Institut du cancer PARIS CARPEM
CANCER RESEARCH FOR PERSONALIZED MEDECINE
AP-HP.Centre-Université de Paris

Université de Paris

Traitements Médicaux Périopératoires

DES ile de France 12 Mai 2023

Marie Wislez

Unité d'oncologie thoracique, Service de Pneumologie, Hôpital Cochin, AP-HP

Equipe "cancer, immune control and escape » Inserm U1138

Université de Paris

Liens d’intérêt

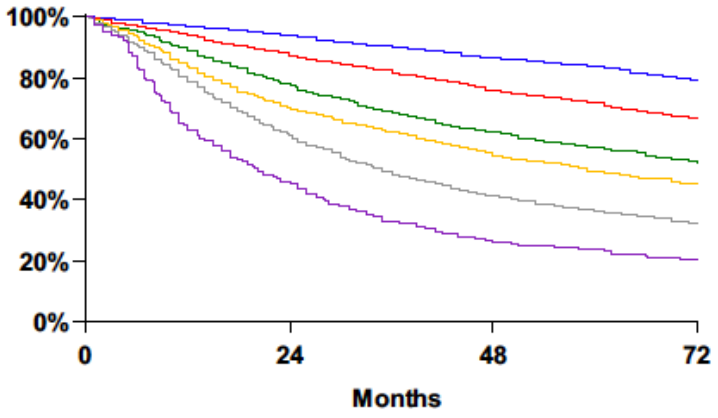
- Activité de conseil ou honoraires au cours des deux dernières années pour les sociétés suivantes : Astra-Zeneca, BMS, MSD, Novartis, Roche, Lilly

Pronostic des stades localisés

7ème édition

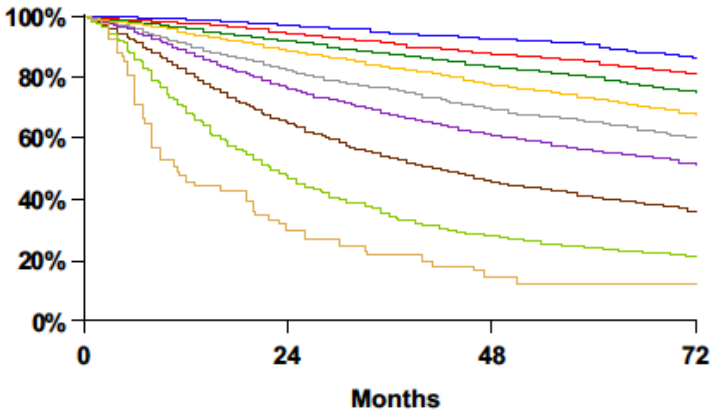
8ème édition

A



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1837 / 11423	NR	94%	83%
IB	2168 / 7711	NR	87%	71%
IIA	1514 / 3702	NR	77%	57%
IIB	1325 / 2776	58.9	70%	49%
IIIA	3467 / 5818	35.0	61%	36%
IIIB	364 / 506	20.0	45%	23%

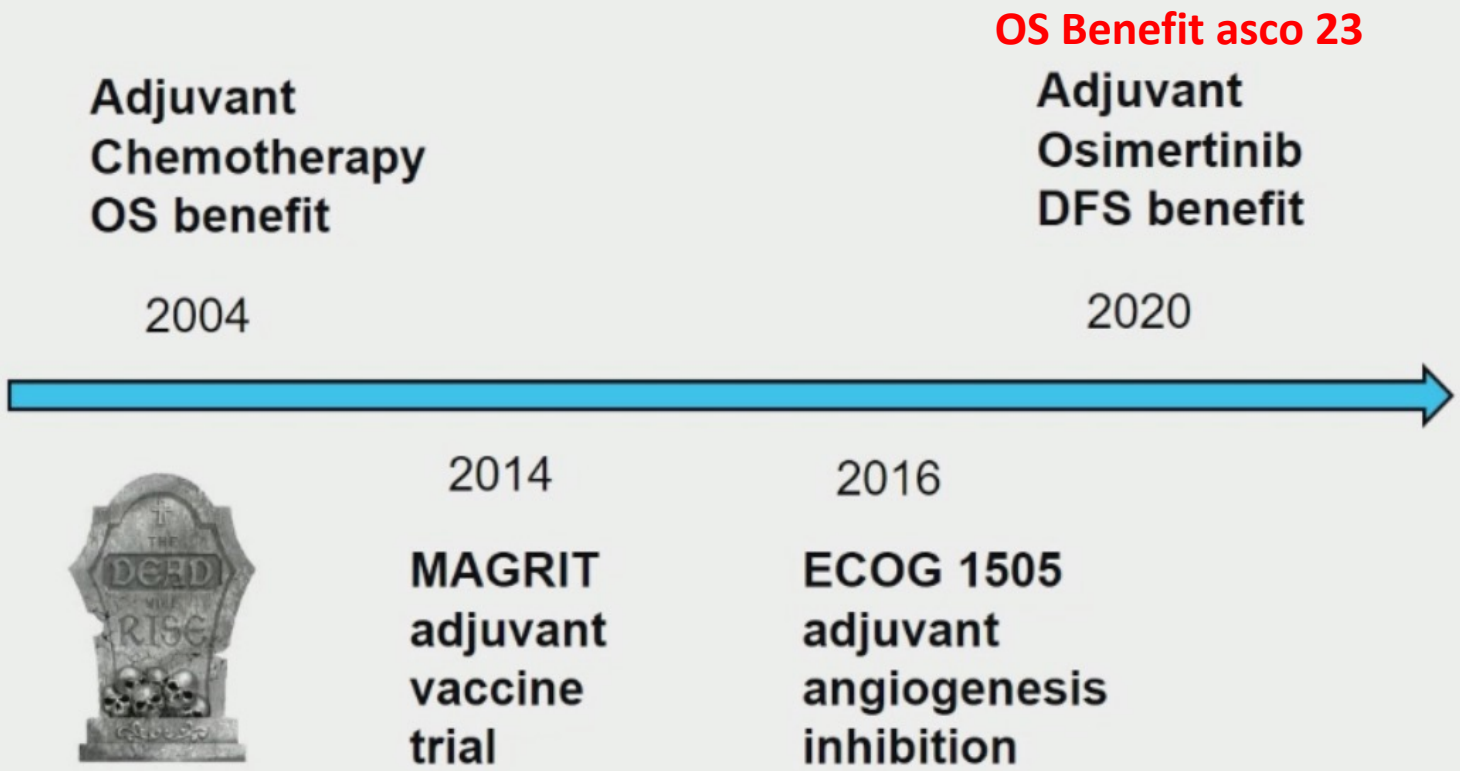
B



Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Goldstraw P et al, J Thorac Oncol 2016

Les stades localisés
les études de phase 3



Neo adjuvant Nivolumab CT CM816 cPR EFS benefit

Adjuvant atezolizumab IMpower 010 DFS benefit

Adjuvant pembrolizumab Keynote 091 DFS benefit

Neo adjuvant Pembro CT & pembro KN 671 cPR EFS benefit

Neo adjuvant Durva CT & Durva Aegan cPR EFS benefit

Neo adjuvant Toripa CT & Toripa NeoTorch cPR EFS benefit

Chimiothérapie adjuvante

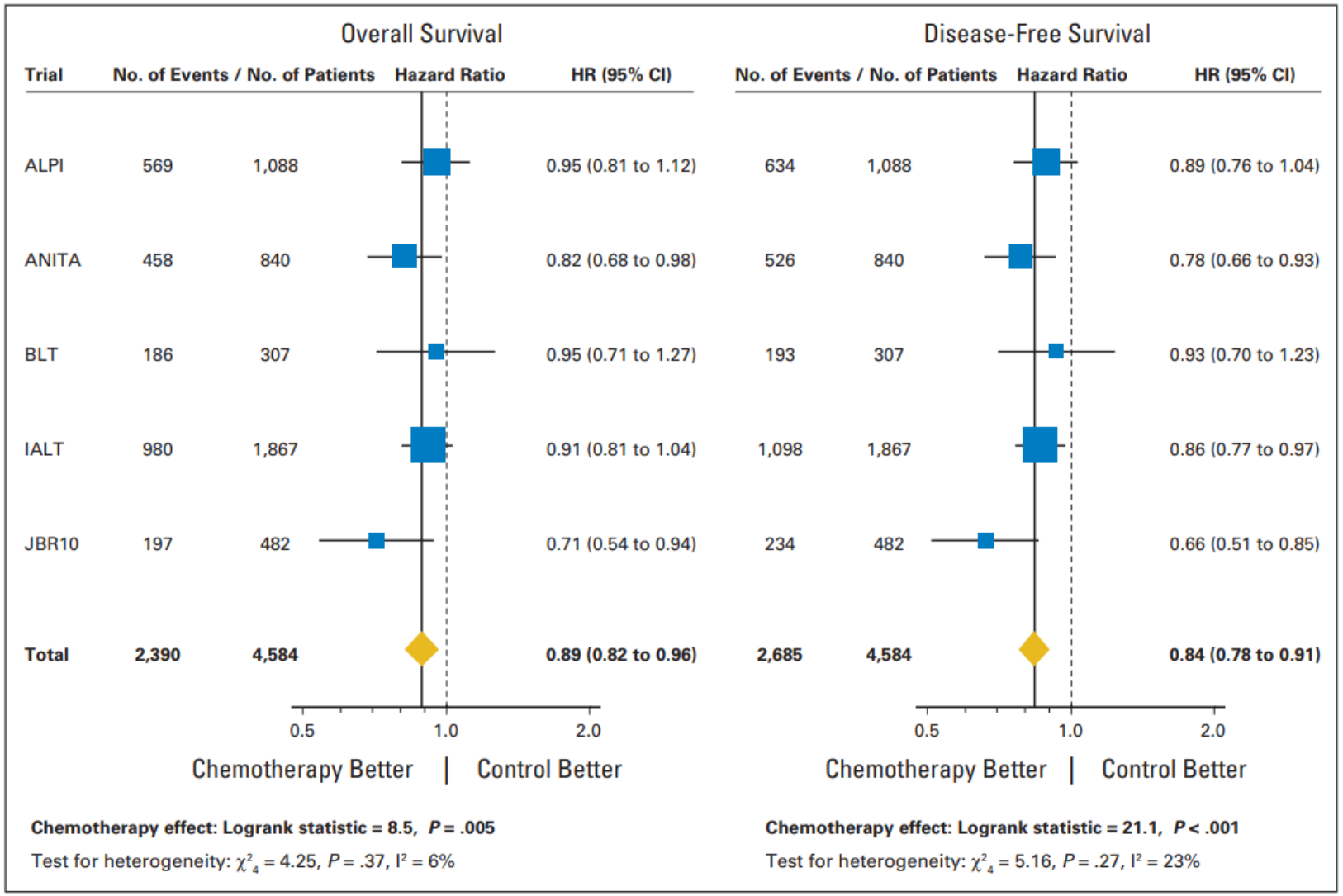
Cisplat 100mg/m²
vindesine et mitomycine

Cisplat 100mg/m²
Vinorelbine 30mg/m²

Cisplat 50-80mg/m² - Vino 30mg/m² ou vindesine ou mitomycine

Cisplat 80-120mg/m² x3-4 - +Vindesine ou Vinblastine ou Vinorelbine (30mg/m²) ou Etoposide

