OPTIMIZING USE OF NEOADJUVANT IMMUNOTHERAPY IN NSCLC

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
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Outline

- Review of neoadjuvant ICI-based studies and translational correlates
- Subgroup analyses in neoadjuvant/perioperative trials
- Perioperative immune-based approaches
- Considerations for optimization of neoadjuvant/perioperative ICI-based therapies

Rationale for Neoadjuvant Immune-Based Therapy in Resectable NSCLC

Scientific:

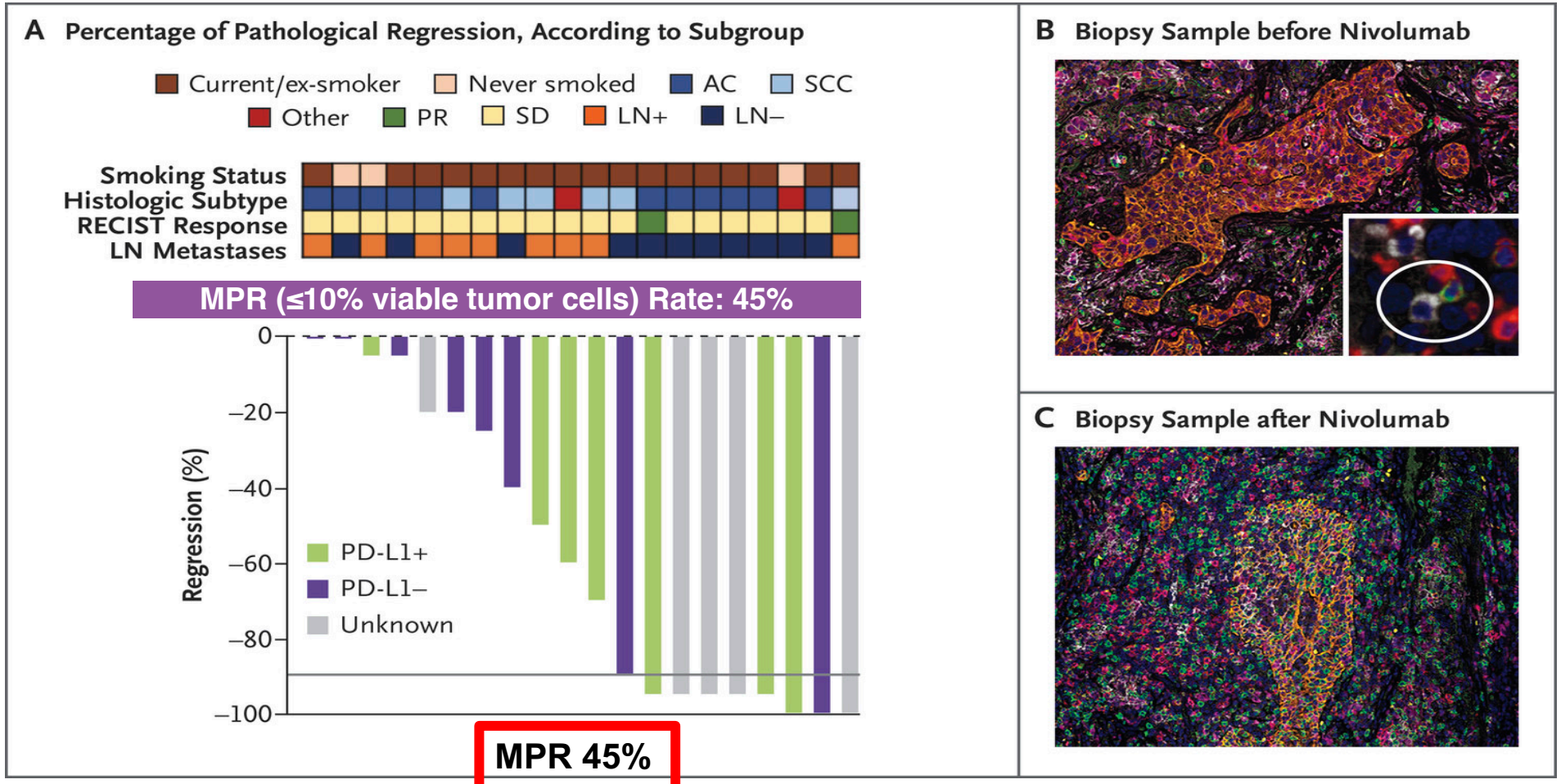
- Tumor upregulation of PD-L1 is critical for the spread and survival of metastases[1]
- Neoadjuvant immunotherapy may activate the immune system robustly prior to surgery[2,3]
- Neoadjuvant combined ICIs are superior to adjuvant therapy and enhance immune infiltration in mice[4,5]

Clinical development of more effective treatments for operable NSCLC[6]:

- Rapid readout of activity based on potential surrogate endpoints (MPR, pCR) of clinical benefit
- Assessment of role of surrogate endpoints (MPR, pCR) at predicting survival benefit
- Translational/biomarker analyses of samples pre- and post-neoadjuvant therapy

1. Chen L et al. *Nat Commun*. 2014;5:5241. 2. McGranahan N et al. *Science*. 2016;351(6280):1463-1469.
3. Topalian SL et al. *Science*. 2020;367(6477):eaax0182. 4. Liu J et al. *Cancer Discovery*. 2016;6(12):1382-1399.
5. Cascone T et al. *Cancer Res*. 2018;78(suppl 13):1719. 6. Chaft JE et al. *Nat Rev Clin Oncol*. 2021;18(9):547-557.

