GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO PRECEPTORSHIP ON LUNG CANCER

First line treatment for advanced NSCLC without oncogenic addiction

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26-27 January 2024, Rabat, Morocco

DECLARATION OF INTERESTS

During the 5 last years, Céline Mascaux received honorary or funding to participate to meeting, or participated to experts groups from Roche, Astrazeneca, Kephren, Bristol-Myers Squibb, Pfizer, Sanofi, MSD, Amgen, Takeda, Janssens

European Patent Application EP19305434.3 was filed on 2 April 2019 by Inserm, Université Paris Descartes, Université Paris Diderot, Sorbonne Université, Université Aix-Marseille, APHM and Université Libre de Bruxelles, and European Patent Application EP19305535.7 was filed on 26 April 2019 by Inserm, Université Paris Descartes, Université Paris Diderot, Sorbonne Université,Université Aix-Marseille, APHM and Université Libre de Bruxelles. The inventors designation is in progress.

Immunotherapy : a very old idea

William Coley

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

MAY, 1893.

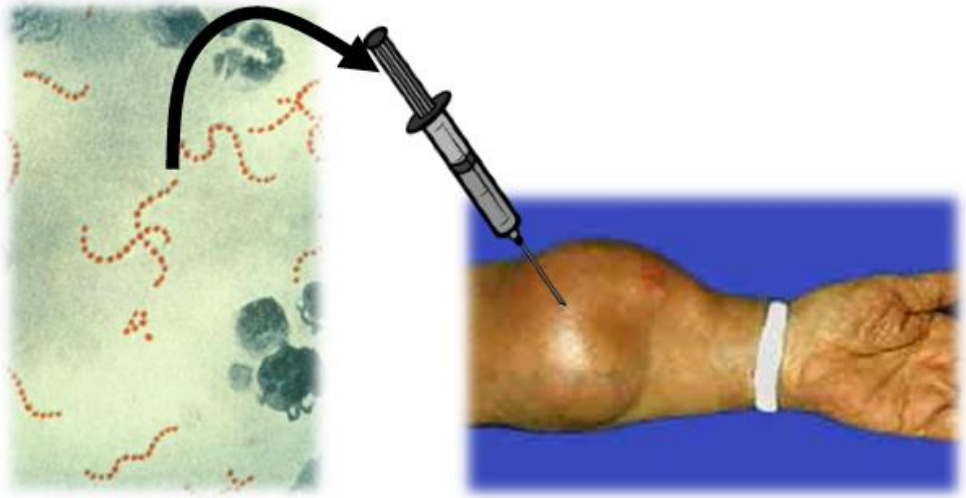
THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

By William B. Coley, M.D.,

Assistant Surgeon to the Hospital for Ruptured and Crippled; Instructor in Surgery in the Post-Graduate Medical School, New York.

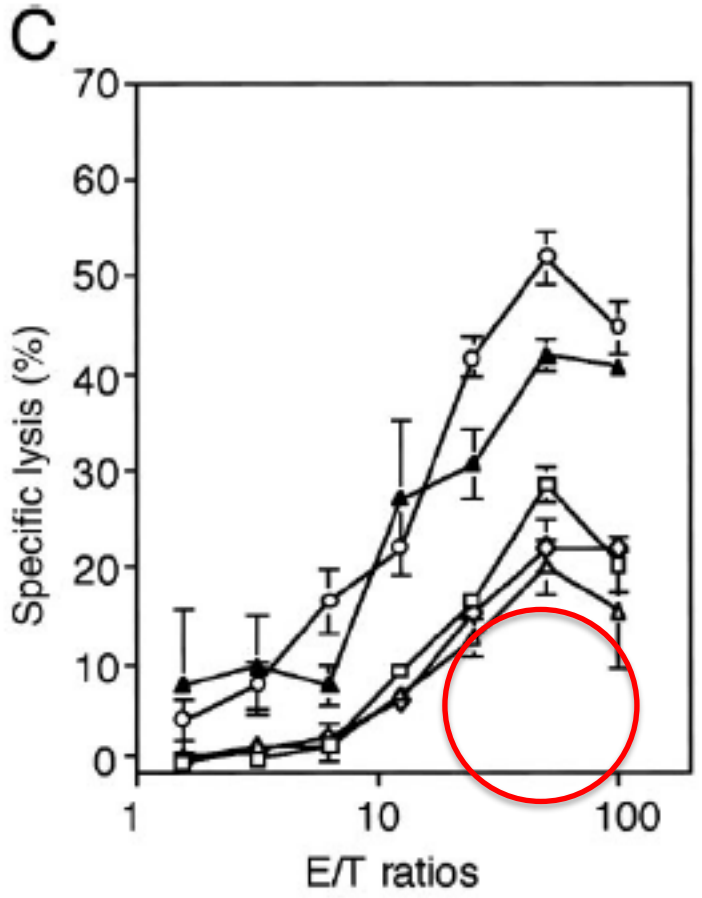
"…on May 2, 1891, I inoculated a case of sarcoma"

"At the end of two weeks, the tumor had disappeared"



Streptococcus pyogenes

PD-L1 : CANCER IMMUNOTOLERANCE

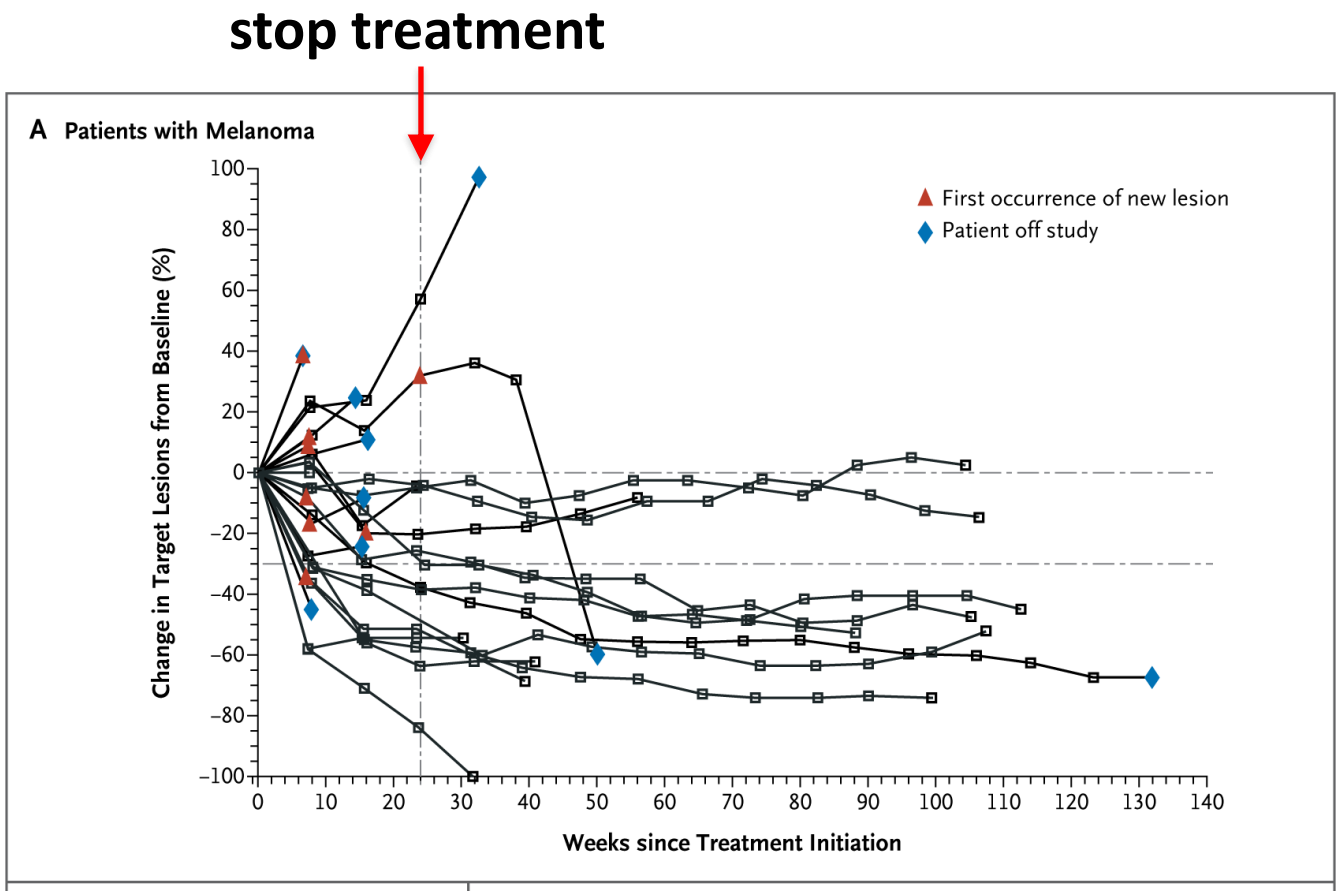


Tumor cells that were transfected for PD-L1 are less destroyed by cytotoxic lysis

Iwai et al. PNAS (2002)

