



# Debate in Early Stage NSCLC: Adjuvant vs Neoadjuvant : Favoring the Adjuvant Concept

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19<sup>th</sup> Annual

# MIAMI CANCER MEETING

JW MARRIOTT MIAMI | MIAMI, FLORIDA

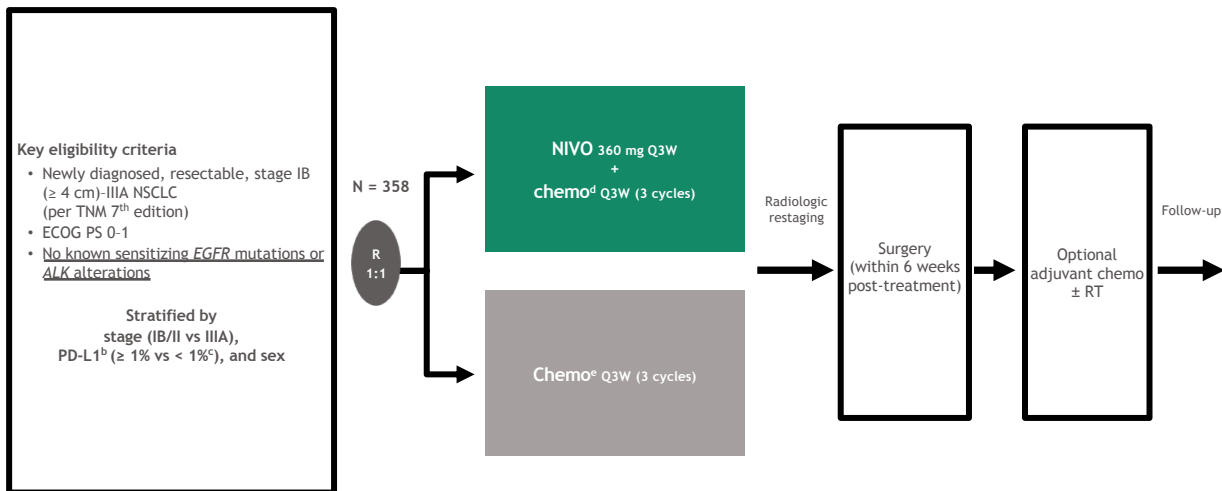
APRIL 28 - 30, 2023

MEC  
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MECC | GLOBAL MEETINGS  
MEETING | EXHIBIT | CONFERENCE | COORDINATION

## Background

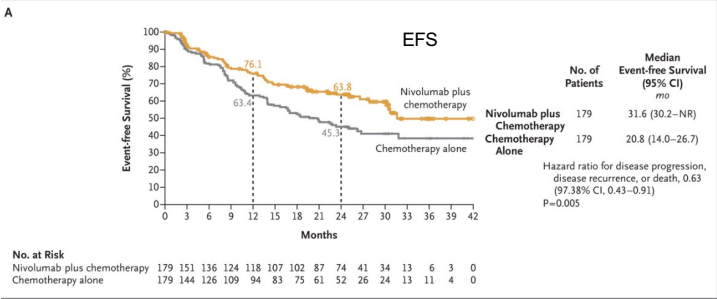
# CM816



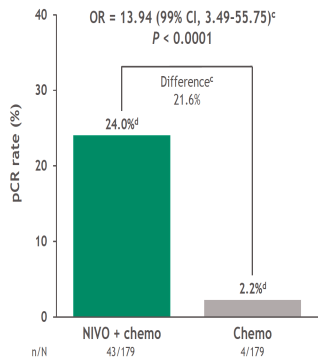
Spicer ASCO 2021 abstr: 8503, Forde NEJM

**63% Stage IIIA**  
**50% PD-L1 >1%**  
**No EGFR/ALK**  
**IO + Chemo**

# CM816 EFS + OS



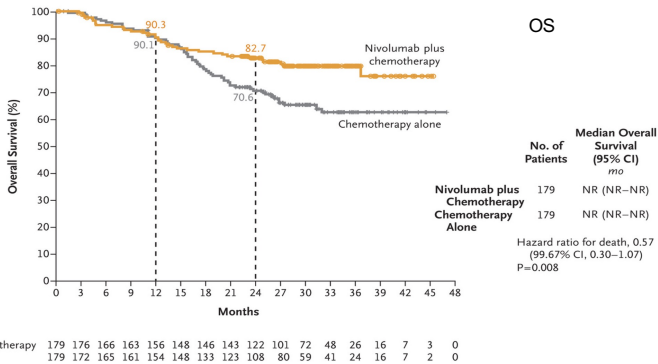
Primary endpoint: ITT (ypT0N0)<sup>b</sup>



• pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

EFS HR 0.63  
97.38% CI (0.43-0.91), p.005

OS HR 0.57  
(99.67% CI 0.30-1.07), p.008

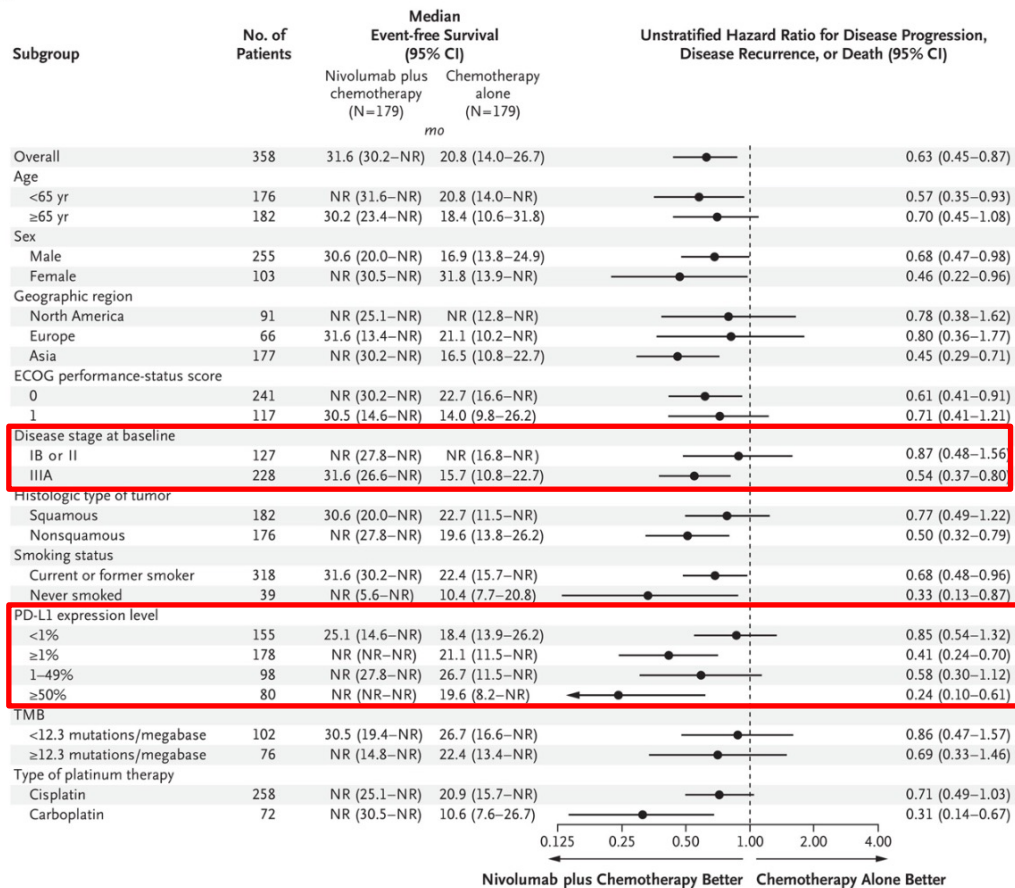


Forde NEJM

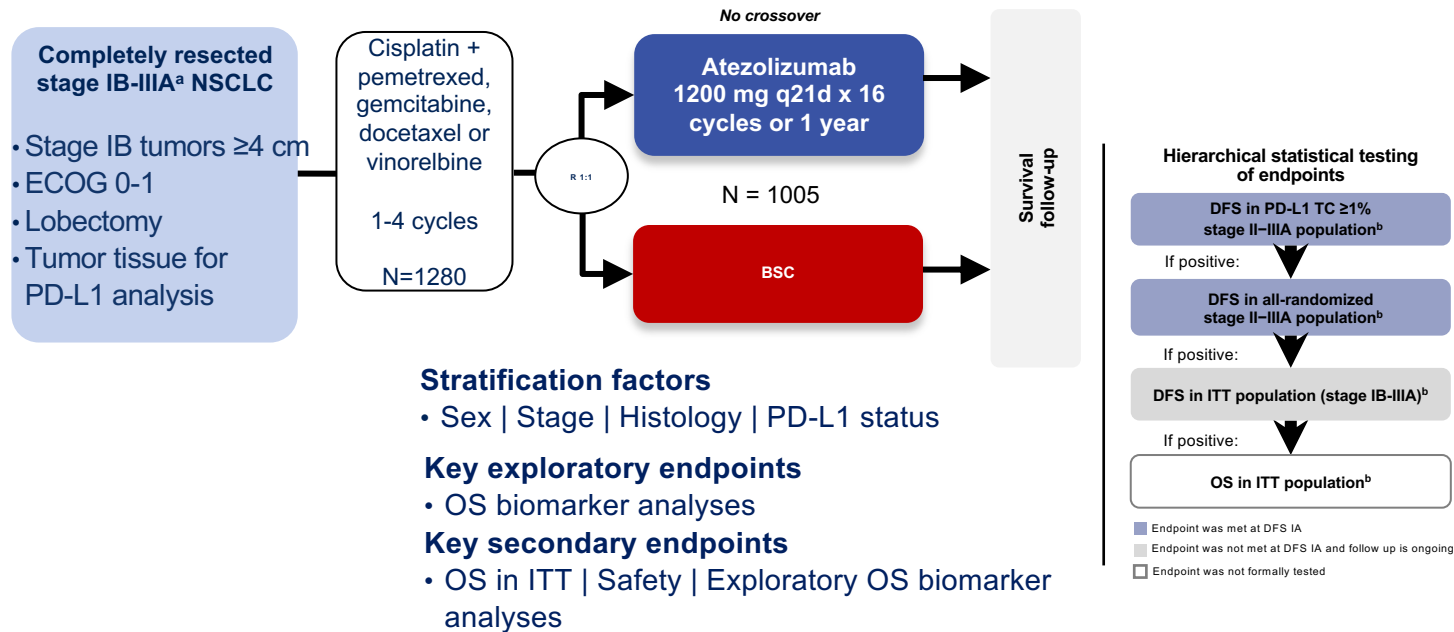
# CM816 subsets

B

Best outcomes  
Stage IIIA  
PD-L1 $\geq$ 50%



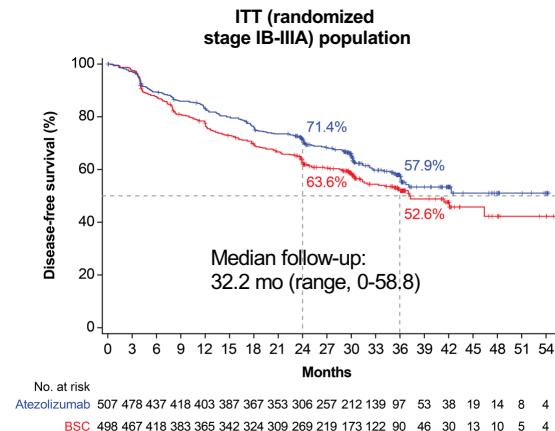
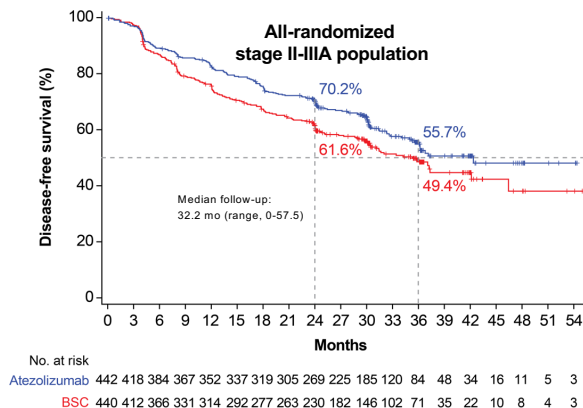
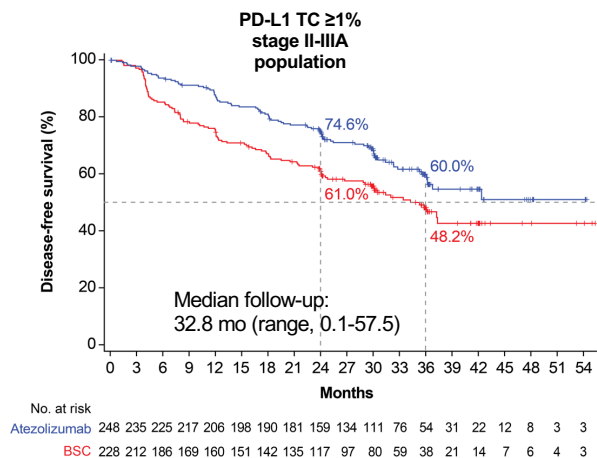
# IMpower010



Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.

<sup>a</sup> Per UICC/AJCC staging system, 7th edition. <sup>b</sup> Two-sided  $\alpha=0.05$ .

# IMpower010: DFS in the PD-L1 TC $\geq 1\%$ <sup>a</sup> stage II-IIIa, all-randomized stage II-IIIa and ITT pop (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 <sup>b</sup>	0.004 <sup>c</sup>	

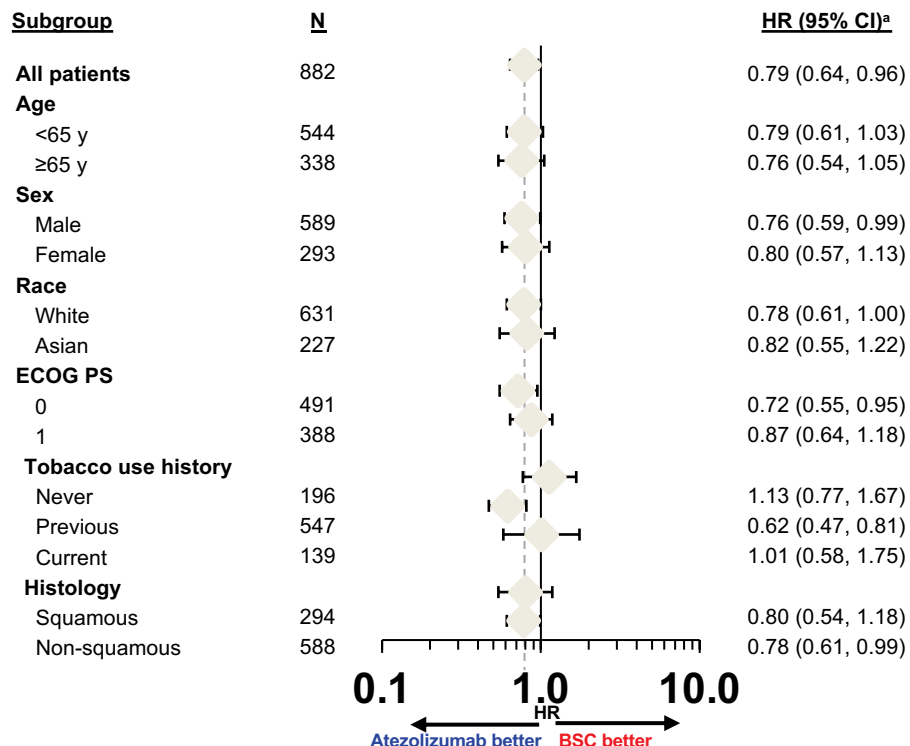
Clinical cutoff: January 21, 2021. <sup>a</sup> Per SP263 assay. <sup>b</sup> Stratified log-rank. <sup>c</sup> Crossed the significance boundary for DFS. <sup>d</sup> The statistical significance boundary for DFS was not crossed.

