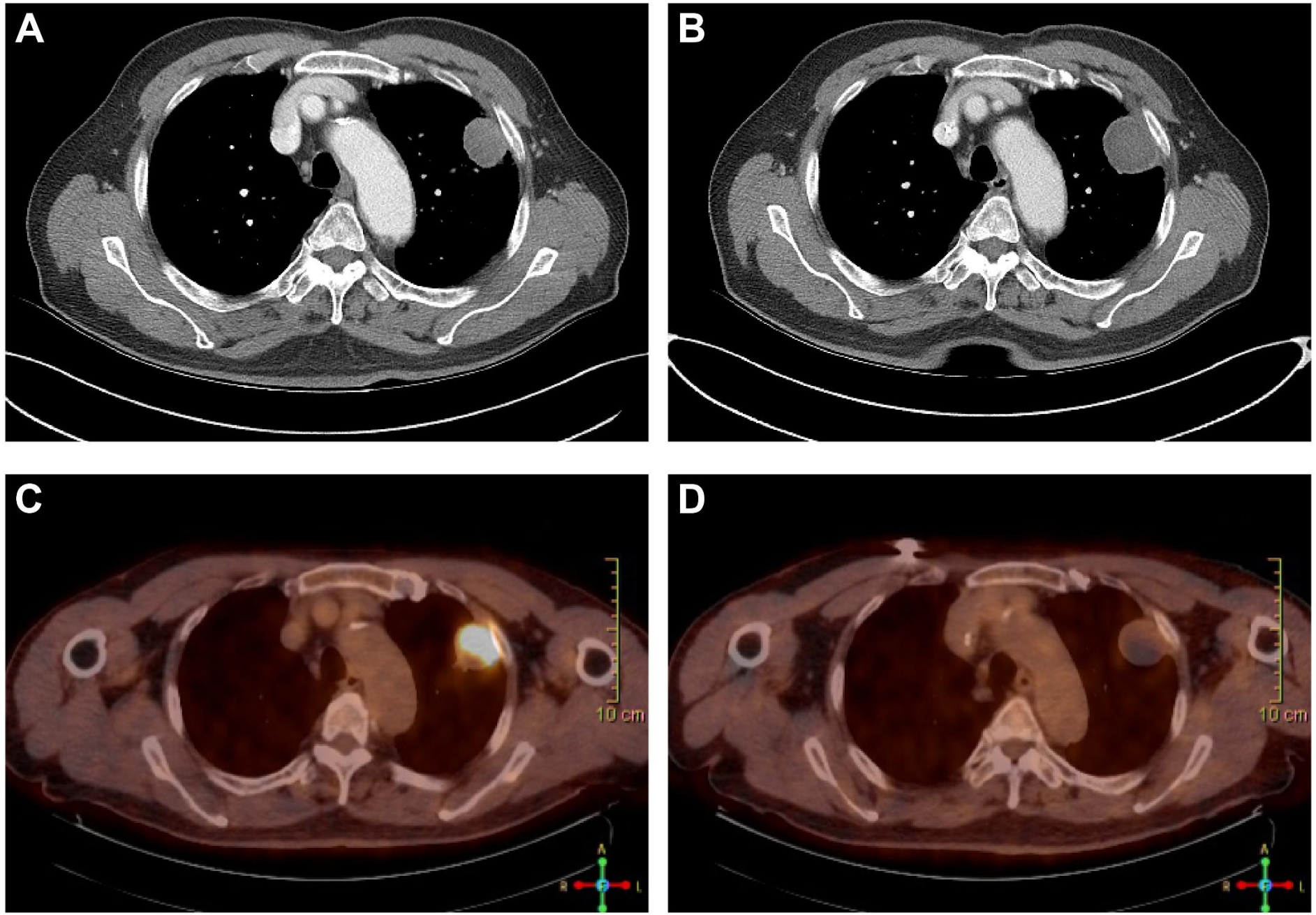
비소세포폐암 환자에서 면역관문억제제를 기반으로 한 선행 항암 요법

고려대학교 구로병원 호흡기내과 최주환

KU MC KOREA UNIVERSITY MEDICAL CENTER

증례

- **환자** : 73세 남자 환자
- **주소** : 간헐적인 객혈로 인해 내원
- **현병력** : 약 한달 전부터 일주일에 한 두차례 정도, 휴지에 묻어나는 양상의 객혈을 주소로 내원함.
- **이학적 소견** : 외래 내원 당시 활력 징후는 혈압 130/80 mmHg, 맥박 70회/분, 호흡수 17회/분, 체온 36.8도였다. 의식은 명료하였으며 청진상 이상소견은 보이지 않음.
- **과거력** : 고혈압
- **영상의학적 소견** : 흉부 CT상 좌상엽 쪽에 3cm 가량에 chest wall invasion의 가능성이 있는 폐암 의심 병변이 확인됨.
- **진단 및 치료** : 조직검사 통해 비소세포폐암 (Adenoca, PD-L1(SP263-100%), PD-L1(SP142-90, 2%) 진단되었으며, stage w/u 상 T3N0M0 확인되어 Neoadj 3C (nivolumab-ipilimumab) 시행하였고, 이후 LULobectomy 시행함, 수술 조직 상 No residual carcinoma (ypT0N0) 확인함.

