Neo-Adjuvant and Adjuvant Immunotherapy for Non-Small Cell Lung Cancer

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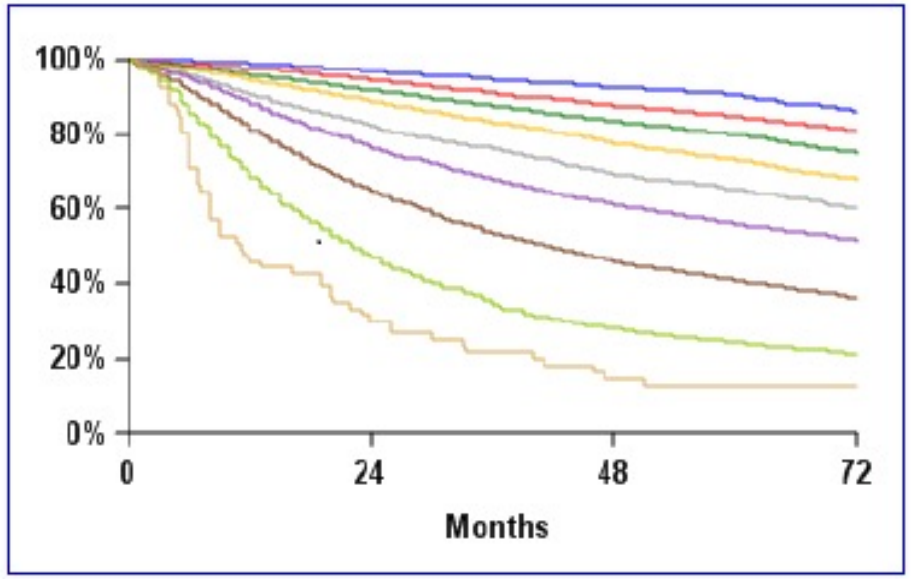
CANCER CENTER of EXCELLENCE Florida HEALTH

Surgery is still the intervention most likely to cure lung cancer

Pathological stage



	Events/N	MST	2 years	5 years
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%

But there is a lot of room for improvement!

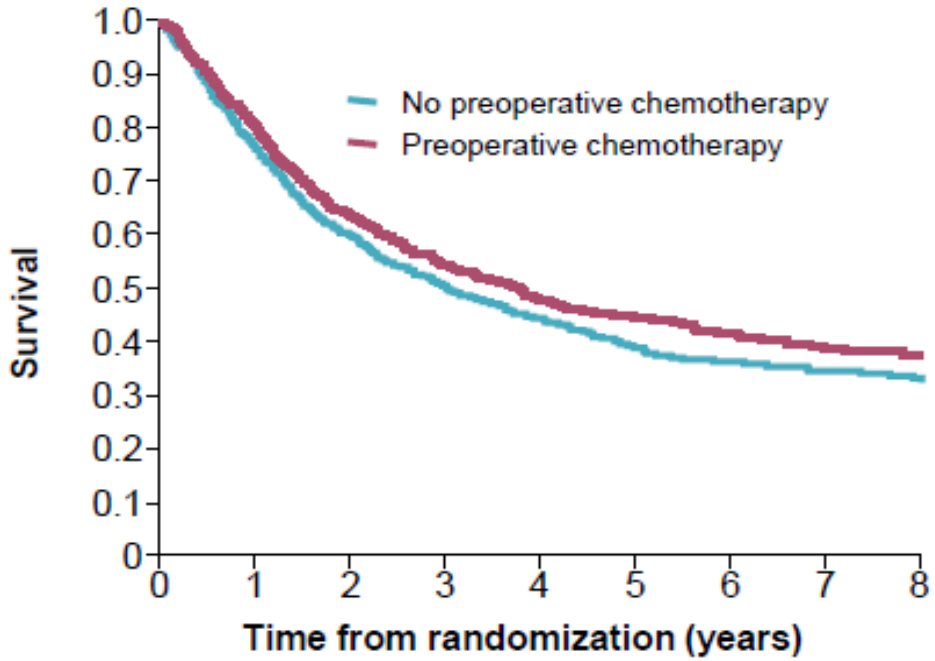
Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.

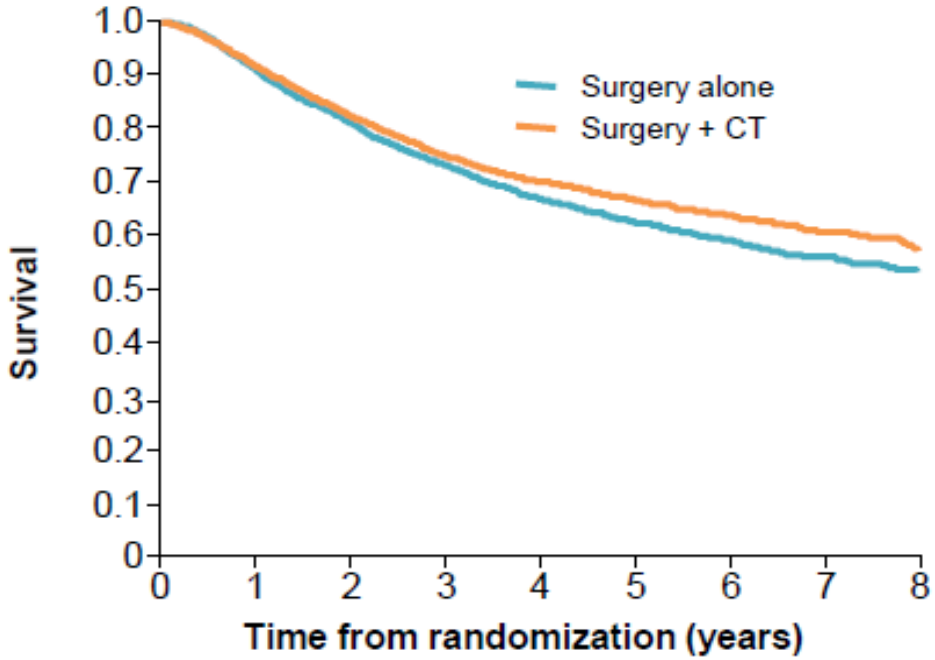
Neoadjuvant Immunotherapy in NSCLC

GECP lung cancer research

LUNG CANCER EARLY STAGES

Background & Current Situation





	N	Absolute Δ5 yr OS	HR	*P* value
Neoadjuvant Trials	2385	5%	0.87 (95% CI 0.78-0.96)	0.007
Adjuvant Trials	8447	4%	0.86 (95% CI 0.81-0.92)	<0.0001

CT RECIST vs. MPR and prediction of OS after neoadjuvant chemotherapy in resectable NSCLC

Methods

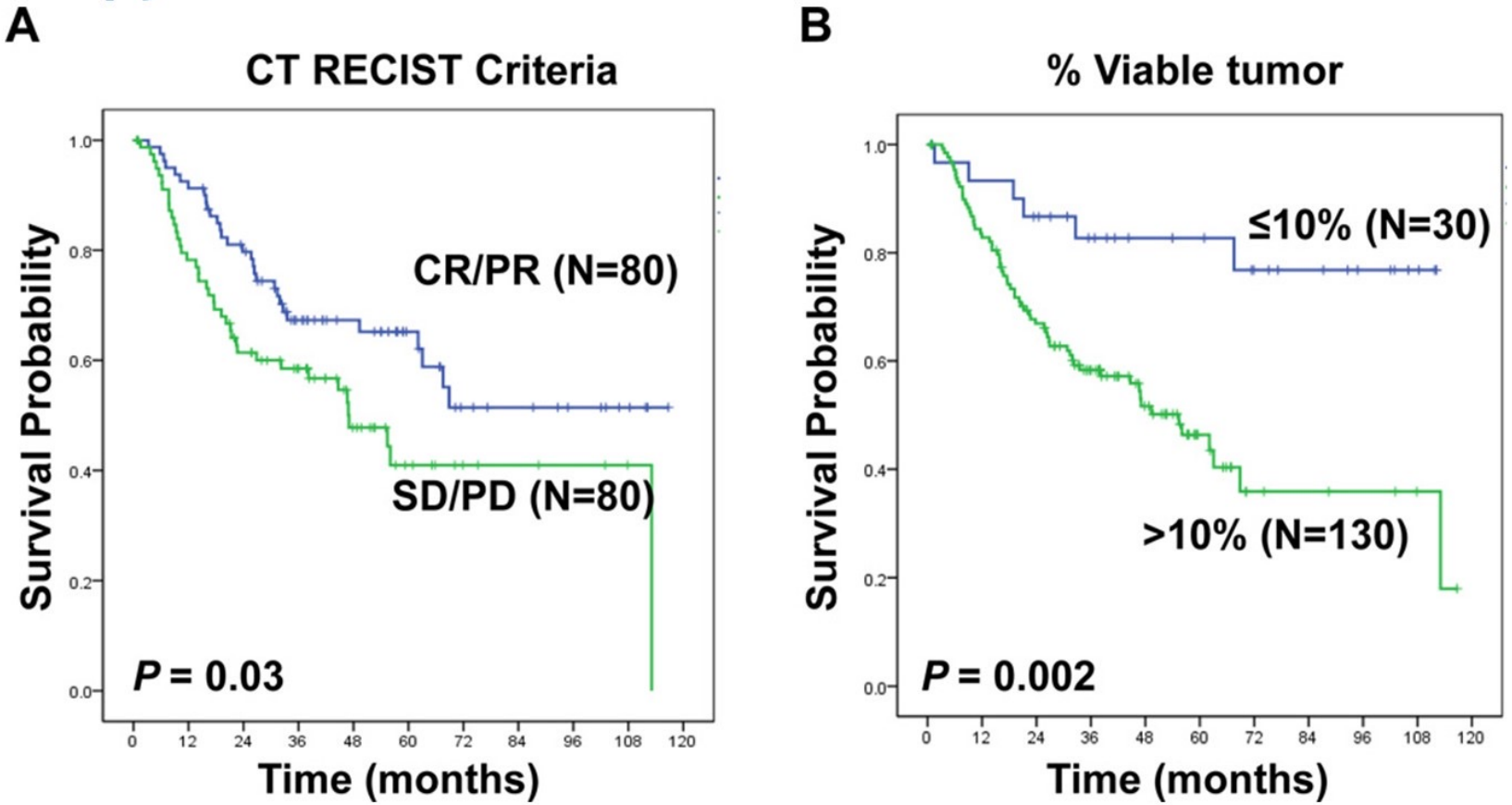
- The University of Texas M.D. Anderson Lung Cancer Collaborative Research Group
- Primary tumor size on CT before and after neoadjuvant chemotherapy in NSCLC.
- N = 160 patients who underwent surgical resection.
- CT-measured response (RECIST) and histopathologic response and OS.
- Major pathologic response (MPR) was defined as ≤10% viable tumor.

Evaluate

- CT RECIST vs. MPR in predicting OS following neoadjuvant chemotherapy

WN William et al J Thorac Oncol. 2013 Feb; 8(2): 222-228

CT RECIST vs. MPR and prediction of OS after neoadjuvant chemotherapy in resectable NSCLC



41% discordance rate between CT RECIST response and histopathologic response.

