



Inserm

Institut national
de la santé et de la recherche médicale
CIC1425 U830



Les inhibiteurs de points de contrôle: application aux cancers pulmonaires

G. Zalcman

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& Unité de Phase I CIC1425/CLIP₂ Paris-Nord
GH Bichat-Claude Bernard, AP-HP.Nord



Liens d'intérêt



Investigateur d'essais cliniques de phases I, II & III promus par Lilly, GSK, Roche, MSD, Merck-Serrono, Pfizer, Astra-Zeneca, Sanofi-Aventis, Pierre Fabre, Boehringer, BMS, Novartis, Ariad, Takeda, Roche... **sans rétribution personnelle**, tous les honoraires ayant été ou étant perçus par mon Institution (Hôpital Bichat-APHP, Centre d'Instigation Clinique CIC1425/CLIP₂ Paris-Nord) ou par l'IFCT en accord avec leurs statuts respectifs et objectifs de recherche...

SUBVENTIONS OU AVANTAGES COLLECTIFS

Lilly, Roche, Pfizer, Astra-Zeneca, Sanofi-Aventis, GSK, BMS, Amgen, Chugai, Pierre Fabre, Boehringer-Ingelheim, Merck-Serono, Chugai, Novartis, Janssen-Cilag, MSD
(Subventions pour l'IFCT dont GZ est président honoraire)

Honoraires pour **“conseils scientifiques”** ou présentations payés à la **Fondation Recherche de l'Assistance-Publique-Hôpitaux de Paris (AP-HP)**: Roche, Astra-Zeneca, Pfizer, MSD, Boehringer-Ingelheim, Inventiva, BMS,

BMS a fourni Nivolumab & Ipilimumab de l'essai DICIPLE IFCT-1701

PAIEMENTS PERSONNELS OU AVANTAGES

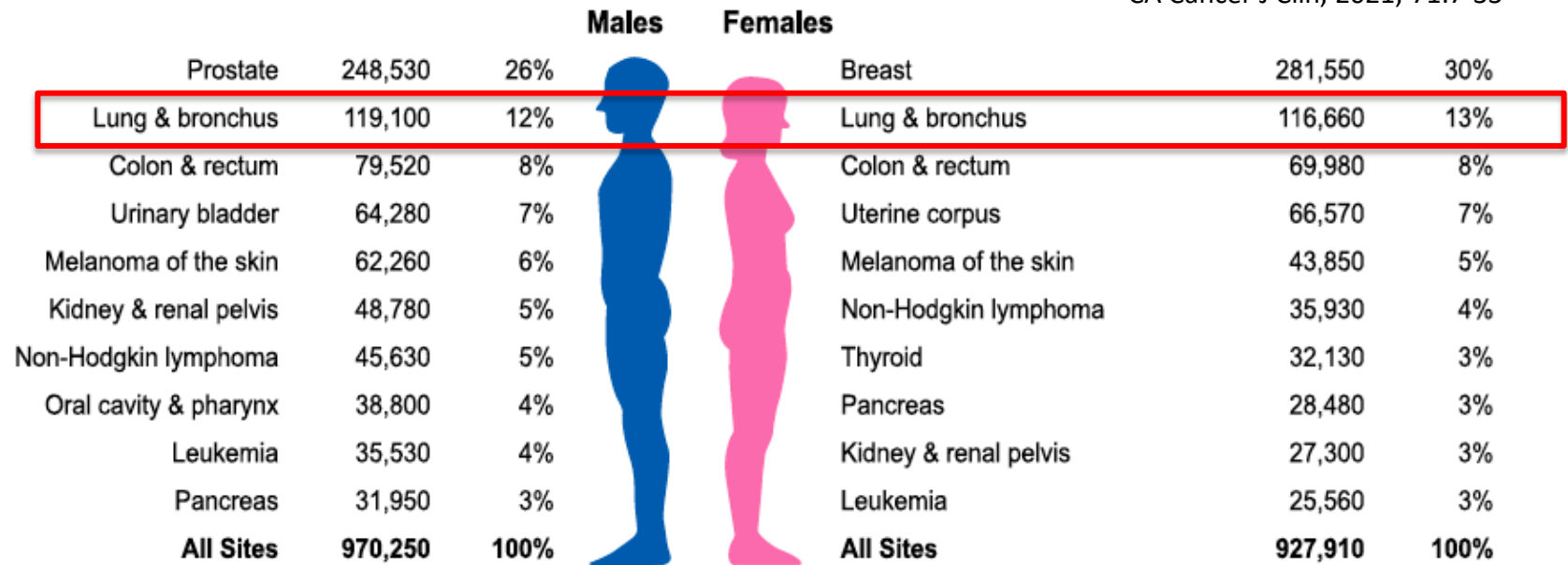
Invitations et hébergement lors de congrès internationaux (ASCO, ESMO, ERS, AACR, WCLC) : Roche, MSD, BMS, Astra-Zeneca, Lilly, Pfizer, Abbvie

Honoraires personnels pour **participation a des conseils scientifiques ou “advisory boards”**: organisés par Lilly, Astra-Zeneca, BMS, Pfizer, Roche, MSD, Boehringer, Inventiva, Paredox Therapeutics

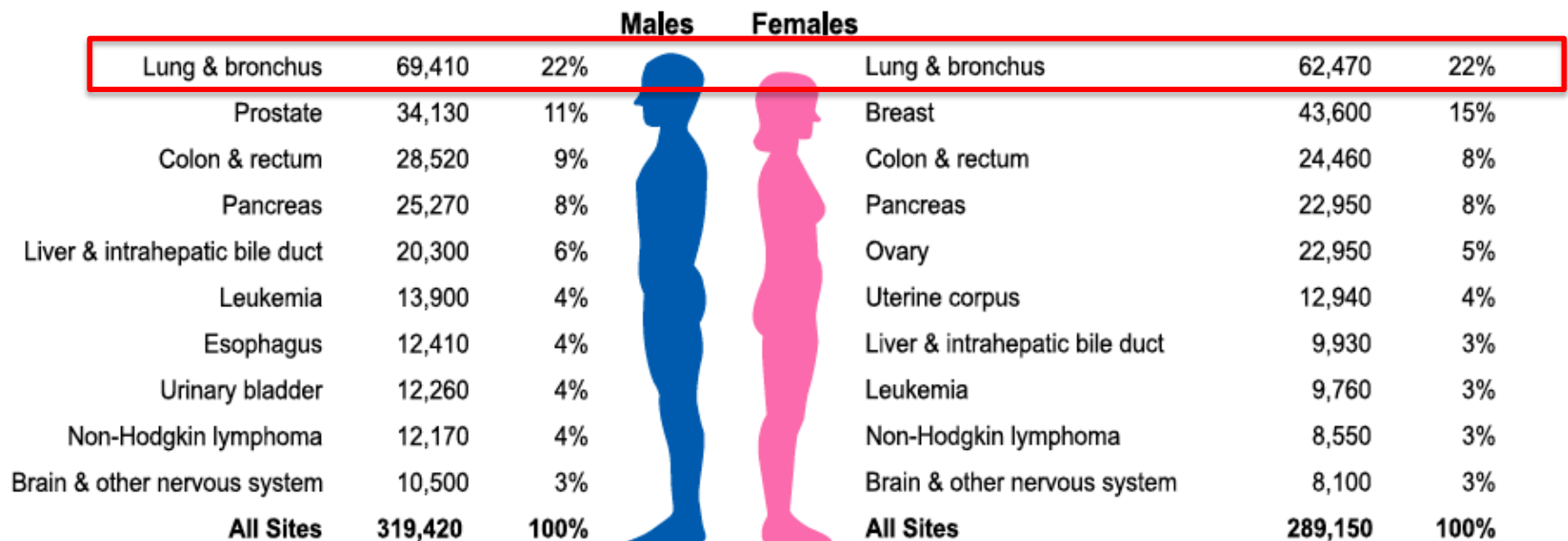
L'ensemble des sommes perçues n'excède pas 15 000 euros au cours des 10 dernières années

Estimated New Cases

Cancer Statistics 2021 Siegel RL *et al.*
CA Cancer J Clin, 2021; 71:7-33



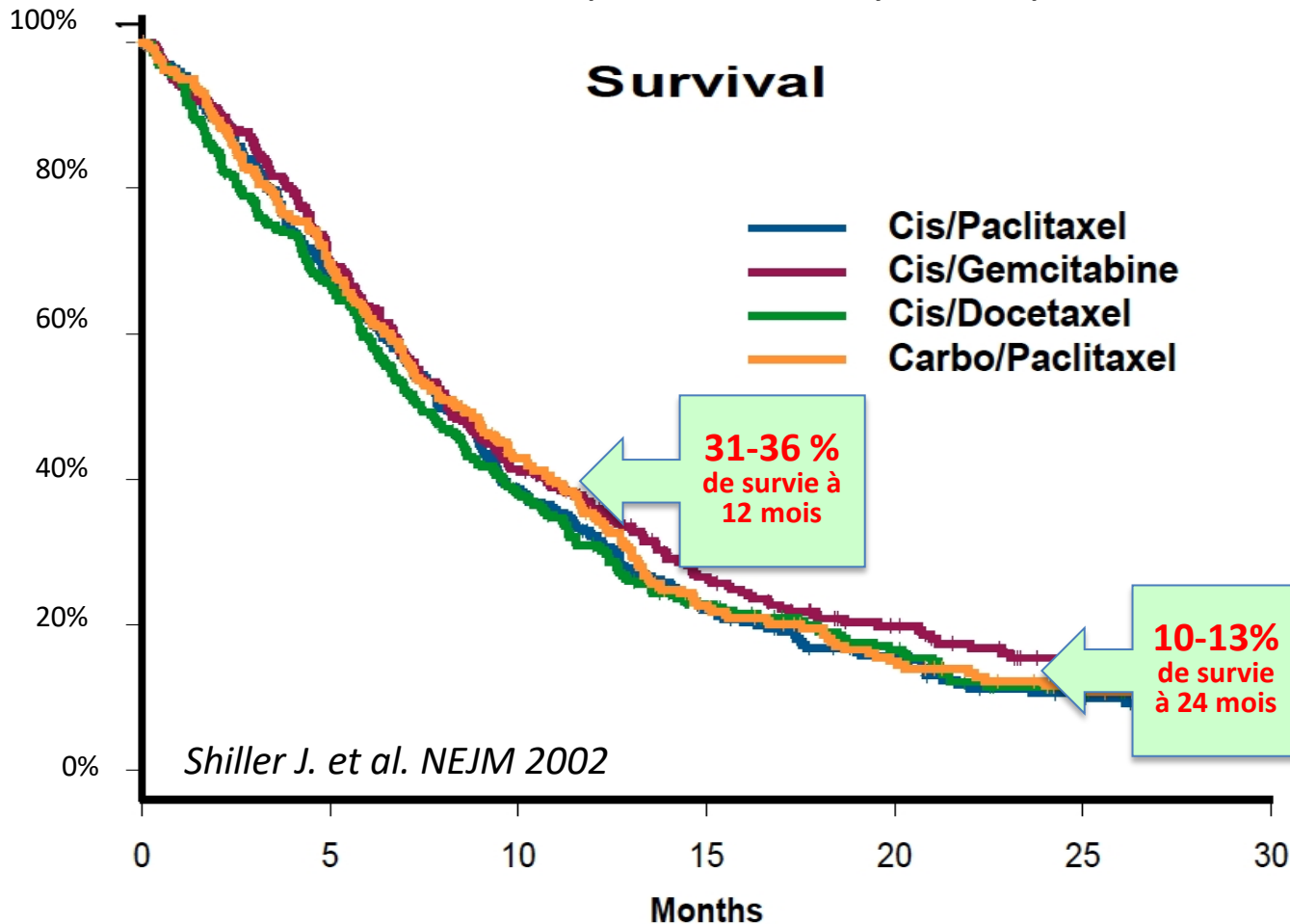
Estimated Deaths



De 2002... à 2019: le chemin parcouru pour les NSCLC stades IV sans mutation addictive

ECOG 1594

doublets de platine avec cytotoxiques de 3^{ème} génération



1^{ère} Étude de « switch » maintenance positive: JMEN

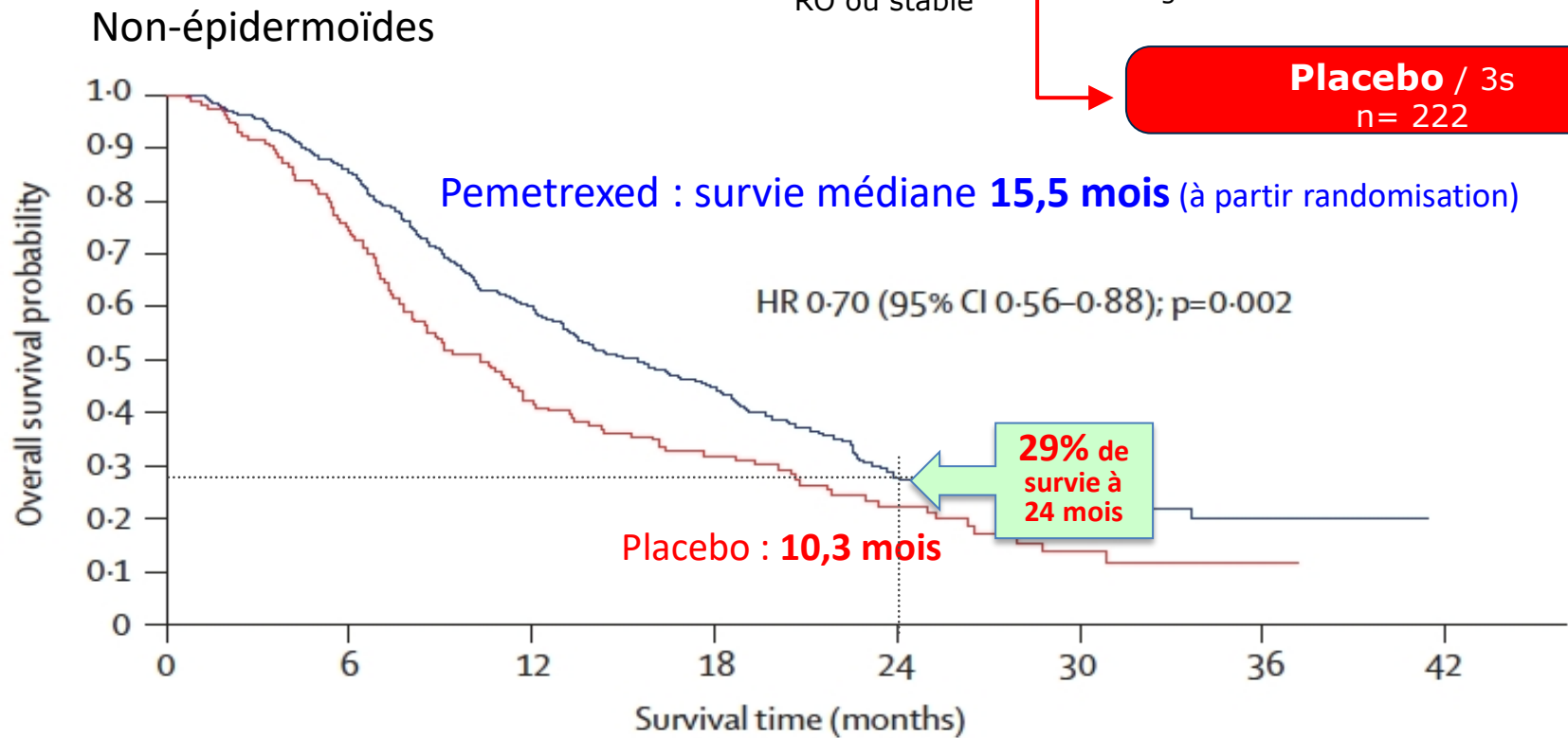
CBNPC, Stade IIIB w, IV
1^o ligne CT **SANS** pemetrexed
PS 0,1
CT à base de sels
Platine 4 cycles
RO ou stable