Neoadjuvant nivolumab is feasible, safe and active in resectable NSCLC

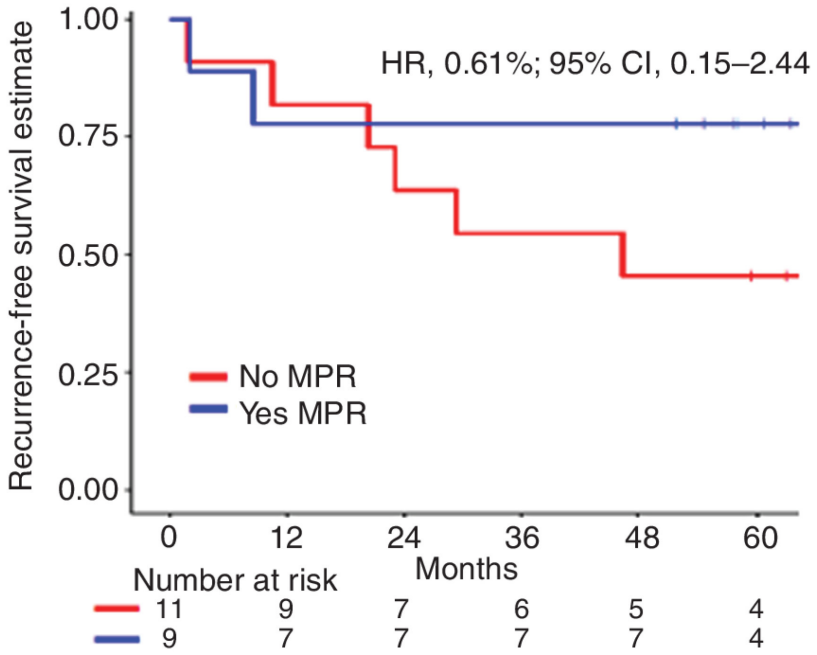


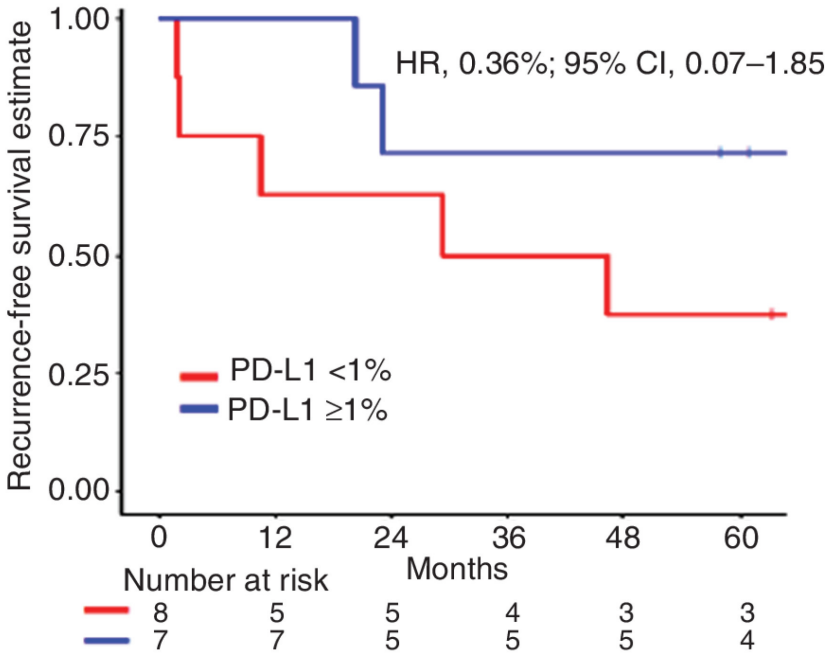
MPR 45%
pCR: 15%

Influx of CD8+-PD-1+ cells in MPR tumors

Forde, PM et al. *N Engl J Med.* 2018

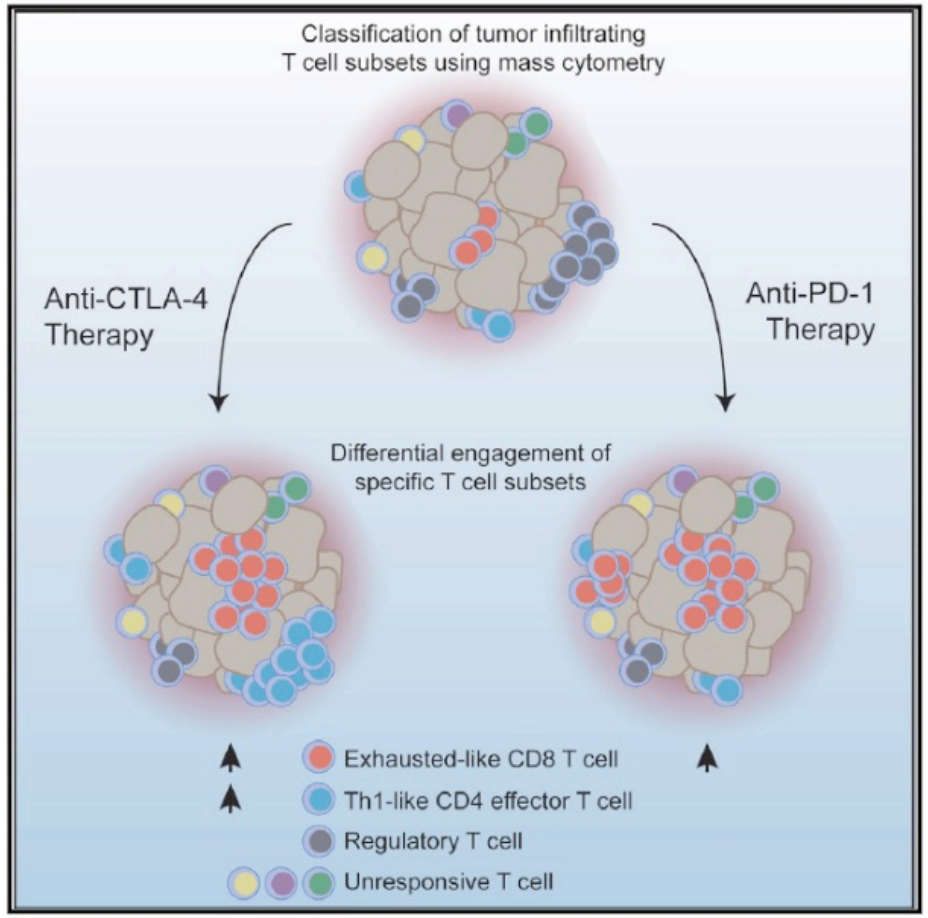
5-yr Survival Outcomes After Neoadjuvant Nivolumab Monotherapy by MPR and PD-L1 status





Rosner S, et al. Clin Cancer Res (2023) 29 (4): 705–710.

Different immune cellular mechanisms in response to distinct ICIs: rationale for combination trials



Anti-PD-1 and anti-CTLA-4 target specific subsets of TIL-T cell populations[1]

- Anti-PD-1 expands exhausted-like CD8 T cell subsets.
- Anti-CTLA-4 expands ICOS+ Th1-like CD4 effector T cells and engages specific subsets of exhausted-like CD8 T cells.[1]

Combination ICIs utilize cellular mechanisms that are partially different vs monotherapies[2]

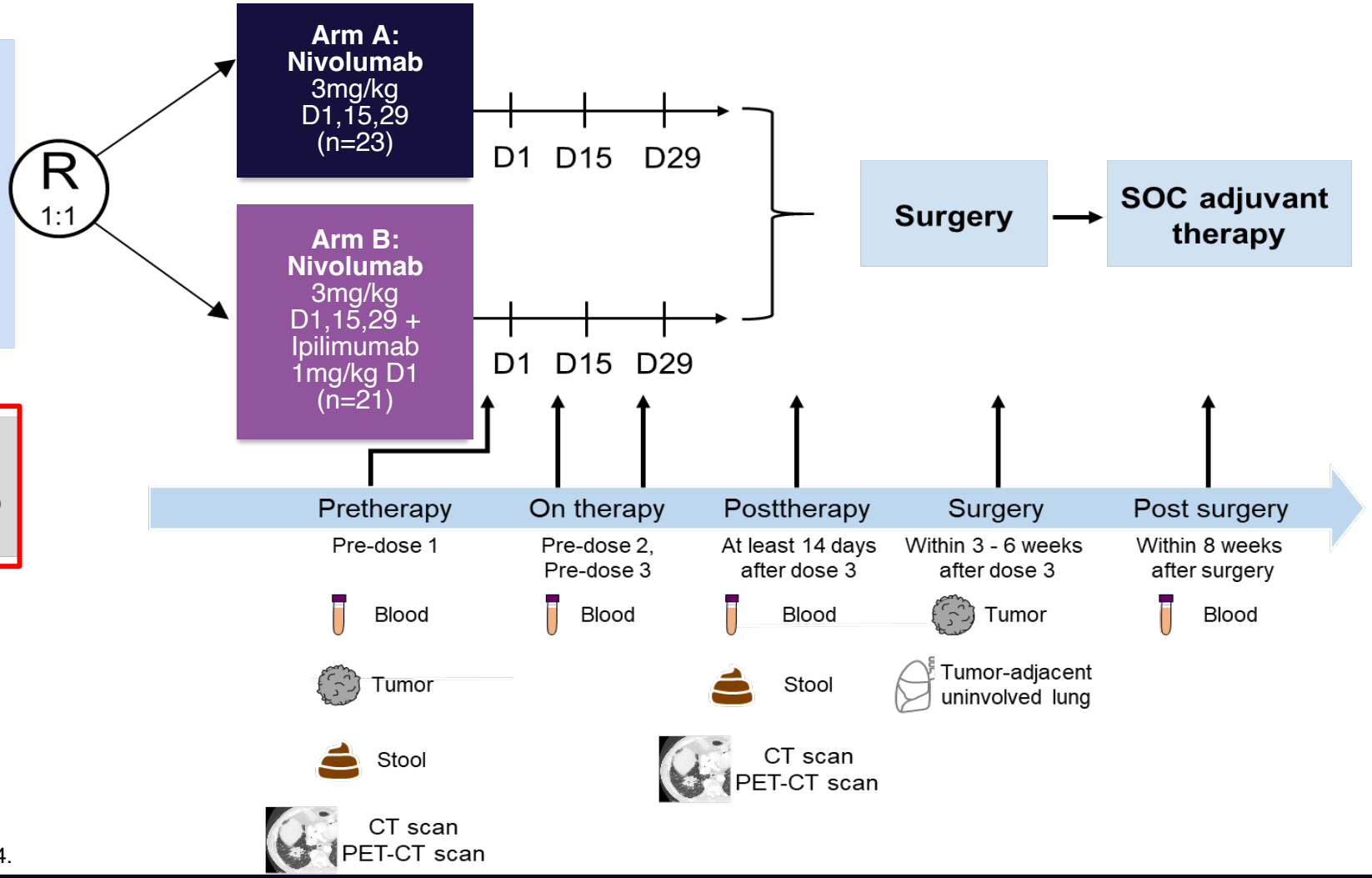
- Activated terminally differentiated effector CD8 TILs expand following combo.
- Combo further increases frequency of Th1-like CD4 effector T cells.

1. Wei S et al. Cell 2017; 2. Wei S et al. PNAS 2019

NEOSTAR: Randomized P2 study of induction ICIs for untreated resectable stage I-IIIA NSCLC

Key Eligibility Criteria
NSCLC Stage I-IIIA N2 single station (AJCC 7th)
No prior systemic therapy
Surgical resectability
ECOG PS 0-1

Stratification
Stage



Primary endpoint:
MPR rate in patients treated with Nivolumab and Nivolumab + Ipilimumab (MPR: ≤10% viable tumor)

PI: Cascone
Co-PI: Sepesi
NCT03158129

Cascone T et al. *Nat Medicine* 2021;27(3):504-514.

Neoadjuvant Nivo plus Ipi meets the prespecified efficacy boundary in patients with resectable NSCLC

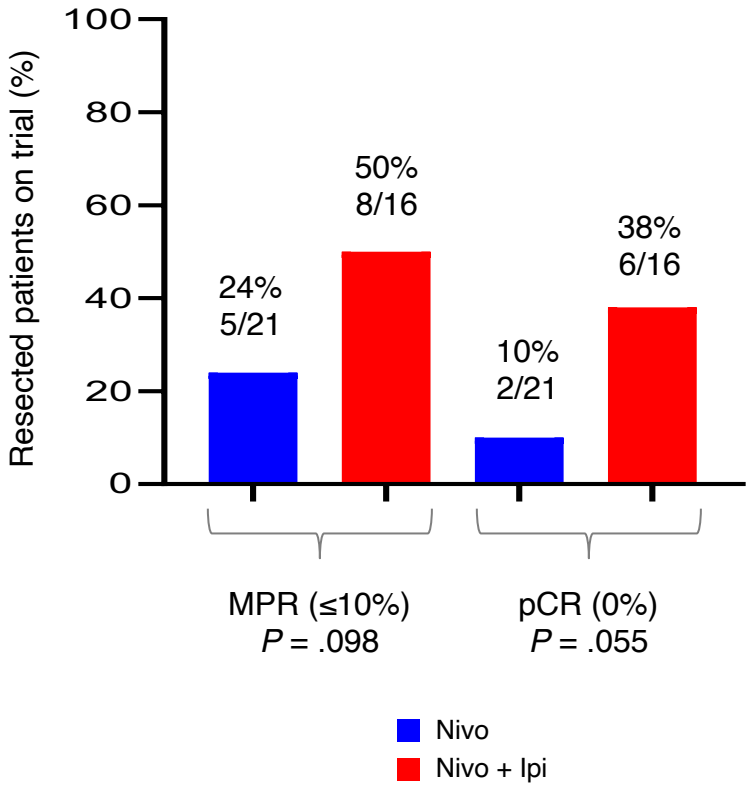
	MPR RATE (%)	
Percentage viable tumor	**Nivo n=23**	**Nivo + Ipi n=21**
0-10 (MPR)	22 (5/23)	38 (8/21)
0 (pCR)	9 (2/23)	29 (6/21)

