The role of predictive biomarker testing in NSCLC: More important than ever!

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Disclosures

- Section author for ‘Pathology of Head and Neck Tumors’ @ *uptodate.com*

Agenda

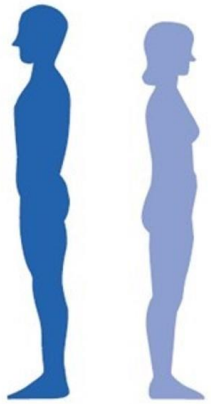
- Background
- Genetic alterations
- PD-L1 IHC
- Specimen considerations

Lung Cancer is Common

Cancer Statistics 2023

Estimated New Cancer Cases in the US in 2023

Male			Female		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All sites	**1,010,310**		**All sites**	**948,000**	



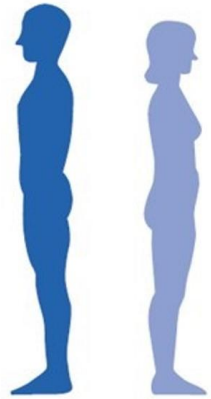
Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Lung Cancer is Common

Cancer Statistics 2023

Estimated Cancer Deaths in the US in 2023

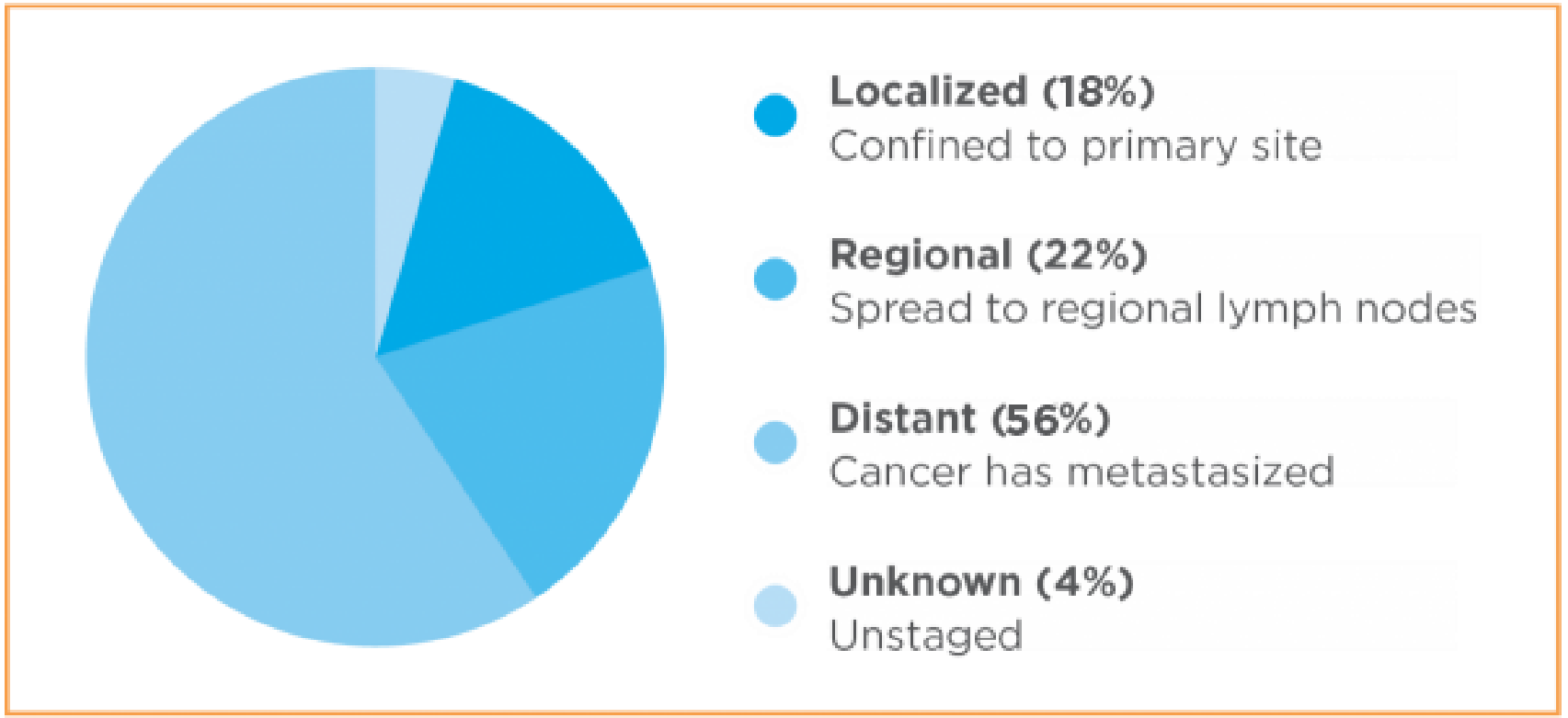
Male		
Lung & bronchus	67,160	21%
Prostate	34,700	11%
Colon & rectum	28,470	9%
Pancreas	26,620	8%
Liver & intrahepatic bile duct	19,000	6%
Leukemia	13,900	4%
Esophagus	12,920	4%
Urinary bladder	12,160	4%
Non-Hodgkin lymphoma	11,780	4%
Brain & other nervous system	11,020	3%
All sites	**322,080**	



Female		
Lung & bronchus	59,910	21%
Breast	43,170	15%
Colon & rectum	24,080	8%
Pancreas	23,930	8%
Ovary	13,270	5%
Uterine corpus	13,030	5%
Liver & intrahepatic bile duct	10,380	4%
Leukemia	9,810	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,970	3%
All sites	**287,740**	

Most lung cancer patients will never undergo resection

PERCENTAGE OF LUNG CANCER DIAGNOSES BY STAGE



A shifting paradigm in metastatic NSCLC

Lung Cancer Diagnosis 2004

- Small cell carcinoma
- Non-small cell carcinoma

Lung Cancer Diagnosis 2023

- Small cell carcinoma
- Non-small cell carcinoma
  - Adenocarcinoma
  - Squamous cell carcinoma

- Molecular testing

- PD-L1 expression (IHC)

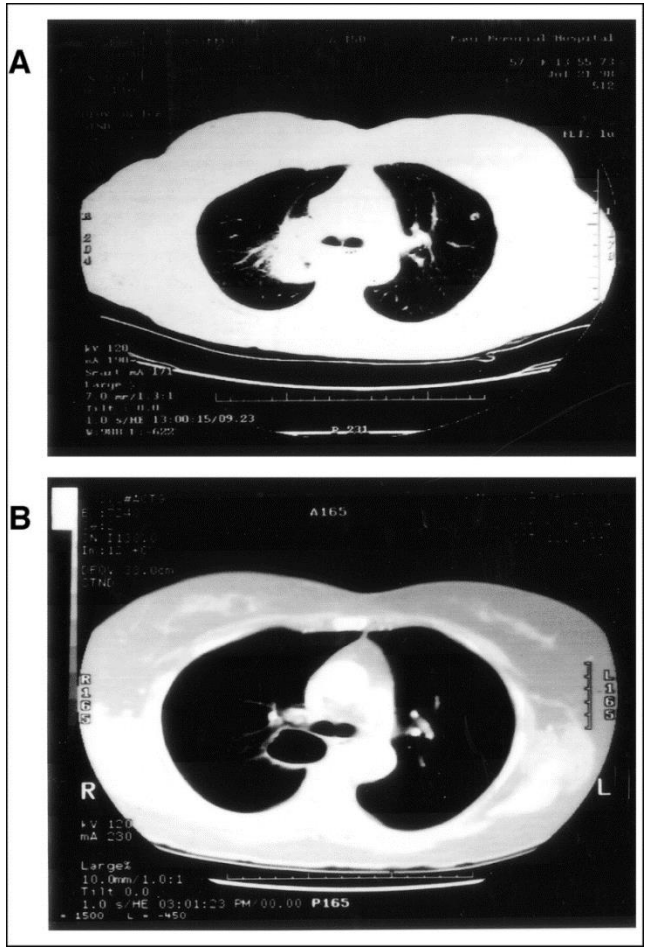
Predictive biomarkers in NSCLC

Predictive biomarker: Data point that can be used to predict response to a therapuetic intervention

- Histologic type (AdenoCA vs Squamous)
- Genetic alterations
- PD-L1 status

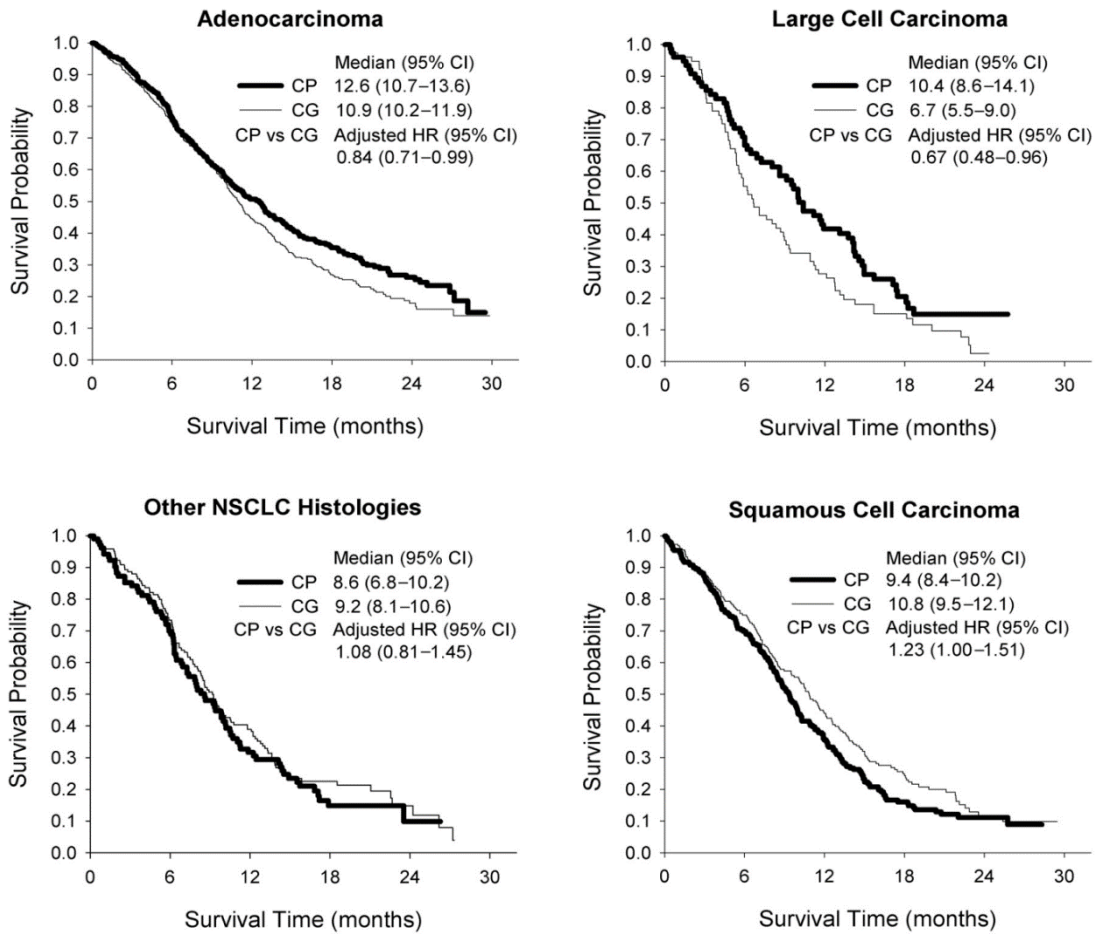
Bevacizumab was associated with severe pulmonary hemorrhage in squamous cell carcinoma

- Severe pulmonary hemorrhage occurred in ~30% of patients with squamous cell carcinoma and 4% of patients with non squamous carcinoma



Johnson D, et al. JCO. 2004.

The therapeutic advantage with pemetrexed is limited to patients with non-squamous histologies



Scagliotti G, et al. The Oncologist. 2009.

National Comprehensive Cancer Network®

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Non-Small Cell Lung Cancer

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

Other Recommended

- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e]
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e]

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- Pembrolizumab/carboplatin/paclitaxel (category 1)[36,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[36,e]

Other Recommended

- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e]
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[8,e]

Predictive biomarkers in NSCLC

Predictive biomarker: Data point that can be used to predict response to a therapuetic intervention

- Histologic type (AdenoCA vs Squamous)
- Genetic alterations
- PD-L1 status

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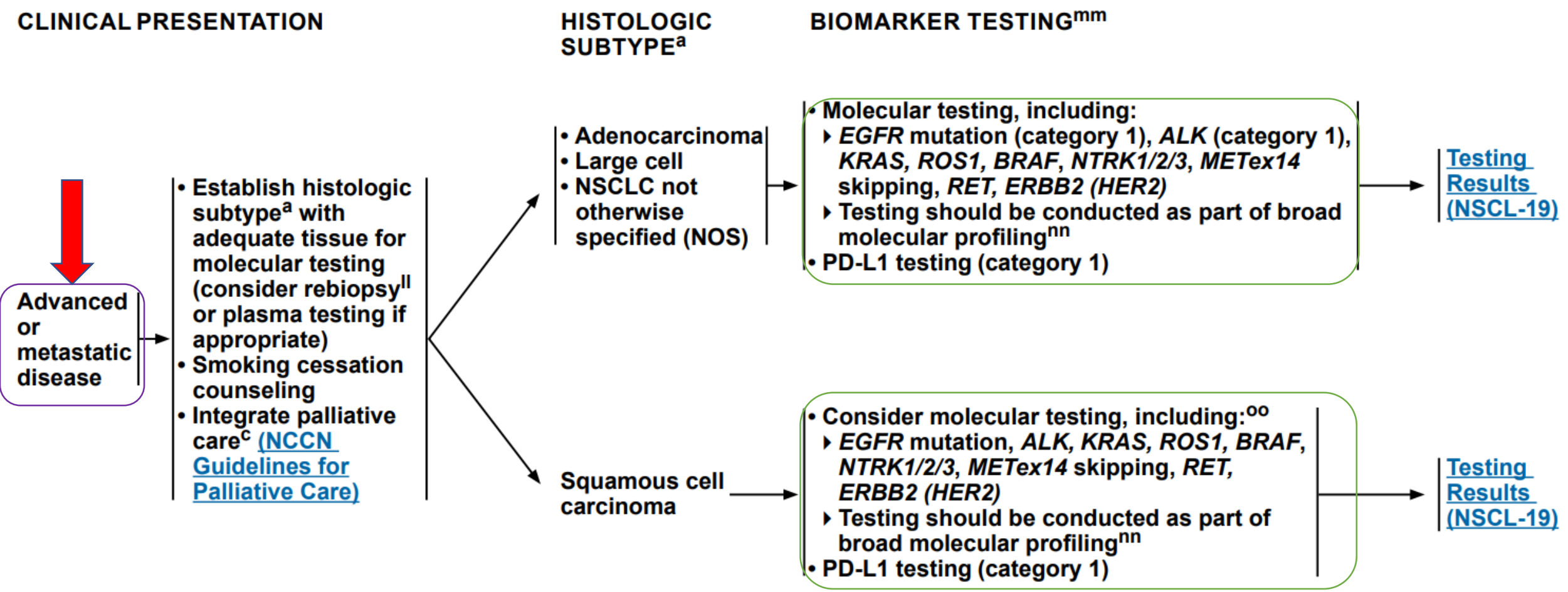
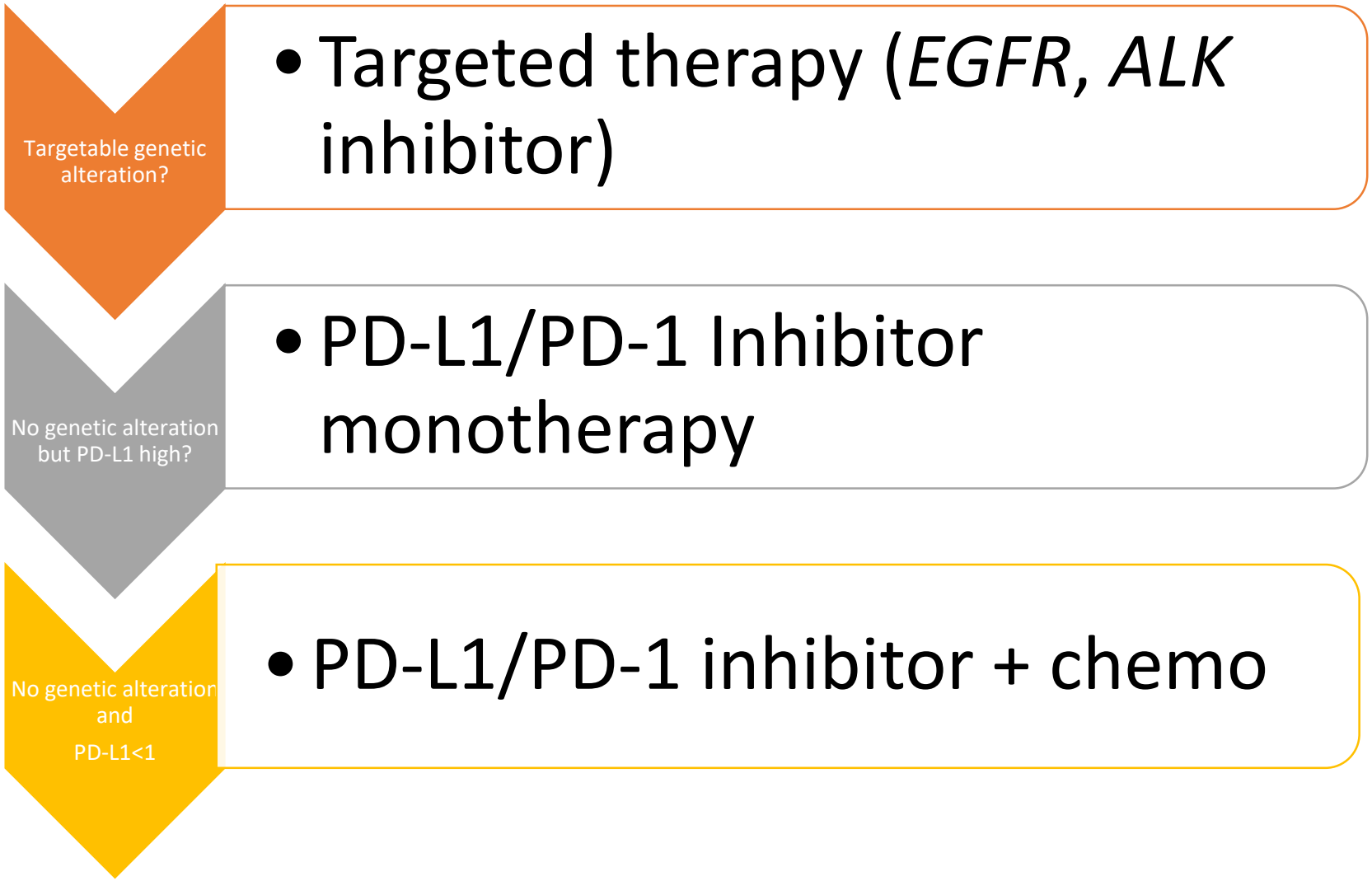
NCCN Guidelines Index
Table of Contents
Discussion

