

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

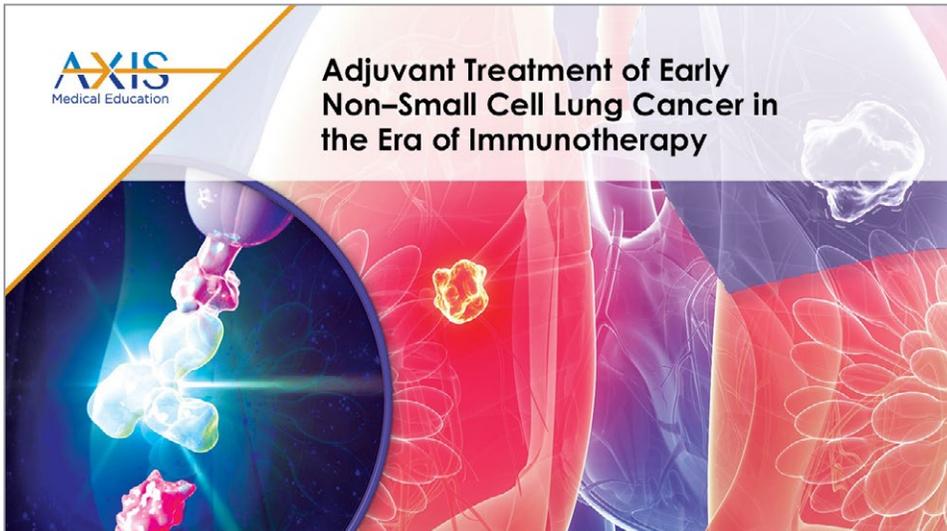
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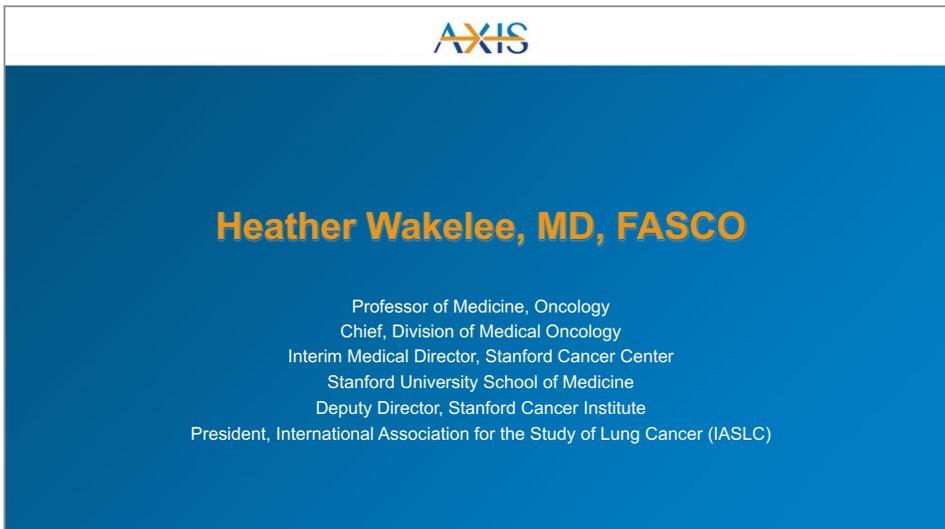
Adjuvant Treatment of Early Non-Small Cell Lung Cancer in the Era of Immunotherapy

Heather Wakelee, MD, FASCO



▶ **Heather Wakelee, MD, FASCO:**

Hello and welcome to this educational activity titled: *Adjuvant Treatment of Early Stage Non-Small Cell Lung Cancer and the Era of Immunotherapy.*



▶ I'm Dr. Heather Wakelee, Professor of Medicine and Chief of the Division of Oncology at Stanford University. I'm also the Deputy Director of the Stanford Cancer Institute, and President of the International Association for the Study of Lung Cancer, IASLC.



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Disclosure of Conflicts of Interest

Consulting or Advisory Role

AstraZeneca, Mirati, Daiichi Sankyo, Blueprint, Merck (uncompensated), Genentech/Roche (uncompensated)

Research Funding to Institution

ACEA Biosciences, Arrys Therapeutics, AstraZeneca/Medimmune, BMS, Clovis Oncology, Genentech/Roche, Helsinn, Merck, Novartis, SeaGen, Pharmacyclics, Xcovery



- ▶ And here are my financial disclosures.

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?
- Conclusion and Reinforcement of Essential Takeaways

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▶ During this activity, we will review the role of immunotherapy in early stage non-small cell lung cancer as adjuvant treatment, recent clinical data for immune checkpoint inhibitors of adjuvant treatment, and recent and ongoing clinical trials for adjuvant and neoadjuvant immune therapy for the treatment of early stage non-small cell lung cancer. Let's get started.

AXIS

Early-Stage NSCLC and the Role of Immunotherapy

▶ To talk about the different stages, it's important that we view the staging criteria and be mindful of the fact that the staging system keeps changing; a lot of it based on work by IASLC and the pathologists in that group.

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

	TNM 7 th Edition	TNM 8 th 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 Mels and Smithuis. *TNM Classification*, 2017.

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- ▶ Here, we see the 8th edition from 2017. The 9th edition will be coming out relatively soon.

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 Dettlerbeck. *J Thorac Cardiovasc Surg*. 2018;155:356-359.

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- ▶ The main things to highlight are when you are meeting a new patient and figuring out the staging, you want to be very mindful of the size of the tumor, but especially the lymph node involvement because that is what really determines stage more than anything when we're dealing with early-stage disease.

Adjuvant Therapy Background

- ▶ When we talk about adjuvant treatment, as well as neoadjuvant treatment, “perioperative therapy,” we always want to keep in mind that the surgery is really the key—the most important part of the treatment. But all of our newer developments for adjuvant and neoadjuvant are there to help improve the outcomes from surgery because although surgery alone can cure a large number of patients, we still have room to go.