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value <sup>b</sup>	0.02 <sup>c</sup>	

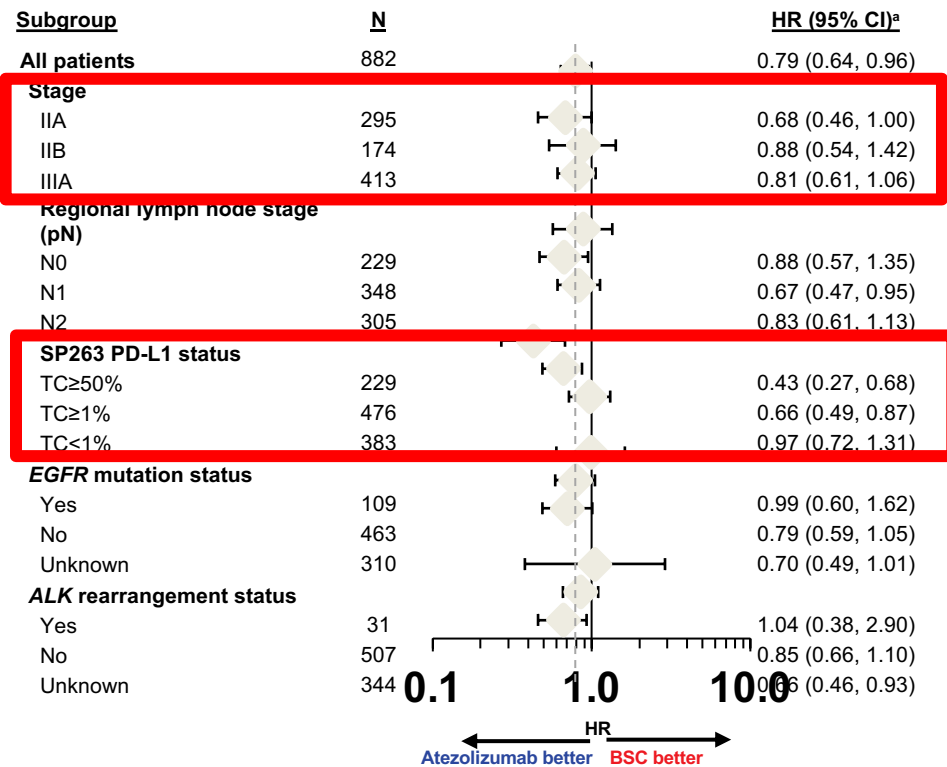
	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value <sup>b</sup>	0.04 <sup>d</sup>	

US FDA approval Oct 15, 2021

# IMpower010: DFS in key subgroups of all-rand stage II-IIIa pop



Clinical cutoff: January 21, 2021. <sup>a</sup> Stratified for all patients; unstratified for all other subgroups.



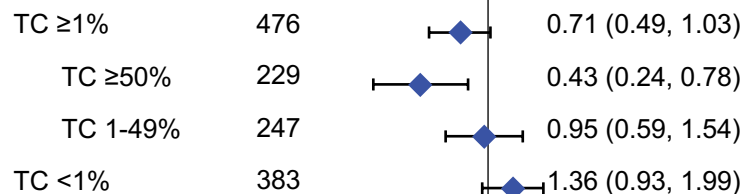


# Impower010 OS by Biomarkers (stage II-IIIa)

(data cutoff: 18 Apr '22, 46 mo follow-up)

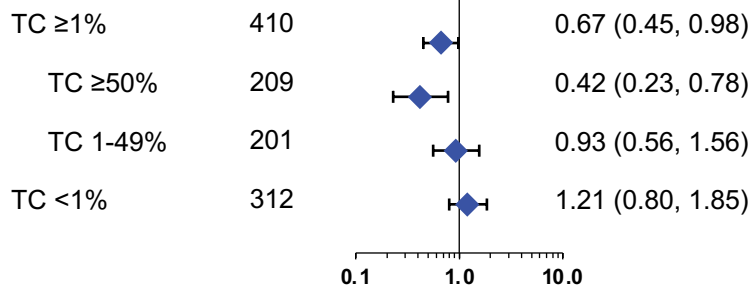
## Subgroup +EGFR/ALK+

### PD-L1 status by SP263<sup>a</sup>

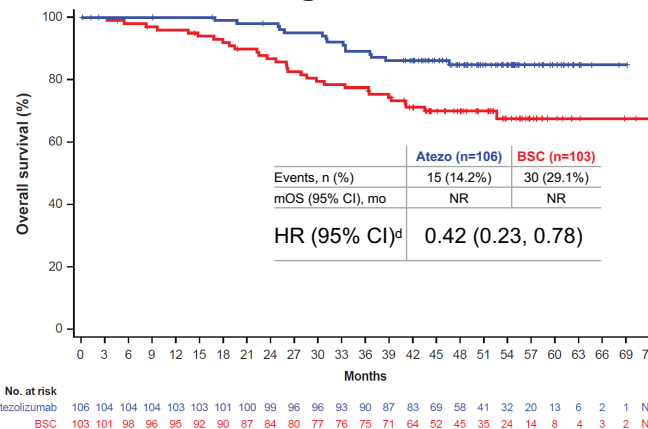


## Subgroup (NO EGFR/ALK+)

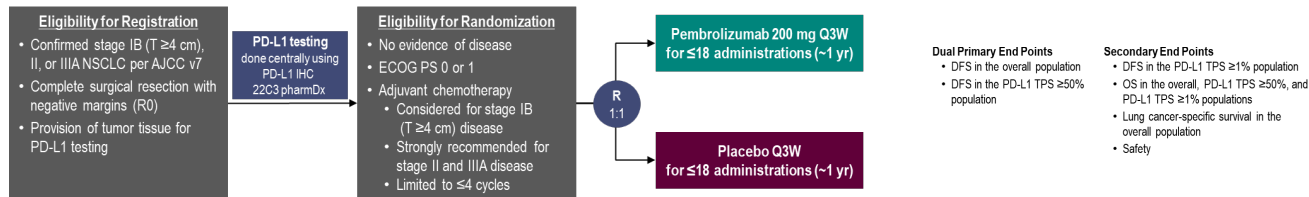
### PD-L1 status by SP263<sup>c</sup>



## OS: PD-L1 TC ≥50% (stage II-IIIa) excluding EGFR/ALK+



# PEARLS/KEYNOTE-091 Study Design



Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range), y	65.0 (31-87)	65.0 (37-85)	64.5 (38-82)	65.0 (37-85)
Male sex	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%

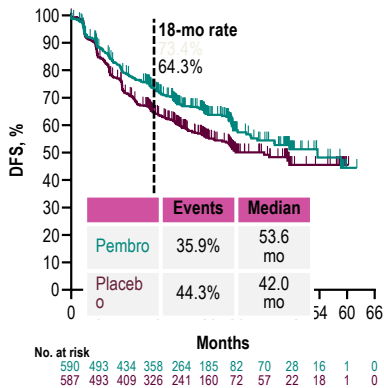
  

Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Current/former smoker	85.3%	88.8%	91.7%	92.1%
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage <sup>a</sup>				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIIA	30.0%	27.6%	31.0%	30.3%
EGFR mutation <sup>a</sup>	6.6%	5.8%	3.6%	3.0%
ALK translocation <sup>a</sup>	1.2%	1.2%	1.8%	0.0%

