Prognostic impact of NGS in NSCLC

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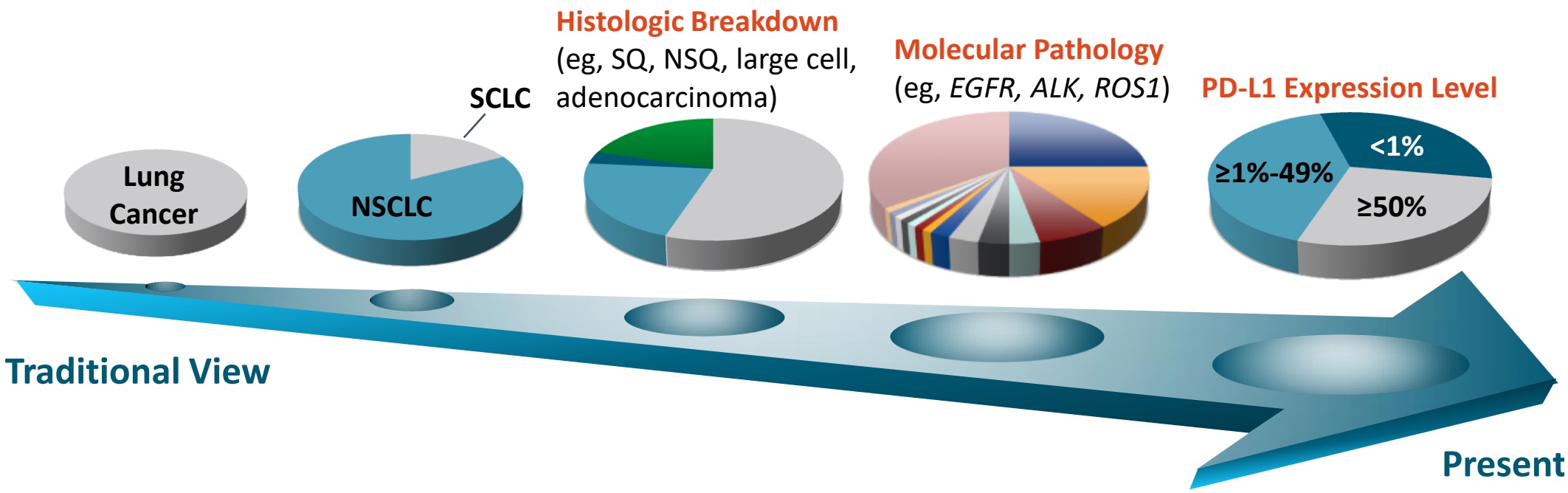
Evolution of Therapy in Lung Cancer

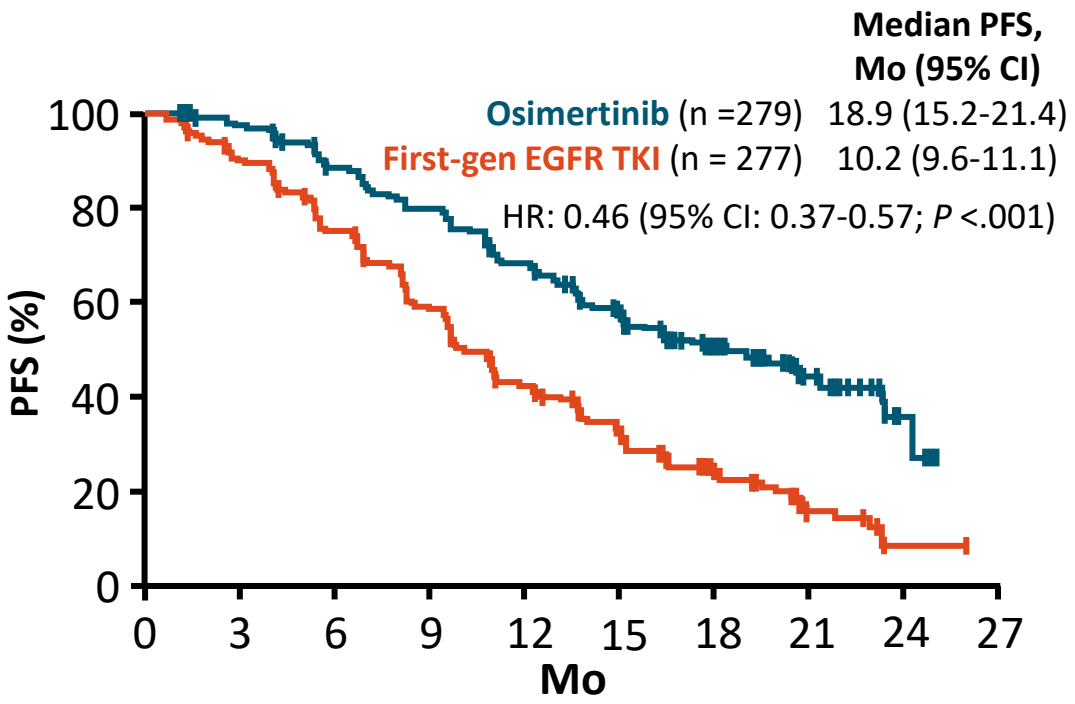
- Not one disease, but many



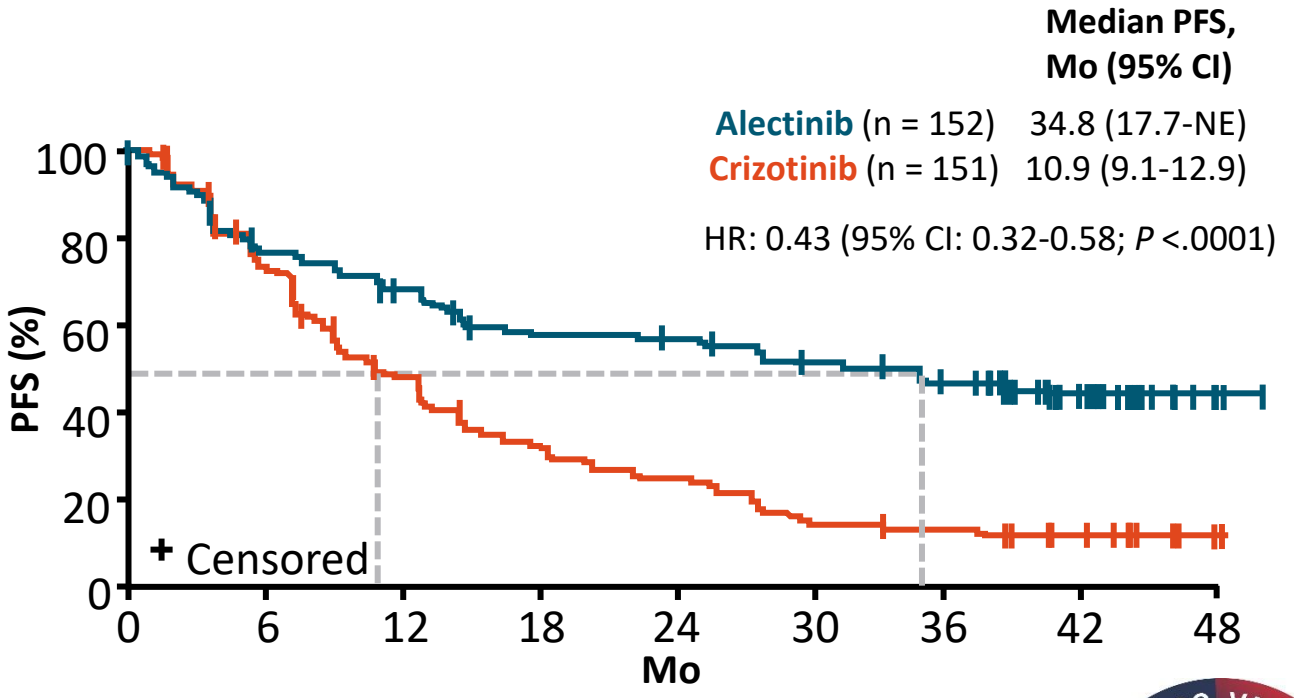
Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11.
Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143.

Impact of Targeted Therapies in Advanced NSCLC

FLAURA: PFS With First-line Osimertinib vs First-Generation EGFR TKI in Advanced *EGFR*+ NSCLC[1]



