the surgery, and continue with Osimertinib after surgery?

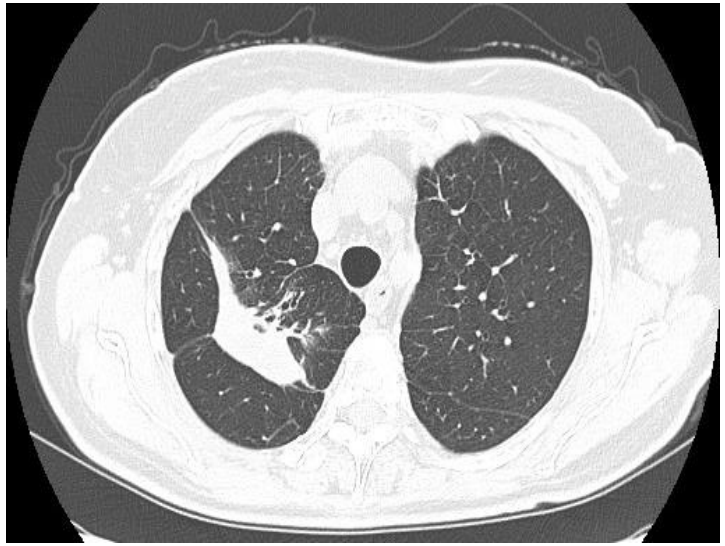




November 2024

February 2025

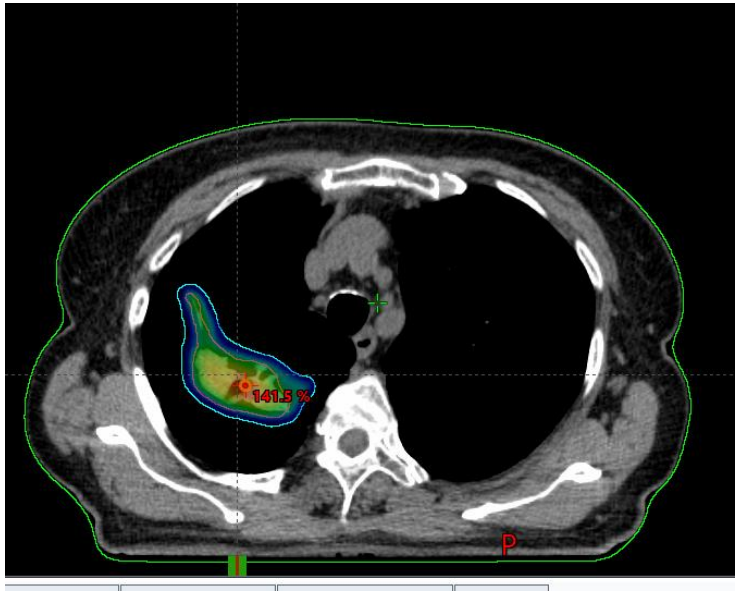


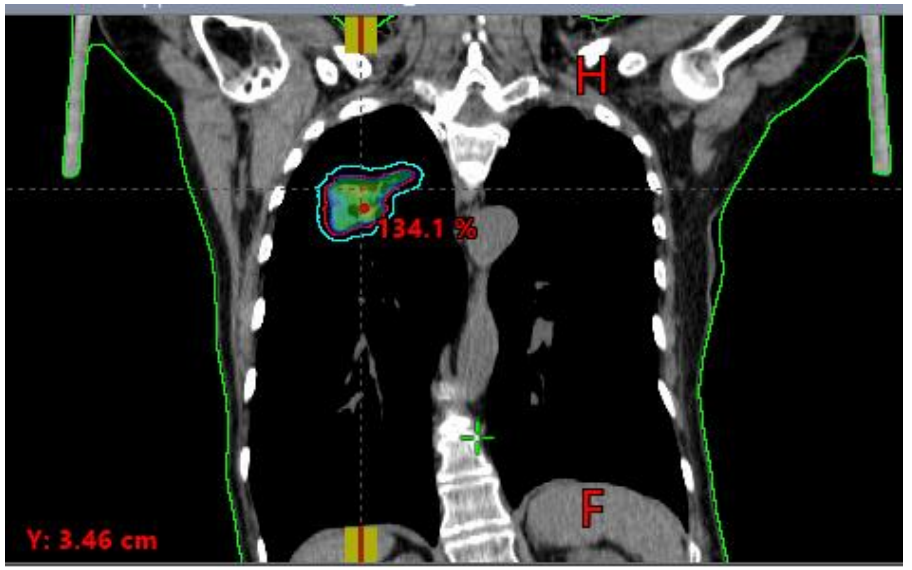


February 2025

MDT

- ❑ SBRT was planned
- ❑ Continuation of Osimertinib





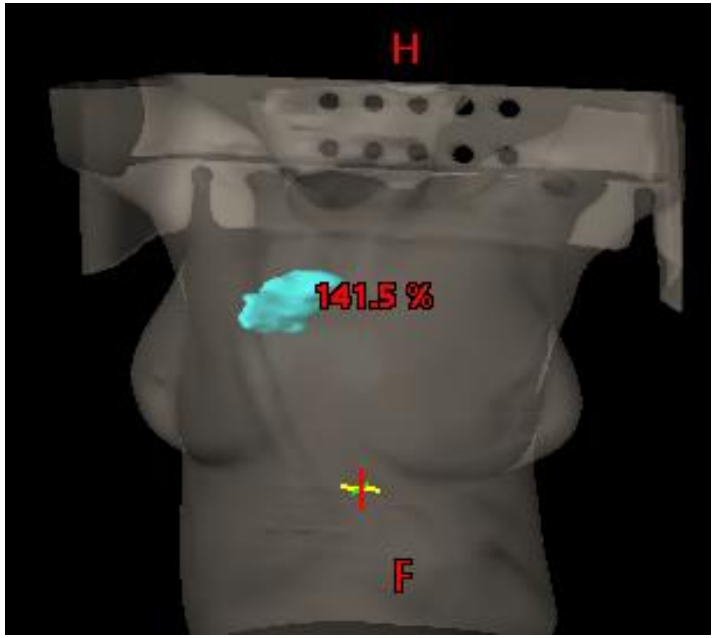
SBRT of the residual Lung mass -11Gy /5Fr DIBH
Total dose 55 Gy-finished on 21/02/2025

Questions to the Faculty

1 . What would be your initial strategy ?

2 . Upon residual mass remaining –what strategy would you adopt ?

3. Any special follow up considerations for this patient ?



THANK YOU !

Oncology and Hematology Department
Todua Clinic

Special Thanks to M. Abuladze for the case

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@Emariamidze –X

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Critical analysis of the case and ESMO CPG recommendations

Egbert Smit MD PhD
Dept Pulmonary Diseases
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Leiden, The Netherlands

2 April 2025

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Conflict of interest

- Personal financial interests: None
- Institutional financial interests:

- Fees have been paid to my institution for speaker engagements and attendance to advisory boards of Astra Zeneca, Bristol Myers Squibb, Bayer, DSI, Eli Lilly, MSD, Merck, Novartis, Pfizer, Takeda, Regeneron, Roche Genentech, Roche Diagnostics.
- Research support: Astra Zeneca, Bristol Myers Squibb, Merck, MSD, Roche Genentech, DSI.
- PI for clinical studies sponsored by Novartis, PharmaMar, Takeda, Bayer, Eli Lilly, Amgen, DSI.

Initial staging – Do we need more information?

ESMO Guidelines

- Complete medical history including smoking history (IV,A)
- CT scan of the chest and upper abdomen (IV,A)
- Imaging of the CNS for all patients with metastatic disease (IV,B); gadolinium enhanced MRI should be considered for all patients (IV,B)
- FDG-PET-CT and brain imaging are recommended for in patients suspected for oligometastatic disease (IV,A). In the presence of a solitairy metastatic site, efforts should be made to obtain pathological proof (IV, A)
- For oligometastatic disease, mediastinal disease should be pathologically proven if this potentially impacts the treatment plan (IV,A)
- If available, multiplex platforms (NGS) for molecular testing are preferable (III,A)

Initial staging – Do we need more information?

ESMO Guidelines

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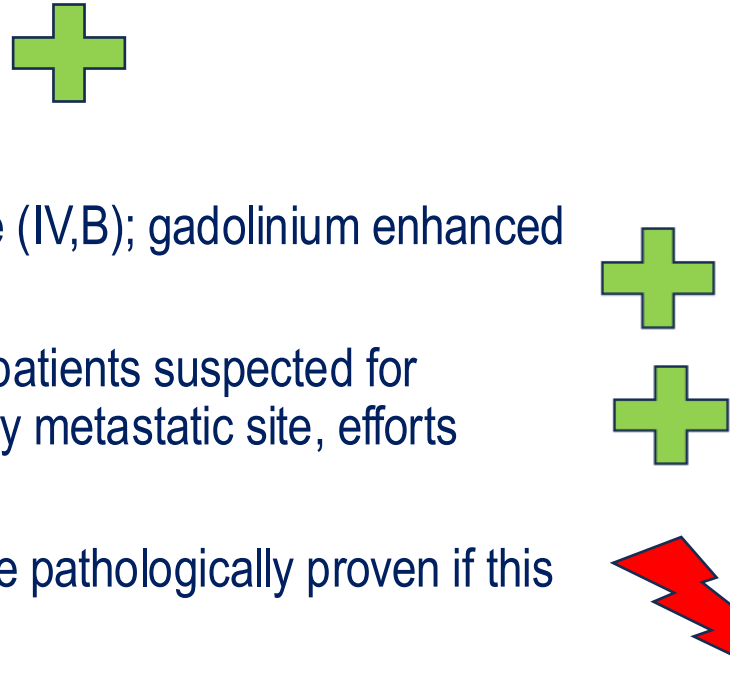
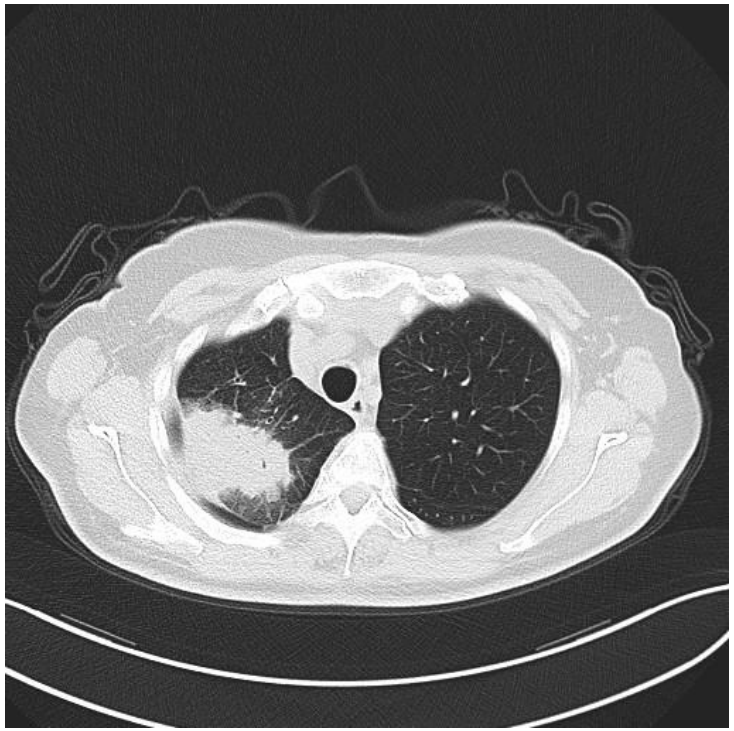
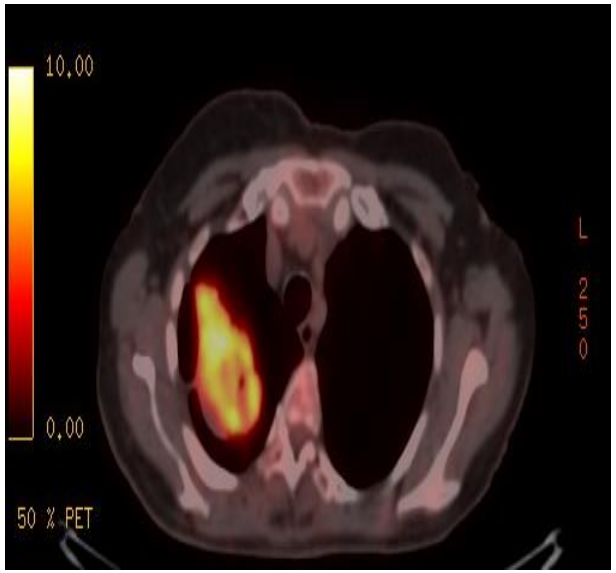


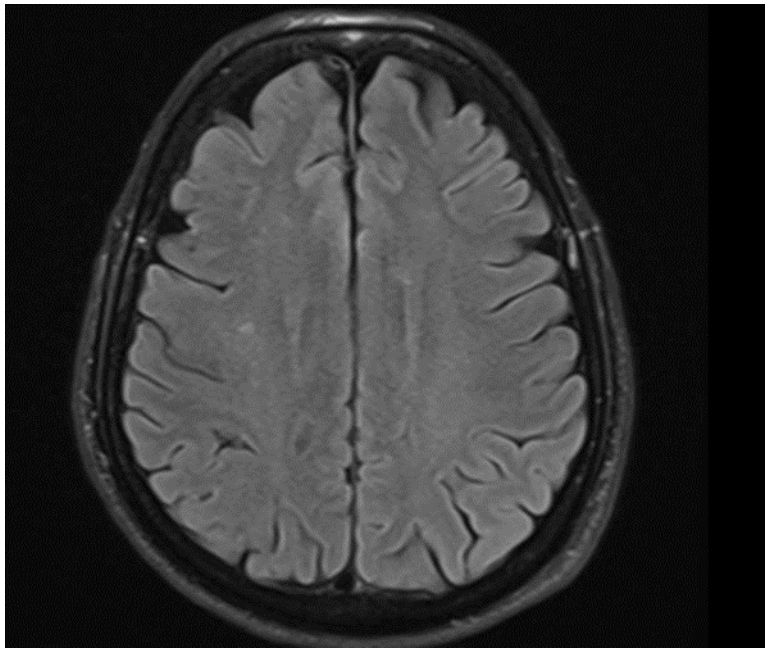
Oligometastatic Disease – European consensus statement

2.3	As the definition is not determined by the type of radical treatment (only by its feasibility), histologic type and genomic background are not taken into account in this definition.
2.4, 2.5, 2.6	The maximum number of metastases/organs involved depends on the possibility of offering a radical intent treatment strategy. On the basis of the systematic review, a maximum of 5 metastases and 3 organs is proposed. The presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition.
2.7, 2.12	Use of risk classification groups or total tumor volume is of interest, but there is a lack of data to formulate a statement.
2.8, 2.9	All organs, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric), and bone marrow involvement are allowed, as these cannot be treated with radical intent.
2.10	Pulmonary metastases are counted as a metastatic site.
2.11	Mediastinal lymph nodes should not count as a metastatic site; mediastinal lymph nodes must be considered as regional disease. However, mediastinal lymph node involvement is of importance in determining whether radical local treatment of the primary may be applied.

