Lung Cancer Advances

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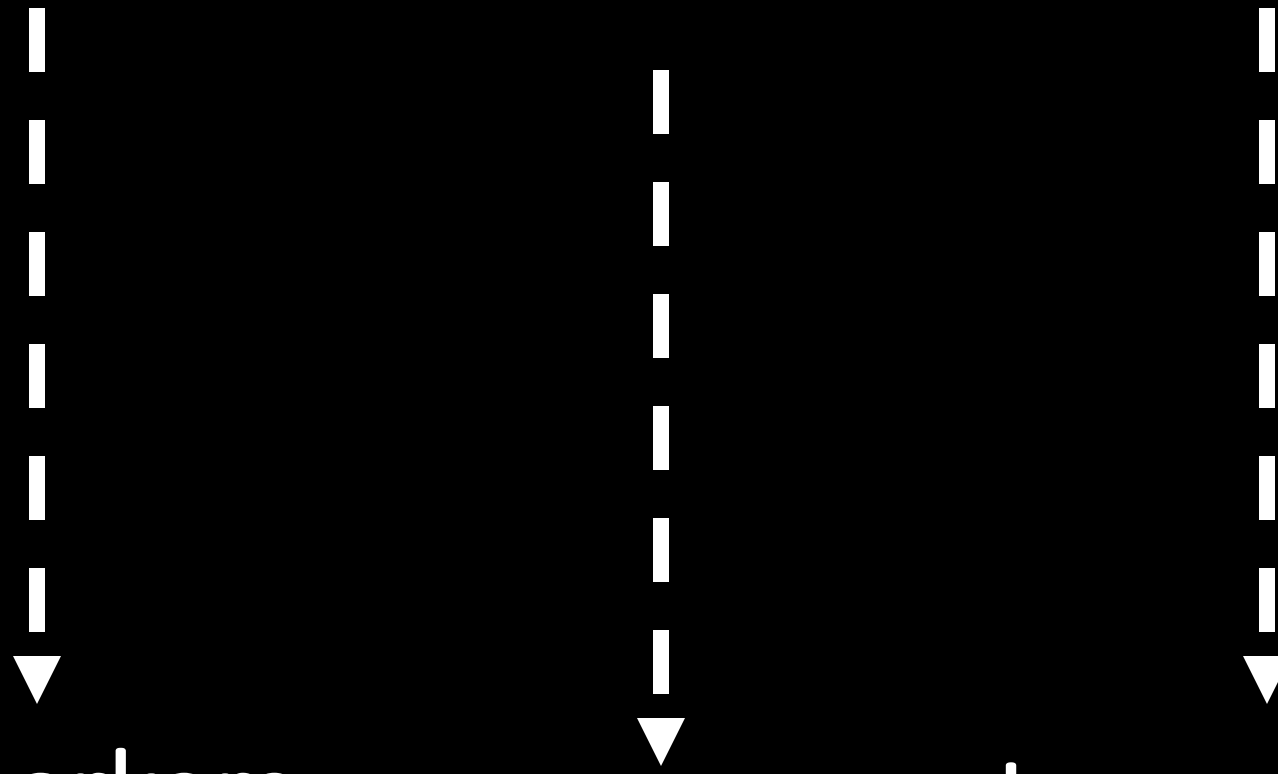
Disclosure of Conflicts of Interest

Jimmy Ruiz, MD has no relevant financial relationships to disclose.

Advances in Metastatic NSCLC



Biomarkers

Precision Oncology

Immunotherapy

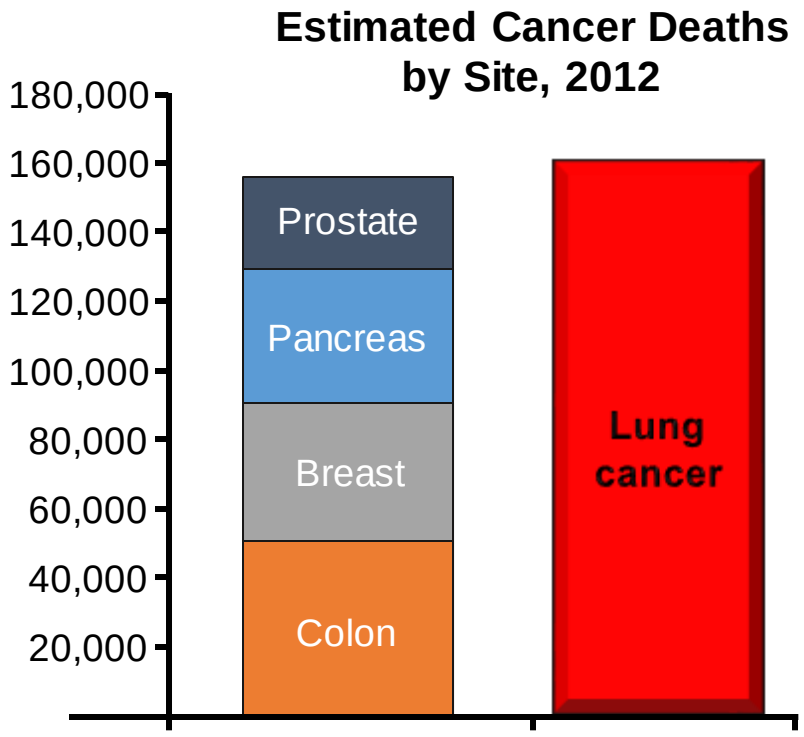
Lung Cancer

- 2.2 million new cases and 1.79 million deaths per year, worldwide.
- Most common cause of cancer-related mortality in US
- Accounts for more deaths than breast, prostate, and colorectal cancers combined
- Median age: 70 years; major risk factor: smoking
  - 25-30,000 never-smoking Americans will develop lung cancer this year
- Advanced stage at the time of diagnosis (low adherence to screening)
- **Histologically and molecularly heterogeneous disease !!!**

International Agency for Research on Cancer. Global Cancer Observatory: cancer today. World Health Organization

Lung Cancer Remains a US Health Burden

- One of the most common cancers and leading cause of cancer deaths
  - New cases, 2016 (estimated): US, 224,390
  - Deaths, 2016 (estimated): US, 158,080
- 5-yr US survival rates
  - Overall: 18%
  - Metastatic: 4%
- The majority of NSCLC present with advanced incurable disease



National Center for Health Statistics. Centers for Disease Control and Prevention

Number of Tobacco Farms by County

- Total US tobacco production grew from 300 million pounds to over a billion pounds from **1860-1909**.
- Production topped at around 2 billion pounds in **1946**
- Tobacco today is grown in 17 states

Majority of tobacco is grown in 3 states (NC, KY, TN) = 79%

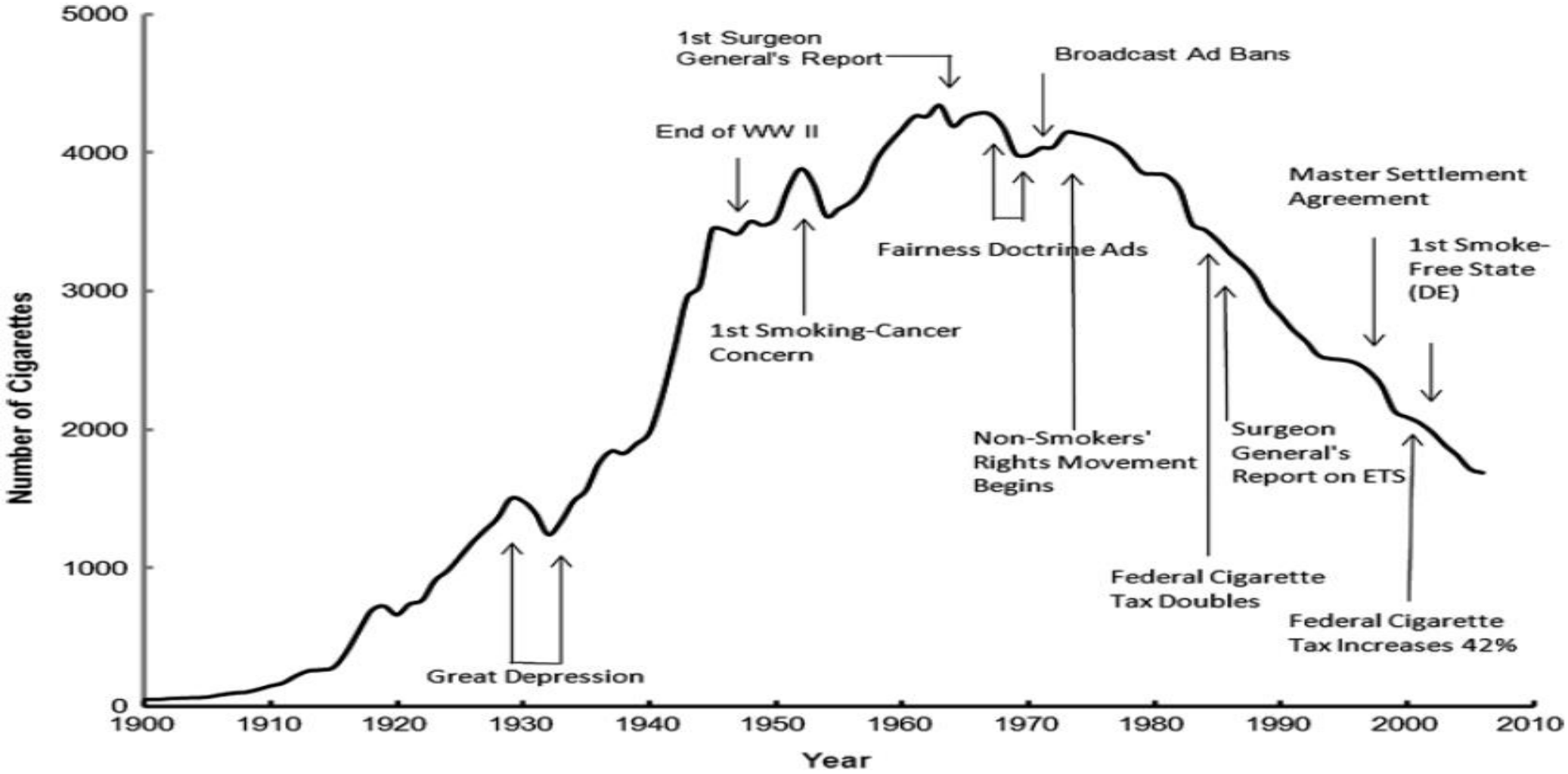
Tobacco production in 6 states (add SC, GA, VA) = 94%

Farms
1 - 100
101 - 250
250 - 500
501 - 700
> 700

US Department of Agriculture. https://www.nass.usda.gov/Charts_and_Maps (access 2020)

https://tobaccofreelife.org/tobacco/tobacco-history/

Adult per capital cigarette consumption in US from 1900-2006

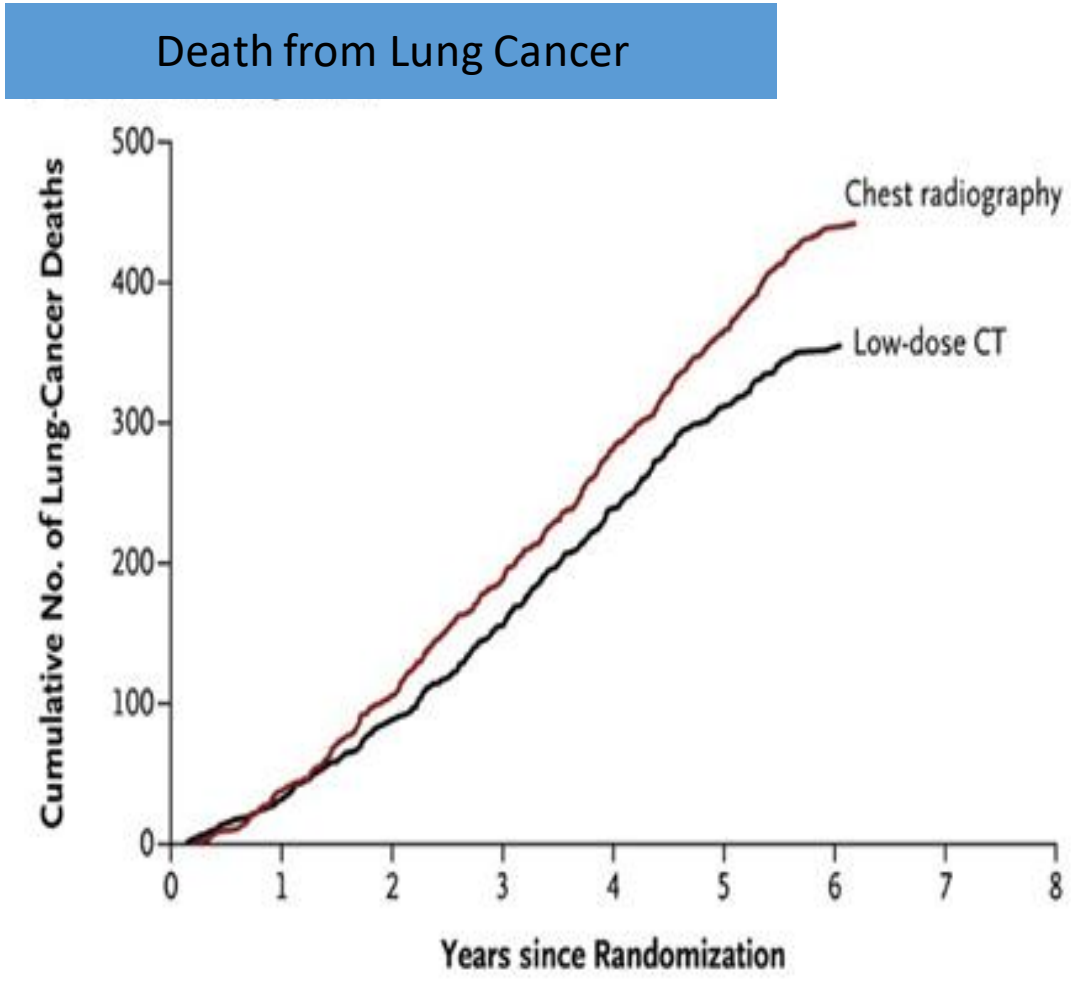


KE Warner et al. 2014: American Journal of Public Health **104**, 83_89

National Lung Screening Trial

- CT Chest versus Chest x-ray
- 53,454 patients enrolled

- Relative Risk reduction of 20% from lung cancer death
- More stage I lung cancer diagnosed compared to chest x-ray arm (63% vs 48%)
- 320 patients screened to prevent one death



Aberle et al. NEJM 2011

Histologically and molecularly heterogeneous

1. More than an Organ specific Dx → Lung cancer
2. More than Histologic Dx → NSCLC (adeno, squam, large cell, etc..)

   vs. SCLC
3. Today there is Biomarker/Molecular Dx:

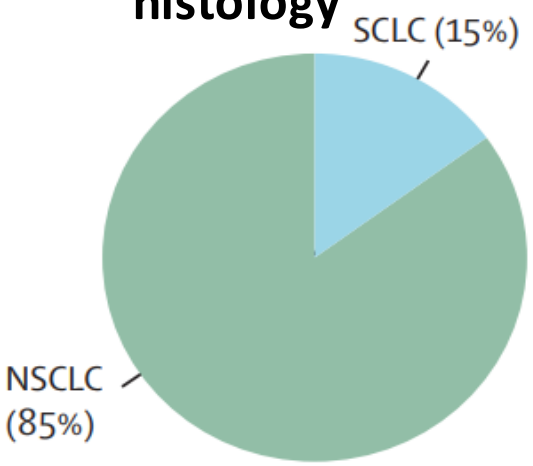
   → Driver mutations/rearrangements/expression/amplifications:

   EGFR, ALK, ROS, BRAF, KRAS, RET, MET, NTRK, HER2, MEK1, PIK3CA

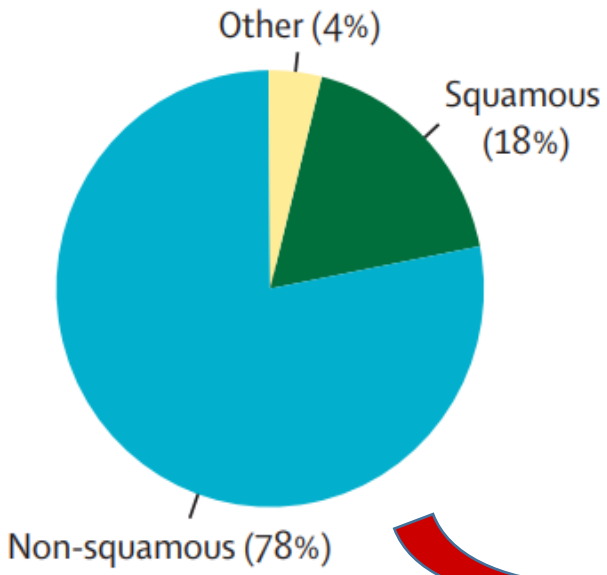
   → PDL1 and TMB

Reck, et al. Lancet 2013; Shukuya and Carbone. J Thorac Oncol 2016; Planchard, et al. Ann Oncol 2018

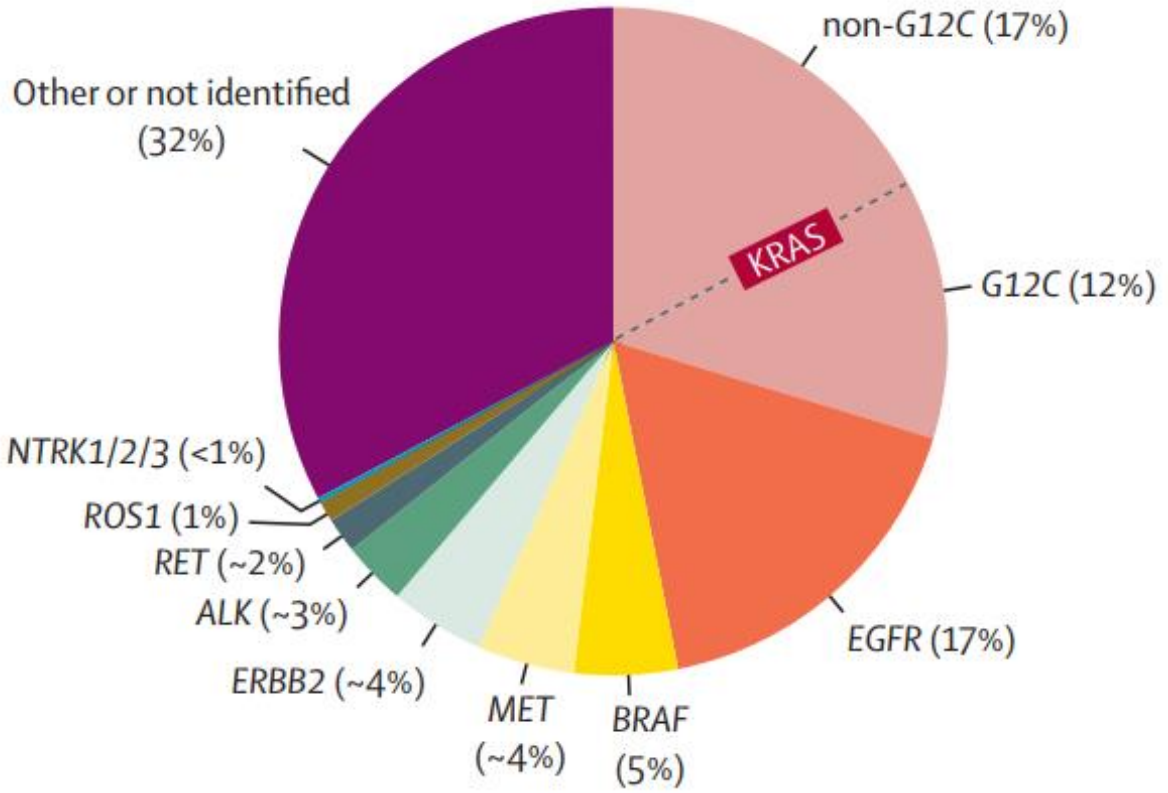
Lung cancer histology



NSCLC histology



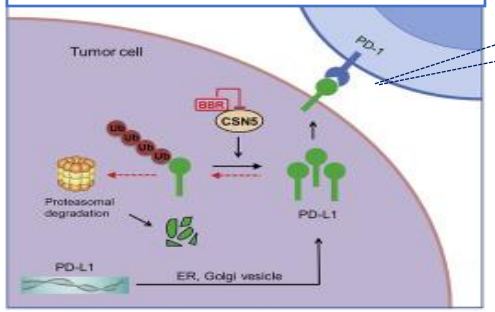
Oncogenic mutations in NSCLC



Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

NSCLC Biomarker Testing

Tumor PD-L1 expression

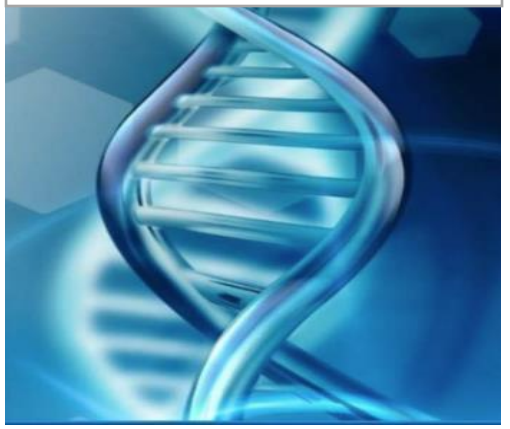


Surface tumor expression
Can be detected by immunohistochemistry

Predictive for immune check point inhibitors (ICIs)
Not the perfect biomarker

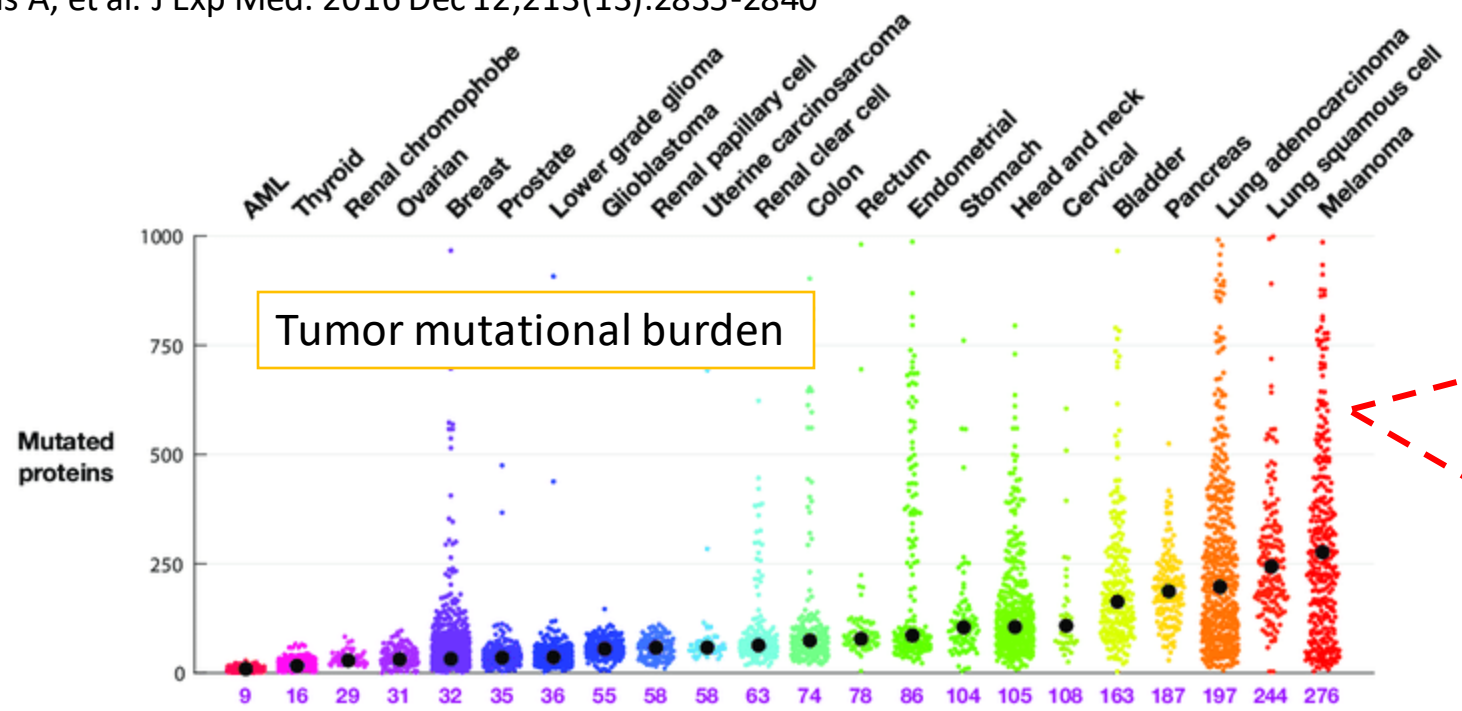
Ribas A, et al. J Exp Med. 2016 Dec 12;213(13):2835-2840

