

# Assessing the Evidence for NSCLC Treatment Today

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**BOSNIA AND HERZEGOVINA LUNG HEALTH CONFERENCE**  
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# Conflict of interest (COI)

I have no of conflicts of interest to disclose.

# Content

- Metastatic NSCLC: non-oncogene & oncogene-addicted
- Unresectable stage III NSCLC: how to build on the PACIFIC standard?
- Resectable NSCLC: novel perioperative therapies in the clinic

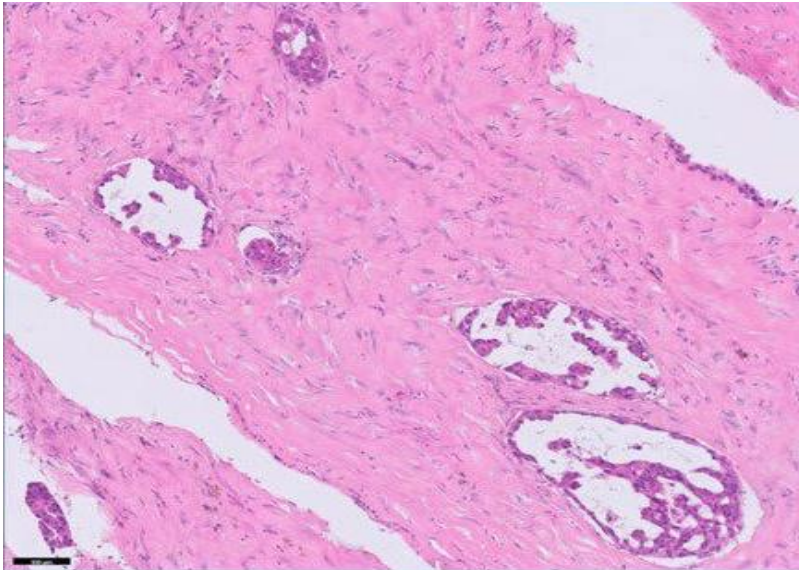
- Metastatic NSCLC

Dual world: non-oncogene & oncogene-addicted

# Dual world of metastatic NSCLC clinical & pathological review

## TARGETED THERAPY Hit the target, not the patient

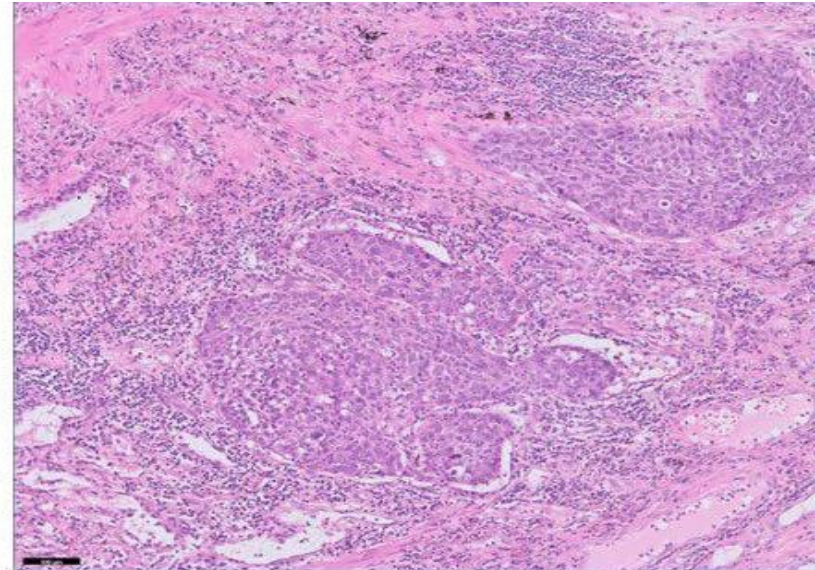
- Mostly adenocarcinoma
- Never/few smokers
- More females
- Good general conditions
- Cold tumor microenvironment (e.g. EGFR and ALK driven tumors)



Pleural biopsy *EGFR*mut+ adenocarcinoma

## IMMUNOTHERAPY Power of the immune system

- All NSCLC histologies
- Heavy smokers
- More males
- Important comorbidity
- Hot tumor microenvironment (especially squamous cell carcinoma)



