Advancements in Systemic Therapy

LUNG CANCER- A JOURNEY TOWARDS LIFE

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PRESENTER DISCLOSURE

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- **Advisory Board: Astra Zeneca, Merck**

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OBJECTIVES

- To understand treatment advances in NSCLC with driver mutations
- To better understand treatment advances in Non-small cell lung cancer (NSCLC) without driver mutations
- To understand advances in Small Cell Lung Cancer (SCLC)

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NSCLC TREATMENT- DOES ONE SIZE FIT ALL?

- Biopsy sample is processed in pathology lab- takes about 7 days for diagnosis
- Biopsy sample, if adequate, then it is sent to Toronto for further biomarker testing
- This can take anywhere between 3-4 weeks, specially longer, if its adenocarcinoma / Non squamous NSCLC
- we focus so much on pathology as one size does not fit all anymore

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CASE

- 56 Yr./M, previously healthy, non-smoker, presents with enlarged supra clavicular LN and SOB
- PET scan shows- multiple lung nodules and lymph nodes in mediastinal area, left supraclavicular area, multiple bony mets, adrenal mets but no mets in liver and brain.
- Biopsy from Left lung mass in Toronto confirms- NSCLC
- Patient is sent for further management to WRCP

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NEXT STEPS?

- Pathology shows met. Adenocarcinoma
- Will you offer chemo to this young pt. with large burden of disease? Biomarkers are not back yet.

- Patient was educated about chemo with f/u in 1 week. Complicated discussion about pros and cons of chemo alone

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Case cont.-

- Biomarkers fortunately came back, and patient is found to have ALK mutation.
- Urgent application for targeted treatment initiated through our drug coordinators
- Patient started on po Brigatinib after one week
- Seen in 3 weeks for f/u– feeling much better, supraclavicular LN not palpable anymore.
- Zometa initiated for bone mets

WHY PATHOLOGY IS SO IMP?

- Pathology is the crux for management and therefore its imp to get a good sample, order a core biopsy to run the immunohistochemistry and biomarker tests.
- If a tumor is peripheral in lung or if you see liver mets/ palpable lymph nodes – order urgent CT guided core biopsy in the hospital
- If a tumor is central/ near airway/ in mediastinum- refer for bronchoscopy / EBUS biopsy- urgent Referral to respirology

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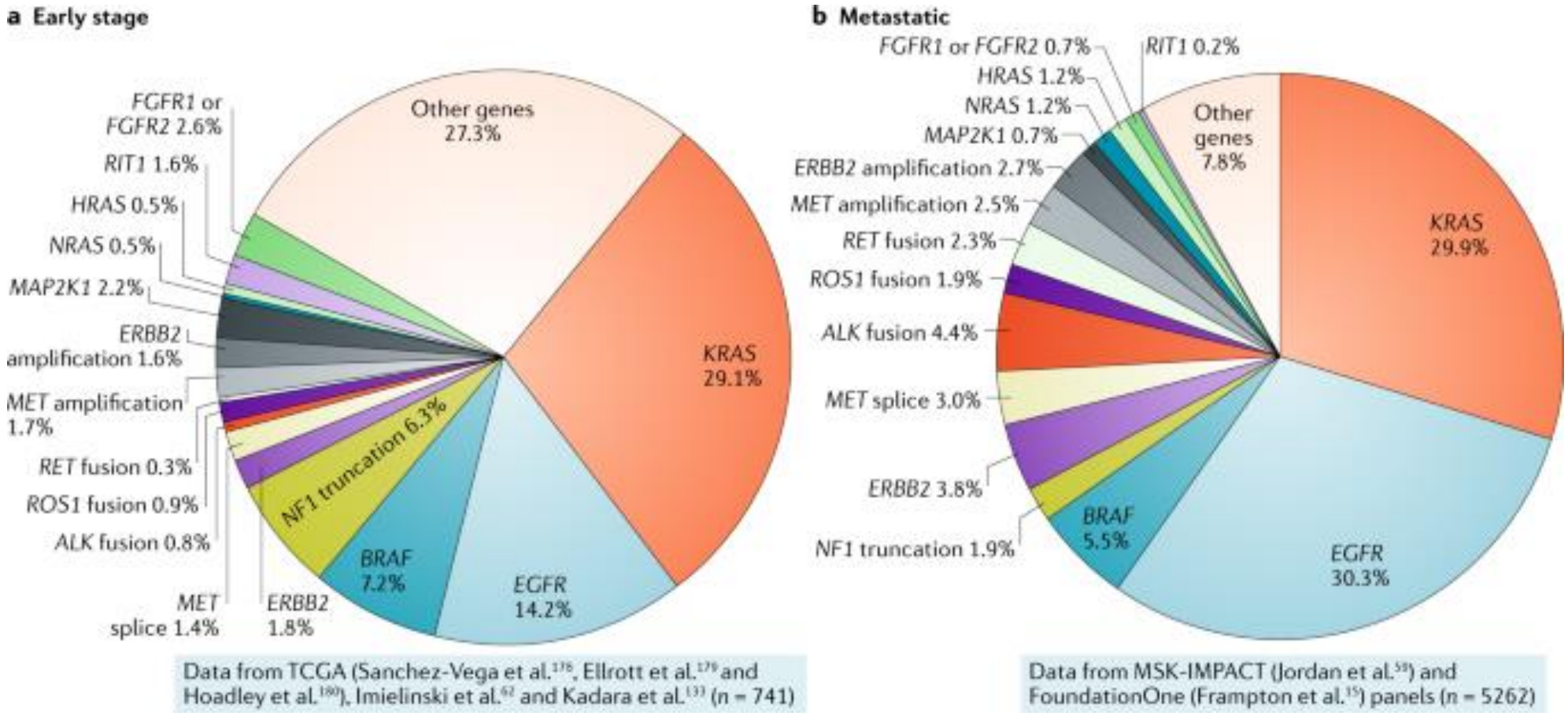
NSCLC- Non-squamous
Oncogene addicted tumors



COMMON TARGETABLE MUTATIONS

- EFGR- Seen in 15-50% of patients based on where you practice in the world. Common in non-smokers, Asians
- ALK- 5-7% -younger, never/ light smokers
- Met – 3-4% sometimes seen in pts progressed on chemo/ immunotherapy
- Ros-1- 1-2 % younger, never smokers
- RET-1-2% younger pts, non-smokers
- KRas / Braf/ Ntrk / Her-2

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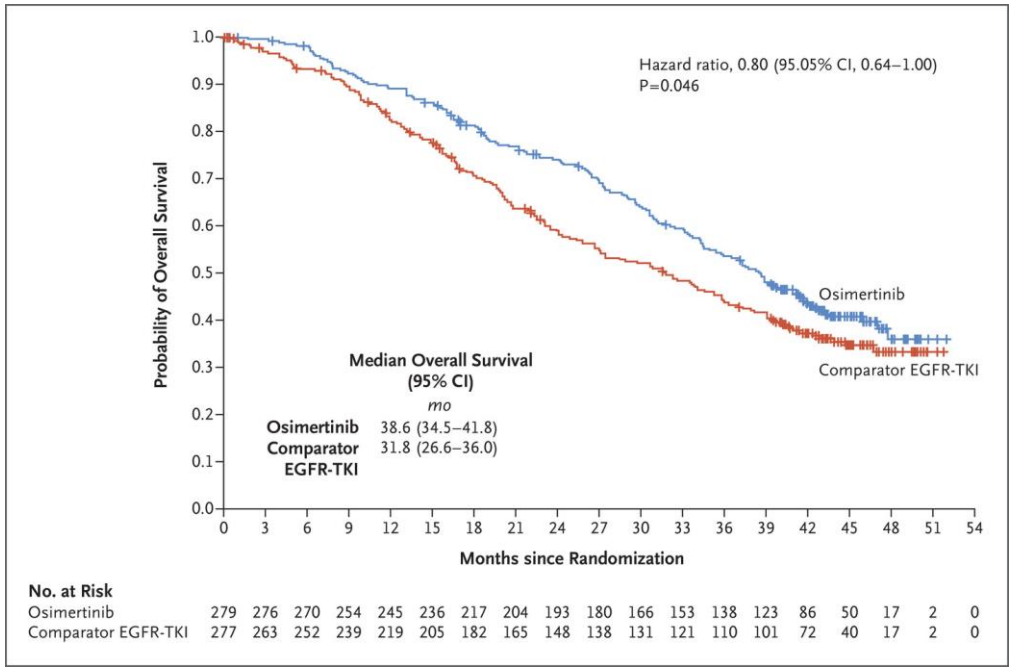
WHY ITS IMPORTANT TO KNOW ABOUT THESE MUTATIONS?

Targeted treatments have changed the outcome and prognosis of Mutated / oncogene addicted lung caners significantly.