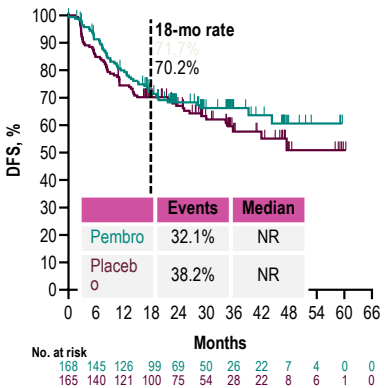
# PEARLS/KN-091:

## Results Second Interim Analysis

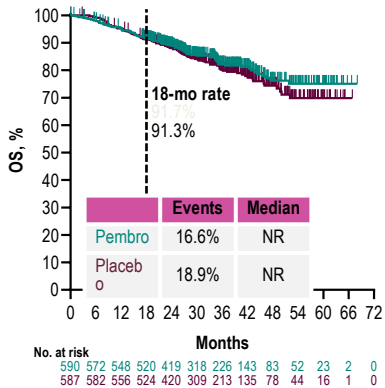
**DFS, Overall Population**  
**HR 0.76 (95% CI 0.63-0.91)**  
**P = 0.0014**



**DFS, PD-L1 TPS ≥50% Population**  
**HR 0.82 (95% CI 0.57-1.18)**  
**P = 0.14**



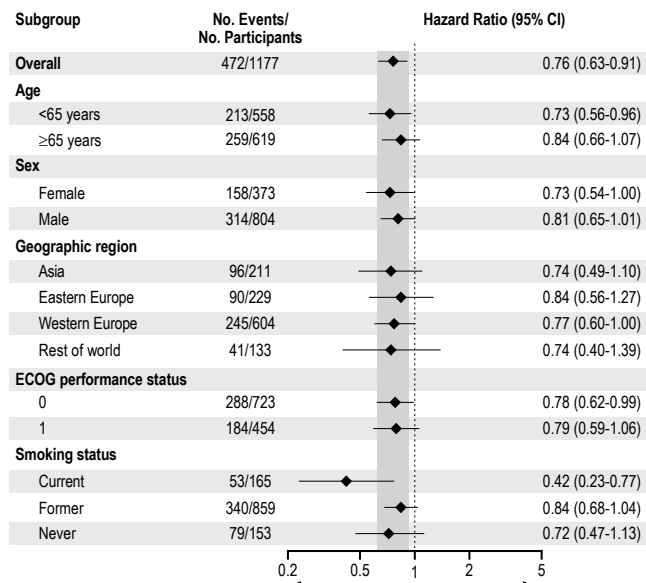
**OS, Overall Population**  
**HR 0.87 (95% CI 0.67-1.15)**  
**P = 0.170**



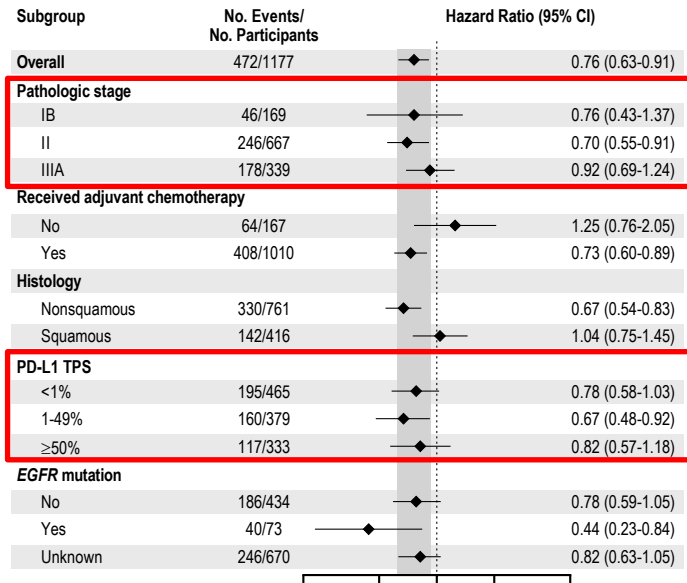
US FDA approval Jan 26, 2023

Impower010 DFS HR: all comer 0.81, PD-L1 ≥50% 0.43

# KN-091 Results: DFS in Subgroups



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





**Debate in Early Stage NSCLC: Adjuvant vs Neoadjuvant :  
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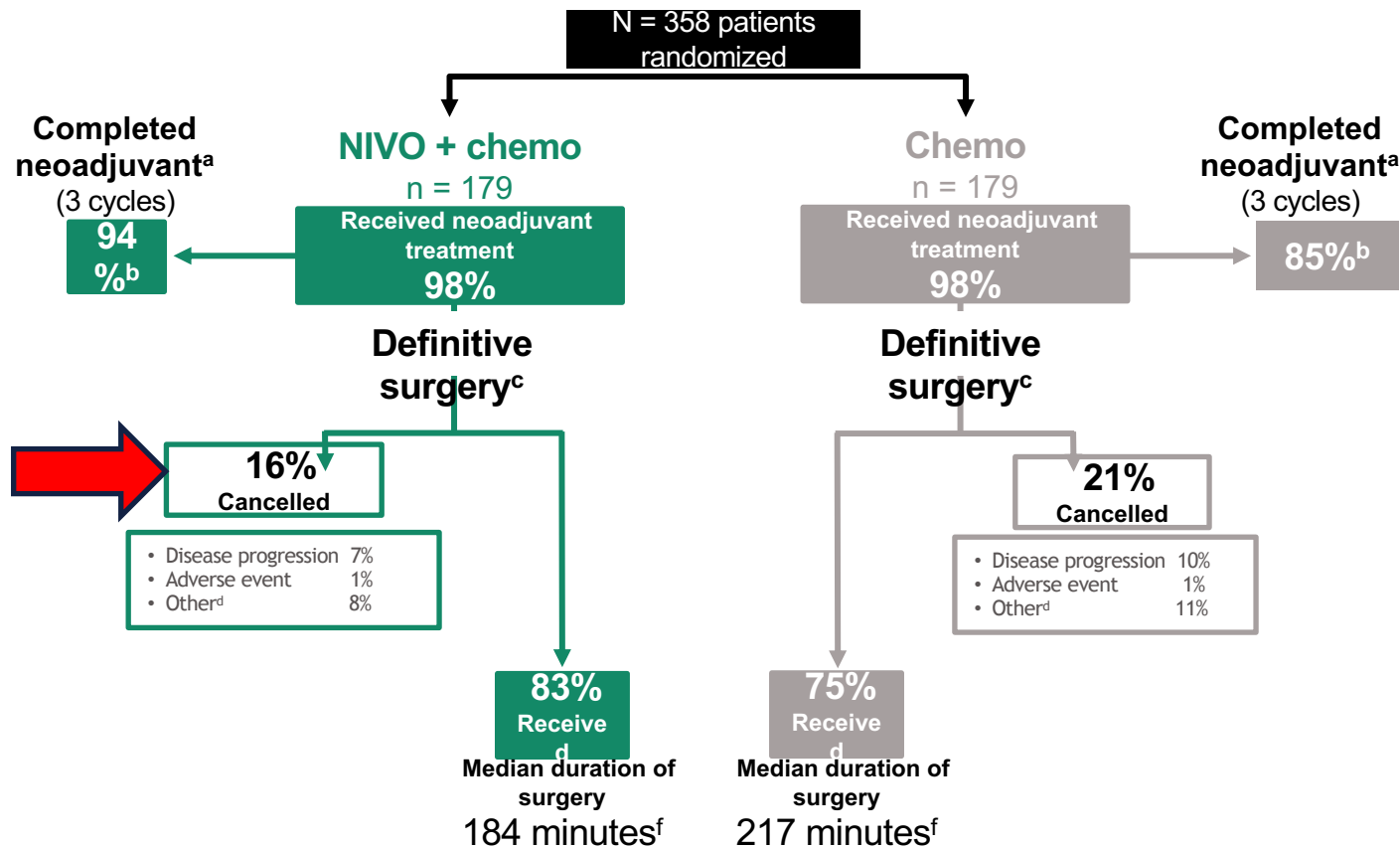
**Risk of Lost Opportunity for Surgery**