WN William et al J Thorac Oncol. 2013 Feb; 8(2): 222-228

MPR and pCR may represent surrogate markers of survival benefit in operable NSCLC

After neoadjuvant platinum-based chemo:

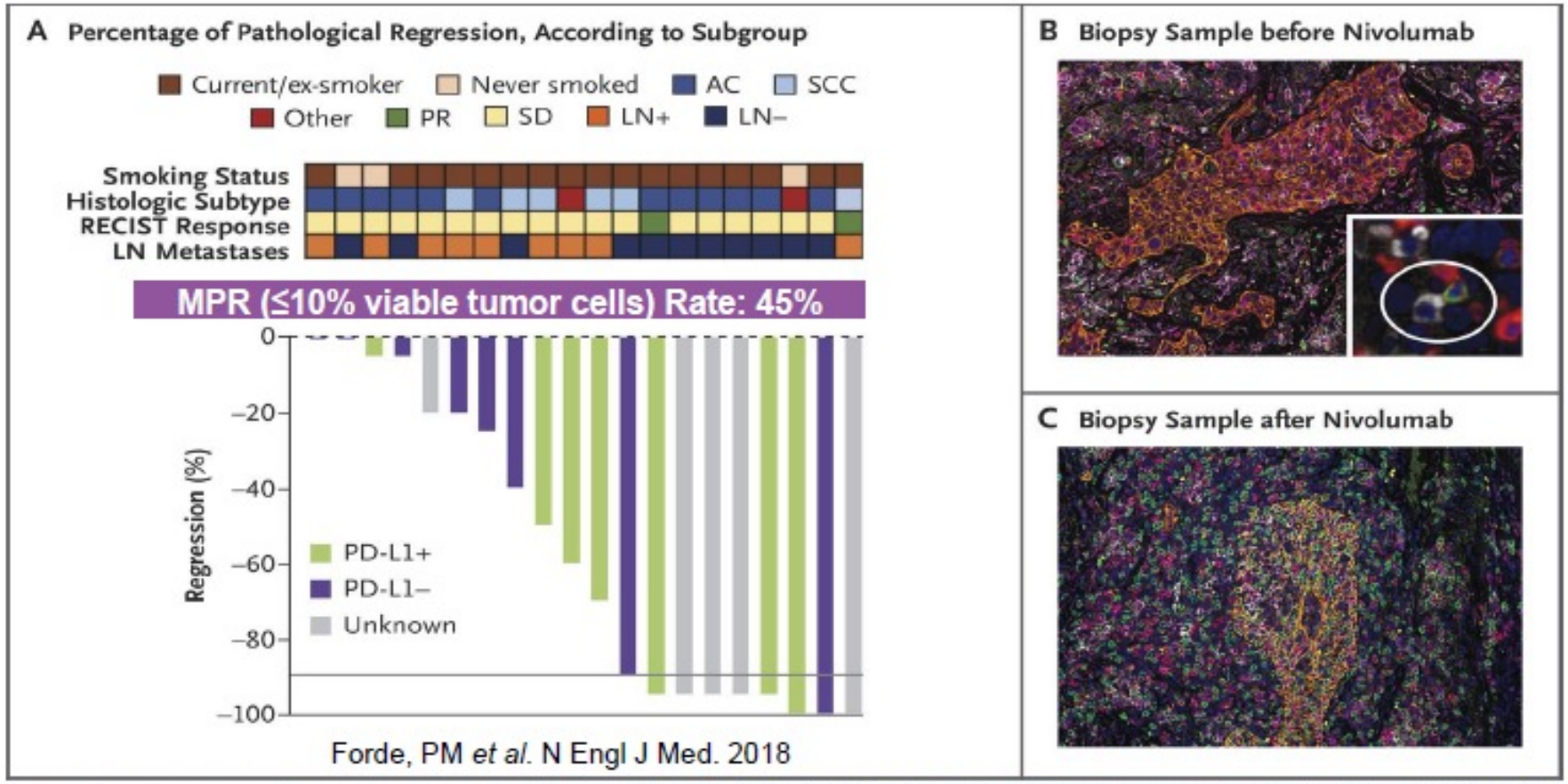
- Historical major pathologic response rates in primary tumors: ~20% (MPR, ≤10% residual viable tumor)[1-3]
- Historical pathological complete response rates: ~4% (pCR, 0% residual viable tumor)[4]

Meta-Analysis: Associations Between pCR/MPR & OS/EFS after neoadjuvant chemo-based therapy[5]

Association	HR (95% CI)	Range of HRs	Patients (n)	Studies (n)
OS, pCR vs no pCR	0.49 (0.42–0.57)	0.13–0.78	6474	20
OS, MPR vs no MPR	0.36 (0.29–0.44)	0.13–0.58	1193	12
EFS, pCR vs no pCR	0.49 (0.41–0.60)	0.26–0.71	2157	11
EFS, pCR vs no pCR	0.52 (0.42–0.66)	0.43–0.60	770	6

1. Pataer A et al. J Thorac Oncol 2012; 2. Chaft JE et al; J Thorac Oncol, 2013; 3. Cascone T et al, Ann Thorac Surg 2018; 4. Hellmann M et al Lancet Oncol 2014; 5. Waser N et al. Oral presentation ESMO 2020.

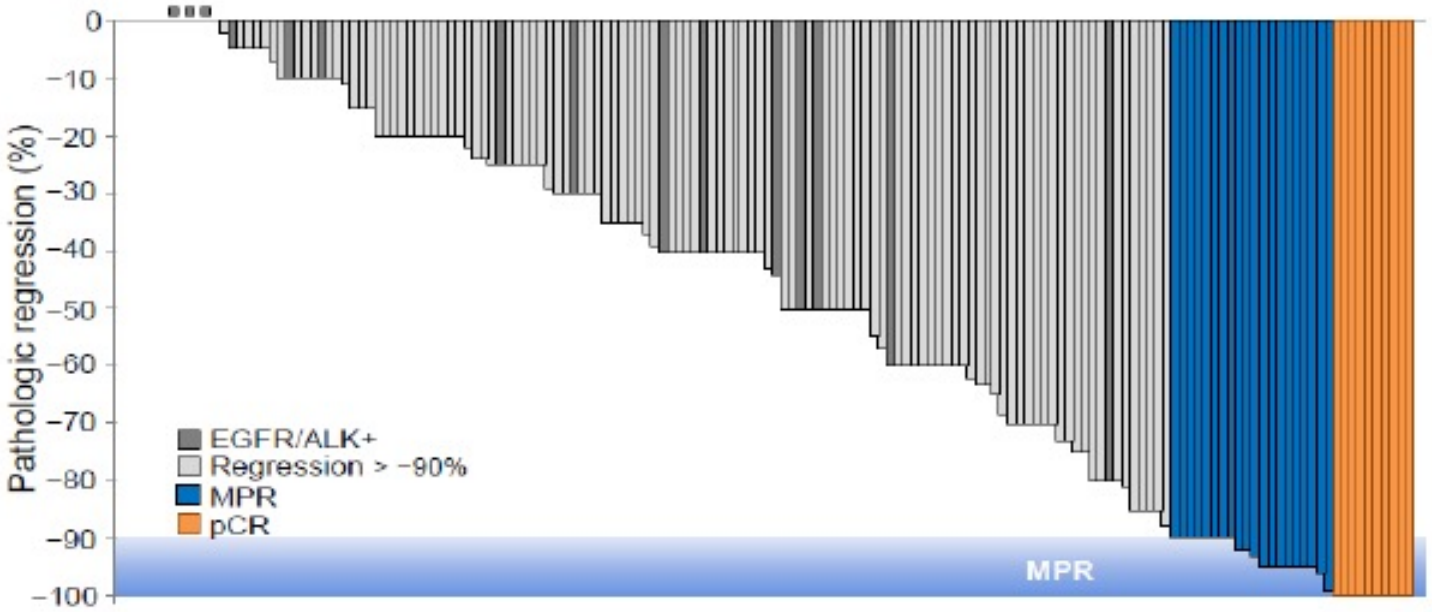
Neoadjuvant nivolumab is feasible, safe and active in operable NSCLC



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

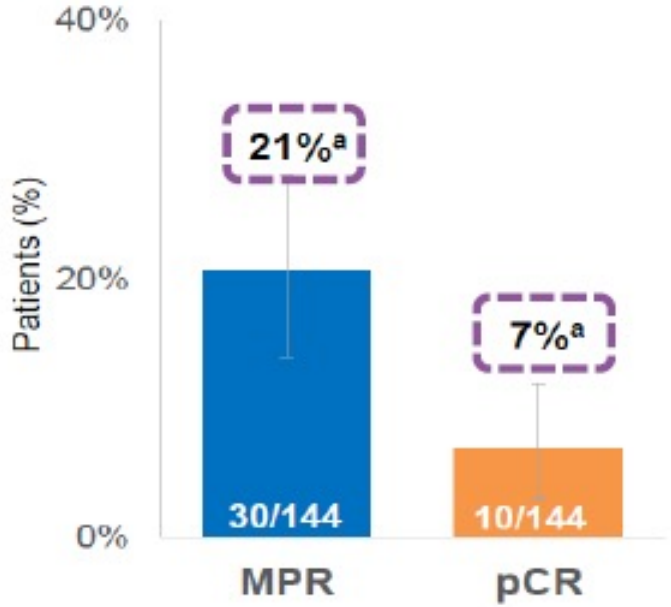
MPR to neoadjuvant atezolizumab in the LCMC3 study

Pathologic response in surgery population (n=159)



Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.
[a] Error bars indicate 95% CI.

Major pathologic response in primary efficacy population (n=144)



Lee JM, *et al*. WCLC 2021

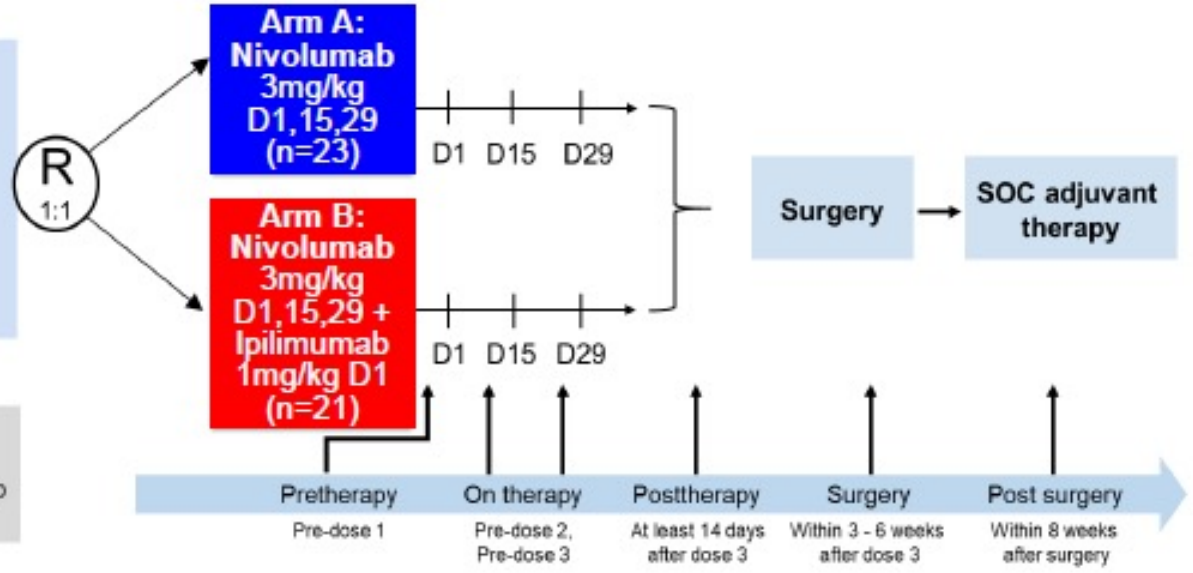
Presented by Dr Jay M. Lee LCMC3: Neoadjuvant Atezolizumab in Resectable NSCLC JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

