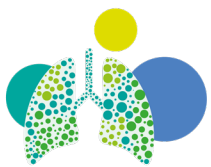




# Immunothérapie des cancers bronchiques

**Julien Mazieres**

CHU de Toulouse, Université Paul Sabatier,  
INSERM UMR1037



**Pôle des voies  
respiratoires**

CHU  
TOULOUSE

Services pneumologie, chirurgie thoracique, ORL



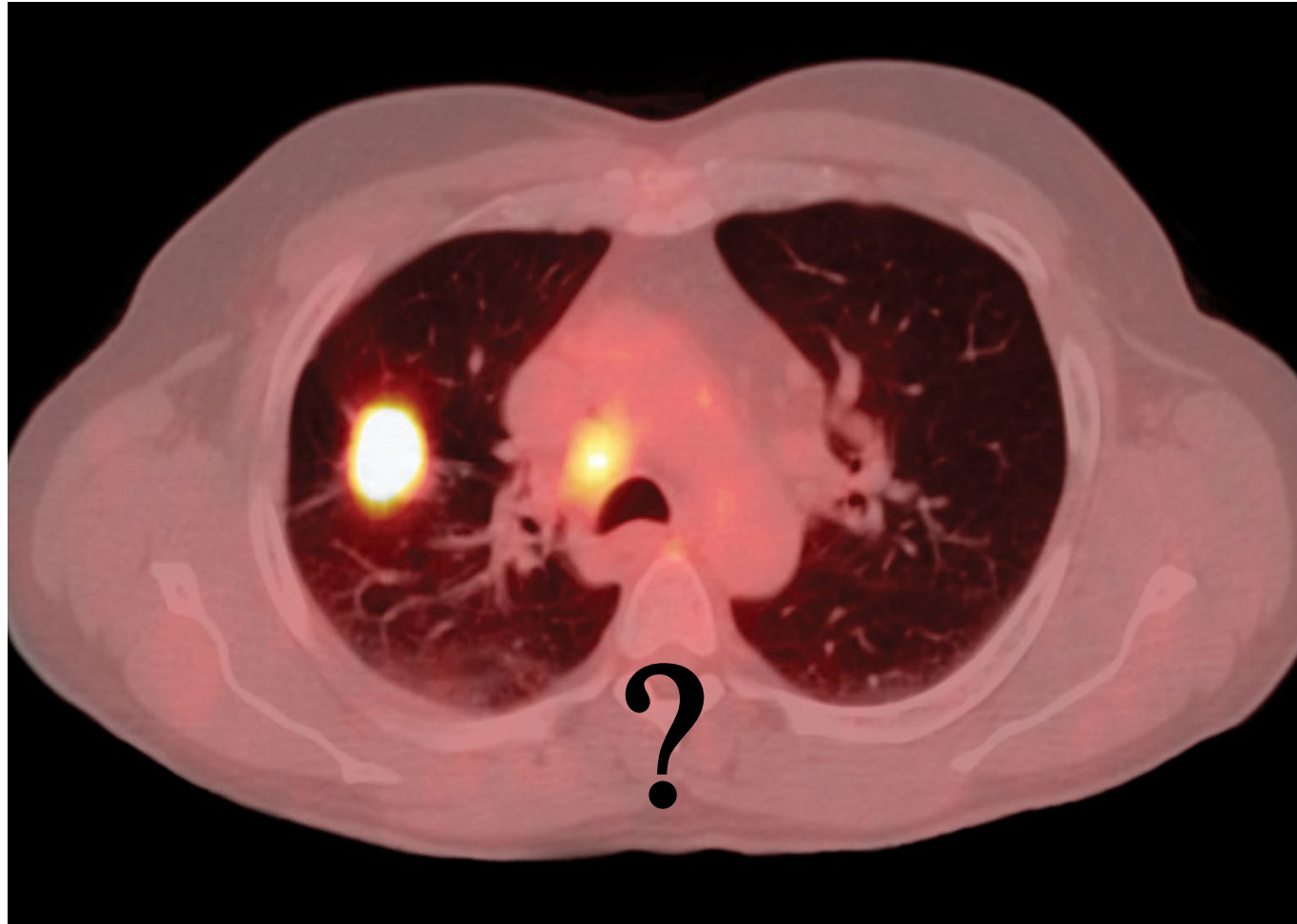
INSTITUT UNIVERSITAIRE  
DU CANCER DE TOULOUSE

# Traitement péri-opératoire des stades précoces

Radio-  
chimiothérapie  
concomitant puis  
immunothérapie ?

Chirurgie suivie de  
chimiothérapie  
adjuvante ?

Chirurgie suivie de  
chimiothérapie  
adjuvante et  
immuno ?



Chimio-  
immunothérapie  
suivi de chirurgie  
puis immuno ?

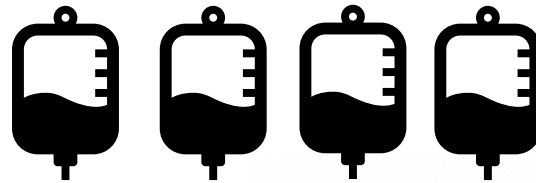
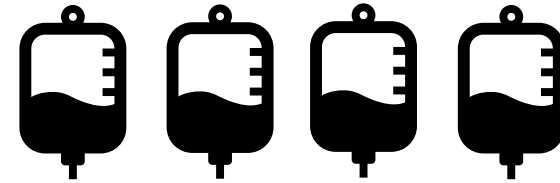
Chimio-  
immunothérapie  
suivi de chirurgie  
seule ?

Si EGFR + Chirurgie  
suivi de CT puis  
osimertinib 3 ans



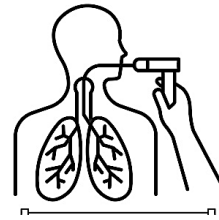
# Traitement péri-opératoire (2022)