EGFR mutated NSCLC

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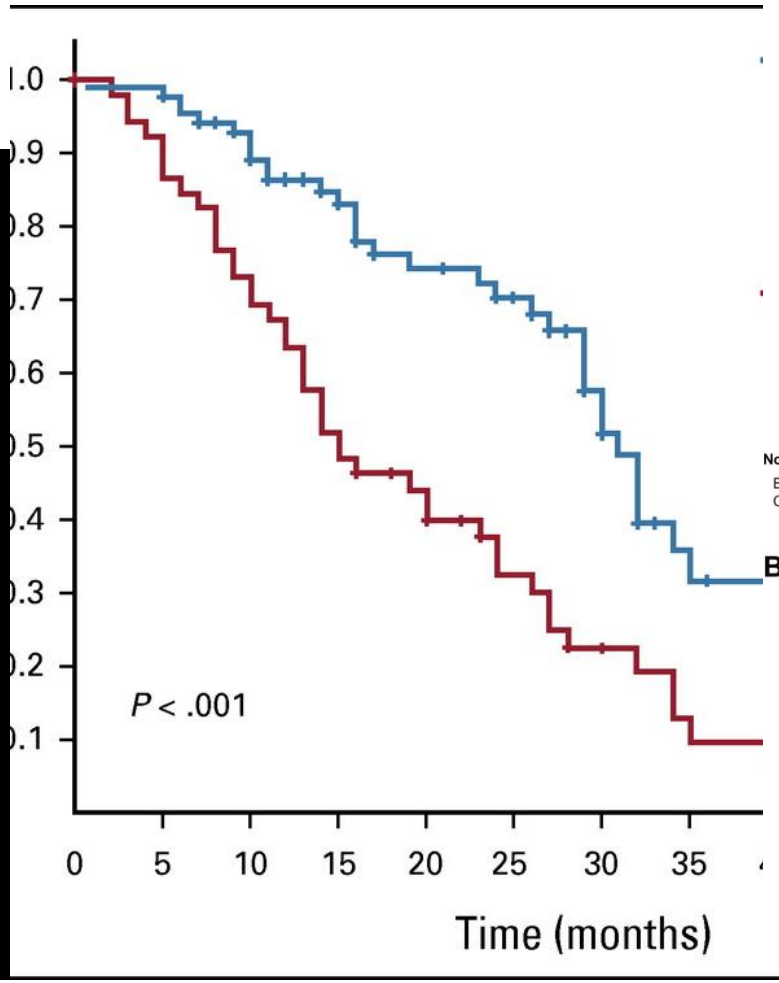
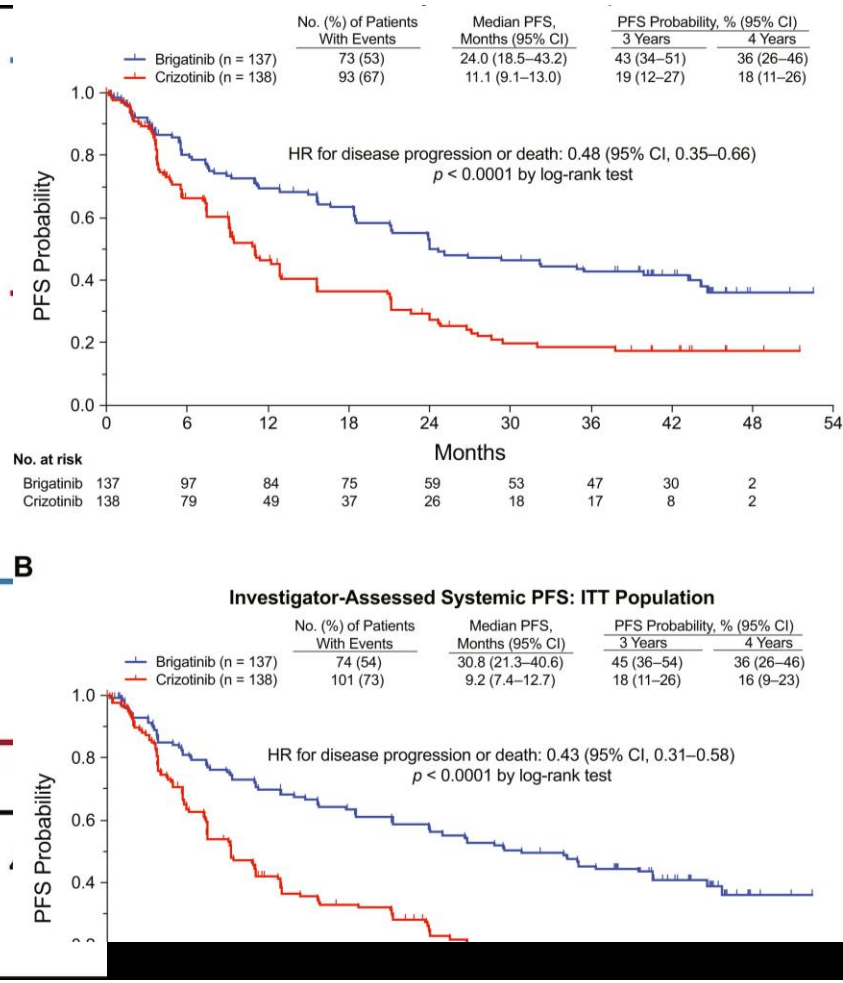
Targeted treatments have changed the outcome and prognosis of ALK Mutated caners significantly.





ONCOGENE ADDICTED TUMORS OUTCOME SUMMARY

- EFGR mutated- With Osimertinib OS 38.6 months after a f/u of 39 months
- Recent advance- EGFR met bispecific antibody Amivantamab + Lazertinib showed PFS 23.7 Vs 16.6 months with Osimertinib, OS data not mature
- ALK- Brigatinib showed median PFS 24 months
- Recent advancement- Lorlarinib Median PFS not reached at @ 5 yr. mark and 5 yr. PFS is 60 Vs 8 months
- Met – tepotinib OR 46% and stable disease 11 months
- Ros-1- median OS 51 months with crizotinib recently repotrectinib showed PFS = 36 months and median os 25 months after 18 months f/u
- RET-Selpercatinib PFS 22 months
- KRas / Braf/ Ntrk / Her-2- Targeted treatment available with good responses

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NSCLC WITHOUT DRIVER MUTATIONS

These include advanced Non-Squamous and Squamous NSCLC. All are tested for PDL-1.

- If Pdl-1 > 50%- Immunotherapy alone
- If pdl-1- 1-49% or <1% - Combination of chemo and immunotherapy is used.
- Why do we test this?

