



# CURRENT ROLE OF ADJUVANT IMMUNOTHERAPY IN NSCLC

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Chief, General Thoracic Surgery

University of Chicago

Endorsed by



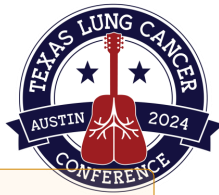
Accredited by



Presented by



# Worldwide Lung Cancer Incidence and Mortality

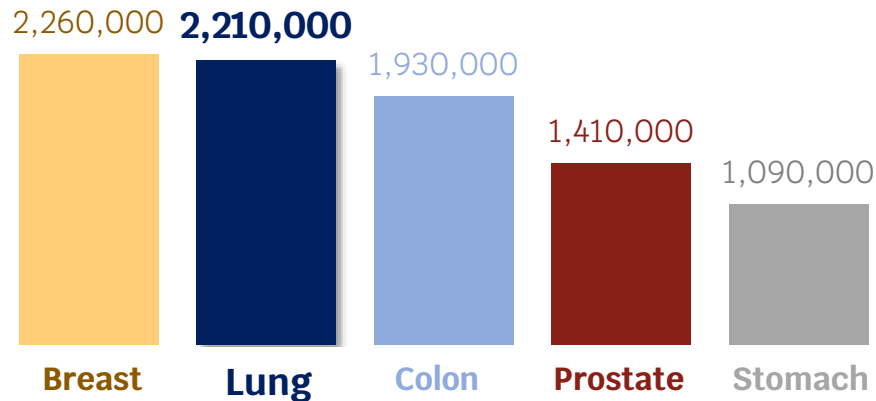


diagnosed with lung cancer in 2020

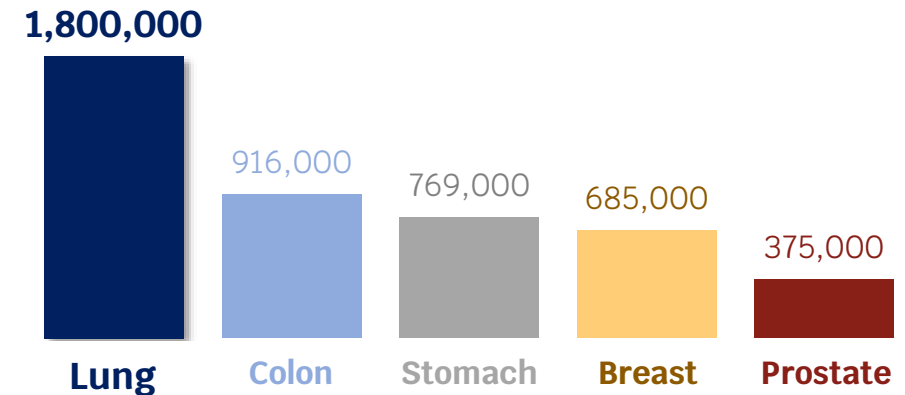


died from lung cancer in 2020

Estimated Cases by Tumor Type

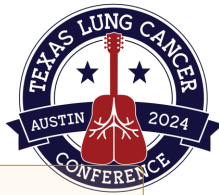


Estimated Deaths by Tumor Type



WHO Cancer Facts 2020

# US Lung Cancer Incidence and Mortality

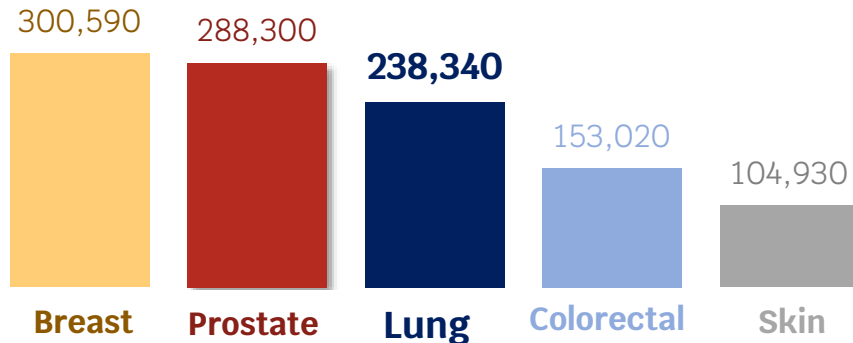


diagnosed with lung cancer in 2023

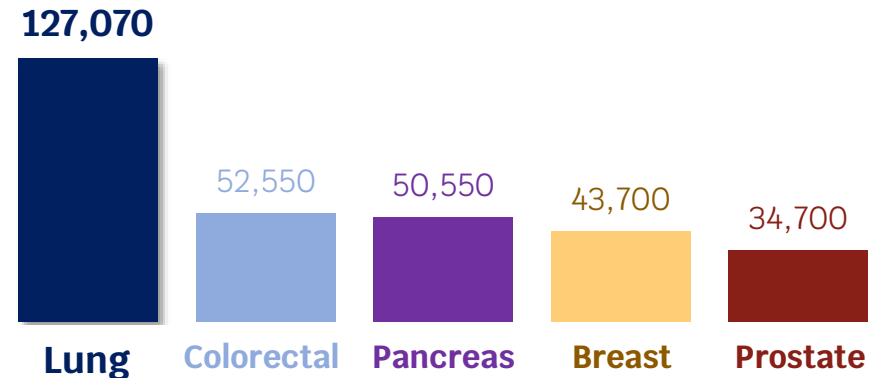


died from lung cancer in 2023

Estimated Cases by Tumor Type

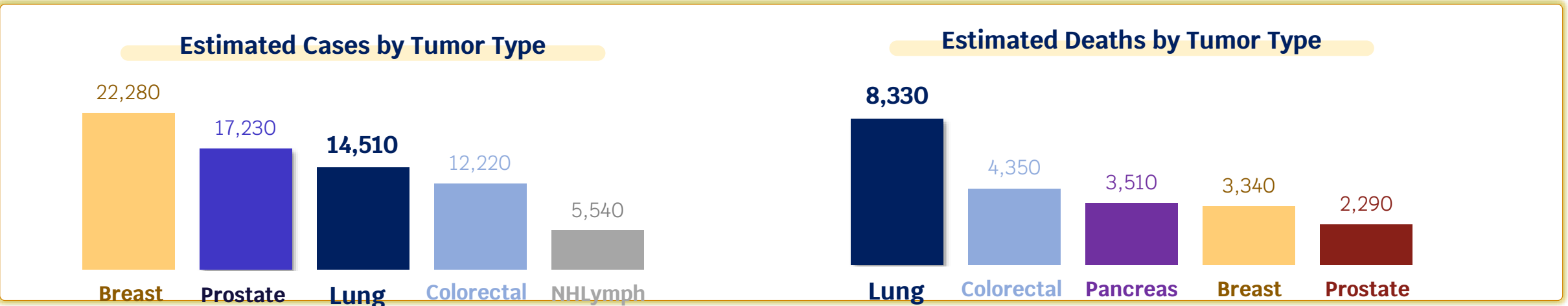
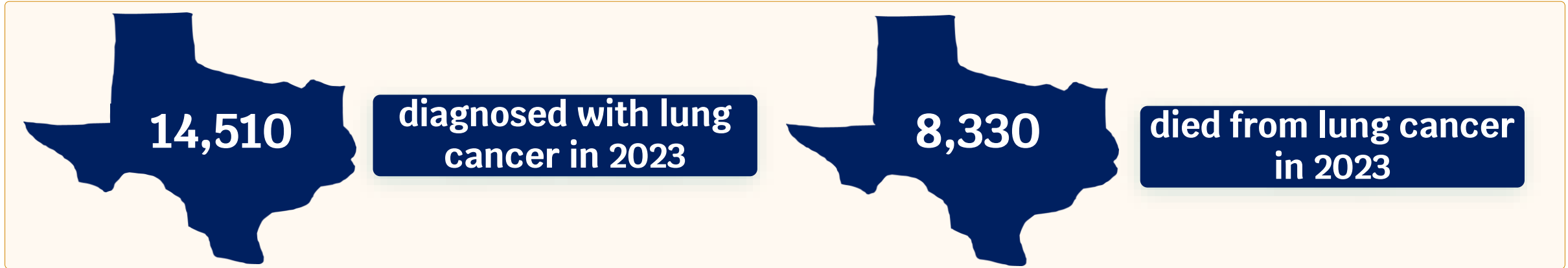
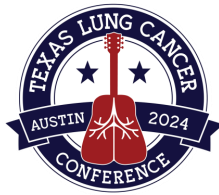


Estimated Deaths by Tumor Type



**1 of every 4 cancer deaths is a lung cancer death**

# Texas Lung Cancer Incidence and Mortality



**1 of every 5 cancer deaths is a lung cancer death**

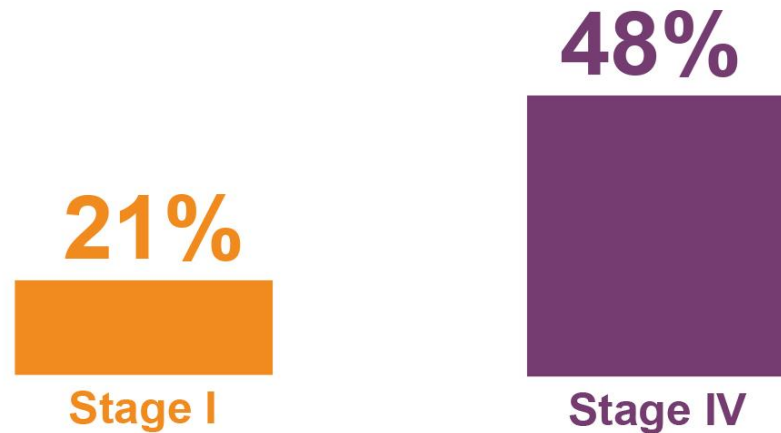
# Poor Prognosis in NSCLC



## Two-pronged problem

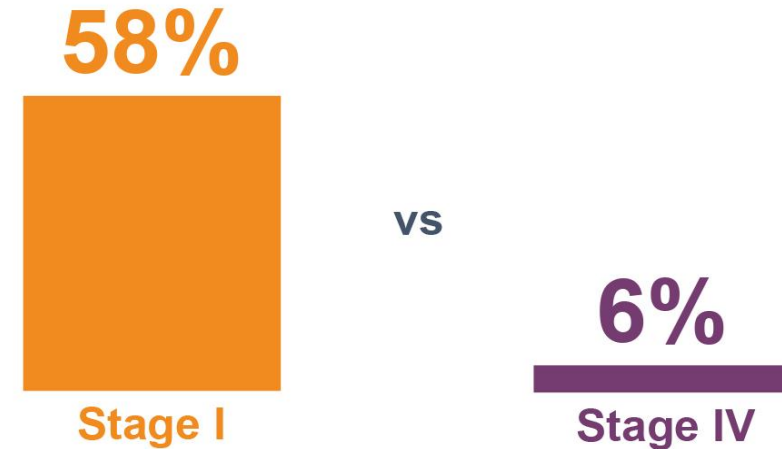
We diagnose pts too late

Stage at Diagnosis



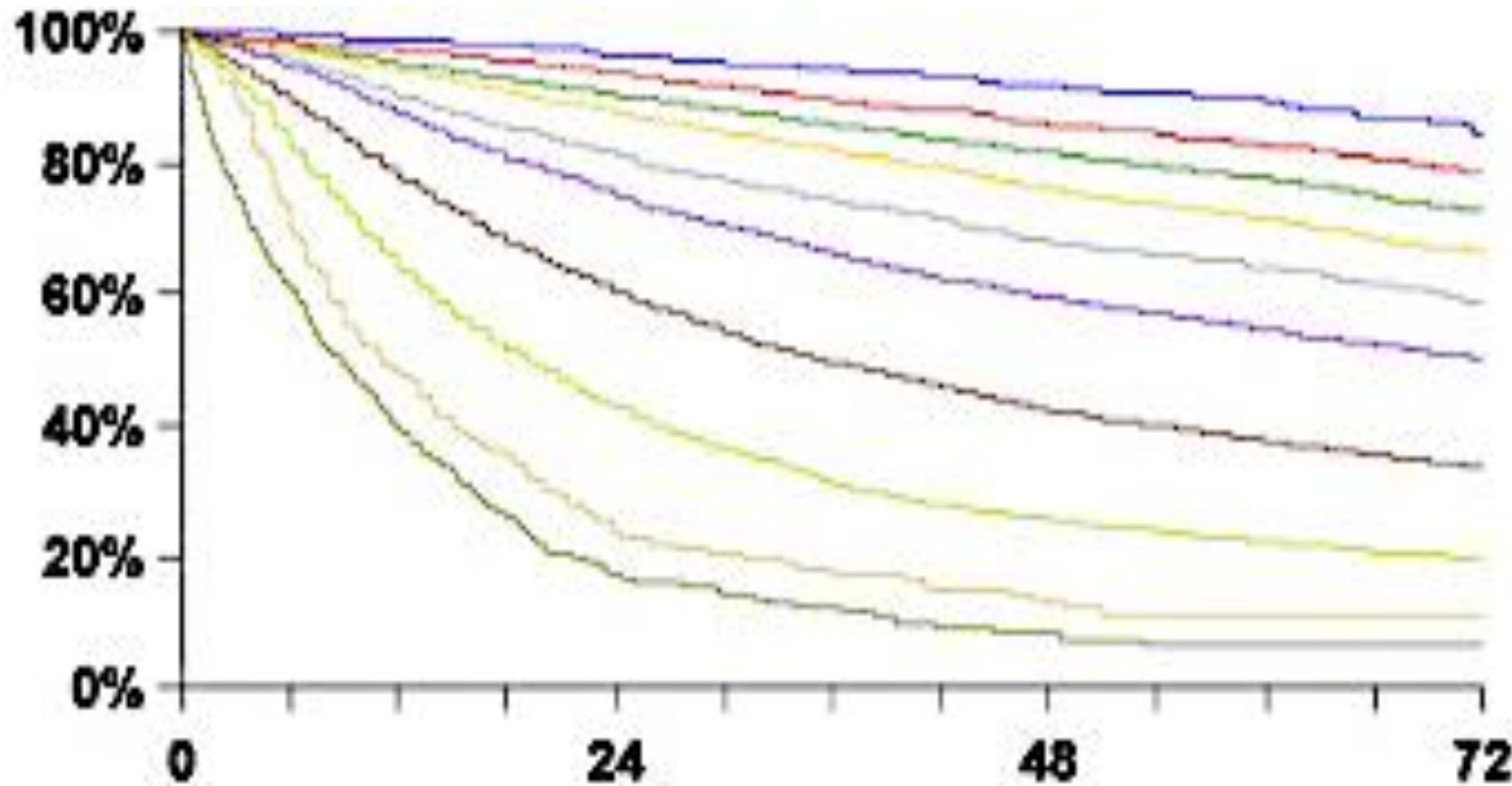
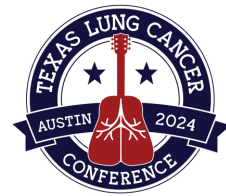
Treatments are ineffective