Dingemans. J. Thor. Oncol. 2019



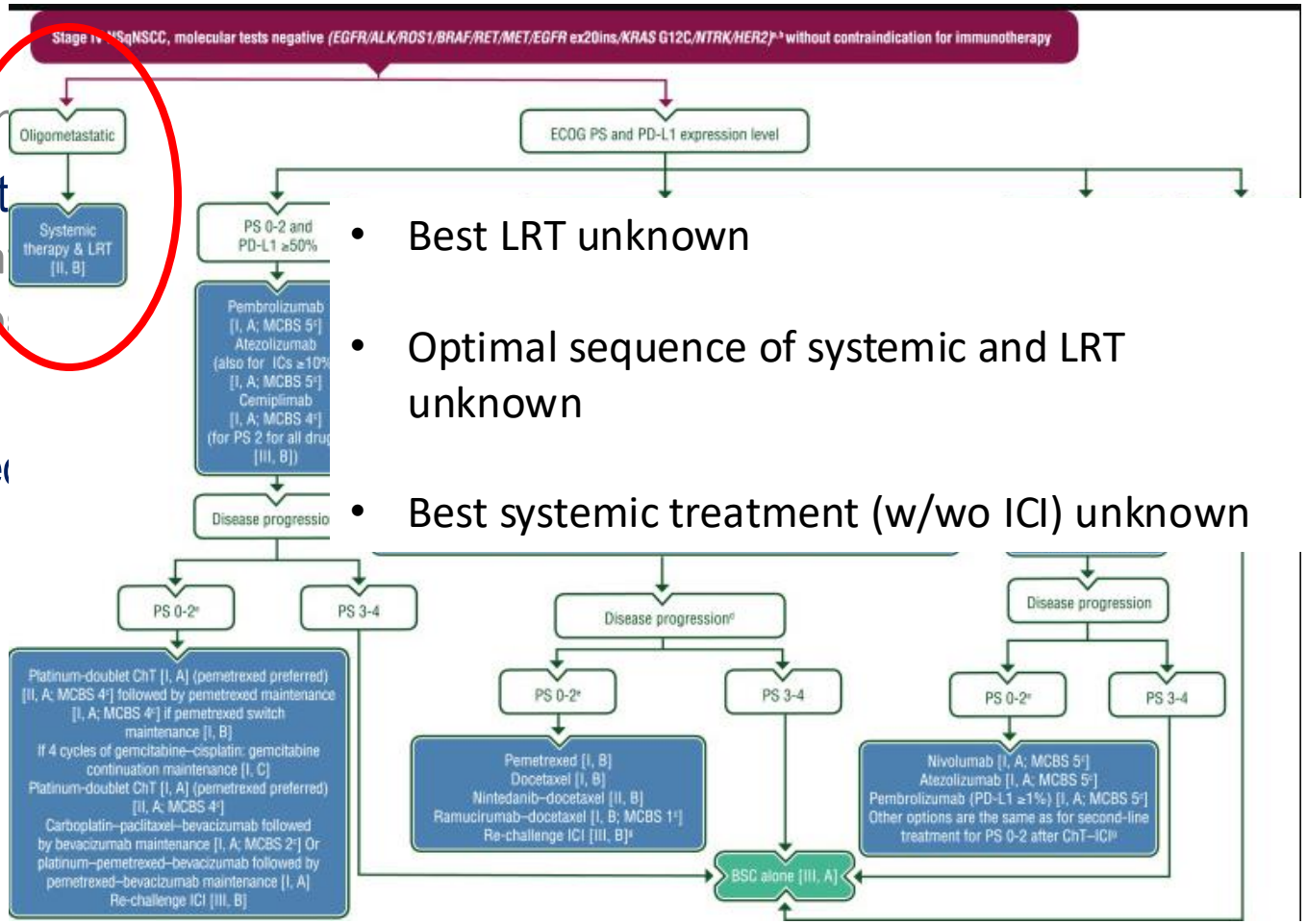




“the LN in TNM; they were Ispilateral Mediastinal and Contralateral Hilar, so N3. They were not pathologically evaluated as the FDG avidity was the same as the primary tumour and our thoracic surgeons didn't rush as to do it”

Initial staging and treatment

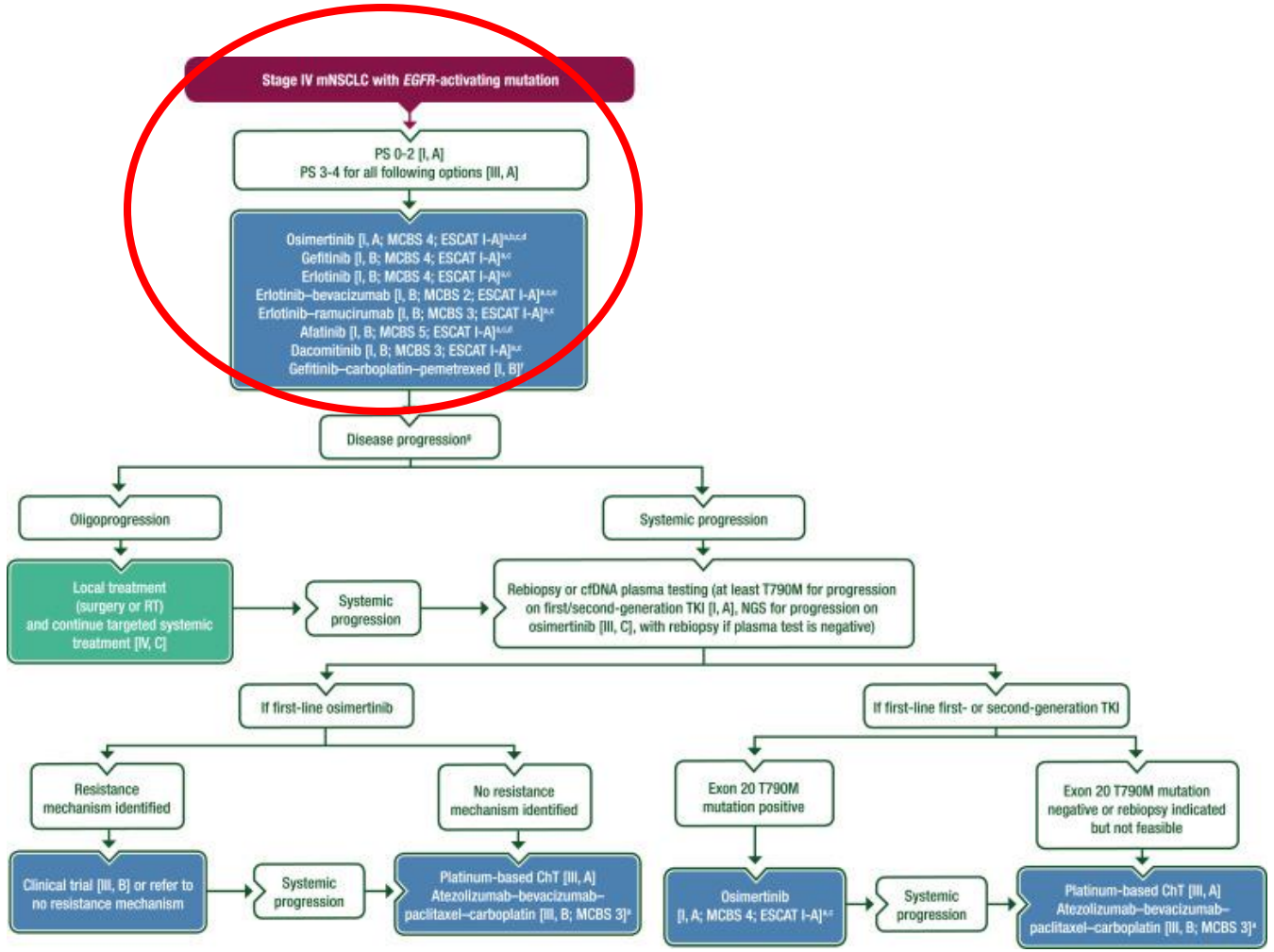
- Adenocarcinoma
  - NGS pendir
- Possibly oligomet
  - No informa
  - No patholo
- Treatment initiate



- Best LRT unknown
- Optimal sequence of systemic and LRT unknown
- Best systemic treatment (w/wo ICI) unknown

Hendriks. Ann. Oncol. 2023

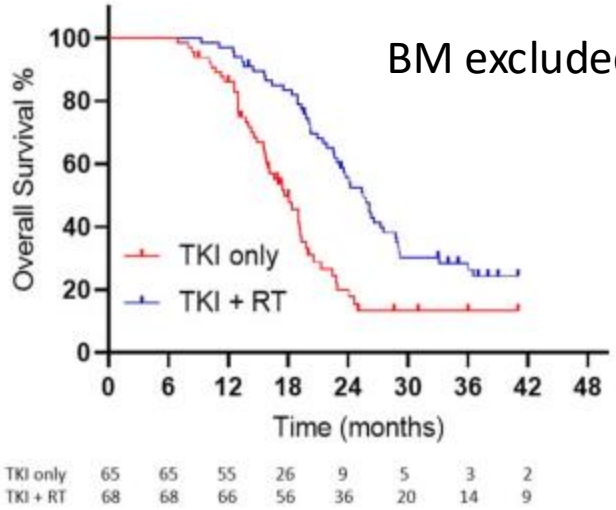
NGS detected an activating EGFR exon 19 del (and TP53) mutation



Hendriks. Ann. Oncol. 2023

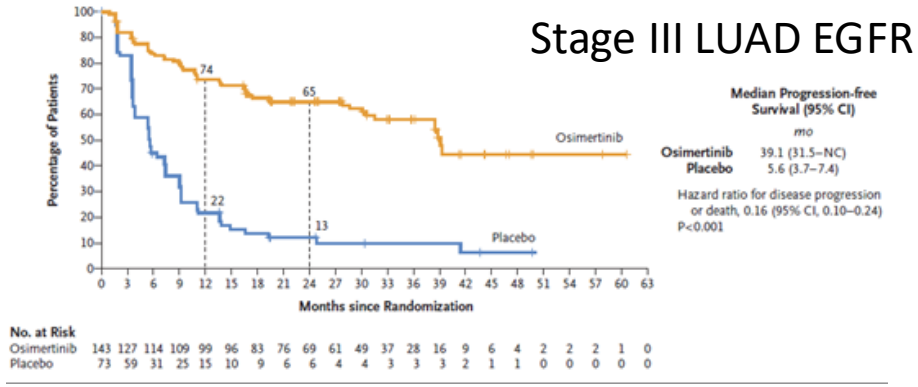
EGFR inhibition and LRT

BM excluded



Wang. JNCI 2023

Stage III LUAD EGFR mut +



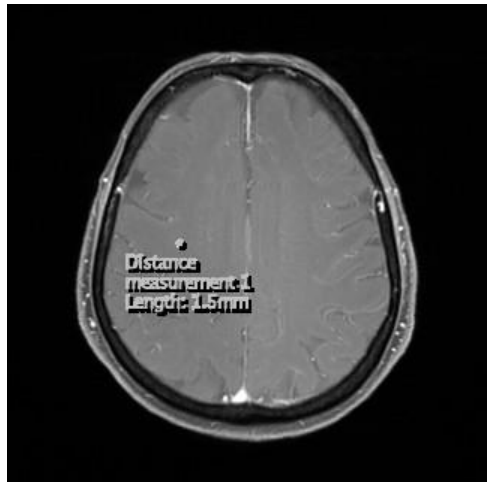
Lu. New Eng. J. Med. 2024

Integral investigations

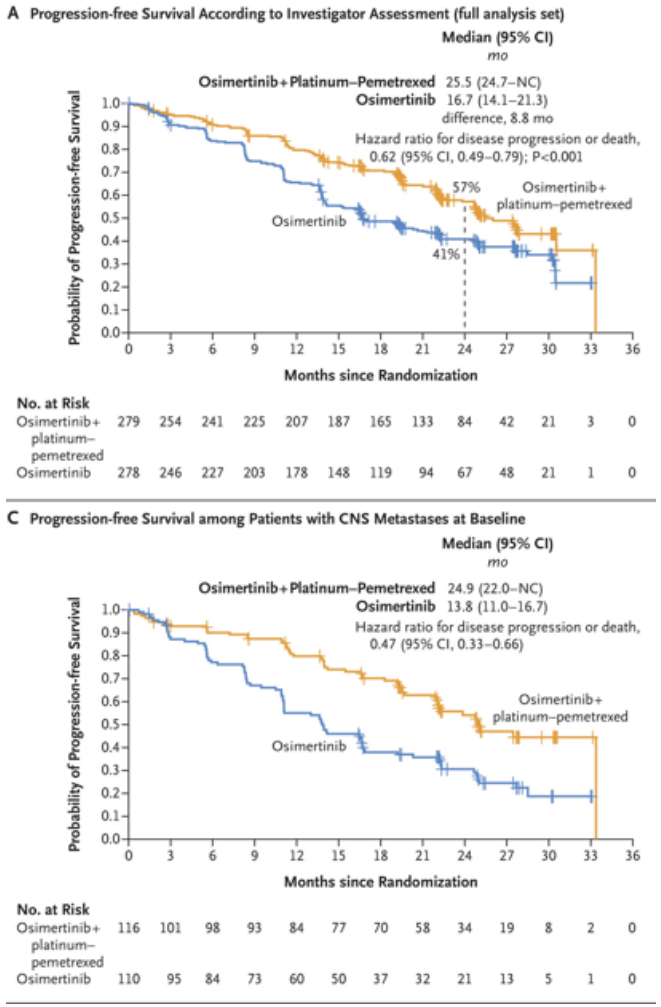
30.12.2024 - 2nd round of chemo – Osimertinib+Pemetrexed+Carboplatin

20.01.2025 - 3rd round of chemo- Osimertinib+Pemetrexed+Carboplatin

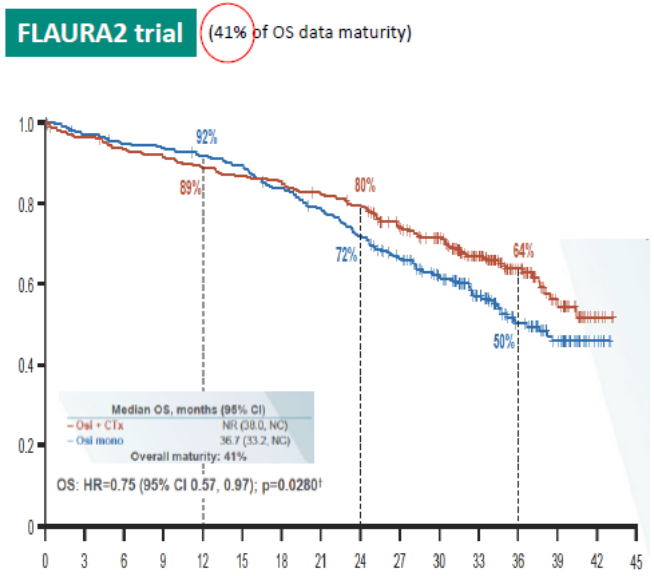
10.02.2025 – 4th round of chemo - Osimertinib+Pemetrexed+Carboplatin