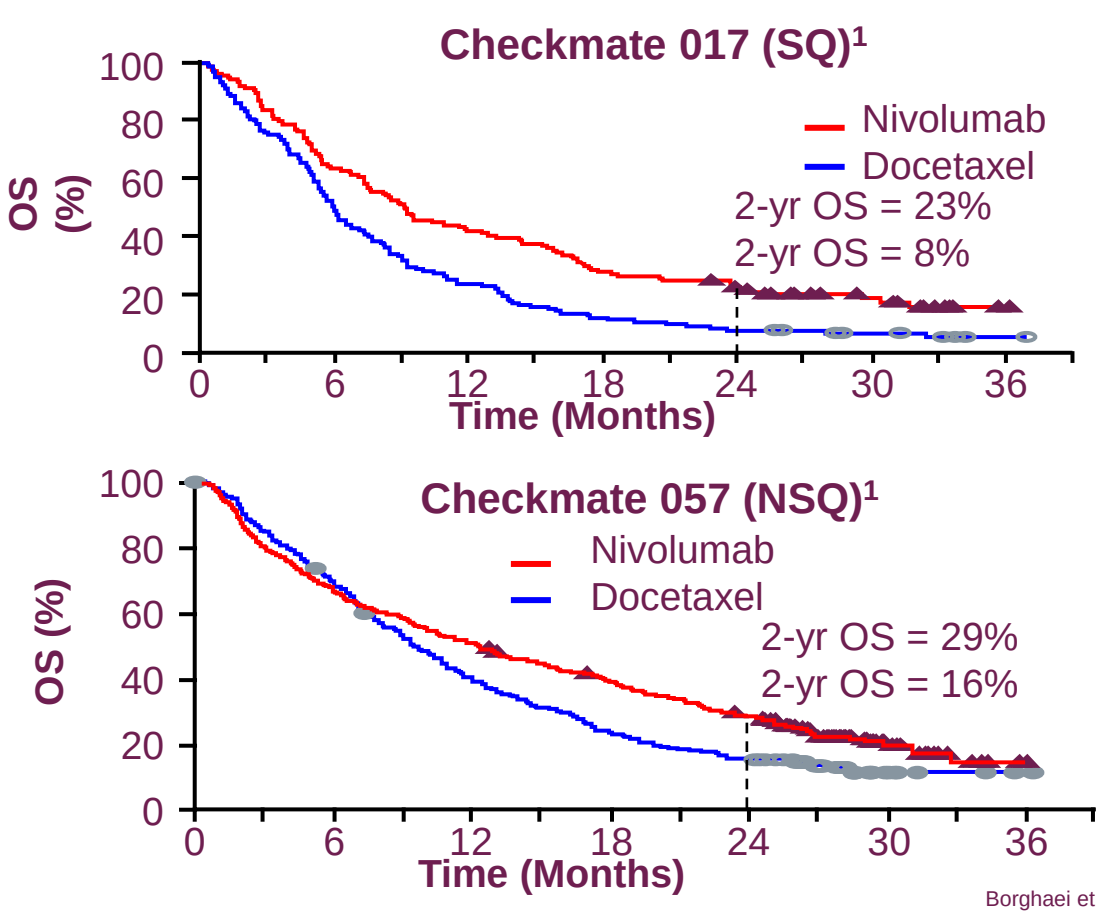
DURABLE RESPONSE BY PD-1 BLOCKADE

"Responses were durable; 20 of 31 responses lasted 1 year or more after stopping therapy."

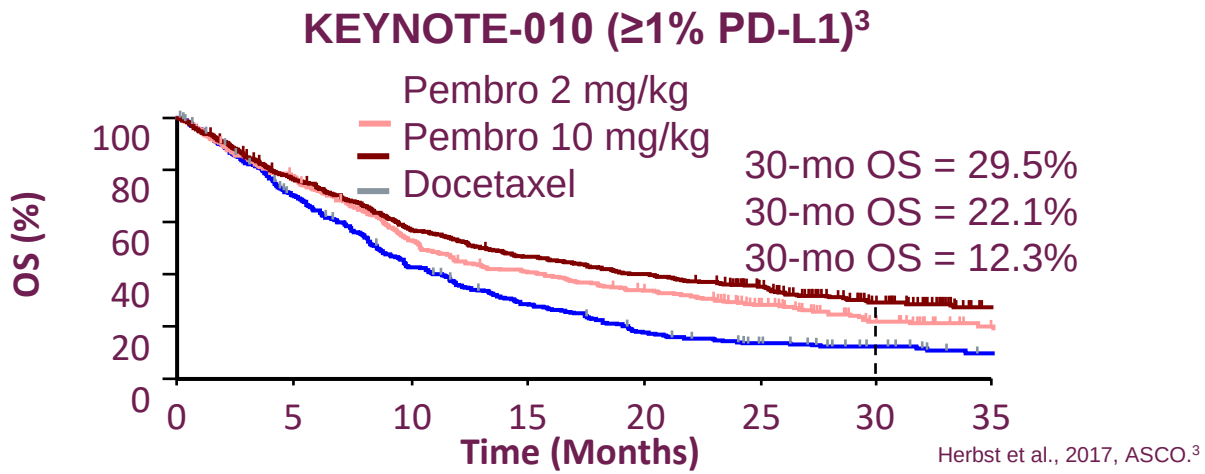


From Topalian et al. NEJM 2012

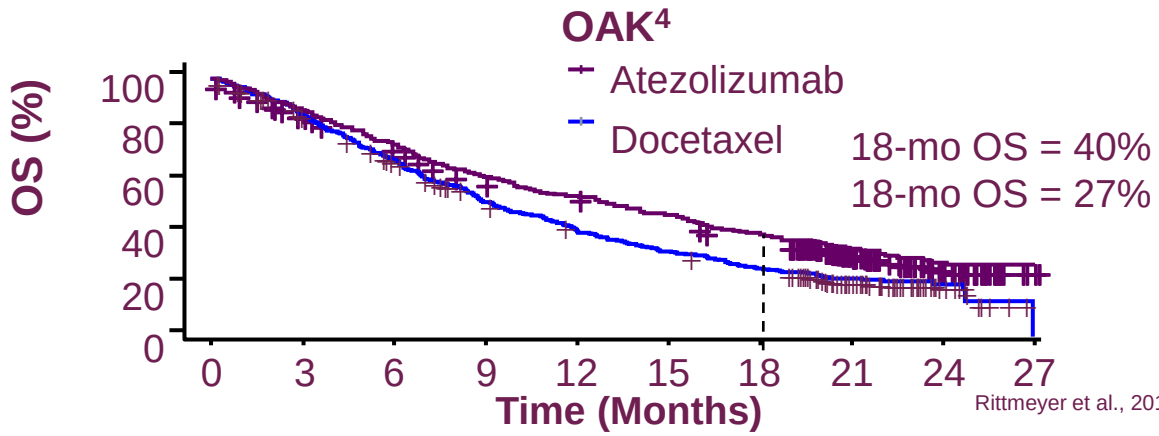
2015-2016: checkpoint inhibitors for previoulsy treated



Borghaei et al., 2016, ASCO.[1]



Herbst et al., 2017, ASCO.[3]

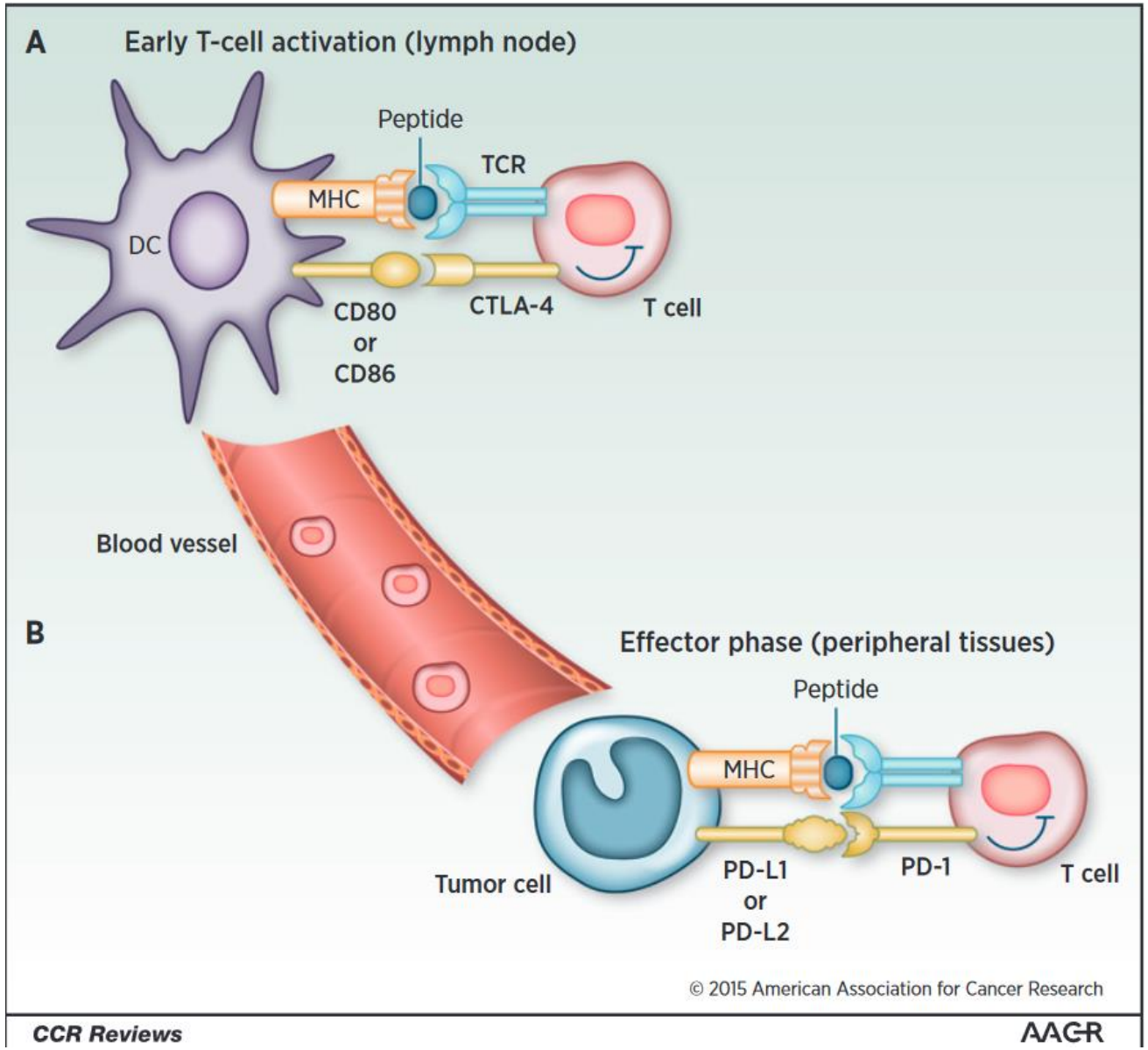


Rittmeyer et al., 2017, *Lancet*.[4]

Immunotherapy… new actors

AntiPD1
Nivolumab
Pembrolizumab
Cemiplimab
Tislelizumab
Camrelizumab
Pidilizumab
Sintilimab
Toripalimab
Dostarlimab

AntiPDL1
Atezolizumab
Avelumab
Durvalumab
Sugemalimab



AntiCTLA4
Ipilimumab
Tremelimumab

Anagnostou, V. K. & Brahmer, J. R. Cancer Immunotherapy: A Future Paradigm Shift in the Treatment of Non–Small Cell Lung Cancer. Clin Cancer Res 21, 976–984 (2015).