Relative 5-Year Survival



Early detection and treatment are critical to improving clinical outcomes in patients with lung cancer

# Lung Cancer Survival by Stage

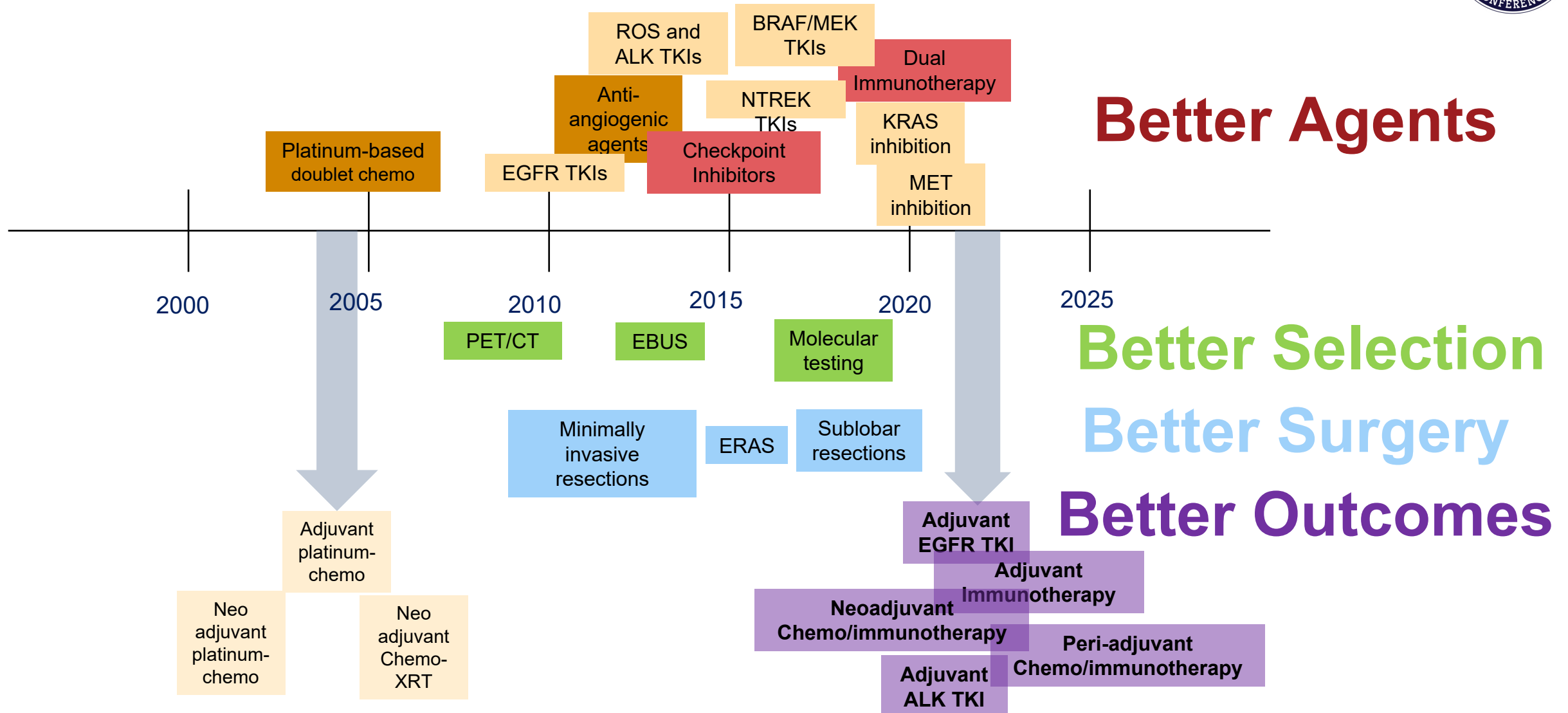
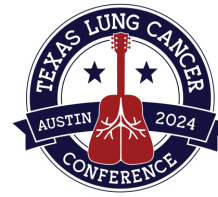


**5y OS**  
**Stage IB: 71%**  
**Stage IIA: 64%**  
**Stage IIB: 55%**  
**Stage IIIA: 37%**

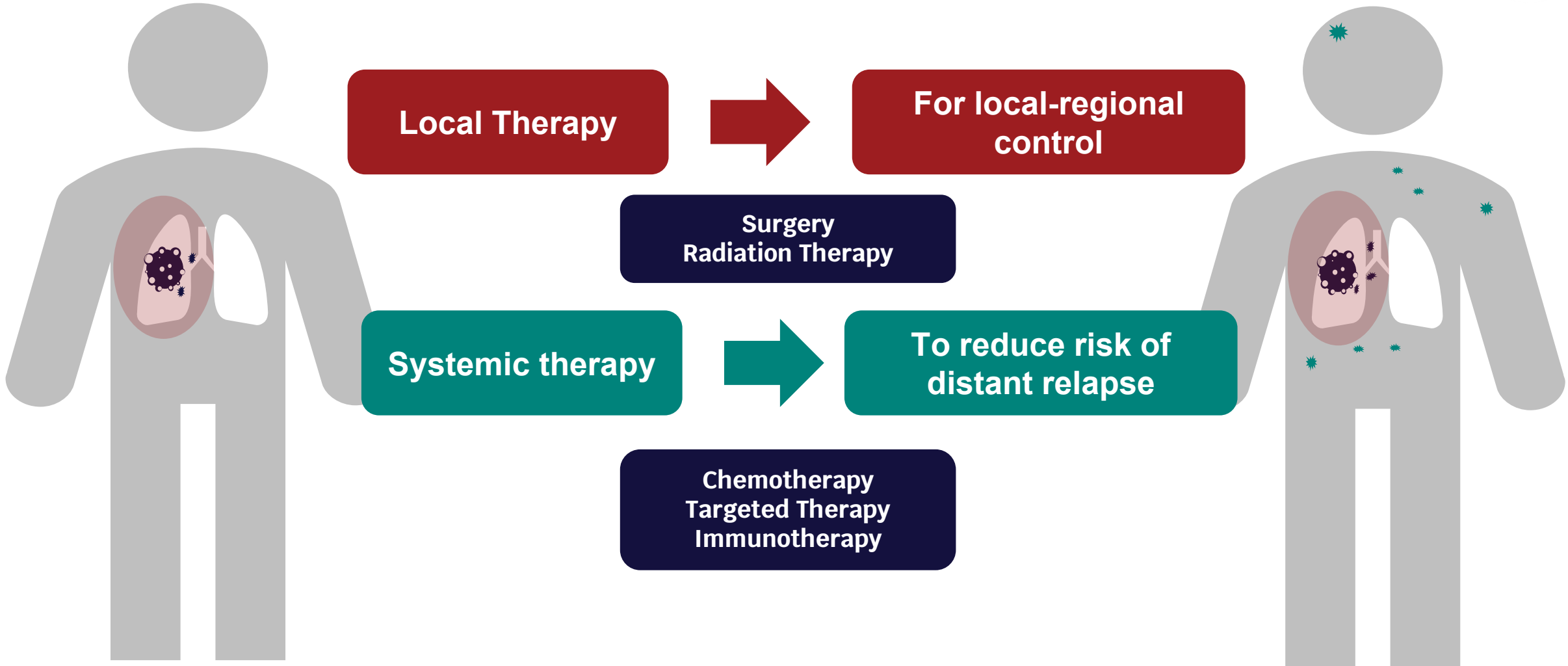
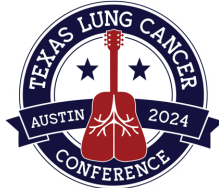
Goldstraw P, JTO, 2016



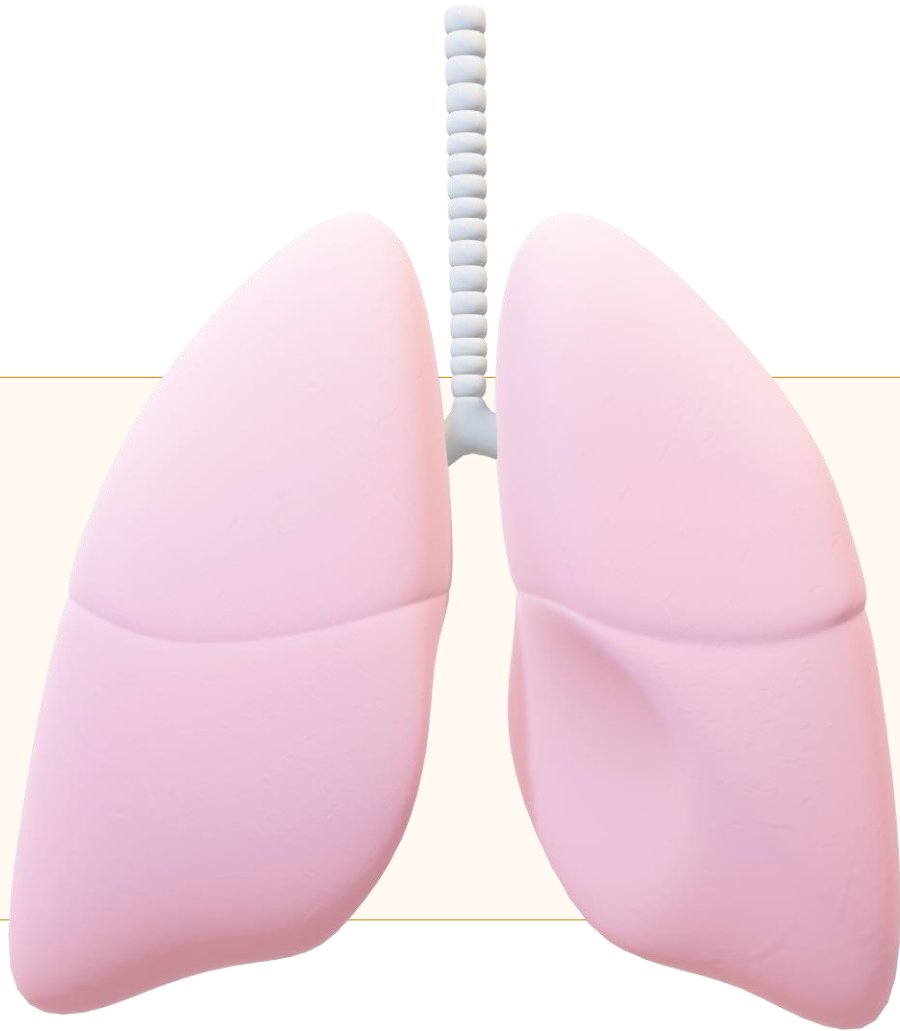
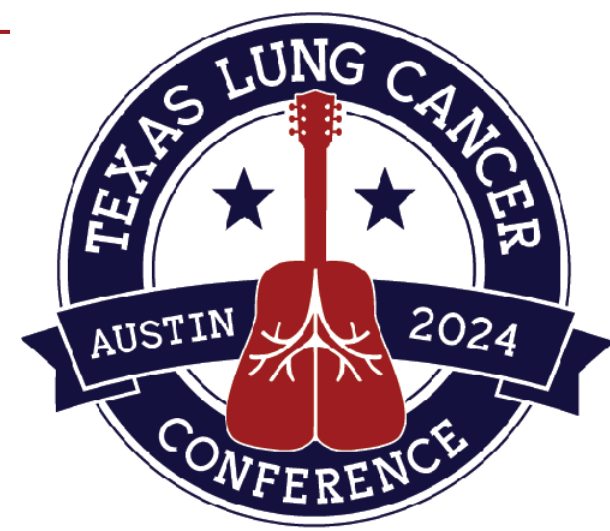
# Updates to Peri-operative Lung Cancer Care



# Curative Therapy for Locally Advanced NSCLC







**Because good surgery is not  
enough to cure patients  
Lung cancer is a systemic disease**

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# Basic NSCLC Treatment Strategies 2022



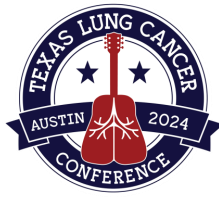
	I <i>Resection alone Consider Sublobar Resection</i>	Resectable Locally Advanced II and IIIA <i>Surgery ± (neo)adjuvant cancer immunotherapy or targeted therapy ± chemotherapy ± RT</i>	Unresectable IIIB/C <i>Chemotherapy/RT ± cancer immunotherapy or targeted therapy</i>	
T and N	N0	N1	N2	N3
T1	IA	IIA	IIIA	IIIB
T2a/b	IB	IIA	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a/b/c	IVA/B/C	IVA/B/C	IVA/B/C	IVA/B/C
<b>IVA/B/C</b> <i>Systemic therapy: cancer immunotherapy; targeted therapy; chemotherapy</i>				

NCCN guidelines for NSCLC v8.



