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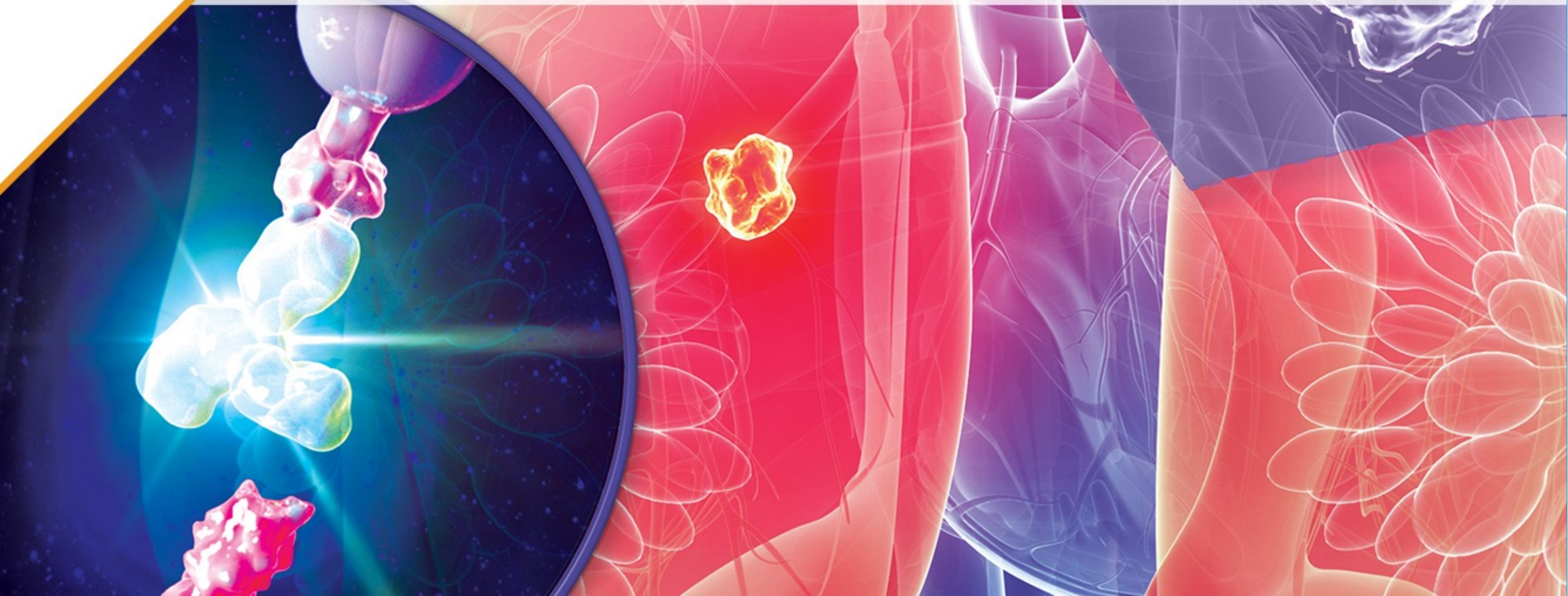
Adjuvant Treatment of Early Non–Small Cell Lung Cancer in the Era of Immunotherapy



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Disclosure of Conflicts of Interest
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Activity Agenda

- Early-Stage NSCLC and the Role of Immunotherapy
- Clinical Advances With Immunotherapies in the Adjuvant Setting
- Case Consultations
- What's on the Horizon in the Neoadjuvant Setting?
- Essential Takeaways

Early-Stage NSCLC and the Role of Immunotherapy

AJCC Staging: Changes From 7th to 8th Edition (2017)

	TNM 7th Edition	TNM 8th Edition
T	-	Tis
	-	Tmi
	-	Tss
	T1a (≤2 cm) →	T1a (≤1 cm)
	T1b (>2-3 cm)	T1b (>1-2 cm)
		T1c (>2-3 cm)
	T2a (>3-5 cm) →	T2a (>3 cm but ≤4 cm)
	T2b (>5-7 cm)	T2b (>4 cm but ≤5 cm)
	T3 (>7 cm) →	T4
	T3 – atelectasis/pneumonitis involving whole lung	T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung
	T3 – tumor involving the main bronchus <2cm distance to carina →	T2 – tumor involving the main bronchus irrespective of distance to carina
	T3 – invasion of the diaphragm →	T4 – invasion of the diaphragm
N	No changes	
M	M1b – distant metastasis →	M1b – single extrathoracic metastasis
		M1c – multiple extrathoracic metastases

AJCC, American Joint Committee on Cancer.
Adapted from Mets and Smithuis. *TNM Classification*. 2017.

AJCC Staging NSCLC 8th Edition (2017)

T/M	Subcategory	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

AJCC, American Joint Committee on Cancer.
Adapted from Detterbeck. *J Thorac Cardiovasc Surg*. 2018;155:356-359.

Adjuvant Therapy Background

Management Approach

Resectable disease

(Stage I-II, *some* IIIA)

- Surgery remains the primary treatment of choice for local (*resectable*) disease
- Data from several phase 3 trials suggest a moderate benefit (~5% at 5 years) from neoadjuvant or adjuvant cisplatin-based chemotherapy for resected stage II and IIIA NSCLC

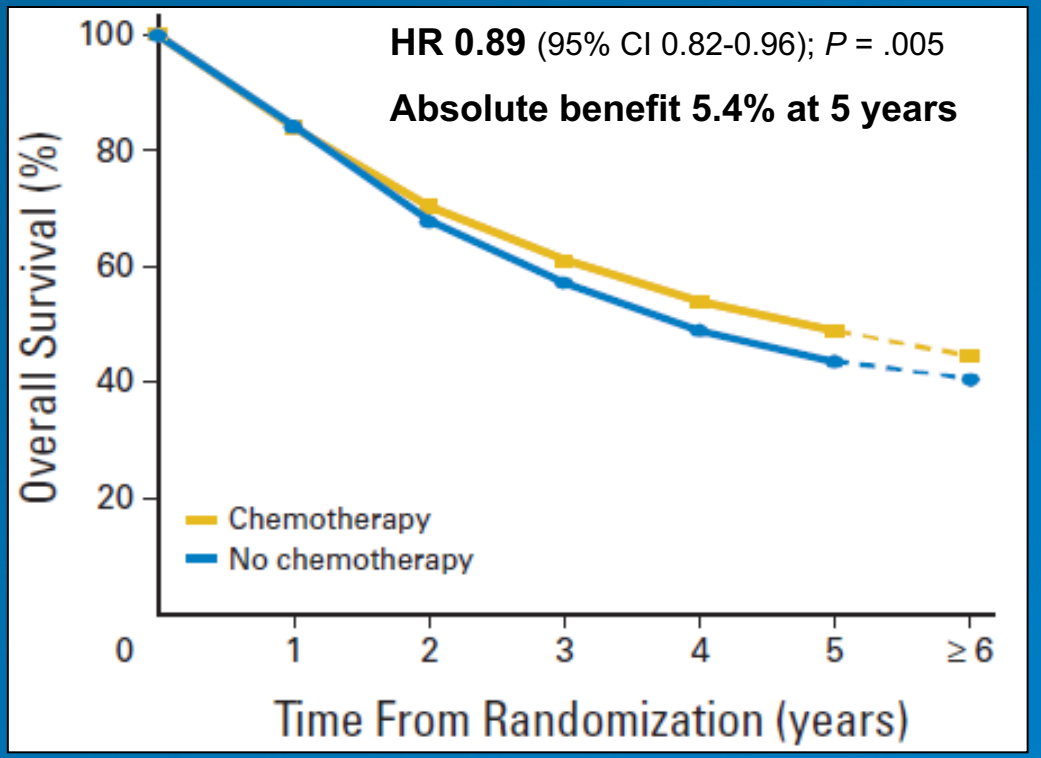
Unresectable disease

(Some IIIA, virtually all IIIB-C)

- Standard treatment for locally advanced, *unresectable* disease includes definitive chemoradiation followed by durvalumab maintenance
- Stage IIIA is a heterogenous disease and includes multiple T and N staging criteria

Meta-Analysis: Lung Adjuvant Cisplatin Evaluation (LACE)

- 5 studies since 1995
  - BLT, ALPI, IALT, JBR.10, ANITA
- Pooled individual data
  - 4,585 patients
- Chemotherapy
  - ↓6.9% lung cancer death
  - ↑1.4% non-cancer death



ALPI, Adjuvant Lung Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; IALT, International Adjuvant Lung Cancer Trial; JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10.
Pignon et al. *J Clin Oncol*. 2008;26:3552-3559.

ADAURA Study Design: Osimertinib as Adjuvant Therapy

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- Confirmed primary non-squamous NSCLC
- *EGFR* Ex19del/L858R**
- Complete resection with negative margins §

Stratification by:
- Stage (IB vs II vs IIIA)
- EGFRm (Ex19del vs L858R)
- Race (Asian vs non-Asian)

Randomization 1:1 (N = 682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 yrs

