NOUVEAUTÉS EN IMMUNOTHÉRAPIE : DE LA TÊTE AUX PIEDS

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1ER NOVEMBRE 2019

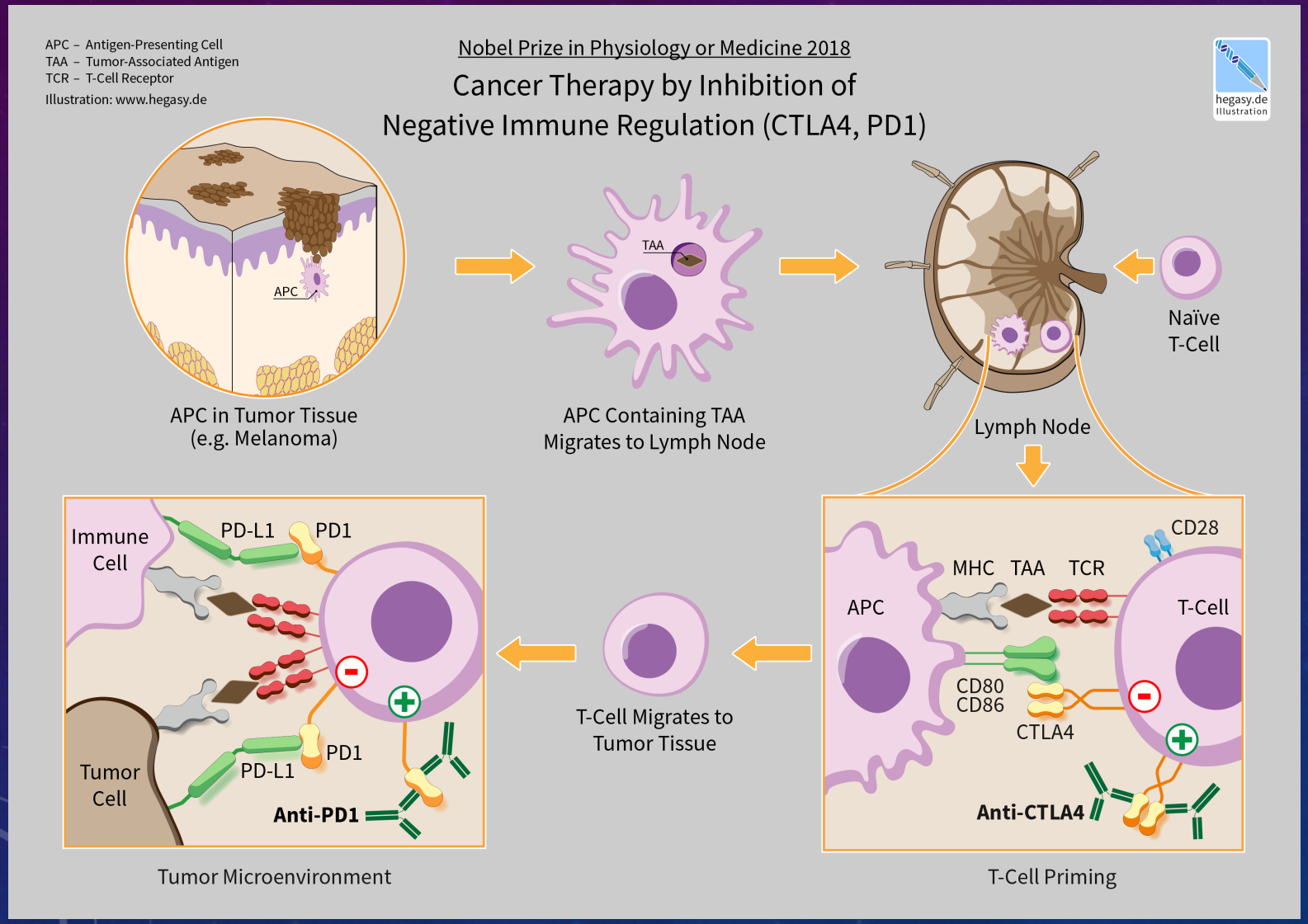
CONFLITS D'INTÉRÊT

Aucun conflit à déclarer

OBJECTIFS

- Revoir brièvement la pharmacologie de l’immunothérapie dans le traitement du cancer;
- Discuter des nouveaux usages cliniques de cette classe de médicaments;
- Aborder certaines données décevantes concernant l’immunothérapie du cancer;
- Présenter les cibles thérapeutiques à venir;
- Discuter des réactions indésirables causées par l’immunothérapie.

PHARMACOLOGIE 101… OU PLUTÔT PD-(L)1 ET CIE



Tiré du site:
www.hegasy.de

ENCORE UNE ANNÉE FASTE POUR L'IMMUNOTHÉRAPIE

- Mélanome malin
- Carcinome épidermoïde cutané
- Carcinome de Merkel
- Une première : le cancer du sein
- CPNPC… et oui encore!
- Carcinome rénal
- Cancer urothélial
- CPPC

MÉLANOME MALIN

Mélanome adjuvant

- Nivolumab X 1 an
- Pembrolizumab X 1 an

Mélanome métastatique

- Données de survie à 5 ans de l’étude Checkmate 067

NIVOLUMAB ADJUVANT : CHECKMATE-238

- Inscrit à la LE en mai 2019
- RCT, phase III, 906 patients
- Mélanome de stade IIIb, IIIc ou IV complètement réséqué
- Randomisés à 1 an de nivolumab 3 mg/kg IV q 2 semaines ou ipilimumab 10 mg/kg IV q 3 semaines X 4 doses puis q 12 semaines
- Objectif principal : Survie sans récidive
- Mise à jour des données: Weber, ASCO 2018, abstract 9502

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

Novembre 2017

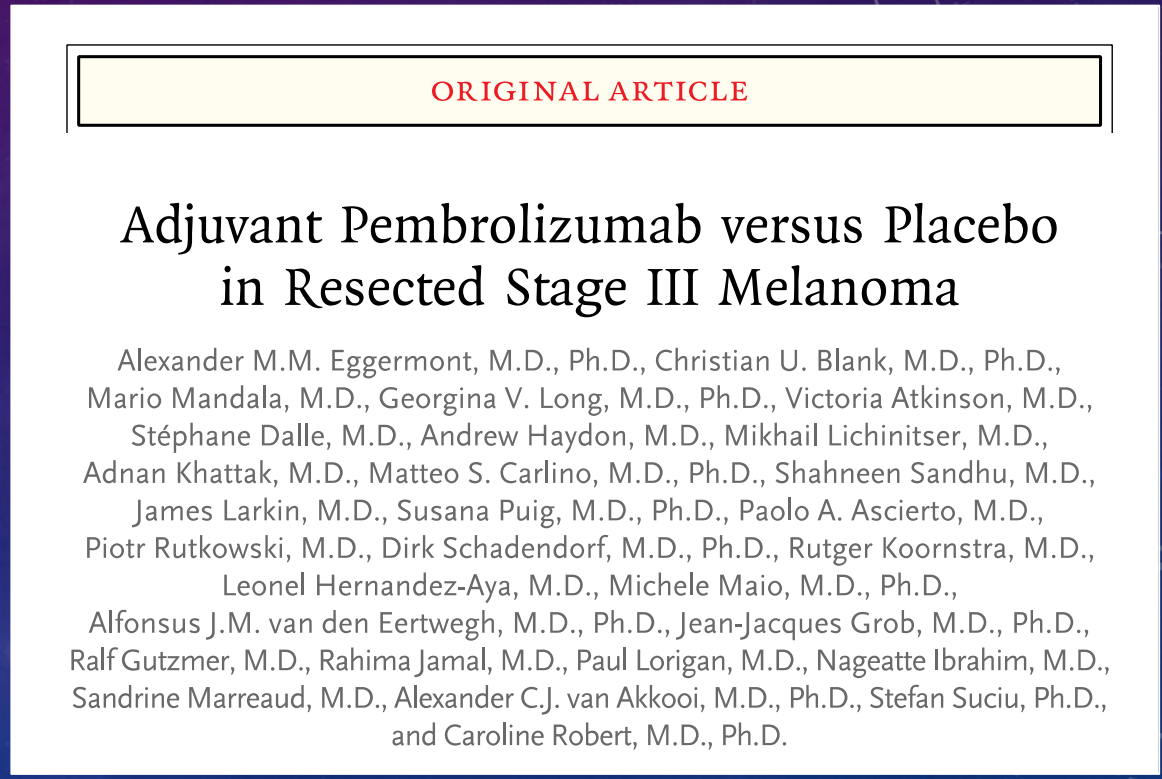
CHECKMATE-238 RÉSULTATS (2018)

Paramètre d'efficacité	Nivolumab	Ipilimumab	RRI (IC95%) et valeur p
Survie médiane sans récidive	30,8 mois	24,1 mois	0,66 (0,54-0,81) P<0,001
Survie sans récidive estimée à 30 mois	60,4%	44,4%	-

Résultats obtenus avec une durée minimale de suivi de 24 mois

PEMBROLIZUMAB ADJUVANT : KEYNOTE-054

- Évaluation favorable de l'INESSS en juin 2019 – ministre sursoit
- Étude de phase III, multicentrique, randomisée et contrôlée contre placébo
- 1019 patients
- Mélanome de stade III ou IV complètement réséqué
- Sujets randomisés à pembrolizumab 200mg IV q3 semaines X 18 doses ou placebo



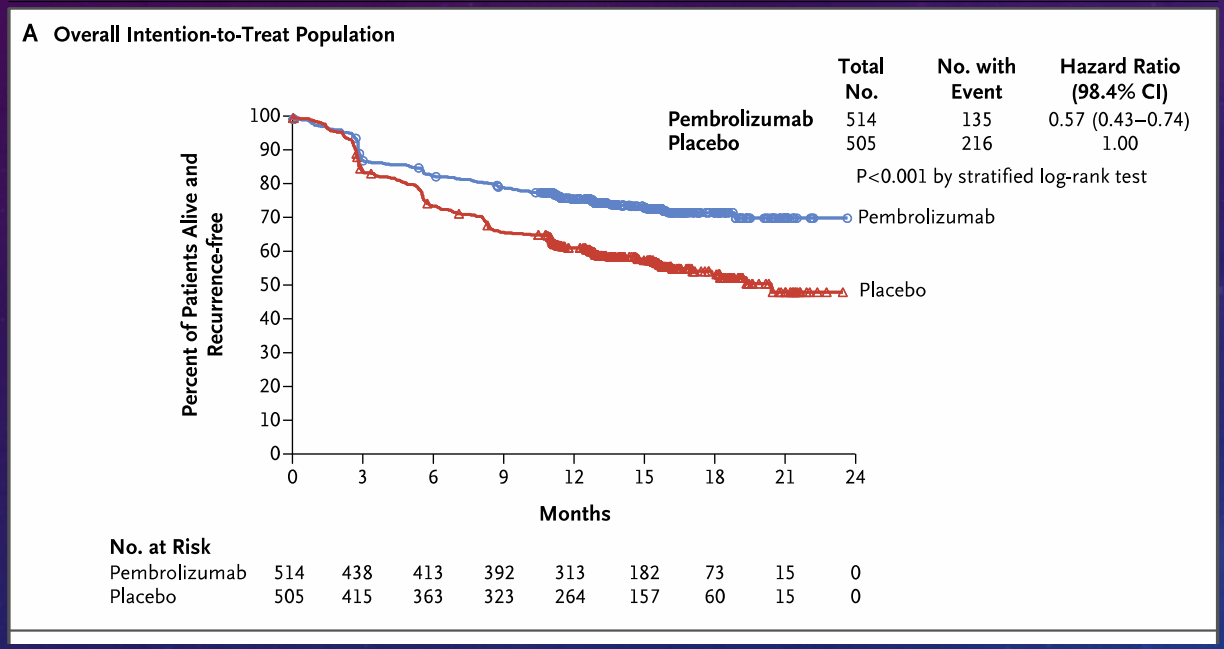
ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., Ph.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.

Avril 2018

RÉSULTATS : KEYNOTE-054



Subgroup	Pembrolizumab	Placebo	Hazard Ratio (99% or 98.4% CI)	P Value for Interaction
	no. of events/total no.			
Tumor PD-L1 expression				0.60
Positive	102/428	176/425	0.54 (0.39–0.74)	
Negative	20/59	27/57	0.60 (0.28–1.28)	
Indeterminate	13/27	13/23	0.80 (0.29–2.19)	
Sex				0.49
Male	86/324	138/304	0.53 (0.37–0.76)	
Female	49/190	78/201	0.62 (0.39–1.00)	
Age				0.86
18 to <65 yr	96/389	154/379	0.57 (0.41–0.80)	
≥65 yr	39/125	62/126	0.55 (0.32–0.93)	
AJCC 2009 melanoma classification				0.69
Stage IIIA	6/77	15/76	0.38 (0.11–1.31)	
Stage IIIB	62/240	97/232	0.58 (0.38–0.88)	
Stage IIIC	67/197	104/197	0.58 (0.38–0.86)	
No. of positive lymph nodes				0.78
1	44/227	80/237	0.53 (0.33–0.86)	
2 or 3	46/177	76/166	0.52 (0.32–0.85)	
≥4	45/110	60/102	0.62 (0.37–1.03)	
Type of positive lymph nodes				0.86
Microscopic	35/187	50/161	0.56 (0.32–0.99)	
Macroscopic	100/327	166/344	0.59 (0.42–0.81)	
Ulceration				0.12
No	62/230	94/251	0.69 (0.45–1.05)	
Yes	64/208	101/197	0.52 (0.35–0.79)	
Not reported	9/76	21/57	0.30 (0.11–0.84)	
Lymph-node and ulceration status				0.35
Microscopic, ulceration	25/94	31/75	0.58 (0.29–1.15)	
Microscopic, no ulceration	10/89	19/85	0.48 (0.17–1.30)	
Macroscopic, ulceration	39/114	70/122	0.51 (0.31–0.86)	
Macroscopic, no ulceration	52/141	75/166	0.79 (0.50–1.26)	
BRAF mutation status				0.89
Wild type	69/233	97/214	0.61 (0.41–0.92)	
V600E mutation	54/186	94/209	0.59 (0.38–0.92)	
All Patients	135/514 (26.3%)	216/505 (42.8%)	0.57 (0.43–0.74)	