# HOW do we incorporate immunotherapies therapy into resectable NSCLC?

# Incorporating Novel Therapies into Resectable NSCLC

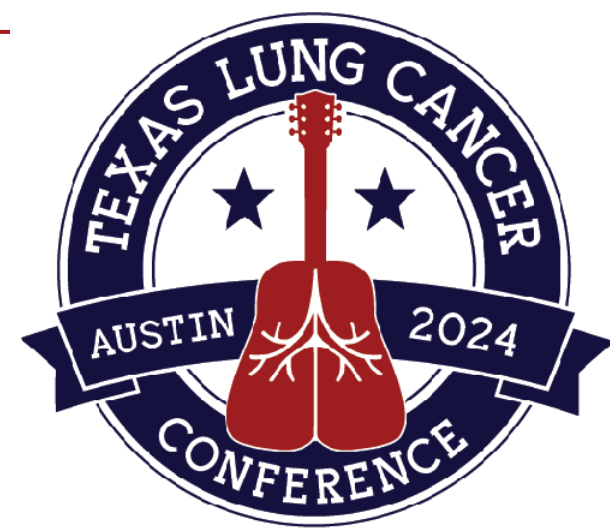


Select appropriate patient

Determine sequencing of therapies

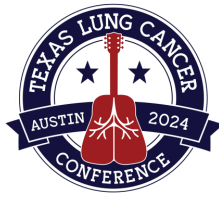
Understanding Evidence

Decrease treatment attrition



# Patient selection

# Emerging Therapies in Resectable NSCLC



## PD-1/PD-L1 inhibitors

Inhibit interactions between PD-1 and PD-L1 that activate T cells to recognize and eliminate cancer cells

Atezolizumab (PD-1)  
Durvalumab (PD-1)  
Nivolumab (PD-L1)  
Pembrolizumab (PD-L1)



## Biomarker-directed therapies

Inhibit oncogenic drivers, which are present in ~64% of patients with NSCLC

Osimertinib (EGFR)  
Alectinib (ALK)

# Surgical Evaluation for NSCLC



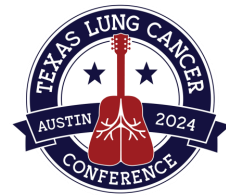
## Staging

- CT
- PET
- EBUS/Med
- Brain MRI

## Physiologic Evaluation

- PFTs
- Cardiac eval
- Exercise testing
- Frailty assessment





# Surgical Evaluation for NSCLC

## Staging

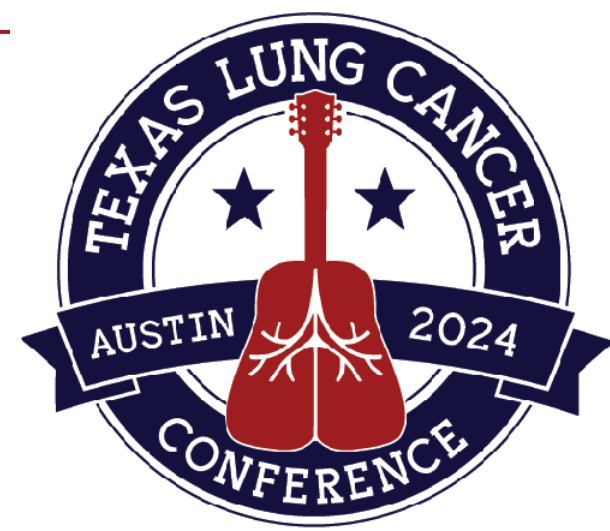
- CT
- PET
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- Brain MRI

## Physiologic Evaluation

- PFTs
- Cardiac eval
- Exercise testing
- Frailty assessment

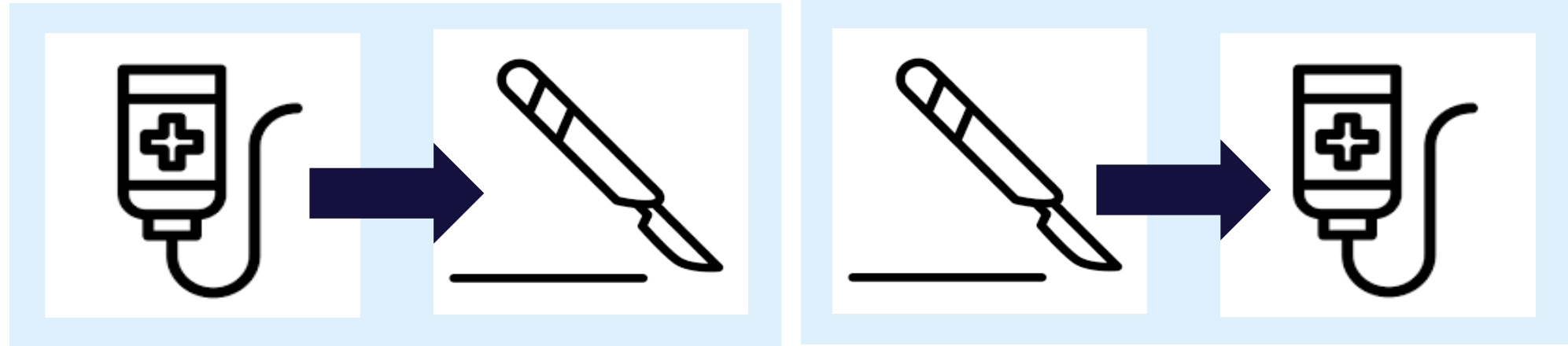
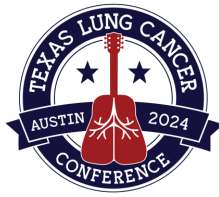
## Biomarker testing

- EGFR
- ALK
- PD-L1
- NGS

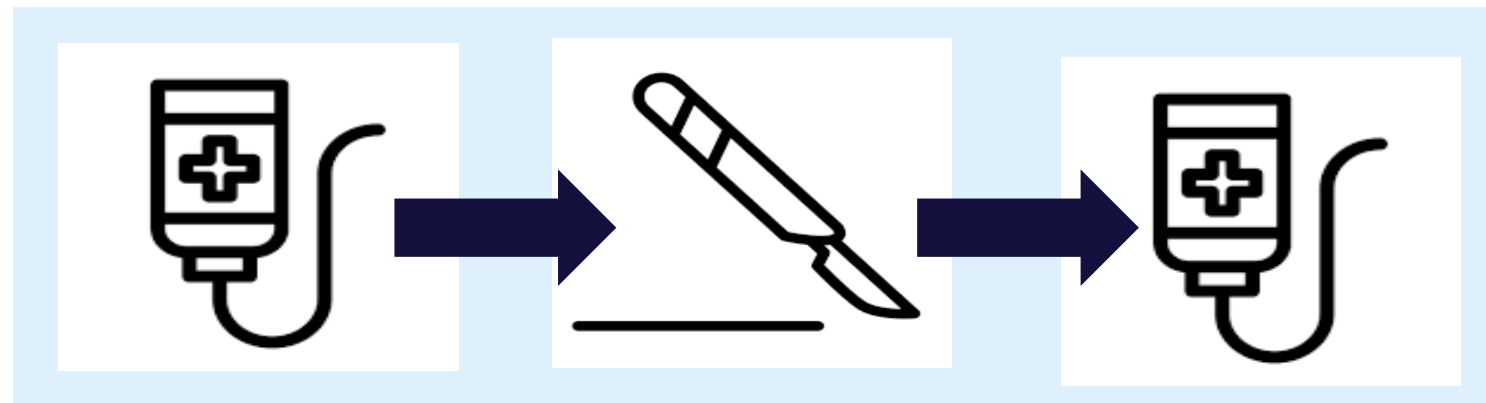


# Sequencing Therapy

# Sequencing Therapy



**NEOADJUVANT or ADJUVANT**



**SANDWICH (PERI-ADJUVANT)**



# Therapeutic Considerations

## NEOADJUVANT

Early eradication of micro-metastatic disease

Healthier patients w/ improved tolerance of drug toxicity

Improved compliance and higher drug exposure

Opportunity for pre- and post-treatment tissue to adjust treatment

Neoadjuvant is standard of care for resectable stage III disease

Presence of whole tumour allows activation of broader & more diverse immune response

## ADJUVANT

Adjuvant is standard of care for resectable stage IB and II disease

No surgical delays

Tumor biomarkers can guide therapeutic decisions

No added hilar and mediastinal fibrosis

No risk of disease progression resulting in missed opportunity for curative surgery

## SANDWICH

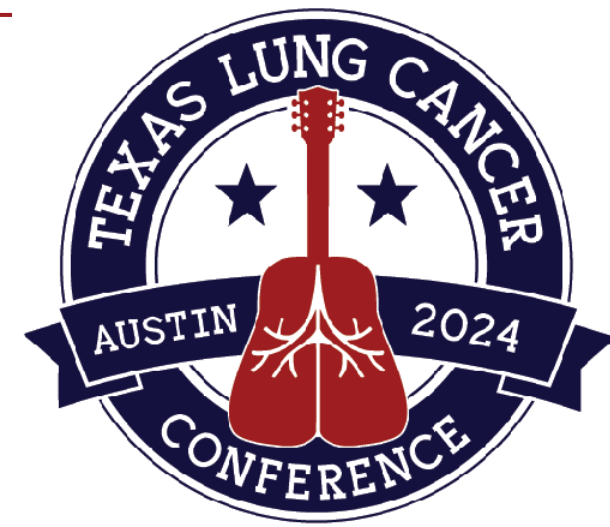
Allows for greatest amount systemic therapy

Early eradication of micro-metastatic disease

Opportunity for pre- and post-treatment tissue to adjust treatment

Tumor biomarkers can guide therapeutic decisions

Presence of whole tumour allows activation of broader & more diverse immune response

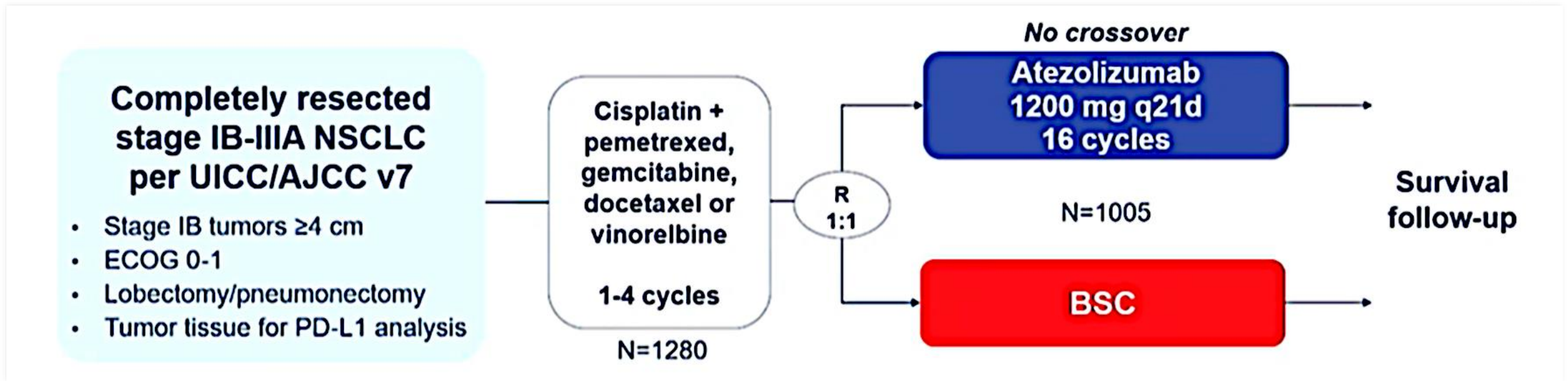
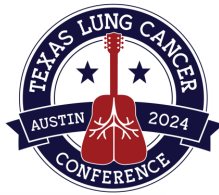


