SELECTION OF ENDPOINTS: IMPACT ON PRACTICE

Julie R Brahmer, MD, MSc, FASCO

Marilyn Meyerhoff Professor of Thoracic Oncology

Johns Hopkins Kimmel Cancer Center

@JulieBrahmer

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Clinical Trial Endpoints in NSCLC Testing Immunotherapy

- **What is Clinically Meaningful? What really matters?**

  Advanced Stage

  - Overall Survival (OS) – Gold Standard – requires large numbers and long followup
    - ?Landmark OS?
  - Progression Free Survival (PFS)
  - Overall Response Rate (ORR)
  - Duration of Response (DOR)

  Early Stage Disease

  - Pathologic Complete Response (pCR)
  - Major Pathologic Response (MPR)
  - Event Free Survival (EFS)
  - Disease Free Survival (DFS)

Surrogate Endpoints

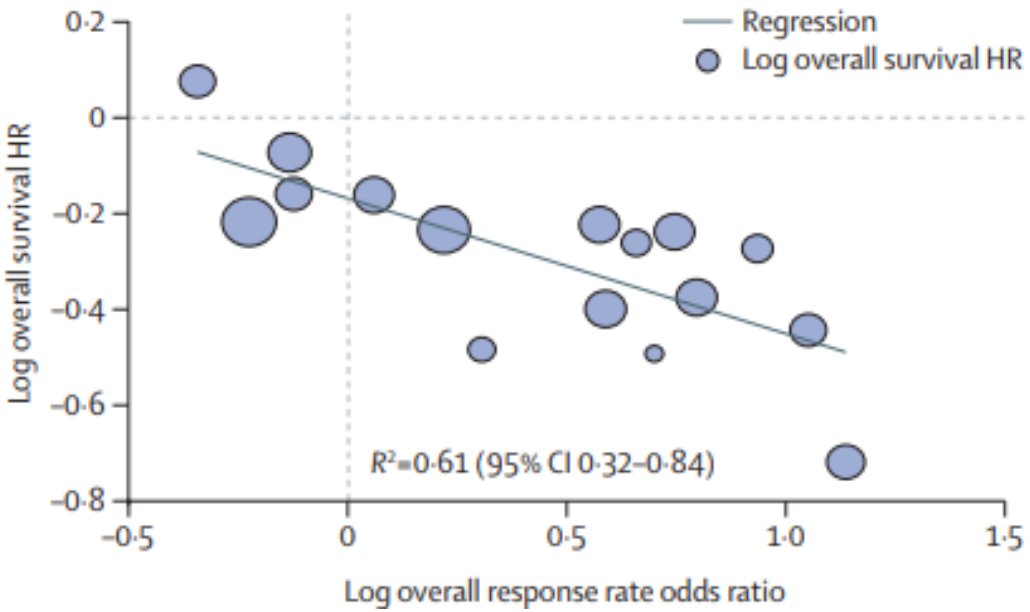
Prentice Criteria

- The treatment intervention must be associated with the surrogate
- The surrogate must be associated with the true outcome
- The surrogate must be able to explain the entirety of the effect on the true outcome
- US Food and Drug Administration (FDA) has adopted a less stringent definition of surrogacy, which requires that a surrogate endpoint be “reasonably likely to predict clinical benefit”

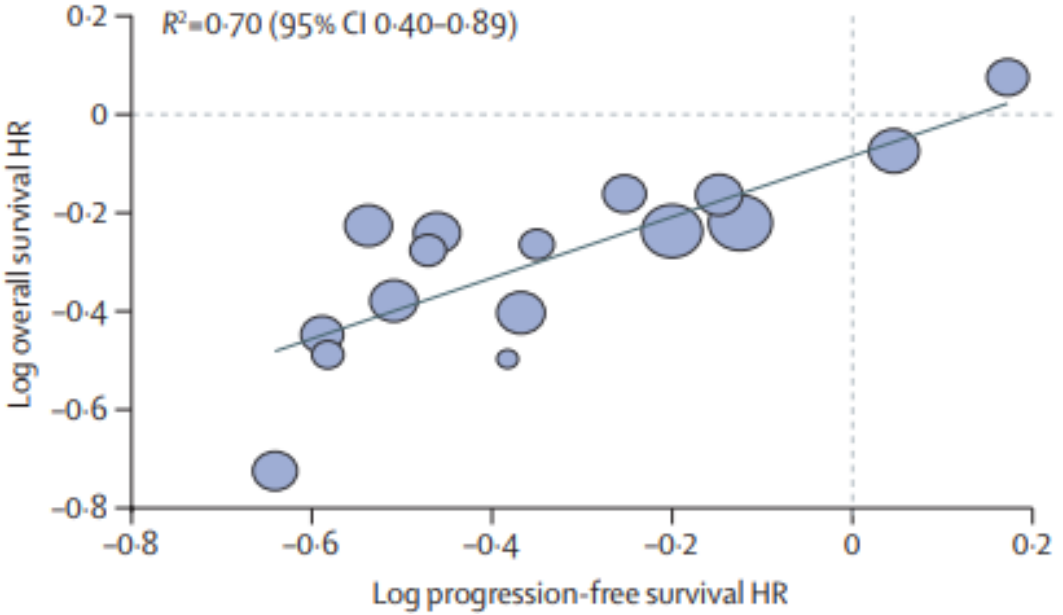
Prentice RL Stat Med 1989; US FDA 21 Code of Federal Regulations, Part 314.530 2013