Molecular Testing



Driver mutations in everyone

NGS Testing Recommended

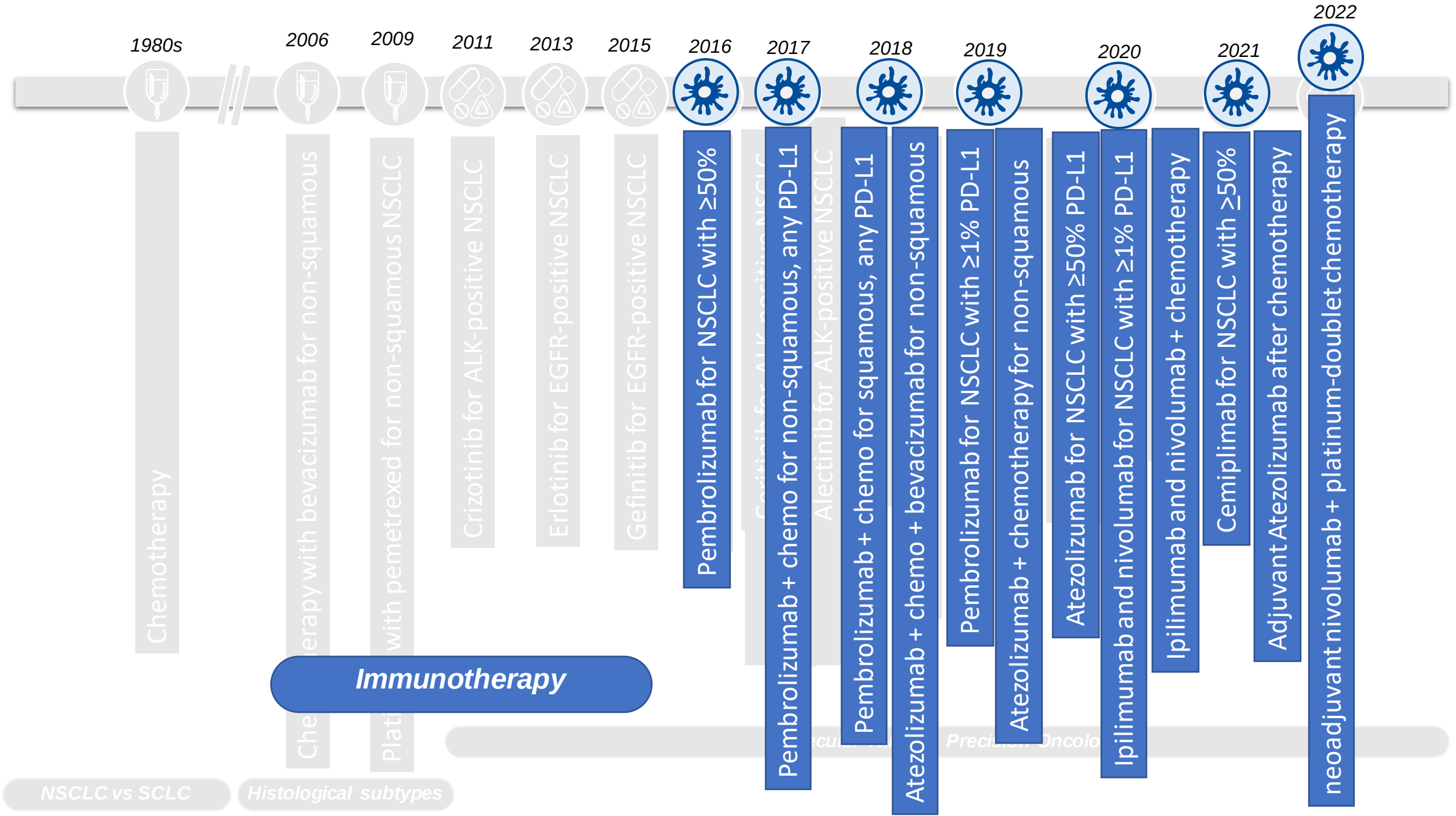


Predictive of response to ICIs

Pembrolizumab has FDA approval in pretreated patients with high TMB (≥10 mutations per megabase)

JC et al. 2019/08/07.1856. 10.3389/fimmu.2019. Frontiers in Immunology

fda.gov accessed Jan 2022


1980s
2006
2009
2011
2013
2015
2016
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2021
2022
Chemotherapy
Chemotherapy with bevacizumab for non-squamous
Platinum with pemetrexed for non-squamous NSCLC
Crizotinib for ALK-positive NSCLC
Erlotinib for EGFR-positive NSCLC
Gefinitib for EGFR-positive NSCLC
Pembrolizumab for NSCLC with ≥50%
Pembrolizumab + chemo for non-squamous, any PD-L1
Alectinib for ALK-positive NSCLC
Pembrolizumab + chemo for squamous, any PD-L1
Atezolizumab + chemo + bevacizumab for non-squamous
Pembrolizumab for NSCLC with ≥1% PD-L1
Atezolizumab + chemotherapy for non-squamous
Atezolizumab for NSCLC with ≥50% PD-L1
Ipilimumab and nivolumab for NSCLC with ≥1% PD-L1
Ipilimumab and nivolumab + chemotherapy
Cemiplimab for NSCLC with ≥50%
Adjuvant Atezolizumab after chemotherapy
neoadjuvant nivolumab + platinum-doublet chemotherapy
Immunotherapy
NSCLC vs SCLC
Histological subtypes

NEWS RELEASES

NCI Press Release

Annual Report to the Nation: Rapid decrease in lung cancer and melanoma deaths lead overall continued decline in cancer death rate

Posted: July 8, 2021

Contact: NCI Press Office
240-760-6600

*"The declines in **lung cancer** and melanoma death rates are the result of progress across the entire cancer continuum — from reduced smoking rates to prevent cancer to discoveries such as targeted drug therapies and immune checkpoint inhibitors," said Karen E. Knudsen, M.B.A., Ph.D., chief executive officer, American Cancer Society.*

CANCER · **Published** July 9, 2021 12:17pm EDT

Overall cancer death rates declining in US, report finds

Death rates for prostate, colorectal and breast cancers still a concern

CNN health Life, But Better Fitness Food Sleep More Audio Live TV

Cancer mortality rates continue to decline amid 'major progress' in lung cancer early detection and treatment

By Deidre McPhillips, CNN

Updated 12:23 PM ET, Wed January 12, 2022

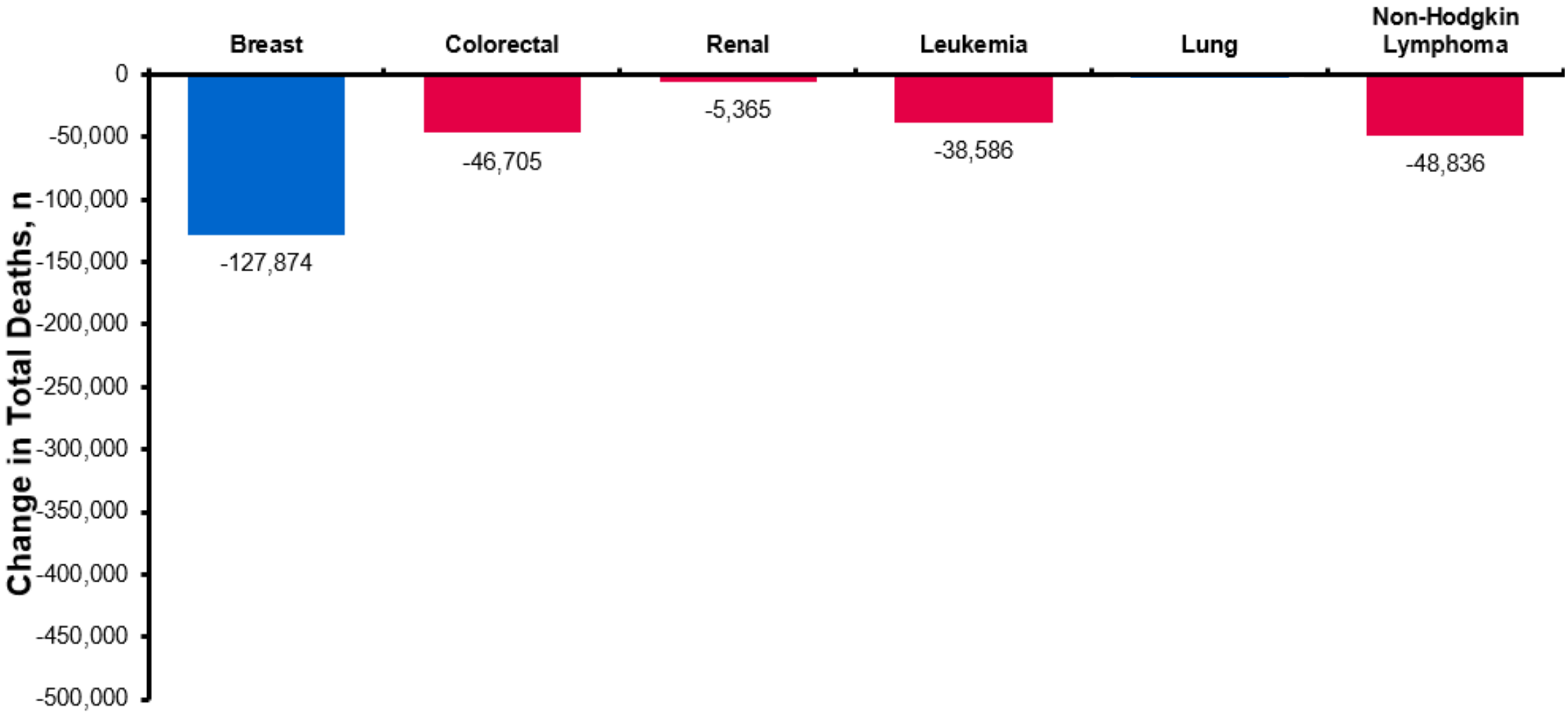
THE WALL STREET JOURNAL.

U.S.

Cancer Death Rate in U.S. Falls by Largest Yearly Amount on Record

Powerful new lung-cancer treatments helped propel overall declines in recent years

Cancer Mortality Reduction

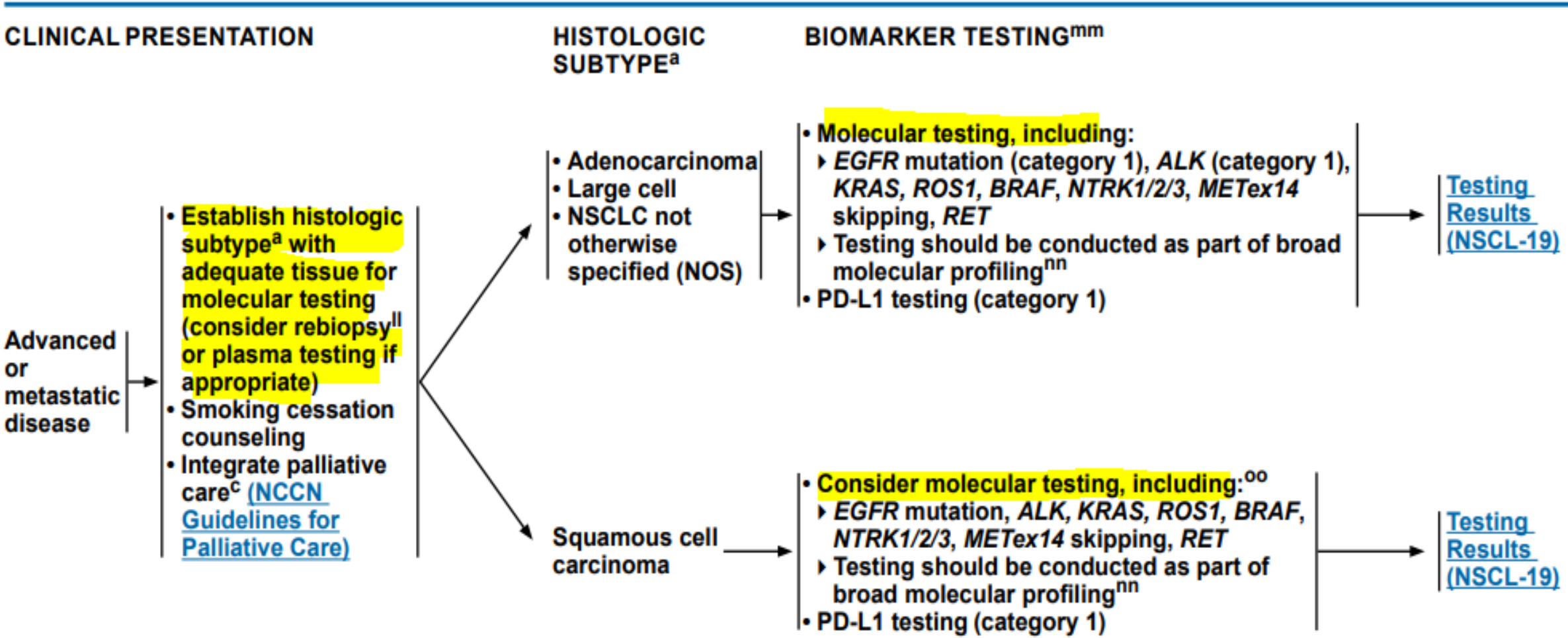


MacEwan JP et al. *J of Med Econ.* 2020.

Biomarkers

“You can’t hit a target you cannot see, and you cannot see a target you do not have.”

- Zig Ziglar


CLINICAL PRESENTATION
HISTOLOGIC SUBTYPE[a]
BIOMARKER TESTING[mm]
Advanced or metastatic disease
• Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[ll] or plasma testing if appropriate)
• Smoking cessation counseling
• Integrate palliative care[c] (NCCN Guidelines for Palliative Care)
• Adenocarcinoma
• Large cell
• NSCLC not otherwise specified (NOS)
• Molecular testing, including:
▸ EGFR mutation (category 1), ALK (category 1), KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET
▸ Testing should be conducted as part of broad molecular profiling[nn]
• PD-L1 testing (category 1)
Testing Results (NSCL-19)
Squamous cell carcinoma
• Consider molecular testing, including:[oo]
▸ EGFR mutation, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET
▸ Testing should be conducted as part of broad molecular profiling[nn]
• PD-L1 testing (category 1)
Testing Results (NSCL-19)

[Thoracic Oncology Original Research]

CHEST

CHEST 2021; 160(6):2293-2303

Knowledge and Practice Patterns Among Pulmonologists for Molecular Biomarker Testing in Advanced Non-small Cell Lung Cancer

Adam H. Fox, MD; James R. Jett, MD; Upal Basu Roy, PhD, MPH; Bruce E. Johnson, MD;

- Substantial differences among pulmonologists' evaluation of advanced NSCLC
- Variation in knowledge of available biomarkers and the importance of targeted therapies
- Differences in institutional coordination likely lead to underutilization of biomarker testing.

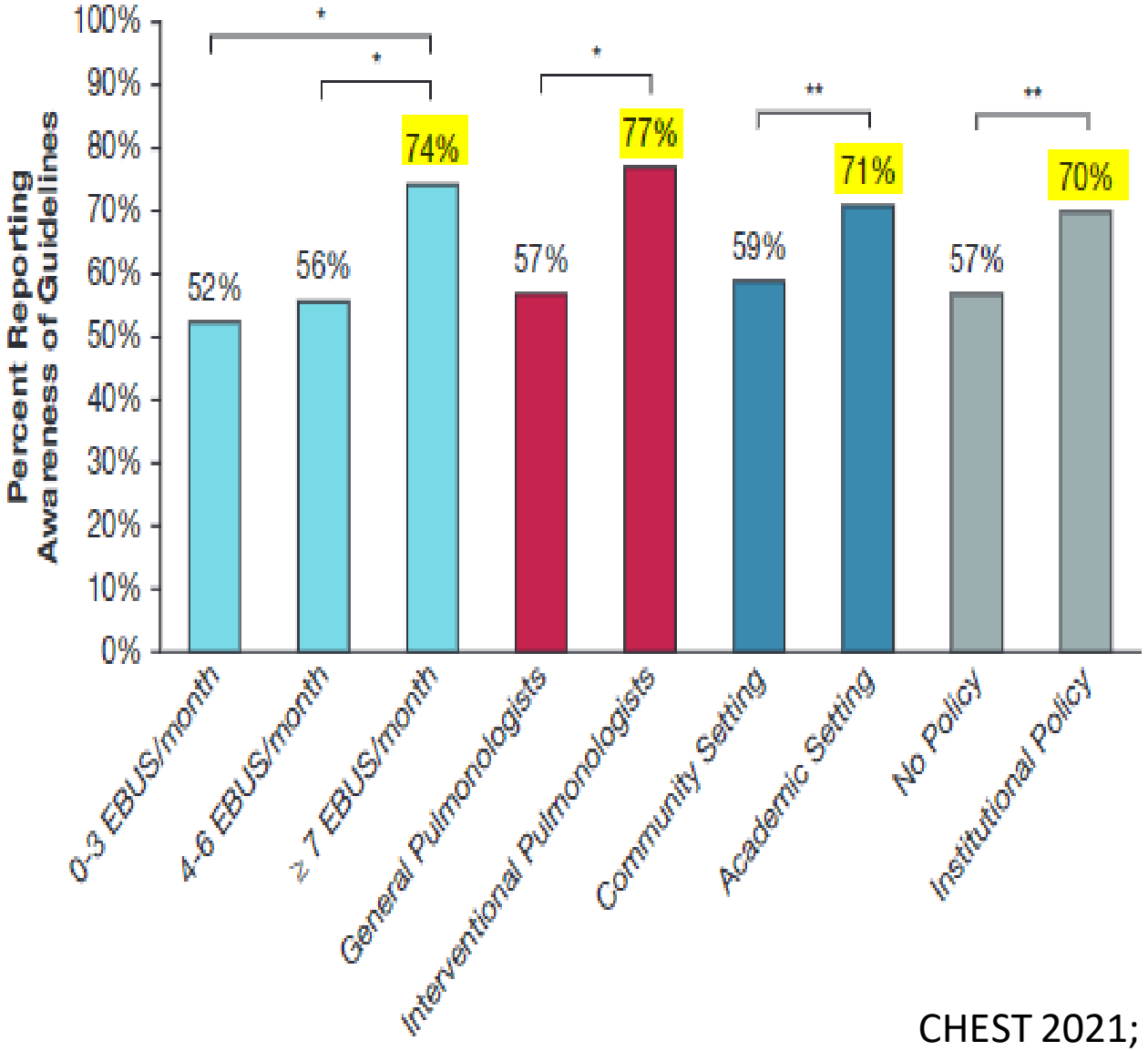
Lack of uniform testing

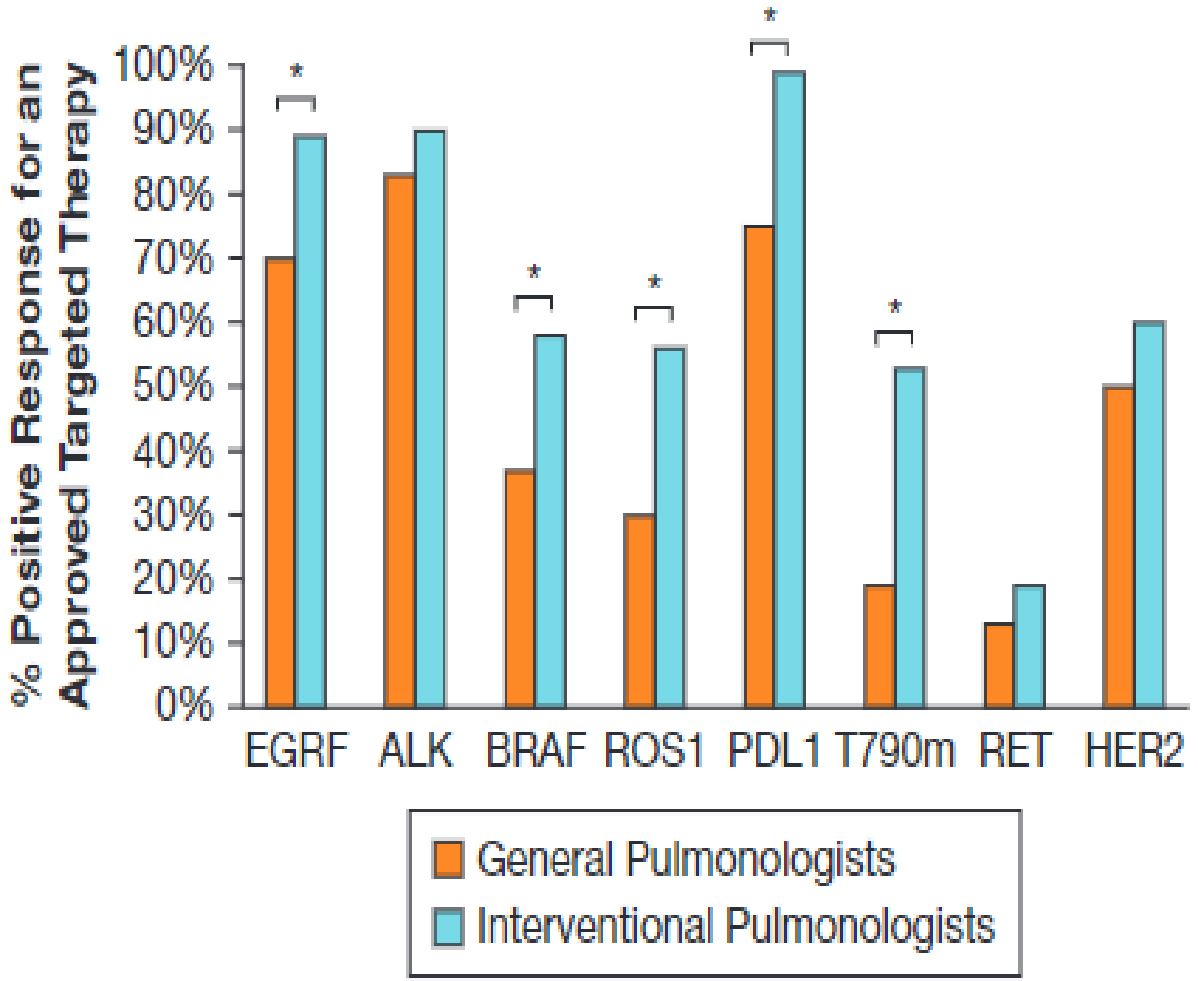
Frequency for Which Biomarkers Were Routinely Tested Outside of Clinical Trials by Practice Setting, Subspecialty Training, and Presence of Institutional Policy (N = 453)

