CURRENT ROLE OF ADJUVANT IMMUNOTHERAPY IN NSCLC

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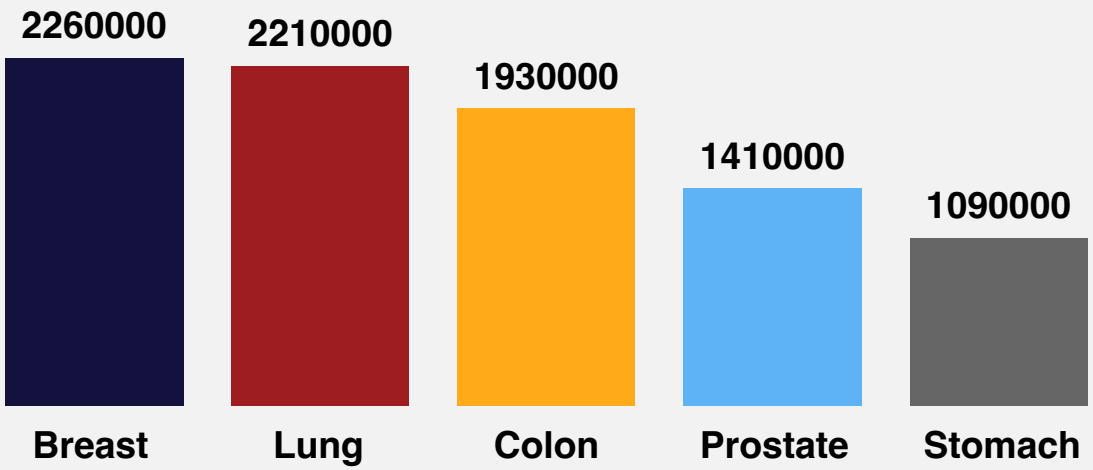
Creating Aha! Moments In Healthcare

Lung Cancer Incidence and Mortality

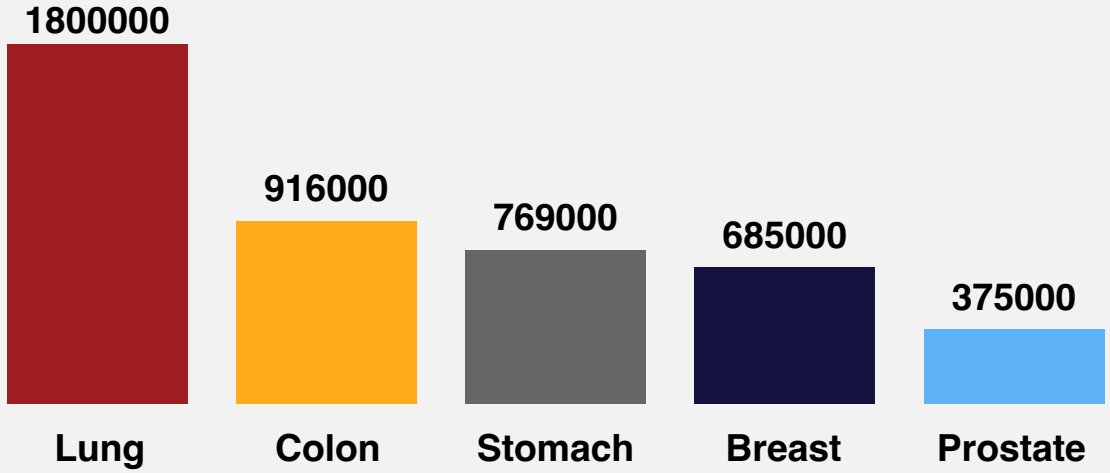
2,210,000 were diagnosed with lung cancer in 2020