IO AS MONOTHERAPY

KEYNOTE 024 : DESIGN DE L'ÉTUDE

Principaux critères d'inclusion

- CBNPC stade IV non traité
- PD-L1 TPS ≥ 50%
- ECOG PS 0-1
- Pas de mutation activatrice de l'*EGFR* ni translocation de ALK
- Pas de métastases cérébrales non traitées
- Pas de maladie auto-immune active nécessitant un traitement systémique

R

1:1
N = 305

Pembrolizumab
200 mg IV toutes les 3 semaines
35 cycles (2 ans)

Rechallenge Pembrolizumab

Pembrolizumab
200 mg Q3W
17 cycles (1 year)

Doublet de chimiothérapie à base de platine
4 – 6 cycles

- Pémétrexed + carboplatine
- Pémétrexed + cisplatine
- Paclitaxel + carboplatine
- Gemcitabine + carboplatine
- Gemcitabine + cisplatine

PD

Crossover *via* pembrolizumab

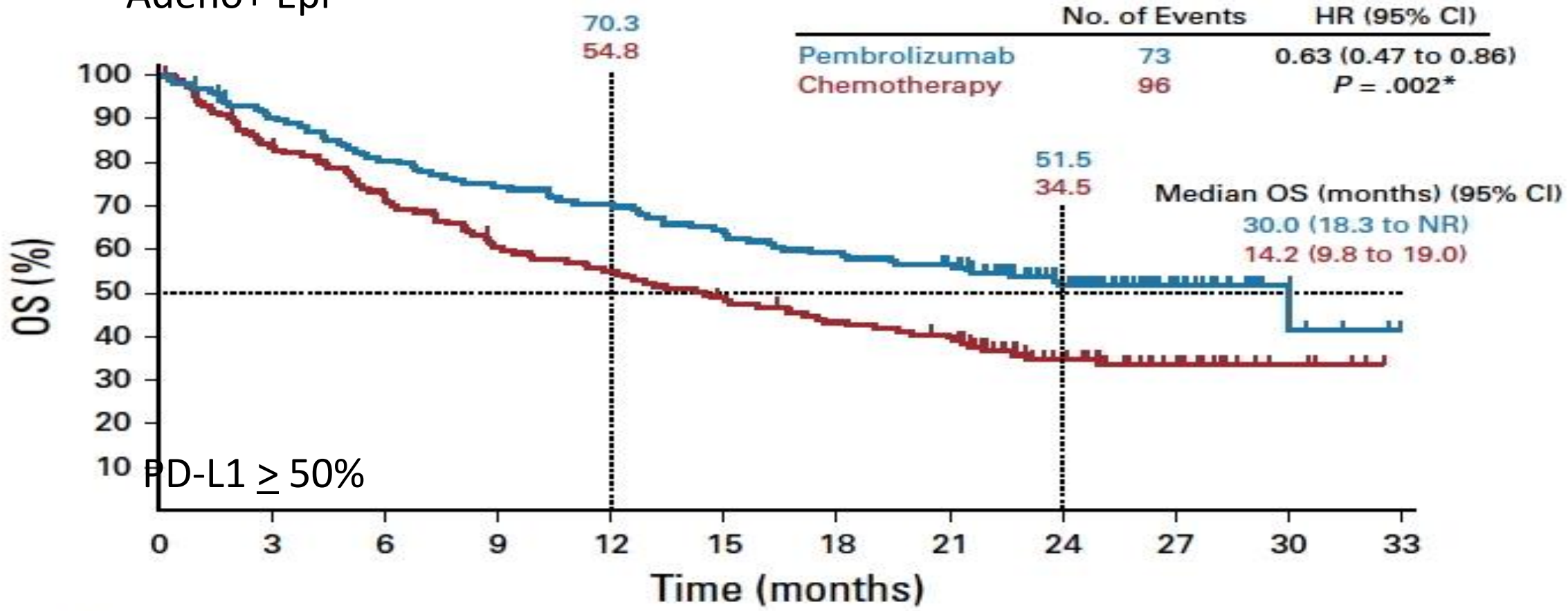
Pembrolizumab
200 mg Q3W
(2 years)

- **Critère principal : SSP** (RECIST v1.1) par comité de revue centralisé indépendant en aveugle)
- **Critère secondaire clé : SG**
- **Autres critères secondaires :** ORR, tolérance, SSP (RECIST v1.1) selon l'investigateur
- **Critère exploratoire :** DDR

J. Brahmer, et al., ESMO® 2020, Abs # LBA51

KN-024: 1st update, JCO, jan 2019

Adéno+ Epi

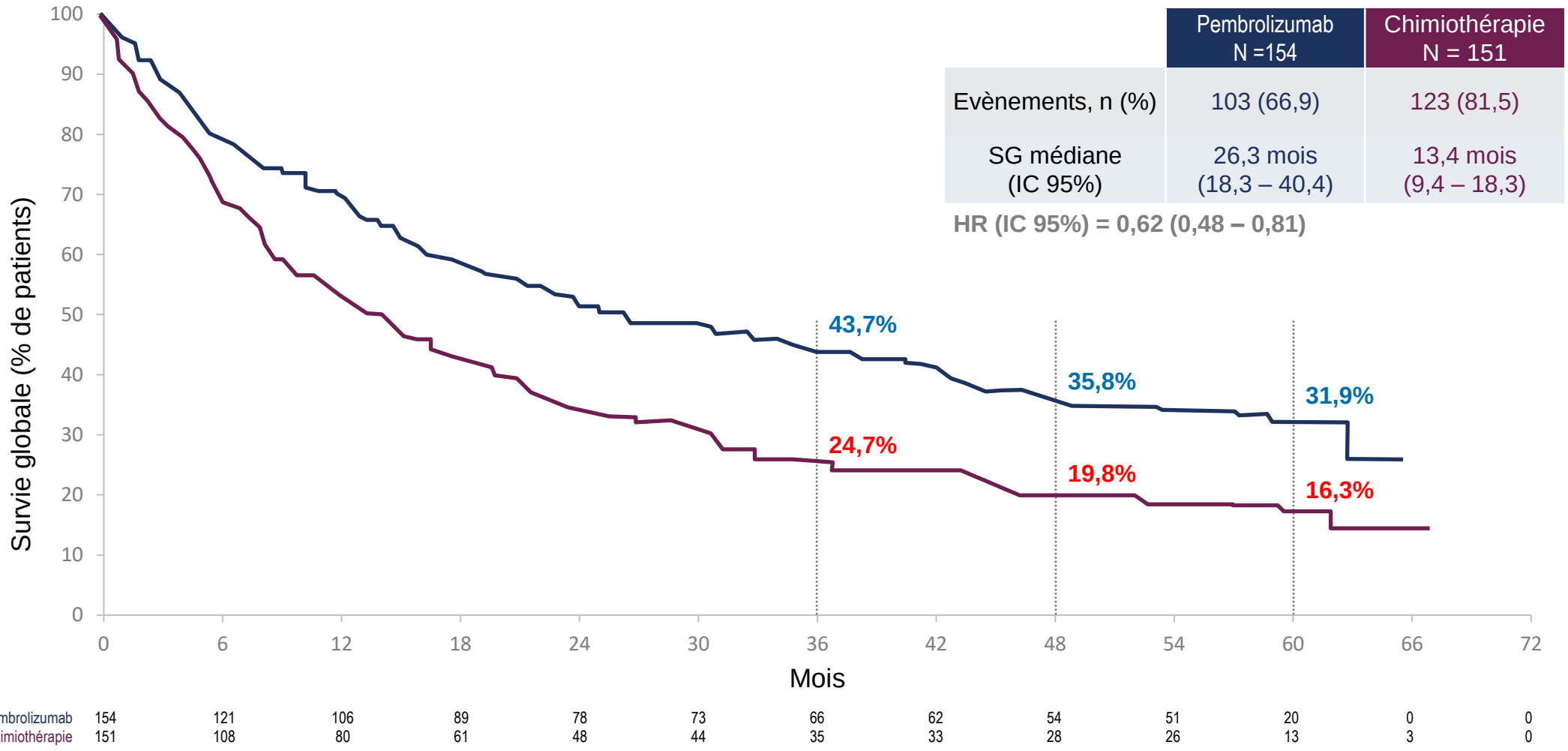


No. at risk:												
Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0
Chemotherapy	151	123	107	88	80	70	61	55	31	16	5	0

KEYNOTE 024 : OVERALL SURVIVAL

	Pembrolizumab N =154	Chimiothérapie N = 151
Evènements, n (%)	103 (66,9)	123 (81,5)
SG médiane (IC 95%)	26,3 mois (18,3 – 40,4)	13,4 mois (9,4 – 18,3)

HR (IC 95%) = 0,62 (0,48 – 0,81)



J. Brahmer, et al., ESMO® 2020, Abs # LBA51

Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial

*Tony S K Mok, Yi-Long Wu, Iveta Kudaba, Dariusz M Kowalski, Byoung Chul Cho, Hande Z Turna, Gilberto Castro Jr, Vichien Srimuninnimit, Konstantin K Laktionov, Igor Bondarenko, Karou Kubota, Gregory M Lubiniecki, Jin Zhang, Debra Kush, Gilberto Lopes, for the KEYNOTE-042 Investigators**