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

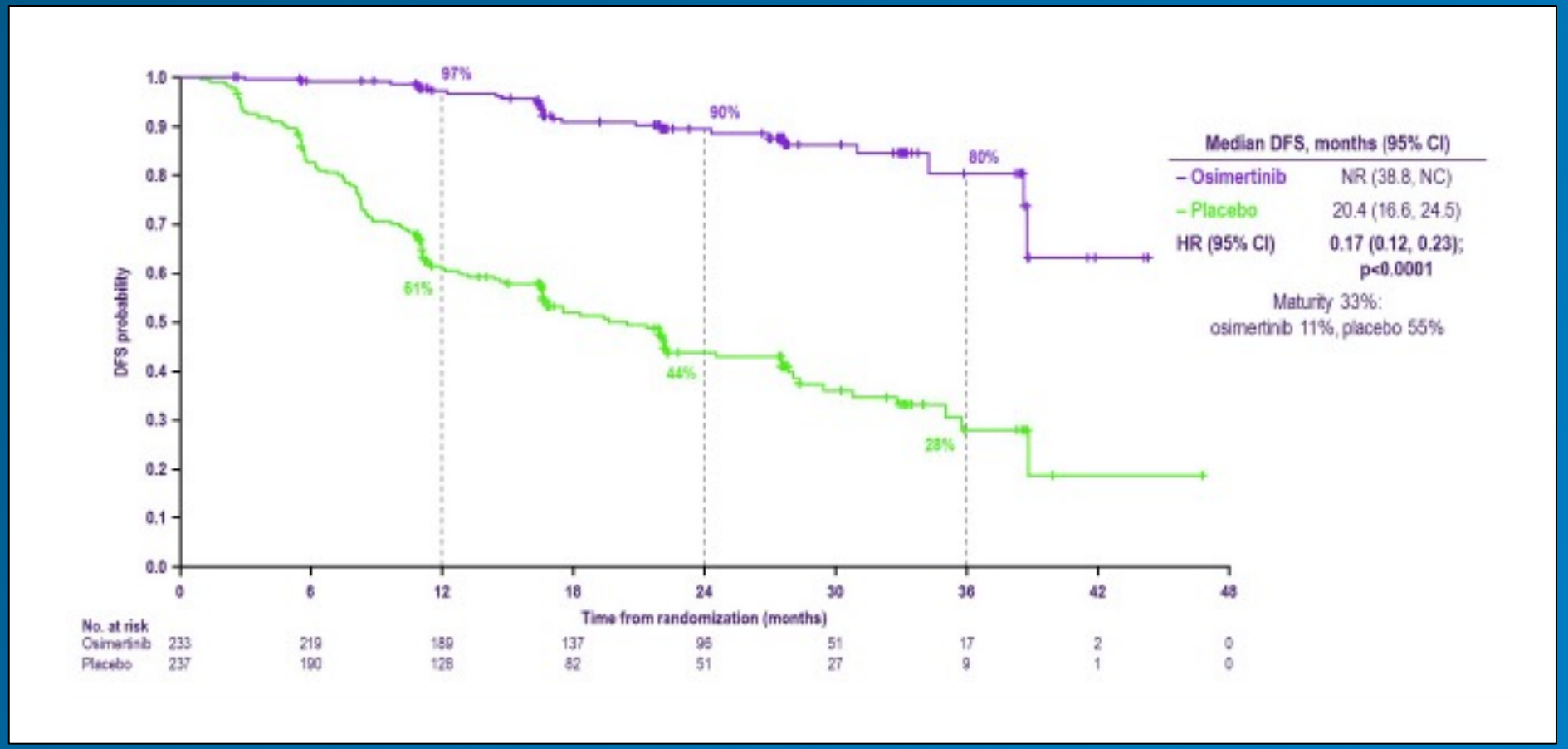
Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- Primary: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- Secondary: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis
- At the time of unblinding, the study had completed enrollment and all patients were followed up for at least 1 year

NCT02511106; ADAURA data cut-off. January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; **Centrally confirmed in tissue; § Patients received a CT scan after resection and within 28 days prior to treatment; ¶ Stage IB/II/IIIA.
CT, computed tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; OS, overall survival; WHO, World Health Organization.
Adapted from Herbst et al. *J Clin Oncol*. 2020;38:LBA5.

ADAURA Primary Endpoint: DFS in Patients With Stage II/IIIA Disease



DFS, disease-free survival; NR, not reached.
Adapted from Herbst et al. *J Clin Oncol*. 2020;38:LBA5.

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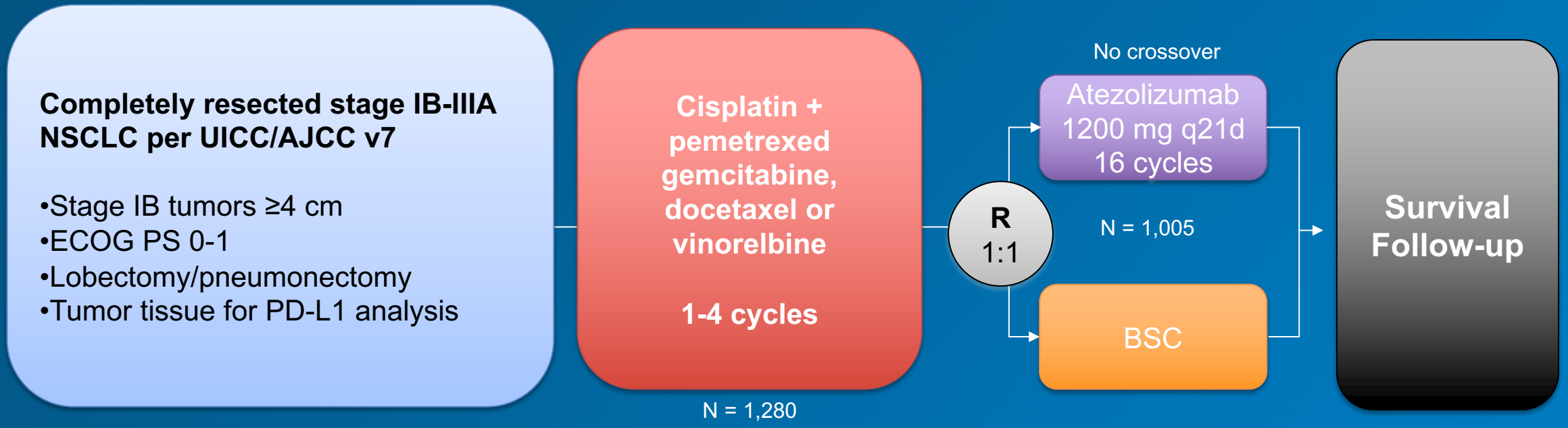
Adjuvant Immunotherapy

IMpower010: Study Design



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- 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

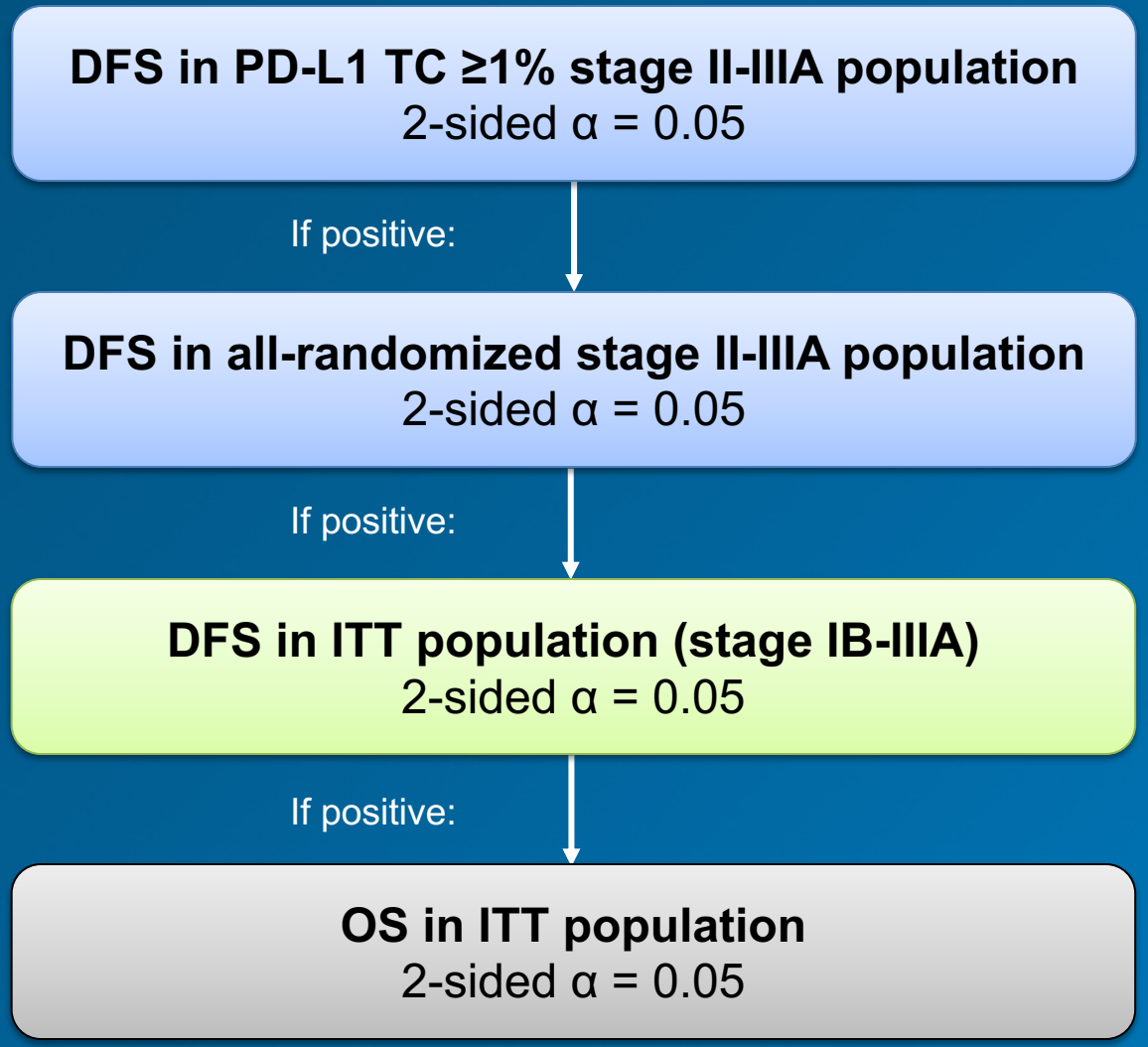
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

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

[a]Per SP142 assay.
Both arms included observation and regular scans for disease recurrence on the same schedule.
BSC, best supportive care; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cells; ITT, intent to treat; OS, overall survival; PD-L1, programmed cell death protein ligand 1; TC, tumor cells.
Adapted from Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500.

IMpower010: Statistical Analysis Plan



- The significance boundary was not crossed at this DFS interim analysis in the ITT population (stage IB-IIIA) and testing will continue to the final DFS analysis in this population

DFS, disease-free survival; ITT, intention to treat; OS, overall survival; PD-L1, programmed cell death protein ligand 1; TC, tumor cells.
Adapted from Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500.