Advanced Stage: First Line ICI Trials-Correlation of Endpoints with Overall Survival

Overall Response



Progression Free Survival

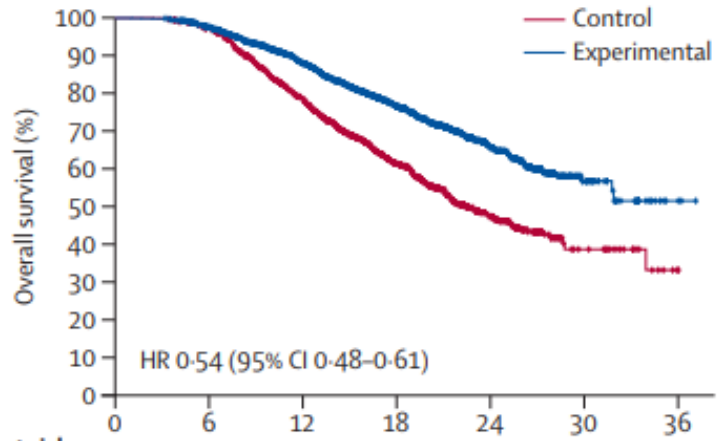


- Log odds ratio of ORR with log HR for OS – R^2=0.61 and Log HR for PFS and OS – R^2=0.70
- Moderate correlation in a pooled analysis of 13 trials of ICI or ICI chemo combinations

Goulart BHL et al Lancet Oncol 2024

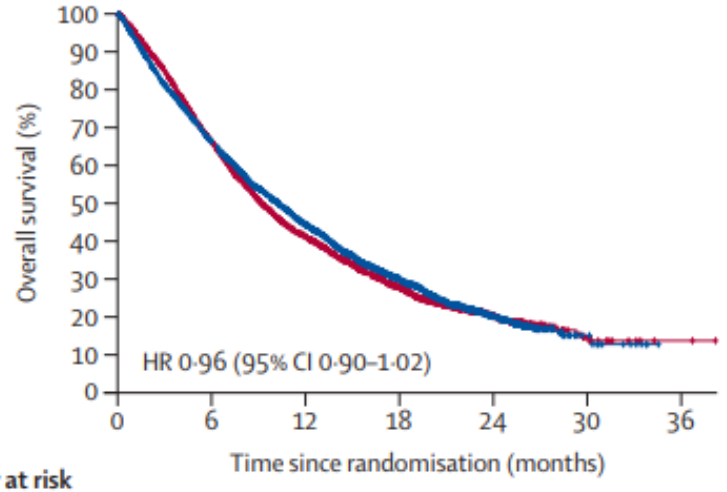
Advanced Stage: First Line ICI Trials-Overall Survival by Response

OS in Responders to ICI



Number at risk (number censored)							
Control	1546 (0)	1478 (25)	1049 (184)	568 (467)	171 (775)	21 (910)	0 (930)
Experimental	2117 (0)	2024 (42)	1556 (323)	864 (848)	279 (1351)	42 (1567)	2 (1605)

OS in Non-responders to ICI



Number at risk (number censored)							
Control	3214 (0)	2000 (171)	1094 (355)	526 (606)	151 (879)	15 (994)	2 (1007)
Experimental	3138 (0)	1981 (132)	1163 (321)	531 (632)	136 (903)	14 (1005)	0 (1017)

