Secondes rencontres d'Oncologie Thoracique en Nouvelle-Aquitaine

Actualité en immunothérapie : 2e ligne

Rémi Veillon
Oncologue Médical
Service des maladies respiratoires

Angoulême, 27 Avril 2018

Liens d'intérêts

depuis 2013

- Participation à des congrès (ASCO, ESMO, WCLC) :
  - Roche, Amgen, Lilly, Boehringer-Ingelheim, Pfizer, MSD, Bristol-Myers Squibb

- Board local d'experts ; animations ou interventions (réunions d'experts, post-congrès) :
  - Boehringer-Ingelheim, Roche, Astra-Zeneca, Bristol-Myers Squibb, MSD, Pfizer

- Consultant
  - MSD

- Honoraires investigateurs dans le cadre de recherche clinique (compte recherche Accelence)
  - Roche, Astra-Zeneca, Takeda, Abbvie, Merck-Serono, Bristol-Myers Squibb, MSD

Le contenu et/ou les opinions exprimées lors de cette présentation ont été réalisés en toute indépendance

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Avant l'immunothérapie

	Adénocarcinomes	Carcinomes épidermoides
1ère ligne	2002 : Bithérapie[1,2] (sels de platine) +/- Bevacizumab[3]	2002 : Bithérapie [1,2] (sels de platine)
	Maintenance : Pemetrexed[4] et/ou Bevacizumab[3]	
2ème ligne	2000 : Docetaxel[5] 2004 : Pemetrexed[6] 2005 : Erlotinib[7]	2000 : Docetaxel[5] 2005 : Erlotinib[7]
Xème ligne	2005 : Erlotinib[7]	

(1) Schiller et al. NEJM 2002 ; 346 : 92 -98
(2) Scagliotti, JCO 2008 ; 26 : 3543-51
(3) Sandler et al. NEJM 2006; 355:2542-50
(4) Paz-Ares, et al. J Clin Oncol 2013 : 23 ; 2895-2902.
(5) Shepherd et al. JCO 2000 ; 18 : 2095-2103
(6) Hanna et al. JCO 2004 ; 22 : 1589-1597
(7) Shepherd et al . NEJM 2005 ; 353 : 123-32

CBNPC : Docetaxel en 2e ligne

- 204 patients (nov 1994 – dec 1998)
- 2e ligne : Docetaxel vs Placebo
- Survie globale : 7,0 vs 4,6 mois (p 0,047)

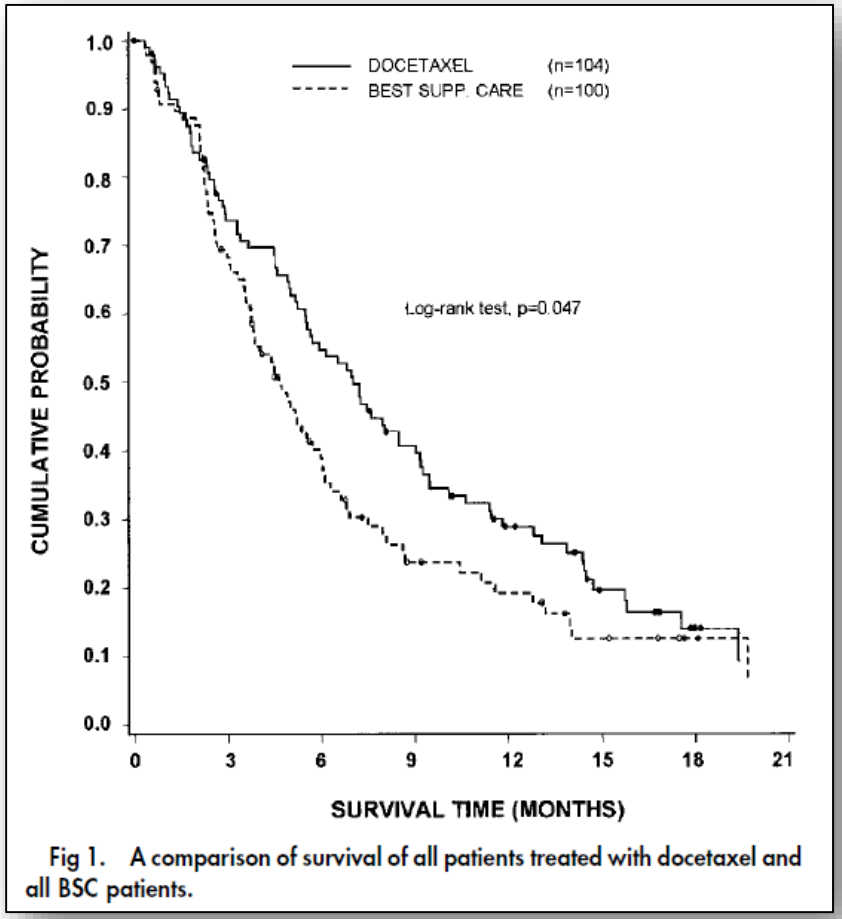

Fig 1. A comparison of survival of all patients treated with docetaxel and all BSC patients.

Shepherd et al. JCO 2000 ; 18 : 2095-2103

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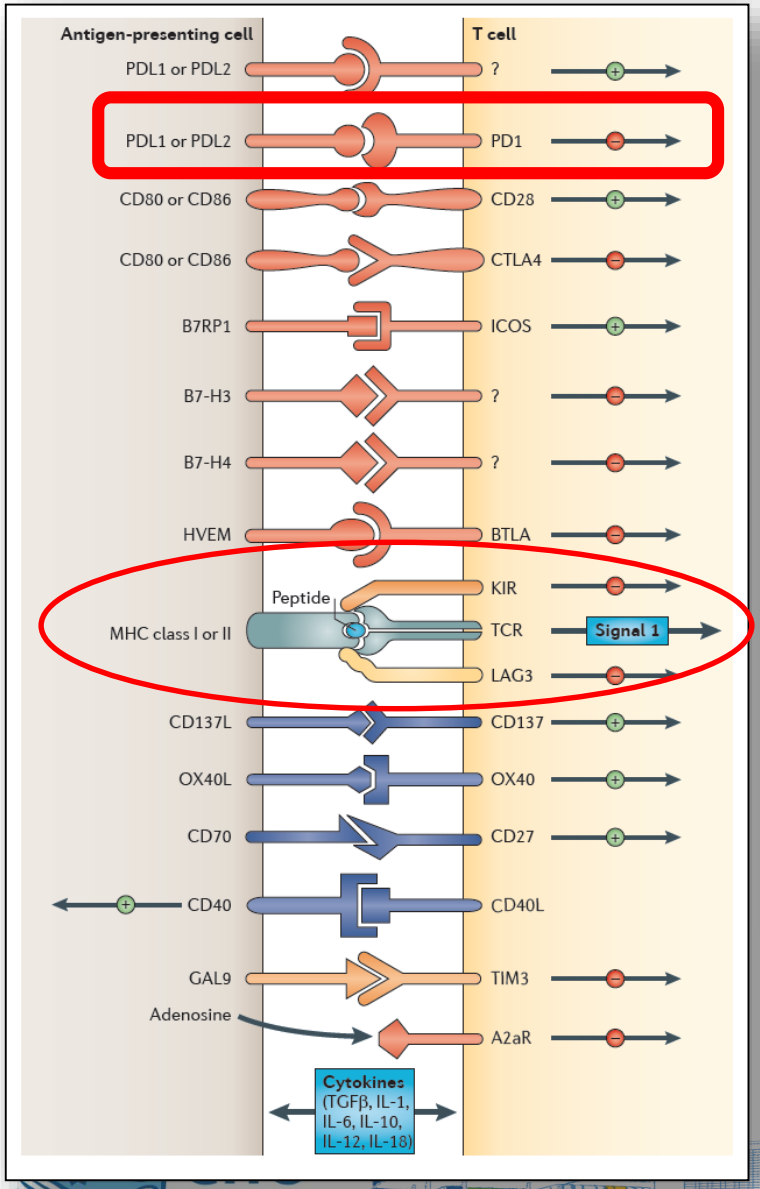
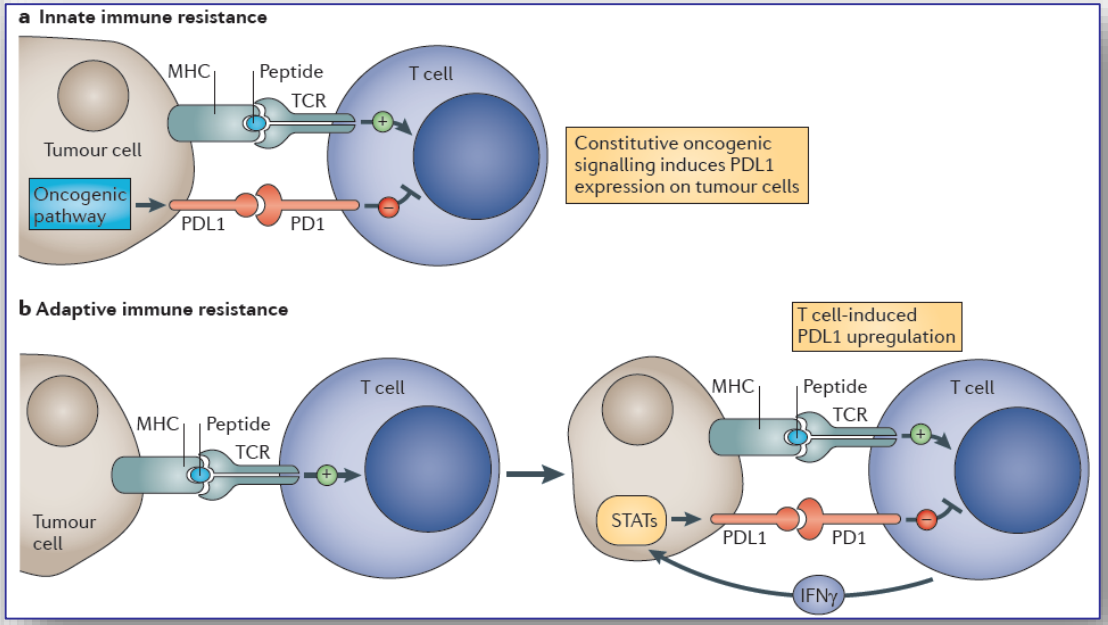
Immunothérapie et CBNPC 2e ligne : anti PD1





Pardoll et al. Nat Rev Cancer 2012 ; 4 : 252-264

Nivolumab

Checkmate 017 (phase III, carcinomes épidermoïdes)

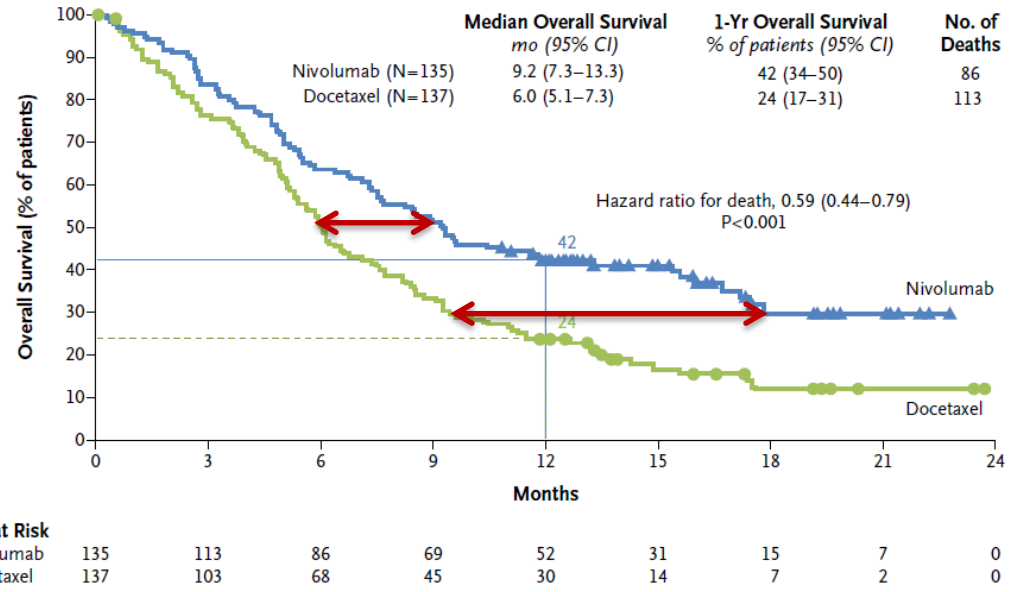


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N=135)	Docetaxel (N=137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.5
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+

- Carcinomes épidermoides bronchiques en 2ème Ligne
- Réponses indépendantes de l'expression IHC de PD-L1

Brahmer et al. N Engl J Med 2015; 373:123-135

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Cancers Bronchiques Non à Petites Cellules (CBNPC)

	Adénocarcinomes	Carcinomes épidermoides
1ère ligne	Bithérapie +/ Bevacizumab +/- maintenance	Bithérapie
2ème ligne	Docetaxel Pemetrexed Erlotinib	Nivolumab