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

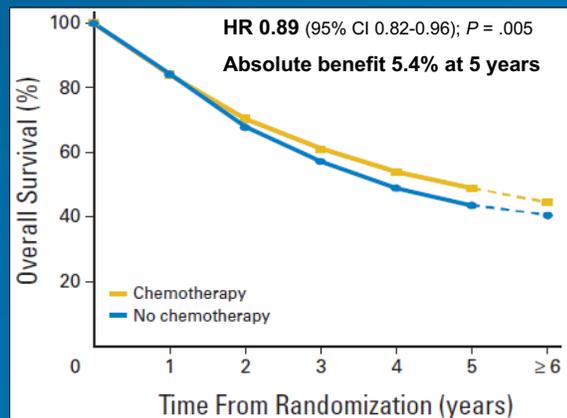
Unresectable disease (*Some* IIIA, virtually all IIIB-C)

- 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

- ▶ Now when we think about the management approach overall for patients who are historically considered having resectable disease, surgery is the primary treatment of choice. There have been multiple phase 3 trials that show that chemotherapy can be helpful, but on the order of only maybe a 5% survival benefit at 5 years. That was based on multiple randomized trials looking at giving adjuvant post operative chemotherapy, as well as neoadjuvant preoperative chemotherapy, where neither approach seemed that different from each other. We also have patients with early-stage disease who do not have resectable disease, and that includes a lot of our patients with stage IIIA and almost all patients with stage IIIB or IIIC disease.

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.

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► Now, going back in time, we do see this chemotherapy benefit of approximately 5% when the chemotherapy is given after surgery. And we spent many years trying to improve upon that, debating what was the best chemotherapy, how could we pick which patients needed chemotherapy, could we add anything to the chemotherapy? I did a big trial

with bevacizumab, but we didn't really make any progress. We were stuck with 4 cycles, cisplatin-based chemotherapy was helpful, we couldn't really pick which patients were more likely to benefit. We just didn't move forward very much.

However, we did start to learn a lot about better treatment for patients with metastatic lung cancer. The biggest

changes that we saw were in our understanding of molecular targets, and how to best treat patients with tumors that had molecular targets. Then of course, the development of immune therapy, which is particularly effective in patients who don't have tumors with molecular targets and sometimes with those as well.

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)

Osimertinib
80 mg, once
daily

Randomization
1:1
(N = 682)

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.

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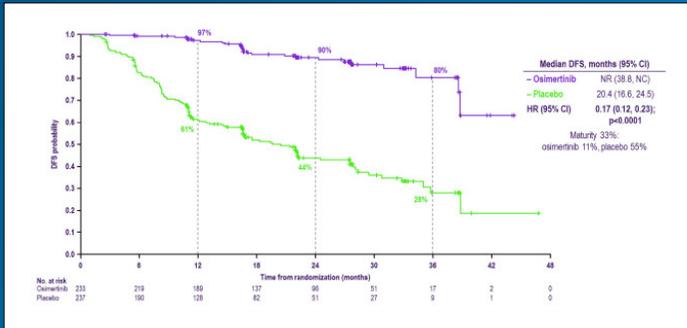
- ▶ The logical steps were to take what we learned in the metastatic setting and transfer it into early-stage disease. And there have been multiple trials looking at the targeted treatment approaches in the perioperative setting. Most of those have been done with the EGFR tyrosine kinase inhibitors (TKIs). There have been a number of studies that looked at giving adjuvant postoperative EGFR TKI trials that were done with gefitinib and erlotinib and others. Those studies showed interesting, significant benefits in disease-free survival, but did not

really show an overall survival benefit. When one looks at the hazard ratios for disease-free survival benefit, they were good, but not phenomenal and really did not change practice.

Then we saw the results of the ADAURA trial. And the ADAURA study used adjuvant osimertinib, the third-generation EGFR TKI, that has become the standard of care first-line option for patients who have activating driver mutations in *EGFR* and are diagnosed with metastatic disease. The ADAURA trial enrolled patients who had completely resected, stage

IB, II, or IIIA non-small cell lung cancer; could or did not need to have had adjuvant chemotherapy; and needed to have an activating driver mutation, including either *EGFR*, exon 19 deletion, or L858R. Patients were randomized to either get osimertinib once daily for a couple of years, actually 3 years, or to get a placebo once daily also for 3 years. And patients were continued on treatment for those 3 years unless they had a recurrence, or discontinued for another reason.

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;38:1BA5.

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► This study showed very, very striking results. The disease-free survival hazard ratio was less than 0.2. You know, we just don't see those sorts of results. But we haven't seen the long-term results yet and there are still some questions.

But we have established that osimertinib is a standard approach now for patients who have undergone a complete resection for early-stage lung cancer with tumors that harbor an activating *EGFR* mutation. The difference is that benefit is particularly seen in patients with stage II and IIIA disease and less so for patients with stage IB. But that is still something that is talked about with patients in that setting.

There are ongoing trials looking at whether we can get similar approaches with very potent ALK inhibitors, as well as long-term follow-up happening with ADAURA to see how this might impact overall survival.

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Adjuvant Immunotherapy

► I'm now going to transition and talk more about immune therapy because that has an impact for a much larger group of patients.

IMpower010: Study Design

Completely resected stage IB-IIIa NSCLC per UICC/AJCC v7

- Stage IB tumors ≥ 4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

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

Cisplatin +
pemetrexed
gemcitabine,
docetaxel or
vinorelbine

1-4 cycles

N = 1,280

R
1:1

No crossover

Atezolizumab
1200 mg q21d
16 cycles

N = 1,005

BSC

Survival
Follow-up

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
 - PD-L1 TC \geq 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 \geq 50% (per SP263) stage II-IIIa population
- 3-y and 5-y DFS in all 3 populations

^aPer 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.

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- ▶ The role of adjuvant immune therapy was just recently established in 2021 with the IMpower010 trial results.

