Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

Adjuvant systemic therapy <u>SHOULD NOT</u> be offered if a pCR is achieved with neoadjuvant therapy for early-stage NSCLC

Joshua E. Reuss, MD
Assistant Professor of Medicine
Georgetown Lombardi Comprehensive Cancer Center

April 6th, 2024


@Joshua_Reuss

NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

My esteemed opponent…

Washington University in St. Louis

St Luke's Cancer Institute

INOVA®

Schar Cancer Institute

Look how far we've come!

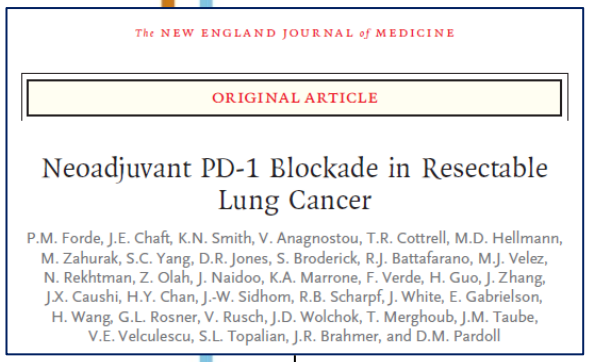
Investigator opens perioperative trial

Trial results published

Provencio *et al.* ASCO 2022

@Joshua_Reuss
Georgetown | Lombardi

Look how far we've come!


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

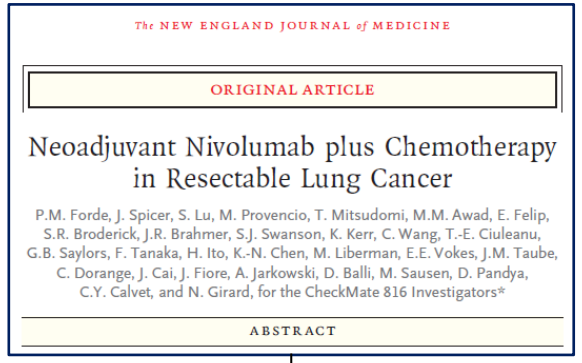
P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

4/2018

7/2021 – positive pCR endpoint from ph3 CheckMate816 trial

10/2021 – FDA approves adjuvant atezolizumab in PD-L1+ resected NSCLC

3/2022 – FDA approves neoadjuvant nivo-chemo in resectable NSCLC


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

4/2022

1/2023 – FDA approves adjuvant pembrolizumab in resected NSCLC

10/2023 – Positive overall survival results for ph3 KEYNOTE-671 trial

10/2023 – FDA approves neoadj/adj pembrolizumab in resectable NSCLC

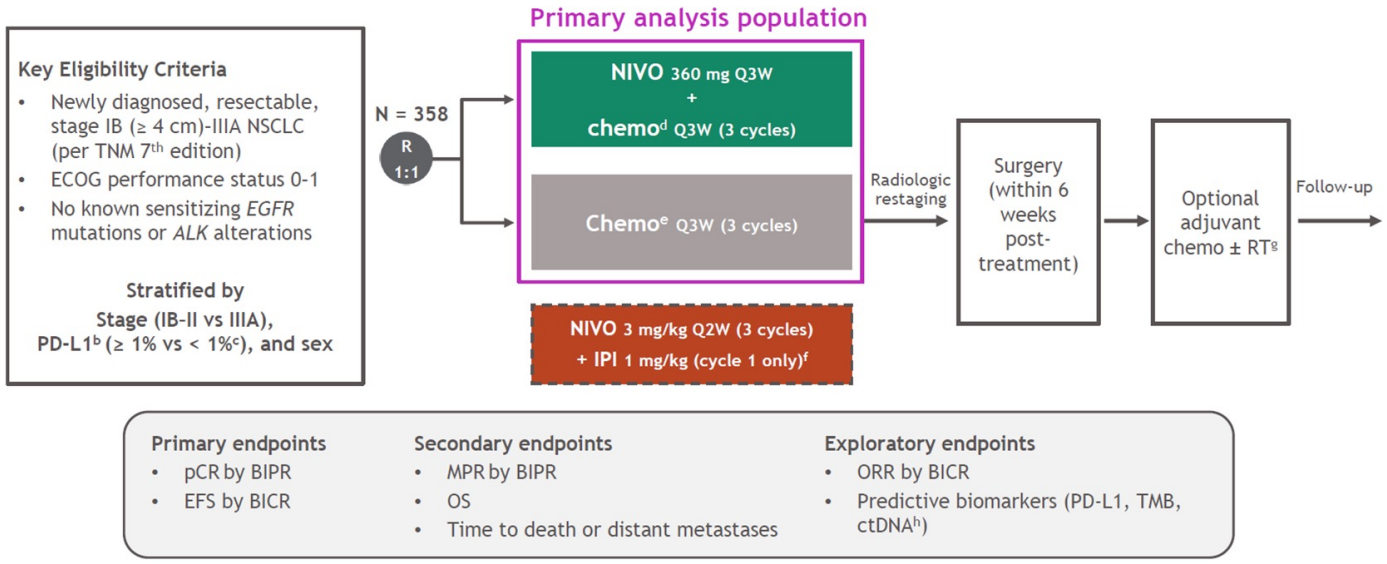
Provencio *et al.* ASCO 2022

@Joshua_Reuss

Georgetown | Lombardi

Phase 3 CheckMate 816 Trial

CheckMate 816 study design[a]

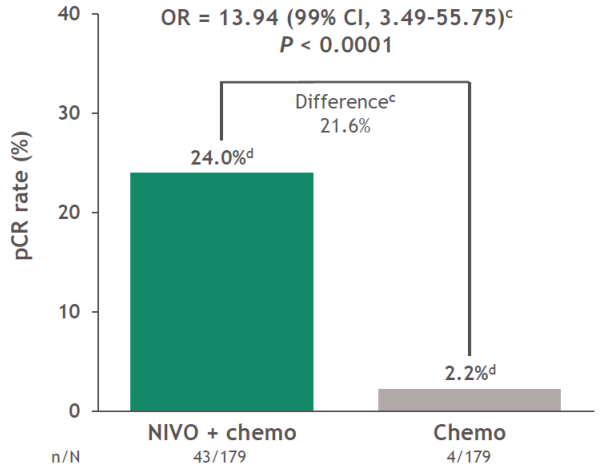


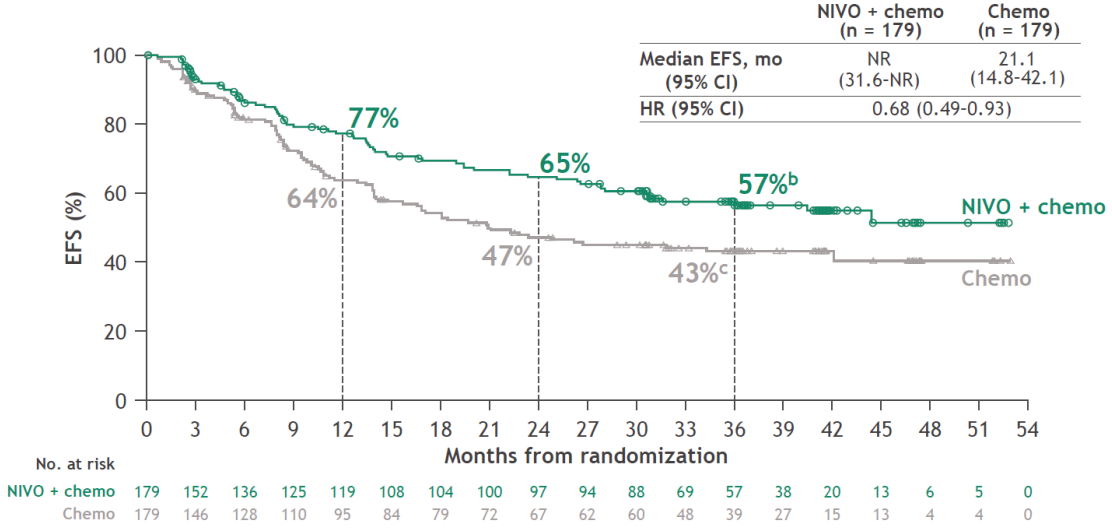
Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Primary endpoint: ITT (ypT0N0)[b]