I	IA
	IB
II	IIA
	IIB
III	IIIA
	IIIB
	IIIC

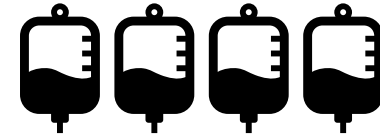


# Traitement péri-opératoire: EGFR

I	IA
	IB
II	IIA
	IIB
III	IIIA
	IIIB
	IIIC



EGFR



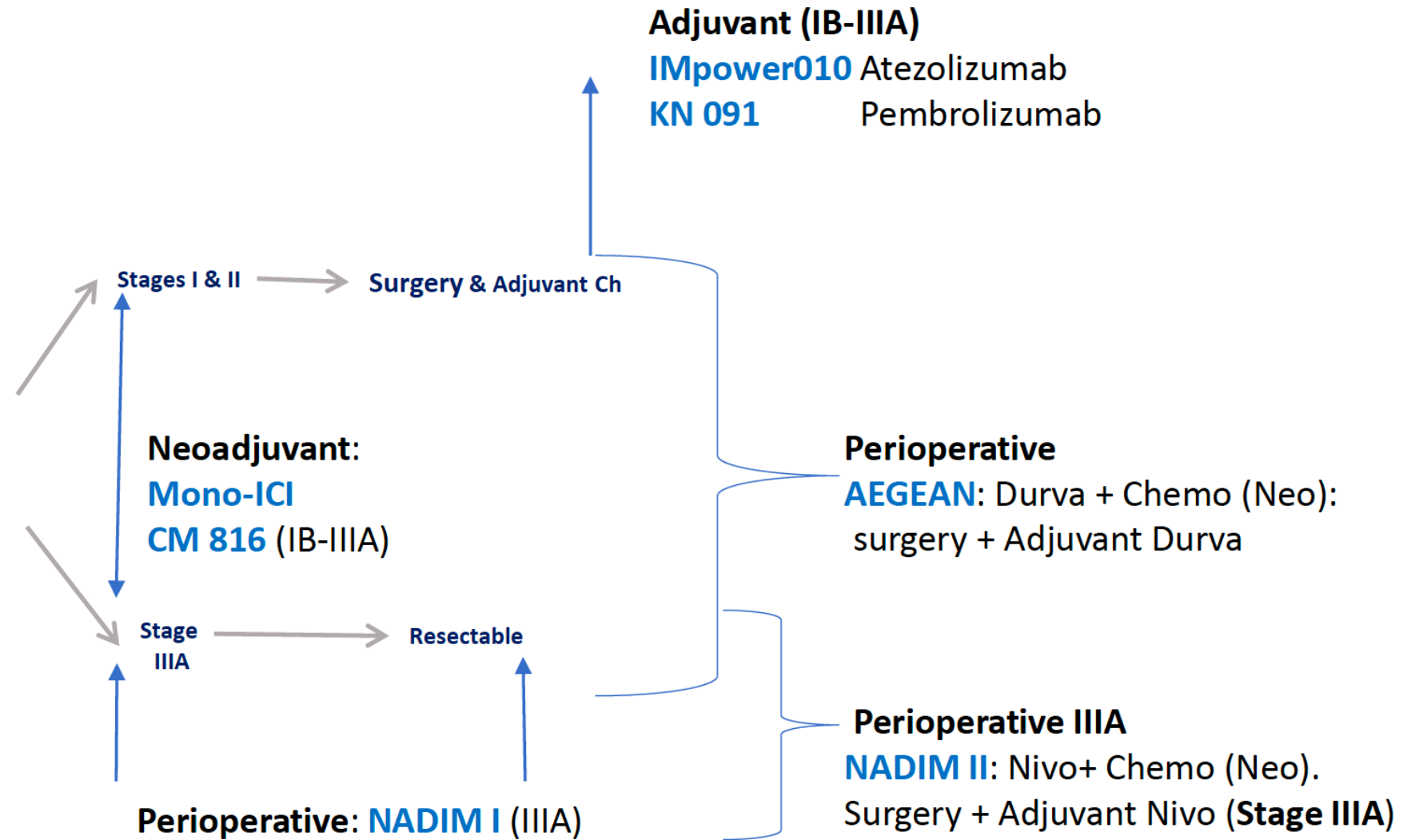
# Immunothérapie péri-opératoire des stades précoces

Stratégie	Adjuvant	Neo-Adjuvant
Pas de délai pour la chirurgie		
TNM pathologique		
Tissus pour les biomarqueurs		
Action rapide sur le <u>priming immunitaire</u>		
Tolérance/compliance		
Délivrance de la molécule ( <u>ganglion</u> )		
Evaluation de l'efficacité individuelle	Non	Imagerie
Analyse précoce de la stratégie	DFS	RR, pRR, DFS



# Immunothérapie péri-opératoire des stades précoces

IASLC	O.S. 60 m
IB	68%
IIA	60%
IIB	53%
IIIA	36%



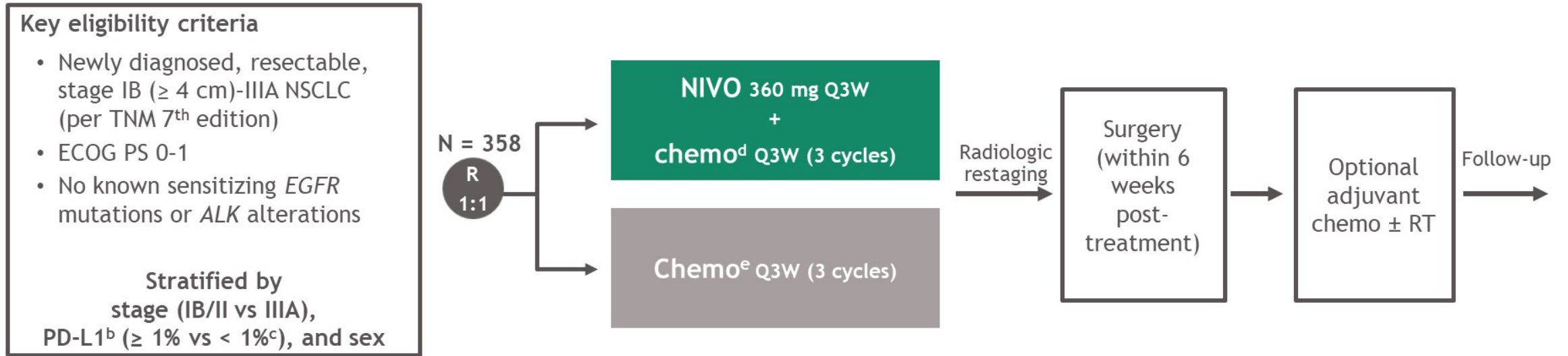
# Études de phase III d'immunothérapie adjuvante dans le CBNPC

Drug/Trial	Description	Stages entered	Description	Primary Endpoint
<b>Nivolumab ALCHEMIST/ANVIL</b>	US NCI, observation as control,	IB (4 cm) – IIIA, after adj chemo and/or radiation	Phase 3 Allows PD-L1+ and PD-L1 -	OS/DFS
<b>Atezolizumab IMPOWER 010</b>	Global, placebo controlled	IB (4 cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS
<b>MEDI4736 BR31</b>	Global, placebo controlled	IB (4 cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS in PD-L1+
<b>Pembrolizumab Keynote-091 Pearls</b>	ETOP/EORTC placebo controlled	IB (4 cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS

## Essais de phase 3 en cours: chimiothérapie dans tous les bras...

Trial Identifier	Lay Title	Sponsor	Stage (ed)	Backbone	Intervention	Primary Endpoints
NCT02998528	Checkmate 816	BMS	IB-III A (7 <sup>th</sup> )	Cis or Carbo + Vin/Peme/Gem/Doce/Pacli	+/- Nivo I+N closed	EFS pCR
NCT03425643	KEYNOTE 671	Merck	IIA-III A (8 <sup>th</sup> )	Cis + Peme or Gem	Pembro or placebo	EFS OS
NCT03456063	IMPOWER 030	Genentech	II-III B (8 <sup>th</sup> )	Cis/Carbo + nab-pac/peme/gem	Atezo or placebo	MPR EFS
NCT03800134	AEGEAN	AstraZeneca	IIA-III B (8 <sup>th</sup> )	Cis + gem or peme Carbo + peme or pacli	Durva or placebo	MPR