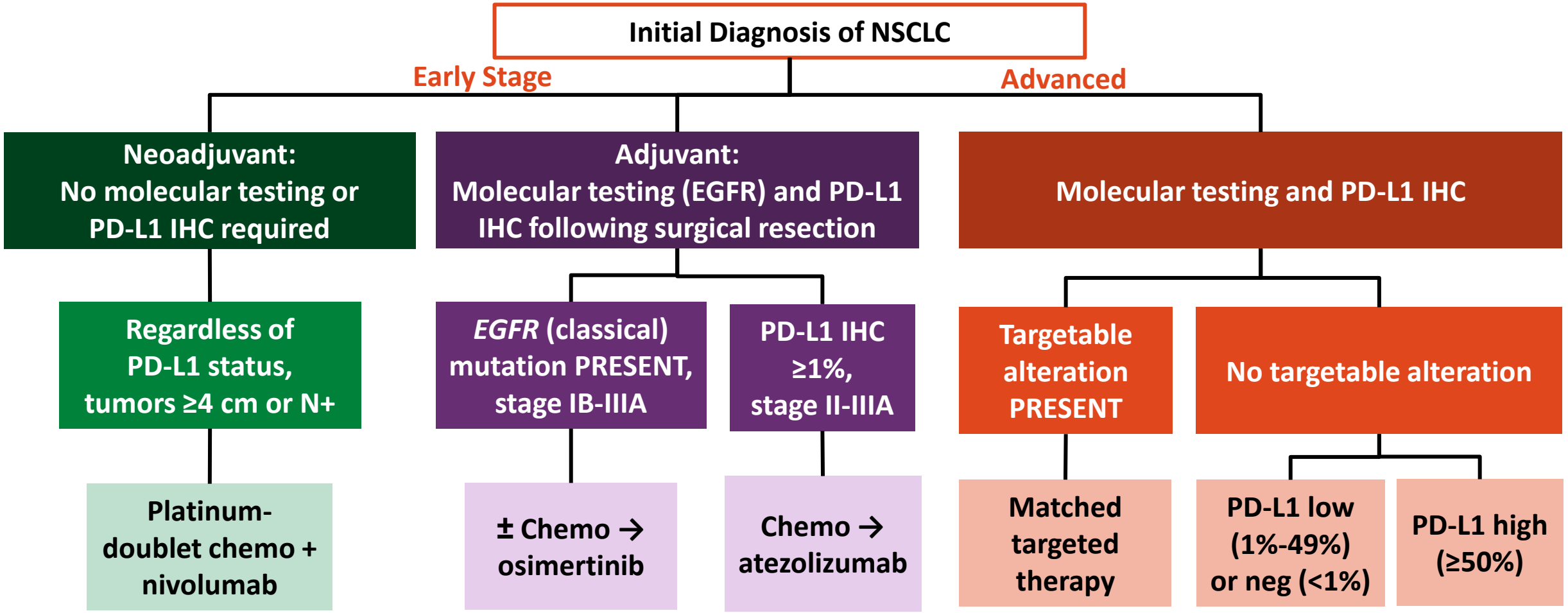
ALEX: PFS With First-line Alectinib vs Crizotinib in Advanced *ALK*+ NSCLC[2]



- ~50% of patients with advanced nonsquamous NSCLC will have a driver mutation targetable with an FDA-approved agent or on a clinical trial[3]

1. Soria. NEJM. 2018;378:113. 2. Mok. Ann Oncol. 2020;31:1056. 3. NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022. nccn.org.

Molecular and PD-L1 Testing at Initial Diagnosis to Guide Treatment in NSCLC

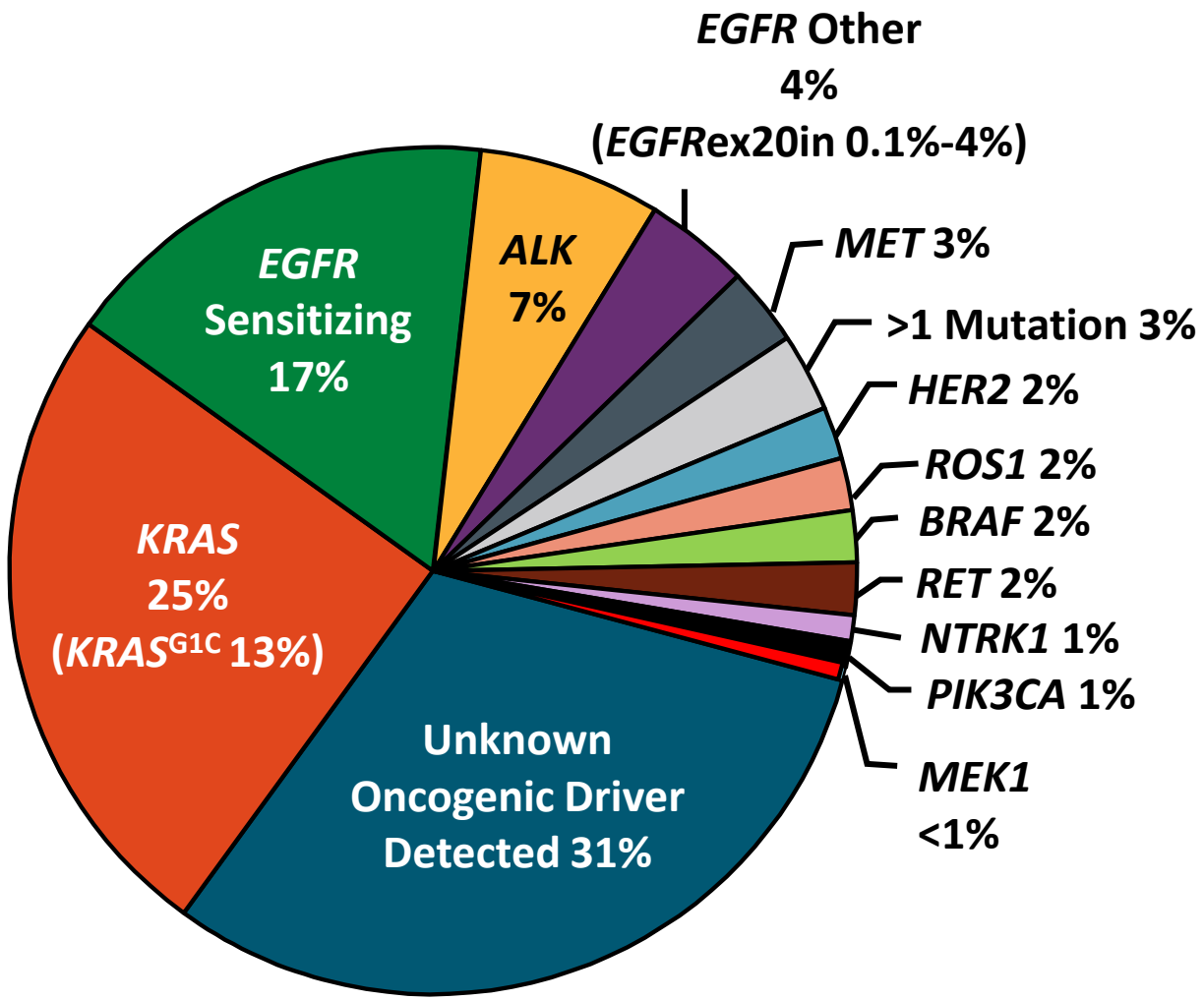


Which Patients Require Biomarker Testing in 2022?

Stage IB-IIIA Nonsquamous, Resectable	EGFR Testing ± NGS—Trials?	*NCCN*
Stage III Nonsquamous, Definitive Chemoradiation	Consider EGFR Testing	*Not Yet Standard— LAURA Study Ongoing*
Advanced/Metastatic		
Nonsquamous	Comprehensive NGS in All Patients	*NCCN*
Squamous	NGS in Selected* Patients *Young, nonsmokers, small sample.	

Simplify View!

~50% of Patients With Advanced Nonsquamous NSCLC Have an Actionable Driver Mutation



Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613.
Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

Tissue Journey: Biopsy to Analysis

Preliminary diagnosis → **Biopsy methods and specimen processing** → **Morphologic assessment** → **Extraction** → **Analysis**

TISSUE
- **Resection**
- **Excision**
- **Small tissue biopsies**

→ **FFPE block**

CYTOLOGY
- **Fine-needle aspiration**
- **Exfoliative cytology** (cells shed from body surfaces)

→ **FFPE block**

LIQUID
- **Liquid biopsies**
  - Blood
  - Cyst fluid

→ **Non–cell block slide**

Histology

Cytology

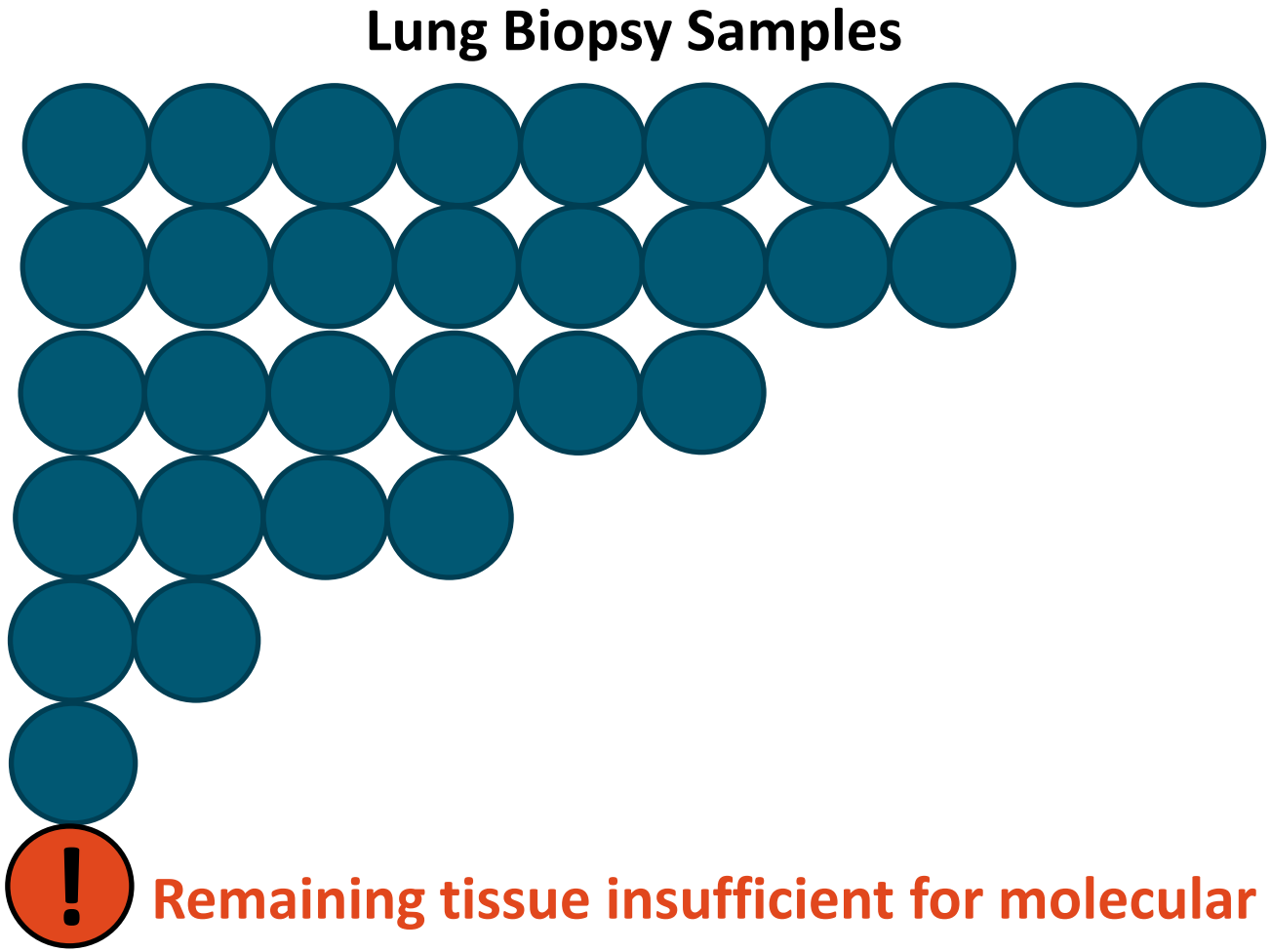
Parallel diagnostics
- IHC (eg, PD-L1, dMMR)
- ISH/FISH

DNA →
RNA →
Protein →

Assessment methods
- PCR
- Cancer gene panels
- MSI
- NGS (WGS, WES, targeted hotspot panel)
- RT-qPCR
- Gene expression panels
- RNA-seq NGS
- Proteomics
- FACS
- Data analytics

Ascierto. J Mol Diagn. 2019;21:756.

