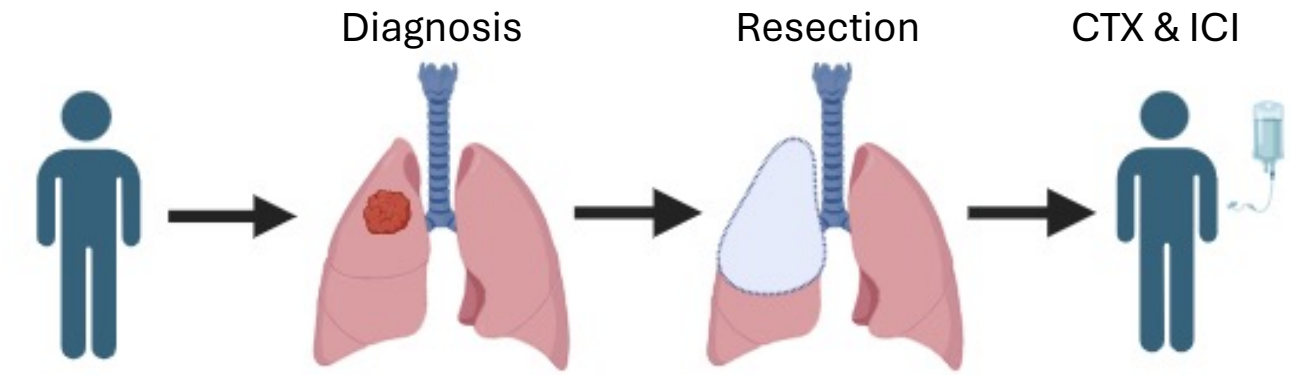
Yes, to Adjuvant ICI after Pathologic Complete Response

INOVA
Schar Cancer Institute

Janakiraman Subramanian MD, MPH

Patient Journey in Resectable NSCLC without Driver Alterations



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS of ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial

ESMO VIRTUAL PLENARY

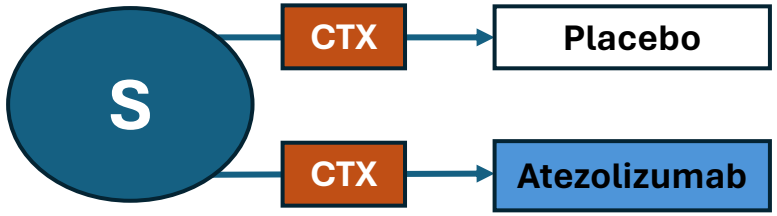
EORTC European Organisation for Research and Treatment of Cancer

The future of cancer therapy

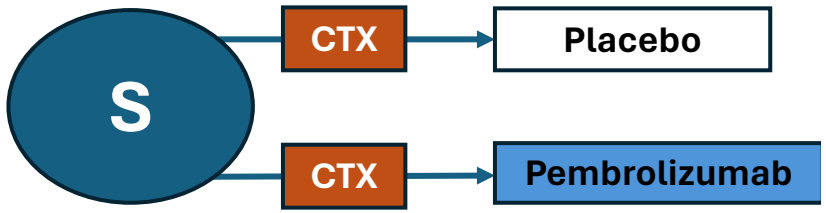
Pembrolizumab Versus Placebo For Early-Stage NSCLC Following Complete Resection and Adjuvant Chemotherapy When Indicated: Randomized, Triple-Blind, Phase 3 EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Study

Adjuvant ICI after Definitive Surgical Resection

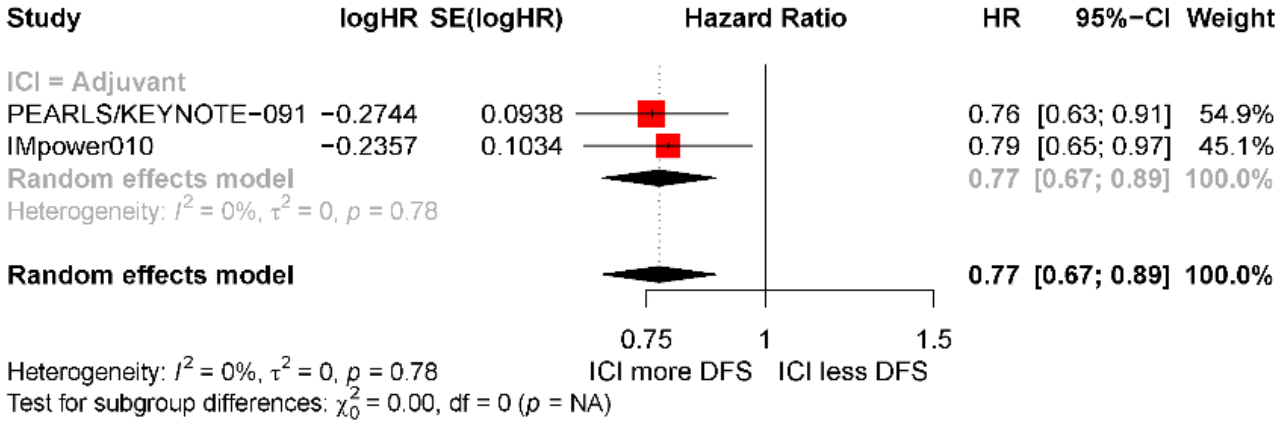
IMpower-010



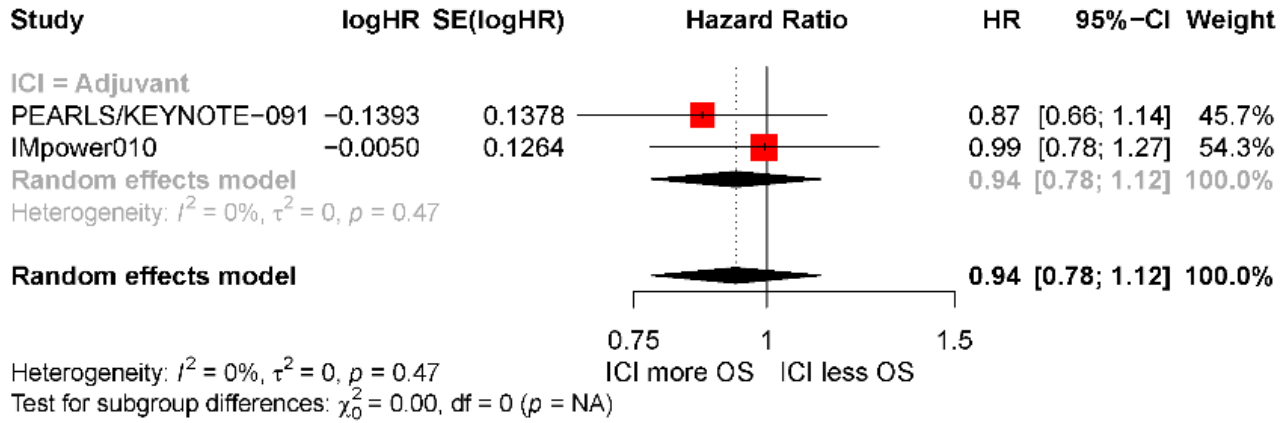
PEARLS/KN-091



Adjuvant DFS



Adjuvant OS



Ponvilawan-Subramanian Clin lung Cancer. 2024

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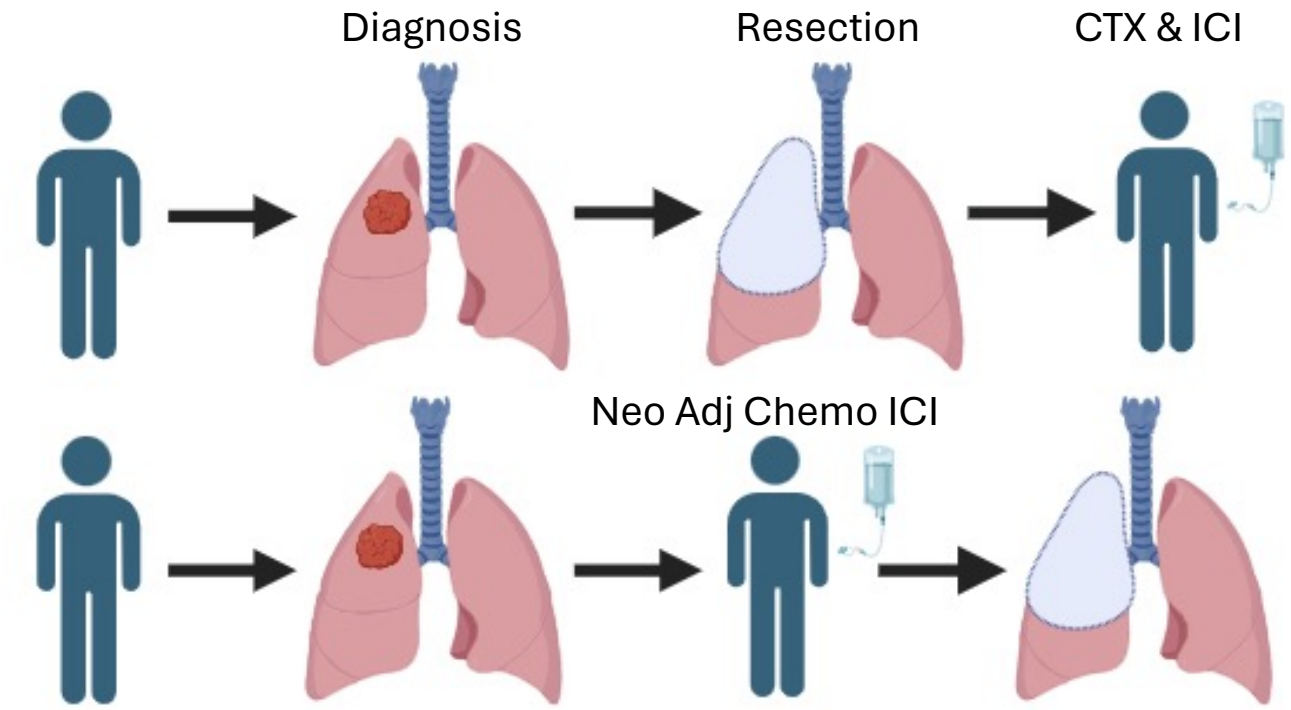

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ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard. for the CheckMate 816 Investigators*