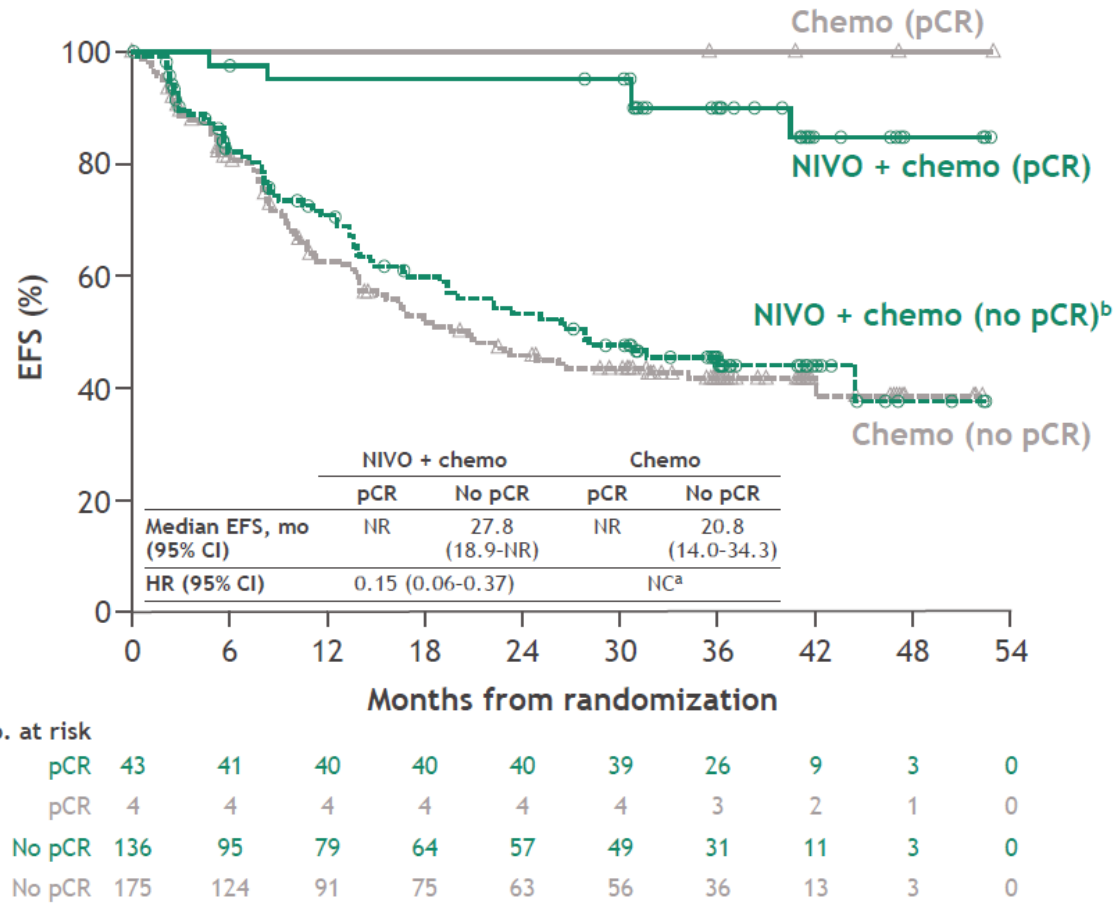


Forde et al. *AACR* 2021, Forde et al *ELCC* 2023

Phase 3 CheckMate 816 Trial

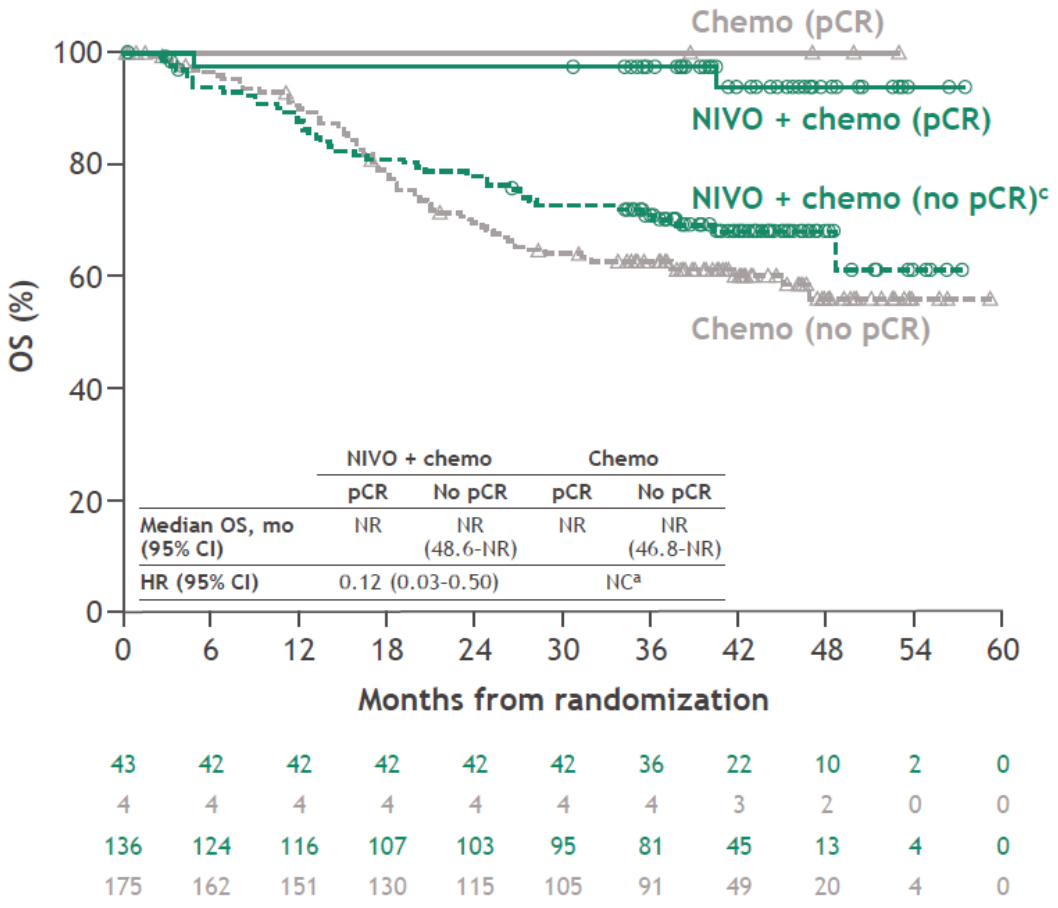
Subgroup analysis by pCR status

EFS



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS, mo (95% CI)	NR	27.8 (18.9-NR)	NR	20.8 (14.0-34.3)
HR (95% CI)	0.15 (0.06-0.37)		NC[a]	

OS



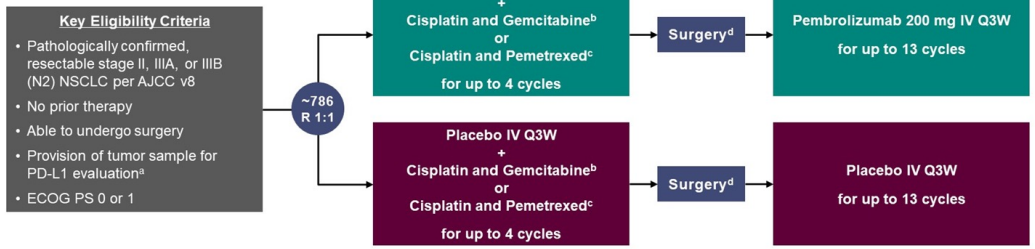
	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo (95% CI)	NR	NR (48.6-NR)	NR	NR (46.8-NR)
HR (95% CI)	0.12 (0.03-0.50)		NC[a]	

