CLINICAL PATHWAYS CONGRESS

CANCER CARE BUSINESS EXCHANGE

September 5–6, 2025
Westin Copley Place
Boston, MA

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Advances in Non-Small Cell Lung Cancer: Optimizing Biomarker-Driven Targeted Therapeutics through Clinical Pathways

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Supported by an independent educational grant from Johnson & Johnson

Disclosures

- **Tejas Patil, MD:** Advisory board – Aadi Biosciences, Astrazeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Caris, Cellworks, Daiichi, Foundation Medicine, Guardant Health, Gilead, Johnson & Johnson, Jazz Pharmaceuticals, Merus, Natera, Nuvation, Pfizer, Regeneron, Rigel, Roche/Genentech, Summit Therapeutics, Takeda; DSMB – Boehringer Ingelheim, Elevation Oncology, Johnson & Johnson, Foundation Medicine; research/grant support – Janssen, Gilead

Learning Objectives

- Explain the role of driver mutations and biomarkers in the pathogenesis and treatment selection of NSCLC in clinical pathways
- Apply clinical guidelines, recent updates, and economic variables guiding NSCLC treatment protocols and their significance for NSCLC clinical pathways
- Implement strategies that align evidence-based best practices and personalized medicine into an interdisciplinary setting for NSCLC care to optimize patient outcomes and streamline treatment pathways

NSCLC = non-small cell lung cancer.

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Advanced NSCLC[a]

Oncogene driver

- **EGFR Exon 19 del / L858R**: Osimertinib monotherapy; osimertinib + platinum pemetrexed; amivantamab + lazertinib
- **EGFR (atypical)**: Afatinib, osimertinib
- **EGFR Exon 20 insertion**: Amivantamab + chemotherapy
- **ALK**: Alectinib, brigatinib, lorlatinib, ensartinib
- **ROS1**: Repotrectinib, taletrectinib, entrectinib, crizotinib
- **RET**: Selpercatinib, pralsetinib
- **BRAF V600E**: Dabrafenib + trametinib, encorafenib + binimetinib
- **MET Exon 14**: Capmatinib, tepotinib
- **NTRK**: Larotrectinib, entrectinib, repotrectinib
- **KRAS G12C†**: Sotorasib, adagrasib
  EGFR Exon 20: Sunvozeritinib
  HER2†: Trastuzumab deruxtecan (T-Dxd), zongertinib
  NRG1: Zenocutuzumab
- **MET IHC [3+]**:Telizotuzumab vedotin
  HER2 IHC [3+]: Trastuzumab deruxtecan (T-Dxd)

No driver mutation

Non-squamous

PDL1 ≥ 50% (including below)
- Pembrolizumab
- Atezolizumab
- Cemiplimab

PDL1 ≥ 1%
- Pembrolizumab + platinum + pemetrexed
- Atezolizumab + carboplatin + abraxane
- Atezolizumab + carboplatin + paclitaxel + bevacizumab
- Nivolumab + ipilimumab
- Nivolumab + ipilimumab + platinum + paclitaxel
- Durvalumab + tremelimumab + platinum chemotherapy

PDL1 < 1% (including all the chemo-ICI options above)
- Ipilimumab + nivolumab + carboplatin + paclitaxel

Squamous

PDL1 ≥ 50% (including below)
- Pembrolizumab
- Atezolizumab
- Cemiplimab

PDL1 ≥ 1%
- Pembrolizumab + carboplatin + paclitaxel
- Pembrolizumab + carboplatin + abraxane
- Nivolumab + ipilimumab
- Nivolumab + ipilimumab + platinum + paclitaxel
- Durvalumab + tremelimumab + platinum chemotherapy

PDL1 < 1% (including all the chemo-ICI options above)
- Ipilimumab + nivolumab + carboplatin + paclitaxel

[a]Locally advanced (not amenable to chemoXRT) or metastatic; †Second line setting only, evolving space regarding HER2 Exon 20 insertions vs HER2 3+ IHC.
EGFR = epidermal growth factor receptor; IHC = immunohistochemistry; PDL1= programmed death ligand 1.

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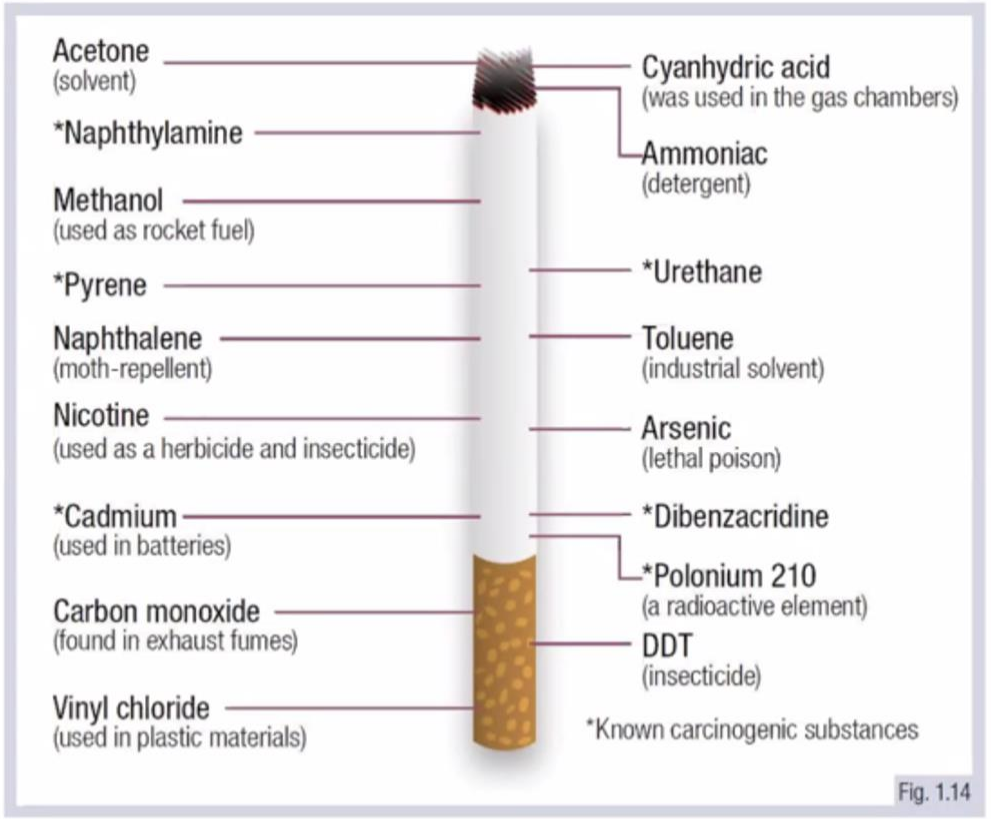
Part 1: NSCLC Overview

Major Risk Factors for Lung Cancer

- Environmental risk factors
  - Tobacco smoking**
    - 50 carcinogens in tobacco smoke
  - Environmental tobacco smoke
  - Biomass burning – wood and coal
  - Air pollution
  - Uranium, radium and radon
  - Occupational exposures: Asbestos, arsenic, beryllium, cadmium, chromium, nickel, radon, silica, diesel



https://oncologypro.esmo.org/education-library/essentials-for-clinicians/thoracic-tumours/risk-factors

Barta JA, et al. *Ann Glob Health*. 2019;85(1):8. Slide courtesy Nina Thomas.

Major Risk Factors for Lung Cancer

- Biologic risk factors
  - Genetics (*de novo T790M*)
  - Solid organ transplantation
  - Alpha 1 antitrypsin deficiency
  - Interstitial lung disease (ILD)
  - HIV or tuberculosis
  - Field cancerization effect
    - Prior HNSCC or lung cancer

HNSCC = head and neck squamous cell carcinoma.

Barta JA, et al. *Ann Glob Health*. 2019;85(1):8.

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Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
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Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
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Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

American Cancer Society. Accessed August 28. 2025. https://www.cancer.org/research/acs-research-news/facts-and-figures-2024.html.

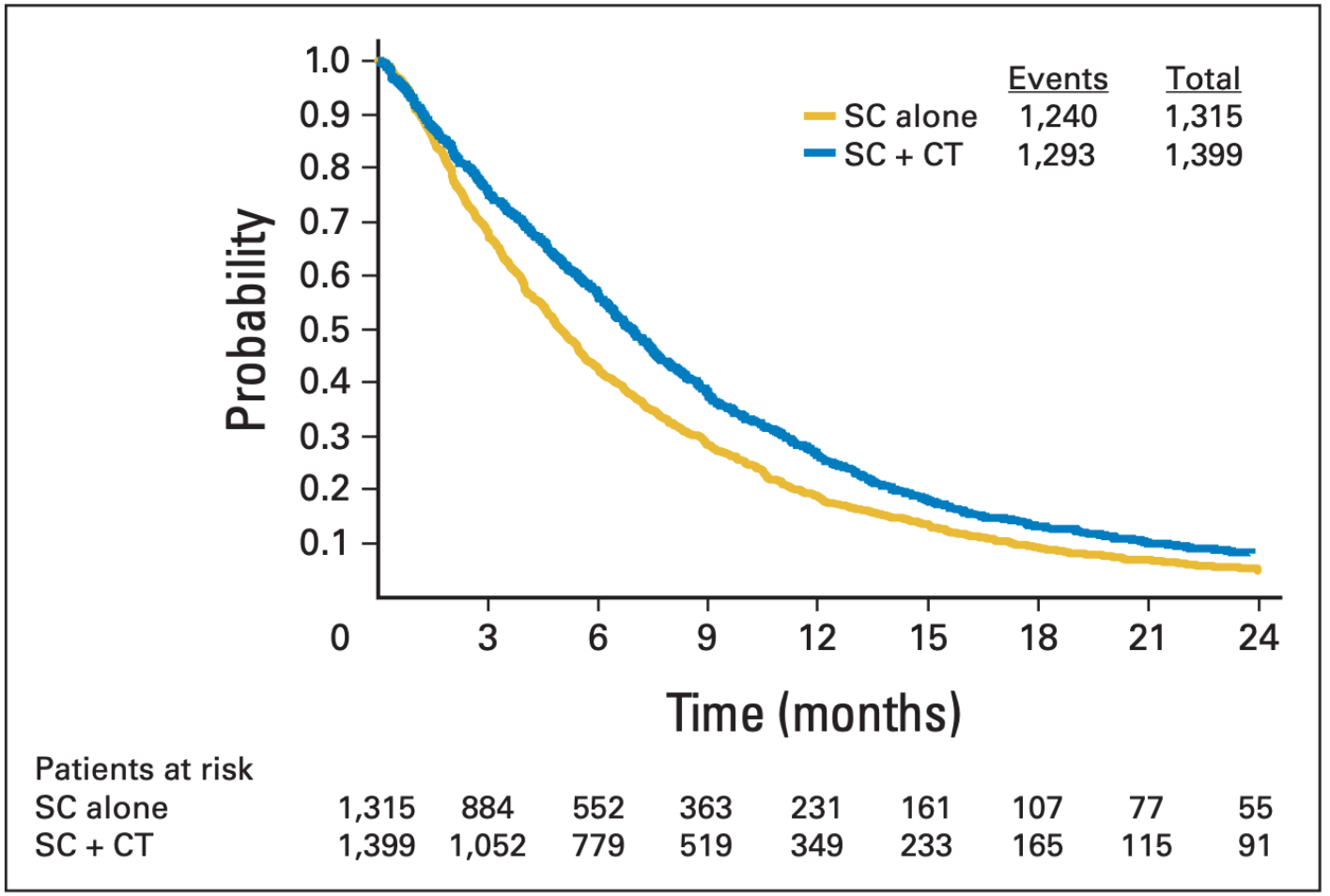
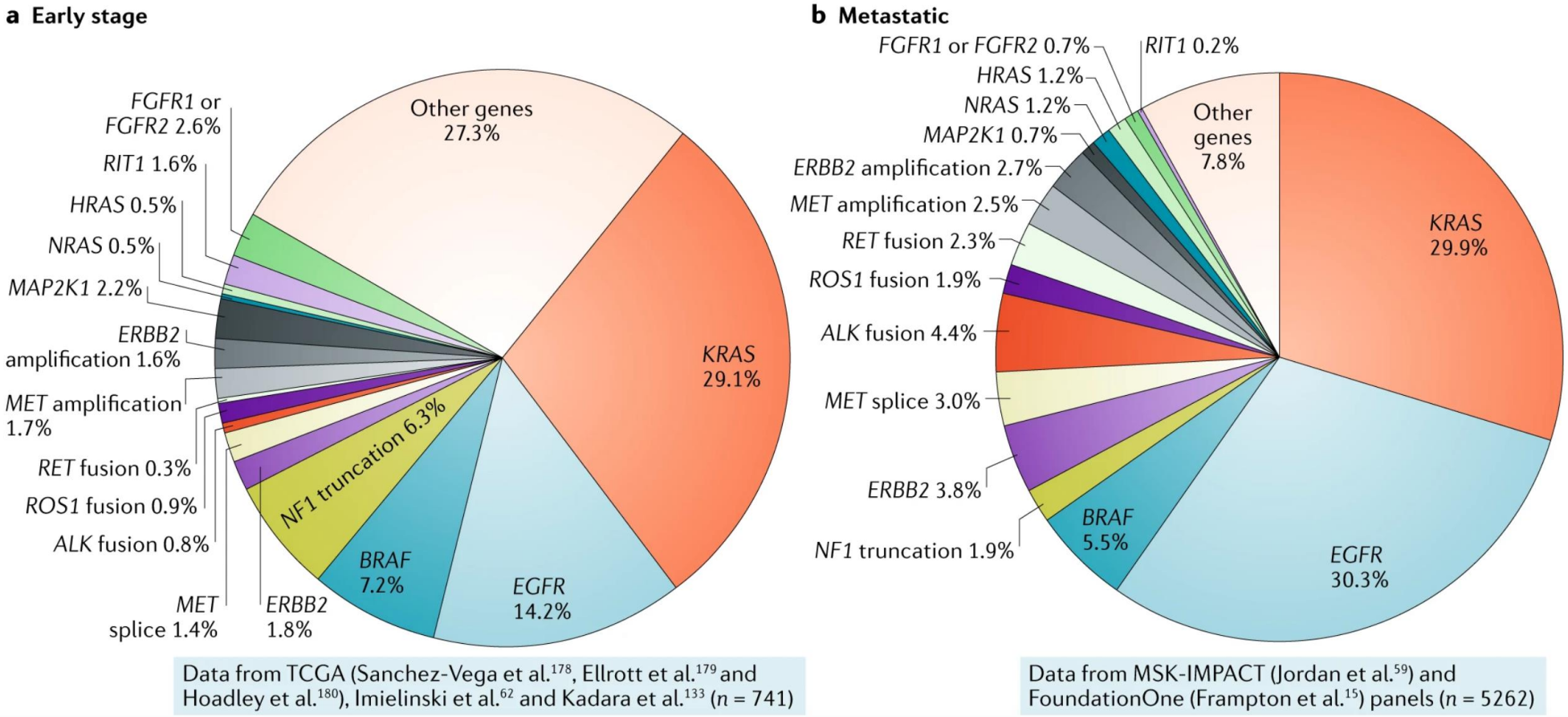


Fig 2. Simple (nonstratified) Kaplan-Meier curve for survival by treatment. SC, supportive care; CT, chemotherapy.

NSCLC Meta-Analyses Collaborative Group. *J Clin Oncol*. 2008;26(28):4617-4625.



*~45% mutations[a] (in early and metastatic setting) targetable with **currently available (as of 2023)** small molecular tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (mABs)*

[a]KRAS G12C at 24%; BRAF V600E at 2%.

Sebastian M, et al. *Lung Cancer*. 2021;154:51-61. Paik PK, et al. *J Clin Oncol*. 2011;29(15):2046-2051. Skoulidis F, et al. *Nat Rev Cancer*. 2019;19(9):495-509.

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Types of Mutations

		Examples
THE CAT ATE THE RAT THE KAT ATE THE RAT	**Silent** *Meaning of sentence is the same*	
THE CAT ATE THE RAT THE HAT ATE THE RAT	**Substitution** *Single amino acid change*	**KRAS G12C**
THE CAT ATE THE RAT THE CCA TET HER AT	**Deletion** *Frameshift - Single amino acid del*	**EGFR Exon 19 del**
THE CAT ATE THE RAT THE ECA TAT ETH ERA T	**Insertion** *Frameshift - Single amino acid ins*	**EGFR Exon 20 ins**
THE CAT ATE THE RAT THE RAT ATE THE CAT	**Translocation** *Chromosomal gene swap*	***EML4-ALK***
THE CAT ATE THE RAT THE CAT CAT CAT CAT CAT ATE THE RAT	**Gene amplification** *Repetitive gene sequences in chromosome*	***ERBB2 amplification***
THE CAT ATE THE RAT THE CAT ATE THE RAT THE CAT ATE THE RAT	**Polysomy** *Unstable chromosome with polypoidy – multiple gene copies*	***Trisomy 8 (AML / MDS)***

Initial Forays into EGFR Therapy

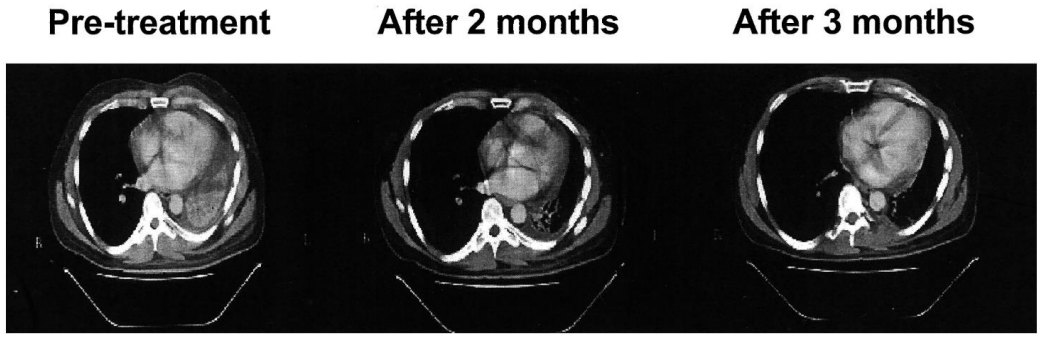
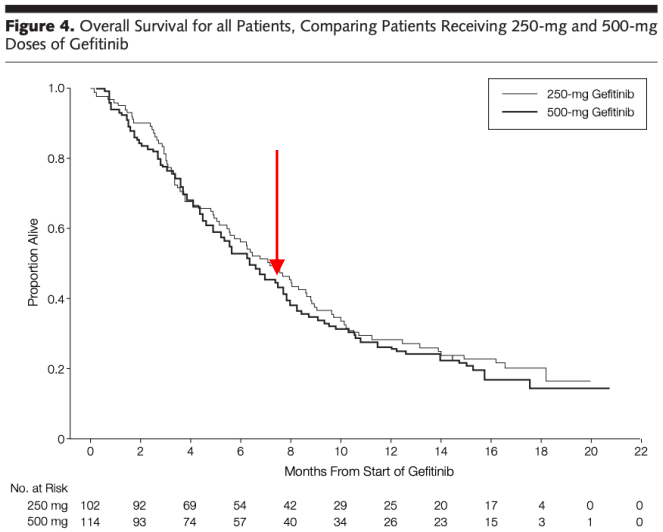
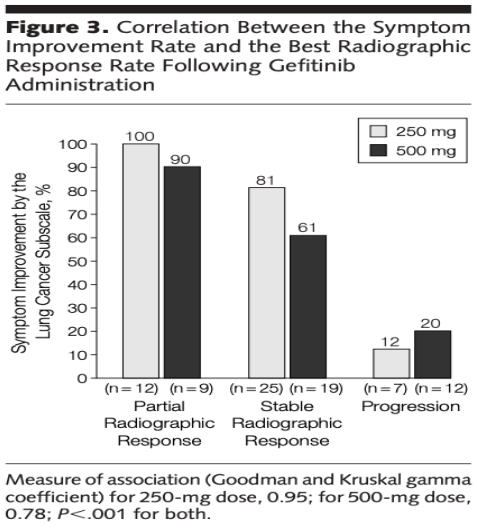
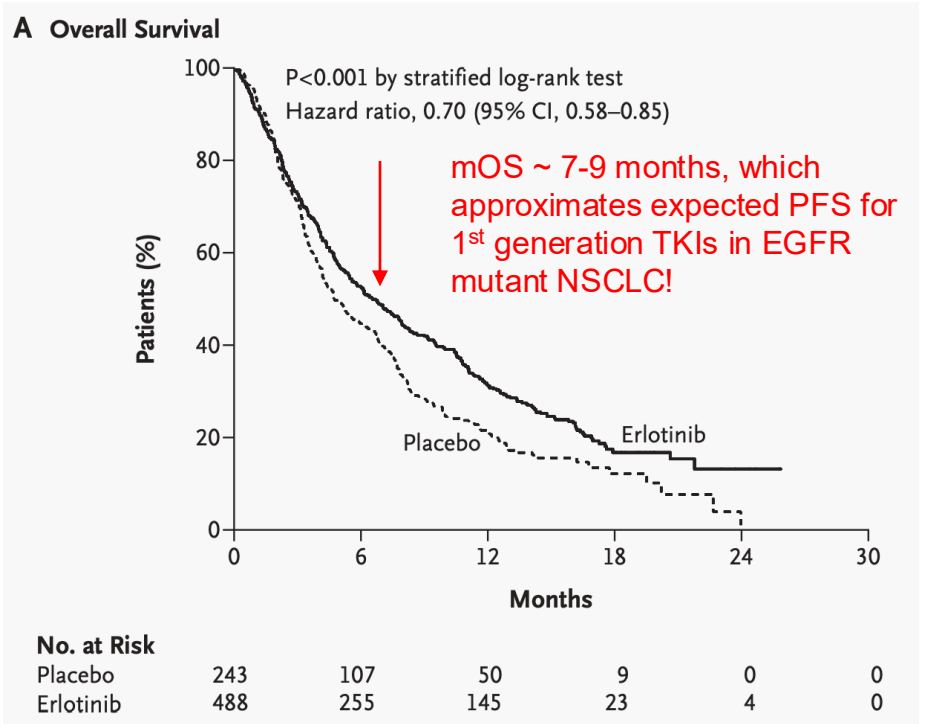


Fig 4. Computed tomography scan of a non–small-cell lung cancer patient before and after treatment with ZD1839 (525 mg/d for 14 d/month).







