TRAITEMENTS SYSTÉMIQUES DES CANCERS BRONCHIQUES NON À PETITES CELLULES : SPÉCIFICITÉS CHEZ LE SUJET ÂGÉ

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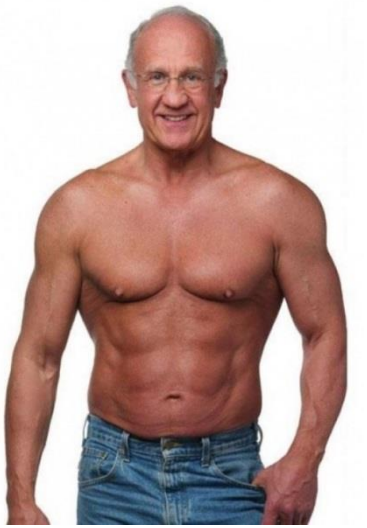
Liens d’intérêt

- Honoraires / advisory board : AstraZeneca, Boehringer-Ingelheim, Bristol-Myers-Squibb, MSD, Novartis, Roche

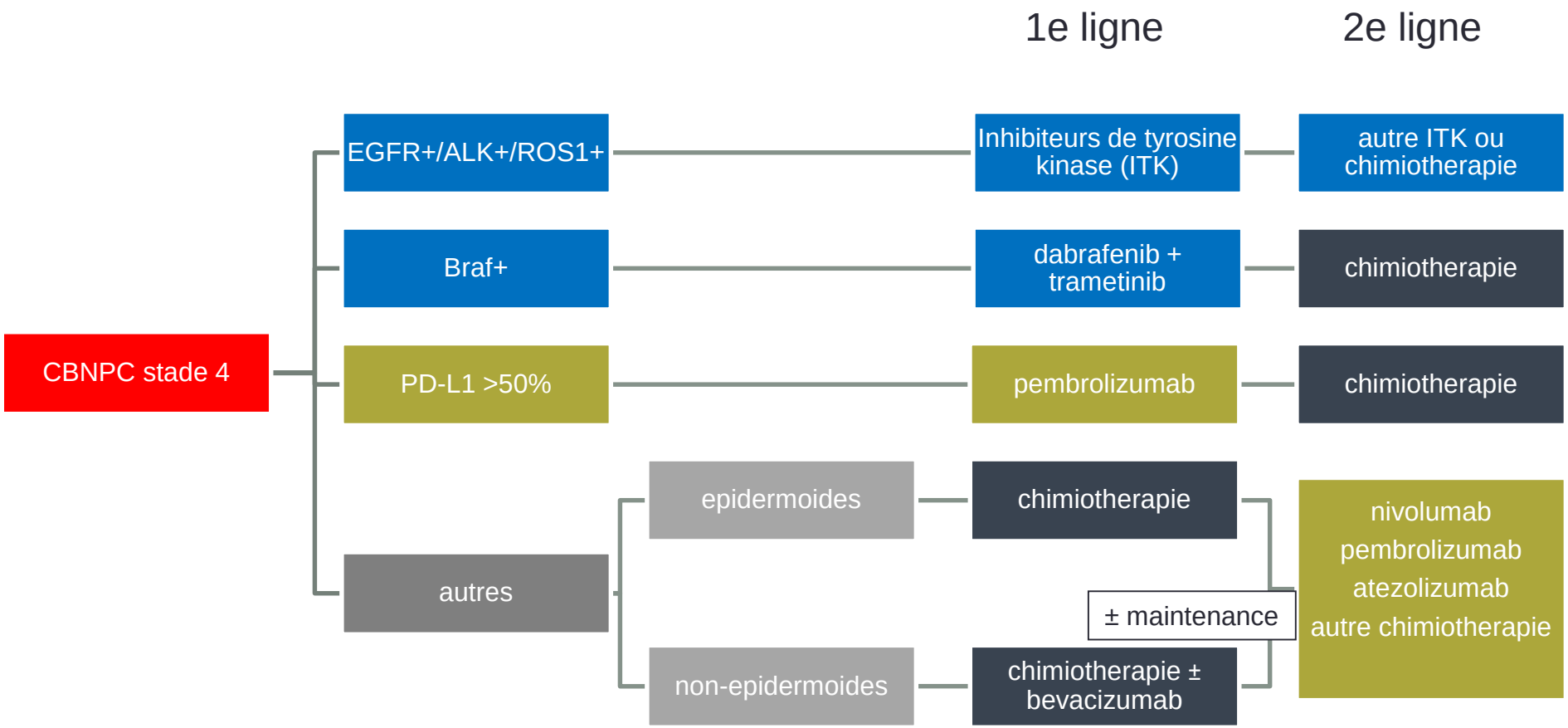
- Subventions recherche (institution) : AstraZeneca, Bristol-Myers-Squibb, Roche

Qu’est-ce qu’un sujet âgé ?

- Pas de limite d’âge consensuelle : 65 ans ? 70 ans ? 80 ans ?



Stratégie thérapeutique des stades 4 en 2018



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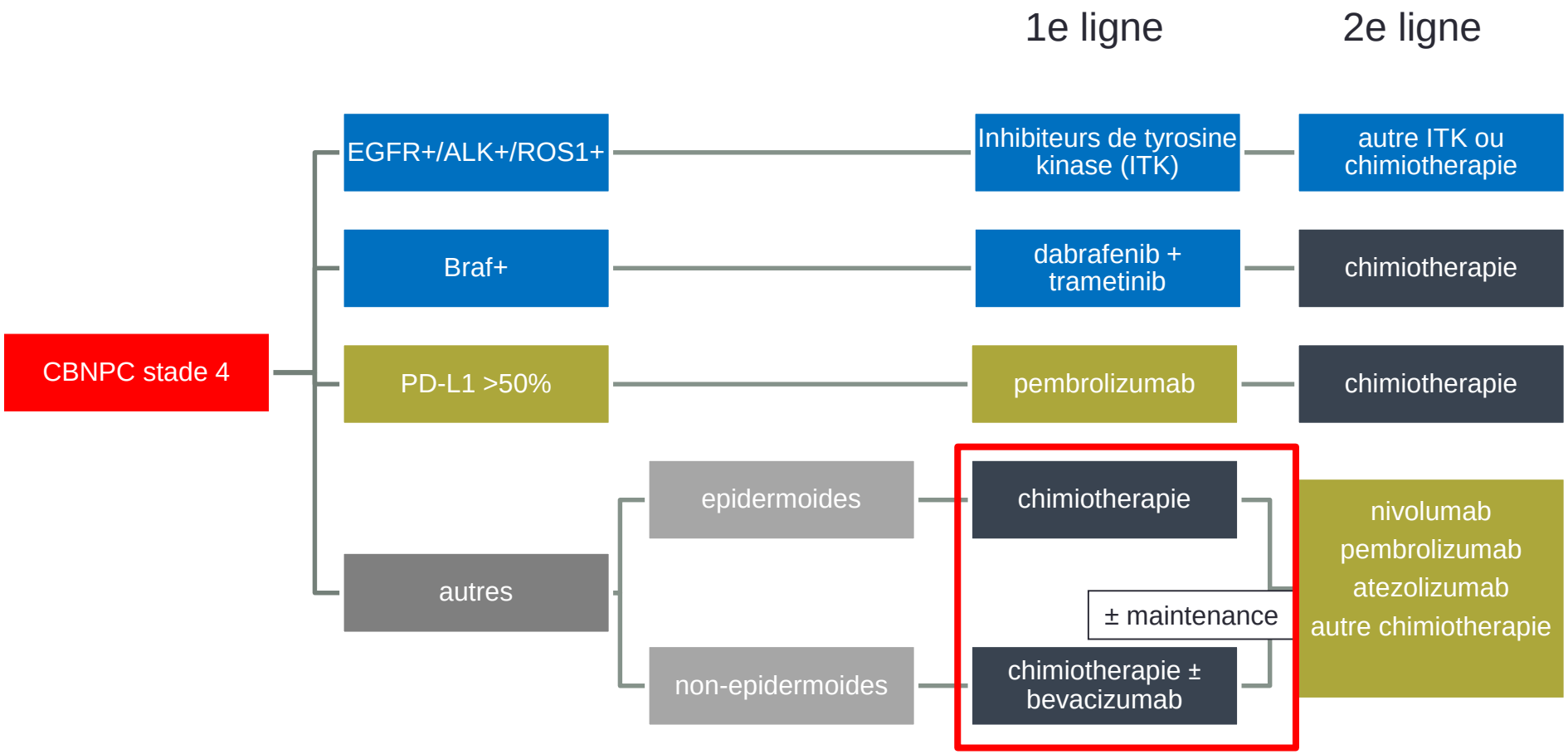
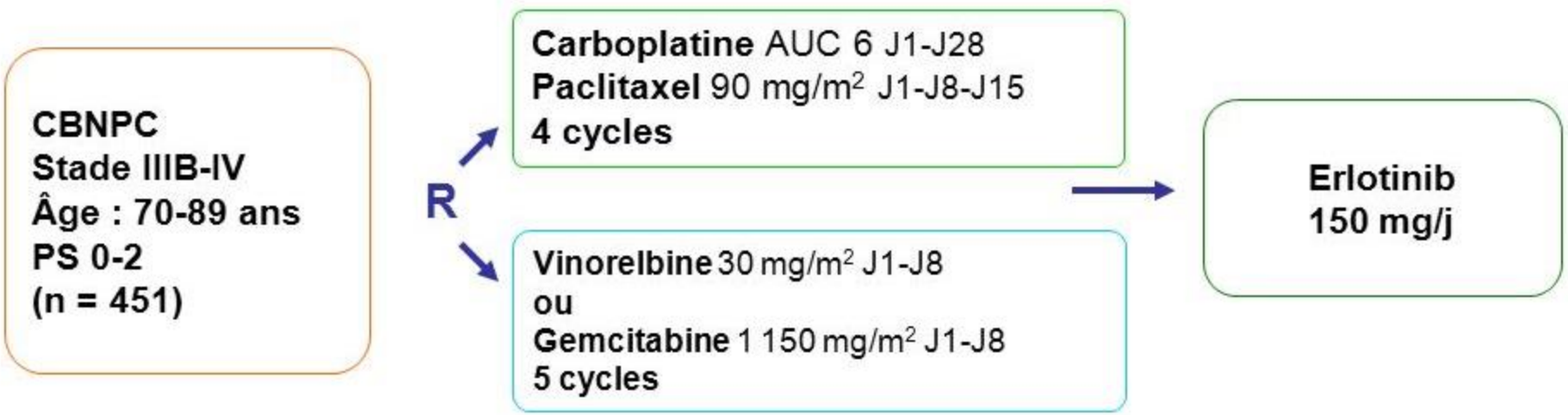
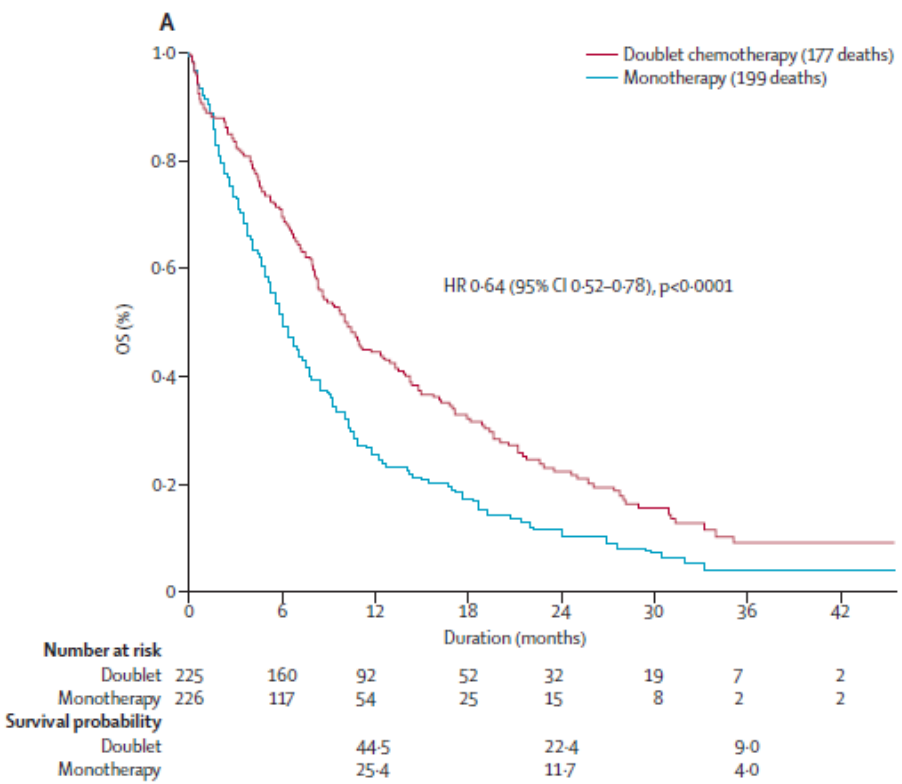


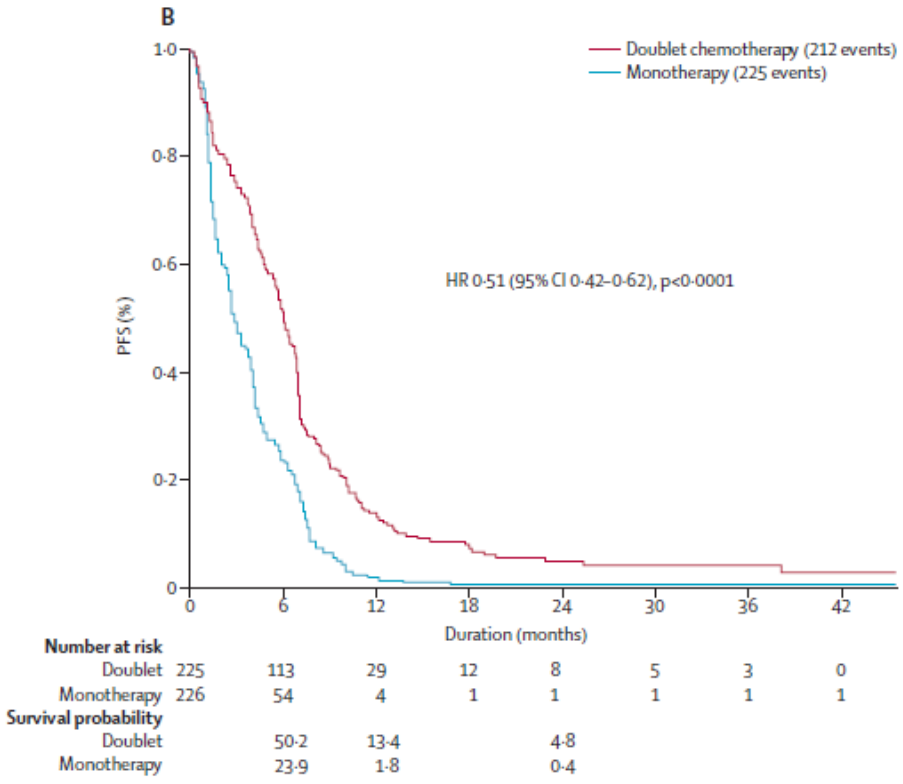
Quelle chimiothérapie en 1e ligne chez les sujets âgés ? IFCT-0501



Quoix Lancet 2011

IFCT-0501 - Résultats





Quoix Lancet 2011

IFCT-0501 - Résultats

Causes of deaths

	Single arm n=226	Doublet arm n=225
Total deaths	199	177
Cause of death		
Cancer	180	147
Intercurrent disease	11	17
Toxic deaths	3 (1.3 %)	10 (4.4 %)
Unknown	5	3