IMpower010: Baseline Characteristics

Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIA)		All randomized (stage II-IIIA)		ITT (stage IB-IIIA)	
		Atezolizumab (n=248)	BSC (n=228)	Atezolizumab (n=442)	BSC (n=440)	Atezolizumab (n=507)	BSC (n=498)
Median (range) age, y	**62 (26-84)**	61 (34–82)	62 (26–84)	62 (33–82)	62 (26–84)	62 (33–83)	62 (26–84)
Age ≥65 y, n (%)	**382 (38.0)**	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	**672 (66.9)**	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	**738 (73.4)**	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75.5)
Asian	**242 (24.1)**	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	**25 (2.5)**	8 (3.2)	6 (2.6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
ECOG PS, n (%)							
0	**556 (55.3)**	140 (56.5)	125 (54.8)	239 (54.1)	252 (57.3)	273 (53.8)	283 (56.8)
1	**446 (44.4)**	107 (43.1)	102 (44.7)	201 (45.5)	187 (42.5)	232 (45.8)	214 (43.0)
Histology, non-squamous, n (%)	**659 (65.6)**	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	**123 (12.2)**	–	–	–	–	65 (12.8)	58 (11.6)
IIA	**295 (29.4)**	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	**174 (17.3)**	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	**413 (41.1)**	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Tobacco use history, n (%)							
Never	**222 (22.1)**	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108 (21.7)
Current/previous	**783 (77.9)**	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC≥1%, n (%)[a]	**535 (54.6)**	248 (100)	228 (100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)
EGFR mutation status, n (%)[b]							
Positive	**117 (11.6)**	23 (9.3)	20 (8.8)	49 (11.1)	60 (13.6)	53 (10.5)	64 (12.9)
Negative	**527 (52.4)**	123 (49.6)	125 (54.8)	229 (51.8)	234 (53.2)	261 (51.5)	266 (53.4)
Unknown[c]	**361 (35.9)**	102 (41.1)	83 (36.4)	164 (37.1)	146 (33.2)	193 (38.1)	168 (33.7)
ALK rearrangement status, n (%)[b]							
Positive	**33 (3.3)**	12 (4.8)	11 (4.8)	14 (3.2)	17 (3.9)	15 (3.0)	18 (3.6)
Negative	**574 (57.1)**	133 (53.6)	121 (53.1)	251 (56.8)	256 (58.2)	280 (55.2)	294 (59.0)
Unknown[c]	**398 (39.6)**	103 (41.5)	96 (42.1)	177 (40.0)	167 (38.0)	212 (41.8)	186 (37.3)

Clinical cutoff: January 21, 2021. [a]26 patients in the ITT population had unknown PD-L1 status as assessed by SP263. [b]For patients with non-squamous NSCLC, *EGFR/ALK* status was assessed locally or centrally. [c]89.2% of patients with unknown *EGFR* status and 80.7% of patients with unknown *ALK* status in the ITT population had squamous NSCLC and were not required to undergo local or central testing.

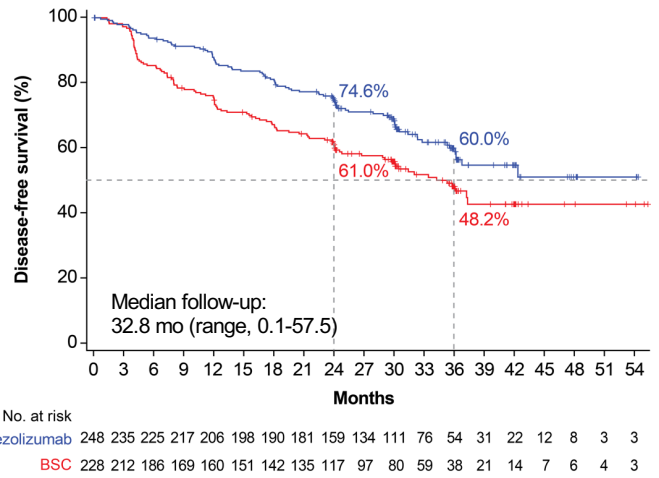
BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.

Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500.

IMpower010: DFS in PD-L1 TC ≥1%[a] Stage II-IIIA

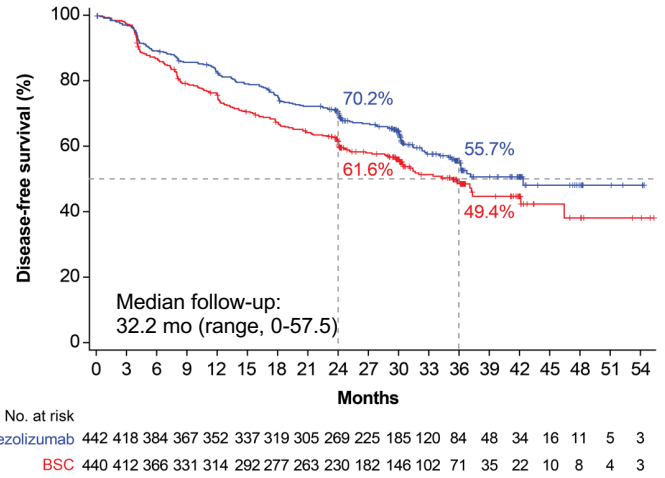
All-randomized Stage II-IIIA and ITT populations (Primary Endpoint)

PD-L1 TC ≥1% stage II-IIIA population



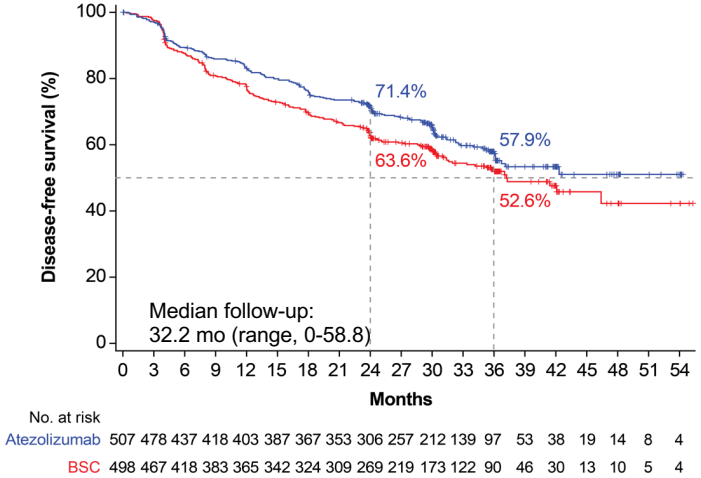
Parameter	Atezolizumab (n = 248)	BSC (n = 228)
Median DFS (95% CI), mo	NE (36.1-NE)	35.3 (29.0-NE)
Stratified HR (95% CI)	0.66 (0.50-0.88)	
***P*[b]**	.004[c]	

All-randomized stage II-IIIA population



Parameter	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*[b]**	.02[c]	

ITT (randomized stage IB-IIIA) population

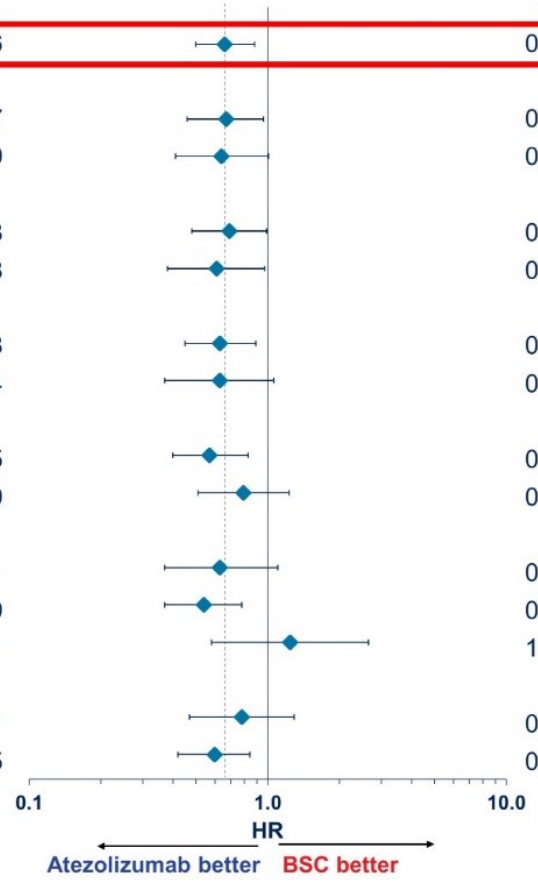


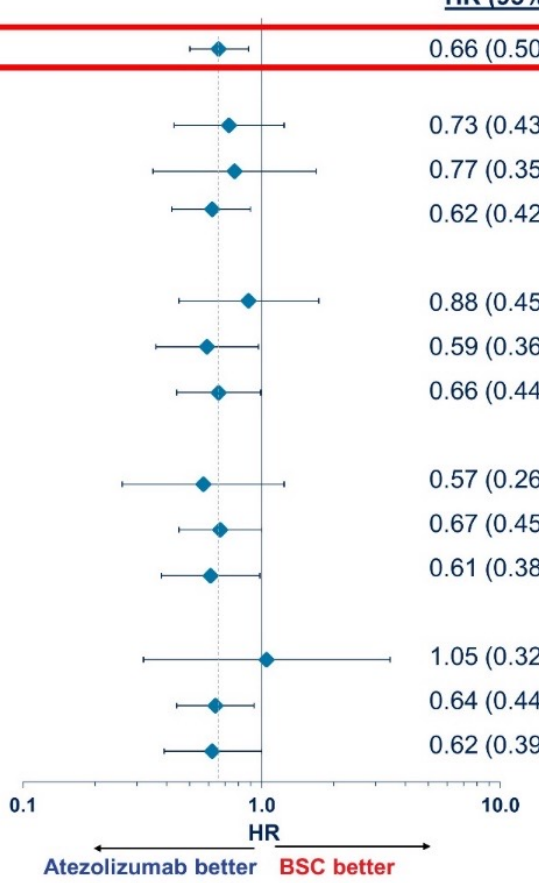
Parameter	Atezolizumab (n = 507)	BSC (n = 498)
Median DFS (95% CI), mo	NE (36.1-NE)	37.2 (31.6-NE)
Stratified HR (95% CI)	0.81 (0.67-0.99)	
***P*[b]**	.04[d]	

Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed.
BSC, best supportive care; DFS, disease-free survival; ITT, intention to treat; NE, not estimable; PD-L1, programmed cell death protein ligand 1; TC, tumor cells.
Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500. Felip et al. *Lancet* 2021;398:1344-1357.

