Best Surgical Approaches for Stage III NSCLC

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Thoracic Surgery | UCLA

Heterogeneity of Stage III NSCLC

Stage III Heterogeneity	Clinical factors			Controversies
Occult (microscopic) vs. Radiographically (clinically) apparent N2	Occult	vs.	Clinical	Are these factors relevant in era of immunotherapy and targeted therapy?
Number of N2 stations	Single	vs.	Multiple (double, triple)	
N2 nodal response to neoadjuvant therapy	N2 down-staging	vs.	N2 persistent Disease	
Extent of resection in N2 disease	Lobectomy	vs.	Pneumonectomy	
Invasive T3 or Invasive T4	N0 or N1	vs.	N2	

Definition of resectable eNSCLC varies in IO clinical trials

Invasive T3/T4, multi-station N2, and pneumonectomy included in most trials

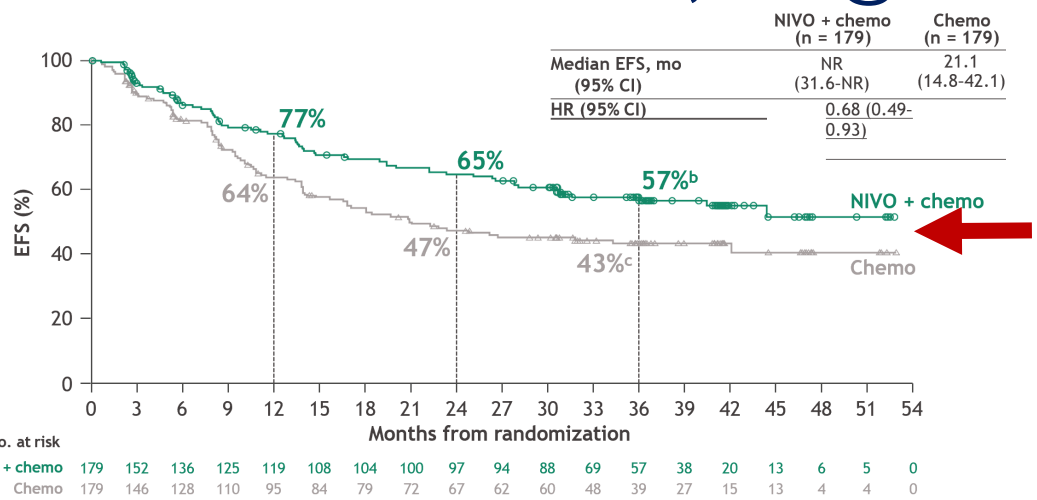
Clinical trial	Neoadjuvant	Adjuvant	N	Stage	Invasive T3	Invasive T4	Multi-station N2	Pneumonectomy
Neoadjuvant								
CheckMate 816	CT + Nivolumab x 3 cycles	None	358	IB-IIIA (7th ed.)	Included	Included	Included	Included
Perioperative (neoadjuvant plus adjuvant)								
KEYNOTE 671	CT + Pembrolizumab x 4 cycles	Pembrolizumab x 1 yr.	786	II-IIIB	Included	Included	Included	Included
AEGEAN	CT + Durvalumab x 4 cycles	Durvalumab x 1 yr.	802	II-IIIB(N2)	Included	Excluded	Included	Excluded
NADIM II	CT + Nivolumab x 3 cycles	Nivolumab x 6 mo.	86	IIIA-B	Included	Included	Included (36.8%)	Included
Neotorch	CT + Toripalimab x 3 cycles	CT + Toripalimab x 1 cycle then Toripalimab x 1 yr.	404	II-IIIC	Included	Included	Included	Included
Adjuvant								
IMpower 010	None	CT mandatory then atezolizumab x 1 yr.	1280	IB-IIIA (7th ed.)	Included	Included	Included	Included
Keynote 091 (PEARLS)	N/A	CT allowed then pembrolizumab x 1 yr.	1177	IB-IIIA (7th ed.)	Included	Included	Included	Included

Study	Neoadjuvant (CT-IO vs. CT)	N	EGFR/ALK	Adjuvant (IO 1Y vs. placebo)	Stage	Primary Endpoint	DFS/EFS HR	OS HR	DFS/EFS	OS
Neoadjuvant										
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)	pCR EFS	0.68	0.62	65% @ 2Y 57% @ 3Y	83% @ 2Y 78% @ 3Y
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Excluded	Durvalumab	IIA-IIIB (8th ed.)	pCR FS	0.68	NR	63% @ 2Y	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)				FS		0.58	0.72	62% @ 2Y	67% @4Y
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)				FS		0.58	NR	70% @1.5Y	NR
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Excluded	Toripalimab + CT (1 cycle), Toripalimab	II-III	EFS MPR	0.40 (stage3)	NR	65% @2Y (stage3)	NR
Adjuvant										
IMpower 010 (WCLC 2022)	N/A	1280	Included	CT mandatory Atezolizumab	II-IIIA (8th ed.)	DFS	0.66 (PD-L1 ≥1%)	NR	75% @ 2Y	NR
Keynote-091 (ESMO 2022)	N/A	1177	Included	CT optional Pembrolizumab	II-IIIA (8th ed.)	DFS	0.76	0.87	73% @ 1.5Y	92%