ASCO 2018
Lancet, 4 Apr. 2019

Objectif principal : SSP et SG

n=1274

Critères d'inclusion
- CBNPC avancé
- Ni EGFR muté ni ALK+
- Expression de PD-L1 ≥ 1 % des cellules tumorales
- ECOG 0-1

Stratification
- PD-L1, 50 % versus 1-49 %
- Asie vs. reste du monde

(n = 637)

R

1:1

(n = 637)

Pembrolizumab 200 mg dose fixe i.v./
3 sem. maximum 35 cycles

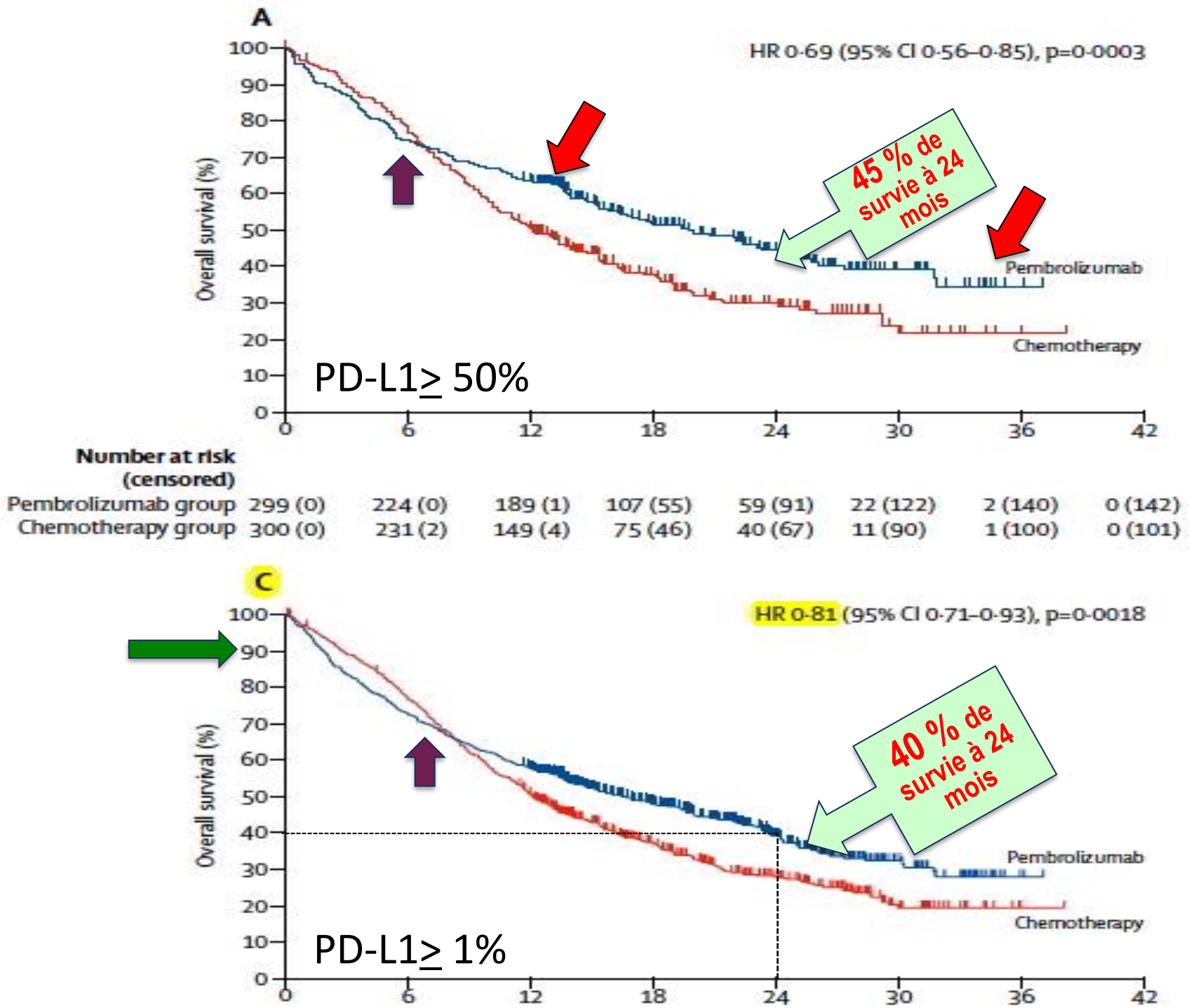
Pas de cross-over possible

Au choix des investigateurs
Carboplatine ASC 5 ou 6
+ **paclitaxel** 200 mg/m²
ou **pémétrexed** 500 mg/m²
maximum 6 cycles

299 x 2 ≥ 50% PD-L1

KN-042

Adéno+ Epi



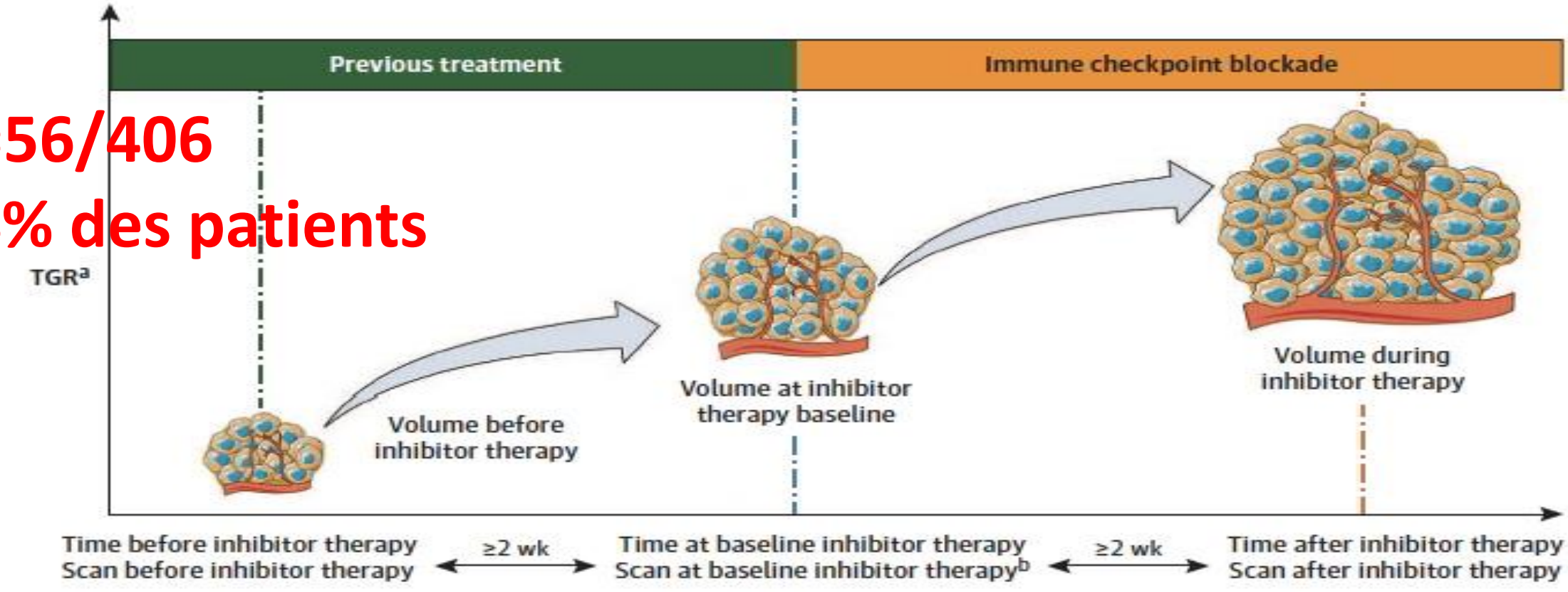
JAMA Oncology | Original Investigation

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 Tessonnier, 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 Ferté, 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