- Pooled analysis of 13 trials of ICI or ICI chemo combinations
- Patient level – Response associated with improved survival

Goulart BHL et al Lancet Oncol 2024

Main Neoadjuvant and Perioperative Studies

Trial	Setting	Drug	Primary endpoint	HR (EFS)	Median EFS (ICI vs placebo)	OS
CM-816	Neoadjuvant	Nivolumab	EFS & pCR	0.63 (0.45,0.87)	31.6 vs 20.8 months	82.7% (2 year)
KN-671	Perioperative	Pembrolizumab	Dual EFS & OS	0.58 (0.46,0.72)	NR vs 17.0 months	67.1% vs 51.5% (4 years)
AEGEAN	Periop	Durvalumab	EFS & pCR	0.68 (0.53,0.88)	NR vs 25.9 months	Not reported
CM-77T	Periop	Nivolumab	EFS	0.58	NR vs 18.4 months	Not reported

- Event Free Survival (EFS) - the time after primary cancer treatment until a complication from cancer or treatment occurs, such as disease progression, recurrence, or treatment discontinuation
- Pros – easy to measure, demonstrates treatment efficacy, earlier endpoint
- EFS surrogacy for OS is controversial

CheckMate-816: Forde PM, N Engl J Med 2022; 386 and Girard N, European Lung Cancer Congress 2023 abst 340. **KEYNOTE-671:** Wakelee H, N Engl J Med 2023; 389:491-503. **AEGEAN: Heymach JV,** N Engl J Med Oct 2023. **CheckMate-77T:** Cascone T, ESMO 2023., Cameron RB et al Ther Adv Med Oncol 2023

Courtesy of Raid Aljumaily, MD

Pathological Surrogate for Survival after Neoadjuvant Therapy

- **Valid:** Improvement in the surrogate outcome should correlate with improvement in OS, including subgroups
- **Reflective:** Surrogate outcome should reflect the biological effect of treatment and the magnitude of the effect of the treatment on OS
- **Moderately Frequent:** Surrogate outcome should be sufficiently frequent to allow statistically relevant assessments with reasonable sample sizes, but sufficiently infrequent enough that improvement is attainable.
- **Defined:** Surrogate outcome should have an unequivocal definition
- **Feasible:** Surrogate outcome should be easily and feasibly assessable with universally acceptable methods
- **Reproducible:** Surrogate outcome should be reproducible with minimal interobserver variability