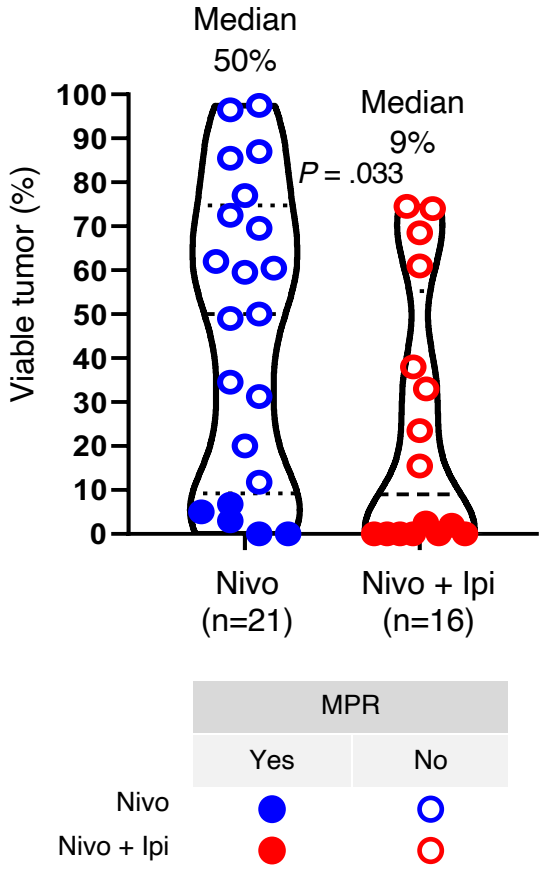
Prespecified trial efficacy boundary: ≥6 MPR

Grade 3-5 TRAEs

Nivo 13%

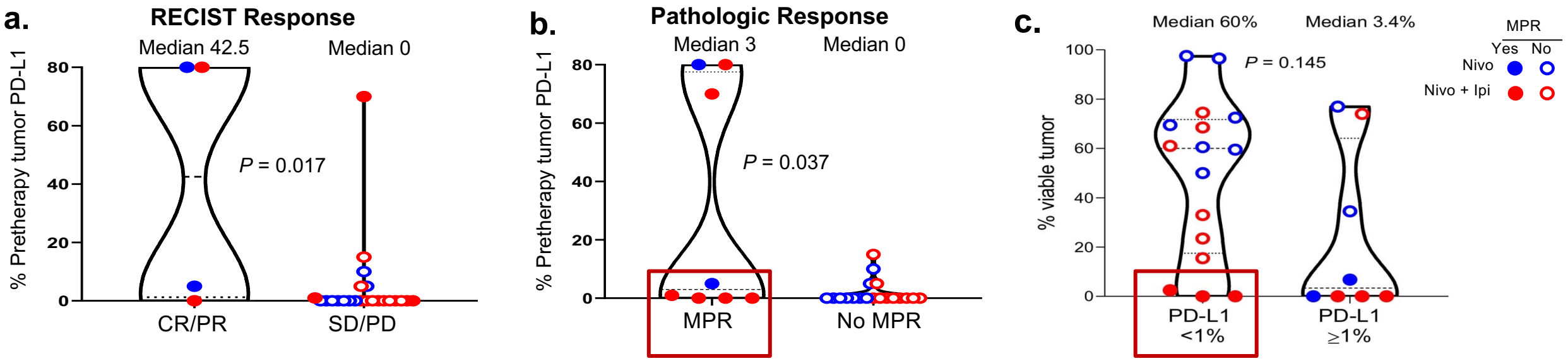
Nivo + Ipi 10%





Cascone T et al. Nat Medicine 2021;27(3):504-514.

Pretreatment tumor PD-L1 expression is associated with responses to neoadjuvant ICIs



Cascone T et al. Nat Medicine 2021;27(3):504-514.

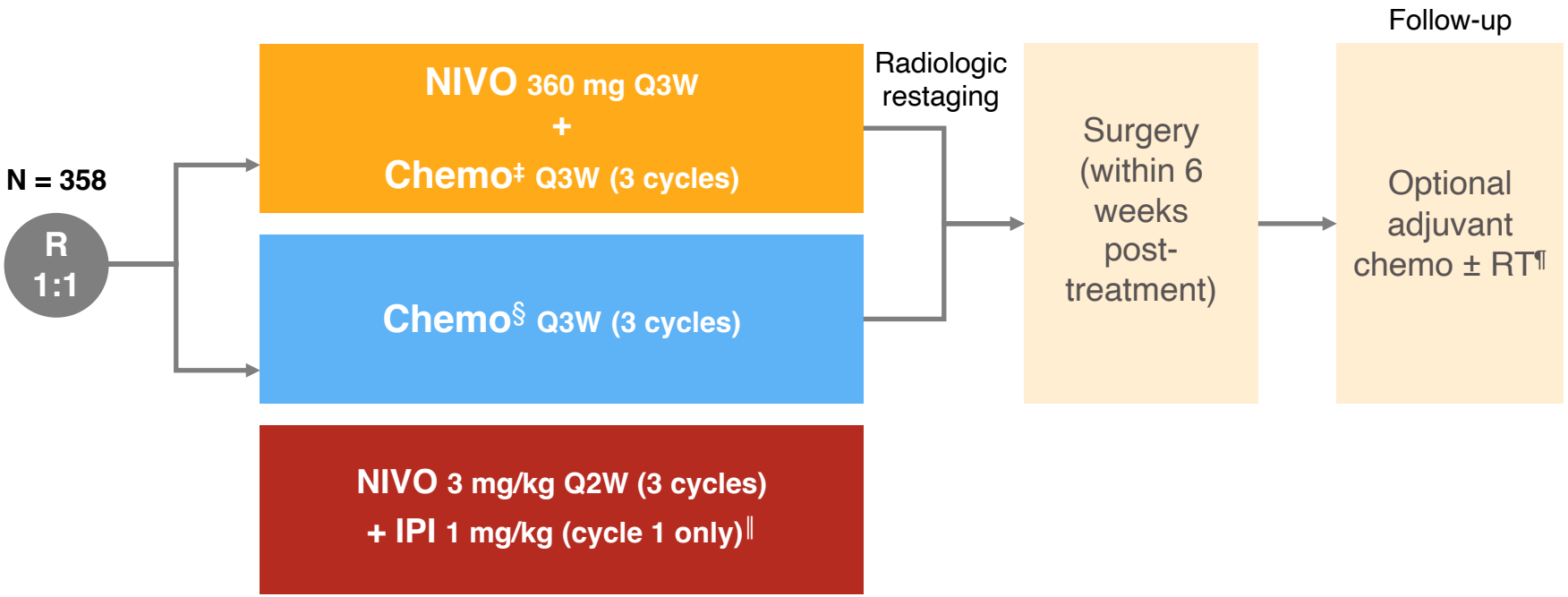
CheckMate 816 study design: Neoadjuvant Nivo + CT for resectable NSCLC

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* (≥ 1% vs < 1%†), and sex



Primary endpoints

- pCR by BIPR
- EFS by BICR

Secondary endpoints

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

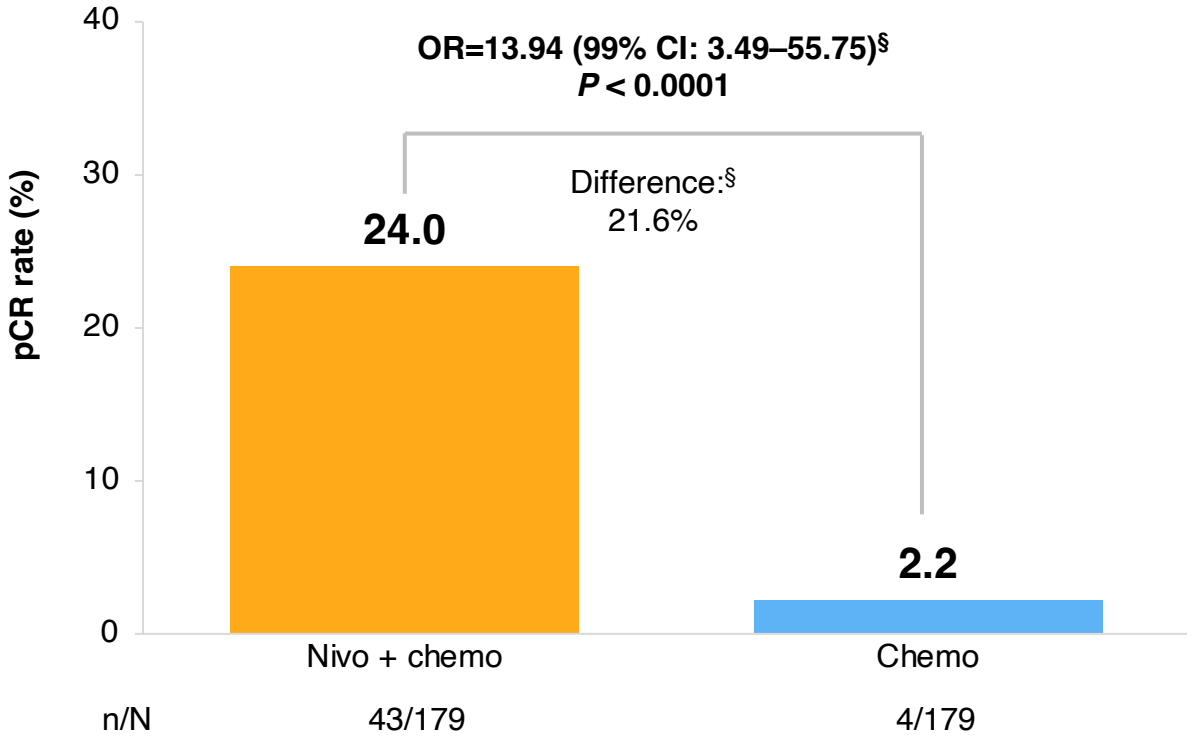
Exploratory endpoints

- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA#)