Bronchial biopsy squamous cell carcinoma

# Dual world of metastatic NSCLC pathological

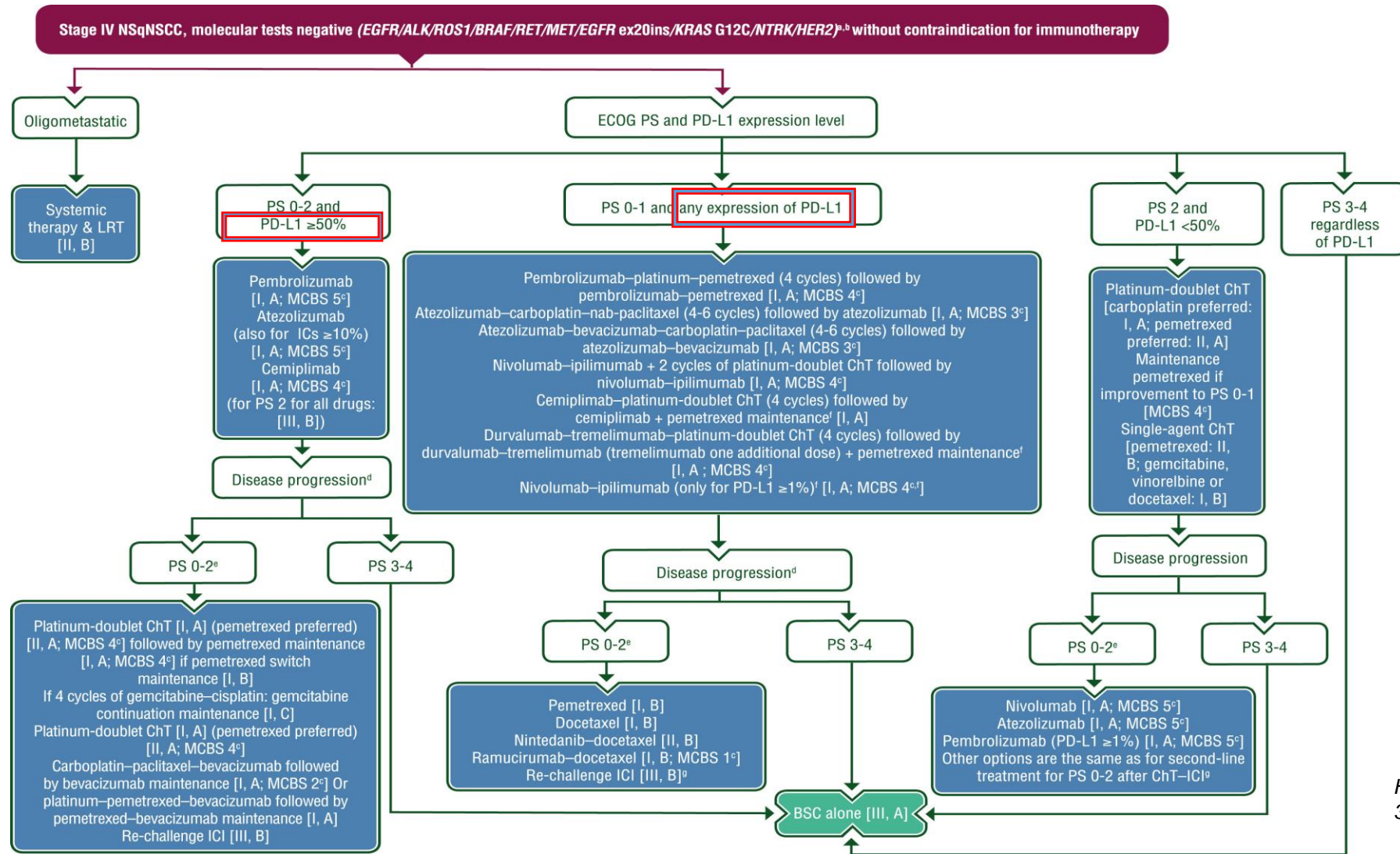
## **Special Articles:**

**Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**

**Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**

Hendriks et al,  
Ann Oncol 34:358-376, 2023  
Ann Oncol 34:339-357, 2023

# Dual world of metastatic NSCLC non-oncogene addicted







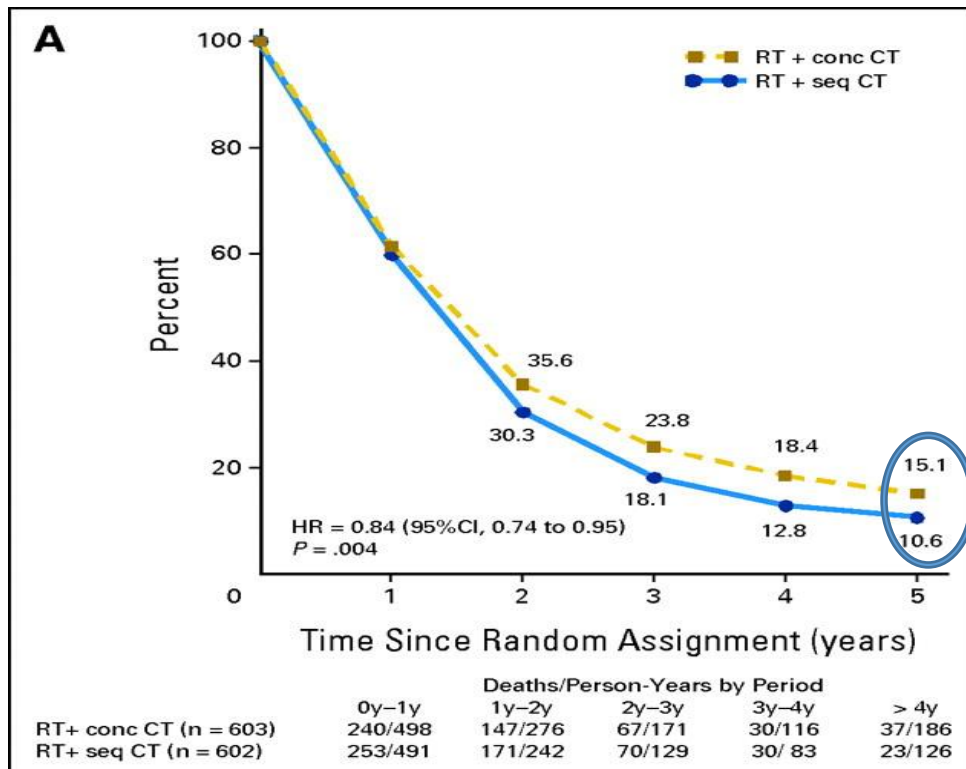
- Unresectable stage III NSCLC

*How to build on the PACIFIC standard?*

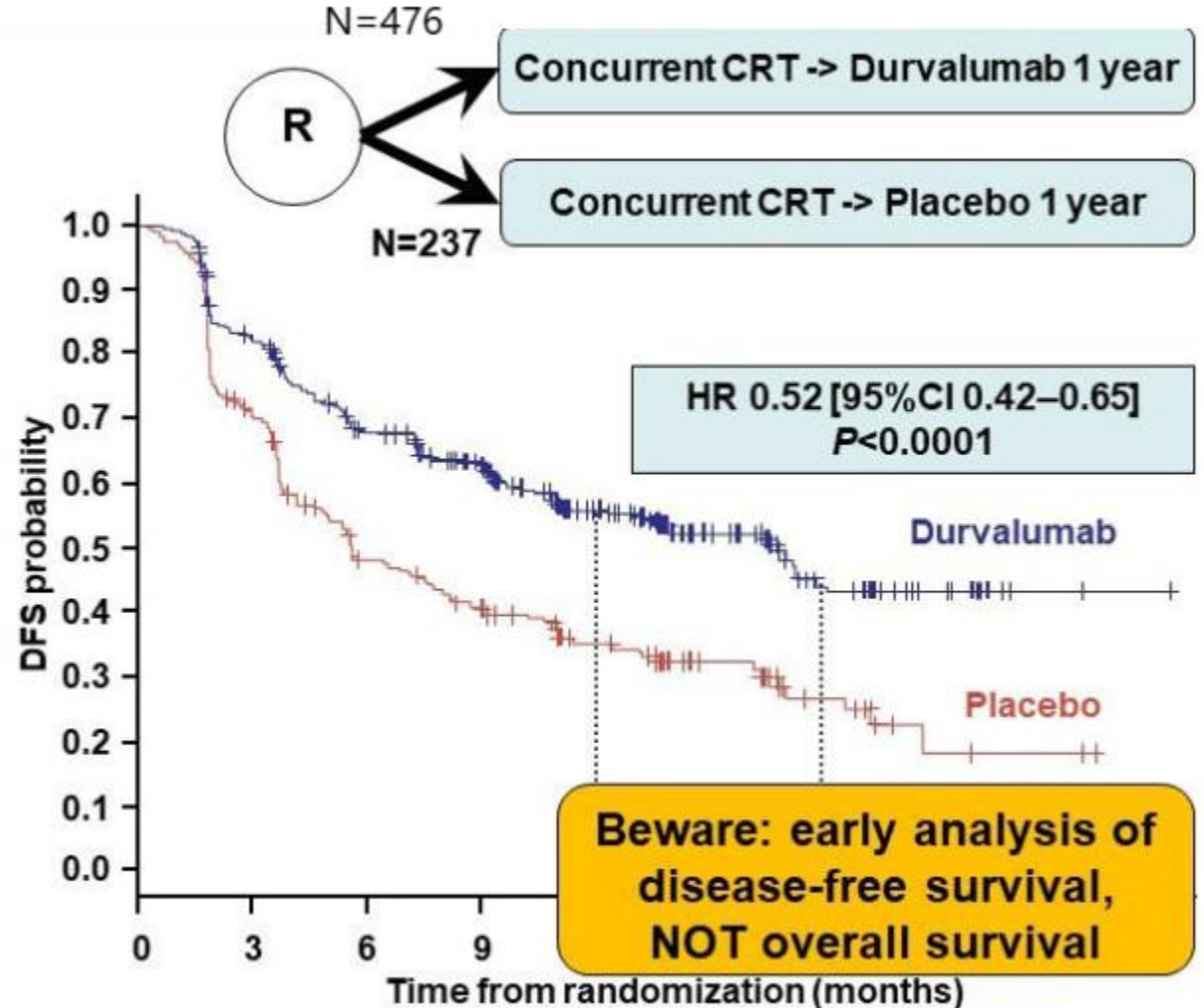
# Unresectable stage III NSCLC

## the PACIFIC progress

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced NSCLC

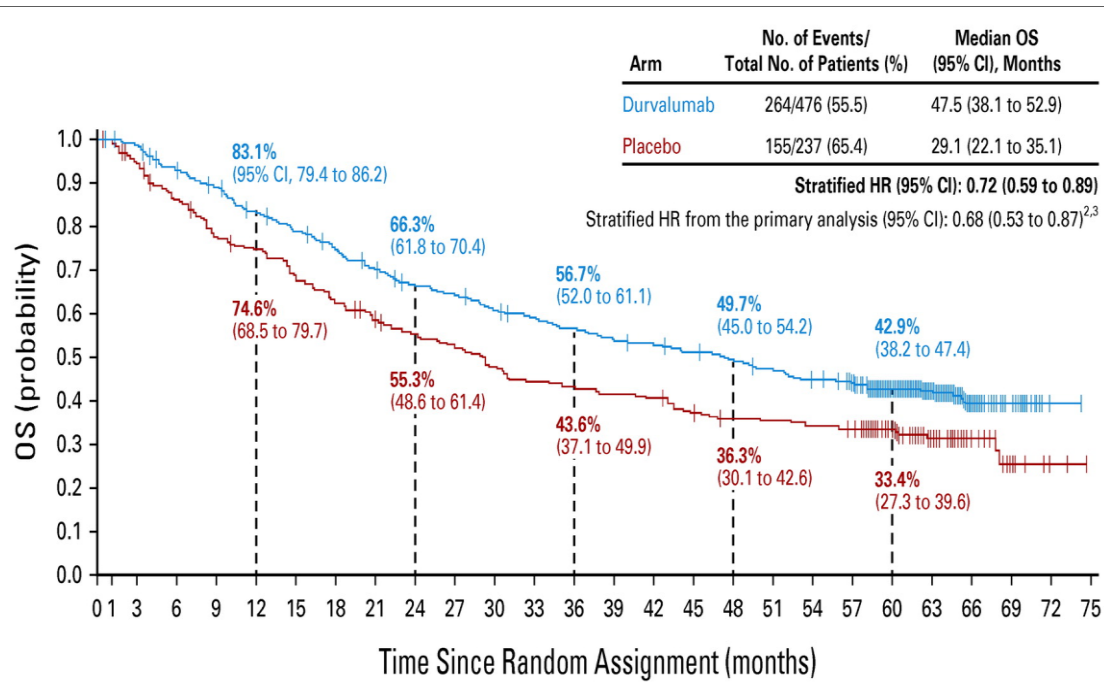


Auperin et al. J Clin Oncol 2010; 28(13):2181-90.



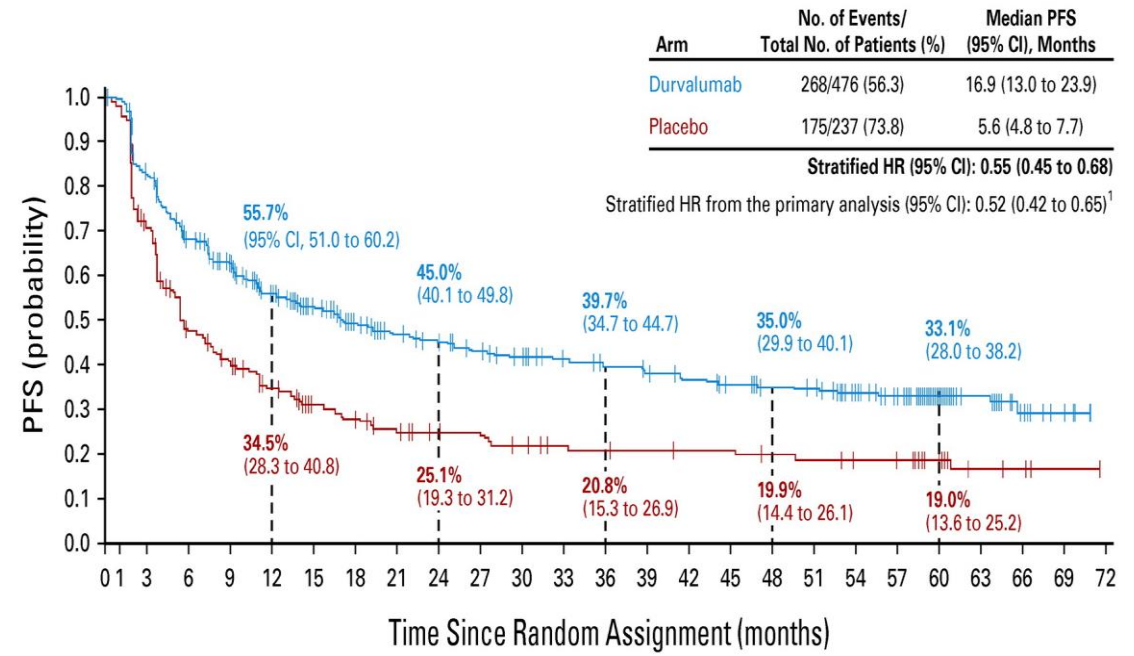
Paz-Ares et al. ESMO 2017.