I mentioned that we had been seeing hints of perioperative benefit of immune therapy with early results from neoadjuvant trials, showing that single agent immune therapy with trials with nivolumab, atezolizumab, pembrolizumab, all showed that there was a benefit and that there would be some patients with a major pathologic response, meaning less than 10% viable tumors at the time of surgery, and that those results were even better when we looked at combined chemotherapy and immune therapy in studies such as NADIM, but we hadn't seen

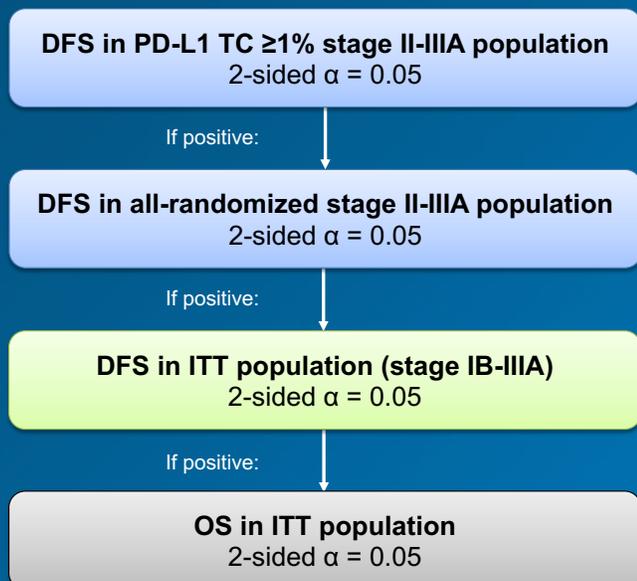
any results from the adjuvant postoperative treatment until IMpower010 results were presented in June 2021.

It's not surprising that neoadjuvant data comes first because you get a sneak peek and see how the tumors have responded. But what we really want to look at is how did the patients benefit, and that's where we have data now from the adjuvant as well as neoadjuvant setting.

The IMpower010 trial enrolled patients with completely resected stage IB, II and IIIa non-small cell lung cancer, they had to have either had a lumpectomy or pneumonectomy, and they needed to have tumor tissue available for PD-L1 (programmed cell death

protein ligand 1) testing. Patients then went on to get up to 4 cycles of a cisplatin-based adjuvant chemotherapy regimen, giving cisplatin with either pemetrexed, gemcitabine docetaxel, or vinorelbine, so trying to mimic what's done in real-world practice. After completion of the chemotherapy, (there were patients who dropped off during the chemotherapy phase because they just didn't want to keep going) patients were then randomized, one to one to either get up to 1 year of atezolizumab at the 1,200-milligram every 3-week dosing or to continue on best supportive care. And just over 1,000 patients were randomized and then continued with follow-up.

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.

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- ▶ The study was designed with a hierarchical statistical testing plan, so that the first group analyzed were those patients whose tumors had some PD-L1 expression of at least 1% and had stage II to IIIa disease, disease-free survival.

That was analyzed, and if it met its statistical significance boundary, then we were to look at allcomers, who

had stage II to IIIa disease regardless of PD-L1 expression of the tumor looking at disease-free survival there. The next step was to look at disease-free survival in all patients on the trial. So that brings in the stage IB patient population. The final analysis is with overall survival.

At the presentations that were initially given at ASCO 2021,

and continued with follow-up at other meetings, the first two primary endpoints were met. The third was in the intent-to-treat population and had not reached statistical significance at the time of presentation, meaning that not enough events had happened in total to be able to call one way or the other, nor has overall survival been presented.

IMpower010: Baseline Characteristics

Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIa)		All randomized (stage II-IIIa)		ITT (stage II-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 (66.5)	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 (33.5)	147 (29.0)	148 (29.7)
IB+IIA	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)	235 (46.4)	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 (8.9)	49 (11.1)	60 (13.6)	53 (10.5)	64 (12.9)
Negative	527 (52.4)	123 (49.6)	125 (54.8)	229 (51.6)	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)	16 (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)	196 (37.3)

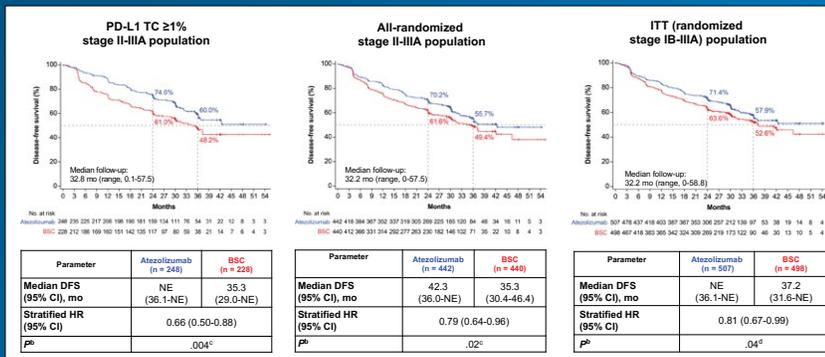
Clinical cutoff: January 21, 2021. ^a26 patients in the ITT population had unknown PD-L1 status as assessed by SP263. ^bFor patients with non-squamous NSCLC, EGFR/ALK status was assessed locally or centrally. ^c89.2% of patients with unknown EGFR status and 80.7% of patients with unknown ALK status in the ITT population had squamous NSCLC and were not required to undergo local or central testing.

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I'm going to back up now and talk a little bit about who actually went on the trial. There were more than 1,000 patients who were randomized. Two-thirds of the patients had non-squamous histology, and most of them had stage II and IIIA disease. More specifically, 12% had stage IB, 41% had stage IIIA, and the rest had stage II. It's also important to note that over half of the patients, 55%, had tumors with some PD-L1 expression of at least 1%. But that means that 45% did not. This trial also allowed enrollment of patients with tumors that had EGFR mutations or ALK translocation, so that was a minority of the patients enrolled on the trial.

IMpower010: DFS in PD-L1 TC ≥1%^a Stage II-IIIa

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

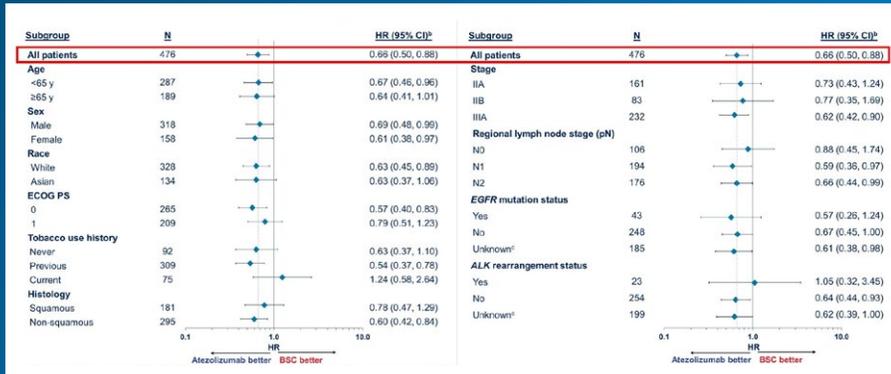


Clinical cutoff: January 21, 2021. ^aPer SP263 assay. ^bStratified log-rank. ^cCrossed the significance boundary for DFS. ^dThe statistical significance boundary for DFS was not crossed.