	Erlotinib (N = 488)	Placebo (N = 243)
Median survival	6.7 mo	4.7 mo
1 year survival	31.2%	21.5%
Objective response rate	8.9%	<1%

PFS = progression-free survival; mOS = mean overall survival.

Ranson M, et al. *J Clin Oncol*. 2002;20(9):2240-2250. Kris MG, et al. *JAMA*. 2003;290(16):2149-58. Shepherd FA, et al. *N Engl J Med*. 2005;353(2):123-132.

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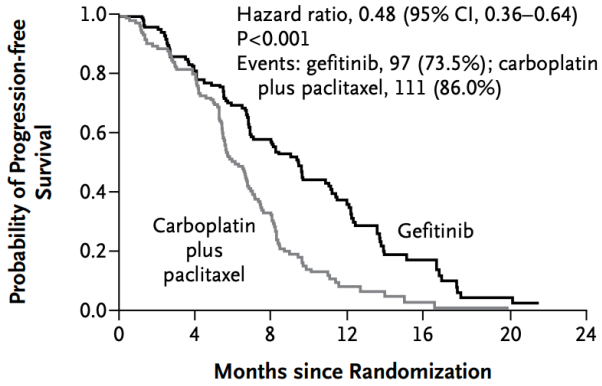
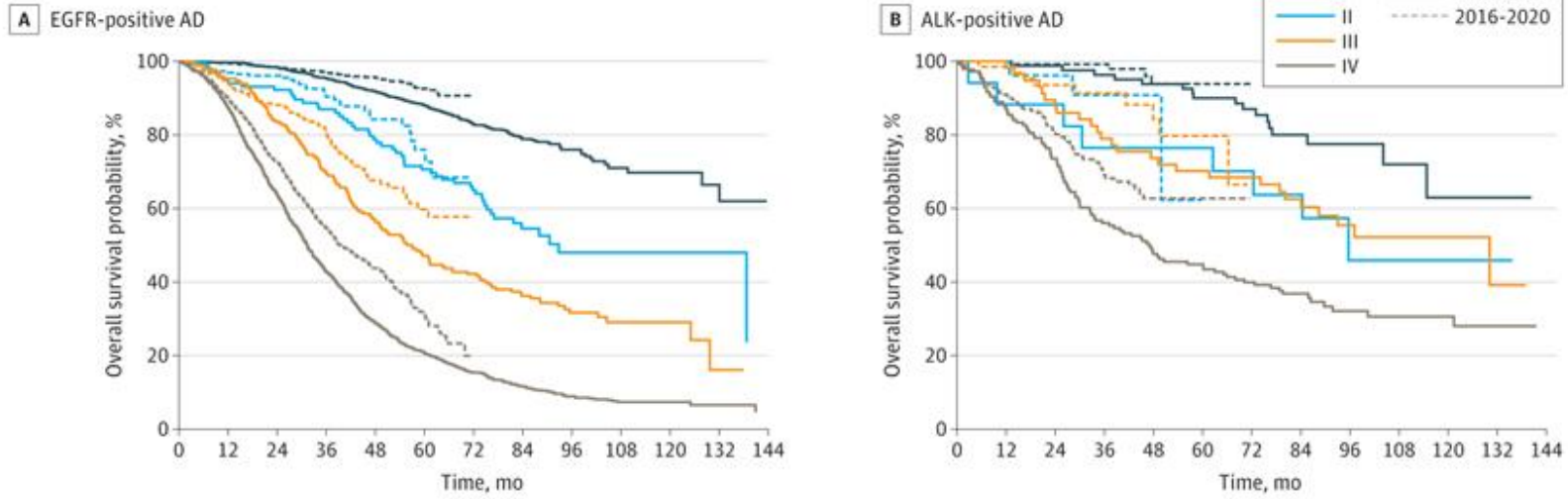
Why Targeted Therapy?

B ***EGFR*-Mutation–Positive**



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0



No. at risk													
Stage I													
2010-2015	1034	1016	985	946	898	811	635	384	169	60	34	15	1
2016-2020	2491	2380	1776	1204	731	280	0	0	0	0	0	0	0
Stage II													
2010-2015	118	110	105	98	87	77	67	37	17	8	5	3	0
2016-2020	262	248	193	119	65	24	0	0	0	0	0	0	0
Stage III													
2010-2015	216	203	178	148	120	97	83	62	35	19	7	2	0
2016-2020	304	278	216	141	77	32	0	0	0	0	0	0	0
Stage IV													
2010-2015	1027	896	652	435	291	206	146	90	47	29	18	5	0
2016-2020	1300	1116	682	385	186	54	0	0	0	0	0	0	0

84	83	79	77	75	70	57	36	22	12	5	1	0
134	129	99	79	46	23	0	0	0	0	0	0	0
17	15	15	13	13	13	11	10	4	1	1	1	0
27	26	18	13	8	0	0	0	0	0	0	0	0
57	57	51	45	42	40	38	28	19	9	7	3	0
69	64	49	37	22	9	0	0	0	0	0	0	0
146	125	105	80	69	64	57	38	23	17	13	7	0
223	196	132	79	43	17	0	0	0	0	0	0	0

A, Survival curves for patients with epidermal growth factor receptor (EGFR) variation are presented. B, Survival curves for patients with anaplastic lymphoma kinase (ALK) variation are presented.

Mok TS, et al. *N Engl J Med*. 2009;361(10):947-57. Chi SA, et al. *JAMA Netw Open*. 2023;6(3):e232002.

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234,580 cases of lung cancer

197,047 (84%) cases of NSCLC

68,966 cases of EGFR mutant NSCLC

66,440 cases of pancreas cancer

Estimated New Cases

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Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
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Key Learning Points

- Comprehensive biomarker testing is critical in NSCLC as it helps inform treatment selection
- Targeted therapy options are available for patients with a variety of actionable genomic alterations in NSCLC
- The use of targeted therapies (in the appropriate patient) improves overall survival

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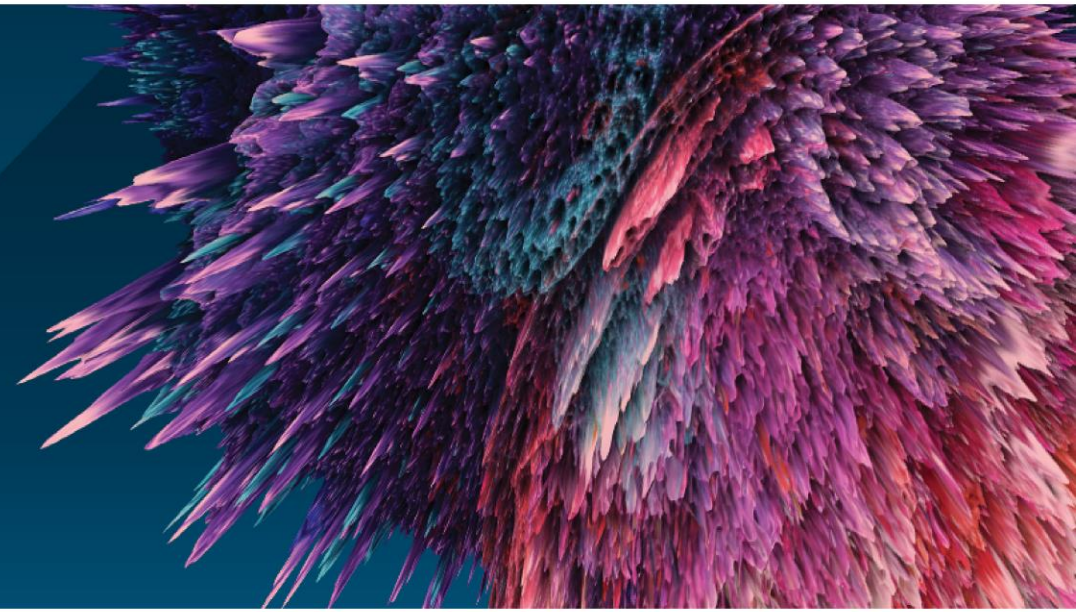
Part 2: Biomarker Testing



Molecular Testing: A Balancing Act

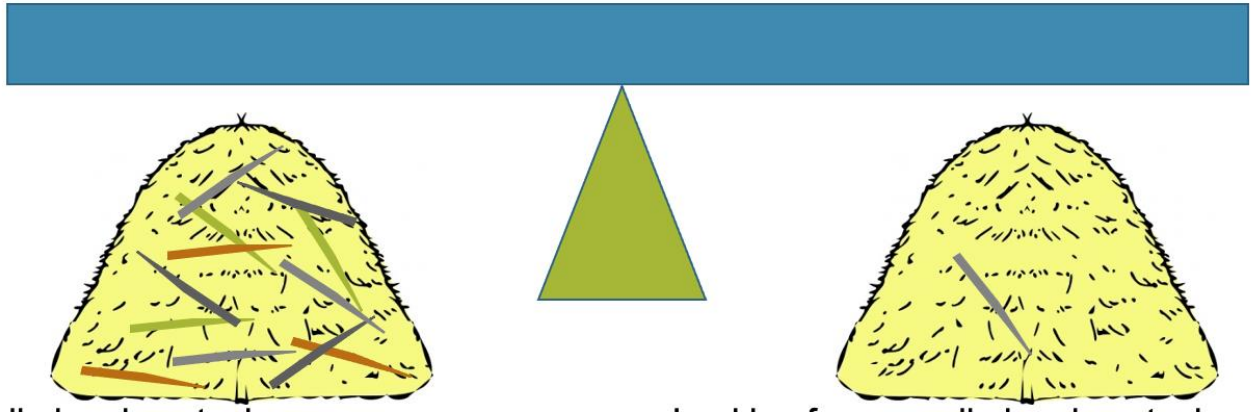
- ***Clinical sensitivity*: How many possible mutations can a test detect?**
  - False negatives are related to mutations which fall outside of test design
  - Example: EGFR test that only looks for L858R and Exon 19 del mutations will not detect G719X or Exon 20 insertions
- ***Analytic sensitivity*: How well can a test detect a rare change among normal?**
  - False negatives are related to few tumor cells relative to non-tumor
  - Example: Pleural cell block with lots of reactive mesothelial cells, few tumor cells

Slide courtesy Dara Aisner, MD PhD.

In Clinician Speak…

Clinical Sensitivity:
How many of the possible changes does the test detect?

Analytic Sensitivity:
How sensitively can the test detect a rare change in a background of normal? [LOD]



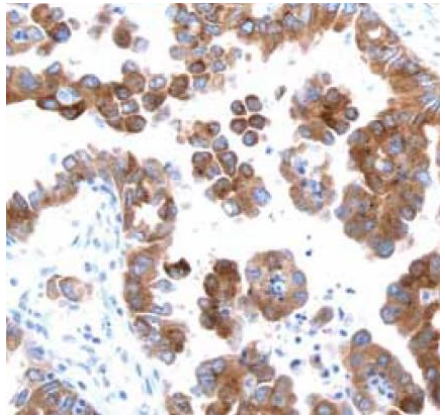
The test can identify needles of many different colors, but needles to exist at a relatively high level

The test can identify only a couple of colors of needles, but can pick them out even when they are very rare

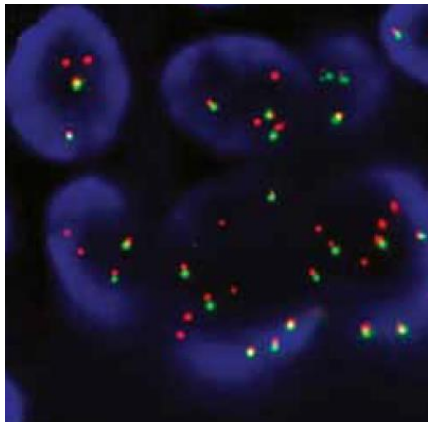
Slide courtesy Dara Aisner, MD PhD.

Testing Methodologies

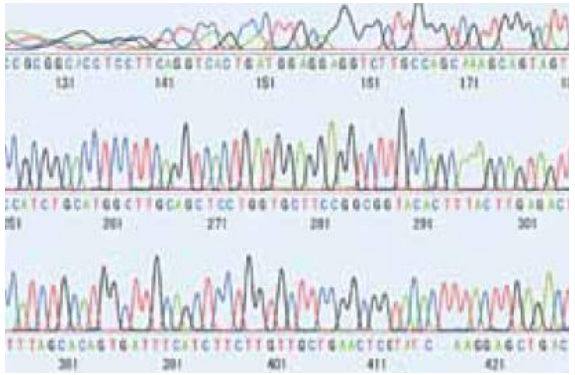
Immunohistochemistry



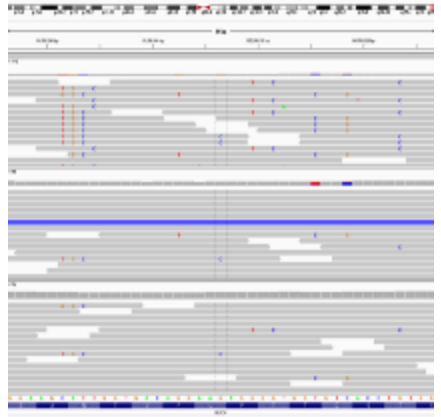
FISH



RT-PCR



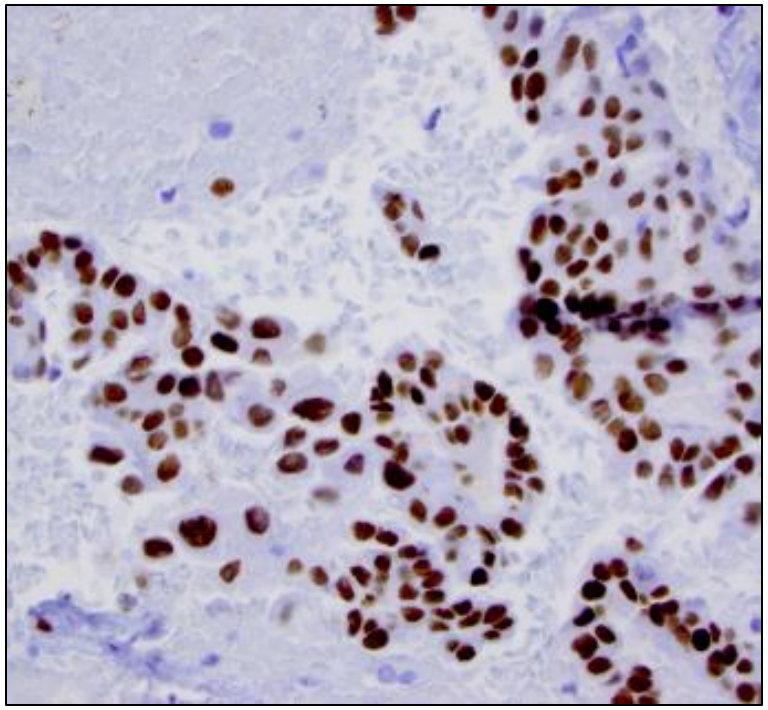
Next Generation Seq



FISH = fluorescence *in situ* hybridization; RT-PCR = reverse transcription-polymerase chain reaction.

Immunohistochemistry

- **Selectively identifies antigens (proteins) in cells of a tissue section by use of specific antibodies**
  - **Step 1:** Tissues are first fixed in formalin,* which chemically cross links the proteins in the tissue, locking all cellular processes, proteins and macromolecules conformationally in their exact location at the time
  - **Step 2:** Epitope retrieval + blocking off-target binding to reduce background noise
  - **Step 3:** Primary antibody (most important step)
  - **Step 4:** Visualization of antibody
    - *Chromogenic IHC*: Antibody is conjugated to an enzyme that can catalyze a color producing reaction
    - *Immunofluorescence*: an antibody is tagged to a fluorophore
  - **Step 5:** Counterstain

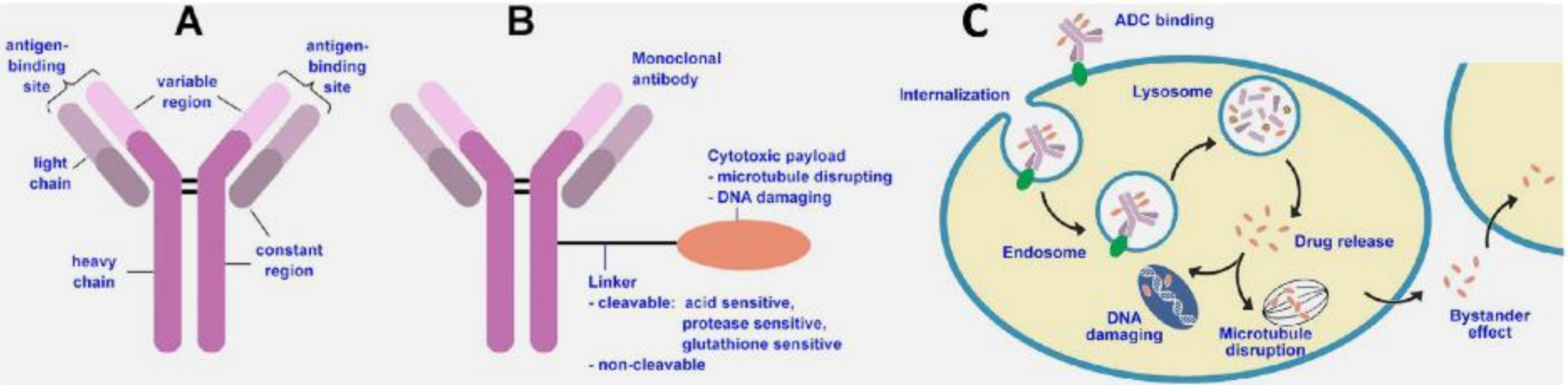


If NSCLC is suspected, standard stains may include: TTF1, Napsin A, p40, p63, CK7, CK20

Magaki S, et al. *Methods Mol Biol*. 2019;1897:289-298.