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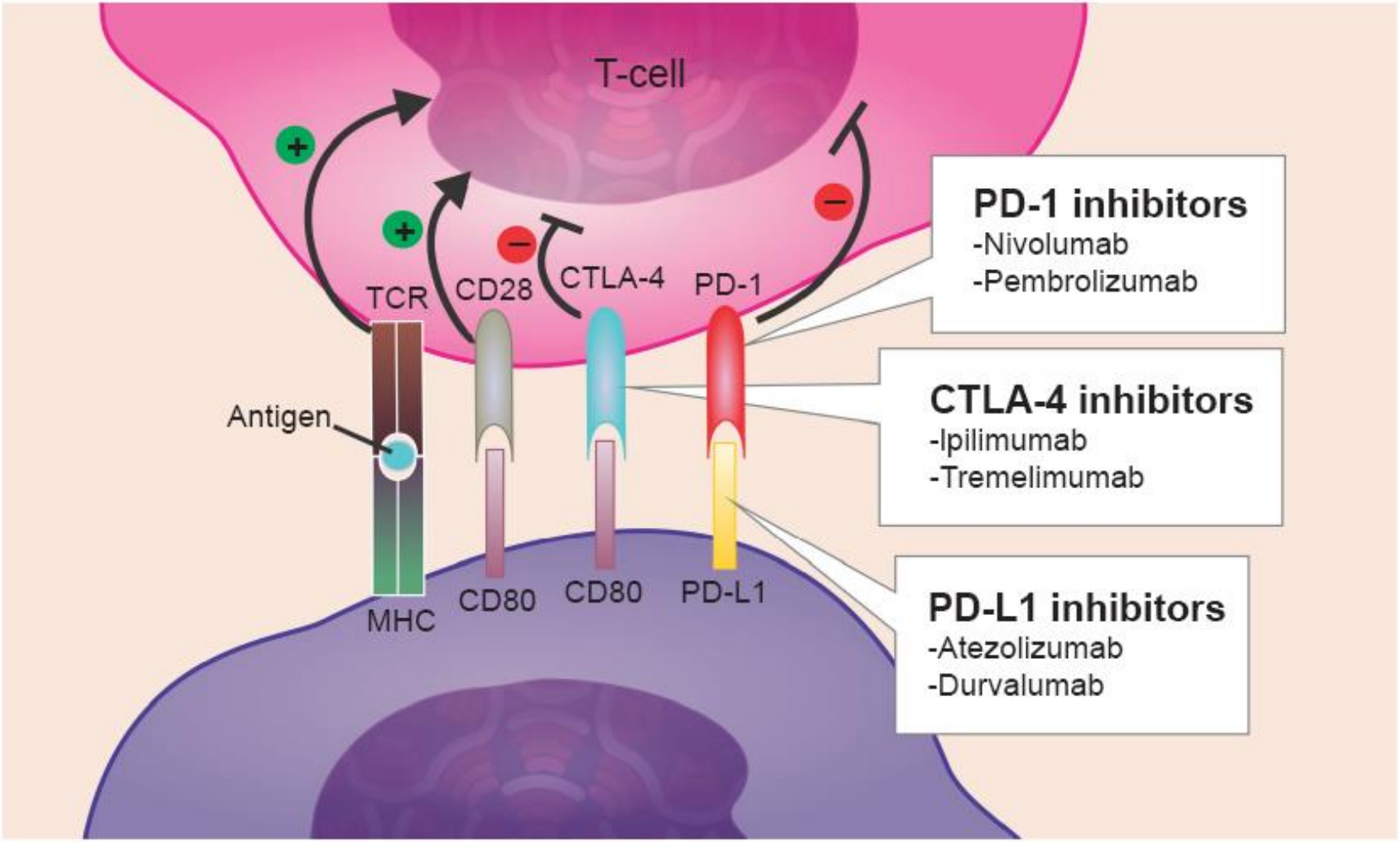
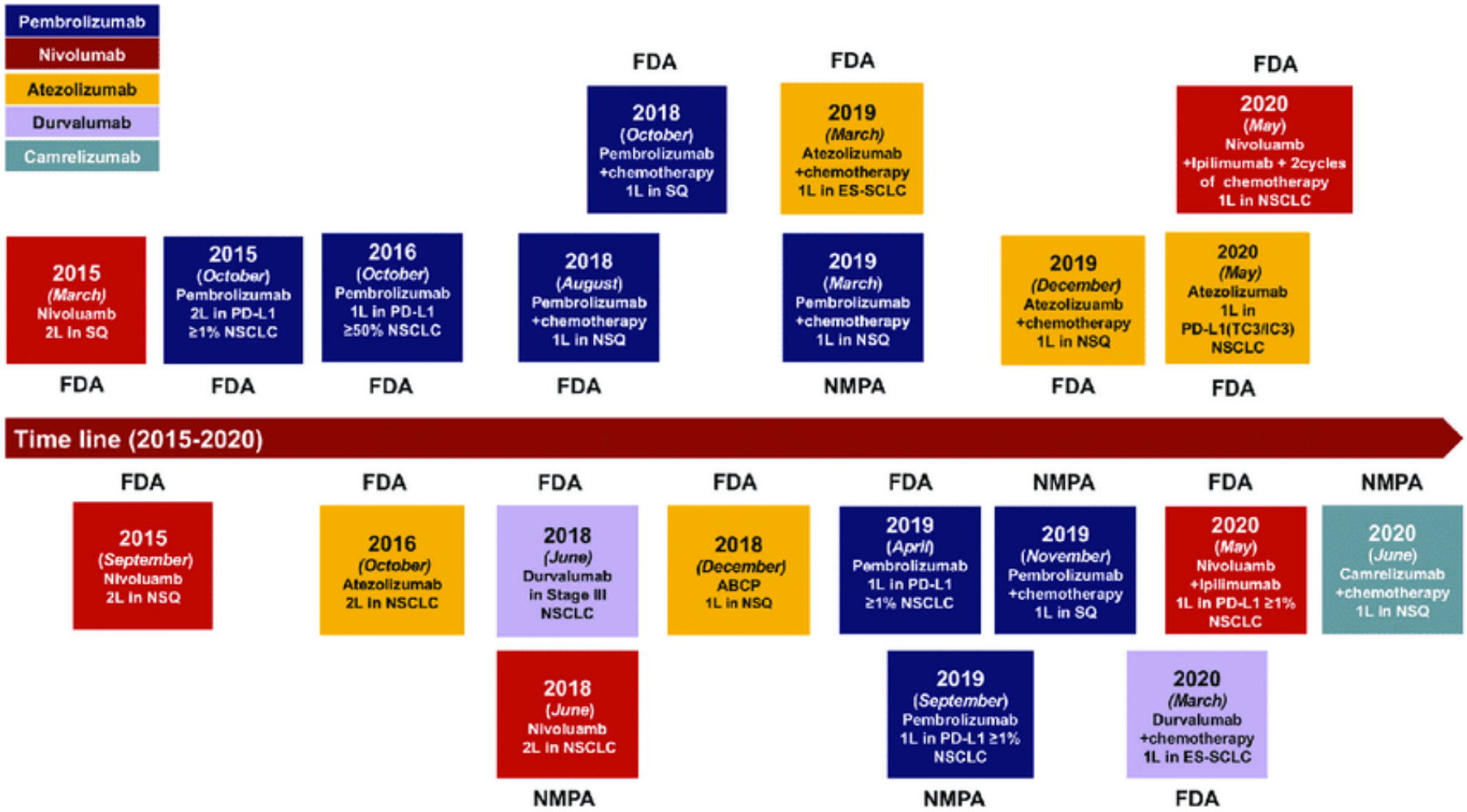
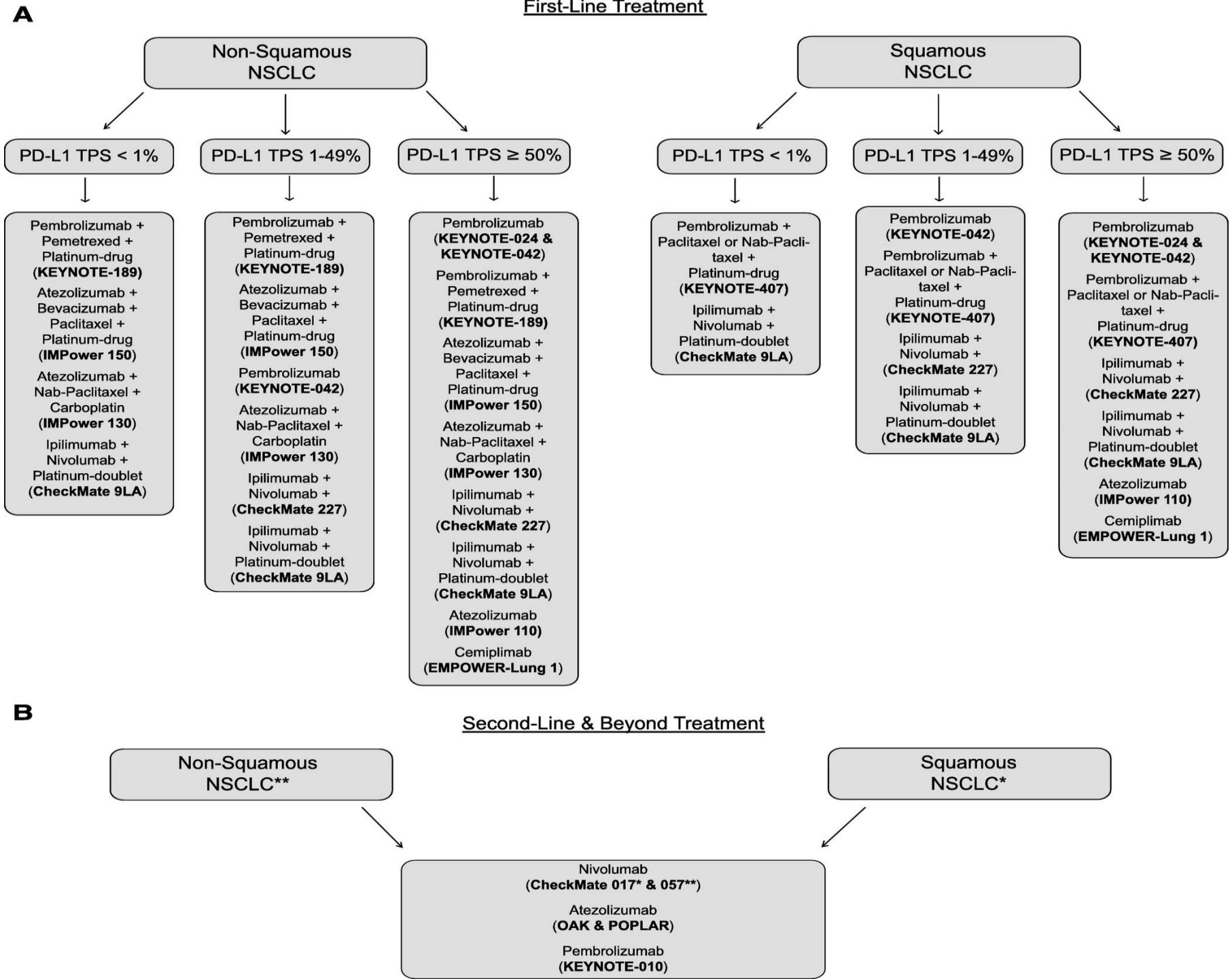


Figure 2 Mechanism of action of immune checkpoint inhibitors.

Notes: T_{regs} depend on the activity of CTLA-4, PD-1, and PD-L1 to induce immunosuppression. Ipilimumab and tremelimumab are monoclonal antibodies that inhibit CTLA-4, while nivolumab, pembrolizumab, atezolizumab, and durvalumab inhibit PD-1 and PD-L1. These drugs act by reducing immuno checkpoint activity on a T_{reg}-rich microenvironment, thus diminishing tumor evasion.

Abbreviations: T_{regs}, regulatory T-cells; TCR, T-cell receptor; MHC, major histocompatibility complex.


Pembrolizumab
Nivolumab
Atezolizumab
Durvalumab
Camrelizumab
FDA
2018 (October) Pembrolizumab +chemotherapy 1L in SQ
FDA
2019 (March) Atezolizumab +chemotherapy 1L in ES-SCLC
FDA
2020 (May) Nivoluamb +Ipilimumab + 2cycles of chemotherapy 1L in NSCLC
2015 (March) Nivoluamb 2L in SQ
FDA
2015 (October) Pembrolizumab 2L in PD-L1 ≥1% NSCLC
FDA
2016 (October) Pembrolizumab 1L in PD-L1 ≥50% NSCLC
FDA
2018 (August) Pembrolizumab +chemotherapy 1L in NSQ
FDA
2019 (March) Pembrolizumab +chemotherapy 1L in NSQ
NMPA
2019 (December) Atezolizuamb +chemotherapy 1L in NSQ
FDA
2020 (May) Atezolizumab 1L in PD-L1(TC3/IC3) NSCLC
FDA
Time line (2015-2020)
FDA
2015 (September) Nivoluamb 2L in NSQ
FDA
2016 (October) Atezolizumab 2L in NSCLC
FDA
2018 (June) Durvalumab in Stage III NSCLC
FDA
2018 (December) ABCP 1L in NSQ
FDA
2019 (April) Pembrolizumab 1L in PD-L1 ≥1% NSCLC
NMPA
2019 (November) Pembrolizumab +chemotherapy 1L in SQ
FDA
2020 (May) Nivoluamb +Ipilimumab 1L in PD-L1 ≥1% NSCLC
NMPA
2020 (June) Camrelizumab +chemotherapy 1L in NSQ
2018 (June) Nivoluamb 2L in NSCLC
NMPA
2019 (September) Pembrolizumab 1L in PD-L1 ≥1% NSCLC
NMPA
2020 (March) Durvalumab +chemotherapy 1L in ES-SCLC
FDA