1,800,000 died from lung cancer in 2020

Estimated Cases by Tumor Type



Estimated Deaths by Tumor Type

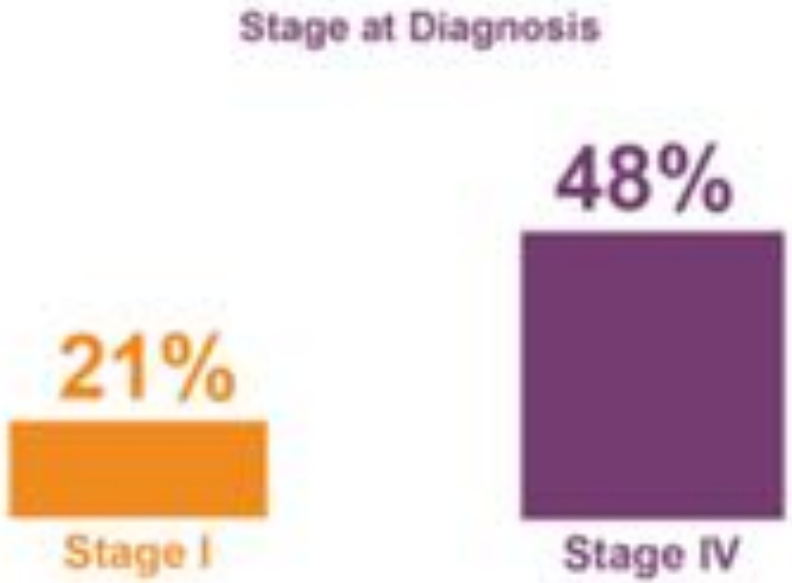


WHO Cancer Facts 2020

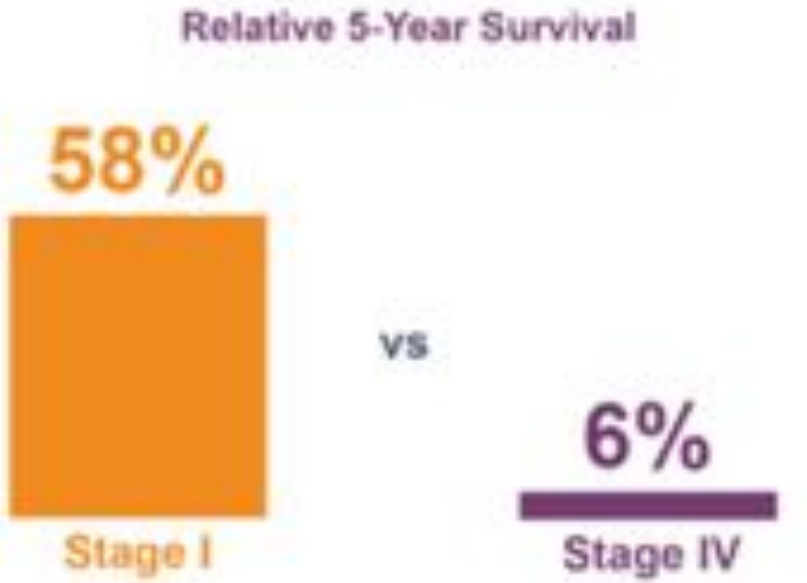
Poor Prognosis in NSCLC

Two-pronged problem

We diagnose pts too late

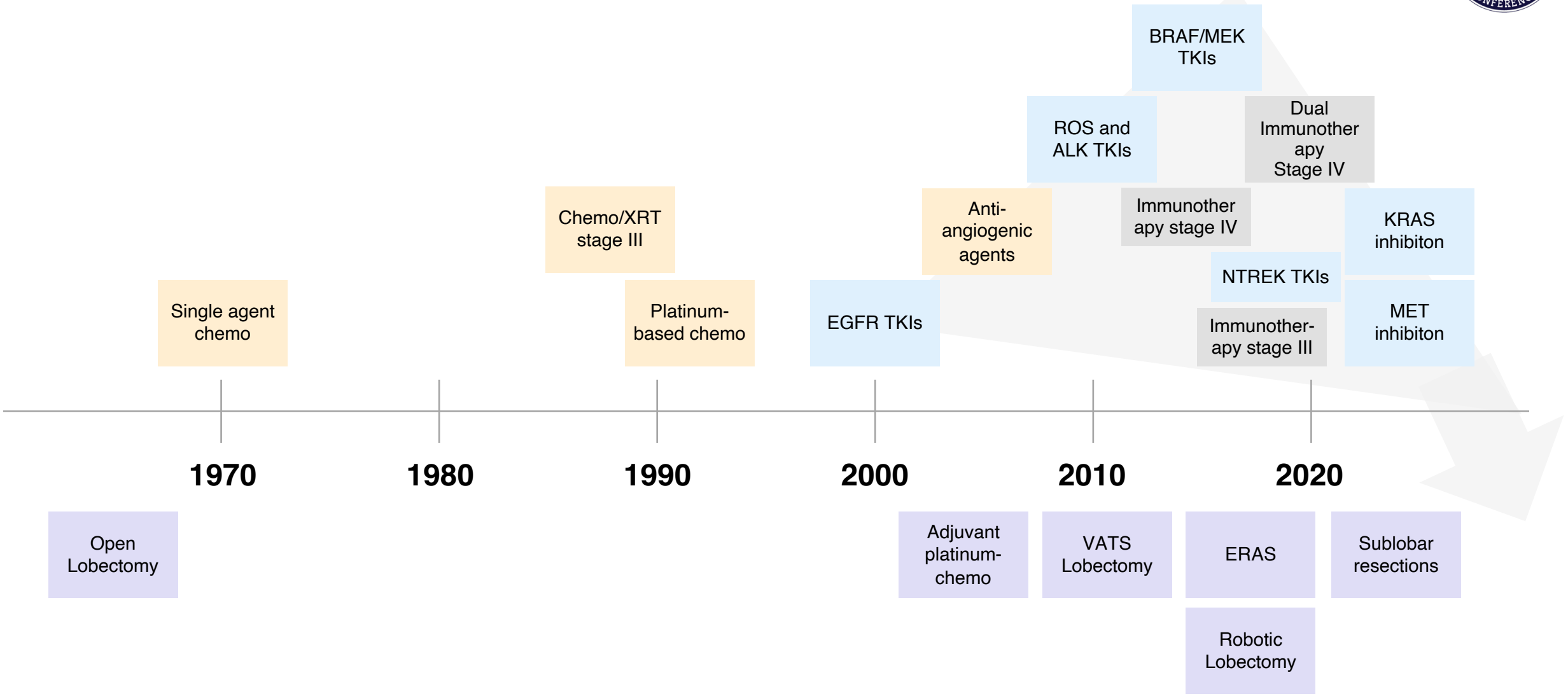


Treatments are ineffective

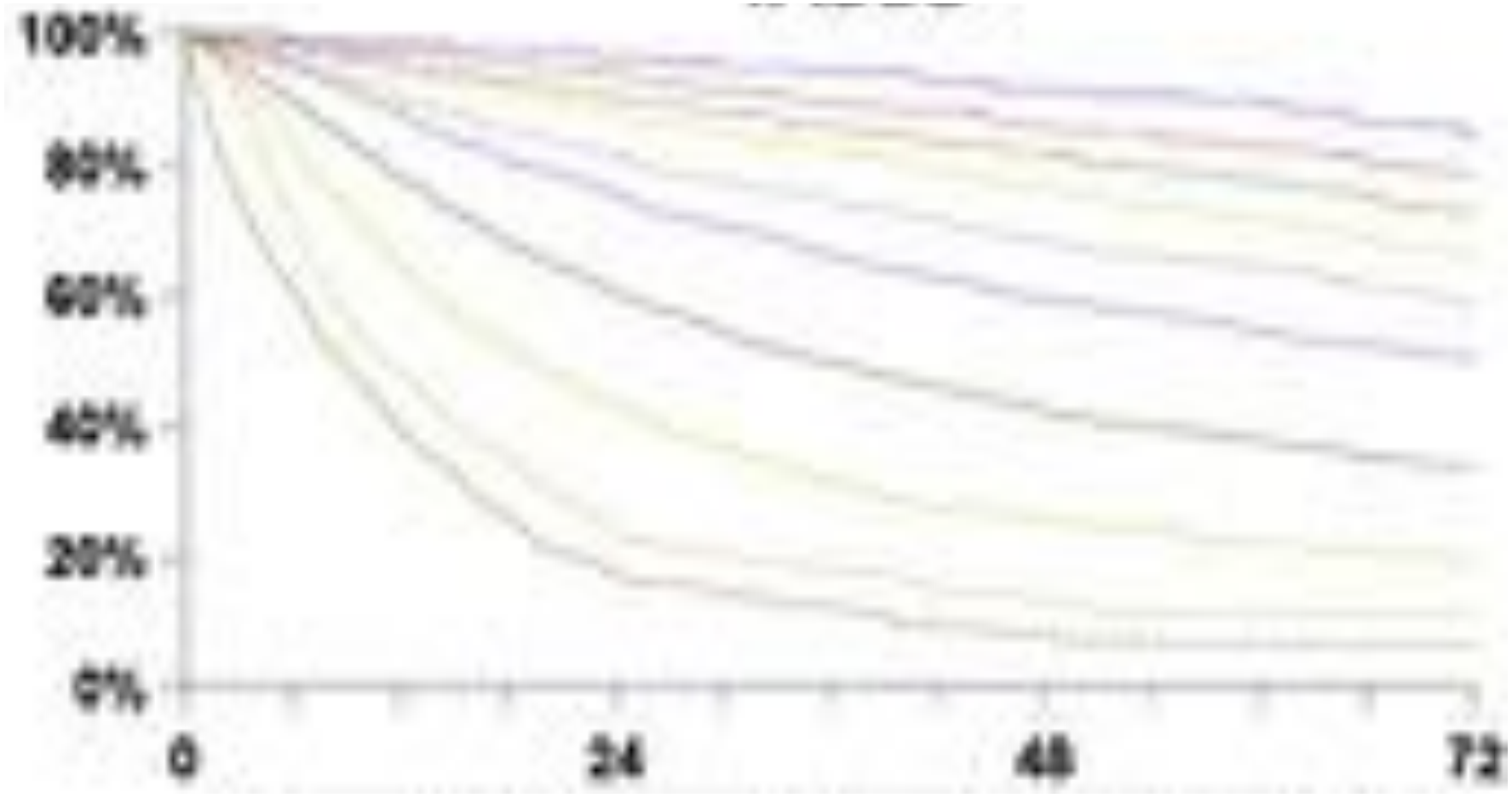


Early detection and treatment are critical to improving clinical outcomes in patients with lung cancer

Milestones in NSCLC Treatment



Lung Cancer Survival by Stage



5y OS

Stage IB: 71%

Stage IIA: 64%

Stage IIB: 55%

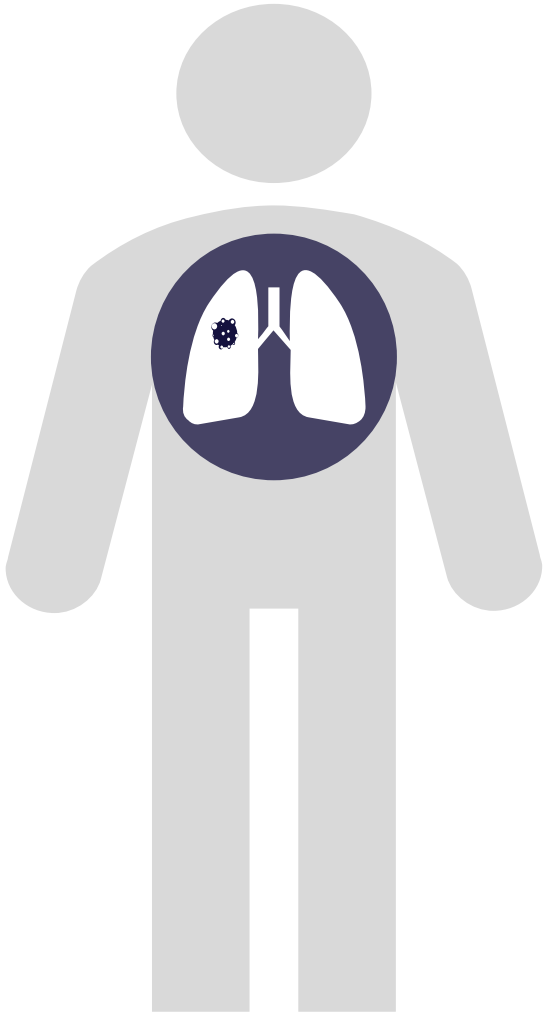
Stage IIIA: 37%

Goldstraw P, JTO, 2016

Treatment for early-stage NSCLC

Local Therapy	→	**For local-regional control**
Systemic therapy	→	**To reduce risk of distant relapse**

- Chemotherapy
- Targeted therapy
- Cancer immunotherapy



Because good surgery is not enough to cure patients

Lung cancer is a systemic disease

Basic NSCLC Treatment Strategies 2022

	IA *Resection alone* ***Consider Sublobar Resection***	**Resectable IB, II and IIIA** *Surgery ±* *(neo)adjuvant* ***cancer immunotherapy or targeted therapy*** *± chemotherapy ± RT*	**Unresectable IIIB/C** *Chemotherapy/RT ±* ***cancer immunotherapy or targeted therapy***

T and N	N0	N1	N2	N3
T1	IA	IIA	IIIA	IIIB
T2a/b	IB / IIA	IIA/IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a/b/c	IVA/B/C	IVA/B/C	IVA/B/C	IVA/B/C

IVA/B/C
*Systemic therapy****: cancer immunotherapy****; **targeted therapy;** chemotherapy*

NCCN guidelines for NSCLC v8.2020 (15 September 2020); Postmus, et al. Ann Oncol 2017

HOW do we incorporate immunotherapies therapy into resectable NSCLC?

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Conquering Thoracic Cancers Worldwide

How to incorporating Novel Therapies into Resectable NSCLC

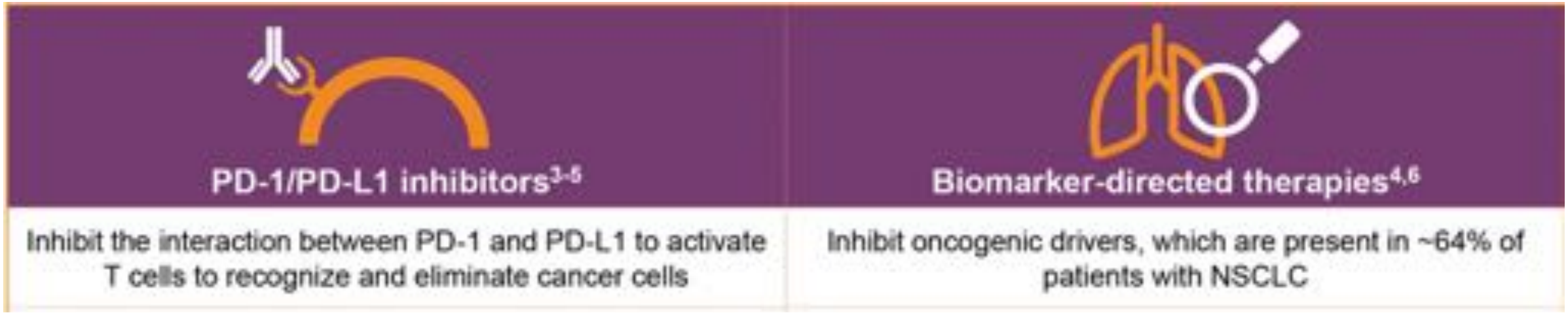
Select appropriate patient

Decide neoadjuvant of adjuvant

Relay importance to the patient

Patient Selection

- Targeted therapies and immunotherapies are typically mutually exclusive
- Approvals for use are dependent on biomarkers
- Increases importance of pre-treatment biopsy for molecular analysis



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
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Physiologic Evaluation

