NEOADJUVANT vs ADJUVANT

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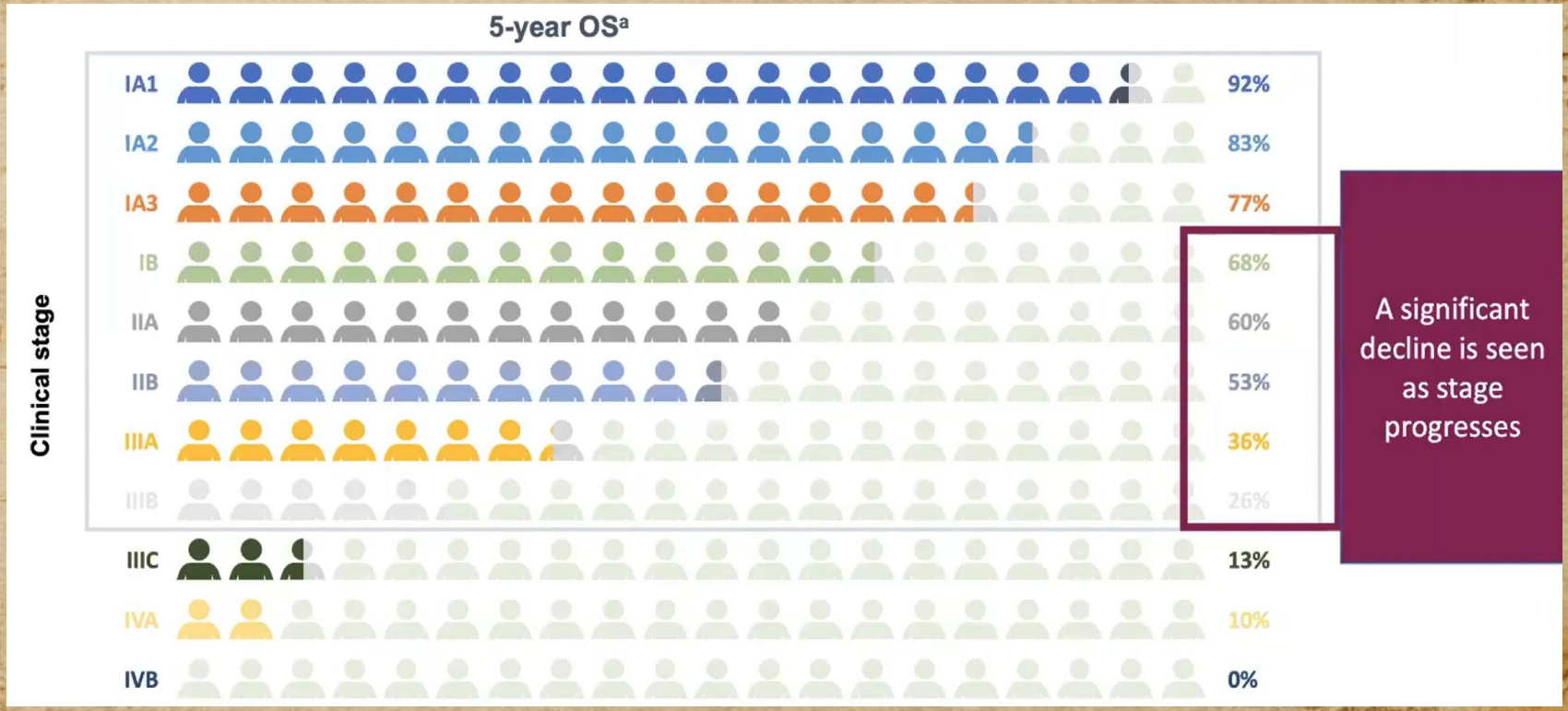
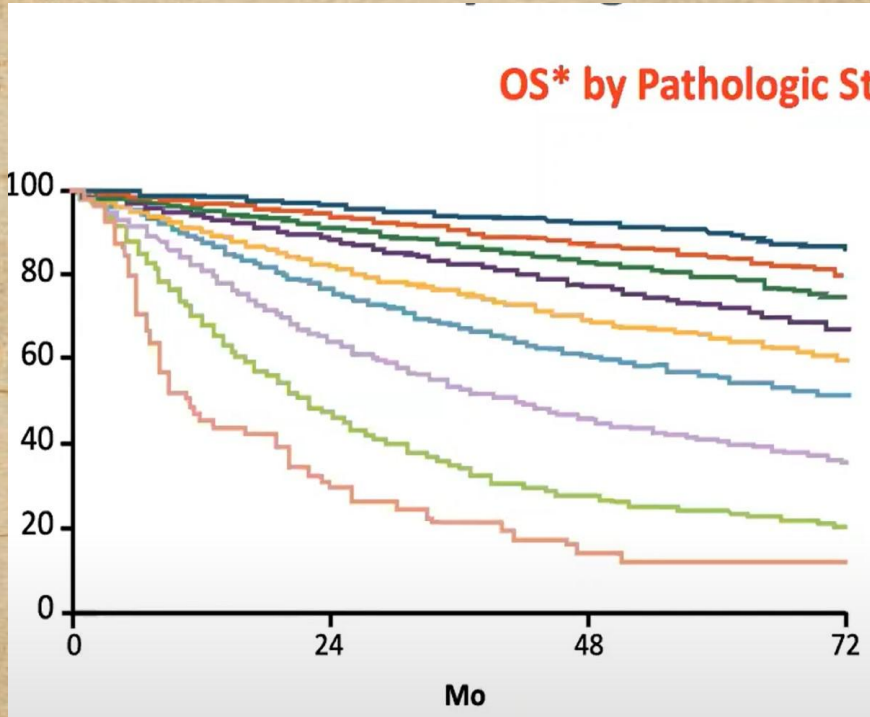
5 YEAR OS OUTCOMES DECREASE WITH INCREASE IN STAGE



Goldstraw P et al , J Thorac Oncol 2016

Outcomes in early NSCLC: room for improvement



Proposed	Events/N	mOS, Mo	24-Mo OS, %	60-Mo OS, %
IA1	139/1389	NR	97	90
IA2	823/5633	NR	94	85
IA3	875/4401	NR	92	80
IB	1618/6095	NR	89	73
IIA	556/1638	NR	82	65
IIB	2175/5226	NR	76	56
IIIA	3219/5756	41.9	65	41
IIIB	1215/1729	22.0	47	24
IIIC	55/69	11.0	30	12

Goldstraw et al, J Thorac Oncol 2016

Recurrence rate is high in early cancer patients

Inspite of Surgery and adjuvant chemotherapy, recurrence rate still remains high across all stages of early lung cancer

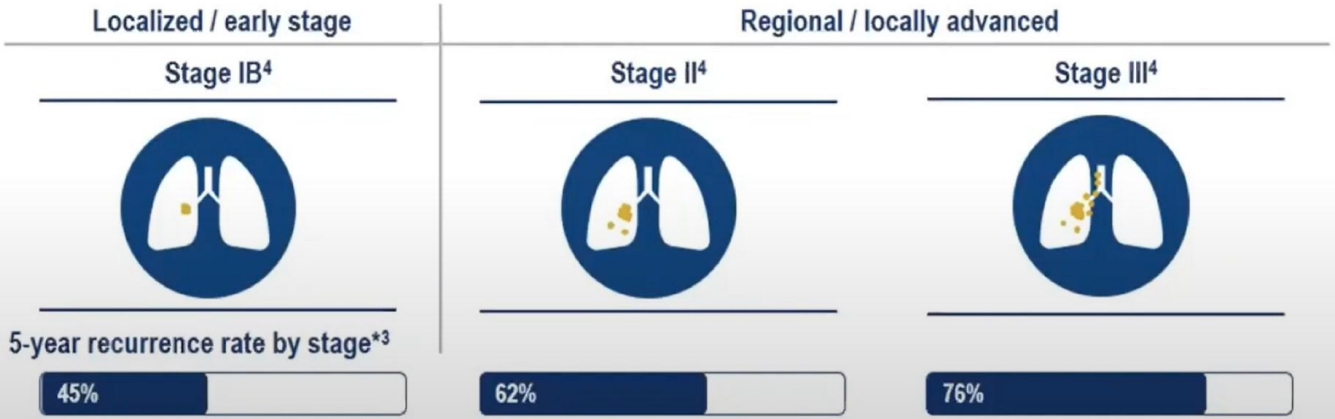


Table 1 Demographic and baseline characteristics of lung cancer patients

Variable	Sub-group	*n* (%)
Age (years) (*n*=1862)	≤45	256 (13.8)
	46-70	1410 (75.7)
	>70	196 (10.5)
Sex (*n*=1862)	Male	1544 (82.9)
	Female	318 (17.1)
Education level (*n*=1518)	Illiterate	416 (27.4)
	Primary level	415 (27.3)
	Secondary level (matric)	370 (24.4)
	Higher secondary	150 (9.9)
	Graduation	126 (8.3)
	Postgraduation	41 (2.7)
Smoking status (*n*=1788)	Never smoker	425 (23.8)
	Current smokers	697 (39)
	Reformed smokers	666 (37.2)
Smoking index (*n*=1136)	<100	95 (8.4)
	100-300	254 (22.4)
	301-600	385 (33.9)
	>600	402 (35.3)
Diagnostic modality (*n*=1772)	Flexible bronchoscopy	890 (50.2)
	CT/USG-guided FNAC/biopsy (lung)	577 (32.6)
	Thoracoentesis	95 (5.4)
	Thoracoscopic Pleural biopsy	19 (1.1)
	Peripheral lymph node sampling	100 (5.6)
	EBUS	47 (2.7)
	Lung biopsy (surgical)	6 (0.3)
	Others	38 (2.1)
Predominant lobe involved (*n*=1467)	Upper lobe	792 (51.3)
	Right middle lobe/lingula	112 (7.7)
	Lower lobe	326 (22.2)
	Others	277 (18.8)
Pathological type (*n*=1862)	ADC	634 (34.0)
	SCC	532 (28.6)
	NCSLC (NOS)	338 (18.1)
	Small cell carcinoma (SCLC)	300 ([illegible])
	Others	[illegible] (3.2)
NSCLC stage TNM staging 7th ed. (before 1st January, 2017)	Stage 1	14 (1.2)
	Stage 2	44 (3.8)
	Stage 3	337 (29.1)
	Stage 4	766 (65.9)

CT: Computed tomography, USG: Ultrasound, FNAC: Fine-needle aspiration cytology, EBUS: Endobronchial ultrasound, ECOG: Eastern cooperative oncology [illegible]roup, KPS: Karnofsky Performance Status Scale, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small [illegible] cancer, NSCLC: Non-SCLC, TNM: Tumor node metastasis, NOS: Not otherwise specified

Mohan et al, Lung India 2020

TNM stage (%)	STAGE I /II	14.6	13.7
	STAGE III	42.8	42.4
	STAGE IV	32.2	36.8

Noronha et al, 2012 TMH-Mumbai

TNM stage	
I and II	46 (3.5)
IIIA	170 (13.1)
IIIB	392 (30.1)
IV	693 (53.3)

Kaur et al, 2017 PGIMER-Chandigarh

Stage III NSCLC: A Heterogeneous Group

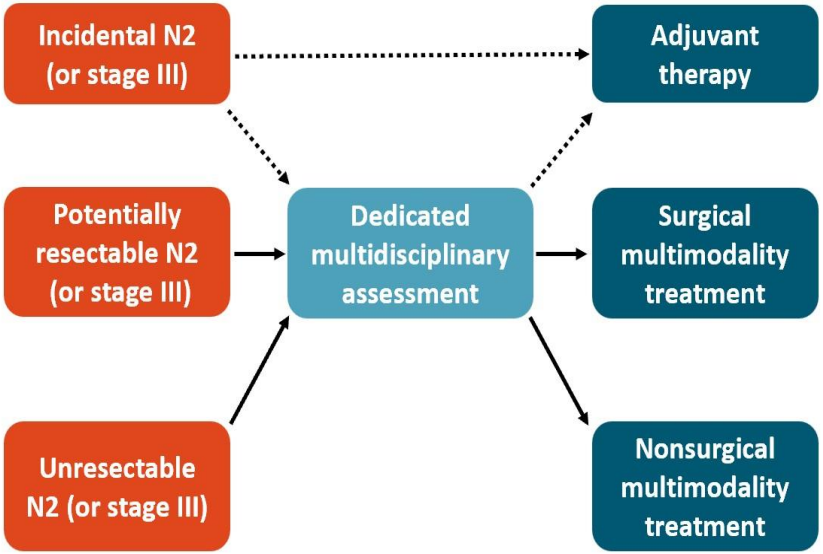
8th Edition AJCC/UICC Stage

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

OS by Pathologic Stage

Stage	mOS, Mo	2-yr OS, %	5-yr OS, %
IIIA	41.9	65	41
IIIB	22.0	47	24
IIIC	11.0	30	12

Approach to Treatment Decisions for Stage III NSCLC



Considerations for Timing of Treatment Options for Early-Stage NSCLC

Neoadjuvant

- Provides earliest opportunity to eradicate micrometastatic disease[1]
- Increased treatment initiation rate and compliance[2]
- Pathologic response provides early indicator of response to therapy and can guide future treatment decisions[3]

Adjuvant

- Allows the fastest time to surgery[4]
- No risk of presurgery complications from systemic therapy[4]
- Enables longer treatment duration for systemic control[5]
- More flexible timing postsurgery provides more recovery time for patients[6]

1. Lewis. Front Oncol. 2018;8:5. 2. Felip. JCO. 2010;28:3138. 3. Hellmann. Lancet Oncol. 2014;15:e42. 4. McElnay. J Thorac Dis. 2014;6 Suppl 2:S224. 5. Yuan. Signal Transduct Target Ther. 2019;4:61. 6. Owen. J Thorac Dis. 2018;10(suppl 3):S404.

- An increased percentage of patients completing the planned dose of chemotherapy.

  vs. op alone –how about planned surgery? / vs. adj tx - Yes

- The ability to treat micrometastatic tumor cell dissemination preoperatively.

  vs. op alone – Yes / vs. adj tx – Yes but why not postoperatively?

