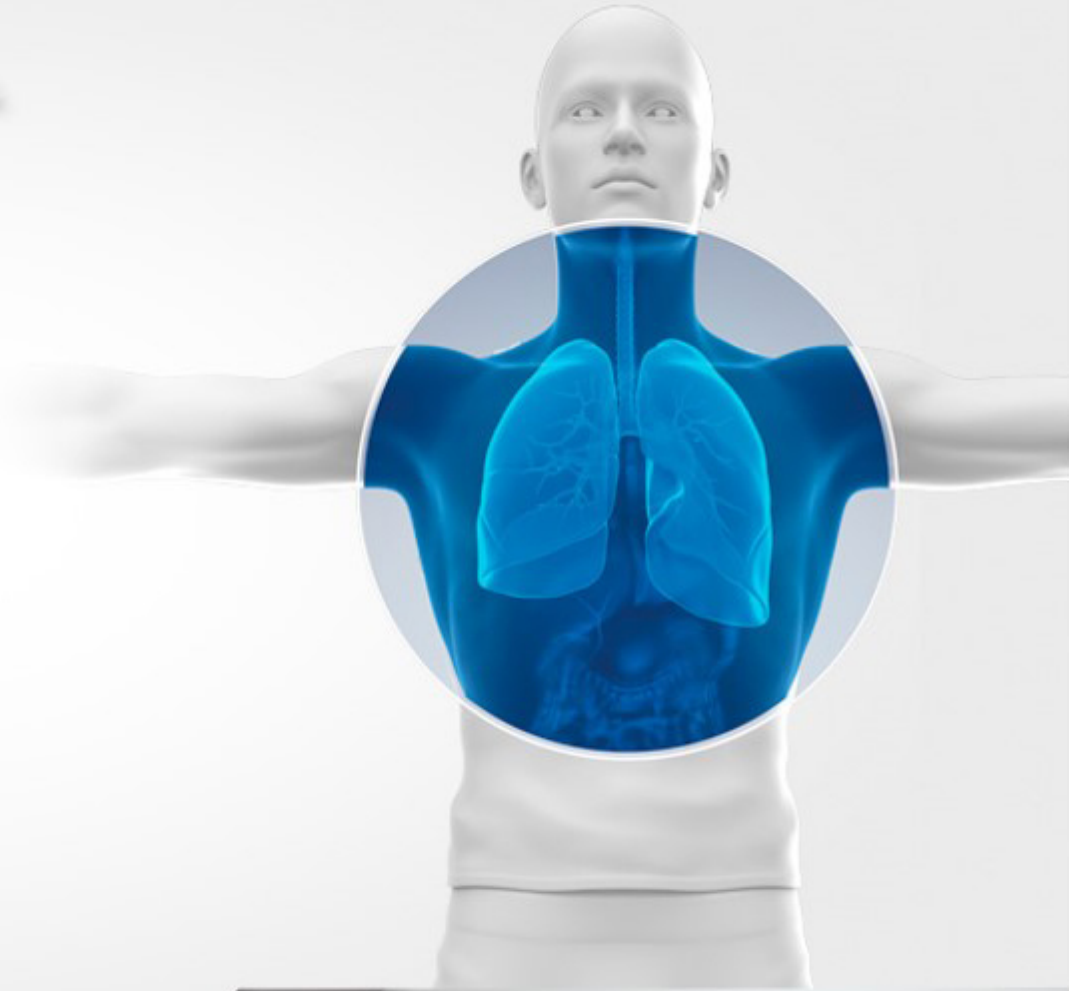




GROUPE FRANÇAIS DE
PNEUMO-CANCÉROLOGIE

17^{ème} réunion

Clinico-
Pathologique
en Oncologie Thoracique



Lecture critique d'article

**JOURNÉES
GFPC
2023**

Présenté par :

Dr Aurélie Swalduz, *Centre Léon Bérard, Lyon*
Pr Florian Guisier, *CHU Rouen*

Liens d'intérêts

- Amgen, Astra Zeneca, BMS, Janssen, MSD, Pfizer, Roche, Sanofi, Takeda, Viatris

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- Pr Olivier Bylicki

The NEW ENGLAND
JOURNAL *of* MEDICINE

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AUGUST 10, 2023

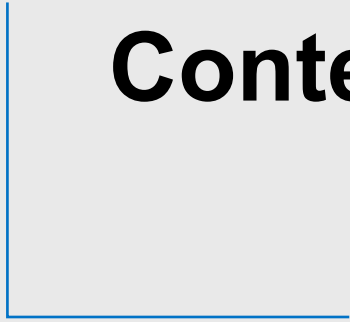
VOL. 389 NO. 6

Perioperative Pembrolizumab
for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Doms, M. Majem, E. Eigendorff,
G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari,
and J.D. Spicer, for the KEYNOTE-671 Investigators*



Contexte



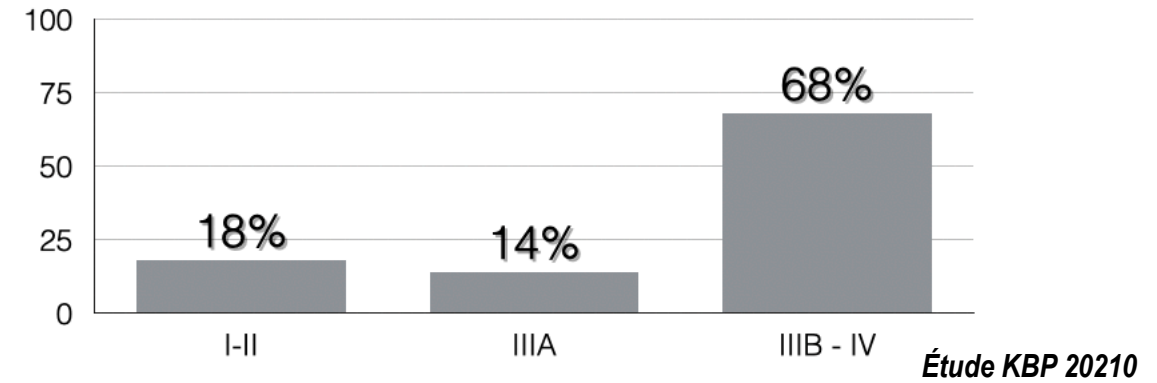
Contexte de l'étude

- CBNPC localisé

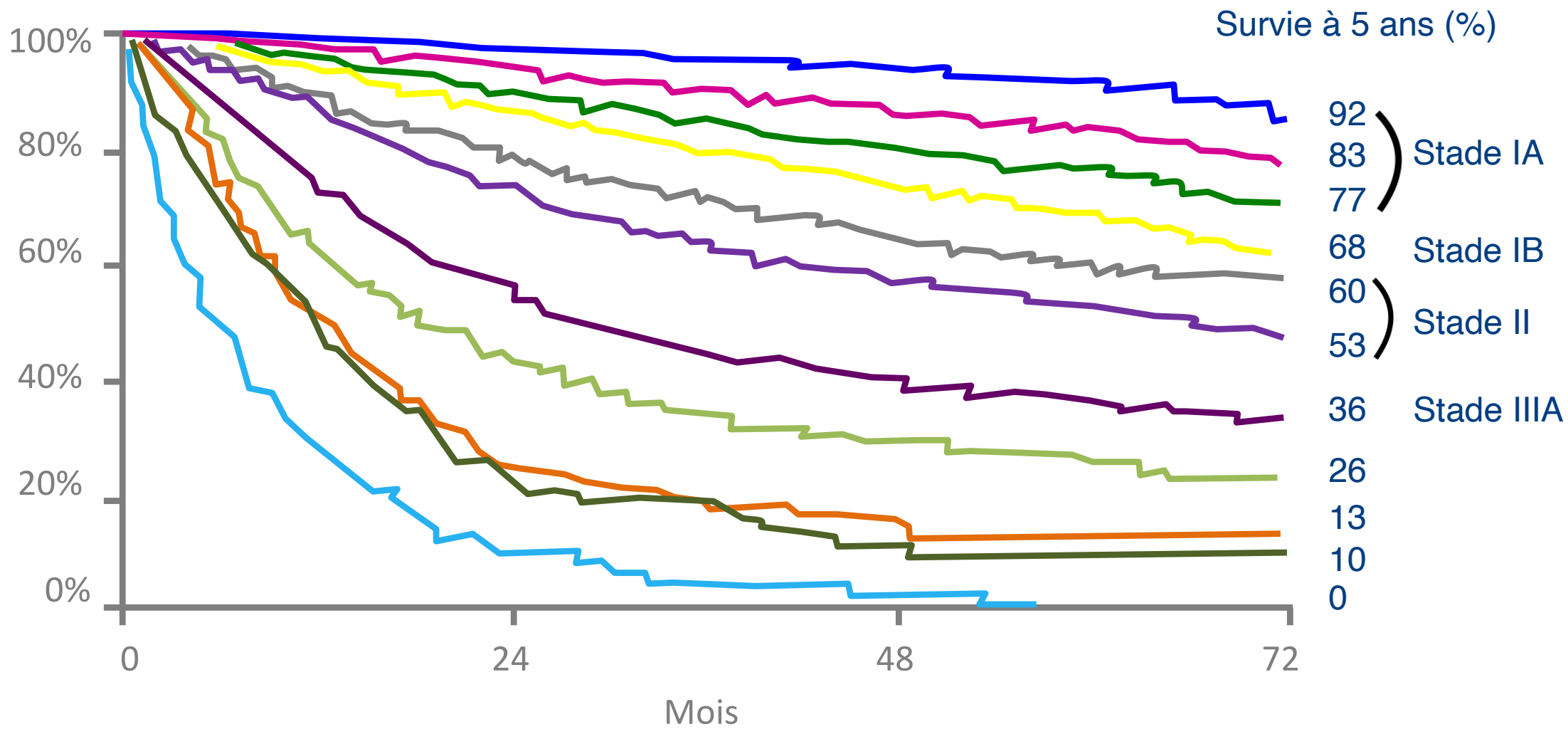
→ 18% des CBNPC en France

→ Taux de récurrence élevé : 45 à 76% pour les stades IB-III

Stade au diagnostic (CBNPC)



Contexte de l'étude



Contexte de l'étude

- CBNPC opéré : taux de récurrence élevé
 - survie globale stade IB 68 % stade IIIA 36%
- Bénéfice réel mais modéré de la chimiothérapie : +5% de survie globale à 5 ans
- Bénéfice de l'immunothérapie dans le CBNPC stade III et IV et III
 - quel effet en situation péri-opératoire ?

Contexte de l'étude

	ADJUVANT		NEOADJUVANT
	IMPOWER 010	KEYNOTE 091	CHECKMATE 816
n	1005 (60% st. III)	1177 (30% st. III)	358 (63% st. III)
Attrition (CT adj ou Chir)	20% non randomisés	>750 screen-fail 14% sans CT	83% opérés (75% avec Pbo)
1-yr EFS	71% (vs 64%)	À 18 mois ; 73% (vs. 64%)	76% (vs 63%)
2-yr EFS	58% (vs 53%)		64% (vs 45%)
MPR / PCR			37% / 24% (vs 9% / 2%)
OS	?	À 18 mois ; 91,7% (vs. 91,3%)	1-yr : 90% (vs 90%) 2-yr : 83% (vs 71%)
Gr 5 TRAE	2% (vs 1%)	0,7% (vs. 0%)	0% (vs 1,7%)

Contexte de l'étude

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2-yr EFS	58% (vs 53%)		64% (vs 45%)
MPR / PCR			37% / 24% (vs 9% / 2%)
OS	St II-III, PD-L1≥50% +15% OS à 4 ans	À 18 mois ; 91,7% (vs. 91,3%)	1-yr : 90% (vs 90%) 2-yr : 83% (vs 71%)
Gr 5 TRAE	2% (vs 1%)	0,7% (vs. 0%)	0% (vs 1,7%)



Objectif :

Démontrer la supériorité d'un traitement néo-adjuvant par chimiothérapie + Pembrolizumab, puis d'un traitement par Pembrolizumab, par rapport à un traitement néo-adjuvant par chimiothérapie seule.