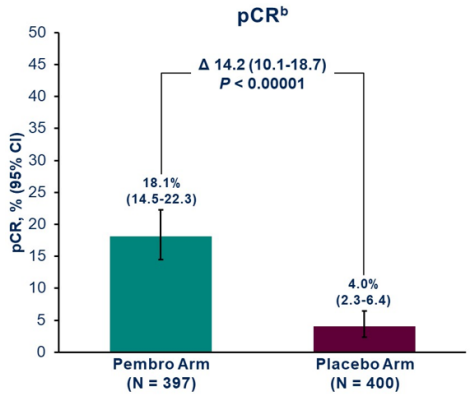
Provencio et al *ESMO* 2023

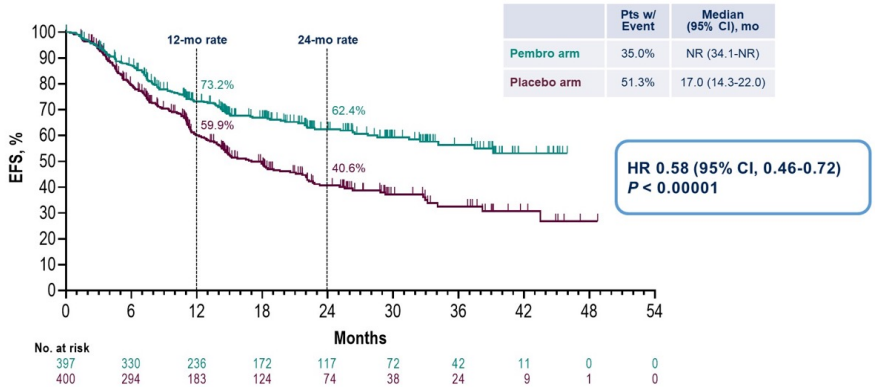
Georgetown | Lombardi

Phase 3 Perioperative chemo-immunotherapy trials

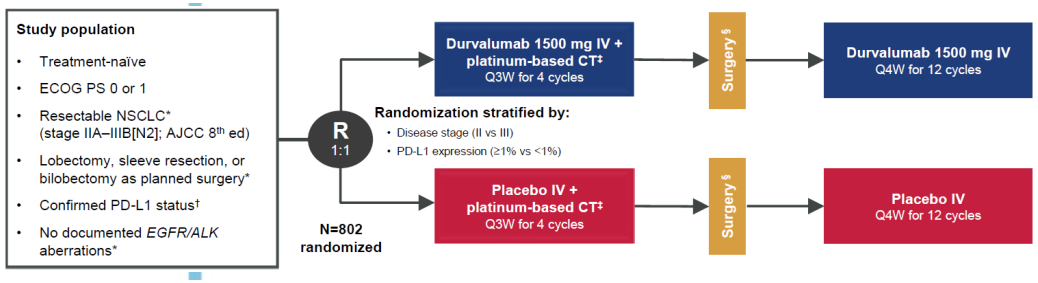
KEYNOTE-671

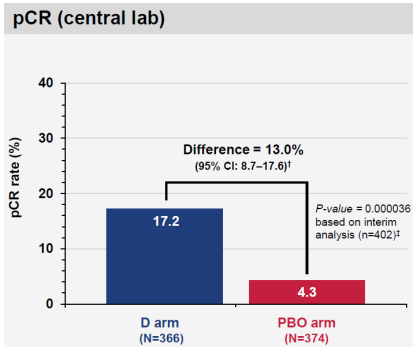


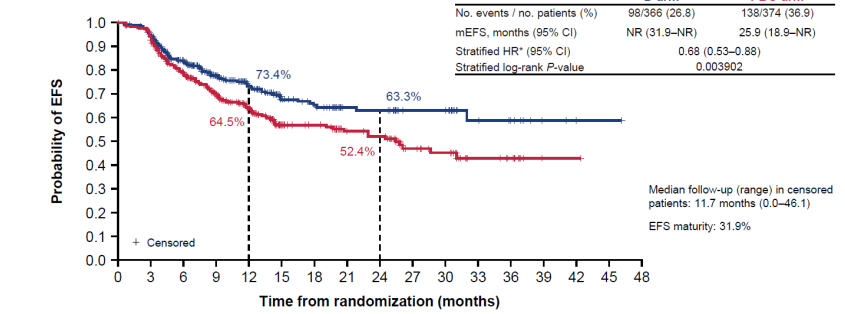




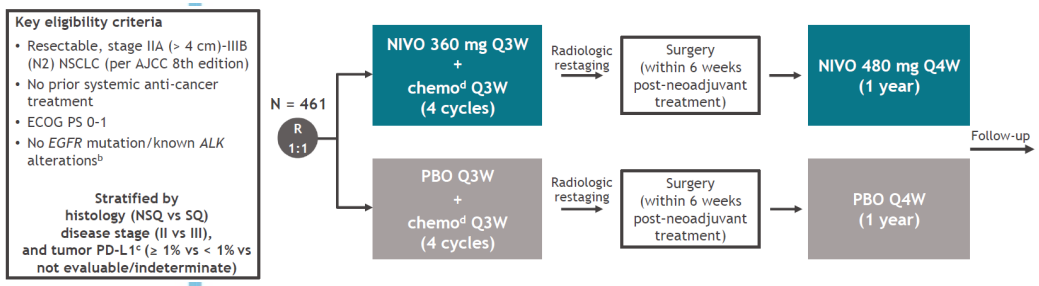
AEGEAN

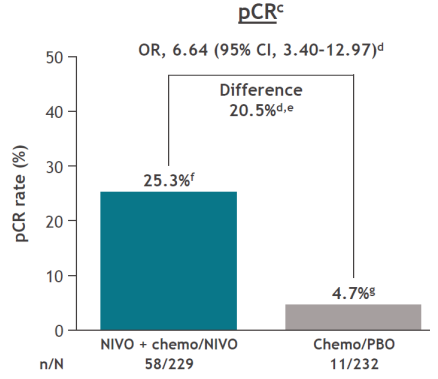


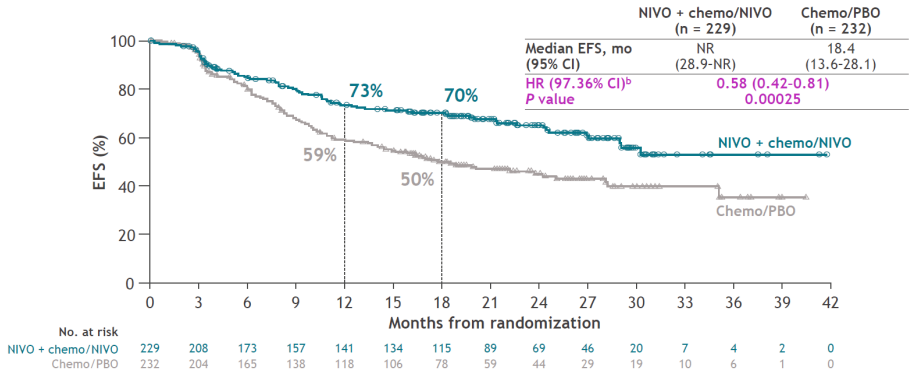




CheckMate 77T





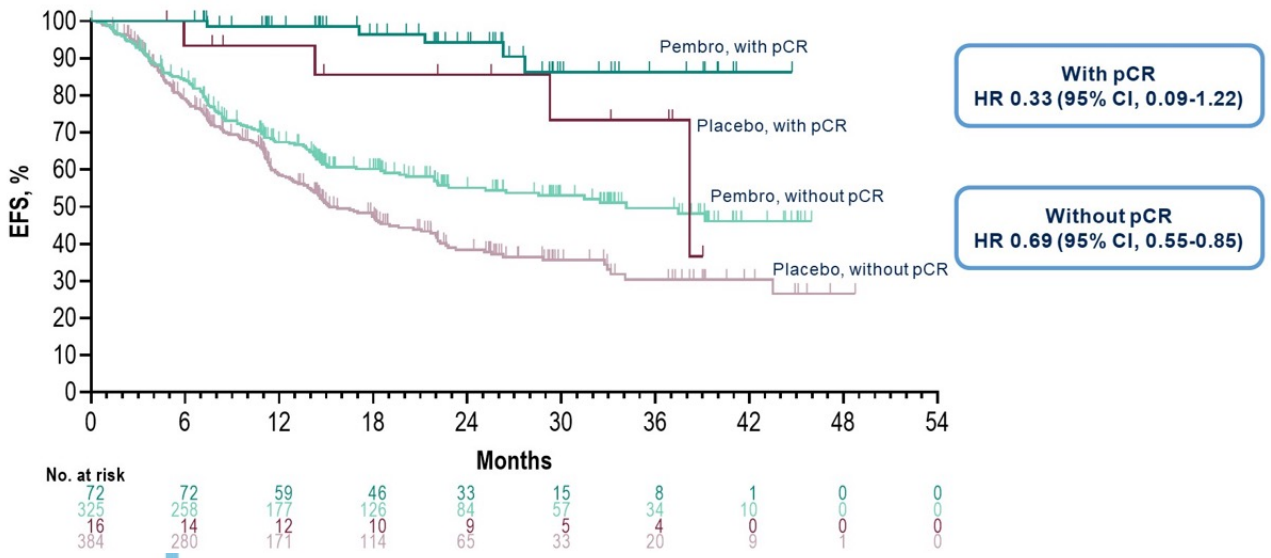


Wakelee et al *ASCO* 2023, Wakelee et al *NEJM* 2023, Heymach et al *AACR* 2023, Heymach et al NEJM 2023, Cascone et al *ESMO* 2023