A
First-Line Treatment
Non-Squamous NSCLC
PD-L1 TPS < 1%
Pembrolizumab + Pemetrexed + Platinum-drug (KEYNOTE-189)
Atezolizumab + Bevacizumab + Paclitaxel + Platinum-drug (IMPower 150)
Atezolizumab + Nab-Paclitaxel + Carboplatin (IMPower 130)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
PD-L1 TPS 1-49%
Pembrolizumab + Pemetrexed + Platinum-drug (KEYNOTE-189)
Atezolizumab + Bevacizumab + Paclitaxel + Platinum-drug (IMPower 150)
Pembrolizumab (KEYNOTE-042)
Atezolizumab + Nab-Paclitaxel + Carboplatin (IMPower 130)
Ipilimumab + Nivolumab + (CheckMate 227)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
PD-L1 TPS ≥ 50%
Pembrolizumab (KEYNOTE-024 & KEYNOTE-042)
Pembrolizumab + Pemetrexed + Platinum-drug (KEYNOTE-189)
Atezolizumab + Bevacizumab + Paclitaxel + Platinum-drug (IMPower 150)
Atezolizumab + Nab-Paclitaxel + Carboplatin (IMPower 130)
Ipilimumab + Nivolumab + (CheckMate 227)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
Atezolizumab (IMPower 110)
Cemiplimab (EMPOWER-Lung 1)
Squamous NSCLC
PD-L1 TPS < 1%
Pembrolizumab + Paclitaxel or Nab-Paclitaxel + Platinum-drug (KEYNOTE-407)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
PD-L1 TPS 1-49%
Pembrolizumab (KEYNOTE-042)
Pembrolizumab + Paclitaxel or Nab-Paclitaxel + Platinum-drug (KEYNOTE-407)
Ipilimumab + Nivolumab + (CheckMate 227)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
PD-L1 TPS ≥ 50%
Pembrolizumab (KEYNOTE-024 & KEYNOTE-042)
Pembrolizumab + Paclitaxel or Nab-Paclitaxel + Platinum-drug (KEYNOTE-407)
Ipilimumab + Nivolumab + (CheckMate 227)
Ipilimumab + Nivolumab + Platinum-doublet (CheckMate 9LA)
Atezolizumab (IMPower 110)
Cemiplimab (EMPOWER-Lung 1)
B
Second-Line & Beyond Treatment
Non-Squamous NSCLC**
Squamous NSCLC*
Nivolumab (CheckMate 017* & 057**)
Atezolizumab (OAK & POPLAR)
Pembrolizumab (KEYNOTE-010)

NSCLC WITHOUT DRIVER MUTATIONS-TREATMENT

- If Pdl-1 > 50%- Immunotherapy alone
- Treatment is based on good evidence that these pts will respond to immunotherapy alone, can avoid chemo upfront.
- Even in real world setting the at 5 yrs. mark OS is doubled 32 Vs 16% with HR 0.62, Median survival=26 Months

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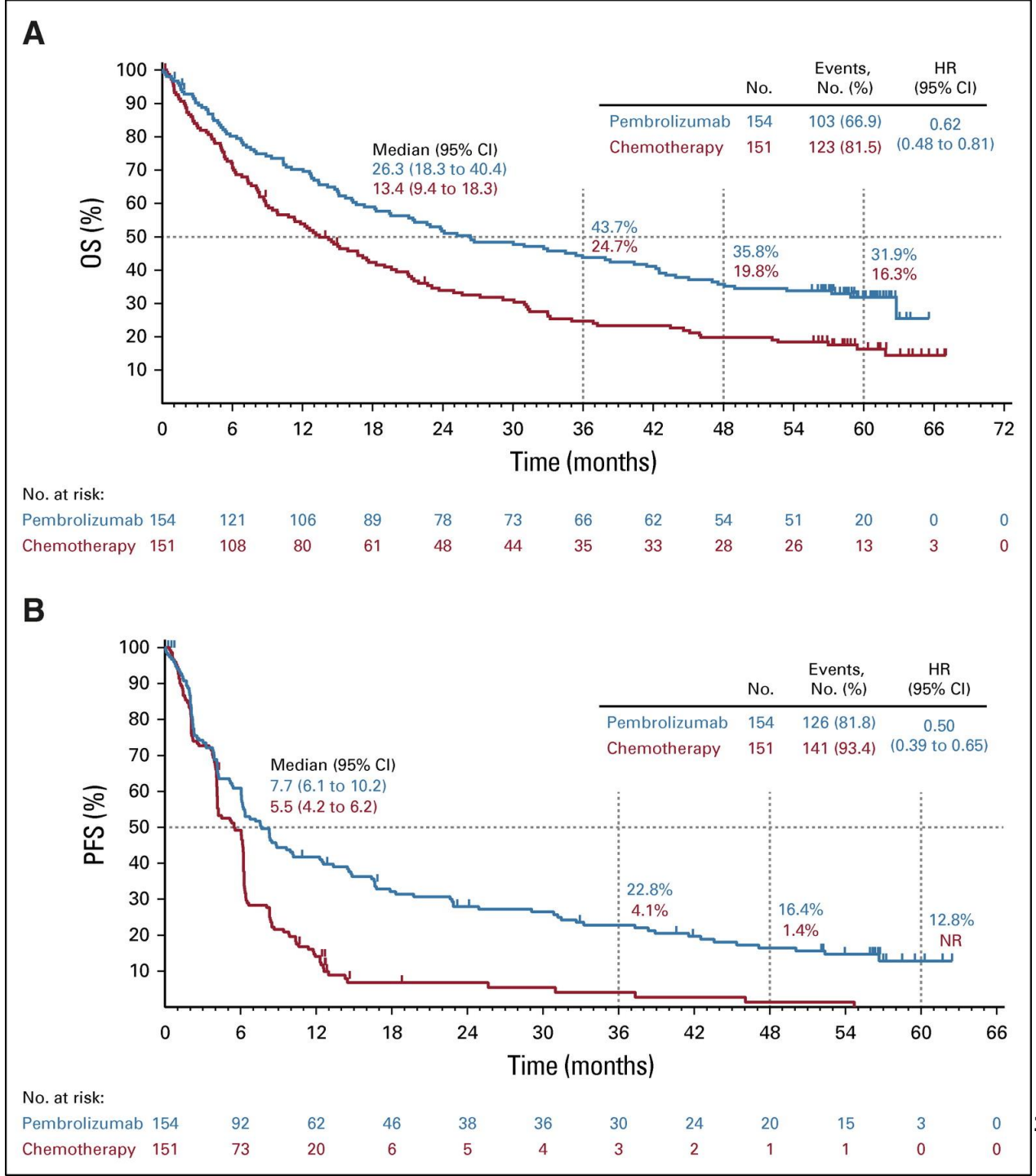
Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%

Journal of Clinical Oncology
Volume 39, Number 21



NSCLC WITHOUT DRIVER MUTATIONS-TREATMENT

- If Pdl-1 is 1-49%- Immunotherapy + chemotherapy combination is used
- Treatment is based on good evidence and patients are living longer.
- various regimens are used with combination followed by maintenance immune therapy+/- chemo based on histology or type of clinical trial

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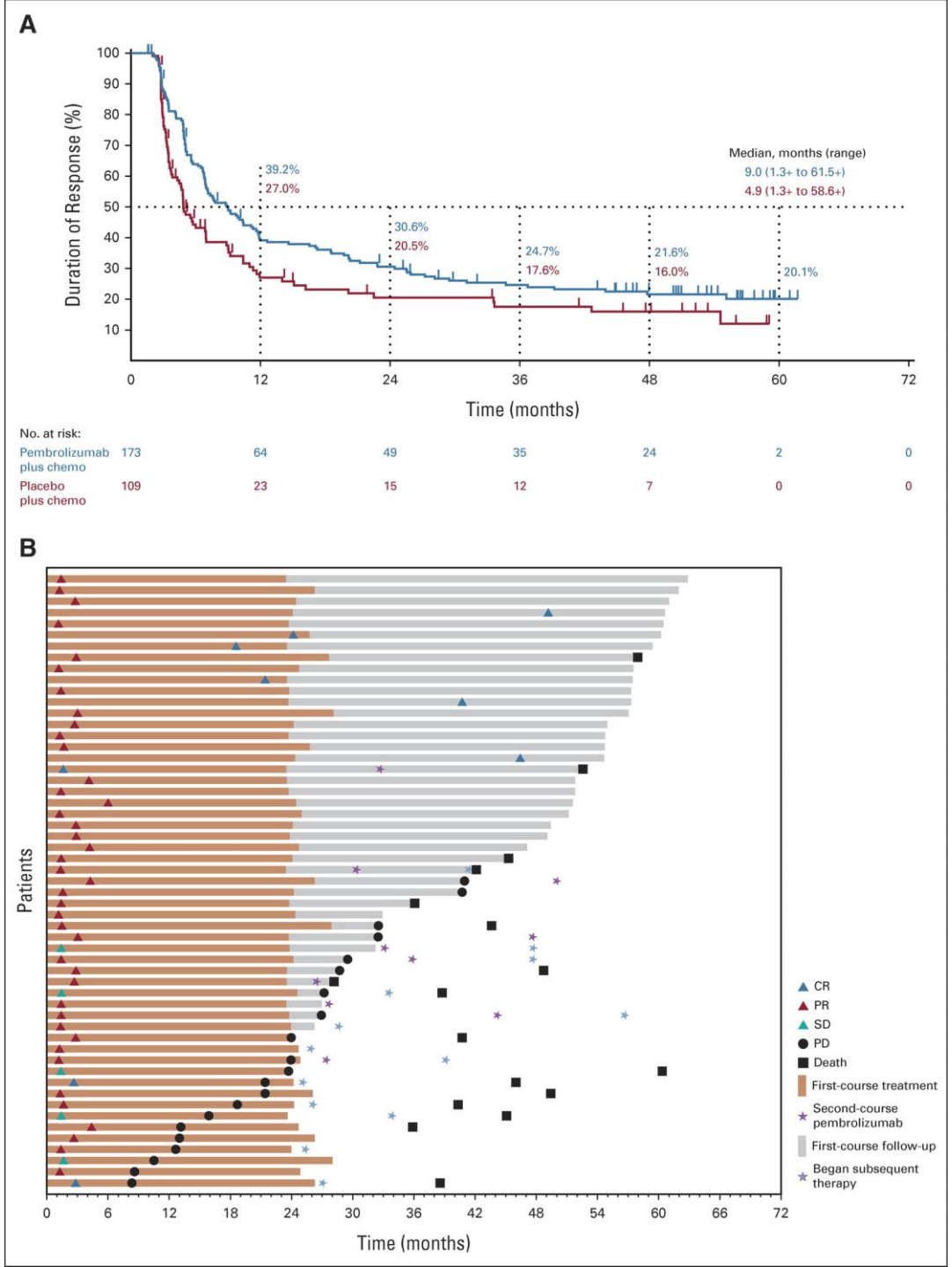
Keynote 407 -5 yrs. update