Brahmer et al. N Engl J Med 2015; 373:123-135

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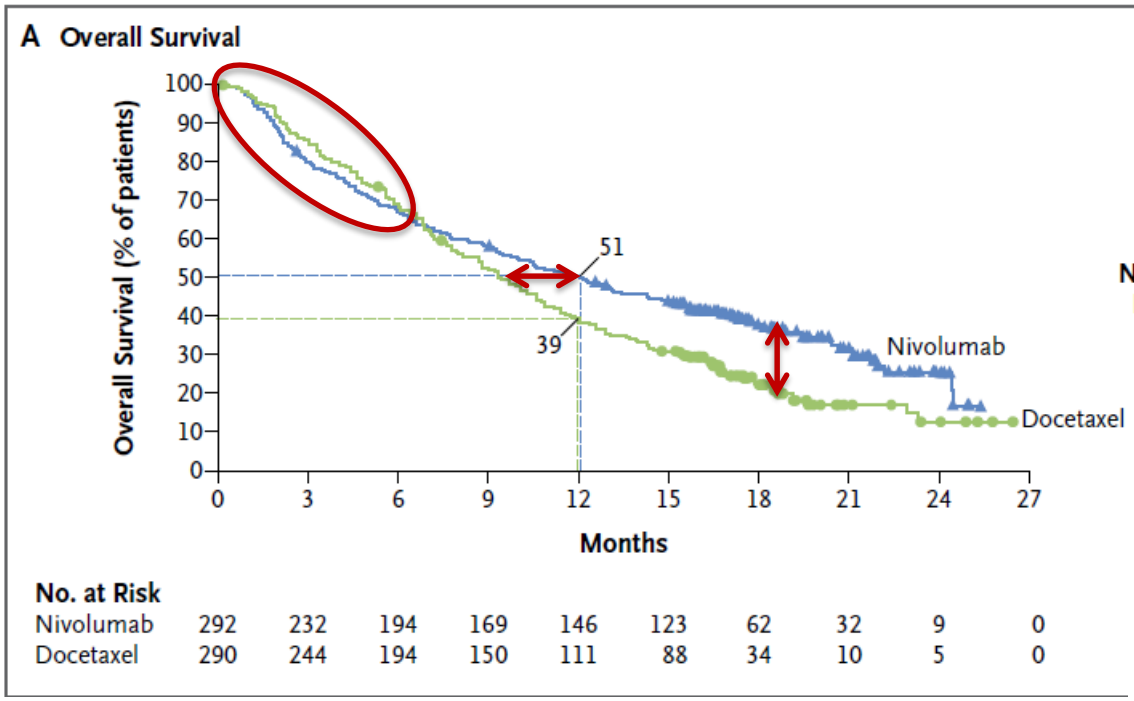
Nivolumab

Checkmate 057 (phase III, carcinomes non-épidermoïdes)



	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

- 2e ligne
- Réponses influencées par l'expression IHC de PD-L1

Table 2. Tumor Response with Nivolumab versus Docetaxel in Patients with Advanced Nonsquamous Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N = 292)	Docetaxel (N = 290)
Objective response†		
No. of patients	56	36
% of patients (95% CI)	19 (15–24)	12 (9–17)
Estimated odds ratio (95% CI)	1.7 (1.1–2.6)	
P value	0.02	
Best overall response — no. (%)		
Complete response	4 (1)	1 (<1)
Partial response	52 (18)	35 (12)
Stable disease	74 (25)	122 (42)
Progressive disease	129 (44)	85 (29)
Could not be determined	33 (11)	47 (16)
Time to response — mo‡§		
Median	2.1	2.6
Range	1.2–8.6	1.4–6.3
Duration of response — mo‡¶		
Median	17.2	5.6
Range	1.8 to 22.6+	1.2+ to 15.2+

Borghaei et al. N Engl J Med 2015; 373:1627-1639

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Cancers Bronchiques Non à Petites Cellules (CBNPC)

	Adénocarcinomes	Carcinomes épidermoides
1ère ligne	Bithérapie +/ Bevacizumab +/- maintenance	Bithérapie
2ème ligne	Docetaxel Pemetrexed Erlotinib Nivolumab	Nivolumab

Borghaei et al. N Engl J Med 2015; 373:1627-1639

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Pembrolizumab

Keynote 10 (phase III, Pembro vs Docetaxel)

- PDL1 > 50%
  - HR 0,54 (Pembro 2mg/kg)
  - HR 0,50 (Pembro 10mg/kg)
  - Médiane : 14,9 vs 17,3 vs 8,2 mois
- PDL1 > 1%
  - HR 0,71 (Pembro 2m/kg)
  - HR 0,61 (Pembro 10mg/kg)
  - Médiane : 10 vs 12,7 vs 8,5 mois

Herbst et al. Lancet 2016 ; 387 : 1540 - 50

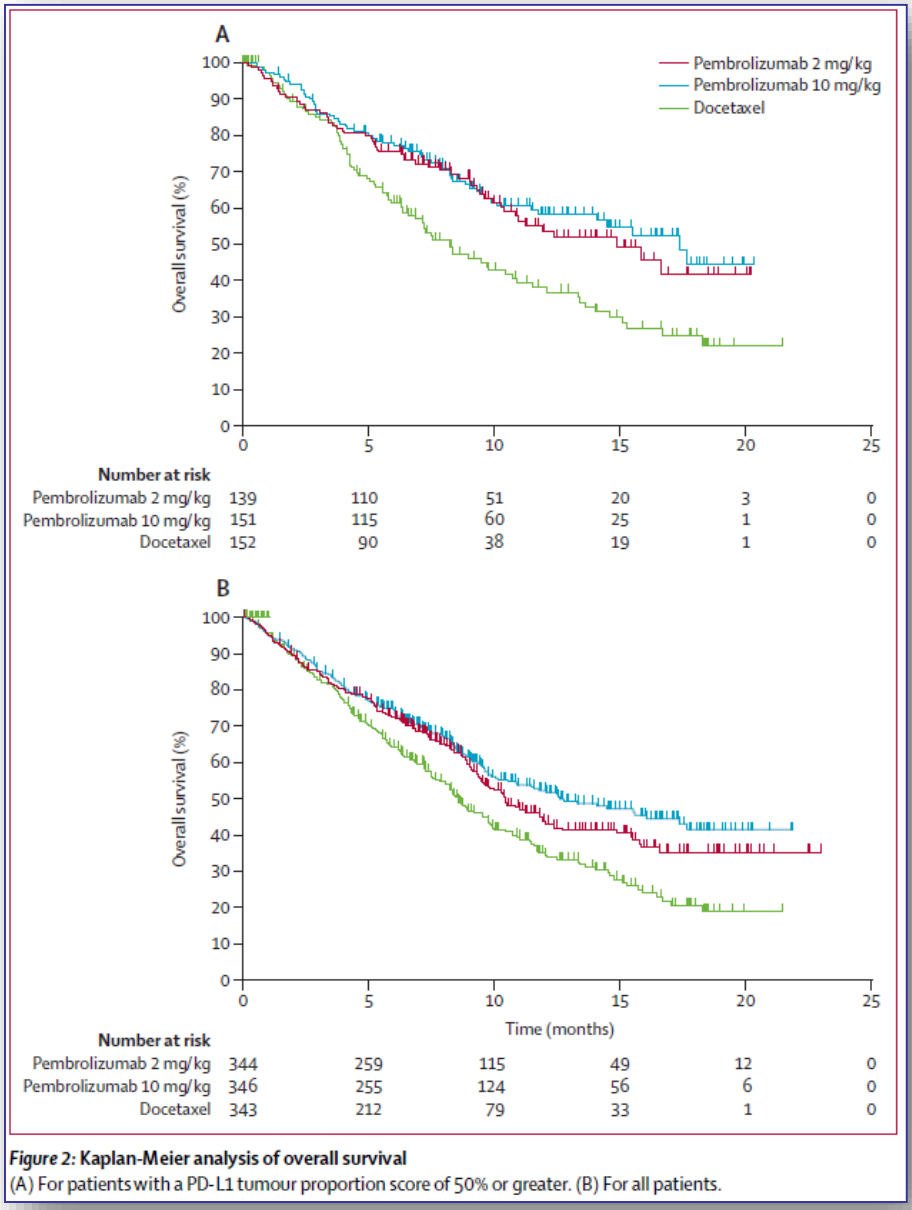

Figure 2: **Kaplan-Meier analysis of overall survival**
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

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Stratégie : Cancers Bronchiques Non à Petites Cellules (CBNPC)

	Adénocarcinomes	Carcinomes épidermoides
1ère ligne	Bithérapie +/ Bevacizumab +/- maintenance	Bithérapie
2ème ligne	Docetaxel Pemetrexed Nivolumab	Nivolumab

Pembrolizumab (PDL1+)

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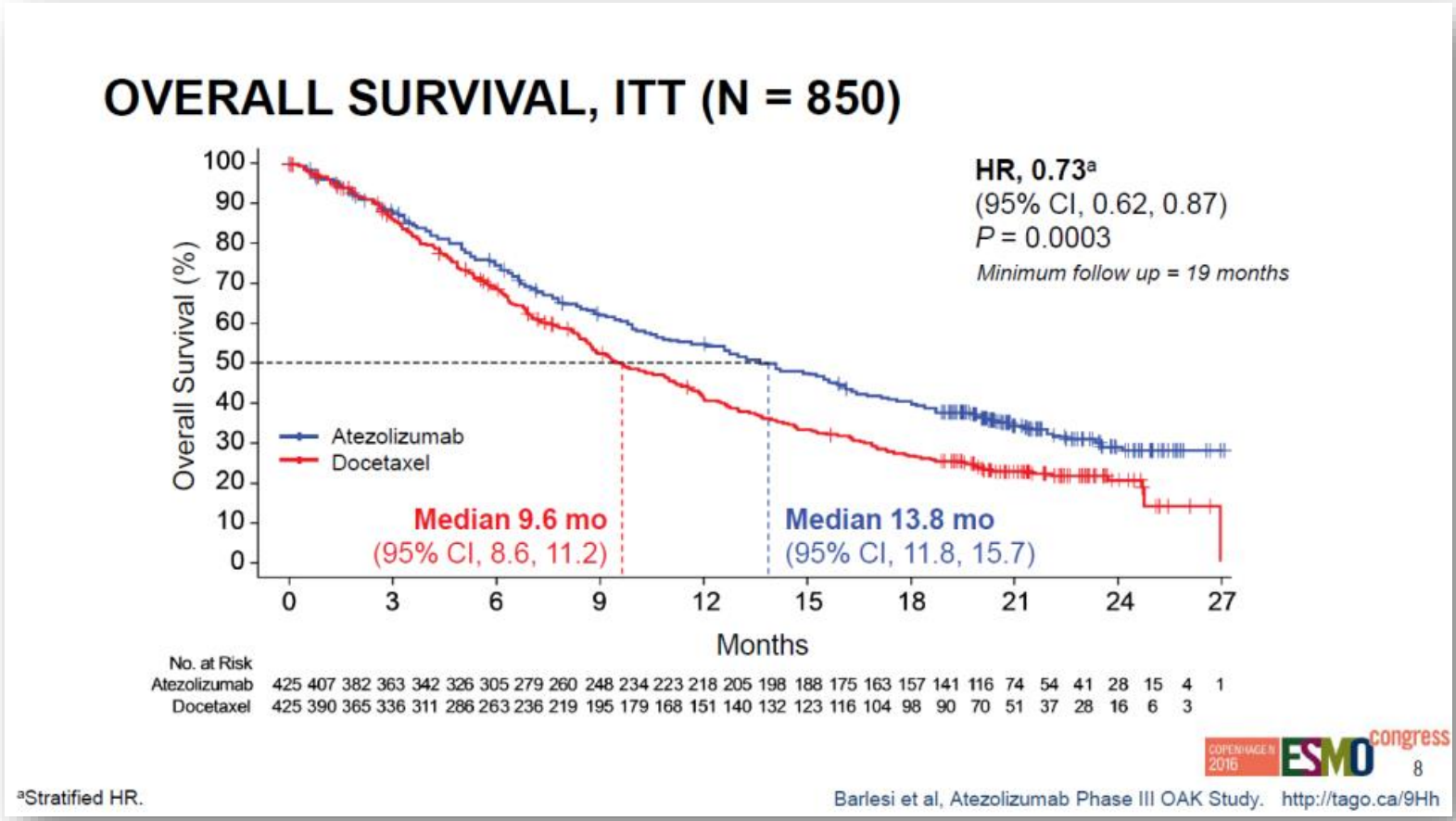
Atezolizumab (étude OAK)

Anti PD-L1



Barlesi – ESMO 2016 ; LBA 44

Rittmeyer et al. Lancet 2017 ; 389 255 - 265

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Stratégie depuis l'arrivée du Pembrolizumab en 1ère ligne

	CBNPC PDL1 >50%	CBNPC PDL1 <50%
1ère ligne	Pembrolizumab(1)	Chimiothérapie
2ème ligne	Chimiothérapie	PDL1 positifs: Pembrolizumab(2) Nivolumab(3,4) ; PDL1 négatifs / inconnus: Chimiothérapie Nivolumab(3,4) ?

?