R

2/1
Etude Double
aveugle

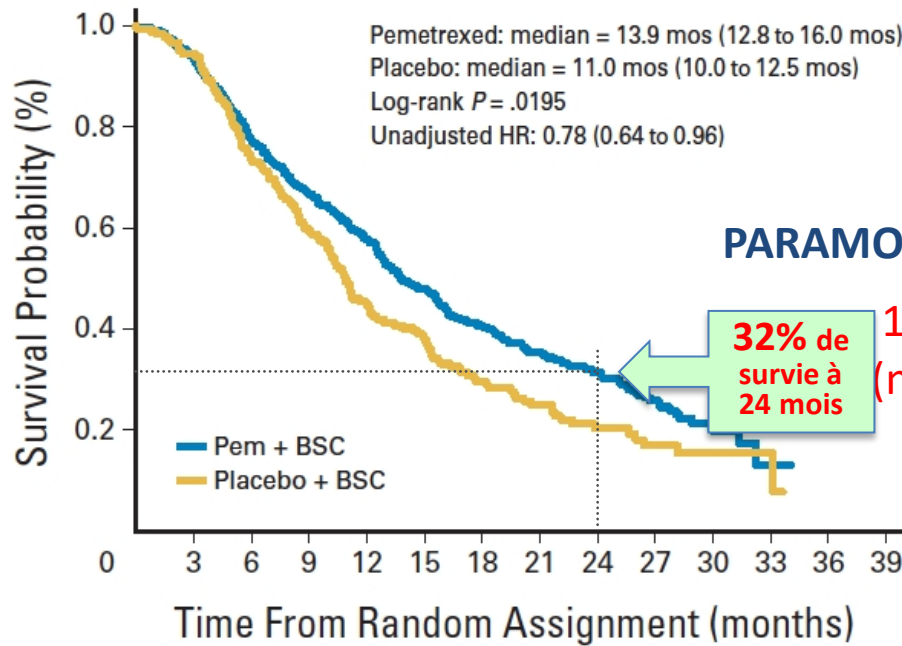
Pemetrexed 500 mg/m²/3s *
n= 441

Placebo / 3s
n= 222



ASCO 2008 - T.E. Ciuleanu et al. Lancet 2009

2012-2013: La maintenance de continuation dans les essais Paramount & Avaperl

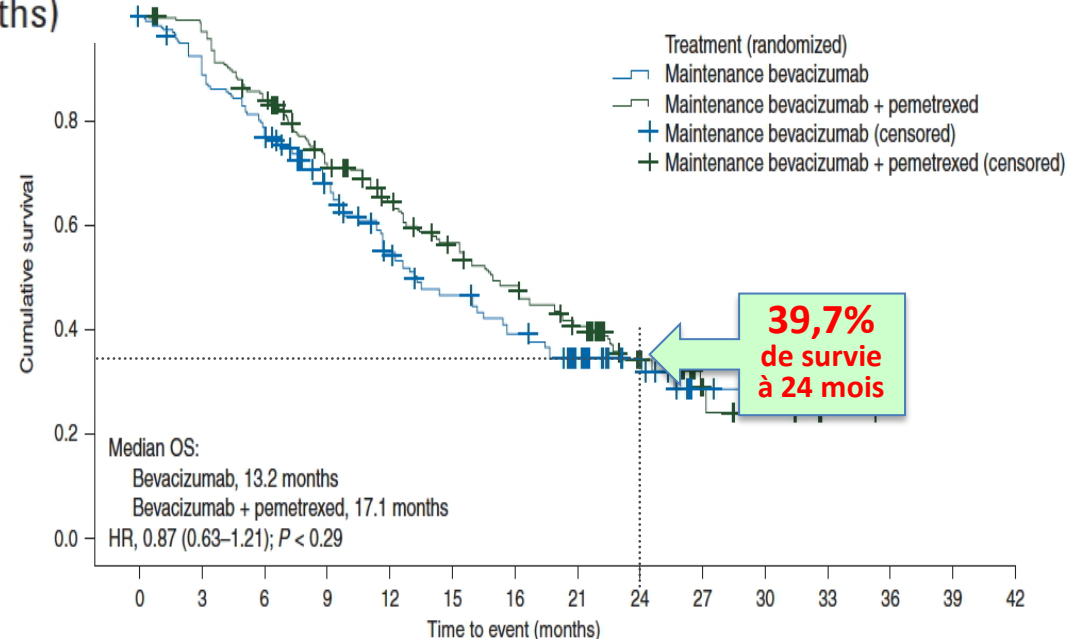


13.9 mois de médiane de SG
(non épidermoïdes)

Paz-Ares L et al. *Lancet Oncol* 2012, *JCO* 2013;
Barlési F. et al. *JCO* 2013, *Ann. Oncol.* 2014

AVAPERL

17,1mois de médiane de SG
depuis la randomisation
(non épidermoïdes éligibles avastin)

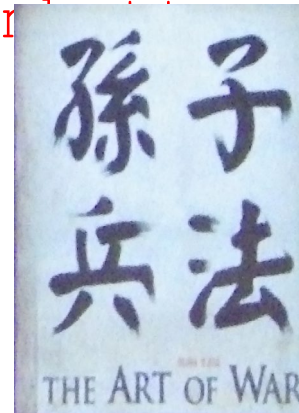


2015: la 2^{ème} révolution thérapeutique dans les cancers broncho-pulmonaires: L'immunothérapie

L'excellence suprême consiste
à casser la résistance de
l'ennemi...sans combattre

Sun Tzu (544-496 av JC)

« L'Art de la Guerre »



Essais de phase 3 de 2^{ème} ligne: CheckMate 017 (épi)

Brahmer J. *et al.* *NEJM*, 31 May 2015

CheckMate 057 (non-épi)

Borghaei H *et al.* *NEJM*, 27 Sept. 2015



Dr. J Allison Dr. T.Honjo

Le ciblage des points de contrôle immunitaires des lympho T cytotoxiques



Anticorps **Anti-PD-1** ciblent les cellules T infiltrant la tumeur (TILs)
Anticorps **Anti-PD-L1** ciblent les cellules tumorales

Anticorps **Anti-CTLA-4** ciblent les lymphocytes T périphériques des ganglions

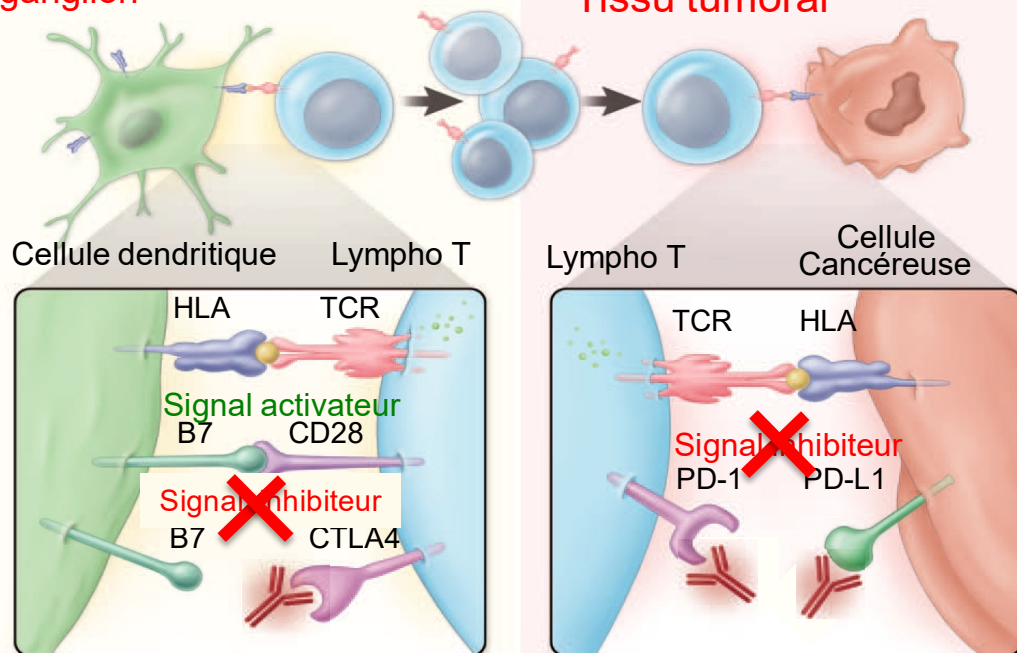


Phase d'amorçage

ganglion

Phase effectrice

Tissu tumoral



PD-1

CTLA-4

Régule l'activité des cellules T effectrices dans les tissus et la tumeur

Régule les étapes précoces de l'activation des lympho T

Exprimé par toutes les cellules sanguines

Exprimé exclusivement par les lympho T

Expression induite c/o les autres lymphocytes: B et cellules NK...

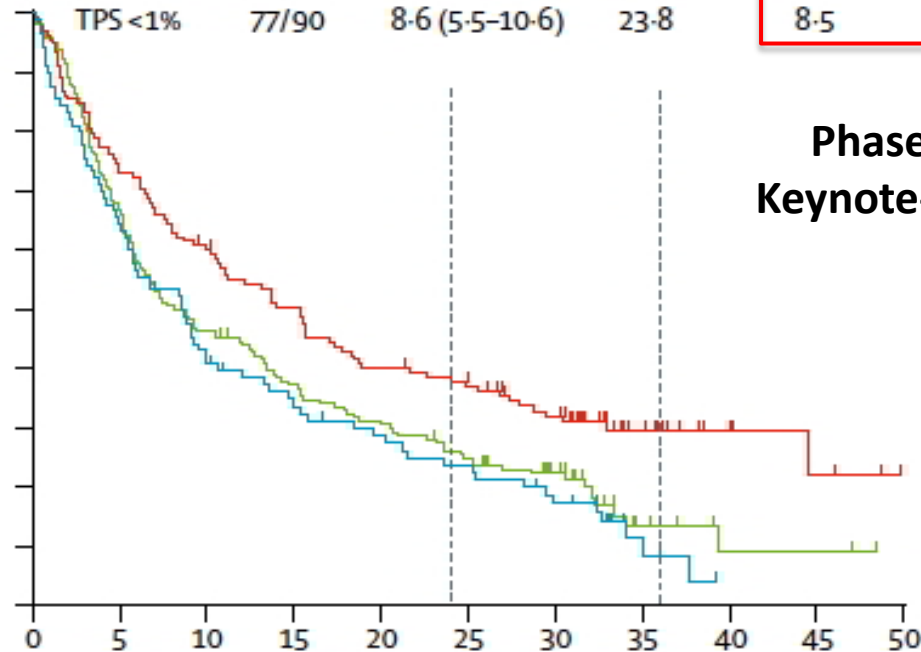
Preuve de principe de l'immunothérapie:

Les longues survies avec anticorps anti-PD1 dans les CBNPC métastatiques traités en 2L où au-delà (2015-2019)

D Previously treated patients

	Events, n/N	Median (95% CI), months	24-month rate, %	36-month rate, %
TPS ≥50%	95/138	15.4 (10.5-18.5)	38.6	29.7
TPS 1-49%	137/168	8.5 (6.0-12.7)	26.2	13.5
TPS <1%	77/90	8.6 (5.5-10.6)	23.8	8.5

Phase I
Keynote-001



138	101	82	68	54	48	38	13	5	3	0
168	112	78	61	51	40	26	6	2	2	0
90	58	36	28	23	19	13	4	0	0	0

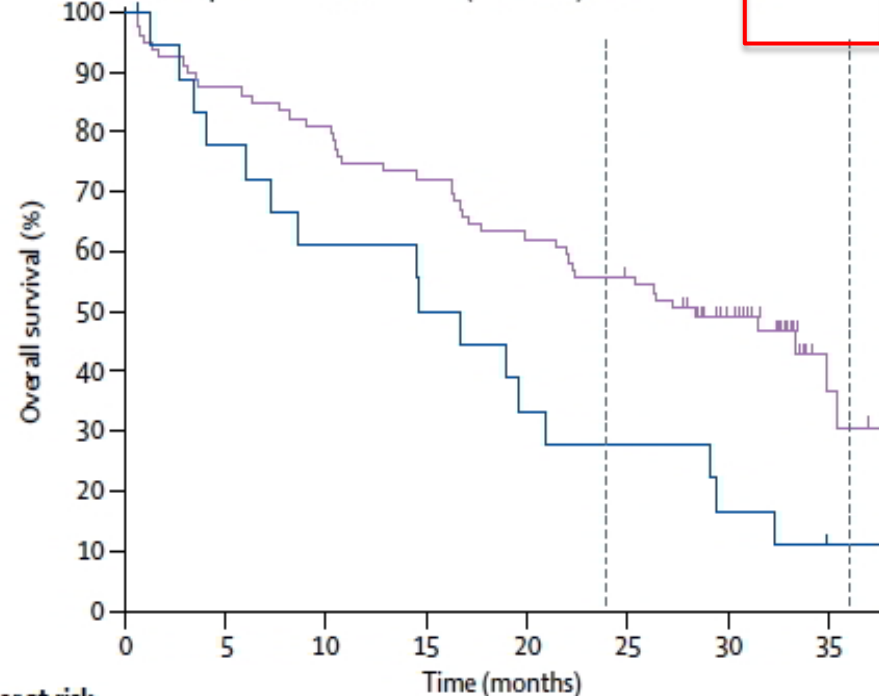
Number at risk

Squamous

Non-squamous

Treatment naive patients

	Events, n/N	Median (95% CI), months	24-month rate, %	36-month rate, %
Squamous	16/19	15.6 (6.0-21.0)	27.8	11.1
Non-squamous	45/79	28.4 (21.5-35.4)	55.7	30.6



19	14	11	9	6	5	3	1
79	69	64	57	49	43	29	6

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D.,
Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D.,
Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D.,
Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D.,
Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D.,
Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D.,
for the KEYNOTE-024 Investigators*

NEJM 9 oct. 2016

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

J Clin. Oncol. 8 Jan. 2019

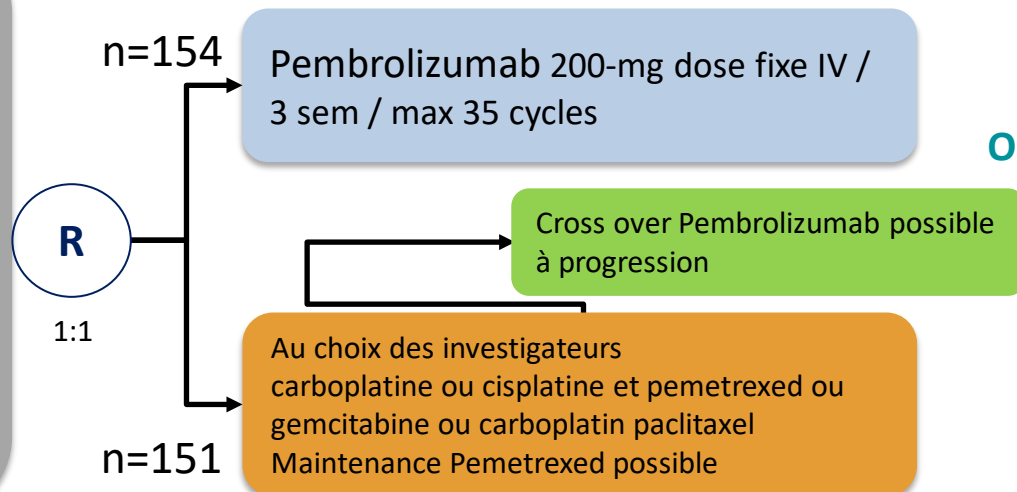
Martin Reck, MD, PhD¹; Delvys Rodríguez-Abreu, MD²; Andrew G. Robinson, MD³; Rina Hui, MBBS, PhD⁴; Tibor Csőszi, MD⁵; Andrea Fülöp, MD⁶; Maya Gottfried, MD⁷; Nir Peled, MD, PhD⁸; Ali Tafreshi, MD⁹; Sinead Cuffe, MD¹⁰; Mary O'Brien, MD¹¹; Suman Rao, MD¹²; Katsuyuki Hotta, MD, PhD¹³; Kristel Vandormael, MSc¹⁴; Antonio Riccio, PhD¹⁵; Jing Yang, PhD¹⁵; M. Catherine Pietanza, MD¹⁵; and Julie R. Brahmer, MD¹⁶

n = 305 Critères d'inclusion

- CBNPC avancé
- Ni EGFR muté ni ALK +
- Expression de PD-L1 $\geq 50\%$ des cellules tumorales
- Pas de maladie auto immune
- Pas de métastases cérébrales nontraitées