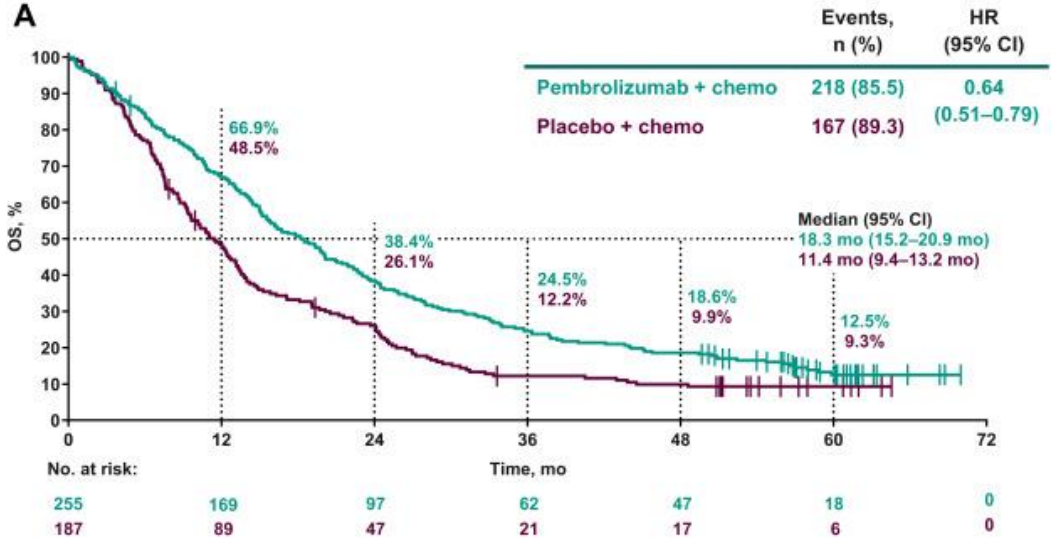
Patients with pdl-1 <50% with squamous NSCLC

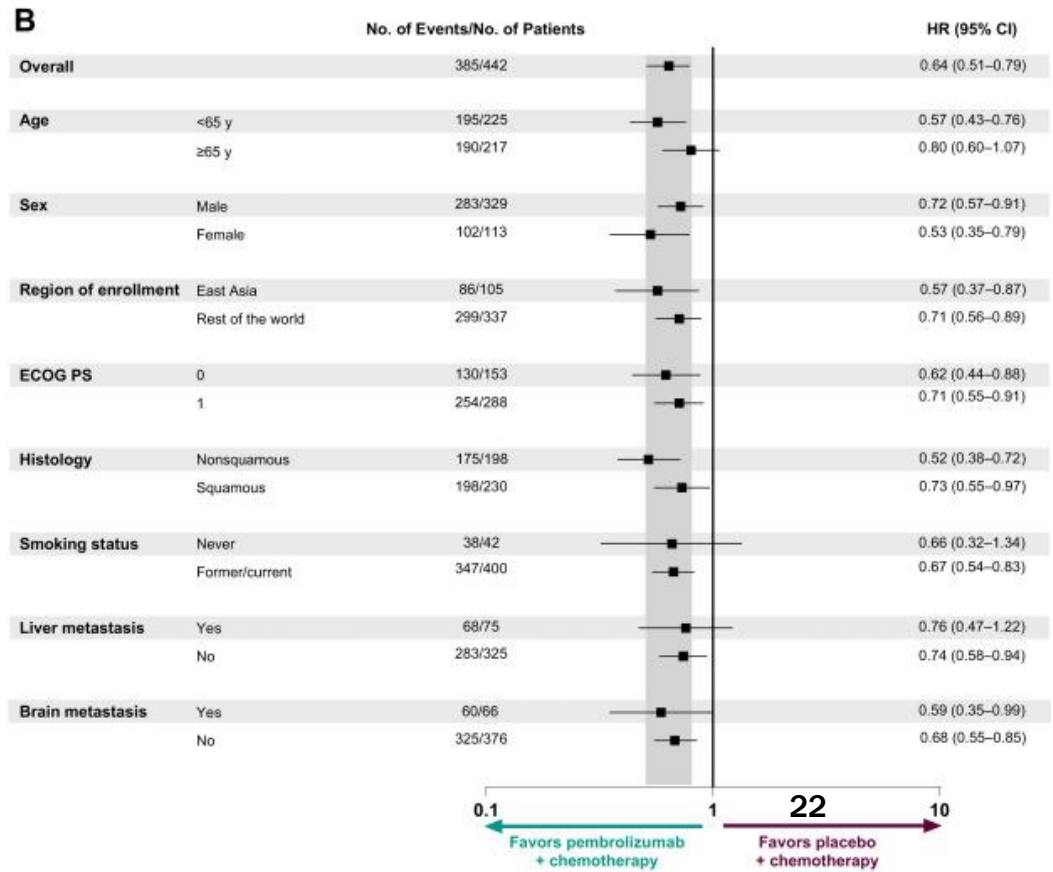
Journal of Clinical Oncology
Volume 41, Number 11



Pembrolizumab Plus Chemotherapy for Metastatic NSCLC With Programmed Cell Death Ligand 1 Tumor Proportion Score Less Than 1%: Pooled Analysis of Outcomes After Five Years of Follow-Up

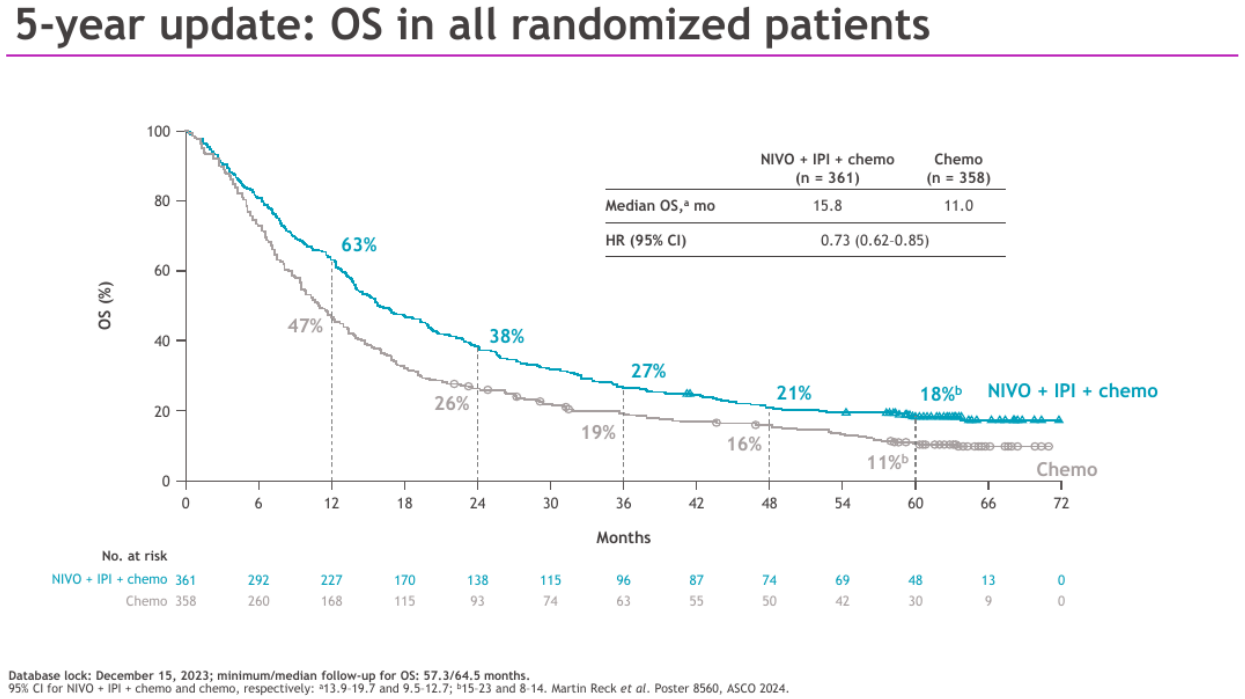
www.jto.org/cms/10.1016/j.jtho.2024.04.011





5 YRS RESULTS OF CHECKMATE 9LA-

WHERE ONLY 2 CYCLES OF CHEMO WERE USED FOLLOWED WITH IMMUNOTHERPY COMBINATION



5-year OS rates, 18% vs. 11%), regardless of tumor programmed death ligand 1 (PD-L1) expression (PD-L1 < 1%, 22% vs. 8%;

histology (squamous, 18% vs. 7%; non-squamous, 19% vs. 12%),

presence of baseline brain metastases (20% vs. 6%).

