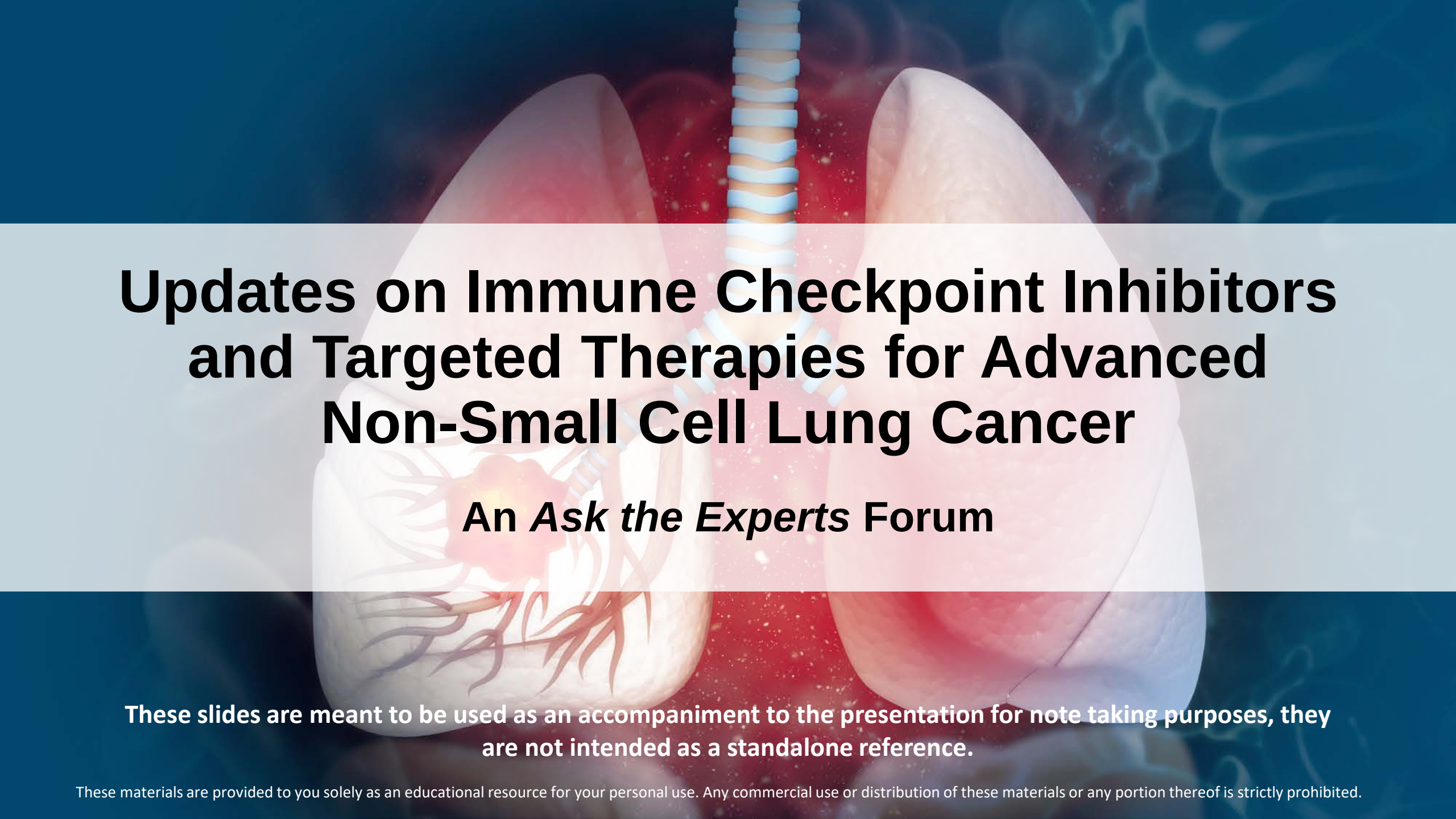
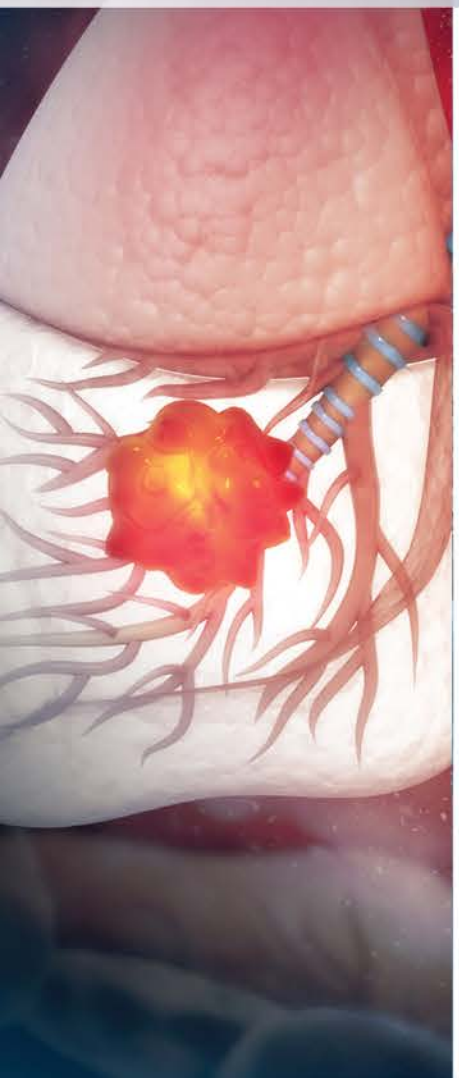


Updates on Immune Checkpoint Inhibitors and Targeted Therapies for Advanced Non-Small Cell Lung Cancer

An *Ask the Experts* Forum

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by
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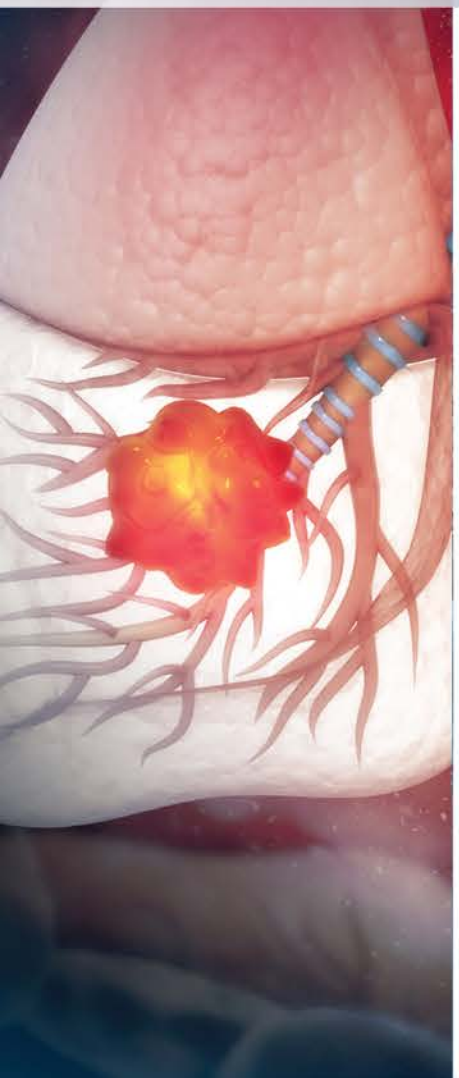
Faculty

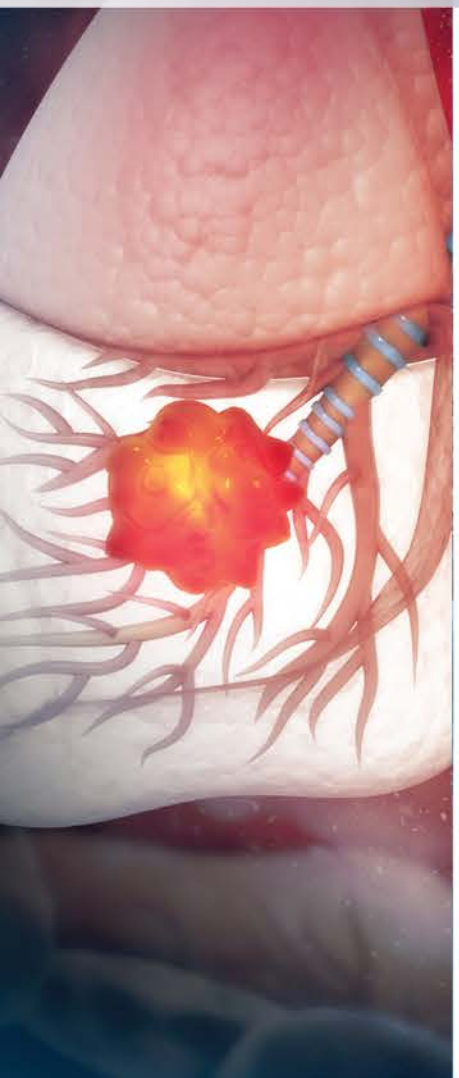


Val R. Adams, PharmD, FCCP, FHOPA, BCOP

Associate Professor of Pharmacy Practice & Science
Markey Cancer Center at the University of Kentucky
Lexington, KY

Dr. Adams is an Associate Professor in the department of Pharmacy Practice and Science in the College of Pharmacy at the University of Kentucky. He is on the graduate faculty and is a member of the Markey Cancer Center where he has a clinical practice site. He co-chairs the protocol review and committee for the NCI Designated Markey Cancer Center. He received his BS in pharmacy from the University of Utah and received his PharmD from the University of Texas. He completed an Oncology residency at the Audie L. Murphy Memorial V.A. Hospital. He then completed a two-year fellowship in immunology and transplantation at the University of Florida.

Faculty

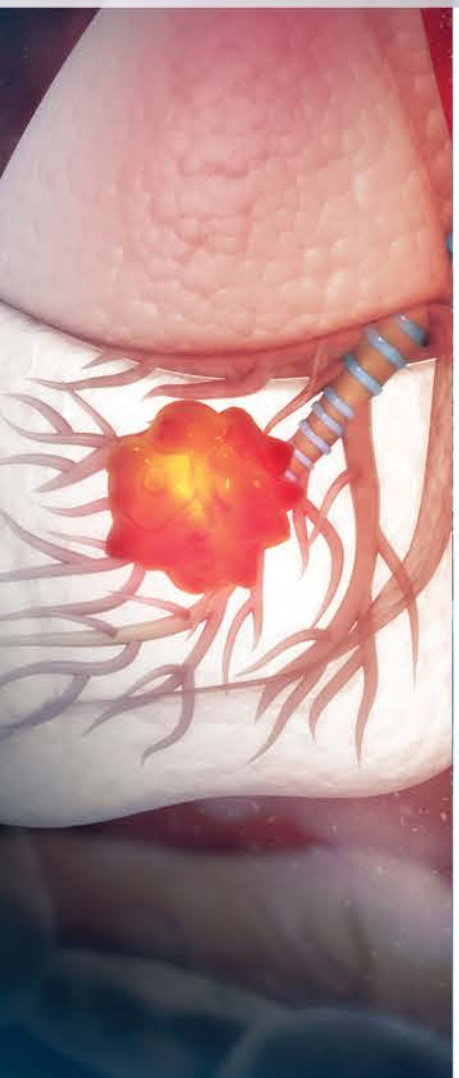


Sandra Cuellar, PharmD, BCOP, FHOPA, FASHP

Clinical Associate Professor, Department of Pharmacy Practice
Oncology Clinical Pharmacist
University of Illinois Hospital and Health Sciences System
Oncology Resident Director, Ambulatory Pharmacy Services
University of Illinois at Chicago College of Pharmacy
Chicago, IL

Dr. Cuellar is a Clinical Associate Professor in the Department of Pharmacy Practice at the University of Illinois at Chicago (UIC) College of Pharmacy. She received her PharmD from the UIC College of Pharmacy, then completed a Pharmacy Practice Residency at University of Kentucky Chandler Medical Center. Following her residency, she completed a specialty oncology residency at MD Anderson Cancer Center in Houston. Dr. Cuellar is a Board-Certified Oncology Pharmacist and works as a clinical oncology pharmacist at UI Health. Dr. Cuellar also serves as the director of the oncology residency program at UI Health.

Disclosures



Dr. Cuellar has disclosed that she has received consulting fees from Pfizer, Genentech, and Eisai.

Dr. Adams has received research funding from Bristol Myers Squibb; and has served as a consultant for Regeneron.

The clinical reviewer, Megan May, PharmD, BCOP has no relevant affiliations or financial relationships with a commercial interest to disclose.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education (CE) activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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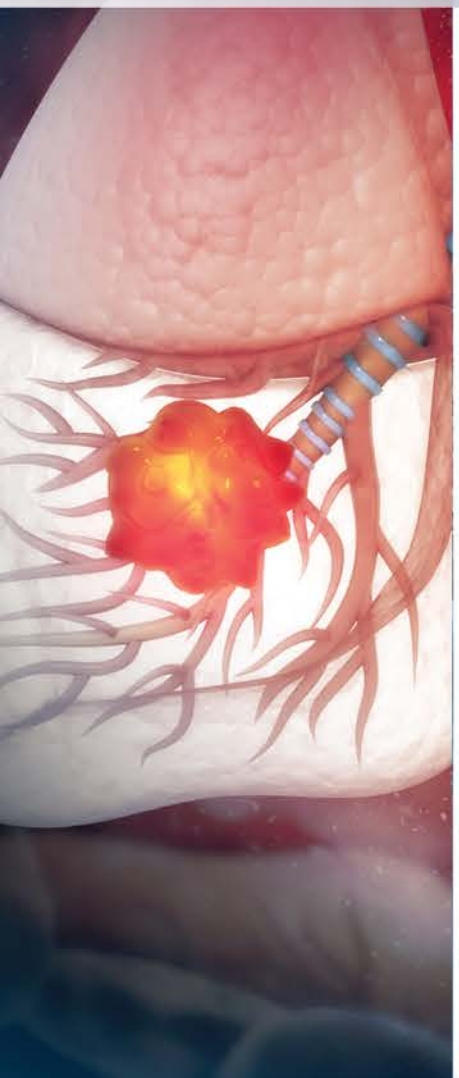

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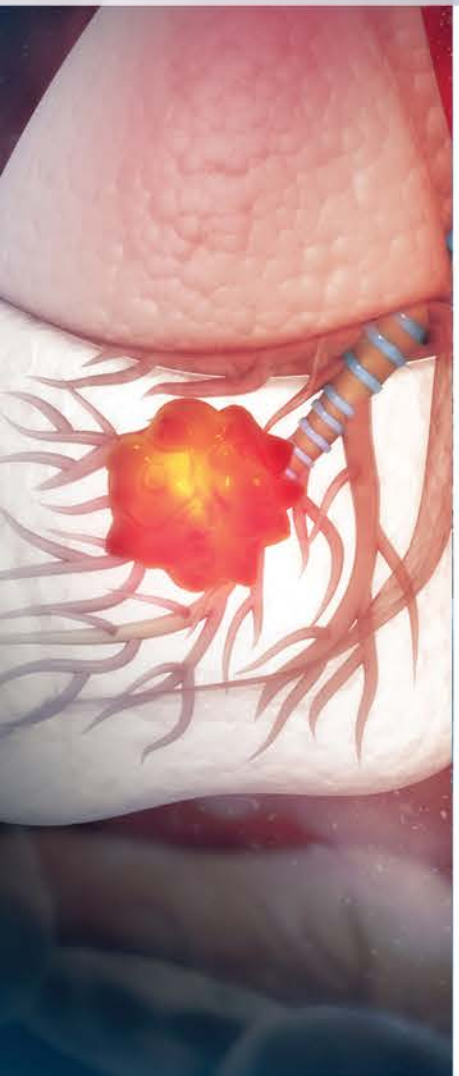
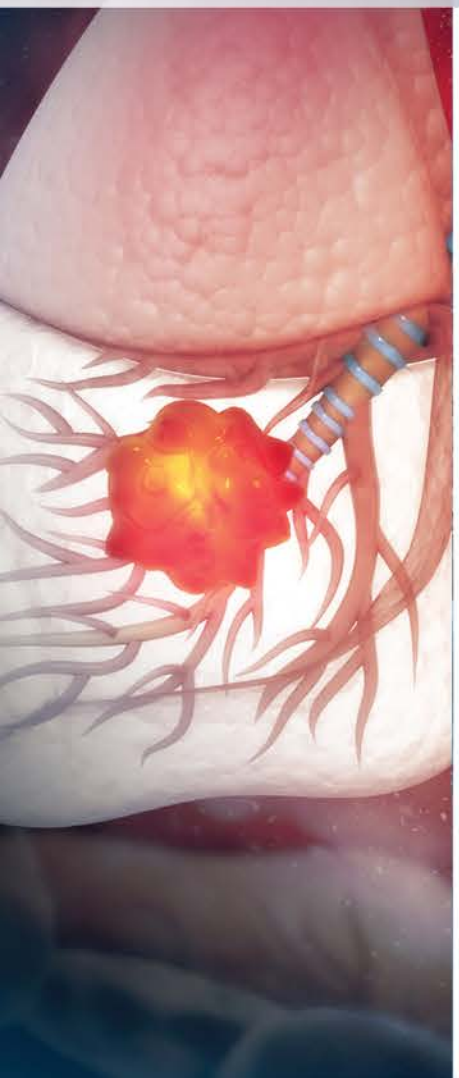
UAN: 0430-0000-21-089-H01-P
Credits: 1.5 hour (0.15 CEU)
Type of Activity: Application

Learning Objectives

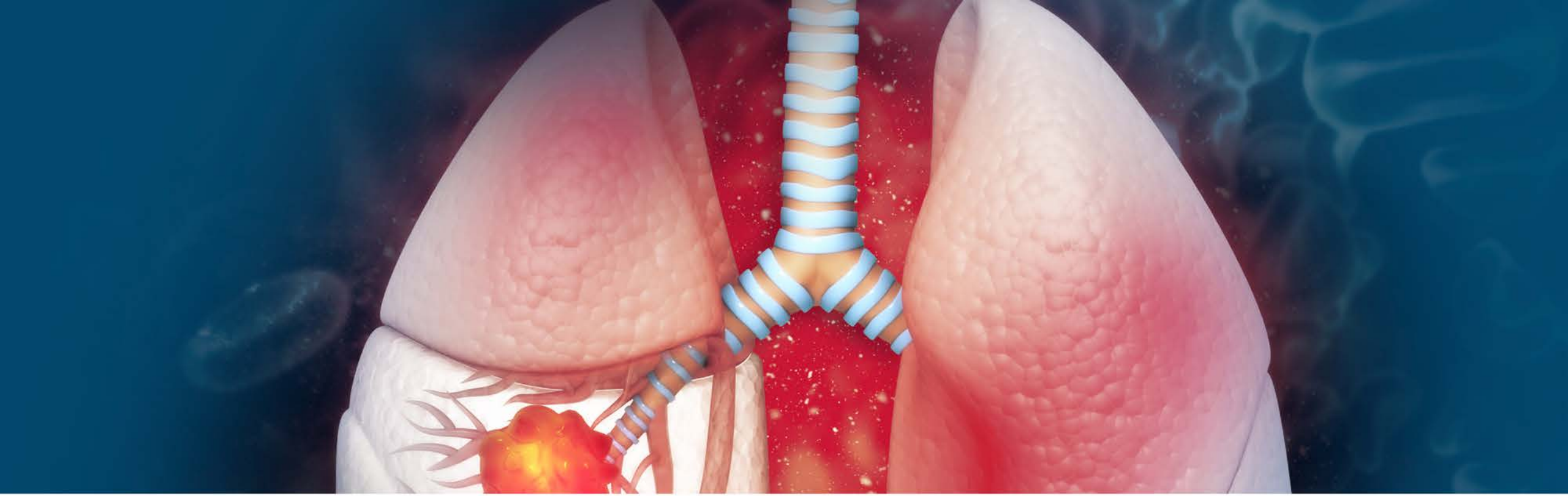


- **Describe** recommended therapeutic regimens for patients with advanced NSCLC
- **Recognize** the role of immunotherapy in the treatment of advanced NSCLC
- **Identify** recommended treatments based on the presence or absence of driver mutations in patients with advanced NSCLC
- **Develop** a therapeutic plan for a patient with advanced NSCLC including monitoring for adverse events and therapy resistance

Frequently Asked Questions

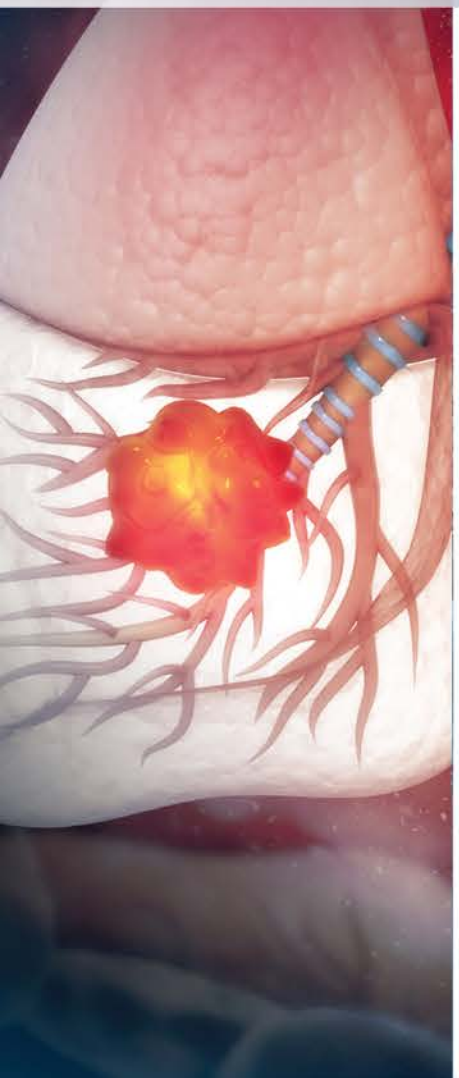


- ***Immunotherapy Alone***
  - Who benefits?
  - What is the benefit?
  - What about dual ICIs?
- ***Chemoimmunotherapy***
  - What is the benefit of adding chemotherapy?
- ***Tumor Analysis Methods***
  - How are tumors tested for driver mutations?
- ***Driver Mutations***
  - How does driver mutations impact treatment selection?
  - How to identify recommended treatment options?
    - KRAS G12C mutation?
    - MET Exon 14 mutation?
    - RET Fusion Positive mutations?
    - EGFR Exon 20 insertion mutations?



Who Benefits from Immunotherapy?