Stratification

- PS : 0 vs 1
- Histologie épi vs non épi
- Asie vs reste du monde

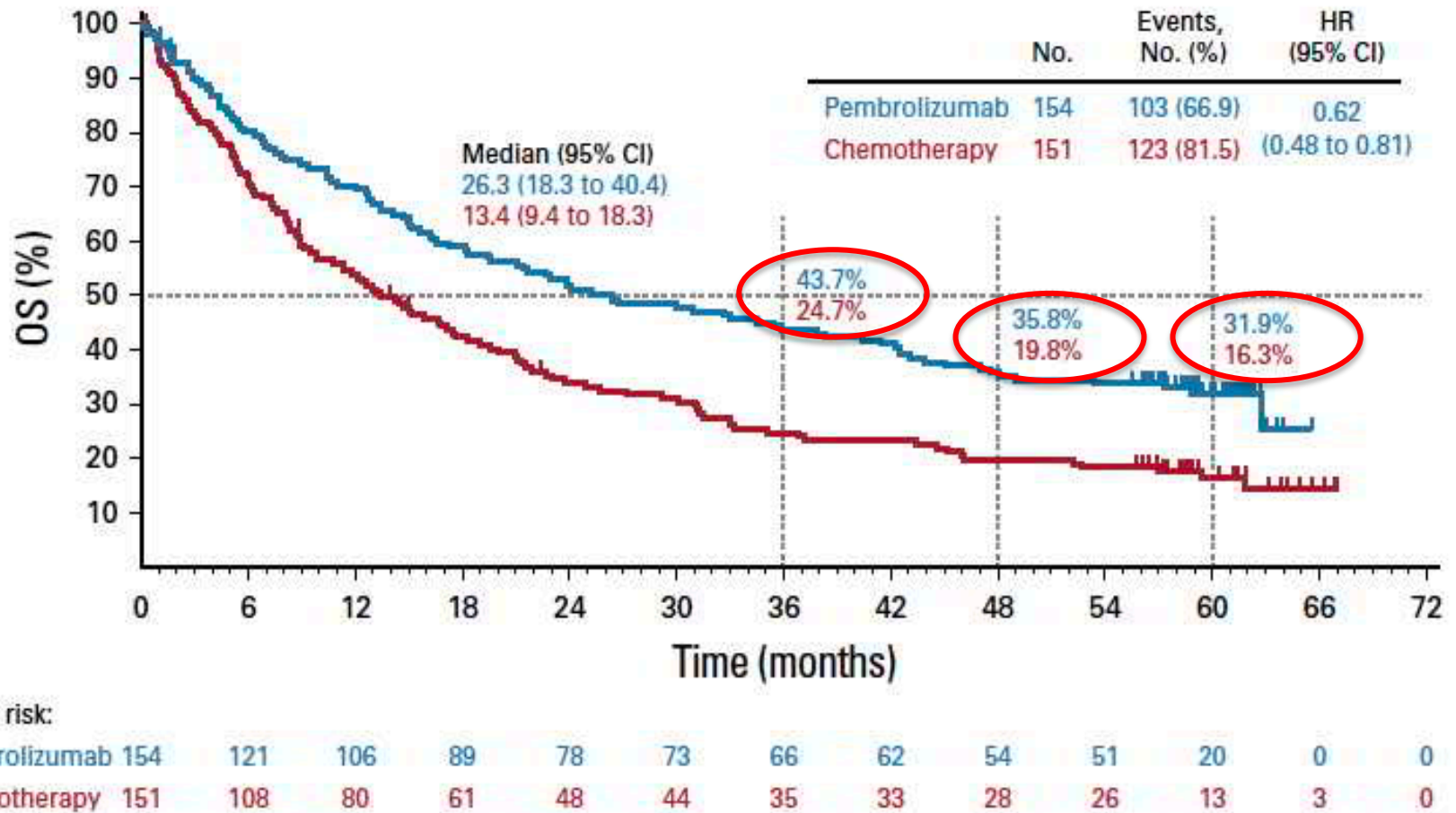


Objectif principal : SSP

KN-024: 2^{eme} update, JCO, avril 2021

Median fu= 59.9 months

Adéno+ Epi

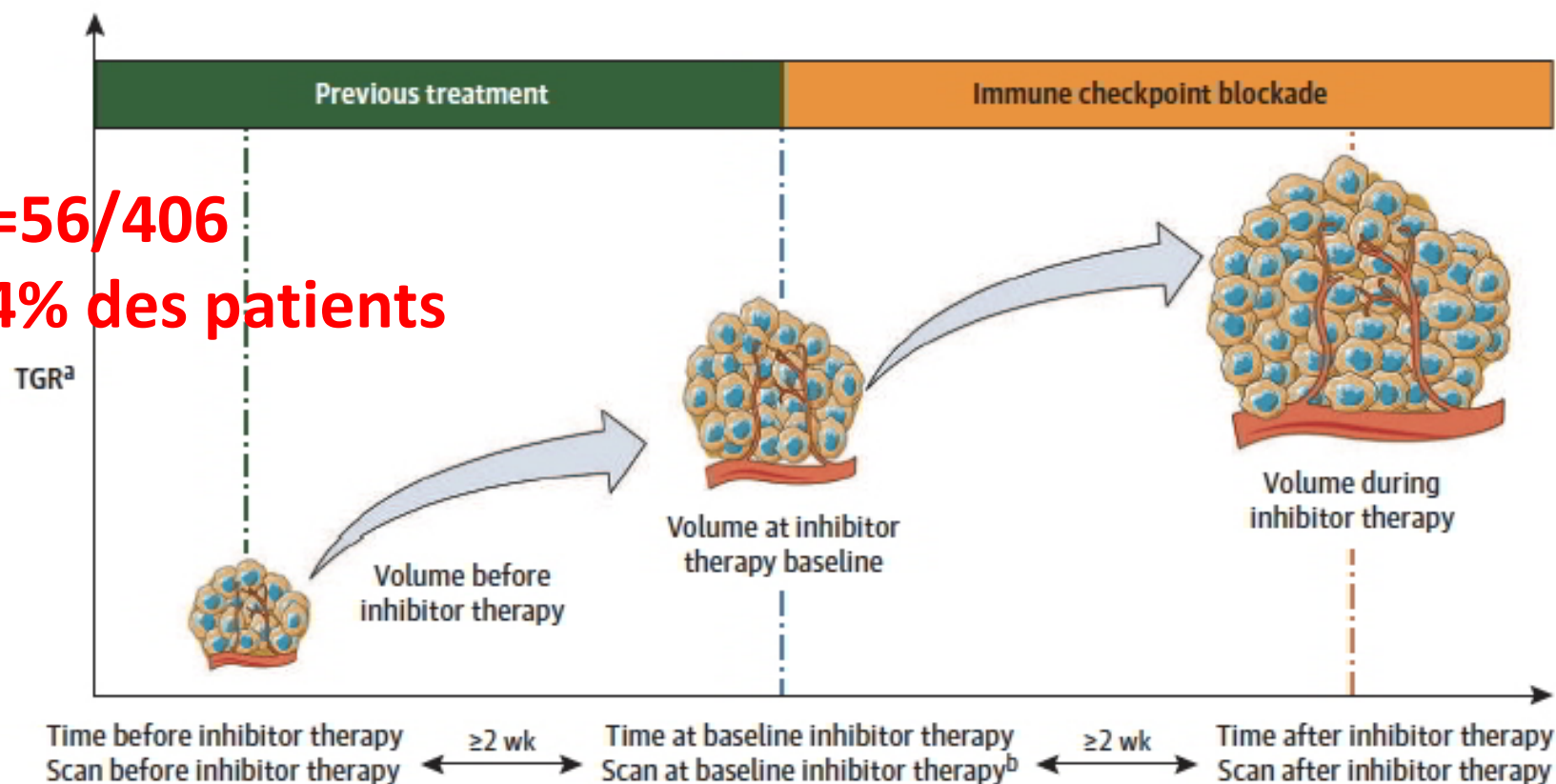


Recul à 5 ans

Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy

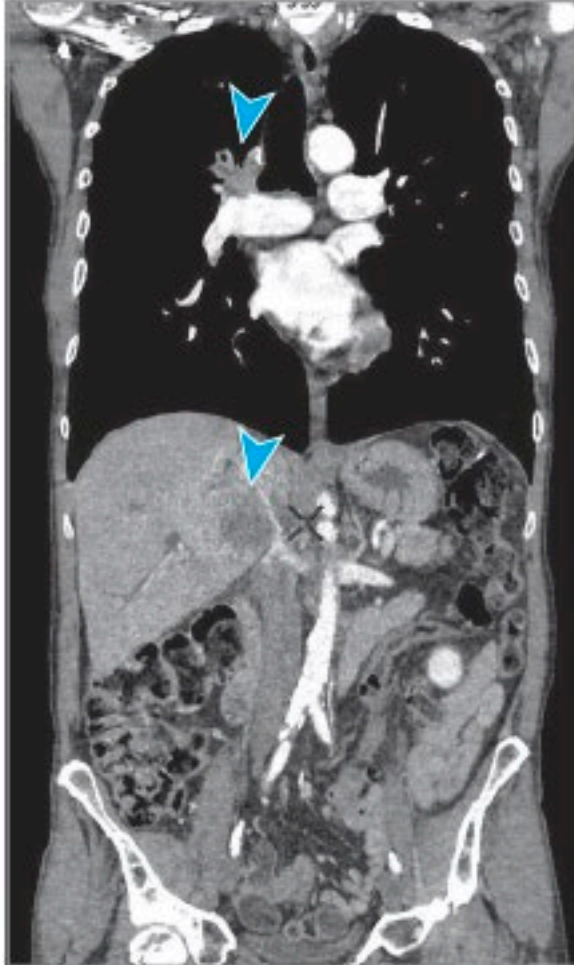
Roberto Ferrara, MD; Laura Mezquita, MD, PhD; Matthieu Texier, MSc; Jihene Lahmar, MD; Clarisse Audigier-Valette, MD; Laurent Tessonier, MD; Julien Mazieres, MD, PhD; Gerard Zalcman, MD, PhD; Solenn Brosseau, MD; Sylvestre Le Moulec, MD; Laura Leroy, MD; Boris Duchemann, MD; Corentin Lefebvre, MD; Remi Veillon, MD; Virginie Westeel, MD, PhD; Serge Koscielny, MSc; Stephane Champiat, MD; Charles Fert , MD, PhD; David Planchard, MD, PhD; Jordi Remon, MD; Marie-Eve Boucher, MD; Anas Gazzah, MD; Julien Adam, MD, PhD; Emilio Bria, MD; Giampaolo Tortora, MD, PhD; Jean-Charles Soria, MD, PhD; Benjamin Besse, MD, PhD; Caroline Caramella, MD

n=56/406
14% des patients

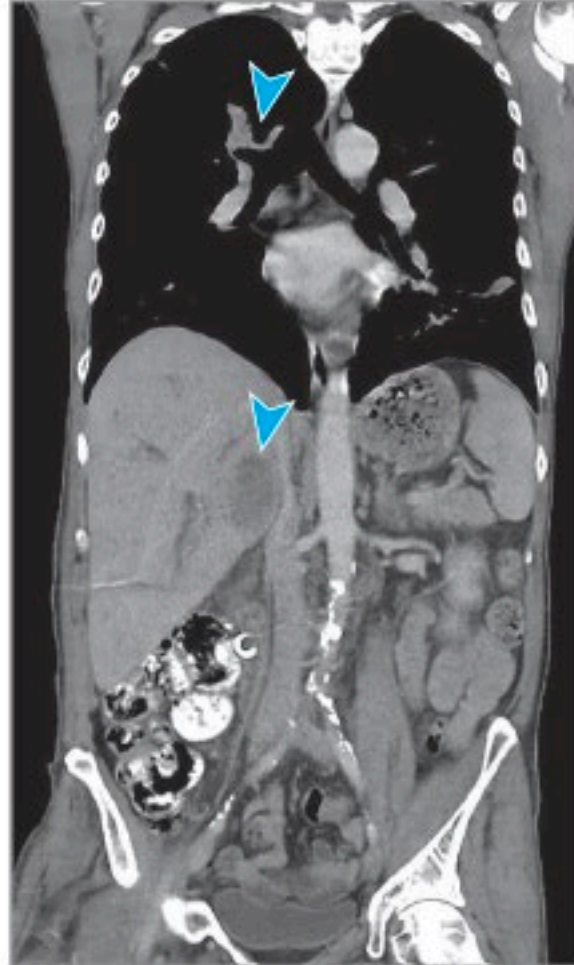


Hyper-progression

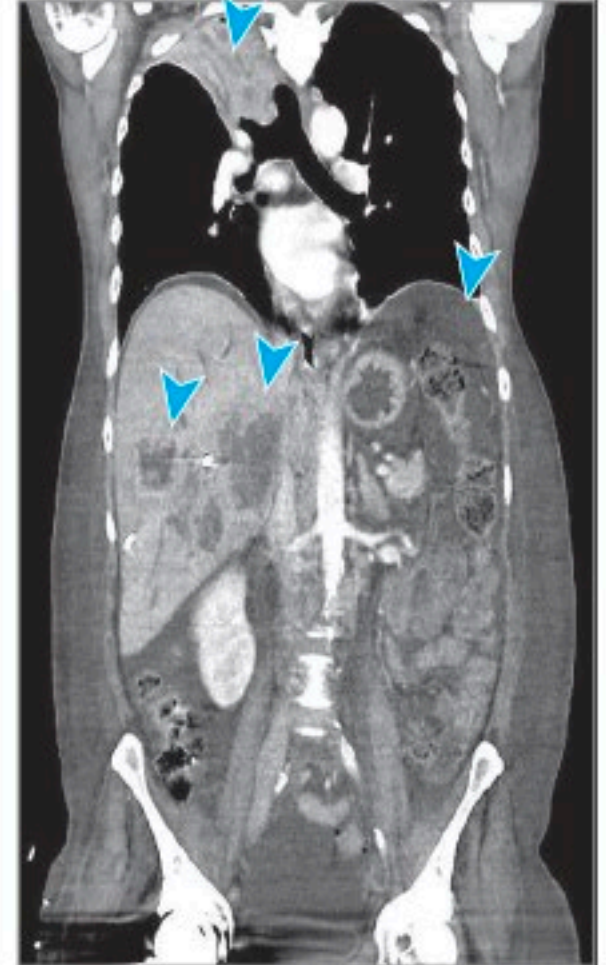
A Before baseline



B At baseline



C During inhibitor therapy



12 weeks

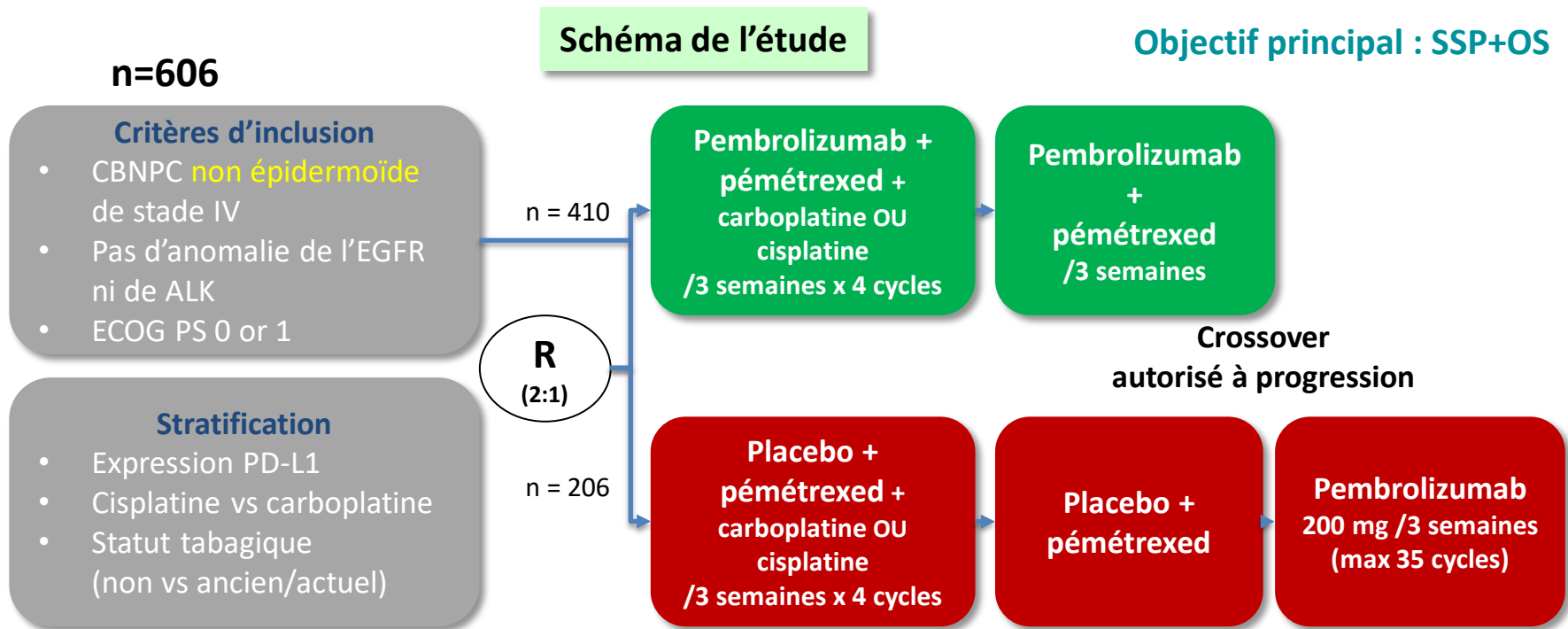


4 weeks upon Tt

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer **Non-SCC**

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino,
for the KEYNOTE-189 Investigators*