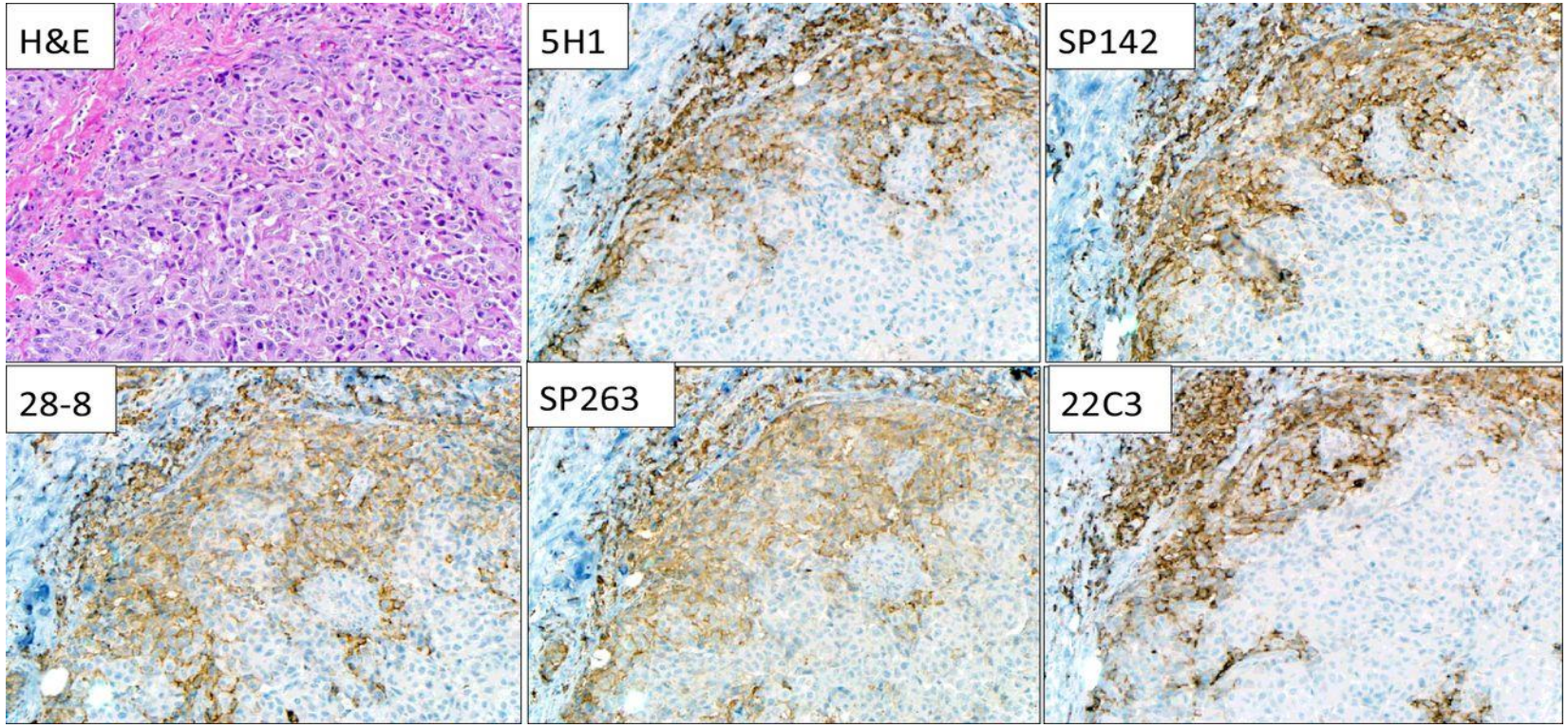
IHC: Practical Applications

- Used to confirm ALK positivity (D5F3 antibody)
- Used to determine PD-L1 tumor proportion score (more on this later)
- (Sometimes) used to determine suitability of antibody drug conjugate



Pacheco JM, Camidge DR. *Lung Cancer.* 2018;124:260-269.

PD-L1 in Lung Cancer



Remember that PD-L1 is a *qualitative* score (both TPS and CPS)
Remember that PD-L1 is a *continuous* variable (not binary) variable

TPS = tumor proportion score; CPS = combined positive score.

Assay Heterogeneity

Table 1. Approved and Investigational PD-L1 Diagnostic Assays in NSCLC

	Nivolumab		Pembrolizumab		Atezolizumab	Durvalumab	Avelumab
Antibody clone	28-8	SP263	22C3	SP263	SP142	SP263	73-10
Assay developer	Dako[5,25]	Ventana[24]	Dako[22,23]	Ventana[24]	Ventana[6]	Ventana[16]	Dako[55]
PD-L1 immunohistochemistry scoring*	TC	TC	TC	TC	TC and/or tumor-infiltrating IC	TC	TC
PD-L1 levels evaluated in clinical trials	TC: ≥ 1%, ≥ 5%, ≥ 10%[5]	TC: ≥ 1%, ≥ 5%, ≥ 10%[5]	TC: ≥ 1%, ≥ 50%[22]	TC: ≥ 1%, ≥ 50%[22]	TC: ≥ 50% (TC3)† IC: ≥ 10% (IC3)†[6,15]	TC: ≥ 25%[16]	TC: ≥ 1%[56]
PD-L1 level in first-line therapy	NA	NA	TC ≥ 50%	TC ≥ 50%	NA	NA	NA
PD-L1 level in second-line therapy	None	None	TC ≥ 1%	TC ≥ 1%	None	NA	NA
Diagnostic status	Complementary: testing not required US/EU: NSQ NSCLC Japan: SQ and NSQ NSCLC	Complementary: testing not required EU: NSQ NSCLC	Companion: testing required US/EU/Japan: SQ and NSQ NSCLC	Companion: testing required EU: SQ and NSQ NSCLC	Complementary: testing not required US/EU: SQ and NSQ NSCLC	Not yet approved for durvalumab	Not yet approved for avelumab
Approved IVD PD-L1 expression levels	US/EU/Japan: all patients eligible	EU: all patients eligible	US/EU/Japan: ≥ 50% (previously untreated); ≥ 1% (previously treated)		US: all patients eligible	Not available for NSCLC	Not available for NSCLC

Abbreviations: IC, immune cells; IVD, in vitro diagnostic; NA, not applicable; NSCLC, non–small-cell lung cancer; NSQ, non-squamous; PD-L1, programmed death-ligand 1; SQ, squamous; TC, tumor cells.
*All assays score cells at any intensity.
†TC0 < 1%, TC1 1% to < 5%, TC2 5% to < 50%, TC3 ≥ 50%, IC0 < 1%, IC1 1% to < 5%, IC2 5% to < 10%, IC3 ≥ 10%.

- **There are multiple assays to test for PD-L1 with different scoring guidelines and thresholds**
  - 28-8 (*ipilimumab* + *nivolumab*): 1%, 5% and 10%
  - 22C3 (*pembrolizumab*): <1%, 1-49%, and ≥50%

Büttner R, et al. *J Clin Oncol*. 2017;35(34):3867-3876.

Caveats with PD-L1 Testing

- **Cytologic materials excluded from PD-L1 assessment in trials**
  - Nearly 1/3 of lung samples are FNAs or from pleural sample
  - How well do FNA reliably represent immune compartment?

- **Potential spatial heterogeneity**
  - To what extent is their concordance between primary and metastatic sites. Some controversy here

- **Potential dynamic heterogeneity**
  - PD-L1 is not a static variable! Cancers and immune microenvironment evolve in response to anti-cancer therapies

FNA = fine needle aspiration.

Sakakibara R, et al. *Clin Lung Cancer*. 2017;18(5):527-534.e1. Cho JH, et al. *Clin Lung Cancer*. 2017;18(6):e473-e479. Ratcliffe MJ, et al. *Clin Cancer Res*. 2017;23(14):3585-3591.

Caveats with PD-L1 Reporting

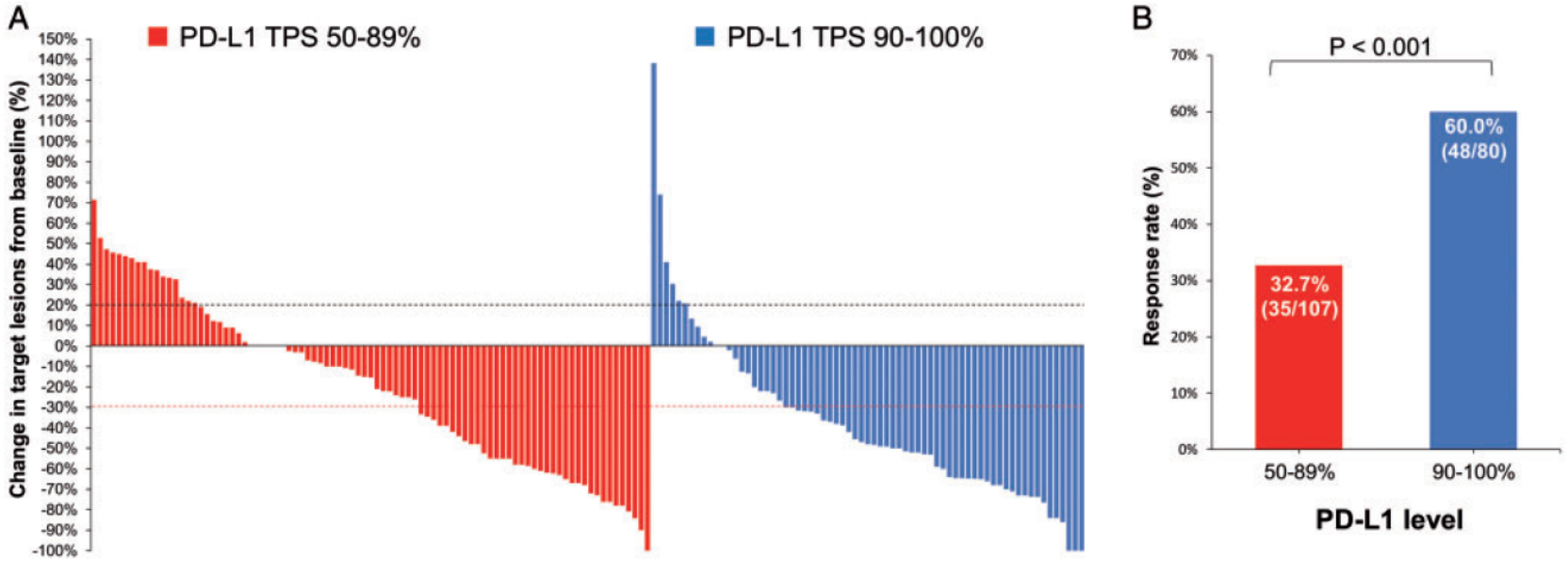


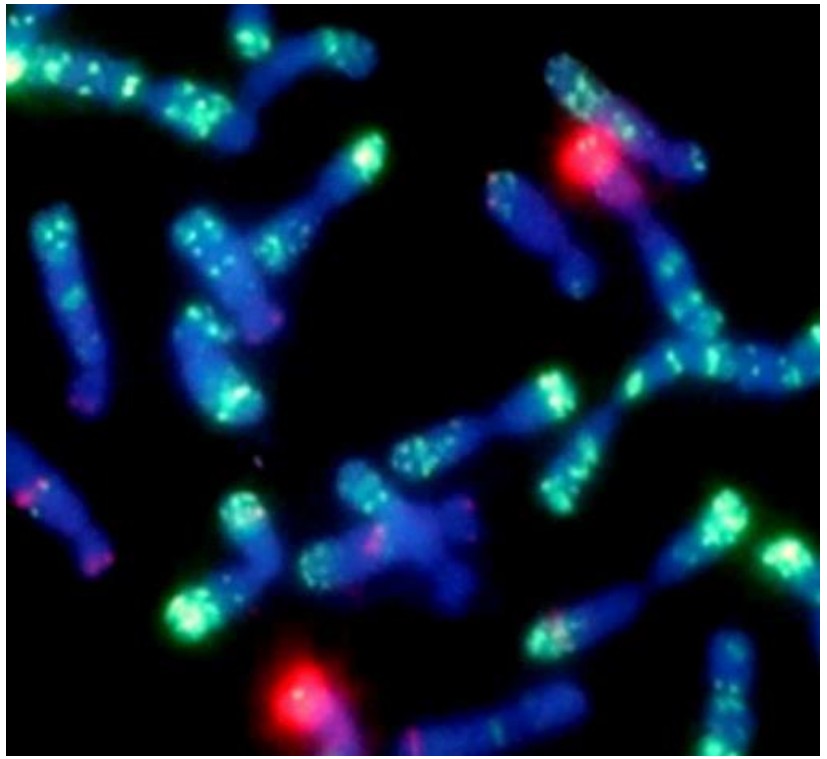
Figure 2. (A) The best objective response to pembrolizumab is shown as a percent change of target lesions from baseline in evaluable patients in patients with a non-small-cell lung cancer programmed death-ligand 1 (PD-L1) expression level of 50%–89% versus 90%–100%. (B) Histograms showing the response rate to first-line pembrolizumab in the PD-L1 expression 50%–89% versus 90%–100% groups.

- **PD-L1 is a continuous variable, but trials will analyze data as categorical variable**
  - KEYNOTE-189: PD-L1 (22C3) <1%, 1-49%, and ≥ 50%
  - Checkmate 227: PD-L1 (28-8) <1% vs >1%

Aguilar EJ, et al. *Ann Oncol*. 2019;30(10):1653-1659.

Fluorescence *in situ* Hybridization

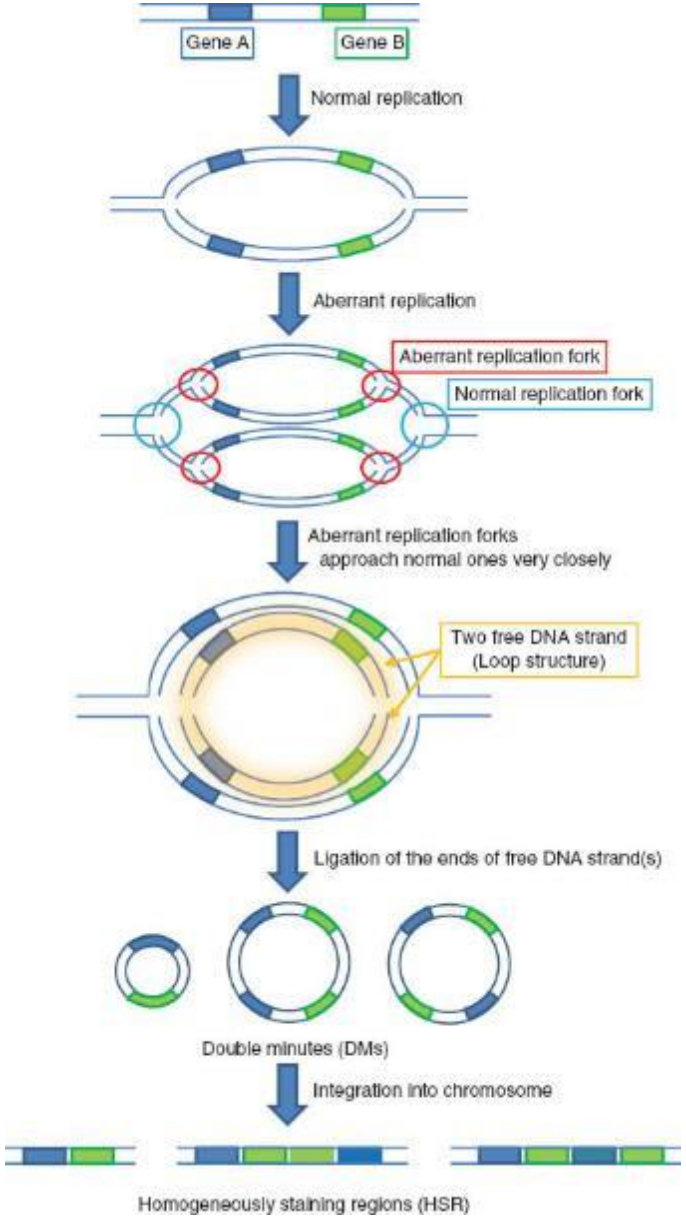
- Requires that extensive testing of normal tissue be performed to understand thresholds
- Combines direct, visually-mapped localization of DNA or RNA with high sensitivity
- Gene fusions
  - *ALK* (≥15% of nuclei out of 100 tested)
  - *ROS1* (≥15% of nuclei out of 100 tested)
  - *RET* (less frequently used)
  - *NTRK*
- Gene amplifications
  - *MET*
  - *ERBB2* (*HER2*)



Minca EC, et al. *J Thorac Oncol*. 2014;9(4):464-8. Shan L, et al. *PLoS One*. 2015;10(3):e0120422.

Gene Amplification

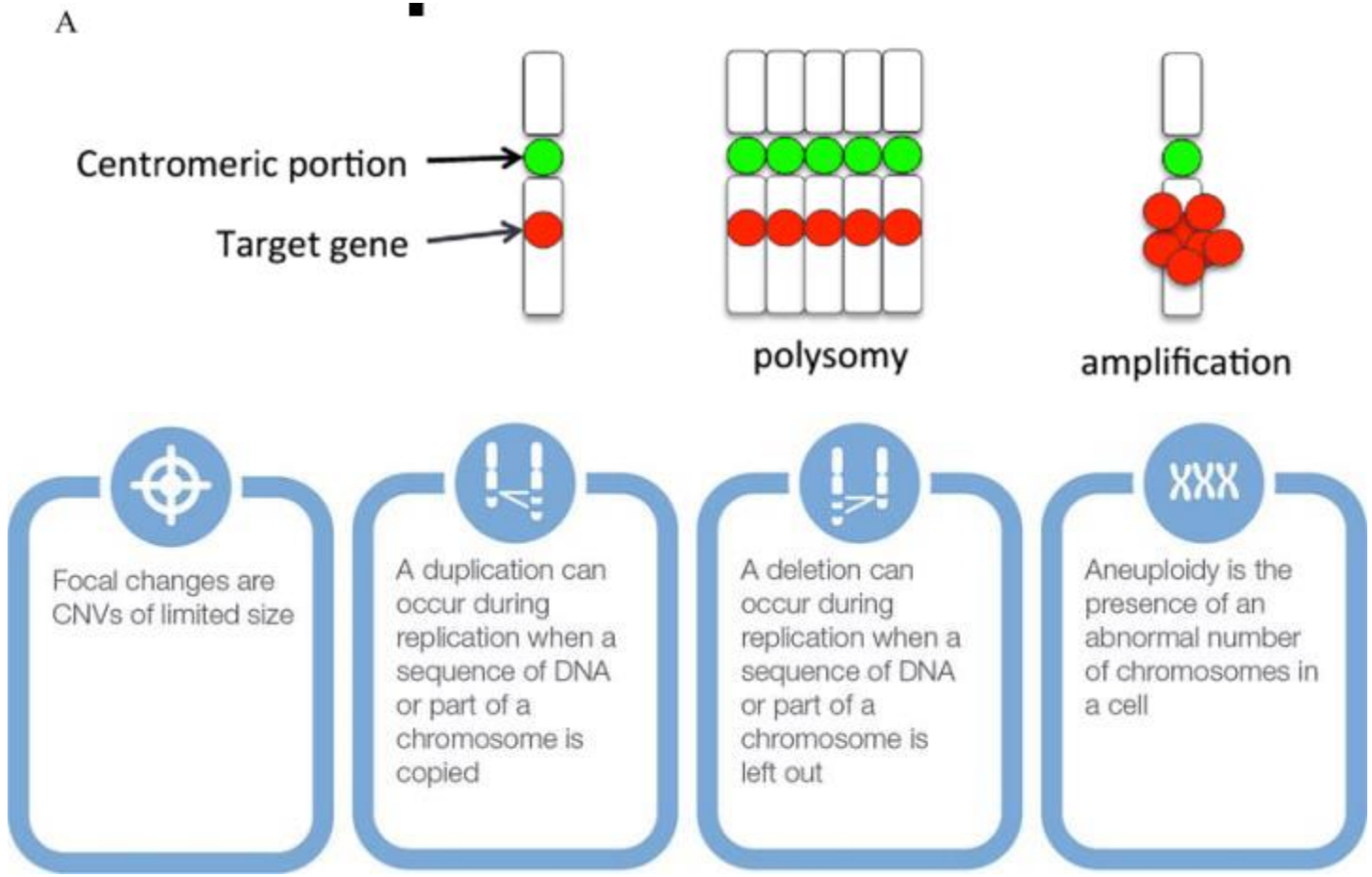
- The gain or loss of gene copies often correlates with a corresponding increase or decrease in the amount of RNA and protein encoded by the gene
- Amplified genes are rare in mammalian cells and within cancer are often the proto-oncogenes
- Gene amplification is an increase in copy number of a restricted region of a chromosome arm. This amplified region is called an "amplicon"
- *Mechanism of gene amplification unknown*
  - Extra-replication + recombination model
  - Breakage-fusion-break model
  - Double rolling-circle replication model
  - Replication fork stalling and template switching (FoSTeS)



Matsui A, et al. *Biomol Concepts*. 2013;4(6):567-582.