The Problem of Insufficient Tissue in Workup for NSCLC



Original

TTF-1, p40 IHC

CDX-2, PAX-8 IHC

CK7, CK20 IHC

GATA-3 IHC

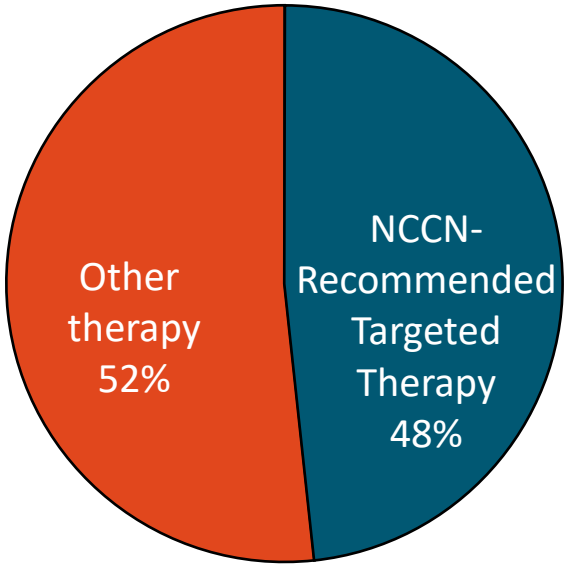
Synaptophysin IHC

Remaining tissue insufficient for molecular testing and PD-L1 IHC

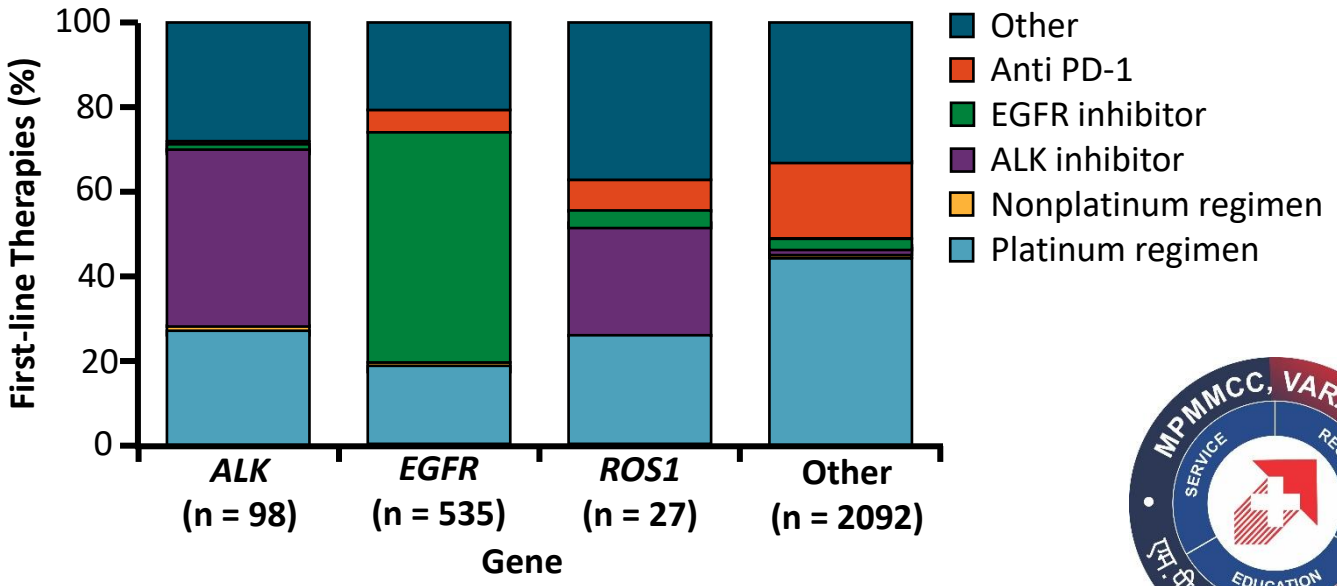
Why Does Upfront Testing Matter?

- Only 48% of patients with advanced NSCLC and a driver mutation received NCCN-recommended targeted therapy[1]
  - Alterations included *EGFR, ALK, ROS1, BRAF, MET, RET, ERBB2*
- Patients with driver mutations who received targeted therapy had an improved OS (18.6 mo vs 11.4 mo; *P* <.001)[1]
- **Always give the best treatment upfront**
  - ~30% of patients will NOT go on to receive second-line treatment[2]

Patients with NSCLC
(N = 1260)



First-line Therapy Received by Driver Mutation



1. Singal. JAMA. 2019;321:1391. 2. Ramalingam. NEJM. 2020;382:41.

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Impact of EGFR exon 19 deletion subtypes on clinical outcomes in EGFR-TKI-Treated advanced non-small-cell lung cancer

Le-Tian Huang, Shu-Ling Zhang, Cheng-Bo Han, Jie-Tao Ma *

Department of Oncology, Shengjing Hospital of China Medical University, Shenyang 110022, China

- Patients with E746_A750del, the most common 19del subtype, had a significantly higher frequency of acquired T790M mutation when treated with first- or second-generation EGFR-TKIs compared to those with other 19del subtypes (RR, 0.76; 95% CI: 0.64–0.89, P = 0.001).

- Patients with E746_A750del subtype have a higher frequency of acquired T790M mutation.

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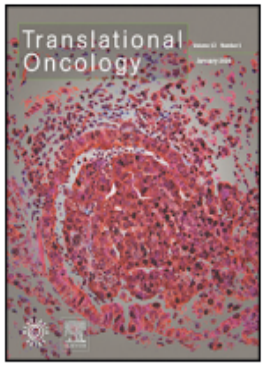


Molecular Characteristics and Clinical Outcomes of EGFR Exon 19 C-Helix Deletion in Non–Small Cell Lung Cancer and Response to EGFR TKIs

Chun-wei Xu [a,1], Lei Lei [b,1], Wen-xian Wang [b,1], Li Lin [c], You-cai Zhu [d], Hong Wang [e], Li-yun Miao [f,*], Li-ping Wang [g,*], Wu Zhuang [h], Mei-yu Fang [b], Tang-feng Lv [a], Yong Song [a,*]

[a] *Department of Respiratory Medicine, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing, Jiangsu 210002, People's Republic of China*

[b] *Department of Chemotherapy, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of*

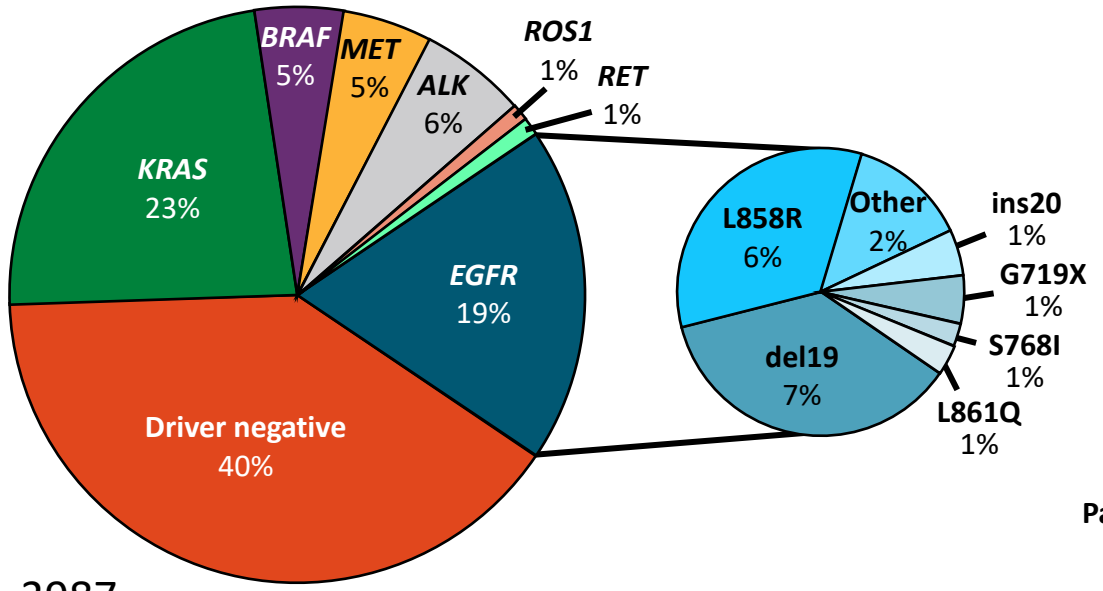
- About 2.5% E19del would occur in the Chelix part of exon 19 which could constructively impact the sensitivity of TKI treatment by activation of TK region.

