Les traitements de seconde ligne des CBNPC, hors addiction oncogénique

PJ Souquet

CH Lyon Sud
Hospices Civils de Lyon

Liens d'intérêt

Amgen, Astellas, Astra Zénéca, Bayer, BMS, I.P. Bocuse, Boehringer-Ingelheim, Chugai, Daichy, P Fabre Oncologie, Lilly, Merck, Merrimack, MSD, Novartis, Pfizer, Roche, Sandoz, Taiho,Takéda

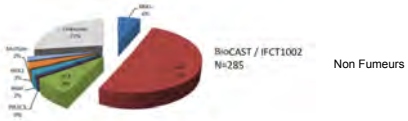
CBNPC de stade IV

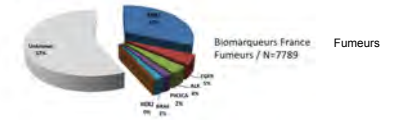
Traitements de première lignes en 2018

15 – 20 %: thérapeutiques ciblées

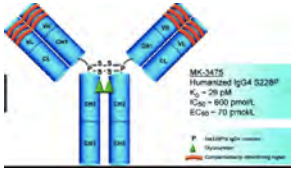
15-20 % : Pembrolizumab (PDL-1 > 50 %)

60-70 %: chimiothérapie





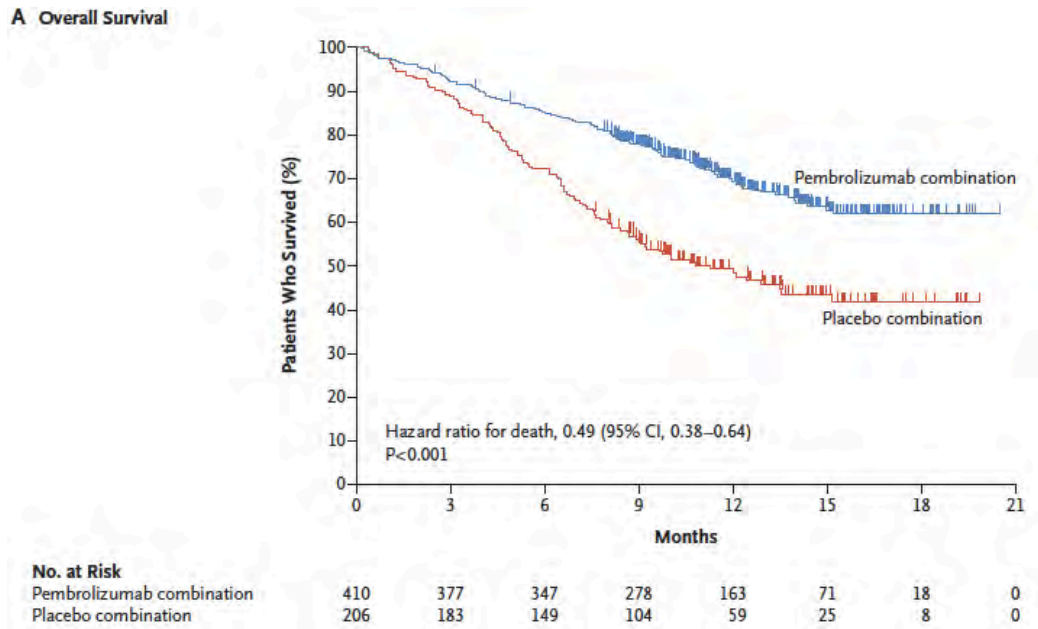
S Couraud et al, Eur. Resp J. 2015
F Barlési, et al Asco 2013, Abstract 8000



CBNPC de stade IV

Chimiothérapie
+
Pembrolizumab

Nouveau standard??



L GANDHI ET AL, KEYNOTE 189 NEJM, 2018

CBNPC de stade IV L2

Quel traitement après une première ligne d'IO ?

Chimiothérapie à base de sels de platine
Association IO + Chimiothérapie ??
Poursuite IO + Traitement local d'un site évolutif ??

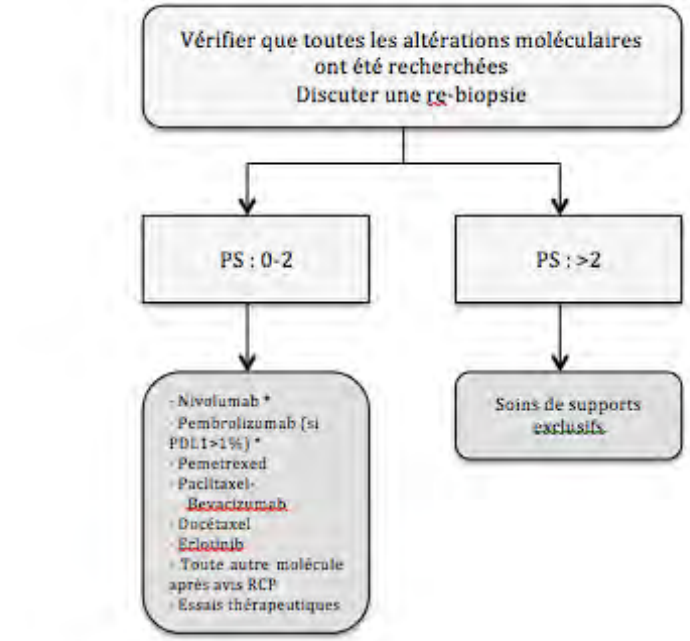
Quel traitement après une association IO + CT???

Combo : PDL1 + Anti CTLA4? Ou autre association??
CT seule?

CBNPC de stade IV L2

CBNPC non épidermoide

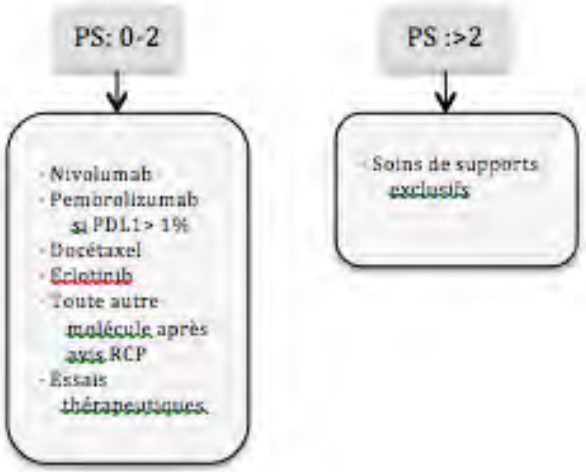
Référentiel en oncologie
Auvergne-Rhône-Alpes



* *si immunothérapie non utilisée en première ligne.*

CBNPC de stade IV L2

CBNPC épidermoides

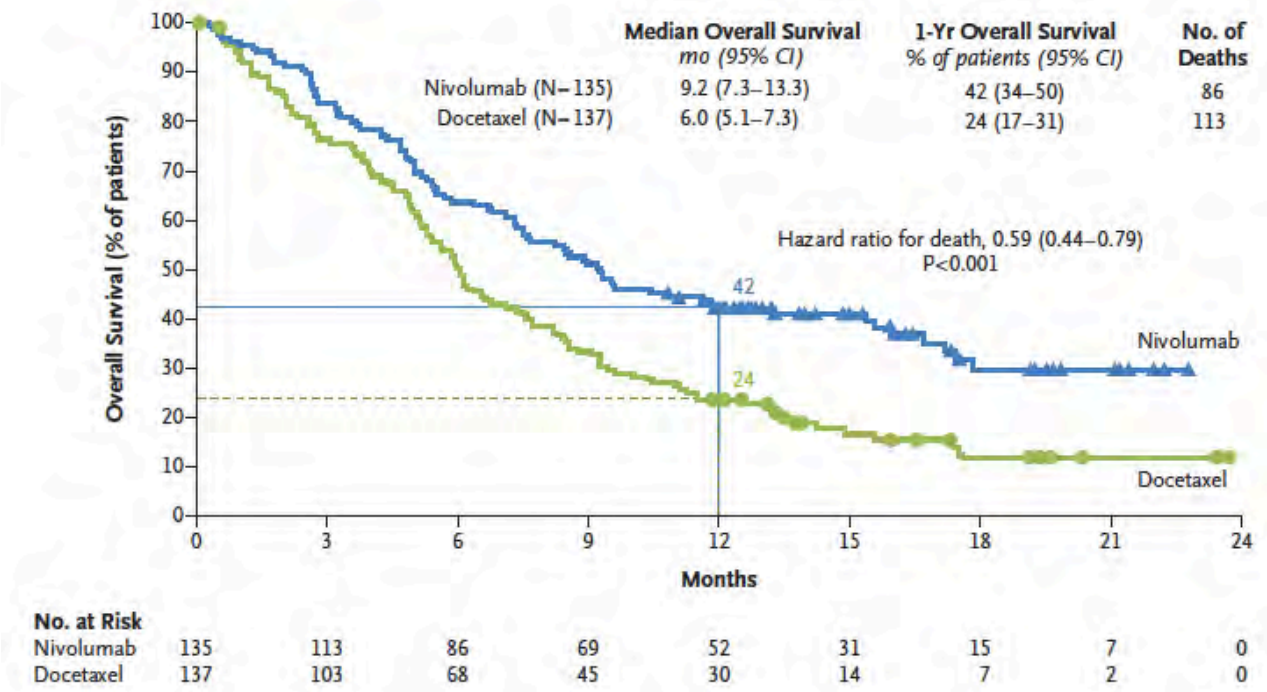


CBNPC de stade IV L2. Epi

CBNPC
épidermoide
Stade IV
Prétraité Sels de
platine
PS:0/1

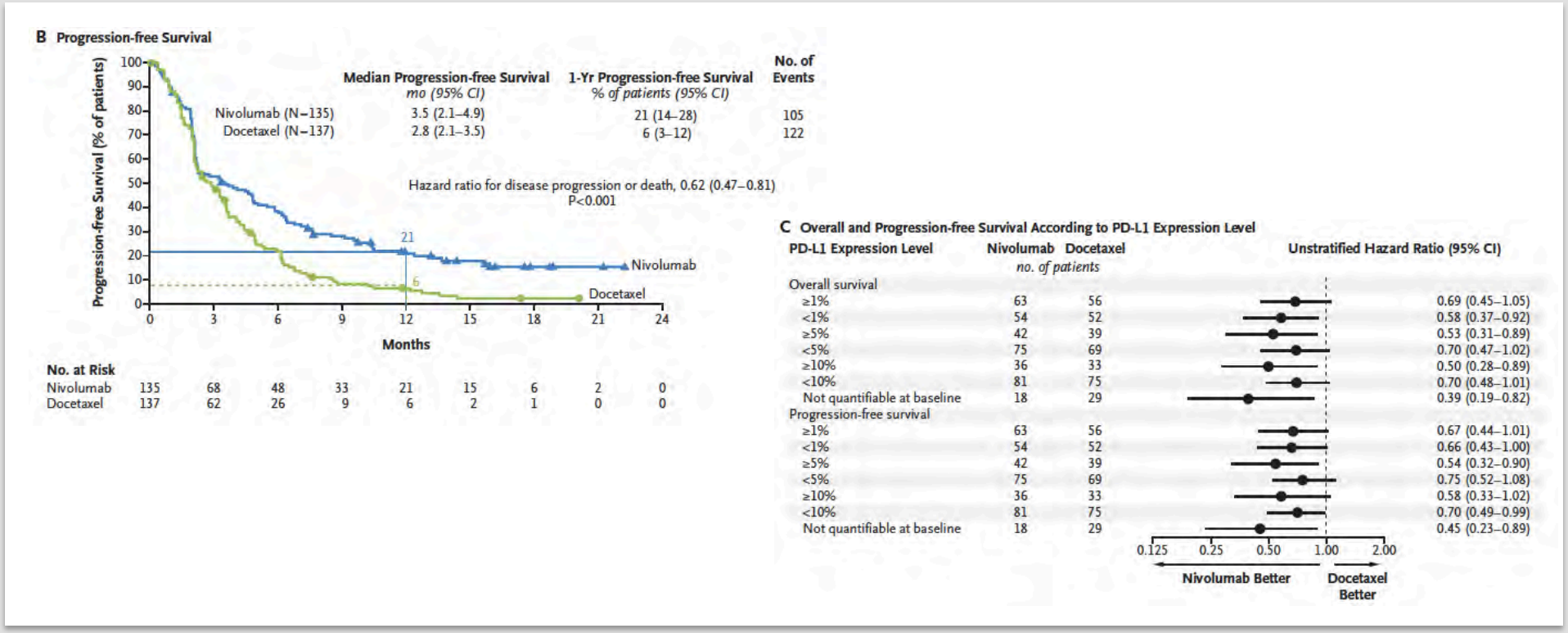
Nivo.