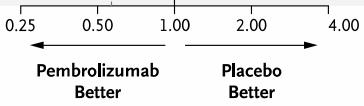
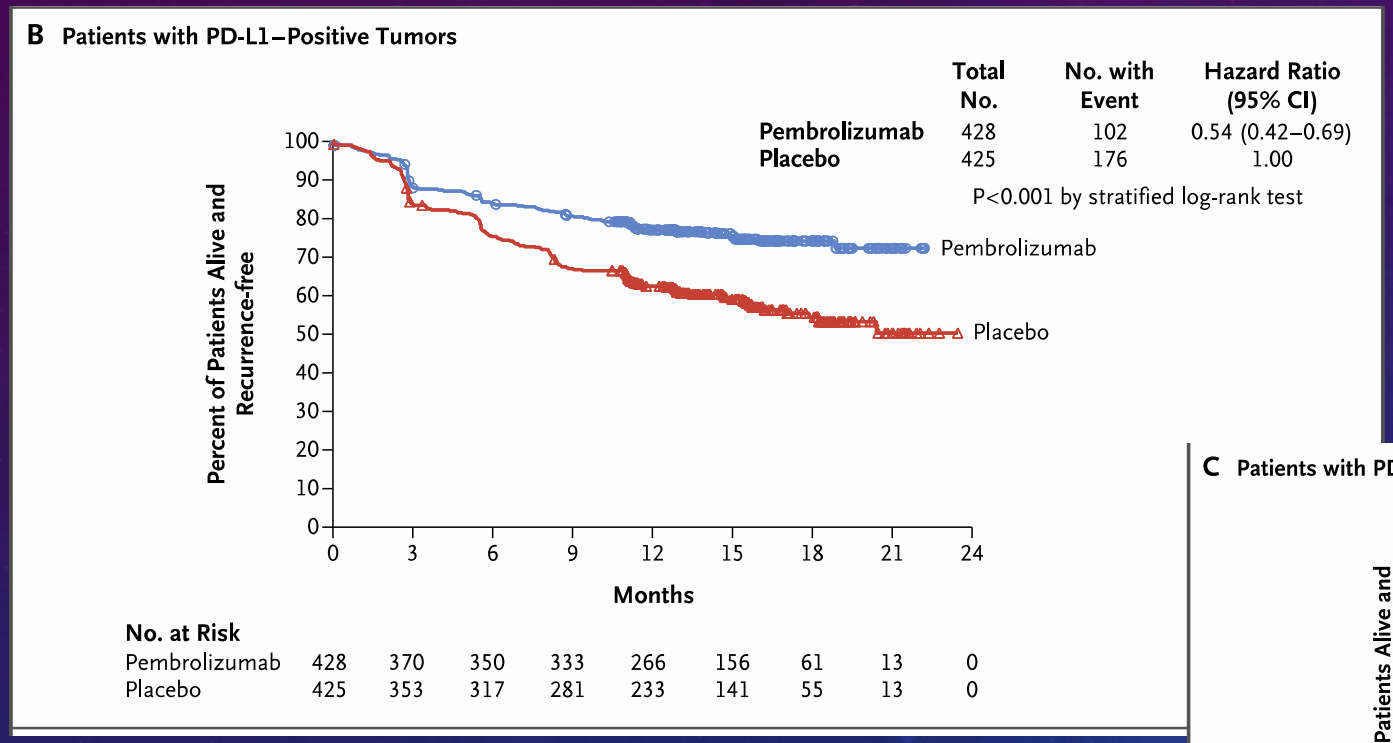
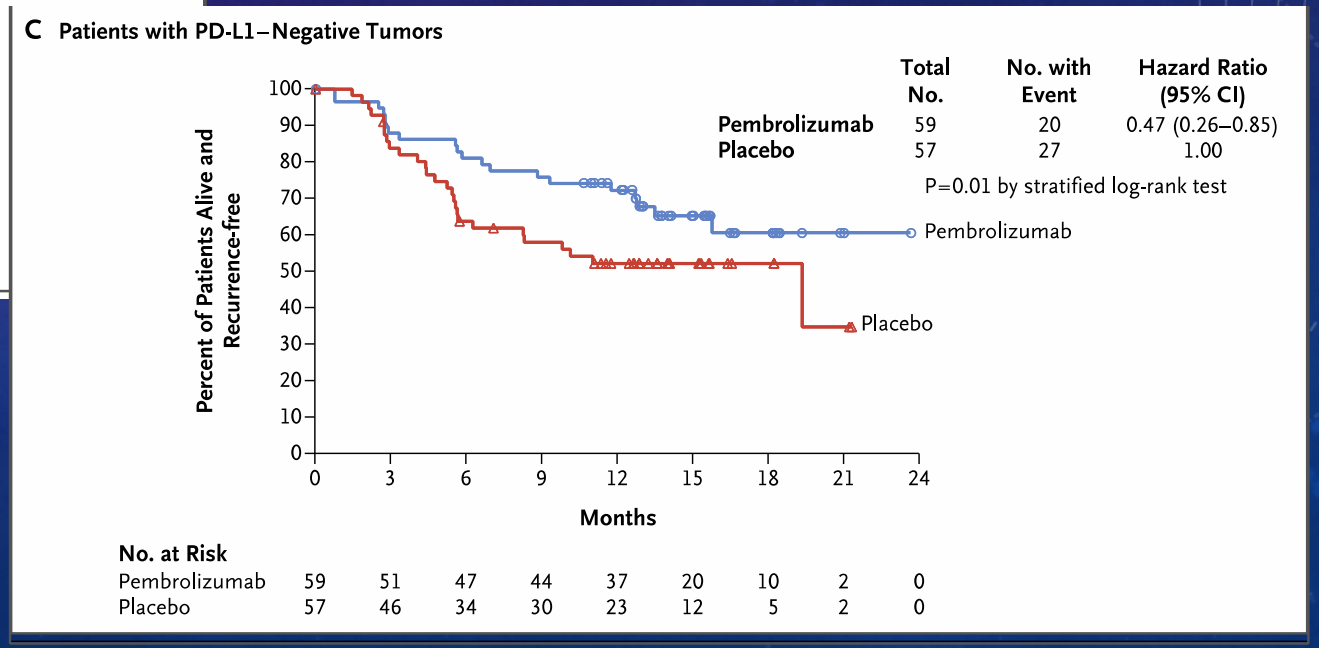


Figure 3. Forest Plot of Recurrence-free Survival According to Subgroup.

An unstratified univariate Cox model was used to estimate the hazard ratios for the risk of recurrence or death in the pembrolizumab group as compared with the placebo group among all the patients. An unstratified Cox model including the trial group, a covariate of interest (e.g., age 18 to <65 vs. ≥65 years) and the interaction term (e.g., age × treatment) was used to perform the interaction test and estimate the hazard ratios for the subgroups. P values were yielded by the test of the treatment difference in the overall intention-to-treat population or by the test of interaction; for each, the Wald test was used. The sizes of the blue boxes are nonlinearly proportional to the numbers of events. The green diamond is centered on the overall hazard ratio (dashed line) and covers its 98.4% confidence interval. In the subgroup analyses, 99% confidence intervals (blue lines) are presented. Data on lymph-node and ulceration status were not available for 133 patients; data on *BRAF* mutation status were not available for 65 patients, and the *BRAF* mutation present differed from V600E in 112 patients. P<0.001 in the unadjusted analysis of the overall effect of pembrolizumab versus placebo on recurrence-free survival. AJCC denotes American Joint Committee on Cancer 2009 classification, 7th edition.[14]

RÉSULTATS : KEYNOTE-054





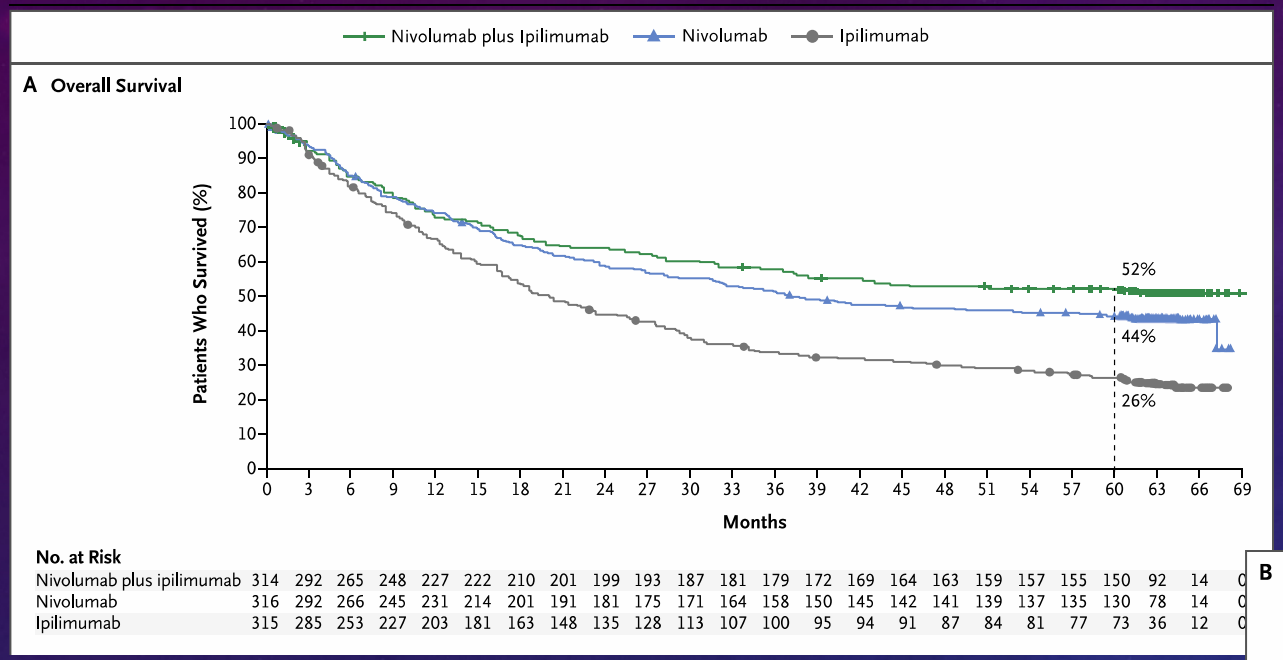
IPILIMUMAB + NIVOLUMAB OÙ EN SOMMES-NOUS EN 2019?

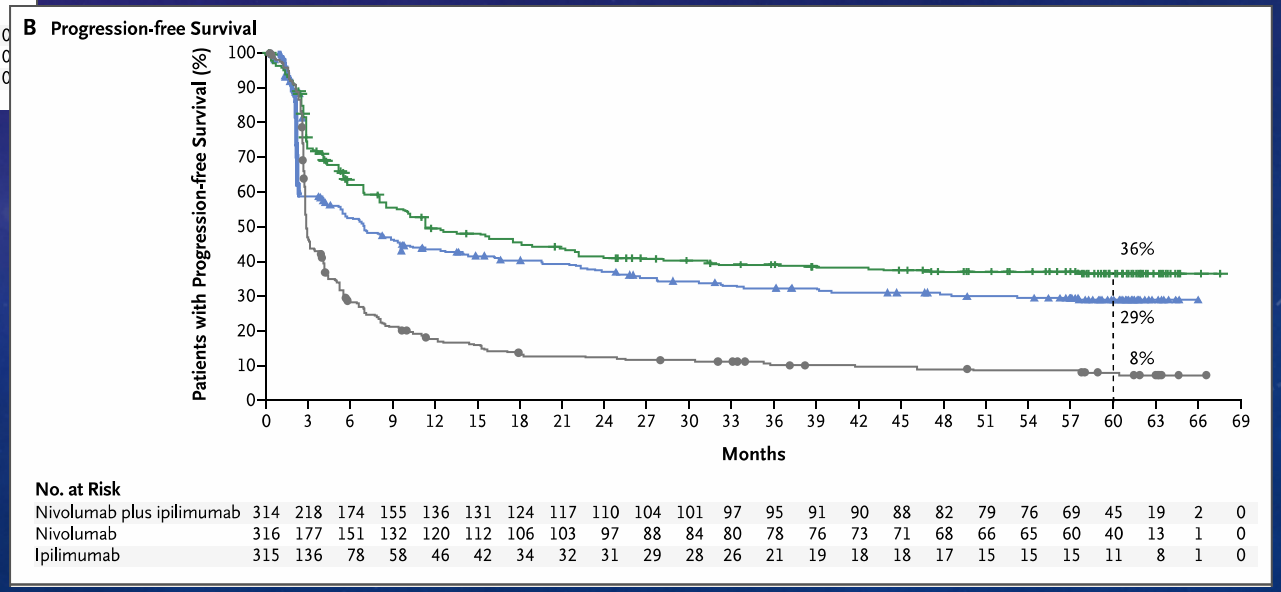
Inscrit à la LE pour le traitement de 1ère intention du mélanome métastatique pour les patients avec un statut PD-L1 de moins de 5% en mai 2019

Réévaluation par l'INESSS et modification du critère de remboursement en octobre 2019 : régime permis peu importe le taux d'expression du PD-L1

Impact budgétaire significatif pour certains établissements

DONNÉES DE SURVIE À 5 ANS DE L'ÉTUDE CHECKMATE 067





Paramètre	Ipi+nivolumab	Nivolumab	Ipilimumab	RRI (IC95%)	Commentaire
Durée médiane de survie globale	> 60 mois	36,9 mois	19,9 mois	0,52 (0,42-0,64) 0,63 (0,52-0,76) 0,83 (0,67-1,03)	Ipi+nivo vs ipi Nivo vs ipi Ipi+nivo vs nivo
Taux de survie à 5 ans	52%	44%	26%		
Durée médiane de SSP	11,5 mois	6,9 mois	2,9 mois	0,42 (0,35-0,51) 0,53 (0,44-0,64) 0,79 (0,64-0,96)	Ipi+nivo vs ipi Nivo vs ipi Ipi+nivo vs nivo
Taux de SSP à 5 ans	36%	29%	8%		

DONNÉES DE SURVIE À 5 ANS DE L'ÉTUDE CHECKMATE 067

CARCINOME ÉPIDERMOÏDE CUTANÉ

Cémiplimab (Libtayo®)

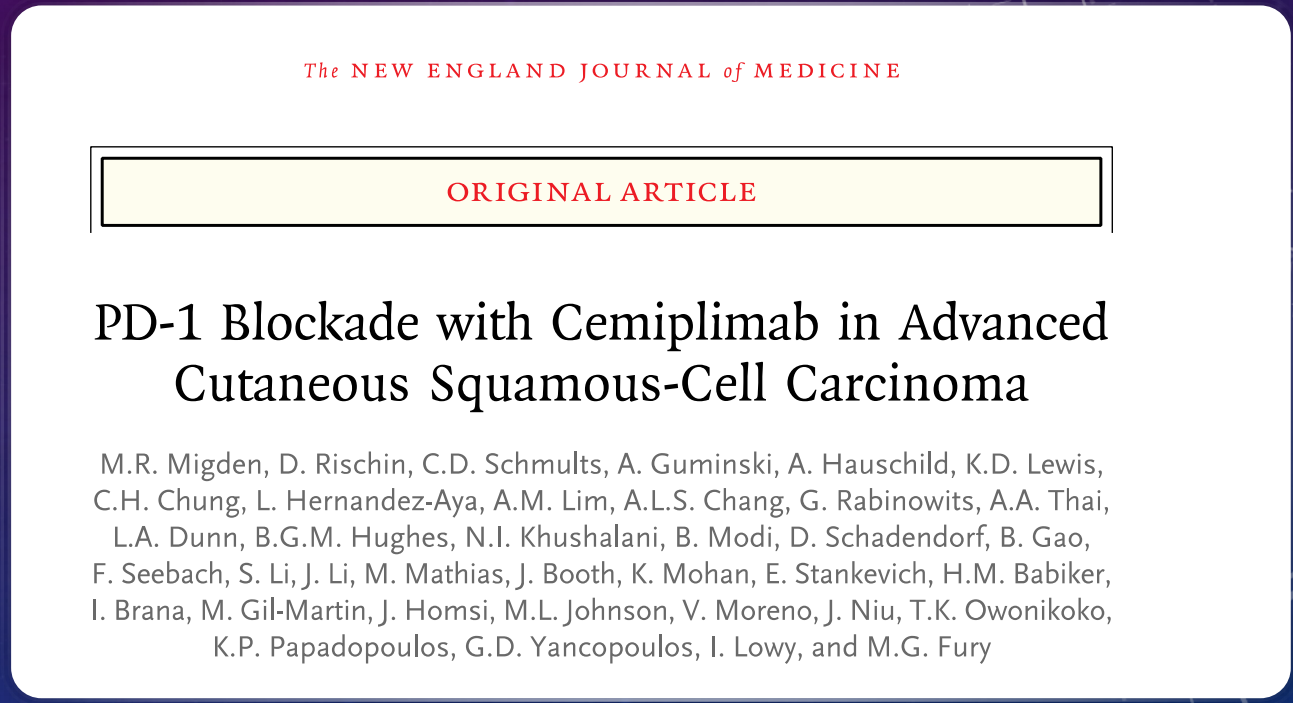
Nouvelle immunothérapie : anti-PD1

Rationnelle : Aucune thérapie systémique n’est approuvée pour ce type de cancer. Le fardeau mutationnel tumoral est élevé ce qui laissait présager une certaine efficacité de l’immunothérapie.