Méthodes



Méthodes - étude randomisée en double aveugle

Key Eligibility Criteria

- Pathologically confirmed, resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC v8
- No prior therapy
- Able to undergo surgery
- Provision of tumor sample for PD-L1 evaluation^a
- ECOG PS 0 or 1

~786
R 1:1

Pembrolizumab 200 mg IV Q3W
+
Cisplatin and Gemcitabine^b
or
Cisplatin and Pemetrexed^c
for up to 4 cycles

Surgery^d

Pembrolizumab 200 mg IV Q3W
for up to 13 cycles

Placebo IV Q3W
+
Cisplatin and Gemcitabine^b
or
Cisplatin and Pemetrexed^c
for up to 4 cycles

Surgery^d

Placebo IV Q3W
for up to 13 cycles

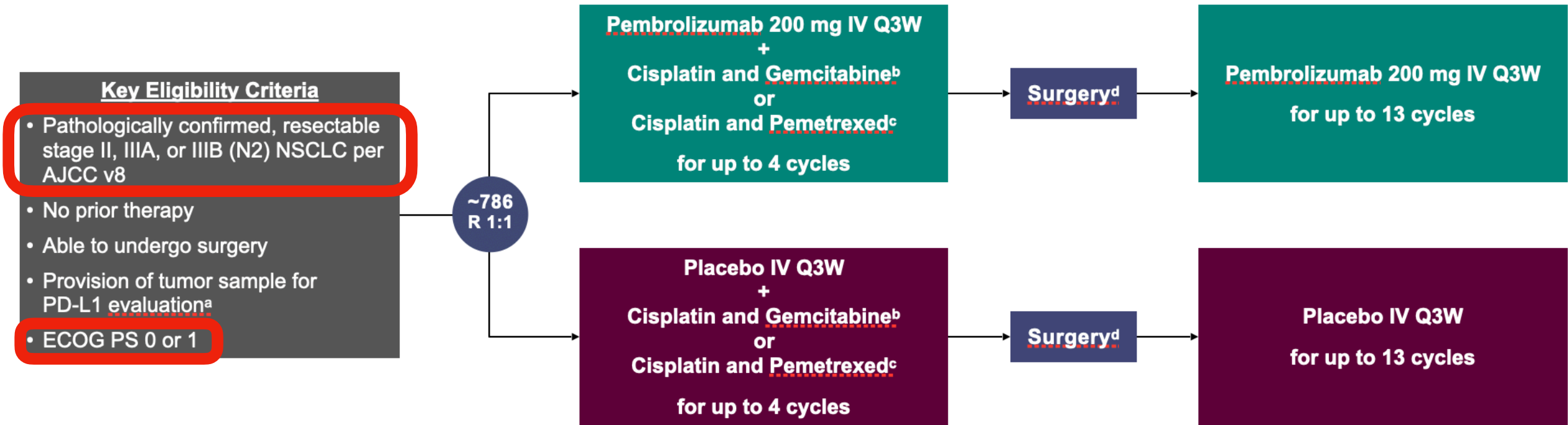
Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS^a (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

Méthodes - sélection des patients



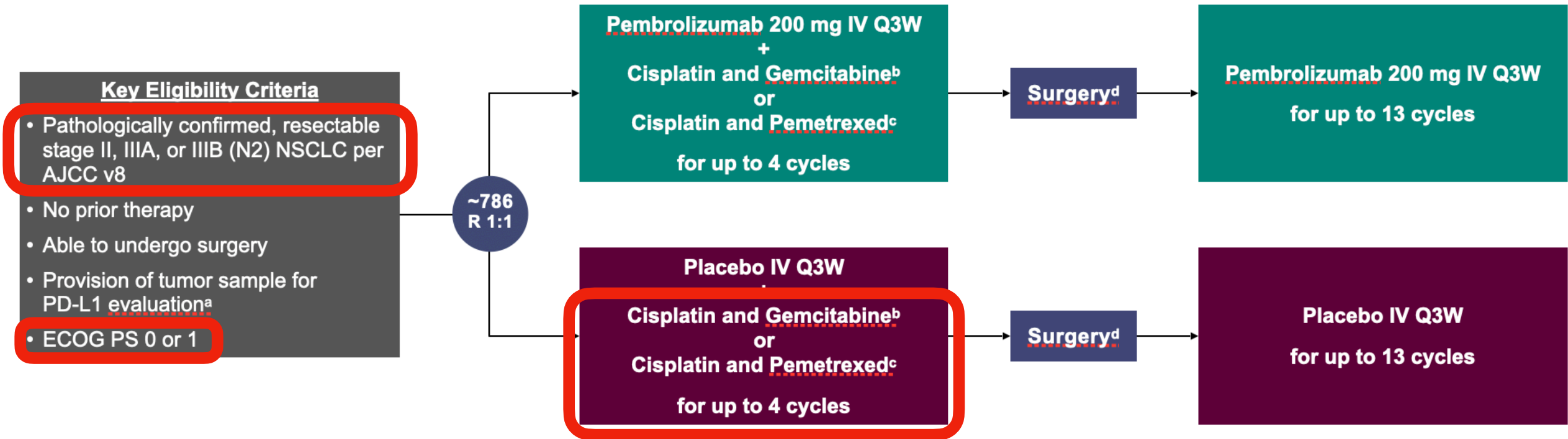
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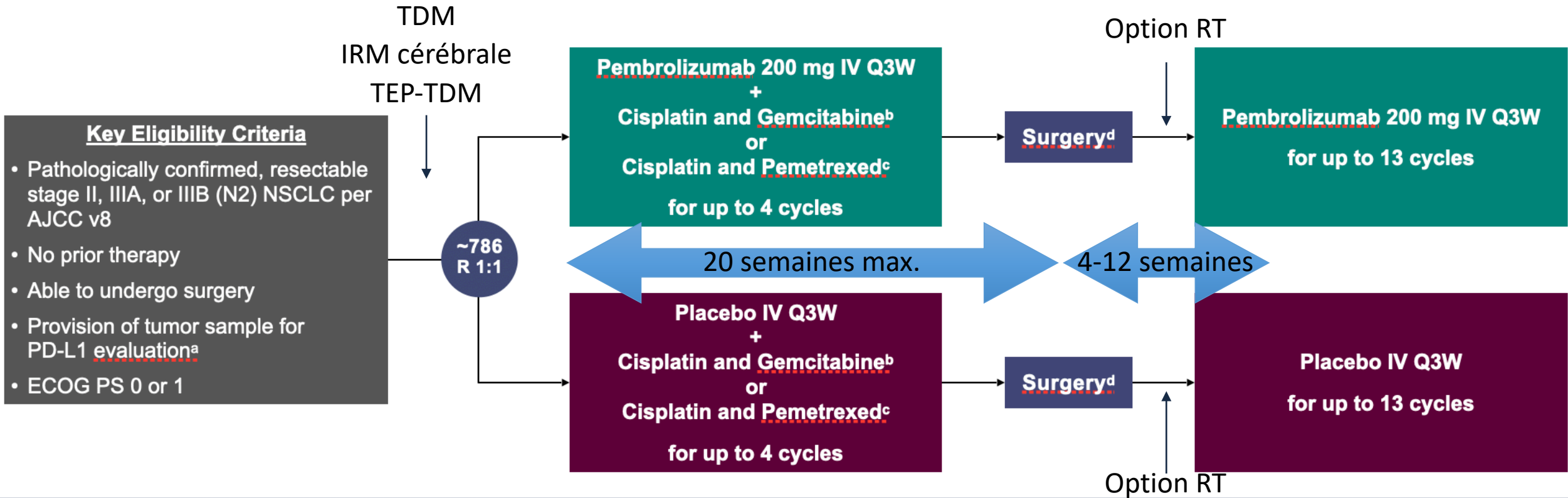
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Dual primary end points: EFS per investigator review and OS

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Méthodes - sélection des patients



Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

Méthodes - critères de jugements

Key Eligibility Criteria

- Pathologically confirmed, resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC v8
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~786
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Pembrolizumab 200 mg IV Q3W
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for up to 4 cycles

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or
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Surgery^d

Placebo IV Q3W
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Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS^a (<50% vs ≥50%)
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- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

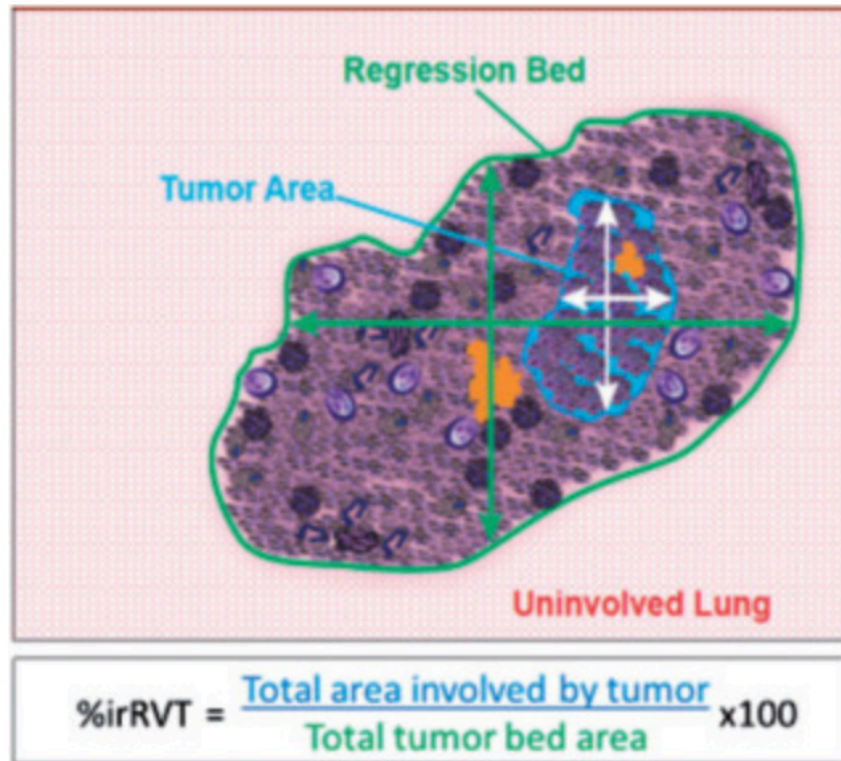
Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

Méthodes - critères de jugement

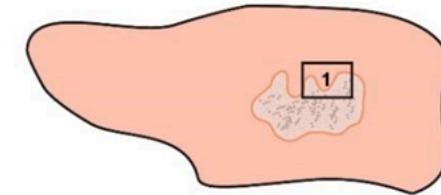
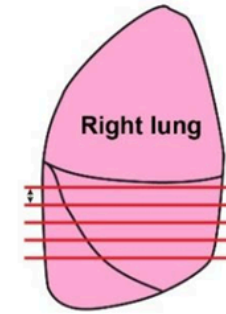
- EFS : Event-Free Survival, c'est à dire le temps entre la randomisation et :
 - Progression locale empêchant de réaliser la chirurgie
ou
 - Tumeur non résécable au moment de la chirurgie
ou
 - Progression (locale ou distance)
ou
 - Récidive (après la chirurgie)
ou
 - Décès

Méthodes - critères de jugement

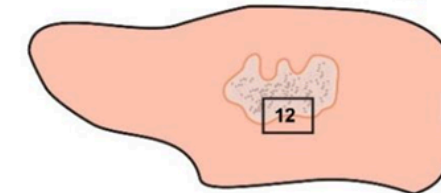
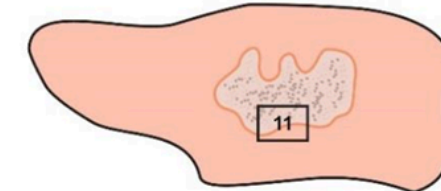
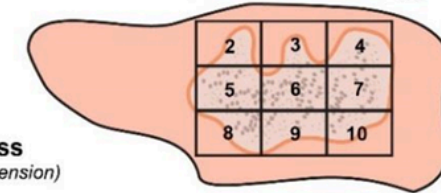
- Réponse pathologique (centralisée, en aveugle)