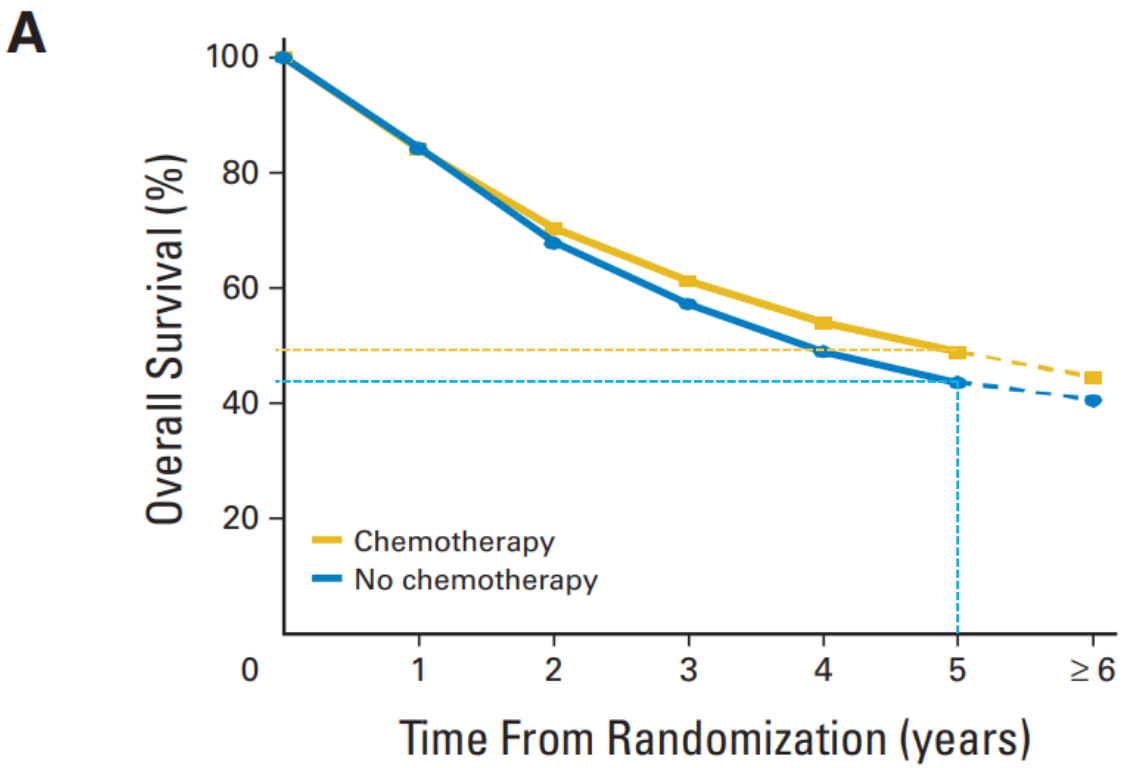
Cisplat 50mg/m² x4 - Vino 25mg/m² x16

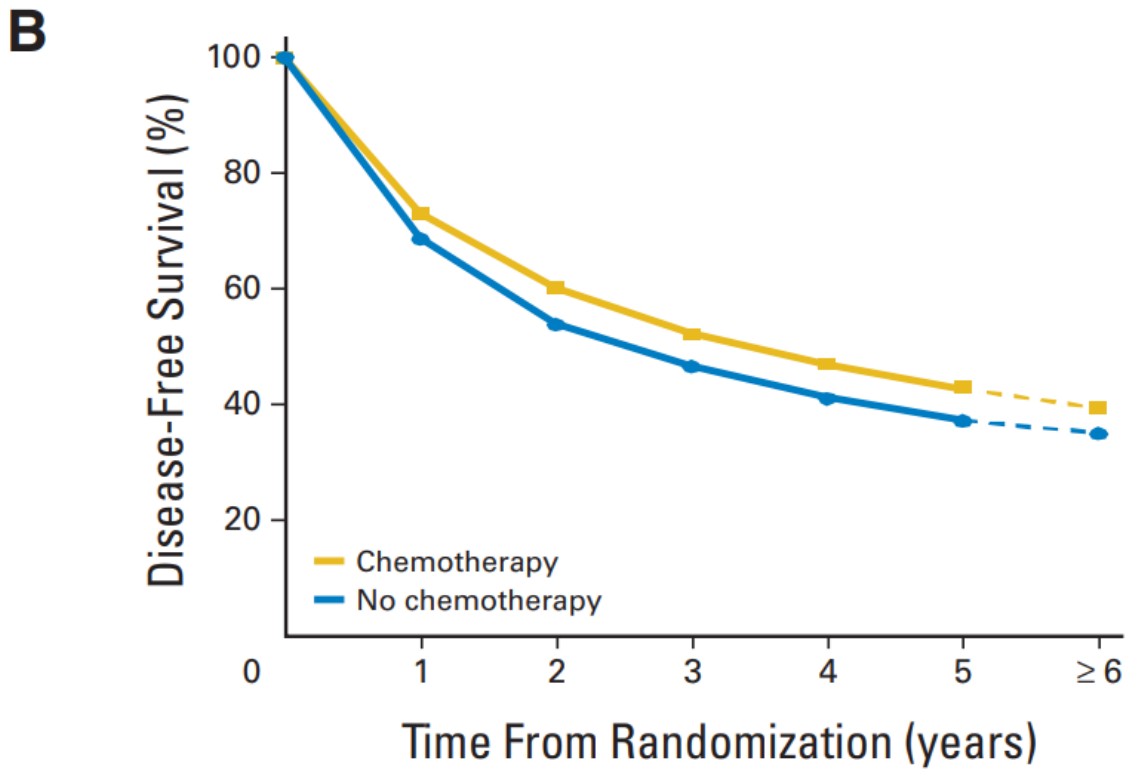


HR 0,89
95% CI 0,82 – 0,96
p=0,005

Pignon JP et al, J Clin Oncol 2008

Chimiothérapie adjuvante





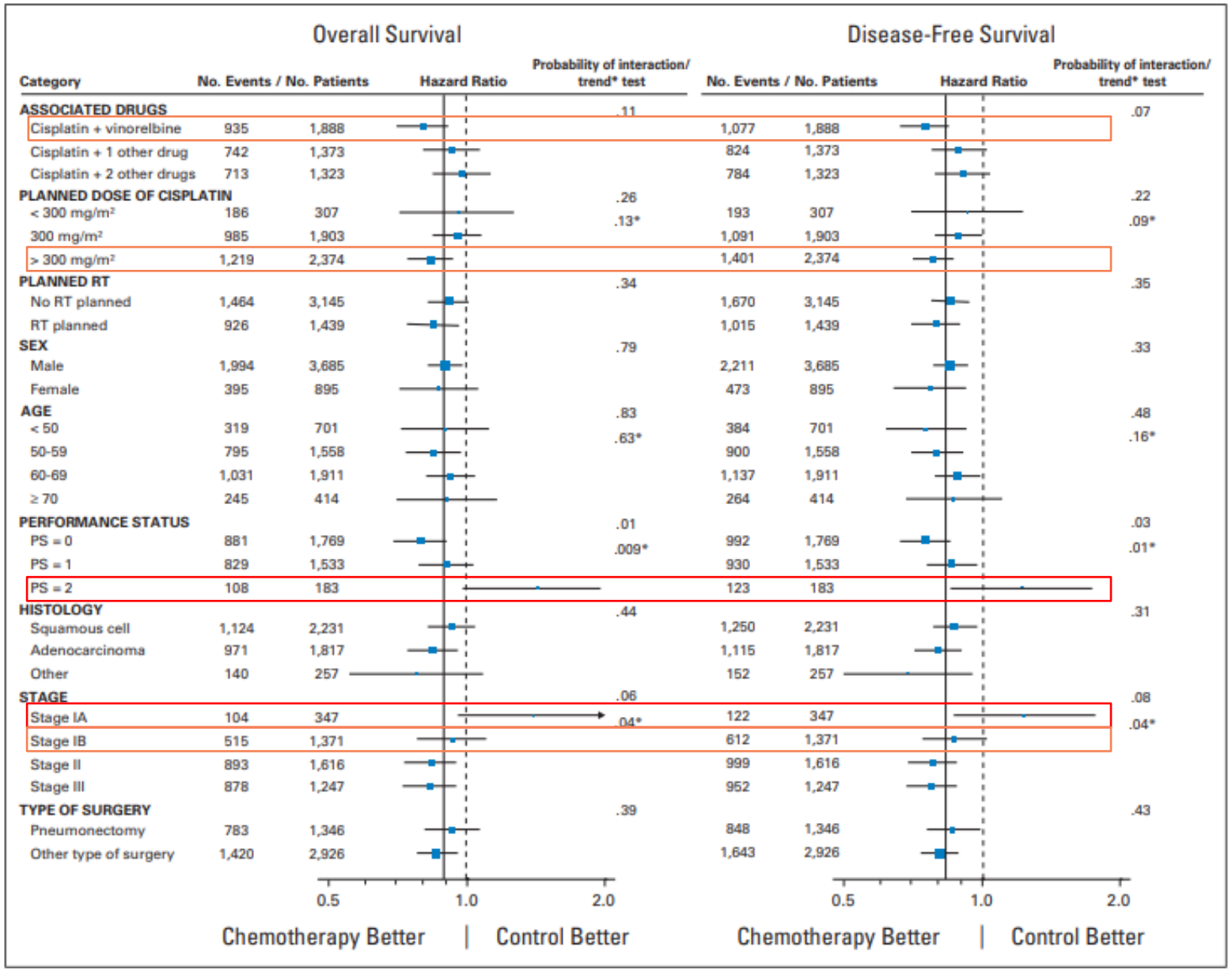
Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Events / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	1,222 / 4,341	163 / 1,396	35 / 610
Chemotherapy	1,047 / 4,627	159 / 1,606	59 / 708

+5% à 5 ans

Pignon JP et al, J Clin Oncol 2008

Chimiothérapie adjuvante



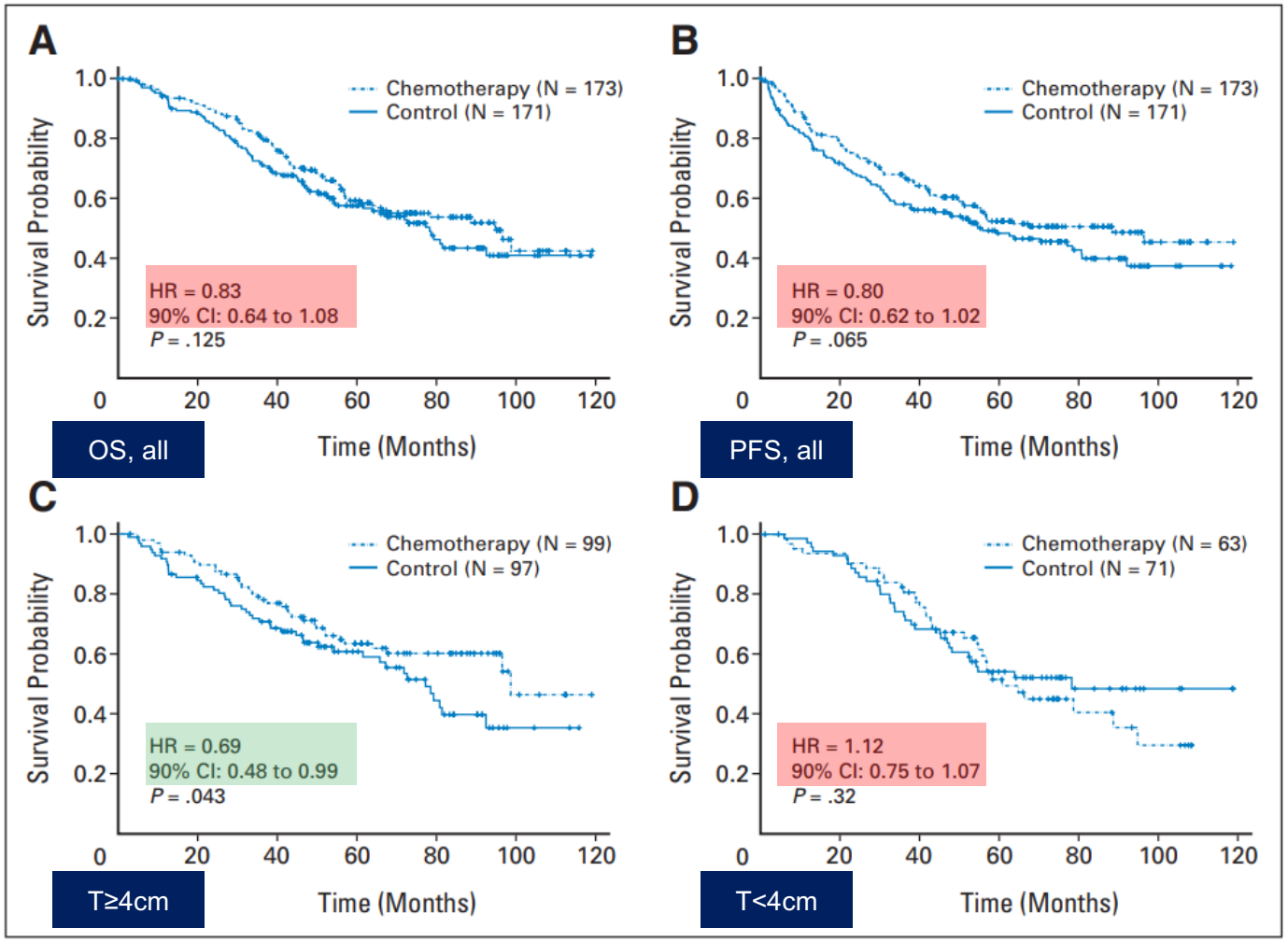
Chimiothérapie adjuvante

Stades IB (T2)
R0

R

Carboplatine AUC 6 + Paclitaxel
200mg/m² x 4 - N=173

Observation
N=171



Strauss JM et al, J Clin Oncol 2008

Chimiothérapie adjuvante

KEY ELIGILITY

- Completely resected non-Sq NSCLC
- Pathological stage II-IIIA (7th TNM)
- ECOG PS 0-1
- Age 20-75 years
- Lobectomy or pneumonectomy with resection of N2 lymph nodes within 3–8 weeks

N=804

RANDOMIZED

1:1

Vinorelbine (25 mg/m2, days 1, 8) +Cisplatin (80 mg/m2, day 1) every 3 weeks, up to 4 cycles

Pemetrexed (500 mg/m2, day 1) +Cisplatin (75 mg/m2, day 1) every 3 weeks, up to 4 cycles

ENDPOINTS

Primary

- Recurrence-free survival

Secondary

- Overall survival
- Rate of treatment completion
- Toxicity

Stratification factors: Gender (female vs. male), Age (<70 years vs. ≥70 years), Pathological stage (II vs. IIIA), EGFR mutation (mutant vs. wild), Institution

PARIS 2022 ESMO congress

Kiyotaka Yoh, MD
National Cancer Center Hospital East

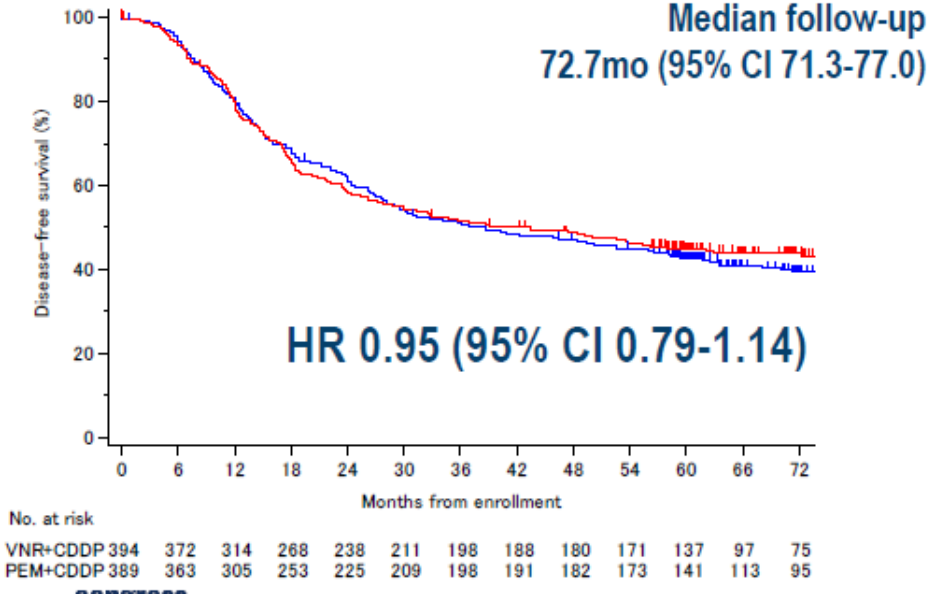
Yoh K et al, ESMO 2022

Chimiothérapie adjuvante

RFS and OS: 5-year follow-up

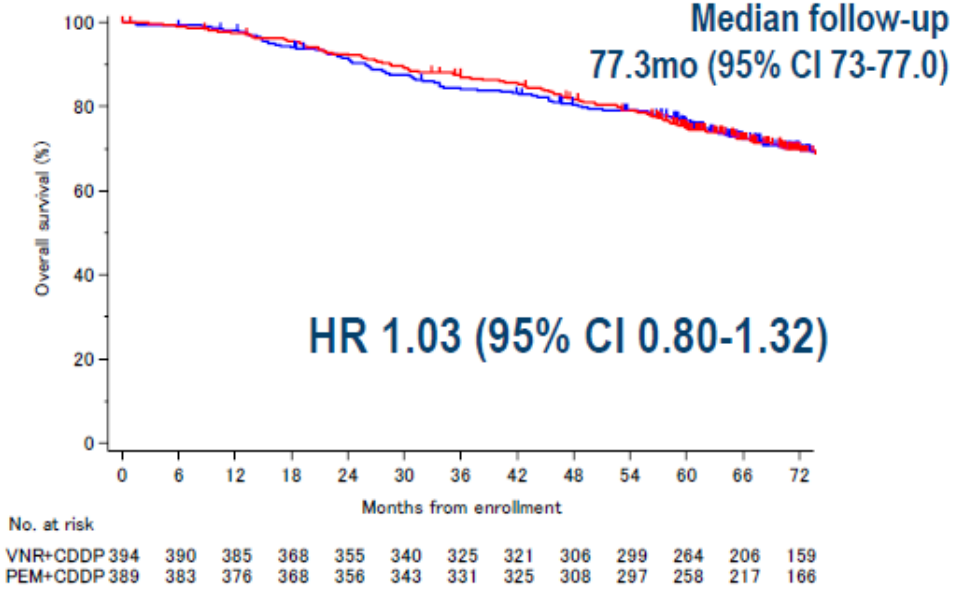
RFS assessed by investigators

	VNR+CDDP (n=394)	PEM+CDDP (n=389)
Number of events	236	220
Median RFS (95%CI)	37.5 mo (28.9-52.6)	43.4 mo (29.0-59.7)
3-year RFS (95%CI)	51.0% (49.5-74.9%)	51.6% (46.5-56.4%)
5-year RFS (95%CI)	42.6% (37.7-47.5 %)	44.9% (39.8-49.8%)



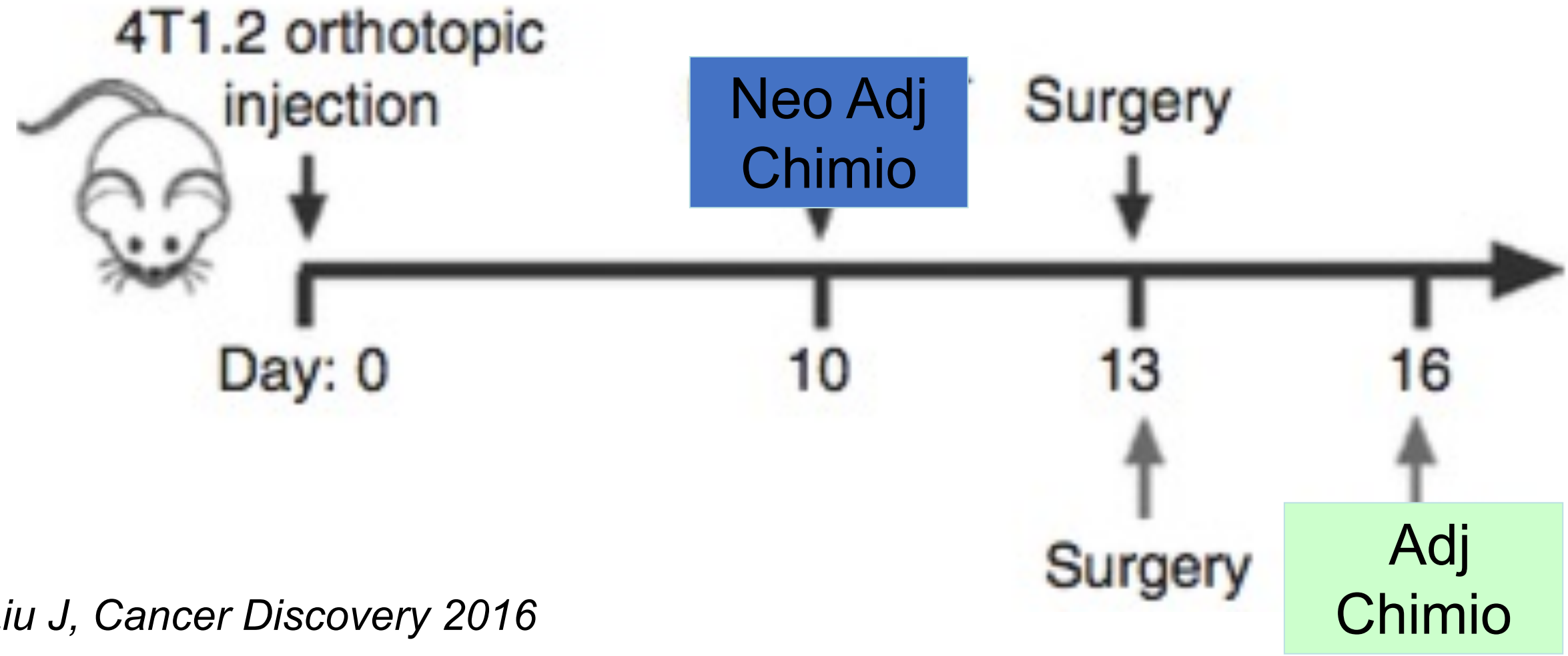
Overall survival

	VNR+CDDP (n=394)	PEM+CDDP (n=389)
Number of events	119	123
Median OS (95%CI)	Not reached (NR-NR)	Not reached (NR-NR)
3-year OS (95%CI)	84.1% (80.0-87.3%)	87.0% (83.2-90.0%)
5-year OS (95%CI)	75.6% (71.0-79.6%)	75.0% (70.3-79.0%)