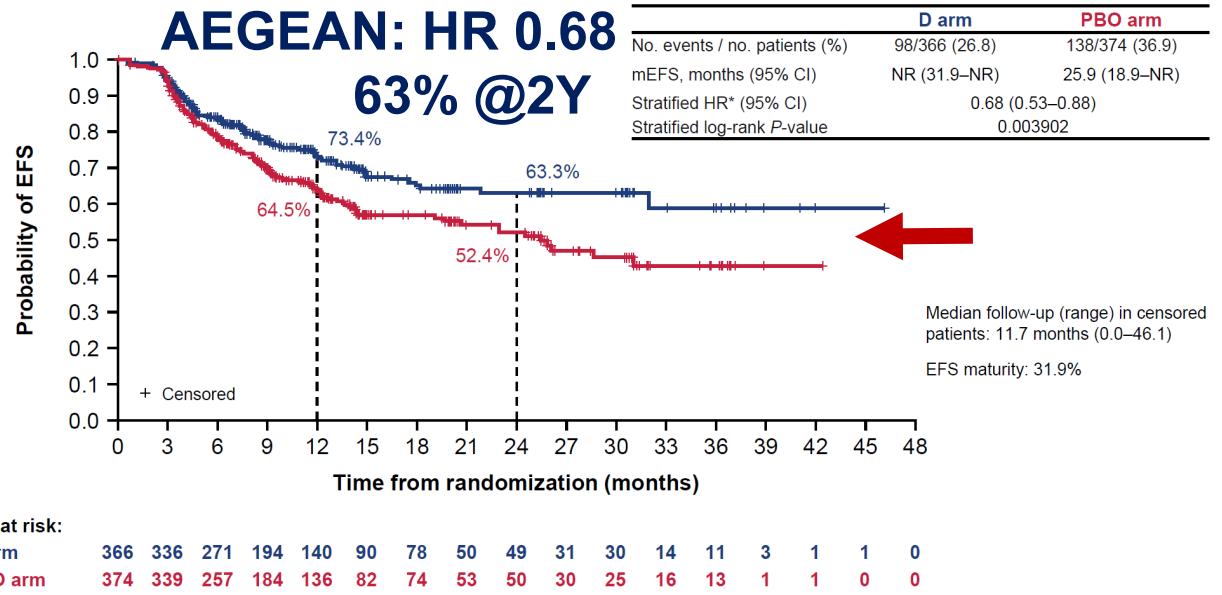
Neoadj./Periop. Trials: EFS HR and EFS% at 2Y are similar