NSCLC WITHOUT DRIVER MUTATIONS- EARLY STAGE TREATMENT

- After a big success in advanced stage there are several trials done in earlier stage to try to cure the more lung cancer patients
- With adjuvant chemotherapy in resected NSCLC from stage IB-IIIA absolute benefit was only 5%
- By offering chemo and immunotherapy combination upfront before surgery (neoadjuvant) or after surgery (adjuvant) benefit is much bigger.

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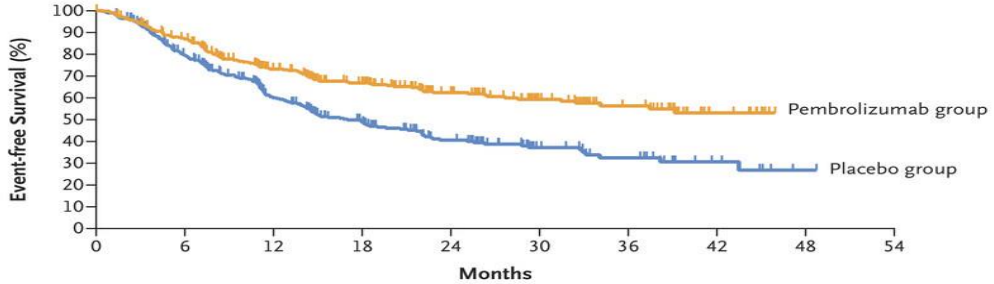
A Event-free Survival

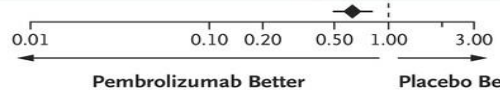


No. at Risk

Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0

B Subgroup Analysis of Event-free Survival

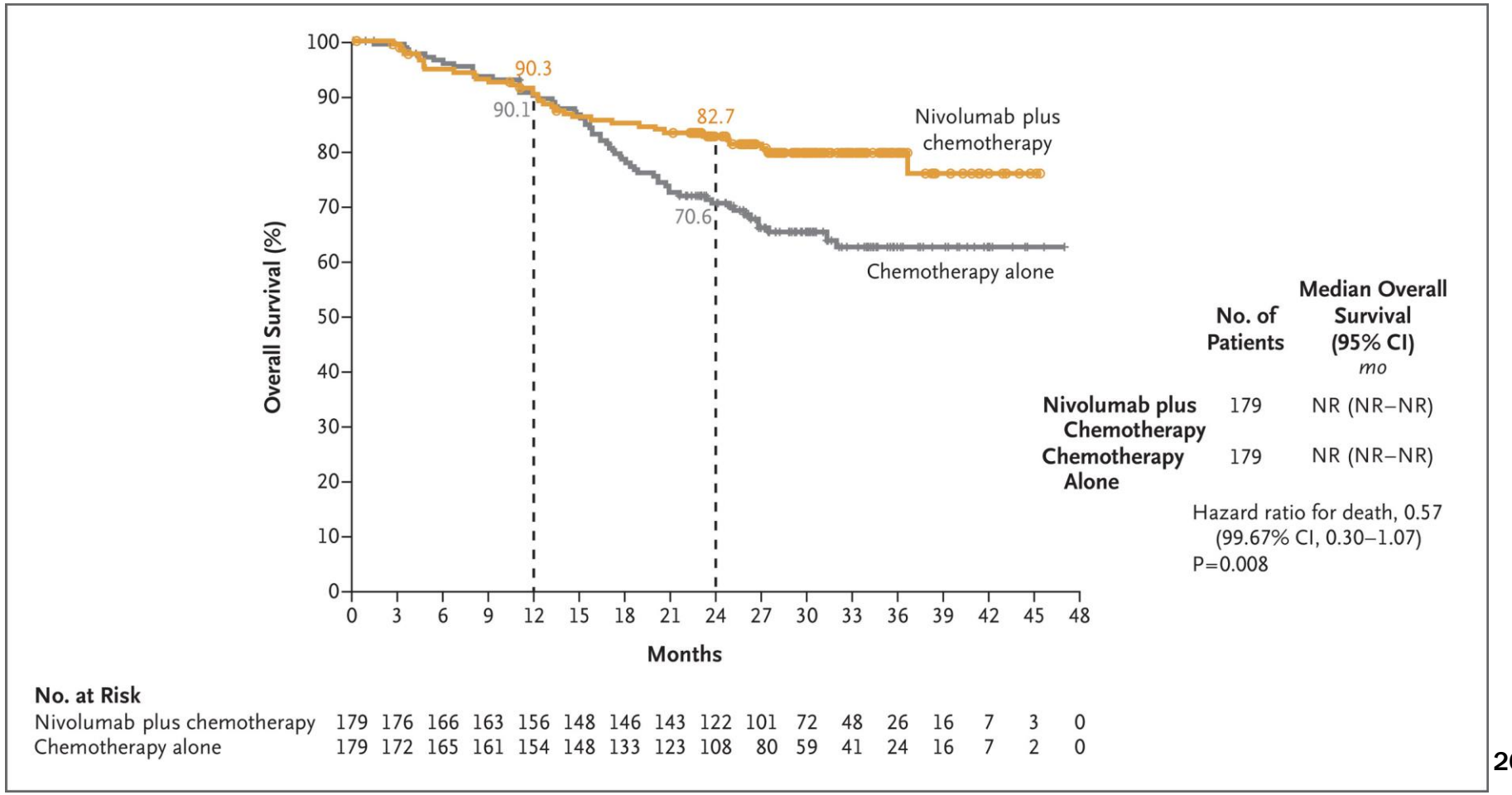
Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)
	no. of events/no. of participants		
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	65/176	92/186	0.64 (0.46–0.88)
Sex			
Female	31/118	55/116	0.44 (0.28–0.68)
Male	108/279	150/284	0.63 (0.49–0.80)
Race			
White	85/250	123/239	0.54 (0.41–0.72)
Other	46/134	70/145	0.62 (0.42–0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45–0.99)
Other	96/274	148/279	0.54 (0.41–0.69)
Smoking status			
Current smoker	37/96	57/103	0.52 (0.34–0.78)
Former smoker	84/247	128/250	0.57 (0.43–0.75)
Never smoked	18/54	20/47	0.68 (0.36–1.30)
Pathological stage			
II	34/118	48/121	0.65 (0.42–1.01)
III	105/279	157/279	0.54 (0.42–0.70)
Histologic features			
Nonsquamous	73/226	107/227	0.58 (0.43–0.78)
Squamous	66/171	98/173	0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)
EGFR mutation			
No	31/111	64/127	0.48 (0.31–0.74)
Yes	1/14	10/19	0.09 (0.01–0.74)
Unknown	107/272	131/254	0.64 (0.49–0.83)
ALK translocation			
No	29/104	76/133	0.41 (0.26–0.62)
Unknown	106/281	128/258	0.63 (0.49–0.82)



Are we achieving cure ?

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer (Checkmate 816)

3 cycles of chemo and immunotherapy given before surgery after 2 yrs. of f/u.



NSCLC WITH DRIVER MUTATIONS- EARLY STAGE TREATMENT

- After a big success in advanced stage can we achieve more in this setting?
- Trials are done with adjuvant Osimertinib for EGFR mutated early stage lung ca
- Trials are done for ALK mutated early stage NSCLC with alectinib