(1) Reck et al. NEJM 2016 ; 375 : 1823 – 33
(2) Herbst et al. Lancet 2016 ; 387 : 1540 - 50
(3) Brahmer et al. N Engl J Med 2015; 373:123-135
(4) Borghaei et al. N Engl J Med 2015; 373:1627-1639

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Choix de la 2e ligne :
PDL1 négatif ou inconnu

- Histologie : Carcinomes épidermoïdes
  - Checkmate 017 : Nivolumab vs Docetaxel

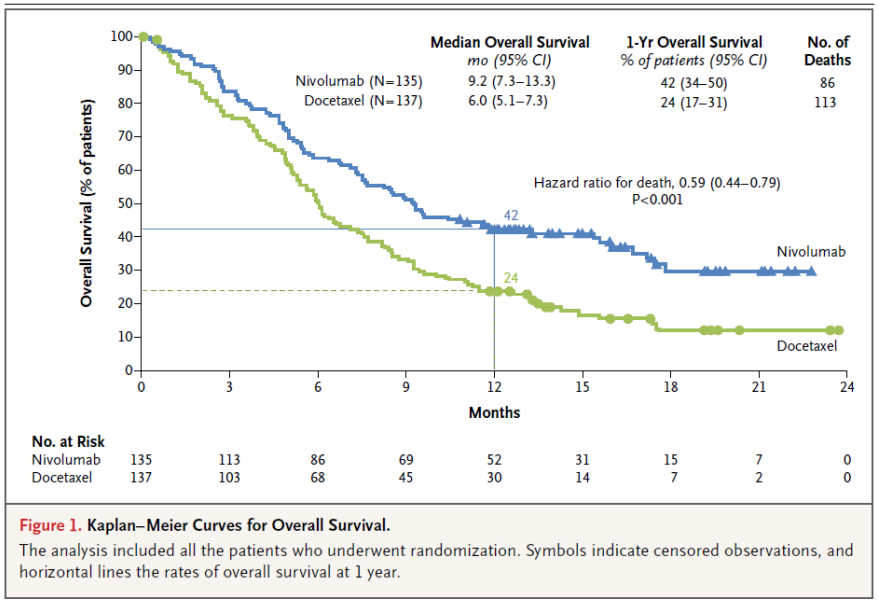

Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Brahmer et al. N Engl J Med 2015; 373:123-135

- Carcinomes non épidermoides ?

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Choix 2e ligne :

PDL1 négatif ou non connu
Carcinomes non épidermoides

- Chimiothérapie ou immunothérapie ?
  - Autres marqueurs prédictifs
    - Tabac
    - Mutation EGFR
  - Etat général ?
  - Réponse à la 1ère ligne ?
  - Chimiothérapie post-immunothérapie ?

Facteur prédictif : Tabac

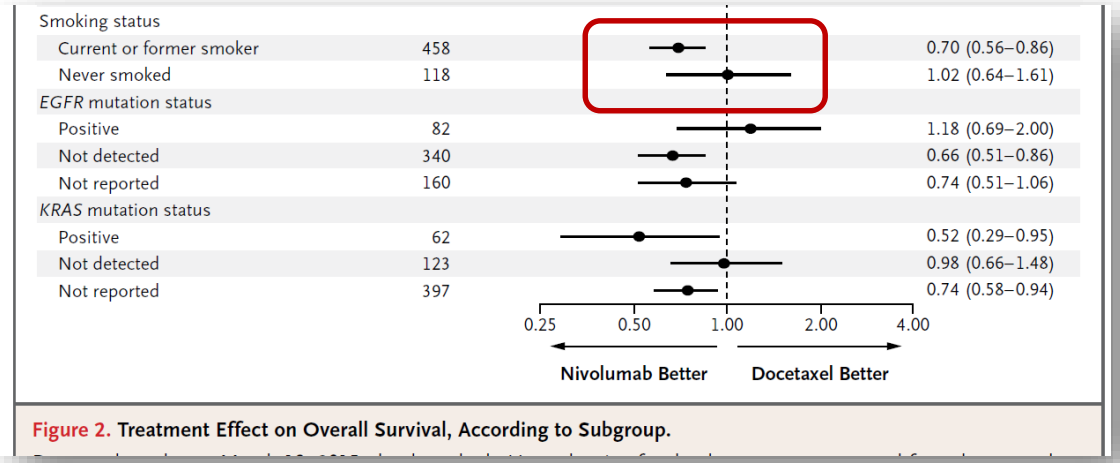


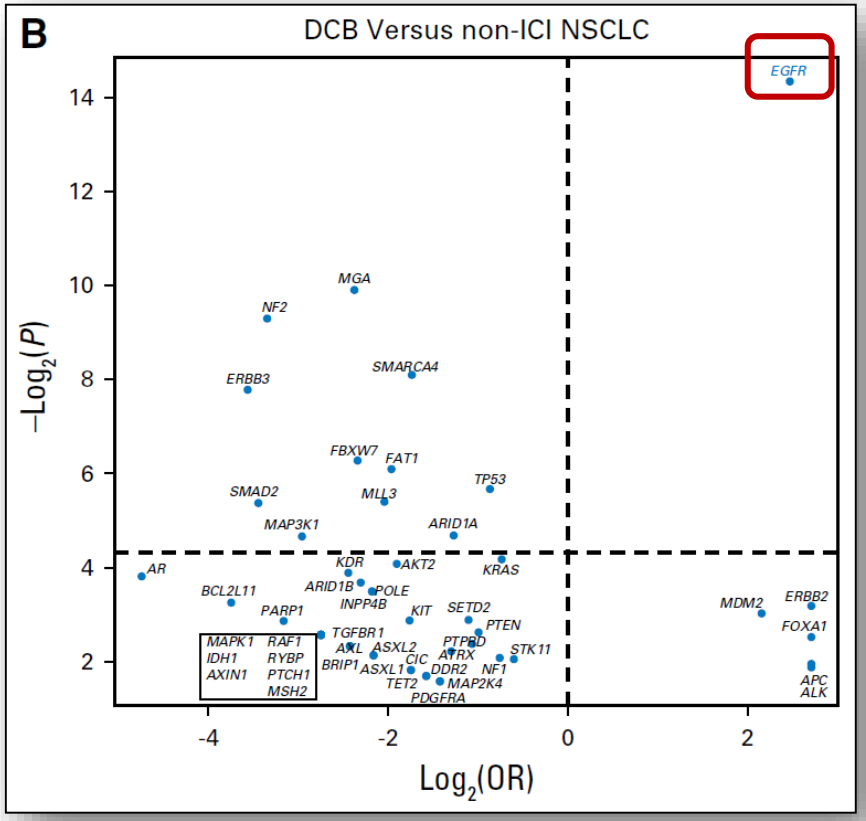
Figure 2. Treatment Effect on Overall Survival, According to Subgroup.

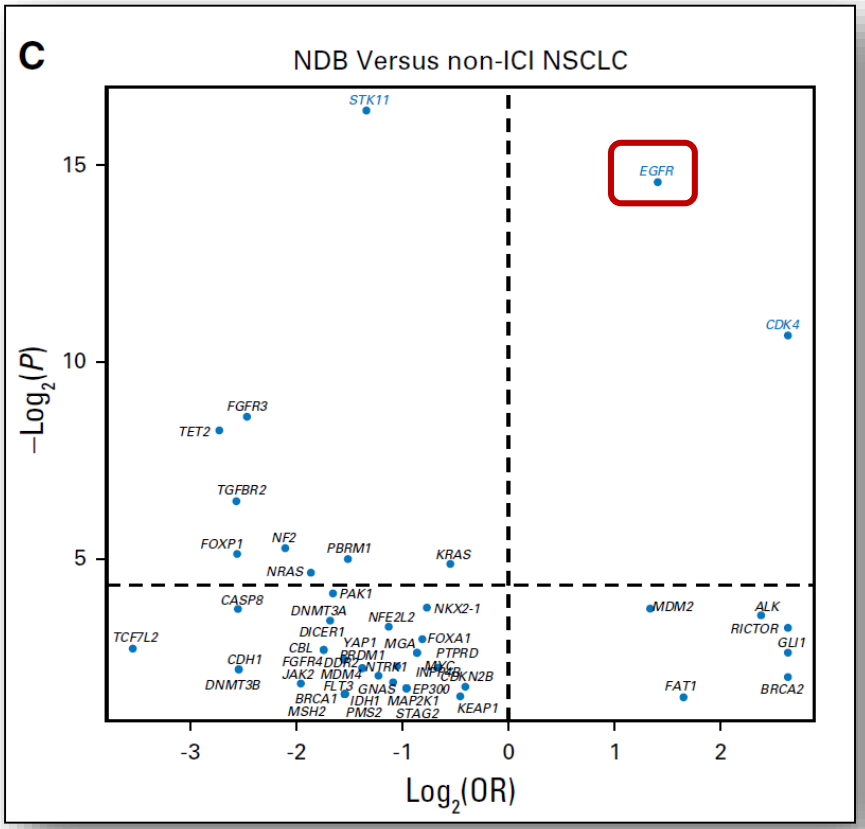
Borghaei et al. N Engl J Med 2015; 373:1627-1639

	No.	ORR — no. (%) [95% CI]
Smoking history		
Never	126	13 (10.3) [5.6-17.0]
Former/current	369	83 (22.5) [18.3-27.1]

Garon et al. N Engl J Med 2015; 372:2018-2028 (app)

Facteur prédictif : EGFR





- EGFR significativement sous représenté dans le groupe de patient répondeur

Rizvi et al. JCO 2018 ; DOI :10.1200/JCO.2017.75.3384

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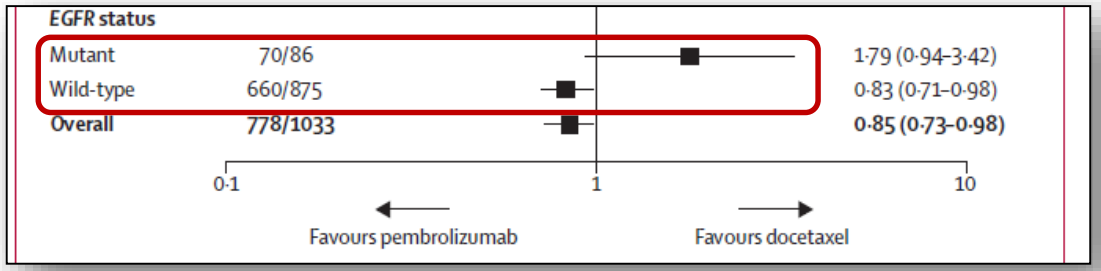
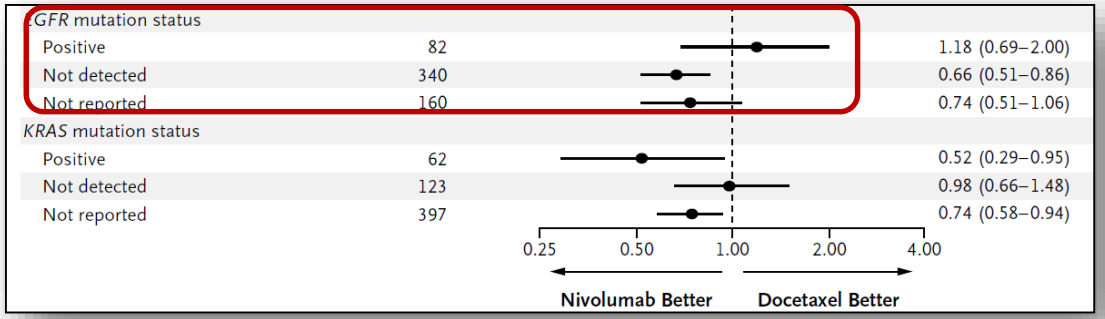
Facteur prédictif : EGFR



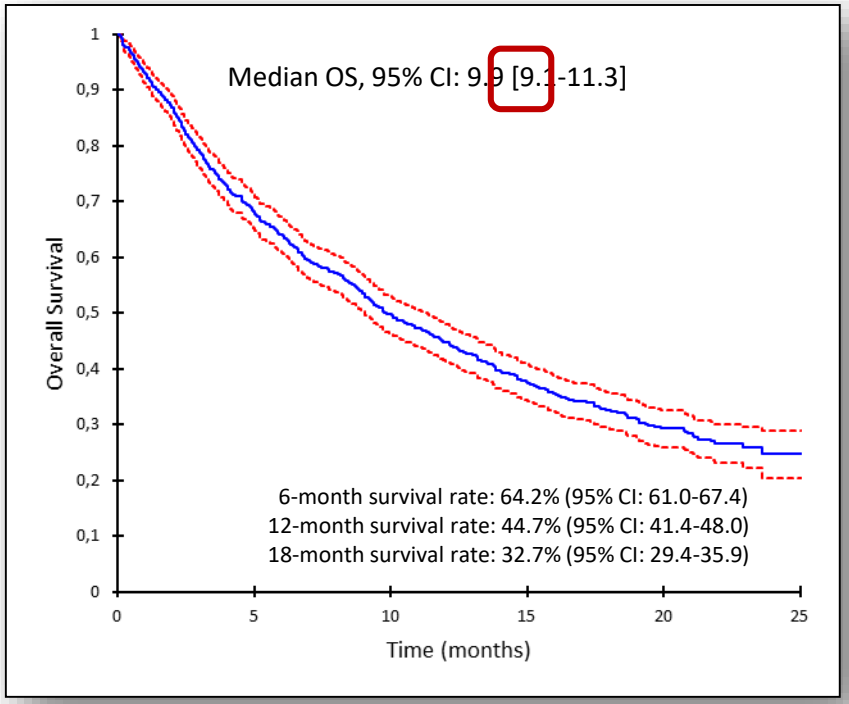
Herbst et al. Lancet 2016 ; 387 : 1540 - 50