EFS in Ph 3 Neoadjuvant or Perioperative IO global trials

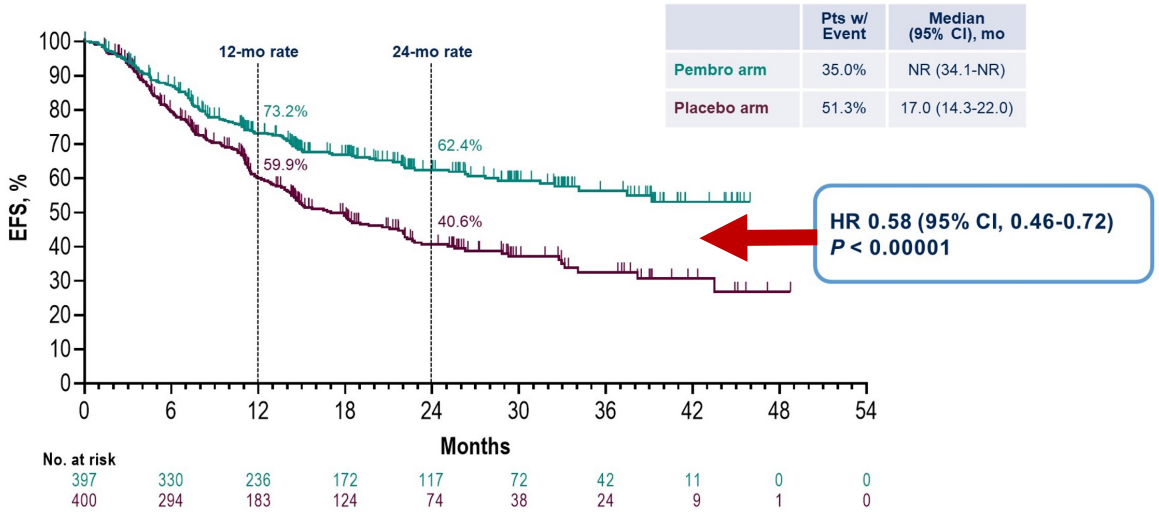
CheckMate 816: HR 0.68; 65% @2Y



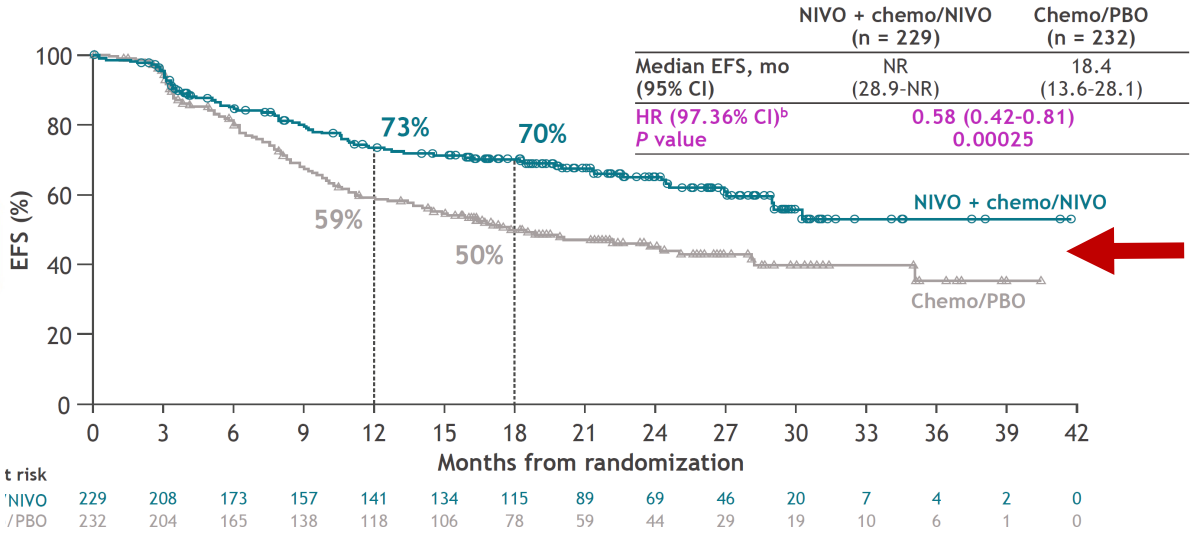
AEGEAN: HR 0.68 63% @2Y



Keynote 671: HR 0.58; 62% @2Y

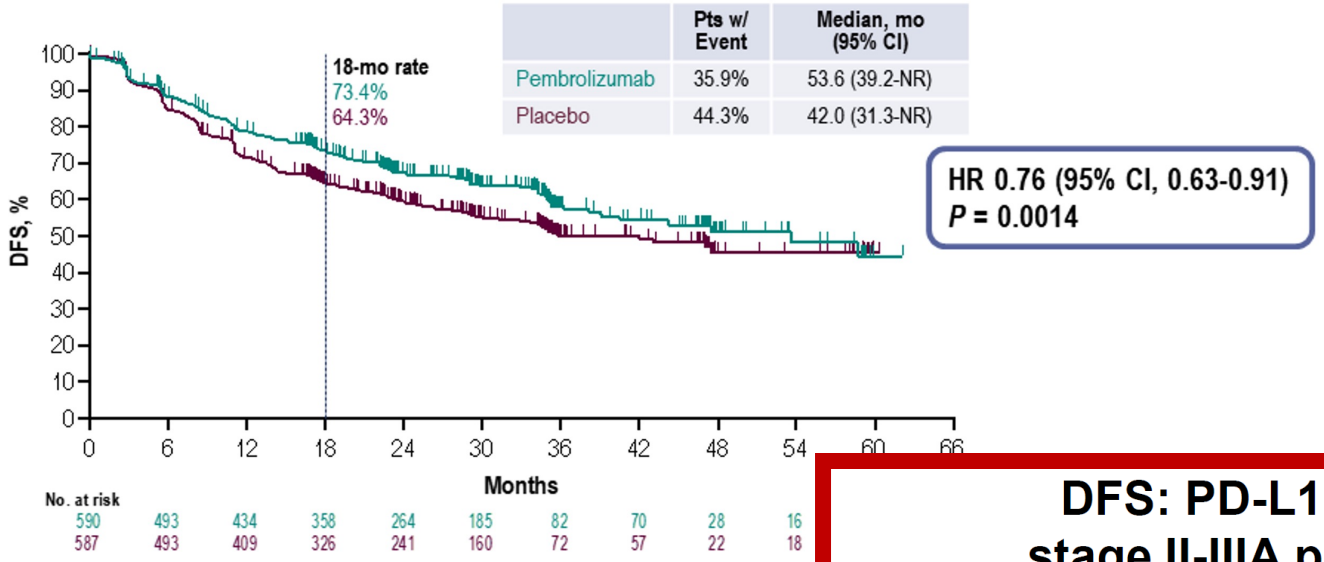


CheckMate 77T: HR 0.58; 70% @1.5Y



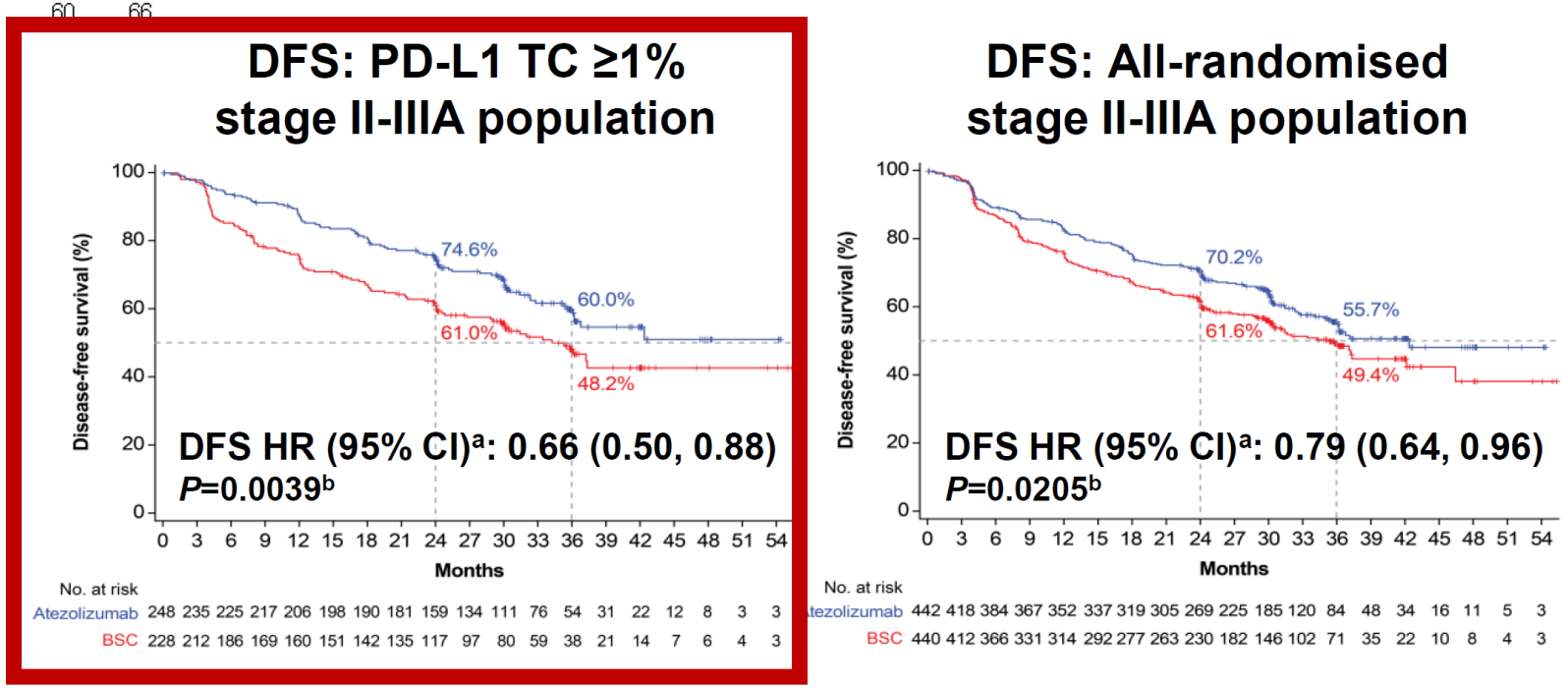
EFS in Ph3 Adjuvant IO trials

Keynote 091: HR 0.76; EFS 73% @1.5Y



EFS benefit in Ph3 adjuvant IO trials are most pronounced in PD-L1 (+)