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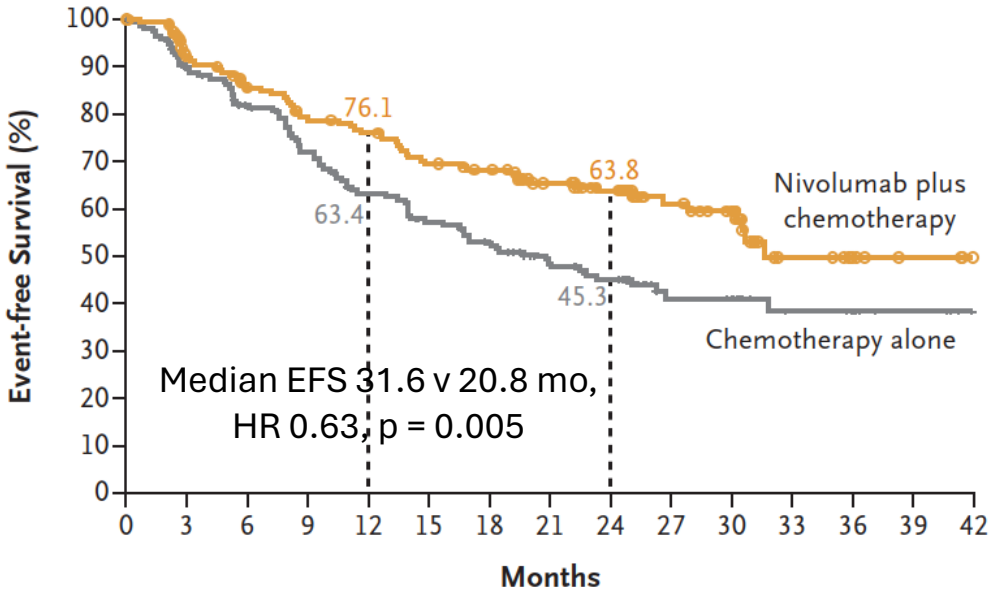
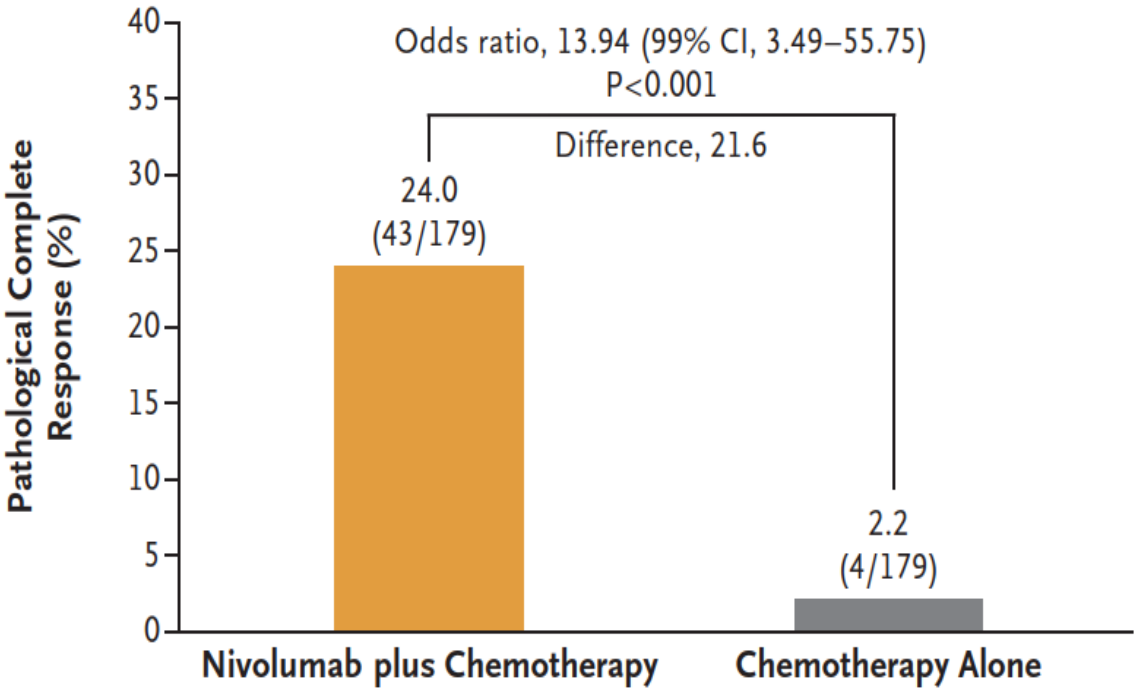


No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0



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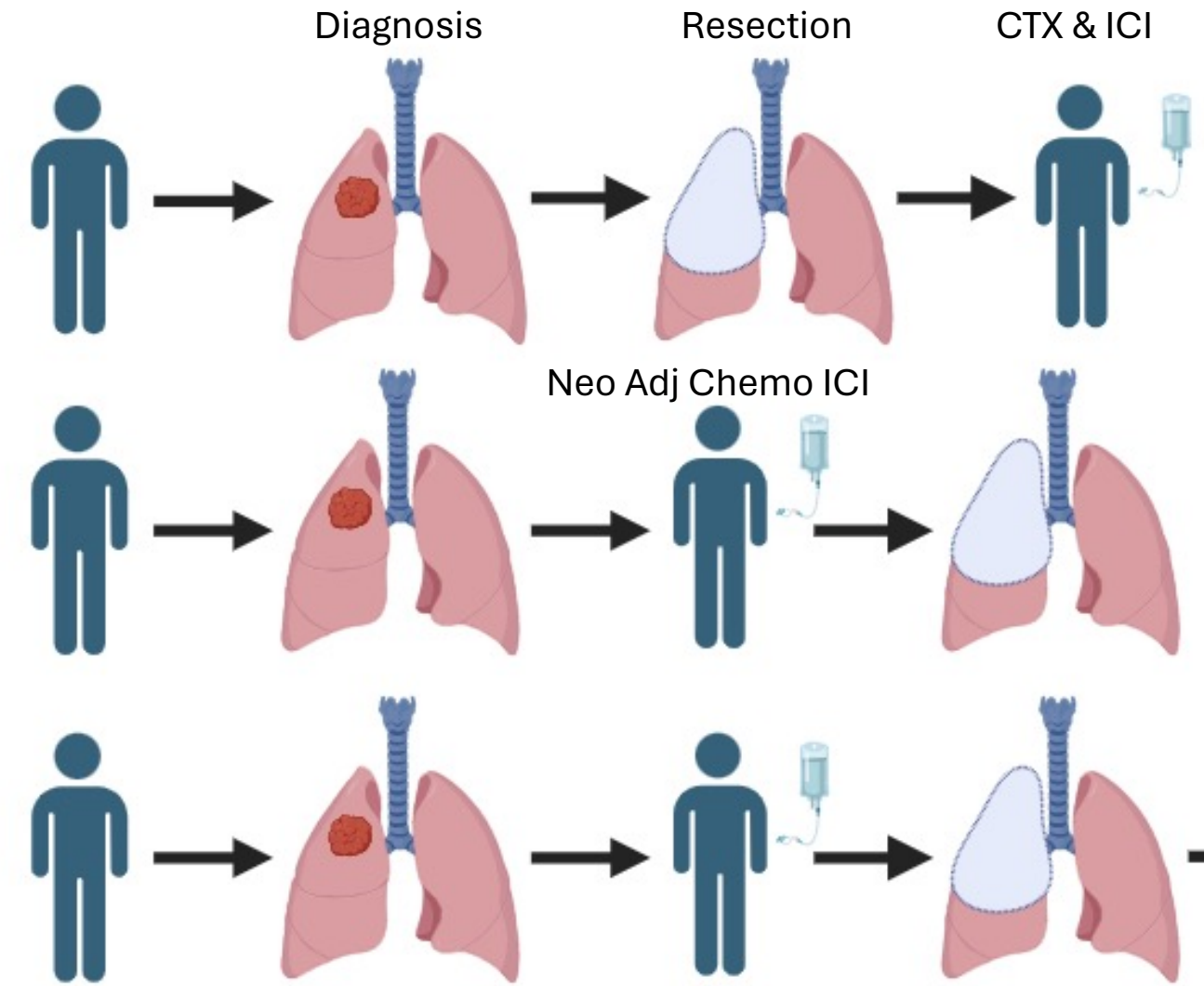