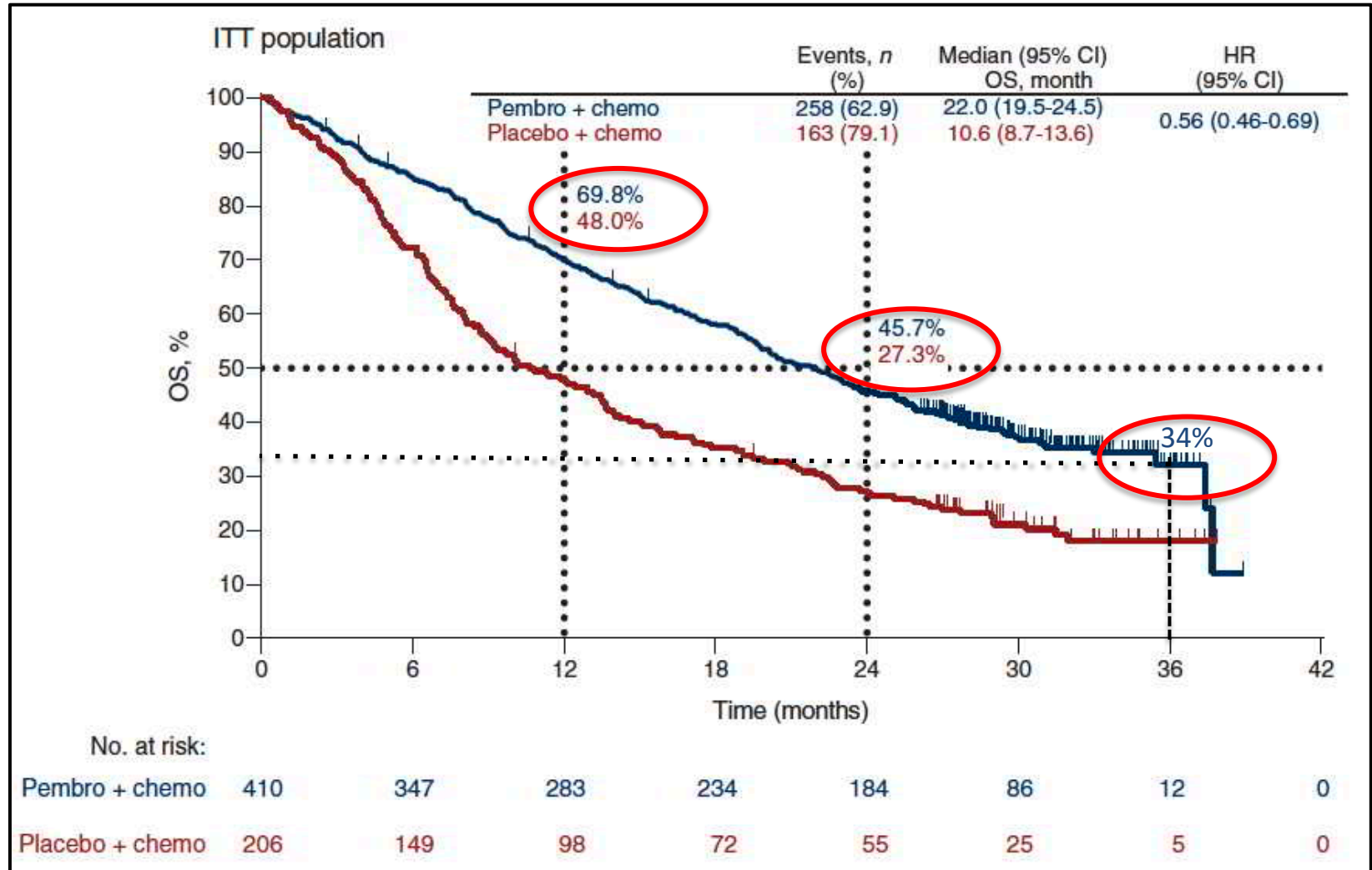
NEJM 16 April. 2018



Actualisation Keynote-189: Ann. Oncol Aug. 2021

Adéno K

31 mois de suivi médian



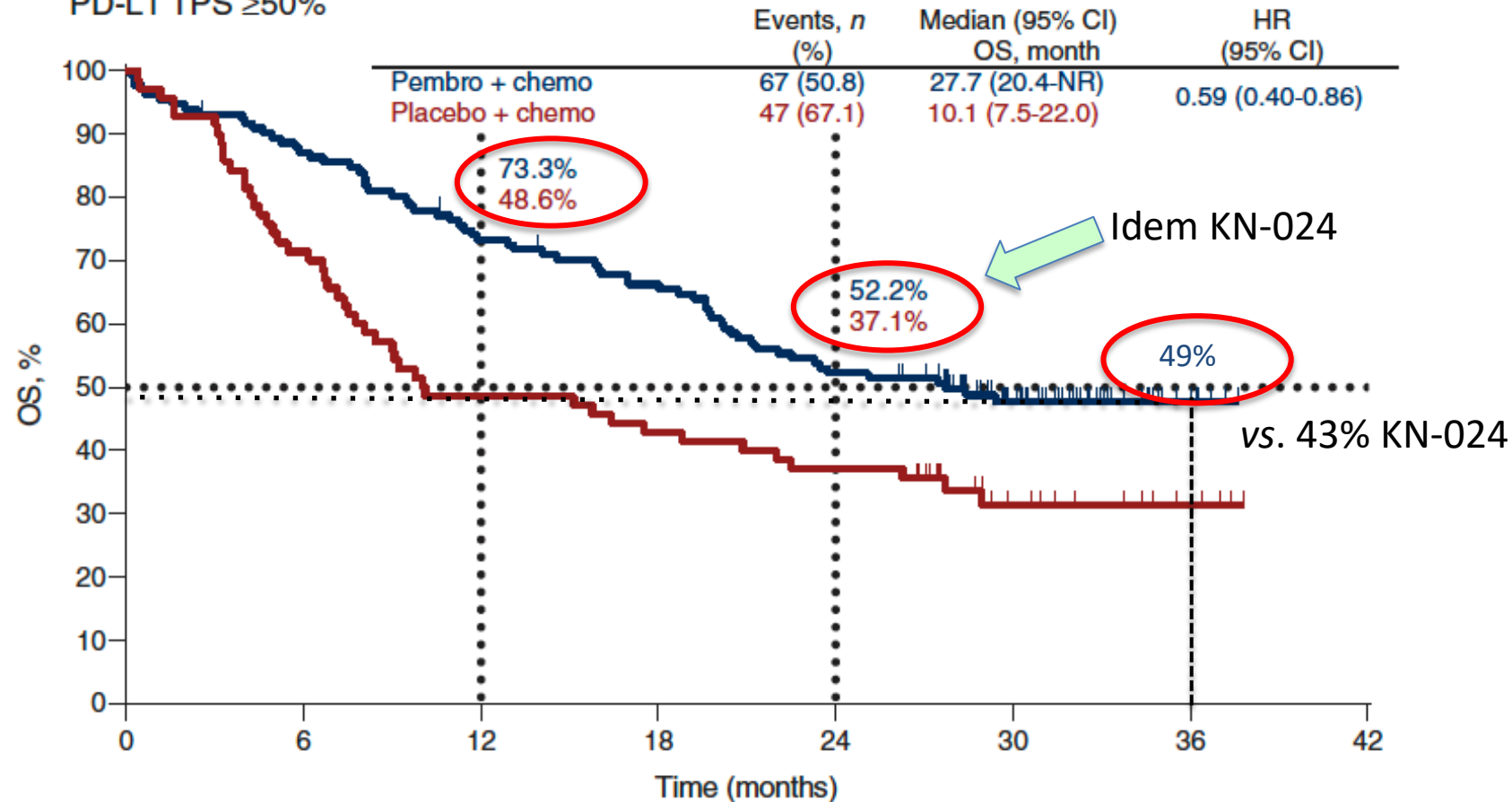
Actualisation Keynote-189: Ann. Oncol Aug. 2021

31 mois de suivi médian

Adéno K

B

PD-L1 TPS $\geq 50\%$



No. at risk:

Pembro + chemo	132	114	95	85	67	38	5	0
Placebo + chemo	70	50	34	30	26	12	4	0

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csőszi, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

NEJM 25 sept. 2018

n=559

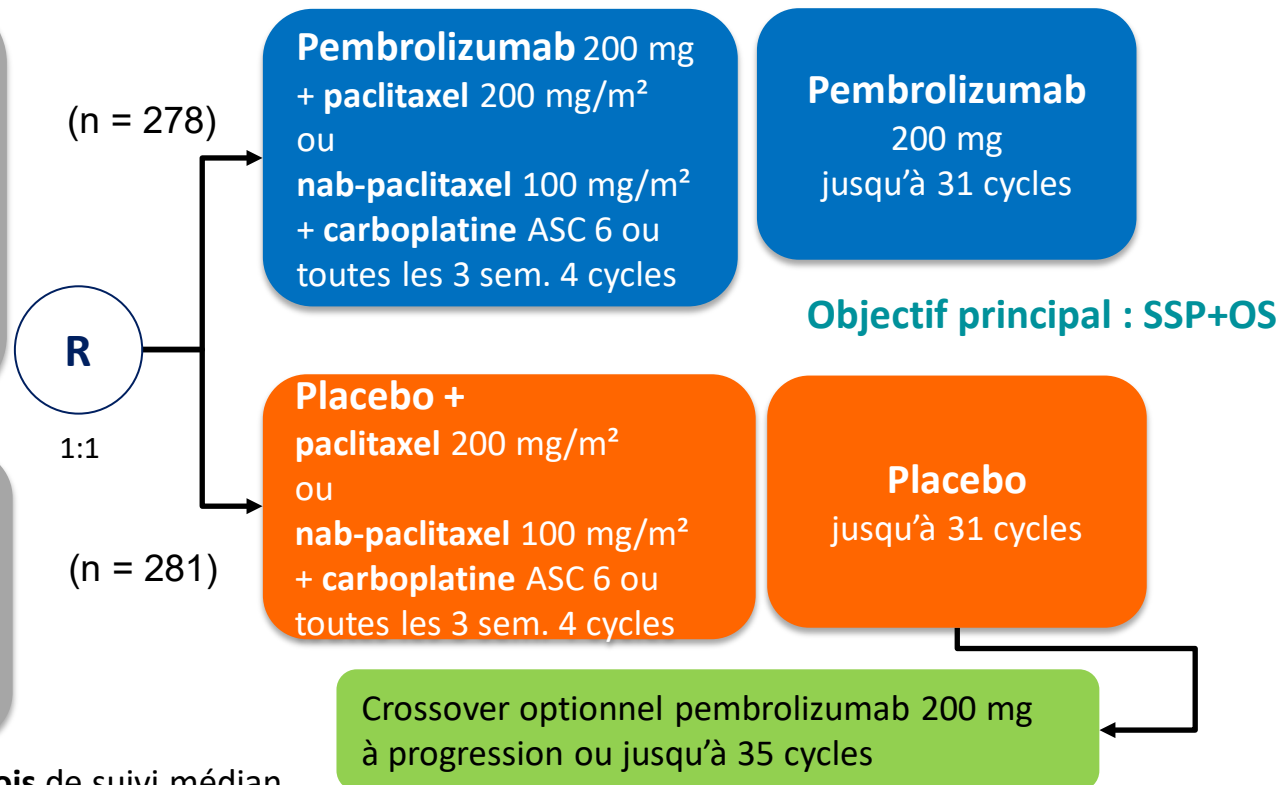
Critères d'inclusion

- CBNPC épidermoïde avancé
- PS OMS 0-1
- Tissus pour IHC PD-L1 Pas de pneumonie sous stéroïdes
- Pas de métastases cérébrales ou de métastases traitées

épidermoïdes

Stratification

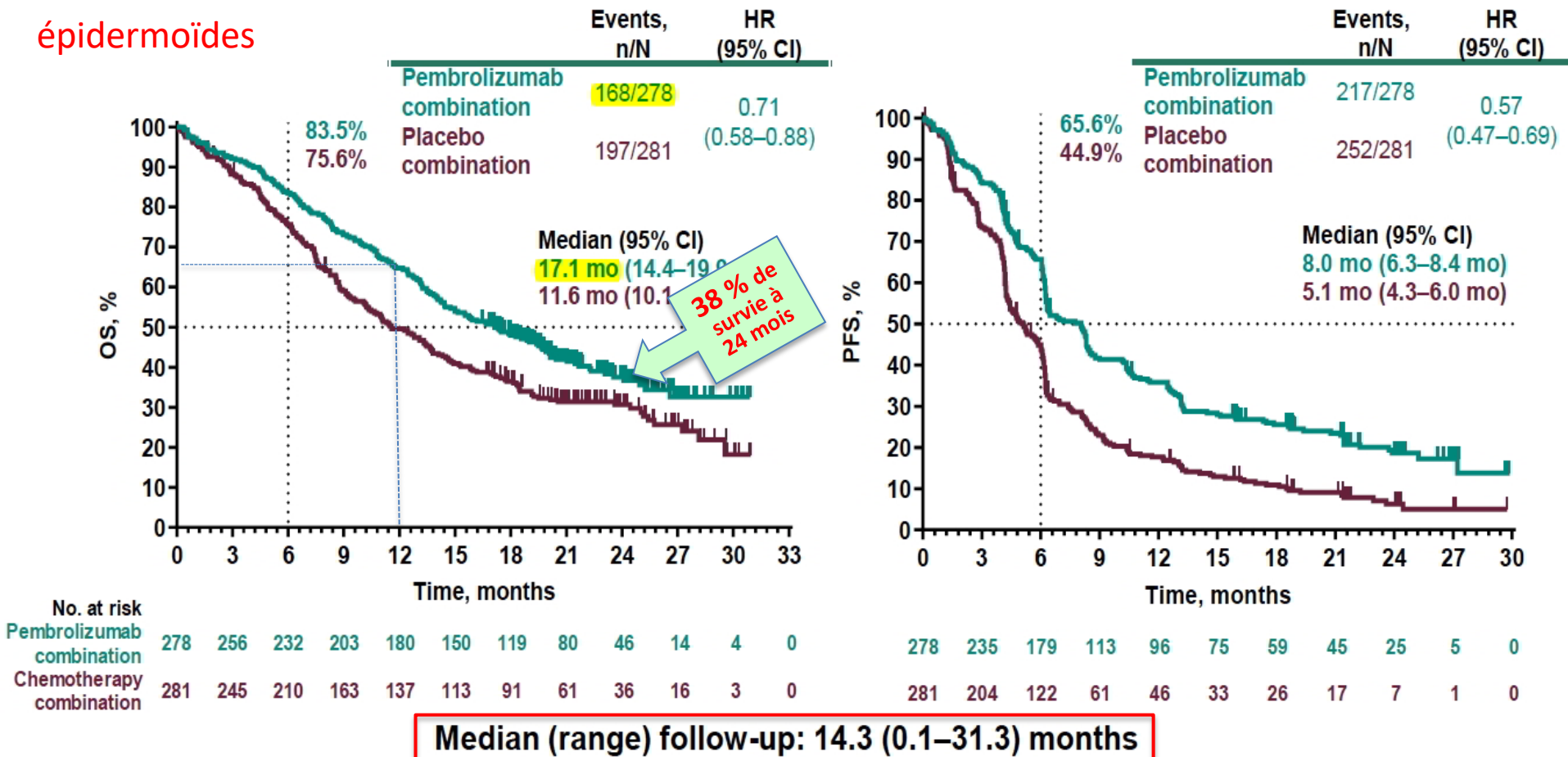
- Expression de PD-L1 (TPS > 1 % versus ≥ 1 %)
- Taxane
- Région géographique



Analyse finale Keynote-407: Paez-Aeres L et al. ESMO 2019

Kaplan-Meier Estimates of OS and PFS^a Overall Study Population Epi

épidermoïdes



^aResponse assessed per RECIST v1.1 by blinded independent central review. Data cutoff date: May 9, 2019.

Quid de la double immunothérapie dans les CBNPC ?

...Pas d'enregistrement Européen sans chimio initiale

2021 ASCO[®]
ANNUAL MEETING

First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: 2-year update from CheckMate 9LA

Martin Reck,¹ Tudor-Eliade Ciuleanu,² Manuel Cobo,³ Michael Schenker,⁴ Bogdan Zurawski,⁵ Juliana Menezes,⁶ Eduardo Richardet,⁷ Jaafar Bennouna,⁸ Enriqueta Felip,⁹ Oscar Juan-Vidal,¹⁰ Aurelia Alexandru,¹¹ Hiroshi Sakai,¹² Arnaud Scherpereel,¹³ Shun Lu,¹⁴ Luis G. Paz-Ares,¹⁵ David P. Carbone,¹⁶ Arteid Memaj,¹⁷ Sathiya Marimuthu,¹⁷ Phuong Tran,¹⁷ Thomas John¹⁸

¹Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany; ²Institutul Oncologic Prof Dr Ion Chiricuta and UMF Iuliu Hatieganu, Cluj-Napoca, Romania; ³Unidad de Gestión Clínica Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain; ⁴SF Nectarie Oncology Center, Craiova, Romania; ⁵Ambulatorium Chemioterapii, Bydgoszcz, Poland; ⁶Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; ⁷Instituto Oncológico de Córdoba, Córdoba, Argentina; ⁸University Hospital of Nantes and INSERM, CRCINA, Nantes, France; ⁹Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; ¹⁰Hospital Universitario La Fe, Valencia, Spain; ¹¹Institute of Oncology Prof Dr Alexandru Trestlioreanu Bucha, Bucharest, Romania; ¹²Saitama Cancer Center, Saitama, Japan; ¹³University of Lille, CHU Lille, INSERM U1189, OncoThAI, Lille, France; ¹⁴Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; ¹⁵Hospital Universitario 12 de Octubre, CNIO-H12o Lung Cancer Clinical Research Unit, Universidad Complutense & CiberOnc, Madrid, Spain; ¹⁶The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; ¹⁷Bristol Myers Squibb, Princeton, NJ, USA; ¹⁸Austin Hospital, Heidelberg, Australia

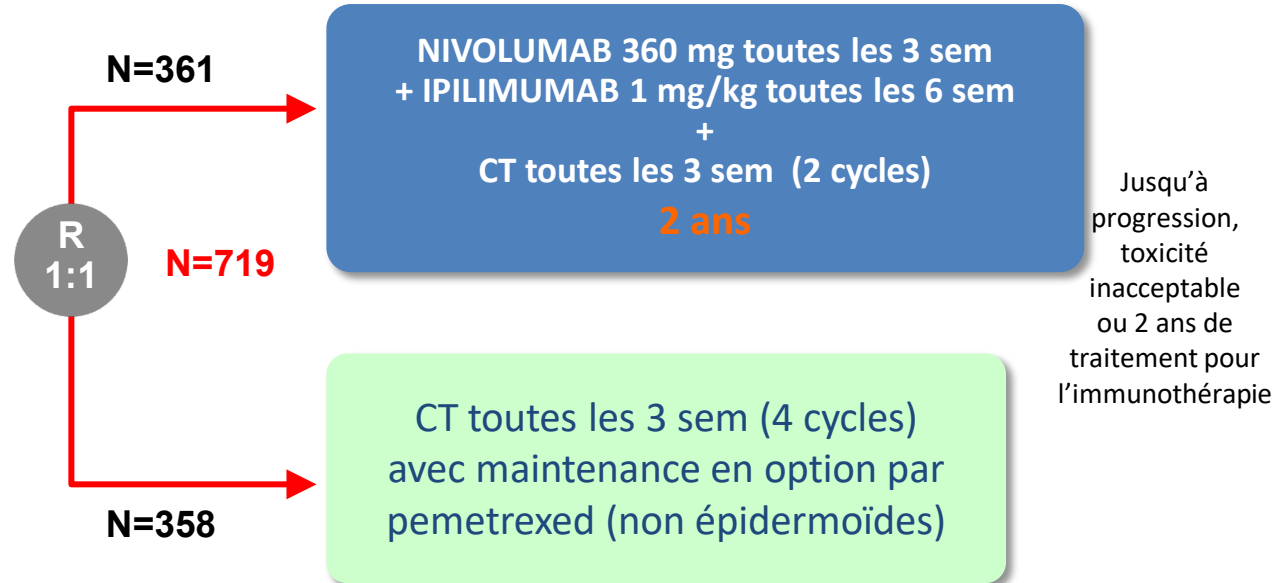
Association nivolumab + ipilimumab + 2 cycles de chimiothérapie versus chimiothérapie (4 cycles) en 1^{ère} ligne du CBNPC de stade avancé: Actualisation à 2 ans de la CheckMate 9LA

Critères d'éligibilité

- CBNPC Stade IV ou en rechute
- Pas de traitement systémique antérieur
- Pas de mutations d' EGFR ni altérations de ALK connues
- ECOG PS 0-1