IMpower 010: HR 0.79; EFS 70% @2Y



Study	Neoadjuvant (CT-IO vs. CT)	N	EGFR/ALK	Adjuvant (IO 1Y vs. placebo)	Stage	Primary Endpoint	DFS/EFS HR	OS HR	DFS/EFS	OS
Neoadjuvant										
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	Excluded (if known)	None	IB-IIIA (7^{th} ed.) II-IIIB (8^{th} ed.)	pCR EFS	0.68	0.62	65% @ 2Y 57% @ 3Y	83% @ 2Y 78% @ 3Y
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Excluded	Durvalumab	IIA-IIIB (8^{th} ed.)	pCR	0.68	NR	63% @ 2Y	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizum (4 cycles)							0.72	62% @ 2Y	67% @4Y
CheckMate 77T (ESMO 2023)	Nivolumab + (4 cycles)							NR	70% @1.5Y	NR
Neotorch (ASCO 2023)	Toripalimab + cycles)			Toripalimab				NR	65% @2Y (stage3)	NR
Adjuvant										
IMpower 010 (WCLC 2022)	N/A	1280	Included	CT mandatory Atezolizumab	II-IIIA (8^{th} ed.)	DFS	0.66	NR	75% @ 2Y	NR
Keynote-091 (ESMO 2022)	N/A	1177	Included	CT optional Pembrolizumab	II-IIIA (8^{th} ed.)	DFS	0.76	0.87	73% @ 1.5Y	92%

Neoadjuvant or perioperative IO and Adjuvant IO are all acceptable standards of care in eNSCLC (FDA approved in USA)

Phase 3 IO trials in eNSCLC: Preoperative Attrition to Surgery

Study	Neoadjuvant (CT-IO vs. CT)	N	Preop. Attrition (Rx arm)	Preop. A (	Time from last dose
Neoadjuvant only					
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	16%		
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (3 cycles)	221	26%		
Perioperative (neoadjuvant + adjuvant)					
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	19%		
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	786	18%		
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	22%		
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	18%		
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT (3-4 cycles)	453	16%		

Historical Neoadjuvant Chemotherapy Trials

Trial	N	Preop. Attrition
SWOG S9900 (ph 3)	169	**10%**
MRC LU22/NVALT 2/EORTC 08012 (ph 3)	247	**9%**
NATCH (ph 3)	199	**9%**
IFCT 0002	267	**4%**
CHEST (ph 3)	127	**13%**
French Cooperative Thoracic Intergroup	179	**7%**
SAKK Lung Cancer Project Group (ph 3)	115	**18%**

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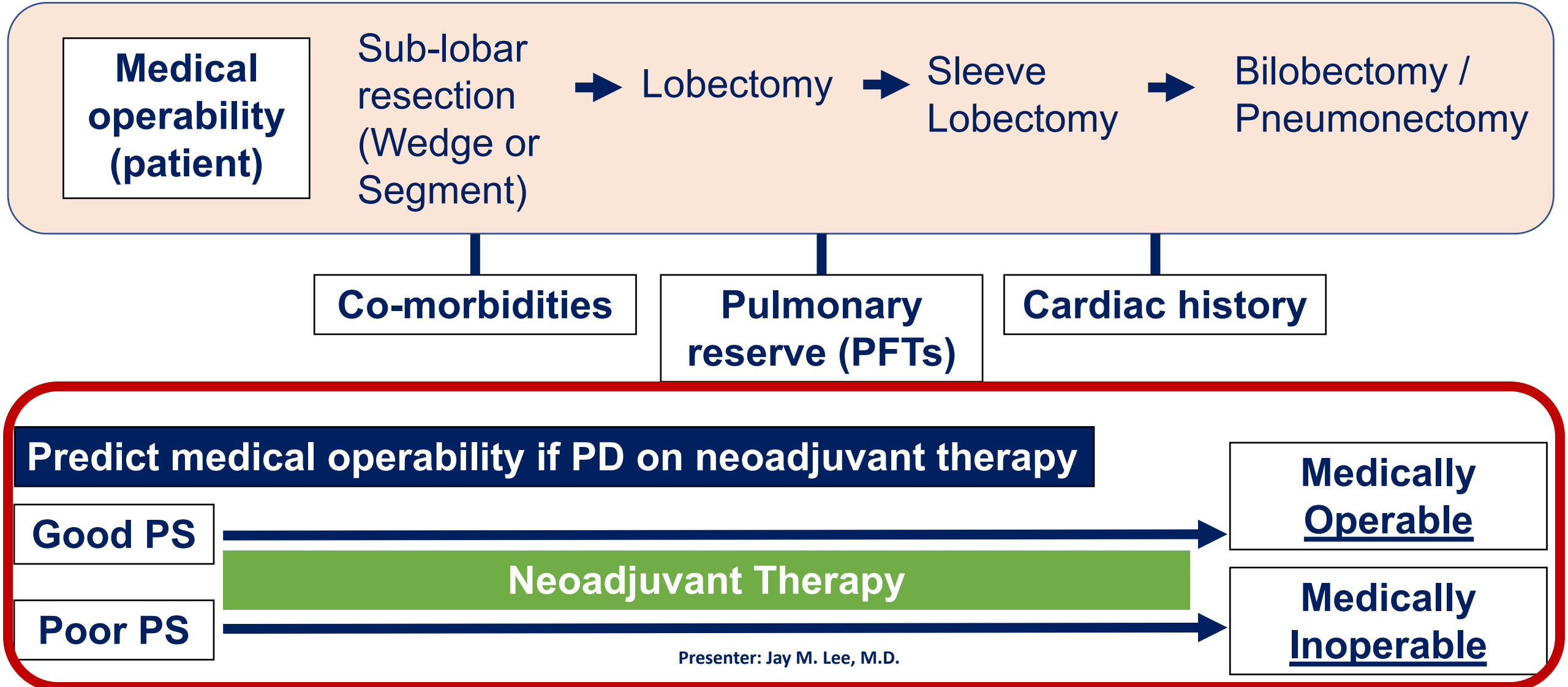
Medical operability (patient)

Impact of Progression of Disease (PD) with Neoadjuvant Therapy

- Determine medical operability before neoadjuvant therapy



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Surgical resectability (tumor and lymph nodes)

- Determine surgical resectability before neoadjuvant therapy

Resectability (tumor and lymph nodes)

Invasive T3 Invasive T4	R0 Resection	→	R1 Resection	→	R2 Resection	
Sub-lobar resection (Wedge or Segment)	→	Lobectomy	→	Sleeve Lobectomy	→	Bilobectomy / Pneumonectomy
Extent of Lymph Node Disease	N0	→ N1	→	Single station N2	→	Multi-station N2 → N3

Predict Surgical Resectability if PD on neoadjuvant therapy

Resectable → **Neoadjuvant Therapy** → **Resectable or Unresectable**

Presenter: Jay M. Lee, M.D.