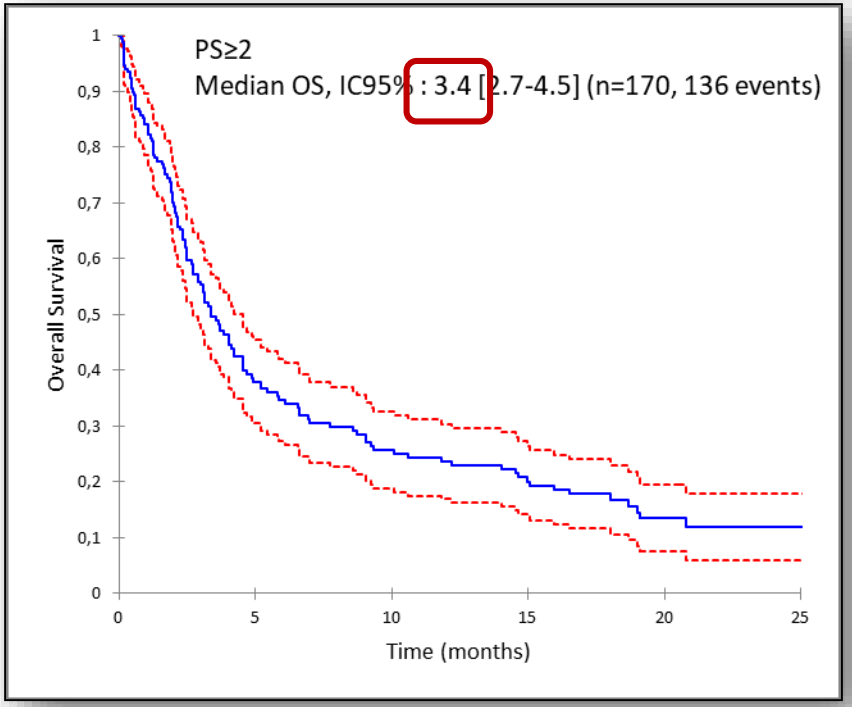


Borghaei et al. N Engl J Med 2015; 373:1627-1639

CLINIVO
(ATU Nivolumab) PS ≥ 2

Best response %, 95%CI	Total (n=121)
Objective response	12.4% [6.5%-18.3%]
Stable Disease	31.4% [23.1%-39.7%]
Disease Control	43.8% [35.0%-52.6%]
Progression	56.2% [47.4%-65.0%]





Girard et al – WCLC 2017 – abstract 9371

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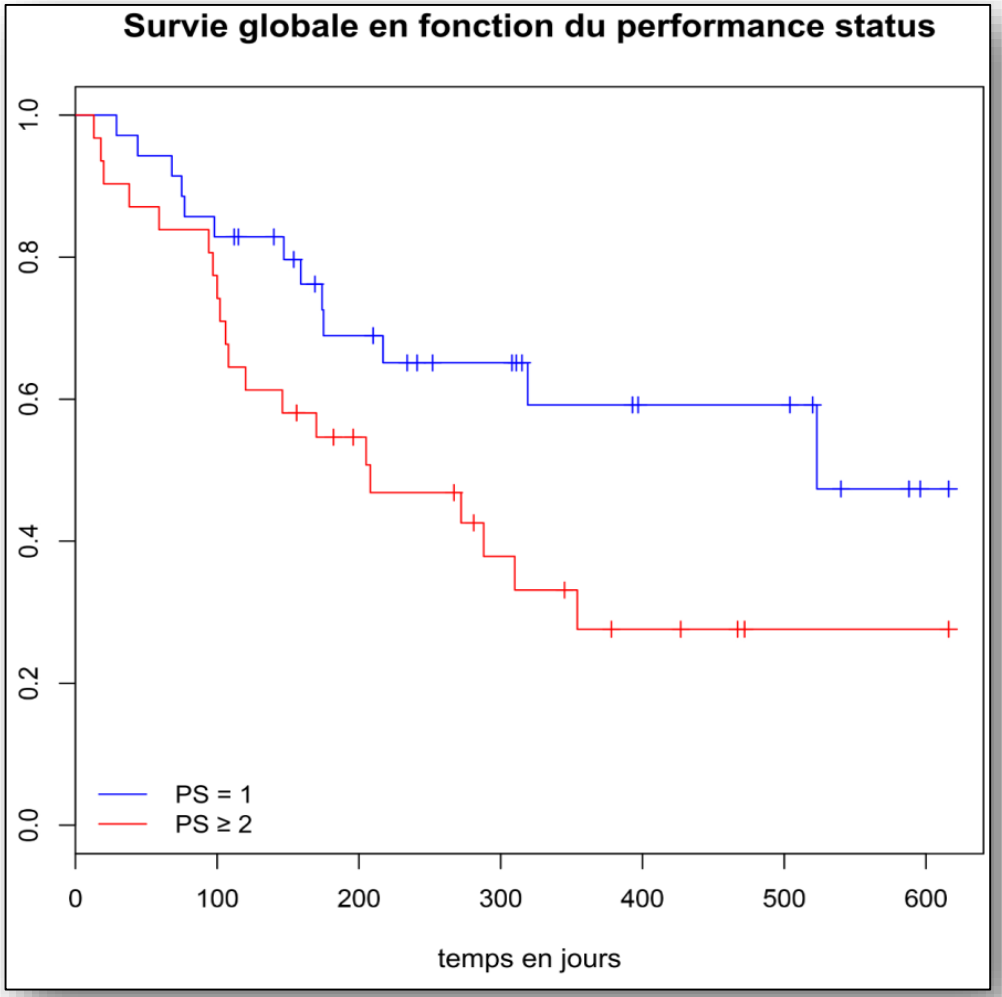
Survie Globale en fonction du PS (2e ligne)

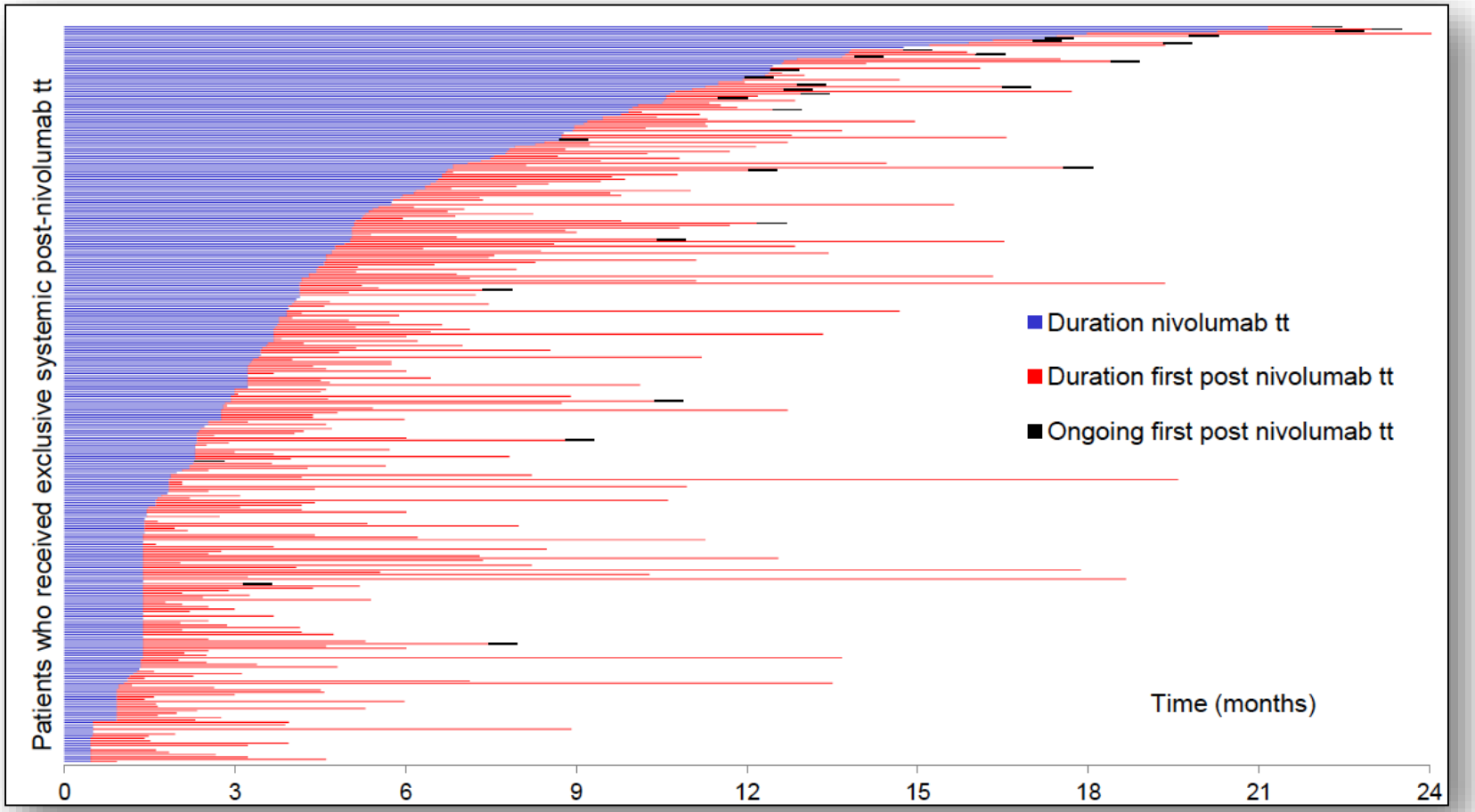
- PS 0-1 : 17,4 mois
- PS ≥ 2 : 6,9 mois

- HR 0.38 IC95% [0.19-0.76] p=0.006



Thèse Pierre Helly-de-Tauriers

Réponse post-immunothérapie



Girard et al – WCLC 2017 – abstract 9371

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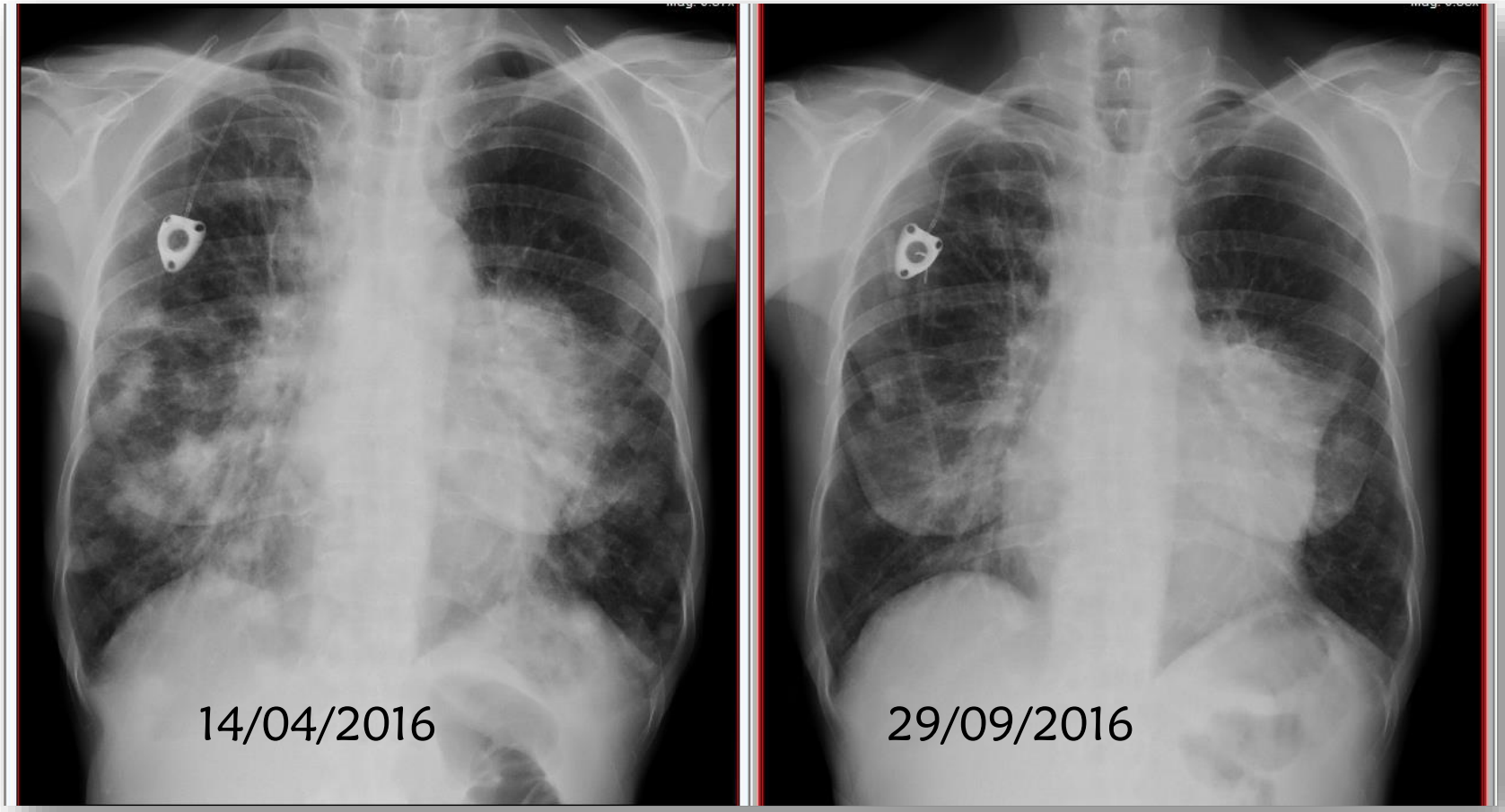
Exemple