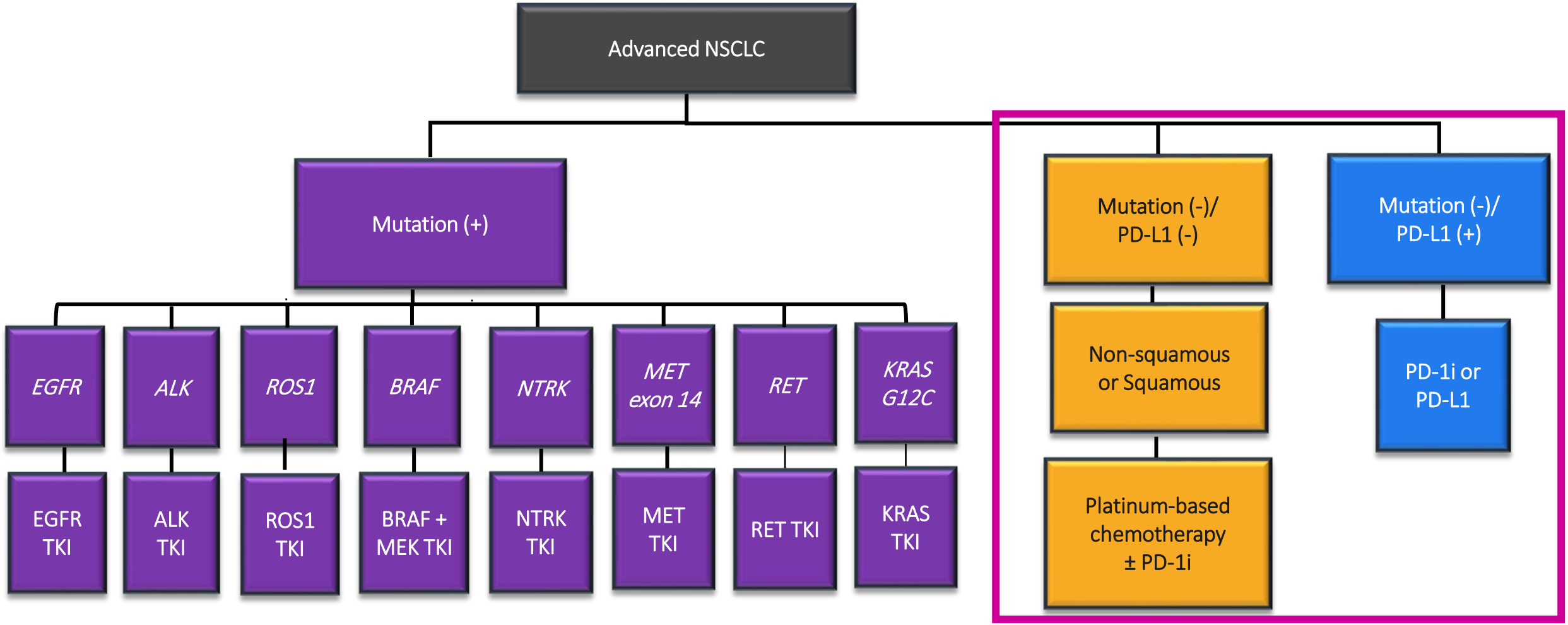
Treatment Modalities by Stage for NSCLC



- Stage I – tumor < 4 cm — SURGERY monitor
- Stage IB – IIIA — SURGERY w/adjuvant or neoadjuvant therapy
- **Stage IIIB – IV — Systemic Treatment w/ Precision Med and/or Chemo IO and/or IO**

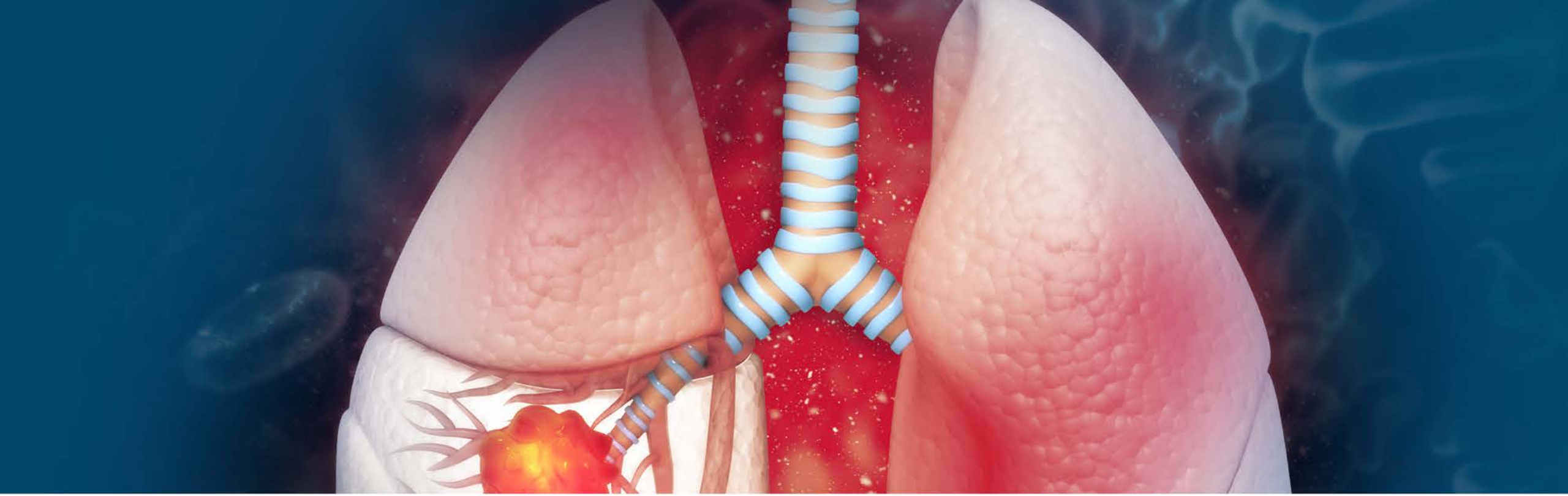
IO = immuno-oncology

Individualized Treatment



PD-L1 = programmed cell death ligand 1; PD1i = PD-1 immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor.

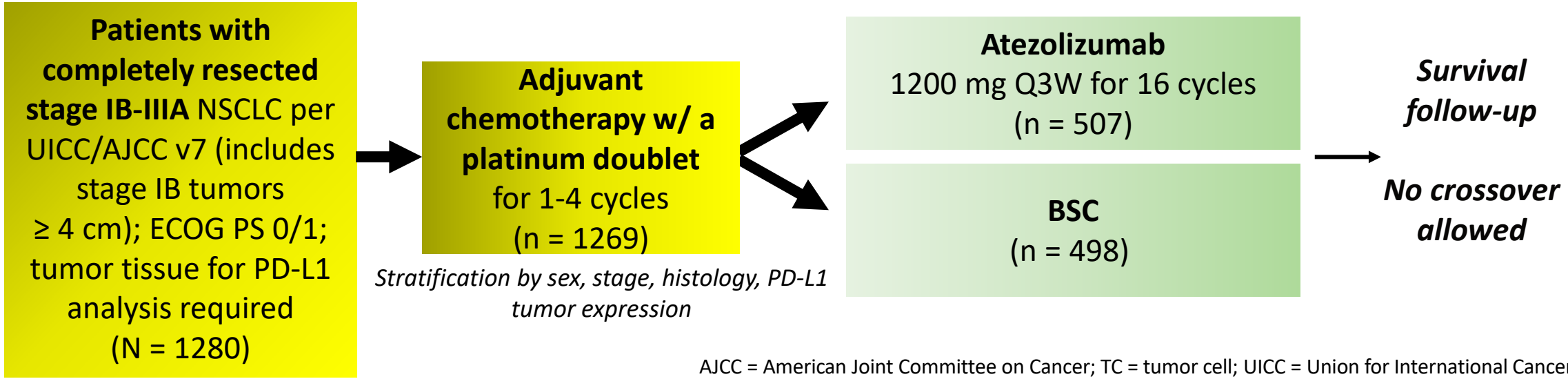
NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf



What is the Benefit of ICI Monotherapy?

IMpower010: Adjuvant Atezolizumab

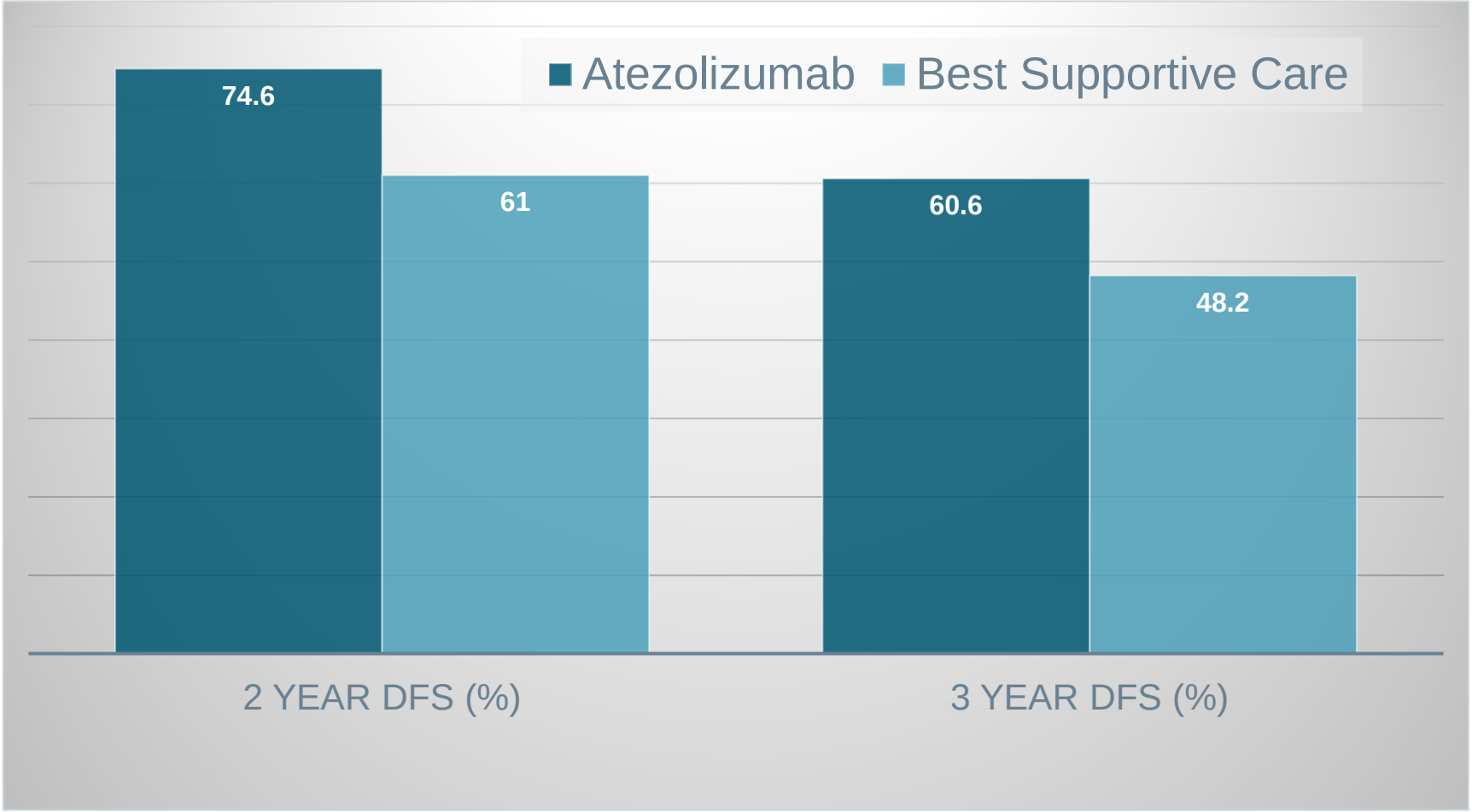
- Primary endpoint: investigator-assessed DFS in 3 populations
  - Stage II-IIIA with PD-L1 TC ≥1%
  - **All randomized stage II-IIIA**
  - ITT population (stage IB-IIIA)
- Key secondary endpoints: OS (ITT); DFS in stage II-IIIA with PD-L1 TC ≥ 50%; 3-year and 5-year DFS in all 3 populations; safety
- Data cutoff for interim analysis: January 21, 2021



AJCC = American Joint Committee on Cancer; TC = tumor cell; UICC = Union for International Cancer Control

Wakelee HA, et al. *J Clin Oncol*. 2021;39:15_suppl, 8500. (ASCO Abstract #8500)

IMpower010: Primary Endpoint
DFS in Stage II-IIIA NSCLC with PD-L1 TC ≥ 1%



	Atezo	BSC
	N=248	n=228
mDFS	NE(36.1-NE)	35.3 (29-NE)

Stratified HR: 0.66 (95% CI: 0.50-0.88; *P* = .004) (crossed significance boundary)

Median follow up: 32.8 mo (range: 0.1-57.5)

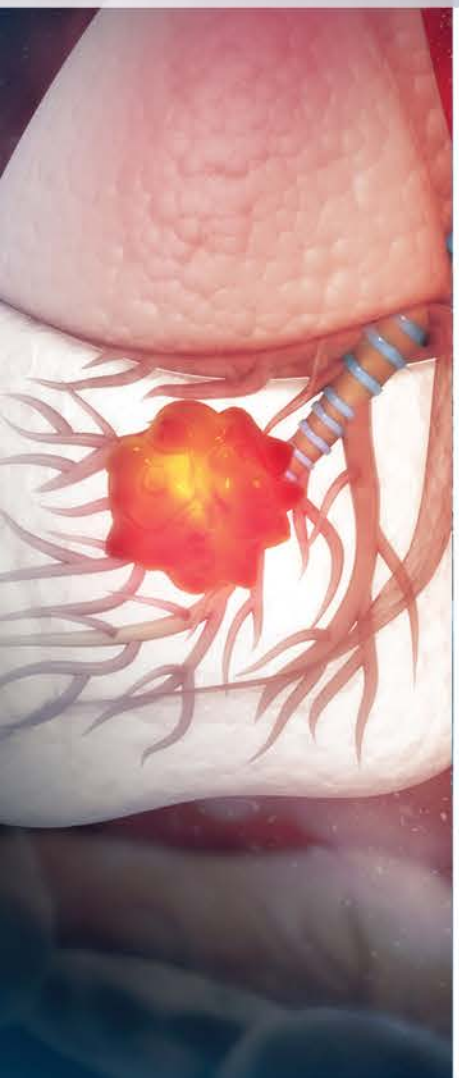
Likely a new standard of Care

But OS data is still immature

DFS = disease free survival, m = median

Wakelee HA, et al. *J Clin Oncol*. 2021;39:15_suppl, 8500. (ASCO Abstract #8500)

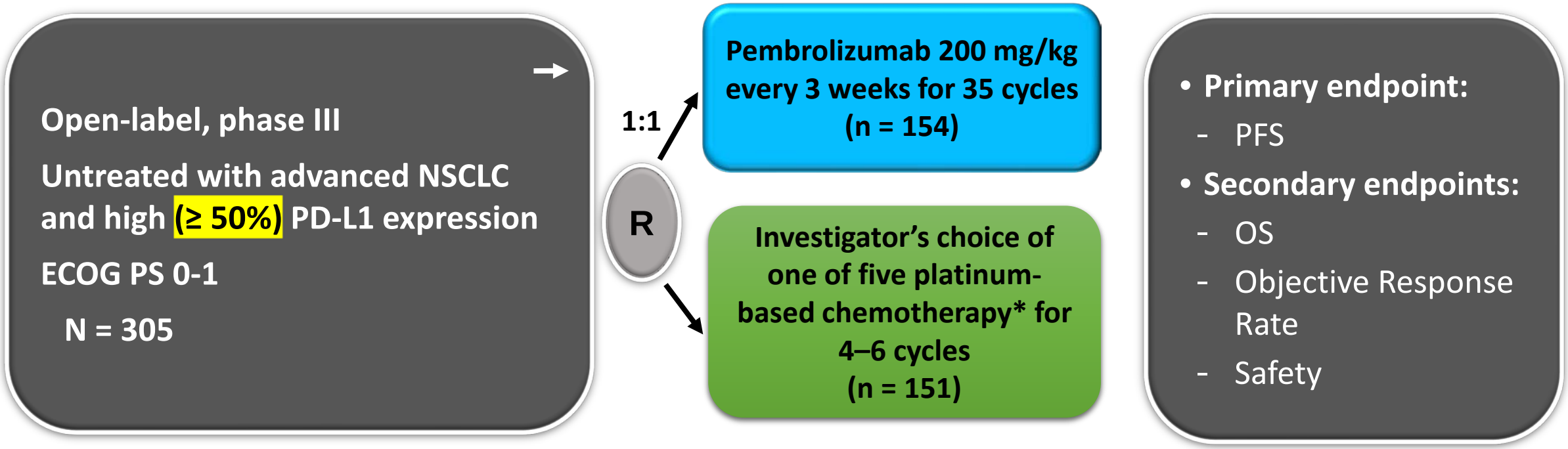
IMpower010: Interim Analysis Conclusions



- Adjuvant atezolizumab achieved a significant DFS benefit in the following patients with resected early-stage NSCLC after adjuvant chemotherapy:
  - Stage II-IIIA NSCLC and PD-L1 TC ≥ 1% (HR: 0.66; 95% CI: 0.50-0.88)
  - All randomized patients with stage II-IIIA (HR: 0.79; 95% CI: 0.64-0.96)
- OS data were immature and not formally tested
- DFS in the ITT population (includes stage IB disease) did not cross significance boundary
  - Follow-up for DFS and OS will continue in the ITT population
- No unexpected safety signals emerged with adjuvant atezolizumab
- Atezolizumab may be considered a practice-changing adjuvant treatment option for patients with stage II-IIIA NSCLC and PD-L1 TC ≥ 1%

KEYNOTE-024 Pembrolizumab vs. Platinum-Based Chemotherapy:

- 23% to 28% of patients with advanced NSCLC have high level of PD-L1 expression; defined as 50% of tumor cells



*carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel

ECOG PS = Eastern Cooperative Oncology Group performance-status

Reck M, et al. *N Engl J Med.* 2016;375:1823-1833.

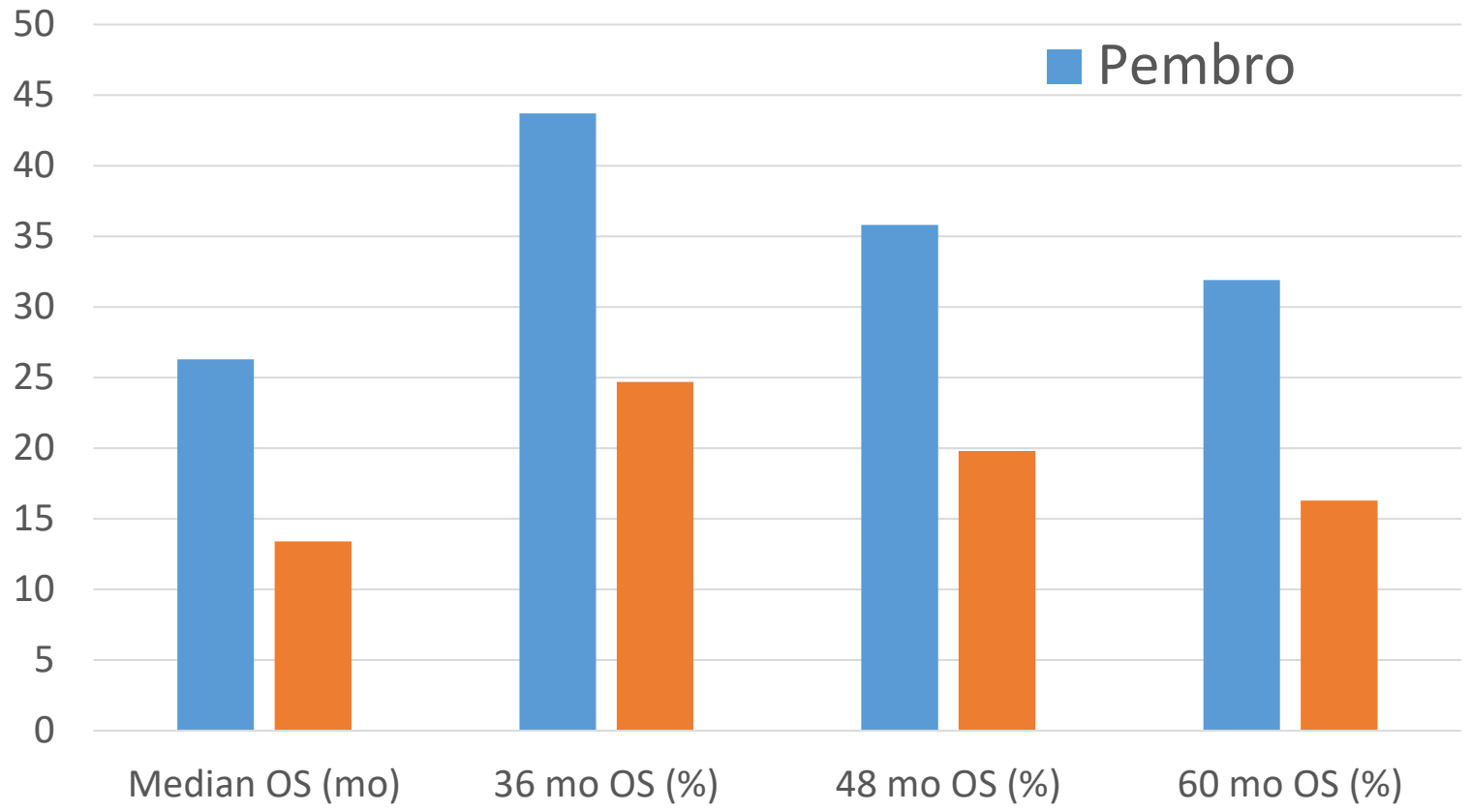
Pembrolizumab vs. Platinum-Based Chemotherapy: OS

Pembrolizumab monotherapy better than platinum doublet

PFS ⇧ by 2 mo

OS ⇧ by 13 mo

Less toxic (G3-5)
31% vs. 53%



Reck M, et al. *J Clin Oncol* 2021;39:2339-2349.