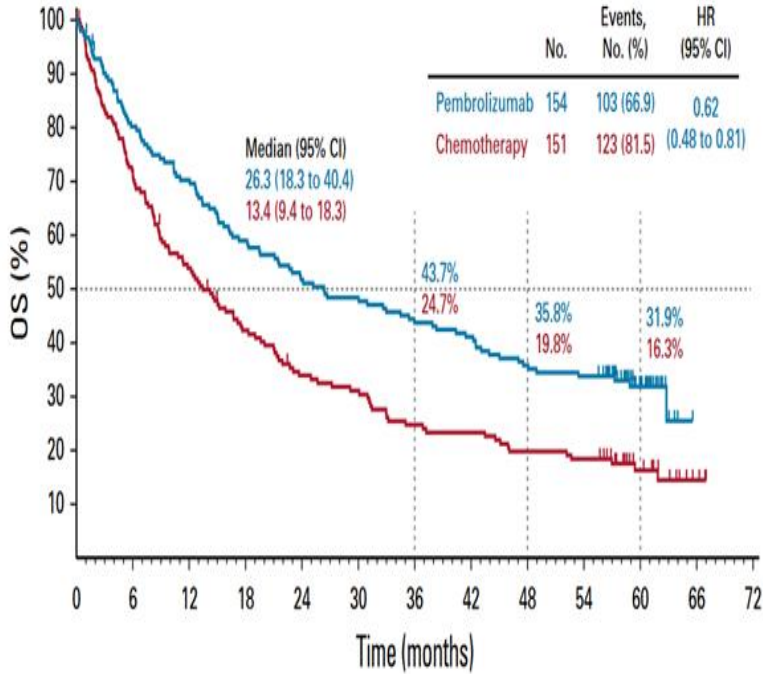
n=56/406

14% des patients

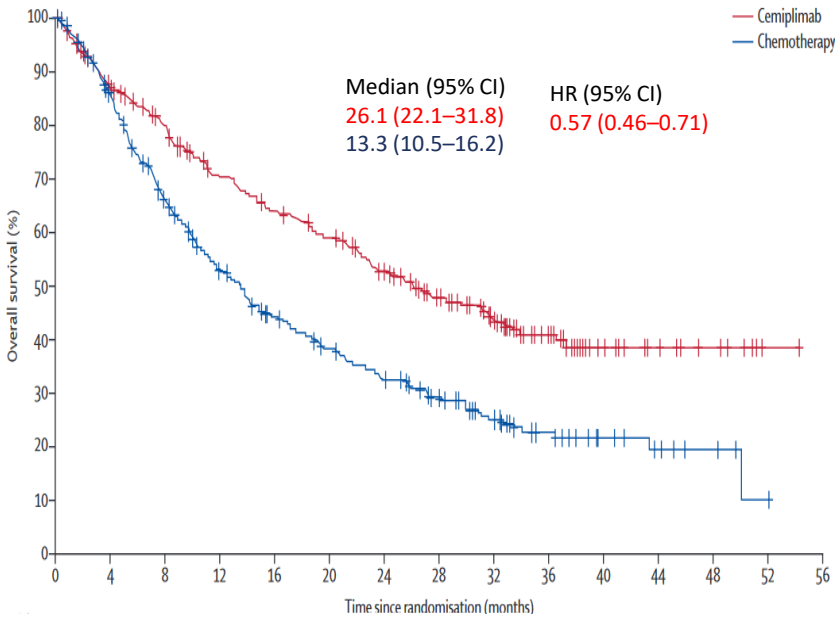


MONOTHERAPY WITH AMM IN EUROPE

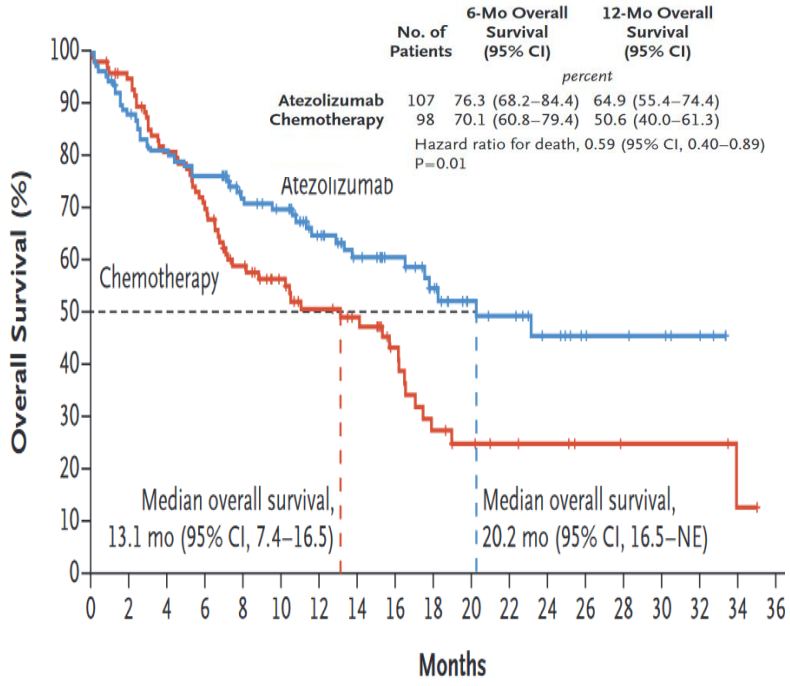
Keynote-024
PDL1>50%



EMPOWER-Lung 1
PDL1>50%



Impower-110
PD-L1 High Expressors

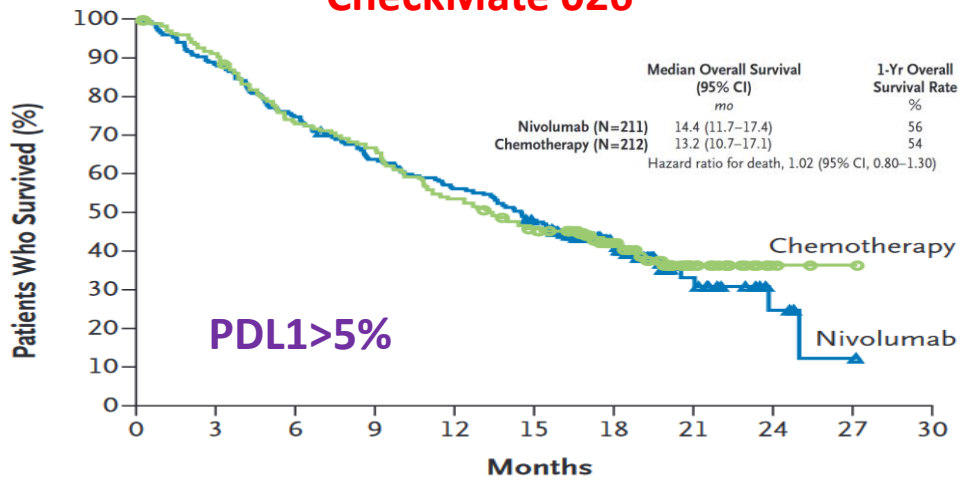


Herbst, R. S. *et al.* Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *New England Journal of Medicine* (2020) / Martin Reck et al., « Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50 », Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 39, no 21 (20 juillet 2021): 2339-49 / Sezer, A. *et al.*.

Özgüroğlu, M. *et al.* First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology* **24**, 989–1001 (2023).

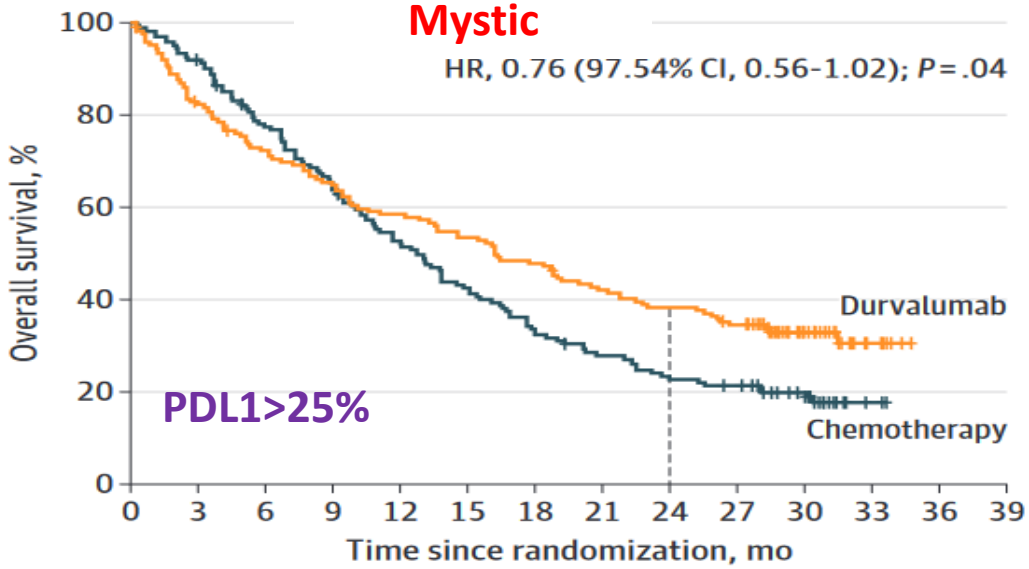
NO monotherapy – PDL1<50%

CheckMate 026



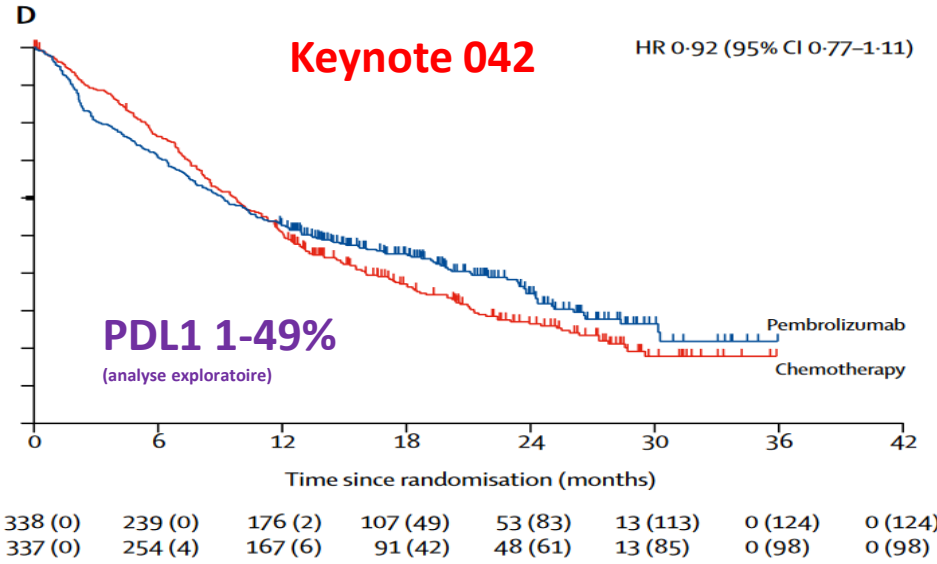
No. at Risk											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Mystic



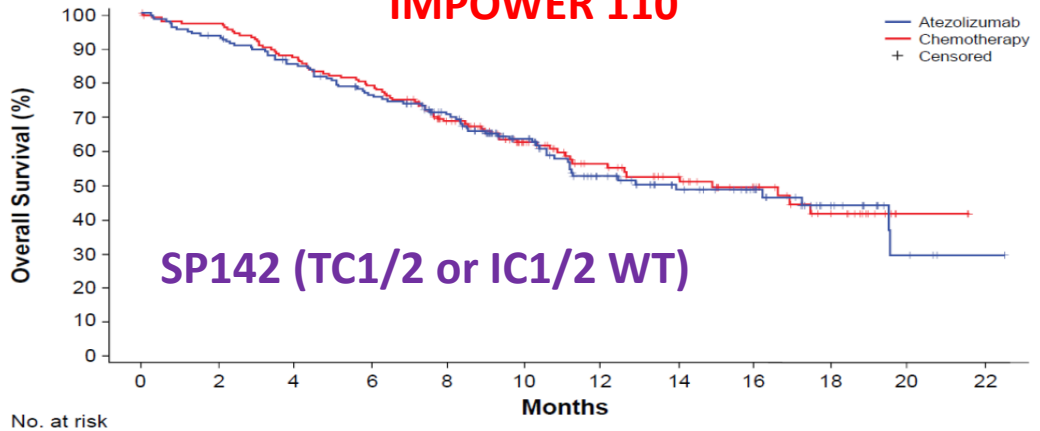
No. at risk													
Durvalumab	163	134	116	104	93	85	76	66	60	53	25	6	0	0
Chemotherapy	162	147	123	101	83	67	53	43	35	32	20	2	0	0