# CheckMate 816 study design<sup>a,1</sup>



## Primary endpoints

- pCR by BIPR
- EFS by BICR

## Key secondary endpoints

- MPR by BIPR
- OS
- Time to death or distant metastases

## Key exploratory endpoints included

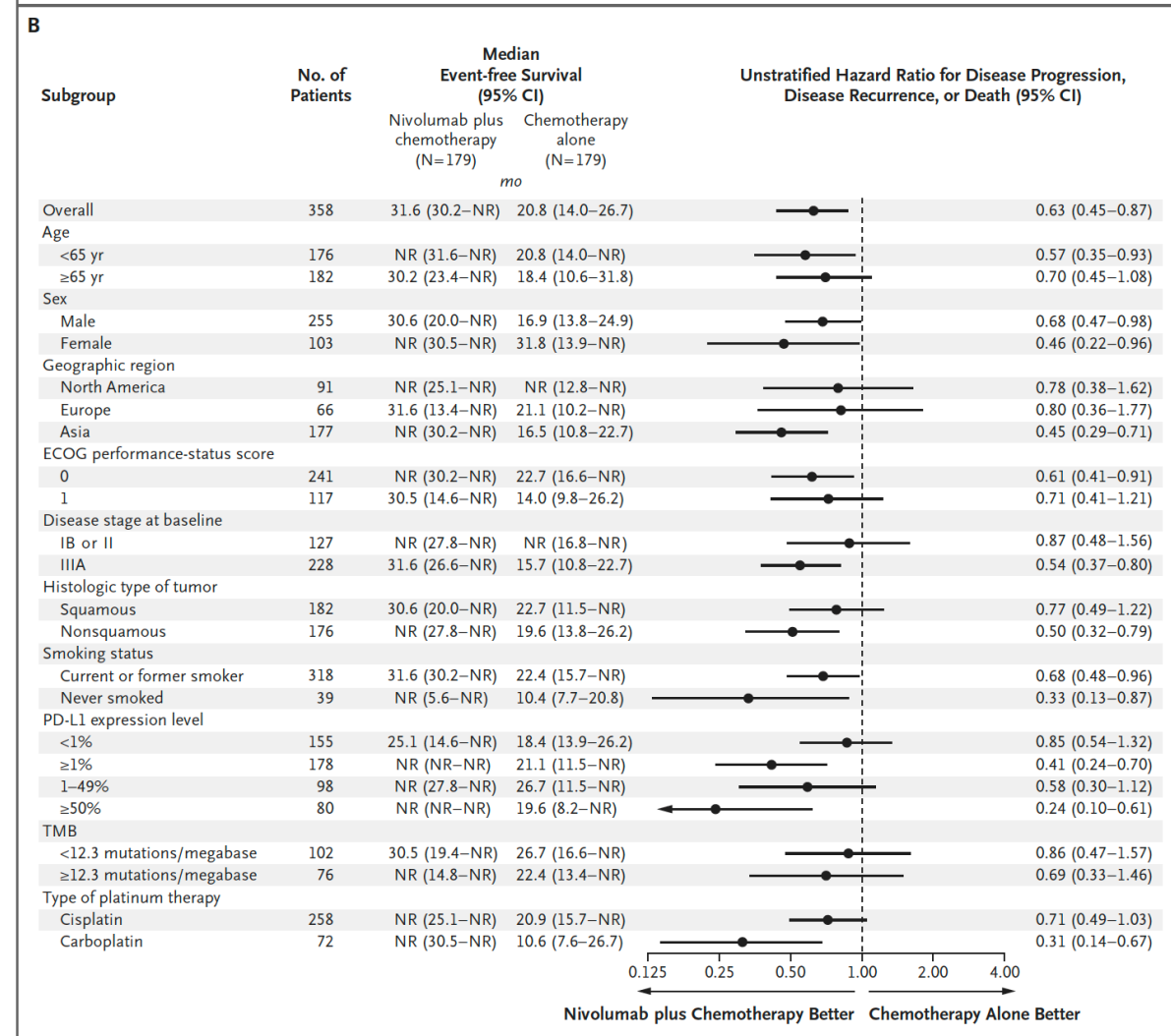
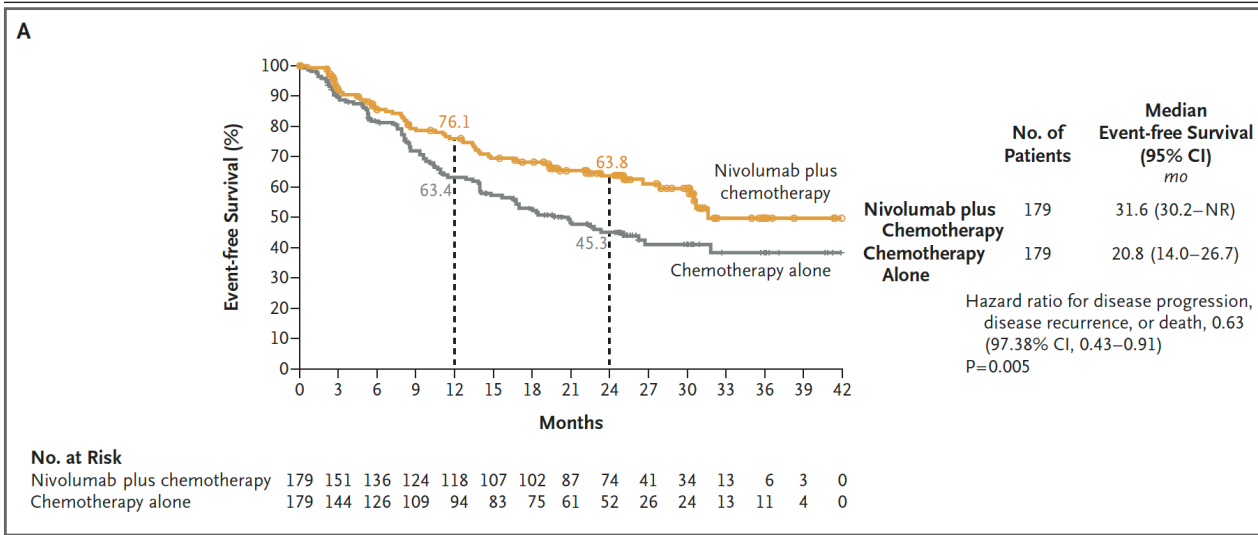
- ORR by BICR
- Feasibility of surgery; peri- and post-operative surgery-related AEs**

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

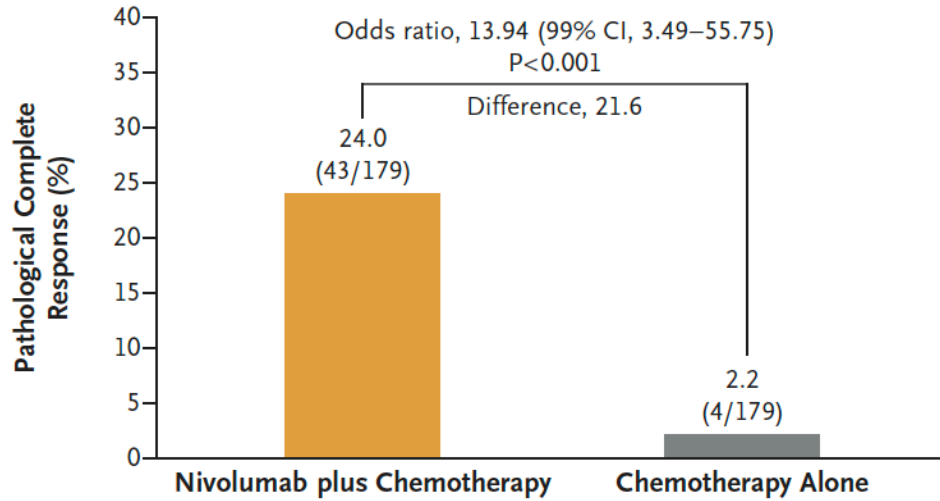
<sup>a</sup>NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; <sup>b</sup>Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); <sup>c</sup>Included patients with PD-L1 expression status not evaluable and indeterminate; <sup>d</sup>NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; <sup>e</sup>Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