Polysomy vs Gene Amplification

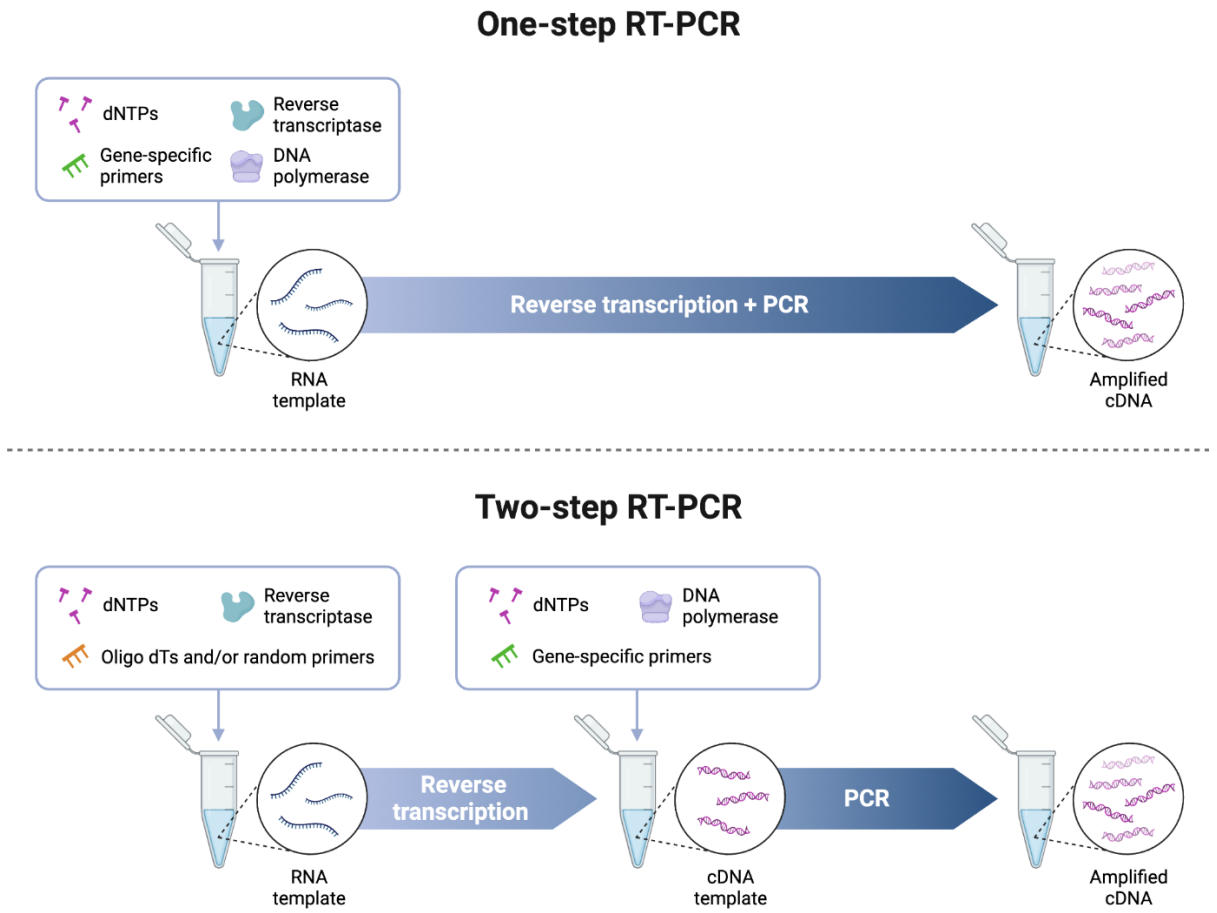
- Gene copy number (GCN) and copy number variation (CNV) are important concepts
- Increased GCN can occur from
  - Polysomy (or aneuploidy)
  - "True" gene amplification
- FISH and NGS have been utilized to distinguish between the two



NGS = next-generation sequencing.
Matsui A, et al. *Biomol Concepts*. 2013;4(6):567-582.

Quantitative PCR

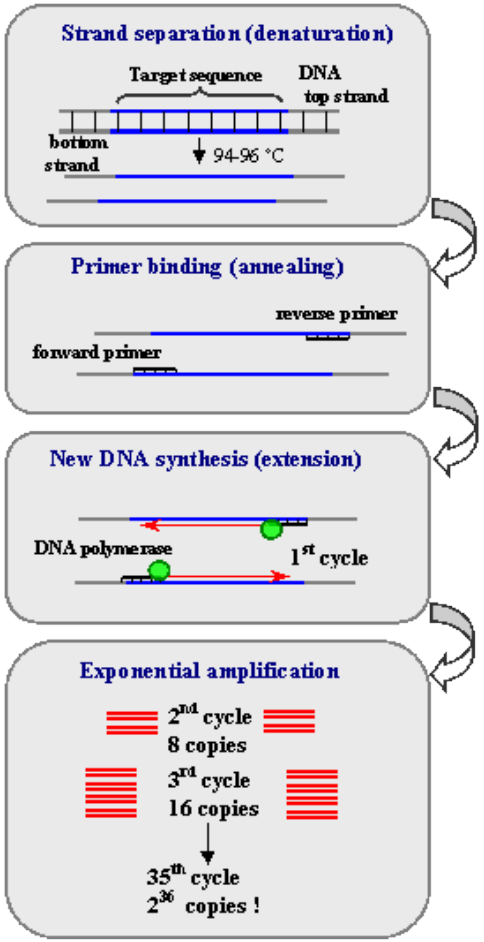
Most useful when looking for *specific* point mutations or deletions



Examples in NSCLC
EGFR L858R
BRAF V600E

Huang E. Accessed August 28, 2025. https://app.biorender.com/biorender-templates/t-61f6fcf776778800a0375e4d.

Think of PCR as "Molecular Photocopying"



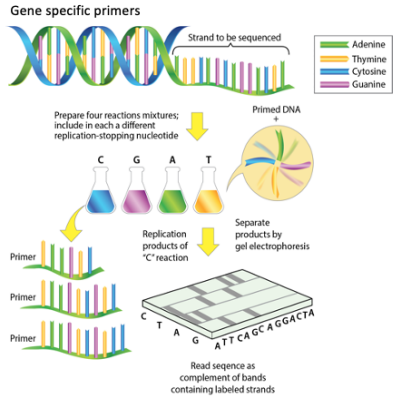
- Identify DNA region of interest
- Identify primers for that region of interest
- Denature DNA by heating
- Use thermostable *Taq* polymerase to create new strands of DNA from primers
- Rinse and repeat

National Library of Medicine (NIH). Accessed August 28, 2025. https://www.ncbi.nlm.nih.gov/probe/docs/techpcr/.

Next Generation Sequencing

- Fundamentally no different than Sanger sequencing or allele PCR, but key difference is massively parallel sequencing
- The key innovation that transforms DNA replication into the DNA-sequencing strategy at the core of both Sanger and NGS is the use of unextendable, **fluorescently labeled** modified bases
- Remember that NGS is a platform and not a standardized test. It depends on probes used in gene panels

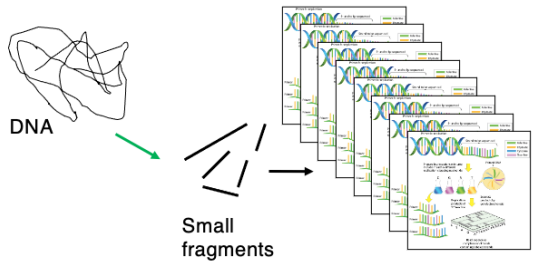
Single gene sequencing (Sanger):



Adapted from http://www.eisenlab.org/FunFly/?page_id=24

Training Residents in Genomics

Genomics: How can you sequence a whole genome?

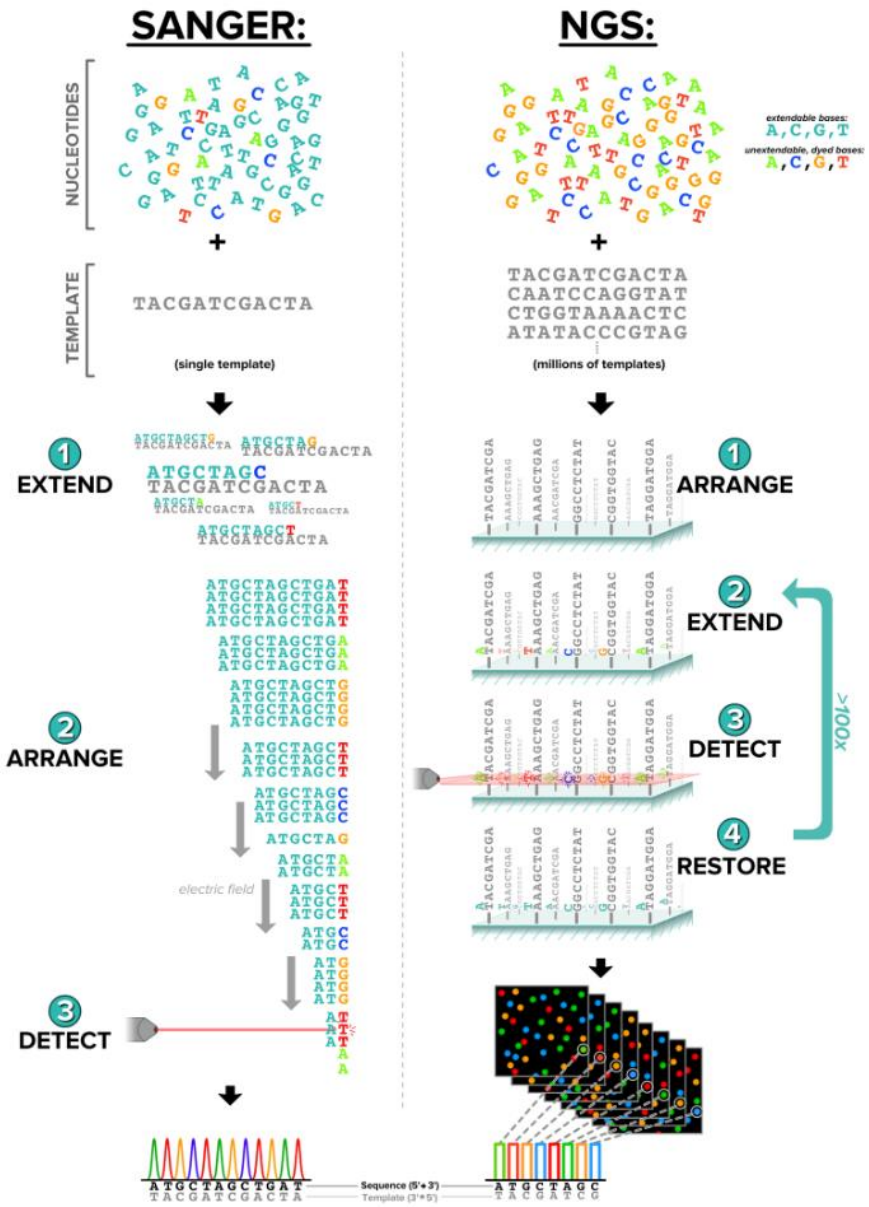


Massively parallel

Muzzey D, et al. *Curr Genet Med Rep*. 2015;3(4):158-165.

- **Sanger sequencing: Size separation**
  - DNA molecules—all originating from the same position on the template
  - Electrical field separates them by size because DNA is negatively charged

- **NGS: Positional separation**
  - Millions of template DNA strands bind to discrete positions on glass slide and remain fixed
  - Extended by single modified base
  - Optical camera resolves position, fluorescent color and intensity at each step



Muzzey D, et al. *Curr Genet Med Rep.* 2015;3(4):158-165.

Depth of Read Critical to Make NGS Calls

- NGS DNA fragments are aligned in reference to human genome
- The number of detected base pairs that align with a known gene sequence *at a given position* is called depth
  - 20X depth = 99.9999% that deviations from genome are real
- Depth is influenced by
  - Relative copy number of DNA in a region
  - Quality of DNA in tissue

Muzzey D, et al. *Curr Genet Med Rep.* 2015;3(4):158-165.

Different Types of NGS

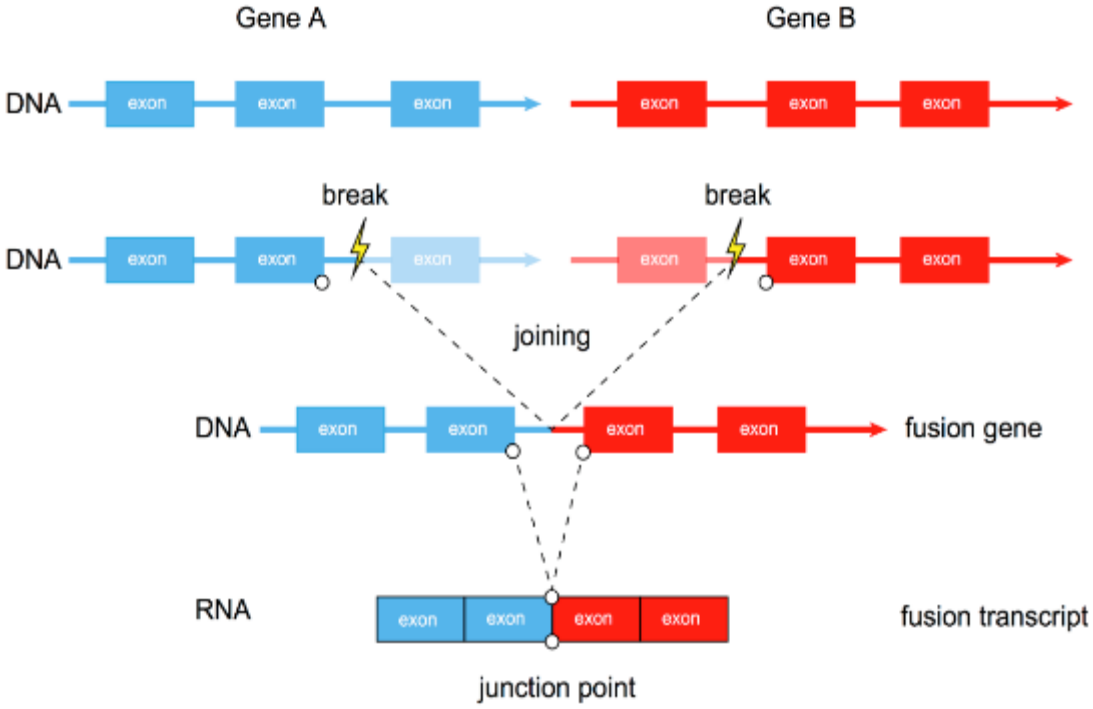
	DNA-NGS (capture)	RNA-NGS (amplicon)	RNA-NGS (capture)
Major strength(s)	• Fusion targets already included in many NGS assays • Does not require a second/separate assay	• Already included in some commercially available assays	• Best performance for challenging fusions
Major weakness(es)	• Significant false negative for challenging fusions *(eg. ROS1-GOPC)*	• Like qRT-PCR, will only detect fusions where there is a primer for the fusion partner	• Performance relies on RNA quality

Davies KD, et al. *J Thorac Oncol*. 2018;13(10):1474-1482.

Gene Fusions (*ALK, ROS1, RET, NTRK, NRG1*)

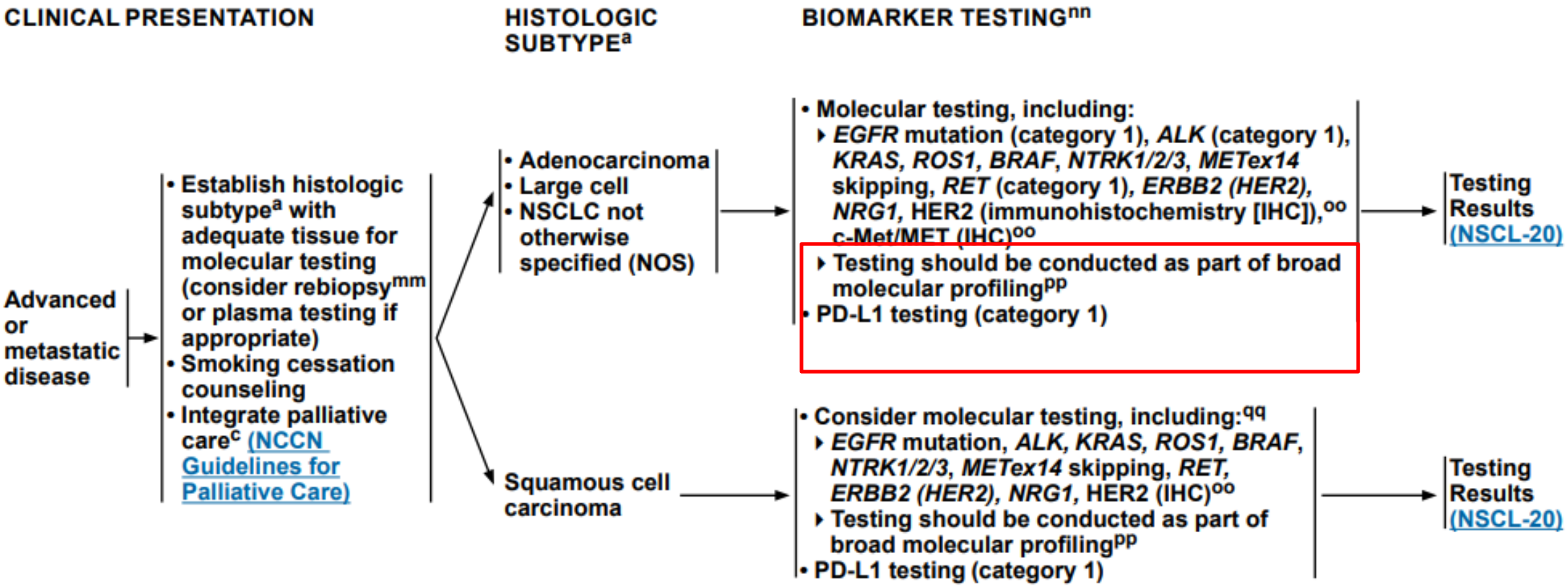
- Gene fusion – a hybrid gene formed erroneous rejoining and replication of DNA. Leads to fused RNA transcript and abnormal (or chimeric) fusion protein

- **Key points**
  - *In general*, fusions (not mutations) are expected to be sensitizing in NSCLC
  - RNA-based NGS potentially better at detecting fusions with novel partners



EML4-ALK → alectinib, brigatinib, lorlatinib
CD74-ROS1 → entrectinib, crizotinib
KIF5B-RET → selpercatinib, pralsetinib
NTRK2-ETV6 → larotrectinib, entrectinib
*CD74-NRG1** → *clinical trials*

***NRG1 fusions unique in that chimeric protein functions as ligand.**
Jackson Laboratory. Accessed August 28, 2025. https://www.tumorfusions.org/.