Keynote 042



338 (0)	239 (0)	176 (2)	107 (49)	53 (83)	13 (113)	0 (124)	0 (124)
337 (0)	254 (4)	167 (6)	91 (42)	48 (61)	13 (85)	0 (98)	0 (98)

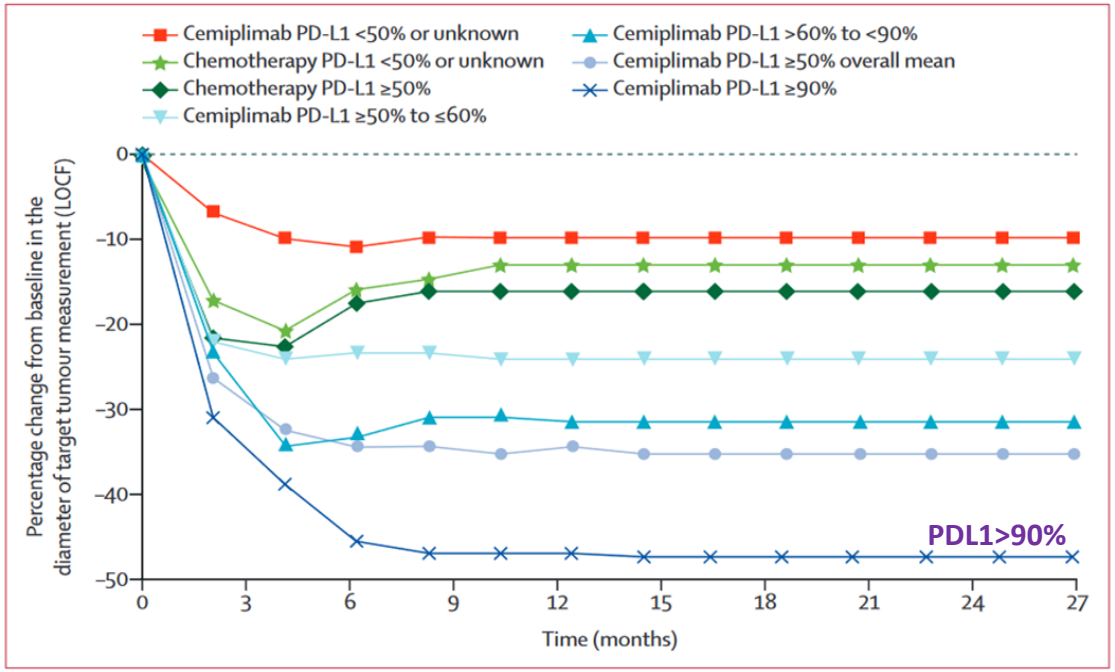
IMPOWER 110

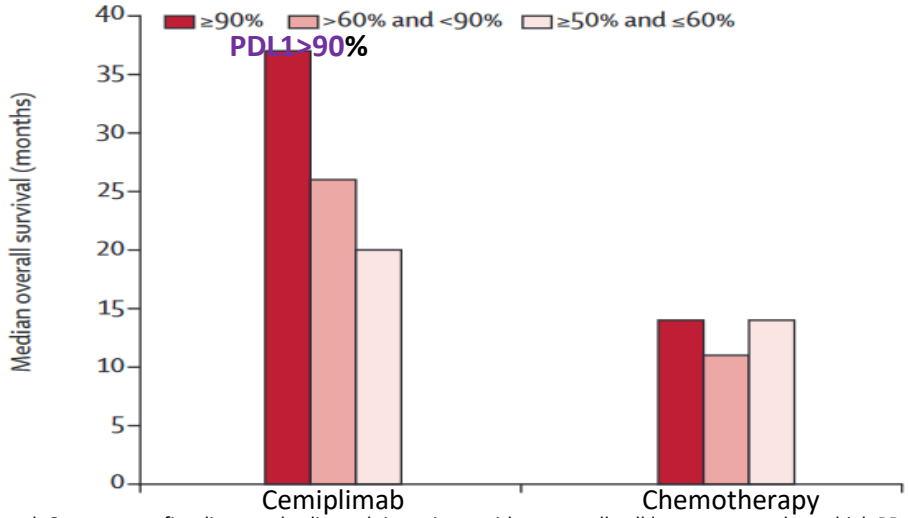


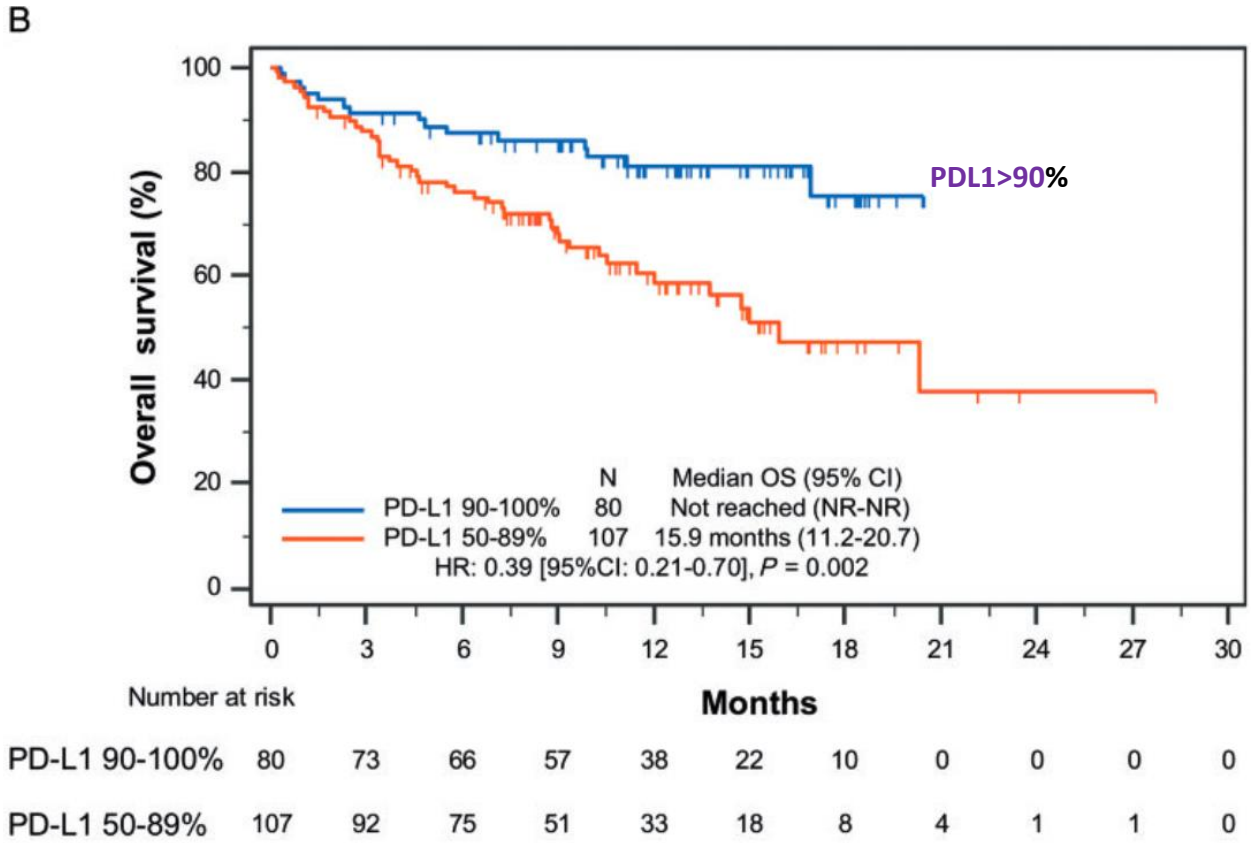
No. at risk											
Atezolizumab	170	158	141	124	104	73	45	34	23	12	4	1
Chemotherapy	179	165	148	134	103	68	46	35	24	12	1	

Carbone, D. P. *et al.* First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **376**, 2415–2426 (2017) / Rizvi, N. A. *et al.* Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer:The MYSTIC Phase 3 Randomized Clinical Trial. *JAMA Oncol* **6**, 661–674 (2020)/ Herbst, R. S. *et al.* Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *New England Journal of Medicine* (2020) / Mok, T. S. K. *et al.* Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* **393**, 1819–1830 (2019).