Stratification selon:

Expression PD-L1 (<1% vs ≥ 1%),
genre, et histologie (épidermoïde vs non épidermoïde)



Objectif principal :

- SG

Objectifs secondaires :

- SSP par Comité de revue indépendant en aveugle
- Taux de réponse Objective par Comité de revue indépendant en aveugle
- Efficacité selon l'expression tumorale de PD-L1

Critère exploratoire:

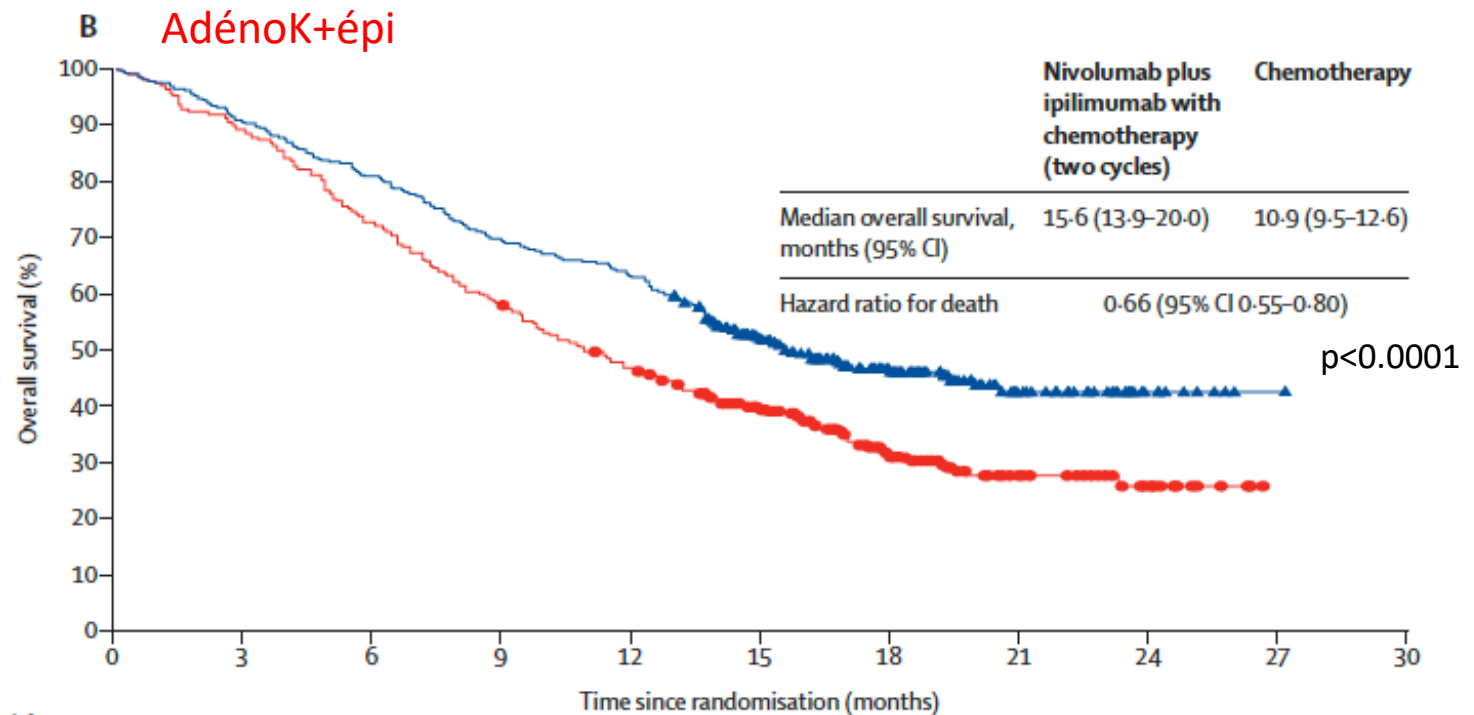
- Tolérance

First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial

Luis Paz-Ares, Tudor-Eliade Ciuleanu, Manuel Cobo, Michael Schenker, Bogdan Zurawski, Juliana Menezes, Eduardo Richardet, Jaafar Bennouna, Enriqueta Felip, Oscar Juan-Vidal, Aurelia Alexandru, Hiroshi Sakai, Alejo Lingua, Pamela Salman, Pierre-Jean Souquet, Pedro De Marchi, Claudio Martin, Maurice Pérol, Arnaud Scherpereel, Shun Lu, Thomas John, David P Carbone, Stephanie Meadows-Shropshire, Shruti Agarwal, Abderrahim Oukessou, Jinchun Yan, Martin Reck

Lancet Oncol 2021; 22: 198–211

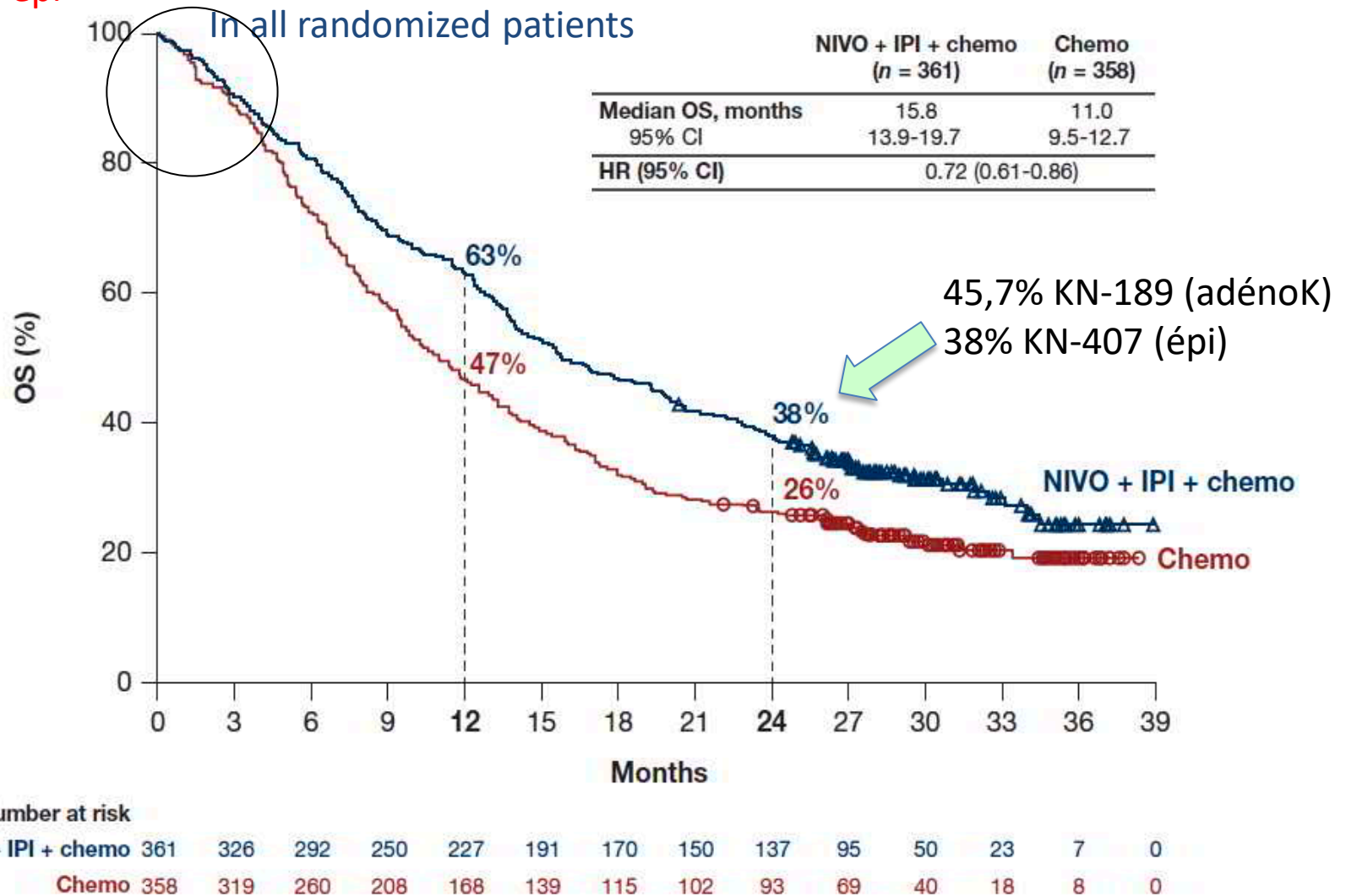
Médiane de suivi = 12,7 mois



	Number at risk (number censored)										
	0	3	6	9	12	15	18	21	24	27	30
Nivolumab plus ipilimumab with chemotherapy (two cycles)	361 (0)	326 (0)	292 (0)	250 (0)	227 (0)	153 (38)	86 (90)	33 (138)	10 (161)	1 (170)	0 (171)
Chemotherapy	358 (0)	319 (0)	260 (0)	208 (0)	166 (2)	116 (27)	67 (56)	26 (91)	11 (105)	0 (116)	0 (116)

CheckMate 9LA: actualisation à 2 ans

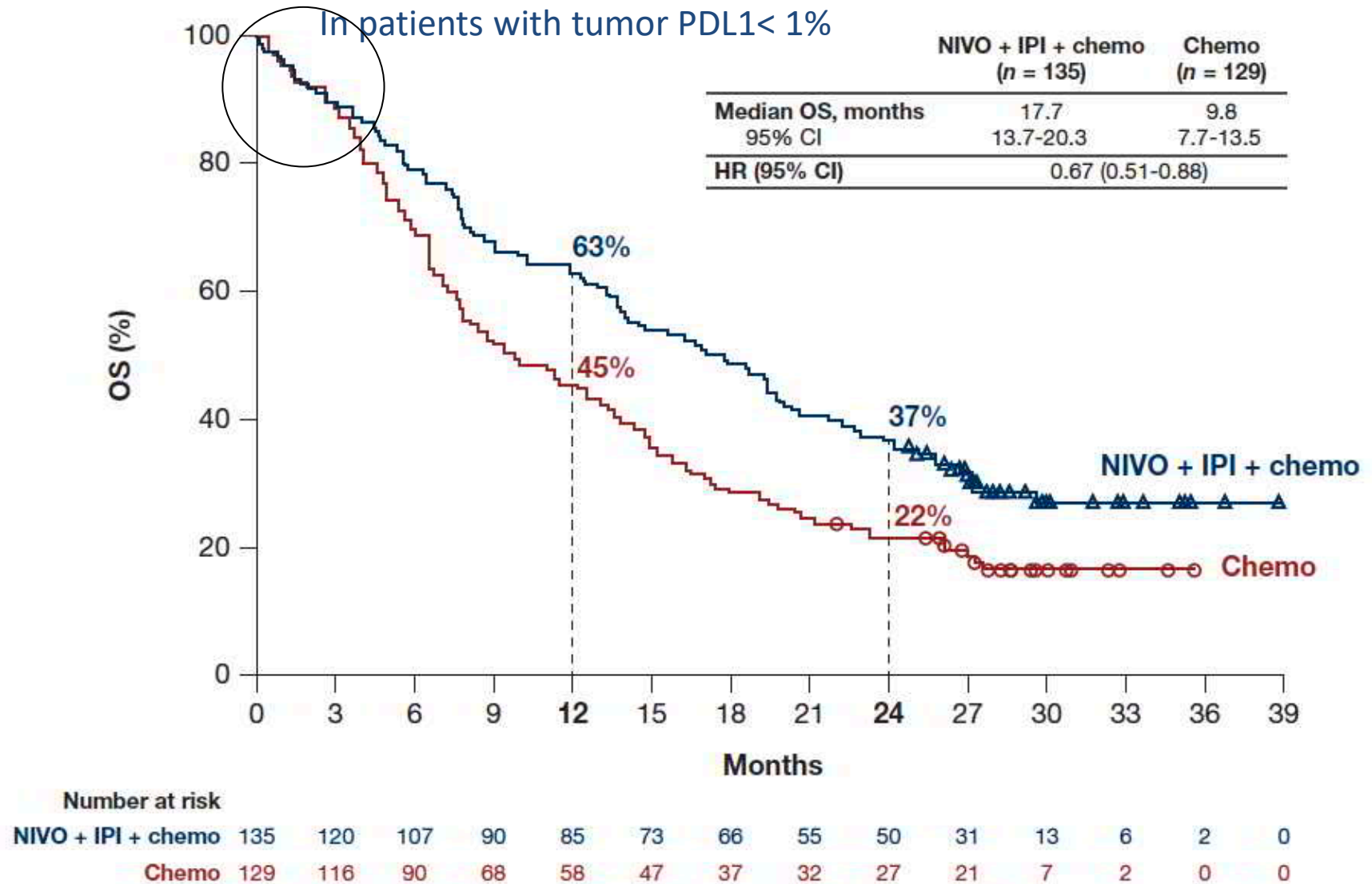
AdénoK+épi



Clôture de base : 18 février 2021 ; suivi minimum/médian pour la SG : 24,4 mois/30,7 mois.

Base de données actualisée au 9 mars 2020 ; suivi minimum : 12,7 mois pour la SG et 12,2 mois pour les autres critères

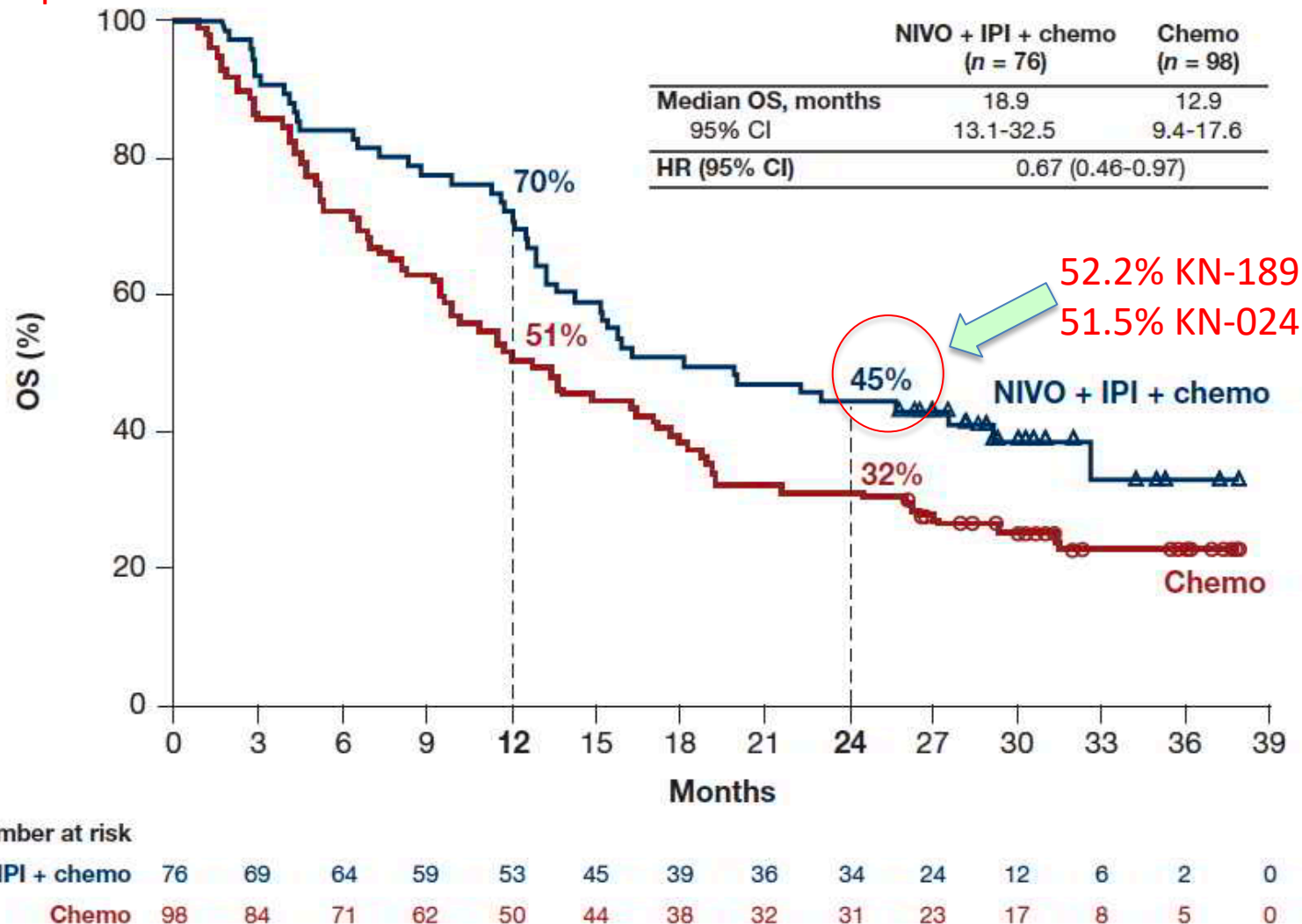
CheckMate 9LA: actualisation à 2 ans



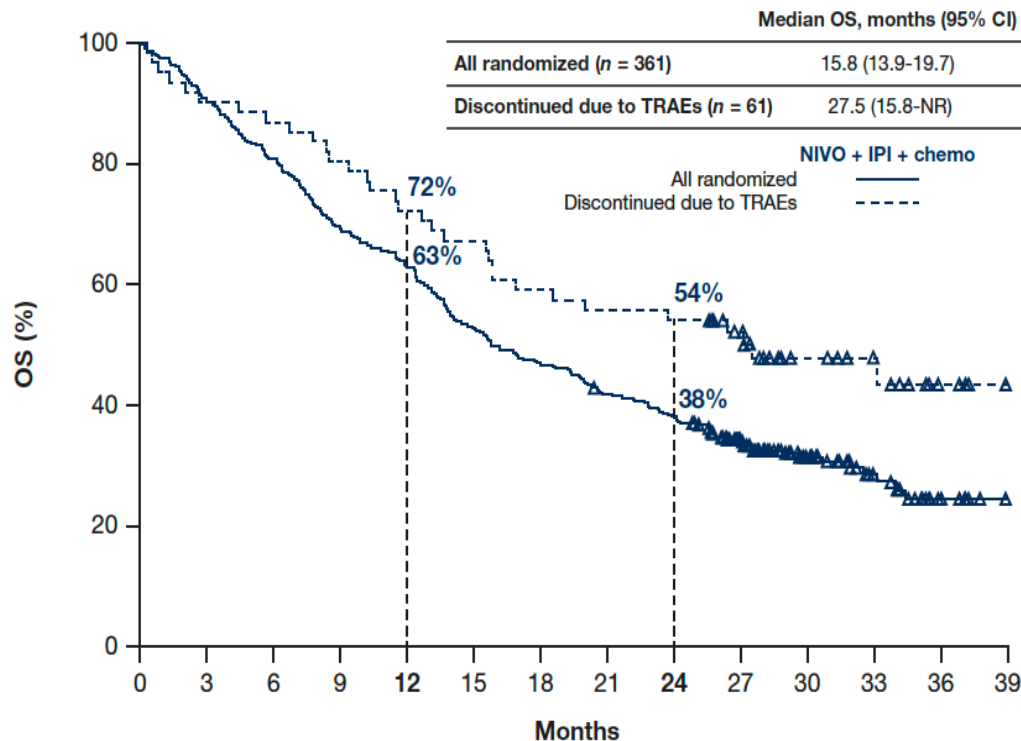
CheckMate 9LA: actualisation à 2 ans

AdénoK+épi

In patients with tumor PDL1>50%



Étude CheckMate 9LA : actualisation à 2 ans



Patients ayant interrompu IPI + NIVO + CT du fait d'un EI lié au traitement

	NIVO + IPI + CT (n = 61)
Survie médiane, mois	27,5
Survie à 2 ans, %	54
RO, n (%)	31 (51)
Durée médiane de réponse après l'arrêt du traitement, mois	14,5
Maintien de la réponse ≥ 1 an après l'arrêt du traitement, %	56

Number at risk (all randomized patients)														
NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Number at risk (patients who discontinued due to TRAEs)														
NIVO + IPI + chemo	61	55	53	49	44	41	36	34	33	26	15	11	4	0

Clôture de base : 18 février 2021 ; suivi minimum/médian pour la SG : 24,4 mois/30,7 mois.