Docé.



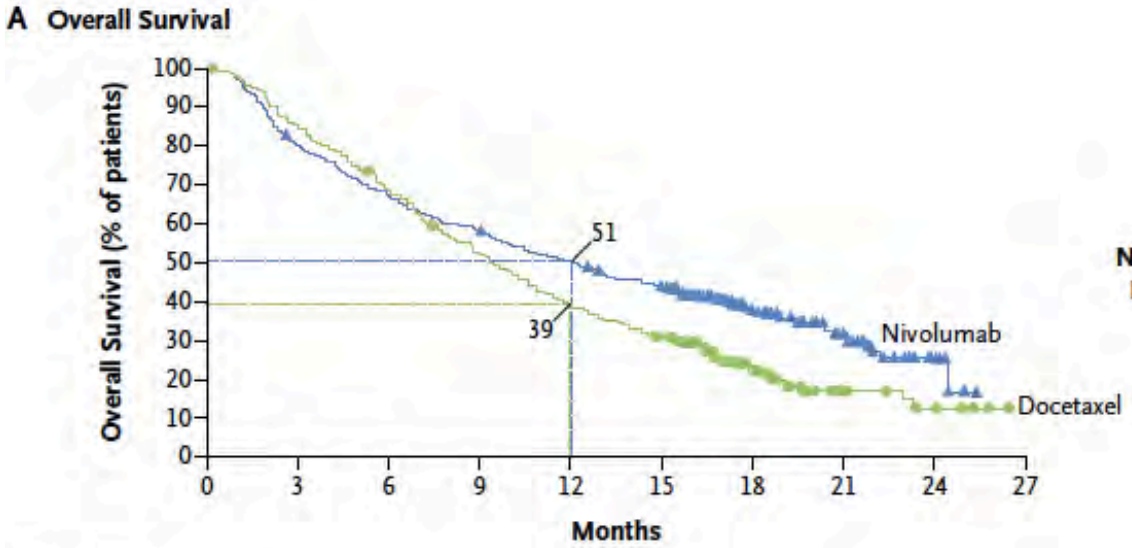
J Brahmer et al, NEJM, 2015

CBNPC de stade IV L2 Epi



J Brahmer et al, NEJM, 2015

CBNPC de stade IV L2 Non épi

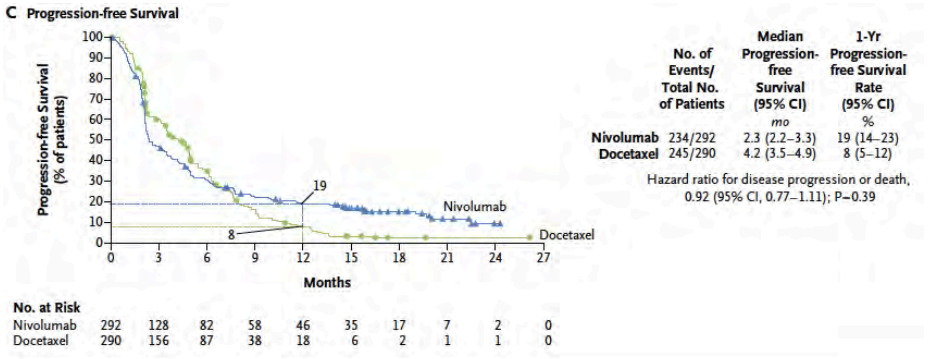


	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P–0.002

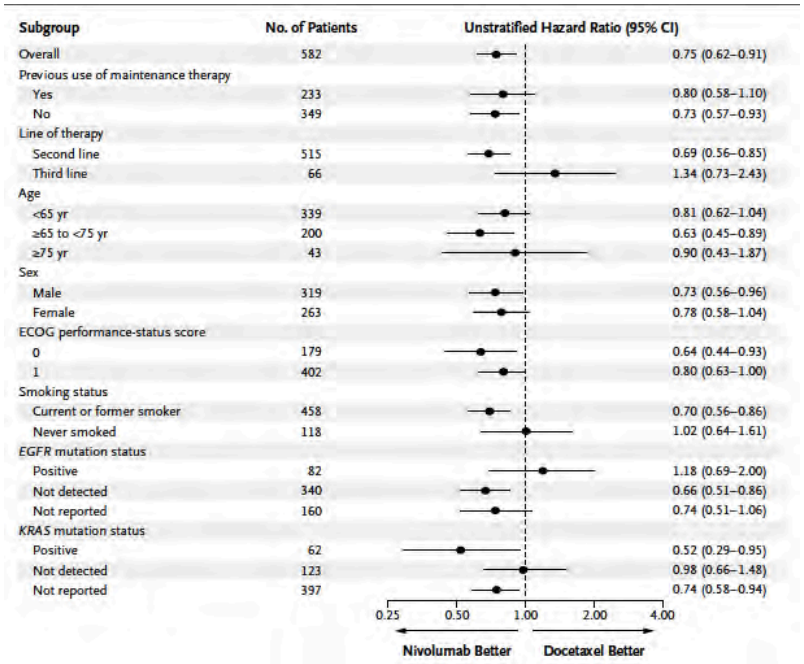
Borghai H et al, NEJM, 2015

CBNPC de stade IV L2 Non Epi.



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39



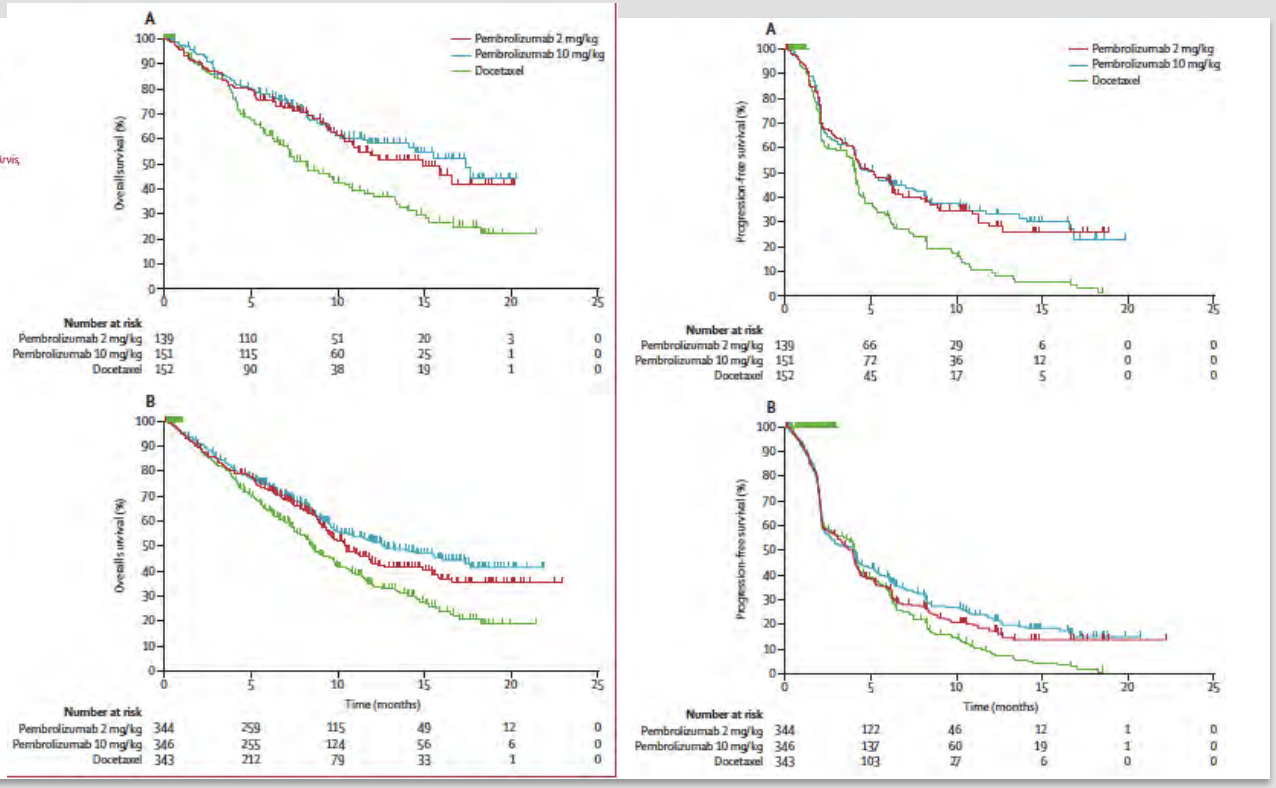
Borghai H et al, NEJM, 2015

CBNPC de stade IV L2

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

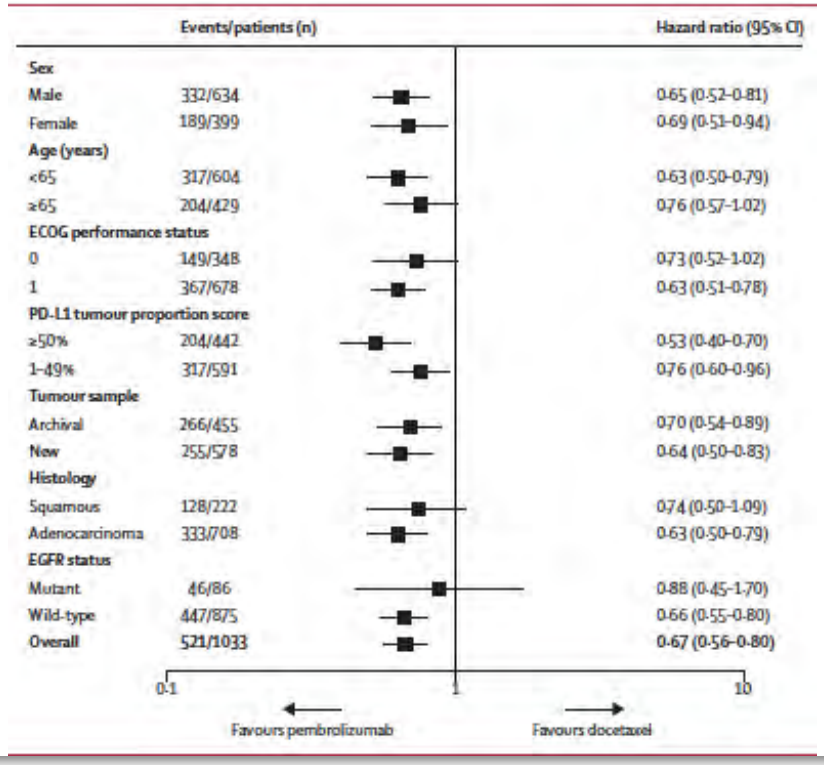
Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