En évaluation à l’INESSS

CÉMIPLIMAB

- Publication des résultats de la cohorte d'expansion de l'étude de phase I et de la phase II de l'étude
- Phase I : patients avec maladie localement avancée ou métastatique
  - But : déterminer la DMT
- Phase II : maladie métastatique uniquement
  - But : RTO



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

Juin 2018

CÉMIPLIMAB

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Expansion Cohorts of the Phase 1 Study (N = 26)	Metastatic-Disease Cohort of the Phase 2 Study (N = 59)
Age		
Median (range) — yr	73 (55–88)	71 (38–93)
≥65 yr — no. (%)	21 (81)	43 (73)
Male sex — no. (%)	21 (81)	54 (92)
ECOG performance status score — no. (%)†		
0	10 (38)	23 (39)
1	16 (62)	36 (61)
Primary site of cutaneous squamous-cell carcinoma — no. (%)		
Head or neck	18 (69)	38 (64)
Arm or leg	5 (19)	12 (20)
Trunk	2 (8)	9 (15)
Penis	1 (4)	0
Previous systemic therapy for cutaneous squamous-cell carcinoma — no. of patients (%)‡		
No regimens	8 (31)	26 (44)
Any regimen	15 (58)	33 (56)
1 regimen	15 (58)	22 (37)
≥2 regimens	0	11 (19)
Previous radiotherapy for cutaneous squamous-cell carcinoma — no. (%)	20 (77)	50 (85)
Extent of cutaneous squamous-cell carcinoma — no. (%)		
Distant metastasis	8 (31)	45 (76)
Regional metastasis only	8 (31)	14 (24)
Locally advanced progression only	10 (38)	0

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.

† Eastern Cooperative Oncology Group (ECOG) performance status scores are measured on a 5-point scale, with higher scores indicating greater disability.

‡ In the phase 1 cohorts, previous systemic therapies were unknown for 3 patients. In the phase 2 cohort, 14 patients had received previous systemic therapy for cutaneous squamous-cell carcinoma with palliative intent.

CÉMIPLIMAB

Table 2. Tumor Response to Cemiplimab, as Assessed by Independent Central Review.*

Outcome	Expansion Cohorts of the Phase 1 Study (N = 26)	Metastatic-Disease Cohort of the Phase 2 Study (N = 59)
Best overall response — no. (%)†		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated‡	3 (12)	7 (12)
Nontarget lesions only§	1 (4)	4 (7)
Objective response — % (95% CI)	50 (30–70)	47 (34–61)
Durable disease control — % (95% CI)	65 (44–83)	61 (47–74)
Median observed time to response (range) — mo¶	2.3 (1.7–7.3)	1.9 (1.7–6.0)

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.

† To determine the tumor response, results of whole-body imaging were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In the phase 2 study, digital medical photographs were evaluated according to protocol-specified composite response criteria.

‡ The data include patients who did not undergo imaging studies after the initiation of therapy or had imaging studies that could not be evaluated by independent central review.

§ The data include patients who had nontarget lesions only (i.e., lesions that could not be measured according to RECIST, version 1.1) and did not have disappearance of all lesions or unequivocal progression.

¶ The data are from patients who had a confirmed complete or partial response.

CARCINOME DE MERKEL

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Céleste Lebbé, Gerald P Linette, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie Cuillerot, Paul Nghiem

Lancet Oncology, 2016

- Avelumab = anti PDL1
- Carcinome de Merkel = cancer cutané rare, agressif et à mauvais px lors de maladie avancée
- Historiquement : doublet de platine comme unique traitement
- Actuellement, avelumab remboursé en traitement de 2^{e} intention du carcinome de Merkel

- Etude JAVELIN Merkel 200
- Essai de phase II, non-comparatif de 88 patients
- Carcinome de Merkel métastatique, réfractaire à la chimiothérapie
- Avelumab 10 mg/kg IV q 2 semaines ad progression
- Objectif principal : RTO

	Confirmed best overall response* (n=88)
Complete response	8 (9%)
Partial response	20 (23%)
Stable disease	9 (10%)
Progressive disease	32 (36%)
Non-complete response/ non-progressive disease†	1 (1%)
Non-assessable‡	18 (20%)
Objective response§	31·8% (21·9–43·1)

Data are n (%) or % (95·9% CI). *Confirmed best overall response was according to independent review committee assessment and Response Evaluation Criteria in Solid Tumors version 1.1. †One patient did not have measurable disease at baseline and thus a best overall response of partial response or stable disease could not be distinguished. ‡Patients not assessable for a confirmed best overall response had no baseline lesions identified by the independent review committee (n=4), baseline but no post-baseline assessments (n=10; four patients died within 6 weeks after the start of treatment and six additional patients discontinued study treatment in the first 6 weeks), all non-assessable post-baseline assessments (n=2), no post-baseline tumour assessment before the start of new anticancer therapy (n=1), or stable disease of insufficient duration (<6 weeks after start date without further tumour assessment; n=1). §A repeated CI for the objective response in the modified intention-to-treat analysis set (95·9% CI for the primary analysis) was calculated to account for the group sequential testing approach.[40]

Table 2: **Confirmed best overall response**

ÉTUDE JAVELIN MERKEL 200 : RÉSULTATS

Taux de survie sans progression estimé à 6 mois	40 % (IC95 % : 29 % à 50 %)
Taux de survie globale estimé à 6 mois	69 % (IC95 % : 58 % à 78 %)

	Confirmed best overall response* (n=88)
Complete respon	
Partial respon	
Stable disea	
Progressive	
Non-compl non-progre	
Non-assess	
Objective re	

Data are n (%) independent r Solid Tumors and thus a bes distinguished no baseline le baseline but n 6 weeks after treatment in t (n=2), no post therapy (n=1) without furthe response in the analysis) was calcu

Table 2: **Confirmed best overall response**

Perspectives futures de l'avelumab en carcinome de Merkel : intéressantes

UNE PREMIÈRE : LE CANCER DU SEIN

- En évaluation à l'INESSS actuellement
- RCT de phase III, 902 patientes
- Cancer du sein métastatique ou inopérable
- Triple négatif
- Objectif principal : SSP et SG pour la population ITT et la population PDL1+

Nab-paclitaxel 100 mg/m^2 jours 1, 8, 15 +/- atézolizumab 840mg jours 1-15 ou placebo ad progression

Cycles de 28 jours

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

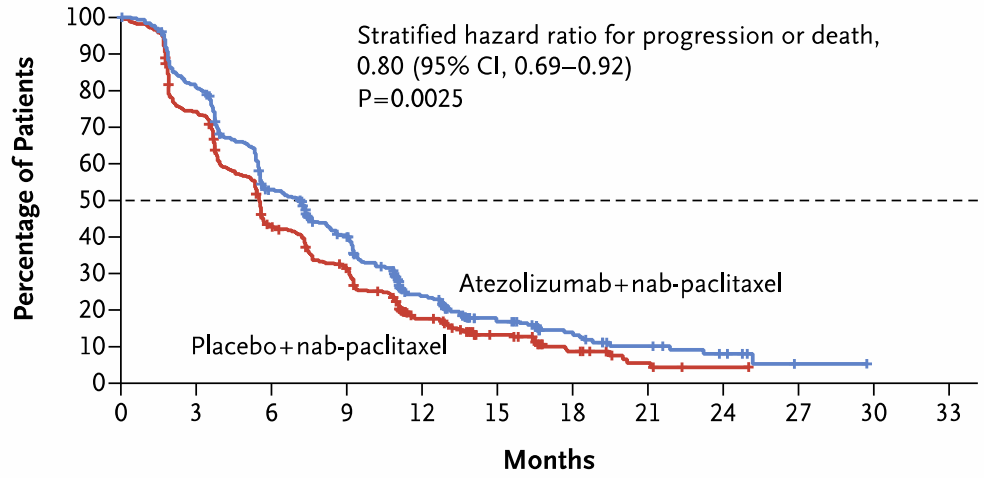
P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

Novembre 2018

IMPASSION 130 : RÉSULTATS SSP

A Progression-free Survival in the Intention-to-Treat Population

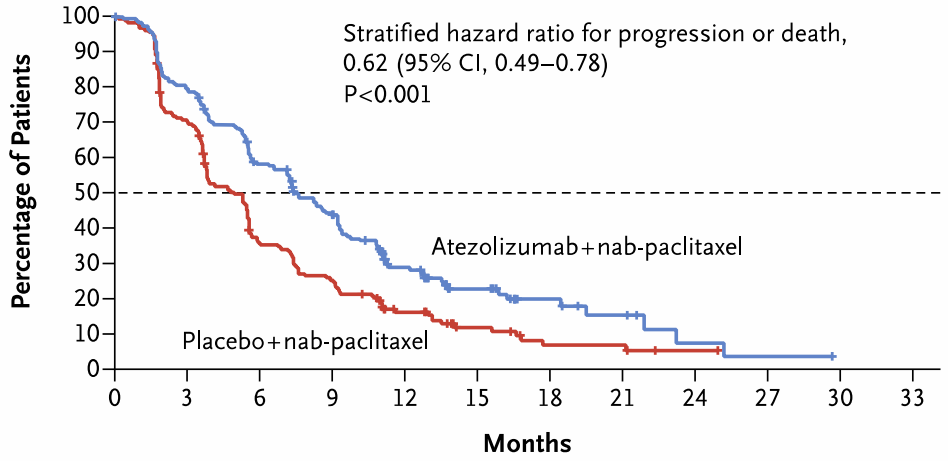
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

B Progression-free Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)

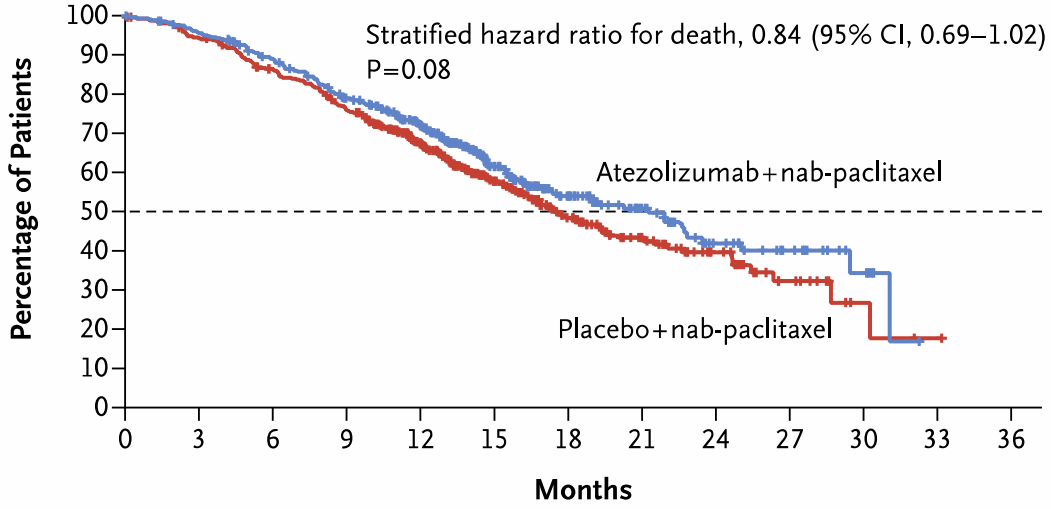


No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

IMPASSION 130 : RÉSULTATS SG

C Overall Survival in the Intention-to-Treat Population

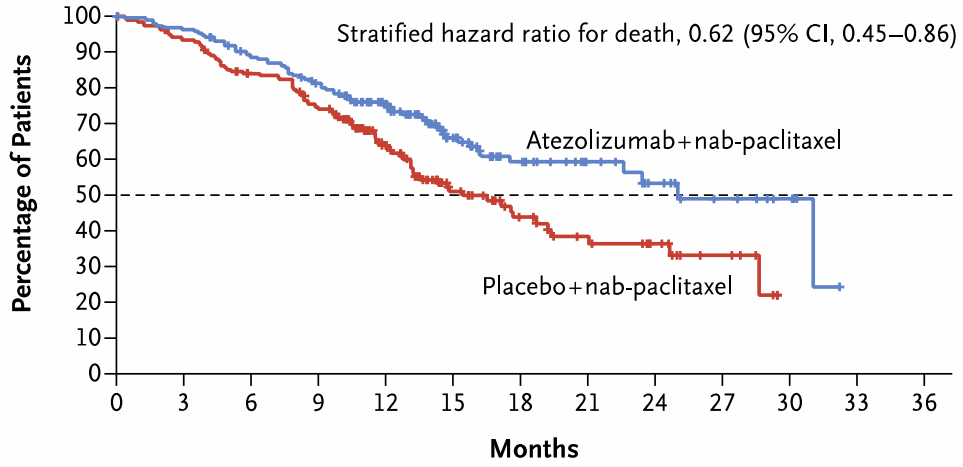
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk													
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

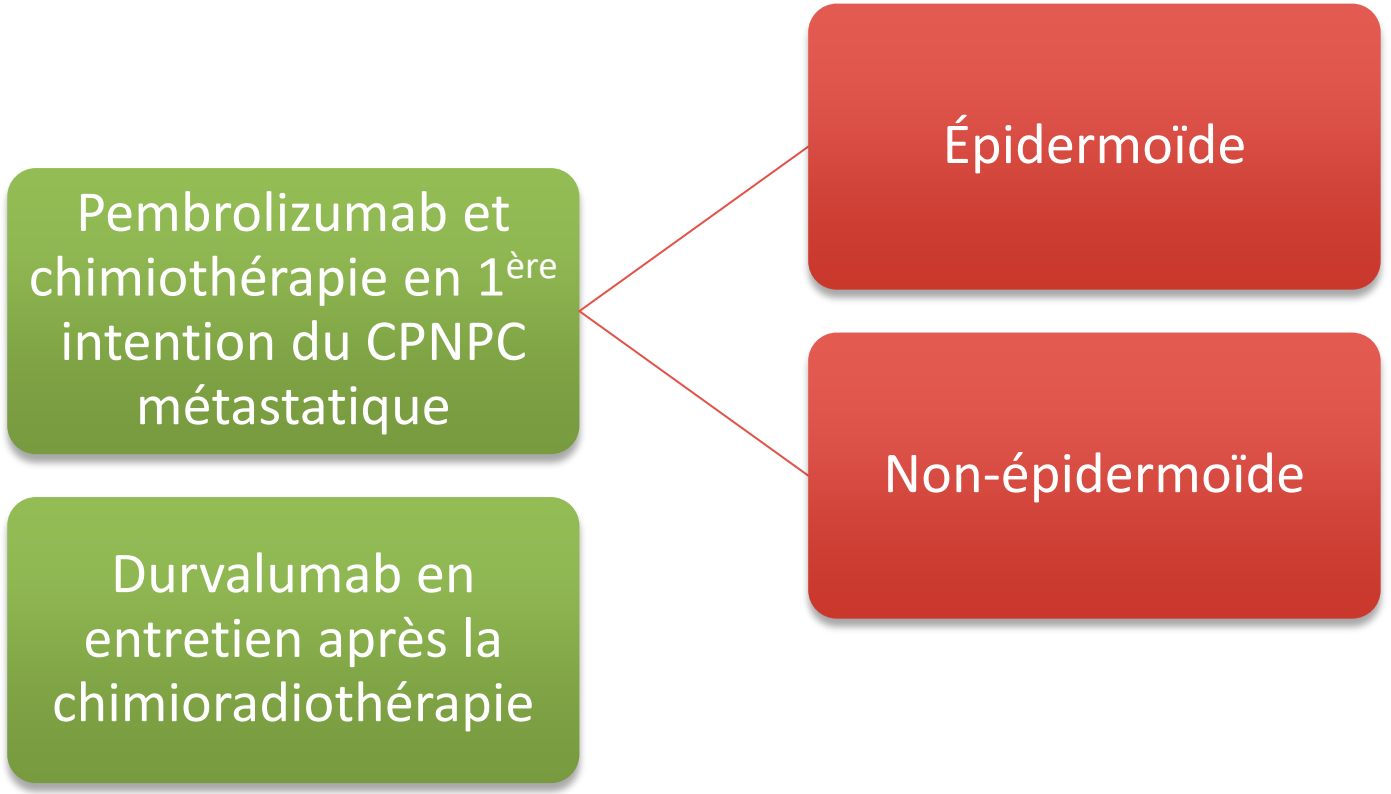
D Overall Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