Combination therapy for St IV NSCLC EGFR mut+



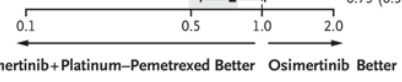
Planchard. New Eng J. Med. 2023



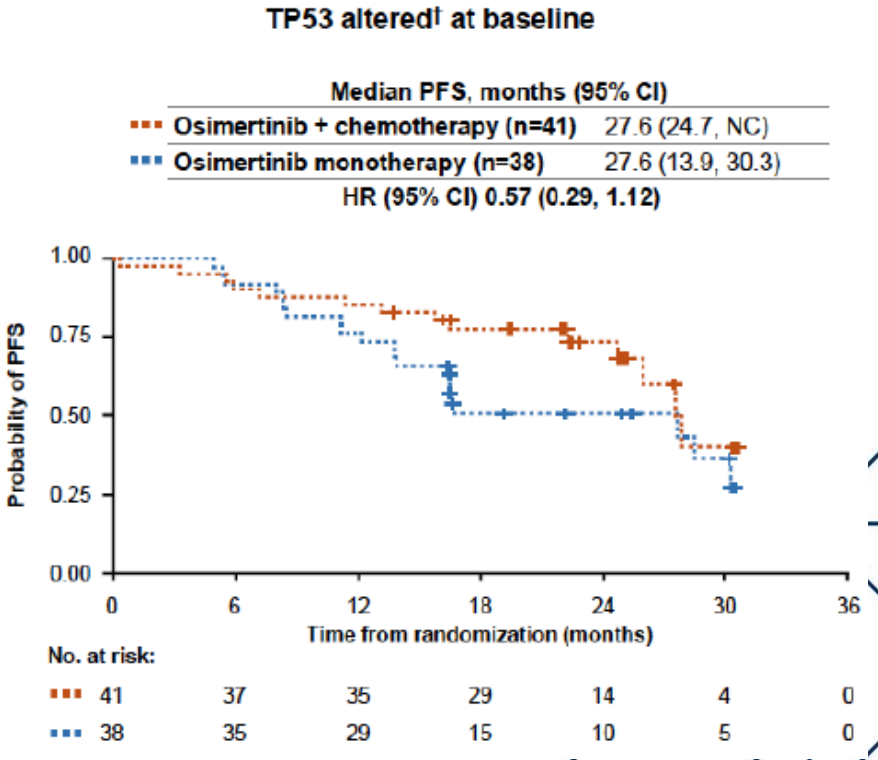
Valdviezo. ELCC 2024

Who benefits most from combination therapy in EGFR mut+

Subgroup	Osimertinib+ Platinum–Pemetrexed	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall			
Stratified log-rank analysis	120/279	166/278	0.62 (0.49–0.79)
Unadjusted Cox proportional-hazards analysis	120/279	166/278	0.62 (0.49–0.78)
Sex			
Male	51/106	73/109	0.54 (0.37–0.77)
Female	69/173	93/169	0.67 (0.49–0.92)
Race			
Asian Chinese	26/71	43/69	0.49 (0.30–0.81)
Asian non-Chinese	54/107	65/107	0.76 (0.53–1.09)
Non-Asian	40/101	58/102	0.55 (0.37–0.83)
Method used for tissue testing			
Central	52/121	67/119	0.73 (0.51–1.05)
Local	68/158	99/159	0.55 (0.40–0.74)
Age at screening			
<65 yr	73/174	97/166	0.59 (0.44–0.80)
≥65 yr	47/105	69/112	0.68 (0.47–0.98)
History of smoking			
Yes	43/91	57/97	0.63 (0.42–0.94)
No	77/188	109/181	0.61 (0.46–0.82)
EGFR mutation at randomization			
Exon 19 deletion	65/172	94/169	0.60 (0.44–0.83)
L858R mutation	55/106	70/107	0.63 (0.44–0.90)
WHO performance-status score			
0	48/101	57/102	0.79 (0.54–1.16)
1	72/178	109/176	0.53 (0.39–0.72)
CNS metastases at baseline			
Yes	52/116	79/110	0.47 (0.33–0.66)
No	68/163	87/168	0.75 (0.55–1.03)



Planchard. New Eng. J. Med. 2023



Yang WCLC 2024

Questions to the Faculty

1. Stop chemo after 4 cycles and continue with Osimertinib without any local treatment?

   No data; median duration of chemotherapy in FLAURA2 11.1 months, Osimertinib 22.3 months

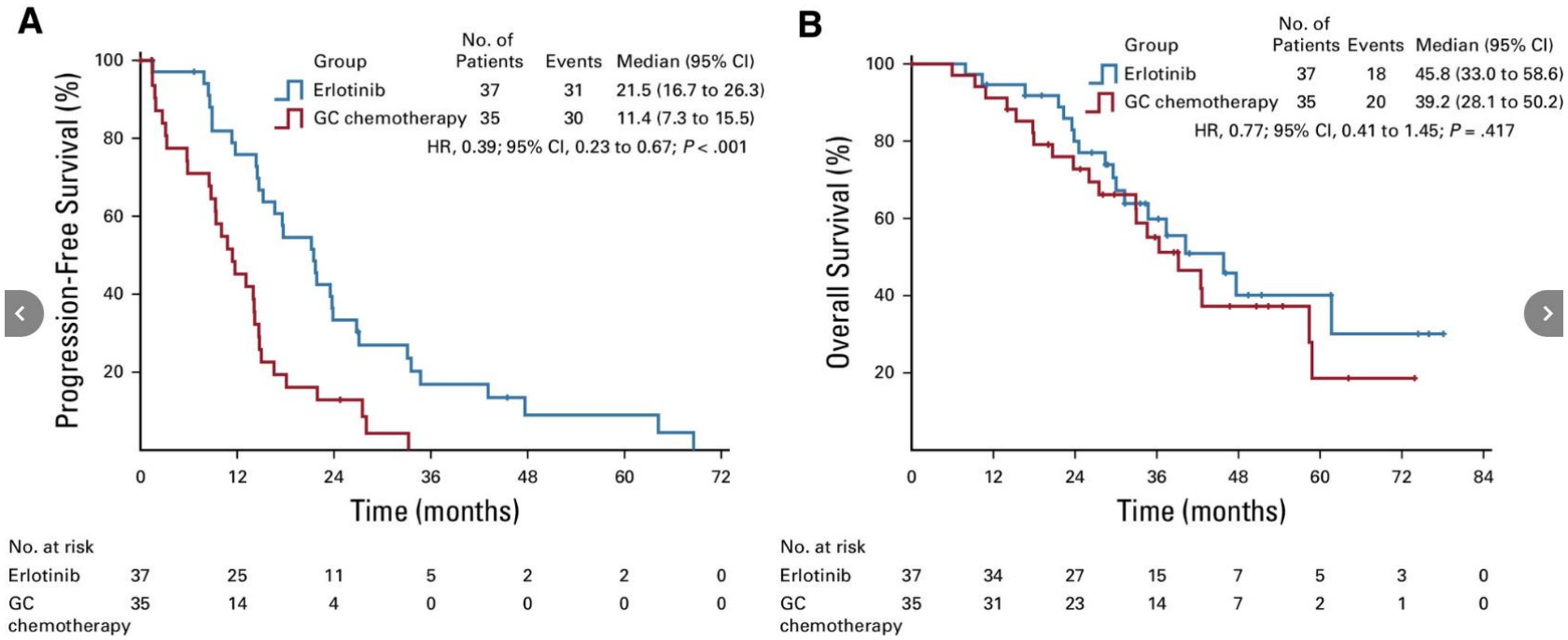
2. Stop Osimertinib temporarily and continue with radical chemo+RT continue Osimertinib after RT?

   “Modified” LAURA approach; combines benefit of LAT and possible survival benefit of “adjuvant” osimertinib

3. Stop chemo after 4 cycles , Perform the surgery, and continue with Osimertinib after surgery?

   Few data

Neoadjuvant EGFR TKI in stage III EGFR mut NSCLC CTONG 1103



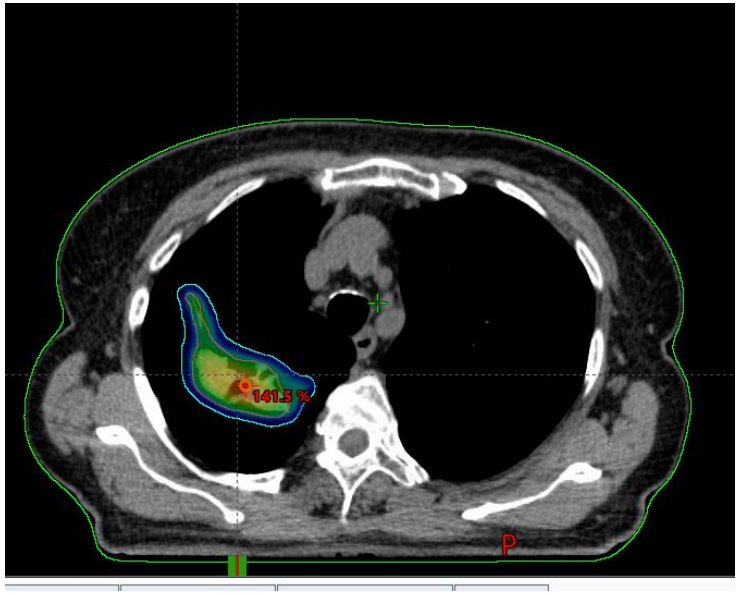
MPR rate in erlotinib arm 9.7%

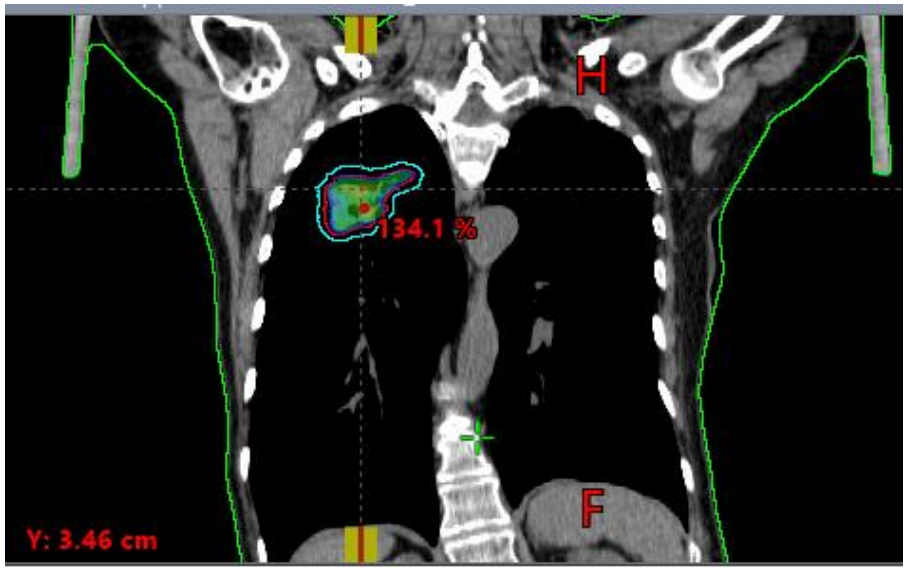
Zhong. J. Clin. Oncol. 2019

February 2025

MDT

- SBRT was planned
- Continuation of Osimertinib





SBRT of the residual Lung mass -11Gy /5Fr DIBH
Total dose 55 Gy-finished on 21/02/2025

Osimertinib followed by SABR – few data

Eligibility

- TKI Naïve, EGFR+ advanced NSCLC.
- Not restricted by number, site or size of metastases.
- No history of interstitial lung disease.
- ECOG ≤2

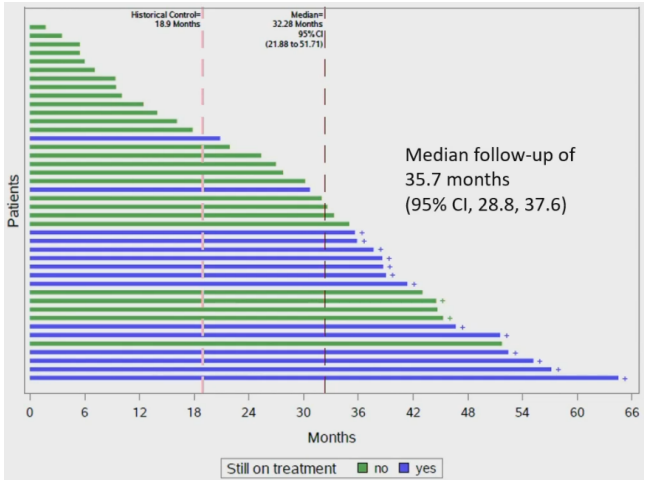
Multicenter, single arm phase 2 IIT

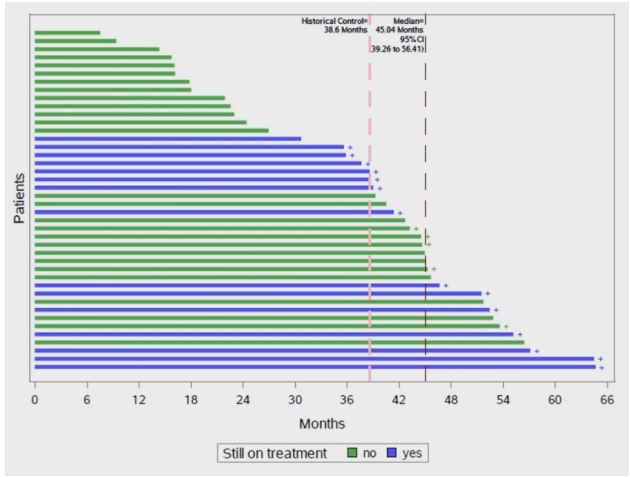
42 patients

Induction	Radiation	Continuation of therapy
Osimertinib X 8weeks	SBRT	Osimertinib

PET/CT

- Median PFS 32.3 mo (FLAURA 18.9 mo)
- Median OS 45 mo (FLAURA 38.6 mo)





Rashdan. ASCO 2024

Safety of Osimertinib + SABR (N=42!)

Grade ≥3 adverse events	Number of patients
Pneumonitis	1 (2%)
Paronychia	1 (2%)
Liver enzyme elevation	1 (2%)
Hyponatremia	1 (2%)
Diarrhea	1 (2%)

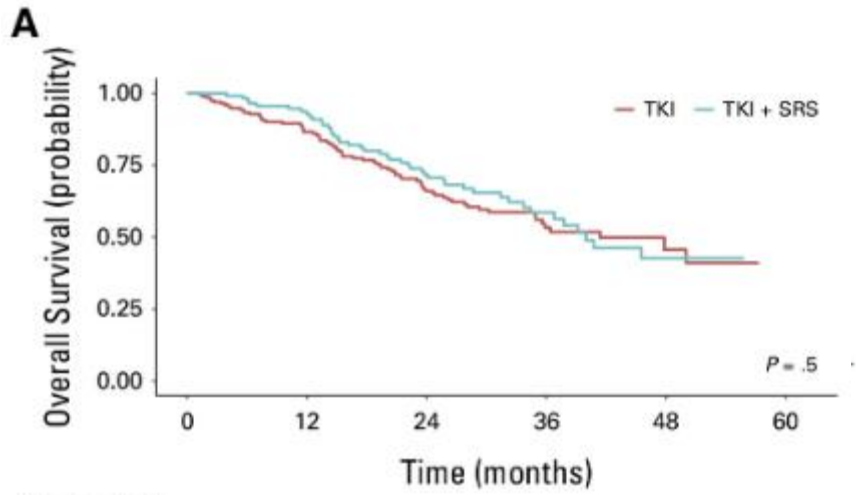
Rashdan. ASCO 2024.

What about the brain metastasis?

- Patients with NSCLC with actionable oncogenic driver alterations such as *EGFR* or *Alk* or *ROS1* rearrangement and asymptomatic or oligosymptomatic BM sould be treated with upfront systemic target therapy. (ESMO : II, B) *Le Rhun. Ann Oncol. 2021*

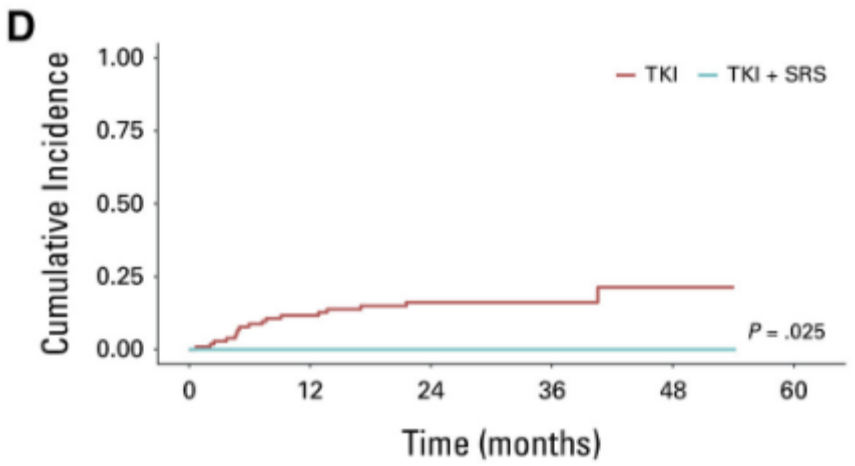
- “No prospective trials have addressed the question of optimal combined modality treatment with systemic therapy”

Retrospective analysis of TKI vs SRS + TKI: no OS benefit, increased local control



Number at risk						
TKI						
At risk	200	147	91	38	11	3
Events	0	25	57	70	73	74
TKI + SRS						
At risk	117	99	66	29	10	4
Events	0	8	29	38	44	44

Overall survival for all patients



Number at risk						
TKI						
At risk	108	69	35	11	2	0
Events	0	12	16	16	17	17
TKI + SRS						
At risk	27	20	11	5	2	1
Events	0	0	0	0	0	0

Local CNS progression patients BM <1 cm

Pike. J. Clin. Oncol. 2024

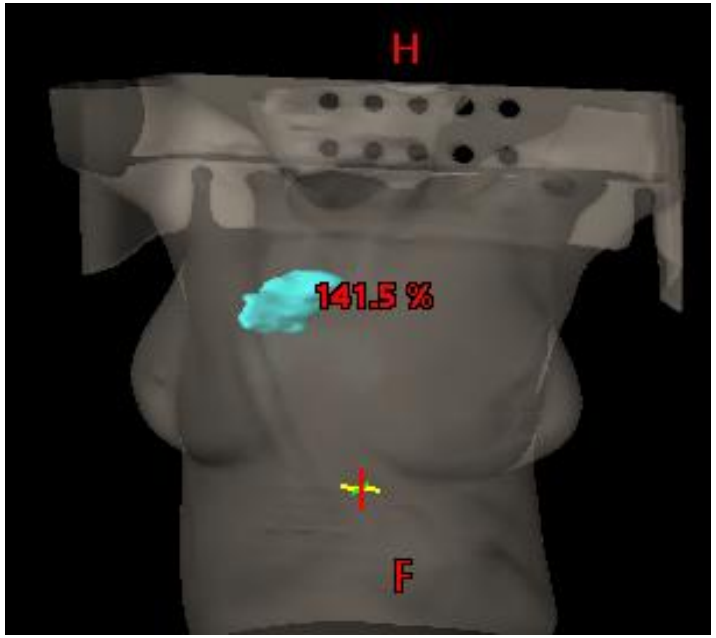
Questions to the Faculty

1 . What would be your initial strategy ?