NEOSTAR: phase 2 study of induction ICB for 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

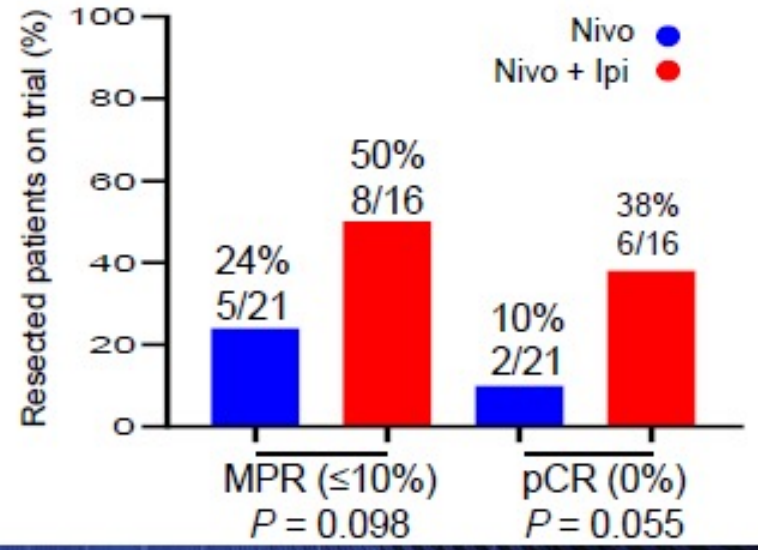
Stratification
Stage

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



Longitudinal tumor- blood, stool and imaging-based biomarkers

	MPR RATE (%) in ITT	
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)

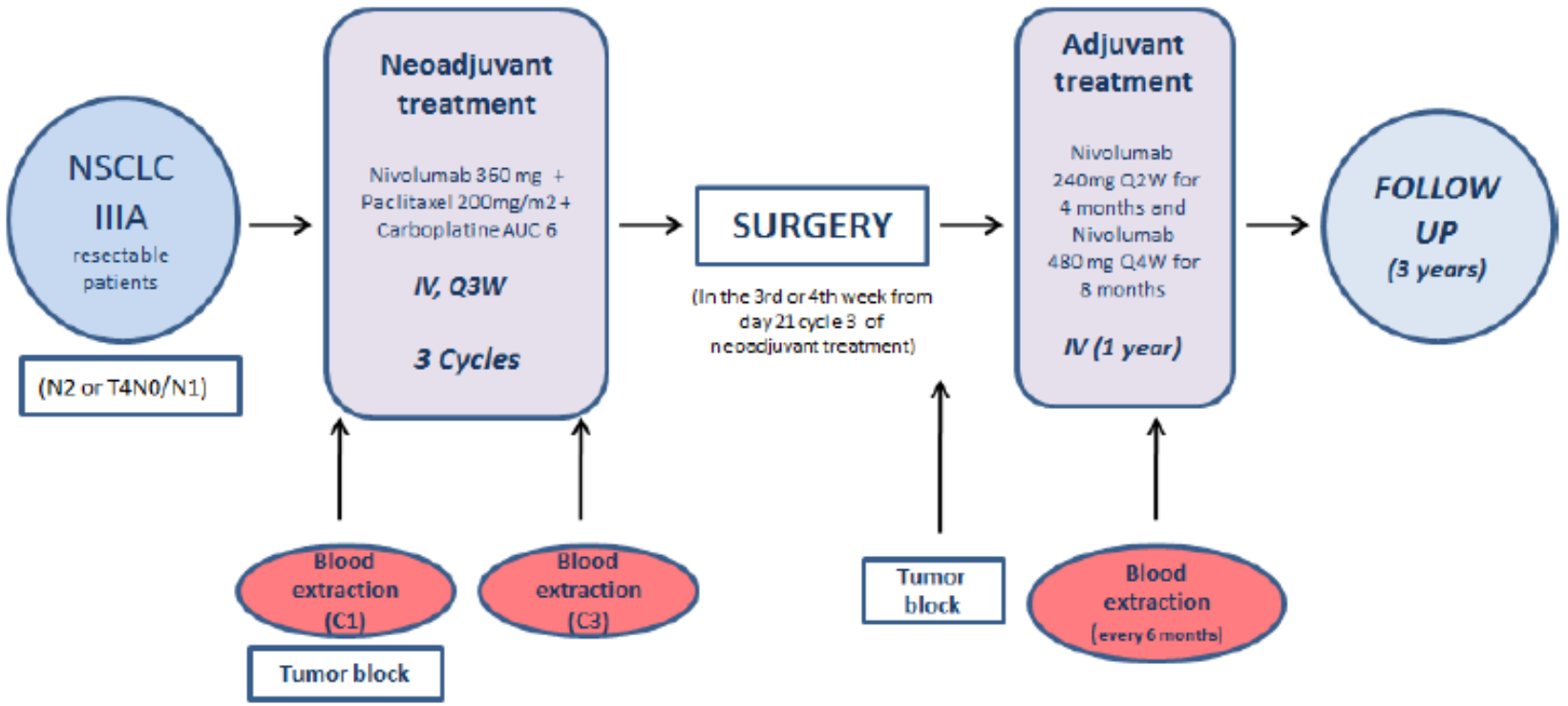


Cascone, T *et al.* Nat Med. 2021

Neoadjuvant Chemo-Immunotherapy
NADIM: Study Design & Endpoints

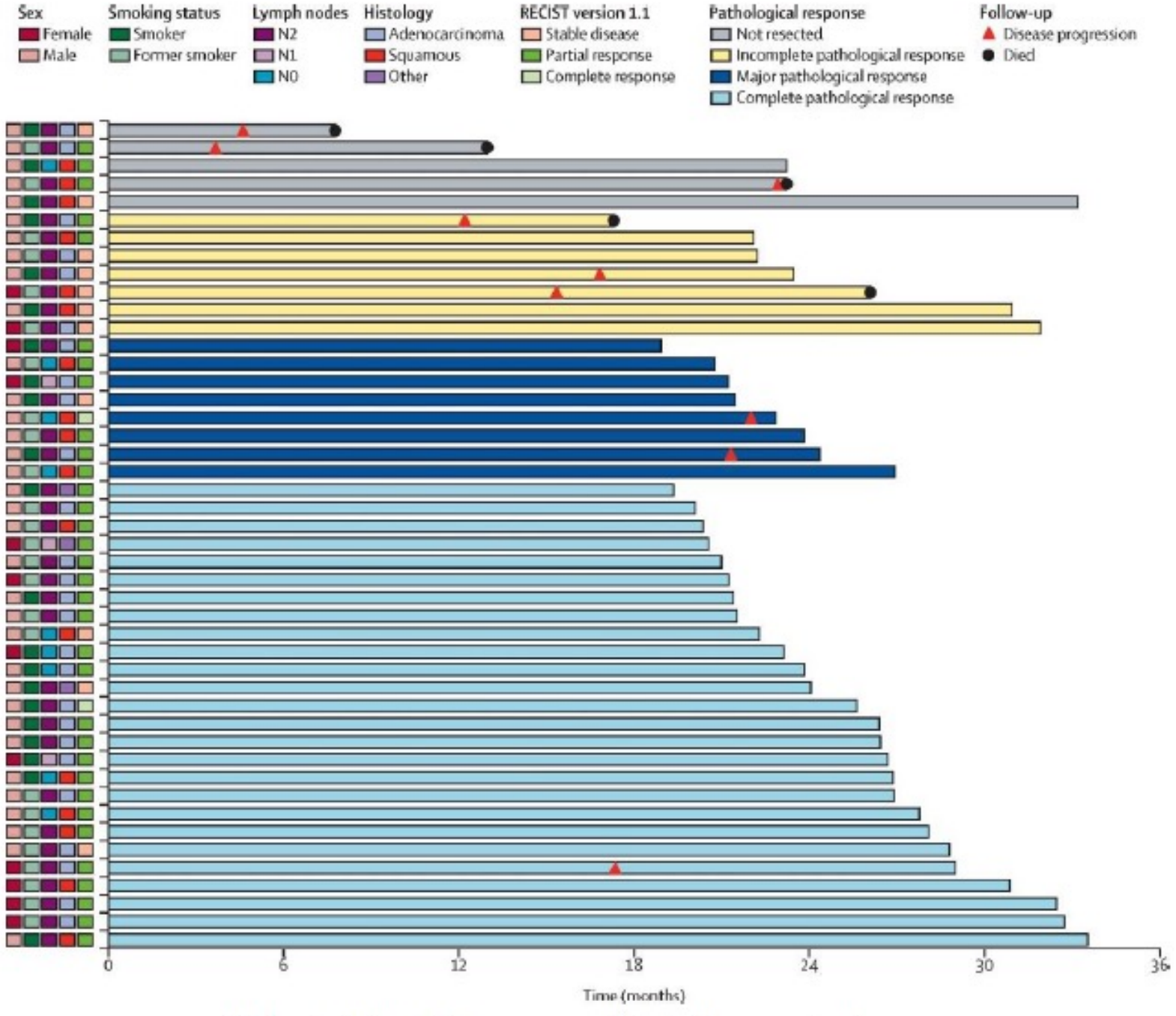
Primary Endpoint:
PFS at 24 months

Secondary Endpoints:
Down-staging rate, complete resection rate, ORR, safety, TTP, OS at 3 years