Biomarker	No. (%)	Comparison by Practice Setting		Comparison by Subspecialty Training		Comparison by Presence of an Institutional Testing Policy	
		Academic Setting (%)	Community Setting (%)	Interventional Pulmonologists (%)	General Pulmonologists (%)	Institutional Policy (%)	Lack of a Policy (%)
EGFR[a]	447 (99)	99	98	100	98	98	100
ALK[a]	430 (95)	97	94	100	94	96	94
BRAF[a]	201 (44)	55[b]	39[b]	70[b]	38[b]	51[b]	38[b]
ROS1[a]	219 (48)	55[b]	45[b]	80[b]	40[b]	55[b]	42[b]
NTRK[a]	57 (13)	17[b]	10[b]	14	12	15[b]	10[b]
PD-L1[a]	347 (77)	84[b]	73[b]	99	71	82[b]	72[b]
ERBB2/ HER2	149 (33)	40[b]	29[b]	41[b]	31[b]	34	32
KRAS	309 (68)	74[b]	65[b]	82[b]	65[b]	70	67
MET	84 (19)	29[b]	13[b]	34[b]	15[b]	20	17
RET	70 (15)	26[b]	10[b]	27[b]	12[b]	18	13
TMB	41 (9)	16[b]	6[b]	18[b]	7[b]	10	9

CHEST 2021; 160(6):2293-2303

Lack of uniform testing





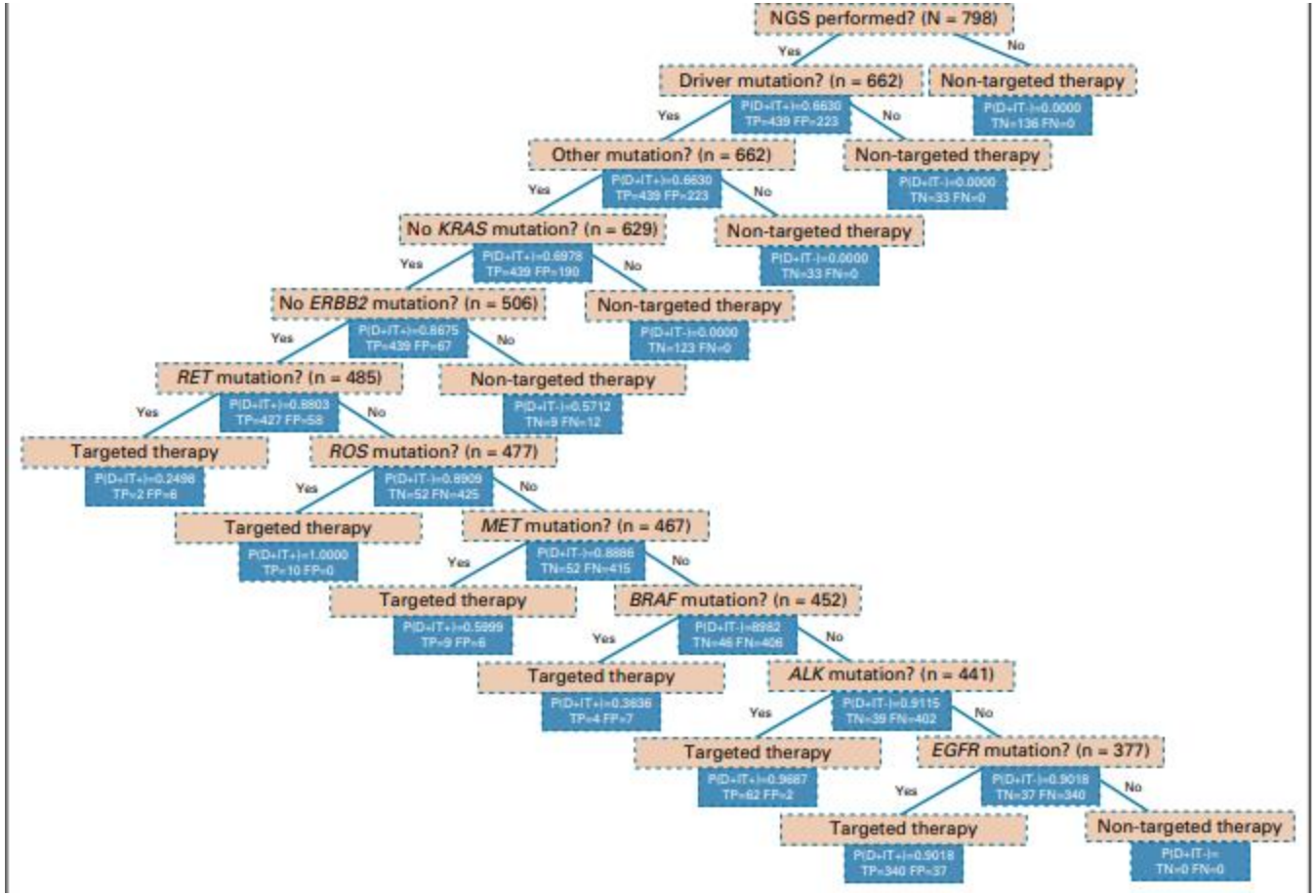
CHEST 2021; 160(6):2293-2303

JCO® Oncology Practice
Volume 17, Issue 2 111

VALUE IN CANCER CARE

Evaluation of Omics-Based Strategies for the Management of Advanced Lung Cancer

Ravi Salgia, MD, PhD[1]; Isa Mambetsariev, BA[1]; Rebecca Pharaon, BA[1]; Jeremy Fricke, BS[1]; Angel Ray Baroz, BS[1]; Iztok Hozo, PhD[2]; Chen Chen, MS[3]; Marianna Koczywas, MD[1]; Erminia Massarelli, MD, PhD[1]; Karen Reckamp, MD, MS[1,4]; and Benjamin Djulbegovic, MD, PhD[5]



Fast-and-frugal decision trees (FFTs)

- Theoretical framework for constructing clinical pathways
- assess the accuracy and the impact of the recommended management strategies on important health outcomes

- FFT-driven targeted therapy decision-making = OS of 38 months

VS.

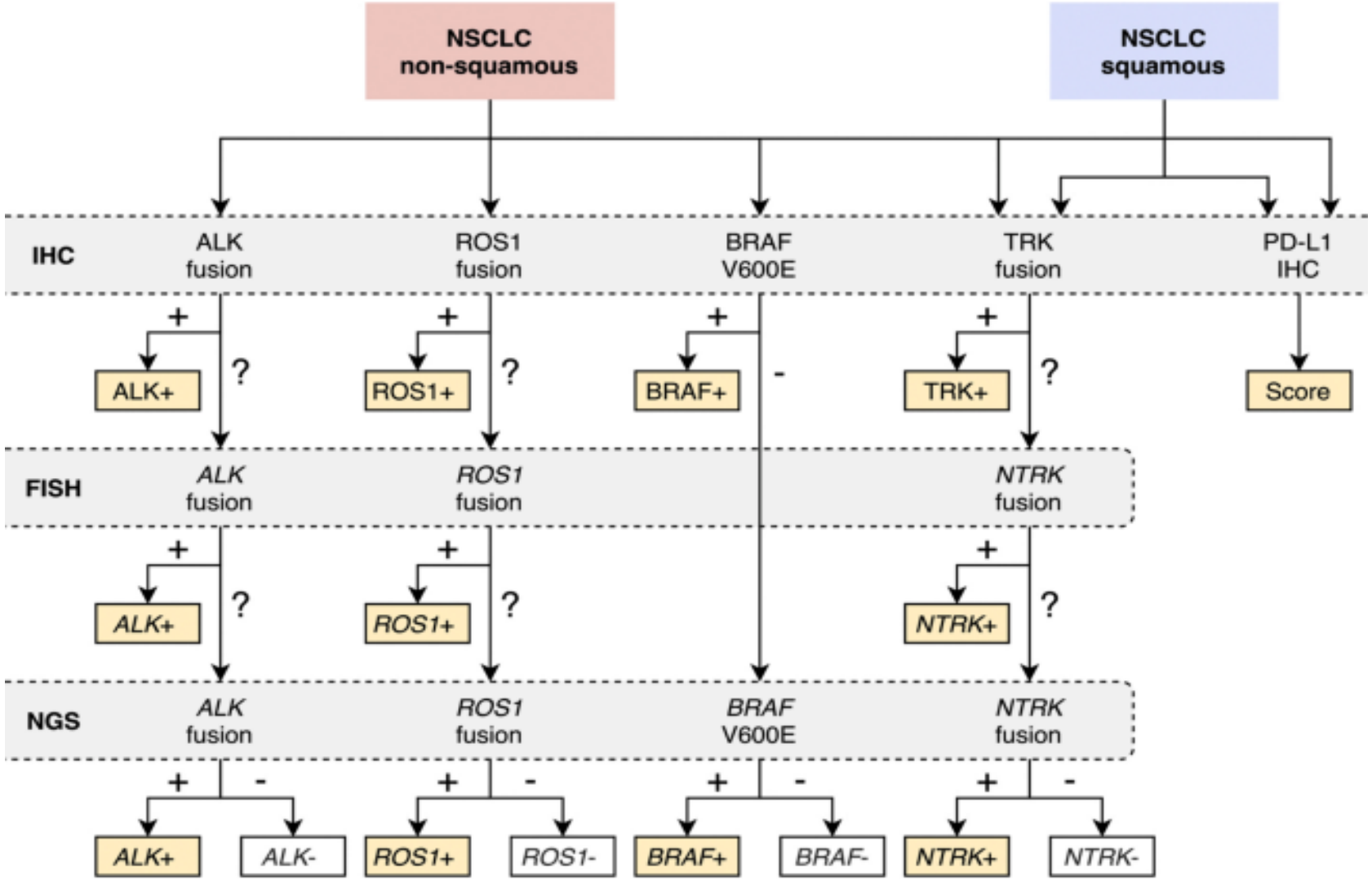
- Nontargeted-therapy decision-making group = OS of 26 months

Review

Precision medicine in non-small cell lung cancer: Current applications and future directions

Soo-Ryum Yang [a,1], Anne M. Schultheis [b,1], Helena Yu [c], Diana Mandelker [a], Marc Ladanyi [a], Reinhard Büttner [b,*]

- Immunohistochemistry a key technique for primary diagnosis
- Reliable tool in the assessment of predictive biomarkers
- advantage of faster and cheaper test results
- Less tissue consumption than any DNA or RNA extraction-based method



Seminars in Cancer Biology 84 (2022) 184–198

Seminars in Oncology

Molecular biomarkers and liquid biopsies in lung cancer

Kamva Sankar[a,†], Mina Zeinali[b,c,d,†], Sunitha Nagrath[b,c,d], Nithva Ramnath[e,]

Expert Opinion: How should the clinician in 2022 utilize ctDNA in the diagnosis and treatment of NSCLC?

- The gold standard for diagnosis of NSCLC remains tissue biopsy.
- The use of ctDNA testing for diagnosis and identification of targetable mutations in advanced NSCLC may be considered in specific circumstances:
  - The patient is medically unfit for invasive testing.
  - There is insufficient tissue from initial tissue biopsy for molecular analysis and subsequent biopsy is not planned.

Circulating Tumor DNA (ctDNA)

vantages

High sensitivity and specificity

Standardized assays

Identification of resistance mutations

allenges

Need for paired tumor to improve specificity

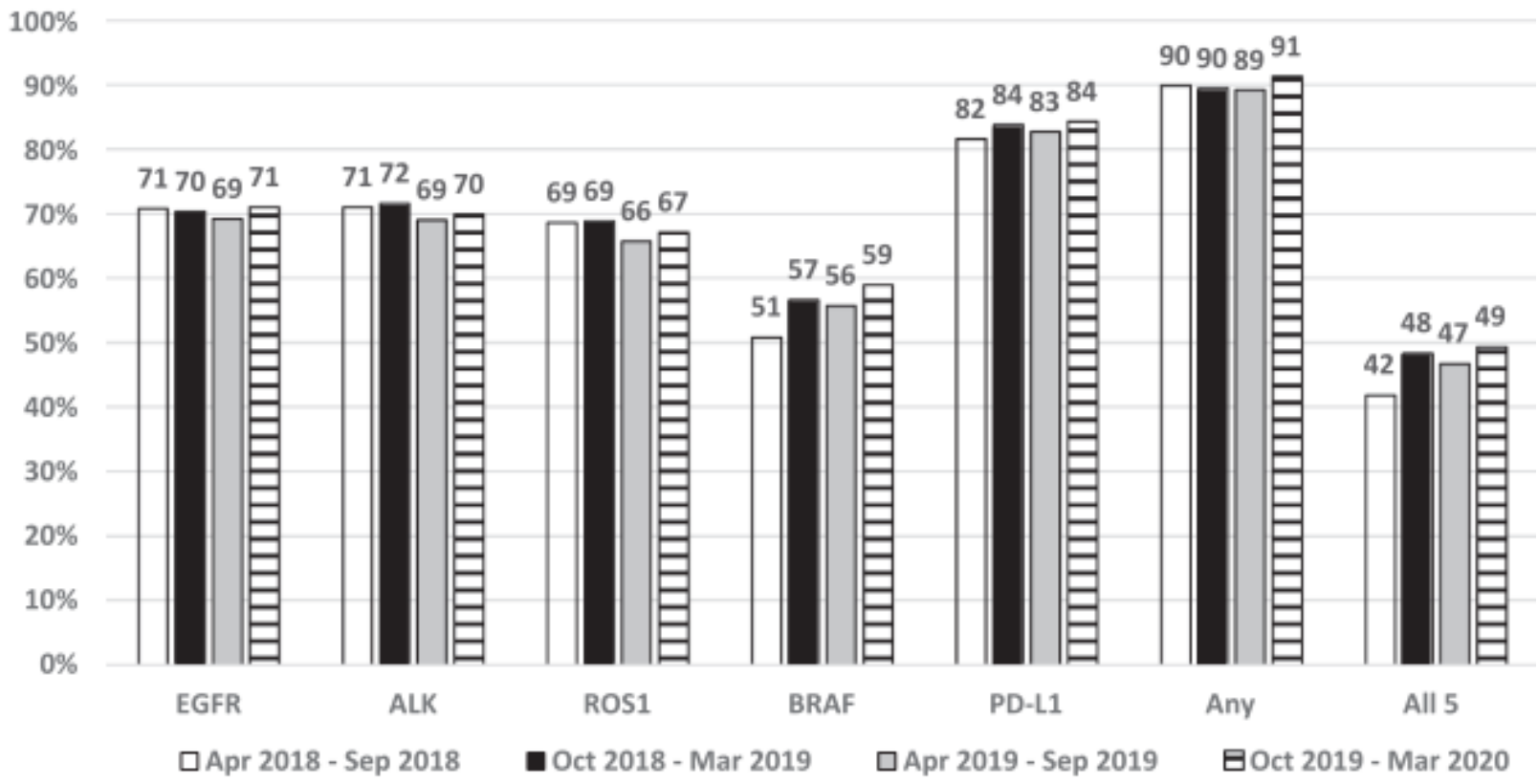
Less stability in circulation

No functional assays

Biomarker testing and tissue journey among patients with metastatic non-small cell lung cancer receiving first-line therapy in The US Oncology Network

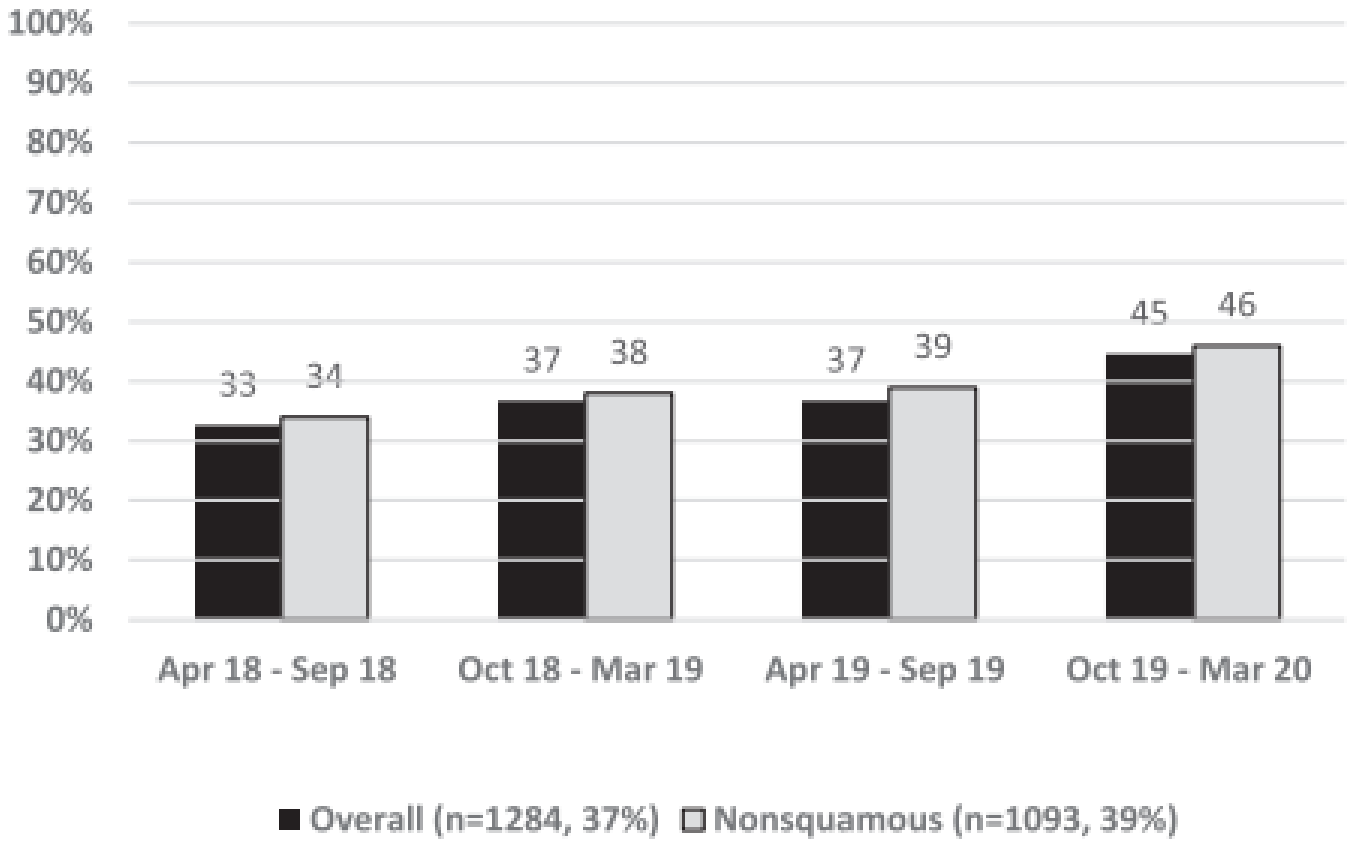
Study Population = 3474

- From practices within the US Oncology Network that utilize the iKnowMed™ EMR
- Dx of mNSCLC
- Initiated a 1L systemic therapy for mNSCLC between 1-April-2018 and 31-March-2020.
- Test results were specifically assessed for EGFR, ALK, ROS1, BRAF, and PD-L1



N.J. Robert et a. Lung Cancer 166 (2022) 197–204

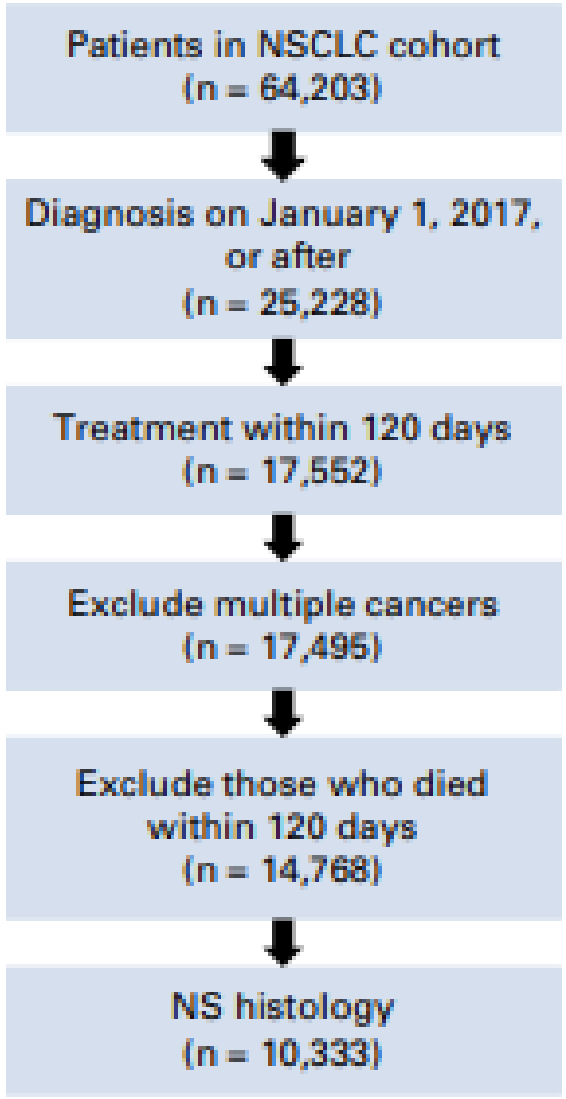
NGS for All Metastatic NSCLC Populations



Concluding Points:

- Decreasing the time from NGS of mNSCLC to 1L initiation
- Including upfront comprehensive testing for all biomarkers may help ensure appropriate and timely treatment decision making

N.J. Robert et a. Lung Cancer 166 (2022) 197–204



	NSCLC Overall (N = 14,768)	White (n = 9,793)	Black (n = 1,288)	*P*, White vs Black
All patients with NSCLC				
Ever tested	11,297 (76.5%)	7,477 (76.4%)	948 (73.6%)	.03
Tested prior to 1L therapy		6,064 (61.9%)	784 (60.9%)	.47
Ever NGS tested	7,185 (48.7%)	4,904 (50.1%)	513 (39.8%)	< .0001
NGS tested prior to 1L therapy		3,081 (31.5%)	332 (25.8%)	< .0001
	Nonsquamous (n = 10,333)	**White (n = 6,705)**	**Black (n = 922)**	***P*, White vs Black**
Patients with nonsquamous NSCLC				
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	.09
Tested prior to 1L therapy		4,881 (72.8%)	662 (71.8%)	.52
Ever NGS tested	5,494 (53.2%)	3,668 (54.7%)	404 (43.8%)	< .0001
NGS tested prior to 1L therapy		2,452 (36.6%)	274 (29.7%)	< .0001

- Underutilization of comprehensive genomic testing - 76%
- Advanced or metastatic NS-NSCLC had biomarker testing at 85.0%
- NGS-based testing is not being in absence of single-gene testing to identify an actionable biomarker.
- Rates of NGS-based testing were low for patients with NSCLC at 48.7%
- Only 35.5% of these patients received it before first line therapy