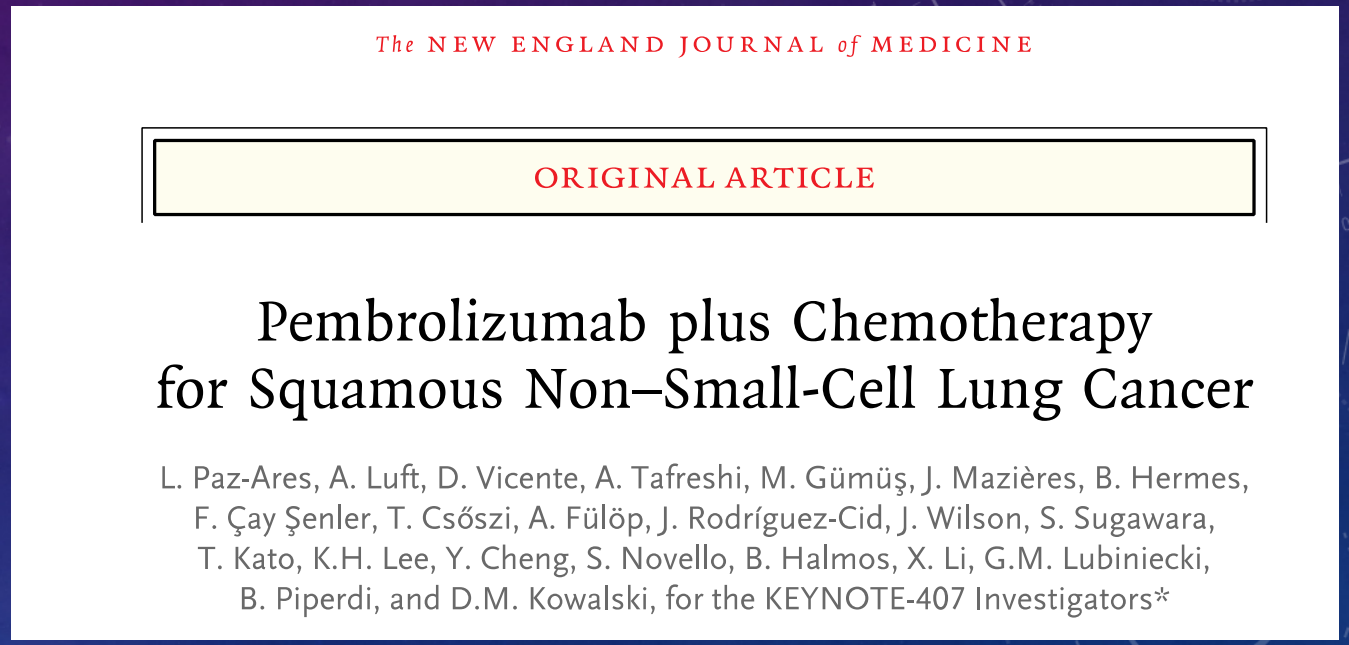
No. at Risk													
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

CPNPC… ET OUI ENCORE!



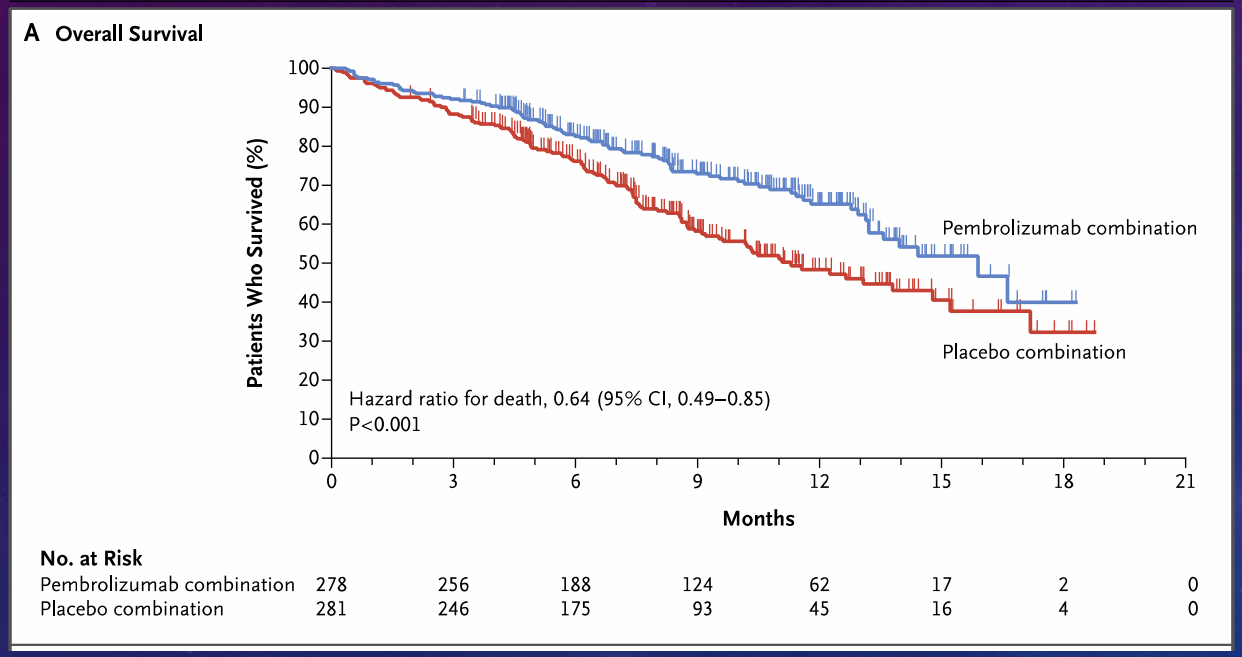
CPNPC MÉTASTATIQUE ÉPIDERMOÏDE

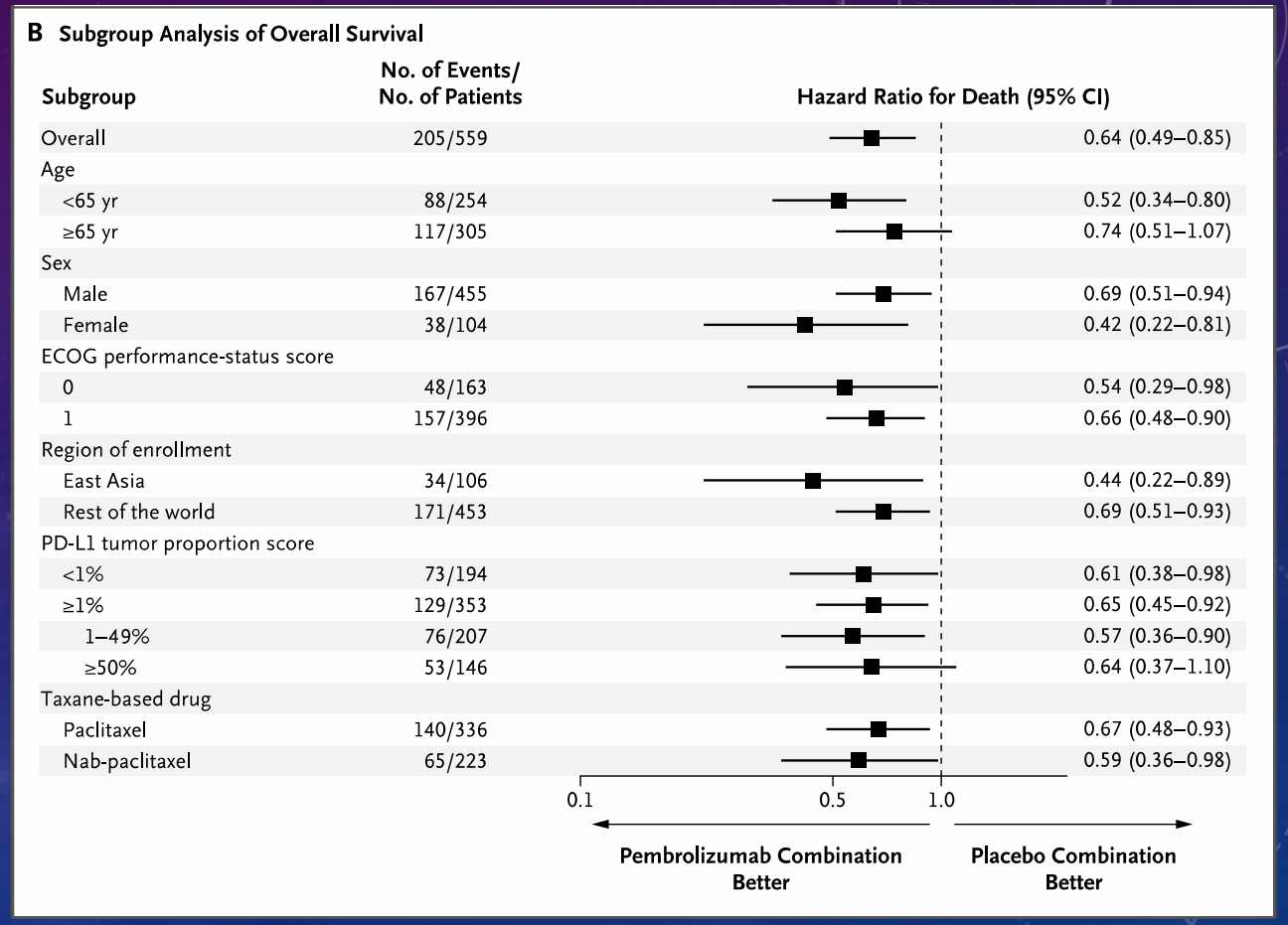
- Évaluation favorable de l'INESSS : ministre sursoit
- RCT de phase III, 559 patients
- CPNPC métastatique, naïf à tout traitement
- Sel de platine + paclitaxel ou nab-paclitaxel X 4 cycles avec ou sans pembrolizumab 200mg IV q 3 semaines X max 35 cycles
- Objectifs principaux : SG et SSP