Yoh K et al, ESMO 2022

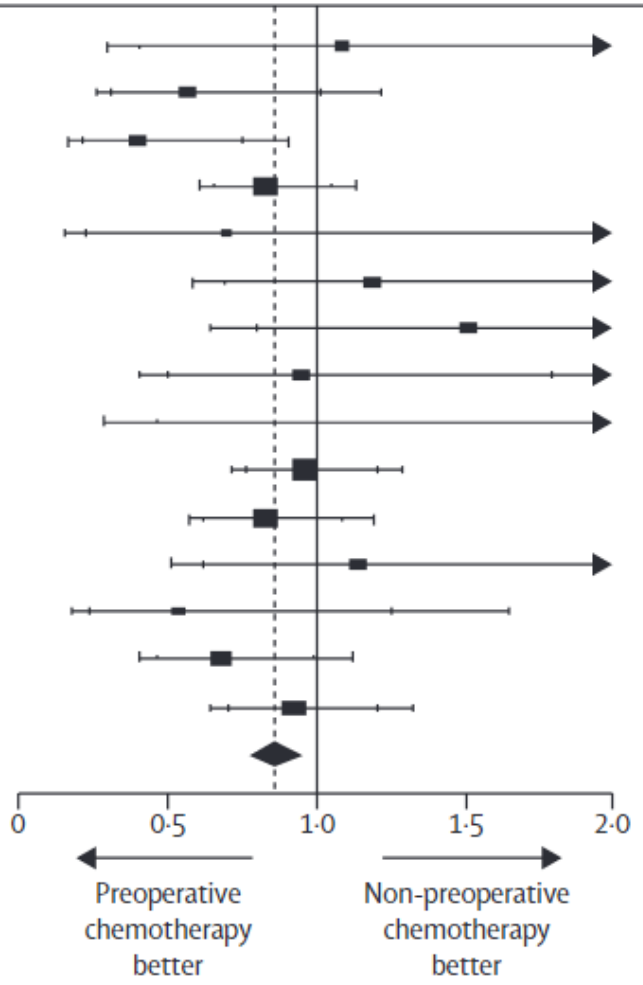
Modèles murins : chimiothérapie



Liu J, Cancer Discovery 2016

Chimiothérapie néo-adjuvante

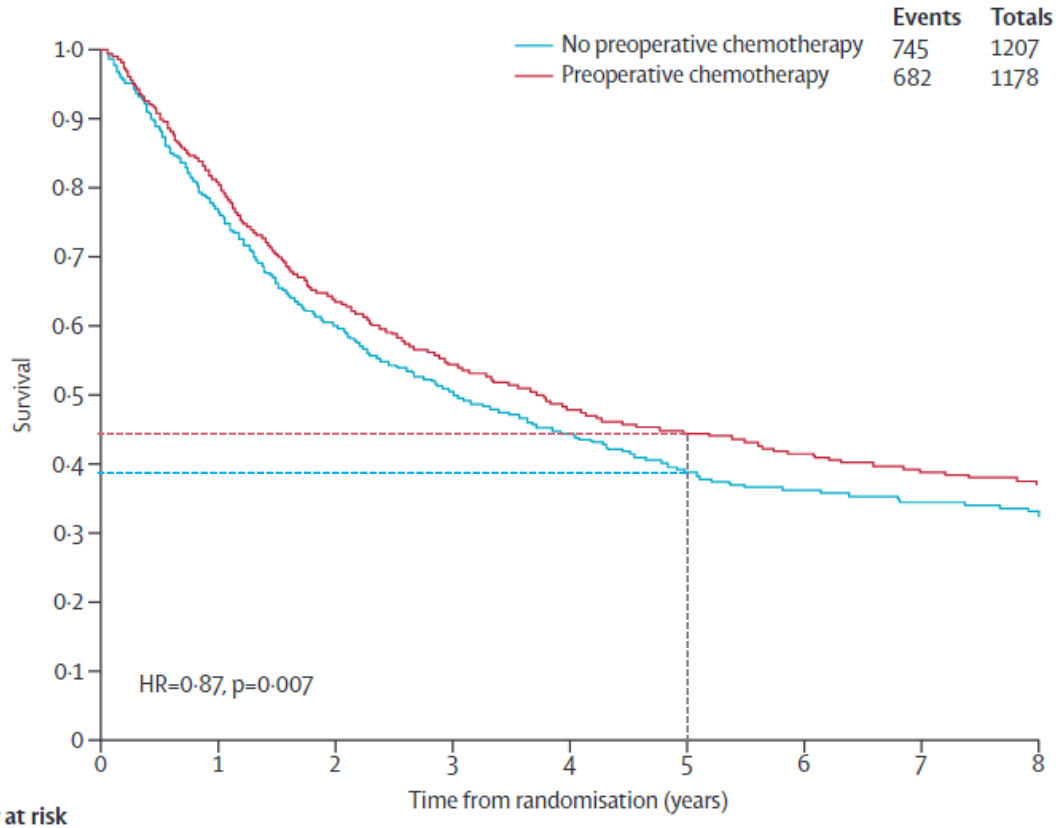
	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	–6·40	11·19	
Spain 1994	19/29	27/30	–8·88	9·65	
MIP-91	137/179	146/176	–12·99	70·22	
SWOG S9015	3/5	12/16	–1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	–0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	–2·92	77·01	
SWOG S9900	93/180	103/174	–9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	–3·31	5·44	
ChEST	45/129	61/141	–10·27	26·39	
NATCH	99/201	109/212	–4·11	51·95	
Total	**682/1178**	**745/1207**	**–50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**



Overall HR
0·87 (0·78–0·96). p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

NSCLC Meta-analysis Collaborative Group. Lancet 2014

Chimiothérapie néo-adjuvante



Number at risk									
No preoperative chemotherapy	1207	893	674	527	409	300	209	147	102
Preoperative chemotherapy	1178	928	712	570	442	346	253	172	123

+5% à 5 ans

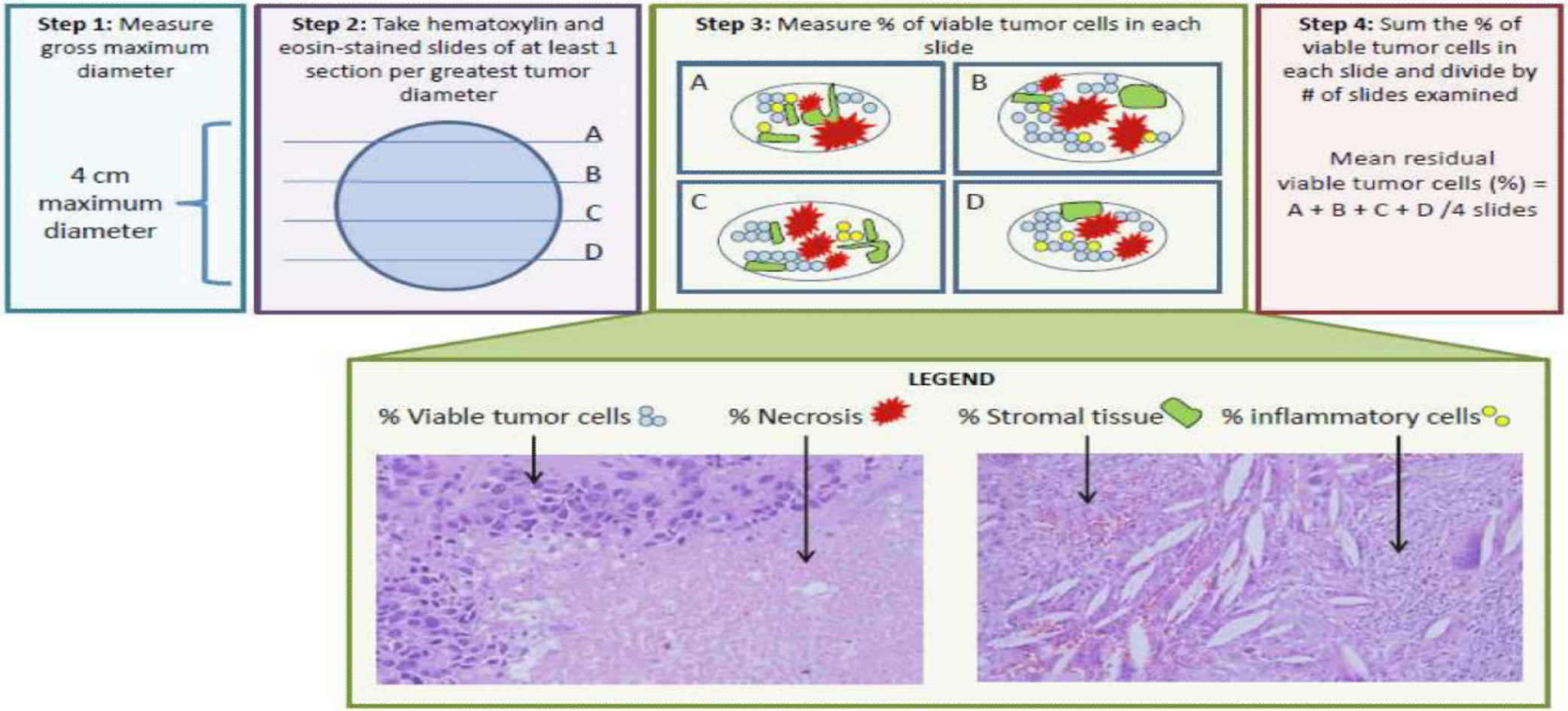
	Number of trials	Number of deaths/ patients	Hazard ratio (95%CI), p value
Survival by planned chemotherapy schedule (n=15 trials)			
Preoperative chemotherapy only	10	1045/1883	0·90 (0·80–1·02), 0·09
Preoperative and postoperative chemotherapy (to responders)	5	382/502	0·78 (0·64–0·95), 0·02
Survival by number of preoperative chemotherapy cycles (n=14 trials)			
2 cycles	6	418/576	0·89 (0·74–1·08), 0·25
3 cycles	8	1002/1799	0·85 (0·75–0·96), 0·01
Survival by chemotherapy regimen (n=14 trials)			
Platinum plus second generation chemotherapy	7	543/694	0·86 (0·72–1·02), 0·08
Platinum plus third generation chemotherapy	6	801/1540	0·85 (0·74–0·97), 0·02
Non-platinum chemotherapy	1	38/62	0·95 (0·50–1·79), 0·87
Survival by the number of chemotherapy agents (n=15 trials)			
Non platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87
Doublet regimen	9	907/1702	0·88 (0·78–1·01), 0·06
Triplet regimen	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25
Survival by chemotherapy regimen and number of chemotherapy agents (n=14 trials)			
Non-platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87
Platinum second generation, doublet	2	68/83	1·08 (0·66–1·76), 0·76
Platinum second generation, triplet	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25
Platinum third generation, doublet	6	801/1540	0·85 (0·74–0·97), 0·02
Survival by cisplatin or carboplatin regimen (n=12 trials)			
Cisplatin-based	7	830/1289	0·83 (0·72–0·95), 0·01
Carboplatin-based	5	492/905	0·90 (0·75–1·07), 0·23

NSCLC Meta-analysis Collaborative Group. Lancet 2014

Chimiothérapie néo- ou adjuvante ?

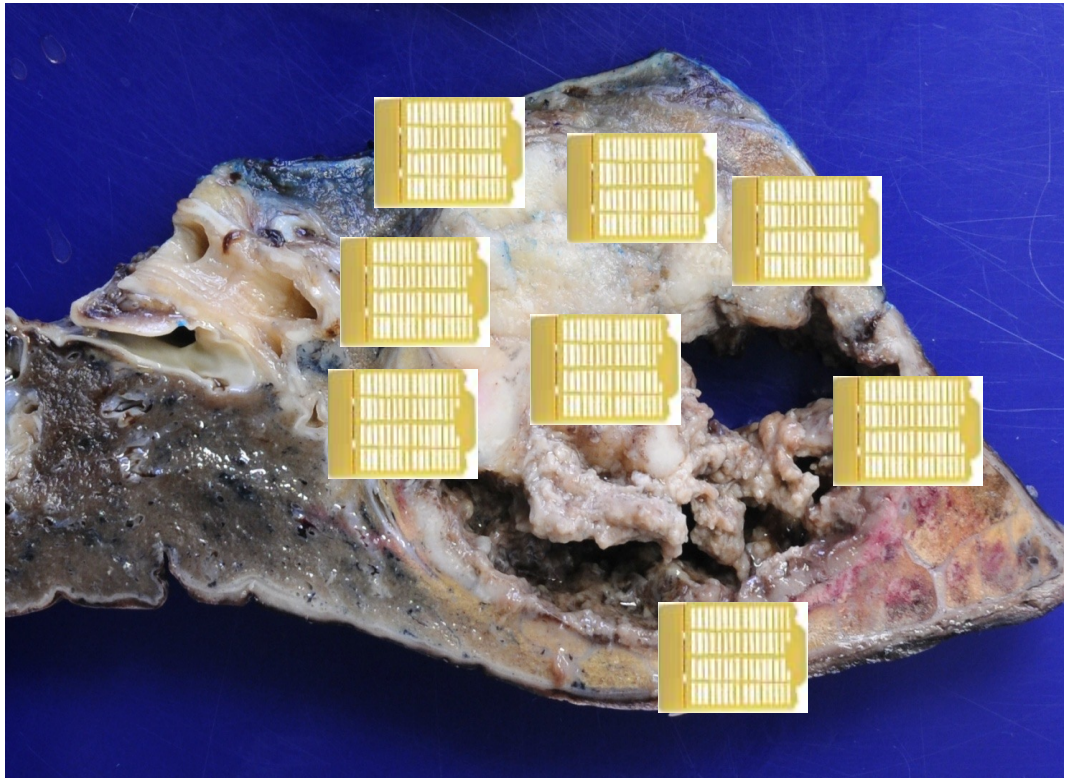
- Contre :
  - mauvais stagging initial
  - possibilité de progression
  - métanalyses
- Pour :
  - faisabilité; toxicité acceptable
  - amélioration de la resecabilité ?
  - introduction plus précoce d’un tt systémique pour traiter les micro-métastases
  - meilleure compliance que la CT adjuvante
  - évaluation de la réponse : réponse histologique

Qu’est ce que la réponse histologique ?

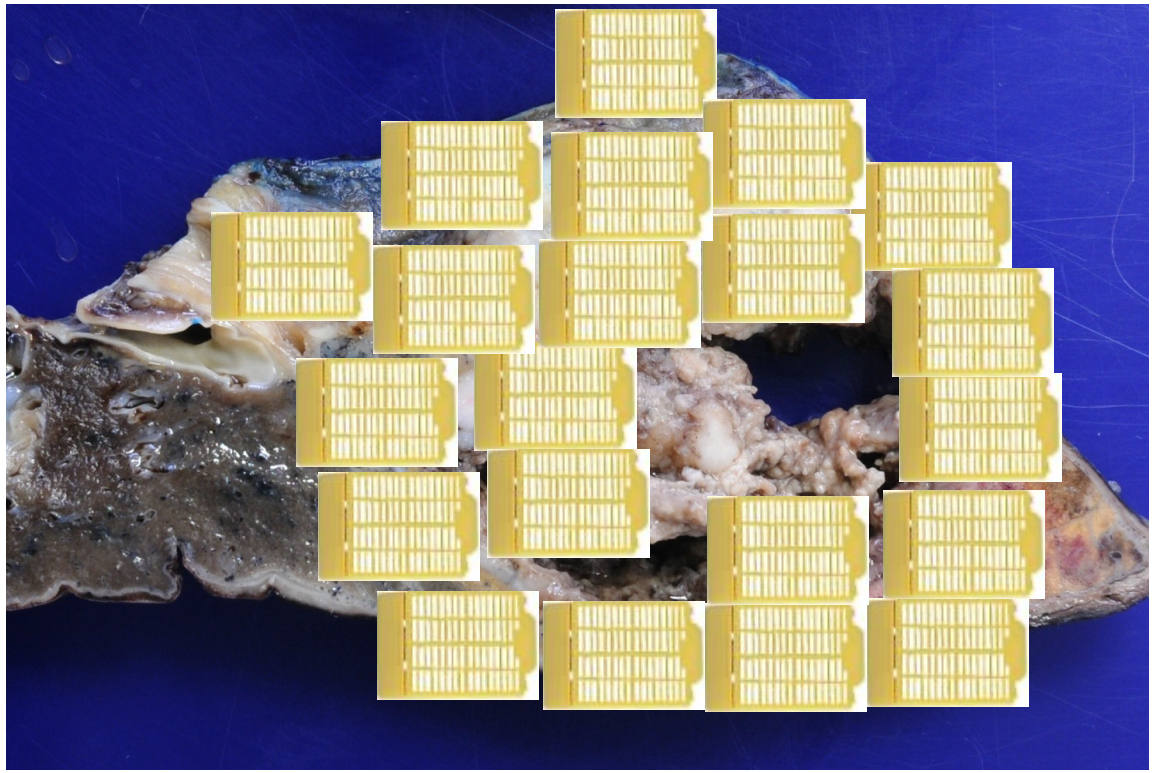


Hellmann M Lancet Oncol 201

Qu’est ce que la réponse histologique ?



Tumor + edge = 8 cm.
<8 paraffin blocks

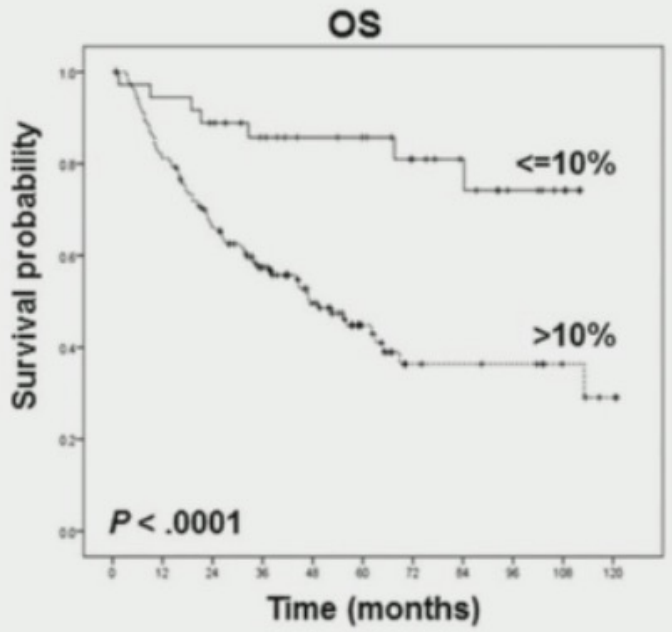


All tumor + edge N
=very high

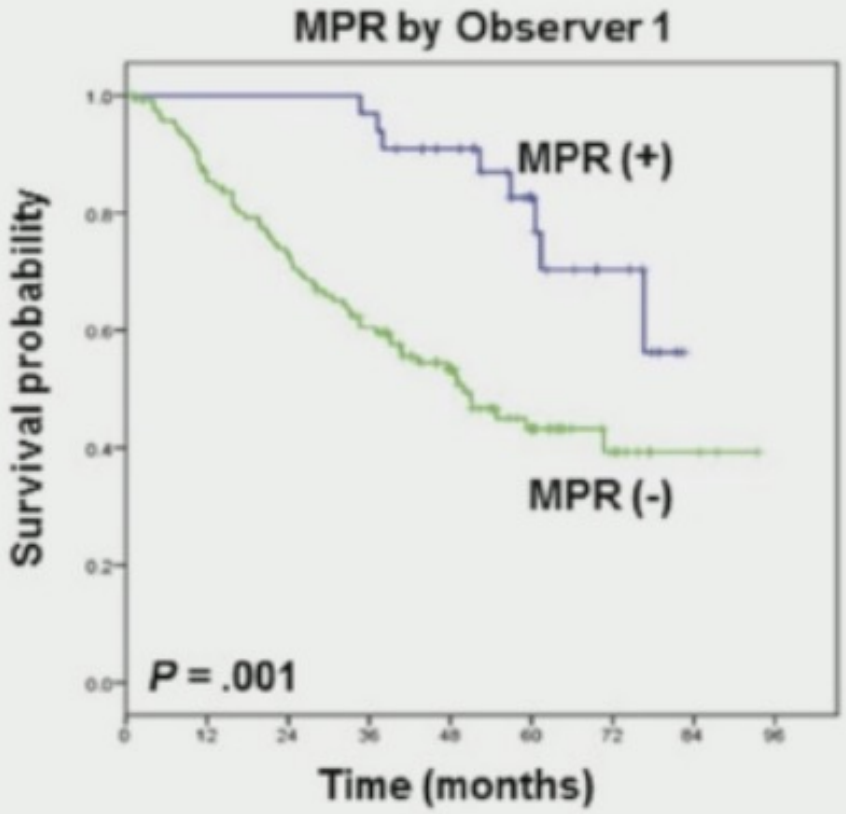
Chimiothérapie néoadjuvante : réponse histologique majeure et survie globale ?

