Mésothéliome pleural: quelle(s) séquence(s) thérapeutique(s)?

JOURNÉES GFPC 2023

Présenté par :

Pr Laurent GREILLIER, *Marseille*

Liens d’intérêts

- Abbvie
- Astra-Zeneca
- Bristol-Myers Squibb
- Boehringer–Ingelheim
- Eli Lilly Oncology
- Janssen
- Roche
- Novartis
- Merck
- MSD
- Pierre Fabre
- Pfizer
- Takeda
- Sanofi

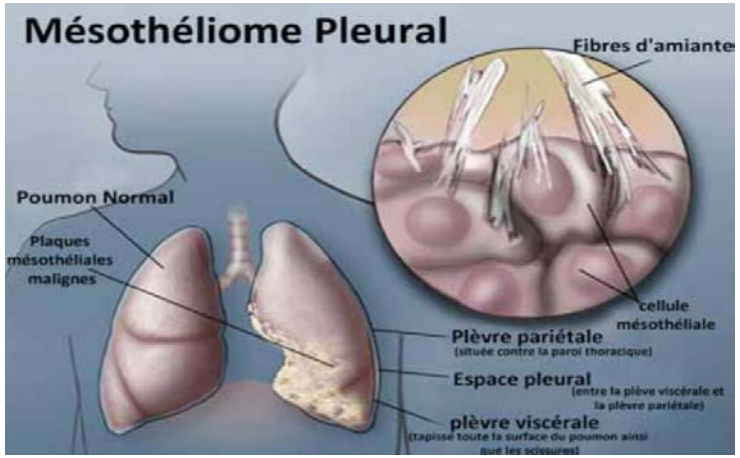
Mésothéliome

• **Tumeur** issue des **cellules mésothéliales** tapissant les séreuses (**pleural** : 80% des cas)

• Tumeur **rare** (#1000 cas/an en France)

• Facteurs de risque :

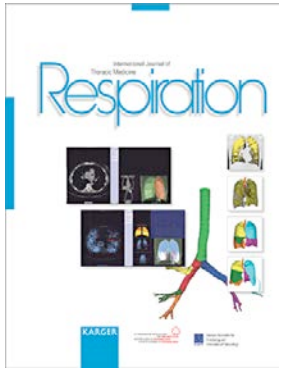
- **Amiante** (latence : **30-40 ans** après exposition)
- Prédisposition génétique possible : perte d'expression du gène de BAP-1 (BRCA1-associated protein 1) …

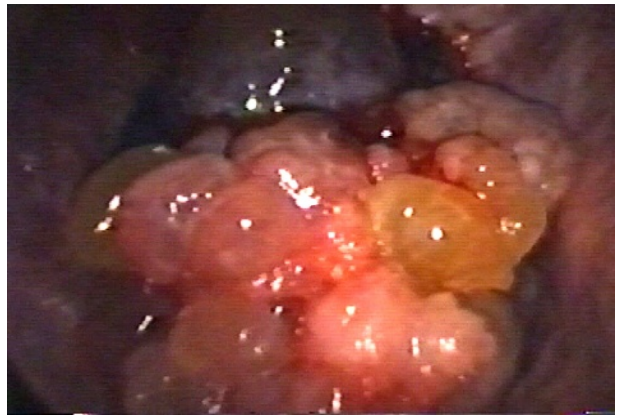


• **Tumeur agressive:** médiane de survie # 12 mois

Prise en charge diagnostique

- Présentation clinique
- Imagerie thoracique
- Cytologie pleurale
- Biopsies pleurales par thoracoscopie
- Anatomopathologie





Greillier L, Respiration 2008

Stratégies thérapeutiques dans le mésothéliome

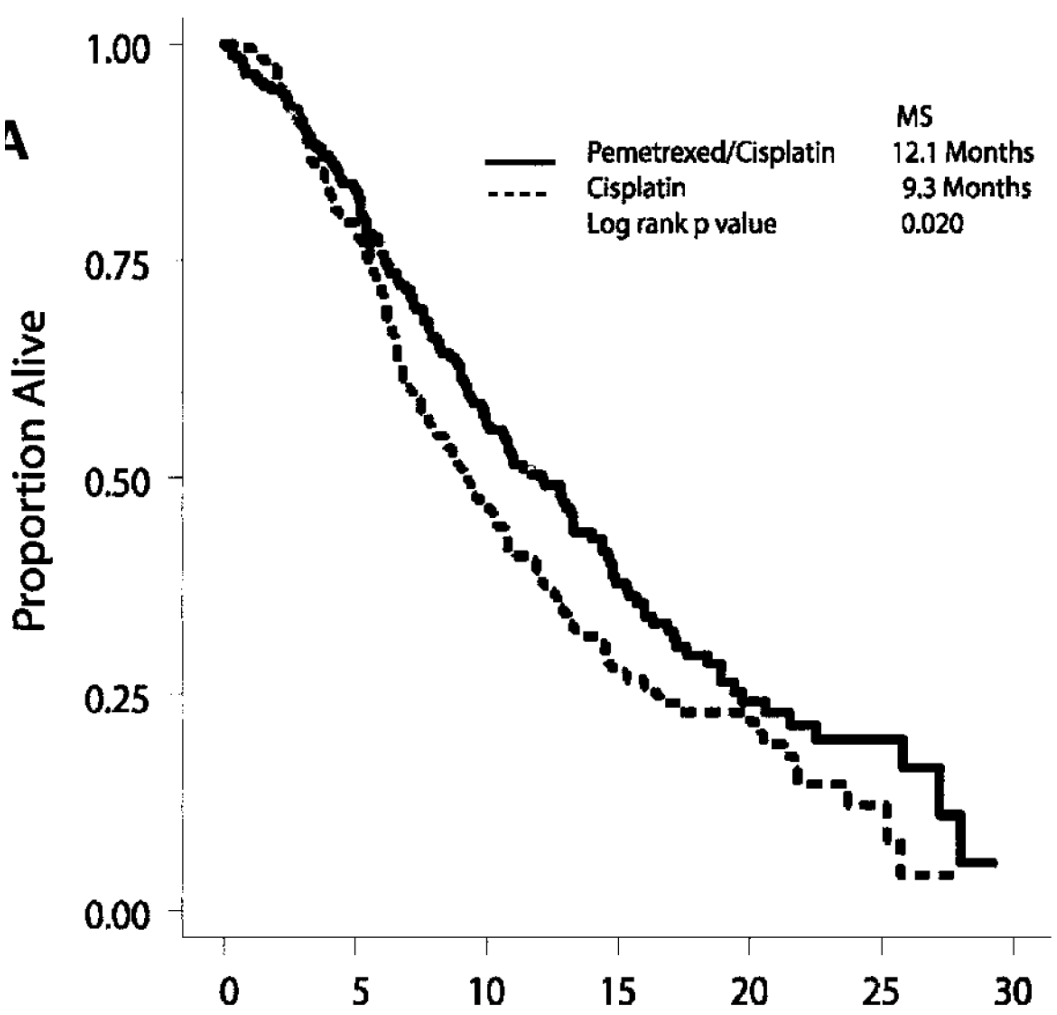
Chimiothérapie

Chimiothérapie de référence

R

Bras A (n=226)
Pemetrexed 500mg/m² + CDDP 75mg/m²

Bras B (n=222)
CDDP 75mg/m²

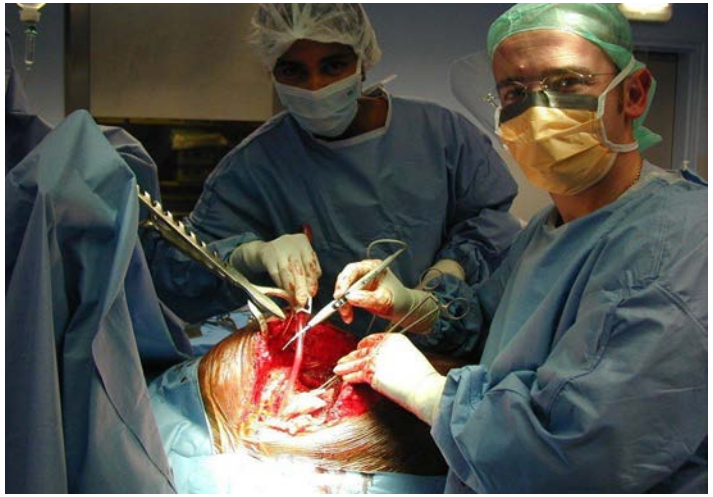


TR: 41,3% vs 16,7% (p<0,001)

SSP: 5,7 vs 3,9 mois (p<0,001)

Vogelzang NJ et al, J Clin Oncol 2003

Stratégies thérapeutiques dans le mésothéliome

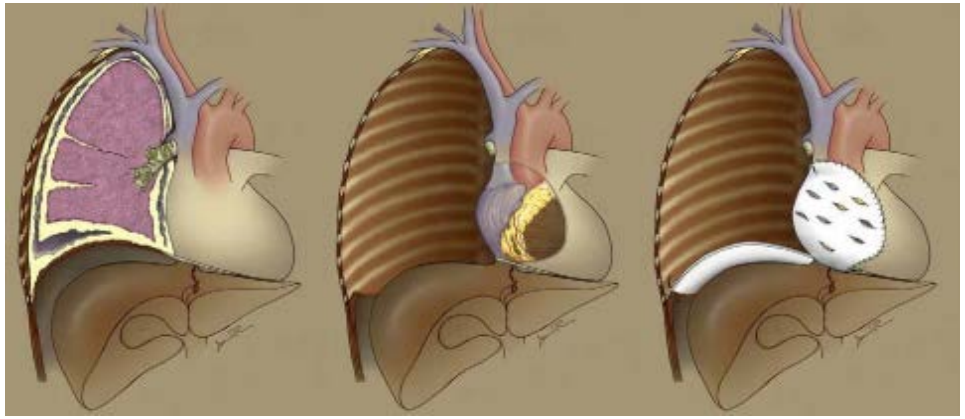


Chirurgie

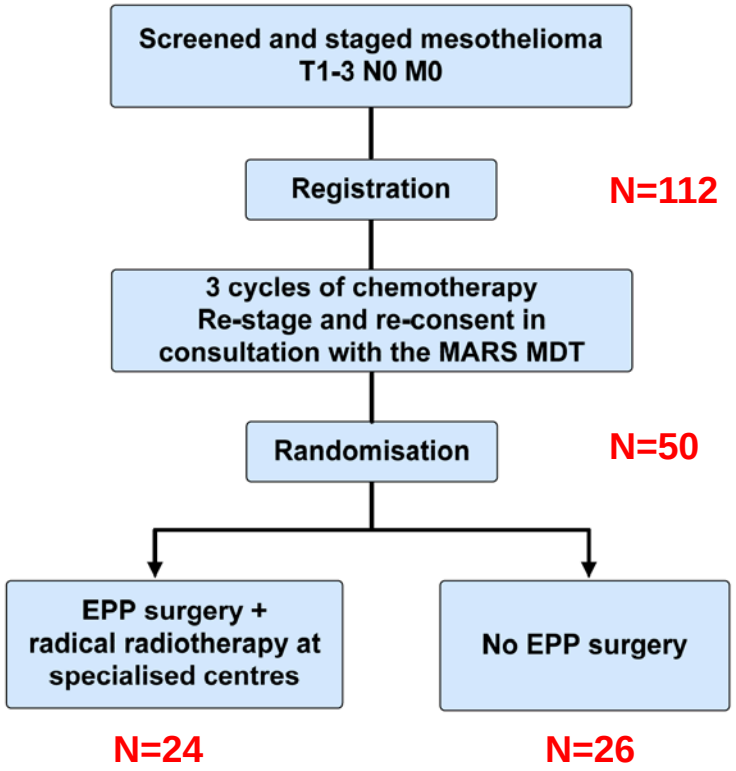
Chimiothérapie

Chirurgie du mésothéliome

- **Pleuro-pneumonectomie élargie**

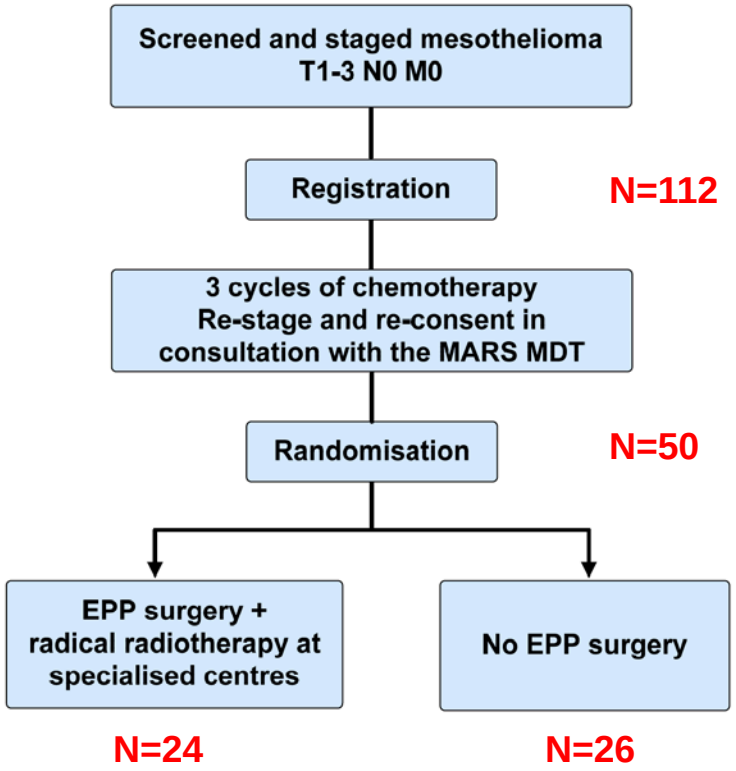


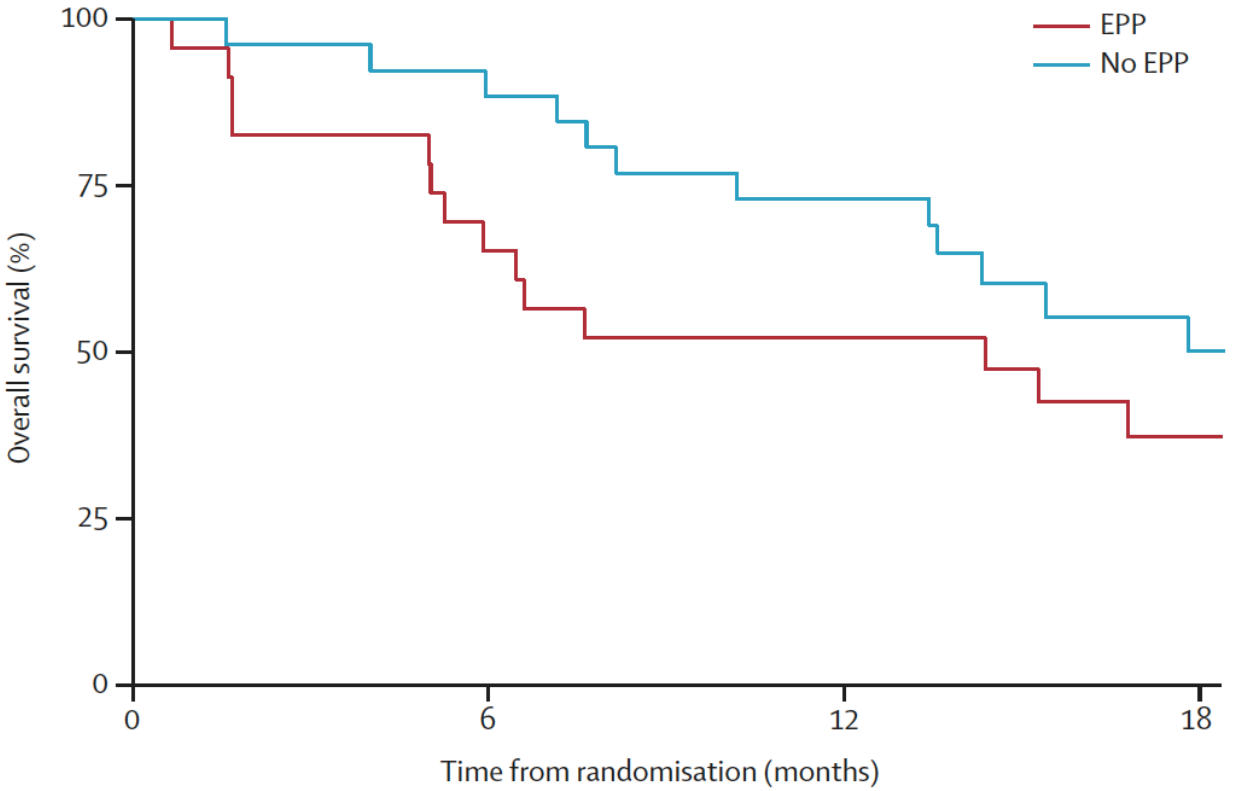
Essai MARS



Treasure T et al, Lancet Oncol 2011

Essai MARS





Number of events/ at risk				
EPP	0/24	8/16	3/12	3/8
No EPP	0/26	3/24	4/20	5/11

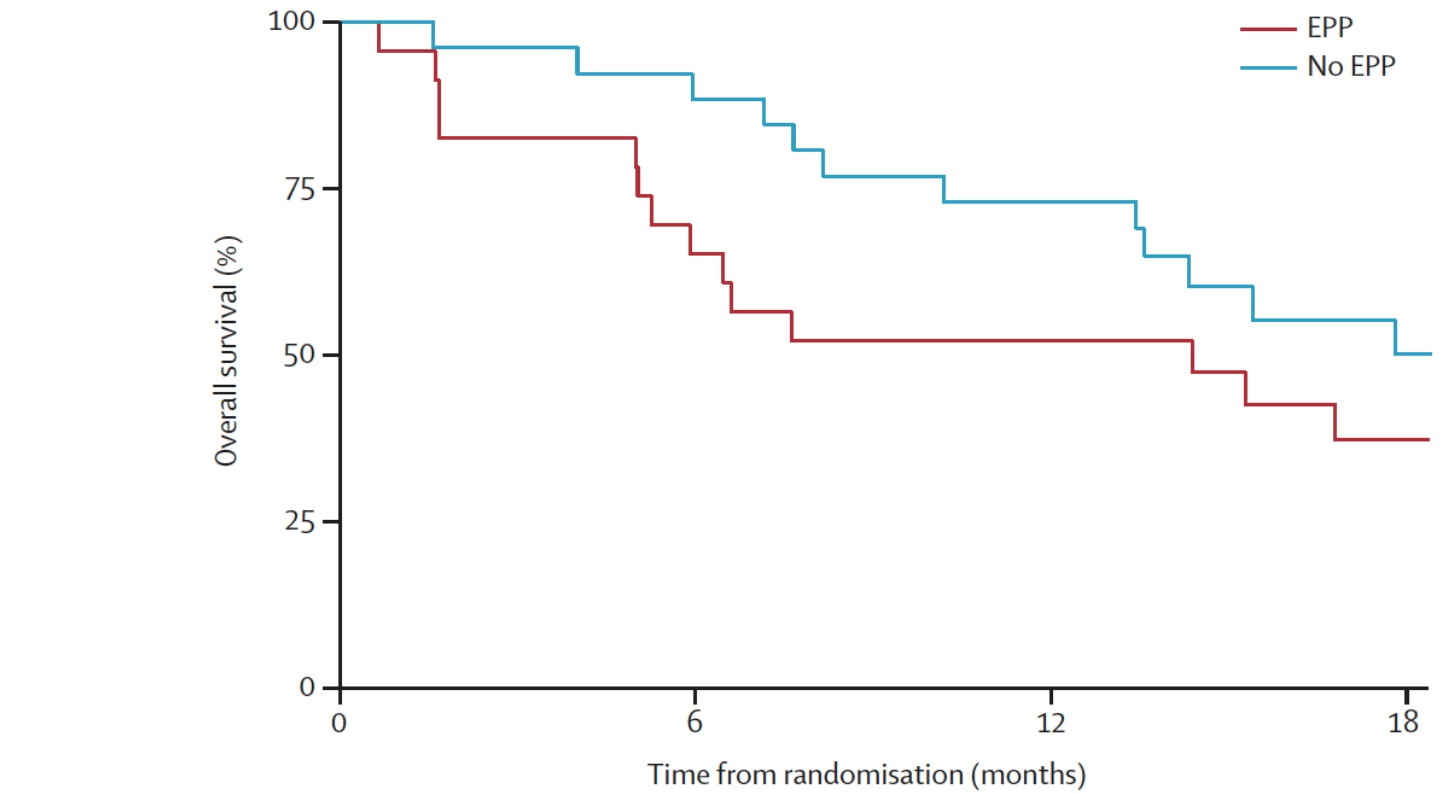
Treasure T et al, Lancet Oncol 2011

Essai MARS

Median OS (R)
EPP = 14.4 mo (5.3-18.7)
No EPP= 19.5 mo (13.4-NR)

Unadj HR = 1.90
(95%CI, 0.92-3.93; p=0.82)

Adj HR = 2.75
(95%CI, 1.21-6.26; p=0.016)



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EPP	0/24	8/16	3/12	3/8
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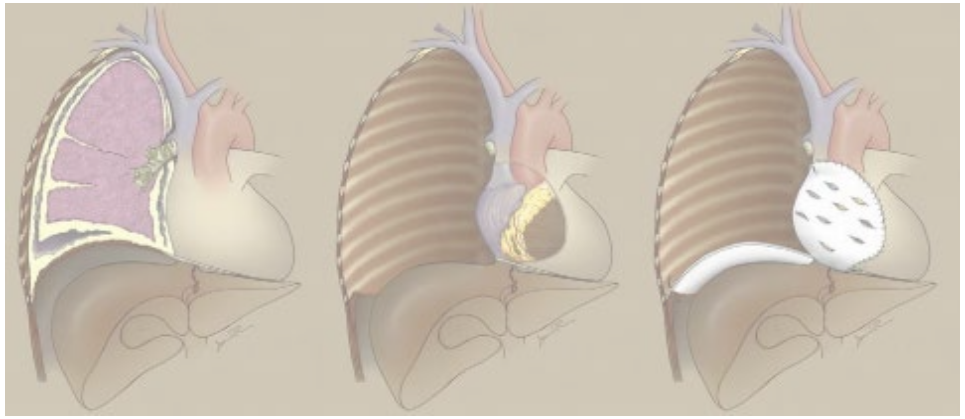
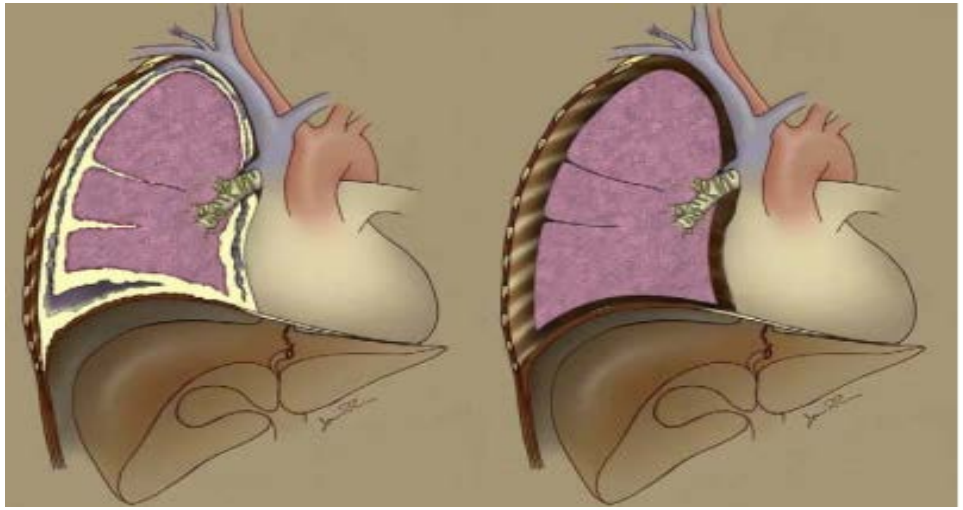
Treasure T et al, Lancet Oncol 2011

Chirurgie du mésothéliome

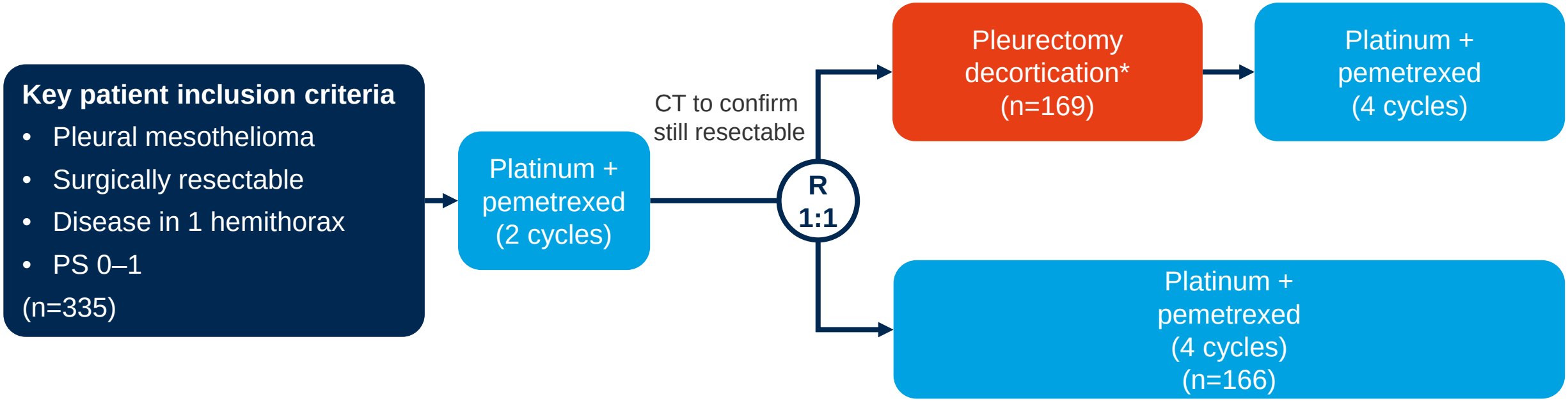
- Pleuro-pneumonectomie élargie



- **Pleurectomie / décortication élargie**



Essai MARS-2



Primary endpoint

- OS

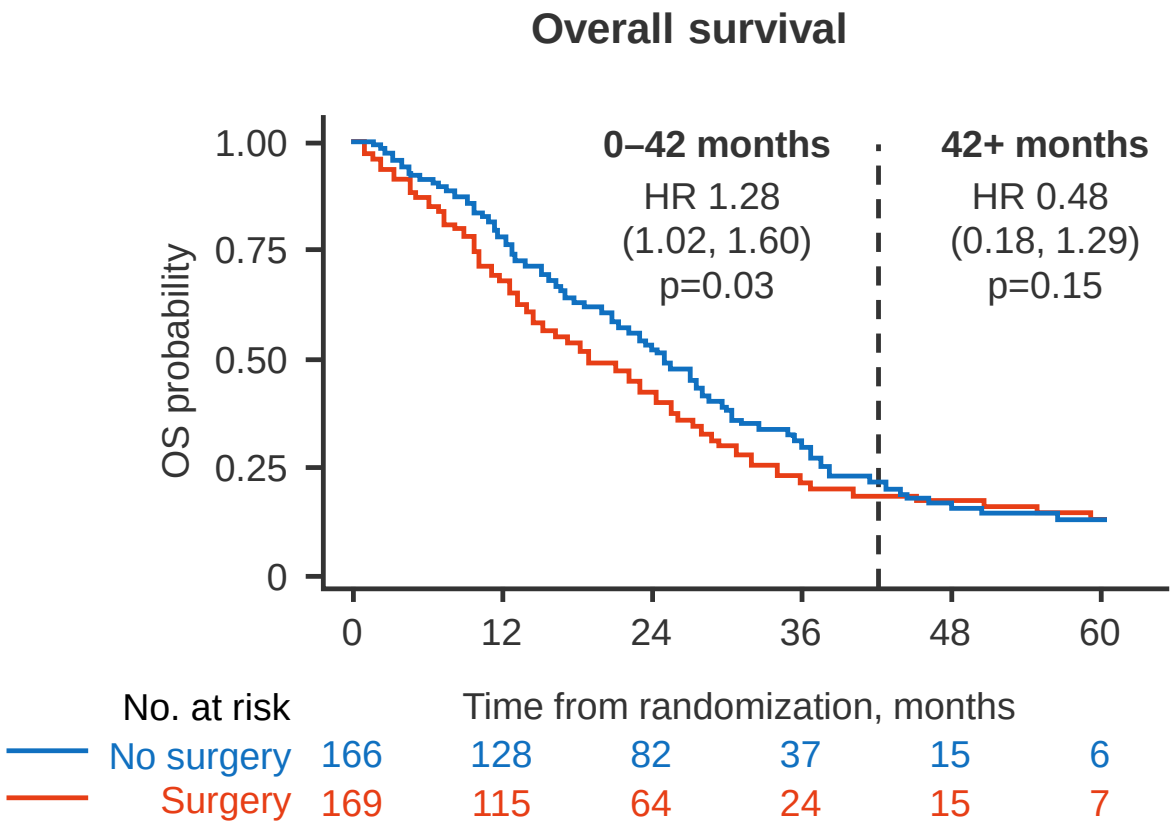
Secondary endpoints

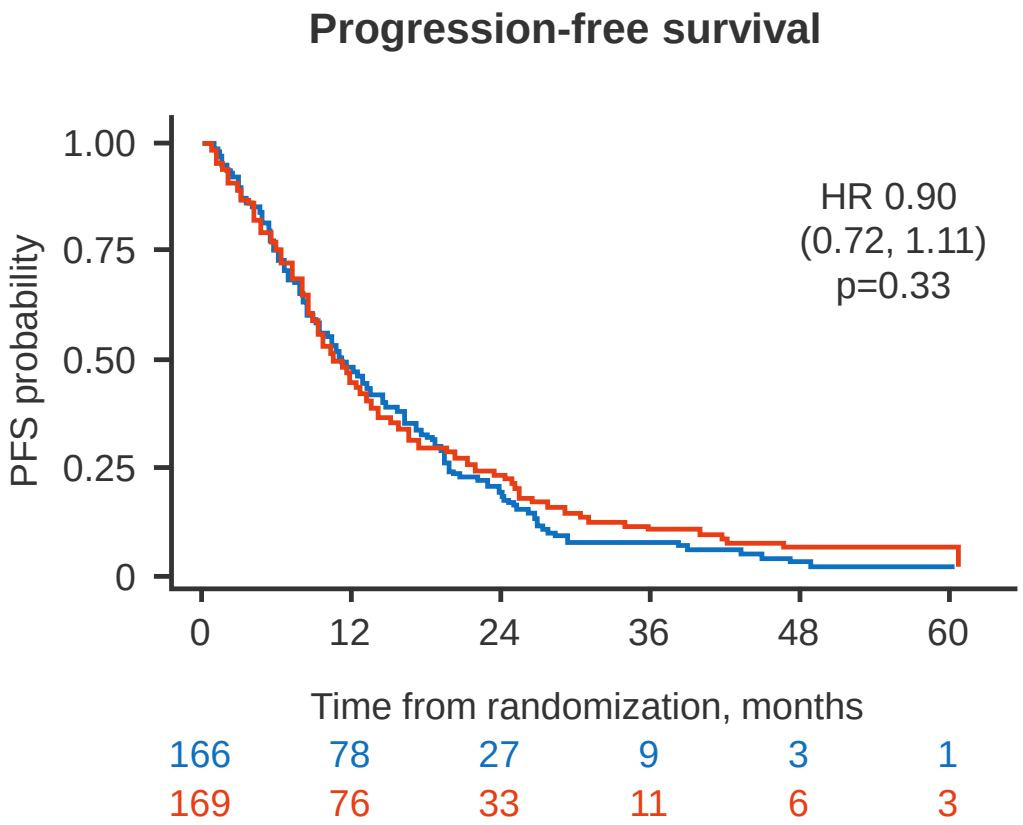
- PFS, QoL, safety

*Removal of all visible disease in the visceral and parietal pleura and if required the ipsilateral hemidiaphragm and pericardium but sparing the lung.