- PFTs
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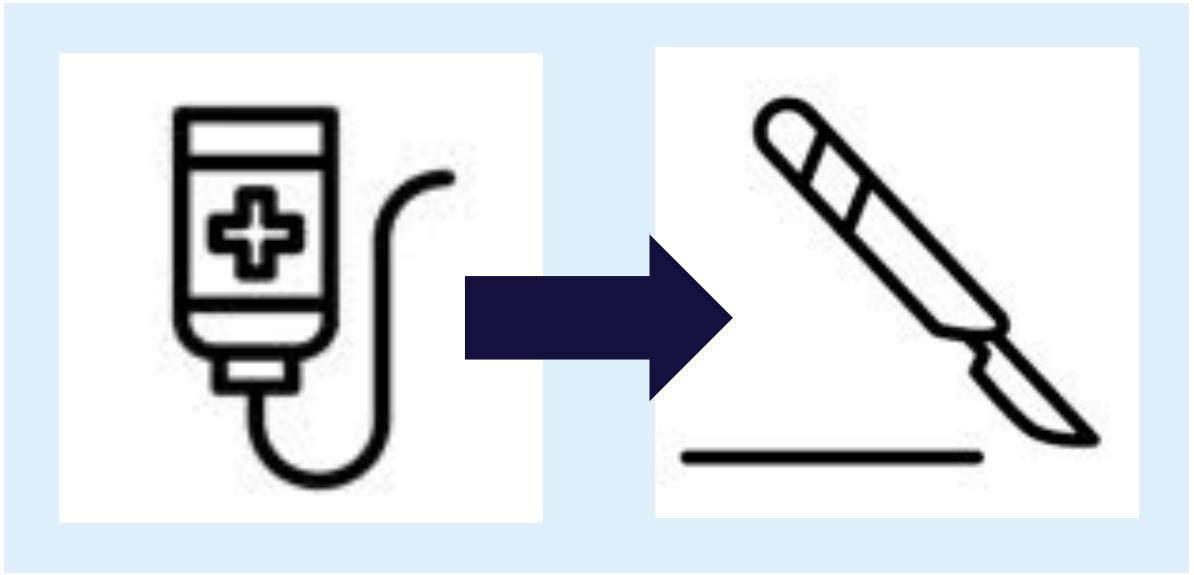
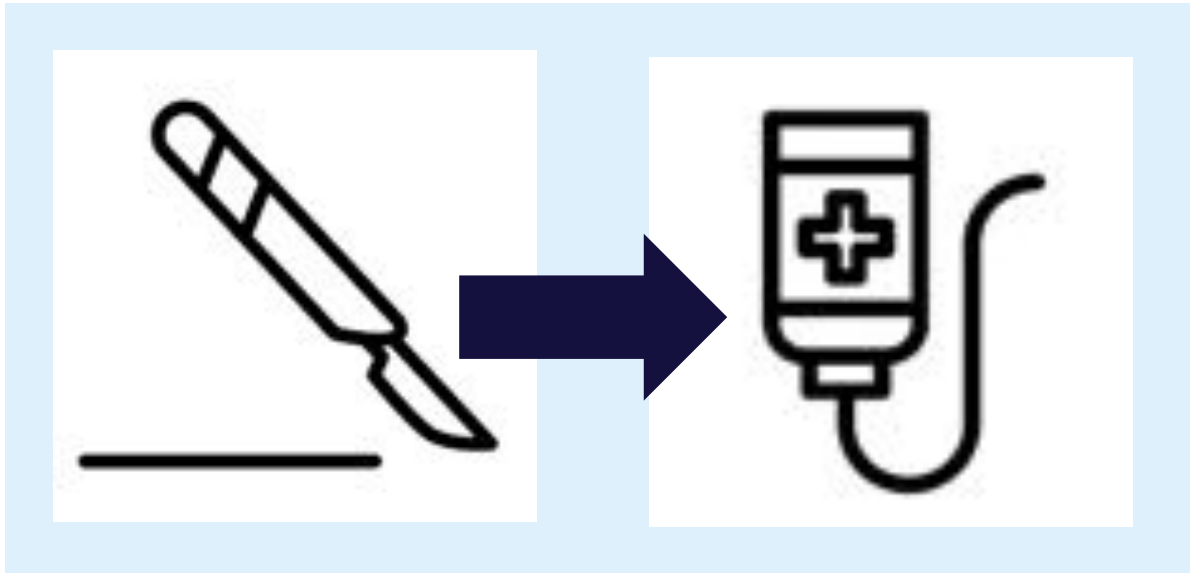
Biomarker testing

- EGFR
- ALK
- PD-L1
- NGS

Sequencing with Resection





NEOADJUVANT or ADJUVANT

Considerations for adjuvant I/O or targeted therapy

PRO	CON
Proven standard of care for resected stage IB and II disease	Poor tolerance and compliance with adjuvant protocols
Tumor biomarkers can guide tx decisions	Longer treatment times
No surgical delays	Need for biomarker testing from resection specimen
No hilar and mediastinal fibrosis	
No risk of disease progression resulting in missed opportunity for curative surgery	
Clinical stage I patients upstaged at resection	

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

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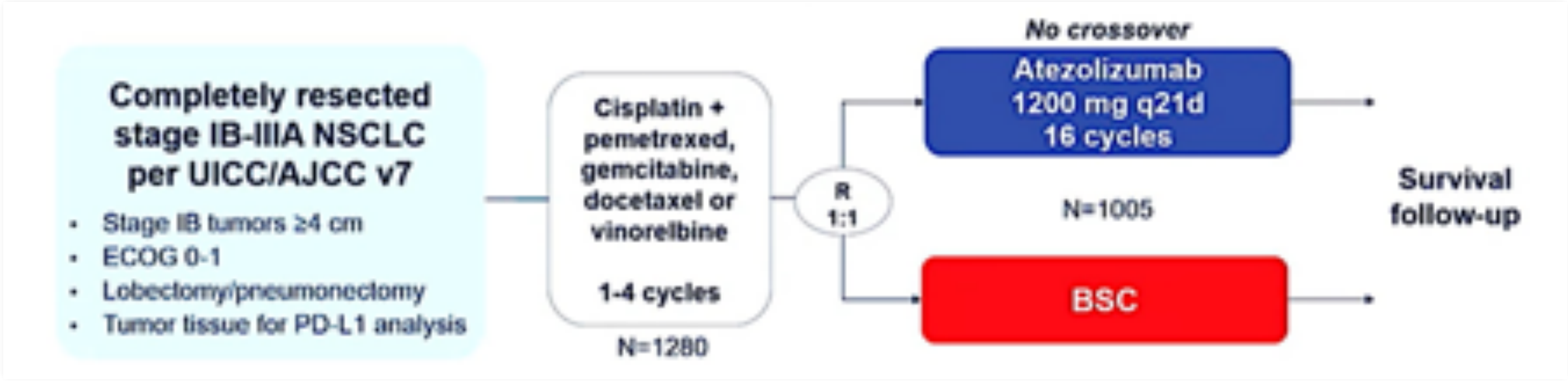
Impower010



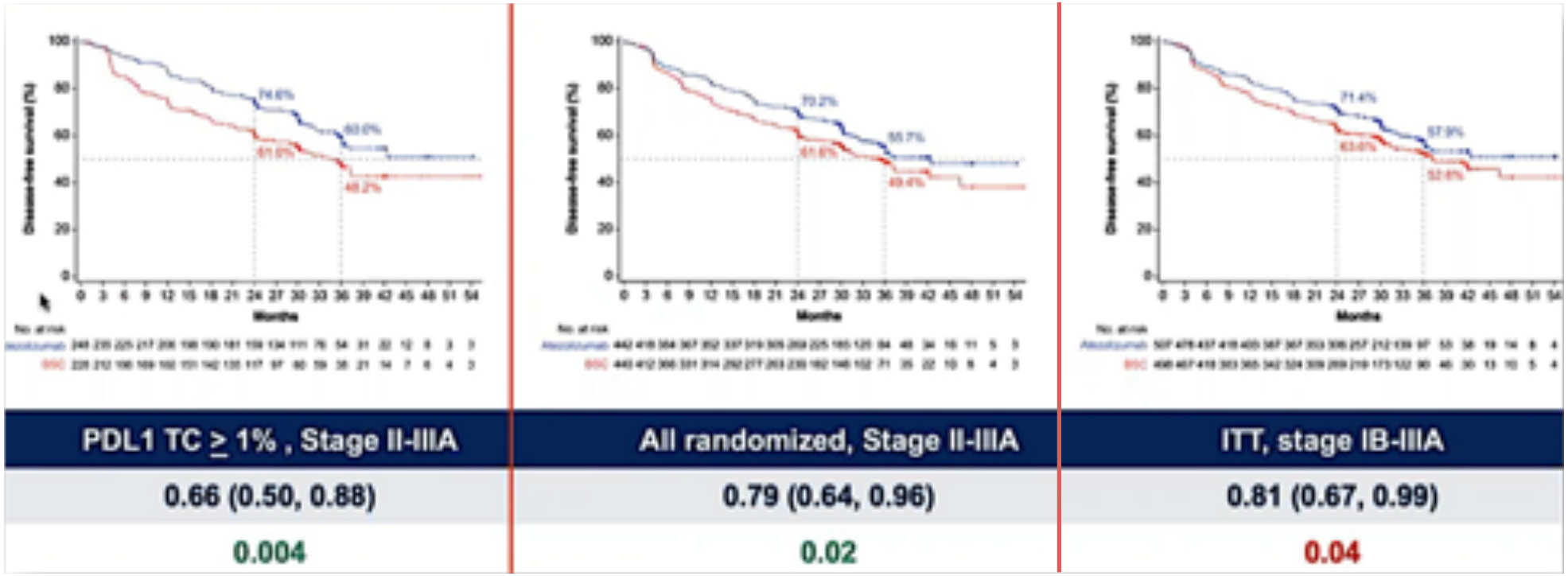
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥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 ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Wakelee, H, ASCO 2021.