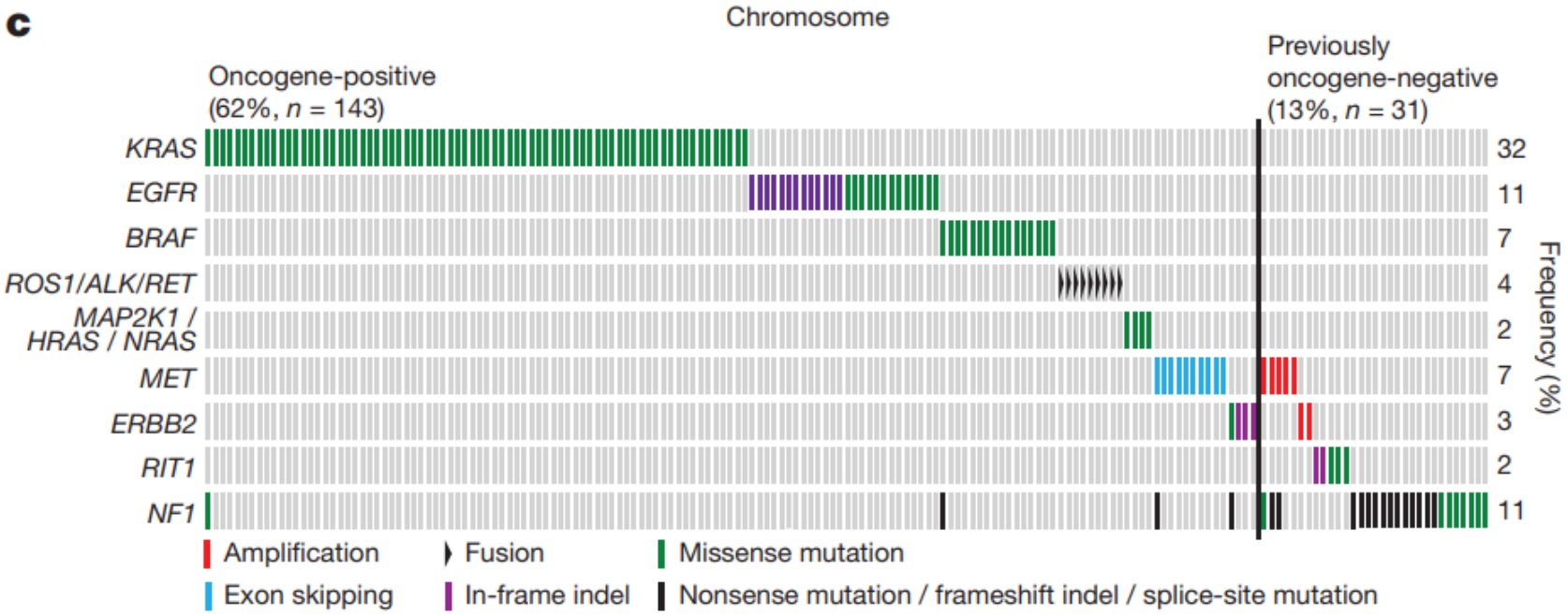


Algorithm for Stage IV NSCLC



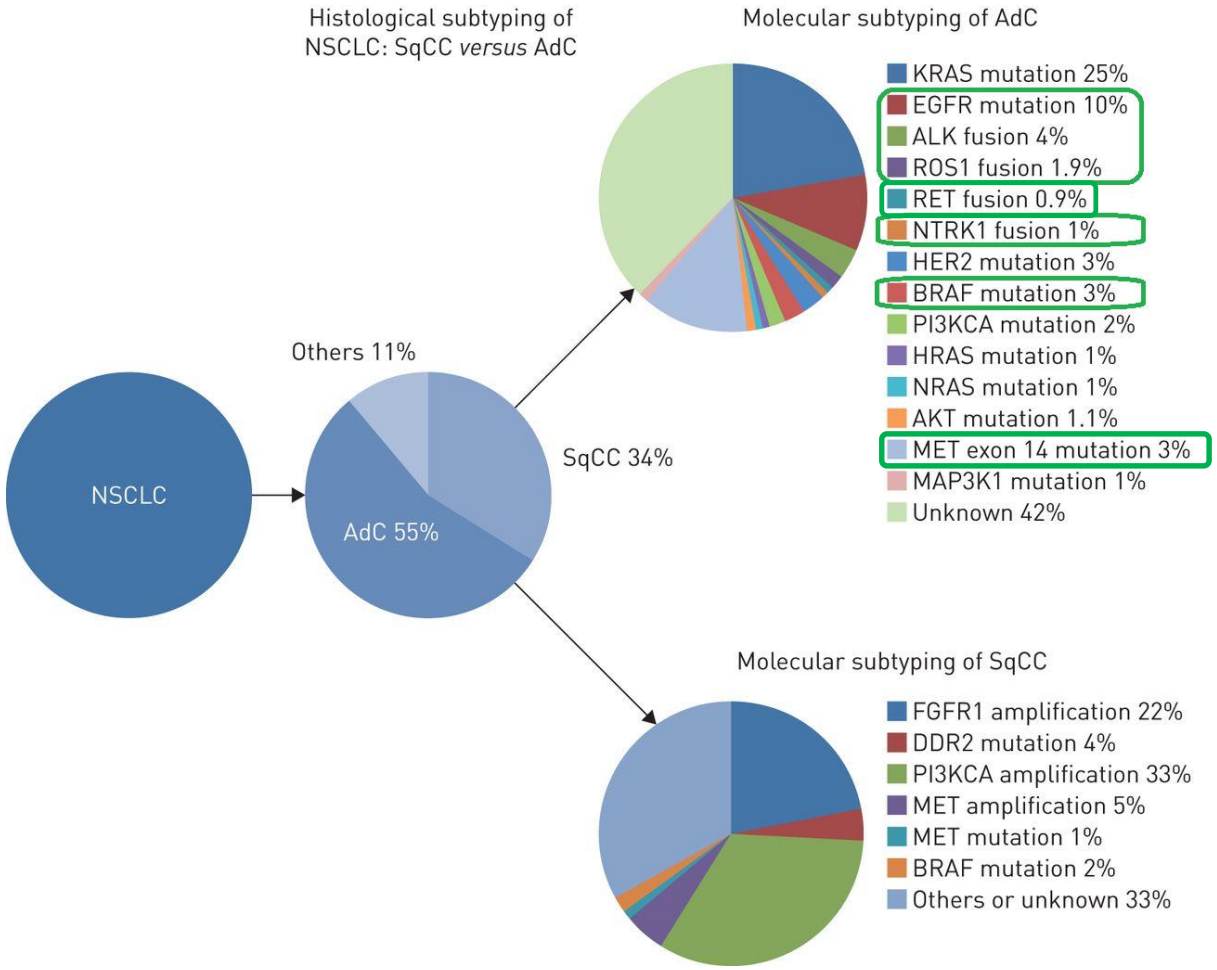
Driver mutations in cancer

- Present in all tumor cells as they are early inciting genetic events
- Define a tumor clinicopathologically
- Generally mutually exclusive

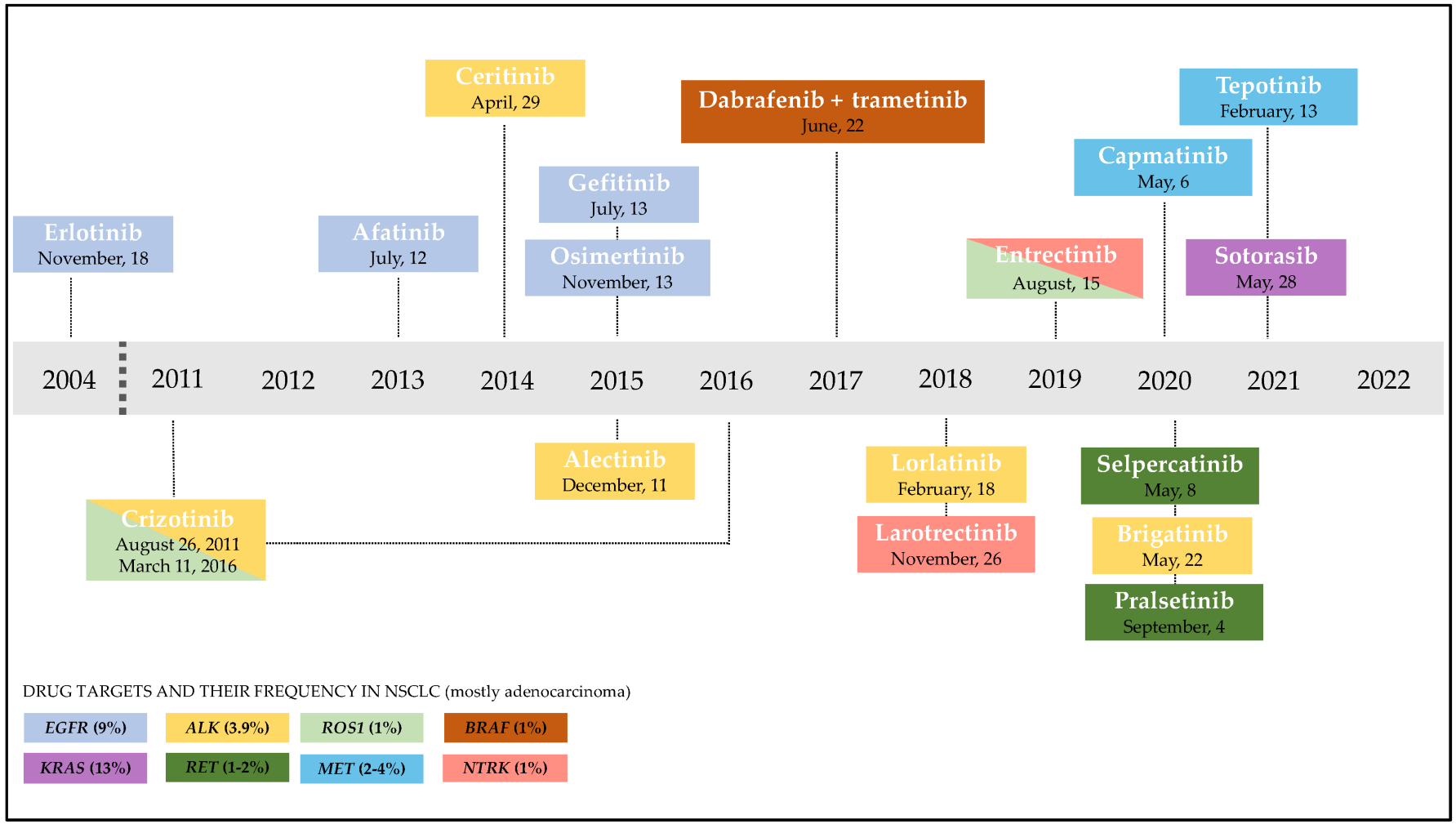


Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014.

Driver mutations in NSCLC



A rapidly evolving array of targeted therapies for NSCLC



Michelotti A, et al. NSCLC as the Paradigm of Precision Medicine at Its Finest: The Rise of New Druggable Molecular Targets for Advanced Disease. Int J Mol Sci. 2022 Jun 17;23(12):6748.

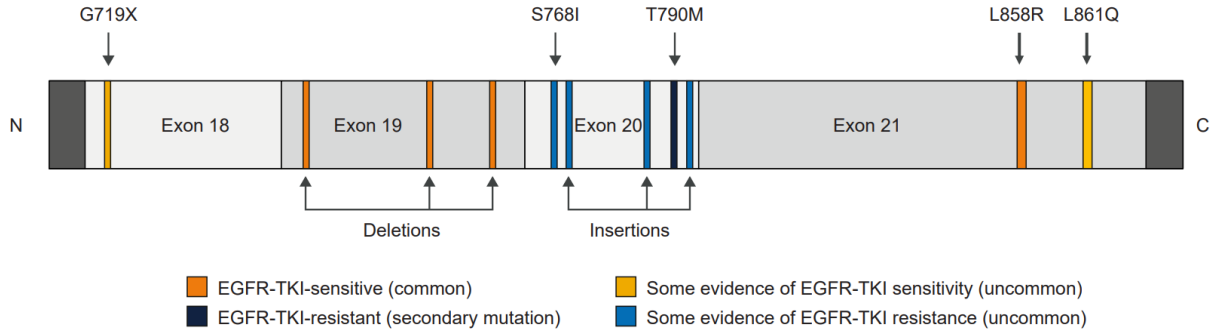
TESTING RESULTS[ll,mm]

EGFR **exon 19 deletion or exon 21 L858R mutation positive**	NSCL-20
EGFR **S768I, L861Q, and/or G719X mutation positive**	NSCL-23
EGFR **exon 20 insertion mutation positive**	NSCL-24
KRAS **G12C mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
ERBB2 (HER2) **mutation positive**	NSCL-35
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

EGFR mutated adenocarcinoma

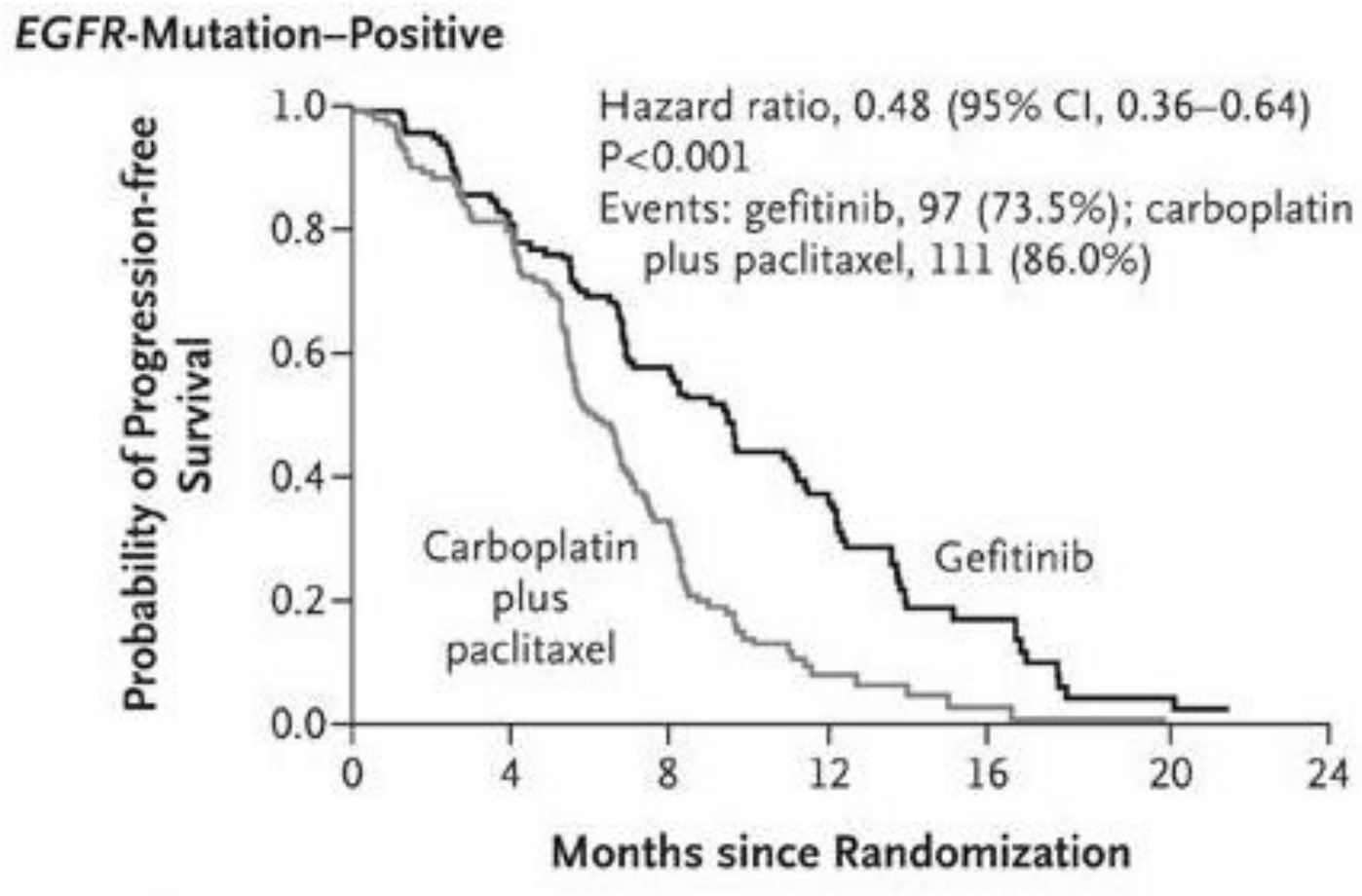
- Present in ~20% of lung adenocarcinoma cases

- 3 Relevant sets of primary mutations
  - Exon 19 deletions/L858R on Chr21 (85% of cases)
  - Uncommon mutations (S768I, L861Q, and/ or G719X)
  - Exon 20 insertions (uncommon) ← Different drugs, 2nd line



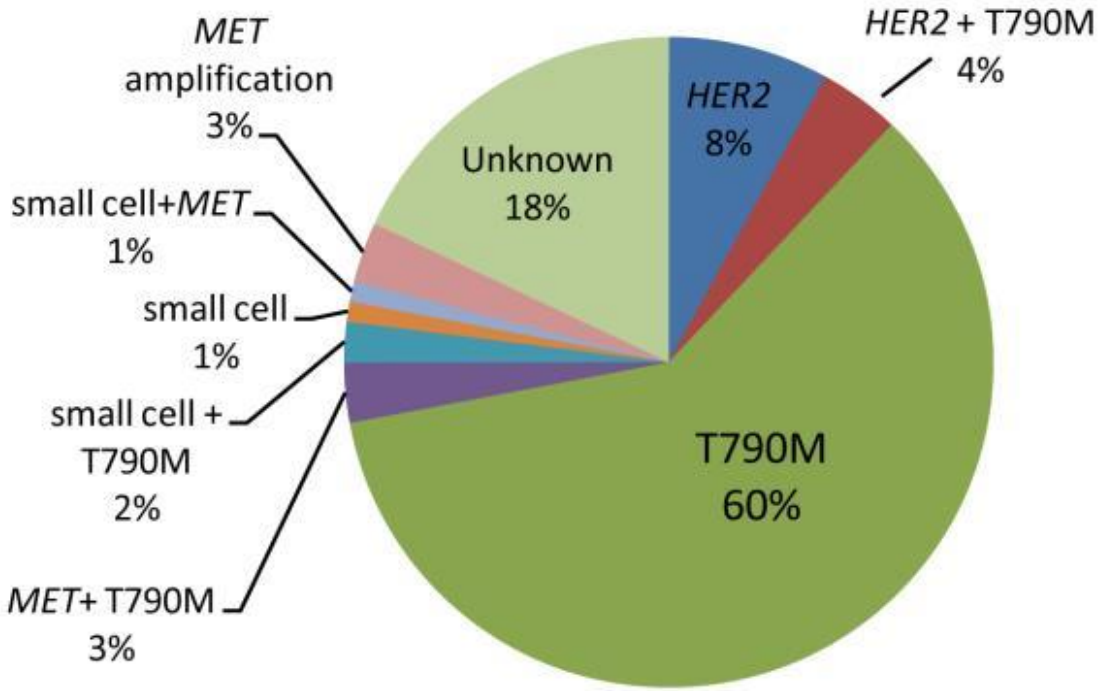
John T, et al. Uncommon EGFR mutations in non-small-cell lung cancer: A systematic literature review of prevalence and clinical outcomes. Cancer Epidemiol. 2022 Feb;76.

