



Multidisciplinary Approaches to Cancer Symposium

The Next Frontier for Systemic Therapy for Non- Small Cell Lung Cancer : Where Do We Go from Here?

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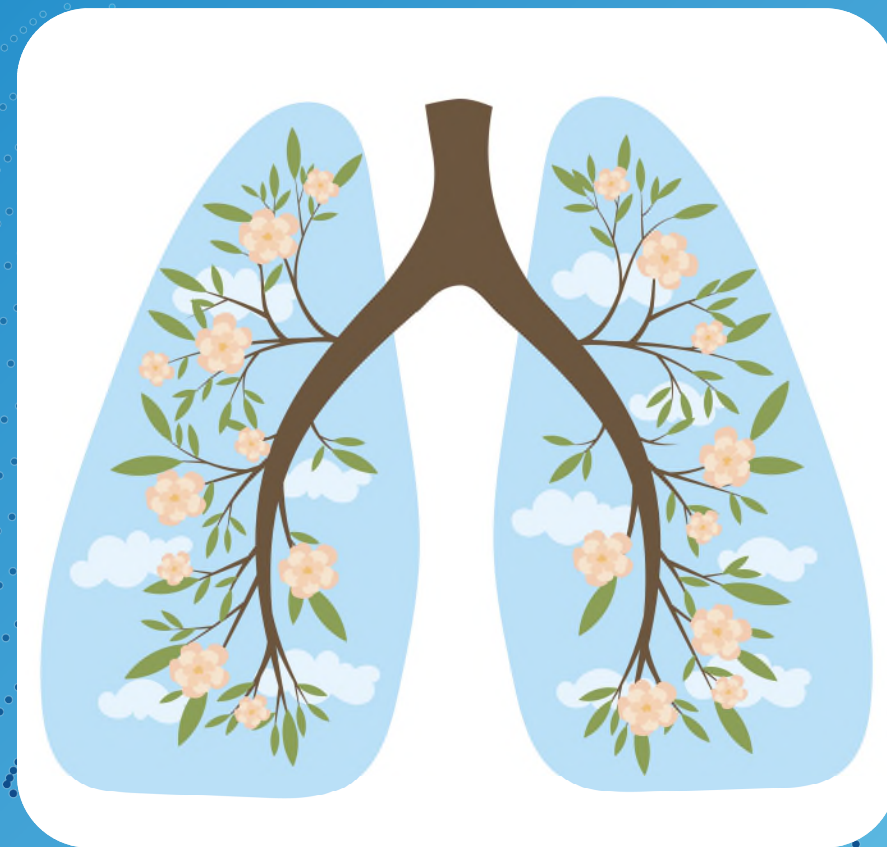
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October 1, 2026



Disclosures

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

I have the following relevant financial relationships to disclose: (for the past 24 months)

- Employee of: N/A
- Consultant for: AbbVie, Amgen, AnHeart, Astra Zeneca, Black Diamond, BMS, Boehringer Ingelheim, Daiichi Sankyo, Exact, Foresight, Foundation Medicine, Guardant, Genentech, Gilead, Guardant, Immunity Bio, Jazz, JNJ, Merck, Nuvalent, Nuvation, Onvivo, Pfizer, Regeneron, Summit, Takeda, Taiho, Tempus
- Speaker's Bureau for: N/A
- Stockholder in: N/A
- Honoraria from: AbbVie, Amgen, AnHeart, Astra Zeneca, Black Diamond, BMS, Boehringer Ingelheim, Daiichi Sankyo, Exact, Foresight, Foundation Medicine, Guardant, Genentech, Gilead, Guardant, Immunity Bio, Jazz, JNJ, Merck, Nuvalent, Nuvation, Onvivo, Pfizer, Regeneron, Summit, Takeda, Taiho, Tempus
- I served as DSMB chair for a Janssen study, uncompensated.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.



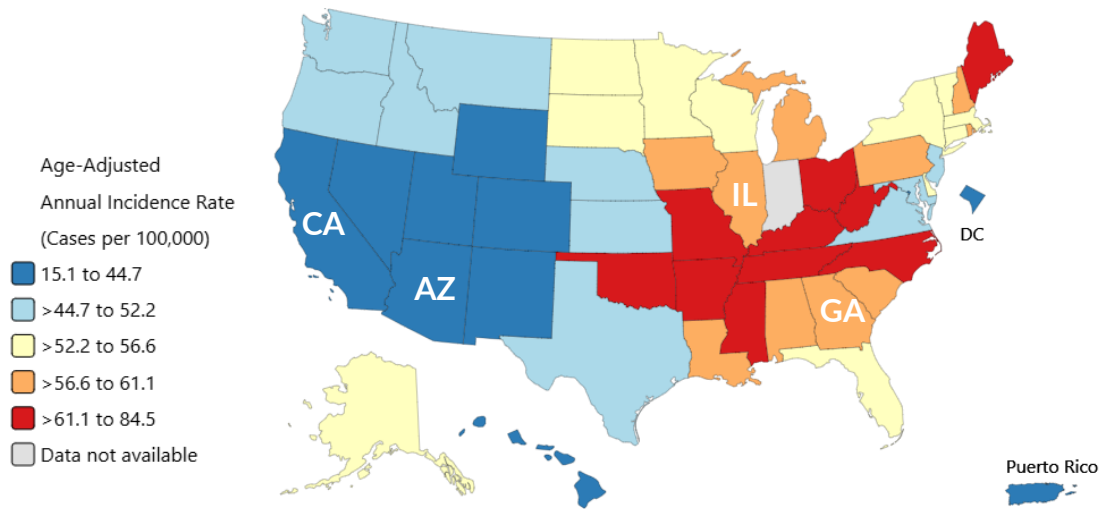
Lung Cancer: remains the #1 cause of cancer related deaths in the USA

A common cancer fraught with poor survival rates, disparities in outcomes, and funding challenges.

Cancer statistics, 2026

Estimated Deaths	Male			Female		
	Lung & bronchus	63,040	19%	Lung & bronchus	61,950	21%
	Prostate	36,320	11%	Breast	42,140	14%
	Colon & rectum	30,110	9%	Pancreas	25,510	9%
	Pancreas	27,230	8%	Colon & rectum	25,120	8%
	Liver & intrahepatic bile duct	19,650	6%	Uterine corpus	14,450	5%
	Leukemia	13,900	4%	Ovary	12,450	4%
	Esophagus	12,940	4%	Liver & intrahepatic bile duct	11,330	4%
	Urinary bladder	12,640	4%	Leukemia	10,010	3%
	Non-Hodgkin lymphoma	11,710	4%	Brain & other nervous system	8,380	3%
	Kidney & renal pelvis	10,200	3%	Non-Hodgkin lymphoma	8,260	3%
	All sites	327,290		All sites	298,850	

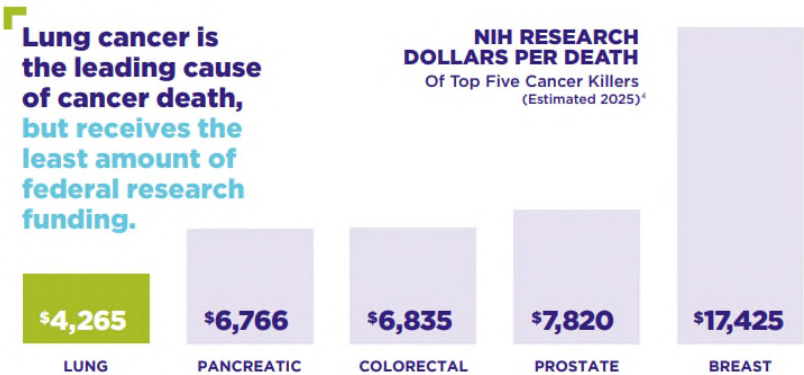
Lung Cancer Incidence Rates by State
(2017-2021)



Created by statecancerprofiles.cancer.gov on 02/15/2026 9:55 pm.