Forde PM et al. N Engl J Med. 2022

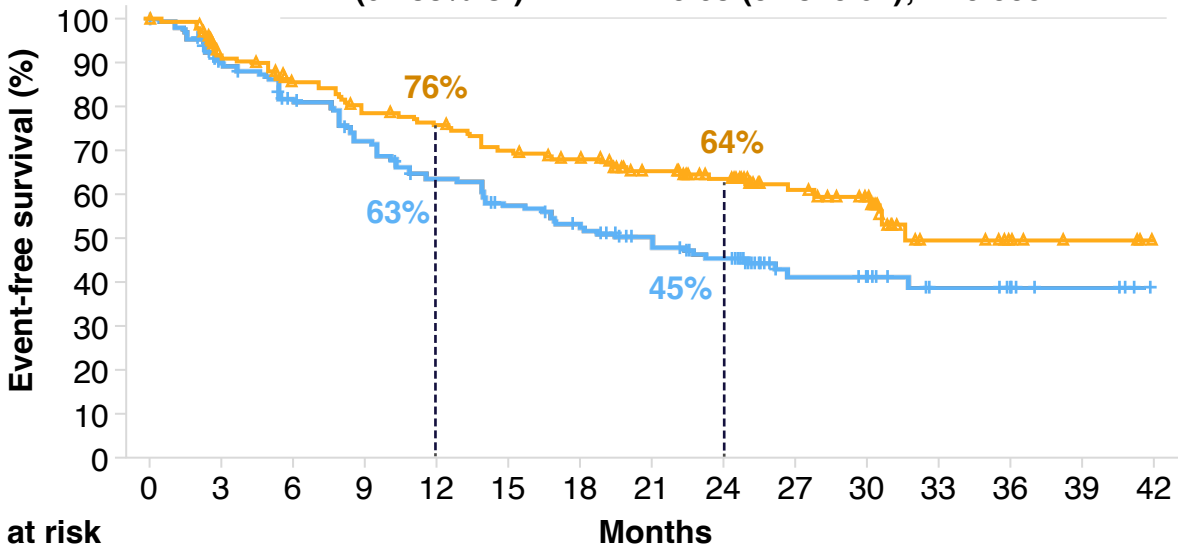
CheckMate 816: Neoadjuvant Nivo + CT improved pCR and EFS in patients with stage IB-IIIA NSCLC

pCR† Rate (ypT0N0)
(Resected + non-resected population)



EFS
PD-L1 AC, stage IB-IIIA

	Nivo + chemo (n=179)	Chemo (n=179)
Median EFS¶, mo	31.6	20.8
HR (97.38% CI)#	0.63 (0.43–0.91); *P*=0.0052**	

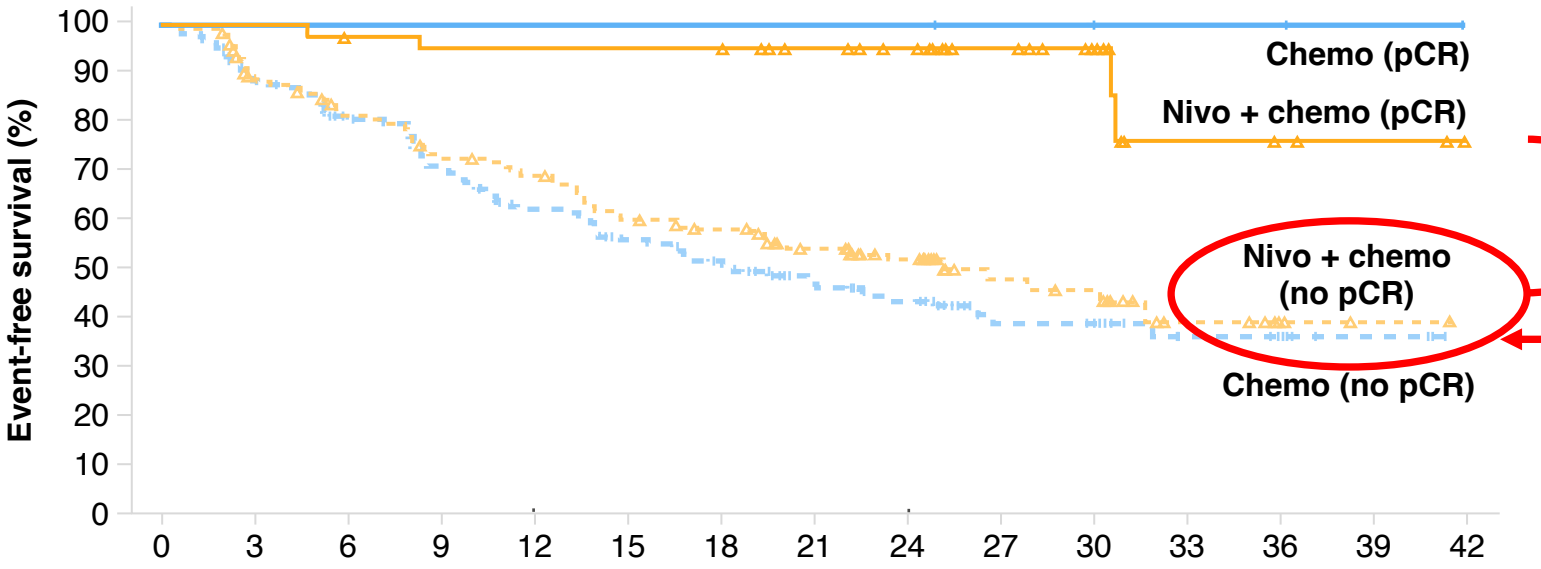


No. at risk															
Nivo + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Forde PM et al. N Engl J Med. 2022

CM 816: pCR May Represent an Early Indicator of EFS Benefit From Neoadjuvant CT+IO

EFS by pCR
PD-L1 AC, stage IB-IIIA



No. at risk															
pCR	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
pCR	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
No pCR	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
No pCR	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

	Nivo + chemo (n=179)		Chemo (n=179)	
	pCR	No pCR	pCR	No pCR
Median EFS, mo	NR	26.6	NR	18.4
HR (95% CI)	0.13 (0.05-0.37)		Not computed	

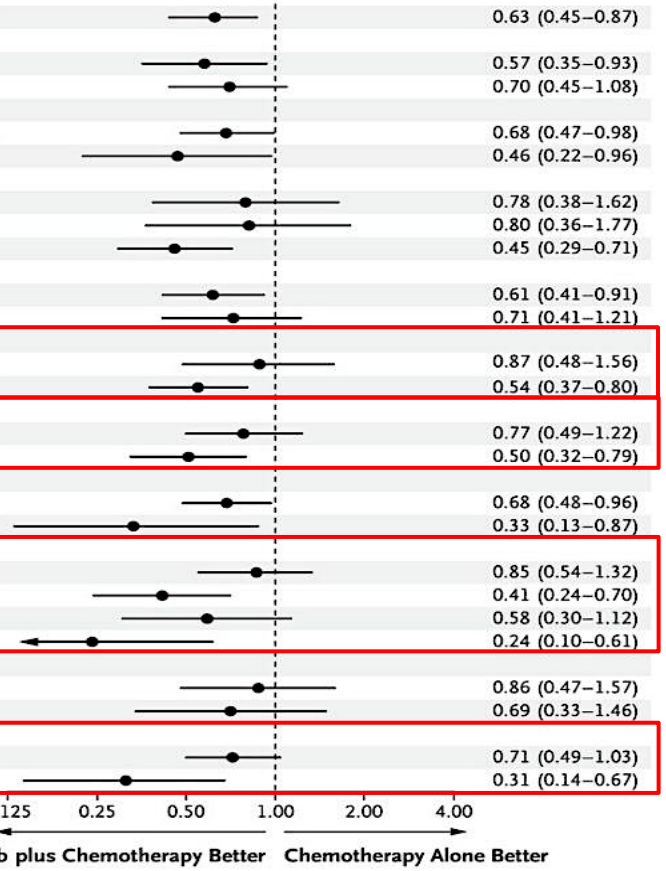
In pts with no pCR

Nivo +CT vs CT: HR 0.84 (0.61, 1.17)

Forde PM, et al. N Engl J Med. 2022;386:1973-1985.