In patients with metastatic NSCLC with an *EGFR* mutation, PFS is superior when treated with a targeted agent



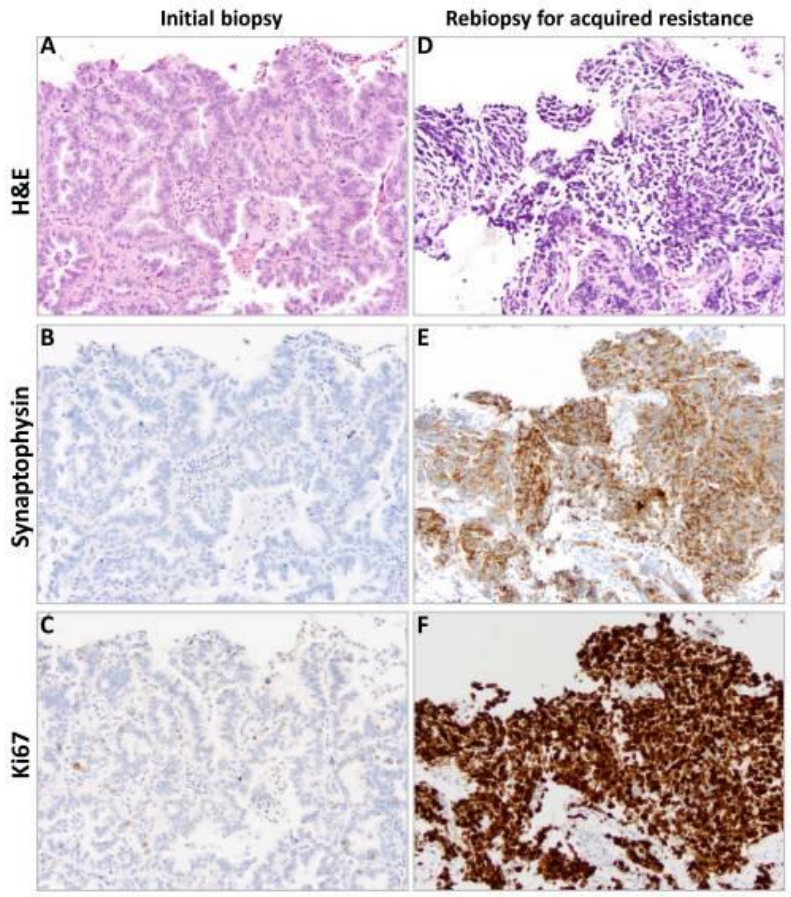
North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010

Patients treated with older *EGFR* inhibitors invariably develop resistance



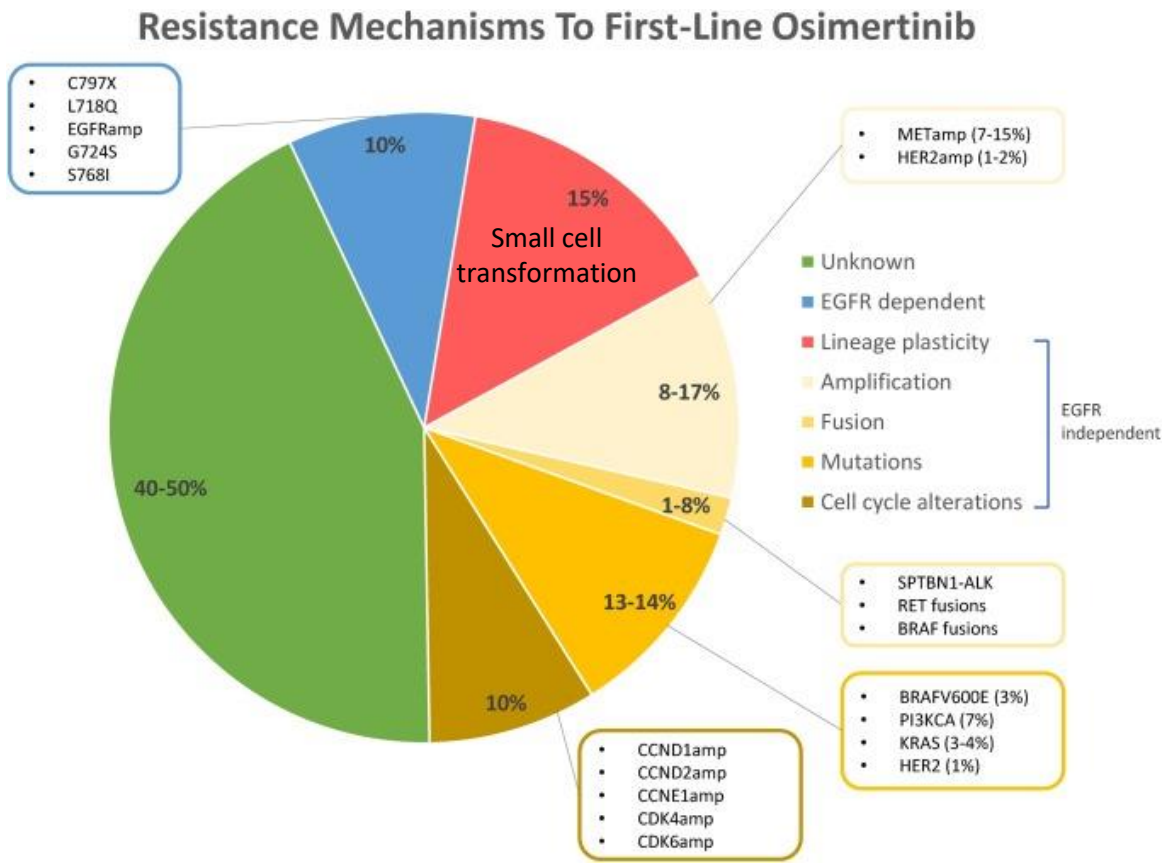
Yu HA, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR–TKI therapy in 155 patients with EGFR–mutant lung cancers. Clin Cancer Res. 2013.

Small cell transformation in patient treated with *EGFR* inhibitor



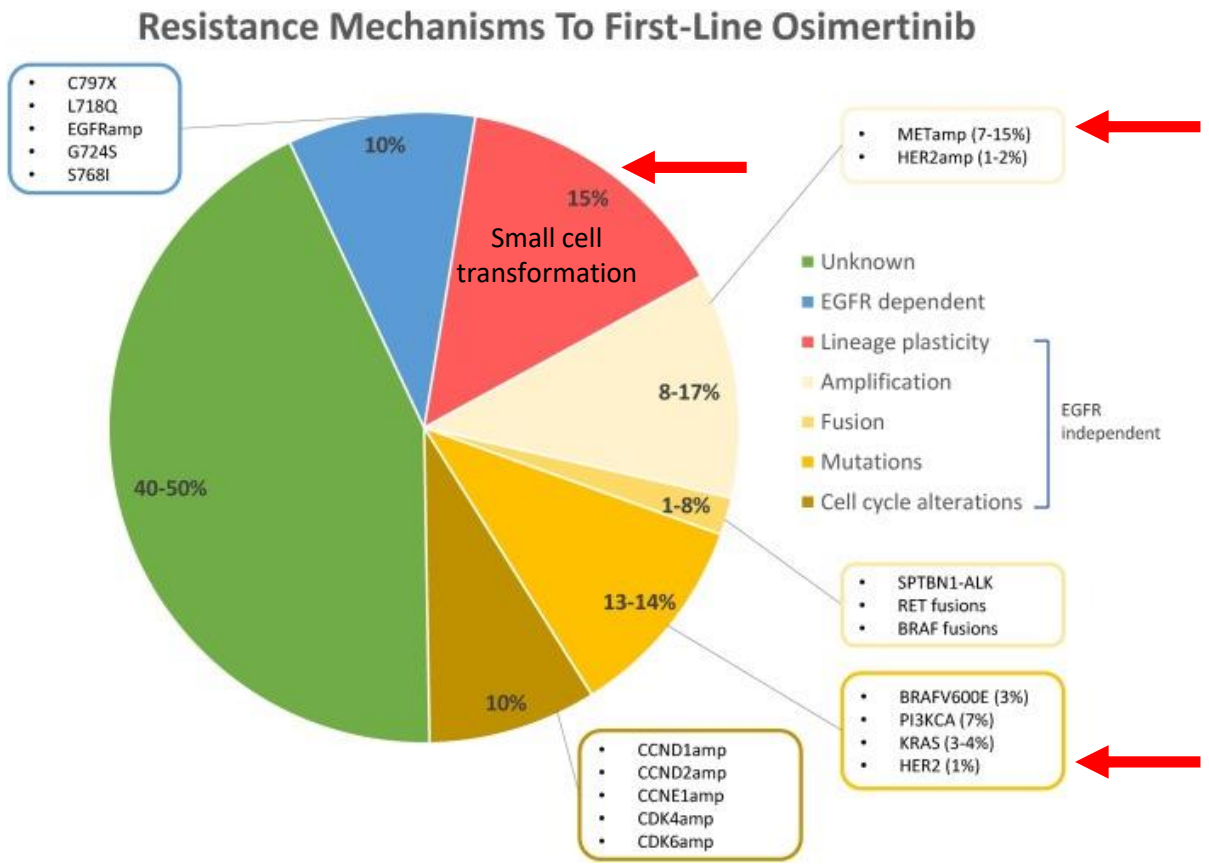
Yu HA, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR–TKI therapy in 155 patients with EGFR–mutant lung cancers. Clin Cancer Res. 2013.

Changing mechanisms of resistance with 3rd Gen *EGFR* inhibitors



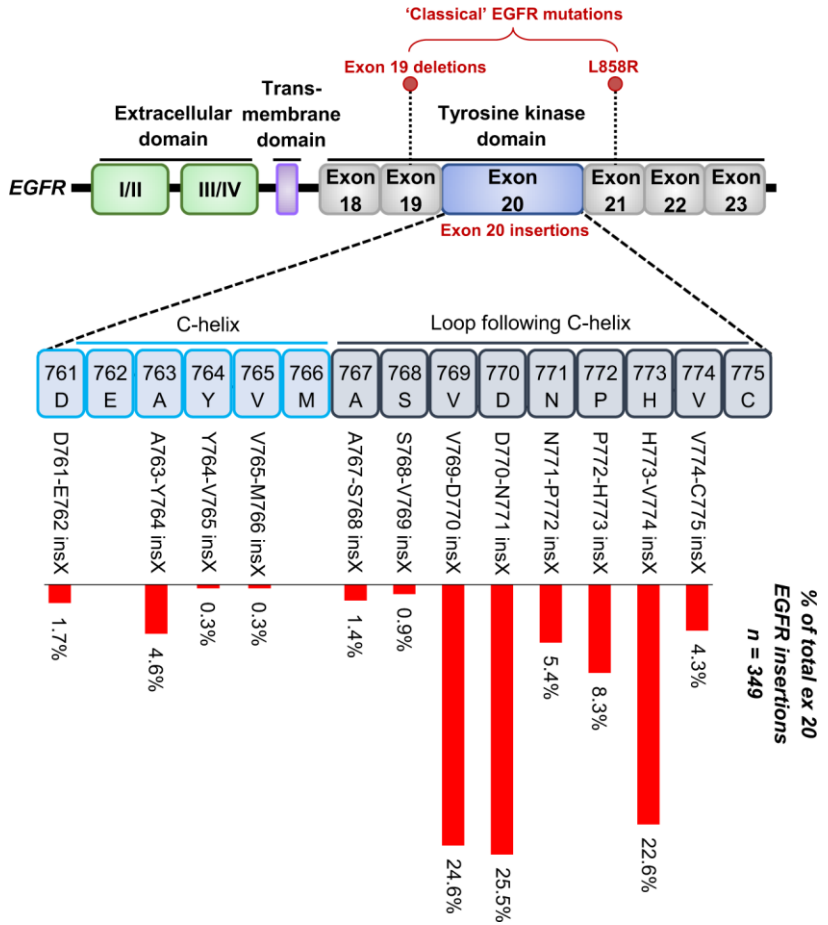
Schmid S, Li JJN, Leighl NB. Mechanisms of osimertinib resistance and emerging treatment options. Lung Cancer. 2020 Sep;147:123-129.

Role of testing for resistance mechanisms in *EGFR* mut NSCLC



Schmid S, Li JJN, Leighl NB. Mechanisms of osimertinib resistance and emerging treatment options. Lung Cancer. 2020 Sep;147:123-129.

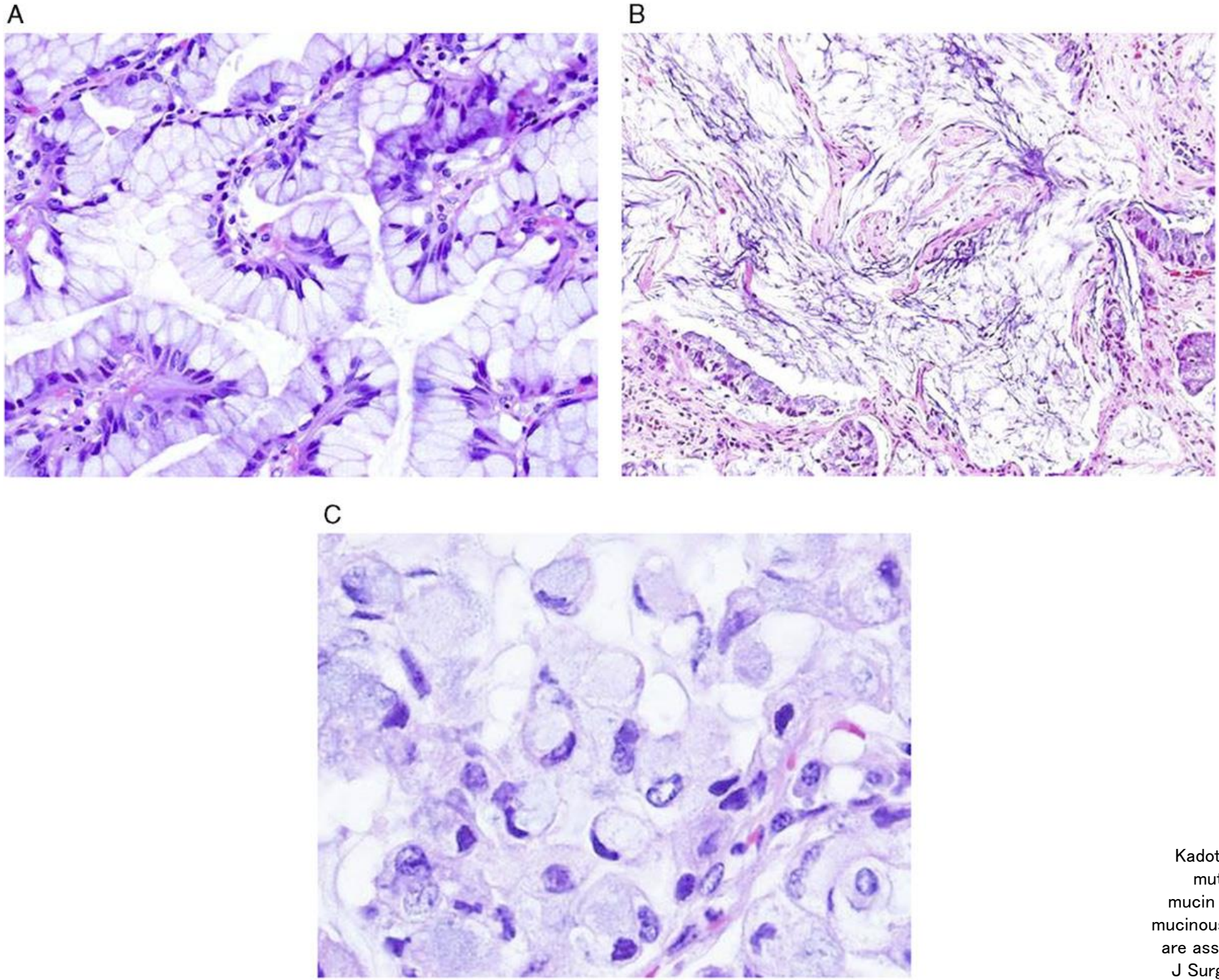
Exon 20 insertions require different therapy (but only approved in 2nd line setting)



Vyse, S., Huang, P.H. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther* **4,** 5 (2019).