# Unresectable stage III NSCLC PACIFIC after 5 years



No. at risk:

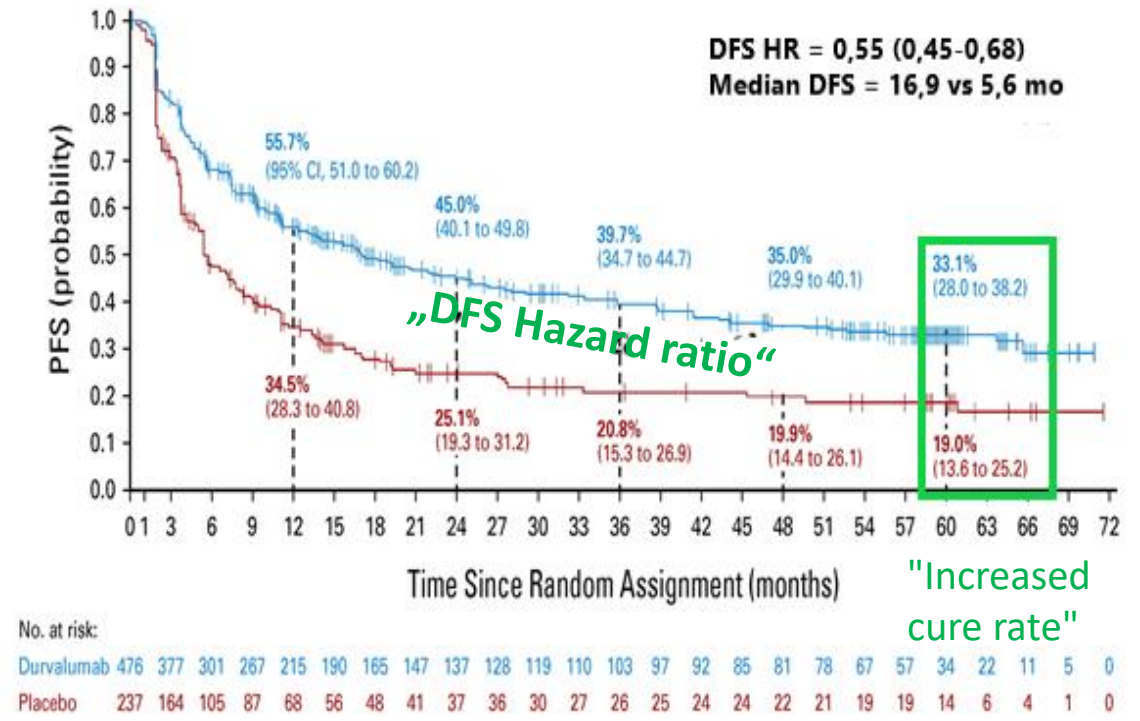
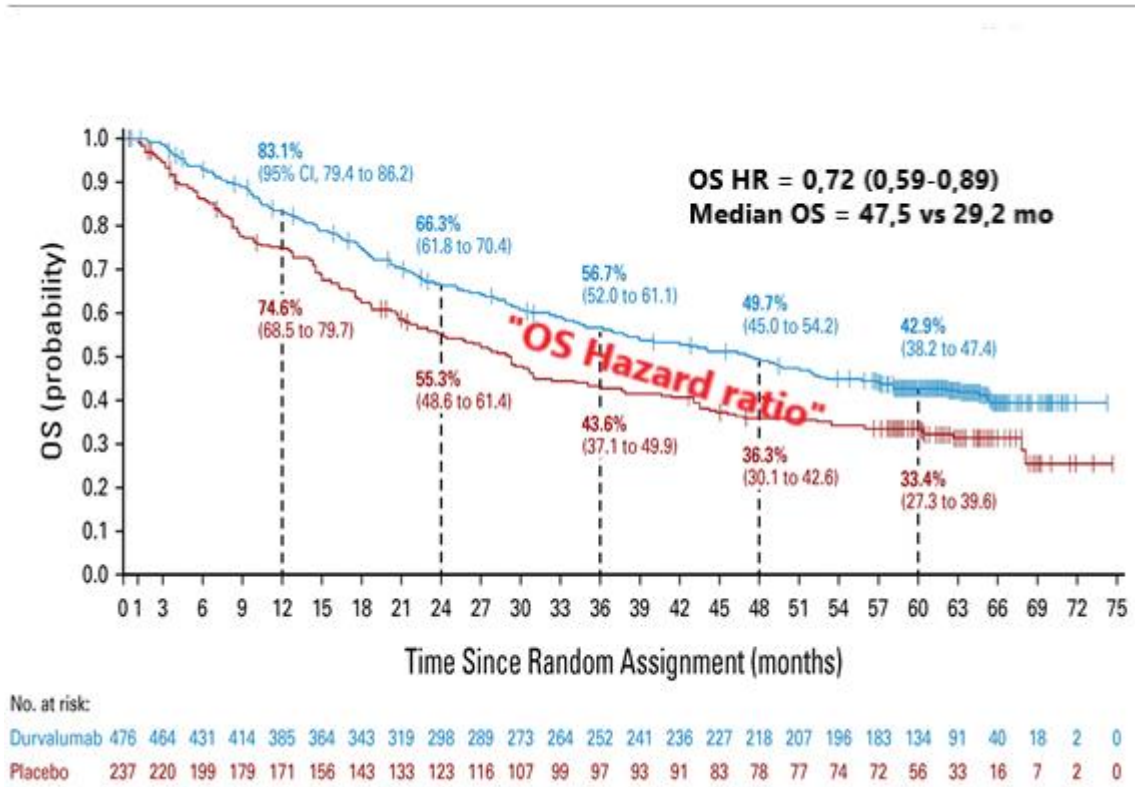
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0



No. at risk:

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

# Unresectable stage III NSCLC lessons from PACIFIC after 5 years



Spigel et al. J Clin Oncol 40: 1303-1311, 2022

# Unresectable stage III NSCLC

## how to build on the PACIFIC standard?

Immunotherapy in unresectable stage III NSCLC: state of the art and novel therapeutic approaches

<b>PACIFIC</b>		<b>Doublet chemotherapy</b> Radiotherapy 60 – 66 Gy	<b>Durvalumab 1 year</b>
<b>CONCURRENT ICI</b>		<b>Doublet chemotherapy</b> Radiotherapy 60 – 66 Gy Immunotherapy	<b>Immunotherapy 1 year</b>
<b>NEOADJUVANT ICI</b>	<b>Immunotherapy</b>	<b>Doublet chemotherapy</b> Radiotherapy 60 – 66 Gy	<b>Immunotherapy 1 year</b>
<b>Combined ICI</b> anti-CTLA4, anti-CD73 anti-NKG2A, anti-TIGIT		<b>Doublet chemotherapy</b> Radiotherapy 60 – 66 Gy	<b>Immunotherapy 1 year</b> <b>Immunotherapy 1 year</b>
<b>De-escalation</b>		<b>Less/No chemotherapy</b> Radiotherapy lower dose	<b>Immunotherapy shorter duration</b>

- Resectable NSCLC  
*Novel perioperative therapies in the clinic*

# Resectable NSCLC

the next wave of progress: (neo)adjuvant therapies



Immuno and target  
therapy in surgical  
NSCLC

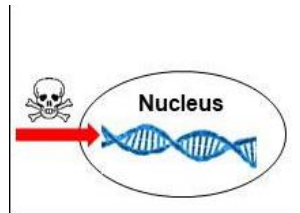
Immuno and target  
therapy in advanced  
NSCLC

# Resectable NSCLC perioperative therapy

## Optimal aim of (neo)adjuvant therapy

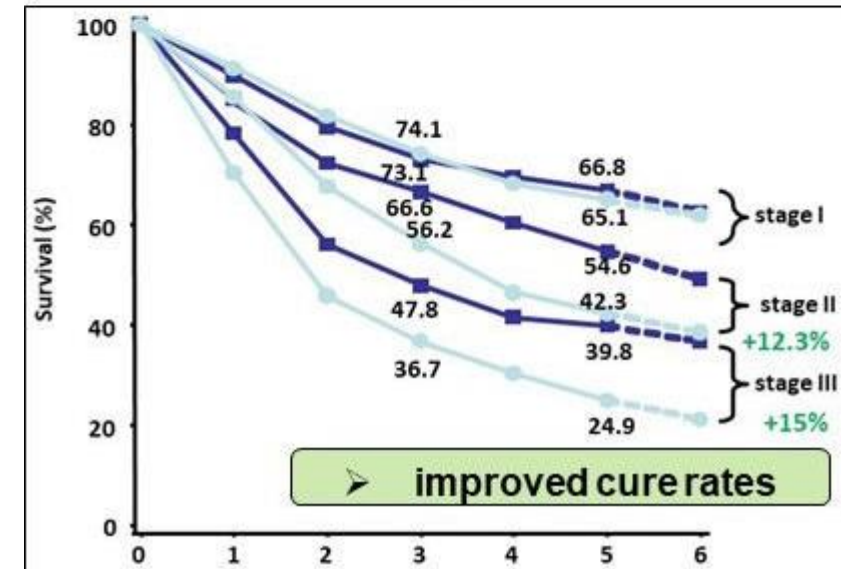
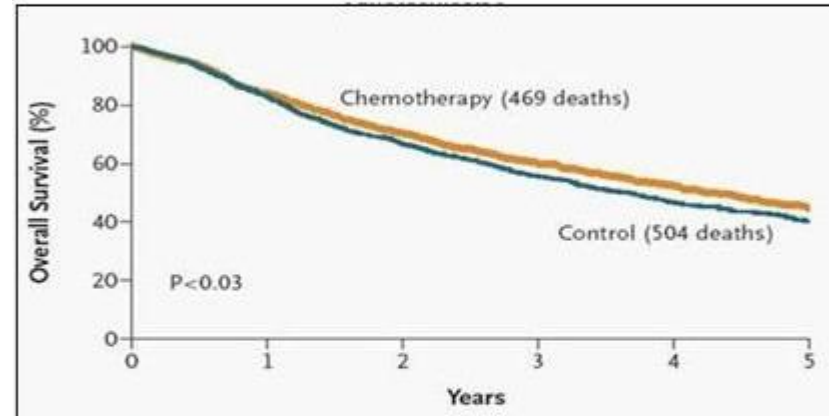
- Eliminate (distant) minimal residual disease
- To improve cure rates ( $\approx 5$  Y OS)
- Along with acceptable safety profile

➤ **Chemotherapy: eliminates MRD**



IALT investigators, N Engl J Med 350:351-360, 2004  
Pignon et al, Ann Oncol 17 Suppl 9:213, 2006  
Pignon et al, J Clin Oncol 26:3552-3559, 2008