Lim E et al, WCLC 2023

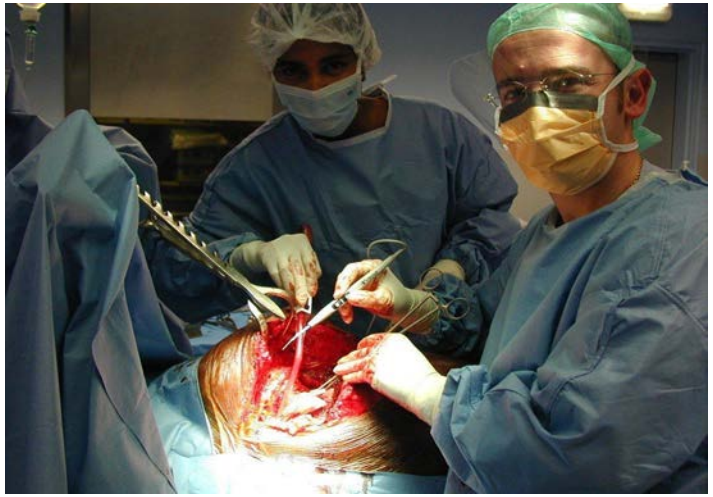
Essai MARS-2





Lim E et al, WCLC 2023

Stratégies thérapeutiques dans le mésothéliome

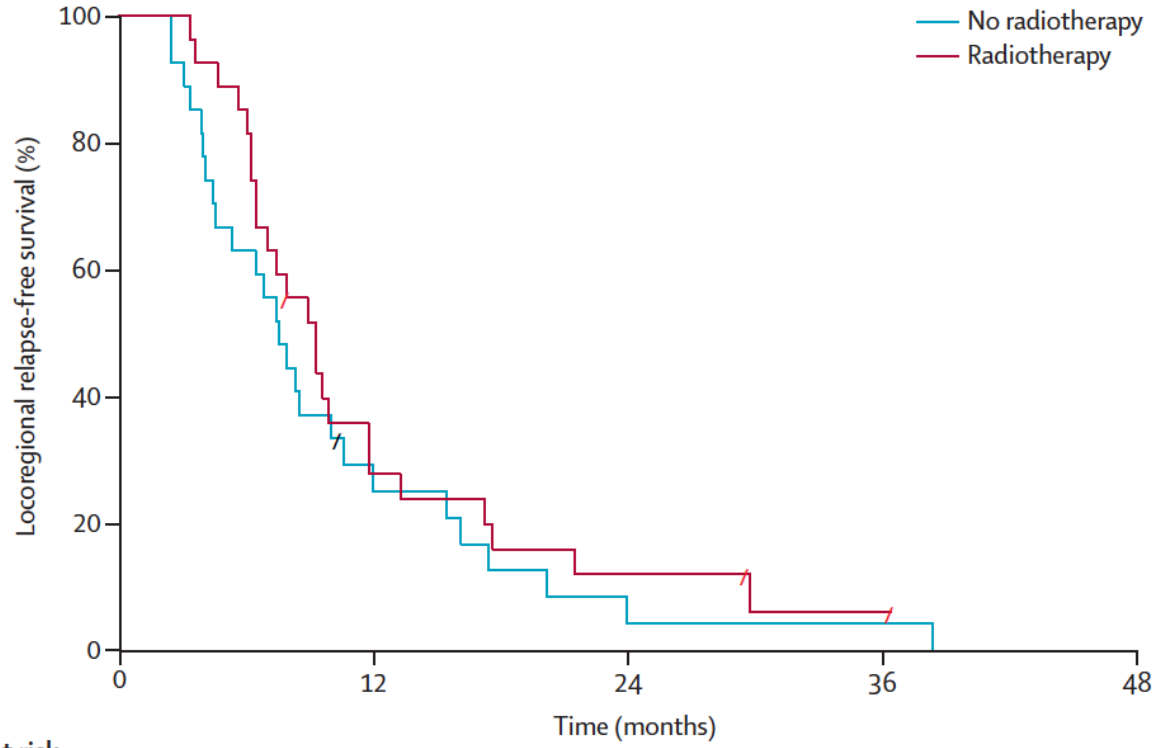


Chirurgie

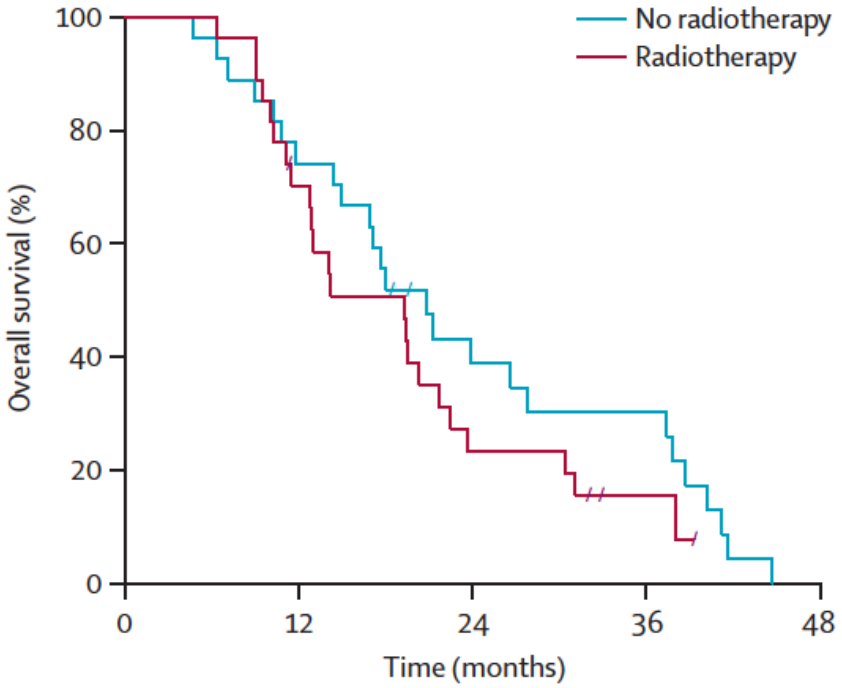
Chimiothérapie

Radiothérapie

Essai SAKK 17/04



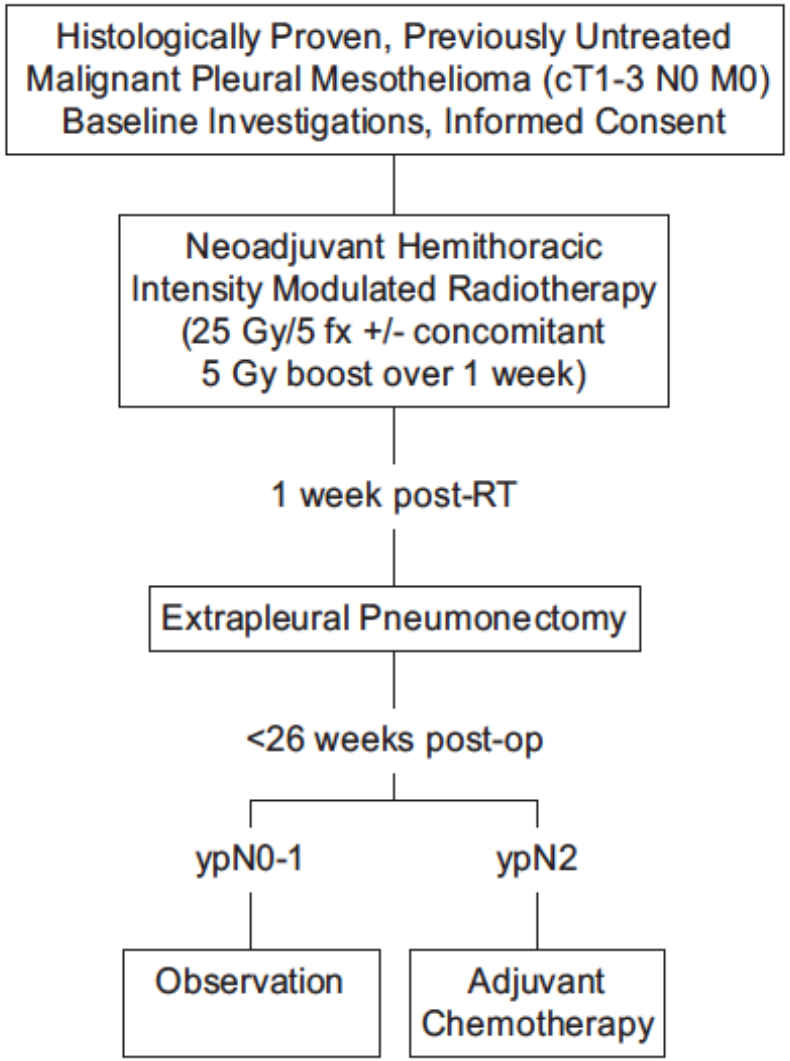
Number at risk					
No radiotherapy	27	7	2	1	0
Radiotherapy	27	7	3	1	0

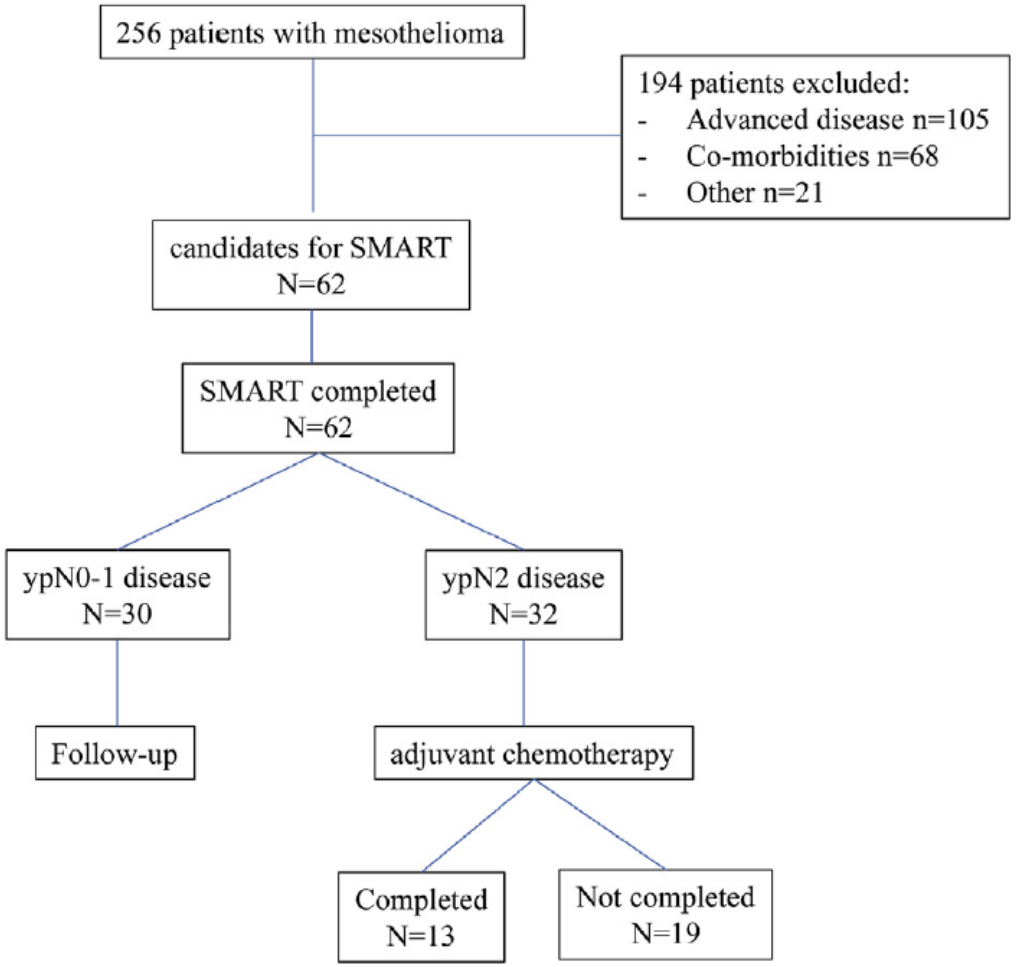


Number at risk					
No radiotherapy	27	20	9	7	0
Radiotherapy	27	18	6	2	0

Stahel RA et al, Lancet Oncol 2015

Approche SMART





Cho JBC RA et al, J Thorac Oncol 2014; de Perrot M et al, J Thorac Cardiovasc Surg 2016

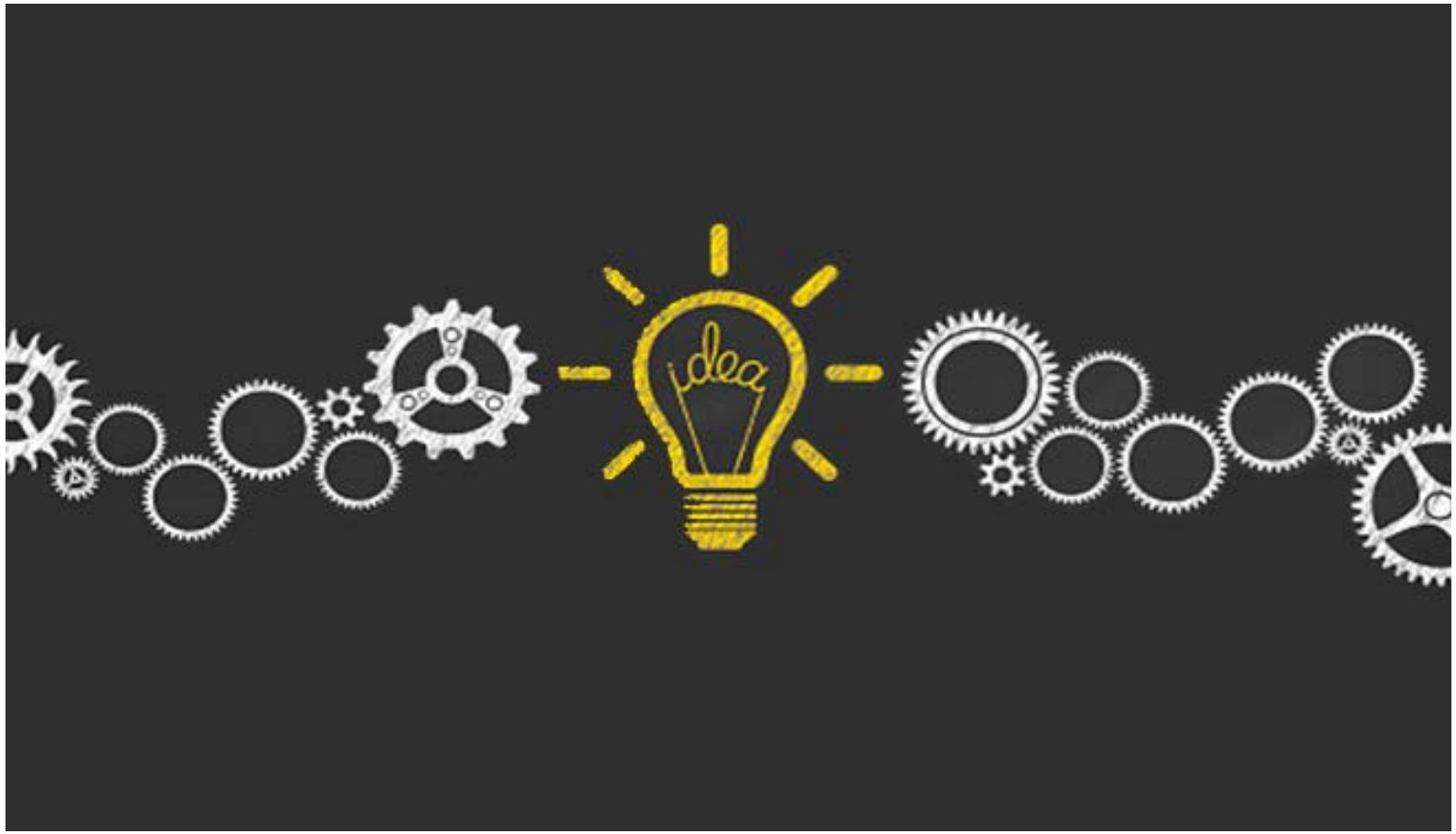
Stratégies thérapeutiques dans le mésothéliome

Chirurgie

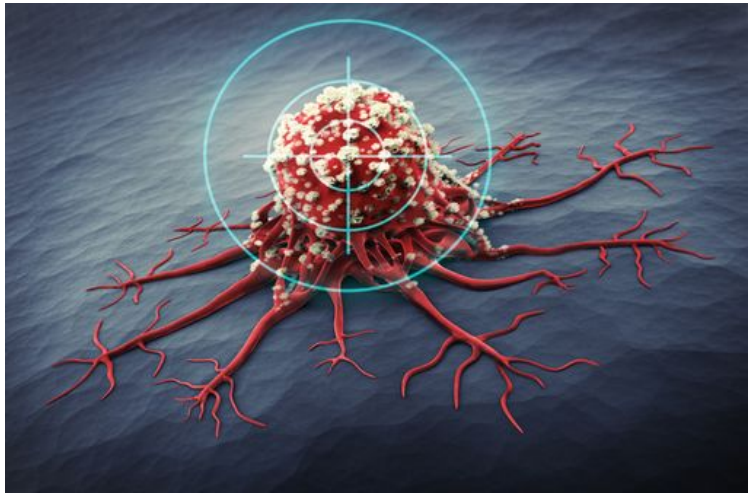
Chimiothérapie

Radiothérapie

Peut-on faire mieux ?



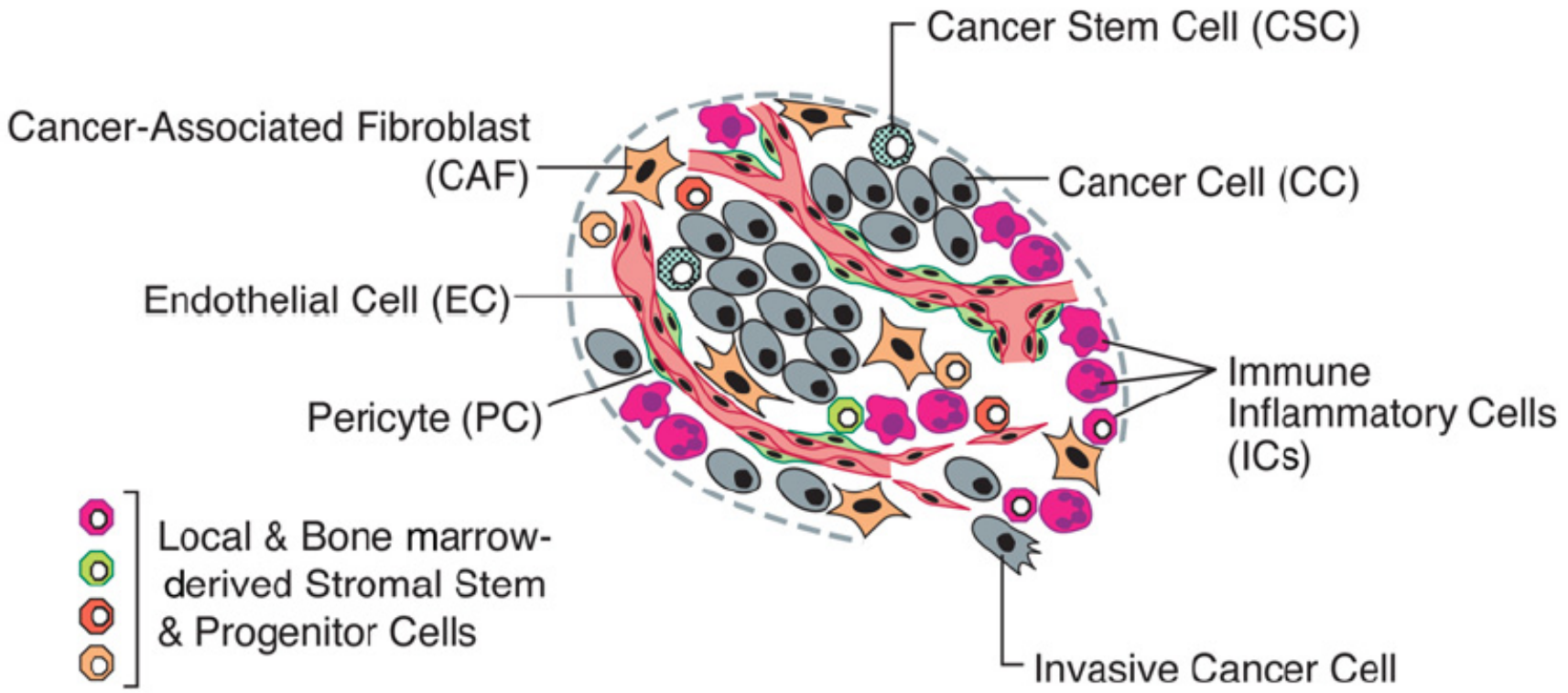
Stratégies thérapeutiques dans le mésothéliome



Thérapies ciblées

Chimiothérapie

Micro-environnement tumoral



Essai MAPS

- **Mésothéliome <u>Pleural</u> Malin**
- Prouvé histologiquement
  ECOG PS 0-2
- Pas de comorbidité cardiovasculaire
- Pas de chimiothérapie antérieure

(n=448)

R 1:1

A

Pemetrexed 500 mg/m² J1
Cisplatine 75mg/m² J1
6 cycles, Q3W
(n=225)

Surveillance

B

Pemetrexed 500 mg/m² J1
Cisplatine 75mg/m² J1
Bevacizumab 15 mg/kg J1
6 cycles, Q3W
(n=223)

Maintenance Bevacizumab
15 mg/kg J1, Q3W
Jusqu'à progression

<u>Stratification</u>: centre, histologie (epithelioide vs. sarcomatoide/mixe), PS (0-1 vs. 2), statut tabagique (fumeur vs. non-fumeur)

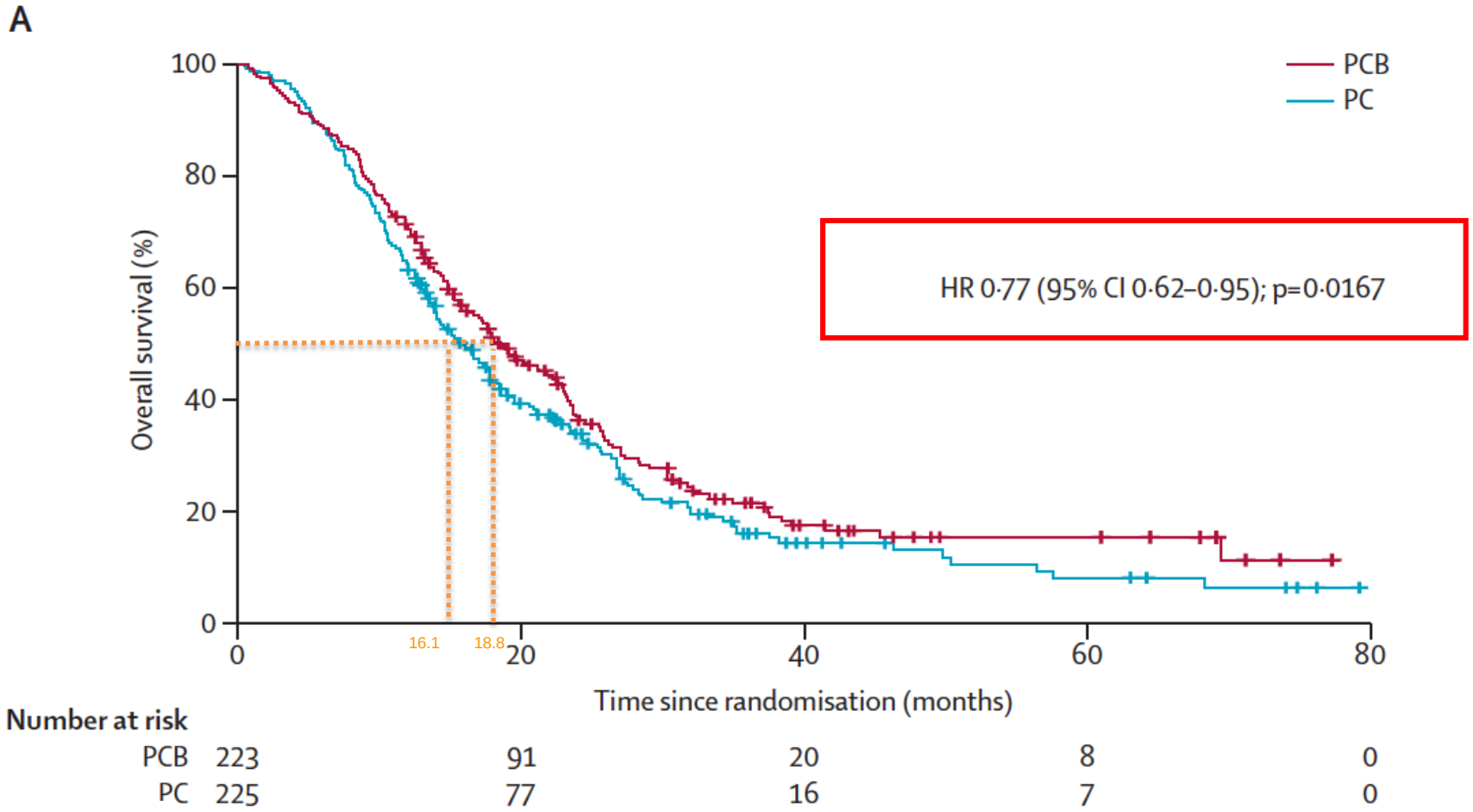
Scanner tous les 3 cycles dans les 2 bras.
Réponse évaluée selon les RECIST modifiés

Objectif principal:
Survie globale

Objectifs secondaires:
Survie sans progression, qualité de vie, toxicité

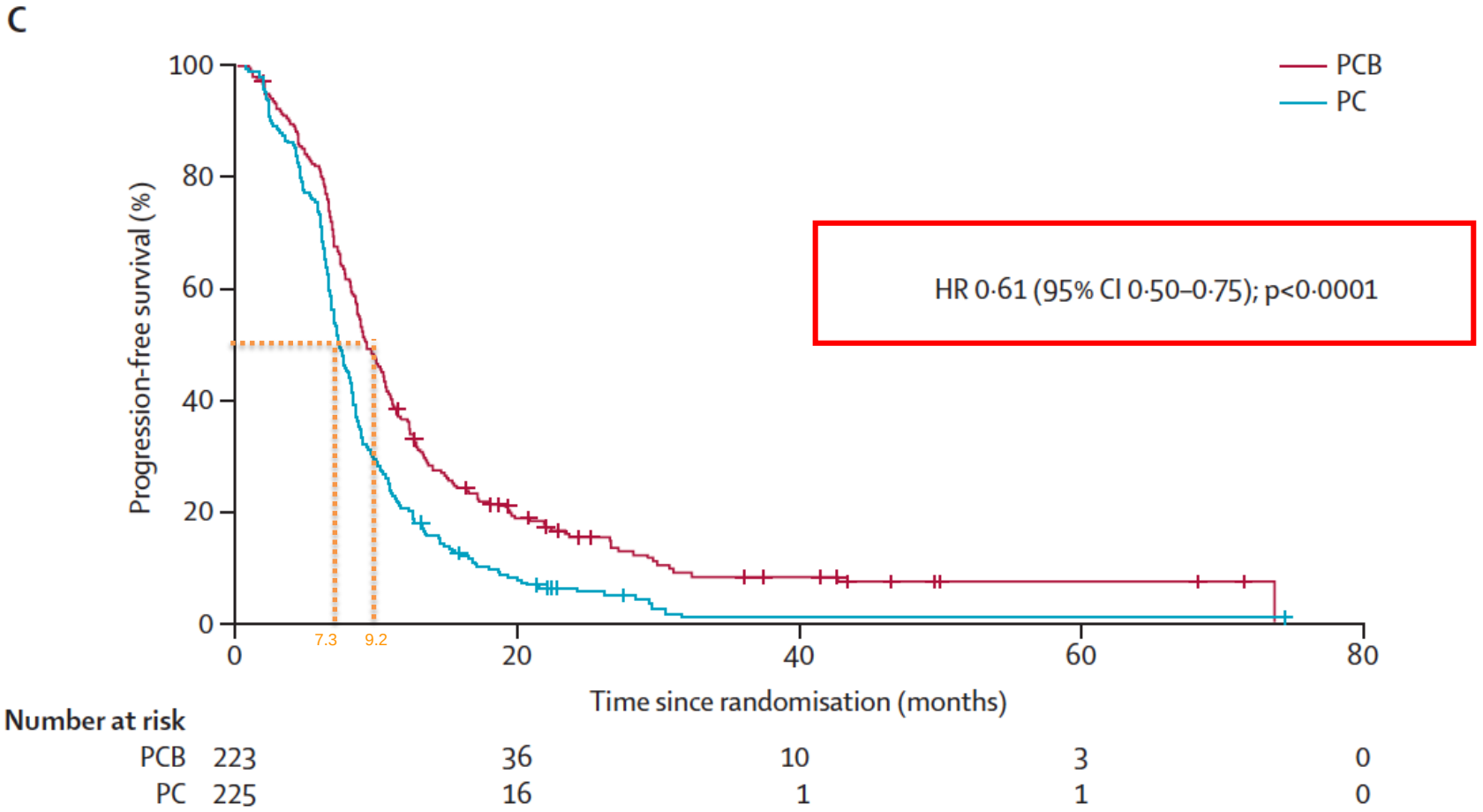
Zalcman G et al, Lancet 2015

Essai MAPS



Zalcman G et al, Lancet 2015

Essai MAPS



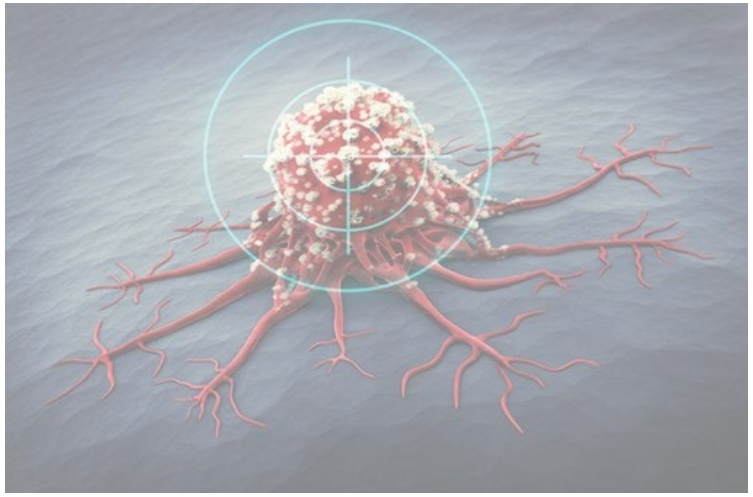
Zalcman G et al, Lancet 2015

Essai MAPS

	PCB (n=222)		PC (n=224)		Difference (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	173 (77·9%)	98 (44·1%)	177 (79·0%)	100 (44·6%)	−1·1% (−8·7 to 6·5)	−0·5% (−9·6 to 8·6)
Febrile neutropenia	4 (1·8%)	4 (1·8%)	7 (3·1%)	7* (3·1%)	−1·3% (−4·7 to 1·8)	−1·3% (−4·7 to 1·8)
Thrombocytopenia	130 (58·6%)	22 (9·9%)	119 (53·1%)	21 (9·4%)	5·4% (−3·8 to 14·5)	0·5% (−5·1 to 6·1)
Anaemia	163 (73·4%)	16 (7·2%)	187 (83·5%)	30 (13·4%)	−10·1% (−17·6 to −2·4)	−6·2% (−11·9 to −0·5)
Asthenia or fatigue	155 (69·8%)	30 (13·5%)	152 (67·9%)	28 (12·5%)	2·0% (−6·6 to 10·5)	1·0% (−5·3 to 7·3)
Weight loss	22 (9·9%)	0	22 (9·8%)	0	0·1% (−5·6 to 5·7)	0 (−1·7 to 1·7)
Anorexia	75 (33·8%)	5 (2·3%)	75 (33·5%)	9 (4·0%)	0·3% (−8·4 to 9·0)	−1·8% (−5·4 to 1·7)
Constipation	47 (21·2%)	2 (0·9%)	44 (19·6%)	1 (0·4%)	1·5% (−6·0 to 9·0)	0·5% (−1·5 to 2·4)
Diarrhoea	37 (16·7%)	1 (0·5%)	26 (11·6%)	2 (0·9%)	5·1% (−1·4 to 11·6)	−0·4% (−2·0 to 1·1)
Oral mucositis	37 (16·7%)	2 (0·9%)	33 (14·7%)	1 (0·4%)	1·9% (−4·9 to 8·7)	0·5% (−1·5 to 2·4)
Nausea or vomiting	174 (78·4%)	18 (8·1%)	172 (76·8%)	18 (8·0%)	1·6% (−6·1 to 9·3)	0·1% (−5·1 to 5·3)
Creatinine concentration increase	86 (38·7%)	8 (3·6%)	63 (28·1%)	4 (1·8%)	10·6% (1·9 to 19·1)	1·8% (−1·4 to 5·3)
Haemorrhage	91 (41·0%)	2† (0·9%)	16 (7·1%)	0	33·8% (26·3 to 41·0)	0·9% (−5·1 to 5·3)
Sepsis	3 (1·4%)	3‡ (1·4%)	3 (1·3%)	3 (1·3%)	<0·1% (−2·7 to 2·7)	<0·1% (−2·7 to 2·7)
Hepatic enzymes	5 (2·3%)	0	3 (1·3%)	1 (0·4%)	0·9% (−1·9 to 3·9)	−0·4% (−2·5 to 1·3)
Cardiovascular AEs	137 (61·7%)	64 (28·8%)	6 (2·7%)	2 (0·9%)	59·0% (51·8 to 65·3)	27·9% (21·9 to 34·2)
Hypertension	125 (56·3%)	51 (23·0%)	3 (1·3%)	0	55·0% (47·9–61·4)	23·0% (17·6 to 28·9)
Arterial and venous thromboembolic events	16 (7·2%)	13 (5·8%)	3 (1·3%)	2 (0·9%)	5·9% (2·2 to 10·1)	5·0% (1·6 to 8·9)