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The take-home from the study was disease-free survival. And when we look at patients whose tumors had some PD-L1 expression and they had stage II to IIIA disease, the disease-free survival hazard ratio was 0.66, highly statistically significant. And this actually is the patient population where we now have an FDA approval to give adjuvant atezolizumab, again, for patients with completely resected stage II to IIIA disease whose tumors have PD-L1 expression of at least 1%. When we look at the all, say II to IIIA patient population regardless of PD-L1 expression, that hazard ratio is 0.79. And in the intention-to-treat, again, we had not seen enough events for statistical significance to be called one way or the other, but that hazard ratio was 0.81.

IMpower010: DFS in Key Subgroups of the PD-L1 TC ≥1%^a Stage II-IIIa Population



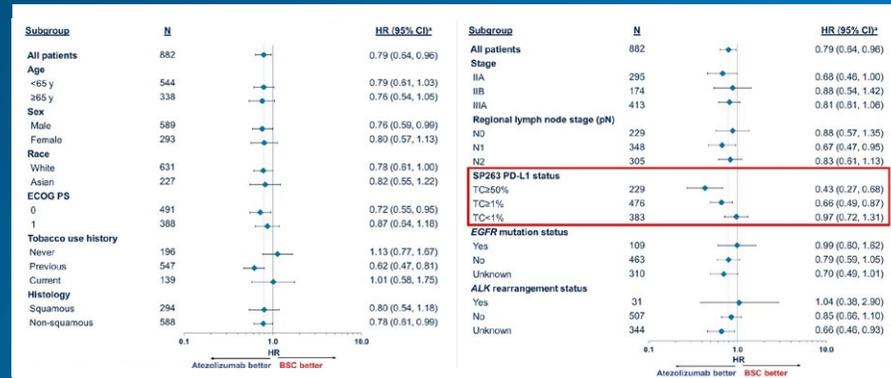
Clinical cutoff: January 21, 2021. ^aPer SP263 assay. ^bStratified for all patients; unstratified for all other subgroups. ^c89.2% and 80.7% of patients in the ITT population with unknown EGFR or ALK status, respectively, had squamous NSCLC and were not required to undergo local or central testing. DFS, 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.

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Looking in more detail at the disease-free survival and the subgroups of patients with PD-L1 of at least 1% and stage II to IIIA, pretty much every subgroup had benefit. There were a couple of outliers who are a little confusing. Patients who were actively smoking did not seem to have as much benefit, but the numbers are small and significance boundaries crossed unity. So I'm unclear what the significance of that was. We also do see that patients who had ALK rearrangement translocations had no benefit regardless of PD-L1 expression. Patients who had tumors with EGFR mutations, though, maybe had benefit if their tumors did have PD-L1 expression, but we are still trying to understand that patient population better.

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



Clinical cutoff: January 21, 2021. ^aStratified 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.

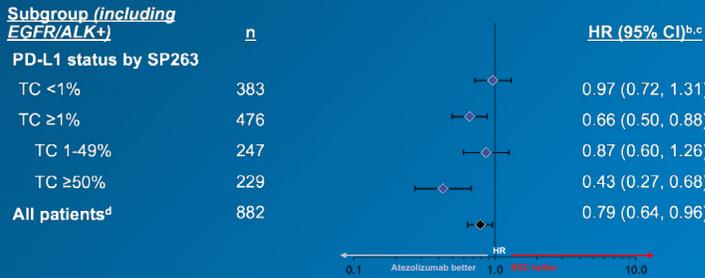
Wakelee et al. *J Clin Oncol*. 2021;39:8500-8500.

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When we look at the disease-free survival in all randomized stage II to IIIA patients, it's very clear that that PD-L1 expression is very important in the outcome of this trial. And patients whose tumors had PD-L1 expression of greater than 50%, had by far the most benefit, the disease-free survival hazard ratio of 0.43. When we look at patients who had no PD-L1 expression in this trial, there was no benefit. And so that's something to keep in mind as we talk about some of the other studies looking at adjuvant immunotherapy.

IMpower010: DFS by PD-L1 Status^a

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



Clinical cutoff: January 21, 2021.

^a Per SP263 assay.

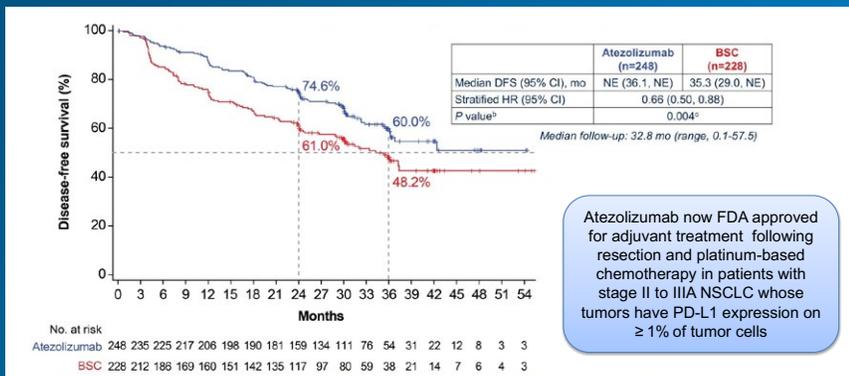
^b Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. ^c DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. ^d 23 patients had unknown PD-L1 status as assessed by SP263. ^e Excluding patients with known EGFR/ALK+ NSCLC. ^f Unstratified for all subgroups. ^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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▶ Going into more detail about PD-L1 expression, patients who had PD-L1 expression less than 1% on their tumor, the disease-free survival hazard ratio in IMpower010 owner was 0.97. But if there's any PD-L1 expression, it was 0.66, mostly driven by the greater than 50% tumor expression of PD-L1 patient population, where that hazard ratio was 0.43. And patients whose tumors had 1% to 49% expression, it was 0.87. So still trying to tease all of that out. But clearly the biggest benefit is seen in those patients with high PD-L1 expression.