Bruno DS, et al. Disparities in Biomarker Testing and Clinical Trial Enrollment Among Patients With Lung, Breast, or Colorectal Cancers in the United States. JCO Precis Oncol. 2022 Jun

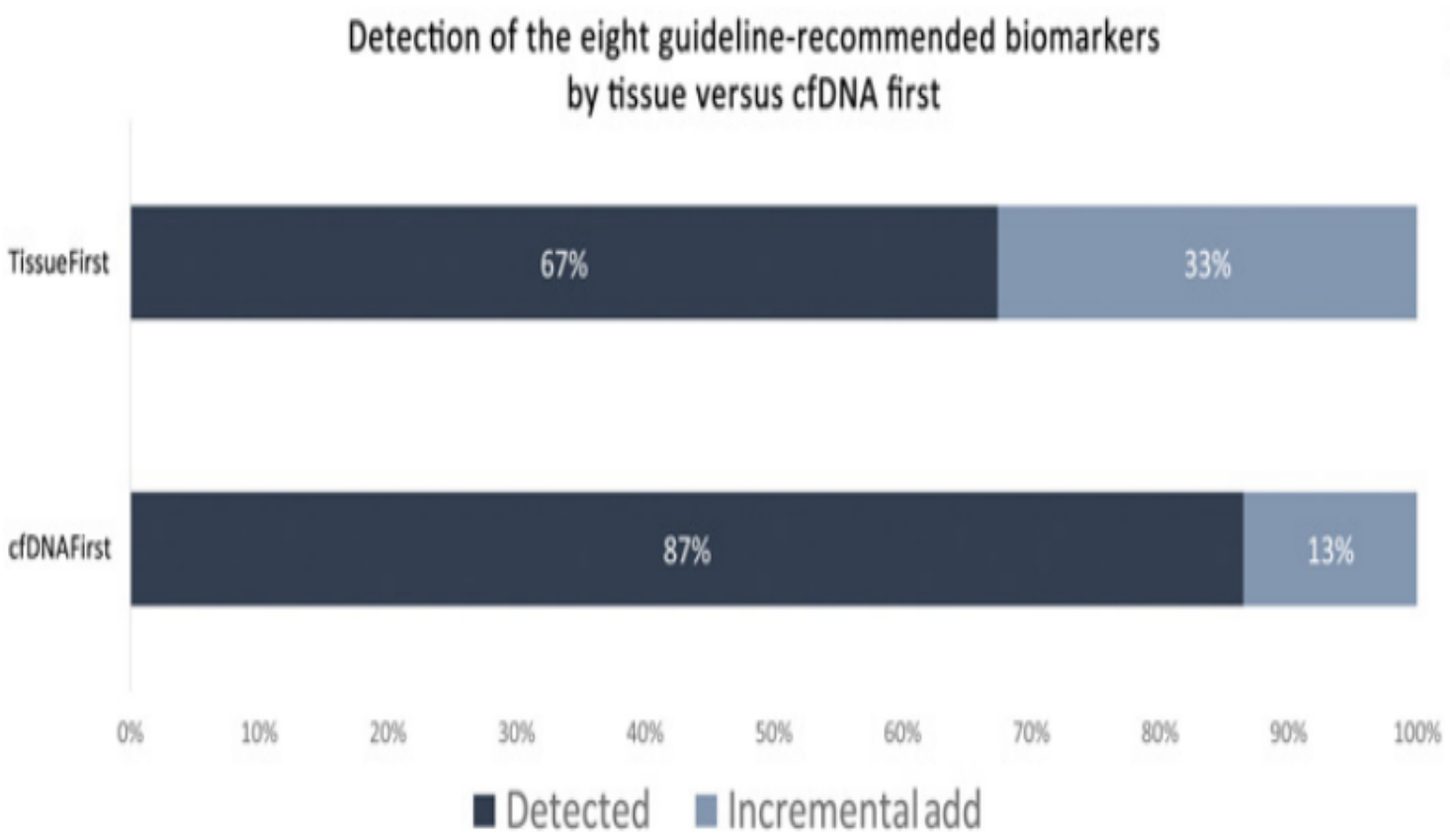
Gene-Guided Treatment Decision-Making in Non-Small Cell Lung Cancer – A Systematic Review

Jatta Saarenheimo[1*†], Heidi Andersen[2,3,4†], Natalja Eigeliene[2,5] and Antti Jekunen[2,5]

- reviews the existing literature to 2021 with extra effort to explore the role of genes and gene-driven therapies as part of decision-making.
- found that with current methods and broad gene panels, patients benefit from early molecular testing of liquid biopsy samples
- 79% of liquid biopsy samples showed somatic mutations based on 8 original studies included in the systematic review
- When both liquid biopsy samples and tissue samples are evaluated, the sensitivity to detect targetable mutations in NSCLC increases
- We recommend early testing with liquid biopsy

Saarenheimo J, et al. (2021) Front. Oncol. 11:754427. doi: 10.3389/fonc.2021.754427

Plasma vs. Tissue Testing for Mutations



- Plasma and tissue testing performed similarly in the detection of guideline-recommended biomarkers (27% versus 21%)
- 98% concordance between plasma and tissue testing for EGFR, ALK, ROS1, and BRAF
- Plasma + tissue testing nearly doubles number of patients identified with targetable mutations

Leighl NB, et al. Clin Cancer Res. 2019 Aug 1;25(15):4691-4700.
Aggarwal C et al. JAMA Oncol. 2018.

Liquid Biopsy

- Simple blood draw to isolate cell-free DNA, circulating tumor cells
- Used Today:
  - Molecular testing when available tissue biopsy inadequate or no available
  - Resistance to TKIs
- Limitations
  - Sensitivity: 70-80%; specificity: ~99%
  - Negative result is **NOT** helpful
- Consider use in parallel with tissue biopsy in populations that may harbor oncogenic driver or in all metastatic NS-NSCLC or in all.

Lowes. Int J Mol Sci. 2016:17

Targeted Therapy

“What greater joy can there be than putting into practice what you have learned.”

- Confucious

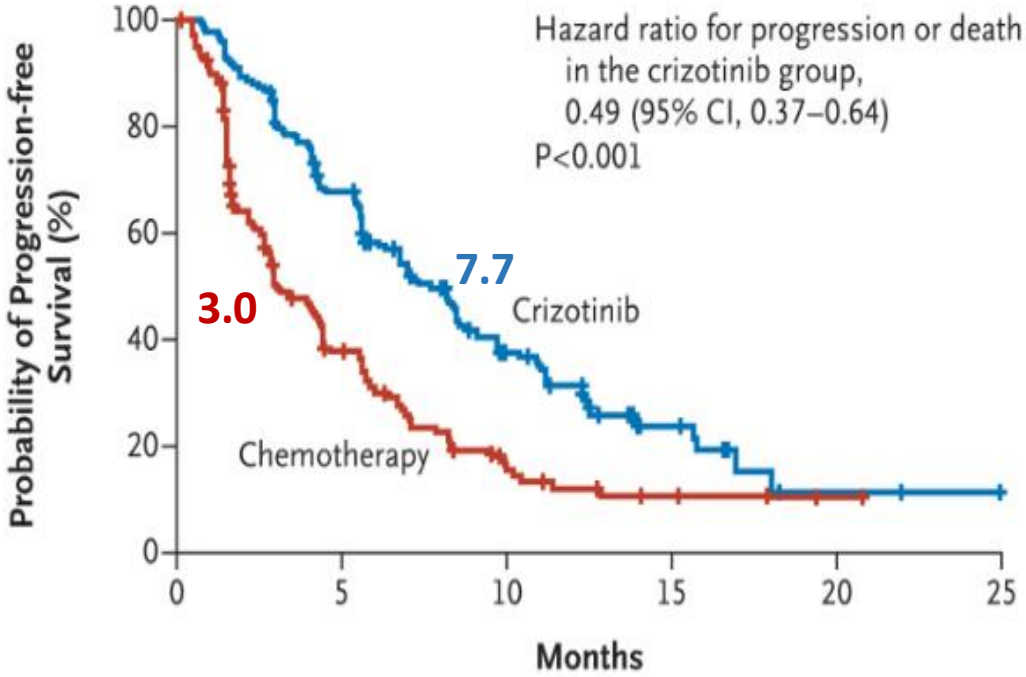
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

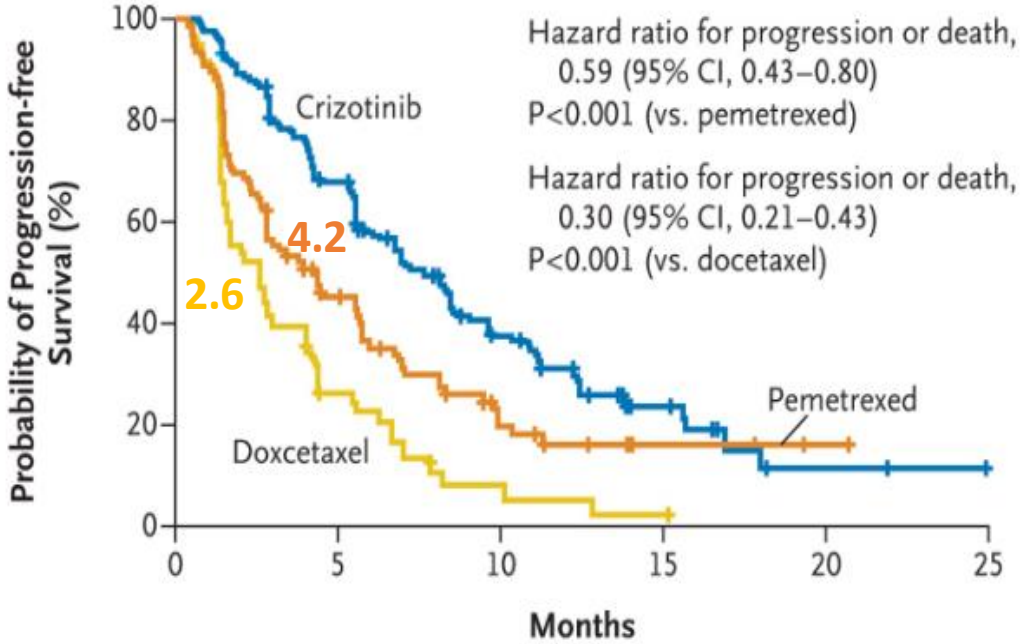
Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D.,

A Progression-free Survival



No. at Risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

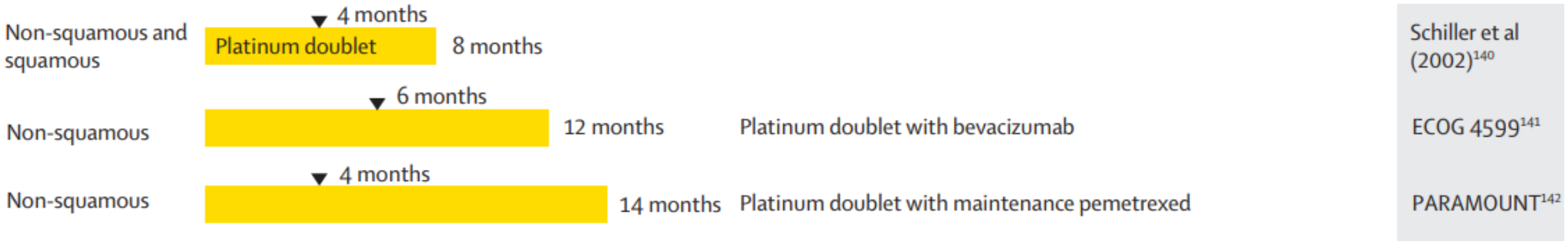
B Progression-free Survival with Crizotinib vs. Pemetrexed or Docetaxel



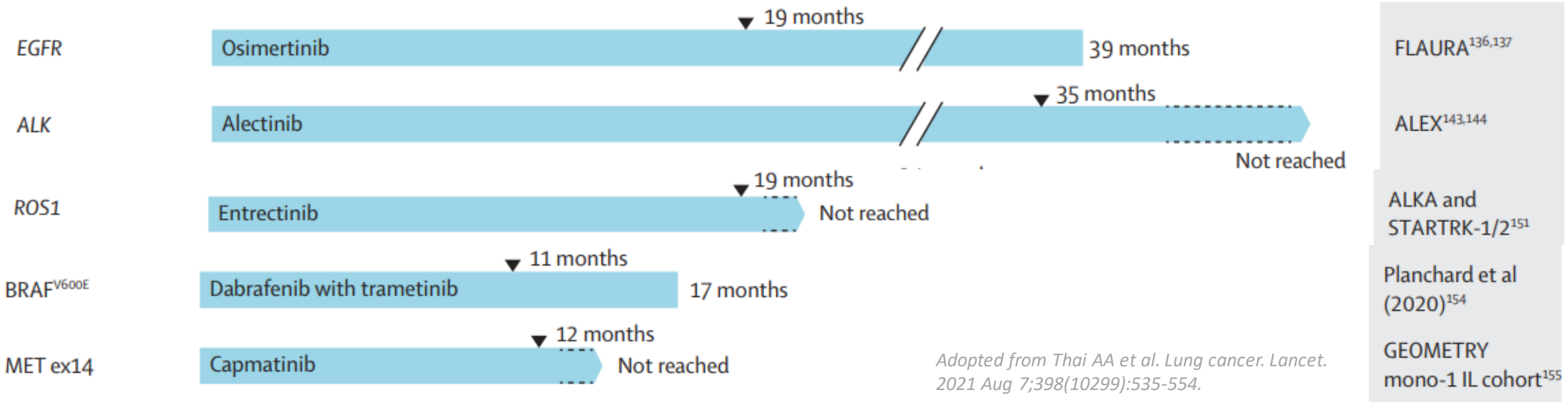
No. at Risk						
Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	2	3	1	0
Docetaxel	72	13	3	1	0	

N Engl J Med 2013; 368:2385-2394

Where we were.

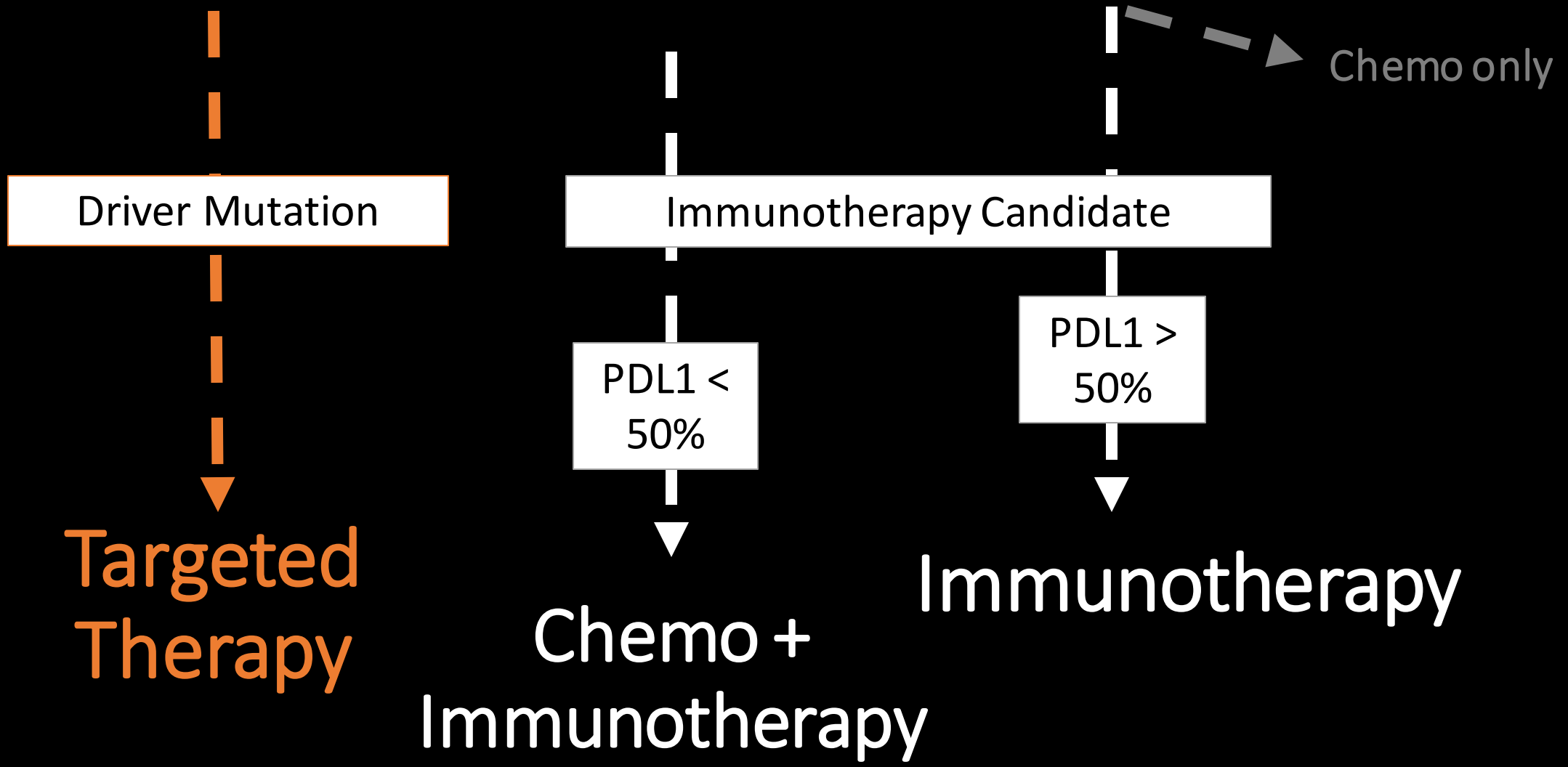


Where we are with targeted therapy.

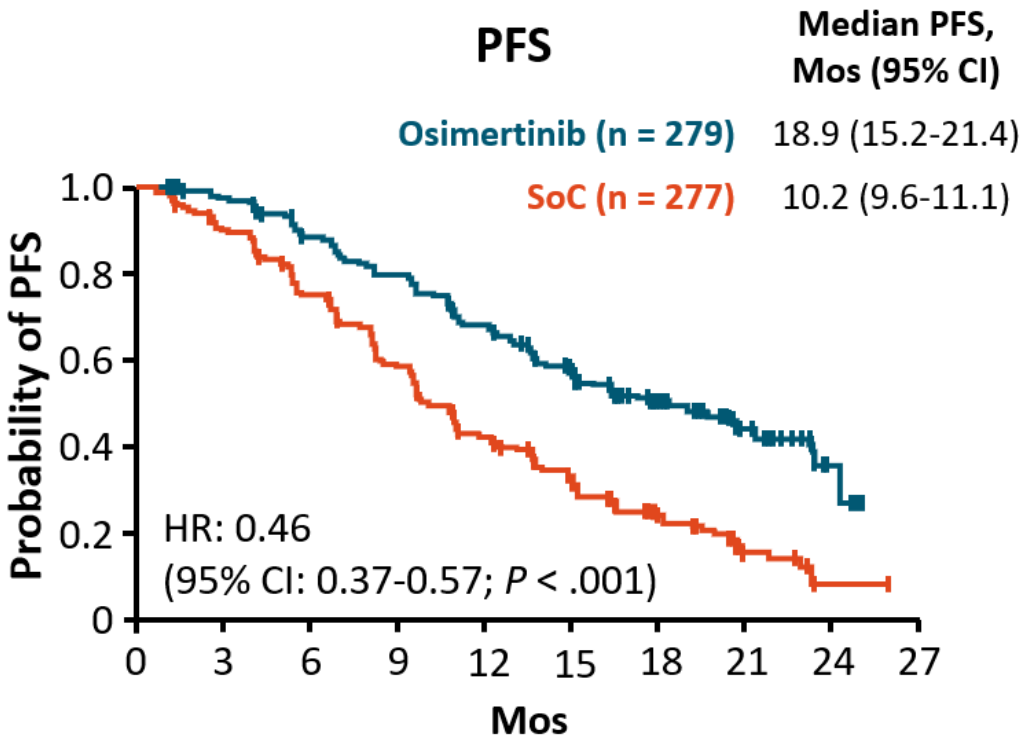


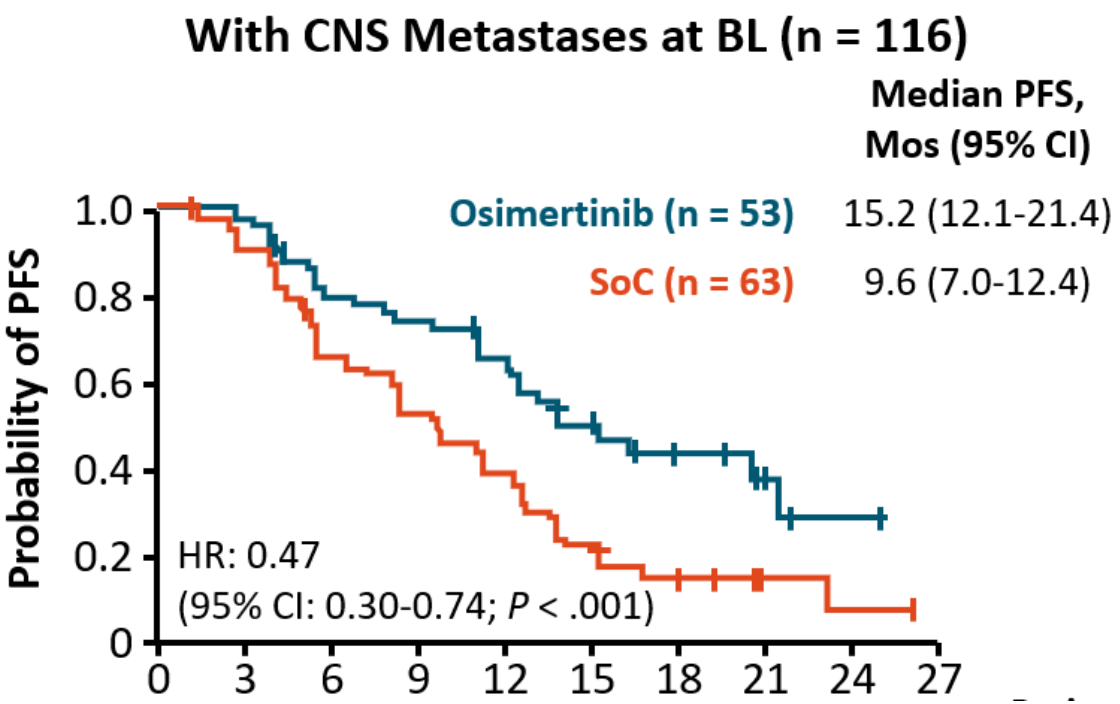
Adopted from Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

Treatment of Metastatic NSCLC



FLAURA: First-line Osimertinib vs Erlotinib or Gefitinib for *EGFR*-Mutated Advanced NSCLC





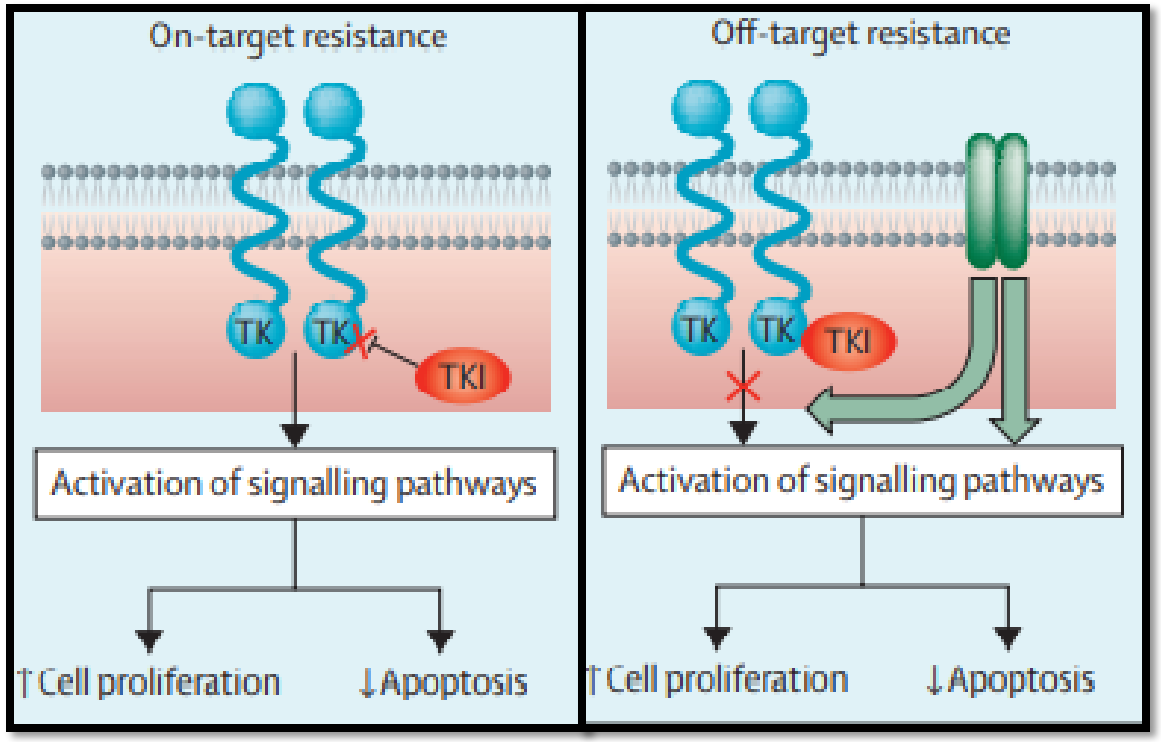
Ramalingam. ESMO 2017. Abstr LBA2_PR. Soria. NEJM. 2018;378:113.