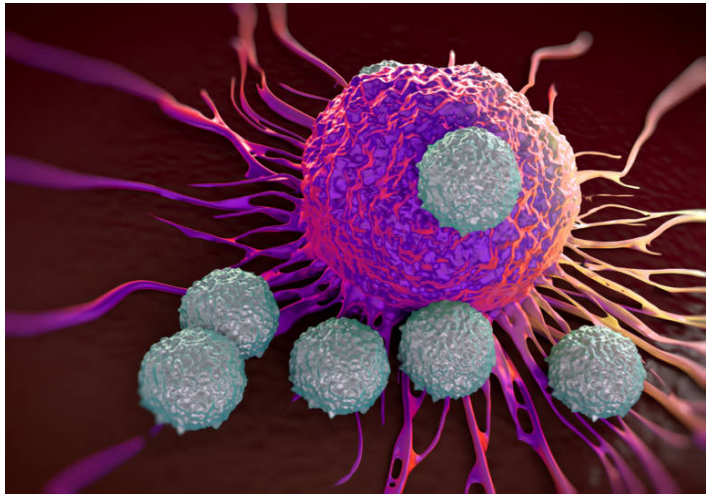
Zalcman G et al, Lancet 2015

Stratégies thérapeutiques dans le mésothéliome



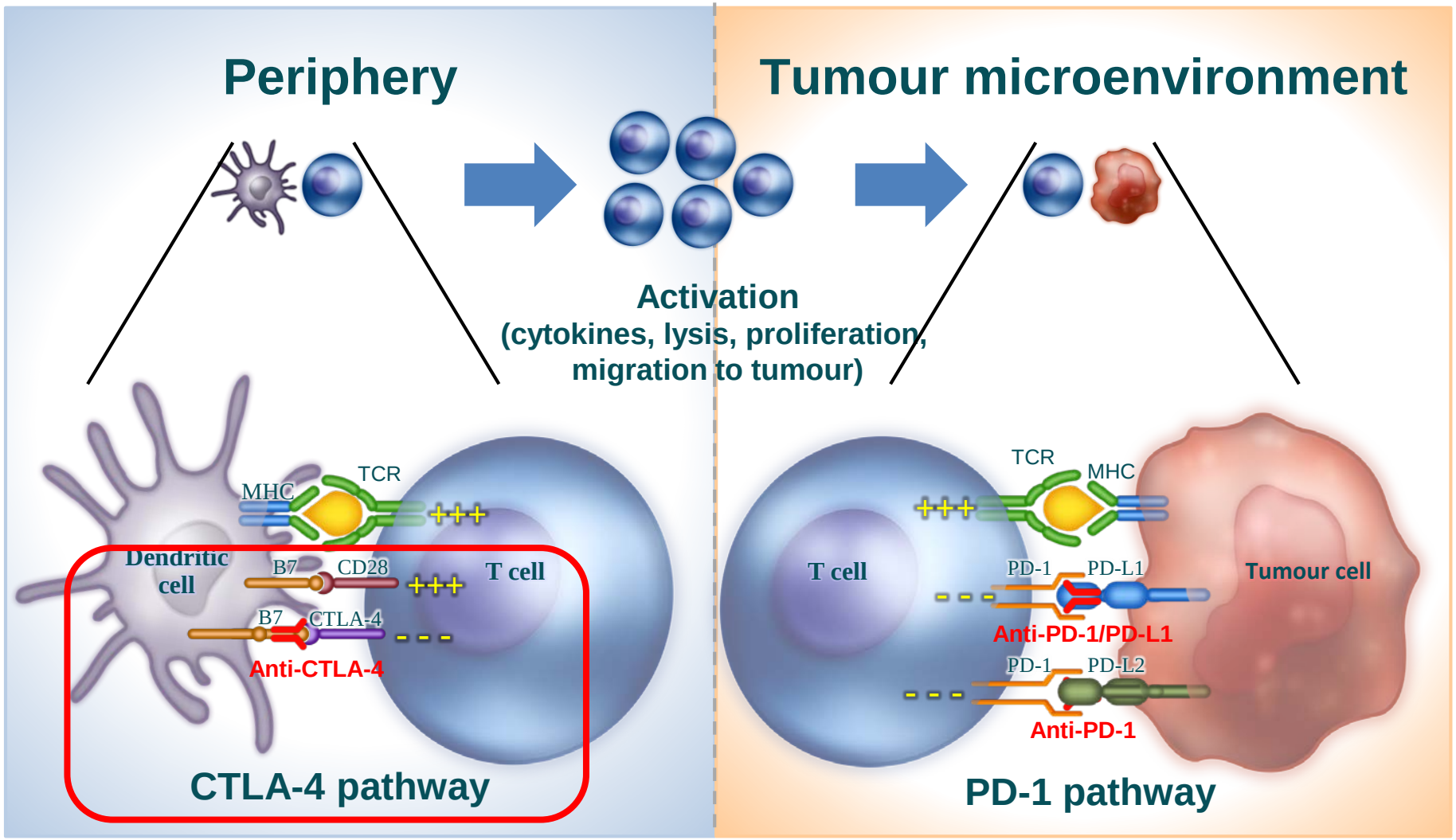
Thérapies ciblées

Chimiothérapie

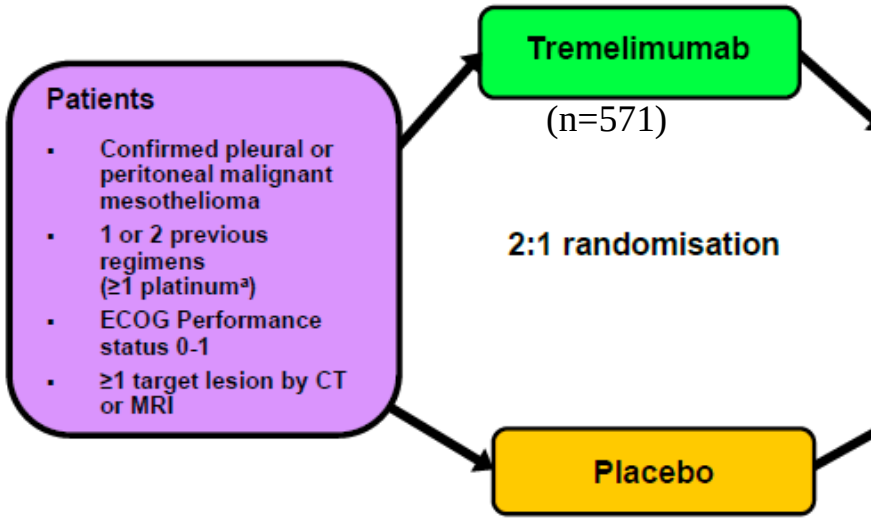


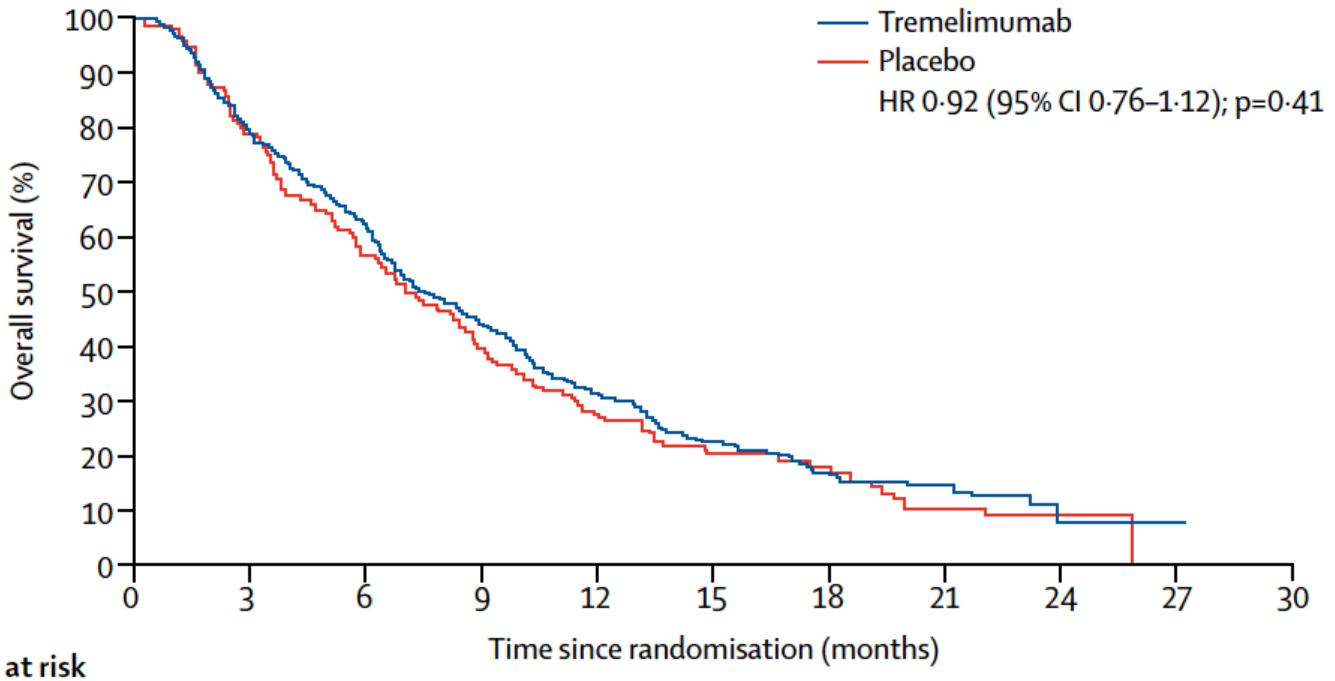
Immunothérapie

Inhibiteurs des points de contrôle de l'immunité



Essai DETERMINE

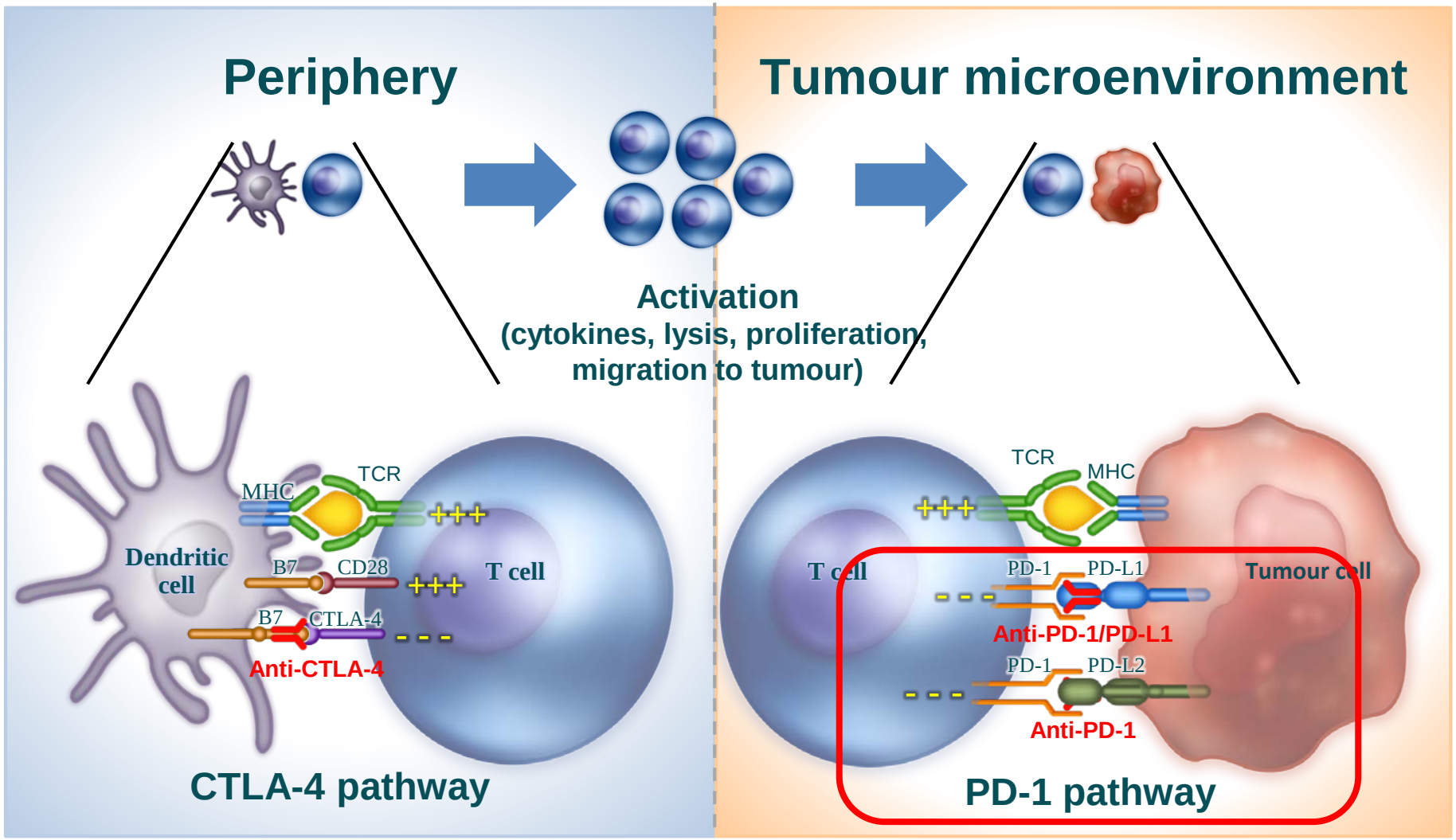




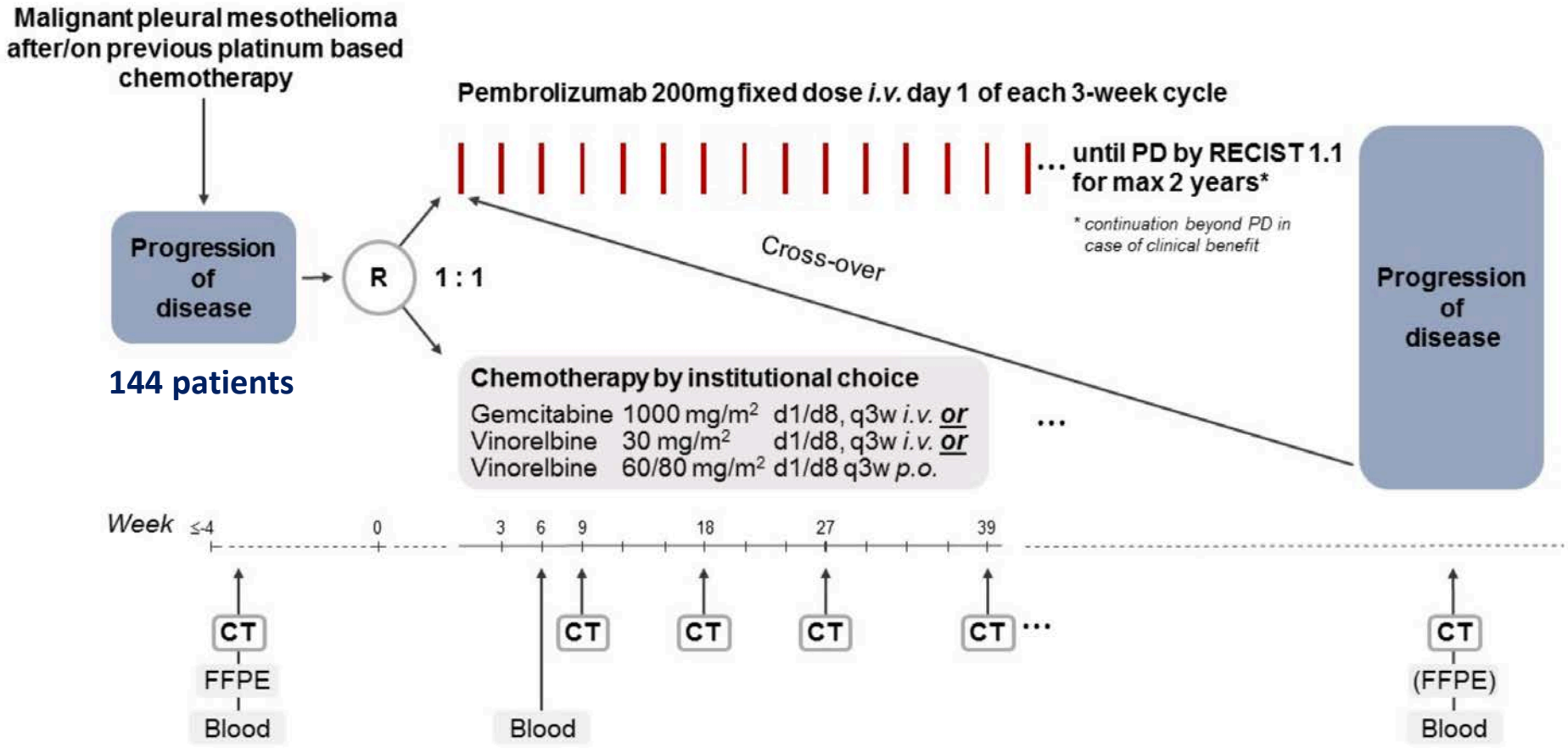
Number at risk (number censored)											
Tremelimumab	382 (0)	300 (6)	232 (11)	163 (13)	116 (13)	69 (29)	36 (48)	16 (63)	3 (72)	1 (74)	0 (75)
Placebo	189 (0)	147 (3)	103 (6)	70 (9)	48 (10)	32 (14)	17 (26)	8 (29)	2 (34)	0 (35)	0 (35)

Maio M et al, Lancet Oncol 2017

Inhibiteurs des points de contrôle de l'immunité



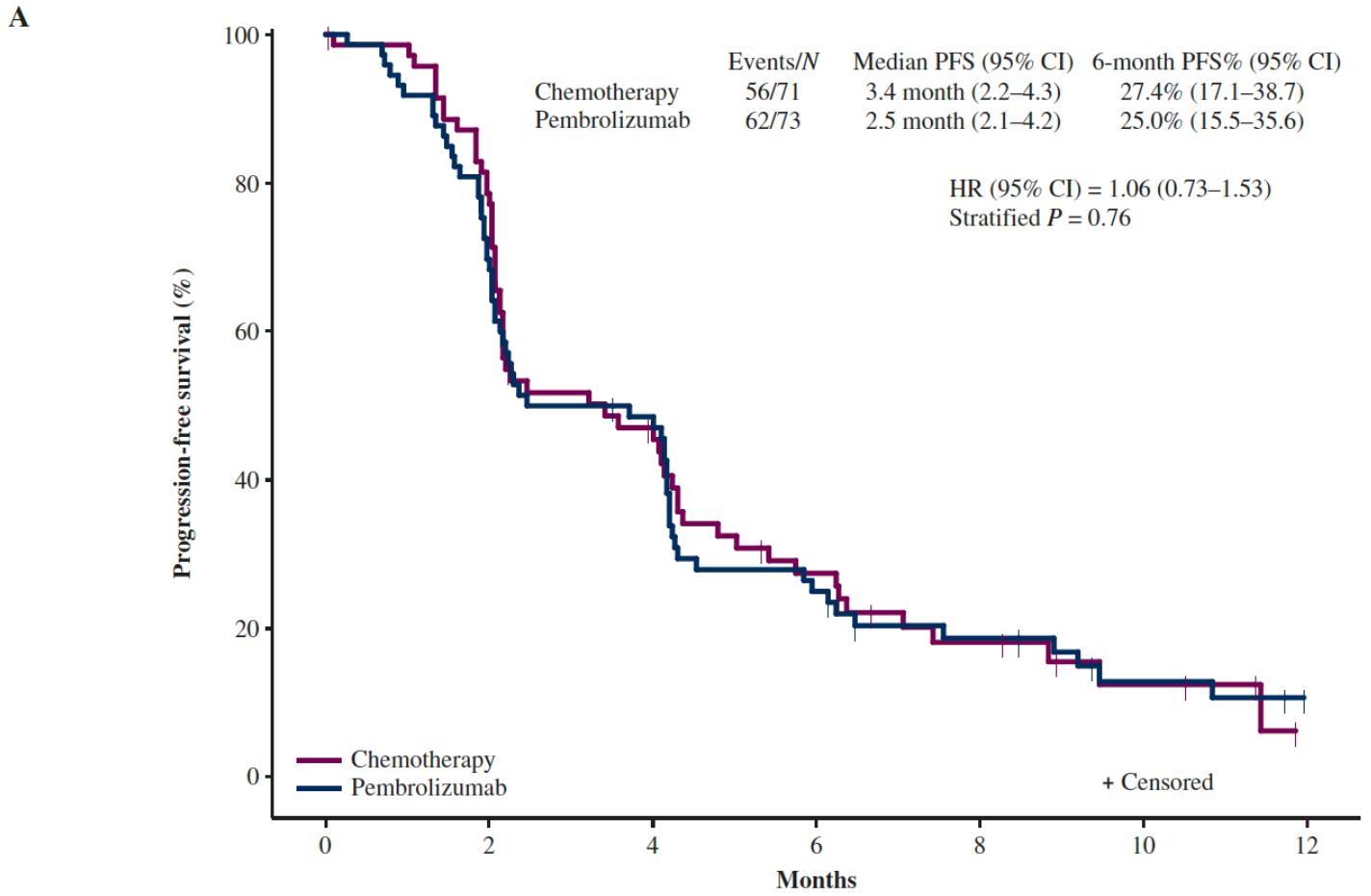
Essai PROMISE-meso



Primary endpoint: Progression-free survival based on independent review

Popat S, Ann Oncol 2020

Essai PROMISE-meso



Popat S, Ann Oncol 2020

Essai CONFIRM

- **Histological diagnosis of Malignant Mesothelioma**
- **Progression after at least 2 previous lines of chemotherapy**
- **Measurable / assessable disease (RECIST 1.1)**
- **ECOG PS 0-1**
- **Weight loss <10%**
- **Age > 18**
- **Available tumor tissue**
- **Exclusion criteria:** history of other malignancy, auto-immune disease, primary immunodeficiency or drug immunosuppression, ILD…

336 patients

R 2:1

Anti-PD-1 Nivolumab
240 mg flat dose (30' IV)
every 2 weeks

→ *until progression or unacceptable toxicity (or 1 year max)*

Placebo
(30' IV)
every 2 weeks

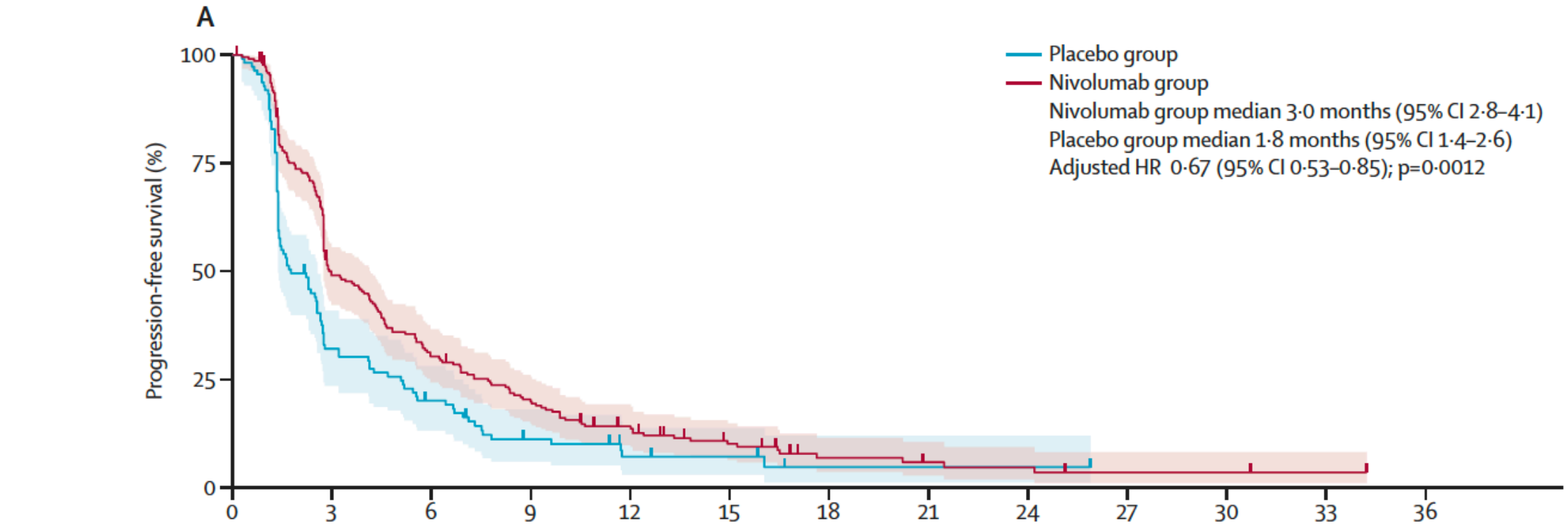
→ *until progression or unacceptable toxicity (or 1 year max)*

→Primary endpoints: OS & IR-PFS

Sponsor: University of Southampton

Fennell D, WCLC 2020

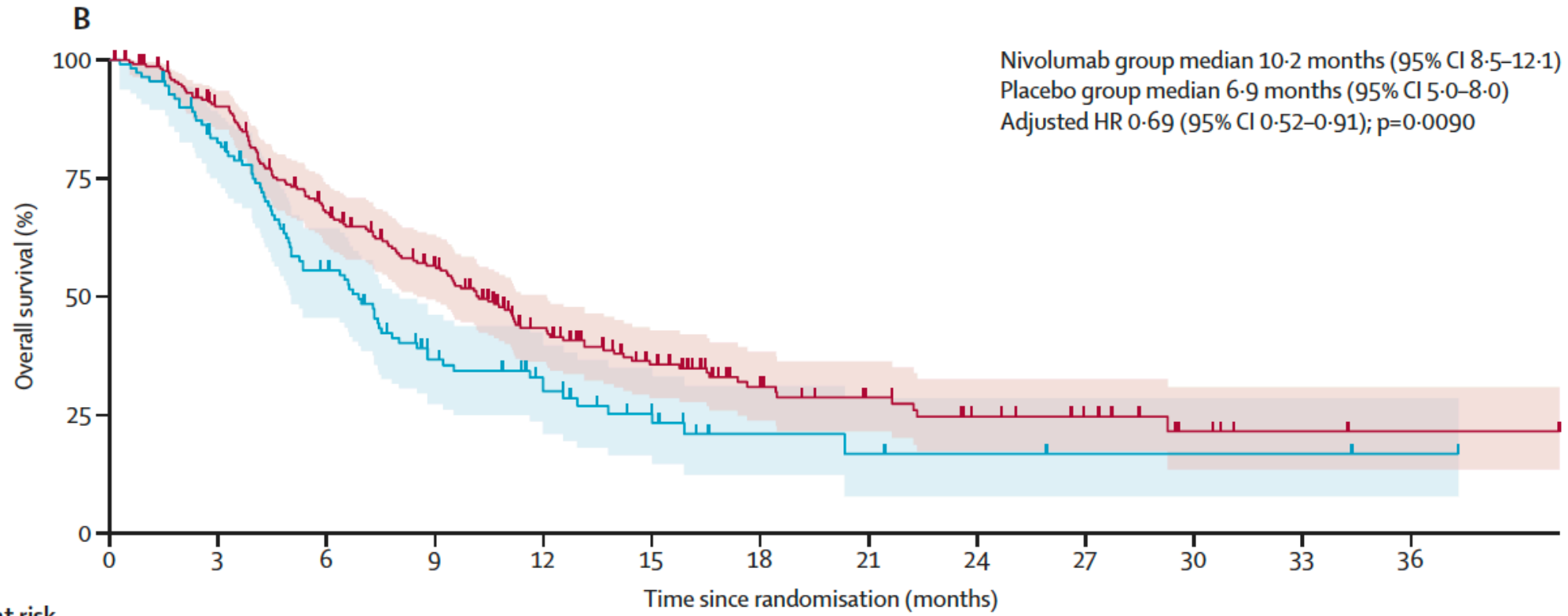
Essai CONFIRM



Number at risk (number censored)													
Placebo group	111 (0)	35 (1)	21 (2)	10 (4)	5 (6)	4 (7)	1 (9)	1 (9)	1 (9)	0 (10)	0 (10)	0 (10)	0 (10)
Nivolumab group	221 (0)	105 (6)	65 (6)	43 (7)	27 (10)	15 (15)	5 (20)	5 (20)	4 (20)	2 (21)	2 (21)	1 (22)	0 (23)

Fennell D, Lancet Oncol 2021

Essai CONFIRM



Number at risk (number censored)													
Placebo group	111 (0)	88 (4)	55 (9)	31 (15)	21 (20)	13 (25)	5 (31)	4 (31)	3 (32)	2 (33)	2 (33)	2 (33)	1 (34)
Nivolumab group	221 (0)	187 (13)	137 (17)	108 (24)	67 (42)	46 (52)	29 (64)	22 (69)	15 (73)	11 (77)	5 (82)	2 (85)	1 (86)

Fennell D, Lancet Oncol 2021

Essai MAPS 2

Randomized, non-comparative phase 2 trial - One-step Fleming design (each arm independently)

- **Histological** diagnosis of **Malignant Pleural Mesothelioma** (Mesopath)
- **Unresectable** cancer with **documented progression after maximum 1 or 2 previous lines of chemotherapy** including pemetrexed/platinum
- **Measurable disease**
- **ECOG PS 0-1**
- **Weight loss <10%**
- **Age > 18 years (M or F)**
- **Available tumor tissue**
- **Exclusion criteria:** history of other malignancy, auto-immune disease, primary immunodeficiency or drug immunosuppression, ILD...