# What is the **evidence for adjuvant immunotherapy?**

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# Impower010



## Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status<sup>a</sup>: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

## Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC  $\geq 1\%$  (per SP263) stage II-IIIa population
  - All-randomized stage II-IIIa population
  - ITT population (stage IB-IIIa)

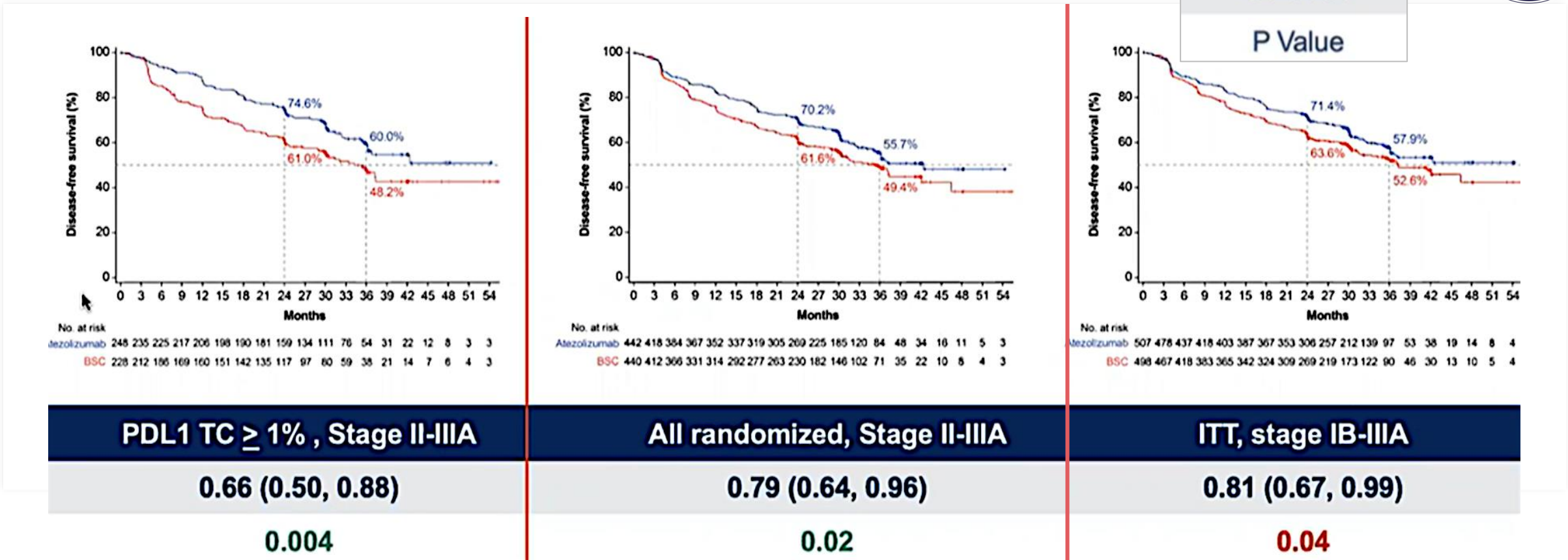
## Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC  $\geq 50\%$  (per SP263) stage II-IIIa population
- 3-y and 5-y DFS in all 3 populations

Felip E, Lancet 2021; Wakelee, H, ASCO 2021;



# Impower010: DFS

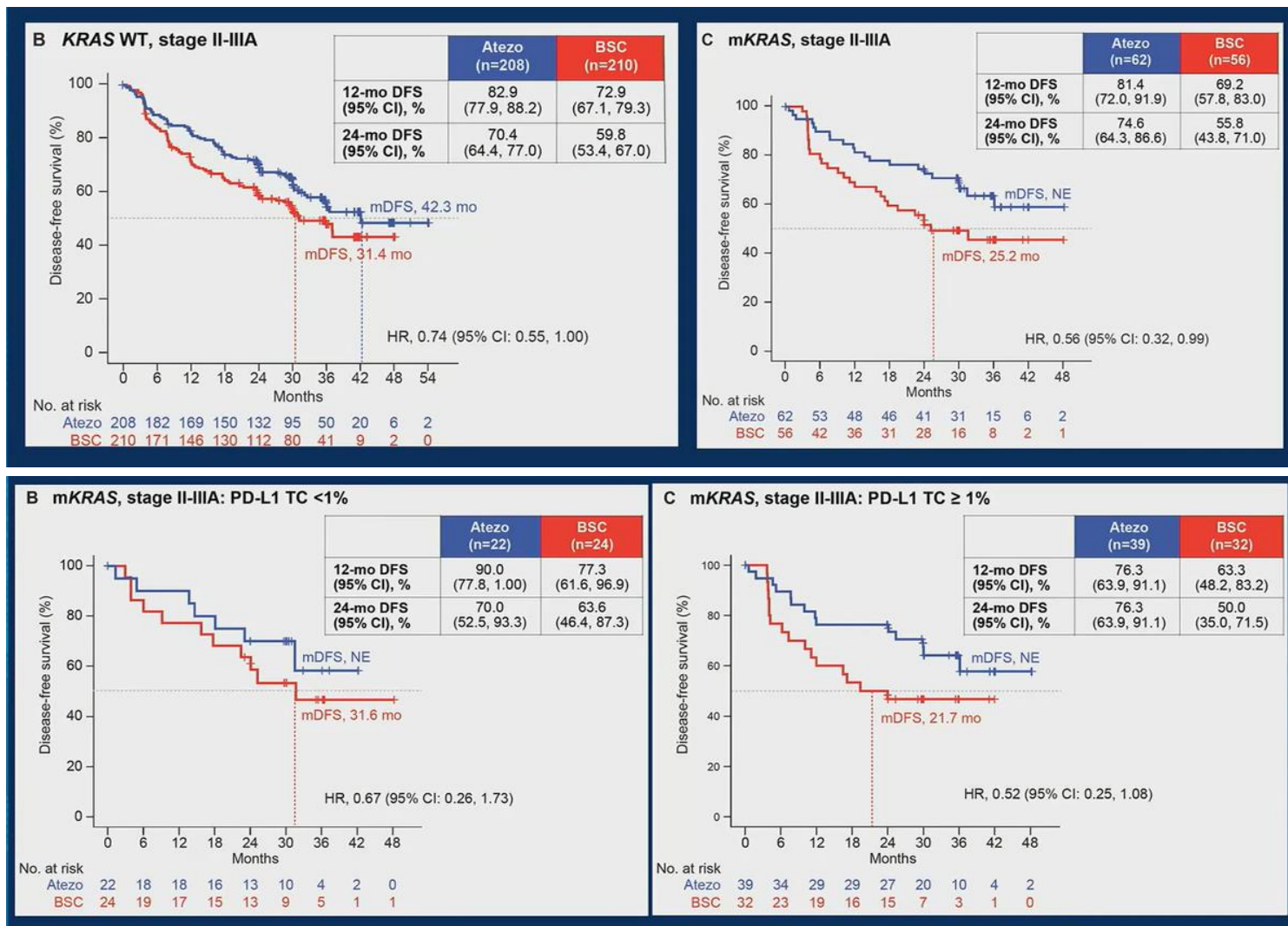


- Adjuvant atezolizumab following resection and adjuvant chemotherapy showed significant improvement in DFS in PD-L1 >1% stage II-III A (HR 0.66) and all randomized stage II-IIA (HR 0.79)

Felip E, Lancet 2021; Wakelee, H, ASCO 2021;



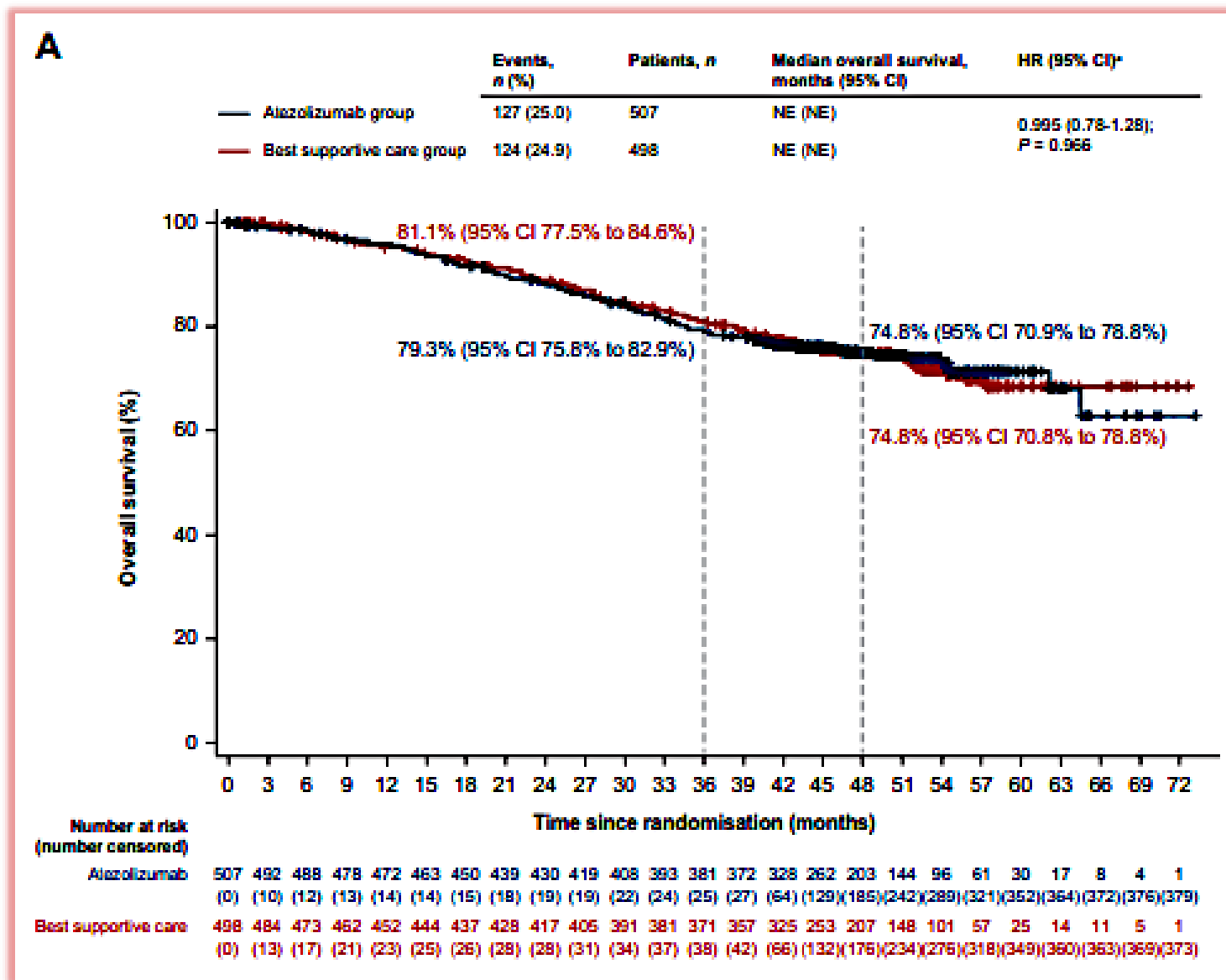
# IMPower010: Outcomes in KRAS Mutated patients



- 603/1005 pts w/ WES
- KRAS mutation 21% (G12C 44%)
- No major difference in demographics from overall study population
- PD-L1 expression higher  
 >1%: 59% vs. 53%  
 ≥50%: 30% vs. 25%