- The ability to evaluate the response to the chemotherapy as a prognostic indicator.

  vs. op alone – Yes / vs. adj tx – Yes

- Increased resectability due to tumor regression.

  vs. op alone – probably No / vs. adj tx – not applicable

Wantanabe et al, JCO 2017

NATCH TRIAL

VOLUME 28 · NUMBER 19 · JULY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

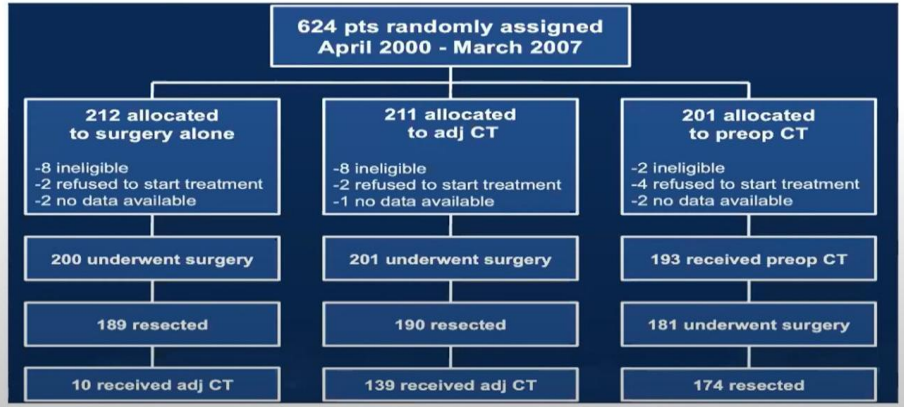
Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non–Small-Cell Lung Cancer

Enriqueta Felip, Rafael Rosell, José Antonio Maestre, José Manuel Rodríguez-Paniagua, Teresa Morán, Julio Astudillo, Guillermo Alonso, José Manuel Borro, José Luis González-Larriba, Antonio Torres, Carlos Camps, Ricardo Guijarro, Dolores Isla, Rafael Aguiló, Vicente Alberola, José Padilla, Abel Sánchez-Palencia, José Javier Sánchez, Eduardo Hermosilla, and Bartomeu Massuti

From the Vall d'Hebron University Hospital; Catalan Institute of Oncology and

Adjuvant *vs* neoadjuvant immunotherapy in early-stage NSCLC: Pathologic *vs* clinical staging

NATCH trial



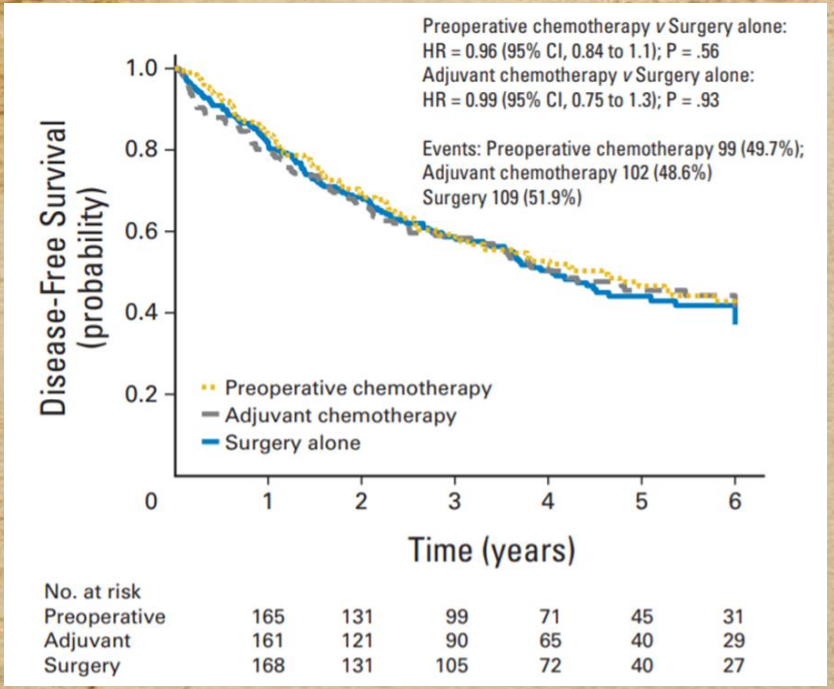
Clinical Stage at Baseline

Clinical stage	Surgery alone (N=210)	Adj CT (N=210)	Preop CT (N=199)
Stage I	154 (73%)	163 (77%)	148 (74%)
T1N0	20 (10%)	30 (14%)	16 (8%)
T2N0	134 (64%)	133 (63%)	132 (66%)
Stage II	52 (25%)	46 (22%)	46 (23%)
T1N1	1 (0.5%)	3 (1%)	4 (2%)
T2N1	25 (12%)	25 (12%)	24 (12%)
T3N0	26 (12%)	18 (9%)	18 (9%)
Stage III	4 (2%)	1 (0.5%)	5 (3%)
T3N1	4 (2%)	1 (0.5%)	4 (2%)
T4N0*	-	-	1 (0.5%)

Pathologic Stages at Surgery

	Surgery (N=200)	Adj CT (N=201)	Preop CT (N=181)
p-CR	-	-	19 (10%)
p-stage I	96 (48%)	105 (52%)	89 (49%)
p-stage II	43 (21%)	45 (22%)	37 (20%)
p-stage T3N1	3 (1.5%)	5 (3%)	1 (0.5%)
p-stage ≥IIIAN2	58 (29%)	46 (23%)	35 (19%)

Felip ASCO 09, JCO 10

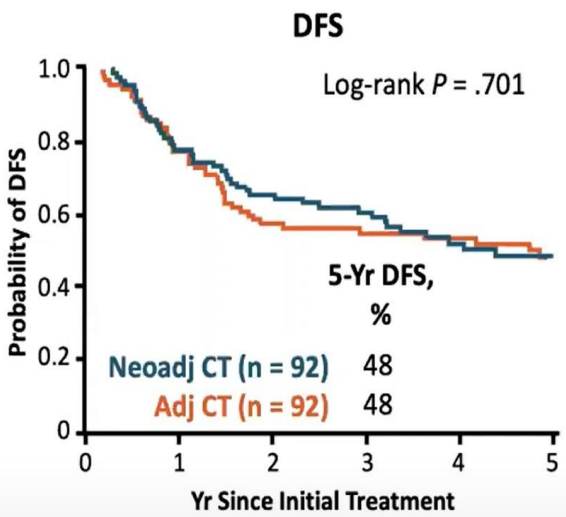


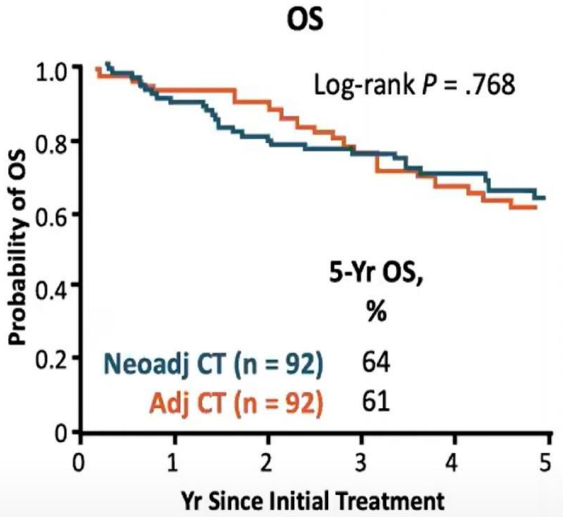
- Patients in the preoperative arm had a nonsignificant trend toward longer disease-free survival than those assigned to surgery alone (5-year disease-free survival 38.3% v 34.1%; hazard ratio [HR] for progression or death, 0.92; P .176)
- Five-year disease-free survival rates were 36.6% in the adjuvant arm versus 34.1% in the surgery arm (HR 0.96; P .74)

- However, more patients were able to receive preoperative than adjuvant treatment.

NeoAdj vs Adj cT2-4N0-1M0 NSCLC

- Retrospective propensity-matched analysis of outcomes with neoadjuvant vs adjuvant chemotherapy for cT2-4N0-1M0 NSCLC with R0 resection (N = 330)





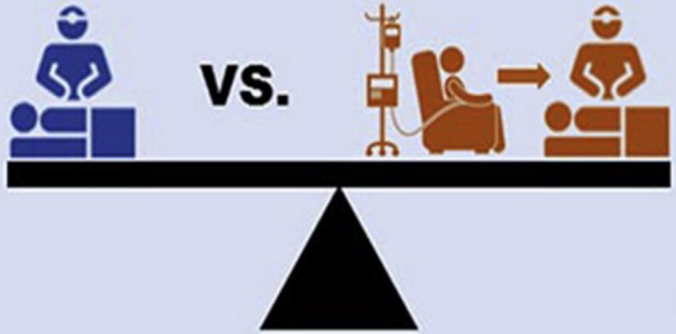
Chemotherapy Tolerance, n (%)	Neoadjuvant (n = 92; 50%)	Adjuvant (n = 92; 50%)	*P* Value
Received full dose of chemotherapy	72 (78)	58 (63)	.014
Received all cycles of chemotherapy	84 (91)	72 (78)	.005
Grade ≥3 AE to chemotherapy	14 (15)	35 (38)	.001

Brandt et al, J Thorac Cardiovasc Surg 2019

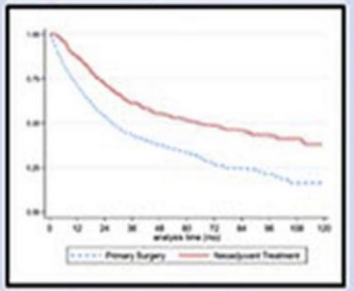
Neoadjuvant treatment is associated with superior outcomes in T4 lung cancers with local extension

It is unclear if patients with clinical T4 lung cancers with local invasion benefit from neoadjuvant treatment prior to surgery

We performed a propensity matched analysis of patients with $cT4_{inv}$ undergoing surgery with vs without neoadjuvant treatment



10.5%
vs
31.3%



Patients who received neoadjuvant treatment had lower rates of positive margin and better overall survival

THE ANNALS OF THORACIC SURGERY
Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

Towe et al

@annalsthorsurg #TSSMN
#VisualAbstract #AnnalsImages

Randomized Trial of Multimodal Prehabilitation for Lung Cancer Surgery

Patient-Reported Outcomes, n (%)	Prehabilitation (n = 52)	Rehabilitation (n = 43)	P Value
SF-36 Mental Summary			
▪ Baseline	72.7 (17.6)	66.8 (22.8)	.18
▪ Preoperative	74.8 (16.4)	68.8 (21.3)	.15
▪ 4 wk after surgery	66.9 (15.2)	60.5 (14.5)	.052
▪ 8 wk after surgery	71.3 (16.9)	70.1 (18.1)	.76
SF-36 Physical Summary			
▪ Baseline	70.3 (16.3)	67.2 (21)	.44
▪ Preoperative	73.7 (17.5)	69.6 (19.8)	.3
▪ 4 wk after surgery	56.6 (13.7)	48.1 (14.3)	.006
▪ 8 wk after surgery	69.3 (15.4)	61.9 (16.3)	.034
SF-36 Total			
▪ Baseline	73 (16.6)	68.1 (22.4)	.26
▪ Preoperative	75.5 (16.6)	70.3 (21.1)	.2
▪ 4 wk after surgery	60.9 (14.5)	53.7 (13.8)	.022
▪ 8 wk after surgery	70.4 (16.4)	66.3 (15.2)	.24

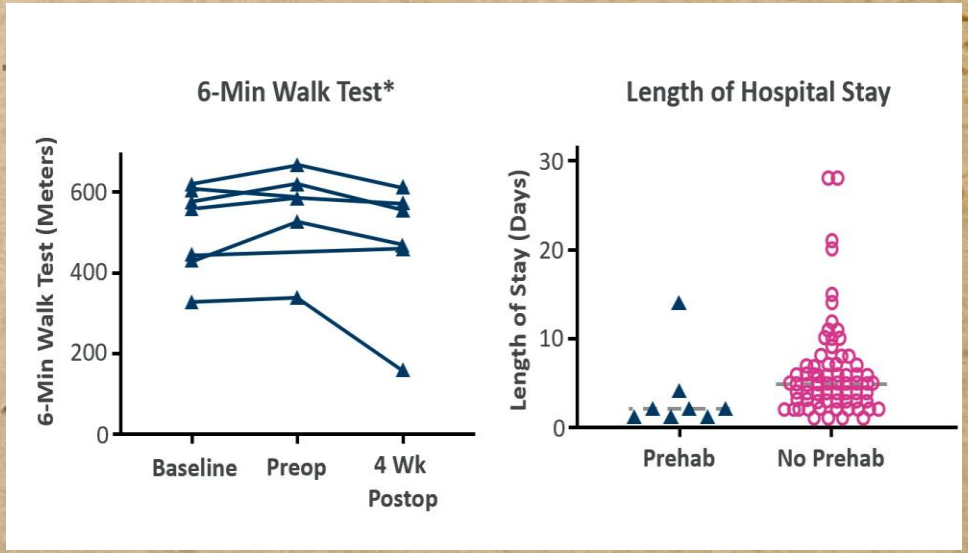
Postoperative Clinical Outcomes	Prehabilitation (n = 52)	Rehabilitation (n = 43)	*P* Value
Median length of hospital stay, days (IQR)	4 (2-5.75)	4 (3-5)	.27
Discharge day, n (%)			
• Postoperative Day 1-2	22 (42)	7 (16)	.0069
• Postoperative Day 3-4	12 (40)	22 (61)	.005
• Postoperative Day 5+	18 (100)	14 (100)	.84
ED visits in 30 days, n (%)	7 (14)	9 (21)	.33
Readmissions in 30 days, n (%)	4 (8)	6 (14)	.32
Death, n (%)	2 (4)	0 (0)	.19
Clavien grade, n (%)			
• 0	25 (48)	17 (40)	
• I	13 (25)	12 (28)	
• II	9 (17)	9 (21)	
• IIIa	2 (4)	3 (7)	
• IIIb	1 (2)	2 (5)	
• V	2 (4)	0 (0)	.66
Median Comprehensive Comorbidity Index (IQR)	8.7 (0-20.9)	8.7 (0-20.9)	.39

- Multimodal prehabilitation initiated 4 wk prior to surgery effective in recovering functional capacity in patients undergoing surgical resection

Ferreira. Ann Thorac Surg. 2020;112:1600.