CA A Cancer J Clinicians, Volume: 76, Issue: 1, First published: 13 January 2026, DOI: (10.3322/caac.70043)

- ~20% of all cancer deaths in the USA.
- Global burden of lung cancer deaths >1 million/year.
- Almost 50% of current patients are diagnosed with metastatic/stage 4 disease, where 5 year overall survival rate is only ~10%.

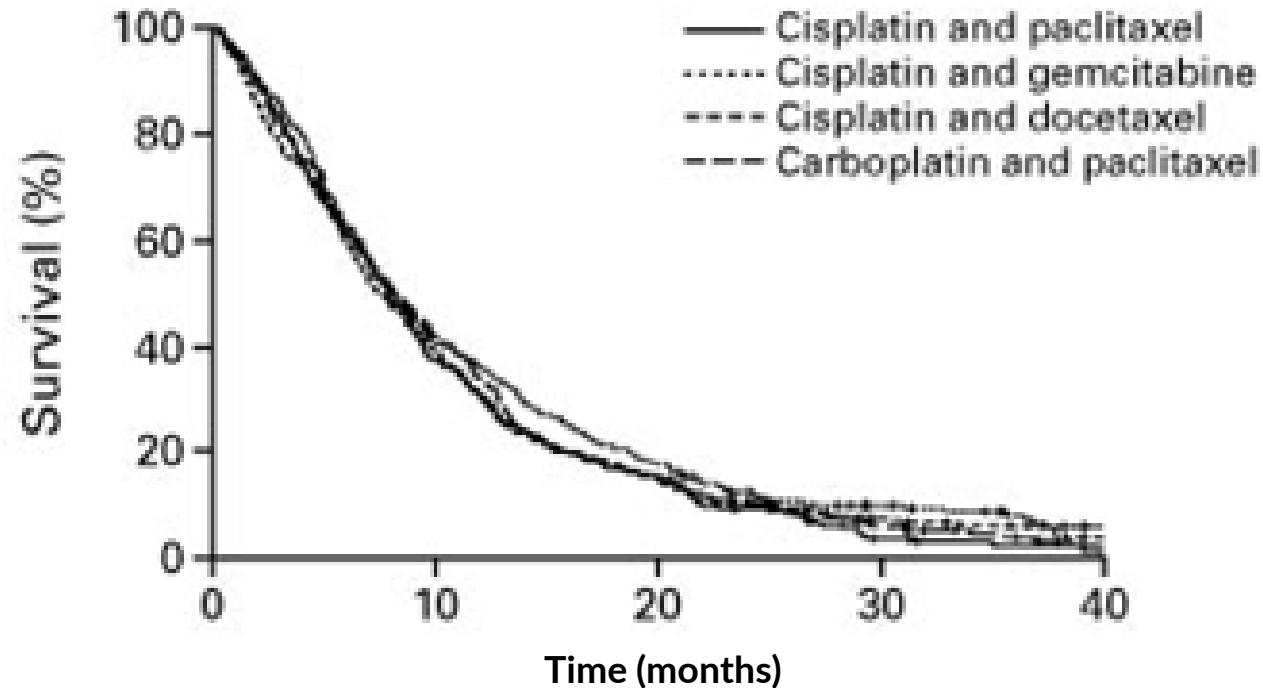


source: GO2 Foundation



Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer

Joan H. Schiller, M.D., David Harrington, Ph.D., Chandra P. Belani, M.D., Corey Langer, M.D., Alan Sandler, M.D., James Krook, M.D., Junming Zhu, Ph.D., and David H. Johnson, M.D. for the Eastern Cooperative Oncology Group



State of the art in 2002

- No breakdown by tumor histology
- No biomarker stratification



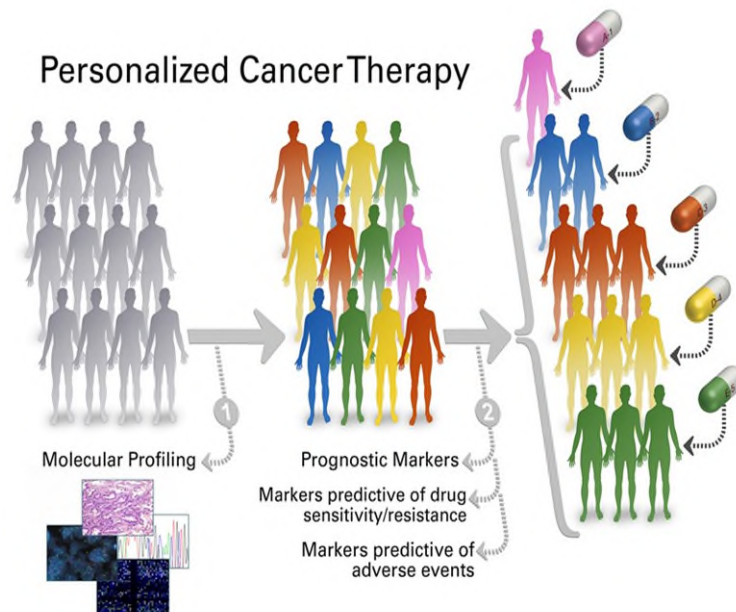
Response rate – 19%

Median Time to Progression – 3.7 months

Median Overall Survival – 8 months

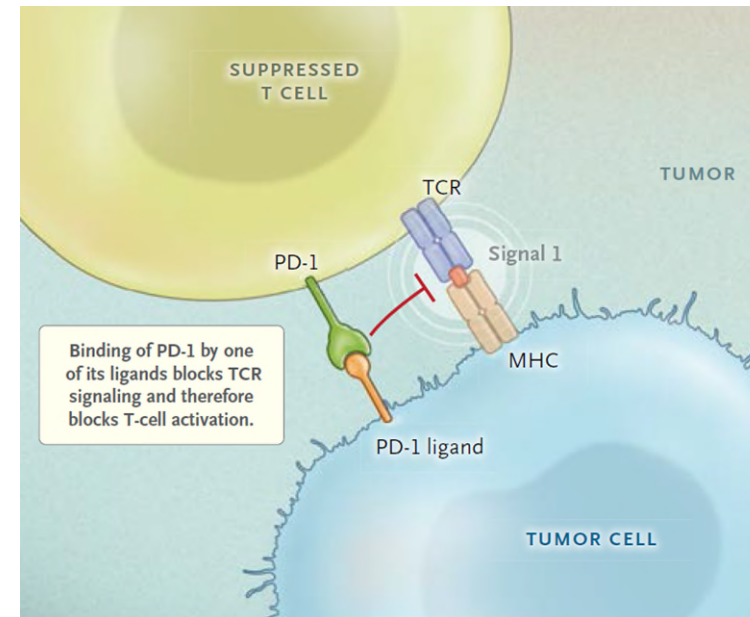
Where do we go from here?

Emergence of Two Treatment Paradigms Have Transformed Lung Cancer Care



Targeted Therapies

Therapies designed to inhibit the function of hyper-activated mutant “driver” oncogenes.



Immune Checkpoint Inhibitors (ICIs)

Therapies aimed to activate anti-tumor immune response.

Treatment for NSCLC has become a sequence of biologic decisions



The “next frontier” is not one target or one drug.
It is a learning system, delivered with equity.

Four transformations that help define current treatment paradigms for NSCLC

Earlier detection

LDCT screening and improved staging create more curative opportunities.

Systemic therapy moves earlier

Adjuvant, neoadjuvant and perioperative strategies redefine cure.

Actionable biology

EGFR, ALK, ROS1, BRAF, MET, RET, NTRK, HER2 and KRAS reshape treatment.

Durable immunity

Checkpoint blockade produces long survival tails for a subset.