Expose All Patients to Toxicity, Regardless of  
Benefit

Over-Treatment

# CM816: Treatment and surgery summary: all randomized patients

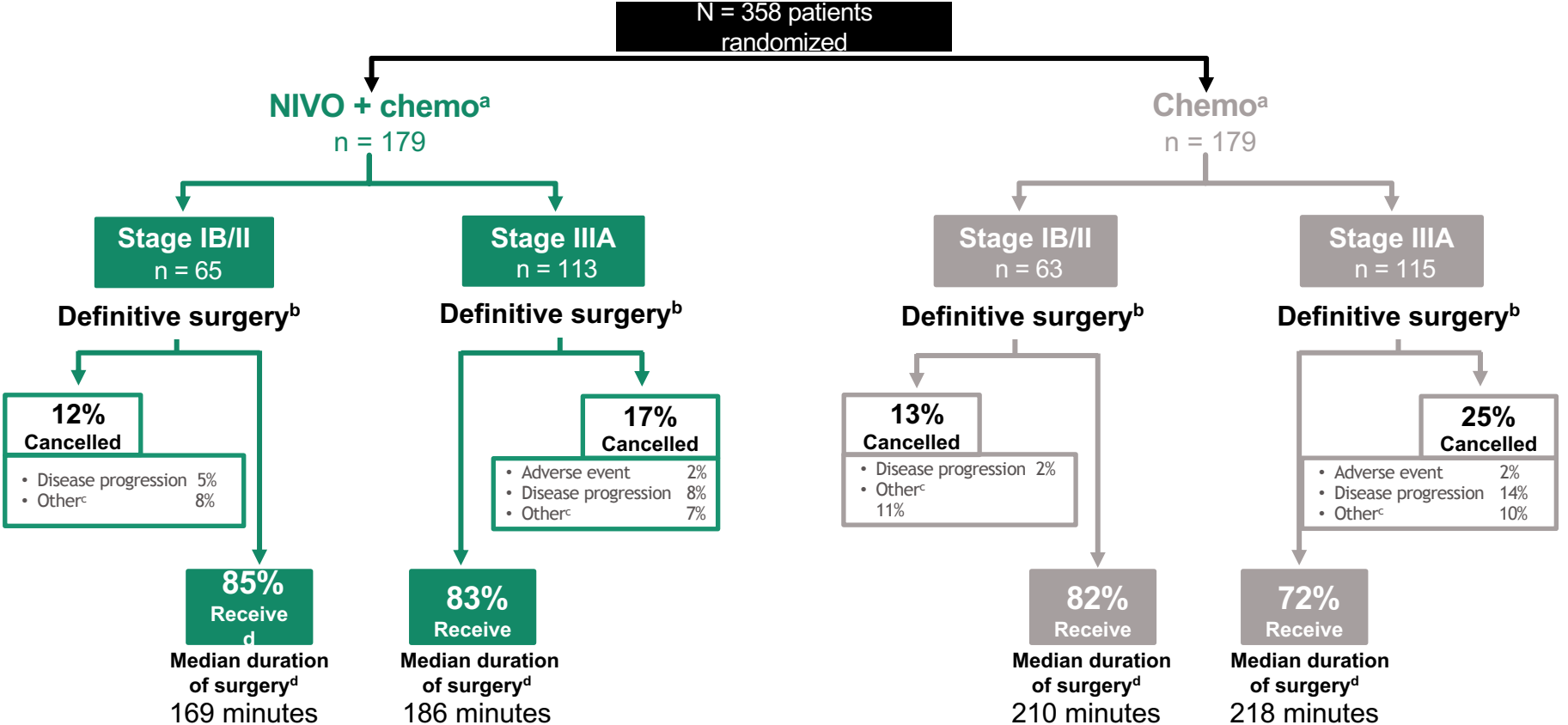
Spicer ASCO 2021



<sup>a</sup>Reasons for patients not completing neoadjuvant treatment: study drug toxicity (6% in the NIVO + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria); <sup>b</sup>Denominator based on patients with neoadjuvant treatment; <sup>c</sup>Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; <sup>d</sup>Other reasons included patient refusal, unresectability, and poor lung function; <sup>e</sup>Median (IQR) time from last dose to definitive surgery; <sup>f</sup>Patients (n) with reported duration of surgery: NIVO + chemo, 122; chemo, 121; IQR for median duration of surgery: NIVO + chemo, 130.0-252.0 minutes; chemo, 150.0-283.0 minutes.

# CM816: Surgery summary: by baseline stage of disease

Spicer ASCO 2021



<sup>a</sup>1 patient with stage IV in each arm; <sup>b</sup>Patients with definitive surgery not reported: NIVO + chemo, 3% (stage IB/II), 0 (stage IIIA); chemo, 5% (stage IB/II), 3% (stage IIIA); <sup>c</sup>Other reasons included patient refusal, unresectability, and poor lung function; <sup>d</sup>Patients (n) with reported duration of surgery: NIVO + chemo, 46 (stage IB/II), 76 (stage IIIA); chemo, 47 (stage IB/II), 74 (stage IIIA); IQR for median duration of surgery: NIVO + chemo, 126.0–275.0 (stage IB/II) and 134.5–245.5 (stage IIIA); chemo, 150.0–267.0 (stage IB/II) and 147.0–290.0 (stage IIIA).

# CM816 Surgery Outcomes summary

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
<b>Patients who received neoadjuvant treatment</b>	176 (98)	176 (98)
<b>Reason off neoadjuvant treatment<sup>a</sup></b>		
Completed (3 cycles)	165 (94)	149 (85)
Study drug toxicity	10 (6)	12 (7)
Disease progression	1 (1)	2 (1)
Other <sup>b</sup>	0	13 (7)
<b>Patients with definitive surgery<sup>c</sup></b>	149 (83)	135 (75)
<b>Type of surgery<sup>d,e</sup></b>		
Lobectomy	115 (77)	82 (61)
Pneumonectomy	25 (17)	34 (25)
Other <sup>f</sup>	29 (19)	35 (26)
<b>R0 resection (negative margins)<sup>d</sup></b>	124 (83)	105 (78)
<b>Patients with cancelled definitive surgery</b>	28 (16)	38 (21)
Disease progression	12 (7)	17 (9)
Adverse event	2 (1)	2 (1)
Other <sup>g</sup>	14 (8)	19 (11)
<b>Patients with delayed surgery<sup>d,h</sup></b>	31 (21)	24 (18)
Administrative reason <sup>d</sup>	17 (11)	8 (6)
Adverse event <sup>d</sup>	6 (4)	9 (7)
Other <sup>d</sup>	8 (5)	7 (5)