Reck M, ASCO 2023

# IMPOver010: OS



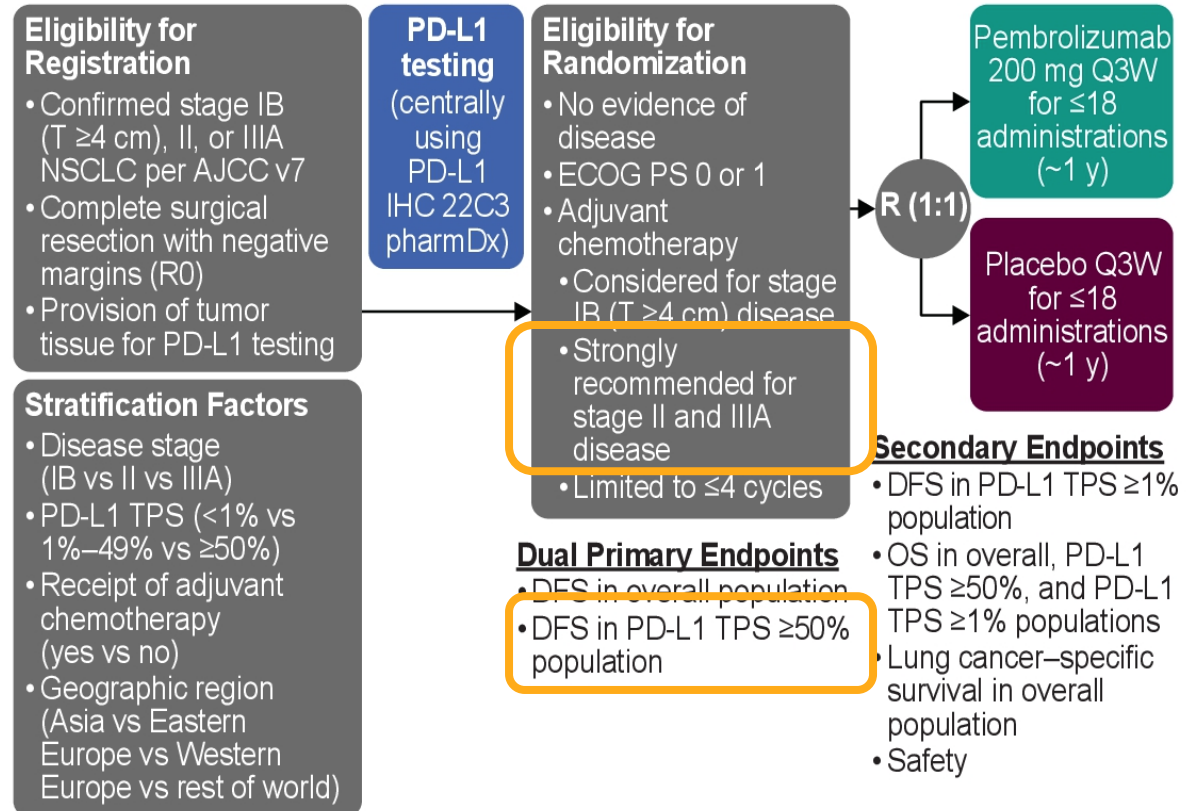
Felip E, Ann Oncol 2023

# PEARLS/KEYNOTE-091



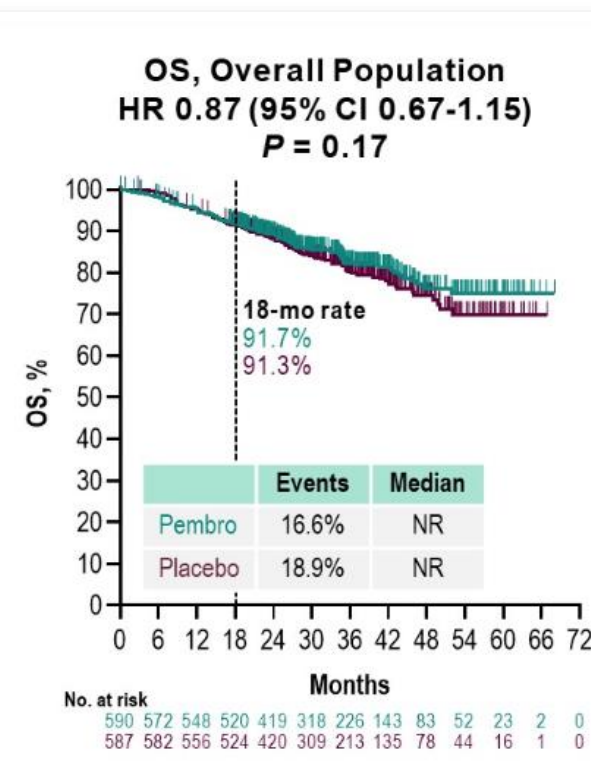
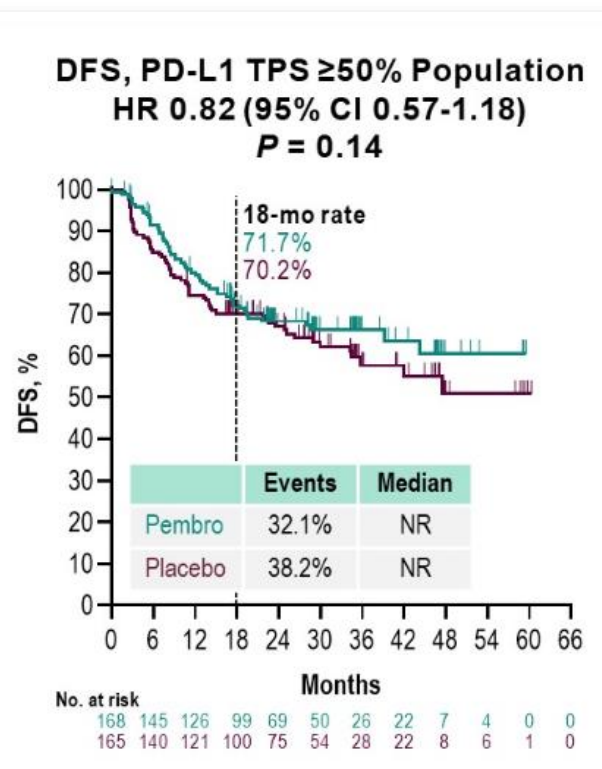
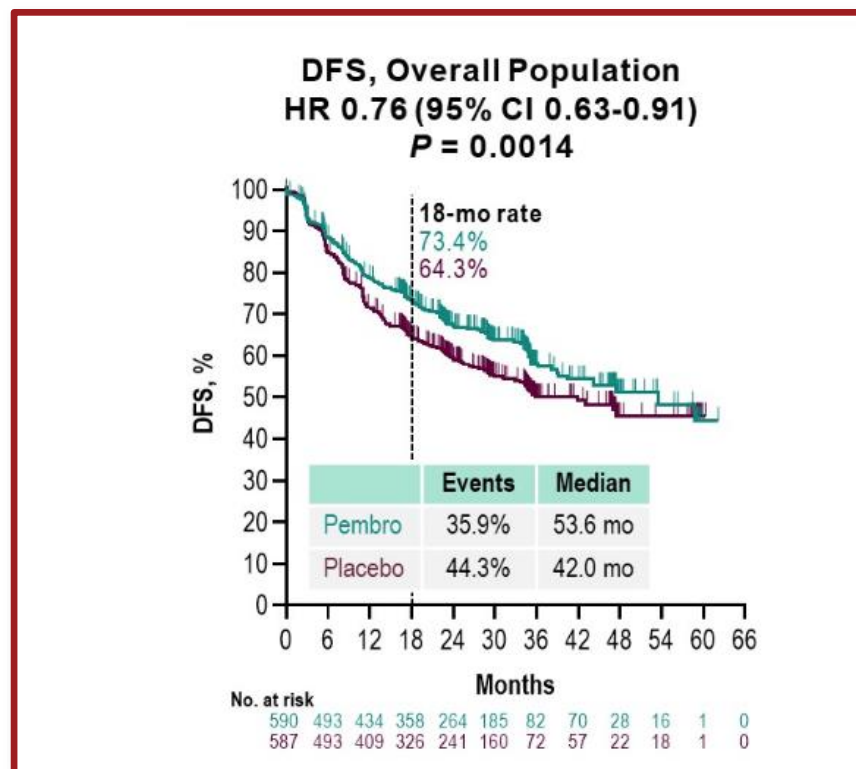
## Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

Mary O'Brien\*, Luis Paz-Ares\*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, A Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murie Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 In



O'Brien M, Lancet Oncol, 2022, ESMO 2022, ASCO 2022

# PEARLS/KEYNOTE-091

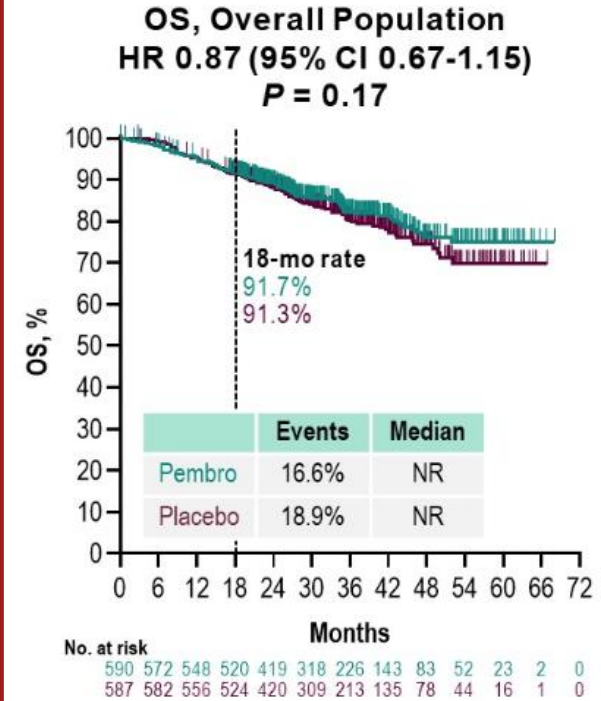
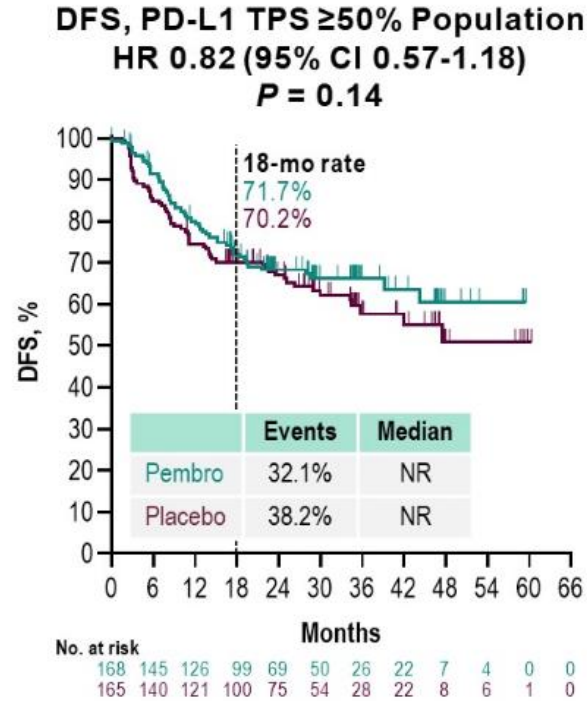
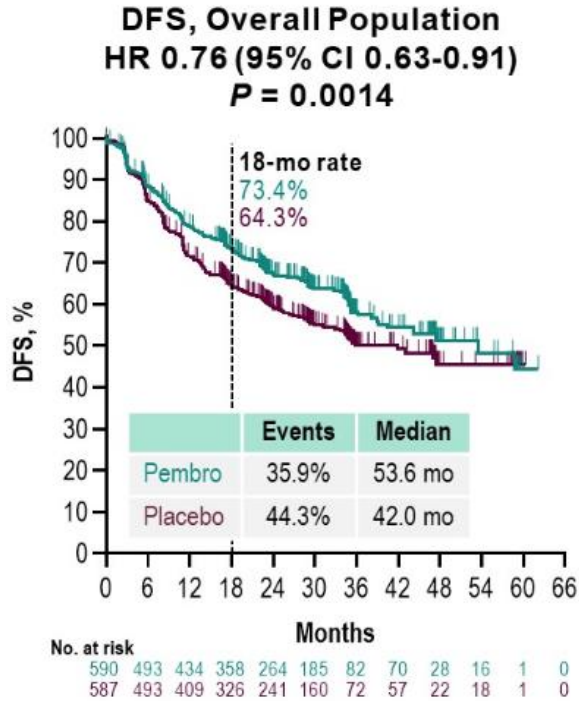
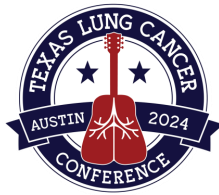


- DFS benefit generally consistent across most protocol-specified subgroups, including PD-L1 TPS <1% (HR 0.78, 95% CI 0.58-1.03) and 1-49% (HR 0.67, 95% CI 0.48-0.92)
- Overall safety profile generally as expected for pembrolizumab monotherapy