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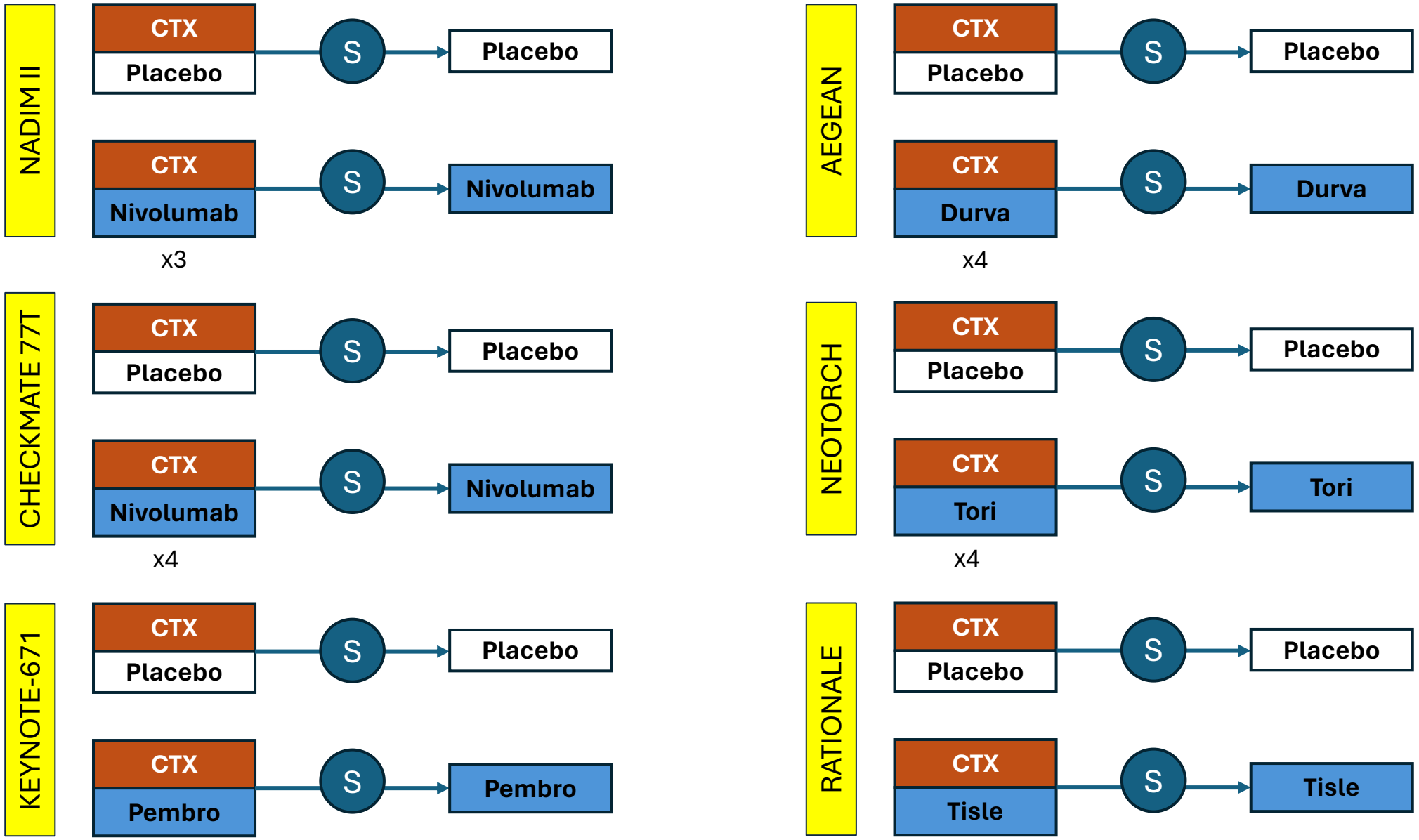
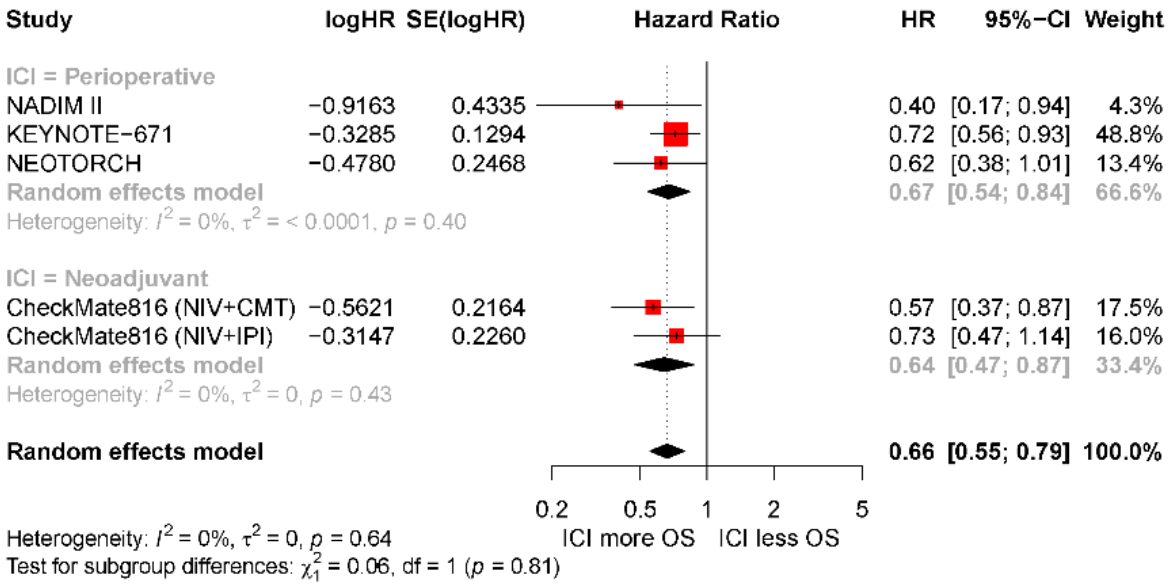
Peri-operative CTX + IO Trials in NSCLC (N = 3000 patients)



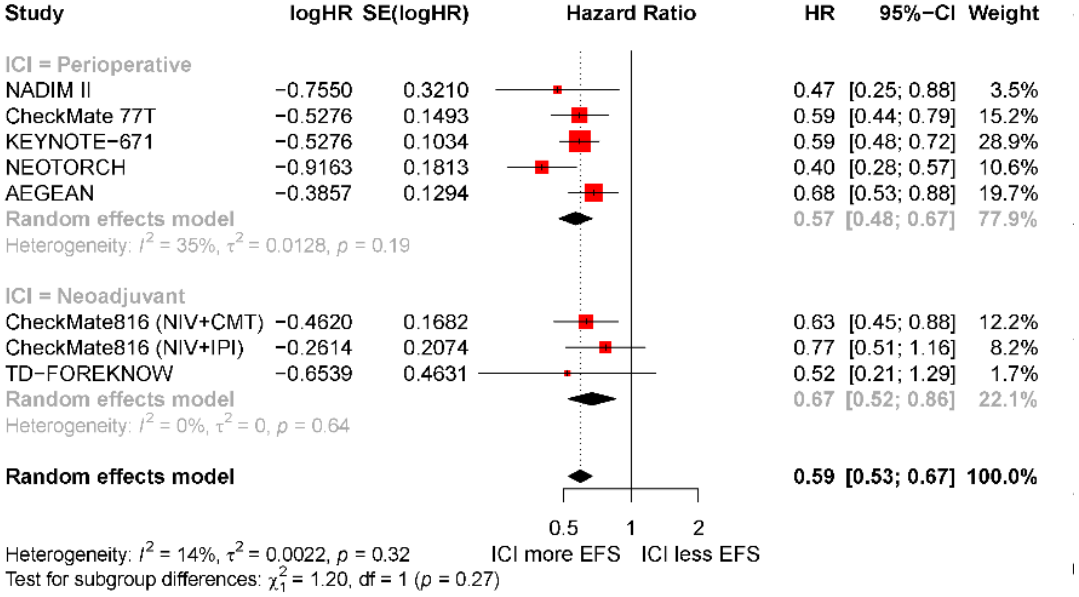
Provencio NEJM 2023, Wakelee NEJM 2023, Yue ESMO 2024
Forde NEJM 2022, Lu JAMA 2024, Cascone ESMO 2023

There is benefit in adding ICI to chemotherapy

Neoadjuvant OS



Neoadjuvant EFS



- Neoadjuvant/Peri-operative chemotherapy ICI improves both OS and EFS
- Compared to adjuvant ICI the magnitude of benefit appears to be better with the Neoadjuvant approach

Ponvilawan-Subramanian Clin lung Cancer. 2024

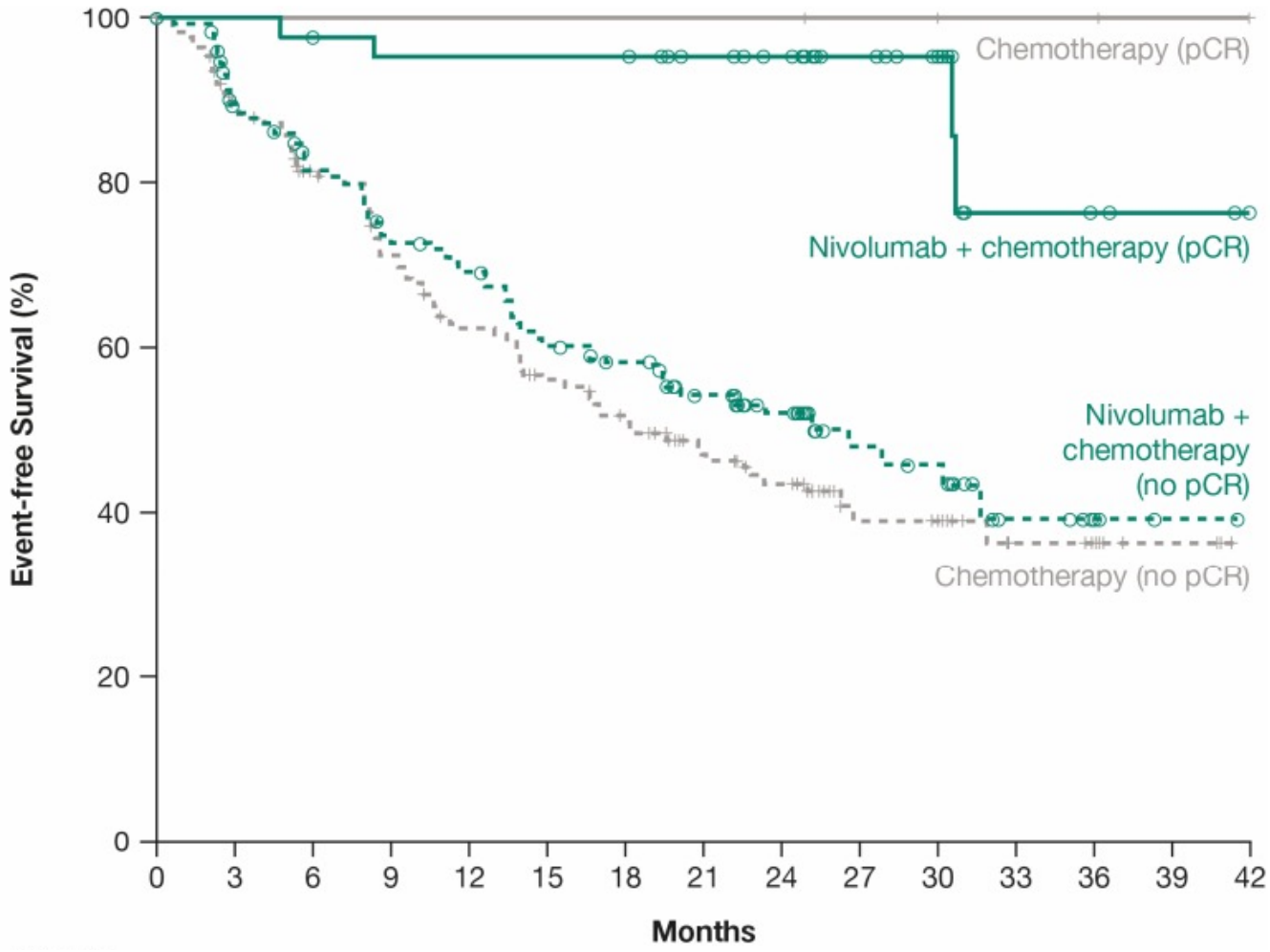
Which is better? Adjuvant or Neoadjuvant

- Adjuvant
  - No delay in curative surgery
  - Accurate surgical staging
  - Avoid neoadjuvant “mission creep”
- Neoadjuvant
  - Intact tumor generates better antitumor response
  - Better tumor response
  - Better resectability
  - More lung sparing surgeries