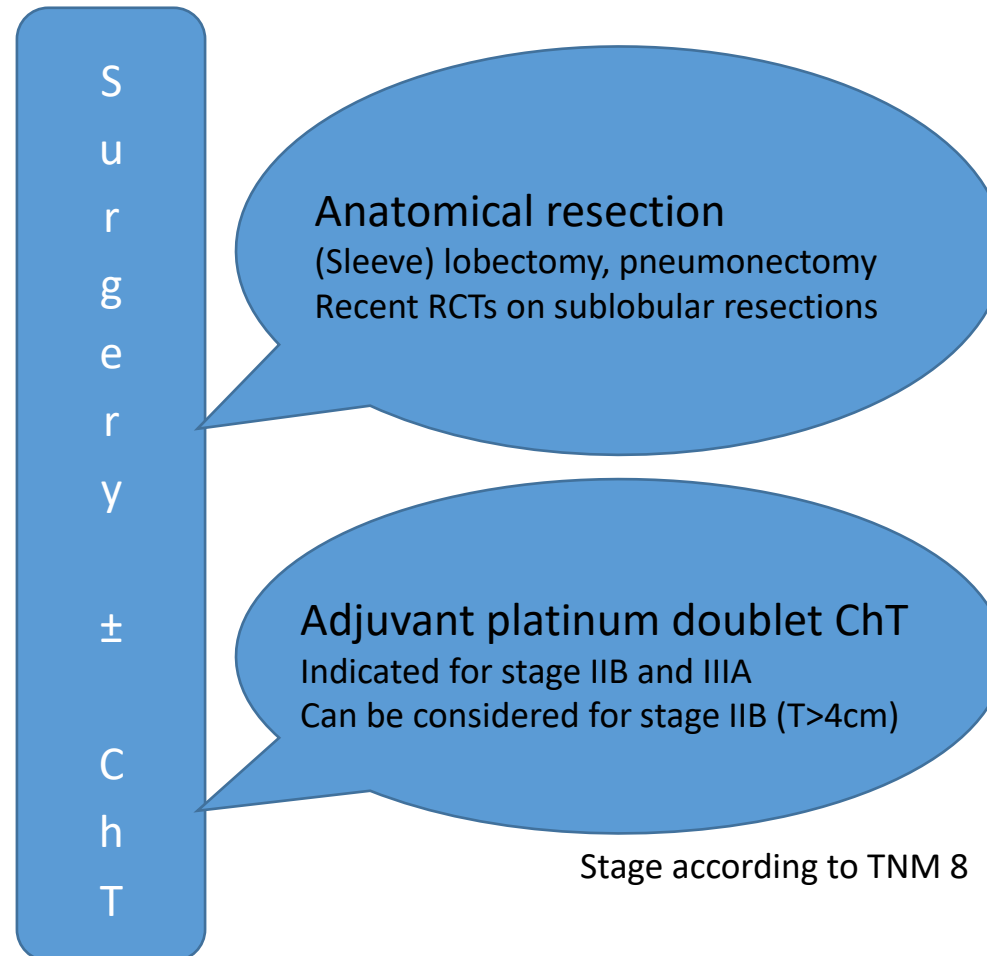
## Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non-Small- Cell Lung Cancer





# Resectable NSCLC state of the art

Early and locally advanced NSCLC:  
ESMO clinical practice guidelines for  
diagnosis, treatment and follow up



# Resectable NSCLC

## RCTs on novel perioperative therapies

- IMpower-10  
vs. observation
- Keynote-091  
placebo controlled
- ADAURA  
placebo controlled

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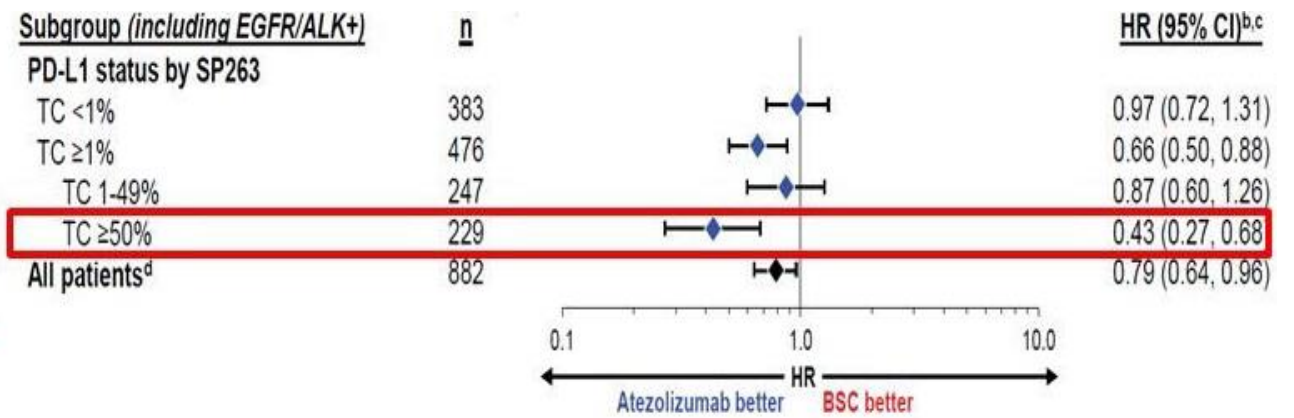
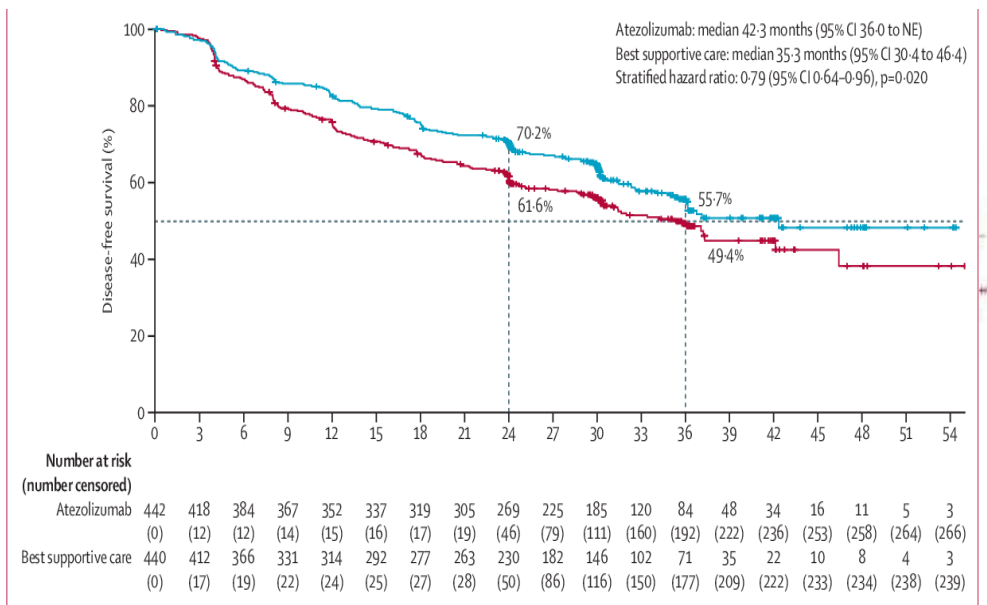
adjuvant

- Chemo th    Atezo for 1 year
- Chemo th recommended    Pembro for 1 year
- Chemo th recommended    Osimertinib up to 3 y

# Resectable NSCLC

## RCTs on adjuvant Atezolizumab

**Stage II – IIIA**  
**HR 0,79 (0,64-0,96) – p=0.02**



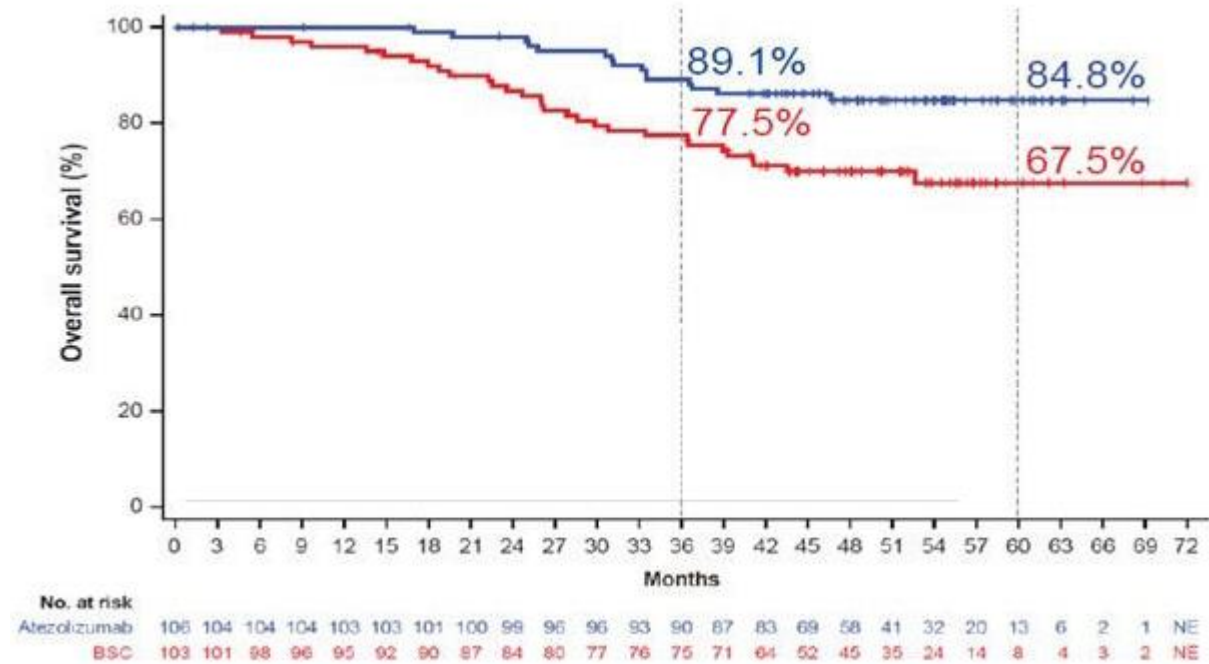
2022 — EMA approved atezolizumab as adjuvant treatment, following complete resection and platinum-based chemotherapy, for NSCLC with PD-L1 ≥50%