	All stages		Stage IB/II		Stage IIIA	
	NIVO + chemo (n = 149)	Chemo (n = 135)	NIVO + chemo (n = 55)	Chemo (n = 52)	NIVO + chemo (n = 94)	Chemo (n = 83)
<b>Patients with delayed surgery,<sup>b,c</sup> n (%)</b> AE	31 (21) 6 (4)	24 (18) 9 (7)	9 (16) 2 (4)	13 (25) 7 (13)	22 (23) 4 (4)	11 (13) 2 (2)
<b>Length of delay in surgery, weeks</b> Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)	2.1 (0.9–2.9)	2.1 (1.3–3.6)	1.9 (0.6–3.0)	2.6 (0.6–4.9)
<b>Of patients with delayed surgery, proportion n (%) with delay of<sup>d</sup></b>						
≤ 2 weeks	17 (55)	11 (46)	4 (44)	6 (46)	13 (59)	5 (46)
> 2 and ≤ 4 weeks	8 (26)	8 (33)	4 (44)	5 (38)	4 (18)	3 (27)
> 4 and ≤ 6 weeks	3 (10)	2 (8)	0	0	3 (14)	2 (18)
> 6 weeks	3 (10)	3 (12)	1 (11)	2 (15)	2 (9)	1 (9)

- Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6–6.0) weeks with NIVO + chemo and 5.0 (4.6–5.9) weeks with chemo for all patients with definitive surgery

<sup>a</sup>Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; <sup>b</sup>Denominator based on patients with definitive surgery; surgery was also delayed due to administration reasons (NIVO + chemo, 11% [all stages], 7% [stage IB/II], 14% [stage IIIA]; chemo, 6% [all stages], 8% [stage IB/II], 5% [stage IIIA]) and other reasons (NIVO + chemo, 5% [all stages], 5% [stage IB/II], 5% [stage IIIA]; chemo, 5% [all stages], 4% [stage IB/II], 6% [stage IIIA]); other reasons included surgeon requested additional pre-operative workup, patient request, impact of COVID-19; <sup>c</sup>Time from last dose of neoadjuvant treatment to surgery > 6 weeks; <sup>d</sup>Denominator based on patients with delayed surgery.



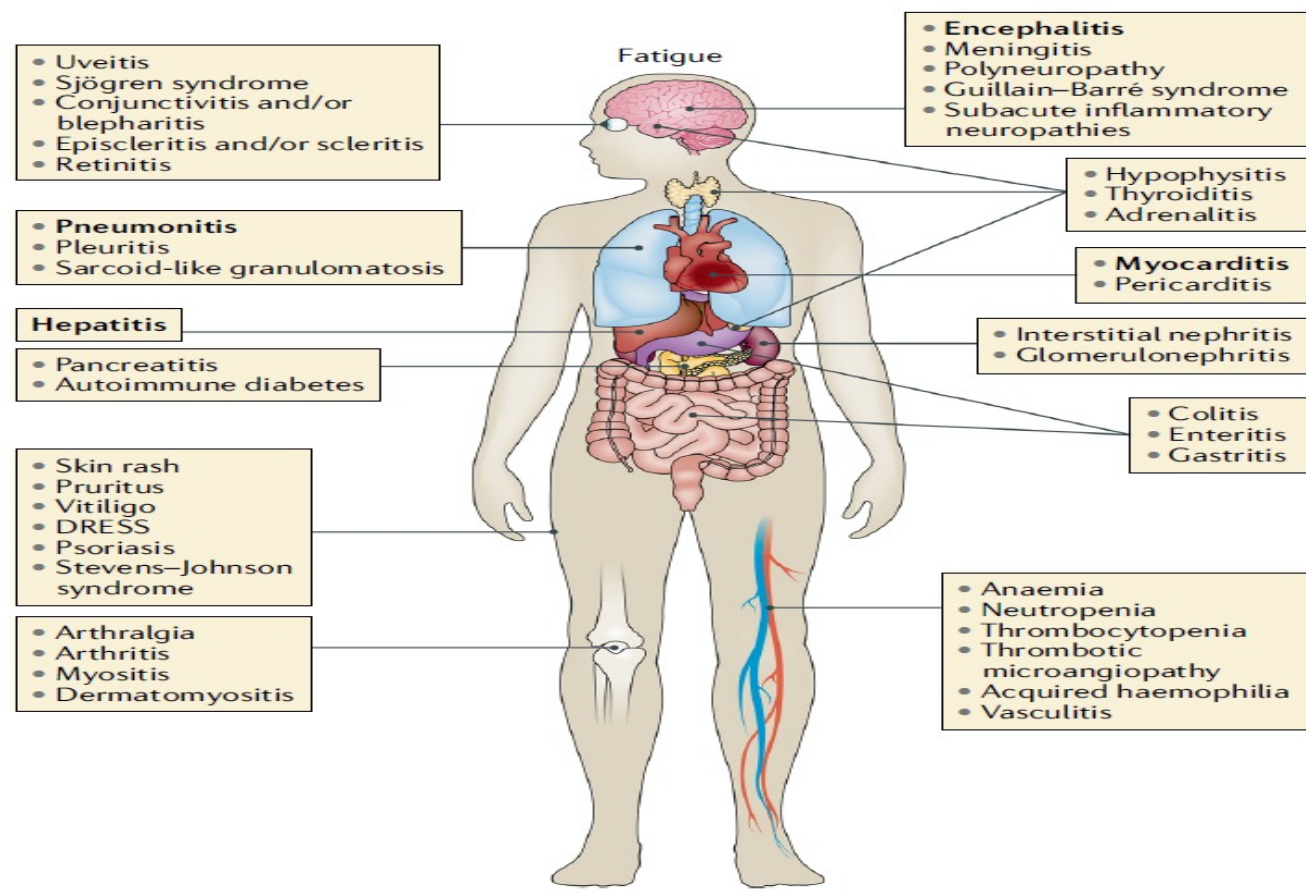
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Risk of Lost Opportunity for Surgery

**Expose All Patients to Toxicity, Regardless of  
Benefit**

Over-Treatment

# Immune-related adverse events by site



# CM816 Adverse events

## Adverse events<sup>a</sup> summary

Patients (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs	92	41	97	44
TRAEs	82	34	89	37
All AEs leading to discontinuation	10	6	11	4
TRAEs leading to discontinuation	10	6	10	3
All SAEs	16	11	14	10
Treatment-related SAEs	12	8	10	8
Surgery-related AEs <sup>b</sup>	41	11	47	15
Treatment-related deaths	0		3 <sup>c</sup>	

- Grade 5 surgery-related AEs<sup>d</sup> were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)
- NIVO + IPI (n = 111): Any grade and grade 3-4 TRAEs were reported in 65% and 14% of patients, respectively
  - Grade 5 surgery-related AEs<sup>d</sup> occurred in 1 patient (due to septic shock [unrelated to study drug per investigator])

# IMpower010: safety summary<sup>a</sup>

n (%)	Atezolizumab (n=495)	BSC (n=495)
Any-cause AE	459 (92.7)	350 (70.7)
Treatment-related AE	335 (67.7)	–
Grade 3-4 AE	108 (21.8)	57 (11.5)
Treatment-related grade 3-4 AE	53 (10.7)	–
Serious AE	87 (17.6)	42 (8.5)
Treatment-related serious AE	37 (7.5)	–
Grade 5 AE	8 (1.6) <sup>b</sup>	3 (0.6) <sup>c</sup>
Treatment-related grade 5 AE	4 (0.8)	–
AE leading to dose interruption of atezolizumab	142 (28.7)	–
AE leading to atezolizumab discontinuation	90 (18.2)	–
Immune-mediated AEs	256 (51.7)	47 (9.5)
Grade 3-4 immune-mediated AEs	39 (7.9)	3 (0.6)
Immune-mediated AEs requiring the use of systemic corticosteroids	60 (12.1)	4 (0.8)

Clinical cutoff: January 21, 2021. AE, adverse event; <sup>a</sup> Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment).