Optimizing Outcomes for Locally Advanced NSCLC Using Neoadjuvant Prehabilitation Therapy

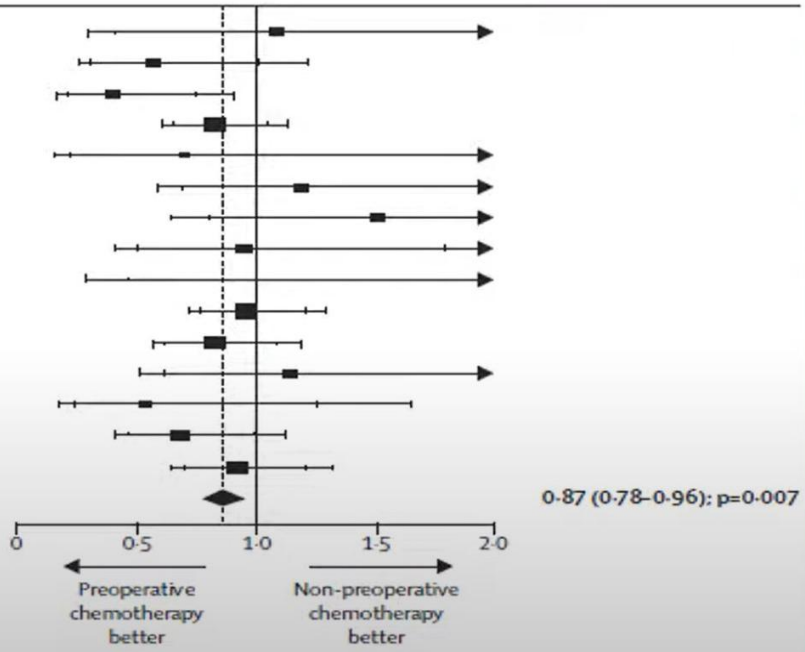
- Retrospective analysis of patients with NSCLC receiving neoadjuvant therapy followed by curative-intent surgery at McGill University Health Center (2015-2020; N = 93)
  - 12 patients screened for prehabilitation program, including physical performance assessment, nutritional status, signs for anxiety/depression
  - 9 patients completed full neoadjuvant rehabilitation program



Schmid. ASCO 2021. Abstr e20545.

Meta-analysis on neoadjuvant chemotherapy

	Preoperative chemotherapy*	Control*	O–E	Variance
France 1990	8/13	8/13	0·32	3·97
MD Anderson 1994	19/28	27/32	−6·40	11·19
Spain 1994	19/29	27/30	−8·88	9·65
MIP-91	137/179	146/176	−12·99	70·22
SWOG S9015	3/5	12/16	−1·04	2·94
JCOG 9209	28/31	25/31	2·25	12·97
Netherlands 2000	23/39	15/40	3·86	9·36
Finland 2003	19/30	19/32	−0·50	9·48
MRC BLT	4/5	3/5	1·26	1·60
MRC LU22	151/258	158/261	−2·92	77·01
SWOG S9900	93/180	103/174	−9·31	48·84
China 2002	26/32	18/23	1·42	10·78
China 2005	8/19	14/21	−3·31	5·44
ChEST	45/129	61/141	−10·27	26·39
NATCH	99/201	109/212	−4·11	51·95
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**



Overall HR
0·87 (0·78–0·96), p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

Lancet 2014

OTHER STUDIES

	No	Limitations	Outcomes
Nagai et al. (JTCVS 2003)	62	Early closure	No difference
Mattson (Ann Oncol 2003)	274	Definitive RT was included	Not presented
Waller (EJCTS 2004)	381	3% neoadjuvant, 97% adjuvant	No difference
Pister (JCO 2010)	354	Early closure	No difference
Scagliotti (JCO 2012)	270	Early closure	Difference in PFS
Felip (JCO 2010)	624	Stage I and II (surgery only vs. neoadjuvant vs. adjuvant)	No difference
deBoer (BJS 1999)	22	Small number / early stage	Not presented

Features of the study

- Individual data meta-analysis
- 15 RCTS
- 2385 patients
- Comprehensive subgroup analysis

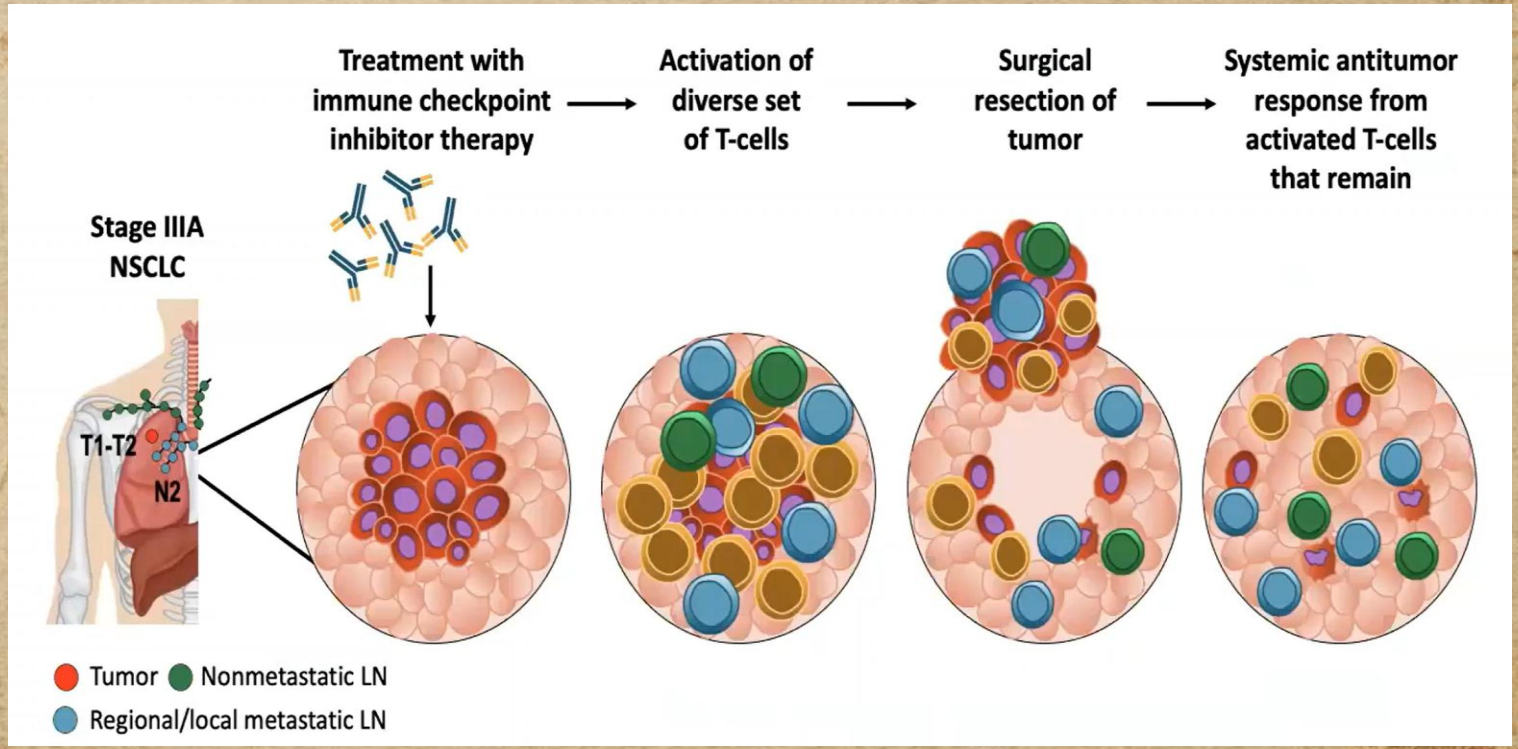
Outcomes

- 5% survival benefit at 5 years
- No difference in chemotherapy (regimen, cycles, or pre- vs. post)
- Preoperative chemotherapy was beneficial in distant metastasis, however interaction effect was greater in postoperative chemotherapy
- Preoperative chemotherapy did not affect complete resection

Limitations

- Inclusion of unpublished data (one from Netherland, two from China)
- Inclusion of inadequate studies
- Squamous cell dominant (50%) and small number of IIIA patients (23%)

Rationale for neoadjuvant immunotherapy



Versluis Nat Med 2020

Arguments for Neoadjuvant ICI followed by resection

Higher antigen load and release from dying cells in untreated tumors

- ✓ Better priming of immune system

Fit host immune system

No significant clonal evolution

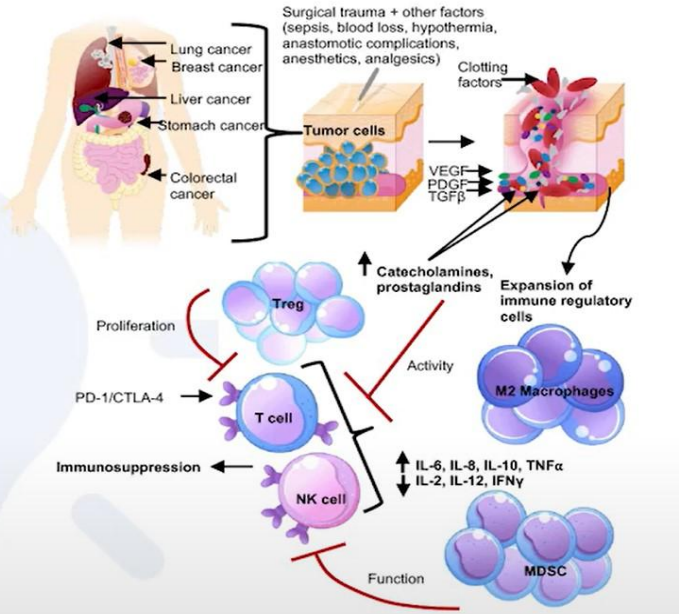
- ✓ Tumor less heterogeneous

Opportunity to accurately study the effects of IO

- ✓ Access to pre and post tissue

Ability to assess efficacy of the therapy

Shorten timeframe to completion of trials (early surrogate for survival?)

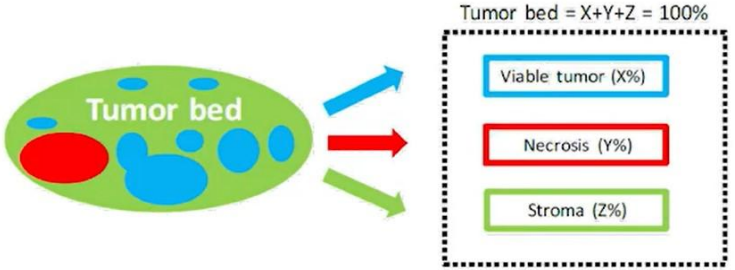


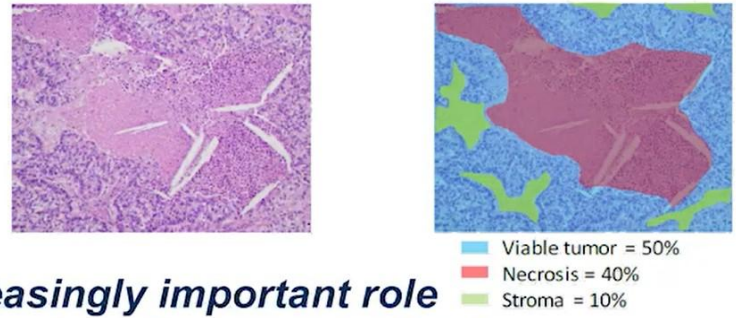
Bakos et al, J Immunother Cancer 2018

IASLC Guidance for pathological assessment of lung cancer specimens following NAT

- **Pathologic complete response (pCR): no viable tumor cells**
- **Major pathologic response (MPR): ≤10% viable tumor cells**

- Used for all systemic therapies, **including immunotherapy**, whether administered alone or in combination in the neoadjuvant setting

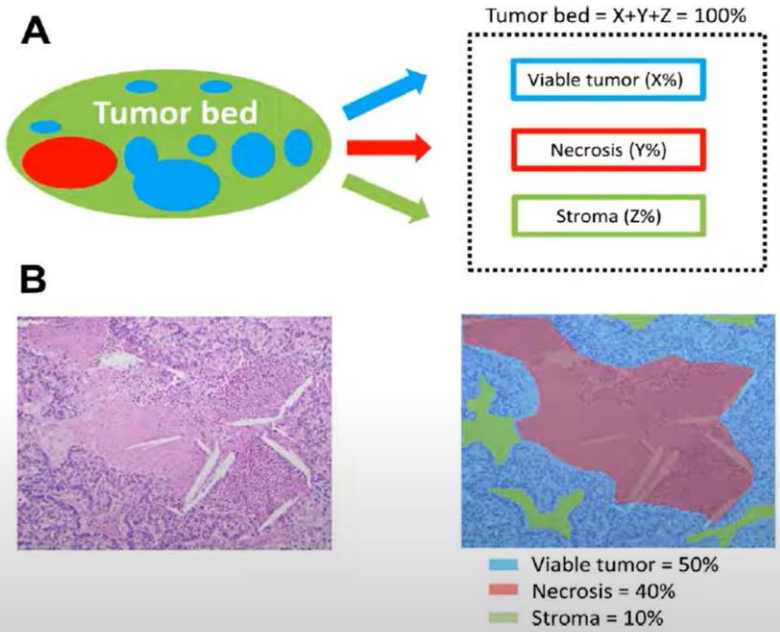


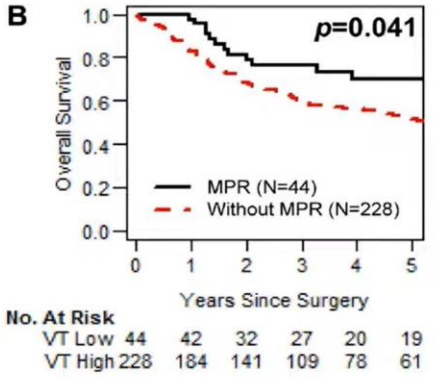


Pathologists will play an increasingly important role in collaborating with surgeons and medical oncologists!

Travis WD et al, J Thorac Oncol 2020

Major pathological response





MPR after neoadjuvant chemotherapy	
Squamous cell carcinoma	26%
Adenocarcinoma	12%

*MPR: ≤ 10% viable tumor

J Thorac Oncol, 2019

PDL-1 BLOCKADE AS INDUCTION IN NSCLC

Study	N	Stages	Neoadjuvant Regimen	All Stages, %			
				MPR	pCR	ORR	Resected
Forde et al[1]	21	I-IIIA	Nivolumab x 2	45*¶	15*	10	95
LCMC3[2,3]	181	IB-IIIB	Atezolizumab x 2	21†	7†	7	88
NEOSTAR[4,5]							
▪ Arm A	23	I-IIIA	Nivolumab x 3	22‡	10‡	22	96
▪ Arm B	21		Nivolumab/Ipilimumab x 3	38	38	19	81
MK3475-223[6]	15	I-II	Pembrolizumab x 1-2	31*	15*	NR	87
Li et al[7]	40	IA-IIIB	Sintilimab x 2	40.5*	16.2*	20	93
NADIM[8]	46	IIIA	Nivo + carbo/pac x 3	83*	63*	76	89
Shu et al[9]	30	IB-IIIA	Atezo + carbo/nab-pac x 2-4§	57‡	33‡‖	63	87
SAKK 16/14[10]	68	IIIA	Cis/doc x 3, then durvalumab x 2	62*	18*	58	81

*Calculated from patients who had complete surgical resection. ¶Stage IIIA MPR: 2/9 (22%). †Calculated from patients in efficacy population who had intended surgery and MPR assessment. ‡ITT. §Patients without PD after 2 cycles received 2 additional cycles. ‖6/10 patients with pCR had stage IIIA disease. Caution should be used with cross trial comparisons.