# Resectable NSCLC

## RCTs on adjuvant Atezolizumab: 5 y OS\* report

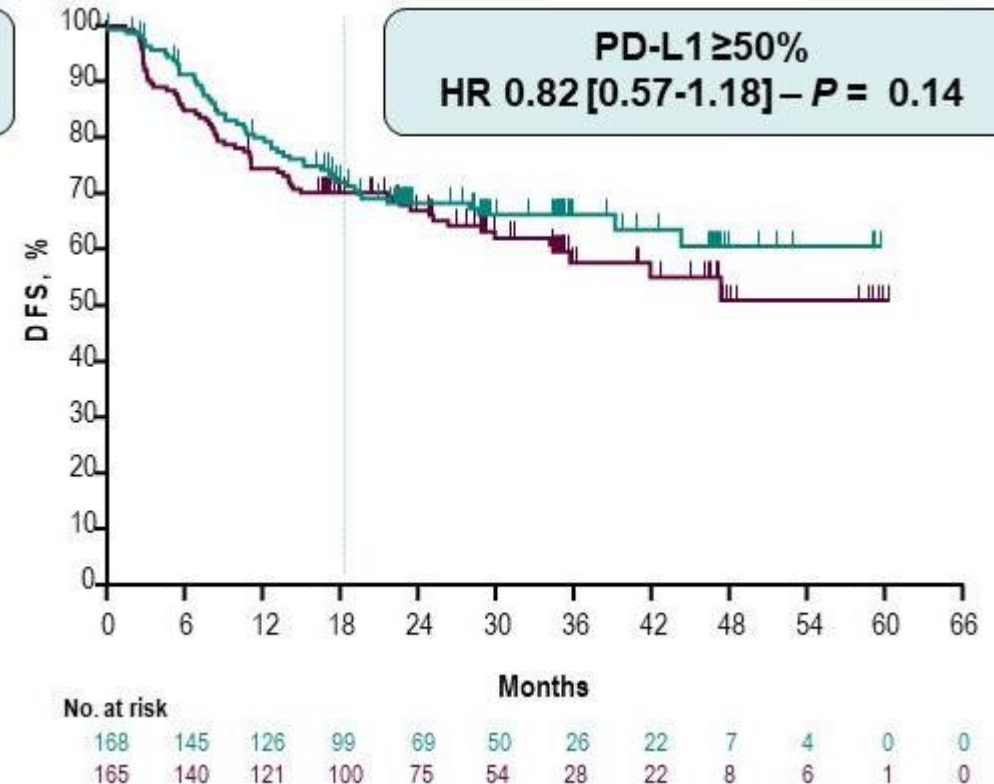
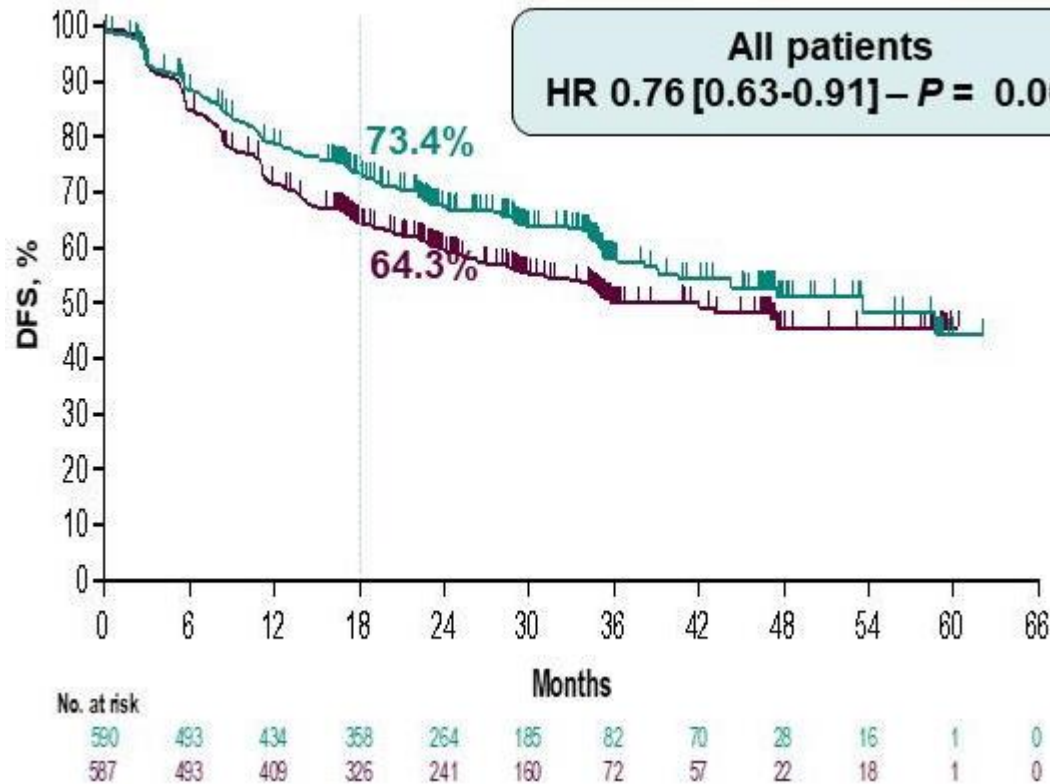
\*follow-up 45 mo [25% maturity]

Stage II-III A & PD-L1  $\geq 50\%$   
HR 0.42 [0.23-0.78]



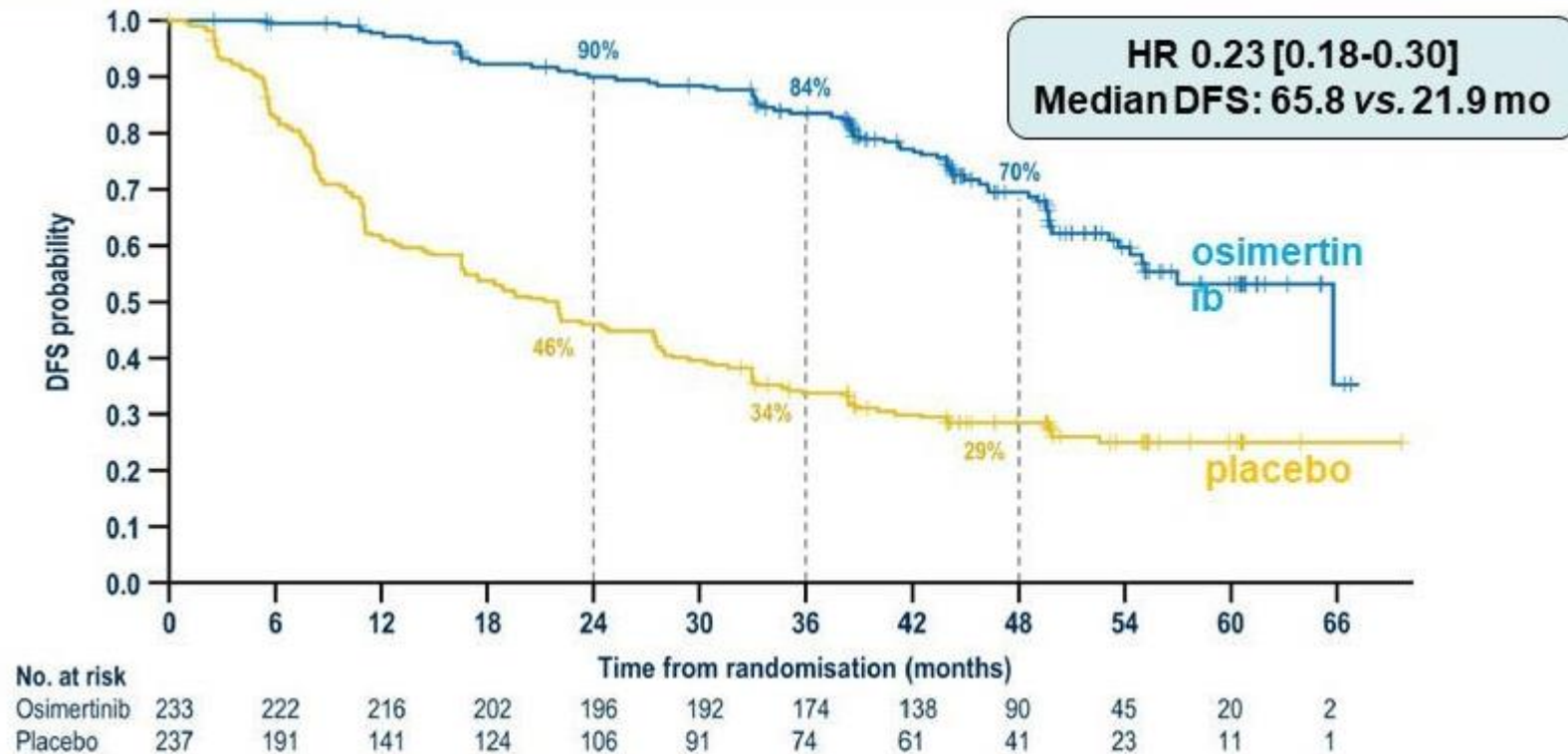
# Resectable NSCLC RCTs on adjuvant Pembrolizumab

\*follow-up 36 mo



# Resectable NSCLC

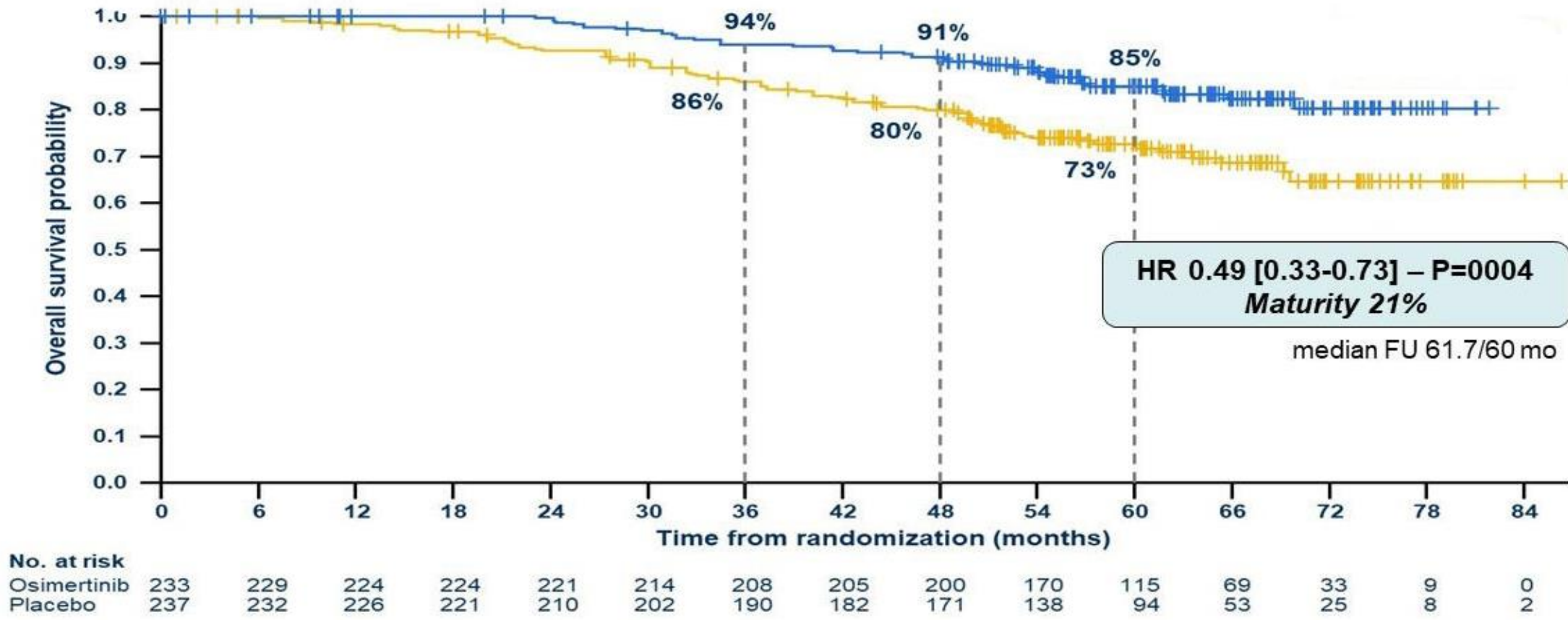
## RCTs on adjuvant Osimertinib in EGFRmut+ resected NSCLC



