ESMO ON AIR

Precision Oncology in Lung Cancer – Diagnostics

ESMO DEEP DIVE WEBINAR SERIES: LUNG CANCER

Thomas John, *Chair*

Peter MacCallum Cancer Centre,
University of Melbourne, Australia

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

5 February 2025

5 min	**Welcome and introduction** Tom John
25 min	**Precision through genomics and beyond (multi-omics)** Celine Mascaux
25 min	**Harnessing liquid biopsy for diagnosis, monitoring** Christian Rolfo
25 min	**Beyond Xray vision – novel imaging technologies and radiomics** Raquel Lopez
15 min	**QnA and Discussion** All speakers

Thomas John
Chair
Peter MacCallum Cancer Centre, University of Melbourne

Celine Mascaux
Speaker
Strasbourg University Hospital

Christian Rolfo
Speaker
The Ohio State University Wexner Medical Center

Raquel Perez Lopez
Speaker
Vall d'Hebron Institute of Oncology

Learning objectives

- To acquire a deeper understanding of the clinical course of lung cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for lung cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO ON AIR

Precision Oncology in Lung cancer – Diagnostics (genomics, transcriptomics (SCLC), plasma, radiomics)

Celine Mascaux

04 février 2025

ESMO EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

ESMO ON AIR

Precision medecine through genomics and beyond (multi-omics)

Celine Mascaux

04 février 2025

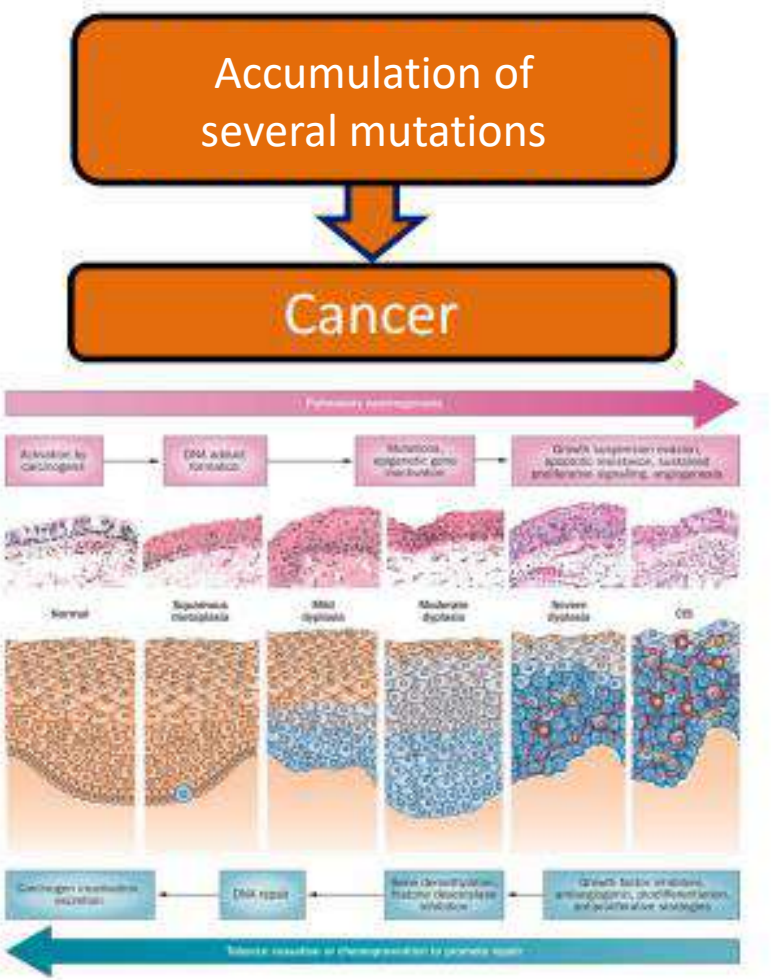
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

WHY
IN WHOM do we analyse tumours for molecular abnormalities ?
HOW

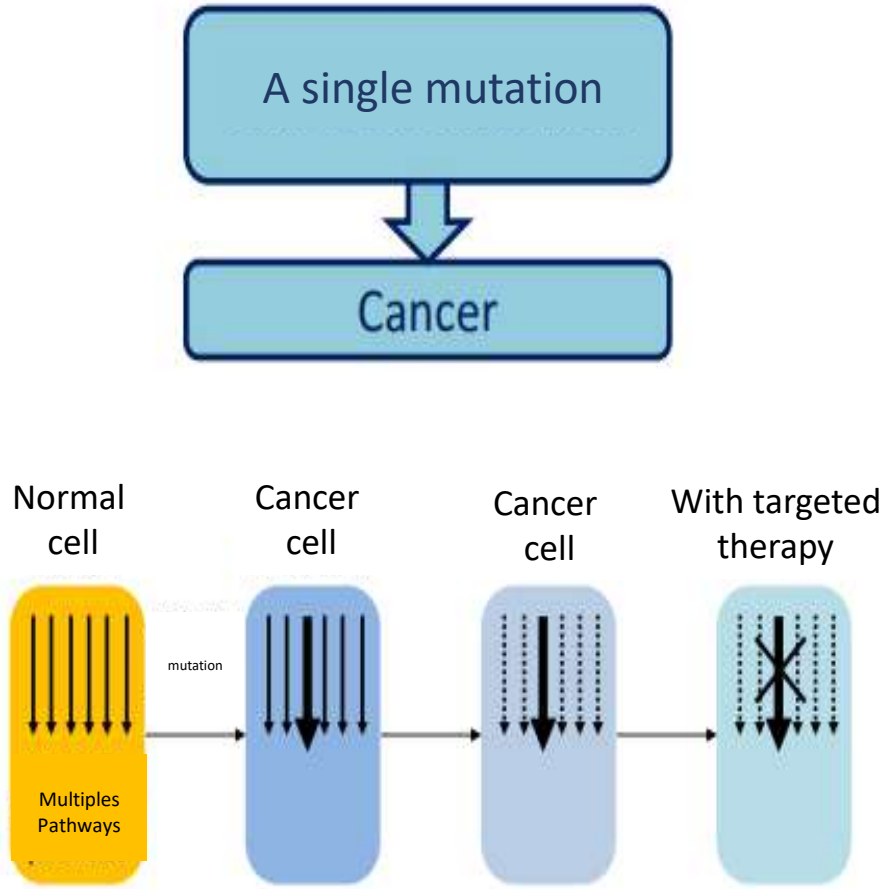
WHY do we analyse tumours for molecular abnormalities ?

Two models of carcinogenesis

Multistep carcinogenesis



Oncogenic addiction

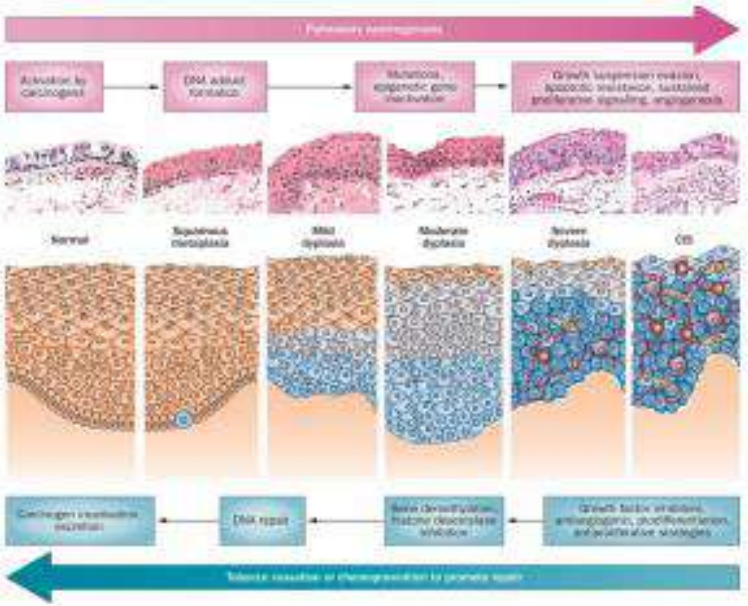


Two models of carcinogenesis

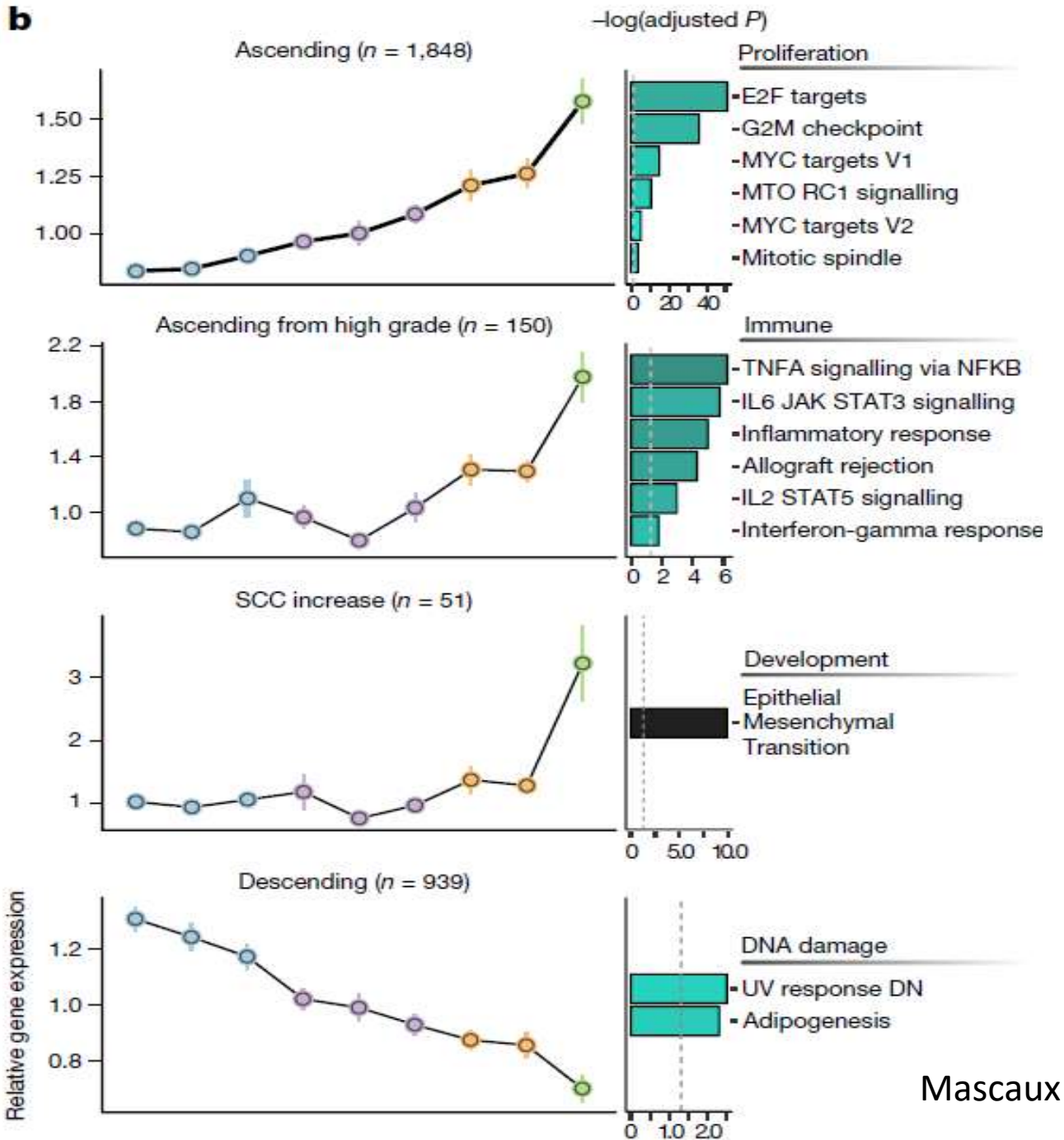
Multistep carcinogenesis

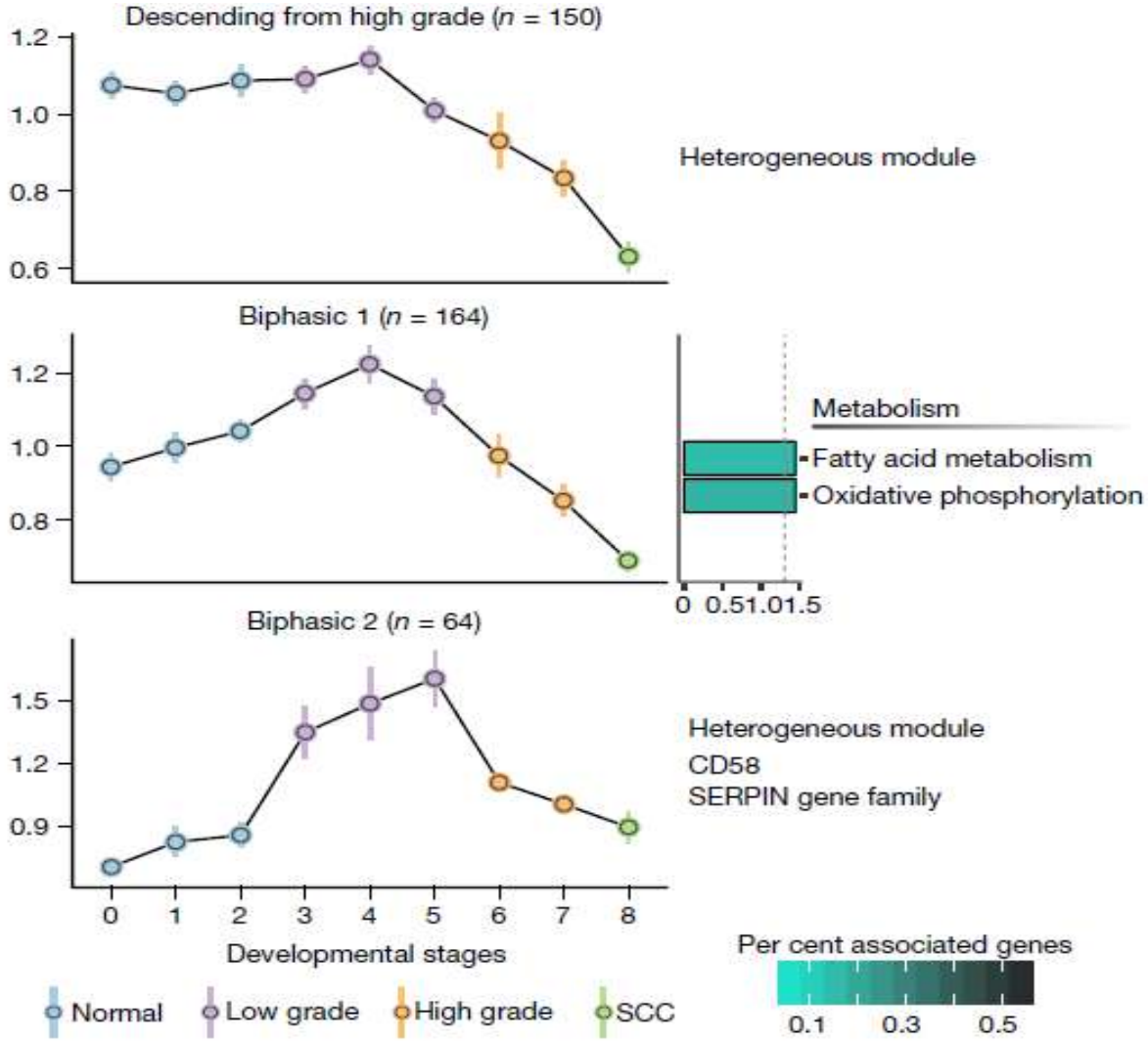
Accumulation of several mutations

Cancer



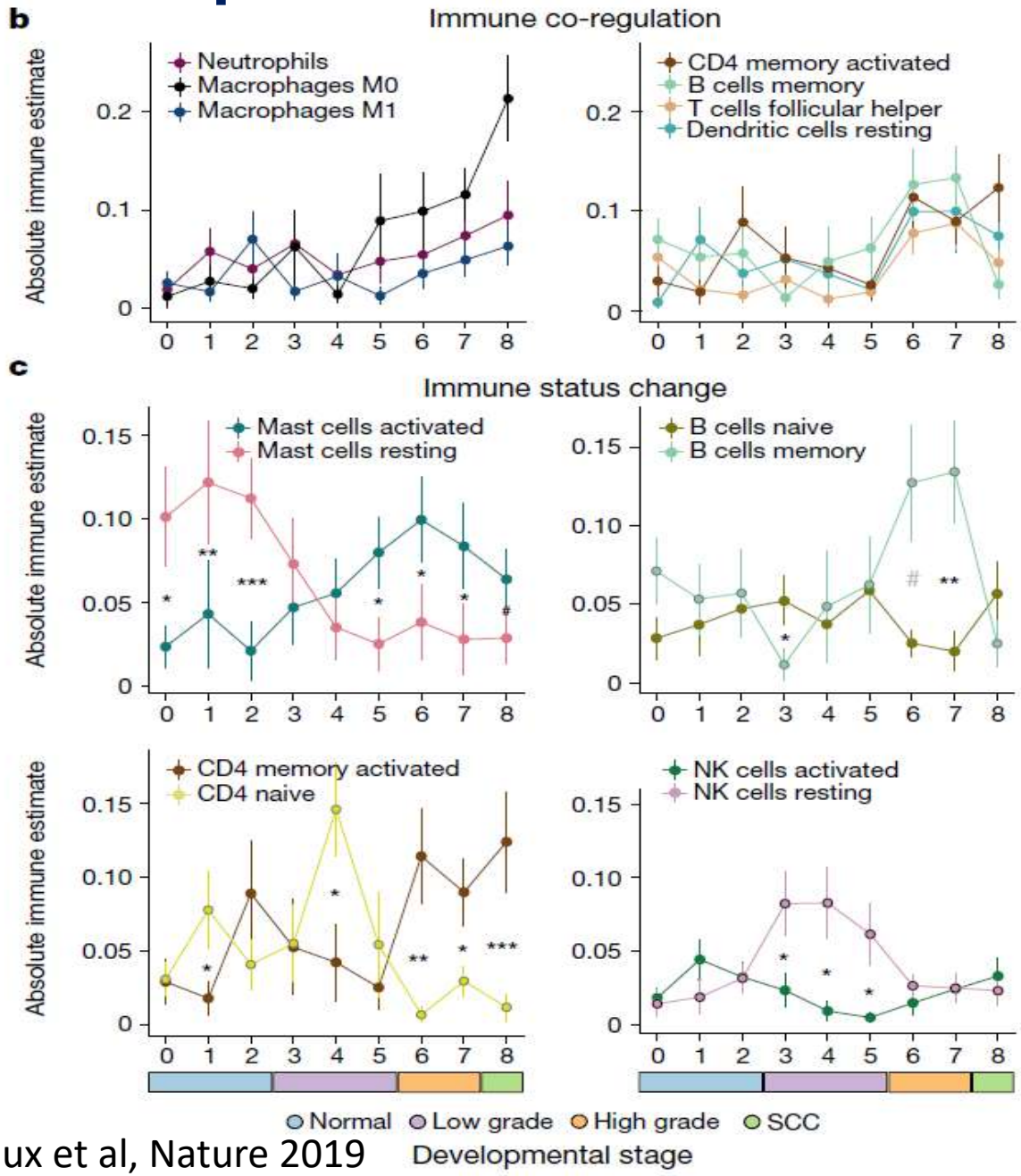
Multi-step carcinogenesis





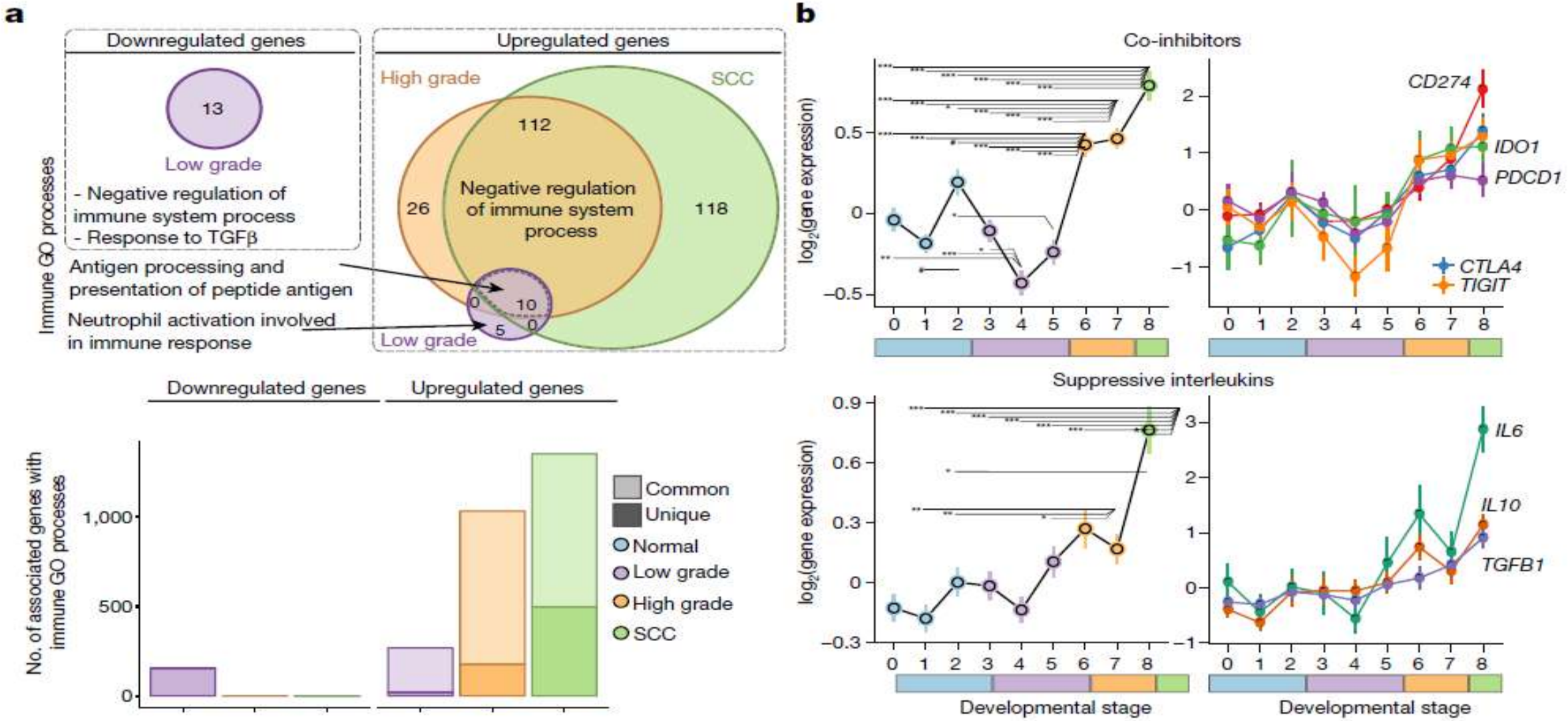
Mascaux et al, Nature 2019

Active immune response



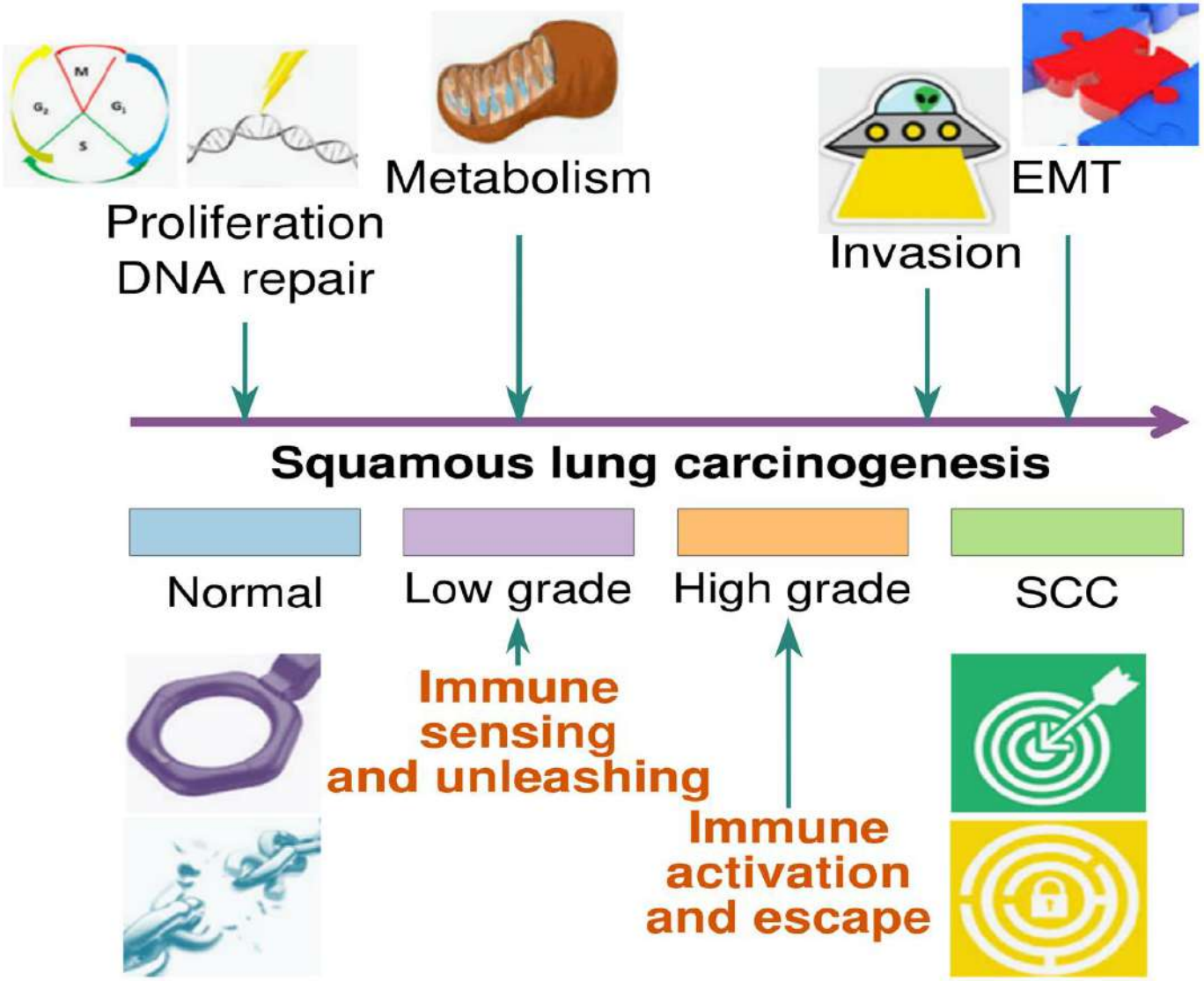
Mascaux et al, Nature 2019

Early inhibition of immune response



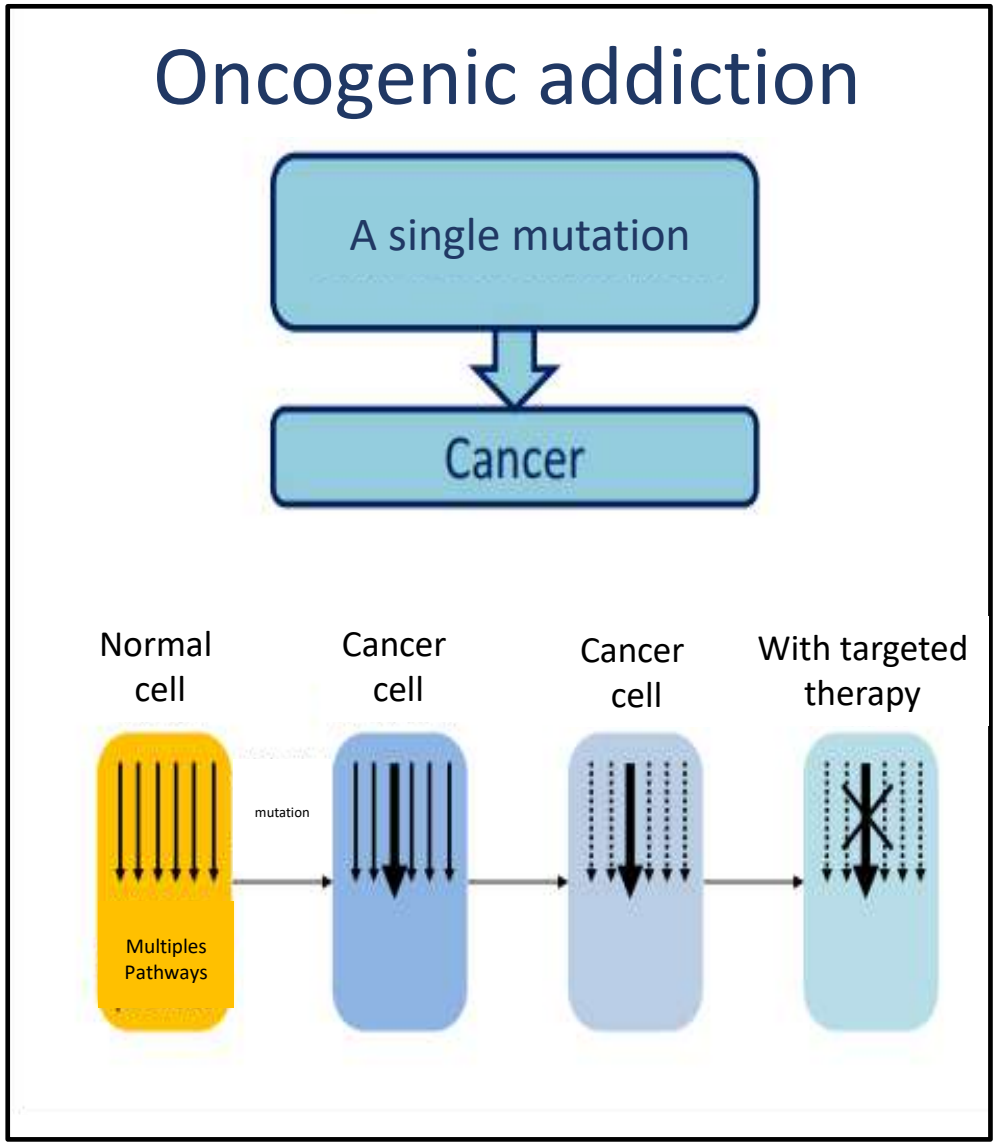
Mascaux et al, Nature 2019

Chronology of molecular pathway of lung carcinogenesis



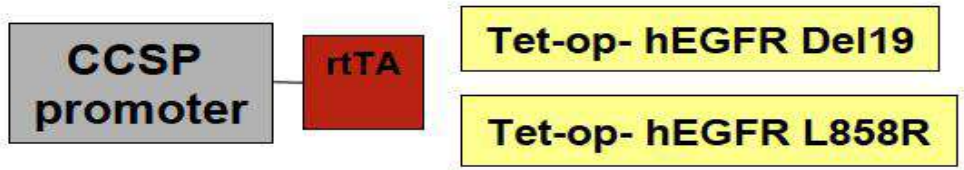
Mascaux et al, Nature 2019

Two models of carcinogenesis



Genetically engineered models of lung cancer

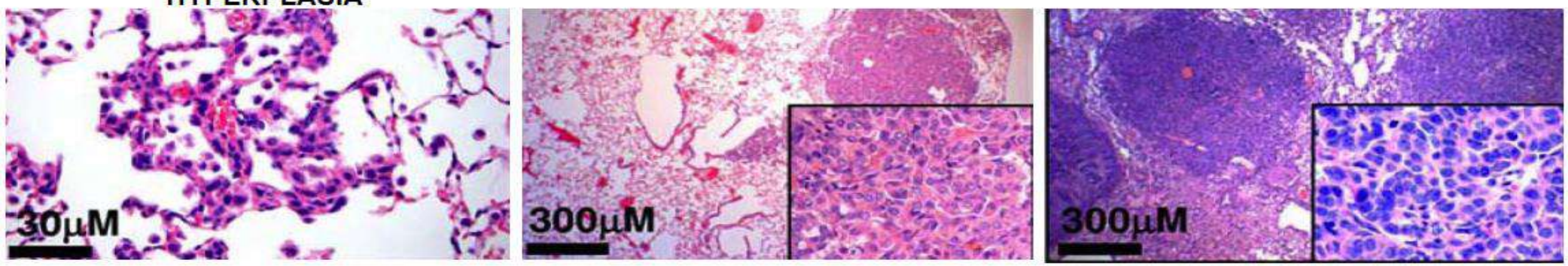
Cell specific inducible hEGFR mutant



✓ Doxycycline administration

3-4 weeks — 5-6 weeks — 8-10 weeks

ATYPICAL ADENOMATOUS HYPERPLASIA | ADENOMA | ADENOCARCINOMA

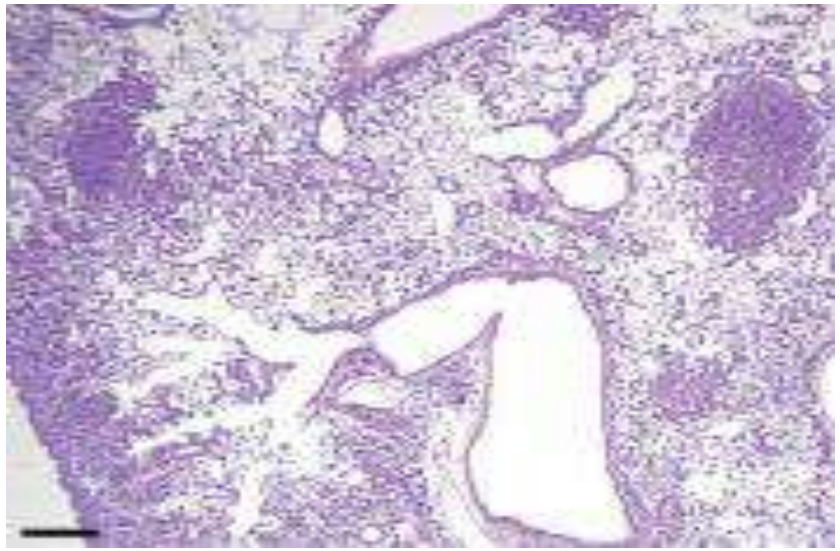


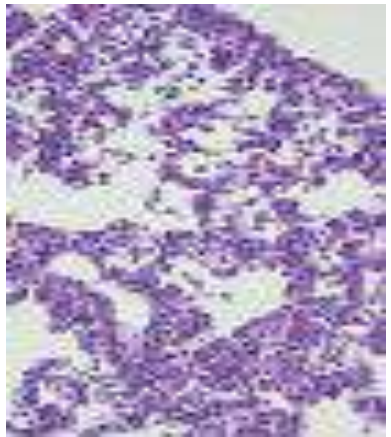
- 100% developed adenocarcinoma with BAC features after 8 or more weeks (SPC+)
- Expression of the hEGFR mutants is essential for tumor maintenance (After 3 weeks of doxycycline withdrawal a complete regression was observed)
- Treatment with TKis (erlotinib or HKI-272) or long term anti-hEGFR antibody (cetuximab) led to tumor regression.

