PERIOPERATIVE IO THERAPY FOR NSCLC

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April 19, 2024

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The Evidence Supporting Perioperative Tx

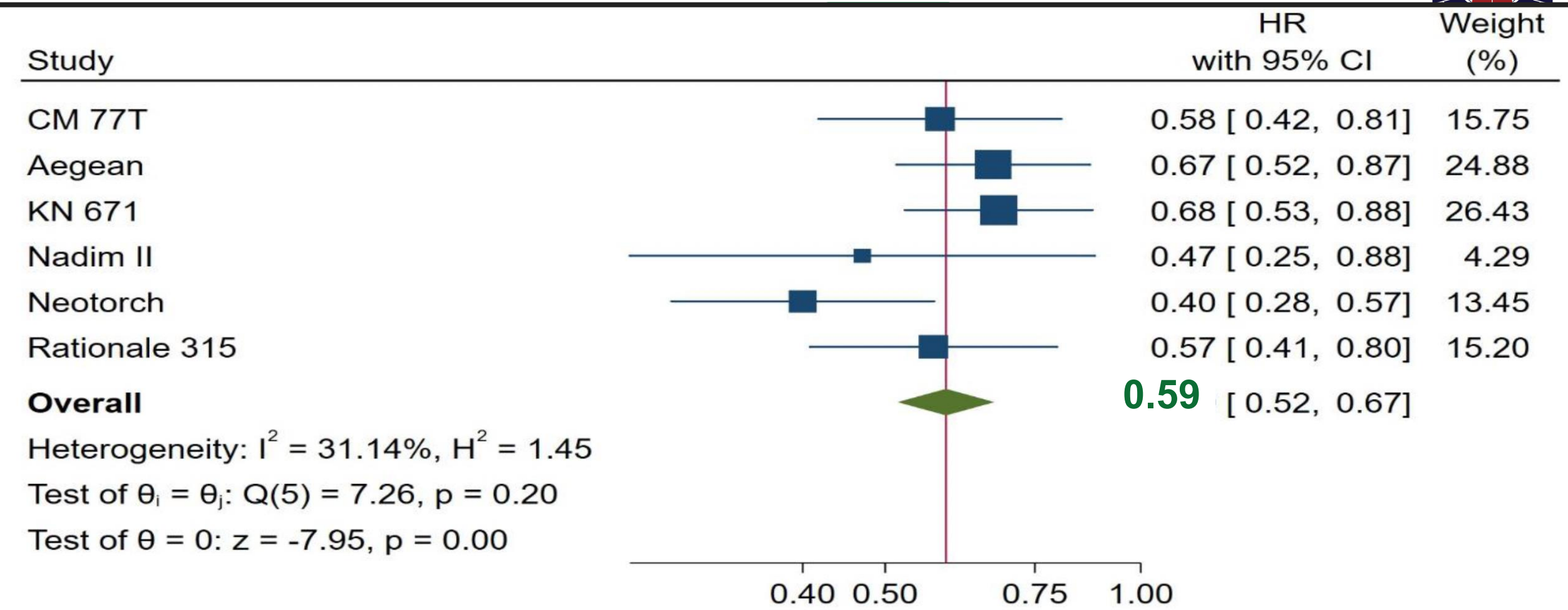
Study	Neoadjuvant (CT-IO vs. CT)	N	EGRF/ ALK	Adjuvant (IO 1Y vs. Placebo)	Stage	Primary Endpoint	DFS/EFS HR	DFS/EFS Rate	OS Rate	OS HR
Neoadjuvant										
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)	pCR EFS	0.68	65% 2Y 57% 3Y	83% 2Y 78% 3Y	0.62
Perioperative (neoadjuvant + adjuvant)										
AEGEA (AACR										NR
Keynot (ASCO (ESMO										0.72
Checkl (ESMO										NR
Neotor (ASCO										NR
RATIO (ESMO										0.62
Adjuvant										
IMpower 010 (WCLC 2022) Felip 2023	N/A	1280	Included	CT mandatory Atezolizumab	II-IIIA (8th ed.)	DFS	0.66 (PD-L1≥1%)	75% 2Y	79% 4Y	0.71* (PDL1-≥1%)
Keynote-091 (ESMO 2022)	N/A	1177	Included	CT optional Pembrolizumab	II-IIIA (8th ed.)	DFS	0.76	73% 1.5Y	82% 3Y	0.87*

Overall has the Strongest Evidence

- 5 Trials
- Consistent numerically favorable DFS
- Only regimen with proven OS benefit