Impower110 Phase 3: Atezolizumab vs. Platinum Pemetrexed Adv/Metastatic Non-Squamous NSCLC

Stage IV Non-squamous NSCLC
Chemotherapy naïve
Stratification:

- Sex
- ECOG PS
- Liver mets
- PD-L1 expression

Key Exclusion Factors: EGFR or ALK mut

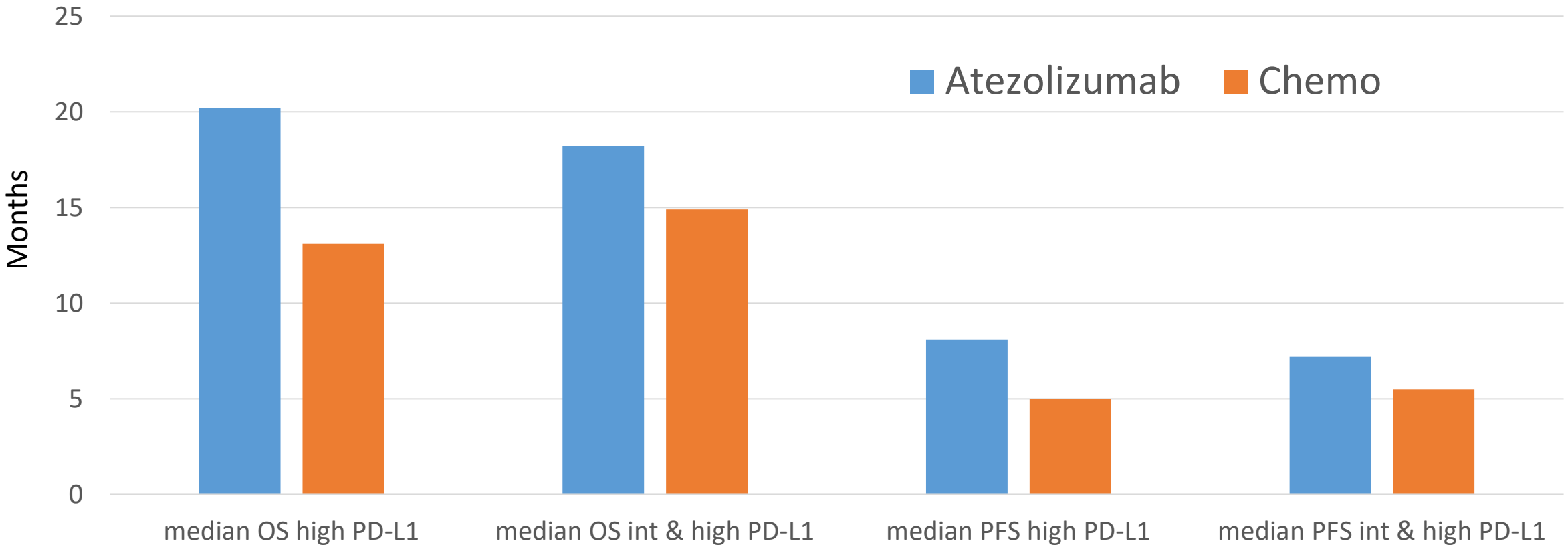
Atezolizumab 1200 mg IV q21d
N=286

Carboplatin AUC6 or Cisplatin 75 mg/m^2
+ Pemetrexed 500 mg/m^2 IV q21d x 4-6 C
Then Pemetrexed 500 mg/m^2 IV q21d
N=263

Primary Endpoint: Overall Survival
Secondary Endpoints include: progression-free survival (PFS), overall response rate (ORR), duration of response (DOR)
Analysis by PD-L1 subgroups (intermediate or high)

Herbst RS, et al. *N Engl J Med.* 2020; 383(14):1328-1339.

Impower110 Phase 3: Atezolizumab vs. Platinum Pemetrexed Adv/Metastatic Non-Squamous NSCLC



Herbst RS, et al. *N Engl J Med.* 2020; 383(14):1328-1339.

EMPOWER-Lung 1 Phase 3: Cemiplimab vs. Platinum Doublet Adv/Metastatic NSCLC

Stage IV Non-squamous NSCLC
Chemotherapy naïve
Stratification:
- Histology
- Geographic Region

Key Exclusion Factors: EGFR or ALK mut

Cemiplimab 350 mg IV q21d
N=355

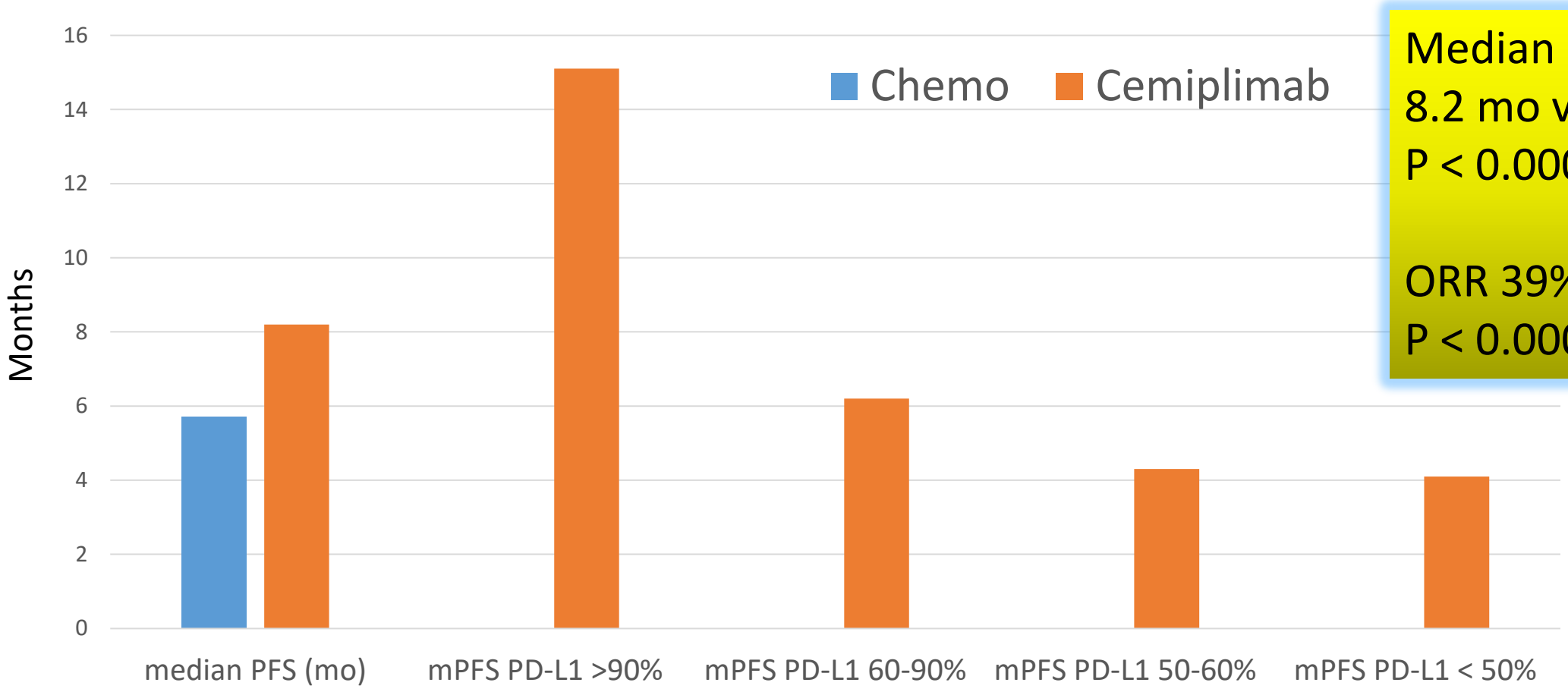
Platinum Doublet: Maintenance pemetrexed allowed
Crossover following disease progression allowed
N=342

Most common doublets: carboplatin/paclitaxel and carboplatin/pemetrexed

Primary Endpoints: OS and PFS
Secondary Endpoints: ORR, DOR, health-related quality of life (HRQOL)

Sezer A, et al. *Lancet.* 2021;397(10274):592-604.

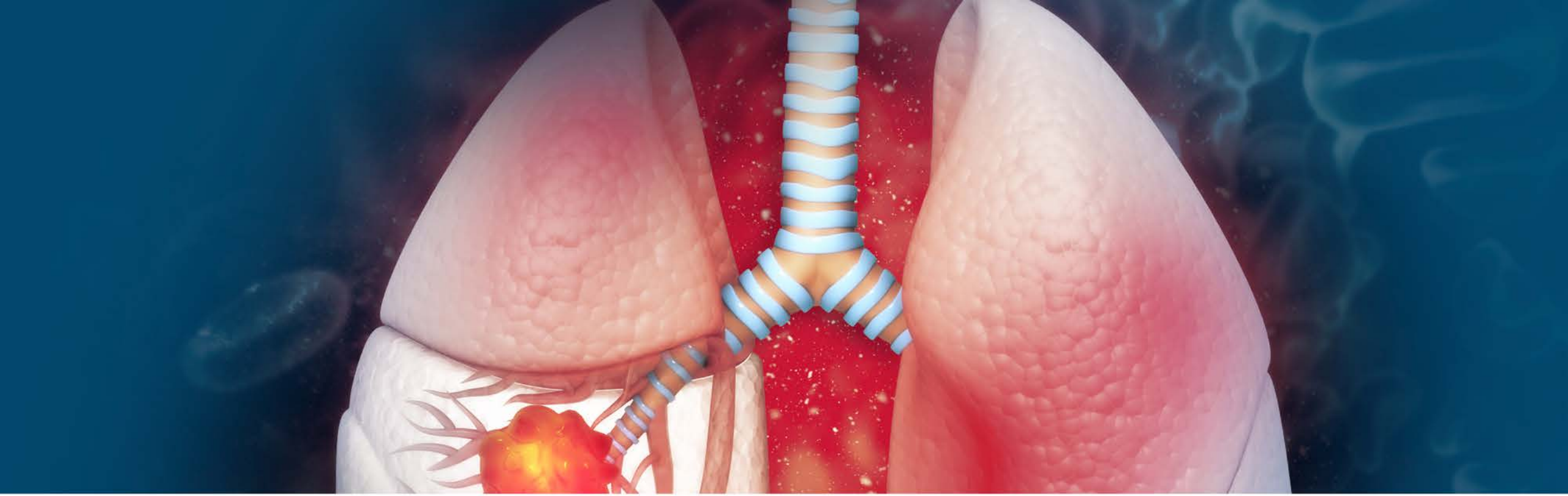
EMPOWER-Lung 1 Phase 3: Cemiplimab vs. Platinum Doublet Adv/Metastatic NSCLC



Median PFS
8.2 mo vs. 5.7 mo
P < 0.0001

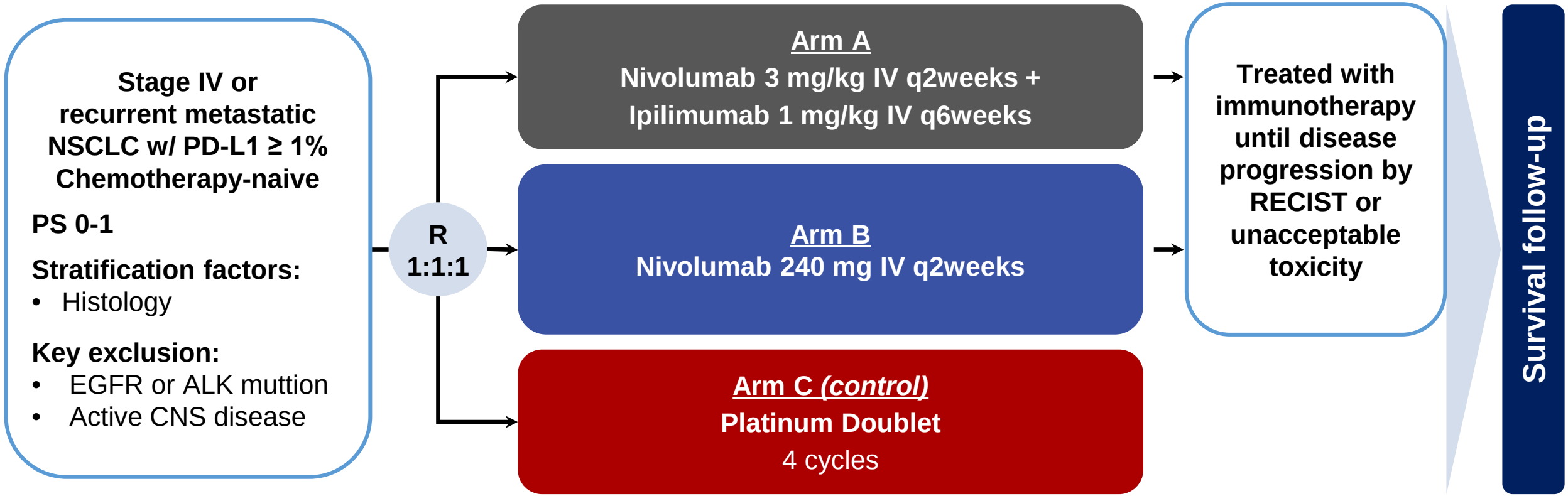
ORR 39% vs. 20%
P < 0.0001

Sezer A, et al. *Lancet.* 2021;397(10274):592-604.



What about Dual ICIs?

CheckMate 227 (Part 1a)



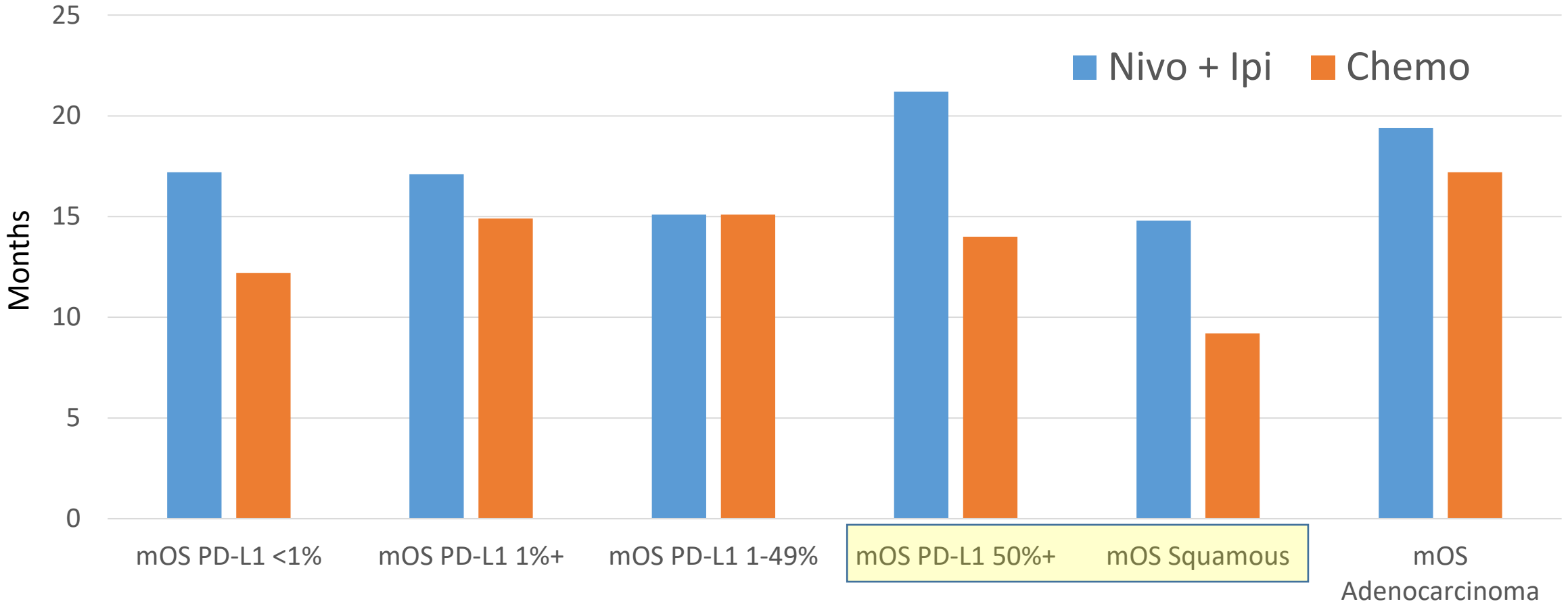
Part 1b included patients with PD-L1 expression < 1%

Primary Endpoint: OS between arm A and C
Secondary Endpoints: PFS, OS with PD-L1 ≥ 50%

RECIST = response evaluation criteria in solid tumors

Hellmann MD, et al. *N Engl J Med.* 2019;381(21):2020-2031.

Results from CheckMate 227



The Greatest Benefit based on HR for subgroups is Squamous histology and PD-L1 > 50%

Hellmann MD, et al. *N Engl J Med.* 2019;381(21):2020-2031.

Guideline-Based Immunotherapy Recommendations for Adv/Metastatic NSCLC

Chemoimmunotherapy by histology (PD-L1 ≥ 1%)

Non-Squamous

- Platinum/pemetrexed/pembrolizumab
- Carboplatin/paclitaxel/bevacizumab/ atezolizumab
- Carboplatin/alb bound paclitaxel/atezolizumab
- Platinum/pemetrexed/nivolumab/ipilimumab

Squamous

- Carboplatin/paclitaxel*/pembrolizumab
- Carboplatin/paclitaxel/nivolumab/ipilimumab

* - paclitaxel or albumin bound paclitaxel

Immunotherapy

PD-L1 ≥ 1%

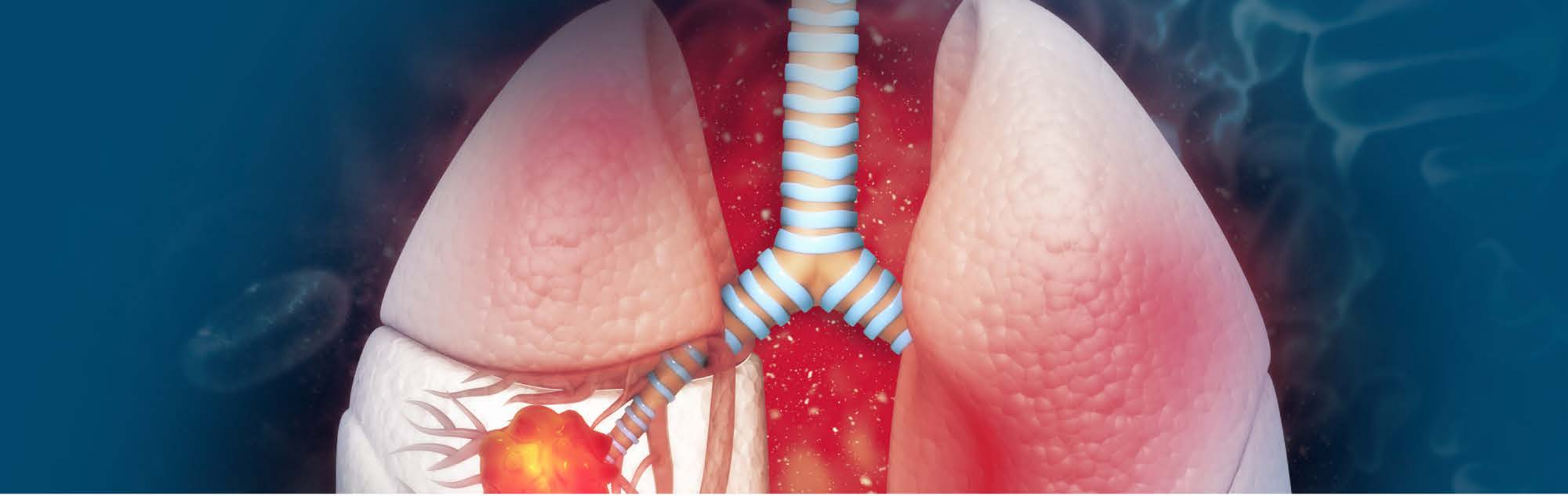
- Pembrolizumab
- Nivolumab/Ipilimumab

PD-L1 ≥ 50%

- Atezolizumab
- Cemiplimab

NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Immunotherapy Alone Questions & Answers



What is the Benefit of Adding Chemotherapy to immunotherapy?

Guideline-Based Immunotherapy Recommendations for Adv/Metastatic NSCLC

Chemoimmunotherapy by histology (PD-L1 ≥ 1%)

Non-Squamous

- Platinum/pemetrexed/pembrolizumab
- Carboplatin/paclitaxel/bevacizumab/ atezolizumab
- Carboplatin/alb bound paclitaxel/atezolizumab
- Platinum/pemetrexed/nivolumab/ipilimumab

Squamous

- Carboplatin/paclitaxel*/pembrolizumab
- Carboplatin/paclitaxel/nivolumab/ipilimumab

* - paclitaxel or albumin bound paclitaxel

Immunotherapy

PD-L1 ≥ 1%

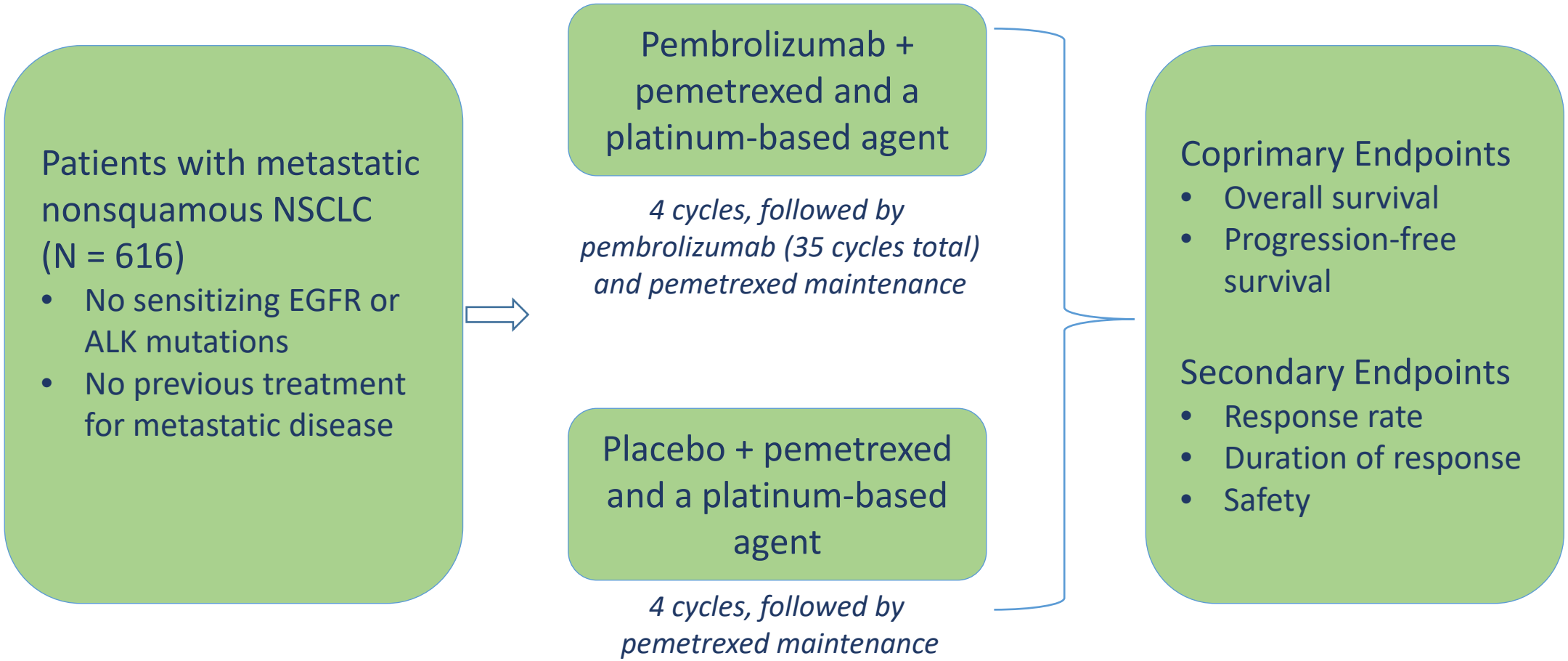
- Pembrolizumab
- Nivolumab/Ipilimumab

PD-L1 ≥ 50%

- Atezolizumab
- Cemiplimab

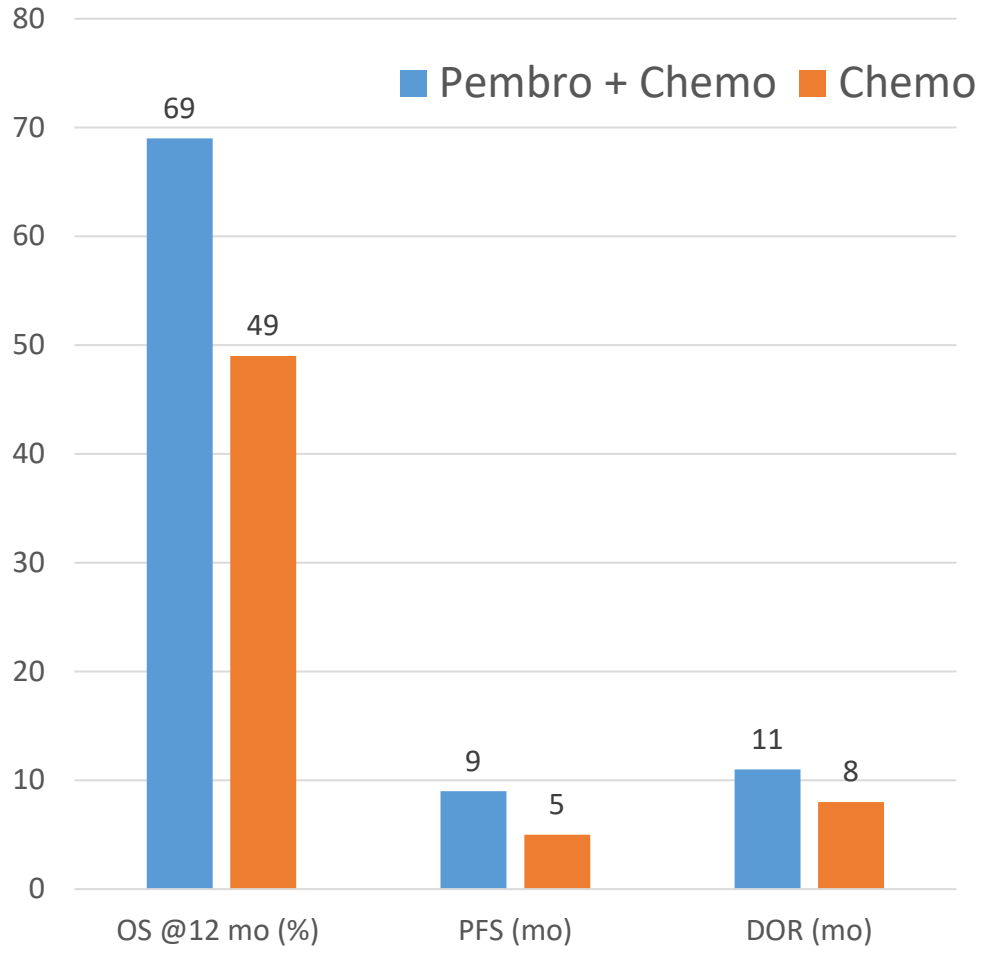
NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Chemotherapy + IO vs. Chemotherapy: Non-Squamous Pembrolizumab—KEYNOTE-189



Gandhi L, et al. *N Engl J Med*. 2018;378:2078-2092.