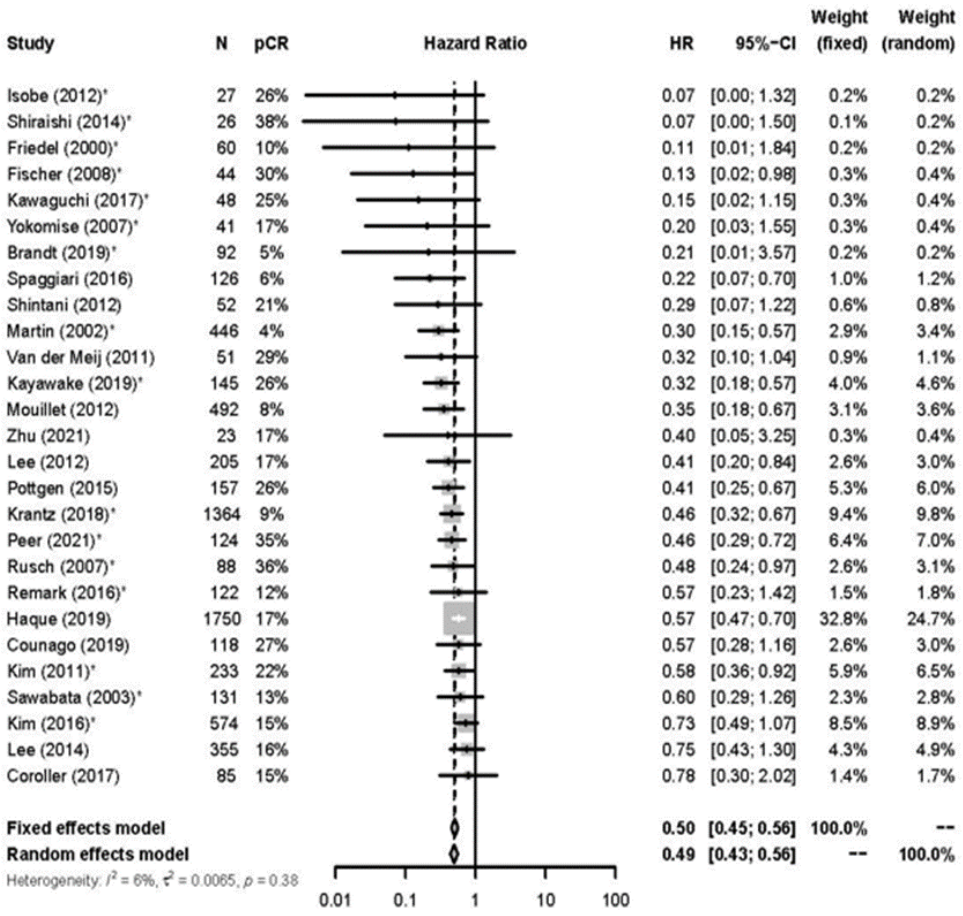
Hellmann MD et al Lancet Oncol 2014

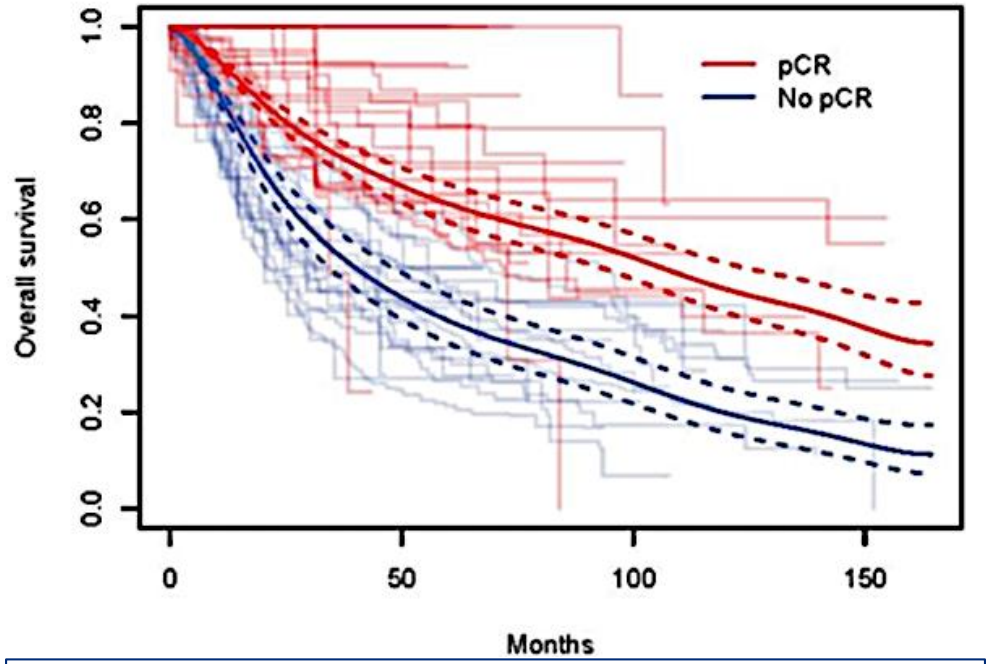
Pathologic Response as a Surrogate Endpoint in Neoadjuvant Studies

- The extent of pathological response must strongly correlate with improved overall survival.
- The pathological response is reflective of the effect of neoadjuvant therapy.
- The degree of pathological response associates with the degree of benefit in overall survival.