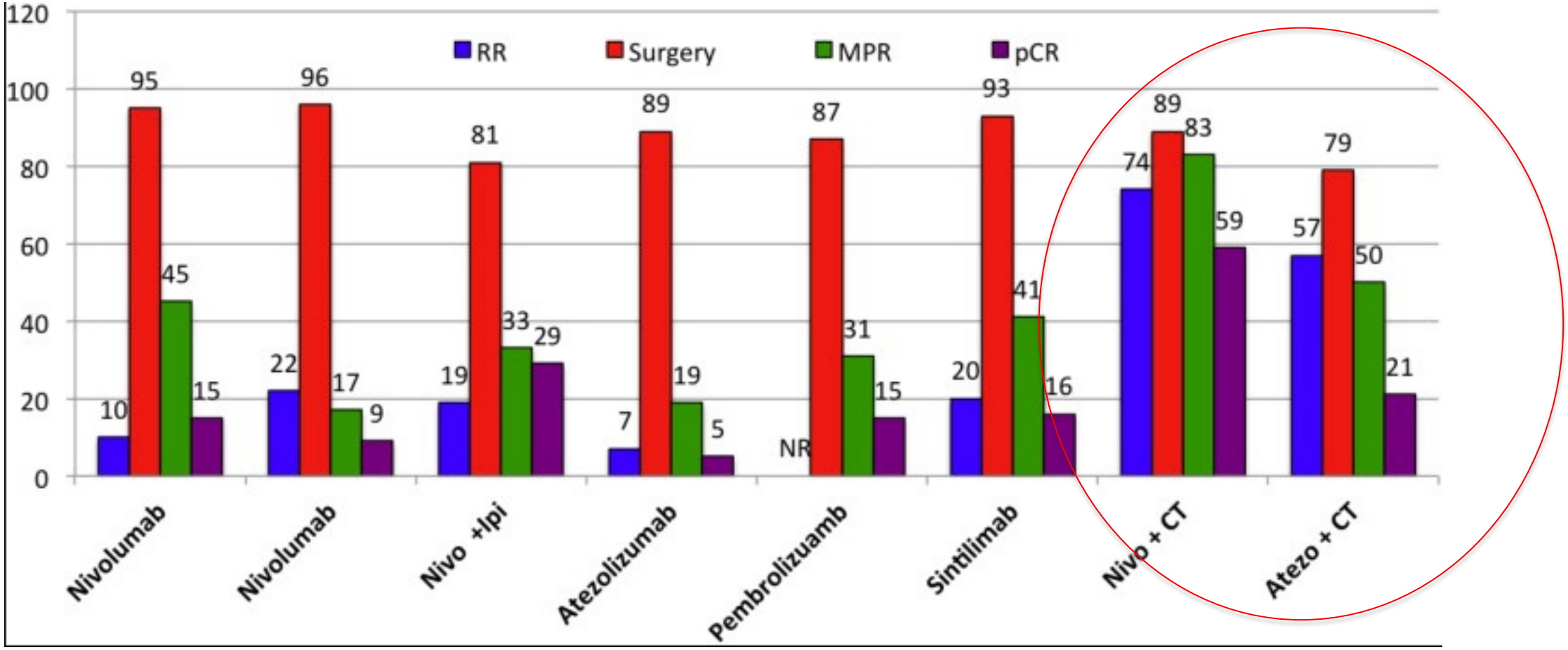
Key Results - NADIM

- 46 patients with clinical stage IIIA enrolled, 74% N2 including 54% multi-station N2
- 30% of pts had ≥G3 toxicity, no delays to surgery due to toxicity
- ORR 76%, 41 of 46 patients underwent R0 resection*. 37/46 (80%) downstaged at resection.
- 24 month PFS – 77% (59.9-87.7)
- 74% (34/46) had MPR and **57% (26/46) pts had pCR**



*2 pts elected not to have surgery, 3 pts had progressive disease

Efficacy of neoadjuvant immune checkpoint inhibitors (ICIs) with or without chemotherapy (CT)



Check

CheckMate 816 study design[a]

FDA approved 3/2022

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 816—Baseline Characteristics

	NIVO + Chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41–82)	65 (34–84)
Female, %	28	29
Region, %*		
North America	23	28
Europe	23	14
Asia	48	51
Stage, %†		
IB–II‡	36	35
IIIA	63	64
Histology, %		
Squamous	49	53
Nonsquamous	51	47
Smoking status, %§		
Current / former	89	88
Never	11	11

	NIVO + Chemo (n = 179)	Chemo (n = 179)
Tumor PD-L1 expression, %¶		
Not evaluable	7	7
<1%	44	43
≥1%	50	50
1%–49%	28	26
≥50%	21	24
TMB, %¶		
Not evaluable / not reported//	51	50
<12.3 mut/Mb	27	30
≥12.3 mut/Mb	22	21

Baseline characteristics in the NIVO + IPI (exploratory) arm were generally similar to the NIVO + chemo and chemo arms

*Rest of the world: 7% of patients in each of the NIVO + chemo and chemo arms. †Disease stage by CRF, with TNM 7th edition used for classification; 1 patient in each of the NIVO + chemo and chemo arms had stage IV disease. ‡Stage IB, IIA, IIB disease: 6%, 17%, and 14% of patients in the NIVO + chemo arm, and 4%, 18%, and 13% in the chemo arm, respectively. §Smoking status unknown: 1 patient in chemo arm. ¶Percentages are based on ITT. //TMB was not analyzed for patients in China, and these patients are included in the "not reported" category.

Abbreviations: ITT, intention to treat; NICO, nivolumab; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.

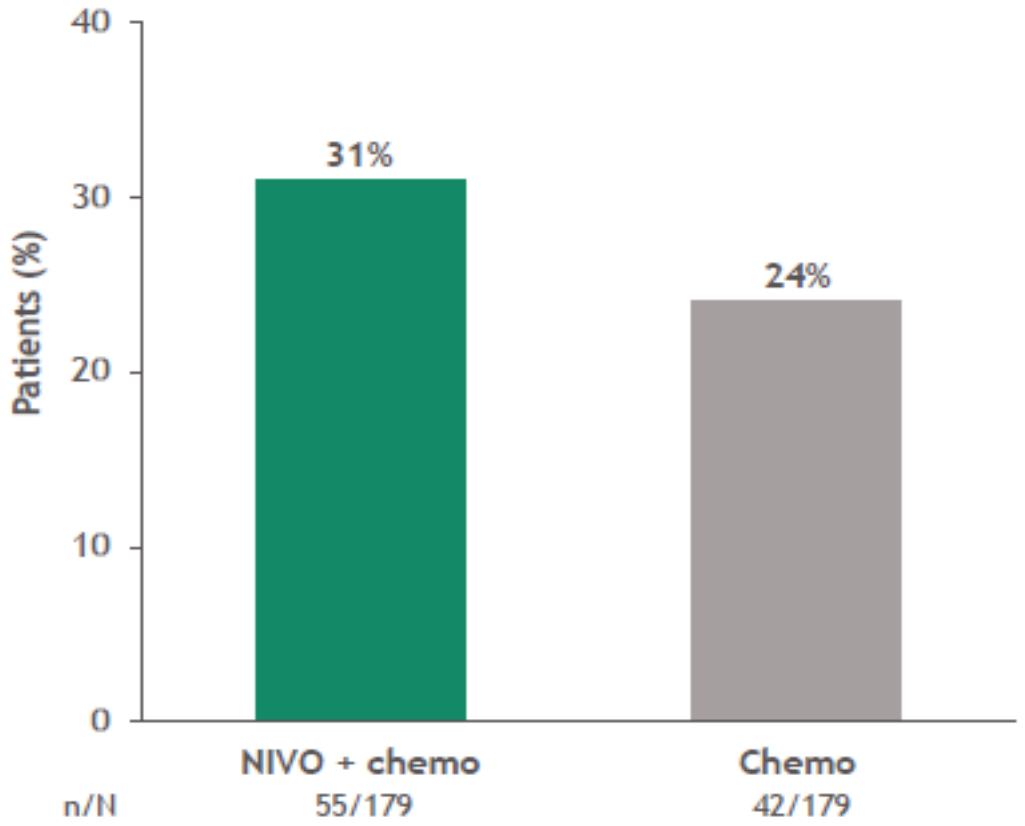
Forde PM, et al. Abstract CT003. Presented at: 2021 AACR; April 10–15, 2021. Graphic courtesy of Patrick Forde, MBBCh.

Objective response rate and radiographic down-staging

Objective response rate

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
ORR[a]	96 (54)[b]	67 (37)[b]
Best overall response		
Complete response	1 (1)	3 (2)
Partial response	95 (53)	64 (36)
Stable disease	70 (39)	88 (49)
Progressive disease	8 (4)	11 (6)
Not evaluable	1 (1)	1 (1)
Not reported	4 (2)	12 (7)

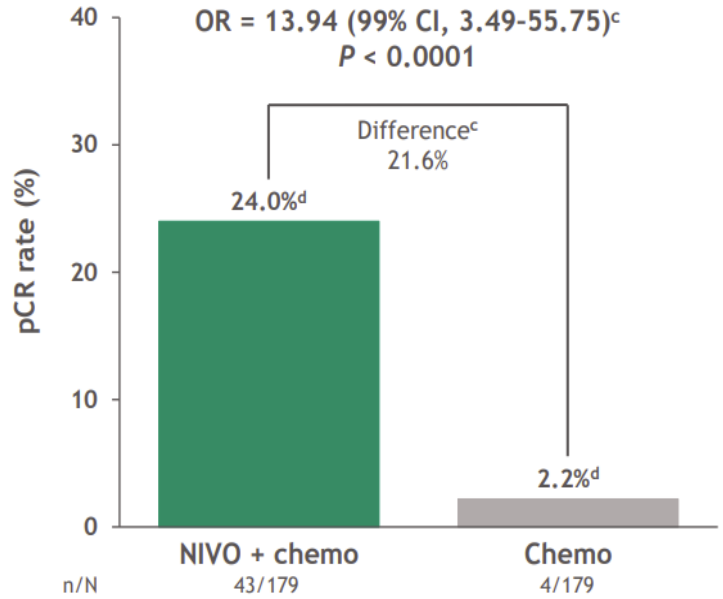
Patients with radiographic down-staging[c]



[a]Objective response rate was up to the presurgical scan; [b]ORR rates 95% CI: NIVO + chemo, 46-61; chemo, 30-45; [c]Decrease in stage from baseline to presurgical scan.

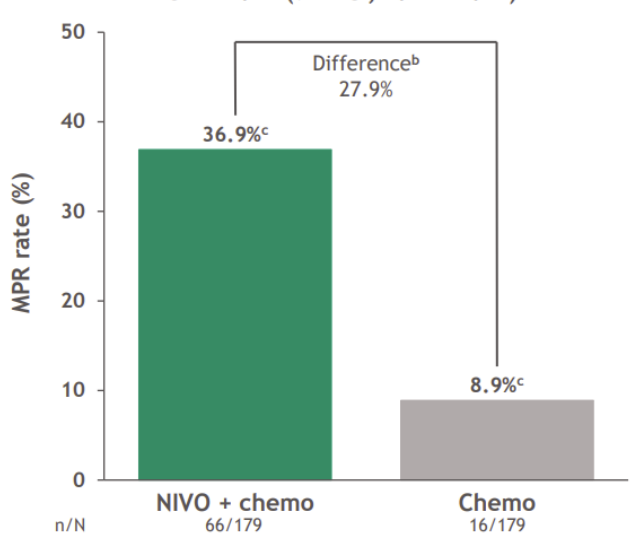
Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo

Primary endpoint: ITT (ypT0N0)[b]



MPR[a] rate with neoadjuvant NIVO + chemo vs chemo

ITT



[a]Per BIPR; MPR: ≤ 10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Calculated by stratified Cochran-Mantel-Haenszel method; [c]MPR rates 95% CI: NIVO + chemo, 29.8-44.4; chemo, 5.2-14.1.

CheckMate 816 Summary—Neoadjuvant Nivolumab Plus Chemotherapy vs Chemotherapy for Resectable NSCLC

- CheckMate 816 showed a statistically significant improvement in the primary endpoint of pCR (OR = 13.94 [99% CI, 3.49–55.75]; *P* <.0001), and benefit was consistent across disease stages, histologies, TMB, and PD-L1 expression levels
  - MPR and ORR were also improved
  - The study reportedly also now positive for EFS
- The addition of neoadjuvant nivolumab to chemotherapy maintained a tolerable safety profile and did not impede the feasibility of surgery
- In an exploratory subset analysis, ctDNA clearance was more frequent with nivolumab plus chemotherapy vs chemotherapy alone and appeared to be associated with pCR
- CheckMate 816 is the first phase III study to show the benefit of neoadjuvant immunotherapy plus chemotherapy combination for resectable NSCLC

Abbreviations: ctDNA, circulating tumor DNA; EFS, event-free survival; MPR, major pathologic response; NSCLC, non-small cell lung cancer; ORR, objective response rate; pCR, pathologic complete response; TMB, tumor mutational burden.