125 patients

R 1:1

Anti-PD-1 Nivolumab
3 mg/kg (1h IV)
every 2 weeks

until progression or unacceptable toxicity (or 2 years max)

CT-scan reassessment: 1rst at Week 12…

Anti-PD-1 Nivolumab
3 mg/kg
every 2 weeks
+ Anti-CTLA4 Ipilimumab
1mg/kg IV D1-D42,
every 6 weeks

until progression or unacceptable toxicity (or 2 years max)

→**Primary Endpoint: Disease Control Rate (DCR) at 12 weeks**

Scherpereel A et al, Lancet Oncol 2019

Essai MAPS 2

Tumor Response assessment after first 12 weeks by a blinded, independent panel of radiologists

in the **first 108 eligible patients**

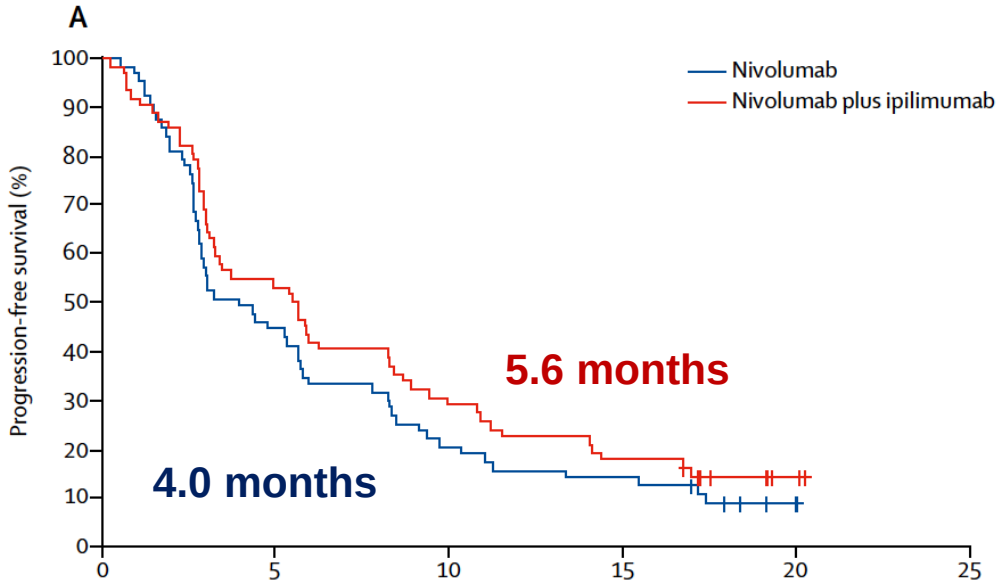
Tumor assessment % [IC95%](n pts)	NIVO Arm (n=54)	NIVO+IPI Arm (n=54)
Objective response	18.5% [8.2-28.9%](10)	25.9% [14.2-37.6%](14)
Stable Disease	25.9% [14.2-37.6%](14)	24.1% [12.7-35.5%](13)
Disease control rate at 12 wks	44.4% [31.2-57.7%](24)	50.0% [36.7-63.3%](27)
Disease Progression	51.9 [38.5-65.2%](28)	42.6% [29.4-55.8%](23)
Not evaluable/not done /missing	3.7% [0.0-8.7%](2)	7.4% [0.4-14.4%](4)

in the **ITT population (125 pts)**

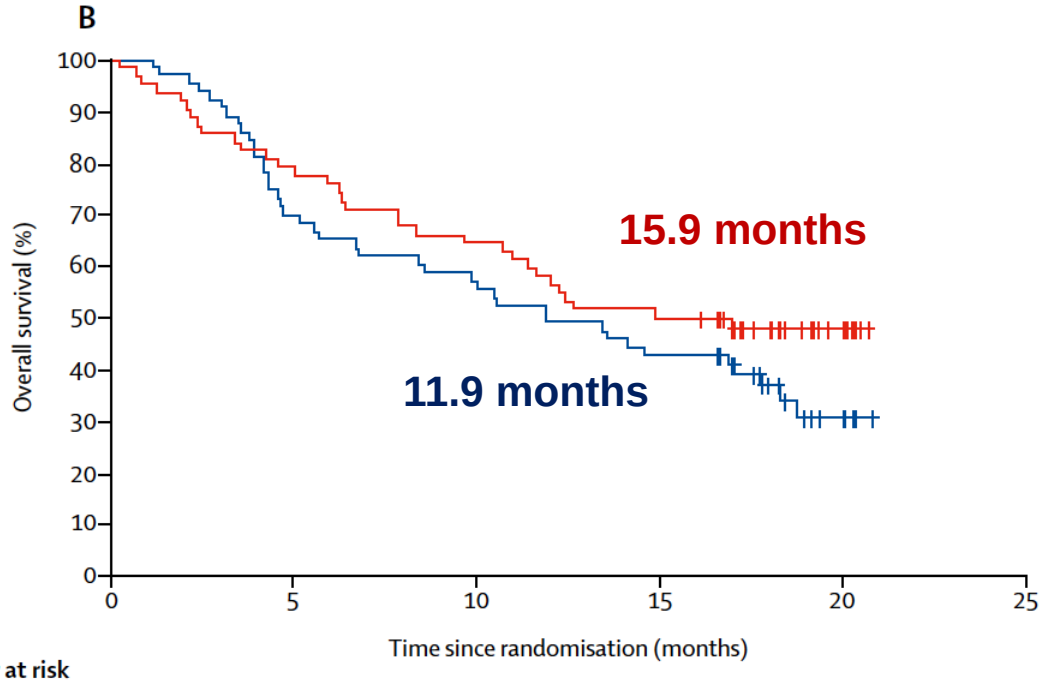
NIVO Arm (n=63)	NIVO+IPI Arm (n=62)
17.5% [8.1-26.8%] (11)	24.2% [13.5-34.9%] (15)
22.2% [12.0-32.5%] (14)	27.4% [16.3-38.5%] (17)
39.7% [27.6-51.8%] (25)	51.6% [39.2-64.1%] (32)
57.1% [44.9-69.4%] (36)	37.1% [25.1-49.1%] (23)
3.2% [0.0-7.5%] (2)	11.3% [3.4-19.2%] (7)

Scherpereel A et al, ASCO 2017; Zalcman G et al, ESMO 2017

Essai MAPS 2



Number at risk (number censored)						
Nivolumab	63 (0)	28 (0)	13 (0)	9 (0)	1 (5)	0 (6)
Nivolumab plus ipilimumab	62 (0)	34 (0)	19 (0)	11 (0)	2 (7)	0 (9)



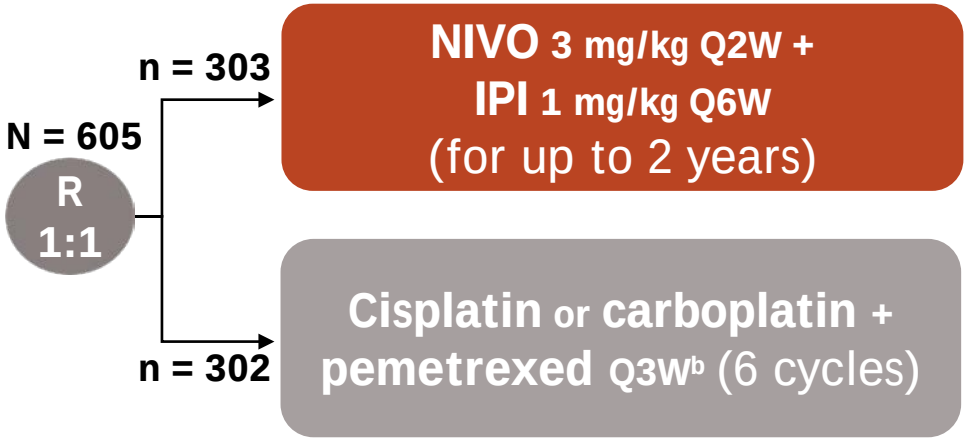
Number at risk (number censored)						
Nivolumab	63 (0)	44 (0)	35 (0)	27 (0)	5 (17)	0 (22)
Nivolumab plus ipilimumab	62 (0)	49 (0)	40 (0)	32 (0)	8 (22)	0 (30)

Scherpereel A et al, Lancet Oncol 2019

Essai Checkmate 743

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0–1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender



Until disease progression, unacceptable toxicity *or* for 2 years for immunotherapy arm

Primary Endpoint
- OS

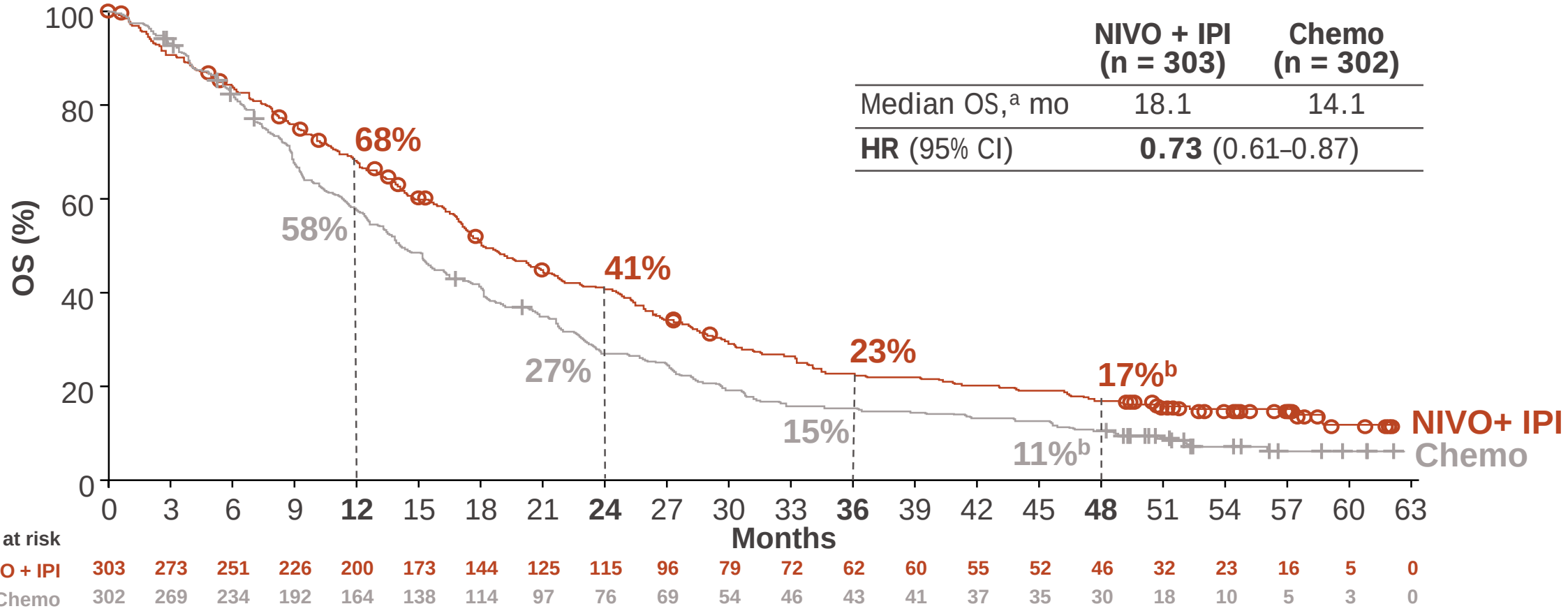
Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

Database lock: April 3, 2020; minimum follow-up for OS: 22.1 months; median follow-up: 29.7 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by PD-L1 IHC 28-8 pharmDx assay from Dako.

Baas P et al, Lancet 2021

Essai Checkmate 743



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	**0.73** (0.61–0.87)	

- 4-year PFS rates were 9% vs 0% with NIVO + IPI vs chemo[c]
- ORR and DOR were consistent with previous database lock[d]; rate of ongoing responders at 4 years was 16% vs 0%, respectively

Minimum / median follow-up for OS: 47.5 months / 55.1 months.

Zalcman G et al, ESMO 2022

Essai MESOIMMUNE – GFPC 04-2021

- National, multicenter, retrospective, non-interventional study

Key eligibility criteria
- Unresectable PM
- No prior systemic therapy
- No opposition to data collection

N = 350

NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W (French EAP: April 2021 - Feb 2022)

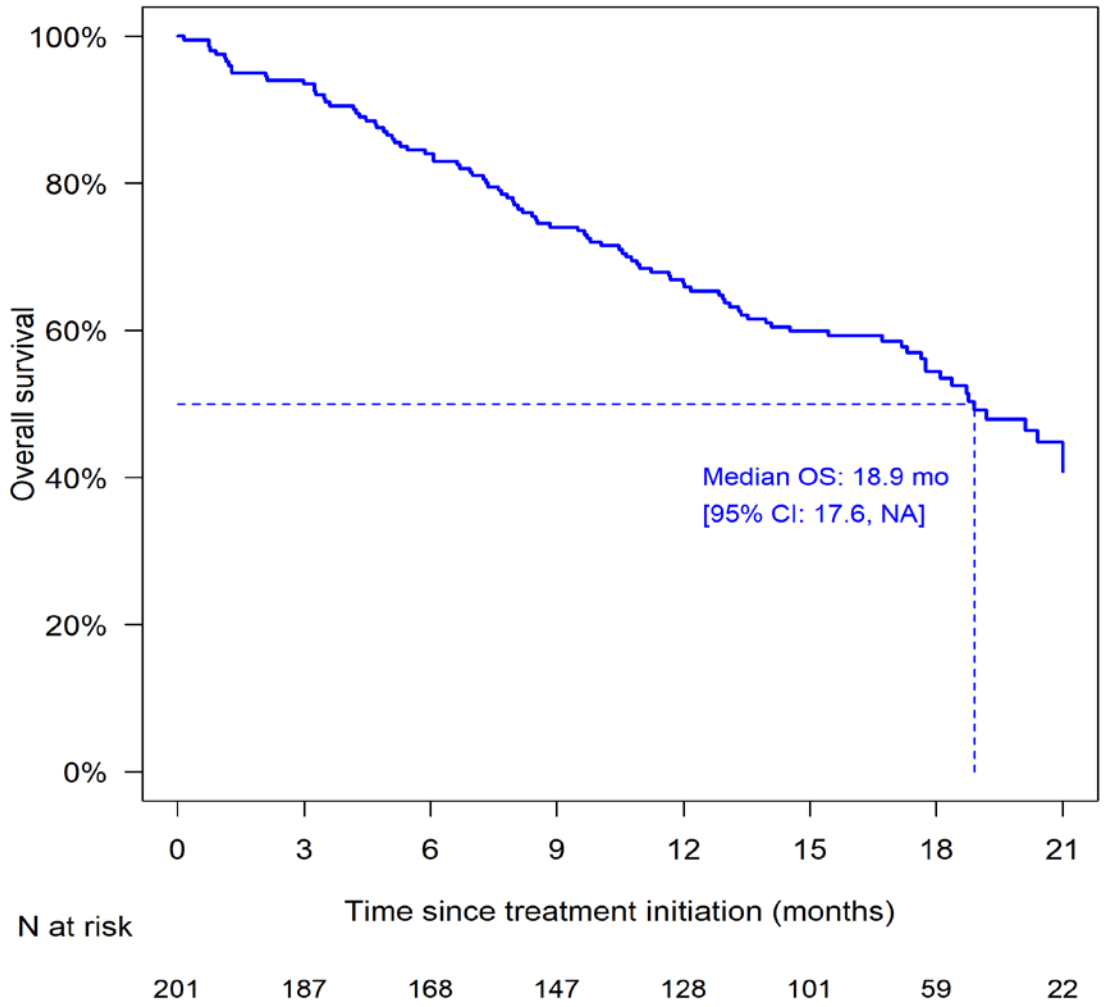
Until disease progression or unacceptable toxicity

Primary endpoint
- rw-PFS

Secondary endpoints
- rw-OS
- ORR
- Safety

Greillier L et al, IMiG 2023

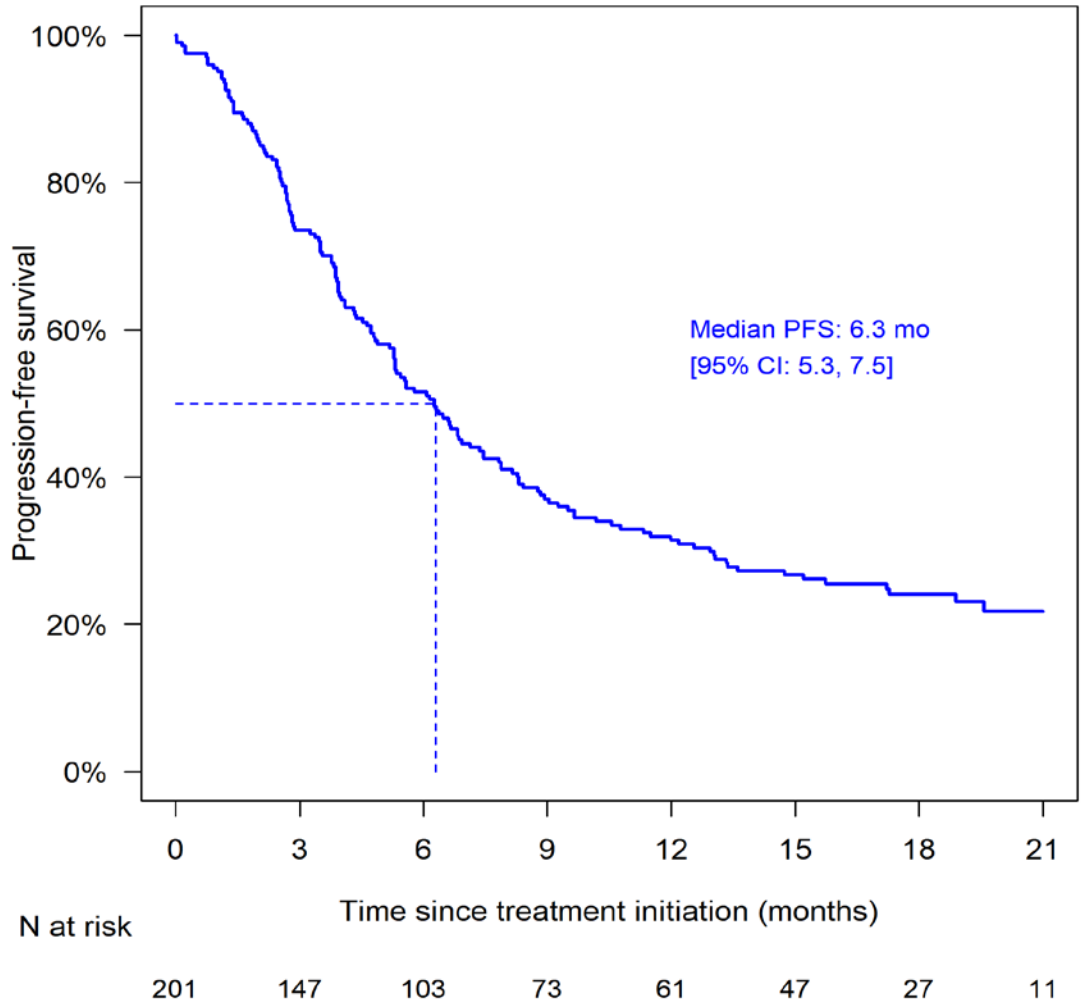
Essai MESOIMMUNE – GFPC 04-2021



Median follow-up: 18.4 months (95%CI 17.7-19.2)

Greillier L et al, IMiG 2023

Essai MESOIMMUNE – GFPC 04-2021



Median follow-up: 18.4 months (95%CI 17.7-19.2)

Greillier L et al, IMiG 2023

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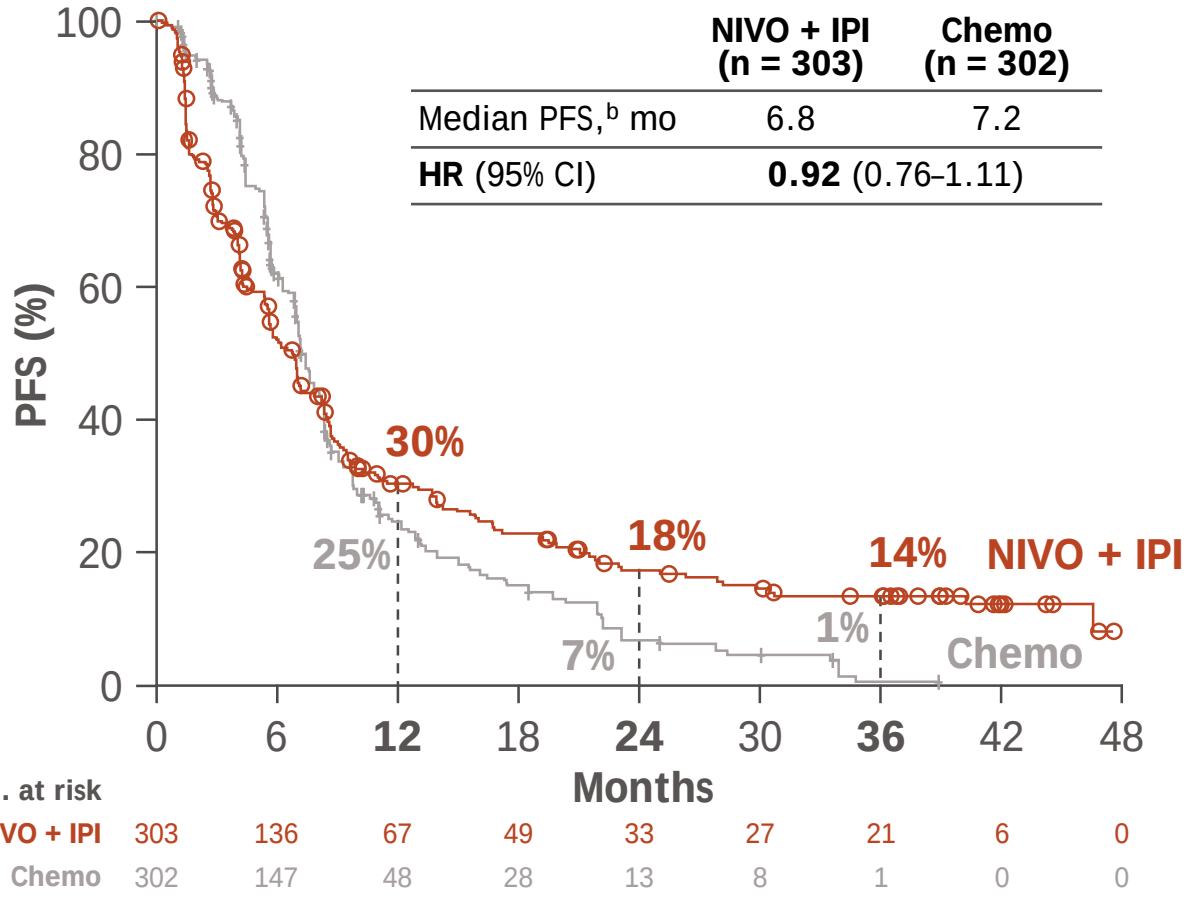
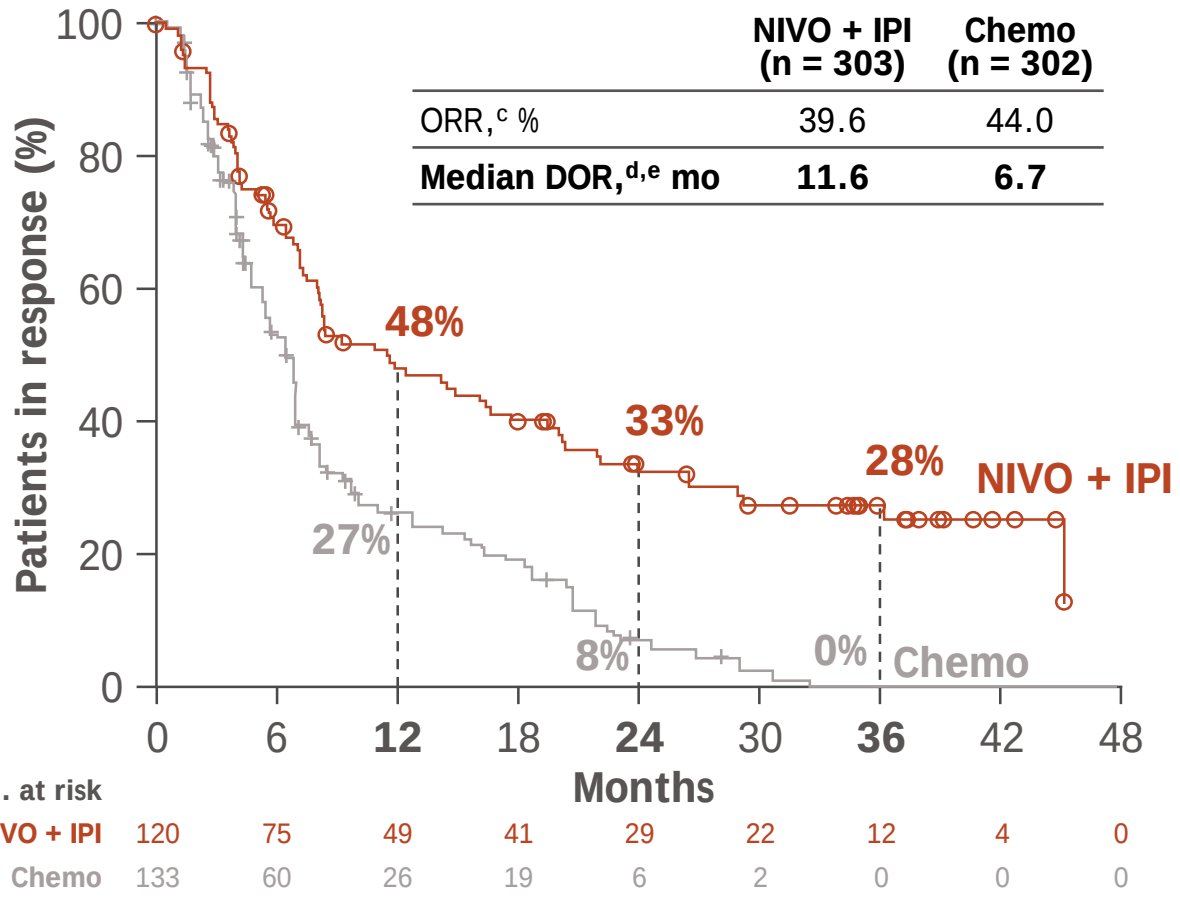
PFS[a]



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median PFS,[b] mo	6.8	7.2
HR (95% CI)	**0.92** (0.76–1.11)	

No. at risk									
NIVO + IPI	303	136	67	49	33	27	21	6	0
Chemo	302	147	48	28	13	8	1	0	0

ORR/DOR[a]



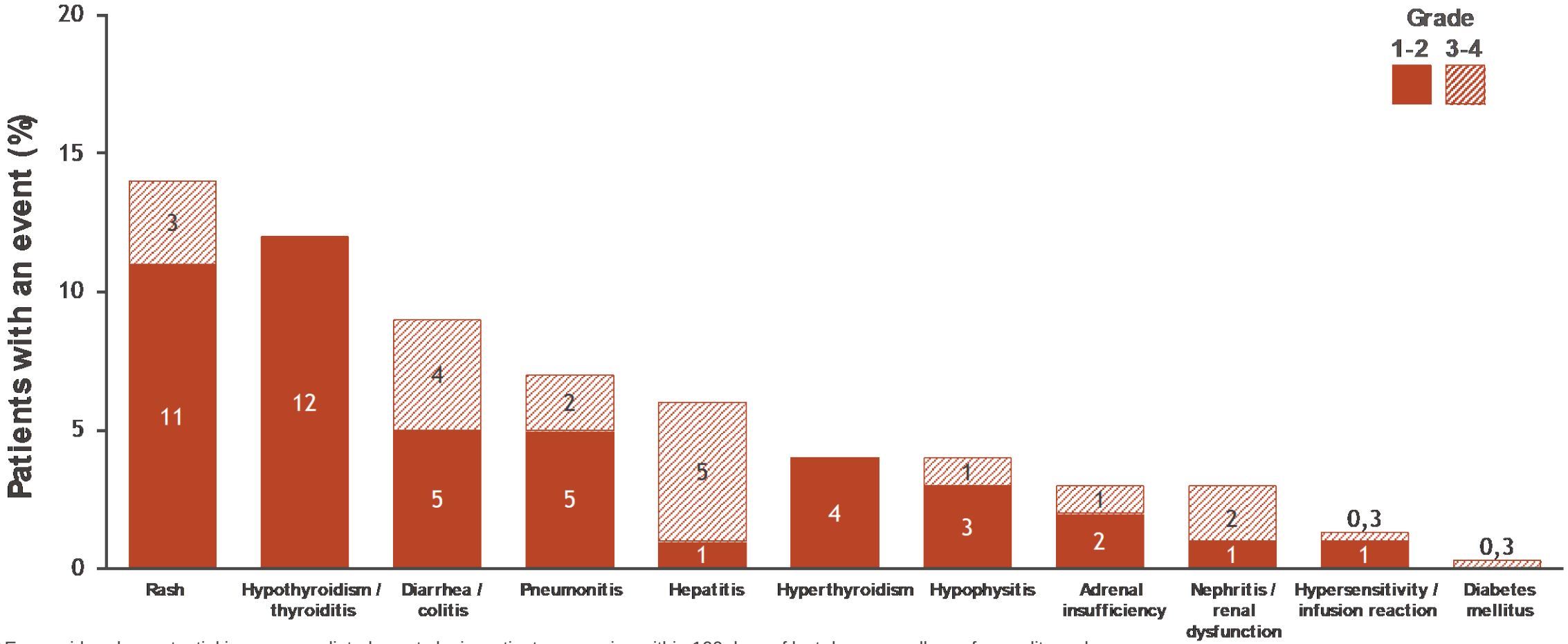
	NIVO + IPI (n = 303)	Chemo (n = 302)
ORR,[c] %	39.6	44.0
Median DOR,[d,e] mo	**11.6**	**6.7**

No. at risk									
NIVO + IPI	120	75	49	41	29	22	12	4	0
Chemo	133	60	26	19	6	2	0	0	0

[a]Per BICR; [b]95% CIs were 5.6–7.4 (NIVO + IPI) and 6.9–8.0 (chemo); [c]8 patients (7 with epithelioid histology and 1 with non-epithelioid histology) treated with NIVO + IPI and 0 patients treated with chemo had CR; [d]DOR was calculated in patients with a response (NIVO + IPI: n = 120, chemo: n = 133); [e]95% CIs were 8.2–16.8 (NIVO + IPI) and 5.6–7.1 (chemo).

Peters S et al, ESMO 2021

Essai Checkmate 743



[a]Includes AEs considered as potential immune-mediated events by investigator occurring within 100 days of last dose regardless of causality and treated with immune-modulating medication, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. CTCAE Version 4.0; MedDRA Version: 25.0.

Zalcman G et al, ESMO 2022

Essai Checkmate 743

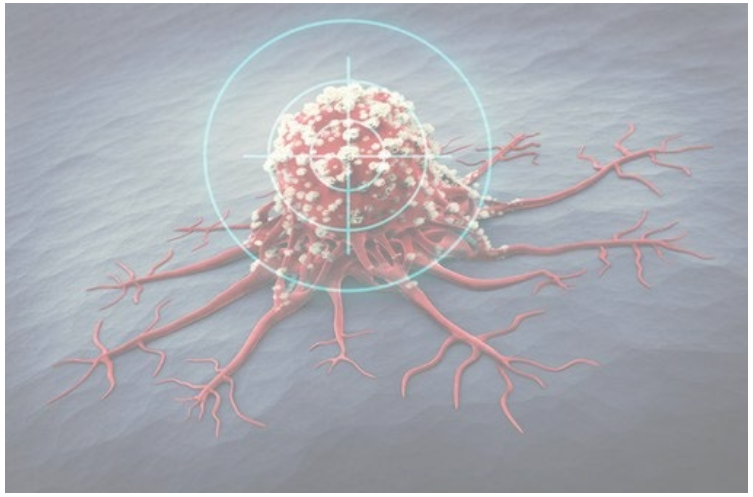
TRAE, %	NIVO + IPI[a] (n = 300)		Chemo[b] (n = 284)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE[c]	80	31	82	32
TRAEs leading to discontinuation of any component of the regimen[c]	23	15	16	7
TRAEs leading to discontinuation of all components of the regimen	17	13	8	5
Serious TRAEs[c]	21	16	8	6
Treatment-related deaths	1[d]		<1[e]	

Person-years of exposure: NIVO + IPI, 220.7; chemo, 94.6.

[a]Median (IQR) doses for treated patients: NIVO 12.0 (5.0–23.5); IPI 4.0 (2.0–7.0); [b]Median (IQR) doses for treated patients: pemetrexed 6.0 (4.0–6.0), cisplatin 5.0 (3.0–6.0), carboplatin 6.0 (4.0–6.0); [c]Includes events reported between first dose and 30 days after last dose of study drug; [d]3 deaths due to NIVO + IPI: pneumonitis, encephalitis, acute heart failure; [e]1 death due to chemo: myelosuppression.

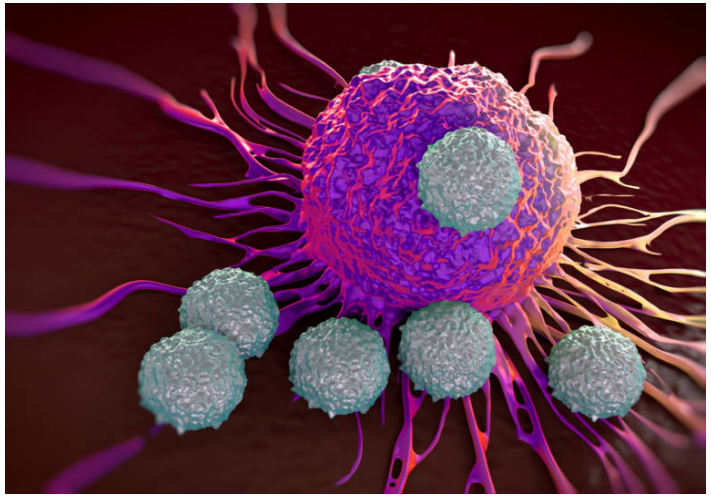
Peters S et al, ESMO 2021

Stratégies thérapeutiques dans le mésothéliome



Thérapies ciblées

Chimiothérapie



Immunothérapie

Essai IND227 – IFCT 1901

Randomized, open-label phase III trial

- **Histological** diagnosis of **Malignant Pleural Mesothelioma**
- **Unresectable advanced and/or metastatic disease**
- **Available tumor tissue**
- **Measurable disease**
- **ECOG PS 0-1**
- **Age > 18 years (M or F)**
- **Exclusion criteria:** history of other malignancy, auto-immune disease, primary immunodeficiency or drug immunosuppression, ILD...