Which is better? Adjuvant or Neoadjuvant

- Adjuvant
  - No delay in curative surgery
  - Accurate surgical staging
  - Avoid neoadjuvant “mission creep”
  - Only 53% are guideline compliant lymph node dissections
  - Low adherence - only 57% receive adjuvant chemotherapy
- Neoadjuvant
  - Intact tumor generates better antitumor response
  - Better tumor response
  - Better resectability
  - More lung sparing surgeries
  - Possible disease progression
  - Delay of surgery & inability to undergo surgery

Checkmate 816 – Outcomes by pCR

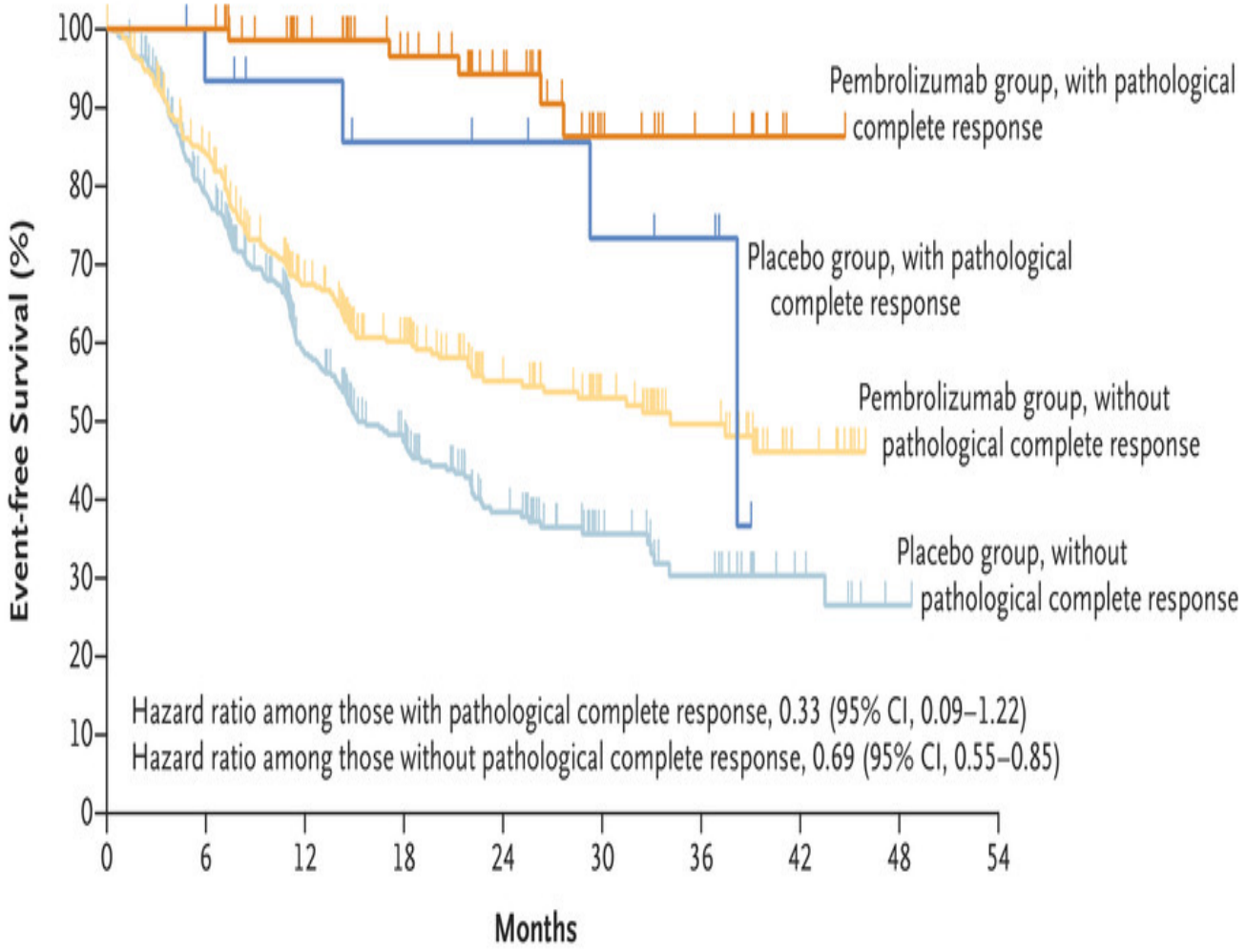


	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	

- Patients with pCR have better EFS
- But at 30 months EFS ~75%
- Outcomes for patients without pCR seem similar with or without nivo!!

Forde NEJM 2022

KN-671 - Outcomes by pCR

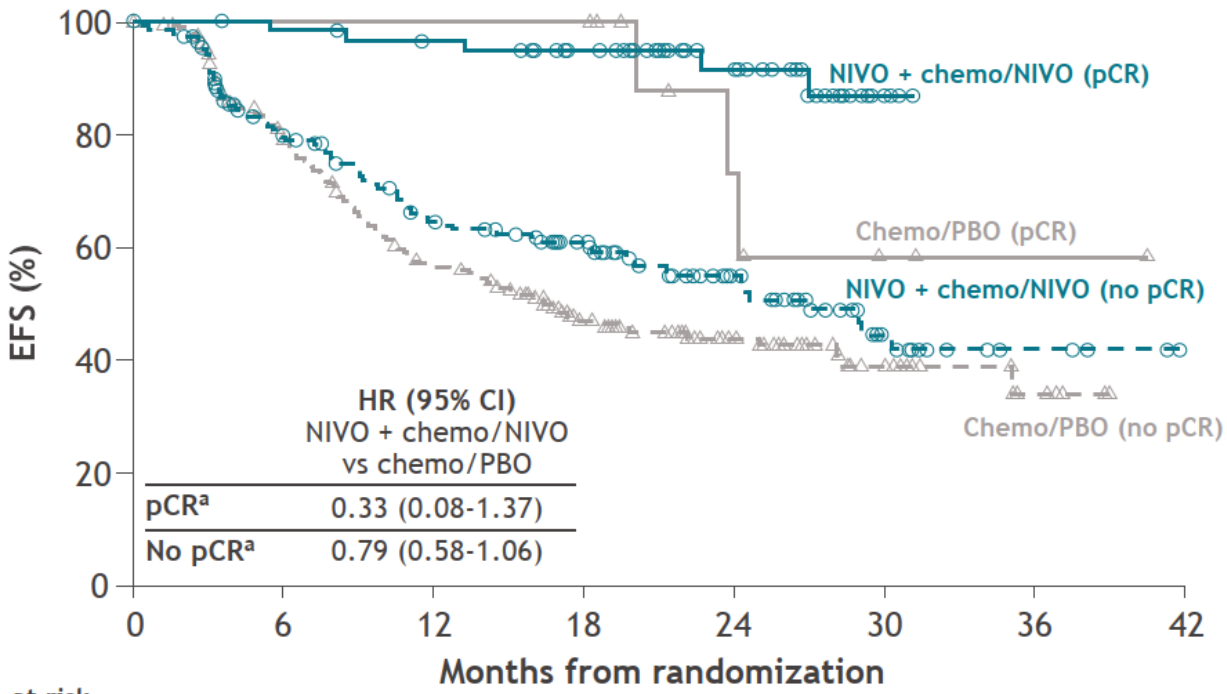


- HR for pCR patients 0.33 (95% CI 0.09-1.22)
- Once again, these patients do better but 2-year EFS ~90%
- But do have recurrent disease

Wakelee NEJM 2023

Exploratory analysis: EFS by pCR and MPR status

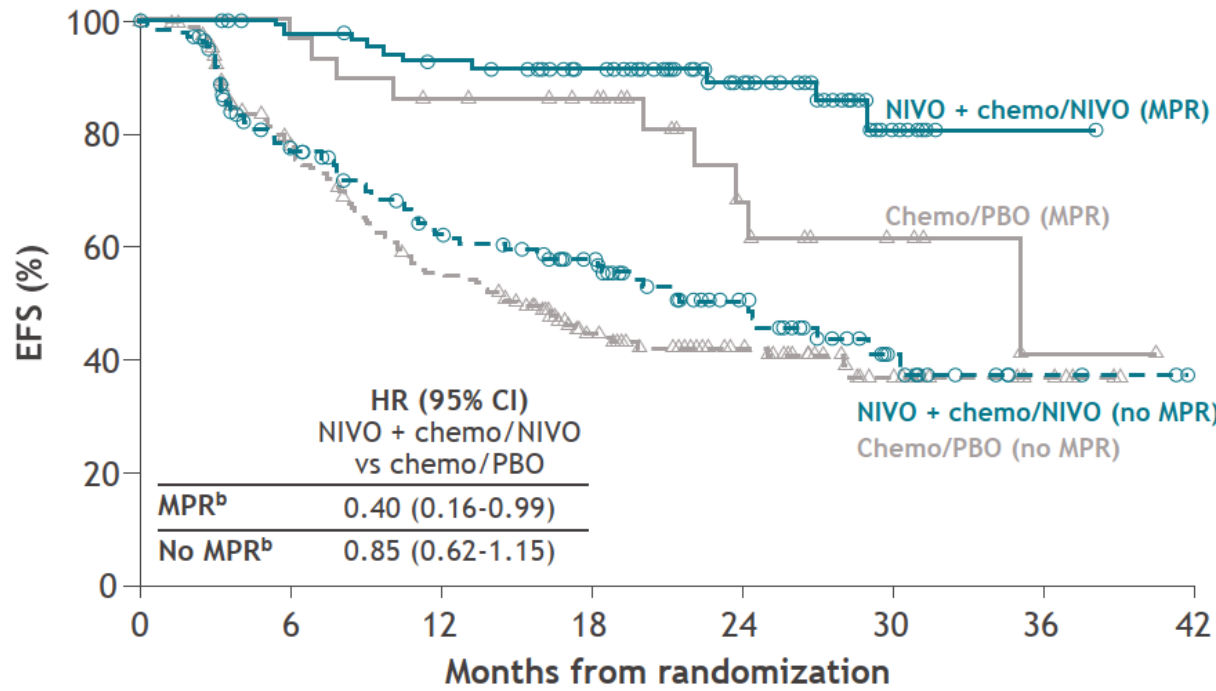
EFS by pCR



No. at risk

pCR	58	56	53	45	28	4	0	0
pCR	11	11	11	11	5	2	1	0
No pCR	171	117	88	70	41	16	4	0
No pCR	221	154	107	67	39	17	5	0