2022 — EMA approved osimertinib as an adjuvant treatment after complete resection with stage IB-IIIA NSCLC with EGFR exon 19 deletion or exon 21 (L858R) mutation

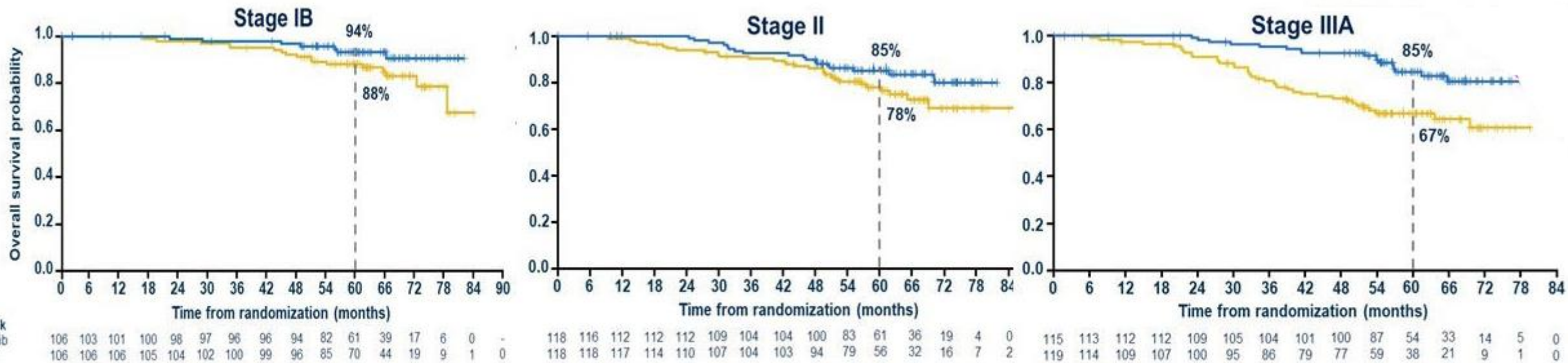
# Resectable NSCLC

## RCTs on adjuvant Osimertinib: OS analysis



# Resectable NSCLC

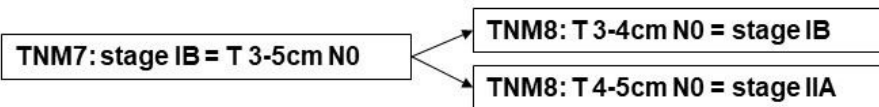
## RCTs on adjuvant Osimertinib: OS analysis