- Adénocarcinome bronchique sous **Paclitaxel** (3e ligne) après échec de l'Avelumab (2e ligne)



Carcinomes non épidermoïde PDL1 négatifs/non connu

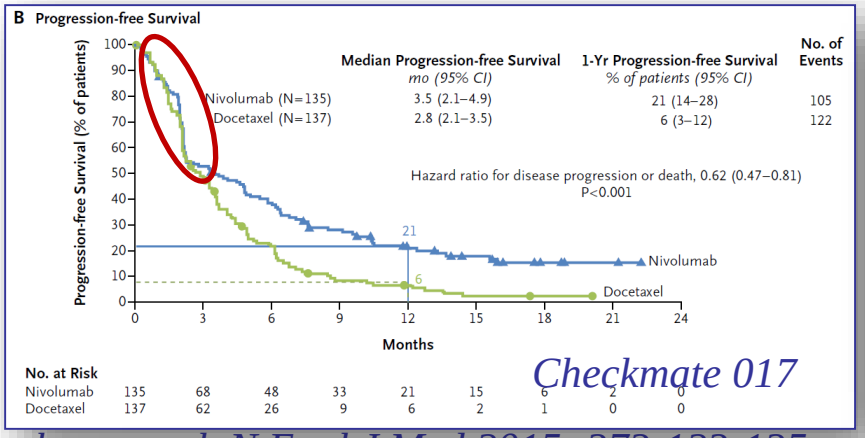
- Pour Nivolumab :
  - Bon état général
  - Gros fumeur
  - Mauvaise réponse à la chimiothérapie
  - Se garder une ligne de chimiothérapie…
- Contre Nivolumab :
  - Prix !
  - Non fumeur / muté EGFR
  - Bonne réponse à la chimiothérapie
  - Risque d'hyper-progression

Quand stopper l'immunothérapie ?

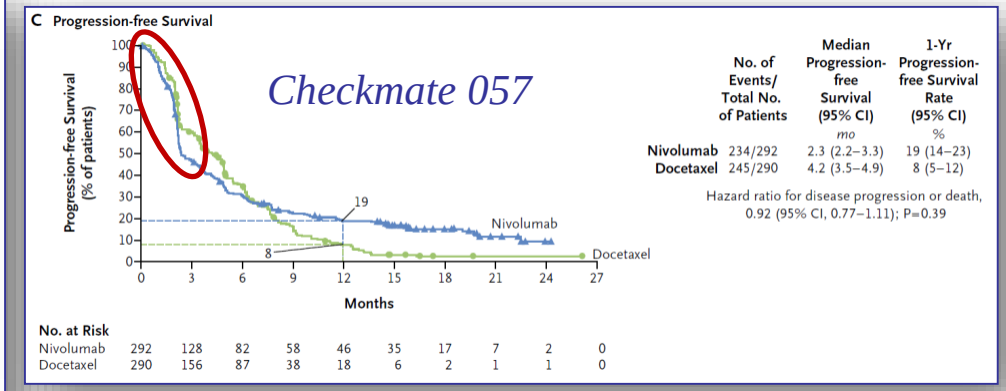
- Chez les non-répondeurs
  - Hyperprogression
  - Pseudo-progression

- Chez les répondeurs

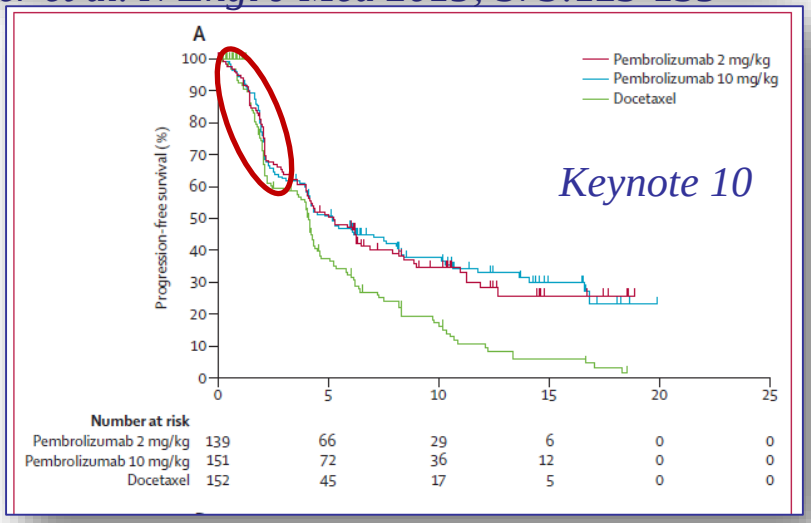
Remarque : survie sans progression



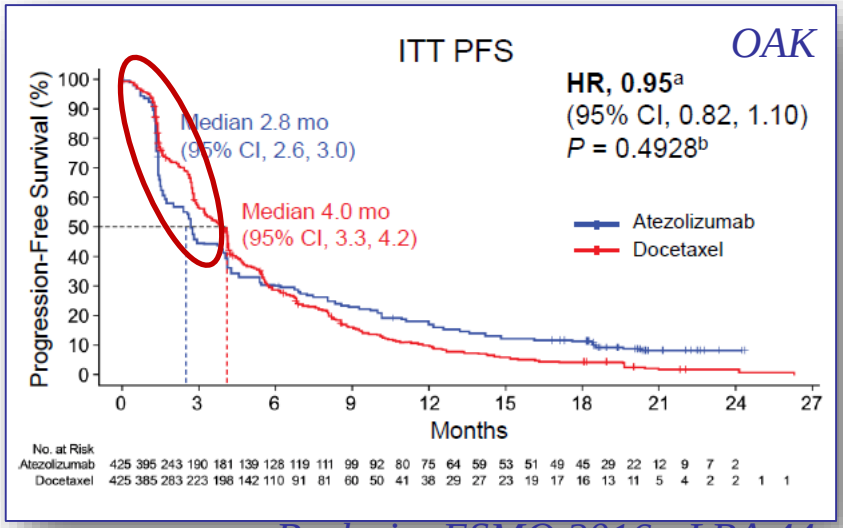
Brahmer et al. N Engl J Med 2015; 373:123-135



Borghaei et al. N Engl J Med 2015; 373:1627-1639



Herbst et al. Lancet 2016 ; 387 : 1540 - 50



Barlesi – ESMO 2016 ; LBA 44

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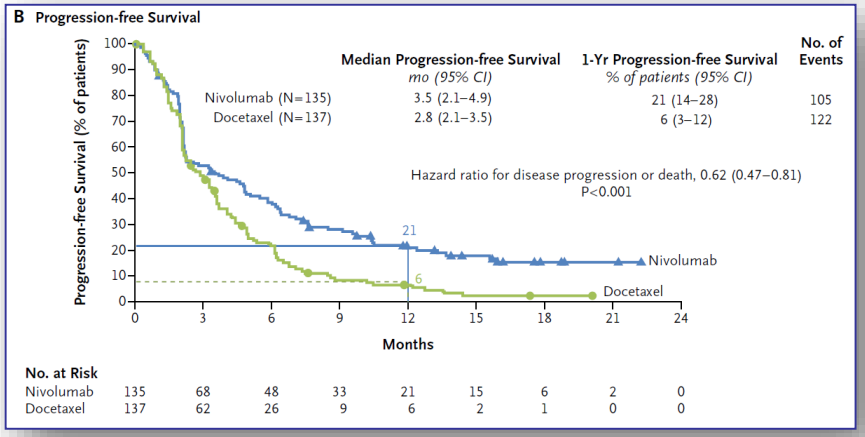
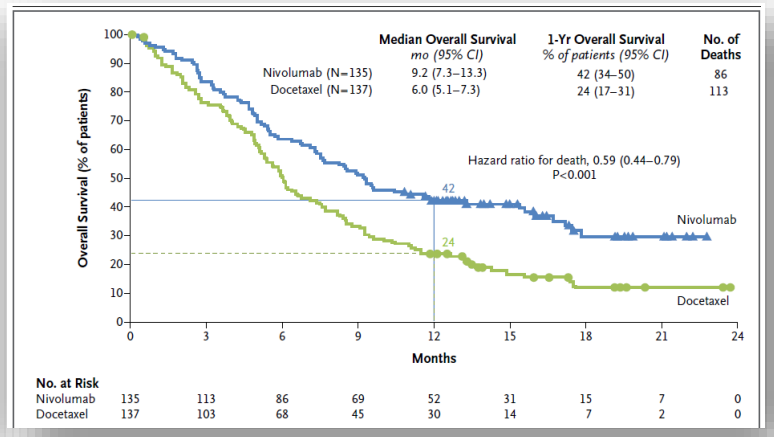
Contraste Survie Sans Progression / Survie Globale





- Efficacité de la chimiothérapie post-immunothérapie
- Ralentissement de la progression
- Pseudo progression
- Hyperprogression

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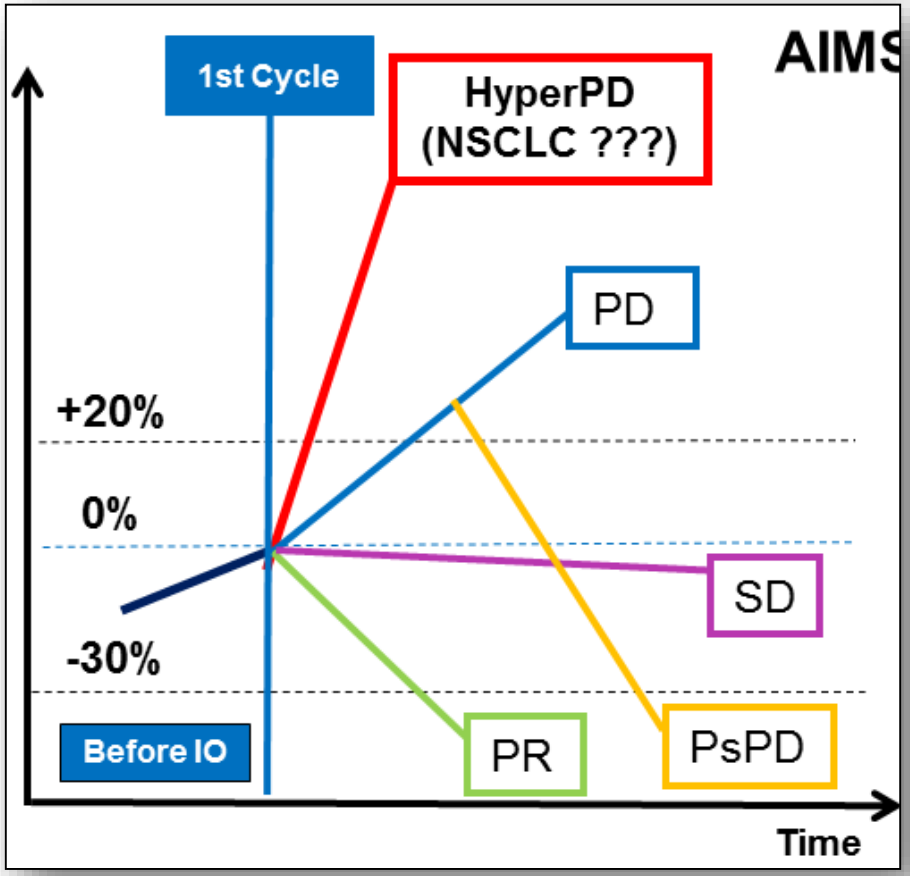
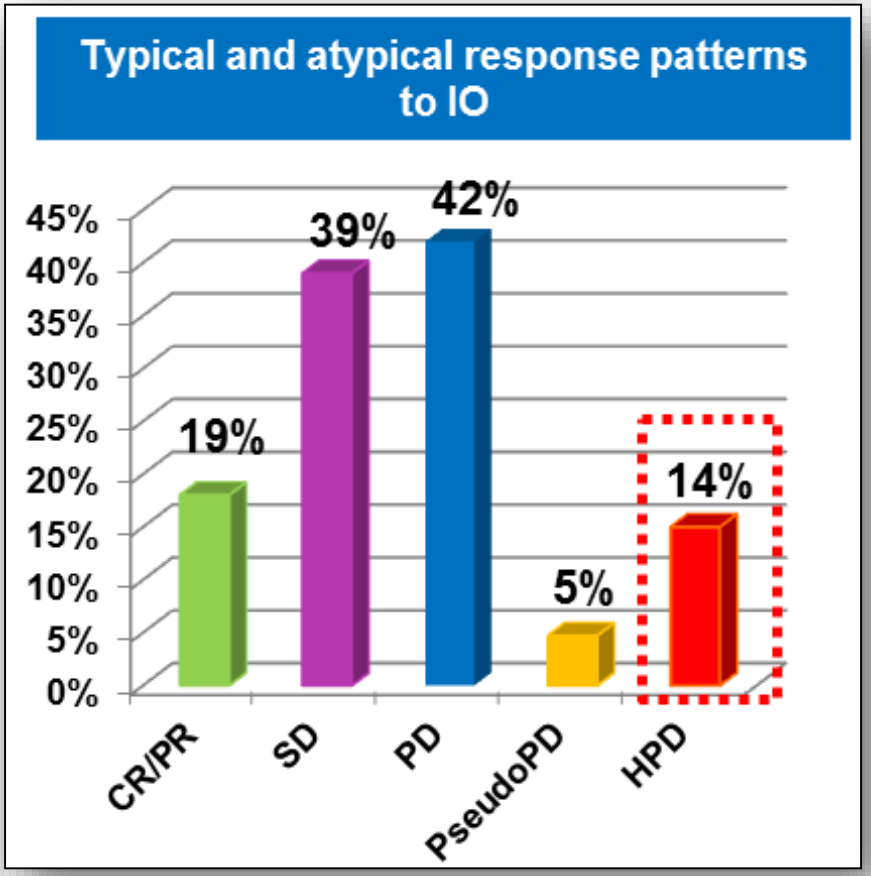
Hyperprogression