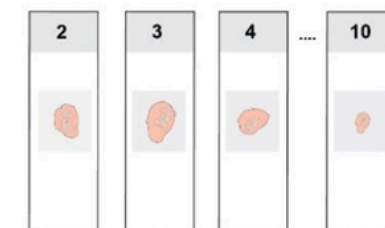
1 cm slices
of lung tissue



Tumor Mass
(4 cm greatest dimension)



Tumor sections for
pathologic response



Méthodes - statistiques (IA1)

- Résultats publiés = 1ère analyse intermédiaire (326 événements)
 - Seuil alpha pour EFS : 0,00462
 - Seuil alpha pour MPR : 0,0001
 - Seuil alpha pour CPR : 0,0001

 - Durée médiane de suivi : 25 mois (min 7,5 ; max 50,6)

Méthodes - statistiques (IA2)

- Résultats présentés à l'ESMO 2023 = 2ème analyse intermédiaire (416 événements)
 - Analyse finale de EFS : non testée au vu de l'IA1
 - Analyse intermédiaire de l'OS : 0,00543

 - Durée médiane de suivi : 36,6 mois (min 18,8 ; max 62)

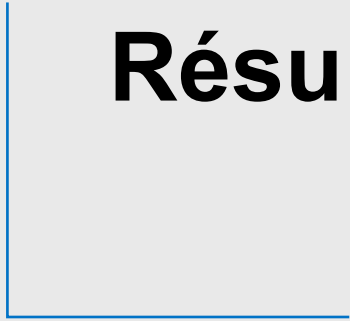


Méthodes





Résultats



Résultats

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N = 397)	Placebo Group (N = 400)
Age		
Median (range) — yr	63 (26–83)	64 (35–81)
<u>≥65 yr — no. (%)</u>	<u>176 (44.3)</u>	<u>186 (46.5)</u>
Male sex — no. (%)	279 (70.3)	284 (71.0)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	1 (0.3)	0
Asian	124 (31.2)	125 (31.2)
Black	6 (1.5)	10 (2.5)
Multiple	3 (0.8)	10 (2.5)
White	250 (63.0)	239 (59.8)
Missing data	13 (3.3)	16 (4.0)
Geographic region — no. (%)		
East Asia	123 (31.0)	121 (30.2)
Other	274 (69.0)	279 (69.8)
ECOG performance-status score — no. (%)‡		
0	253 (63.7)	246 (61.5)
1	144 (36.3)	154 (38.5)
Smoking status — no. (%)		
Current smoker	96 (24.2)	103 (25.8)
Former smoker	247 (62.2)	250 (62.5)
Never smoked	54 (13.6)	47 (11.8)

Résultats

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N=397)	Placebo Group (N=400)
Pathological stage at baseline — no. (%)		
II	118 (29.7)	121 (30.2)
III	279 (70.3)	279 (69.8)
III A	217 (54.7)	225 (56.2)
III B	62 (15.6)	54 (13.5)
Tumor stage — no. (%)		
T1	55 (13.9)	61 (15.2)
T2	106 (26.7)	126 (31.5)
T3	121 (30.5)	109 (27.2)
T4	115 (29.0)	104 (26.0)
Node stage — no. (%)		
N0	148 (37.3)	142 (35.5)
N1	81 (20.4)	71 (17.8)
N2	168 (42.3)	187 (46.8)
Histologic features — no. (%)		
Nonsquamous	226 (56.9)	227 (56.8)
Squamous	171 (43.1)	173 (43.2)
PD-L1 tumor proportion score — no. (%)		
≥50%	132 (33.2)	134 (33.5)
<50%	265 (66.8)	266 (66.5)
1–49%	127 (32.0)	115 (28.8)
<1%	138 (34.8)	151 (37.8)

Amendement 07/2019
Inclusion des IIIB

Résultats

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Characteristic	Pembrolizumab Group (N=397)	Placebo Group (N=400)
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<1%	138 (34.8)	151 (37.8)

Amendement 07/2019
Inclusion des IIIB

EGFR : 3,5% vs 4,8%
Inconnu pour 63-68%
ALK : 3,0% vs 2%
Inconnu pour 65-70%

Résultats

		Pembrolizumab Group	Placebo Group
Screening	Patients screened	1364	
	Randomized (intention-to-treat population)	397	400
↓			
Neoadjuvant Treatment	Received ≥1 dose of neoadjuvant treatment (as-treated population)	396	399
	Completed 4 cycles of pembrolizumab or placebo	295 (74.5%)	297 (74.4%)
	Completed ≥3 cycles of pembrolizumab or placebo	346 (87.4%)	348 (87.2%)
	Continued to surgery and/or radiotherapy	342 (86.4%)	335 (84.0%)
	Discontinued all study therapy permanently	54 (13.6%)	64 (16.0%)
↓			
In-Study Surgery and/or In-Study Radiotherapy*	Underwent in-study surgery	325 (82.1%)	317 (79.4%)
	Underwent in-study radiotherapy	35 (8.8%)	53 (13.3%)
	Discontinued all study therapy permanently following surgery	45 (11.4%)	60 (15.0%)
	Discontinued all study therapy permanently following radiotherapy	7 (1.8%)	8 (2.0%)
↓			
Adjuvant Treatment	Received ≥1 dose of adjuvant treatment	290 (73.2%)	267 (66.9%)
	Completed adjuvant treatment	160 (40.4%)	141 (35.3%)
	Discontinued adjuvant treatment	88 (22.2%)	81 (20.3%)
	Adjuvant treatment ongoing	42 (10.6%)	45 (11.3%)

Résultats

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	Adjuvant treatment ongoing	42 (10.6%)	45 (11.3%)

Résultats - patients n'ayant pas été opérés

	Pembrolizumab Group (N = 397)	Placebo Group (N = 400)
	<i>no. (%)</i>	
No in-study surgery	71 (17.9)	82 (20.5)
<u>Adverse event</u>	25 (6.3)	17 (4.2)
Clinical progression*	1 (0.3)	1 (0.2)
<u>Local progression</u> preventing surgery	0	6 (1.5)
New non-study anticancer therapy	0	1 (0.2)
Participant refusal	4 (1.0)	3 (0.8)
Physician decision	16 (4.0)	20 (5.0)
<u>Progressive disease</u> †	15 (3.8)	26 (6.5)
Withdrawal of consent	10 (2.5)	8 (2.0)

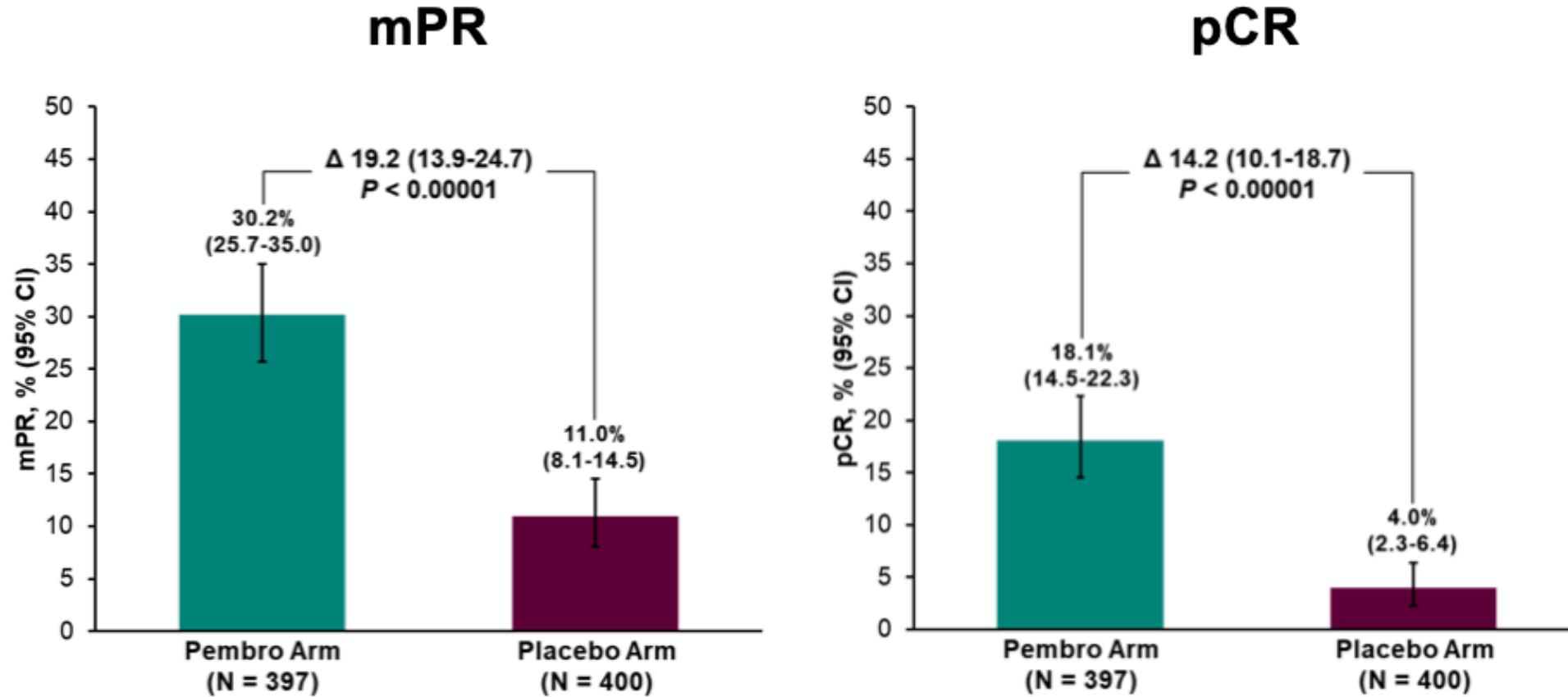
*Worsening of clinical status felt to be related to disease progression in the absence of radiographic evidence of disease progression.

†Radiographic disease progression.

Résultats - Chirurgie

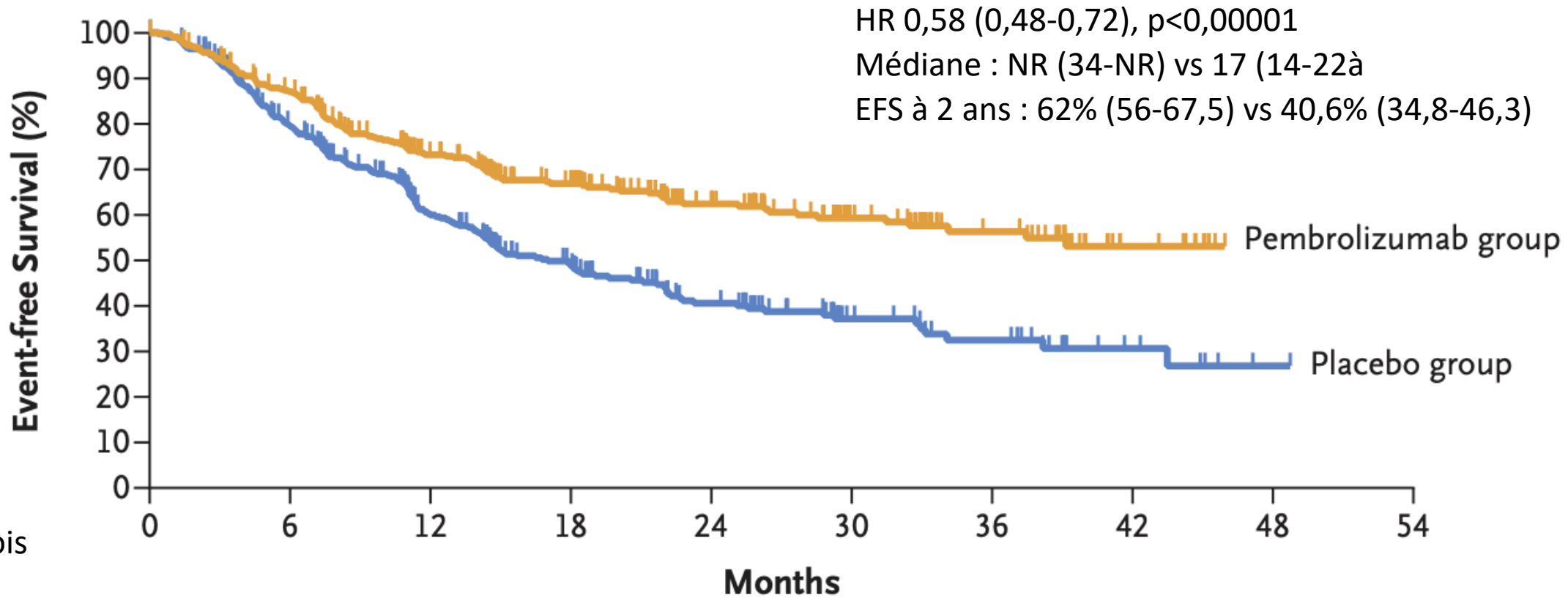
	Pembrolizumab Group (N = 325)	Placebo Group (N = 317)
	<i>no. (%)</i>	
Lobectomy	256 (78.8)*	238 (75.1)†
Bilobectomy	26 (8.0)	26 (8.2)
Pneumonectomy	37 (11.4)	39 (12.3)
Exploratory thoracotomy	4 (1.2)	13 (4.1)
Segmentectomy	1 (0.3)	0
Wedge resection	1 (0.3)	0
Lymph node dissection only	0	1 (0.3)‡