Phase 3 Perioperative chemo-immunotherapy trials

EFS Subgroup analysis by pCR status

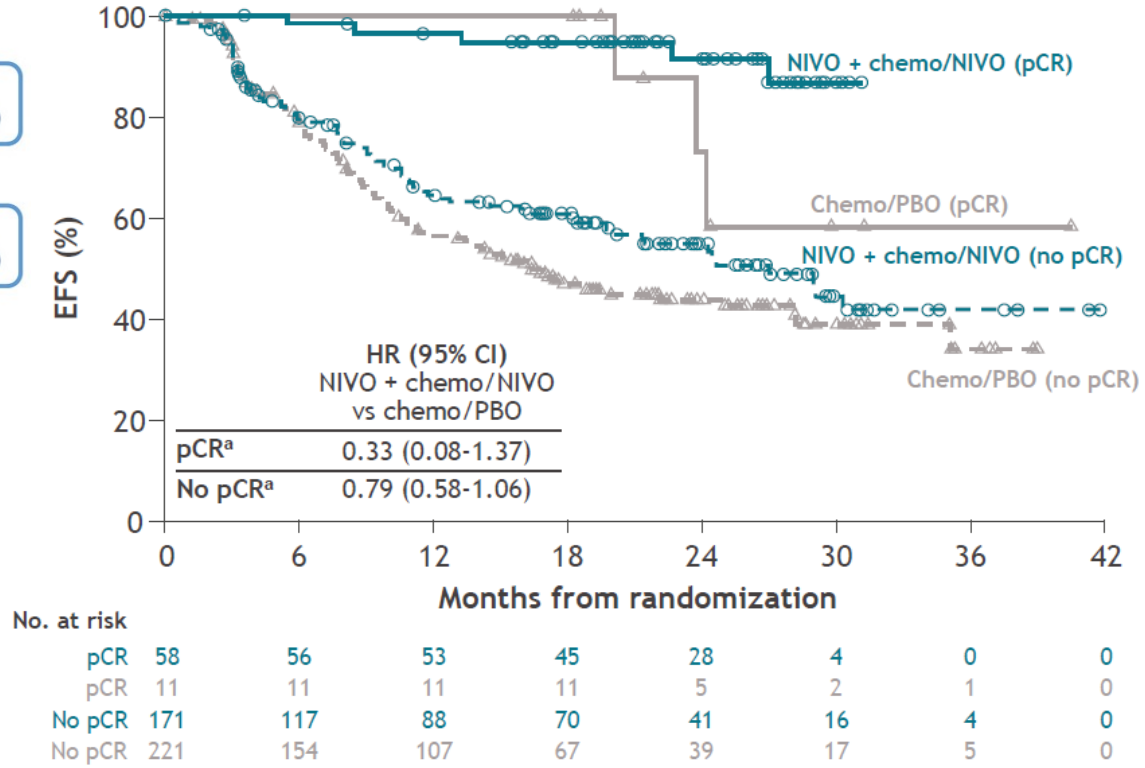
KEYNOTE-671



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

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

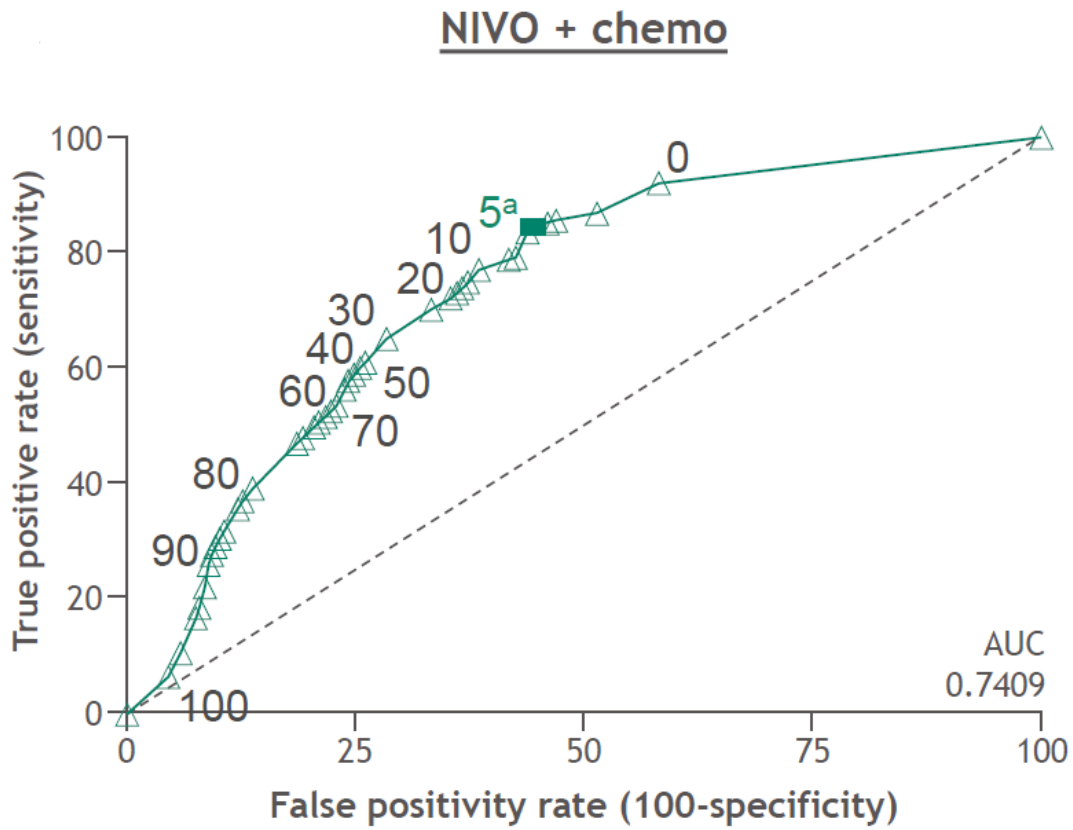
CheckMate 77T

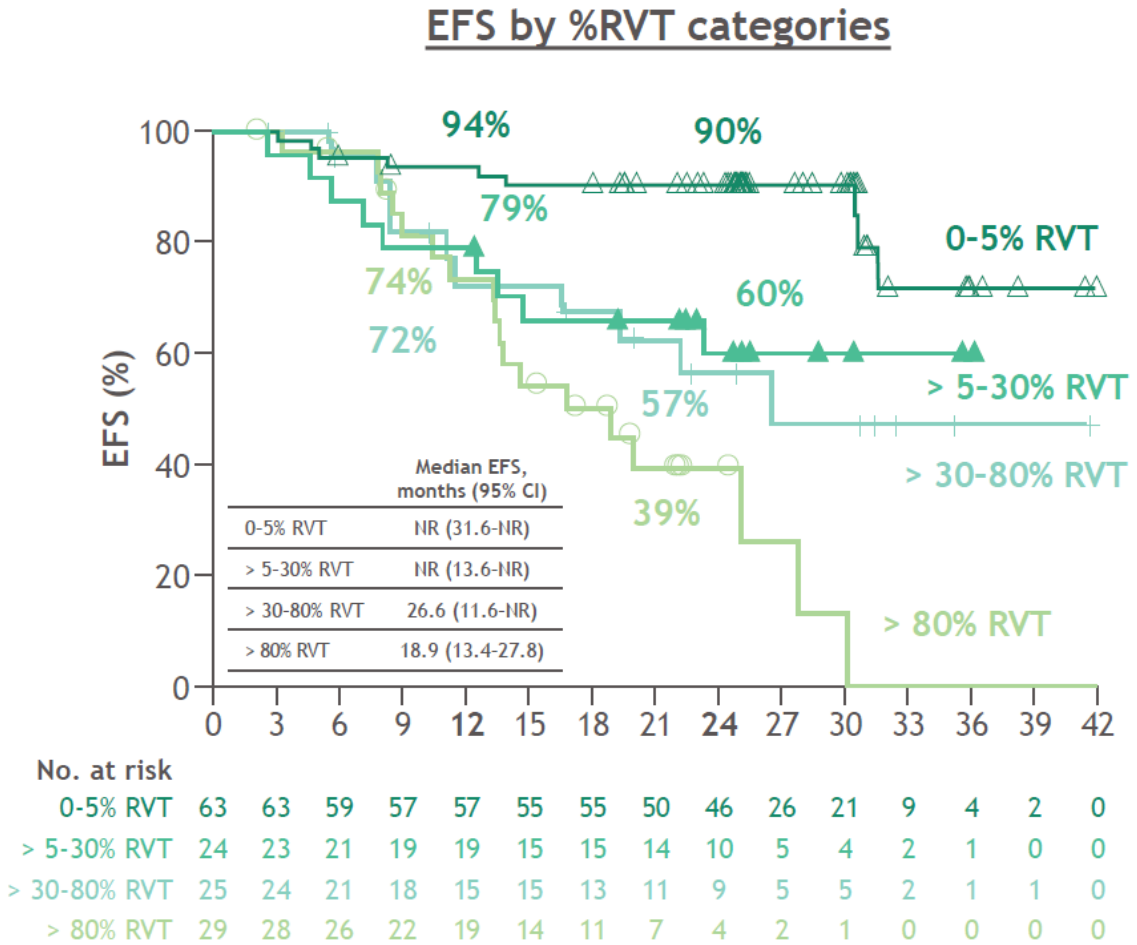