Pembrolizumab—KEYNOTE-189



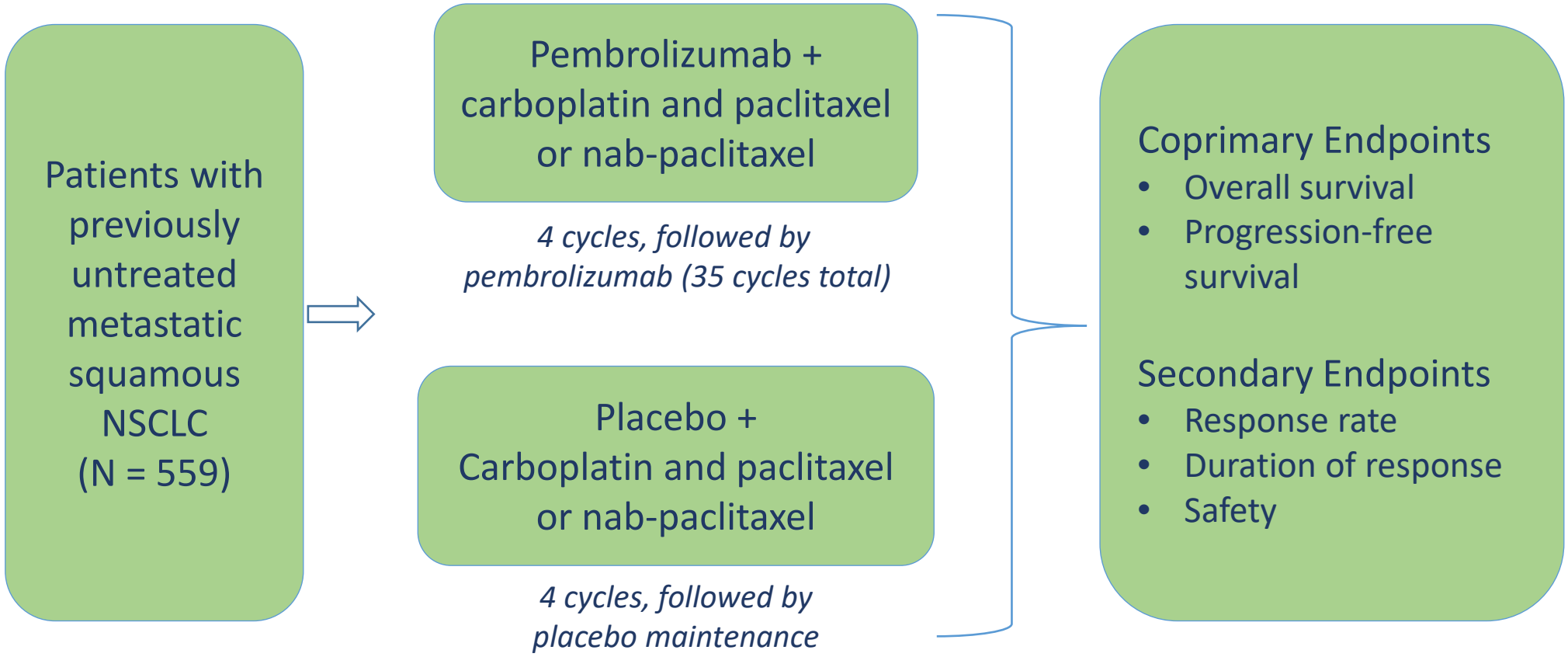
- Significant improvement in OS seen with pembrolizumab
  - Estimated 12-mo OS: 69.2% vs. 49.4%
  - Improvement seen in all PD-L1 categories evaluated
- Improvements also seen with pembrolizumab for
  - Median PFS (8.8 mo vs. 4.9 mo)
  - Response rate (47.6% vs. 18.9%)
  - Duration of response (median 11.2 mo vs. 7.8 mo)

Addition of pembrolizumab to standard platinum doublet chemotherapy in patients with previously untreated metastatic nonsquamous NSCLC results in significantly longer OS and PFS

OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival DOR = duration of response

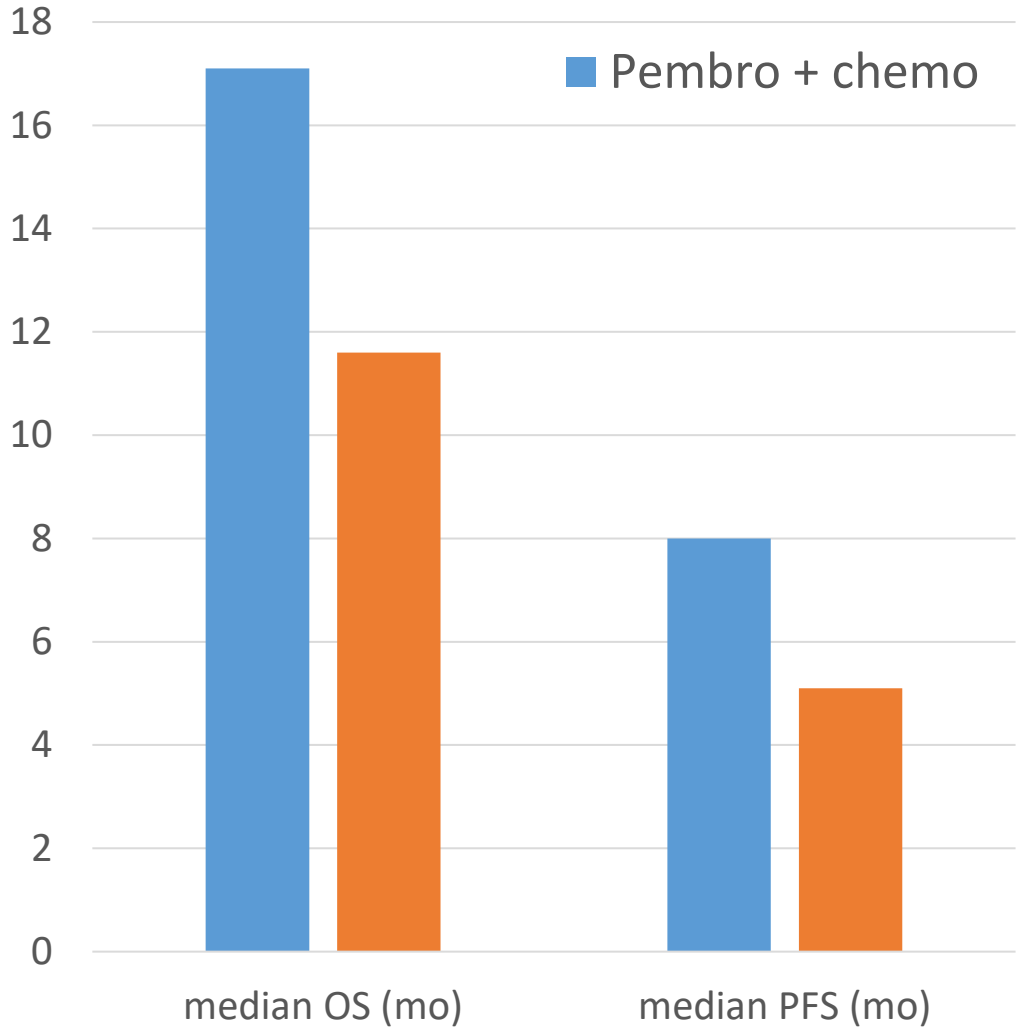
Gandhi L, et al. *N Engl J Med*. 2018;378:2078-2092.

Chemotherapy + IO vs. Chemotherapy: Squamous Pembrolizumab—KEYNOTE-407



Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-2051.

Pembrolizumab—KEYNOTE-407



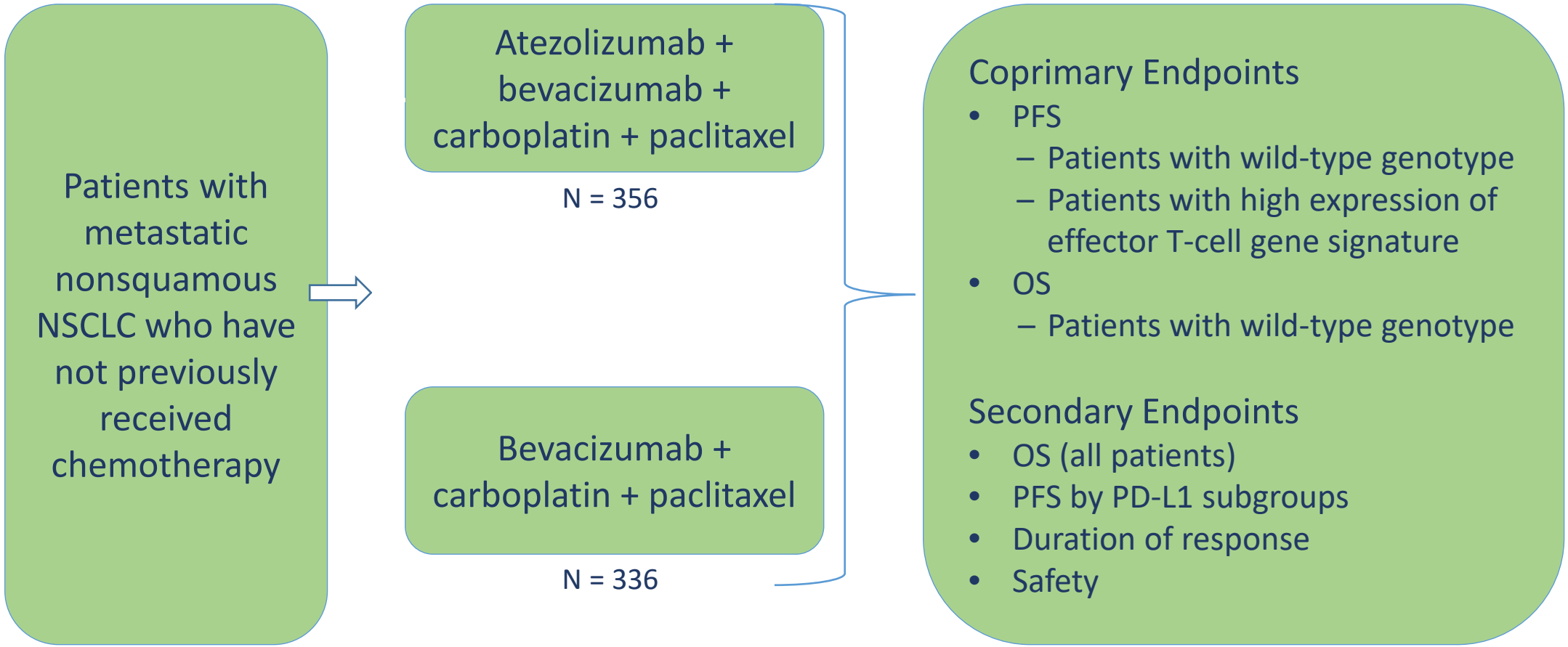
- Significant improvement in OS seen with pembrolizumab
  - Median OS: 17.1 mo vs. 11.6 mo HR 0.71 (0.58-0.88)
- Significant improvement also seen in PFS with addition of pembrolizumab
  - Median PFS: 8.0 mo vs. 5.1 mo HR 0.57 (0.47-0.69)
- Improvements also seen with pembrolizumab for response rate and duration of response

Addition of pembrolizumab to chemotherapy with carboplatin and paclitaxel (or nab-paclitaxel) significantly improves OS and PFS in patients with previously untreated metastatic squamous NSCLC

HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Paz-Ares L, et al. J Thorac Oncol. 2020;15:1657-69.

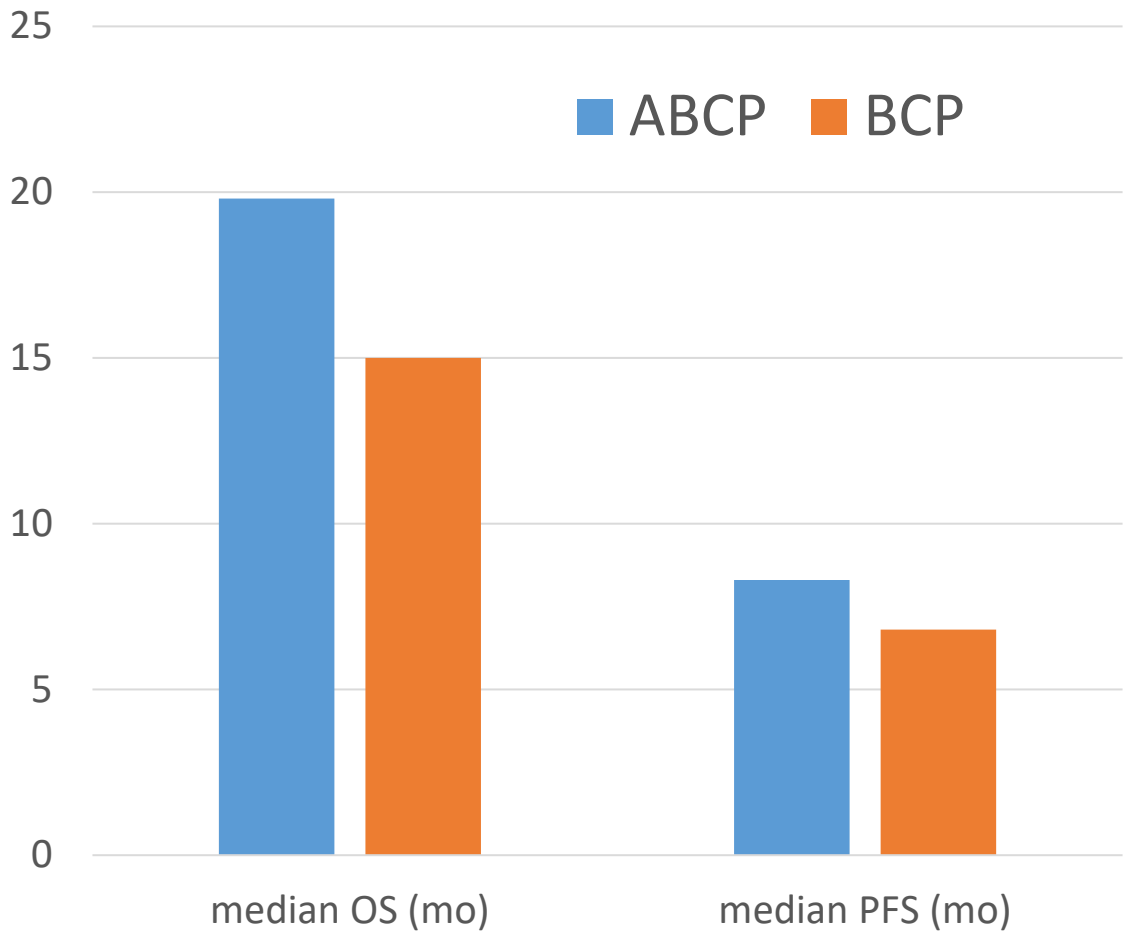
Chemotherapy + IO vs. Chemotherapy: Non-Squamous
Atezolizumab—Impower150



OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival

Socinski MA, et al. *N Engl J Med*. 2018;378:2288-2301.

Atezolizumab—Impower150



ABCP = Atezolizumab/bevacizumab/carboplatin/paclitaxel
BCP = Bevacizumab/carboplatin/paclitaxel

- Significant improvement in PFS with addition of atezolizumab
  - Median PFS: 8.4 mo vs. 6.8 mo (HR 0.62, *P* <.001)
  - Improvements seen in all PD-L1 expression cohorts
- Atezolizumab improved median OS in the wild-type genotype patient population (no *EGFR* or *ALK* mutations)
  - Median OS: 19.8 months vs. 15 months (HR 0.8, 0.68-0.95)

Addition of atezolizumab to bevacizumab and chemotherapy significantly improves PFS and OS in patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK mutation status

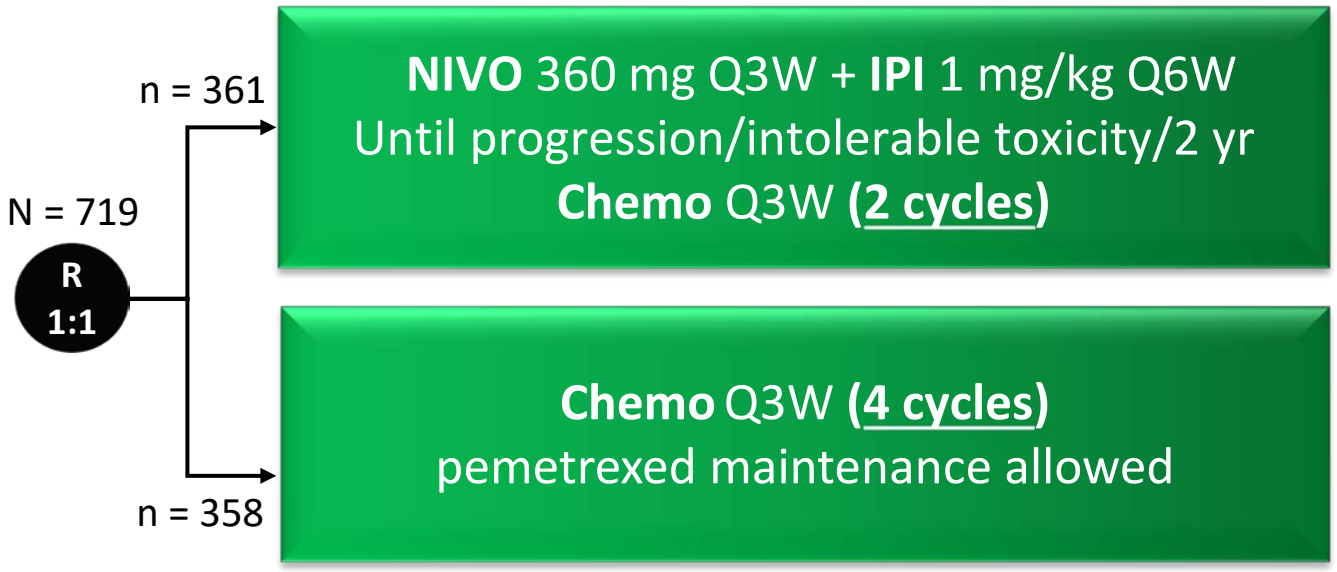
Socinski M, et al. J Thorac Oncol. 2021;S1556-0864(21)02322-4.