RESPONSE TO ANTI PD(L)1 ACCORDING TO PD-L1 EXPRESSION



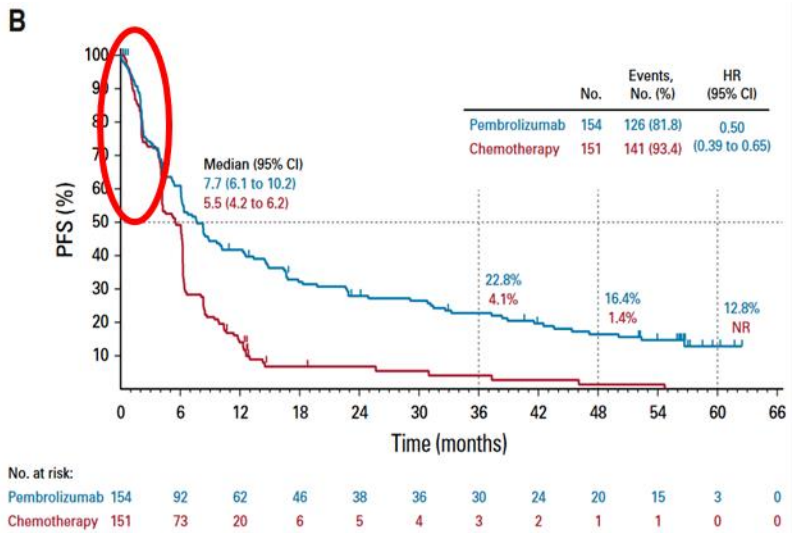




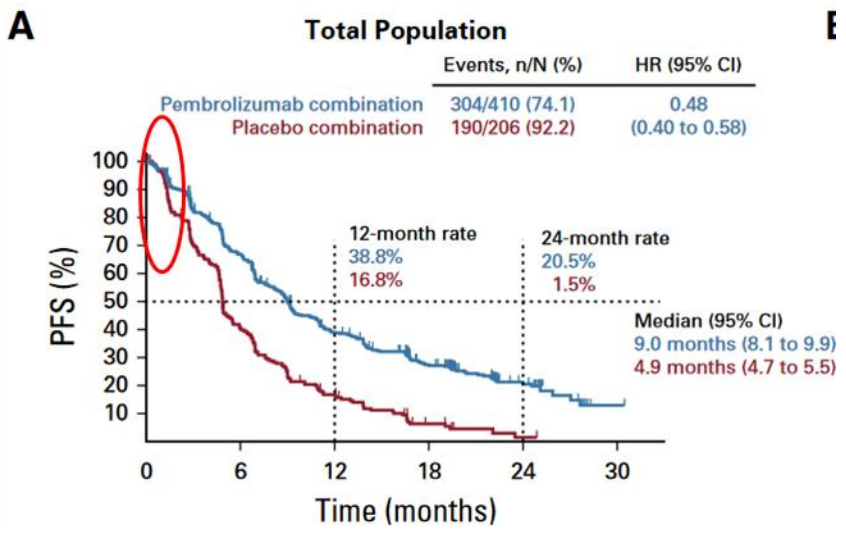
Aguilar, E. J. et al. Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. Ann Oncol 30, 1653–1659 (2019) / Sezer, A. *et al.* Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *The Lancet* **397**, 592–604 (2021) / Özgüroğlu, M. *et al.* First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology* **24**, 989–1001 (2023).

PDL1 > 50% : mono or combo ?

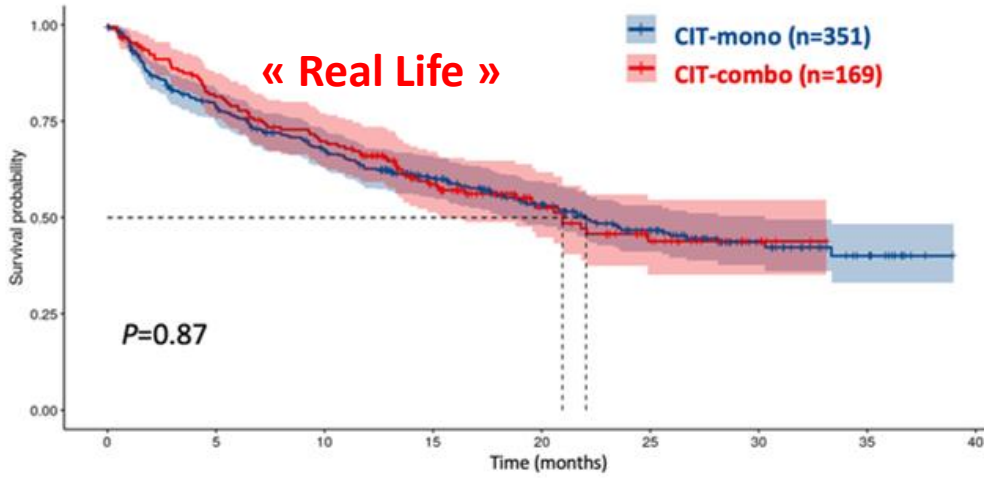
KN - 024

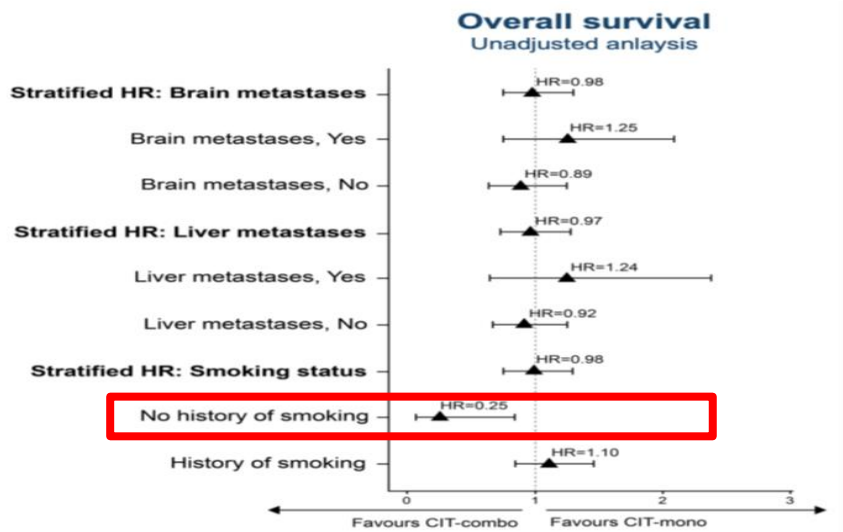


KN - 189



« Real Life »



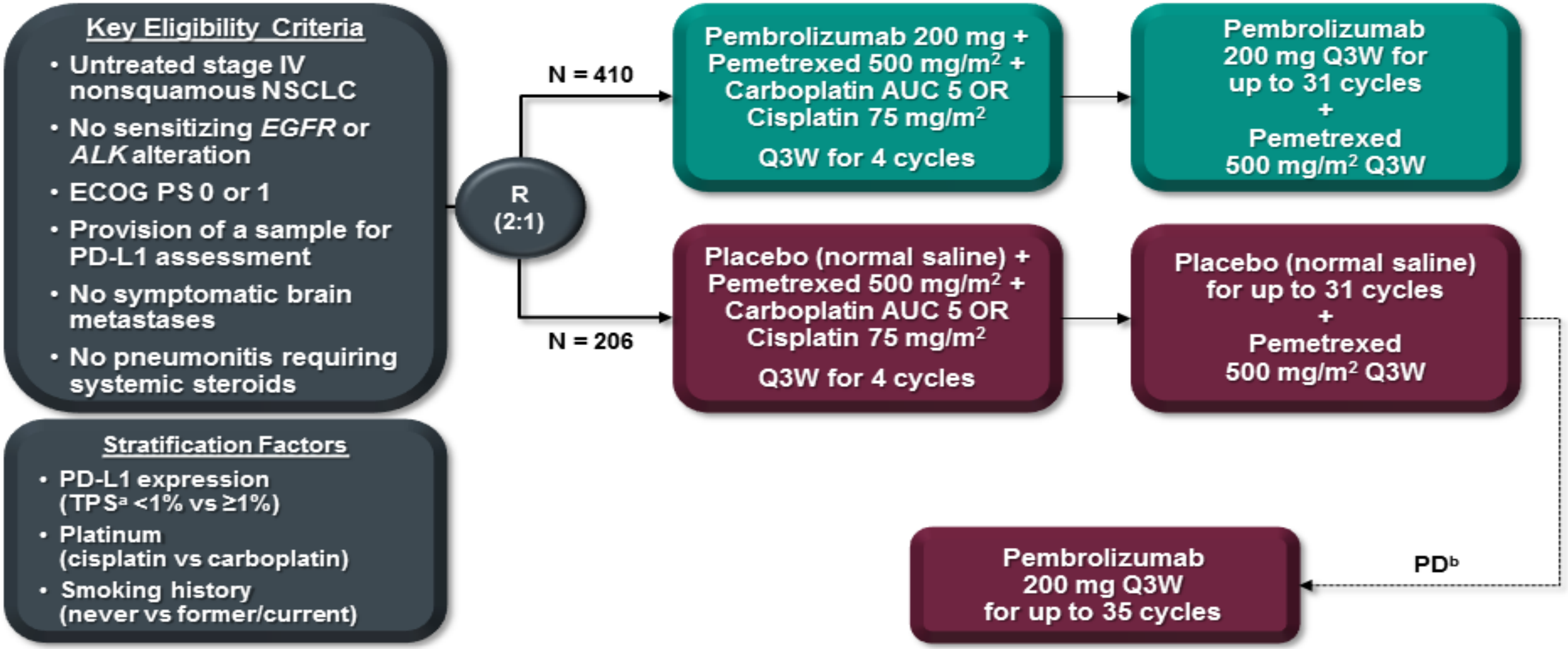


Martin Reck et al., « Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50 », *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 39, nº 21 (20 juillet 2021): 2339-49 Shirish Gadgeel et al., « Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer », *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 38, nº 14 (10 mai 2020): 1505-17 / M. Pérol et al., « Effectiveness of PD-(L)1 Inhibitors Alone or in Combination with Platinum-Doublet Chemotherapy in First-Line (1L) Non-Squamous Non-Small-Cell Lung Cancer (Nsq-NSCLC) with PD-L1-High Expression Using Real-World Data », Annals of Oncology: Official Journal of the European Society for Medical Oncology, 23 février 2022, S0923-7534(22)00124-7

IO AS COMBINAISON

Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)