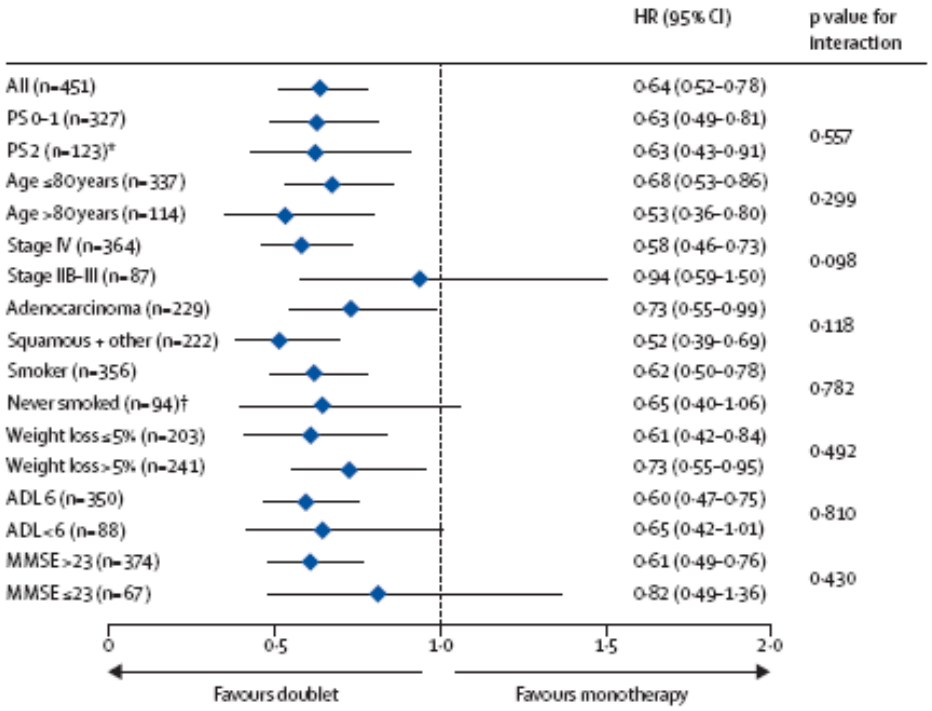
Early deaths (within 3 months)

	Single arm n=226	Doublet arm n=225	p
No	166	188	**0.012**
Yes	60 (26.5%)	37 (16.4%)	

Quoix Lancet 2011

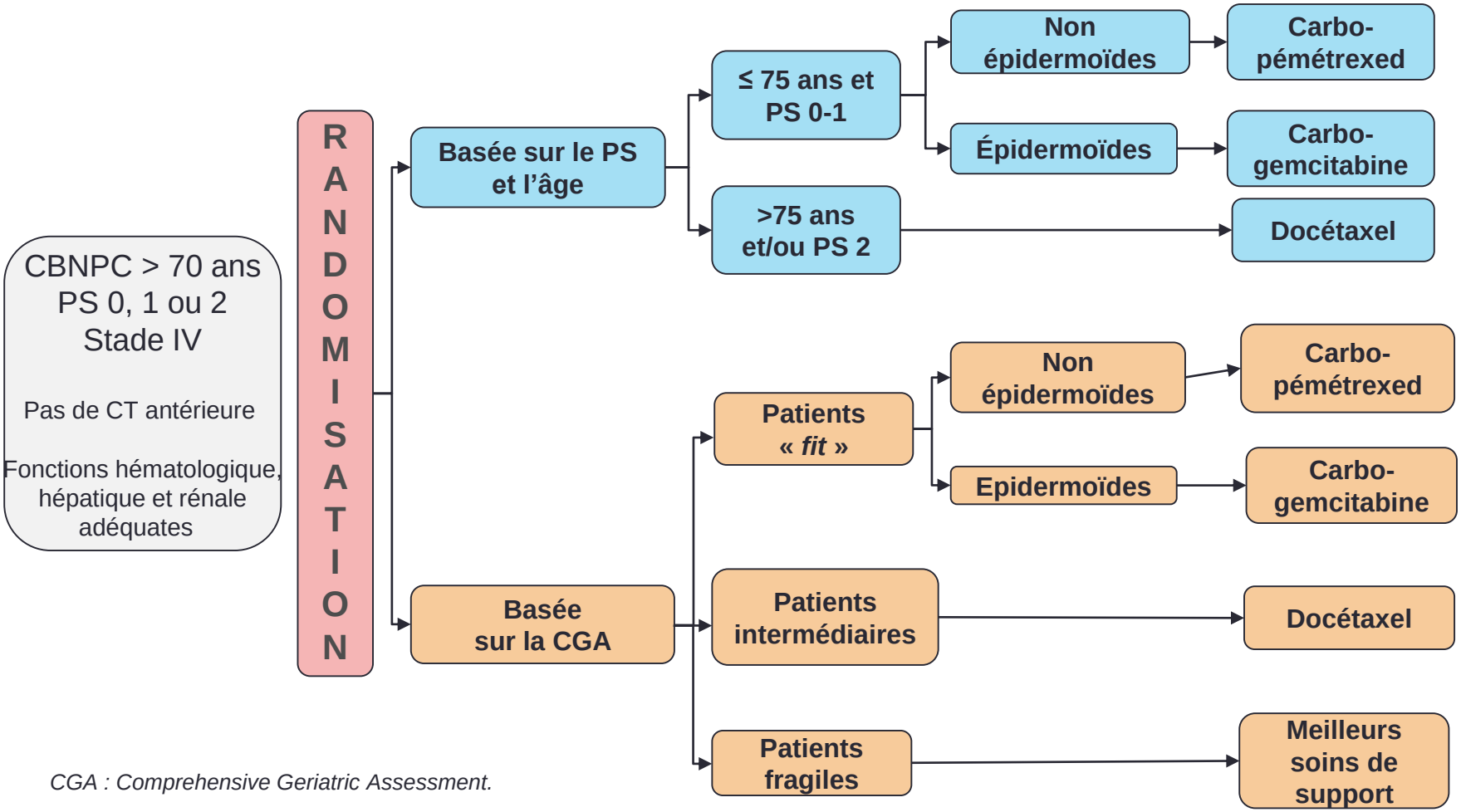
Scores gériatriques

	Number of patients	Univariate analysis (n=451)		Multivariate analysis (n=430*)	
		HR (95% CI)	p value	HR (95% CI)	p value
Treatment					
Doublet chemotherapy	225	0·64 (0·52–0·78)	<0·0001	0·62 (0·51–0·77)	<0·0001
Monotherapy	226	1·00	..	1·00	..
Sex					
Male	333	1·00	..	..	..
Female	118	0·77 (0·61–0·97)	0·026	..	..
Age (years)					
≤80	337	0·91 (0·72–1·14)	0·415	..	..
>80	114	1·00	..	..	..
Performance status score					
0–1	327	0·48 (0·38–0·60)	<0·0001	0·58 (0·46–0·74)	<0·0001
2†	123	1·00	..	..	..
Disease stage					
III‡	87	0·95 (0·74–1·23)	0·719	..	..
IV	364	1·00	..	..	..
Histology					
Adenocarcinoma	229	0·67 (0·55–0·83)	0·0002	0·79 (0·63–0·98)	0·029
Squamous and other	222	1·00	..	1·00	..
Smoking status					
Never smoked	94	0·65 (0·50–0·85)	0·001	0·68 (0·51–0·90)	0·007
Ever smoked§	356	1·00	..	1·00	..
MMSE					
≤23	67	1·00	..	..	..
>23	374	0·67 (0·51–0·88)	0·005	..	..
ADL score					
<6	88	1·00	..	1·00	..
6	350	0·59 (0·46–0·76)	<0·0001	0·67 (0·51–0·87)	0·003
CCI					
≤2	341	0·87 (0·69–1·10)	0·250	..	..
>2	110	1·00	..	..	..
BMI (kg/m²)					
≤20	52	1·00	..	..	..
>20–≤26	249	0·87 (0·63–1·21)	0·422	..	..
>26–≤30	99	0·74 (0·51–1·08)	0·119	..	..
>30	51	0·78 (0·51–1·19)	0·241	..	..
Weight loss before randomisation (%)					
≤5	203	0·56 (0·45–0·69)	<0·0001	0·70 (0·56–0·88)	0·002
>5	241	1·00	..	1·00	..



Quoix Lancet 2011

Valeur prédictive de l'évaluation gériatrique : essai ESOGIA (GFPC-GECP 08-02)



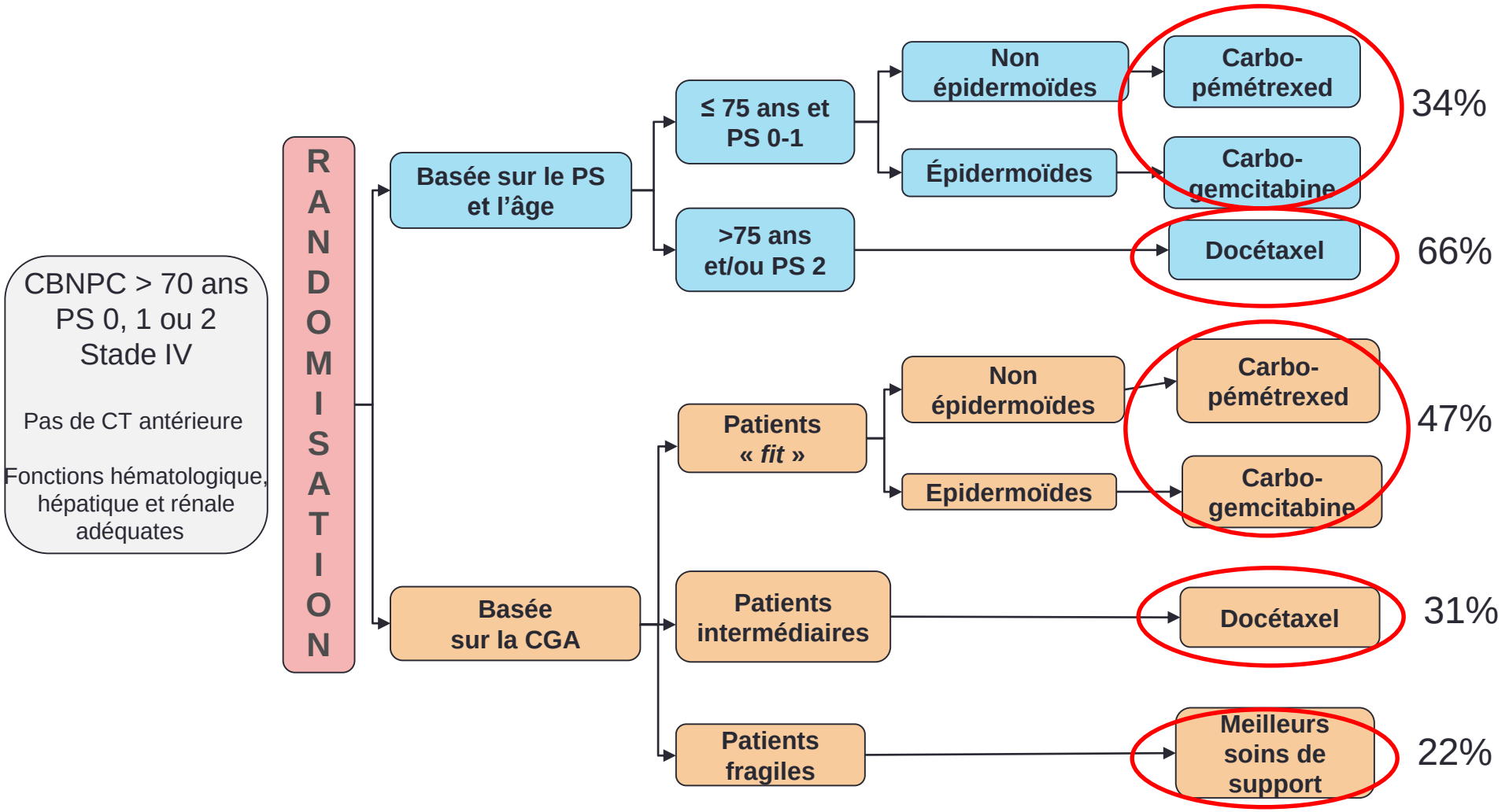
CGA : Comprehensive Geriatric Assessment.

Corre J Clin Oncol 2016

Comprehensive Geriatric Assessment

	Patients éligibles	Patients intermédiaires	Patients fragiles
ADL	6	6	≤ 5
IADL	0	1	≥ 2
Cognition **Schultz-Larsen mini MM-SE** **Folstein MM-SE ≤ 23**	> 23	> 23	≤ 23
Chutes à répétition	Non	Non	Oui
Incontinence urinaire ou fécale	Non	Non	Oui
Index de comorbidités de Charlson	0-1	2-3	≥4 (≥3 si >80 ans)
Score de dépression GDS 5	0-1	2-3	4-5

Corre J Clin Oncol 2016



CGA : Comprehensive Geriatric Assessment.

Corre J Clin Oncol 2016

ESOGIA - Résultats

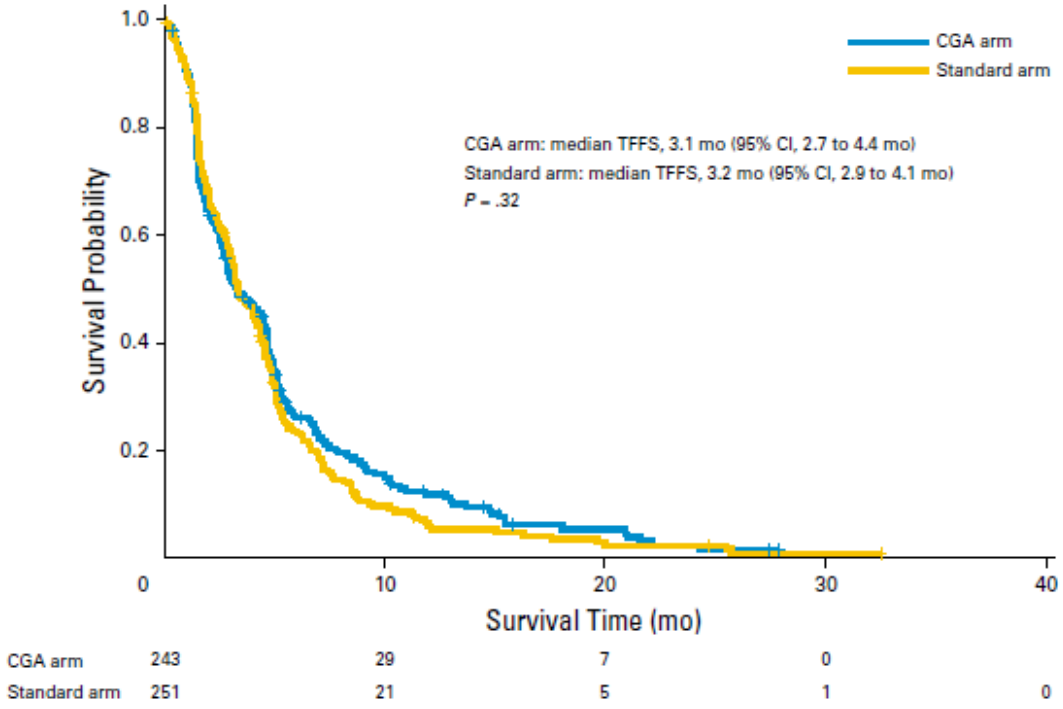


Table 4. Grade 3 or 4 Toxicities

Toxicity	% of Patients: Standard Arm (n = 251)	% of Patients: CGA Arm (n = 243)	P
All grades	93.4	85.6	.01
Grade 3-4	71.3	67.9	.41
Grade 3-4 neutropenia			.41
All	11.1	13.2	
Doublet	16.0	25.2	
Monotherapy	8.0	5.3	
BSC	—	0	
Grade 3-4 febrile neutropenia			.22
All	5.6	3.3	
Doublet	11.0	5.4	
Monotherapy	2.4	2.6	
BSC	—	0	
Grade 3-4 anemia			.87
All	11.2	10.7	
Doublet	21.6	16.2	
Monotherapy	5.5	6.6	
BSC	—	5.3	
Grade 3-4 thrombocytopenia			.04
All	3.6	7.8	
Doublet	7.9	17.1	
Monotherapy	1.2	0	
BSC	—	0	
Grades 3-4 asthenia			.34
All	10.8	13.6	
Doublet	7.9	14.4	
Monotherapy	12.3	15.8	
BSC	—	8.9	
Grade 3-4 anorexia			.27
All	4.0	6.2	
Doublet	0	10	
Monotherapy	6.0	5.3	
BSC	—	0	
Grade 3-4 nausea/vomiting			.46
All	3.6	4.9	
Doublet	1.1	8.1	
Monotherapy	4.9	2.6	
BSC	—	1.8	
Grade 3-4 peripheral sensory neuropathy			.62
All	1.2	0.4	
Doublet	0	0	
Monotherapy	1.8	1.3	
BSC	—	0	

Le choix de la chimiothérapie basée sur une échelle gériatrique simplifiée pour les patients >70 ans avec CBNPC de stade IV n'apporte pas de bénéfice en terme de survie ou de toxicité grave