Current ESMO guideline advocates Osimertinib single agent (I, A)

2 . Upon residual mass remaining –what strategy would you adopt ?

3. Any special follow up considerations for this patient ?



Questions to the Faculty

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My strategy: discuss with radiotherapist whether LAT of the primary and mediastinal lymph nodes is feasible. If yes: CCRT, adjuvant Osimertinib and SRS BM

2 . Upon residual mass remaining –what strategy would you adopt ?

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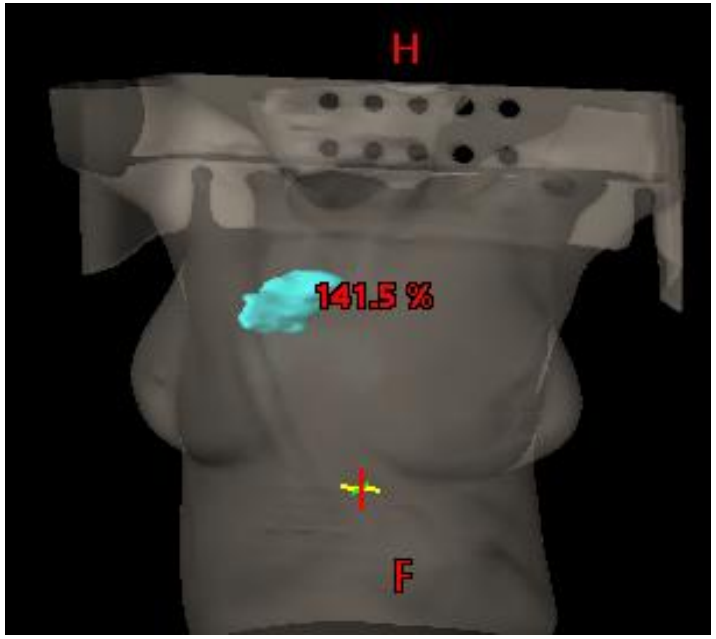


Questions to the Faculty

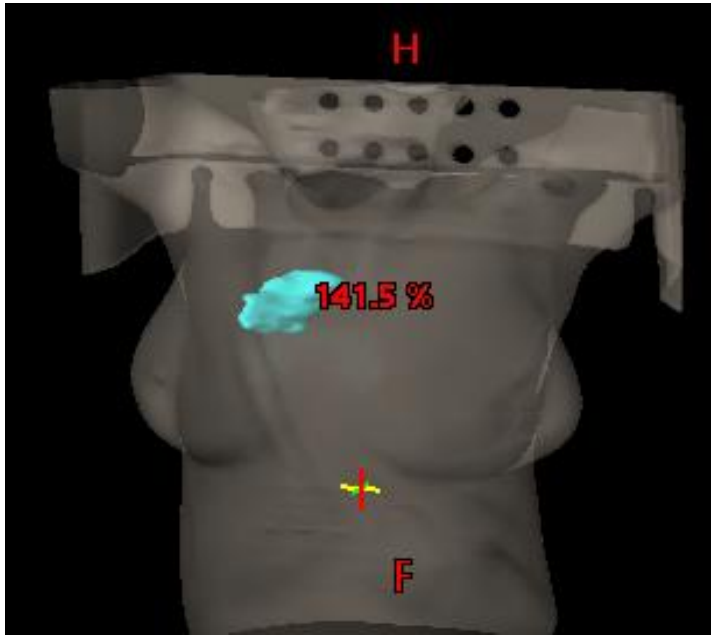
1 . What would be your initial strategy ?

Current ESMO guideline advocates Osimertinib single agent (I, A)

My strategy: discuss with radiotherapist whether LRT of the primary and mediastinal lymph nodes is feasible. If yes: CCRT, adjuvant Osimertinib and SRS BM

2 . Upon residual mass remaining –what strategy would you adopt ? Continue osimertinib

3. Any special follow up considerations for this patient ?



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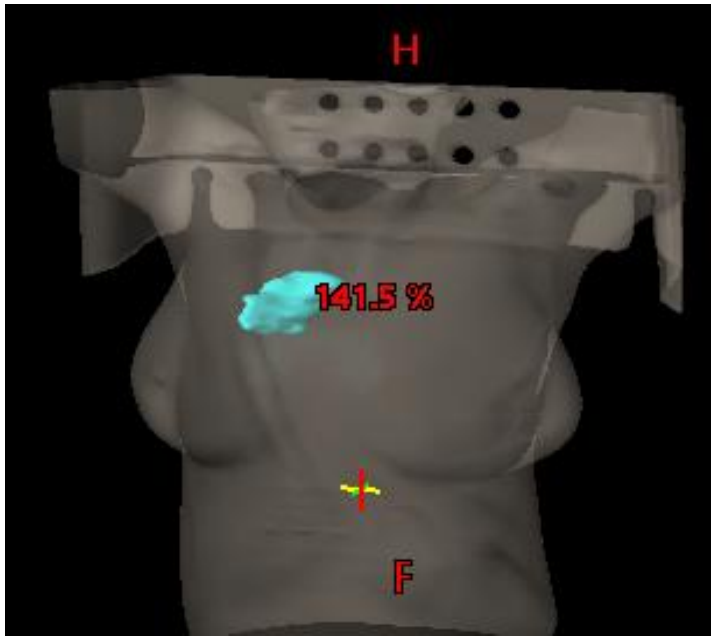
None



ESMO ON AIR

Considerations related to Guideline implementation in everyday clinical practice

Mila Petrova, MD, PhD

MHAT Nadezhda Hospital

Sofia, Bulgaria

26 Mar 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

DOI

Speaker/Advisory/Investigator: MSD, Astra Zeneca, Pfizer, Elli Lilly, Novartis, BMS

Outline

1. Molecular testing in adeno NSCLC
2. First line options for treatment in EGFR+ NSCLC
3. Oligometastatic disease
4. Take home message

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

Outline

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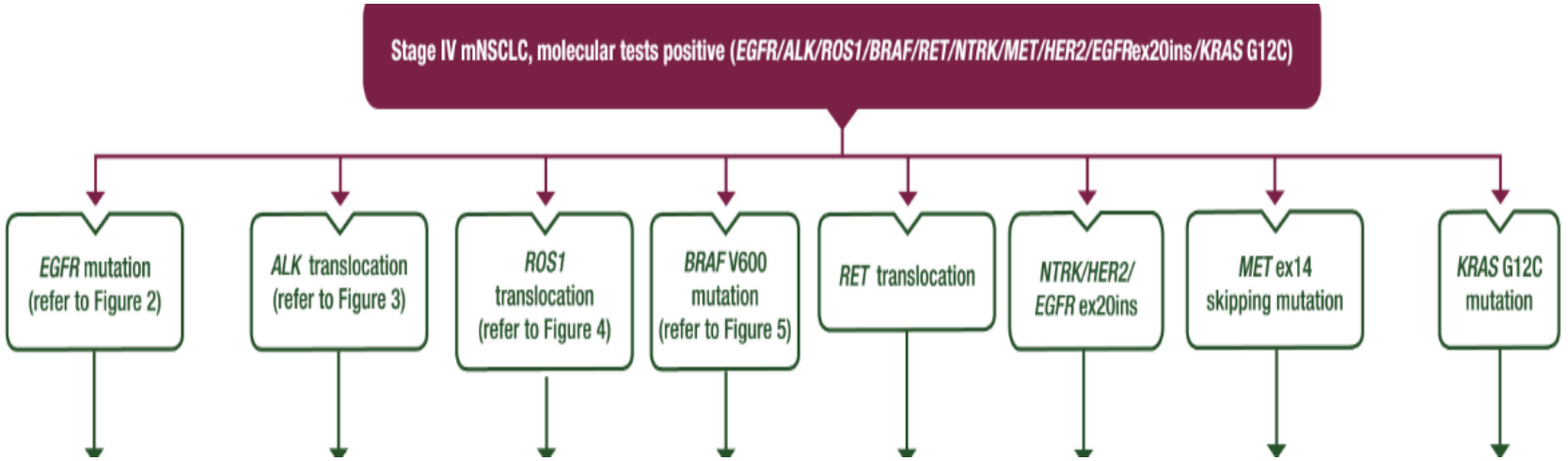
4. Take home message

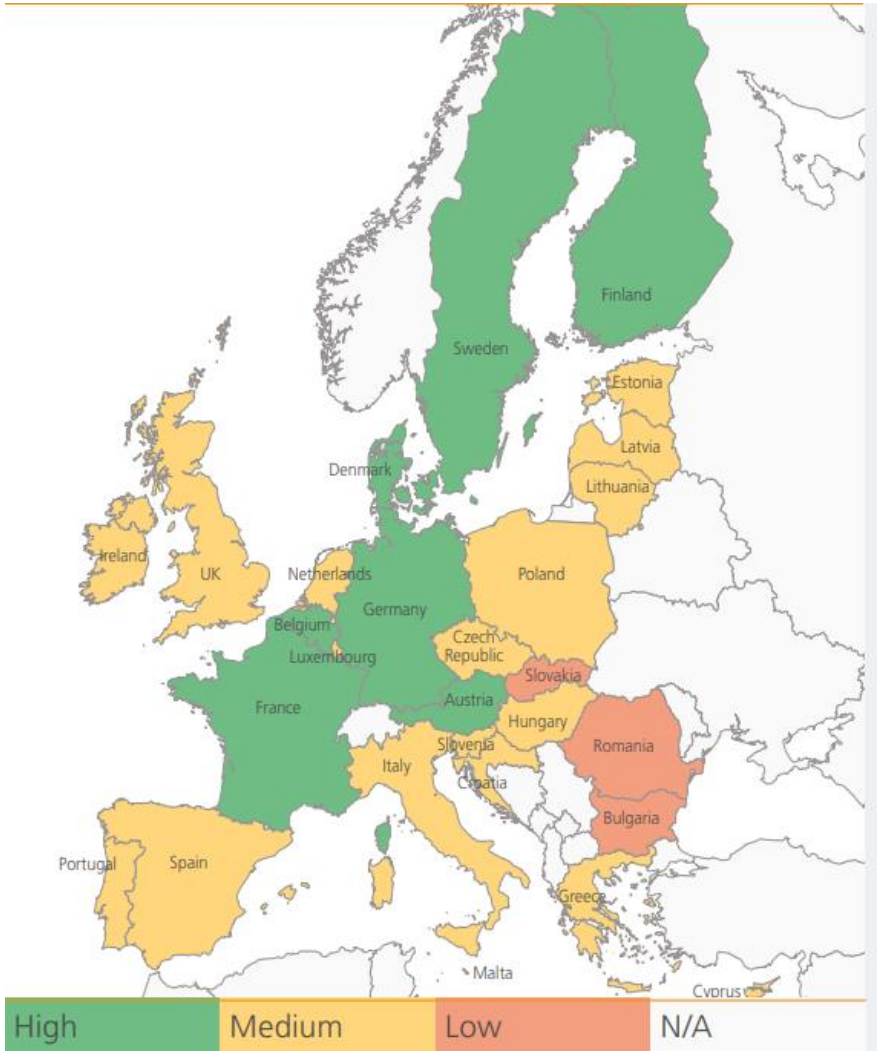


- *EGFR* mutation status should be determined [I, A]. Test methodology should have adequate coverage of mutations in exons 18-21, including those associated with resistance to some therapies [III, A]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [I, A].
- The availability of TKIs effective against T790M-mutated recurrent disease makes T790M testing on disease relapse on first- or second-generation EGFR TKIs mandatory [I, A].
- Testing for *ALK* rearrangements should be carried out [I, A].
- Detection of the *ALK* translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have been accepted as an equivalent alternative to FISH for ALK testing.
- Testing for *ROS1* rearrangements should be carried out [II, A]. Detection of the *ROS1* translocation by FISH remains a standard; IHC may be used as a screening approach [IV, A].
- *BRAF* V600 mutation status testing should be carried out [II, A].
- Testing for *NTRK* rearrangements should be carried out [II, A]. Screening for *NTRK* rearrangements may use IHC or NGS, with appropriate testing follow-up to validate a positive result [II, A].
- Testing for *MET* exon 14 skipping mutations, MET amplifications, *RET* rearrangements, *KRAS* G12C mutations and *HER2* mutations should be carried out [II, A].
- If available, multiplex platforms (NGS) for molecular testing are preferable [III, A].