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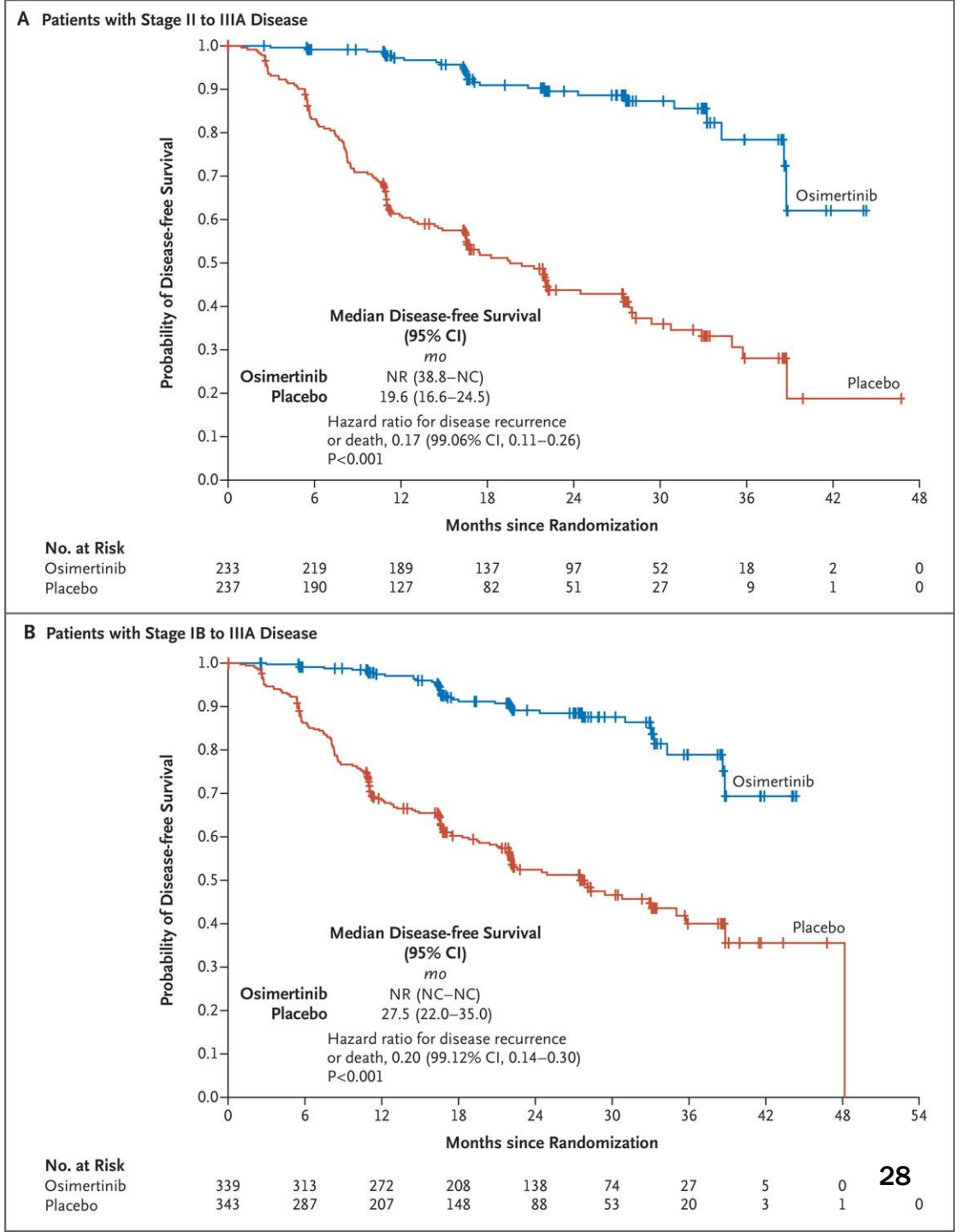
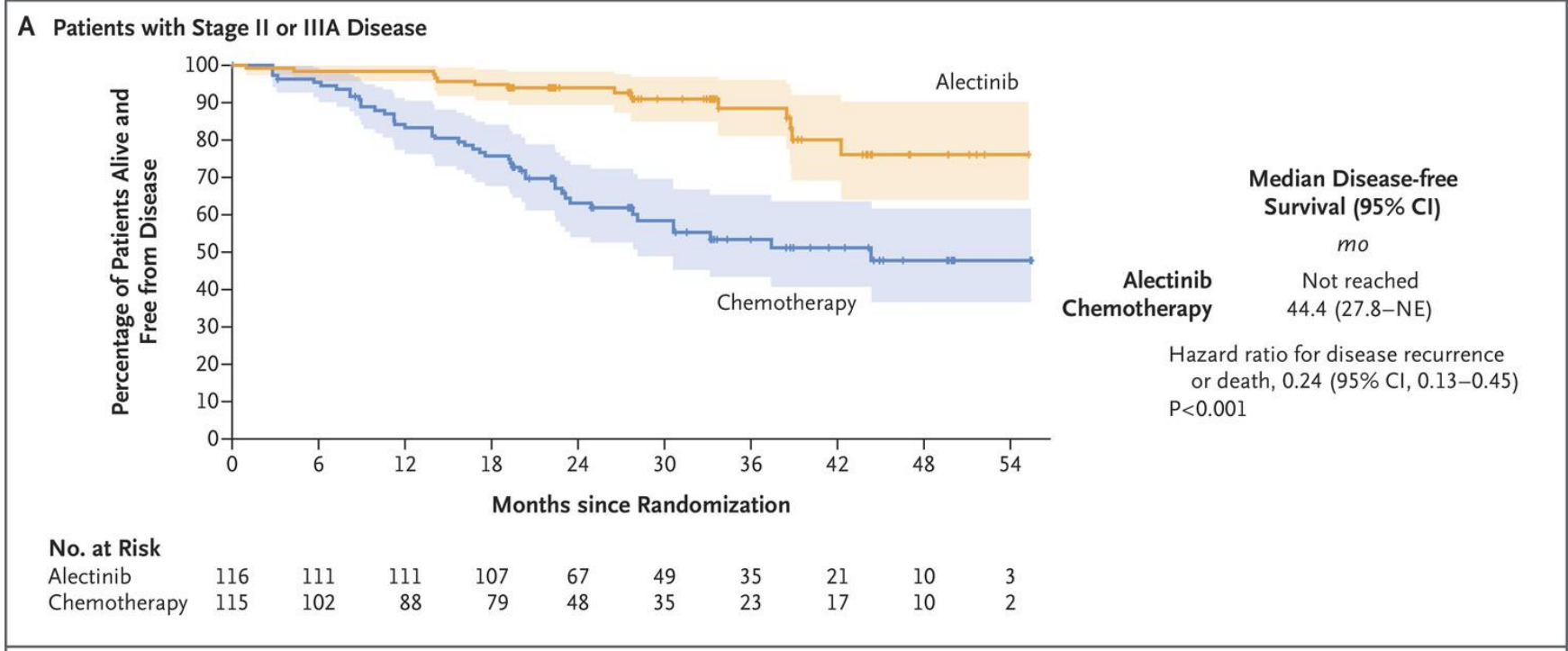
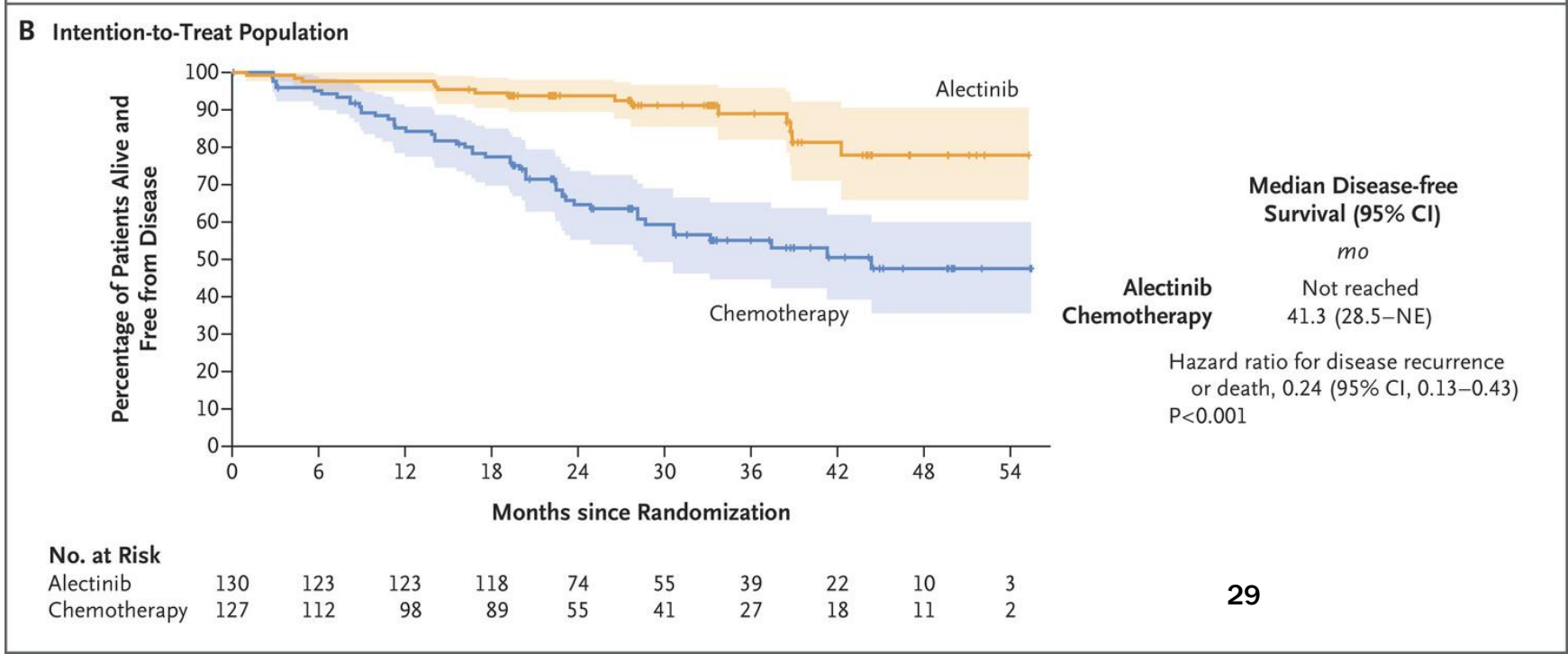
Adaura trial with adjuvant Osimertinib with EGFR mutated early stage NSCLC after surgery



Alina trial-with adjuvant Alectinib in ALK positive early stage NSCLC

Received adjuvant po Alectinib





SCLC – TREATMENT FOR ADVANCED AND LIMITED STAGE DISEASE

- Is there anything for this difficult to treat cancer?
- Yes- Durvalumab in extensive stage SCLC did show benefit in this tough to treat disease
- More recently durvalumab has also shown benefit in early stage disease post chemo / RT
- New drug called tarlatamab (bispecific T cell engager or BiTE) is approved for second line setting in advanced stage