Progress is real. Delivery remains uneven.



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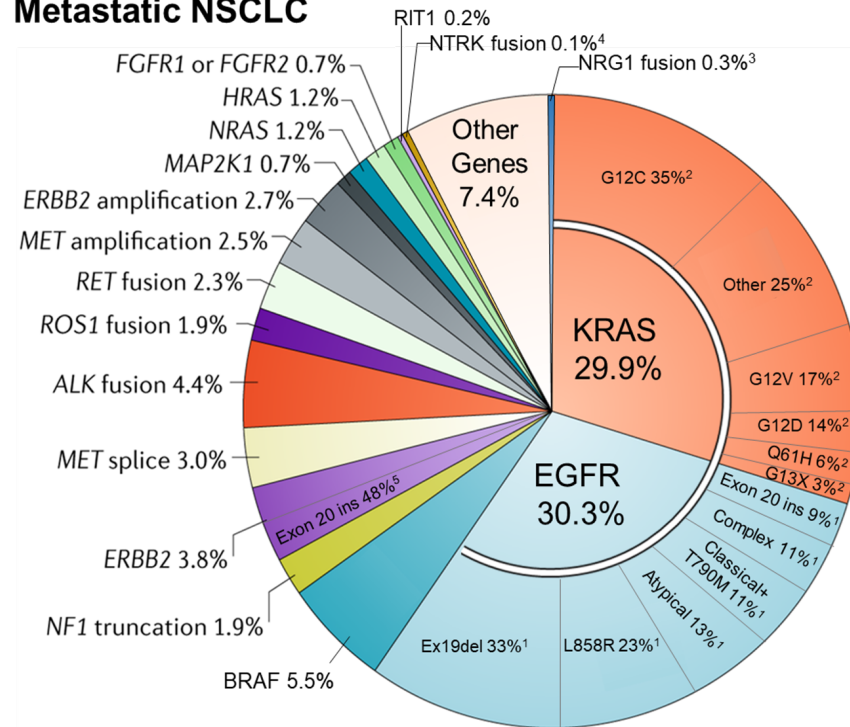
Checkpoint blockade produces long survival tails for a subset.

Current status and the next frontier of biomarker driven care in treatment of NSCLC.



Biomarker Driven Care in Non-Small Cell Lung Cancer (2026)

Metastatic NSCLC



Current status of care:

- Multi-panel gene testing (DNA/RNA) + IHC for select therapeutic markers on tumor sample (+/- ctDNA)
- Single biomarker → therapeutic selection

Targets with FDA-approved biomarker driven therapies

Gene biomarkers

- ALK fusions
- BRAF p.V600E
- EGFR “typical” (ex19del, L858R)
- EGFR “non-classical” (L861Q, G719x, S786I)
- EGFR exon 20 insertions
- HER2 kinase domain
- KRAS p.G12C
- MET exon14 skipping alterations
- NRG1 fusions
- NTRK 1/2/3 fusions
- RET fusions
- ROS1 fusions

Proteins

- PD-L1 expression (IHC)
- HER2 expression (IHC)
- MET expression (IHC)

Adapted from Skoulidis and Heymach 2019 Nat Rev Can

¹ Robichaux et al 2020 WCLC

² Mack et al 2020 Cancer

³ Jonna et al 2019 Clin Can Res

⁴ Russo et al 2020 Precis Cancer Med

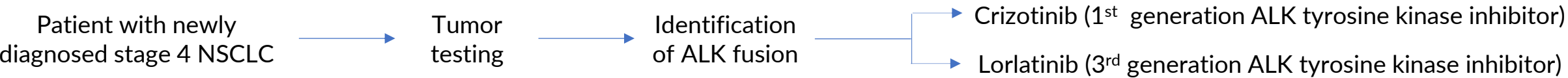
⁵ Robichaux et al 2019 Cancer Cell



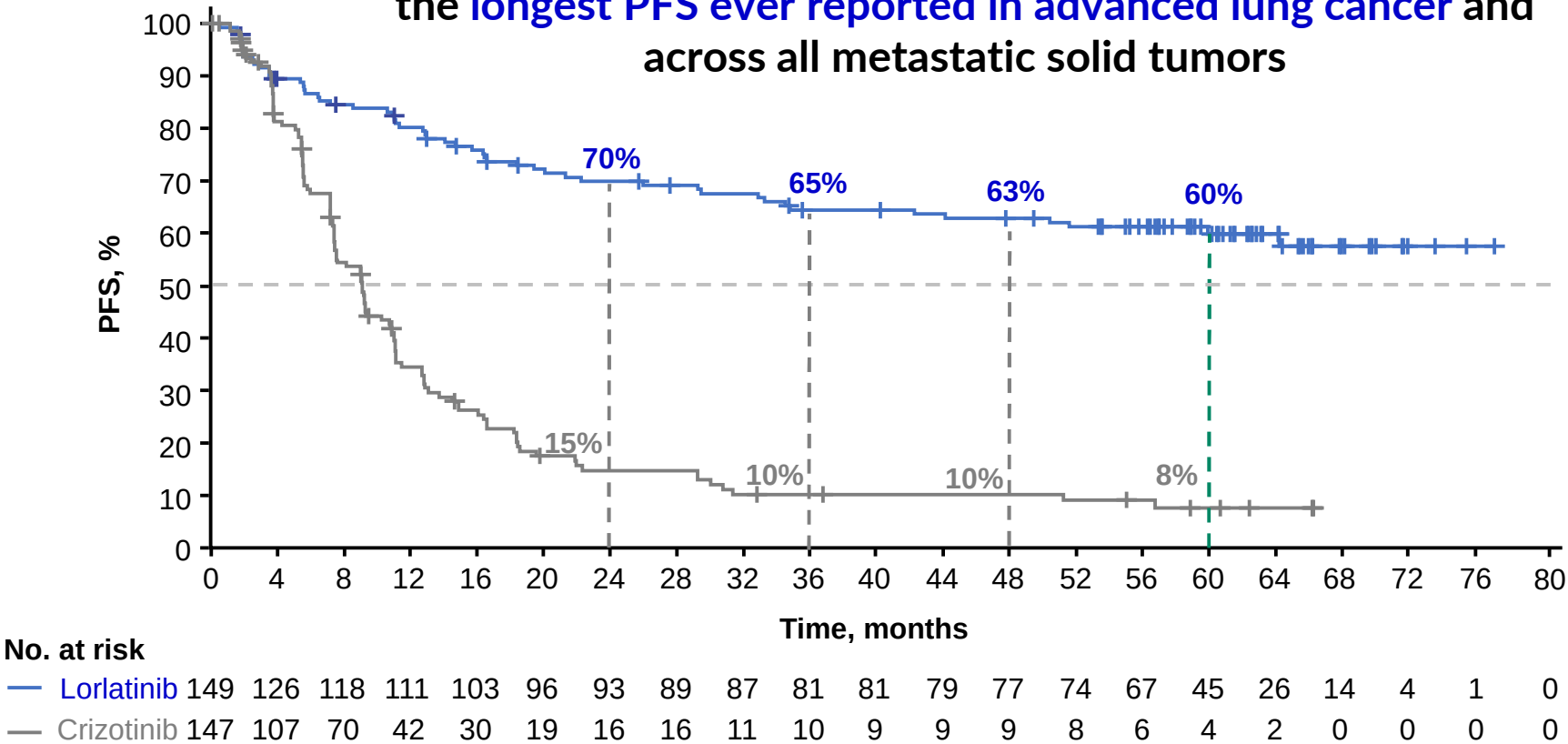
Current biomarker matched FDA-approved drugs in NSCLC