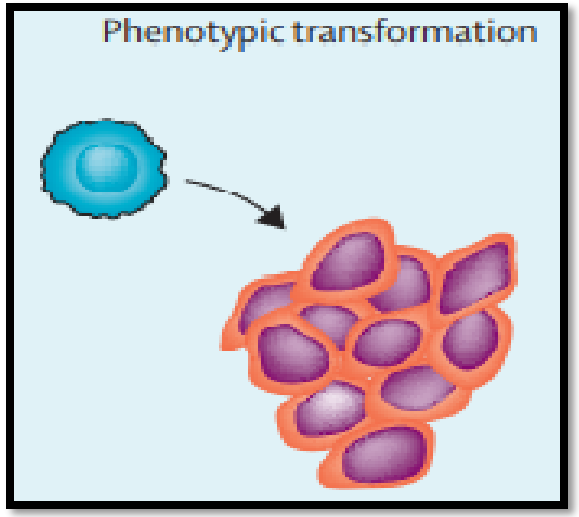
Targeted Therapy Resistance

- On-target resistance: target gene changes like gene amplification or second site mutations that interfere with drug binding.

- Off-target resistance: reactivation of downstream oncogenic signaling pathways, despite ongoing inhibition of the target kinase.

- Phenotypic transformation: transformation from NSCLC to SCLC.





Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

Acquired Resistance to Osimertinib

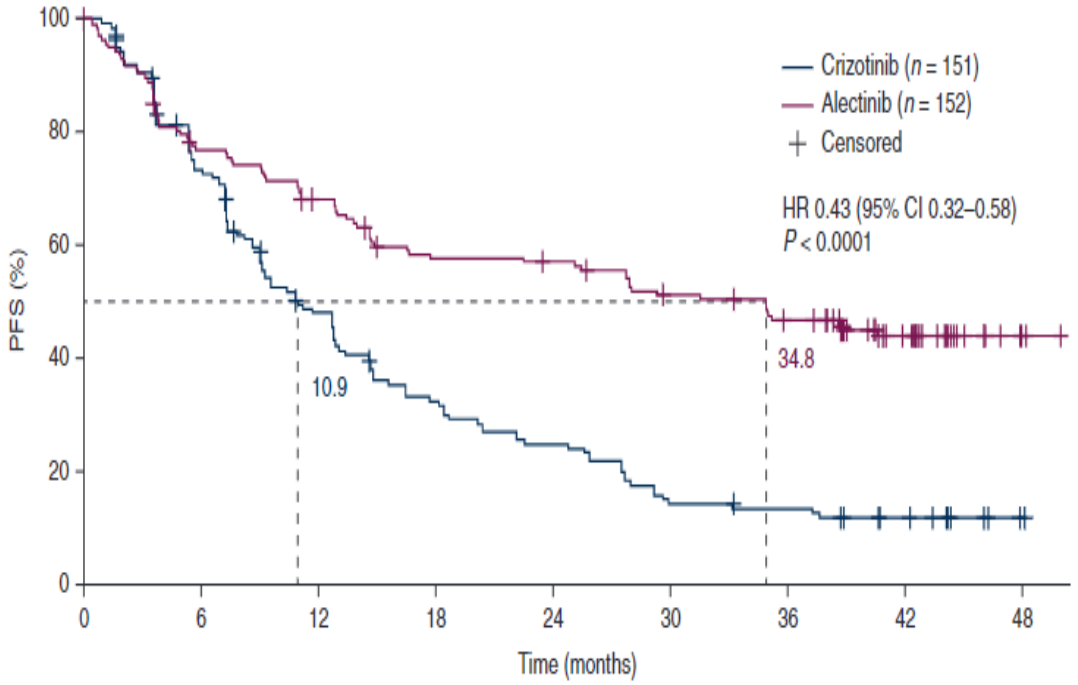
- Repeat biopsy after osimertinib not SoC at present time
- Potential options based on result
  - MET inhibitor
  - First-generation EGFR TKI for C797S
  - Chemotherapy (platinum/ etoposide) for SCLC transformation
- Clinical trials in development

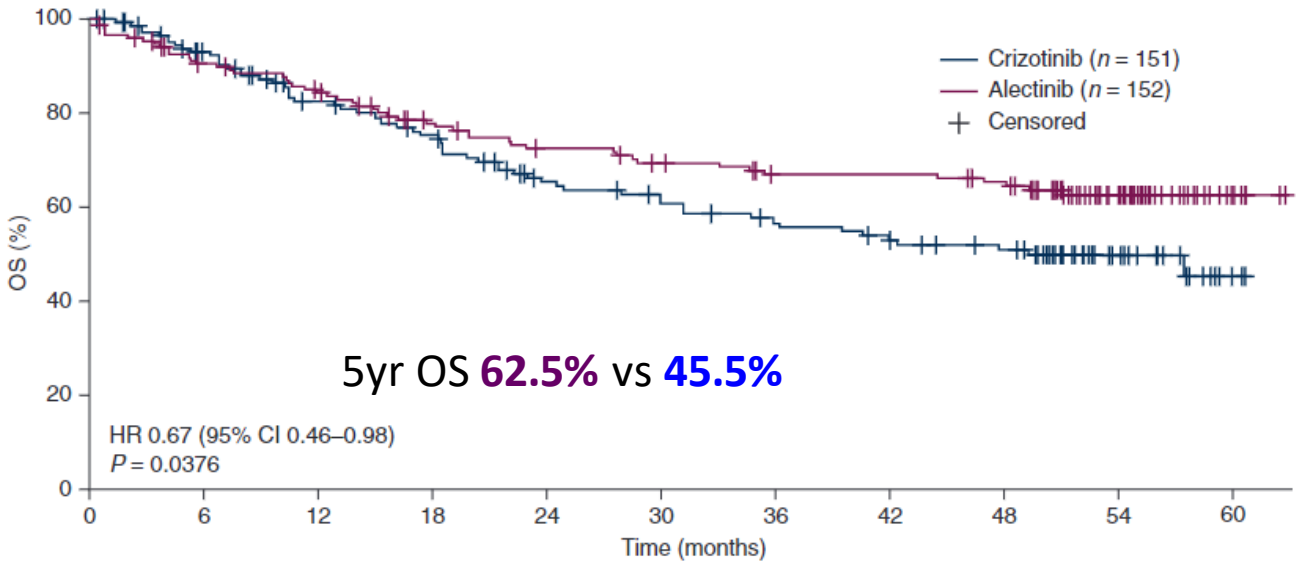
Mechanism of Acquired Resistance in Osimertinib-Resistant Patients (N = 32)

- *MET* amp: 7 (22%)
- T790M/C797S: 6 (19%)
- Loss of T790M: 11 (34%)
- No T790M: 3 (9%)

Piotrowska. Cancer Discov. 2018;8:1529

ALEX Trial: Alectinib Vs Crizotinib in ALK+ Advanced NSCLC





5yr OS **62.5%** vs **45.5%**

Mok T, et. al. Ann Oncol. 2020 Aug;31(8):1056-1064.

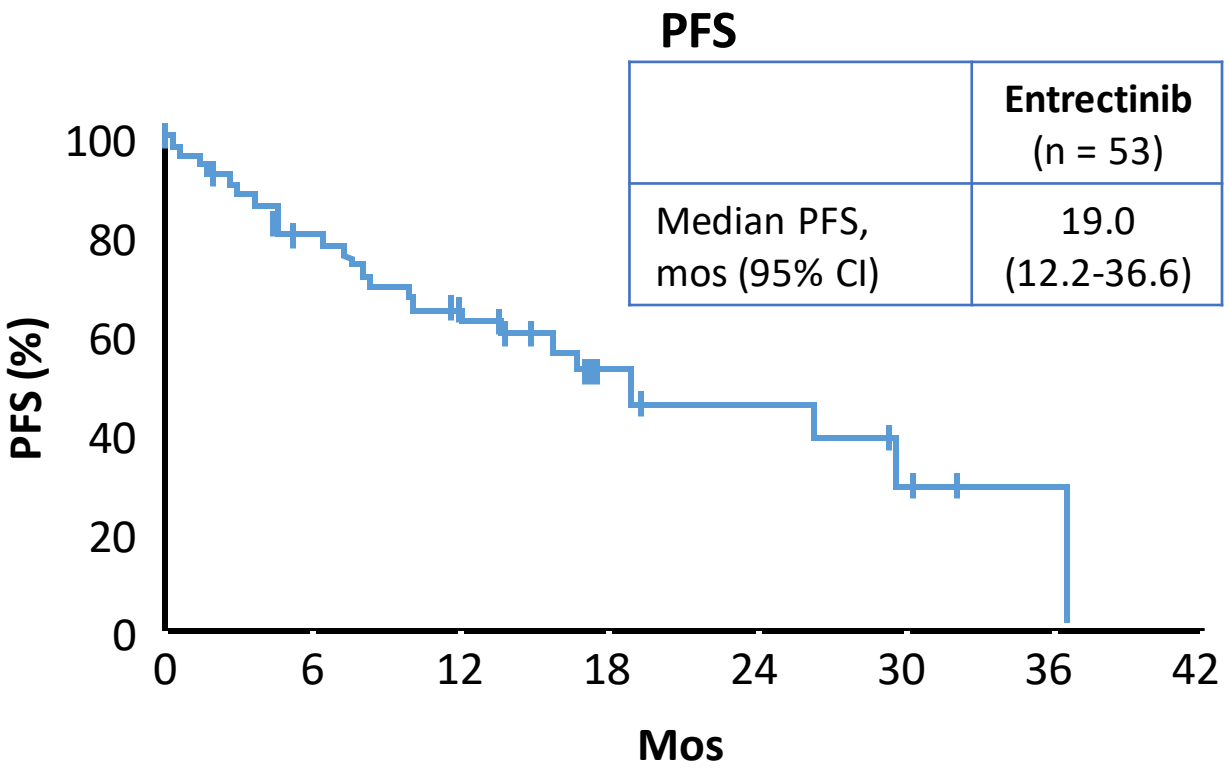
Lorlatinib: Active Against *ALK* Resistance Mutations

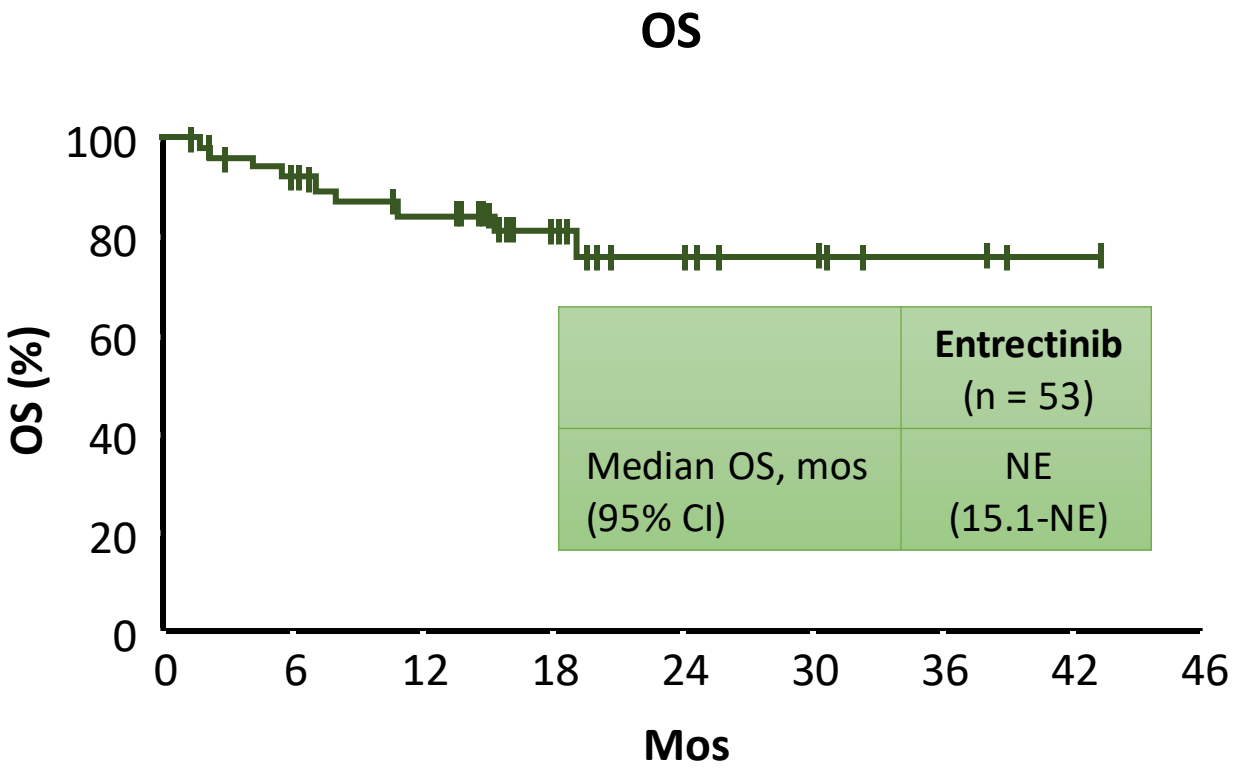
Cellular ALK phosphorylation mean IC_{50} (nmol/L)					
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0

Cellular ALK phosphorylation mean IC_{50} (nmol/L)					
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

Gainor. Cancer Discov. 2016. 6:1118.

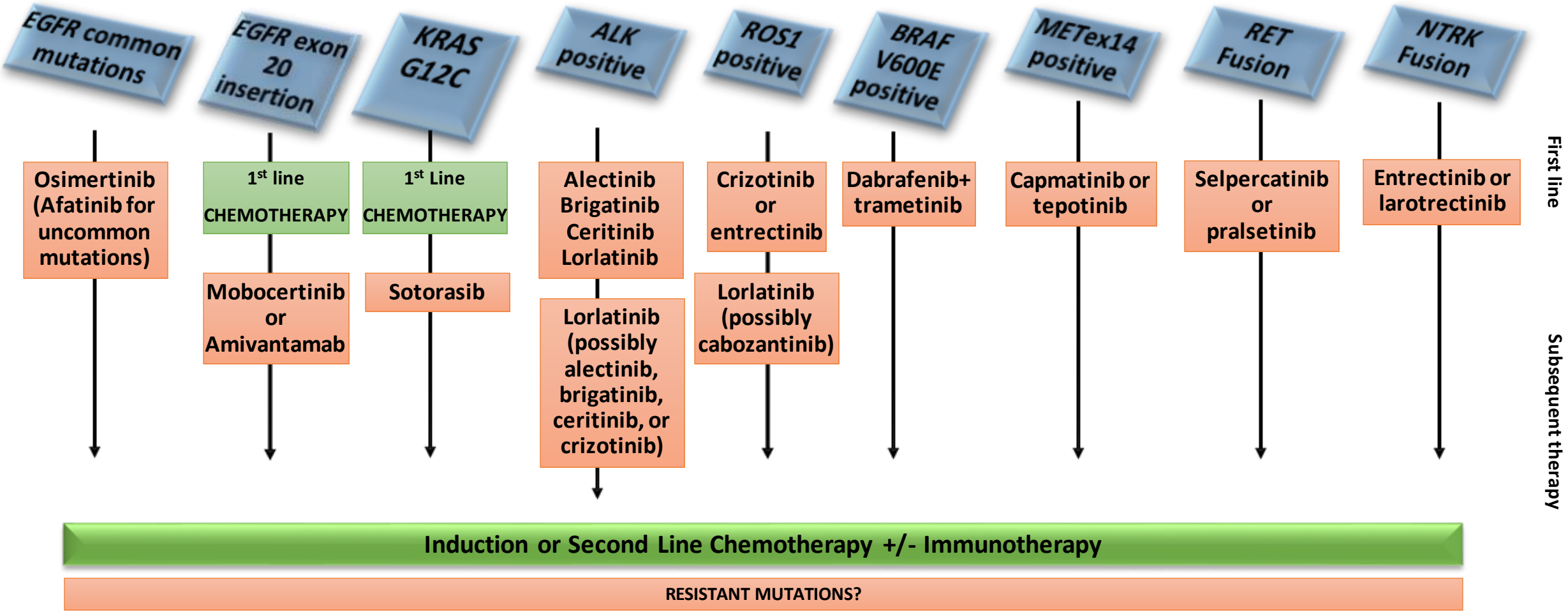
Entrectinib in *ROS1* Rearrangement–Positive NSCLC: Survival





Drilon. Lancet Oncol. 2020;21:261.

Targeted Therapies for Biomarker–Positive NSCLC



NCCN Guidelines Version 3.2022 Non-Small Cell Lung Cancer

Targeted Therapy In Metastatic NSCLC

Test for all genomic alterations to identify driver mutations with comprehensive genomic testing

- When → at the time of diagnosis
- Where → in the clinic
- How → logistical pathways or ordering strategies (make it easy)

Testing tissue and plasma in parallel may increase molecular yields and are complementary

Immunotherapy mostly ineffective in these populations and may pose a risk of toxicity if exposure is sequential

Targeted therapy are more effective than standard chemotherapy

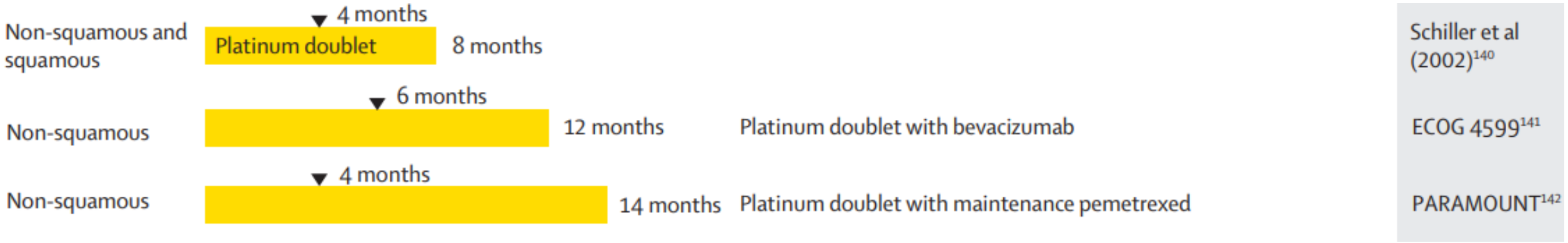
NCCN Guidelines Version 3.2022 Non-Small Cell Lung Cancer

Immunotherapy

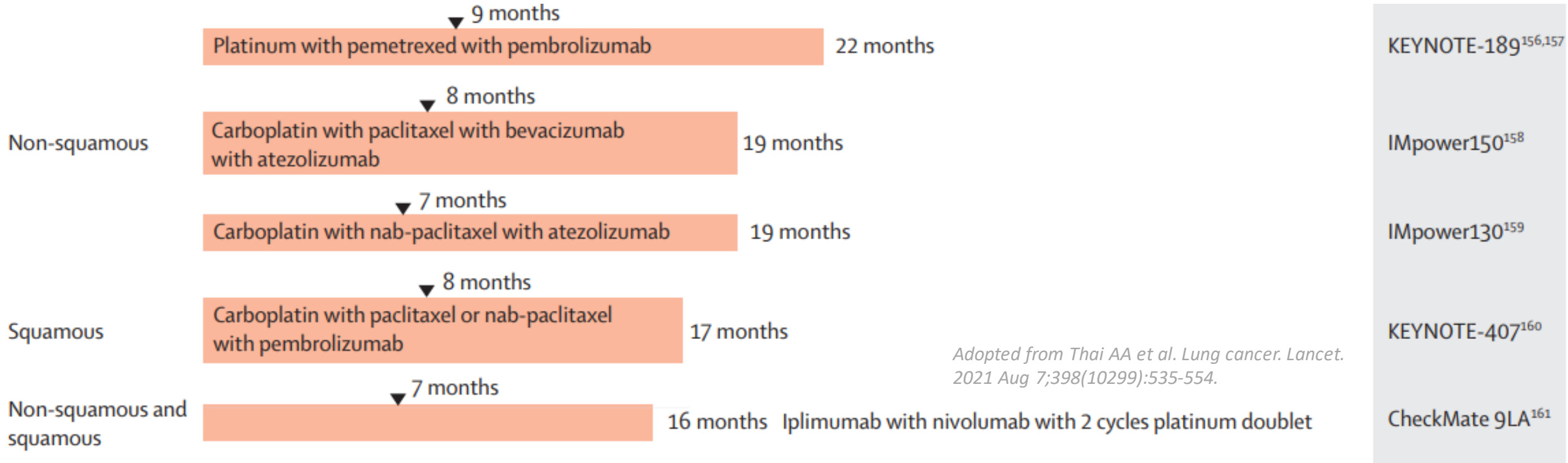
“There is an invisible strength within us; when it recognizes two opposing objects of desire, it grows stronger.”

- Rumi

Where we were.