Ji et al. Cancer Cell 2006 9(6):485-95

Mouse Lung Adenocarcinomas Induced by Sensitive EGFR Mutations Respond to Down-regulation of the Receptors or Erlotinib

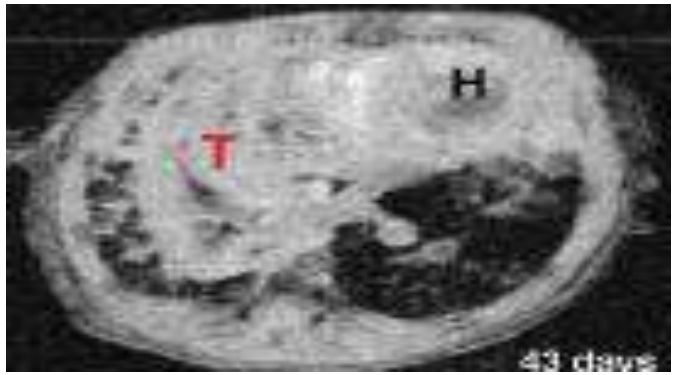
Histopathology



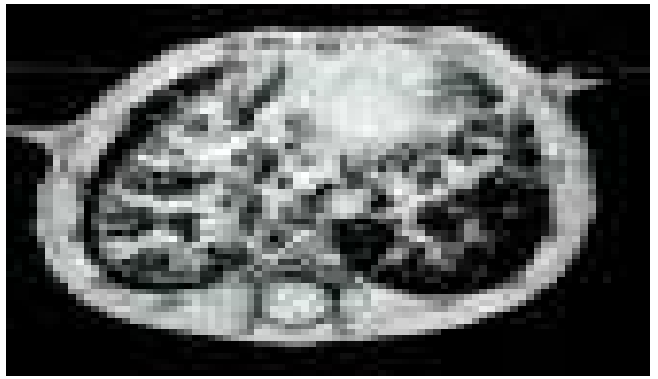


Tumor Response (MRI)

7 weeks ON dox

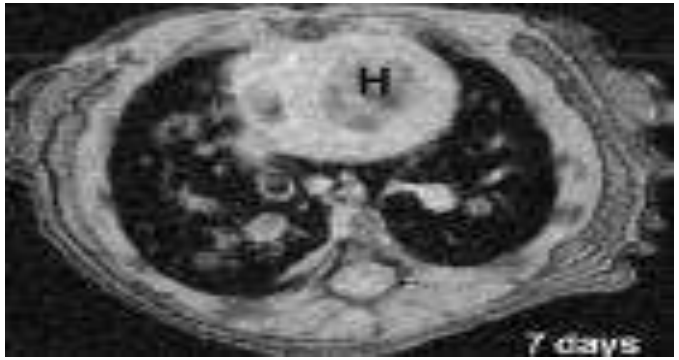


9 weeks on dox

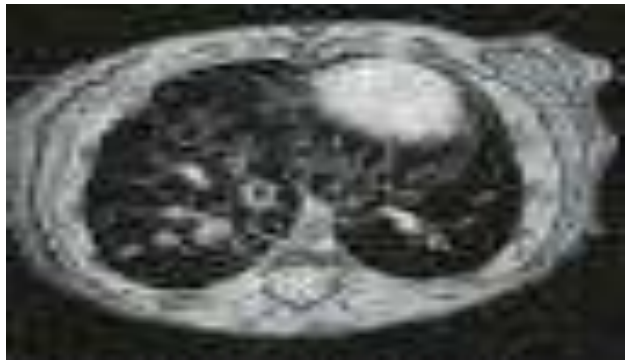


10 weeks on dox

1 week OFF dox

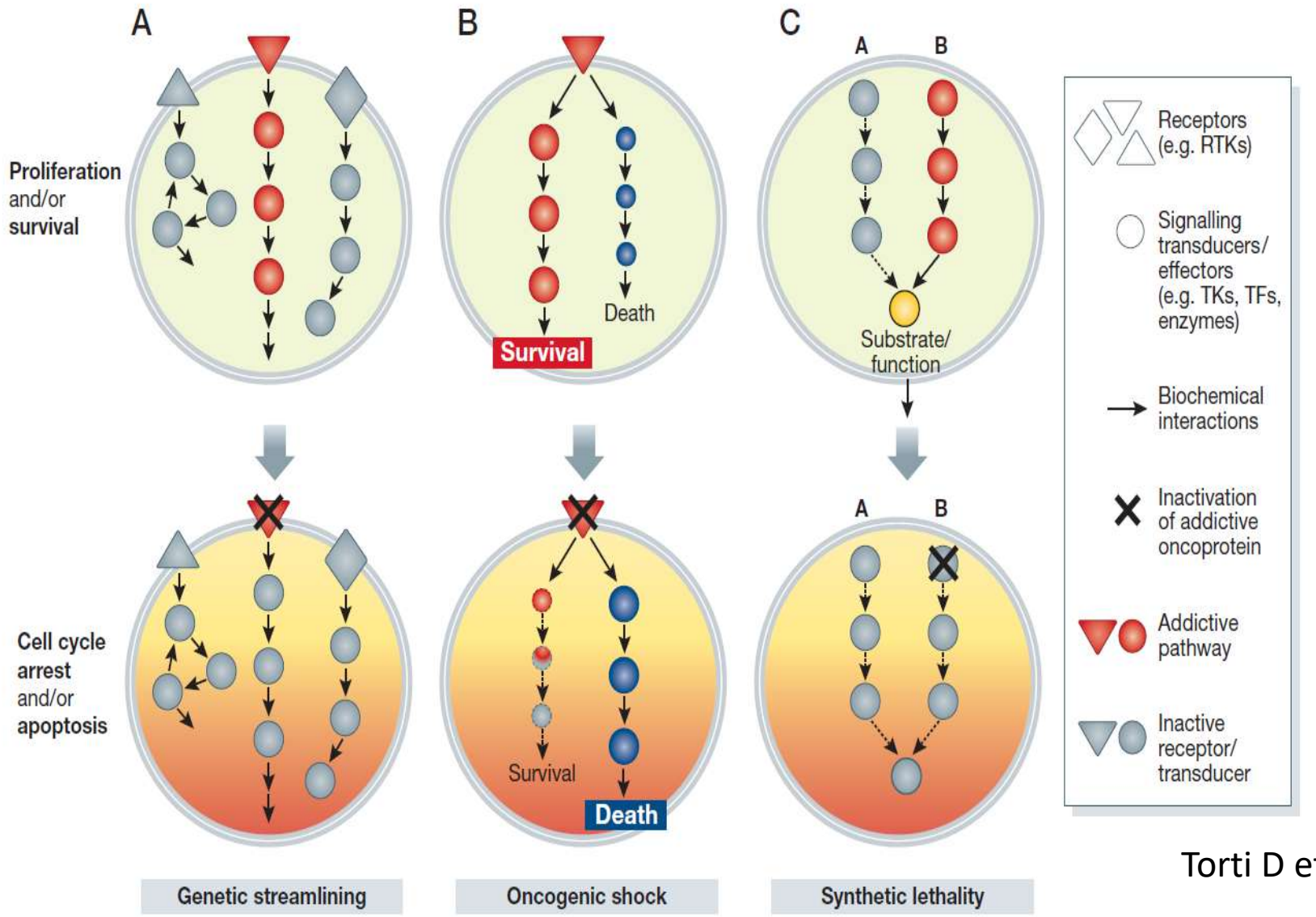


1 week on Erlotinib



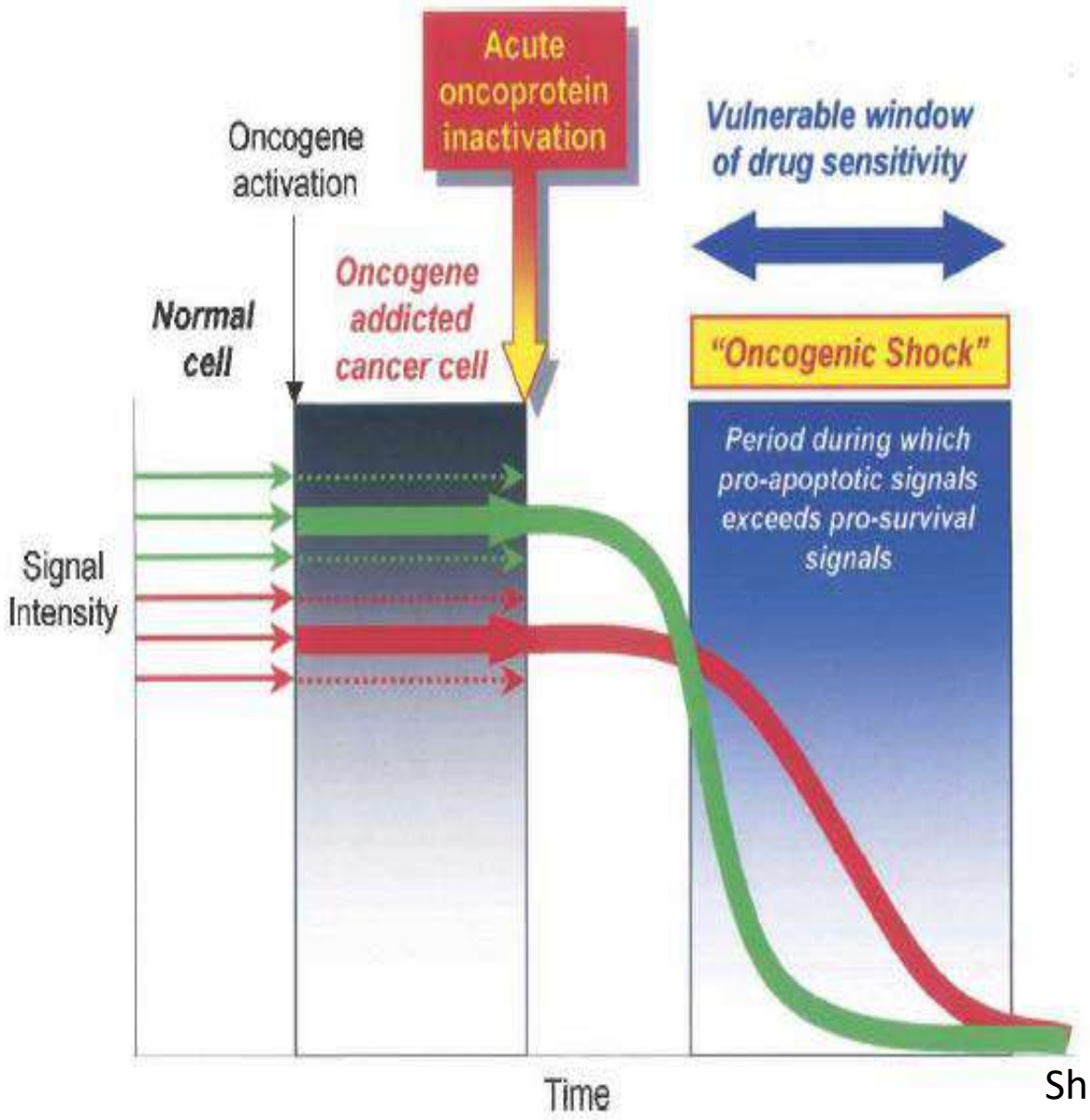
Ji et al.:Genes and Dev 2006:20:1496-510

Models of oncogenic addiction



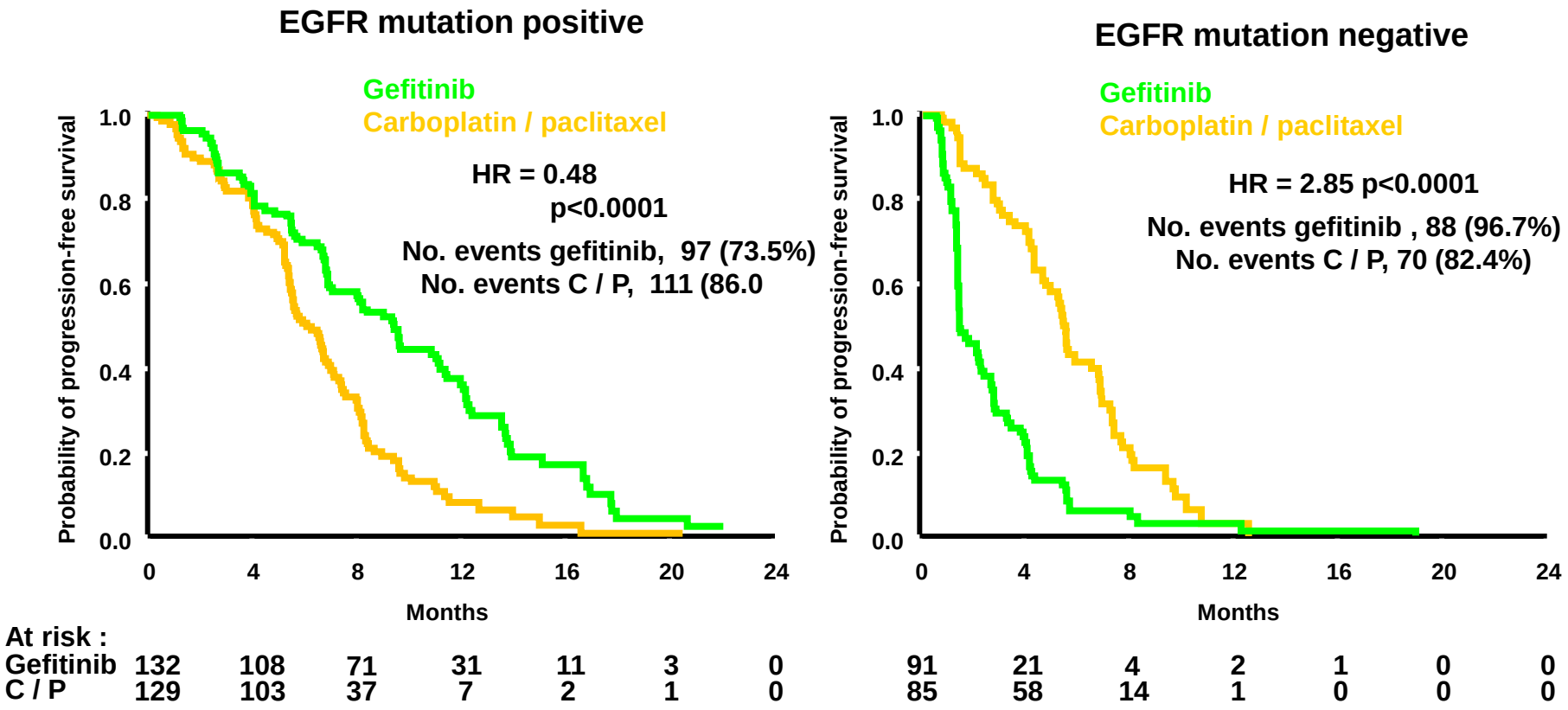
Torti D et al, EMBO 2011

The oncogenic shock



Sharma SV et al, Genes and dev 2007

IPASS: Progression-Free Survival in *EGFR* Mutation Positive and Negative Patients



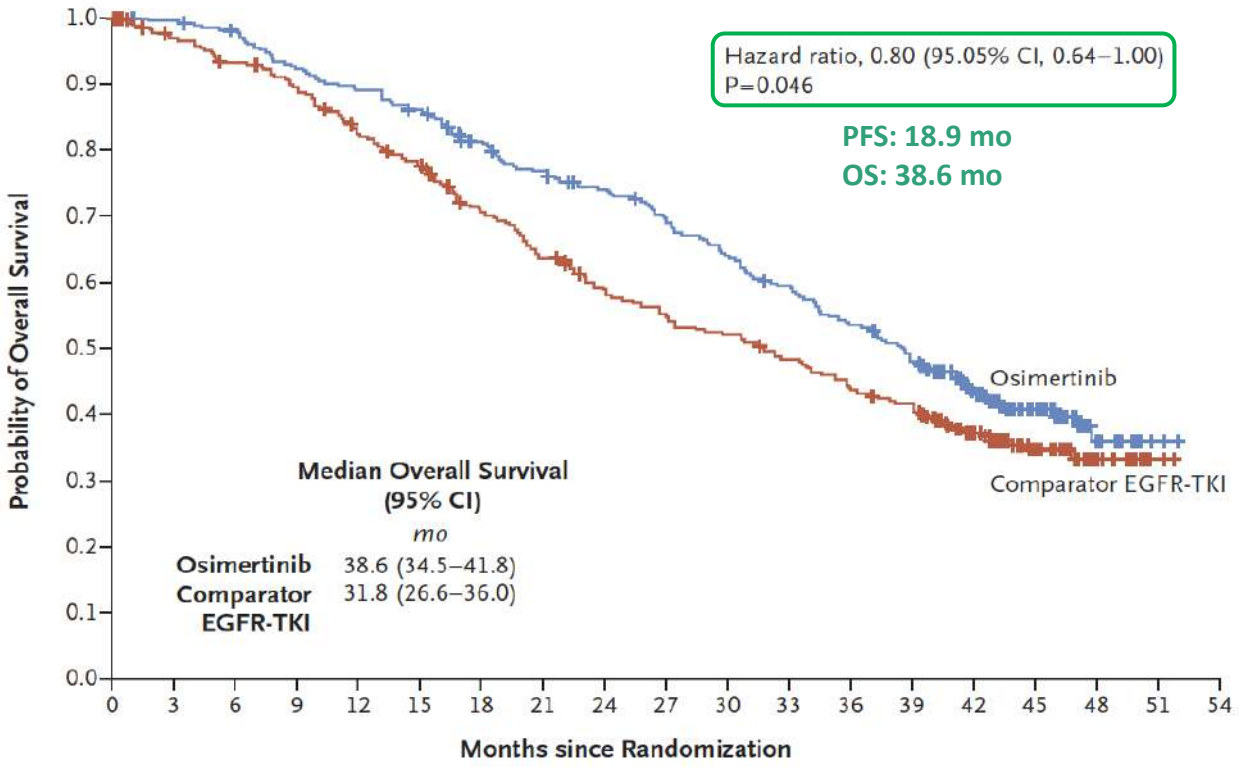
Treatment by subgroup interaction test, p<0.0001

Fukuoka et al. Proc ASCO, 2009

FLAURA Phase III 1st line treatment, osimertinib *vs* gefitinib/erlotinib

Advanced NSCLC, common EGFR mutation, double blind, amendment for osimertinib cross-over

Overall survival



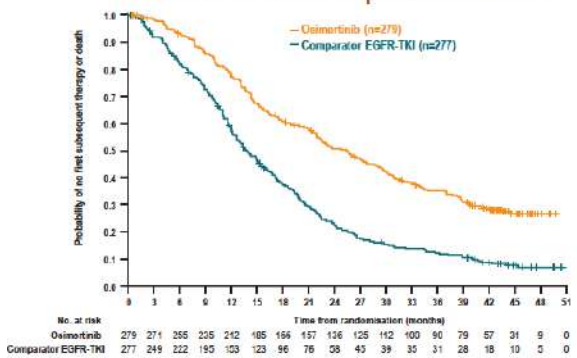
No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Table 1. Overall Survival and Continuation of First-Line Trial Drug.*

Variable	Osimertinib (N=279)	Comparator EGFR-TKI (N=277)
Patients continuing to receive first-line trial drug — no. (%)		
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

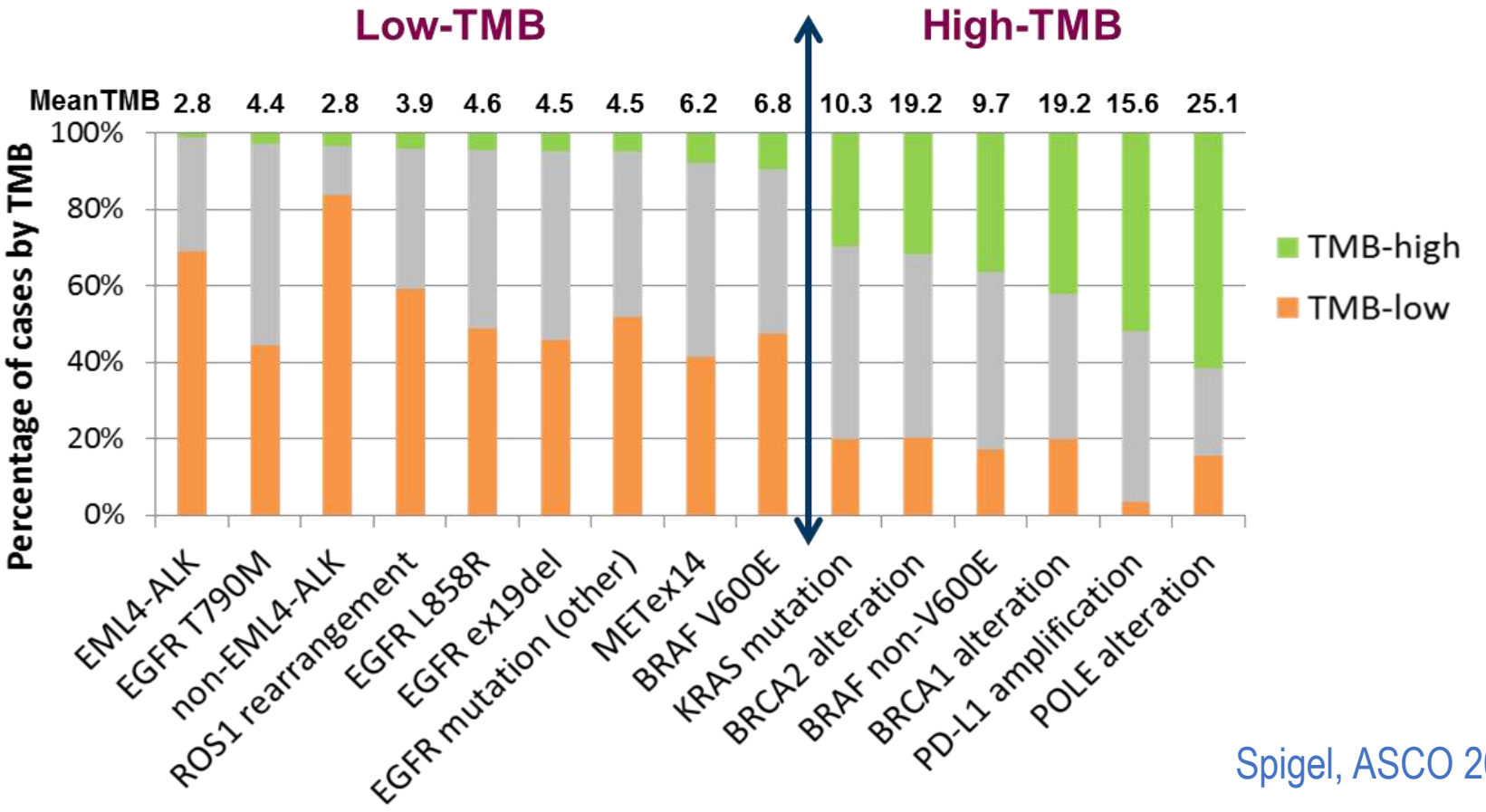
Time to first subsequent treatment*



Time to first subsequent therapy or death	Events	Median, months (95% CI)
Osimertinib	194	25.5 (22.0, 29.1)
Comparator EGFR-TKI	242	13.7 (12.3, 15.7)
HR (95% CI)		0.478 (0.393, 0.581) p<0.0001

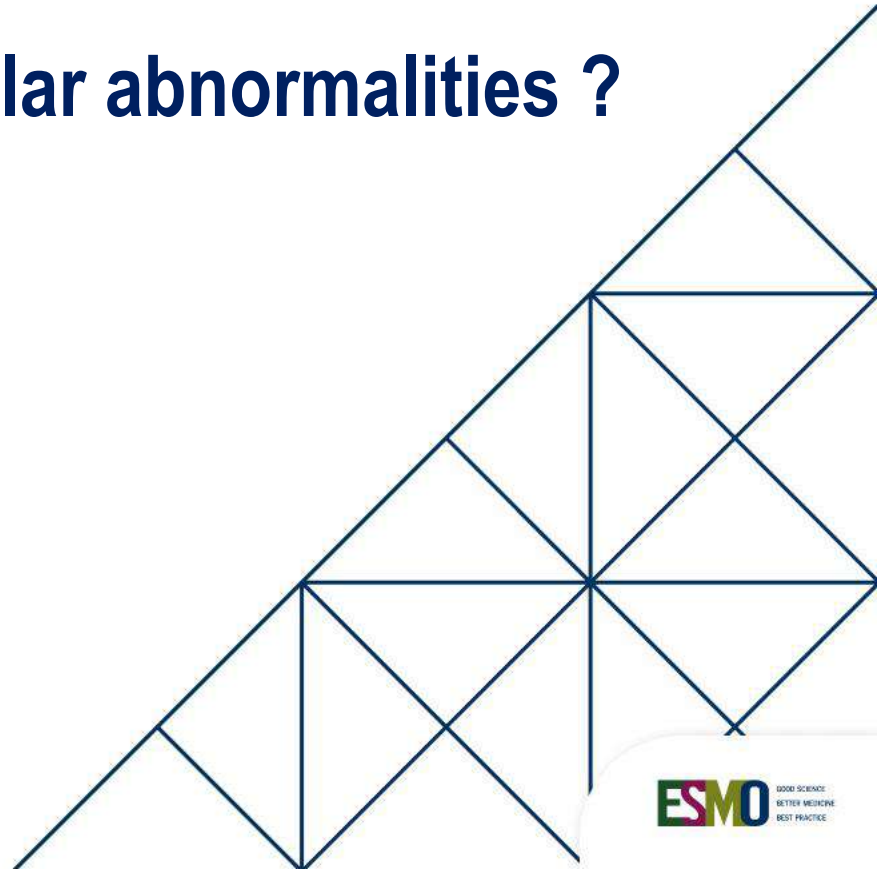
Hendriks LE, Ann Oncol 2022, Epub Dec; Ramalingam S, N Engl J Med 2020, 382:41

TMB high versus low and oncogenic addiction

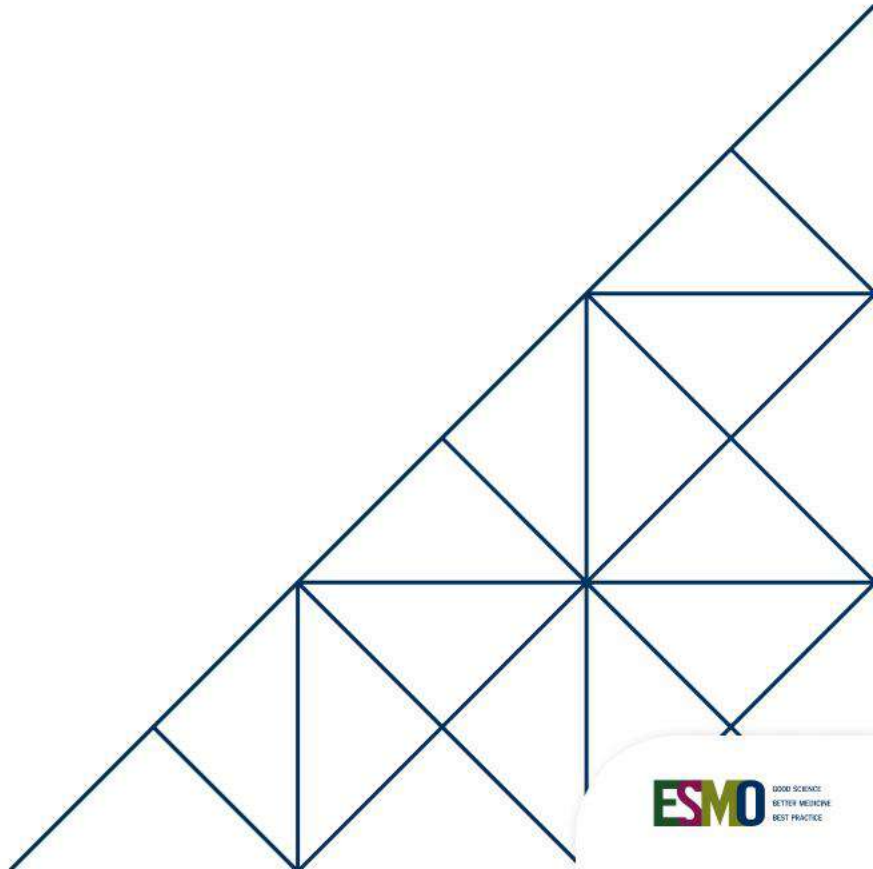


Spigel, ASCO 2016

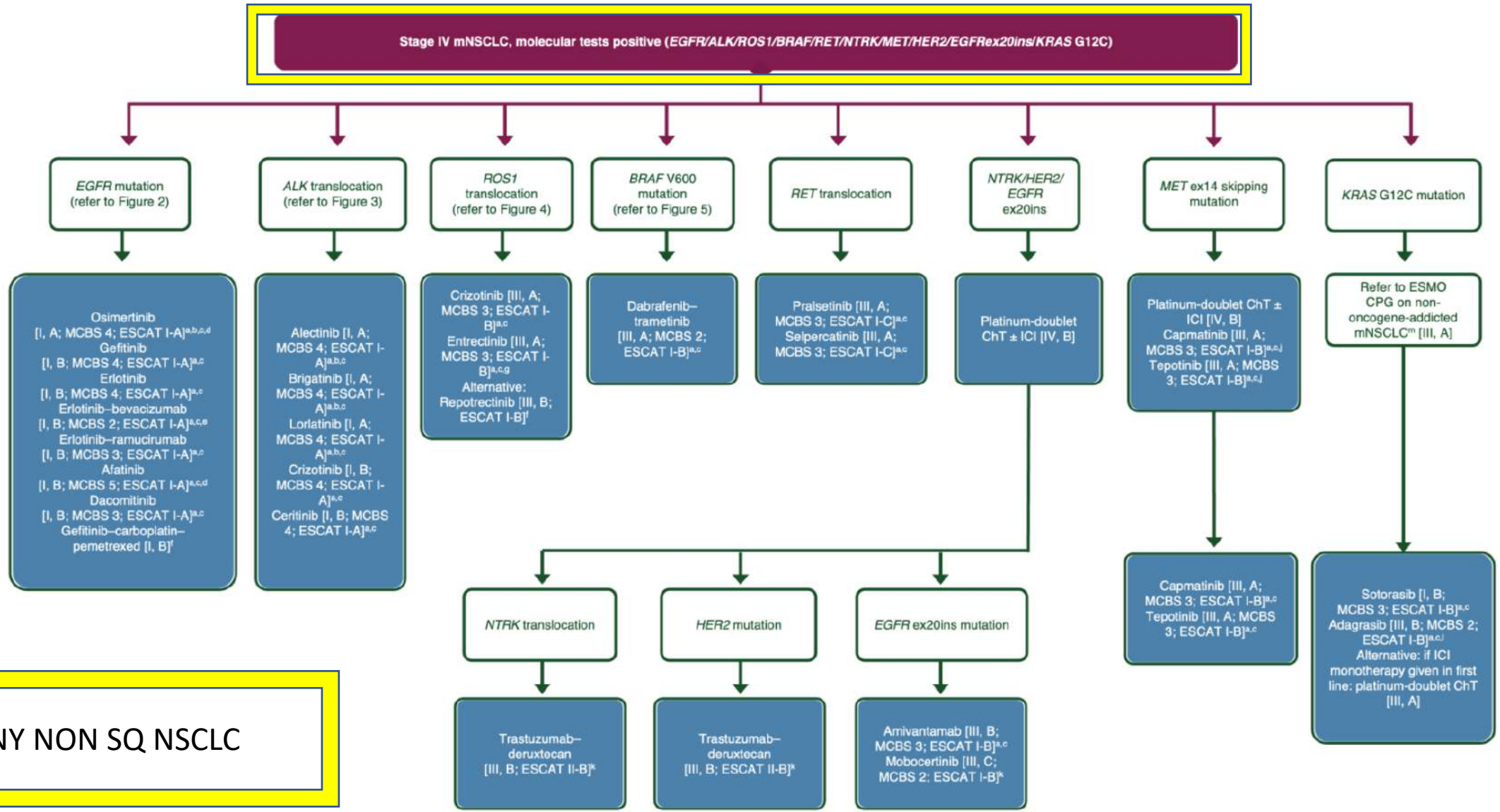
IN WHOM do we analyse tumours for molecular abnormalities ?



ADVANCED STAGES NSCLC

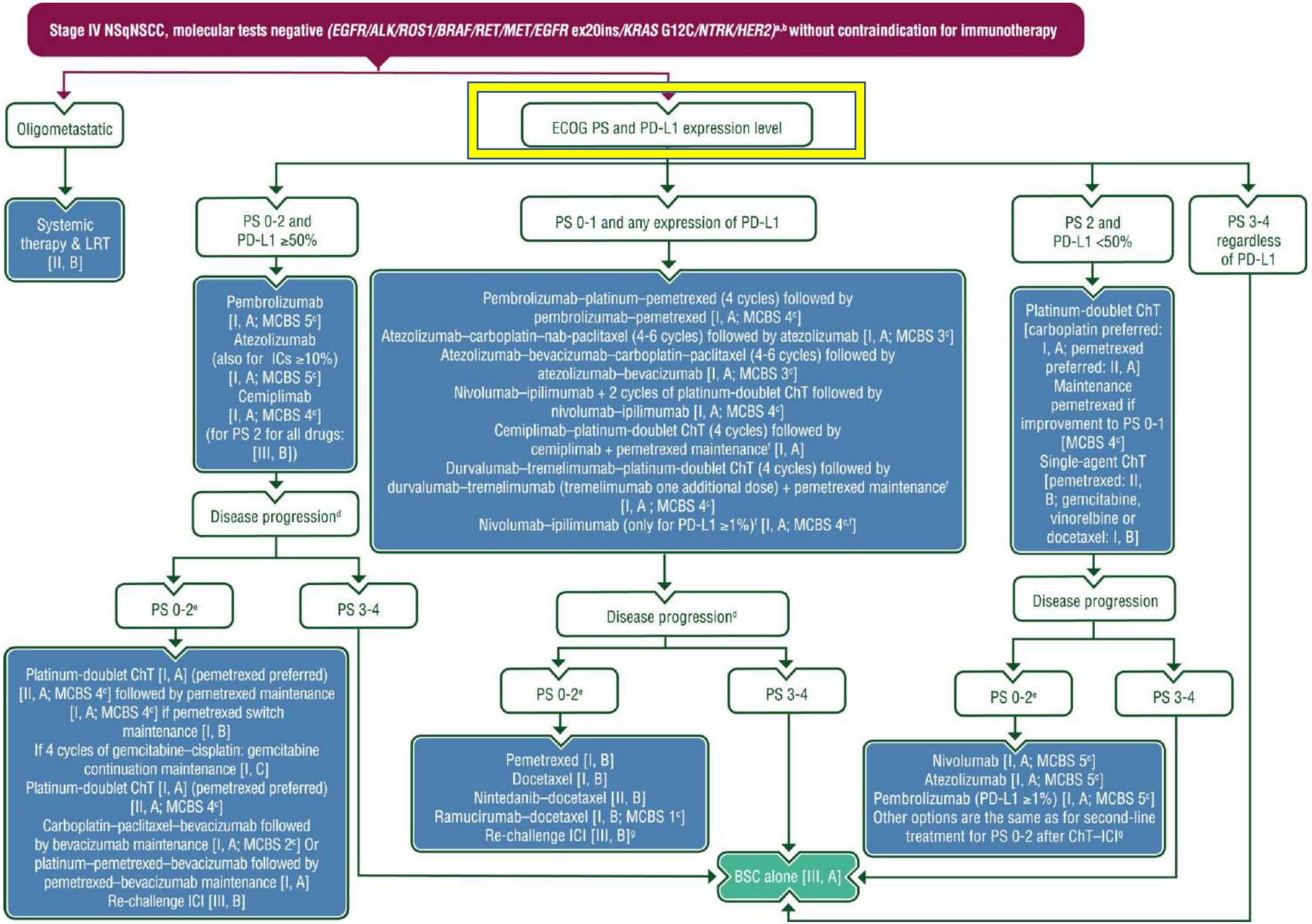


Targeted Therapies in Advanced NSCLC: ESMO guidelines

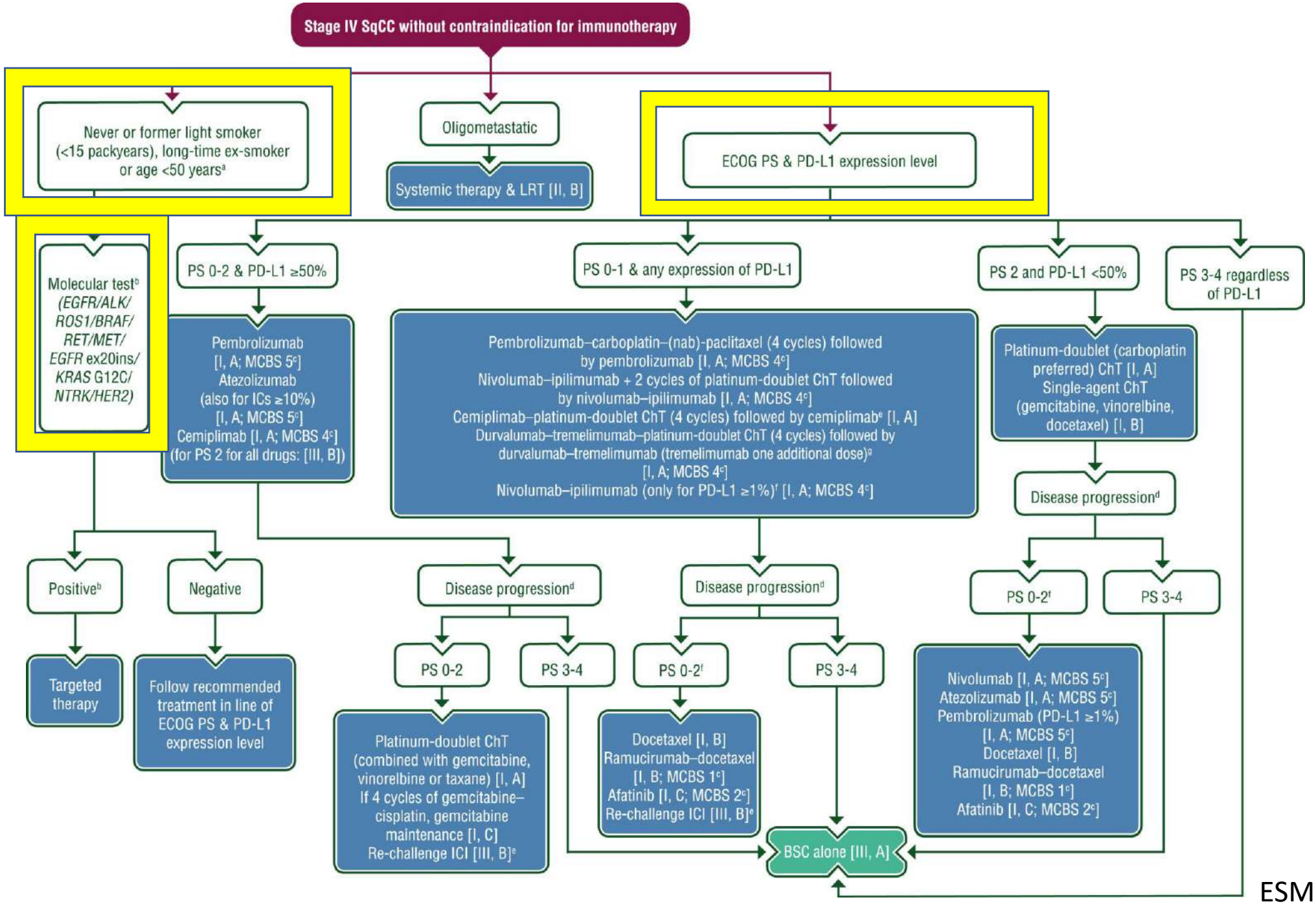


ANY NON SQ NSCLC

ChT = chemotherapy; ESCAT = ESMO Scale for Clinical Actionability of molecular Targets; ESMO = European Society for Medical Oncology; ICI = immune-checkpoint inhibitor; MCBS = ESMO-Magnitude of Clinical Benefit Scale.
Reproduced with permission from Hendriks LE, et al. Ann Oncol. 2023;34:339-357.