1. Forde. NEJM. 2018;378:1976. 2. Kwiatkowski. ASCO 2019. Abstr 8503. 3. Lee. WCLC 2020. Abstr PS01.05. 4. Cascone. ASCO 2019. Abstr 8504. 5. Cascone. Nat Med. 2021;504. 6. Bar. ASCO 2019. Abstr 8534. 7. Li. JTO. 2020;15:816. 8. Provencio. Lancet Oncol. 2020;21:1413. 9. Shu. Lancet Oncol. 2020;21:786. 10. Rothschild. JCO. 2021;39:2872.

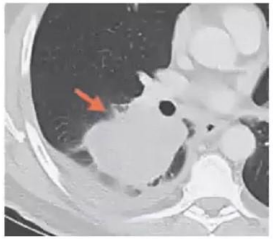
Selected phase 3 neoadjuvant chemotherapy + anti PDL-1 studies

Trial Identifier and Status	Study Title (Planned Accrual)	Stage (Edition)	Backbone	Intervention	Adjuvant Immunotherapy Treatment	Primary Endpoints
NCT02998528 Completed accrual Q4 2019	CheckMate -816 N = 360	IB-IIIA (7th)	3 cycles of cisplatin or carboplatin + vinorelbine/pemetrexed/docetaxel/paclitaxel	± Nivolumab (nivolumab + ipilimumab closed)	No	EFS pCR
NCT03425643 Accrual ongoing	KEYNOTE-671 N = 786	IIA-IIIB (8th)	4 cycles of cisplatin + pemetrexed or gemcitabine	Pembrolizumab or placebo	13 x 3-wk cycles of pembrolizumab/placebo	EFS OS
NCT03456063 Accrual ongoing	IMpower030 N = 450	II-IIIB (8th)	4 cycles of cisplatin/carboplatin + nab-paclitaxel/pemetrexed/gemcitabine	Atezolizumab or placebo	16 x 3-wk cycles of atezolizumab or BSC	EFS
NCT03800134 Accrual ongoing	AEGEAN N = 800	IIA-IIIB (8th)	3-4 cycles of cisplatin + gemcitabine or carboplatin + paclitaxel or pemetrexed + cisplatin or pemetrexed + carboplatin	Durvalumab or placebo	Adjuvant durvalumab or placebo	pCR EFS
NCT04025879 Accrual ongoing	CA209-77T N = 452	II-IIIB (8th)	3-4 cycles of cisplatin/carboplatin + pemetrexed/docetaxel or paclitaxel	Nivolumab or placebo	Adjuvant nivolumab or placebo	EFS

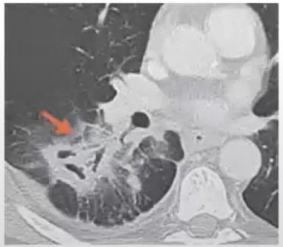
PD L1 Blockade as Preoperative Therapy

- Pilot study of 2 preoperative nivolumab doses in untreated, resectable stage I-IIIA NSCLC (n = 21)

Chest CT: Patient With Stage IIB sqNSCLC

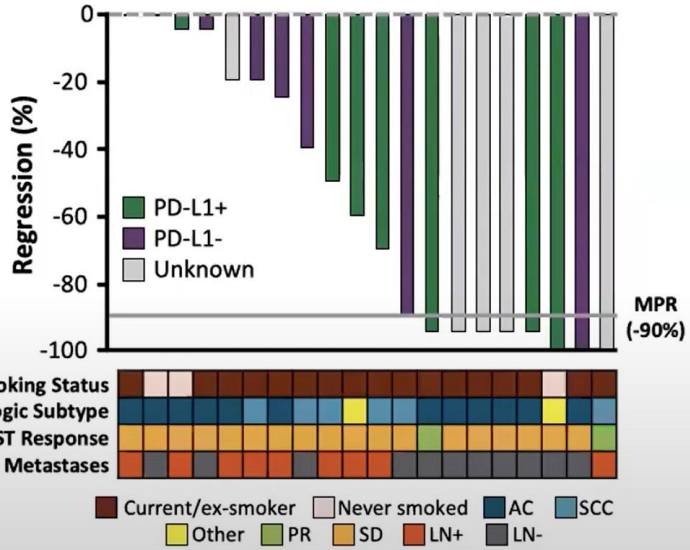


Before Nivolumab

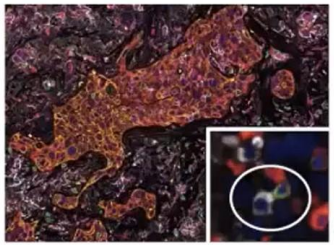


Wk 4 (Before Surgery)

Pathological Regression in Resected Primary Tumor by Subgroup (n = 20)



Multiplex Immunofluorescence*



Biopsy Before Nivolumab

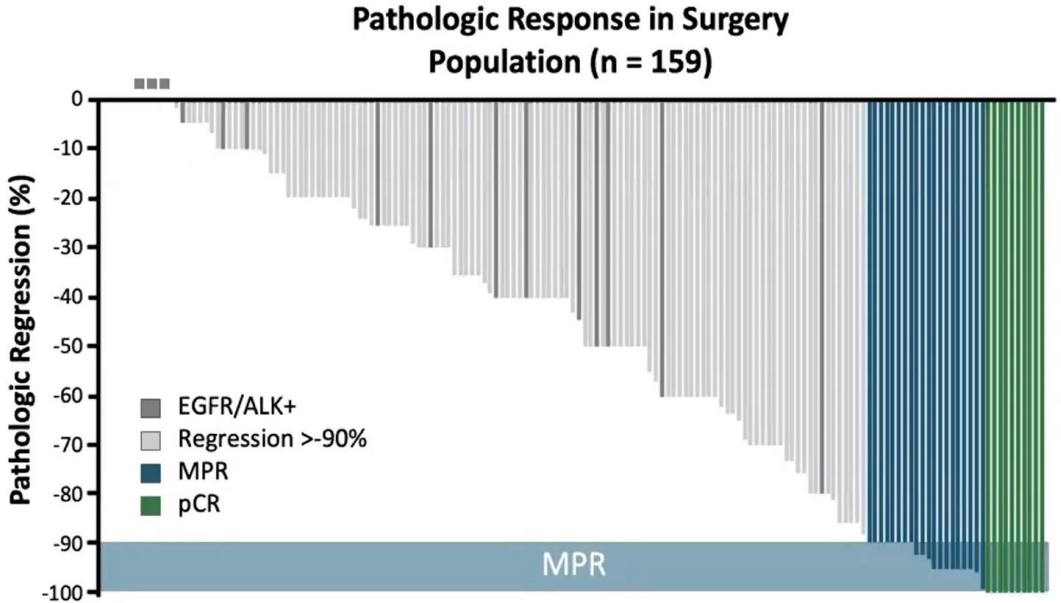
Biopsy After Nivolumab

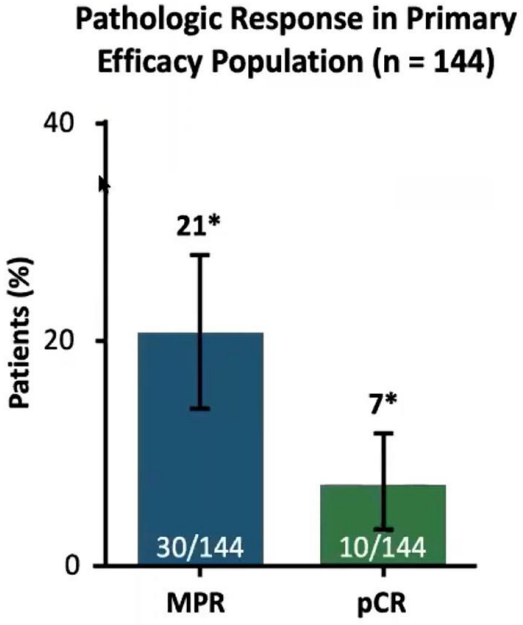
Cytokeratin+ tumor cells (orange), CD68+ macrophages (magenta), FoxP3+ regulatory T cells (yellow), CD8+ T cells (green), PD-1+ cells (red), and PD-L1+ cells (white).

Forde et al NEJM 2018

LCMC3-NEOADJUVANT ATEZOLIZUMAB IN RESECTABLE NSCLC

- Phase II study of 2 preoperative atezolizumab doses in untreated, resectable stage IB-IIIB NSCLC (N = 181)

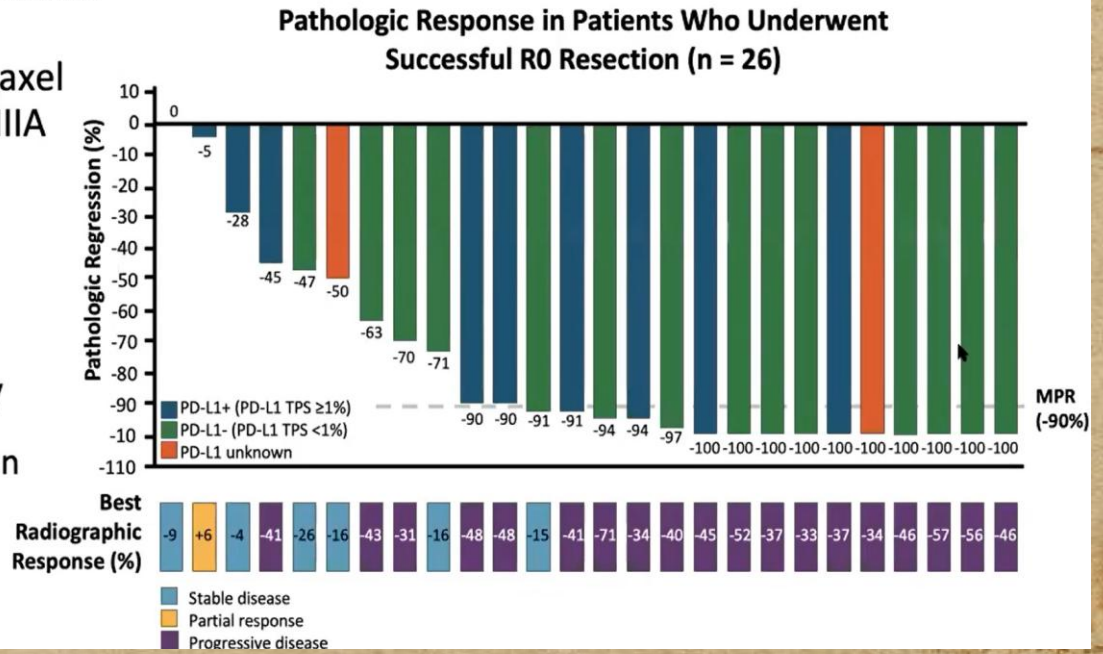




Lee WCLC 2020

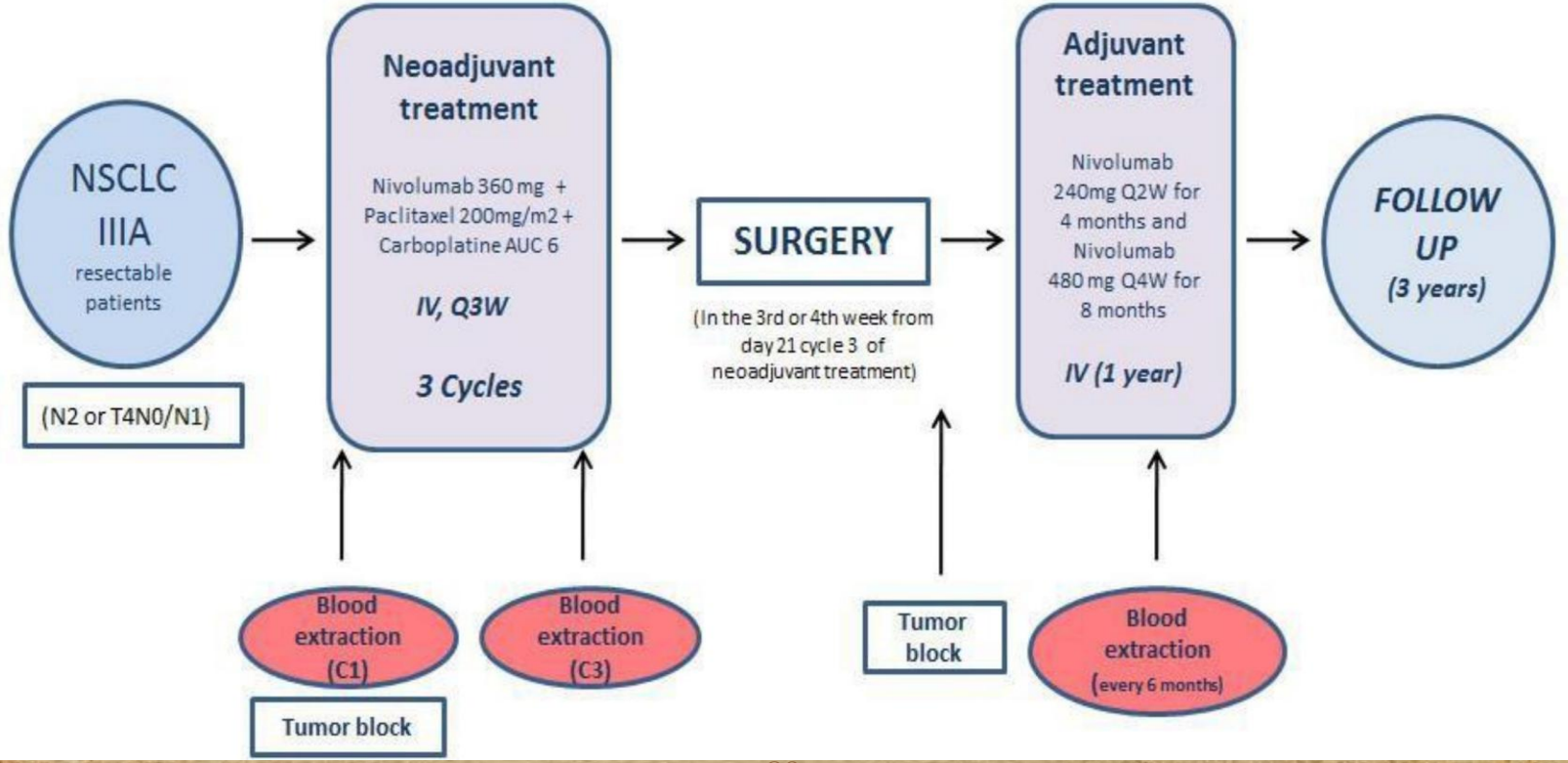
ATEZOLIZUMAB+CT IN EARLY STAGE RESECTABLE NSCLC

- Phase II trial of preoperative atezolizumab with carboplatin/nab-paclitaxel in resectable stage IB-IIIA NSCLC (N = 30)
  - Stage IIIA: 77%
- Outcomes
  - 97% taken to surgery
  - 87% with R0 resection
  - 57% achieved MPR