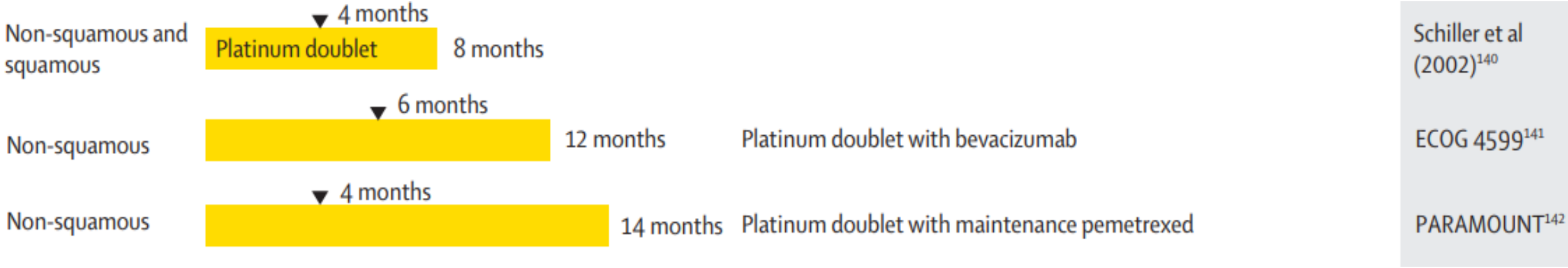


Where we are w/**chemo-**immunotherapy.

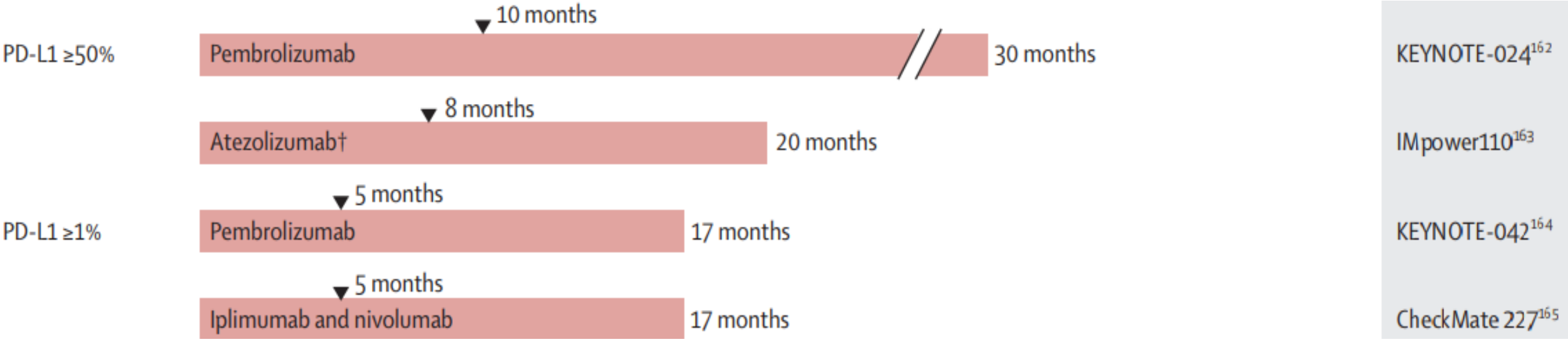


Adopted from Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

Where we were.

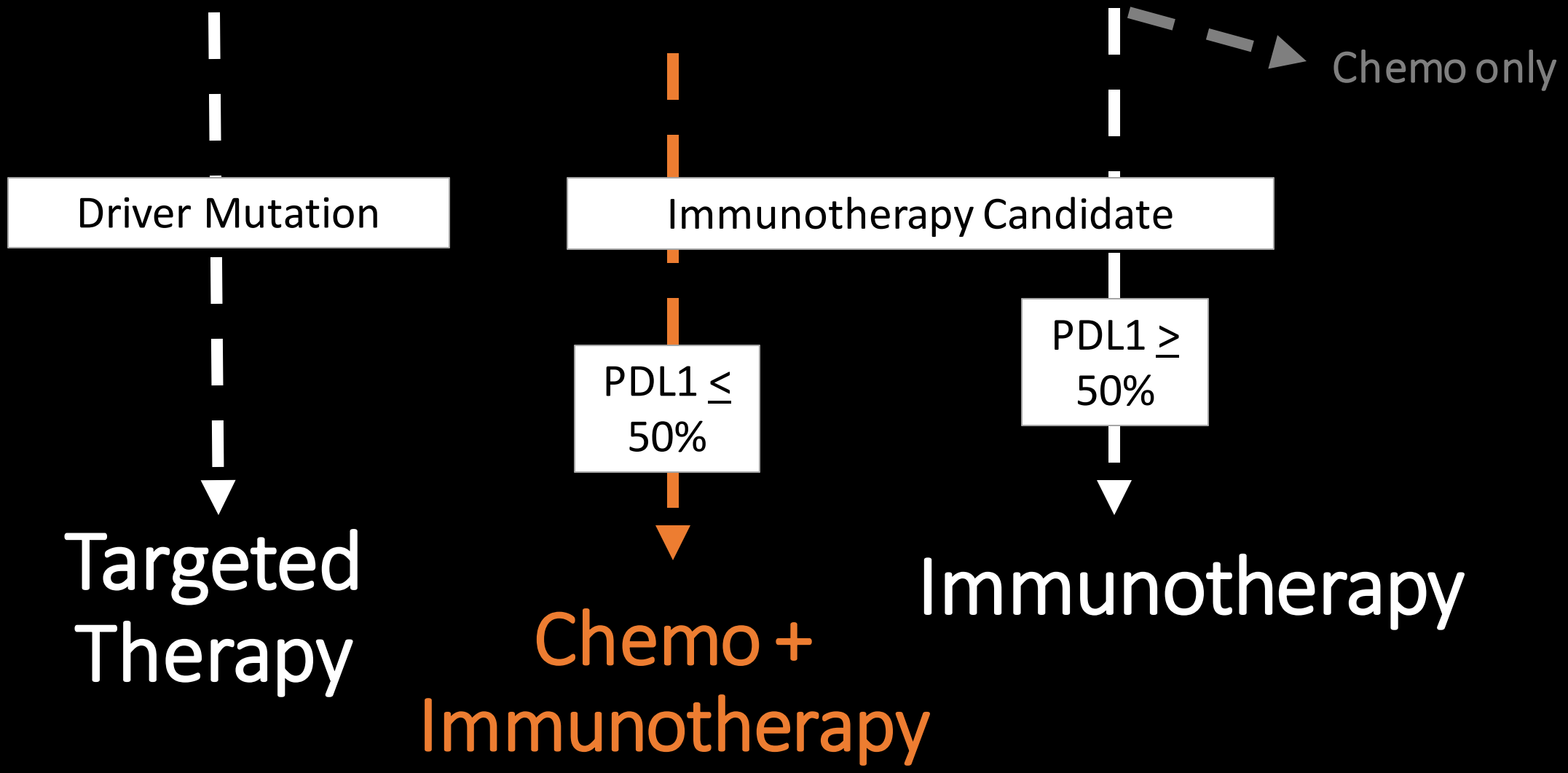


Where we are w/immuno-**mono**therapy.



Adopted from Thai AA et al. Lung cancer. Lancet. 2021 Aug 7;398(10299):535-554.

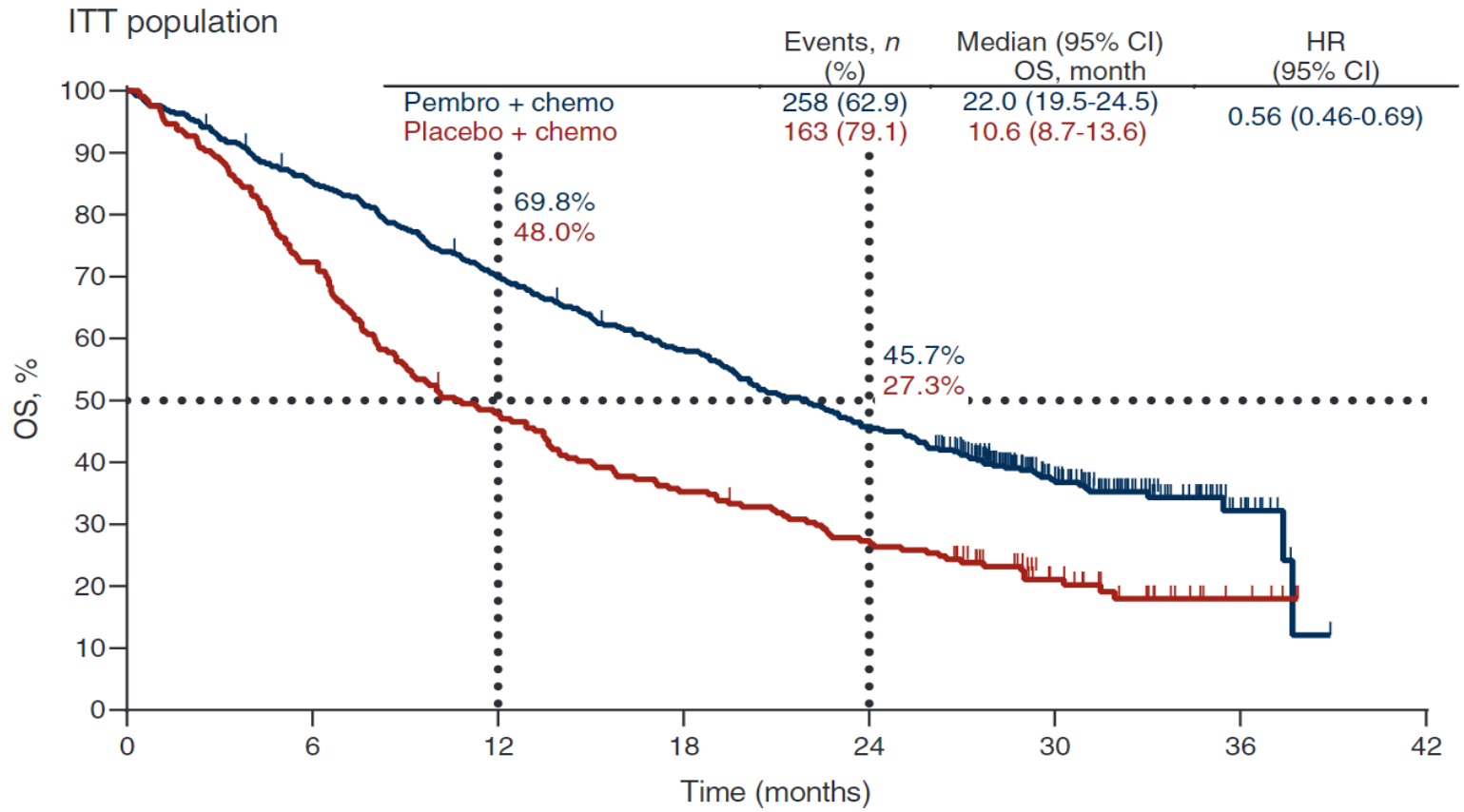
Treatment of Metastatic NSCLC



KEYNOTE-189: 1st line Pembrolizumab + CT vs Placebo + CT in Stage IV Nonsquamous NSCLC

no actionable *EGFR/ALK* mutations;
no symptomatic CNS mets or pneumonitis requiring tx
(N = 616)

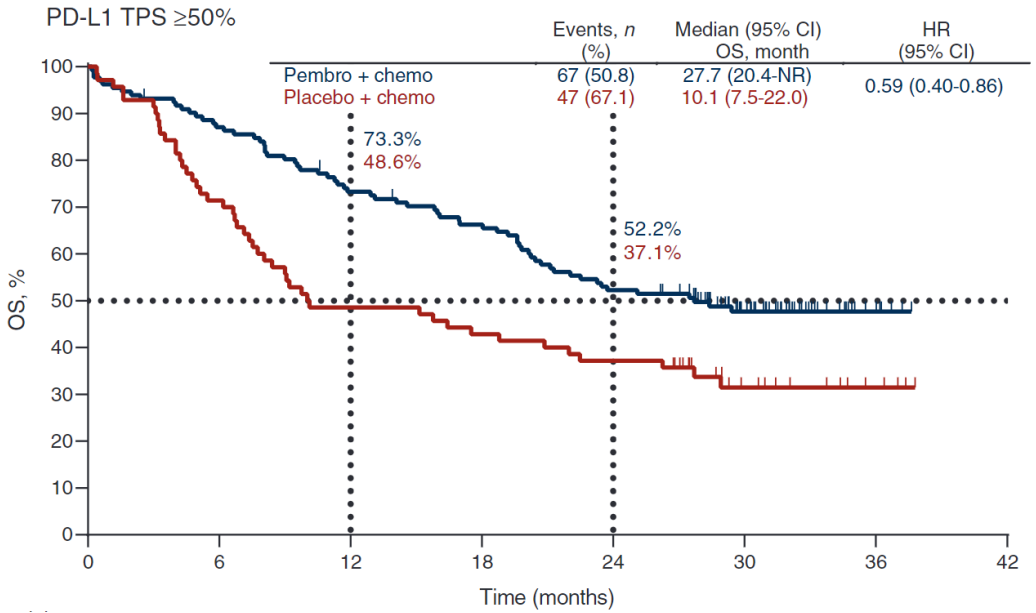
Primary endpoints: OS, PFS by BICR
Secondary endpoints: ORR, DoR, safety

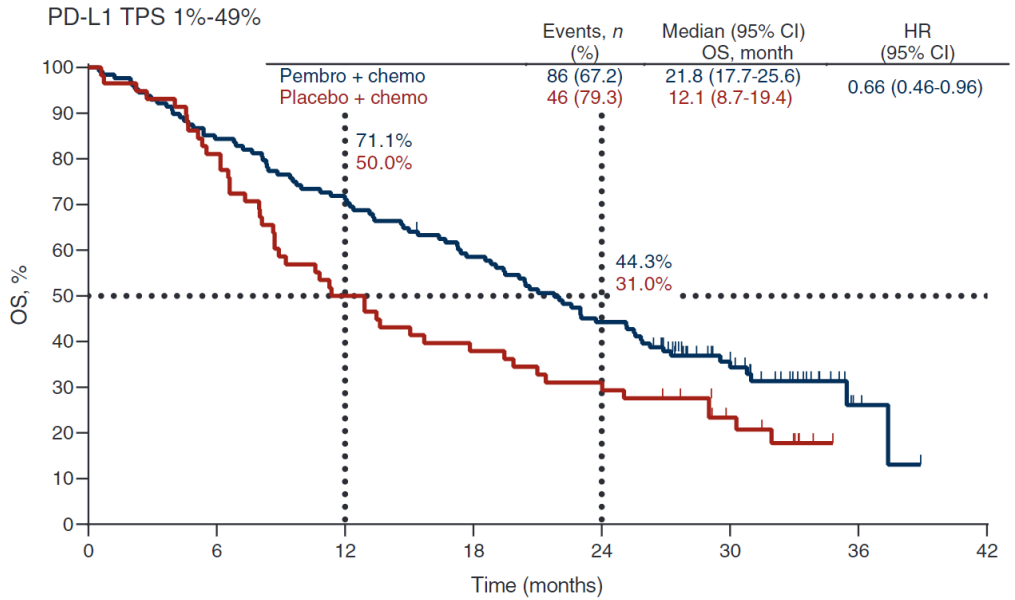


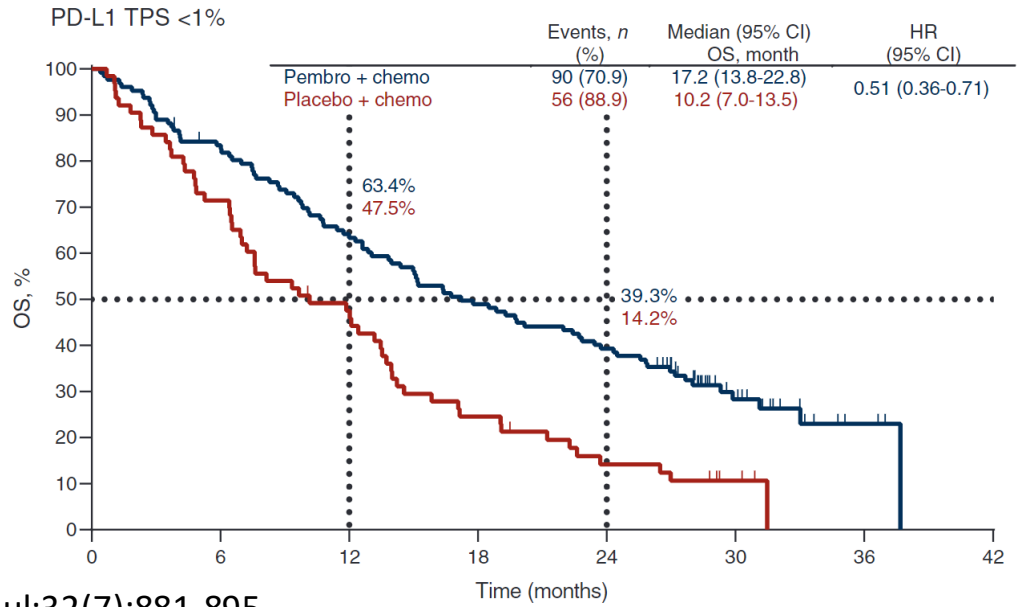
No. at risk:								
Pembro + chemo	410	347	283	234	184	86	12	0
Placebo + chemo	206	149	98	72	55	25	5	0

Rodríguez-Abreu D, et al. Ann Oncol. 2021 Jul;32(7):881-895.

KEYNOTE-189







Rodríguez-Abreu D, et al. Ann Oncol. 2021 Jul;32(7):881-895.

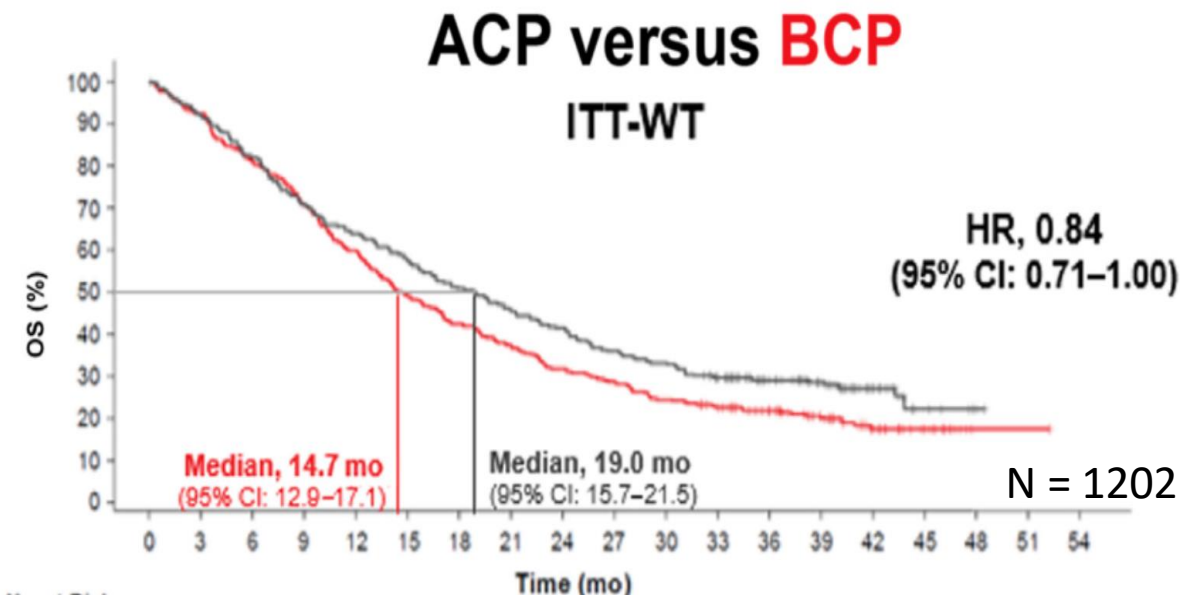
IMpower150: Addition of Atezolizumab to Carbo/Pac + Bevacizumab in Advanced NSCLC - NonSquamous

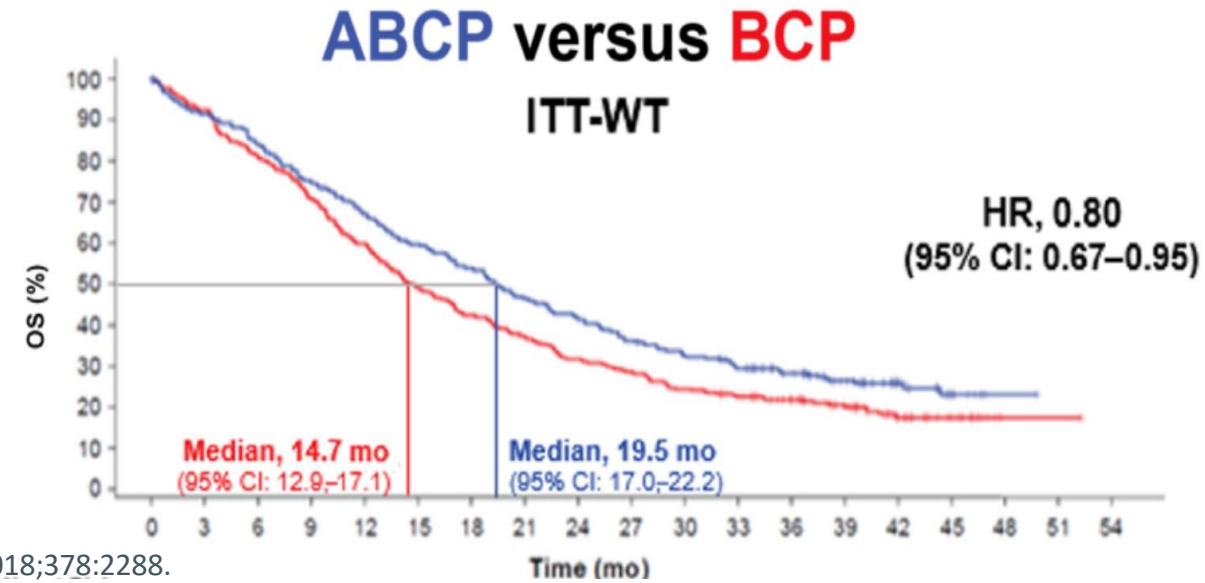
Primary endpoints: PFS, OS
Secondary endpoints: PFS (IRF), ORR, OS at Yrs 1 and 2, QoL, safety, PK

Stratified by sex, PD-L1 expression, liver mets

4-6 cycles followed by Maintenance therapy (no crossover allowed)

Atezolizumab until PD or loss of benefit and/or bevacizumab until PD

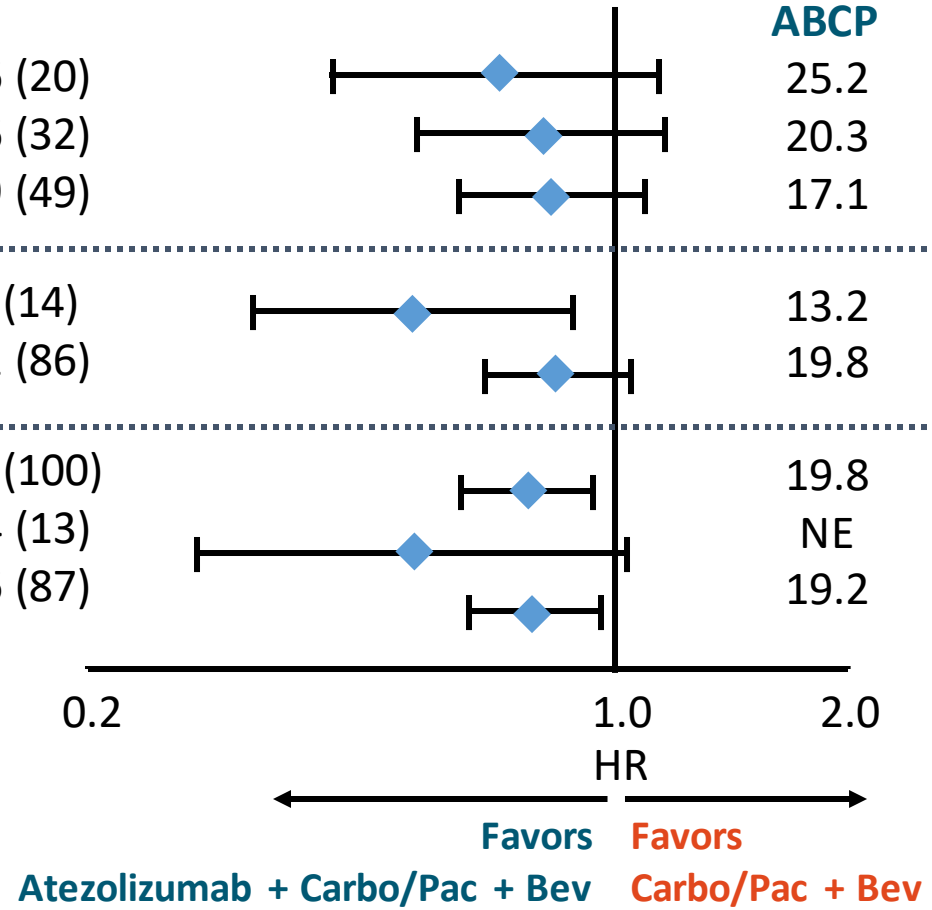




Reck. ESMO I-O Congress 2017. Abstr LBA1_PR. Kowanetz. AACR 2018. Abstr CT076. Socinski. NEJM. 2018;378:2288.