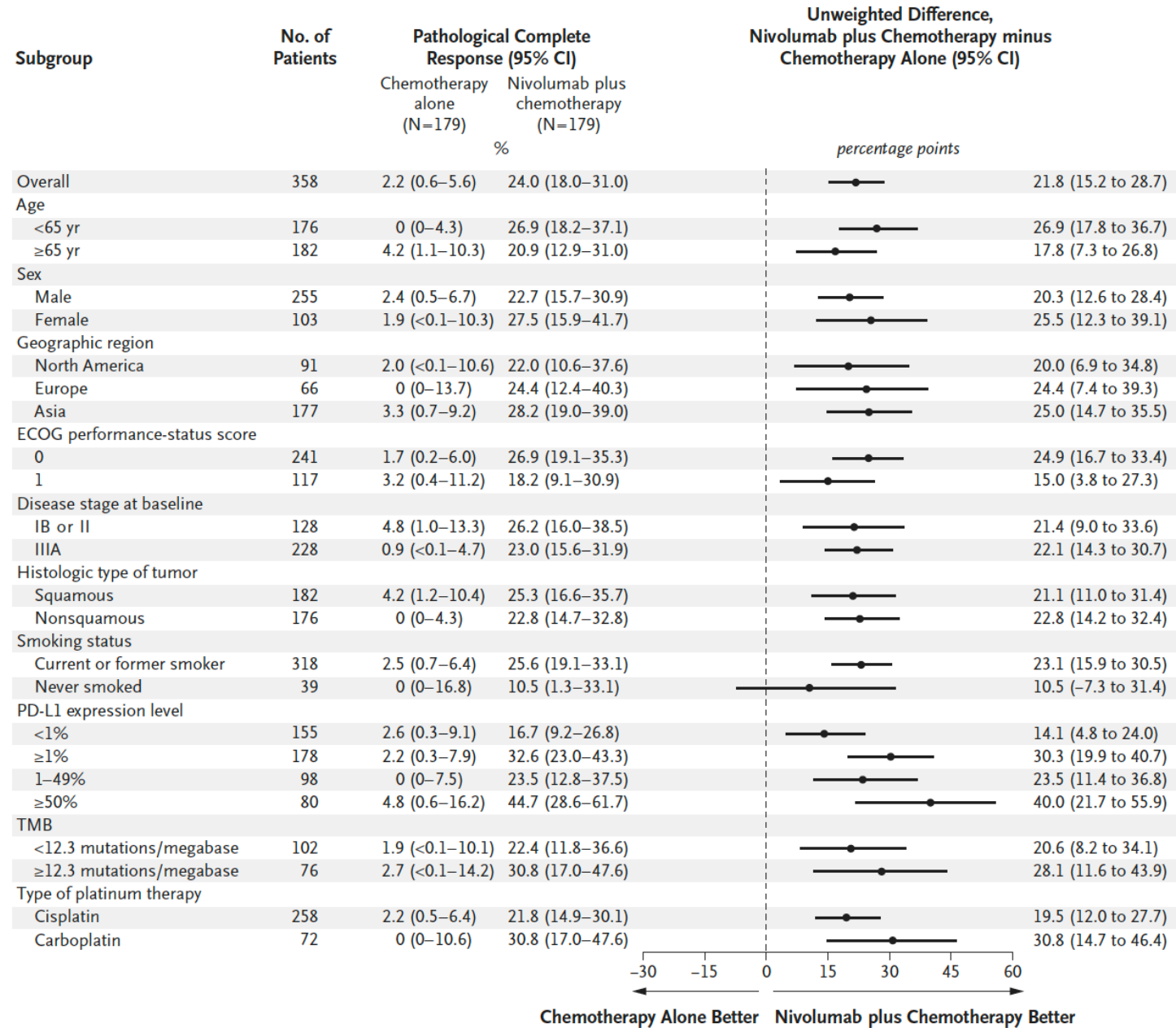
# CheckMate 816 study



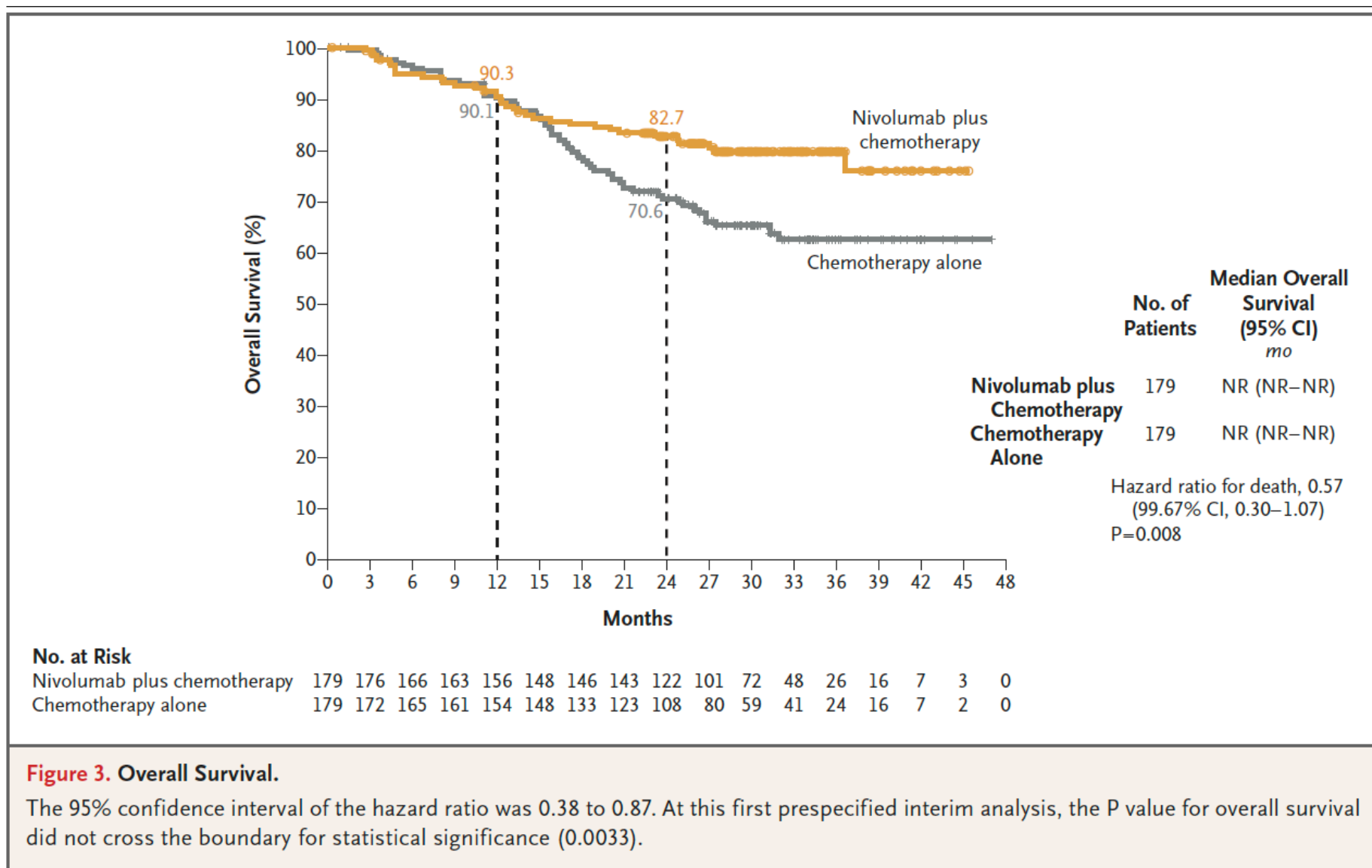
# CheckMate 816 study



B



# CheckMate 816 study



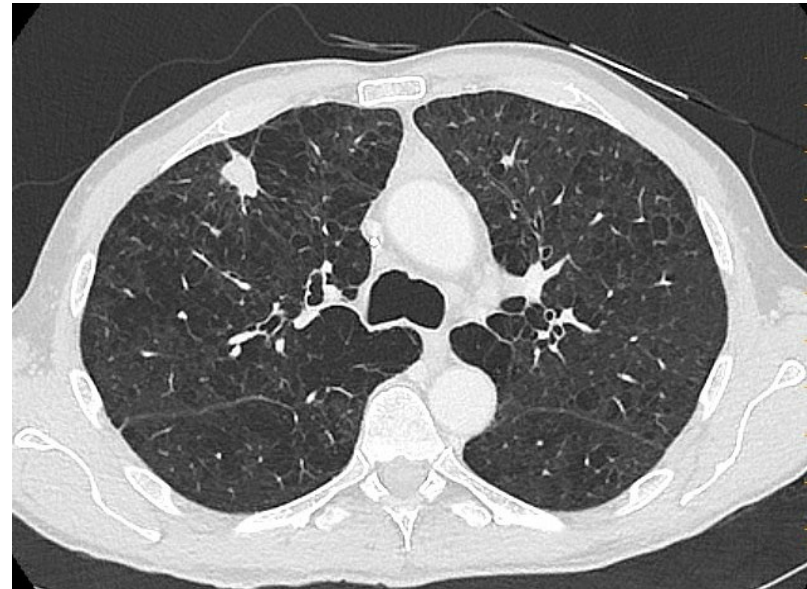
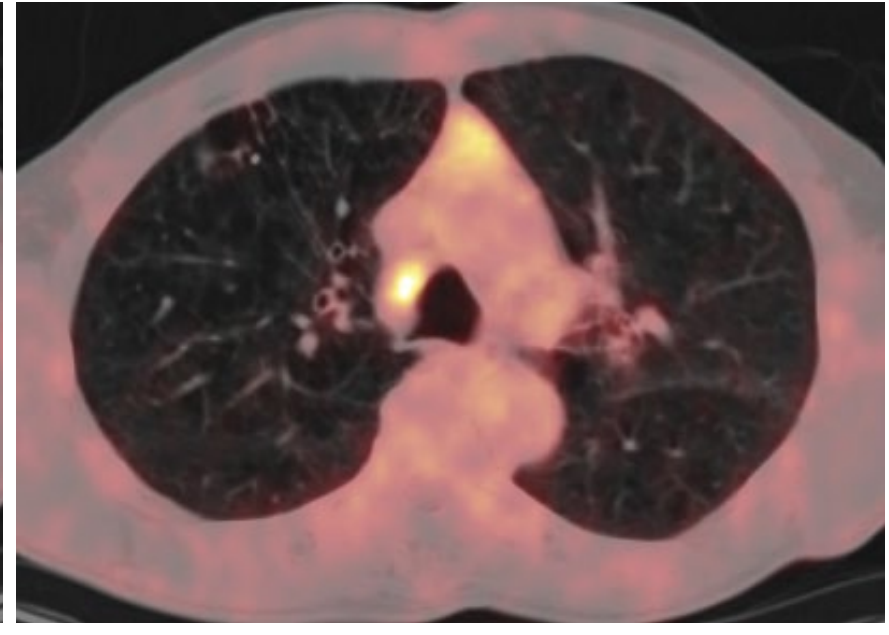
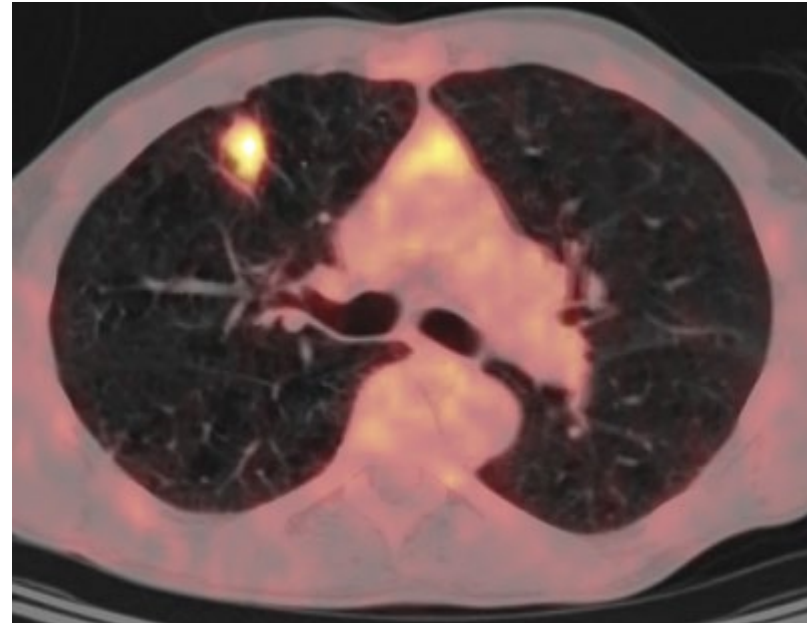
**Figure 3. Overall Survival.**

The 95% confidence interval of the hazard ratio was 0.38 to 0.87. At this first prespecified interim analysis, the P value for overall survival did not cross the boundary for statistical significance (0.0033).