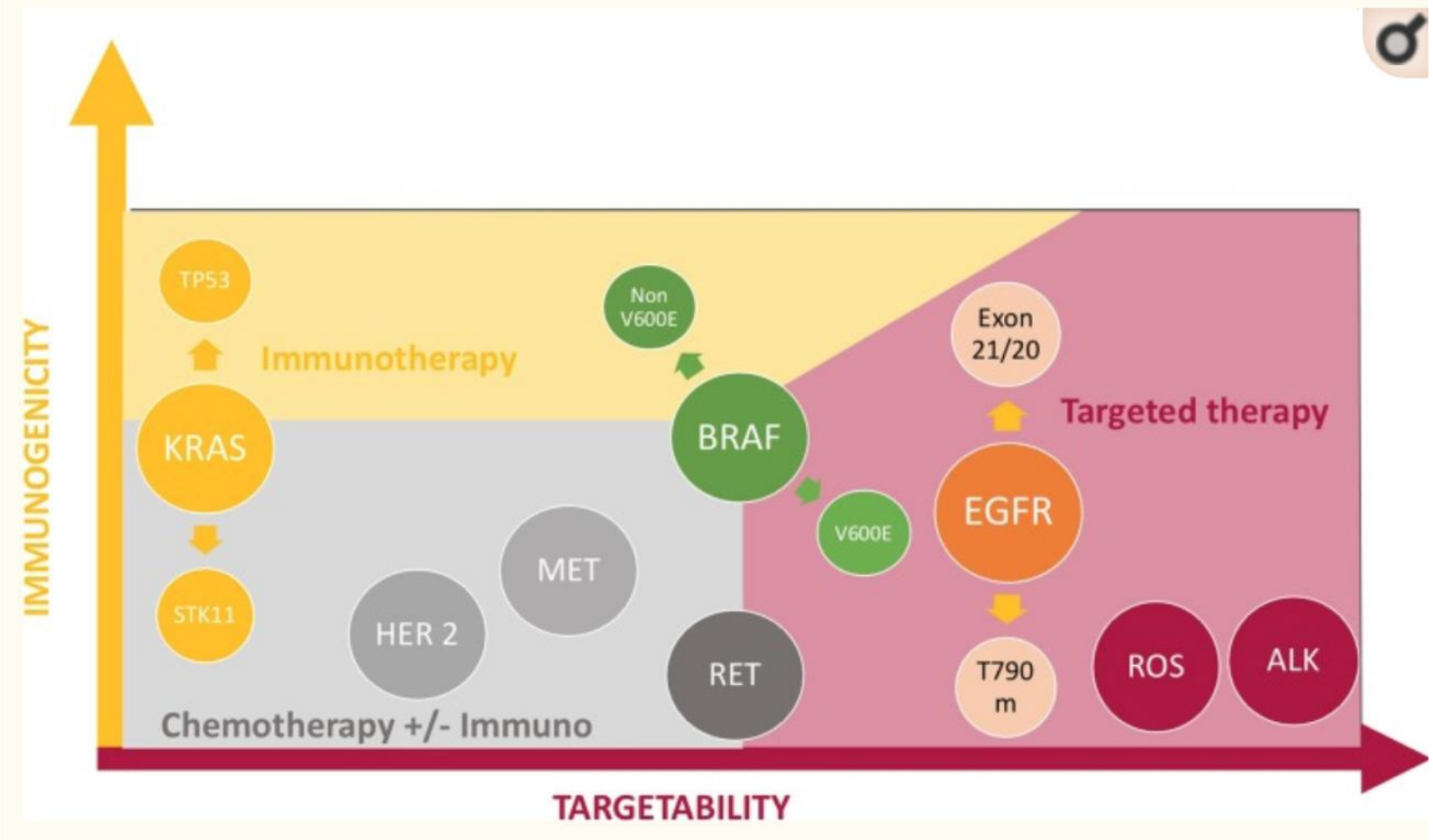
Key Learning Points

- Appreciate different methods for biomarker testing
  - IHC used for testing PD-L1
- Recognize that the National Comprehensive Cancer Network® (NCCN®) recommends broad based biomarker profiling (including DNA and RNA based approaches)
- Optimal strategies for biomarker prioritization continue to evolve

CLINICAL PATHWAYS CONGRESS | CANCER CARE BUSINESS EXCHANGE

Part 3: Treatment Considerations

A Word on Waiting for Molecular Testing



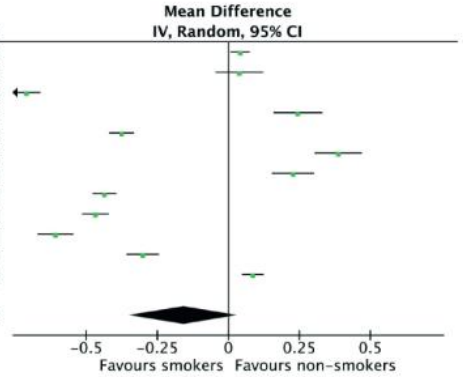
Mhanna L, et al. *Curr Treat Options Oncol*. 2019;20(7):60.

Caution with ICI Monotherapy in Never Smokers

A Comparison of HR (OS) between smokers and non-smokers

Study or Subgroup	smokers log[HR]	SD	Total	non-smokers log[HR]	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Achim Rittmeyer 2016	-0.30110509	0.09348545	694	-0.34249031	0.21224072	156	8.4%	0.04 [0.01, 0.08]
D.P. Carbone 2017	0.05826891	0.11913852	475	0.01980263	0.32492504	59	8.3%	0.04 [-0.05, 0.12]
Fabrice Barlesi 2018	-0.18632958	0.11600412	657	0.52472853	0.28374091	133	8.4%	-0.71 [-0.76, -0.66]
Fabrice Barlesi 2018-2	-0.18632958	0.12475812	511	-0.43078292	0.35760167	67	8.3%	0.24 [0.16, 0.33]
H. Borghaei 2015	-0.35667494	0.10943765	458	0.01980263	0.23533706	118	8.4%	-0.38 [-0.42, -0.33]
Howard West 2019	-0.21072103	0.11494529	548	-0.597837	0.38801708	84	8.3%	0.39 [0.30, 0.47]
L. Gandhi 2018	-0.61618614	0.10929965	543	-0.84397007	0.32116197	73	8.3%	0.23 [0.15, 0.30]
Luis Paz-Ares 2019	-0.31471075	0.08397495	614	0.12221763	0.24093408	132	8.4%	-0.44 [-0.48, -0.40]
M.D. Hellmann 2019	-0.26136476	0.09257793	674	0.20701417	0.2442688	107	8.4%	-0.47 [-0.52, -0.42]
Martin Reck 2020	-0.4780358	0.09098851	622	0.13102826	0.31578427	97	8.3%	-0.61 [-0.67, -0.55]
Ramaswamy Govindan 2017	-0.12783337	0.09272982	656	0.17395331	0.26291453	83	8.3%	-0.30 [-0.36, -0.24]
Yi-Long Wu 2019	-0.31471075	0.1414058	354	-0.40047757	0.22188029	150	8.4%	0.09 [0.05, 0.12]
Total (95% CI)			**6806**			**1259**	**100.0%**	**-0.16 [-0.35, 0.03]**

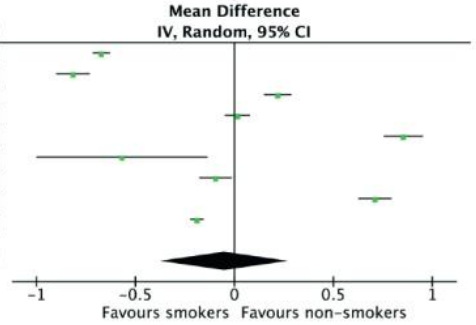
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 1758.52$, df = 11 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 1.64 (P = 0.10)



B Comparison of HR (PFS) between smokers and non-smokers

Study or Subgroup	smokers log[HR]	SD	Total	non-smokers log[HR]	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Caicun Zhou 2019	-0.73396918	0.18065945	257	-0.0618754	0.24141405	155	11.4%	-0.67 [-0.72, -0.63]
D.P. Carbone 2017	0.10436002	0.11373407	475	0.92028275	0.33286207	59	11.3%	-0.82 [-0.90, -0.73]
Fabrice Barlesi 2018-2	-0.49429632	0.10001074	511	-0.71334989	0.2892101	67	11.3%	0.22 [0.15, 0.29]
Howard West 2019	-0.4462871	0.09528406	548	-0.46203546	0.29672214	84	11.3%	0.02 [-0.05, 0.08]
L. Gandhi 2018	-0.61618614	0.14007852	543	-1.46967597	0.43020381	73	11.3%	0.85 [0.75, 0.95]
Martin Reck 2016	-0.67334455	0.15584415	281	-0.10536052	1.08012921	24	9.5%	-0.57 [-1.00, -0.14]
Robert Jotte 2020	-0.35667494	0.08706713	627	-0.26136476	0.31254465	55	11.3%	-0.10 [-0.18, -0.01]
S.J. Antonia 2017	-0.52763274	0.11232445	649	-1.23787436	0.3405615	64	11.3%	0.71 [0.63, 0.79]
Yi-Long Wu 2019	-0.32850407	0.12385404	354	-0.13926207	0.19588539	150	11.4%	-0.19 [-0.22, -0.16]
Total (95% CI)			**4245**			**731**	**100.0%**	**-0.05 [-0.37, 0.27]**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 1709.96$, df = 8 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 0.31 (P = 0.75)



ICI = immune checkpoint inhibitor; OS = overall survival; HR = hazard ratio.
Zhao W, et al. *Front Oncol.* 2021;11:703143.

Higher iRAE with Sequential Immunotherapy and Targeted Therapy

- Remember that checkpoint inhibitors have long half lives!
- Multiple studies have shown marked increase in immune toxicity when TKI is given after checkpoint inhibitor therapy
- Especially in **never/light smoker** with lung cancer, my practice
  - If clinically stable → wait for molecular testing (NGS) to rule out "drive oncogenes" such as *EGFR, ALK, ROS1, RET*
  - If symptomatic (needs urgent therapy) → start chemotherapy for 1-2 cycles and *hold immunotherapy* until molecular results

iRAE = immune-related adverse events; TKI = tyrosine kinase inhibitor.

Schoenfeld AJ, et al. *Ann Oncol*. 2019;30(5):839-844. Oshima Y, et al. *JAMA Oncol*. 2018;4(8):1112-1115. Lin JJ, et al. *J Thorac Oncol*. 2019;14(1):135-140.

FLAURA2 Phase III Study

Pts with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles), followed by maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)*
n=279

Randomisation 1:1 (N=557)

Osimertinib 80 mg (QD)
n=278

Primary endpoint:

- PFS by investigator assessment per RECIST 1.1†‡

Key secondary endpoints:

- OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5), PFS2†

Pts with CNS metastases which were asymptomatic (not requiring steroids) or had a stable neurological status for ≥2 weeks after completion of definitive treatment and steroids, if received, were allowed

Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met
- Brain imaging mandatory at baseline (all pts; 84% received MRI) and progression for all pts, and at scheduled assessments until progression for pts with baseline CNS metastases
- All CNS scans were assessed by neuroradiologist CNS BICR using modified RECIST guidance

Key exploratory endpoints by CNS BICR (modified RECIST 1.1): CNS PFS, CNS ORR, CNS DoR, CNS DCR and change in CNS tumour size

- **CNS full analysis set (cFAS):** pts with ≥1 measurable (≥10 mm) and / or non-measurable CNS lesion at baseline (osi + CTx n=118; osi mono n=104)
- **CNS evaluable-for-response set (cEFR):** pts with ≥1 measurable (≥10 mm) CNS lesion at baseline (osi + CTx n=40; osi mono n=38)

*Pemetrexed maintenance continued until a discontinuation criterion was met; †Efficacy analyses were in the full analysis set, defined as all pts randomized to study; comparison between treatment arms was regardless of the treatment actually received. The safety analysis set was defined as all randomized pts who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; ‡The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level.

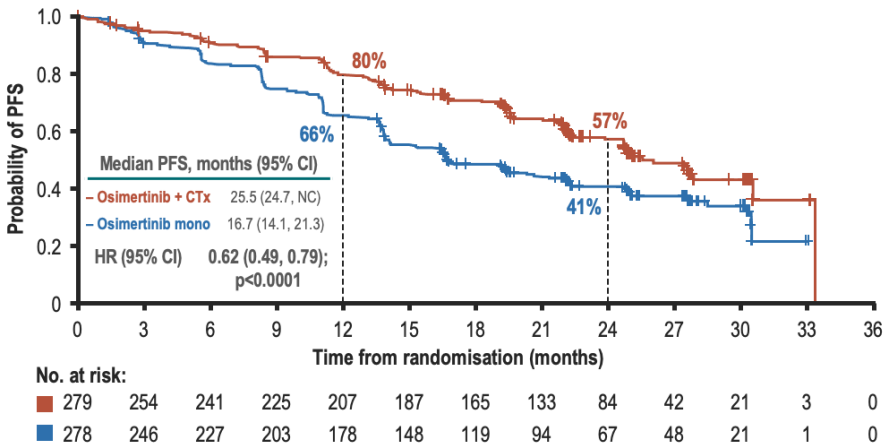
AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CTCAE, Common Terminology Criteria for AEs; CTx, chemotherapy; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; Ex19del, exon 19 deletion; HRQoL, health-related quality of life; mono, monotherapy; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; osi, osimertinib; PFS, progression-free survival; PFS2, second progression-free survival; pts, patients; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; WHO PS, World Health Organization performance status

Planchard D, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; November 29, 2023; Madrid, Spain. LBA68.

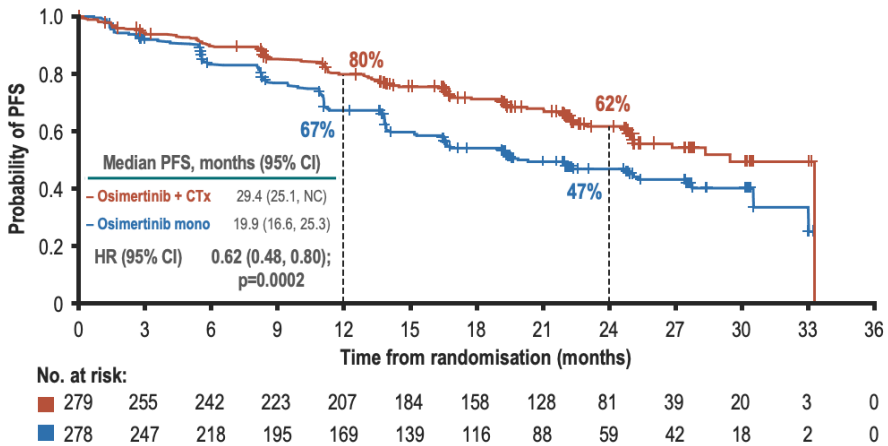
1L OSIMERTINIB WITH THE ADDITION OF CTx SIGNIFICANTLY IMPROVES PFS VS OSIMERTINIB MONOTHERAPY

- Osimertinib with the addition of platinum-pemetrexed has demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy in pts with EGFRm advanced NSCLC[1]
  - Per investigator assessment, median PFS was improved by ~8.8 months with osimertinib + CTx vs osimertinib monotherapy
  - Per BICR, median PFS was improved by ~9.5 months with osimertinib + CTx vs osimertinib monotherapy

PFS per investigator assessment



PFS per BICR assessment

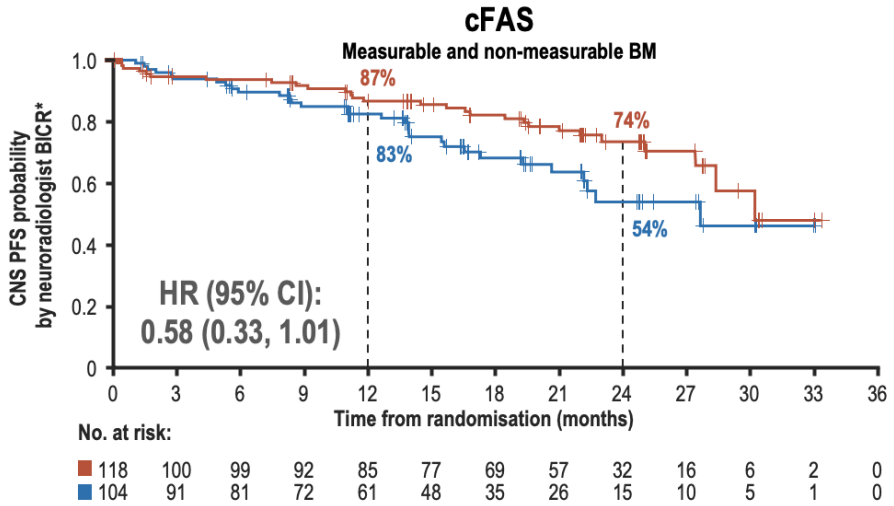


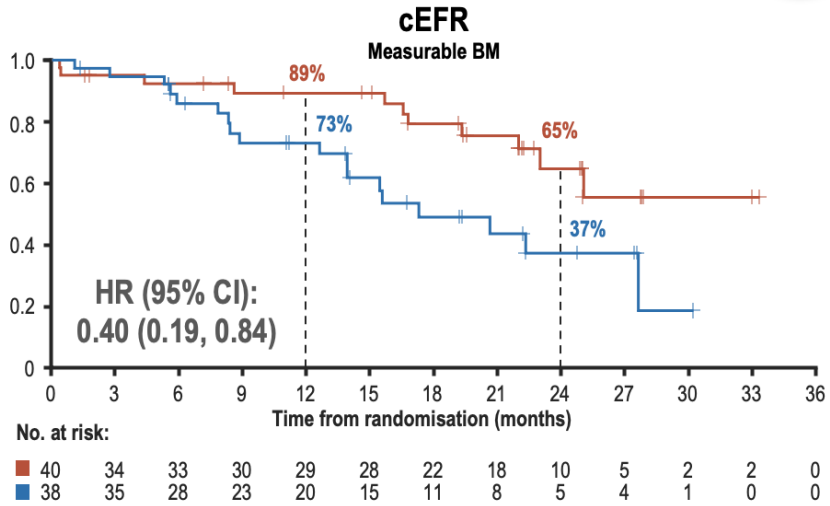
1. Jänne et al. WCLC 2023: abstract / presidential symposium PL03.13

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.

Planchard D, et al. Presented at: ESMO Congress; November 29, 2023; Madrid, Spain. LBA68.

OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED IMPROVED CNS PFS VS OSIMERTINIB BY CNS BICR





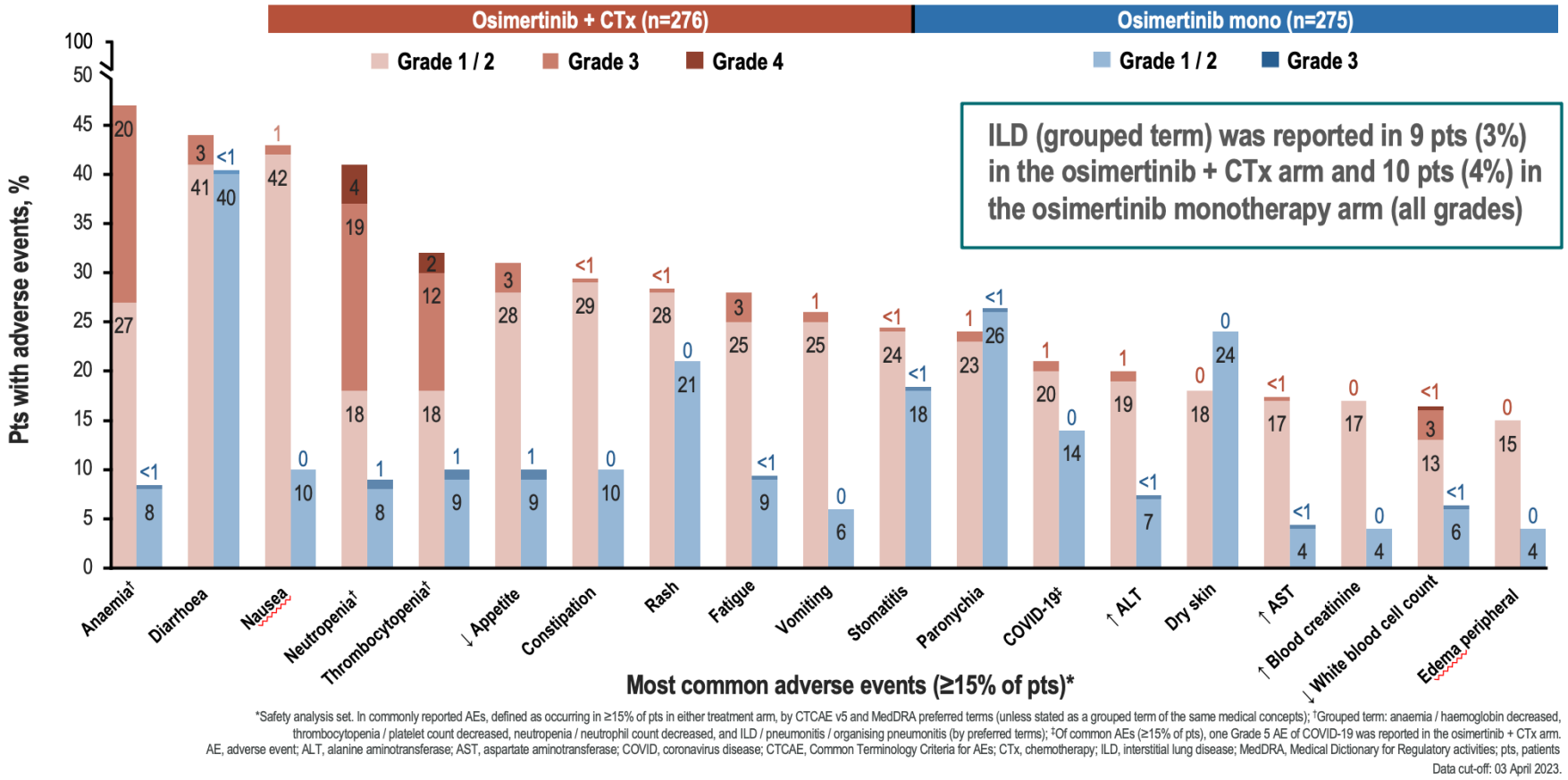
	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
n (%)†	Osi + CTx (n=118)	Osi mono (n=104)	Osi + CTx (n=40)	Osi mono (n=38)
Any CNS RECIST progression‡	11 (9)	20 (19)	5 (13)	13 (34)
Progression in CNS target lesions	2 (2)	7 (7)	2 (5)	7 (18)
Progression in non-target CNS lesions	0	4 (4)	0	3 (8)
Progression due to new CNS lesions	9 (8)	12 (12)	3 (8)	6 (16)
Death without CNS progression	17 (14)	11 (11)	6 (15)	5 (13)

*Median follow-up for CNS PFS in the cFAS was 20.1 months (range 0-33.3) in the osimertinib + platinum-pemetrexed arm and 13.9 months (0-33.1) in the osimertinib monotherapy arm. CNS PFS data maturity was 27% (59/222 events across both arms);
†Only includes CNS progression events that occurred within two consecutive scheduled visits (plus visit window) of the last CNS assessment or randomisation; ‡Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive.