Résultats - Réponse pathologique



Résultats - Survie sans événement (IA1)

IA 1

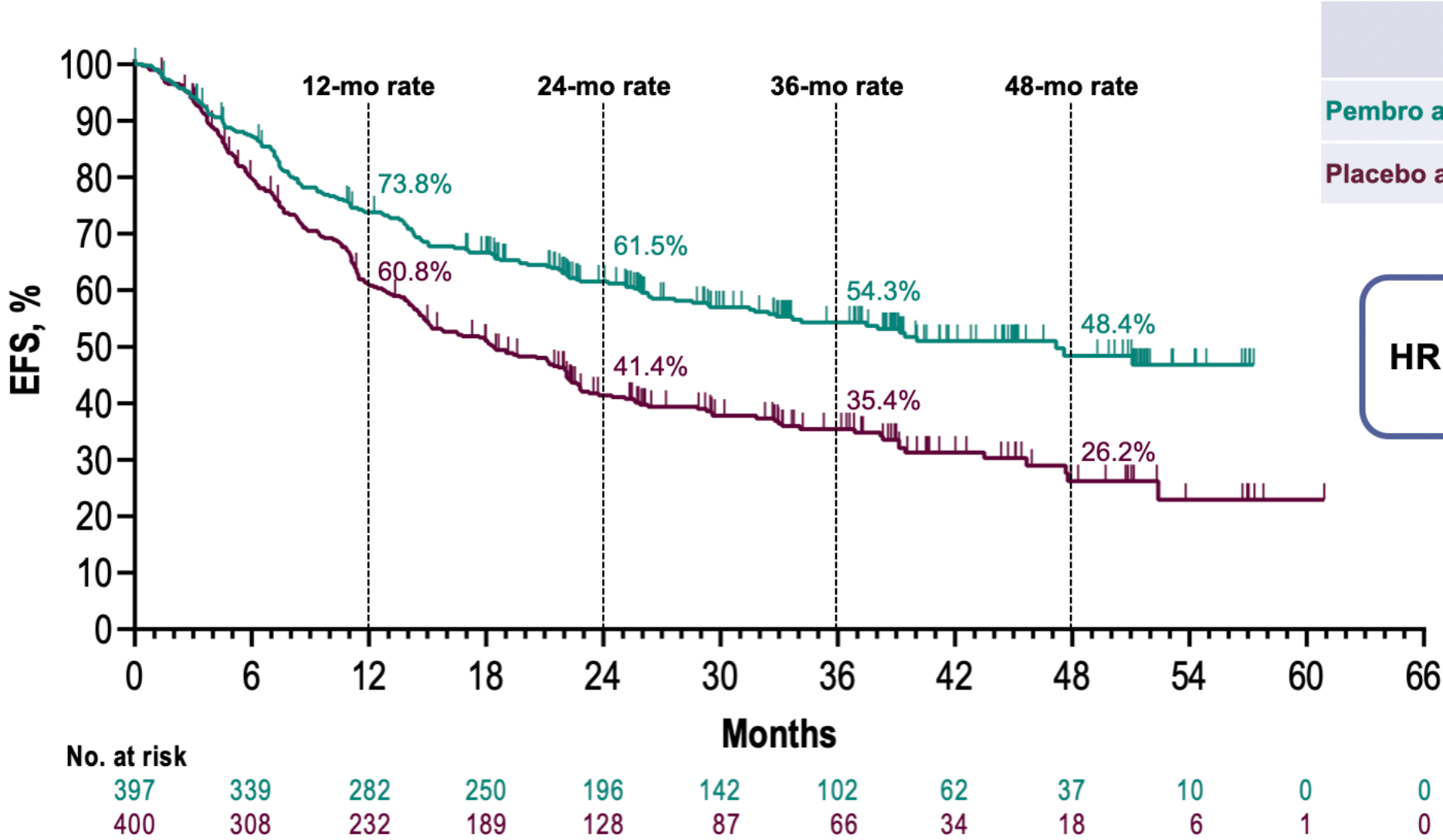


Suivi médian 24 mois

No. at Risk

Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0

Résultats - Survie sans événement (IA2)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

HR 0.59 (95% CI, 0.48-0.72)

Suivi médian 36 mois

Résultats - Types d'événements

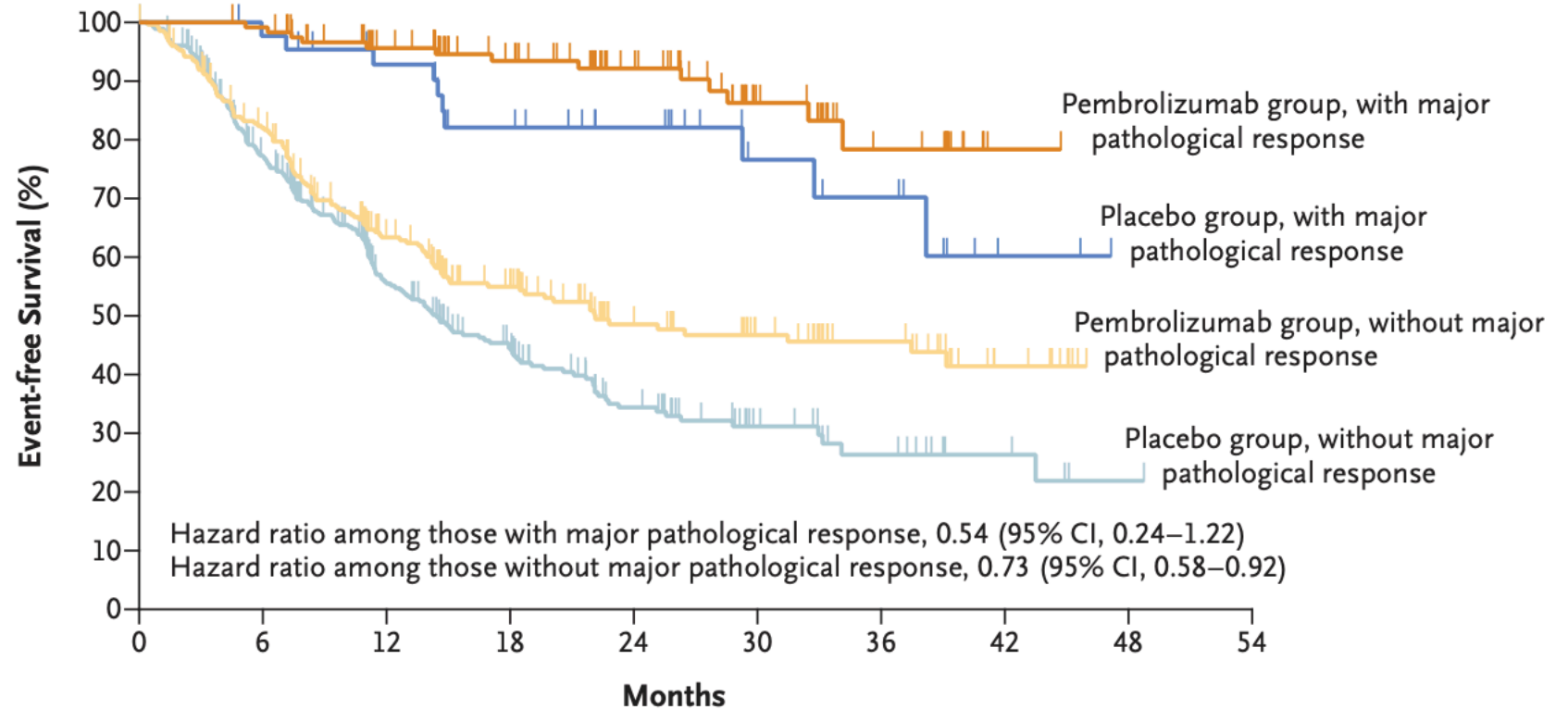
	Pembrolizumab Group (N = 397)	Placebo Group (N = 400)
	<i>no. (%)</i>	
<u>No event</u>	258 (65.0)	195 (48.8)
<u>Event</u>	139 (35.0)	205 (51.2)
<u>Disease progression or recurrence</u>	94 (23.7)	155 (38.8)
Local disease progression preventing surgery	0	6 (1.5)
<u>Inability to resect the tumor</u>	5 (1.3)	15 (3.8)
<u>Death</u>	40 (10.1)	29 (7.2)

Résultats

Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)	
	<i>no. of events/no. of participants</i>			
All patients	139/397	205/400		0.58 (0.46–0.72)
Age				
<65 yr	74/221	113/214		0.53 (0.39–0.71)
≥65 yr	65/176	92/186		0.64 (0.46–0.88)
Sex				
Female	31/118	55/116		0.44 (0.28–0.68)
Male	108/279	150/284		0.63 (0.49–0.80)
Race				
White	85/250	123/239		0.54 (0.41–0.72)
Other	46/134	70/145		0.62 (0.42–0.89)
Geographic region				
East Asia	43/123	57/121		0.66 (0.45–0.99)
Other	96/274	148/279		0.54 (0.41–0.69)
Smoking status				
Current smoker	37/96	57/103		0.52 (0.34–0.78)
Former smoker	84/247	128/250		0.57 (0.43–0.75)
Never smoked	18/54	20/47		0.68 (0.36–1.30)
Pathological stage				
II	34/118	48/121		0.65 (0.42–1.01)
III	105/279	157/279		0.54 (0.42–0.70)
Histologic features				
Nonsquamous	73/226	107/227		0.58 (0.43–0.78)
Squamous	66/171	98/173		0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)				
<50%	107/265	142/266		0.64 (0.49–0.82)
≥50%	32/132	63/134		0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)				
<1%	63/138	80/151		0.77 (0.55–1.07)
≥1%	76/259	125/249		0.47 (0.36–0.63)
PD-L1 TPS				
<1%	63/138	80/151		0.77 (0.55–1.07)
1–49%	44/127	62/115		0.51 (0.34–0.75)
≥50%	32/132	63/134		0.42 (0.28–0.65)