Mr AB 66 ans  
60 PA actif  
ATCD lymphome 2009 2 lignes chimio,  
en RC  
BPCO VEMS 62% TLCO 59% VO2Max  
22ml/Kg/min  
ADK cT1c pN2 M0 PDL1 55%

2 cycles Carboplatine Alimta  
Pembrolizumab

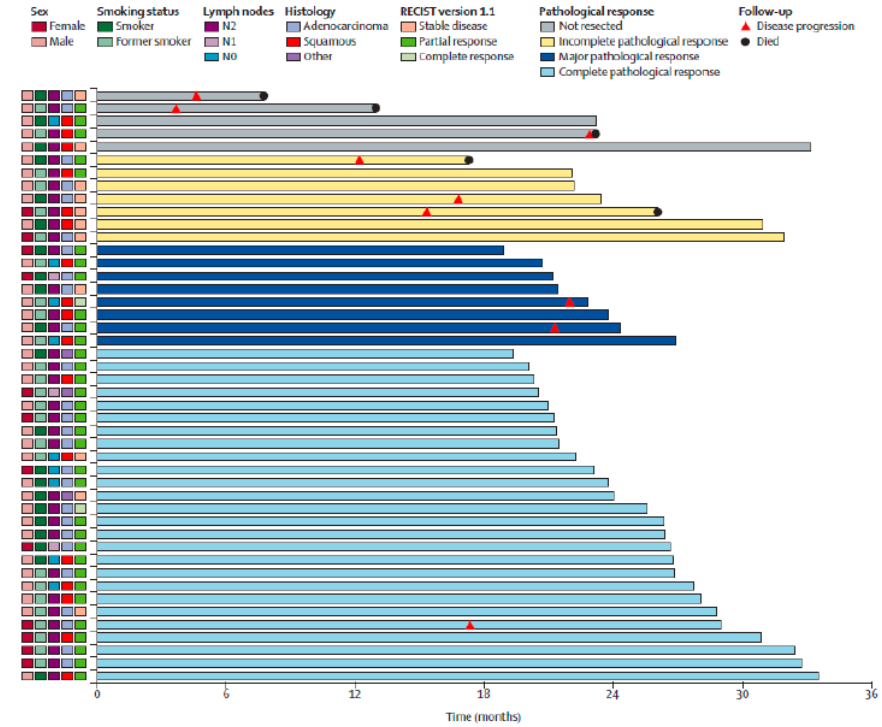
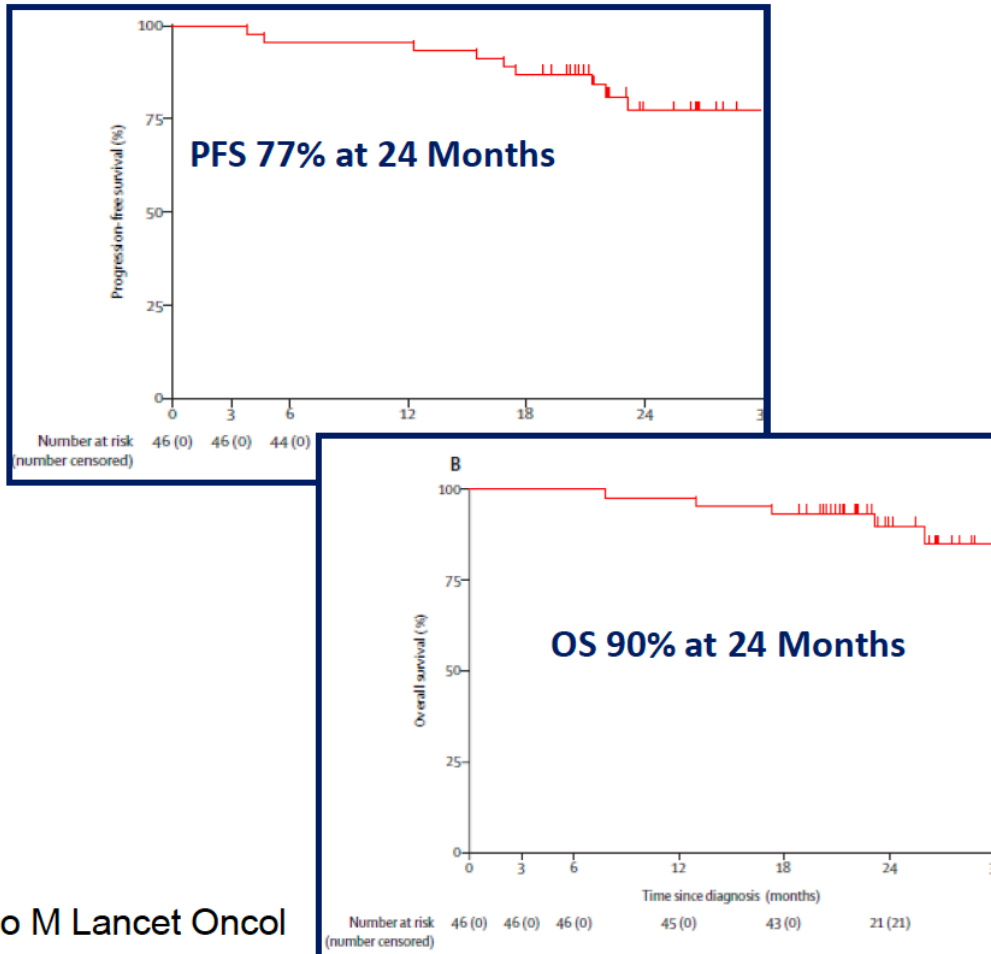
Lobectomie supérieure droite +  
curage le 02/11.  
Anapath : yTONOM0  
Anapath : 0/33N+, infiltration  
ganglionnaire diffuse et  
probablement pulmonaire par le  
lymphome B de la zone marginale.