Shu et al, Lancet 2020

NADIM: Study design & Flow-chart



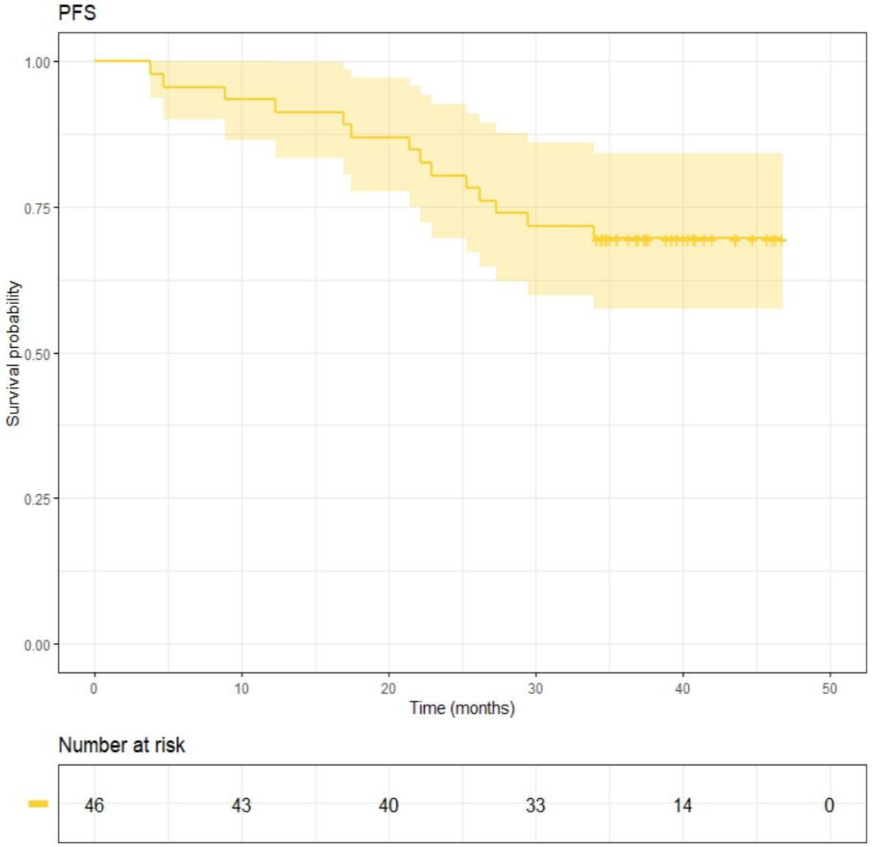
STUDY OBJECTIVES

- **The primary endpoint was**
  - ✓ **Progression-free survival (PFS) at 24 months: 77.1% (95% CI 59.9-87.7) with median duration o follow-up was 24.0 mo (IQR 21.4-28.1) (ITT population)**

- **Secondary endpoints were**
  - ✓ **Down-staging rate: 90% , Complete resection rate: 89% and ORR RECIST 1.1: 76% ORR**
  - ✓ **Pathological response: MPR: 82.9%, CPR: 63%**
  - ✓ **Safety and tolerability profile: 30% (14) had adverse event of grade 3 or worse**
  - ✓ **Surgical outcome and operative and post-operative complications: 29% . No post-surgery mortality**
  - ✓ **To explore the expression of biomarkers and relation with response and survival: PDL1 and TMB**

- **Overall Survival at 3 years**

RESULTS: PFS



ITT population:

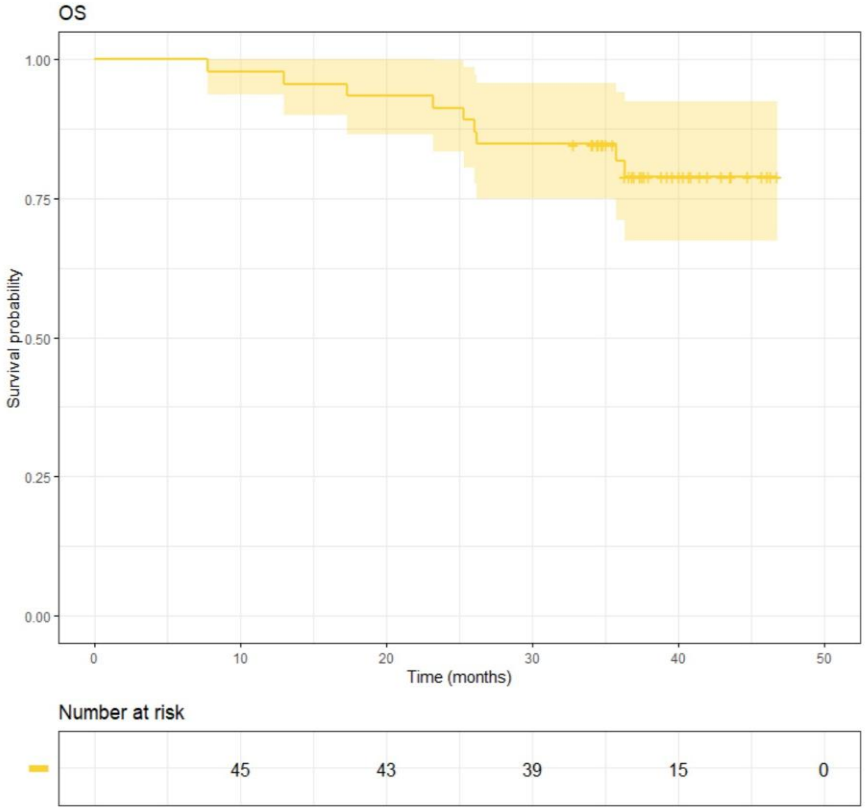
- **PFS 69.6%** (95%CI: 54.1-80.7%) **at 36 and 42 months.**

PP population:

- **PFS 81.1%** (95%CI: 64.4-90.5%) **at 36 and 42 months.**

The median PFS for patients who had progressive disease was 21.4 months (95% CI: 8.8–26.2 months)

RESULTS: OS



ITT population:

- **OS 81.9%** (95% CI: 66.8-90.6%) **at 36 months.**
- **OS 78.9%** (95%CI: 63.1-88.6%) **at 42 months.**

PP population:

- **OS 91.0%** (95%CI: 74.2-97.0%) **at 36 months.**
- **OS 87.3%** (95%CI: 69.3-95.1%) **at 42 months.**

Neoadjuvant Adverse Events (chemo+Nivo)

Grade 1-2 TRAEs (>7%)	N=46	%
Fatigue	23	50
Alopecia	16	35
Nausea	15	33
Diarrhea	11	24
Arthralgia	11	24
Vomiting	8	17
Myalgia	8	17
Paresthesia	8	17
Constipation	8	17
Anorexia	8	17
Anemia	7	15
Peripheral sensory neuropathy	7	15
Pruritus	6	13
Platelet count decrease	4	9
Rash	3	7

Grade 3-4 TRAEs	N= 46	%
Febrile neutropenia	3	7
Lipase increased	3	7
Neutrophil count decreased	3	7
Serum amylase increased	2	4
Alopecia	1	2
GGT increased	1	2
Immune system disorders	1	2
Rash maculo-papular	1	2
Renal and urinary disorders	1	2

- ❖ Most TRAEs were grade 1 or 2
- ❖ No fatal (grade 5) TRAEs occurred
- ❖ **Only one patient decided to withdraw from the study and only received 2 cycles**

Adjuvant Adverse Events (Nivo)

Grade 1-2 TRAEs	N=37	%
Skin disorders[1]	25	68
Fatigue	20	54
Amylasa/Lipasa increase	13	35
Diarrhea	11	30
Arthralgia/Myalgia	8	22
Endocrine disorders[2]	6	16
Flu like symptoms	6	16
Blood and lymphatic system disorder[3]	6	16
Nausea/vomitting	6	16
Anorexia	5	14
Pain/weakness	5	14
Constipation	4	11
Pneumonitis	3	8
Edema	2	5
Papilledema	2	5
Others[4]	13	35

Grade 3-4* TRAEs	N=37	%
Lipase increased	9	24
Serum amylase increased	3	8
Adrenal insufficiency	1	3

* these AEs were present in 5 of 37 patients

- Most TRAEs were grade 1 or 2
- No fatal (grade 5) TRAEs occurred

Discontination Reasons	N= 8	%
Toxicity	4	50
Patient/PI decisión	3	38
Other	1	12

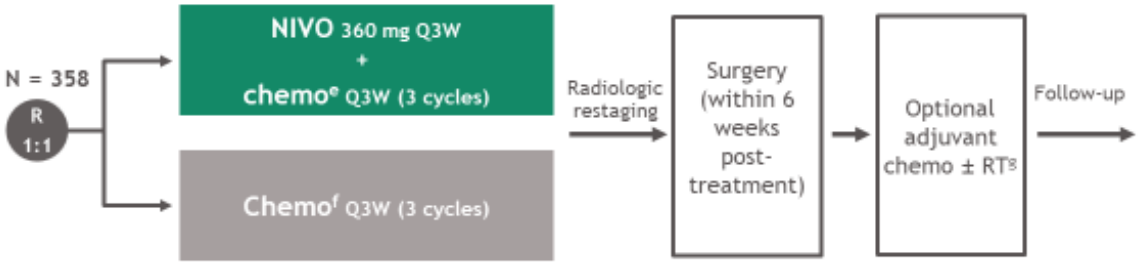
[1] Pruritus (8), rash (4), erythema multiforme (1), other skin alterations (12)
[2] Hypothiroidism (4), hyperthiroidism (1), other endocrine disorders (1)
[3] Anemia (2), platelet count decrease (1), others (3)
[4] Dry eye and mouth (4), dysgeusia-mucositis (4), others (5)

CheckMate 816 study design[a]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per AJCC 7th edition[b])
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

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



Primary endpoints
- pCR by BIPR
- **EFS[h] by BICR**

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

Key exploratory analysis
- **EFS by pCR status**

Database lock: October 20, 2021; minimum follow-up: 21 months for NIVO + chemo and chemo arms; median follow-up, 29.5 months.

[a]NCT02998528; [b]TNM Classification of Malignant Tumors 7th edition; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Included patients with PD-L1 expression status not evaluable and indeterminate; [e]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [f]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [g]Per healthcare professional choice; [h]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

Neoadjuvant immunotherapy: CheckMate 816

Table 1. **Characteristics of the Patients at Baseline.**

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
Age		
Median (range) — yr	64 (41–82)	65 (34–84)
Distribution — no. (%)		
<65 yr	93 (52.0)	83 (46.4)
≥65 yr	86 (48.0)	96 (53.6)
Sex — no. (%)		
Male	128 (71.5)	127 (70.9)
Female	51 (28.5)	52 (29.1)
Geographic region — no. (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world*	12 (6.7)	12 (6.7)
ECOG performance-status score — no. (%)†		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Disease stage — no. (%)‡		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histologic type of tumor — no. (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Smoking status — no. (%)§		
Never smoked	19 (10.6)	20 (11.2)
Current or former smoker	160 (89.4)	158 (88.3)
PD-L1 expression level — no. (%)¶		
Could not be evaluated	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
Tumor mutational burden — no. (%)‖		
Could not be evaluated or was not reported	91 (50.8)	89 (49.7)
<12.3 mutations per megabase	49 (27.4)	53 (29.6)
≥12.3 mutations per megabase	39 (21.8)	37 (20.7)
Type of platinum therapy — no. (%)		
Cisplatin	124 (69.3)	134 (74.9)
Carboplatin	39 (21.8)	33 (18.4)

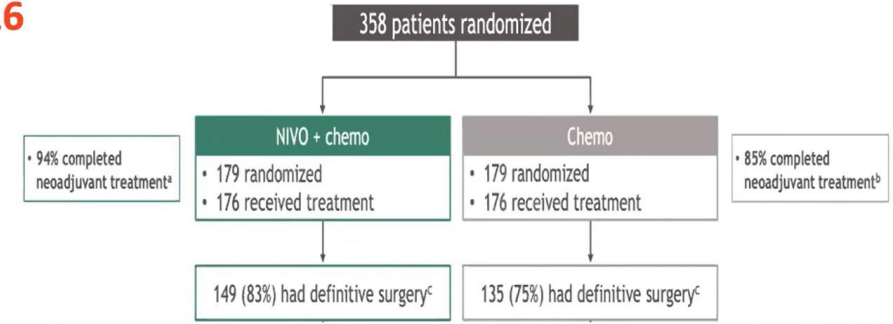
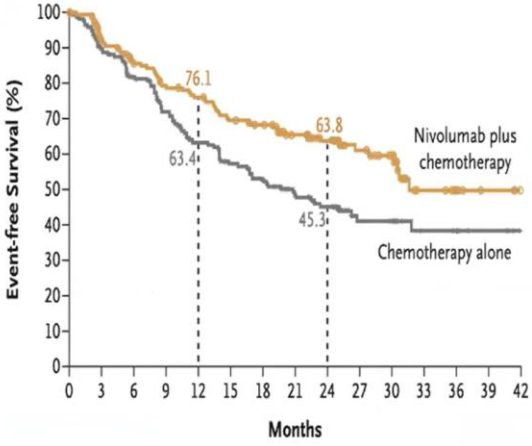


Table 2. **Adverse Events.***

Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

Girard AACR 22, Forde NEJM 22

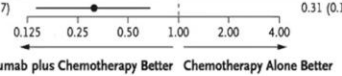
Neoadjuvant immunotherapy: CheckMate 816



	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)

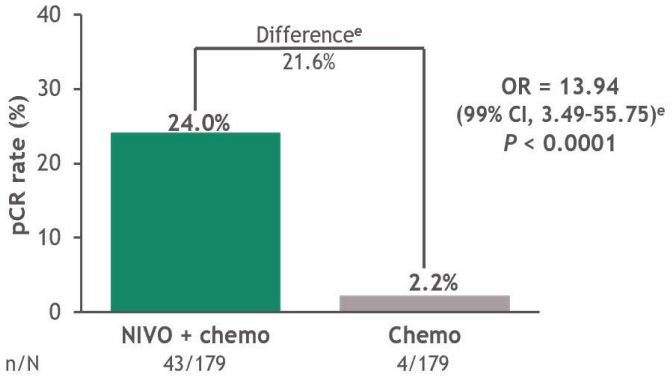
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

Subgroup	No. of Patients	Median Event-free Survival (95% CI) mo: Nivolumab plus chemotherapy (N=179)	Median Event-free Survival (95% CI) mo: Chemotherapy alone (N=179)	Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
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)