CBNPC toute histologie
L1 par sels de platine
PS: 0/1
1034 patients
PDL1> 0%

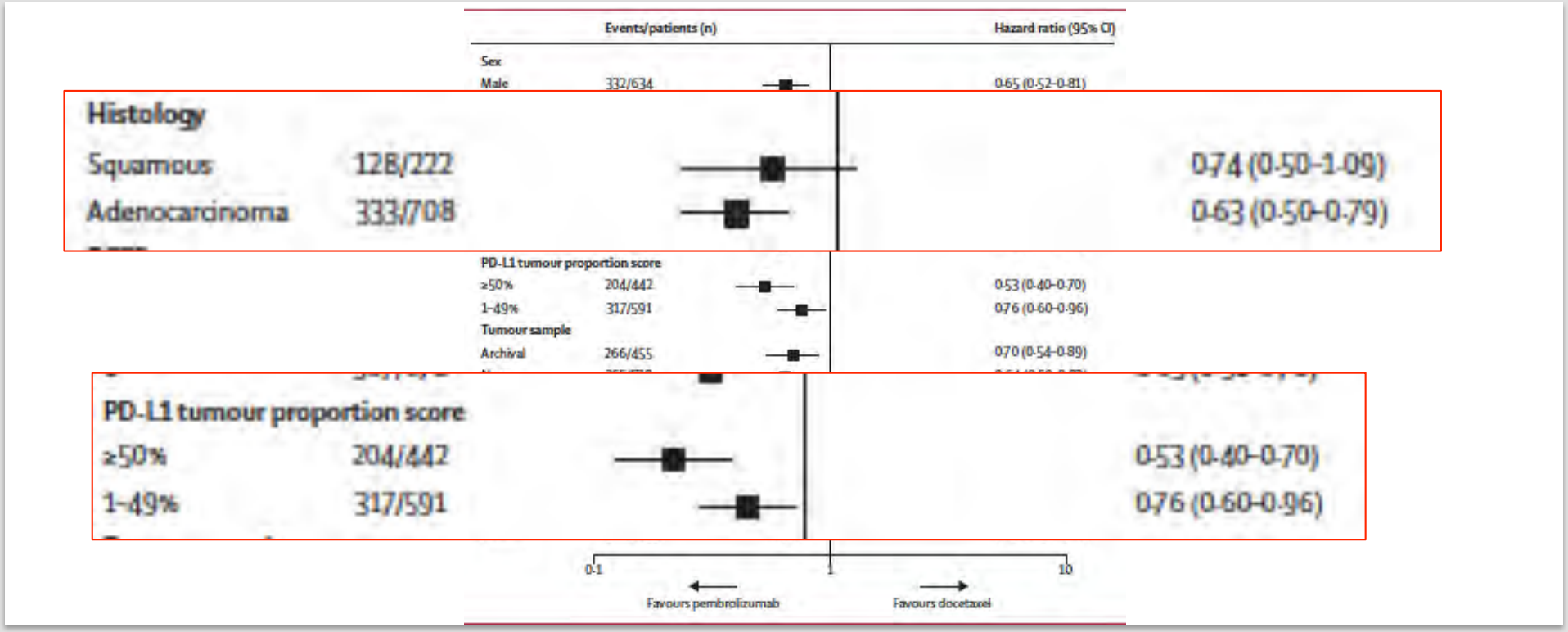


RS Herbst et al, Lancet Avril 2016

CBNPC de stade IV L2

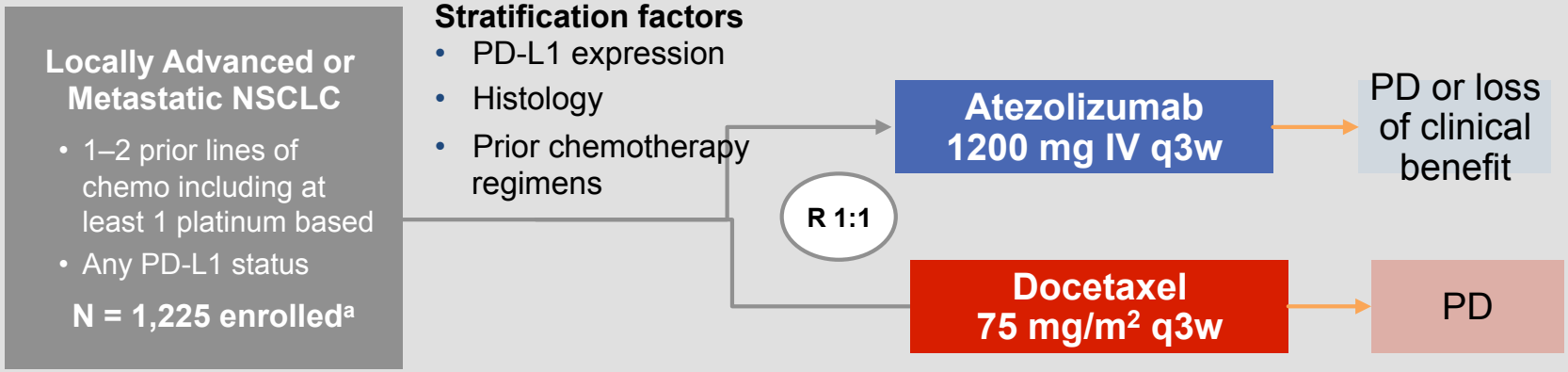


CBNPC de stade IV L2



CBNPC de stade IV L2

Phase III OAK study design

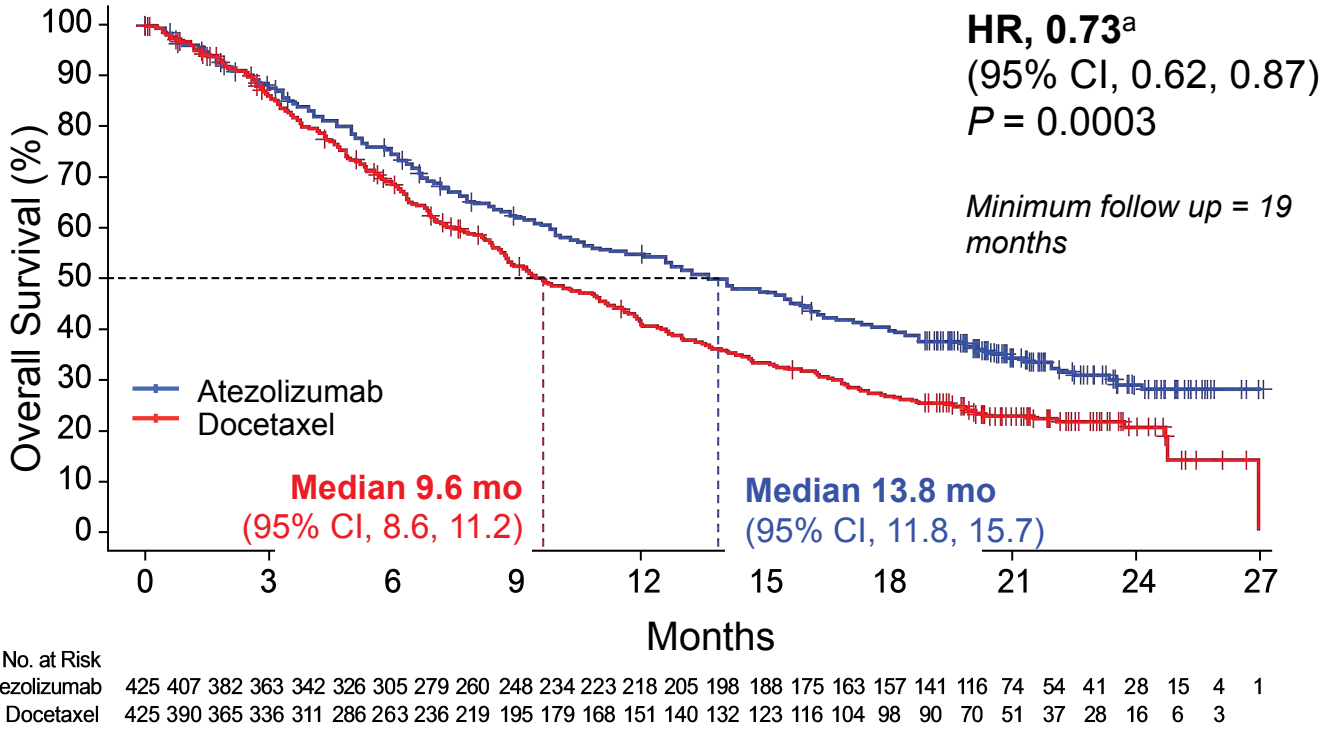


Primary Endpoints (first 850 enrolled patients):

- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

CBNPC de stade IV L2



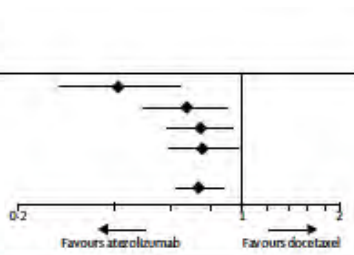
Rittmeyer et al, Lancet, 2017, 289(10066

CBNPC de stade IV L2

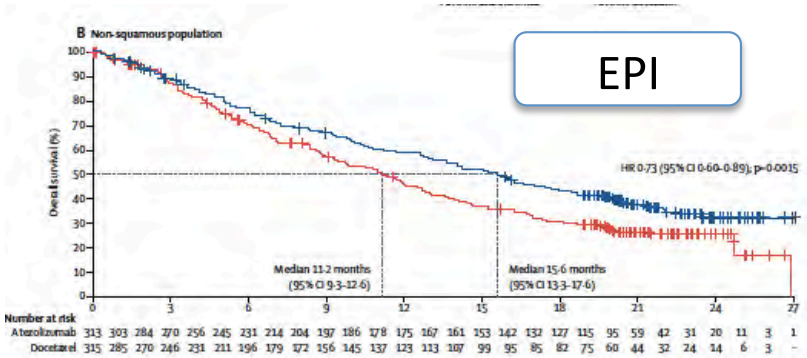
Efficacité pour tout niveau d'expression de PDL1 TC et IC