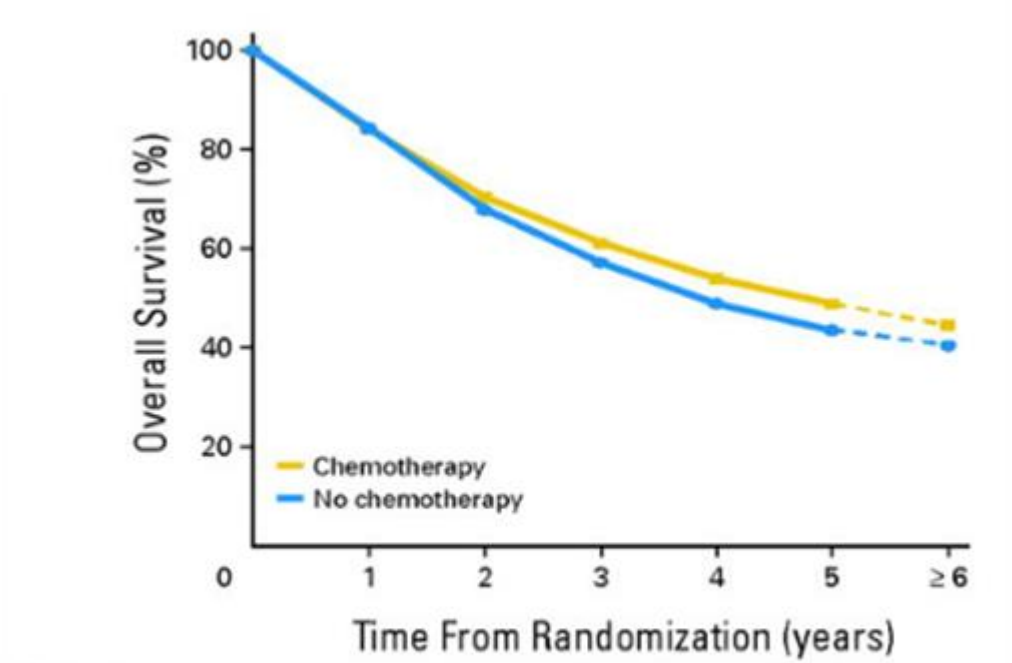

A
B
C
10 cm
D
10 cm

Journal of Clinical Oncology

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

- 5RCTs (4,584 pts), cisplatin-based chemotherapy, R0

- Absolute effect of chemotherapy at 5 years was a decrease of 6.9% for lung cancer death and an increase of 1.4% for non–lung cancer death



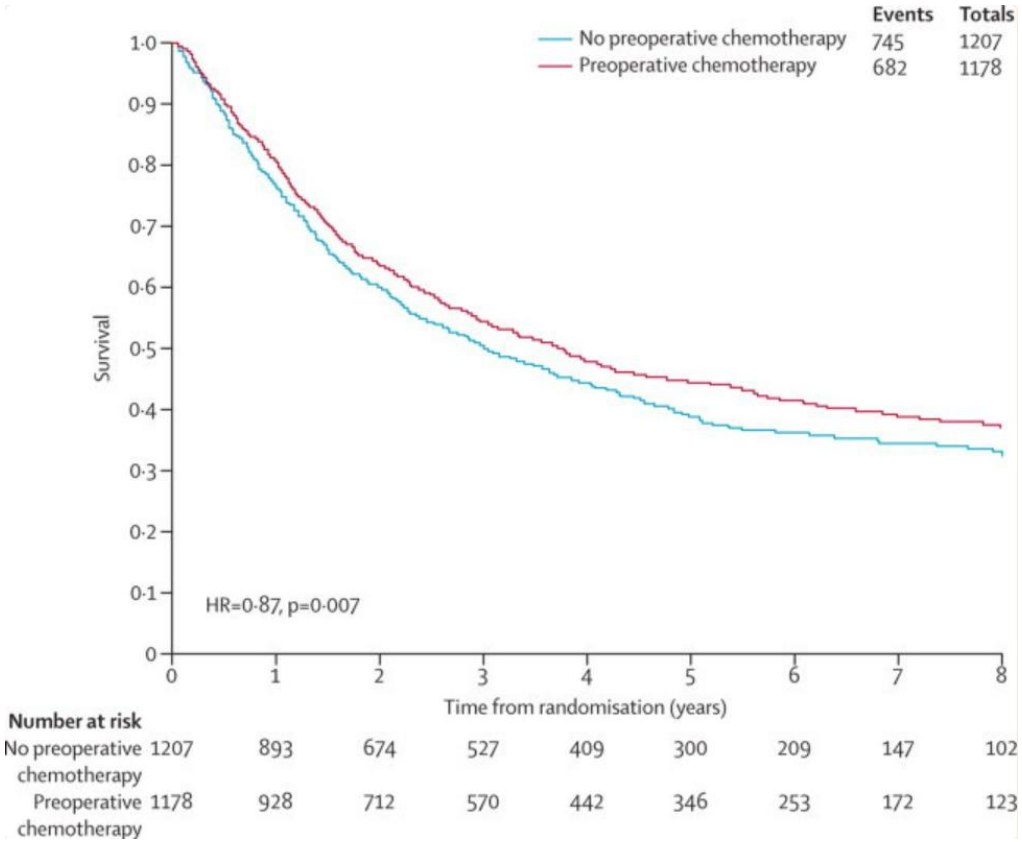
Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Lancet

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

- 15RCTs (2,385 pts), stage IB-IIIA

- The evidence for neoadjuvant chemotherapy results showed that improved the 5-year overall survival by 5%



Number at risk									
No preoperative chemotherapy	1207	893	674	527	409	300	209	147	102
Preoperative chemotherapy	1178	928	712	570	442	346	253	172	123

J Thorac Oncol.