O'Brien M, *Lancet Oncol*, 2022, *ESMO* 2022, *ASCO* 2022



# PEARLS/KEYNOTE-091

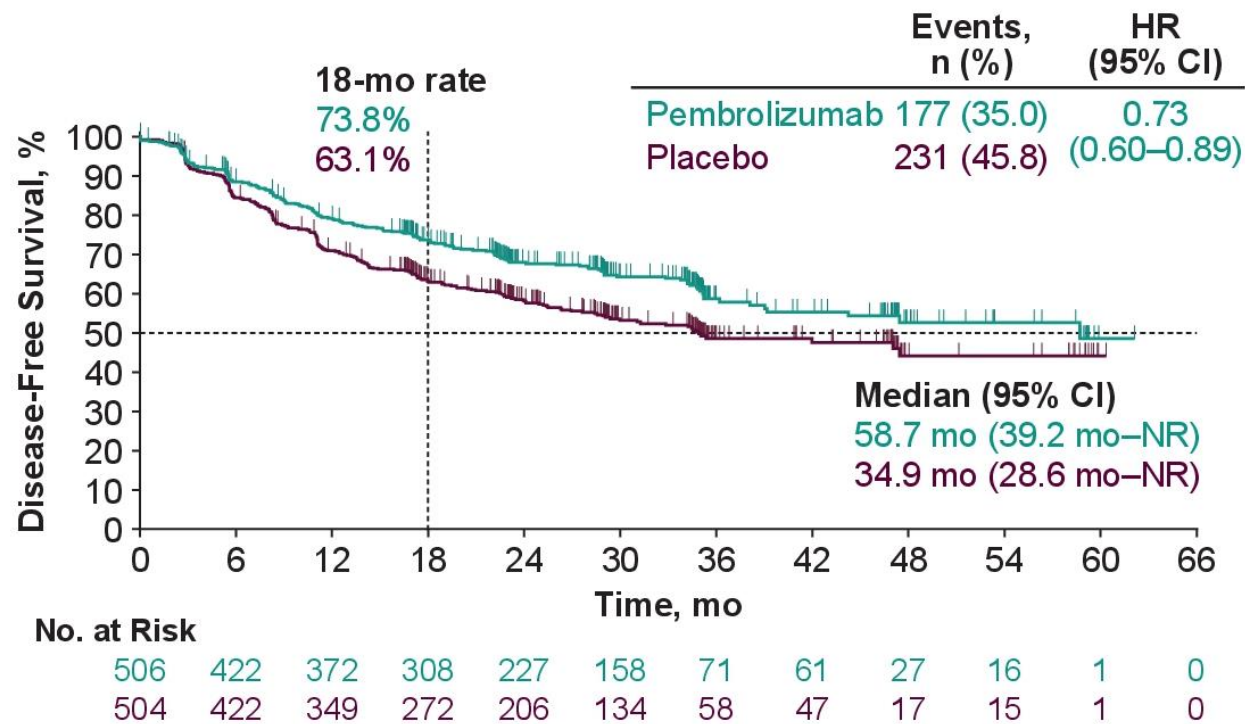


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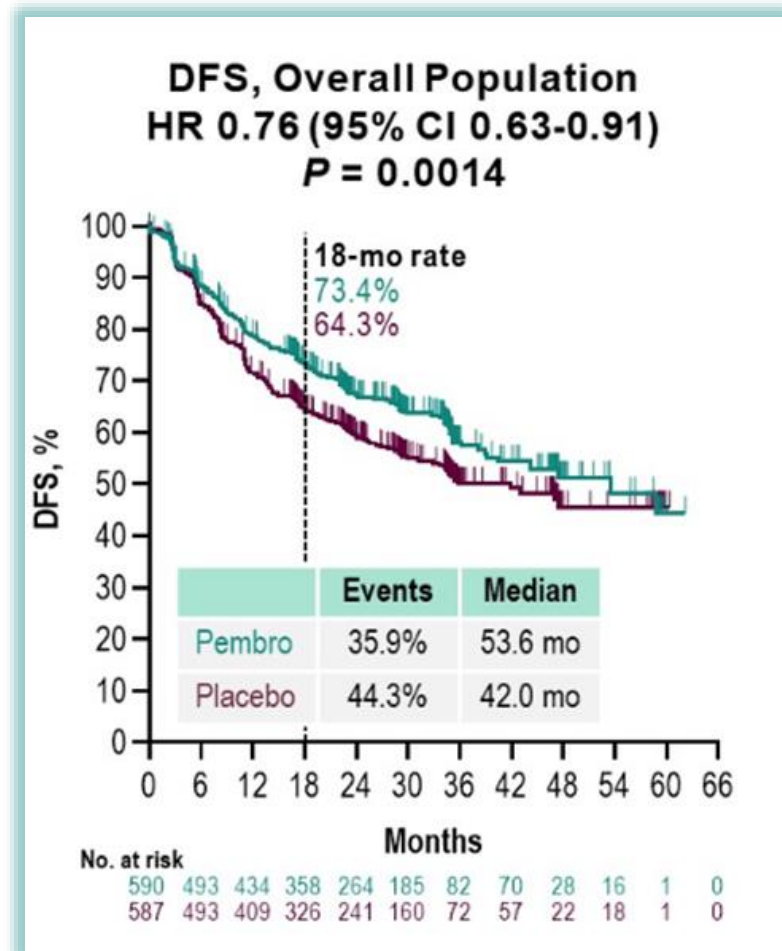
O'Brien M, Lancet Oncol, 2022, ESMO 2022, ASCO 2022

# Pembrolizumab vs Placebo for Early-Stage Non-Small-Cell Lung Cancer After Resection and Adjuvant Therapy: Subgroup Analysis of Patients Who Received Adjuvant Chemotherapy in the Phase 3 PEARLS/KEYNOTE-091 Study

**Figure 3. Disease-free survival in patients who received ≥1 cycle of adjuvant chemotherapy**



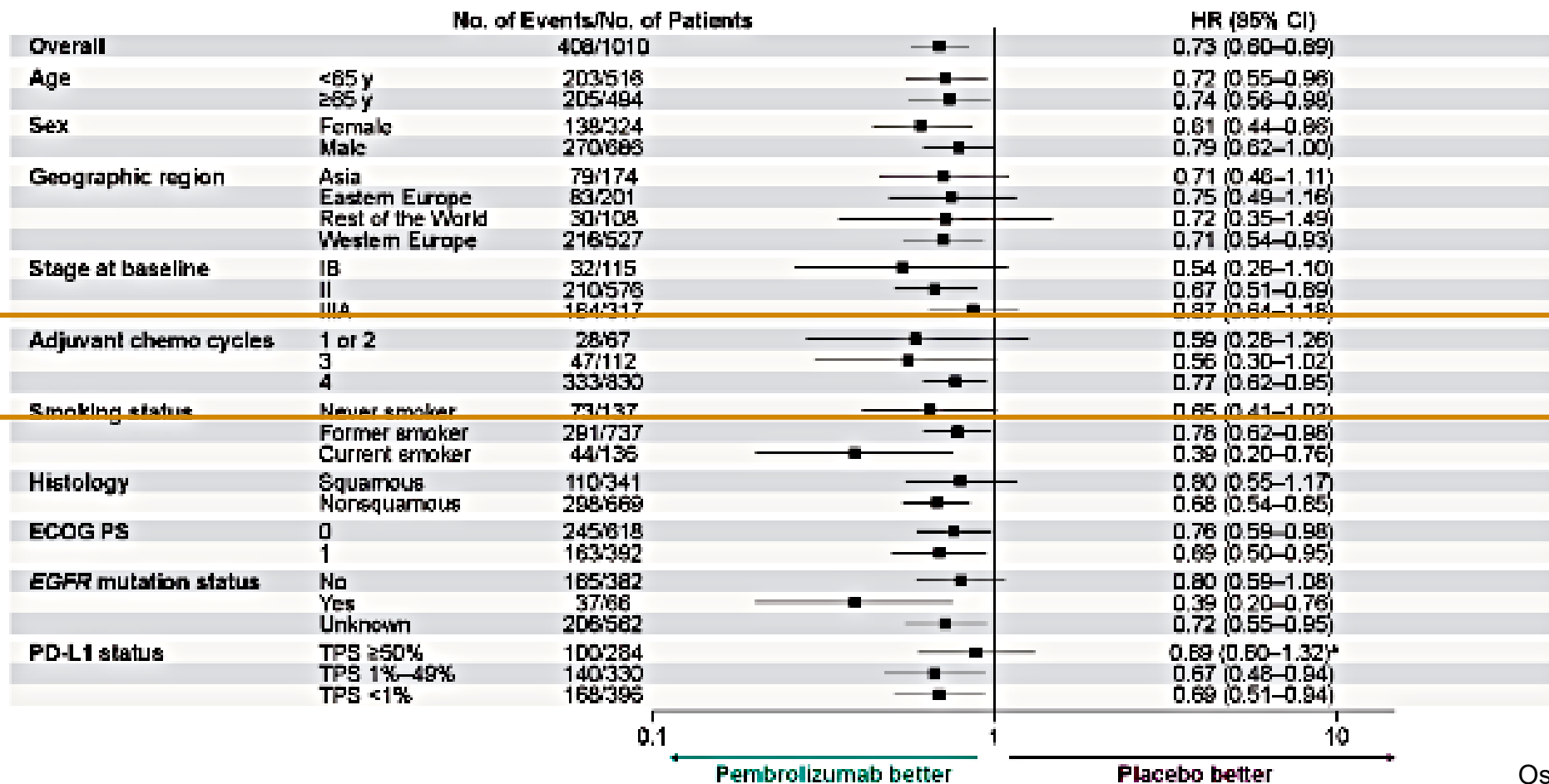
NR, not reached.



ed >  
all study

Oselin K, ASCO 2023

# Pembrolizumab vs Placebo for Early-Stage Non-Small-Cell Lung Cancer After Resection and Adjuvant Therapy: Subgroup Analysis of Patients Who Received Adjuvant Chemotherapy in the Phase 3 PEARLS/KEYNOTE-091 Study



Oselin K, ASCO 2023





# How do trials compare?

Trial	IMpower-010	KEYNOTE-091/PEARLS
Population	Resected stage IB-IIIa • 40% stage IIIa • 41% PD-L1 negative • 23% never smokers	Resected stage IB-IIIa • 30% stage IIIa • 39% PD-L1 negative • 15% never smokers
Design	Phase 3, randomized 1:1 to atezolizumab (507 pts) vs best supportive care (498 pts)	Phase 3, randomized 1:1 to pembrolizumab (590 pts) vs placebo (587 pts)
Endpoints	1. DFS in stage II-IIIa PD-L1 $\geq$ 1% 2. DFS in all stage II-IIIa pts 3. DFS in ITT, stage IB-IIIa pts	1. DFS in ITT, stage IB-IIIa 2. DFS in PD-L1 TPS $\geq$ 50%
Results	1. HR 0.66, CI [0.5, 0.88]; $P = .0039$ 2. HR 0.79, CI [0.64, 0.96]; $P = .02$ 3. HR 0.81, CI [0.67, 0.99]; $P = .04^a$	1. HR 0.76, CI [0.63, 0.91]; $P = .0014$ 2. HR 0.82, CI [0.57, 1.18]; $P = .14^a$
Median DFS	1. NE vs 35.3 mo 2. 42.3 vs 35.3 mo 3. NE vs 37.2 mo <sup>a</sup>	1. 53.6 vs 42 mo 2. NR vs NR <sup>a</sup>
PD-L1 assay	SP263, Ventana	22C3, Agilent
Adjuvant chemotherapy	Mandatory	Considered