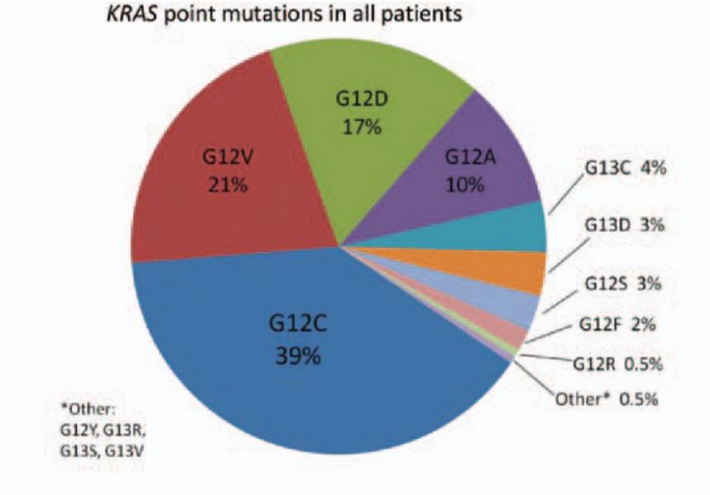
KRAS mutated adenocarcinoma

- Older Smokers, tend to do poorly
- Tend to be TTF1-
- Small molecule *KRAS* inhibitor recently approved, but only 2nd line and for G12C mutation

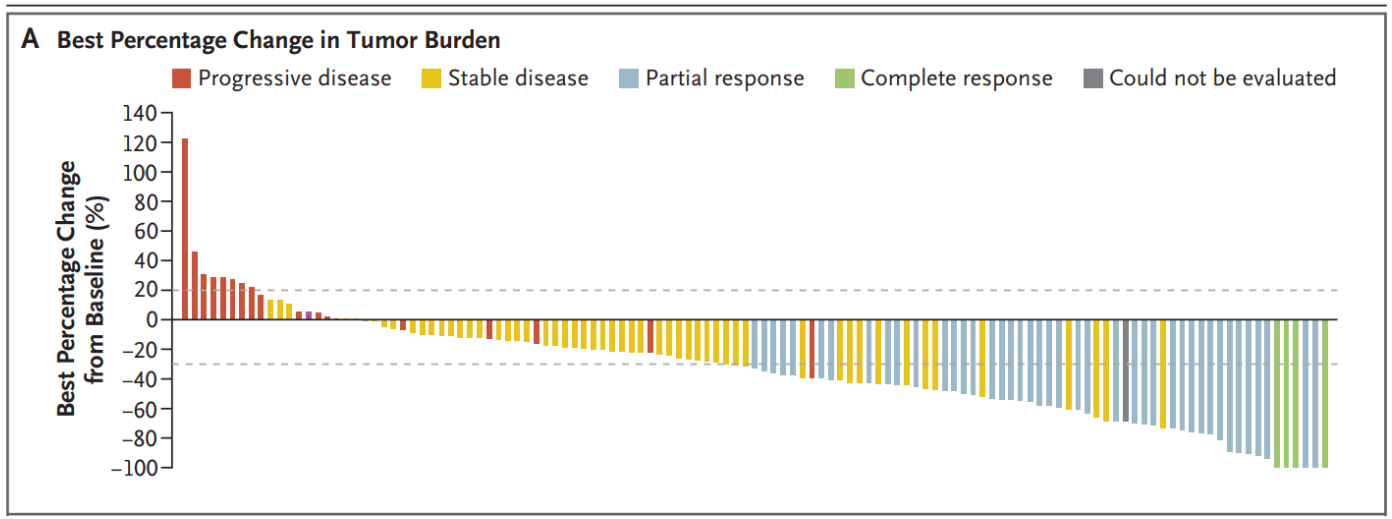


Kadota K, et al.. Associations between mutations and histologic patterns of mucin in lung adenocarcinoma: invasive mucinous pattern and extracellular mucin are associated with KRAS mutation. Am J Surg Pathol. 2014 Aug;38(8):1118–27

About 1/3 of patients with previously treated metastatic G12C adenoCA will respond to sotorasib



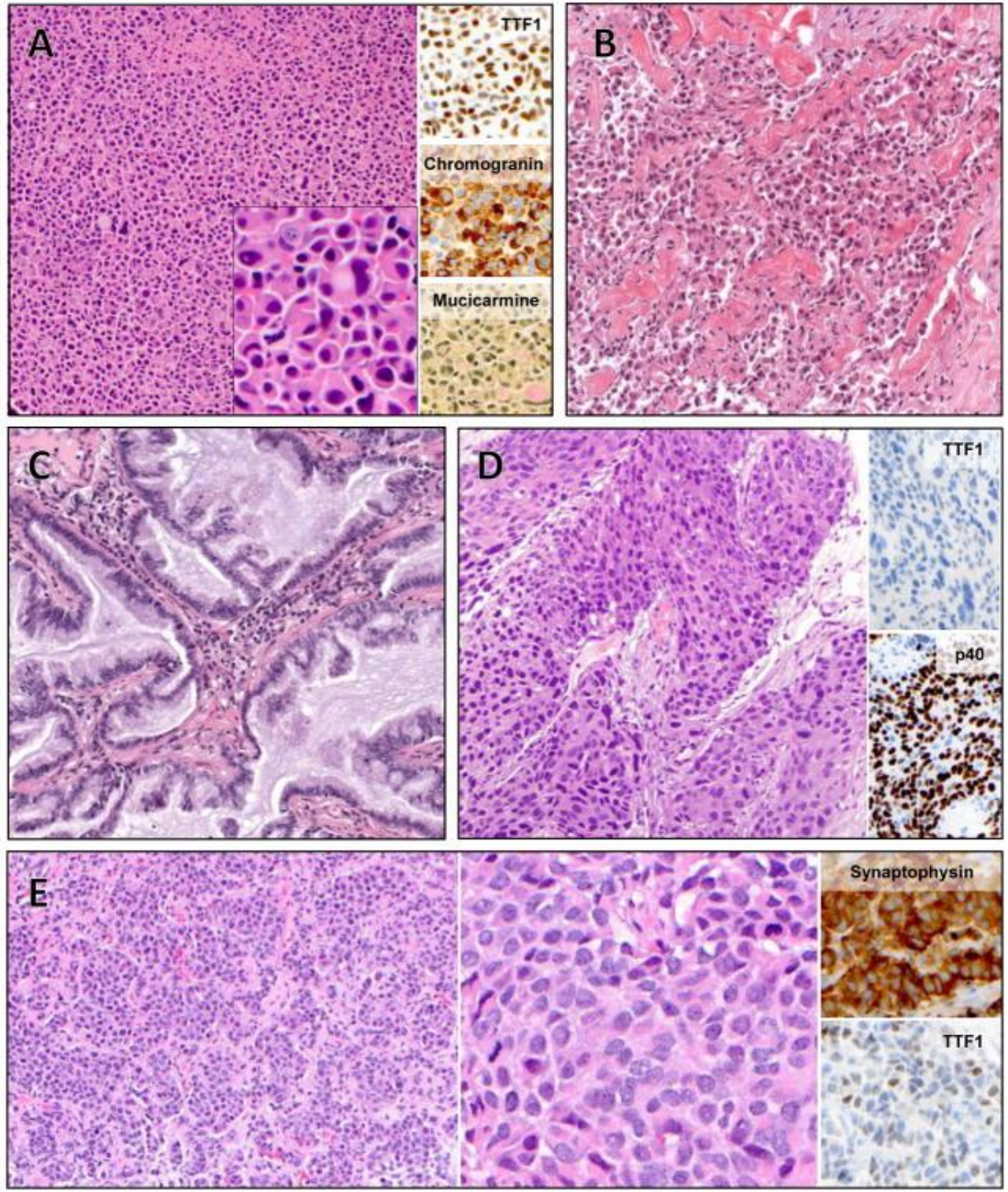
Yu HA, et al. Prognostic impact of KRAS mutation subtypes in 677 patients with metastatic lung adenocarcinomas. J Thorac Oncol. 2015 Mar;10(3):431-7.



Skoulidis F, et al. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. N Engl J Med. 2021 Jun 24;384(25):2371-2381.

NSCLC with *NTRK* rearrangements

- May be seen in smokers or non smokers
- Very rare, <1% of cases of lung adenocarcinoma
- Rearrangements may involve *NTRK1, NTRK2*, or *NTRK3*
- Morphologically heterogeneous (squamous, NE)
- Treated with *NTRK* inhibitor (larotrectinib)



Farago AF, et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. JCO Precis Oncol. 2018.

TESTING RESULTS[ll,mm]

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2nd line	*EGFR* exon 20 insertion mutation positive	NSCL-24
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	ALK rearrangement positive	NSCL-26
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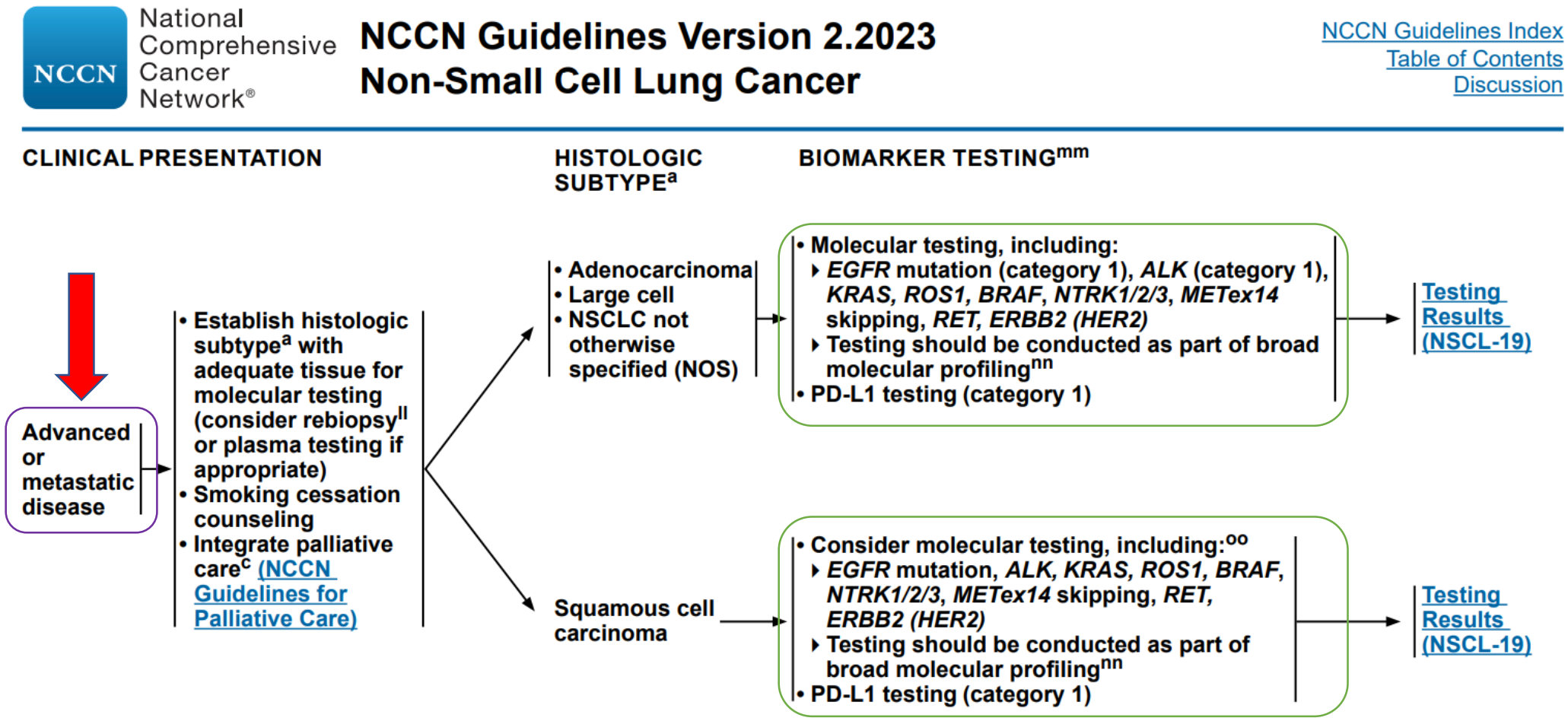
	RET rearrangement positive	NSCL-34
2nd line	*ERBB2 (HER2)* mutation positive	NSCL-35
	PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
	PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

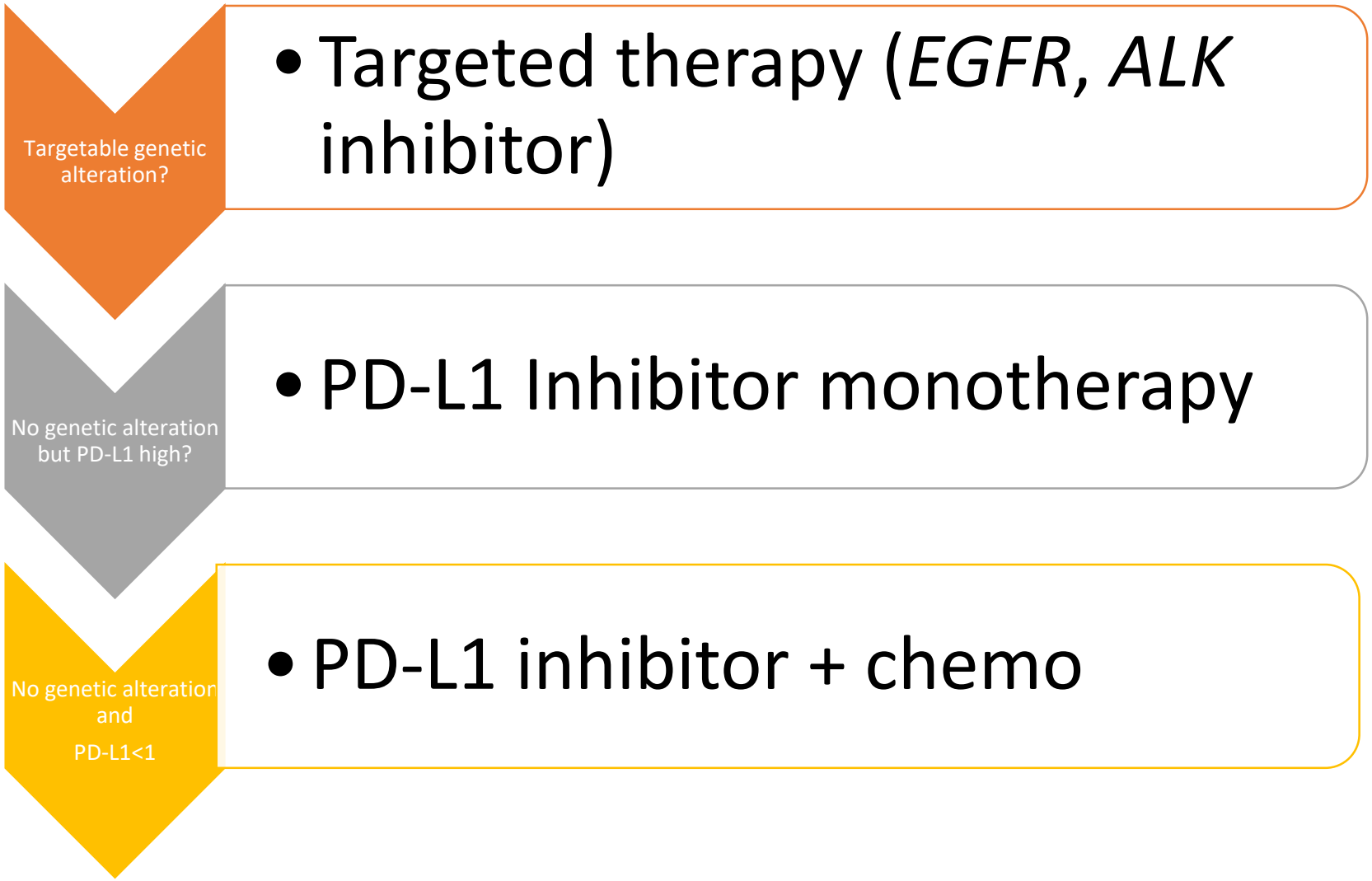
Is molecular testing indicated in squamous cell carcinoma?



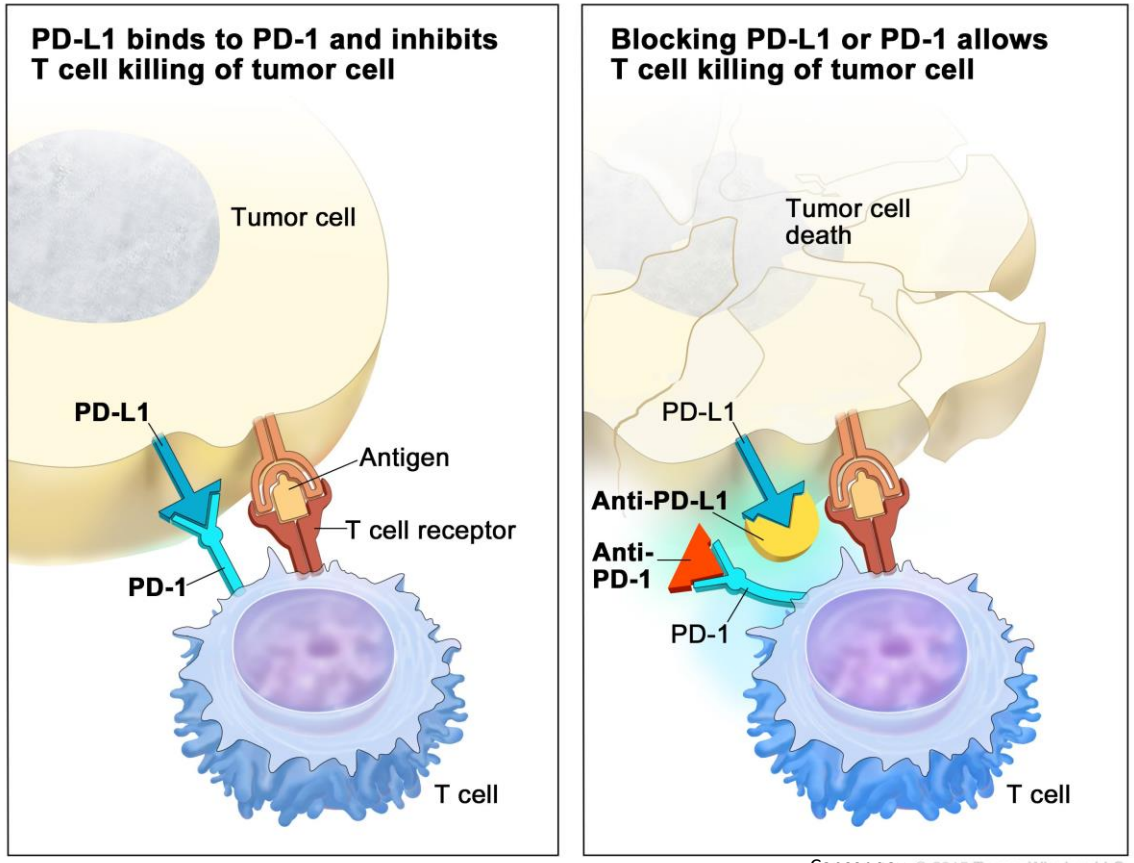
Is molecular testing indicated in squamous cell carcinoma?