Phase 3 IO trials in eNSCLC: Subset Hazard Ratios for EFS

Study	Neoadjuvant (CT-IO vs. CT)	Stage II	Stage IIIA	Stage IIIB	PD-L1 < 1%	PD-L1 1-49%	PD-L1 ≥ 50%	SQ	Non-SQ	TMB <12.3 m/mb	TMB ≥ 12.3 m/mb
Neoadjuvant											
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	0.87 (IB/II 7th)	0.54	NA	0.85	0.58	0.24	0.77	0.50	0.86	0.69
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Perioperative (neoadjuvant + adjuvant)											
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	0.76	0.57	0.83	0.76	0.70	0.60	0.71	0.69	NR	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	0.65	0.54	0.52	0.77	0.51	0.42	0.57	0.58	NR	NR
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	0.81	0.51		0.73	0.76	0.26	0.46	0.72	NR	NR
Neotorch (ASCO 2023)	Toripalimab + CT	NA									
RATIONALE-315 (ESMO 2023)											

Periop. IO improves EFS HR subsets who are poor responders to Neoadj. CT-IO only; Reflect both neoadj. adj. phases of IO.

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Phase 3 IO trials in eNSCLC: Subset Hazard Ratios for EFS

Study	Neoadjuvant (CT-IO vs. CT)	Stage II	Stage IIIA	Stage IIIB	PD-L1 < 1%	PD-L1 1-49%	PD-L1 ≥ 50%	SQ	Non-SQ	TMB <12.3 m/mb	TMB ≥ 12.3 m/mb
Neoadjuvant											
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	0.87 (IB/II 7th)	0.54	NA	0.85	0.58	0.24	0.77	0.50	0.86	0.69
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)										
Perioperative (neoadjuvant + adju											
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)										
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)										
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)										
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)										
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT (3-4 cycles)										

Poor responders to Neoadj. CT-IO:

- Stage IB/II(7th ed.); stage II (8th ed.)
- PD-L1 <1%
- Squamous
- Low TMB

Use biomarkers to predict response to neoadjuvant CT-IO and impact on medical operability (patient) and surgical resectability (tumor)

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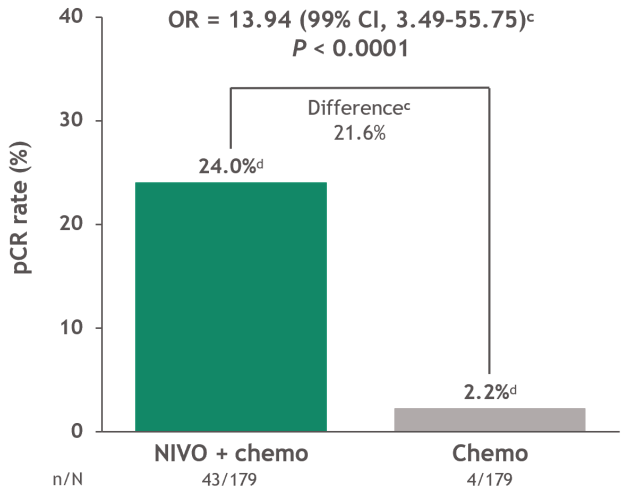
pCR is similar in neoadjuvant vs. perioperative ph3 IO trials

CT-IO X 3 cycles

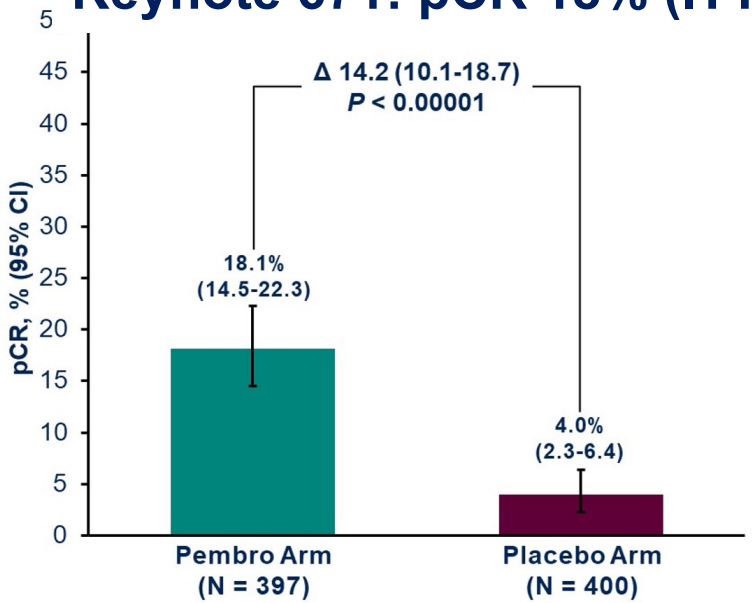
CheckMate 816: pCR 24% (ITT)



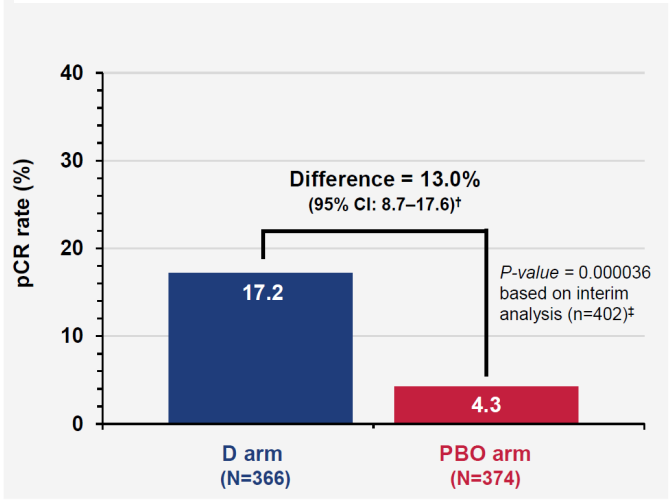
VS.