EFS by MPR

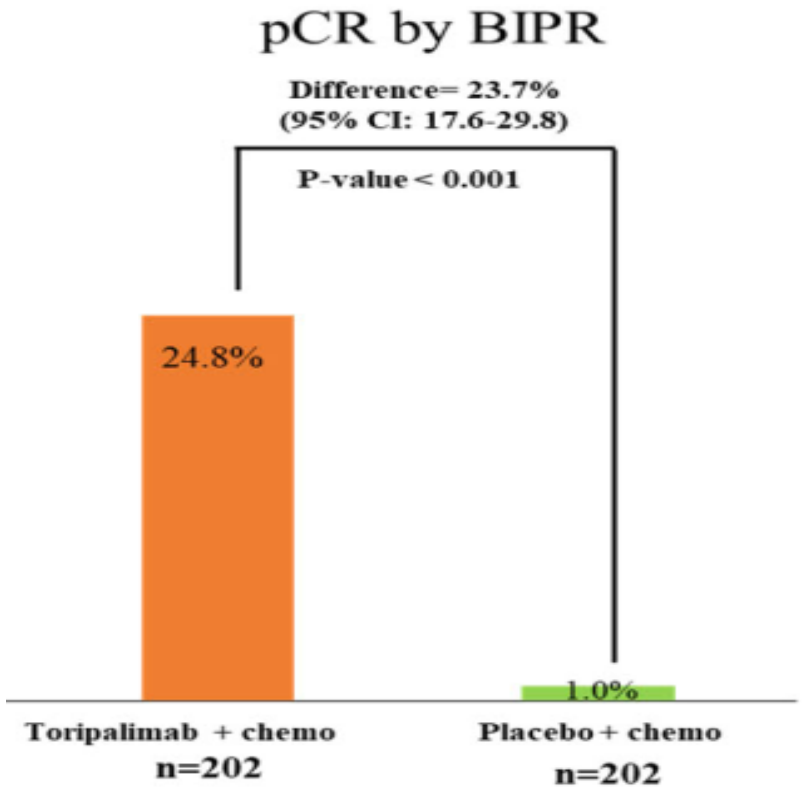


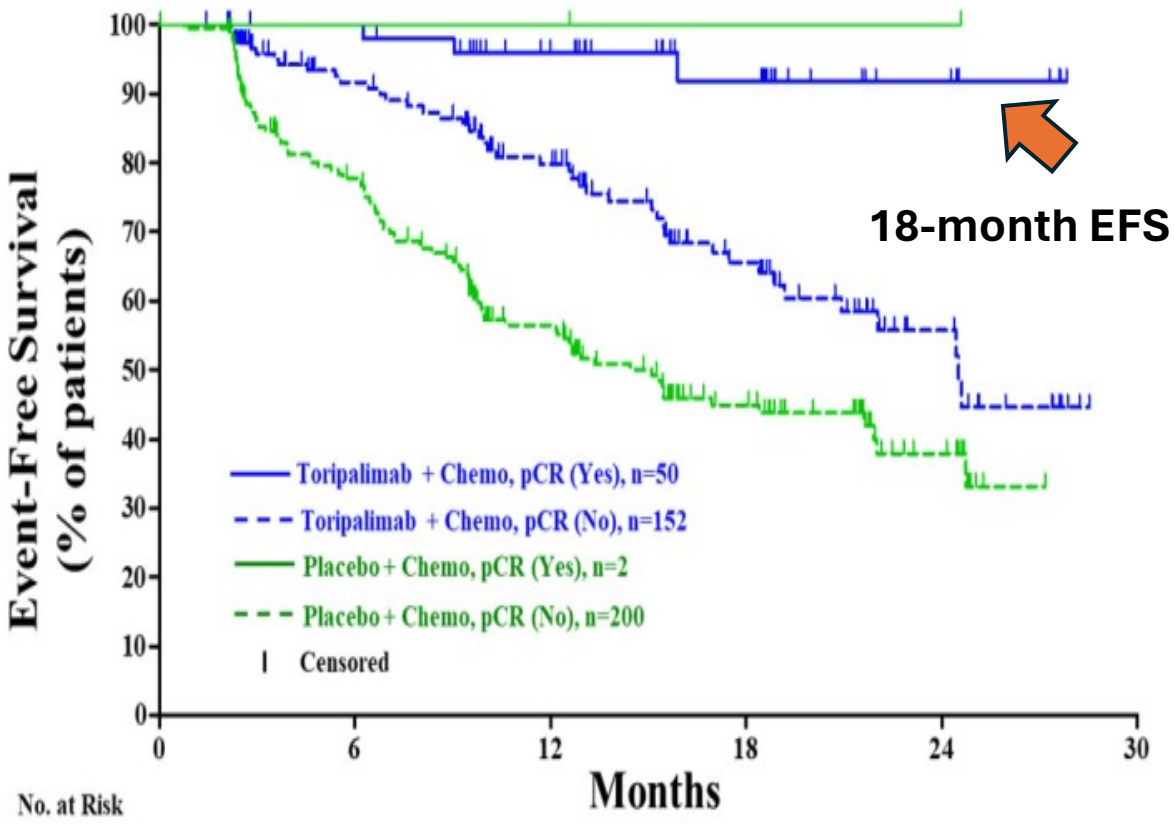
MPR	81	76	70	59	37	8	1	0
MPR	28	27	23	20	10	5	1	0
No MPR	148	97	71	56	32	12	3	0
No MPR	204	138	95	58	34	14	5	0

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

[a]HR (95% CI), 0.14 (0.06-0.35) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.32 (0.10-1.00) in the chemo/PBO arm. [b]HR (95% CI), 0.18 (0.09-0.35) in patients with MPR vs those without in the NIVO + chemo/NIVO arm and 0.40 (0.20-0.78) in the chemo/PBO arm.

NEOTORCH



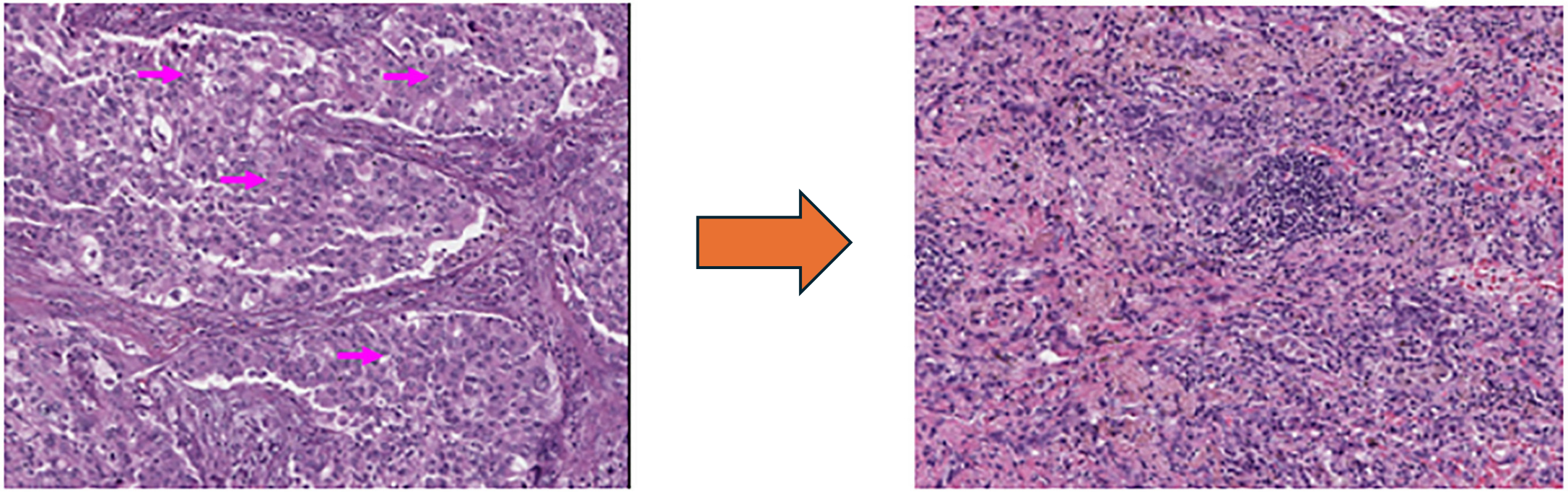


18-month EFS ~ 90%

Lu JAMA 2024

What is pathologic complete response?

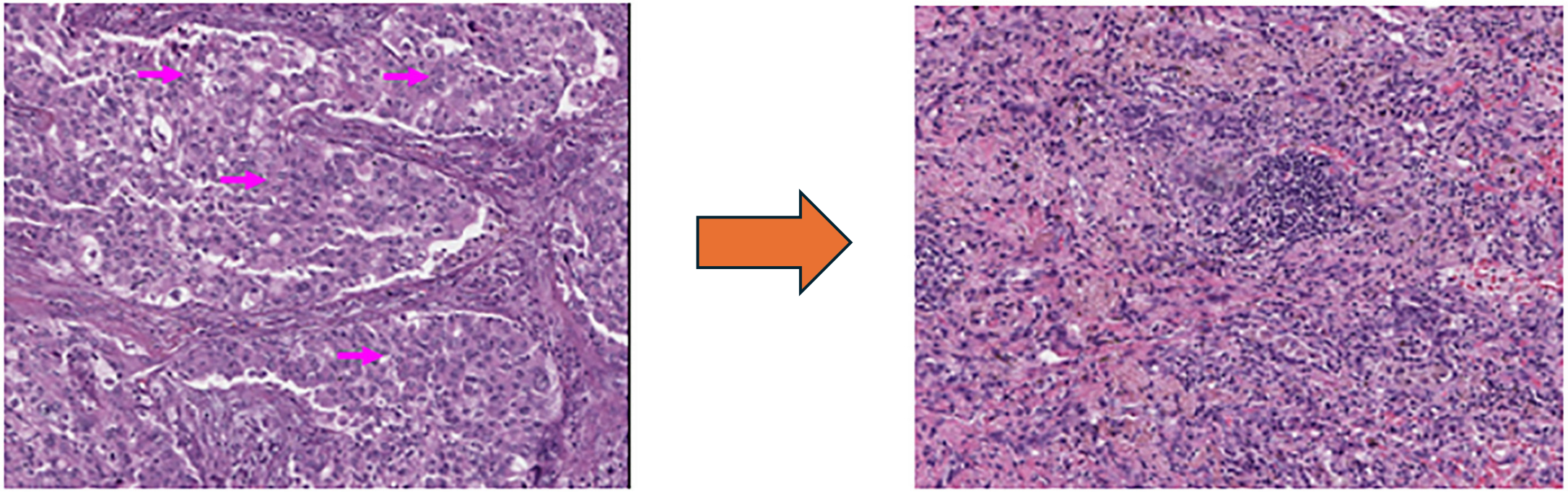
- pCR = no residual viable (0%) tumor cells in the resected tumor & lymph nodes after treatment



Pataer JTO CRR 2022

What is pathologic complete response?