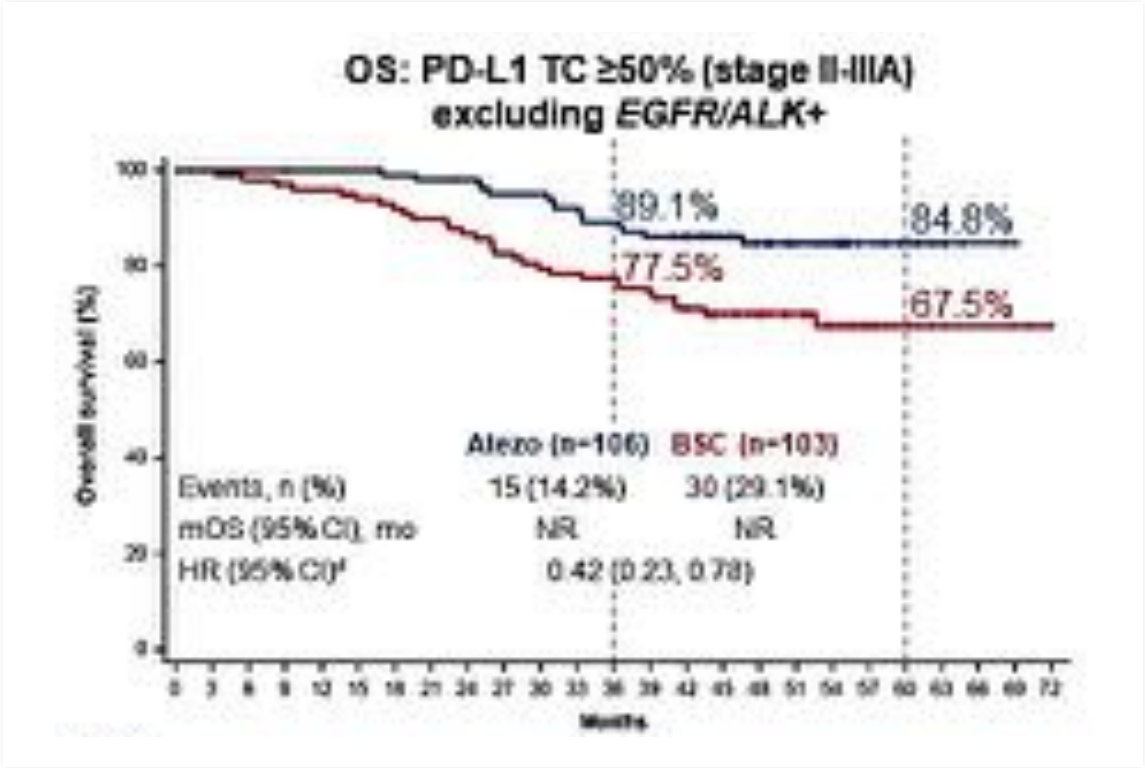
Impower010: DFS

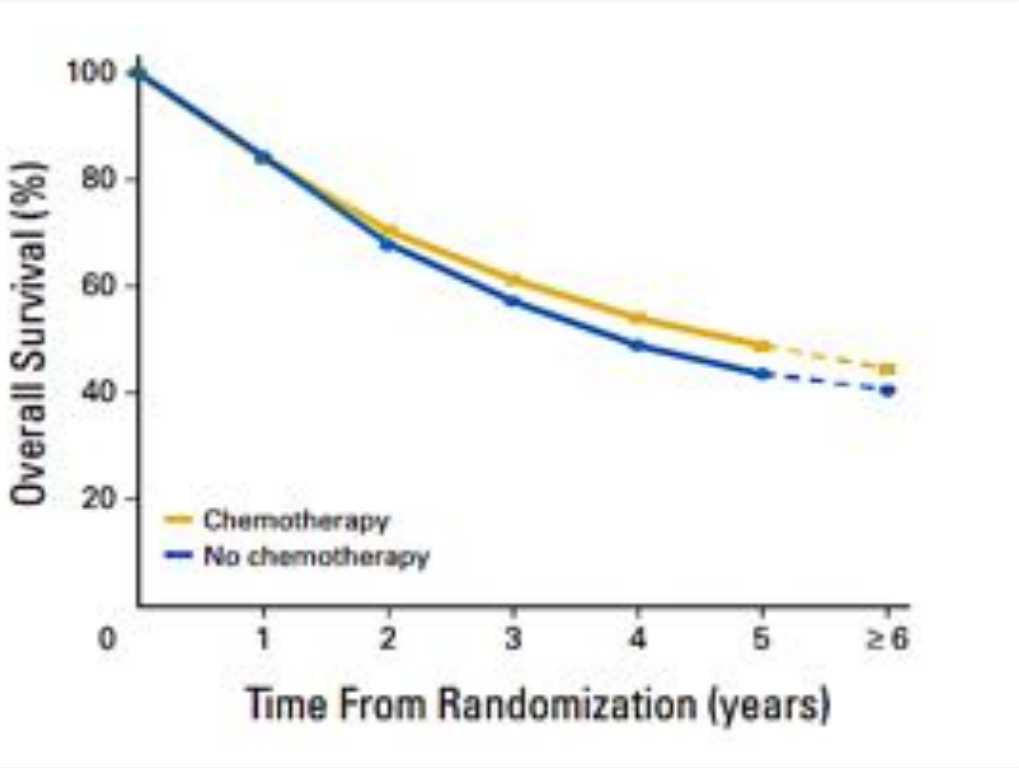


- Adjuvant atezolizumab following resection and adjuvant chemotherapy showed significant improvement in DFS in PD-L1 >1% stage II-IIIA (HR 0.66) and all randomized stage II-IIA (HR 0.79)
- Safety profile similar to prior atezolizumab monotherapy

Wakelee, H, ASCO 2021.

Adjuvant I/O: Impower010 early OS data





IMPower010
1103 pts IB- IIIA
Surgery + chemo I/O vs Surgery + chemo
85% OS @ 36 month

LACE analysis
4584 pts IB-IIIA
Surgery + cisplatin chemo
<60% OS @ 36 month

Pigon JP, JCO 2016; Felipe E, Lancet WCLC 2022.

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, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡

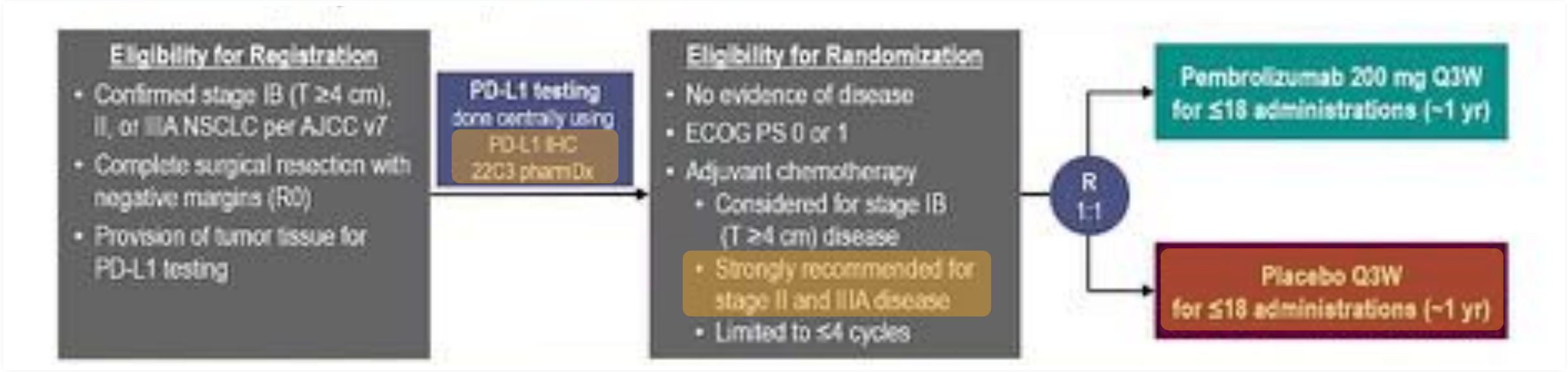
2022 ASCO ANNUAL MEETING

PARIS 2022 ESMO congress

FDA

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

PEARLS/KEYNOTE-091



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

O'Brien M, ESMO 2022, ASCO 2022

PEARLS/KEYNOTE-091: Demographics

Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range), y	65.0 (31-87)	65.0 (37-85)	64.5 (38-82)	65.0 (37-85)
Male sex	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%

Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Current/former smoker	85.3%	88.8%	91.7%	92.1%
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage[a]				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIA	30.0%	27.6%	31.0%	30.3%
EGFR mutation[b]	6.6%	5.8%	3.6%	3.0%
ALK translocation[c]	1.2%	1.2%	1.8%	0.0%

O'Brien M, ASCO 2022

PEARLS/KEYNOTE-091: Treatment

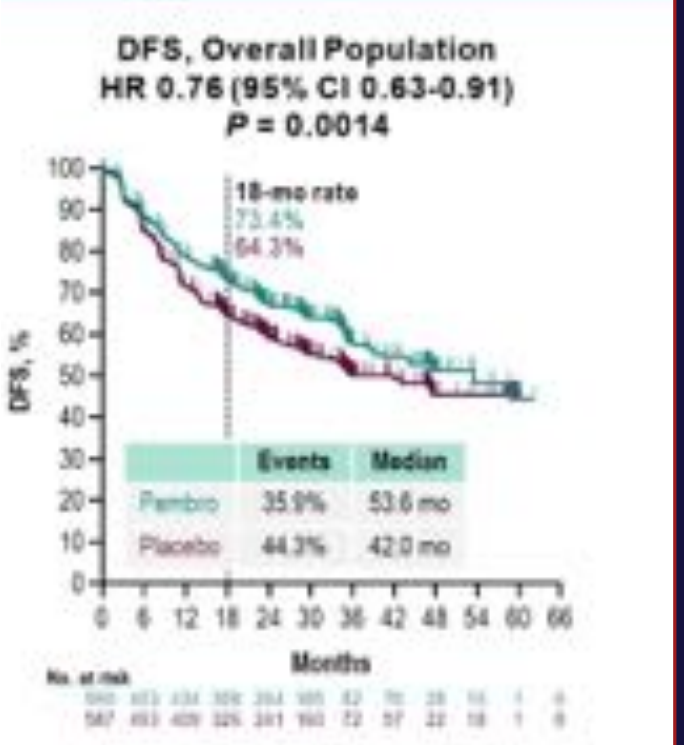
	Pembro (N = 590)	Placebo (N = 587)
Type of surgery, n (%)		
Bilobectomy	47 (8.0)	45 (7.7)
Lobectomy	461 (78.1)	464 (79.0)
Pneumonectomy	65 (11.0)	62 (10.6)
Other	17 (2.9)	16 (2.7)
pN status, n (%)		
0	233 (39.5)	257 (43.8)
1	233 (39.5)	223 (38.0)
2	124 (21.0)	107 (18.2)
Tumor size, n (%)		
≤4 cm	252 (42.7)	239 (40.7)
>4 cm	337 (57.1)	348 (59.3)
Missing	1 (0.2)	0

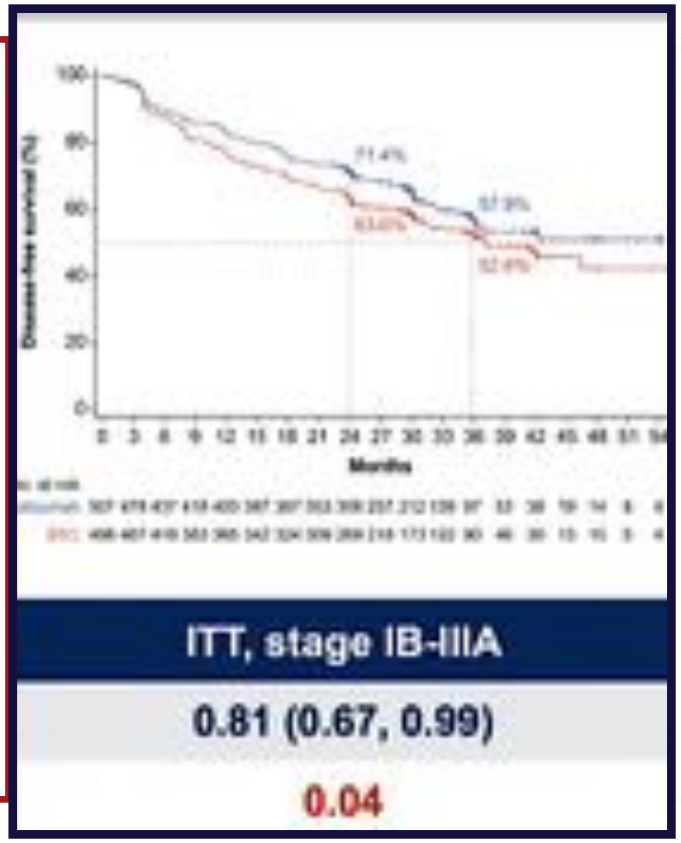
	Pembro (N = 590)	Placebo (N = 587)
Received adjuvant chemotherapy		
No, n (%)	84 (14.2)	83 (14.1)
Reason for not receiving, n		
Participant refused	36	30
Physician decision[a]	46	47
Unknown	2	6
Disease stage in those who did not receive, n		
IB	24	30
II	48	43
IIIA	12	10
Yes, n (%)	506 (85.8)	504 (85.9)
1-2 cycles	35 (5.9)	32 (5.5)
3-4 cycles	471 (79.8)	472 (80.4)