- p.T751_I759delinsS seemed to have intrinsic resistance to gefitinib, and PFS was only 2.0 months.

- Case reports: Good response to Afatinib and Osimertinib.

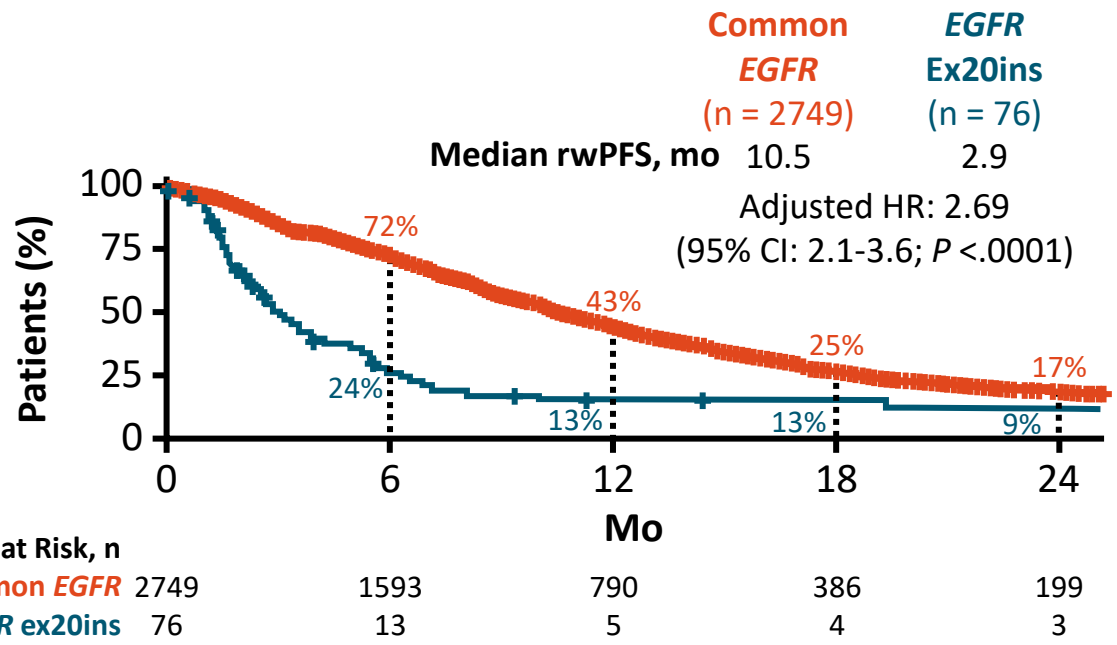
EGFR Exon 20 Insertions in Advanced NSCLC

Frequency of *EGFR* Exon 20 Insertion Mutations in Advanced NSCLC



N = 3987

Real-World PFS for *EGFR* Ex20ins+ vs *EGFR* L858R/ Ex19del+ Adv NSCLC with 1L EGFR TKI Therapy (n = 2825)*

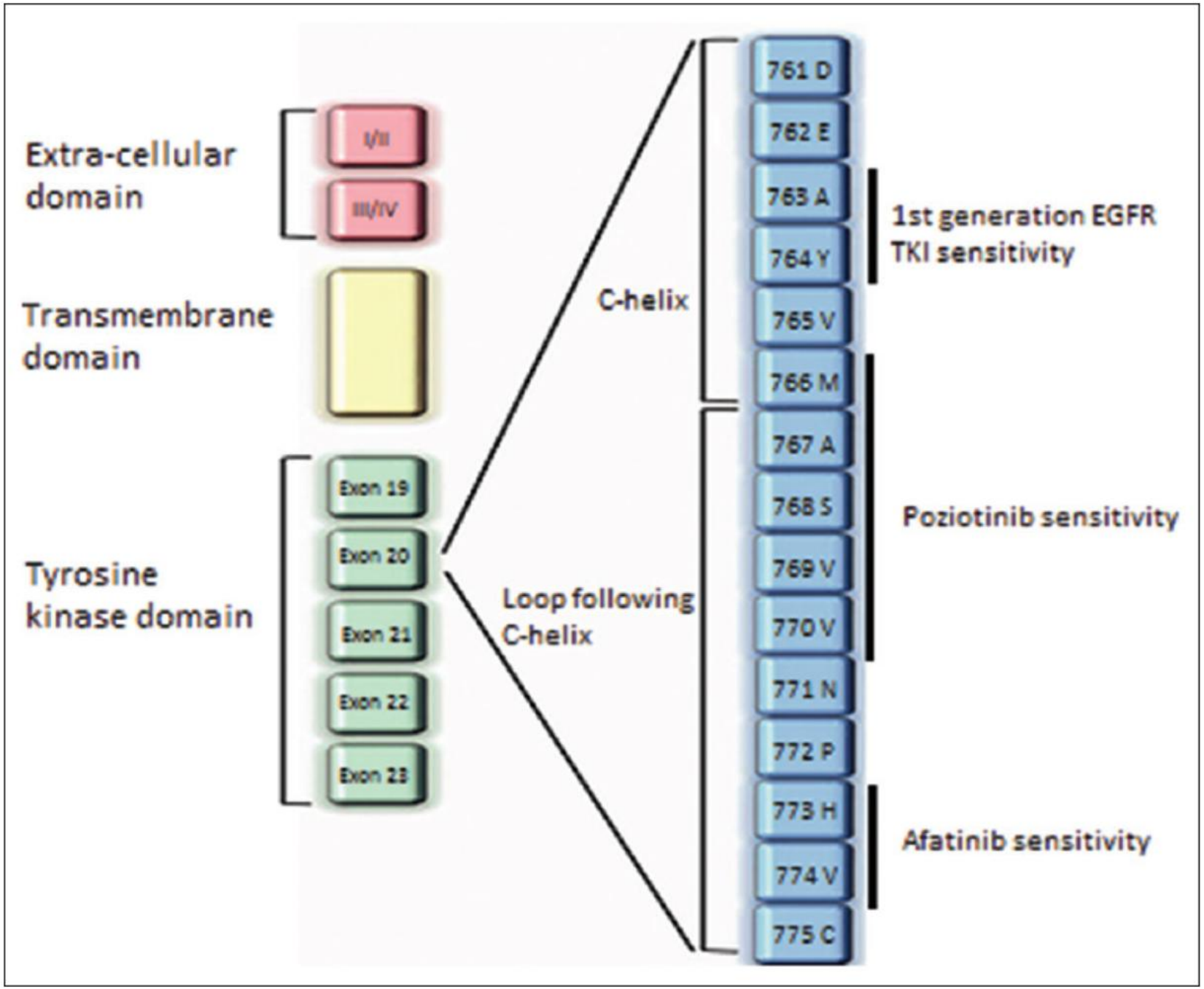


*Stratified by l

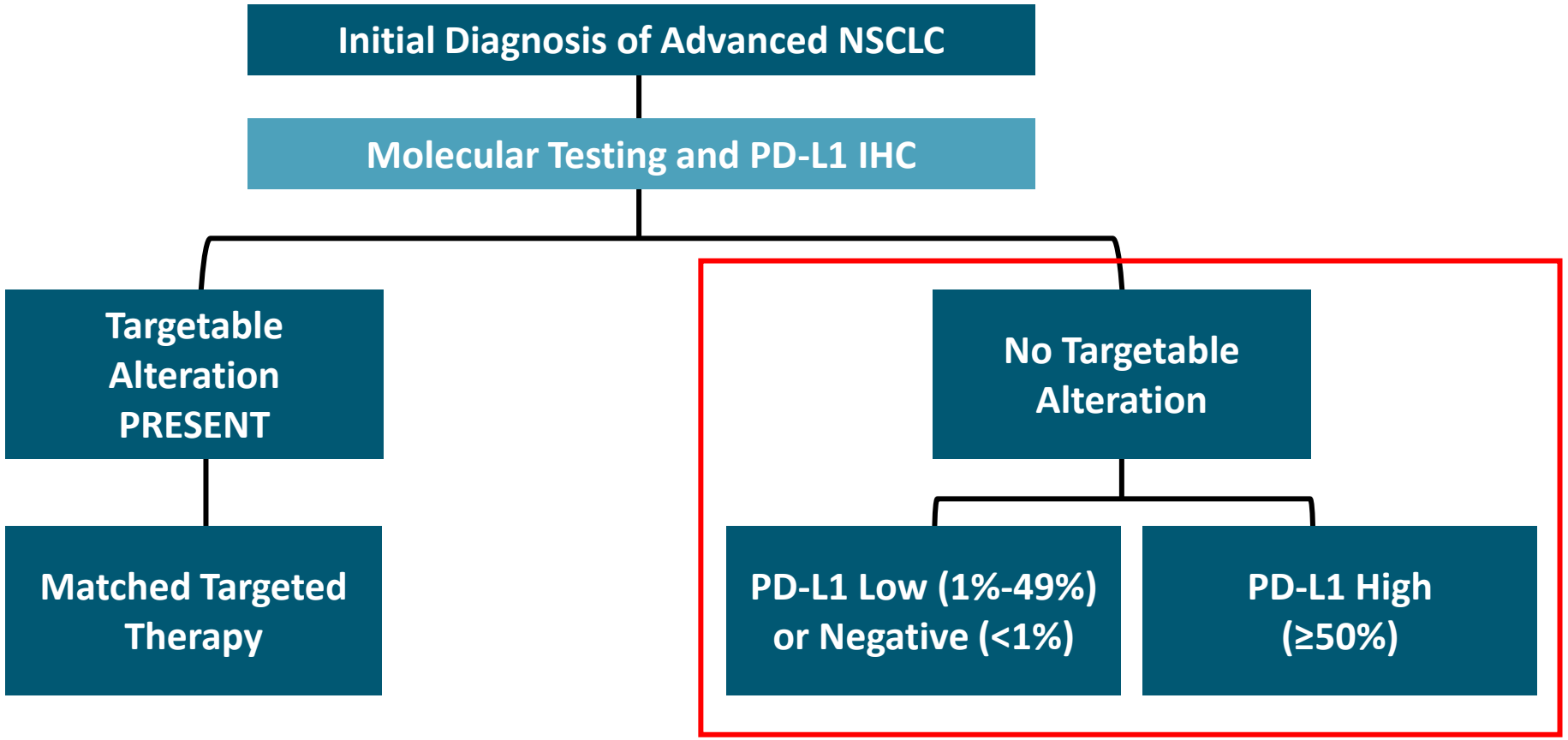
- *EGFR* exon 20 insertions account for 1% of actionable biomarkers in advanced NSCLC, ~10% of *EGFR* mutations

Meador. Cancer Discov. 2021;11:2145. Bazhenova. Lung Cancer. 2021;162:154.