MPR is shown to predict OS in neoadjuvant chemotherapy and chemo/VEGF lung cancer trials (Pataer, JTO 2012, Weissferdt et al Clin Lung Cancer 2020, Chaft JTO 2014)

It is not yet known if the same stands true for IO



Pataer, JTO 2012



Weissferdt et al Clin Lung Cancer 2(

Association linéaire entre réponse histologique majeure et survie globale

réponse histologique et risque de décès

Percentage of residual viable tumor following neo-adjuvant chemotherapy	Hazard Ratio for death
1-10%	1.00
11-30%	2·51 (95% CI 0·91-6·96)
31-50%	3·39 (95% CI 1·40-8·22)
51-70%	4·57 (95% CI 1·98-10·52)
71-100%	4·78 (95% CI 2·06-11·11)

Hellmann M Lancet Oncol 2014

Les stades localisés
les études de phase 3

Adjuvant Chemotherapy OS benefit

2004

Adjuvant Osimertinib DFS benefit
OS Benefit asco 23

2020

2014

MAGRIT adjuvant vaccine trial

2016

ECOG 1505 adjuvant angiogenesis inhibition

Neo adjuvant Nivolumab CT CM816 cPR EFS benefit

Adjuvant atezolizumab IMpower 010 DFS benefit

Adjuvant pembrolizumab Keynote 091 DFS benefit

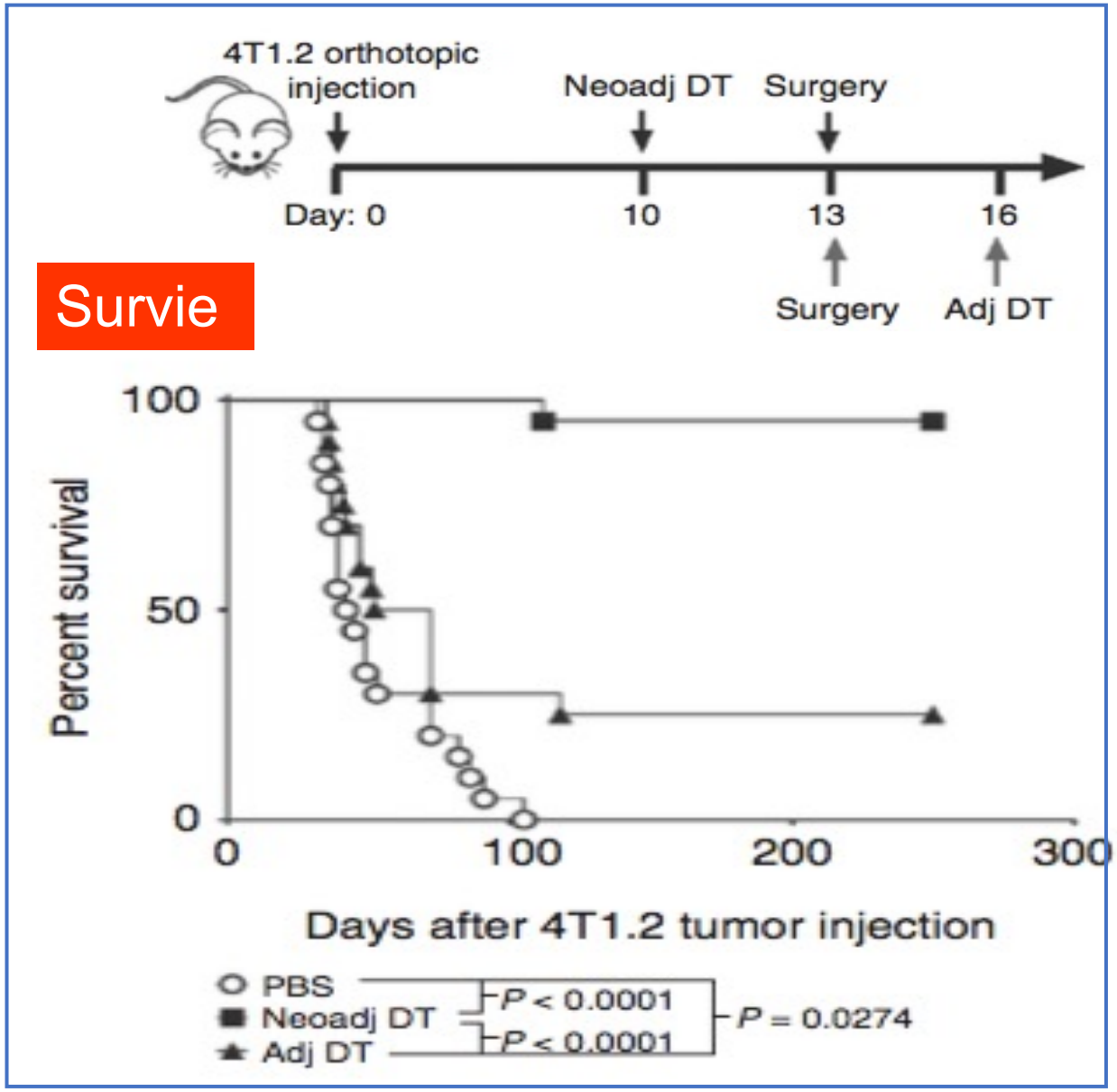
Neo adjuvant Pembro CT & pembro KN 671 cPR EFS benefit

Neo adjuvant Durva CT & Durva Aegan cPR EFS benefit

Neo adjuvant Toripa CT & Toripa NeoTorch cPR EFS benefit

Immunothérapie néo- ou adjuvante *rationnel préclinique*

- Présence d'une forte charge antigénique et relarguage de néo antigènes par les cellules tumorales : meilleure stimulation du système immunitaire
- Système immunitaire de l' hôte indemne



Liu J, Cancer Discovery 2016
Bakos, Journal of Immunotherapy of Cancer 2018

Phase 2 : Immunothérapie néoadjuvante

Ph 2 studies	Stage	Delay to surgery	First objective	Operated (%) R0 (n)	MPR /pCR	90-Day mortality	PD-L1 w/ MPR
Forde P (n=22)	IB-IIIA	4 wks after 1st dose	MPR	21 (95%) 20 R0	45% 15%	NR	no
LCMC3 (n=180) n=101 interim	IB-IIIB	4 wks after 1st dose	% pts with delayed surgery	159 (88%) 145 R0	19% 5%	NR	no
Neostar (n=44) arm A (n=23)	IA-IIIA	3 wks	MPR	22 (96%) 22 R0	19% 10%	0	yes
IFCT Ionesco (n=50)	IB-IIIA	2 to 14 days	R0	43 (86%) 41 R0	19% 7%	4 (9%)	no
Princeps (n=30)	I – IIIA (>2 cm)	4 wks	Safety (2 mo post atezo)	30 (100%) 29 R0	14% 0%	0 (30-day)	yes
Sintilimab (n=40)	IA-IIIB	2 to 14 days	Safety	37 (92.5%) 36 R0	40% 16%	NR	yes (stromal cells)
Reuss JITC (n=9)	IA-III	2 to 4 wks 6 wks	Safety	6 (67%) NR R0	33% 33%	1 ARDS	yes
Neostar (n=44) arm B (n=21)	IA-IIIA	3 wks 6 wks	MPR	17 (81%) 17 R0	44% 38%	0	yes

Phase 2 : Immunothérapie néoadjuvante

Ph 2 studies	Stage	Delay to surgery	First objective	Operated (%)	MPR /pCR	90-Day	PD-L1 w/
Forde P (n=22)	IB-IIIA	4 wks after 1st dose	MPR				
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Neostar (n=44) arm A (n=23)	IA-IIIA	3 wks	MPR				
IFCT Ionesco (n=50)	IB-IIIA	2 to 14 days	R0				
Princeps (n=30)	I – IIIA (>2 cm)	4 wks	Safety (2 mo post atezo)				
Sintilimab (n=40)	IA-IIIB	2 to 14 days	Safety				
Reuss JITC (n=9)	IA-III	2 to 4 wks 6 wks	Safety				
Neostar (n=44) arm B (n=21)	IA-IIIA	3 wks 6 wks	MPR	17 (81%) 17 R0	44% 38%	0	yes

- Multi / monocentrique
- Petits effectifs
- Objectifs principaux
  - réponse histologique vs patients opérés
- Mortalité à 90 jours
- Type histologique C épidermoïde
  - Comorbidités
  - Tabac
  - Tumeurs proximales
  - Pneumonectomie
  - Nombre de cycles
  - Délais entre le dernier cycle et la chirurgie

Ph 2 studies	Stage	Delay to surgery	First objective	Operated (%) R0 (n)	MPR pCR	90-Day mortality	PD-L1 w/ MPR
				21 (95%) 20 R0	45% 15%	NR	no
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				37 (92.5%) 36 R0	40% 16%	NR	yes (stromal cells)
				6 (67%) NR R0	33% 33%	1 ARDS	yes
arm B (n=21)		6 wks		17 (81%) 17 R0	44% 38%	0	yes

Réponse histologique

Faisabilité de la chirurgie

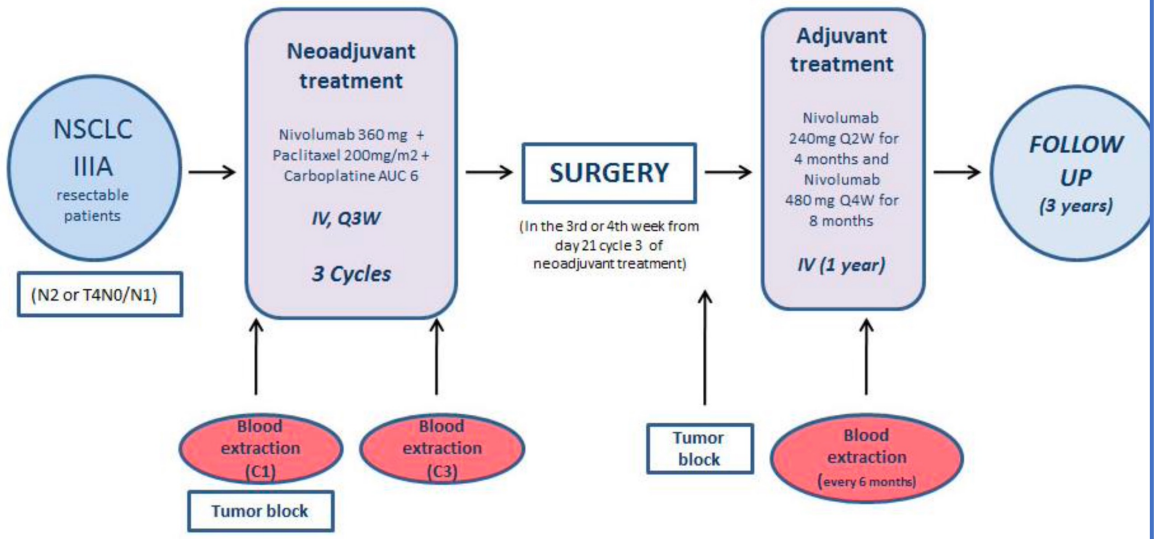
Réponse histologique associée à la survie

L'immunothérapie néoadjuvante impacte-t-elle la chirurgie?

- Complexité de la chirurgie ?
- Flare-up médiastinal
- Effets indésirables immuns

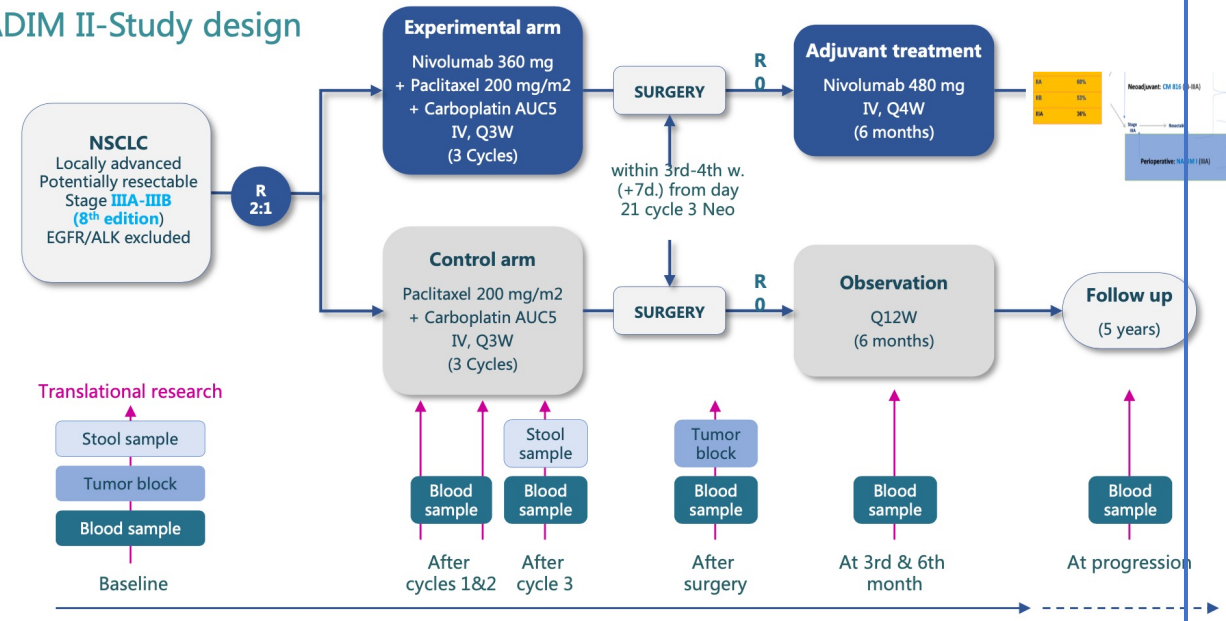
Phase 2 : Chimio Immuno néoadjuvante NADIM trial puis NADIM 2 trial

NADIM: Study design & Flow-chart



46 patients

NADIM II-Study design

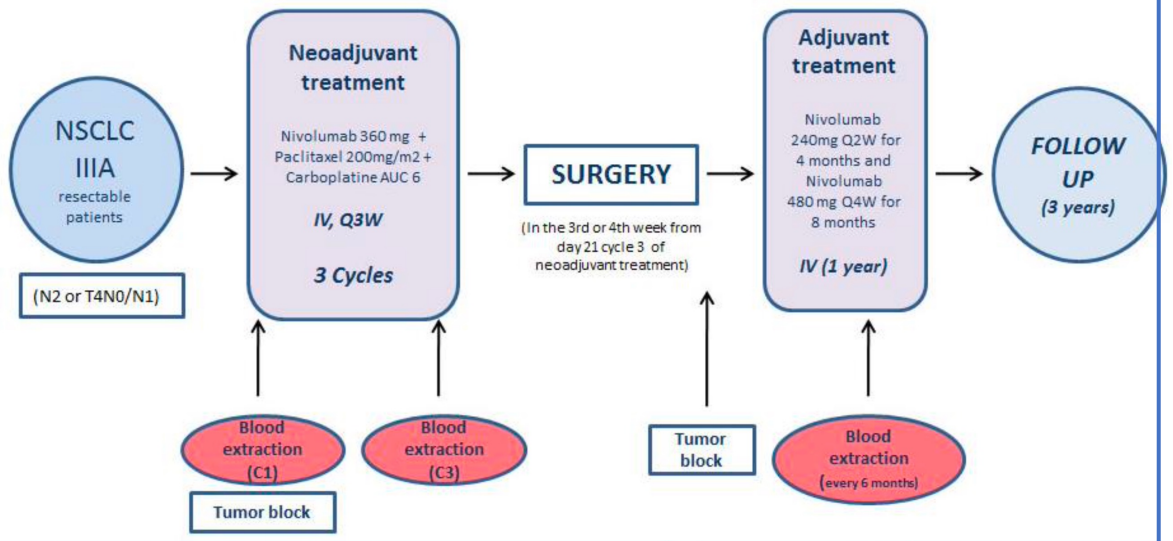


86 patients

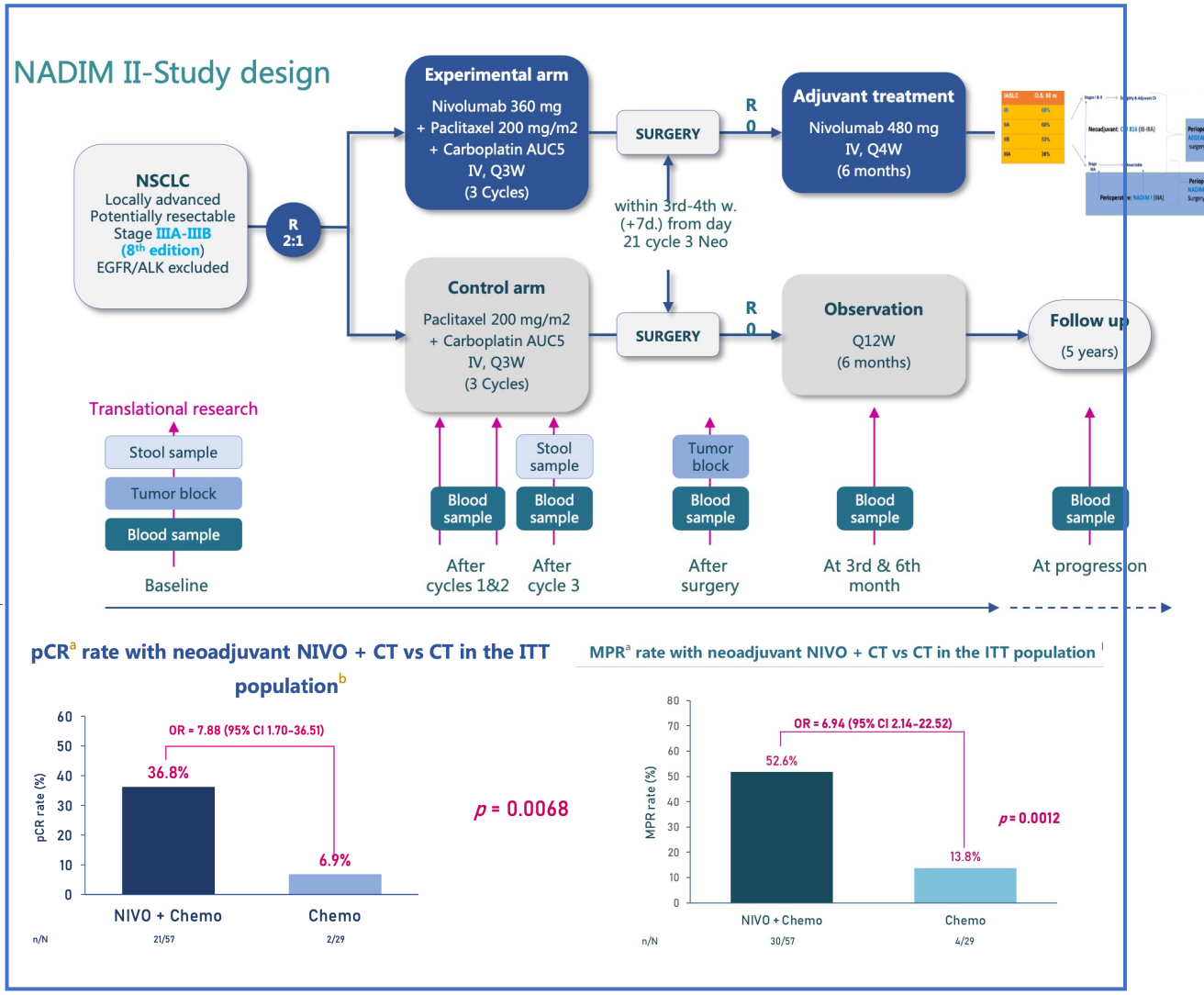
Provencio, Lancet Oncol 2020;