<sup>b</sup> Interstitial lung disease\*; pneumothorax; multiple organ dysfunction syndrome\*; cerebrovascular accident; arrhythmia; myocarditis\*; acute myeloid leukemia\*; acute cardiac failure. <sup>c</sup> Pneumonia; pulmonary embolism; cardiac tamponade and septic shock in the same patient. \*, Treatment related per investigator.

# IMpower010: immune-mediated AEs<sup>a</sup>

imAEs occurring in ≥1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any grade	Grade 3-4	Any grade	Grade 3-4
Any immune-mediated AEs	256 (51.7) <sup>b</sup>	39 (7.9%)	47 (9.5)	5 (0.6)
Rash	91 (18.4)	7 (1.4)	11 (2.2)	0
Hepatitis (diagnosis and laboratory abnormalities)	86 (17.4)	20 (4.0)	22 (4.4)	1 (0.2)
Hepatitis (laboratory abnormalities)	81 (16.4)	16 (3.2)	21 (4.2)	1 (0.2)
Hepatitis (diagnosis)	7 (1.4)	4 (0.8)	1 (0.2)	0
Hypothyroidism	86 (17.4)	0	3 (0.6)	0
Hyperthyroidism	32 (6.5)	2 (0.4)	4 (0.8)	0
Pneumonitis	19 (3.8) <sup>c</sup>	4 (0.8)	3 (0.6)	0
Infusion-related reaction	7 (1.4)	1 (0.2)	0	0
Adrenal insufficiency	6 (1.2)	2 (0.4)	0	0

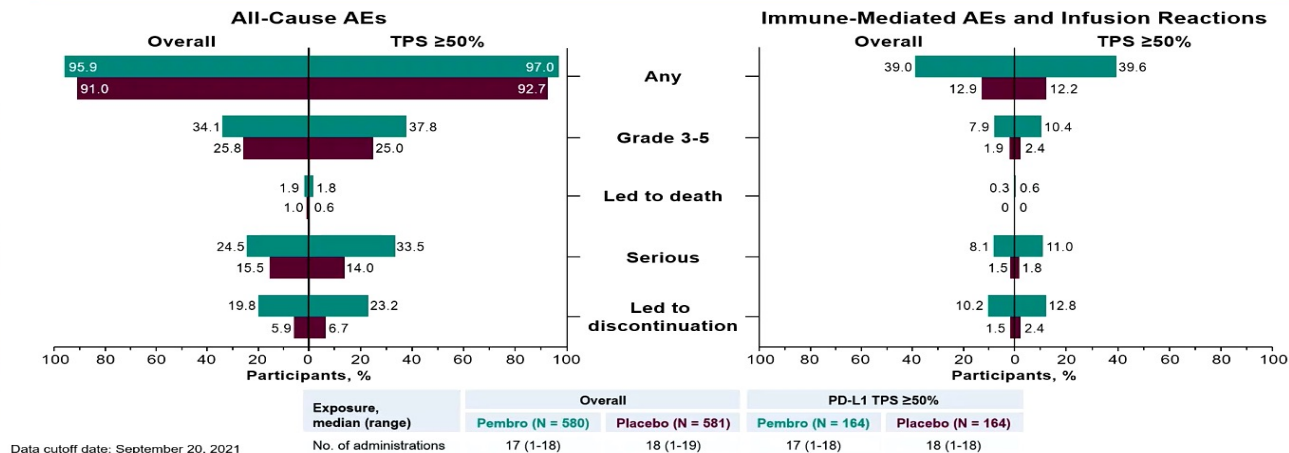
imAEs occurring in <1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any Grade	Grade 3-4	Any grade	Grade 3-4
Meningoencephalitis	4 (0.8)	3 (0.6)	0	0
Colitis	4 (0.8)	2 (0.4)	1 (0.2)	0
Diabetes mellitus	4 (0.8)	0	1 (0.2)	0
Myositis (myositis and rhabdomyolysis)	4 (0.8)	0	1 (0.2)	0
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Encephalitis	2 (0.4)	2 (0.4)	0	0
Severe cutaneous adverse reaction	2 (0.4)	0	0	0
Autoimmune hemolytic anemia	2 (0.4)	0	0	0
Myocarditis	2 (0.4) <sup>c</sup>	0	0	0
Meningitis	2 (0.4)	1 (0.2)	0	0
Guillain-Barre syndrome	1 (0.2)	1 (0.2)	0	0
Ocular inflammatory toxicity	1 (0.2)	0	1 (0.2)	1 (0.2)
Hypophysitis	1 (0.2)	0	0	0
Nephritis	1 (0.2)	0	0	0
Vasculitis	0	0	1 (0.2)	1 (0.2)

Clinical cutoff: January 21, 2021. <sup>a</sup> Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). <sup>b</sup> Includes 2 (0.4%) Grade 5 events. <sup>c</sup> Includes 1 (0.2%) Grade 5 event.

# KN-091 Toxicity

## Summary of Adverse Events and Exposure: Overall and PD-L1 TPS $\geq 50\%$ Populations



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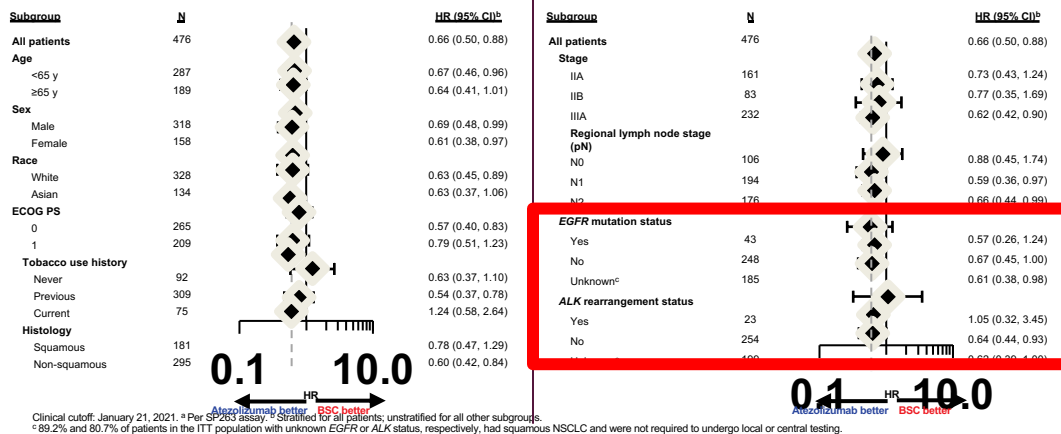