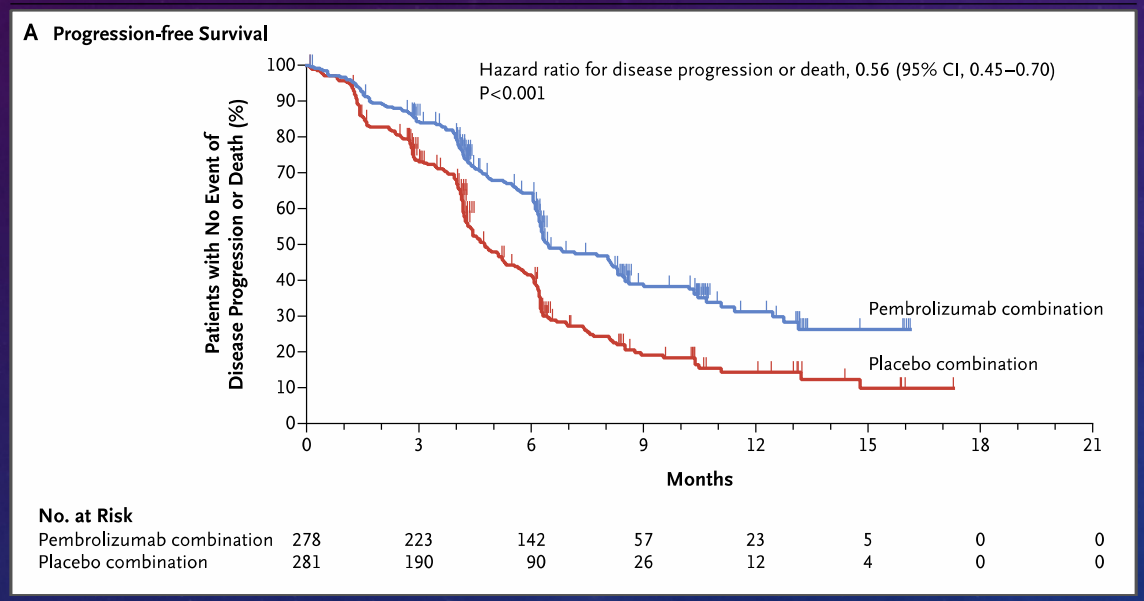
Novembre 2018

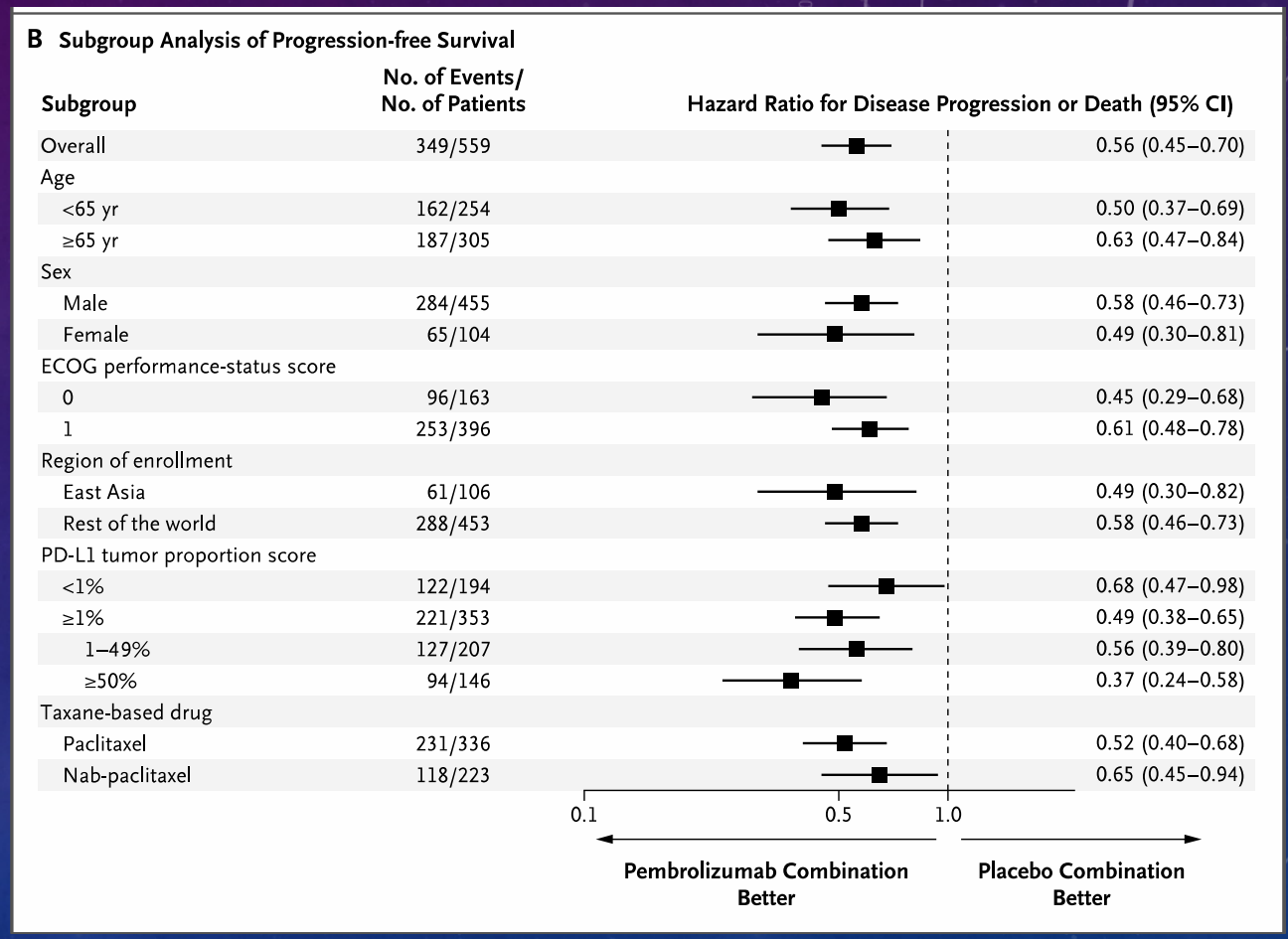
KEYNOTE-407: RÉSULTATS





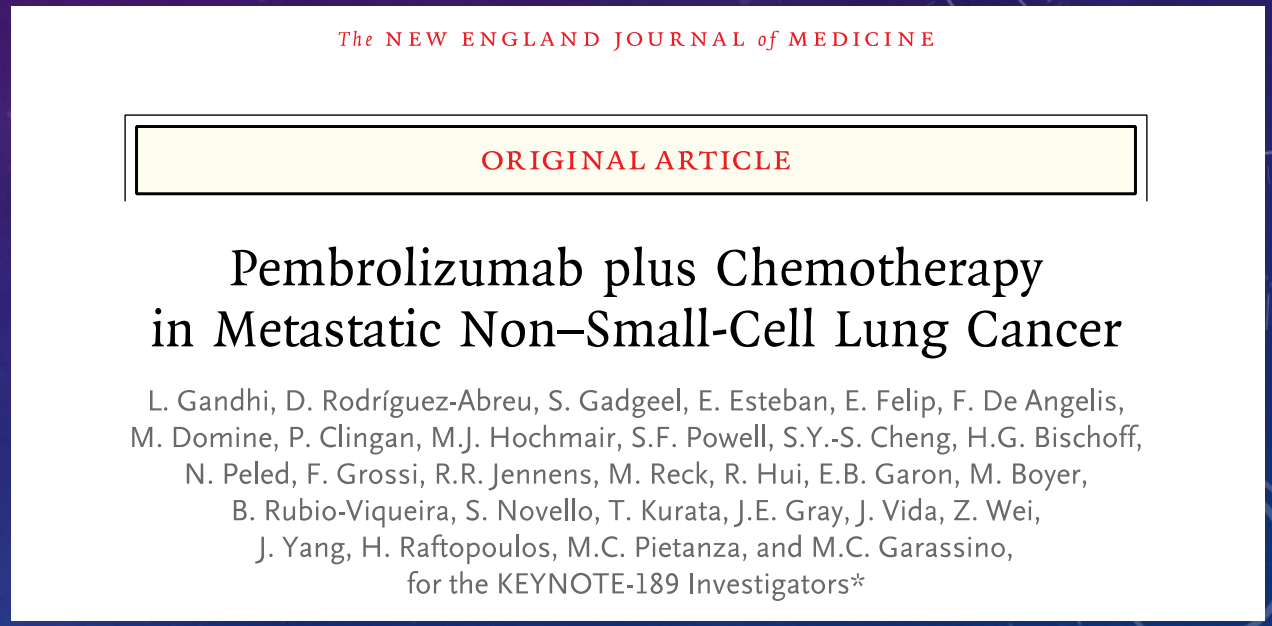
KEYNOTE-407: RÉSULTATS





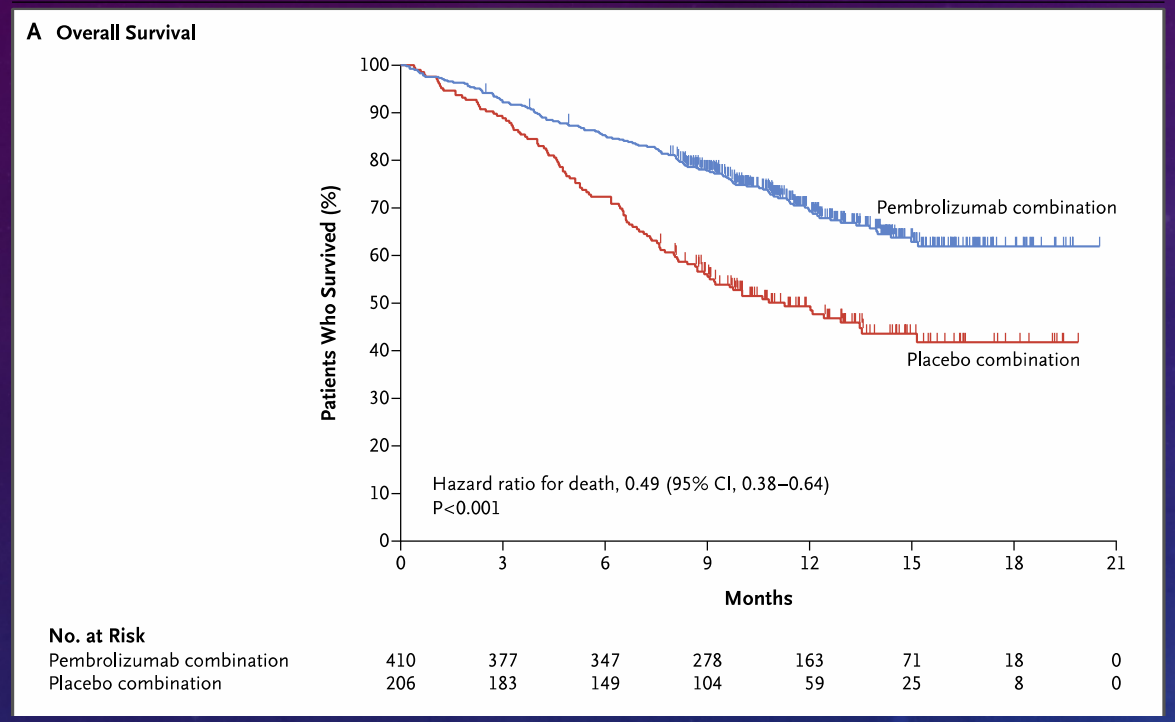
CPNPC MÉTASTATIQUE NON-ÉPIDERMOÏDE

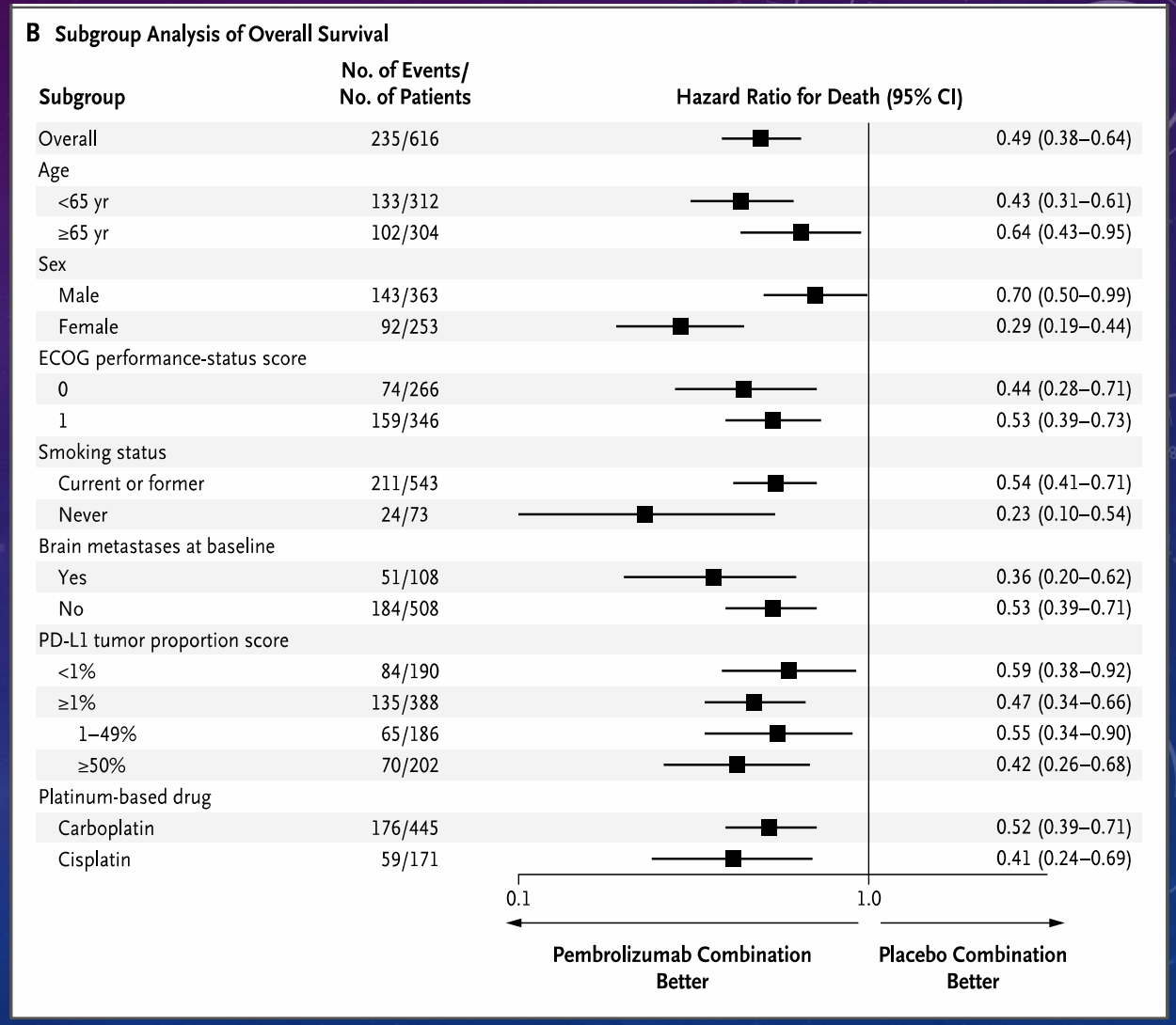
- Évaluation favorable de l'INESSS : ministre sursoit
- RCT de phase III, 616 patients
- CPNPC métastatique, EGFR -, ALK – naïf à tout traitement
- Sel de platine + pemetrexed X 4 cycles avec ou sans pembrolizumab 200mg IV q 3semaines X max 35 cycles
- Maintenance de pemetrexed pour tous
- Objectifs principaux : SG et SSP



Mai 2018

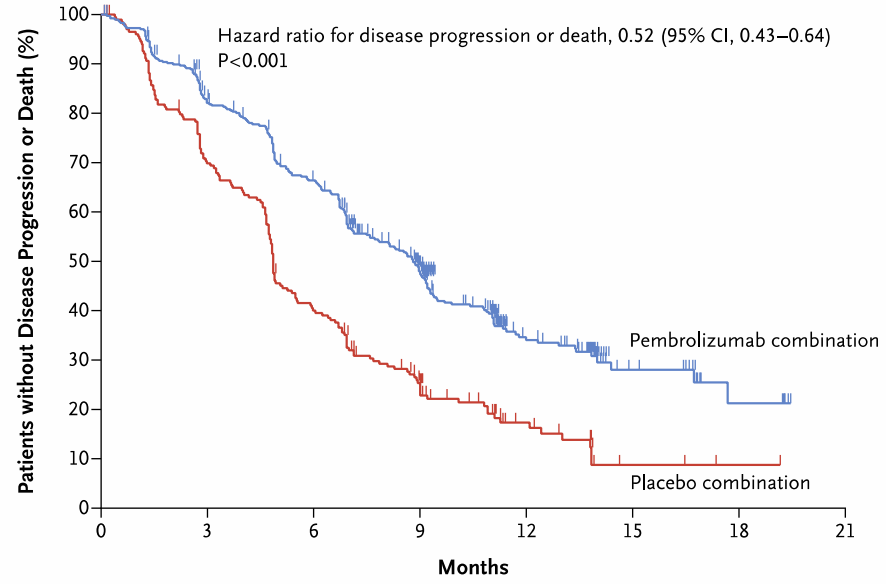
KEYNOTE-189: RÉSULTATS





KEYNOTE-189: RÉSULTATS

A Progression-free Survival

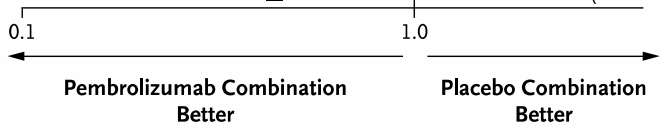


No. at Risk

Pembrolizumab combination	410	322	256	149	60	17	5	0
Placebo combination	206	141	80	40	16	3	1	0

B Subgroup Analysis of Progression-free Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	410/616	0.52 (0.43–0.64)
Age		
<65 yr	224/312	0.43 (0.32–0.56)
≥65 yr	186/304	0.75 (0.55–1.02)
Sex		
Male	236/363	0.66 (0.50–0.87)
Female	174/253	0.40 (0.29–0.54)
ECOG performance-status score		
0	158/266	0.49 (0.35–0.68)
1	250/346	0.56 (0.43–0.72)
Smoking status		
Current or former	365/543	0.54 (0.43–0.66)
Never	45/73	0.43 (0.23–0.81)
Brain metastases at baseline		
Yes	81/108	0.42 (0.26–0.68)
No	329/508	0.53 (0.43–0.67)
PD-L1 tumor proportion score		
<1%	146/190	0.75 (0.53–1.05)
≥1%	238/388	0.44 (0.34–0.57)
1–49%	114/186	0.55 (0.37–0.81)
≥50%	124/202	0.36 (0.25–0.52)
Platinum-based drug		
Carboplatin	299/445	0.55 (0.44–0.70)
Cisplatin	111/171	0.44 (0.30–0.65)

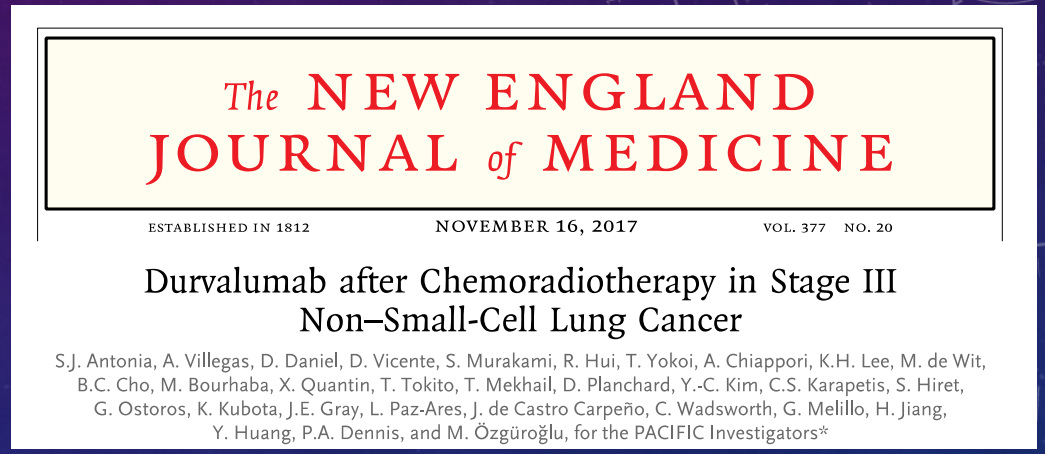


UNE QUESTION DEMEURE

Quoi faire avec les patients dont la tumeur exprime le PDL1 à 50% ou plus?