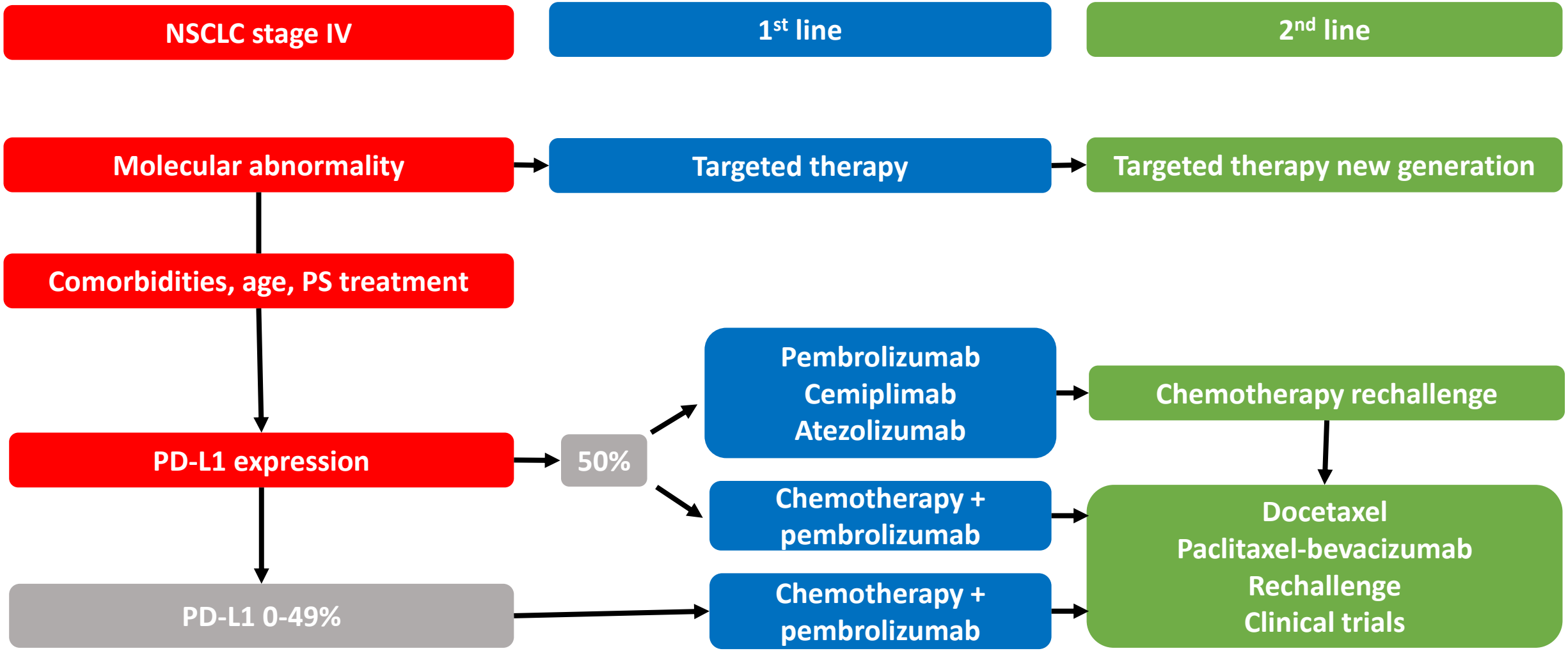


ESMO Guidelines 2024

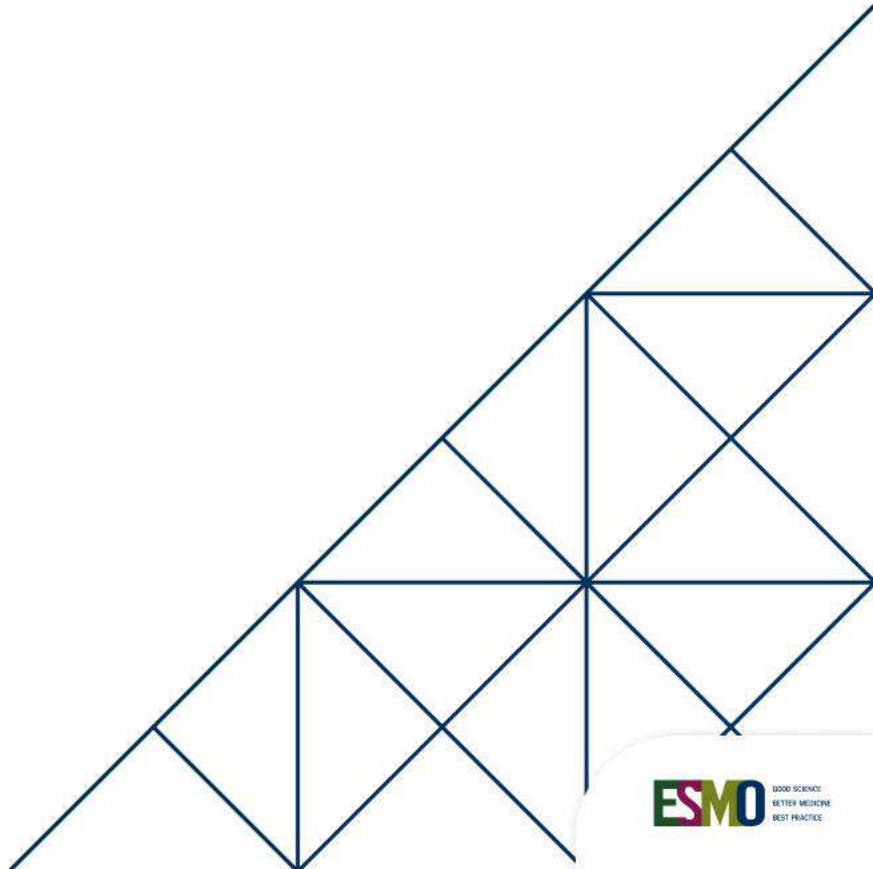


ESMO Guidelines 2024

ALGORITHM IN STAGES IV NSCLC



EARLY STAGES NSCLC



Neoadjuvant and Adjuvant Treatments for Early Stage Resectable NSCLC: Consensus Recommendations From the International Association for the Study of Lung Cancer

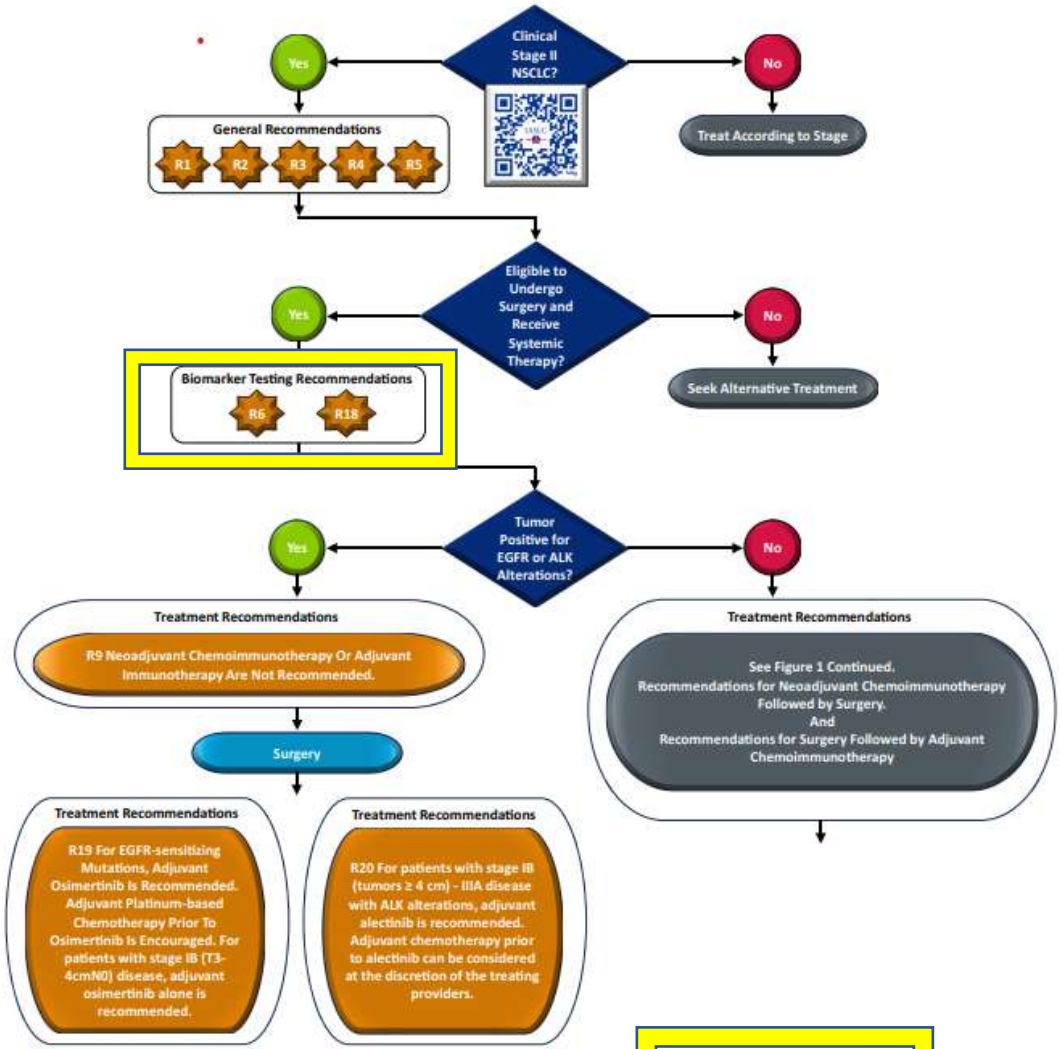


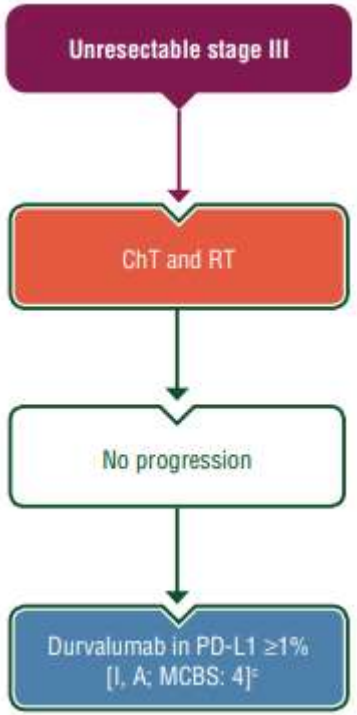
Figure 1. Workflow for neoadjuvant or adjuvant thera for clinical stage II NSCLC.

Figure 2. Workflow for neoadjuvant or adjuvant thera for clinical stage III NSCLC.

	Expert Panel Agreement, %	Open Comment Agreement, %
For patients being considered for neoadjuvant or adjuvant systemic therapy, at a minimum, determination of *EGFR* and *ALK* alteration status is required. Tumor proportion score measurement for determination of PD-L1 status should also be considered.	100	93
For patients with TKI-sensitizing *EGFR* or *ALK* alterations, neoadjuvant chemoimmunotherapy or adjuvant immunotherapy is not recommended.	95	89
In the light of ongoing trials in populations with specific driver alterations and with extrapolation of the limited efficacy of PD-1 and PD-L1 inhibitors in patients with driver alterations, in addition to assessing *EGFR* and *ALK* alteration status, biomarker testing for other oncogenic drivers is highly encouraged in patients with early stage disease.	94	91
For patients with stage II or IIIA disease with *EGFR*-sensitizing mutations, adjuvant osimertinib is recommended. Adjuvant platinum-based chemotherapy before osimertinib is encouraged. For patients with stage IB (T3-4cmN0) disease, adjuvant osimertinib alone is recommended.	94	92
For patients with stages IB (tumors ≥ 4 cm) to IIIA disease with ALK alterations, adjuvant alectinib is recommended. Adjuvant chemotherapy before alectinib can be considered at the discretion of the treating providers.	95	ND

Spicer et al, JTO 2024

Unresectable stage III

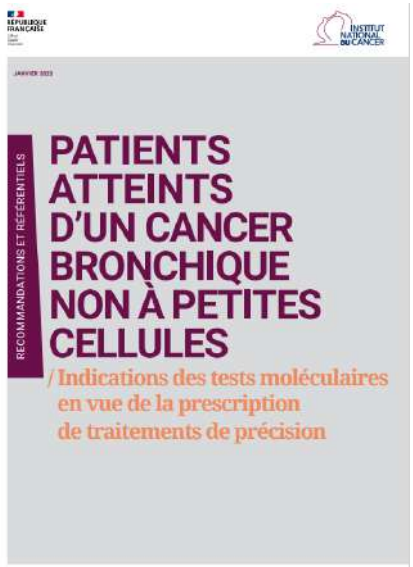


Unresectable locally advanced NSCLC

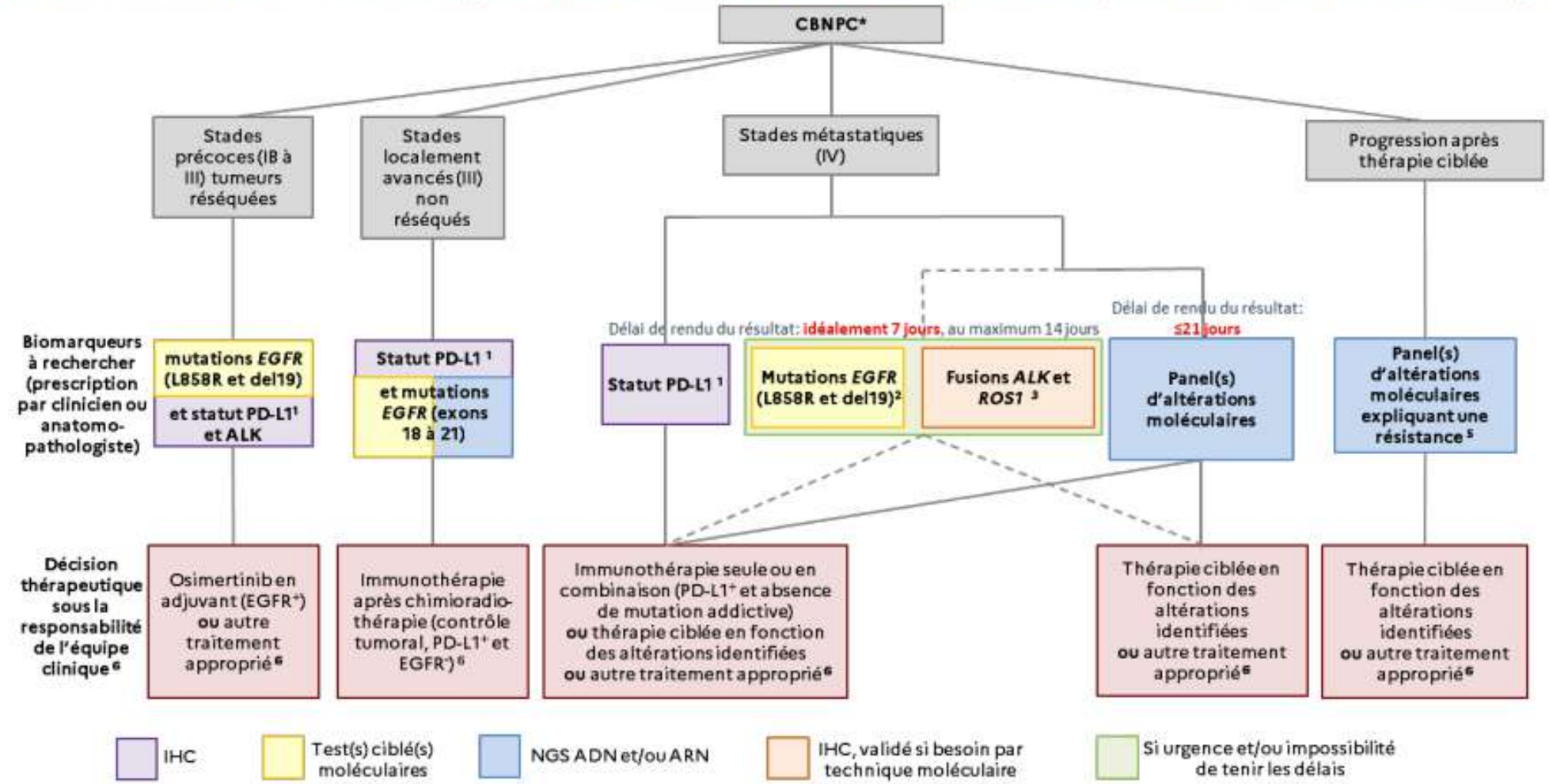
The phase III PACIFIC trial randomised (2 : 1) 713 patients with unresectable, locally-advanced NSCLC without disease progression within the first 42 days after concurrent chemoradiotherapy, to consolidative durvalumab for 1 year or placebo.[8] After a median follow-up of 34.2 months, the median OS for durvalumab was reached (47.5 months versus 29.1 months for placebo, HR 0.72, 95% CI 0.59-0.89), and the estimated 5-year OS rates were 42.9% versus 33.4% for durvalumab versus placebo, respectively. The median PFS was 16.9 months for durvalumab and 5.6 months for placebo (HR 0.55, 95% CI 0.45-0.68) with a 5-year PFS rate of 33.1% versus 19.0%, respectively.[8]

A *post hoc* exploratory analysis of the mature survival data requested by licensing European authorities observed that the benefit with durvalumab was not evident in patients with PD-L1 expression <1%. The significance of this observation is disputed.[9]

In France



Arbre décisionnel : biomarqueurs nécessaires au traitement des patients atteints de cbnpc



HOW do we analyse tumours for molecular abnormalities ?

ESCAT

ESMO Scale for Clinical Actionability of Molecular Targets

Ensure precision medicine based on biomarkers analyzed in NGS with a sufficient level of evidence (ESCAT I//II).

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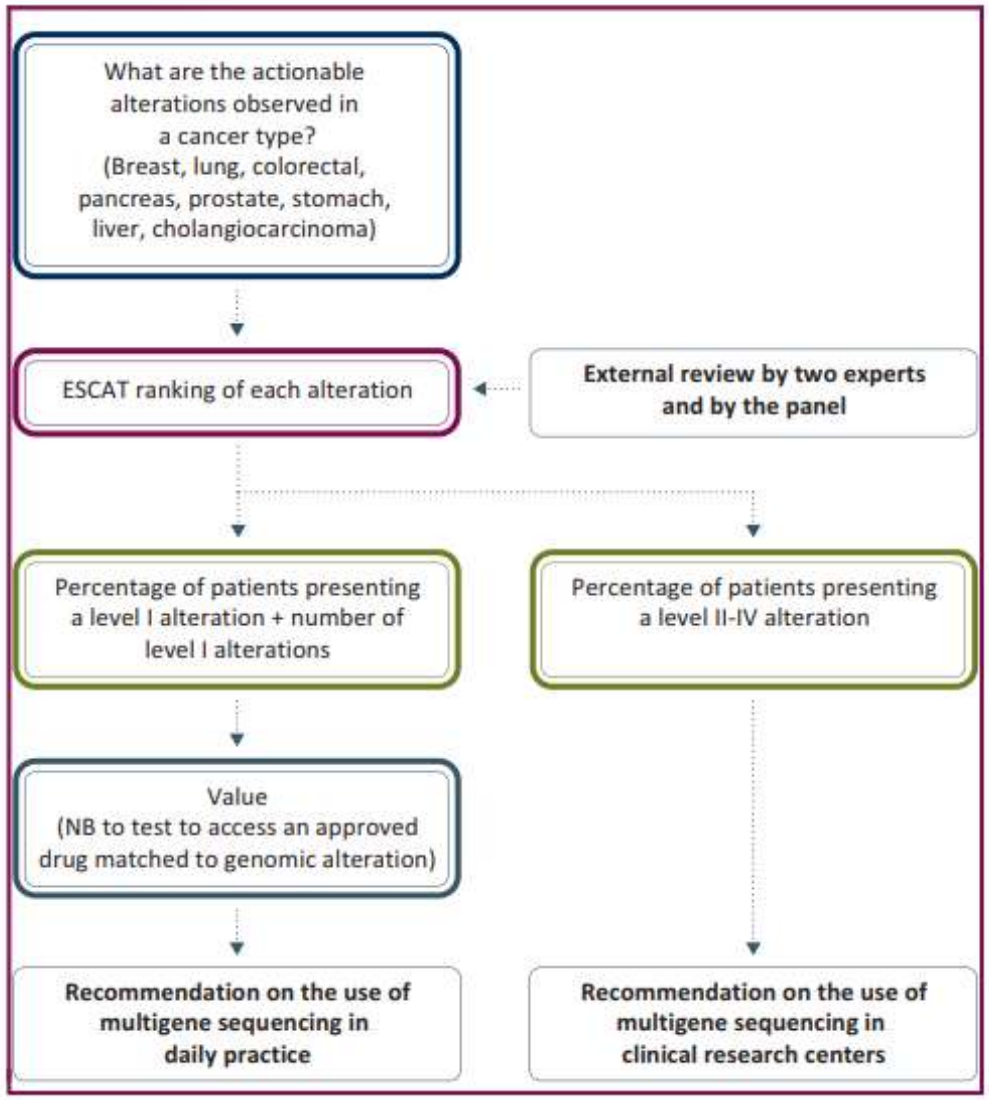
Mosele et al, Ann of Oncol, 2020

Methods to develop recommendation about NGS in daily practice



Mosele et al, Ann of Oncol, 2020

Which biomarkers do we test in first line for advanced NSCLC

Table 3A. List of genomic alterations level I/II/III according to ESCAT in advanced non-squamous non-small-cell lung cancer (NSCLC)

Gene	Alteration	Prevalence	ESCAT	References
EGFR	Common mutations (*Del19, L858R*)	15% (50%–60% Asian)	IA	Midha A, et al. *Am J Cancer Res.* 2015[26]
	Acquired *T790M* exon 20	60% of *EGFR* mutant	IA	Mok T, et al. *J Clin Oncol.* 2018[27]
	Uncommon *EGFR* mutations (*G719X* in exon 18, *L861Q* in exon 21, *S768I* in exon 20)	NSCLC	IB	Soria J-C, et al. *N Engl J Med.* 2018[28]
		10%	IIB	Ramalingam S, et al. *N Engl J Med.* 2020[29]
	Exon 20 insertions	2%		Mok T, et al. *N Engl J Med.* 2017[30] Yang JC-H, et al. *Lancet Oncol.* 2015[31] Cho J, et al. *J Thorac Oncol.* 2018[32] Cardona A, et al. *Lung Cancer.* 2018[33] Heymach J, et al. *J Thorac Oncol.* 2018[34]
ALK	Fusions (mutations as mechanism of resistance)	5%	IA	Solomon B, et al. *J Clin Oncol.* 2018[35] Soria J-C, et al. *Lancet.* 2017[36] Peters S, et al. *N Engl J Med.* 2017[37] Zhou C, et al. *Ann Oncol.* 2018[38] Camidge D, et al. *N Engl J Med.* 2018[39]
MET	Mutations *ex 14 skipping*	3%	IB	Tong J, et al. *Clin Cancer Res.* 2016[40] Drilon A, et al. *Nat Med.* 2020[41]
	Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumours)	3%	IIB	Camidge D, et al. *J Clin Oncol.* 2018[52]
BRAF^{V600E}	Mutations	2%	IB	Planchard D, et al. *Lancet Oncol.* 2016[42] Planchard D, et al. *Lancet Oncol.* 2017[43] Planchard D, et al. *J Clin Oncol.* 2017[44]
ROS1	Fusions (mutations as mechanism of resistance)	1%–2%	IB	Shaw A, et al. *N Engl J Med.* 2014[45] Shaw A, et al. *Ann Oncol.* 2019[46] Drilon A, et al. *Lancet Oncol.* 2020[47]
NTRK	Fusions	0.23%–3%	IC	Drilon A, et al. *N Engl J Med.* 2018[48] Hong D, et al. *Lancet Oncol.* 2020[49] Doebele RC, et al. *Lancet Oncol.* 2020[50]
RET	Fusions	1%–2%	IC	Drilon A, et. *J Thorac Oncol.* 2019[51]
KRAS^{G12C}	Mutations	12%	IIB	Barlesi F, et al. *Lancet.* 2016[53] Fakih M, et al. *J Clin Oncol.* 2019[54]
ERBB2	Hotspot mutations Amplifications	2%–5%	IIB	Hyman D, et al. *Nature.* 2018[55] Wang Y, et al. *Ann Oncol.* 2018[56] Tsurutani J, et al. *J Thorac Oncol.* 2018[57]
BRCA 1/2	Mutations	1.2%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]
PIK3CA	Hotspot mutations	1.2%–7%	IIIA	Cancer Genome Atlas Research Network. *Nature.* 2014[60] Vansteenkiste J, et al. *J Thorac Oncol.* 2015[62]
NRG1	Fusions	1.7%	IIIB	Duruisseaux M, et al. *J Clin Oncol.* 2019[59]

Mosele MF, Ann Oncol 2020

Which biomarkers do we test in first line for advanced NSCLC

Table 3B. List of genomic alterations level I/II/III according to ESCAT in advanced squamous NSCLC

Gene	Alteration	Prevalence	ESCAT	References
NTRK	Fusions	0.23%–3%	IC	Drilon A, et al. *N Engl J Med.* 2018[48] Hong D, et al. *Lancet Oncol.* 2020[49] Doebele RC, et al. *Lancet Oncol.* 2020[50]
PIK3CA	Hotspot mutations	16%	IIIA	Cancer Genome Atlas Research Network, *Nature.* 2012[61] Vansteenkiste J, et al. *J Thorac Oncol.* 2015[62]
BRCA 1/2	Mutations	1.2%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets.

Mosele MF, Ann Oncol 2020

SPECIAL ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

M. F. Mosele[1,2], C. B. Westphalen[3], A. Stenzinger[4], F. Barlesi[1,2,5], A. Bayle[5,6,7,8], I. Bièche[9], J. Bonastre[7,8], E. Castro[10], R. Dienstmann[11,12,13], A. Krämer[14,15], A. M. Czarnecka[16,17], F. Meric-Bernstam[18], S. Michiels[7,8], R. Miller[19,20], N. Normanno[21], J. Reis-Filho[22†], J. Remon[2], M. Robson[23], E. Rouleau[24], A. Scarpa[25], C. Serrano[11], J. Mateo[11] & F. André[1,2,5*]

Summary of recommendations

No changes have been made to the indication of carrying out tumour NGS in patients with advanced non-squamous NSCLC in daily practice, as the working group has already recommended tumour NGS in these patients. However, with the inclusion of new genomic alterations categorised as ESCAT level I, it is crucial to carefully consider the optimal approach for tumour NGS implementation in the clinical management of patients with advanced non-squamous NSCLC.

Mosele MF, Ann Oncol 2024

ESCAT I/II

Table 2. List of genomic alterations level I/II according to ESCAT in advanced non-squamous non-small-cell lung cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
EGFR	Common mutations (deletion exon 19, p.L858R)	15% Caucasian 50% Asian 30% LATAM	IA	First-, second- and third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs EGFR-MET bispecific antibodies + chemotherapy ± EGFR TKIs (after PD on third-generation EGFR TKIs)	Midha et al., *Am J Can Res* 2015[12] Arrieta et al., *J Thorac Oncol* 2015[13] Soria et al., *N Engl J Med* 2018[14] Ramalingam et al., *N Engl J Med* 2020[15] Cho et al., *Ann Oncol* 2023[16] Passaro et al., *Ann Oncol* 2024[17]
	Acquired p.T790M mutation in exon 20	60% after first- or second-generation EGFR TKIs	IA	Third-generation EGFR TKIs	Mok et al., *N Engl J Med* 2017[18] Papadimitrakopoulou et al., *Ann Oncol* 2020[19]
	Exon 20 insertions	2%	IA	EGFR-MET bispecific antibodies or TKIs	Park et al., *J Clin Oncol* 2021[20] Zhou et al., *N Engl J Med* 2023[21]
	Uncommon mutations (p.G719 variants in exon 18, p.L861Q in exon 21, p.S768I in exon 20)	10%	IB	Second- and third-generation EGFR TKIs	Cho et al., *J Clin Oncol* 2020[22] Yang et al., *Front Oncol* 2022[23]
ALK	Fusions	5%	IA	ALK TKIs	Mok et al., *Ann Oncol* 2020[24] Shaw et al., *N Engl J Med* 2020[25] Camidge et al., *J Thorac Oncol* 2021[26] Horn et al., *JAMA Oncol* 2021[27] Solomon et al., *Lancet Respir Med* 2023[28]
KRAS	Mutations (p. G12C)	12%	IA	KRAS ^{G12C} TKIs	Jänne et al., *N Engl J Med* 2022[29] de Langen et al., *Lancet* 2023[30]
RET	Fusions	1%-2%	IA	RET TKIs	Subbiah et al., *Clin Can Res* 2021[31] Griesinger et al., *Ann Oncol* 2022[32] Drilon et al., *J Clin Oncol* 2023[33] Zhou et al., *N Engl J Med* 2023[34]
ROS1	Fusions	1%-2%	IB	ROS1 TKIs	Shaw et al., *Ann Oncol* 2019[35] Shaw et al., *Lancet Oncol* 2019[36] Drilon et al., *JTO Clin Res Rep* 2022[37]
BRAF	Mutations (p. V600E)	2%	IB	BRAF TKIs + MEK TKIs	Planchard et al., *J Thorac Oncol* 2022[38] Riely et al., *J Clin Oncol* 2023[39]
MET	Mutations exon 14 skipping	3%	IB	MET TKIs	Drilon et al., *Nat Med* 2020[40] Wolf et al., *J Clin Oncol* 2021[41] Lu et al., *Lancet Respir* 2021[42] Thomas et al., *J Thorac Oncol* 2022[43] Wolf et al., *Ann Oncol* 2022[44]
	Focal amplifications	5% as primary 15% as mechanism of acquired resistance on EGFR TKIs	IIB	MET TKIs + third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs	Yu et al., *Ann Oncol* 2021[45] Bauml et al., *J Clin Oncol* 2021[46] Shu et al., *J Clin Oncol* 2022[47] Marmarelis et al., *J Thorac Oncol* 2022[48] Hartmaier et al., *Cancer Discov* 2023[49] Tan et al., *J Clin Oncol* 2023[50]
ERBB2	Hotspot mutations	3%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., *Nature* 2018[51] Li et al., *N Engl J Med* 2022[52]
NRG1	Fusions	<1%	IIB	Anti-HER2/HER3 bispecific antibody	Schram et al., *JCO* 2022[53]

ADC, antibody–drug conjugates; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; LATAM, Latin America; PD, progressive disease; TKIs, tyrosine kinase inhibitors.

Mosele MF, Ann Oncol 2024

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AL					26
KR					
RE					
RO					37
BR					2[38]
MI					3
	Focal amplifications	5% as primary 15% as mechanism of acquired resistance on EGFR TKIs	IIB	MET TKIs + third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs	Won et al., *Ann Oncol* 2022 Yu et al., *Ann Oncol* 2021[45] Bauml et al., *J Clin Oncol* 2021[46] Shu et al., *J Clin Oncol* 2022[47] Marmarelis et al., *J Thorac Oncol* 2022[48] Hartmaier et al., *Cancer Discov* 2023[49] Tan et al., *J Clin Oncol* 2023[50]
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What do the ESMO Guidelines recommend?

1. **Molecular Testing**

- **Broad based NGS testing and PD-L1 tumor expression at stage IV diagnosis**[1]

  - RNA-based NGS preferred

  - Targets should include *EGFR*, ***KRAS***^{G12C}, *BRAF*^{V600E}, *ERBB2*, *MET* (ex14, amplification), *ALK*, *ROS1*, *TRK*, *RET* translocation

- **Plasma cfDNA testing recommended**[2]**;** reflex to tissue testing if negative

2. **Treatment**[3,4]

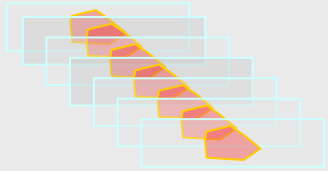
ICI + Chemo (PD-L1 1%)

Mosele MF, Ann Oncol 2024

Bloc selection by the pathologist

HES : % CT

Small pieces 10µ



slides

Nucleic acid extraction
Molecular biology

DNA
RNA

FISH

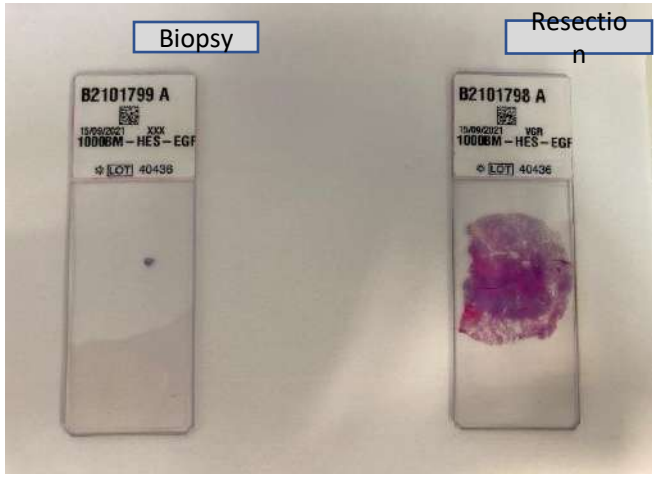
DNA

IHC

Protein expression

Analyses of mutations/fusions/amplifications

Quality of the tissue (fixation, treatment, time since sampling)
Quantity of available material
Tumour cellularity (%)

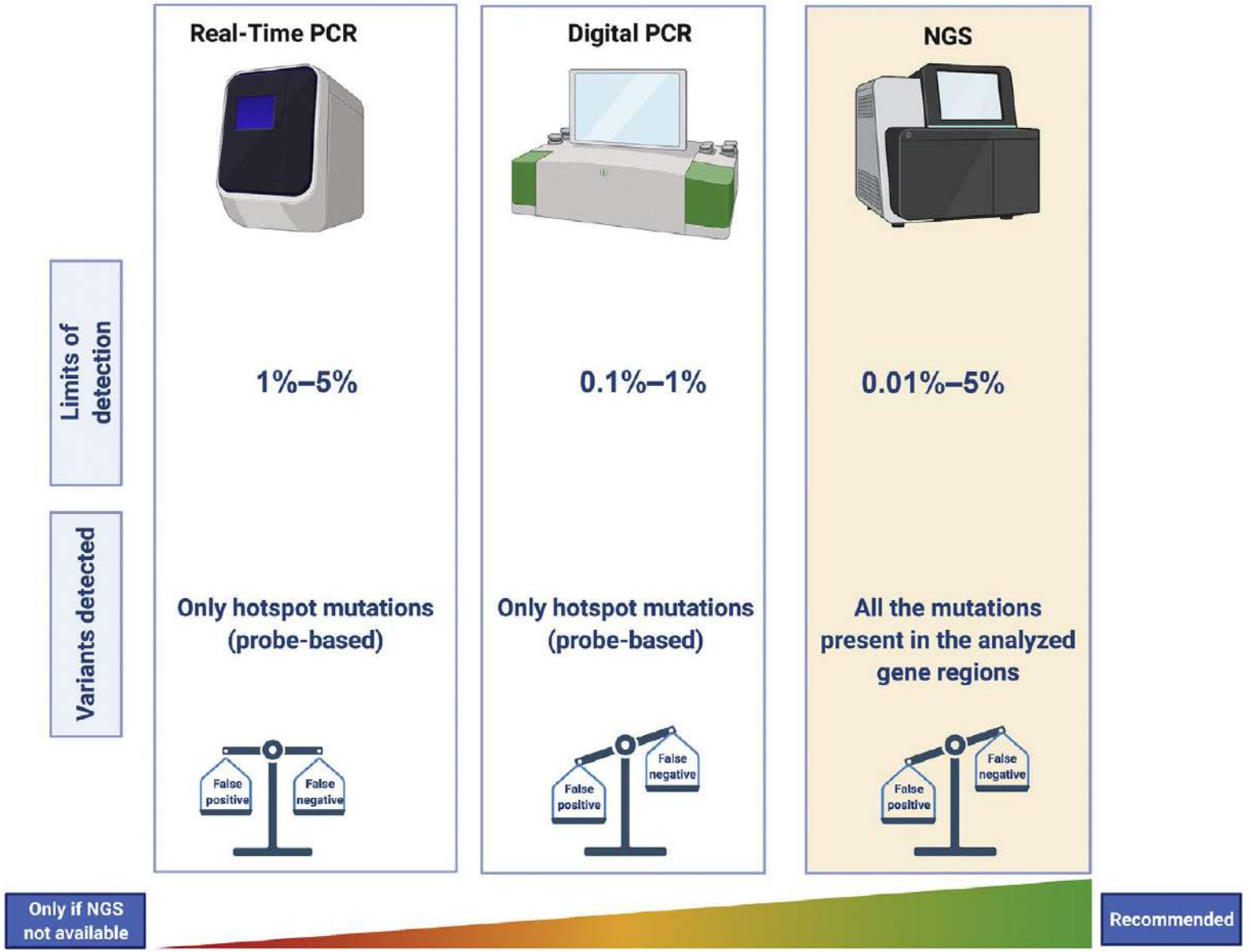


With sequential approach of testing
Risk of lack of tissue

For small sample, prefer high throughput techniques (NGS +++)

Biomarkers, molecular targets and methods for testing according to ESCAT scores

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score[a,b]
EGFR mutations (ex19 deletion or exon 21 L858R)[55-67]	Sanger sequencing or NGS	EGFR TKI	I-A
EGFR T790M resistance mutation[68]	Sanger sequencing or NGS	EGFR TKI	I-A
Non-exon 19 deletion/exon 21 L858R sensitising *EGFR* mutations[69, 70]	Sanger sequencing or NGS	EGFR TKI	I-B
EGFR exon 20 insertion mutations[71, 72]	Sanger sequencing or NGS	EGFR TKI EGFR MET Bispecific antibody	I-B
ALK rearrangements[70, 73-77]	IHC FISH RNA-based NGS	ALK TKI	I-A
ROS1 rearrangements[78-81]	IHC (only screening) FISH RNA-based NGS	ROS1 TKI	I-B
BRAF V600 mutations[82]	Sanger sequencing or NGS	BRAF + MEK TKI	I-B
RET rearrangements[83, 84]	FISH RNA-based NGS (preferably)	RET TKI	I-C
MET exon 14 skipping mutations[85, 86]	NGS (RNA-based NGS might detect more cases compared with DNA-based NGS)	MET TKI	I-B
MET amplification[85]	IHC ISH	MET TKI	II-B
HER2 mutations[87, 88]	NGS	Antibody–drug conjugate	II-B
KRAS G12C mutations[89]	NGS	KRAS G12C inhibitor	I-B
NTRK rearrangements[90, 91]	IHC for screening RNA-based NGS	NTRK inhibitors	I-C
NRG1 fusions[92]	RNA-based NGS	HER inhibitors	III-A



Rolfo C, JTO 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

REVIEW

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

Table 2. Summary recommendations

Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.	It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in breast, pancreatic and hepatocellular cancers where level II—IV alterations are numerous.	Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Breast cancers	No current indication for tumour multigene		

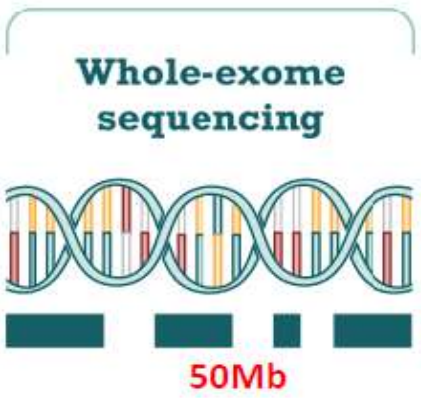
Mosele MF, Ann Oncol 2020

NGS approaches

ADN

WGS

WES

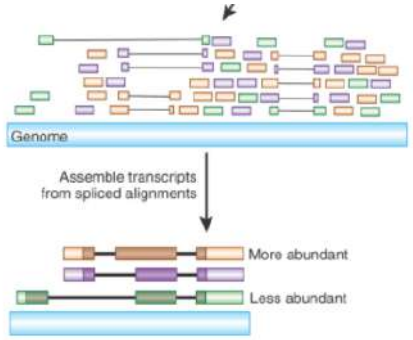


Panel of genes of DNA

Kb- some Mb

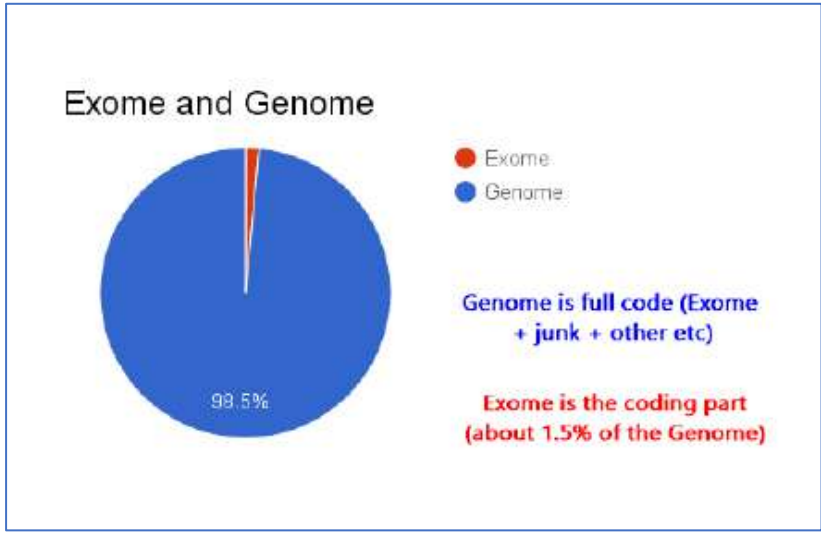
ARN

RNASeq



Targetted RNASeq Panel of genes

Variable size
(30-500 genes)

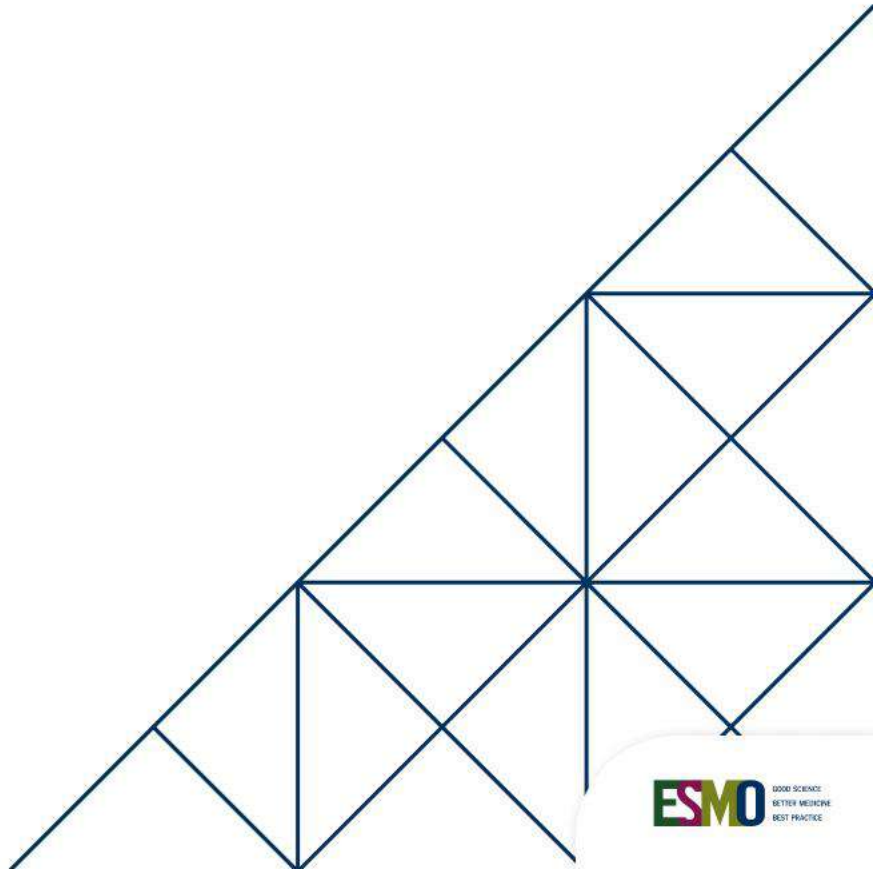


Advantages and disadvantages of the different next-generation sequencing methods for detection of fusion genes

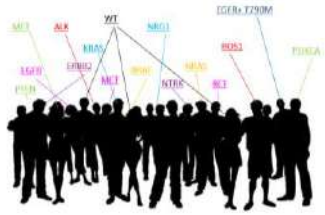
Library	Nucleic acid	Input*	Genetic alterations detected
Hybrid capture based	DNA	High (≥50 ng)	Break points of translocations (limited if long introns)
Hybrid capture based	RNA	High (≥40 ng)	Fusions (partner independent)
Amplicon based	RNA	Low (≥10 ng)	Fusions (only known fusion partners)
Anchored Multiplex Sequencing	RNA	Low (≥10 ng)	Fusions (partner independent)

* Minimum nucleic acid input suggested by manufacturers. Higher input is recommended when possible to increase the sensitivity of the test.