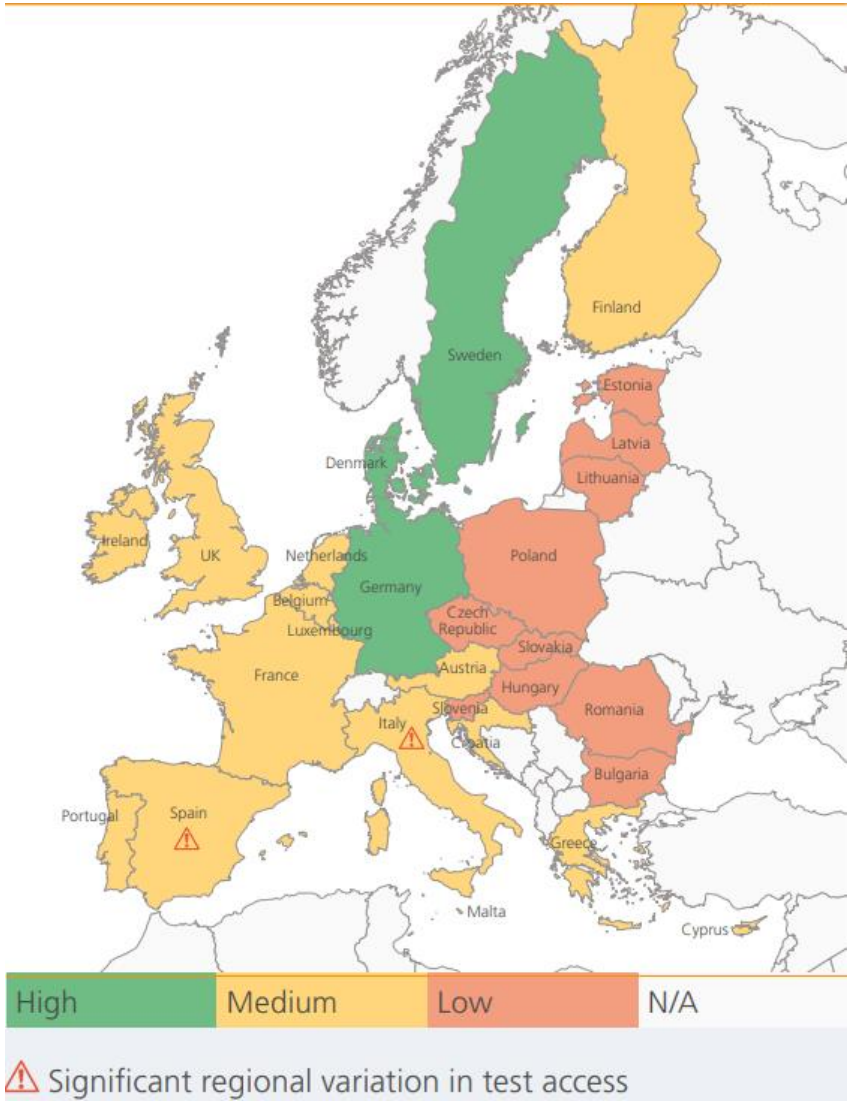
ESMO Guidelines, Hendriks et al, 2023

Availability of single biomarker test and multi biomarker tests

Single biomarker test access



Multi-biomarker test access



- **Single biomarker tests:**

PD-L, HER2, ALK, MMR/MSI, BRCA, EGFR, NTRK, BRAF

- **Multi-biomarker test Technologies:**

Complex genomic signatures

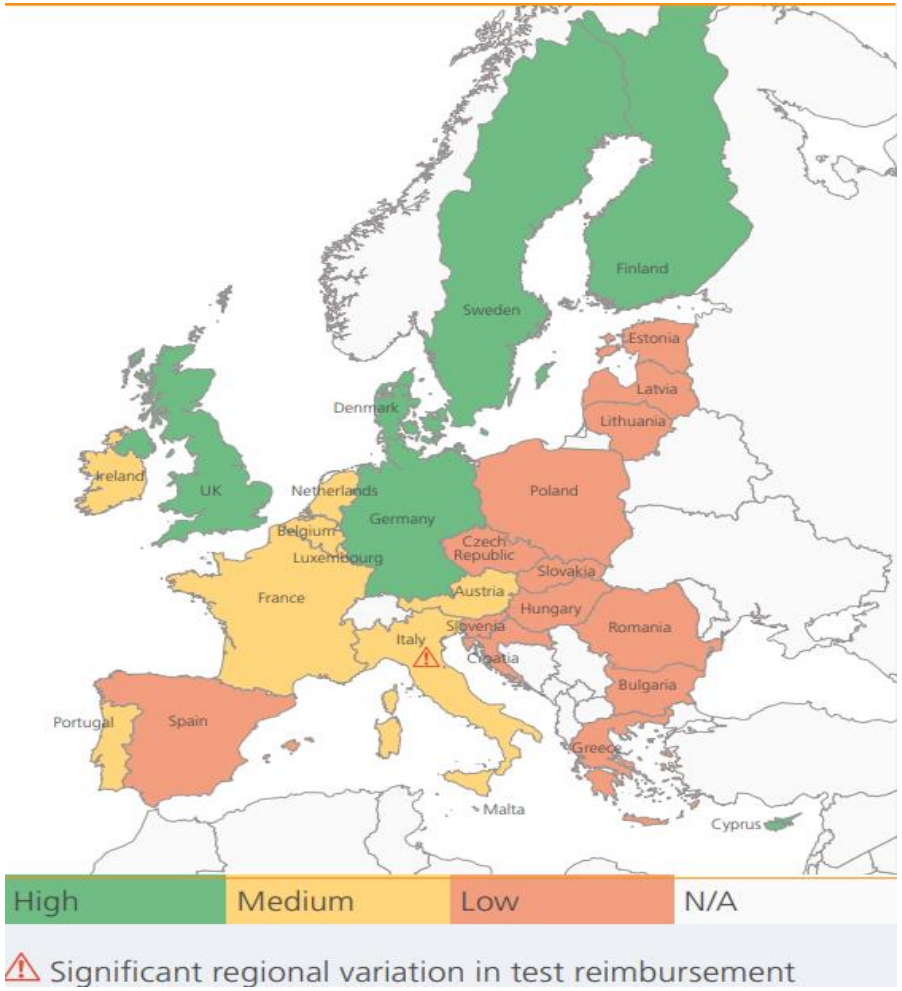
NGS hotspot (up to 12 genes)

NGS comprehensive panel

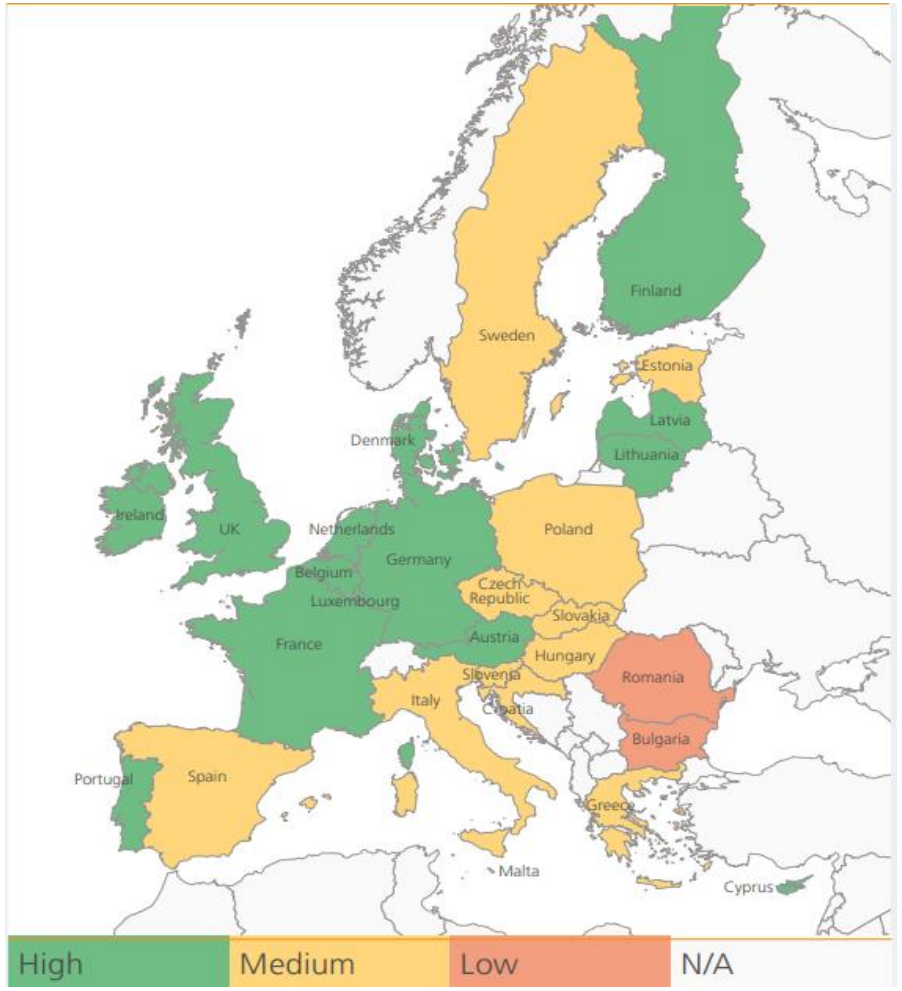
ESMO ON AIR

Unlocking the potential of precision medicine in Europe, Report by IQNPath, ECPC, EFPIA, 2021

Multi Biomarker test Reimbursement

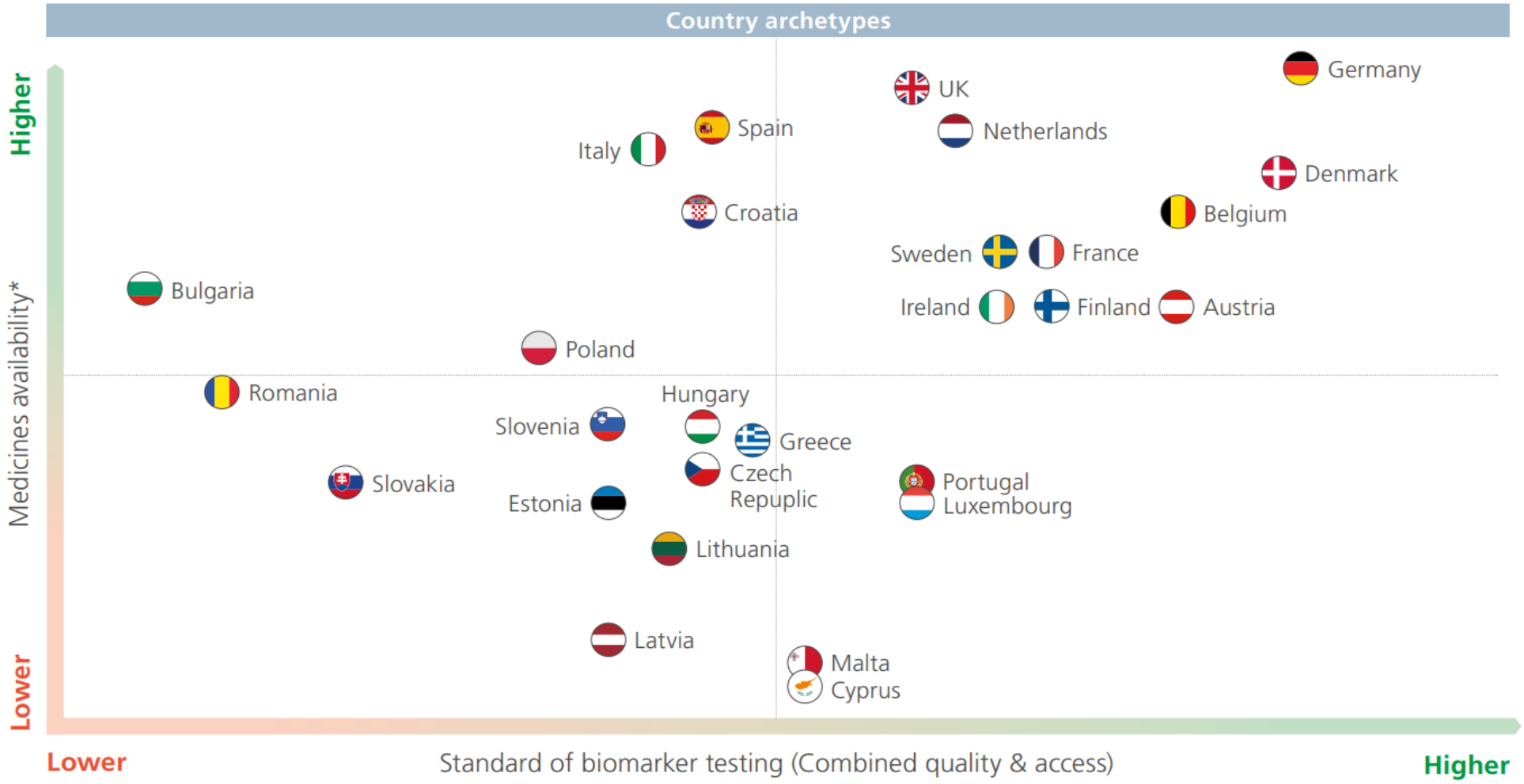


Biomarker test Quality



Unlocking the potential of precision medicine in Europe, Report by IQNPath, ECPC, EFPIA, 2021

Aggregate Performance on precision medicine availability vs biomarker testing



Note: * Focused on precision medicines; high score defined as being commercially launched and publicly reimbursed
Source: L.E.K. research and analysis

ESMO ON AIR

Unlocking the potential of precision medicine in Europe, Report by IQNPath, ECPC, EFPIA, 2021

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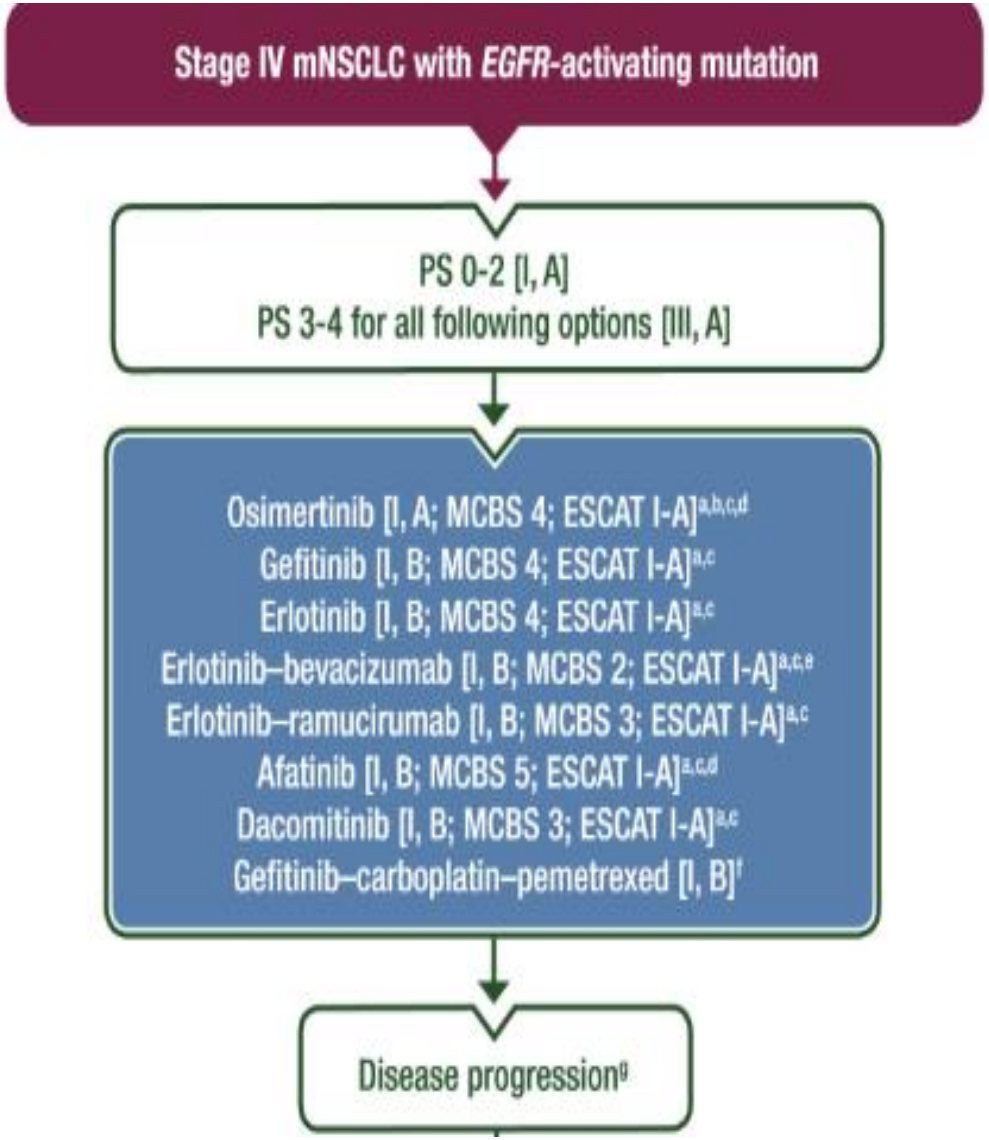
4. Take home message