CT-IO X 4 cycles

Keynote 671: pCR 18% (ITT)

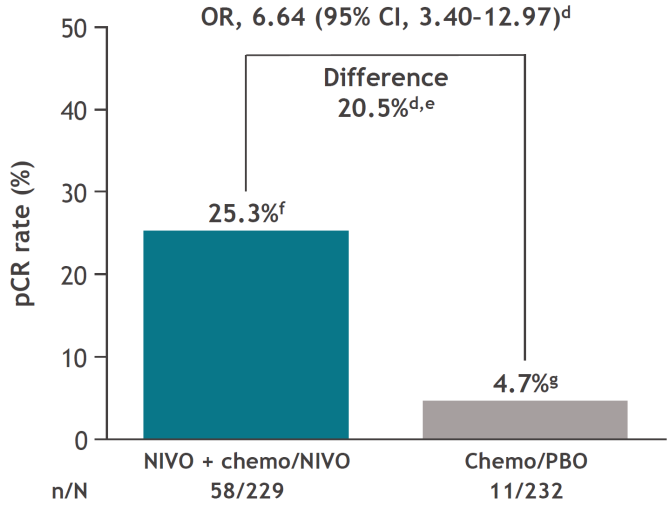


AEGEAN: pCR 17% (mITT)



- 3 (neoadjuvant) vs. 4 cycles (perioperative) of preop. CT-IO did not change pCR: 24 vs. 17-25%

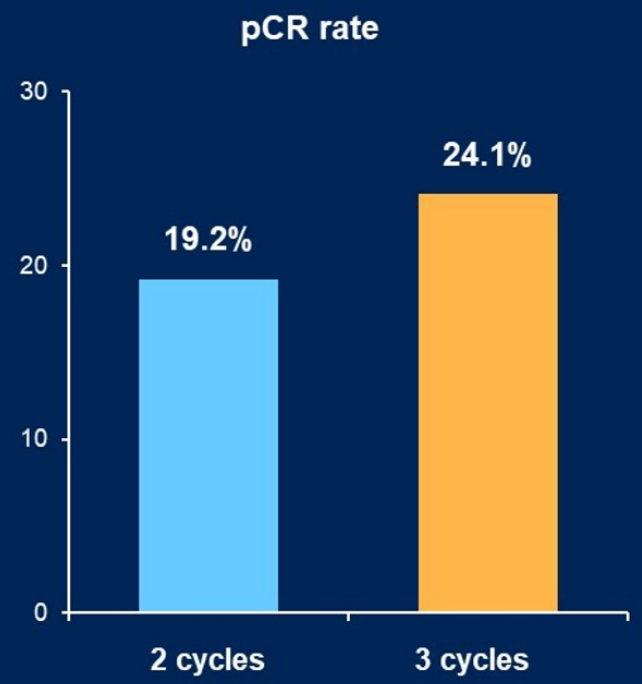
CheckMate 77T: pCR 25% (ITT)



Forde AACR 2020. Heymach AACR 2023. Wakelee ASCO 2023. Cascone ESMO 2023.

Two cycles versus three cycles of neoadjuvant sintilimab plus platinum-doublet chemotherapy in patients with resectable non-small-cell lung cancer (neoSCORE): a randomized, single center, two-arm phase II trial

2 vs. 3 cycles of neoadjuvant sintilimab plus CT did not show significant difference in pCR



- Three cycles treatment presented a **4.9%** increase in pCR rate in comparison to two cycles

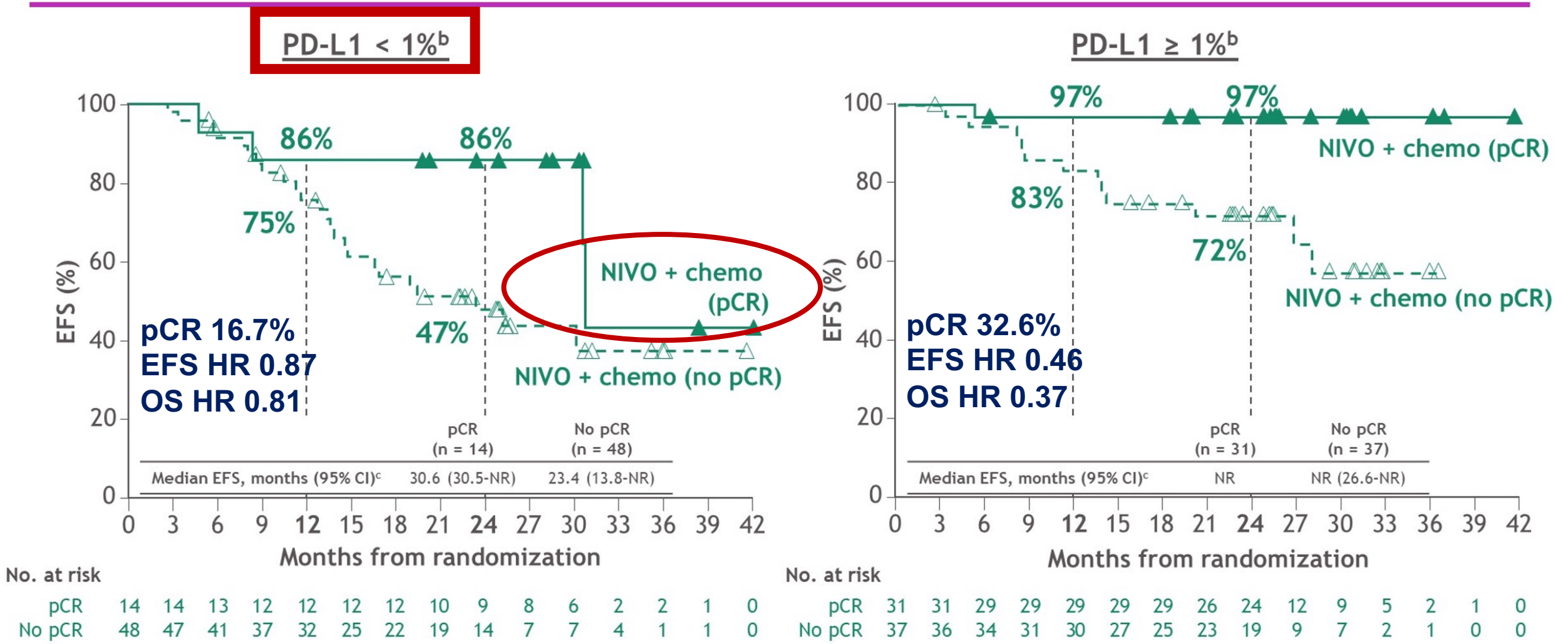
Pathological response, n(%)	Total, n=55	2 cycles, n=26	3 cycles, n=29	*P* value*
pCR	12（21.8%） (95% CI：11.8-35.0%)	5（19.2%） (95% CI：6.6-39.4%)	7（24.1%） (95% CI：10.3-43.5%)	0.660