And the future ?



Emergent biomarkers



Current biomarkers

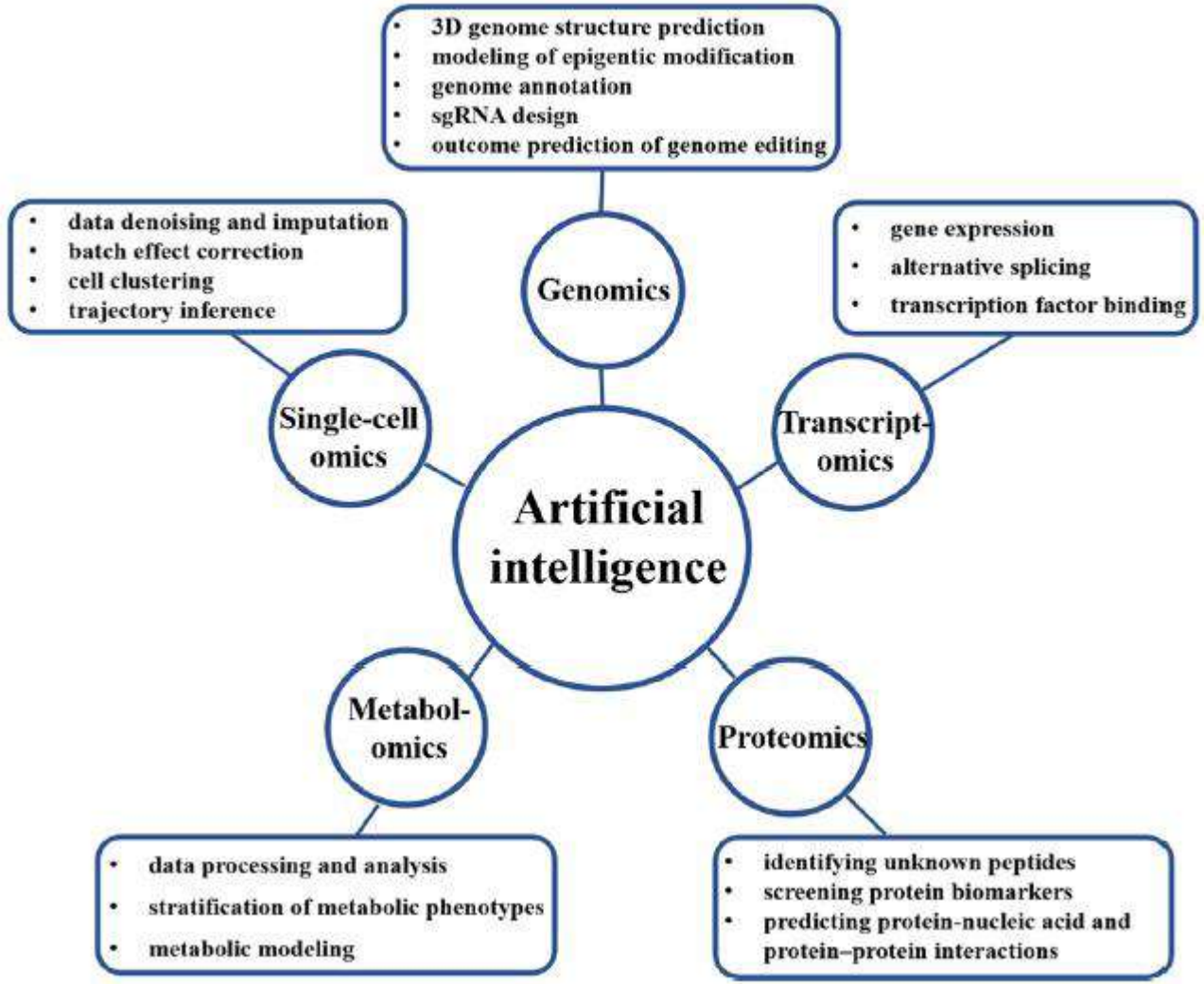
ALK	BRAF V600
EGFR	MET
ROS1	KRAS G12C
ERBB2 mutations	RET
NTRK	PD-L1

Emerging biomarkers

STK11	TP53
KEAP1	TMB
MAP2K1	PIK3CA
BRAF non-V600	NRG1
BRCA1/2	ERBB2 amplifications

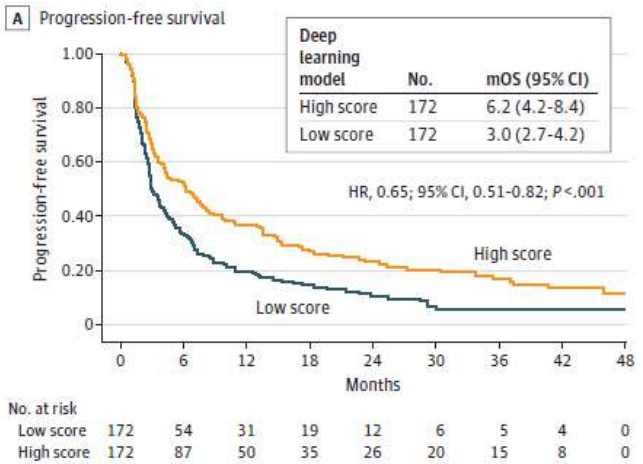
Vincent D. de Jager Lancet 2024

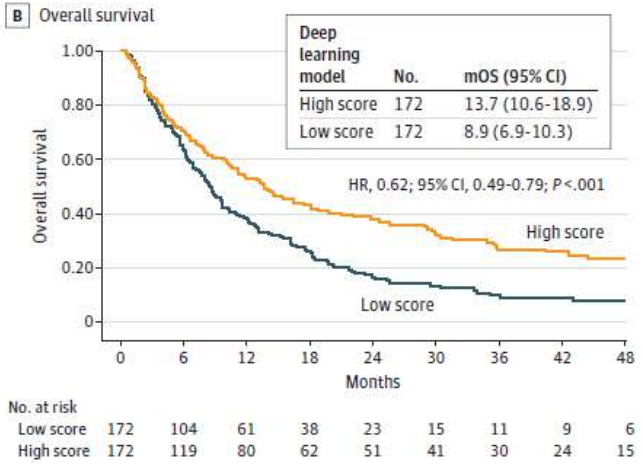
Application of IA technologies to single-omics analysis

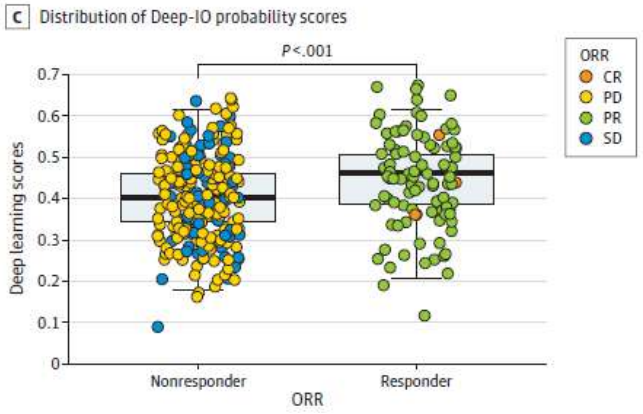


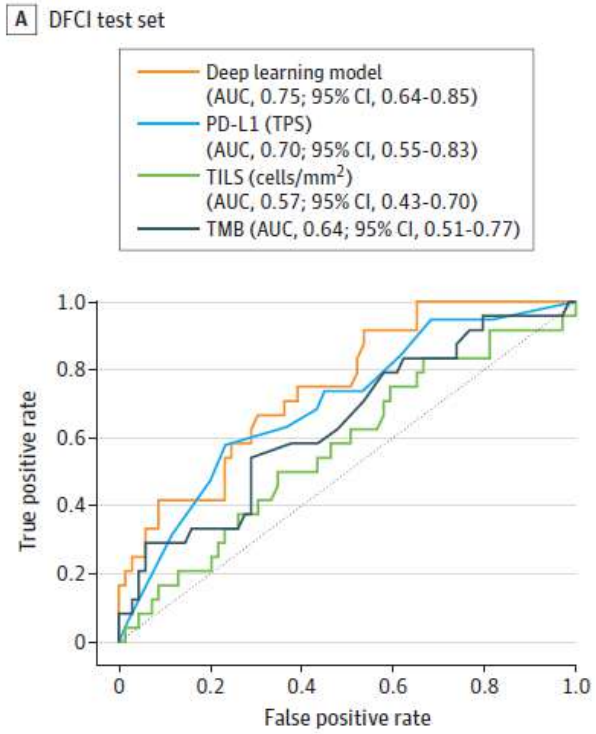
He et al. Semin Cancer Biol, 2023

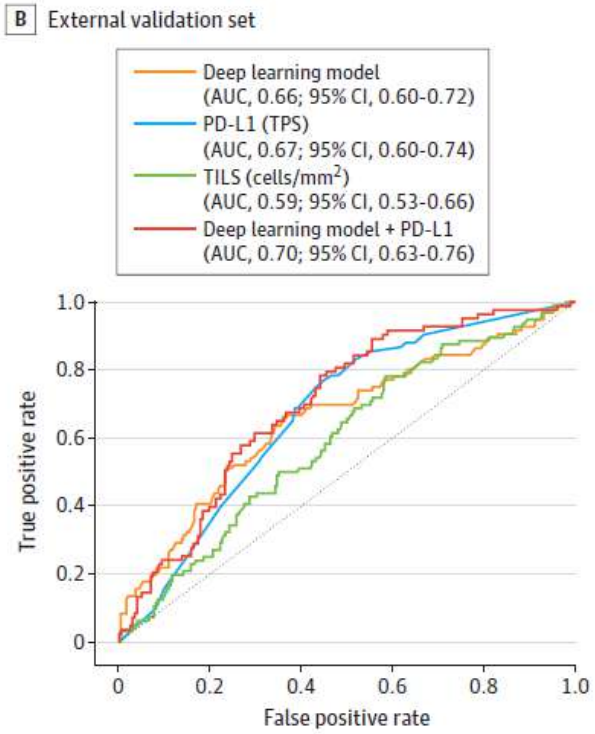
IA Guided precision medicine

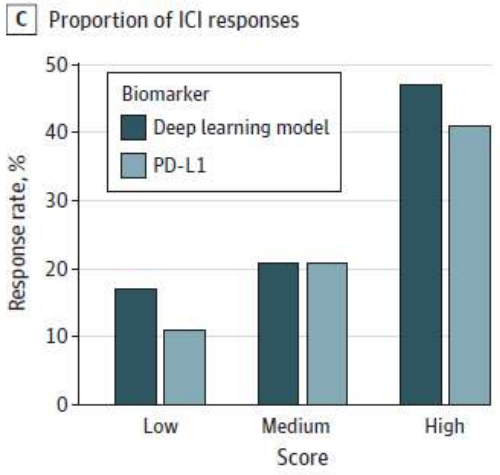


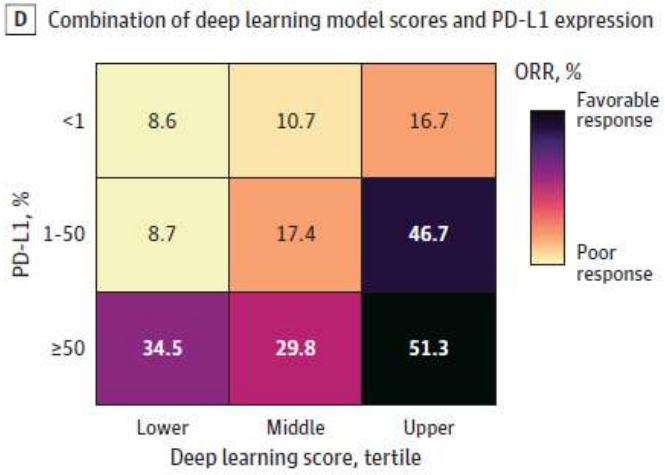












Rakaee et al. JAMA Oncol. 2024

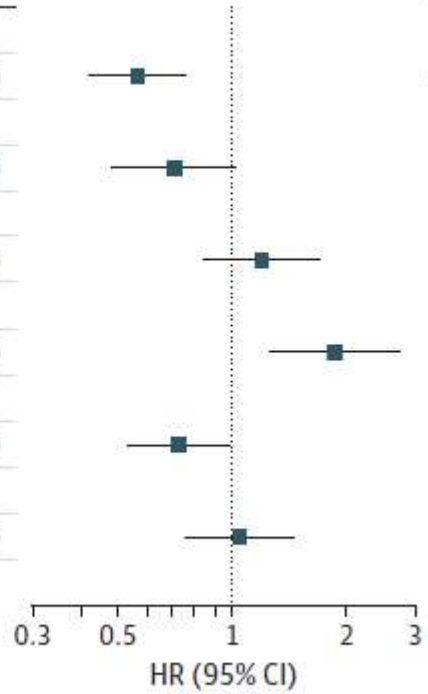
IA Guided precision medicine

Multivariable Analysis in the Validation Cohort

A Cox proportional hazard model of PFS in validation cohort

Variable	HR (95% CI)	*P* value
Deep learning model		
> vs ≤Median	0.56 (0.42-0.76)	<.001
PD-L1		
≥ vs <50%	0.70 (0.48-1.03)	.07
ICI line		
≥2 vs 1	1.20 (0.85-1.70)	.31
ECOG		
≥2 vs 0-1	1.87 (1.26-2.77)	.002
Sex		
Female vs male	0.72 (0.53-0.99)	.04
Histology		
LUSC vs LUAD	1.05 (0.75-1.45)	.79

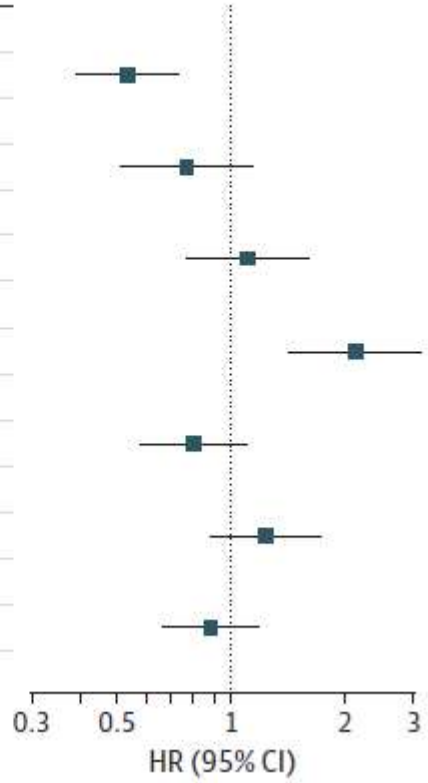
No. of events, 212; C-index = 0.65



B Cox proportional hazard model of OS in validation cohort

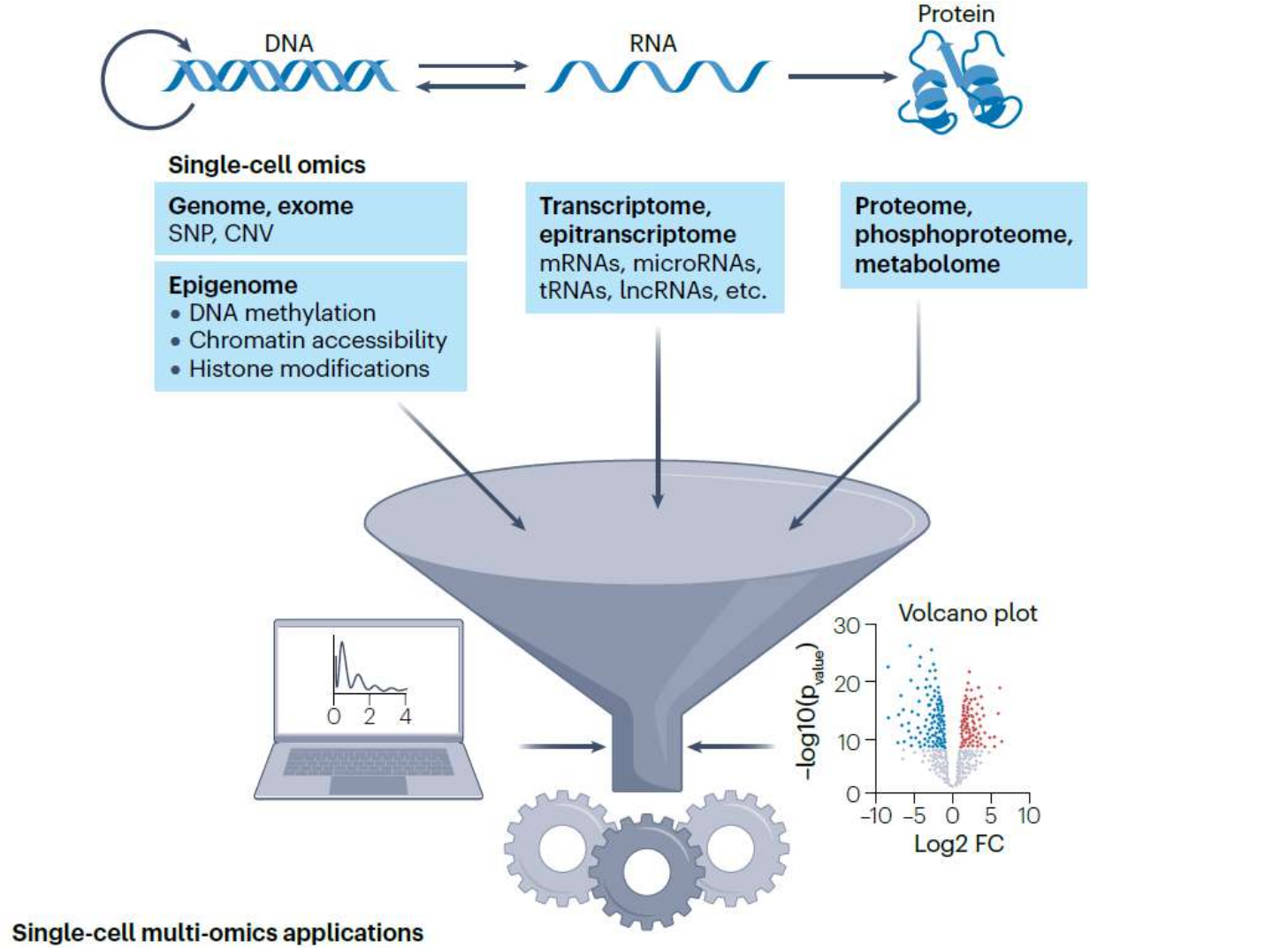
Variable	HR (95% CI)	*P* value
Deep learning model		
> vs ≤Median	0.53 (0.39-0.73)	<.001
PD-L1		
≥ vs <50%	0.76 (0.51-1.14)	.18
ICI line		
≥2 vs 1	1.11 (0.77-1.61)	.58
ECOG		
≥2 vs 0-1	2.13 (1.42-3.18)	<.001
Sex		
Female vs male	0.80 (0.58-1.10)	.17
Histology		
LUSC vs LUAD	1.23 (0.88-1.73)	.23
Age		
> vs ≤median	0.88 (0.66-1.19)	.41

No. of events, 197; C-index = 0.64



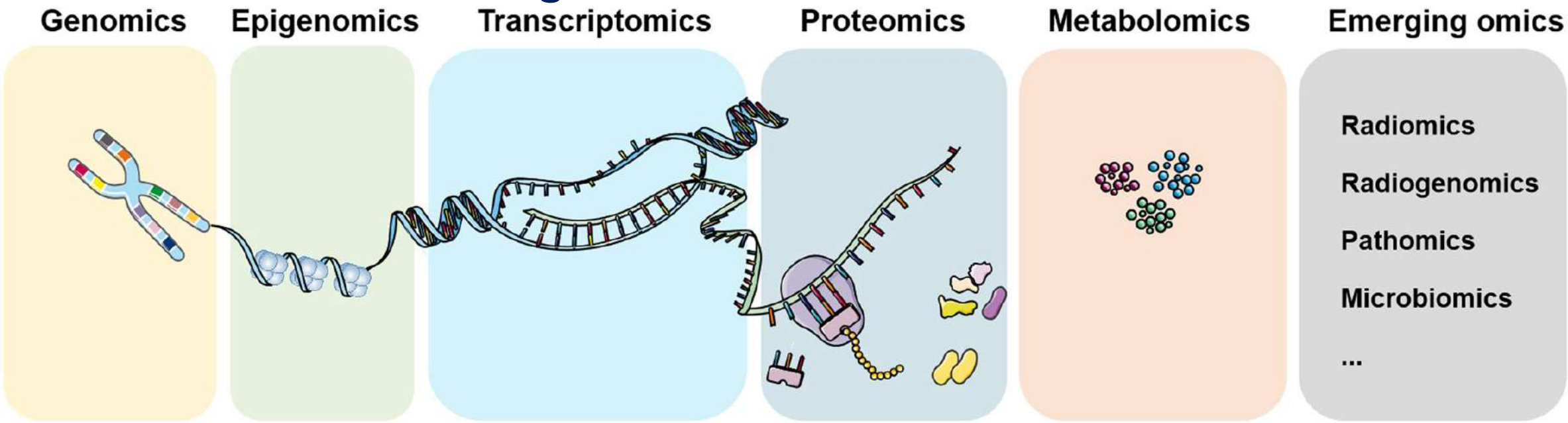
Rakaee et al. JAMA Oncol. 2024

Multi-omics



Baysoy et al. Nat Rev Mol Cell Biol. 2023

Multi-omics technologies



The information provided by omics technologies

- point mutations
- small insertions/deletions
- genomic rearrangements
- viral-genome insertions
- structural variants
- copy-number variants

- DNA modifications
- histone modifications and variants
- nucleosome occupancy
- chromatin interactions
- chromatin domains

- gene expression
- noncoding RNAs
- alternative splicing
- alternative polyadenylation
- gene fusions
- allele-specific expression
- RNA editing
- endogenous retrotransposon transcription

- identification and quantitation of proteins
- protein modifications

- identification and quantitation of metabolites
- drug metabolism and toxicity
- cancer metabolic reprogramming
- immunometabolism

- cell composition, cell morphology, and spatial context
- quantitative features from digital images
- microenvironment information

Representative techniques

- WGS
- WES

- WGBS
- ChIP-seq
- MeRIP-Seq
- ATAC-seq
- 3C and derivatives

- Microarray
- RNA-seq

- MS-based proteomics technology
- SMPS

- NMR spectroscopy
- MS-based metabolomics technology

- PET/CT, MRI, Dermoscopic images, Mammograms, H&E
- WMS, 16S rRNA gene sequencing

Multi-omics technologies have been developed to profile genome sequences, epigenetic features, transcription expression, protein and metabolite abundance, and more. Additional information from an individual can be captured by emerging omics technologies, such as radiomics, pathomics, and microbiomics. The corresponding representative technologies are enumerated. Whole-genome sequencing (WGS), whole-exome sequencing (WES), whole-genome bisulfite sequencing data (WGBS), chromatin immunoprecipitation sequencing (ChIP-seq), methylated RNA immunoprecipitation sequencing (MeRIP-seq), assay for transposase-accessible chromatin using sequencing (ATAC-seq), chromosome conformation capture (3C) technology, mass spectrometry (MS)-based proteomics technology, single-molecule protein sequencing (SMPS) technologies, Nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS)-based metabolomics technology, positron emission tomography(PET)/computed tomography (CT) scans, magnetic resonance imaging (MRI), Hematoxylin and eosin staining (H&E), and whole metagenome sequencing (WMS).

He et al. Semin Cancer Biol, 2023

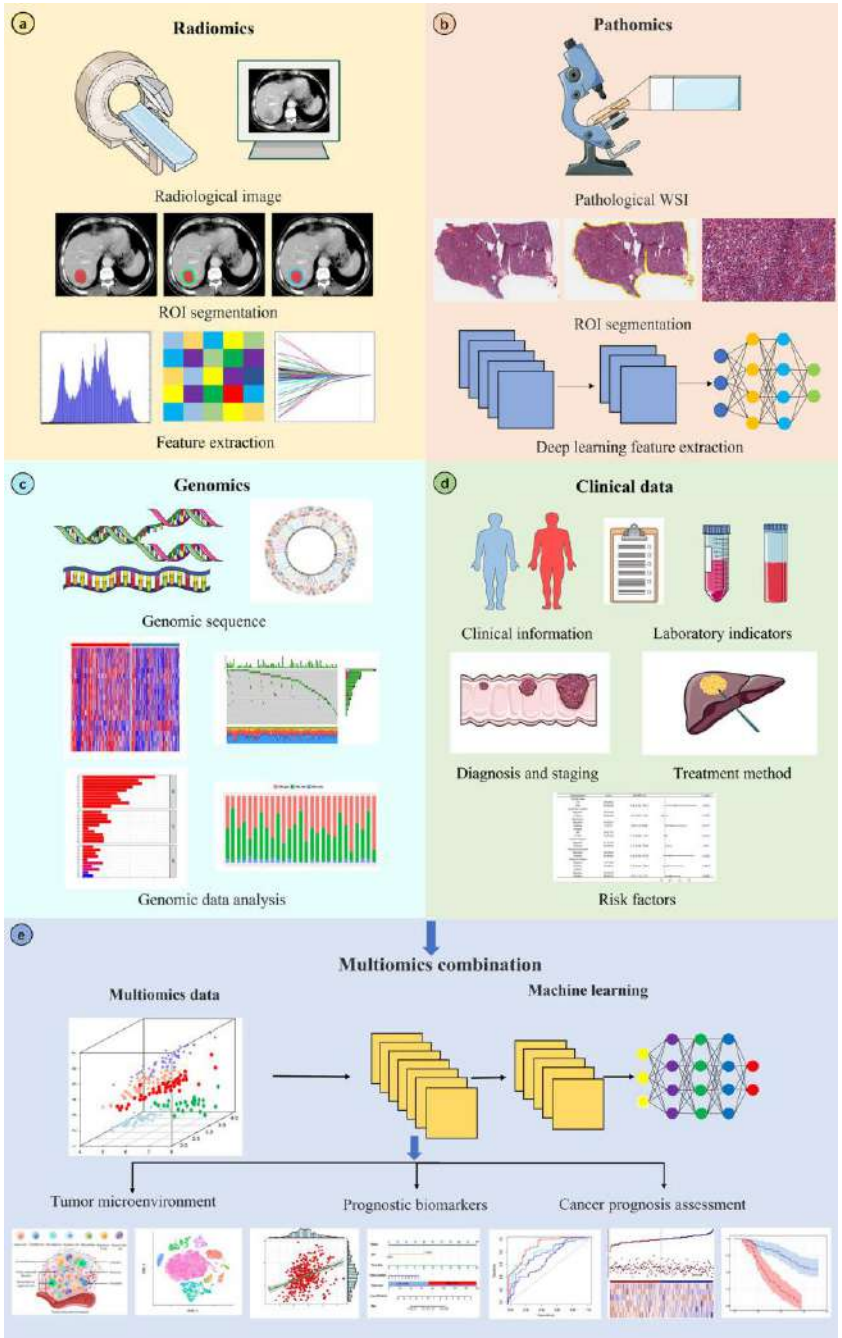
A Radiomics process mainly includes image acquisition, region of interest (ROI) segmentation, radiomics feature extraction

B Pathomics process includes acquisition of pathological images, whole slide images (WSI) ROI segmentation, extraction features of deep learning

C Genomics process mainly includes acquisition of genomics data, analysis of genomics data, etc.

D Clinical data include demographic information, laboratory examination, diagnosis and staging, treatment method, etc.

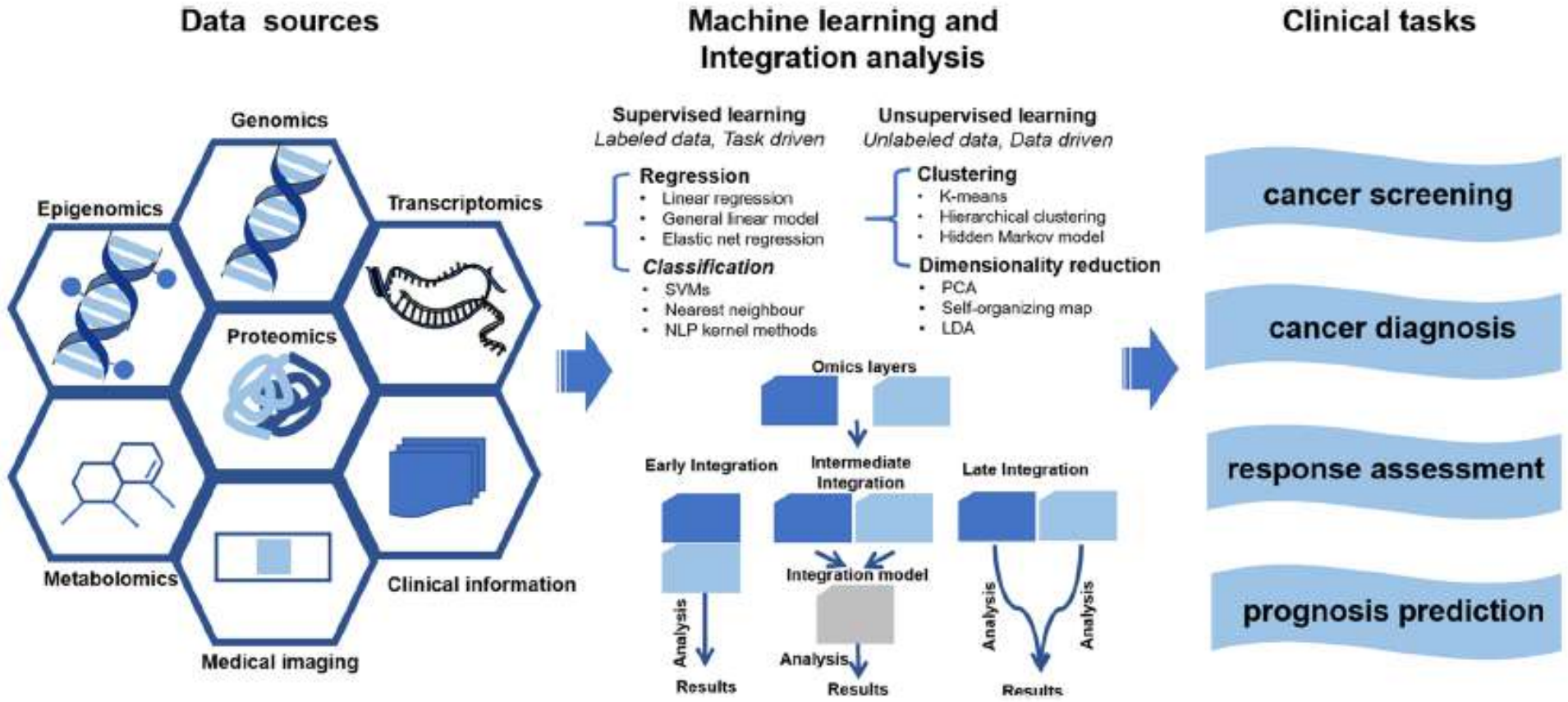
E Multiomics combinations.
Multiomics data are fused by machine learning methods to construct combinatorial models for tumor microenvironment exploration and cancer prognosis evaluation, and to develop comprehensive prognosis biomarkers



Multi-omic combinations

Kang et al. J Transl Med. 2023

Artificial intelligence support of multi-level biomedical data integration workflow



The data acquired in multi-omics studies can be integrated with other complementary modality data, including medicinal imaging, and clinical information (left panel). ML methods can be divided broadly into supervised learning and unsupervised learning. Representative ML methods are listed (middle panel). Data integration strategies for multi-omics include early, intermediate, and late integration (middle panel). AI-based multi-omics analysis has the potential to aid precision medicine. Key applications of AI-based multi-omics analysis in cancer precision medicine are shown (right panel). Support vector machines (SVMs), natural language processing (NLP) kernel methods, principal component analysis (PCA), and latent dirichlet allocation (LDA).

He et al. Semin Cancer Biol, 2023

Conclusions

- Biomarkers testing according to level of evidence (ESCAT)

- Testing in non squamous and light or non smokers squamous lung carcinomas
- Advanced stage and nowadays for early stages

- NGS approaches with panel of genes
- RNA seq preferred as testing for gene fusions

- Perspective of integration of multi-omics and IA

ESMO DEEP DIVE:
LUNG CANCER

PRECISION ONCOLOGY IN LUNG CANCER - DIAGNOSTICS

Harnessing liquid biopsy for diagnosis, monitoring

Christian Rolfo, MD, PhD, MBA, Dr.hc.
Professor of Medicine
Director Division Medical Oncology
Associate Director for Early Phase Clinical Trials
The James Comprehensive Cancer Center, The Ohio State University

ESMO WEBINAR SERIES

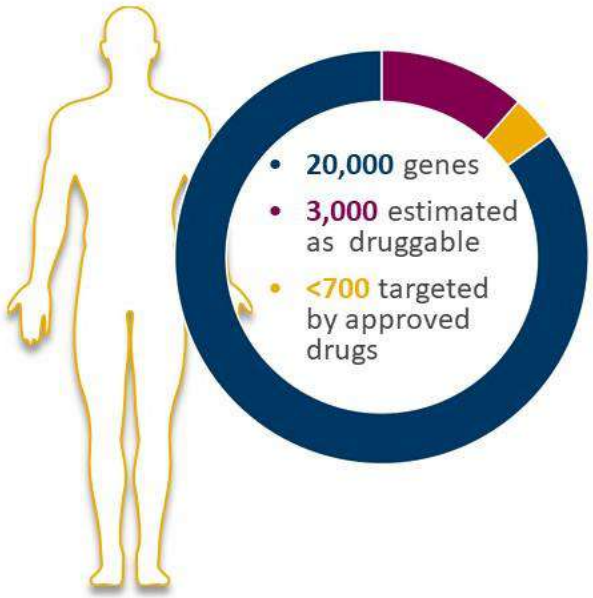
ESMO

Disclosures

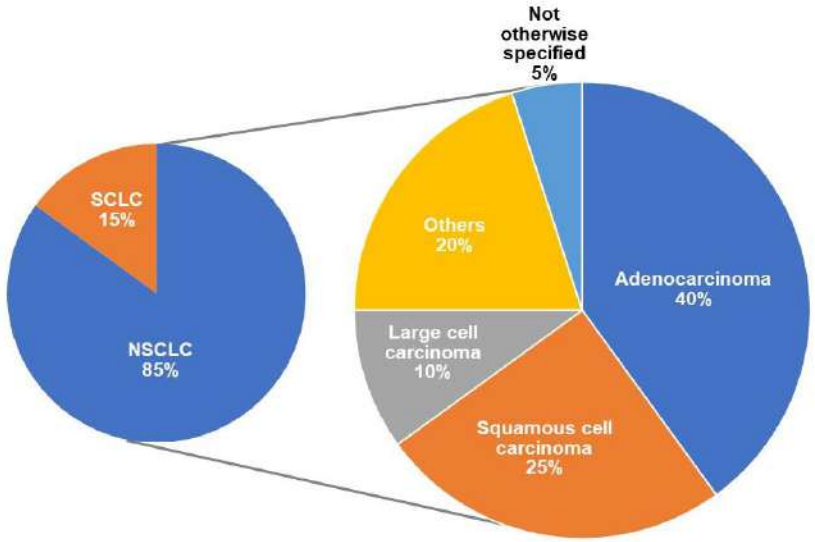
- Advisory Board: AstraZeneca, Daiichi Sankyo, Regeneron and Novocure; Bristol-Myers Squibb (BMS), Novartis, Invitae, Guardant Health,COR2ED, Bayer, Boehringer Ingelheim, Abbvie, Invitae, Janssen, EMD Serono
- Research Grant: Astra Zeneca, Thermo Fisher, Oncohost, Lung Cancer Research Foundation, National Foundation for Cancer Research, and U54 (National Institute of Health)
- Research collaboration: GuardantHealth, Foundation Medicine, Roche Diagnostics, EMD Serono
- Scientific advisory board member of Imagene
- Leadership roles: in International Society of Liquid Biopsy, The European School of Oncology, International Association for Study of Lung Cancer, and Oncology Latin American Association.
- Editor role: Editor in chief of CROH and Honorary editor at Journal of Liquid Biopsy Elsevier. Editorial board Lung Cancer and ILCN (IASLC).