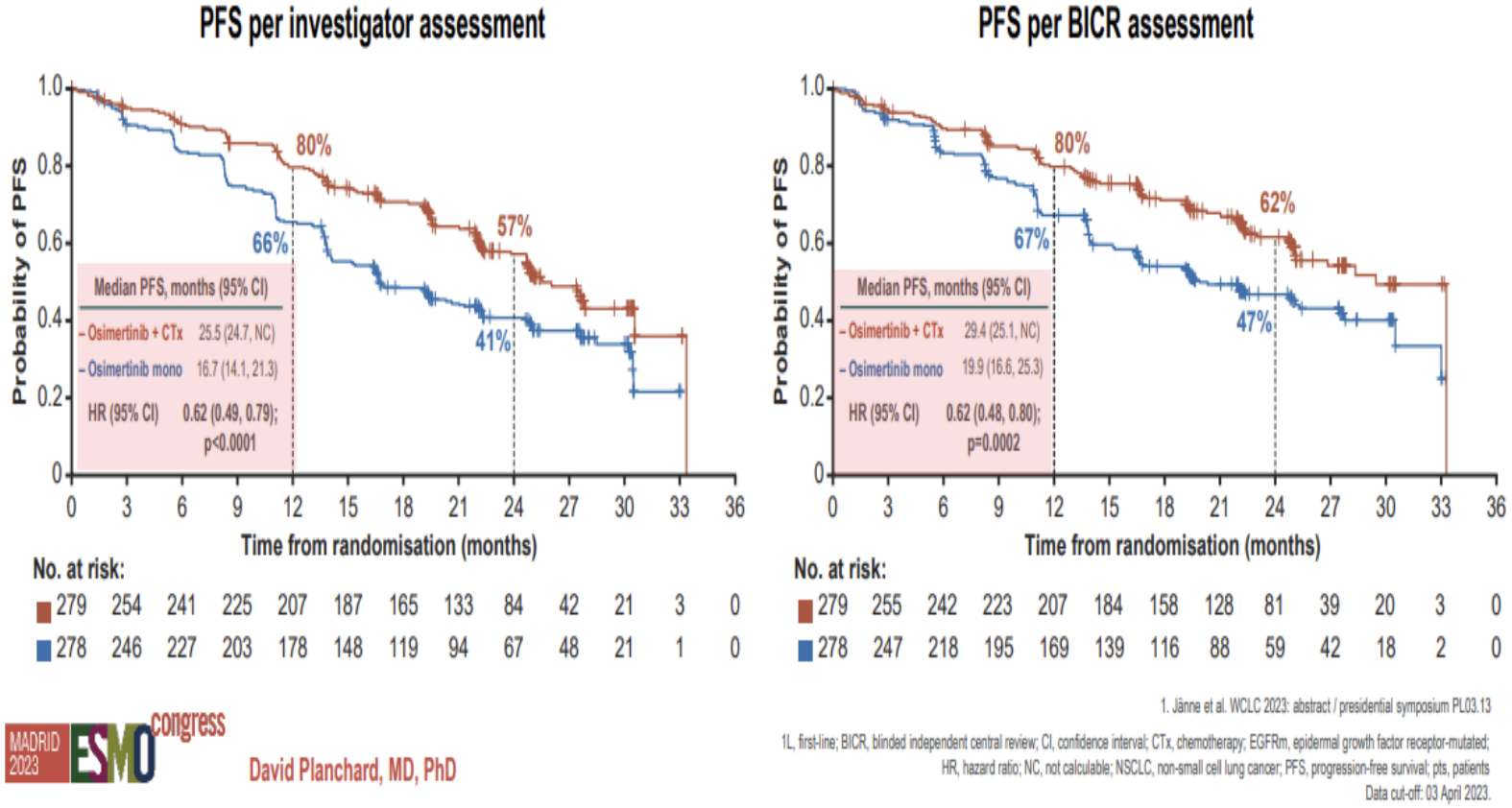
ESMO Guidelines, Hendriks et al, 2023

SUPERIORITY of EGFR TKI as 1st line

	Trial	EGFR TKI	Comparative therapy	N	EGFR mutaiton	ORR* (%)	PFS* (months)	OS* (months)
1st-Gen TKI	IPASS	Gefitinib	Car/Pac	1217	261	71 vs 47 *P*<0.001	9.5 vs 6.3 HR 0.48 (0.36-0.64)	21.6 vs 21.9 HR 1.00 (0.76-1.33)
	NEJ002		Car/Pac	224	224	74 vs 31 *P*<0.001	10.8 vs 5.4 HR 0.32 (0.24-0.44)	27.7 vs 26.6 HR 0.89 (0.63-1.24)
	WJTOG 3405		Cis/Doc	172	172	62 vs 32 *P*<0.0001	9.2 vs 6.3 HR 0.0.5 (0.34-0.71)	36 vs 39 HR 1.19 (0.77-1.83)
	EURTAC	Erlotinib	Cis/Doc or Cis/Gem	173	173	58 vs 15 *P*-value NR	9.7 vs 5.2 HR 0.37 (0.25-0.54)	22.9 vs 19.6 HR 0.92 (0.63-1.35)
	OPTIMAL		Gem/Car	165	154	83 vs 36 *P*<0.0001	13.1 vs 4.6 HR 0.16 (0.10-0.26)	22.8 vs 27.2 HR 1.19 (0.83-1.71)
	ENSURE		Gem/Cis	217	216	63 vs 34 *P*=0.0001	11.0 vs 5.6 HR 0.42 (0.27-0.66)	26.3 vs 25.5 HR 0.91 (0.61-1.31)
2nd-Gen TKI	LUX-Lung 3	Afatinib	Pem/Cis	345	308	69 vs 44 *P*=0.001	13.6 vs 6.9 HR 0.41 (0.31-0.56)	31.6 vs 28.2 HR 0.78 (0.58-1.06)
	LUX-Lung 6		Gem/Cis	364	324	74 vs 31 *P*<0.0001	13.7 vs 5.6 HR 0.26 (0.19-0.36)	23.6 vs 23.5 HR 0.83 (0.62-1.09)
	LUX-Lung 7		Gefitinib	319	319	70 vs 56 *P*=0.0083	11.0 vs 10.9 HR 0.73 (0.57-0.95	27..9 vs 24.5 HR 0.86 (0.66-1.12)
	ARCHER 1050	Dacomatinib	Gefitinib	452	452	75 vs 72 *P*=0.423	14.7 vs 9.2 HR 0.59 (0.47-0.74)	34.1 vs 26.8 HR 0.76 (0.58-0.99)
3rd-Gen TKI	FLAURA	Osimertinib	Gefitinib or Erlotinib	556	500	80 vs 76 *P*=0.24	18.9 vs 10.2 HR 0.46 (0.37-0.57)	38.6 vs 31.8 HR 0.80 (0.64-
	LASER 301	Lazertinib	Gefitinib	393	393	76 vs 76	20.6 vs 9.7 HR 0.45 (0.34-0.58	Immature

N Engl J Med. 2009;361:947-57; J Clin Oncol. 2011;29:2866-74; N Engl J Med. 2010;362:2380-98; Lancet Oncol. 2010;11:121-8; J Clin Oncol. 2014;32[suppl]:abstract 8117; Lancet Oncol. 2012;13:239-46; ESMO 2014. Abstract 1273P; Lancet Oncol. 2011;12:735-42; J Clin Oncol. 2012;30[suppl]:abstract 7520; Ann Oncol. 2015;26:1883-9; J Clin Oncol. 2013;31:3327-34; Lancet Oncol. 2014;15:213-22; Lancet Oncol 2015;16:141-51; Lancet Oncol. 2016;17[5]:577-89; Ann Oncol 2017;28(2):270-7; Lancet Oncol. 2017;18(11):1454-66; J Clin Oncol. 2018;36(22):2244-50; N Engl J Med. 2018;378(2):113-25.

FLAURA 2: PFS



1. Jänne et al. WCLC 2023: abstract / presidential symposium PL03.13

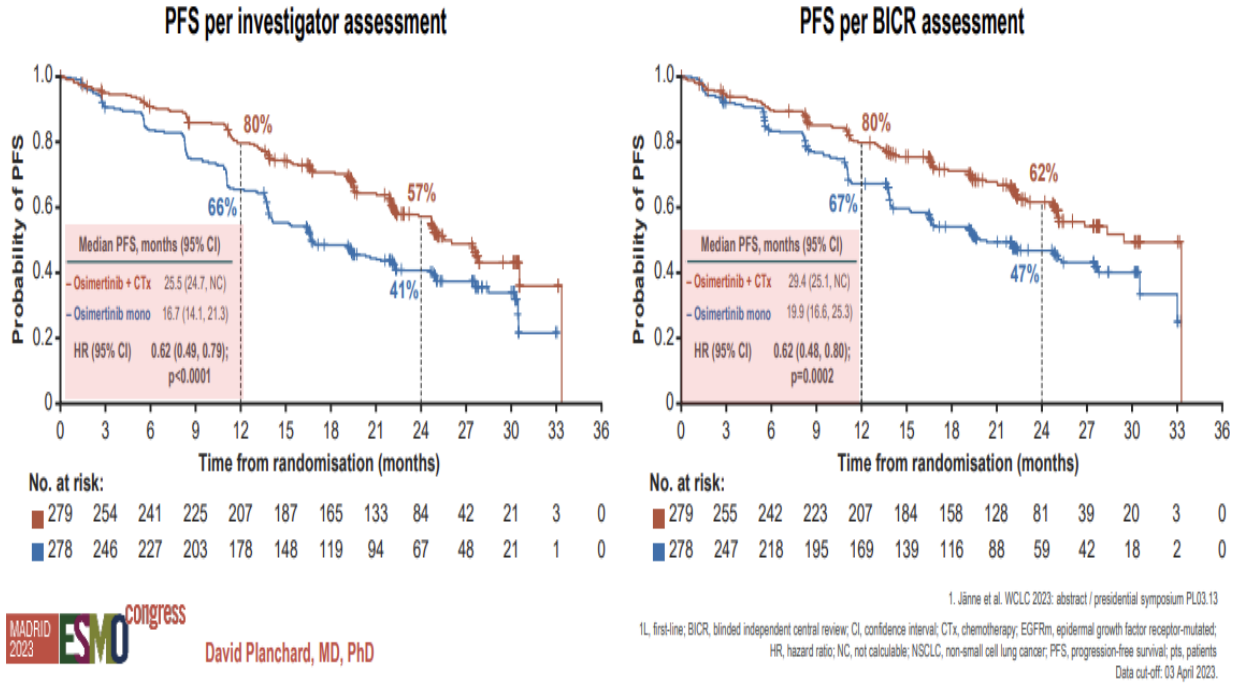
1L, first-line; BICR, blinded independent central review; CI, confidence interval; CTx, chemotherapy; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; pts, patients
Data cut-off: 03 April 2023.

Osi+platinum based chemotherapy and pemetrexed significantly improved mPFS by 9.5 mos per BICR

MADRID 2023 ESMO congress

David Planchard, MD, PhD

FLAURA 2: PFS according to CNS metastases



MADRID 2023 ESMO congress

David Planchard, MD, PhD

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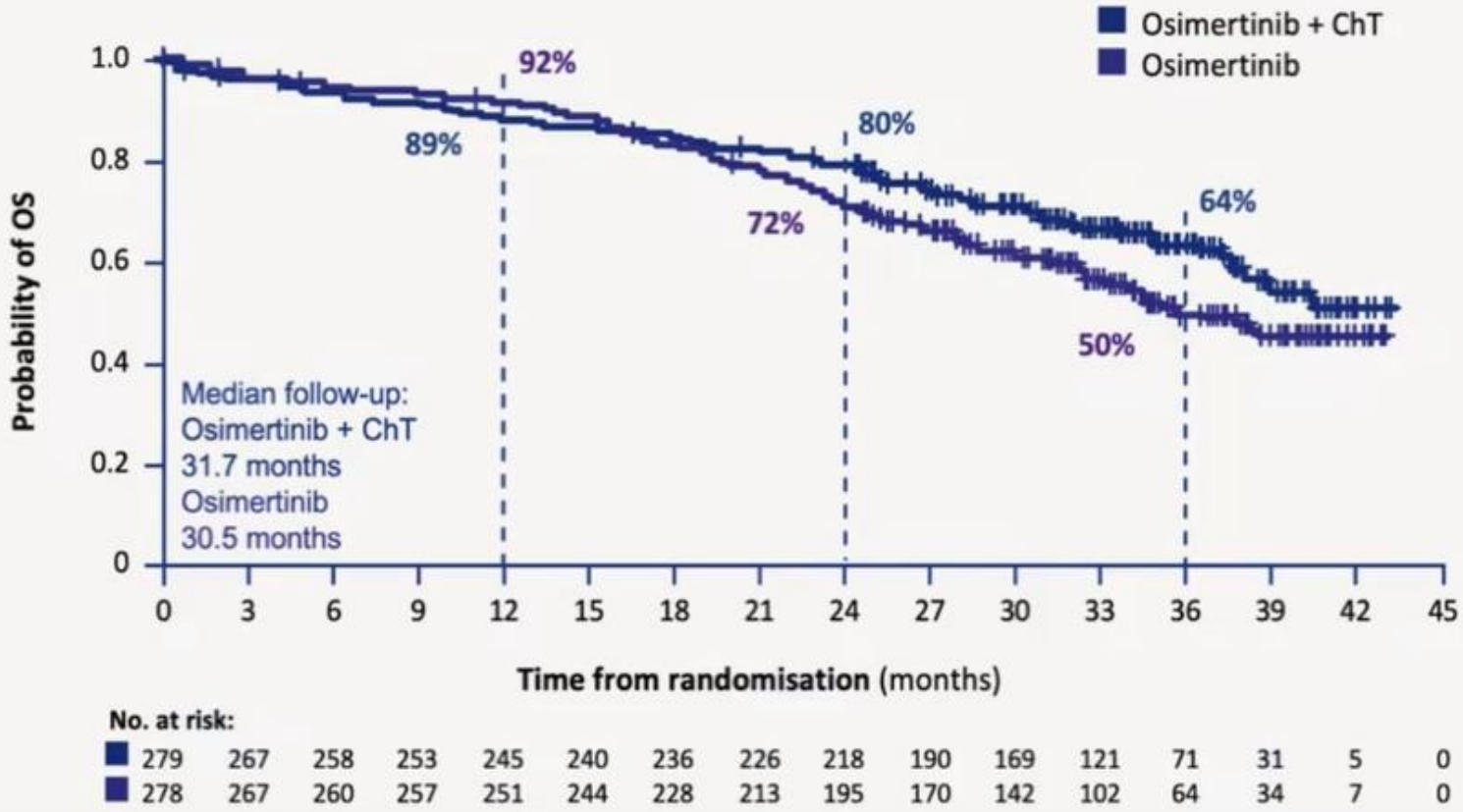
Data cut-off: 03 April 2023.

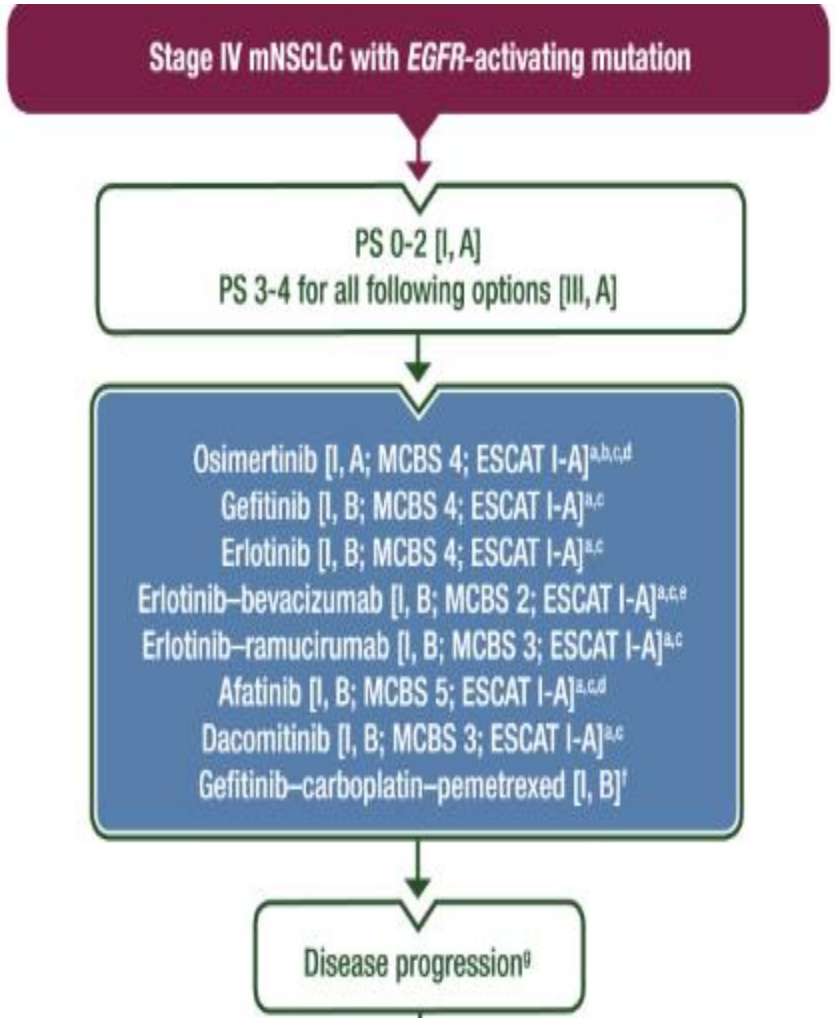
Endpoint	Osimertinib + platinum-pemetrexed (n=279)	Osimertinib monotherapy (n=278)
mPFS per INV, months (95% CI)		
Overall population	**25.5** (24.7–NC)	**16.7** (14.1–21.3)
	HR 0.62 (95% CI, 0.49–0.79); p<0.0001	
With CNS metastases	**24.9** (22.0–NC)	**13.8** (11.0–16.7)
	HR 0.47 (95% CI, 0.33–0.66)	
Without CNS metastases	**27.6** (24.7–NC)	**21.0** (16.7–30.5)
	HR 0.75 (95% CI, 0.55–1.03)	
mOS, months (95% CI)		
Overall population	**NR** (31.9–NC)	**NR** (NC–NC)
	HR 0.90 (95% CI, 0.65–1.24); p=0.5238	

CNS metastases not a stratification factor!!!