Hellmann MD et al Lancet Oncol 2014

Pathological response and clinical outcomes in NSCLC: Meta-analysis

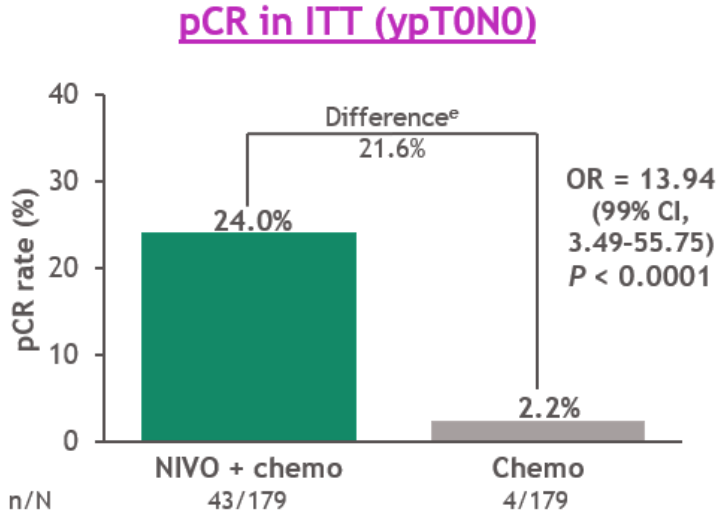


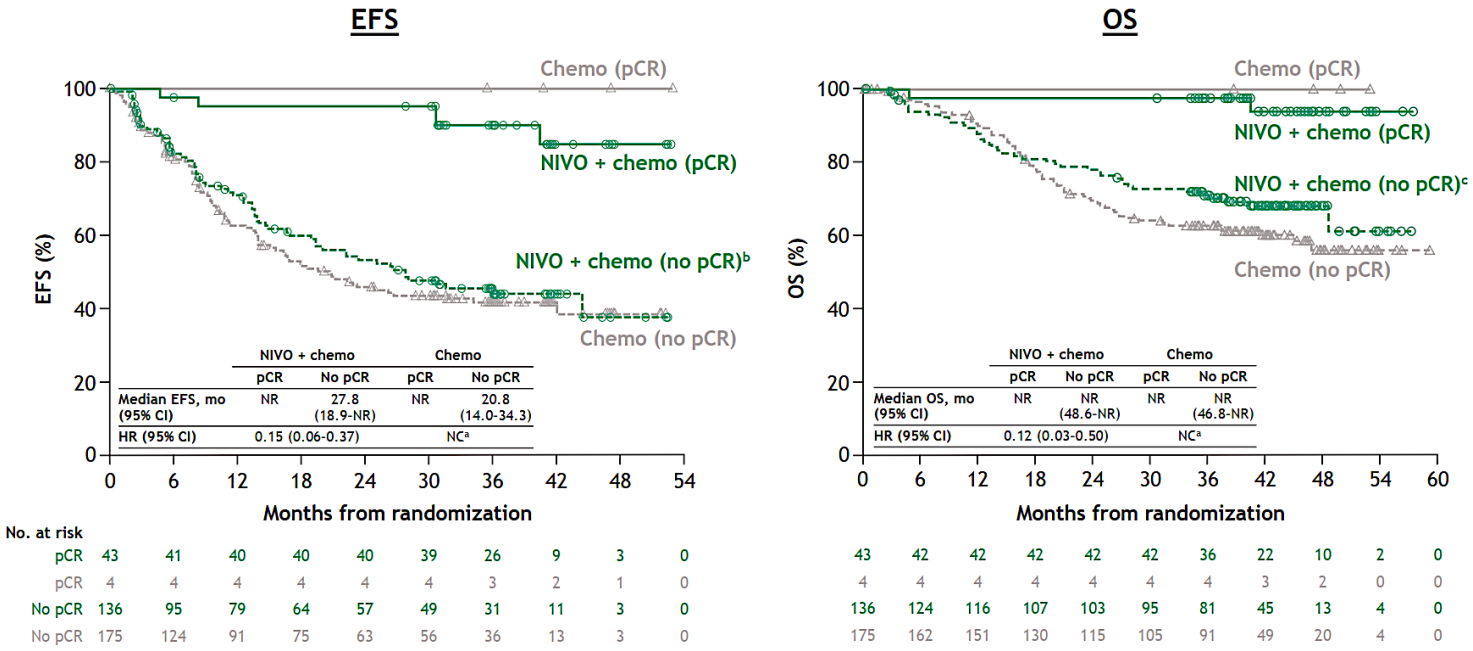


Figures: (a) Forest plot representation of the overall hazard ratios (HRs) estimates with 95% confidence intervals for the association of pCR with overall survival, by study and pooled based on aggregated data meta-analysis. (b) KM estimates of OS for patients with or without a pCR, by study and pooled based on individual patient data meta-analysis.