IMpower010 more stage III

KEYNOTE larger and placebo controlled

All KEYNOTE 1<sup>o</sup> endpoints inclusive of stage IB

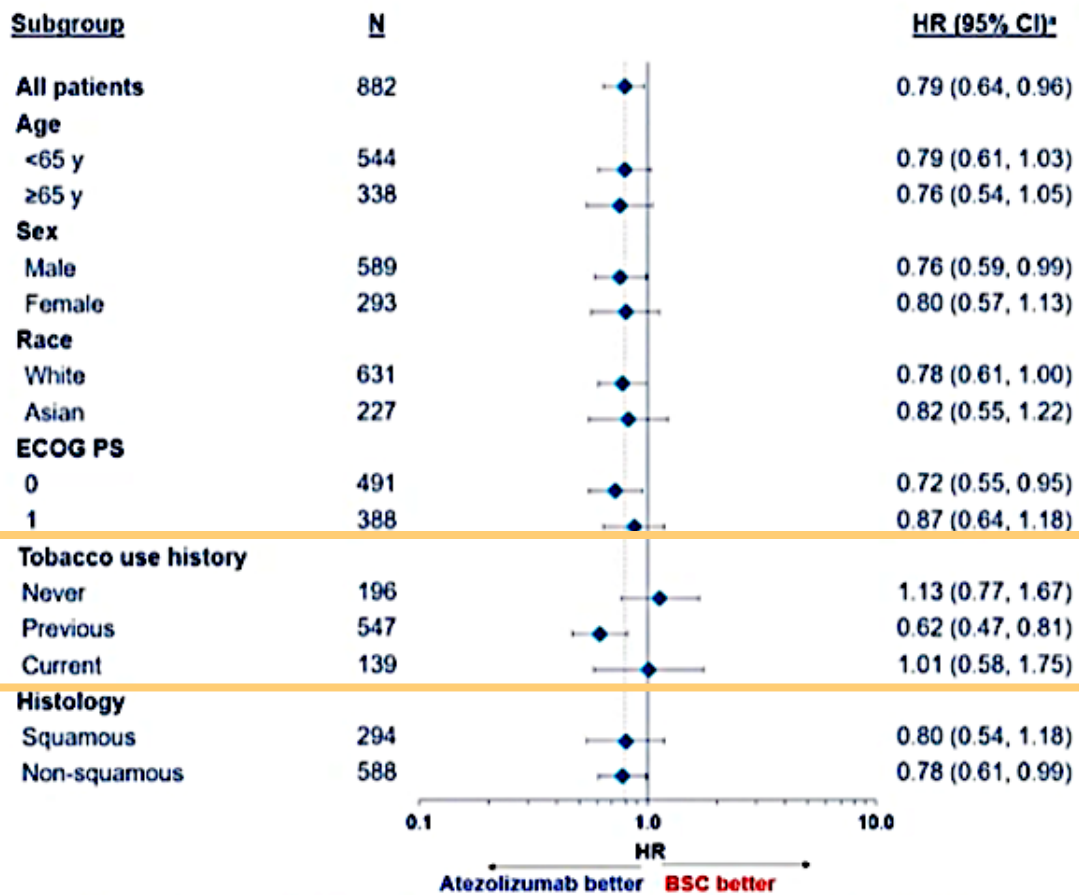
KEYNOTE control arm performed well

Different PD-L1 assays

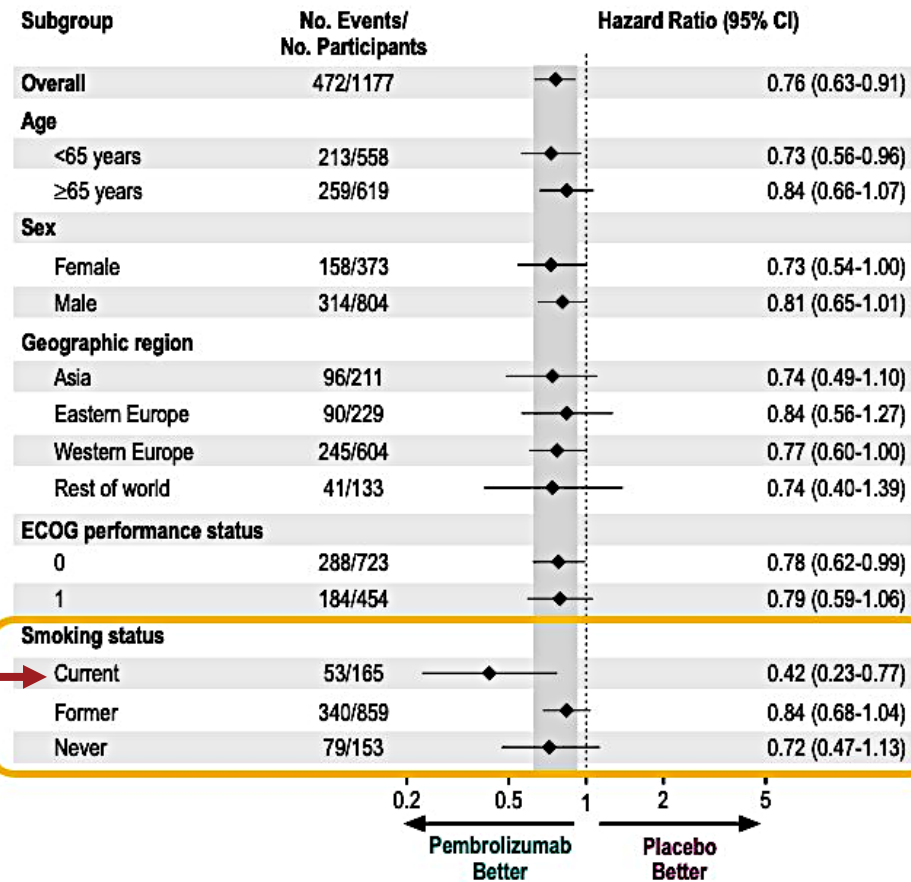
15% KEYNOTE no chemo, 50% carboplatin

# How do trials compare?

## IMpower010

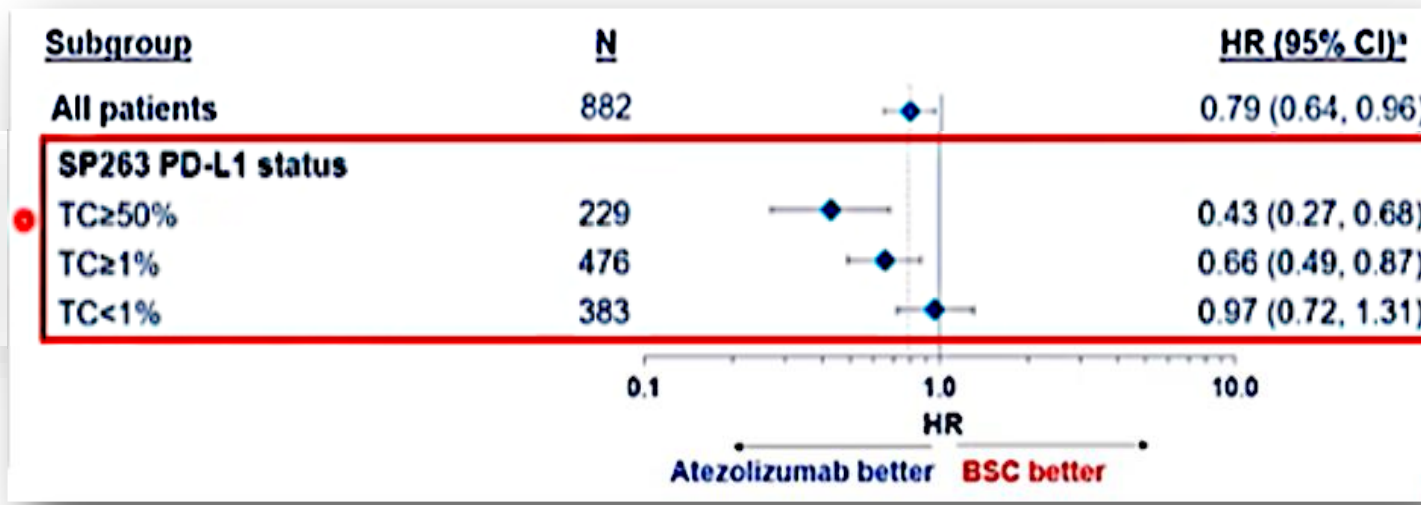


## PEARLS/KEYNOTE-091

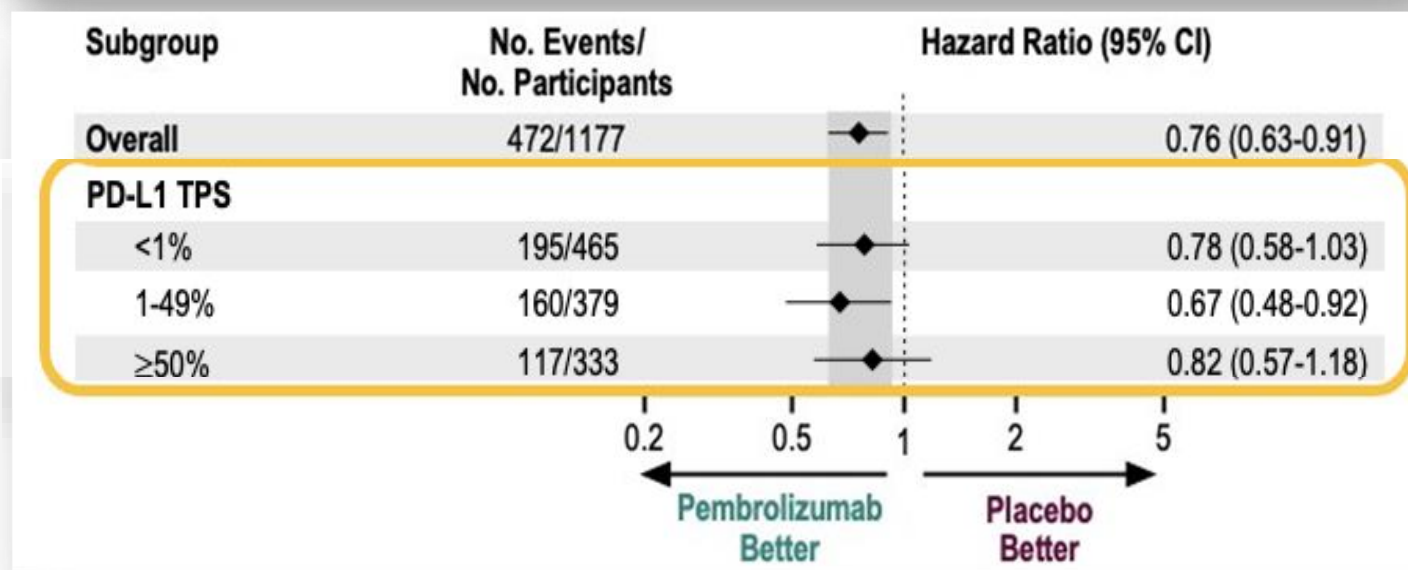


Felip E, Lancet 2021; Wakelee, H, ASCO 2021; O'Brien M, Lancet Oncol, 2022, ESMO 2022, ASCO 2022

# IMpower010

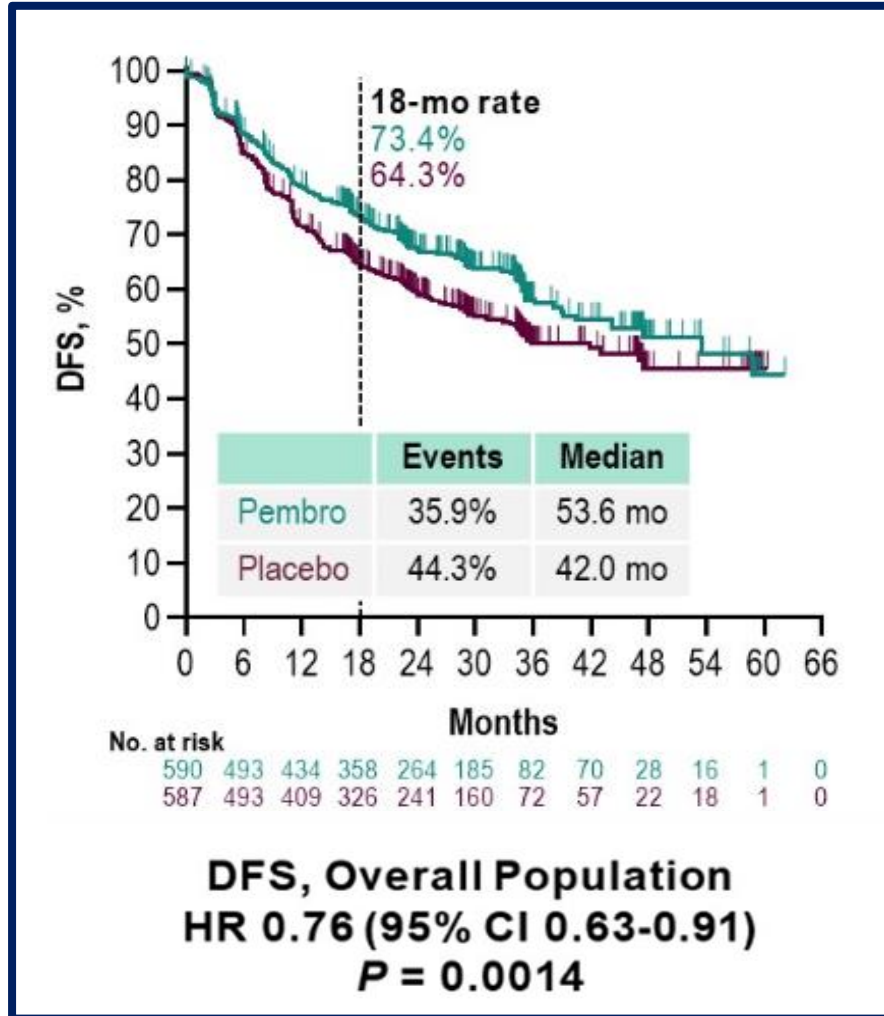


# PEARLS KEYNOTE-091



Felip E Lancet 2021; O'Brien M, Lancet Oncol 2022

# How do the trials compare?



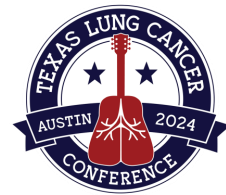
O'Brien M, ASCO 2022; Wakelee H, ASCO 2021



# FDA Approved Adjuvant Immunotherapy for NSCLC



	PD-L1 < 1%		PD-L1 1-49%		PD-L1 > 50%	
IB (>4cm)						
II						
IIIA						



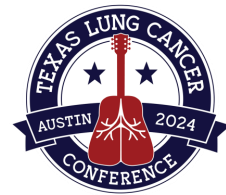
# FDA Approved Adjuvant Immunotherapy for NSCLC

	PD-L1 < 1%		PD-L1 1-49%		PD-L1 > 50%	
<b>IB (&gt;4cm)</b>						
<b>II</b>			<b>Atezolizumab</b>		<b>Atezolizumab</b>	
<b>IIIA</b>			<b>Atezolizumab</b>		<b>Atezolizumab</b>	

## Atezolizumab

DFS HR 0.66 (95%CI 0.50-0.88) p=0.0039

Stage II-III A, PD-L1 > 1%



# FDA Approved Adjuvant Immunotherapy for NSCLC

	PD-L1 < 1%		PD-L1 1-49%		PD-L1 > 50%	
<b>IB (&gt;4cm)</b>		<b>Pembrolizumab</b>		<b>Pembrolizumab</b>		<b>Pembrolizumab</b>
<b>II</b>		<b>Pembrolizumab</b>	<b>Atezolizumab</b>	<b>Pembrolizumab</b>	<b>Atezolizumab</b>	<b>Pembrolizumab</b>
<b>IIIA</b>		<b>Pembrolizumab</b>	<b>Atezolizumab</b>	<b>Pembrolizumab</b>	<b>Atezolizumab</b>	<b>Pembrolizumab</b>