Region of EGFR Exon 20 insertion

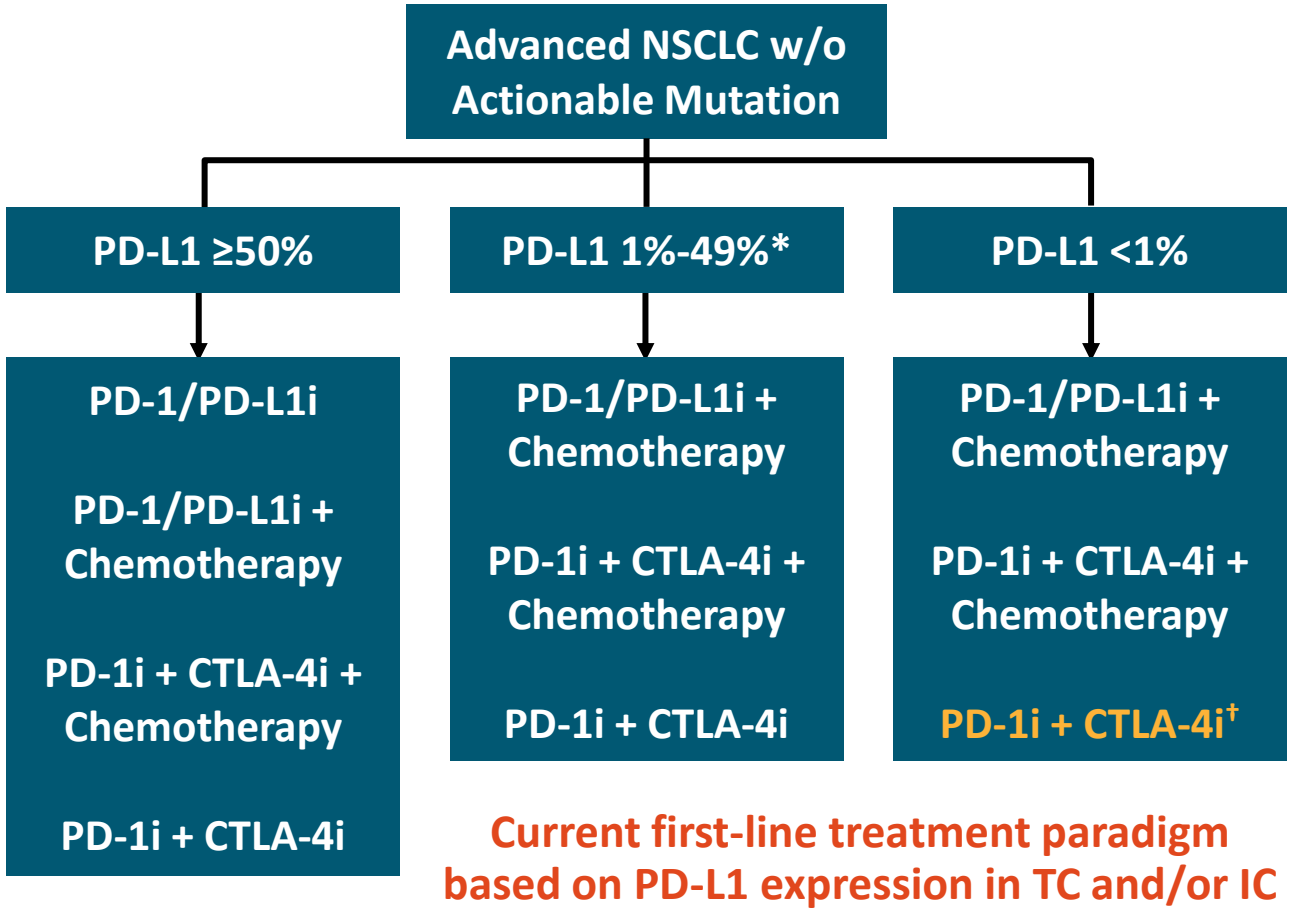


Molecular and PD-L1 Testing Should Be Done at Initial Diagnosis of Advanced NSCLC to Guide 1L Tx Decisions



2022 Paradigm for Immunotherapy in Advanced NSCLC Without an Actionable Mutation

Updated



Current first-line treatment paradigm based on PD-L1 expression in TC and/or IC

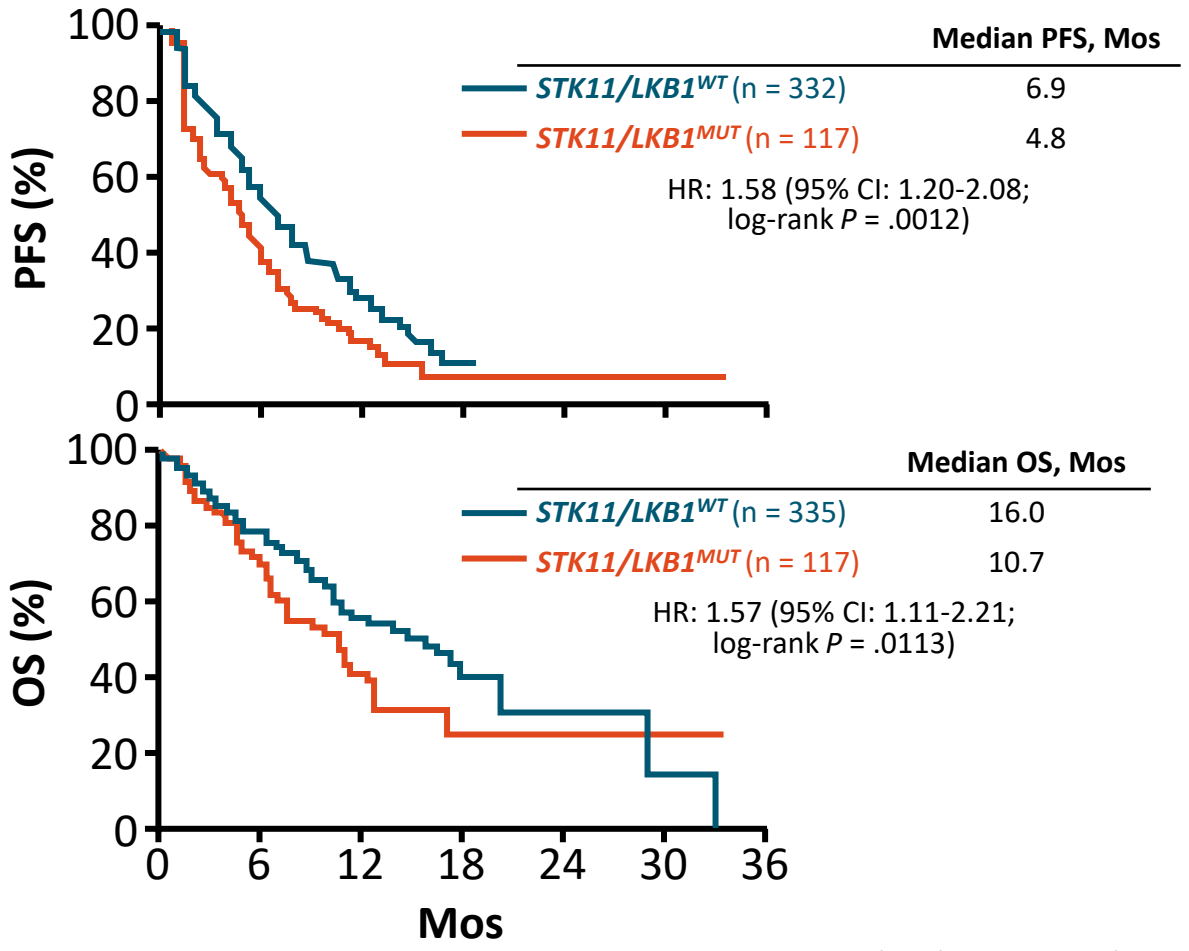
- ICI monotherapy: pembrolizumab,* atezolizumab, cemiplimab
- ICI + chemotherapy
  - Pembrolizumab/carboplatin or cisplatin/pemetrexed (Nsq)
  - Atezolizumab/carboplatin/paclitaxel/ bevacizumab (Nsq)
  - Atezolizumab/carboplatin/nab-paclitaxel (Nsq)
  - Pembrolizumab/carboplatin/taxane (Sq)
  - Nivolumab/ipilimumab + 2 cycles of CT (Sq/Nsq)
- ICI combination: nivolumab/ipilimumab

*Single-agent pembrolizumab also approved for ≥1% PD-L1 but not broadly recommended by experts; guideline-recommended for PD-L1 1-49% if poor PS or contraindications to combining w/CT. †Not an FDA approved indication, but guideline recommended.