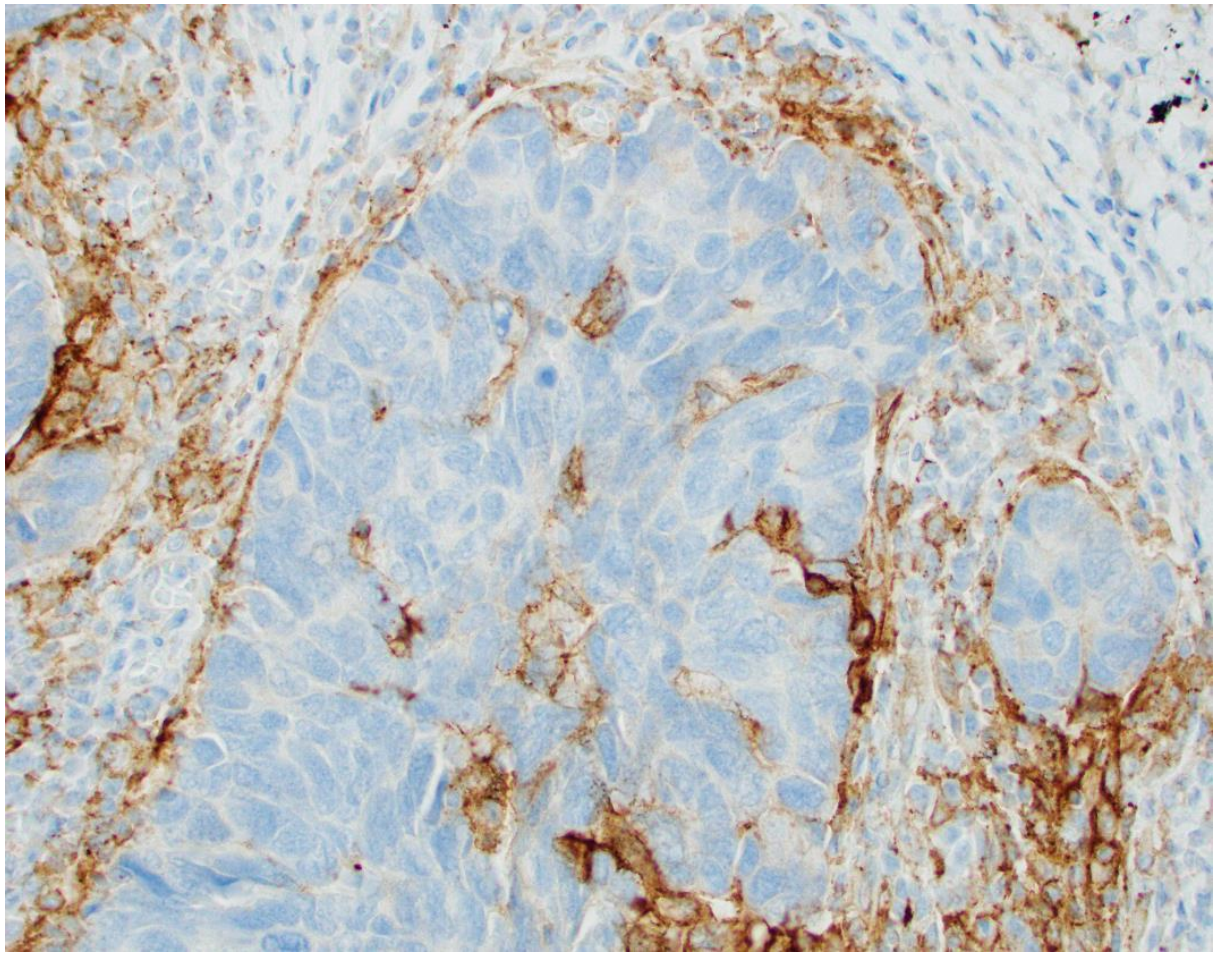
- Not mandatory but may be of value, particularly in small biopsies
  - A few targetable genetic alterations (*NTRK1/2/3*, *METex14*) are present at low frequencies in squamous cell CA
  - May miss an unsampled glandular component in an adenosquamous CA (young, non smokers in particular)

Algorithm for Stage IV NSCLC



PD-L1 inhibitors: A revolution in oncology





Role of PD-L1 inhibitors in patients with Stage IV disease w/o a targetable genetic alteration

- 2016 - **Pembrolizumab originally indicated as monotherapy for TPS>50**

(KEYNOTE 024)

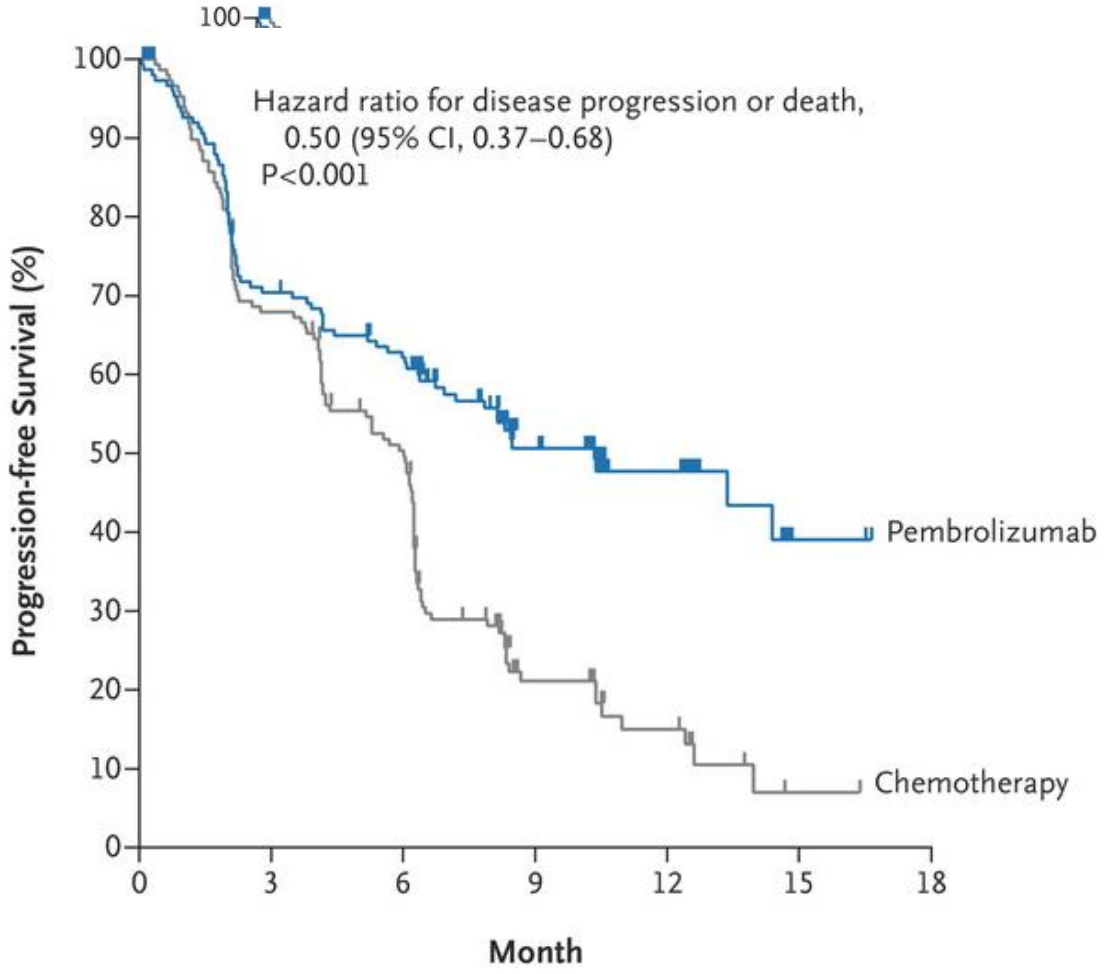
- 2018 - **Pembrolizumab + chemo combo therapy indicated irrespective of PD-L1 score in NSCLC**

(KEYNOTE 189, KEYNOTE 407)

- 2019 – **Pembrolizumab monotherapy indication expanded to TPS>1**

(KEYNOTE 042)

PD-L1 inhibitors as first line therapy in metastatic NSCLC

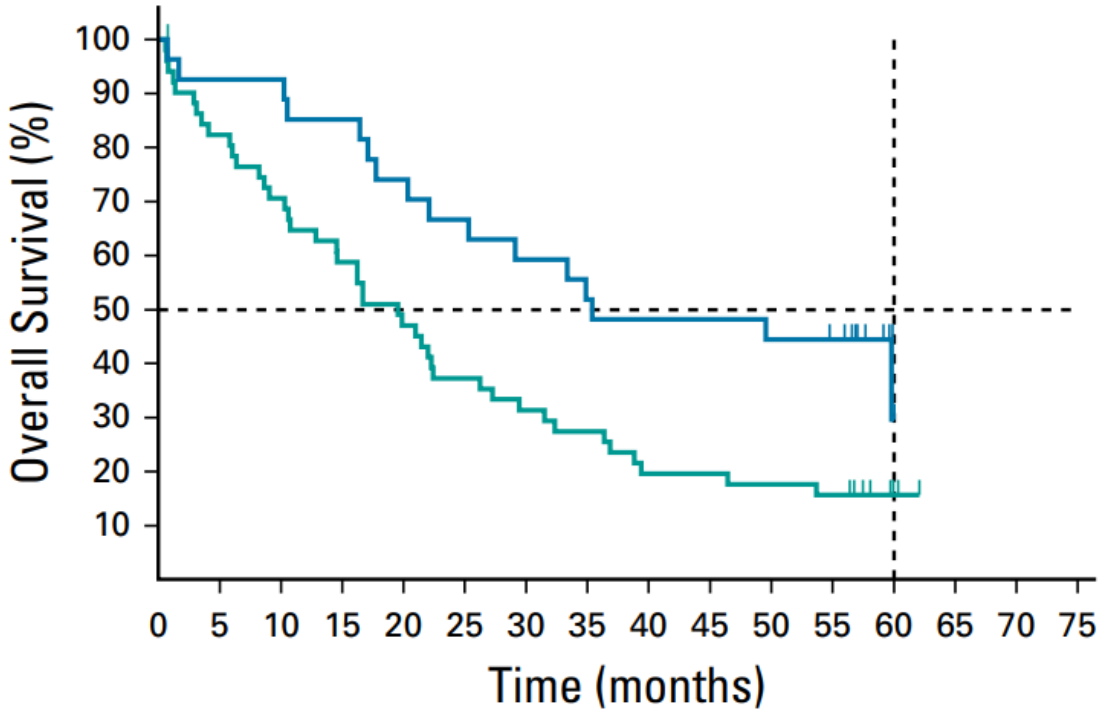


Reck M, et al.. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823-1833.

Almost 30% of patients with mNSCLC and PD-L1 > 50% are alive after 5 years

C

	Events, n/N	Median OS, mo (95% CI)	5-Year OS Rate, % (95% CI)
TPS ≥ 50%	17/27	35.4 (20.3 to 63.5)	29.6 (7.7 to 56.1)
TPS 1–49%	43/52	19.5 (10.7 to 26.3)	15.7 (7.3 to 26.9)



Garon EB, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019

Role of PD-L1 inhibitors in patients with Stage IV disease w/o a targetable genetic alteration

- PD-L1 TPS>50 – Pembrolizumab, Atezolizumab, Cemiplimab monotherapy
- PD-L1 TPS1-49 – PD-L1 inhibitor + chemo, or Pembrolizumab monotherapy if a poor candidate for chemo
- PD-L1 TPS<1 – PD-L1 inhibitor + chemo

Differences between PD-L1 and genetic alteration testing

PD-L1

- IHC based
- Continuous variable
- May change over time and vary at different sites
- Heterogeneously expressed

Genetic alterations

- Mostly PCR/NGS based
- Binary variable
- Usually does not change over time
- Uniformly present throughout tumor

Role of pathology: Selecting patients for monotherapy with PD-L1 inhibitor

- What test (antibody clone) to use?
- What specimen to use?
- How to score?

ORIGINAL ARTICLE

Multicenter Comparison of 22C3 PharmDx (Agilent) and SP263 (Ventana) Assays to Test PD-L1 Expression for NSCLC Patients to Be Treated with Immune Checkpoint Inhibitors

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[c]*Pathology Unit, University of Campania Luigi Vanvitelli, Naples, Italy*
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ABSTRACT

Introduction: Among the several agents targeting the programmed cell death 1 (PD-1) pathway, pembrolizumab is currently the only one approved for the treatment of patients with NSCLC in association with a companion diagnostic assay, the anti–PD-L1 immunohistochemical (IHC) 22C3 PharmDx (Agilent Technologies, Santa Clara, CA) using the Dako Autostainer (Dako, Carpinteria, CA). However, the Dako platform is not present in each pathology department, and this technical limitation is a major problem for the diffusion of the PD-L1 IHC predictive test for pembrolizumab.

data obtained with the 22C3 and SP263 clones at the cutoff of 1% or higher was mainly related to the lower (about 80%) interrater agreement at this cutoff with each clone.

Conclusions: These results indicate a high correlation between PD-L1 IHC expression data obtained with the Agilent PD-L1 IHC 22C3 pharmDx and the Ventana PD-L1 (SP263) tests in NSCLC and suggest that the two assays could be utilized interchangeably as an aid to select patients for first-line and second-line treatment with pembrolizumab and potentially with other anti–PD-1/PD-L1 checkpoint inhibitors.

Marchetti A, et al. Multicenter Comparison of 22C3 PharmDx (Agilent) and SP263 (Ventana) Assays to Test PD–L1 Expression for NSCLC Patients to Be Treated with Immune Checkpoint Inhibitors. J Thorac Oncol. 2017

ORIGINAL ARTICLE

PD-L1 Assays 22C3 and SP263 are Not Interchangeable in Non–Small Cell Lung Cancer When Considering Clinically Relevant Cutoffs

An Interclone Evaluation by Differently Trained Pathologists

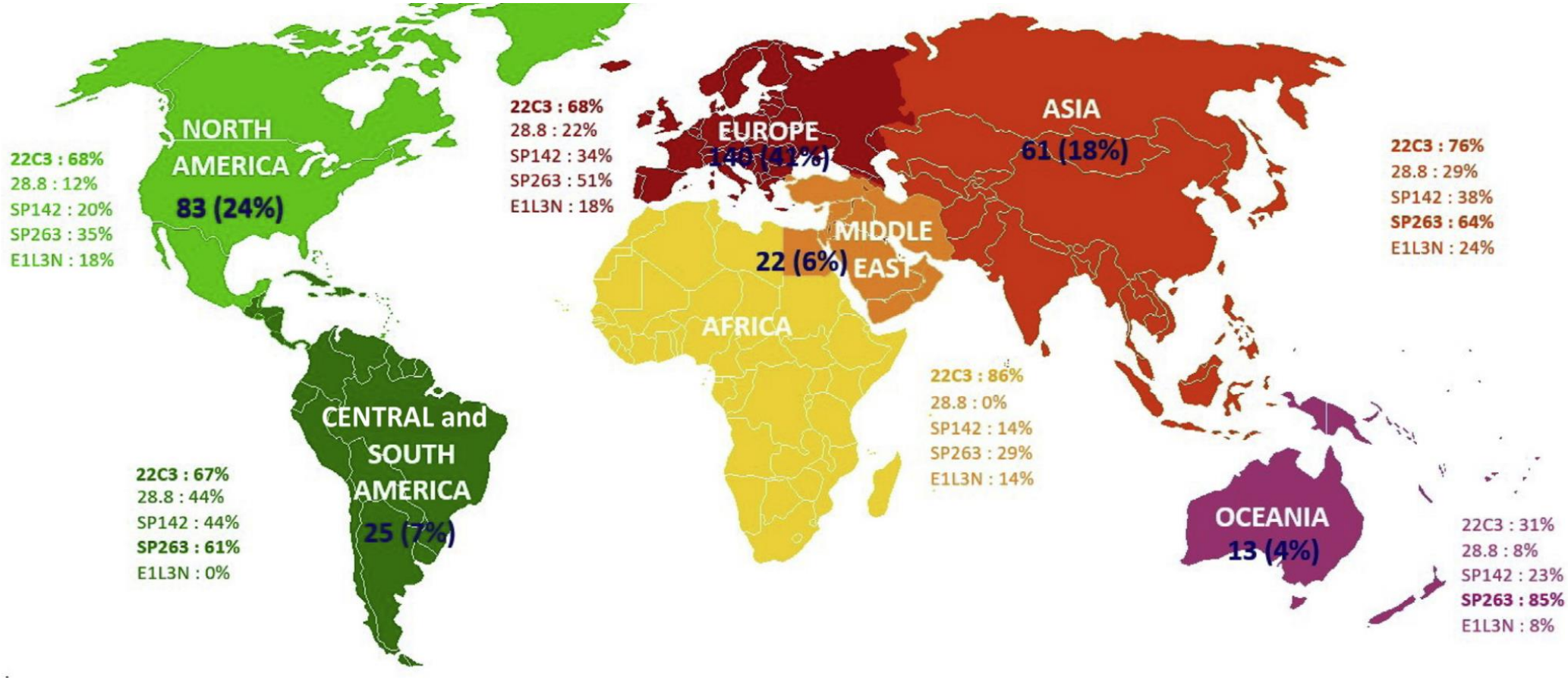
Enrico Munari, MD, PhD, Giulio Rossi, MD,† Giuseppe Zamboni, MD,*‡ Gianluigi Lunardi, MD,§ Marcella Marconi, BS,* Marco Sommaggio, BS,* George J. Netto, MD,‖ Mohammad O. Hoque, PhD,¶ Matteo Brunelli, MD, PhD,‡ Guido Martignoni, MD,‡# Michael C. Haffner, MD, PhD,** Francesca Moretta, MD,†† Maria C. Pegoraro, MD,‡‡ Alberto Cavazza, MD,§§ Giuseppina Samogin, BS,‖‖ Vanna Furlan, BS,‖‖ Francesca R. Mariotti, PhD,¶¶ Paola Vacca, PhD,¶¶ Lorenzo Moretta, MD,¶¶ and Giuseppe Bogina, MD**