IMpower010: DFS in Key Subgroups of the PD-L1 TC ≥1%[a] Stage II-IIIA Population

Subgroup	N	HR (95% CI)[b]
All patients	476	0.66 (0.50, 0.88)
Age		
<65 y	287	0.67 (0.46, 0.96)
≥65 y	189	0.64 (0.41, 1.01)
Sex		
Male	318	0.69 (0.48, 0.99)
Female	158	0.61 (0.38, 0.97)
Race		
White	328	0.63 (0.45, 0.89)
Asian	134	0.63 (0.37, 1.06)
ECOG PS		
0	265	0.57 (0.40, 0.83)
1	209	0.79 (0.51, 1.23)
Tobacco use history		
Never	92	0.63 (0.37, 1.10)
Previous	309	0.54 (0.37, 0.78)
Current	75	1.24 (0.58, 2.64)
Histology		
Squamous	181	0.78 (0.47, 1.29)
Non-squamous	295	0.60 (0.42, 0.84)
Stage		
IIA	161	0.73 (0.43, 1.24)
IIB	83	0.77 (0.35, 1.69)
IIIA	232	0.62 (0.42, 0.90)
Regional lymph node stage (pN)		
N0	106	0.88 (0.45, 1.74)
N1	194	0.59 (0.36, 0.97)
N2	176	0.66 (0.44, 0.99)
***EGFR* mutation status**		
Yes	43	0.57 (0.26, 1.24)
No	248	0.67 (0.45, 1.00)
Unknown[c]	185	0.61 (0.38, 0.98)
***ALK* rearrangement status**		
Yes	23	1.05 (0.32, 3.45)
No	254	0.64 (0.44, 0.93)
Unknown[c]	199	0.62 (0.39, 1.00)





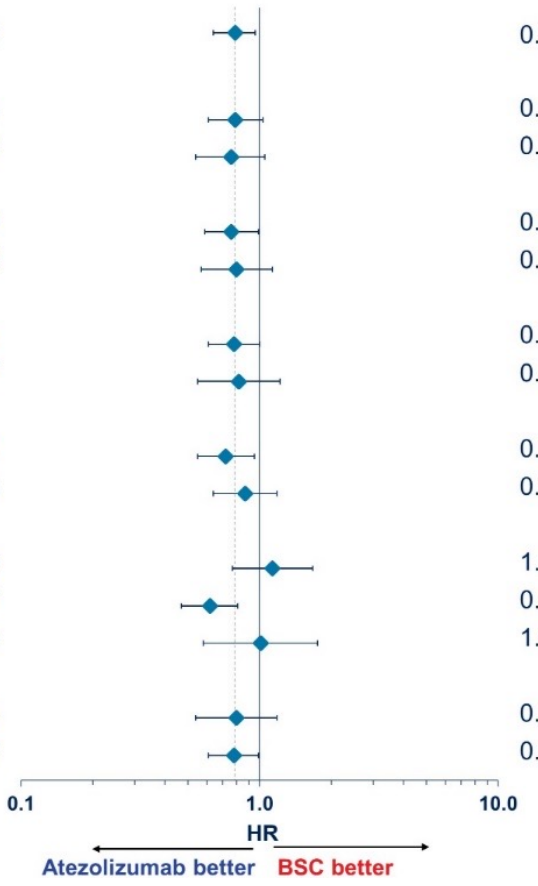
Clinical cutoff: January 21, 2021. [a]Per SP263 assay. [b]Stratified for all patients; unstratified for all other subgroups. [c]89.2% and 80.7% of patients in the ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo local or central testing.

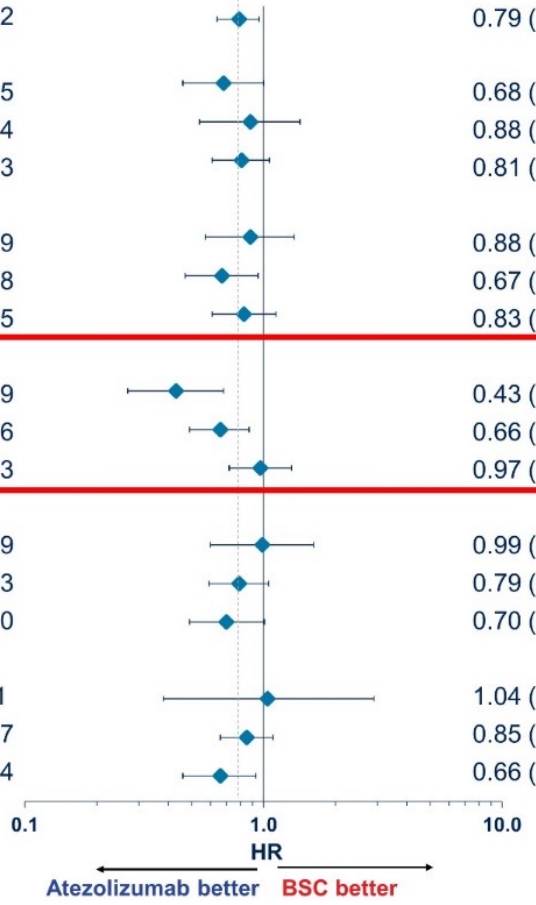
DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.

Wakelee et al. *J Clin Oncol.* 2021;39(15_suppl):8500-8500.

IMpower010: DFS in Key Subgroups of the All-Randomized Stage II-IIIA Population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.79 (0.64, 0.96)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Tobacco use history		
Never	196	1.13 (0.77, 1.67)
Previous	547	0.62 (0.47, 0.81)
Current	139	1.01 (0.58, 1.75)
Histology		
Squamous	294	0.80 (0.54, 1.18)
Non-squamous	588	0.78 (0.61, 0.99)
All patients	882	0.79 (0.64, 0.96)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	463	0.79 (0.59, 1.05)
Unknown	310	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)





Clinical cutoff: January 21, 2021. [a]Stratified for all patients; unstratified for all other subgroups.
BSC, best supportive care; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand 1; TC, tumor cells.
Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500.

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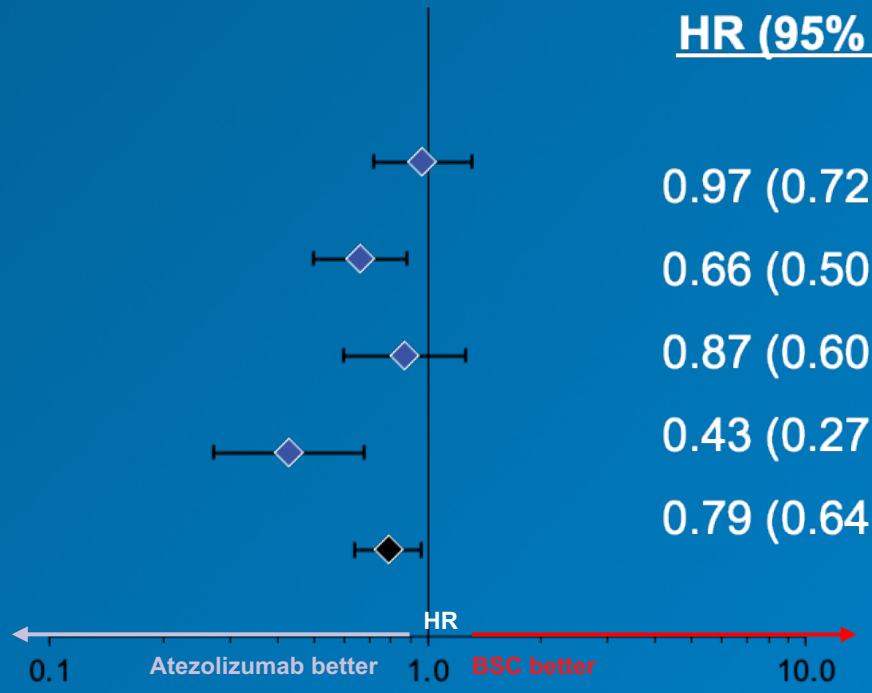
IMpower010: DFS by PD-L1 Status[a]

All-randomized Stage II-IIIA Population (with and without known *EGFR/ALK*+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



Clinical cutoff: January 21, 2021.
[a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.
ALK, anaplastic lymphoma kinase; BSC, best supportive care; DFS, disease-free survival; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death protein ligand 1; TC, tumor cells.
Felip et al. *Lancet* 2021;398:1344-1357.

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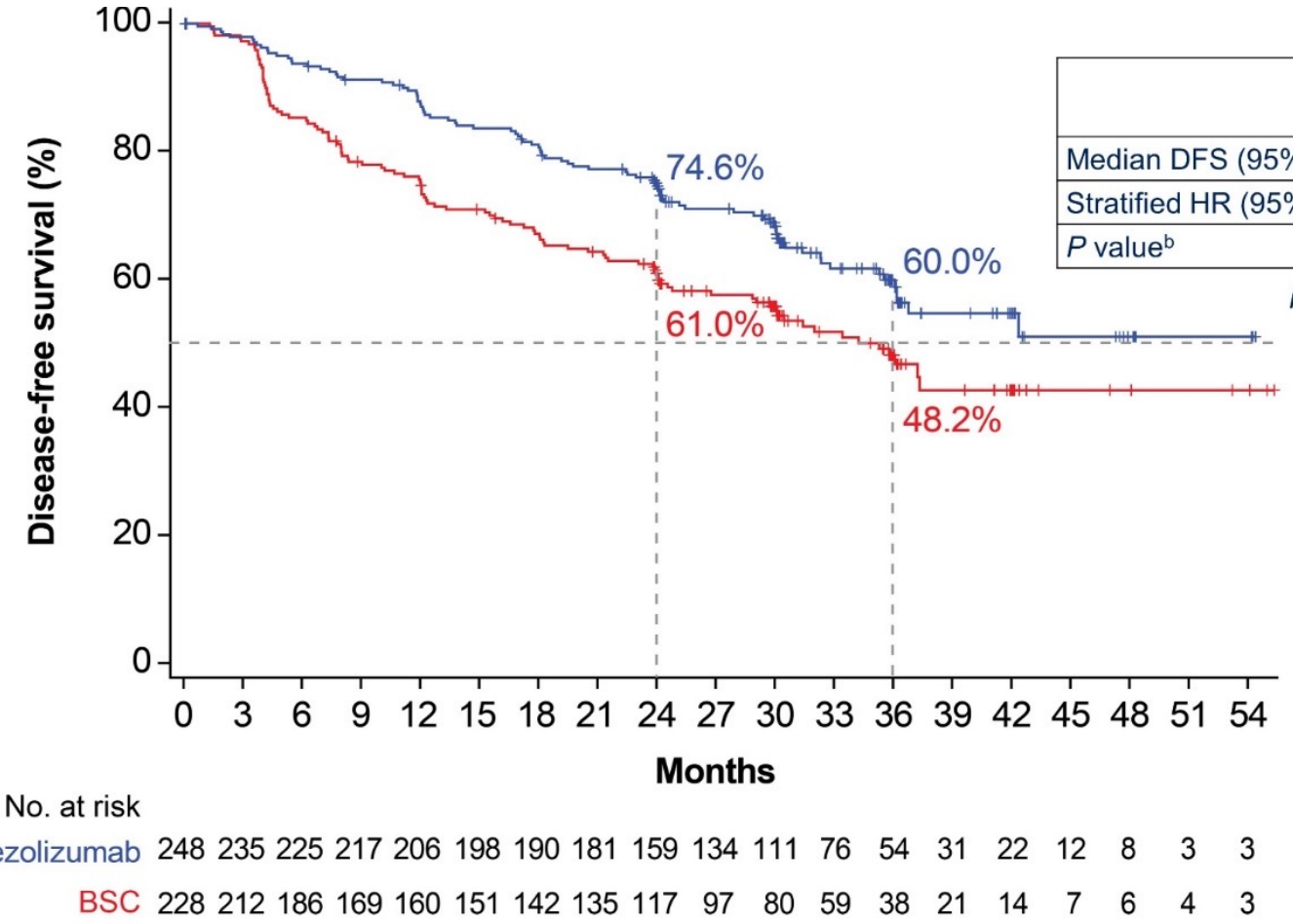
IMpower010: DFS in the PD-L1 TC ≥1%[a] Stage II-IIIA Population (Primary Endpoint)