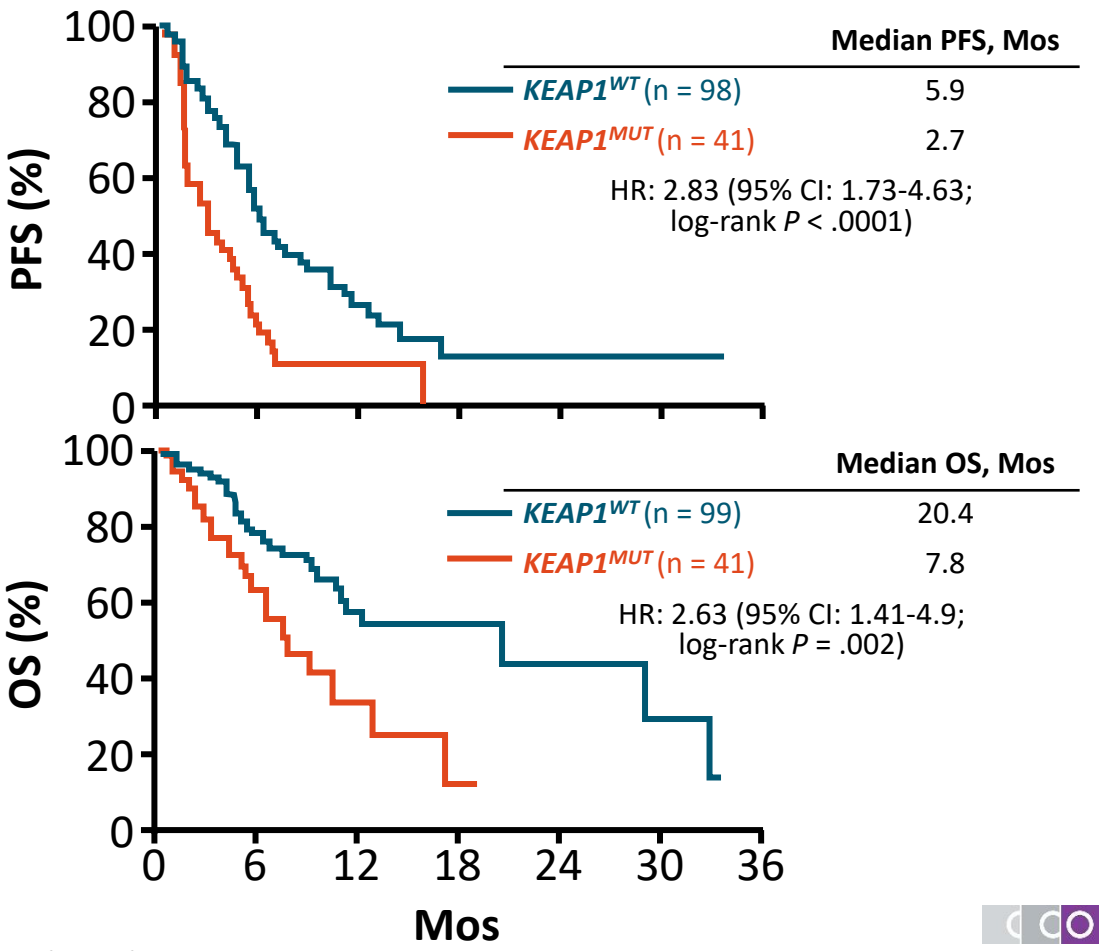
NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022. nccn.org.

STK11 and *KEAP1* Genomic Alterations Associated With Inferior Clinical Outcomes With Pembro + CT in Nonsq NSCLC

STK11 Genomic Alterations



KEAP1 Genomic Alterations

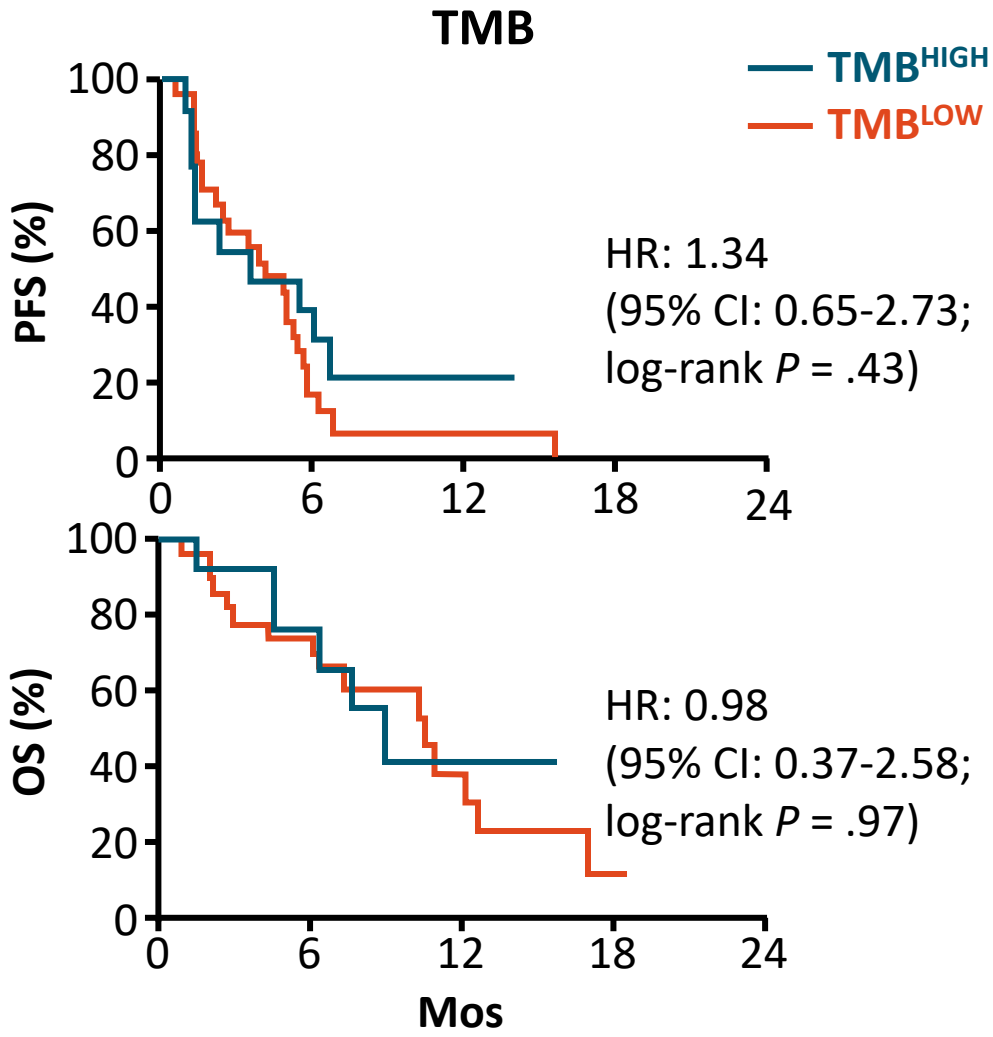


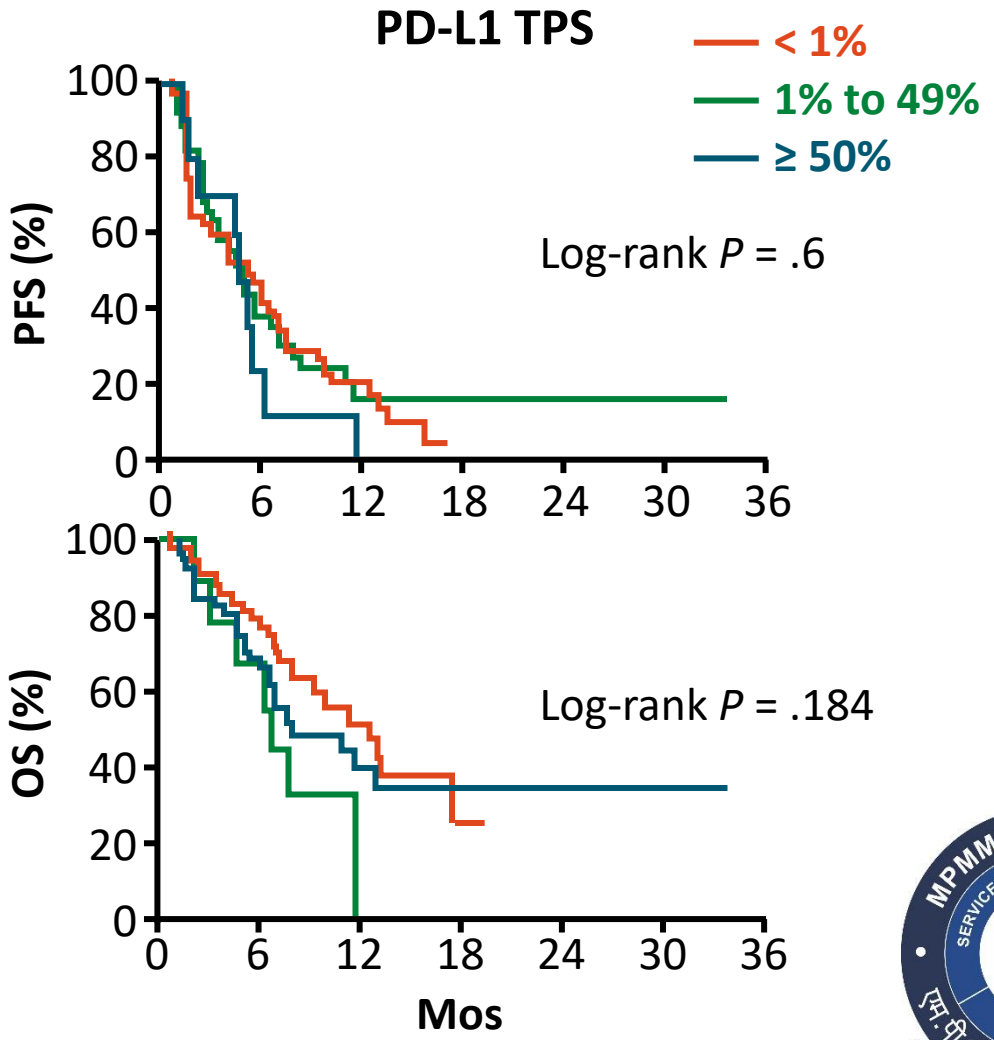
CT: carboplatin or cisplatin/paclitaxel.