Can we reduce preop cycles to decrease preop. attrition to surgery?

Qui et al. ASCO 2022

CheckMate 816 (neoadjuvant nivolumab)

EFS by pCR status (primary tumor) and tumor PD-L1 expression[a]: NIVO + chemo



pCR in PD-L1 < 1% have same EFS as no pCR (and Chemo alone arm)

Minimum follow-up: 21 months; median follow-up: 29.5 months.

[a]Path-evaluable patient population; [b]Subgroup analyses were not performed for the chemo arm because of small sample sizes; [c]HRs were not computed because of low number of events

When to give adjuvant therapy after neoadjuvant CT-IO?

Importance of pathologic regression, PD-L1, and ctDNA status

Adjuvant therapy:

- How effective is adjuvant checkpoint inhibitor monotherapy after neoadjuvant CT-IO?
- Should we escalate adjuvant therapy (combination checkpoint inhibitors, mRNA vaccines, ADCs)?
- Should we abandon IO and switch to targeted therapy? (postoperative NGS testing)

CheckMate 816 (neoadjuvant nivolumab)

CheckMate 816 (NIVO + chemo in resectable NSCLC): 3-y efficacy and safety by definitive surgery status

Subsequent therapy summary

~7-17% of patients at relapse received targeted therapy

Patients, n (%)	With definitive surgery		Without definitive surgery	
	NIVO + chemo (n = 149)	Chemo (n = 135)	NIVO + chemo (n = 30)	Chemo (n = 44)
Any subsequent therapy	32 (22)	59 (44)	17 (57)	28 (64)
Subsequent radiotherapy	14 (9)	26 (19)	11 (37)	18 (41)
Subsequent surgery	4 (3)	7 (5)	1 (3)	1 (2)
Subsequent systemic therapy	26 (17)	52 (38)	15 (50)	23 (52)
Immunotherapy	14 (9)	31 (23)	1 (3)	16 (36)
Targeted therapy	10 (7)	23 (17)	5 (17)	4 (9)
Chemotherapy	23 (15)	28 (21)	14 (47)	19 (43)

Minimum/median follow-up, 32.9/41.4 months.

IMpower 010: adjuvant atezolizumab following chemotherapy in resected stage II-IIIA NSCLC with PD-L1 TC ≥ 1%

~15% of patients at relapse receive targeted TKI therapy
~10% of patients at relapse receive targeted mAb therapy

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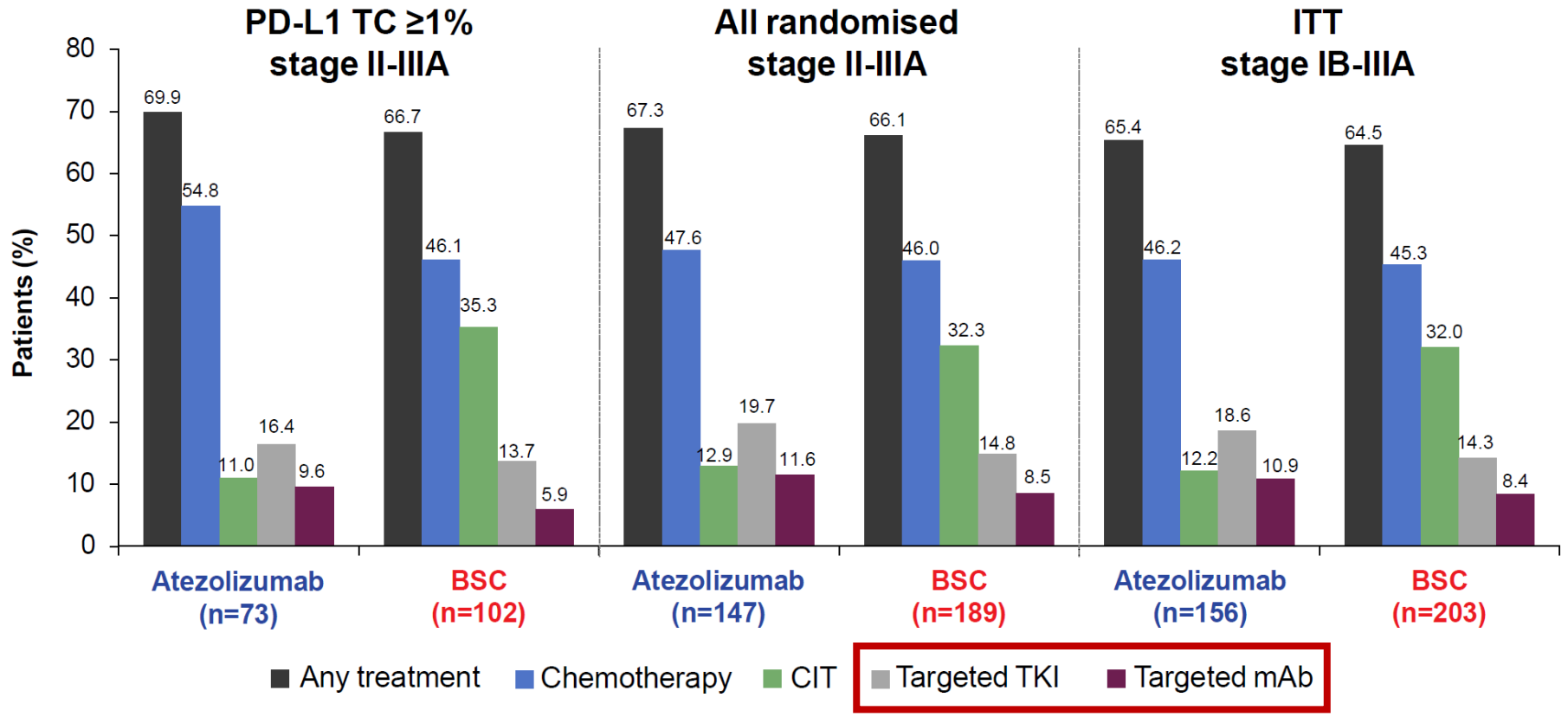
Post-relapse systemic non-protocol anticancer therapy