Forde PM, et al. Abstract CT003. Presented at: 2021 AACR; April 10–15, 2021.

Ongoing Phase III Trials of Neoadjuvant Chemotherapy Plus PD-1/PD-L1 Antibody in NSCLC

PD-1/PD-L1 Antibody	Trial (Estimated Enrollment)	Stage (AJCC ed)	Backbone	Neoadjuvant IO Intervention	Adjuvant IO Intervention	Primary Endpoints
Nivolumab	CheckMate 816[1] (N = 350)	IB–IIIA (7^{th})	Platinum-doublet chemotherapy	+/- Nivolumab IPI + NIVO (closed)	No	pCR EFS
	CheckMate 7TT[2] (N = 452)	II–IIIB (8^{th})	Platinum-doublet chemotherapy	Nivolumab or placebo	Nivolumab or placebo	EFS
Pembrolizumab	KEYNOTE-671[3] (N = 786)	IIA–IIIB (8^{th})	Platinum-doublet chemotherapy	Pembrolizumab or placebo	Pembrolizumab or placebo	EFS OS
Atezolizumab	IMpower030[4] (N = 450)	II–IIIB (8^{th})	Platinum-doublet chemotherapy	Atezolizumab or placebo	Atezolizumab or BSC	EFS
Durvalumab	AEGEAN[6] (N = 800)	IIA-IIIB (8^{th})	Platinum-doublet chemotherapy	Durvalumab or placebo	Durvalumab or placebo	pCR EFS

1. CheckMate 816 positive for both pCR and EFS endpoints at 1^{st} interim analysis – BMS press release Nov 2021

Abbreviations: AJCC, American Joint Commission on Cancer; BSC, best supportive care; ed, edition; EFS, event-free survival; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer. OS, overall survival; pCR, pathologic complete response; PD-1, PD-L1, programmed death ligand 1. PD-L1, programmed death ligand 1. 1. ClinicalTrials.gov. Accessed 8/12/21 at: https://clinicaltrials.gov/ct2/show/NCT02998528 2. ClinicalTrials.gov. Accessed 8/12/21 at: https://clinicaltrials.gov/ct2/show/NCT04025879 3. ClinicalTrials.gov. Accessed 8/12/21 at: https://clinicaltrials.gov/ct2/show/NCT03425643 4. ClinicalTrials.gov. Accessed 8/12/21 at: https://clinicaltrials.gov/ct2/show/NCT03456063 5. ClinicalTrials.gov. Accessed 8/12/21 at: https://clinicaltrials.gov/ct2/show/NCT03800134

ADJUVANT IMMUNOTHERAPY IN NSCLC

The Unmet Need in Early-Stage and Locally Advanced NSCLC

A retrospective review of complete surgical resection for early-stage (N=1294) and stage IIIA (N=346) NSCLC[a] found[1,2]:

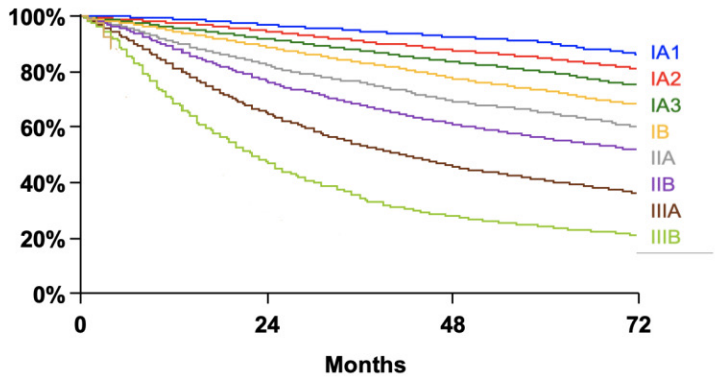
Recurrence Rates by Stage[1,2]

20% for patients with stage I or II NSCLC[1]

52% for patients with stage IIIA NSCLC[2]

A review of a global database of NSCLC (N=25,911 with pathological staging[b]) found[3]:

Overall Survival by Pathological Stage[b]

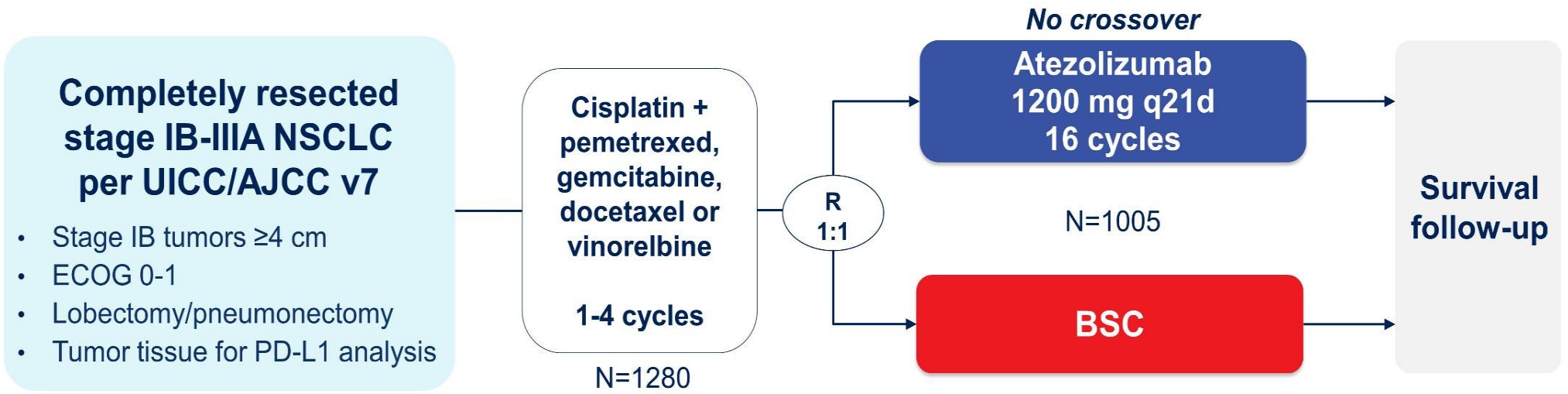


60-month survival decreased from **90%** for stage IA1 to **24%** for stage IIIB[3]

[a]Based on 7th edition AJCC cancer staging. [b]Based on the proposed 8th edition AJCC cancer staging.
AJCC=American Joint Committee on Cancer.

1. Lou F, et al. *J Thorac Cardiovasc Surg*. 2013;145:75-81; 2, Lou F, et al. *Ann Thorac Surg*. 2014;98:1755-1760; 3. Goldstraw P, et al. *J Thorac Oncol*. 2016;11:39-51.

IMpower010: study design



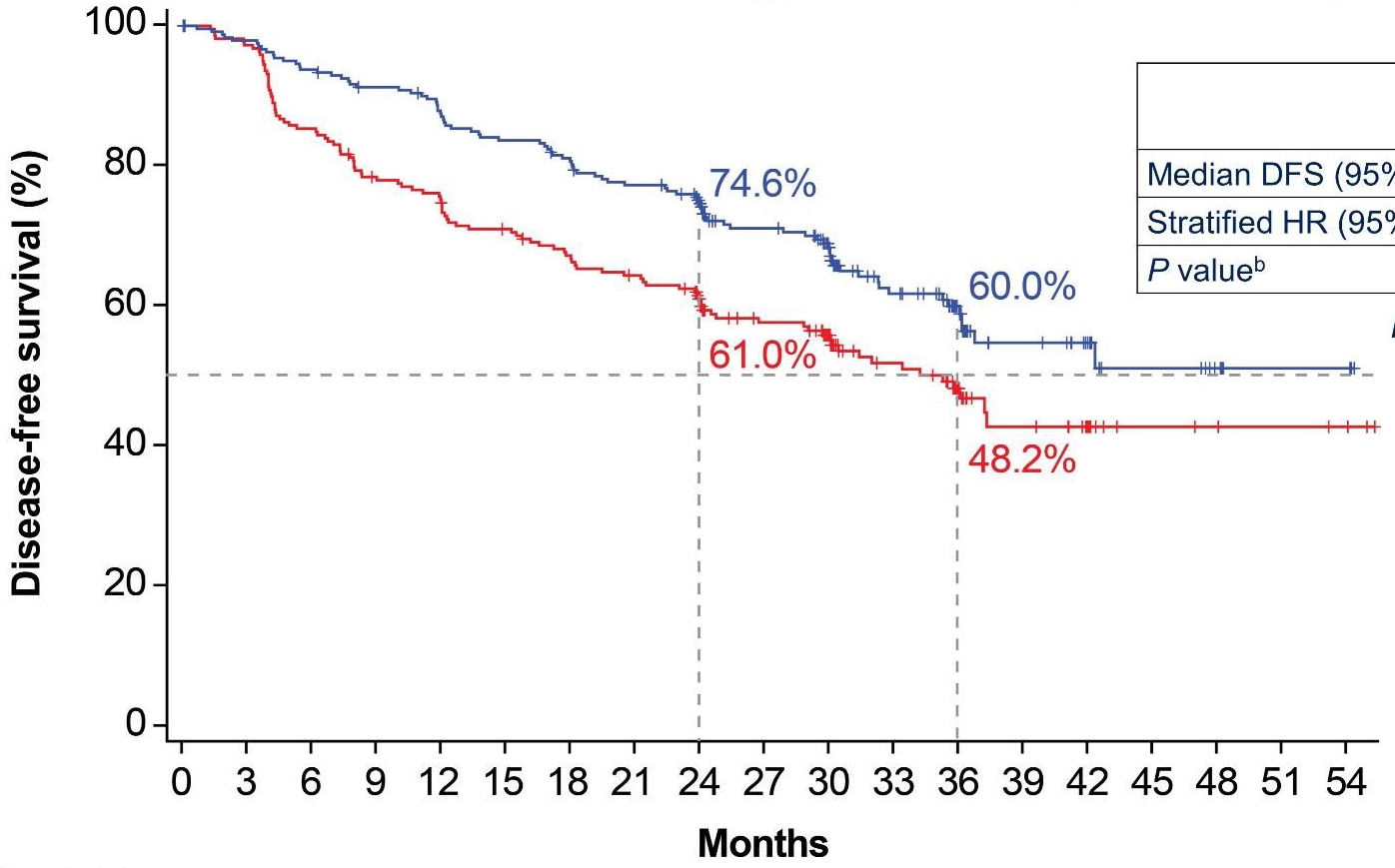
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)