* Not significant

Peri-operative Event Free Survival Curves



ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Luis Paz-Ares

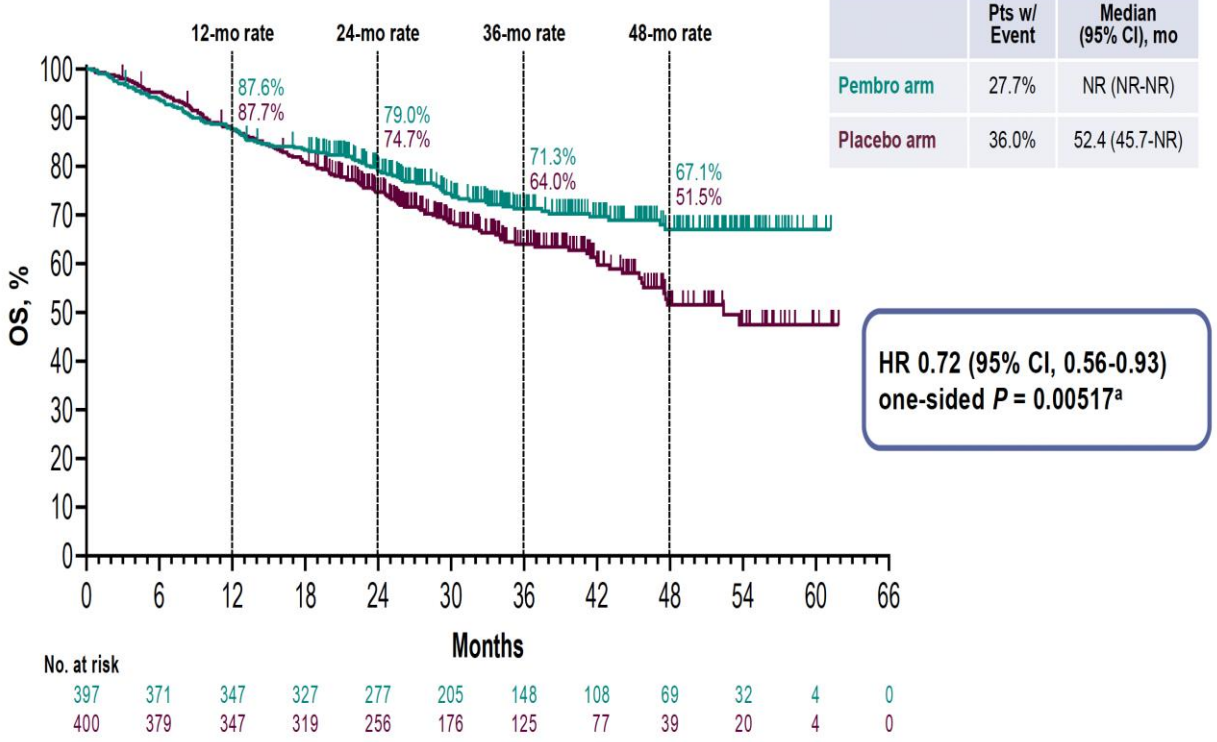
Forde et al NEJM, Spicer et al ESMO 2023; Heymach et al ASCO 2023; Lu et al ASCO Plenary 2023; Provencio et al NEJM 2023

Heymach J, et al. NEJM 2023; Wakelee H, et al. NEJM 2023; Cascone T, et al. ESMO 2023; Yue D, et al. ESMO virtual plenary 2024

KEYNOTE-671

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

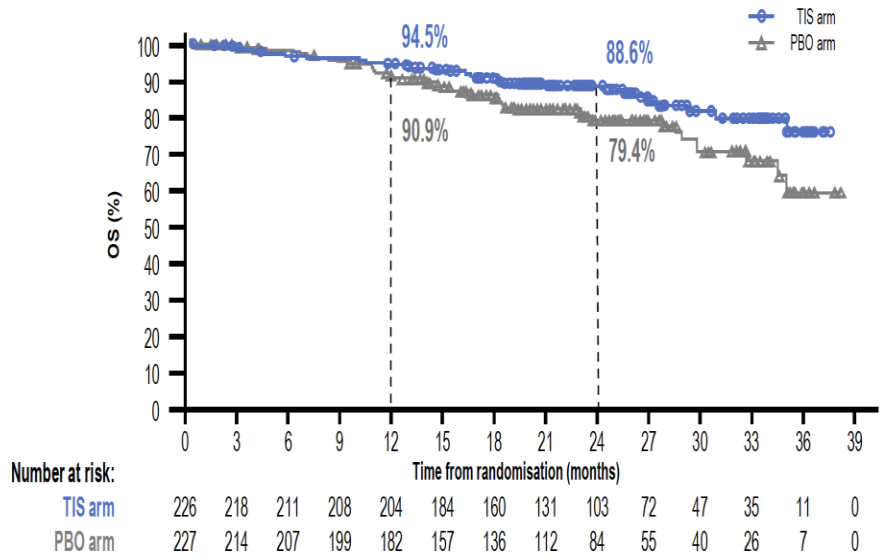
RATIONALE 315

Overall Survival

ITT Analysis Set

Median FU 22.0 months (range .1-38.4)

	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS arm	31 (13.7)	NR (NE, NE)	0.62 (0.39, 0.98)	0.0193
PBO arm	45 (19.8)	NR (35.0, NE)		



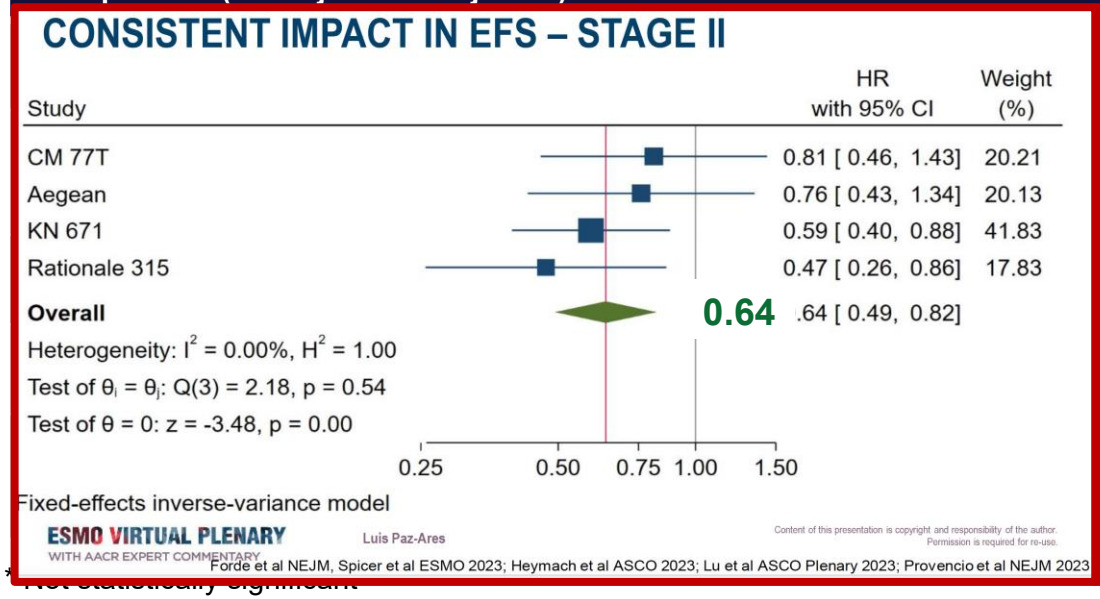
AWAITING OVERALL SURVIVAL FROM OTHER TRIALS