**Atezolizumab**  
 DFS HR 0.66 (95%CI 0.50-0.88) p=0.0039  
 Stage II-III A, PD-L1 > 1%

**Pembrolizumab**  
 DFS HR 0.76 (95%CI 0.63-0.91) p=0.0014  
 Stage IB(>4cm)-III A, regardless PD-L1



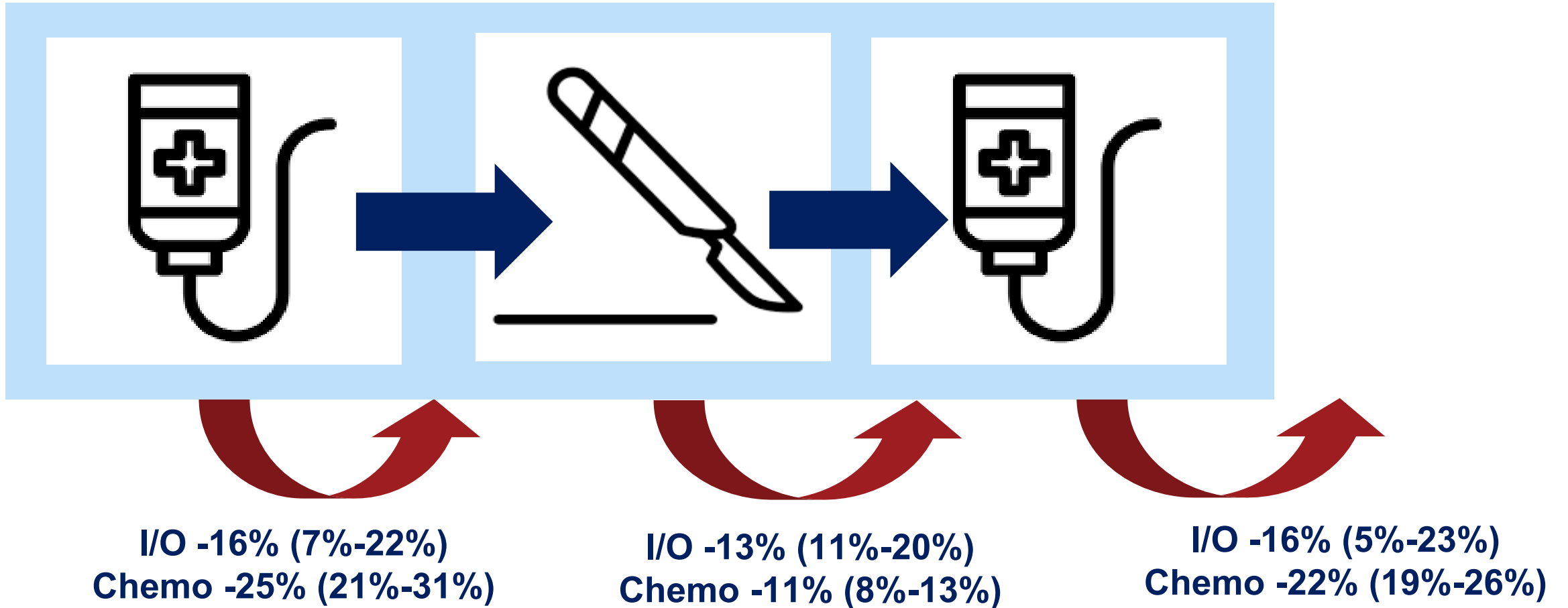
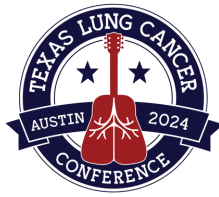


# Decrease treatment-related attrition

Endorsed by



# Therapeutic Attrition



Heymach J, AACR 2023; Wakelee H, NEJM 2023; Lu S, ASCO 2023; Provencio M, NEJM 2023.

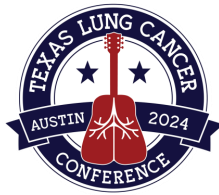
# Adjuvant Therapy Compliance in Chemotherapy Era



Author	Years	Data Set	Stages	#	% adjuvant
Kassam (2007)	2004-2005	Toronto, CA	IB-IIIa	89	37%
Younis (2008)	2005	Nova Scotia, CA	II-III	41	54%
Massard (2009)	2004-2005	Paris, France	IA-IIIa	219	40%
Shukuya (2010)	2005-2007	Shizuoka, Japan	IB-IIIa	109	31%
Cuffe(2012)	2004-2006	Ontario, CA	I-IV	3351	31%
Teh (2014)	2008-2013	Oxford, UK	IB-IV	126	35%
Williams (2014)	2004-2008	VA, USA	IB-IIIa	3318	29%
Berry (2015)	2006-2012	Duke, USA	II-IIIa (N1)	162	57%
Barni (2015)	2010-2012	AIOM, Italy	II-IIIa	99	59%
Rajaram (2016)	2002-2011	NCDB, USA	IB-IIIa	48250	47%
Ahmad (2017)	1998-2010	NCDB, USA	T3N0	824	31%
Chouaid (2018)	2009-2011	France, Germany, UK	IB-IIIa	831	48%
Nelson (2019)	2006-2017	MDACC, USA	II-III	471	47%
Farrow (2020)	2006-2013	NCDB, USA	II-III	13462	70%
Toubat (2020)	2004-2014	NCDB, USA	T1-3N1	14892	54%
Rodriguez-Quintero (2023)	2006-2018	NCDB, USA	IB-IIIa	2305	52%

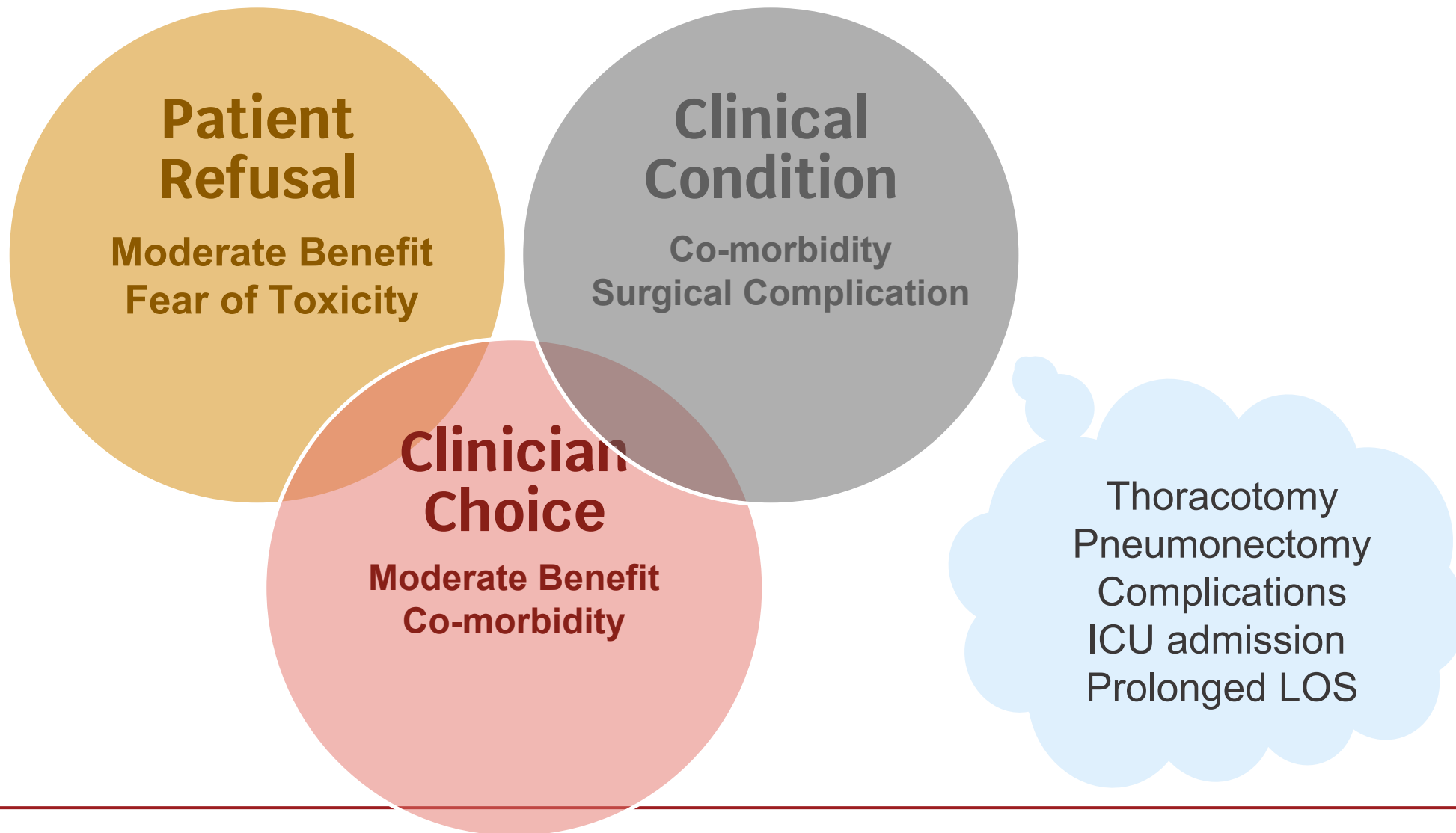


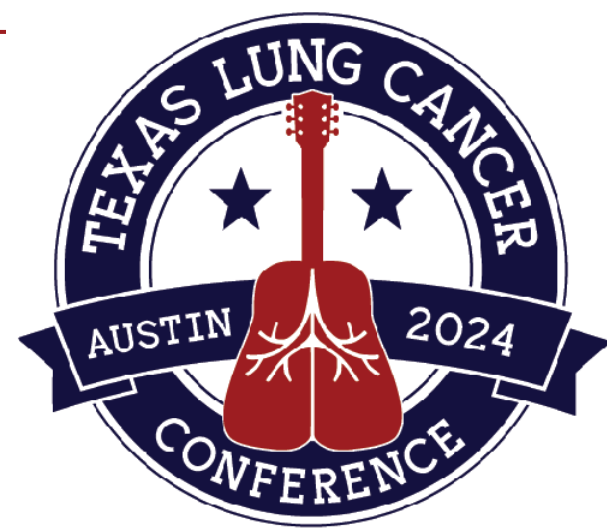
# Need to RIOT



# Return to Intended Oncologic Treatment

# Reasons for Non-Receipt of Adjuvant Therapy





# What is coming?

Endorsed by



# Peri-operative Immunotherapy Landscape



## Neoadjuvant

CheckMate-816

## Peri-adjuvant

AEGEAN

NeoTorch

Keynote-671

CheckMate 77T

## Adjuvant

IMPower010

PEARLS/Keynote-091

ANVIL

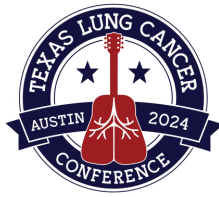
BR31

ALCHEMIST chemo I/O

Mermaid

IMPower030

# Adjuvant Immunotherapies



## CONCLUSIONS

- Two approved agents, both for use after adjuvant chemotherapy
- Associated with significant disease-free survival improvements
- Pembrolizumab: IB-IIIA regardless of PD-L1 staining (HR 0.76)
- Atezolizumab: II-IIA with PD-L1 staining > 1% (HR 0.66)
- Need to improve RIOT rates for resected NSCLC
- Many unanswered questions remain

PD-L1 low or negative tumors

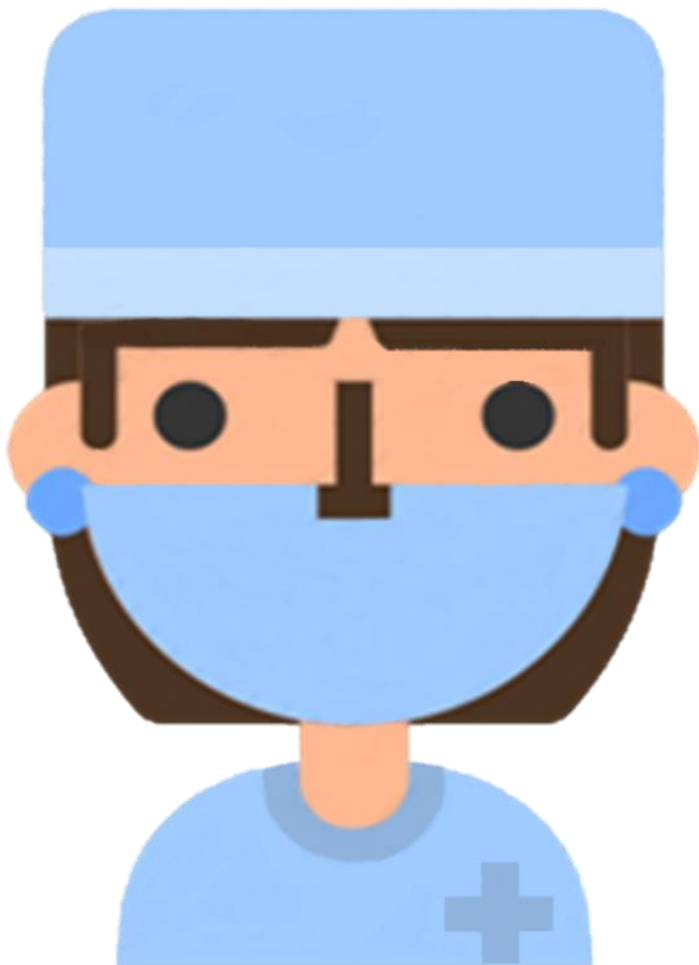
Sequencing of therapy

Need for adjuvant after neoadjuvant

Role of pathologic response of MRD







**THANK YOU**

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