440 patients
(91 patients en France)

R 1:1

Cisplatin 75mg/m² *
+ Pemetrexed 500 mg/m²
+ Pembrolizumab 200 mg
in 21 day cycles for up to six cycles

Cisplatin 75mg/m² *
+ Pemetrexed 500 mg/m²
in 21 day cycles for up to six cycles

Pembrolizumab until progression or unacceptable toxicity (or 2 years max)

CT-scan reassessment: every 6 weeks for 3 assessments then every 12 weeks

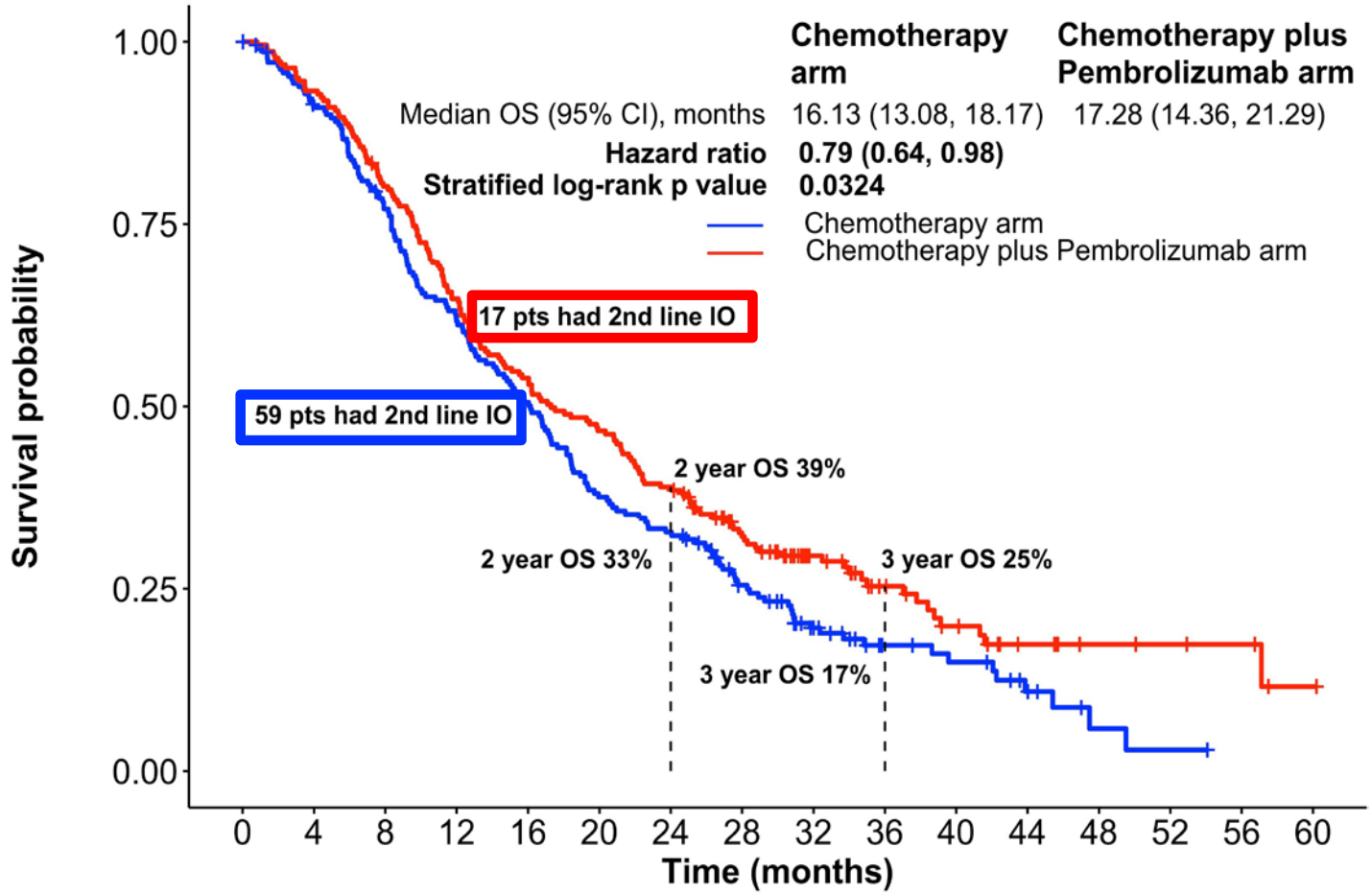
Follow-up

→Primary Endpoint: Overall survival

* Le carboplatine est autorisé après discussion avec le sponsor

Chu Q, Greillier L et al, Lancet 2023

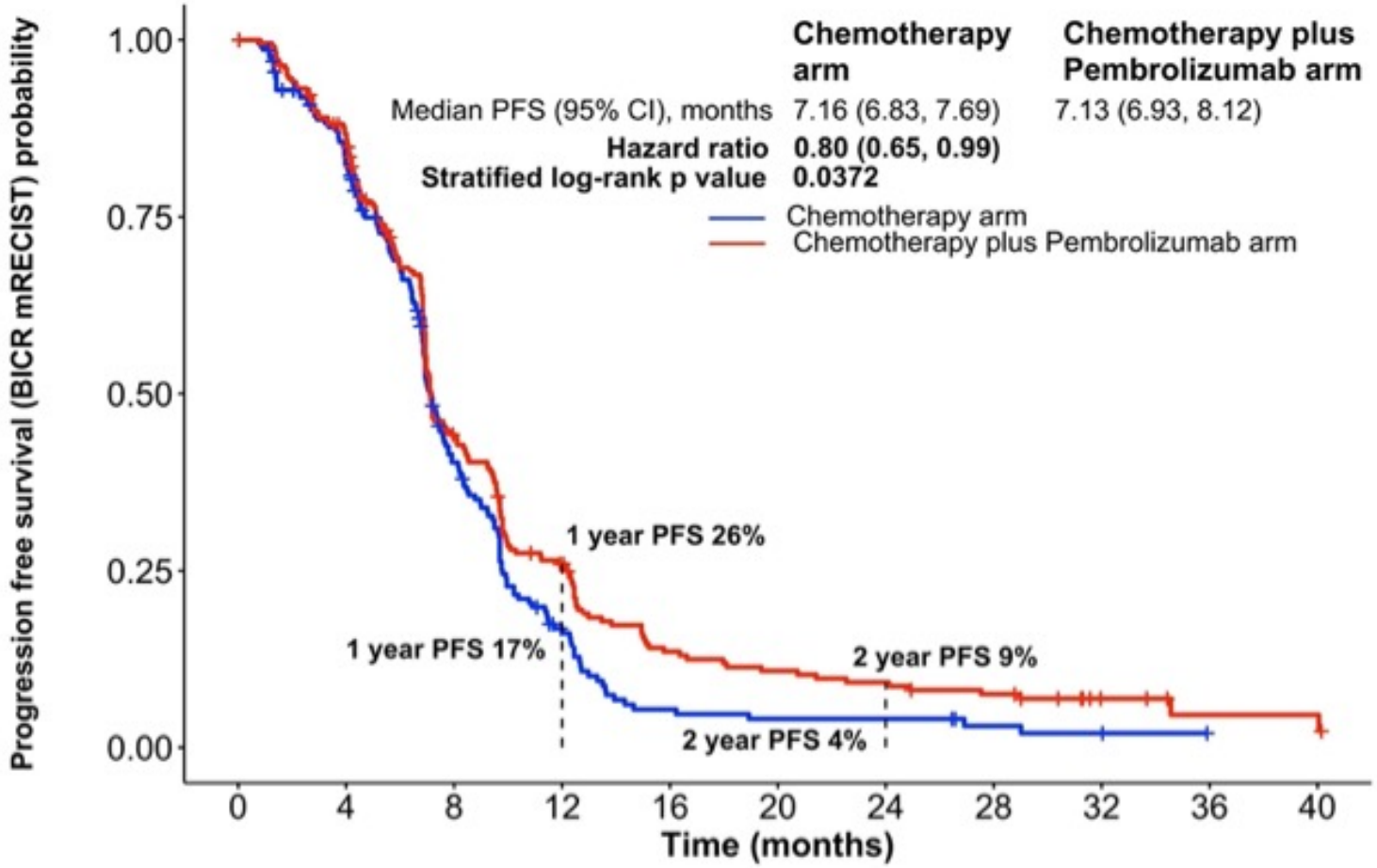
Essai IND227 – IFCT 1901



Patients enrolled Jan 2017-Sept 2020
Median follow up 16.16 months
All pts discontinued all study drugs

Chu Q, Greillier L et al, Lancet 2023

Essai IND227 – IFCT 1901



Chu Q, Greillier L et al, Lancet 2023

Essai IND227 – IFCT 1901

Response		CP (N=218)	CPP (N=222)	P-value
Complete Response		**0**	**2 (1%)**	**P< 0.0001**
Partial Response		**83 (38%)**	**136 (61%)**	
Stable disease/non-CR/PD		103 (47%)	70 (32%)	
Disease Progression		11 (5%)	9 (4%)	
Response could not be assigned	Total	21 (10%)	5 (2%)	
	Never treated/WOC[1]	7 (3%)	0	
	Other reasons[2]	9 (4%)	3 (1%)	
	No baseline images uploaded	5 (2%)	2 (1%)	
Duration of CR/PR (mths)	Median (95% CI)	5.5m (4.2-6)	5.8m (5.5-7)	P=0.185
	Range	0.03, 25.1	0.03, 38.9	

1. Withdrawal of consent/refusal after random assignment
2. Not assessed after baseline/lesions obscured

Includes patients with imaging for central review

Chu Q, Greillier L et al, Lancet 2023

Essai IND227 – IFCT 1901

Adverse Event	CP (n = 211)			CPP (n = 222)		
	Grade[2] 1-2	Grade 3	Grade 4 [3]	Grade 1-2	Grade 3	Grade 4[3]
Any	141 (67%)	**31 (15%)**	**1(<1%)**	138 (65%)	**50 (23%)**	**10 (5%)**
Nausea	93 (44%)	2 (1%)	0	99 (45%)	10 (5%)	0
Fatigue	100 (47%)	12 (6%)	0	97 (44%)	15 (7%)	0
Diarrhea	**18 (9%)**	**3(1%)**	**0**	**48 (22%)**	**3 (1%)**	**0**
Mucositis oral	32 (15%)	2 (1%)	0	42 (19%)	0	0
Vomiting	29 (14%)	2 (1%)	0	40 (18%)	3 (1%)	0
Anorexia	36 (17%)	2 (1%)	0	38 (17%)	0	0
Constipation	27 (13%)	0	0	36 (16%)	0	0
Pruritus	**7 (3%)**	**0**	**0**	**33 (15%)**	**0**	**0**
Rash maculo-papular	**14 (7%)**	**1 (<1%)**	**0**	**28 (13%)**	**2 (1%)**	**0**
Dysgeusia	27 (13%)	0	0	26 (12%)	0	0
Watering eyes	14 (7%)	0	0	26 (12%)	0	0
Peripheral sensory neuropathy	17 (8%)	0	0	24 (11%)	0	0
Anemia	0	0	0	0	4 (2%)	1 (<1%)
Febrile neutropenia	**0**	**2 (1%)**	**0**	**0**	**8 (4%)**	**3 (1%)**

Canadian Cancer Trials Group IFCT

Chu Q, Greillier L et al, Lancet 2023

Hôpitaux Universitaires de Marseille | ap·hm

CRCM Centre de Recherche en Cancérologie de Marseille

Aix*Marseille université

Essai IND227 – IFCT 1901

Pooled AE term	CP N=211 : All Causality		CPP N = 222			
	All (%)	≥ grade 3 (%)	All (%)		≥ grade 3 (%)	
			All Causality			
Skin toxicity	18%	<1%	36%	**26%**	1%	**1%**
Diarrhea/colitis	14%	1%	32%	**22%**	3%	**3%**
Chills/fever	12%	<1%	31%	**8%**	-	**-**
Sensory neuropathy	15%	-	24%	**8%**	-	**-**
Abdominal Pain	9%	<1%	18%	**6%**	3%	**1%**
Joint Pain/Inflammation	2%	-	13%	**8%**	1%	**1%**
Ototoxicity	11%	<1%	13%	**2%**	<1%	**0%**
Myositis, muscle	5%	-	10%	**4%**	1%	**<1%**
Hypothyroidism	2%	-	9%	**7%**	-	**-**
Cognitive	7%	<1%	7%	**1%**	<1%	**0%**
Infusion reactions	1%	-	5%	**3%**	-	**-**
Pneumonitis	-	-	5%	**5%**	2%	**2%**
Nephritis/AKI	1%	-	4%	**3%**	2%	**1%**
Hepatitis	-	-	2%	**2%**	2%	**2%**
Thrombocytopenia	<1%	<1%	2%	**0%**	2%	**0%**
Motor neuropathy	<1%	-	2%	**1%**	<1%	**<1%**

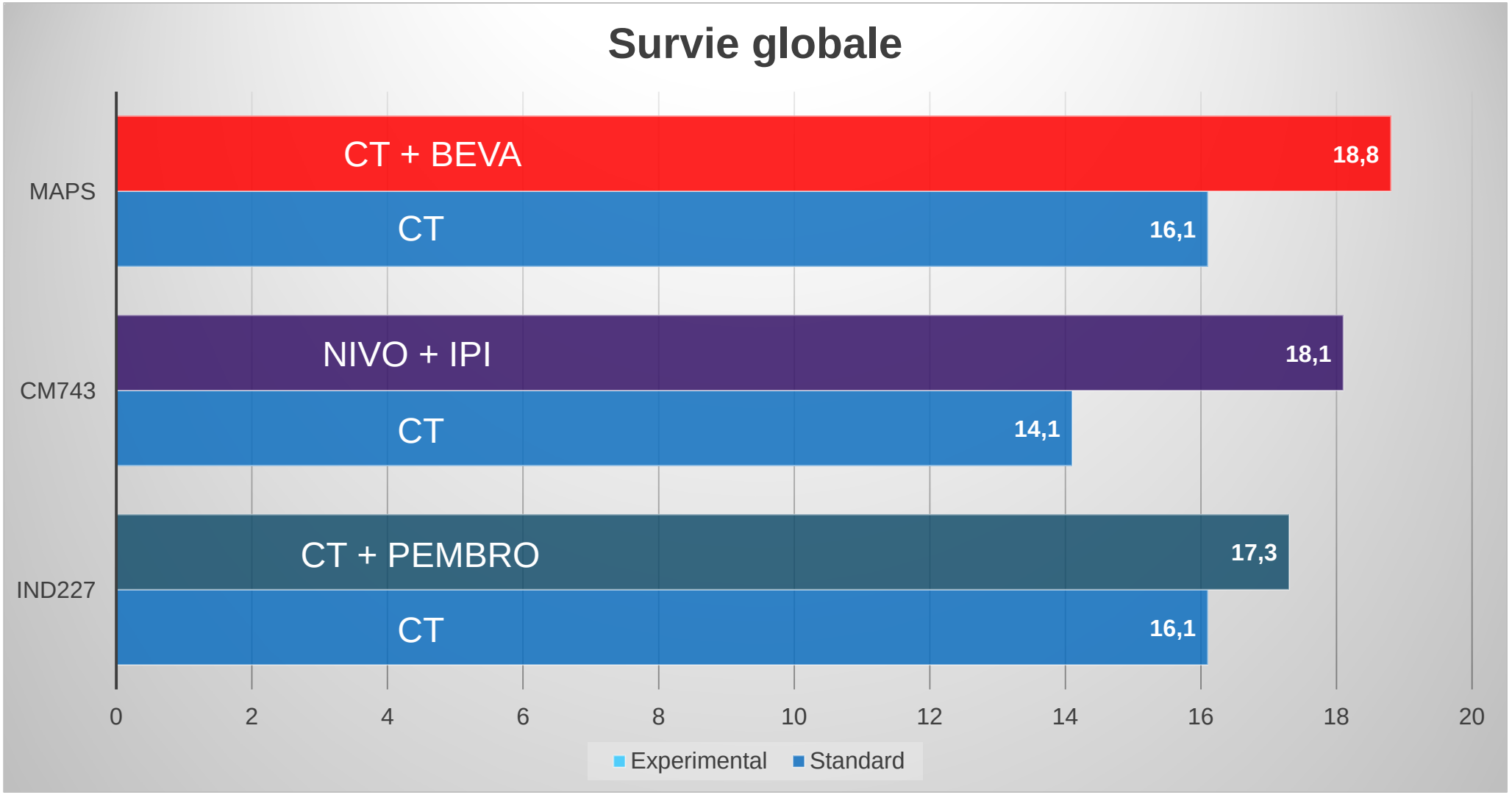
Essai IND227 – IFCT 1901

	Chemotherapy alone (n=211)		Chemotherapy plus pembrolizumab (n=222)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Discontinued any protocol therapy due to adverse event	42 (20%)	13 (6%)	82 (37%)	37 (17%)
Discontinued any protocol treatment due to adverse event (excluding platinum)	14 (7%)	7 (3%)	62 (28%)	33 (15%)
Discontinued platinum for adverse event	42 (20%)	13 (6%)	58 (26%)	21 (9%)
Death due to adverse event (all causes)	11 (5%)	..	14 (6%)	..
Death due to related adverse event	2 (1%)	..	7 (3%)	..
Death within 24 h of onset of a related adverse event	1 (<1%)	..	2 (1%)	..

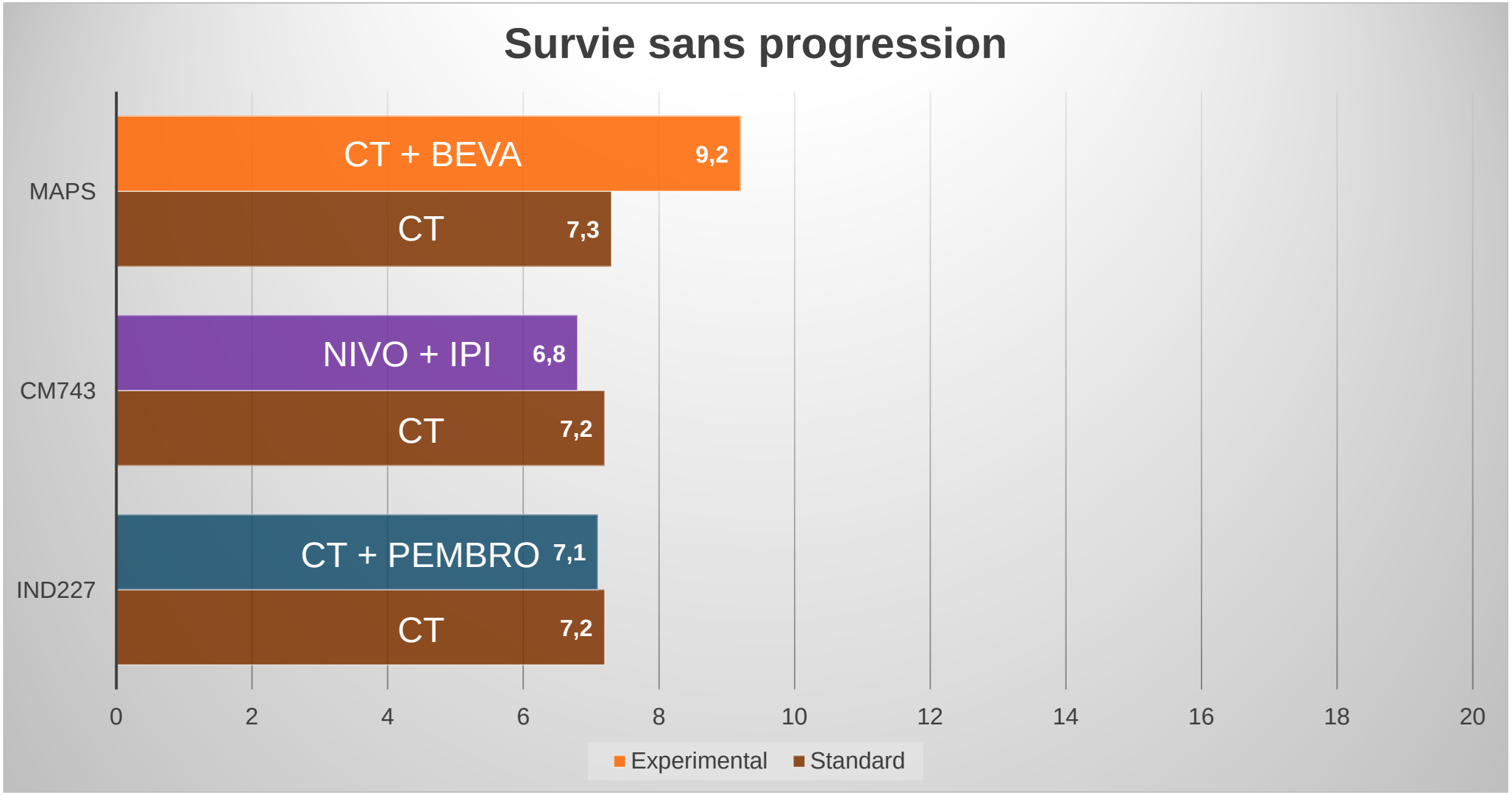
Chu Q, Greillier L et al, Lancet 2023

Quelle(s) stratégie(s) ?

Quelle(s) stratégie(s) ?



Quelle(s) séquence(s) thérapeutiques ?



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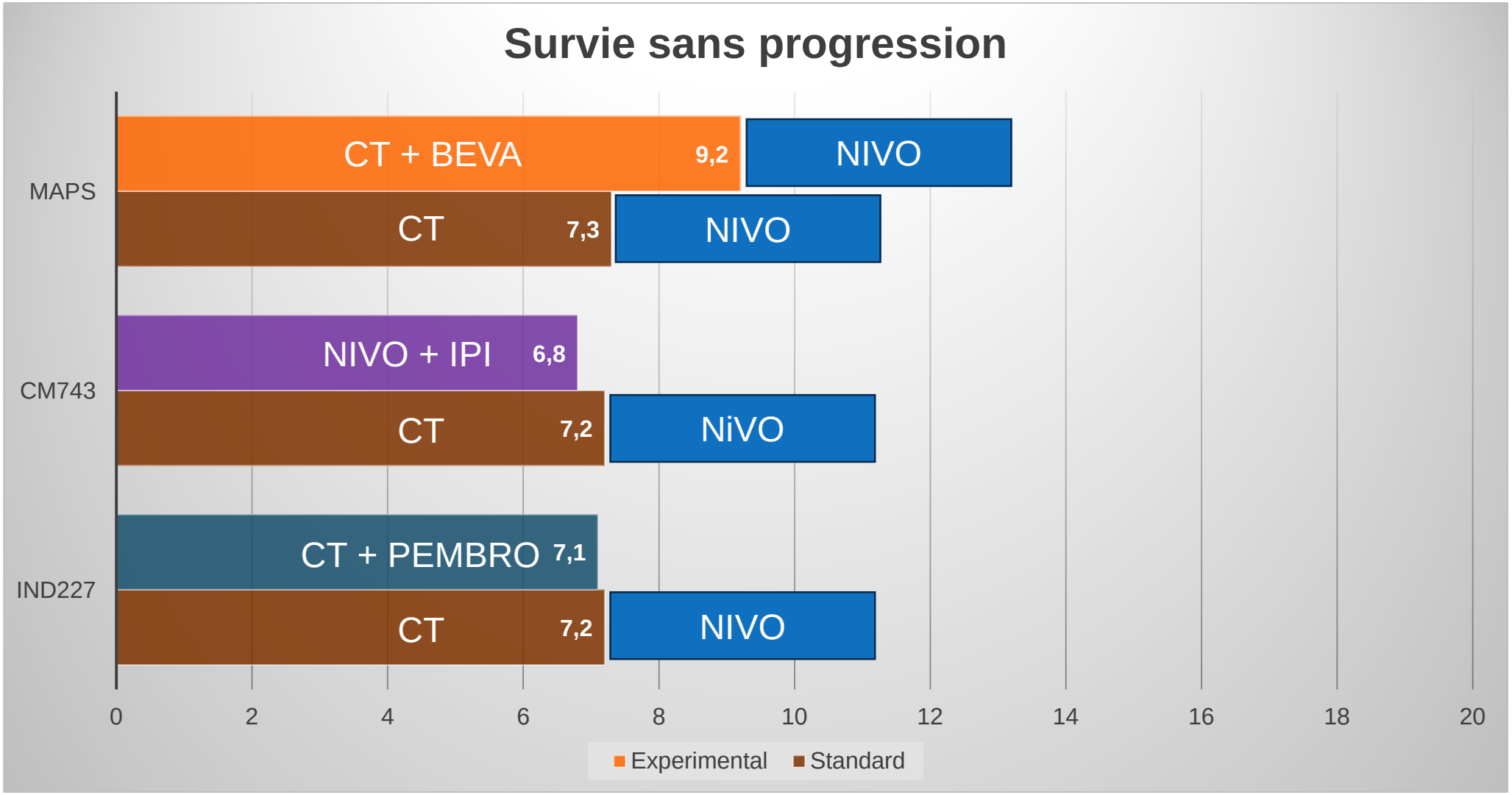

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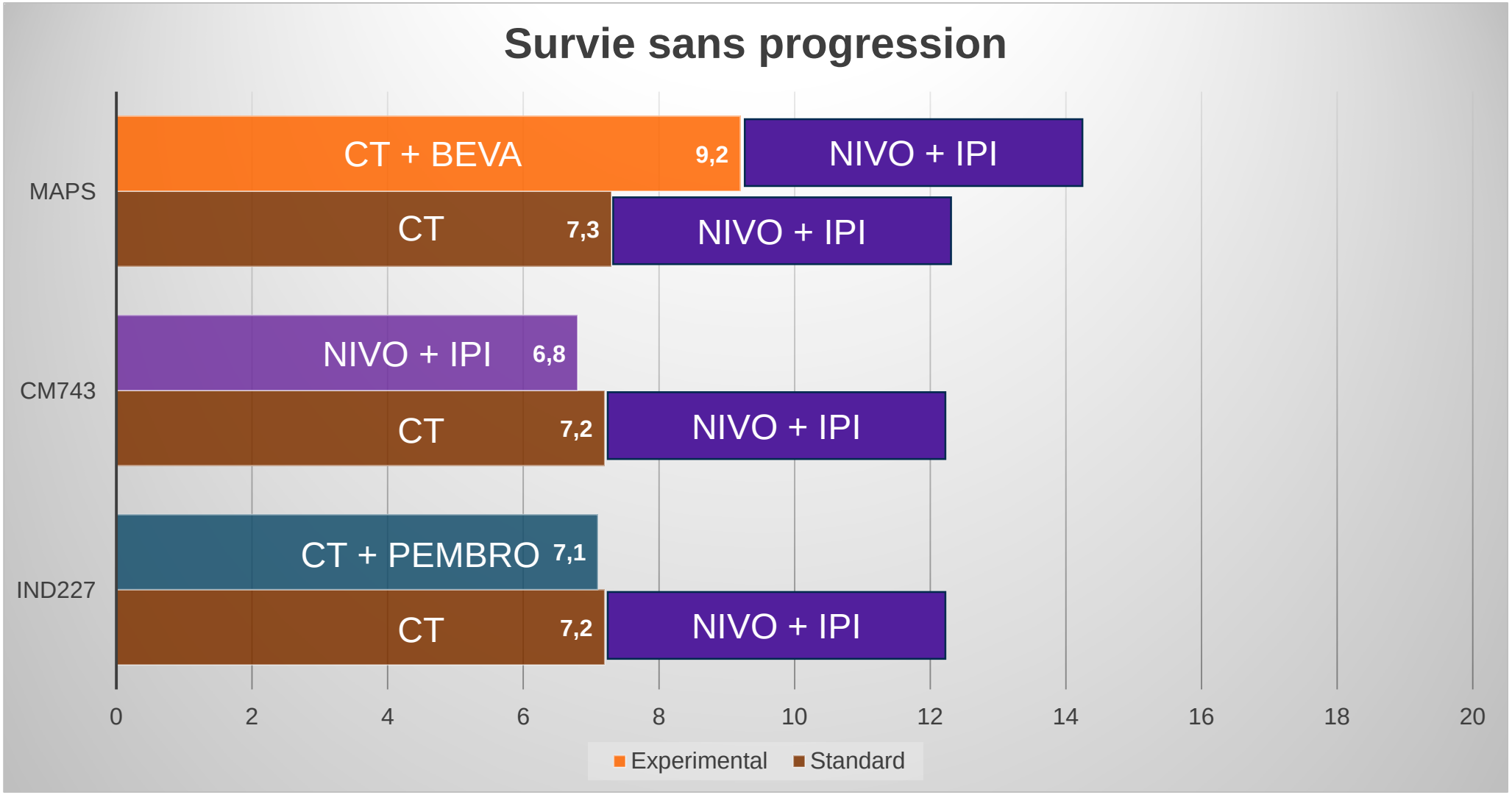

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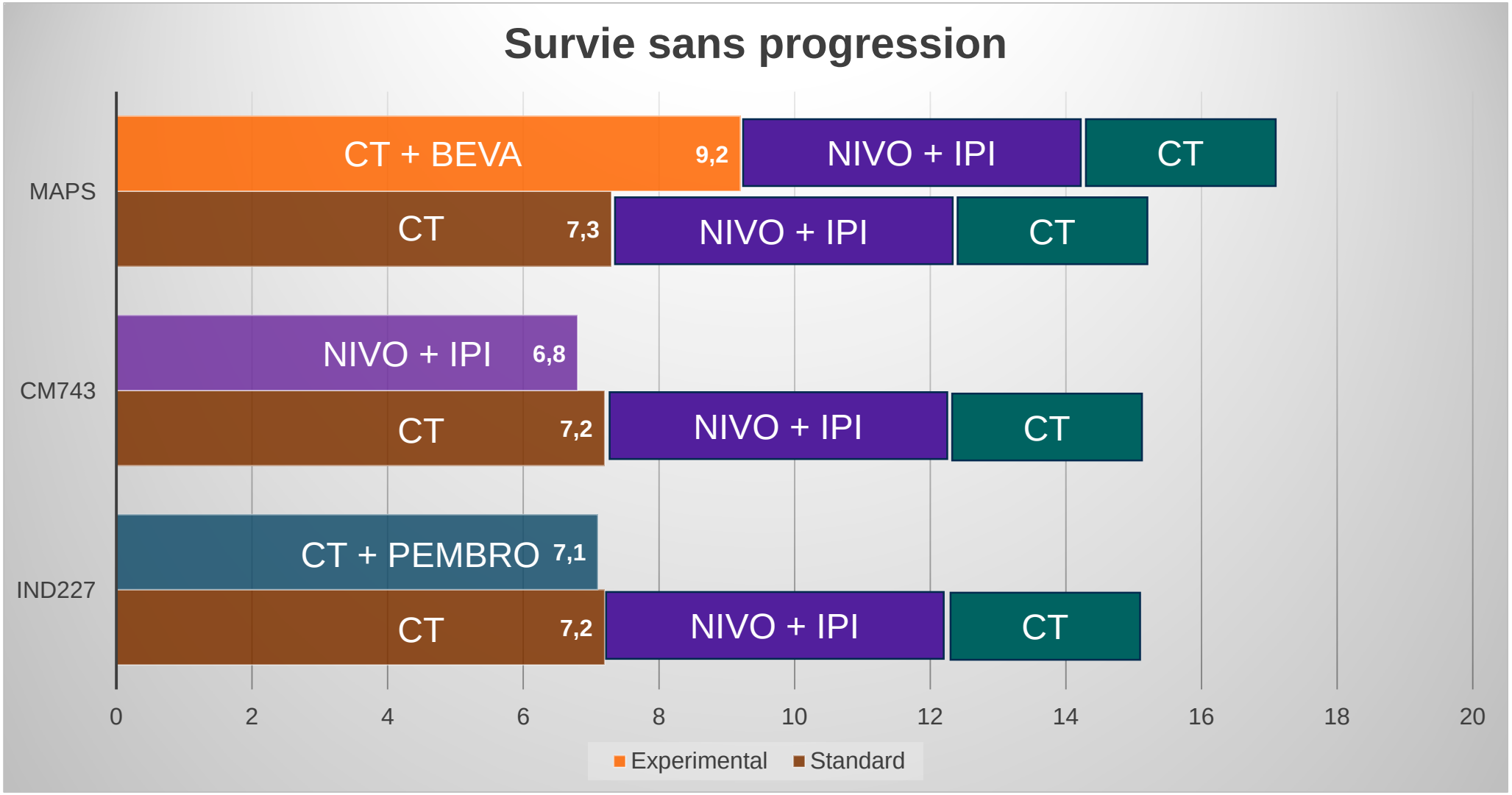