Résultats - EFS selon statut MPR

Event-free Survival According to Major Pathological Response



No. at Risk

With major pathological response

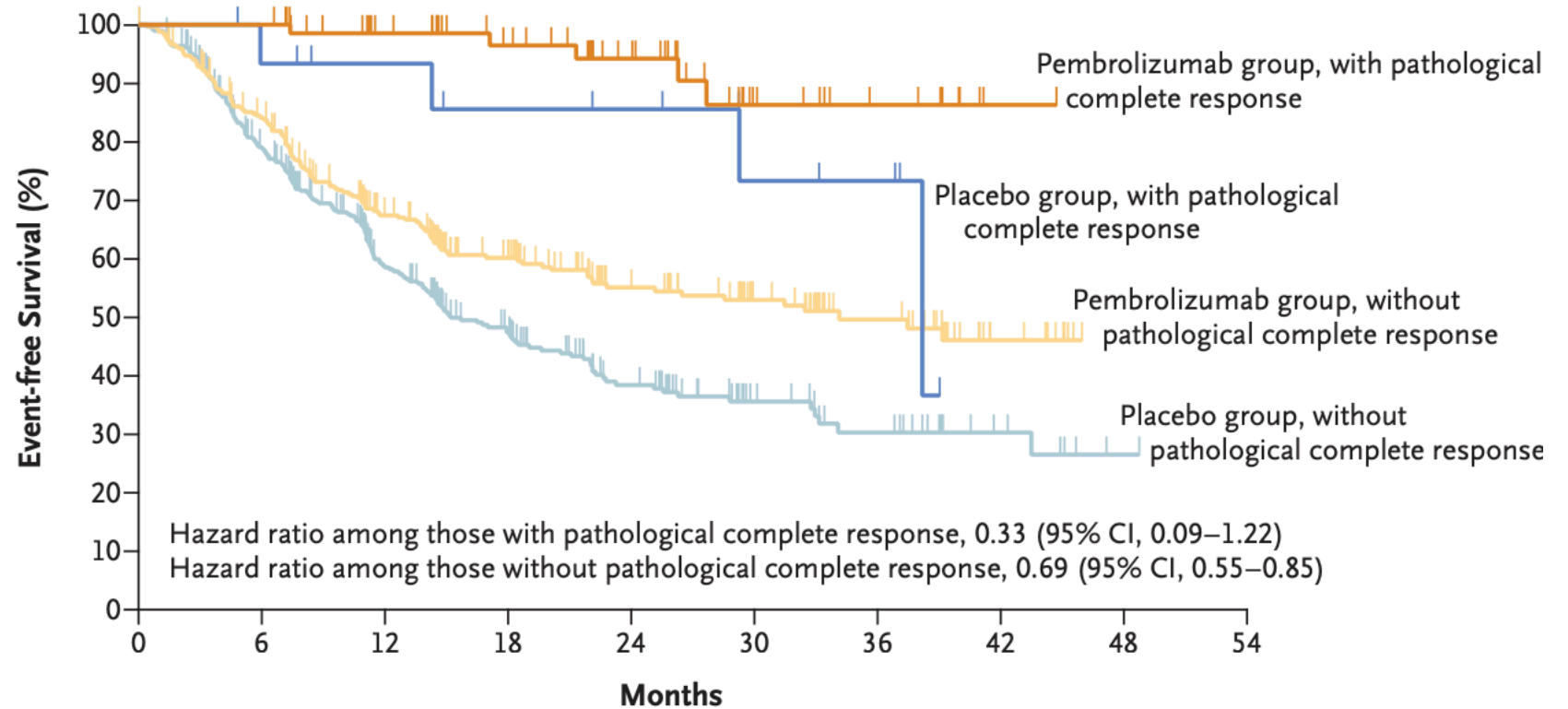
Pembrolizumab group	120	117	99	79	60	30	15	1	0	0
Placebo group	44	42	36	28	22	12	10	2	0	0

Without major pathological response

Pembrolizumab group	277	213	137	93	57	42	27	10	0	0
Placebo group	356	252	147	96	52	26	14	7	1	0

Résultats - EFS selon statut PCR

Event-free Survival According to Pathological Complete Response



No. at Risk

With pathological complete response										
	0	6	12	18	24	30	36	42	48	54
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

Résultats - Tolérance

Event	Pembrolizumab Group (N = 396)	Placebo Group (N = 399)
	<i>number of participants (percent)</i>	
Any treatment-related adverse event	383 (96.7)	379 (95.0)
Grade 3–5 treatment-related adverse event	178 (44.9)	149 (37.3)
Serious treatment-related adverse event	70 (17.7)	57 (14.3)
Treatment-related adverse event that led to death	4 (1.0) [†]	3 (0.8) [‡]
Treatment-related adverse event that led to discontinuation of all trial treatment	50 (12.6)	21 (5.3)

Résultats - Tolérance

Table S7. Treatment-Related Adverse Events that Occurred During the Neoadjuvant/Surgery Treatment Phase (As-Treated Population)

	Pembrolizumab Group (N = 396)	Placebo Group (N = 399)
	<i>no. (%)</i>	
Any treatment-related adverse event	379 (95.7)	374 (93.7)
Grade 3-5	161 (40.7)	146 (36.6)
Serious	56 (14.1)	52 (13.0)
Led to death	3 (0.8)*	3 (0.8)†

Table S8. Treatment-Related Adverse Events that Occurred During the Adjuvant Treatment Phase (As-Treated Population)

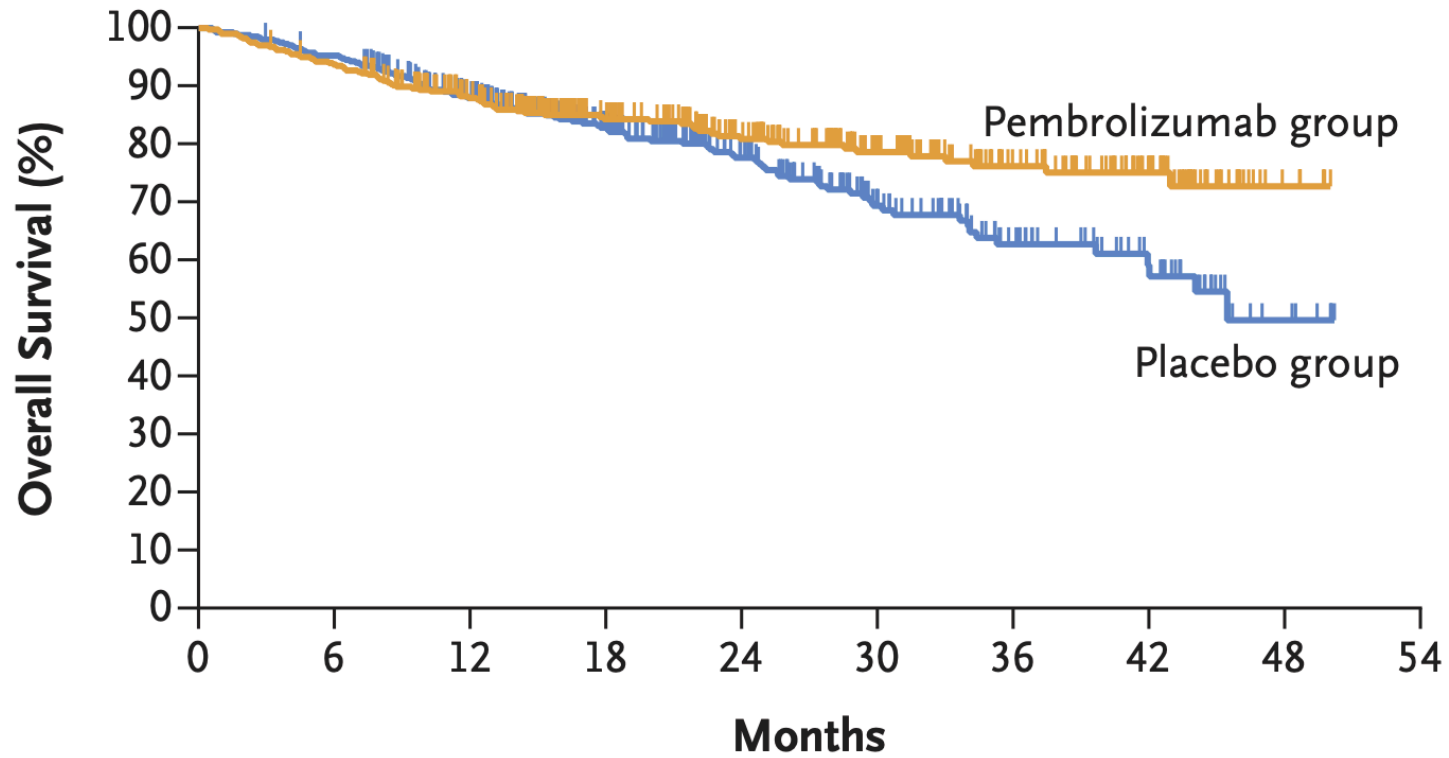
	Pembrolizumab Group (N = 290)	Placebo Group (N = 267)
	<i>no. (%)</i>	
Any treatment-related adverse event	158 (54.5)	85 (31.8)
Grade 3-5	29 (10.0)	15 (5.6)
Serious	16 (5.5)	7 (2.6)
Led to death	1 (0.3)*	0

Résultats - Tolérance

Table S10. Causes of All-Cause Mortality in the Post-Operative Period (Participants Who Underwent In-Study Surgery)

	Pembrolizumab Group (N = 325)	Placebo Group (N = 317)
	<i>no. (%)</i>	
Any death within 30 days of surgery^a	6 (1.8)	2 (0.6)
Pulmonary embolism	2 (0.6)	0
Pulmonary hemorrhage due to arterial injury during surgery	1 (0.3)	0
Pulmonary sepsis	1 (0.3)	0
Respiratory failure	1 (0.3)	1 (0.3)
Septic shock	1 (0.3)	0
Pneumonia	0	1 (0.3)
Any death within 31-90 days of surgery^b	7 (2.2)	3 (0.9)
<u>Malignant neoplasm progression</u> ?	3 (0.9)	1 (0.3)
Cardiac arrest	1 (0.3)	0
Pulmonary hemorrhage	1 (0.3)	0
Immune-mediated lung disease	1 (0.3)	0
Unexplained death ^c	1 (0.3)	0
Acute respiratory failure	0	1 (0.3)
Septic shock	0	1 (0.3)

Résultats - Survie globale (IA1)