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

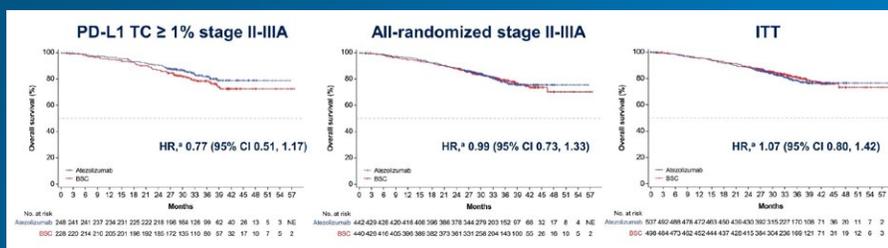


Clinical cutoff: January 21, 2021. ^a Per SP263 assay. ^b Stratified log-rank. ^c Crossed the significance boundary for DFS. BSC, best supportive care; DFS, disease-free survival; FDA, US Food & Drug Administration; NE, not evaluable; PD-L1, programmed cell death protein ligand 1; TC, tumor cells. Wakelee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

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▶ So coming back to the patients with completely resected stage II to IIIa disease, PD-L1 expression of at least 1%, that disease-free survival hazard ratio was 0.66, and the US FDA has granted approval for use of atezolizumab in that patient population.

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. *Stratified.
DFS, disease-free survival; ITT, intention to treat; OS, overall survival; PD-L1, programmed cell death protein ligand 1; TC, tumor cell.

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▶ Still waiting for the overall survival data, but the initial survival curves do seem to be separating in a positive way.

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	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 Administration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.

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▶ I'm now going to mention there are multiple other ongoing phase 3 trials looking at adjuvant immune therapy. We have recently learned that the PEARLS trial/KEYNOTE-091 using adjuvant pembrolizumab in a very similar study designed to the IMpower010 with adjuvant atezolizumab. The PEARLS trial was also positive for disease-free survival in all comers.

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.

▶ What we know from that study is that that benefit was seen regardless of PD-L1 expression. And in the press release, they go on to mention that patients whose tumors had PD-L1 expression greater than 50%, did not have a statistically significant benefit. So, there's a lot to still be learned as we hear further about this. But if the PEARLS trial turns out to be as positive as the press release indicates, it's very likely that we'll be seeing adjuvant pembrolizumab as an option in the future as well. In the PEARLS trial, adjuvant treatment with pembrolizumab significantly improved disease-free survival, reducing the risk of disease recurrence or death by 24% compared to placebo in patients with stage IB to IIIA non-small cell lung cancer following surgical resection regardless of PD-L1 expression, with a hazard ratio of 0.76. The median DFS was 53.6 months for pembrolizumab versus 42.0 months for placebo.

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 Administration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.



▶ Coming later will be the nivolumab-adjuvant nivolumab study; the ANVIL component of the NCTN US cooperative groups study. And then we have the BR31 study with adjuvant durvalumab, and we are still awaiting those results.

Case Consultations

► So with that, I'm now going to move into some cases. Because it's great to hear all of that data but it gets overwhelming as we go through all those disease-free survival hazard ratios. What does it mean in real life when we're dealing with a patient in front of us?

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

► So the first case is a 52-year-old, Asian American man who has an extensive smoking history and presented with hemoptysis. He had a chest x-ray done which showed a right upper lobe mass. CT scan confirmed this mass 4.5 centimeters in size. And he was seen to have a right paratracheal lymph node on PET scan, in addition to the primary mass and no other PET positive areas. Brain MRI was negative. He went to surgical resection and had a right upper lobectomy, complete resection. PD-L1 of the tumor 70%; *EGFR*, *ALK*, *ROS* all negative. He did have a *KRAS* G12A mutation identified.

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.

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- ▶ So we do the staging. This was this stage T2b, N2, stage IIIA lung adenocarcinoma and PD-L1 70%. No driver mutations other than this *KRAS G12A*. So the question is: Would you give adjuvant chemotherapy? Would you offer adjuvant immune therapy?

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

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- ▶ He went on to receive 4 cycles of adjuvant cisplatin/pemetrexed, a mild peripheral neuropathy developed; he was subsequently started on adjuvant atezolizumab, hypothyroidism developed so he was started on hypothyroid replacement therapy but otherwise tolerated it well and is still being followed up this time.

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.

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▶ With case 2, we have a 57-year-old woman with a remote history of tobacco use. She quit 15 years ago. She has 3 months of cough. CT scan of her chest showed a 5.7-centimeter right upper lobe mass, slightly enlarged right-sided hilar nodes. She underwent a bronchoscopic biopsy of the right hilar lymph nodes, which unfortunately showed that she had adenocarcinoma of the lung. PD-L1 expression was 1%. Further evaluation with CT, MRI brain showed no other evidence of distant metastatic disease and she was thought to have a T2, N1 stage IIIA disease.

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
- 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.

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▶ So based on the stage IIIA disease, she underwent resection with medial mediastinal lymph node dissection, then had adjuvant cisplatin/pemetrexed and adjuvant atezolizumab for 1 year.

I think we want to be thinking through the fact that, at this time, we have adjuvant atezolizumab but it's very likely that other immune checkpoint inhibitors will be approved in the near future. Again, we've only so far heard about the

PEARLS trial with adjuvant pembrolizumab, waiting to hear about the data with adjuvant nivolumab, adjuvant durvalumab. And then we will have the difficult task of trying to tease through all the results and what does it mean with different PDL-1 expression levels? How do we choose among agents?

However, coming back to case 2, the other part of that question is what about molecular testing? So what if we had identified an

EGFR L858R mutation in this patient? Would we then have considered adjuvant osimertinib versus continuing with an adjuvant immune checkpoint inhibitor? We still need to see more data before we really know what to do. At this point though, the standard of care would be to give adjuvant osimertinib until we learn more about what does it mean to have *EGFR*-mutated lung cancer with PDL-1 expression. And in that setting, what's our best treatment option?

Neoadjuvant Immunotherapy: Future Directions

► Now I'm going to talk a little bit more about neoadjuvant treatment.