- or is it a function of the pathologist's time?



Pataer JTO CRR 2022

IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy

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REVIEW

IASLC

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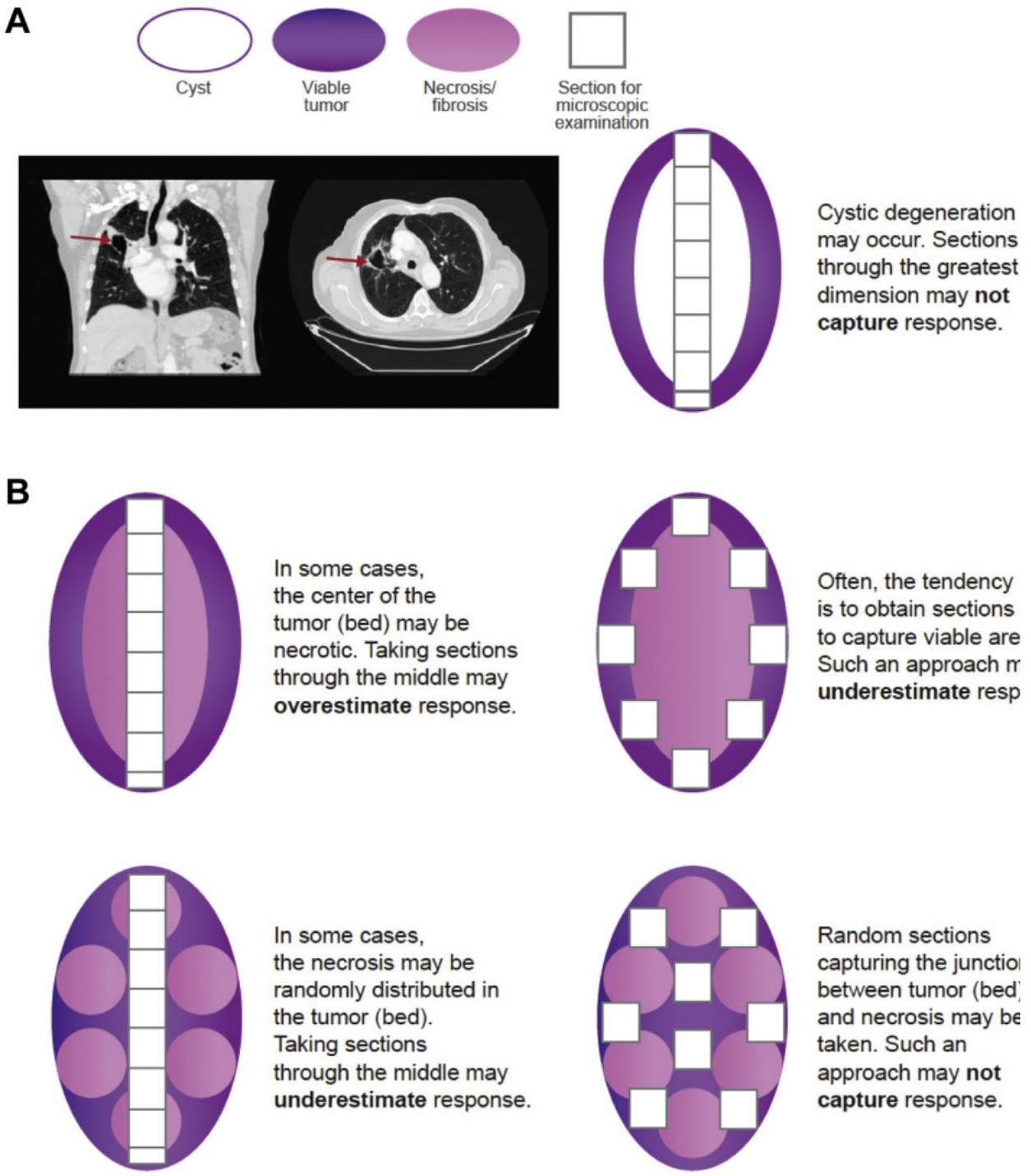
- 11 recommendations
- Recommend a multi-D approach
  - Integrate imaging and gross path
  - Pathologist encouraged to get input from thoracic surgeon
- Number of prospective studies evaluating this methodology = 0

Is pathologic CR a valid surrogate endpoint?

Saqi JTO Clin Res Rep 2022



Is pathologic CR a valid surrogate endpoint?

- Can mPR and pCR be surrogate endpoints for survival?
- Maybe!!
  - There is variability in guidelines for assessing pathologic response
  - Inter-observer variability
  - Several challenging scenarios
    - Extracellular Mucin – “Tumor” or “Stroma”
    - Are fibrovascular cores - “Tumor” or “Stroma”
    - What constitutes “regression bed”
    - Cystic changes in tumor bed
    - Hilar tumors

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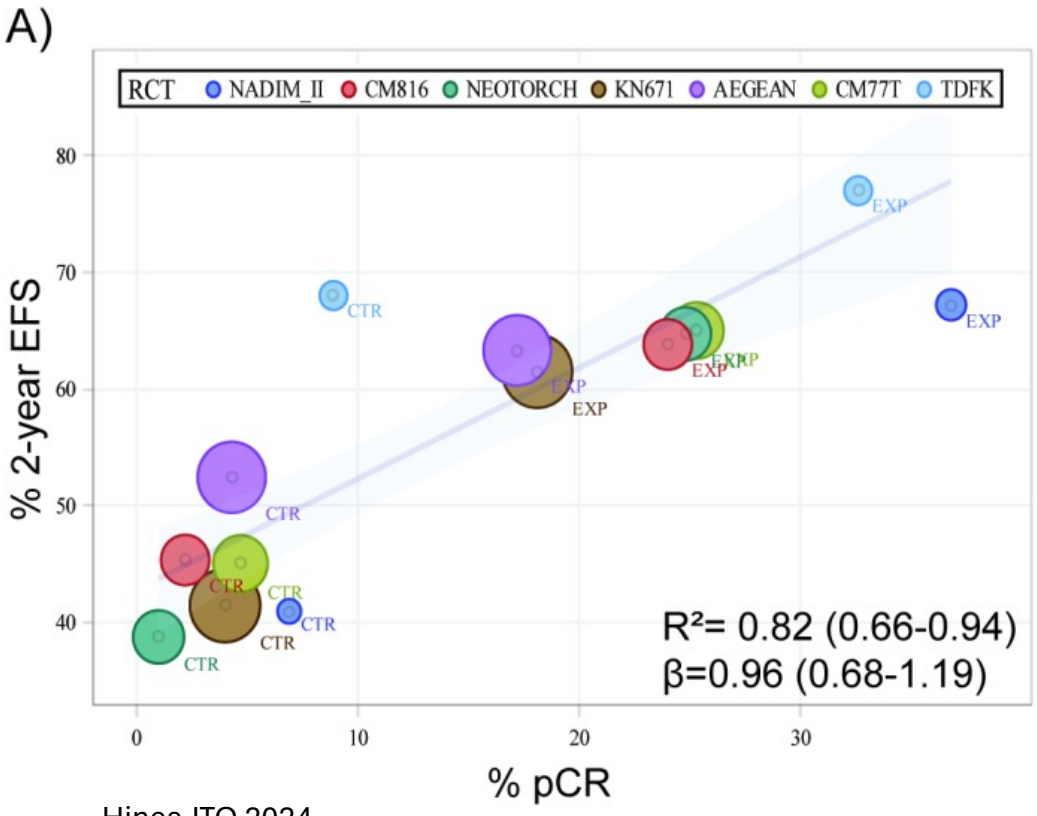