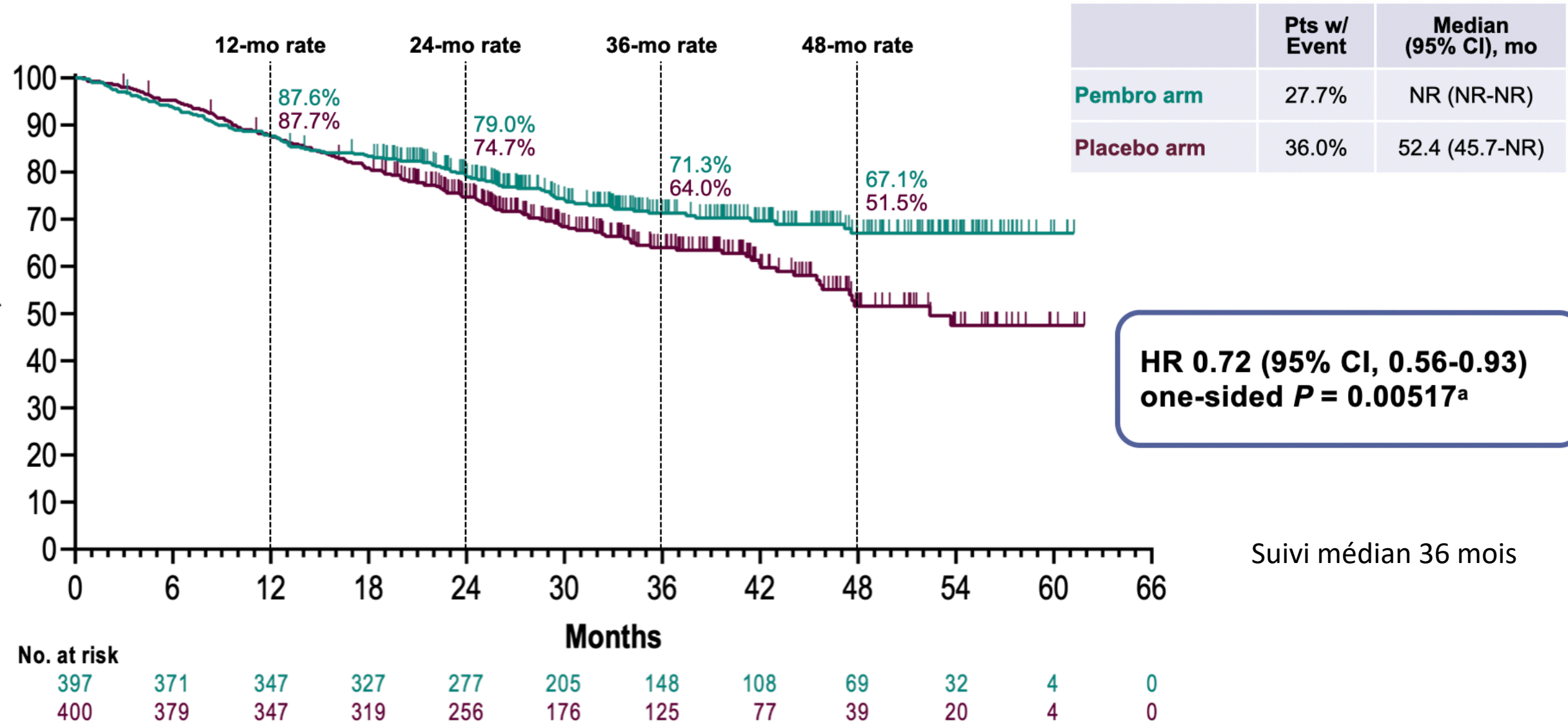


Suivi médian 24 mois

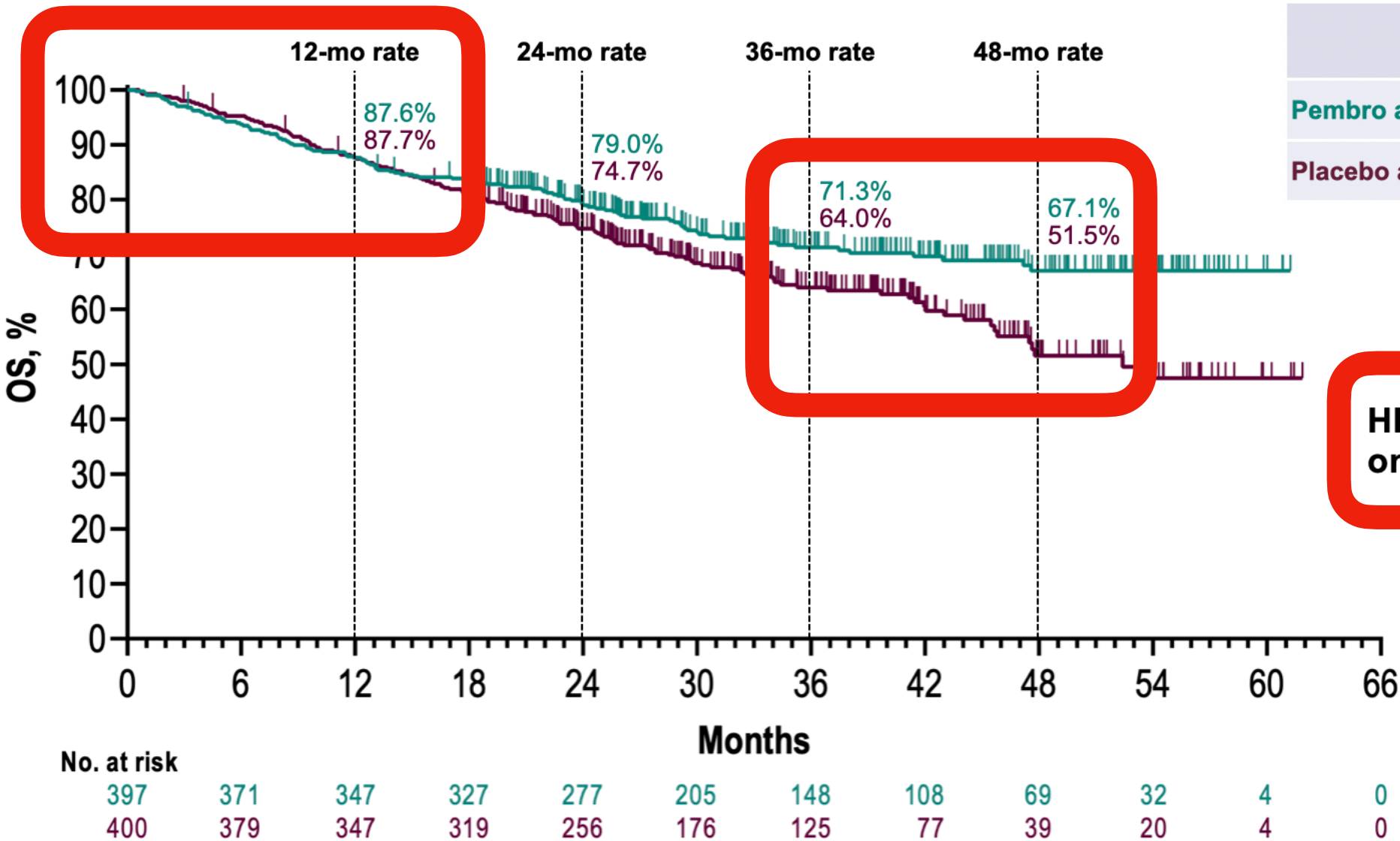
No. at Risk

Pembrolizumab group	397	370	313	232	170	118	76	41	5	0
Placebo group	400	379	316	225	153	91	54	30	6	0

Résultats - survie globale (IA2)



Résultats - survie globale (IA2)



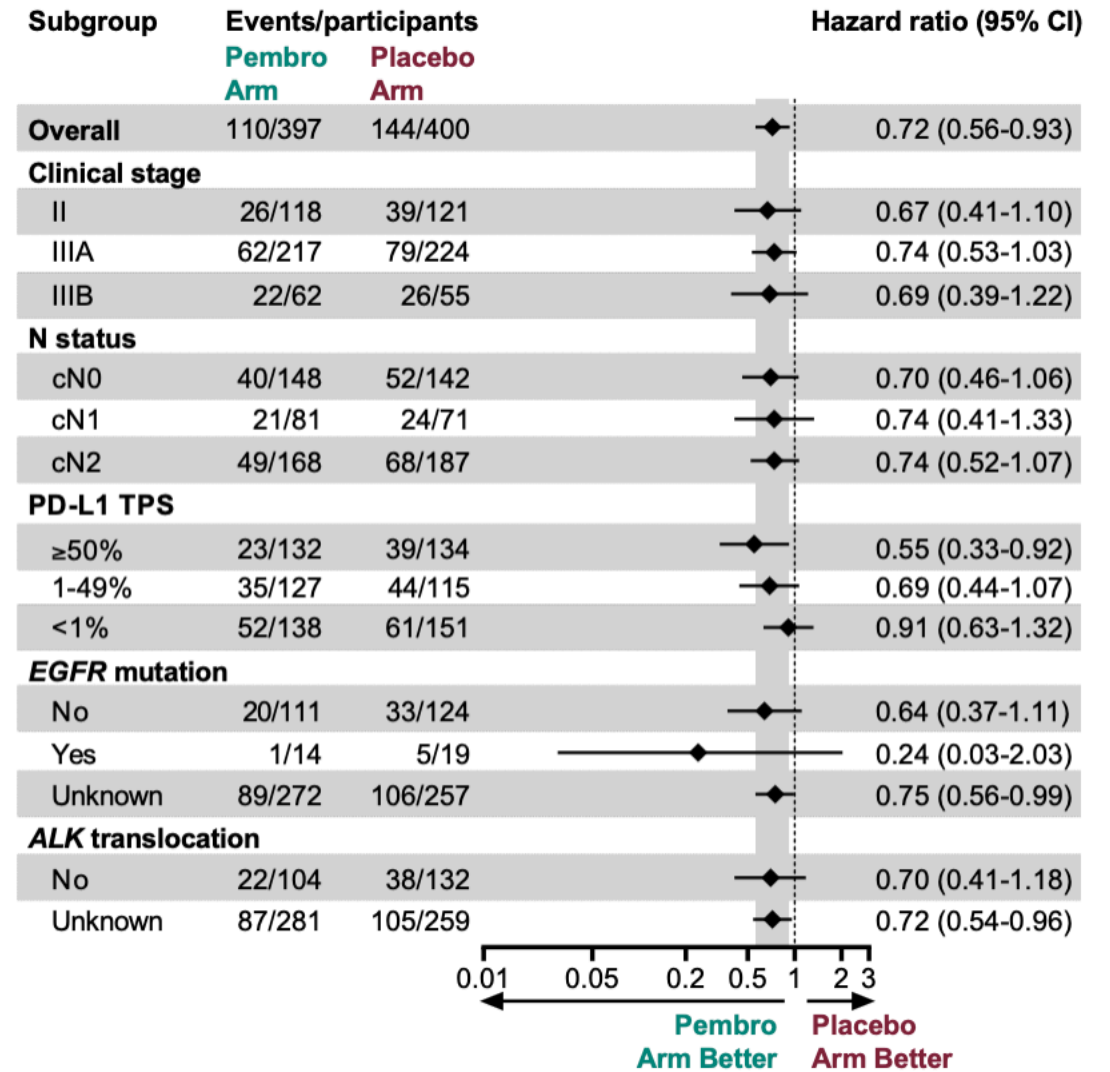
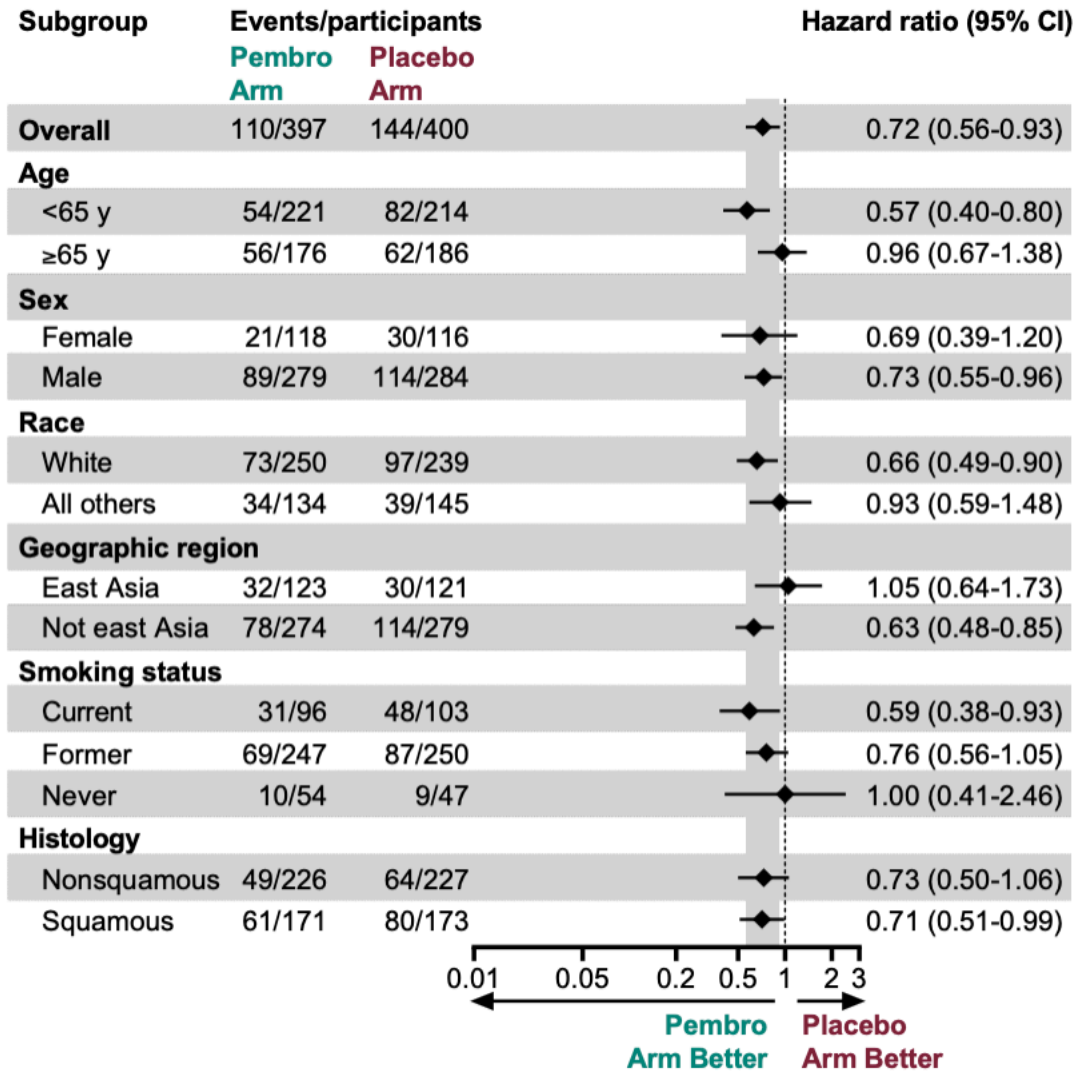
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