Munari E et al. PD-L1 Assays 22C3 and SP263 are Not Interchangeable in Non-Small Cell Lung Cancer When Considering Clinically Relevant Cutoffs: An Interclone Evaluation by Differently Trained Pathologists. Am J Surg Pathol. 2018

Each FDA approved drug is linked to a specific antibody clone (companion diagnostic)

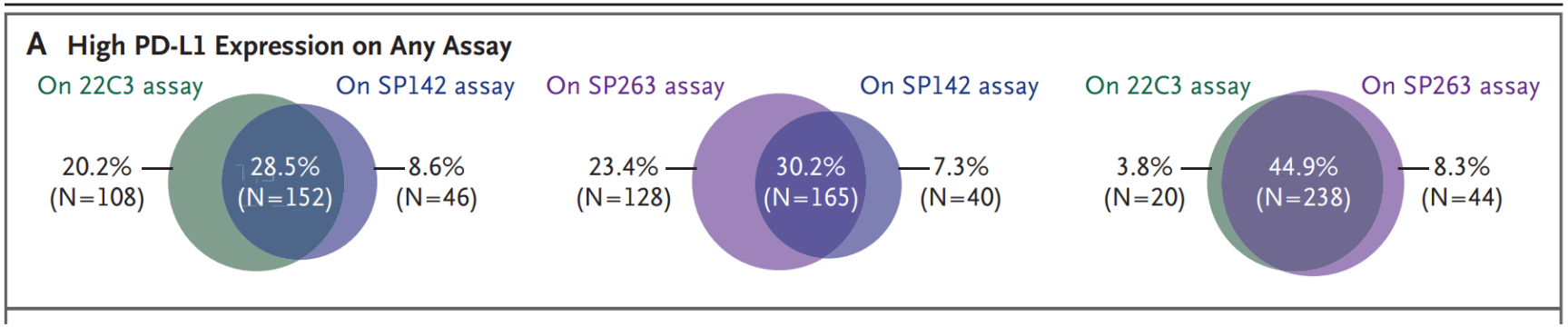
Drug	Clinical Setting	Clinical Trial	CDx	Cutpoint	Year
Pembrolizumab	Stage IV	KEYNOTE 042 (KEYNOTE 024)	22c3 (Dako) (22c3)	TPS>1 (TPS>50)	2019 (2016)
Atezolizumab	Stage IV	IMpower 110	SP142 (Ventana)	TPS>50 or ICA>10	2020
Atezolizumab	Stage IB-IIIA, adjuvant	IMpower 010	SP263 (Ventana)	TPS>1	2021
Nivolumab+ Ipilimumab	Stage IV	CHECKMATE 227	28-8 (Dako)	TPS>1	2020
Cemiplimab	Stage IV	Study 1624	(22c3) (Dako)	TPS>50	2021

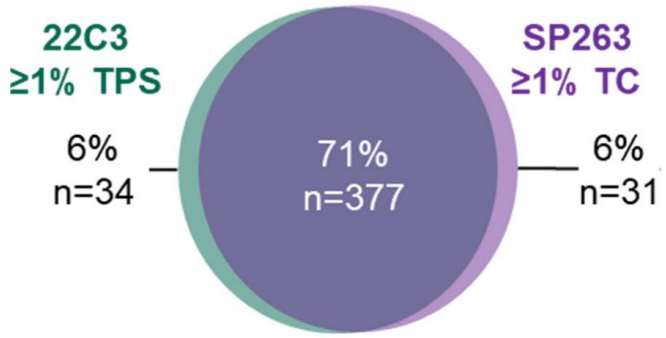
Antibody utilization by region



Mino-Kenudson M, et al. The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC. J Thorac Oncol. 2021

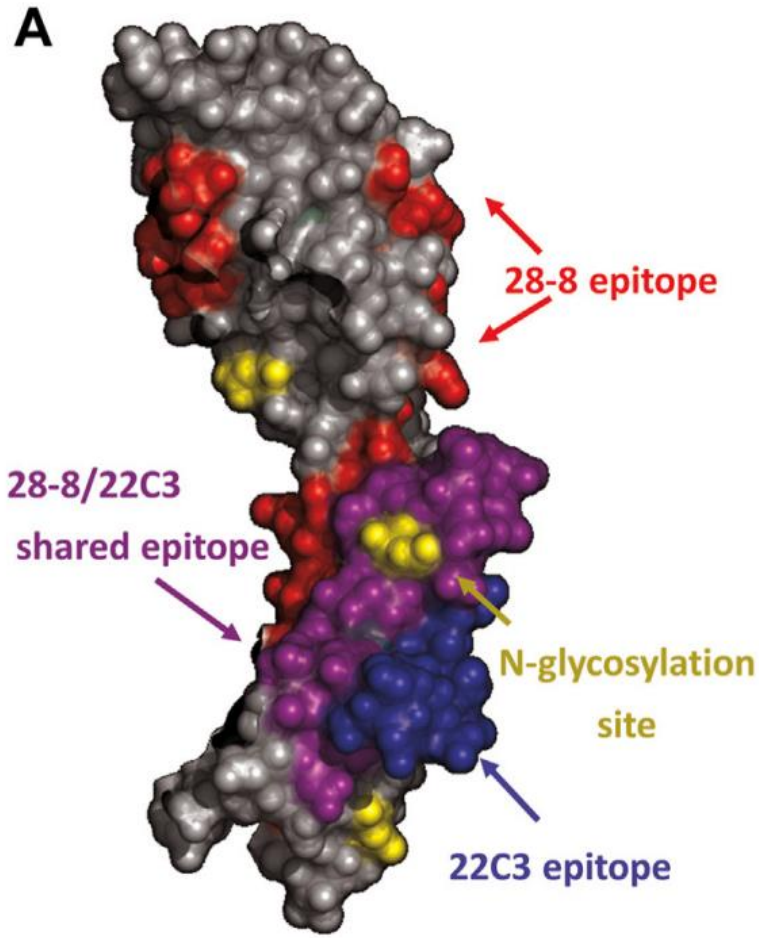
SP263 and 22c3 tend to agree, SP142 underscores (IMpower 110)





Herbst RS, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

Staining directed against PD-L1 extracellular domain antigens is labile

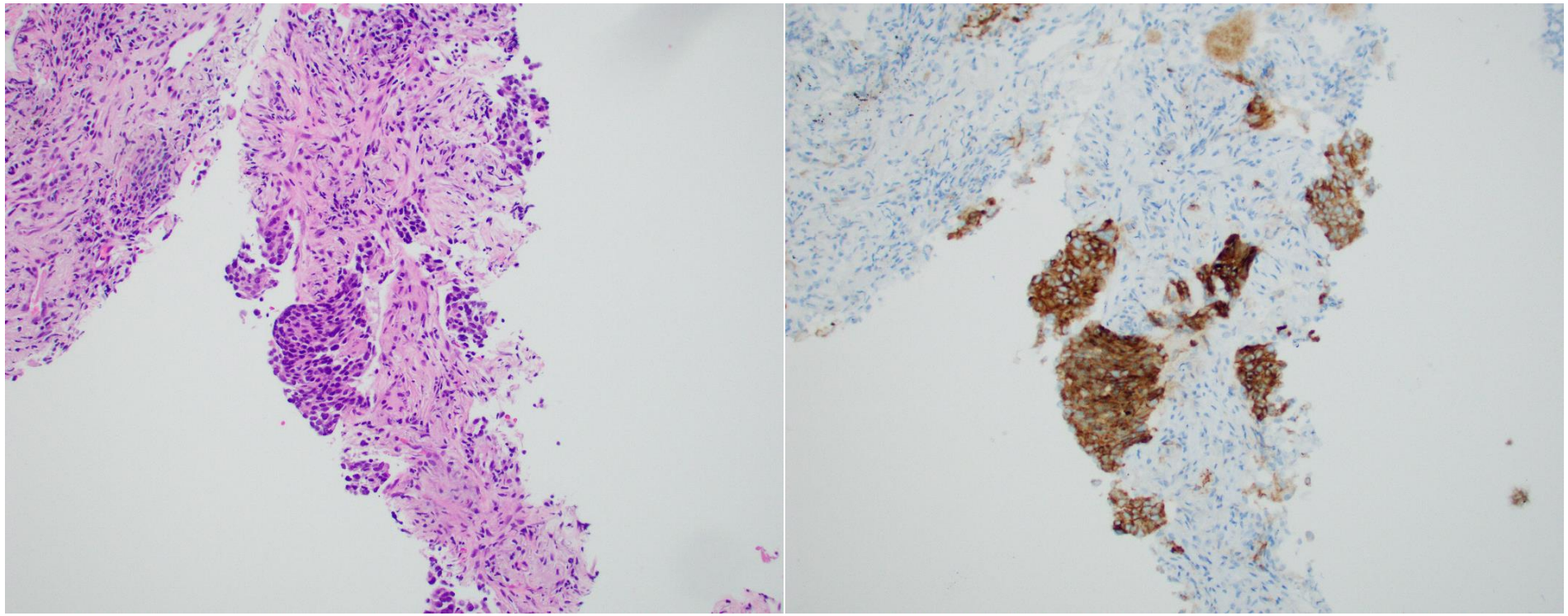


Lawson NL, et al. Impact of Decalcification, Cold Ischemia, and Deglycosylation on Performance of Programmed Cell Death Ligand-1 Antibodies With Different Binding Epitopes: Comparison of 7 Clones. Mod Pathol. 2023 May 23;36(9)

Role of pathology: Selecting patients for monotherapy with PD-L1 inhibitor

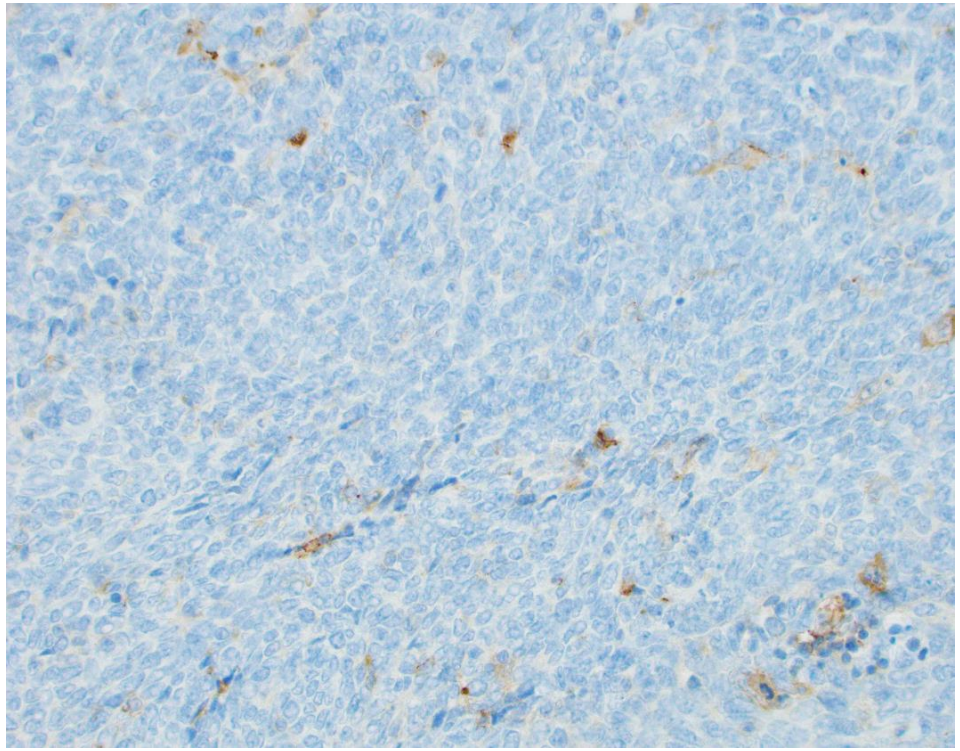
- What test (antibody clone) to use?
  - 22c3 and SP263 have the best concordance and have FDA approved NSCLC indications
  - SP142 tends to underscore
  - SP142 and SP263 are most robust
- What specimen to use?
- How to score?

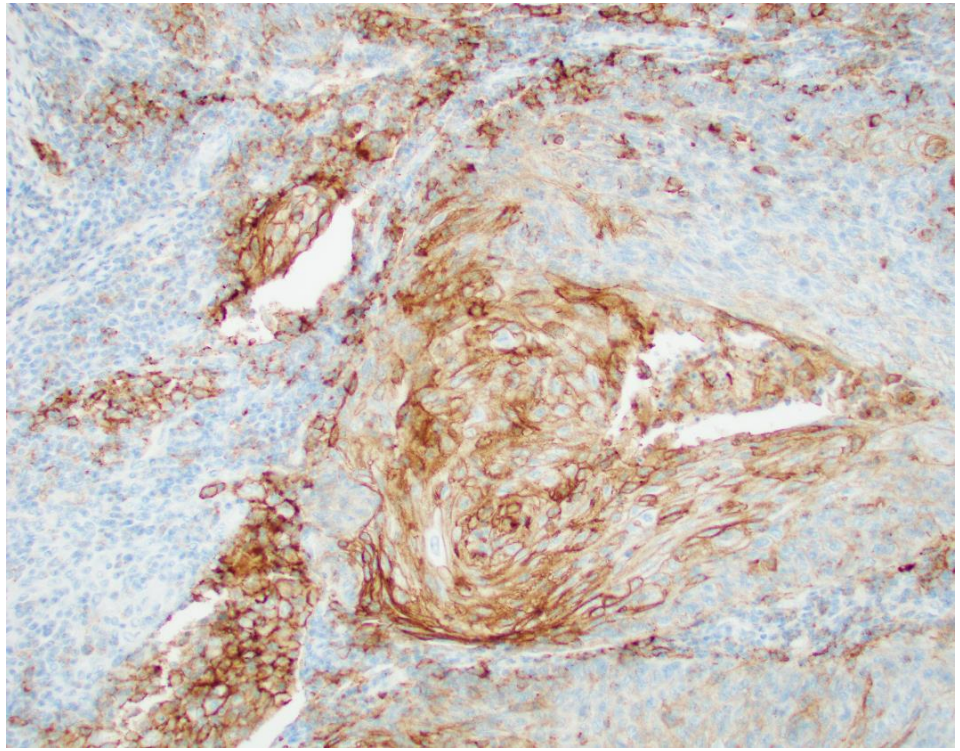
PD-L1 staining of tumor cells



TPS=100

Temporal and geographic heterogeneity



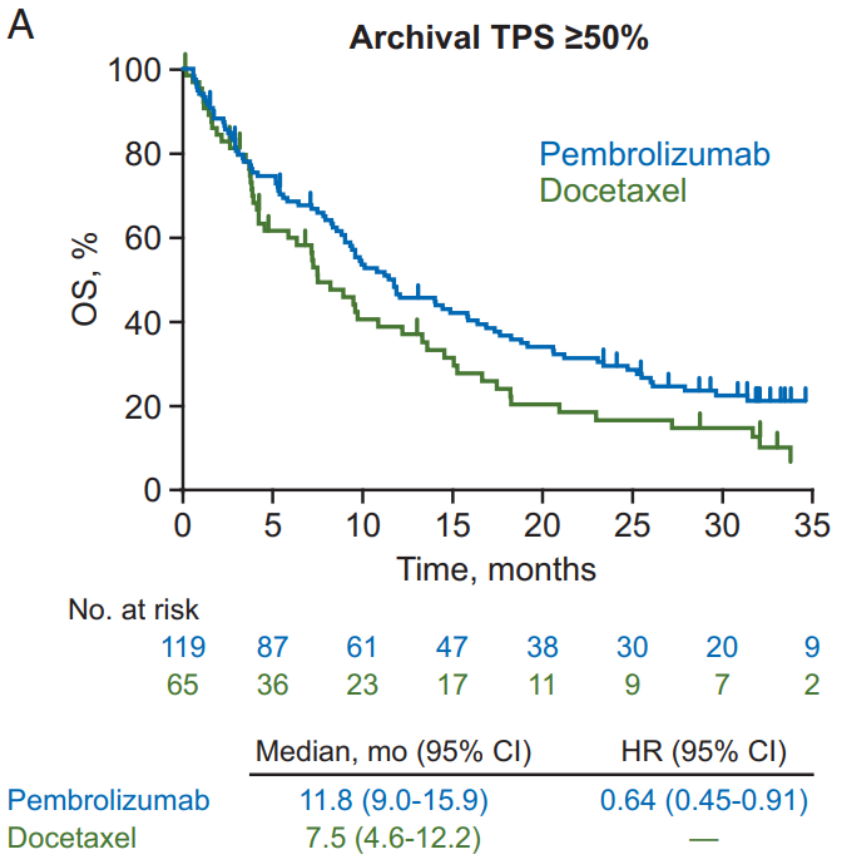


TPS=??