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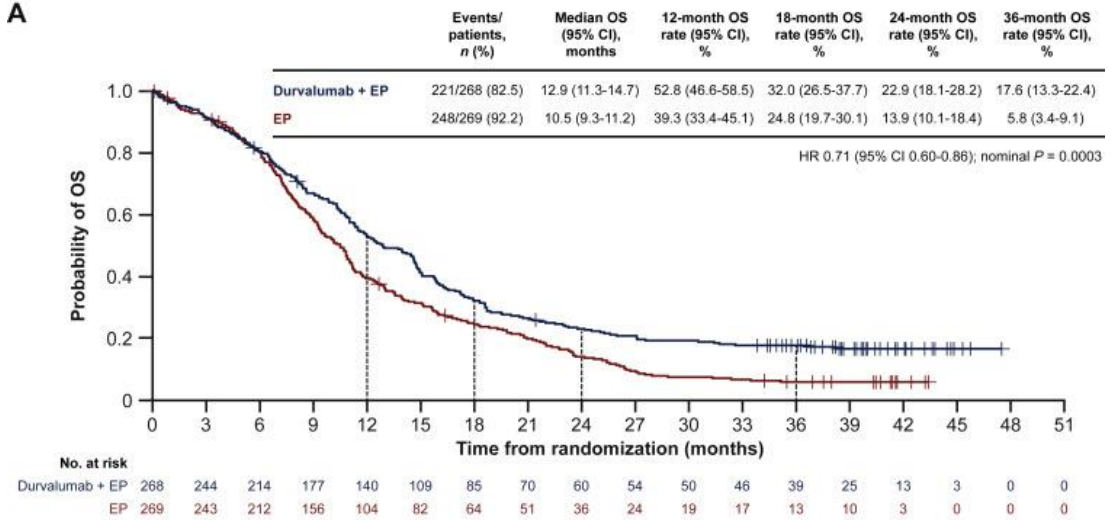
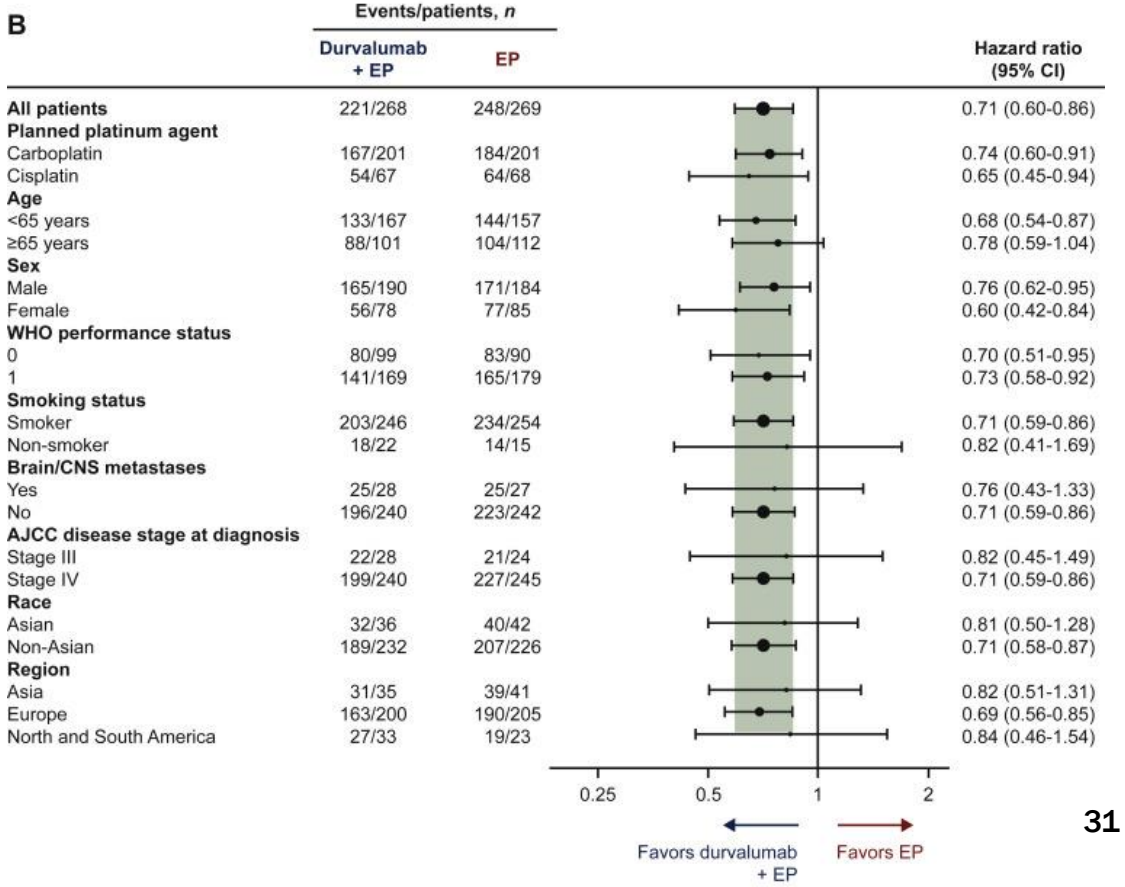
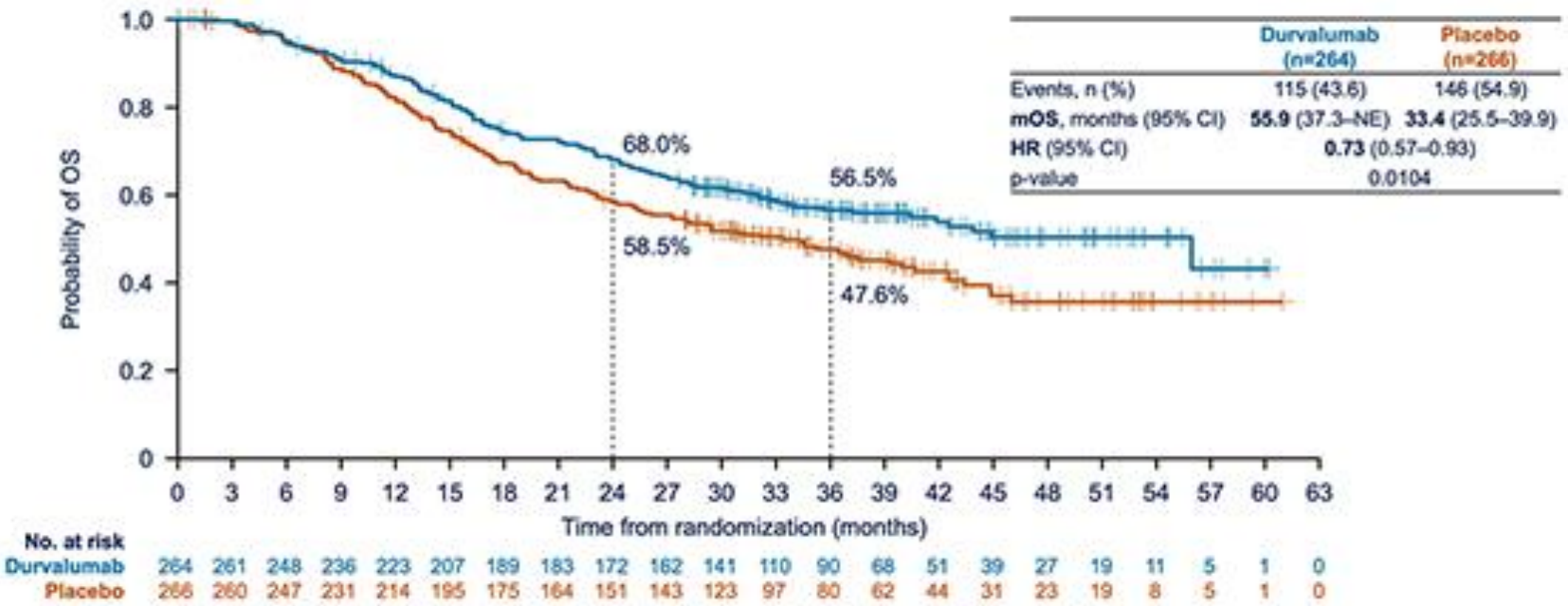
Caspian trial extensive stage SCLC

3 year OS survival updates





Adriatic – Durvalumab as consolidation therapy post chemo RT in limited stage SCLC



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

SUMMARY

- Lung cancer treatment has changed significantly with lots of options for all different subtypes of Lung Cancer.
- Even if they have advanced disease, they have a good chance to control disease longer and achieve better quality of life, with improvement in survival.
- Please do not prognosticate them at the diagnosis, as its difficult. They need to see med onc and need to have a full discussion about newer treatments, which can work wonderfully.
- We are not too far from cure.

Links to ASCO Guideline

1.Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline
Authors: Humera Khurshid, MD, Nofisat Ismaila, MD , Jessica Bian, MD , Raetasha Dabney, MD, Millie Das, MD , Peter Ellis, MD Jill Feldman, BS, MA, Christine Hann, MD, PhD https://orcid.org/0000-0002-1467-5557, Swati Kulkarni, MD, Janessa Laskin, MD, **Publication**: Journal of Clinical Oncology
Volume 41, Number 35

2.Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.2
November 12, 2024

3.Therapy for Stage IV Non–Small Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2023.3
Authors: Ishmael A. Jaiyesimi, MD, MS, Natasha B. Leighl, MD , Nofisat Ismaila, MD , Krishna Alluri, MD , Narjust Florez, MD Shirish Gadgeel, Gregory Masters, MD, Jyoti D. Patel, MD https://orcid.org/0000-0002-7550-2094**AUTHORS INFO & AFFILIATIONS**
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Thank you.