CheckMate 9LA

Randomized Phase III

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1 (< 1% vs. ≥ 1%), sex, and histology (SQ vs. NSQ)



Primary endpoint

- OS

Secondary endpoints

- PFS by BICR
- ORR by BICR
- Efficacy by tumor PD-L1 expression

Demographics:

- Median age: 65
- Never Smoker: 13% to 14%
- PD-L1 expression:
  - < 1% = 40%
  - 1% to 49% = 38%
  - ≥ 50% = 22%

Reck M, et al. *J Clin Oncol.* 2020;38:15_suppl, 9501. (ASCO Abstract #9501)

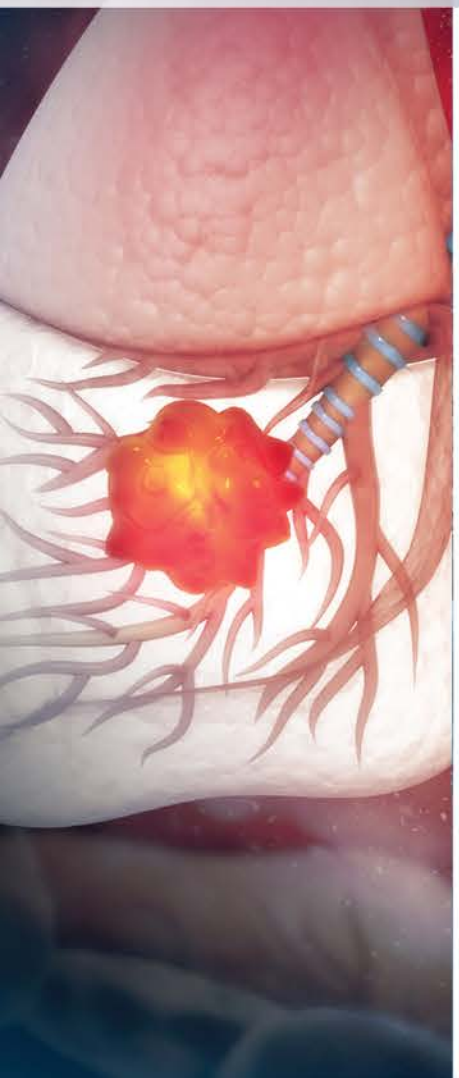
BICR = blinded independent central review; NSQ = non-squamous; SQ = squamous

Overall Survival Subgroup Analysis (Minimum F/U 12.7 mo)

Overall and Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI + chemo n = 361	Chemo n = 358		
All randomized (N = 719)	**15.6**	**10.9**	**0.66**	**(0.55-0.8)**
Never smoker (n = 98)	14.1	17.8	1.14	(0.66 – 1.97)
Smoker (n = 621)	15.6	10.4	0.62	(0.5-0.75)
Squamous (n = 227)	14.5	9.1	0.62	(0.45-0.86)
Non-squamous (n = 492)	17.0	11.9	0.69	(0.55-0.87)
Liver metastases (n = 154)	10.2	8.1	0.83	(0.57-1.2)
No liver metastases (n = 565)	19.4	12.4	0.64	(0.51-0.8)
Bone metastases (n = 207)	11.9	8.3	0.74	(0.53-1.01)
No bone metastases (n = 512)	20.5	12.4	0.65	(0.51-0.82)
PD-L1 < 1% (n = 264)	16.8	9.8	0.62	(0.45-0.85)
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64	(0.5-0.82)
PD-L1 1% to 49% (n = 233)	15.4	10.4	0.61	(0.44-0.84)
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66	(0.44-0.99)

Reck M, et al. *J Clin Oncol.* 2020;38:15_suppl, 9501. (ASCO Abstract #9501)

FDA Pooled Analysis: Background



- Options for patients with previously untreated adv/met NSCLC, no targetable mutations, and low PD-L1 expression (1% to 49%):
  - Various IO-only or chemo-IO regimens
- Unclear whether select patient subgroups with low PD-L1 expression achieve better outcomes with chemo + IO or IO alone
- FDA's retrospective exploratory pooled analysis compared OS and PFS outcomes between chemo-IO and IO-only in patients with adv/met NSCLC and PD-L1 expression 1% to 49%, both in the overall population and in select patient subgroups

adv/met = advanced/metastatic; IO = immuno-oncology

Akinboro O, et al. *J Clin Oncol.* 2021;39:15_suppl, 9001. (ASCO Abstract #9001)

FDA Pooled Analysis: Study Design

- Data pooled from 8 first-line advanced NSCLC RCTs (N = 6010)
  - anti-PD-(L)1 monotherapy
  - Anti-PD-(L)1 therapy plus chemotherapy
- Population defined by tumor PD-L1 expression 1% to 49% (n = 2108)[a]
- Key outcomes of interest: OS, PFS

RCT Leading to Approval	Experimental Arm*†
IO alone	
▪ KEYNOTE-042	Pembro
▪ CheckMate 227	Nivo + ipi
Chemo-IO	
▪ KEYNOTE-189	Pembro + chemo
▪ KEYNOTE-407	Pembro + chemo
▪ KEYNOTE-021 (Cohort G)	Pembro + chemo
▪ IMpower150	Atezo + bev + chemo
▪ IMpower130	Atezo + chemo
▪ CheckMate 9LA	Nivo + ipi + chemo

*Chemo: platinum doublet.

†Control arm in all trials was platinum-doublet chemo, except IMpower150, which was bevacizumab + platinum-doublet chemo

[a]PD-L1 expression defined by tumor cell staining (i.e., TPS)

RCT = randomized controlled trial; TPS = tissue polypeptide specific antigen

Akinboro O, et al. *J Clin Oncol.* 2021;39:15_suppl, 9001. (ASCO Abstract #9001)

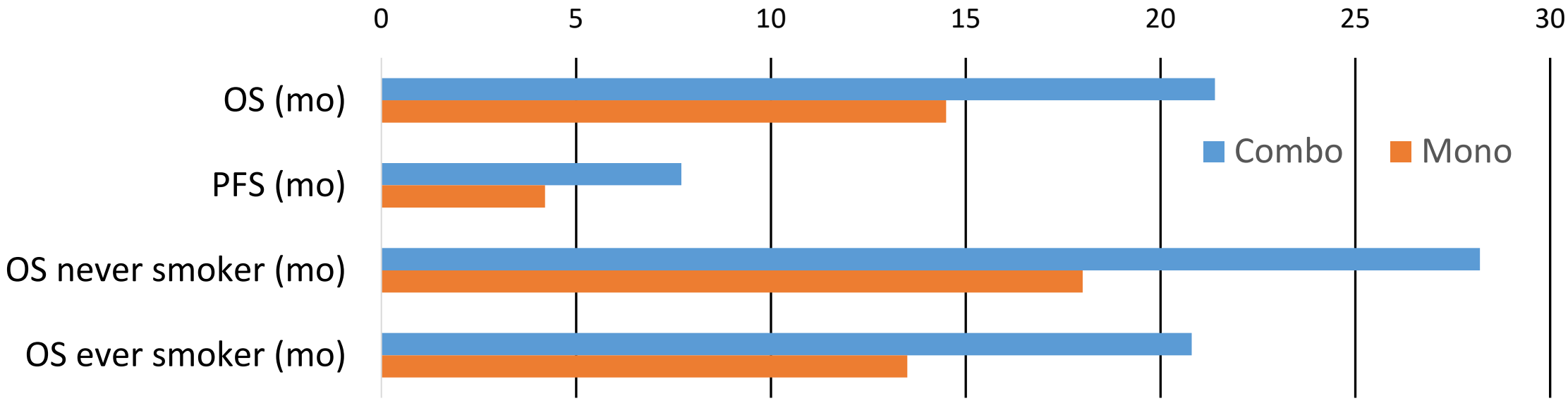
FDA Pooled Analysis: Patient Characteristics

Characteristic, %	Chemo-IO (n = 639)	IO Alone (n = 529)	Chemo (n = 940)	Total (N = 2108)
Age				
▪ < 65 years	48	53	53	51
▪ 65 to 74 years	40	36	36	37
▪ ≥ 75 years	11	11	12	12
Female	35	31	32	33
Race				
▪ White	88	69	78	79
▪ Asian	9	23	19	17
▪ Black/African American	2	2	2	2
Current/prior smoker	91	81	84	85
ECOG PS ≥1	62	67	67	65
Nonsquamous histology	77	63	64	68
Stage IV	89	91	92	91

Akinboro O, et al. *J Clin Oncol*. 2021;39:15_suppl, 9001. (ASCO Abstract #9001)

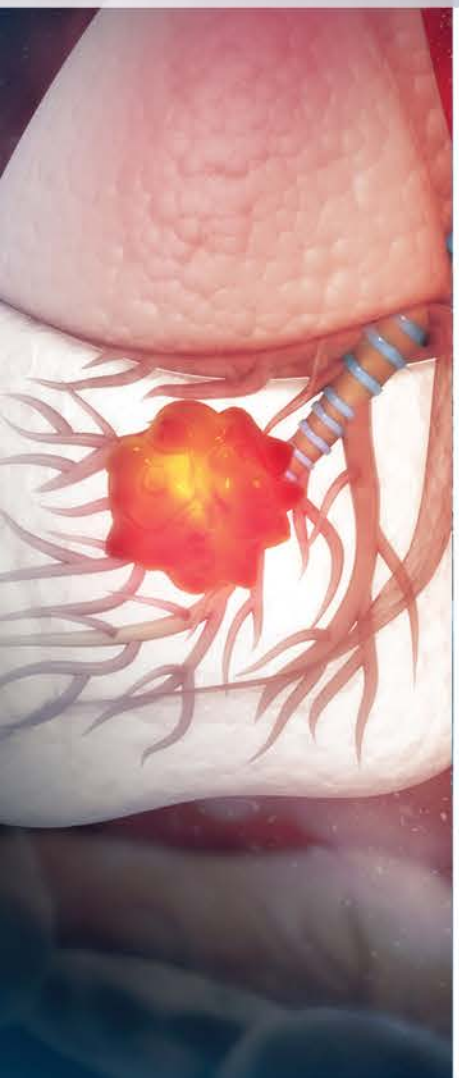
FDA Pooled Clinical Trial Data

- Patients treated with PD1/PD-L1 inhibitor as monotherapy (mono) or in combination with chemotherapy (combo)
- 2108 patients identified with a PD-L1 of 1-49% expression: 529 mono, 639 combo – median f/u was 12.1 months



Akinboro O, et al. *J Clin Oncol*. 2021;39(15 Suppl):9001.

FDA Pooled Analysis: Conclusions



- FDA-approved chemo-IO regimens may improve OS and PFS compared with IO alone in most patients with newly diagnosed adv/met NSCLC and PD-L1 expression 1% to 49%
  - Includes those aged 65-74 years and with ECOG PS 1
  - Exception: aged ≥ 75 years, similar outcomes with chemo-IO and IO alone
- Results question IO alone as control in new first-line RCTs in patients with adv NSCLC and PD-L1 expression 1% to 49%
- Future analyses: chemo-IO vs. IO alone in additional subgroups according to race/ethnicity, *KRAS* mutations, and safety outcomes across subgroups

Akinboro O, et al. *J Clin Oncol*. 2021;39:15_suppl, 9001. (ASCO Abstract #9001)

Guideline-Based Immunotherapy Recommendations for Adv/Metastatic NSCLC

Chemoimmunotherapy by histology (PD-L1 ≥ 1%)

Non-Squamous

- Platinum/pemetrexed/pembrolizumab
- Carboplatin/paclitaxel/bevacizumab/ atezolizumab
- Carboplatin/alb bound paclitaxel/atezolizumab
- Platinum/pemetrexed/nivolumab/ipilimumab

Squamous

- Carboplatin/paclitaxel*/pembrolizumab
- Carboplatin/paclitaxel/nivolumab/ipilimumab

* - paclitaxel or albumin bound paclitaxel

Immunotherapy

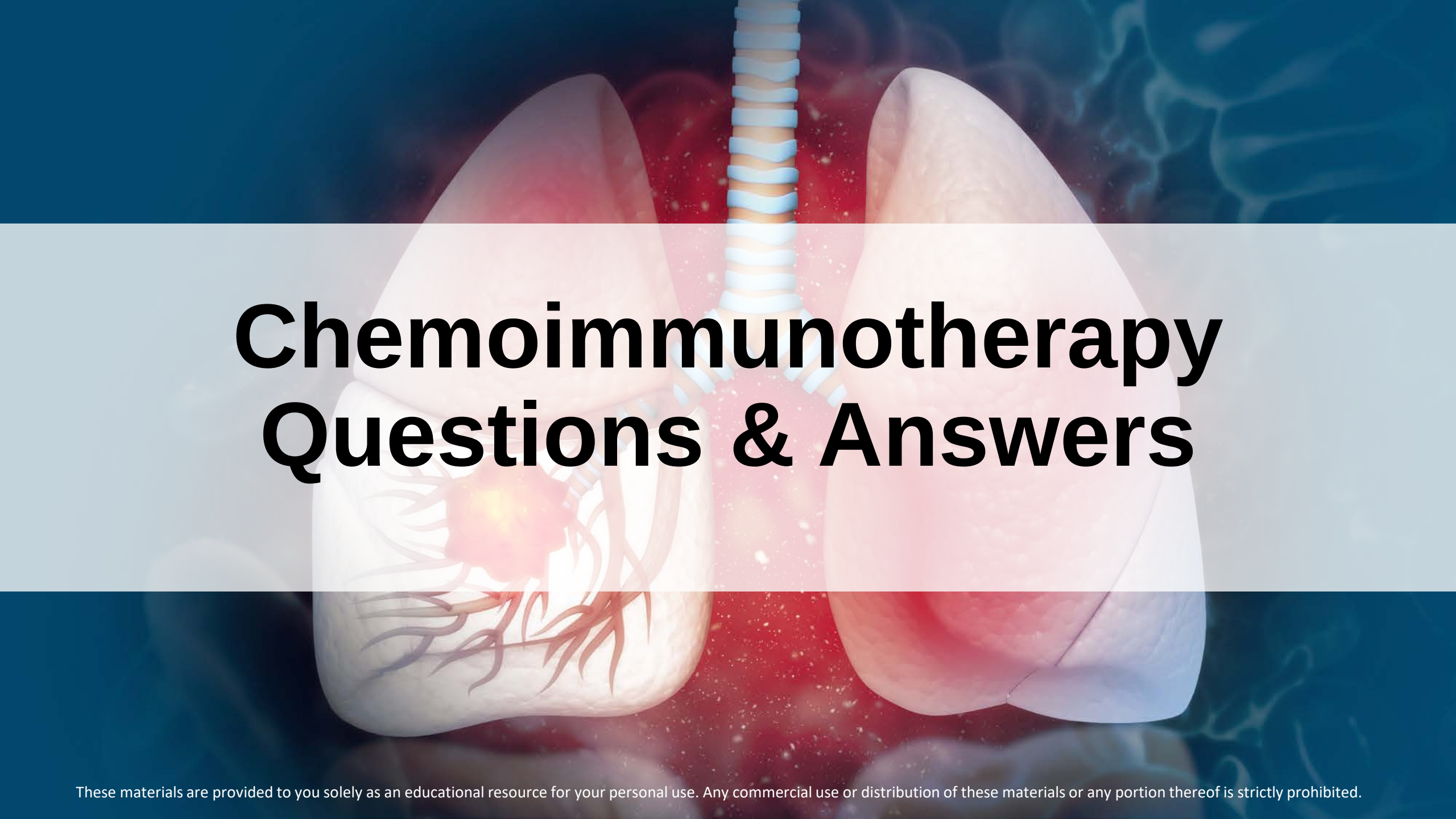
PD-L1 ≥ 1%

- Pembrolizumab
- Nivolumab/Ipilimumab

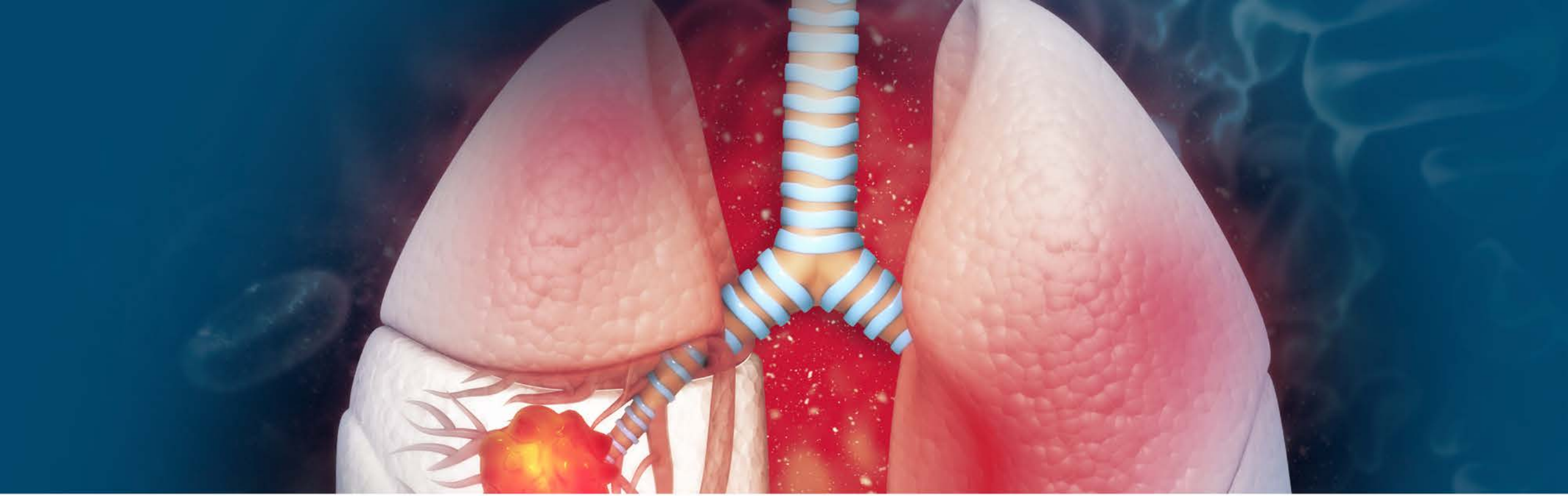
PD-L1 ≥ 50%

- Atezolizumab
- Cemiplimab

NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

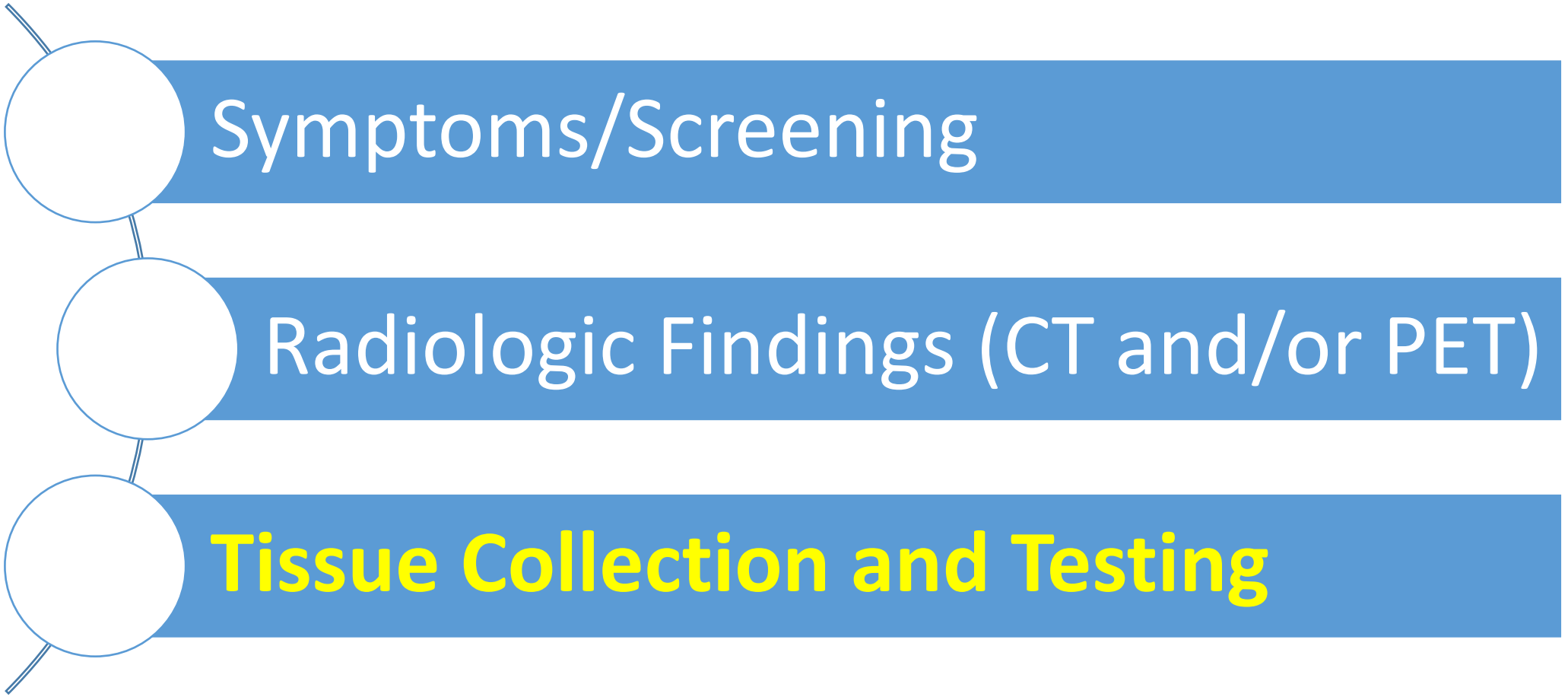


Chemoimmunotherapy Questions & Answers



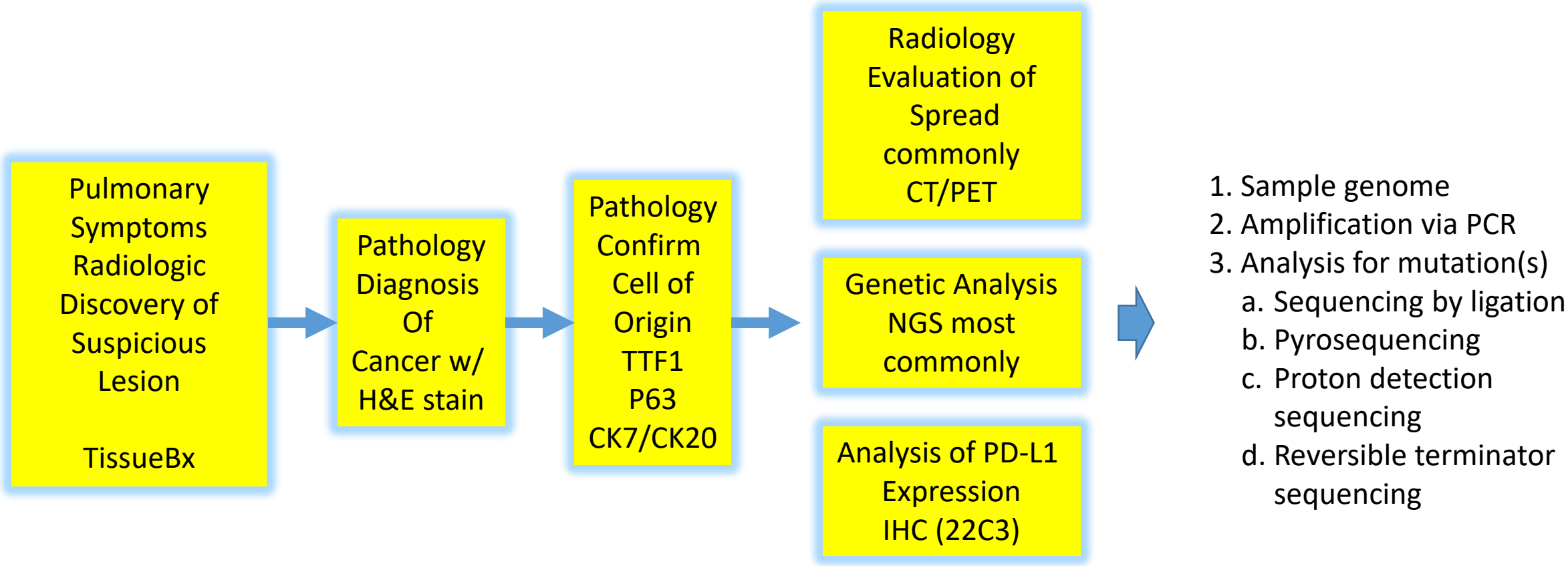
How are Tumors Tested for Driver Mutations?