Wakelee H, et al. NEJM 2023, Yue D, et al. ESMO virtual plenary 2024

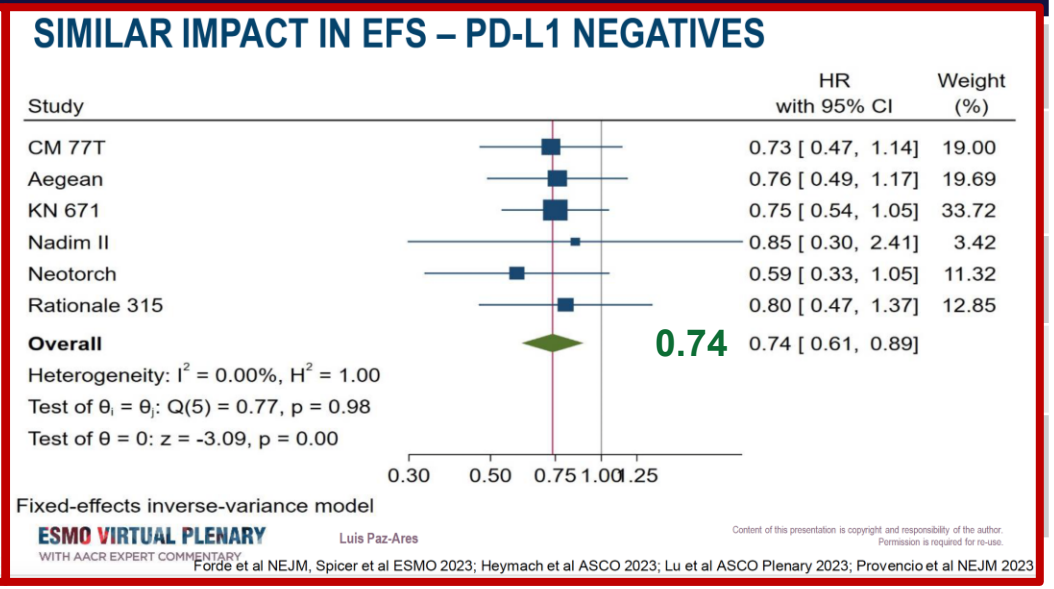
Who needs a perioperative regimen?

Patient Selection

Study	Neoadjuvant (CT-IO vs. CT)	N	Stage II	Stage IIIA	Stage IIIB	PD-L1 <1%	PD-L1 1-49%	PD-L1 ≥50%	SQ	Non-SQ
Neoadjuvant										
Checkmate 816 (ELCC 2023	Nivolumab + CT (3 cycles)	358	0.87 (IB/II 7th)	0.54	NA	0.85	0.58	0.24	0.77	0.50
Perioperative (neoadjuvant + adjuvant)										



Forde et al NEJM, Spicer et al ESMO 2023; Heymach et al ASCO 2023; Lu et al ASCO Plenary 2023; Provencio et al NEJM 2023



Forde et al NEJM, Spicer et al ESMO 2023; Heymach et al ASCO 2023; Lu et al ASCO Plenary 2023; Provencio et al NEJM 2023

*Not statistically significant

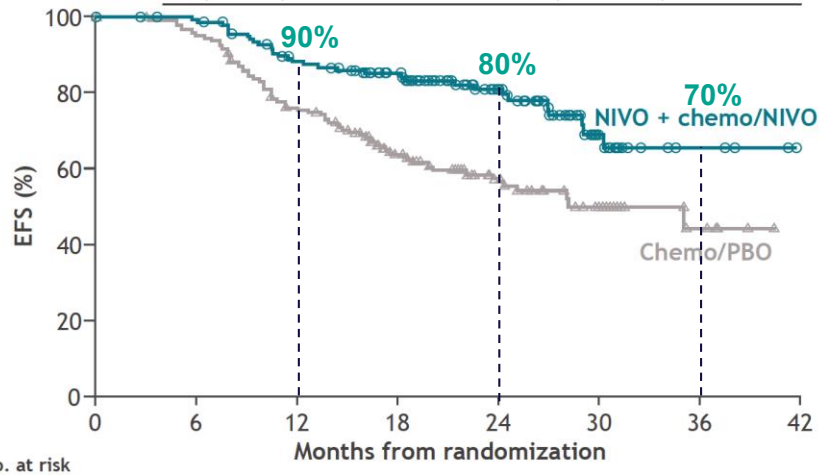
What is the contribution of the adjuvant component?