FLAURA 2: OS 2nd Interim Analysis



mOS, months (95% CI)		
Osimertinib + ChT	NR (38.0–NE)	HR, 0.75 (95% CI, 0.57–0.97); p=0.028*
Osimertinib	36.7 (33.2–NE)	



Since Dec 2024 EMA Approval of Osimertinib+platinum-based chemotherapy and Pemetrexed

Gap b/n clinical trials and real practice

Patients from clinical trials:

ECOG PS 0-1

Relatively homogeneous population

Adequate bone marrow, kidney and liver function

Controlled comorbidity profile

Patients from routine practice:

ECOG PS 1 and more

Heterogeneous population with small subgroup close to the trial

Underrepresented patients with cardio-vascular, lung, HIV infection, autoimmune diseases

Elderly patients

Co-medication – corticosteroids, opiods, antibiotics, herbal intake

Implementation of FLAURA 2 in daily practice?

Reimbursement and access

Increased toxicity

Prolonged hospital stay

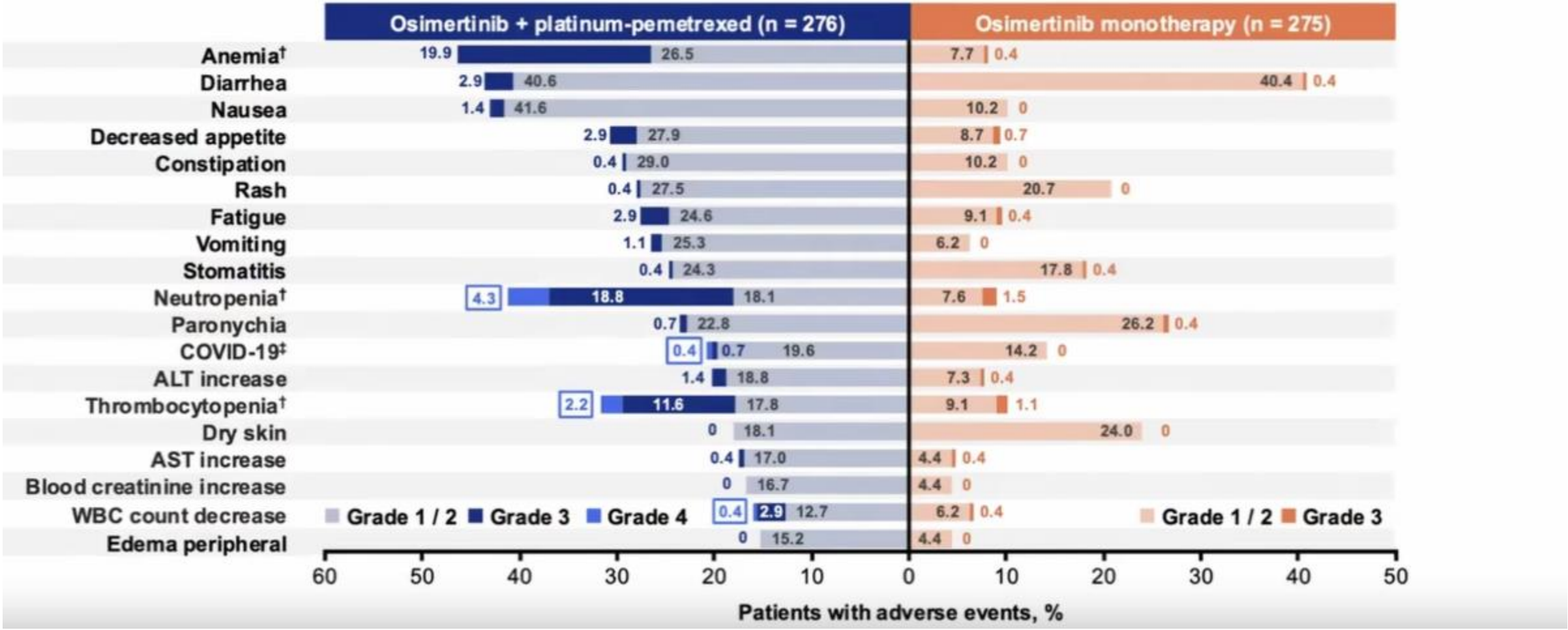
Nurses`and pharmacists` shortage

Improved PFS

Improved PFS in pts with CNS mets

Improved OS

Implementation of FLAURA 2 in daily practice? - Toxicity



Implementation of FLAURA 2 in daily practice? - Staff

We currently face a shortage of 1.2 million doctors, nurses and midwives across the EU, and there is a decline in interest in nursing careers across more than half of EU countries. The action launched today shows our commitment to addressing the shortage of nurses in Member States – European Health Union

Nurses from Bulgaria, Greece, Poland and Spain are underpaid and tempted to work in Switzerland, Austria, Germany, Belgium and the Netherlands - WHO

Need for pharmacists around Europe, in Ireland the situation is critical – Akram Ahmad, Healthcare Carrer Coach

Implementation of FLAURA 2 in daily practice? – Hospital Stay

Chemotherapy +Osimertinib requires:

- prolonged stay at the oncology department
- mandatory IV infusions (not all patients with port-a-cath)
- mandatory blood tests before every treatment cycle
- additional intake of folic acid and Vit B12
- intensity of monitoring

Implementation of FLAURA 2 in daily practice?

BTOG Patient Preference

I was diagnosed at 40, I have two young children. There is nothing I wouldn`t do to have more time with them….

Chemo scares me, while osi allows you to live contras but…. I would probably opt for osi and chemo

I was diagnosed at 72, so I would have to question whether the side effects are really worth it….

I would be reluctant to have chemo alongside Osi ….I can live a normal life on Osi and the side effects with the chemo added sound quite dire…

I think I`d have lots of questions about pros and contras, but would like to have the opportunity to be able to make an informed choice….

Implementation of FLAURA 2 in daily practice? Reimbursement and Access

YES – Germany, Austria, New Zealand, USA

NO – UK, Italy, Romania, Bulgaria, Sweden, Serbia, Hungary, Slovakia, Spain, Macedonia

Outline

1. Molecular testing in adeno NSCLC
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3. **Oligometastatic disease**
4. Take home message

Oligometastatic disease – definition by EORTC

Relevant for patients for whom a **radical treatment** is **technically feasible** with **acceptable toxicity**, taking into account **all sites**, that may modify the course of the disease, leading to a **long-term disease control**

No consensus on **maximum nr** of metastases

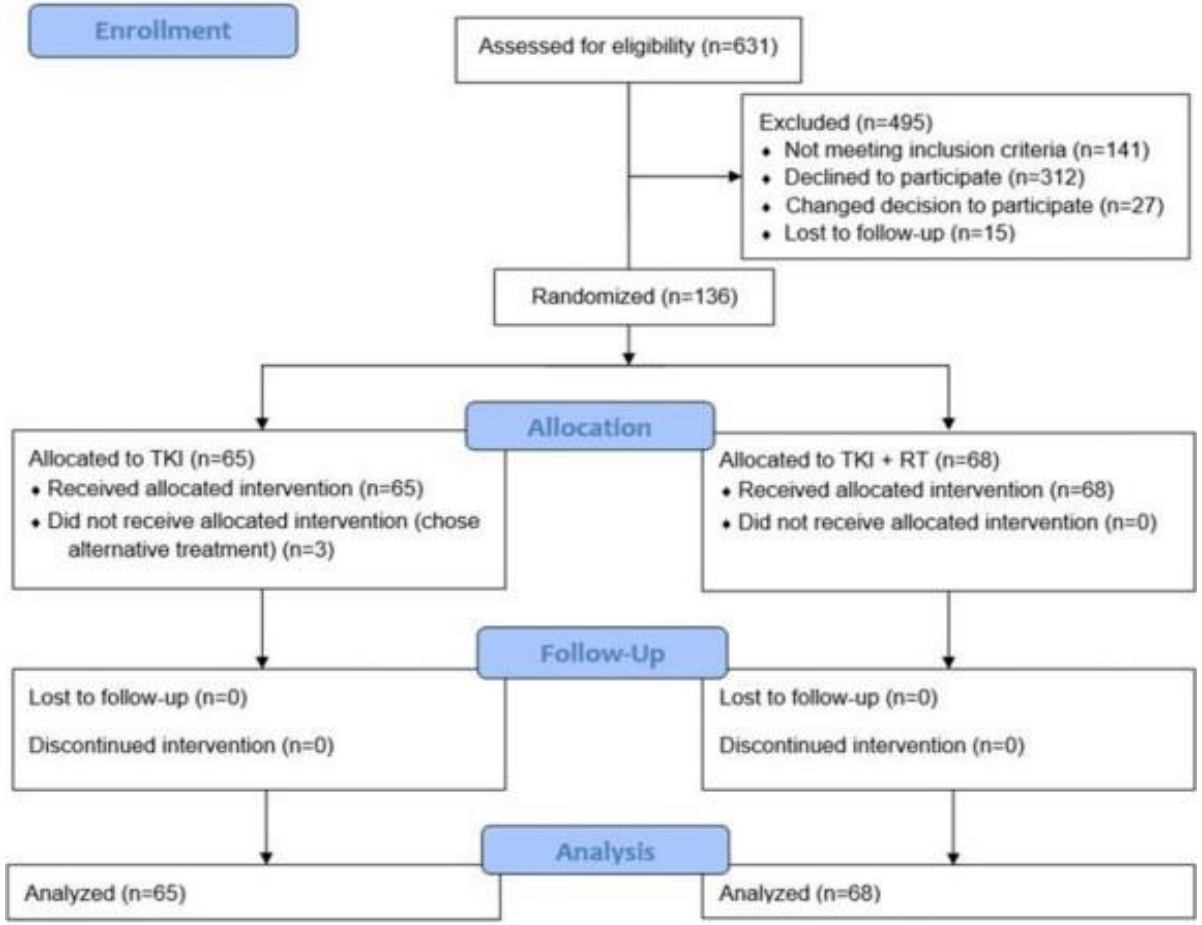
Max nr metastases depends on possibility to radically treat all sites with acceptable toxicity, based on review **max 5 mets in 3 organs** proposed. Diffuse serosal mets and bone marrow mets excluded

MANDATORY: FDG-PET CT; Brain imaging (MRI)

Intermediate state
Possible benefit of Local Ablative Therapy

Dingemans, Hendriks et al, JTO 2019

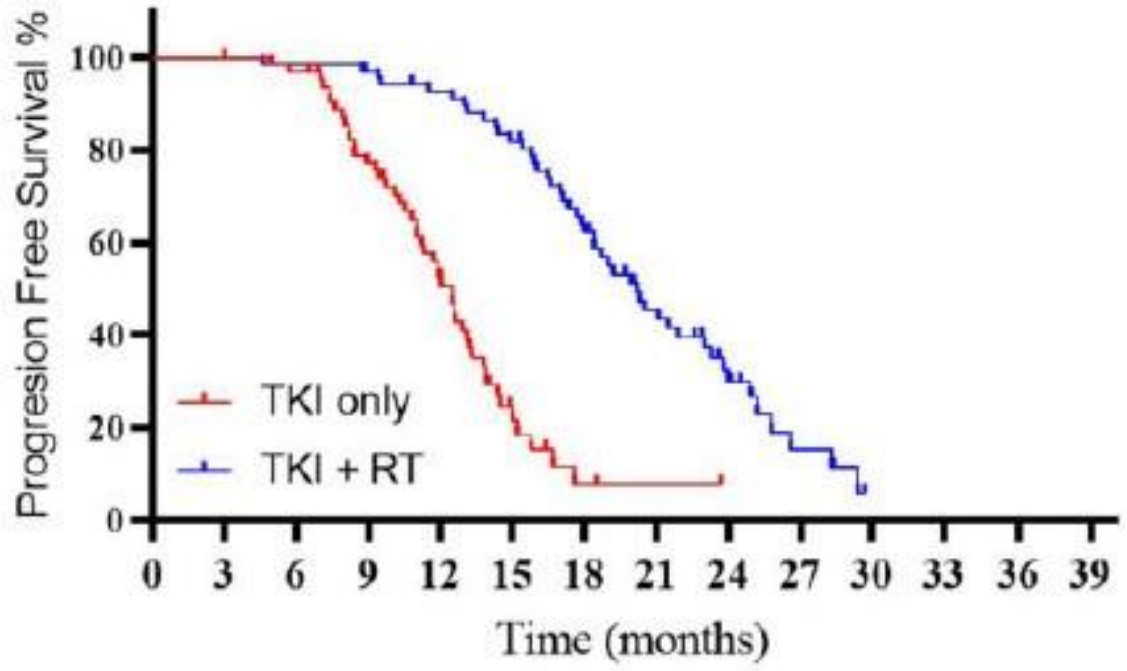
SINDAS TRIAL



- Phase III randomized trial in EGFR mutation positive oligometastatic NSCLC Primary endpoint was PFS
- 133 patients enrolled from 2016-2019

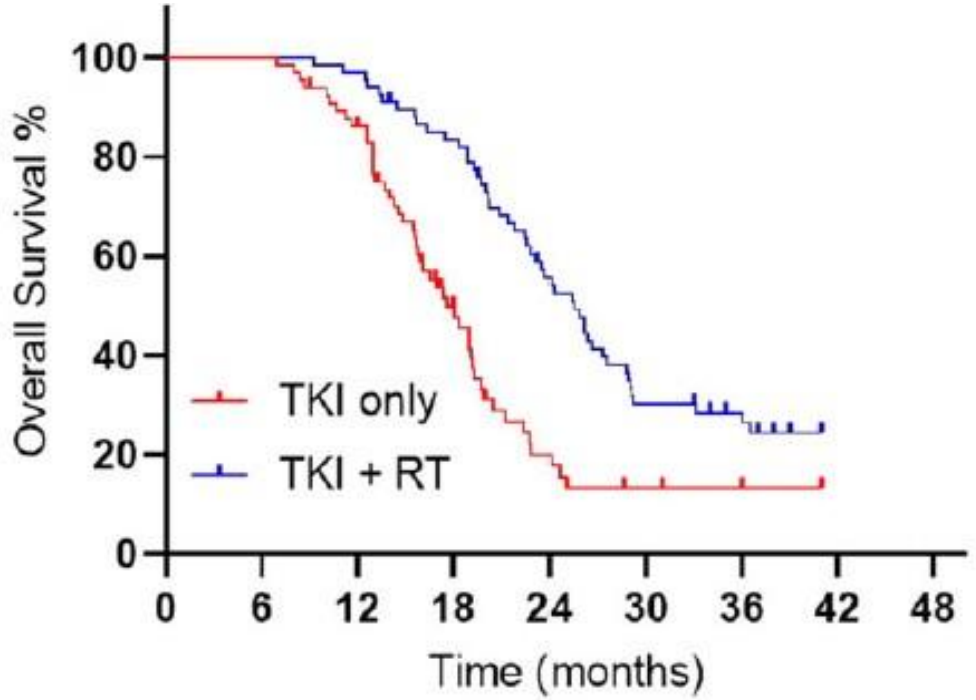
Wang et al JNCI 114(5) 2022

SINDAS TRIAL



TKI only	65	65	62	48	28	8	3	2	1	0	0
TKI + RT	68	67	67	65	60	51	37	22	12	5	1

Figure 2. Kaplan-Meier curves illustrating progression-free survival between arms. RT = radiation therapy; TKI = tyrosine kinase inhibitor.