	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)

Atezolizumab now FDA approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells

Clinical cutoff: January 21, 2021. [a]Per SP263 assay. [b]Stratified log-rank. [c]Crossed the significance boundary for DFS.
BSC, best supportive care; DFS, disease-free survival; FDA, US Food & Drug Administration; NE, not evaluable; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.
Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500; FDA News Release, 2021.

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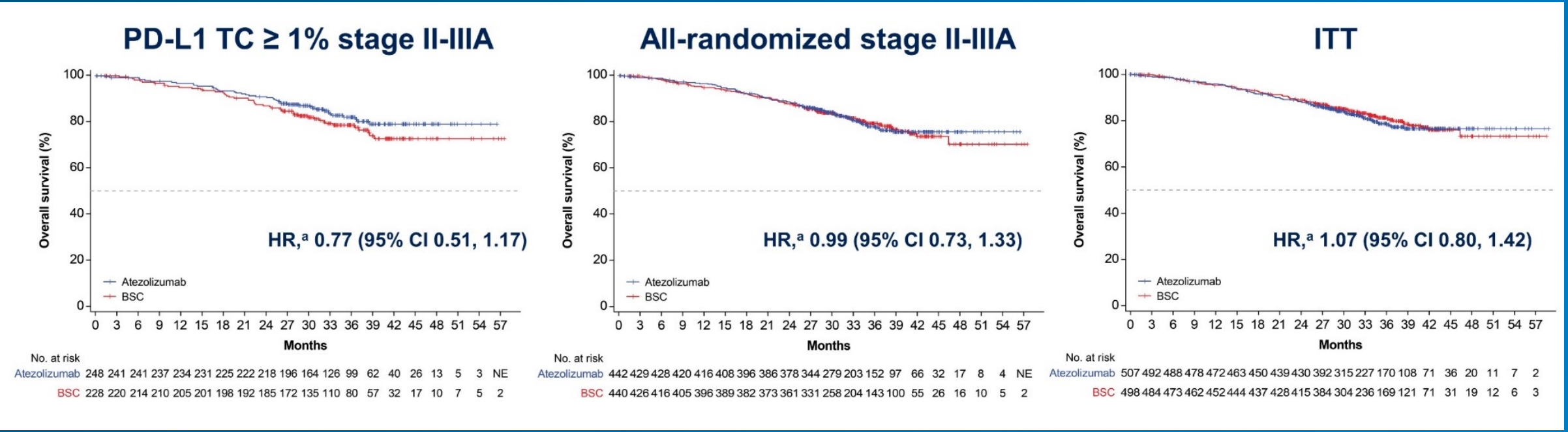
IMpower010: Early OS Data at Interim DFS Analysis



- 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.
DFS, disease-free survival; ITT, intention to treat; OS, overall survival; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.
Wakelee et al. *J Clin Oncol.* 2021;39:8500-8500.

AXIS Medical Education

Adjuvant Phase 3 Immunotherapy NSCLC Trials

Trial	PD-1/PD-L1 Inhibitor	Sample Size	Chemo specified	PORT	Placebo	Endpoint	Status (as of Feb 2022)
IMpower010 (NCT02486718)	Atezolizumab	1,280 (1,127) Fully Accrued	Yes	No	No	DFS in all DFS in Stage II/IIIA DFS in PD-L1+*	FDA approved in Oct 2021 as adjuvant treatment in PD-L1 ≥1% stage II/IIIA disease
EORTC141/ PEARLS/ KEYNOTE-091 (NCT02504372)	Pembrolizumab	1,080 Fully Accrued	No	?	Yes	DFS in all† DFS in PD-L1 high	Active, not recruiting Positive interim analysis in January 2022
EA5142/ANVIL (NCT02595944)	Nivolumab	903 (was 714) Fully Accrued	No	Yes	No	DFS & OS DFS in PD-L1 ≥50%	Active, not recruiting
BR.31 (NCT02273375)	Durvalumab	1,360 (was 1,180) Fully Accrued	No	No	Yes	DFS in PD-L1+ DFS in all	Active, not recruiting

*Press Release March 2021. Positive for DFS in the PD-L1+ population. †Press Release January 2022. Positive for DFS regardless of PD-L1 expression.
DFS, disease-free survival; FDA, US Food & Drug Adminisration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.

PEARLS/KEYNOTE-091: Disease-Free Survival Update

- **Adjuvant** treatment with **pembrolizumab** led to a **statistically significant improvement in DFS** vs placebo in patients with stage **IB to IIIA** NSCLC following resection, **regardless of PD-L1 expression**, meeting one of the dual primary endpoints of the trial
- Median DFS:
  - Pembrolizumab: 53.6 months
  - Placebo: 42.0 months
  - HR = 0.76
- Pembrolizumab reduced the risk of disease recurrence or death by 24% compared to placebo
- Additional results from the interim analysis showed that pembrolizumab also **improved DFS** compared with placebo in patients whose tumors did express **PD-L1** with a tumor proportion score of **50% or higher**; however, this was **not found to meet statistical significance** per the prespecified statistical plan for the trial

DFS, disease-free survival; PD-L1, programmed cell death protein ligand 1.

Adjuvant Phase 3 Immunotherapy NSCLC Trials

Trial	PD-1/PD-L1 Inhibitor	Sample Size	Chemo specified	PORT	Placebo	Endpoint	Status (as of Feb 2022)
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*Press Release March 2021. Positive for DFS in the PD-L1+ population. †Press Release January 2022. Positive for DFS regardless of PD-L1 expression.
DFS, disease-free survival; FDA, US Food & Drug Adminisration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.

Case Consultations

Case 1

- A 52-year-old Asian man with an extensive smoking history presents with hemoptysis
- CXR showed RUL mass
- CT confirmed 4.5 x 4 x 3 cm RUL mass and a solitary LN (right paratracheal 1.7 x 1.3)
- Brain MRI negative; PET otherwise negative
- Underwent a RUL lobectomy
- R0 resection – lung adenocarcinoma
  - PD-L1 70%
  - *EGFR*/*ALK*/*ROS1* negative
  - *KRAS* G12A mutation identified

CT, computed tomography; CXR, chest X-ray; LN, lymph node; MRI, magnetic resonance imaging; PD-L1, programmed cell death protein ligand 1; PET, positron emission tomography; RUL, right upper lobe.

Case 1, cont.

- R0 resection revealed T2bN2 stage IIIA lung adenocarcinoma
  - PD-L1 70%
  - *EGFR/ALK/ROS1* negative
  - *KRAS* G12A mutation identified
- Would you offer adjuvant chemotherapy?
- Would you offer adjuvant immunotherapy?

PD-L1, programmed cell death protein ligand 1.

Case 1: Conclusion

- He tolerated 4 cycles of adjuvant cisplatin/pemetrexed chemotherapy but developed mild peripheral neuropathy
- Subsequently, he started adjuvant atezolizumab
- He then developed mild (asymptomatic) hypothyroidism and was started on thyroid replacement therapy

Case 2

- 57-year-old woman with remote history of tobacco use (quit >15 years ago) presents with persistent, non-productive cough for 3 months
- CT chest shows 5.7 cm right upper lobe mass with slightly enlarged right-sided hilar lymph nodes
- Bronchoscopic biopsy of right hilar lymph node confirms adenocarcinoma of lung origin, PD-L1 1%
- CT A/P and MRI brain for staging detect no distant disease, confirming stage T3N1, IIIA disease

A/P, abdomen/pelvis; CT, computed tomography; CXR, chest X-ray; MRI, magnetic resonance imaging; PD-L1, programmed cell death protein ligand 1.

Case 2, cont.

- Based on stage IIIA (N1) disease, she underwent primary tumor resection with mediastinal lymph node dissection, followed by adjuvant cisplatin/pemetrexed x 4 cycles, followed by maintenance atezolizumab x 1 year per the IMpower010 trial
- Other immune checkpoint inhibitors may be approved soon, such as adjuvant pembrolizumab in the PEARLS trial

- But what if I told you that molecular testing identified an *EGFR* L858R mutation?
- Would your recommendation for management change for this patient?

EGFR, epidermal growth factor receptor.