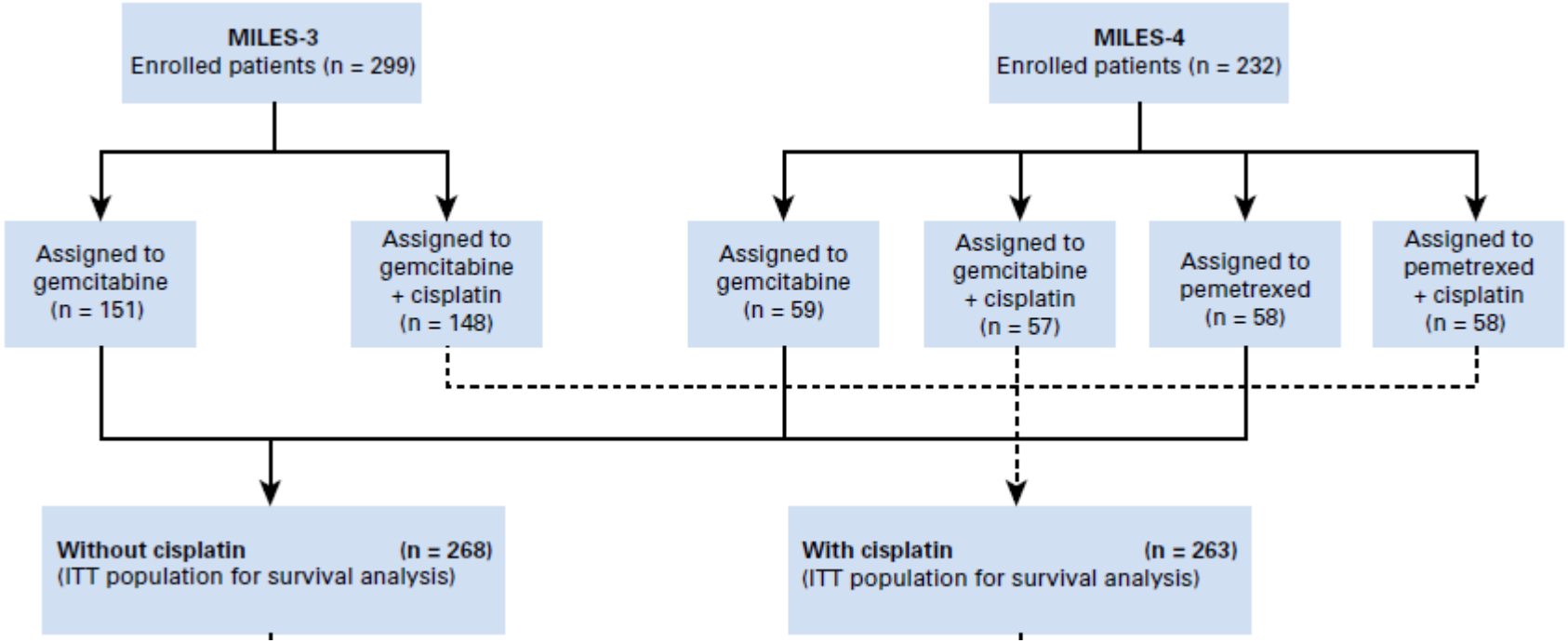
Corre J Clin Oncol 2016

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

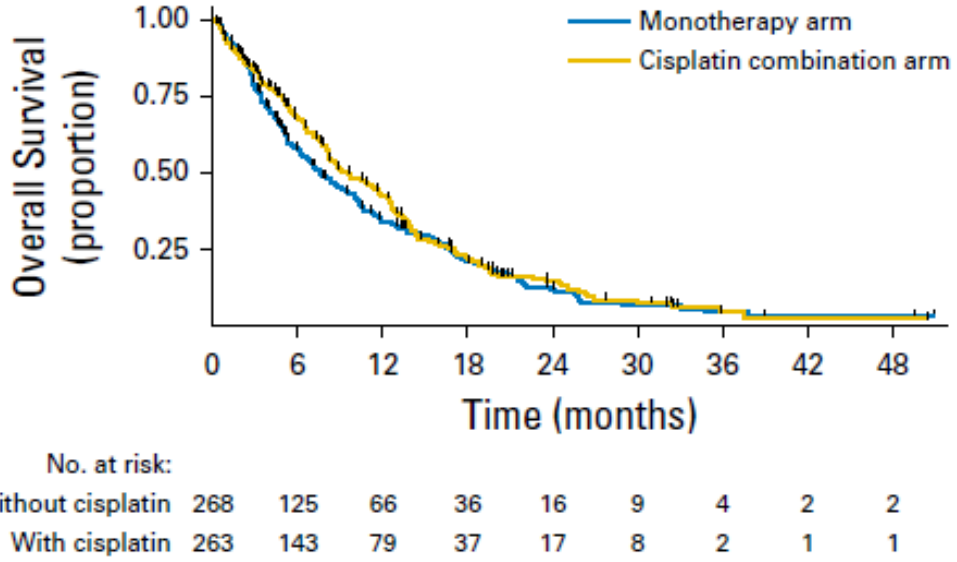
ORIGINAL REPORT

Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials



Gridelli J Clin Oncol 2018

Characteristic	Without Cisplatin (n = 268) No.	%	With Cisplatin (n = 263) No.	%
Age, years				
< 75	131	48.9	139	52.8
75-80	108	40.3	101	38.4
≥ 80	29	10.8	23	8.7
Sex				
Male	215	80.2	203	77.2
Female	53	19.8	60	22.8
Performance status				
0	114	42.5	116	44.1
1	154	57.5	147	55.9
Histotype				
Squamous	79	29.5	78	29.7
Nonsquamous	189	70.5	185	70.3
Stage				
IIIB	20	7.5	16	6.1
IV	248	92.5	247	93.9
Smoking habit				
Current smokers	73	27.2	66	25.1
Former smokers	159	59.3	160	60.8
Never Smokers	36	13.4	34	12.9
Unknown	0		3	1.1
ADL score				
6	202	75.4	200	76.1
< 6	26	9.7	24	9.1
Unknown	40	14.9	39	14.8
Percent of IADL independency				
100	84	31.3	76	28.9
99-75	52	19.4	62	23.6
74-50	67	25.0	61	23.2
49-25	24	9.0	22	8.4
< 25	1	0.4	1	0.4
Unknown	40	14.9	41	15.6
Companion drug				
Gemcitabine	210	78.3	205	77.9
Pemetrexed	58	21.6	58	22.1



- Un doublet à base de cisplatine ne semble pas apporter de bénéfice chez les sujets âgés
- Toxicité supérieure au carboplatine +++
- Ces résultats ne remettent pas en cause les résultats de l'essai IFCT-0501

first-line treatment in clinical practice. This result fully supports

« most fit elderly patients (…) may be offered carboplatin-based doublets" (*P. Bunn JCO 2018*)

ternative in selected cases, with caution regarding potential toxicity.

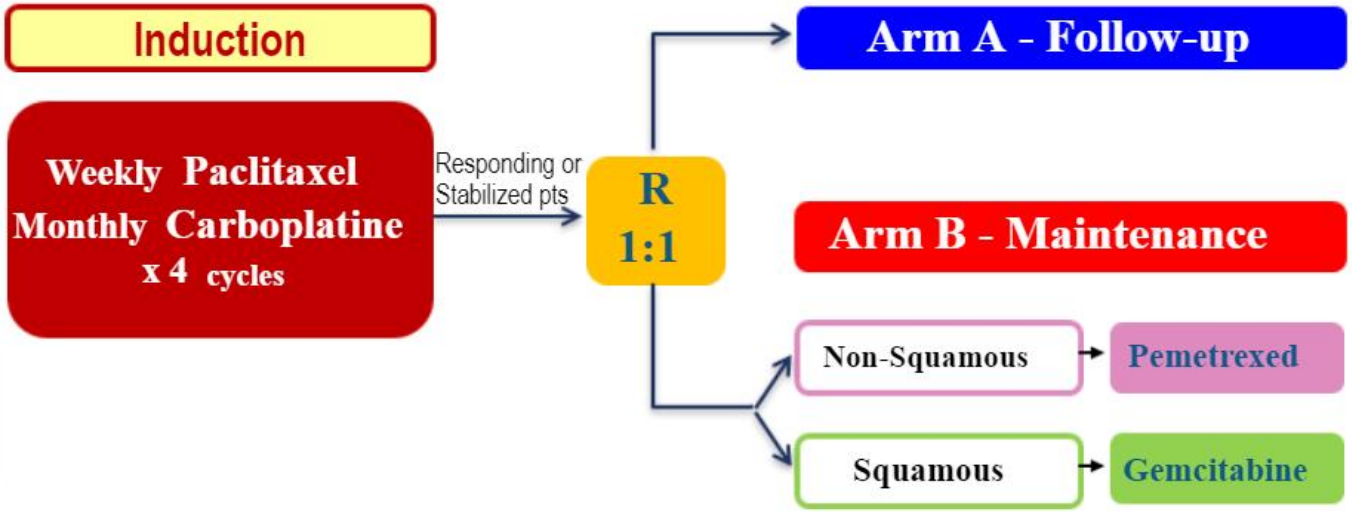
Gridelli J Clin Oncol 2018

Chimiothérapie de maintenance

IFCT-1201 MODEL trial

Randomized, comparative phase 3 trial

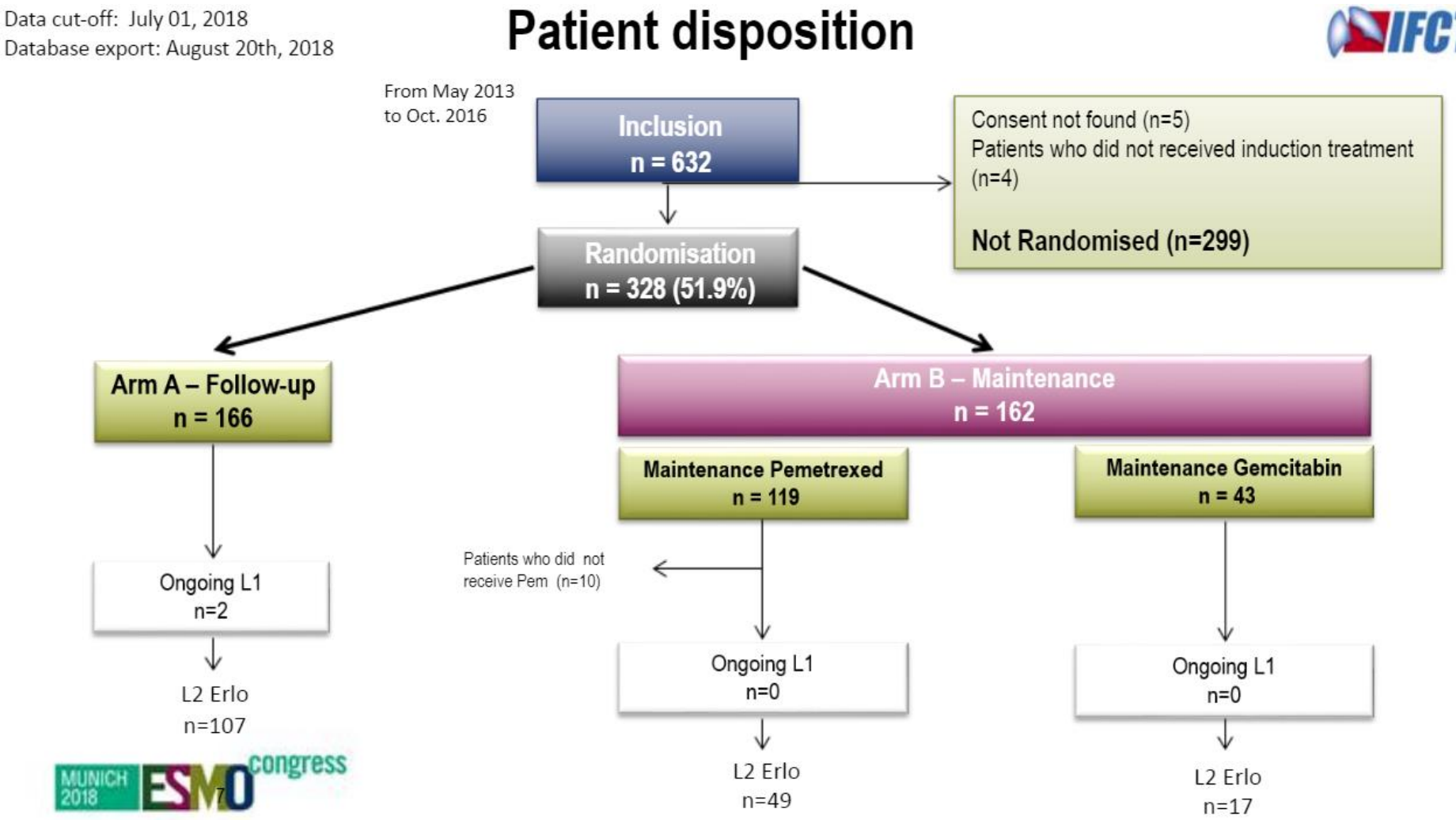
- Histological or cytological diagnosis of NSCLC
- With stage IIIB unresectable and non-irradiable or stage IV
- Without EGFR/ALK mutations (or unknown)
- Measurable disease (RECIST 1.1)
- Age ≥ 70 years and < 90 years
- MMS > 23
- PS 0-2



- Carboplatine : AUC 6 D1 = D29
- Paclitaxel : 90 mg/m², D1=D8=D15=D29
- Gemcitabine 1150 mg/m² D1=D8=D22
- Pemetrexed 500 mg/m² D1 = D22