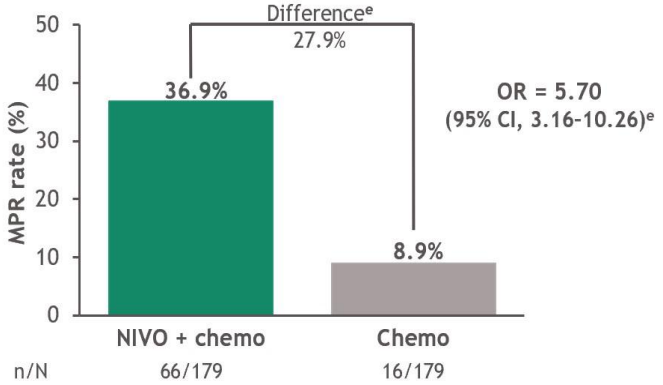


Girard AACR 22, Forde NEJM 22

pCR[b,c] in ITT (ypT0N0)[d]



MPR[b,f] in ITT[d]



- Here, we present additional efficacy data as well as key surgical outcomes in all randomized patients and by stage of disease

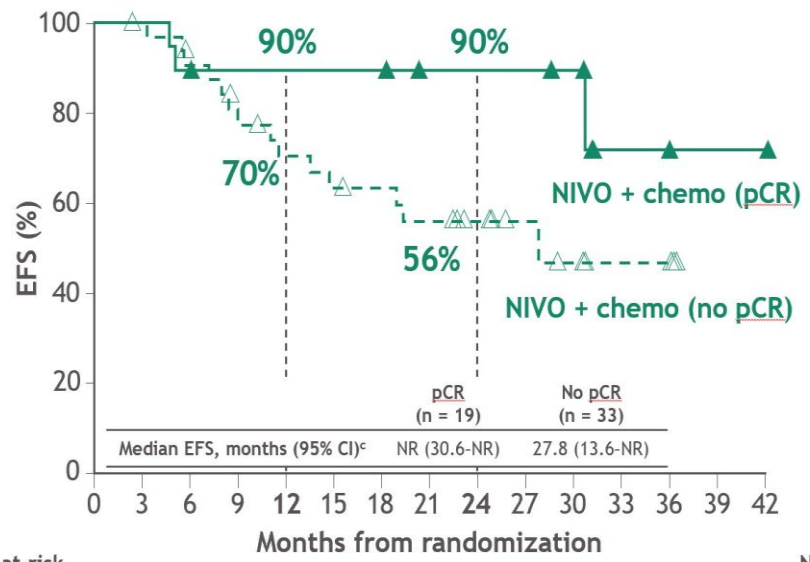
[a]NCT02998528; [b]Per BIPR; [c]Pathological complete response (pCR): 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes (≥ 5 stations, including ≥ 3 mediastinal, were recommended); [d]ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis; [e]Calculated by stratified Cochran-Mantel-Haenszel method; [f]Major pathological response (MPR): ≤ 10% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes (≥ 5 stations, including ≥ 3 mediastinal, were recommended).

1. Forde PM, et al. *N Engl J Med* 2018;378:1976-1986; 2. Provencio M, et al. *Lancet Oncol* 2020;21:1413-1422; 3. Shu C, et al. *Lancet Oncol* 2020;21:786-795; 4. Cascone T, et al. *Nat Med* 2021;27:504-514; 5. Forde PM, et al. Oral presentation at: American Association for Cancer Research; April 8-10, 2021; virtual. Abstract 5218.

3

C

Baseline stage IB-II: NIVO + chemo[b]

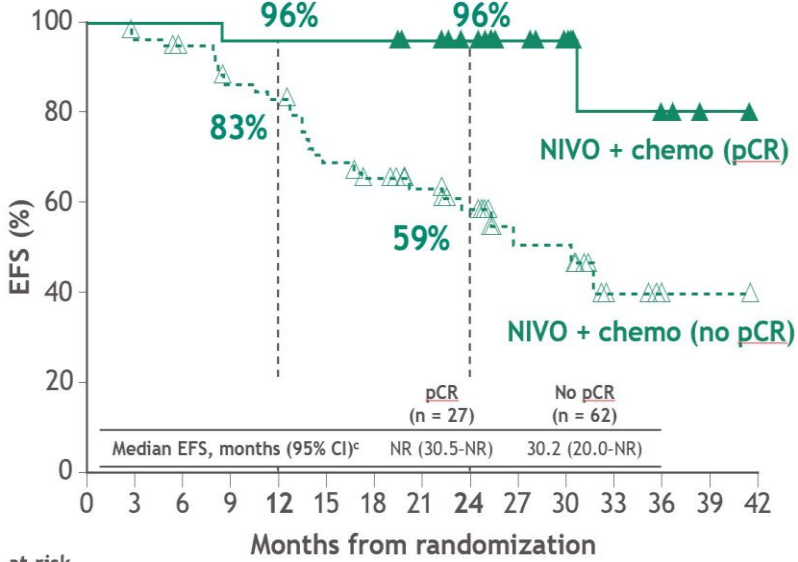


No. at risk

pCR	19	19	16	16	16	16	16	14	14	7	6	2	1	1	0
No pCR	33	32	28	24	20	18	17	15	11	6	4	2	1	0	0

D

Baseline stage IIIA: NIVO + chemo[b]



No. at risk

pCR	27	27	27	26	26	26	26	23	20	13	9	5	3	1	0
No pCR	62	60	56	50	48	39	35	30	24	12	12	4	1	1	0

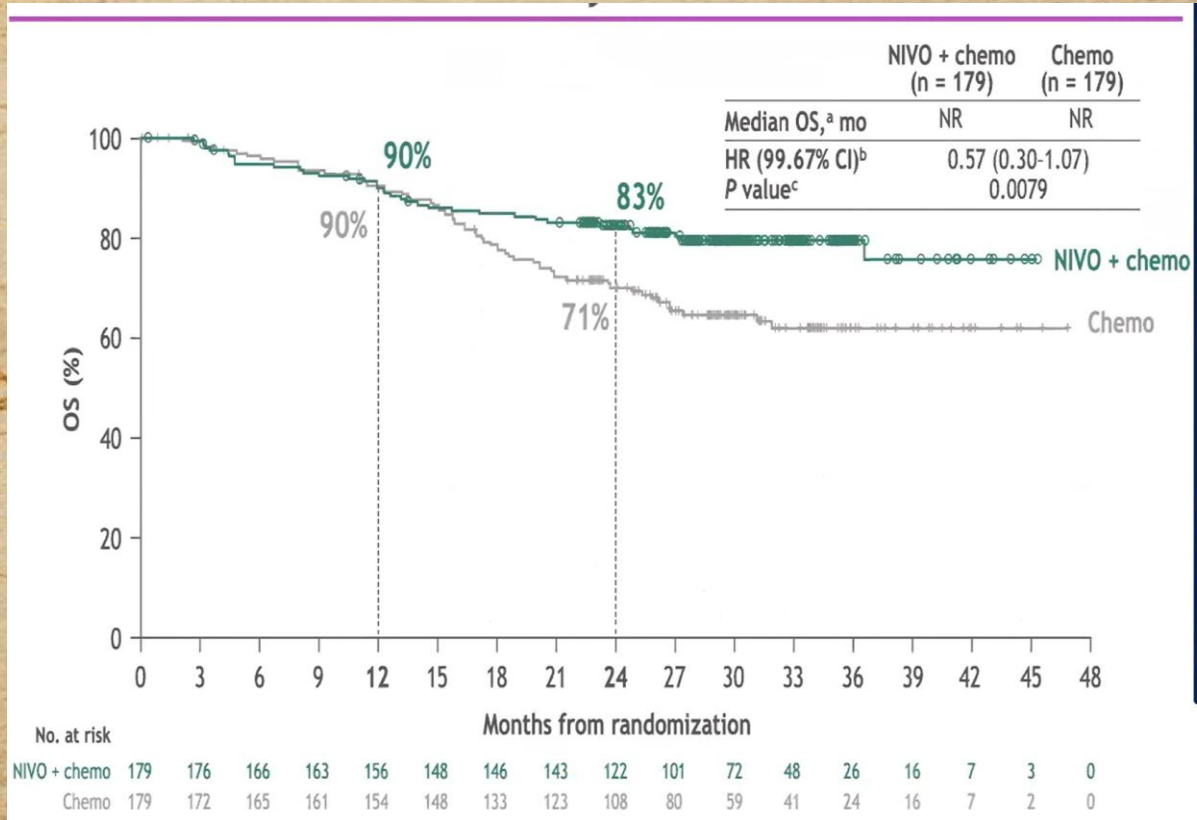
Minimum follow-up: 21 months; median follow-up: 29.5 months.

[b]Subgroup analyses were not performed for the chemo arm because of small sample sizes; [c]HRs were not computed because of low number of events for the pCR subgroups.

NR, not reached.

12

OS-INTERIM ANALYSIS



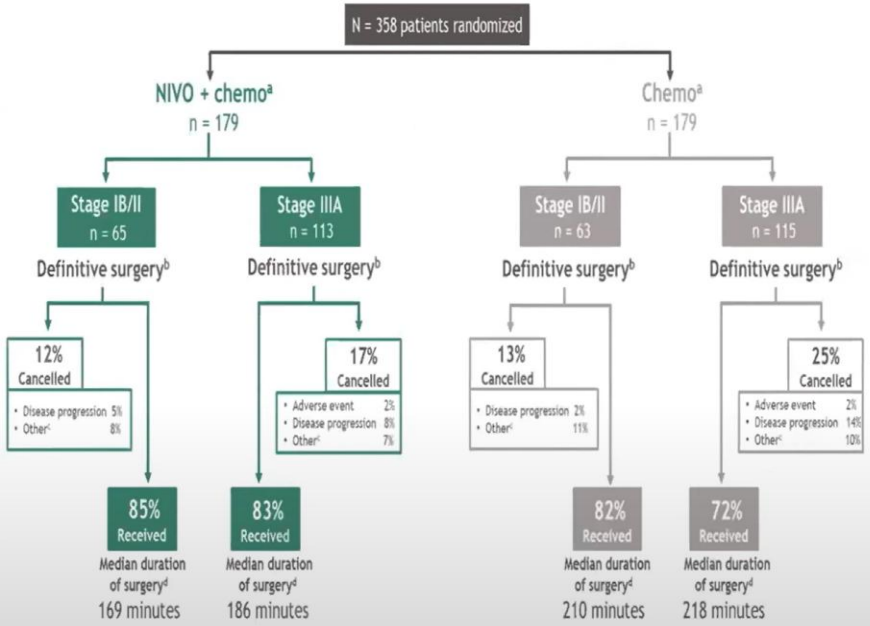
Minimum follow-up: 21 months; median follow-up, 29.5 months.

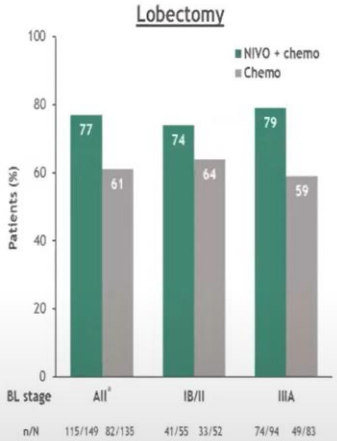
[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo); [b]95% CI = 0.38-0.87; [c]Significance boundary for OS (0.0033) was not met at this interim analysis.

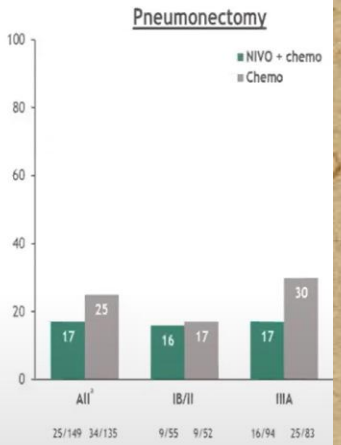
CheckMate 816 is the first phase 3 study with a neoadjuvant immunotherapy–based combination for resectable NSCLC to show improved EFS and pCR, along with promising OS results

These results support neoadjuvant NIVO in combination with CT as a new SoC for patients with resectable NSCLC

Girard AACR 22

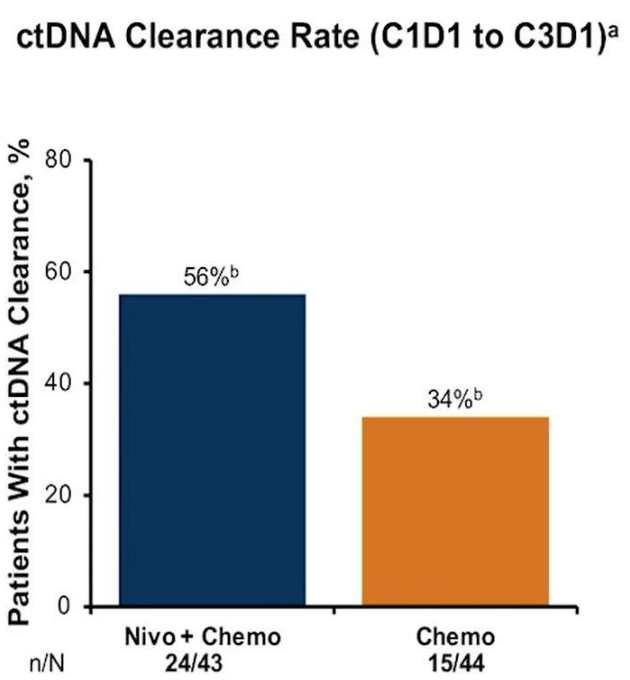


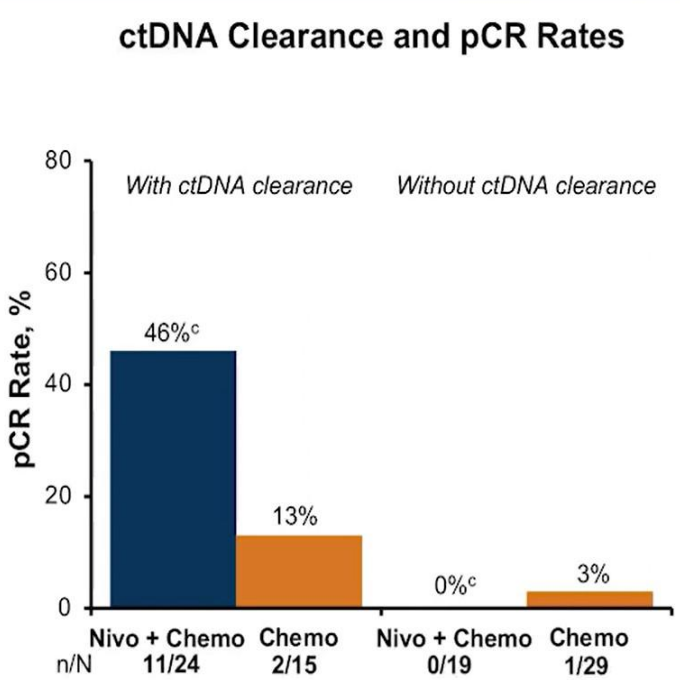




Spicer ASCO 21

CHECKMATE 816-ctDNA CLEARANCE





[a] Performed using tumor-guided personalized ctDNA panel (ArcherDX personalized cancer monitoring); 90 patients were ctDNA evaluable and 87 had detectable ctDNA at C1D1; main reasons for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma. [b] ctDNA clearance 95% CI: nivo + chemo, 40-71; chemo, 20-50. [c] pCR rates 95% CI for nivo + chemo; with ctDNA clearance, 26-67; without ctDNA clearance, 0-18.