DURVALUMAB POST RADIO-CHIMIO

- Inscrit à la LE en octobre 2019
- RCT de phase III
- 713 sujets randomisés
- Patients atteints d'un CPNPC de stade III traité par radiochimiothérapie
- Randomisé à un an de durvalumab 10 mg/kg IV q 2 semaines ou un placebo
- Objectifs principaux : SG et SSP

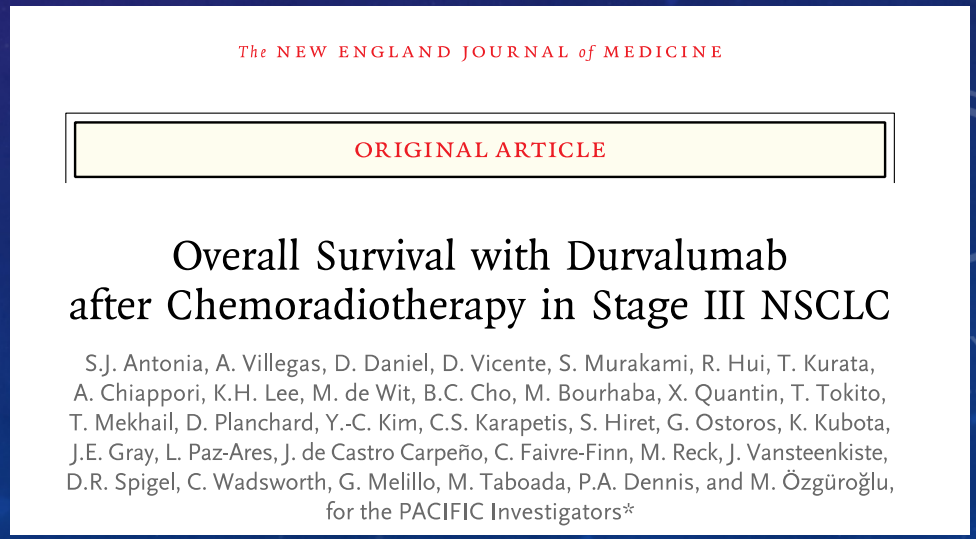


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

ÉTUDE PACIFIC : RÉSULTATS

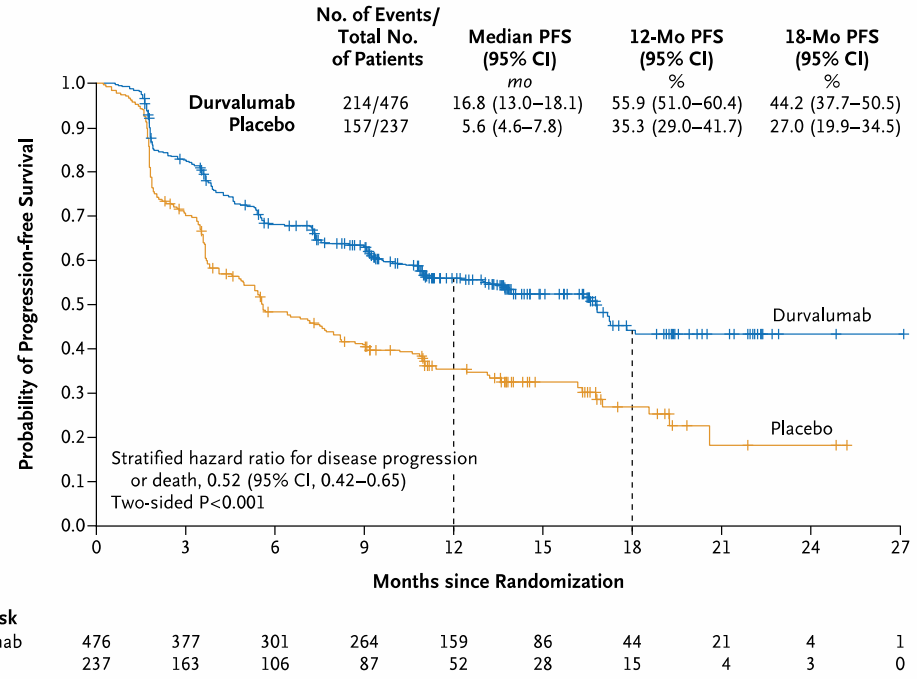


Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

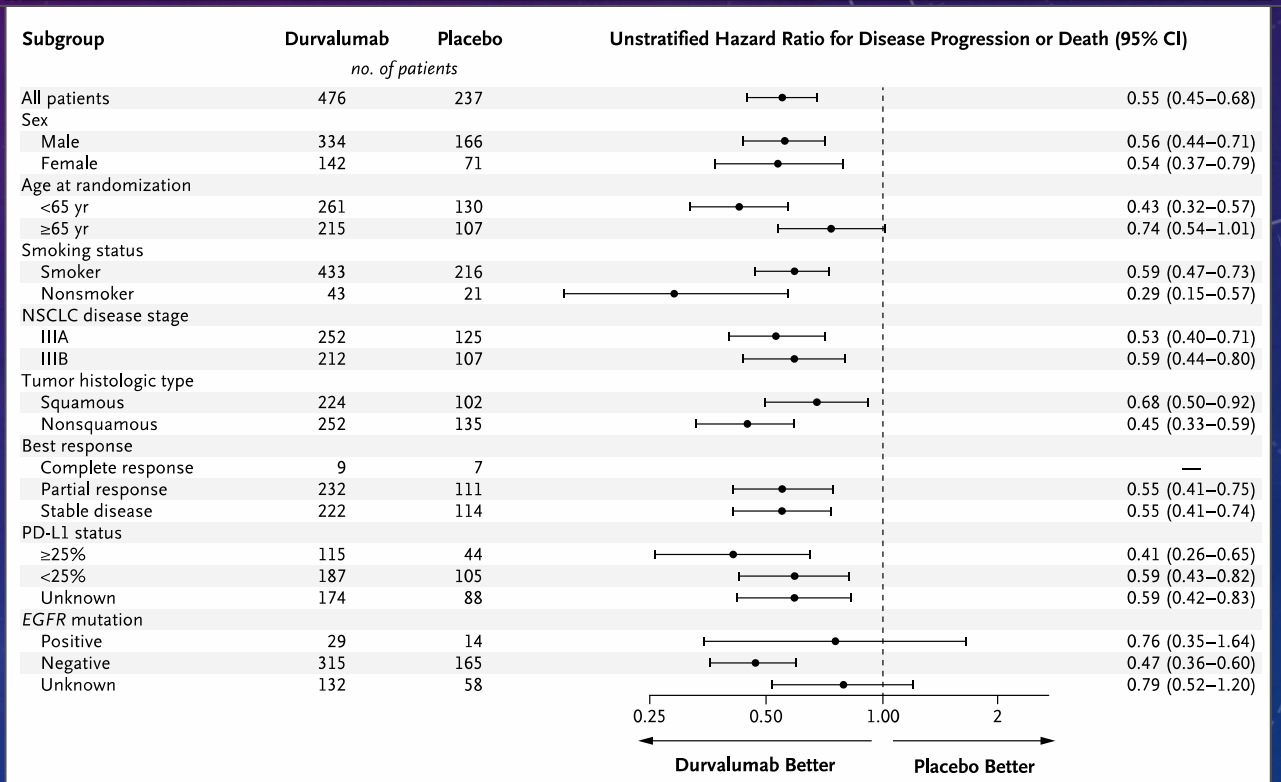


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Progression-free survival was defined according to RECIST, version 1.1, and assessed by means of blinded independent central review. The hazard ratio and 95% confidence interval were not calculated for the complete response because this subgroup had less than 20 events. EGFR denotes epidermal growth factor receptor, and PD-L1 programmed death ligand 1.

ÉTUDE PACIFIC : RÉSULTATS

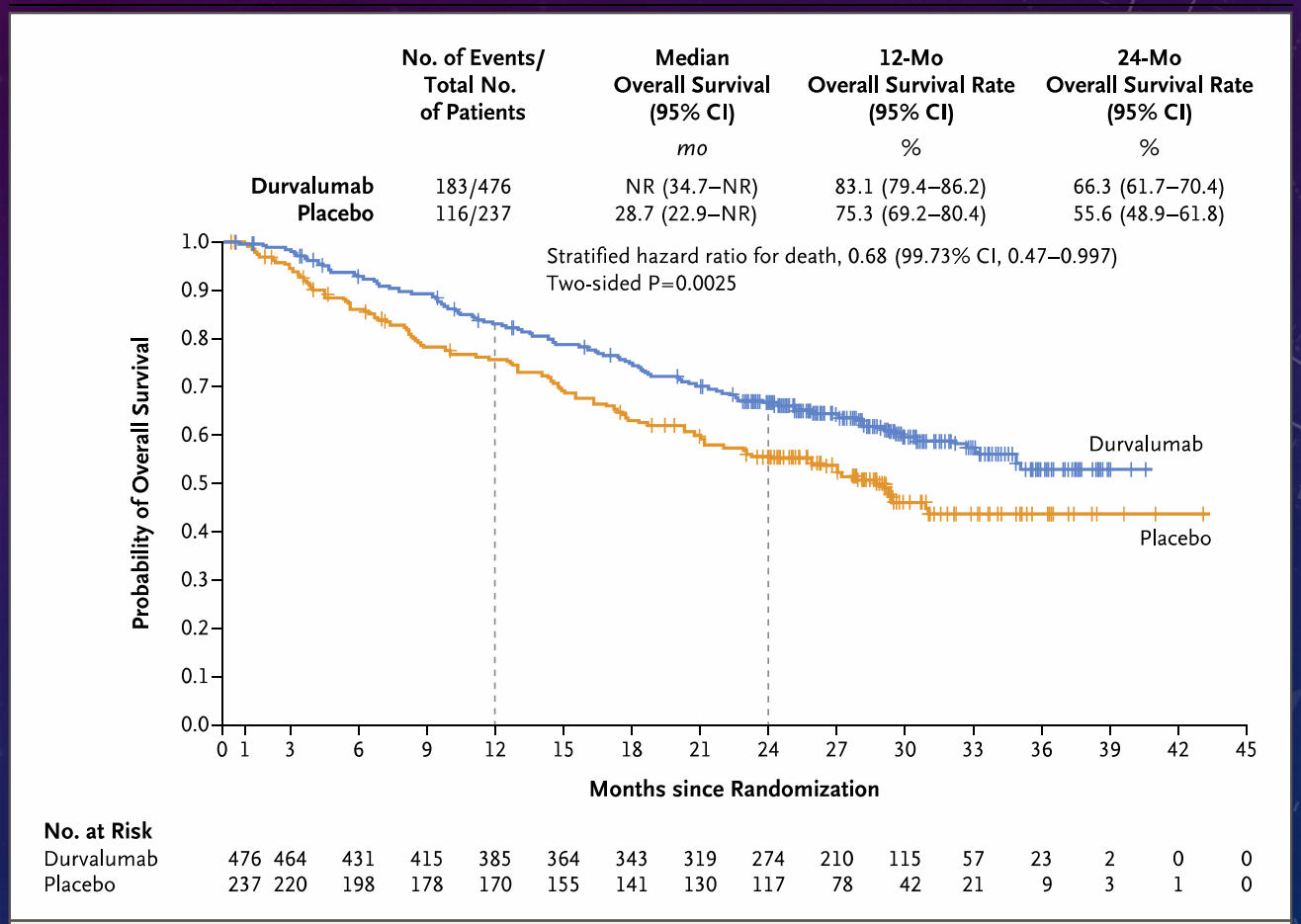


Figure 2. Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for overall survival. Tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of overall survival. The intention-to-treat population included all the patients who underwent randomization. In this analysis of overall survival, the hazard ratio and its corresponding confidence interval of $100[1-\alpha]\%$, with adjustment for the interim analysis, are presented. NR denotes not reached.

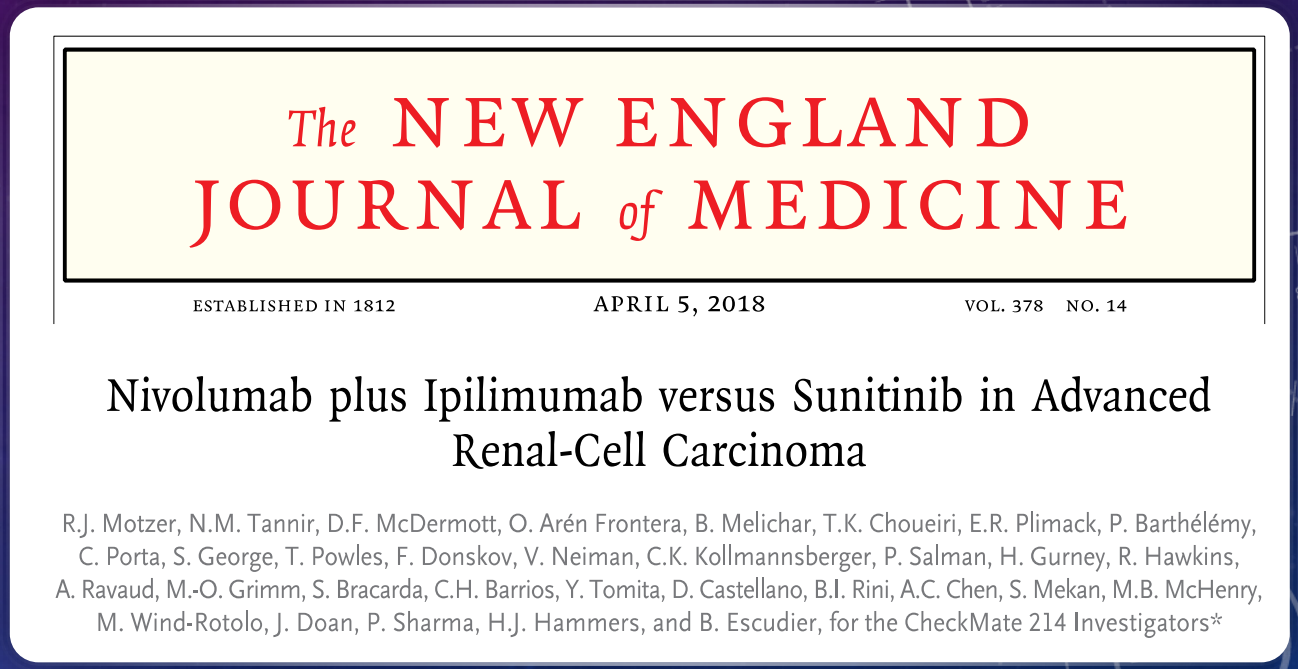
CARCINOME RÉNAL : IPILIMUMAB + NIVOLUMAB

- Inscription à la LE en mai 2019
- Traitement de 1ère intention du cancer rénal à cellules claires
- RCT de phase III, 1096 patients
- Objectif principal : SG, RTO, SSP dans la population à pronostic intermédiaire ou mauvais

Ipilimumab 1 mg/kg + nivolumab 3 mg/kg IV q 3 semaines X 4 doses suivi de nivolumab 3 mg/kg IV q 2 semaines ad progression

OU

Sunitinib 50 mg PO 28/42 jours ad progression



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2018 VOL. 378 NO. 14

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

SCORE IMDC : COMMENT LE CALCULER

Présence de :

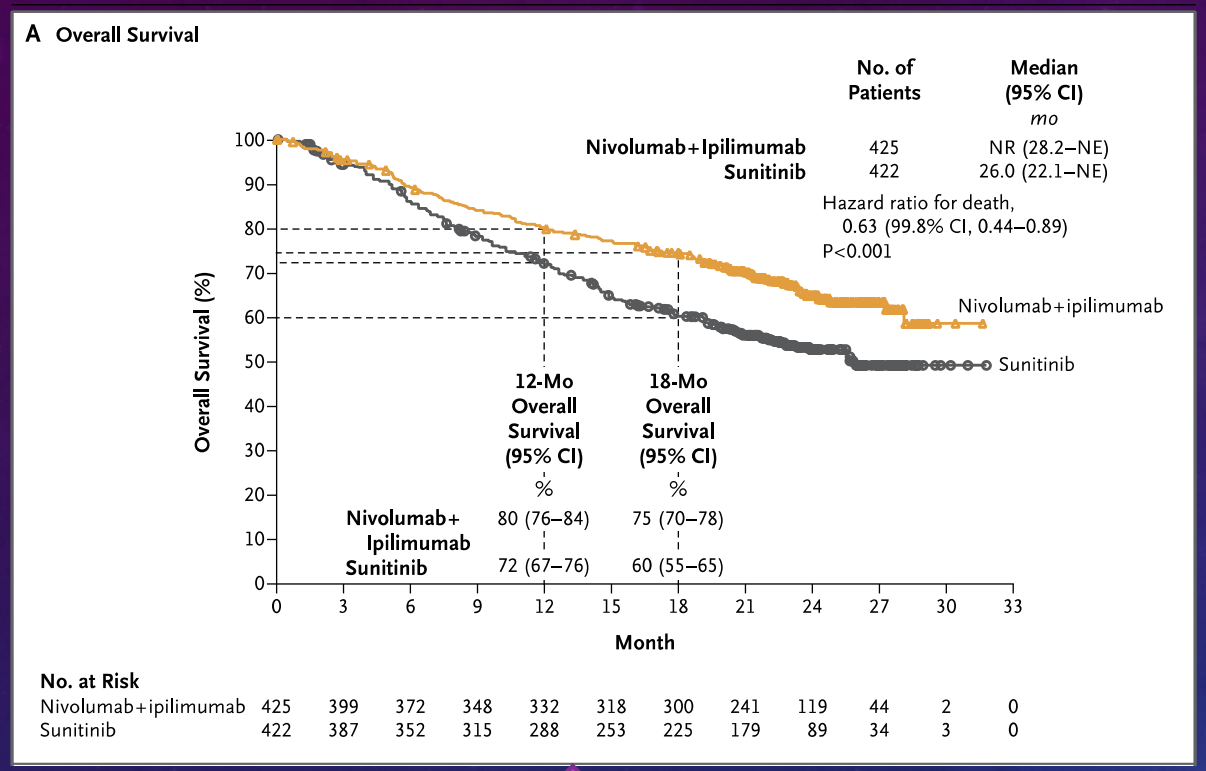
- < 1 an entre le diagnostic et l'initiation d'un traitement systémique
- Karnofsky < 80%
- Hémoglobine < LIN
- Hypercalcémie
- ANC > LSN
- PLT > LSN