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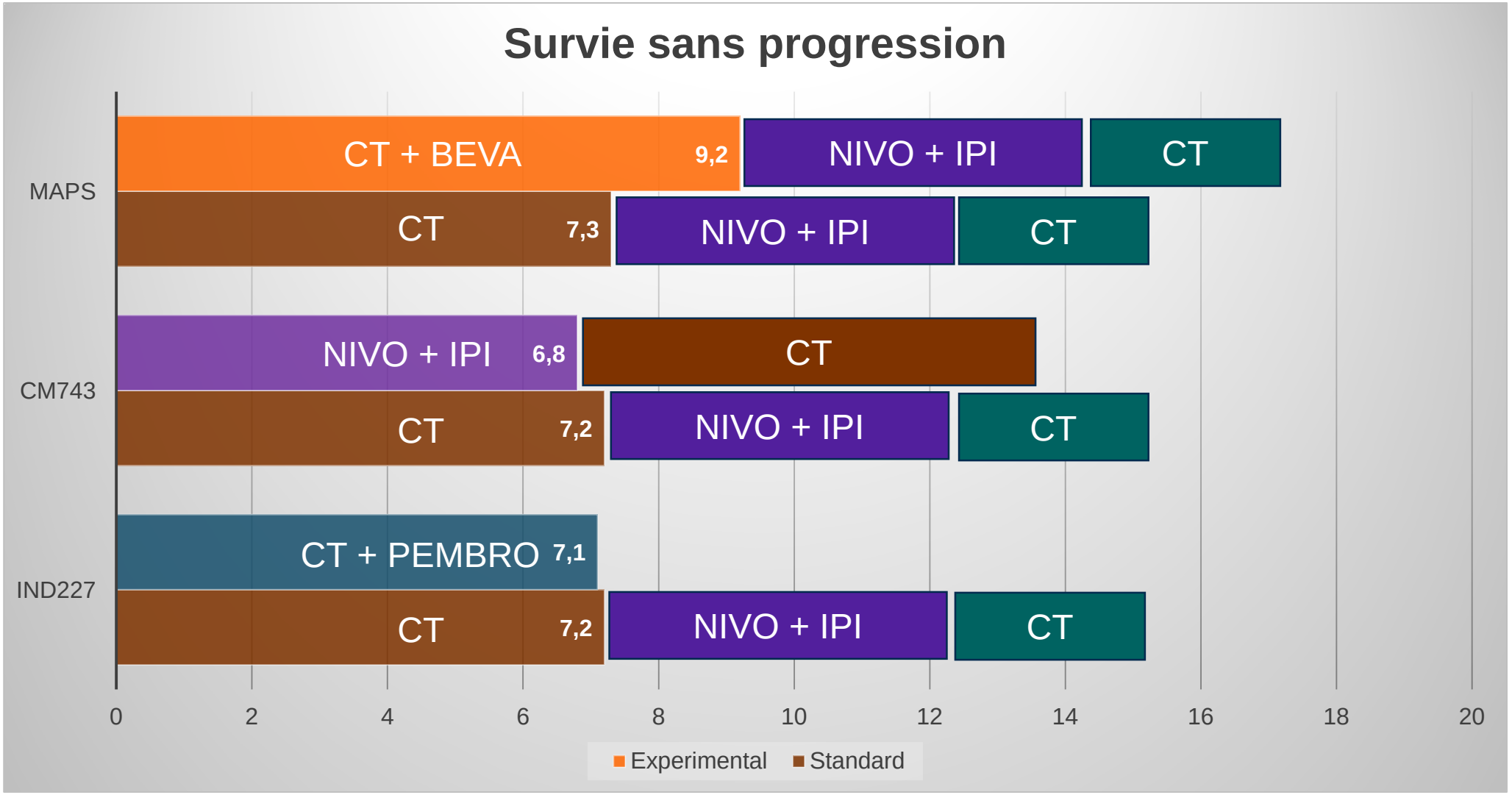

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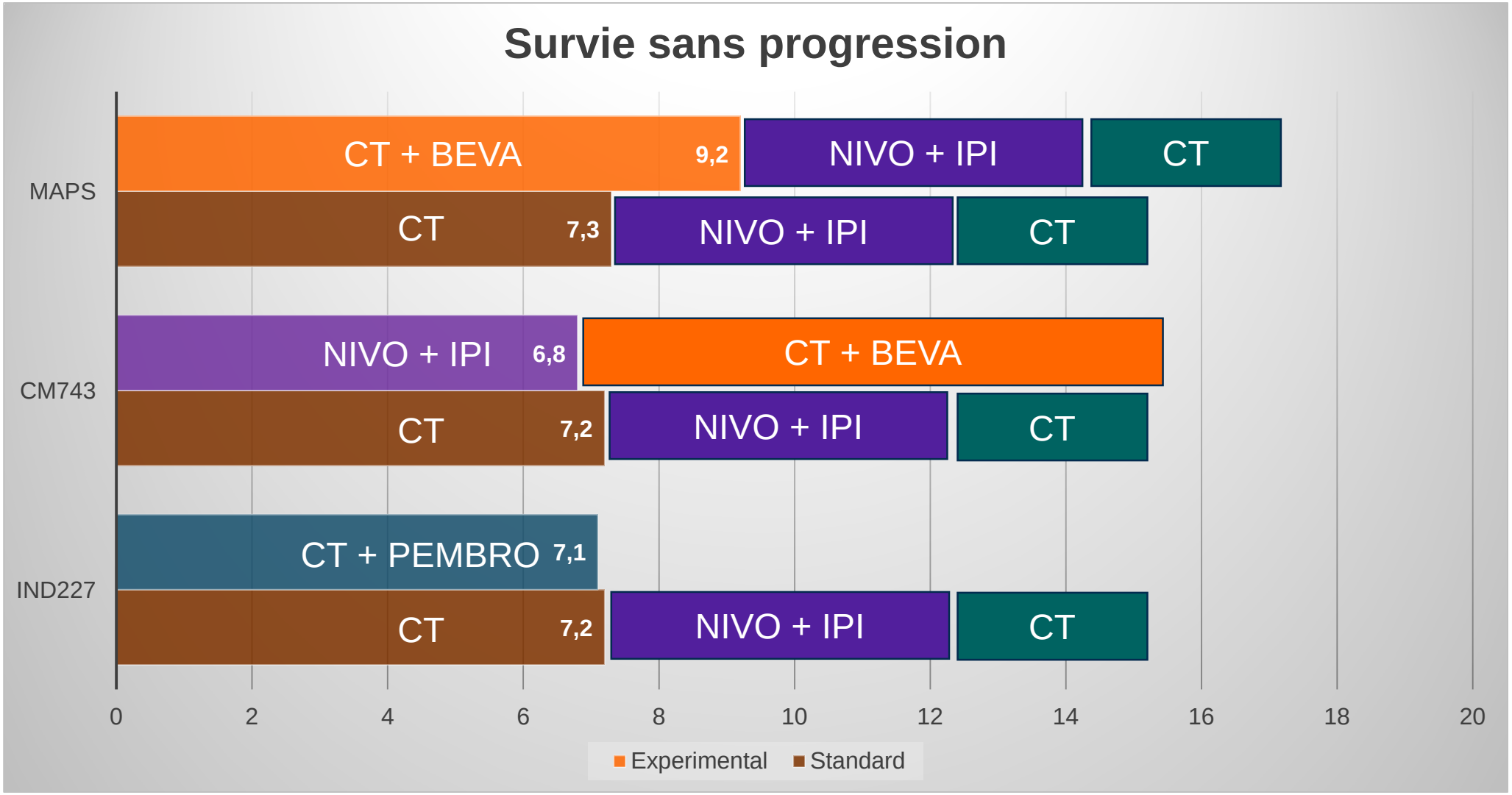
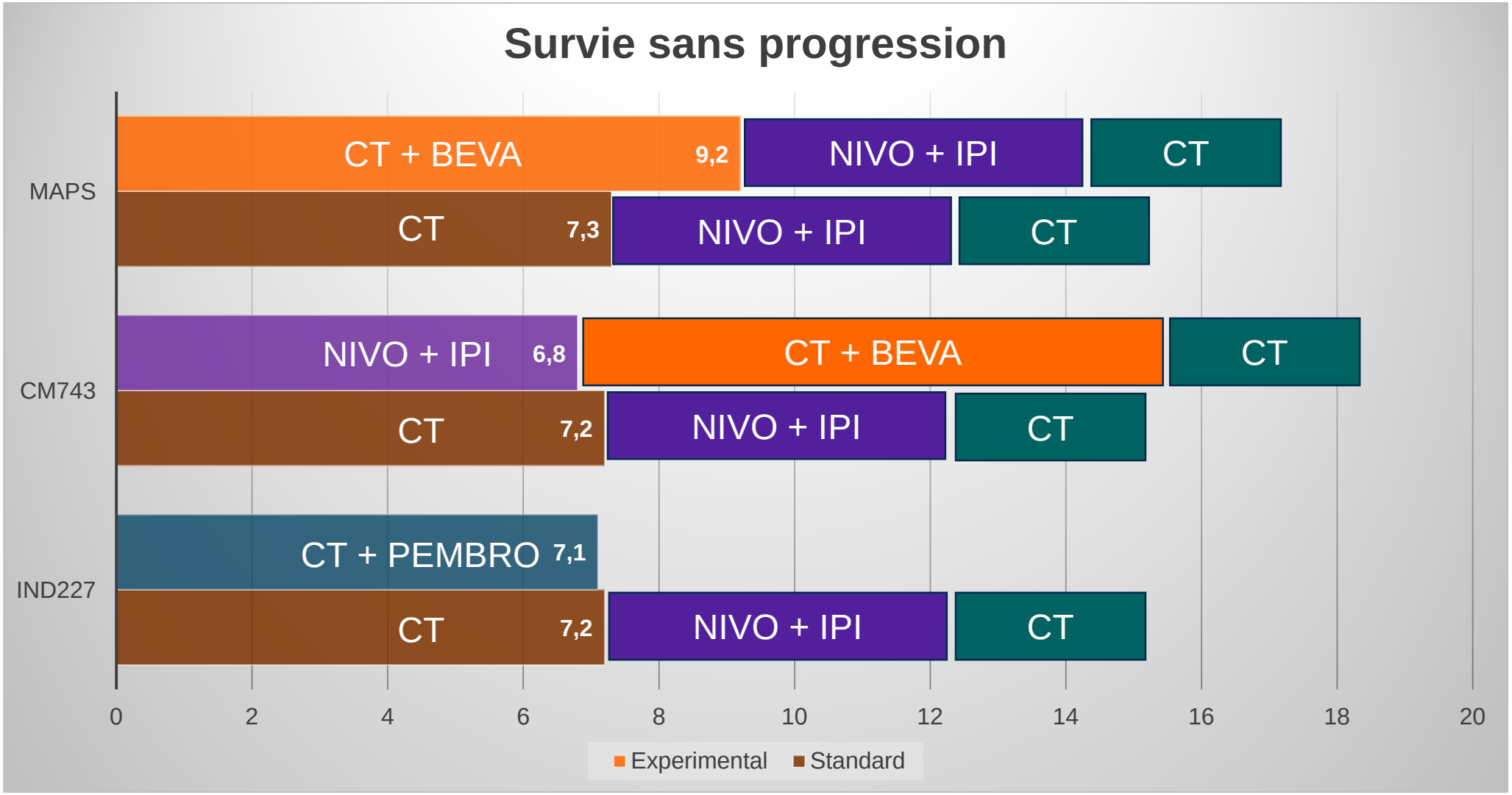


Essai MESOIMMUNE – GFPC 04-2021

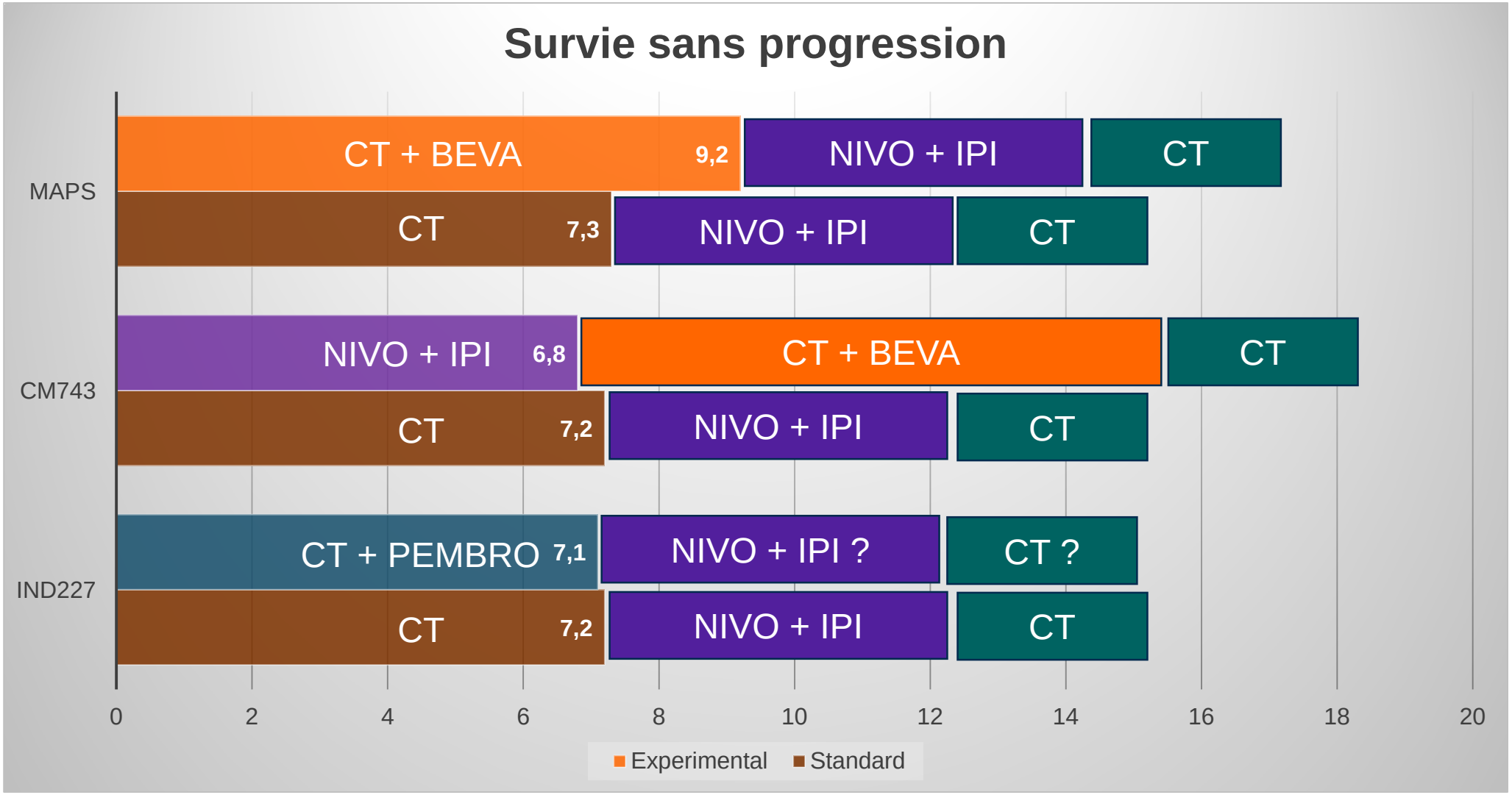
	Nivolumab + Ipilimumab N=201
Disease progression	152 (**75.6%**)
Second-line treatment	101/152 (**66.5%**)
Type of treatment (N=101)	
Platinum/Pemetrexed/Bevacizumab	43 (**42.5%**)
Platinum/Pemetrexed	43 (**42.5%**)
Mono-chemotherapy	11 (**10.9%**)
Pemetrexed	7
Gemcitabine	2
Navelbine	2
Clinical Trial	1 (**0.9%**)
NA	3 (2.7%)

Greillier L et al, IMiG 2023

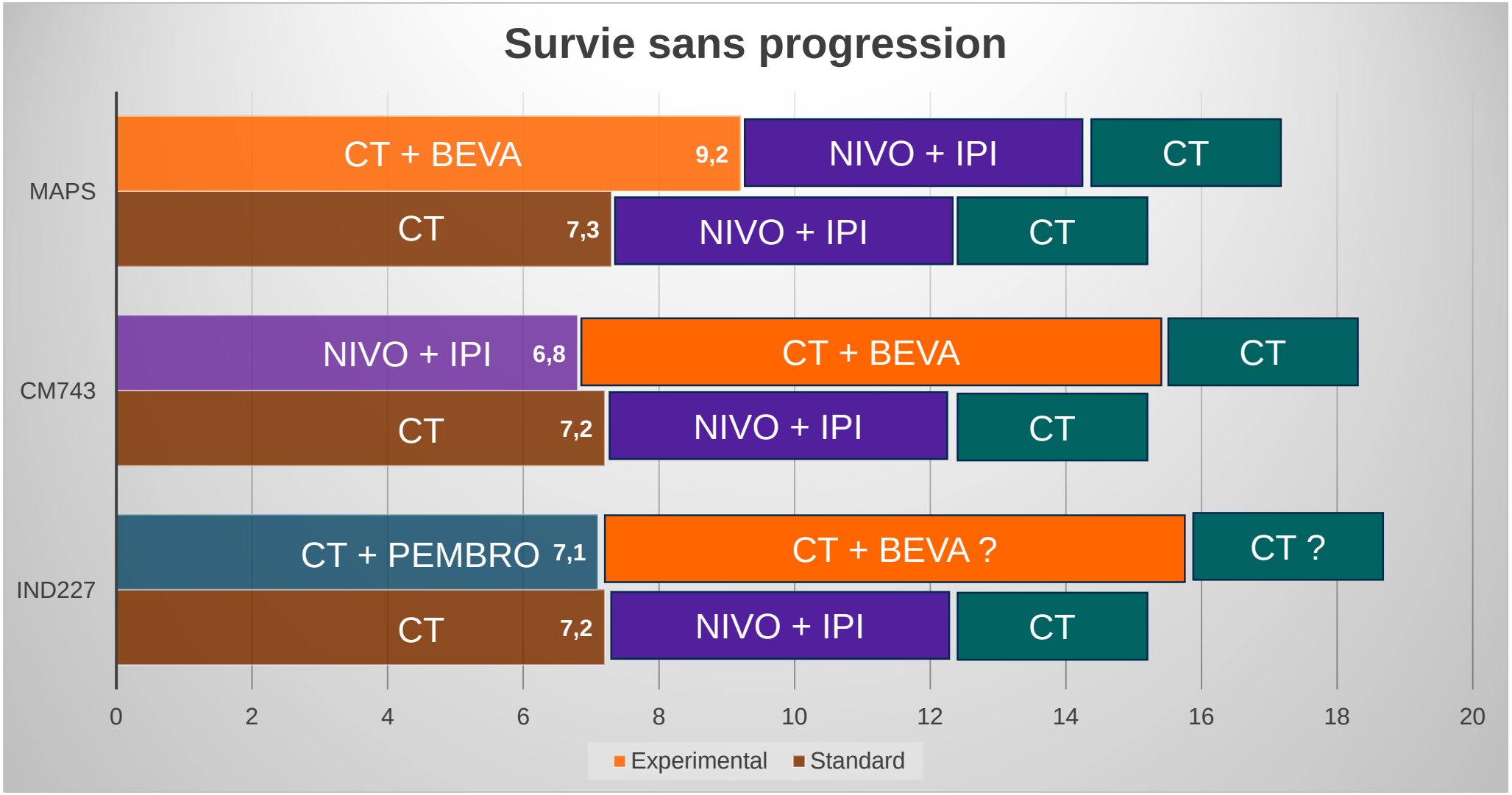
Quelle(s) séquence(s) thérapeutiques ?



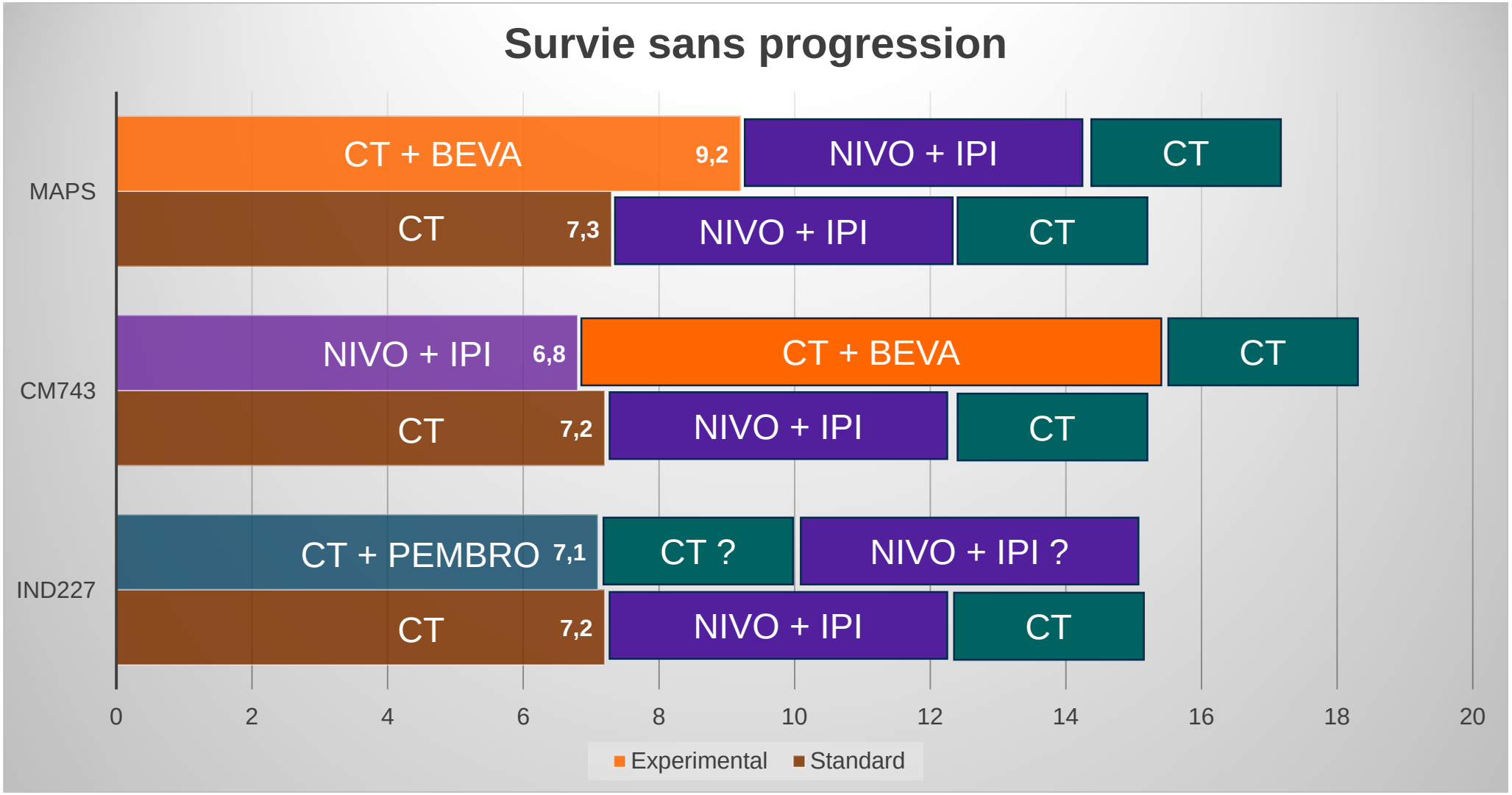
Quelle(s) séquence(s) thérapeutiques ?



Quelle(s) séquence(s) thérapeutiques ?



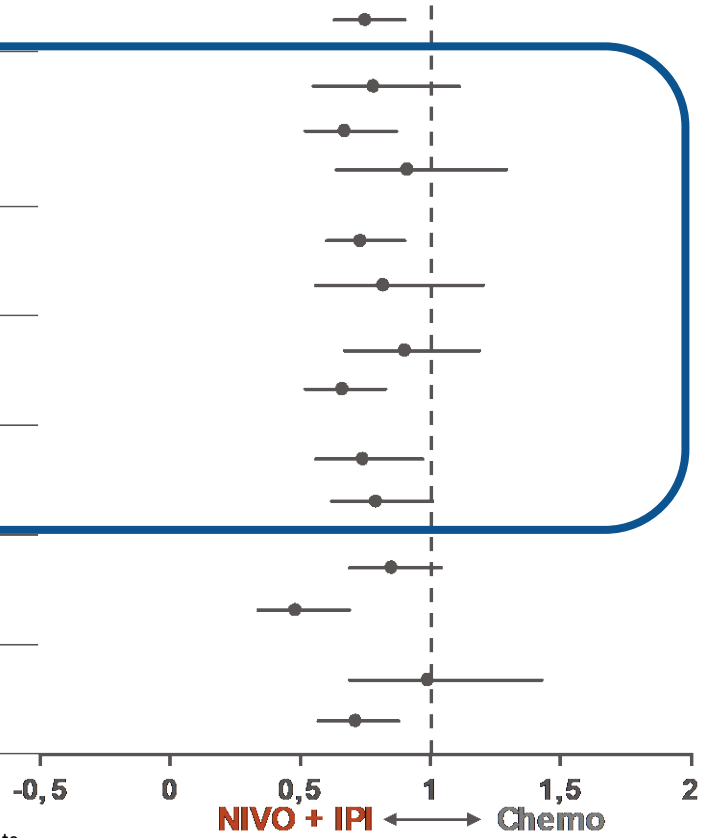
Quelle(s) séquence(s) thérapeutiques ?



Quelle(s) stratégie(s) ???

Sélection clinique?

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI (n = 303)	Chemo (n = 302)	
All randomized (N = 605)	18.1	14.1	0.75[a]
< 65 years (n = 167)	17.2	13.3	0.78
≥ 65 to < 75 years (n = 281)	20.3	14.5	0.67
≥ 75 years (n = 157)	16.9	15.5	0.91
Male (n = 467)	**17.5**	**13.7**	**0.73**
Female (n = 138)	**21.1**	**18.0**	**0.82**
ECOG PS 0 (n = 242)	20.7	19.5	0.90
ECOG PS ≥ 1[b] (n = 363)	17.0	11.6	0.66
Never smoker (n = 249)	17.9	14.1	0.74
Former smoker[c] (n = 318)	17.6	14.9	0.79
Epithelioid (n = 455)	**18.2**	**16.7**	**0.85**
Non-epithelioid[d,e] (n = 150)	**18.1**	**8.8**	**0.48**
PD-L1 < 1% (n = 135)	17.3	16.6	0.99
PD-L1 ≥ 1%[f] (n = 451)	18.0	13.3	0.71



Minimum follow-up: 35.5 months.
Bold text indicates study stratification factors.
[a]Stratified HR, 0.73; [b]One patient in the chemotherapy group had a baseline ECOG PS of 2 (protocol deviation); [c]26 patients were current smokers; smoking status of 12 patients was unknown; [d]Includes sarcomatoid, mixed, and other; [e]One patient was changed from epithelioid to non-epithelioid after the primary analysis; [f]PD-L1 expression level was not reported for 19 patients.

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Sélection histologique ?

Subgroup	Median OS, mo		Unstratified HR
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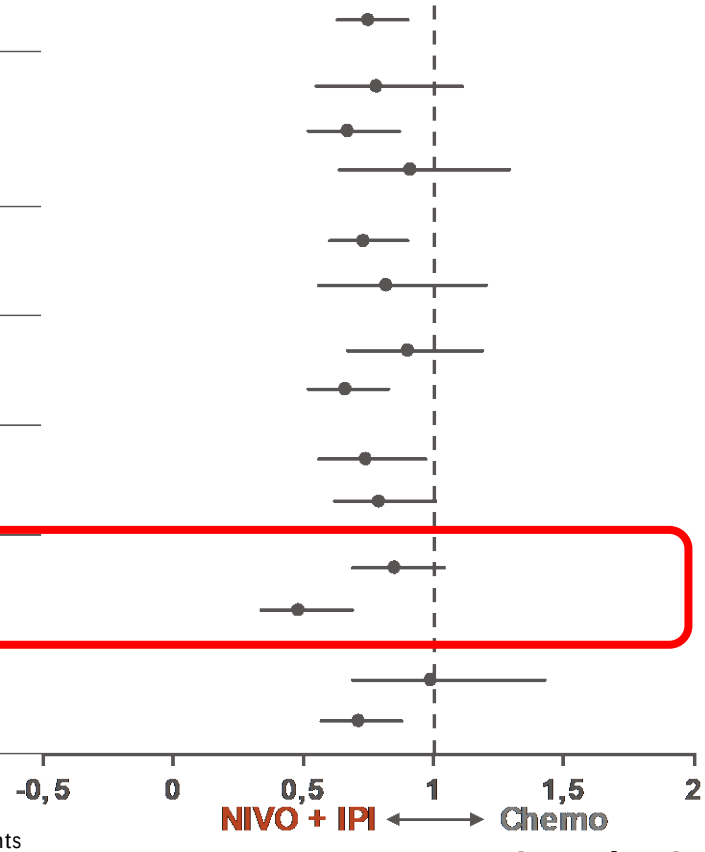

Minimum follow-up: 35.5 months.
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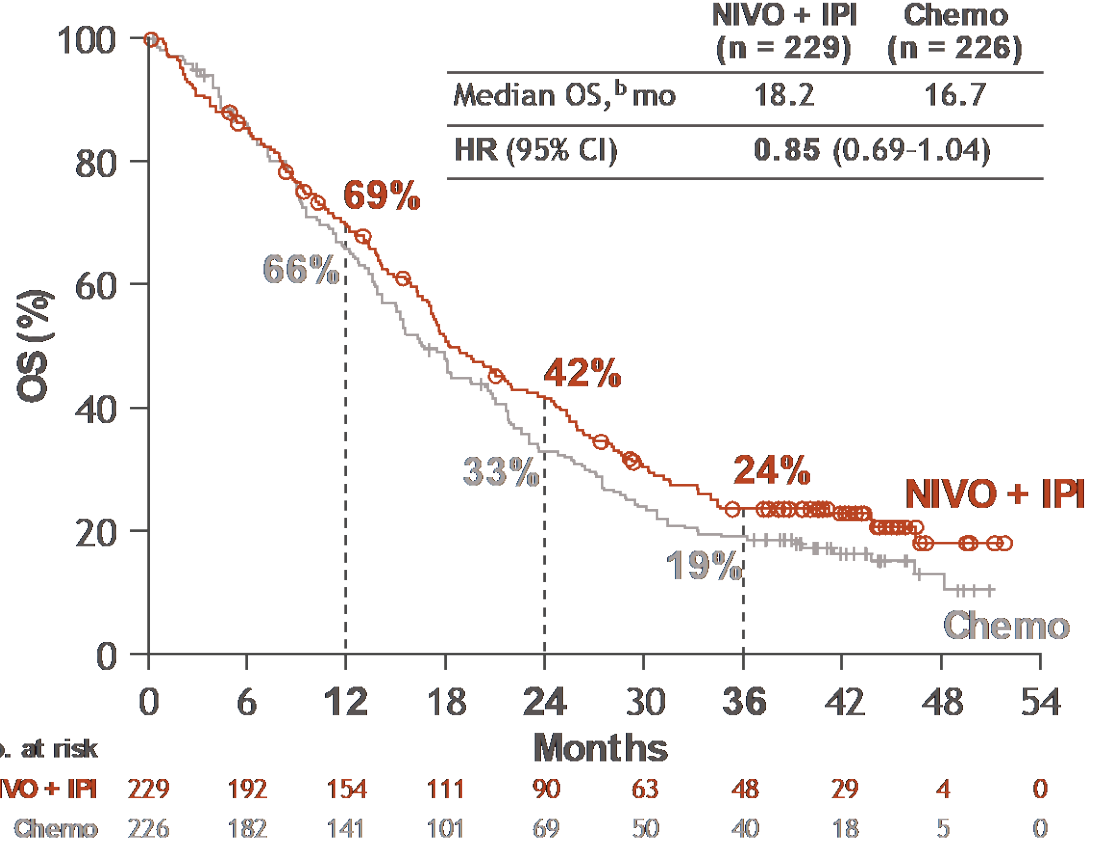
Sélection histologique ?