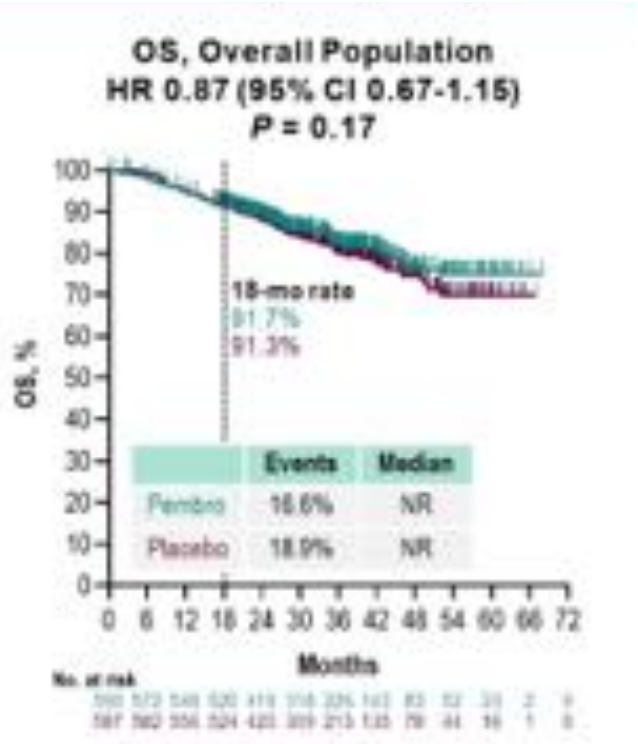
	Pembro (N = 590)	Placebo (N = 587)
Type of adjuvant platinum, n (%)		
Carboplatin-based only	184 (31.2)	171 (29.1)
Cisplatin-based only	301 (51.0)	307 (52.3)
Carboplatin- and cisplatin-based	21 (3.6)	26 (4.4)
Adjuvant regimen, n (%)		
Carboplatin + paclitaxel	60 (10.2)	75 (12.8)
Carboplatin + vinorelbine	81 (13.7)	70 (11.9)
Cisplatin + gemcitabine	27 (4.6)	30 (5.1)
Cisplatin + vinorelbine	241 (40.8)	250 (42.6)
Other	97 (16.4)	79 (13.5)

O'Brien M, ASCO 2022

PEARLS/KEYNOTE-091



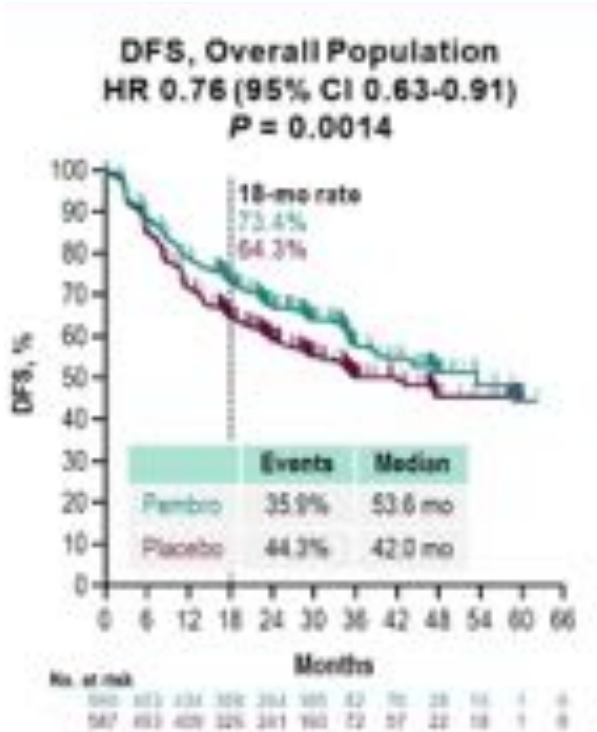


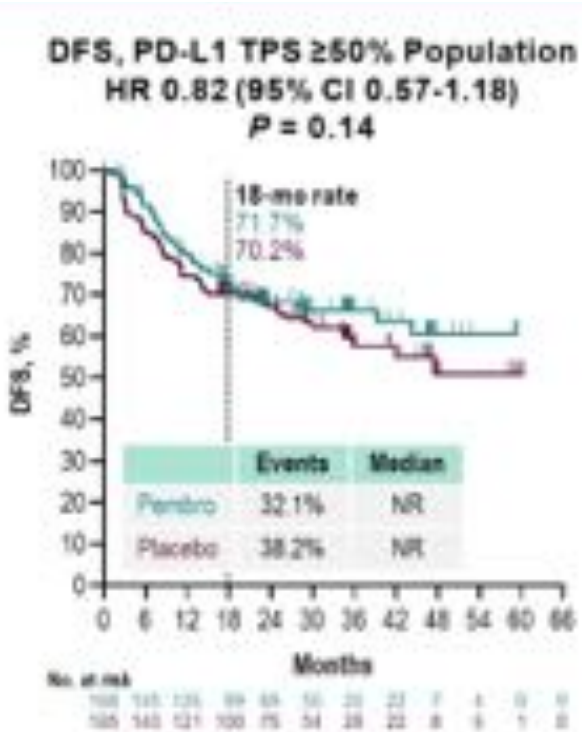


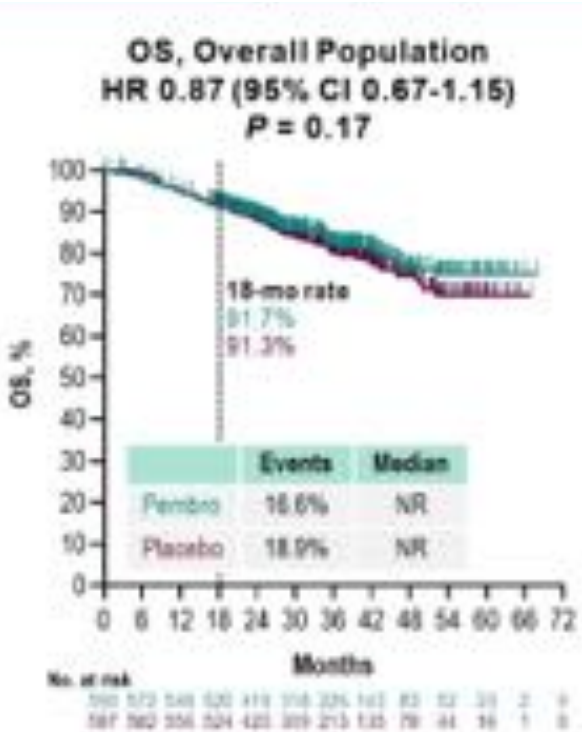
- DFS benefit generally consistent across most protocol-specified subgroups, including PD-L1 TPS <1% (HR 0.78, 95% CI 0.58-1.03) and 1-49% (HR 0.67, 95% CI 0.48-0.92)
- Overall safety profile generally as expected for pembrolizumab monotherapy

O'Brien M, ASCO 2022

PEARLS/KEYNOTE-091







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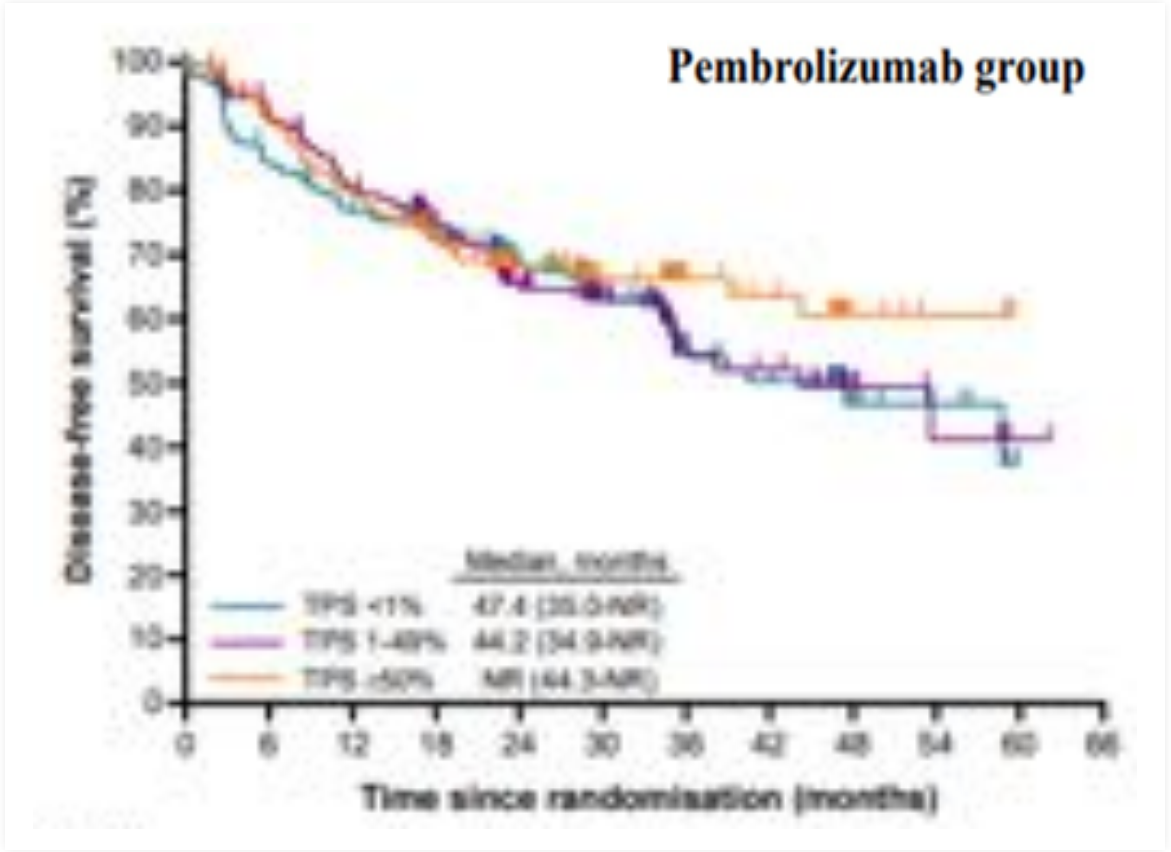
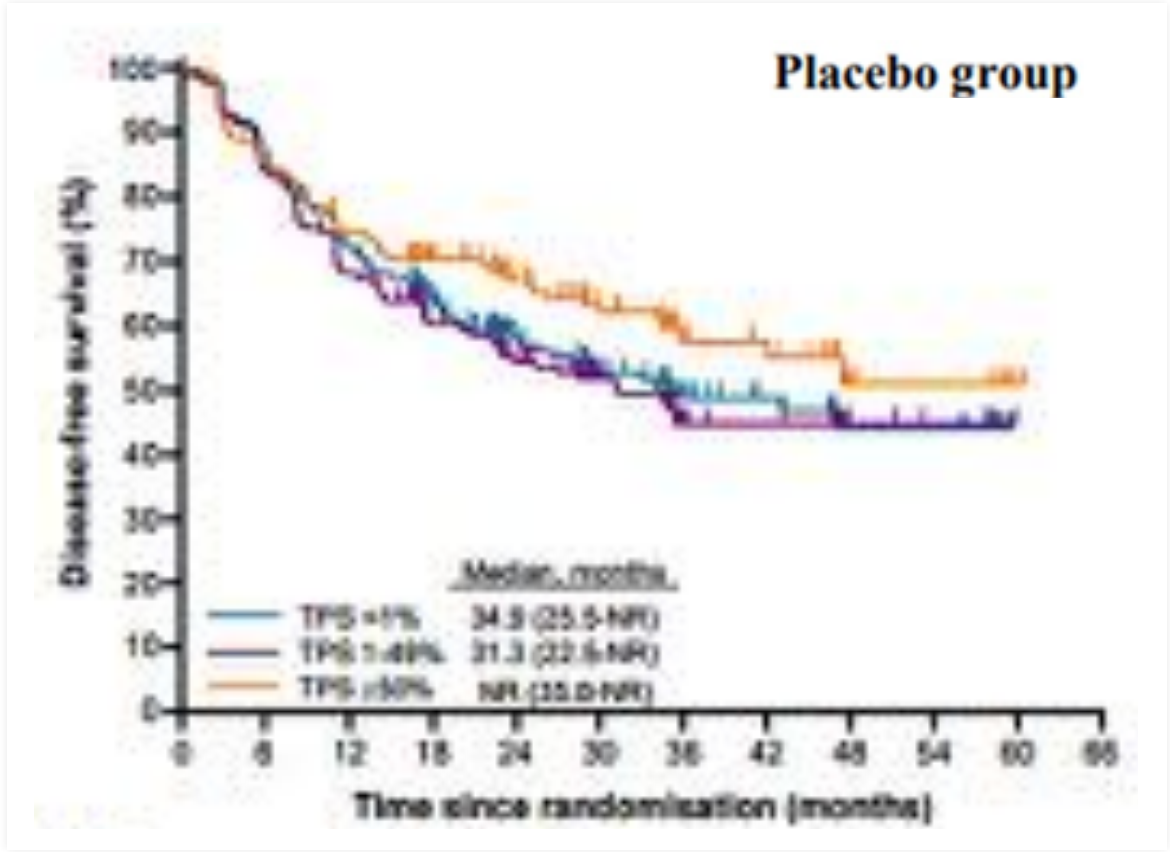
O'Brien M, ASCO 2022