F

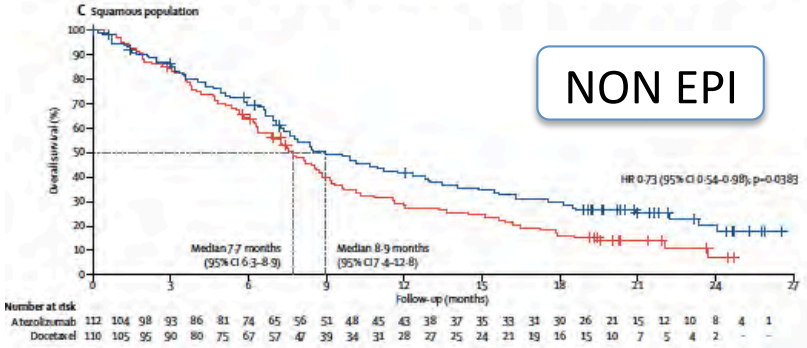
	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73 (0·62–0·87)



EPI

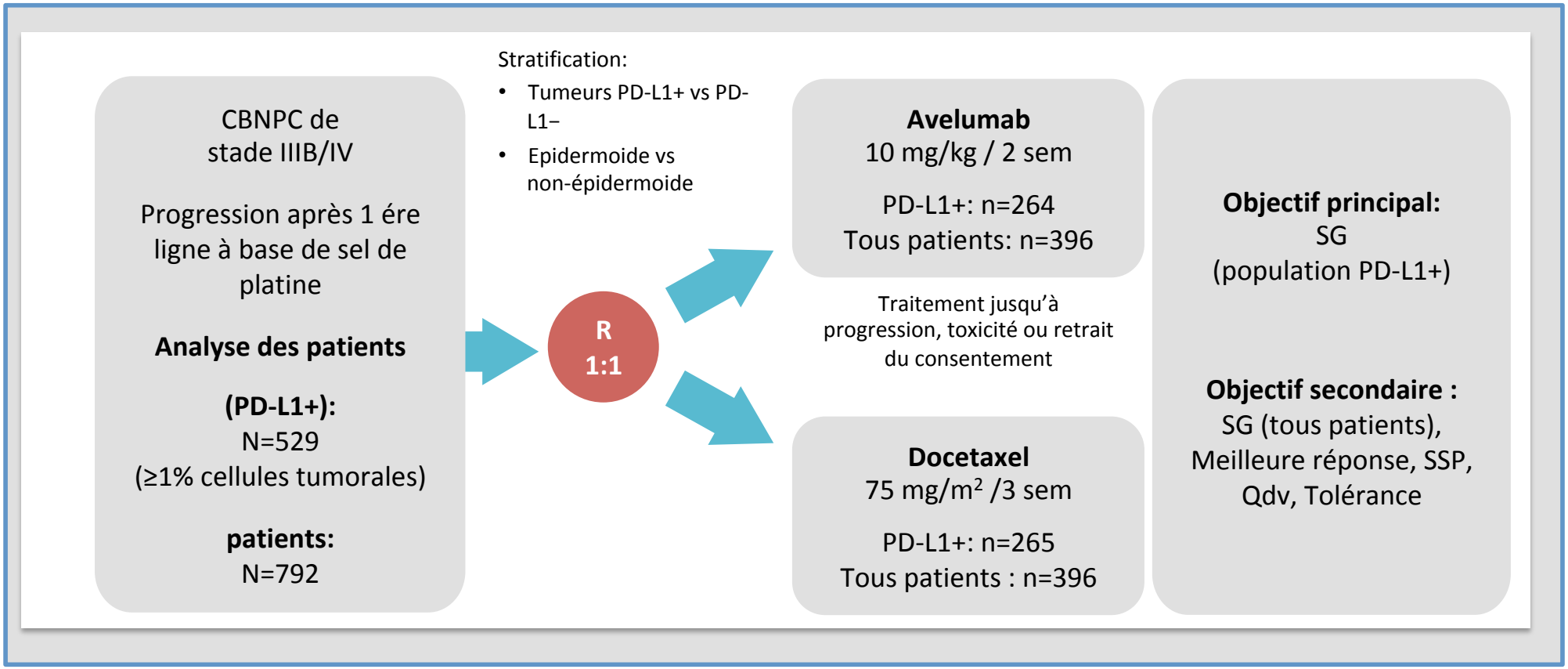


NON EPI



Rittmeyer et al, Lancet, 2017, 289(10066

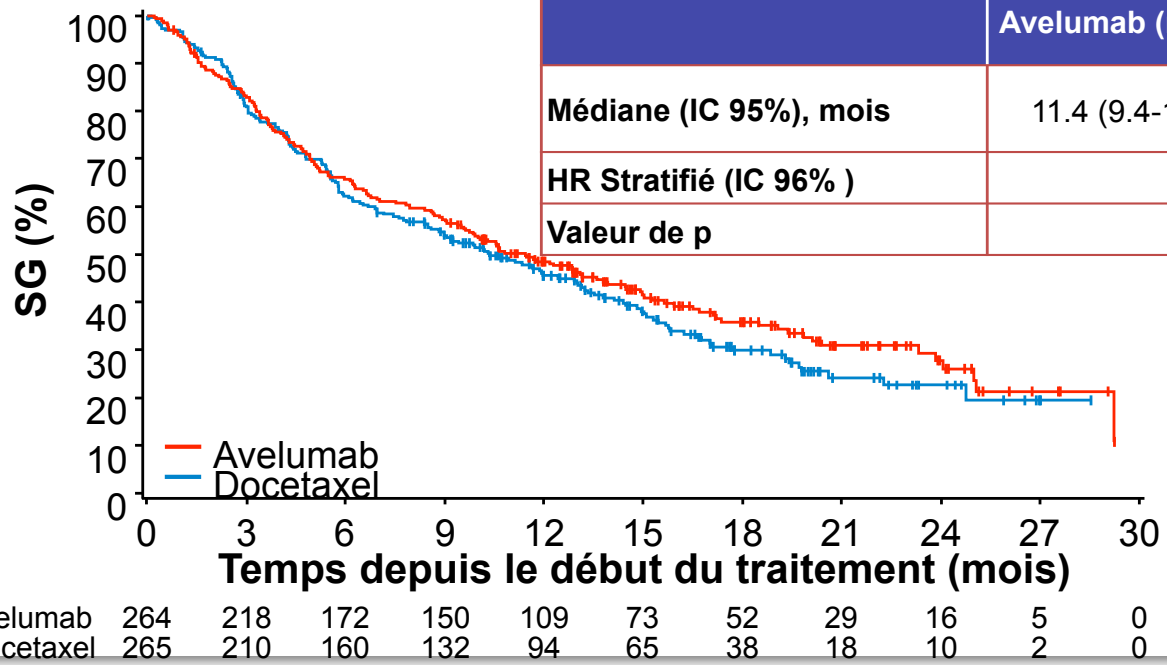
CBNPC de stade IV L2



WCLC 2018 – D'après Barlesi F et al., abstr. OA05.05, actualisé

CBNPC de stade IV L2

SG dans la populationPD-L1+ (≥1%)

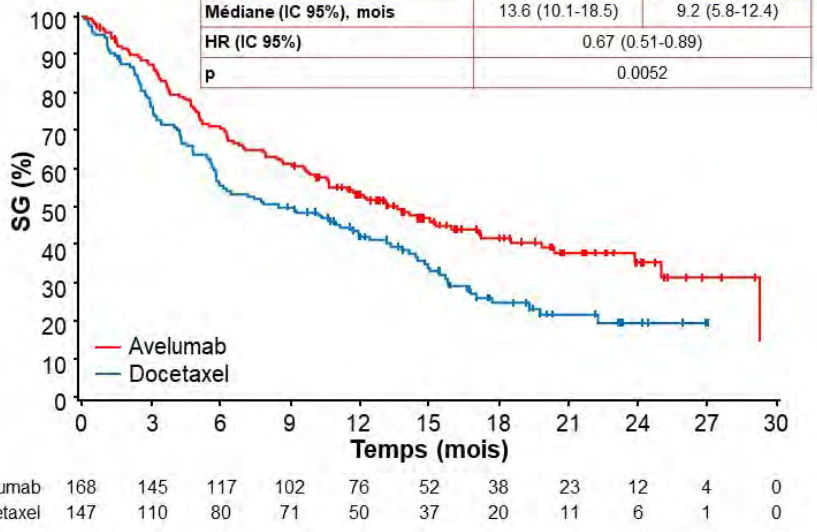


	Avelumab (n=264)	Docetaxel (n=265)
Médiane (IC 95%), mois	11.4 (9.4-13.9)	10.3 (8.5-13.0)
HR Stratifié (IC 96%)	0.90 (0.72-1.12)	
Valeur de p	0.1627	

CBNPC de stade IV L2

≥50% PD-L1+

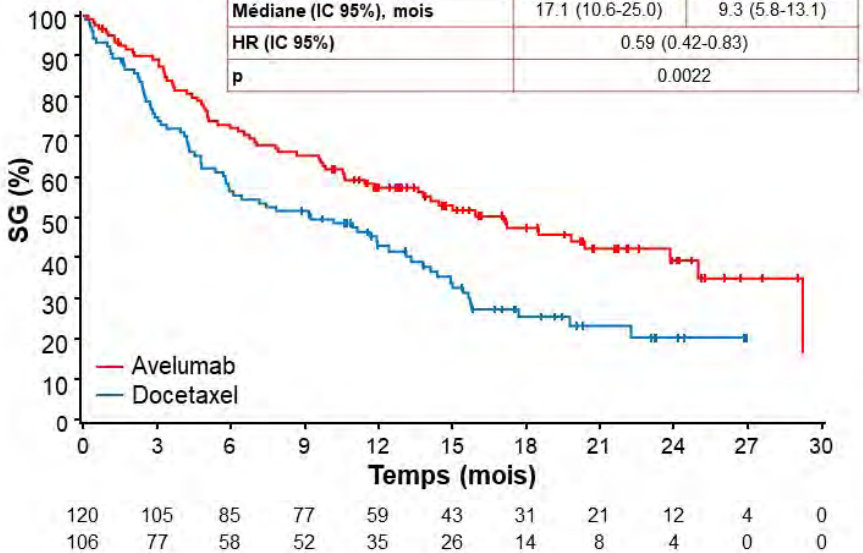
	Avelumab (n=168)	Docetaxel (n=147)
Médiane (IC 95%), mois	13.6 (10.1-18.5)	9.2 (5.8-12.4)
HR (IC 95%)	0.67 (0.51-0.89)	
p	0.0052	



Avelumab	168	145	117	102	76	52	38	23	12	4	0
Docetaxel	147	110	80	71	50	37	20	11	6	1	0

≥80% PD-L1+

	Avelumab (n=120)	Docetaxel (n=106)
Médiane (IC 95%), mois	17.1 (10.6-25.0)	9.3 (5.8-13.1)
HR (IC 95%)	0.59 (0.42-0.83)	
p	0.0022	



	120	105	85	77	59	43	31	21	12	4	0
	106	77	58	52	35	26	14	8	4	0	0

Avelumab

- 10 mois MS du Docétaxel
- 36 % de cross over dans le bras Docétaxel
- Critères d'inclusion