ALK fusions - Alectinib (2nd gen TKI) - Brigatinib (2nd gen TKI) - Ceritinib (2nd gen TKI) - Crizotinib (1st gen TKI) - Ensartinib (2nd gen TKI) - Lorlatinib (3rd gen TKI)	BRAF V600E mut - Dabrafenib - Dabrafenib + Trametinib - Encorafenib + binimetinib - Vemurafenib	EGFR ex19del, L858R - Afatinib (2nd gen TKI) - Amivantamab (EGFR/MET bispecific ab) - Dacomitinib (2nd gen TKI) - Erlotinib (1st gen TKI) - Gefitinib (1st gen TKI) - Lazertinib (3rd gen TKI) - Osimertinib (3rd gen TKI)	EGFR exon 20 insertions - Amivantamab (EGFR/MET bispecific ab) - Sunvozertinib	EGFR ‘uncommon’ mut Afatinib (2nd gen TKI)
HER2 mut - Sevabertinib - Trastuzumab Deruxtecan - Zongertinib	KRAS G12C mut - Adagrasib (1st gen inhibitor) - Sotorasib (1st gen inhibitor)	MET exon 14 skipping mut - Capmatinib (2nd gen inhibitor) - Crizotinib (1st gen inhibitor) - Tepotinib (2nd gen inhibitor)	NRG1 fusions Zenocutuzumab (HER2/HER3 bispecific)	NTRK 1/2/3 fusions - Entrectinib - Larotrectinib - Repotrectinib
RET fusions - Pralsetinib - Selpercatinib	ROS1 fusions - Crizotinib (1st gen TKI) - Entrectinib (2nd gen TKI) - Repotrectinib (2nd gen TKI) - Taletrectinib (3rd gen TKI) - Zidesamtinib (4th gen TKI)	Protein Biomarkers MET expression by IHC HER2 expression by IHC PD-L1 expression by IHC - Telisotuzimab Vedotin - Trastuzumab Deruxtecan - Stratification of 1st line use of PD1/PDL1 immune checkpoint inhibitor antibodies, such as pembrolizumab and nivolumab		

An example of the success of biomarker driven therapies: First line lorlatinib in patients with stage IV ALK fusion positive NSCLC



Lorlatinib leads to a **>7 years of PFS** in 1L ALK+ aNSCLC, the **longest PFS ever reported in advanced lung cancer** and across all metastatic solid tumors

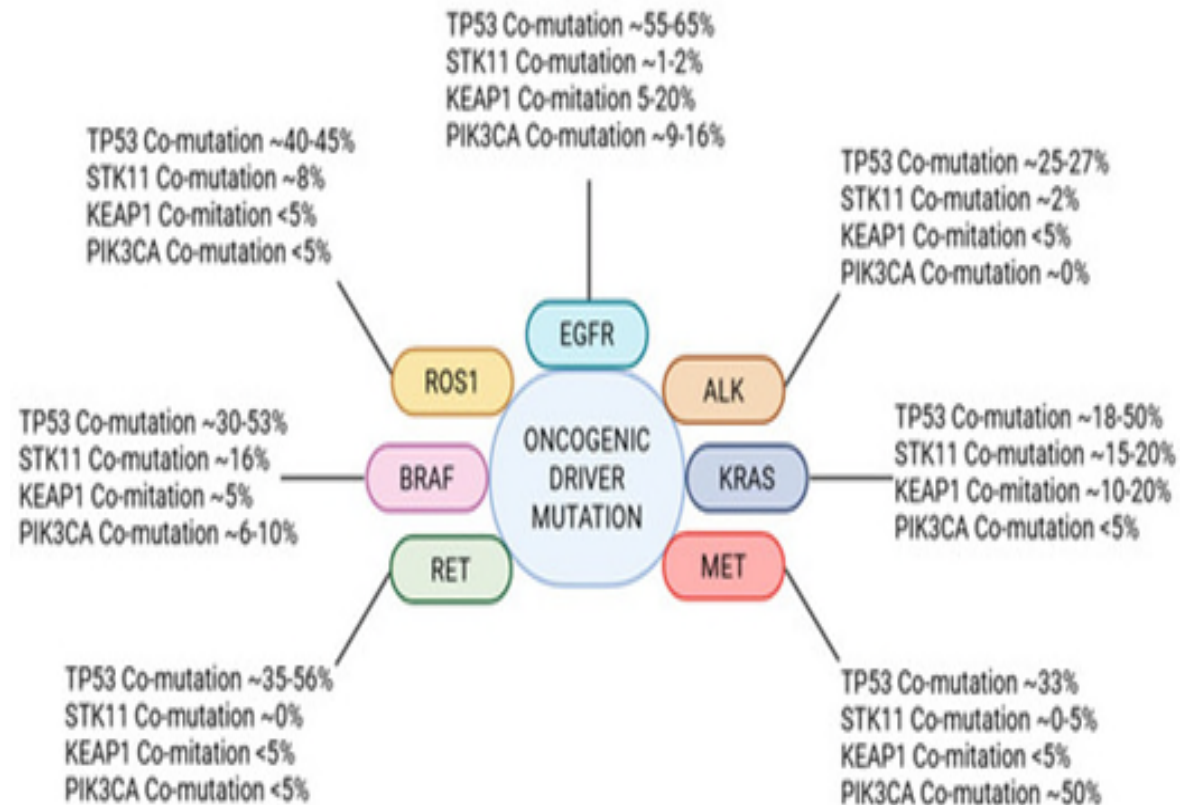


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
mPFS (95% CI), months	NR (64.3–NR)	9.1 (7.4–10.9)
HR (95% CI)	0.19 (0.13–0.27)	