Preoperative versus Postoperative Chemotherapy in Patients with Resectable Non-small Cell Lung Cancer: Systematic Review and Indirect Comparison Meta-Analysis of Randomized Trials

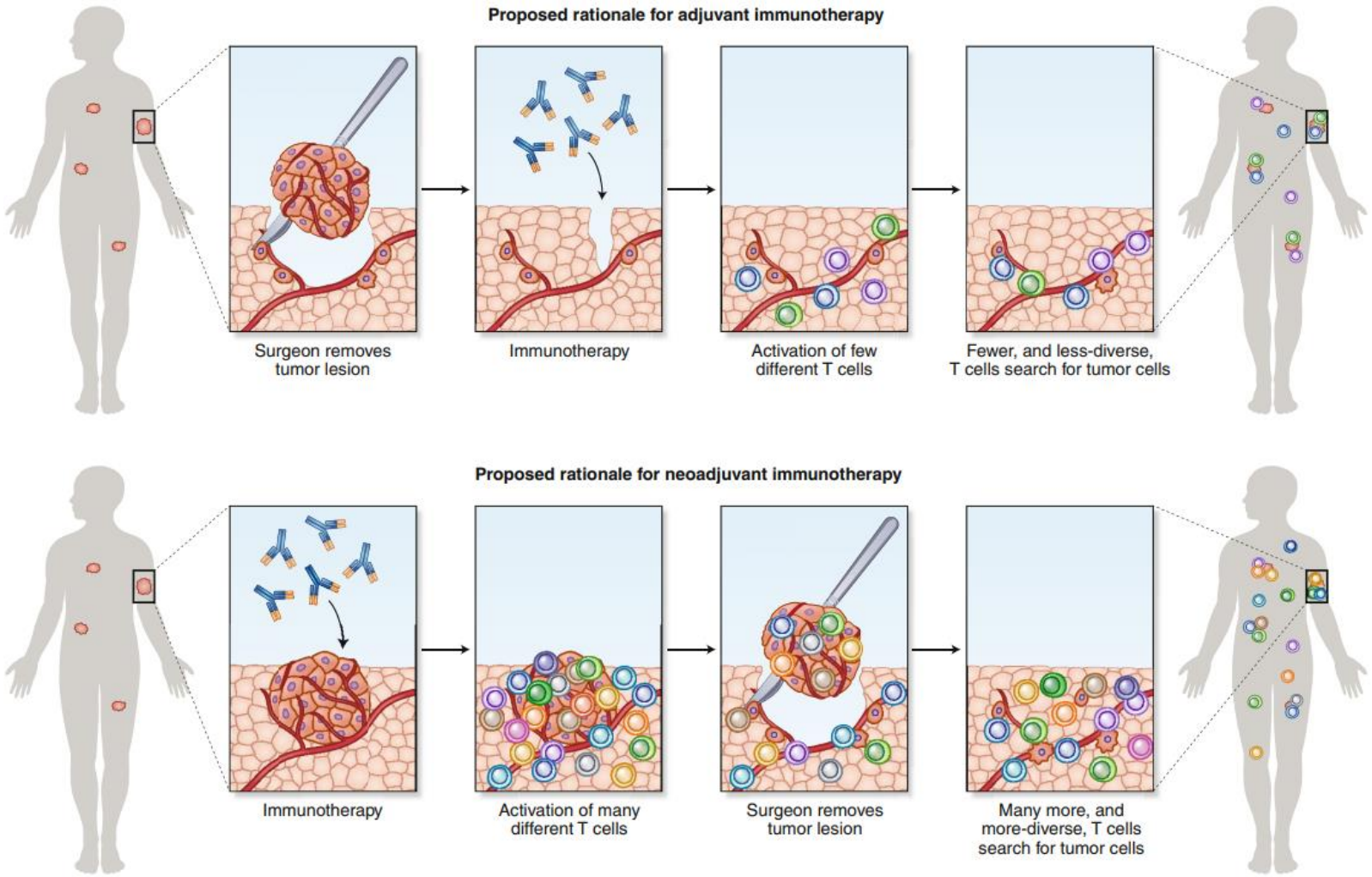
- 32 RCTs (22 ADJ RCTs vs 10 Neo-ADJ RCTs), 10,000 pts

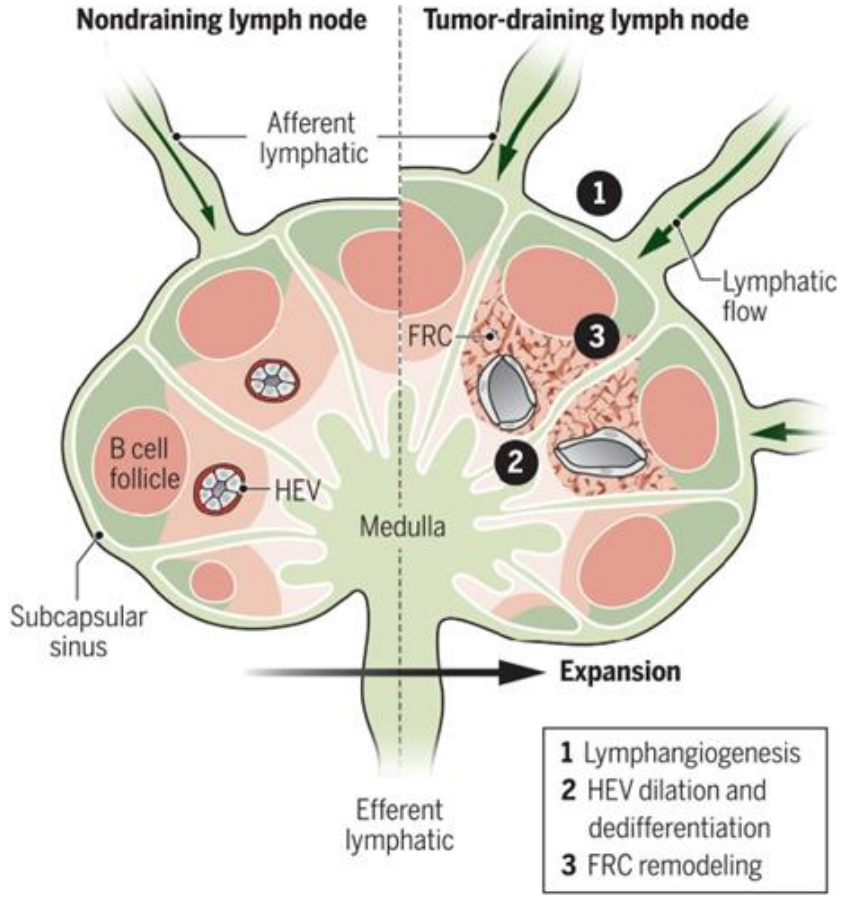
- There was no evidence of a difference in overall and disease-free survival between the timing of administration of chemotherapy