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

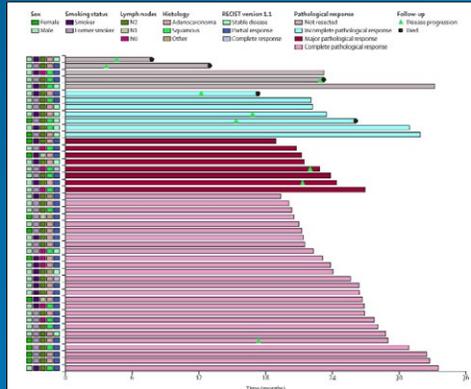
CNS, central nervous system; GI, gastrointestinal; LFT, liver function test; MPR, major pathologic response; PD, progressive disease; PR, partial response; SD, stable disease.
Forde et al. *N Engl J Med*. 2018;378:1976-1986.

► We've talked a little bit about this earlier, but to put in a little bit more detail with neoadjuvant nivolumab, this was really the first step. So nivolumab given with 3 milligrams per kilogram for just 2 doses, resulted in a 10% partial response rate by imaging and a major pathological response rate of 43%. Meaning that 43% of the patients who were on this study showed less than 10% viable tumors at the time of their surgical resection. That's pretty exciting. And this is really what launched this interest in neoadjuvant therapy. Subsequent trials have shown a closer to maybe 20% major pathological response rate with single-agent checkpoint inhibitors. So, the field is moving forward now with combinations with chemotherapy and checkpoint inhibitors in the neoadjuvant setting.

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

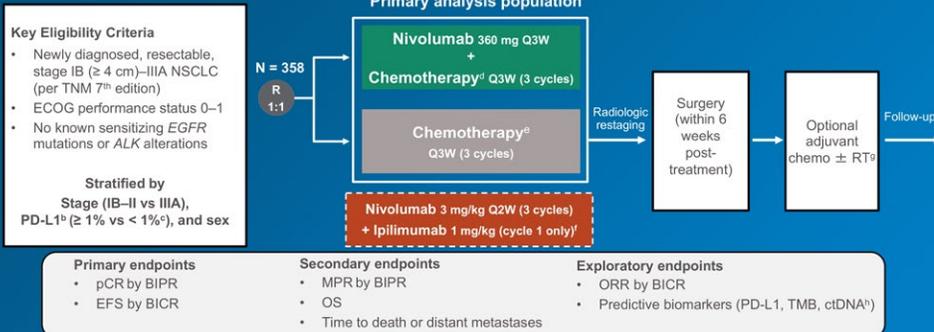


MPR, major pathological response; pCR, pathologic complete response; PFS, progression-free survival. Adapted from Provencio et al. *Lancet Oncol*. 2020;21:1413-1422.

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▶ The NADIM trial, a Spanish study, enrolled 46 patients who got neoadjuvant nivolumab and carboplatin/paclitaxel chemotherapy. There were some patients with delays related to having to pause, to get their treatment, recover. But they all got to surgery on time. And remarkable progression-free survival and overall survival at now 2 and 3 years are being reported. A major pathologic response rate that was over 70%, so 74%. Over half of patients, 57%, had a pathologic complete response, no viable tumor after just 3 doses of chemotherapy nivolumab. So really exciting.