Wakelee et al *ASCO* 2023, Wakelee et al *NEJM* 2023, Cascone et al *ESMO* 2023

@Joshua_Reuss
Georgetown | Lombardi

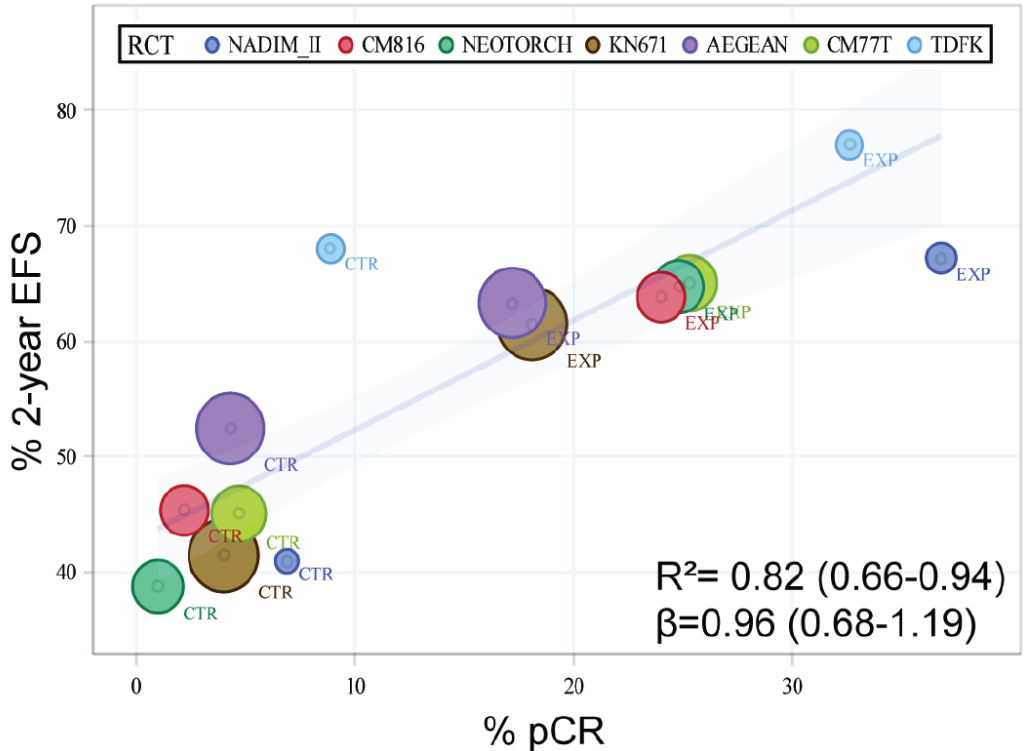
Is pCR predictive of improved EFS with neoadjuvant chemo-immunotherapy?





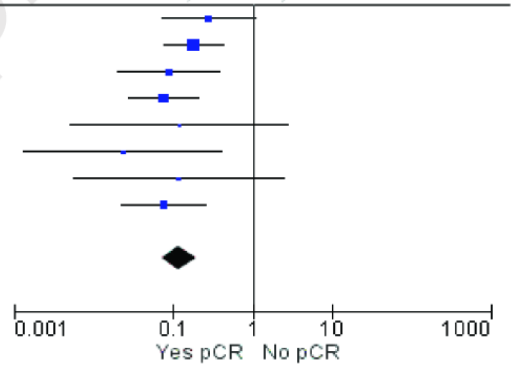
Provencio *et al.* ASCO 2022

Is pCR predictive of improved EFS with neoadjuvant chemo-immunotherapy?