TABLE 3. Estimated 5-yr Survival Probability, Impact on Survival and Limits of the Difference Between Postoperative and Preoperative Administration

		Postoperative Chemotherapy			Preoperative Chemotherapy			Difference (Postoperative versus Preoperative)		
Stage	5-yr Survival Reported	Expected	Lower 95% CI	Upper 95% CI	Expected	Lower 95% CI	Upper 95% CI	Expected	Upper 95% CI	Lower 95% CI
IA	73	78.4	76.4	80.3	78.1	73.7	81.8	−0.30	−4.23	4.51
IB	54	63.2	59.8	66.4	62.7	55.2	69.0	−0.51	−7.20	7.68
IIA	**48**	**58.5**	**54.6**	**62.0**	**57.9**	**49.4**	**64.9**	**−0.58**	**−8.14**	**8.68**
IIB	**38**	**50.5**	**45.9**	**54.7**	**49.8**	**39.7**	**58.2**	**−0.69**	**−9.71**	**10.35**
IIIA	**25**	**40.1**	**34.5**	**45.3**	**39.3**	**27.0**	**49.4**	**−0.84**	**−11.75**	**12.52**
IIIB	19	35.3	29.3	40.9	34.4	21.2	45.3	−0.91	−12.68	13.53
IV	21	36.9	31.0	42.3	36.0	23.1	46.7	−0.88	−12.37	13.19

All numbers are given as a percentage. Bold font indicates the tumour stage for which the data is most applicable.

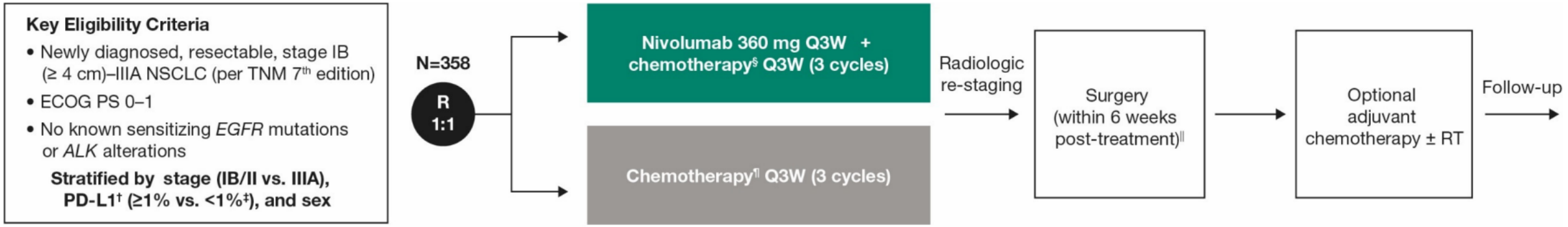




Nat Med 2020 Apr;26(4) 475-484

Science Immunology 2021

Checkmate 816 study design



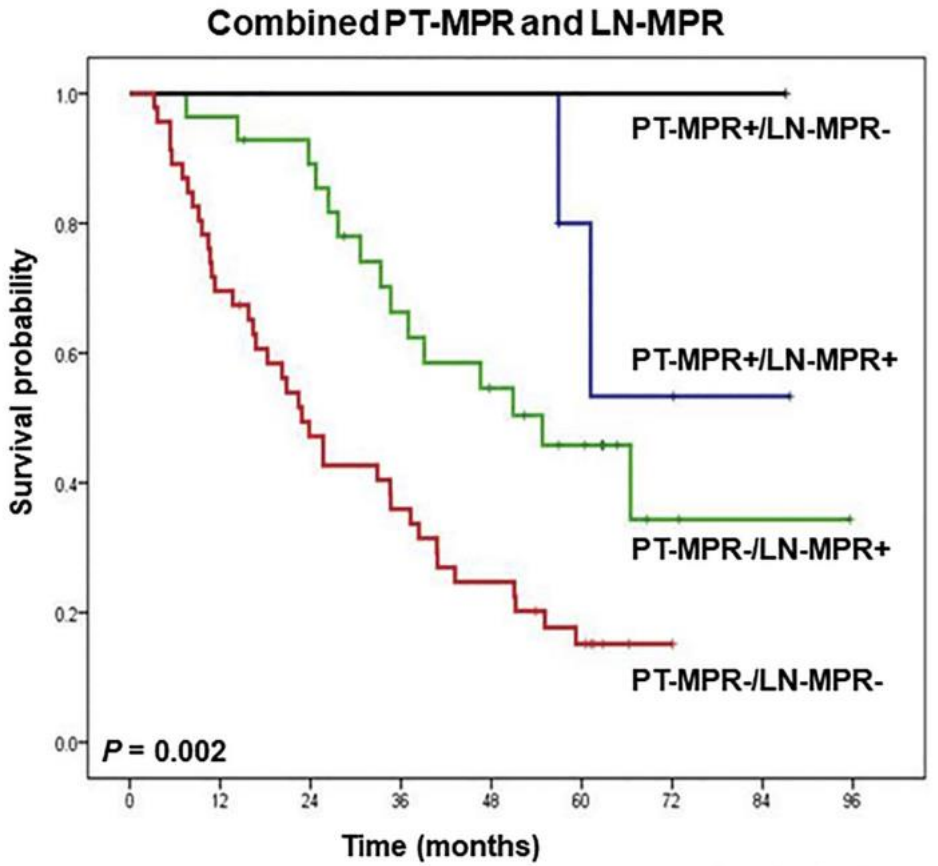
Primary Endpoints
- pCR by BIPR
- EFS by BICR