# Immunothérapie péri-opératoire des stades précoces

## Neoadjuvant chemotherapy and nivolumab in resectable nonsmall-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco,



Incomplete Pathologic Response	7 (17.1%)
Major Pathologic Response	34 (82.9%)
Complete Pathologic Response	26 (63.4%)

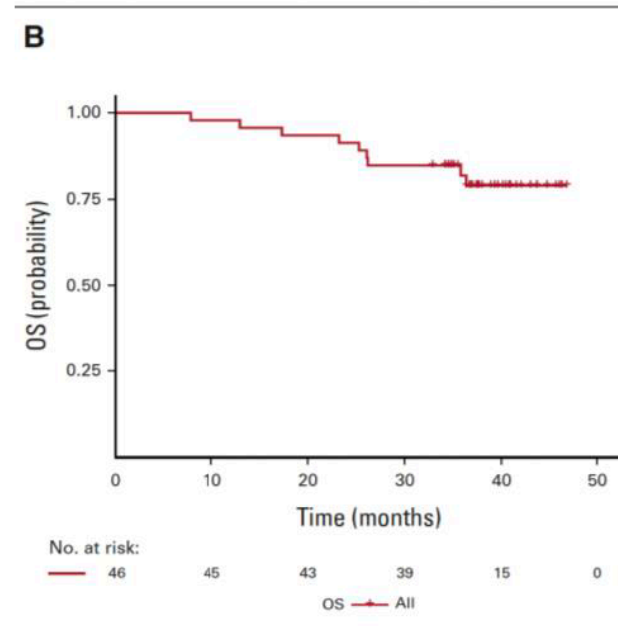
# Immunothérapie péri-opératoire des stades précoces

original reports

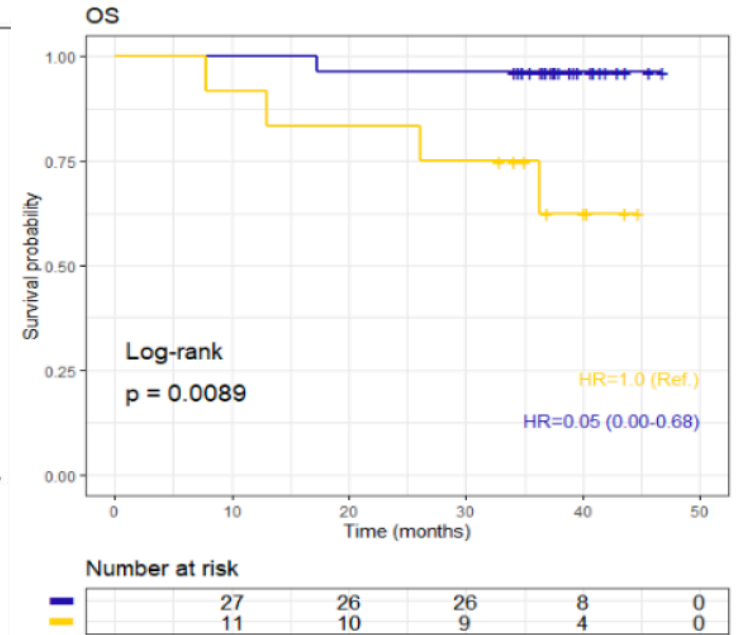
## Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial)

Mariano Provencio, MD, PhD<sup>1</sup>; Roberto Serna-Blasco, MSc<sup>1</sup>; Ernest Nadal, MD<sup>2</sup>; Amelia Insa, MD<sup>3</sup>; M. Rosario García-Campelo, MD<sup>4</sup>; Joaquín Casal Rubio, MD<sup>5</sup>; Manuel Dómine, MD<sup>6</sup>; Margarita Majem, MD<sup>7</sup>; Delvys Rodríguez-Abreu, MD<sup>8</sup>; Alex Martínez-Martí, MD<sup>9</sup>; Javier De Castro Carpeño, MD<sup>10</sup>; Manuel Cobo, MD<sup>11</sup>; Guillermo López Vivanco, MD<sup>12</sup>; Edel Del Barco, MD<sup>13</sup>; Reyes Bernabé Caro, MD<sup>14</sup>; Nuria Viñolas, MD<sup>15</sup>; Isidoro Barneto Aranda, MD<sup>16</sup>; Santiago Viteri, MD<sup>17</sup>; Eva Pereira, MSc<sup>18</sup>; Ana Royuela, PhD<sup>1</sup>; Virginia Calvo, MD<sup>1</sup>; Javier Martín-López, MD<sup>1</sup>; Francisco García-García, PhD<sup>19</sup>; Marta Casarrubios, MSc<sup>1</sup>; Fernando Franco, MD<sup>1</sup>; Estela Sánchez-Herrero, MSc<sup>1,20</sup>; Bartomeu Massuti, MD<sup>21</sup>; Alberto Cruz-Bermúdez, PhD<sup>1</sup>; and Atocha Romero, PhD<sup>1</sup>

OS at 36 months was 81.9% (95% CI, 66.8 to 90.6) in the intention-to-treat population, rising to 91.0% (95% CI, 74.2 to 97.0) in the per-protocol population