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CNS, central nervous system; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; osi, osimertinib; PFS, progression-free survival; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumours
Data cut-off: 03 April 2023.

Planchard D, et al. Presented at: ESMO Congress; November 29, 2023; Madrid, Spain. LBA68.

MORE AEs ≥GRADE 3 WERE OBSERVED IN THE OSIMERTINIB + CTx ARM, MAINLY DRIVEN BY HAEMATOLOGICAL TOXICITIES



*Safety analysis set. In commonly reported AEs, defined as occurring in ≥15% of pts in either treatment arm, by CTCAE v5 and MedDRA preferred terms (unless stated as a grouped term of the same medical concepts); †Grouped term: anaemia / haemoglobin decreased, thrombocytopenia / platelet count decreased, neutropenia / neutrophil count decreased, and ILD / pneumonitis / organising pneumonitis (by preferred terms); ‡Of common AEs (≥15% of pts), one Grade 5 AE of COVID-19 was reported in the osimertinib + CTx arm.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID, coronavirus disease; CTCAE, Common Terminology Criteria for AEs; CTx, chemotherapy; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory activities; pts, patients
Data cut-off: 03 April 2023.

Planchard D, et al. Presented at: ESMO Congress; November 29, 2023; Madrid, Spain. LBA68.

FLAURA2: Take-Home Points

- Large phase 3 clinical of osimertinib vs osimertinib + platinum / pemetrexed chemotherapy
- Improved PFS and ORR with the combination of osimertinib + platinum / pemetrexed vs osimertinib alone
- There was improved CNS control (CNS PFS, CNS DoR, and CNS ORR) – *however…*
  - **More severe AEs, although clinically manageable**
  - **Is this enough to justify upfront chemotherapy (with all toxicities that ensue) given the wide availability of SRS to manage upfront or oligoprogressive brain metastases?**
- Can we better identify underlying risk factors that warrant the use of this combination strategy?

CNS = central nervous system; DoR = duration of response; ORR = objective response rate; SRS = stereotactic radiosurgery; AE = adverse event.

For Whom Should We Intensify?

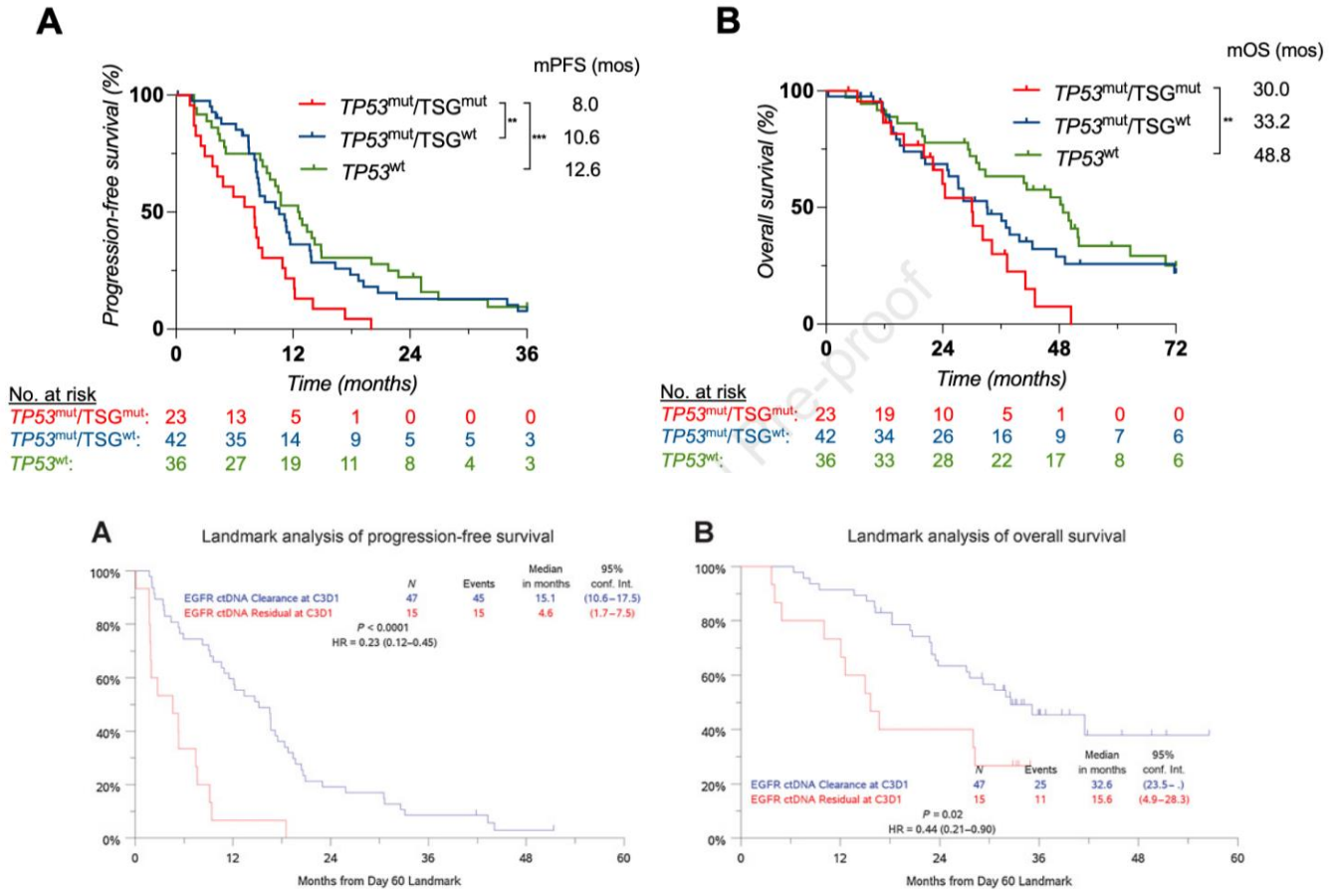


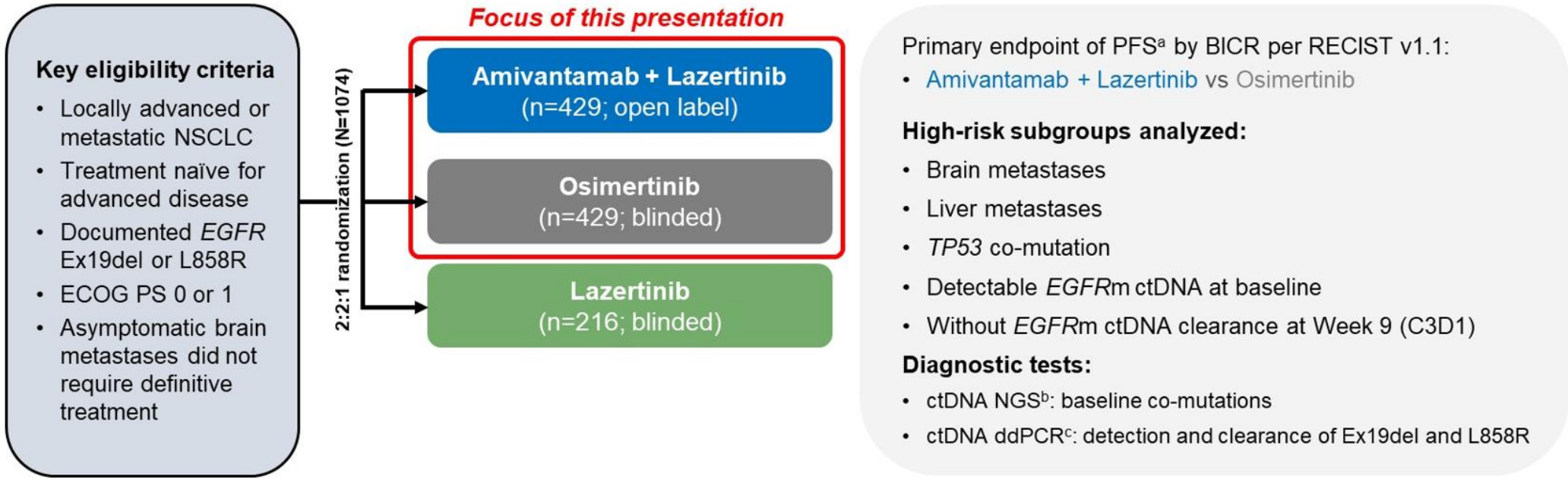
Figure 2.
Kaplan–Meier analysis of PFS (**A**) and OS (**B**) for patients with *EGFR* MAF clearance (blue lines) or residual (red lines) ctDNA at C3D1 (8 weeks). All patients here were baseline positive for mutant *EGFR* ctDNA.

- Co-occurring TP53 + tumor suppressor genes associated with poor prognosis on osimertinib
- Failure to clear EGFR ctDNA (with afatinib + cetuximab) at 8 weeks associated with poor prognosis
- **Need to incorporate prognostic variables in calculus of whether to use upfront chemotherapy**

Stockhammer P, et al. *J Thorac Oncol*. 2024;19(2):240-251. Mack PC, et al. *Clin Cancer Res*. 2022;28(17):3752-3760.

Mariposa Study Design and Methods

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI[4,5]



MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080). [a]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS. The lazertinib arm was included to assess contribution of components. ddPCR. C3D1 is Cycle 3 Day 1. Each cycle was 28 days.

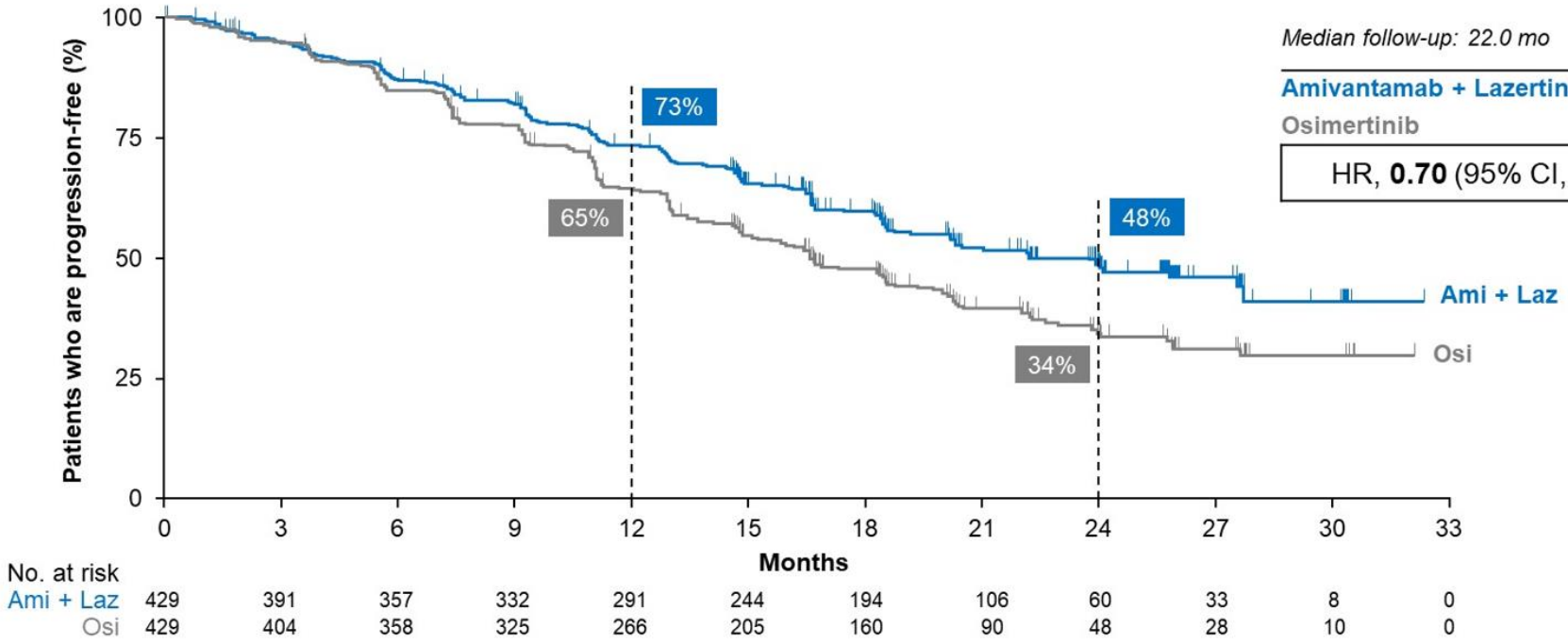
ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; NGS, next-generation sequencing.

1. Moores SL, et al. *Cancer Res.* 2016;76(13):3942-3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19(10):2044-2056. 3. Yun J, et al. *Cancer Discov.* 2020;10(8):1194-1209. 4. Ahn MJ, et al. *Lancet Oncol.* 2019;20(12):1681-1690. 5. Cho BC, et al. *J Thorac Oncol.* 2022;17(4):558-567.

Felip E, et al. *JCO.* 2024;42:8504-8504.

Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 mo	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

Amivantamab + lazertinib also meaningfully improved PFS2 and DoR vs osimertinib in MARIPOSA

Data cutoff: August 11, 2023.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

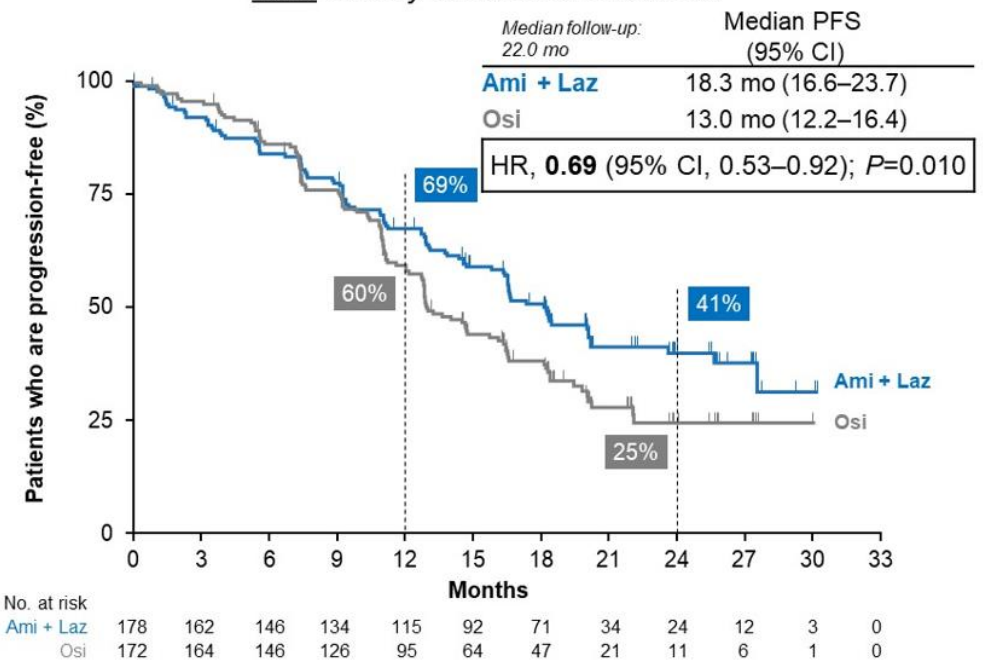
BICR = blinded, independent, central review.
Felip E, et al. *JCO.* 2024;42:8504-8504.

PFS by Baseline Metastases

- In the amivantamab + lazertinib arm, 41% of patients had a history of brain metastases vs 40% in the osimertinib arm
- Osimertinib showed a median PFS of 13.0 mo in patients with a history of brain metastases
- Amivantamab + lazertinib reduced the risk of progression or death by 31% in this subgroup

History of brain metastases is NOT same as intracranial response!

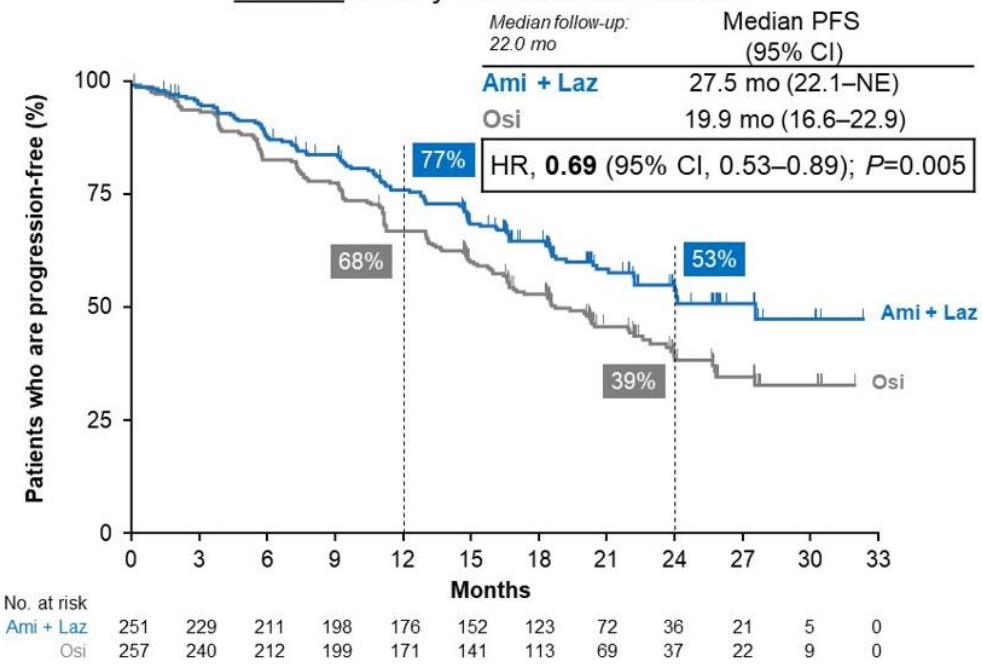
With History of Brain Metastases



Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

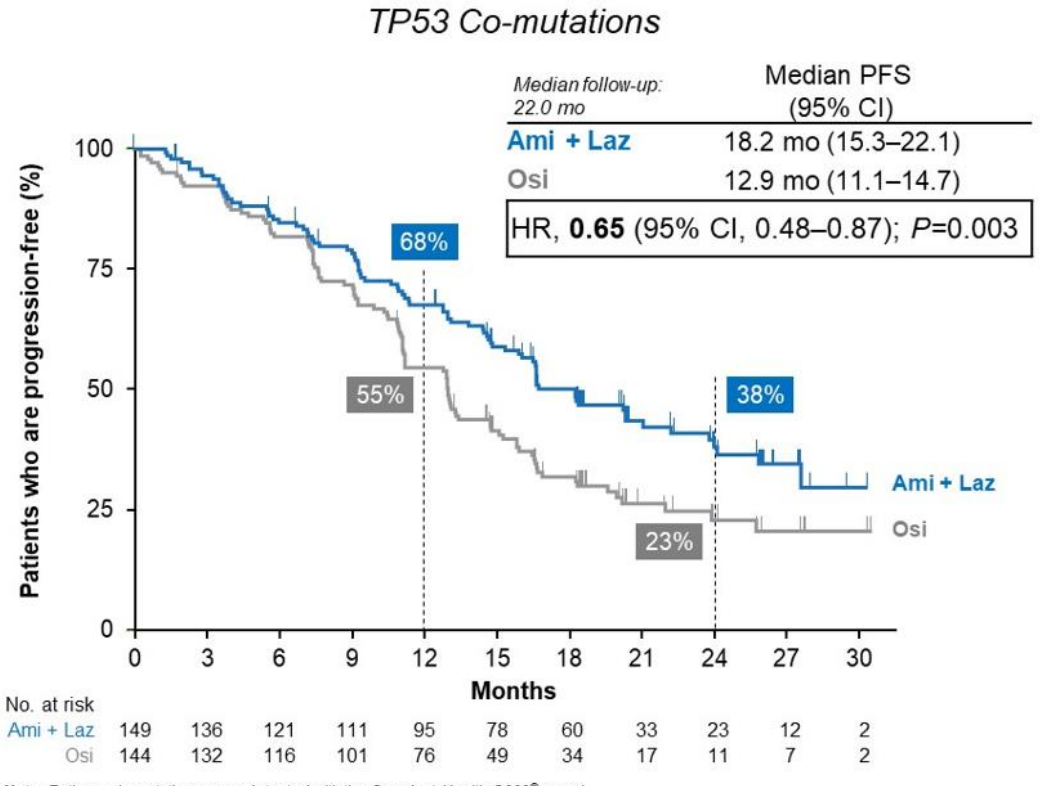
Without History of Brain Metastases

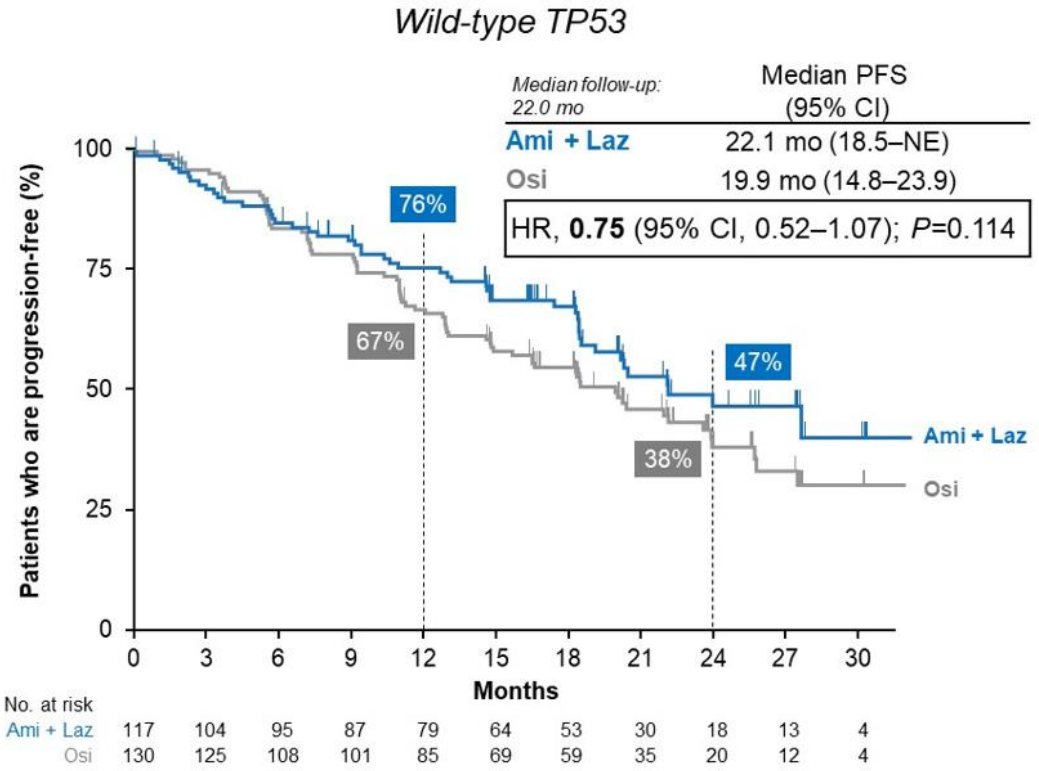


Felip E, et al. *JCO.* 2024;42:8504-8504.