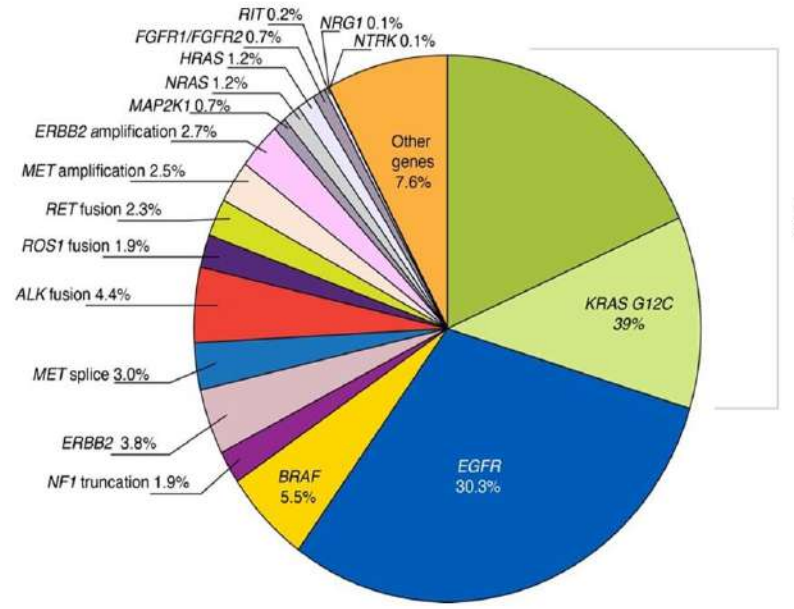
WHY TESTING?

SMALL MOLECULES HAVE TRANSFORMED HOW WE TREAT HUMAN CANCER



Landscape of Lung Cancer





PD-L1 expression
(Tumor mutational burden)

Galbraith S. ASCO 2024

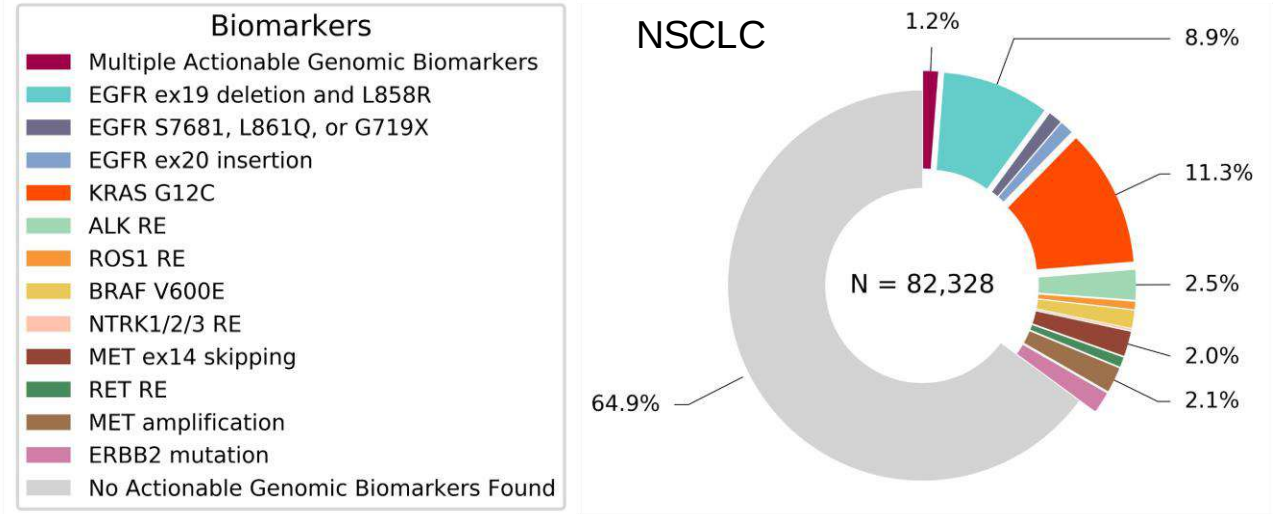
Molecular profiling across histologies in lung cancer across 80.000 pts with lung cancer

Study design and patients selection

This was an observational retrospective analysis of:

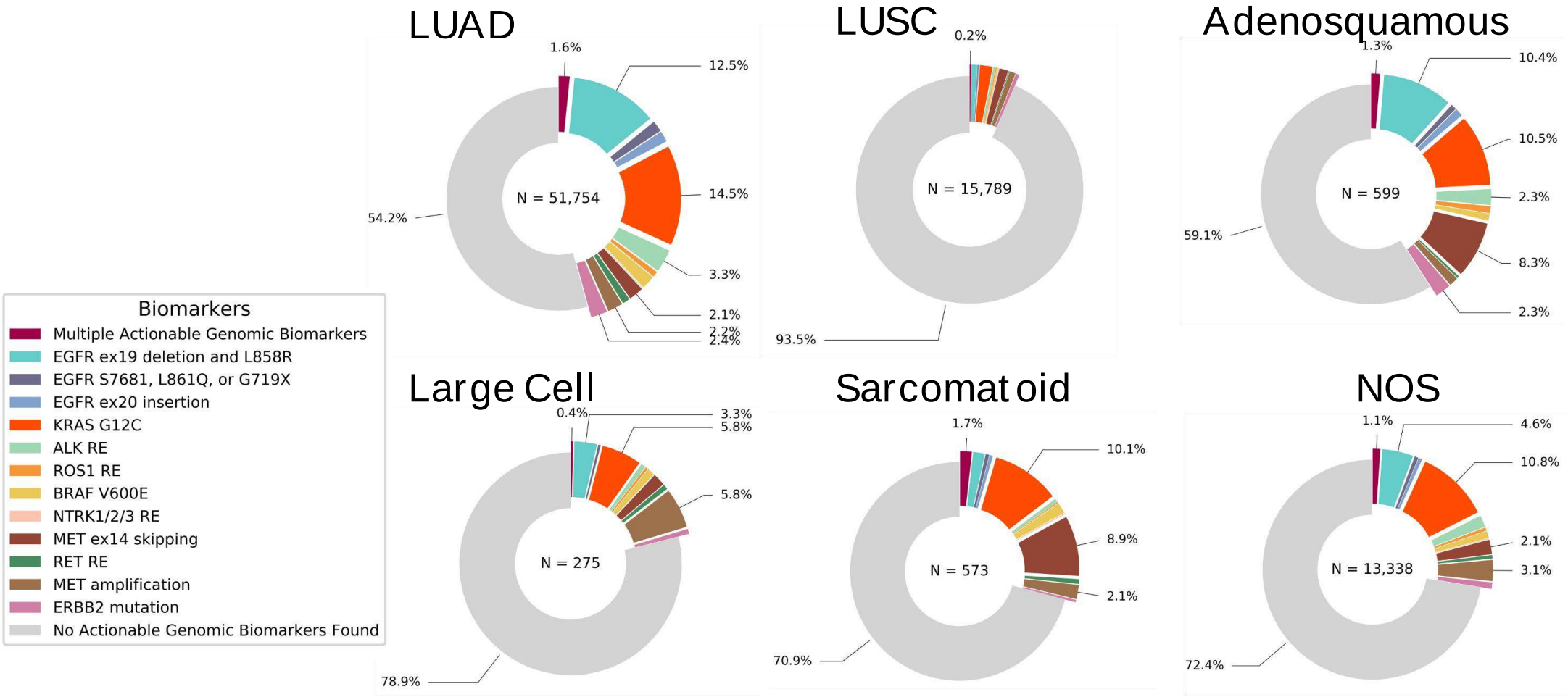
Patients tested at Foundation Medicine Inc laboratory (Cambridge, MA) between 2014 and 2022 (n = 82,328)

- Histologically confirmed non-small cell lung cancer of any age, sex and race.
- Tissue tested using FoundationOne/Foundation CDx (F1/F1CDx).
- +/- Clinical and demographic data Western Institutional Review Board Protocol No. 20152817.



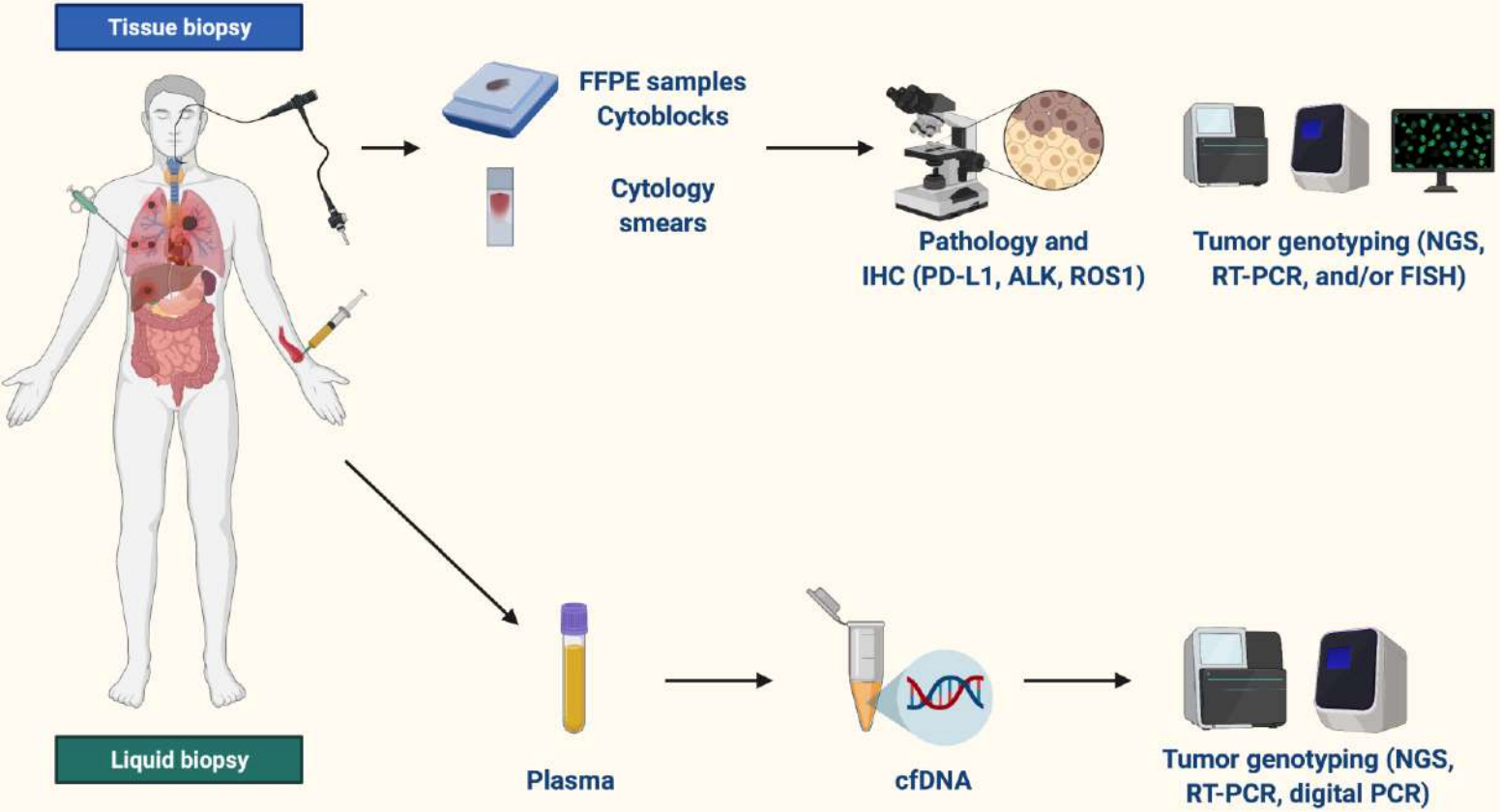
Russo A (Rolfo C), et al. ASCO 2024

Distribution of genomic alterations across histologies



Russo A (Rolfo C), et al. ASCO 2024

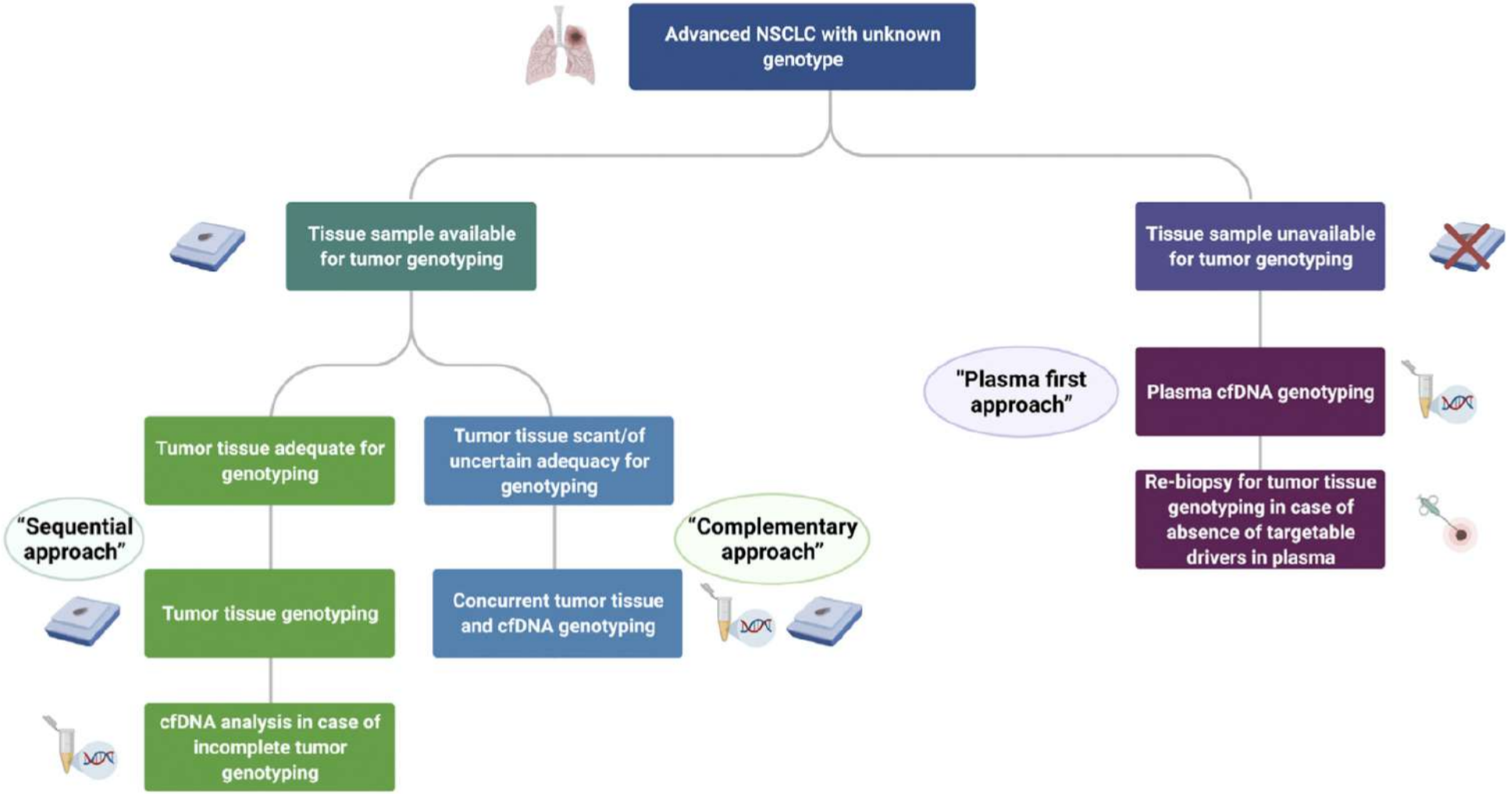
Tissue vs. Liquid biopsy



	Advantages	Disadvantages
Tissue biopsy	✓Pathology information ✓Assessment of DNA and non-DNA biomarkers ✓PD-L1 assessment	✓Longer TAT ✓Limited tissue quantities ✓Invasive ✓At PD, re-biopsy not always feasible ✓Tumor heterogeneity
Liquid biopsy (cfDNA)	✓High concordance rate ✓ Rapid TAT ✓Minimally invasive ✓Repeatable over time ✓Better capture tumor hetereogenity and clonal evolution	✓Non-DNA biomarkers not evaluable ✓Increased costs if used concurrently with tissue testing ✓False negatives

Rolfo C, et al. J Thorac Oncol 2021;16(10):1647-1662.

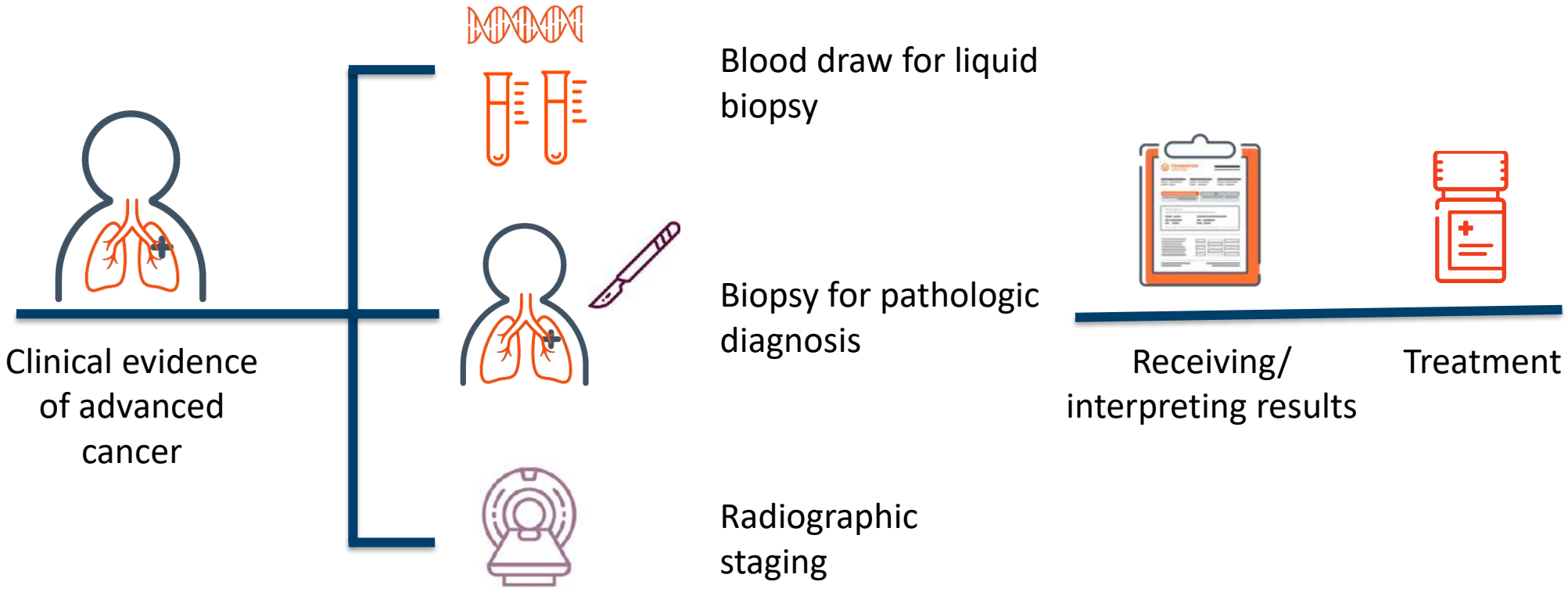
Diagnostic algorithm for liquid biopsy use in treatment-naive advanced/metastatic NSCLC



Rolfo et al, JTO 2021 Oct;16(10):1647-1662

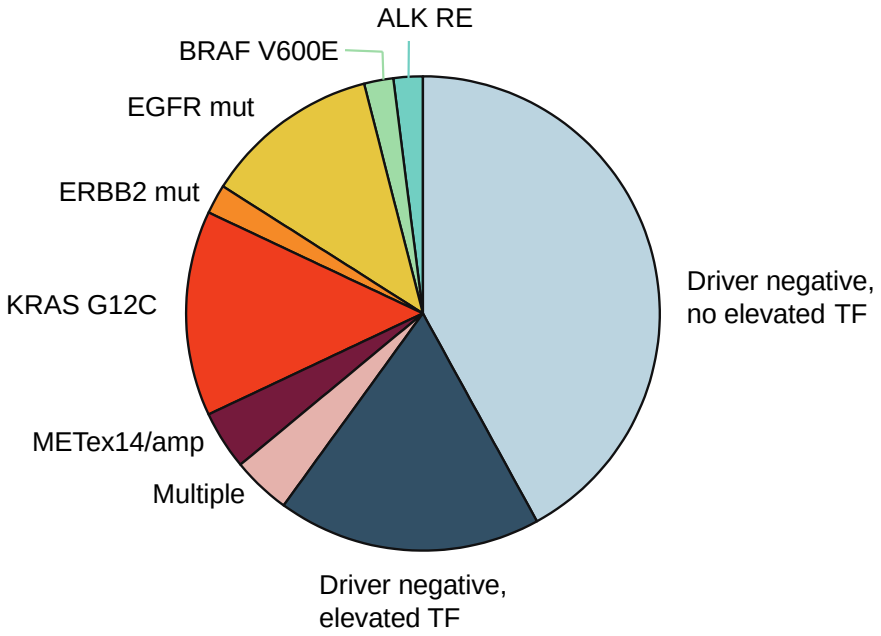
Expedited diagnostic odyssey

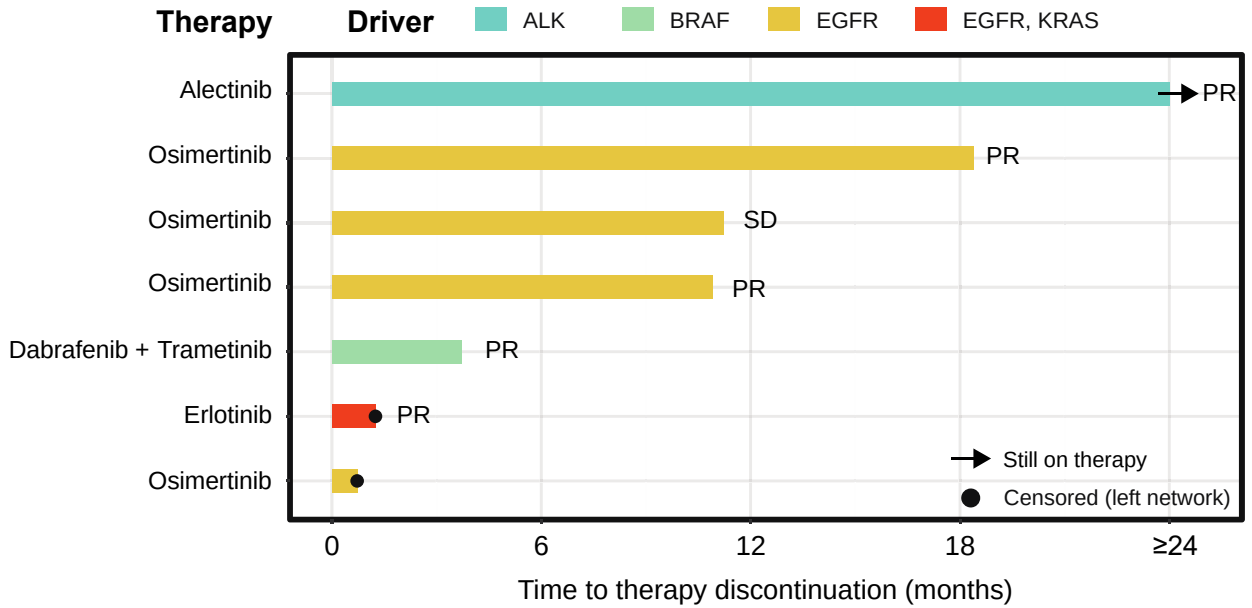
stacking diagnostic steps may be able to shorten the diagnostic odyssey



Russo A. et al (Rolfo C.) JCO PO, Feb 2024

36% of early LBX samples were positive for an actionable NCCN driver





9 (18%) of patients were NCCN driver negative with estimated tumor fraction (TF) ≥ 10% (presumed true negatives)

7 driver+ patients received a 1L matched targeted therapy with a median TTD of 11 months and real-world response (PR) in majority of patients

Russo A. et al (Rolfo C.) JCO PO, Feb 2024

ctDNA tumor fraction informs the relative benefit from reflex to TBx CGP

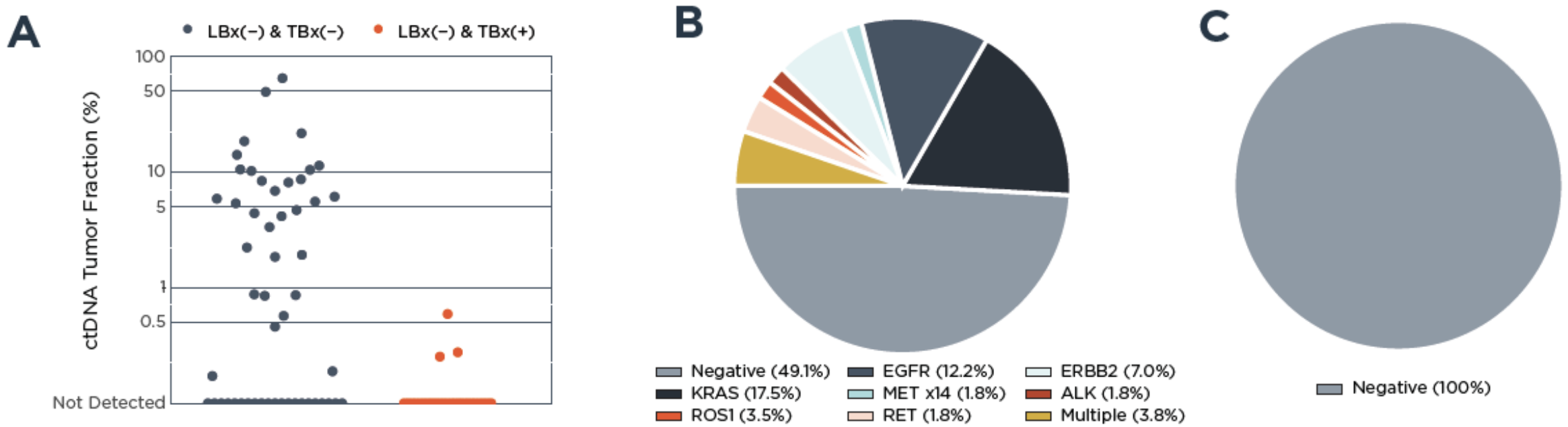
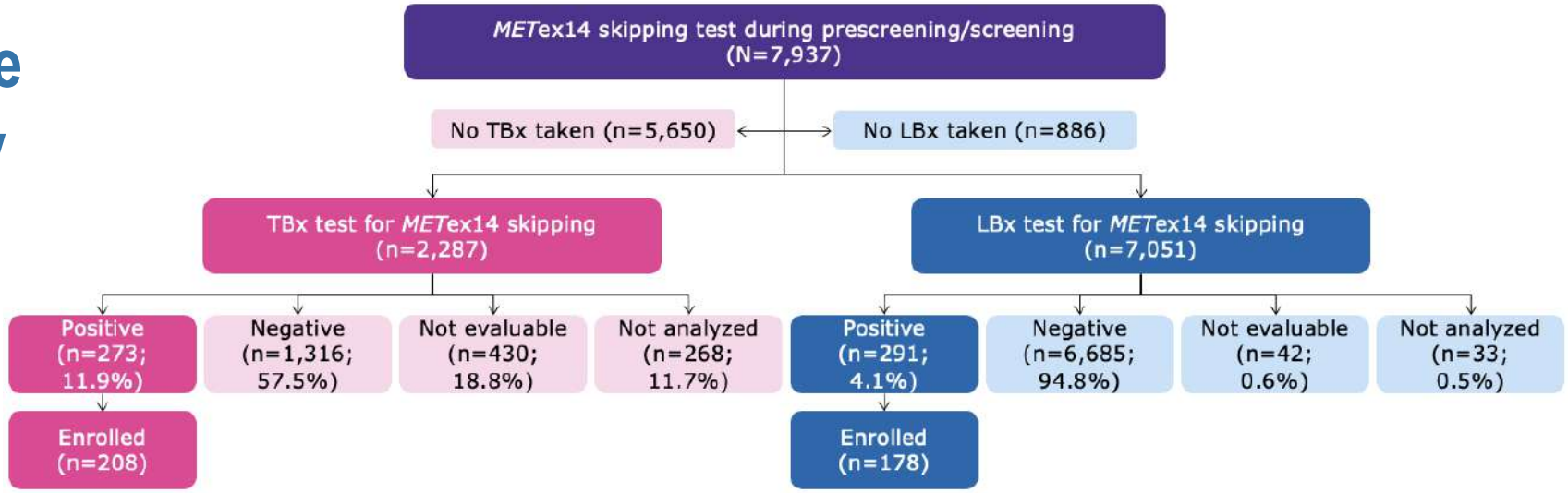


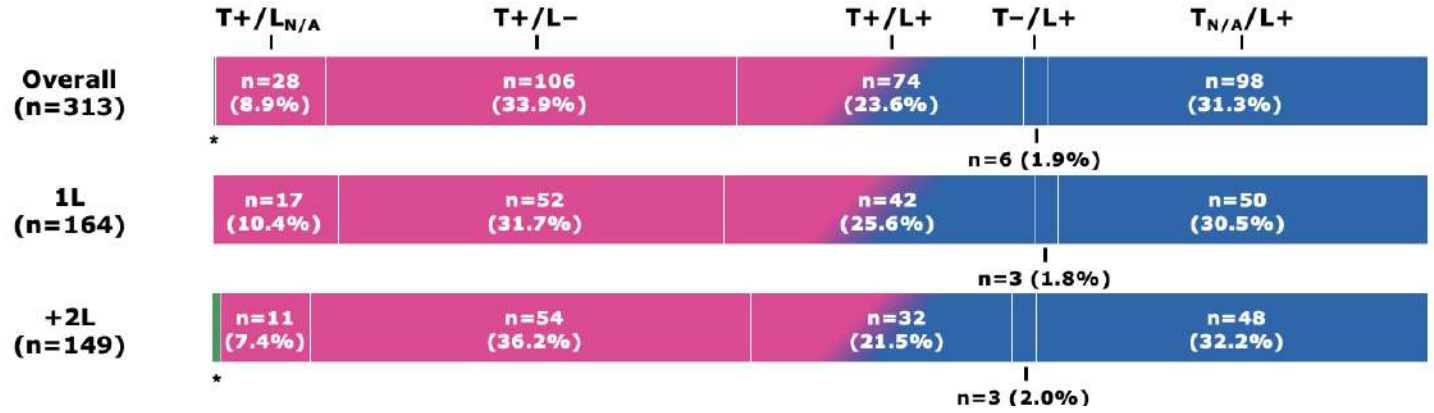
Figure 7: A) 24/81 (30%) patients with reflex TBx after negative LBx had a LBx TF ≥1% and, given high NPV for driver alterations, might have avoided reflex to confirmatory TBx. **B)** Amongst patients with TF <1%, 51% (29/57) of patients had a driver mutation detected on TBx reflex while **C)** no driver mutations (0%) were seen for patients with TF ≥1%

Rolfo C et al, Clin Cancer Research, April 10, 2024

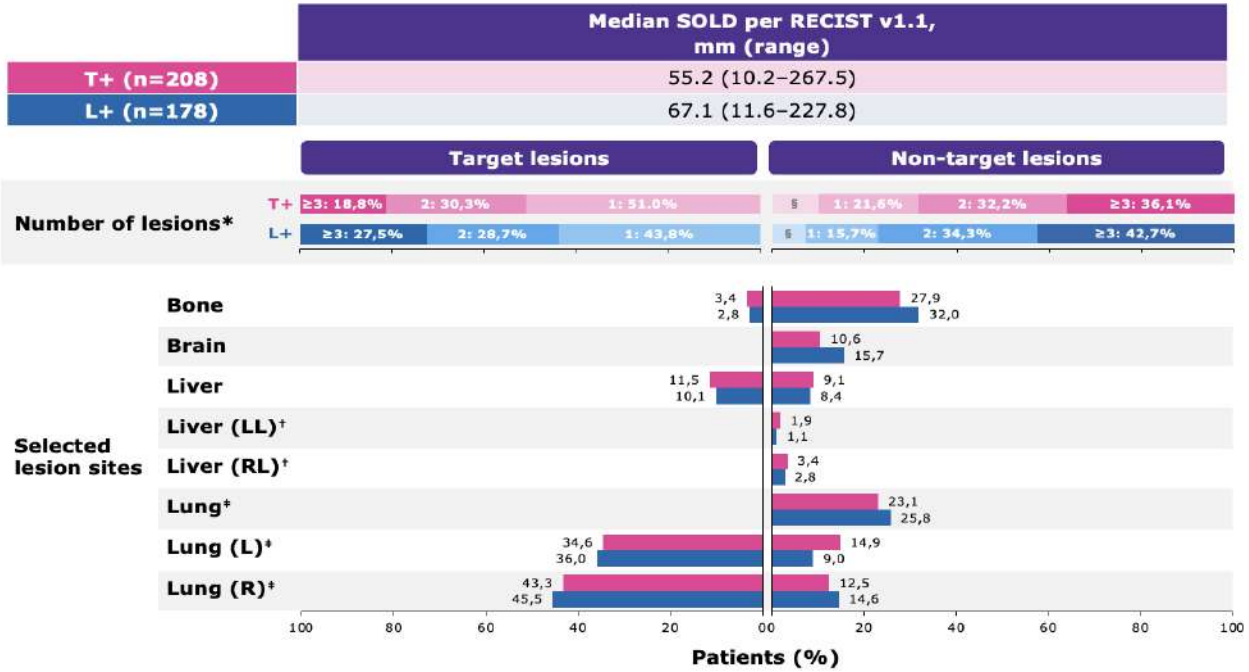
Liquid biopsies (lbx) and tissue biopsies (tbx) for identifying *MET* exon 14 skipping (*met*ex14) in advanced NSCLC: analyses from the phase II VISION study of tepotinib

Prognostic Value of Liquid Biopsy





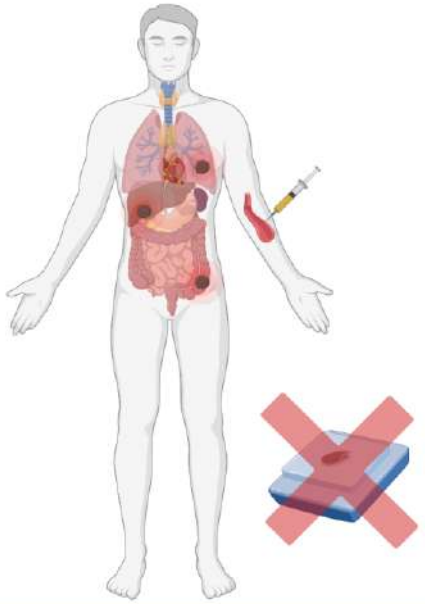
Rolfo C. ASCO 2023



IRC	1L		+2L	
	T+/L– (n=52)	T+/L+ (n=42)	T+/L– (n=54)	T+/L+ (n=32)
ORR, % (95% CI)	57.7 (43.2, 71.3)	64.3 (48.0, 78.4)	44.4 (30.9, 58.6)	53.1 (34.7, 70.9)
mDOR, months (95% CI)	ne (10.4, ne)	19.4 (7.6, ne)	12.6 (5.1, 20.8)	9.9 (4.4, 15.4)
mPFS, months (95% CI)	22.1 (14.8, ne)	12.1 (7.8, 49.7)	13.8 (8.2, 24.9)	8.2 (5.5, 13.7)
mOS, months (95% CI)	32.7 (15.3, ne)	28.5 (14.2, ne)	20.8 (15.6, 32.5)	19.8 (10.0, 26.5)

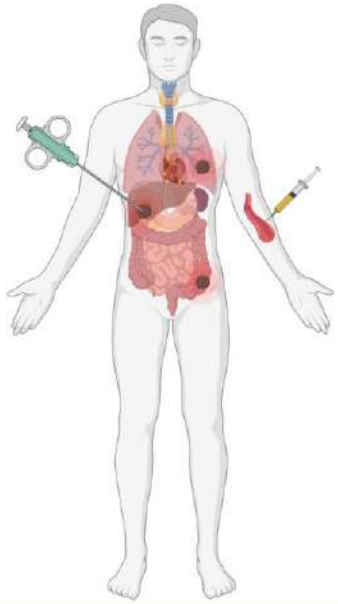
Rolfo C. ASCO 2023

Potential utility of liquid biopsy in *NTRK* fusion-positive NSCLCs



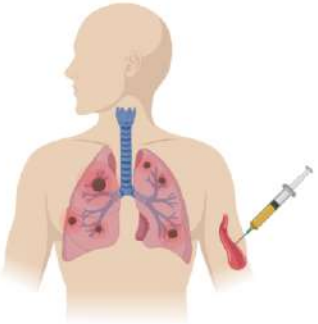
Identification of *NTRK* fusions in patients with insufficient tissue for comprehensive genotyping

Rescue of a significant proportion of undetected *NTRK* fusion positive patients



Identification of the mechanisms of acquired resistance to TRK inhibitors as alternative to tissue re-biopsy

Secondary *NTRK* mutations
Off-target mechanisms

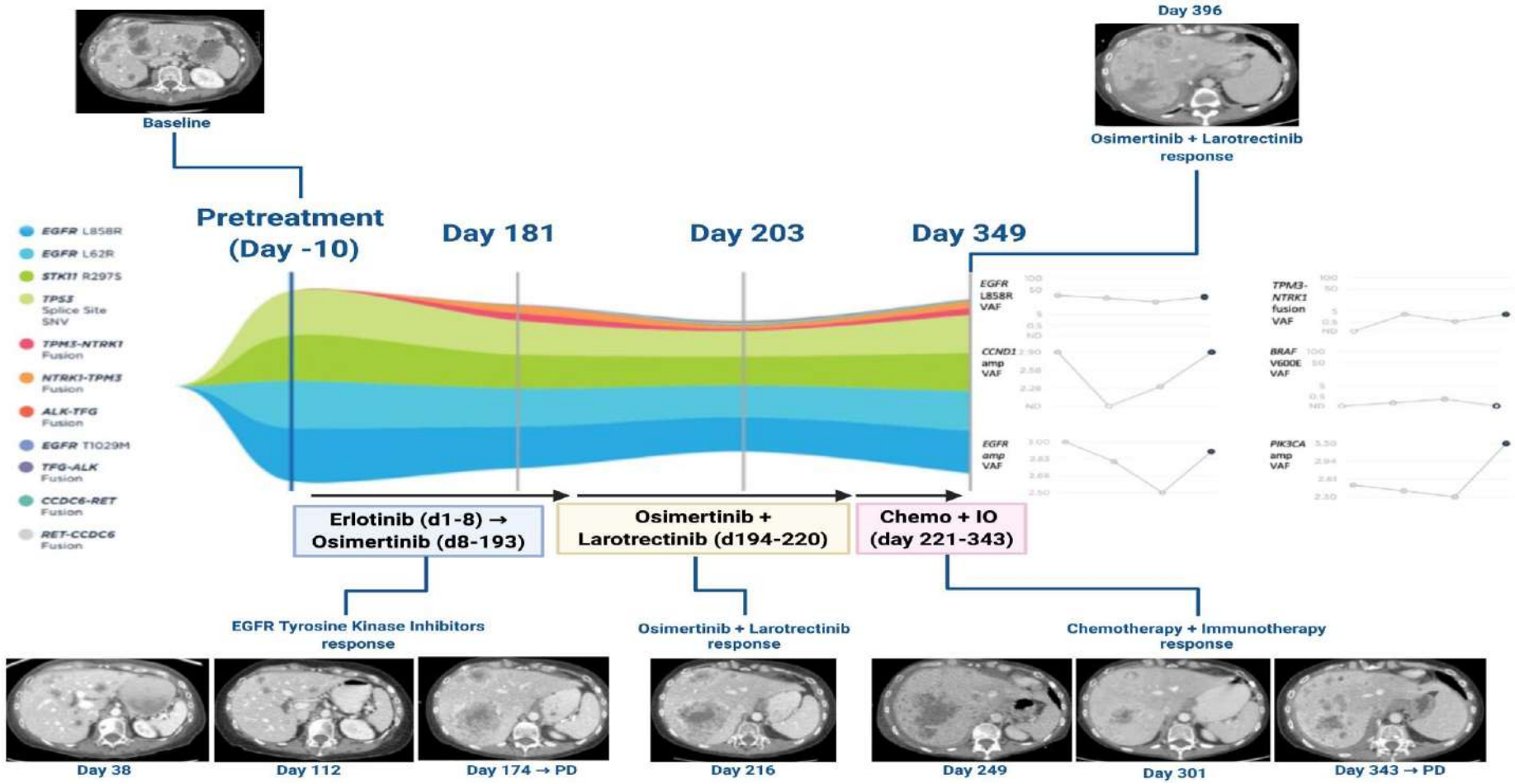


Identification of *NTRK* fusions as mechanisms of resistance to EGFR TKIs and other targeted therapies

Clinical trial enrollment
Tailored strategies

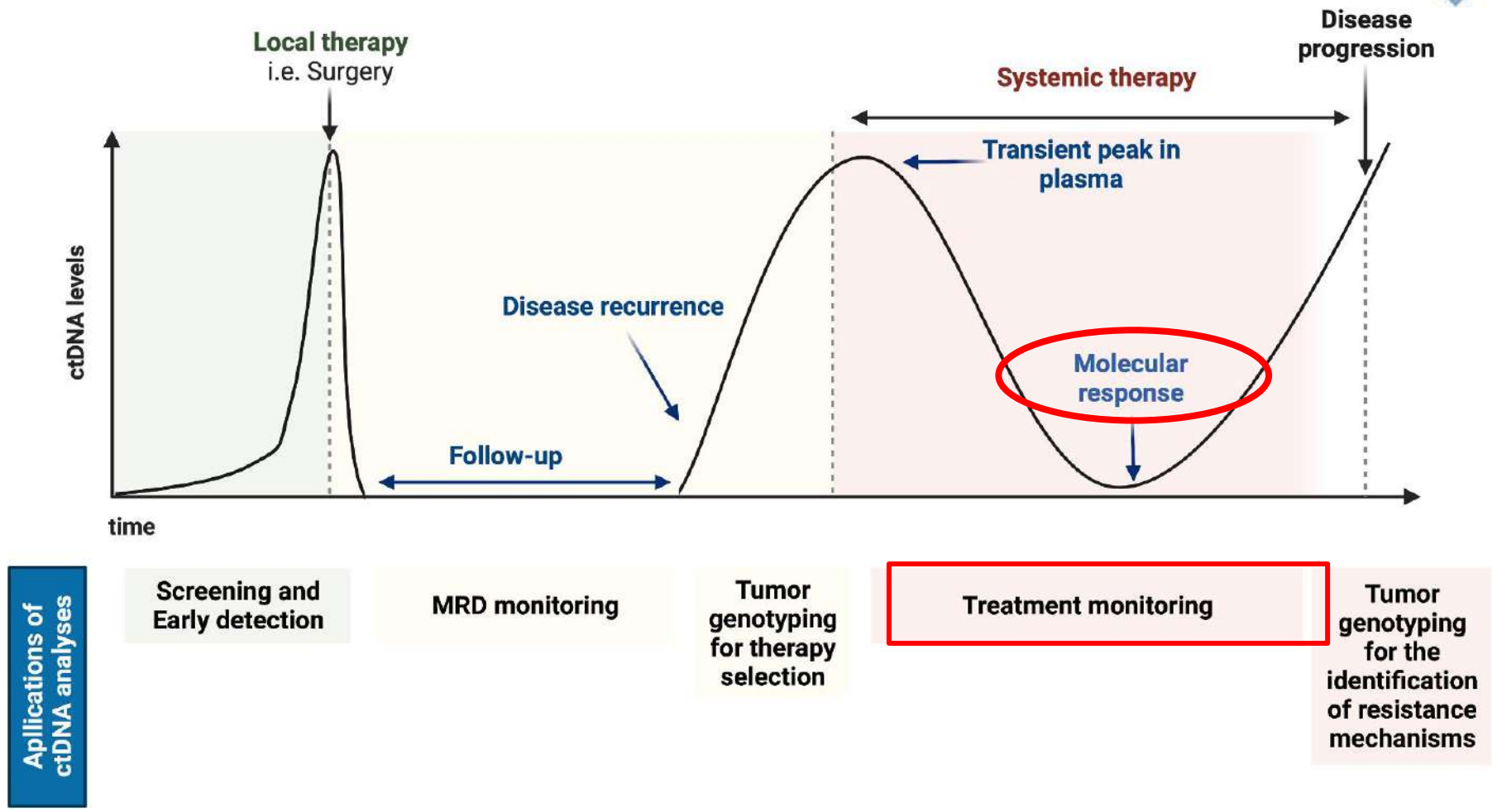
Rolfo C, et al, Br J Cancer 2021

NTRK fusions as mechanism of resistance



Rolfo C, et al, Br J Cancer 2021

Potential clinical applications of LB in lung cancer management



Malapelle U, et al. Lung Cancer. 2022;172:53-64.