Quoix ESMO 2018 abstract #3420

IFCT-1201 MODEL



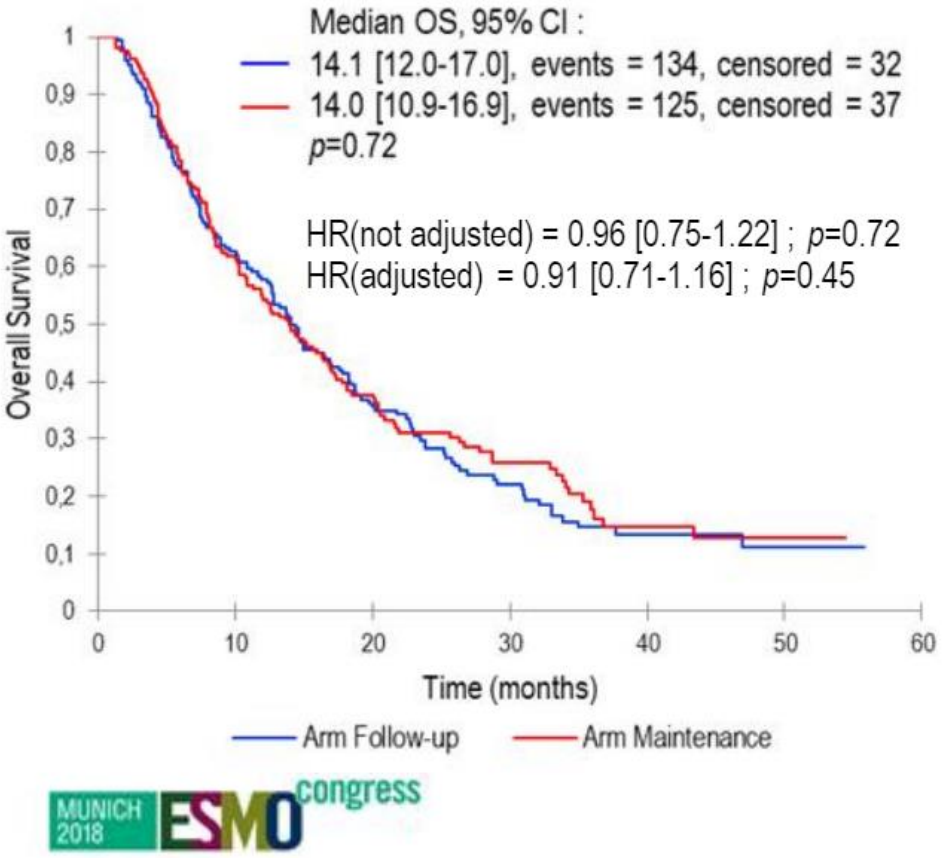
Quoix ESMO 2018 abstract #3420

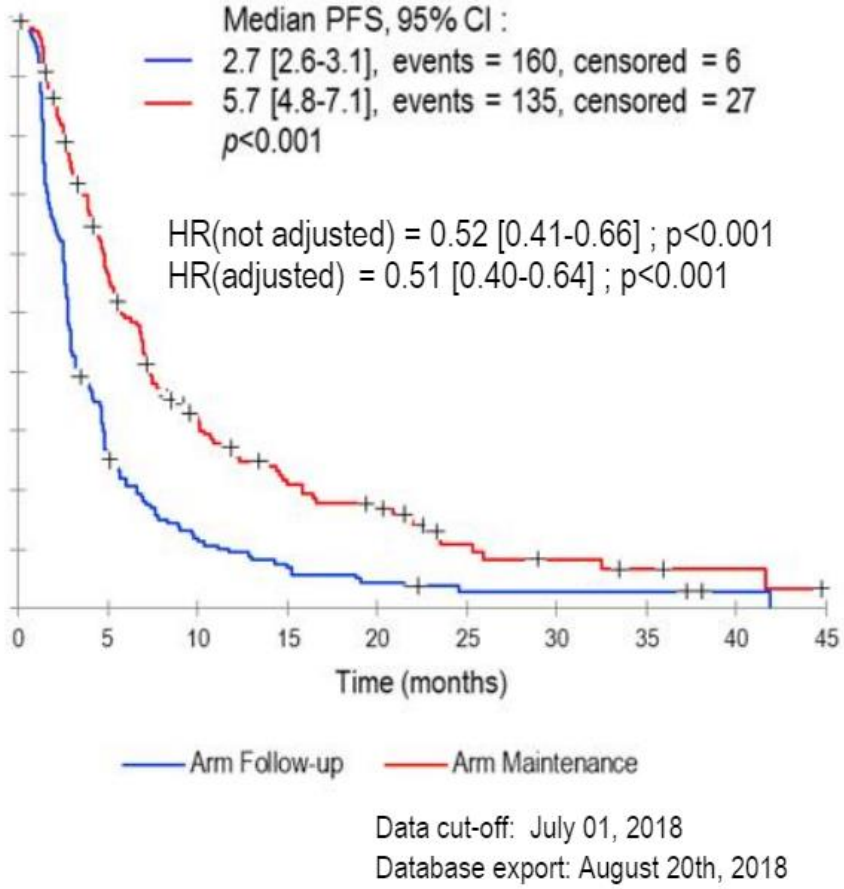
IFCT-1201 MODEL

	Arm Follow-up (N=166)	Arm Maintenance (N=162)	Maintenance (PEM) (N=119)	Maintenance (GEM) (N=43)
Performance Status at randomisation N(%)				
0-1	135 (81.3)	130 (80.2)	93 (78.2)	37 (86.0)
2	31 (18.7)	32 (19.8)	26 (21.8)	6 (14.0)
Age				
< 80 years	130 (78.3)	127 (78.4)	92 (77.3)	35 (81.4)
≥ 80 years	36 (21.7)	35 (21.6)	27 (22.7)	8 (18.6)
Histology subtype N(%)				
Squamous	46 (27.7)	44 (27.2)	1 (0.8)	43 (100)
Non Squamous	120 (72.3)	118 (72.8)	118 (99.2)	0
Response after 4 cycles of induction chemotherapy N(%)				
Complete response	1 (0.6)	1 (0.6)	0	1 (2.3)
Partial response	87 (52.4)	76 (46.9)	49 (41.2)	27 (62.8)
Stabilisation	76 (45.8)	83 (51.2)	68 (57.1)	15 (34.9)
Progression	2 (1.2)	1 (0.6)	1 (0.8)	0
Non Evaluable	0	1 (0.6)	1 (0.8)	0

Quoix ESMO 2018 abstract #3420

IFCT-1201 MODEL





MUNICH 2018 ESMO congress

Quoix ESMO 2018 abstract #3420

IFCT-1201 MODEL

	Arm Follow-up	Arm Maintenance
N	166	162
Ongoing L1	2	0
Patients who could receive second-line treatment	164	162
Patients with second-line systemic post-treatment	133 (81.1%)	103 (63.6%)
Erlotinib	**109 (66.5%)**	**68 (42.0%)**
Nivolumab	**11 (6.7%)**	**22 (13.6%)**
Pemetrexed	6 (3.7%)	3 (1.8%)
Crizotinib	2 (1.2%)	1 (0.6%)
Gefitinib	1 (0.6%)	2 (1.2%)
Vinorelbine	1 (0.6%)	2 (1.2%)
Docetaxel	1 (0.6%)	1 (0.6%)
Gemcitabine	1 (0.6%)	1 (0.6%)
Carboplatin plus pemetrexed	1 (0.6%)	0
Capmatinib	0	1 (0.6%)
Clinical Trial	0	1 (0.6%)
Paclitaxel	0	1 (0.6%)
Exclusive radiotherapy	10 (6.1%)	10 (6.2%)
No second-line treatment	21 (12.8%)	49 (30.2%)

MUNICH 2018 ESMO congress

Quoix ESMO 2018 abstract #3420

IFCT-1201 MODEL

Drug-related Adverse Events (AE) for induction (n=623)

ALL grade	**579 (92.9%)**
Grade 3	235 (37.7%)
Grade 4	110 (17.7%)
Grade 5	12 (1.9%)*

* 2 Febrile neutropenia, 4 Sepsis, 1 Gastrointestinal haemorrhage , 1 Myocardial infarction, 2 Pancytopenia, 1 Febrile bone marrow aplasia, 1 Lung disorder

Drug-related Adverse Events (AE) for maintenance

	Arm Follow-up (N=166)	Maintenance Pemetrexed (N=109)	Maintenance Gemcitabine (N=43)
ALL grade	**87 (52.4%)**	**103 (94.5%)**	**41 (95.3%)**
Grade 3	4 (2.4%)	34 (31.2%)	20 (46.5%)
Grade 4	0 (0%)	20 (18.3%)	2 (4.6%)
Grade 5	0 (0%)	2 (1.8%)*	0 (0%)

*: 1 Febrile neutropenia and 1 Sepsis

Quoix ESMO 2018 abstract #3420

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

Elderly patients

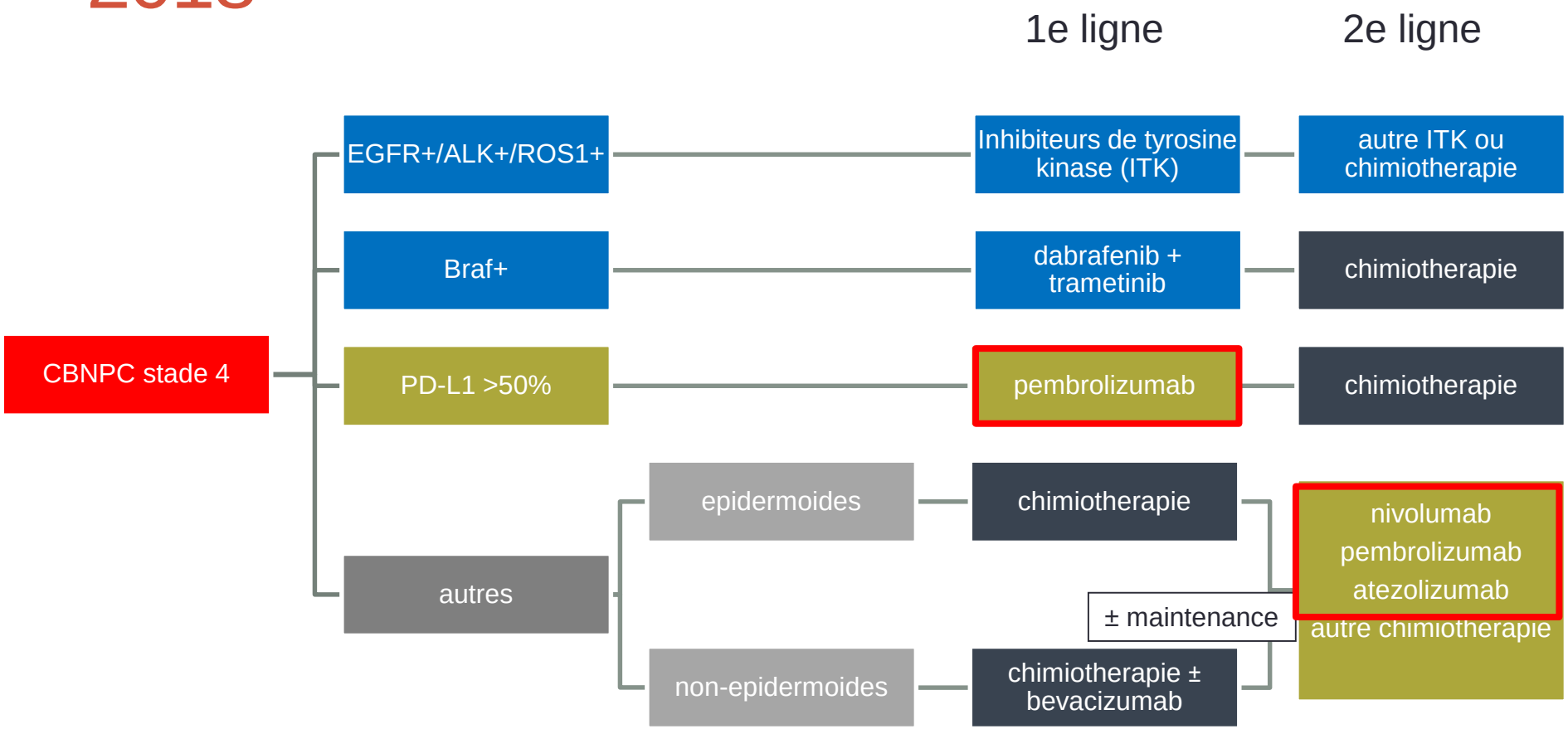
≥70ans

arms in this study [146]. Carboplatin-based doublet ChT is recommended in eligible elderly patients with PS 0–2 and with adequate organ function [I, A]. For those patients not eligible for doublet ChT, single-agent ChT remains the standard of care [I, B].

Planchard Ann Oncol 2018

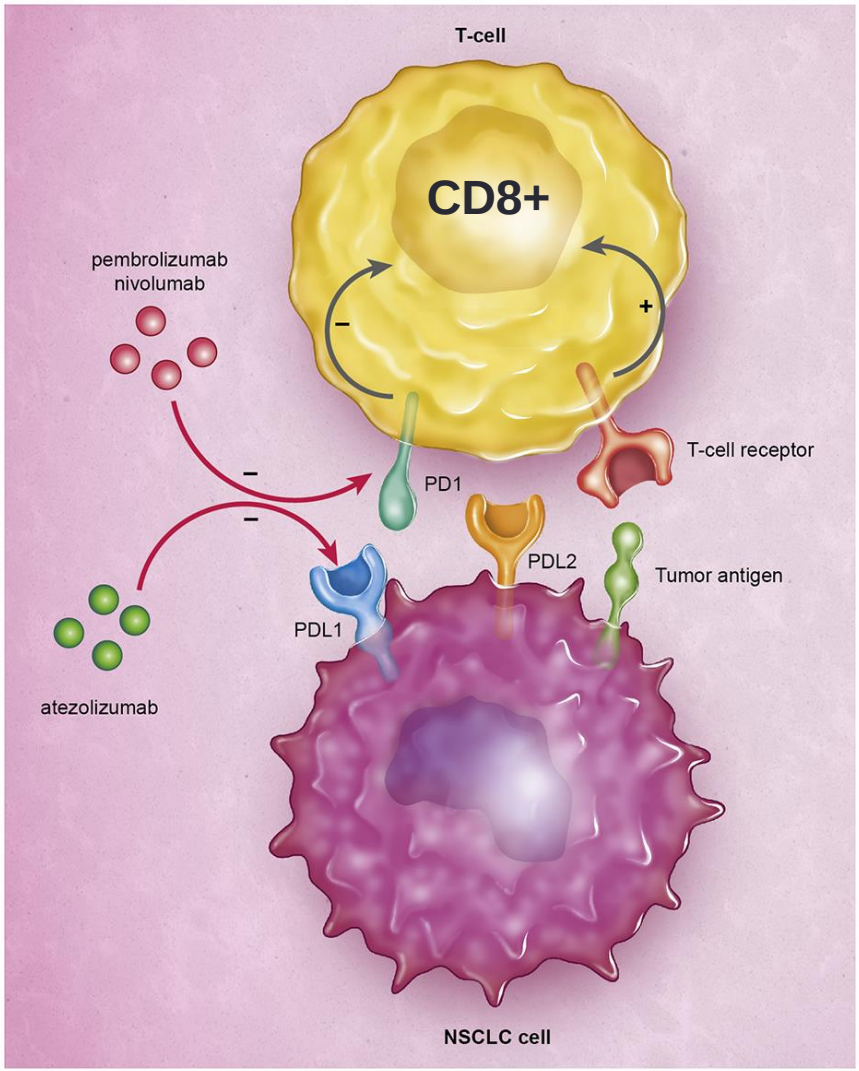
Switch maintenance chemotherapy should not be recommended in elderly patients with advanced NSCLC

Stratégie thérapeutique des stades 4 en 2018



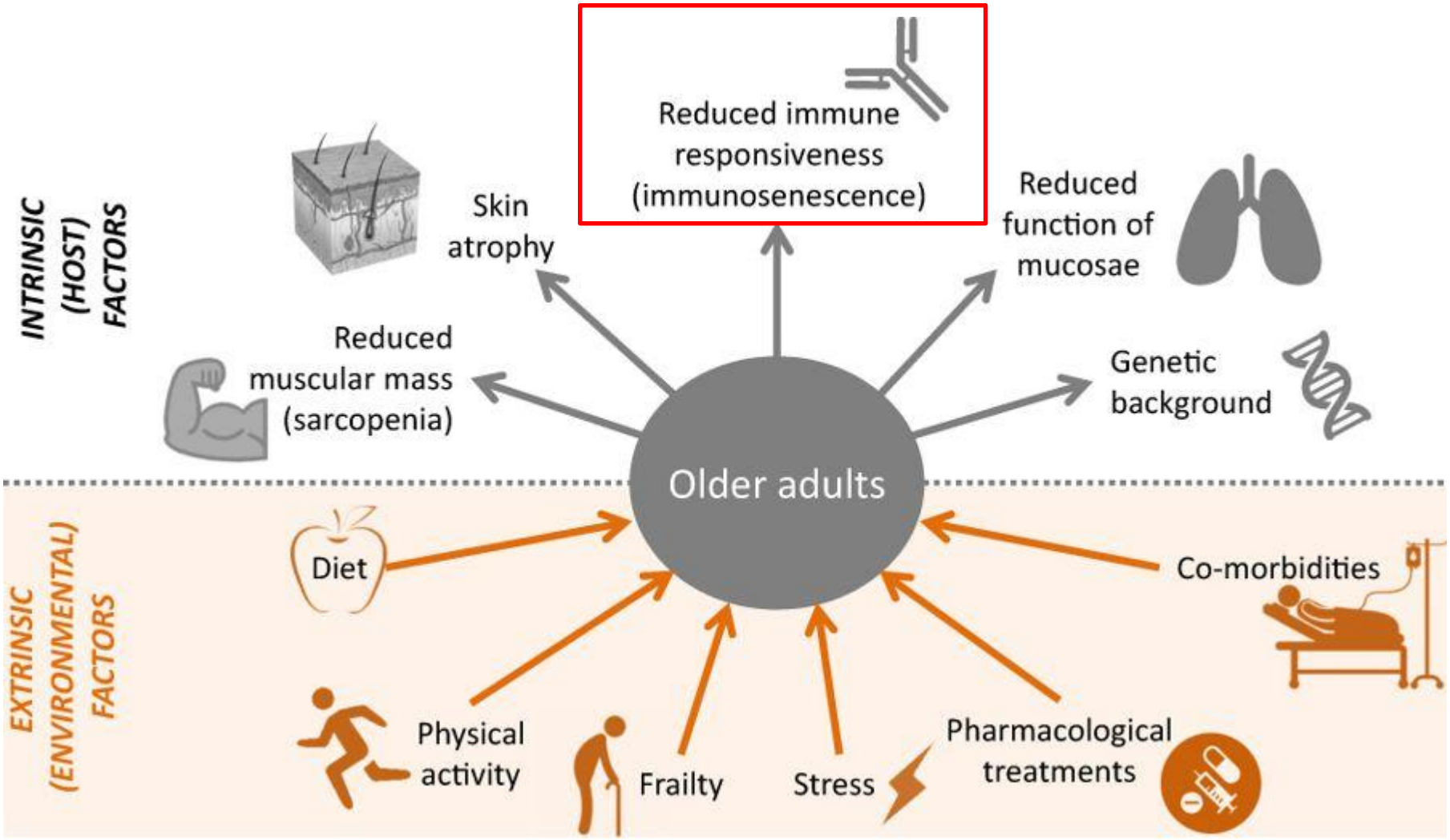
Aucun essai randomisé spécifique pour les sujets âgés
Analyses de sous-groupe des essais d'enregistrement (pas de stratification sur l'âge)