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

Key Exploratory Endpoints Included
- ORR by BICR
- Feasibility of surgery; peri- and post-operative surgery-related AEs
- Predictive biomarkers (PD-L1, TMB, ctDNA**)

- Pathological Response
  - Pathologic complete response (**pCR**) : 0% residual viable tumor
  - Major pathologic response (**MPR**) : ≤ 10% residual viable tumor

- Pathological assessment in CheckMate 816
  - pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes
  - MPR: ≤ 10% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes



Groups	Survival rate	
	4-year	5-year
A. PT-MPR+ (≤10%)/LN-MPR- (>70%) (n=1)	100%	100%
B. PT-MPR+ (≤10%)/LN-MPR+ (≤70%) (n=5)	100%	80%
C. PT-MPR- (>10%)/LN-MPR+ (≤70%) (n=26)	55%	45%
D. PT-MPR- (>10%)/LN-MPR- (>70%) (n=43)	25%	15%

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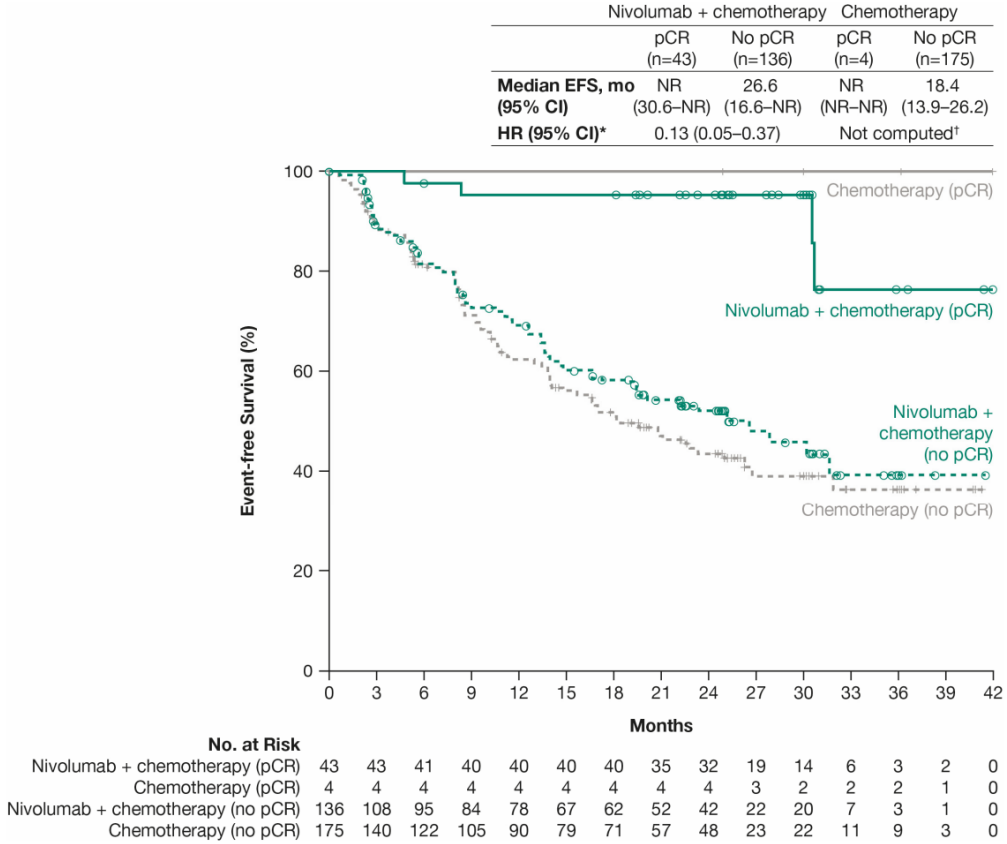
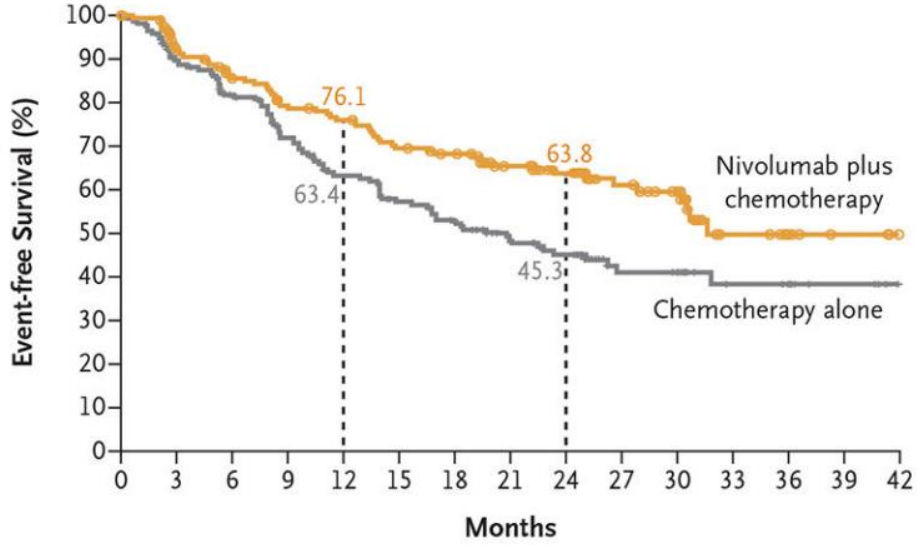
- Pathological Response
  - Pathologic complete response (**pCR**) : 0% residual viable tumor
  - Major pathologic response (**MPR**) : ≤ 10% residual viable tumor