**HR 0.72 (95% CI, 0.56-0.93)
 one-sided P = 0.00517^a**

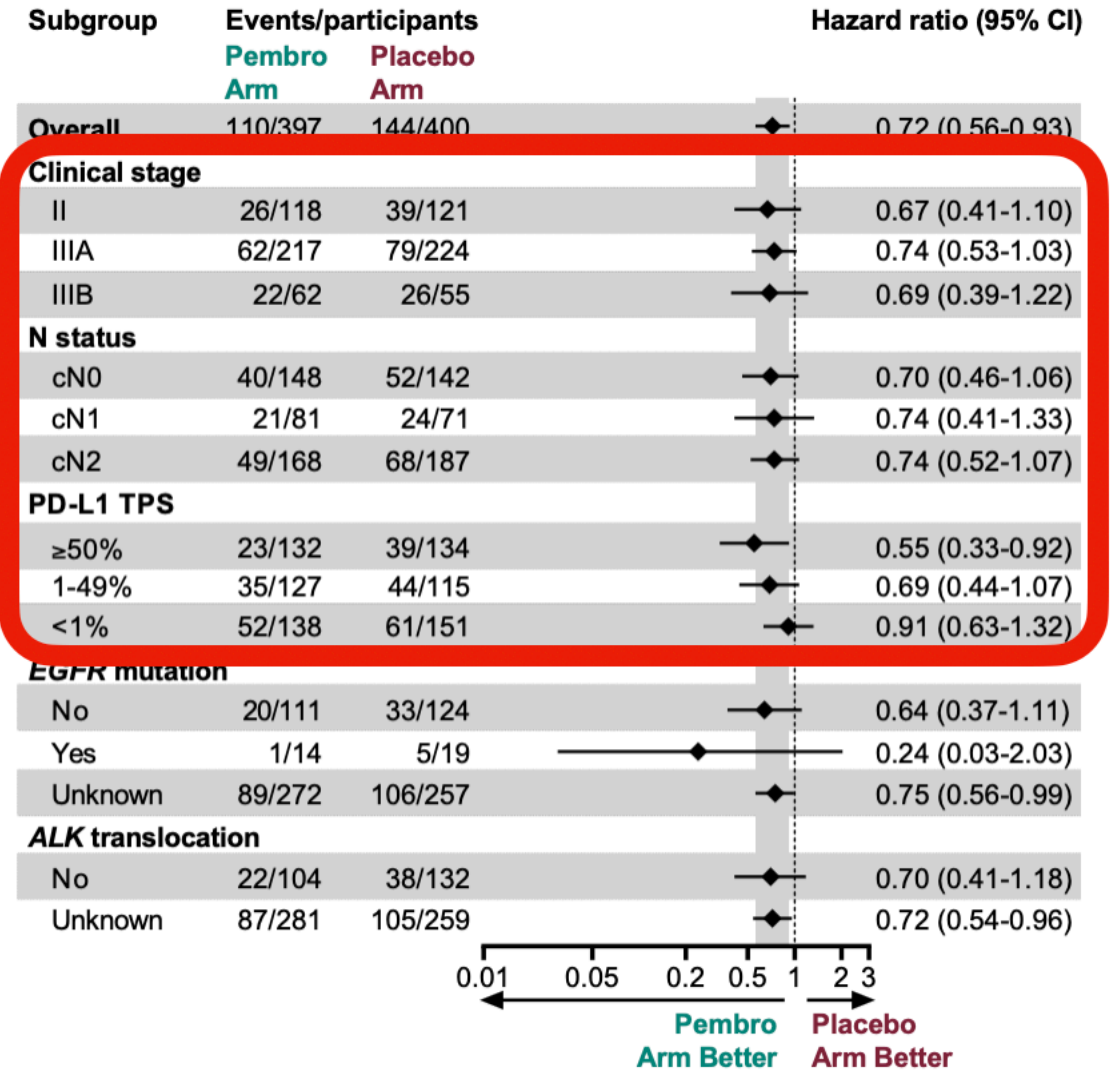
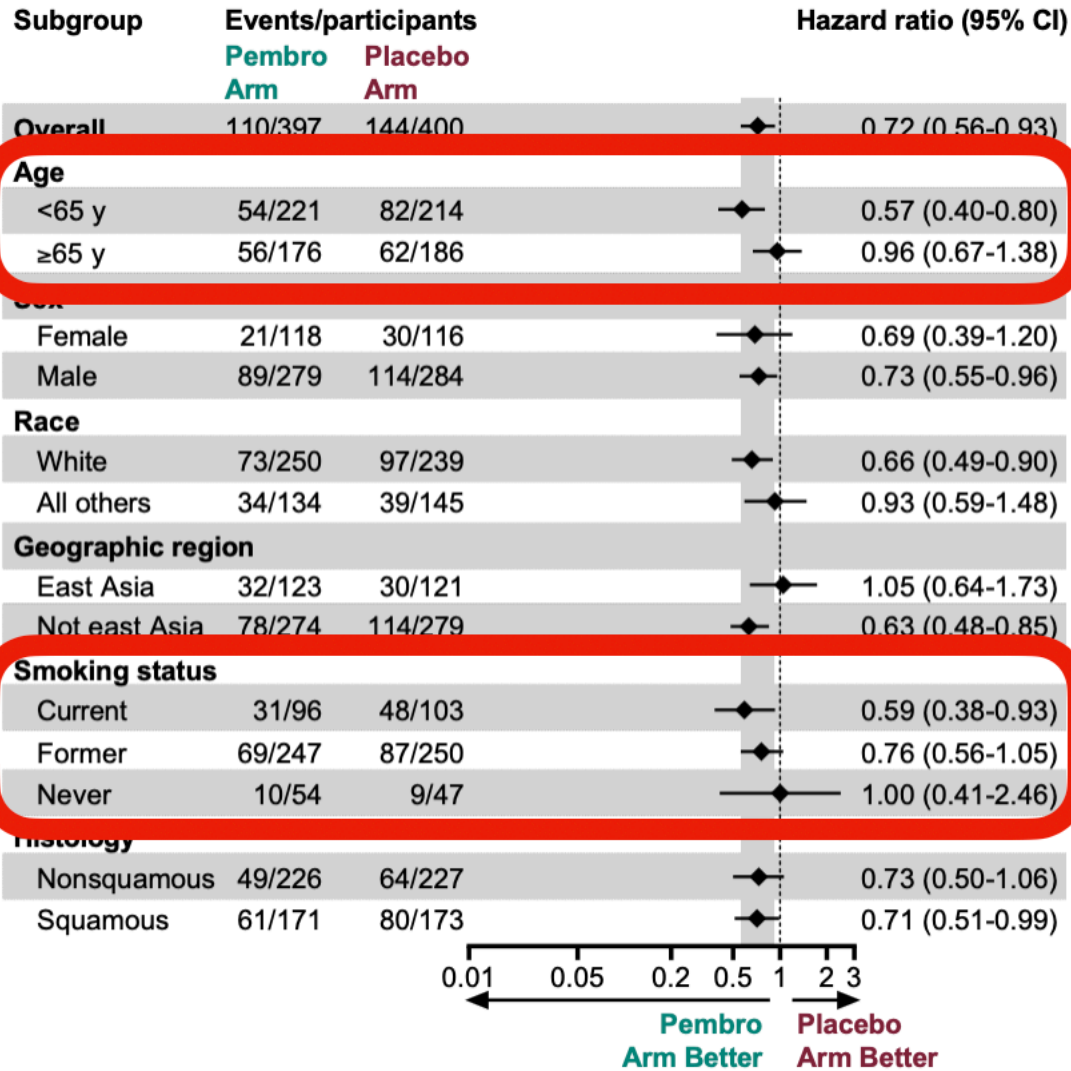
Suivi médian 36 mois

Seuil alpha=0,00543

Résultats

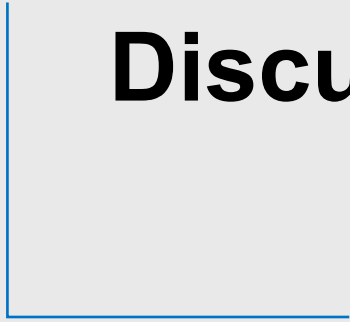


Résultats





Discussion



Discussion - conclusion

- Essai de phase 3, randomisé contre placebo
 - Démonstration d'un bénéfice statistiquement significatif sur l'EFS et l'OS

Discussion - points de vigilance

- Essai de phase 3, randomisé contre placebo
 - Démonstration d'un bénéfice statistiquement significatif sur l'EFS et l'OS


→  20% de patients non opérés

→  20% de mortalité pendant la phase de traitement dans les 2 bras

Discussion

- Essai de phase 3, randomisé contre placebo
 - Démonstration d'un bénéfice statistiquement significatif sur l'EFS et l'OS