Base de données actualisée au 9 mars 2020 ; suivi minimum : 12,7 mois pour la SG et 12,2 mois pour les autres critères.

Le temps des “me too”

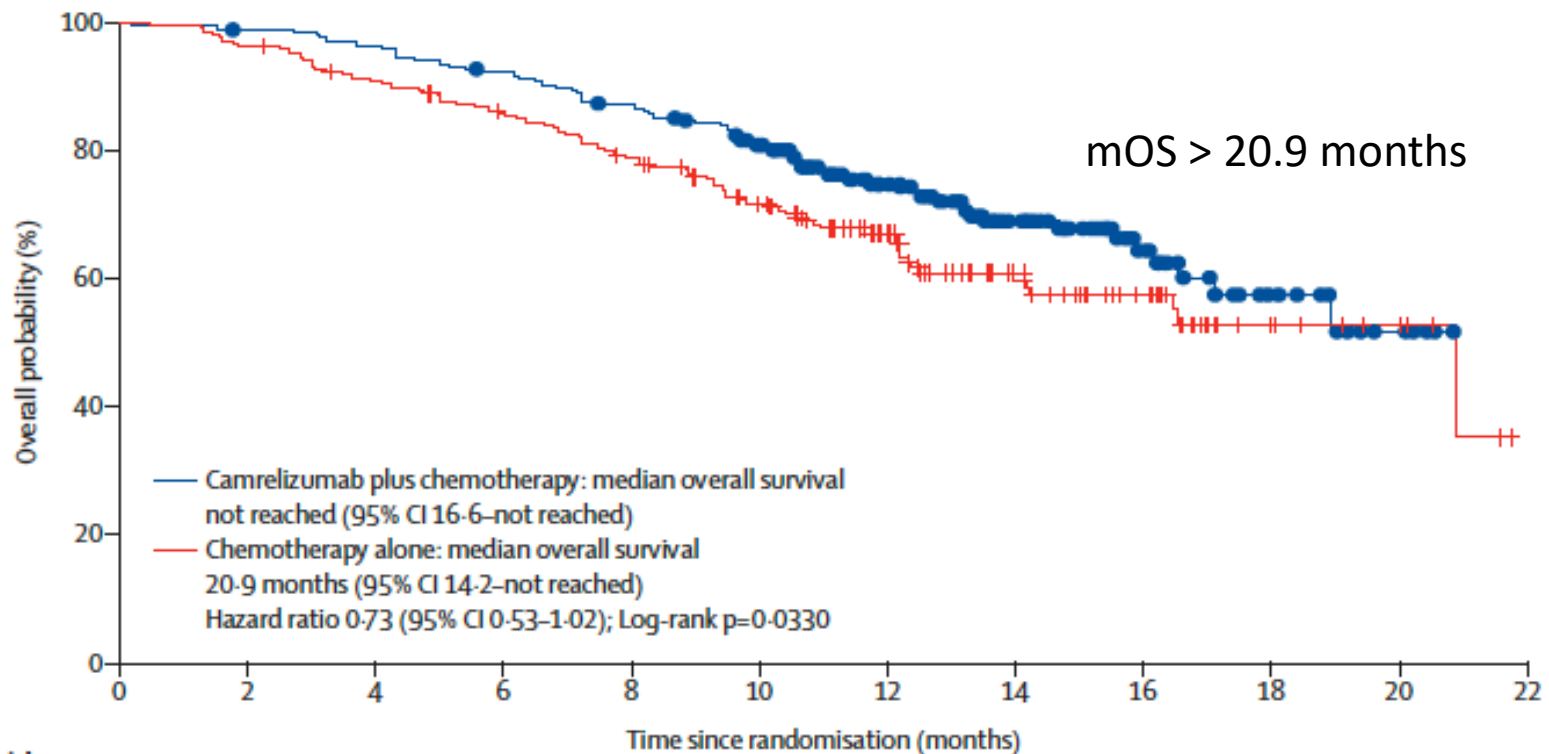
Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial

Zhou C. *et al.*

Lancet Respir Med 2021
9: 305-14

Médiane de suivi= 11.9 mo

Tout PD-L1



	Number at risk (number censored)											
Camrelizumab plus chemotherapy	205 (0)	202 (2)	196 (8)	187 (16)	176 (26)	155 (39)	109 (49)	75 (57)	37 (60)	15 (63)	5 (64)	0 (64)
Chemotherapy alone	207 (0)	199 (8)	186 (19)	173 (29)	158 (43)	134 (57)	94 (65)	57 (73)	32 (76)	12 (78)	6 (78)	0 (89)

Le temps des “me too”

Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer A Phase 3 Randomized Clinical Trial

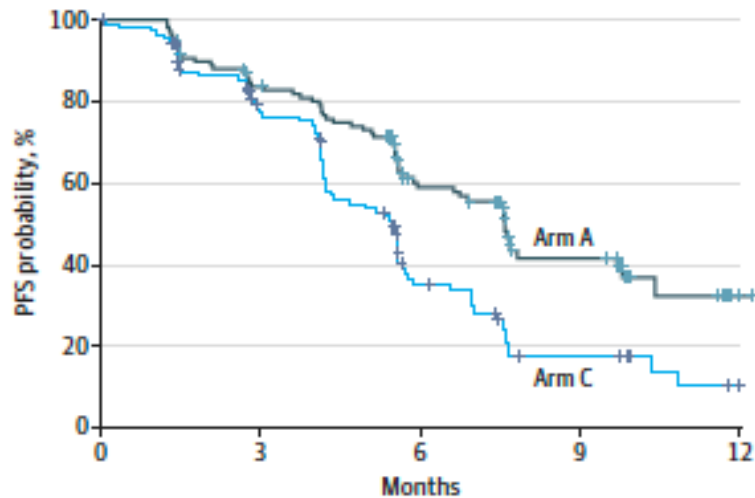
JAMA Oncol. doi:10.1001/jamaoncol.2021.0366

Published online April 1, 2021.

Wang J *et al.*

A Tislelizumab plus PC vs PC

Source	Events, No. (%)	Median (95% CI)	Hazard ratio (95% CI)	P value
Arm A	60 (50.0)	7.6 (6.0-9.8)	0.52 (0.37-0.74)	<.001
Arm C	76 (62.8)	5.5 (4.2-5.7)		

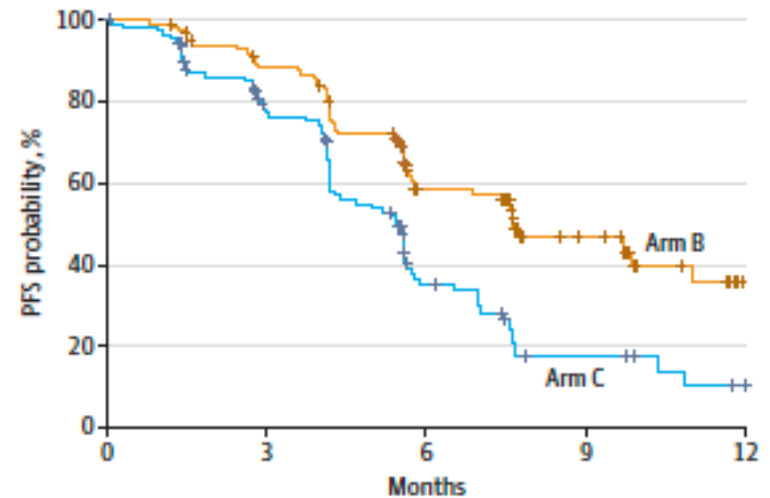


No. at risk

Arm A	120	95	50	23	1
Arm C	121	74	27	10	0

B Tislelizumab plus nab-PC vs PC

Source	Events, No. (%)	Median (95% CI)	Hazard ratio (95% CI)	P value
Arm B	56 (47.1)	7.6 (5.8-11.0)	0.48 (0.34-0.68)	<.001
Arm C	76 (62.8)	5.5 (4.2-5.7)		



No. at risk

Arm B	119	98	47	23	1
Arm C	121	74	27	10	0

Median PFS= 7.6 months

Comment comparer ces traitements/statégies ?



En comparant leur tolérance ?

Mais attention: plus la médiane de suivi est courte moins il y aura de toxicités rapportées... même si le maximum des tox immuno-médiées apparaissent dans le 1^{er} quadrimestre

Safety Summary of Treatment-Related AEs in All Patients Treated With NIVO + IPI, Chemo, or NIVO: CheckMate-227

TRAE, %	NIVO + IPI (n = 576)		Chemo (n = 570)		NIVO ^b (n = 391)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	77	33	82	36	66	19
TRAE leading to discontinuations	18.1%	12.3%	9	5	12	7
Most frequent TRAEs (≥15%)						
Diarrhea	2	2	10	1	12	< 1
Rash	2	2	5	0	11	1
Fatigue	2	2	19	1	11	< 1
Decreased appetite	10	< 1	36	2	6	< 1
Nausea	4	1	33	12	3	< 1
Anemia	4	0	15	< 1	2	0
Constipation	< 1	0	17	10	< 1	0
Neutropenia						
Treatment-related deaths	1.4%		1.1%		1 %	

- With 18 months of follow-up, the safety profile was consistent with the previous report¹ and did not increase
- Median duration of treatment was 4.2 mo (0.03–25.5) with NIVO + IPI, 2.6 mo (0.03–37.6+) with chemo, and 4.6 mo (0.03–25.5) with NIVO.

- Treatment-related deaths in the NIVO + IPI arm (n = 8) were: **pneumonitis (n = 4)**, shock, myocarditis, acute tubular necrosis, and cardiac tamponade; deaths in the chemo arm (n = 6) were: sepsis (n = 2), febrile neutropenia with sepsis, multiple brain infarctions, interstitial lung disease, and thrombocytopenia; deaths in the NIVO arm (n = 2) were: pneumonitis, and critical neutropenia with sepsis.

Le codage/étiquetage des toxicité compte !

2,4% de colites grade 3-4
(3,9 % ds KN-024; <1% ds KN-042; 5,2% ds KN-189; 2,8% ds IMpower150)

Table S10. Treatment-Related Select AEs with Nivolumab plus Ipilimumab and Nivolumab in All Treated Patients.

Treatment-Related Select AEs*	All Treated Patients			
	Nivolumab plus Ipilimumab [†] (N=576)		Nivolumab [‡] (N=391)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	<i>number of patients (percent)</i>			
Skin	196 (34.0)	24 (4.2)	83 (21.2)	4 (1.0)
Endocrine	137 (23.8)	24 (4.2)	51 (13.0)	2 (0.5)
Gastrointestinal	105 (18.2)	14 (2.4)	50 (12.8)	4 (1.0)
Hepatic	91 (15.8)	47 (8.2)	42 (10.7)	15 (3.8)
Pulmonary	48 (8.3)	19 (3.3)	30 (7.7)	6 (1.5)
Renal	25 (4.3)	4 (0.7)	6 (1.5)	3 (0.8)
Hypersensitivity/Infusion reaction	23 (4.0)	0	17 (4.3)	2 (0.5)

Minimum follow-up was 28.3 months.

*Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; includes events reported between first dose and 30 days after last dose of study drug.

8,2% de cytolyse

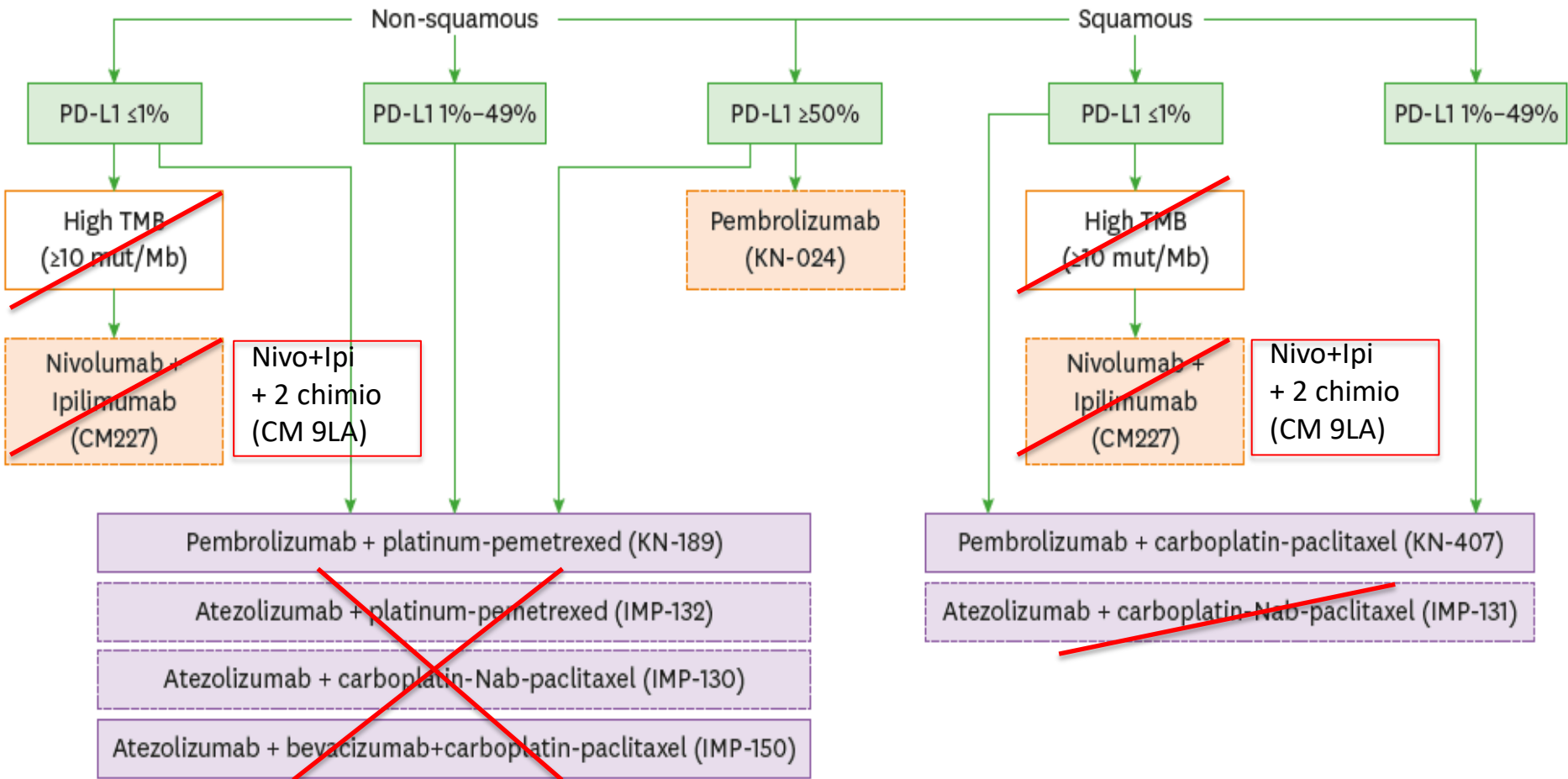
Grade 3-4

(1% ds KN-189 et KN-042)

3,3% de pneumopathies (PHS) grade 3-4

(2,6% ds KN-024, 3.1% ds KN-042; 2,7% ds KN-189)

La prise en charge des CBNPC métastatiques sans mutation addictive... s'est simplifiée