CM 77T

Exploratory analysis: EFS by adjuvant treatment status

Adjuvant

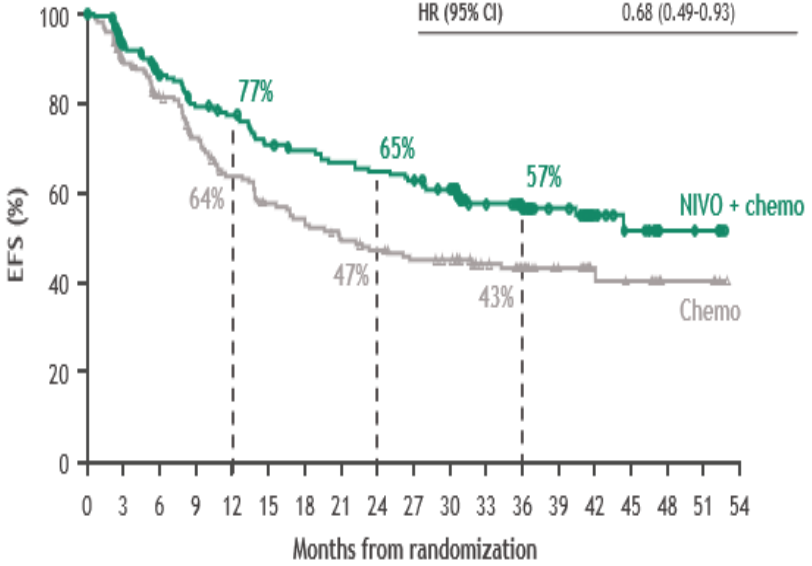
	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	



No. at risk								
NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

CM 816

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

Median follow-up (range): 25.4 months (15.7-44.2).

[a]HR (95% CI), 0.17 (0.11-0.27) in those who received adjuvant treatment vs those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10-0.22) in the chemo/PBO arm.

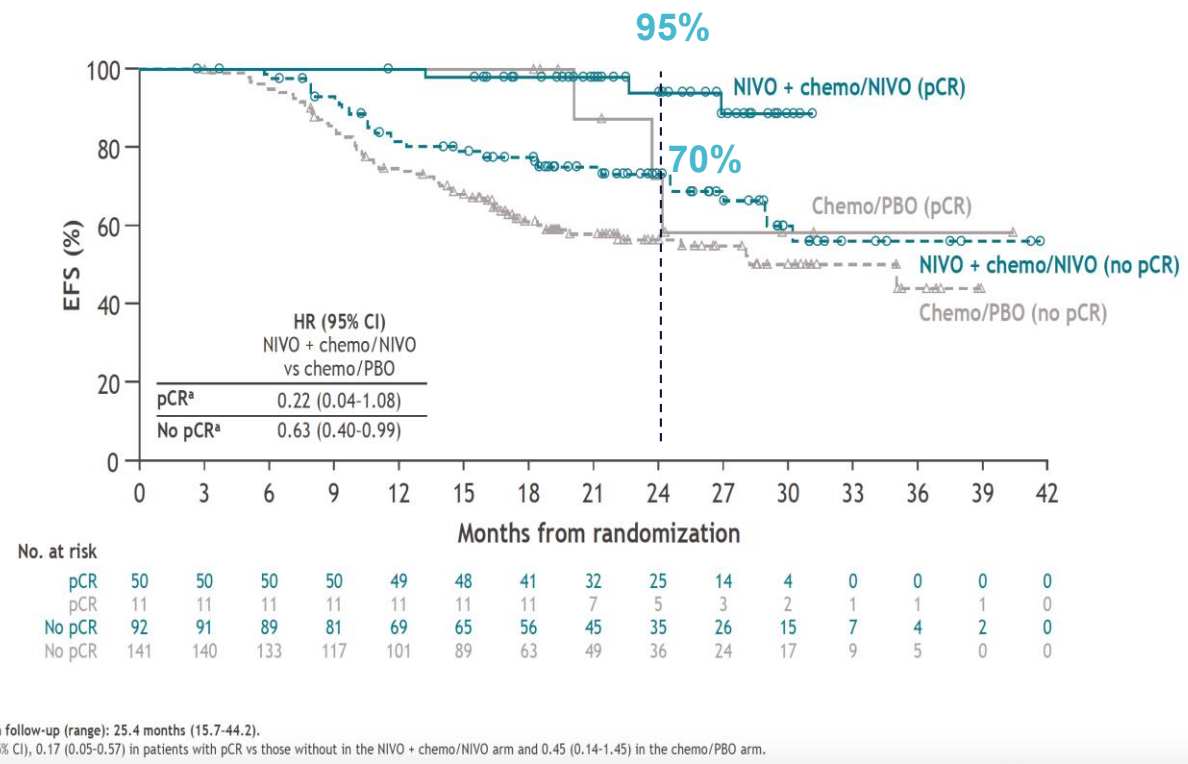
Cascone T, et al. ESMO 2023;

Who Needs a Perioperative Regimen?