Liquid biopsy can capture the dynamic evolution of resistance mechanisms to EGFR TKIs

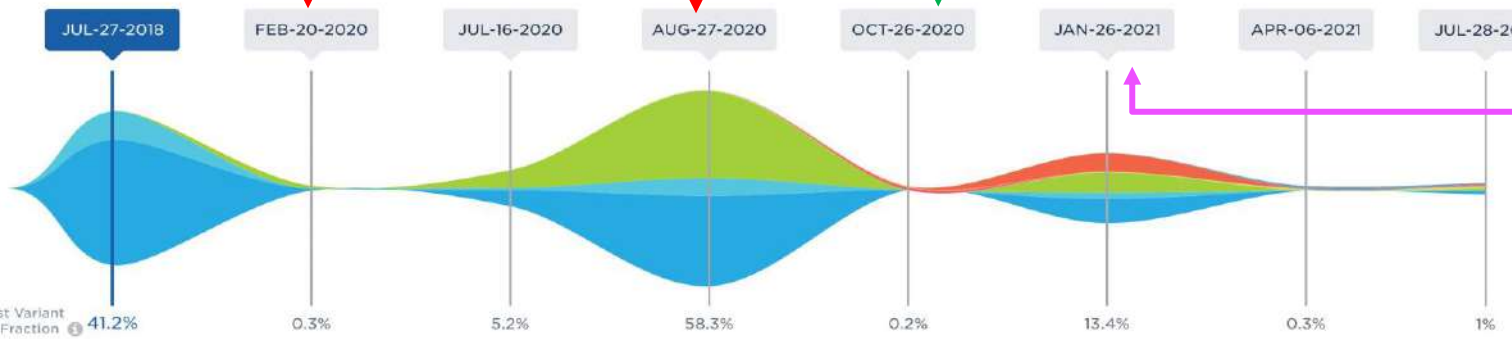
Osimertinib start with an intracranial CR and extracranial PR

After 18 mos oligo-PD (LN mets) → SBRT and continued osi

Further disease progression → osimertinib stopped; switch to erlotinib

PET/CT in Nov. 2020: CR

52-year-old never smoker female; diagnosed in July 2018 with cT4 N3 M1c lung adenocarcinoma (stage IVB).

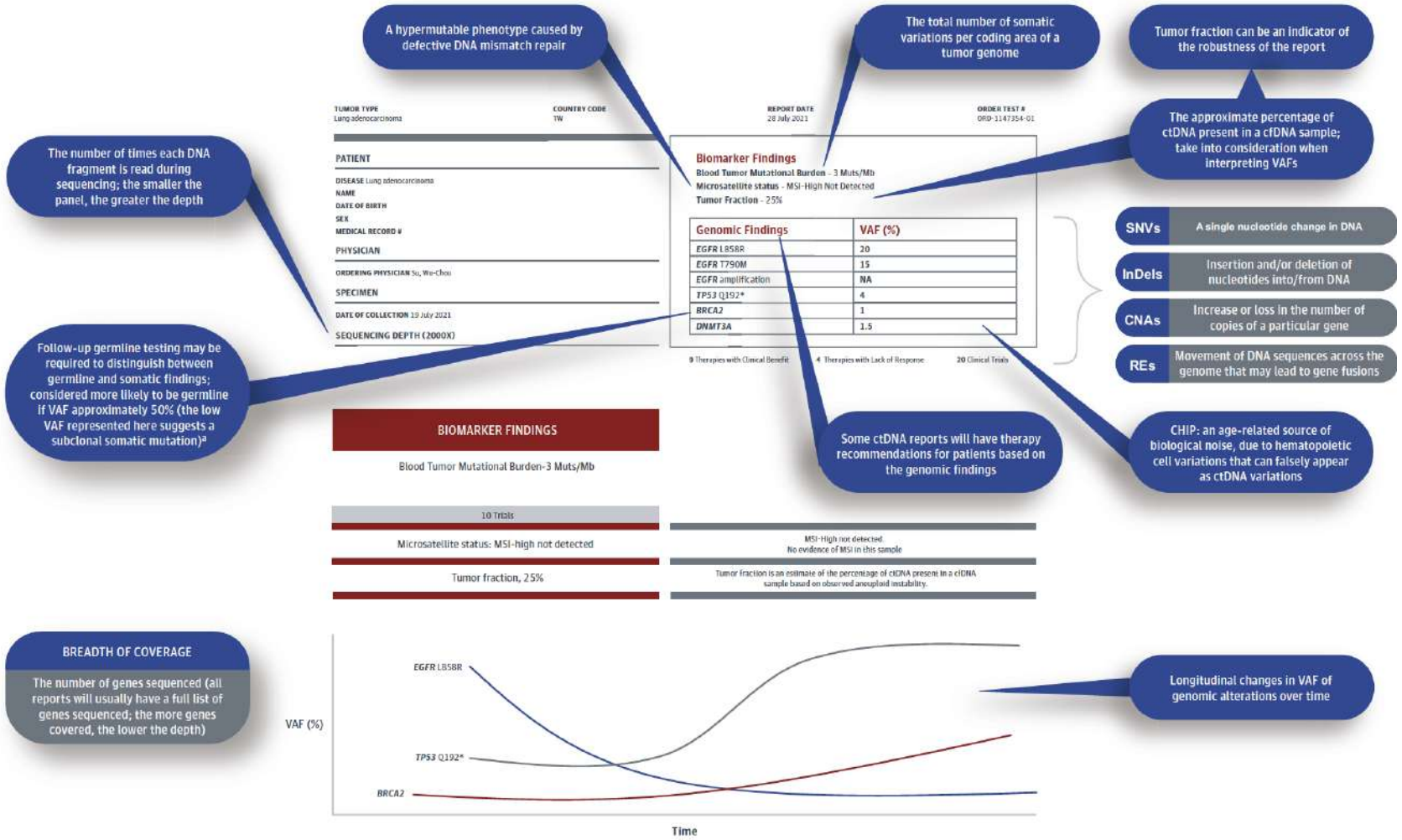


Erlotinib discontinuation → platinum-based chemo start

Genetic Alteration	% cfDNA or amplification							
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND	13.4%	ND	1%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%	ND	0.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%	0.3%	0.6%
EGFR T790M	ND	ND	ND	ND	ND	9.6%	ND	0.4%
TP53 C275Y	ND	ND	ND	ND	ND	ND	0.1%	0.2%
ARID1A F1728F	ND	ND	ND	ND	ND	ND	0.3%	0.2%
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%	ND	0.2%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND	ND	-
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND	0.1%	ND

Russo A (Rolfo C) et al. Clin Lung Cancer 2023

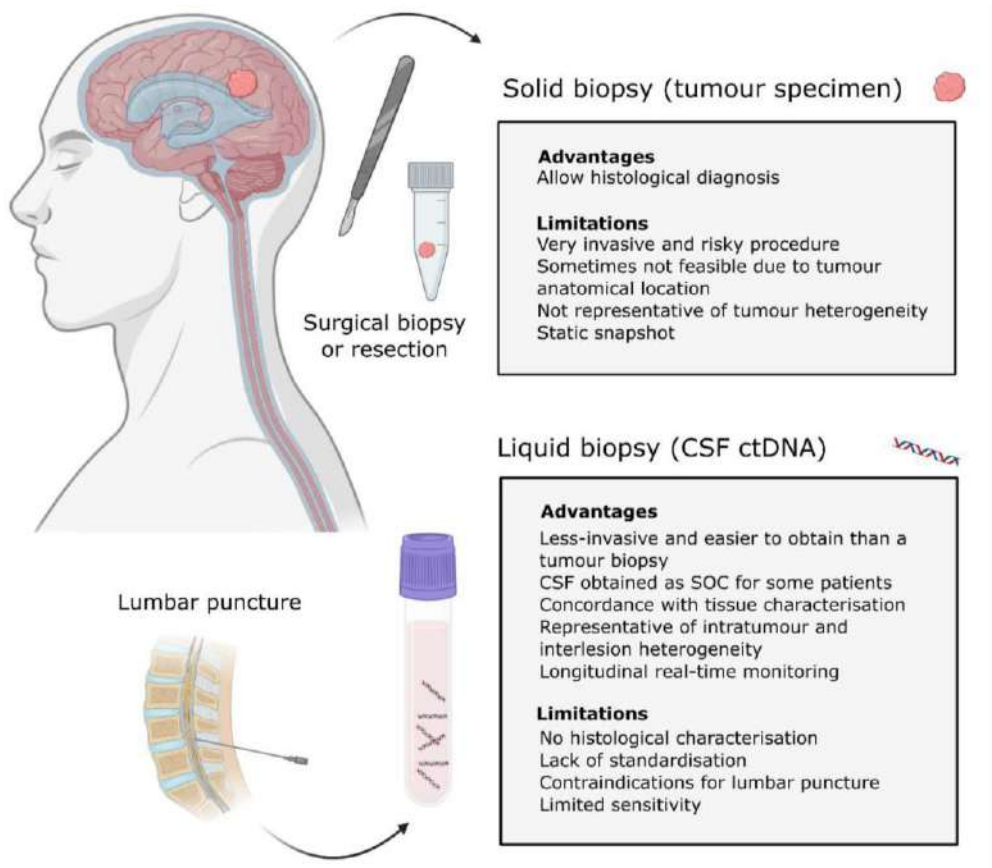
A sample of ctDNA report with key elements



Krebs MG (Rolfo C) et al. JAMA oncol 2022

Special situations: brain metastasis in TKI resistance

CSF demonstrates superiority of cell-free DNA over cell pellet genomic DNA for molecular profiling



Solid biopsy (tumour specimen)

Advantages
Allow histological diagnosis

Limitations
Very invasive and risky procedure
Sometimes not feasible due to tumour anatomical location
Not representative of tumour heterogeneity
Static snapshot

Liquid biopsy (CSF ctDNA)

Advantages
Less-invasive and easier to obtain than a tumour biopsy
CSF obtained as SOC for some patients
Concordance with tissue characterisation
Representative of intratumour and interlesion heterogeneity
Longitudinal real-time monitoring

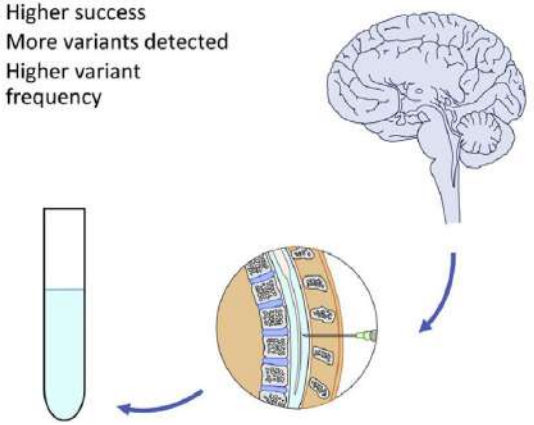
Limitations
No histological characterisation
Lack of standardisation
Contraindications for lumbar puncture
Limited sensitivity

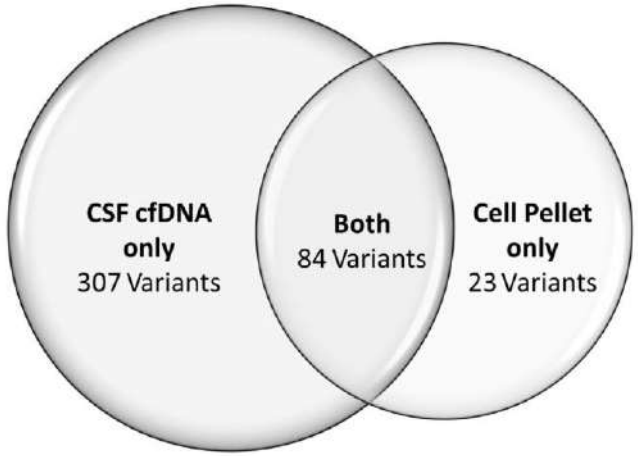
Effective in establishing CNS involvement:
- >97% cases with mutational profile matching primary tumor
- >70% of cases profiled had mutations

New findings compared with primary tumor in >17% demonstrating:
- Resistance mechanisms
- Clonal evolution
- New primary diagnoses

More informative than tumor cell profiling from same CSF sample
- Higher success
- More variants detected
- Higher variant frequency

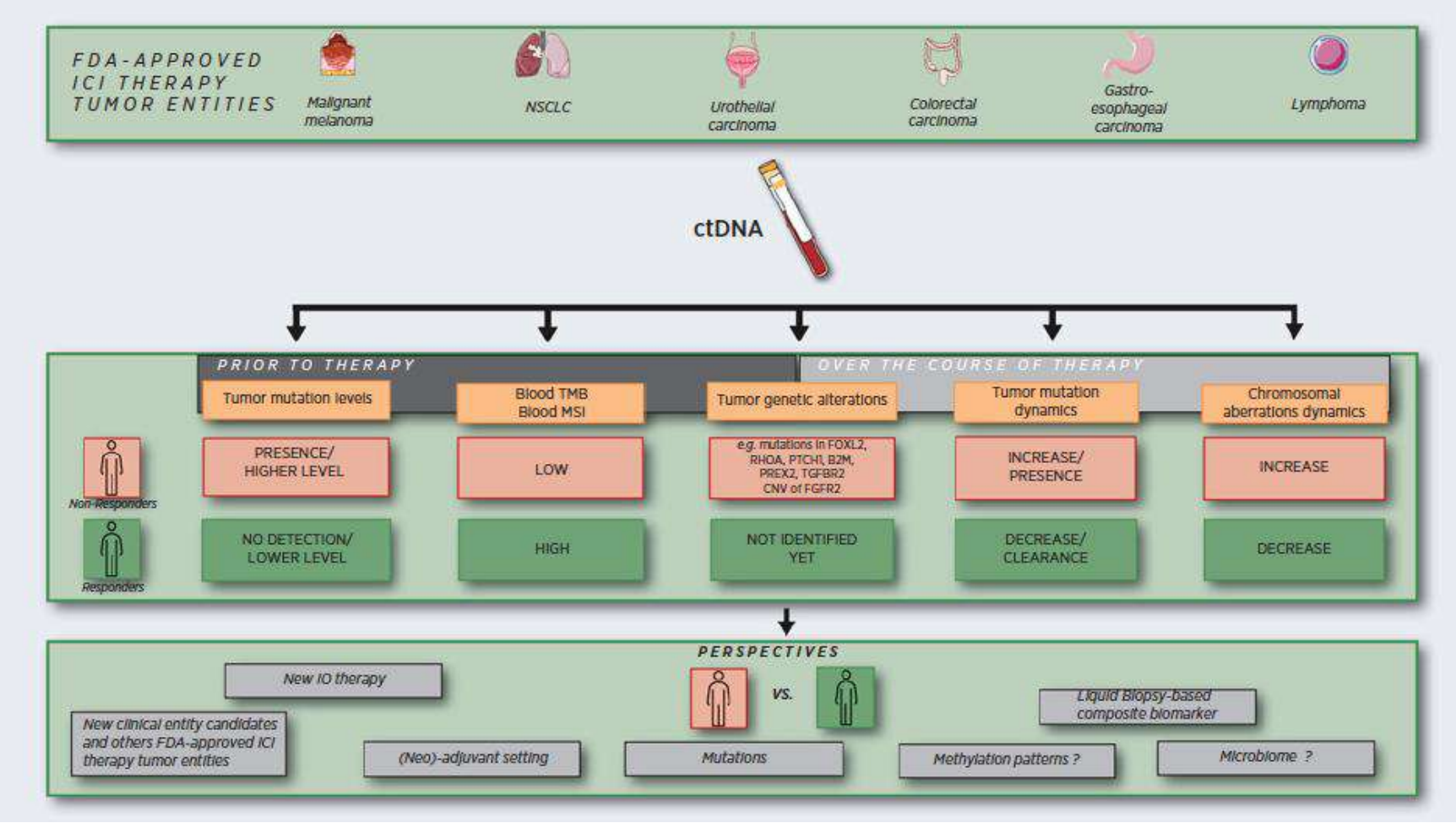
Meaningful results generated even in samples with:
- Very Low input DNA
- Normal CSF cytology





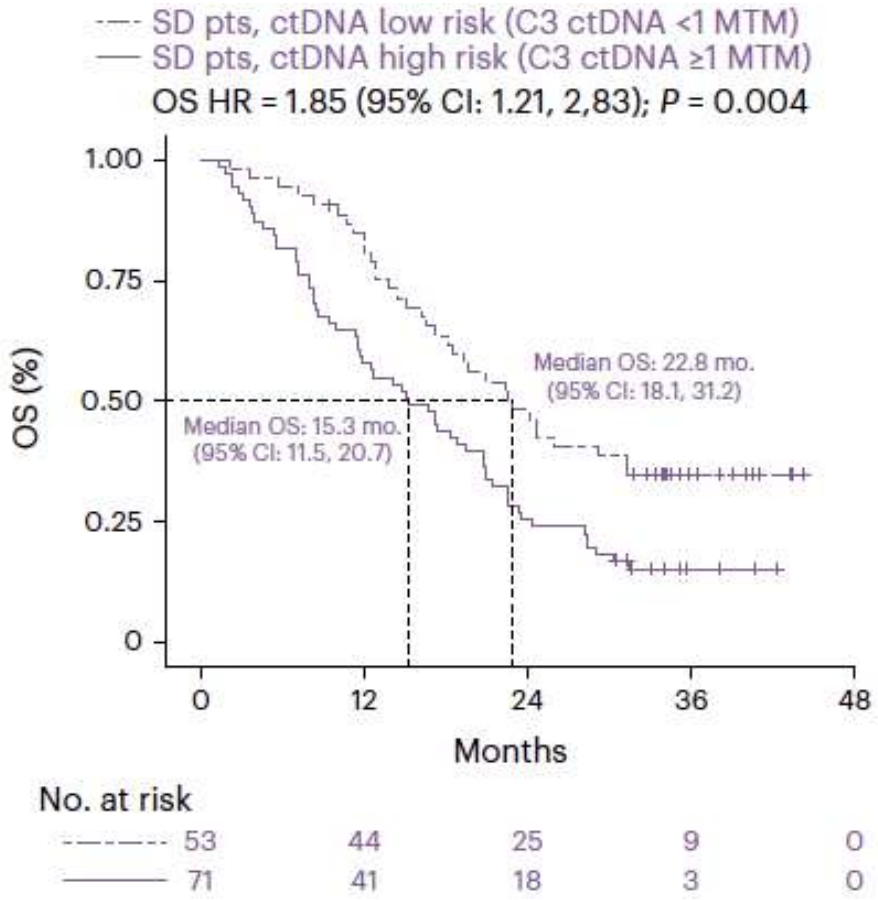
*Escudero et al, Cancers **2021**, 13(9), 1989; Bale et al (Arcila M.) J Mol Diagn . 2021 Jun;23(6):742-752*

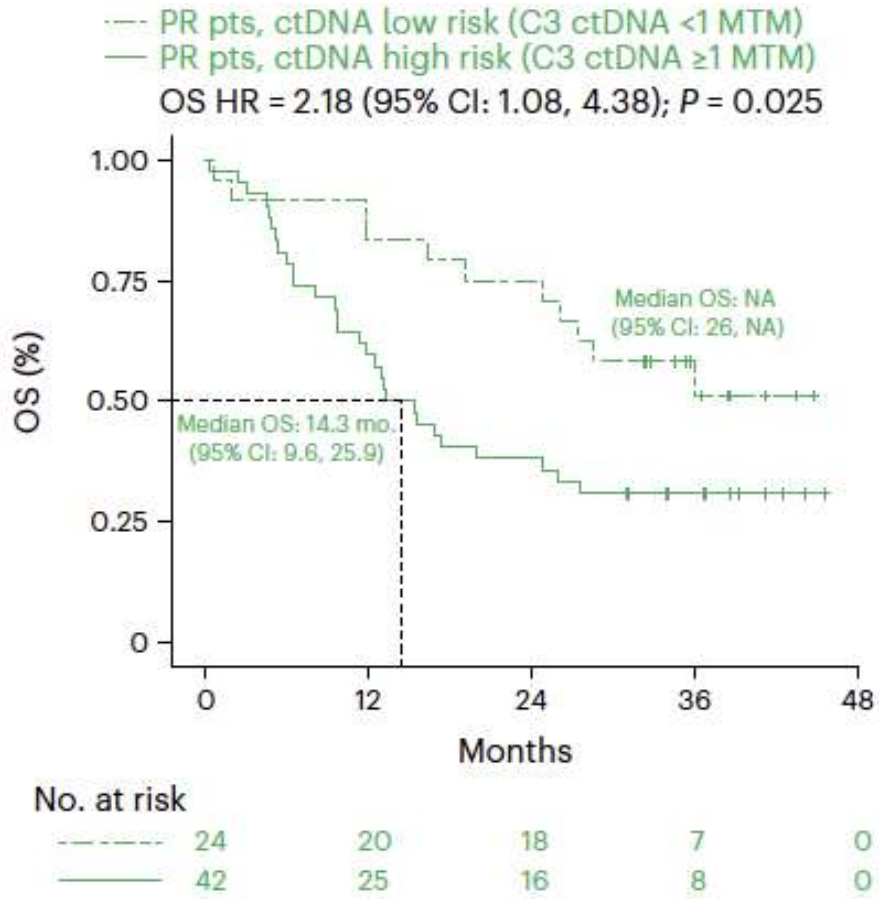
Use of liquid biopsy in immunotherapy



Stadler J, et al. Cancer Res 2022

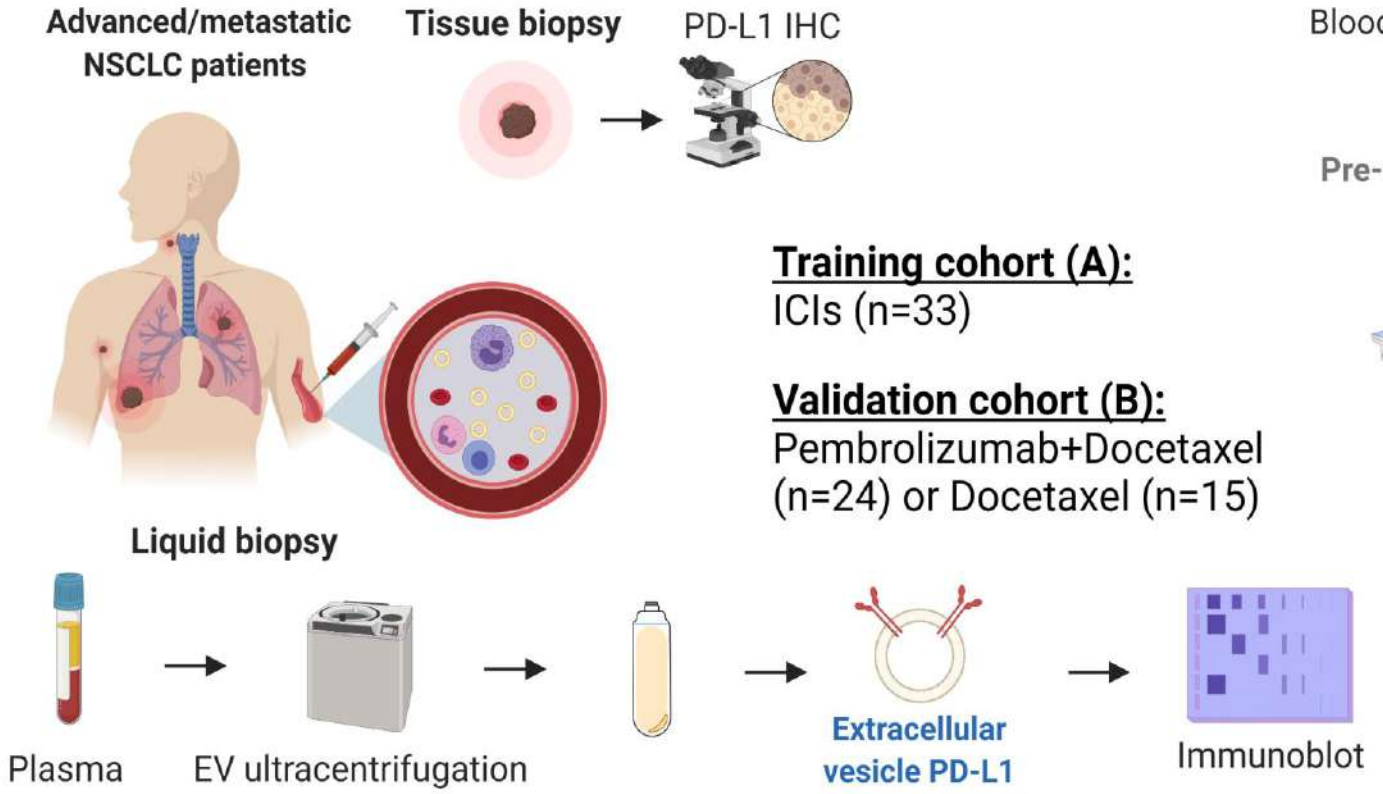
Lack of ctDNA Clearance Is Associated with Poorer Outcomes





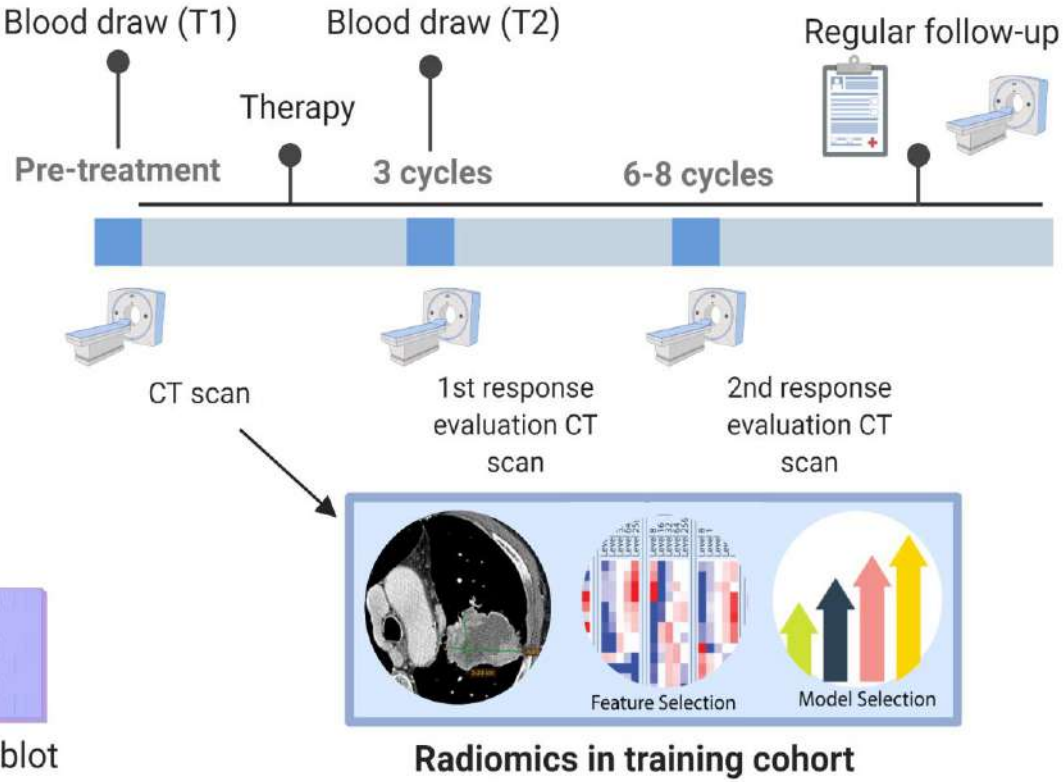
Assaf ZJF, et al. Nat Med. 2023;29(4):859-868.

EV PD-L1 as a predictor for immunotherapy response and outcome



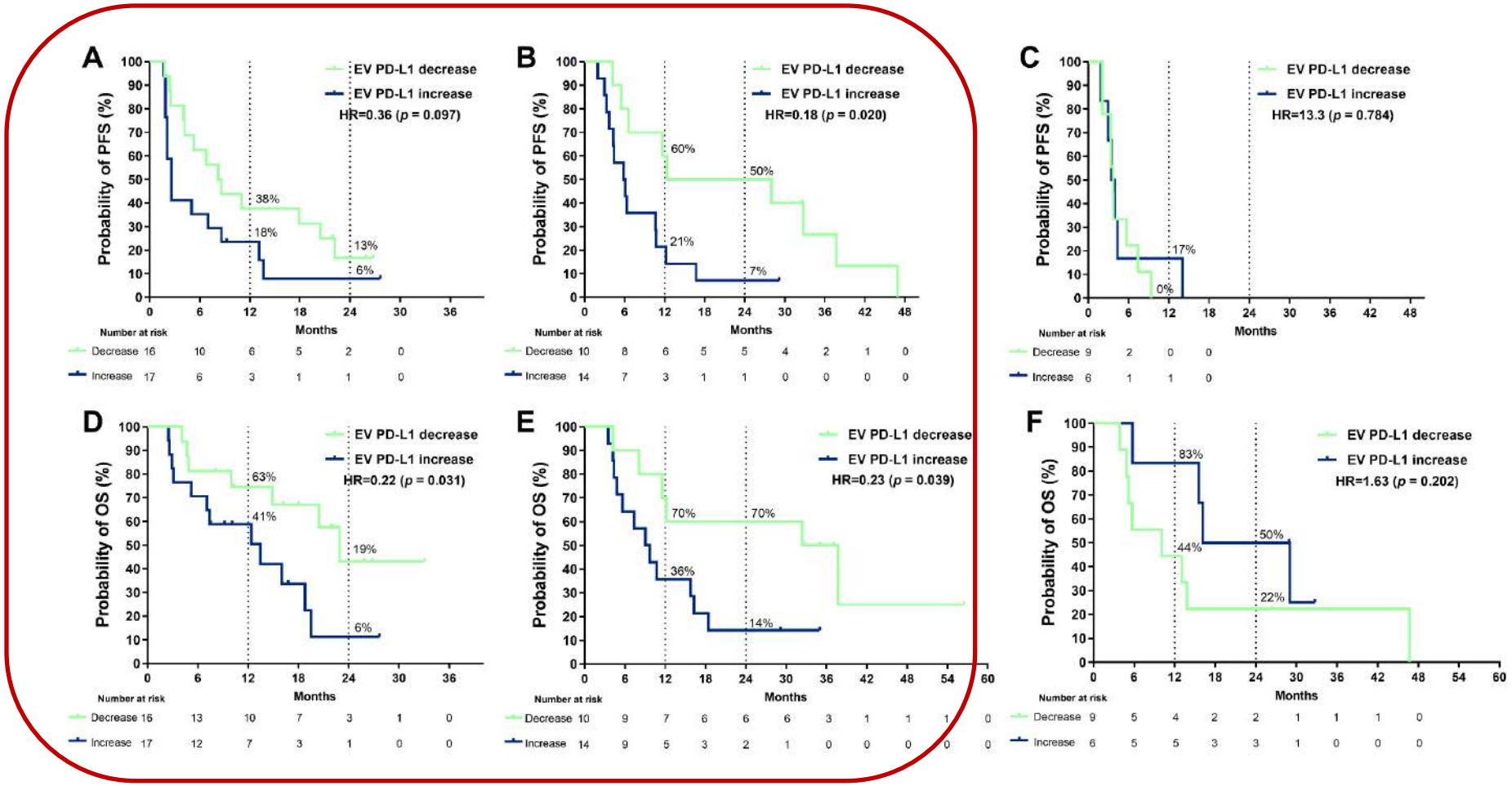
Training cohort (A):
ICIs (n=33)

Validation cohort (B):
Pembrolizumab+Docetaxel (n=24) or Docetaxel (n=15)



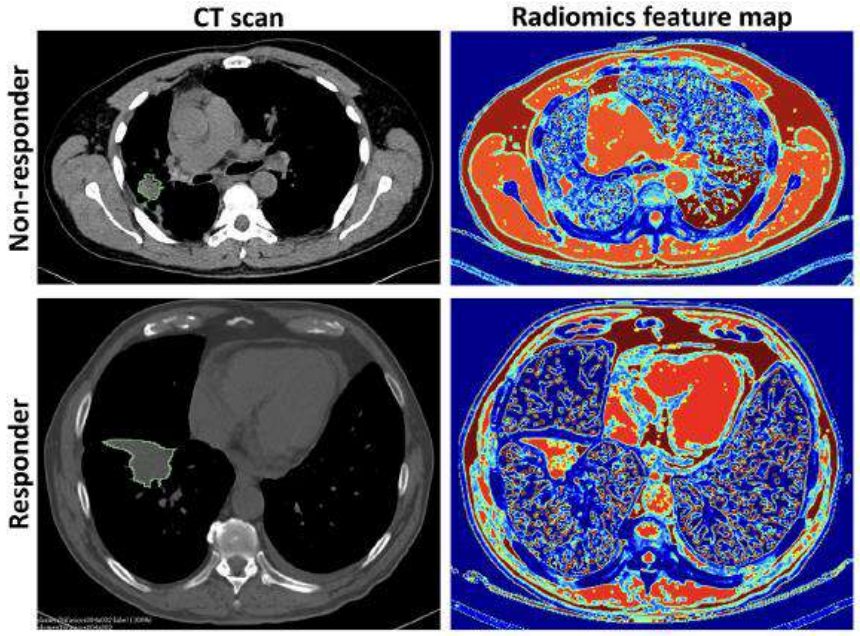
de Miguel-Perez et al. (Rolfo) J Exp Clin Cancer Res (2022) 41:186