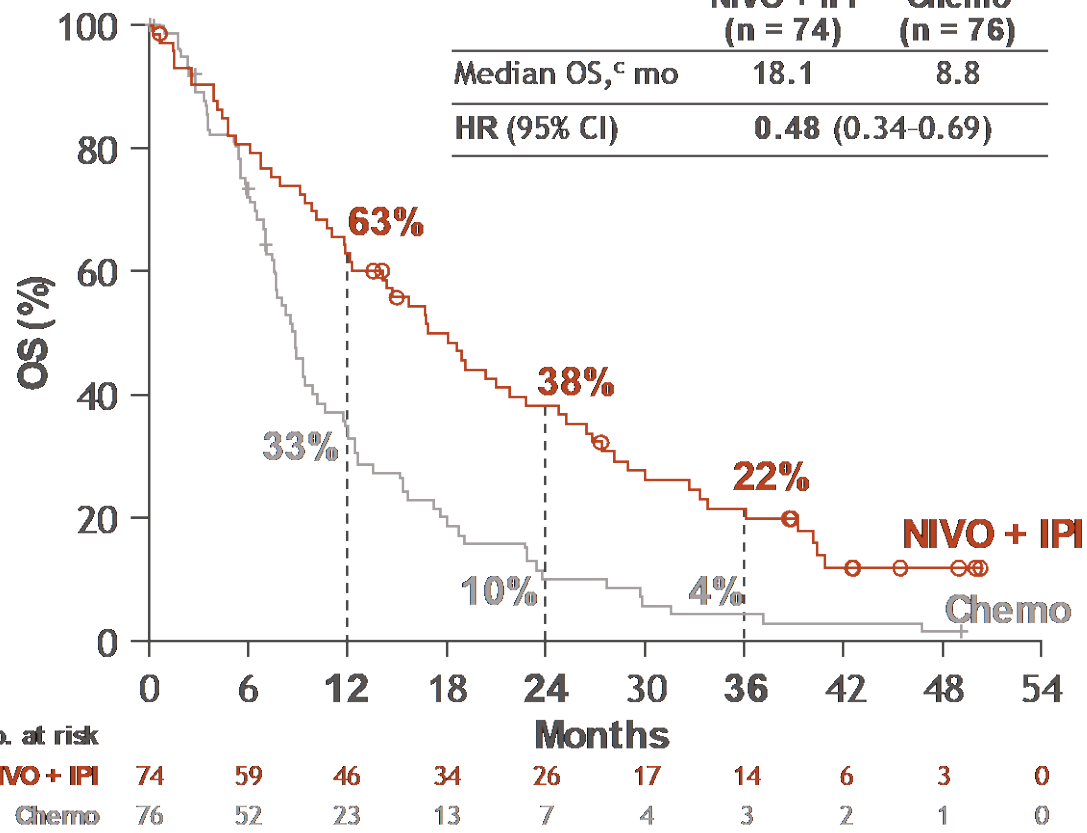
Epithelioid

	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	**0.85** (0.69–1.04)	



Non-epithelioid

	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[c] mo	18.1	8.8
HR (95% CI)	**0.48** (0.34–0.69)	



Minimum follow-up: 35.5 months.

In patients with epithelioid histology, subsequent systemic therapy was received by 47% in the NIVO + IPI arm vs 44% in the chemo arm; subsequent immunotherapy was received by 4% vs 22%; subsequent chemotherapy was received by 45% vs 35%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 39% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 5% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.

[a]Histology per CRF; [b]95% CIs were 16.9–21.9 (NIVO + IPI) and 14.9–20.3 (chemo); [c]95% CIs were 12.2–22.8 (NIVO + IPI) and 7.4–10.2 (chemo).

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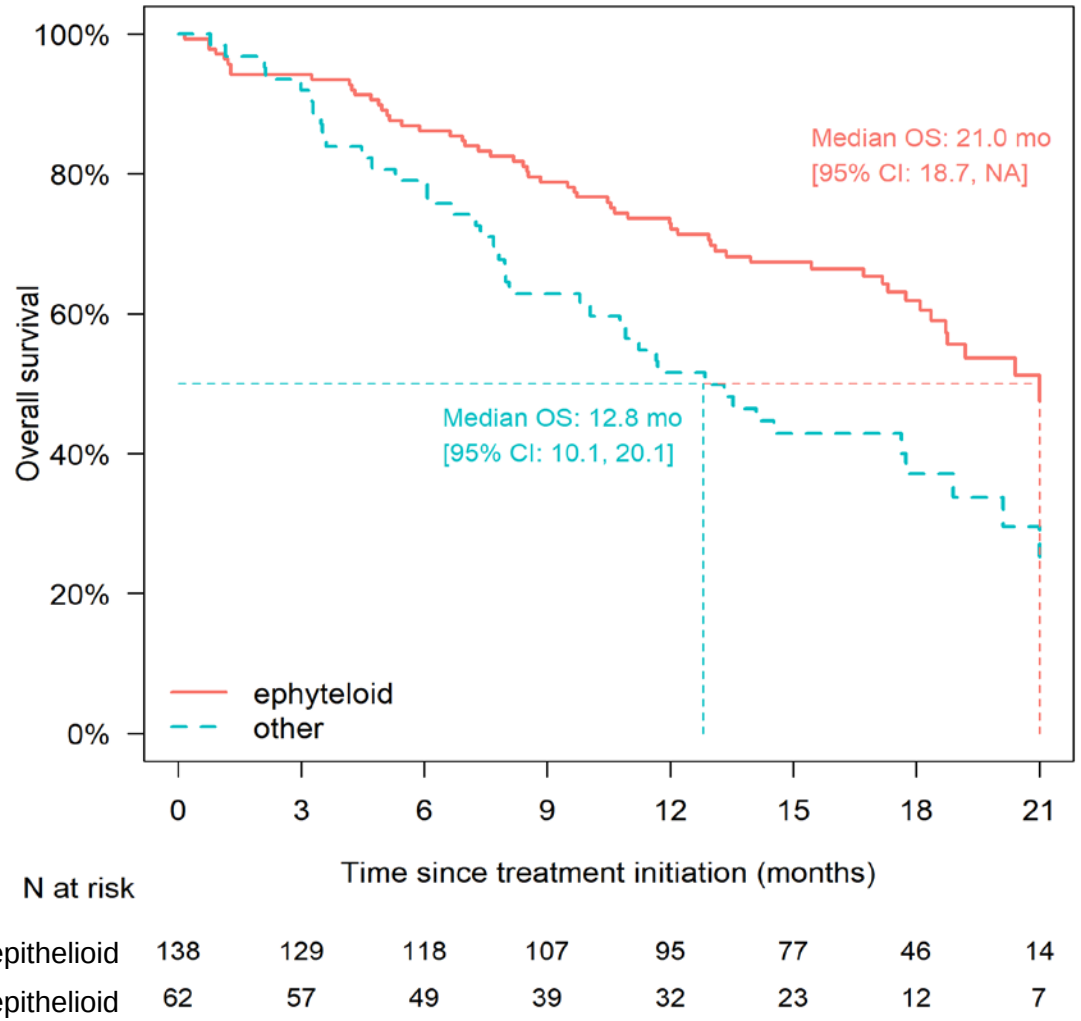
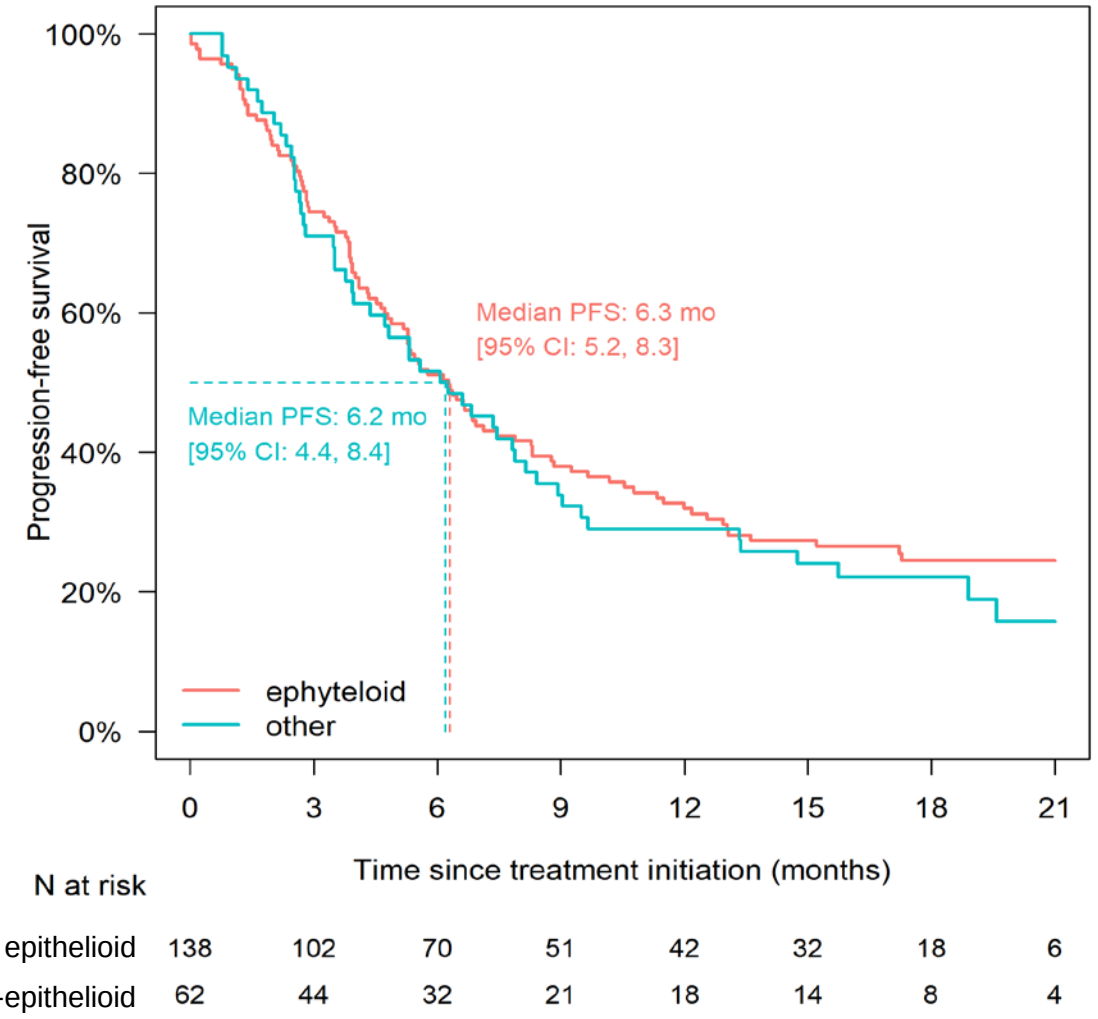


Median follow-up: 18.4 months (95%CI 17.7-19.2)

Greillier L et al, IMiG 2023

Essai MESOIMMUNE – GFPC 04-2021



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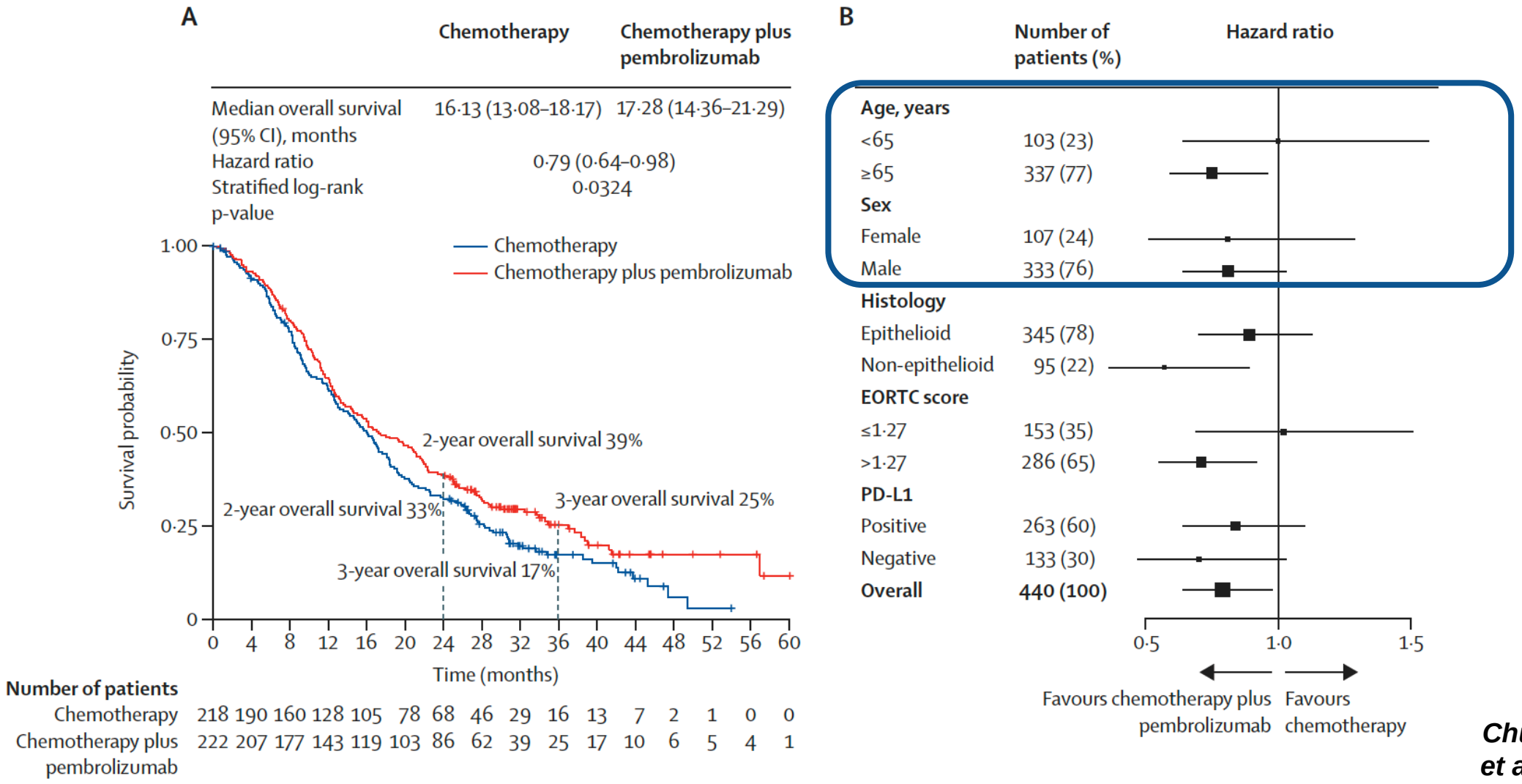
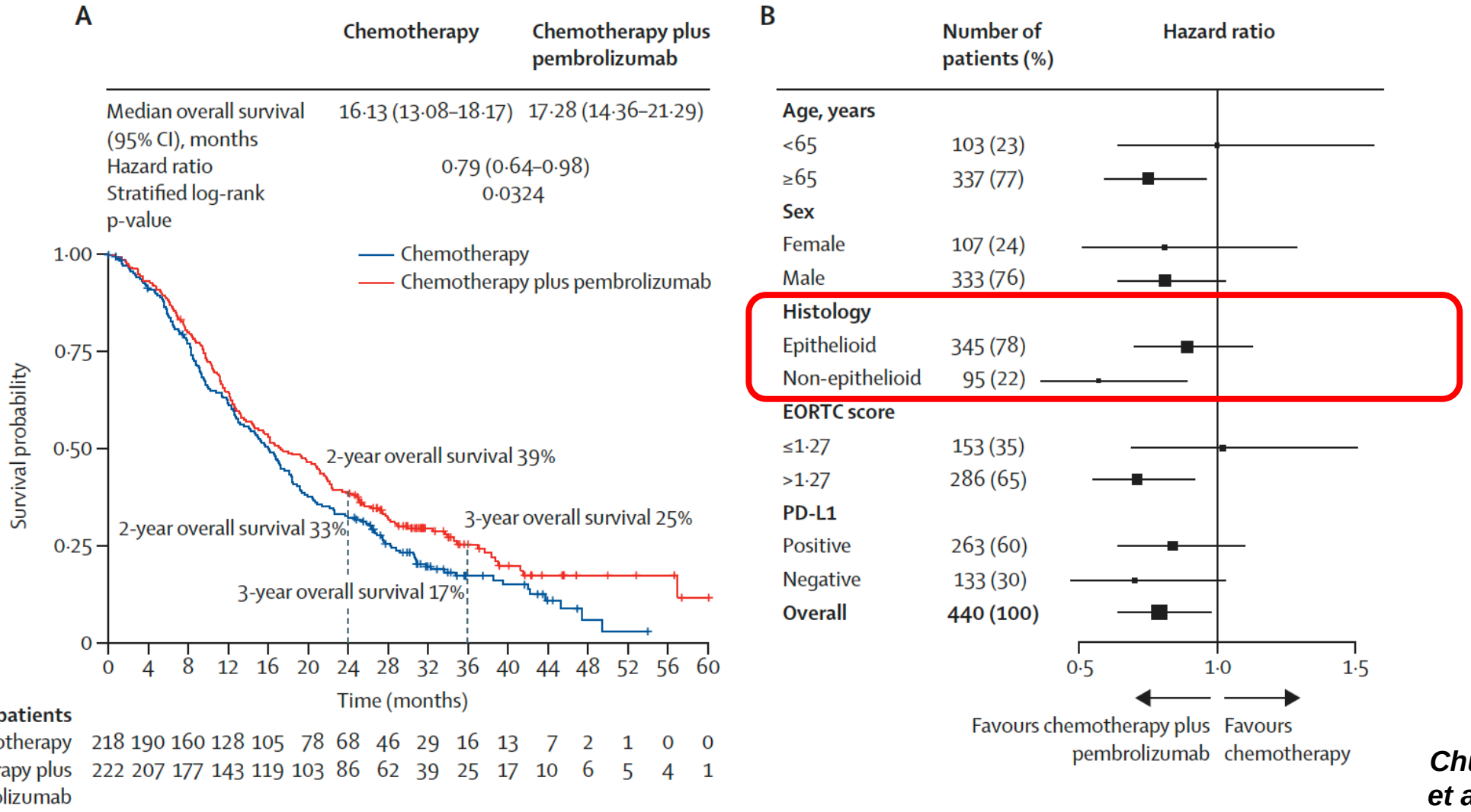
Greillier L et al, IMiG 2023

Sélection clinique ?



Chu Q, Greillier L et al, Lancet 2023

Sélection histologique ?

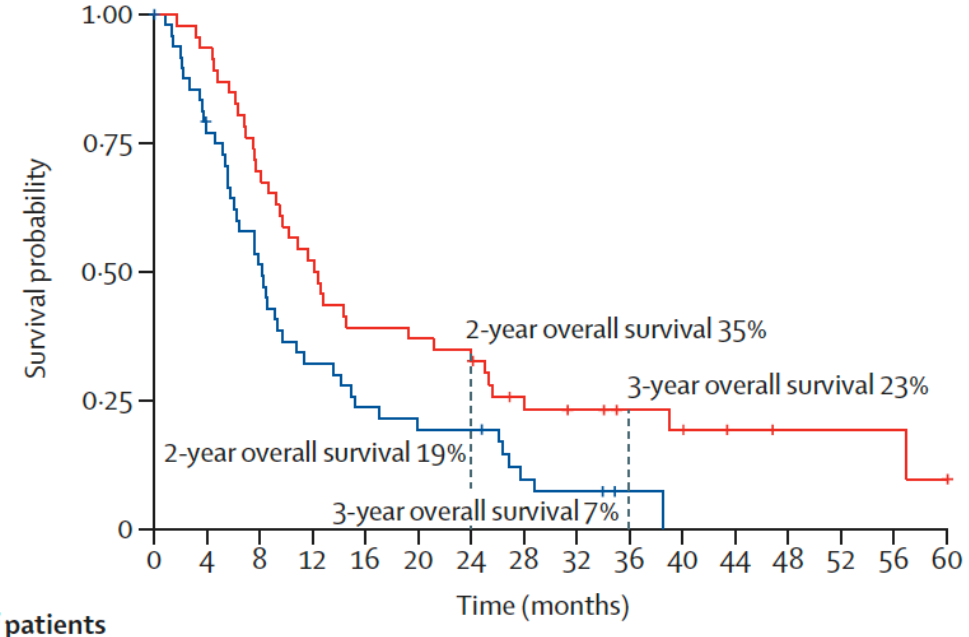


Chu Q, Greillier L et al, Lancet 2023

Sélection histologique ?

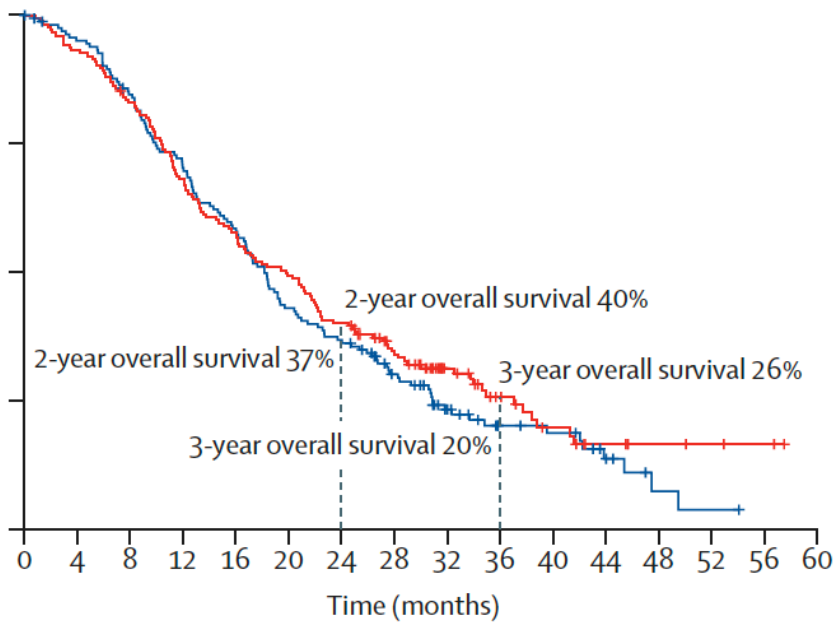
C Exploratory analyses: non-epithelioid (n=95)

	Chemotherapy	Chemotherapy plus pembrolizumab
Median overall survival (95% CI), months	8·21 (5·85–10·8)	12·3 (8·67–21·2)
Hazard ratio	0·57 (0·36–0·89)	



D Exploratory analyses: epithelioid (n=345)

	Chemotherapy	Chemotherapy plus pembrolizumab
Median overall survival (95% CI), months	18·2 (16·0–20·4)	19·8 (16·0–22·2)
Hazard ratio	0·89 (0·7–1·13)	



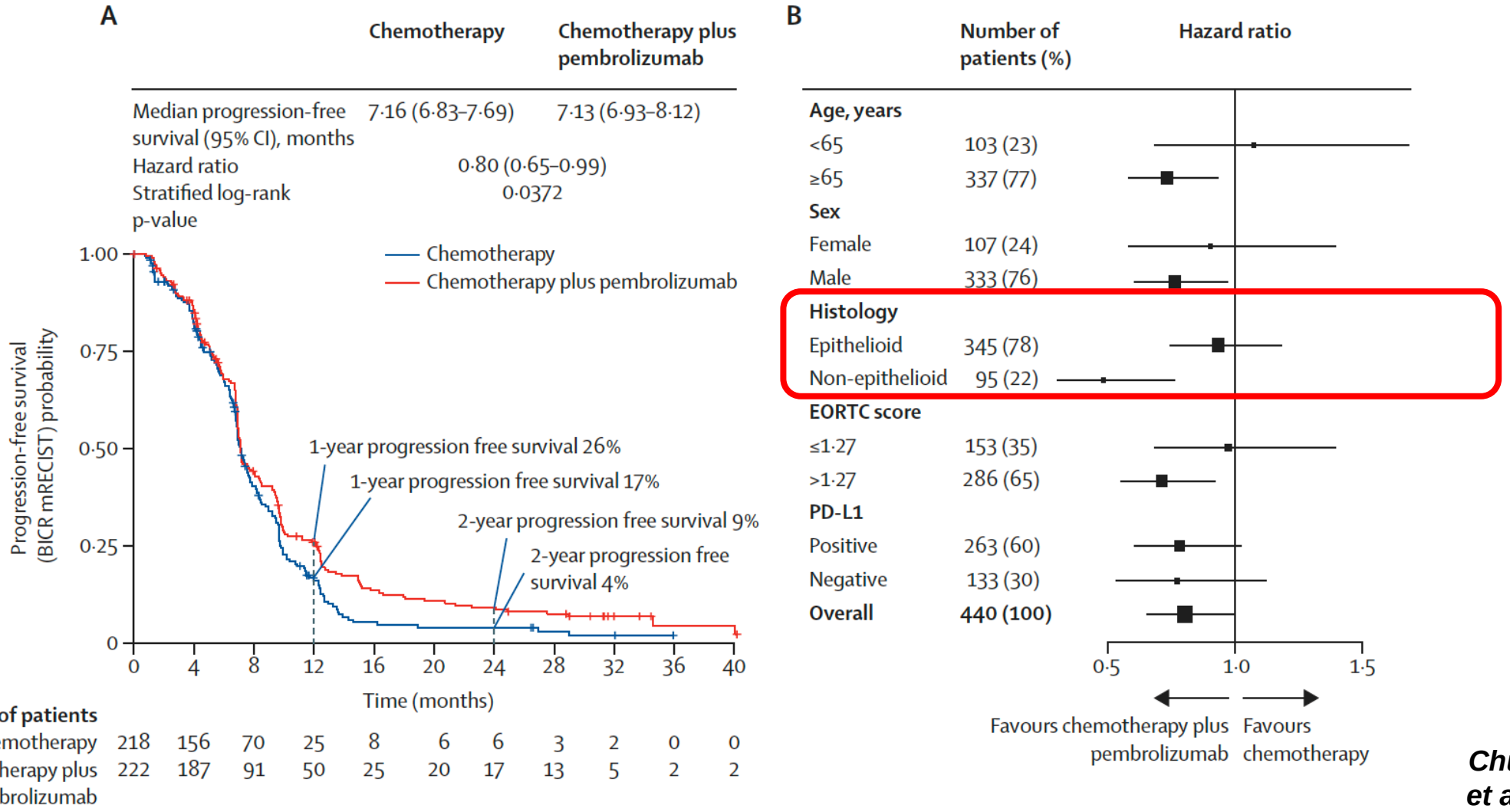
Number of patients

Chemotherapy	49	36	24	15	11	9	9	4	3	1	0	0	0	0	0	0
Chemotherapy plus pembrolizumab	46	43	32	24	18	17	16	10	8	6	5	3	2	2	2	1

Chemotherapy	169	154	136	113	94	69	59	42	26	15	13	7	2	1	0	0
Chemotherapy plus pembrolizumab	176	164	145	119	101	86	70	52	31	19	12	7	4	3	2	0

Chu Q, Greillier L et al, Lancet 2023

Sélection histologique ?

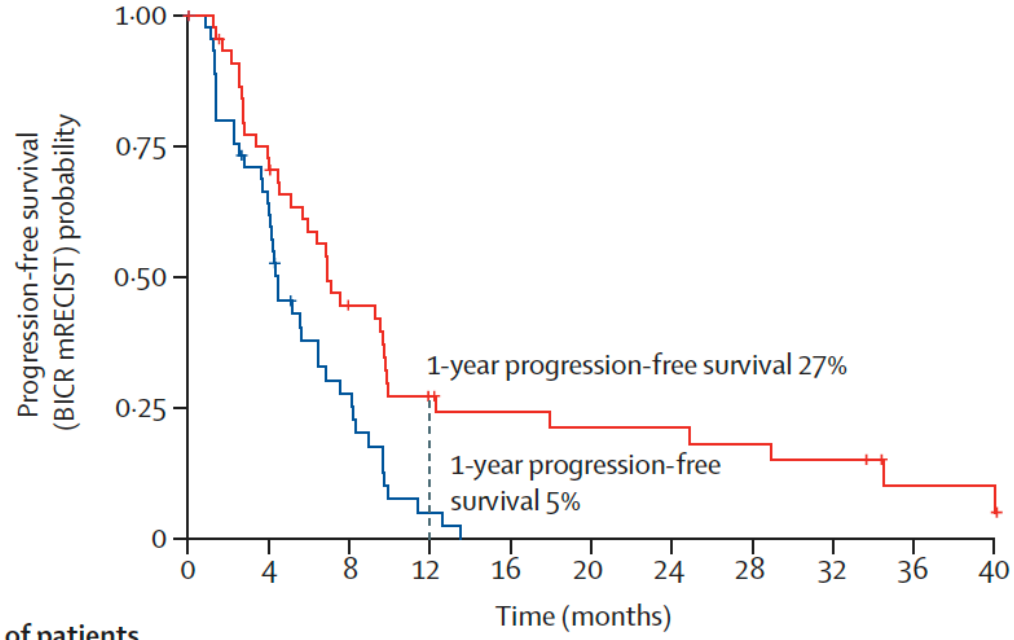


Chu Q, Greillier L et al, Lancet 2023

Sélection histologique ?

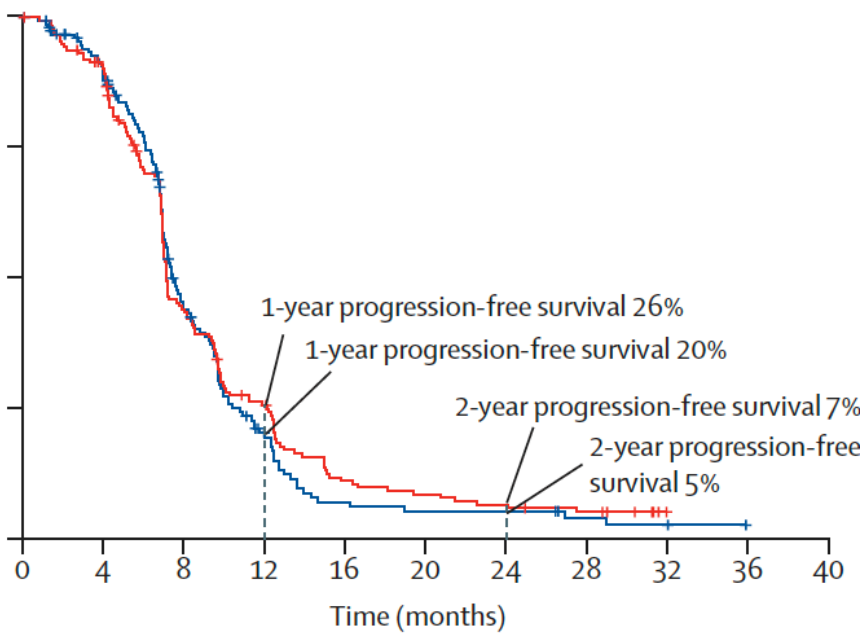
C Exploratory analyses: non-epithelioid (n=95)

	Chemotherapy	Chemotherapy plus pembrolizumab
Median progression-free survival (95% CI), months	4·47 (3·98–6·44)	6·93 (4·53–9·73)
Hazard ratio	0·48 (0·3–0·76)	



D Exploratory analyses: epithelioid (n=345)

	Chemotherapy	Chemotherapy plus pembrolizumab
Median progression-free survival (95% CI), months	7·39 (6·97–8·38)	7·13 (6·93–8·12)
Hazard ratio	0·93 (0·74–1·18)	



Number of patients

Chemotherapy	49	28	11	2	0	0	0	0	0	0	0	169	128	59	23	8	6	6	3	2	0	0
Chemotherapy plus pembrolizumab	46	32	18	10	8	7	7	6	5	2	2	176	155	73	40	17	13	10	7	0	0	0

Chu Q, Greillier L et al, Lancet 2023

Sélection selon PD-L1?