	Docétaxel	Pemetrexed	Paclitaxel+ bevacizumab	Docétaxel+ nindétanib	Docétaxel+ ramucirumab	Erlotinib	Afatinib
Dose	75 mg/m2 J1/21	500 mg/m2 J1/21	Paclitaxel 90 mg/m2 J1,8 et 15 Bevacizumab 10 mg/kg J1 et 15 / 28 jours	Docétaxel 75 mg/m2 J1/21 Nindétanib 200mgx2/J J2-22	Docétaxel 75 mg/m2 Ramucirumab 10mg/kg J1/21	150 mg/j	40 mg/j
Phase III	**Vs placebo**	Vs Docétaxel	Vs Docetaxel	Vs Docétaxel	Vs Docétaxel	**Vs placebo**	Vs Erlotinib
Histologie	Toutes	Toutes	Adénocarcinome	Toutes	Toutes	Epidermoide	Epidermoide
Résultats	**N**=272 **SG** :9,2 vs 6 m* (HR : 0,62) **SSP** :3,5 vs 2,8 m* (HR : 0,62) **RO** : 20 vs 9 % **Tox G3-4** : 8 vs 56%	**N**= 571 **SG** :8,3 vs 7,9 m **SSP** :2,9 vs 2,9 m **RO** : 9,1 vs 8,8% **Toxicités** moindres avec le Pemetrexed	**N**= 166 **SG** : 9,9 vs 10,8 m **SSP** : 5,4 vs 3,9 m* (HR 0,62) **RO** : 22,5 vs 5,5 % * **Toxicités** : Moindre neutropénie Plus neuropathie	**N**=1314 **SG** 12,6 vs 10,3 * (ADK) (HR 0,83) **SSP** 3,7 vs 2,4 m* (HR 0,83) **RO** : 4,4 vs 3,3 % Toxicités: augmentées avec nindétanib	**N**= 1253 **SG** 10,5 vs 9,1 m* (HR 0,86) **SSP** :3,4 vs 2,7 m* (HR :0,79) **RO** : 23 vs 14% * **Toxicités** : augmentation neutropénie	**N**= 731 **SG** : 6,7 vs 4,7 m* (HR :0,70) **SSP** :2,2 vs 1,8 m* (HR :0,61) **RO** : 8, 9 vs 0,7 %* **Toxicités** : attendues avec erlotinib	**N**=795 **SG** : 7,9 vs 6,8 m* (HR 0,81) **SSP:** 2,6 vs 1,9 m* (HR : 0,81) **RO** : 6 vs 3% **Toxicités** : identiques
Commentaire		Etude de non infériorité	En 2° ou 3° ligne. Cross over autorisé 1° ligne avec bévacizumab autorisée	Pas de remboursement dans cette indication	Pas de remboursement dans cette indication		AMM obtenu mais pas de remboursement dans cette indication

CBNPC de stade IV L2

	Nivolumab	Pembrolizumab	Atézolizumab	Durvalumab	Avélumab
Type d'anticorps	Anti PD1 IgG4	Anti PD1 IgG4	Anti PDL1 IgG1 modifiée	Anti PDL1 IgG1 modifiée	Anti PDL1 IgG1
Dose recommandée (CBNPC)	3 mg/kg / 14 j 240 mg / 14 j	2 mg/kg / 21 j 200 mg / 21 j	1200 mg/ 21 j	10 mg/kg/ 14 j (Adjuvant stade III)	10 mg/kg/ 14 j
Test expression PDL1	Dako 28-8	Dako 22C3	Ventana SP142	Ventana SP 263	Dako 73-10

Les Questions ???

- IO en 2° ligne ou en 3° ligne ?
- Y a t'il une différence entre les IO??

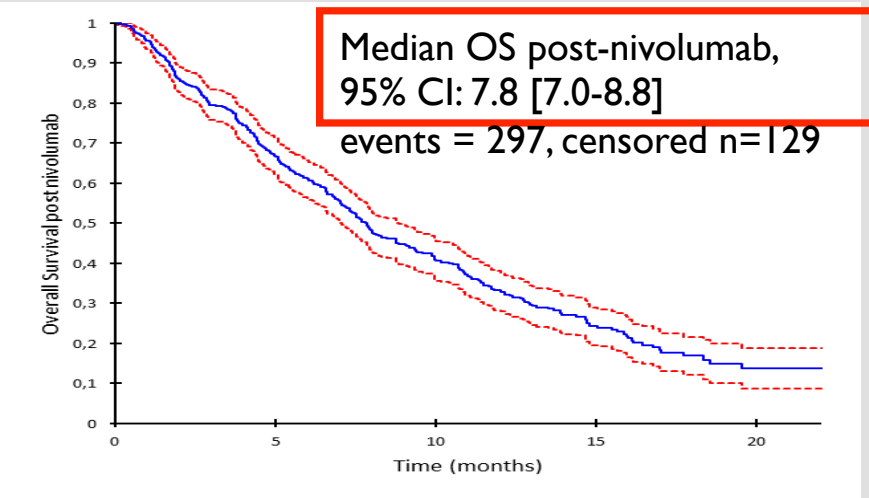
IMMUNOTHERAPIE : L2 OU L x ?

Exclusive systemic tt	**N=319 (75%)**		
Single agent chemotherapy	n=210 (49 %)	Docetaxel	61 (14%)
		Gemcitabine	64 (15%)
		Paclitacel +/ bevacizumab	38 (9%)
		Vinorelbine	24 (6%)
		Pemetrexed	20 (5%)
		Other	3 (1%)
Platin-based doublet	n=35 (8%)	Platin-Paclitaxel	21 (5%)
		Other	14 (3%)
Targeted therapy	n=57 (13%)	Erlotinib	43 (10%)
		Other	14 (3%)
Nivolumab rechallenge	n=15 (4%)		
Other/unknown systemic tt	n=2 (0.5%)		
Surgery +/- radiotherapy +/- systemic tt	**N=100 (24%)**		
Unknown tt	**N=7 (2%)**		

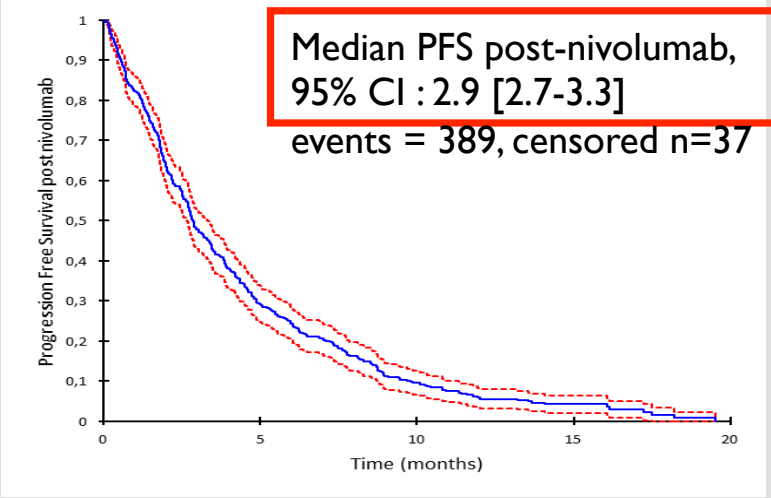
9371 - N. Girard et al.
IFCT - 1502 CLINIVO: Real - life experience with nivolumab in 600 patients (pts) with advanced Non - Small Cell Lung Cancer (NSCLC).

IMMUNOTHERAPIE : L2 OU L x ?

- Best response to first post-nivolumab systemic tt (n=319) was: ORR=16.2 %; SD=42.3%; PD=41.5%.



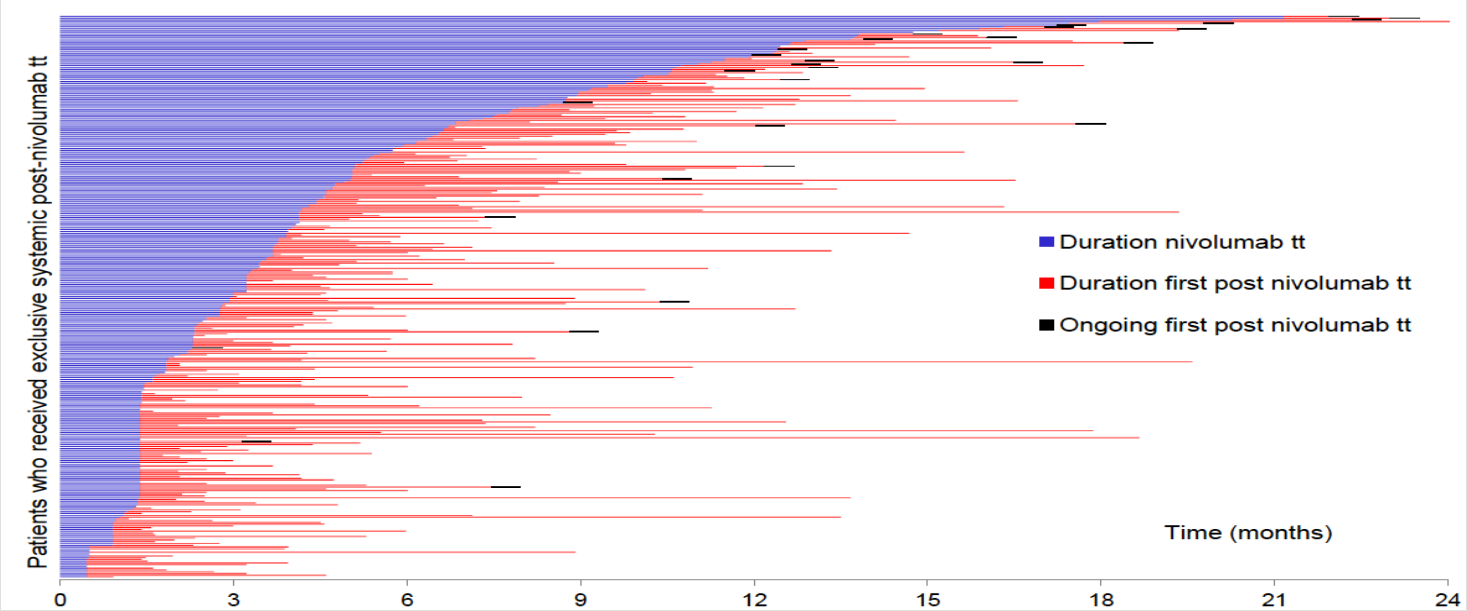
Median OS post-nivolumab,
95% CI: 7.8 [7.0-8.8]
events = 297, censored n=129



Median PFS post-nivolumab,
95% CI : 2.9 [2.7-3.3]
events = 389, censored n=37

IMMUNOTHERAPIE : L2 OU L x??