Score calculé	Pronostic	Durée médiane de survie
0	Bon	43,2 mois
1-2	Intermédiaire	22,5 mois
≥ 3	Mauvais	7,8 mois

Heng 2013

CHECKMATE 214: RÉSULTATS

Survie sans progression



Survie globale

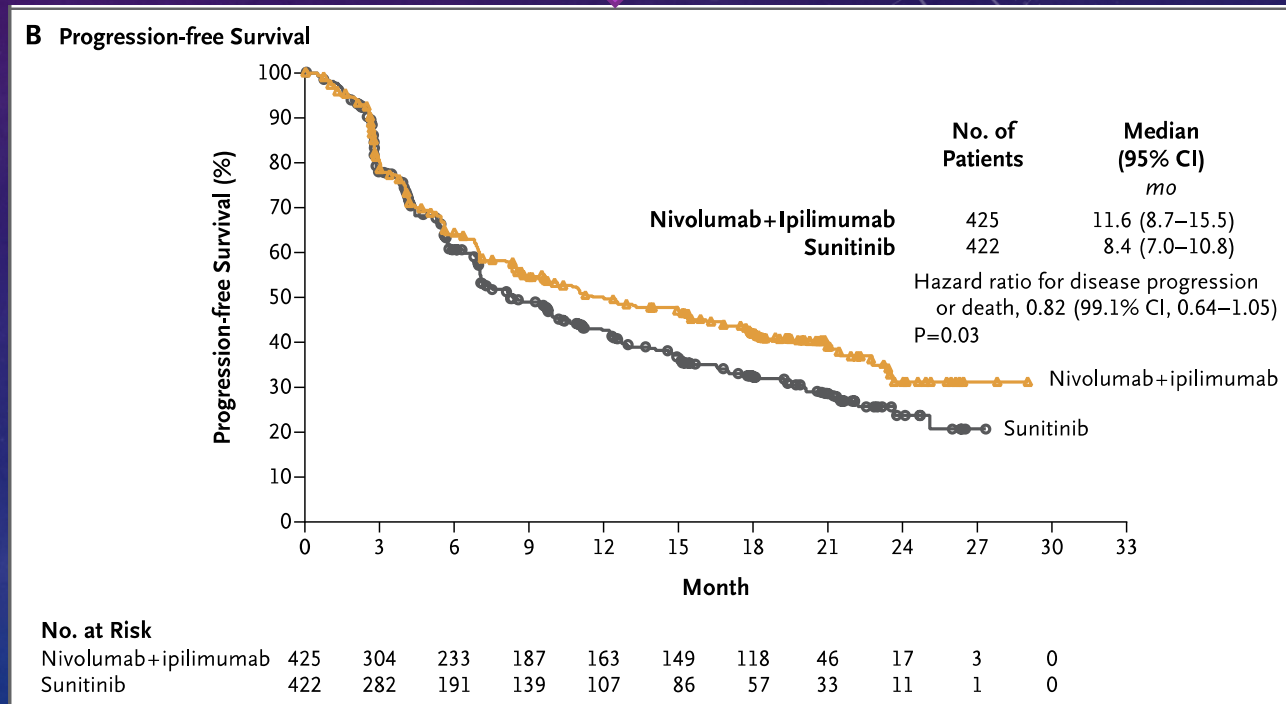


Figure 1. Overall Survival and Progression-free Survival among IMDC Intermediate- and Poor-Risk Patients.

Progression was defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1. For progression-free survival, the between-group difference did not meet the prespecified threshold (P=0.009) for statistical significance. IMDC denotes International Metastatic Renal Cell Carcinoma Database Consortium, NE not estimable, and NR not reached.

CHECKMATE 214: RÉSULTATS

Table 2. Antitumor Activity in IMDC Intermediate- and Poor-Risk Patients.*

Variable	Nivolumab plus Ipilimumab (N = 425)	Sunitinib (N = 422)
Confirmed objective response rate — % (95% CI)†	42 (37–47)‡	27 (22–31)‡
Confirmed best overall response — no. (%)†		
Complete response	40 (9)‡§	5 (1)‡§
Partial response	137 (32)	107 (25)
Stable disease	133 (31)	188 (45)
Progressive disease	83 (20)	72 (17)
Unable to determine or not reported	32 (8)	50 (12)
Median time to response (range) — mo	2.8 (0.9–11.3)	3.0 (0.6–15.0)
Median duration of response (95% CI) — mo	NR (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response — no./total no. (%)	128/177 (72)	71/112 (63)

* NE denotes not estimable, and NR not reached.
† Response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent radiology review committee.
‡ P<0.001 for the difference between groups.
§ The analysis of the between-group difference in complete response was exploratory.

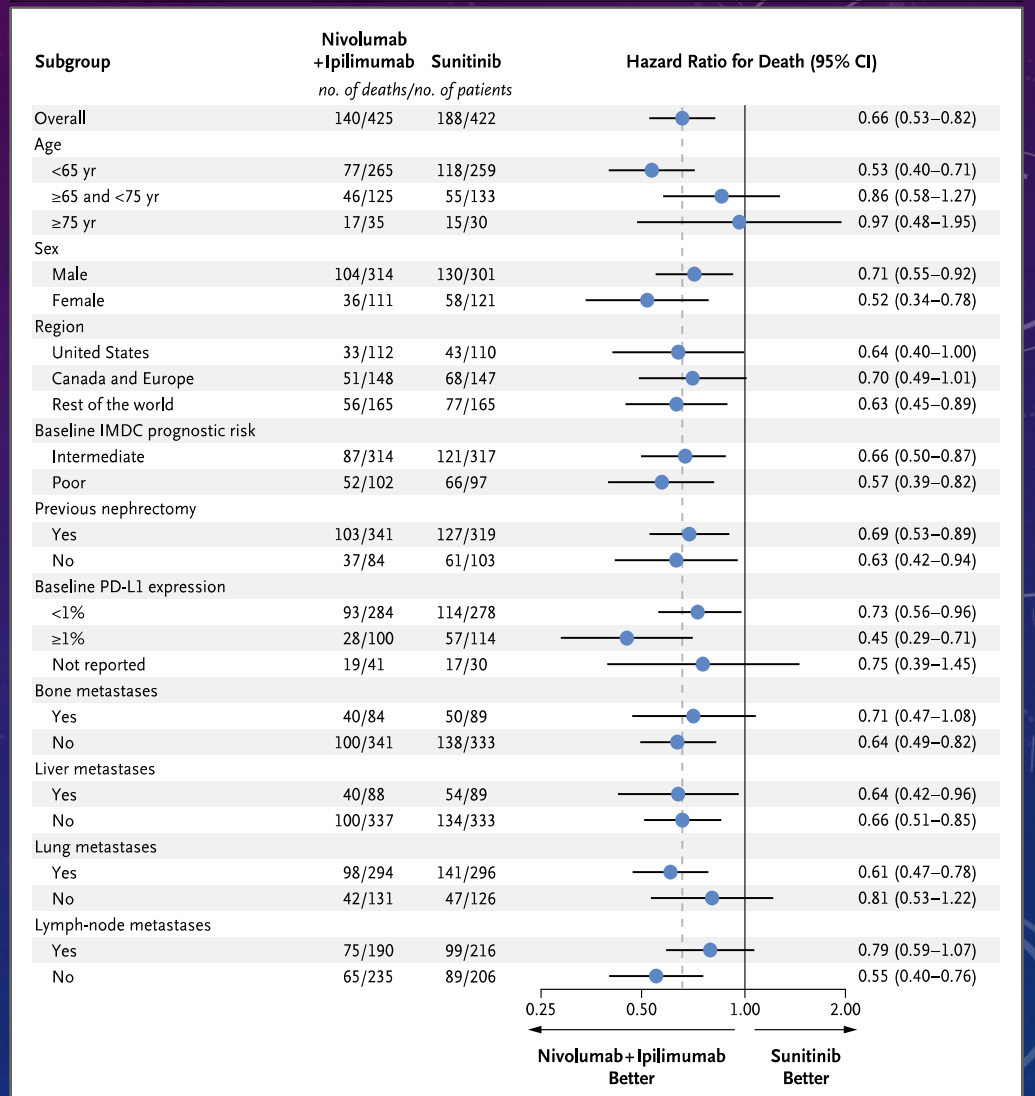
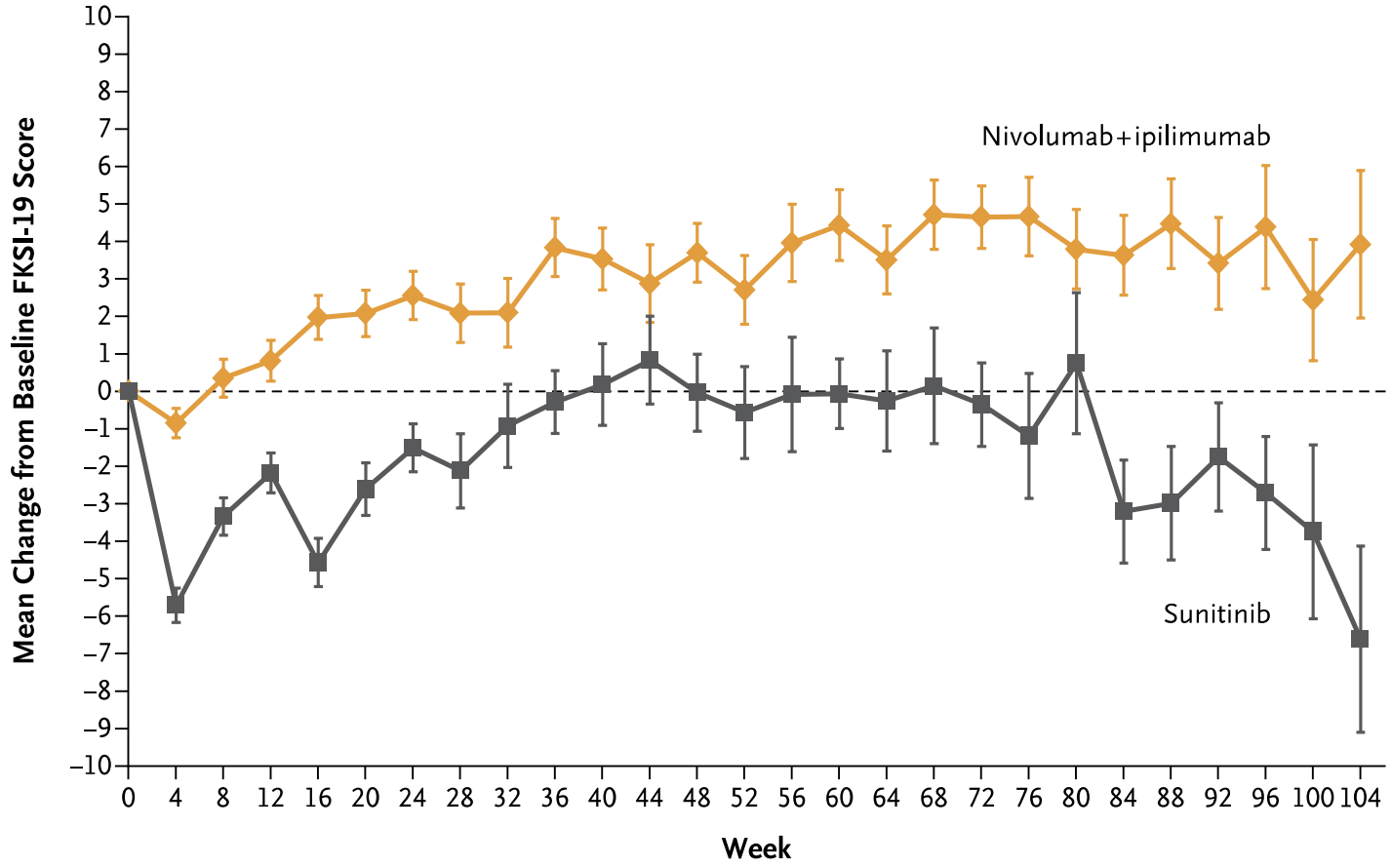


Figure 2. Subgroup Analysis of Overall Survival among IMDC Intermediate- and Poor-Risk Patients.

Patients with intermediate risk had an IMDC score of 1 or 2, and those with poor risk had a score of 3 to 6. IMDC risk scores are defined by the number of the following risk factors present: a Karnofsky performance-status score of 70 (on a scale from 0 to 100, with lower scores indicating greater disability; patients with a performance-status score of <70 were excluded from the trial), a time from initial diagnosis to randomization of less than 1 year, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium concentration of more than 10 mg per deciliter (2.5 mmol per liter), an absolute neutrophil count above the upper limit of the normal range, and a platelet count above the upper limit of the normal range. Bone, liver, lung, and lymph-node metastases were not protocol-prespecified subgroups. PD-L1 denotes programmed death ligand 1.

QDV



No. at Risk

Nivolumab+ipilimumab	425	347	281	239	212	180	166	152	143	139	125	108	76	44
Sunitinib	422	371	284	221	184	147	127	113	104	93	80	64	43	26

Figure 3. Health-Related Quality of Life in IMDC Intermediate- and Poor-Risk Patients.

Scores on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19) range from 0 to 76, with higher scores indicating fewer symptoms. Only time points for which data were available for five or more patients are shown. The number at risk shows the number of randomly assigned patients who were in the trial at each respective time point. I bars indicate standard errors.