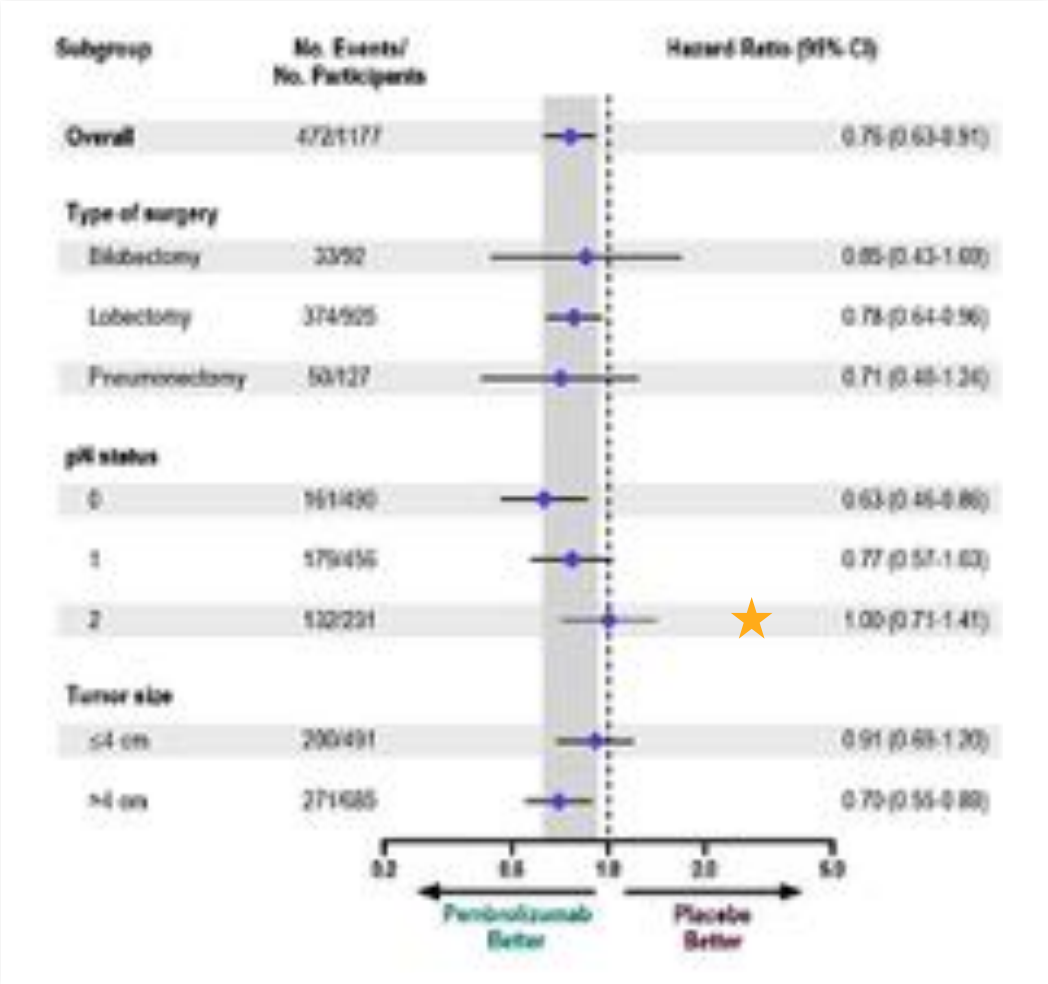
PEARLS/KEYNOTE-091: DFS by PD-L1

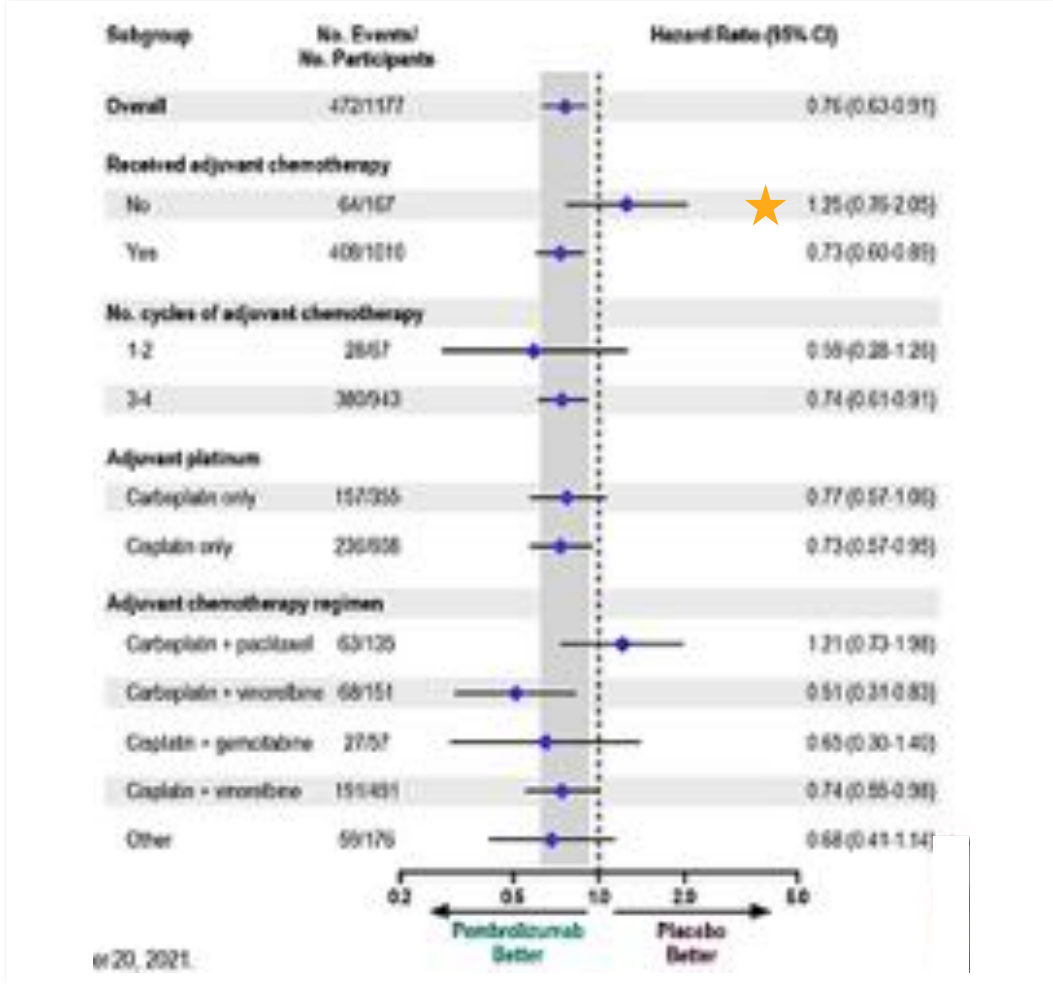




O'Brien M, Lancet Oncol 2022

PEARLS/KEYNOTE-091: Subgroup Analysis by Disease Burden and Treatment





O'Brien M, ASCO 2022

How do the **trials compare?**

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Table. Impower-010 vs KEYNOTE-091/PEARLS Data

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 ≥ 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 ≥ 50%
Results	1. HR 0.66, CI [0.5, 0.88]; $P = .0009$ 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[a]	1. 53.6 vs 42 mo 2. NR vs NR[a]
PD-L1 assay	SP263, Ventana	22C3, Agilent
Adjuvant chemotherapy	Mandatory	Considered