Common Sequence of Diagnostic and Treatment Events



CT = computerized tomography; PET = positron emission tomography.

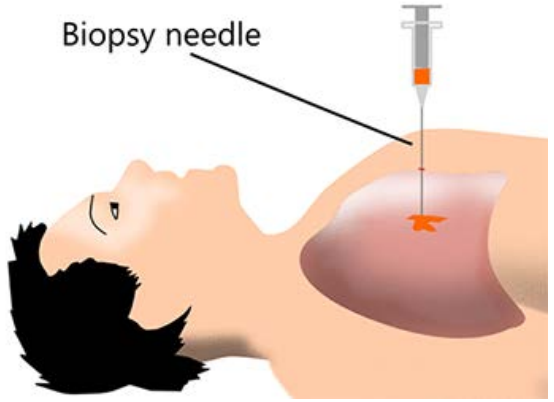
Initial Evaluation, Diagnosis and Staging



1. Sample genome
2. Amplification via PCR
3. Analysis for mutation(s)
   a. Sequencing by ligation
   b. Pyrosequencing
   c. Proton detection sequencing
   d. Reversible terminator sequencing

UpToDate: Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer Thomas, KW, et al. – accessed 10/21/2021
https://www.technologynetworks.com/genomics/articles/an-overview-of-next-generation-sequencing-346532 - Accessed 9/28/21

Sampling Challenges



- Lung cancer biopsies are less cellular than other solid tumors
- Bone biopsies yield poor sample due to decalcification, which degrades DNA
- Quality assurance of genomic medicine (multiple platforms, validation?)
- Logistical: timing of DNA sequencing can take weeks; centralized versus send out to distant laboratory
- QNS: Quality or quantity not sufficient (need 10% to 20% of viable cancer cells in sample for reliable results)

QNS = quantity not sufficient.

Vanderlaan PA, et al. *Lung Cancer*. 2014;84(1):39-44.; Hiley CT, et al. *Lancet*. 2016;388(10048):1002-1011.

NSCLC: Tissue Testing Methods and Targets

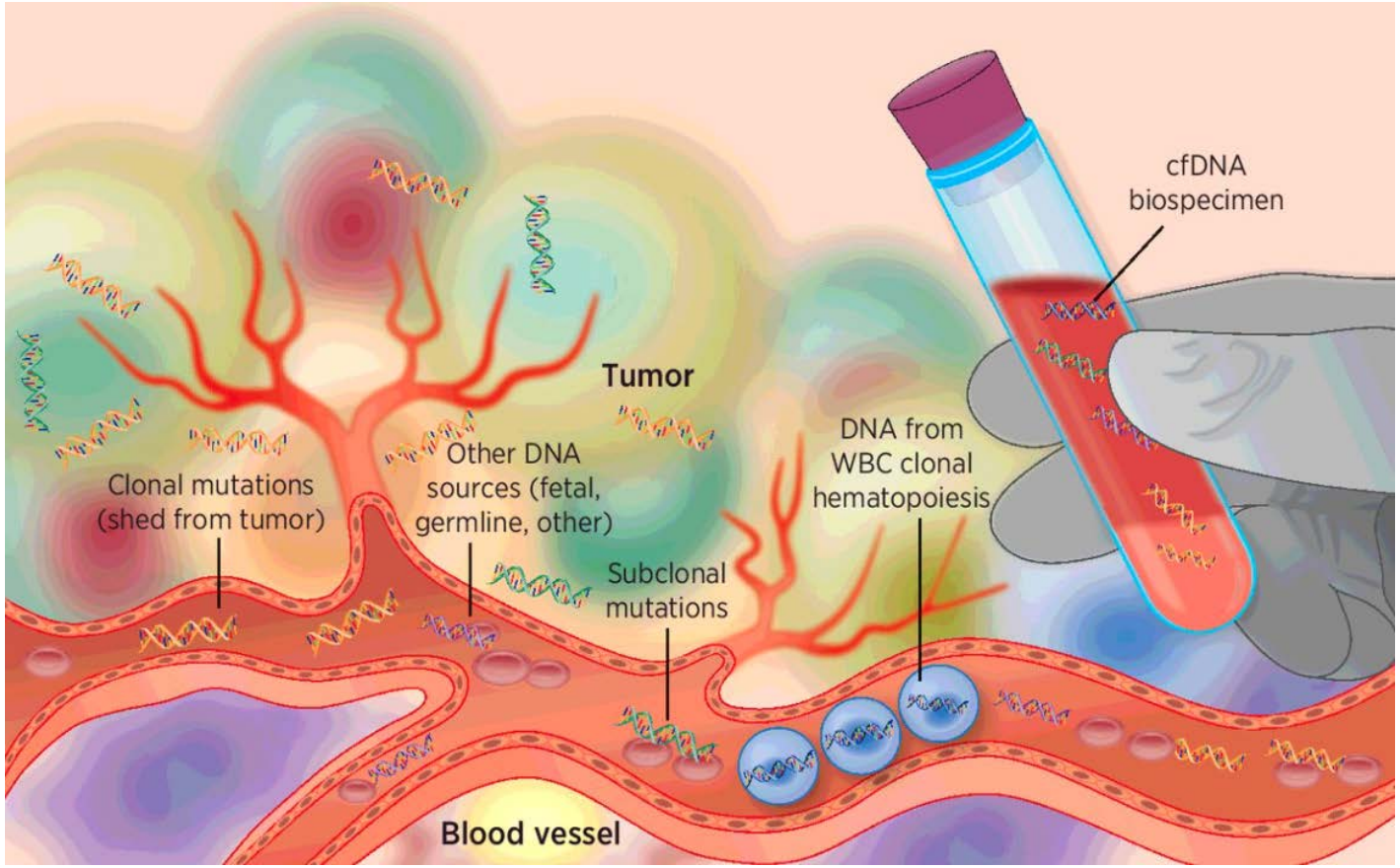
Biomarker/ Targetable Pathway ↓ / Testing Method →	Tissue allele-specific PCR	FISH testing	IHC testing	NGS DNA tumor seq.	Plasma ctDNA PCR	NGS plasma seq ctDNA	NGS RNA tumor seq
EGFR (sensitize and T790M)	++	0	**0**	**++**	+	+	+
HER2 mutation	++	0	**0**	**++**	+	+	+
METex14 mutation	++	0	**0**	**++**	+	+	++
BRAF mutation	++	0	**0**	**++**	+	+	+
KRAS mutation	++	0	**0**	**++**	+	+	+
ALK rearrangements	0	++	**++**	**+**	+	+	++
ROS1 rearrangement	0	++	**0**	**+**	0	+	++
MET amplification	0	++	**0**	**+**	0	+	+
RET rearrangement	0	++	**0**	**+**	+	+	++
PD-L1 expression	0	0	**++**	**0**	0	0	0
NTRK	0	++	**0**	**+**	0	+	++

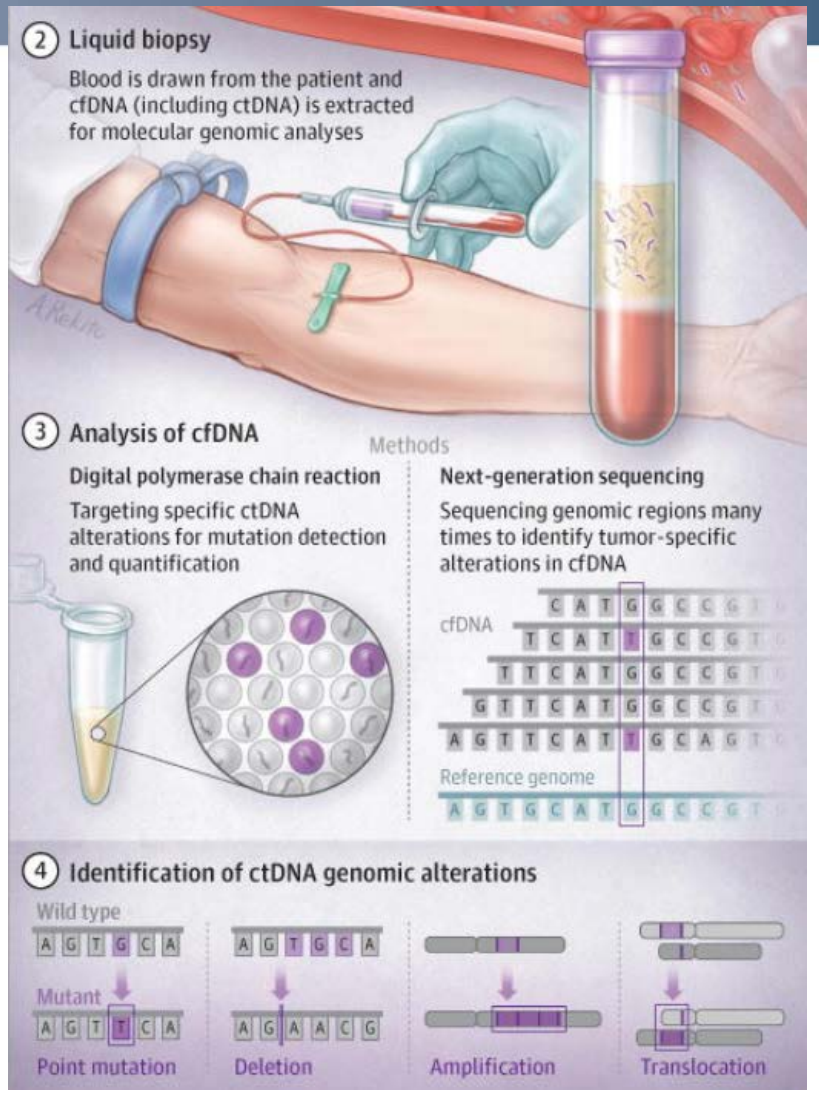
Each test requires specific # of tumor cells to sequence; ++ = most sensitive; + = less sensitive; 0 = not appropriate.

ALK = anaplastic lymphoma kinase; ctDNA = circulating tumor DNA; EGFR: epidermal growth factor receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; NGS = next generation sequencing; NRG1 = neuregulin 1; NTRK = neurotrophic receptor tyrosine kinase; PCR = polymerase chain reaction; PD-L1 = programmed cell death-ligand 1.

Sequist LV, et al. UpToDate. https://www.uptodate.com/contents/personalized-genotype-directed-therapy-for-advanced-non-small-cell-lung-cancer

What is a “Liquid Biopsy”?

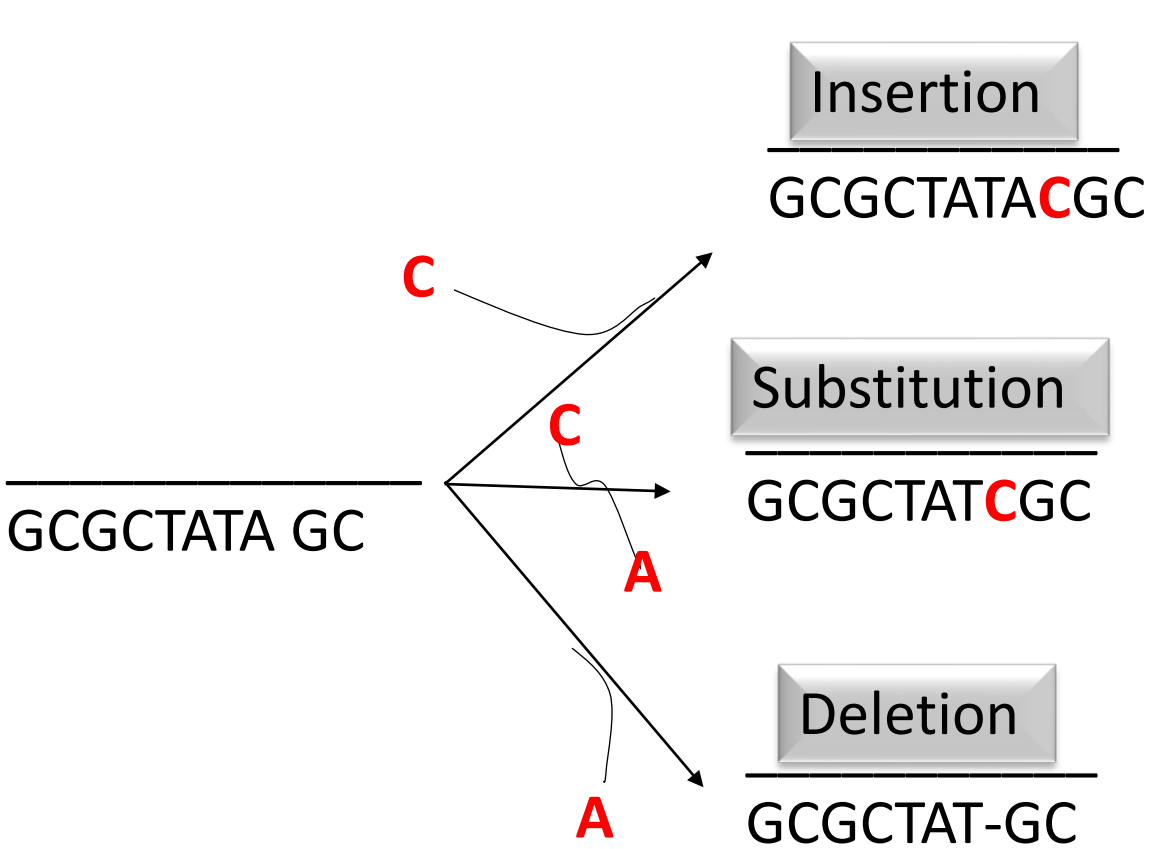


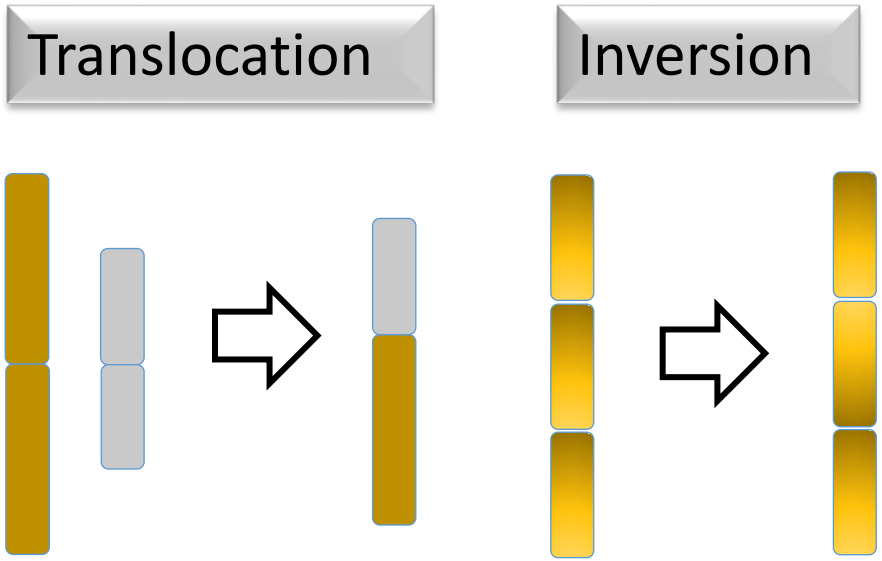


cfDNA = cell-free DNA; WBC = white blood cell

Bauml J, et al. *Clin Cancer Res*. 2018;24(18):4352-4354.; Husain H, et al. *JAMA*. 2017;318(13):1272-1274.

Accuracy of Liquid Biopsy



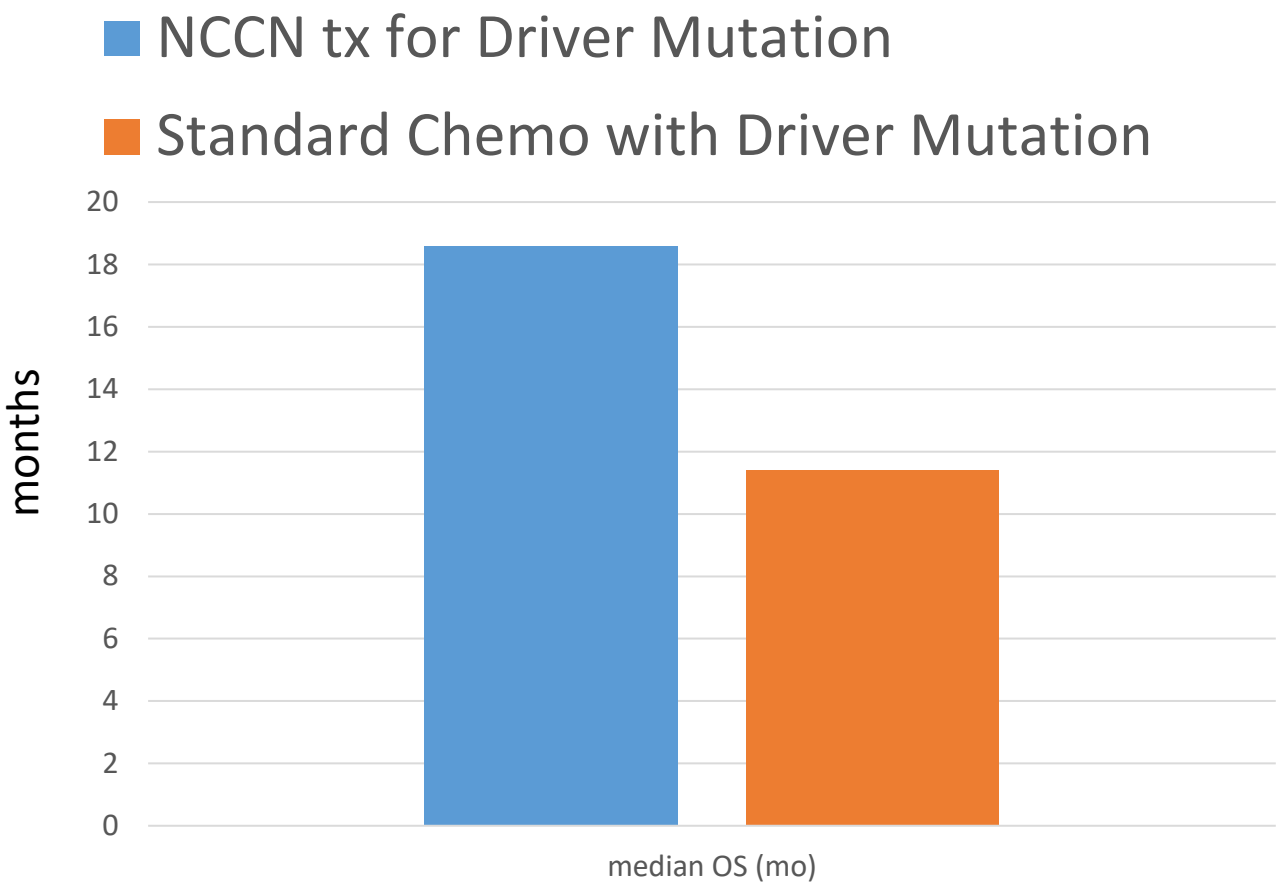


Positive predictive agreement between liquid and tissue biopsy is > 90%

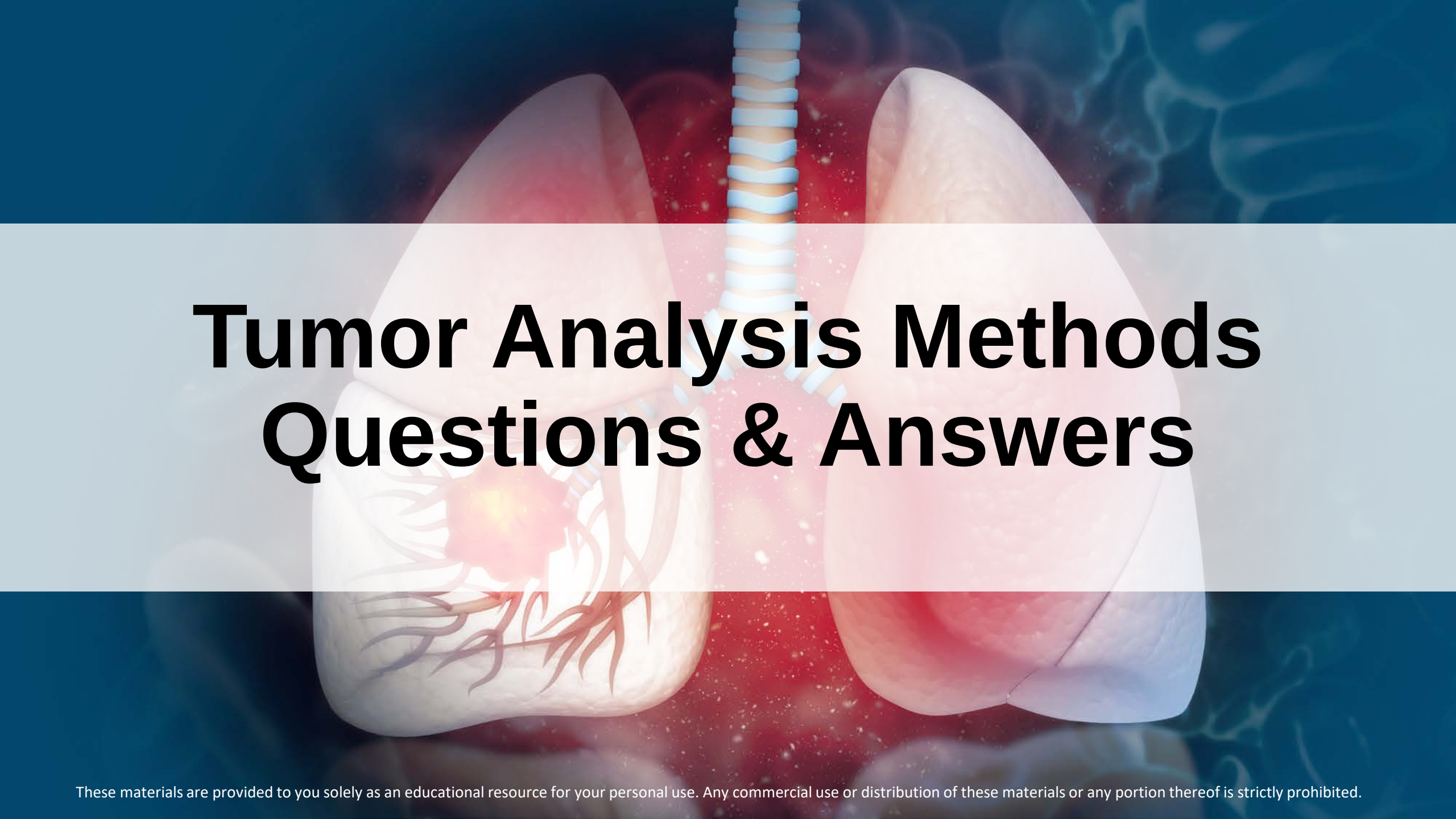
FoundationOne Liquid CDx. http://info.foundationmedicine.com/hubfs/FMI%20Labels/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf.