Inhibiteurs des points de contrôle immunitaire



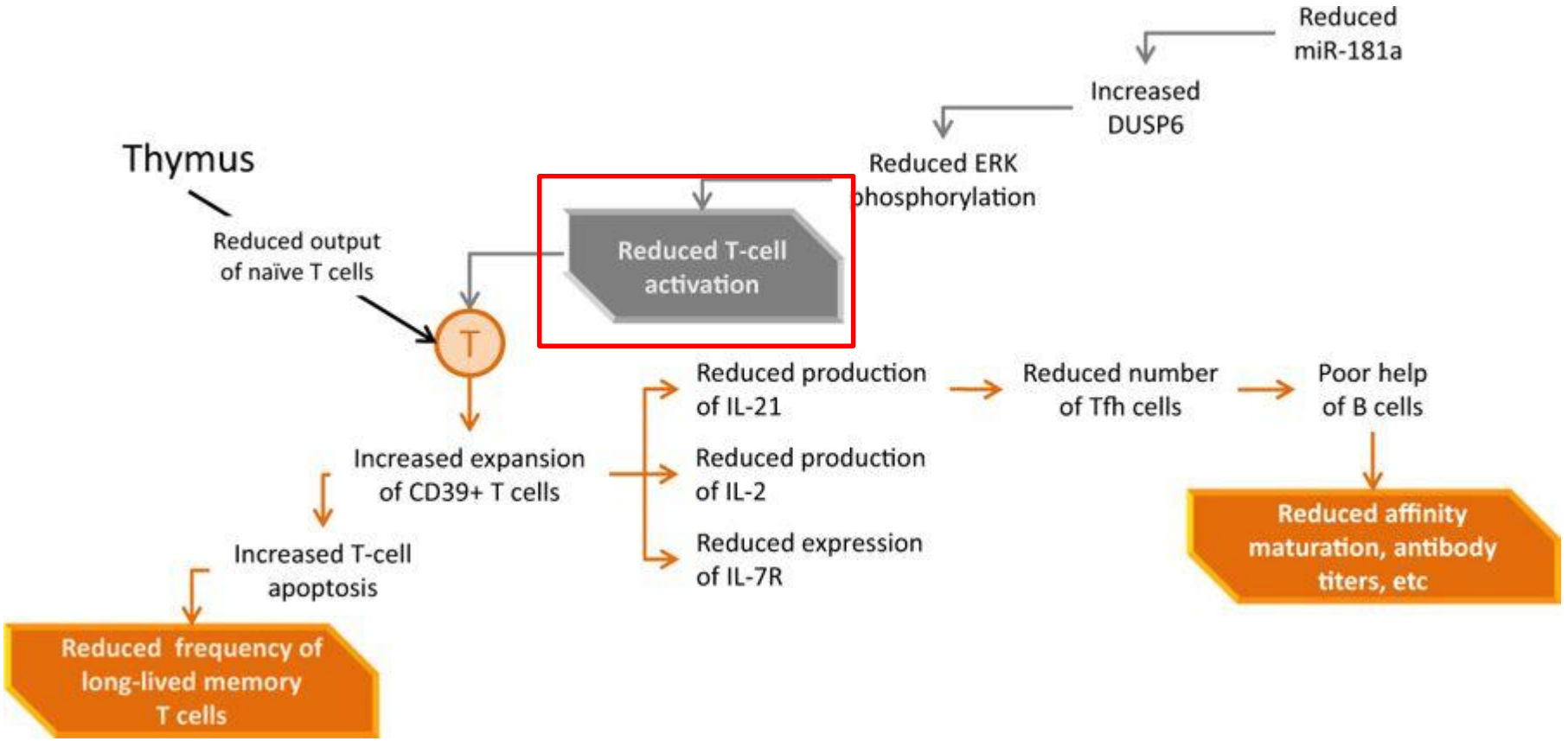
Giroux Leprieur Eur J Cancer 2017

Immunosénéscence



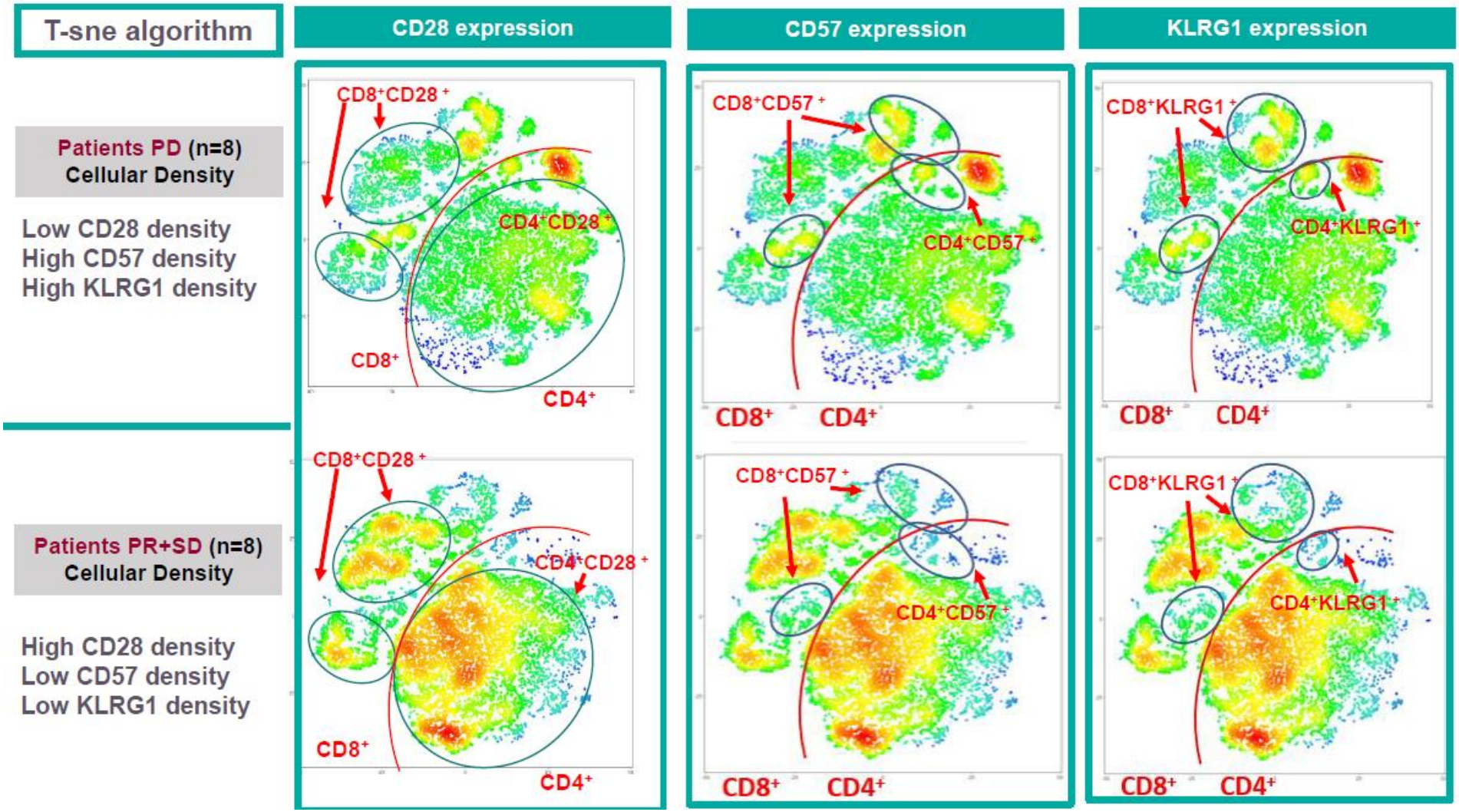
Del Giudice NPJ Aging Mech Dis 2017

Immunosénéscence



Del Giudice NPJ Aging Mech Dis 2017

Evaluation de l'immunosénéscence



Ferrara ESMO 2018 abstract #1416P

Patients characteristics	Total (N=37)	SIP - (N=25)	SIP + (N=12)	p-value
Age				0.62
≥ 65	12 (32%)	7 (28%)	5 (42%)	
< 65	25 (68%)	18 (72%)	7 (58%)	
Smoking history				0.39
Non-smokers	5 (14%)	2 (8%)	3 (25%)	
Former	19 (51%)	13 (52%)	6 (50%)	
Current	13 (35%)	10 (40%)	3 (25%)	
Histology				0.51
Adenocarcinoma	31 (84%)	22 (88%)	9 (75%)	
NSCLC-Other	3 (8%)	1 (4%)	2 (17%)	
Squamous	3 (8%)	2 (8%)	1 (8%)	
PD-L1 status				0.67
PDL-1 < 1% (tumor cells)	8 (22%)	4 (25%)	4 (36%)	
PDL-1 ≥ 1% (tumor cells)	19 (51%)	12 (75%)	7 (64%)	
Unknown	10 (27%)	9	1	
N° of met sites baseline				0.13
≤ 2	22 (59%)	17 (68%)	5 (42%)	
> 2	15 (41%)	8 (32%)	7 (58%)	
Performance status (ECOG)				0.73
< 2	28 (76%)	19 (76%)	9 (75%)	
≥ 2	9 (24%)	6 (24%)	3 (25%)	

L'immunosénéscence

- **Est associée à une moins bonne réponse aux ICI**
- **Mais n'est pas associée à l'âge !**

Ferrara ESMO 2018 abstract #1416P

Checkmate-017

- Stade IIIB/IV CBNPC épidermoïdes
- ECOG PS 0-1
- 1ère ligne avec platine obligatoire
- Expression de PD-L1

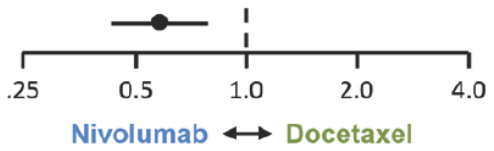
R

Nivolumab 3 mg/kg IV J1-J15 jusqu'à Prog. ou Tox. inacceptable
N = 135

- **Objectif Principal**
  - → SG
- **Objectifs Secondaires**
  - → Taux de réponse global
  - → SSP
  - → Effets secondaires

de

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)



r NEJM 2015

Chemckmate-057

- Stade IIIB/IV CBNPC non-épi
- ECOG PS 0-1
- 1ère ligne avec platine

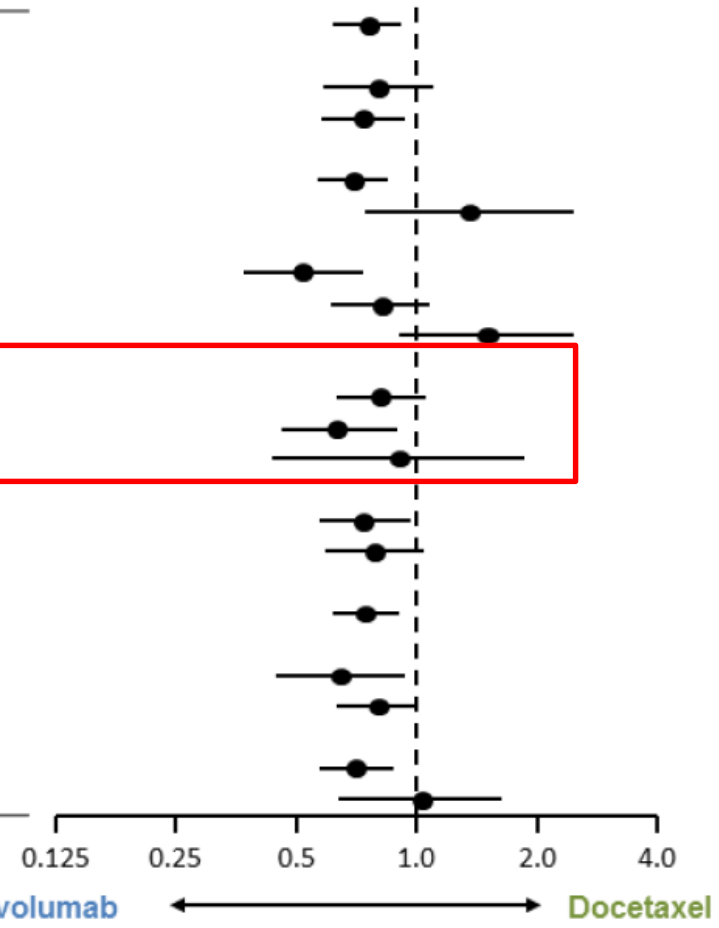
→

Nivolumab 3 mg/kg IV J1-J15 jusqu'à Prog. ou Tox. inacceptable N=292

→

- Objectif Principal
  → SG
- Objectifs Secondaires

	N	Unstratified HR (95% CI)
Overall	**582**	**0.75 (0.62, 0.91)**
Prior Use of Maintenance Therapy		
Yes	233	0.80 (0.58, 1.10)
No	349	0.73 (0.57, 0.93)
Line of Therapy		
Second Line	515	0.69 (0.56, 0.85)
Third Line	66	1.34 (0.73, 2.43)
Region		
US/Canada	215	0.52 (0.37, 0.72)
Europe	269	0.81 (0.61, 1.07)
Rest of World	98	1.49 (0.91, 2.45)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Sex		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Race		
White	533	0.74 (0.61, 0.91)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)