- HPD : 56 patients sur 406 (16%)
- Pseudo progression : 19 patients sur 406 (4,6%)

Ferrara et al – WCLC 2017 – abstract MA 10.11
Ferrara et al – ESMO 2017 – abstract 1306PD

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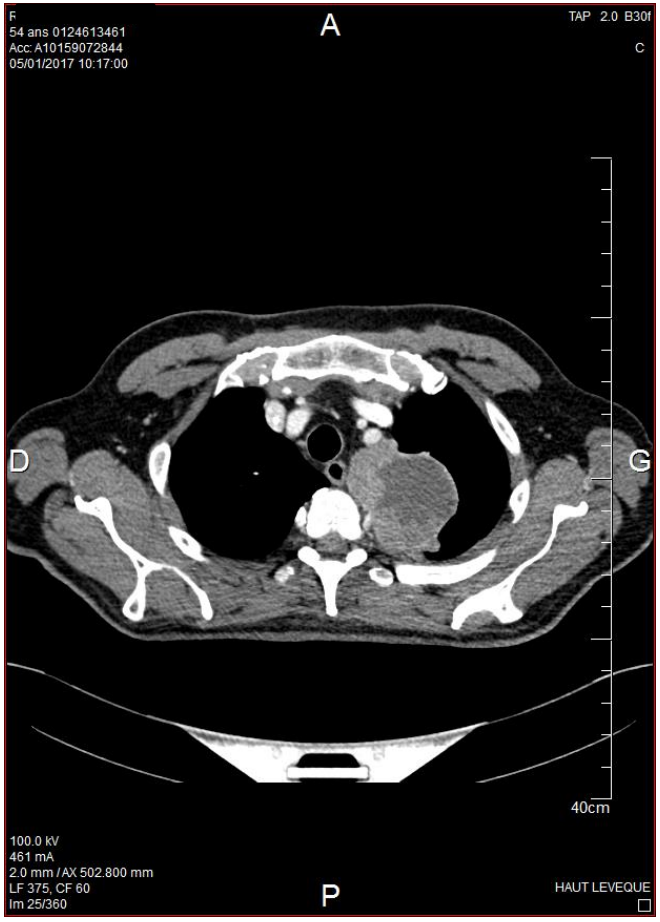
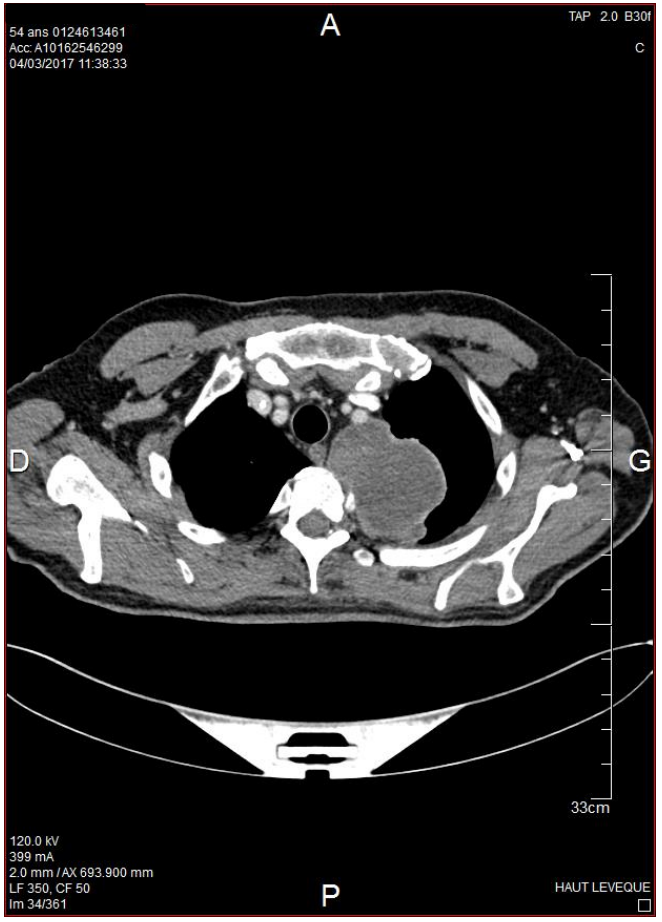
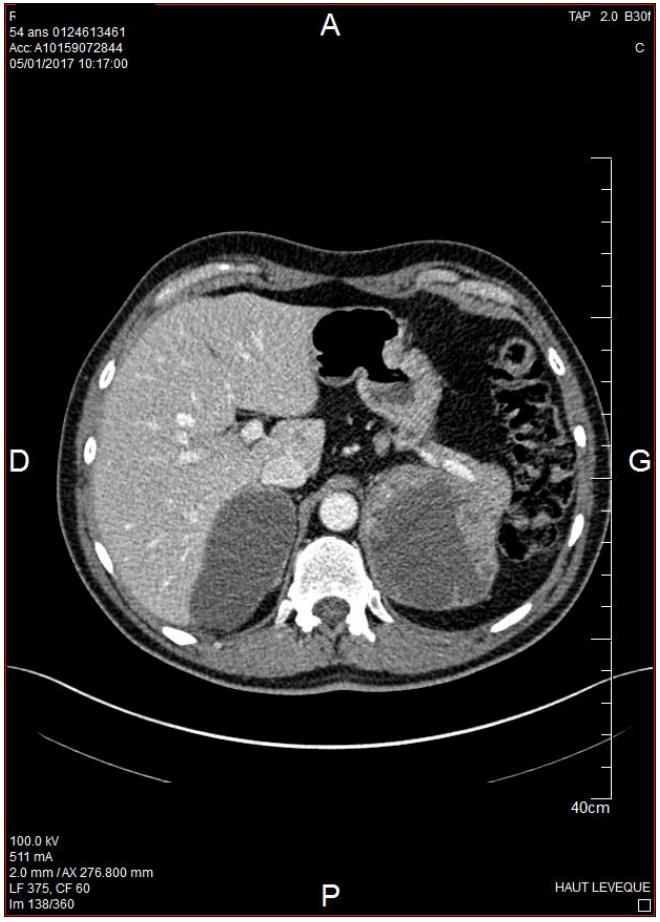
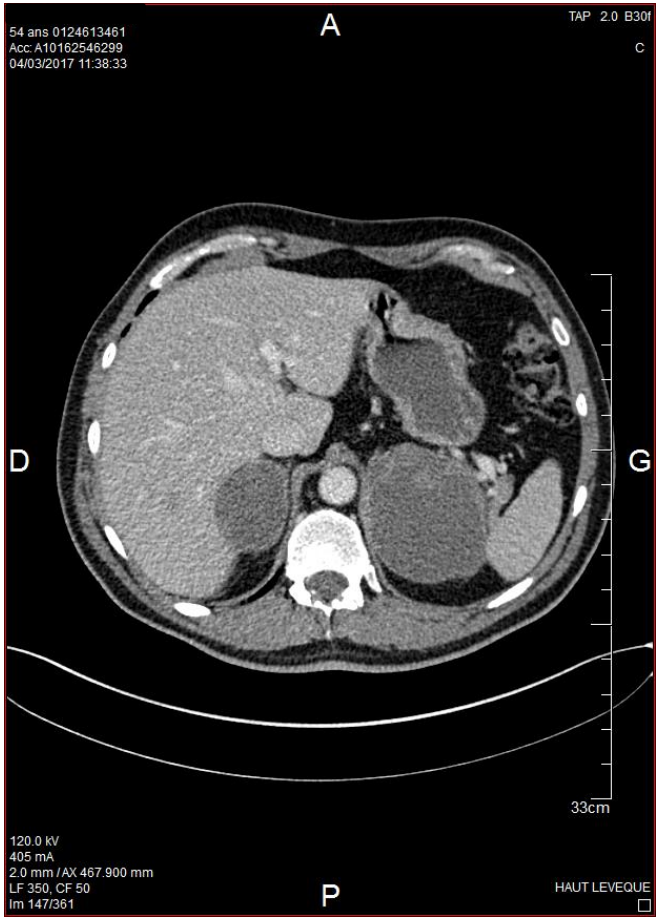
Ralentissement de la progression









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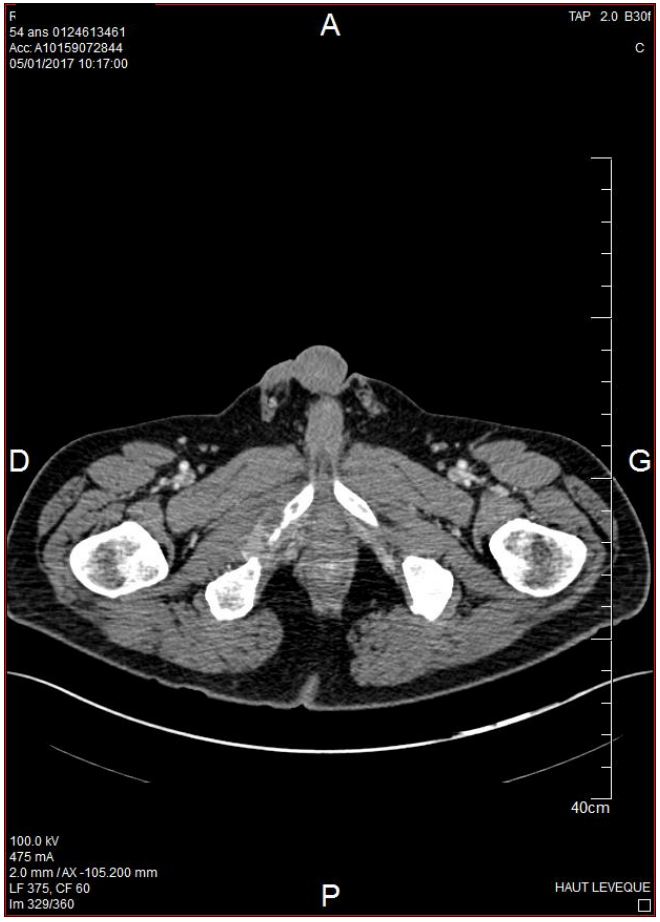