PFS by *TP53* Co-Mutations and Wild-Type *TP53*

- Osimertinib showed a median PFS of 12.9 mo in patients with *TP53* co-mutations at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 35% in this subgroup





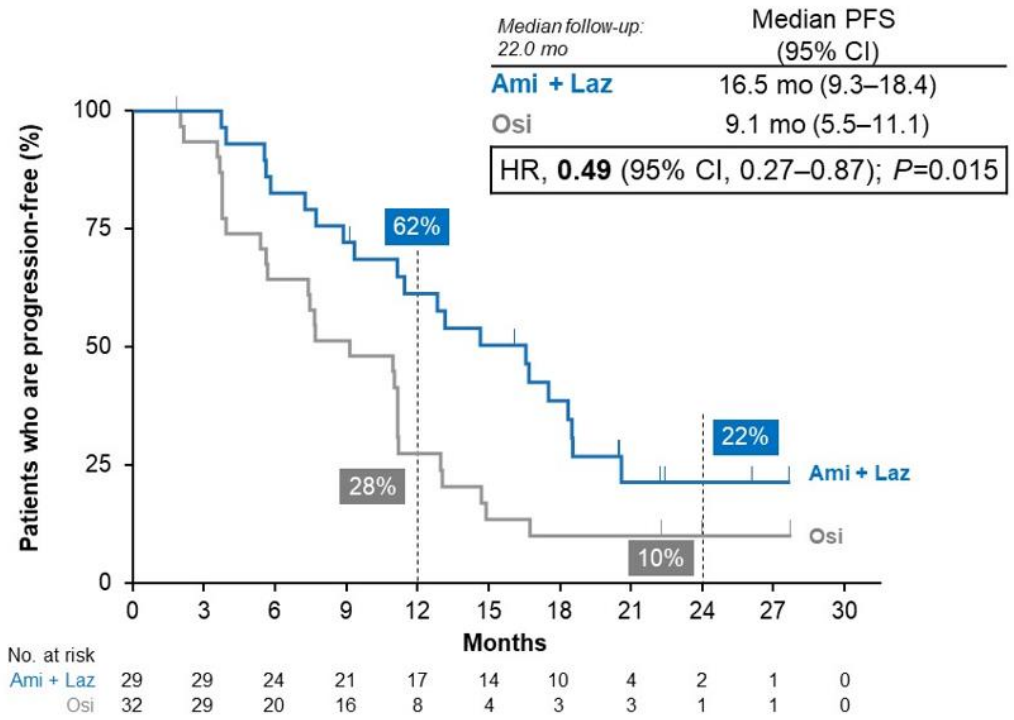
Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

Felip E, et al. *JCO.* 2024;42:8504-8504.

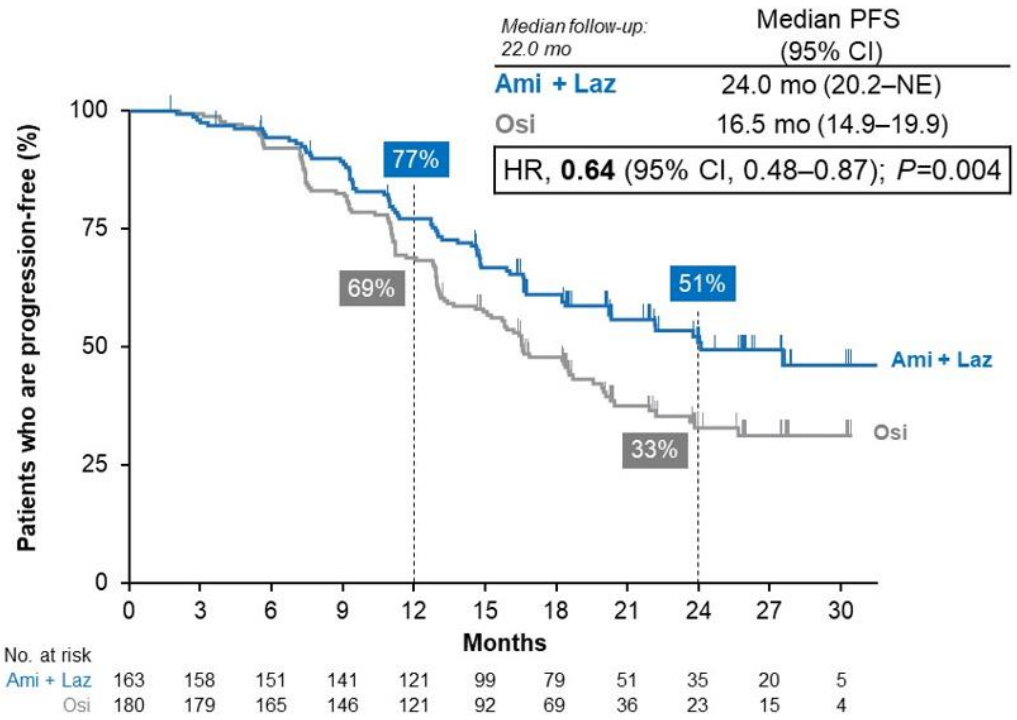
PFS without and with Cleared EGFRm ctDNA[a] at Wk 9 (C3D1)

- Osimertinib showed a median PFS of 9.1 mo in patients without cleared *EGFR*m ctDNA[a] at Week 9
- Amivantamab + lazertinib reduced the risk of progression or death by 51% in this subgroup

Without Cleared EGFRm ctDNA[a] at Week 9



With Cleared EGFRm ctDNA[a] at Week 9



Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; Osi, osimertinib.

Felip E, et al. *JCO.* 2024;42:8504-8504.

CLINICAL PATHWAYS CONGRESS | CANCER CARE BUSINESS EXCHANGE

AEs from Mariposa

Table 3. Adverse Events.*

Event	Amivantamab–Lazertinib (N=421)		Osimertinib (N=428)	
	All	Grade ≥3	All	Grade ≥3
	number of patients (percent)			
Any event	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event	205 (49)		143 (33)	
Any event resulting in death		34 (8)		31 (7)
Event leading to interruption of any trial agent	350 (83)		165 (39)	
Event leading to dose reduction of any trial agent	249 (59)		23 (5)	
Event leading to discontinuation of any trial agent	147 (35)		58 (14)	
Adverse events reported in ≥15% of the patients in either group†				
Paronychia	288 (68)	46 (11)	121 (28)	2 (<1)
Infusion-related reaction	265 (63)	27 (6)	0	0
Rash	260 (62)	65 (15)	131 (31)	3 (1)
Hypoalbuminemia	204 (48)	22 (5)	26 (6)	0
Increased alanine aminotransferase	152 (36)	21 (5)	57 (13)	8 (2)
Peripheral edema	150 (36)	8 (2)	24 (6)	0
Constipation	123 (29)	0	55 (13)	0
Diarrhea	123 (29)	9 (2)	190 (44)	3 (1)
Dermatitis acneiform	122 (29)	35 (8)	55 (13)	0
Stomatitis	122 (29)	5 (1)	90 (21)	1 (<1)
Increased aspartate aminotransferase	121 (29)	14 (3)	58 (14)	5 (1)
Covid-19	111 (26)	8 (2)	103 (24)	9 (2)
Decreased appetite	103 (24)	4 (1)	76 (18)	6 (1)
Pruritus	99 (24)	2 (<1)	73 (17)	1 (<1)
Anemia	96 (23)	16 (4)	91 (21)	7 (2)
Nausea	90 (21)	5 (1)	58 (14)	1 (<1)
Hypocalcemia	88 (21)	9 (2)	35 (8)	0
Asthenia	78 (19)	12 (3)	46 (11)	4 (1)
Pulmonary embolism	73 (17)	35 (8)	20 (5)	10 (2)
Fatigue	70 (17)	6 (1)	42 (10)	4 (1)
Muscle spasms	70 (17)	2 (<1)	32 (7)	0
Dry skin	67 (16)	1 (<1)	60 (14)	1 (<1)
Thrombocytopenia	66 (16)	1 (<1)	84 (20)	5 (1)
Cough	65 (15)	0	88 (21)	0
Pain in extremity	64 (15)	1 (<1)	22 (5)	0
Dyspnea	51 (12)	6 (1)	68 (16)	17 (4)
Leukopenia	26 (6)	1 (<1)	66 (15)	0

Key highlights

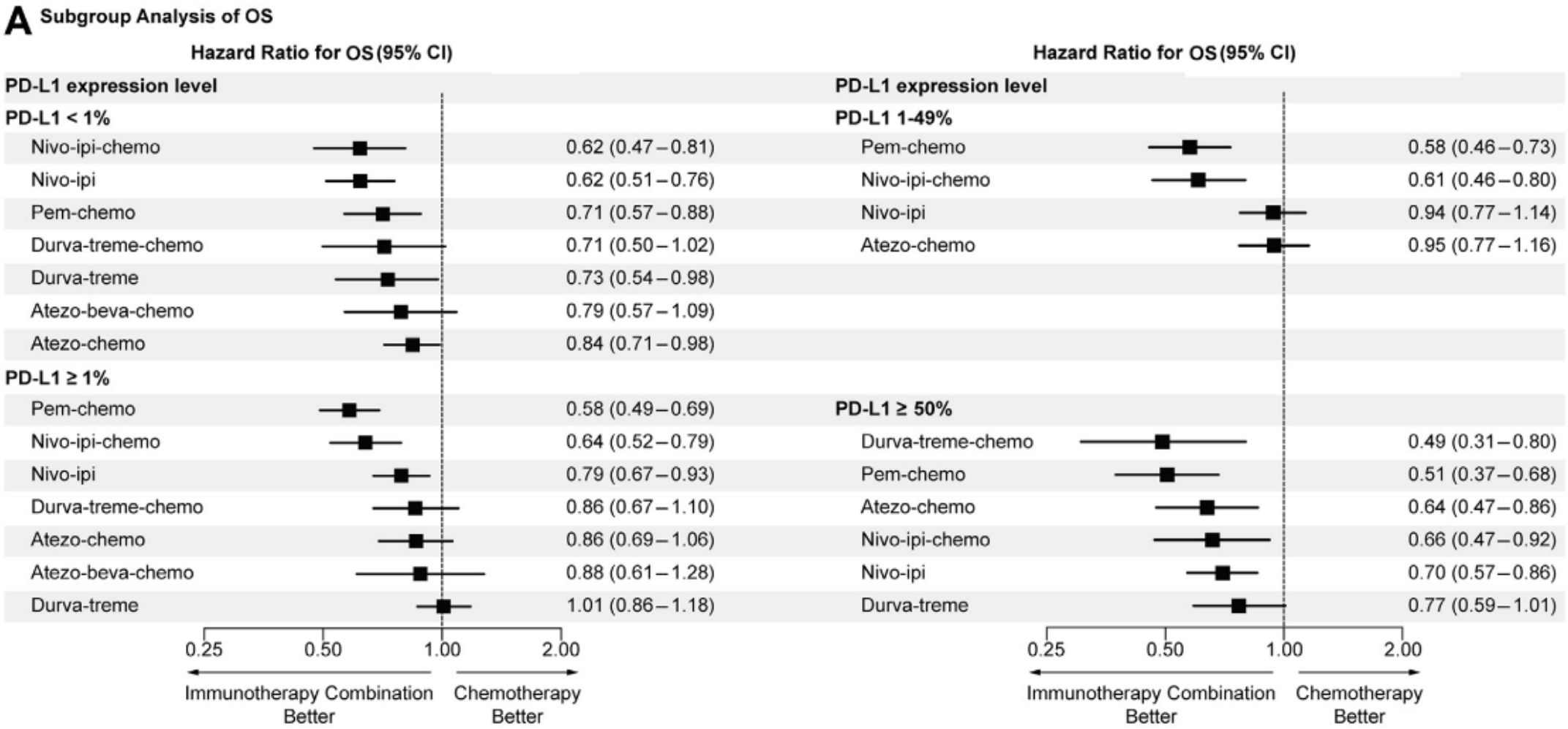
Event	Amivantamab + Lazertinib	Osimertinib
Dose reductions	59%	5%
Dose discontinuation	35%	14%
Rash (≥ Grade 3)	15%	1%
Rash (any grade)	62%	31%
Infusion reaction (any grade)	68%	0%
Diarrhea (any grade)	29%	44%
Pulmonary embolism	17%	5%
Peripheral edema	36%	6%

Improvements in PFS for amivantamab + lazertinib come at expense of worse toxicities

Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

MARIPOSA: Take-Home Points

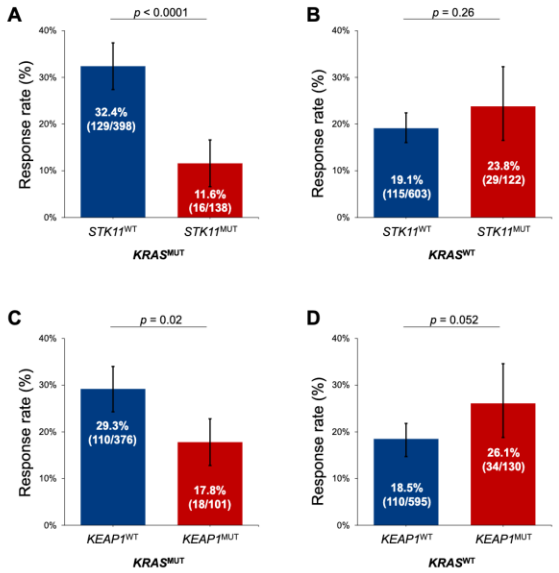
- Well designed phase 3 clinical trial that shows ORR and PFS benefit for patients receiving *first line* amivantamab + lazertinib in patients with sensitizing EGFR mutations
- Control arm performed as expected
  - *Outcomes from osimertinib was comparable to FLAURA (mPFS 18 months)*
- History of brain metastases ≠ intracranial response
  - *Need to see specifics! How many patients had intracranial metastases that were <u>both</u> asymptomatic and measurable (>1cm)*
  - *What is IC-ORR, median duration of intracranial response, etc.*
- Adverse event profile is a concern for MARIPOSA
  - *Patients will be on this treatment for approximately two years!*
- In high-risk patients (TP53 mutations, failure to clear EGFR ctDNA) – should we use MARIPOSA vs FLAURA-2?

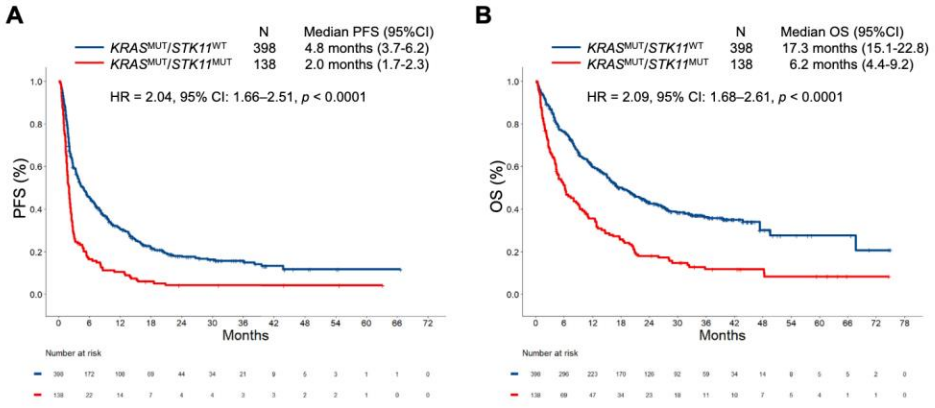


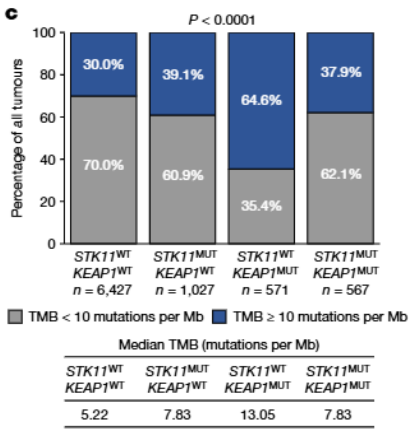
Liu L, et al. *J Thorac Oncol*. 2021;16(7):1099-1117.