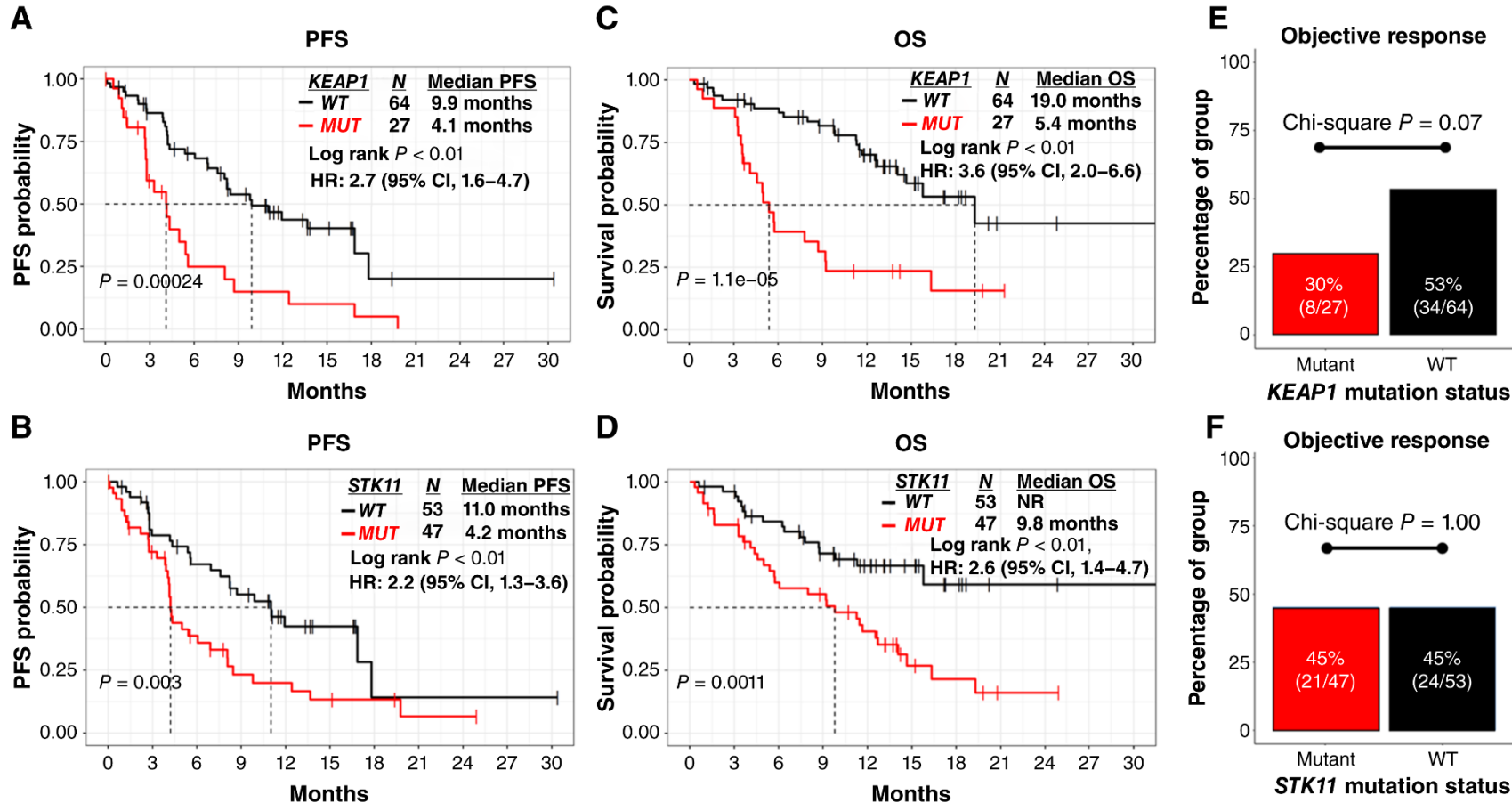
Median f/u time = 60.2 months

Challenging the current status of biomarker driven care in NSCLC: is the single gene → single drug paradigm sufficient?

- Cancer is a disease of multiple mutations
- Driver mutations and tumor suppressors commonly coexist with additional genetic alterations that may influence tumor behavior and therapeutic outcomes.
- Co-mutations may modify:
 - Tumor aggressiveness
 - Immune micro-environment
 - Drug sensitivity or resistance
 - Risk of relapse
- Co-mutations serve as key drivers of tumor heterogeneity

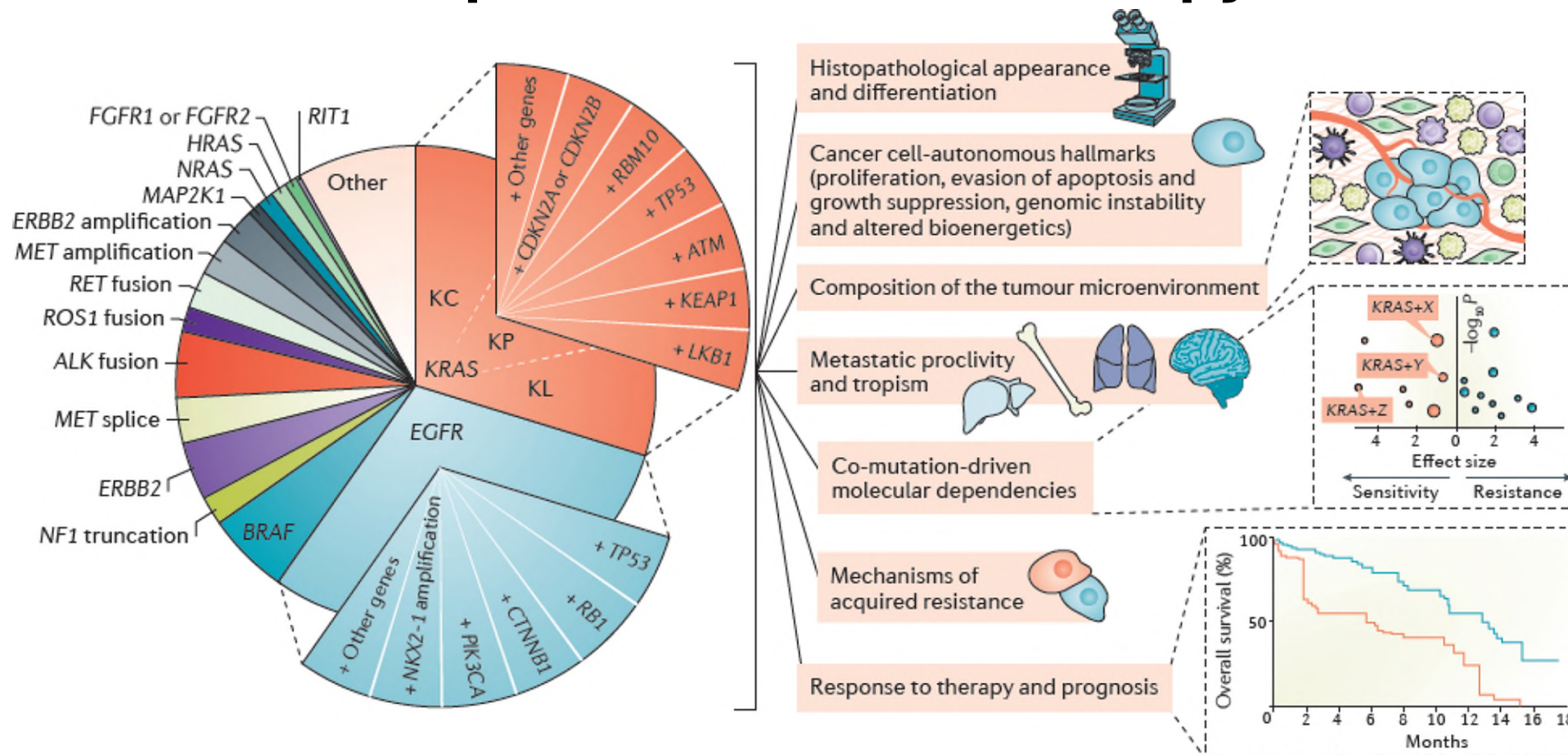


Clinical outcomes to treatment with the KRAS G12C inhibitor, adagrasib, according to KEAP1 and STK11 co-mutation status



- Data from the KRYSTAL-1 trial
- KEAP1 mutant and STK11 mutant → define patients with KRAS G12C-mutant NSCLC with worse outcomes to adagrasib.**
- Patients whose tumors have increased NRF2 signaling—defined by transcriptome sequencing—also have significantly shorter PFS and OS upon treatment with adagrasib (PFS 4.2 months; OS 6.5 months) → data not shown.

The 'Next Frontier' in Actionable Biology / Biomarker Development in NSCLC Therapy



Next-generation model for the molecular stratification for NSCLC:

Inform personalized treatment strategies using integration of multiple demographic, histopathological, and multi-omic data points

The 'Next Frontier' will also require innovative medicinal chemistry to build therapies / combinations beyond the classic TKI and checkpoint paradigms



“Success” will require better target biology, therapeutic index, and biomarker-defined selection.



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Actionable biology

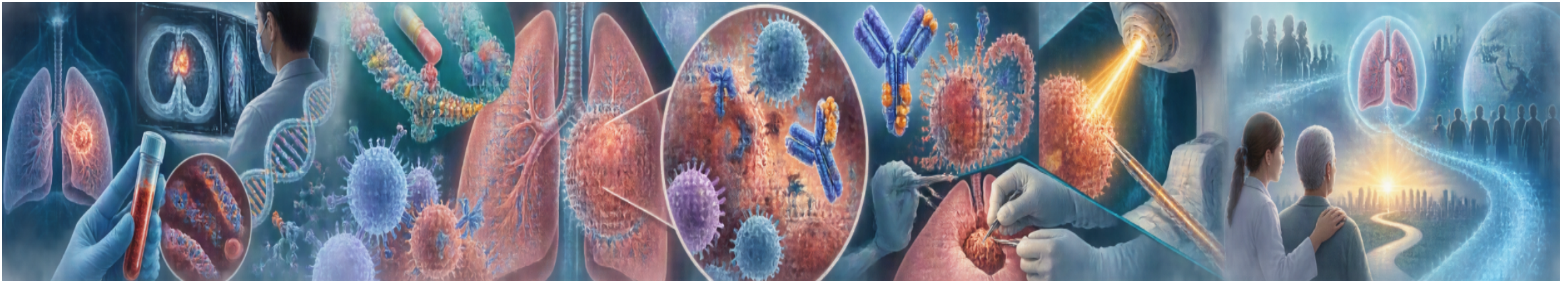
EGFR, ALK, ROS1, BRAF, MET, RET, NTRK, HER2 and KRAS reshape treatment.