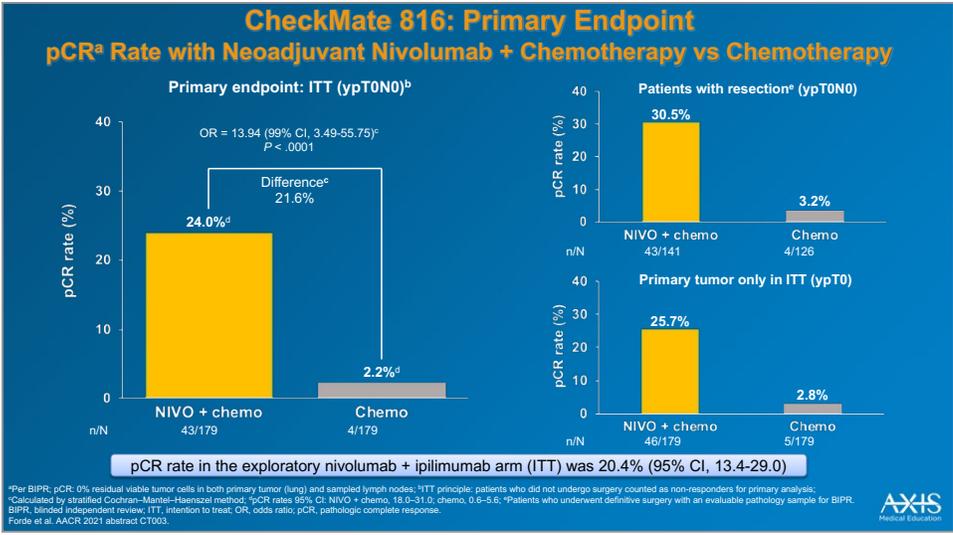
Phase 3 CheckMate 816: Study Design^a



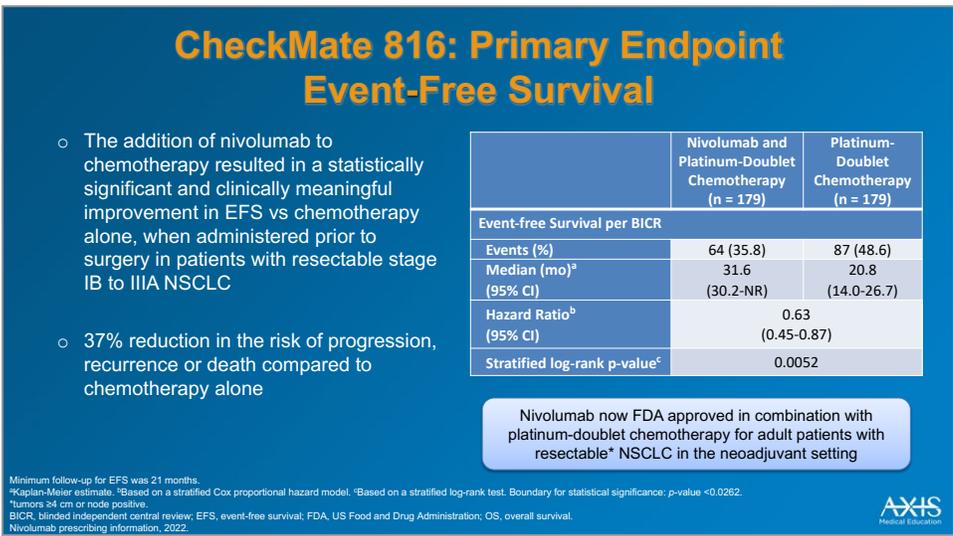
ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathological review; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EGFR, epidermal growth factor receptor; MPR, major pathological response; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand 1; RT, radiotherapy; TMB, tumor mutational burden; TMA, tumor/odes/metastases. Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms. ^aNCT02998528; ^bDetermined by the PD-L1 IHC 28-8 pharmDx assay (Dako); ^cIncluded patients with PD-L1 expression status not evaluable and indeterminate; ^dNSQ, pemetrexed + cisplatin or paclitaxel + carboplatin; SQ, gemcitabine + cisplatin or paclitaxel + carboplatin; ^eVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; Randomized exploratory arm (enrollment closed early); ^fPer healthcare professional choice; ^gPerformed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring). Forde et al. ACR Annual Meeting 2021 abstract CT003.

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▶ That led to the randomized phase 3 CheckMate 816 study, which was for patients with potentially resectable disease, who received chemotherapy or chemotherapy plus nivolumab for 3 cycles.



► When we saw the results of the CheckMate 816 in 2021, we saw that the major pathologic response rate was quite good—24%. So, one-fourth of patients had no viable tumor. The addition of nivolumab did not in any way interfere with patients being able to go to surgery. In fact, surgeries tended to be faster and more complete when the patients had had the combination neoadjuvant therapy.



► We now know that the event-free survival was also in favor of the combination. The FDA has approved nivolumab in combination with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the neoadjuvant setting.

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-III A (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-III B	cisplatin/carboplatin/paclitaxel/pemetrexed/docetaxel	nivolumab or placebo	EFS	Recruiting
NCT03425643	KEYNOTE-671	IIA-III A (8 th)	cisplatin + pemetrexed or gemcitabine	pembrolizumab or placebo	EFS OS	Active, not recruiting
NCT03456063	IMpower030	II-III B (8 th)	cisplatin/carboplatin + nab-paclitaxel/pemetrexed/gemcitabine	atezolizumab or placebo	MPR EFS	Active, not recruiting
NCT03800134	AEGEAN	IIA-III B (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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► There are multiple other ongoing studies looking at other neoadjuvant approaches. So this would be neoadjuvant with a combination of chemotherapy plus pembrolizumab, chemotherapy plus atezolizumab, chemotherapy plus or minus durvalumab, and chemotherapy plus or minus nivolumab we already heard about. I will mention that nivolumab plus ipilimumab, the CTLA-4 drug, was one of the arms of CheckMate 816 but did not show any advantage and that was not continued. So, the jury will be out about whether in the neoadjuvant setting, it's going to be chemo plus single-agent checkpoint inhibitor, or chemo plus combinations. And that'll be something that'll be looked at further.

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/III A DFS in PD-L1+*	FDA approved in Oct 2021 as adjuvant treatment in PD-L1 ≥1% stage II/III A 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
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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 Administration; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PORT, post-operative radiotherapy.

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► I will also mention that so far in the adjuvant setting, we've only seen data with single-agent immune checkpoint inhibitors given after chemotherapy, and that was from the IMpower010 atezolizumab and the KEYNOTE-091 with pembrolizumab.

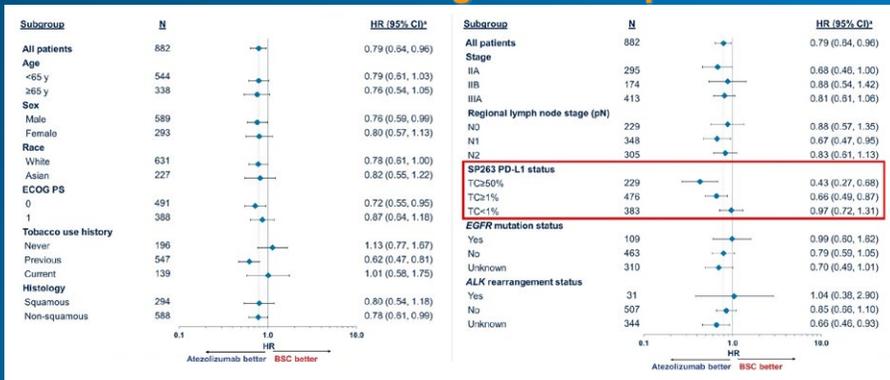
The next steps are going to be adding chemotherapy plus immune checkpoint inhibitors. In fact, we've already talked about the NCTN study with the ALCHEMIST trial or ANVIL with the adjuvant nivolumab was one of the arms. There's a new arm being added that is looking at chemotherapy plus or minus pembrolizumab. And so that will be one of the first chemo plus immune checkpoint inhibitors trials in the adjuvant setting, and more will certainly be coming. And then we'll have to figure out should we give adjuvant or neoadjuvant chemo plus immune checkpoint inhibitor, immune checkpoint inhibitor alone, chemo alone. Lots and lots of ongoing questions.

Molecular Subsets

PD-L1
Driver mutations
What other biomarkers are needed?