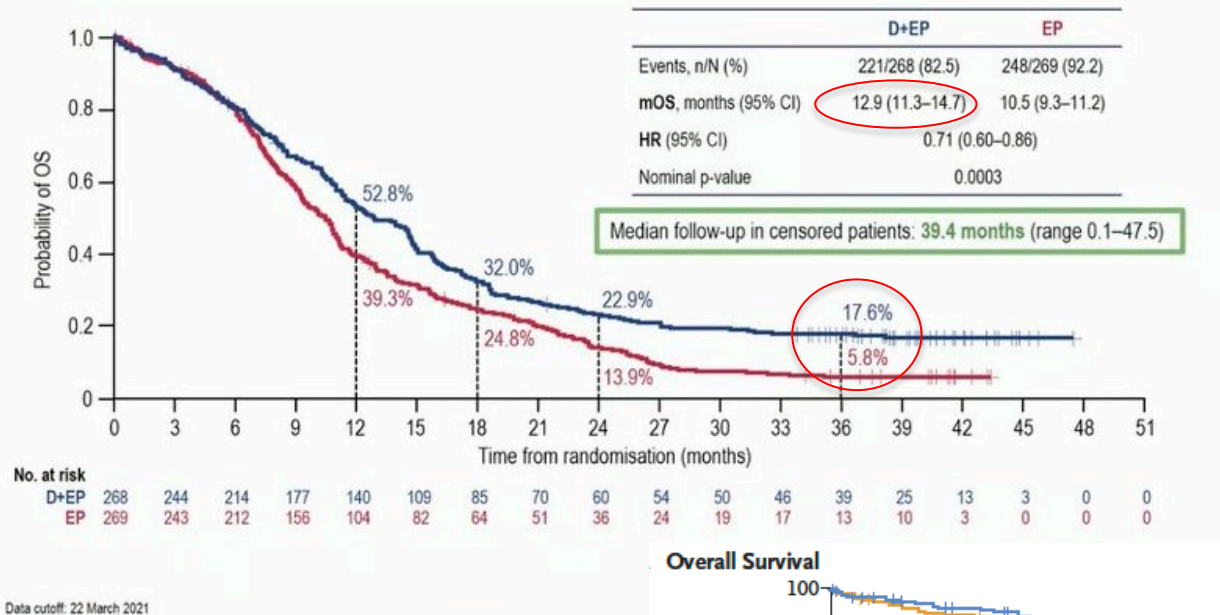
Les autres indications en cancérologie thoraciques: le futur proche

- **Les carcinomes à petites cellules métastatiques:**
 - 2 essais de phase 3 positifs (**Atezolizumab, Durvalumab**) avec VP16/sel de platine
 - Gain de médiane de survie globale= 2 mois
- **Les CBNPC localement avancés** (stades III): 1 essai de phase 3 de **durvalumab** après RT-CT (PACIFIC)
- Les CBNPC opérables de stade IB à IIIA : 4 essais de phase 2 d'immuno (+/-CT) néo-adjuvante
 - 1 essai publié de phase 3 d'immuno adjuvante (Impower-010: **Atezoluzimab**): DFS
 - 1 essai (presse) de phase 3 de **Nivolumab**-CT néoadjuvante (CM-816): EFS
- Les mésothéliome: 1 essai de phase 3 de double immunothérapie (**Nivo+Ipi**) publié (CM-743)
-  Tumeurs thymiques

CBPC métastatiques: + 2 mois de médiane de SG

2021 ESMO congress

3-year Overall Survival Update: D+EP vs EP



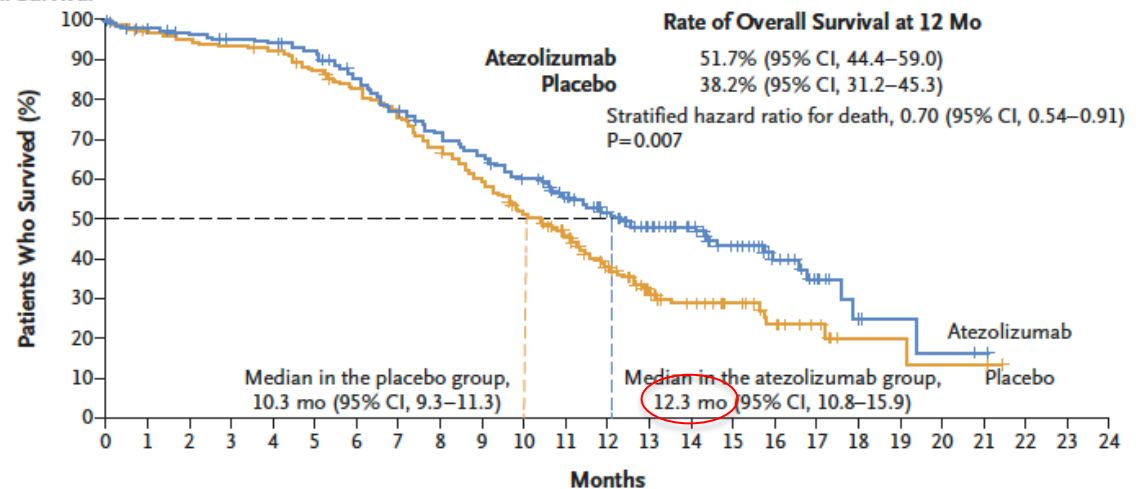
Caspian phase 3 trial
(durvalumab)

Paz-Ares L. *et al.* Lancet 2019

Impower-133 phase 3 trial (Atezolizumab)

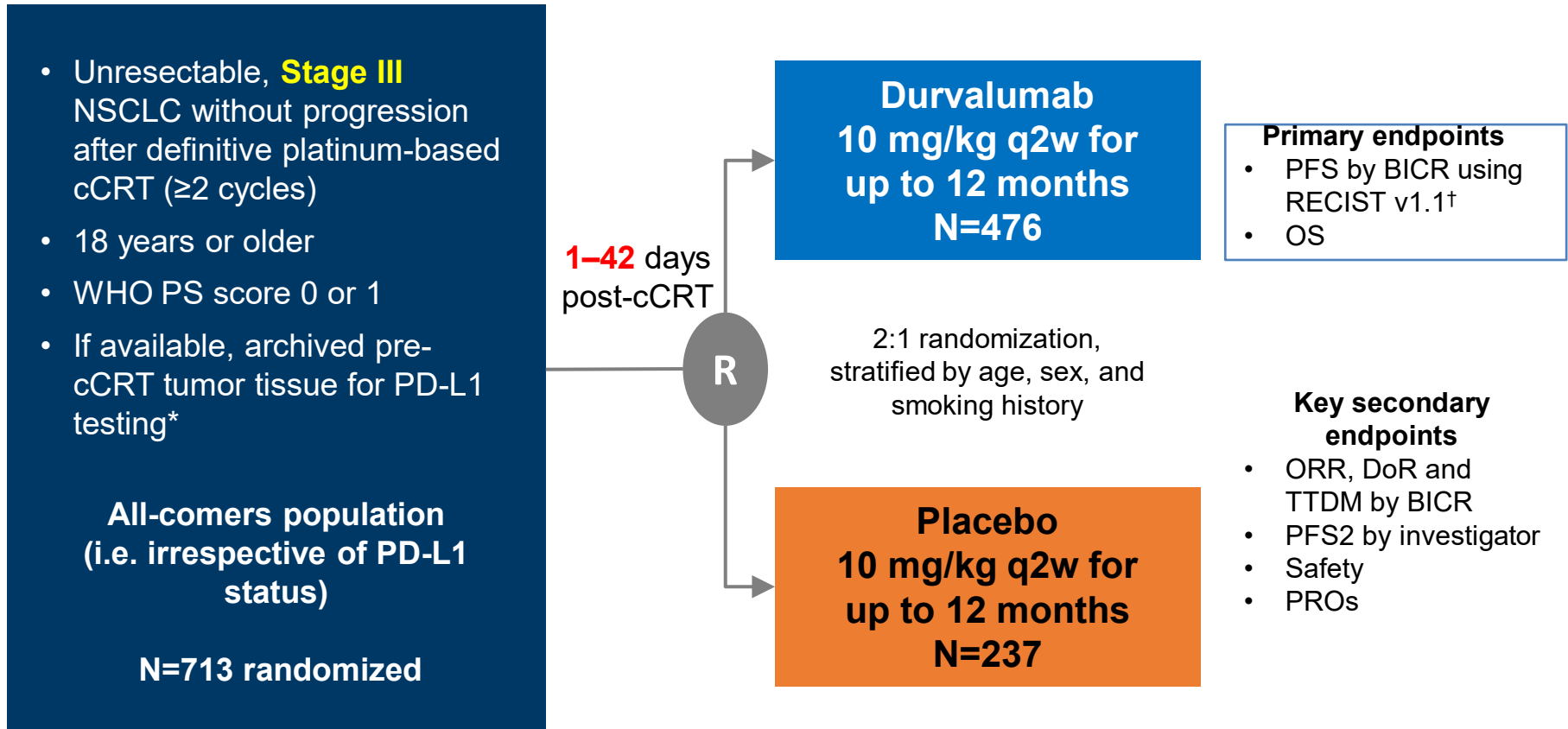
Horn L *et al.* 2018, NEJM

Overall Survival



PACIFIC: Study Design

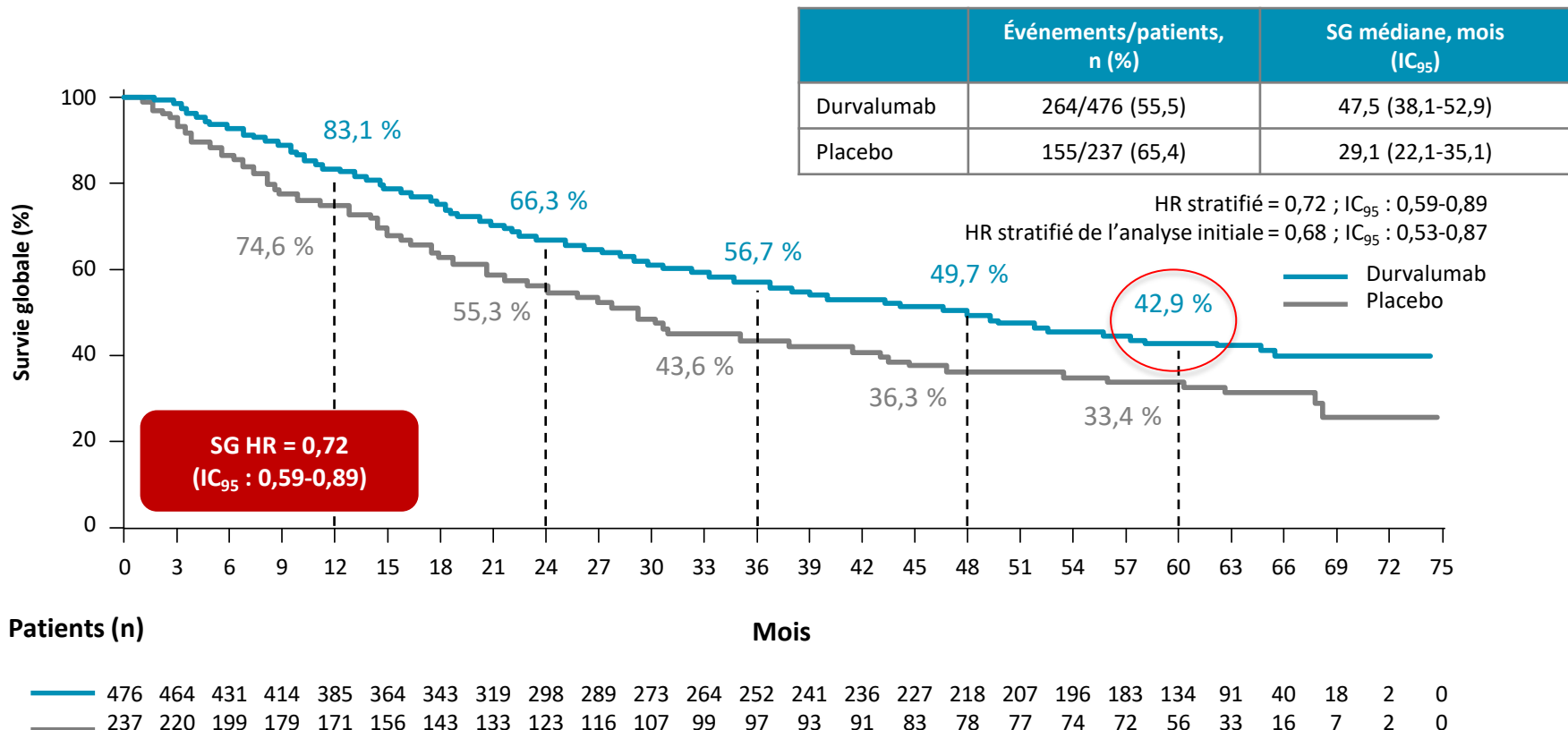
Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study¹



*Using the Ventana SP263 immunohistochemistry assay

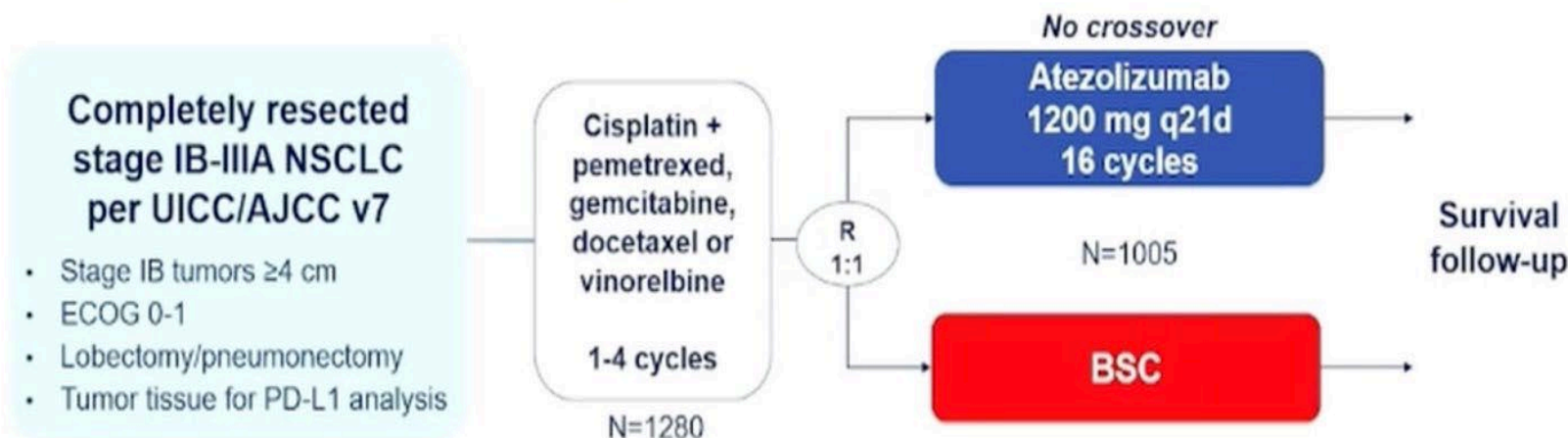
[†]Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

Étude PACIFIC : actualisation à 5 ans !



Analyse 5 ans après la randomisation du dernier patient : date de point 11 janvier 2021.

IMpower010: study design



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status^a: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
 - PD-L1 TC ≥1% (per SP263) stage II-IIIa population
 - All-randomized stage II-IIIa population
 - ITT population (stage IB-IIIa)

Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIa population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.

ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. ^aPer SP142 assay.