IMpower010 more stage III

KEYNOTE larger and placebo controlled

All KEYNOTE 1º endpoints inclusive of stage IB

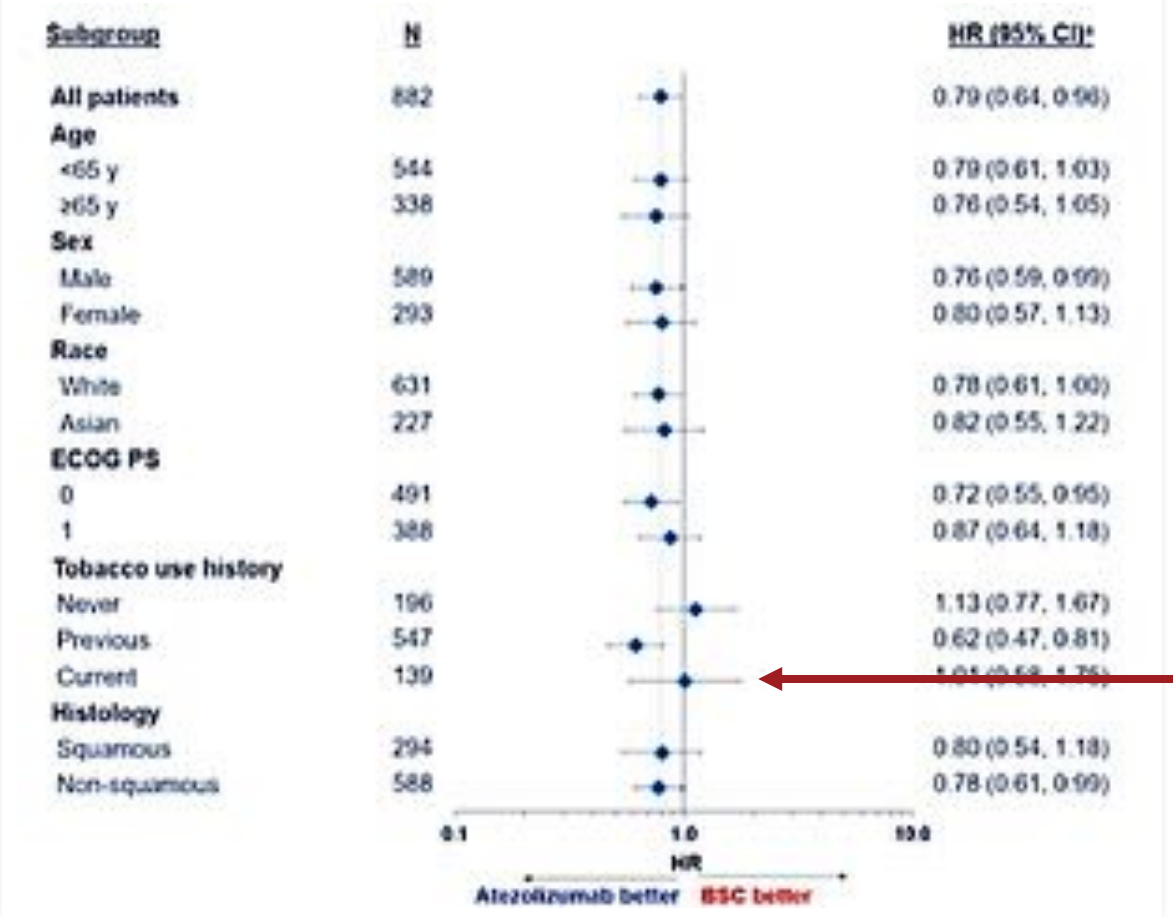
KEYNOTE control arm performed well

Different PD-L1 assays

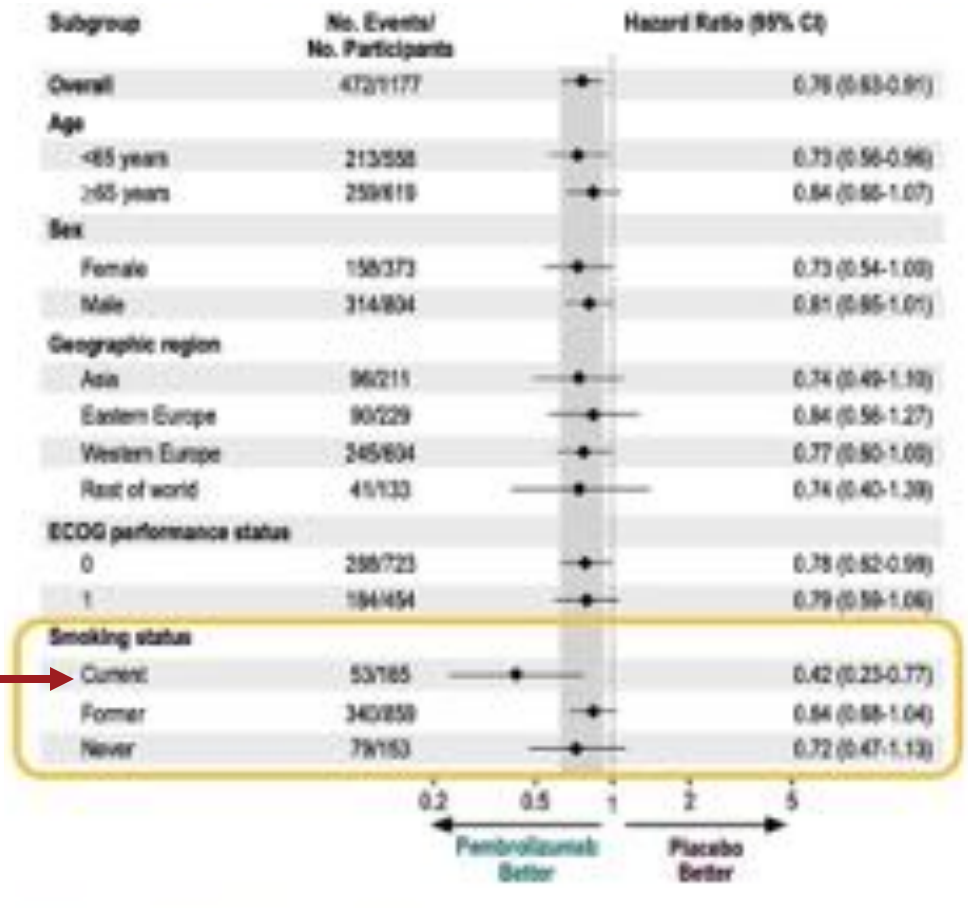
15% KEYNOTE no chemo, 50% carboplatin

DFS Subgroups Analysis

IMpower010



PEARLS/KEYNOTE-091



O'Brien M, ASCO 2022

DFS Subgroups Analysis

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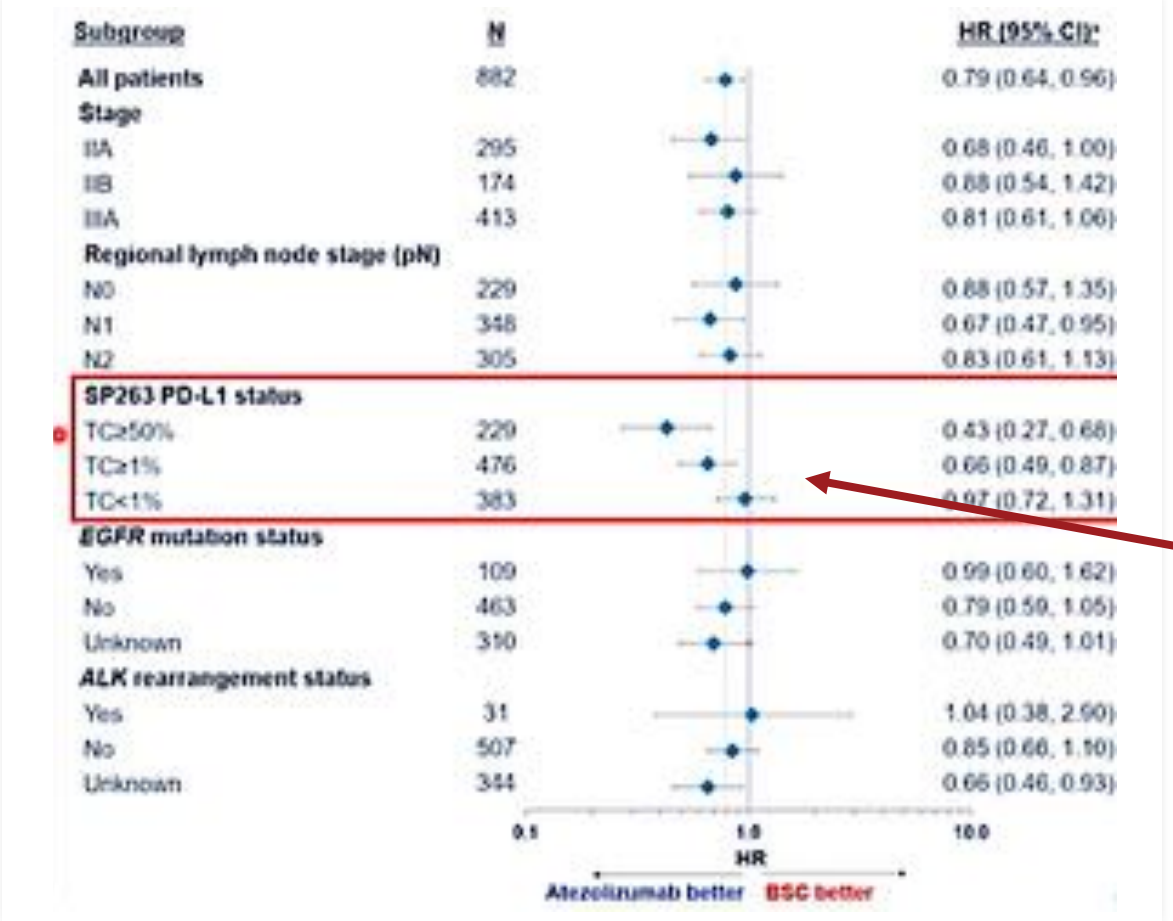