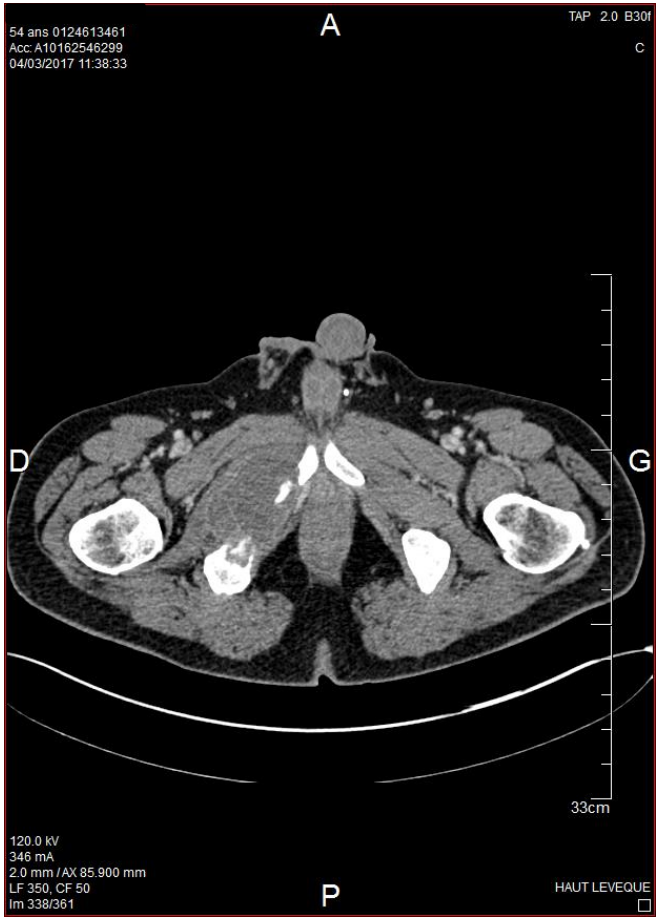

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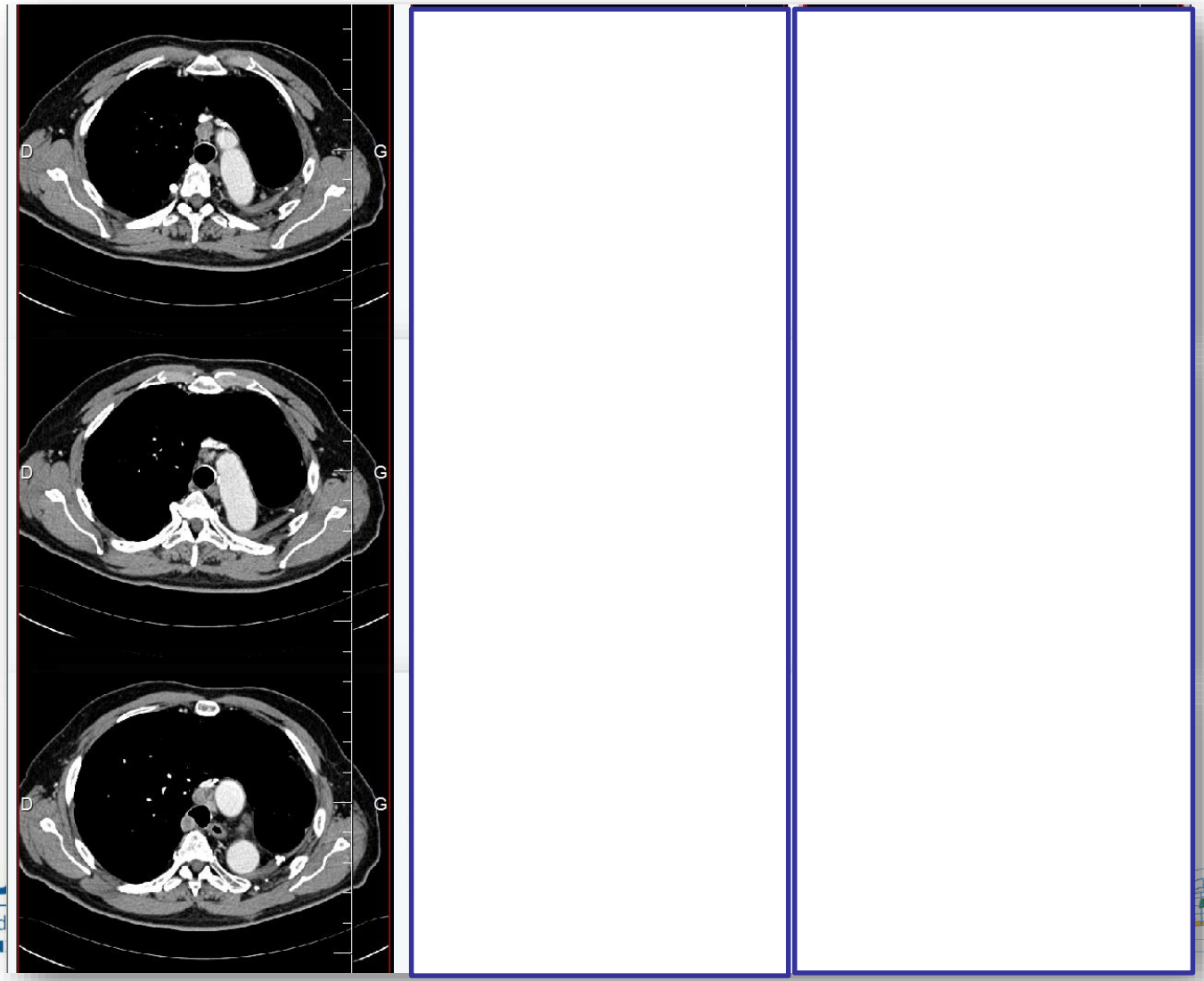
Pseudo-progression

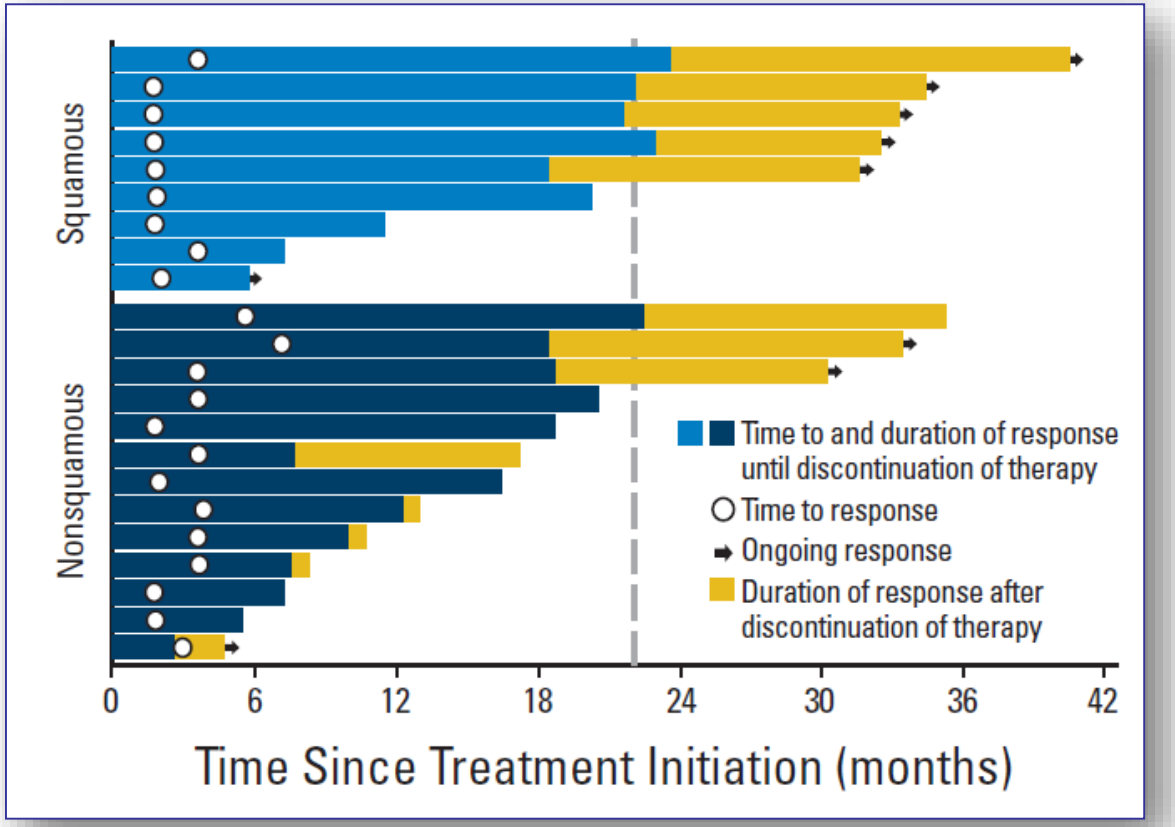
- Carcinome épidermoïde bronchique sous Nivolumab en 2e ligne

14/03/2016 26/09/2016 20/12/2016



Arrêt du traitement chez les patients répondeurs ?

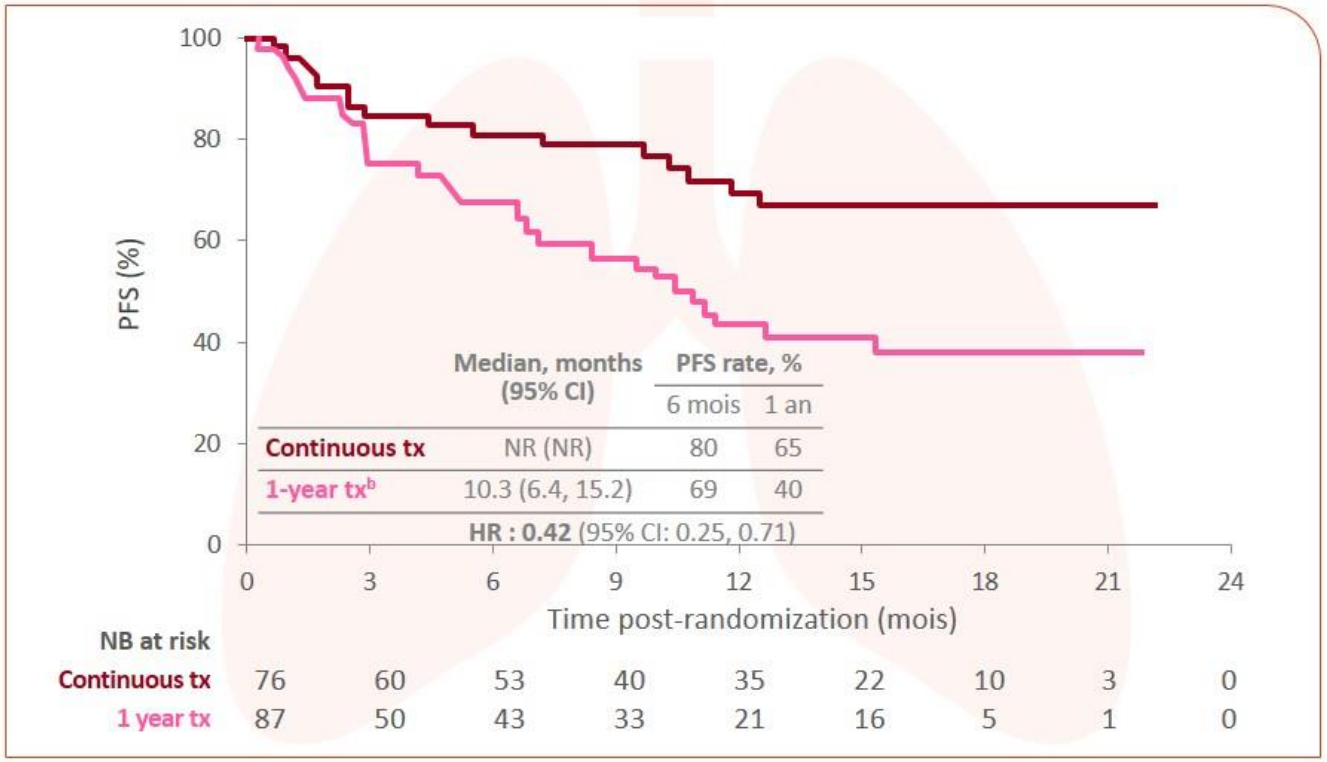
- Nivolumab en phase I
- 18 arrêts de traitement en situation de réponse
- 9 patients en réponse post-traitement supérieur à 9 mois



Gettinger et al. JCO 2015 ; 33 : 2004-12

Arrêt du traitement chez des répondeurs

CheckMate 153 : survie sans progression poursuite du Nivolumab *vs* interruption à 1 an



Spigel D.R. *et al.* - *ESMO® 2017* - Abs. 1297

Spiegel et al. ESMO 2017 – Abs.#1297

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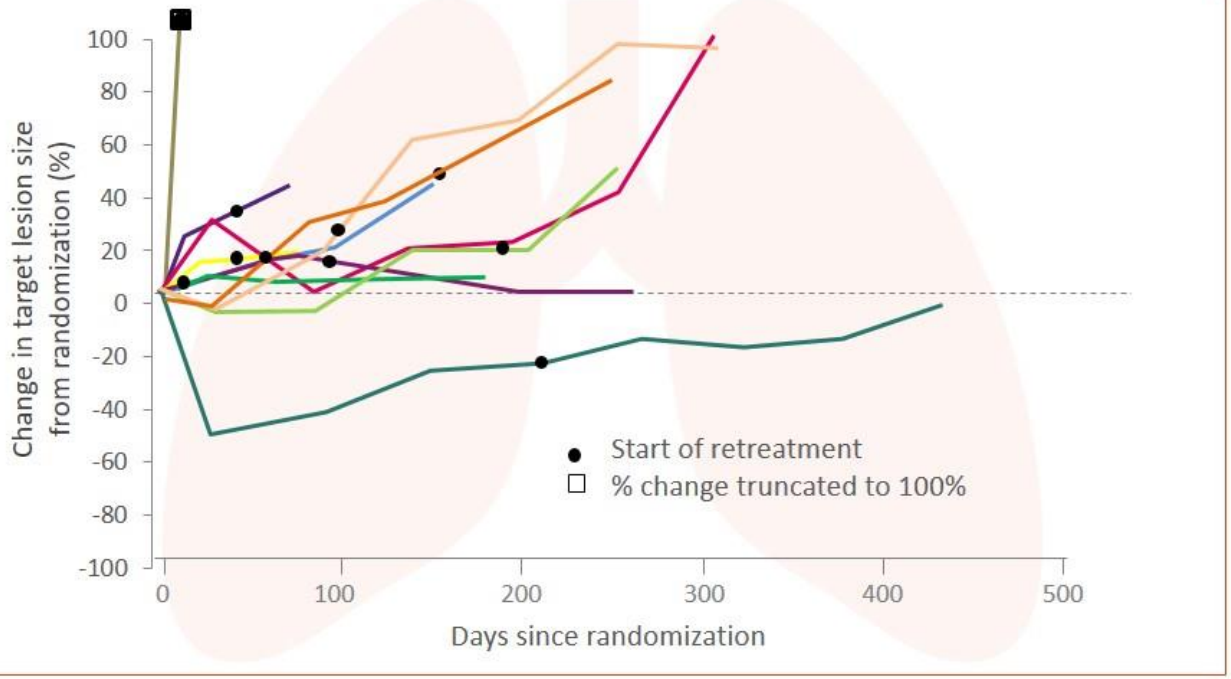
Arrêt du traitement chez des répondeurs