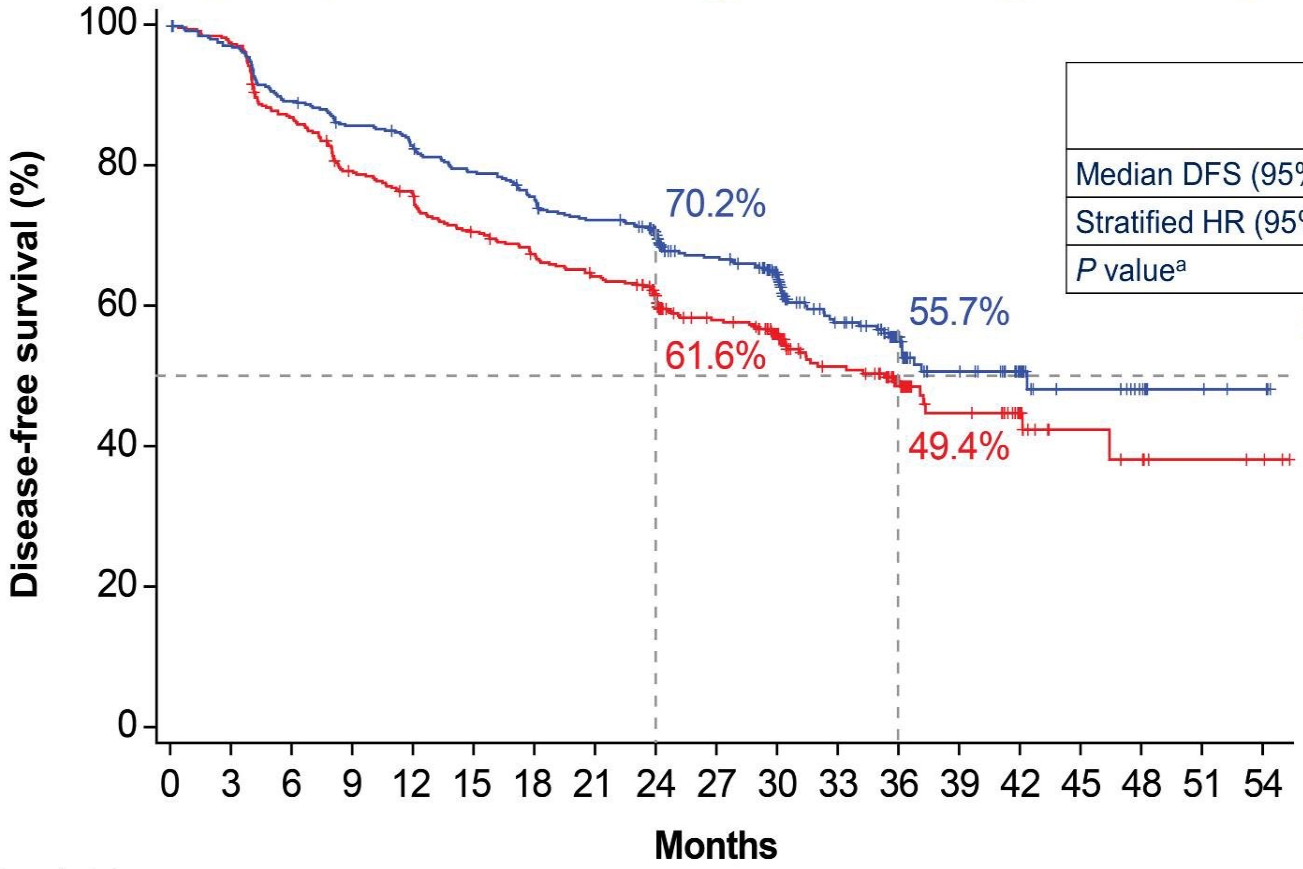


	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)

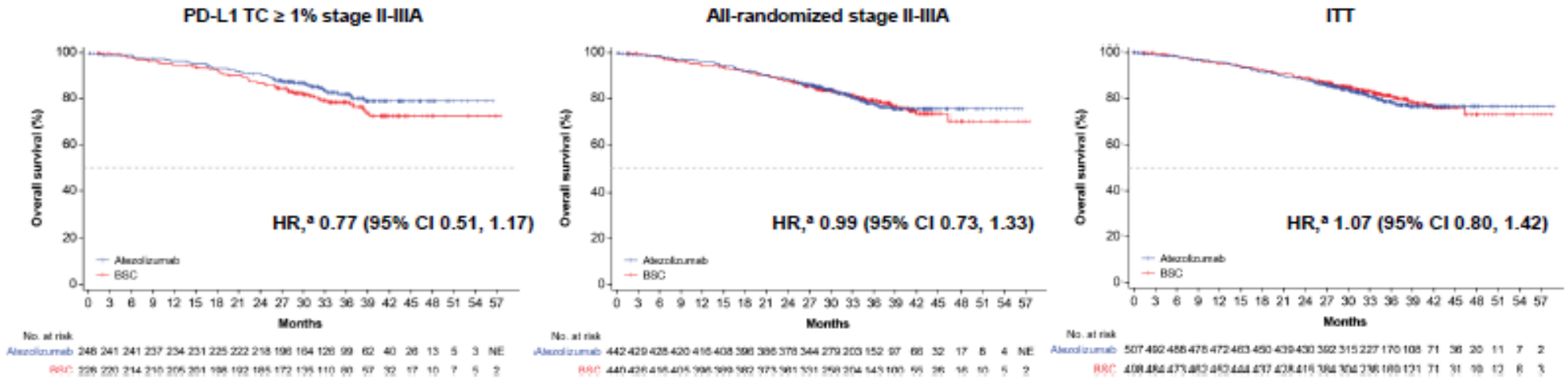


	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

IMpower010: early OS data at interim- Exploratory DFS analysis

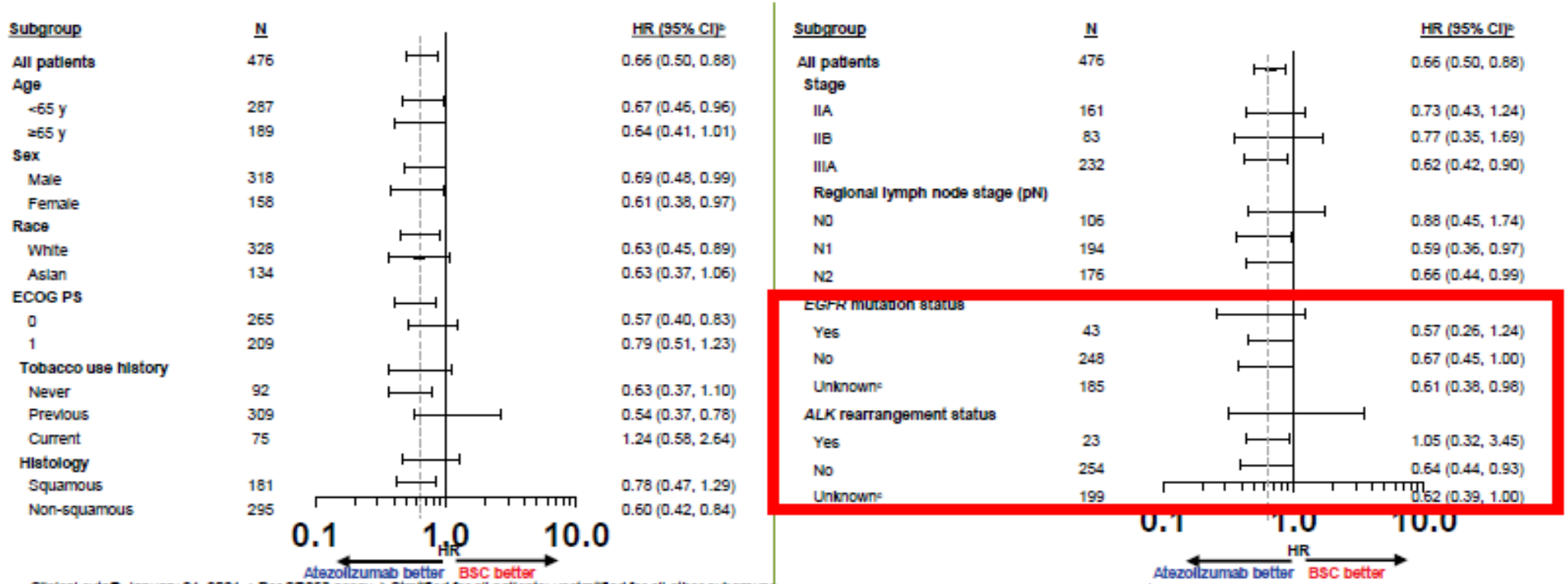


- OS data were immature at this pre-planned DFS interim analysis
  - OS in the ITT population was not formally tested
  - A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Clinical cutoff: January 21, 2021. [a] Stratified.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; https://bit.ly/33t6JJ; Felip Lancet 2021

IMpower010: DFS in key subgroups of the PD-L1 TC ≥1%[a] stage II-IIIA population



Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified for all patients; unstratified for all other subgroups.
[c] 89.2% and 80.7% of patients in the ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo local or central testing.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; https://bit.ly/33t6JJ; Felip Lancet 2021

IMpower010: conclusions

- IMpower010 is the first Phase III study of cancer immunotherapy to demonstrate DFS improvement in the adjuvant NSCLC setting after platinum-based chemotherapy
  - Adjuvant atezolizumab following complete resection and adjuvant chemotherapy showed statistically significant DFS benefit in the PD-L1 TC ≥1% stage II-IIIA (HR, 0.66; 95% CI: 0.50, 0.88) and all-randomized stage II-IIIA (HR, 0.79; 95% CI: 0.64, 0.96) populations, with enriched clinical benefit in patients whose tumors express PD-L1
- IMpower010 will continue for DFS and OS analyses in the ITT population
  - DFS in the ITT population, including patients with stage IB disease, did not cross the significance boundary at this interim DFS analysis
  - At this pre-planned interim DFS analysis, OS data were immature and not formally tested
- The safety profile of atezolizumab was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy
- Atezolizumab may be considered a practice-changing adjuvant treatment option for patients with PD-L1 TC ≥1% stage II-IIIA NSCLC

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration

- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization

- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

- Pembrolizumab 200 mg Q3W for 18 administrations (~1 yr)
- Placebo Q3W for 18 administrations (~1 yr)

Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ESMO VIRTUAL PLENARY

ClinicalTrials.gov number, NCT02504372.