Skoulidis. ASCO 2019. Abstr 102.

Slide credit: clinicaloptions.com

TMB and PD-L1 Independent of Clinical Outcomes With Pembro + CT in *STK11*^{MUT} and/or *KEAP1*^{MUT} Nonsq NSCLC

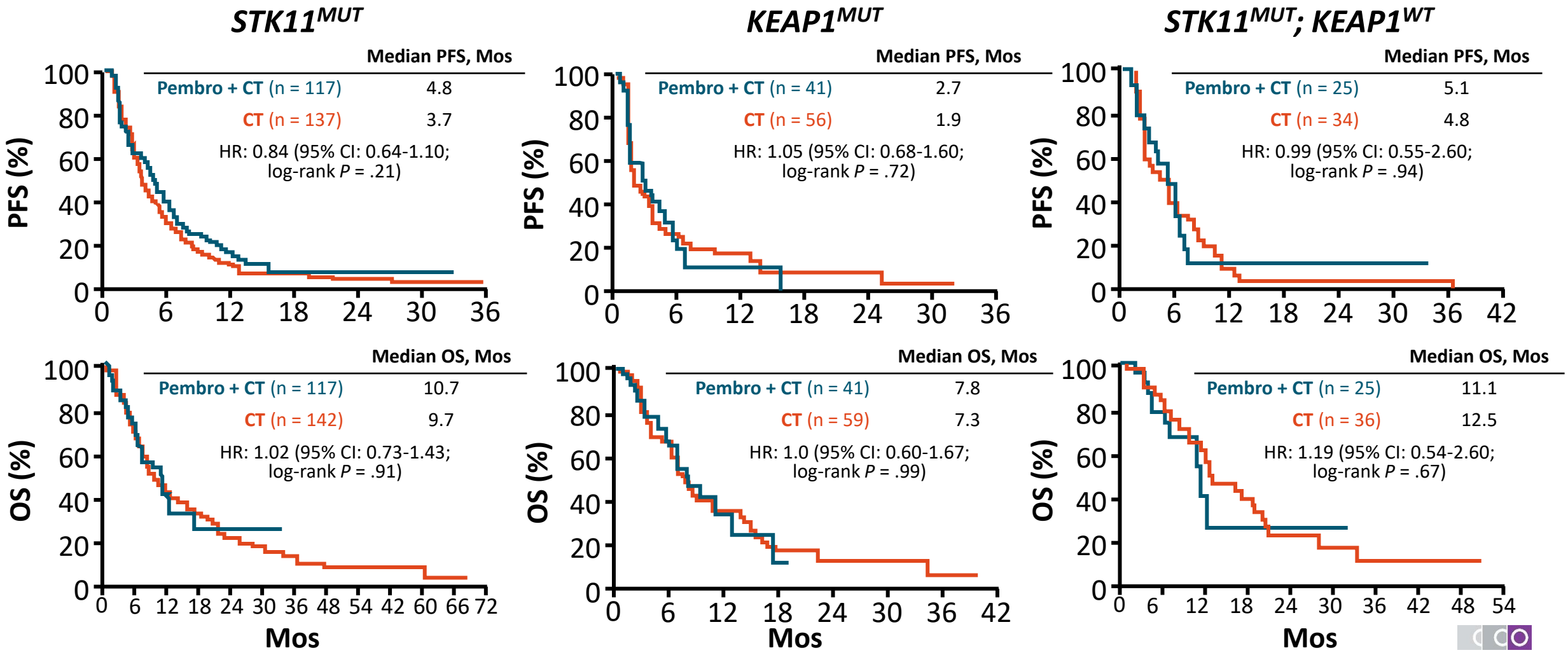




Skoulidis. ASCO 2019. Abstr 102.

CT: carboplatin or cisplatin/paclitaxel.

Survival With Pembro + CT vs CT in *STK11*^{MUT} and *KEAP1*^{MUT} Genomically Defined Subsets of Nonsq NSCLC