Dr. Heather A. Wakelee

Presented By: IMpower010 Interim Analysis
<https://bit.ly/33t6JJP>

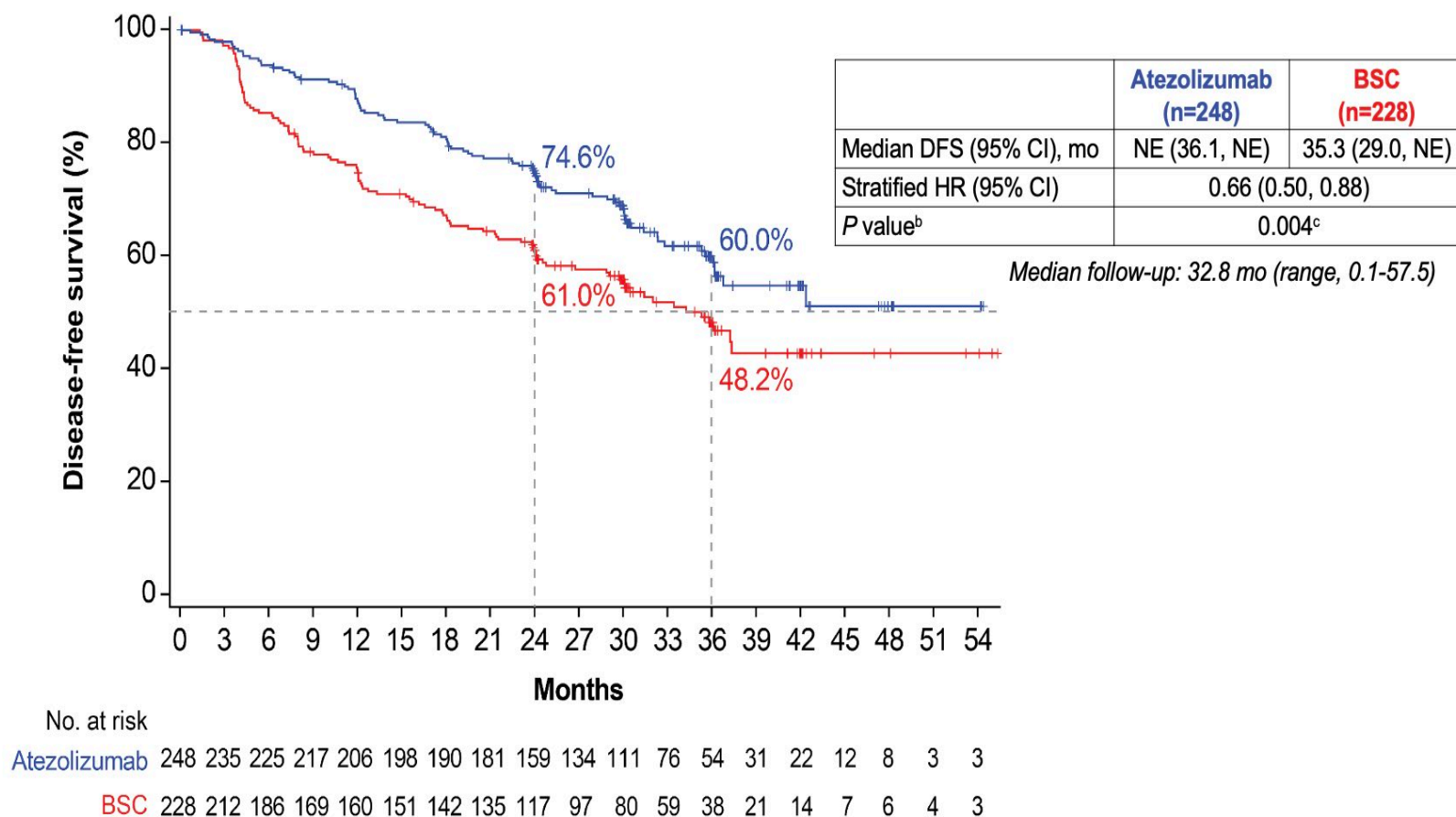
#ASCO21

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2021 ASCO
ANNUAL MEETING

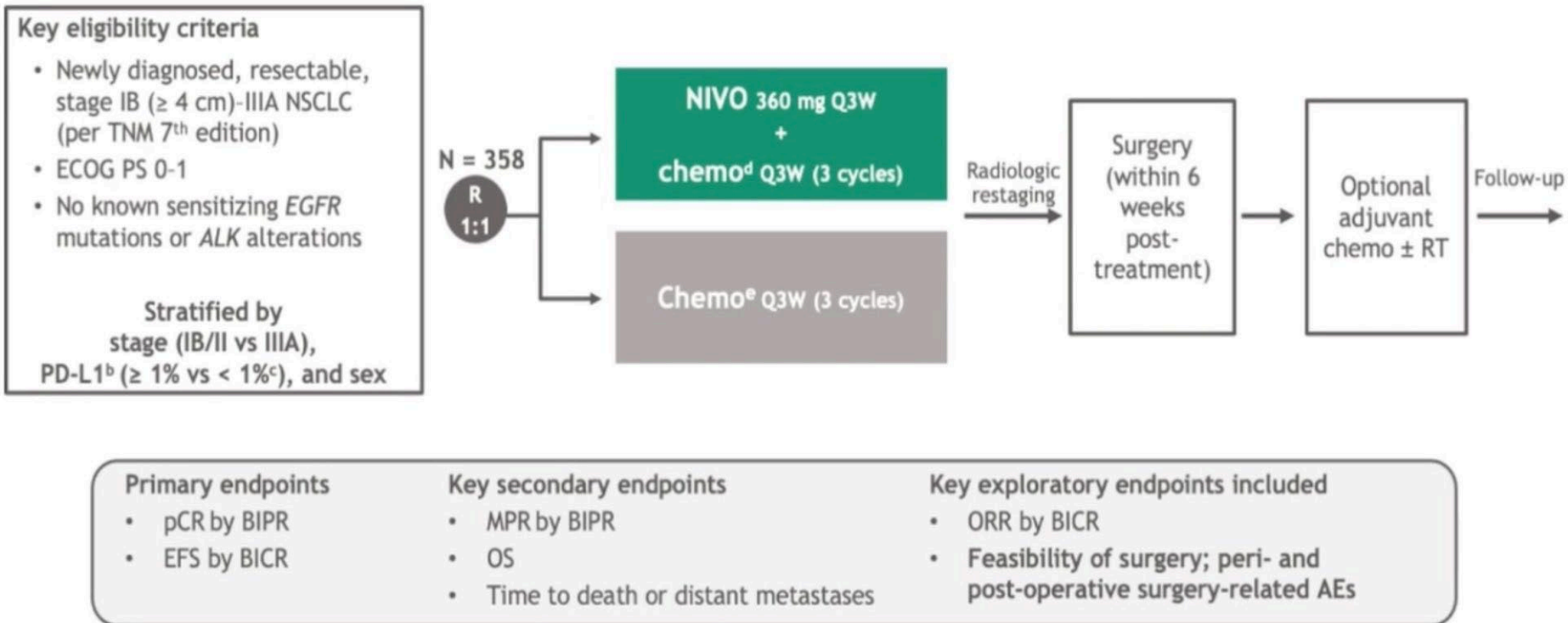
IMpower010: DFS in the PD-L1 TC $\geq 1\%$ ^a stage II-IIIa population (primary endpoint)

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Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. ^a Per SP263 assay. ^b Stratified log-rank. ^c Crossed the significance boundary for DFS.

CheckMate 816 study design^{a,1}



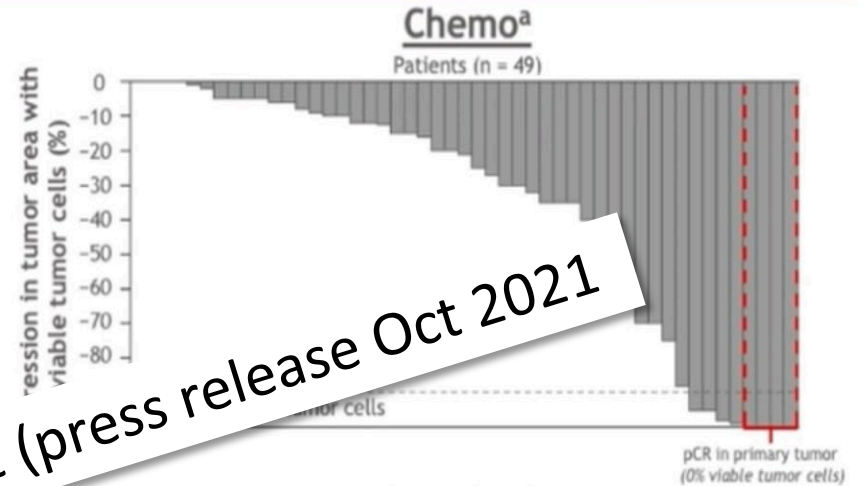
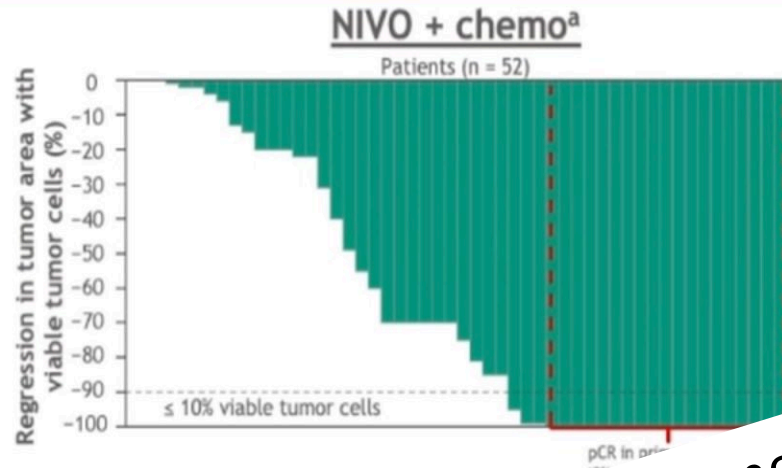
Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

^aNCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; ^bDetermined by the PD-L1 IHC 28-8 pharmDx assay (Dako); ^cIncluded patients with PD-L1 expression status not evaluable and indeterminate; ^dNSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; ^eVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

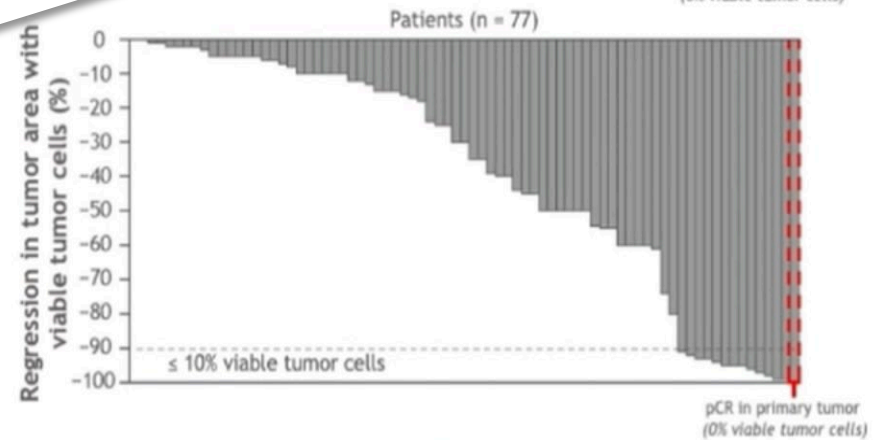
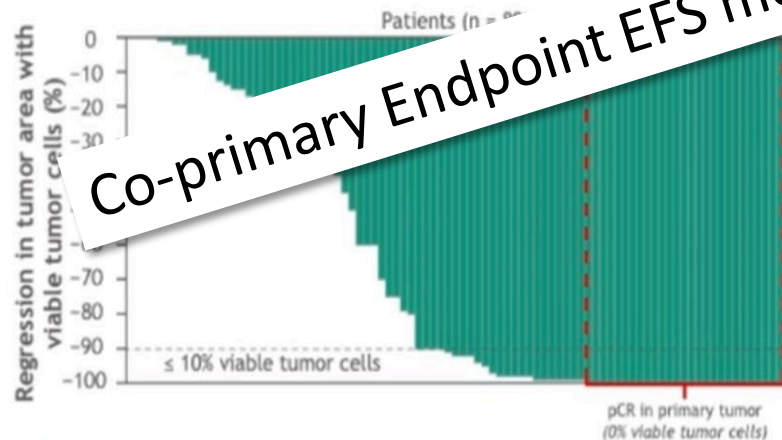
1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

Depth of pathological regression in primary tumor by stage^a

Stage
IB/II



Stage
IIIA



Co-primary Endpoint EFS met (press release Oct 2021)

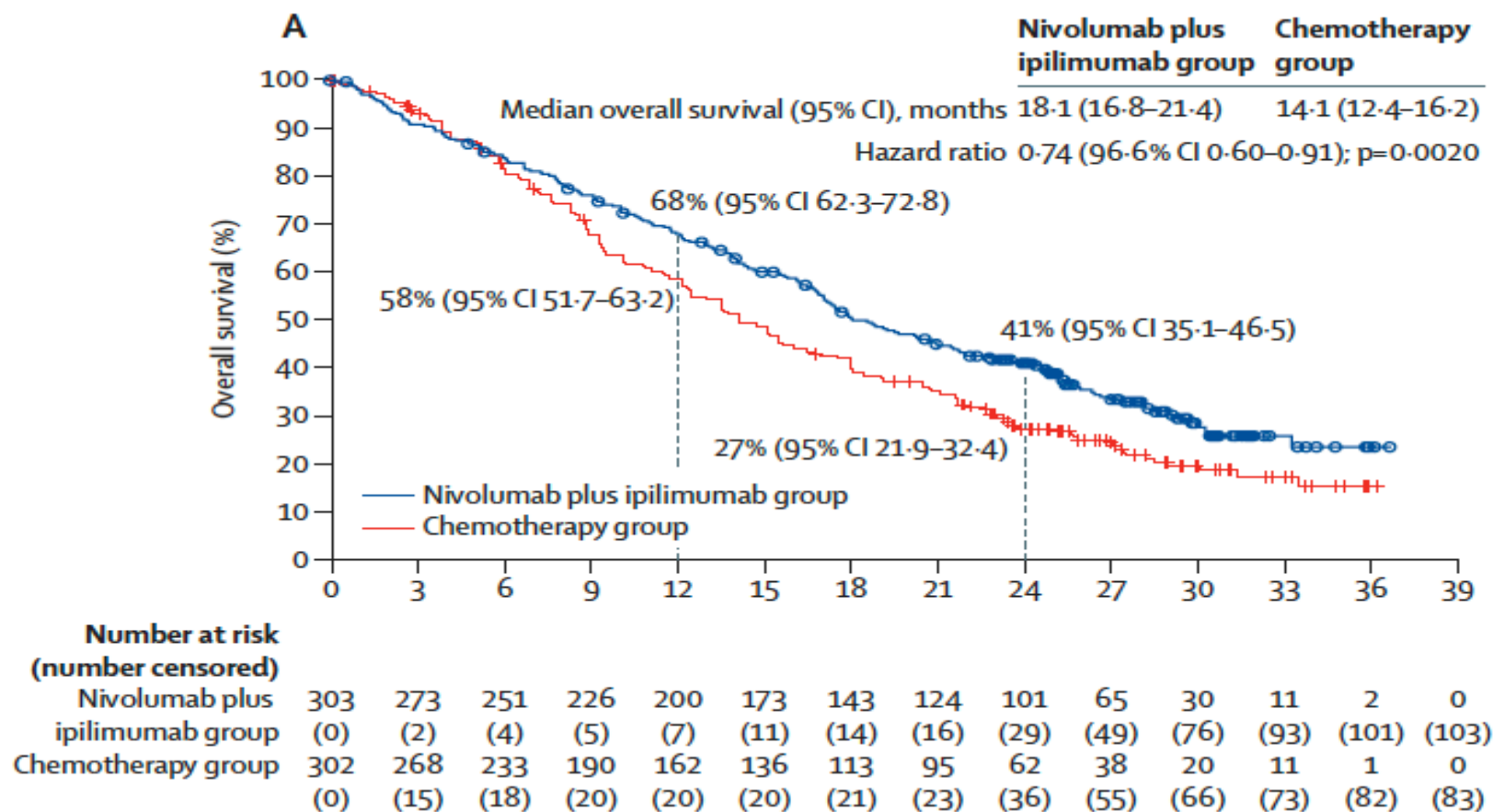
- The median residual viable tumor percentage in stage IB/II and IIIA was 28% and 8% with NIVO + chemo vs 79% and 70% with chemo, respectively

^aResponse-evaluable patients.

First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

Paul Baas, Arnaud Scherpereel, Anna K Nowak, Nobukazu Fujimoto, Solange Peters, Anne S Tsao, Aaron S Mansfield, Sanjay Popat, Thierry Jahan, Scott Antonia, Youssef Oulkhovir, Yolanda Bautista, Robin Cornelissen, Laurent Greillier, Francesco Grossi, Dariusz Kowalski, Jerónimo Rodríguez-Cid, Praveen Aanur, Abderrahim Oukessou, Christine Baudalet, Gérard Zalcman

Lancet 2021



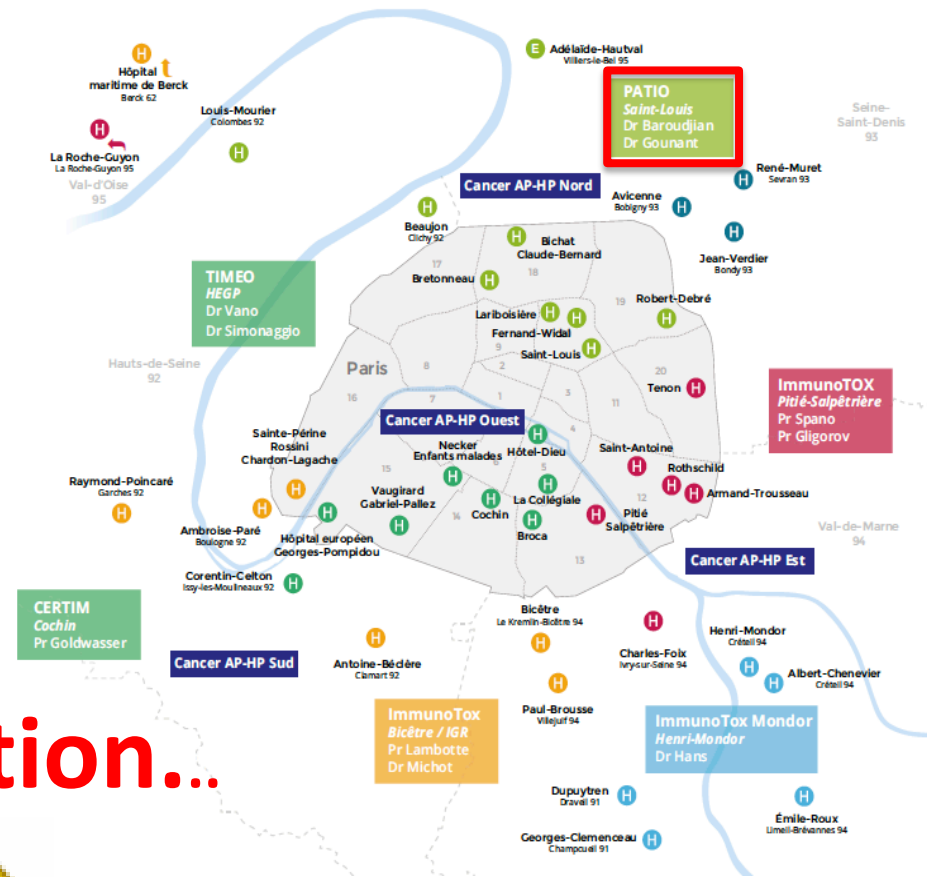
FINALEMENT....

Traitez les tous...? Mais combien de temps ??





LES RCP D'IMMUNOTOXICITÉS PAR TERRITOIRE GÉOGRAPHIQUE



Merci de votre attention...



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