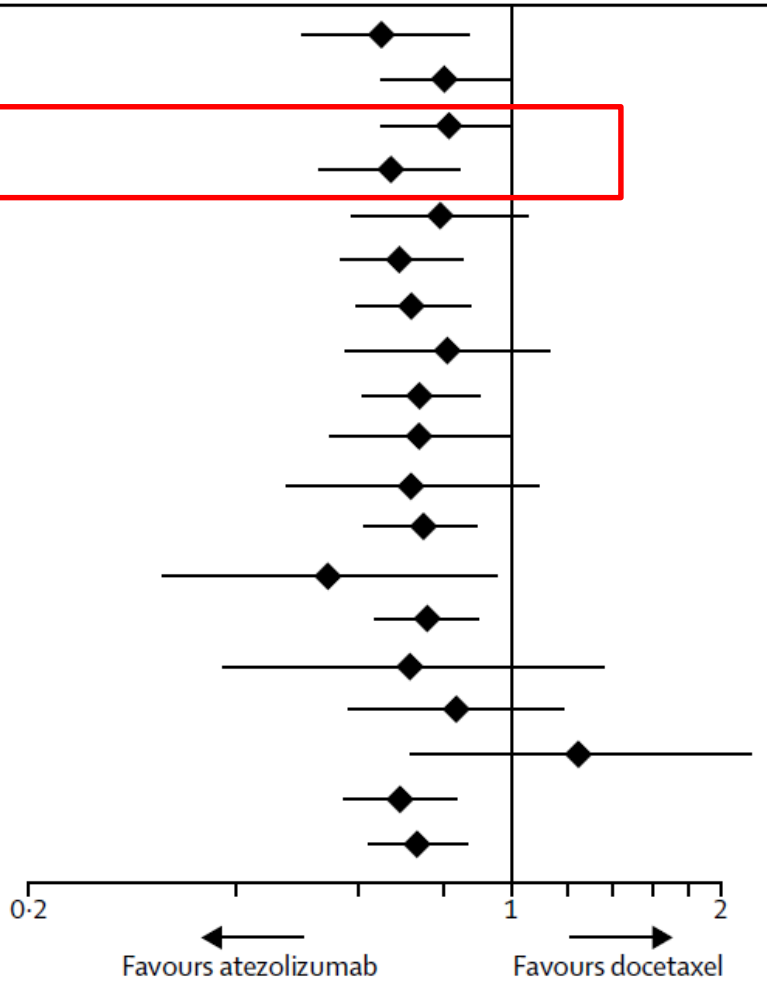


OAK

Progression

A

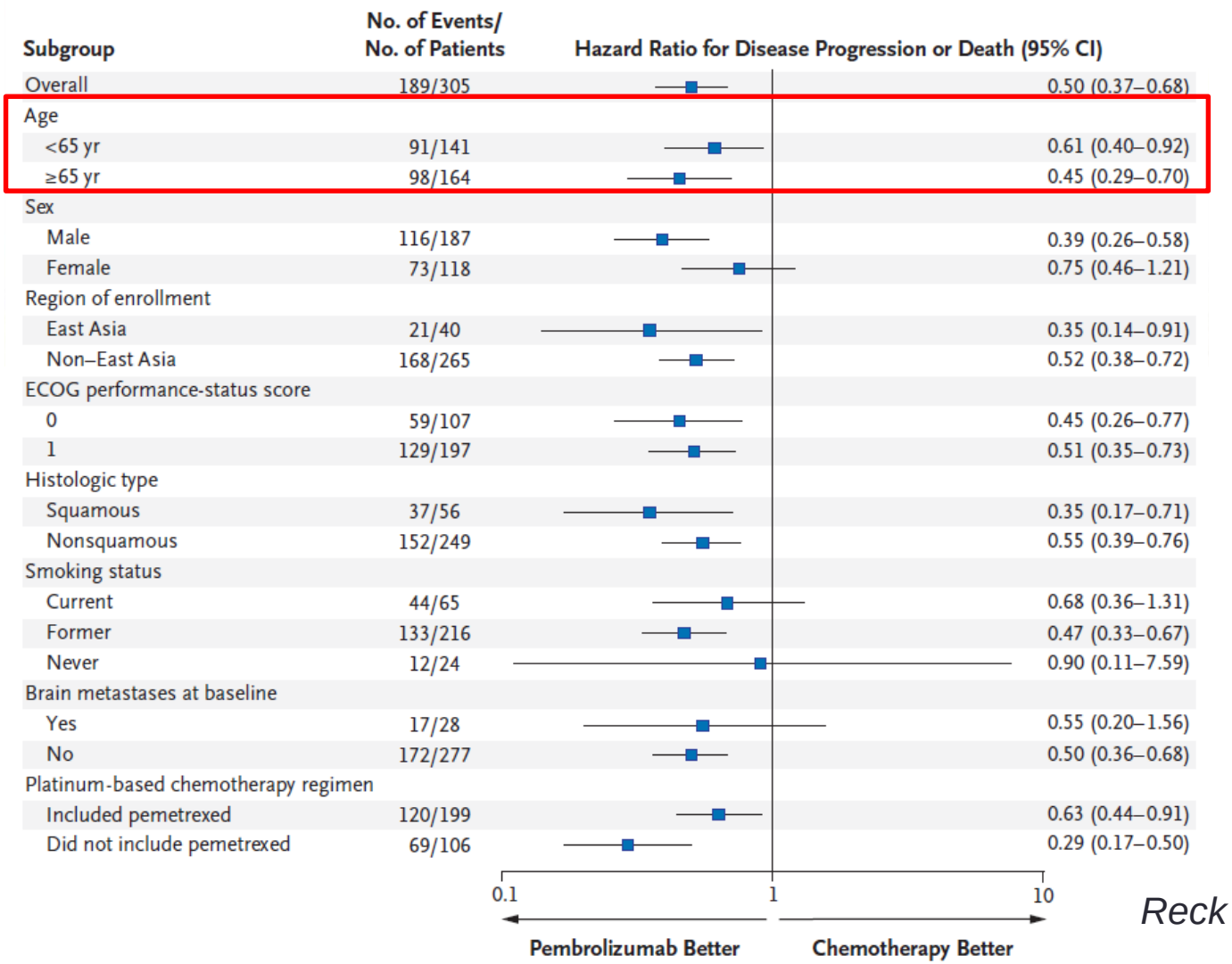
	n (%)	Median overall survival (months)	
		Atezolizumab	Docetaxel
Female	330 (39)	16·2	11·2
Male	520 (61)	12·6	9·2
<65 years old	453 (53)	13·2	10·5
≥65 years old	397 (47)	14·1	9·2
ECOG PS 0	315 (37)	17·6	15·2
ECOG PS 1	535 (63)	10·6	7·6
1 previous therapy	640 (75)	12·8	9·1
2 previous therapies	210 (25)	15·2	12·0
Non-squamous	628 (74)	15·6	11·2
Squamous	222 (26)	8·9	7·7
Never smokers	156 (18)	16·3	12·6
Current or previous smokers	694 (82)	13·2	9·3
CNS metastases	85 (10)	20·1	11·9
No CNS metastases	765 (90)	13·0	9·4
KRAS mutant	59 (7)	17·2	10·5
KRAS wildtype	203 (24)	13·8	11·3
EGFR mutant	85 (10)	10·5	16·2
EGFR wildtype	628 (74)	15·3	9·5
ITT	**850 (100)**	**13·8**	**9·6**



Keynote-024

- CBNPC avancé
- Ni EGFR muté ni ALK+
- Expression de PD-L1

Pembrolizumab 200 mg dose fixe i.v.



Reck NEJM 2016

RESEARCH ARTICLE Open Access

Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis

Rawad Elias[1], Anita Giobbie-Hurder[2], Nadine Jackson McCleary[3], Patrick Ott[3], F. Stephen Hodi[3] and Osama Rahma[3*]

	Study Name	Drug	Phase	Malignancy	First line	Arm 1	Arm 2	Arm 3	Patient' number	Age median	Age range	Age mean	n (%) < 65 y	n (%) ≥ 65 y
Rittmeyer 2016 [33]	OAK	Atezolizumab	3	NSCLC	N	Atezolizumab 1200 mg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W		850	64	33–85	63	453 (53)	397 (47)
Fehrenbacher 2016 [26, 34]	POPLAR	Atezolizumab	2	NSCLC	N	Atezolizumab 1200 mg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W		287	62	36–84	61.5	174 (61)	113 (39)
Brahmer 2015 [5]	Checkmate-017	Nivolumab	3	S-NSCLC	N	Nivolumab 3 mg/kg Q 2 W	Docetaxel 75 mg/m^2 Q 3 W		272	63	39–85	63	152 (56)	120 (44)
Borghaei 2015 [6]	Checkmate-057	Nivolumab	3	NS-NSCLC	N	Nivolumab 3 mg/kg Q 2 W	Docetaxel 75 mg/m^2 Q 3 W		582	62	21–85	NR	339 (58)	243 (42)
Motzer 2015 [4]	Checkmate-025	Nivolumab	3	RCC	N	Nivolumab 3 mg/kg Q 2 W	Everolimus 10 mg daily		821	62	18–88	61.3	497 (61)	324 (39)
Robert 01–2015 [29]	Checkmate-066	Nivolumab	3	Melanoma	Y	Nivolumab 3 mg/kg Q 2 W	Dacarbazine 1000 mg/m^2 Q 3 W		418	65	18–87	62.7	200 (48)	218 (52)
Ferris 2016 [7]	Checkmate-141	Nivolumab	3	H&N	N	Nivolumab 3 mg/kg Q 2 W	Chemotherapy		361	60	28–83	59.1	248 (69)	113 (31)
Herbst 2016 [8]	Keynote-010	Pembrolizumab	2/3	NSCLC	N	Pembrolizmab 2 mg/kg Q 3 W	Pembrolizumab 10 mg/kg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W	1033	NR	NR	62	604 (58)	429 (42)
Robert 06–2015 [9]	Keynote-006	Pembrolizumab	3	Melanoma	N	Pembrolizumab 10 mg/kg Q 2 W	Pembrolizumab 10 mg/kg Q 3 W	Ipilimumab 3 mg/kg Q 3 W	834	NR	NR	60.3	467 (56)	367 (44)

n=5458

Elias J Immun Cancer 2018

Survie sans progression

≥65 ans

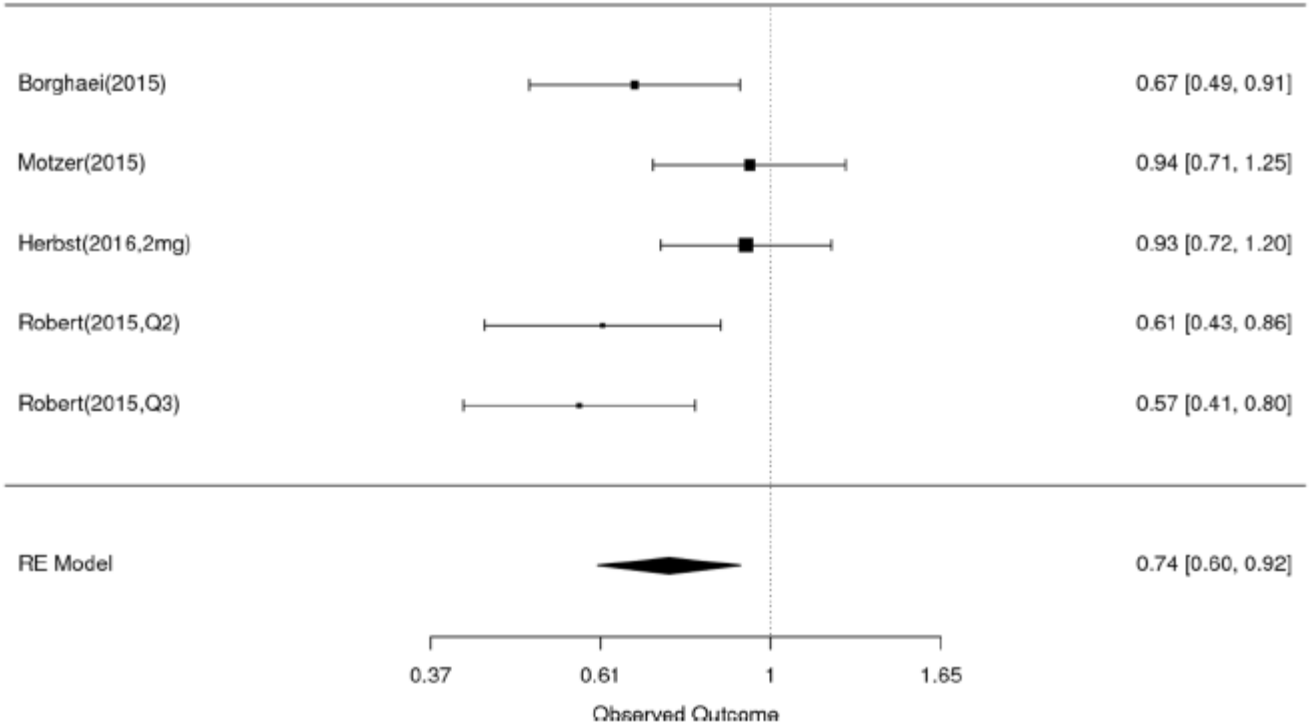


Table 3 Summary of HR for PFS by Age

Age	HR (95% CI)
Age < 65 years	0.73 (0.61 to 0.88)
Age ≥ 65 years	0.74 (0.60 to 0.92)

Elias J Immun Cancer 2018

Survie globale

≥ 65 ans

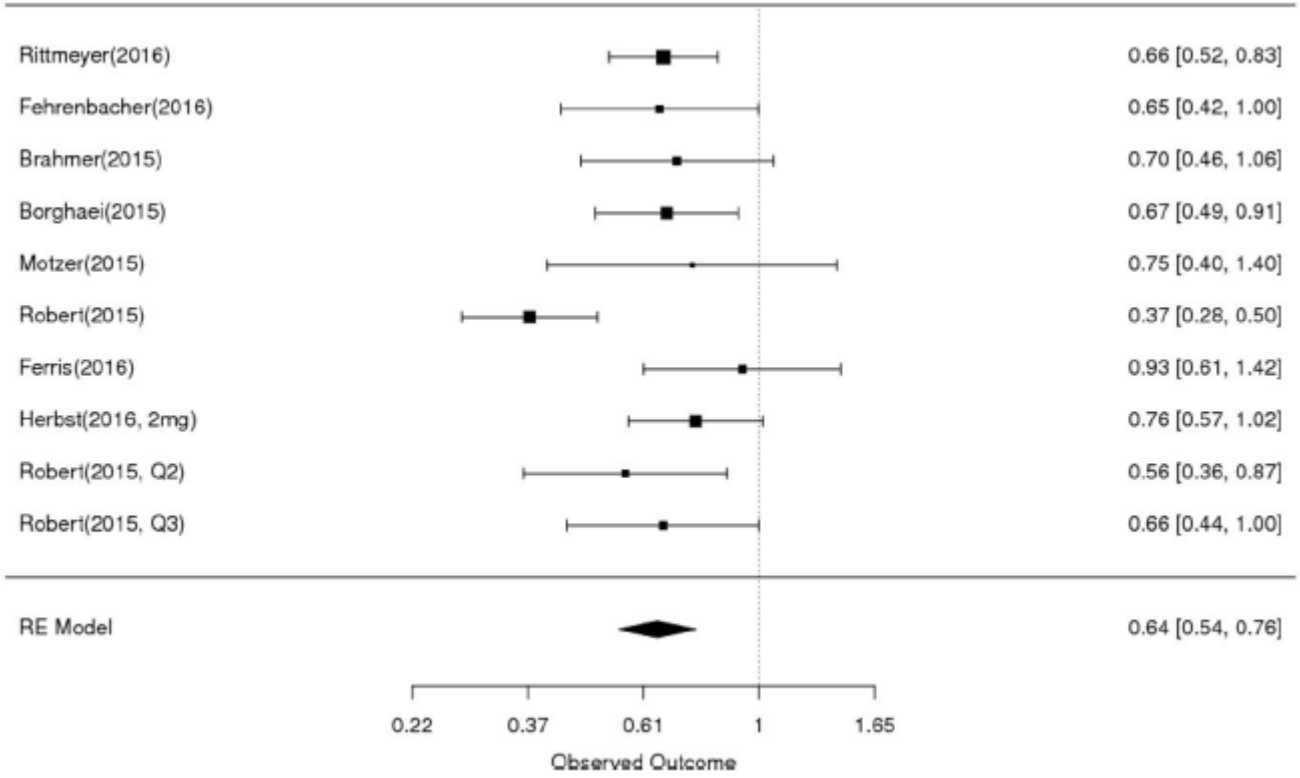


Table 2 Summary of HR for OS by Age

Age	HR (95% CI)
Age < 65 years	0.68 (0.61 to 0.75)
Age ≥ 65 years	0.64 (0.54 to 0.76)

Elias J Immun Cancer 2018

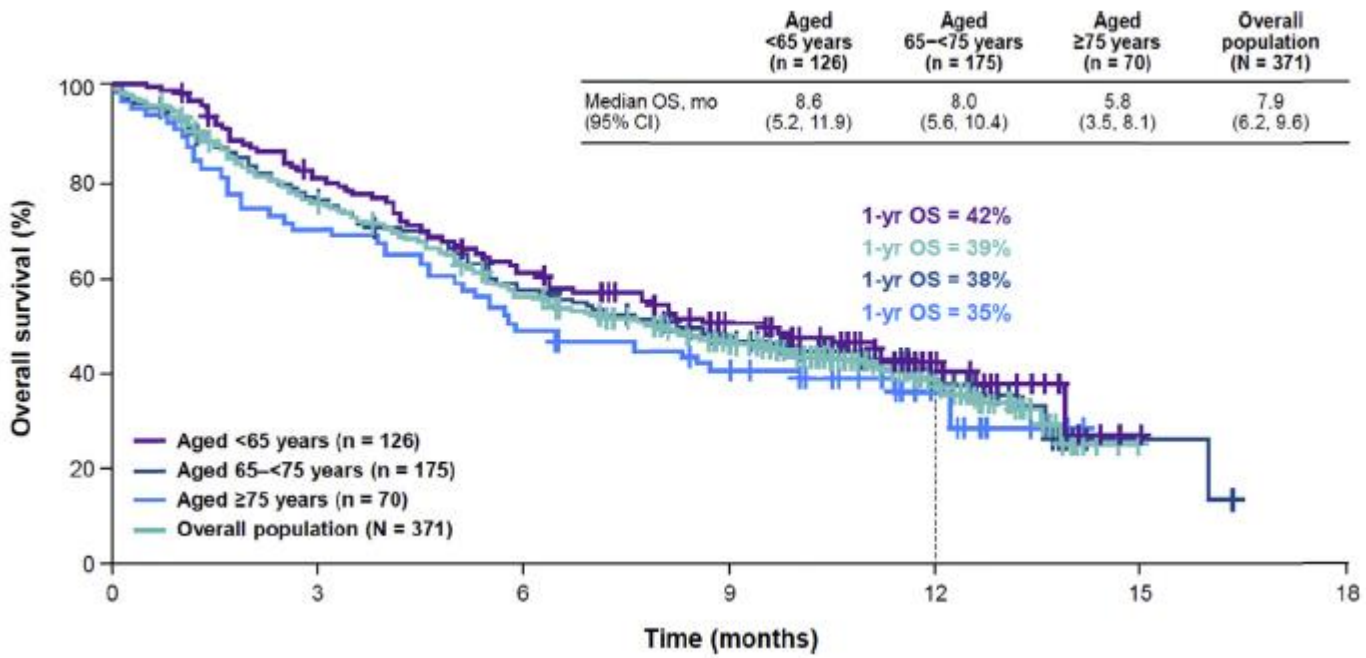
L’immunothérapie (monothérapie) chez les sujets âgés semble aussi efficace que chez les sujet jeunes à partir des données des essais cliniques (population générale)