Rosner S et al. JTO:CRR. 2022

Outcomes by Path CR in NSCLC: CheckMate 816 Nivolumab plus Chemotherapy

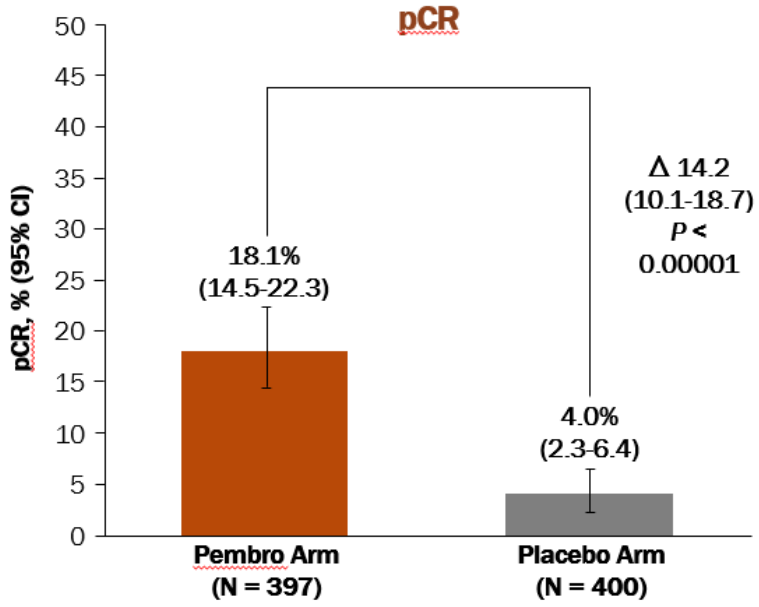


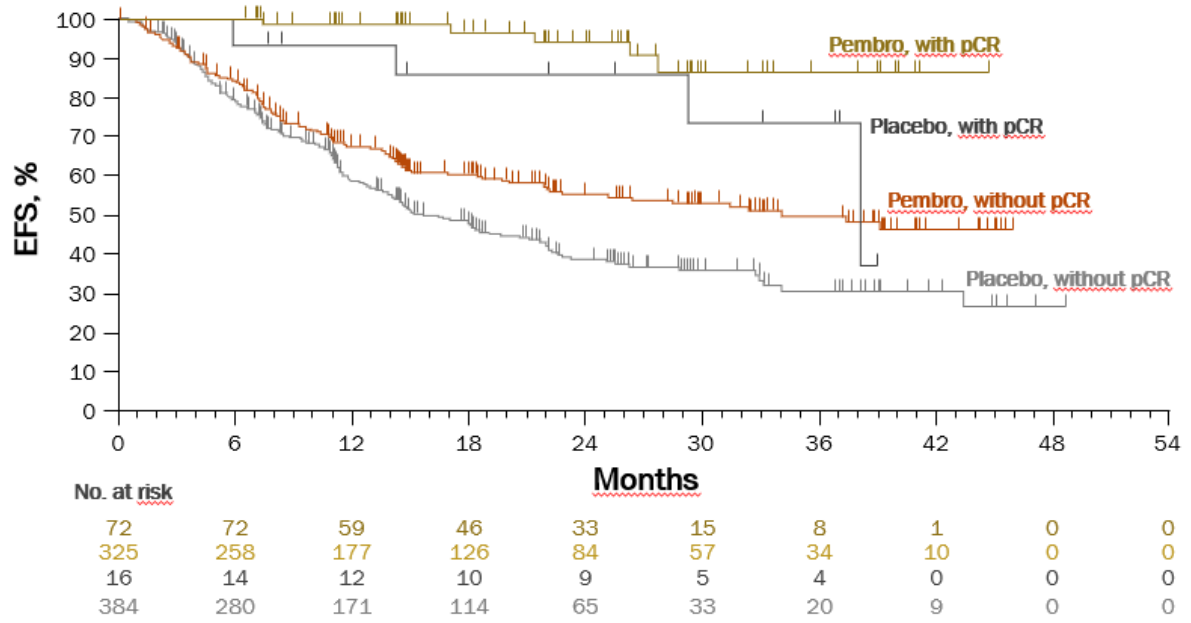


pCR=0% residual viable tumor cells in both primary tumor (lung) and sampled LN (≥ 5 stations, including ≥ 3 mediastinal, were recommended)