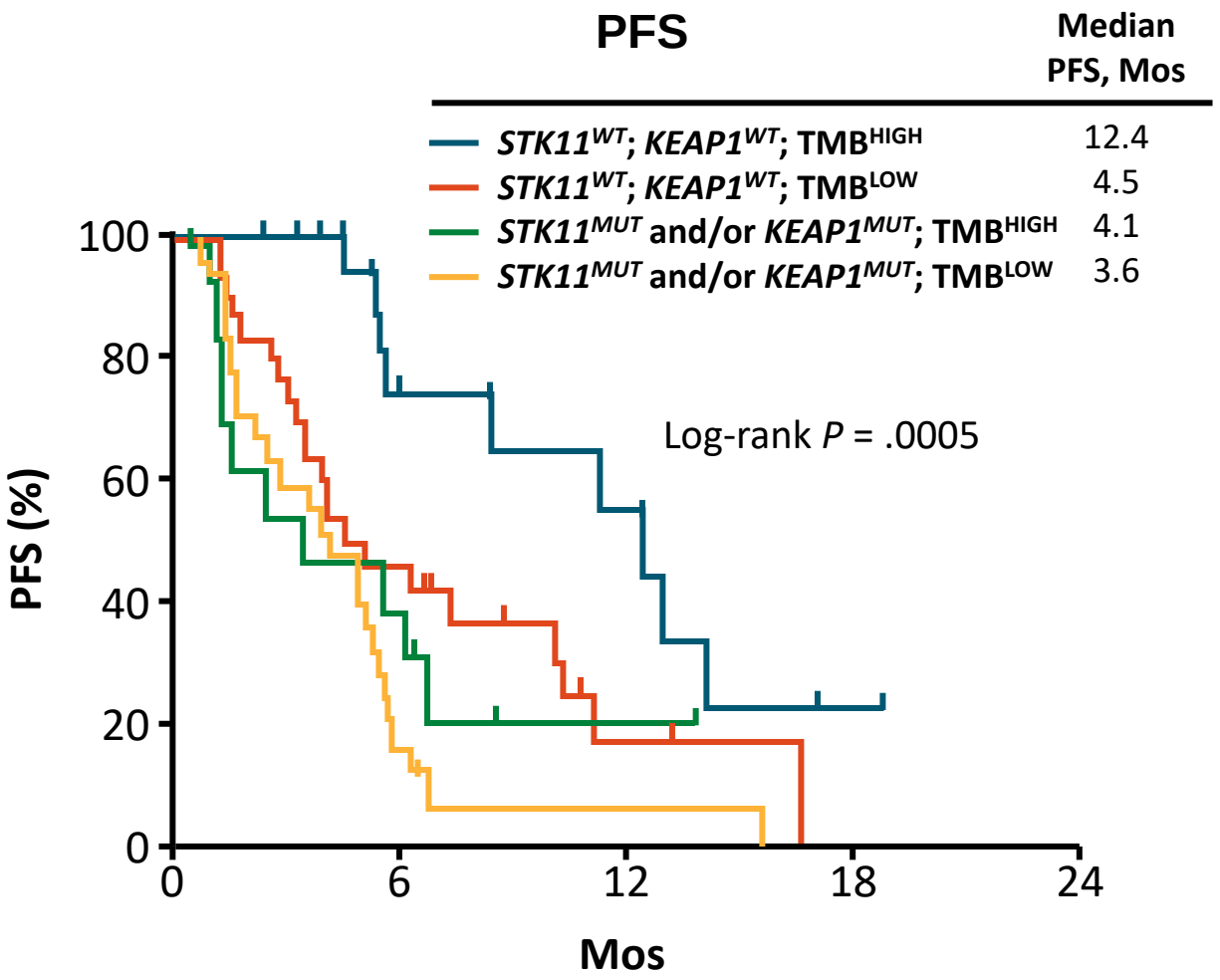


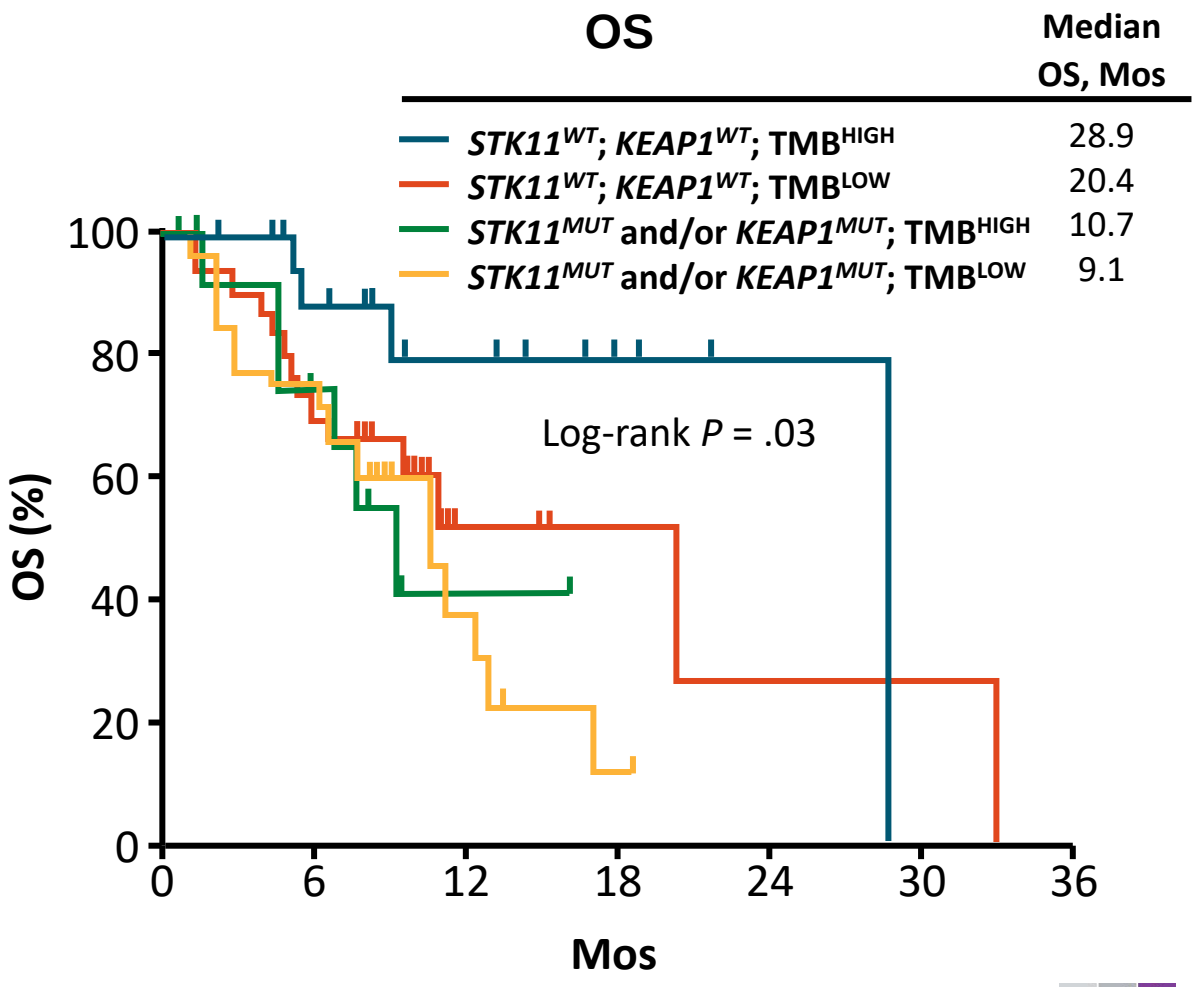
Skoulidis. ASCO 2019. Abstr 102.

CT: carboplatin or cisplatin/paclitaxel.

Slide credit: clinicaloptions.com

Integration of *STK11* and *KEAP1* Genomic Alterations With TMB and Other Biomarkers: Toward a Composite Panel?





Skoulidis. ASCO 2019. Abstr 102.

Slide credit: clinicaloptions.com

nature COMMUNICATIONS

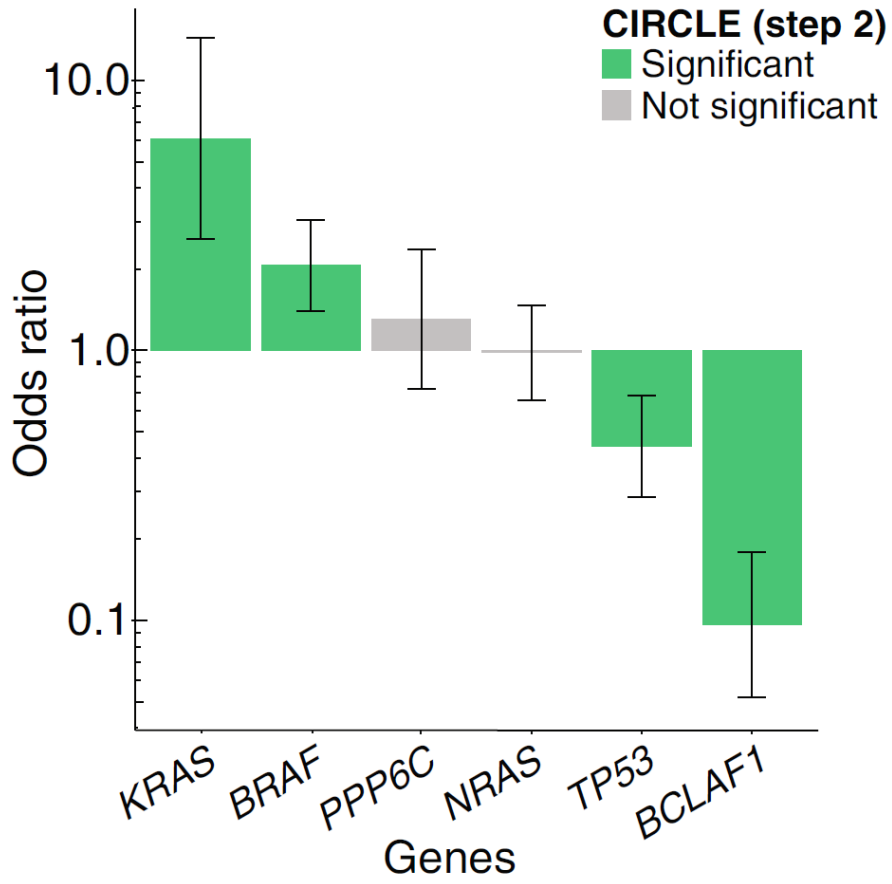
ARTICLE

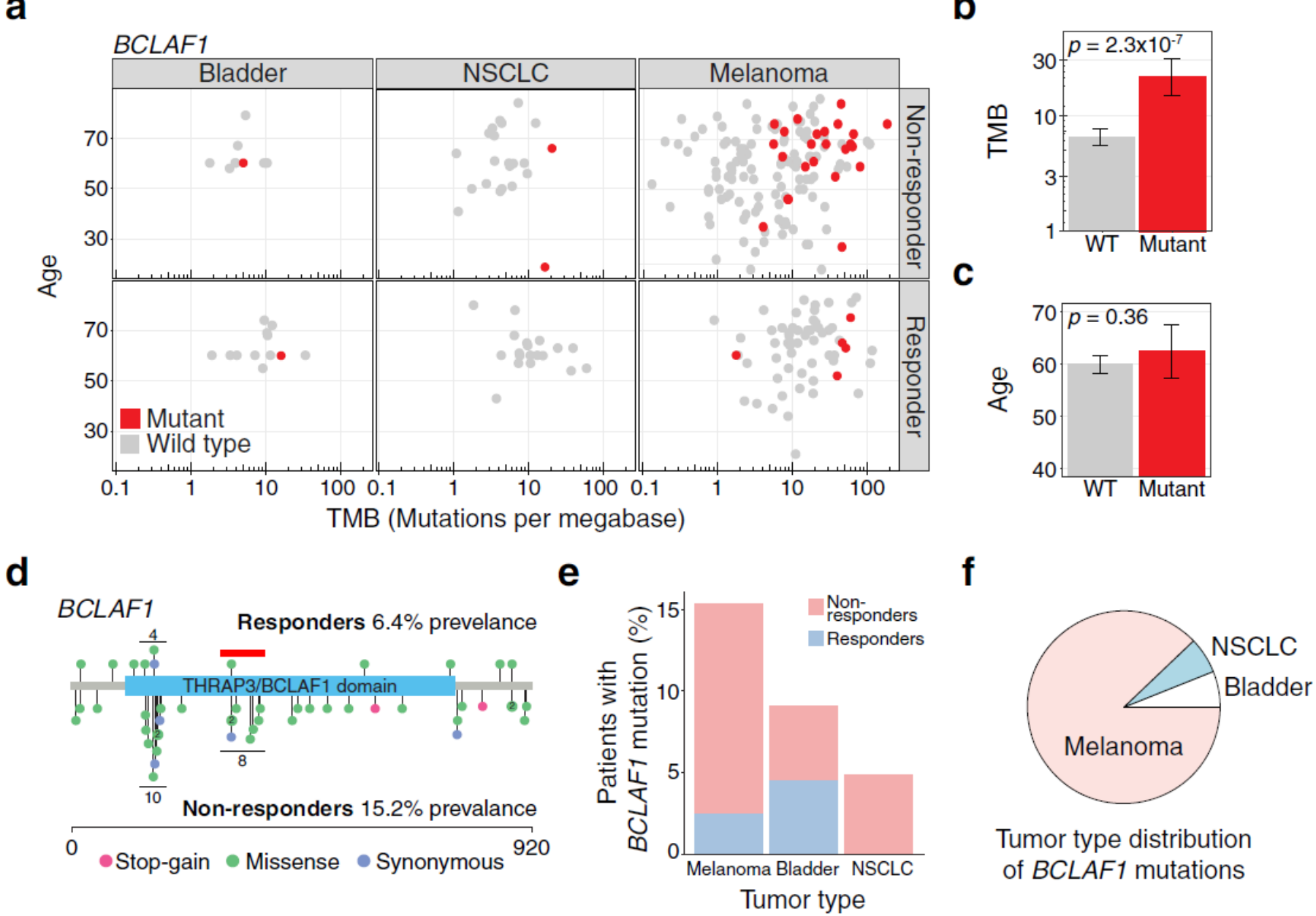
https://doi.org/10.1038/s41467-022-31055-3 OPEN

Recurrent somatic mutations as predictors of immunotherapy response

Zoran Z. Gajic[1,2,3], Aditya Deshpande[1,4,5], Mateusz Legut[1,2,3], Marcin Imieliński[1,5]✉ & Neville E. Sanjana[1,2,3]✉

Odds ratios (ORs) of response to ICB therapy in patients with a high or moderate impact mutation in the indicated gene





3 *BCLAF1* mutations identify a subset of non-responders with high tumor mutational burden (TMB). a Age, TMB and tumor typ responders with (*red*) and without (*gray*) *BCLAF1* mutations. **b** TMB of patients with ($n = 33$) and without ($n = 239$) mutations in

CHOOSING WISELY REMAINS THE KEY

THANKS and GREETING FROM TMH VARANASI