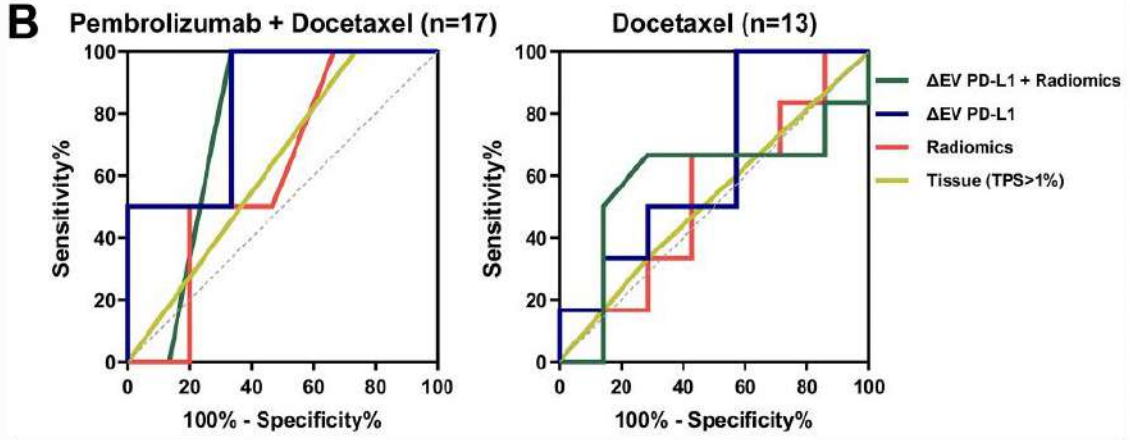
EV PD-L1 and survival outcomes



de Miguel-Perez et al. (Rolfo) J Exp Clin Cancer Res (2022) 41:186

Validation of a multiomic model of plasma extracellular vesicle PD-L1 and radiomics for prediction of response to immunotherapy in NSCLC



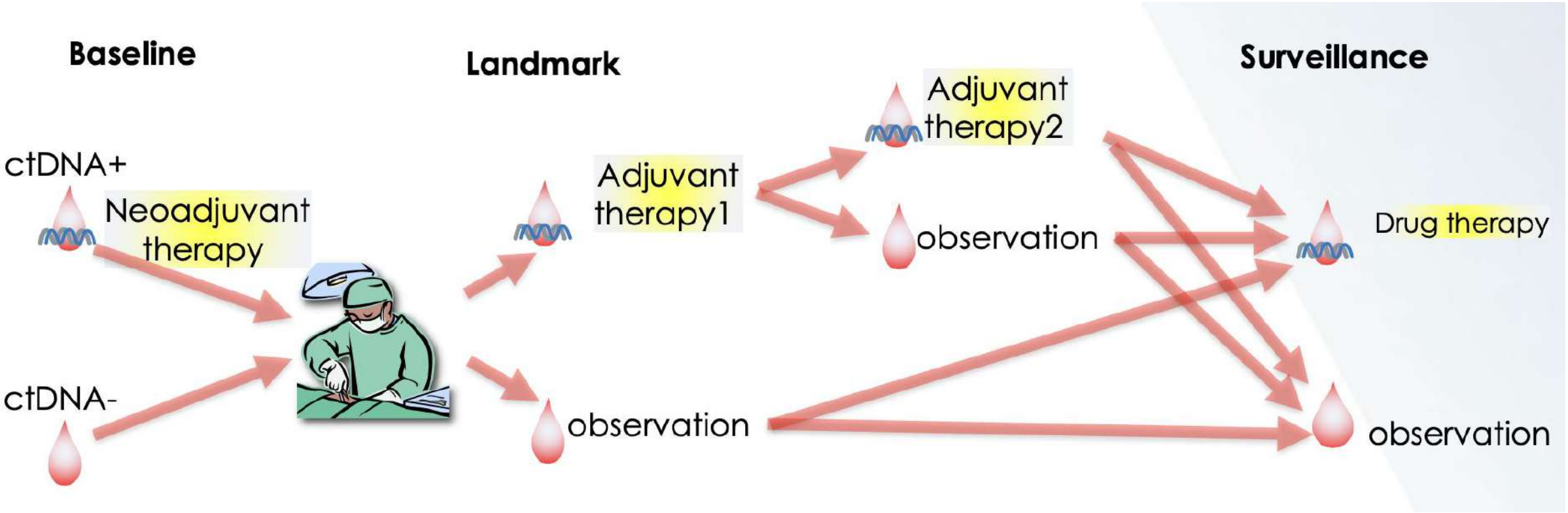


Predictive models for Durable RECIST response (21±3 weeks)								
Cohort:	Pembrolizumab + Docetaxel (n=17)				Docetaxel (n=13)			
Biomarker	AUC	Sensitivity	Specificity	Accuracy	AUC	Sensitivity	Specificity	Accuracy
ΔEV PD-L1 + Radiomics	76.7%	100%	66.7%	70.6%	53.6%	42.9%	83.3%	69.2%
ΔEV PD-L1	83.3%	50%	100.0%	94.1%	54.8%	28.6%	83.3%	61.5%
Radiomics	61.7%	50%	80%	76.5%	57.1%	42.9%	83.3%	53.8%
Tissue PD-L1 ≥1%	63.3%	100%	26.7%	35.3%	52.4%	28.6%	66.6%	46.2%

This multiparametric model showed high sensitivity and specificity at identifying non-responders to ICIs and outperformed tissue PD-L1, being directly correlated with tumor change.

de Miguel-Perez et al. (Rolfo) Journal of Experimental & Clinical Cancer Research (2024) 43:81

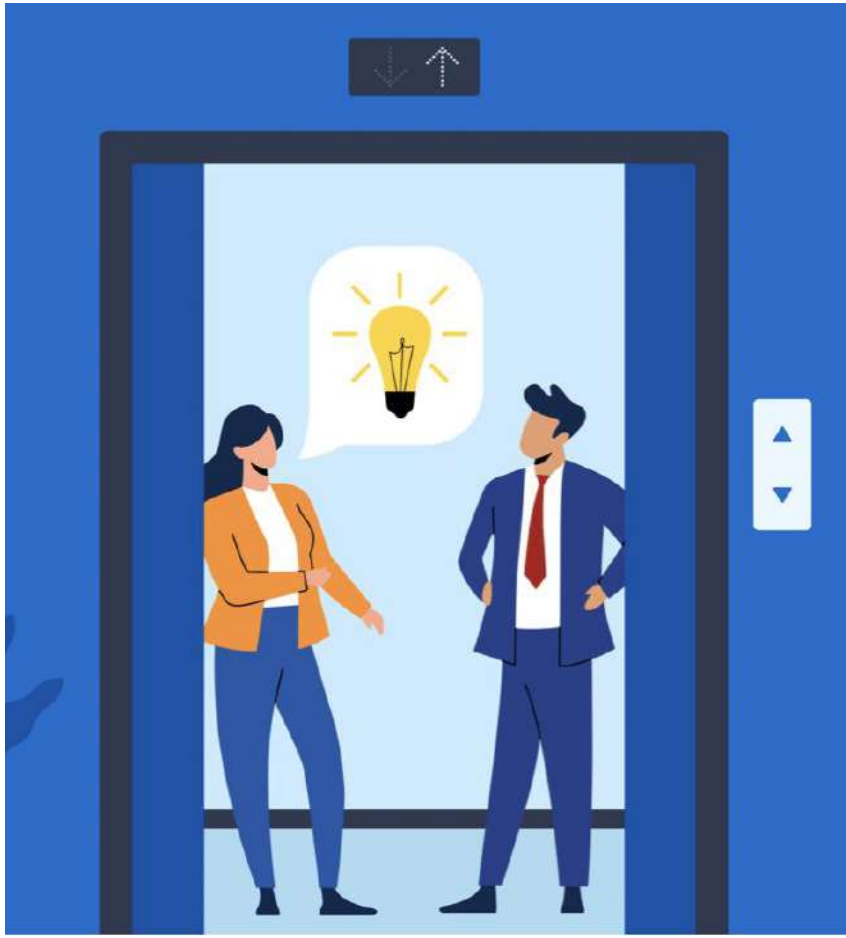
DNA guided perioperative management in the future



Modified from Soh, Hamada Fujino, and Mitsudomi, Cancers (Basel) . 2021

Take home message… my elevator pitch

- Liquid Biopsy is an important tool for diagnosis and monitoring.
- A good opportunity to incorporate LB in immunotherapy assesment
- Integrating liquid biopsy in clinical trials is a necessity
- Use of analytes beyond ctDNA opening the door for biology understanding.



Rolfo Lab

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

The James

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COMPREHENSIVE CANCER CENTER

ACKNOWLEDGEMENTS TEAM AND COLLABORATIONS

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ESMO DEEP DIVE: LUNG CANCER

PRECISION ONCOLOGY IN LUNG CANCER – DIAGNOSTICS

Beyond Xray vision – novel imaging technologies and radiomics

Raquel Perez-Lopez

Team Leader – Radiomics Group Vall d'Hebron Institute of Oncology (VHIO). Barcelona (Spain)

ESMO WEBINAR SERIES

DECLARATION OF INTERESTS

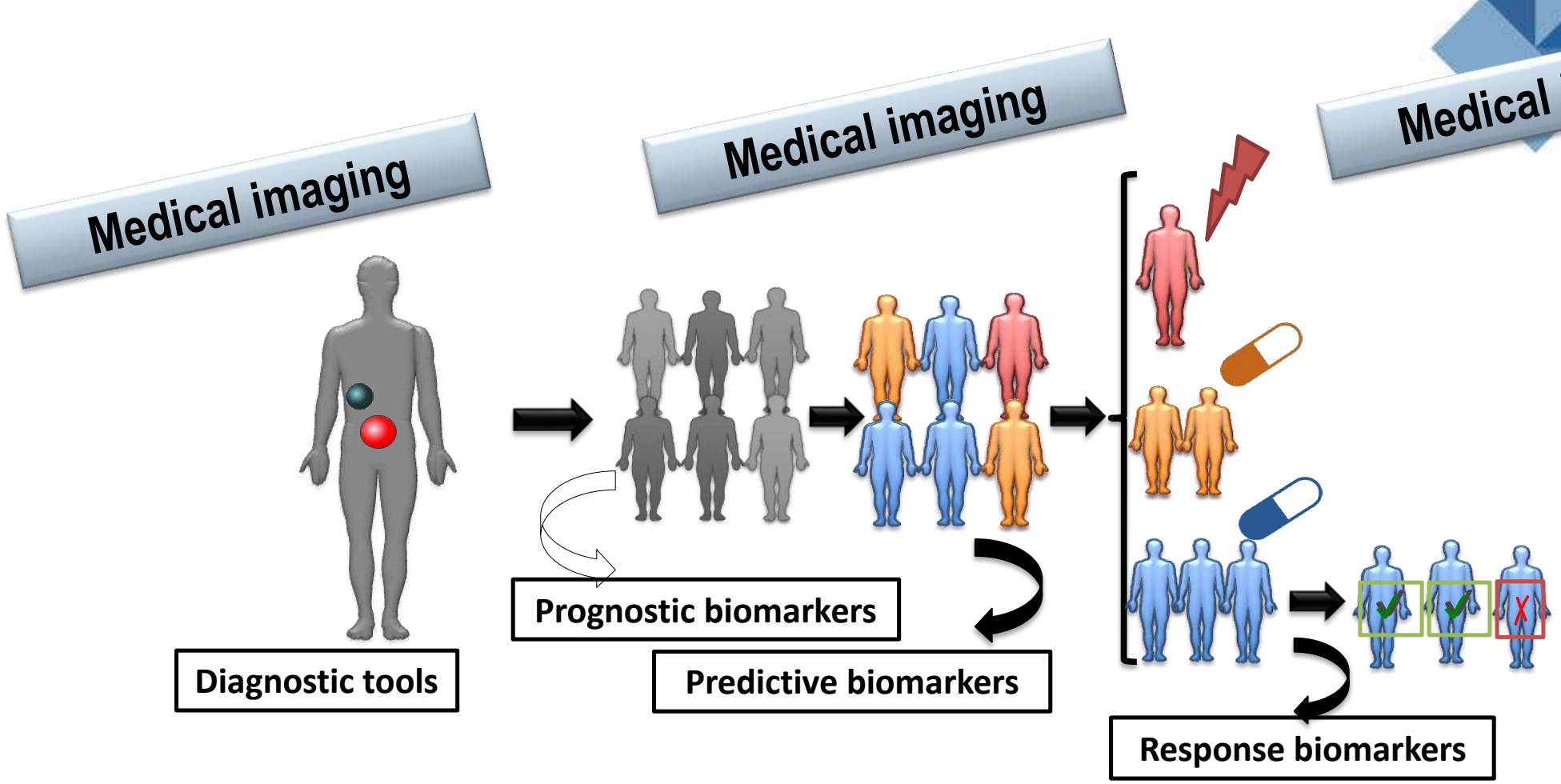
Raquel Perez-Lopez

Employment: Vall d'Hebron Institute of Oncology and Vall d'Hebron Hospital

Research Funding: CRIS Foundation, FERO Foundation, LaMarató Foundation, La Caixa Foundation, Carlos III Instituto de Investigacion, European Commission Horizon Program.

Grant support: AstraZeneca, Roche

Steering committee / advisor role: AstraZeneca, Roche



Clinical Decision Support (CDS) systems

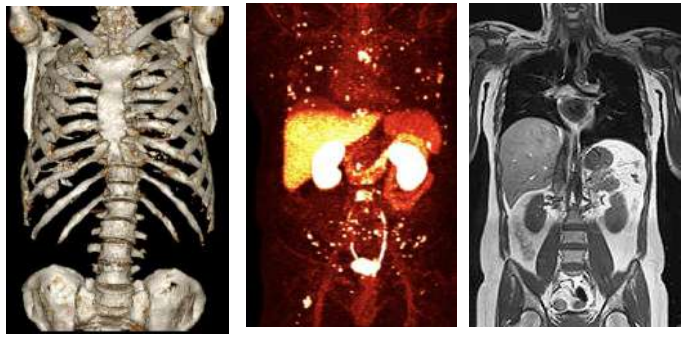
Computer-Aided Diagnosis (CAD) systems

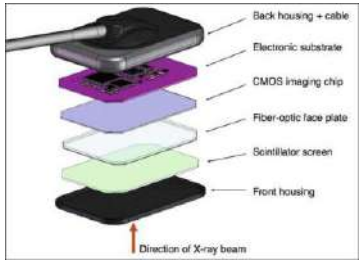
Therapeutic Decision Support (TDS) systems

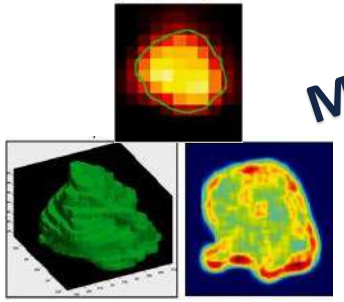
X-ray era

Digital era

Radiomics era







Machine learning

Deep-learning

CNNs

Transformers

Founadtion models

XIX century › **XX century** › **XXI century**

1895 (X-ray)

1950 (PET)

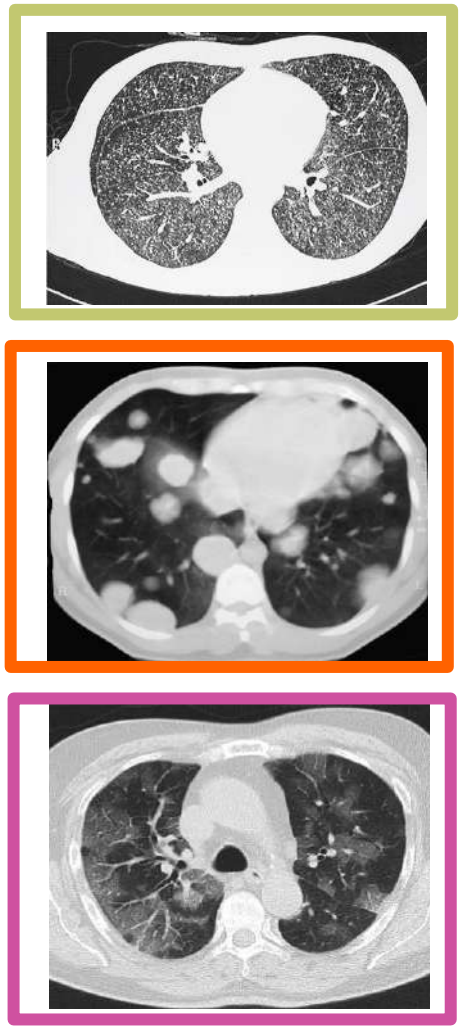
1973 (MRI)

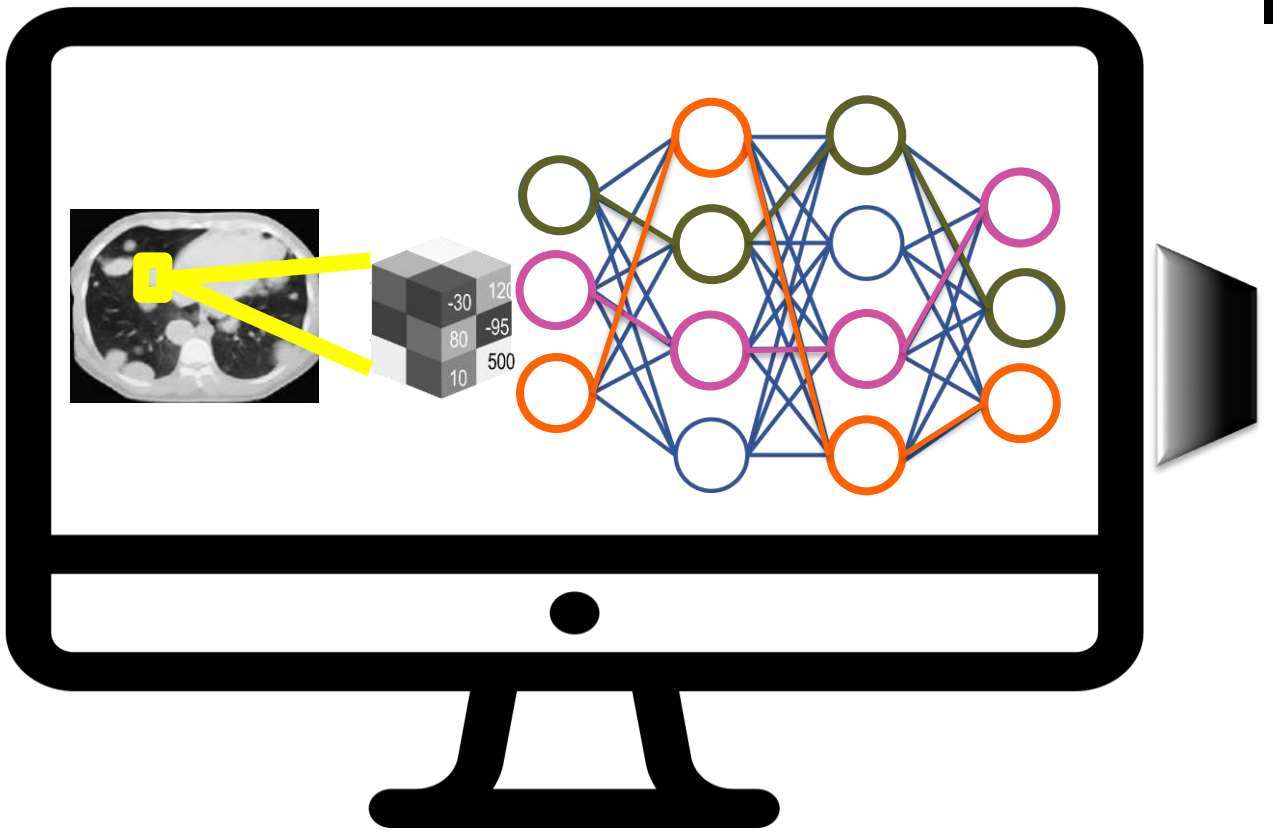
2000

2010

2012

2025





DIAGNOSIS

Tuberculosis

ESMO DEEP DIVE: LUNG CANCER

DETECTION & DIAGNOSIS

LUNG CANCER SCREENING PROGRAM

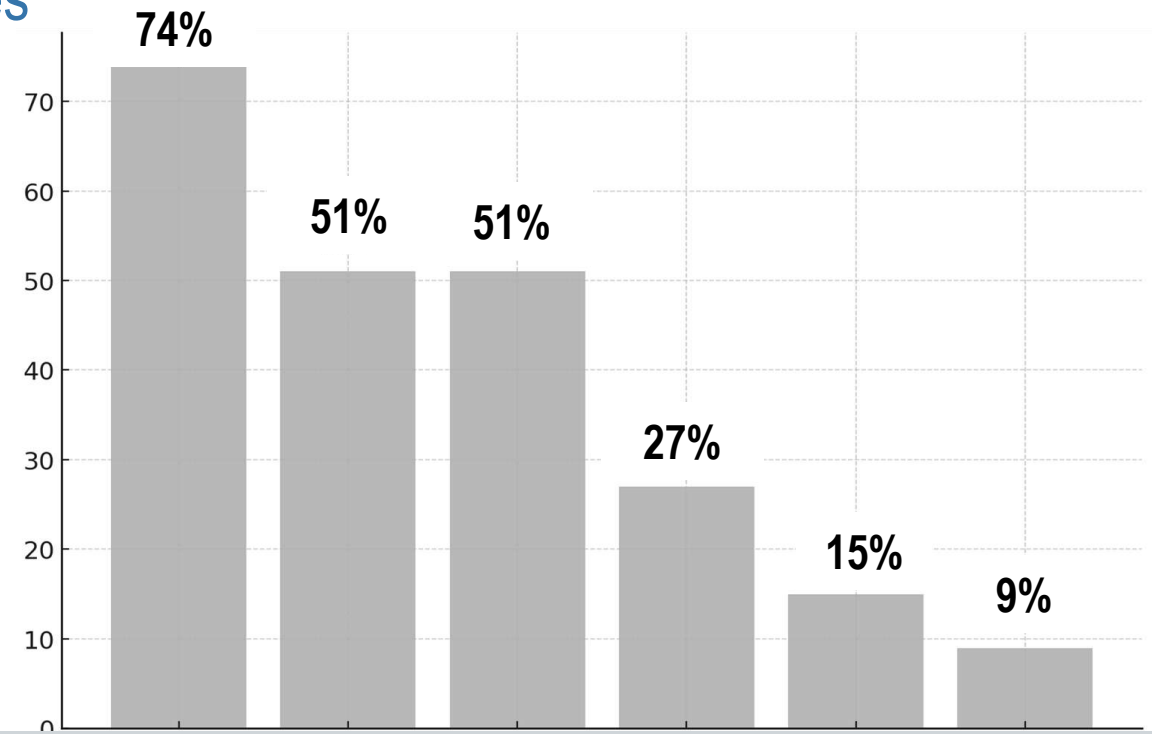
Inclusion criteria

	Recruitment period	Inclusion criteria	Primary comparison	Key outcomes
Randomised trials				
NLST[2]	2002–04	Age 55–74 years; ≥30 pack-year smoking history; currently smoke or quit <15 years ago	Annual low-dose CT *vs* chest radiography for 3 years (n=53 454)	20% reduction in lung cancer-related mortality with low-dose CT
NELSON[3]	2003–06	Age 50–74 years; >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years; currently smoke or quit ≤10 years ago	Low-dose CT at baseline and in year 1, year 3, and year 5·5 *vs* no screen (n=15 789)	24% reduction in lung cancer-related mortality with low-dose CT in men

Field JK, et al. Lancet Reg Health Eur 2021. PMID: 34806061
de Koning HJ, et al. N Engl J Med 2020. PMID: 31995683
NSLT Research Team. N Engl J Med 2011. PMID: PMID: 21714641

LUNG CANCER SCREENING PROGRAM

Prevalence of pulmonary lung nodules



Study	PANCAN	UKLS	NELSON	NLST	MILD	DLCST
Nodule size cutoff	1mm	3mm	4mm	4mm	5mm	5mm

Field JK, et al. Lancet Reg Health Eur 2021. PMID: 34806061

de Koning HJ, et al. N Engl J Med 2020. PMID: 31995683

NSLT Research Team. N Engl J Med 2011. PMID: PMID: 21714641

LUNG CANCER SCREENING PROGRAM

Lung nodule malignancy risk

Lung-RADS® v2022

American College of Radiology™

Lung-RADS	Category Descriptor	Findings	Management
0	**Incomplete** Estimated Population Prevalence: ~1%	Prior chest CT examination being located for comparison (see note 9)	Comparison to prior chest CT;
		Part or all of lungs cannot be evaluated	Additional lung cancer screening CT imaging needed;
		Findings suggestive of an inflammatory or infectious process (see note 10)	1-3 month LDCT
1	**Negative** Estimated Population Prevalence: 39%	**No lung nodules OR**	12-month screening LDCT
		Nodule with benign features: • Complete, central, popcorn, or concentric ring calcifications **OR** • Fat-containing	
2	**Benign** - Based on imaging features or indolent behavior Estimated Population Prevalence: 45%	**Juxtapleural nodule:** • < 10 mm (524 mm^3) mean diameter at baseline or new **AND** • Solid; smooth margins; and oval, lentiform, or triangular shape	
		Solid nodule: • < 6 mm (< 113 mm^3) at baseline **OR** • New < 4 mm (< 34 mm^3)	
		Part solid nodule: • < 6 mm total mean diameter (< 113 mm^3) at baseline	
		Non solid nodule (GGN): • < 30 mm (< 14,137 mm^3) at baseline, new, or growing **OR** • ≥ 30 mm (≥ 14,137 mm^3) stable or slowly growing (see note 7)	
		Airway nodule, subsegmental - at baseline, new, or stable (see note 11)	
		Category 3 lesion that is stable or decreased in size at 6-month follow-up CT **OR** Category 4B lesion proven to be benign in etiology following appropriate diagnostic workup	
3	**Probably Benign** - Based on imaging features or behavior Estimated Population Prevalence: 9%	**Solid nodule:** • ≥ 6 to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** • New 4 mm to < 6 mm (34 to < 113 mm^3)	6-month LDCT
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) at baseline **OR** • New < 6 mm total mean diameter (< 113 mm^3)	
		Non solid nodule (GGN): • ≥ 30 mm (≥ 14,137 mm^3) at baseline or new	
		Atypical pulmonary cyst: (see note 12) • Growing cystic component (mean diameter) of a thick-walled cyst	
		Category 4A lesion that is stable or decreased in size at 3-month follow-up CT (excluding airway nodules)	
4A	**Suspicious** Estimated Population Prevalence: 4%	**Solid nodule:** • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm^3) at baseline **OR** • Growing < 8 mm (< 268 mm^3) **OR** • New 6 to < 8 mm (113 to < 268 mm^3)	3-month LDCT; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** • New or growing < 4 mm (< 34 mm^3) solid component	
		Airway nodule, segmental or more proximal - at baseline (see note 11)	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst **OR** • Multilocular cyst at baseline **OR** • Thin- or thick-walled cyst that becomes multilocular	
4B	**Very Suspicious** Estimated Population Prevalence: 2%	**Airway nodule,** segmental or more proximal - stable or growing (see note 11)	Referral for further clinical evaluation
		Solid nodule: • ≥ 15 mm (≥ 1767 mm^3) at baseline **OR** • New or growing ≥ 8 mm (≥ 268 mm^3)	Diagnostic chest CT with or without contrast; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component; tissue sampling; and/or referral for further clinical evaluation Management depends on clinical evaluation, patient preference, and the probability of malignancy (see note 13)
		Part solid nodule: • Solid component ≥ 8 mm (≥ 268 mm^3) at baseline **OR** • New or growing ≥ 4 mm (≥ 34 mm^3) solid component	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst with growing wall thickness/nodularity **OR** • Growing multilocular cyst (mean diameter) **OR** • Multilocular cyst with increased loculation or new/increased opacity (nodular, ground glass, or consolidation)	
		Slow growing solid or part solid nodule that demonstrates growth over multiple screening exams (see note 8)	
4X	Estimated Population Prevalence: < 1%	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion for lung cancer (see note 14)	
S	**Significant or Potentially Significant** Estimated Population Prevalence: 10%	**Modifier:** May add to category 0-4 for clinically significant or potentially clinically significant findings unrelated to lung cancer (see note 15)	As appropriate to the specific finding

American College of Radiology Committee on Lung-RADS®. Lung-RADS Assessment Categories 2022. Available at https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf

LUNG CANCER SCREENING PROGRAM

AI-aided lung nodule malignancy risk assessment

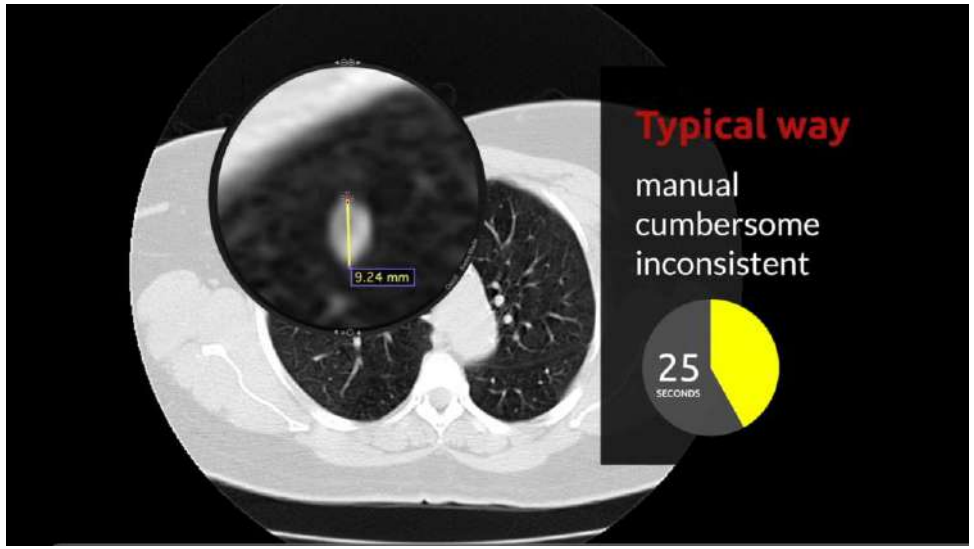


TABLE 4 The latest artificial intelligence-based methods for classifying benign and malignant nodules.

Year	Authors	Data source	Method	Quality index	Quality index value
2016	Petousis et al.[112]	NLST dataset	DBNs Including three expert-driven DBNs and two DBNs derived from structure learning methods	AUC	>0.75
2018	Filho et al.[77]	LIDC-IDRI	Topology-based phylogenetic diversity indices are proposed for features engineering and selection. Feature data are fed to 2D CNNs	Accuracy AUC	0.9263 0.934
2018	Causey et al.[90]	LIDC-IDRI	Training 3D CNN models and collecting output features. A 3D CNN is then used for malignancy classification based on quantitative image features	AUC	0.99
2018	Dey et al.[91]	LIDC-IDRI	Performance comparison between 3D DCNN and 3D DenseNet variants	Accuracy AUC	0.899 0.9459
2019	Balagurunathan et al.[113]	NLST dataset	Optimal linear classifiers	AUC	0.85
2019	Al-Shabi et al.[114]	LIDC-IDRI	Deep Local-G lobal networks containing residual blocks and non-local blocks	AUC	0.9562
2019	Chen et al.[115]	LIDC-IDRI	Using Med3D models pre-trained on ResNets, initialize classification networks using Med3D models	Accuracy	0.9192
2020	Harsono et al.[81]	LIDC-IDRI	Integrated modified pre-trained inflated 3D ConvNet with FPN	AUC	0.8184
2020	Yang et al.[116]	LIDC-IDRI	Self-attention transformer based on 3D DenseNets and MIL algorithms	AUC	0.932
2021	Yu et al.[103]	LIDC-IDRI	Res-trans networks	Accuracy AUC	0.9292 0.9628
2021	Halder et al.[117]	LIDC-IDRI	Two-path morphological 2D CNN	Accuracy AUC	0.9610 0.9936
2019	Xie et al.[78]	LIDC-IDRI	MV-KBC model can learn 3-D lung nodule characteristics by decomposing a 3D nodule into nine fixed views	Accuracy AUC	0.916 0.957
2018	Zhu et al.[50]	LIDC-IDRI	R-CNN-GBM	Accuracy	0.9274
2019	Nasrullah et al.[61]	LIDC-IDRI	CMixNet-GBM	Sensitivity	0.94
2023	Mikhael et al.[118]	NLST	3D Resnet	AUC	0.92
2023	Bushara et al.[119]	LIDC	LCD-CapsNet	Accuracy AUC	0.94 0.989
2023	Irshad et al.[120]	Exasens dataset	An IGWO-based DCNN model	Accuracy Sensitivity	98.27% 97.67%

Quanyang W, et al. Cancer Med. 2024. PMID: 38581113

FDA APPROVED AI-ENABLED MEDICAL DEVICES

692 U.S. Food and Drug Administration (FDA) approved AI-enabled medical devices

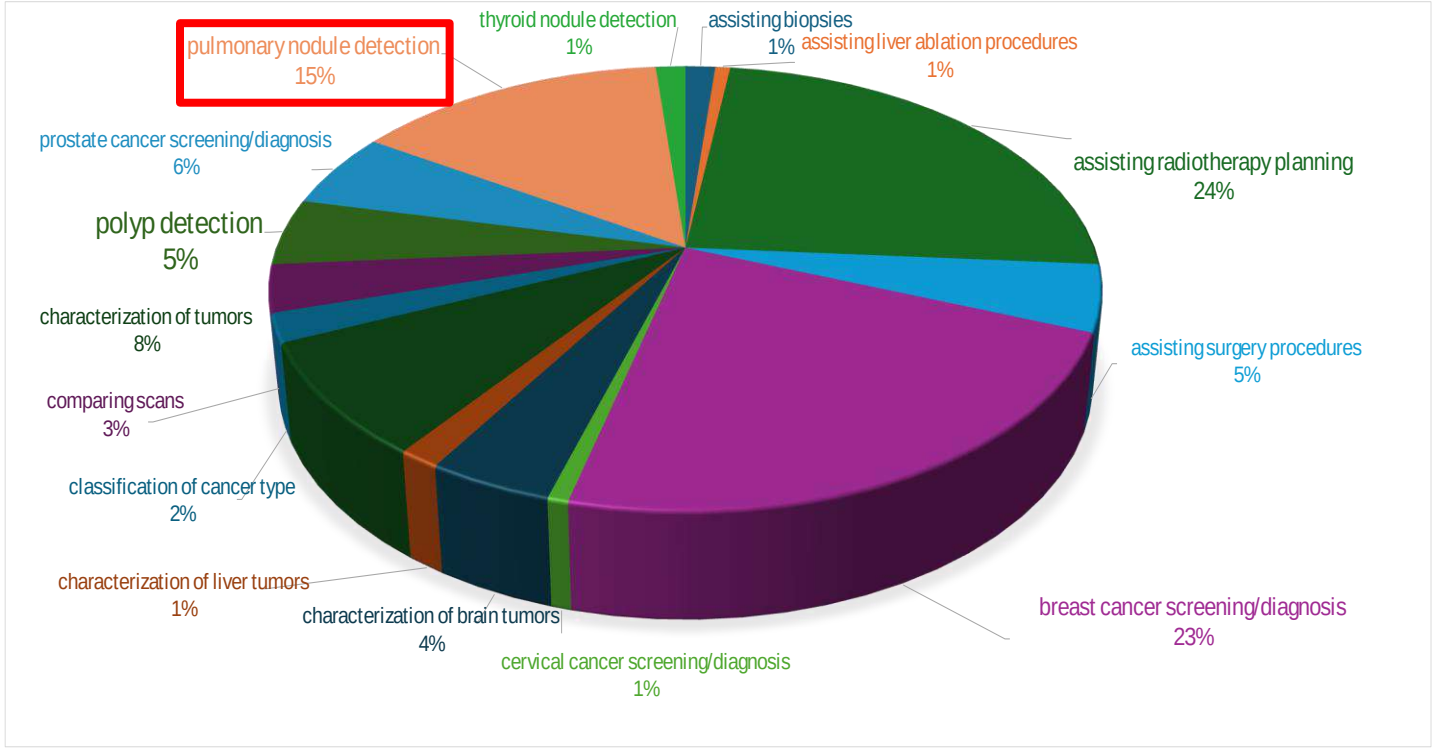
531 in the field of imaging

146 applicable in oncology

135 medical imaging

4 pathology-based

7 colonoscopy-based



https://radiology.healthairegister.com/

Joshi G et al, Electronics 2024. doi: 10.3390/electronics13030498

** Updated 19 October, 2023*

ESMO DEEP DIVE:
LUNG CANCER

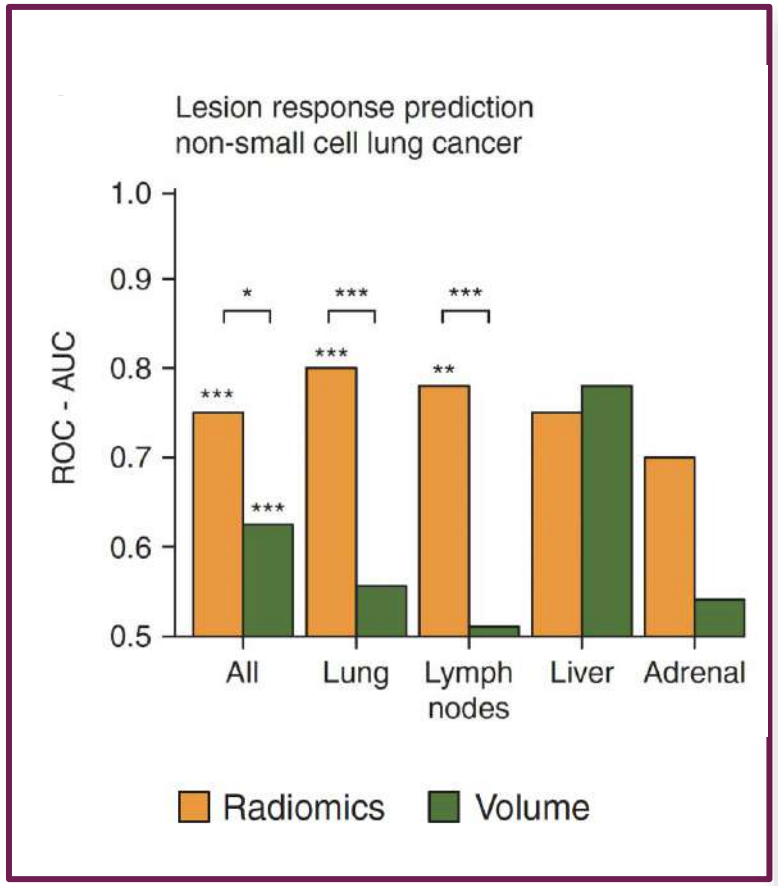
ENHANCED RESPONSE PREDICTIONS AND ON-TREATMENT EVALUATION

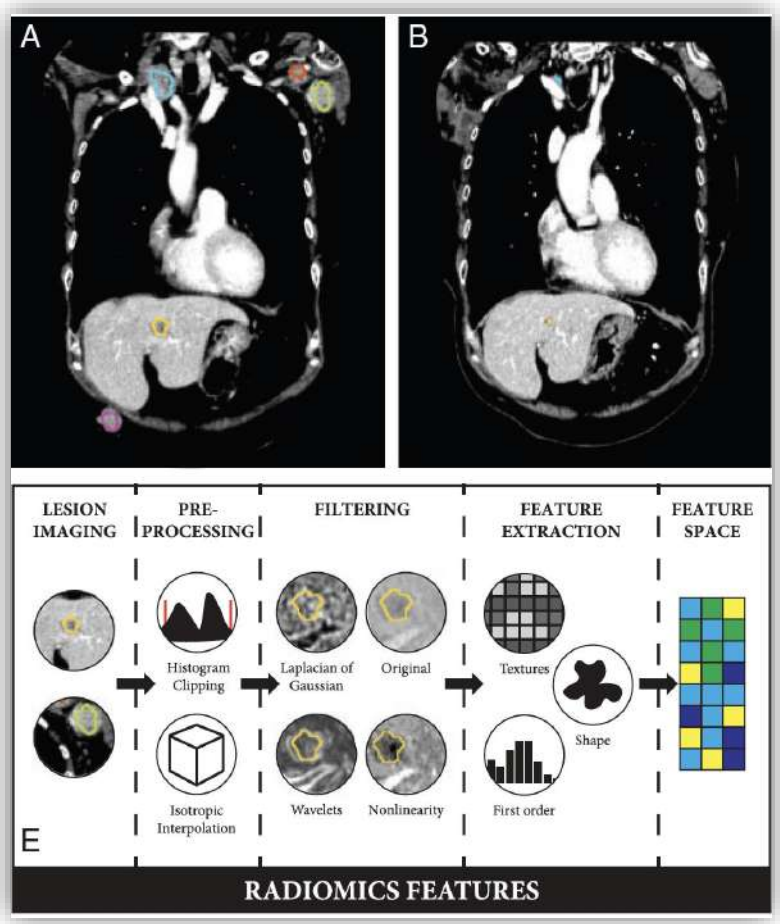
Computational analysis of standard imaging