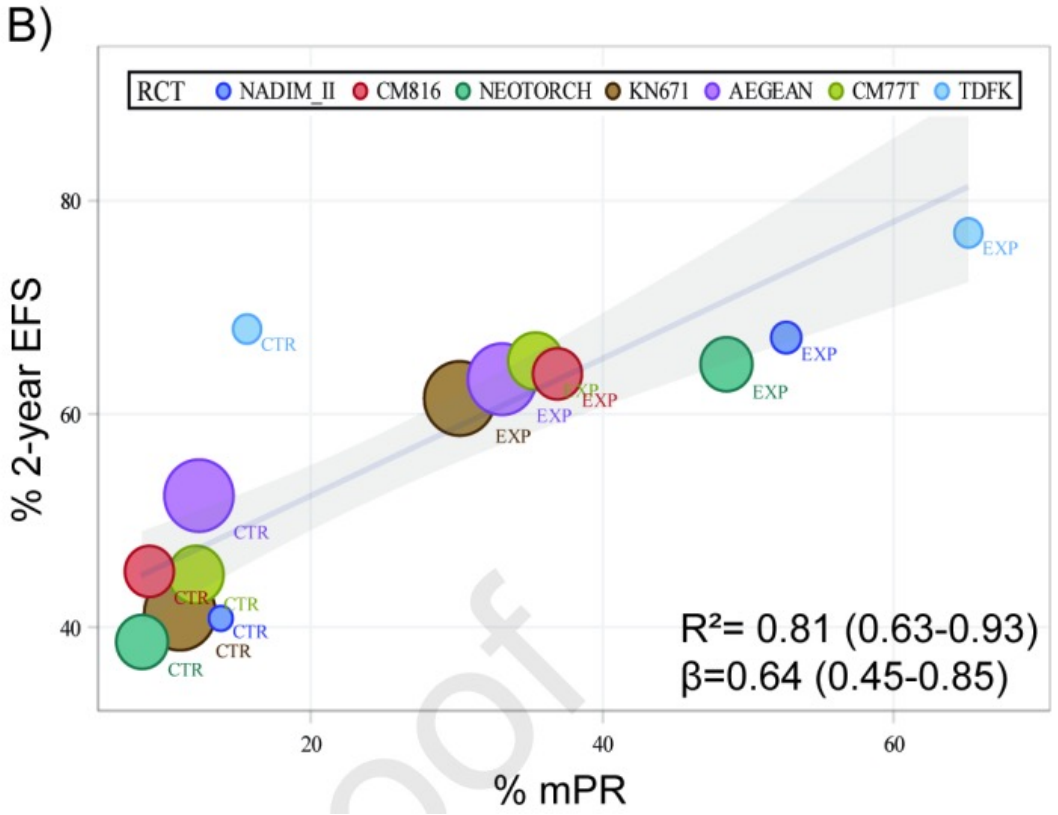

Hines JTO 2024

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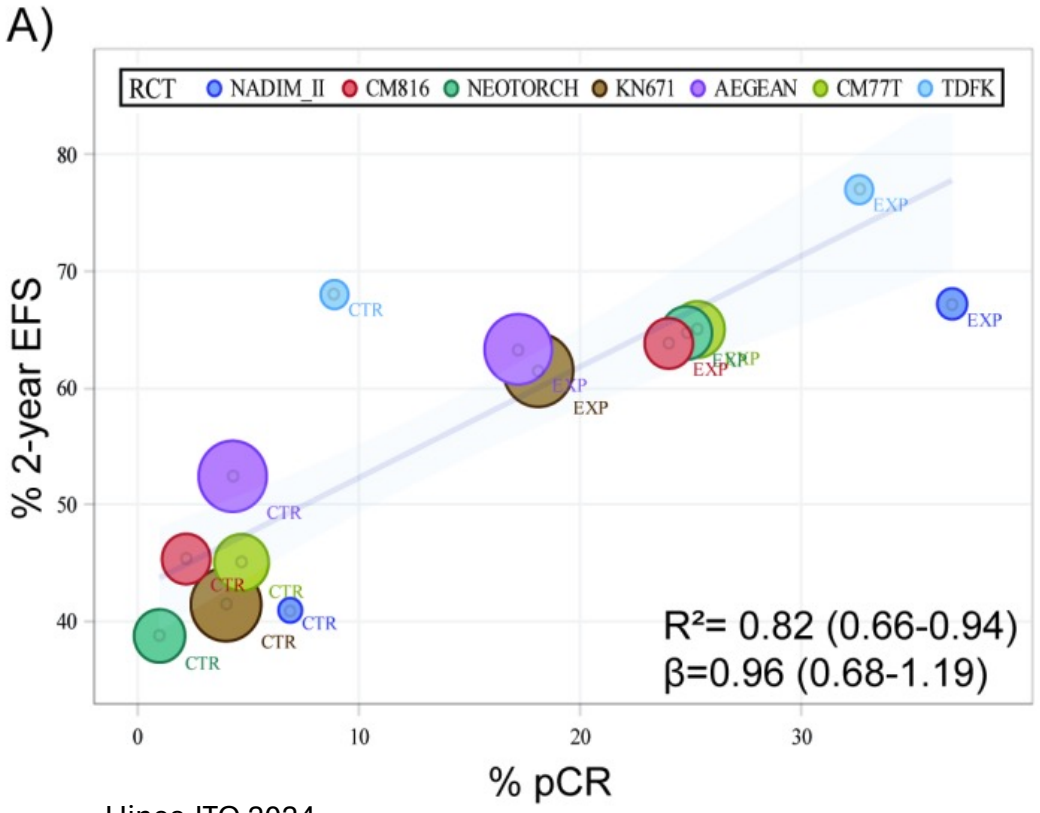
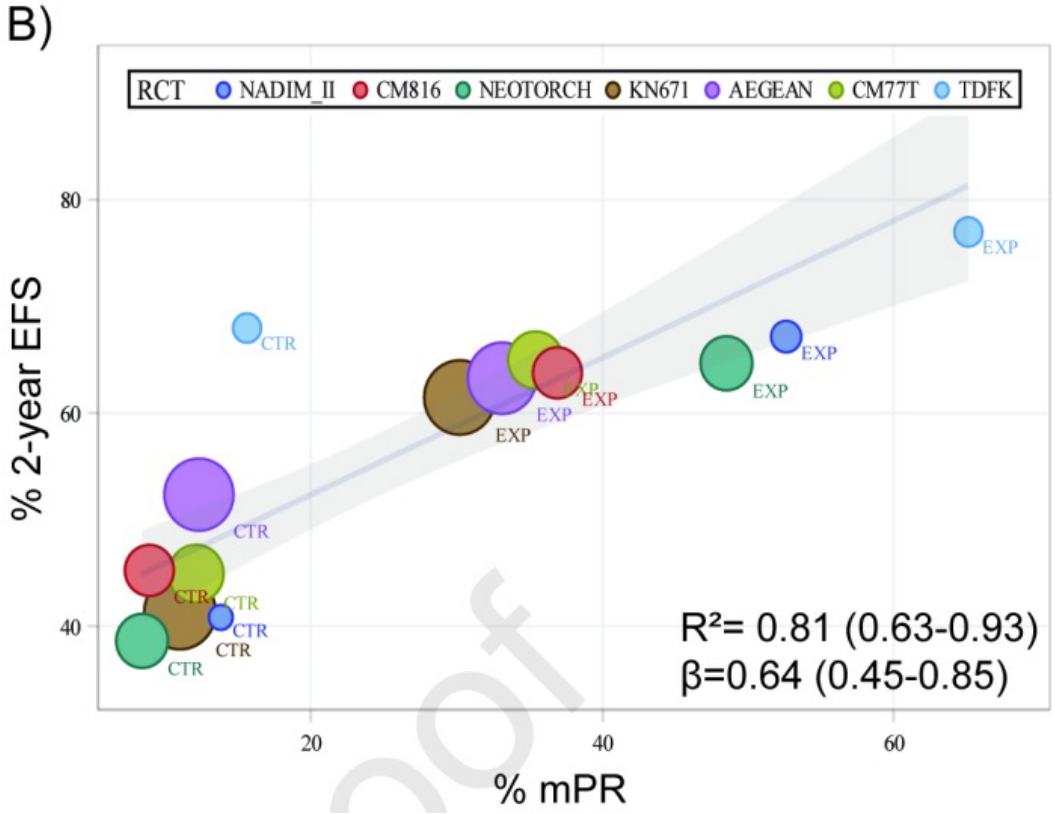
- Maybe !! There is a positive correlation with 2-year EFS





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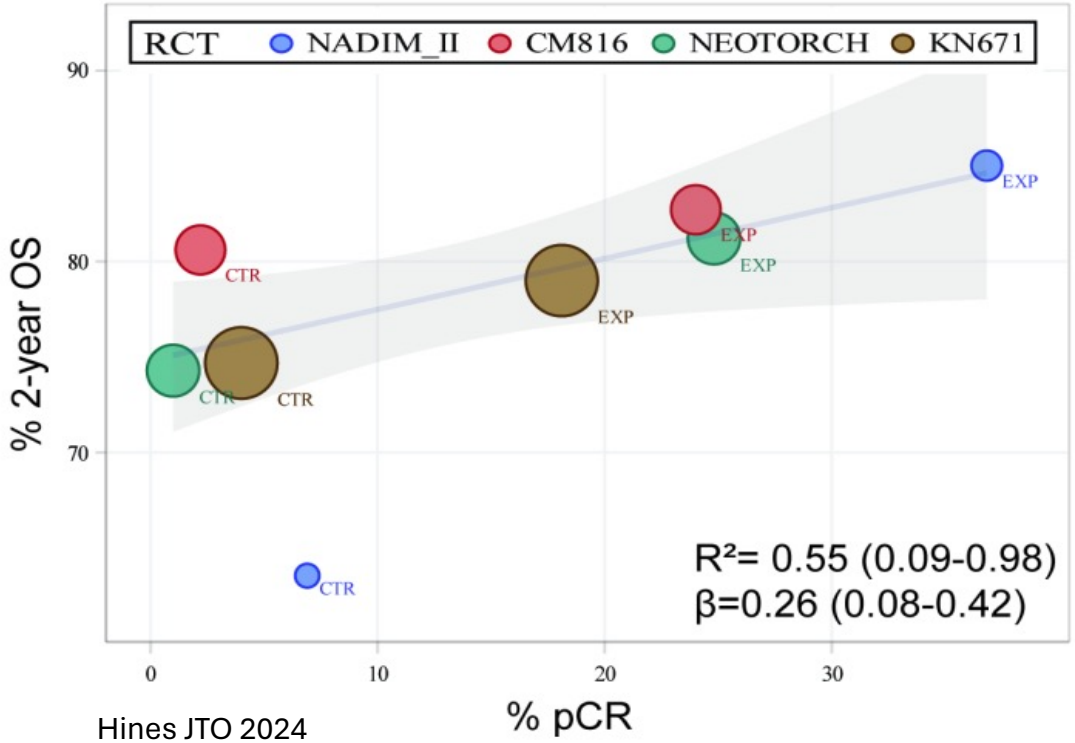
Is pathologic CR a valid surrogate endpoint?

- Can mPR and pCR be surrogate endpoints for survival?
- Maybe !! There is a positive correlation with 2-year EFS
- No correlation with OS!!