Treatment Effect – Pathological Complete Response

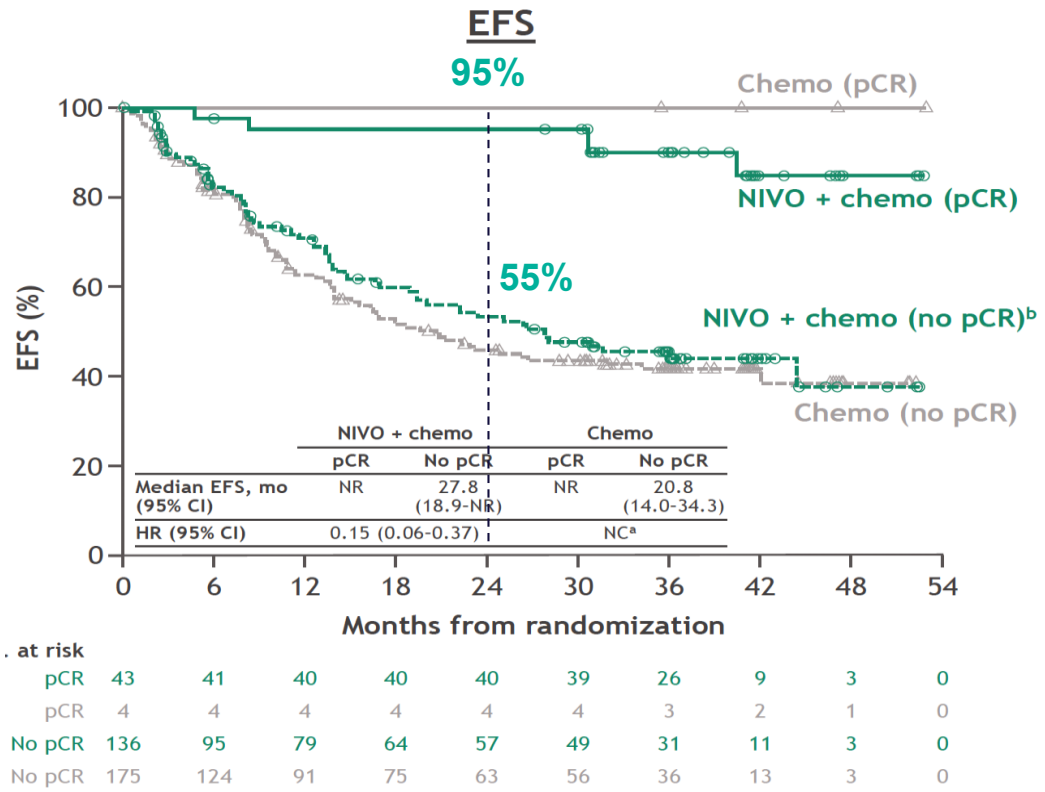
CM 77T

Exploratory analysis: EFS by pCR status in patients who received adjuvant treatment



Median follow-up (range): 25.4 months (15.7-44.2).
[a]HR (95% CI), 0.17 (0.05-0.57) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.45 (0.14-1.45) in the chemo/PBO arm.

CM 816

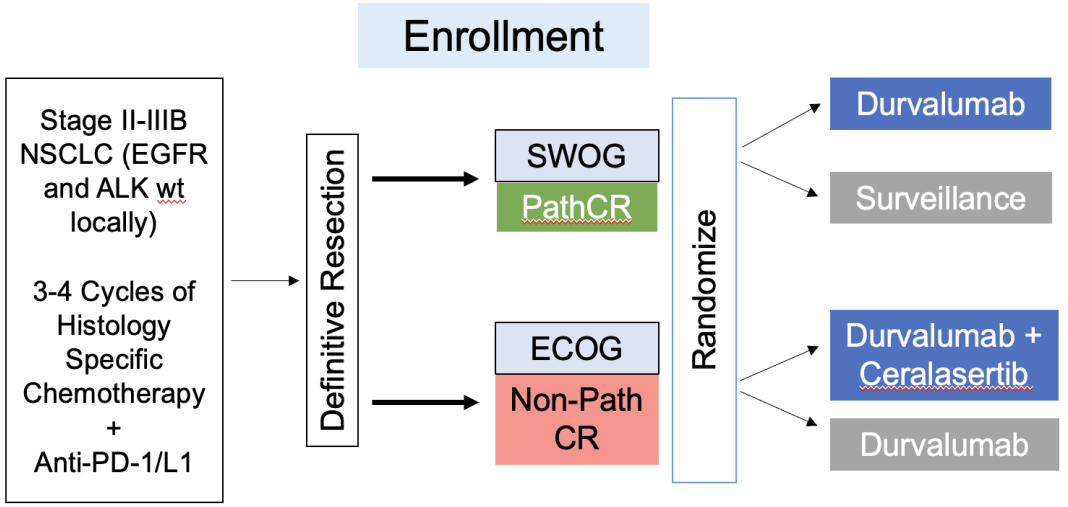


Forde P, et al. NEJM 2022; Cascone T, et al. ESMO 2023;

Tailoring Perioperative Treatment by Pathological Response

Study	Regimen	N	pCR	No pCR
Neoadjuvant				
Checkmate 816 (ELCC 2023	Nivolumab + CT (3 cycles)	179	43 pts 24%	136 pts 76%
Perioperative (neoadjuvant + adjuvant)				
AEGEAN (AACR 2023)	Durvalumab + CT	366	63 pts 17.2%	303 pts 82.8%
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT	397	72 pts 18.1%	325 pts 81.2%
CheckMate 77T (ESMO 2023)	Nivolumab + CT	229	58 pts 25.3%	171 pts 74.7%
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT	226	92 pts 40.7%	134 pts 59.3%

Combined ECOG/SWOG CLEAR-INSIGHT SCHEMA



Perioperative vs Adjuvant Therapy

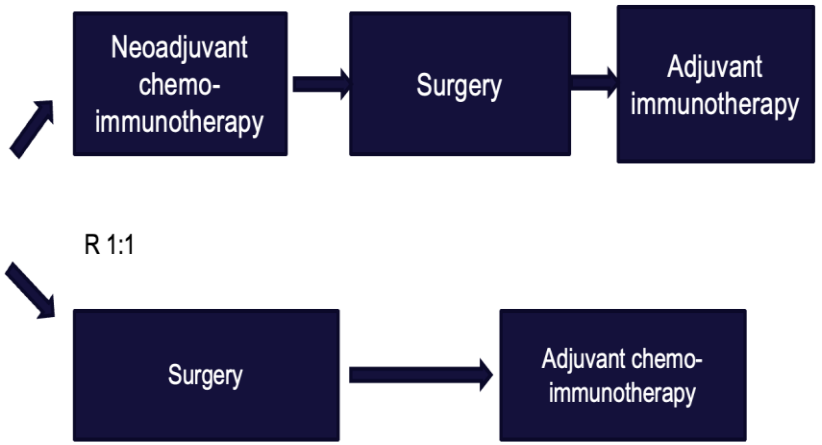
Different groups of patients went on perioperative versus adjuvant trials