IMpower150: OS by Subgroup

Subgroup	n (%)*	Median OS, Mos		HR
		ABCP	BCP	
PD-L1 high (TC3 or IC3) WT	136 (20)	25.2	15.0	0.70
PD-L1 low (TC1/2 or IC1/2) WT	226 (32)	20.3	16.4	0.80
PD-L1 negative (TC0 and IC0) WT	339 (49)	17.1	14.1	0.82
Liver metastases WT	94 (14)	13.2	9.1	0.54
No liver metastases WT	602 (86)	19.8	16.7	0.83
ITT (including *EGFR/ALK*+)	800 (100)	19.8	14.9	0.76
EGFR/ALK+ only	104 (13)	NE	17.5	0.54
ITT WT	696 (87)	19.2	14.7	0.78



*For prevalence, ITT WT (n = 696) used for PD-L1, liver metastases groups; ITT (n = 800) for rest.

Socinski. NEJM. 2018;378:2288.

IMpower130: Carboplatin/nab-Paclitaxel ± Atezolizumab in Advanced Nonsquamous NSCLC

Randomized, multicenter, open-label phase III study
Crossover allowed

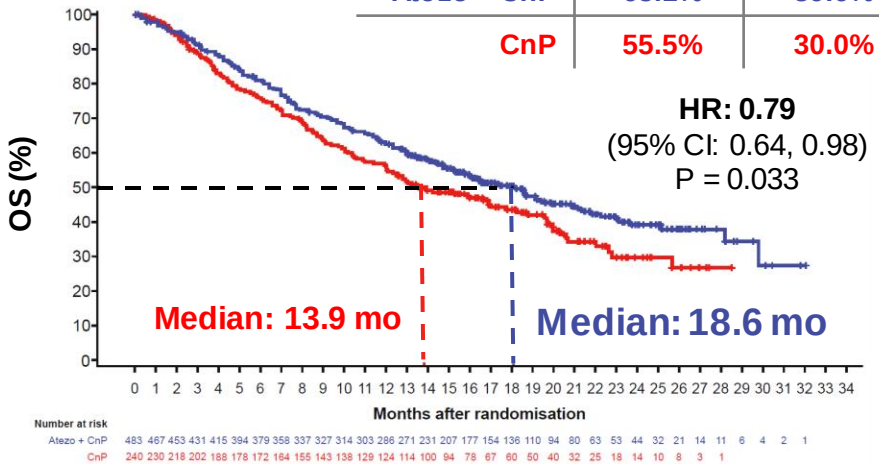
Stratified by sex, baseline liver metastases, tumor PD-L1 expression

Primary endpoint: PFS (investigator assessed), OS in wild-type *EGFR*/*ALK* patients

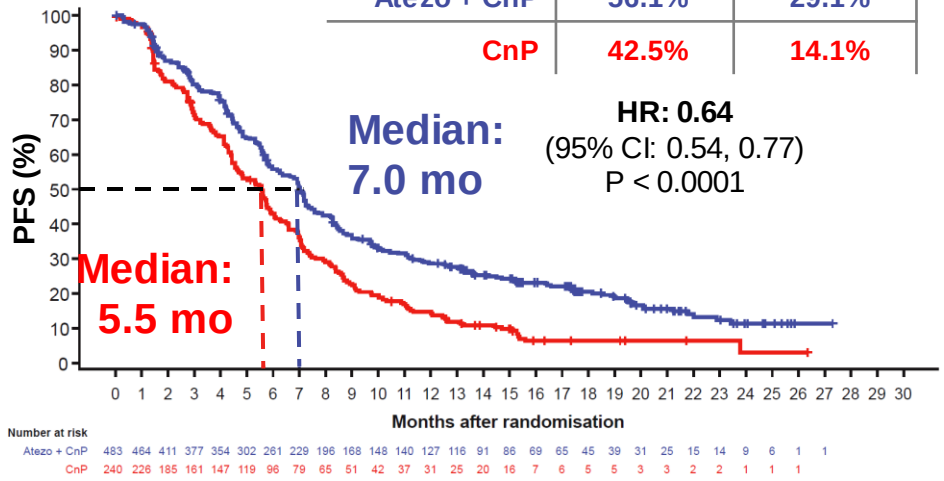
Secondary endpoints: PFS and OS in ITT and by PD-L1 expression in ITT wild-type populations; ORR and DoR; 1-yr and 2-yr OS, time to deterioration in lung cancer symptoms

N = 724

OS (%)	1 year	2 years
Atezo + CnP	63.1%	39.6%
CnP	55.5%	30.0%



PFS (%)	6 months	12 months
Atezo + CnP	56.1%	29.1%
CnP	42.5%	14.1%



West. Lancet Oncol. 2019;20:924. Atezolizumab PI. 2019.

KEYNOTE-407: Advanced Squamous NSCLC

Randomized, double-blind phase III trial

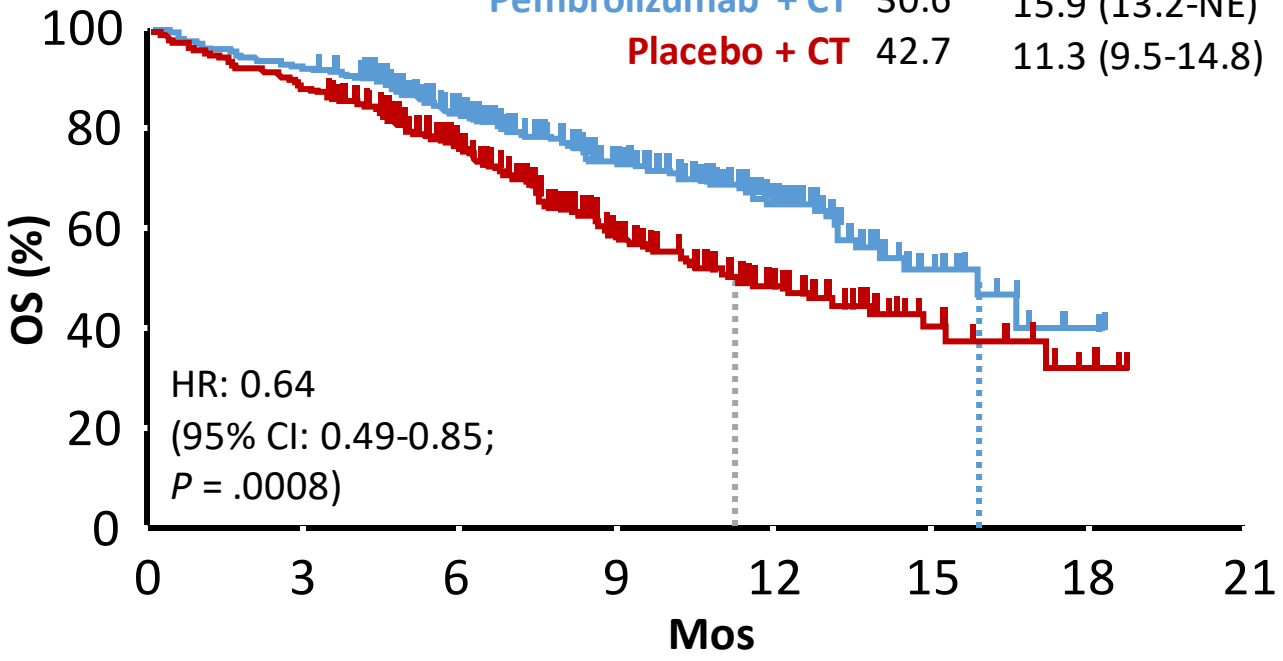
Crossover allowed

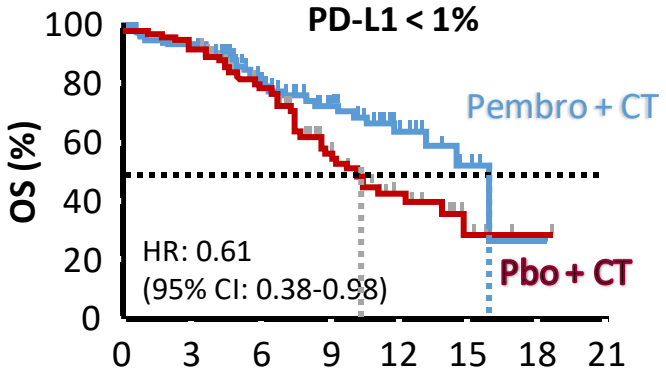
Primary: PFS and OS / Secondary: ORR and DoR/Safety

OS (ITT)

N = 559

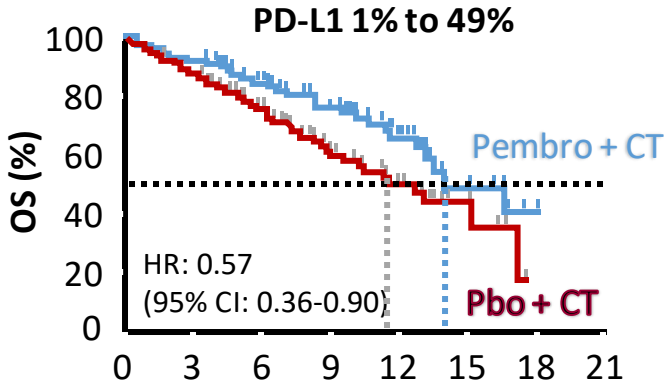
	Events, %	Median OS, Mos (95% CI)
Pembrolizumab + CT	30.6	15.9 (13.2-NE)
Placebo + CT	42.7	11.3 (9.5-14.8)





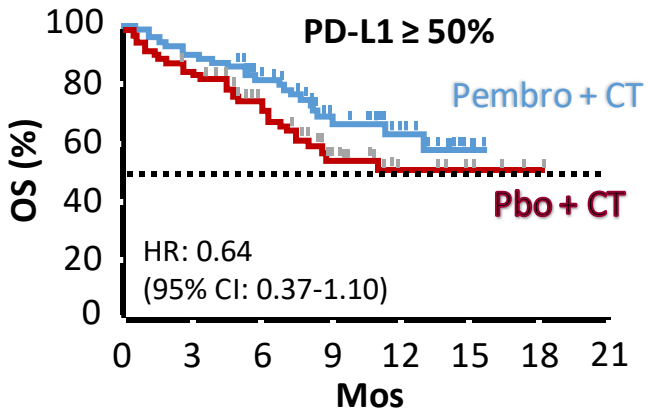
Median OS, Mos (95% CI)

15.9 (13.1-NE)
10.2 (8.6-13.8)



Median OS, Mos (95% CI)

14.0 (12.8-NE)
11.6 (8.9-17.2)



Median OS, Mos (95% CI)

NR (11.3-NE)
NR (7.4-NE)

Paz-Ares. ASCO 2018. Abstract 105. Paz-Ares. NEJM. 2018;379:2040.

Chemo-Immunotherapy Outcomes in Metastatic NSCLC

Chemotherapy + Immunotherapy

Trial	Control	Histology	Med OS control/Inv	HR Inv Arm
KeyNote -189	Carbo/Pem	Non-Squam	10.6/22	0.60
IMPower -150	Carbo/Pac/Bev	Non-Squam	14.7/19.2	0.80
IMPower -130	Carbo/nabPac	Non-Squam	13.9/18.6	0.79
KeyNote -407	Carbo/taxane	Squam	11.3/15.9	0.64

Rodríguez-Abreu D, et al. Ann Oncol. 2021 Jul;32(7):881-895.

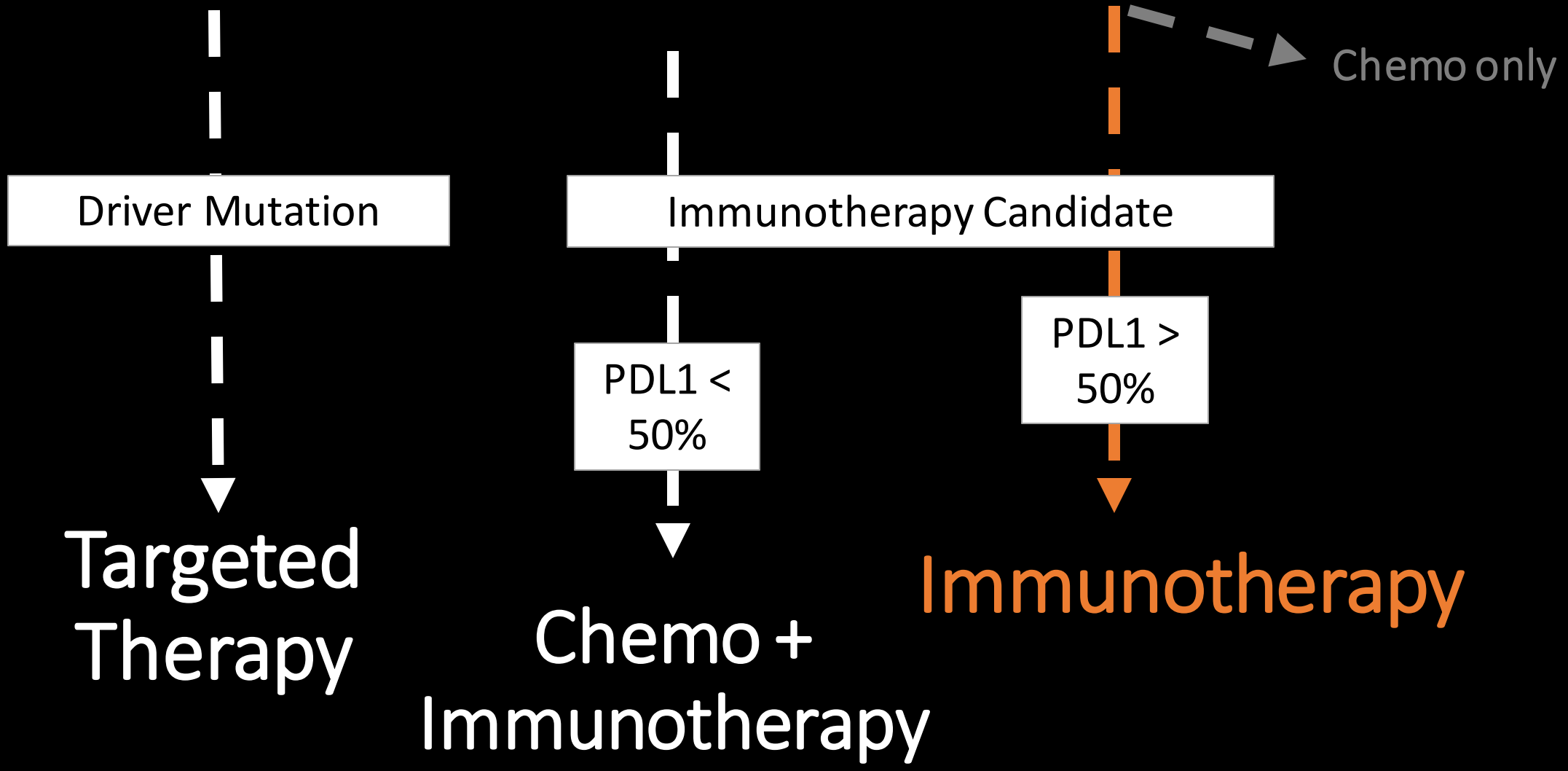
Reck. ESMO I-O Congress 2017. Abstr LBA1_PR. Kowanetz. AACR 2018. Abstr CT076. Socinski. NEJM. 2018;378:2288

West. Lancet Oncol. 2019;20:924. Atezolizumab PI. 2019.

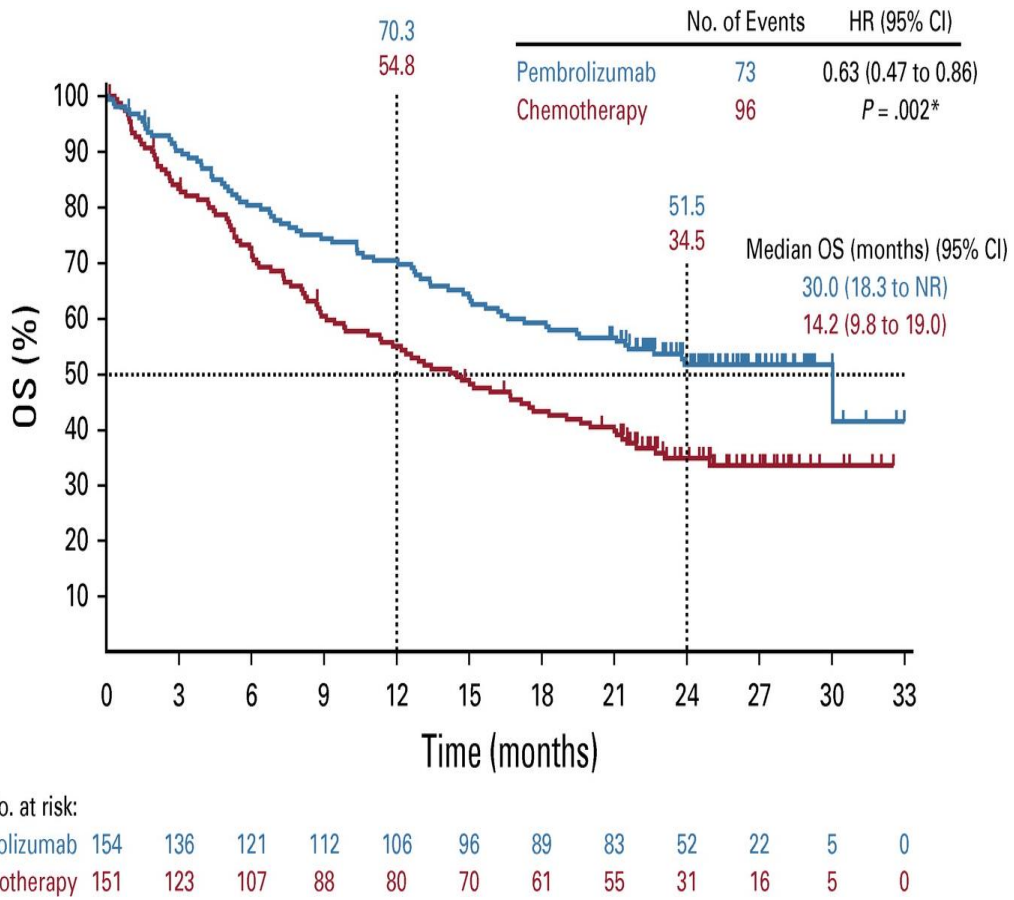
Paz-Ares. ASCO 2018. Abstract 105.

Paz-Ares. NEJM. 2018;379:2040.

Treatment of Metastatic NSCLC

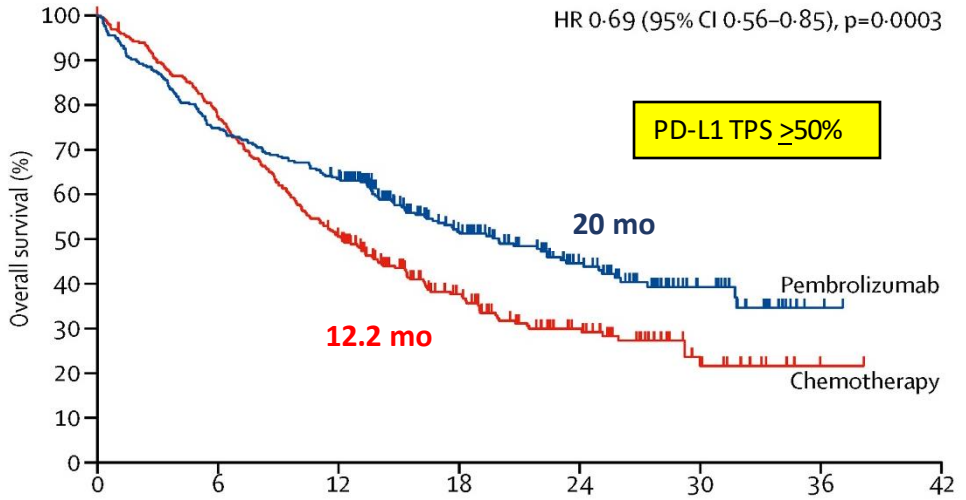


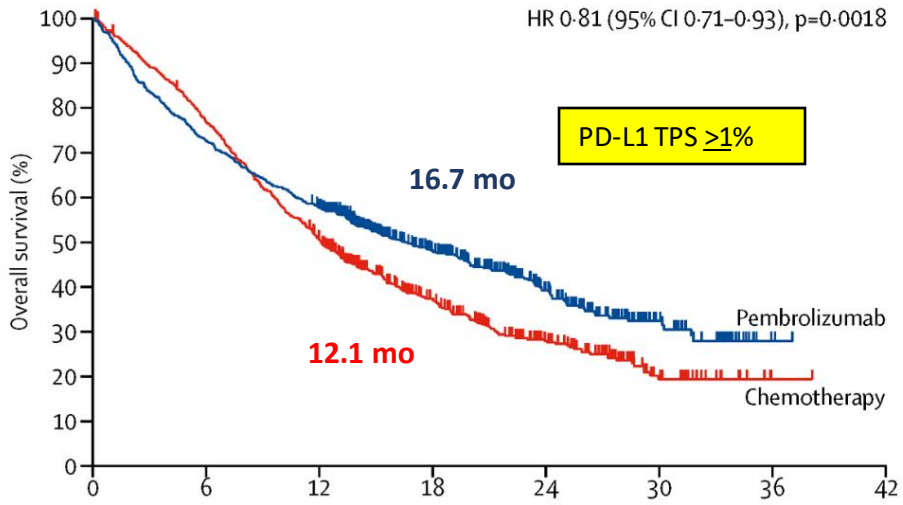
Keynote-024: 1st Line Pembrolizumab vs. Chemotherapy in stage IV NSCLC



Reck M, et al. Updated Analysis of KEYNOTE-024;J Clin Oncol. 2019 Mar 1;37(7):537-546.