Duration of nivolumab and first post-nivolumab treatment

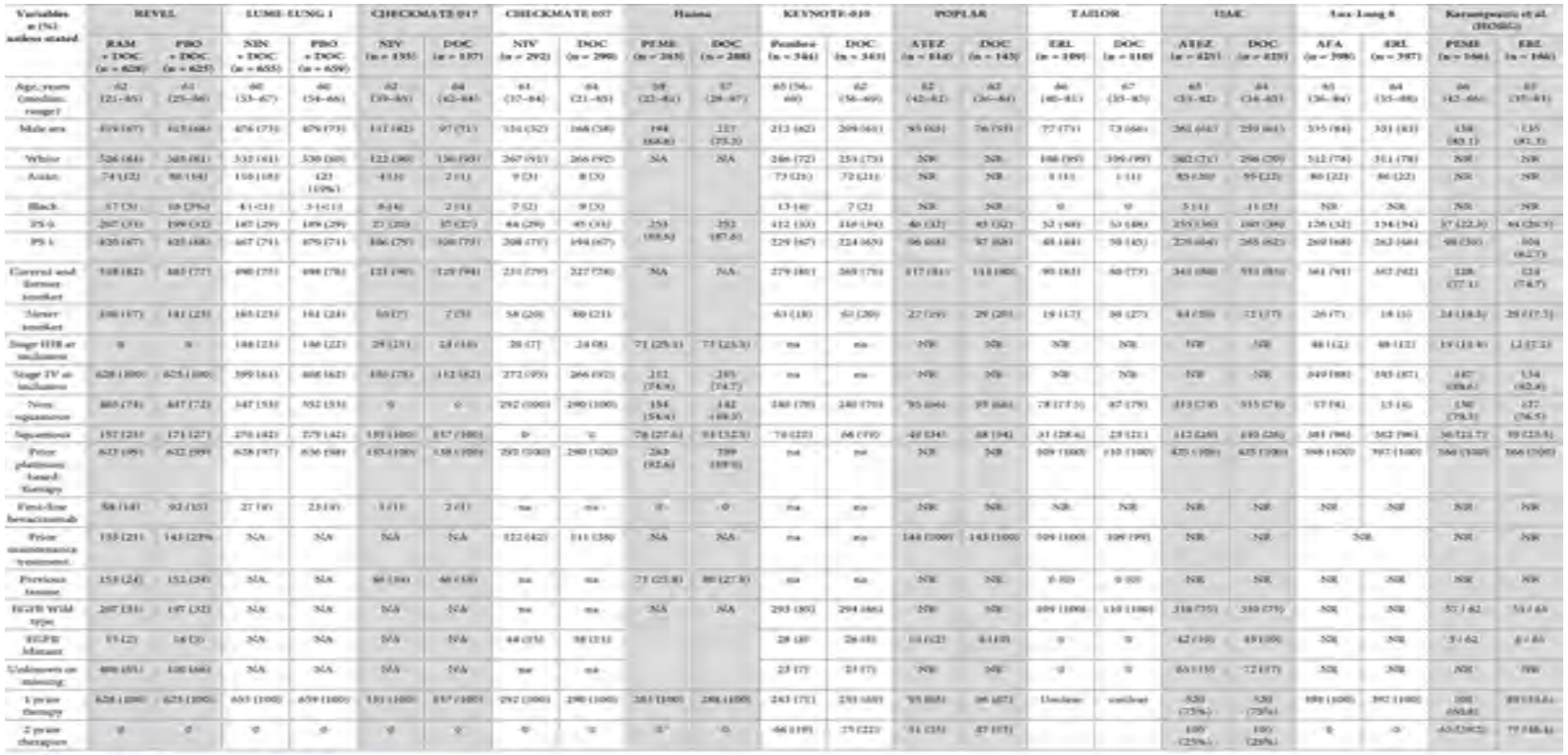


CBNPC de stade IV

NOMBREUSES REVUES SYSTEMATIQUES ET « META-ANALYSES »

N TOMOHIRO et al	The Oncologist 2017
PM ELLIS et al	Clin Lung Cancer 2017
M KHAN et al	Medicine 2018
F PASSIGLIA et al	Int J Cancer 2018
P CREQUIT et al	**BMC Médecine 2017**
X ARMOIRY et al	**Plos One 2018**

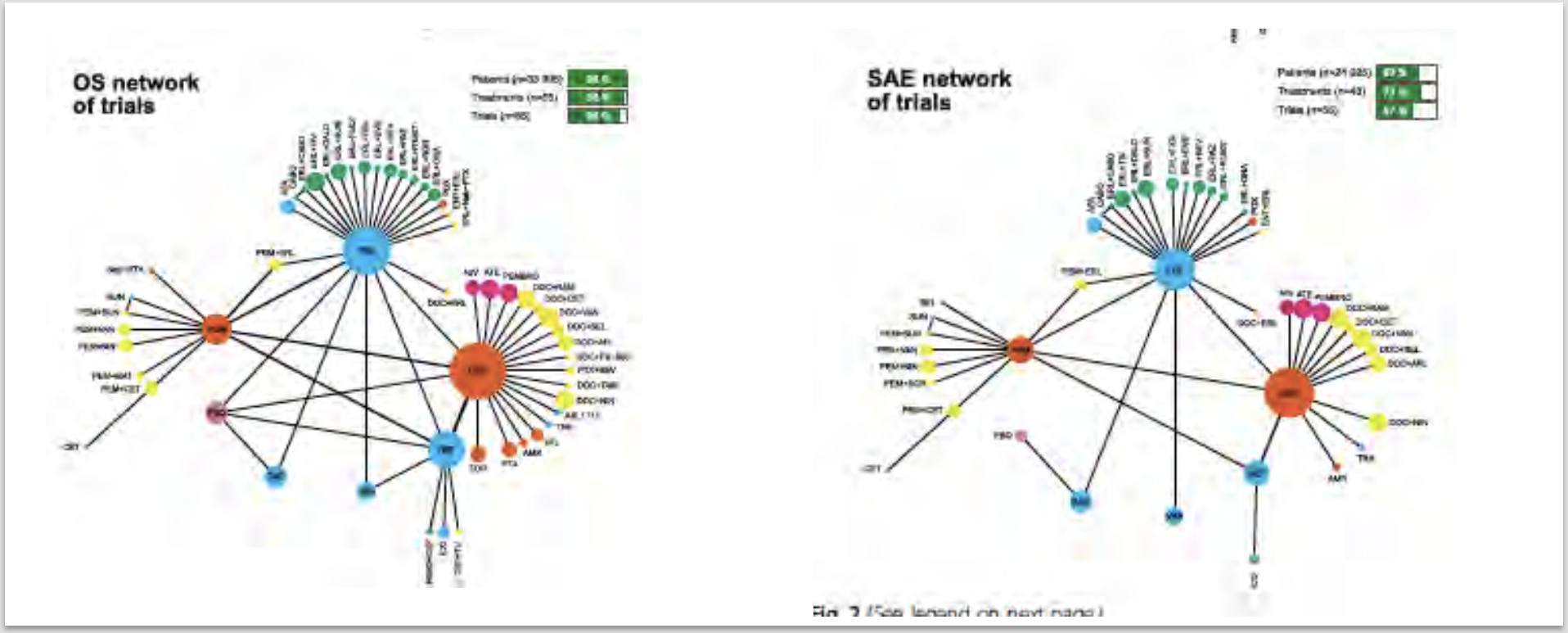
Table 1. Characteristics of included studies.



https://doi.org/10.1371/journal.pone.0199575.t001

Armoiry X, Tsertsvadze A, Connock M, Royle P, Melendez-Torres GJ, et al. (2018) Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PLOS ONE 13(7): e0199575. https://doi.org/10.1371/journal.pone.0199575
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199575

CBNPC de stade IV L2



P CREQUIT et al, BMC Médecine, 2017

CBNPC de stade IV L2

Efficacité

Docetaxel	0.53 (0.26-1.09)	0.45 (0.19-1.16)	0.76 (0.56-1.06)	1.02 (0.68-1.47)	0.97 (0.59-1.59)	1.03 (0.72-1.48)
1.03 (0.92-1.17)	[illegible]	0.85 (0.44-1.71)	1.43 (0.69-2.88)	1.90 (0.80-4.30)	1.82 (0.75-4.36)	1.94 (0.82-4.35)
1.01 (0.89-1.16)	0.98 (0.84-1.13)	[illegible]	1.67 (0.65-4.10)	2.23 (0.81-5.83)	2.14 (0.74-5.91)	2.26 (0.83-5.85)
1.04 (0.94-1.14)	1.00 (0.88-1.14)	1.02 (0.90-1.16)	[illegible]	1.34 (0.79-2.14)	1.28 (0.70-2.27)	1.37 (0.83-2.14)
0.69 (0.56-0.83)	0.67 (0.52-0.83)	0.68 (0.53-0.86)	0.66 (0.53-0.83)	[illegible]	0.95 (0.52-1.81)	1.01 (0.61-1.75)
0.71 (0.56-0.90)	0.69 (0.53-0.89)	0.70 (0.54-0.92)	0.68 (0.53-0.88)	1.03 (0.77-1.40)	[illegible]	1.06 (0.58-1.96)
0.73 (0.62-0.87)	0.71 (0.57-0.87)	0.72 (0.58-0.88)	0.70 (0.56-0.85)	1.06 (0.82-1.37)	1.03 (0.77-1.36)	[illegible]

Effets secondaires

P CREQUIT et a, BMC Médecine, 2017

CBNPC de stade IV L2

Docetaxel	1.10 (0.72-1.73)	1.24 (0.76-2.08)	1.45 (0.97-2.15)	2.02 (0.98-4.27)	2.15 (0.80-5.67)	1.01 (0.49-2.07)
1.04 (0.87-1.24)	Pemetrexed	1.13 (0.69-1.83)	1.32 (0.82-2.03)	1.84 (0.78-4.29)	1.96 (0.65-5.54)	0.91 (0.39-2.07)
1.06 (0.87-1.29)	1.02 (0.83-1.27)	Erlotinib	1.17 (0.70-1.88)	1.63 (0.67-3.96)	1.74 (0.57-5.08)	0.81 (0.34-1.92)
1.03 (0.88-1.20)	0.99 (0.83-1.18)	0.97 (0.79-1.18)	Gefitinib	1.39 (0.61-3.29)	1.48 (0.51-4.28)	0.69 (0.31-1.59)
0.78 (0.59-1.02)	0.75 (0.54-1.03)	0.74 (0.52-1.02)	0.76 (0.55-1.03)	Bevacizumab	1.06 (0.31-3.53)	0.50 (0.18-1.36)
0.88 (0.61-1.26)	0.85 (0.57-1.26)	0.83 (0.55-1.25)	0.85 (0.58-1.27)	1.13 (0.72-1.79)	Pemetrexed+cisplatin	0.47 (0.14-1.57)
0.95 (0.73-1.23)	0.91 (0.66-1.25)	0.89 (0.64-1.23)	0.92 (0.68-1.25)	1.21 (0.83-1.79)	1.07 (0.69-1.68)	Docetaxel+cisplatin