Phase 2 : Chimio Immuno néoadjuvante NADIM trial puis NADIM 2 trial

NADIM: Study design & Flow-chart



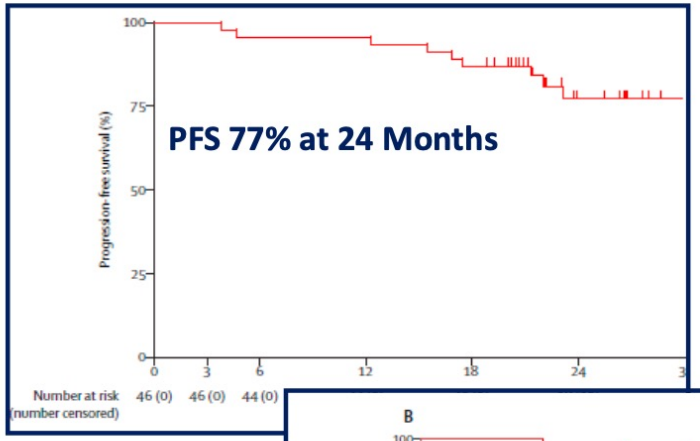
Incomplete Pathologic Response	7 (17·1 %)
Major Pathologic Response	34 (82·9 %)
Complete Pathologic Response	26 (63·4 %)

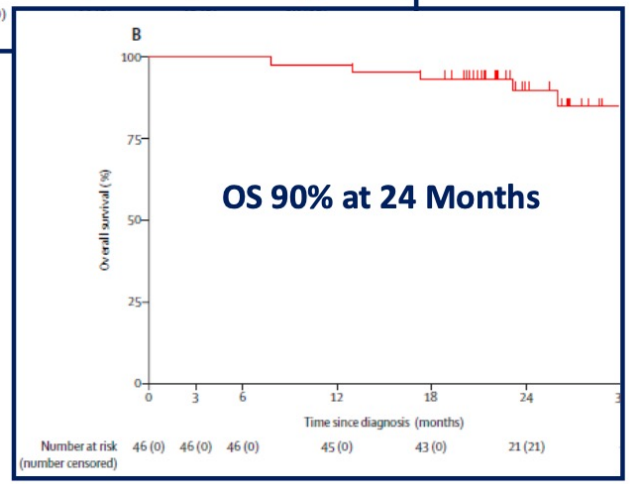


Provencio, Lancet Oncol 2020;

Phase 2 : Chimio Immuno néoadjuvante NADIM trial puis NADIM 2 trial

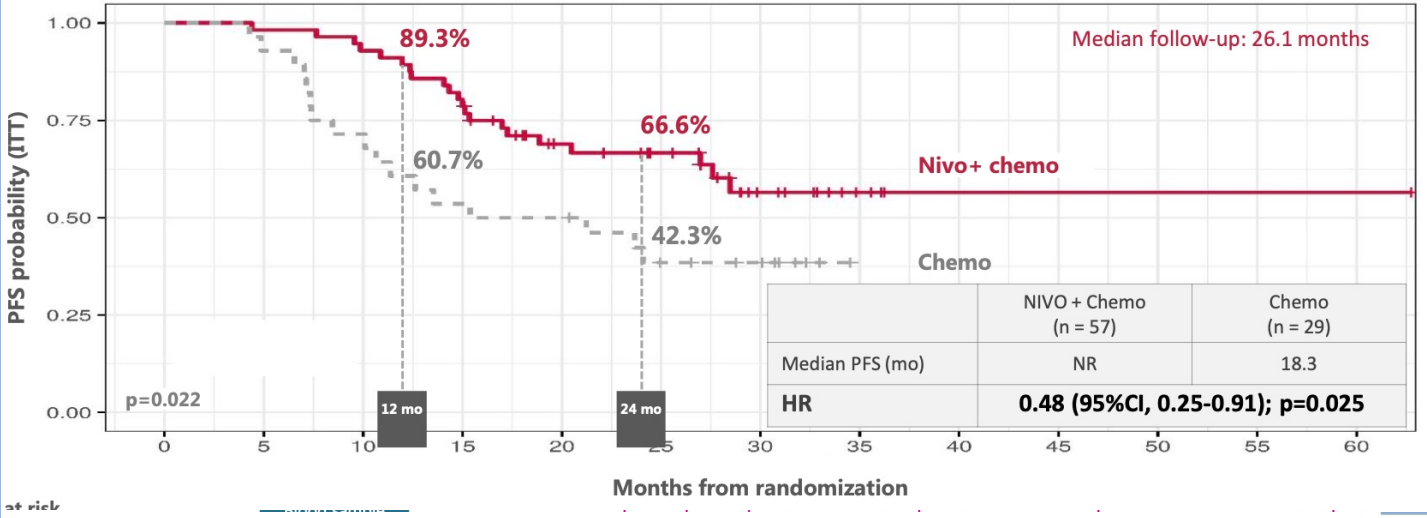
NADIM



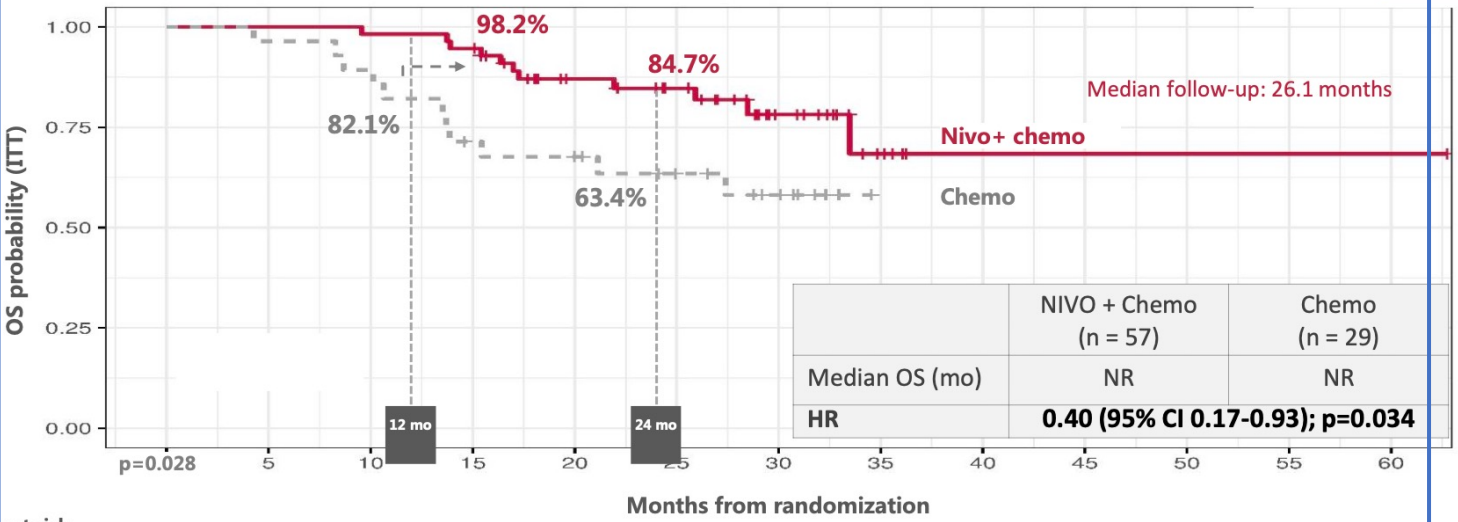


Provencio M Lancet Oncol

NADIM 2



	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	**0.48 (95%CI, 0.25-0.91); p=0.025**	



	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	**0.40 (95% CI 0.17-0.93); p=0.034**	

Phase 3 : Chimio Immuno néoadjuvante versus chimiothérapie

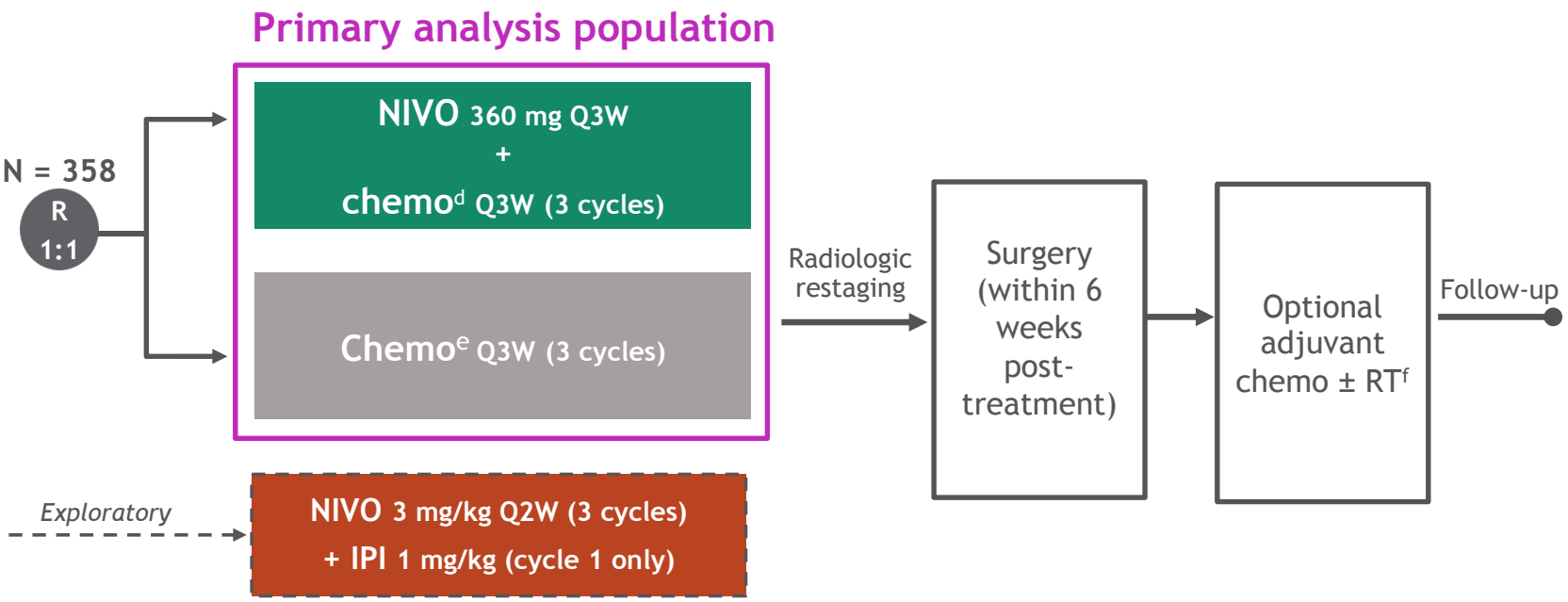
Sponsor	NCT#	stage	Treatment	Primary end point	N
CM 816	02998528	IB-IIA	Nivo/Ipi vs. Nivo/Chemo vs. Chemo	EFS pCR	350
IMPOWER 030	03456063	II-IIIB	Atezolizumab + chemo vs chemo+Placebo	MPR EFS	450
KN 671	03425643	IIB-IIIA	Pembro/chemo vs chemo	EFS, OS	786
Agean	03800134	IIA-IIIB	Durva/Chemo vs. Chemo	MPR EFS	800
Neotorch	04158440	II -III	Toripalumab/chemo vs. Chemo	MPR EFS	404

CheckMate-816 : Neoadjuvant immunotherapy

Key Eligibility Criteria

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

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



Primary endpoints
- pCR by BIPR
- EFS by BICR

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

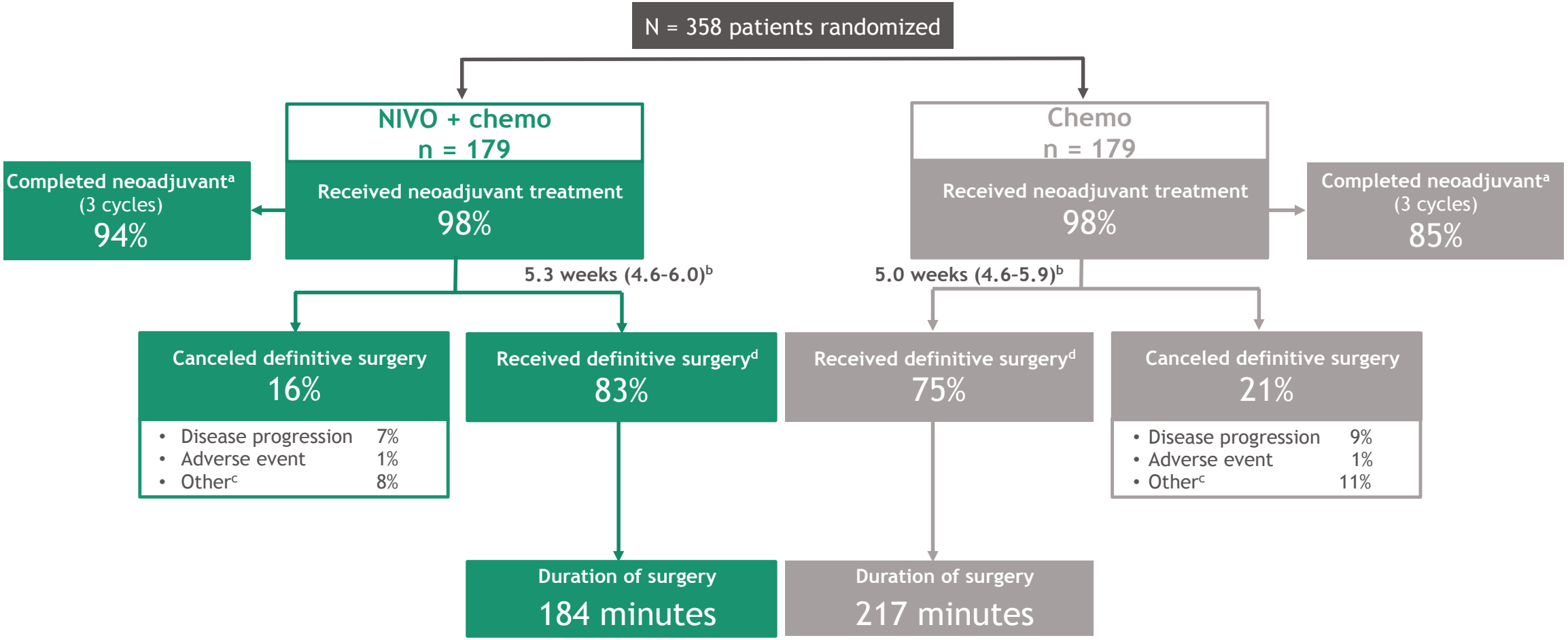
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[g])

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

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

Forde et al. AACR 2021; Spicer et al. ASCO 2021

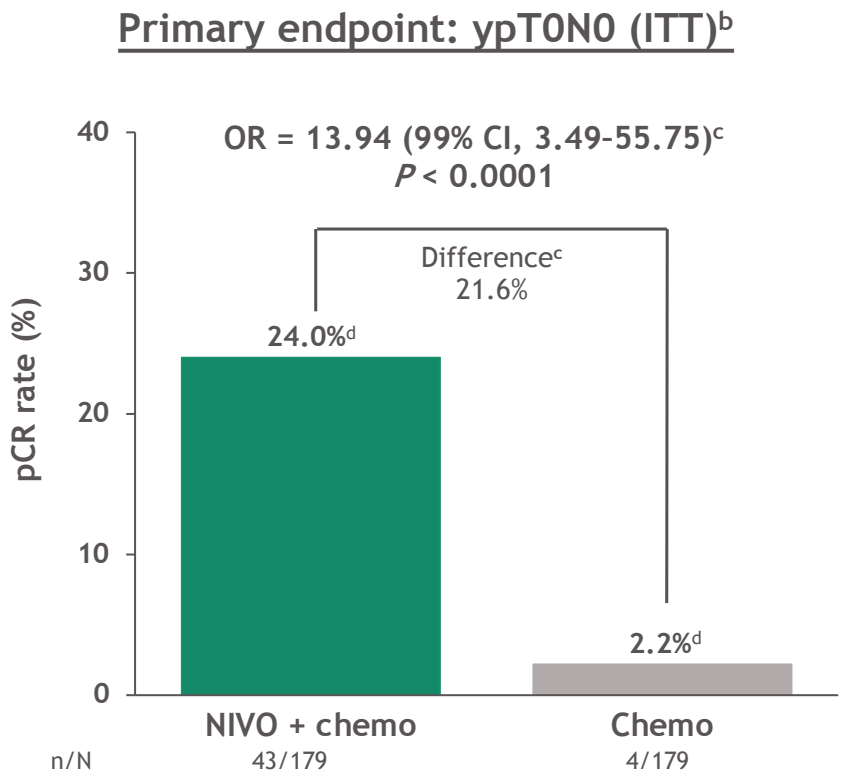
CheckMate-816 : Neoadjuvant immunotherapy



[a]Additional reasons for patients being off 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); [b]Median (IQR) time from last dose to definitive surgery; [c]Other reasons included patient refusal, unresectability, and poor lung function; [d]Patients with definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%.