Study or Subgroup	pCR Yes Events	Total	pCR No Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CM77T_CH	3	11	126	221	12.6%	0.28 [0.07, 1.09]
CM77T_CH_IO	7	58	74	171	32.2%	0.18 [0.08, 0.42]
KEY671_CH	2	16	238	384	10.3%	0.09 [0.02, 0.39]
KEY671_CH_IO	4	72	143	325	21.6%	0.07 [0.03, 0.21]
NADIM_CH	0	2	17	27	2.3%	0.12 [0.01, 2.75]
NADIM_CH_IO	0	21	18	36	2.8%	0.02 [0.00, 0.41]
NEOTORCH_CH	0	2	126	200	2.5%	0.12 [0.01, 2.49]
NEOTORCH_CH_IO	3	50	70	152	15.7%	0.07 [0.02, 0.25]
Total (95% CI)		**232**		**1516**	**100.0%**	**0.12 [0.07, 0.19]**
Total events	19		812			

Heterogeneity: Tau² = 0.00; Chi² = 5.40, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 8.73 (P < 0.00001)

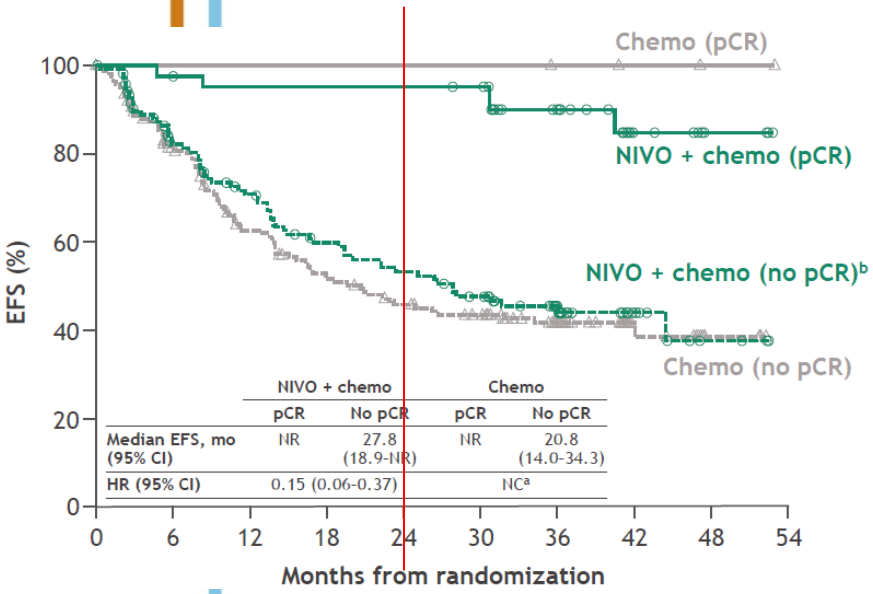


Hines *et al.* JTO 2024

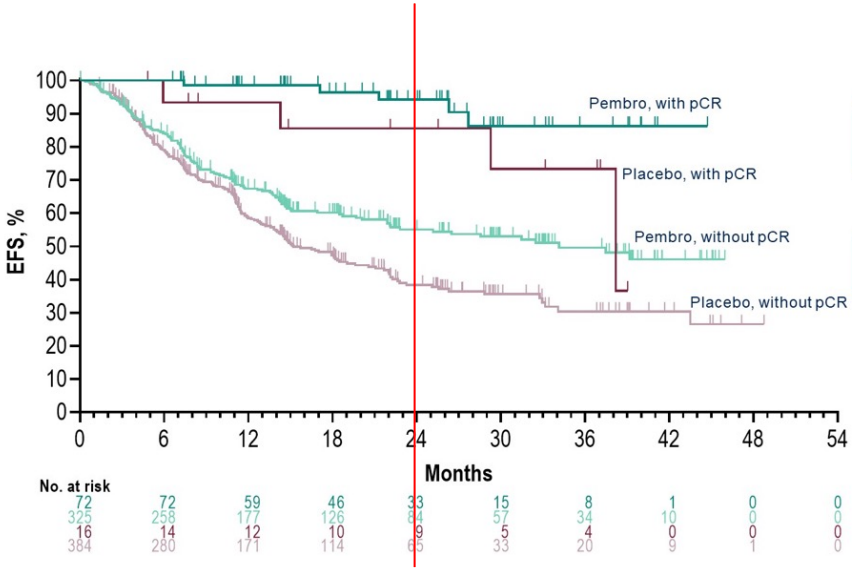
@Joshua_Reuss
Georgetown | Lombardi

Nearly identical EFS curves for pCR subgroups of CheckMate 816, KEYNOTE-671, and CheckMate 77T Trials!

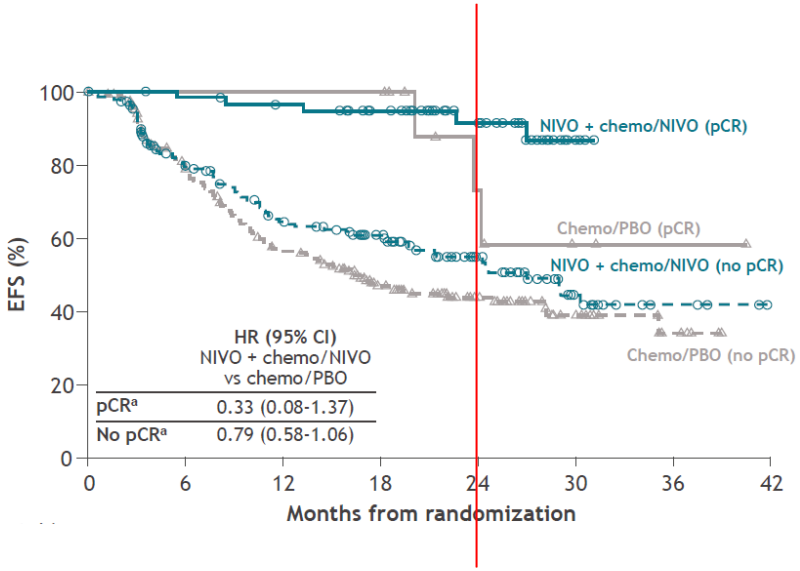
CheckMate 816



KEYNOTE-671



CheckMate 77T



2-year EFS ~90%

Provencio *et al.* ESMO 2023, Wakelee *et al.* ASCO 2023, Cascone *et al.* ESMO 2023

@Joshua_Reuss
Georgetown | Lombardi

To choose my regimen, how can I predict who will have a pCR?

How you achieve a pCR with immunotherapy doesn't matter!

PEMBRO

Nivolumab

@Joshua_Reuss

Georgetown | Lombardi

But what about cross-trial comparisons?

As close to a pure cross-trial comparison as we can get!

Forde et al. *AACR* 2021, Cascone et al. *ESMO* 2023

CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358

R 1:1

Primary analysis population

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)
- NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

CheckMate 77T[a] study design

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)

N = 461

R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → NIVO 480 mg Q4W (1 year)
- PBO Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → PBO Q4W (1 year)

Follow-up

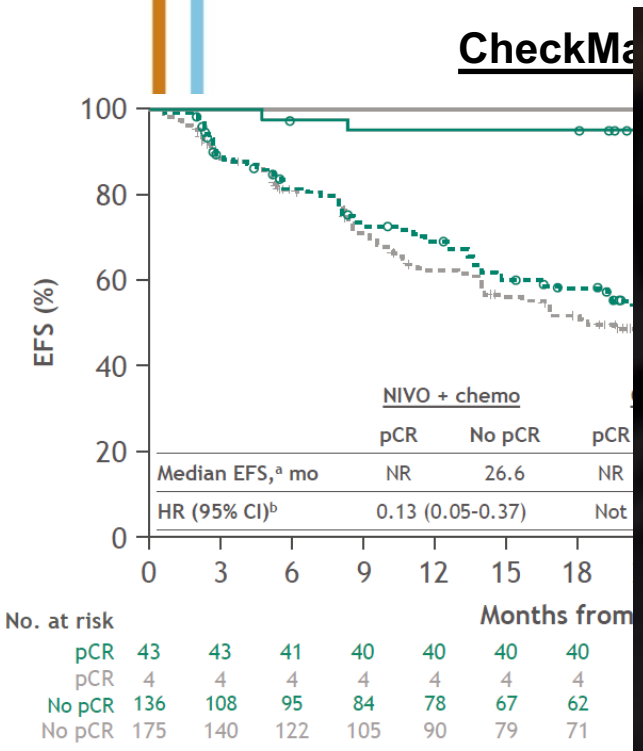
Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