SSP

RO

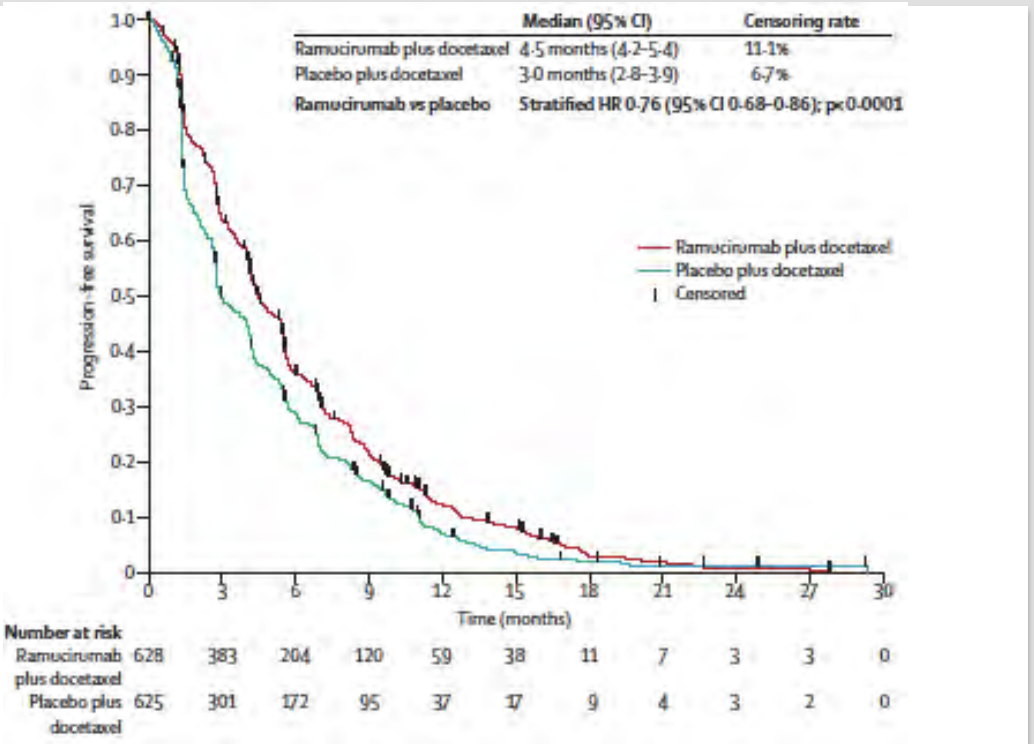
P CREQUIT et a, BMC Médecine, 2017

CBNPC de stade IV L2

Le meilleur taux de réponse
23 % vs 14 %

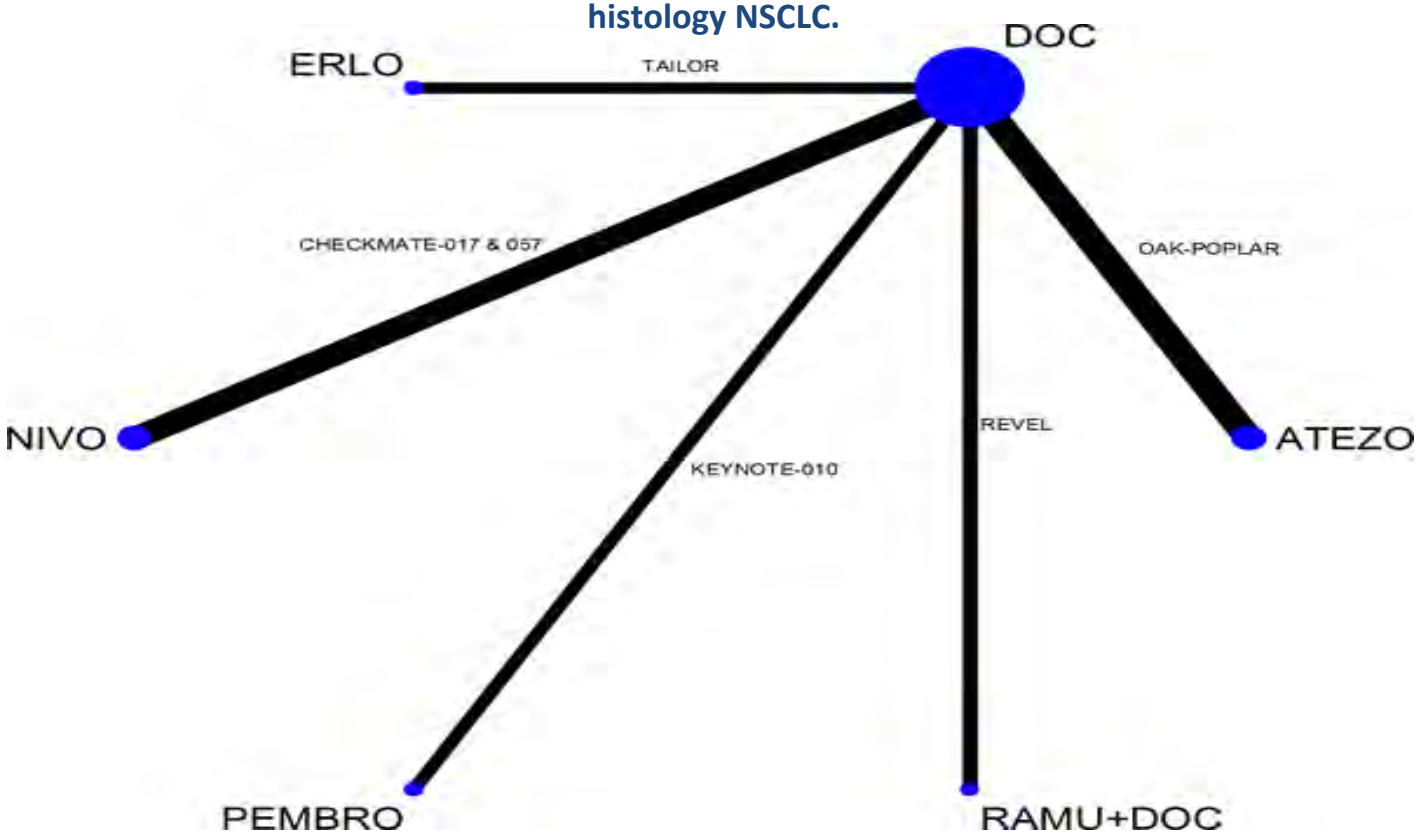
La meilleure survie sans progression..

Docétaxel-Ramucirumab



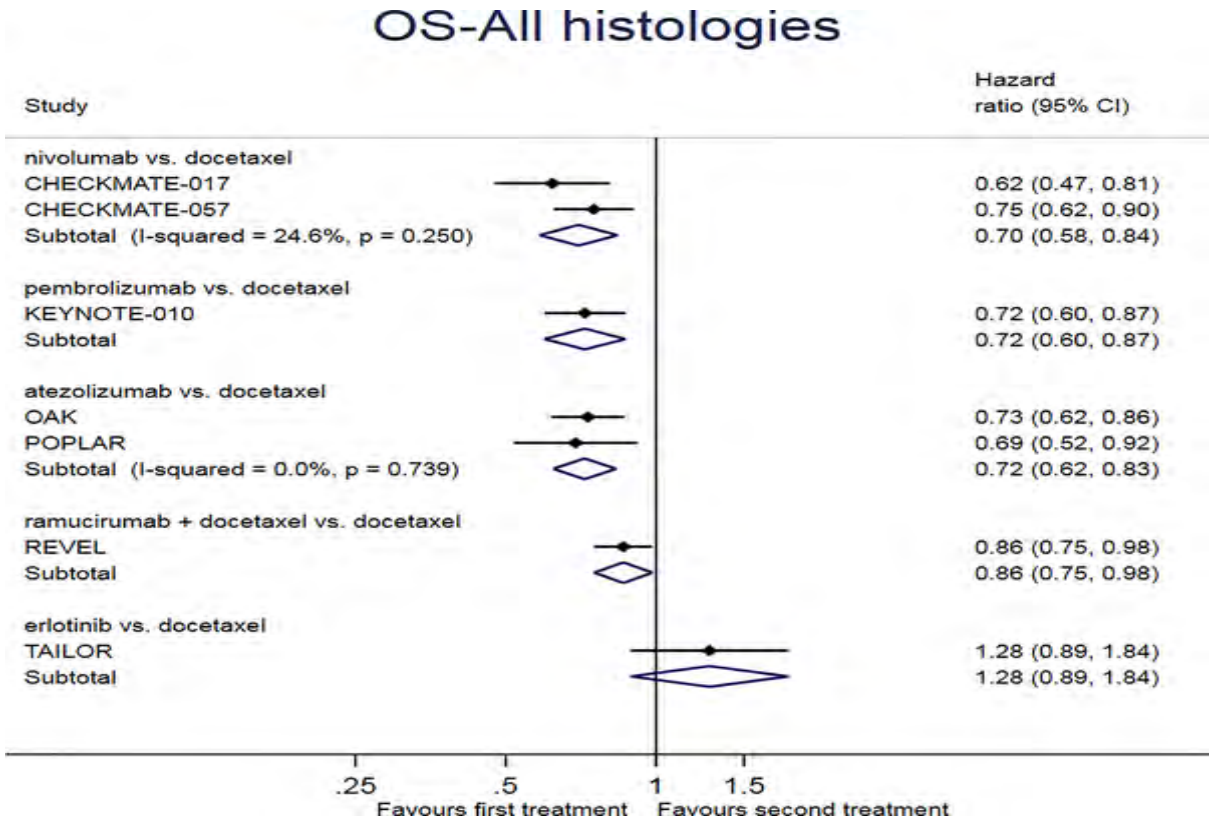
EB Garon et al, Lancet , 2014

Fig 2. Network of studies comparing effectiveness (OS, PFS) and safety (grade 3–5 drug-related AE) outcomes in all-histology NSCLC.



Armoiry X, Tsertsvadze A, Connock M, Royle P, Melendez-Torres GJ, et al. (2018) Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PLOS ONE 13(7): e0199575. https://doi.org/10.1371/journal.pone.0199575
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199575

Fig 3. Pairwise meta-analyses, OS in all-histology NSCLC.



Armoiry X, Tsertsvadze A, Connock M, Royle P, Melendez-Torres GJ, et al. (2018) Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PLOS ONE 13(7): e0199575. https://doi.org/10.1371/journal.pone.0199575
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199575

Table 2. Network meta-analyses: PFS, OS, grade 3–5 AE in all-histology NSCLC.