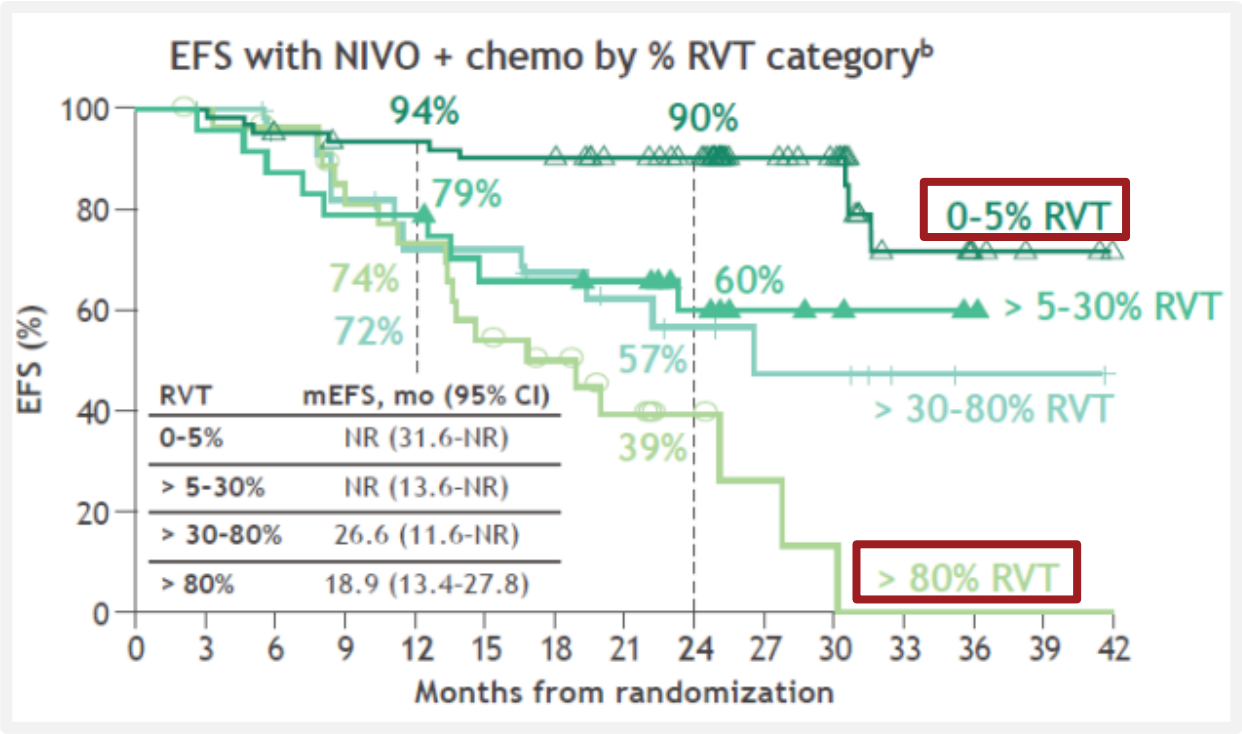
CM-816: EFS Benefit From Neoadjuvant Chemo + Nivo vs Chemo Across Subgroups

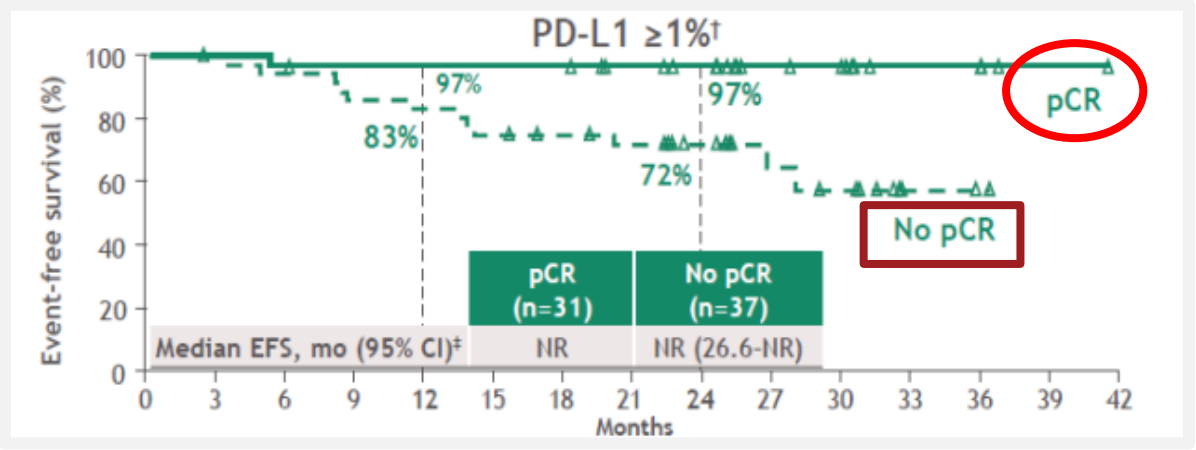
Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)

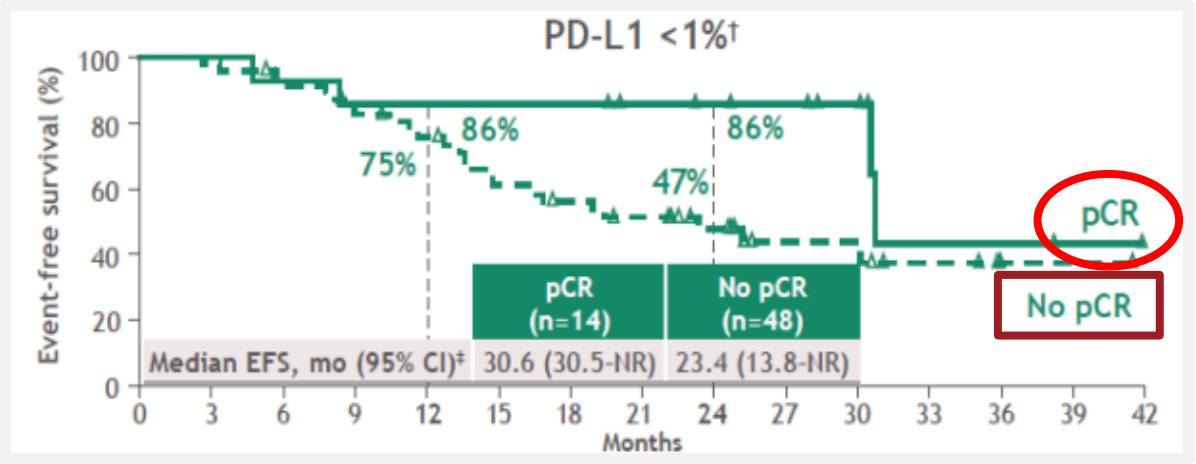


Forde PM, et al. N Engl J Med. 2022;386:1973-1985.

CM816: Impact of pathological regression depth and PD-L1 status on survival outcomes