Table S8. Pathological Response in Patients Who Underwent Resection.*

	Nivolumab plus Chemotherapy (N = 141)	Chemotherapy (N = 126)
	number of patients (percent) (95% CI)	
pCR†	43 (30.5) (23.0–38.8)	4 (3.2) (0.9–7.9)
MPR‡	66 (46.8) (38.4–55.4)	16 (12.7) (7.4–19.8)

* Patients who underwent definitive surgery with an evaluable pathology sample for blinded independent pathological review.
† Pathological complete response (pCR): 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes.
‡ Major pathological response (MPR): ≤10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes.





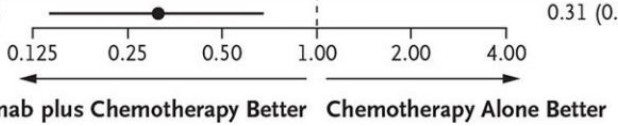
	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

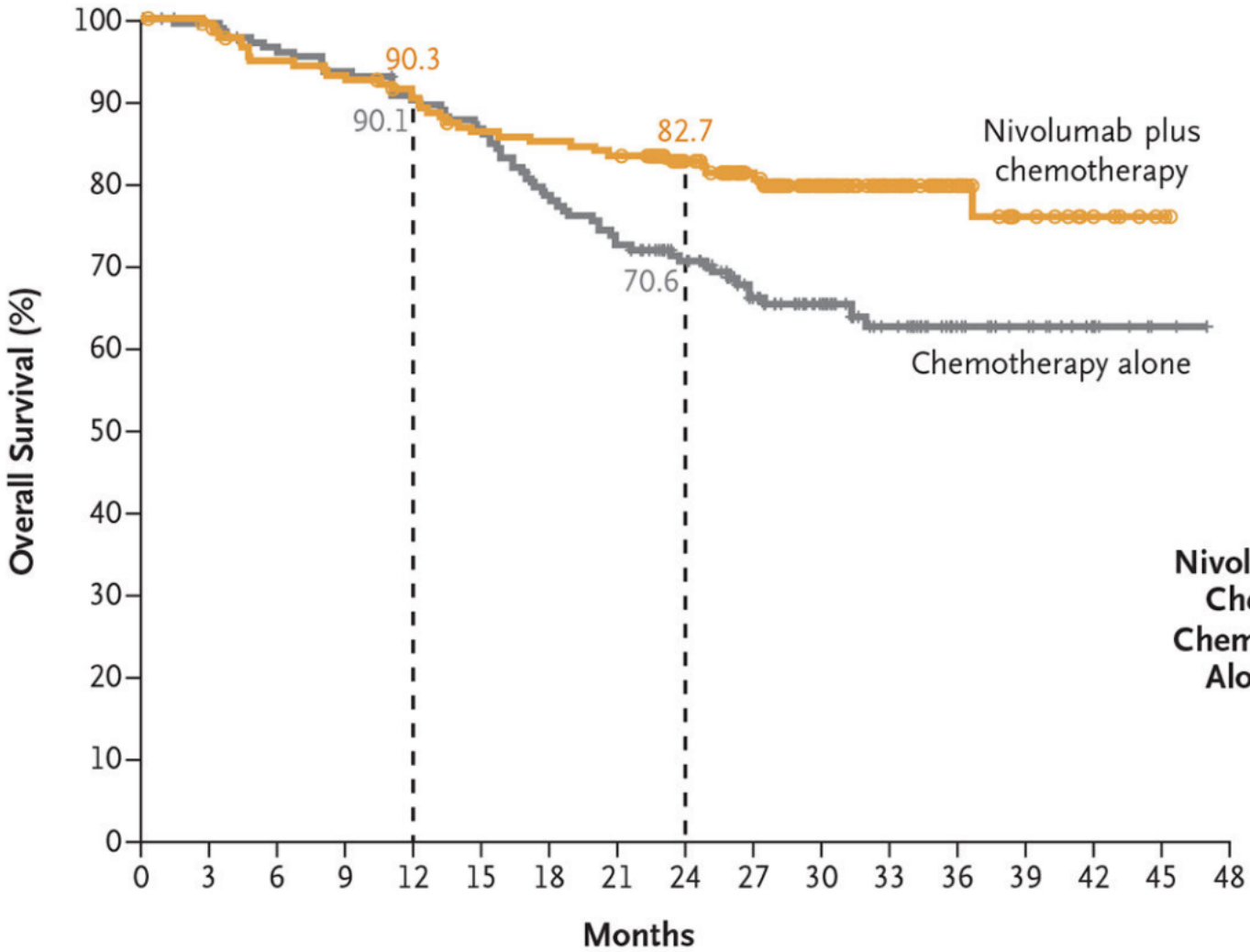
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

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

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)