Trial	N	Stage III A/B
CM 77T	461	64% (IIIB not reported separately)
AEGEAN	740	71% (25% IIIB)
KN 091	1177	29% (IIIA only)
IMpower 010	1005	41% (IIIA only)

Perioperative versus Adjuvant Systemic Therapy in Patients with Resectable Non-Small cell Lung Cancer - PROSPECT LUNG

- Resectable NSCLC
- Stage II-IIIB (AJCC8th) single St N2, T1-T3 & **T4 by size and non-invasive**
- Candidates for treatment modalities
- ECOG PS: 0-2

Stratification:
- Stage II vs III
- PD-L1 ≥1 vs <1 or unknown



Primary endpoint: rwEFS & OS (dual endpoints)
Key secondary endpoints:
pCR rate in the perioperative arm, rates of surgical resection & pCR, G ≥ 3 TRAEs & chance of longer survival rwEFS between 3-5 years

Heymach J, et al. NEJM 2023; Cascone T, et al. ESMO 2023; Felip E, et al. Lancet 2021; O'brien M, et al. Lancet Oncol 2022

Toxicity of Perioperative Therapy
(vs Neoadjuvant or Adjuvant)

Study	Neoadjuvant TRAE GR 3- 4	Neoadjuvant Treatment Mortality	Adjuvant TRAE GR 3-4	Adjuvant Treatment Mortality	Financial Toxicity ICER QALY
Neoadjuvant					
CheckMate 816 (ELCC 2023)	36%	0	-	-	$32,846*
Perioperative (neoadjuvant + adjuvant)					
Keynote-671 (ASCO 2023) (ESMO 2023)	41%	0.8%	10%	0.3%	$94,222
CheckMate 77T (ESMO 2023)	27%	1%	8%	0	-
Adjuvant					
IMpower 010 (WCLC 2022) Felip 2023	-	-	11%	.8%	$46,850
Keynote-091 (ESMO 2022)	-	-	NR	.7%	-

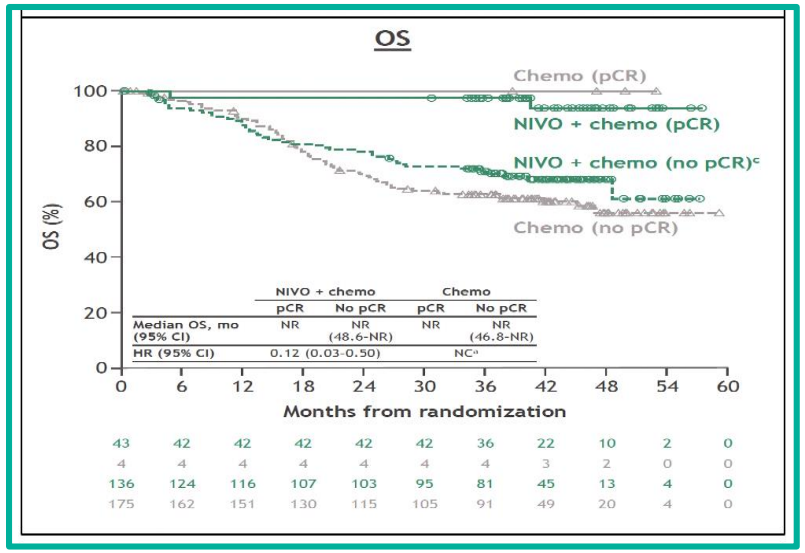
* Canadian dollars

Nivolumab (Opdivo) CADTH Reimbursement Recommendation Canadian Agency for Drugs and Technologies in Health, 2023);Tian W, et al. Fron Immmunol 2023; Das, M, et al. Immunotherapy 2023

Future Directions:

Validating cPR as an Early Endpoint for Survival

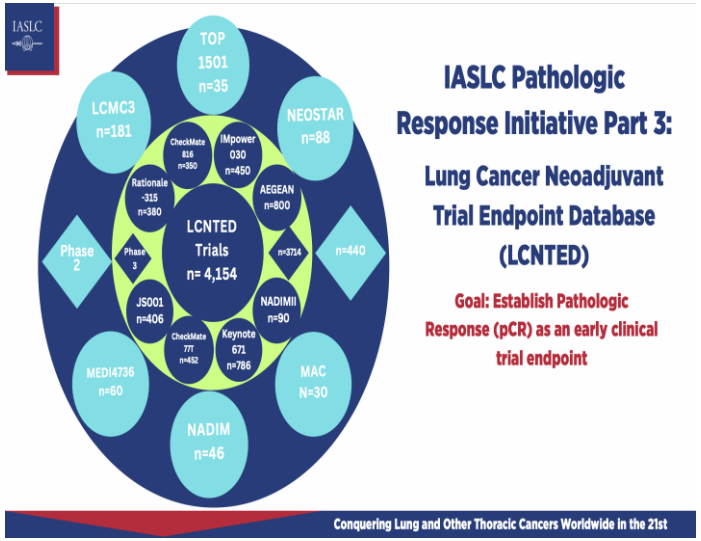
CM 816



95% Overall Survival at 3YRS

Requires large numbers for statistical robustness to determine the:

- I-Association: The association between the surrogate end point (pCR) and the true end point (eg, EFS or DRFS).
- T-Association: The association between the effect of treatment on the surrogate end point (eg, odds ratio for pCR), and the effect of treatment on the true end point (eg, hazard ratio for EFS or DRFS).