Forde et al, AACR 2021

Adverse events[a] summary

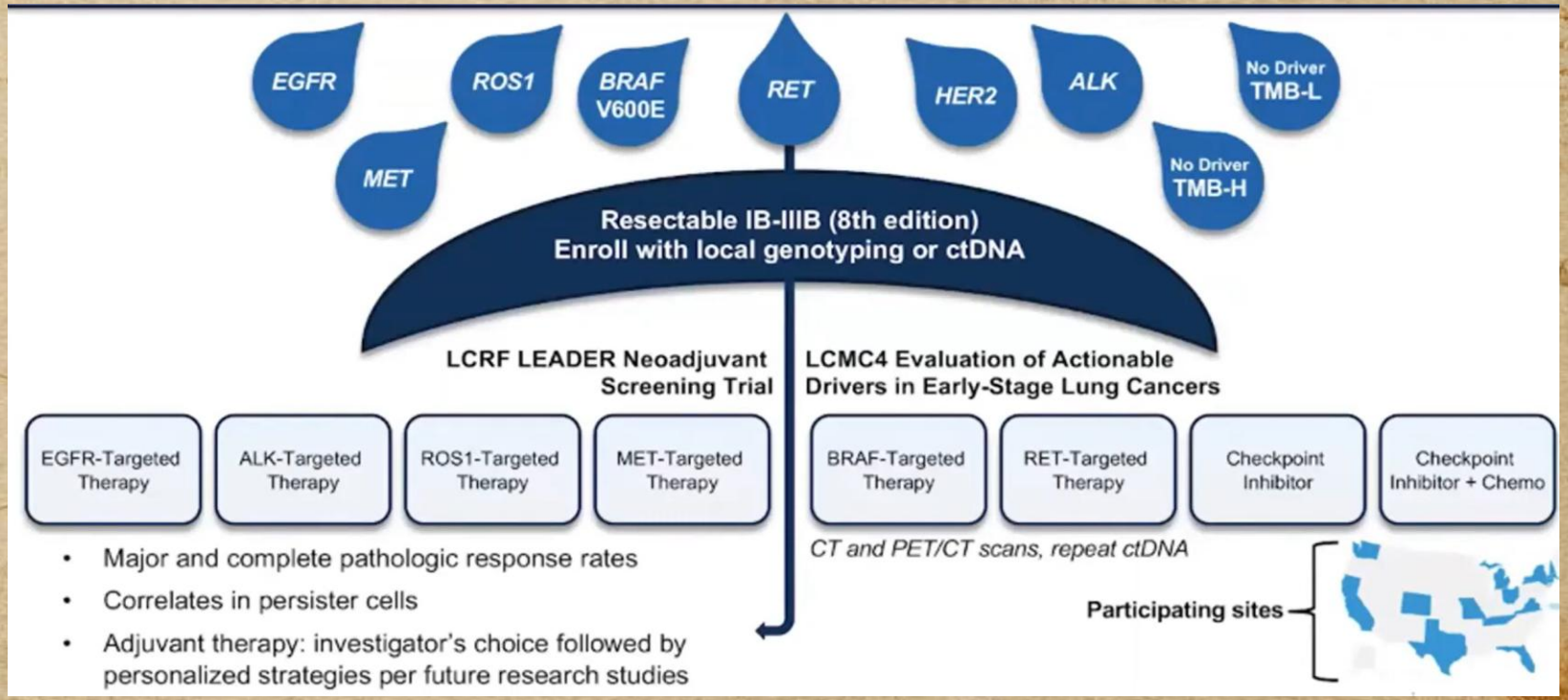
Patients (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs	93	41	97	44
TRAEs	82	34	89	37
All AEs leading to discontinuation	10	6	11	4
TRAEs leading to discontinuation	10	6	10	3
All SAEs	17	11	14	10
Treatment-related SAEs	12	8	10	8
Surgery-related AEs[b,c]	42	11	47	15
Treatment-related deaths[d]	0		2	

- Grade 5 surgery-related AEs[e] were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)

[a]Includes events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per CTCAE Version 4.0; MedDRA Version 24.0; [b]Includes events reported up to 90 days after definitive surgery; [c]Denominator based on patients with definitive surgery (n = 149 in the NIVO + chemo group, n = 135 in the chemo group); [d]Treatment-related deaths (not limited to 30 days window after last neoadjuvant dose) in the chemotherapy arm were due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis, and pneumonia; [e]Grade 5 AEs are defined as events that led to death within 24 hours of AE onset.

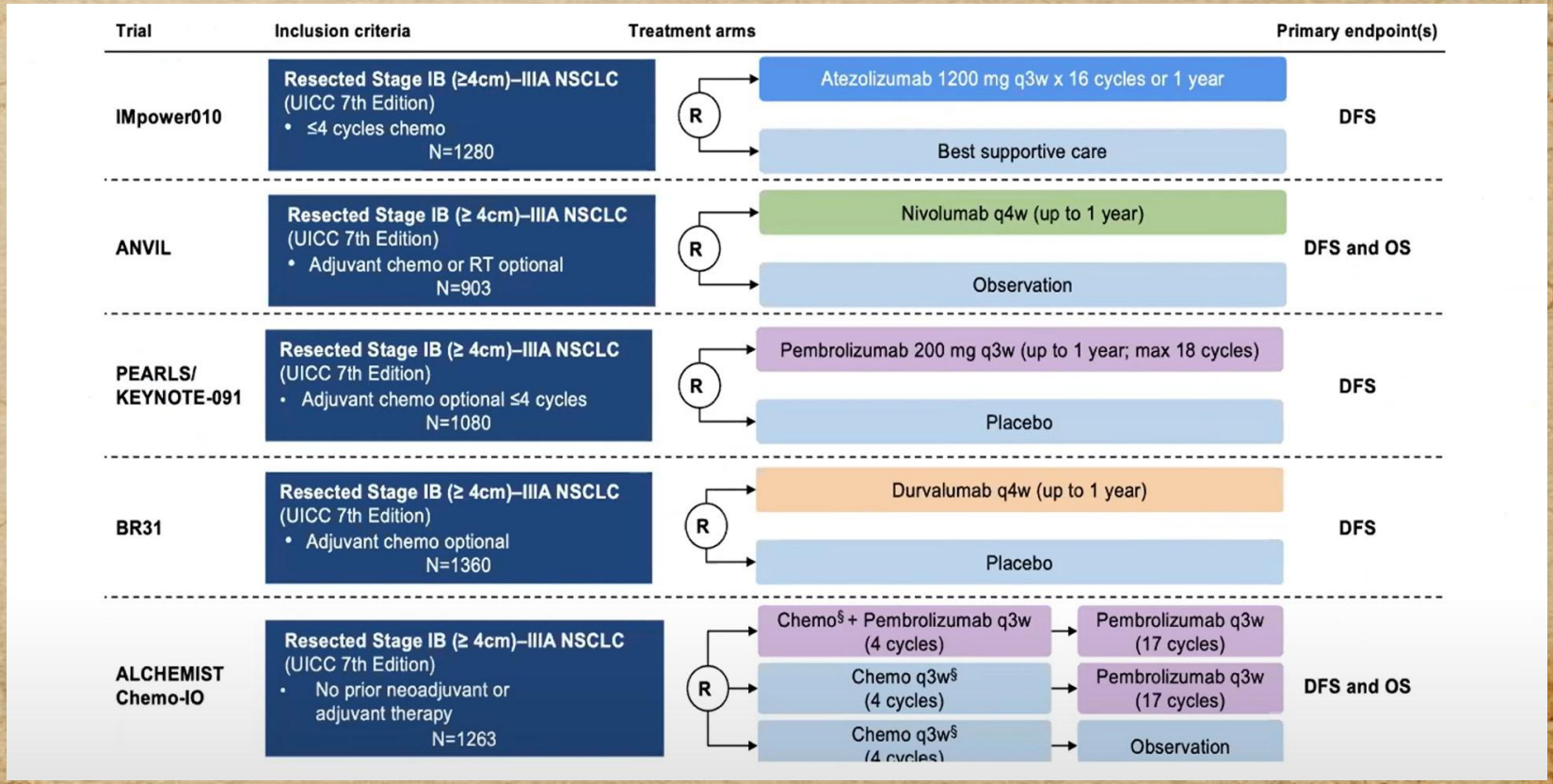
- What about lung with targetable mutations????

LCMC4 LEADER AND NEOADJUVANT TRIALS

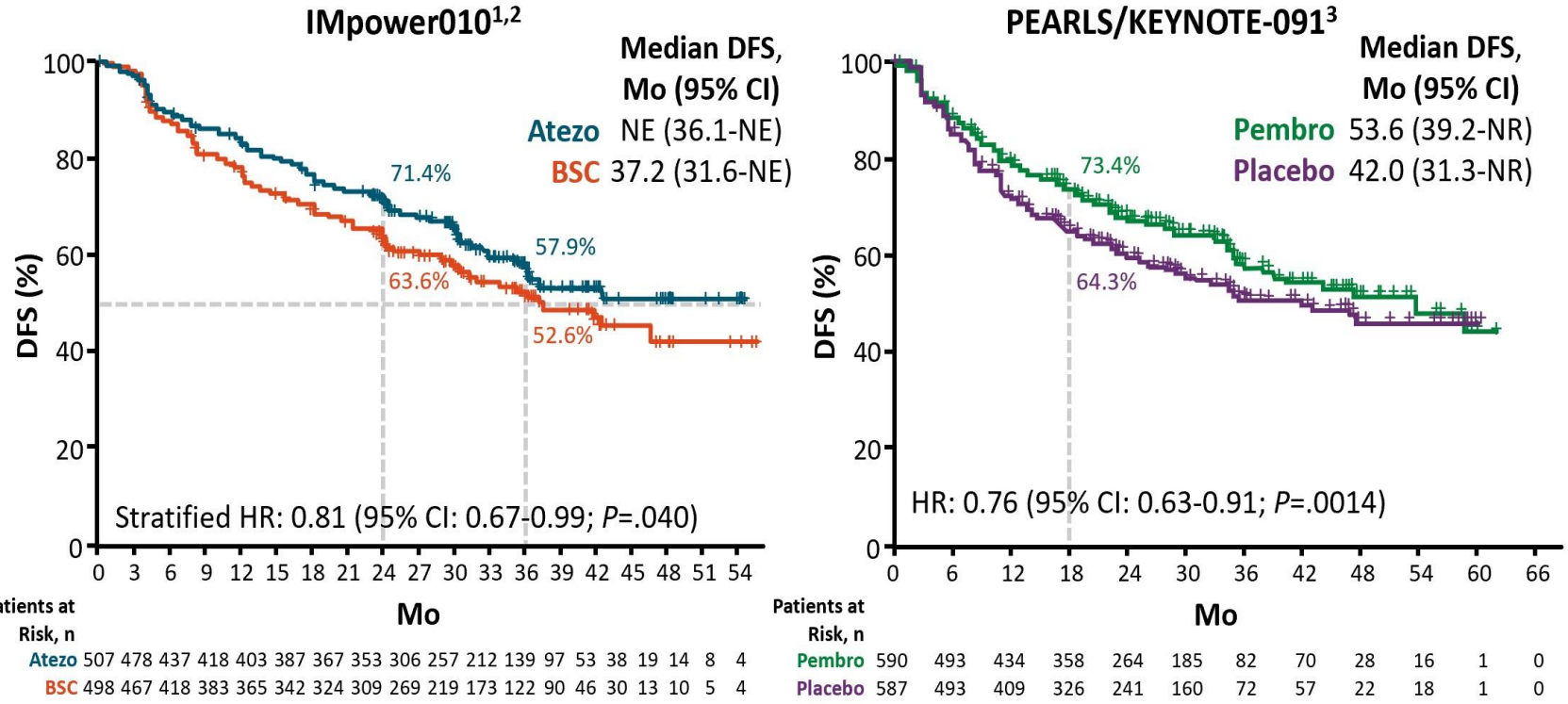


Blumenthal et, J Thorac Oncol 2018

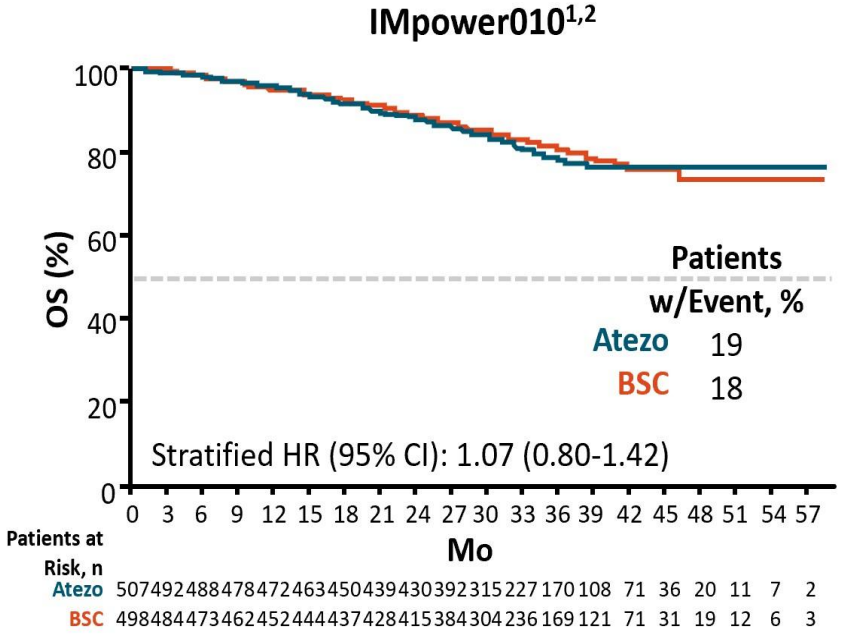
ADJUVANT IMMUNOTHERAPY TRIALS

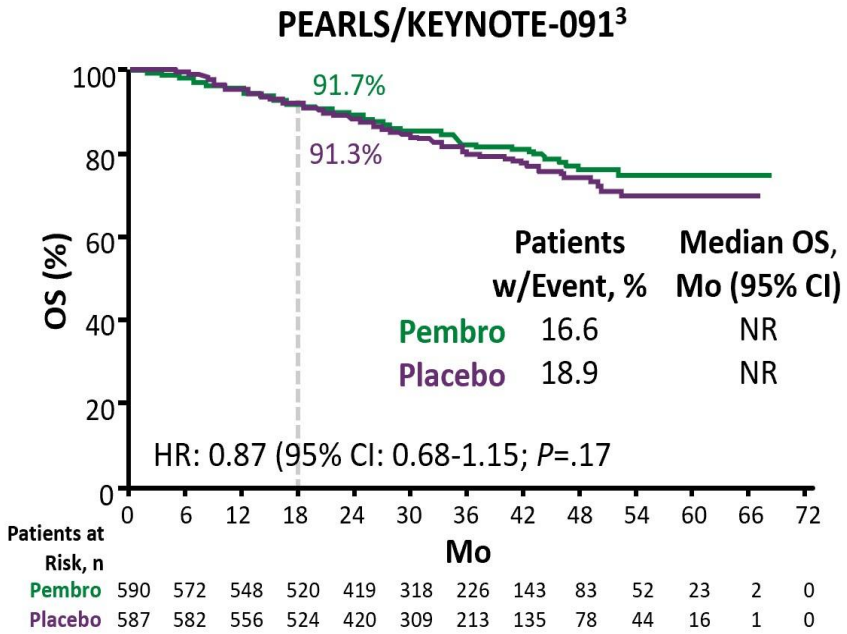


Adjuvant IO Trials: DFS in Overall Population (ITT)