	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

No. at Risk

Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

ICIs + CTx

94% completed neoadjuvant treatment

149 (83%) had definitive surgery

- 85% received definitive surgery in stage IB/II

- 83% received definitive surgery in stage IIIA

  ① 79% received Lobectomy in stage IIIA

  ② 17% received Pneumonectomy in stage IIIA

  ③ Minimal invasive -> open : 11% in IIIA

CTx

85% completed neoadjuvant treatment

135 (75%) had definitive surgery

- 82% received definitive surgery in stage IB/II

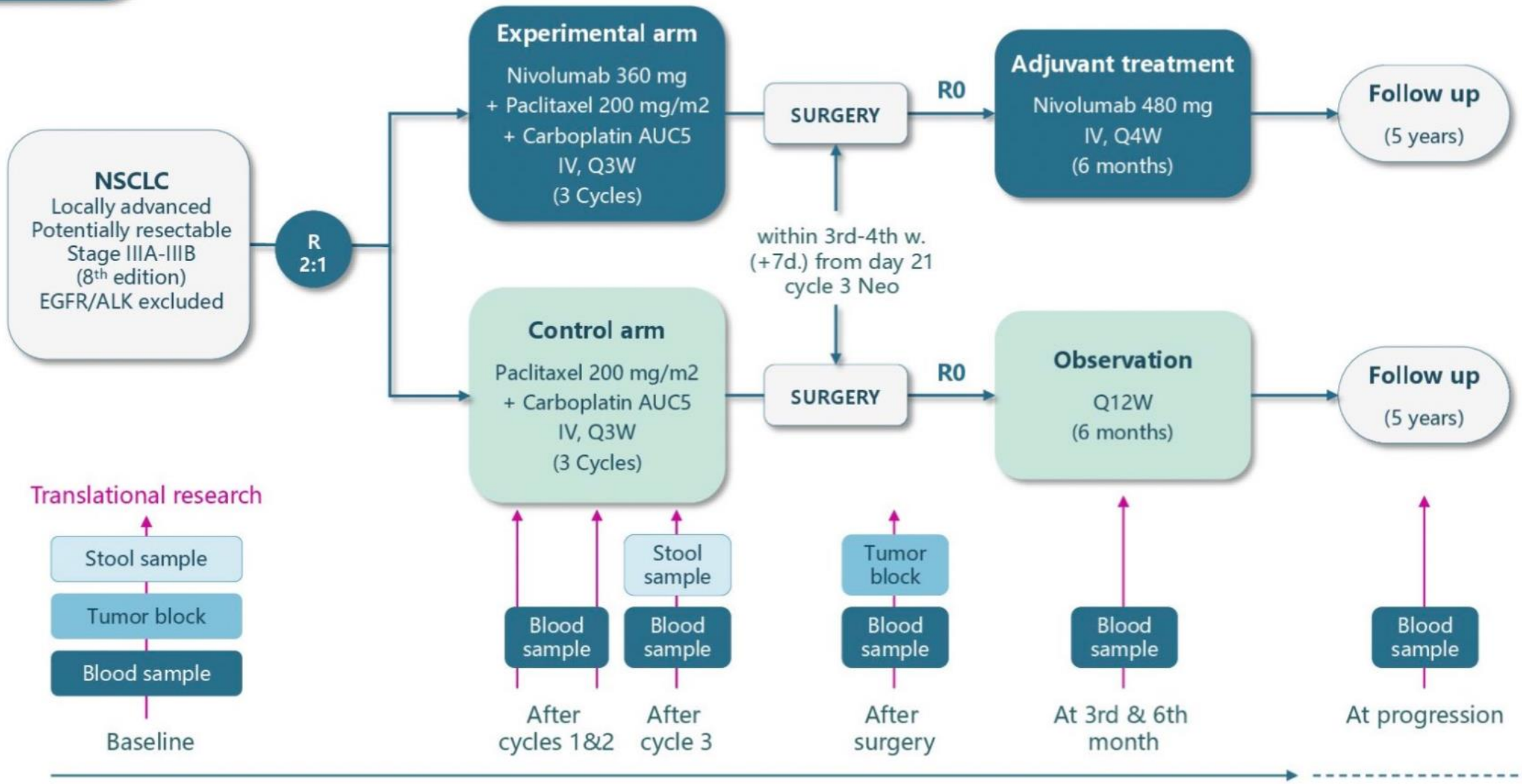
- 72% received definitive surgery in stage IIIA

  ① 59% received Lobectomy in stage IIIA

  ② 30% received Pneumonectomy in stage IIIA

  ③ Minimal invasive -> open : 20% in IIIA

NADIM II Study design



NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

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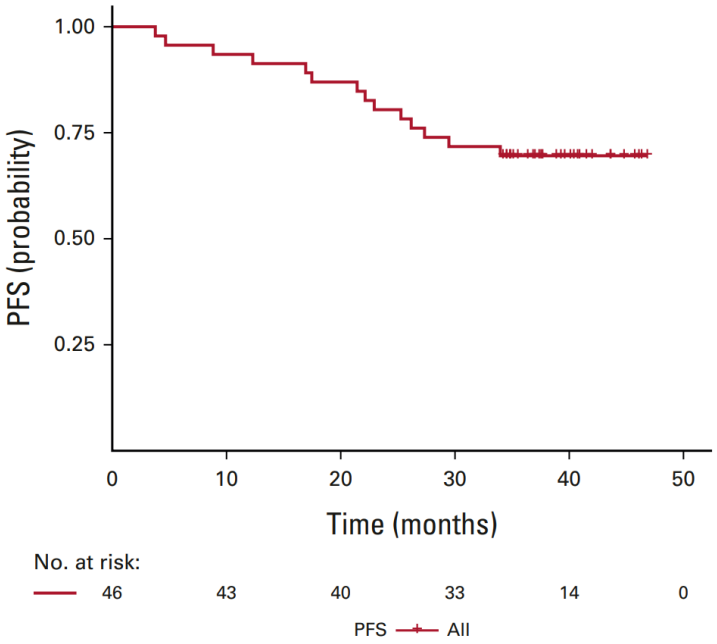