**HR 0.44 [0.17-1.02]**

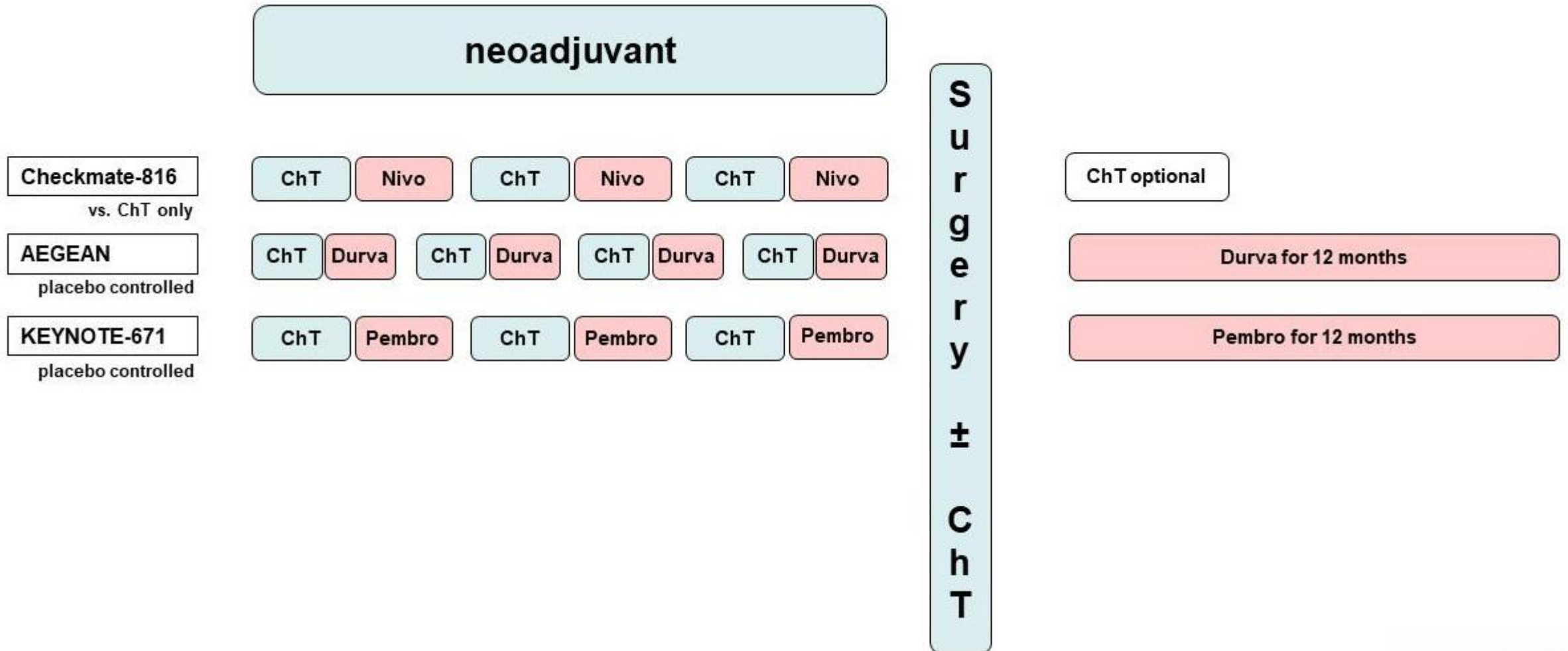
**HR 0.63 [0.34-1.12]**

**HR 0.37 [0.20-0.64]**



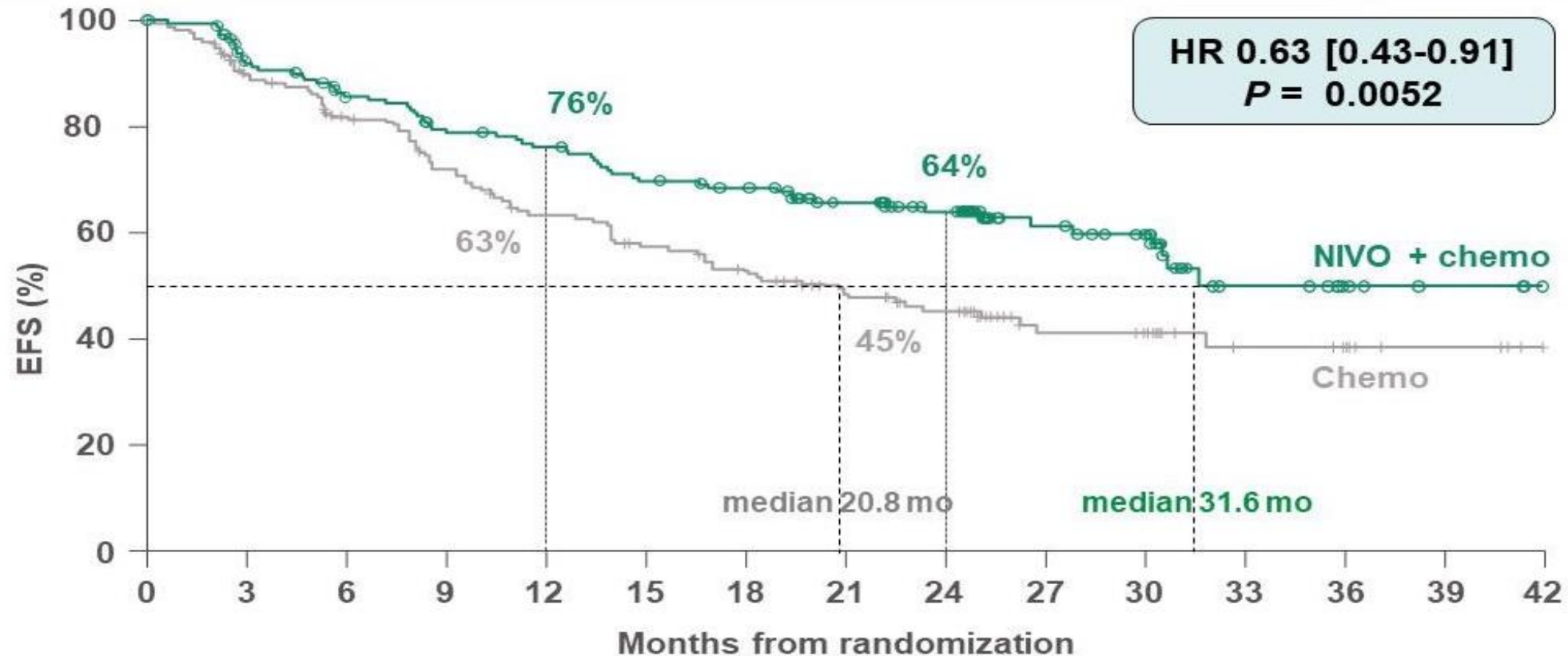


# Early stage NSCLC RCTs on novel perioperative therapies



# Resectable NSCLC

## RCTs on neoadjuvant ChT + Nivolumab

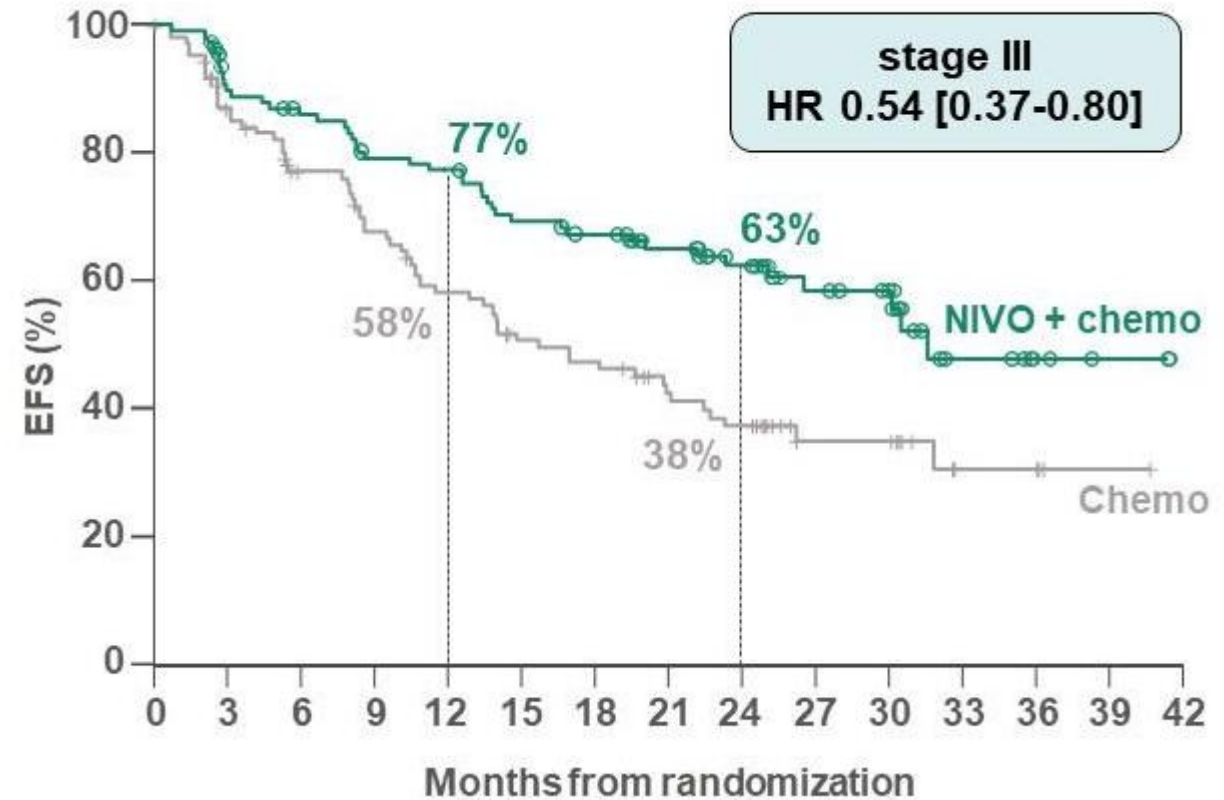
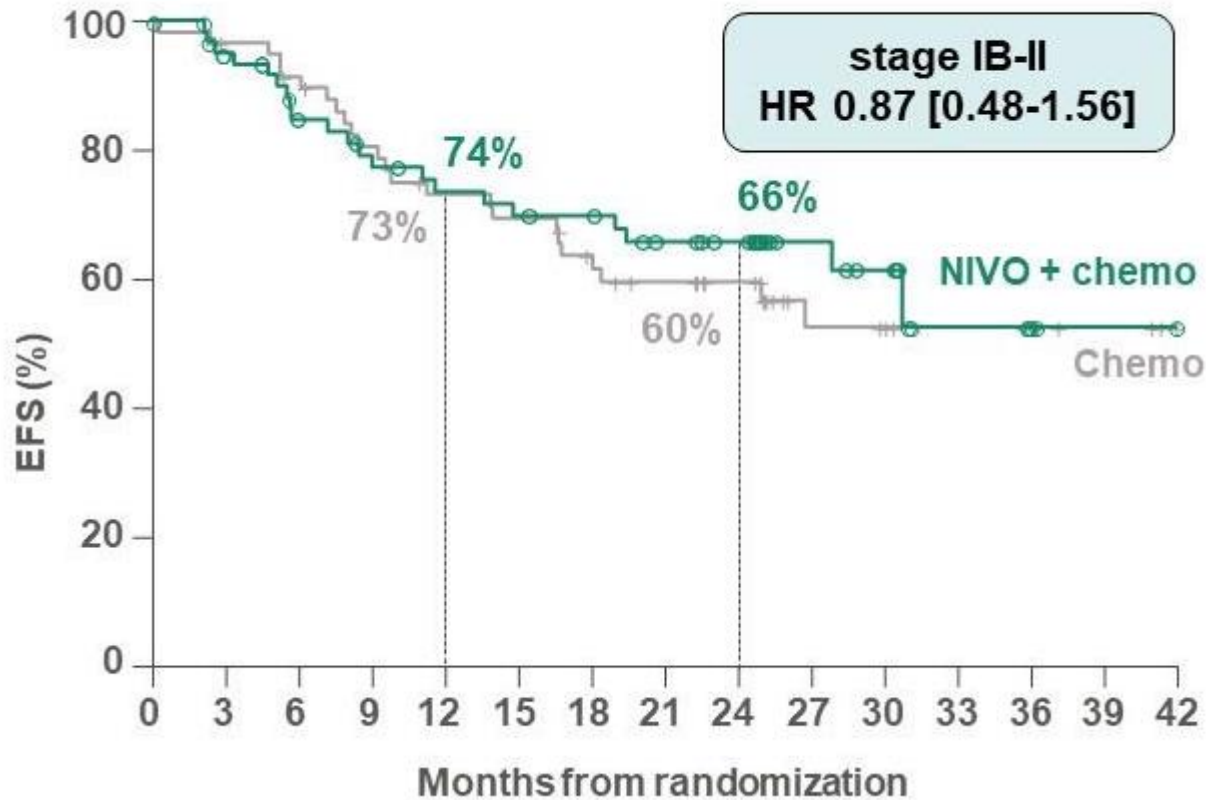


**PD-L1 <1%: HR 0.85 [0.54-1.32]**

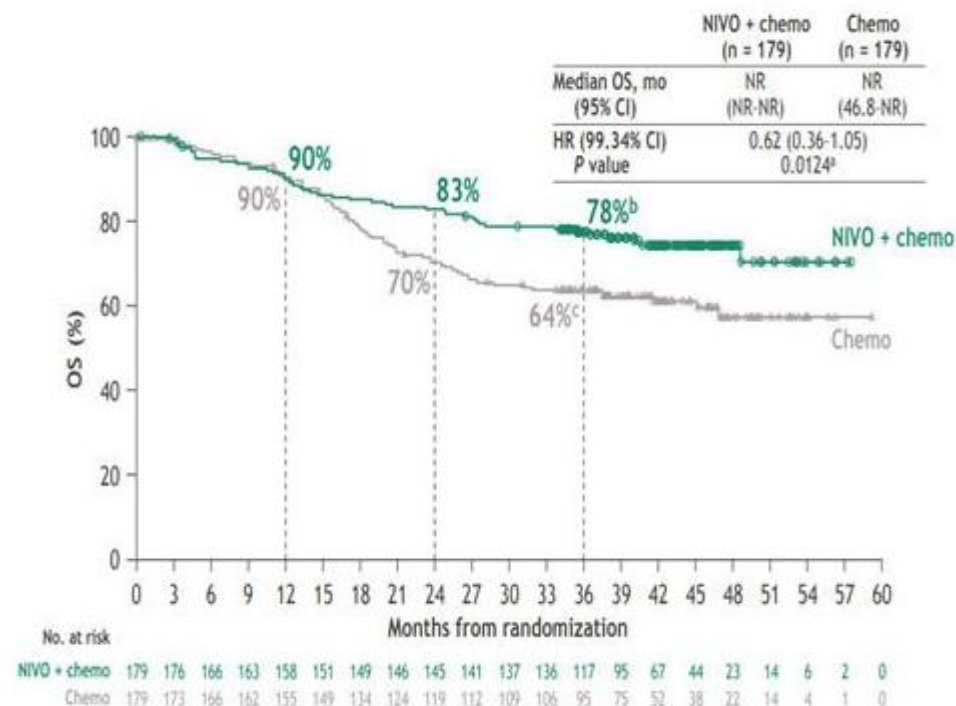
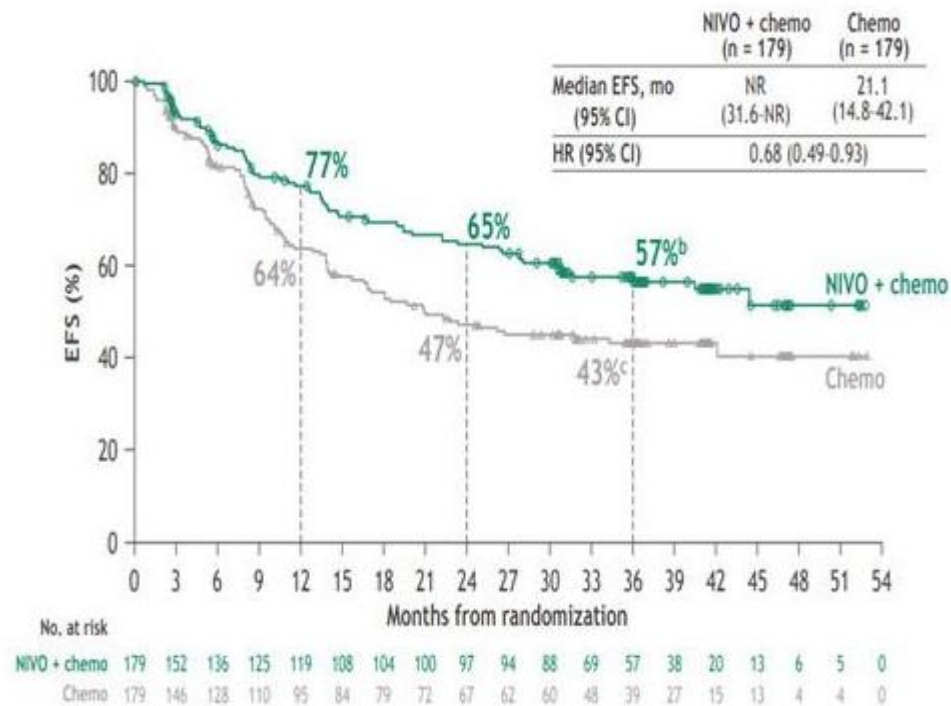
**PD-L1 1-49%: HR 0.58 [0.30-1.12]**