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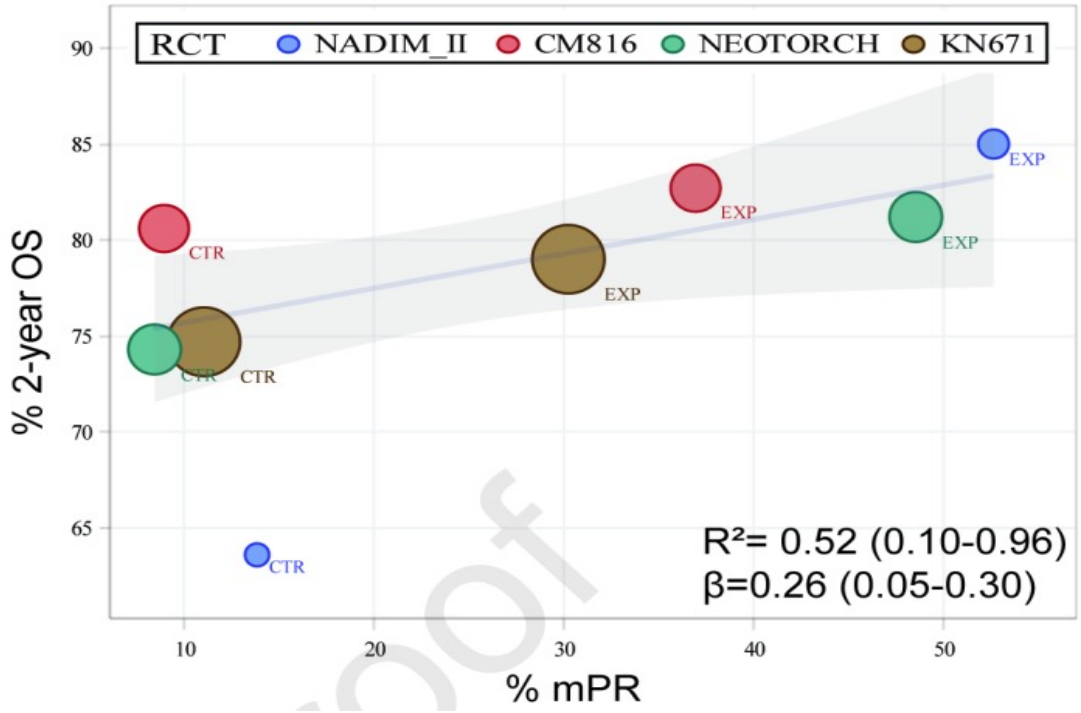
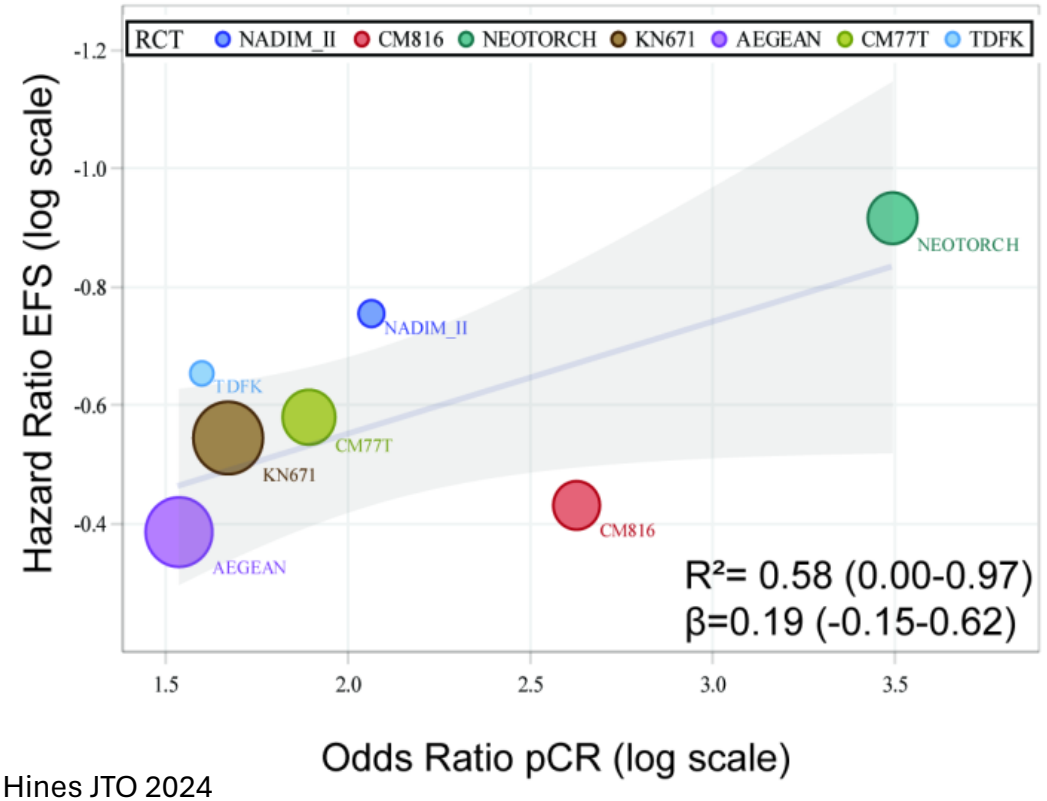
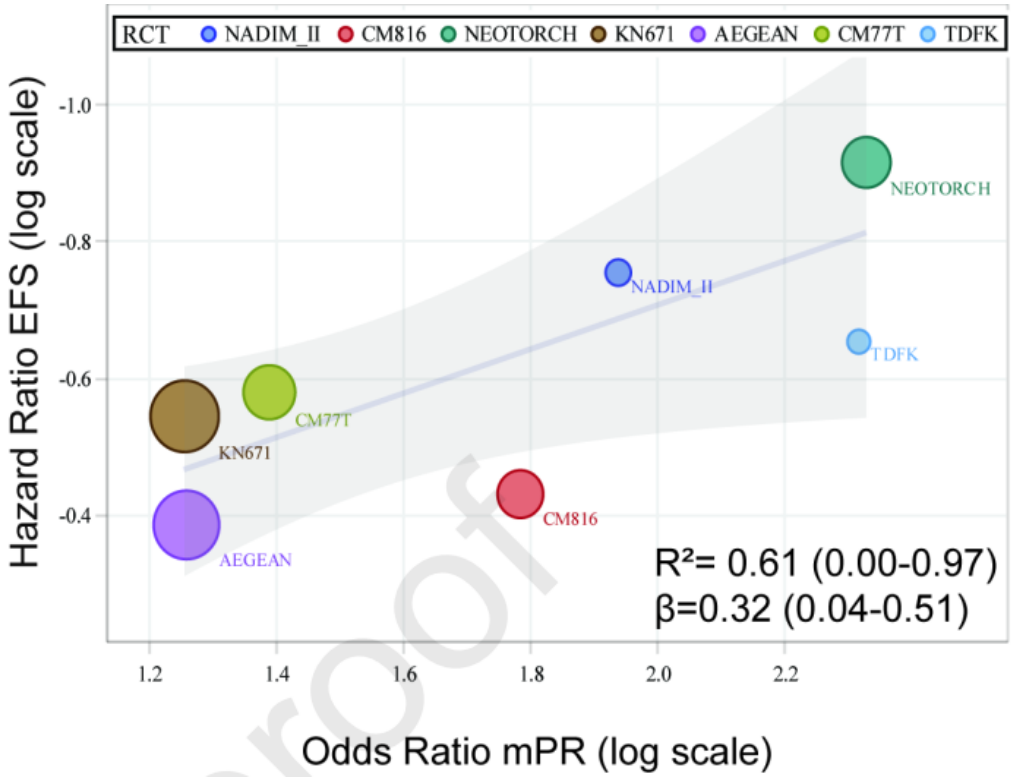


Is pathologic CR a valid surrogate endpoint?

- Can mPR and pCR be surrogate endpoints for survival?
- Interestingly there is no correlation at individual study level





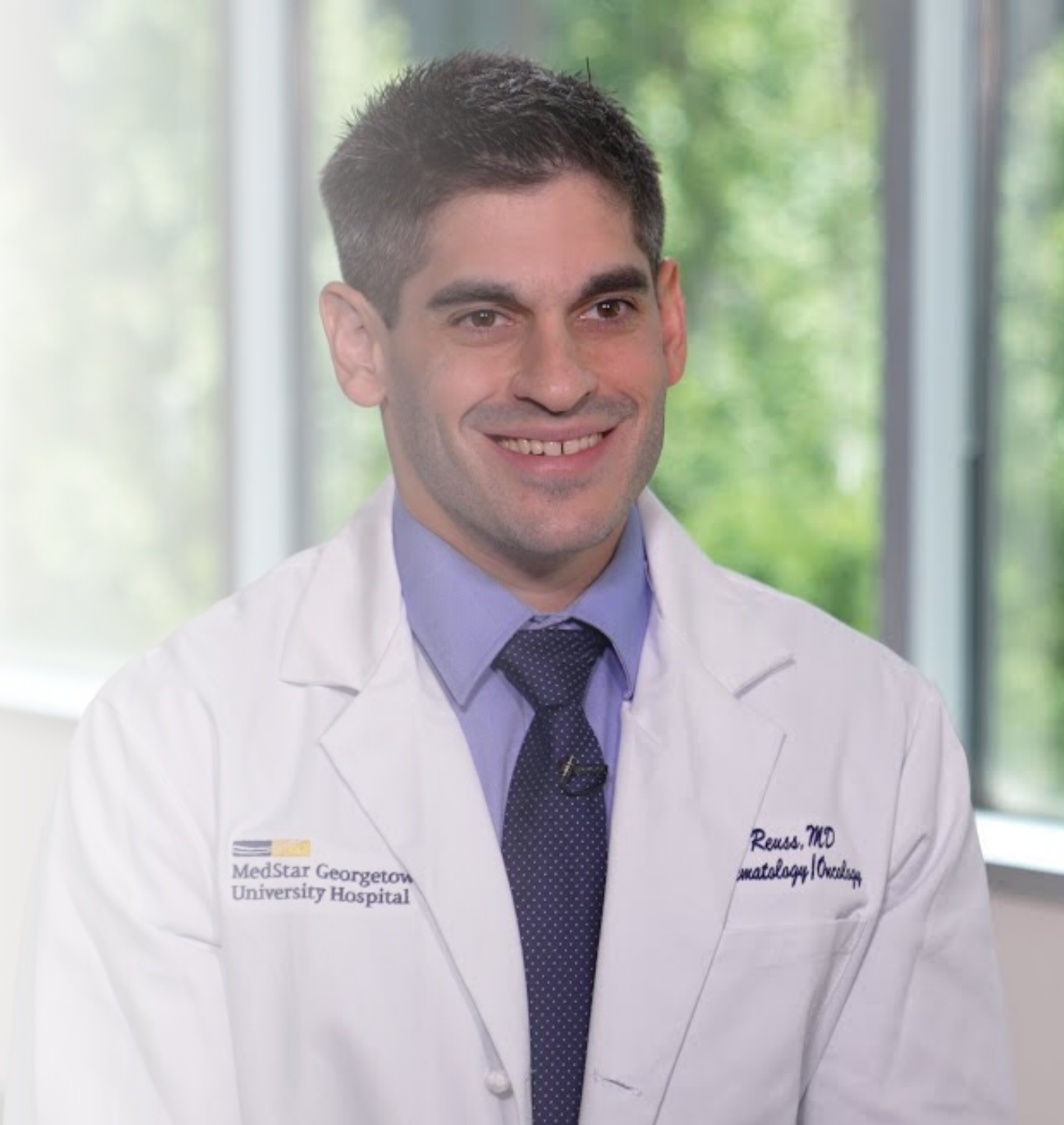
Hines JTO 2024

Conclusion

- pCR after neoadjuvant chemo ICI is associated with better survival
- But pCR does not equal “cure” and that’s current evidence
- pCR and MPR assessment needs standardization
  - IMpower030 sub study – to eval IASLC standards for assessing MPR & pCR and address some of the previously noted challenging scenarios
- There is risk for IrAEs with extended ICI treatment and the duration of adjuvant ICI is not well established
- This calls for shared decision making

Coming up next

- Joshua Reuss, MD, thoracic medical oncologist at MedStar Georgetown University Hospital.



He is going to ask you to trust him!!

He is going to ask you to trust him!!

TRUST ME, I KNOW WHAT I AM DOING!