Baseline Characteristics, Overall Population

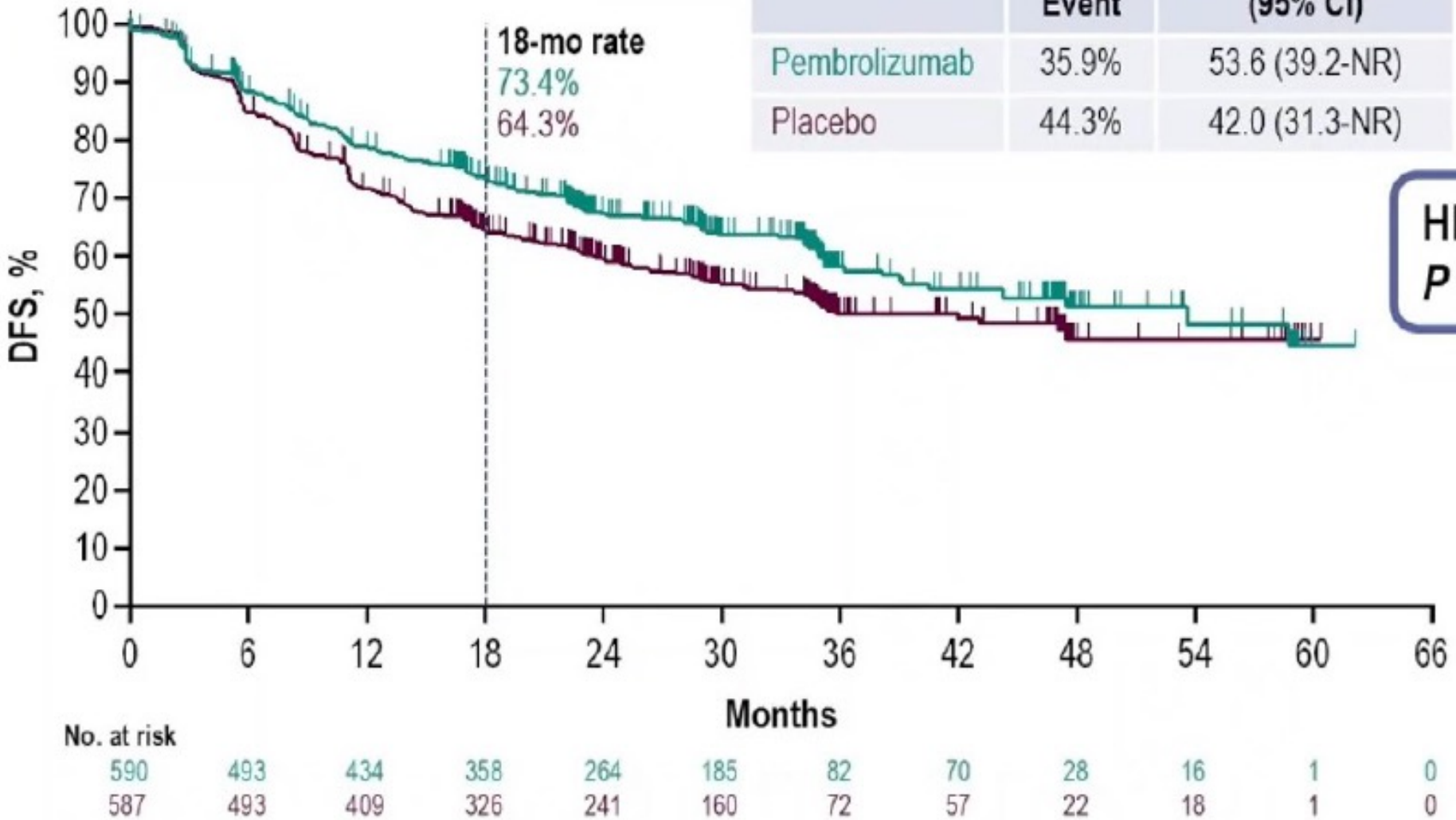
	Pembrolizumab (N = 590)	Placebo (N = 587)
Age, median (range)	65 y (31-87)	65 y (37-85)
Male	401 (68.0%)	403 (68.7%)
Geographic region		
Asia	106 (18.0%)	105 (17.9%)
Eastern Europe	116 (19.7%)	113 (19.3%)
Western Europe	303 (51.4%)	301 (51.3%)
Rest of world	65 (11.0%)	68 (11.6%)
ECOG PS 1	210 (35.6%)	244 (41.6%)
Current/former smoker	503 (85.3%)	521 (88.8%)
***EGFR* mutation**[a]	39 (6.6%)	34 (5.8%)
***ALK* translocation**[b]	7 (1.2%)	7 (1.2%)
Nonsquamous histology	398 (67.5%)	363 (61.8%)
Pathologic stage[c]		
IB	84 (14.2%)	85 (14.5%)
II	329 (55.8%)	338 (57.6%)
IIIA	177 (30.0%)	162 (27.6%)
Received adjuvant chemotherapy		
Yes	506 (85.8%)	504 (85.9%)
No	84 (14.2%)	83 (14.1%)
PD-L1 TPS		
<1%	233 (39.5%)	232 (39.5%)
1-49%	189 (32.0%)	190 (32.4%)
≥50%	168 (28.5%)	165 (28.1%)

[a] *EGFR* status unknown for 333 (56.4%) in pembro arm and 337 (57.4%) in placebo arm.
[b] *ALK* status unknown for 357 (60.5%) in pembro arm and 390 (66.4%) in placebo arm.
[c] 2 (0.3%) participants in the placebo group had stage IV disease.

Data cutoff date: September 20, 2021

DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



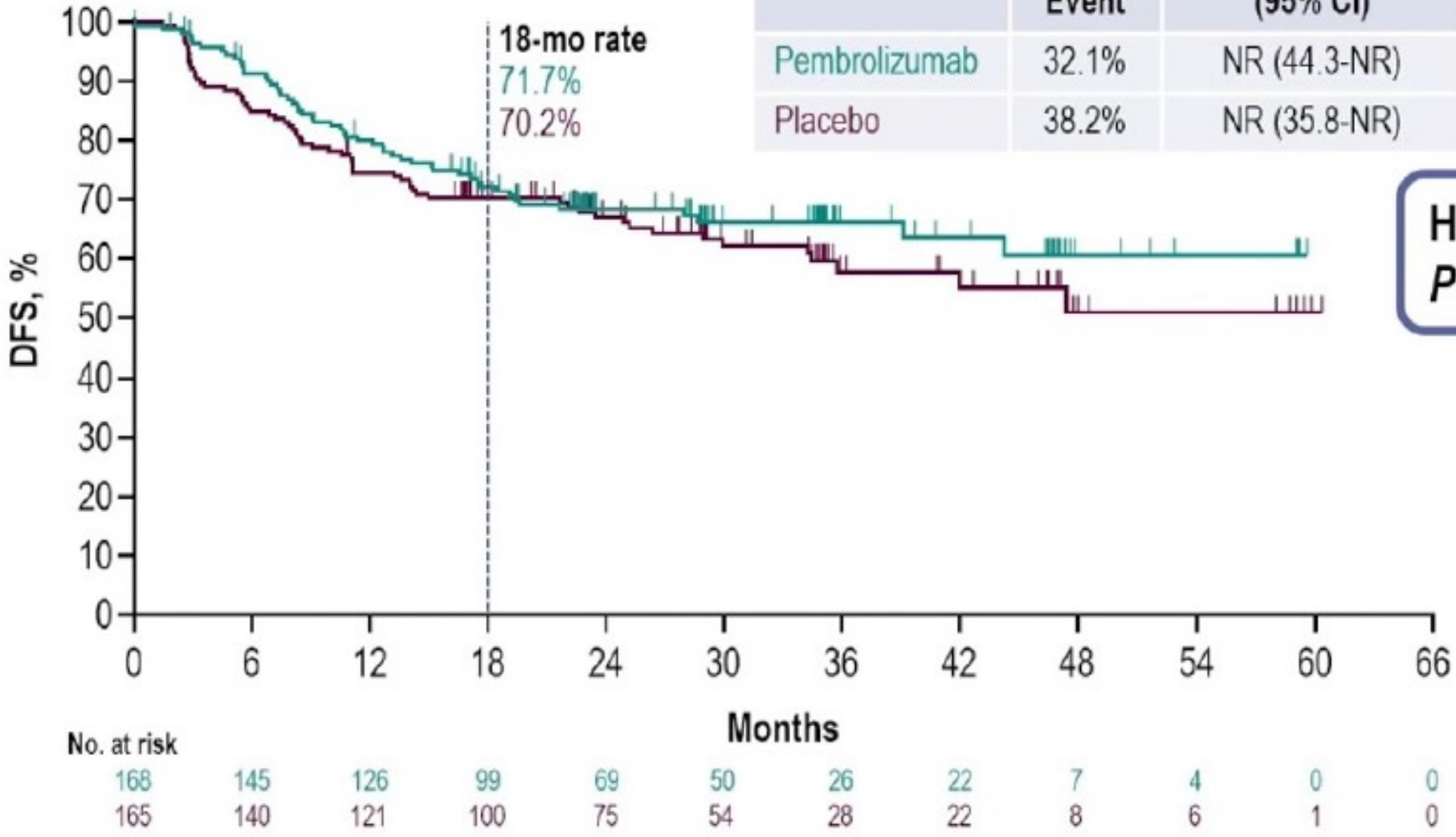
HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

DFS, PD-L1 TPS ≥50% Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)



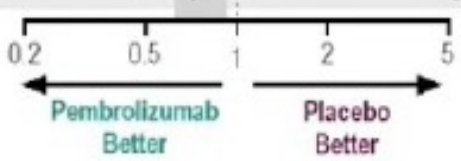
HR 0.82 (95% CI, 0.57-1.18)
P = 0.14

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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)

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	84/167	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)



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

Summary of Adverse Events

	Pembrolizumab (N = 580)	Placebo (N = 581)
Any	556 (95.9%)	529 (91.0%)
Grade 3-5	198 (34.1%)	150 (25.8%)
Led to death	11 (1.9%)	6 (1.0%)
Treatment-related	4 (0.7%)[a]	0 (0.0%)
Serious	142 (24.5%)	90 (15.5%)
Led to treatment discontinuation	115 (19.8%)	34 (5.9%)
Led to treatment interruption	221 (38.1%)	145 (25.0%)

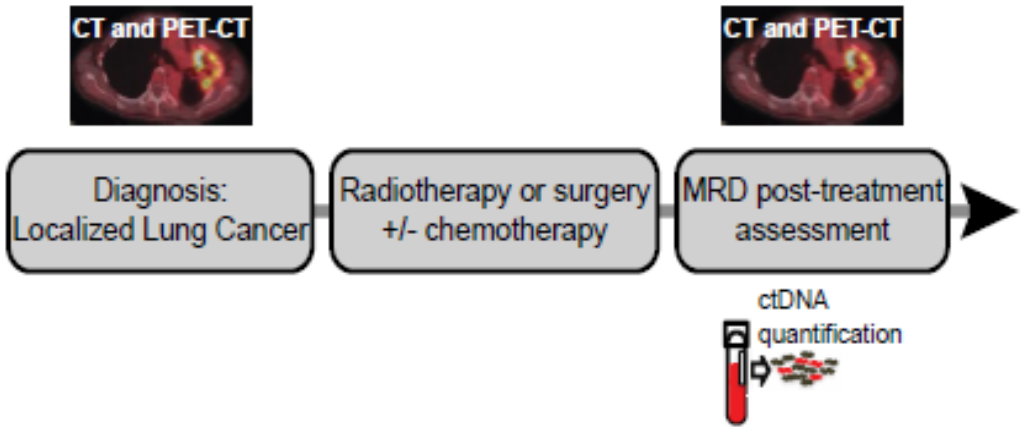
[a] 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