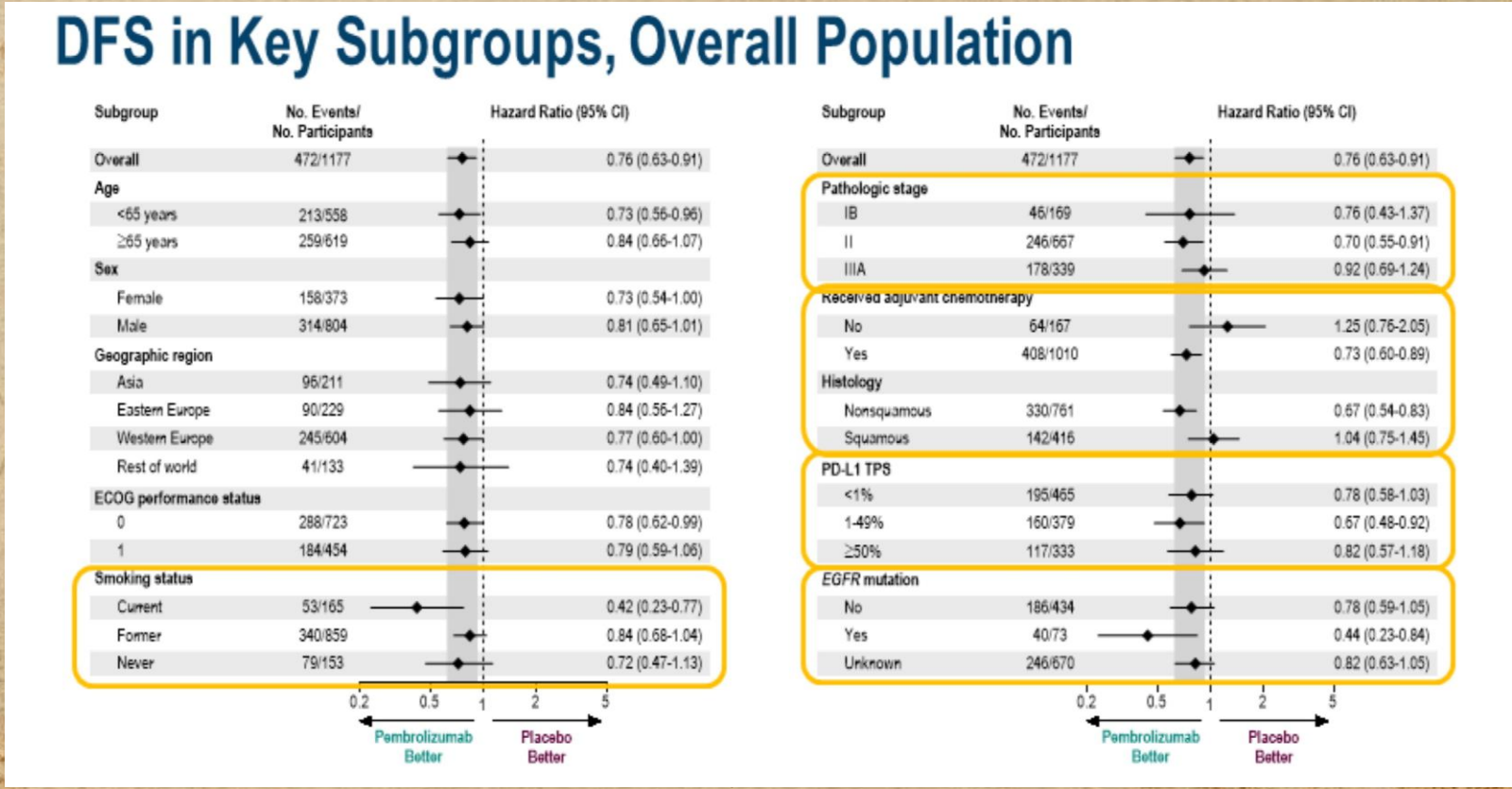
Adjuvant IO Trials: OS in Overall Population (ITT)



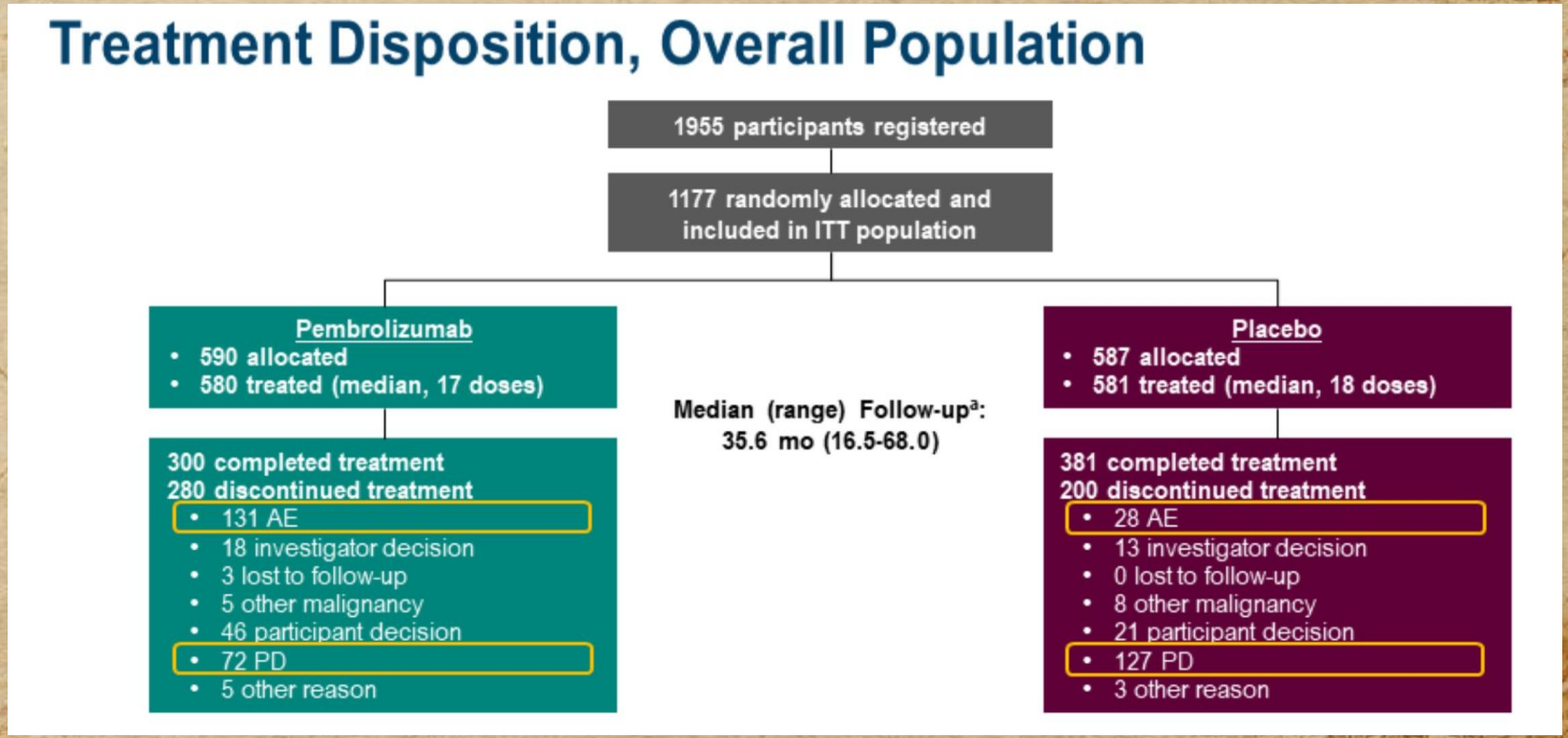


OS not formally tested in the ITT population because DFS in ITT population was not statistically improved and data immature

KEYNOTE 091


DFS in Key Subgroups, Overall Population
Subgroup
No. Events/ No. Participants
Hazard Ratio (95% CI)
Overall 472/1177 0.76 (0.63-0.91)
Age
<65 years 213/558 0.73 (0.56-0.96)
≥65 years 259/619 0.84 (0.66-1.07)
Sex
Female 158/373 0.73 (0.54-1.00)
Male 314/804 0.81 (0.65-1.01)
Geographic region
Asia 96/211 0.74 (0.49-1.10)
Eastern Europe 90/229 0.84 (0.56-1.27)
Western Europe 245/604 0.77 (0.60-1.00)
Rest of world 41/133 0.74 (0.40-1.39)
ECOG performance status
0 288/723 0.78 (0.62-0.99)
1 184/454 0.79 (0.59-1.06)
Smoking status
Current 53/165 0.42 (0.23-0.77)
Former 340/859 0.84 (0.68-1.04)
Never 79/153 0.72 (0.47-1.13)
0.2 0.5 1 2 5
Pembrolizumab Better
Placebo Better
Subgroup
No. Events/ No. Participants
Hazard Ratio (95% CI)
Overall 472/1177 0.76 (0.63-0.91)
Pathologic stage
IB 46/169 0.76 (0.43-1.37)
II 246/667 0.70 (0.55-0.91)
IIIA 178/339 0.92 (0.69-1.24)
Received adjuvant chemotherapy
No 64/167 1.25 (0.76-2.05)
Yes 408/1010 0.73 (0.60-0.89)
Histology
Nonsquamous 330/761 0.67 (0.54-0.83)
Squamous 142/416 1.04 (0.75-1.45)
PD-L1 TPS
<1% 195/465 0.78 (0.58-1.03)
1-49% 160/379 0.67 (0.48-0.92)
≥50% 117/333 0.82 (0.57-1.18)
EGFR mutation
No 186/434 0.78 (0.59-1.05)
Yes 40/73 0.44 (0.23-0.84)
Unknown 246/670 0.82 (0.63-1.05)
0.2 0.5 1 2 5
Pembrolizumab Better
Placebo Better

COMPLIANCE KEYNOTE 091



Adjuvant IO Trials: Summary of Adverse Events

IMpower010[1,2]

AE, n (%)	Atezo (n = 495)	BSC (n = 495)
Any grade AE ▪ TRAE	459 (92.7) 335 (67.7)	350 (70.7) --
Grade 3/4 AE ▪ Grade 3/4 TRAE	108 (21.8) 53 (10.7)	57 (11.5) --
Serious AE ▪ Treatment-related serious AE	87 (17.6) 37 (7.5)	42 (8.5) --
Grade 5 AE ▪ Treatment-related grade 5 AE	8 (1.6)* 4 (0.8)*	3 (0.6)† --
AE leading to atezo dose interruption	142 (28.7)	
AE leading to atezo discontinuation	90 (18.2)	
Any grade immune-mediated AE ▪ Grade 3/4 immune-mediated AE ▪ Immune-mediated AE requiring systemic corticosteroid use‡	256 (51.7) 39 (7.9) 60 (12.1)	47 (9.5) 3 (0.6) 4 (0.8)

PEARLS/KEYNOTE-091[3]

AE, n (%)	Pembro (n = 580)	Placebo (n = 581)
Any	556 (95.9)	529 (91.0)
Grade 3-5 AE	198 (34.1)	150 (25.8)
AE leading to death ▪ Treatment related	11 (1.9) 4 (0.7)§	6 (1.0) 0
Serious AE	142 (24.5)	90 (15.5)
AE leading to treatment d/c	115 (19.8)	34 (5.9)
AE leading to treatment interruption	221 (38.1)	145 (25.0)

§n = 1 each: myocarditis with cardiogenic shock, myocarditis with septic shock, pneumonia, and sudden death.

*n = 1 each related to atezolizumab: ILD, multiple organ dysfunction syndrome, myocarditis, and AML; n = 1 each: pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia, pulmonary embolism, and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

Immunotherapy in stage IB NSCLC

IMpower010

	Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=507)	Best supportive care (n=498)
Stage		
IB	65 (13%)	58 (12%)
IIA	147 (29%)	148 (30%)
IIB	90 (18%)	84 (17%)
IIIA	205 (40%)	208 (42%)

DFS in patients in the stage I-II–IIIA population

ITT (randomised Stage IB-IIIA)	1005	0.81 (0.67, 0.99)[b]

The statistical significance boundary for DFS was not crossed

Wakelee ASCO 21, Felip Lancet 21

PEARLS/KEYNOTE-091

IASLC

	Pembrolizumab (N = 590)	Placebo (N = 587)
Pathologic stage[c]		
IB	84 (14.2%)	85 (14.5%)
II	329 (55.8%)	338 (57.6%)
IIIA	177 (30.0%)	162 (27.6%)

Paz Ares ESMO VIRTUAL PLENARY March 22

CM816

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
Disease stage — no. (%)‡		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)

Subgroup	No. of Patients	Median Event-free Survival (95% CI) Nivolumab plus chemotherapy	Median Event-free Survival (95% CI) Chemotherapy alone	Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
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)

Forde NEJM 22

- Path CR – NADIM (63%)
  CHECKMATE 816 (24% vs 2.2%)

- Compliance- IMPOWER 010 (65%)
  CHECKMATE 816 (94%)
  NADIM (100%)

FUTURE DIRECTIONS

- 54% of NADIM trial patients had multistage N2. Almost 50% of PACIFIC patients had Stage IIIA disease- were these patients operable?

- Future is tailoring of treatment and duration depending on ctDNA, Pathological response and Radiomics

NEOADJUVANT

ADJUVANT

ONCOLOGISTS


Thank
you!