Neoadjuvant Immunotherapy: Future Directions

Neoadjuvant Nivolumab: The First Step

- Feasibility N = 21
- Nivolumab 3 mg/kg x 2 doses (every 2 weeks)
- Did not delay or interfere with surgery

Efficacy (N=21)	n (%)
PR	2 (10%)
SD	18 (86%)
PD	1 (5%)
MPR	9/20 (45%)

Drug-related Adverse Events N = 22	Any Grade n (%)
Fever	1 (5)
Thyroid dysfunction	1 (5)
GI	
Anorexia/dysgeusia	2 (9)
Vomiting/diarrhea	1 (5)
LFT abnormality	1 (5)
Pneumonia	0
Infusion reaction	1 (5)
CNS (delirium)	1 (5)

~20% MPR rate in subsequent single-agent neoadjuvant immunotherapy trials

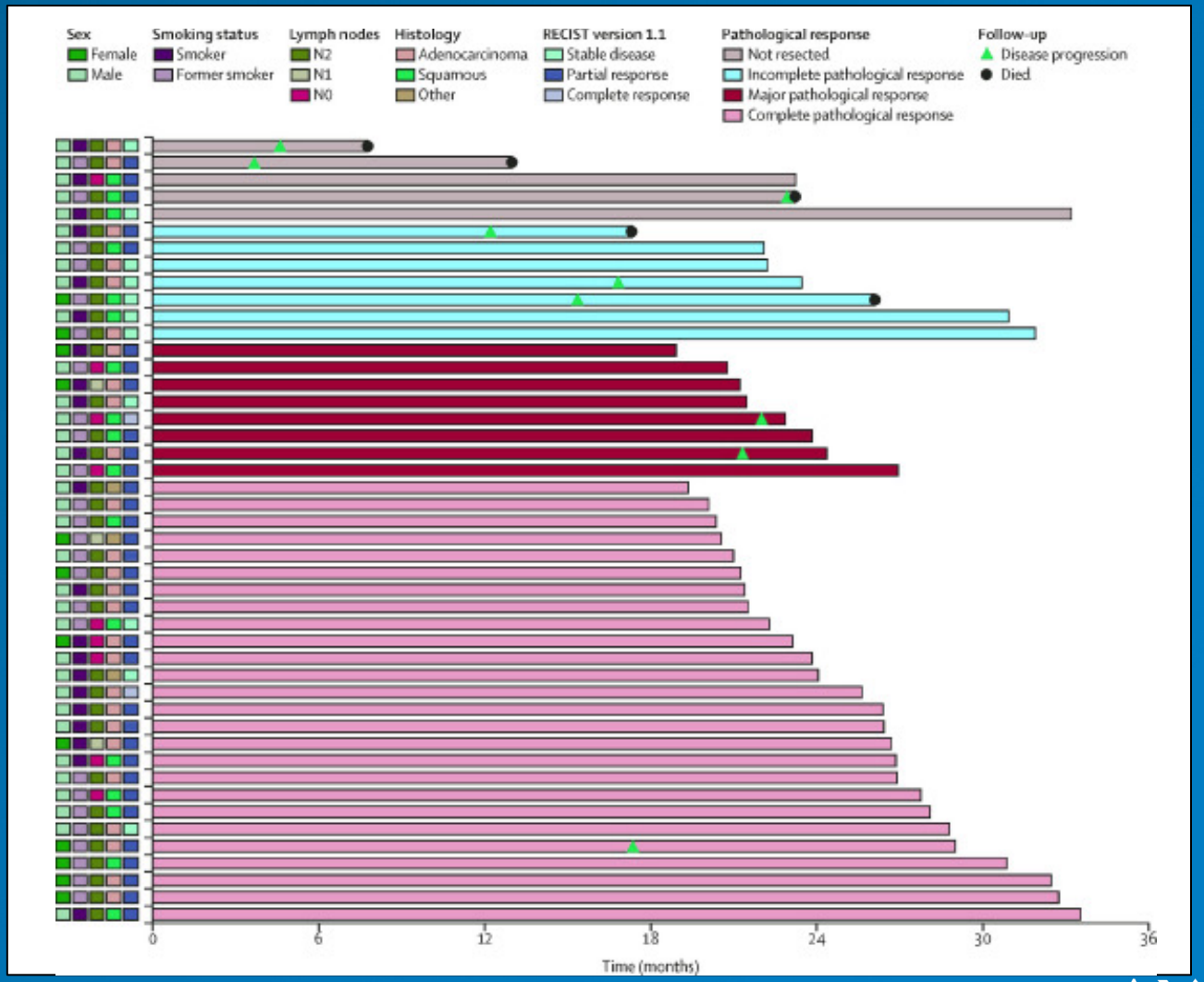
CNS, central nervous system; GI, gastrointestinal; LFT, liver function test; MPR, major pathologic response; PD, progressive disease; PR, partial response; SD, stable disease.

Forde et al. *N Engl J Med*. 2018;378:1976-1986.

Phase 2 NADIM Trial: Neoadjuvant Nivolumab + Carboplatin Paclitaxel

Key Results:

- 46 patients with clinical stage IIIA enrolled, 74% N2
- 30% of patients had Grade 3 or higher toxicity but no delays in surgery
- 24-month PFS: 77%
- 74% (34/46) had MPR
- 57% (26/46) had pCR



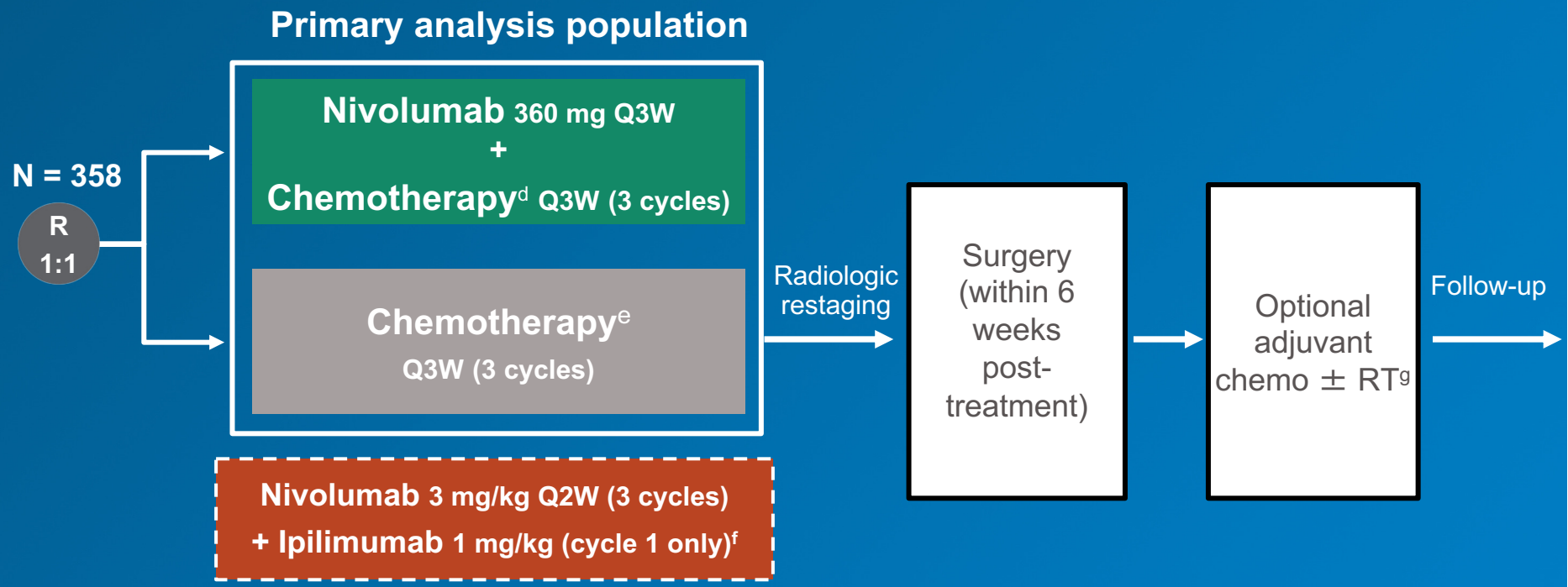
MPR, major pathologic response; pCR, pathologic complete response; PFS, progression-free survival.
Adapted from Provencio et al. *Lancet Oncol*. 2020;21:1413-1422.

Phase 3 CheckMate 816: Study Design[a]

Key Eligibility Criteria

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

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



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])

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathological review; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EGFR, epidermal growth factor receptor; MPR, major pathological response; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death ligand 1; RT, radiotherapy; TMB, tumor mutational burden; TNM, tumor/nodes/metastases.

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

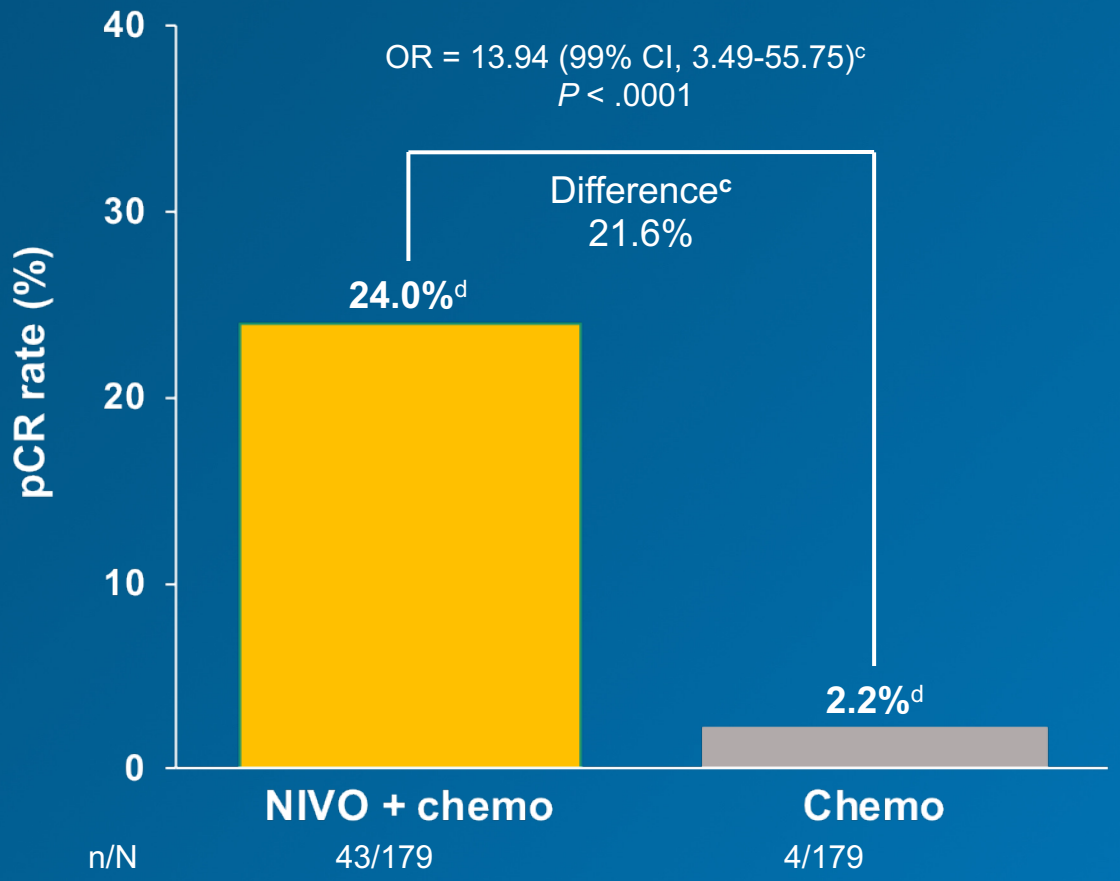
[a]NCT02998528; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [f]Randomized exploratory arm (enrollment closed early); [g]Per healthcare professional choice; [h]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).