Modification de la taille des lesions cible après reprise du traitement



Spigel D.R. *et al.* - *ESMO® 2017* - Abs. 1297

Spiegel et al. ESMO 2017 – Abs.#1297

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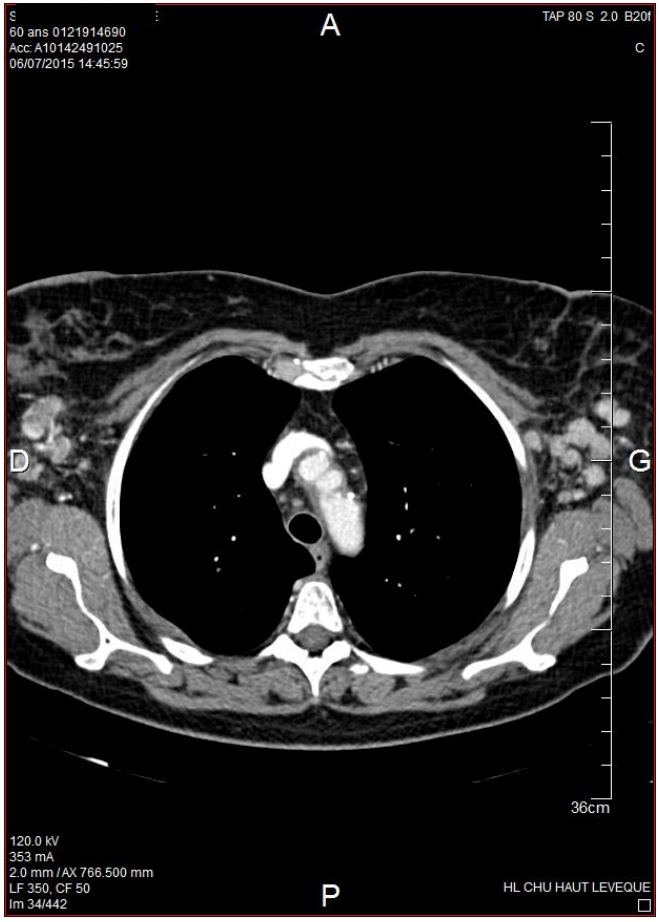
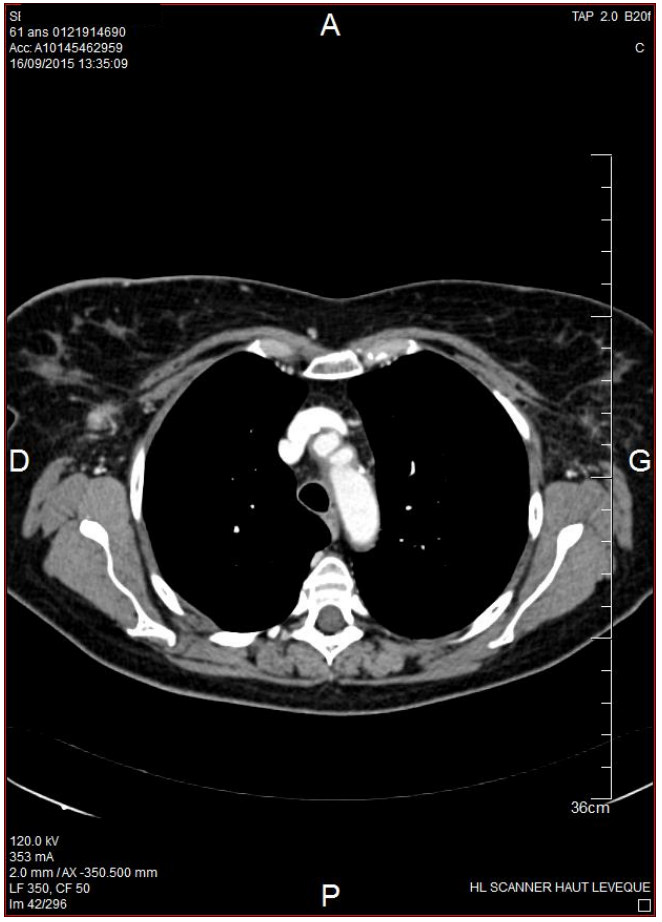
Mme S. : Nivolumab 1ère séquence :





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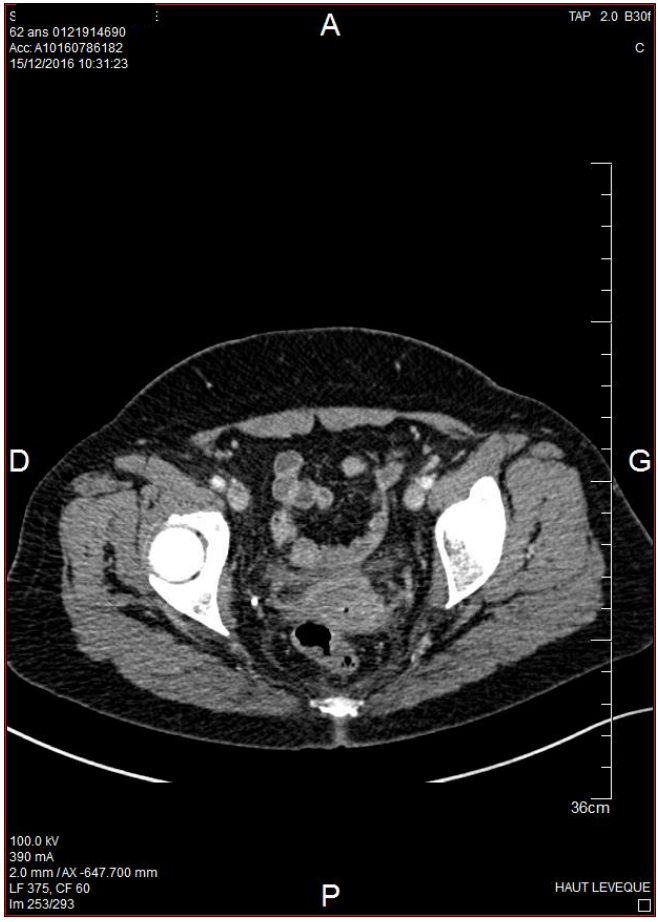

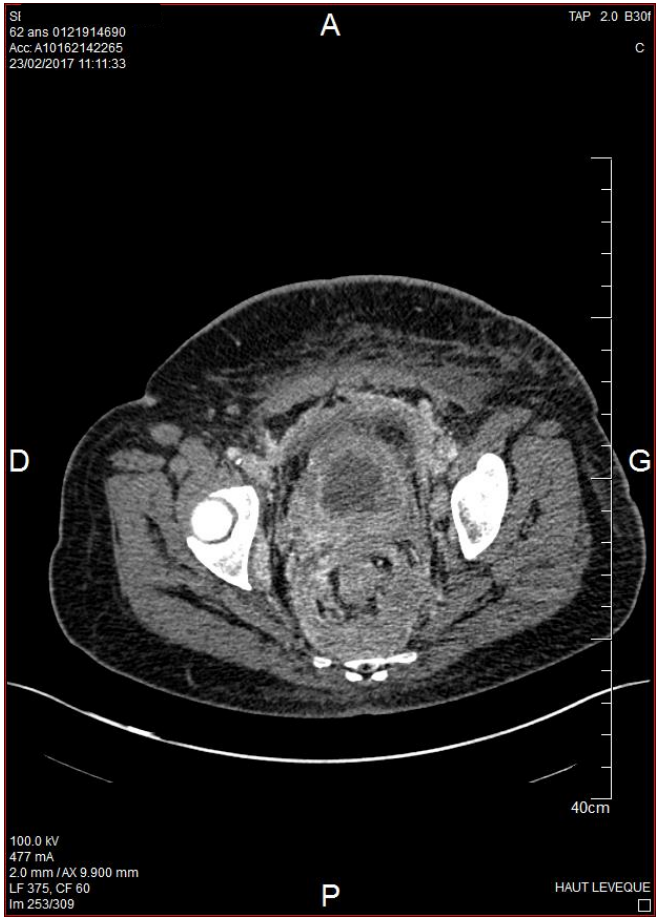

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Merci de votre attention

Pembrolizumab et métastases cérébrales

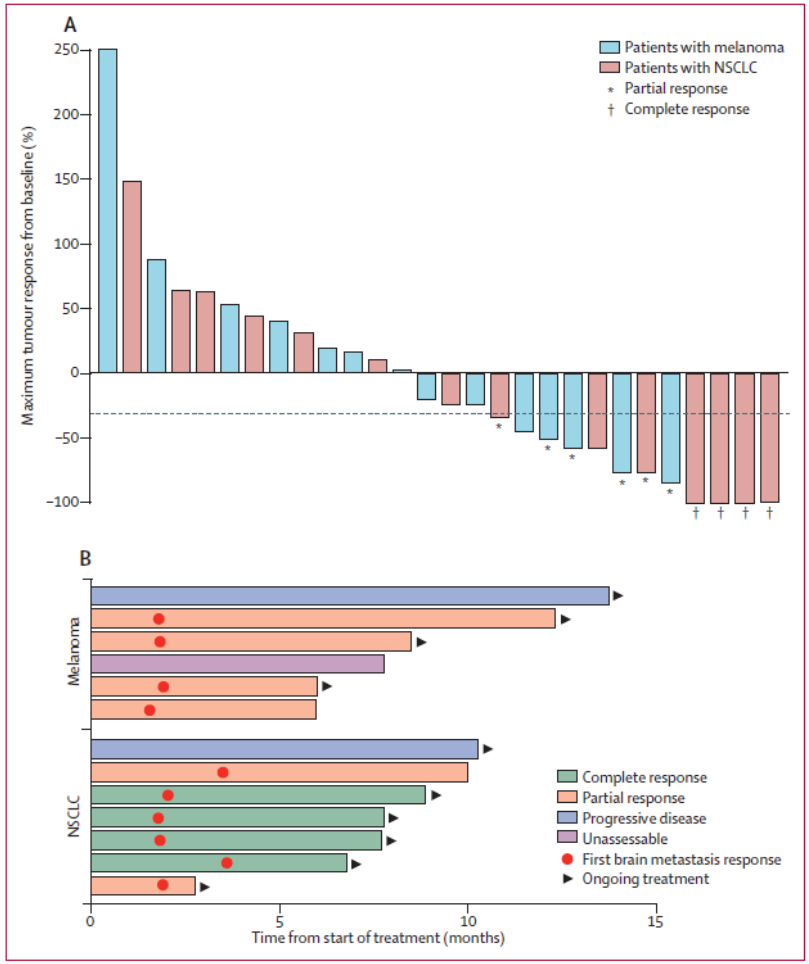

Figure: **Brain metastasis response in assessable patients with melanoma or NSCLC**
(A) Best brain metastasis response by modified RECIST in assessable patients. The dashed line represents the −30% cut-off that defines an objective response. Two patients, one with melanoma and one with NSCLC, had progressive disease despite more than 30% shrinkage of target lesions due to the development of new brain metastases and unequivocal progression of non-target lesions, respectively. Eight patients were unassessable for brain response because of rapid systemic progression (melanoma, n=3; NSCLC, n=4) and intralesional haemorrhage (melanoma; n=1). (B) Time to brain metastasis response and duration of treatment. Bars represent individual patients who achieved a brain metastasis response or remained on trial for 6 months or longer. Three patients remained on treatment for 6 months or longer because of clinical benefit despite having either disease progression or being unassessable because of haemorrhagic lesions in the brain. NSCLC=non-small-cell lung cancer.

- Phase II
- PDL1 +
- Métastases cérébrales non traitées, asymptomatiques, sans corticoïdes
- Mélanome :
  - 4/18 réponses (22%)
- CBNPC
  - 6/18 réponses (33%)
  - 4 non évaluables (progression systémique) 2 stables, 6 progressions
- Bonne corrélation réponse cérébrale / réponse extra cérébrale

Goldberg et al. Lancet Oncol 2016 17 :976-983