Forde P, et al. NEJM 2022

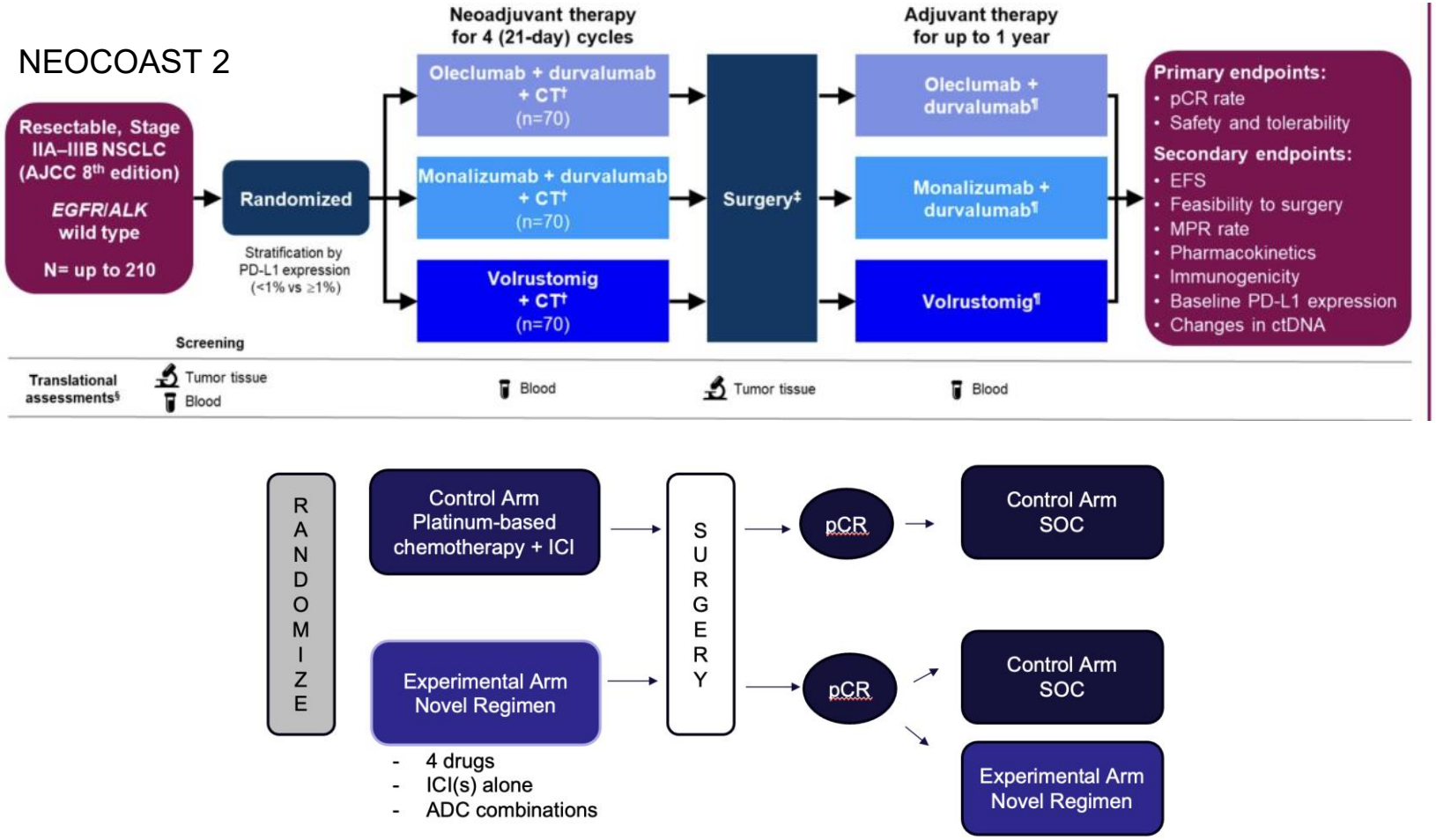
Future Directions

– Drug Development and Evaluation of Perioperative Regimens

Increasing the cPR rate

Trial	cPR
CM 816	24%
KN 671	18.1%
AEGEAN	17.2%
CM 77T	25.3%
RATIONALE 315	40.7%

What % cPR do we to make a GO - NO GO decision?



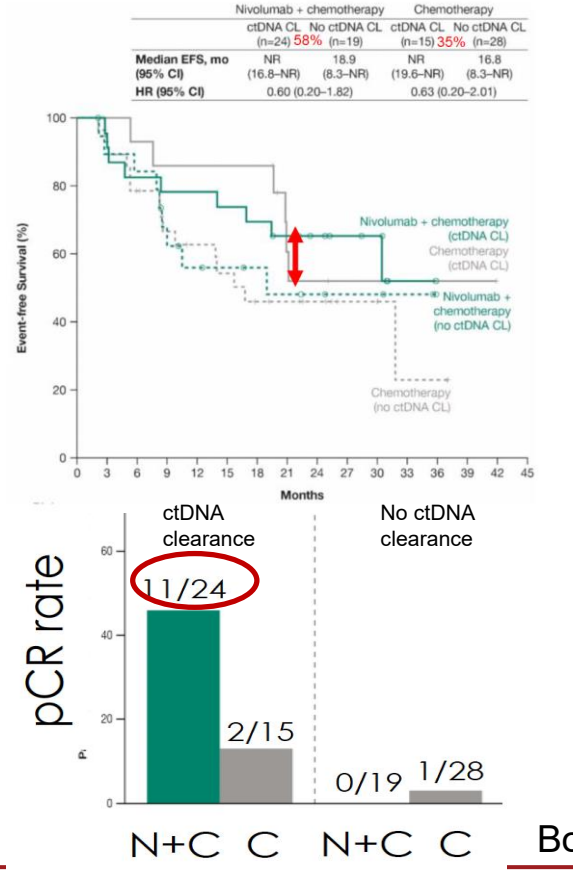
Forde P, et al. NEJM 2022; Heymach J, et al. NEJM 2023; Wakelee H, et al. NEJM 2023; Cascone T, et al. ESMO 2023; Yue D, et al. ESMO virtual plenary 2023