Durable immunity

Checkpoint blockade produces long survival tails for a subset.

Current status and the next frontier of early stage disease in NSCLC.

Precision care for NSCLC now spans the disease continuum



LOCALIZED

surgery / SBRT

RESECTABLE

perioperative or adjuvant
systemic therapy

STAGE III

multimodality +
consolidation

METASTATIC

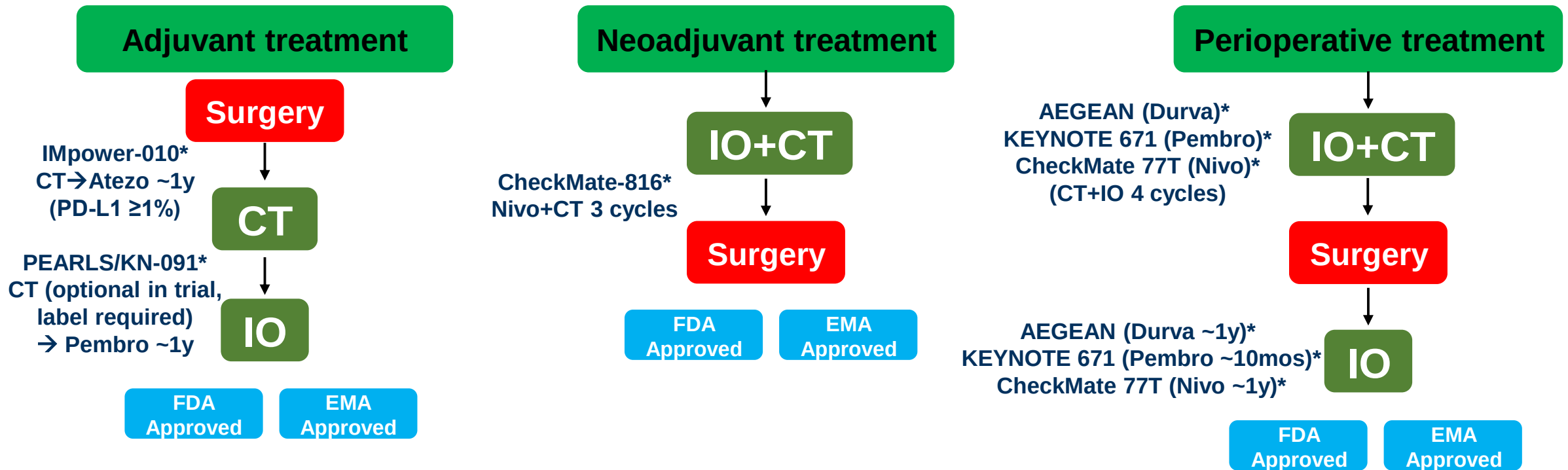
driver-directed or immune-
based therapy

PROGRESSION

mechanism-led sequencing
+ local control

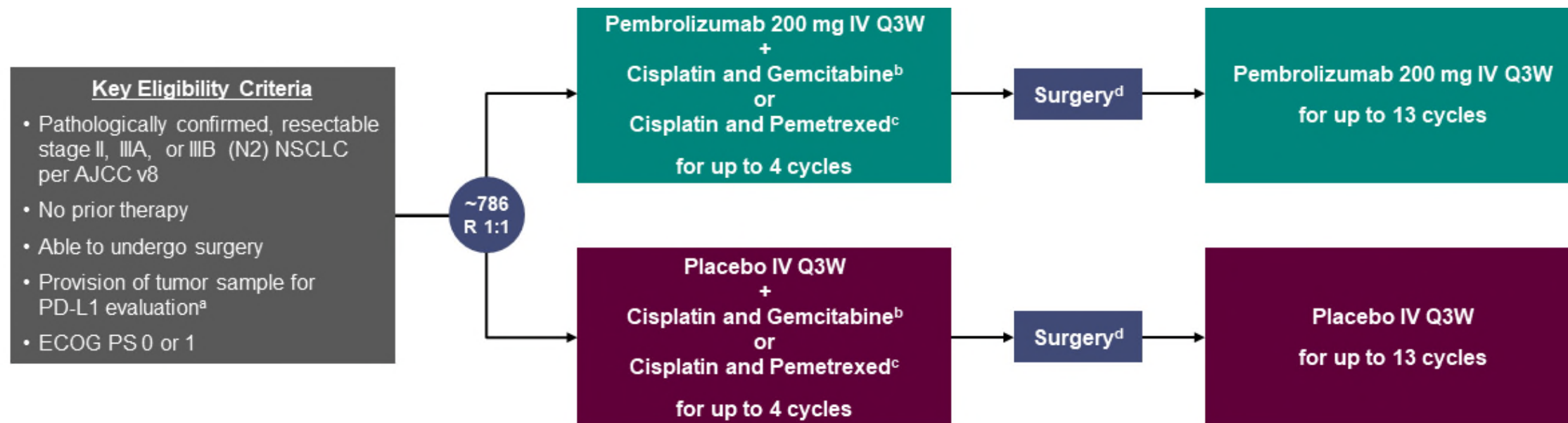
- **Significant advances in utilization of both targeted therapies and immunotherapy in early stage NSCLC.**
- **For sake of time, will focus on advances in immunotherapy.**

Treatment landscape for early-stage resectable NSCLC with no AGAs or IO-sensitive AGAs



- AGAs: actionable genomic alterations
- *SOC regimen
- CT: chemotherapy
- IO: immuno-oncology therapy

KEYNOTE-671: Perioperative pembro in resectable NSCLC



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS^a (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety