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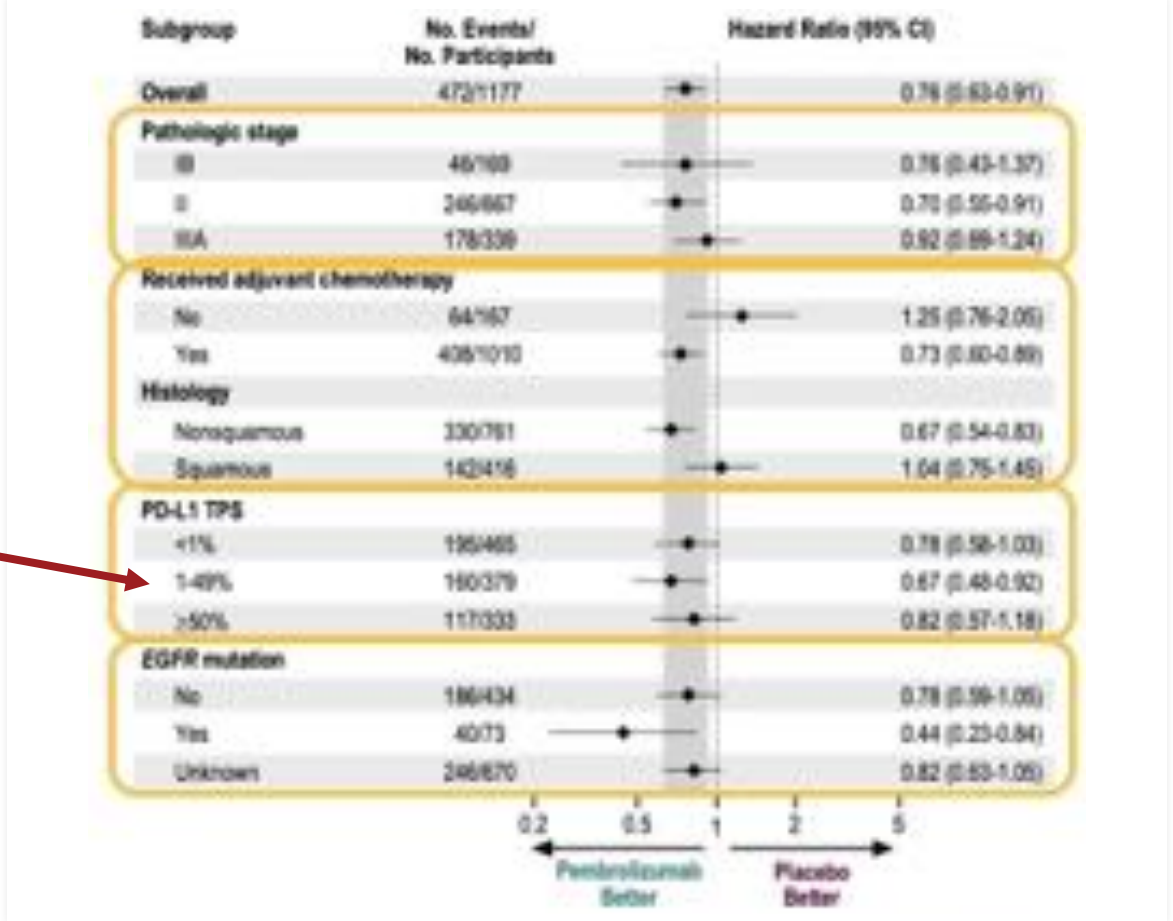

Wakelee H, ASCO 2021, O'Brien M, ESMO 2022

FDA Approved Adjuvant Immunotherapy for NSCLC

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

Pembrolizumab
DFS HR 0.76 (95%CI 0.63-0.91) p=0.0014
Stage IB-IIIA, regardless PD-L1

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

Atezolizumab
DFS HR 0.81 (95%CI 0.67-0.99) p=0.04
Stage IB-IIIA, regardless of PD-L1

What is coming?

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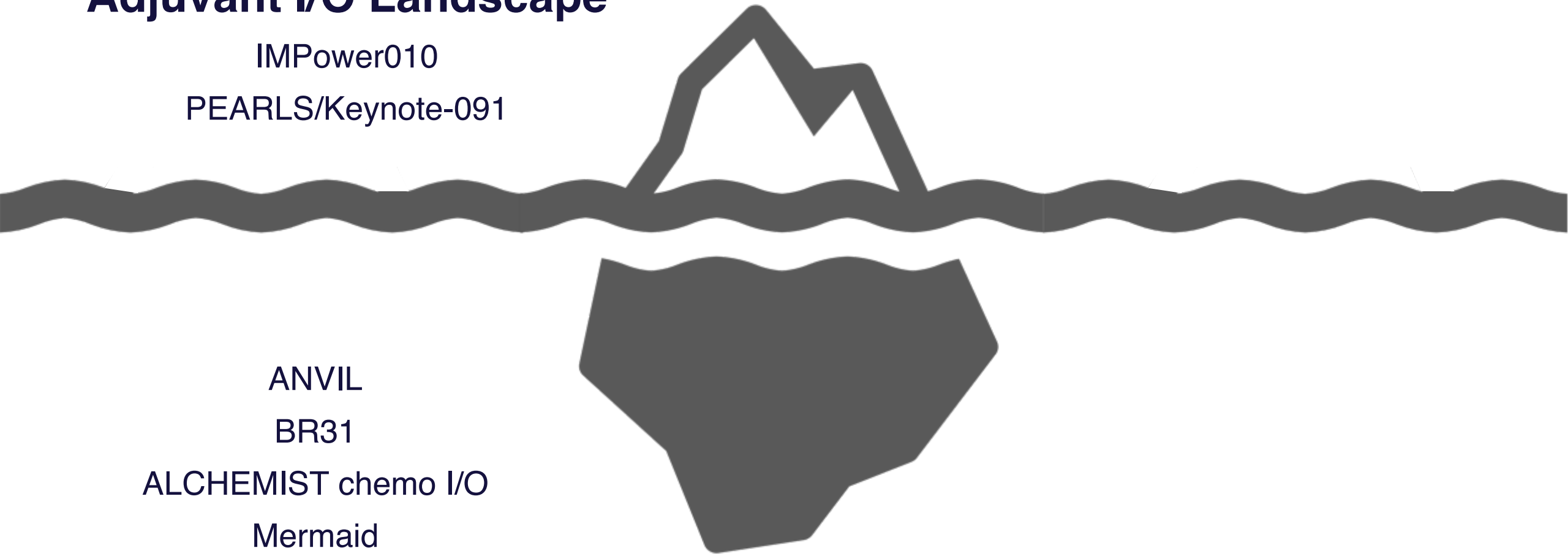
Conquering Thoracic Cancers Worldwide

Adjuvant I/O Landscape

IMPower010

PEARLS/Keynote-091



ANVIL

BR31

ALCHEMIST chemo I/O

Mermaid

Phase III adjuvant I/O trials

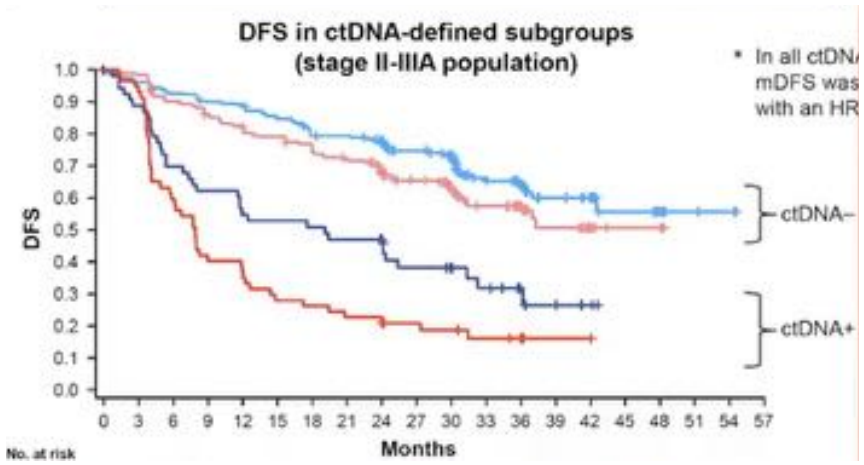
Trial	Inclusion criteria	Treatment arms	Primary endpoint(s)
IMpower010	**Resected Stage IB (≥4cm)–IIIA NSCLC** (UICC 7th Edition) • ≤4 cycles chemo N=1280	R → Atezolizumab 1,200 mg q3w x 16 cycles or 1 year R → Best supportive care	**DFS**
ANVIL	**Resected Stage IB (≥ 4cm)–IIIA NSCLC** (UICC 7th Edition) • Adjuvant chemo or RT optional N=903	R → Nivolumab q4w (up to 1 year) R → Observation	**DFS and OS**
PEARLS/ KEYNOTE-091	**Resected Stage IB (≥ 4cm)–IIIA NSCLC** (UICC 7th Edition) • Adjuvant chemo optional ≤4 cycles N=1177	R → Pembrolizumab 200mg q3w (up to 1 year; max 18 cycles) R → Placebo	**DFS**
BR31	**Resected Stage IB (≥ 4cm)–IIIA NSCLC** (UICC 7th Edition) • Adjuvant chemo optional* N=1360	R → Durvalumab q4w (up to 1 year) R → Placebo	**DFS**
ALCHEMIST Chemo IO	**Resected Stage IB (≥ 4cm)–IIIA NSCLC‡** (UICC 7th Edition) • No prior neoadjuvant or adjuvant therapy N=1263	R → Chemo + pembrolizumab q3w (4 cycles) → Pembrolizumab q3w (17 cycles) R → Chemo q3w (4 cycles) → Pembrolizumab q3w (17 cycles) R → Chemo q3w (4 cycles) → Observation	**DFS and OS**
MERMAID-1	**Resected stage II–III NSCLC** • No prior adjuvant therapy or durvalumab therapy N=332	R → Durvalumab + chemo R → Placebo + chemo	**DFS in MRD+**

www.clinicaltrials.gov; September 2020

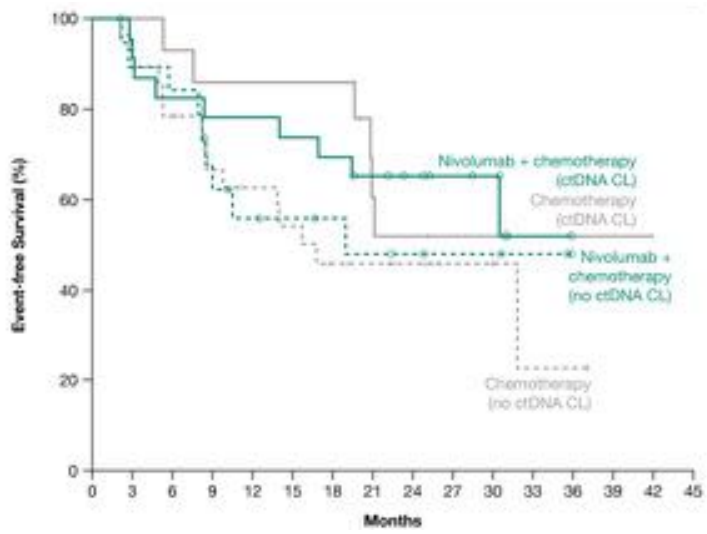
ctDNA

- ctDNA clearance was exploratory endpoint in IMPower010 and CheckMate 816
- post-treatment clearance was associated improved DFS, EFS and pCR.
- Today's ctDNA assays insensitive to low disease levels
- Currently-
  - ctDNA clearance ***should not*** serve as a marker to de-escalate therapy
  - ctDNA persistence of following initial therapy ***could*** serve as a marker for earlier escalation of therapy

IMPower010



CheckMate 816



Adjuvant Immunotherapies

CONCLUSIONS

- Two approved agents
- Both for use after adjuvant chemotherapy
- Associated with significant disease free survival improvements
- Pembrolizumab indicated in IB-IIIA regardless of PD-L1 staining (HR 0.76)
- Atezolizumab indicated in II-IIA with PD-L1 staining > 1% (HR 0.66)
- More work for surgeons
  - Requires understanding agents and indication
  - Biomarker testing is essential
  - Procedures can be more challenging
- Embrace the change, not going away

THANK YOU

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