Testing and Survival

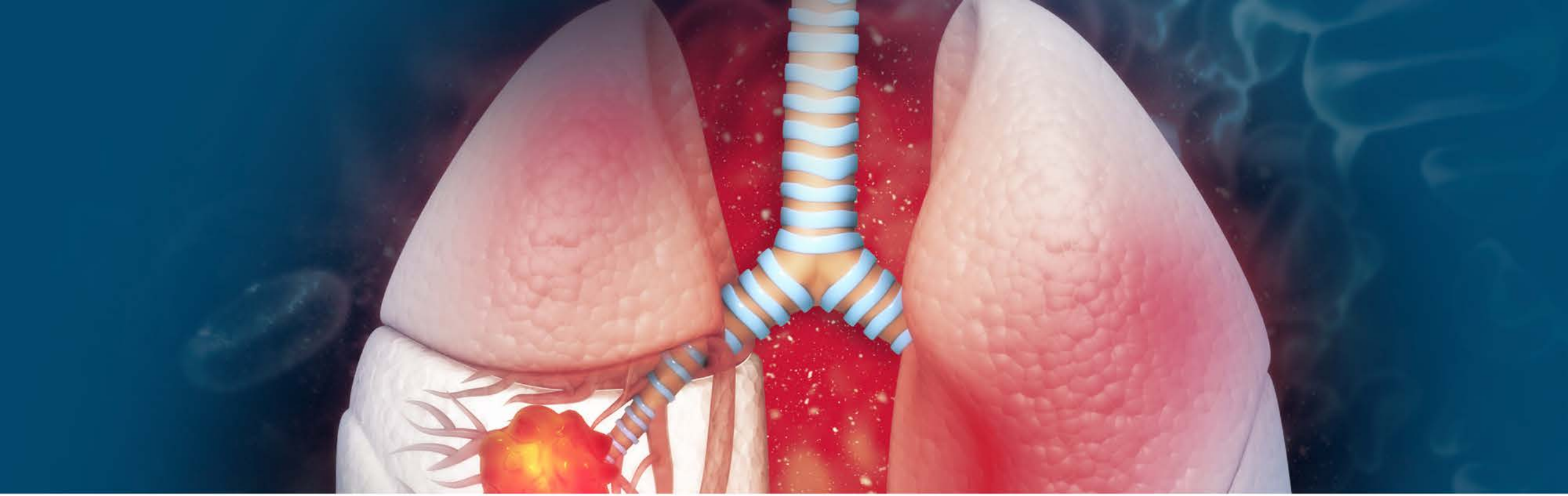
- Many studies show that patients who get chemotherapy rather than targeted therapy specific to their driver mutation do much worse
- Testing and treatment has been incorporated into guidelines
- Following the guidelines improves survival



KM = Kaplan-Meier; NCCN = National Comprehensive Cancer Network; OS = overall survival. Singal G, et al. *JAMA*. 2019;321(14):1391-1399.

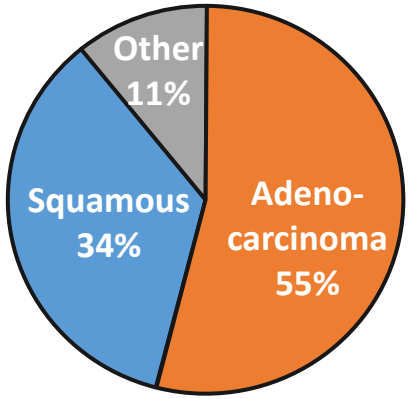


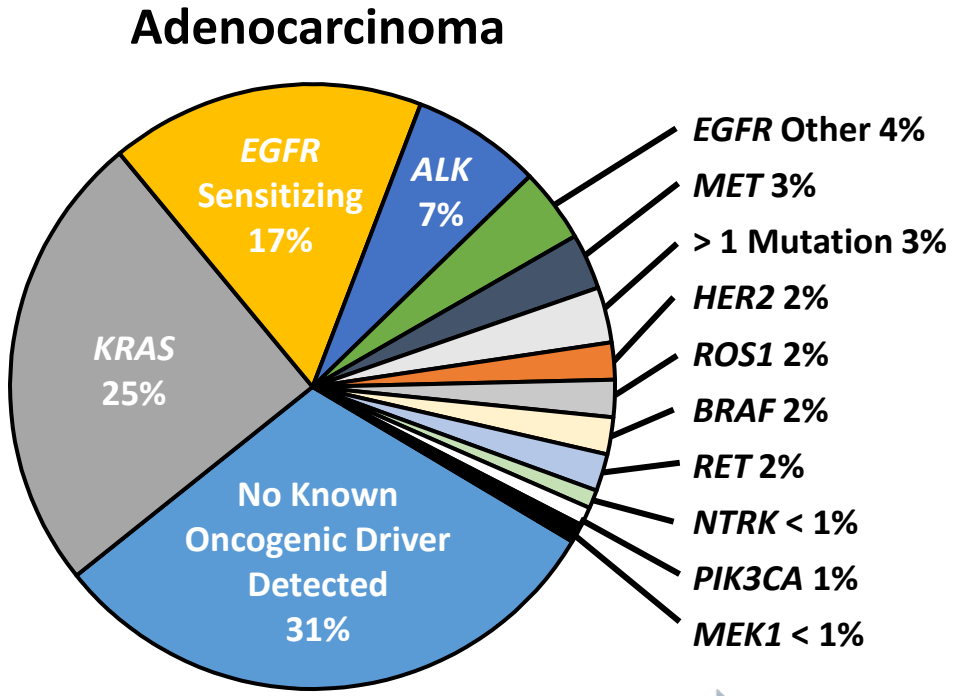
Tumor Analysis Methods Questions & Answers



How does Driver Mutations Impact Treatment Selection?

Non-Small Cell Lung Cancer

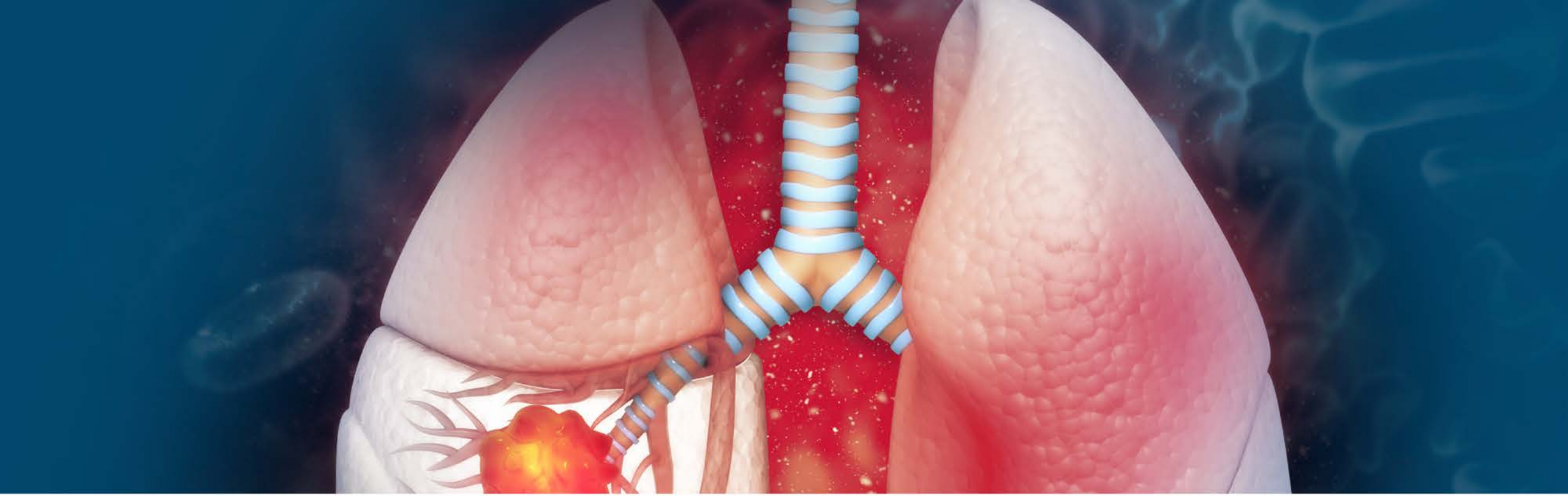




Then — Histology-Based Subtyping — Now

Actionable oncogenic drivers are found in ~40% of patients with adenocarcinoma

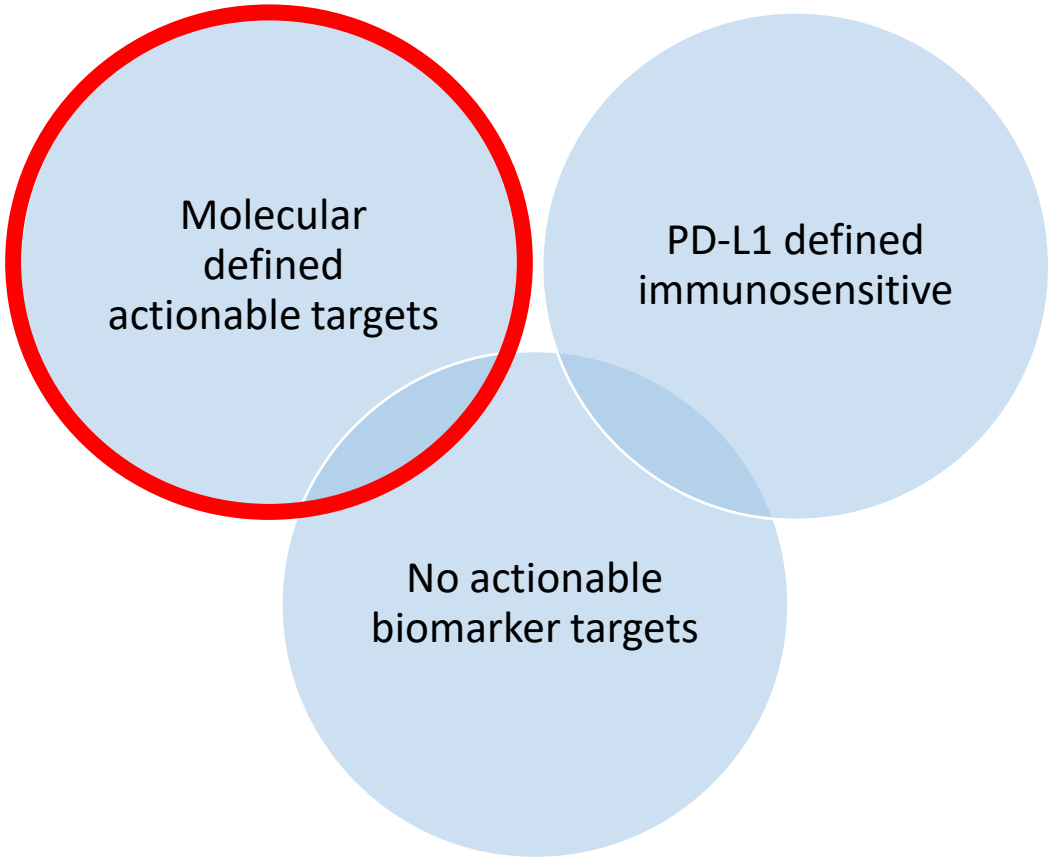
Li T et al. *J Clin Oncol*. 2013;31(8):1039-1049.;
Tsao AS, et al. *J Thorac Oncol*. 2016;11(5):613-638.



Identifying Recommended Treatments Based on Driver Mutations

Biomarker-Based Treatment Selection

- Biomarkers divided NSCLC into 3 groups



Predictive Biomarker: indicative of therapeutic efficacy because there is an interaction between the biomarker and therapy on patient outcome

Prognostic Biomarker: indicative of patient survival independent of treatment received because the biomarker is an indicator of tumor aggressiveness

Riely GL. *J Natl Compr Canc Netw*. 2017;15(5S):686-688.

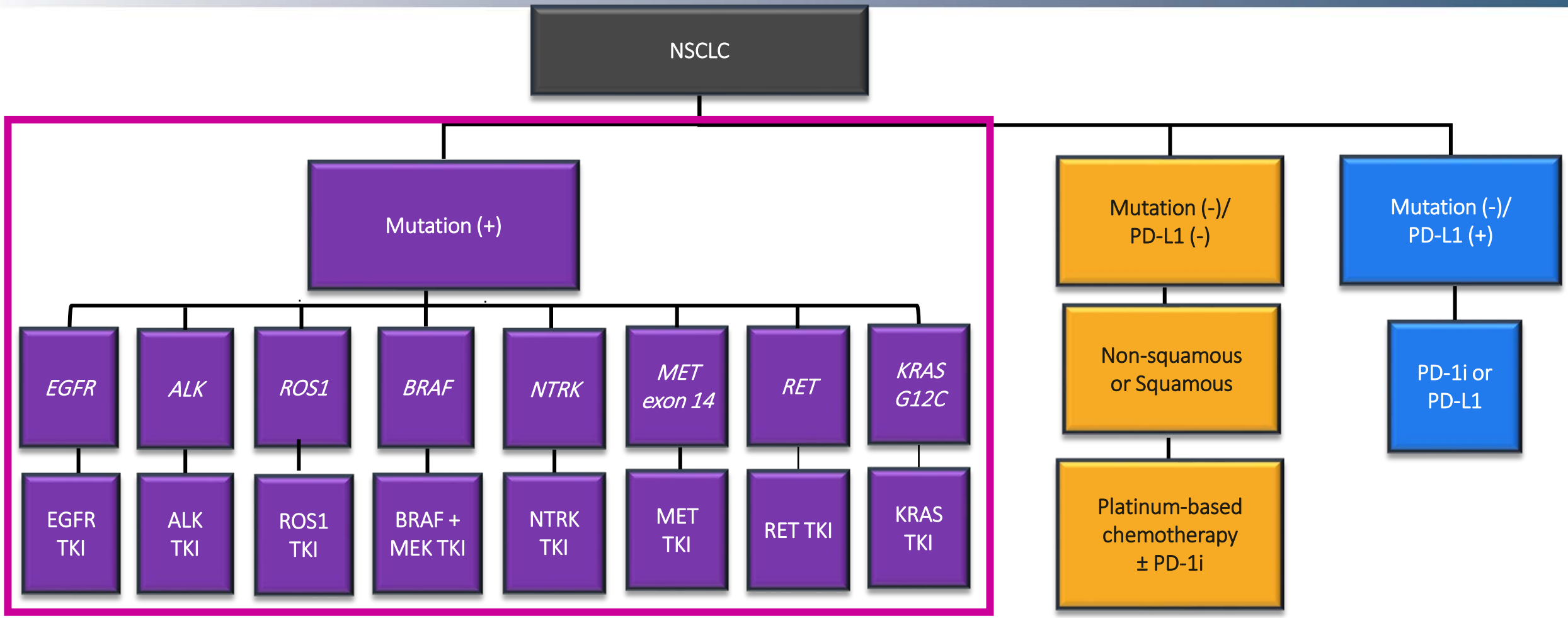
Why is Testing Important?

- NCCN recommends NGS testing as part of boarder molecular profiling
- All patients with metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified
  - Minimum of EGFR, ALK, ROS1, BRAF, METex14, RET, NTRK1/2/3
- Singal G, et al.: Used a clinicogenomic database to determine association of patient characteristics and tumor genomics with clinical outcomes among 4,064 patients with advanced NSCLC
  - 85% treated in community setting
- Results: 48.3% of patients with advanced NSCLC with an NCCN-driver mutation received NCCN-recommended therapy

	NCCN Directed Therapy N = 575	Did not receive NCCN-directed therapy N = 560	P value
Median OS	18.6 months	11.4 months	< 0.001

Singal G, et al. *JAMA*. 2019;321(14):1391-1399.

Individualized Treatment



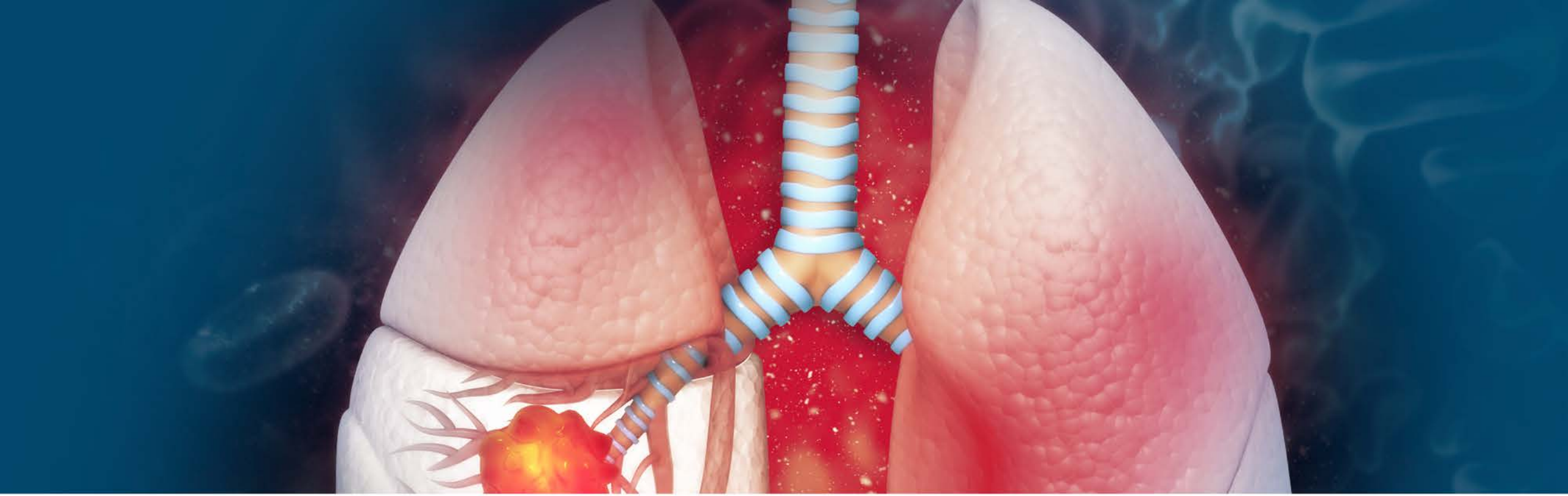
PD-L1 = programmed cell death ligand 1; PD1i = PD-1 immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor.

NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

FDA-Approved Targeted Therapies

EGFR (exon 19 del or L858R)	EGFR exon 20 insertion	ALK	ROS 1	BRAF V600E	NTRK	RET	MET exon 14	KRASG12C
Afatinib	Amivantamab	Alectinib	Ceritinib	Dabrafenib + Trametinib	Entrectinib	Pralsetinib	Capmatinib	Sotorasib
Dacomitinib	Mobocertinib	Brigatinib	Crizotinib		Larotrectinib	Selpercatinib	Crizotinib	
Gefitinib		Ceritinib	Entrectinib			Cabozantinib	Tepotinib	
Erlotinib		Crizotinib	Lorlatinib			Vandetanib		
Osimertinib		Lorlatinib						

NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf



What are options for KRAS G12C mutation?

Sotorasib

Indication

- KRAS G12C-mutated locally advanced or metastatic NSCLC
- Received at least 1 prior systemic therapy

Dosing and Drug Interactions

- 960 mg once daily until progression or unacceptable toxicity
- DDI: avoid PPIs and H2RAs

Adverse Effects and Monitoring Parameters

- AE: diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, cough
- Monitoring: CBC, LFTs, urine protein, Na, Ca

AE = adverse effect; CBC = complete blood count; DDI = drug-drug interaction; H2RA = histamine-2 receptor antagonist; LFT = liver function test; PPI = proton pump inhibitor.

Lumakras [package insert]. Amgen, Inc.;2021.

CodeBreaK 100 Trial: Sotorasib

Study Design

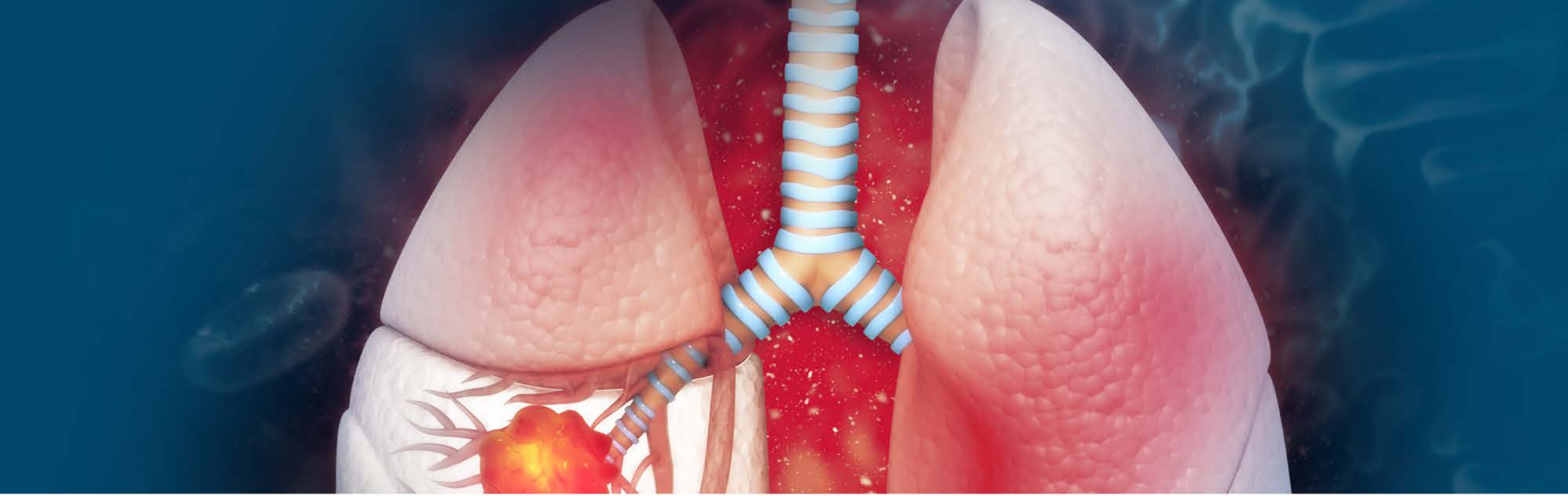
- Single-arm, phase 2, open label, multi-center
  - 960 mg PO once daily
- Locally advanced or metastatic NSCLC
- KRAS G12C mutation
- Progressed on immunotherapy and/or platinum-based chemotherapy

Results

- N = 126
- ORR: 37.1% (95% CI, 28-45%)
- mDOR: 10 months
- mPFS 6.8 months
- Disease control rate: 80.6%

mDOR = median duration of response; mPFS = median progression-free survival; ORR = overall response rate

https://www.amgen.com/newsroom/press-releases/2021/06/results-from-phase-2-codebreak-100-show-lumakras-sotorasib-is-the-first-and-only-kras-g12c-inhibitor-with-overall-survival-data



What are options for MET Exon 14 mutation?