↓ = 46). ITT, intention-to-treat; OS, overall survival; PFS, progression-free



Clearers — Clearers — Non-clearers

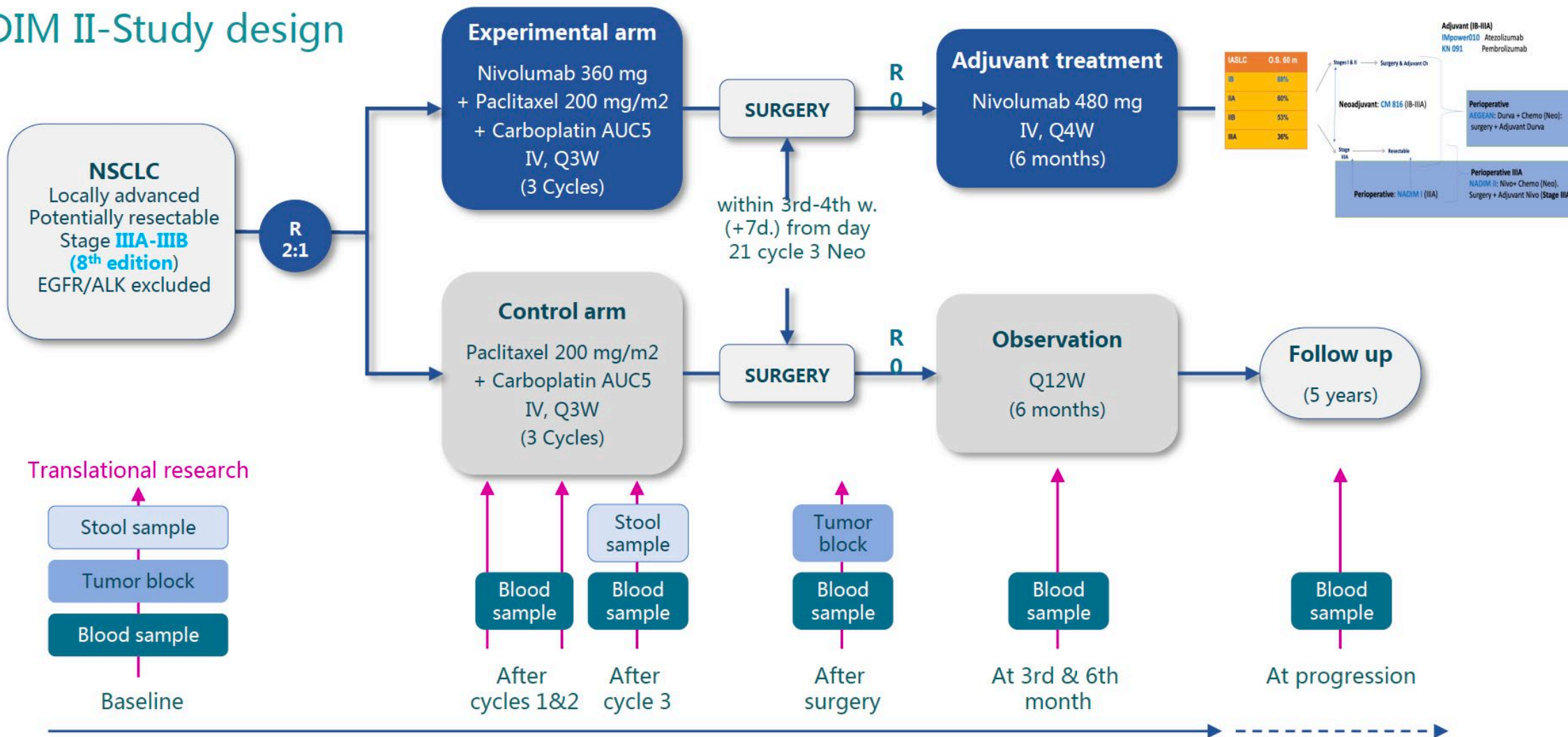


**TABLE 2.** Prognostic Value of Tumor Response to Treatment Assessments on the Basis of CT Scans, Pathologic Evaluation, and ctDNA (landmark analysis)

Survival surrogate	No.	PFS			OS						
		HR (PFS) <sup>a</sup>	95% CI <sup>a</sup>	P <sup>a</sup>	HR (OS) <sup>a</sup>	95% CI <sup>a</sup>	P <sup>a</sup>				
Undetectable ctDNA after treatment	40	0.26	0.07 to 0.93	.038	0.63	0.45 to 0.81	0.04	0.00 to 0.55	.015	0.82	0.61 to 1.00

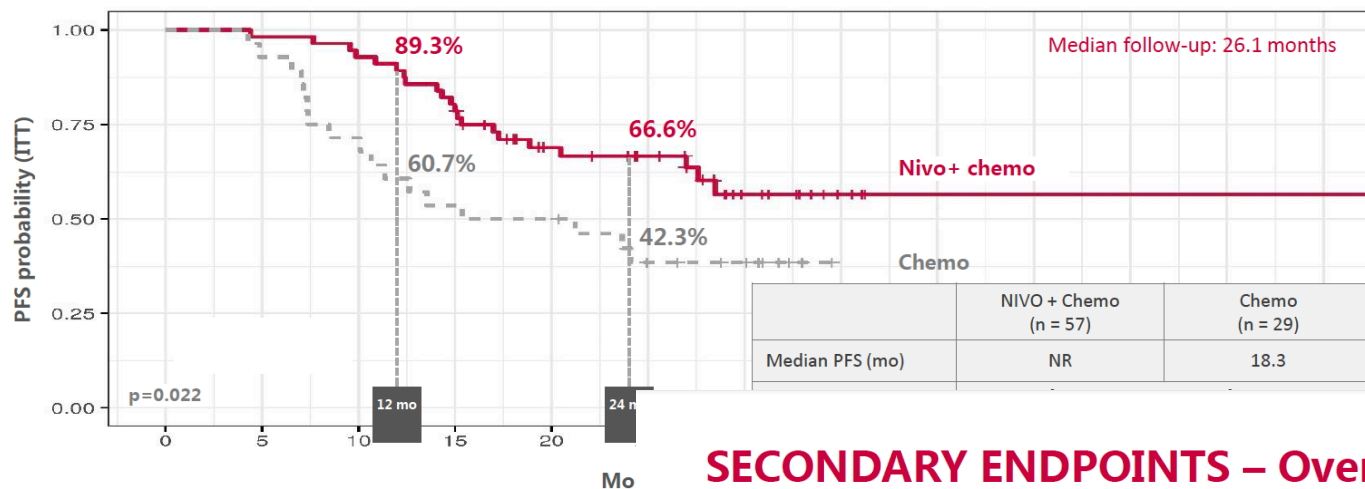
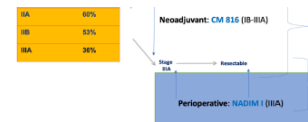
# Immunothérapie péri-opératoire des stades précoces

## NADIM II-Study design



# Immunothérapie péri-opératoire des stades précoces

## SECONDARY ENDPOINTS – Progression-free survival

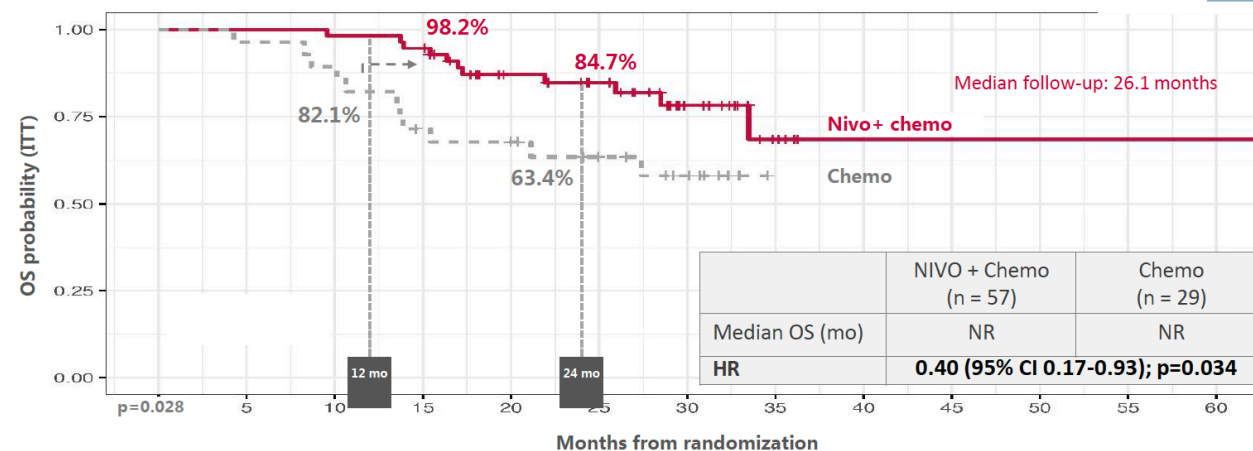
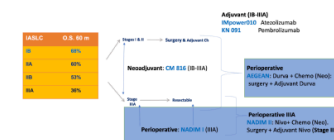


Number at risk

	0	5	10	15	20	24
Nivo + chemo	56	55	52	44	30	
Chemo	28	26	20	15	14	

Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recur

## SECONDARY ENDPOINTS – Overall survival



Number at risk

	0	5	10	15	20	24	30	35	40	45	50	55	60
Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

# Traitement péri-opératoire des stades précoces Adjuvant

## Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csósz, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McClelland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators\*

	Atezolizumab group (n=495)	Best supportive care group (n=495)
<b>Adverse event</b>		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
<b>Immune-mediated adverse events</b>		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Data are n (%). \*Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