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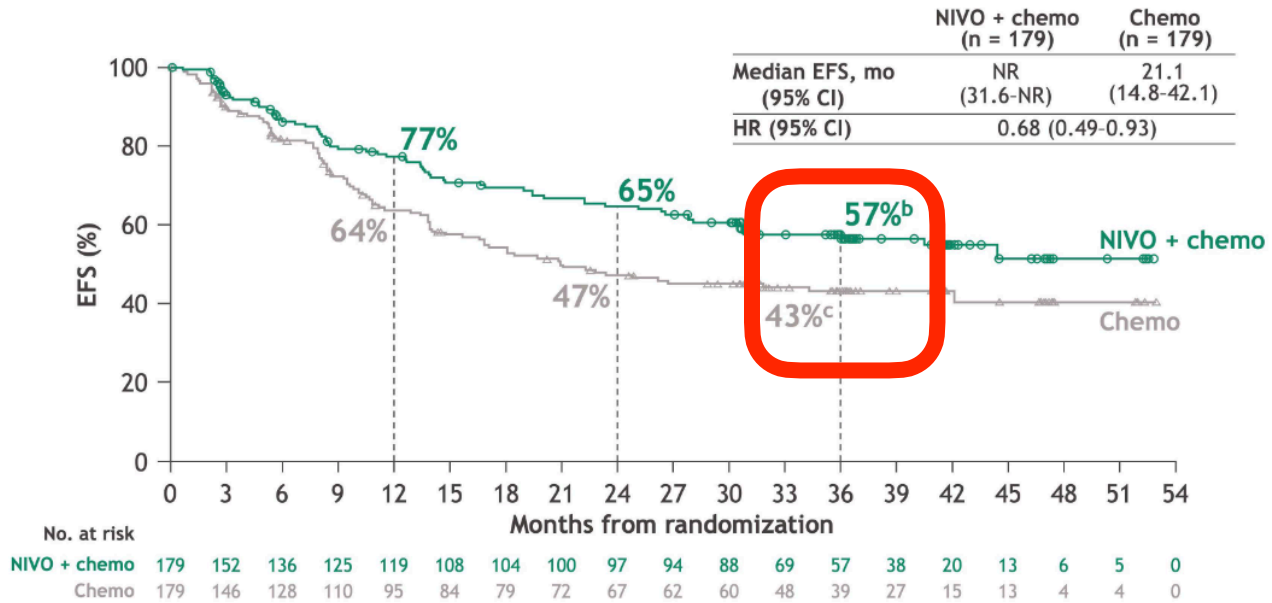
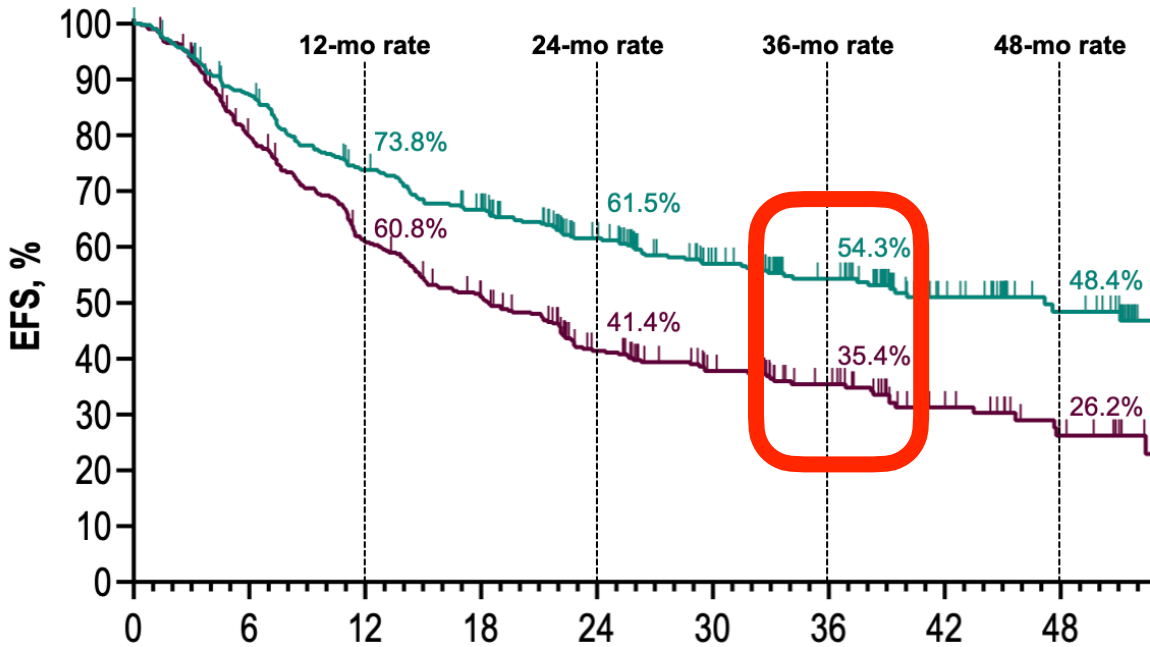
→ Causes de mortalité chez les ≥ 65 ans ?

→ **Effet de la phase adjuvante ?**

Discussion

KN671

CM816



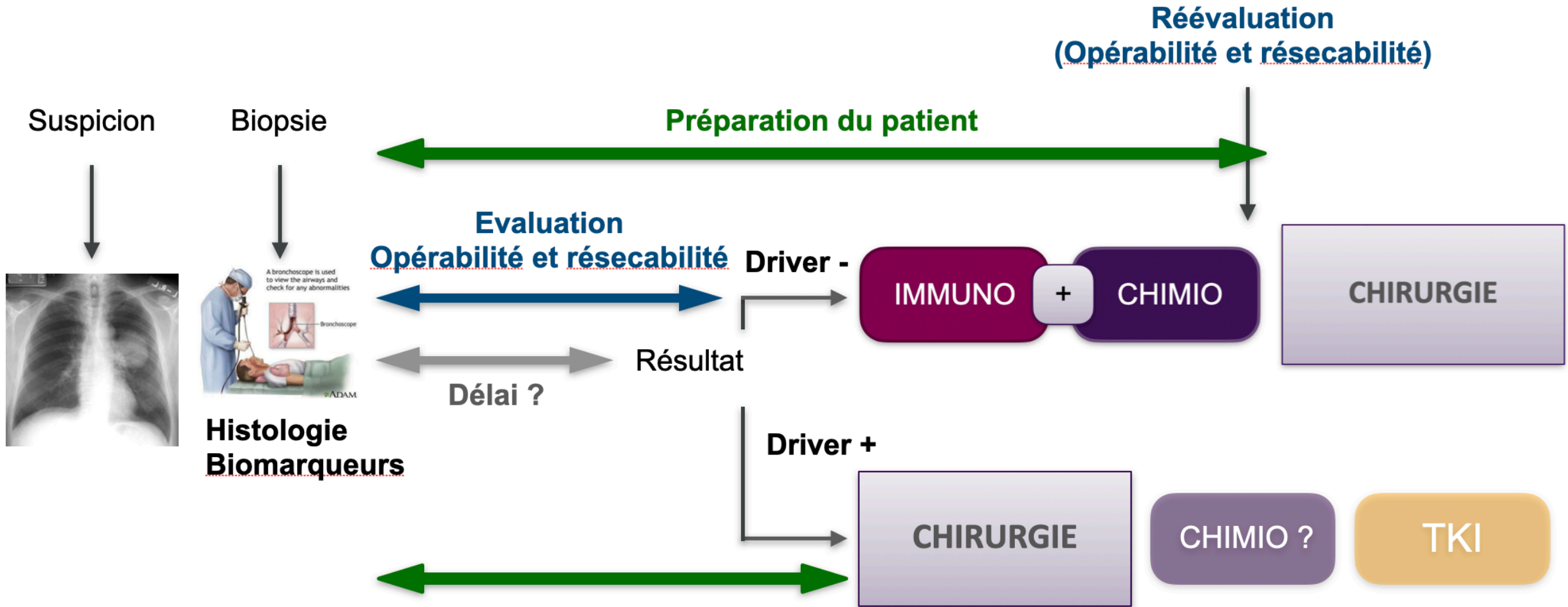
Discussion

	ADJUVANT		NEOADJUVANT	NEOADJUVANT + ADJUVANT			
	IMPOWER 010	KEYNOTE 091	CHECKMATE 816	AEGEAN	KEYNOTE 671	CHECKMATE 77T	NEOTORCH
n	1005 (60% st. III)	1177 (30% st. III)	358 (63% st. III)	802 (70% st. III)	786 (70% st. III)	461 (64% st. III)	500 (100% st. III ?)
Attrition (CT adj ou Chir)	20% non randomisés	>750 screen-fail 14% sans CT	83% opérés (75% avec Pbo)	81% opérés (81% avec Pbo)	82% opérés (79% avec Pbo)	78% opérés (77% avec Pbo)	82% opérés (73% avec Pbo)
1-yr EFS	71% (vs 64%)	À 18 mois ; 73% (vs. 64%)	76% (vs 63%)	73% (vs 64%)	73% (vs 59%)	73% (vs 59%)	81% (vs 56%)
2-yr EFS	58% (vs 53%)		64% (vs 45%)	63% (vs 52%)	62% (vs 41%)	?	67% (vs 46%)
MPR / PCR			37% / 24% (vs 9% / 2%)	33% / 17% (vs 12% / 4%)	30% / 18% (vs 11% / 4%)	35% / 25% (vs 12% / 5%)	48% / 25% (vs 8% / 1%)
OS	St II-III, PD-L1≥50% +15% OS à 4 ans	À 18 mois ; 91,7% (vs. 91,3%)	1-yr : 90% (vs 90%) 2-yr : 83% (vs 71%)	?	3-yr: 71% (vs 64%) 4-yr: 67% (vs 51%)	?	1-yr: 94% (vs 90%) 2-yr: 81% (vs 74%)
Gr 5 TRAE	2% (vs 1%)	0,7% (vs. 0%)	0% (vs 1,7%)	1,8% vs 0,5%	1% vs 0,8%	1% vs 0%	0,5% vs 0%

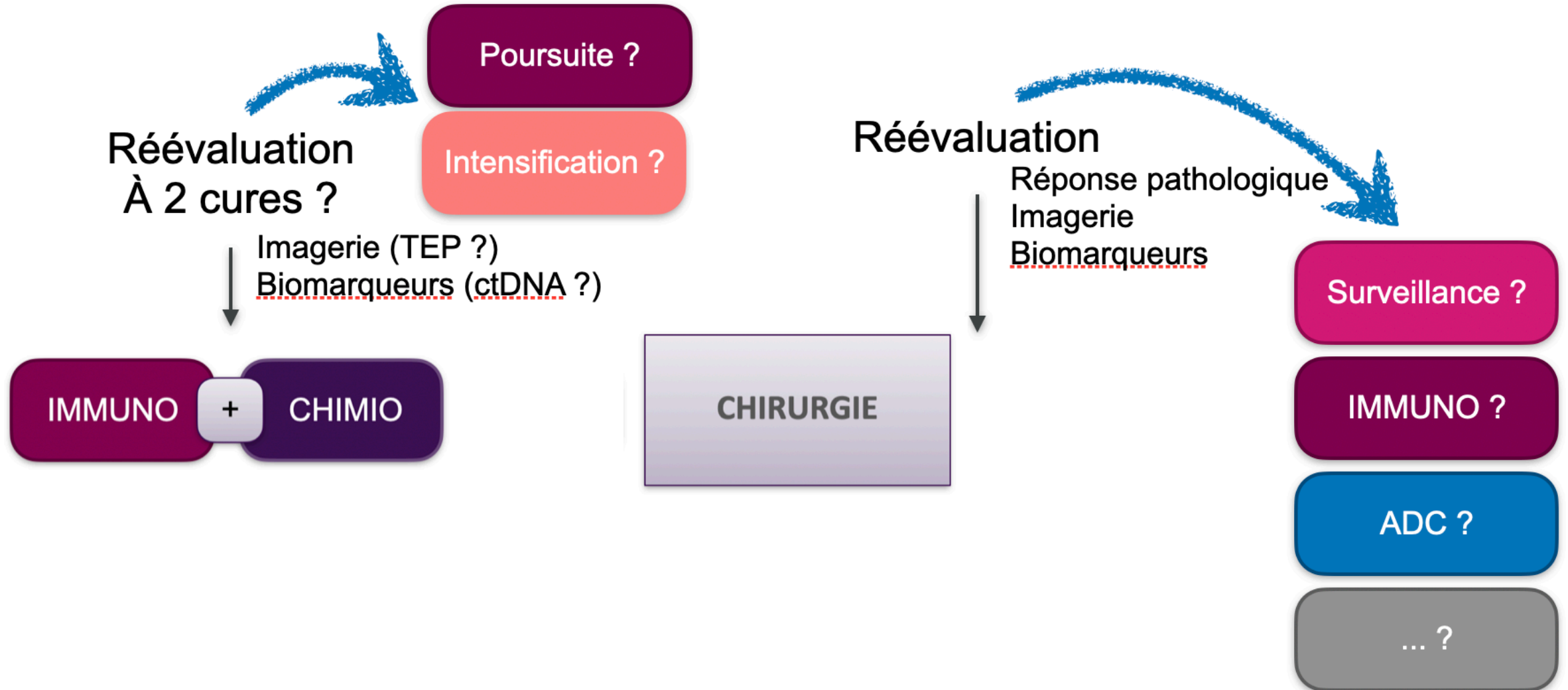
Discussion

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Discussion - implications pratiques



Discussion - aller plus loin ?



Lecture critique d'article

**JOURNÉES
GFPC
2023**

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