Forde P et al AACR 2020; Provencio M et al ESMO 2023

Outcomes by Path CR in NSCLC: KeyNote 671 Pembrolizumab + Chemotherapy





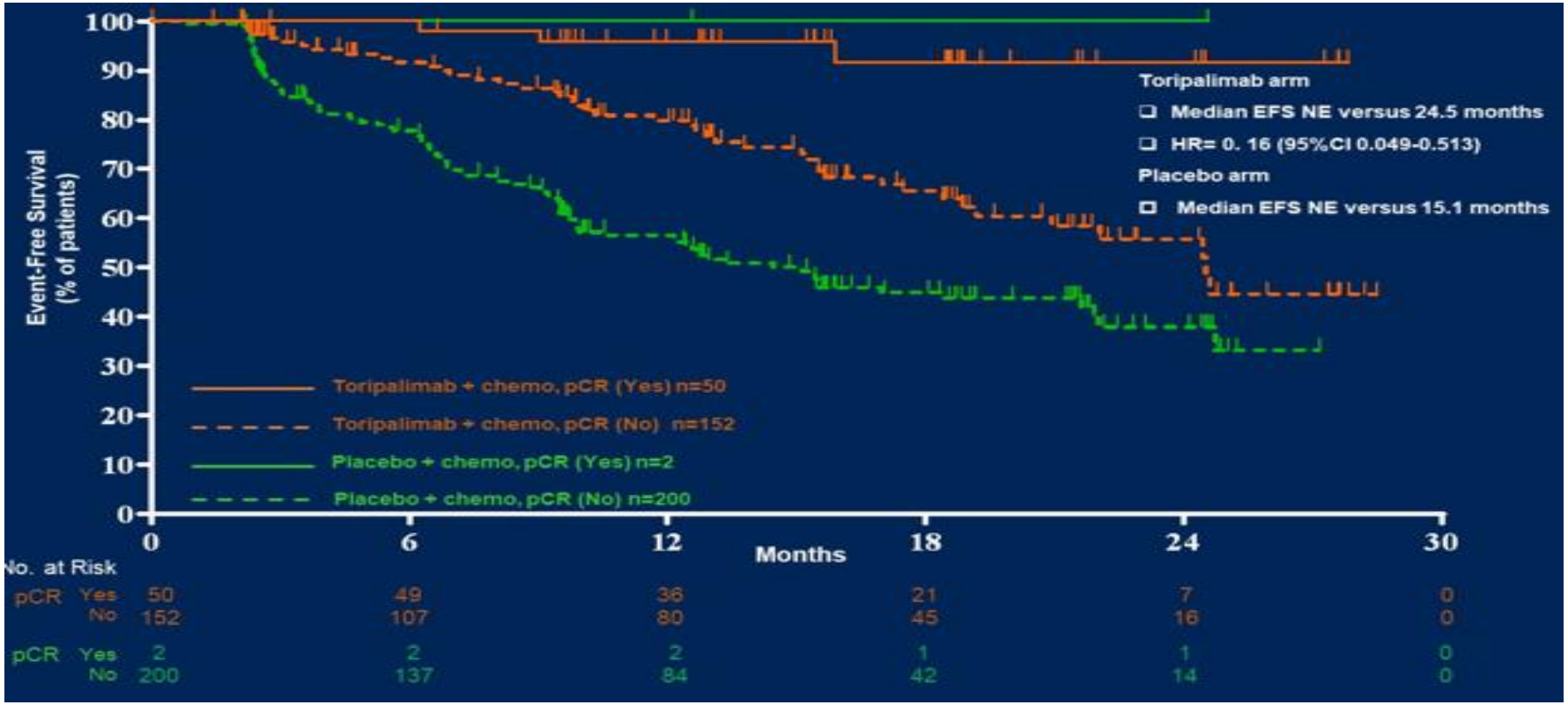
With pCR
HR 0.33
(95% CI, 0.09-1.22)

Without pCR
HR 0.69
(95% CI, 0.55-0.85)