Future Directions

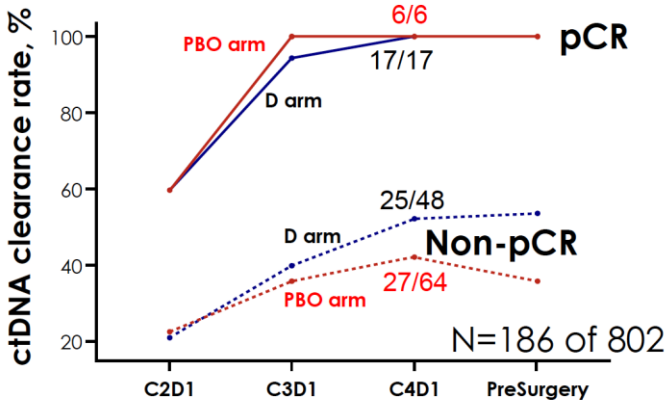
– Drug Development and Evaluation of Perioperative Regimens

Increasing the cPR rate (Can ctDNA be helpful?)

CM 816
ctDNA clearance after 3 cycles



AEGEAN
ctDNA clearance after 4 cycles



Durvalumab+CTx			Placebo+CTx	
	pCR	Non-pCR	pCR	Non-pCR
ctDNA clearance	17	25	6	27
No clearance	0	23	0	37

- Patients who clear their ctDNA with neoadjuvant tx are more likely to achieve a cPR.
- Can increasing ctDNA clearance rates be used as a complimentary tool to assess drug efficacy.
- Can ctDNA be used to risk stratify patients?
- Awaiting a sensitive assay!

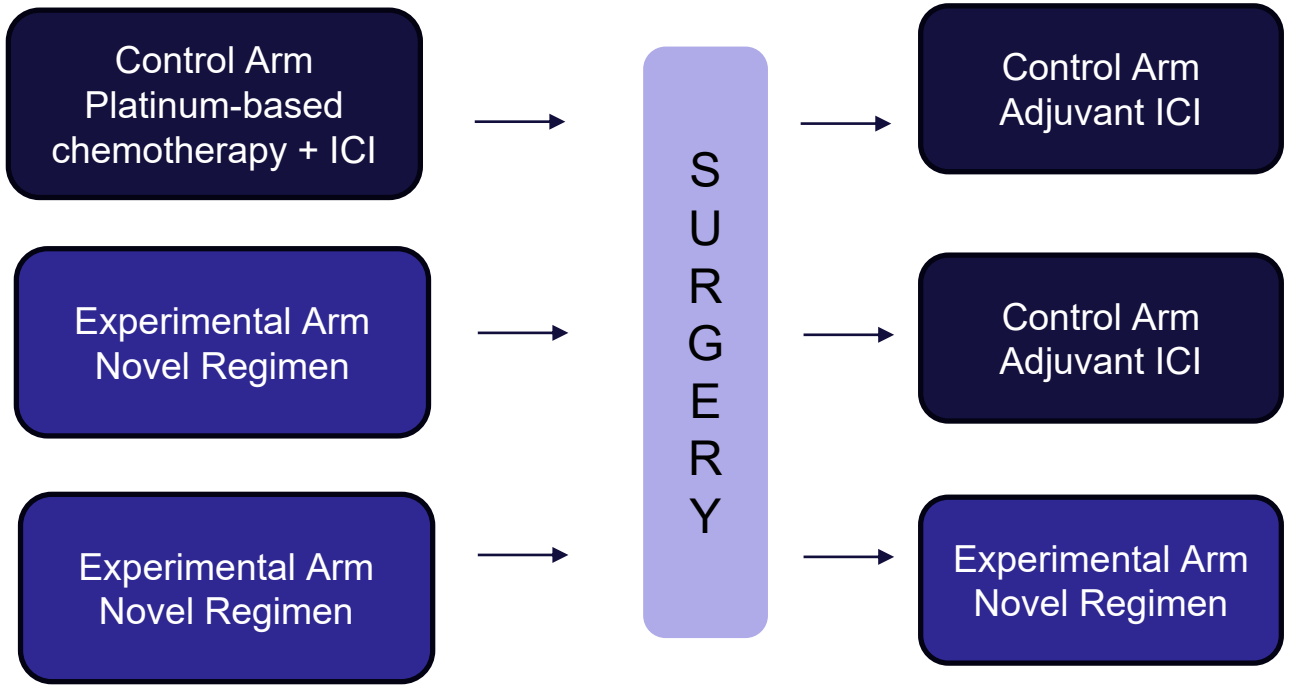
Both studies used ArcherDX (WES tumor informed assay)

Forde P, et al NEJM 2022; Reck M, ESMO 2023

Future Directions

– Drug Development and Evaluation of Perioperative Regimens

Isolating the contribution of the adjuvant component



Summary

- A perioperative regimen is the only regimen that has shown an overall statistically significant survival advantage.
- Many patients need a perioperative regimen (non-cPR, persistent ctDNA positive)
- An initial decision to recommend a perioperative regimen should be made by a multidisciplinary team (MDT).
- All patients with a perioperative plan should be re-presented to a MDT after neoadjuvant systemic treatment followed by surgery to determine if adjuvant therapy is warranted (adaptive treatment).
- Future perioperative studies are focused on:
  - -novel regimens that can increase the cPR (and ctDNA clearance rates)
  - -to determine who needs the adjuvant component
  - -developing efficacious adjuvant regimens

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