**Table 2: Safety summary in the safety evaluable population**

PDL1 +

Tous

ITT

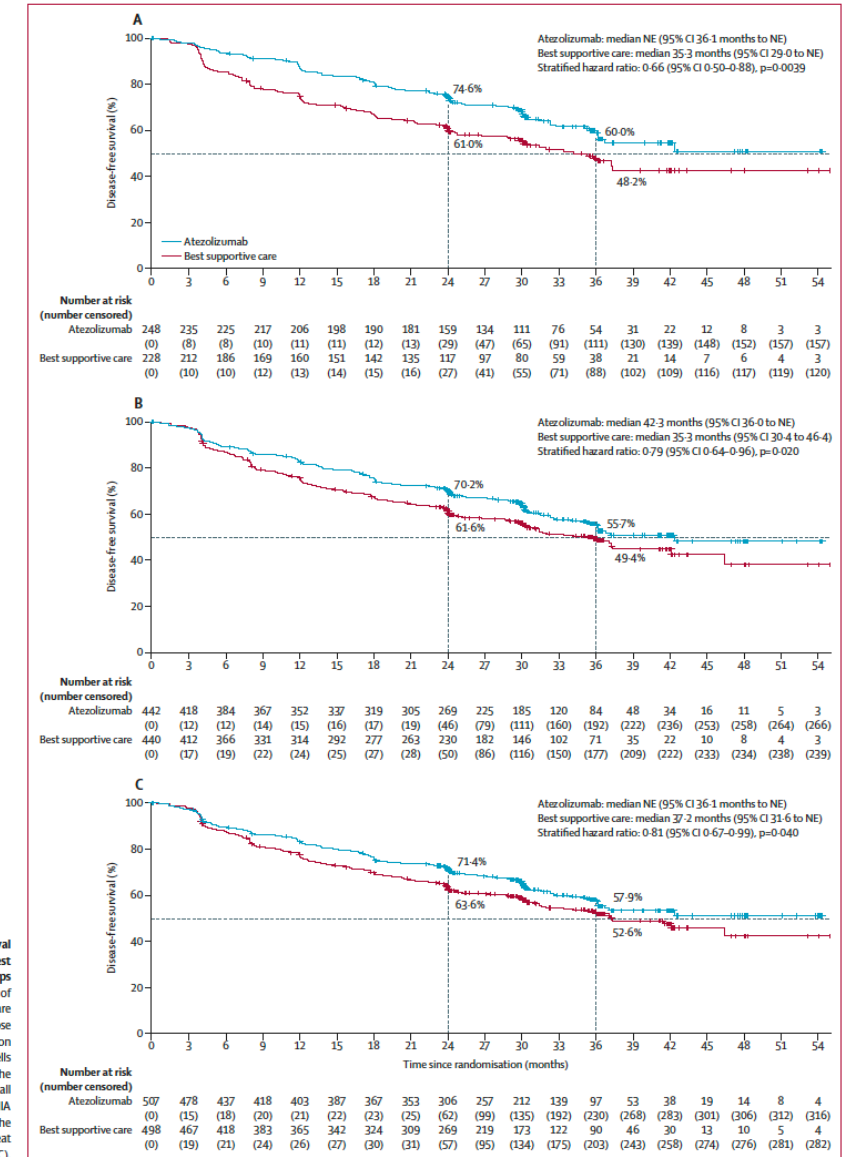
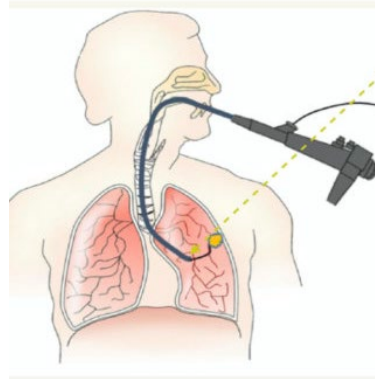


Figure 2: Disease-free survival in the atezolizumab and best supportive care groups  
Kaplan-Meier estimates of disease-free survival are shown for patients whose tumours expressed PD-L1 on 1% or more of tumour cells (per the SP263 assay) in the stage II-IIIa population (A), all patients in the stage II-IIIa population (B), and the intention-to-treat population (C).

# Traitement péri-opératoire: immunothérapie

I	IA
	IB
II	IIA
	IIB
III	IIIA
	IIIB
	IIIC



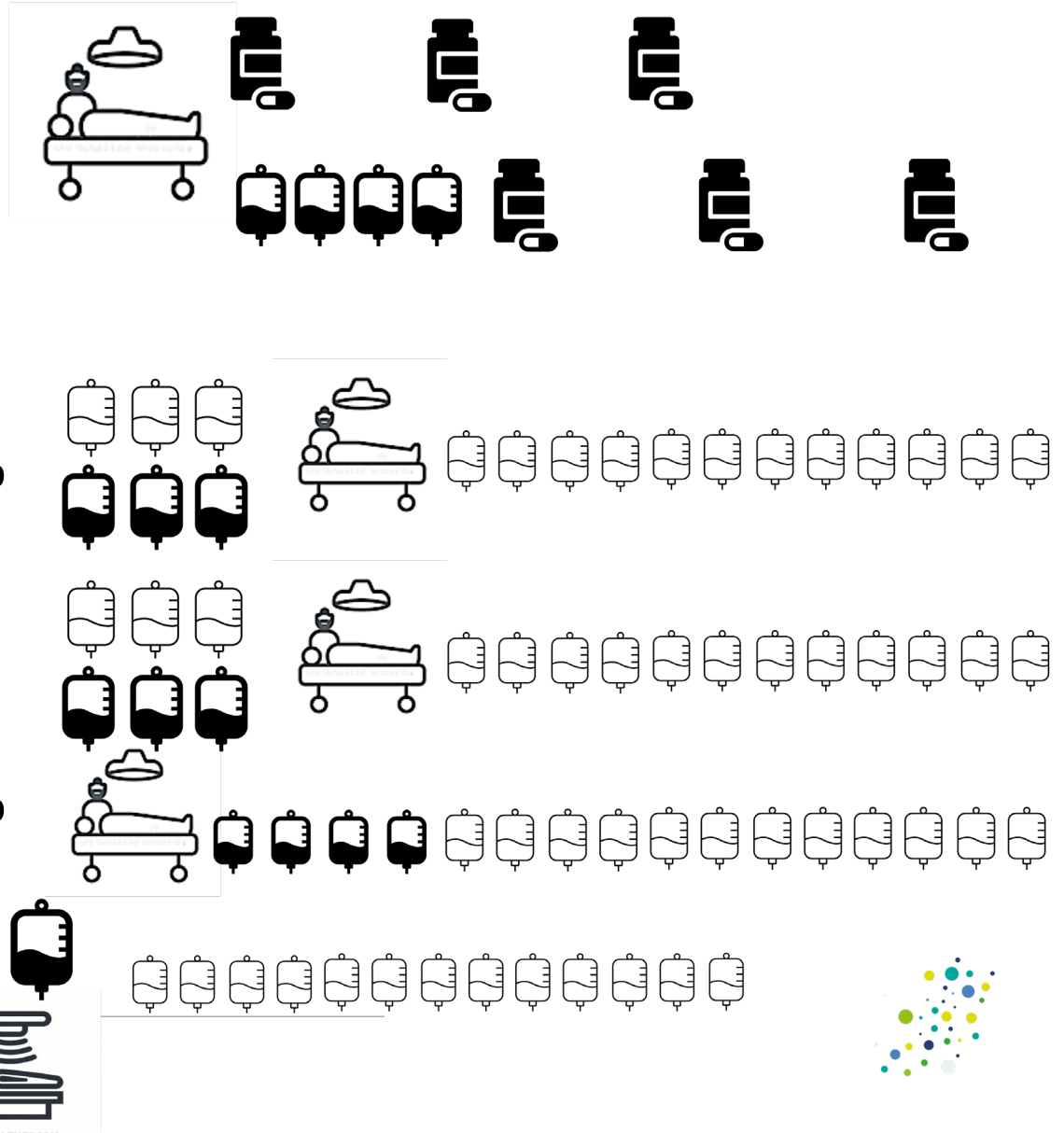
EGFR  
(ALK)

< 50%

PDL1

> 50%

Résécabilité



# Perspectives

- Combinaison de nouvelles immunothérapies
- Vaccins personnalisés
- Monitoring du ctDNA
- Facteur prédictifs moléculaires
- Identifier les patients en CPR avant la chirurgie
- Déterminer le meilleur traitement chez les patients ayant ou n'ayant pas une CPR
- Traitement adjuvant optimal selon réponse initiale en pré-op