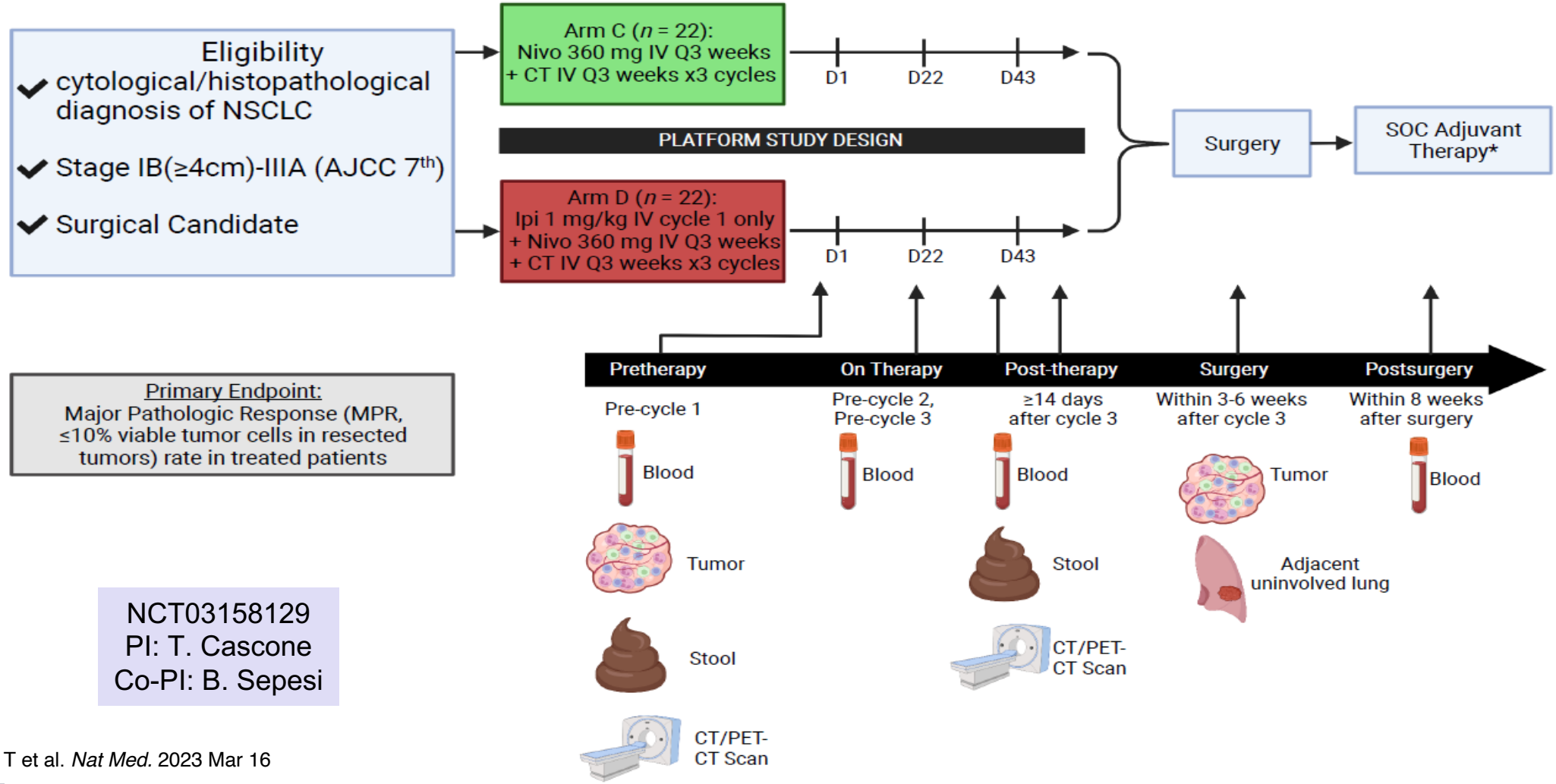






Provencio-Pulla M et al. Poster presentation at ASCO 2022. Abstract LBA8511

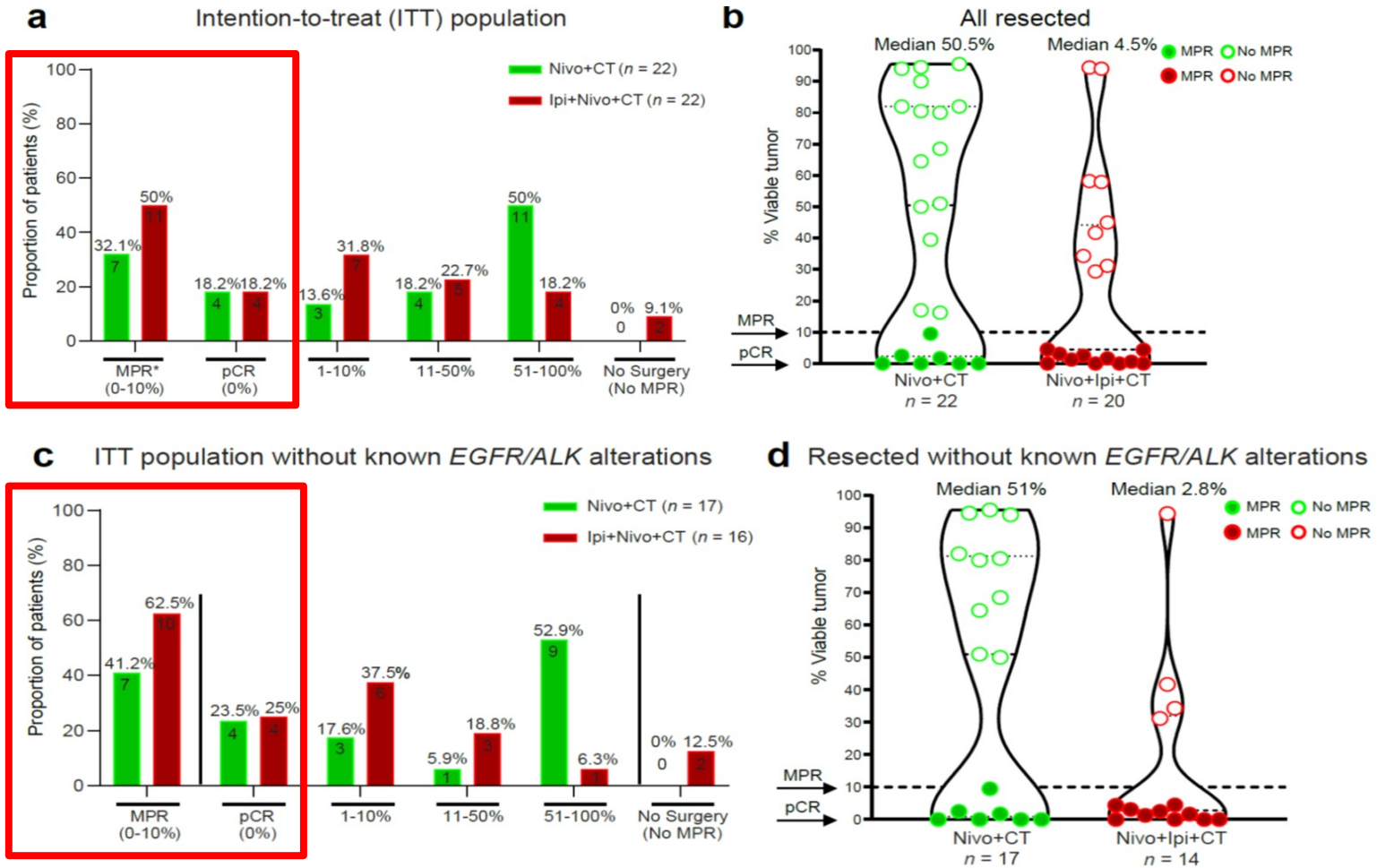
NEOSTAR P2 platform trial: Modular single-arm studies using MPR to rapidly test promising neoadjuvant therapies



NCT03158129
PI: T. Cascone
Co-PI: B. Sepesi

Cascone T et al. *Nat Med.* 2023 Mar 16

NEOSTAR Platform: Neoadjuvant Ipi+Nivo+Chemo results in higher MPR rates than Nivo+Chemo in NSCLC

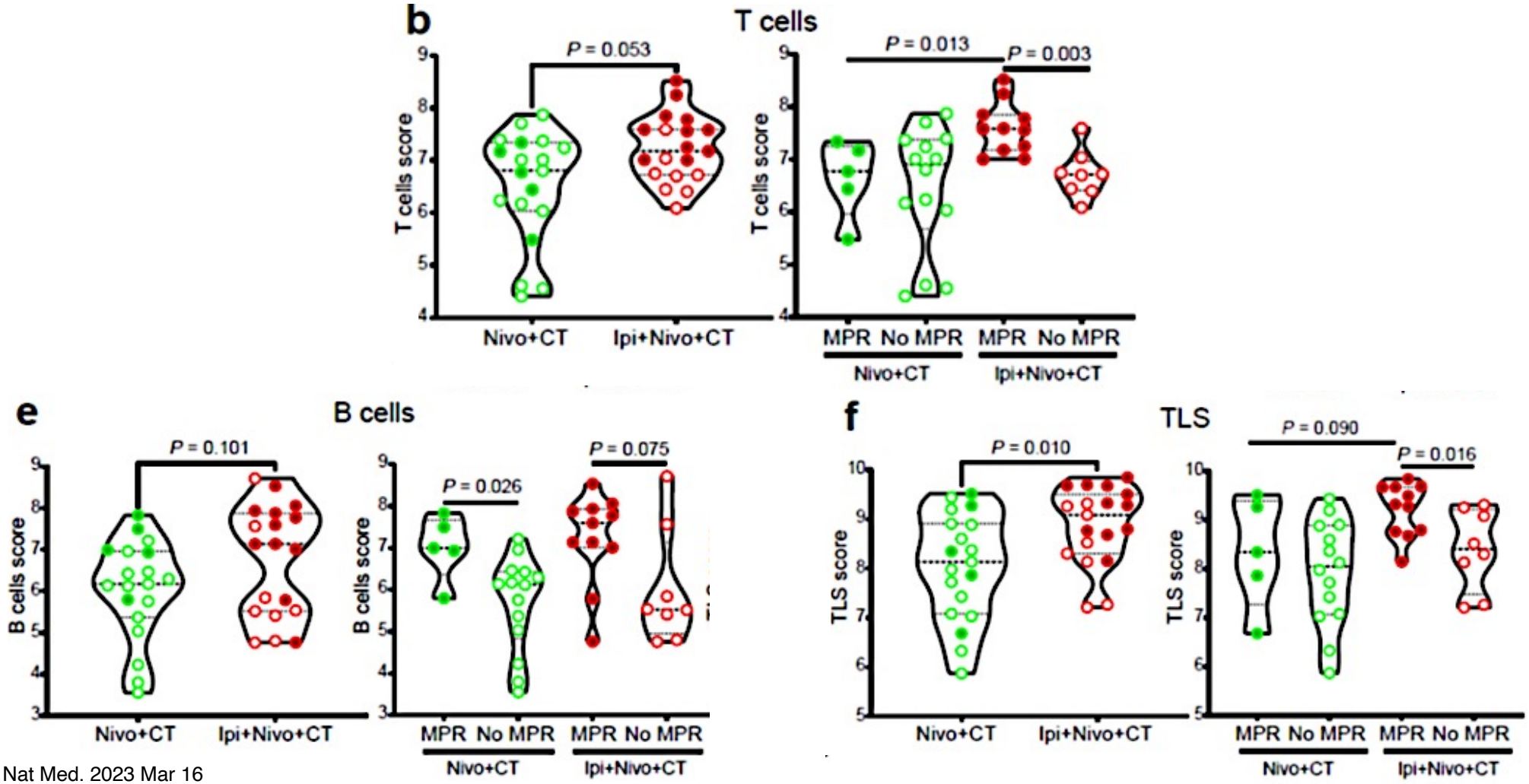


ITT population:
Nivo+CT ITT MPR rate: 32.1%
Ipi+Nivo+CT: MPR rate 50%

Pts without known *EGFR/ALK* alterations:
Nivo+CT ITT: MPR rate: 41.2%;
Ipi+Nivo+CT: MPR rate 62.5%

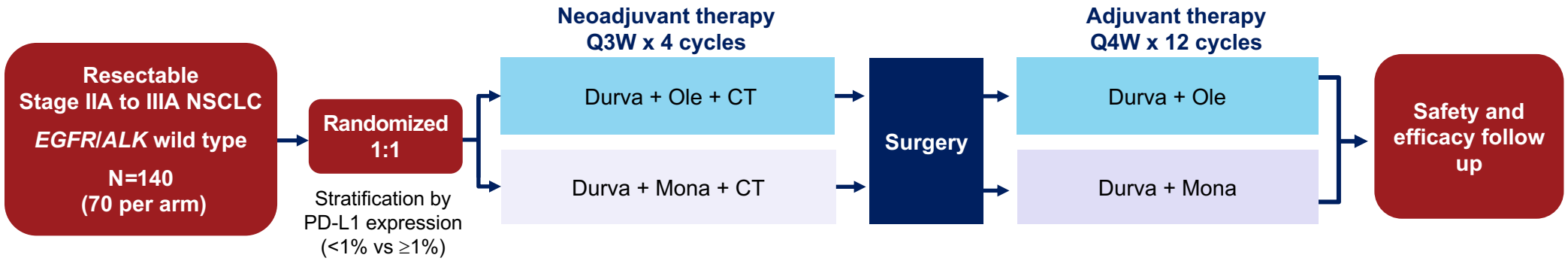
Cascone T et al. Nat Med. 2023 Mar 16

Enhanced immune T, B cell and TLS scores in tumors treated with Ipi+Nivo+CT and responders