Use of nivolumab in elderly patients with advanced squamous non–small-cell lung cancer: results from the Italian cohort of an expanded access programme

Characteristics	Aged <65 years (n = 126)	Aged 65–<75 years (n = 175)	Aged ≥75 years (n = 70)	Overall population (N = 371)
Sex, n (%)				
Male	93 (74)	144 (82)	61 (87)	298 (80)
Female	33 (26)	31 (18)	9 (13)	73 (20)
Median age, years (range)	59 (31–64)	70 (65–74)	77 (75–91)	68 (31–91)
Smoking status, n (%)				
Smoker	33 (26)	35 (20)	15 (21)	83 (22)
Former smoker	67 (53)	107 (61)	51 (73)	225 (61)
Never smoker	15 (12)	14 (8)	2 (3)	31 (8)
Unknown	11 (9)	19 (11)	2 (3)	32 (9)
ECOG Performance Status, n (%)				
0	57 (45)	64 (37)	13 (19)	134 (36)
1	61 (48)	101 (58)	53 (76)	215 (58)
2	8 (6)	10 (6)	4 (6)	22 (6)
Site of metastasis, n (%)				
Bone	46 (37)	56 (32)	18 (26)	120 (32)
CNS	23 (18)	13 (7)	1 (1)	37 (10)
Liver	23 (18)	30 (17)	10 (14)	63 (17)
Comorbidities, n (%)		113 (65)	45 (64)	219 (59)
Acute myocardial infarction	2 (2)	7 (4)	4 (6)	13 (4)
COPD	27 (21)	49 (28)	25 (36)	101 (27)
Diabetes	11 (9)	24 (14)	9 (13)	44 (12)
High blood pressure	2 (2)	7 (4)	2 (3)	11 (3)
Hypercholesterolaemia	6 (5)	9 (5)	4 (6)	19 (5)
Hypertension	26 (21)	48 (27)	24 (34)	98 (26)
Ischaemic heart disease	5 (4)	21 (12)	3 (4)	29 (8)
Number of prior systemic therapies, n (%)				
1	48 (38)	74 (42)	40 (57)	162 (44)
2	43 (34)	56 (32)	21 (30)	120 (32)
3	29 (23)	31 (18)	8 (11)	68 (18)
≥4	6 (5)	14 (8)	1 (1)	21 (6)

Grossi Eur J Cancer 2018

Treatment outcome	Aged <65 years (n = 126)	Aged 65–<75 years (n = 175)	Aged ≥75 years (n = 70)	Overall population (N = 371)
Objective response rate, n (%)	23 (18)	31 (18)	13 (19)	67 (18)
Disease control rate,[a] n (%)	62 (49)	83 (48)	30 (43)	175 (47)
Best response, n (%)				
Complete response	3 (2)	1 (1)	0	4 (1)
Partial response	20 (16)	30 (17)	13 (19)	63 (17)
Stable disease	39 (31)	52 (30)	17 (24)	108 (29)
Progressive disease	63 (50)	88 (50)	38 (54)	189 (51)
Could not be determined	1 (1)	4 (2)	2 (3)	7 (2)



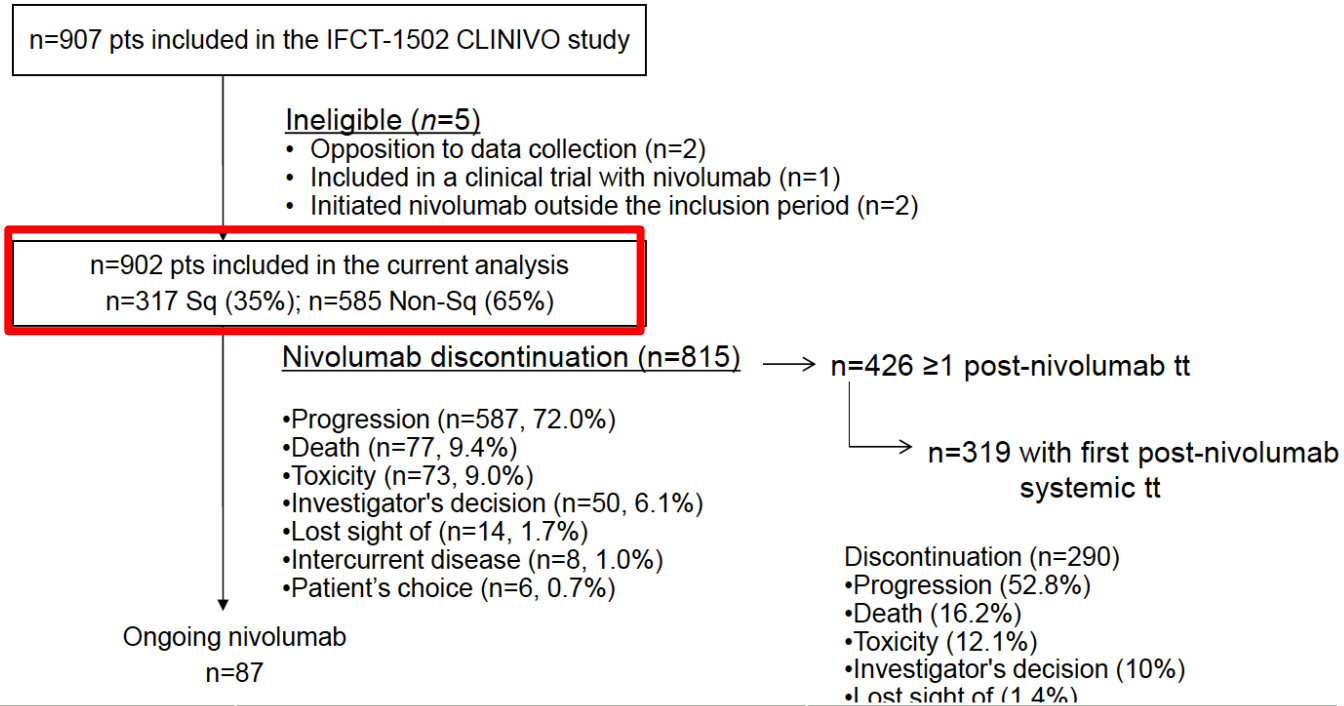
Grossi Eur J Cancer 2018

Characteristics	Univariate, HR (95% CI)	Multivariate, HR (95% CI)
Gender (male versus female)	1.67 (1.05–2.64) p = 0.03	
Age (≥75 versus 65-<75)	1.15 (0.82–1.61) p = 0.42	
Smoking habits (current/former versus never)	1.68 (0.86–3.30) p = 0.13	
Brain mets (yes versus no)	1.08 (0.55–2.11) p = 0.83	
Liver mets (yes versus no)	1.59 (1.09–2.33) p = 0.02	1.53 (1.05–2.79) p = 0.03
Bone mets (yes versus no)	2.06 (1.49–2.83) p < 0.0001	2.03 (1.47–2.79) p < 0.0001
ECOG PS (2 versus 0–1)	1.69 (0.94–3.05) p = 0.08	
Previous therapies (≥2 versus 1)	0.80 (0.59–1.09) p = 0.15	

Discontinuation	Aged <65 years (n = 126)	Aged 65–<75 years (n = 175)	Aged ≥75 years (n = 70)	Overall population (N = 371)
Discontinued treatment, n (%)	92 (73)	133 (76)	56 (80)	281 (76)
Reason for discontinuation, n (%)[a]				
Progressive disease	55 (60)	82 (62)	30 (54)	167 (59)
Death	18 (20)	35 (26)	15 (27)	68 (24)
Any-cause AE or serious AE	4 (4)	10 (8)	6 (11)	20 (7)
Treatment-related AE	4 (4)	7 (5)	3 (5)	14 (5)
Other	15 (16)	6 (5)	5 (9)	26 (9)

Grossi Eur J Cancer 2018

IFCT-1502 CLINIVO



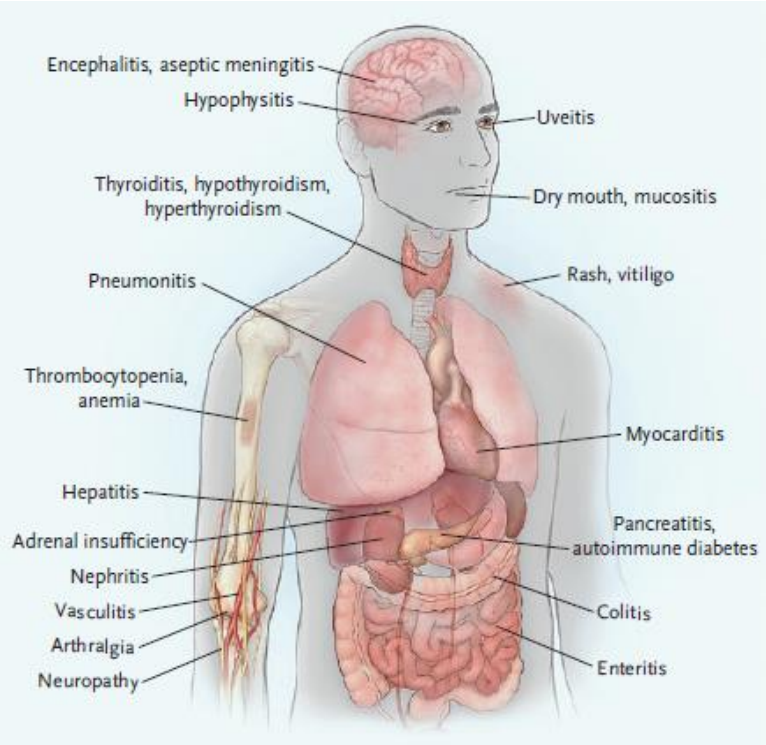
	Univariate analysis			Multivariate analysis (n=889)		
Characteristics	HR	95% CI	p	HR	95% CI	p
ECOG PS						
≥2 (vs 0/1)	2.24	1.85-2.72	<0.0001	2.21	1.82-2.69	<0.0001
Brain metastasis						
Yes (vs No)	1.39	1.15-1.68	0.001	1.38	1.15-1.67	0.0007

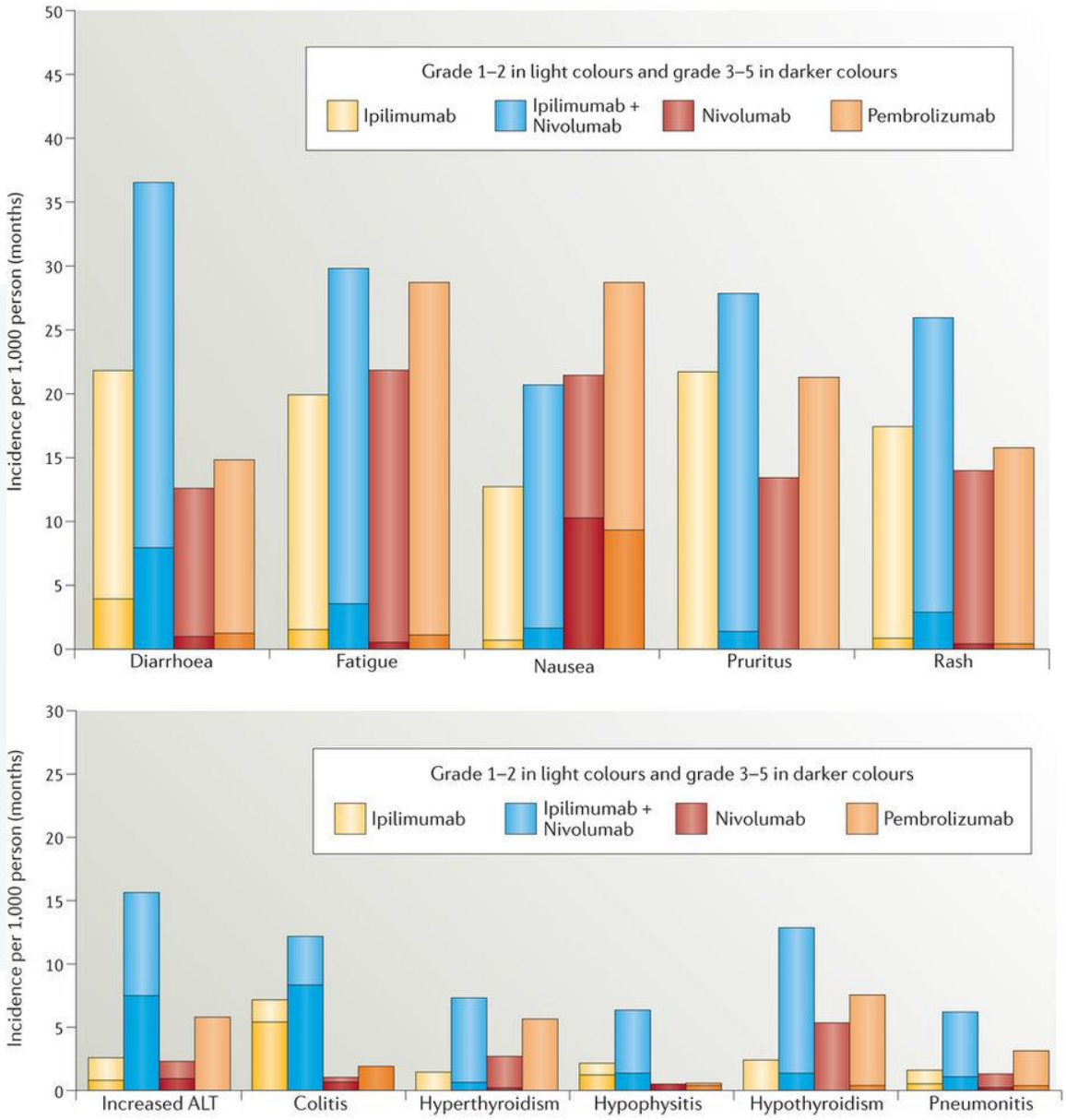
Gender, **age at initiation of nivolumab**, smoking history, TNM stage, histology were not associated with OS.

Girard WCLC 2017 abstract 9371

L’immunothérapie (monothérapie) chez les sujets âgés semble aussi efficace que chez les sujets jeunes à partir des données de la « vraie vie »

Toxicités des ICI





Boutros Nature Rev Clin Oncol 2016 ; Postow NEJM 2018

Toxicités des ICI – rapports FDA

8.5 Geriatric Use

Of 3145 patients with melanoma, NSCLC, or HNSCC who were treated with KEYTRUDA in clinical studies, 43% were 65 years and over and 12% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

8.5 Geriatric Use

Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older.

8.5 Geriatric Use

Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Toxicités patients âgés et nivolumab

	Patients < 65 yrs (N=616) n%	Patients ≥ 65 yrs (N=414) n%	Patients ≥ 70 yrs (N=212) n%
Grade 1-2 Adverse Events	584 (94.8)	394 (95.2)	202 (95.3)
Grade 3-5 Adverse Events	360 (58.4)	259 (62.6)	152 (71.7)
Serious Adverse Events	313 (50.8)	242 (58.5)	123 (58.0)
All Adverse Events leading to Discontinuation	89 (14.4)	71 (17.1	42 (19.8)
AEs Requiring Treatment with Immune Modulating Medication	256 (41.5)	196 (47.3)	110 (51.9)
Select irAE's where immune modulating medication was initiated			
Diarrhea/colitis	15 (2.4)	17 (4.1)	11 (5.2)
Pneumonitis	23 (3.7)	8 (1.9)	5 (2.4)
Hepatitis	8 (1.3)	3 (0.7)	1 (0.5)
Nephritis and renal dysfunction	6 (1.0)	8 (1.9)	7 (3.3)
Rash	47 (7.6)	34 (8.2)	22 (10.4)

Checkmate-025 (rein)
Checkmate-066 (mélanome)
Checkmate-017 (CBNPC)
Checkmate-057 (CBNPC)

Singh ASCO 2016 abstr #10010

Toxicités patients âgés et nivolumab

Table 6. Univariate and multivariate analysis of the risk of occurrence of grade 3–4 toxicity with nivolumab (n = 67).