Wakelee H et al ASCO 2023

Outcomes by Path CR in NSCLC: Neotorch

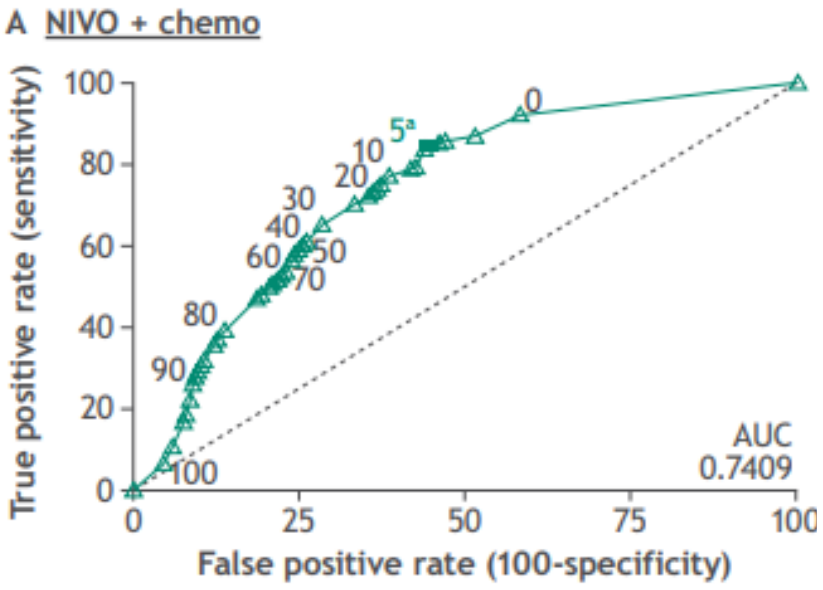
Neotorch



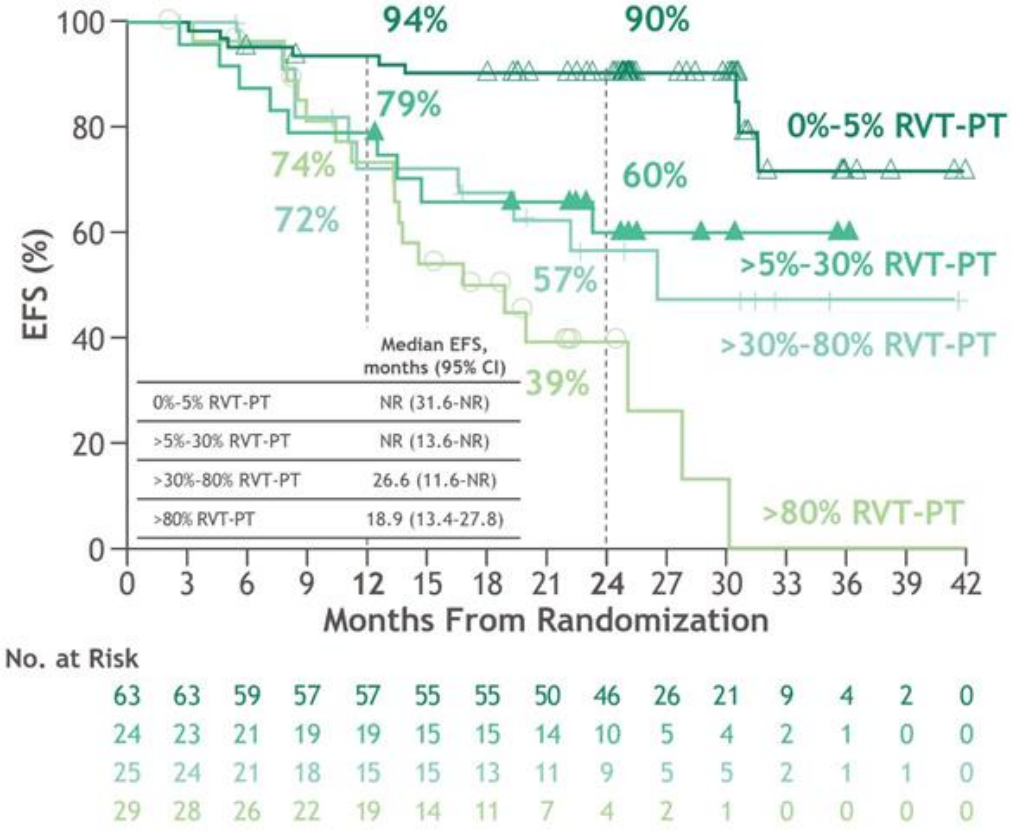
Lu S et al, ASCO Annual Meeting 2023

Path CR in NSCLC as a Surrogate Endpoint and Beyond - %RVT

ROC Curve



ROC curve analysis of 2-year EFS rate by %RVT in the path-evaluable patient population



- % RVT will require technology to make it practical.
- Standardization of assessment may accelerate clinical trial endpoint evaluation and mitigate inter-reader variability
- Increased scalability as therapies become standard of care

Provencio M et al ESMO 2023 & ASCO 2022; Deutsch J et al ESMO 2022; Deutsch JS, et al. Nat Med 10-30-2023

Conclusions

- Gold standard endpoint remains overall survival.
- Advanced Disease – PFS would be a surrogate but may miss OS benefit at times.
- Early Stage Disease –EFS may correlate with OS but more data is needed. pCR may correlate with EFS but more data needed to correlate with OS.

Thank You!