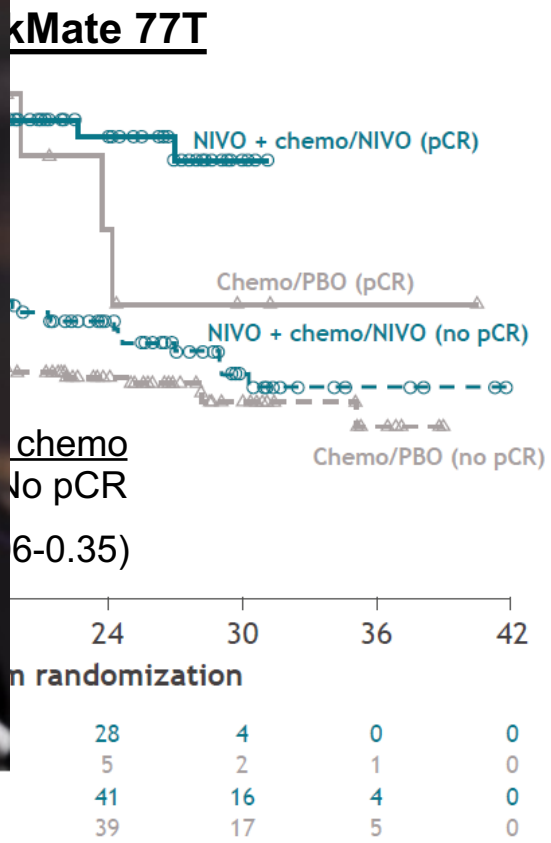
Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

The EFS analyses in pCR subgroups of CheckMate 816 and CheckMate 77T are impressively similar!



Median follow-up: 29.5mo



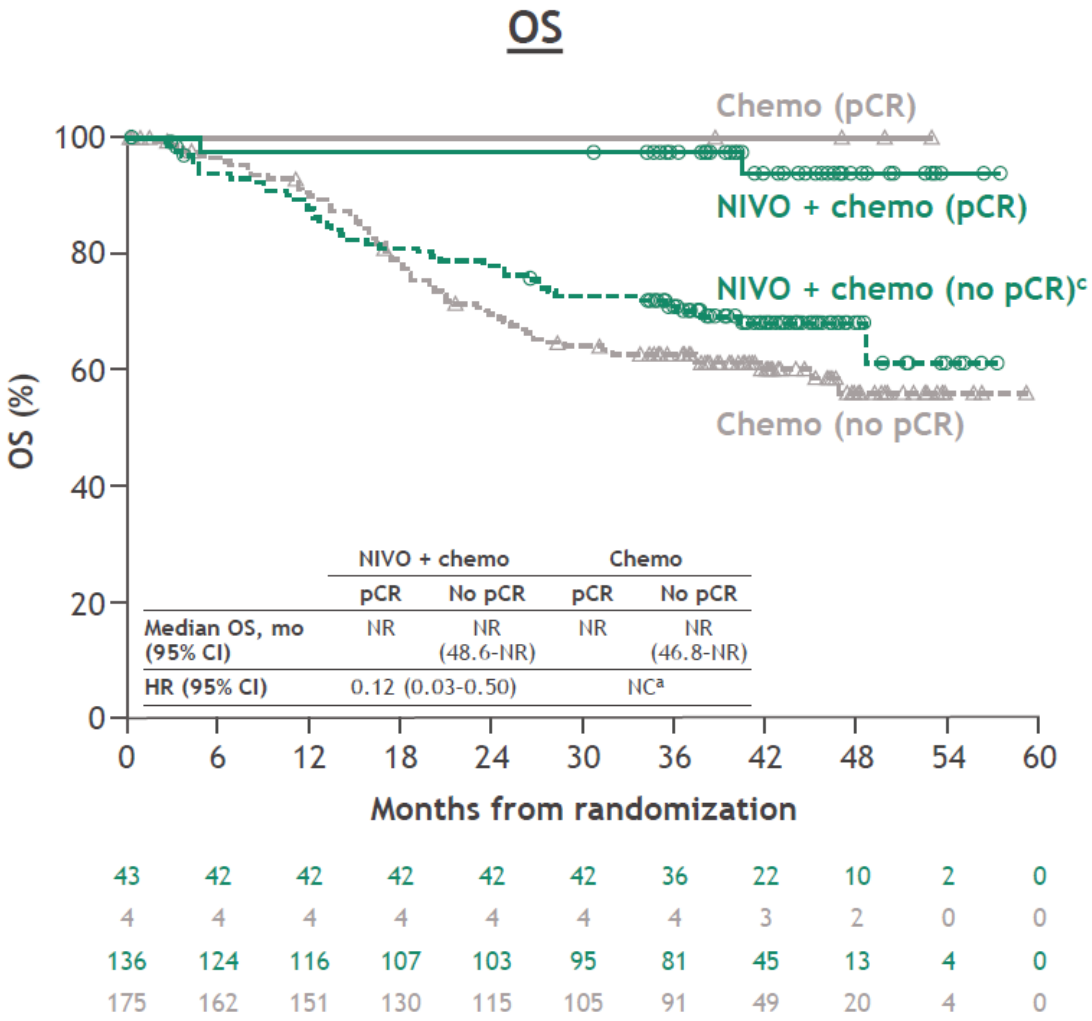
Median follow-up: 25.4mo

Girard et al. *AACR* 2022, Cascone et al *ESMO* 2023

Interim Overall Survival analysis by pCR status from CheckMate 816

But KEYNOTE-671 is the *only* perioperative trial that is positive for overall survival.

There are no overall survival subgroup analyses from KN-671 by pCR status!



Provencio et al. *ESMO* 2023

@Joshua_Reuss

Georgetown | Lombardi

How much do the results of perioperative trials *truly reflect* the adjuvant therapy component?

	KEYNOTE-671[1]	AEGEAN[2]	CheckMate 77T[3]
Completed adjuvant treatment	40.4%	24.0%	60%
Discontinued adjuvant treatment	22.2%	18.6%	34%
Adjuvant treatment ongoing	10.6%	23.2%	6%

1 – Wakelee et al *ASCO* 2023, 2 – Heymach et al *AACR* 2023, 3 – Cascone et al *ESMO 2023*

Who are these?

@Joshua_Reuss
Georgetown | Lombardi

Does additional adjuvant therapy subject patients who achieved pCR and are cured to needless toxicity?

Is there a financial cost?