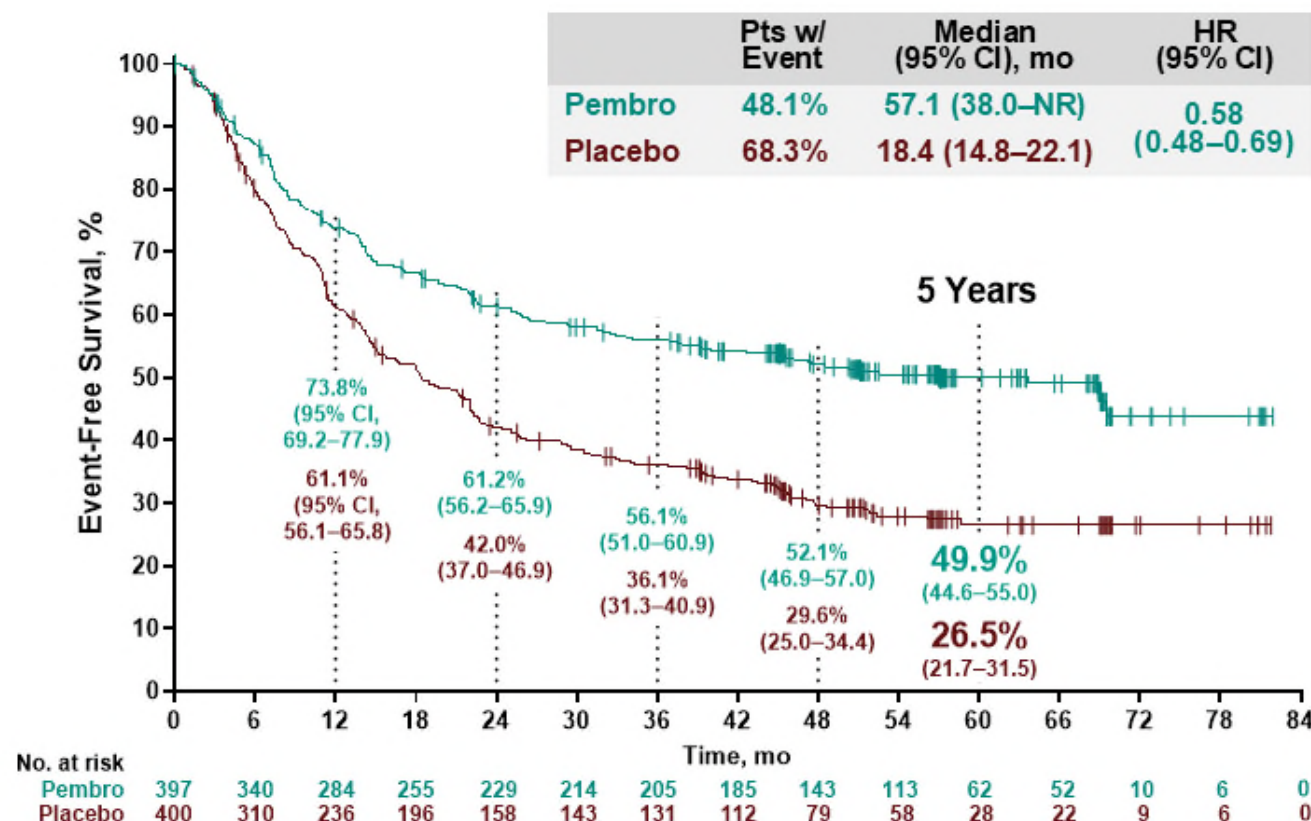
Neoadjuvant pembrolizumab + chemo followed by adjuvant pembrolizumab is approved in the US for patients with stage II, IIIA, or IIIB (T3-4N2) NSCLC



Neoadjuvant pembro + chemo followed by pembro monotherapy as adjuvant treatment for resectable NSCLC at high risk of recurrence in adults.

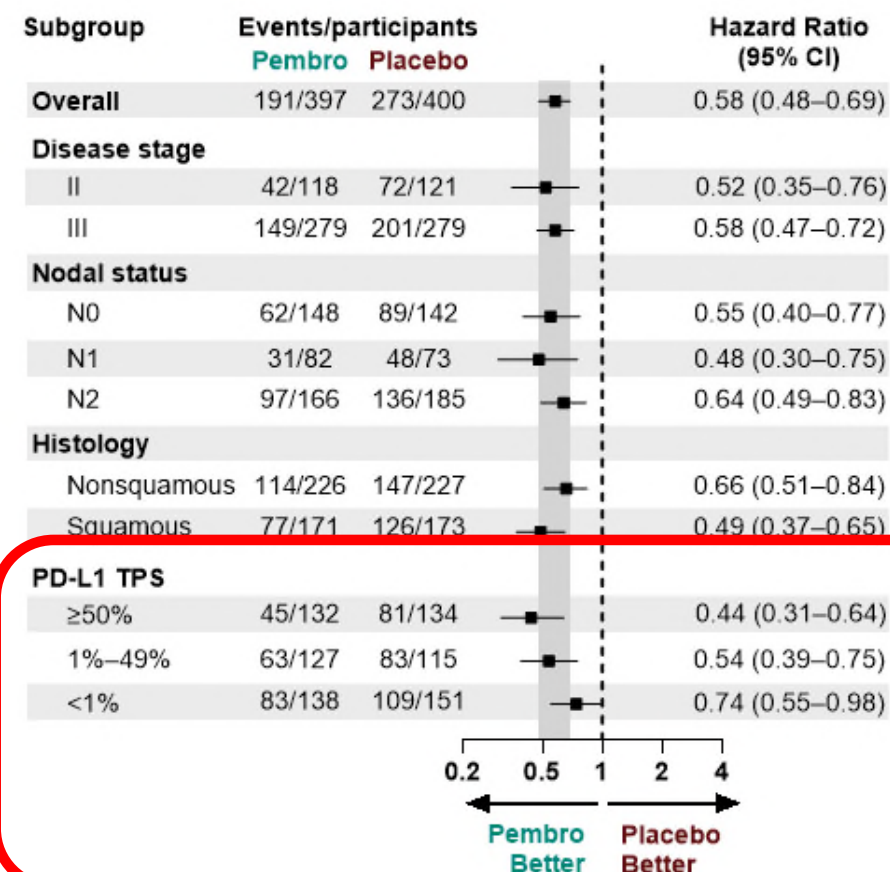
KEYNOTE 671 Perioperative pembro: 5 yr EFS updates

Overall Population



^aAssessed per RECIST version 1.1 by investigator assessment.
Median time from randomization to data cutoff was 60.4 (range, 42.6–85.8) months.
Data cutoff date: July 3, 2025.