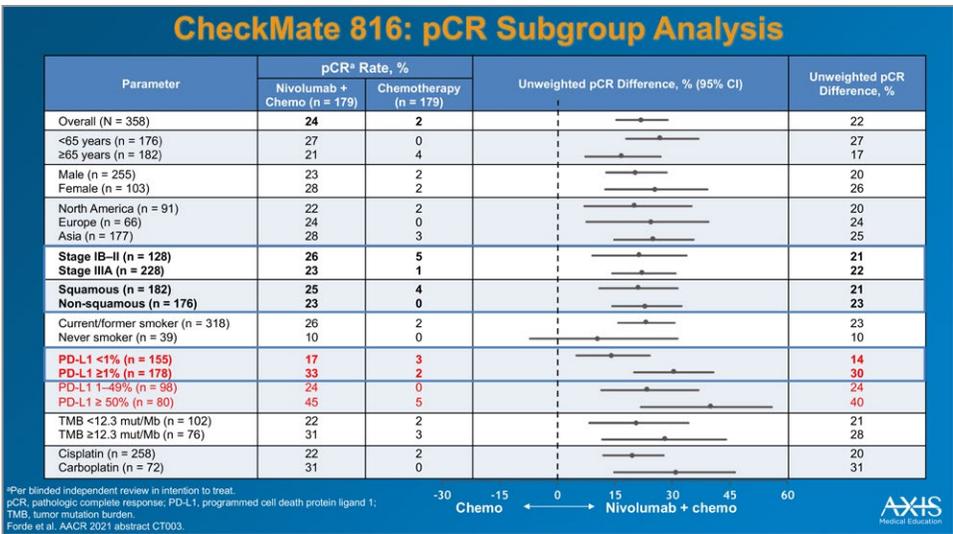
► I'm now going to turn to talk a little bit more about the molecular subsets looking at PD-L1 levels, looking at molecular drivers.

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

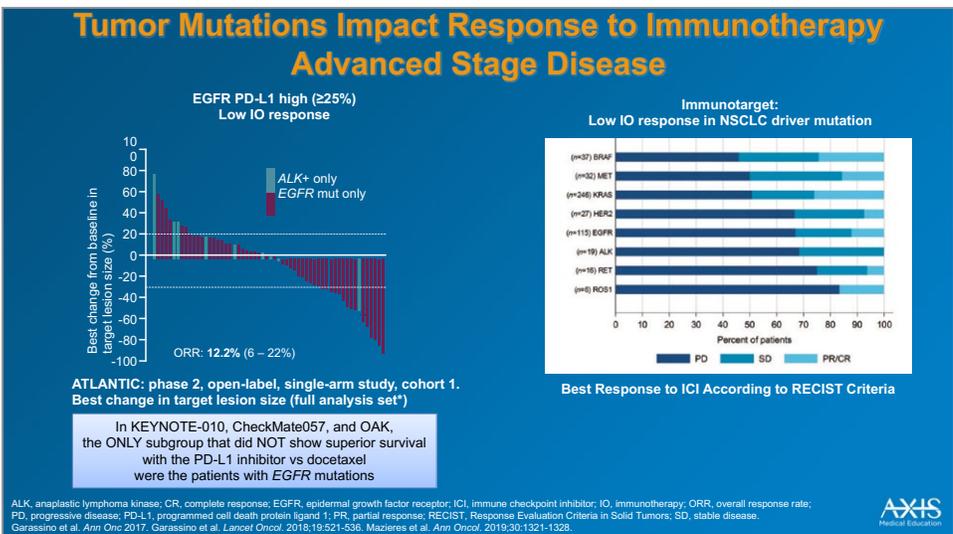


► I've talked already about the importance of PD-L1 level in the IMpower010 study.

Clinical cutoff: January 21, 2021. *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.



▶ When we look at the CheckMate 816 trial, this is the neoadjuvant chemo and nivolumab study, we see that the PD-L1 levels mattered here as well. Regardless of PD-L1, there was benefit with the combination of chemo plus the nivolumab. However, there was more benefit for patients whose tumors had higher expression of PD-L1. So that PD-L1 level did seem to matter. We know from the KEYNOTE-091 press release, that maybe PD-L1 levels don't matter as much in that trial. But we haven't seen the details yet to try to understand how that fits into the rest of these other studies. And we're, of course waiting for multiple ongoing trials to read out to try to fully understand the story of PD-L1 expression and perioperative immune checkpoint inhibitors.



▶ We know that patient's tumors can have PD-L1 expression, but they also can have driving mutations. And sometimes, the PD-L1 expression is more important or equally important, and sometimes that driver mutation is all that matters. So, we do know that in patients whose tumors

have ALK translocations or ROS1, PD-L1 levels can be high, but that does not mean that they're going to respond to a checkpoint inhibitor. It's really important that we know the whole story of the tumor, not just the PD-L1 level, but also what's going on with the driver mutation. If I see a patient who

has ALK translocation, ROS1, I'm not going to give them an immune checkpoint inhibitor, even if their PD-L1 expression is 95%.

In the setting of other drivers, such as KRAS, we know that PD-L1 can matter and that checkpoint inhibitors work well. Others that are more complicated, well, what about EGFR? In general, patients whose tumors have EGFR mutations are less likely to benefit. But if they have high PD-L1 maybe they do. In the metastatic setting, we know there's some patients who benefit in early-stage disease. Still trying to figure all that out. So, there is a lot to learn about still in this. It's a very, ever-growing complexity type of situation, but really exciting developments for our patients.

Conclusions

▶ With that, I'm going to give you a few take-home messages.

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.

▶ Neoadjuvant immune therapy is promising, with proven improvements in major pathologic response, pathologic complete response, and event-free survival. Nivolumab is now FDA approved in combination with platinum-doublet chemotherapy as neoadjuvant treatment for patients with resectable NSCLC as a result of the CheckMate 816 trial. Adjuvant immune therapy confers proven disease-free survival benefit with atezolizumab in patients whose tumors were stage II to IIIa and had PD-L1 expression of at least 1%. Adjuvant pembrolizumab sounds like

it will be an option in the near future as well, maybe regardless of PD-L1 expression, but we're still waiting for more data. Atezolizumab has been approved as an adjuvant treatment now following platinum-based chemotherapy. And as mentioned, pembrolizumab will likely also be an option in the near future.

And likely we'll also be seeing positive data with the other immune checkpoint inhibitors that are ongoing in studies, but we don't know when we'll see that data. And the benefit might be even more in the adjuvant setting when we combined chemo and immune

therapy together, but data forthcoming.

Patient and tumor-specific biomarkers are necessary to predict benefit. We need to really understand PD-L1. We need to fully understand the tumor mutation relevance, and there are a lot of other factors that go into determining immune responses. These are the host factors as well as other tumor-specific factors. DNA and minimal residual disease technology may help predict those in need of additional therapy. But we are a ways away yet from having that as a standard treatment practice.



Thank You

Thank you for participating in this activity!

- ▶ So again, thank you very much for your participation in this activity.

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