TKI only	65	65	55	26	9	5	3	2
TKI + RT	68	68	66	56	36	20	14	9

Figure 3. Kaplan-Meier curves illustrating overall survival between arms. RT = radiation therapy; TKI = tyrosine kinase inhibitor.

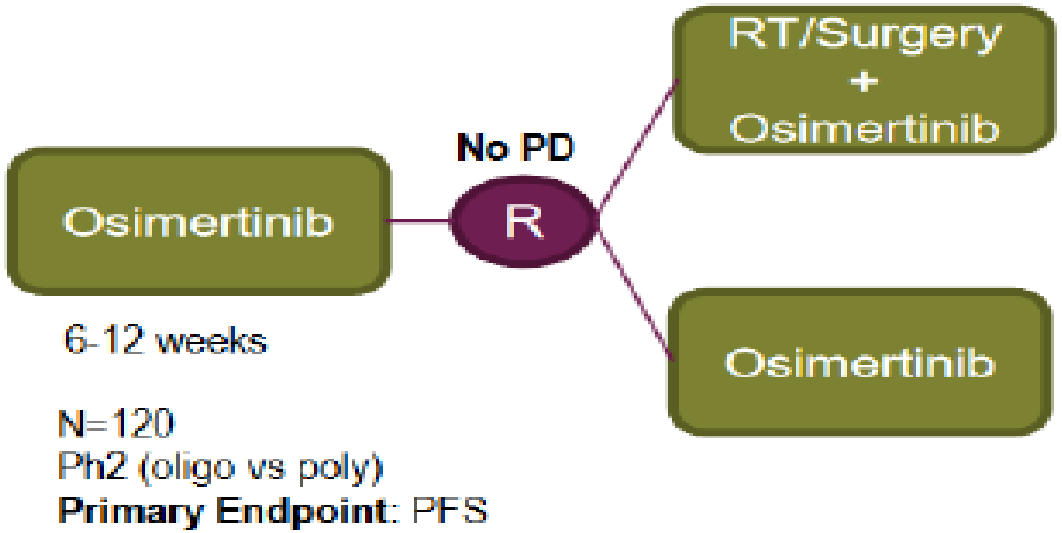
Wang et al JNCI 114(5) 2022

NORTHSTAR TRIAL

EGFRmut

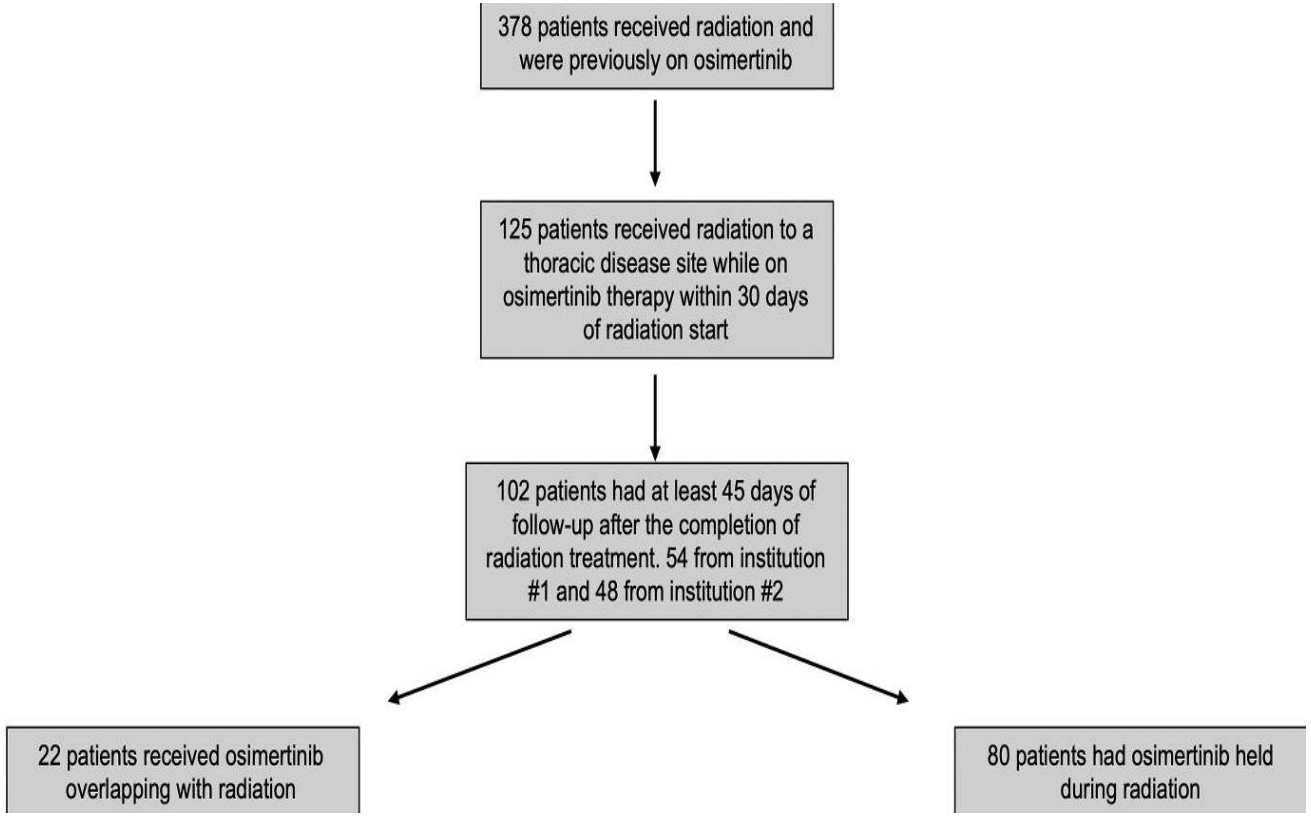
NORTHSTAR trial design (NCT03410043)

Osimertinib + SBRT/Surgery vs Osimertinib



Gomez, Ann Oncology 2018

Pneumonitis with Osimertinib and Thoracic Radiotherapy – multi-institutional study



The median clinical follow-up was 10.2 months (range: 1.9–53.2).

A total of 16 patients (15.7%) developed any-grade pneumonitis, and 14 (13.7%) developed CTCAE grade 2+ pneumonitis

Among the 22 patients who received osimertinib overlapping with TRT (Thoracic radiotherapy) , two (9.1%) developed grade 2+ pneumonitis, compared with 12 (15.0%) of the 80 patients for whom osimertinib was held during TRT (p = 0.729, Fisher's exact test)

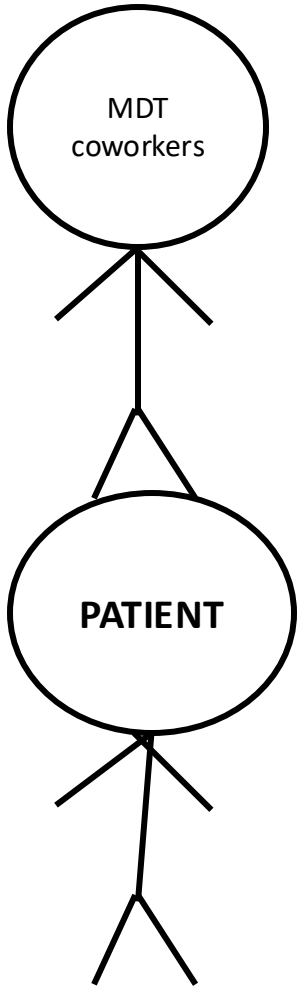
The median time to grade 2+ pneumonitis was 3.2 months (range: 1.5–6.3 mo).

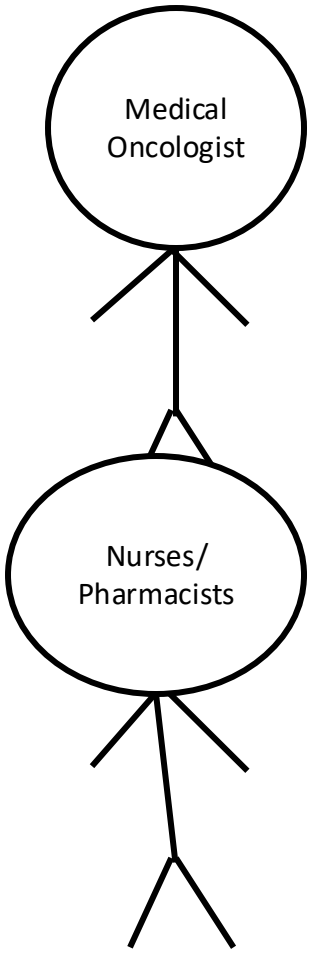
JTO Clin Res Rep L.I. Banla; 2023 Aug 17; 4(10)

Outline

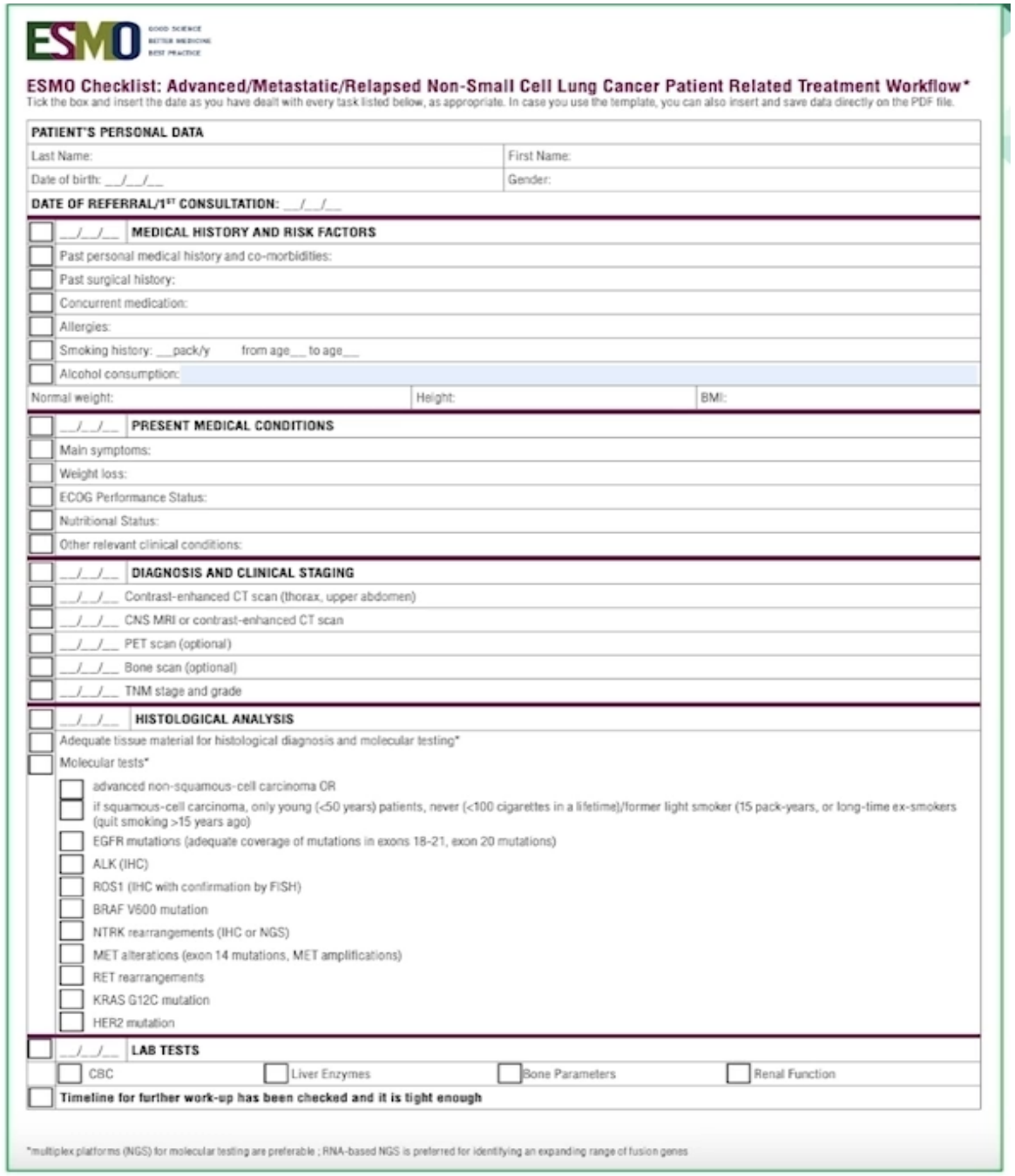
1. Molecular testing in adeno NSCLC
2. First line options for treatment in EGFR+ NSCLC
3. Oligometastatic disease
4. **Take home message**

TAKE HOME MESSAGE


MDT
coworkers
PATIENT


Medical
Oncologist
Nurses/
Pharmacists

ESMO CHECKLIST



ESMO Checklist: Advanced/Metastatic/Relapsed Non-Small Cell Lung Cancer Patient Related Treatment Workflow*

Tick the box and insert the date as you have dealt with every task listed below, as appropriate. In case you use the template, you can also insert and save data directly on the PDF file.

PATIENT'S PERSONAL DATA

Last Name:	First Name:
Date of birth: __/__/__	Gender:

DATE OF REFERRAL/1ST CONSULTATION: __/__/__

- ☐ __/__/__ **MEDICAL HISTORY AND RISK FACTORS**
  - ☐ Past personal medical history and co-morbidities:
  - ☐ Past surgical history:
  - ☐ Concurrent medication:
  - ☐ Allergies:
  - ☐ Smoking history: __pack/y from age__ to age__
  - ☐ Alcohol consumption:

Normal weight:	Height:	BMI:

- ☐ __/__/__ **PRESENT MEDICAL CONDITIONS**
  - ☐ Main symptoms:
  - ☐ Weight loss:
  - ☐ ECOG Performance Status:
  - ☐ Nutritional Status:
  - ☐ Other relevant clinical conditions:
- ☐ __/__/__ **DIAGNOSIS AND CLINICAL STAGING**
  - ☐ __/__/__ Contrast-enhanced CT scan (thorax, upper abdomen)
  - ☐ __/__/__ CNS MRI or contrast-enhanced CT scan
  - ☐ __/__/__ PET scan (optional)
  - ☐ __/__/__ Bone scan (optional)
  - ☐ __/__/__ TNM stage and grade
- ☐ __/__/__ **HISTOLOGICAL ANALYSIS**
  - ☐ Adequate tissue material for histological diagnosis and molecular testing*
  - ☐ Molecular tests*
    - ☐ advanced non-squamous-cell carcinoma OR
    - ☐ if squamous-cell carcinoma, only young (<50 years) patients, never (<100 cigarettes in a lifetime)/former light smoker (15 pack-years, or long-time ex-smokers (quit smoking >15 years ago)
    - ☐ EGFR mutations (adequate coverage of mutations in exons 18-21, exon 20 mutations)
    - ☐ ALK (IHC)
    - ☐ ROS1 (IHC with confirmation by FISH)
    - ☐ BRAF V600 mutation
    - ☐ NTRK rearrangements (IHC or NGS)
    - ☐ MET alterations (exon 14 mutations, MET amplifications)
    - ☐ RET rearrangements
    - ☐ KRAS G12C mutation
    - ☐ HER2 mutation
- ☐ __/__/__ **LAB TESTS**
  - ☐ CBC ☐ Liver Enzymes ☐ Bone Parameters ☐ Renal Function
- ☐ **Timeline for further work-up has been checked and it is tight enough**

*multiplex platforms (NGS) for molecular testing are preferable ; RNA-based NGS is preferred for identifying an expanding range of fusion genes

THANKS FOR LISTENING

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