Forde et al. AACR 2021; Spicer et al. ASCO 2021

CheckMate-816
Primary endpoint: pCR



CM-816: Exploratory Biomarker da

- **pCR rates favored N+CT across PD-L1 levels, although higher rat**
  - PD-L1 expression as expected (49.7% pts with ≥1%; 22.3% pts with ≥50%)
  - For comparison, in BR31: 57.8% pts with ≥1%; 24.1% pts with ≥50%)

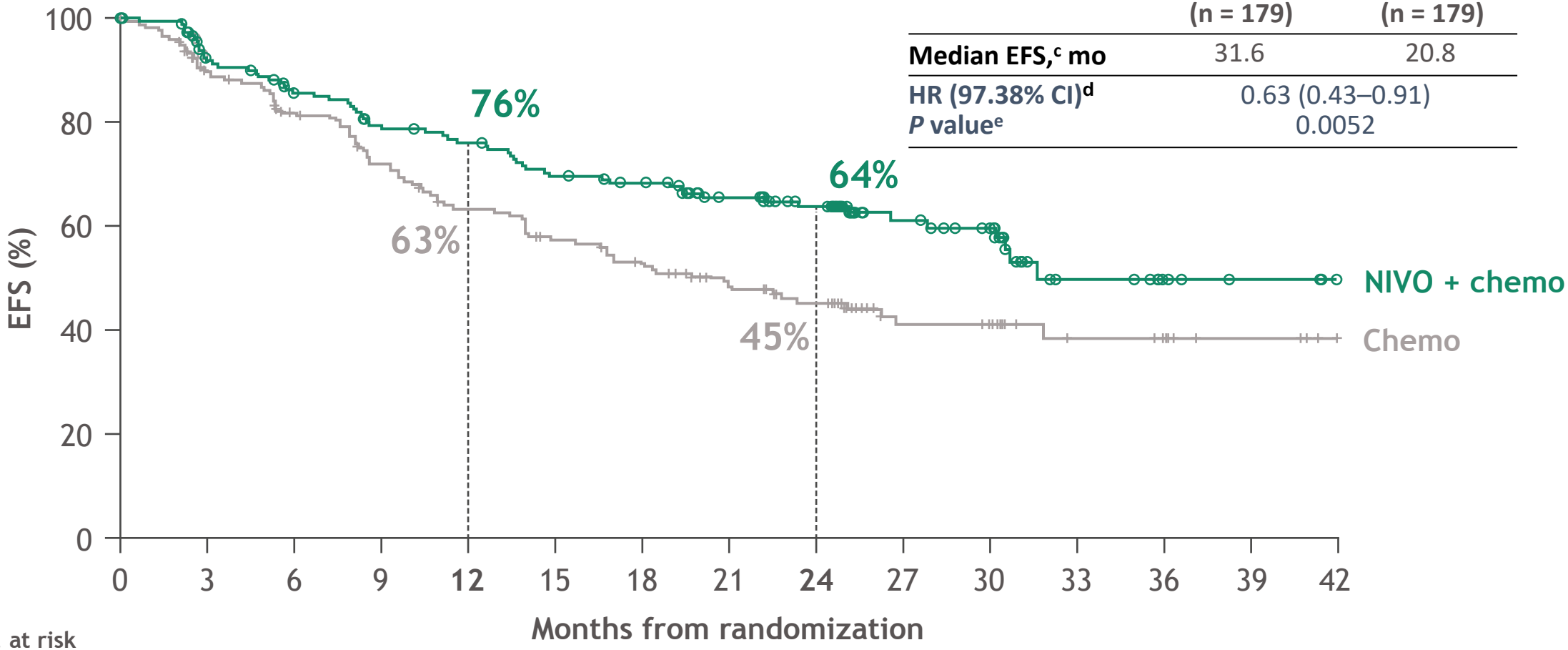
	pCR[a] rate, %		Unweighted pCR diffe
	NIVO + chemo (n = 179)	Chemo (n = 179)	
PD-L1 < 1% (n = 155)	17	3	
PD-L1 ≥ 1% (n = 178)	33	2	
PD-L1 1-49% (n = 98)	24	0	
PD-L1 ≥ 50% (n = 80)	45	5	
TMB < 12.3 mut/Mb (n = 102)	22	2	
TMB ≥ 12.3 mut/Mb (n = 76)	31	3	

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

[a]per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]ITT principle: patients w
stratified Cochran-Mantel-Haenszel method; [d]pCR rates 95% CI: NIVO + chemo, 18.0–31.0; chemo, 0.6–5.6; [e]Patients who underv

CheckMate-816
Primary endpoint: EFS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43–0.91)	
***P* value[e]**	0.0052	



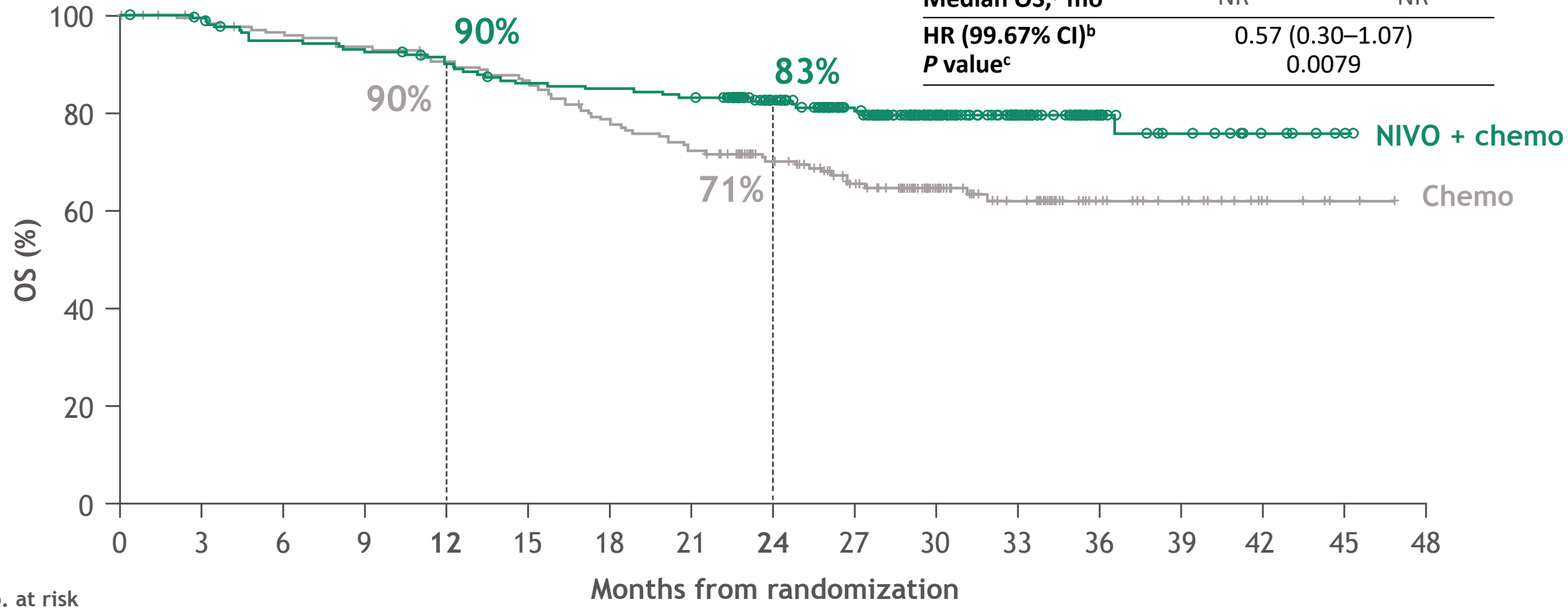
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
NIVO + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2-NR (NIVO + chemo) and 14.0-26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

CheckMate-816
Overall survival: interim analysis

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30–1.07)	
***P* value[c]**	0.0079	



No. at risk																	
NIVO + chemo	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemo	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

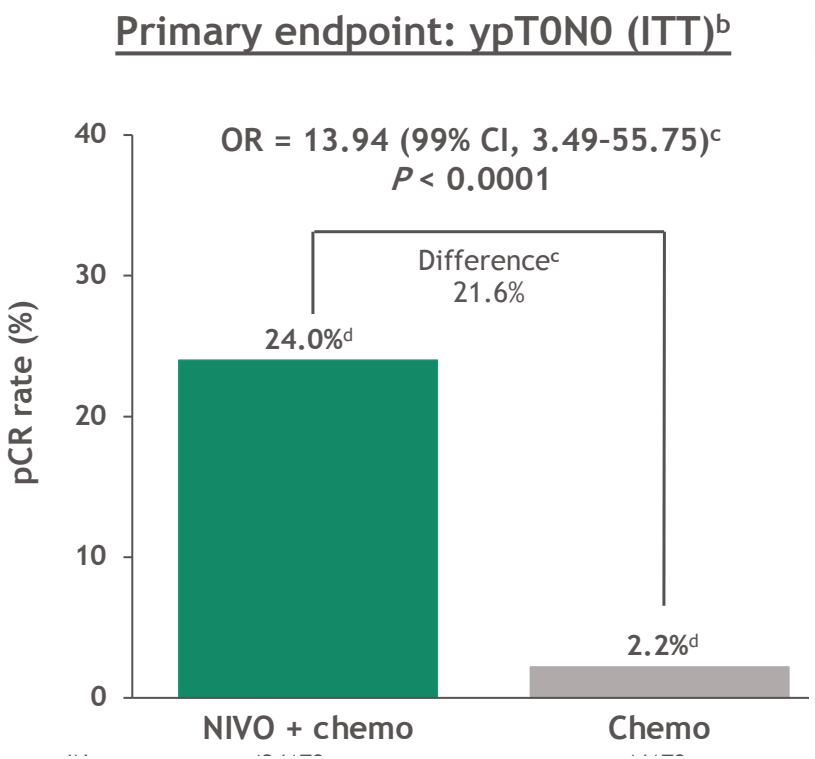
Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo); [b]95% CI = 0.38-0.87; [c]Significance boundary for OS (0.0033) was not met at this interim analysis.

Autres études de phase 3 : réponse histologique complète

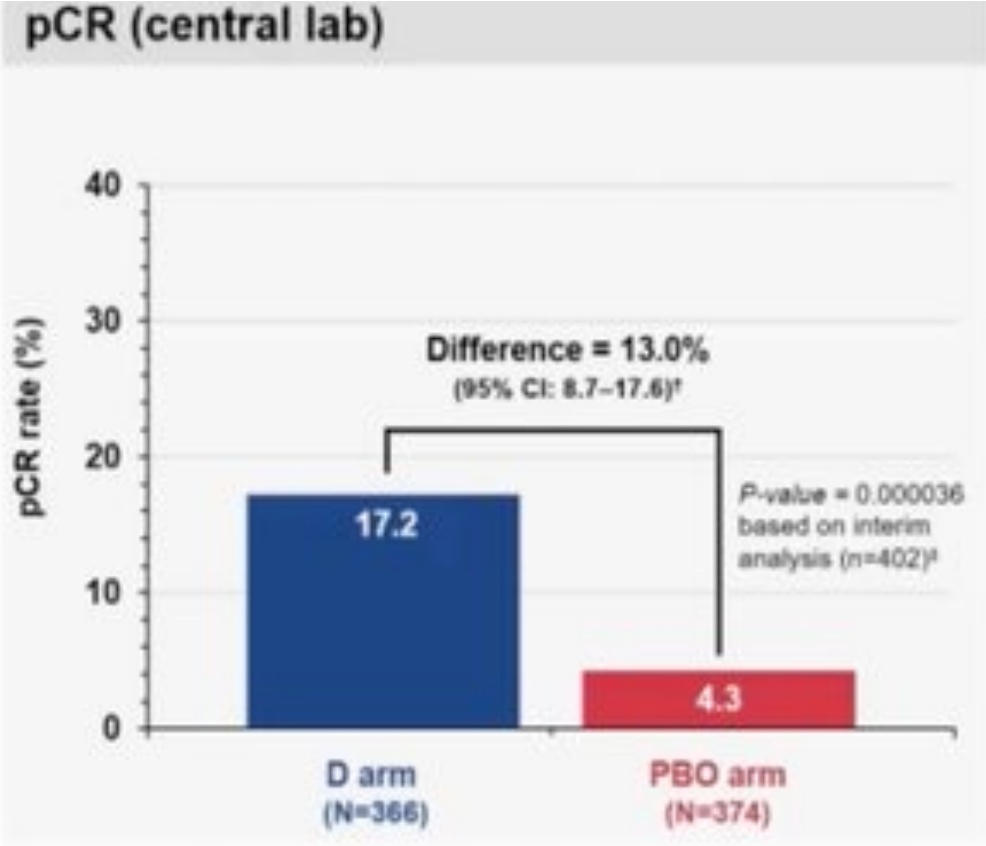
CheckMate-816

Nivolumab-CT (3 cycles)
& Surveillance



Aegan

Durvalumab-CT (4 cycles)
& Durva



Neotorch

Toripalumab CT (3 + 1 cycles)
& Toripa

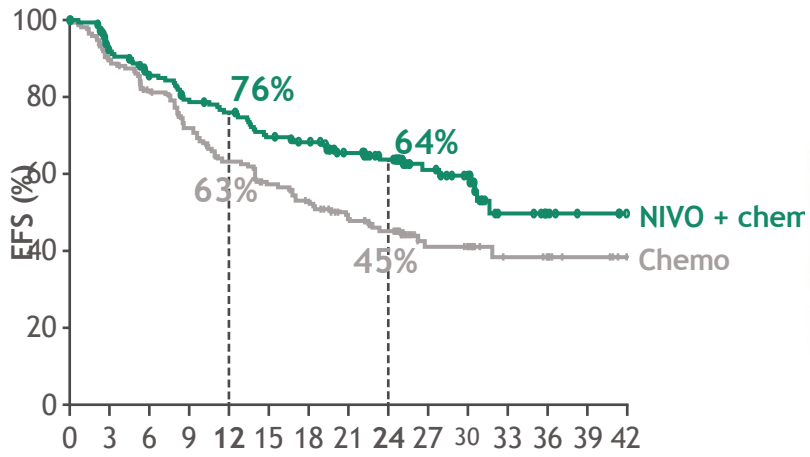
Toripalimab + Chemo （N=202）	Placebo + Chemo （N=202）
50 (24.8)	**2 (1.0)**
19.0, 31.3	0.1, 3.5
23.7 (17.6, 29.8)	
＜0.0001	

pCR assessed by BIPR
n (%)
95% CI
Stratified analysis
Difference between arms (95% CI)
P value

Autres études de phase 3 : survie sans évènement

CheckMate-816

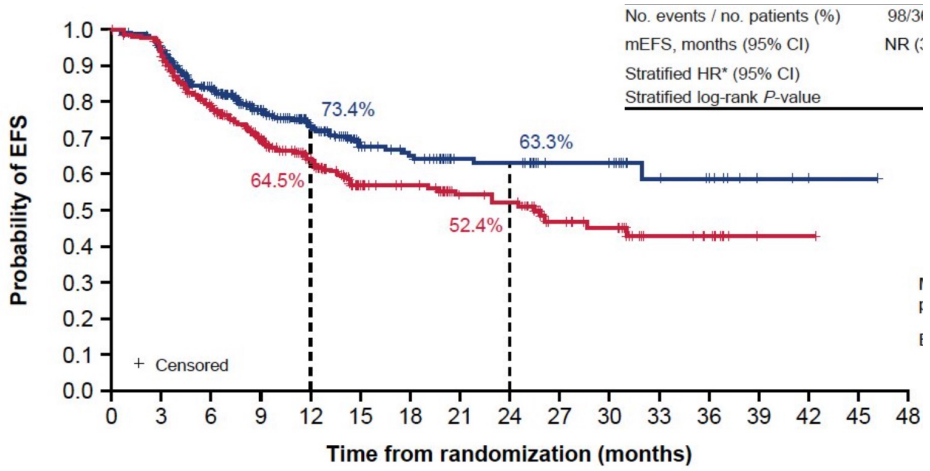
Nivolumab-CT (3 cycles)
& Surveillance



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43–0.91)	
***P* value[e]**	0.0052	

Aegan

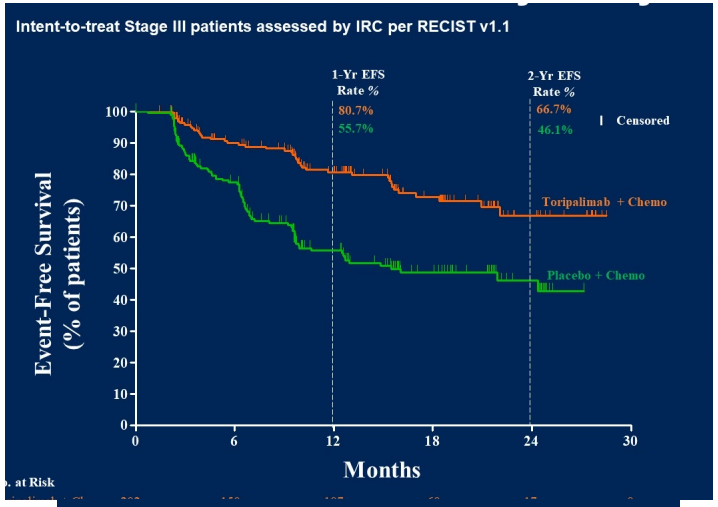
Durvalumab-CT (4 cycles)
& Durva



	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	

Neotorch

Toripalumab CT (3 + 1 cycles)
& Toripa



	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	43/202	NE (NE, NE)
Placebo + Chemo	87/202	15.5 (9.9, NE)

Median follow-up: 18.25 months

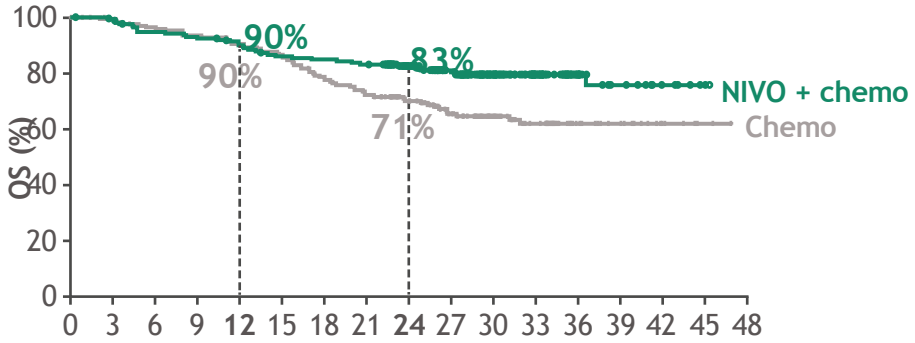
HR 0.40 (95%CI 0.271, 0.572)

nominal P<0.0001

Autres études de phase 3 : survie globale

CheckMate-816

Nivo CT 3 cycles
& Surveillance



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30–1.07)	
***P* value[c]**	0.0079	

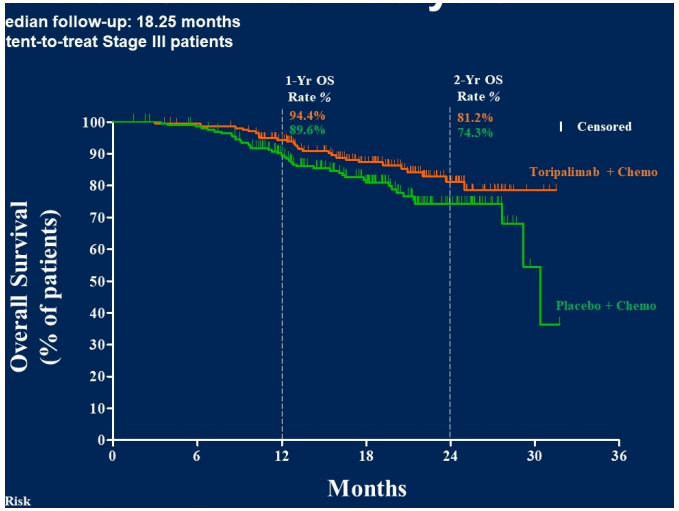
Aegan

Durvalumab CT 4 cycles
& Durva

?