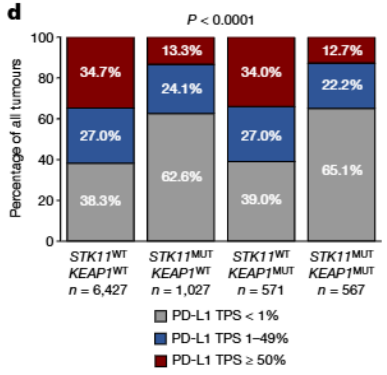
CLINICAL PATHWAYS CONGRESS | CANCER CARE BUSINESS EXCHANGE

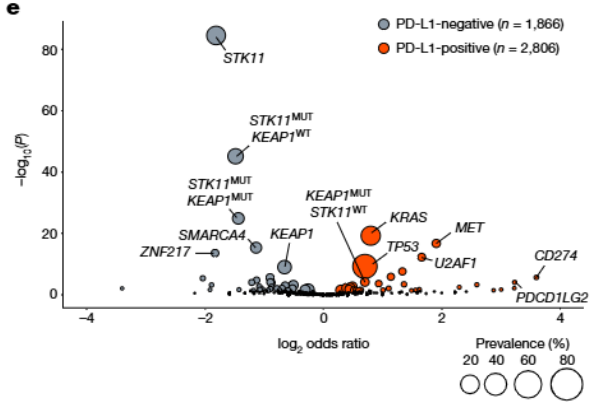
STK11, *KEAP1*, and *SMARCA4* Negative Prognostic Markers to ICIs in NSCLC

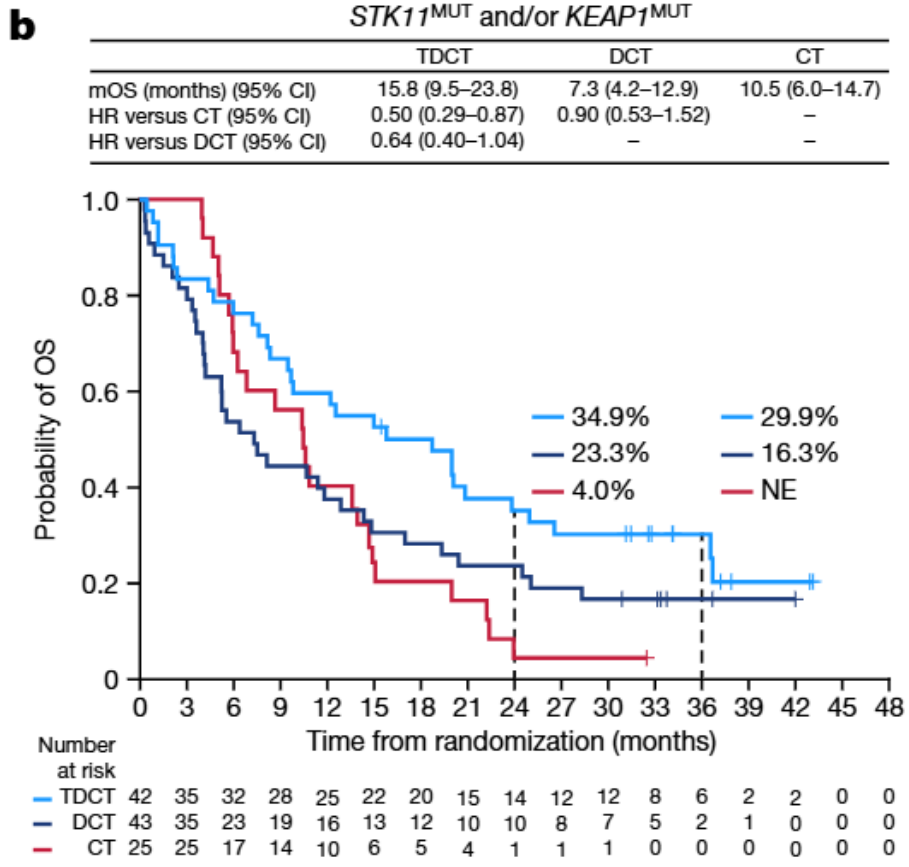












Ricciuti B, et al. *J Thorac Oncol*. 2022;17(3):399-410. Skoulidis F, et al. *Nature*. 2024;635(8038):462-471.

CLINICAL PATHWAYS CONGRESS | CANCER CARE BUSINESS EXCHANGE

Personal Practice Perspective for PD-L1 ≥ 50%

ICI monotherapy	Chemotherapy + ICI
Heavy smoker	Never smoker or light smoking history
Minimally symptomatic	Symptomatic and would be benefit from cytoreduction from chemotherapy
KRAS mutation without STK11, KEAP1, TP53	+/- KRAS mutation with STK11, KEAP1, TP53 with *possible* preference for PD1/CTLA4 combo
CKD Stage III or borderline renal dysfunction	Excellent renal function

CKD = chronic kidney disease.

Key Learning Points

- Comprehensive molecular testing is important in treatment selection
- For patients with EGFR mutant NSCLC, appreciate the importance of intensification strategies with a focus on FLAURA2 and MARIPOSA
- Recognize that chemotherapy with ICIs is standard of care for patients without actionable alterations
- Appreciate evolving role of identifying high risk somatic alterations that confer poor prognosis to first line therapies

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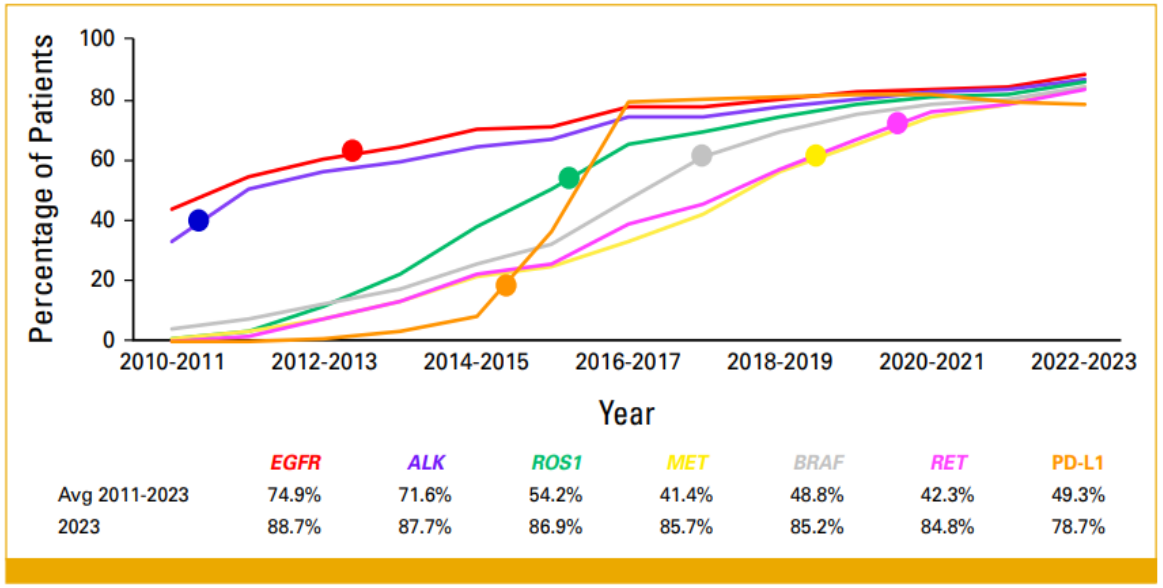
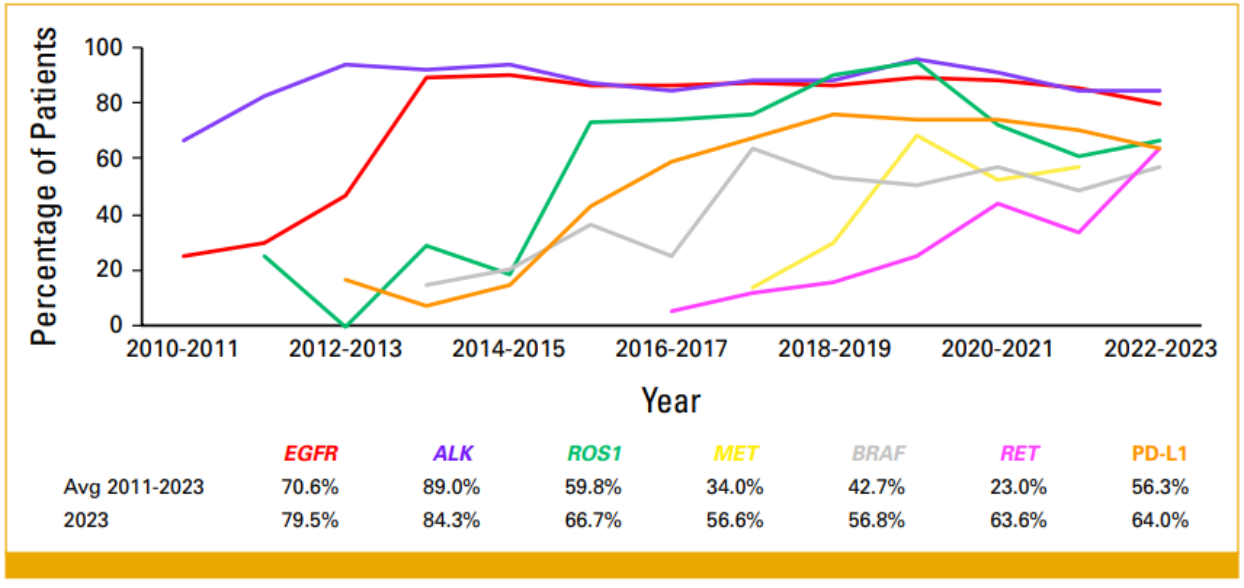
Part 4: Clinical Pathways

Biomarker Testing Remains Sub-Optimal



	EGFR	ALK	ROS1	MET	BRAF	RET	PD-L1
Avg 2011-2023	74.9%	71.6%	54.2%	41.4%	48.8%	42.3%	49.3%
2023	88.7%	87.7%	86.9%	85.7%	85.2%	84.8%	78.7%

FIG 1. Percentage of patients receiving biomarker testing by year of test. Circles represent the year of first FDA approval of a biomarker-informed therapy for each biomarker. FDA, US Food and Drug Administration.



	EGFR	ALK	ROS1	MET	BRAF	RET	PD-L1
Avg 2011-2023	70.6%	89.0%	59.8%	34.0%	42.7%	23.0%	56.3%
2023	79.5%	84.3%	66.7%	56.6%	56.8%	63.6%	64.0%

FIG 2. Percentage of patients receiving FDA-approved biomarker-informed therapy in any line by year of biomarker test. Lines start at different points based on when biomarker test (either tissue or blood) for biomarker became available by the FDA. FDA, US Food and Drug Administration.

- In real world, smoking history remains a significant determinant of whether patients receive biomarker tests or biomarker-informed therapies, such as those targeting ALK, EGFR, and PD-L1
- Biomarker testing for MET Exon 14 and BRAF V600E remains low, around 56%

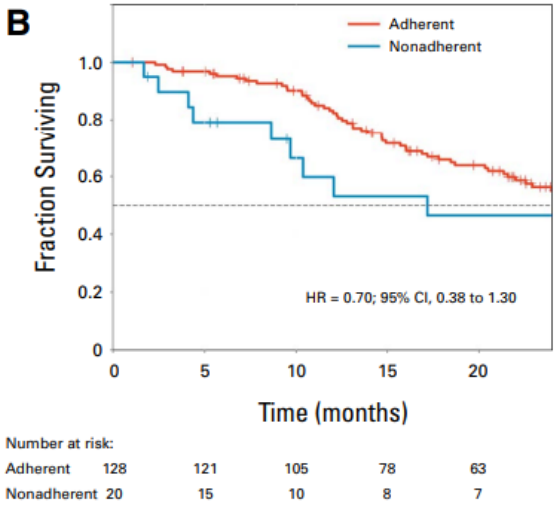
Dennis MJ, et al. *JCO Precis Oncol.* 2025;9:e2400449.

Sub-Optimal Biomarker Testing Leads to Worse Outcomes

A

		Therapy, n (%)		
		Targeted	Nontargeted	Total
Variant, n (%)	Targetable variant	86.3% (n = 201)	13.7% (n = 32)	233
	No targetable variant	4.9% (n = 57)	95.1% (n =1117)	1174
	Total	258	1149	

B



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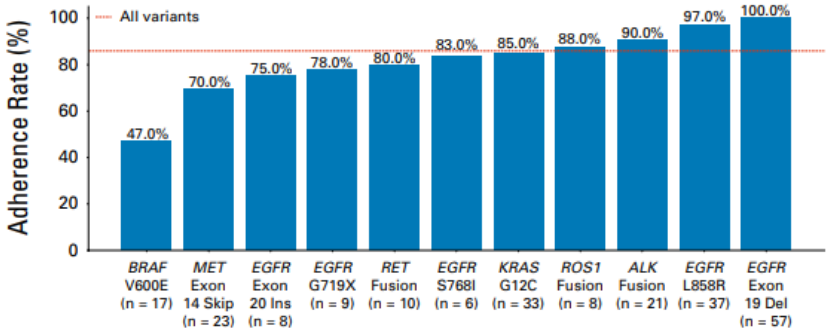

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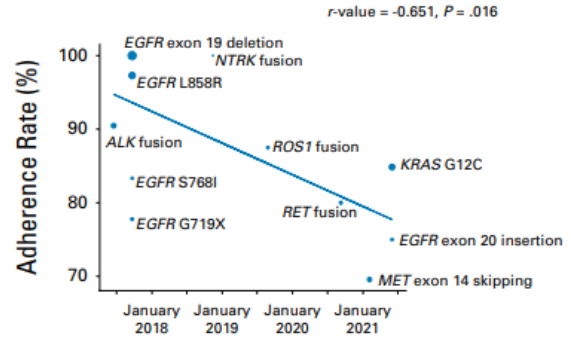
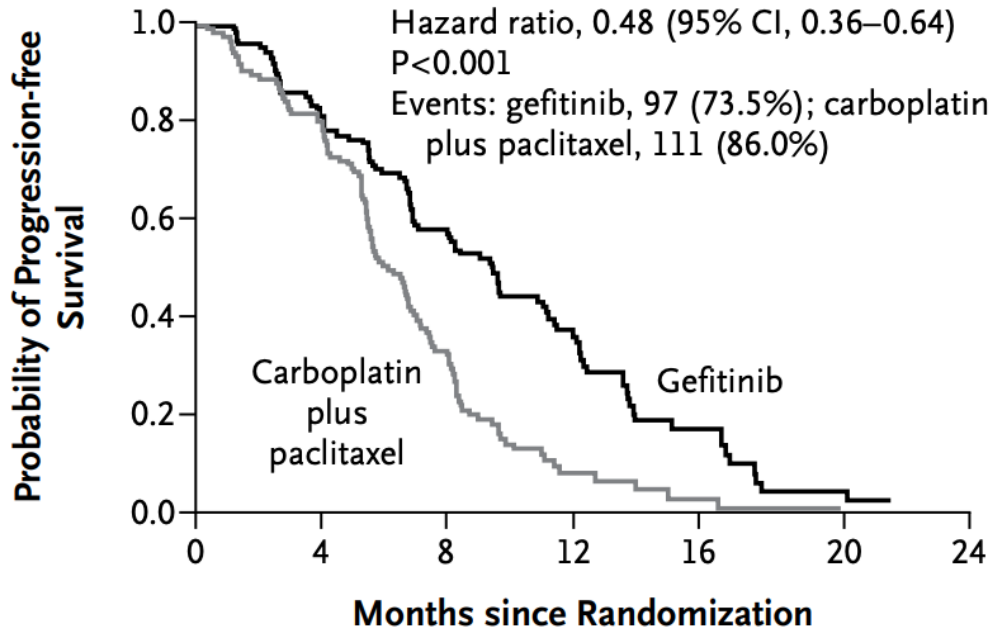


- Approximately 14% of patients with NSCLC who have an actionable genomic alteration do not receive targeted therapy
- Patients who are non-adherent to guidelines have worse overall survival
- There is a lag between when a genomic variant is listed in NCCN and when oncologists start using appropriate targeted therapy

Ben-Shachar R, et al. *JCO Oncol Pract*. 2025:OP2400880.

QoL Is Improved with Proper Treatment Selection

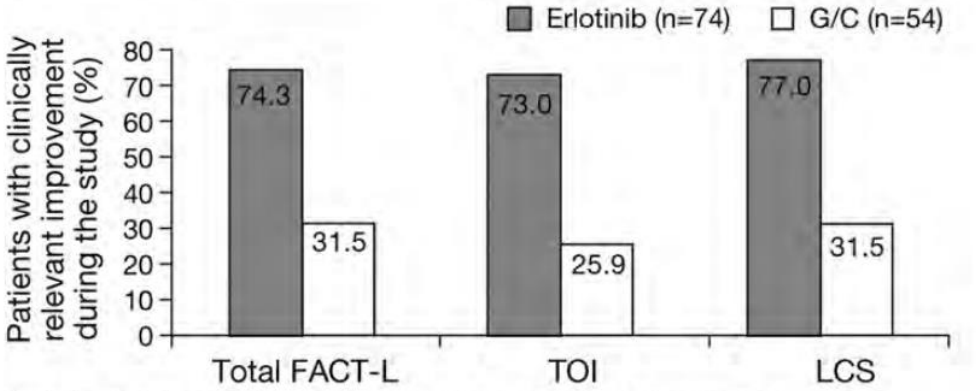
B ***EGFR*-Mutation–Positive**



No. at Risk

Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

	Odds ratio (95% CI)		
Covariates	Total FACT-L	TOI	LCS
PS, smoking history and gender	6.73 (3.01–15.04), $P < 0.0001$	7.46 (3.33–16.72), $P < 0.0001$	7.22 (3.23–16.13), $P < 0.0001$
EGFR mutation type, smoking history and histological type	6.69 (3.01–14.85), $P < 0.0001$	8.07 (3.57–18.26), $P < 0.0001$	7.54 (3.38–16.85), $P < 0.0001$

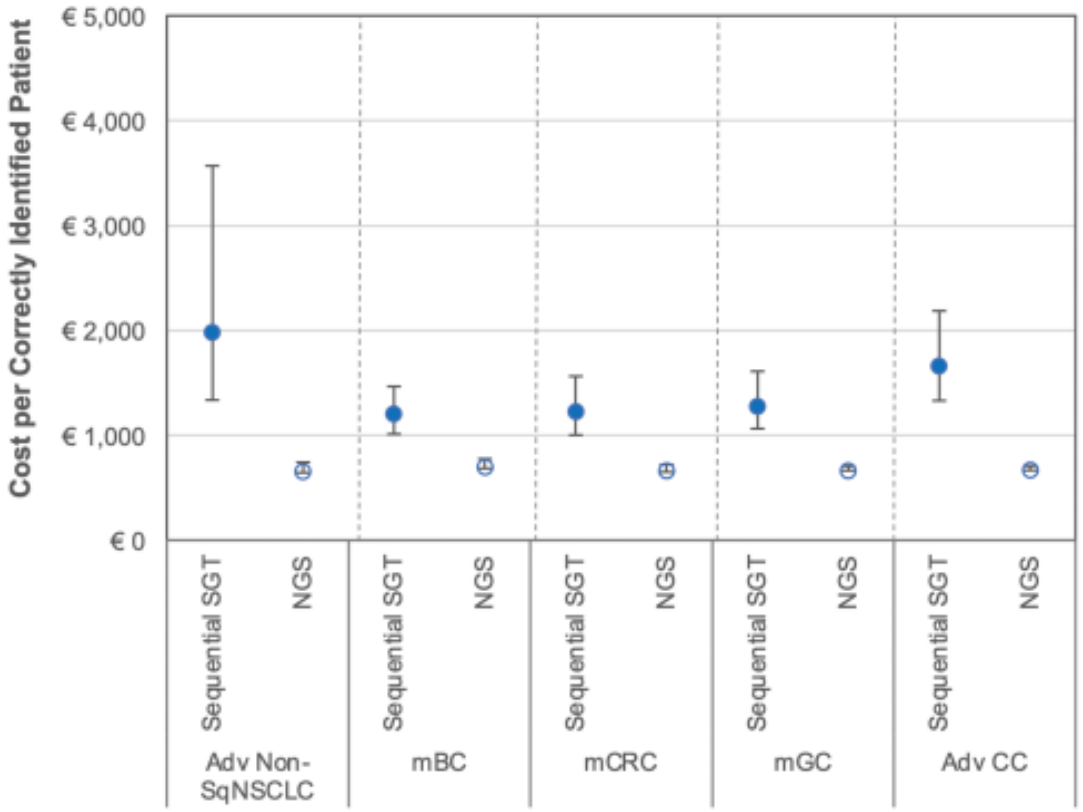


Includes all patients with a baseline and ≥1 post-baseline QoL assessment.

FACT-L = Functional Assessment of Cancer Therapy-Lung. G/C = gemcitabine/carboplatin treatment group. LCS = Lung cancer subscale. PS = performance status. QoL = quality of life. TOI = Trial Outcome Index.

Chen G, et al. *Ann Oncol*. 2013;24(6):1615-1622. Mok TS, et al. *N Engl J Med*. 2009;361(10):947-957.

Economic Impacts of Biomarker Testing



- Broad based molecular profiling (using NGS) is more cost effective than sequential, single gene testing for advanced NSCLC
- Allows for identification of actionable genomic alterations which leads to accurate therapeutic selection!

Figure 2. Tumor types favoring next-generation sequencing (NGS) over sequential single gene testing (SGT) in cost per correctly identified patient. Error bars, 95% CI. Adv, advanced; CC, cholangiocarcinoma; mBC, metastatic breast cancer; mCRC, metastatic colorectal carcinoma; mGC, metastatic gastric cancer; sqNSCLC, squamous non–small cell lung cancer.

Stenzinger A, et al. *Oncologist*. 2023;28(5):e242-e253.

CLINICAL PATHWAYS CONGRESS | CANCER CARE BUSINESS EXCHANGE

Key Learning Points

- Real world biomarker testing rates are below what is recommended within consensus guidelines for metastatic NSCLC
  - Approximately 14% of patients with NSCLC who have an actionable genomic alteration do not receive targeted therapy
- Incorrect therapy selection leads to worse outcomes
- There is both a quality of life and financial benefit to correctly identifying actionable genomic alterations and selecting the appropriate targeted therapy in NSCLC

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THANK YOU

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