	Univariate analysis			Multivariate analysis		
	Grade 3–4	No grade 3–4	*p-value*[¥]	HR [CI95%]		*p-value*[¥]
Age (years)						
<70	16 (24)	23 (34)	0.881			
≥70	12 (18)	16 (24)				
Gender						
Male	22 (33)	24 (36)	0.138			
Female	6 (9)	15 (22)				
Smoking history						
Current smokers	10 (15)	19 (28)	0.559			
Former smokers	14 (21)	15 (22)				
Never smokers	4 (6)	5 (8)				
Histological subtypes						
Adenocarcinoma	13 (19)	34 (51)	0.001	1		
Squamous-cell carcinoma	12 (18)	5 (8)		2.51	0.71–8.94	0.154
Others	3 (4)	0		18.56	0.32–1086.23	0.160
Mutation status						
EGFR	0	0	0.213			
ALK	0	0				
Kras	5 (7)	16 (23)				
Braf	0	1 (1)				
HER2	1 (1)	1 (1)				
WT	22 (33)	23 (34)				
Stage						
IIIB	3 (4)	7 (11)	0.412			
IV	25 (37)	32 (48)				

(…)

Etude rétrospective, bicentrique, CBNPC

Dumenil PlosOne 2018

Toxicités patients ≥80 ans

	Ipi (N = 74)		Anti-PD1 (N = 24)		Nivo+Ipi (N = 8)	
Age - yr						
Mean, range	84, (80-93)		86, (80-94)		82, (80-87)	
Sex -no. (%)						
Male	55(74.3)		16(66.7)		2 (25)	
Female	19(25.7)		8 (33.3)		6 (75)	
Toxicity	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
All AEs	65(87.8)	22(29.7)	21(87.5)	5(20.8)	7(87.5)	5(62.5)
Diarrhea	32(43.2)	13(17.6)	2(8.3)	1(4.2)	5(62.5)	2(25)
Transaminitis	41(55.4)	10(13.5)	0(0)	0(0)	6(75)	2(25)
Pruritus	0(0)	0(0)	7(29.2)	0(0)	3(37.5)	0(0)
Rash	28(37.8)	4(5.4)	8(33.3)	0(0)	5(62.5)	1(12.5)
Pneumonitis	0(0)	0(0)	2(8.3)	0(0)	2(25)	0(0)
Arthralgia/Myalgia	0(0)	0(0)	4(16.7)	0(0)	1(12.5)	0(0)
Hypophysitis	4(5.4)	2(2.7)	0(0)	0(0)	0(0)	0(0)

Etude rétrospective, MSKCC, mélanome

Friedman ASCO 2016 abstr #10009

L’immunothérapie chez les sujets âgés ne semble pas significativement plus toxique que chez les sujets jeunes à partir des données des essais cliniques et des données de la « vraie vie »

Demain, les combinaisons ICI + chimio ?

CLINICAL PRACTICE GUIDELINES

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

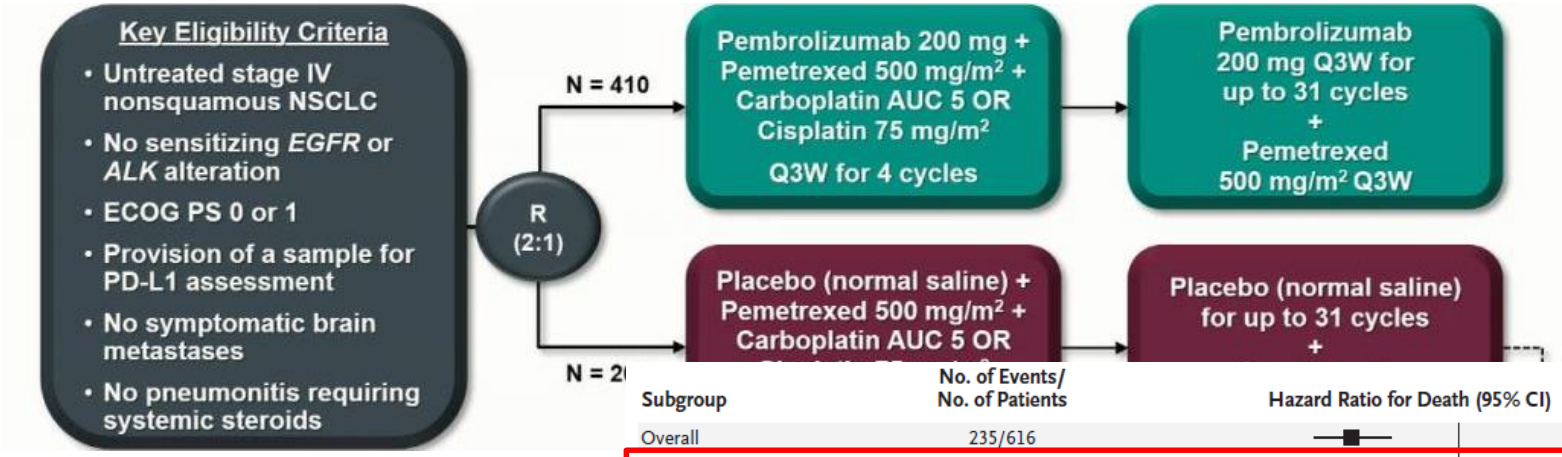
D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

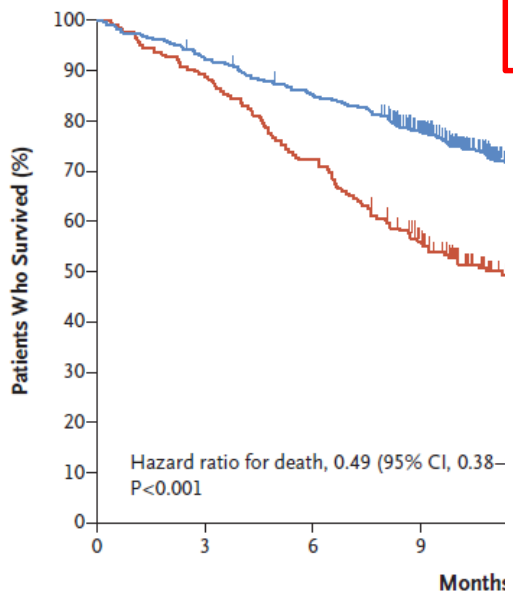
First-line treatment of NSCLC without actionable oncogenic driver regardless of PD-L1 status

- Combinations of platinum-based ChT and anti-PD-(L1) inhibitors have reproducibly demonstrated superiority to standard platinum-based ChT. In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%.

Planchard Ann Oncol 2018

Keynote-189

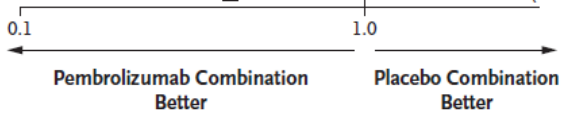




No. at Risk

Pembrolizumab combination	410	377	347	278
Placebo combination	206	183	149	104

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 yr	133/312	0.43 (0.31–0.61)
≥65 yr	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current or former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain metastases at baseline		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)



ImPower-150

CBNPC de stade IV non épidermoïde

Non traité par chimiothérapie[a]

Tout statut PD-L1

Facteurs de stratificat

- Sexe
- Express
- Métasta hépatiq

N

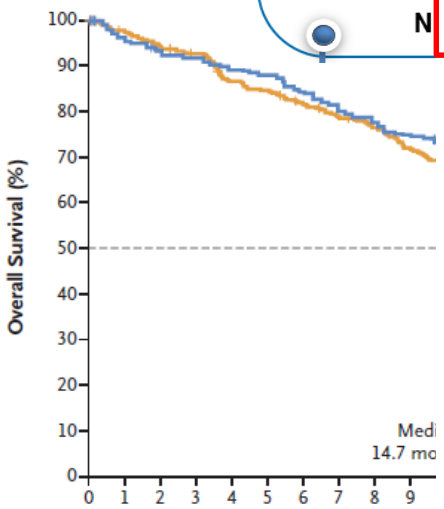
R 1:1:1

A : atezolizumab + carboplatine + paclitaxel
4-6 cycles

→ **atezolizumab**

B : atezolizumab + carboplatine + paclitaxel + bevacizumab

→ **atezolizumab +**

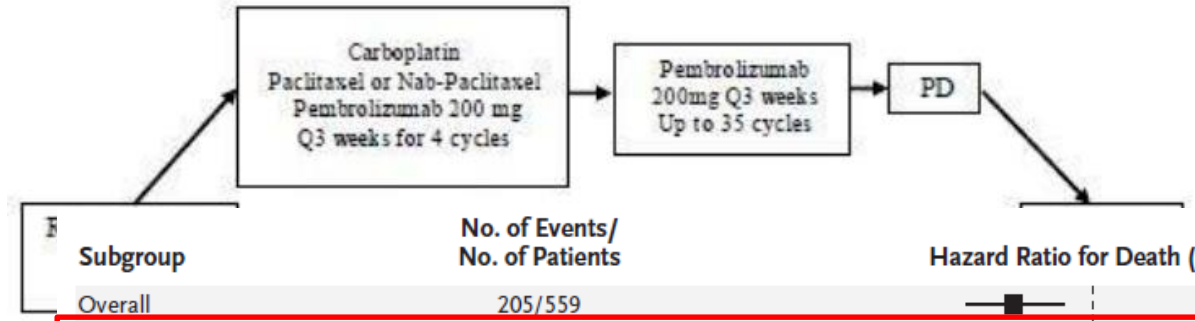


Subgroup	n (%)	HR	Median PFS, mo ABCP	BCP
Male	425 (61)	0.55	8.4	6.8
Female	267 (39)	0.73	8.2	6.8
< 65 years	375 (54)	0.65	8.0	6.8
65–74 years	248 (36)	0.52	9.7	6.9
75–84 years	64 (9)	0.78	9.7	6.8
ECOG PS 0	282 (41)	0.55	11.1	8.0
ECOG PS 1	404 (58)	0.64	7.2	6.0
Current/previous smoker	584 (84)	0.58	8.3	6.8
Never smoker	108 (16)	0.80	8.3	8.3
Liver metastases	94 (14)	0.42	7.4	4.9
No liver metastases	598 (86)	0.63	8.3	7.0
KRAS mutant	80 (12)	0.50	8.1	5.8
KRAS WT	124 (18)	0.47	9.7	5.8
KRAS unknown	488 (71)	0.67	8.3	7.1
ITT-WT	692 (100%)	0.62	8.3	6.8

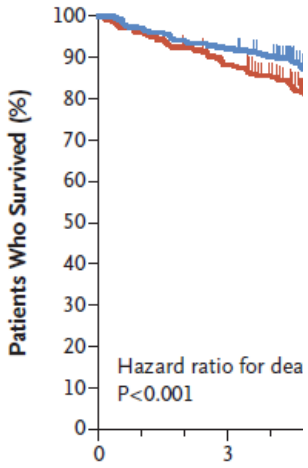
No. at Risk

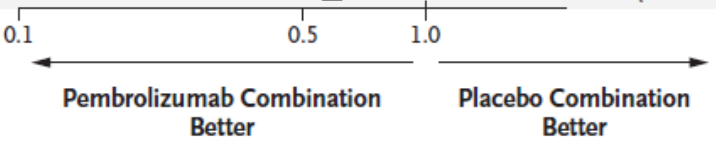
ABCP	359	339	328	323	314	310	296	284	273	264
BCP	337	326	315	308	287	280	268	255	247	233

Keynote-407



Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	205/559	0.64 (0.49–0.85)
Age		
<65 yr	88/254	0.52 (0.34–0.80)
≥65 yr	117/305	0.74 (0.51–1.07)
Sex		
Male	167/455	0.69 (0.51–0.94)
Female	38/104	0.42 (0.22–0.81)
ECOG performance-status score		
0	48/163	0.54 (0.29–0.98)
1	157/396	0.66 (0.48–0.90)
Region of enrollment		
East Asia	34/106	0.44 (0.22–0.89)
Rest of the world	171/453	0.69 (0.51–0.93)
PD-L1 tumor proportion score		
<1%	73/194	0.61 (0.38–0.98)
≥1%	129/353	0.65 (0.45–0.92)
1–49%	76/207	0.57 (0.36–0.90)
≥50%	53/146	0.64 (0.37–1.10)
Taxane-based drug		
Paclitaxel	140/336	0.67 (0.48–0.93)
Nab-paclitaxel	65/223	0.59 (0.36–0.98)



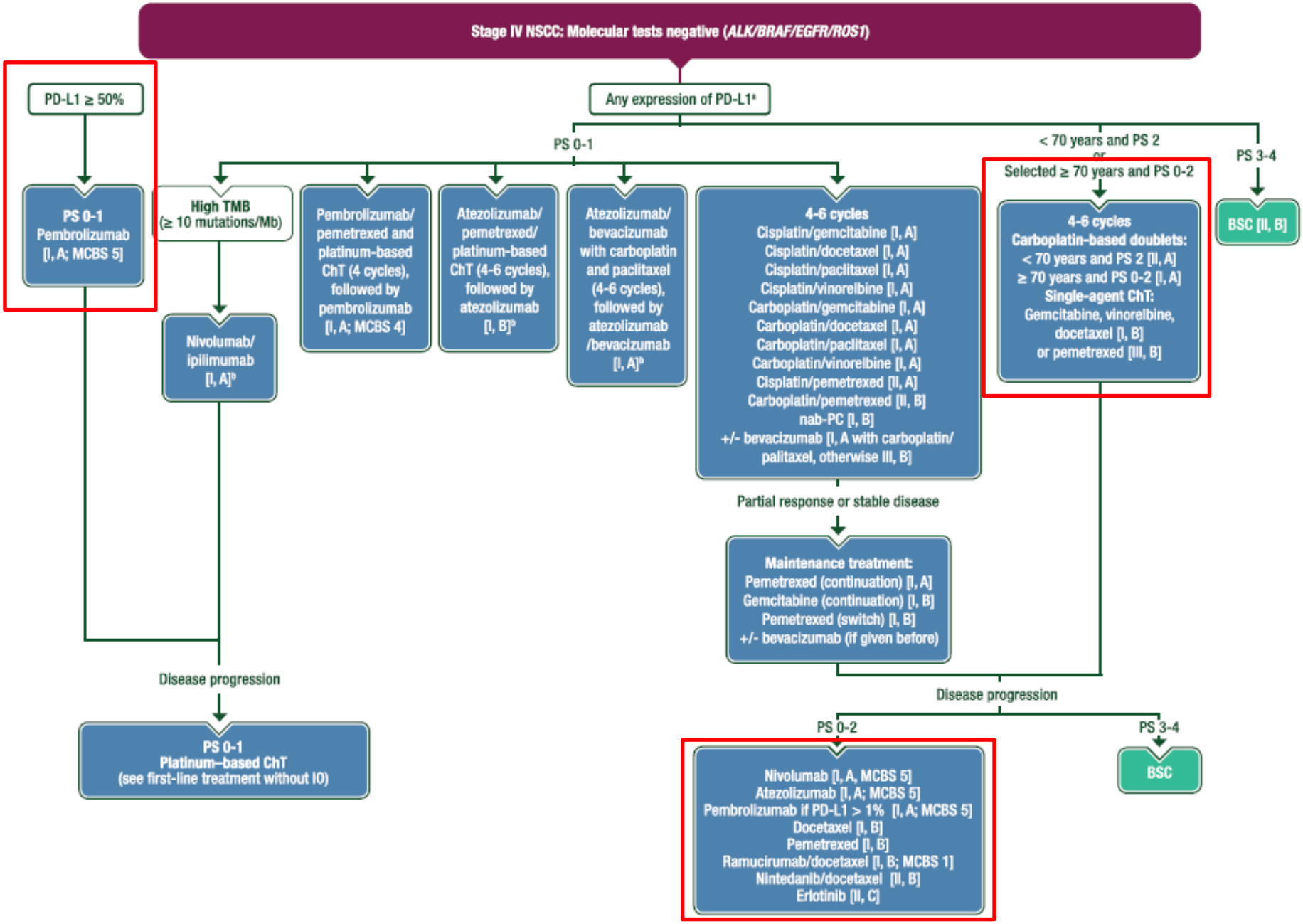


No. at Risk

Pembrolizumab combination	278	256
Placebo combination	281	246

L’immunothérapie en combinaison avec la chimiothérapie chez les sujet âgé semble aussi efficace que chez le sujet jeune à partir des premières données des essais cliniques (population générale)

Pas de données disponibles sur un potentiel surcroît de toxicité



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Conclusion

- La prise en charge des CBNPC du sujet âgé repose sur :
  - Une démarche diagnostique identique aux autres patients (PS, PDL1, biologie moléculaire)
  - Une chimiothérapie par carboplatine – paclitaxel hebdomadaire si possible
  - Une immunothérapie par pembrolizumab si PDL1 ≥50%
  - Une thérapie ciblée si addiction oncogénique
- La valeur prédictive des autres scores gériatriques reste incertaine (hors MMSE ?) pour la chimiothérapie cytotoxique, et inconnue pour l'immunothérapie
- Pas d'indication à une chimiothérapie de maintenance
- Il est nécessaire de développer des essais prospectifs testant l'immunothérapie (combinaisons ++) dans cette population (efficacité, toxicités)