CARCINOME RÉNAL : PEMBROLIZUMAB + AXITINIB

- En évaluation à l'INESSS
- Traitement de 1ère intention du cancer rénal à cellules claires
- RCT de phase III, 861 patients
- Objectif principal : SG, SSP
- Analyse intérimaire des résultats

Pembrolizumab 200mg IV q 3 semaines (max 35 cycles) + axitinib 5mg BID ad progression

OU

Sunitinib 50 mg PO 28/42 jours ad progression

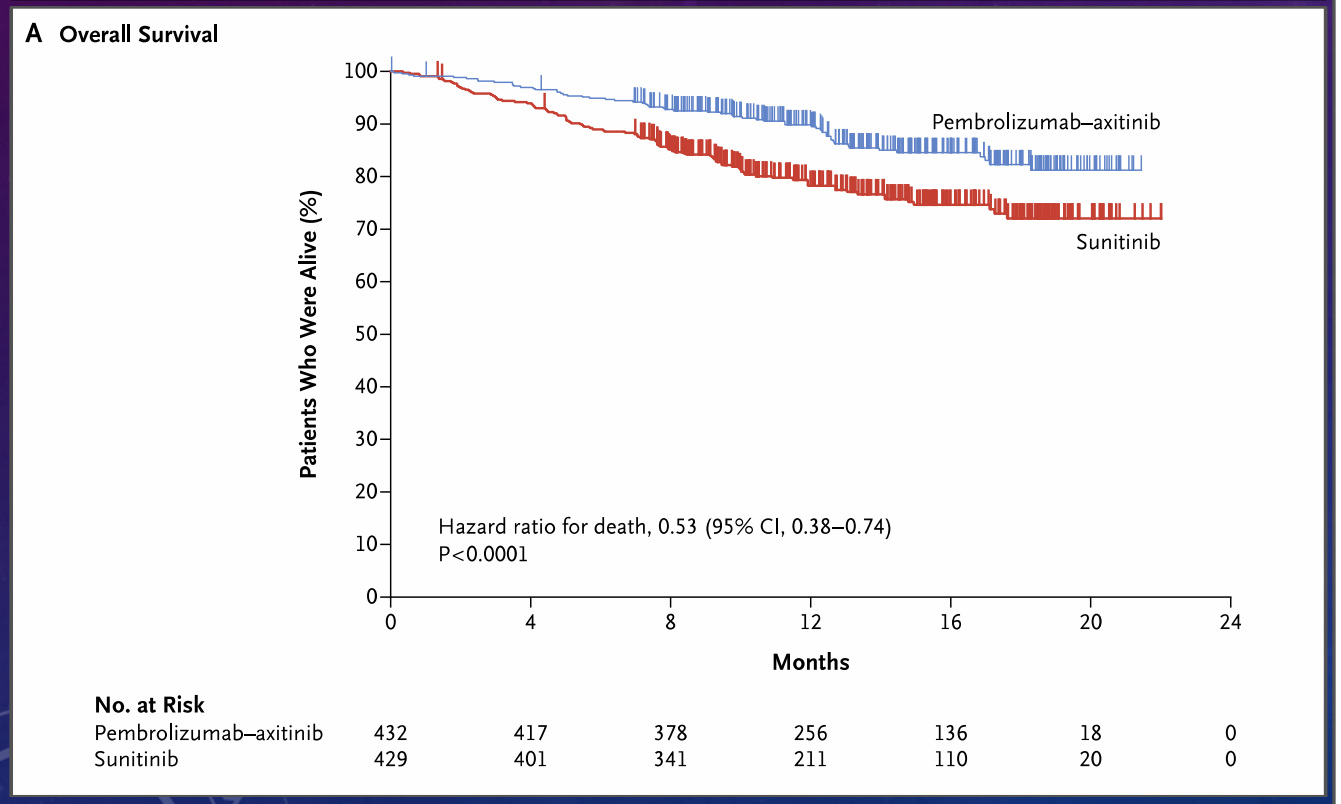
ORIGINAL ARTICLE

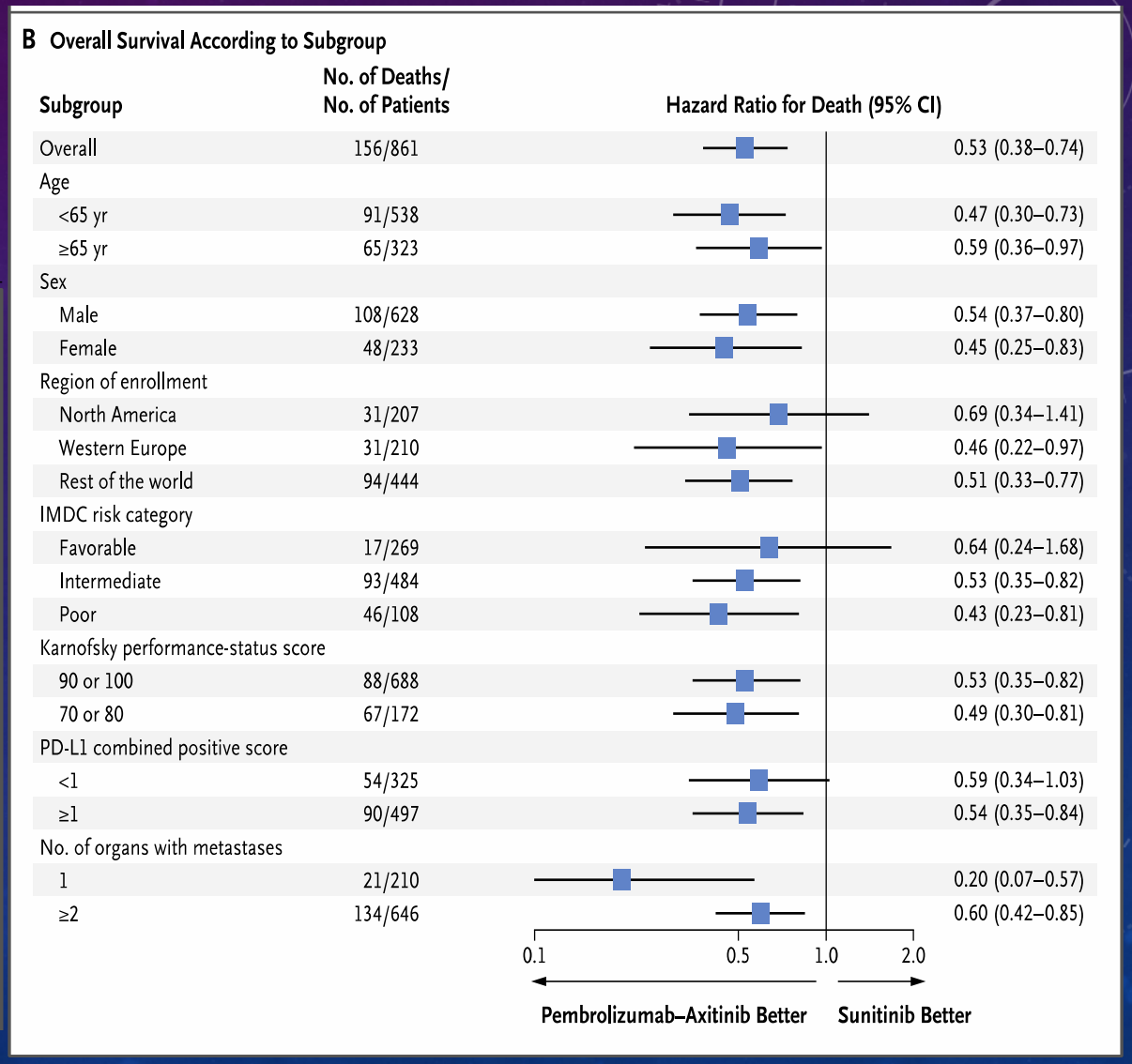
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

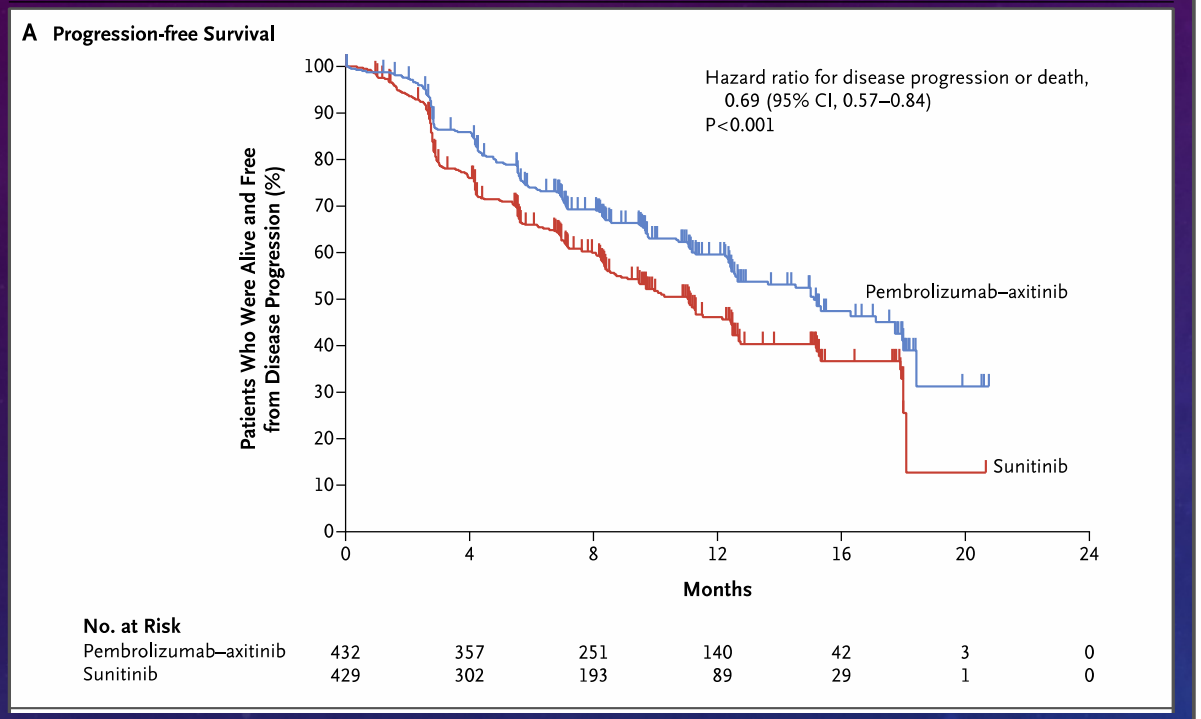
Mars 2019

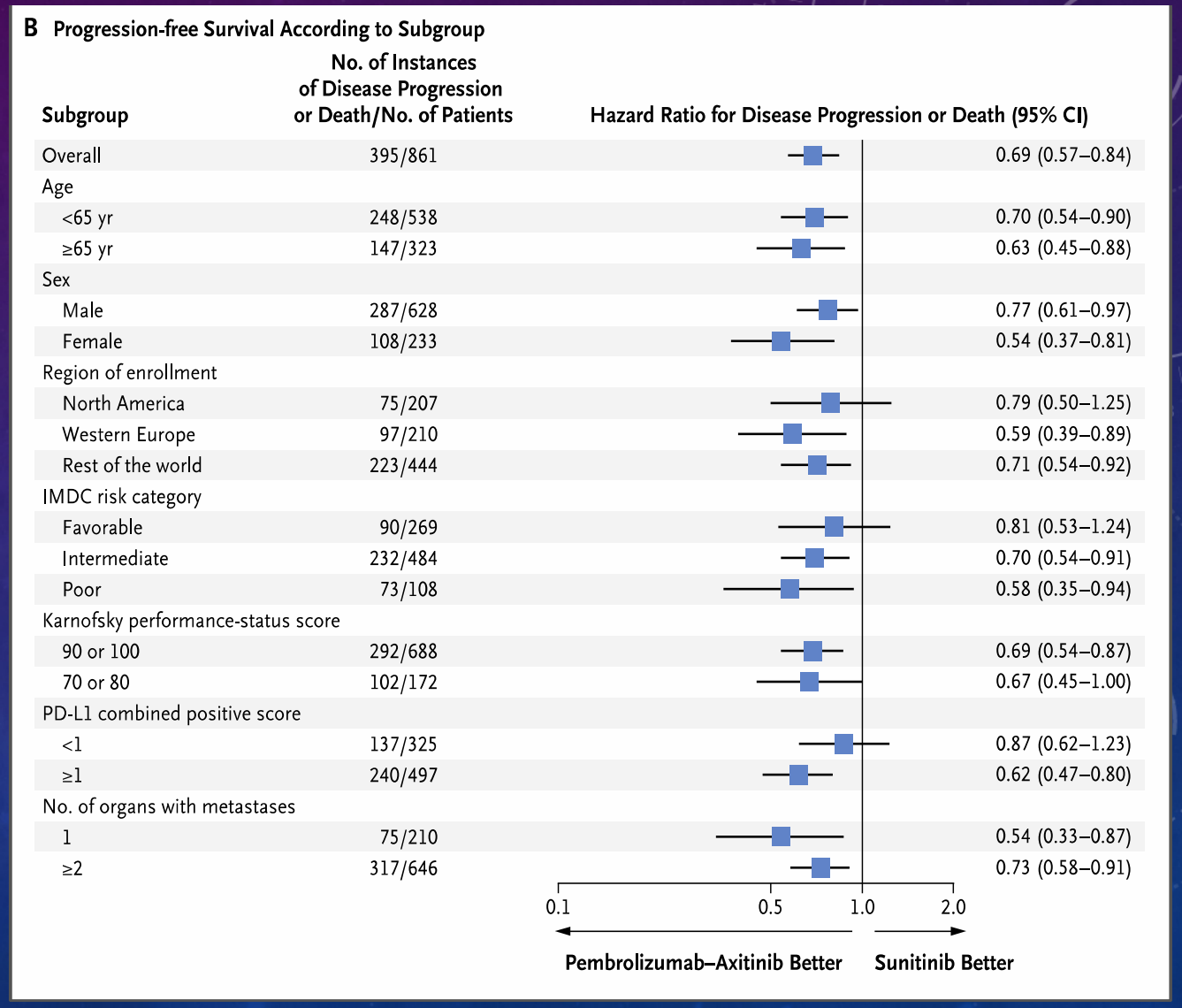
KEYNOTE-426 : RÉSULTATS SG





KEYNOTE-426 : RÉSULTATS SSP





RÉSUMONS!

- Mélanome malin
  - Adjuvant : Nivolumab X 1 an (LE)
  - Adjuvant : pembrolizumab X 1 an (évaluation INESSS)
  - Métastatique : Ipi+nivo (LE)
- Carcinome épidermoïde cutané avancé/métastatique
  - Cémiplimab (évaluation INESSS)
- Carcinome de Merkel avancé/métastatique
  - Avelumab 2^{e} intention (LE)
- Cancer du sein inopérable/métastatique triple négatif
  - Atézolizumab + nab-paclitaxel (Évaluation INESSS)
- CPNPC métastatique
  - Épidermoïde : pembrolizumab + sel de platine/paclitaxel (ministre sursoit)
  - Non-épidermoïde : pembrolizumab + sel de platine/pemetrexed (ministre sursoit)
- CPNPC stade III post radiochimio
  - Durvalumab X 1 an (LE)
- RCC métastatique
  - Px mauvais ou intermédiaire : ipi-nivo (LE)
  - Tous px : pembro-axitinib (évaluation INESSS)

L’IMMUNOTHÉRAPIE, C’EST EFFICACE PARTOUT NON?

- Cancer urothélial: pembrolizumab en 1ère intention
- CPPC-E : chimio+ atézolizumab en 1ère intention
- Carcinome hépatocellulaire : nivolumab ou pembrolizumab en maladie R/R
- Cancer de la prostate : ipilimumab en maladie avancée

PARENTHÈSE SUR LE PEMBROLIZUMAB

Indication reconnue par Santé Canada

Pour le traitement, en monothérapie, des adultes atteints de l'un des cancers non résécables ou métastatiques associés à une forte instabilité microsatellitaire (IMS) ou
à une déficience du système de réparation des mésappariements (SRM) suivants :

- Cancer colorectal caractérisé par des tumeurs ayant progressé après un traitement avec une fluoropyrimidine, de l'oxaliplatine et de l'irinotécan;
  - N=61, suivi médian de 13,2 mois, RTO 28%, durée médiane de la réponse non-atteinte
  - 82% des patients en réponse à 6 mois et plus
- Cancer de l'endomètre caractérisé par des tumeurs ayant progressé après un traitement antérieur et qui ne peut être traité d'aucune autre manière acceptable.
  - N=24, suivi médian de 8,4 mois, RTO 54$, durée médiane de la réponse non-atteinte
  - 100% des patients en réponse à 6 mois et plus

LA DOUBLE IMMUNOTHÉRAPIE, C'EST TOXIQUE HEIN?

L'EXPÉRIENCE CHU DE QUÉBEC – UNIVERSITÉ LAVAL AVEC LA DOUBLE-IMMUNOTHÉRAPIE

PERSPECTIVES FUTURES

BTLA

ICOS

4-1BB

VISTA

CD40

Cibles potentielles

TIM-3

CD-28

OX40

GITR

LAG-3

CD47

CONCLUSION

- L’immunothérapie demeure importante dans le traitement de plusieurs types de cancers
- Ce n’est que la pointe de l’iceberg
  - Plusieurs études en cours : nouveaux sites tumoraux
  - Nouvelles cibles à l’étude
  - Nouvelles combinaisons à l’étude
  - Facteurs prédictifs de réponse ne sont que partiellement connus
- L’accès aux traitements se fait de plus en plus rapidement… trop rapidement?
- L’innocuité de la classe est mieux maitrisée
- Certaines études déçoivent… défient nos hypothèses
- Seule certitude : sujet chaud pour les années à venir!