Cascone T et al. Nat Med. 2023 Mar 16

NeoCOAST-2 P2R platform trial testing novel I-O agents in combination with PD-L1 blockade + CT

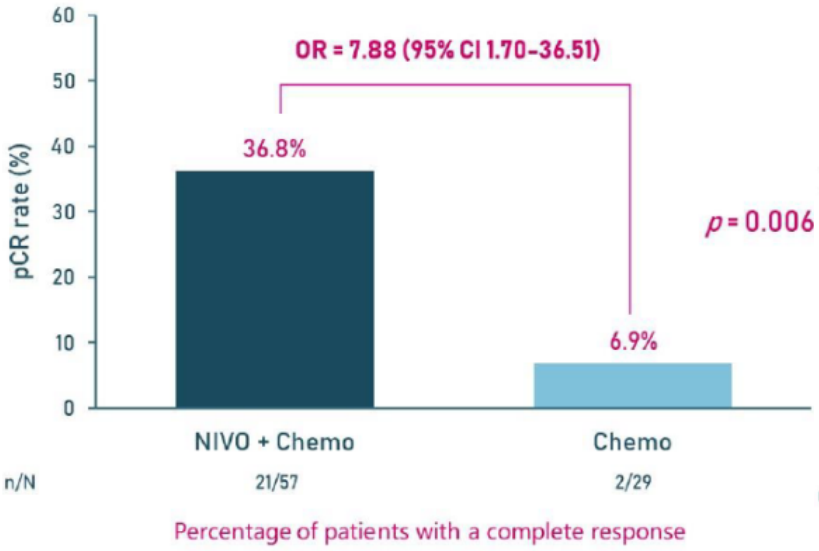


- NeoCOAST-2 (NCT05061550) is a phase 2, randomized study of neoadjuvant durvalumab combined with chemotherapy and either ole or mona, followed by surgery and adjuvant durva plus ole or mona, in patients with resectable, Stage IIA–IIIA NSCLC.[1]
  - Primary endpoints: pCR, safety and tolerability
  - Secondary endpoints: EFS, DFS, OS, and ORR per RECIST v1.1; MPR; feasibility of surgery; pharmacokinetics; immunogenicity; baseline tumor PD-L1 expression; changes in ctDNA
  - Recruitment initiated in January 2022.

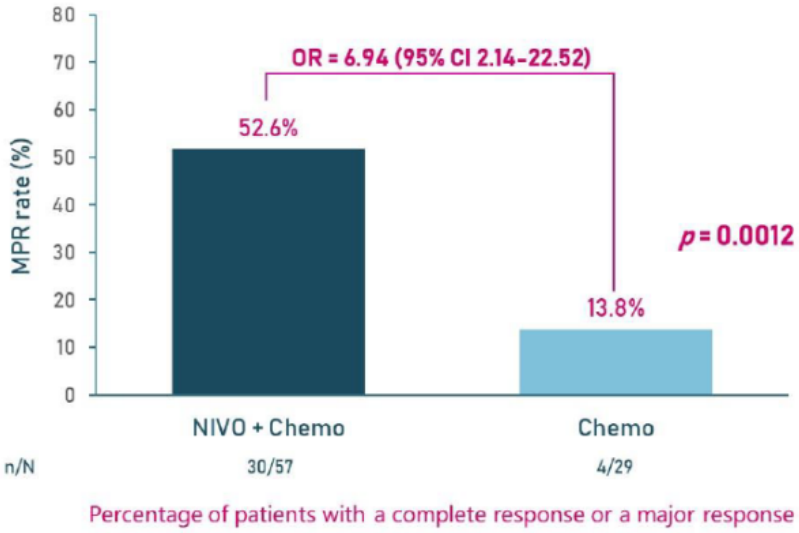
Cascone T, et al. AACR 2022 (poster CT124).

Primary Outcomes Following Perioperative Nivo + Chemo in NADIM 2 P2R Trial

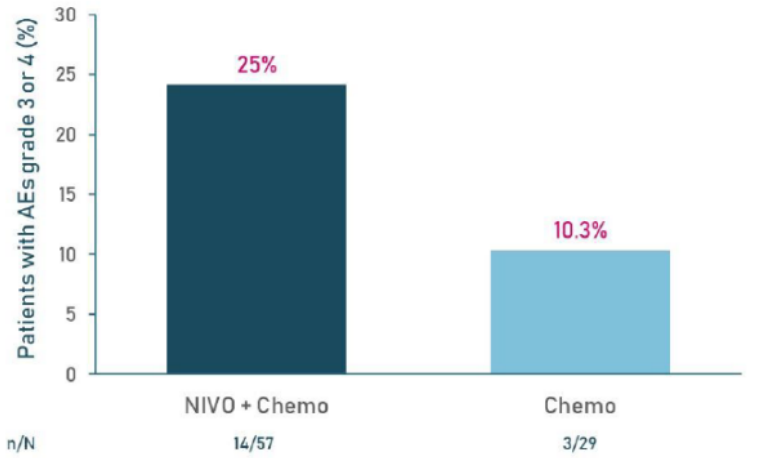
NADIM 2 pCR



NADIM 2 MPR



Adverse events G 3-4 summary (ITT population)

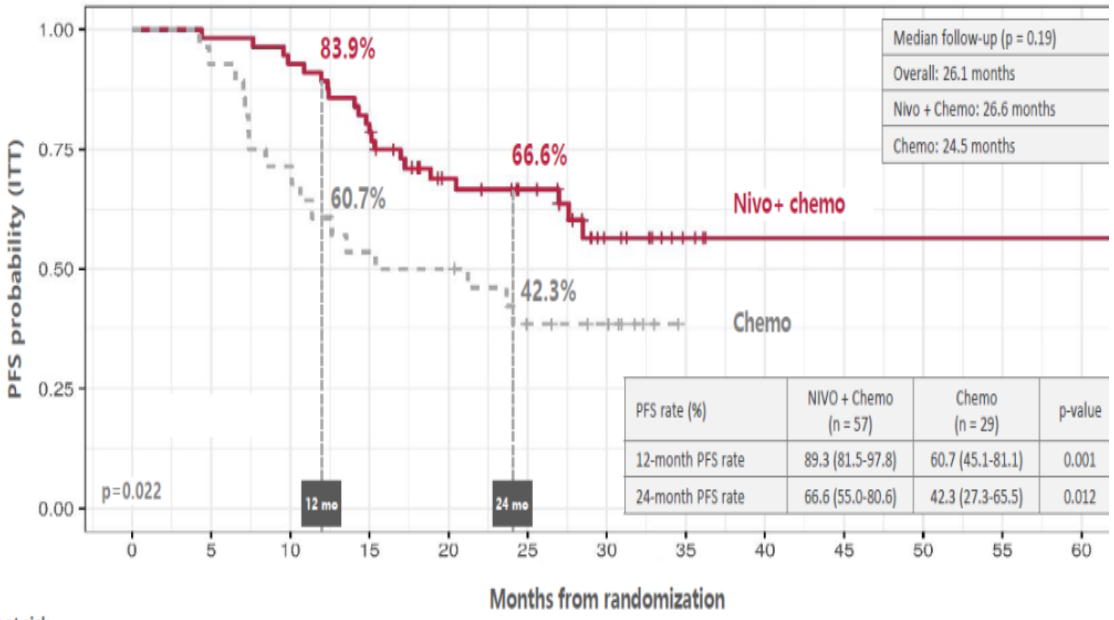


No grade 5 treatment-related adverse events were observed

Provencio-Pulla M et al. 2022 ASCO Annual Meeting.

Secondary Outcomes Following Perioperative Nivo + Chemo in NADIM 2 Trial

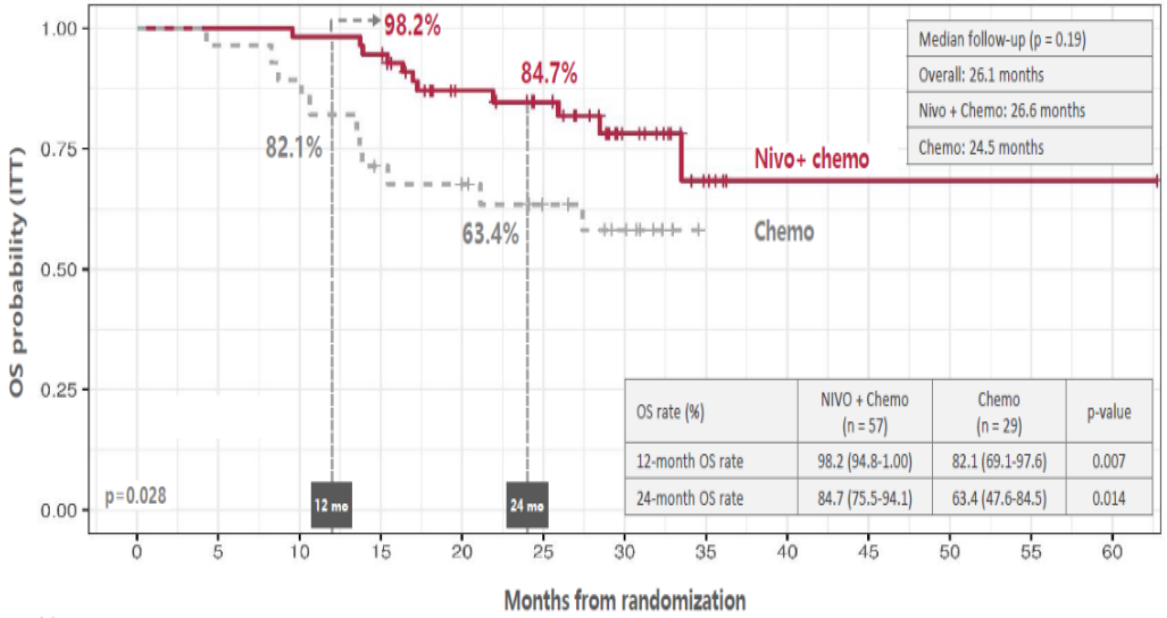
NADIM 2 PFS



PFS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month PFS rate	89.3 (81.5-97.8)	60.7 (45.1-81.1)	0.001
24-month PFS rate	66.6 (55.0-80.6)	42.3 (27.3-65.5)	0.012