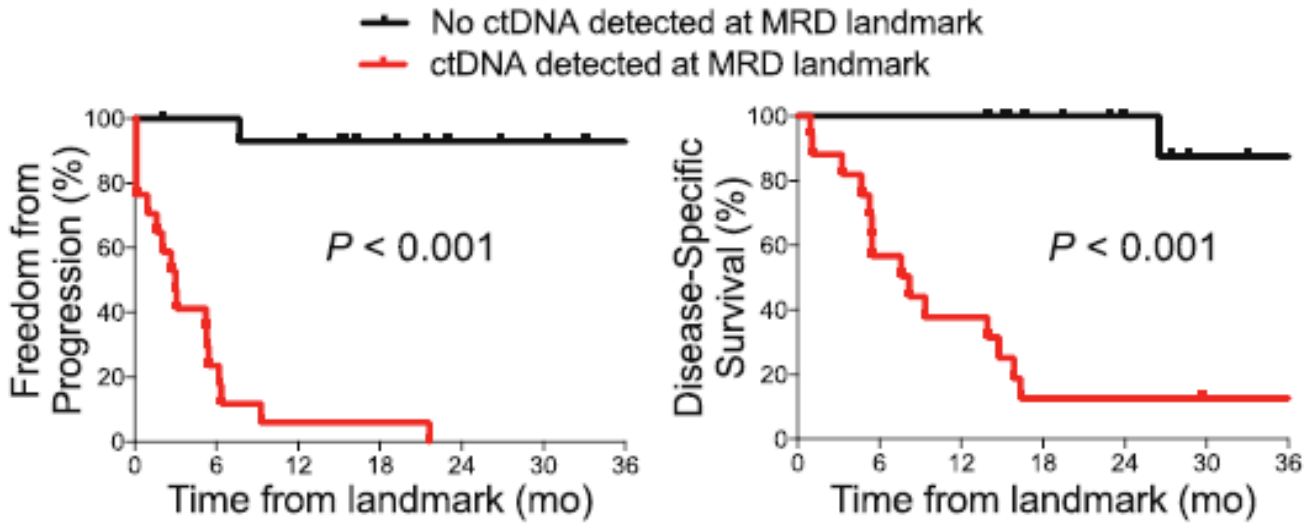
Data cutoff date: September 20, 2021

Summary and Conclusions

- Pembrolizumab provided statistically significant, clinically meaningful DFS improvement versus placebo in the overall population
  - Median DFS of 53.6 months with pembrolizumab vs 42.0 months with placebo (HR, 0.76)
  - Generally consistent DFS benefit in participants with PD-L1 TPS <1%, 1-49%, and ≥50%
  - OS data are immature
  - DFS in the PD-L1-defined populations and OS will be tested at future analyses according to the analysis plan
- Pembrolizumab safety profile as expected
- **Data suggest pembrolizumab has the potential to be a new adjuvant treatment option for patients with stage IB (T ≥4 cm) to IIIA NSCLC following complete resection and adjuvant chemotherapy when recommended, regardless of PD-L1 expression**

ctDNA Minimal Residual Disease in Localized Lung Cancer

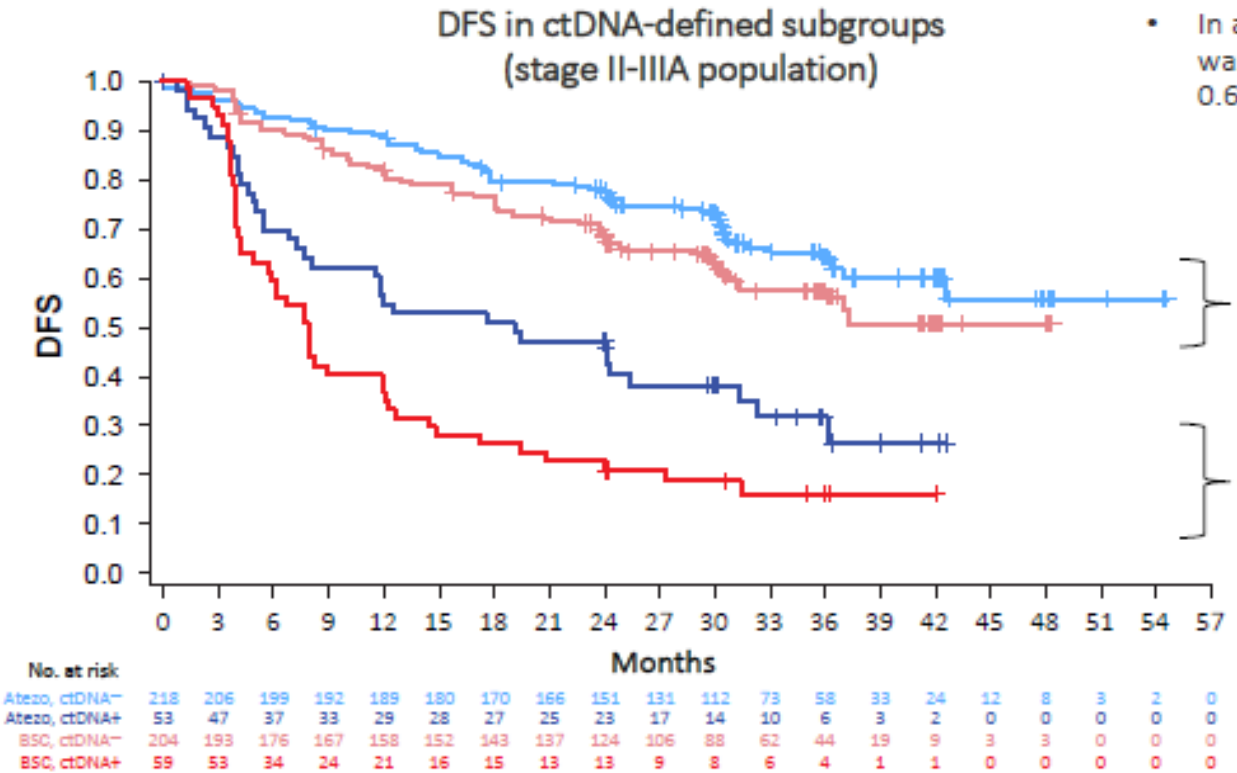




Residual ctDNA after completion of therapy is associated with an extremely high risk of recurrence

Chaudhuri et al. *Cancer Discovery* 2017

IMpower010 ctDNA MRD Analysis



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Benefit of consolidation immunotherapy is strongest in ctDNA-positive patients

Zhou et al. *ESMO Immuno-Oncology* 2021

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A081801

INTEGRATION OF IMMUNOTHERAPY INTO ADJUVANT THERAPY FOR RESECTED NSCLC: ALCHEMIST CHEMO-IO

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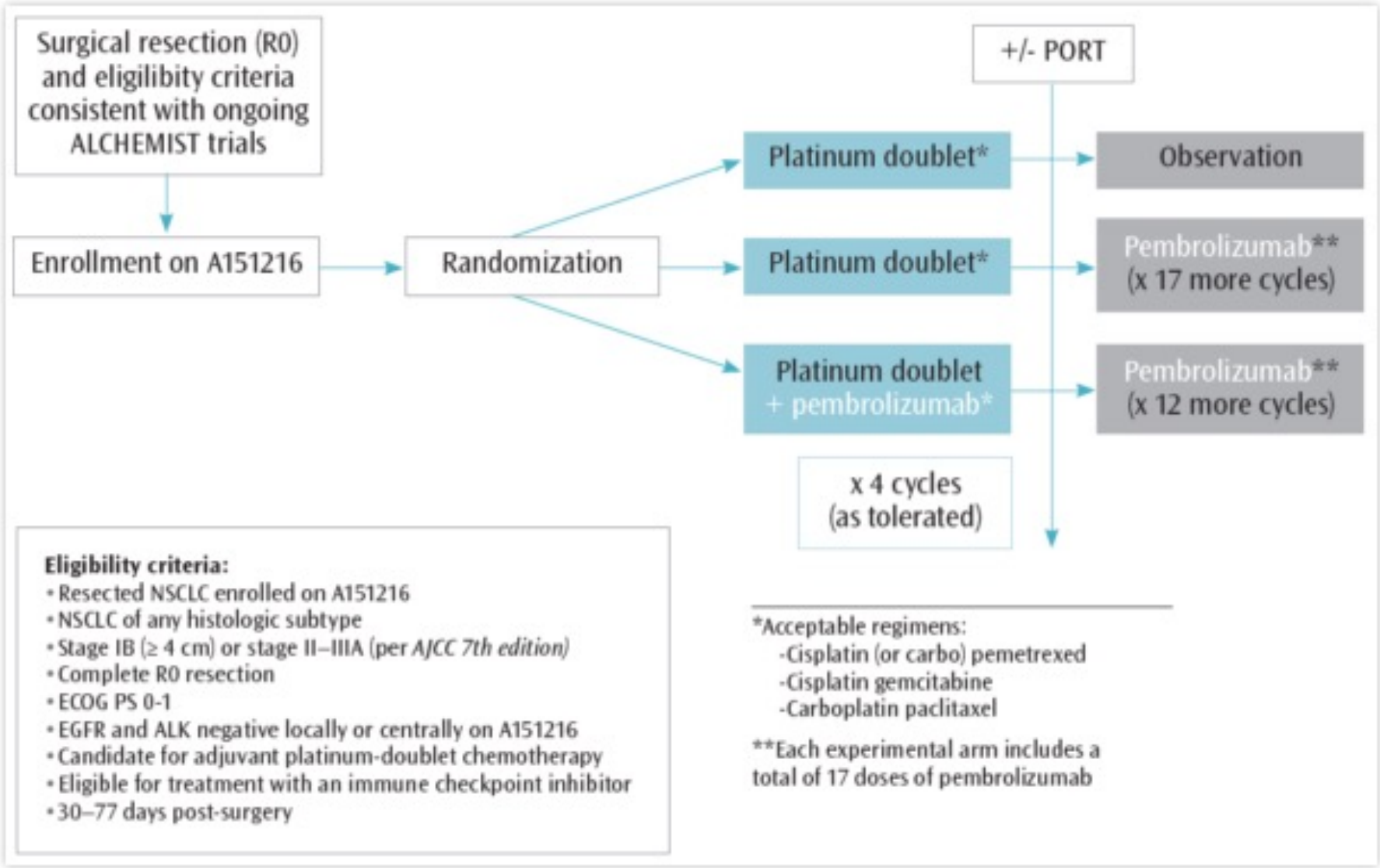
Figure 1. Schema: ALCHEMIST CHEMO-IO



Adjuvant PD-1/PD-L1 IO trials

Drug/Trial	Description	Stages entered	Description	Primary endpoint
Nivolumab	US, NCI (ECOG), Observational control	IB (4cm)-IIIA After Adj Chemo +/- radiation	Phase 3 Allows PD-L1 +/-	OS/DFS
Atezolizumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Durvalumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Pembrolizumab PEARLS KN-091	ETOP/EORTC, Placebo Controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS

1) Adjuvant IO therapy with proven DFS benefit in PD-L1+ stage II-IIIA NSCLC pts
2) Adjuvant IO + chemotherapy trials needed
3) Patient and tumor specific biomarkers necessary to predict benefit
    - -Improve upon PD-L1
    - -Fully understand tumor mutation relevance
    - -Many other factors
4) ctDNA and other biomarkers to select patients who need therapy

Pre-operative vs. Postoperative IO: General considerations

- **Both have the disadvantage that you are treating a lot of people who may be cured by surgery alone with expensive drugs for a long time**
  - No robust biomarkers for relapse or benefit from IO
- **Postoperative:**
  - No delay or potential interference with the most effective regimen (surgery)
  - Longest experience, more accurate staging
  - Patients/surgeons don't like to delay surgery
- **Preoperative:**
  - Ability to assess antitumor efficacy of the intervention, – may not need postoperative IO if pCR
  - Early systemic therapy
  - Intact nodal drainage and tumor might be a benefit for immunity/IO therapy
  - Access to pre- and post biospecimens for research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