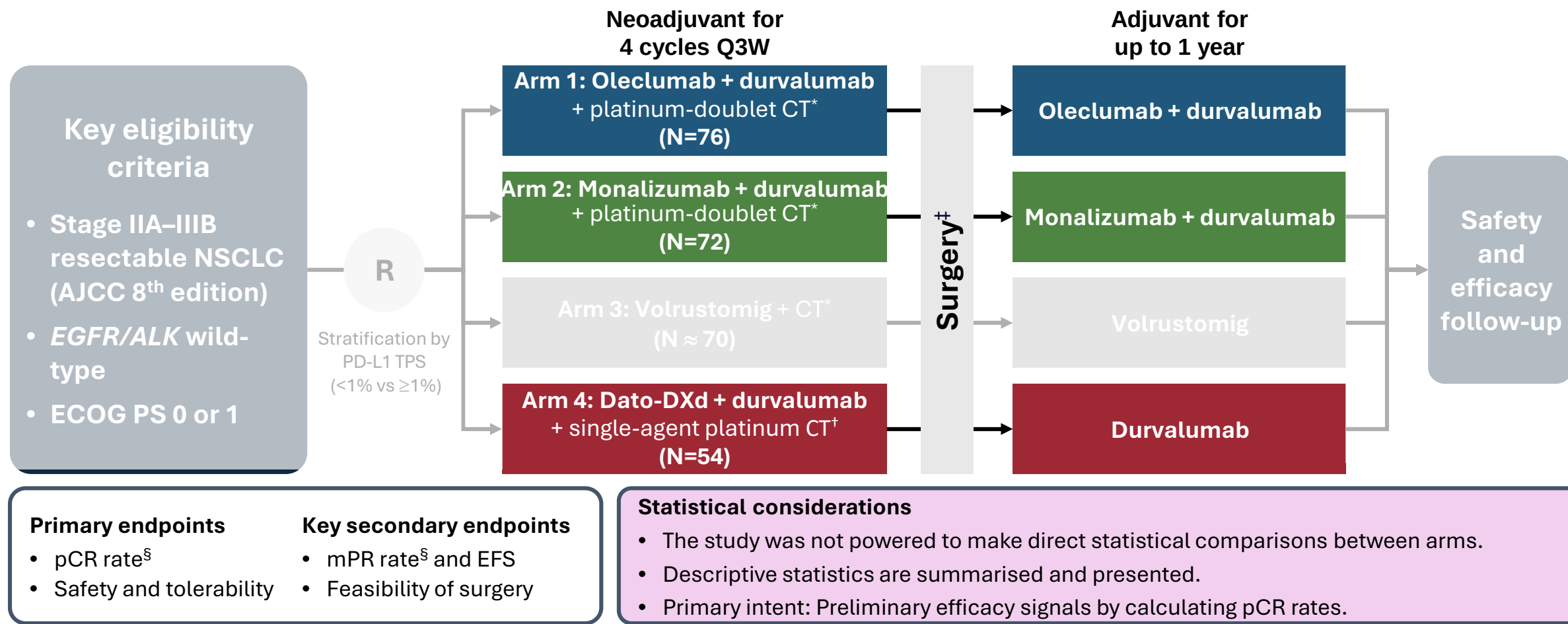
Key Subgroups



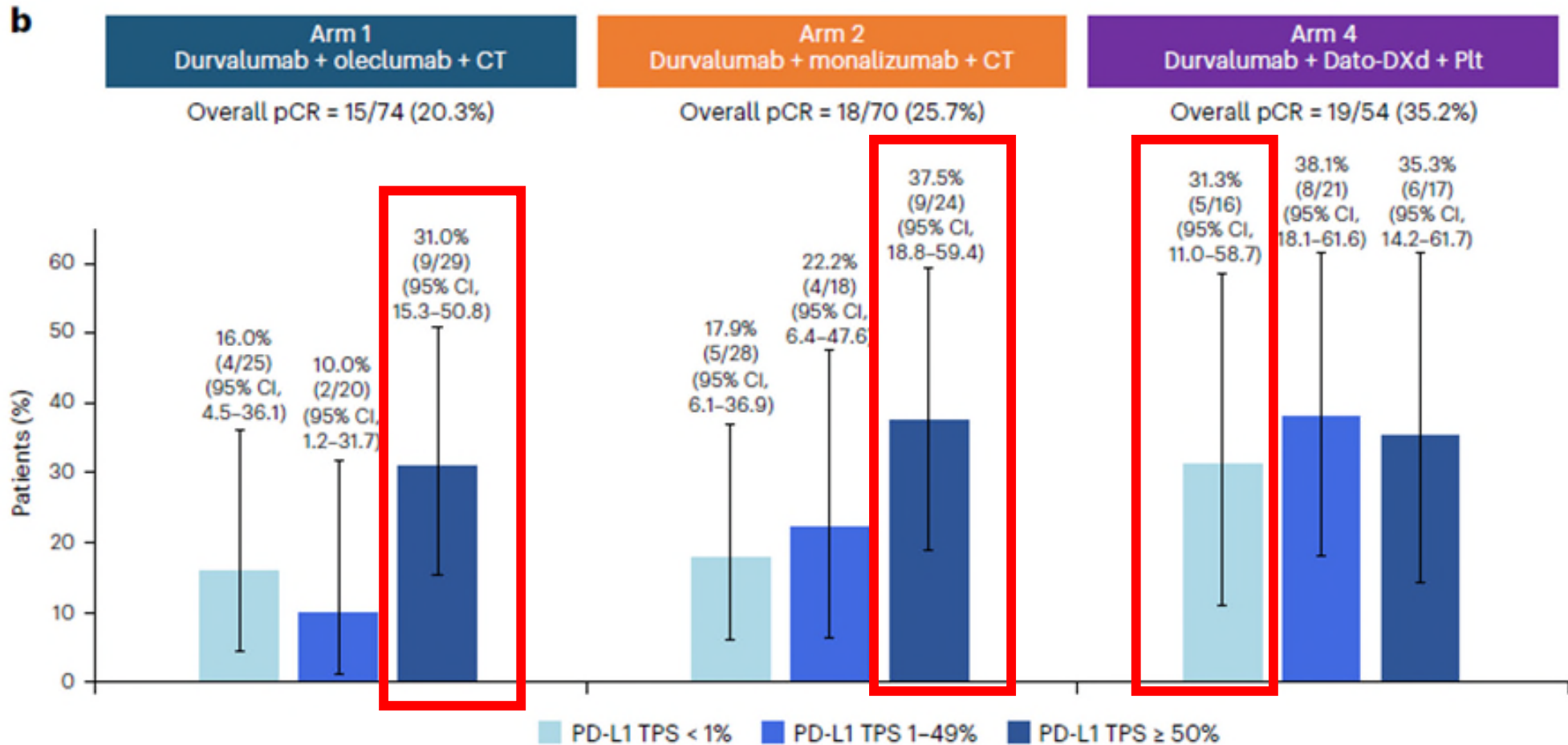
**Challenging the current status of
chemo/PD(L)1 perioperative treatment in
NSCLC:**

**Can therapy intensification drive increased
pCR rates in biomarker select group,
especially PD-L1 low tumors?**

NeoCOAST-2: Multi-arm platform study of novel perioperative treatment combinations in NSCLC



NeoCOAST-2: pCR rates across baseline PD-L1 TPS in mITT population



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Four “ceilings” that limit full deployment of existing and emerging advances in NSCLC

Incomplete Uptake of Screening

Low rates of lung cancer screening for USPSTF screen eligible patients.
(Screening dependent on tobacco history)

Therapeutic Resistance

Heterogeneity, bypass signaling, lineage plasticity, tumor heteroclonality

Lack of model systems that recapitulate patient biology

Preclinical models for enhanced precision.

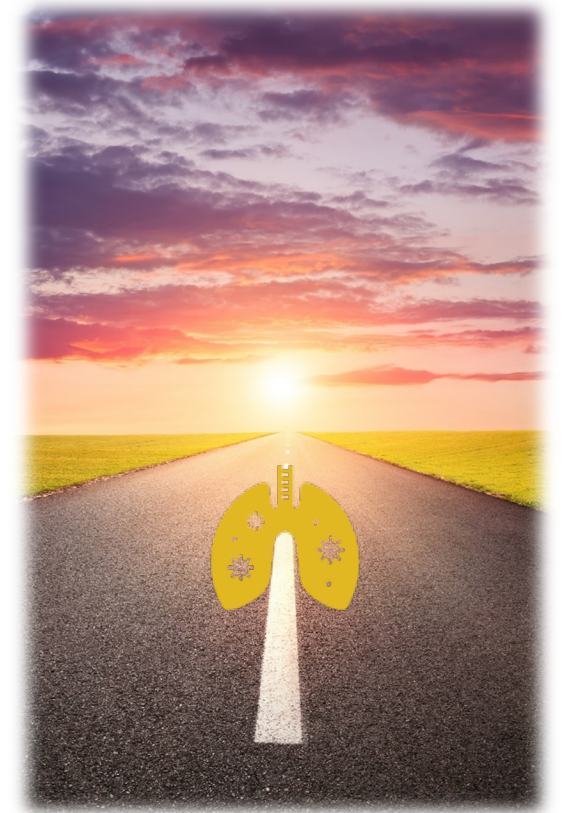
Lack of Access to care

Testing, trial access and subspecialty care remain inconsistent
Insurance (or lack thereof)



On the Horizon for Systemic Therapies for Patients with Lung Cancer

- Next generation targeted therapies → increased on target potency
- Novel targets
 - KRAS non-G12C mutations (i.e., KRAS G12D, G12V, Q61H)
 - SMARCA4
 - MTAP deletions
 - RBM10
 - SCLC protein biomarkers (DLL3, SEZ6, ASCO1, NEUROD1)
 - Others...
- Improved biomarker stratification → moving beyond one target : one drug approach. (example: concomitant KRAS G12C and STK11 mutations).
- Novel classes of systemic therapies
 - PROTACS (targeted protein degraders)
 - Bi- and Tri-specific antibodies
 - Cellular therapies (CAR-T, CAR-NK)
 - Cancer vaccines
- Enhanced monitoring with “liquid biopsy” surveillance → blood tests to help us track disease, monitor response and resistance.
- MRD testing in early and late stage disease → and, importantly, clinical utility of testing MRD beyond prognostic information.



This is a small flavor of a huge topic!
Thank you for your kind attention!

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