Forde et al. AACR Annual Meeting 2021 abstract CT003.

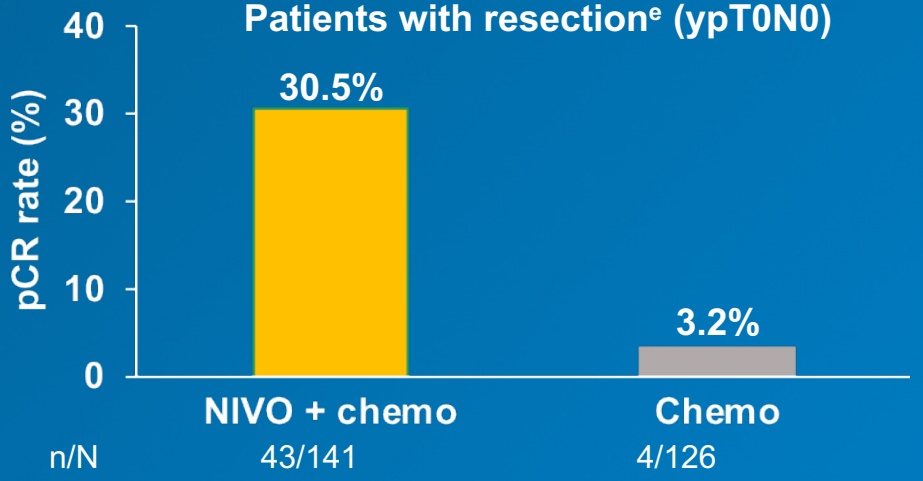
CheckMate 816: Primary Endpoint

pCR[a] Rate with Neoadjuvant Nivolumab + Chemotherapy vs Chemotherapy

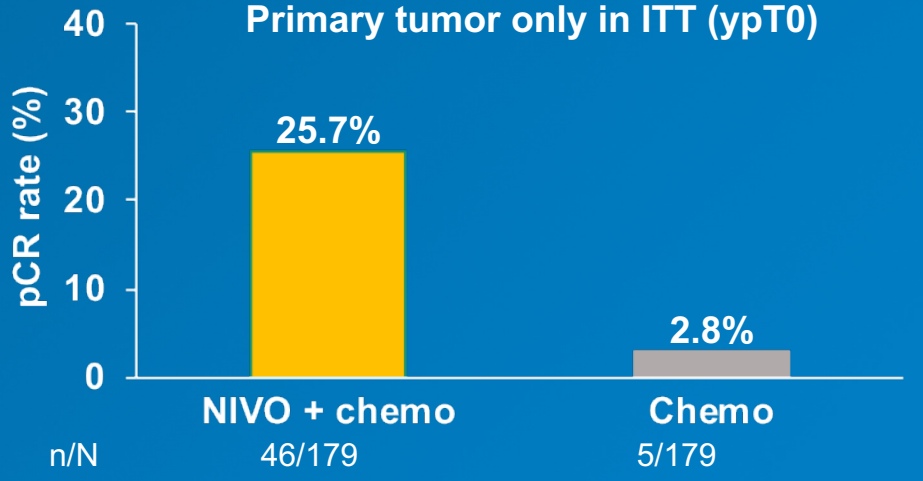
Primary endpoint: ITT (ypT0N0)[b]



Patients with resection[e] (ypT0N0)



Primary tumor only in ITT (ypT0)



pCR rate in the exploratory nivolumab + ipilimumab arm (ITT) was 20.4% (95% CI, 13.4-29.0)

[a]Per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis; [c]Calculated by stratified Cochran–Mantel–Haenszel method; [d]pCR rates 95% CI: NIVO + chemo, 18.0–31.0; chemo, 0.6–5.6; [e]Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.
BIPR, blinded independent review; ITT, intention to treat; OR, odds ratio; pCR, pathologic complete response.
Forde et al. AACR 2021 abstract CT003.

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CheckMate 816: Primary Endpoint Event-Free Survival

- The addition of nivolumab to chemotherapy resulted in a statistically significant and clinically meaningful improvement in EFS vs chemotherapy alone, when administered prior to surgery in patients with resectable stage IB to IIIA NSCLC
- 37% reduction in the risk of progression, recurrence or death compared to chemotherapy alone

	Nivolumab and Platinum-Doublet Chemotherapy (n = 179)	Platinum-Doublet Chemotherapy (n = 179)
Event-free Survival per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (mo)[a] (95% CI)	31.6 (30.2-NR)	20.8 (14.0-26.7)
Hazard Ratio[b] (95% CI)	0.63 (0.45-0.87)	
Stratified log-rank p-value[c]	0.0052	

Nivolumab now FDA approved in combination with platinum-doublet chemotherapy for adult patients with resectable* NSCLC in the neoadjuvant setting

Minimum follow-up for EFS was 21 months.
[a]Kaplan-Meier estimate. [b]Based on a stratified Cox proportional hazard model. [c]Based on a stratified log-rank test. Boundary for statistical significance: *p*-value <0.0262.
*tumors ≥4 cm or node positive.
BICR, blinded independent central review; EFS, event-free survival; FDA, US Food and Drug Administration; OS, overall survival.
Nivolumab prescribing information, 2022.

Neoadjuvant Phase 3 Immunotherapy NSCLC Trials

Trial Identifier	Lay Title	Stage (ed)	Backbone	Intervention	Primary Endpoints	Status (as of March 2022)
NCT02998528	CheckMate 816	IB-IIIA (7^{th})	cisplatin or carboplatin + vincristine/pemetrexed/ gemcitabine/docetaxel/paclitaxel	+/- nivolumab (ipilimumab + nivolumab closed)	EFS* pCR*	FDA approved in March 2022 as neoadjuvant treatment
NCT04025879	CheckMate 77T	II-IIIB	cisplatin/carboplatin/paclitaxel/ pemetrexed/docetaxel	nivolumab or placebo	EFS	Recruiting
NCT03425643	KEYNOTE-671	IIA-IIIA (8^{th})	cisplatin + pemetrexed or gemcitabine	pembrolizumab or placebo	EFS OS	Active, not recruiting
NCT03456063	IMpower030	II-IIIB (8^{th})	cisplatin/carboplatin + nab-paclitaxel/pemetrexed/ gemcitabine	atezolizumab or placebo	MPR EFS	Active, not recruiting
NCT03800134	AEGEAN	IIA-IIIB (8^{th})	cisplatin + gemcitabine or pemetrexed carboplatin + pemetrexed or paclitaxel	durvalumab or placebo	MPR	Recruiting

*Reported positive.
EFS, event-free survival; FDA, US Food and Drug Administration; MPR, major pathologic response; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death protein ligand 1.

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Adjuvant Phase 3 Immunotherapy NSCLC Trials

Trial	PD-1/PD-L1 Inhibitor	Sample Size	Chemo specified	PORT	Placebo	Endpoint	Status (as of Feb 2022)
IMpower010 (NCT02486718)	Atezolizumab	1,280 (1,127) Fully Accrued	Yes	No	No	DFS in all DFS in Stage II/IIIA DFS in PD-L1+*	FDA approved in Oct 2021 as adjuvant treatment in PD-L1 ≥1% stage II/IIIA disease
EORTC141/ PEARLS/ KEYNOTE-091 (NCT02504372)	Pembrolizumab	1,080 Fully Accrued	No	?	Yes	DFS in all† DFS in PD-L1 high	Active, not recruiting Positive interim analysis in January 2022
EA5142/ANVIL (NCT02595944)	Nivolumab	903 (was 714) Fully Accrued	No	Yes	No	DFS & OS DFS in PD-L1 ≥50%	Active, not recruiting
BR.31 (NCT02273375)	Durvalumab	1,360 (was 1,180) Fully Accrued	No	No	Yes	DFS in PD-L1+ DFS in all	Active, not recruiting

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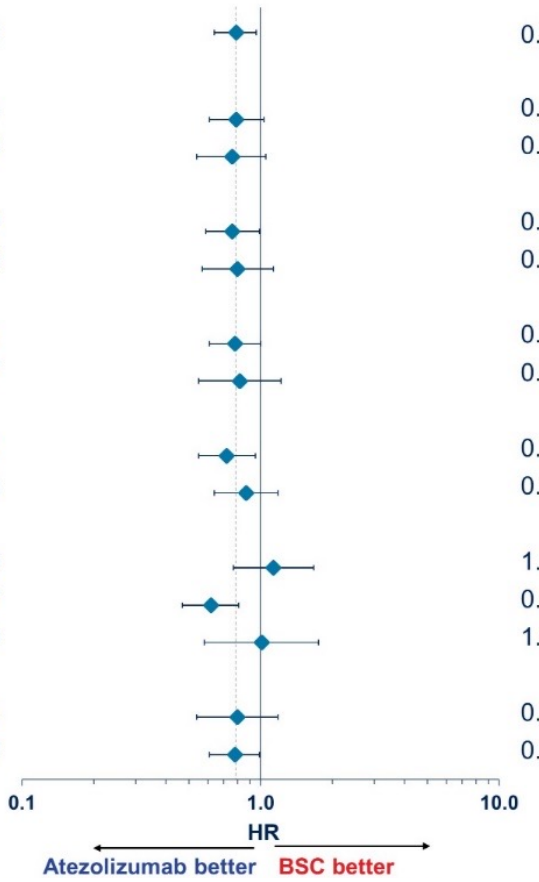
DFS, disease-free survival; FDA, US Food & Drug Adminisration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.