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI (n = 303)	Chemo (n = 302)	
All randomized (N = 605)	18.1	14.1	0.75[a]
< 65 years (n = 167)	17.2	13.3	0.78
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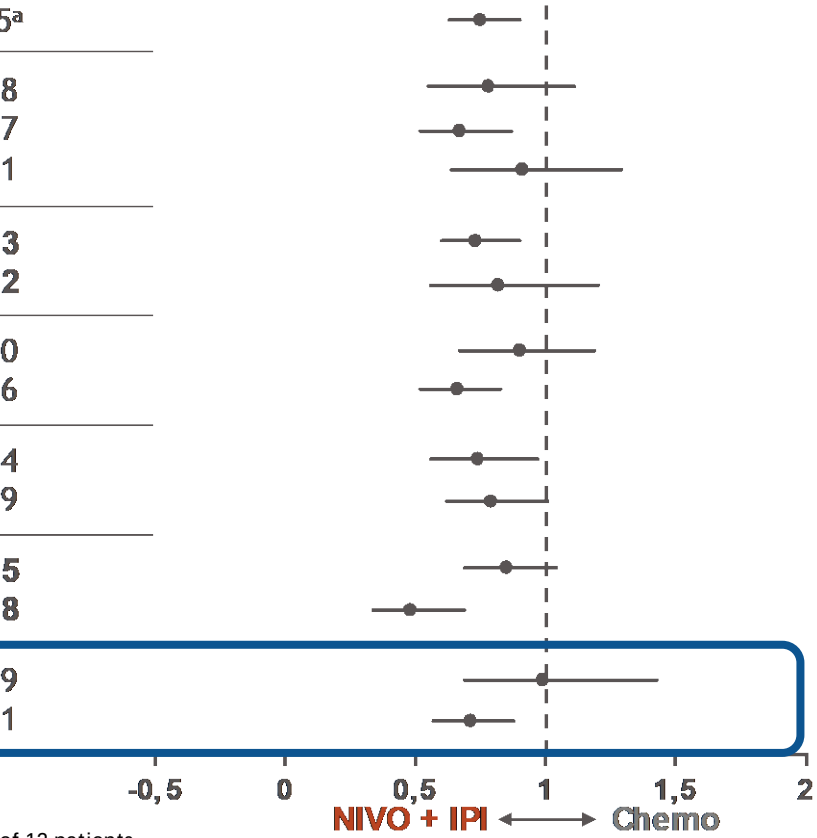

Minimum follow-up: 35.5 months.
Bold text indicates study stratification factors.
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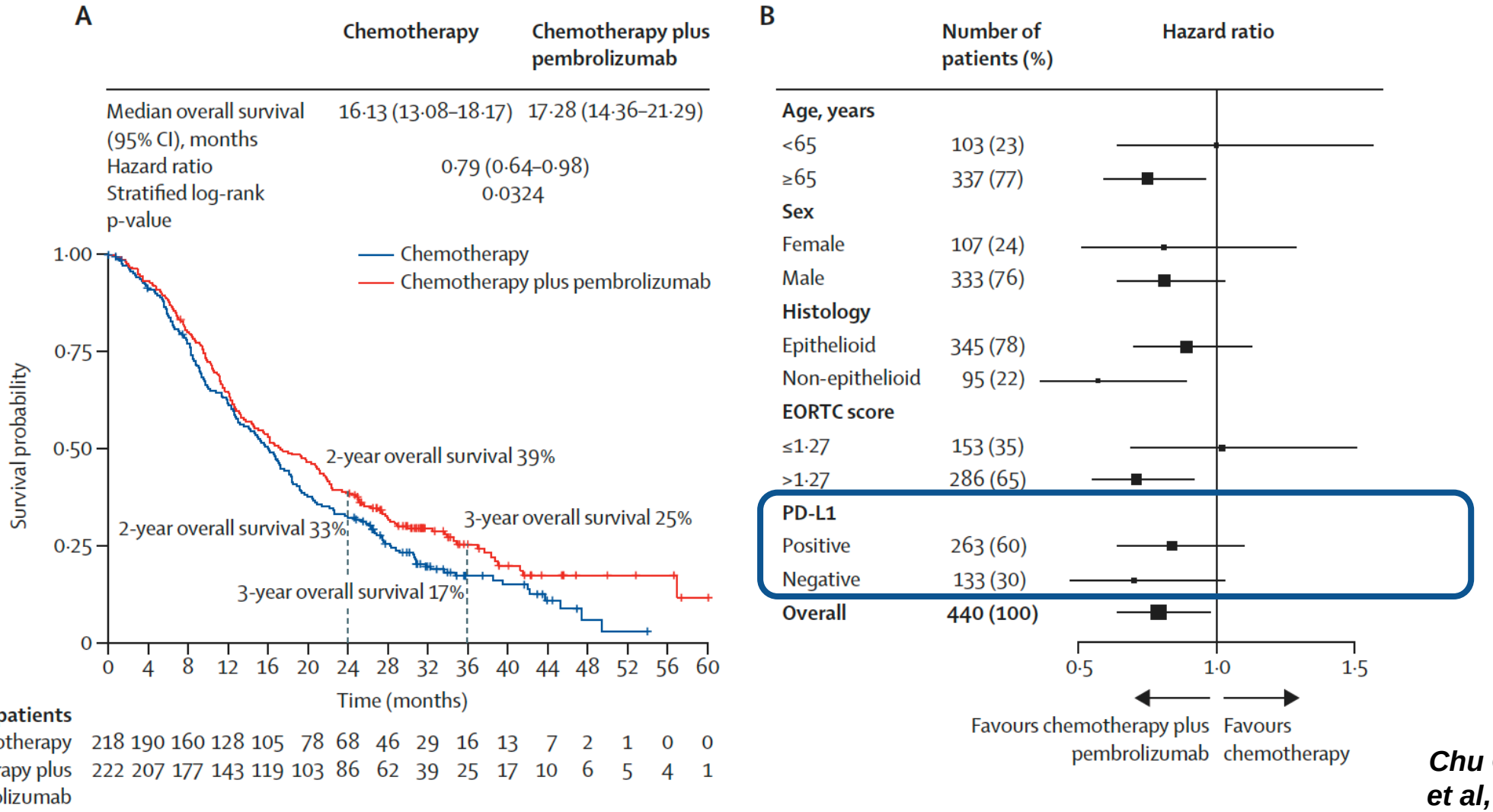
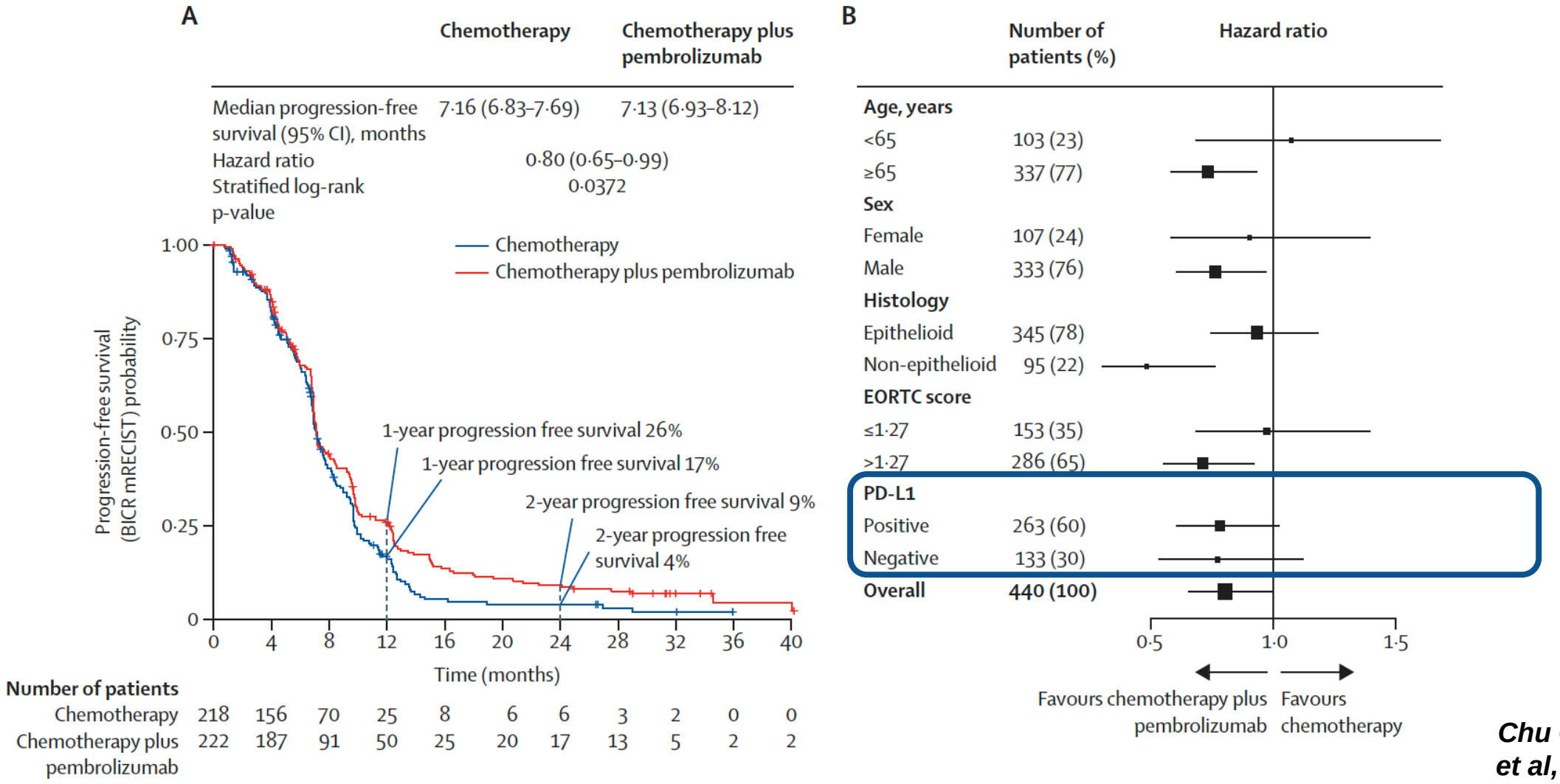
Sélection selon PD-L1?



Chu Q, Greillier L et al, Lancet 2023

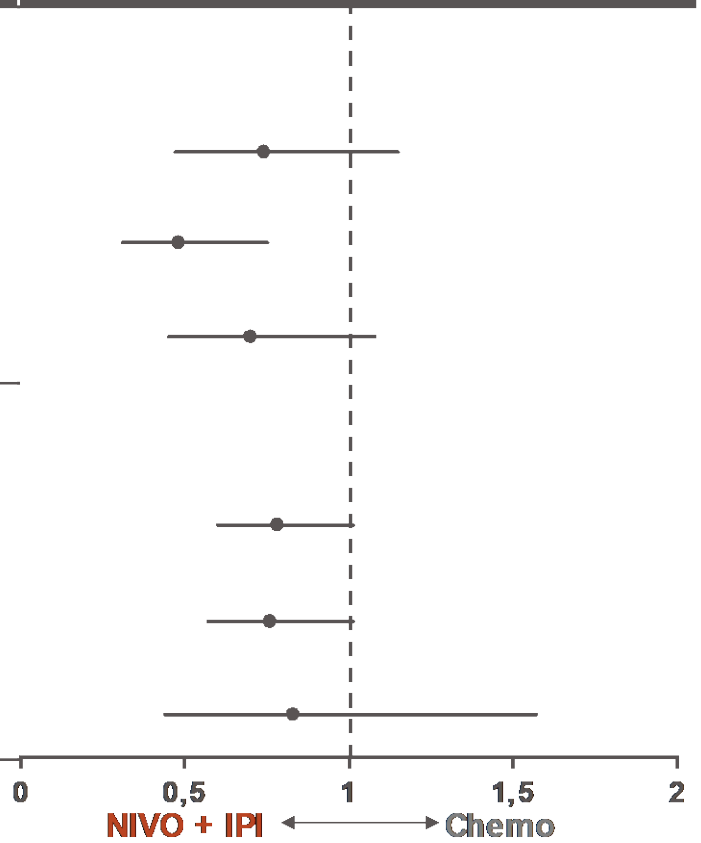
Sélection selon PD-L1?



Chu Q, Greillier L et al, Lancet 2023

Sélection selon d'autres biomarqueurs ?

Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI	Chemo		
Tissue TMB tertile[a]				
Low[b] (n = 103)	19.3	18.0	0.74	
Intermediate[c] (n = 97)	17.9	9.9	0.48	
High[d] (n = 95)	17.1	14.1	0.70	
LIPI score[e]				
Good[f] (n = 293)	21.6	16.3	0.78	
Intermediate[g] (n = 233)	17.1	14.1	0.76	
Poor[h] (n = 47)	6.1	6.0	0.83	



Minimum follow-up: 35.5 months.

The inflammation signature measures expression of *CD8A, STAT1, LAG3, and CD274 (PD-L1)*. Inflammation signature z-score was stratified into high and low inflammation based on the median.

[a]Evaluated in RNA-evaluable population; performed via RNA sequencing on baseline tumor samples; [b]95% CIs were 12.0–18.6 (low) and 16.9-33.2 (high); [c]95% CIs were 11.1–20.8 (low) and 9.5–15.2 (high).

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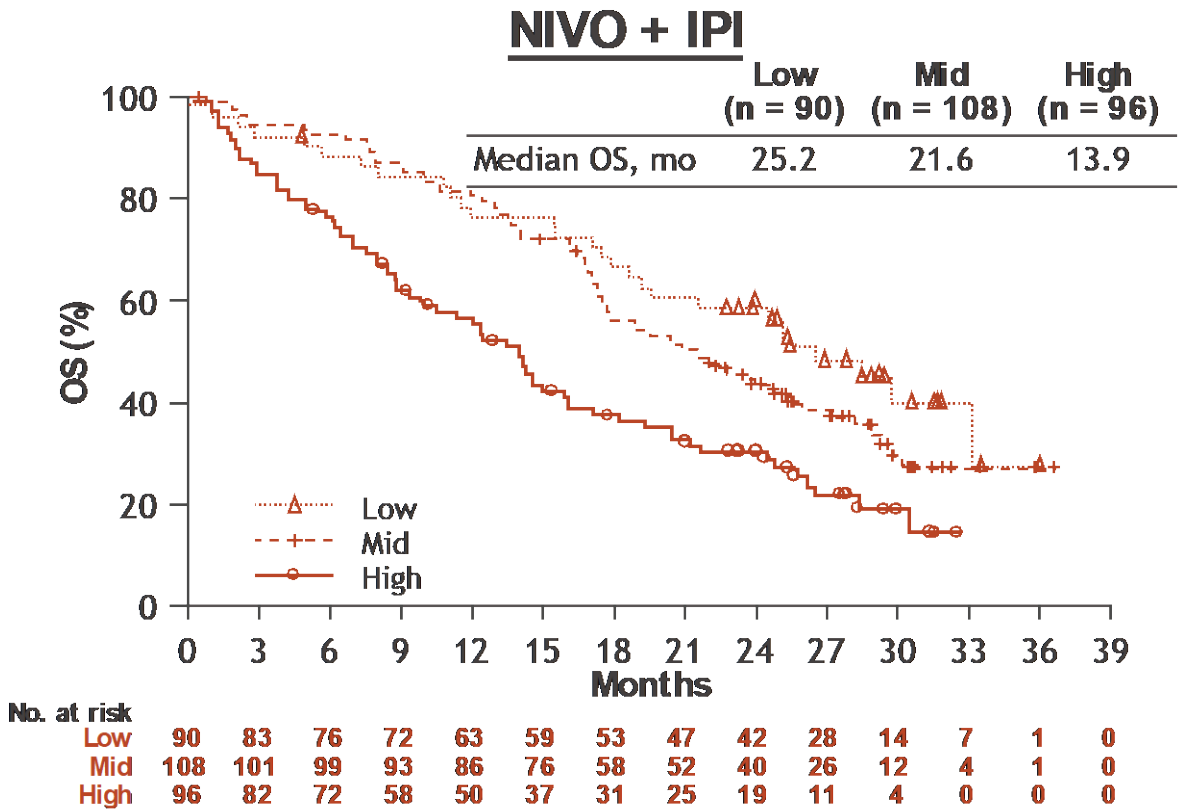
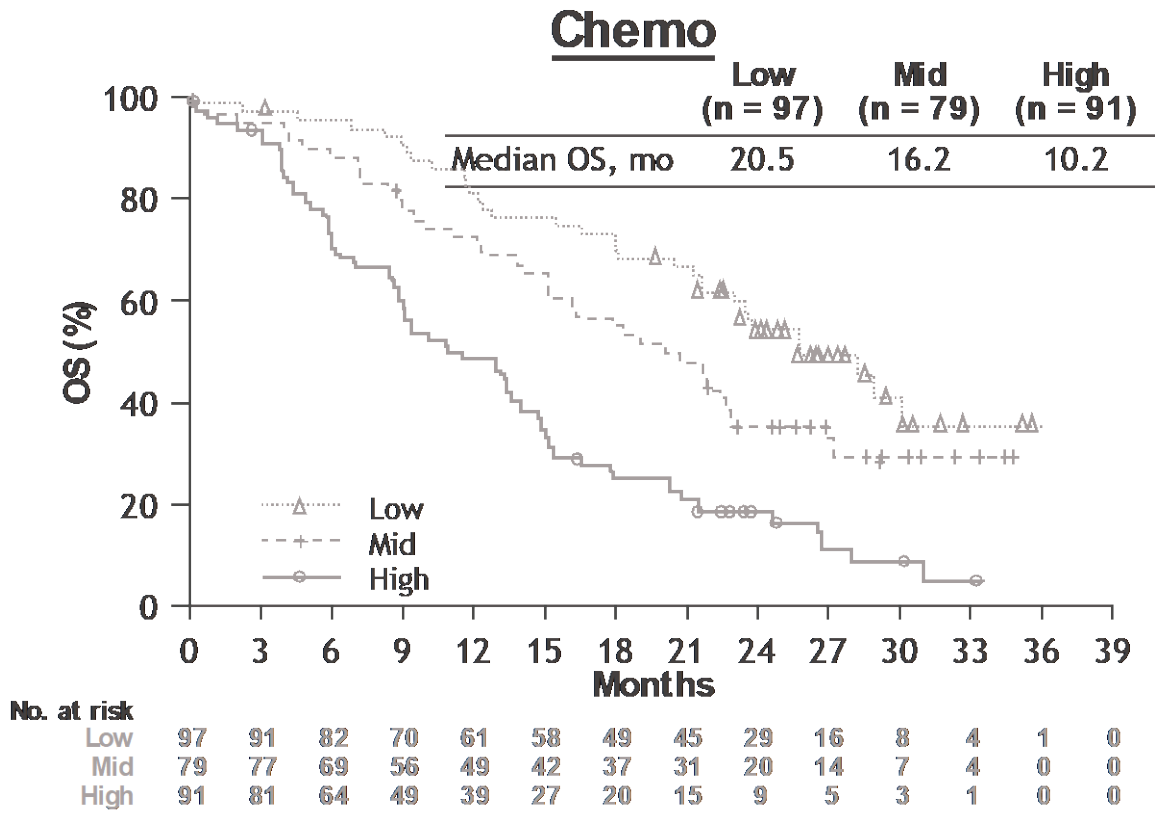
Sélection selon d'autres biomarqueurs ?



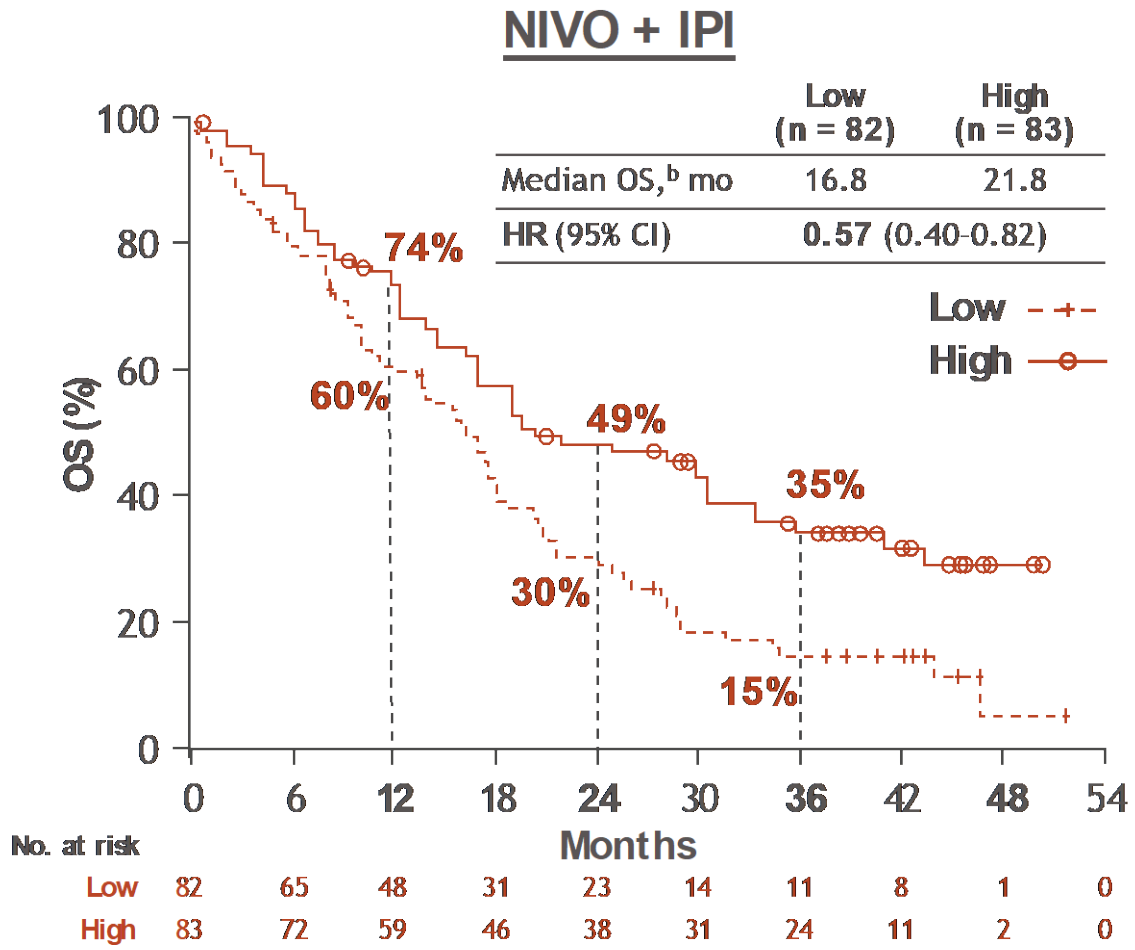


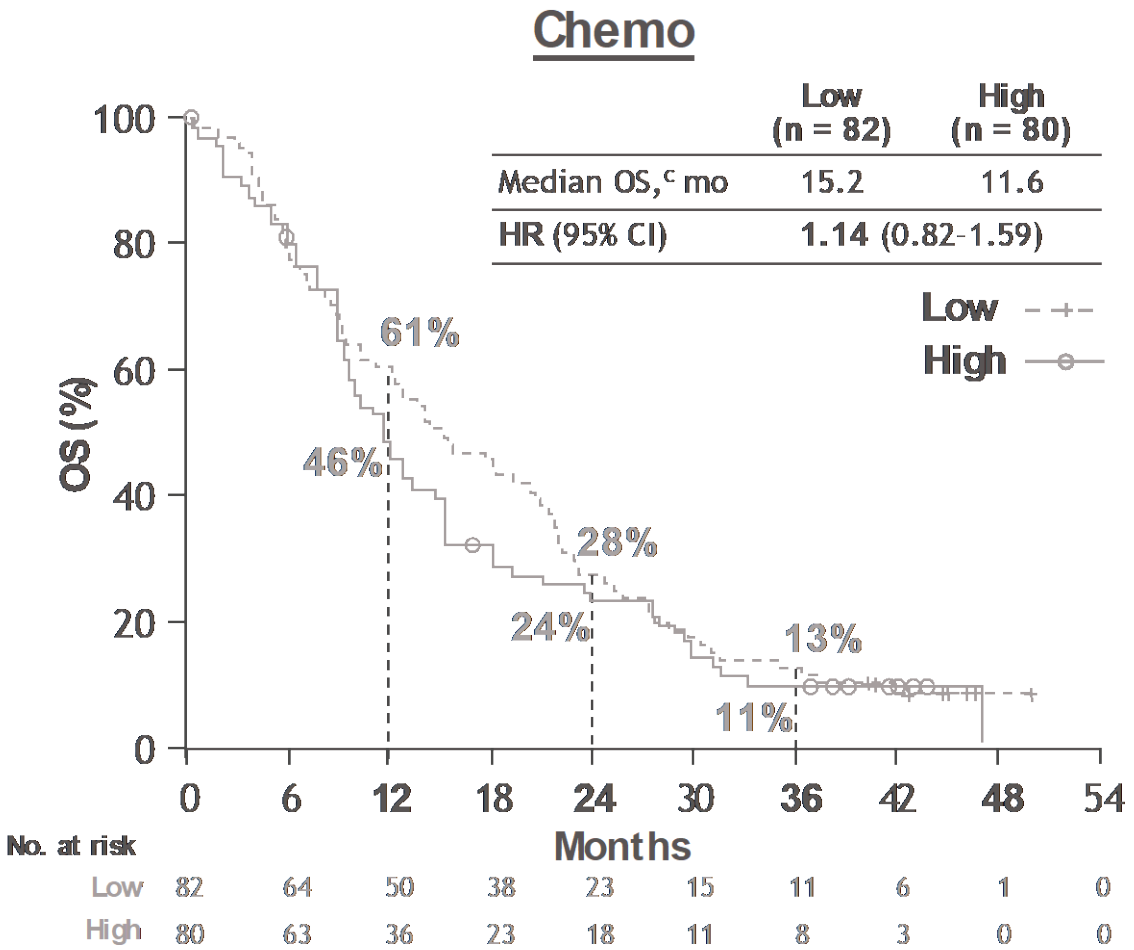
Minimum / median follow-up for OS: 47.5 months / 55.1 months.

[a]Quantified using an ELISA-based methodology on patient serum samples; low, mid, and high subgroups were split by tertile median soluble mesothelin levels; [b]97% (n/N = 294/303) and 88% (267/302) of patients had evaluable baseline soluble mesothelin levels in the NIVO + IPI and chemo arms, respectively; [c]Epithelioid histology: median OS for low, mid, and high soluble mesothelin level: 27.7 (n = 50), 21.7 (n = 86), and 13.9 (n = 85) months for the NIVO + IPI arm, respectively, and 25.9 (n = 61), 20.8 (n = 57), and 11.6 (n = 79) for the chemo arm, respectively; [d]Non-epithelioid histology: median OS for low, mid, and high soluble mesothelin level were 18.6 (n = 40), 20.3 (n = 22), and 12.3 (n = 11) months for the NIVO + IPI arm, respectively, and 8.6 (n = 36), 9.3 (n = 22), and 8.4 (n = 12) for the chemo arm, respectively.

Zalcman G et al, ESMO 2022

Sélection selon d'autres biomarqueurs ?





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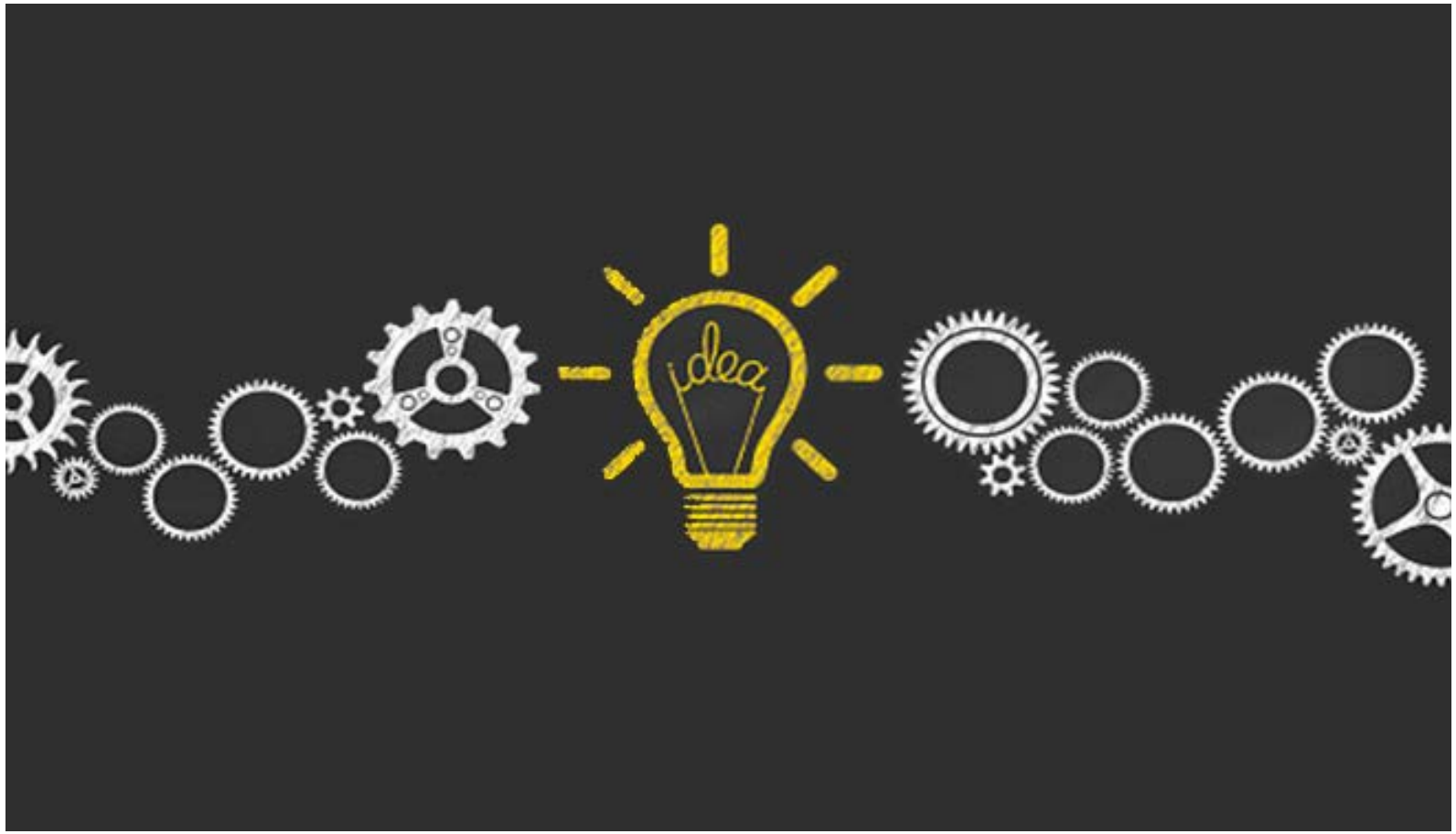
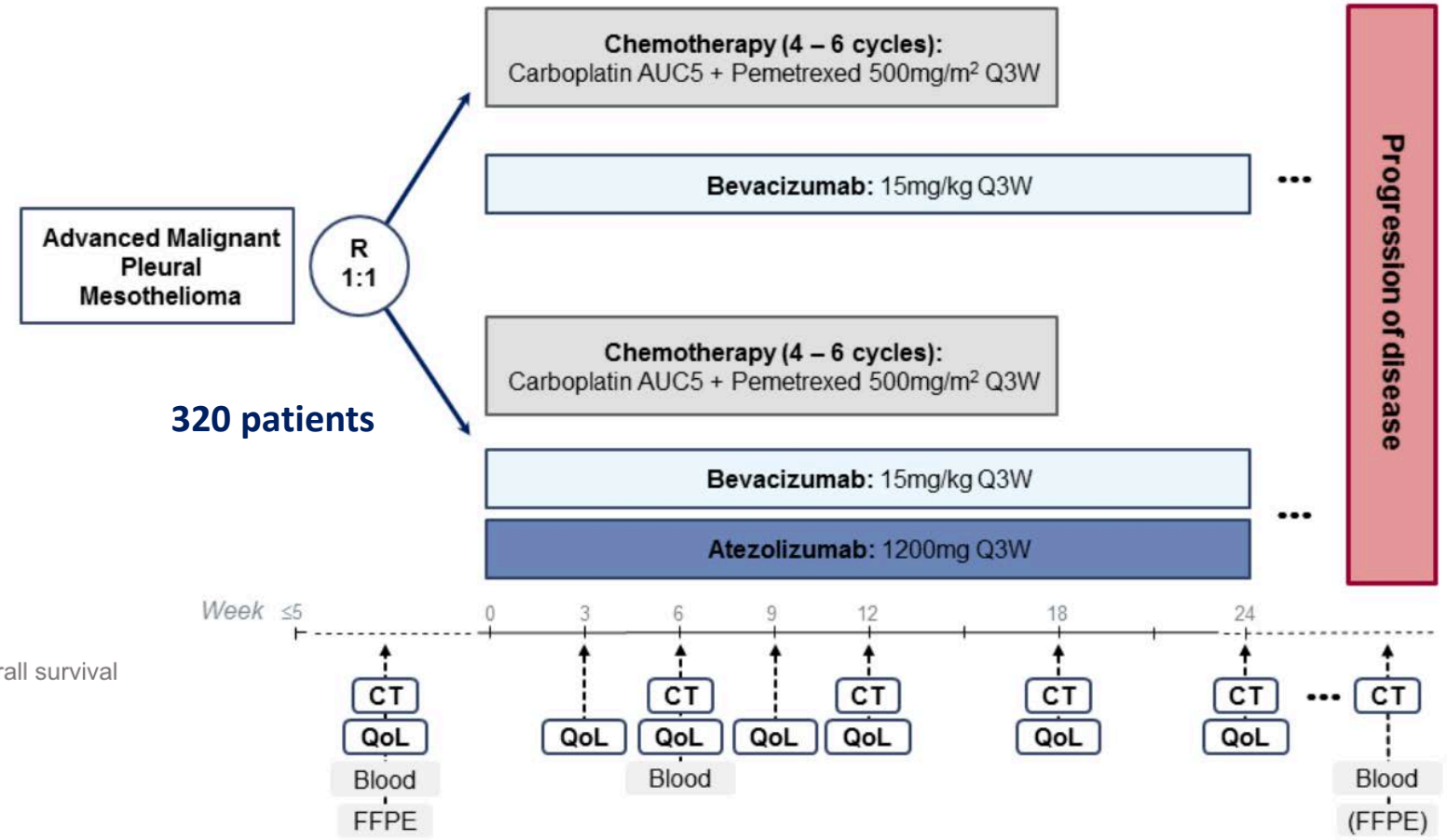
Peut-on faire ENCORE mieux ???



Essai BEAT-Meso

etop
Information | Research



Primary endpoint: Progression free survival & Overall survival

Secondary endpoints:
- Response rate
- Disease control rate
- Time to treatment failure
- Duration of response
- Safety and tolerability
- Patient reported outcome
- Quality of life

EudraCT number: 2018-002180-25

Hôpitaux Universitaires de Marseille | ap-hm
CRCM Centre de Recherche en Cancérologie de Marseille
Aix*Marseille université

Conclusions

NETMESO
Réseau National Expert pour le Mésothéliome Pleural Malin

Merci pour votre attention

laurent.greillier@ap-hm.fr