Clinical cutoff: 21 January 2021. CIT, cancer immunotherapy; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

Neoadjuvant vs. Adjuvant Treatment Related Adverse Events (TRAE)

Presenter: Jay M. Lee, M.D.

	Neoadjuvant				Adjuvant			
Study	**CT-IO TRAE Gr. 3-4**	**CT TRAE Gr. 3-4**	**CT-IO Mortality**	**CT Mortality**	**IO TRAE Gr. 3-4**	**PBO TRAE Gr. 3-4**	**IO Mortality**	**PBO Mortality**
Neoadjuvant only								
CheckMate 816 (ELCC 2023)	36%	38%	0%	2%	NA	NA	NA	NA
CheckMate 816 (ESMO 2023)	14% (Ipi/Nivo)	36%	0% (Ipi/Nivo)	0%	NA	NA	NA	NA
Perioperative								
AEGEAN (AACR 2023)	NR	NR	NR	NR	NR	NR	NR	NR
Keynote-671 (NEJM 2023)	41%	37%	0.8%	0.8%	10%	5.6%	0.3%	0%
CheckMate 77T (ESMO 2023)	27%	23%	1%	0%	8%	3%	0%	0%
Neotorch (ASCO 2023)								
RATIONALE-315 (ESMO 2023)								
Adjuvant only								
IMpower 010 (Lancet 2021)	NA	NA	NA	NA	11%	12%	0.8%	0.6%
Keynote-091 (Lancet 2022)	NA	NA	NA	NA	NR	NR	NR	NR

In Periop. Trials, Gr. 3/4 TRAE are greater in Neoadjuvant vs. Adjuvant IO phase (Concurrent CT-IO vs. CT then IO)

Phase 3 IO trials in eNSCLC: Systemic therapy disposition

Presenter: Jay M. Lee, M.D.

	Neoadjuvant Therapy				Adjuvant Therapy					
	Received		Completed		Received		Completed		On-going	
Study	CT-IO	CT	CT-IO	CT	IO	PBO	IO	PBO	IO	PBO
Neoadjuvant only										
CheckMate 816 (NEJM 2022)	98%	98%	94% (C3)	85% (C3)	NA	NA	NA	NA	NA	NA
CheckMate 816 (ESMO 2023)	98% (Ipi/Nivo)	96%	91% (Ipi/Nivo)	86%	NA					NA
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)	100%	99%	87%	89%	66%					24%
Keynote-671 (ASCO 2023)	99%	99%	75%	74%	73%					11%
CheckMate 77T (ESMO 2023)	99%	99%	85%	89%	62%				T)	3% (ITT)
Neotorch (ASCO 2023)	100%	100%	87% (C3)	92% (C3)	71%					10%
RATIONALE-315 (ESMO 2023)	100%	99%	93%	93%	NR	NR	NR	NR	NR	NR
Adjuvant only										
IMpower 010 (Lancet 2021)	NA	NA	NA	NA	98%	99%	64%	75%	0%	0%
Keynote-091 (Lancet 2022)	NA	NA	NA	NA	98%	99%	51%	65%	0%	0%

Neoadj./Periop. Trials: 6-25% of patients will not be able to complete intended neoadjuvant therapy

Phase 3 IO trials in eNSCLC: Systemic therapy disposition

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	Neoadjuvant Therapy				Adjuvant Therapy					
	Received		Completed		Received		Completed		On-going	
Study	CT-IO	CT	CT-IO	CT	IO	PBO	IO	PBO	IO	PBO
Neoadjuvant only										
CheckMate 816 (NEJM 2022)	98%	98%	94% (C3)	85% (C3)	NA	NA	NA	NA	NA	NA
CheckMate 816 (ESMO 2023)	98% (Ipi/Nivo)	96%	91% (Ipi/Nivo)	86%	NA	NA	NA	NA	NA	NA
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)					66%	64%	24%	21%	23%	24%
Keynote-671 (ASCO 2023)					73%	67%	40%	35%	11%	11%
CheckMate 77T (ESMO 2023)					62%	66%	37% (ITT)	40% (ITT)	3% (ITT)	3% (ITT)
Neotorch (ASCO 2023)					71%	65%	44%	33%	12%	10%
RATIONALE-315 (ESMO 2023)	100%	99%	93%	93%	NR	NR	NR	NR	NR	NR
Adjuvant only										
IMpower 010 (Lancet 2021)	NA	NA	NA	NA	98%	99%	64%	75%	0%	0%
Keynote-091 (Lancet 2022)	NA	NA	NA	NA	98%	99%	51%	65%	0%	0%

Periop. Trials:
27-38% of patients do not start intended adjuvant therapy

Conclusions

- Neoadjuvant, Perioperative, and Adjuvant IO approaches are all acceptable SOC
- “Surprise N2” patients will (by default) receive adjuvant therapy
- Definition of resectability (tumor) remains controversial
- Determine medical operability (patient) and resectability (tumor) upfront before neoadjuvant therapy
- Preoperative attrition to surgery is a concern with neoadjuvant therapy
- Use predictors of response to neoadjuvant CT-IO and impact on medical operability (patient) and resectability (tumor) to determine preoperative therapy vs. upfront surgery
- Oncogene addicted NSCLC with known poor responsiveness to IO should not undergo neoadjuvant CT-IO; Consider (perioperative) targeted therapy trial or upfront surgery
- Interpretation of pCR after neoadjuvant therapy requires PD-L1 expression to guide adjuvant therapy
- We need to be selective about who receive preoperative therapy