Number at risk													
Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

NADIM 2 OS



OS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month OS rate	98.2 (94.8-1.00)	82.1 (69.1-97.6)	0.007
24-month OS rate	84.7 (75.5-94.1)	63.4 (47.6-84.5)	0.014

Number at risk													
Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

Provencio-Pulla M et al. 2022 WCLC Meeting.

The Neo-adjuvant treatment landscape will expand as IO-based therapies are further explored in NSCLC

Completed and Ongoing Select Phase 3 trials

Resectable NSCLC

Neoadjuvant

Trial	Regimen
CheckMate 816	Nivolumab + chemo

Adjuvant

Trial	Regimen
KEYNOTE-091/PEARLS	Pembro
IMpower010	Atezolizumab
CCTC BR31	Durvalumab
CANOPY-A	Canakinumab
ANVIL	Nivolumab
MERMAID-1	Durvalumab + chemo
MERMAID-2	Durvalumab

Perioperative

Trial	Regimen
CheckMate 77T	Nivolumab + chemo → Nivolumab
KEYNOTE-671	Pembrolizumab + chemo → Pembrolizumab
IMpower030	Atezolizumab + chemo → Atezolizumab
AEGEAN	Durvalumab + chemo → Durvalumab

Advantages of perioperative immunotherapy:
Continuous treatment throughout the surgical setting
Enhanced micrometastatic disease killing
Greater impact on EFS/OS w/o concerning toxicity?

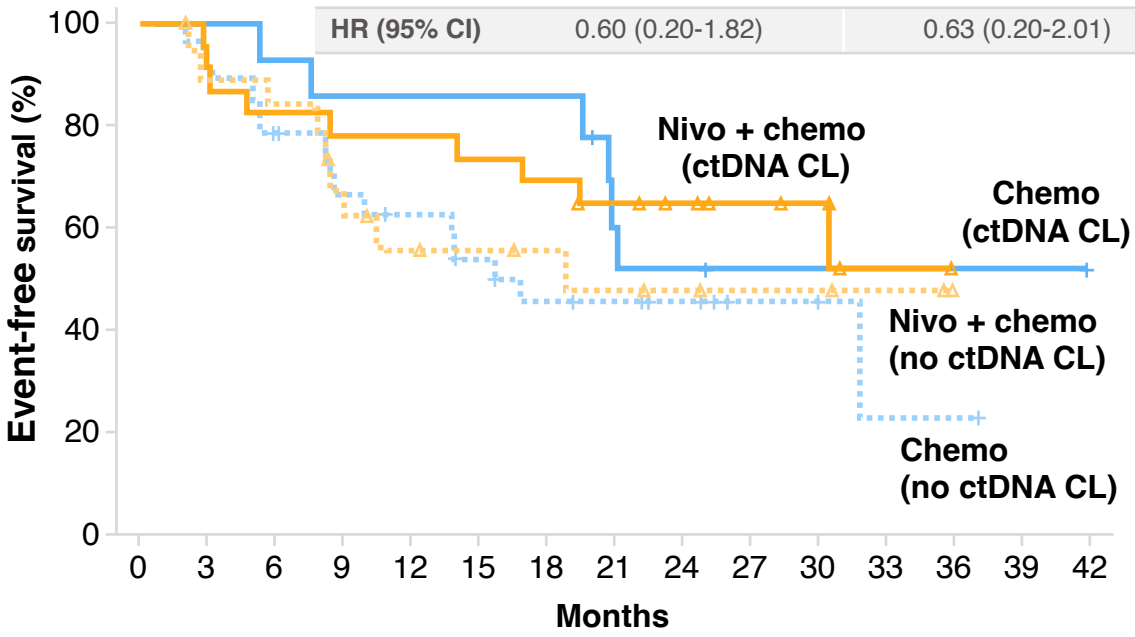
Aegean Press release: Positive EFS 3/9/23
KEYNOTE-671 Press release: Positive EFS 3/1/23
Adapted from ESMO IO Satellite Symposium 2022.

How to Utilize ctDNA for Treatment Decisions after Neoadjuvant Chemo-IO?

Optimize ctDNA testing at baseline, post neoadj and surgery to guide therapy across subgroups

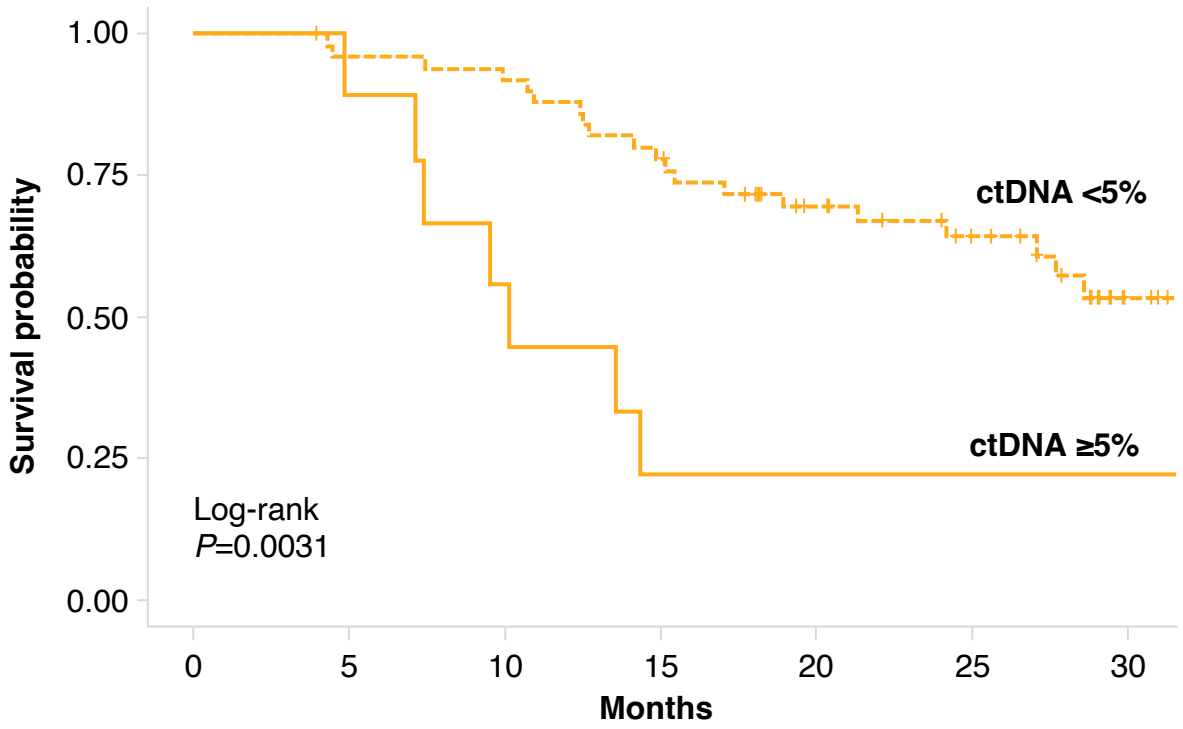
CM816: ctDNA clearance post neoad CT+IO and EFS

	Nivo + chemo		Chemo	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
mEFS, mo	NR	18.9	NR	16.8
HR (95% CI)	0.60 (0.20-1.82)		0.63 (0.20-2.01)	



Forde PM, et al. N Engl J Med. 2022;386:1973-1985.

NADIM 2: PFS by baseline ctDNA post periop CT+IO



Romero A et al. Oral presentation at WCLC 2022. Abstract MA06.03.

Take-Home Points From Neoadjuvant ICI-Based Therapy Studies in Resectable NSCLC

- Neoadjuvant ICI combinations are overall safe, feasible, and induce higher MPR and pCR rates than either CT historical controls or ICI as monotherapy
- CheckMate 816 P3R: pCR and EFS benefit with neoadjuvant IO + chemo in pts with *EGFR/ALK* wt tumors
- Positive EFS with perioperative Chemo-IO in P3R trials: results to be presented
- Importance of building longitudinal pan-sample collections on neoadjuvant/perioperative trials for novel target (B cell/TLS?) and biomarker discovery

Considerations to optimize neoadjuvant/perioperative ICI-based therapy

- pCR

Surveillance with imaging +/- ctDNA/MRD monitoring

  - Near pCR/MPR?

- no pCR

Continue IO +/- ctDNA monitoring or change treatment strategy in the adjuvant setting:

  - Nonresponders (High %RVT?); PD-L1 <1%, select molecular subsets→ CTLA-4 blockade potentially useful?

- What is the role of RT in the neo-adjuvant setting?

- Clinical and financial toxicity

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