Capmatinib

Indication

- Metastatic NSCLC with MET exon 14 skipping mutation

Dosing and Drug Interactions

- 400mg BID until progression or unacceptable toxicity
- DDI: avoid use with strong & moderate CYP3A inducers

Adverse Effects and Monitoring

- AE: peripheral edema, nausea/vomiting, fatigue, dyspnea, decreased appetite
- Monitoring: renal function, LFTs, CBC, electrolytes, glucose, amylase

Tabrecta [package insert]. Novartis Pharmaceuticals Corporation;2020.

GEOMETRY Mono-1
Capmatinib: MET Exon 14 Skipping

Study Design

- Phase II multi-cohort trial
  - Capmatinib 400mg PO BID
- Stage IIIB or IV NSCLC
- *MET* exon 14 skipping mutation or *MET* amplification
- Treatment naïve and pretreated (2^{nd}/3^{rd} line)

Results (*MET* exon 14 skipping only)

- N = 69 Previous treatment, N = 28 Treatment naïve
- ORR%
  - Previous treatment: 41%
  - Treatment naïve: 68%
- mPFS
  - Previous treatment: 5.4 months (95% CI, 4.2-7.0)
  - Treatment naïve: 12.4 months (95% CI, 8.2-not estimated)

Wolf J, et al. *N Engl J Med*. 2020;383(10):944-957.

Tepotinib

Indication

- Metastatic NSCLC with MET exon 14 skipping mutation

Dosing and Drug Interactions

- 450mg once daily with food until progression or unacceptable toxicity
- DDI: avoid use with strong CYP3A inducers and P-gp inhibitors

Adverse Effects and Monitoring

- AE: edema, nausea, fatigue, diarrhea, musculoskeletal pain, dyspnea
- Monitoring: serum creatinine, LFTs, electrolytes, amylase, CBC

P-gp = P-glycoprotein.

Tepmetko [package insert]. EMD Serono, Inc.;2021.

VISION
Tepotinib: MET Exon 14 Skipping

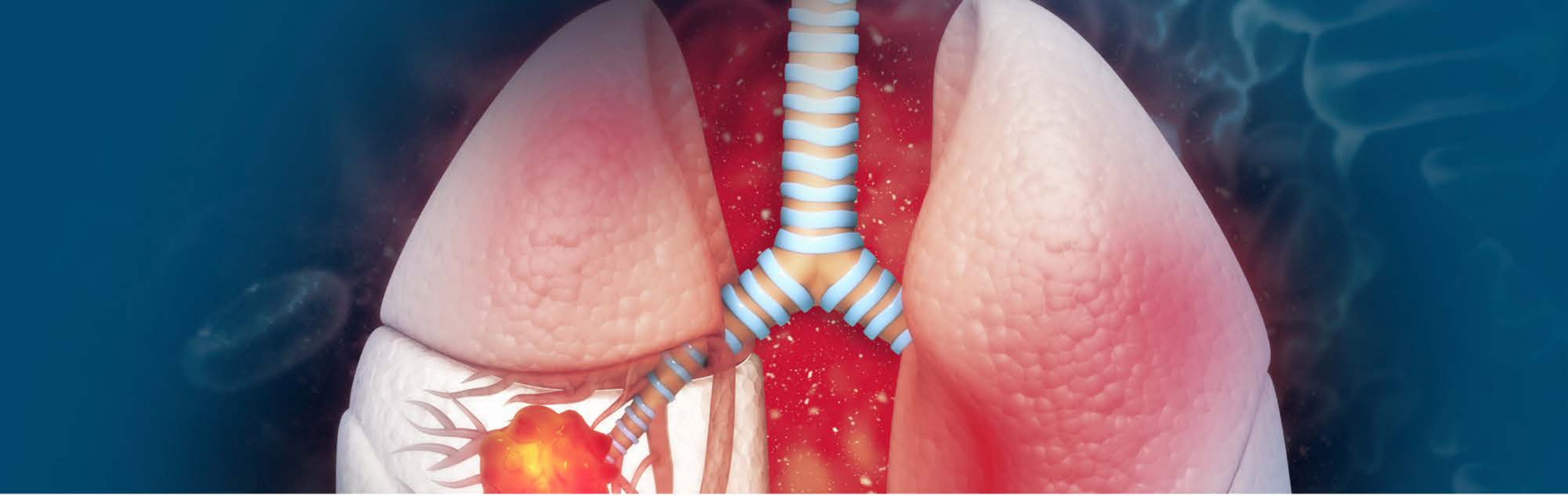
Study Design

- Phase II multi-cohort
  - Tepotinib 500 mg PO once daily
- Stage IIIB/IV NSCLC
- MET exon 14 skipping mutation
- Treatment naïve and pretreated (2^{nd}/3^{rd} line)

Results

- N = 66 Liquid biopsy
  - ORR 48.5%
  - DoR: 9.9 mo, PFS 8.5 months
- N = 60 Tissue biopsy
  - ORR 50%
  - DoR 15.7 months, PFS 11.0 months

Paik PK, et al. *N Engl J Med*. 2020;383(10):931-943



What are Options for RET Fusion Positive Mutations?

Selpercatinib

Indication

- Metastatic NSCLC with RET fusion positive mutation

Dosing and Drug Interactions

- 120 mg PO BID (< 50 kg) or 160mg PO BID (≥ 50 kg) until progression or unacceptable toxicity
- DDI: avoid acid reducers and strong/moderate CYP3A inducers & inhibitors

Adverse Effects and Monitoring

- AE: fatigue, edema, constipation, diarrhea, hypertension, dry mouth, rash
- Monitoring: serum creatinine, CBC, electrolytes, cholesterol

Retevmo [package insert]. Lilly USA, LLC;2021.

LIBRETTO-001
Selpercatinib: RET Fusion Positive

Study Design

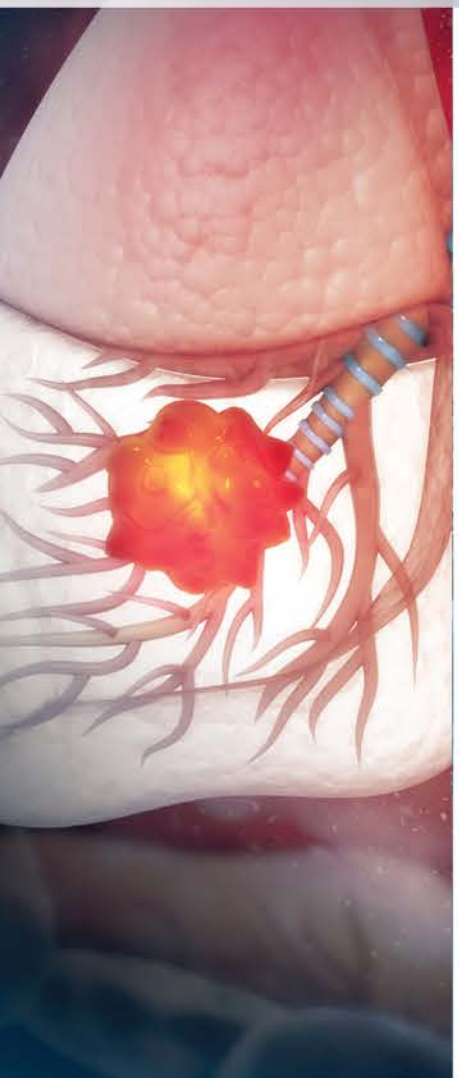
- Phase I/II
  - Selpercatinib 160 mg PO BID (phase II)
- Stage IIIB/IV NSCLC
- RET fusion
- Treatment naïve and prior platinum chemo

Results

- N = 39 Treatment naïve
  - ORR: 85% (95% CI, 70 – 94)
  - mDOR: NE (95% CI, 12 – NE)
  - mPFS: NE (95% CI, 13.8 mo – NE)
- N = 105 Previous Treatment
  - ORR: 64% (95% CI, 54 – 73)
  - mDOR: 17.5 mo (95% CI, 12 – NE)
  - mPFS: 16.5 mo (95% CI, 13.7 – NE)

Drilon A, et al. *N Engl J Med*. 2020;383(9):813-824.

Pralsetinib



Indication

- Metastatic RET fusion-positive NSCLC

Dosing and Drug Interactions

- 400 mg once daily on empty stomach until progression or unacceptable toxicity
- DDI: avoid coadministration with strong CYP3A4 inducers or inhibitors

Adverse Effects and Monitoring

- AE: fatigue, constipation, musculoskeletal pain, hypertension
- Monitoring: CBC, LFTs, serum creatinine, electrolytes

Gavreto [package insert]. Blueprint Medicines Corporation;2020.

ARROW
Pralsetinib: RET Fusion Positive

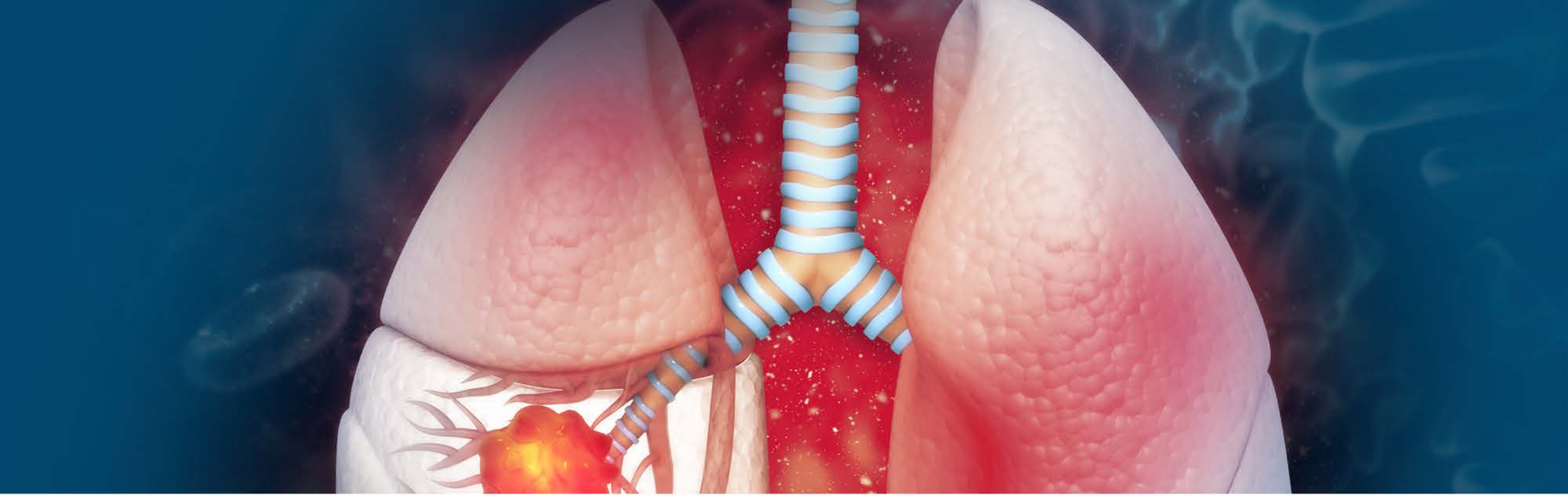
Study Design

- Phase I/II multi-cohort trial
  - Pralsetinib 400mg PO once daily (phase II)
- Unresectable locally advanced or metastatic NSCLC
- RET fusion-positive
- Treatment naïve and pretreated

Results

- n = 114
- ORR %: 70%
  - N = 87 Previously treated
  - N = 27 Treatment naive
- mDOR (mo): treatment naive
  - Not reach (95% CI 11.3 - NR)

Gainor JF, et al. *Lancet Oncol*. 2021;22(7):959-969. DOI: 10.1200/JCO.2020.38.15_suppl.9515 *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 9515-9515.



What are Options for EGFR Exon 20 Insertion mutations?

EGFR exon 20 insertions comprise 4-10% of EGFR-mutant NSCLC and refractory to 1st/2nd generation EGFR TKIs

CHRYSALIS: Amivantamab

- Anti-EGFR-MET bispecific antibody
- Phase I (n = 39)
- ORR: 36% (95% CI, 21-53)
- mPFS
  - Prior platinum chemotherapy: 8.6 mo (95% CI, 3.7 – 14.8)
  - Response-evaluable patients: 8.3 mon (95% CI, 3.0 – 14.8)
- Dosing: IVPB, weight-based dosing
- Pre-medications required
- AE: rash, infusion reactions, paronychia, cough, nausea/vomiting, constipation, edema, stomatitis, dyspnea, musculoskeletal pain
- Monitoring: CBC, electrolytes, LFTs

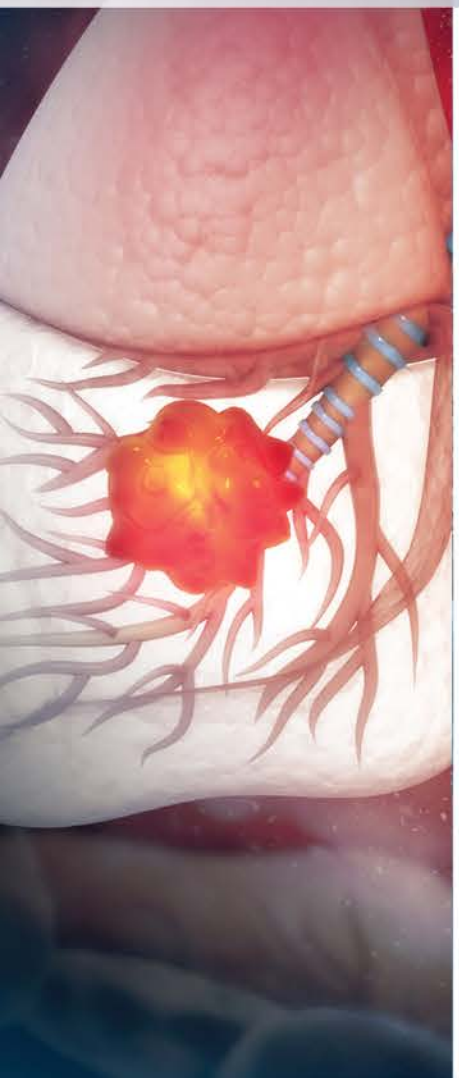
EXCLAIM Phase I/II: Mobocertinib

- Phase I/II (n = 28)
- ORR: 43%
- mPFS: 7.3 months
- Dosing: 160 mg PO once daily until progression or unacceptable toxicity
- Boxed Warnings: QTc prolongation & Torsades de points
- AE: Diarrhea, stomatitis, nausea/vomiting, rash, paronychia, musculoskeletal pain, cough, fatigue,
- Monitoring: CBC, renal function, LFTS, electrolytes
- DDI: CYP3A4 inducers/inhibitors and medications that prolong QTc

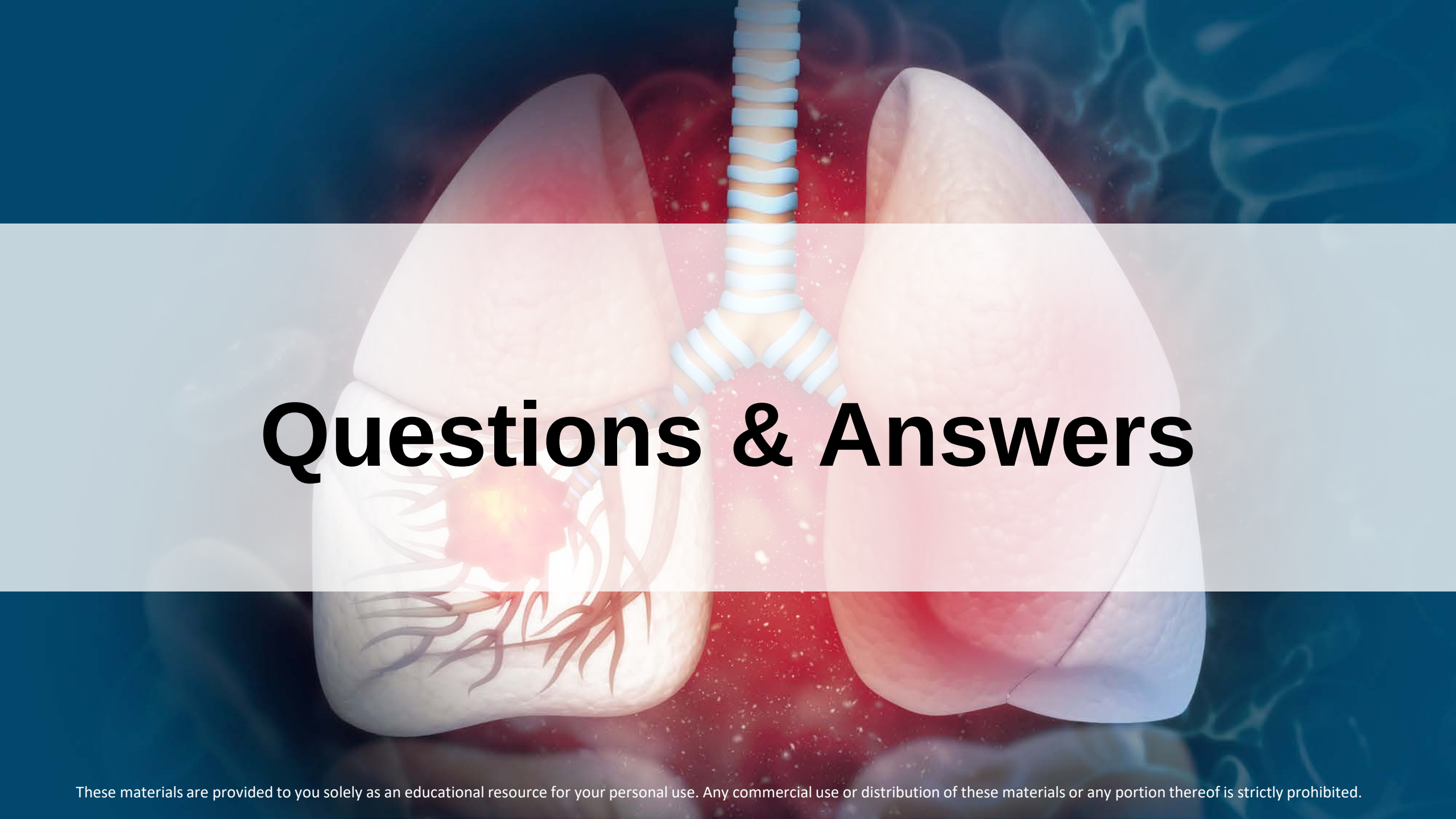
IVPB = intravenous piggyback

Cho JH, et al. *J Clin Oncol*. 2020;38:15_suppl, 9512.;
Riely G, et al. *Ann Oncol*. 2020;31(suppl 4):S754-S840.

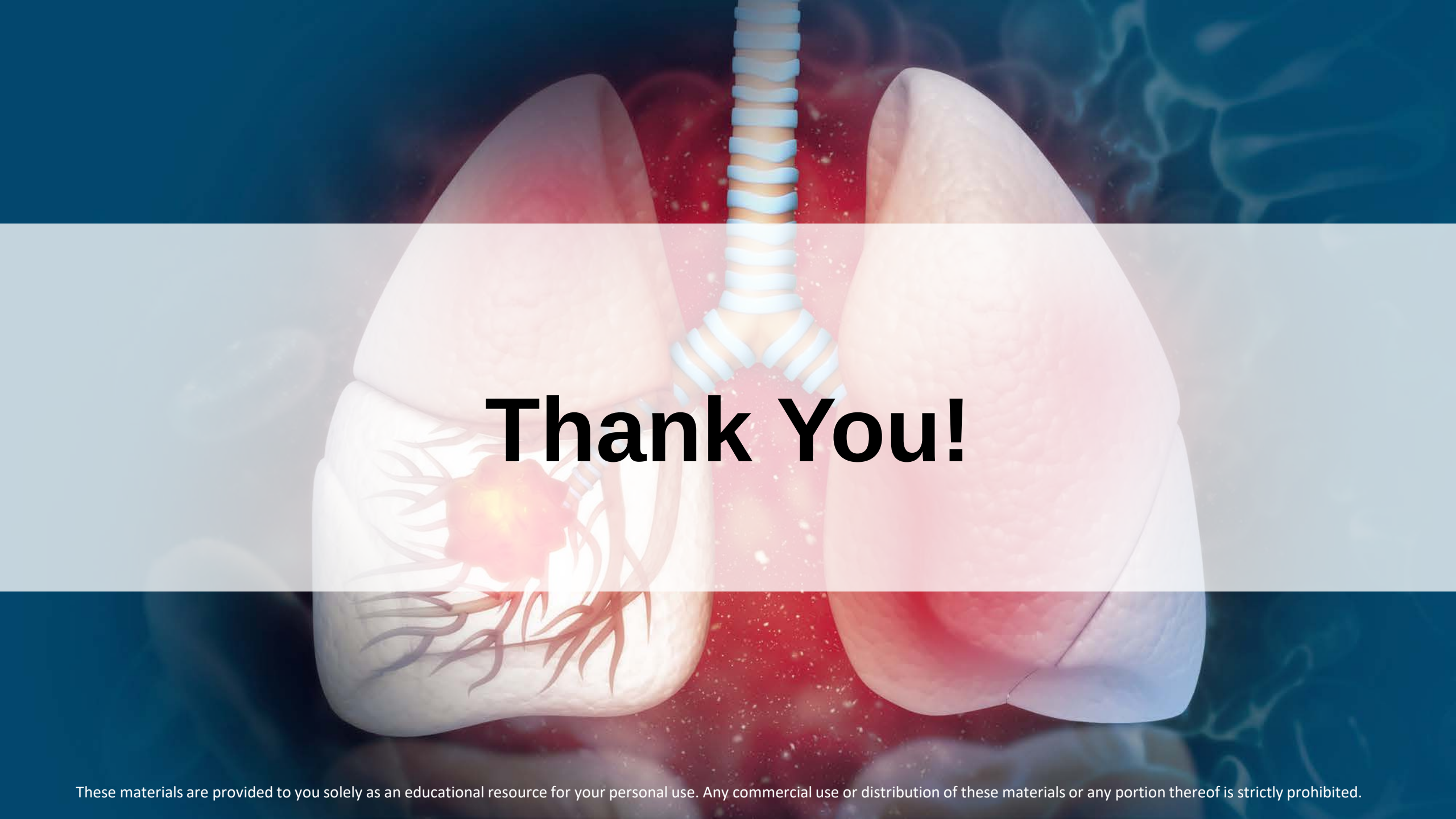
Summary



- NSCLC is a heterogeneous disease with multiple actionable biomarkers
  - Improved efficacy outcomes demonstrated with targeted therapies for NSCLC with driver mutations
- Biomarker testing should be conducted in all eligible patients with advanced NSCLC
- Recommend appropriate target-based therapy to optimize efficacy outcomes
- Role of the pharmacist
  - Dosing, administration, monitoring parameters, counseling, drug interactions



Questions & Answers



Thank You!