Neotorch

Toripalumab CT 4 cycles
& Toripa CT 1 cycle & Toripa



	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	28/202	NE (NE, NE)
Placebo + Chemo	48/202	30.4 (29.2, NE)

HR 0.62 (95% CI 0.381, 0.999)

nominal P=0.0502

Phase 3 : ICI monothérapie versus placebo/BSC situation adjuvante

Trial	NCT	Drug	Stage	Target Accrual	Phase	Endpoint
PEARLS	NCT02504372	S with or without CT→ Pembrolizumab vs Placebo	IB-IIIA	1080	III	DFS
BR31	NCT02273375	S with or without CT→ Durvalumab vs Placebo	IB-IIIA	1360	III	DFS, DFS in PD-L1 positive
ANVIL	NCT02595944	S with or without CT→ Nivolumab vs Observation	IB-IIIA	903	III	DFS, OS
IMpower010	NCT02486718	S with CT→ Atezolizumab vs Best Supportive Care	IB-IIIA	1280	III	DFS

S: surgery. CT: adjuvant chemotherapy. DFS: disease free survival.

IMpower 010 : Adjuvant immunotherapy

2021 ESMO congress

IMpower010 study design

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

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

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

No crossover

Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

Stratification factors

- Sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumour expression status (TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1)[a]

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomised stage II-IIIA population
  3. ITT (all-randomised stage IB-IIIA) population

Key secondary endpoints

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

Hierarchical statistical testing

DFS in PD-L1 TC ≥1% stage II-IIIA population[b]

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomised stage IB-IIIA)

If positive:

OS in ITT population[b] (all-randomised stage IB-IIIA)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumour-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

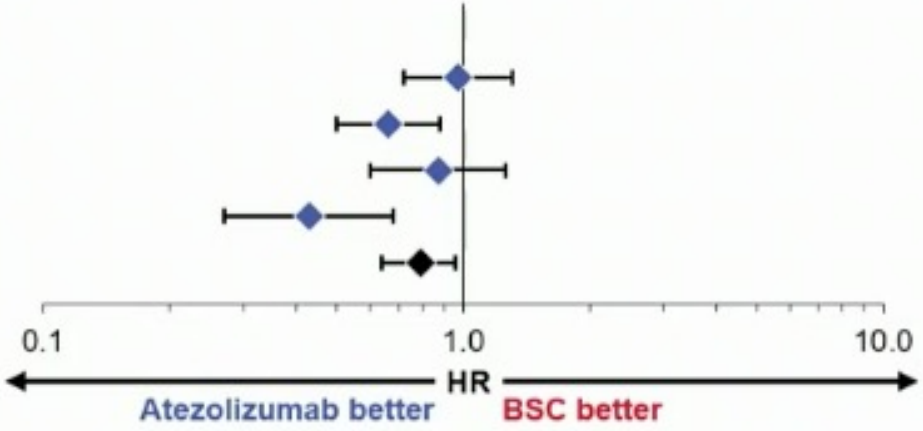
Felip et al. IMpower010 Relapse Patterns.
https://bit.ly/3mNMSAi

IMpower 010 : Adjuvant immunotherapy

DFS by PD-L1 status[a]

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

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



IMpower 010 : Avis de la commission de transparence

Avis de la CT du 14 décembre 2022

Documents : 4

Historique des avis

TÉLÉCHARGER L'AVIS

ÉCOUTER

AJOUTER À MA SELECTION

TECENTRIQ (atézolizumab) - Cancer bronchique non à petites cellules (CBNPC)

AVIS SUR LES MÉDICAMENTS - Mis en ligne le 20 janv. 2023

Nature de la demande

Extension d'indication

Nouvelle(s) indication(s).

L'essentiel

Avis défavorable au remboursement en monothérapie dans le traitement adjuvan
complète et chimiothérapie à base de platine, des patients adultes atteints d'un c
non à petites cellules (CBNPC) avec un risque élevé de récidive, dont les tumeurs
expression de PD-L1 ≥ 50 % sur les cellules tumorales (TC) et qui ne présentent pa
EGFR muté ou réarrangement du gène ALK (ALK-positif).

Quelle place dans la stratégie thérapeutique ?

de chirurgie d'emblée avec résection complète, notamment l'association cisplatine-vinorelbine ou cisplatine-pemetrexed (uniquement dans le CBNPC non-épidermoïde). Il n'est pas recommandé de chimiothérapie adjuvante en cas de stade I.

En l'absence de mutation EGFR, la suite de la prise en charge consiste en une surveillance.

Place du médicament

Prenant en compte :

- les limites méthodologiques majeures associées aux analyses d'efficacité réalisées dans la population finalement retenue pour l'AMM (notamment analyses en sous-groupes, post-hoc, non ajustées pour la multiplicité, sans interaction recherchée, utilisant un critère de stratification différent de ceux utilisés dans la randomisation), ne permettant d'en tirer aucune conclusion formelle ;
- le contexte de situation adjuvante, dans laquelle une proportion estimée entre 37% et 63% des patients ne va pas rechuter (quasi équivalent de guérison), sans prise en charge additionnelle ;
- le surcroît de toxicité associé à l'utilisation de TECENTRIQ (atezolizumab), par rapport à la surveillance, dans le contexte de situation adjuvante évoqué ci-dessus ;

la Commission de la Transparence estime que TECENTRIQ (atezolizumab) n'a pas de place dans la stratégie thérapeutique actuelle.

Service Médical Rendu (SMR)

Insuffisant	Le service médical rendu par TECENTRIQ (atezolizumab) est insuffisant pour justifier d'une prise en charge par la solidarité nationale dans l'indication de l'AMM.

Amélioration du service médical rendu (ASMR)

Sans objet

Pearls / Keynote-091 : Adjuvant immunotherapy

Randomized, Triple-Blind, Phase 3 Trial

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

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

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

R 1:1

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

Placebo Q3W for ≤18 administrations (~1 yr)

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

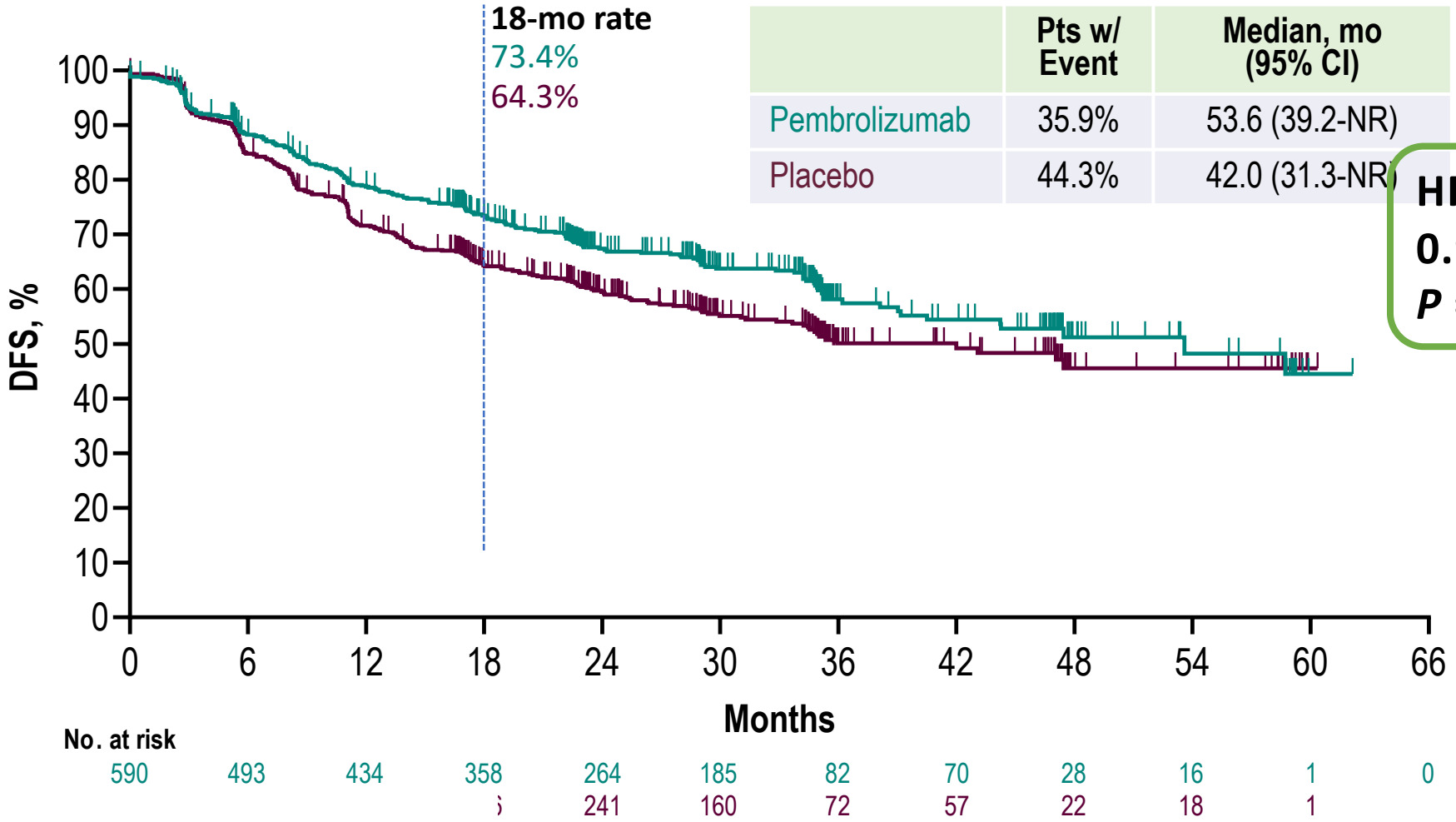
Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