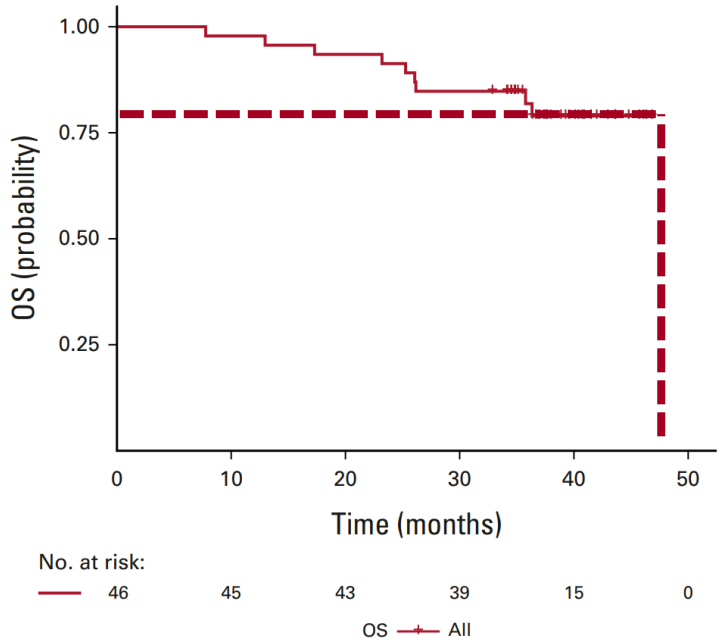

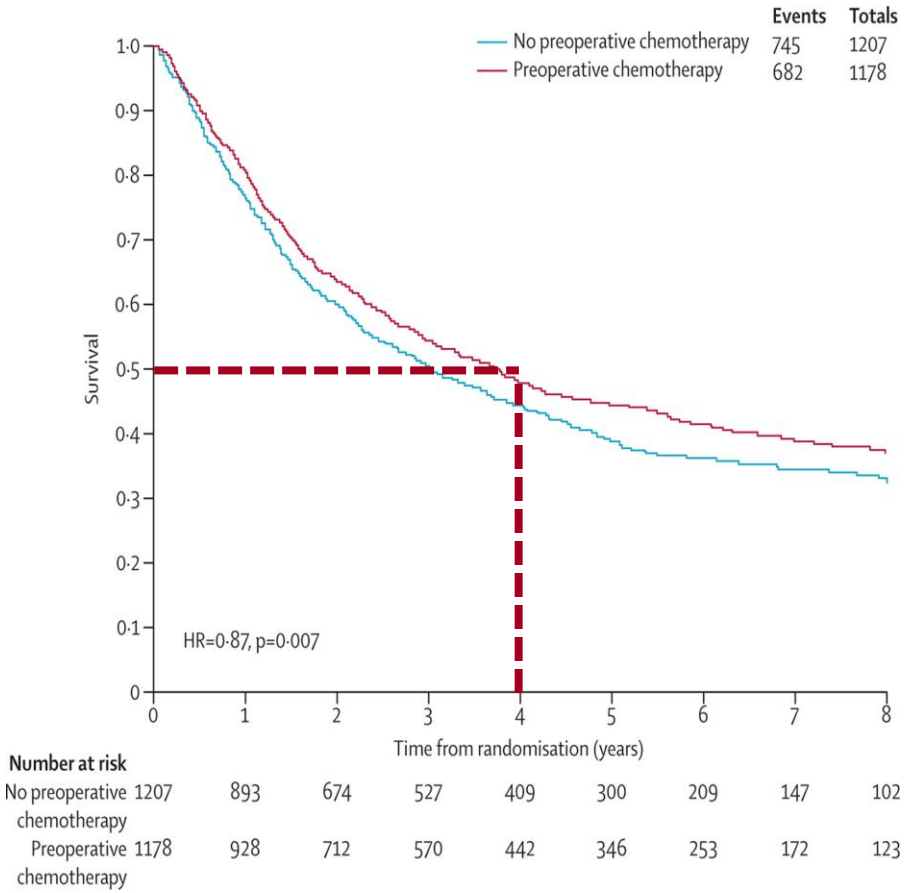

The Lancet 2014 3831561-1571DOI

- Pathologic complete response (**pCR**) : 0% residual viable tumor
- Major pathologic response (**MPR**) : ≤ 10% residual viable tumor

- NADIM II : pCR (63.4%), MPR (82.9%)
- Checkmate 816 : pCR (30.5%), MPR (46.8%)
- CTx alone : pCR (3.2%), MPR (12.7%)

Study	Stage	Patients numbers	*Regimens*	MPR (%)	pCR (%)	R0 resection (%)
NADIM (NCT03081689)	IIIA	41	Nivo + platinum doublet 3 cycles – Nivo (adj) 1year	83.0	63.0	89.1
CheckMate816 (NCT02998528)	IB to IIIA	179	Nivo + platinum doublet 3 cycles	36.9	24.0	83.2
KEYNOTE 671	II to IIIB	397	Pembro + cisplatin doublet 4cycles – Pem (adj) 13 cycles	30.2	18.1	92.0
LCMC3 (NCT02927301)	IB to IIIB	147	Atezo mono 2 cycles	20.4	6.8	82.3
NEOMUN (NCT03197467)	II to IIIA	15	Pembro mono 2cycles	27.0	13.0	100

Biomarker

- PD-L1 expression
  - NADIM II : The expression of PD-L1 in tumor cells was not associated with improved PFS or OS
  - Checkmate 816 : A benefit with nivolumab plus chemotherapy was seen across PD-L1 subgroups
  - Neostar : PD-L1 expression was not different between pretreatment biopsy and surgical resection
- TMB
  - NADIM II : TMB assessment was not associated with survival outcomes
- ctDNA (ctDNA clearance, ctDNA in pretreatment sample)

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	*P*[a]	HR (OS)[a]	95% CI[a]	*P*[a]
Basal ctDNA < 1%	43	9	12	0.20	0.06 to 0.63	.006	0.07	0.01 to 0.39	.002
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

감사합니다.