Keynote-042: 1st Line Pembrolizumab vs. Chemotherapy in stage IV NSCLC with PD-L1 TPS ≥ 1%

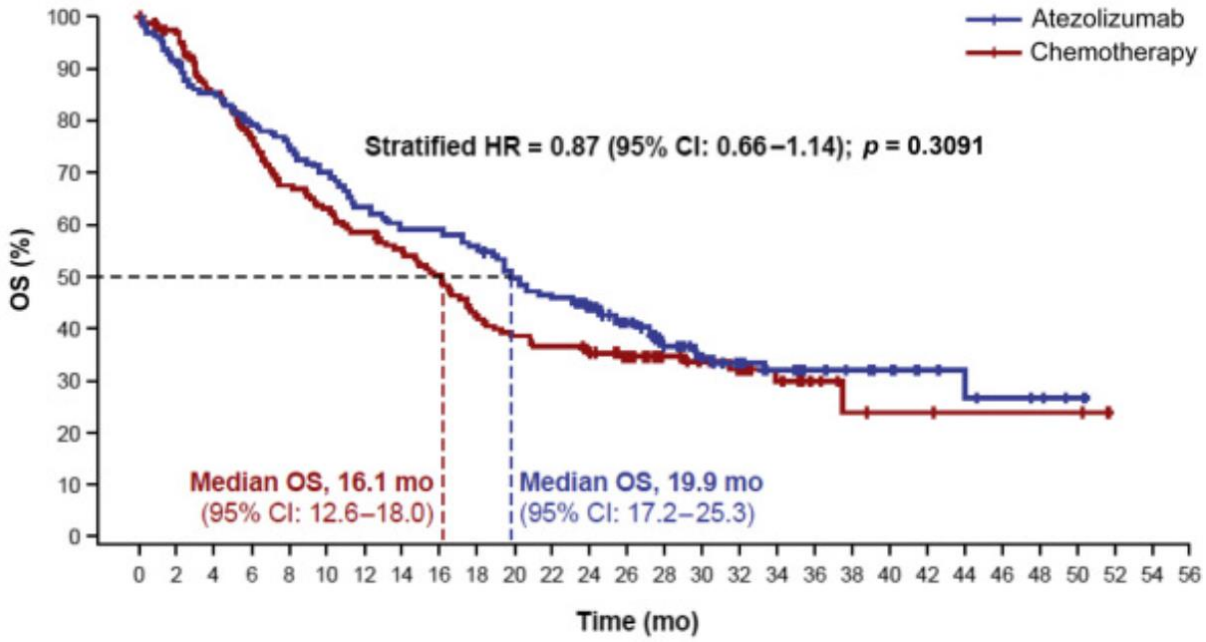




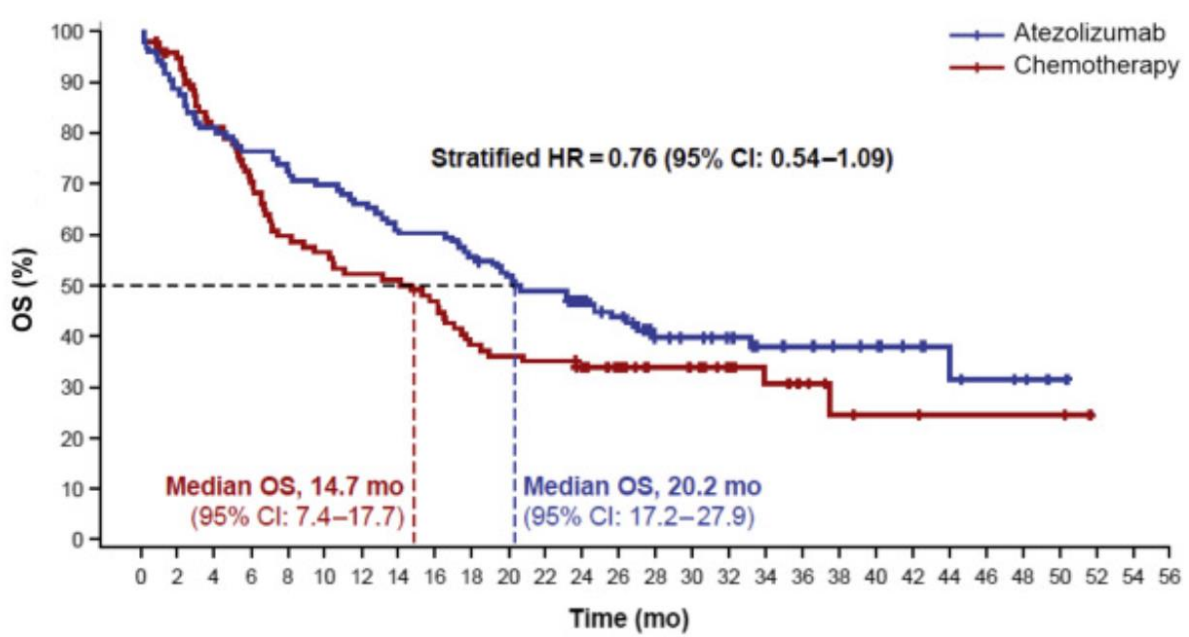
Mok TSK, et al. KEYNOTE-042. Lancet. 2019 May 4;393(10183):1819-1830.

Impower 110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1–Selected NSCLC

high-or-intermediate PD-L1 expression
≥5% PD-L1 expression on TC or IC

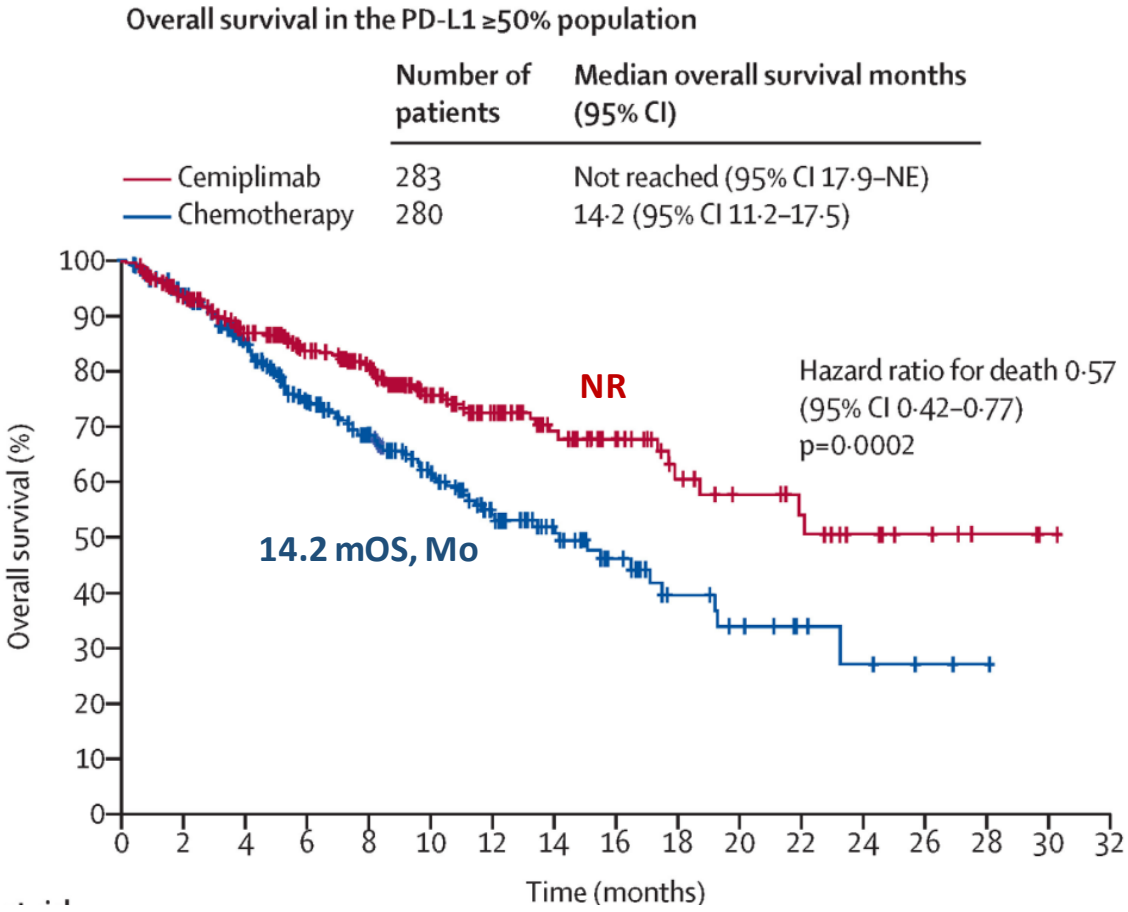


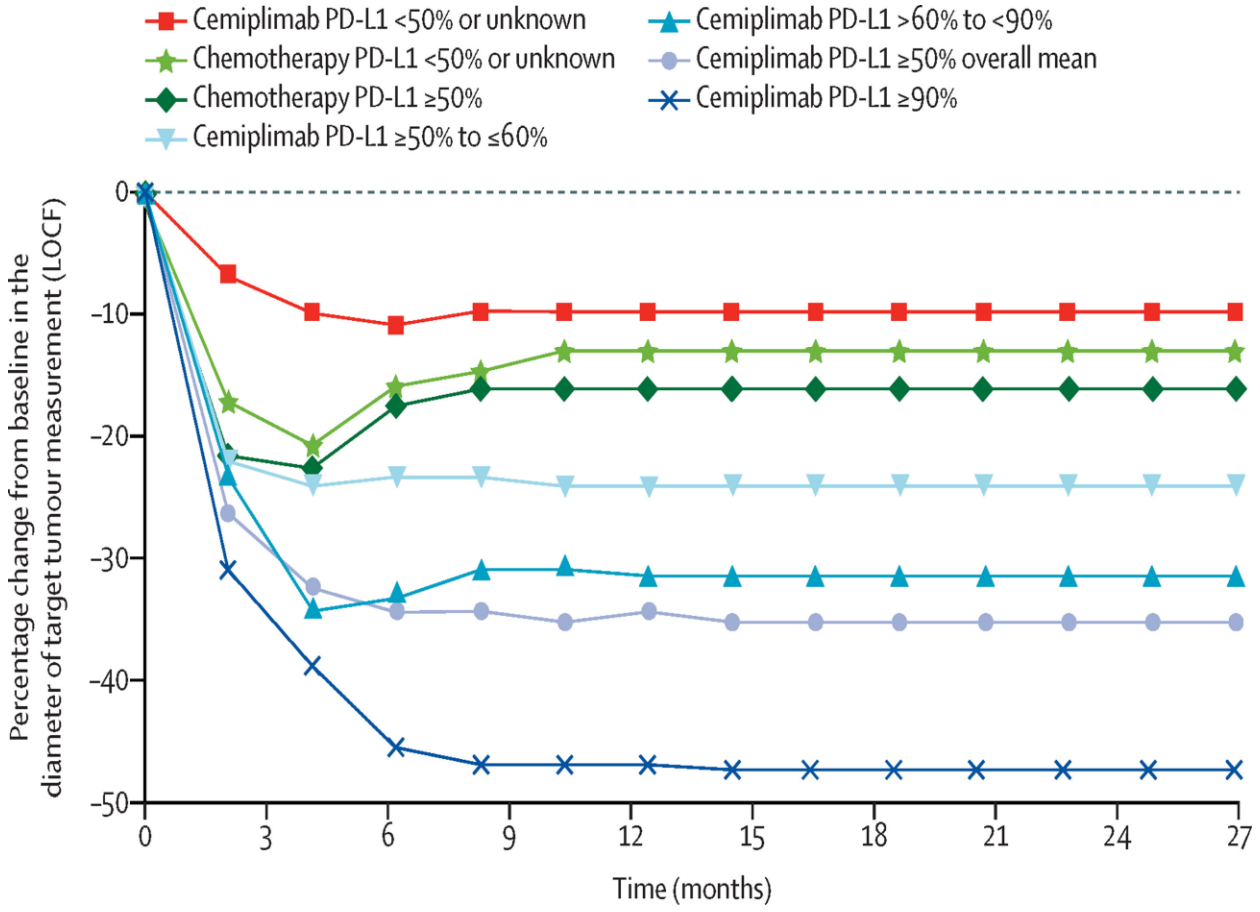
high PD-L1 expression (≥50% PD-L1 expression on TC or ≥10% PD-L1 expression on IC)



Jacek Jassem, et al. IMpower110, Journal of Thoracic Oncology, Volume 16, Issue 11, 2021,Pages 1872-1882,ISSN 1556-0864

Cemiplimab monotherapy for 1st line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%





Sezer A, et. al.. Lancet. 2021 Feb 13;397(10274):592-604.

Response Rates based on monotherapy Immunotherapy and Immuno-chemotherapy

Immunotherapy as monotherapy

Trial	PD-L1	ORR
KN-024	>50%	45%
KN-042	>50%	40%
IMPower110	TC3/IC3	38%
EMPOWER	>50%	35%
CM-227	PD-L1 >1%	36%
CM-227	PD-L1 <1%	27%

Immunotherapy + Chemo

Trial	PD-L1	ORR
KN-189	>50%	61%
KN-407	>50%	58%
IMPower150	TC3/IC3	69%
IMPower132	TC3/IC3	72%
IMPower131	TC3/IC3	60%

Reck M, et al. Updated Analysis of KEYNOTE-024;J Clin Oncol. 2019 Mar 1;37(7):537-546.
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Immuno-monotherapy in metastatic NSCLC

Guide to immuno-monotherapy use

- Low volume disease burden
- Symptom Control
- Very High PDL1 expression

Who not to treat with immuno-monotherapy

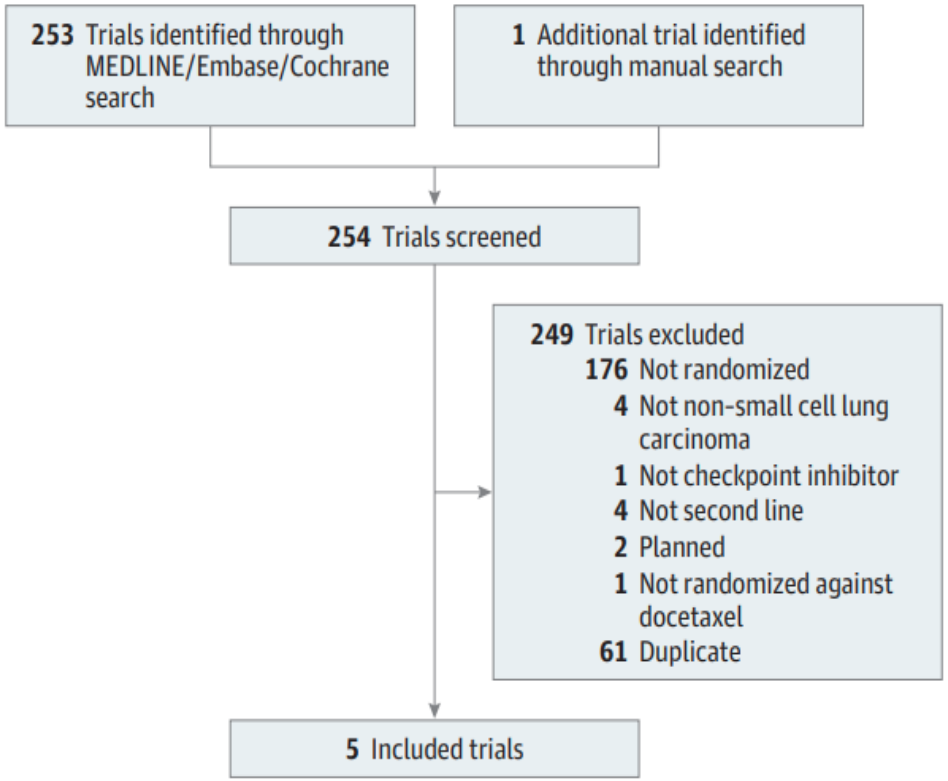
- Large disease burden
- Uncontrolled symptoms
- PDL1 <50%

Where Targeted Therapy Intersects with Immunotherapy

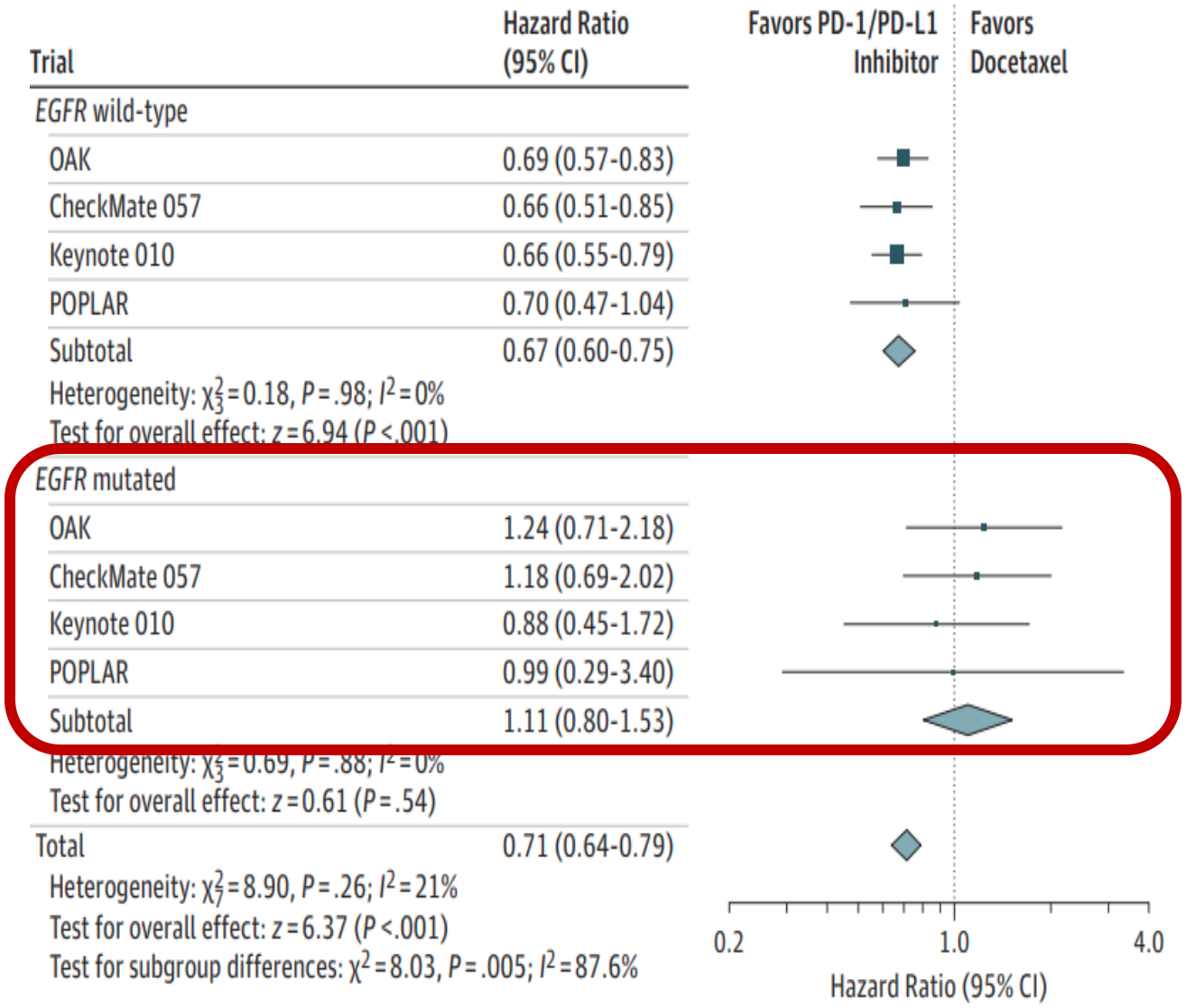
"To look at the cross section of any plan of a big city is to look at something like the section of a fibrous tumor."

- Frank Lloyd Wright

Systematic Review and Meta-analysis



Trials	Treatment Comparison	Median OS, mo[a]	Patients, No. (%) *EGFR* Mutation	*KRAS* Mutation	Squamous Carcinoma
CheckMate 017,[5] 2015	Nivolumab vs docetaxel	9.2 vs 6.0			272 (100)
CheckMate 057,[4] 2015	Nivolumab vs docetaxel	12.2 vs 9.4	82 (14)	62 (11)	0
Keynote 010,[6] 2016	Pembrolizumab vs docetaxel	10.4 vs 12.7[b] vs 8.5[c]	86 (8)		222 (21)
OAK,[7] 2017	Atezolizumab vs docetaxel	13.8 vs 9.6	85 (10)	59 (7)	222 (26)
POPLAR,[8] 2016	Atezolizumab vs docetaxel	12.6 vs 9.7	18 (6)	27 (9)	97 (34)



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ORIGINAL ARTICLE

A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

A. Lisberg, MD, A. Cummings, MD, J. W. Goldman, MD, K. Bornazyan, BS,

- Enrollment ceased due to lack of efficacy at 11 of 25 planned patients
- Only 1 patient (9%), where report of *EGFR* mutation was in error, achieved an objective response to pembrolizumab despite 8/11 patients (73%) having PD-L1 ≥ 50%
- Two deaths within 6 months of enrollment, including one attributed to pneumonitis.

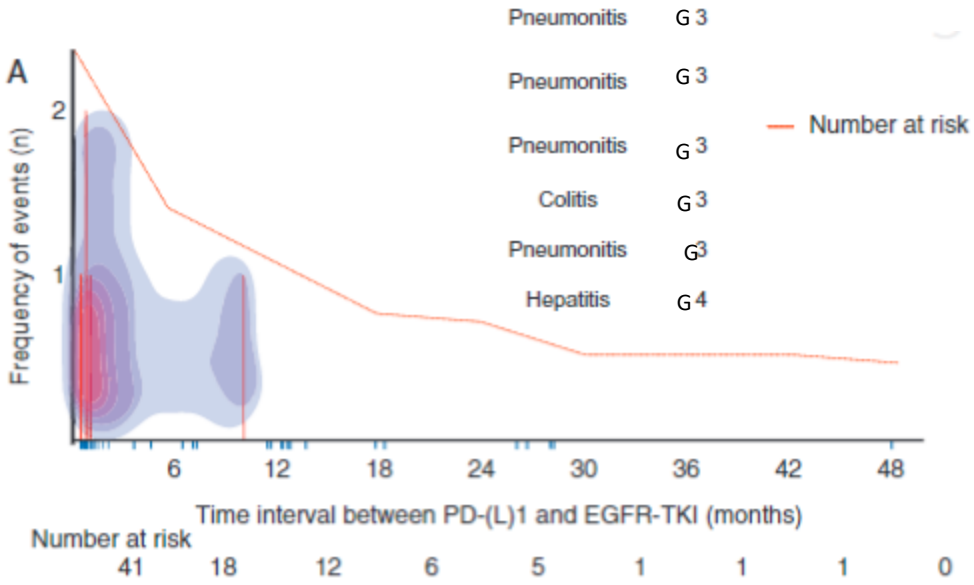
Journal of Thoracic Oncology Vol. 13 No. 8: 1138-1145

ORIGINAL ARTICLE

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A. J. Schoenfeld[1], K. C. Arbour[1], H. Rizvi[1], A. N. Iqbal[1], S. M. Gadgeel[2], J. Girshman[3], M. G. Kris[1],

- 126 patients treated with the EGFR TKI osimertinib within 3 mos of PD-(L)1 blockade, 24% developed a severe irAE, including pneumonitis



Annals of Oncology 30: 839–844, 2019

In Conclusion

Advances in Metastatic NSCLC

The characteristic of scientific progress is our knowing that we did not know
– Gaston Bachelard

Biomarkers

Precision Oncology

Immunotherapy

We need more comprehensive genomic testing

We need more therapeutic options to overcome immunotherapy resistance

Any Questions?

Extra Slides