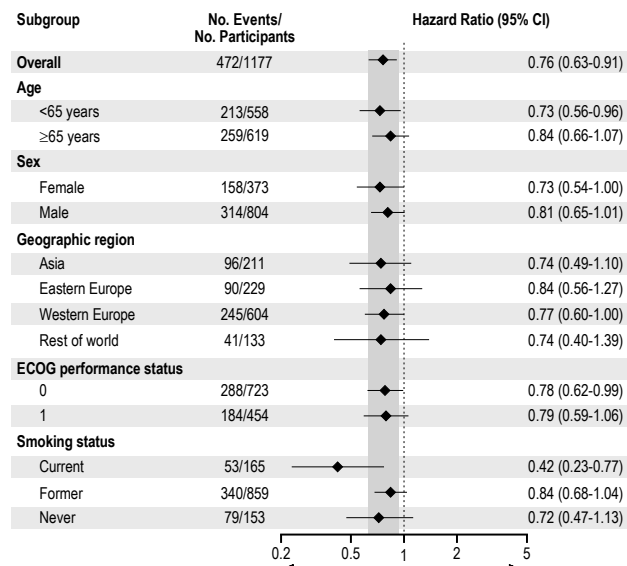
# Surrogates: Driver Mutations

**With Neo-Adjuvant you will NOT  
likely know full tumor details  
before you start**

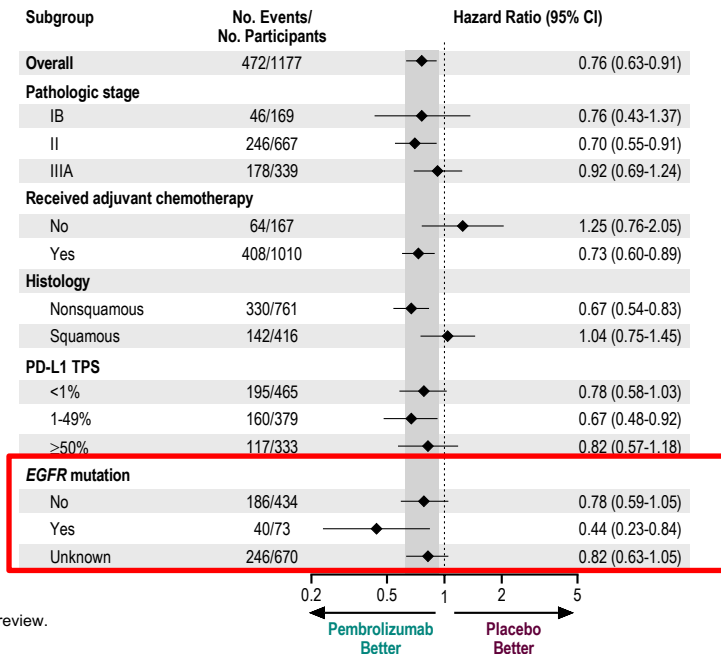
## IMpower010: DFS in key subgroups of the PD-L1 TC $\geq 1\%$ <sup>a</sup> stage II-III A population



# KN-091 Driver Mutation and other Subsets



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

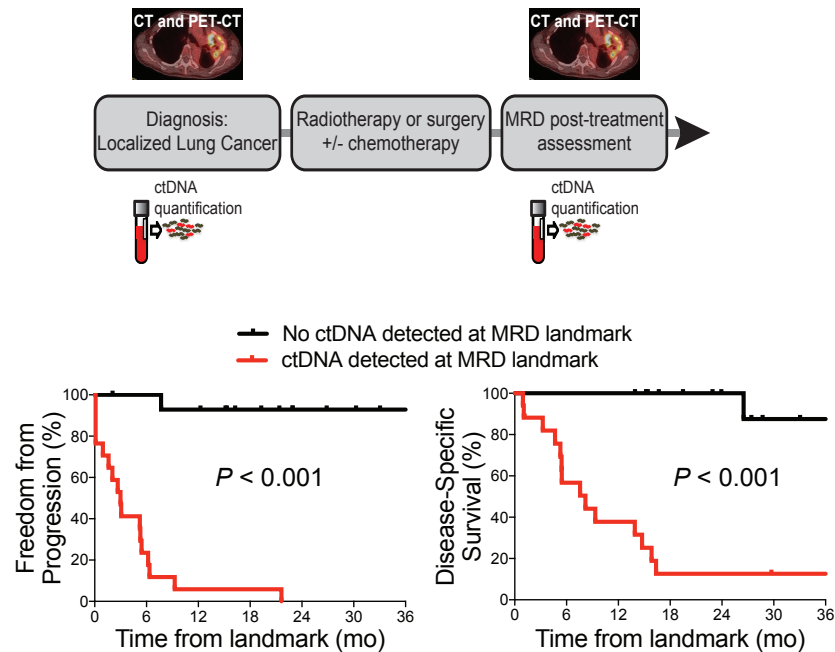




# Surrogates: ctDNA

## How do we avoid overtreatment

# The Promise of MRD



M. Diehn / Stanford

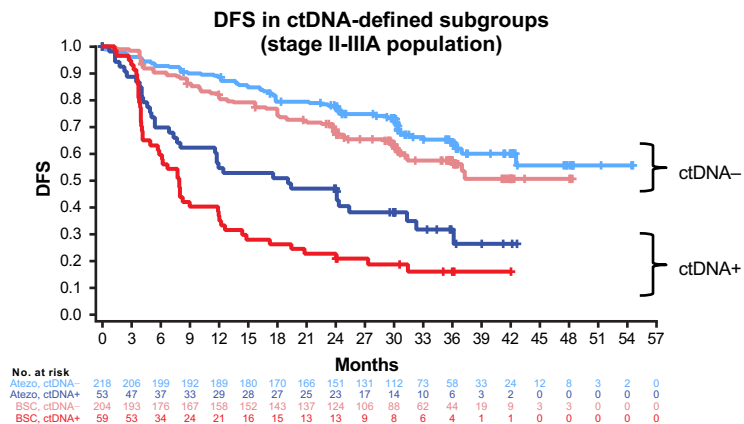
Chaudhuri et al *Cancer Discovery* 2017

# IMpower010 ctDNA data

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

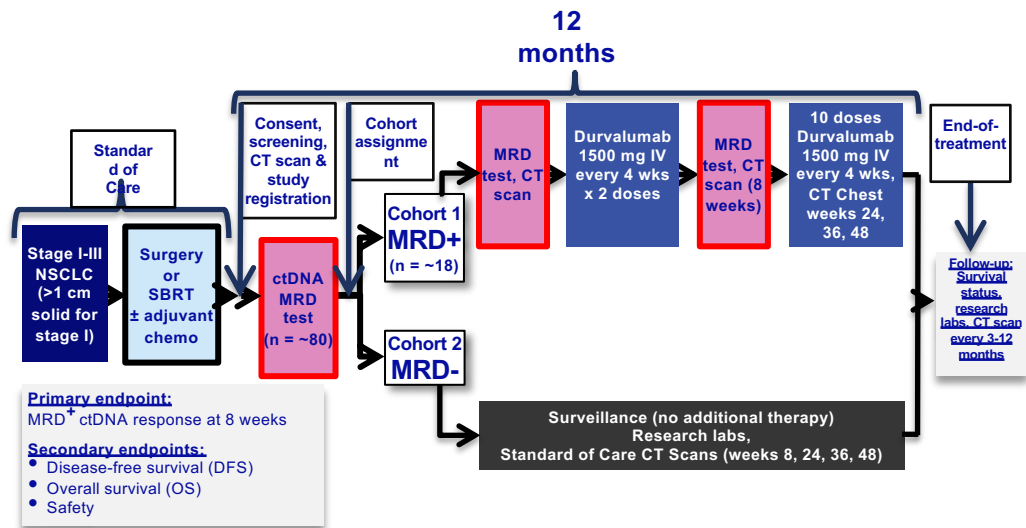
ctDNA-	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

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



Zhou C et al, ESMO IO 2021

# Adjuvant Durvalumab for Early Stage NSCLC with ctDNA MRD after surgery – ongoing trial



PIs: Neal and Diehn

**Debate in Early Stage NSCLC: Adjuvant vs Neoadjuvant :  
Favoring the Adjuvant Concept**

**Risk of Lost Opportunity for Surgery – the  
definitive therapy**

**Expose All Patients to Toxicity, Regardless  
of Benefit – Long-term risk is real**

**Over-Treatment - Less opportunity to select who  
will actually benefit (ctDNA, driver mutation  
analysis, etc.)**





Debate in Early Stage NSCLC: Adjuvant vs Neoadjuvant :  
**Favoring the Adjuvant Concept**

**Or maybe this debate is less relevant:  
The PERI-OPERATIVE TRIALS ARE HERE!!!**

AEGEAN + EFS	(AACR)
Neotorch + EFS	(April 20 ASCO virtual Plenary)
KN-671 + EFS	(ASCO)



# **Debate in Early Stage NSCLC: Adjuvant vs Neoadjuvant : Favoring the Adjuvant Concept**

**Use the right treatment to achieve the best possible outcome for every patient**

**Do not give any more treatment than is necessary to achieve cure**