Pembrolizumab dose	Cost/infusion
200mg every 3 weeks	$11,115.04
400mg every 6 weeks	$22,230.08

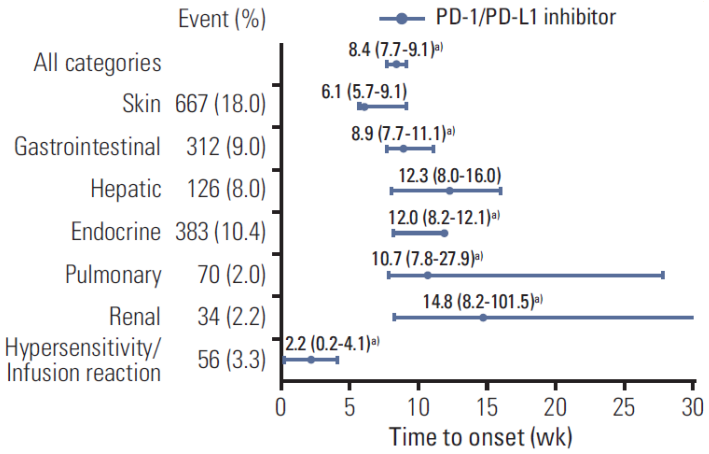
Source: https://www.keytruda.com/financial-support/

$11,115.04/dose x 13 doses = **$144,495.52**

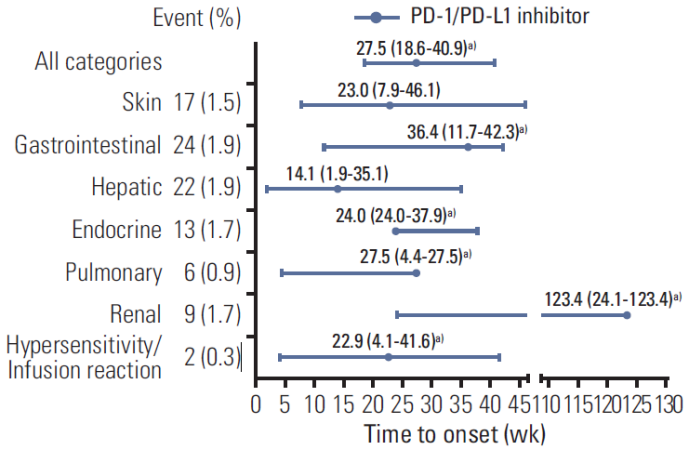
Are there treatment-related toxicities that subject patients to serious risk?

PD-1 monotherapy

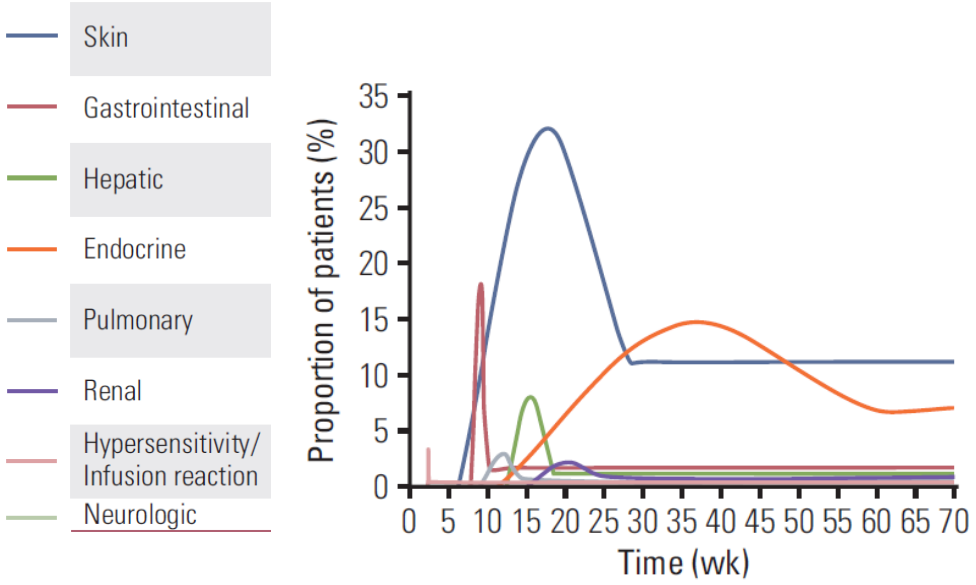
All grade irAEs



Grade ≥ 3 irAEs



PD-1 monotherapy



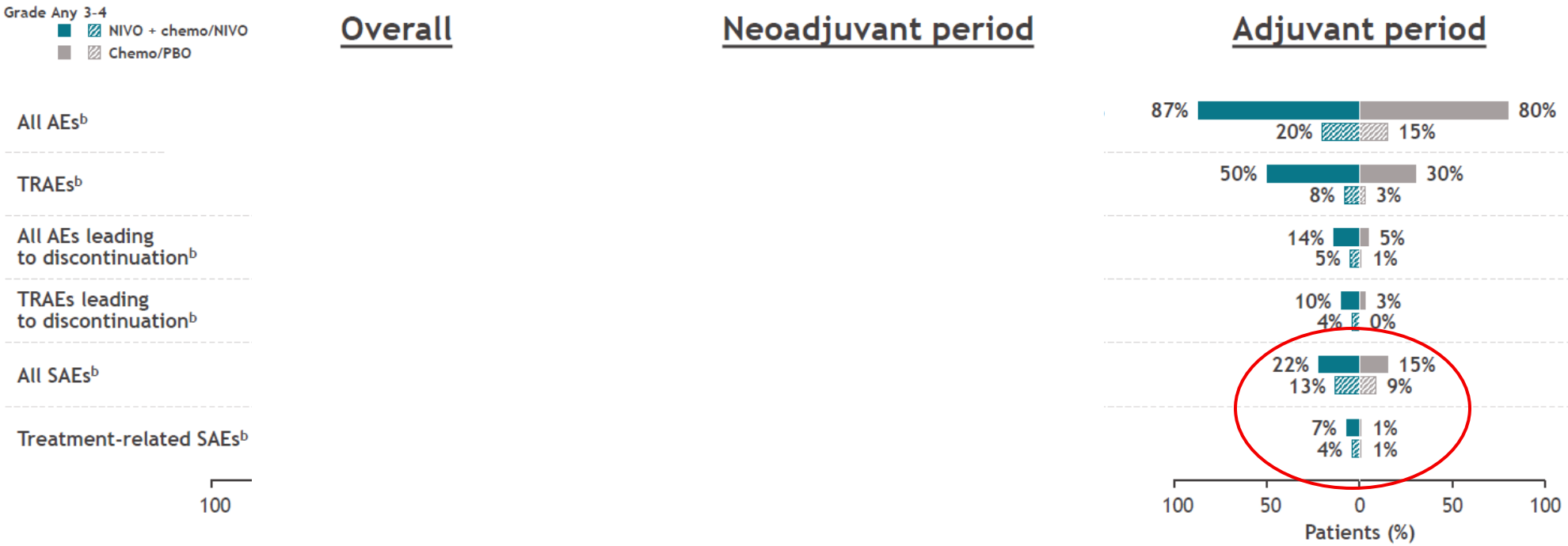
Tang et al. *Cancer Res Treat*. 2021

@Joshua_Reuss
Georgetown | Lombardi

Are there treatment-related toxicities that subject patients to serious risk?

Phase 3 CheckMate 77T Trial

Safety summary[a] across study phases



- Any-grade surgery-related AEs occurred in 73 (41%) and 69 (39%) patients in the NIVO + chemo/NIVO and chemo/PBO arms, respectively; 21 (12%) patients in each arm experienced grade 3-4 events[c]
- Treatment-related deaths occurred in 2 (1%) patients in the NIVO + chemo/NIVO arm (1 due to grade 5[d] pneumonitis and 1 due to grade 4 pneumonitis, both occurring after completion of neoadjuvant treatment)

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

[a]AEs per CTCAE v4.0 and MedDRA v26.0. [b]Includes events reported between the first dose and 30 days after the last dose of study treatment. [c]Includes events reported within 90 days after definitive surgery. Percentages calculated from treated patients who had definitive surgery (n = 178 in the NIVO + chemo/NIVO arm; n = 178 in the chemo/PBO arm). Grade 5 surgery-related AEs: NIVO + chemo/NIVO, 3 (2%) patients (1 each due to acute myocardial infarction, postprocedural hemorrhage, and septic shock); chemo/PBO, 1 (1%) patient (due to pneumonia); all were unrelated to study drug per investigator. [d]AEs that led to death within 24 hours of onset.

Should adjuvant therapy be offered if a pCR is achieved with neoadjuvant chemo-immunotherapy in resected NSCLC?

Just Say **NO!**

THANK YOU!

GEORGETOWN UNIVERSITY

Lombardi Comprehensive Cancer Center

@Joshua_Reuss

Georgetown | Lombardi