OS comparisons (*Findings are expressed as HR (95% CI), use of random-effects model.*)

Drug	SUCRA	Nivo	Atezo	Pembro	Ramu+Doc	Doc	Erlo
Nivo	0.82		0.98 (0.79,1.21)	0.98 (0.77,1.25)	0.82 (0.67,1.00)	0.71 (0.61,0.82)	0.55 (0.37,0.82)
Atezo	0.77			1.00 (0.79,1.27)	0.84 (0.69,1.02)	0.72 (0.62,0.83)	0.56 (0.38,0.83)
Pembro	0.77				0.84 (0.67,1.05)	0.72 (0.60,0.87)	0.56 (0.37,0.85)
Ramu+Doc	0.42					0.86 (0.75,0.98)	0.67 (0.46,0.99)
Doc	0.18						0.78 (0.54,1.12)
Erlo	0.02						

PFS comparisons (*Findings expressed as HR (95% CI), use of random-effects model.*)

Drug	SUCRA	Ramu +Doc	Nivo	Pembro	Atezo	Doc	Erlo
Ramu + Doc	0.84		0.98 (0.68,1.41)	0.86 (0.58,1.29)	0.80 (0.57,1.14)	0.76 (0.58,0.99)	0.55 (0.35,0.88)
Nivo	0.81			0.88 (0.60,1.29)	0.82 (0.59,1.13)	0.77 (0.61,0.99)	0.56 (0.36,0.88)
Pembro	0.57				0.93 (0.64,1.35)	0.88 (0.65,1.18)	0.64 (0.39,1.03)
Atezo	0.45					0.95 (0.76,1.18)	0.69 (0.44,1.06)
Doc	0.31						0.72 (0.50,1.06)
Erlo	0.02						

Grade 3–5 AE comparisons (*Findings are expressed as RR (95% CI), use of random-effects model.*)

Drug	SUCRA	Nivo	Atezo	Pembro	Erlo	Doc	Ramu+Doc
Nivo	1		0.55 (0.38,0.79)	0.52 (0.34,0.81)	0.46 (0.29,0.72)	0.18 (0.14,0.25)	0.17 (0.12,0.23)
Atezo	0.68			0.95 (0.66,1.38)	0.83 (0.55,1.23)	0.34 (0.28,0.41)	0.31 (0.25,0.38)
Pembro	0.63				0.87 (0.54,1.39)	0.35 (0.26,0.48)	0.32 (0.23,0.44)
Erlo	0.49					0.41 (0.29,0.58)	0.37 (0.26,0.53)
Doc	0.2						0.91 (0.85,0.97)
Ramu+Doc	0						

Note: The table must be read as the drug on the column against the drug on the row. For example the PFS HR of ramucirumab+docetaxel against nivolumab is 0.98 (95%CI 0.68, 1.41).

https://doi.org/10.1371/journal.pone.0199575.t002

Armoiry X, Tsertsvadze A, Connock M, Royle P, Melendez-Torres GJ, et al. (2018) Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PLOS ONE 13(7): e0199575. https://doi.org/10.1371/journal.pone.0199575
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199575

PLOS ONE

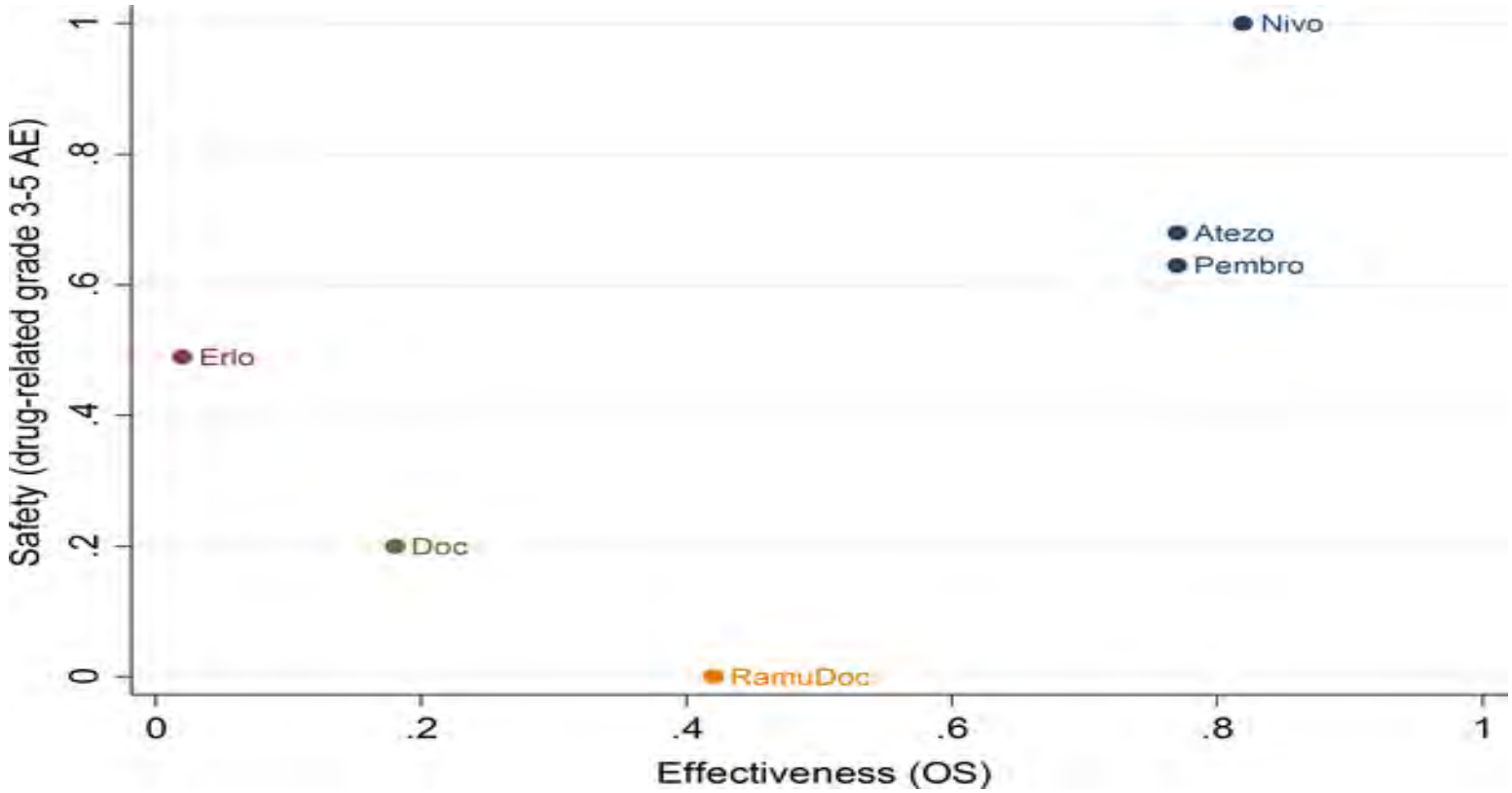
CBNPC de stade IV L2

SUCRA (surface under cumulative Ranking Curve) :

Epidermoide Nivo > ? Mais faible nombre d'épi dans certaines études

Non épidermoide Nivo =Pembro =Atézo > Pem > Ninde+ Doc,= Ramu+Doc> Doc

Fig 4. Clustered ranking plot on effectiveness (OS) and safety (grade 3–5 drug-related AE) both expressed as SUCRAS.



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https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199575

CBNPC de stade IV L2

MOINS D'EFFETS SECONDAIRES G3-G4-G5 avec le Nivolumab vs Pembro ou Atézo???
MEME TAUX D'EFFETS SECONDAIRES G1-G5 entre les 3 IO…

BIAIS: 1 visite médicale J1 – J15 – J29 – J43 – bilan vers J 55

1 visite médicale J1 – J22 – J43 – bilan vers J 60

Importance de la surveillance médicale, notamment au début du traitement

Hospices Civils de Lyon

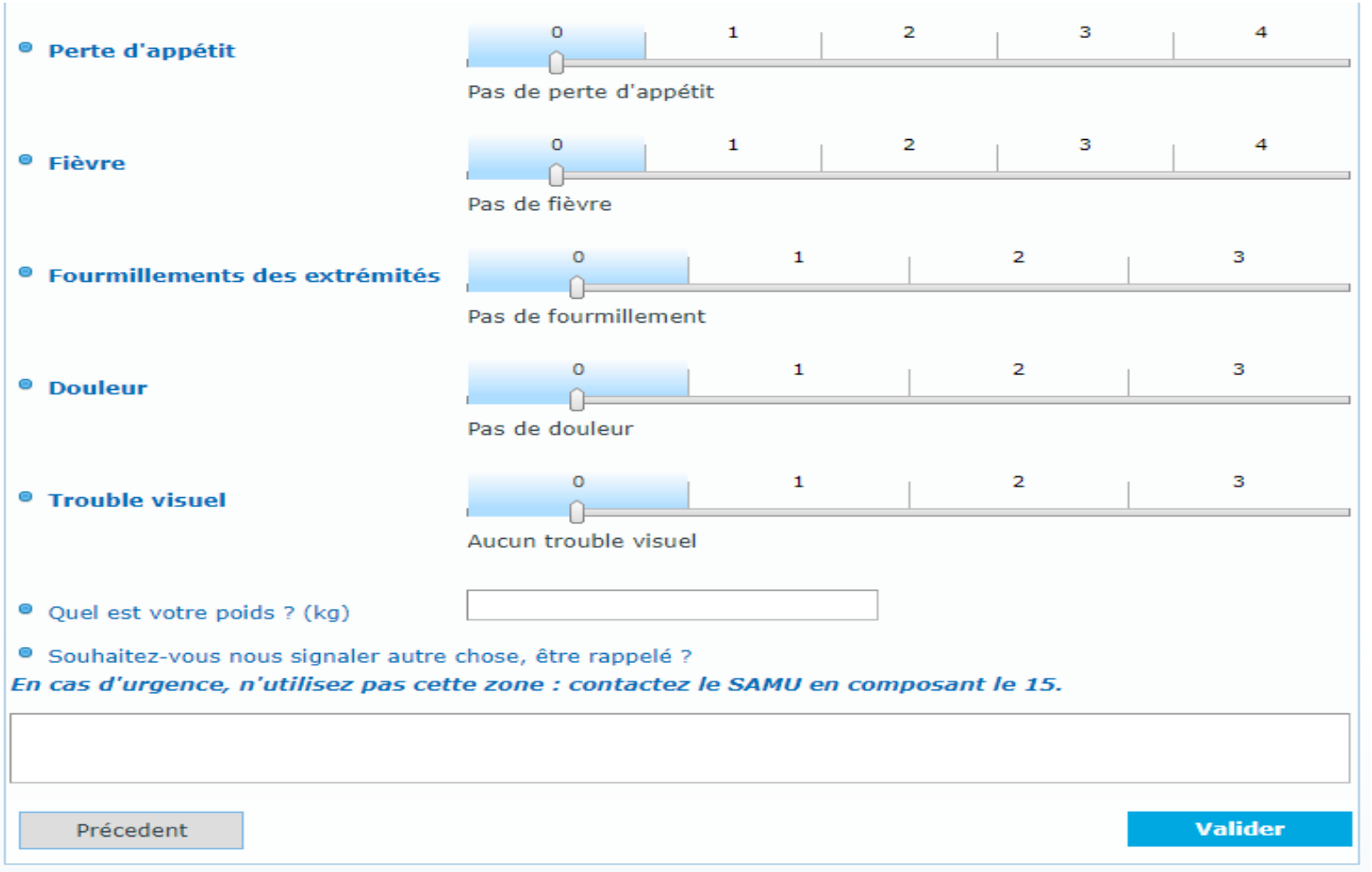
INSTITUT DE CANCÉROLOGIE

IMMUCARE

Surveillance Web guidée

>> suite page suivante

Suite


Perte d'appétit
0 1 2 3 4
Pas de perte d'appétit
Fièvre
0 1 2 3 4
Pas de fièvre
Fourmillements des extrémités
0 1 2 3
Pas de fourmillement
Douleur
0 1 2 3
Pas de douleur
Trouble visuel
0 1 2 3
Aucun trouble visuel
Quel est votre poids ? (kg)
Souhaitez-vous nous signaler autre chose, être rappelé ?
En cas d'urgence, n'utilisez pas cette zone : contactez le SAMU en composant le 15.
Précedent
Valider

CBNPC de stade IV L2

Nivolumab: 1053 € les 100mg: 240 mg/14 jours: 7581,6 Euros pour 6 semaines

Pembrolizumab: 2672 € les 100 mg soit par 6 semaines 10 688 Euros

Atézolizumab??

Nivolumab 1 HJ de plus, 1 VSL, 1 bio / 6 semaines que Pembrolizumab = moins de 3100 Euros…. .

MERCI POUR ATTENTION