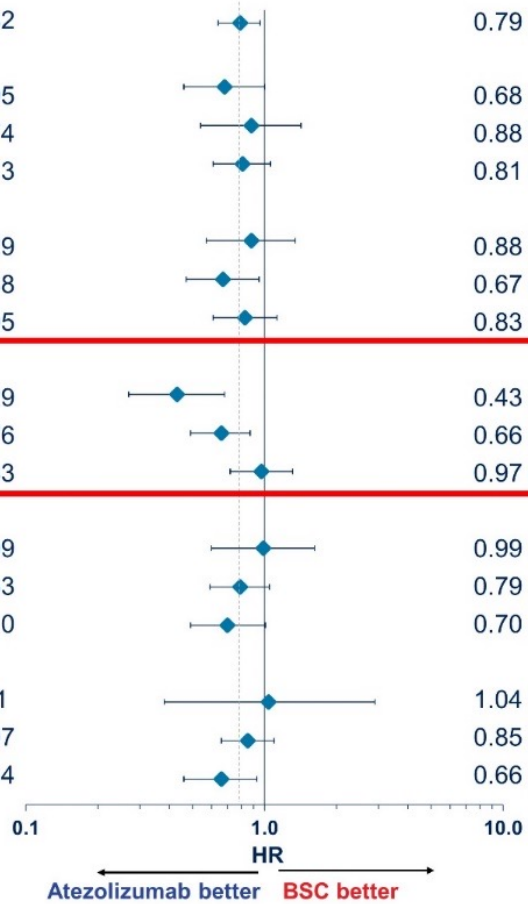
Molecular Subsets

PD-L1
Driver mutations
What other biomarkers are needed?

IMpower010: DFS in Key Subgroups of the All-Randomized Stage II-IIIA Population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.79 (0.64, 0.96)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Tobacco use history		
Never	196	1.13 (0.77, 1.67)
Previous	547	0.62 (0.47, 0.81)
Current	139	1.01 (0.58, 1.75)
Histology		
Squamous	294	0.80 (0.54, 1.18)
Non-squamous	588	0.78 (0.61, 0.99)
All patients	882	0.79 (0.64, 0.96)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	463	0.79 (0.59, 1.05)
Unknown	310	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)





Clinical cutoff: January 21, 2021. [a]Stratified for all patients; unstratified for all other subgroups.
ALK, anaplastic lymphoma kinase; BSC, best supportive care; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.
Wakelee et al. *J Clin Oncol.* 2021;39(15_suppl):8500-8500.

CheckMate 816: pCR Subgroup Analysis

Parameter	pCR[a] Rate, %		Unweighted pCR Difference, % (95% CI)	Unweighted pCR Difference, %
	Nivolumab + Chemo (n = 179)	Chemotherapy (n = 179)		
Overall (N = 358)	**24**	**2**		22
<65 years (n = 176)	27	0		27
≥65 years (n = 182)	21	4		17
Male (n = 255)	23	2		20
Female (n = 103)	28	2		26
North America (n = 91)	22	2		20
Europe (n = 66)	24	0		24
Asia (n = 177)	28	3		25
Stage IB–II (n = 128)	**26**	**5**		**21**
Stage IIIA (n = 228)	**23**	**1**		**22**
Squamous (n = 182)	**25**	**4**		**21**
Non-squamous (n = 176)	**23**	**0**		**23**
Current/former smoker (n = 318)	26	2		23
Never smoker (n = 39)	10	0		10
PD-L1 <1% (n = 155)	**17**	**3**		**14**
PD-L1 ≥1% (n = 178)	**33**	**2**		**30**
PD-L1 1–49% (n = 98)	24	0		24
PD-L1 ≥ 50% (n = 80)	45	5		40
TMB <12.3 mut/Mb (n = 102)	22	2		21
TMB ≥12.3 mut/Mb (n = 76)	31	3		28
Cisplatin (n = 258)	22	2		20
Carboplatin (n = 72)	31	0		31

[a]Per blinded independent review in intention to treat.
pCR, pathologic complete response; PD-L1, programmed cell death protein ligand 1; TMB, tumor mutation burden.
Forde et al. AACR 2021 abstract CT003.

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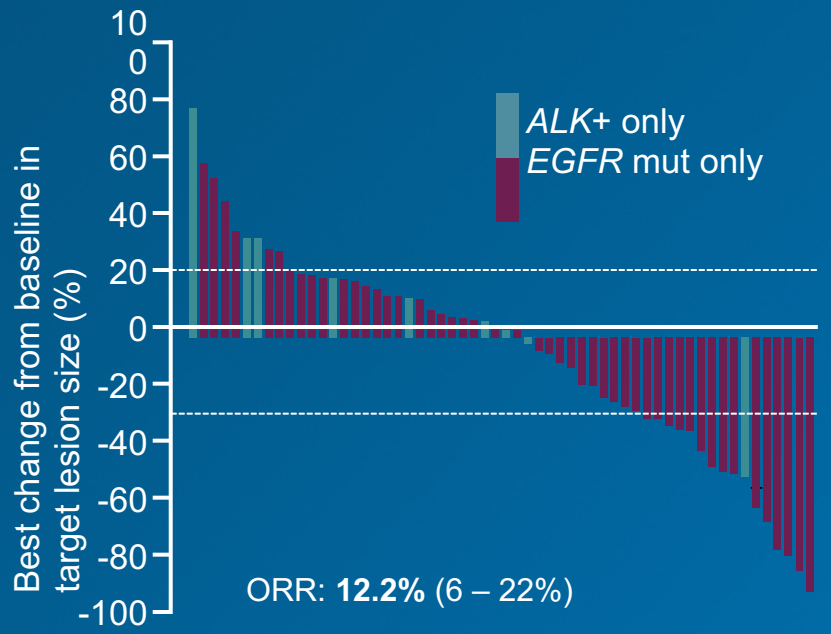
Tumor Mutations Impact Response to Immunotherapy Advanced Stage Disease

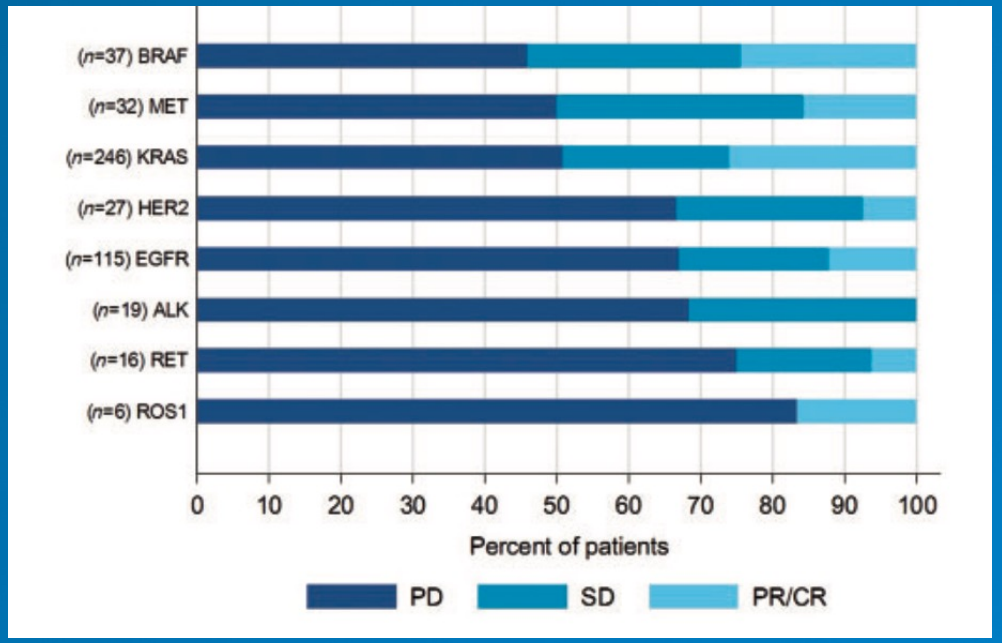
EGFR PD-L1 high (≥25%)
Low IO response



ATLANTIC: phase 2, open-label, single-arm study, cohort 1.
Best change in target lesion size (full analysis set*)

In KEYNOTE-010, CheckMate057, and OAK,
the ONLY subgroup that did NOT show superior survival
with the PD-L1 inhibitor vs docetaxel
were the patients with *EGFR* mutations

Immunotarget:
Low IO response in NSCLC driver mutation



Best Response to ICI According to RECIST Criteria

ALK, anaplastic lymphoma kinase; CR, complete response; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IO, immunotherapy; ORR, overall response rate; PD, progressive disease; PD-L1, programmed cell death protein ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Garassino et al. *Ann Onc* 2017. Garassino et al. *Lancet Oncol*. 2018;19:521-536. Mazieres et al. *Ann Oncol*. 2019;30:1321-1328.

Conclusions

Perioperative Immunotherapy in NSCLC

- **Neoadjuvant immunotherapy** confers proven improvements in MPR, pCR, and EFS
  - Nivolumab now FDA approved in combination with platinum-doublet chemotherapy as neoadjuvant treatment for patients with resectable NSCLC, regardless of PD-L1 status (CheckMate 816 trial)
- **Adjuvant immunotherapy** confers proven DFS benefit in PD-L1+ stage II-IIIA NSCLC
  - Atezolizumab had been approved as adjuvant treatment following platinum-based chemotherapy in PD-L1+ (IMpower010 trial)
  - Pembrolizumab may also become approved in adjuvant setting (PEARLS trial)
- Patient and tumor-specific biomarkers are necessary to predict benefit
  - Improve upon PD-L1
  - Fully understand tumor mutation relevance
  - Many other factors
- ctDNA/MRD technology may help predict those in need of additional therapy

ctDNA, circulating tumor DNA; DFS, disease-free survival; EFS, event-free survival; FDA, US Food and Drug Administration; MRD, minimal residual disease; MPR, major pathologic response; MRD, minimal residual disease; pCR, pathologic complete response; PD-L1, programmed cell death protein ligand 1.

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Adjuvant Treatment of Early Non–Small Cell Lung Cancer in the Era of Immunotherapy