**PD-L1 ≥50%: HR 0.24 [0.10-0.61]**

# Resectable NSCLC RCTs on neoadjuvant ChT + Nivolumab



# Resectable NSCLC RCTs on neoadjuvant ChT + Nivolumab



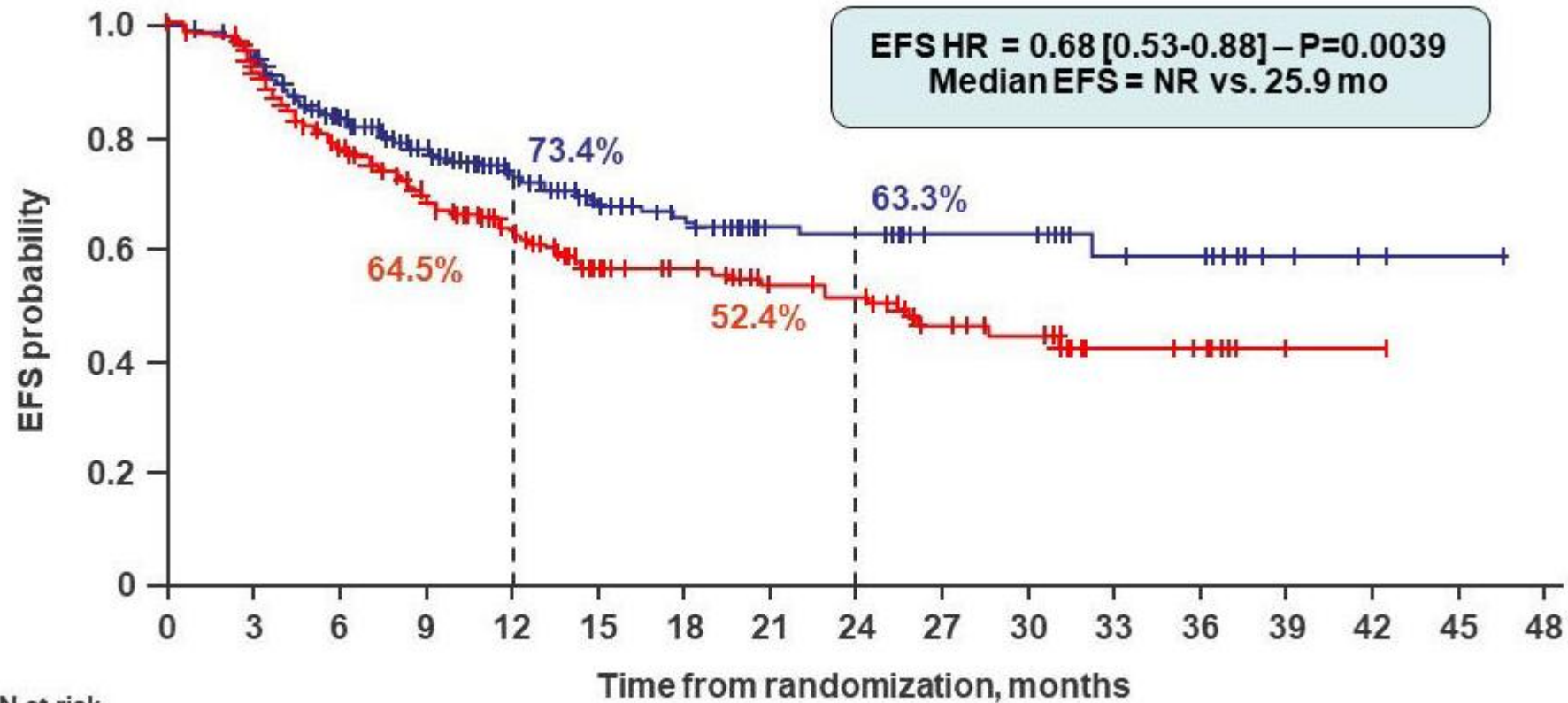
➤ **May 26, 2023 – CHMP positive advice for Nivolumab in combination with platinum-based chemotherapy for neoadjuvant treatment of resectable NSCLC at high risk of recurrence and with PD-L1 ≥ 1%**

# Resectable NSCLC

## RCTs on perioperative ChT + Durvalumab

AACR 2023

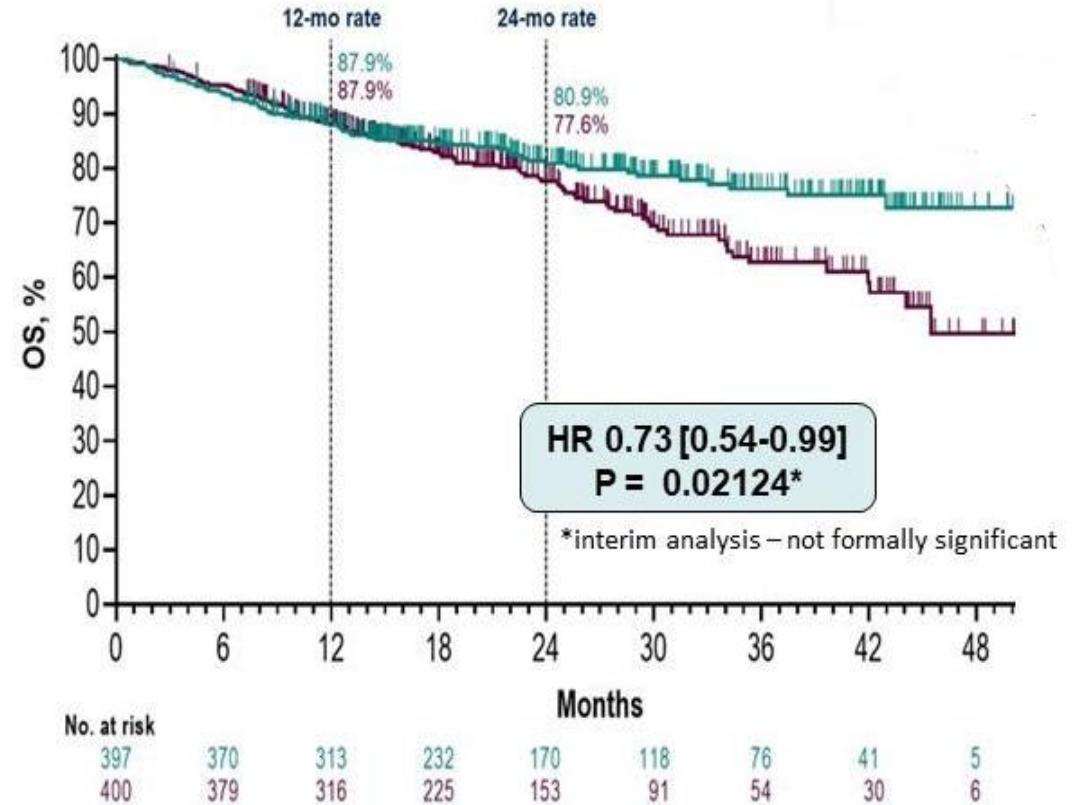
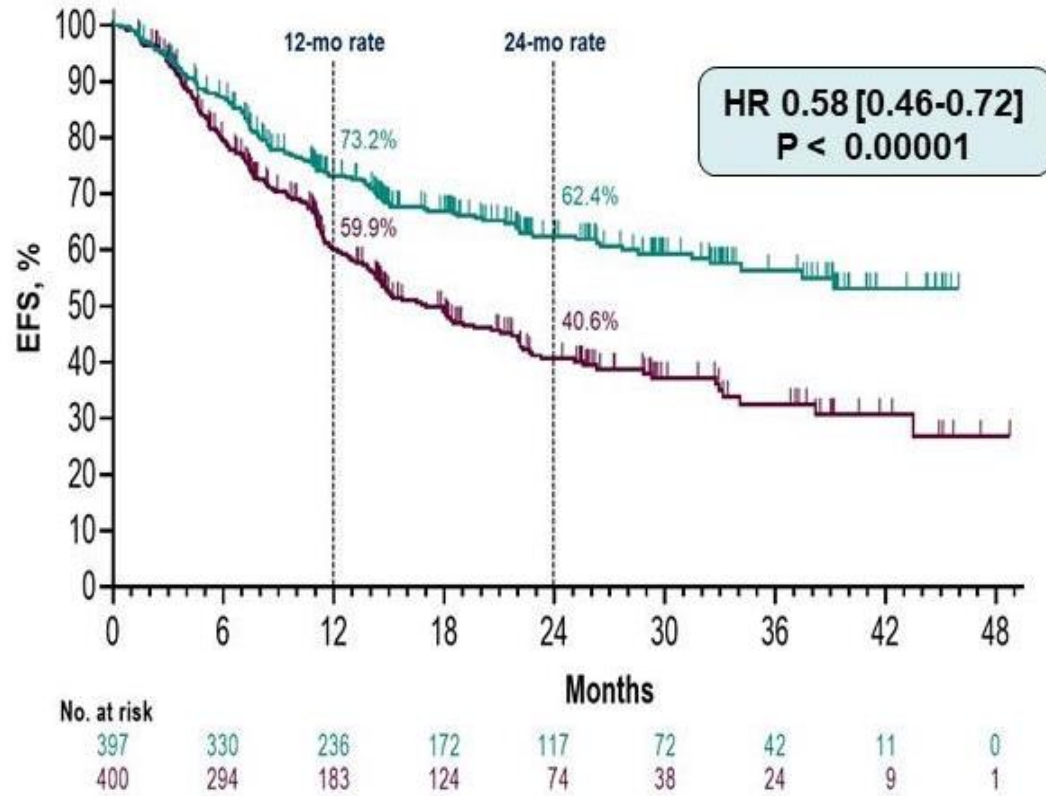
median FU 11.7 mo



N at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Durva + CT	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Plac + CT	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

# Resectable NSCLC

## RCTs on perioperative ChT + Pembrolizumab



# Take-Home Message No 1



- In unresectable stage III NSCLC treated with CRT, consolidation immunotherapy with Durvalumab was proven to improve cure rates,
- In resectable stage II-III A NSCLC with complete resection + adjuvant ChT
  - Adjuvant immunotherapy improved DFS (Atezolizumab EMA approved in PD-L1  $\geq 50\%$ )
- In resectable stage II-III A NSCLC with complete resection + adjuvant ChT
  - Adjuvant osimertinib improved OS in EGFR mutated NSCLC (EMA approved)
  - First trial showing clear OS benefit with targeted therapy in resected NSCLC
- In resectable stage II-III B(N2) NSCLC
  - Neoadjuvant chemo-immunotherapy improved EFS compared to ChT alone (Nivolumab now has CHMP recommendation)
  - Similar results are for perioperative chemo-immunotherapy with Durvalumab and Pembrolizumab

# Take-Home Message No 2



-> benefit of ICI for all

- **Three types of medically fit patients**
  - **Resectable:** most patients with stage I (N0) and stage II (N1)
    - Preferred strategy: direct resection. For N1: adjuvant ChT. Adjuvant ICI if PD-L1  $\geq 50\%$  \*  
\* adjuvant therapy may be considered in case of N0 and T >4 cm
  - **Potentially resectable:** some patients with stage II (N1), some with stage IIIA-B (N2)
    - Preferred strategy: neoadjuvant chemo-immuno therapy -> surgery -> consolidation ICI to be considered
  - **Unresectable:** many patients with stage IIIA-B and all with stage IIIC (N3)
    - Preferred strategy: chemoradiotherapy -> Durvalumab 1 year
- This judgment **REMAINS the unique privilege of your multidisciplinary tumor board**
  - Patients considered for neo-adjuvant chemo+ICI should be considered operable upfront by the MDTB



Thank you