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

Paz Ares L, ESMO virtual meeting 2022

Pearls / Keynote-091 : Adjuvant immunotherapy

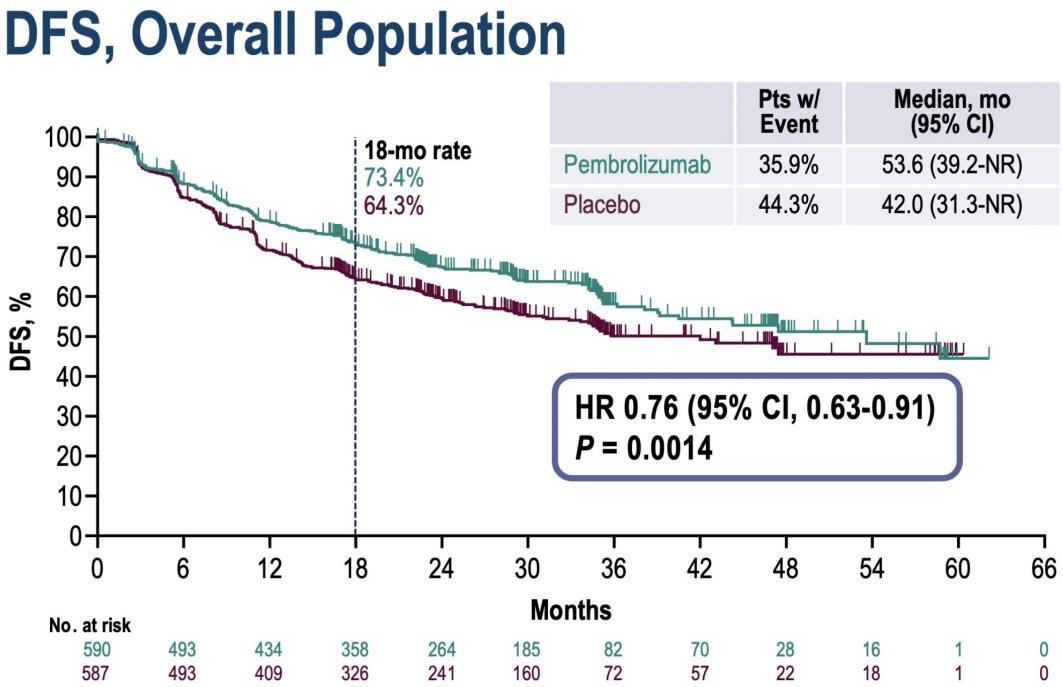
survie sans récidive

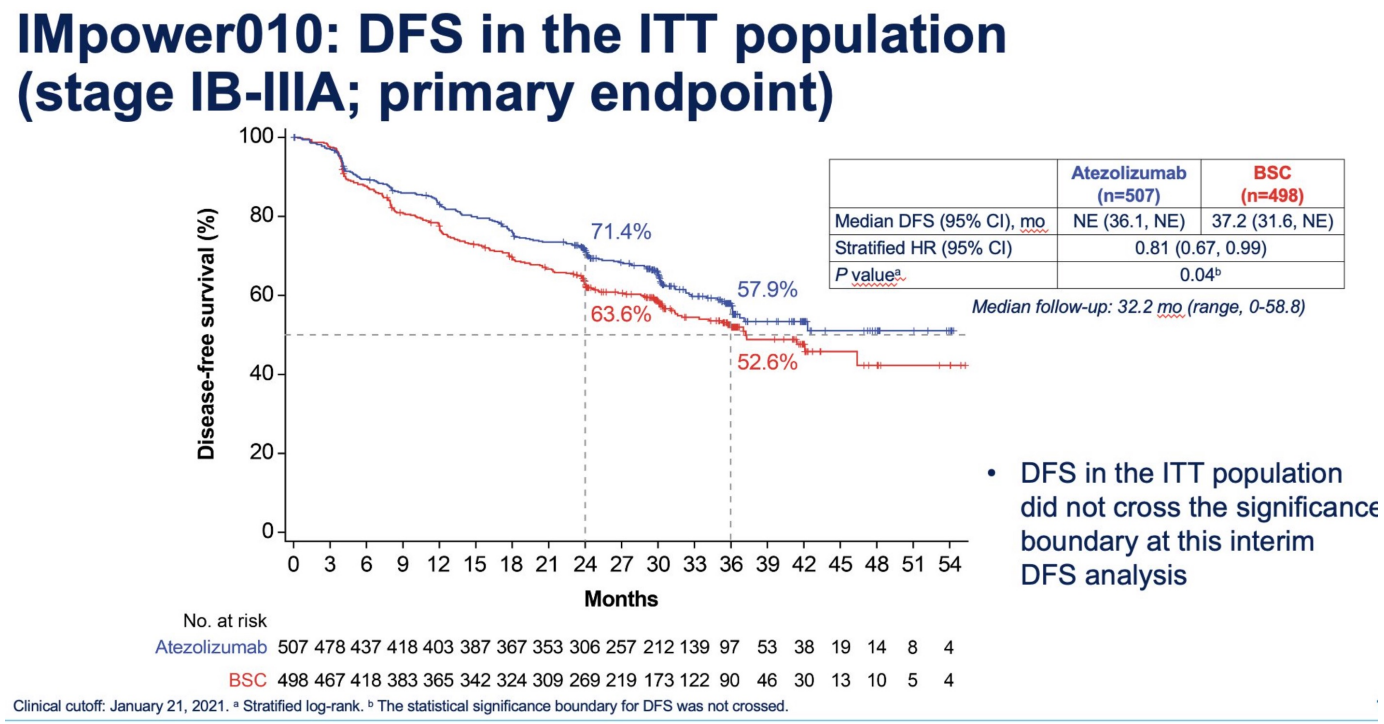


	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

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

Pearls/Keynote-091 et Impower 010
survie sans récidive



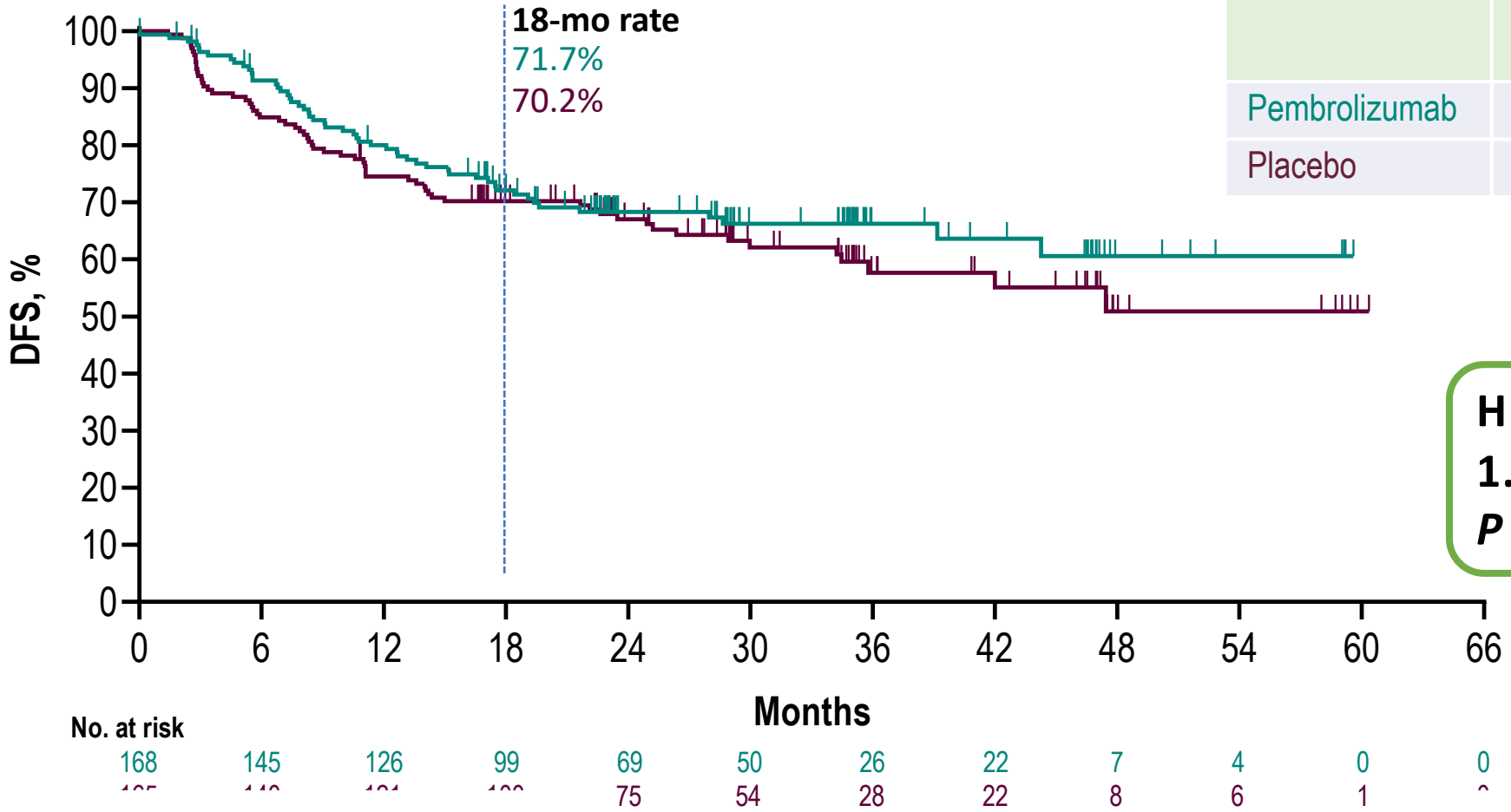


- DFS in the ITT population did not cross the significance boundary at this interim DFS analysis

Paz Ares L, ESMO virtual meeting 2022

Similar HR for DFS in IMpower 010

Pearls / Keynote-091 : Adjuvant immunotherapy
survie sans récidive chez les PDL1 ≥ 50%



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

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

TKI EGFR en adjuvant

TRIALS	STAGE	INTERVENTION	Duration	COMPARASION	DFS	OS
EVAN	IIIA	Erlotinib (n=51)	2 years	Vinorelbine + Cisplatin (n=51)	2-year DFS 81.4% vs. 44.6% RR 1·823, p=0·0054	5-year OS 84.2m vs. 61.1m HR 0.318, 95% CI, Phase II, Small cohort
ADJUVANT	II-IIIA	Gefitinib (n=111)	2 years	Vinorelbine + Cisplatin (n=111)	Median DFS 28.7m vs. 18.0m HR 0.6, p=0·0054	5-year OS 75.5 vs. 62.8 mons HR=0.92, p=0.674 Not significant
IMPACT	II-III	Gefitinib (n=116)	2 years	Vinorelbine + Cisplatin (n=116)	Median DFS 35.9m vs. 25.0m HR 0.92, p=0·63	5-year OS 78.0% vs. 74.6% HR=1.03, p=0·98 Not significant
ADAURA	IB-IIIA	Osimertinib (n=339)	3 years	Placebo (n=343)	Median DFS NR vs. 27.5m HR 0.20, p<0.001	NA

More highly potent EGFR-TKIs at later lines may impact survival and trial of adjuvant

Osimertinib is still pending for OS.

TKI EGFR en adjuvant

Adjuvant Osimertinib versus Placebo (ADAURA)

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

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO PS 0 / 1
Confirmed primary non-squamous NSCLC
Ex19del / L858R‡
MRI or CT scan of the brain prior to surgery or randomization
Complete resection with negative margins¶
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Adjuvant chemotherapy use was per physician and patient choice, and should have consisted of a platinum-based doublet for ≤4 cycles

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: three years

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

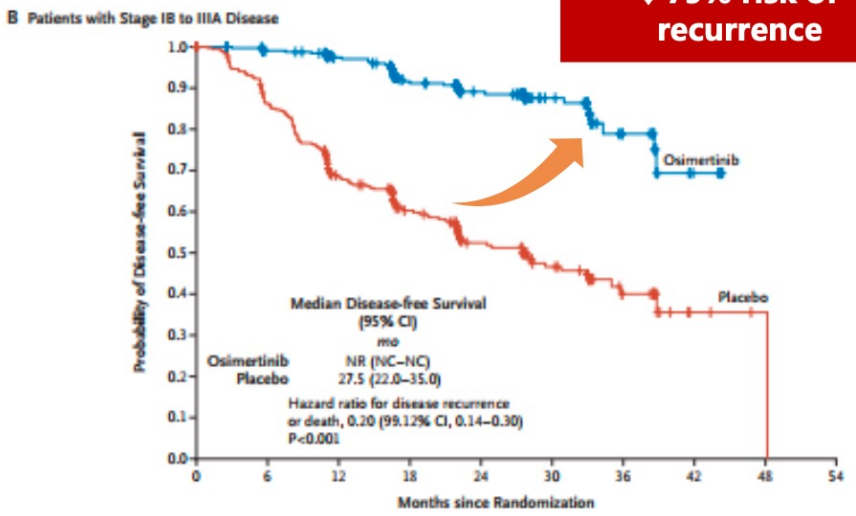
Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

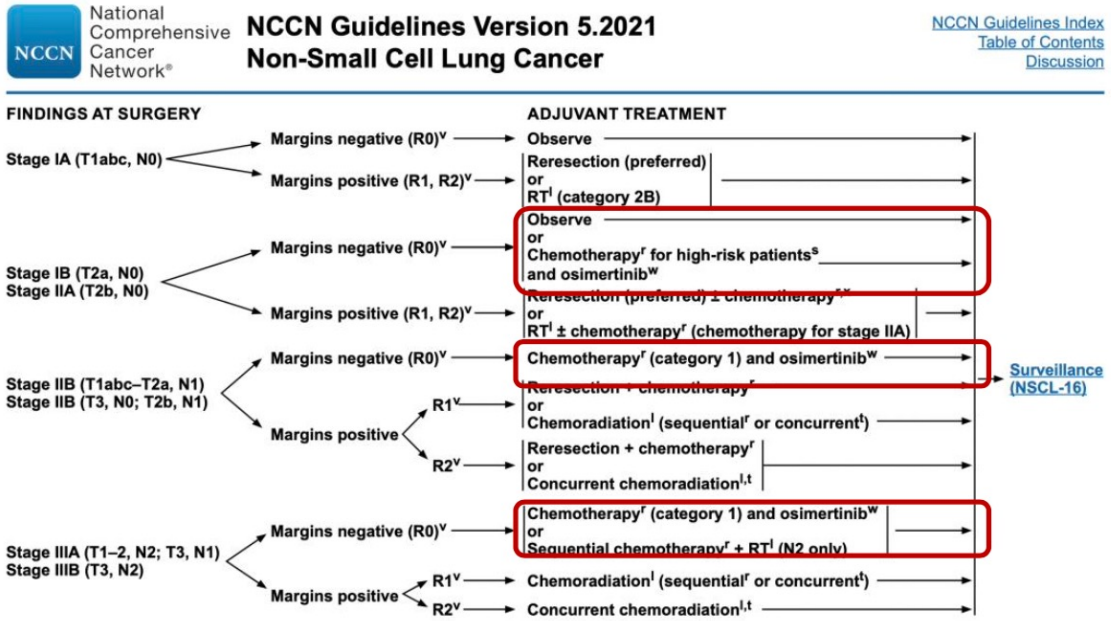
3rd generation EGFR-TKI

Treatment duration: 3 years

With and without chemotherapy

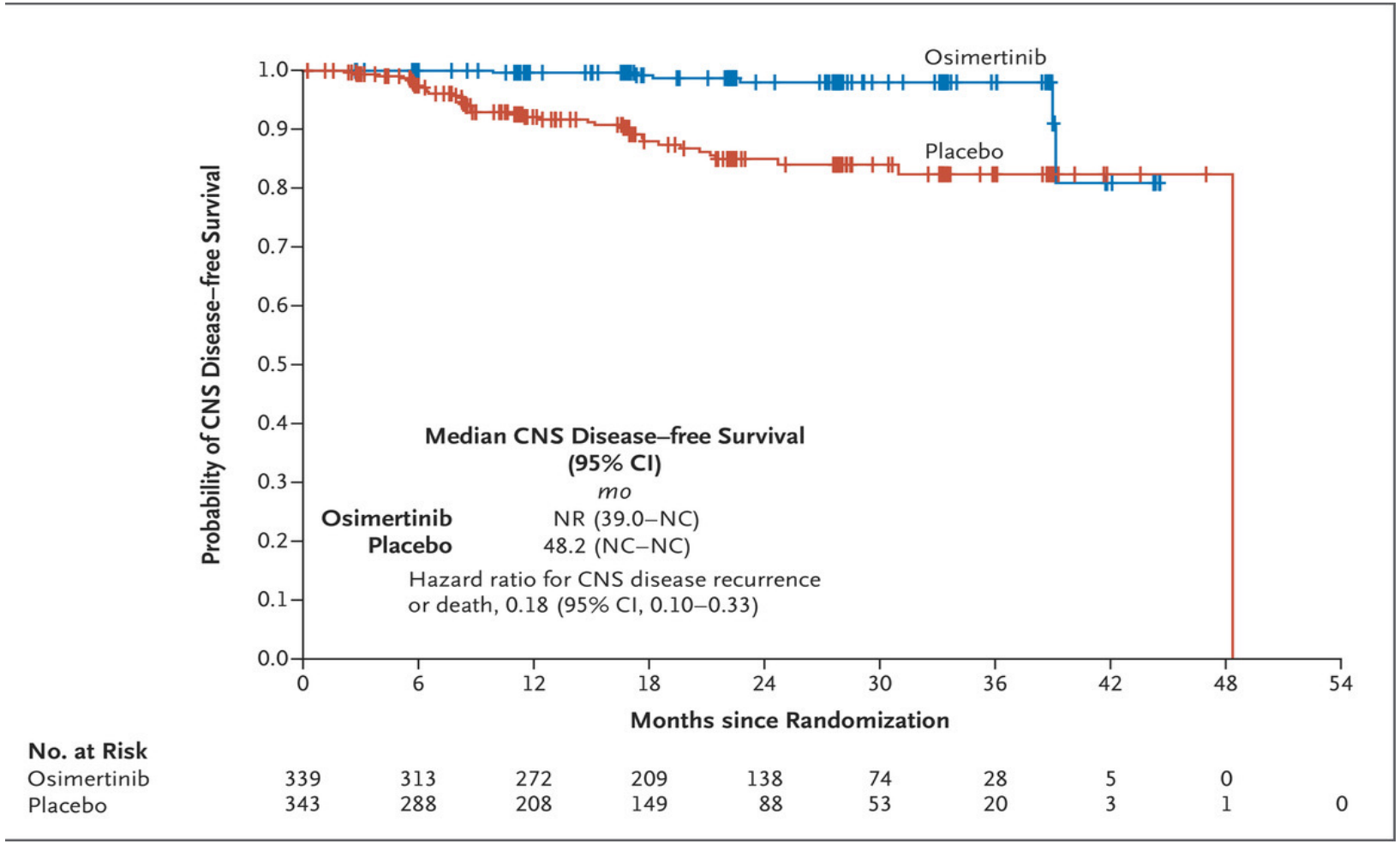
↓ 79% risk of recurrence





2020 ASCO, Presented By Roy Herbst Wu YL et al. 2020 N Engl J Med. 2021 NCCN Guideline, Version 5

TKI EGFR en adjuvant ADAURA
Central Nervous System DFS



Y Wu et al. N Engl J Med 2020;383:1711-1723.

TKI EGFR en adjuvant ADAURA

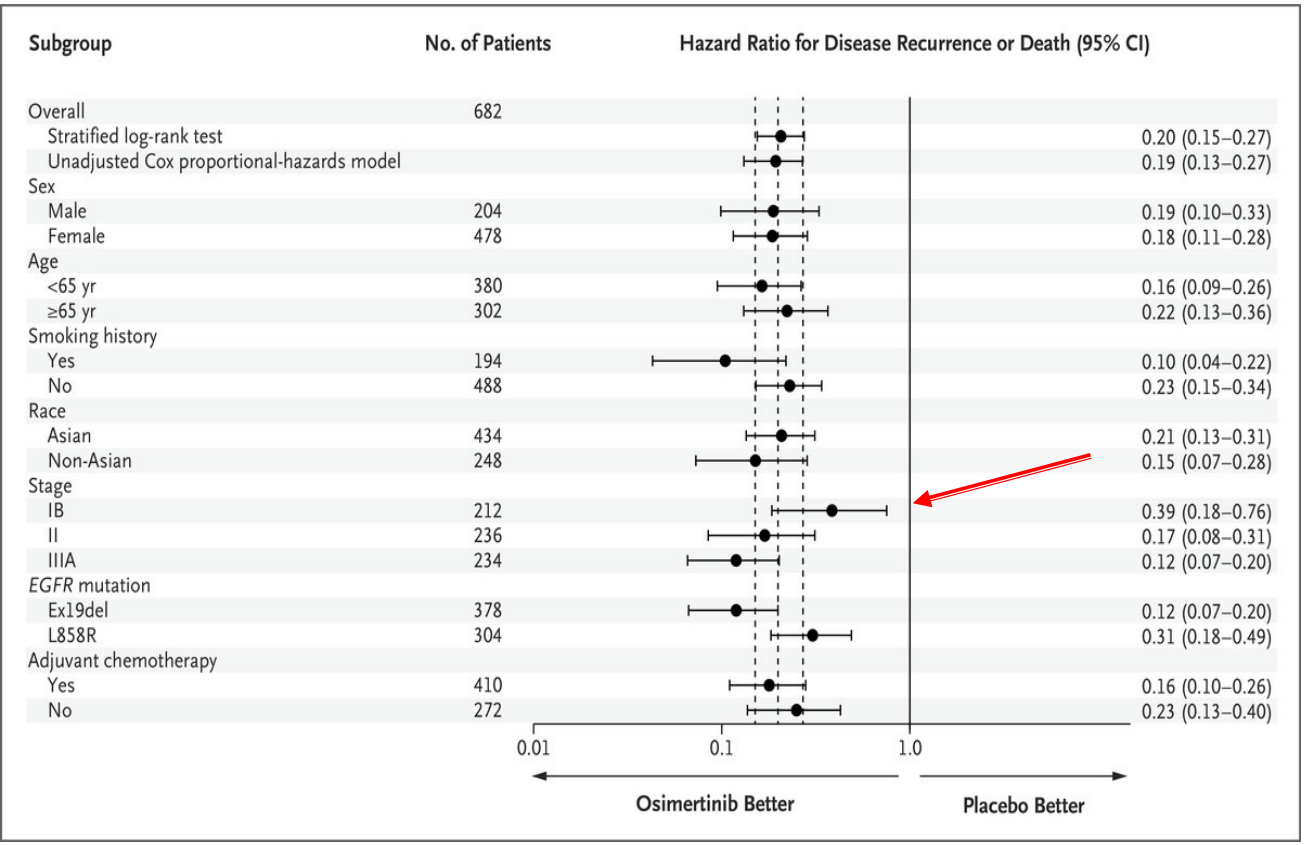


Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

* Listed are adverse events that were reported in at least 10% of the patients in either trial group, according to the maximum Common Terminology Criteria for Adverse Events grade and preferred term. The safety analyses included all the patients who received at least one dose of osimertinib or placebo (safety analysis set). None of the adverse events reported in at least 10% of the patients in either trial group were determined to be grade 4 or higher.

Y Wu et al. N Engl J Med 2020;383:1711-1723.

TKI EGFR en adjuvant ADAURA

ADAURA - Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC).

ABSTRACTS & PRESENTATIONS

2023 ASCO Annual Meeting - Plenary Session

Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC).

Abstract: LBA3

ASCO 2023 (27-04-2023)

https://meetings.asco.org/abstracts-presentations/219805

Tagrisso (osimertinib) - AstraZeneca, Solid Tumor, Non Small Cell Lung Cancer, Lung Cancer, Oncology, EGFR mutation, EGFR, AstraZeneca

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- IO CT neoadjuvant
  - Adjuvant : ? quelle durée ?
  - Quel stade?
  - PD-L1
- TKI EGFR
  - Adjuvant
  - OS : amplitude benefice

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