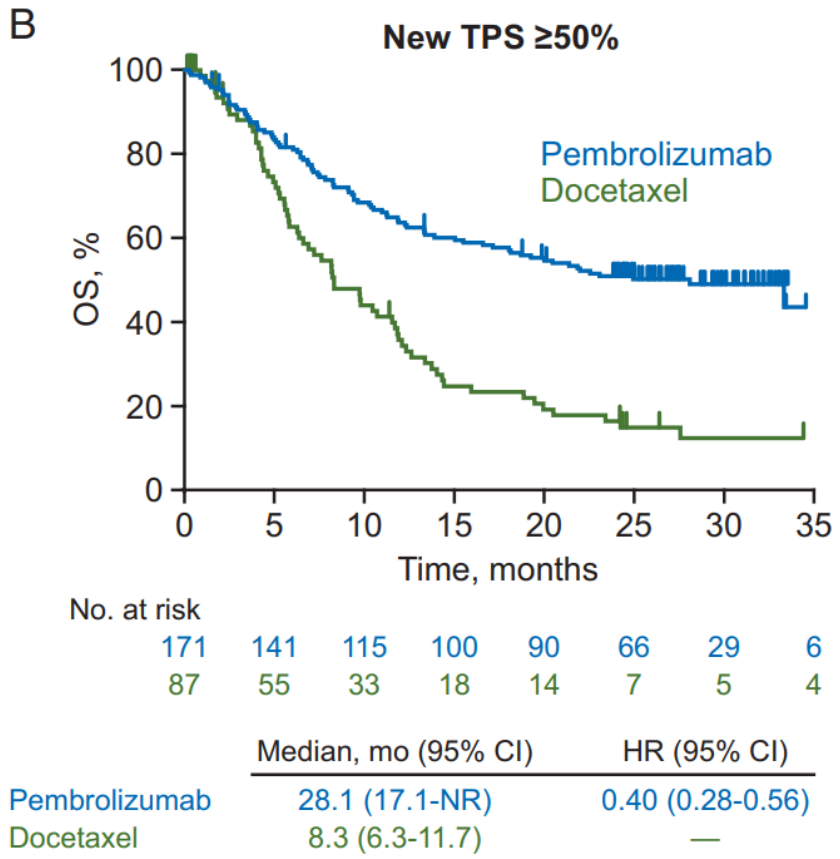
Testing of small biopsies vs cell blocks vs resections

- Clinical trials for patient's with metastatic disease did not utilize resection material
- Although results often differ based on site of disease, no good data in regards to which site will predict response to therapy
- Assays are validated for use in formalin fixed paraffin embedded material

Trend towards better predictive value in new versus archival specimens



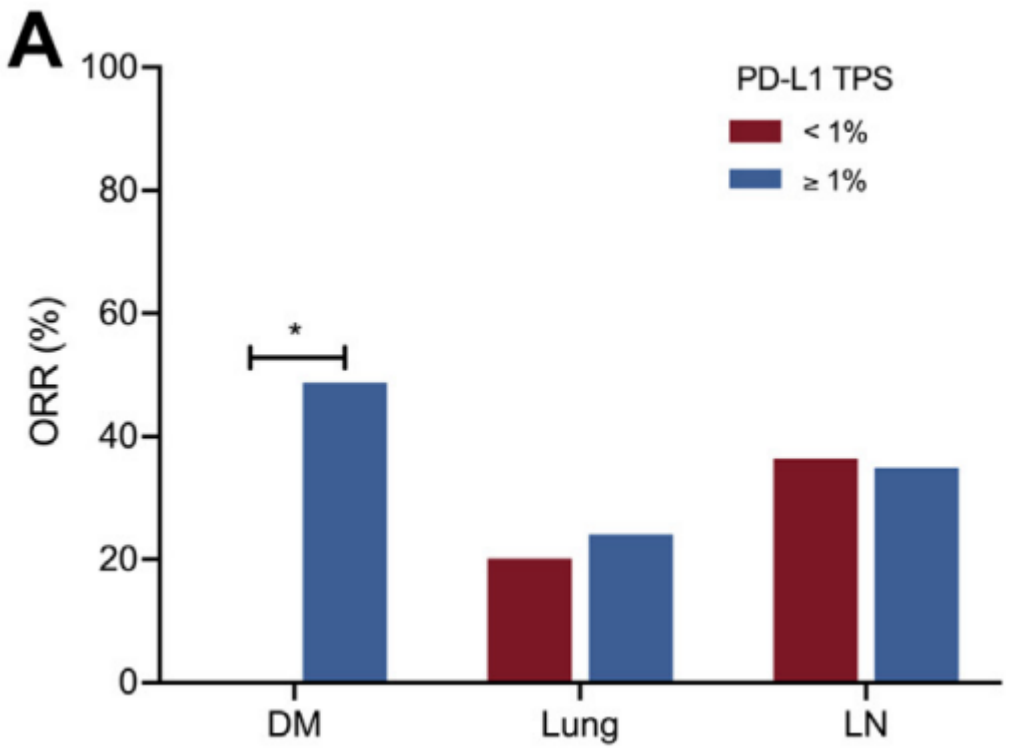
	Median, mo (95% CI)	HR (95% CI)
Pembrolizumab	11.8 (9.0-15.9)	0.64 (0.45-0.91)
Docetaxel	7.5 (4.6-12.2)	—

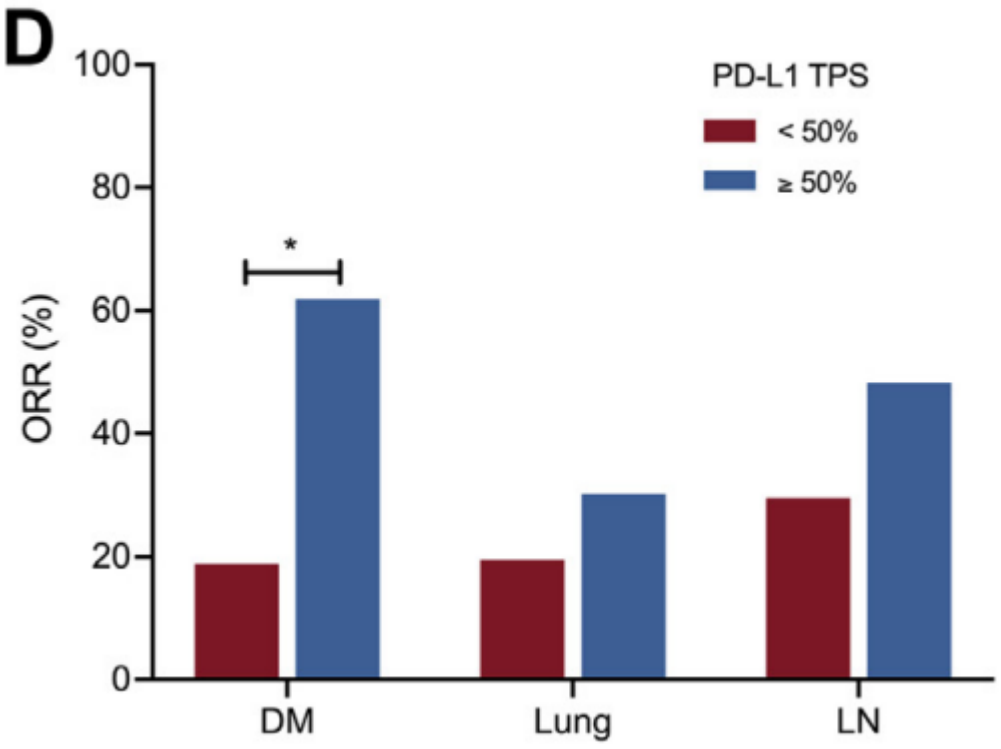


	Median, mo (95% CI)	HR (95% CI)
Pembrolizumab	28.1 (17.1-NR)	0.40 (0.28-0.56)
Docetaxel	8.3 (6.3-11.7)	—

Herbst RS, et al. Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial. Ann Oncol. 2019 Feb 1;30(2):281-289.

PD-L1 IHC may have better predictive value at non nodal sites of metastatic disease





Hong L, et al. Programmed Death-Ligand 1 Heterogeneity and Its Impact on Benefit From Immune Checkpoint Inhibitors in NSCLC. J Thorac Oncol. 2020 Sep;15(9):1449-1459.

Role of pathology: Selecting patients for monotherapy with PD-L1 inhibitor

- What test (antibody clone) to use?
  - 22c3 and SP263 have the best concordance and have FDA approved NSCLC indications
  - SP142 tends to underscore
- What specimen to use?
  - New biopsies may have more predictive value than archival tissue
  - Distant sites of metastatic dz may have more predictive value than primary tumor or regional LN
  - Be very wary of testing anything other than FFPE

ctDNA can be helpful, but is inferior to direct testing of tumor

www.nature.com/modpathol

USCAP

ARTICLE

Check for updates

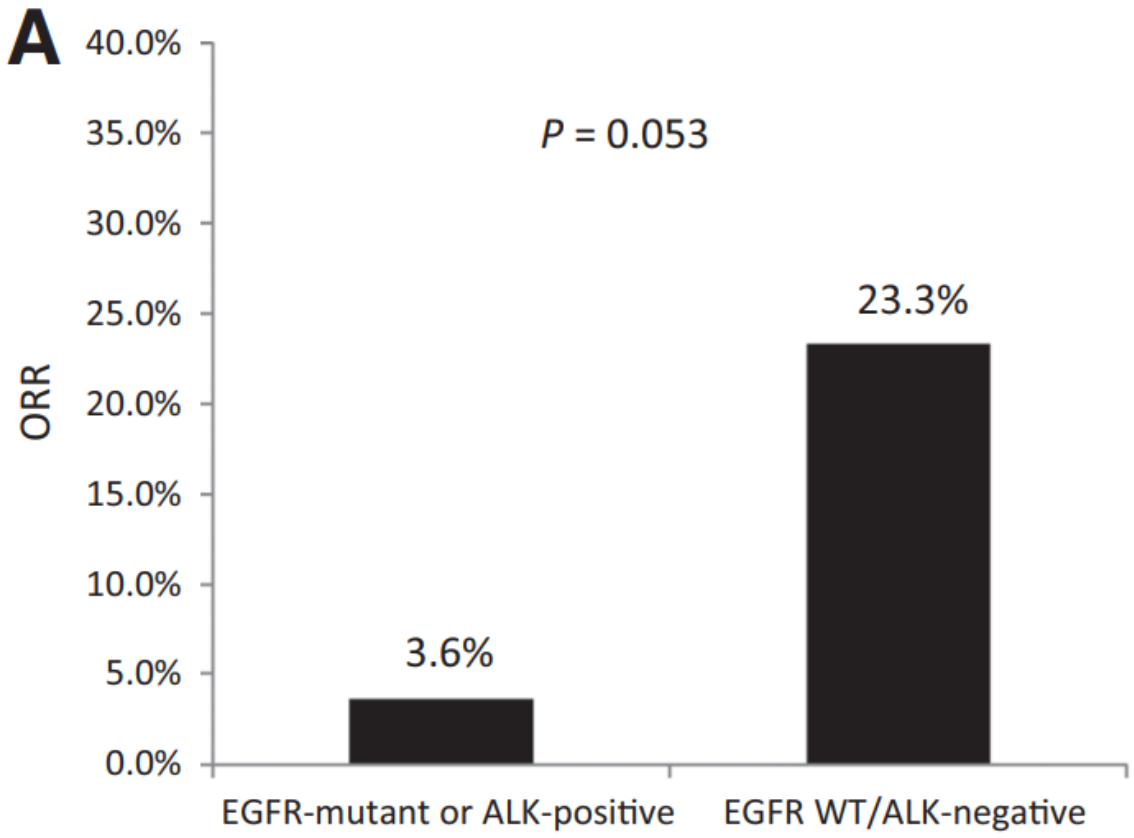
Comparison of solid tissue sequencing and liquid biopsy accuracy in identification of clinically relevant gene mutations and rearrangements in lung adenocarcinomas

Lawrence Hsu Lin[1,4], Douglas H. R. Allison[1,4], Yang Feng[2], George Jour[1], Kyung Park[1], Fang Zhou[1], Andre L. Moreira[1], Guomiao Shen[1], Xiaojun Feng[1], Joshua Sabari[3], Vamsidhar Velcheti[3], Matija Snuderl[1] and Paolo Cotzia[1]✉

Screening for therapeutic targets is standard of care in the management of advanced non-small cell lung cancer. However, most molecular assays utilize tumor tissue, which may not always be available. "Liquid biopsies" are plasma-based next generation sequencing (NGS) assays that use circulating tumor DNA to identify relevant targets. To compare the sensitivity, specificity, and accuracy of a plasma-based NGS assay to solid-tumor-based NGS we retrospectively analyzed sequencing results of 100 sequential patients with lung adenocarcinoma at our institution who had received concurrent testing with both a solid-tissue-based NGS assay and a commercially available plasma-based NGS assay. Patients represented both new diagnoses (79%) and disease progression on treatment (21%); the majority (83%) had stage IV disease. Tissue-NGS identified 74 clinically relevant mutations, including 52 therapeutic targets, a sensitivity of 94.8%, while plasma-NGS identified 41 clinically relevant mutations, a sensitivity of 52.6% ($p < 0.001$). Tissue-NGS showed significantly higher sensitivity and accuracy across multiple patient subgroups, both in newly diagnosed and treated patients, as well as in metastatic and nonmetastatic disease. Discrepant cases involved hotspot mutations and actionable fusions including those in *EGFR*, *ALK*, and *NTRK1*. In summary, tissue-NGS detects significantly more clinically relevant alterations and therapeutic targets compared to plasma-NGS, suggesting that tissue-NGS should be the preferred method for molecular testing of lung adenocarcinoma when tissue is available. Plasma-NGS can still play an important role when tissue testing is not possible. However, given its low sensitivity, a negative result should be confirmed with a tissue-based assay.

Modern Pathology (2021) 34:2168–2174; https://doi.org/10.1038/s41379-021-00880-0

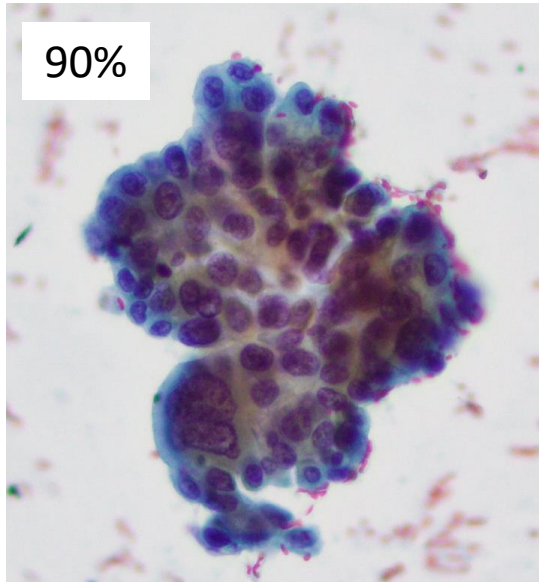
PD-L1 monotherapy has minimal benefit in patients whose tumors harbor *ALK* and *EGFR* alterations

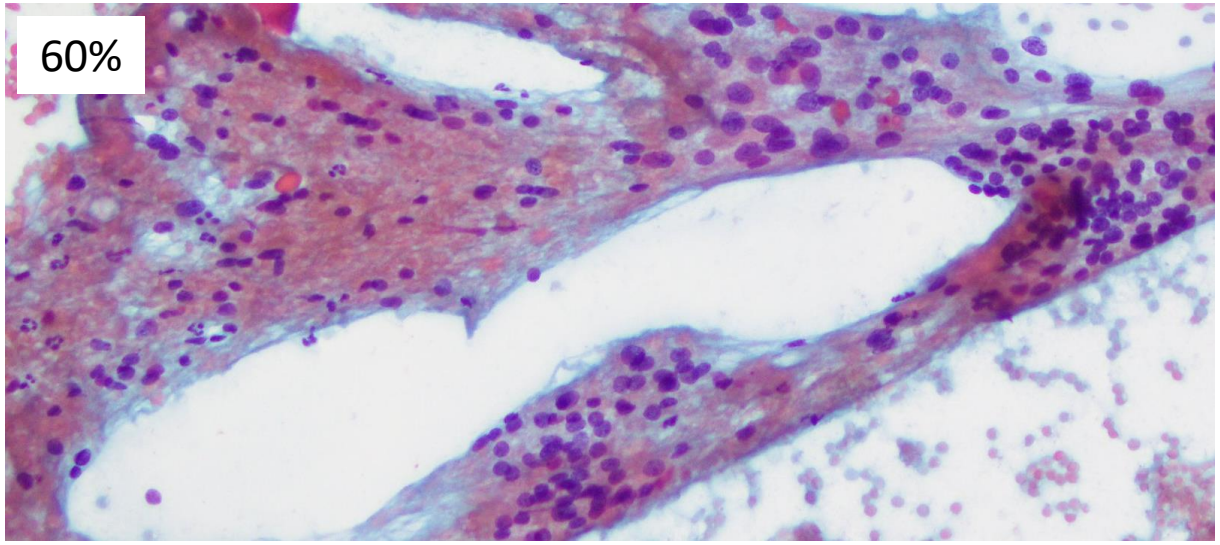


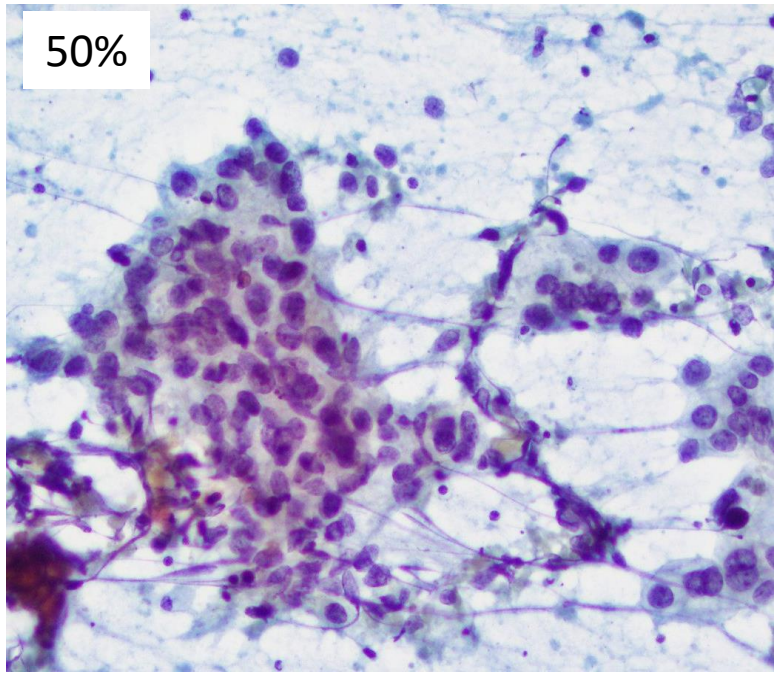
Gainor JF, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res. 2016 Sep 15;22(18):4585-93.