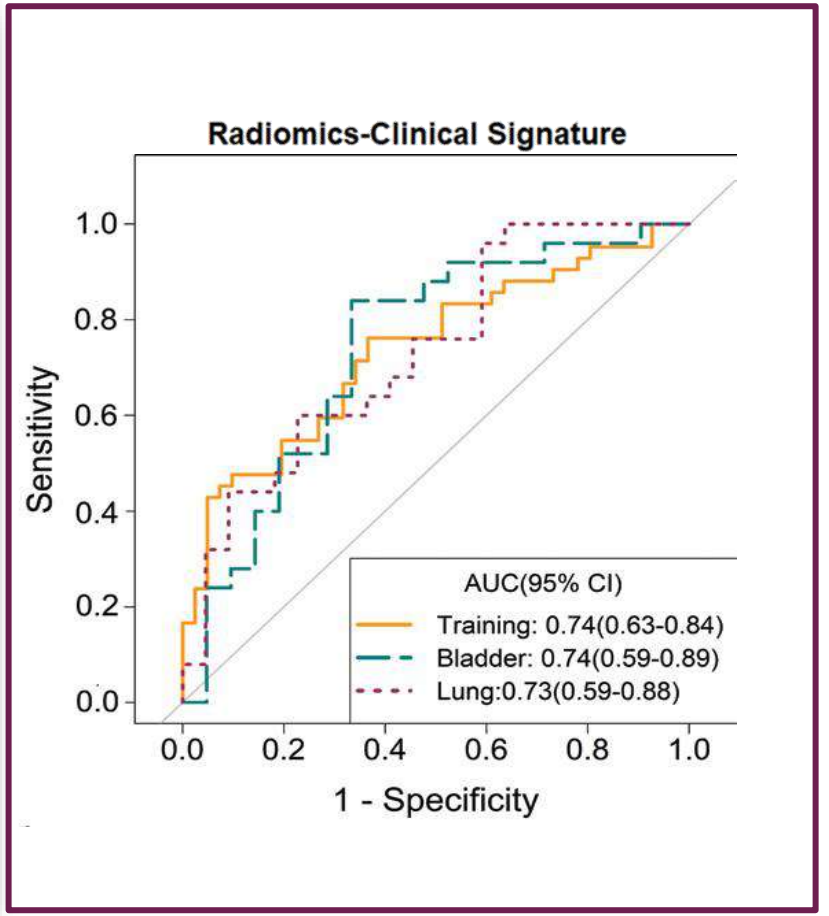
ESMO WEBINAR SERIES

IMMUNE-RADIOMICS SIGNATURES

End-to-end signature for response prediction





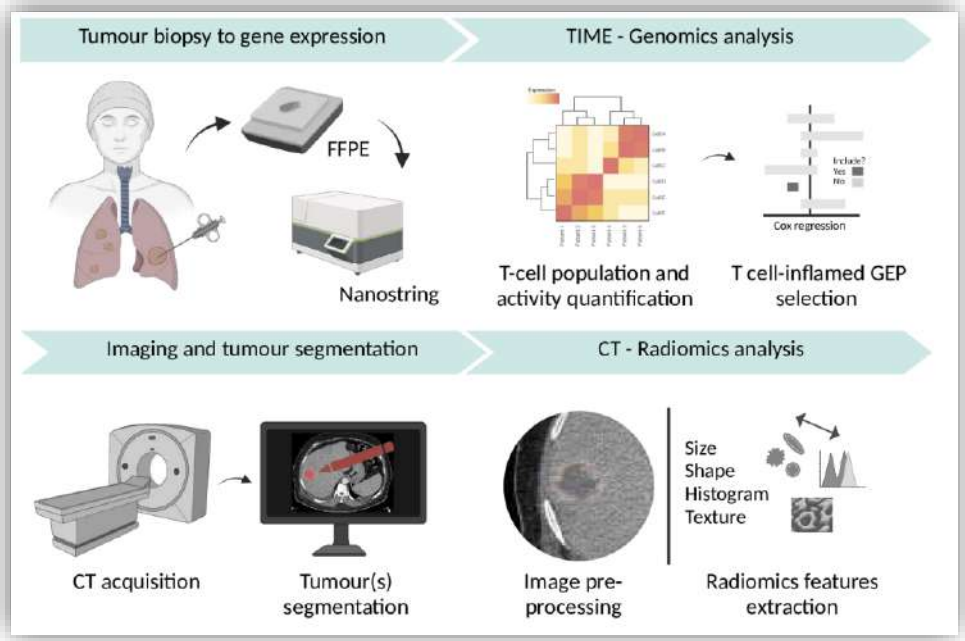


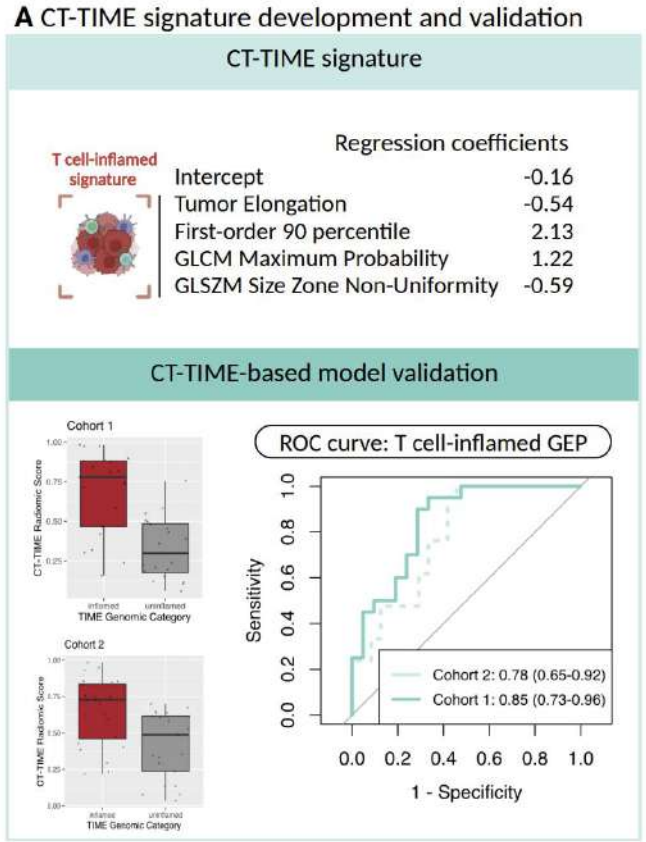
Trebeschi S, et al. Ann Oncol. 2019. PMID: 30895304

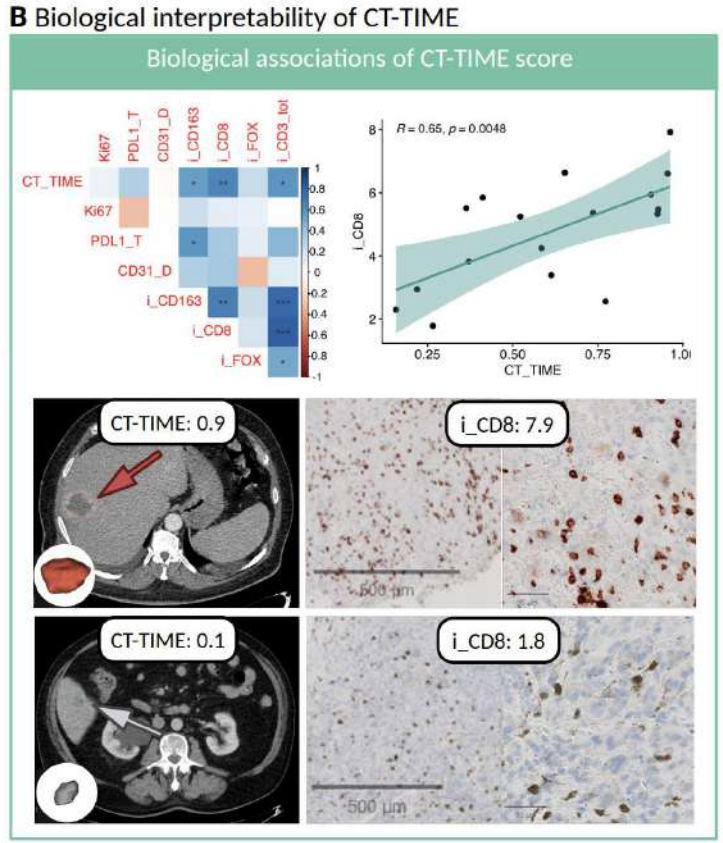
Ligero M, et al. Radiology. 2021.PMID: 33497314

IMMUNE-RADIOMICS SIGNATURES

Biomarker prediction



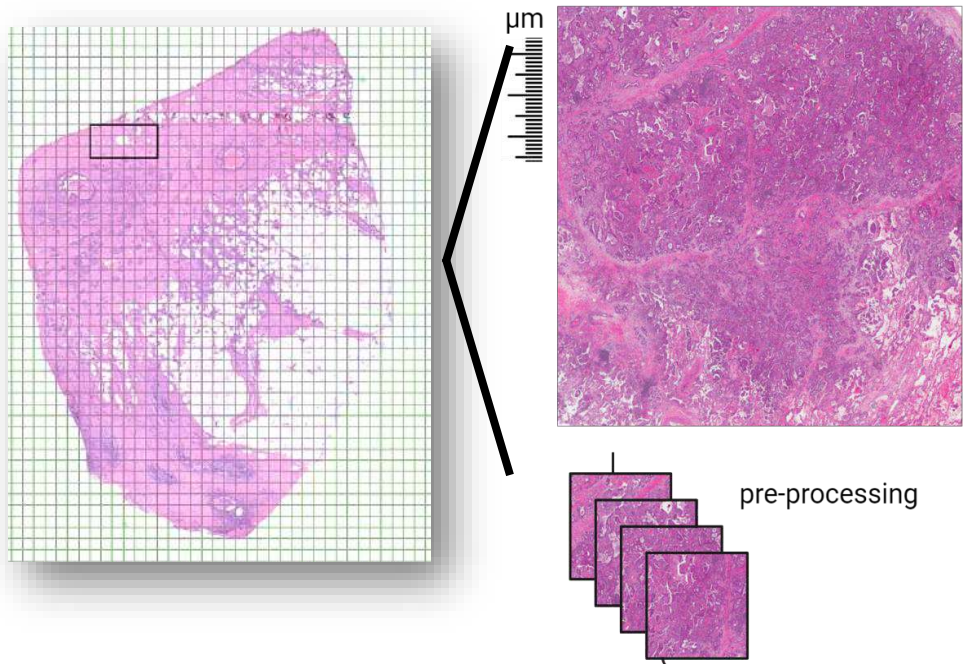


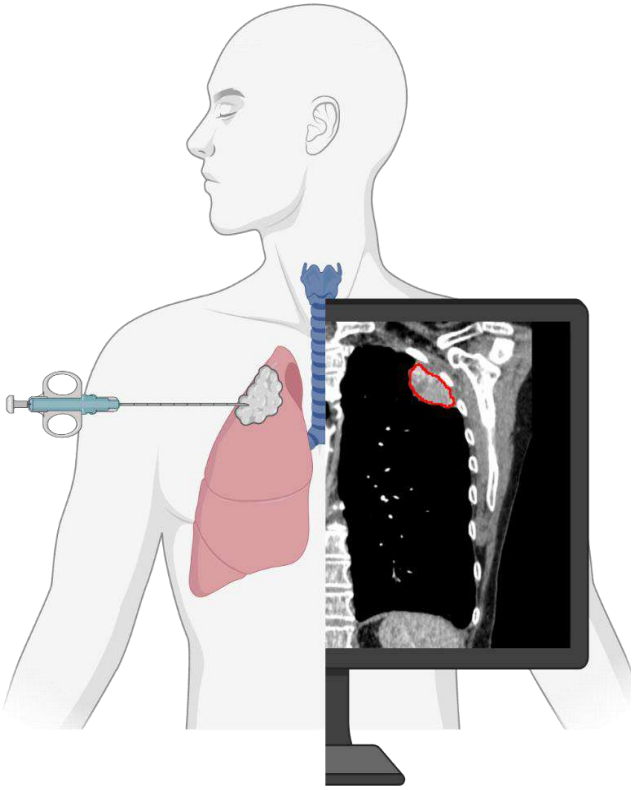


Bernatowicz K, et al. J Immunother Cancer. 2025. PMID: 39800381

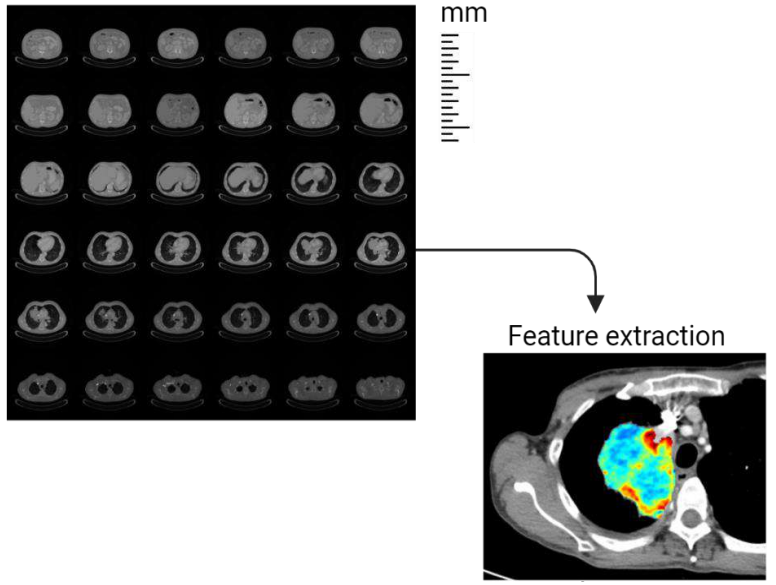
Pathology and radiology provide valuable information at different scales

Histopathology images





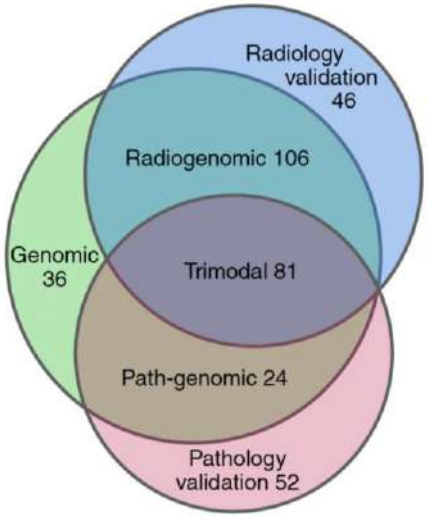
Radiology images

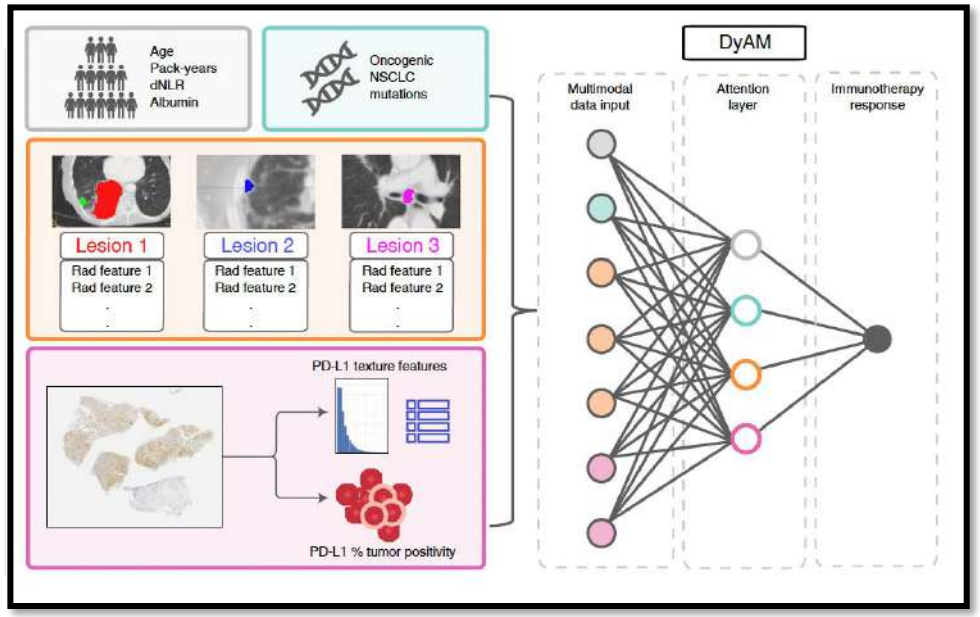


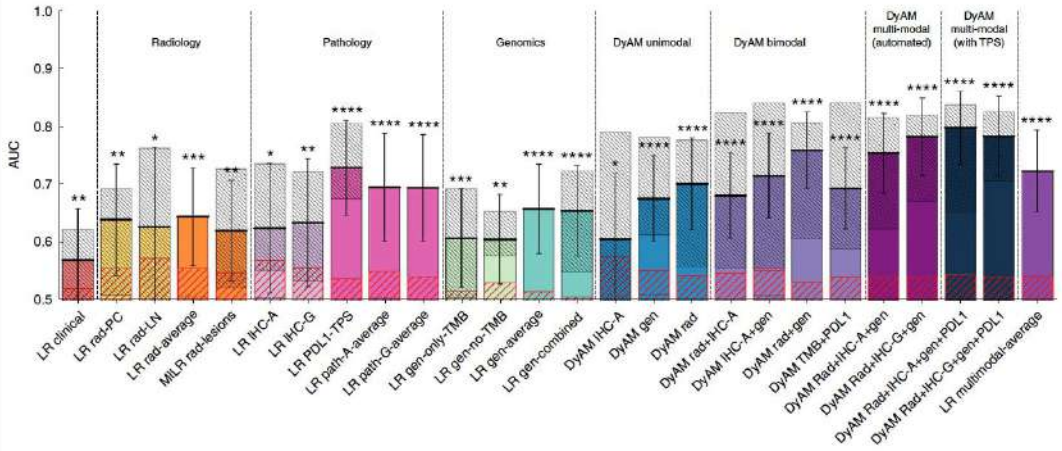
Perez-Lopez R, et al .Nat Rev Cancer. 2024. PMID: 38755439
Ghaffari Laleh N, et al. Clin Cancer Res. 2023. PMID: 36083132

Multimodal data integration improves AI-model performace

Response prediction to PD-L1 inhibitors in NSCLC







Vanguri RS, et al. Nat Cancer. 2022.PMID: 36038778

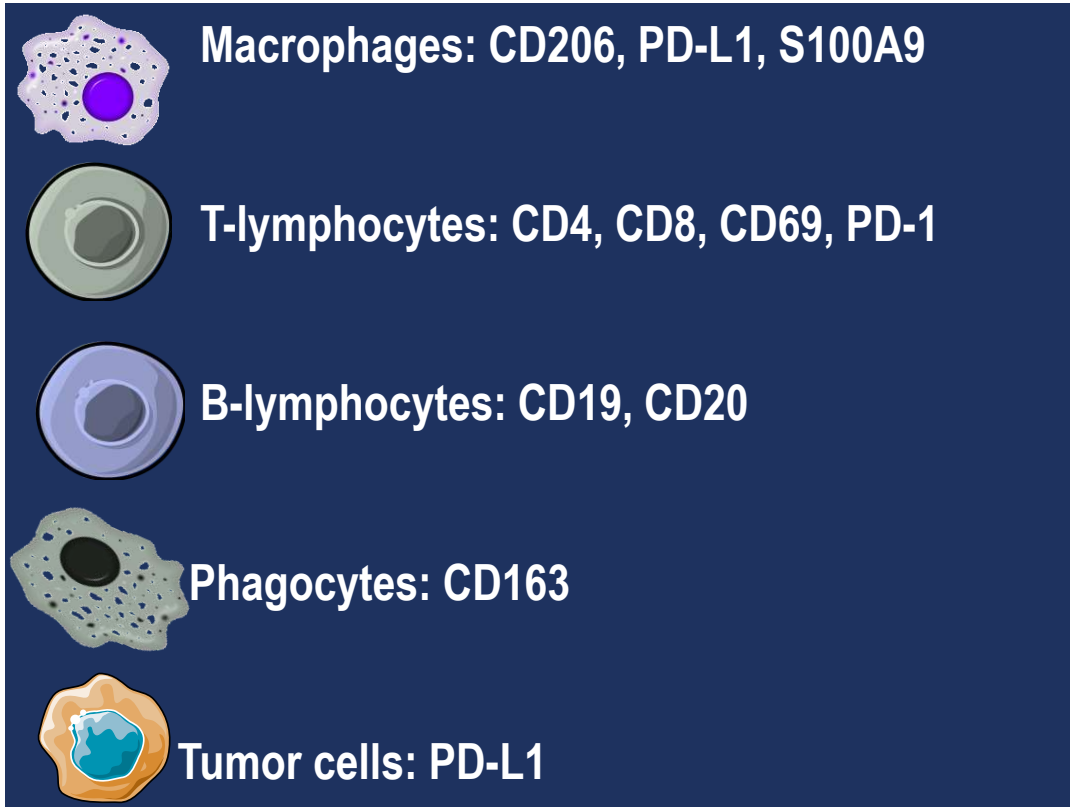
ESMO DEEP DIVE:
LUNG CANCER

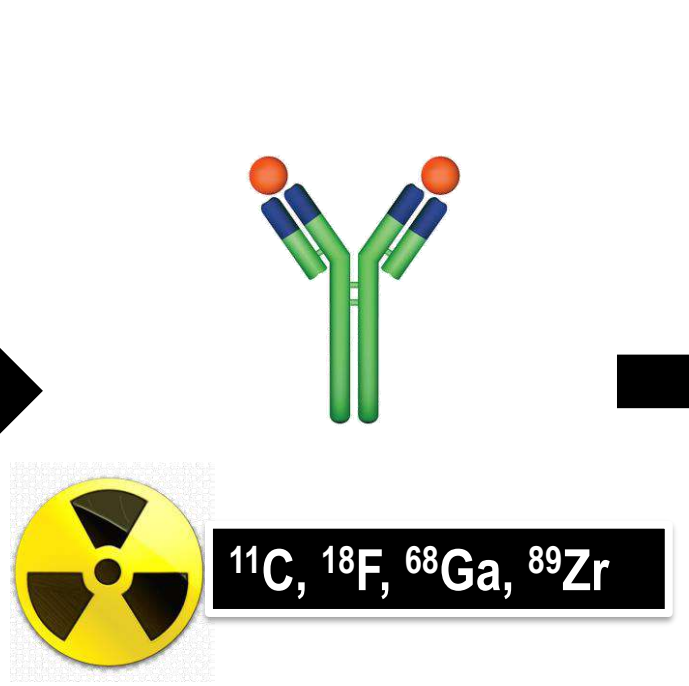
ENHANCED RESPONSE PREDICTIONS AND ON-TREATMENT EVALUATION

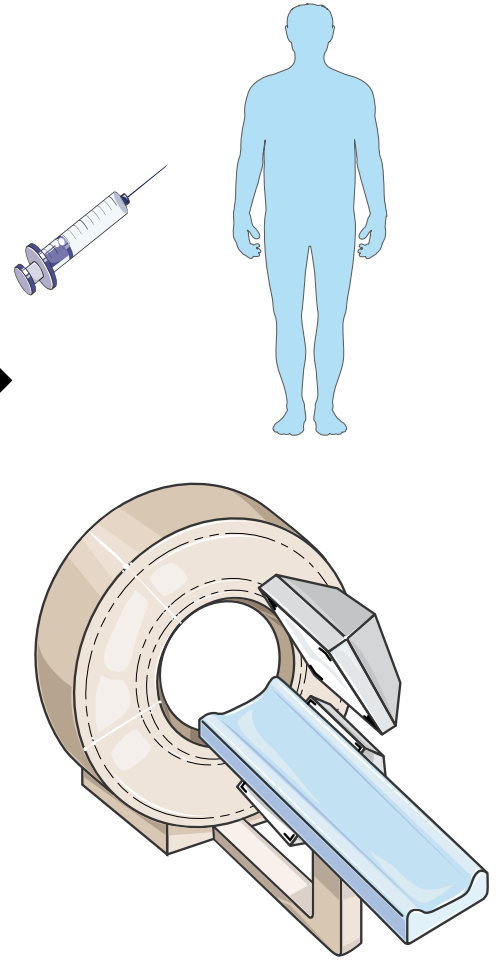
Advanced imaging techniques

ESMO WEBINAR SERIES

Imaging of immune cell dynamics with immunotracers

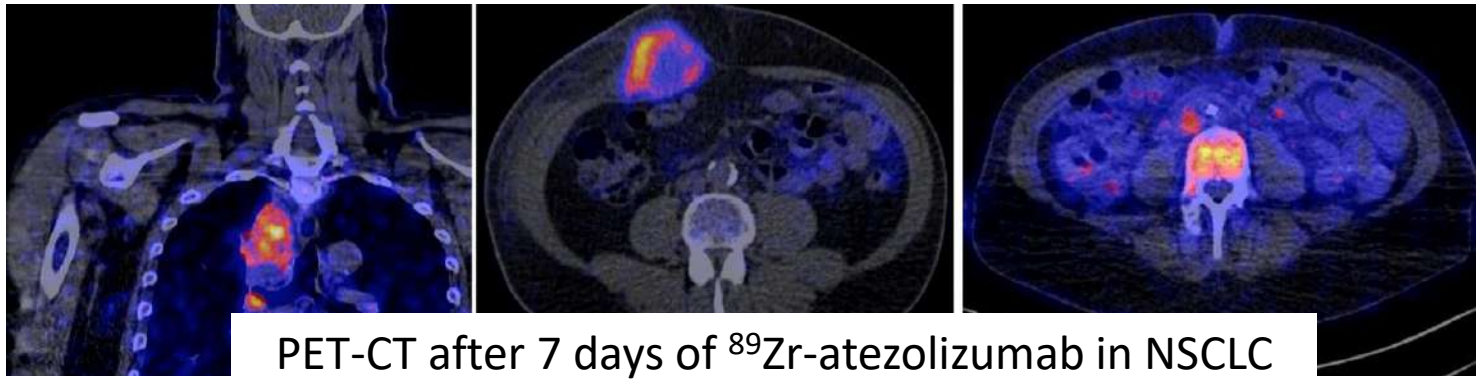




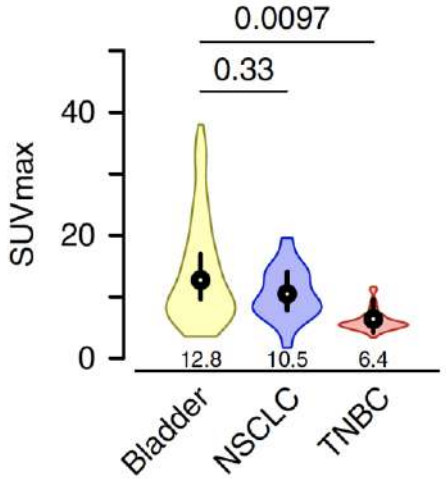


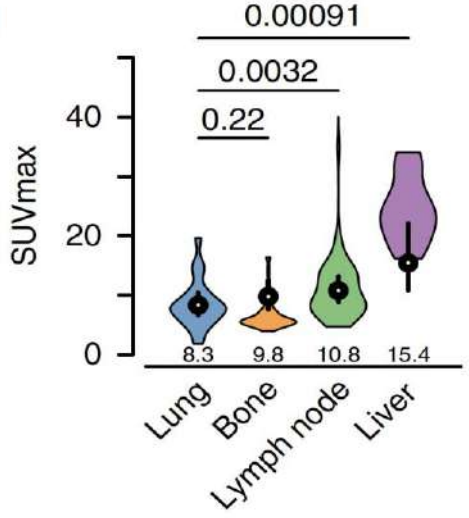
^{89}Zr-atezolizumab PET-CT for assessing response to PD-L1 inhibition

22 patients with
non-small cell lung cancer (NSCLC), bladder cancer or triple-negative breast cancer (TNBC)



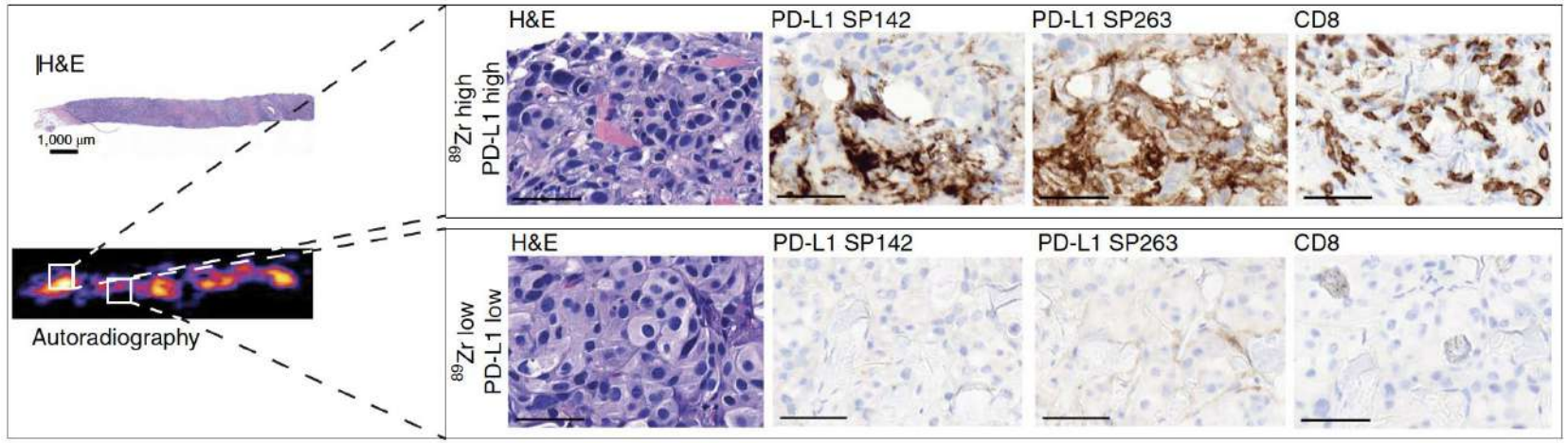
PET-CT after 7 days of ^{89}Zr-atezolizumab in NSCLC

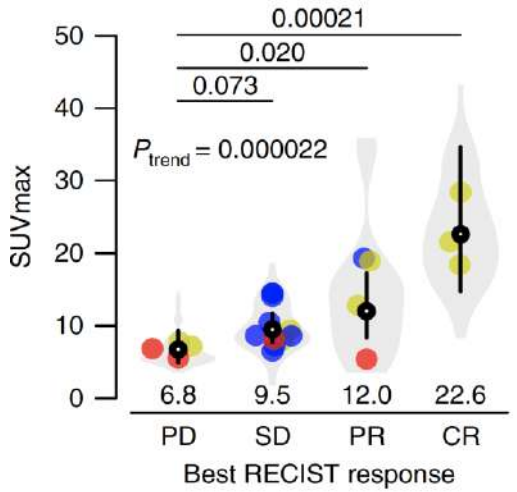


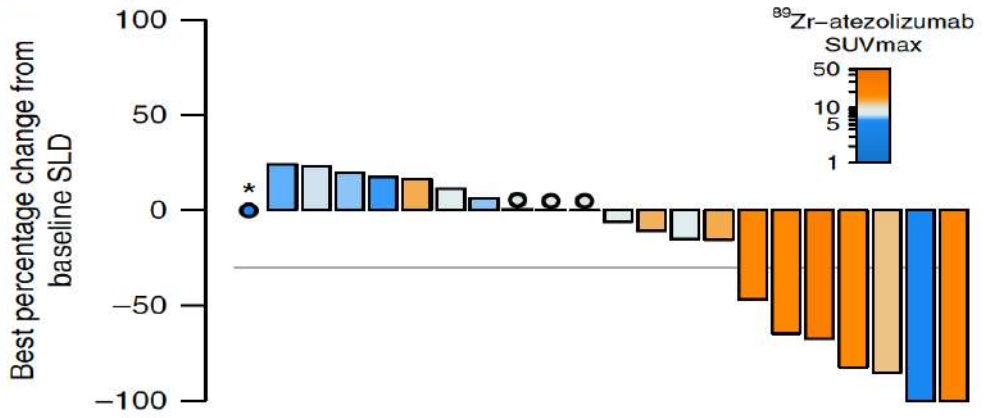


Bensch F, et al. Nat Med. 2018. PMID: 30478423

^{89}Zr-atezolizumab PET-CT for assessing response to PD-L1 inhibition





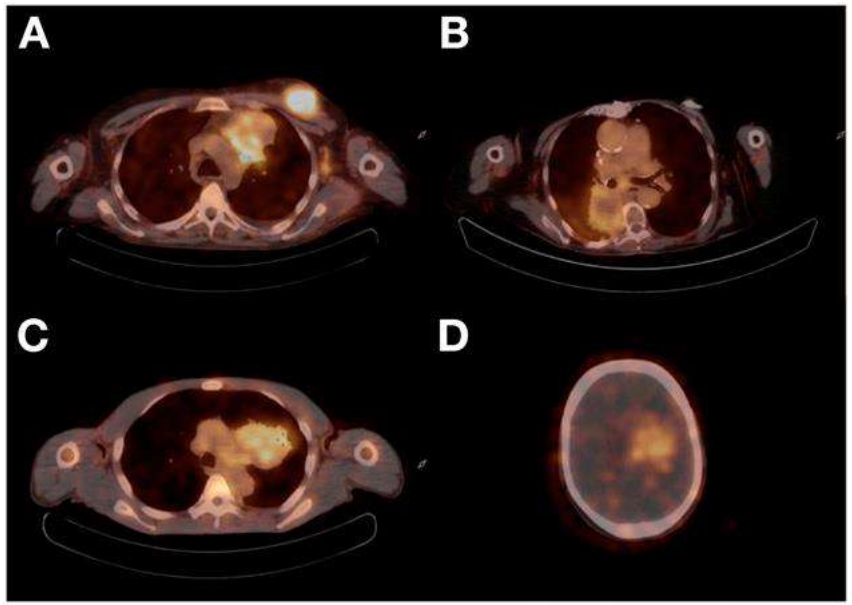


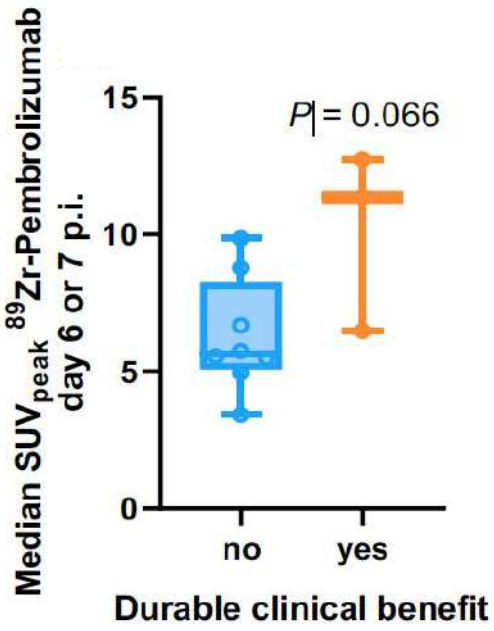
Bensch F, et al. Nat Med. 2018. PMID: 30478423

^{89}Zr-pembrolizumab PET-CT for assessing response to PD-1 inhibition

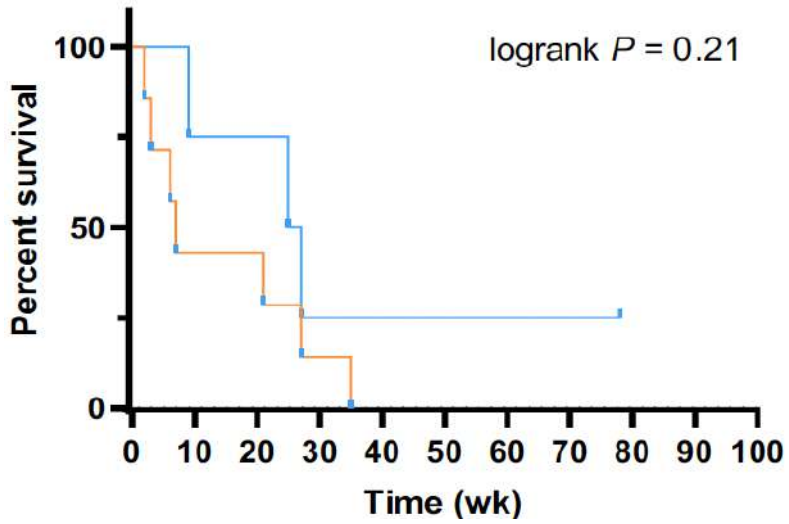
12 NSCLC patients eligible for pembrolizumab monotherapy as first- or later-line therapy

SUVpeak on day 6-7, when tumour uptake was the highest and blood-pool activity was the lowest (best tumour-to-background ratio)





PR or SD > 6 months



Niemeijer AN, et al. J Nucl Med. 2022. PMID: 34272316

Take home messages

- AI-driven tools **enhance lung nodule detection** and size measurements.
- AI models are advancing the ability to **distinguish between benign and malignant nodules.** These improvements are expected to further refine risk assessment in the near future, reducing unnecessary follow-ups and invasive biopsies.
- AI and advanced imaging techniques may help immunotherapy selection by providing non-invasive, real-time insights into the tumour microenvironment.

Radiomics Group
Vall d'Hebron Institute of Oncology

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AGAUR

Instituto de Salud Carlos III

European Commission

La Marató 3

Obra Social
Fundación "la Caixa"

rperez@vhio.net

https://vhio.net/pf/radiomics-group/

ESMO DEEP DIVE: LUNG CANCER

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

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