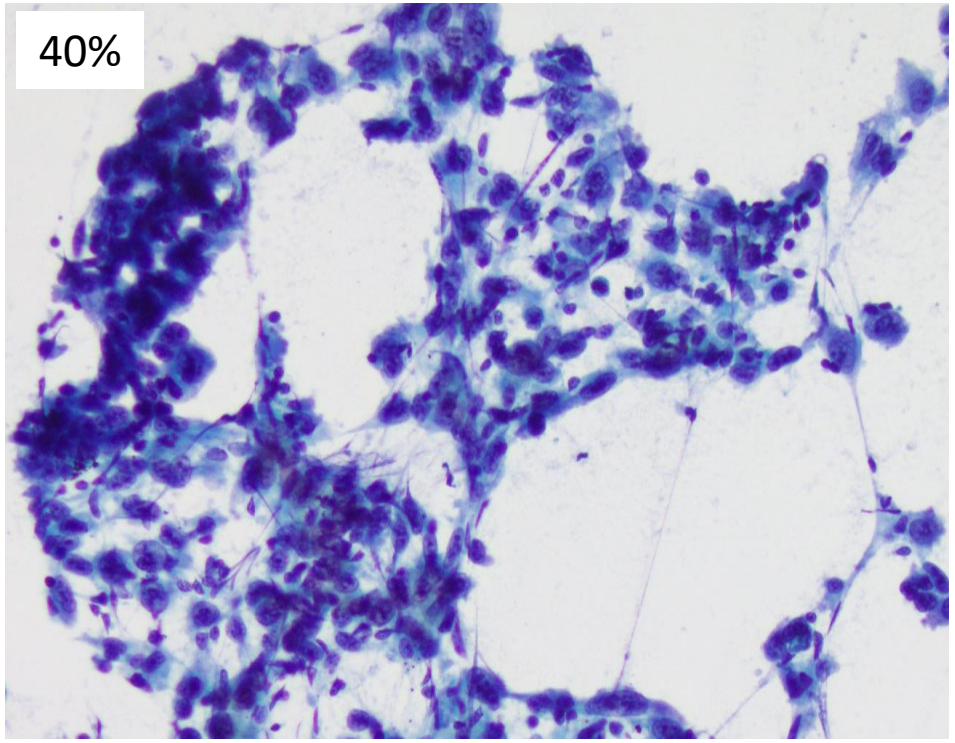
Specimen requirements for molecular studies

- Single gene vs multigene assay
- Tissue quantity dependant on platform
  - Ion Torrent vs Illumina
- Typically 20% tumor cellularity
- Can be performed on aspirate smears if validated









Courtesy of Dr Mir Alikhan

Is ancillary testing of small biopsies worthwhile outside of the Stage IV setting?

YES!!!

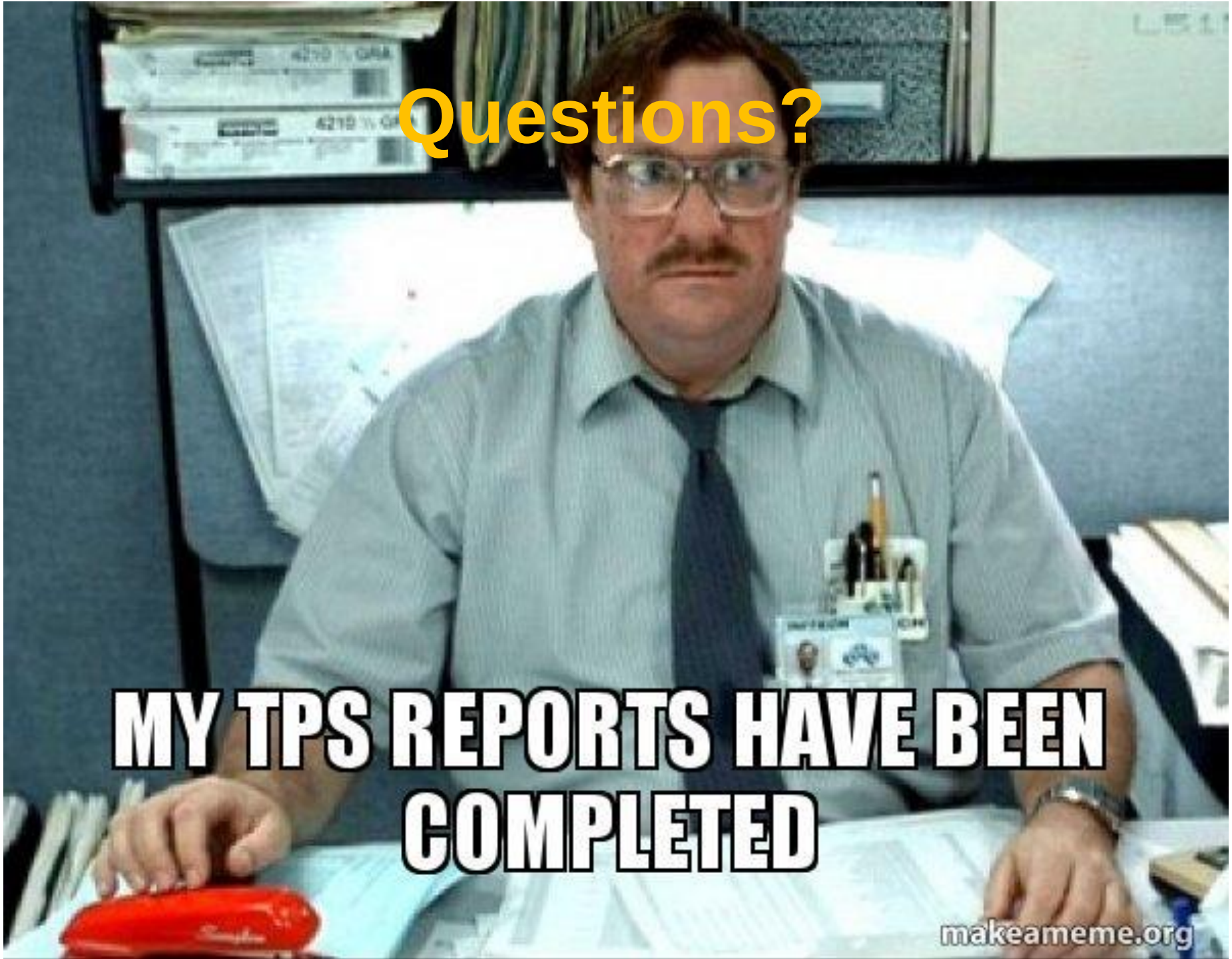
- Stage IIIB: Predict response to maintenance durvalumab (low response rate in *ALK/EGFR* mutant patients and TPS<1)

- Stage IB-IIIA: Predict response to neoadjuvant atezolizumab + chemo (low response rate in *ALK/EGFR* mutant patients and patients TPS<1)

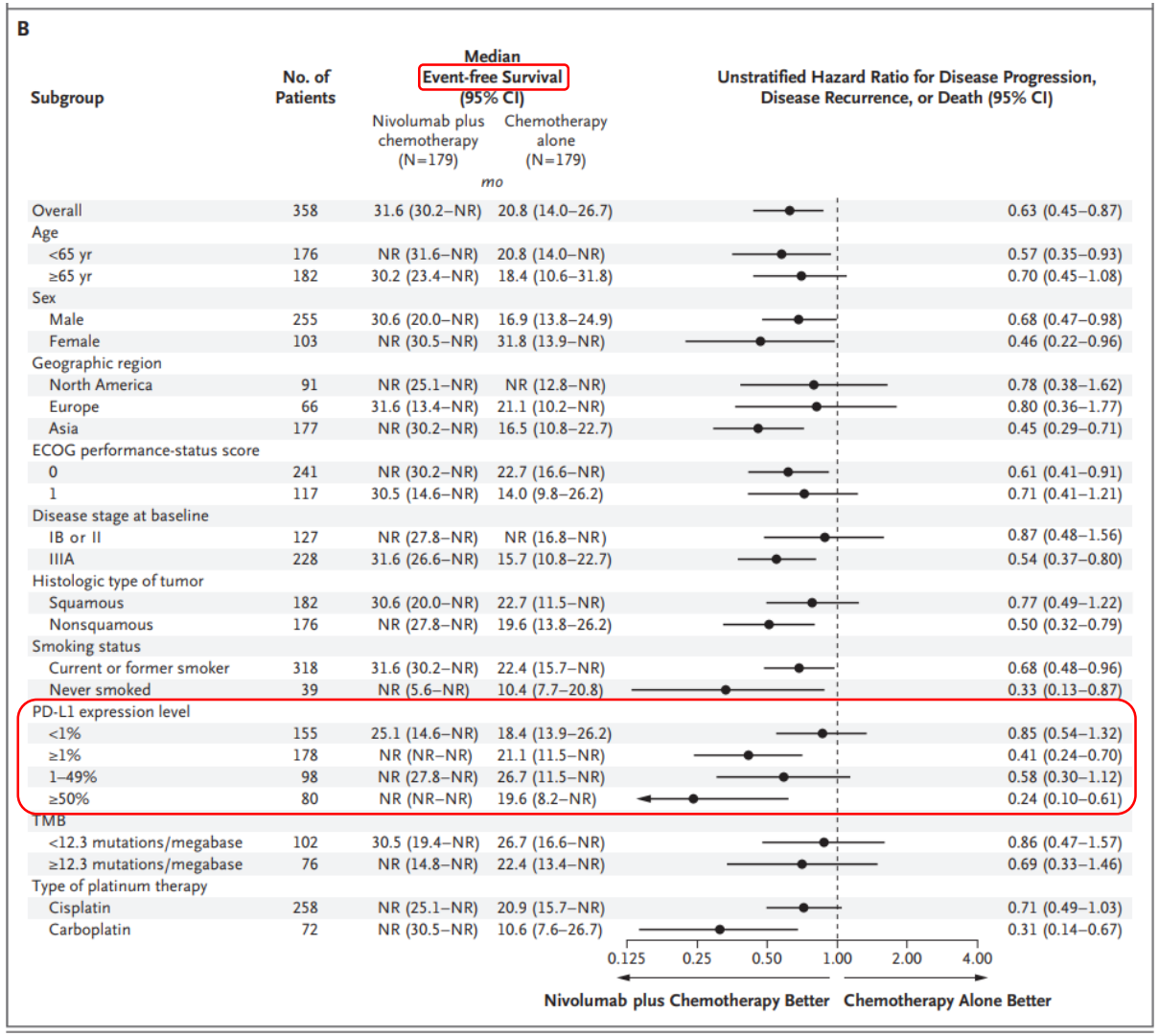
Closing points

- Predictive biomarker testing in NSCLC increasingly makes the role of (cyto)pathology more relevant than ever

- Triage of tissue for both PD-L1 IHC as well as molecular testing is extremely important in driving first line therapy


Questions?
MY TPS REPORTS HAVE BEEN COMPLETED
makeameme.org

Value of PD-L1 IHC in the neoadjuvant setting

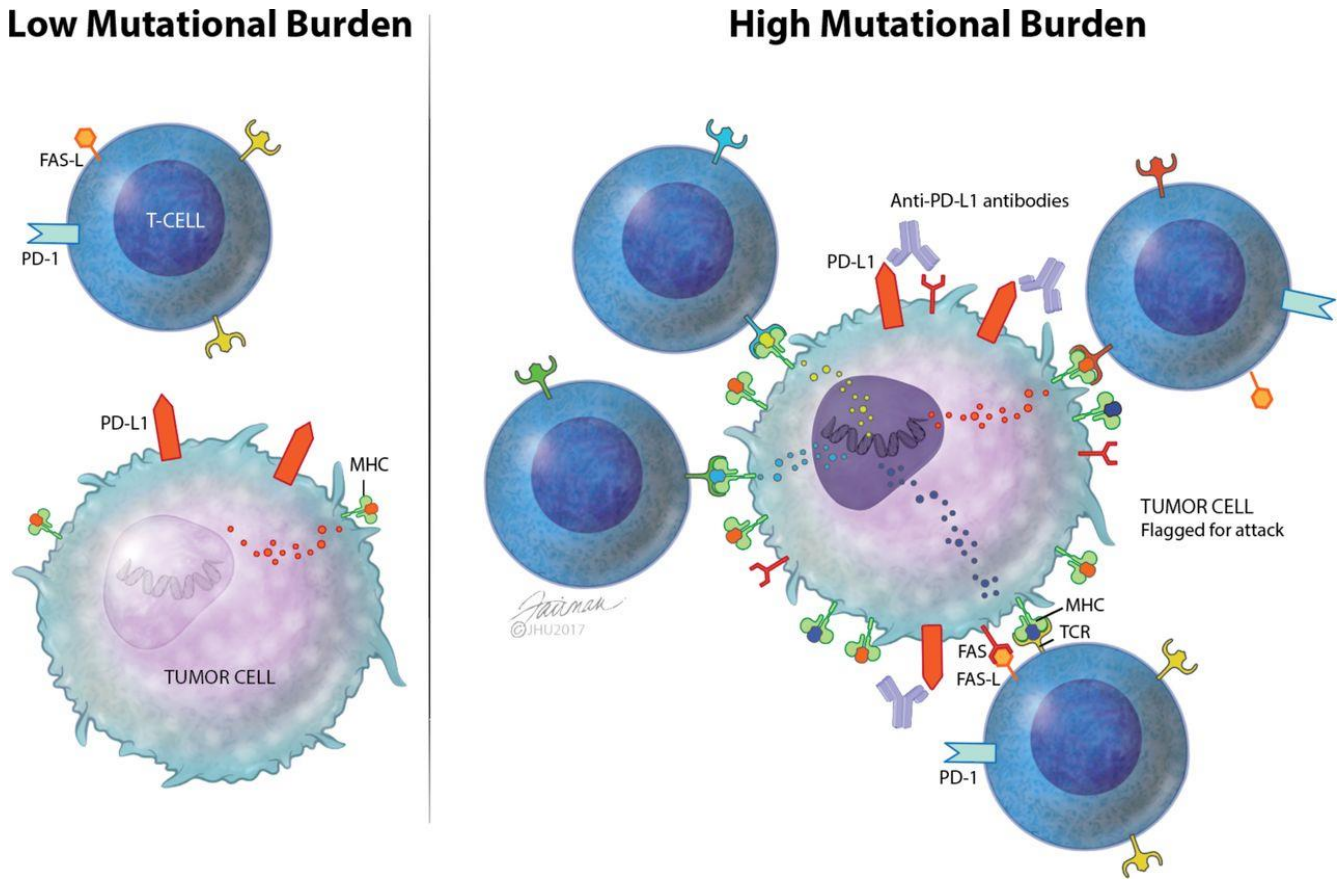


B

Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)

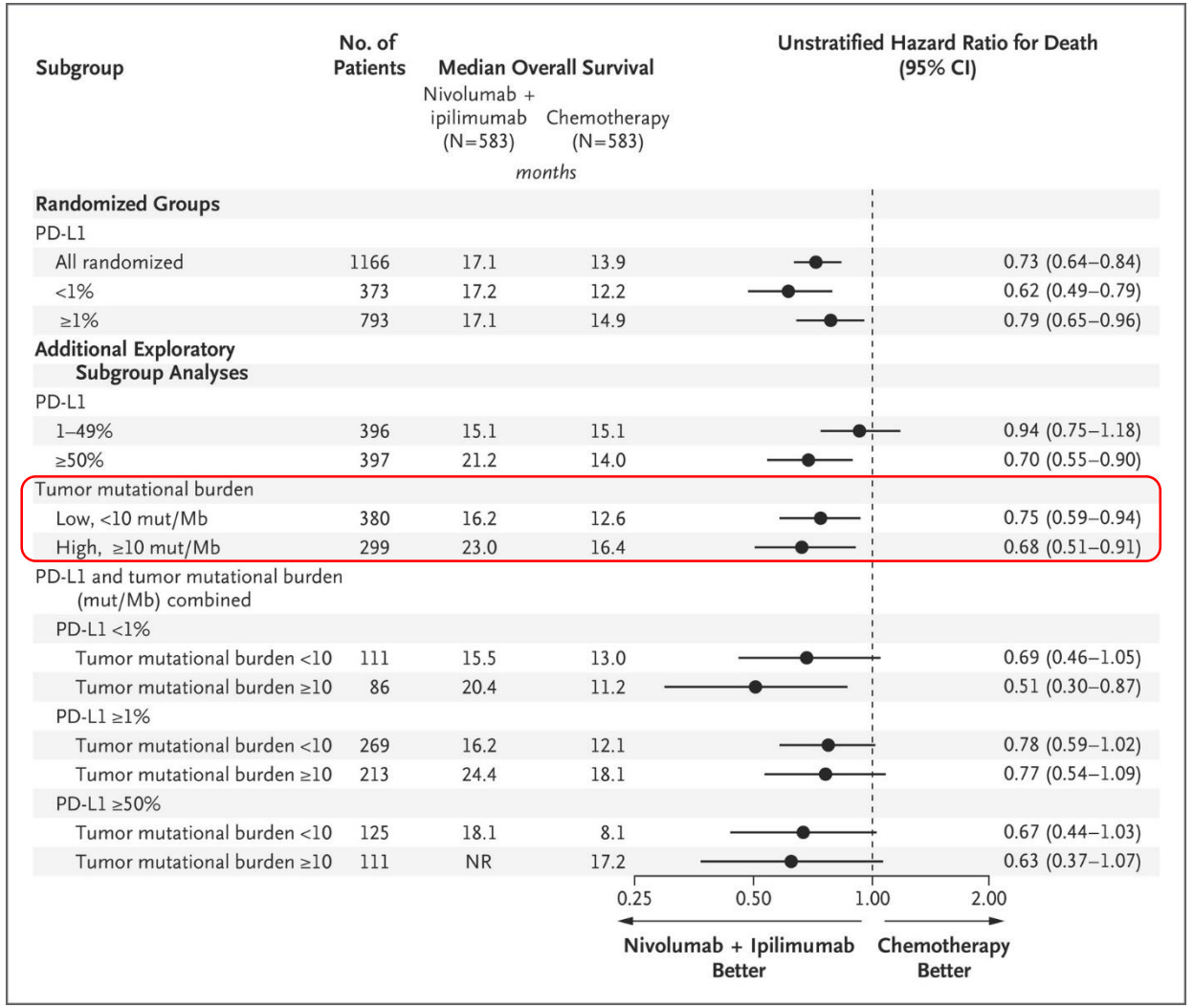
Forde PM, et al. CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985.

Tumor mutational burden as a biomarker?



Sharabi A, et al. Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. Oncologist. 2017

KEYNOTE 227: Early data showed PFS benefit in TMB high, but no OS difference in final data



Subgroup	No. of Patients	Median Overall Survival (months)		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab + ipilimumab (N=583)	Chemotherapy (N=583)	
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)

Hellmann MD, Paz-Ares L, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019 Nov 21;381(21):2020-2031.

extras

- Braf response to ici is 23%
- Ntrk is .2% of nsclc
- Impower 010 post hoc sp263
- 19% pdl1 change from primary to met, usually it turns negative
- **Impact of Decalcification, Cold Ischemia, and Deglycosylation on Performance of Programmed Cell Death Ligand-1 Antibodies With Different Binding Epitopes: Comparison of 7 Clones**