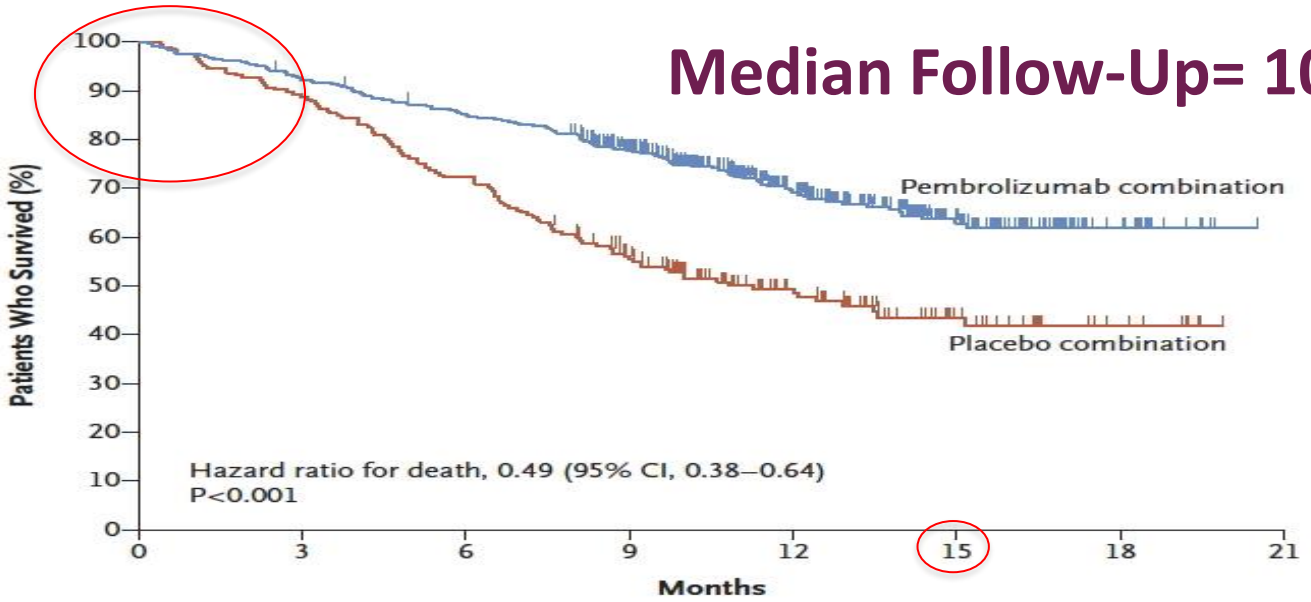


[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded independent central radiology review and all safety criteria had to be met.

Adéno

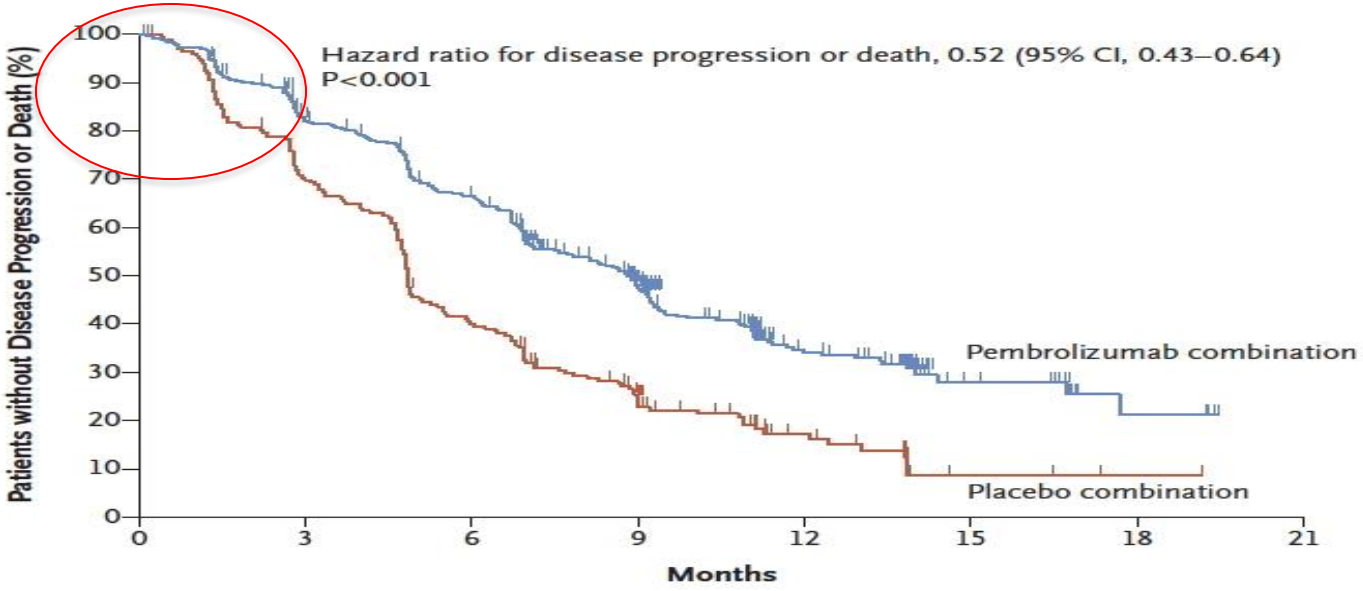
Median Follow-Up= 10,5 mois (0,2-20,4)

Overall Survival



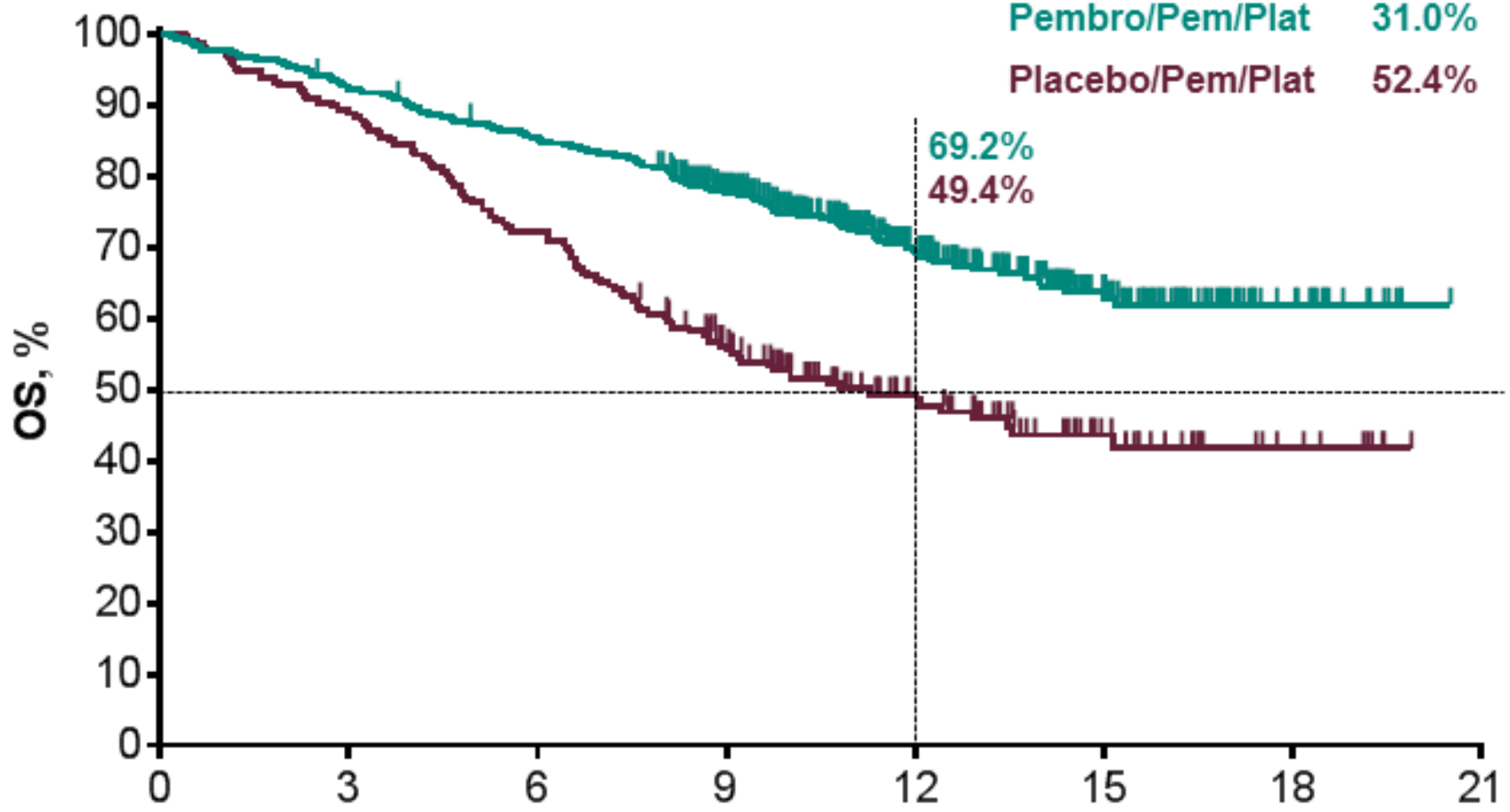
No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

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

Overall Survival, ITT



	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	31.0%	0.49 (0.38-0.64)	<0.00001
Placebo/Pem/Plat	52.4%		

Median (95% CI)
NR (NE-NE)
11.3 mo (8.7-15.1)

No. at Risk							
410	377	347	278	163	71	18	0
206	183	149	104	59	25	8	0

Data cutoff date: Nov 8, 2017.

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

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

R

1:1

(n = 278)

Pembrolizumab 200 mg
+ **paclitaxel** 200 mg/m²
ou
nab-paclitaxel 100 mg/m²
+ **carboplatine** ASC 6 ou
toutes les 3 sem. 4 cycles

Pembrolizumab
200 mg
jusqu'à 31 cycles

(n = 281)

Placebo +
paclitaxel 200 mg/m²
ou
nab-paclitaxel 100 mg/m²
+ **carboplatine** ASC 6 ou
toutes les 3 sem. 4 cycles

Objectif principal : SSP+OS

Placebo
jusqu'à 31 cycles

Crossover optionnel pembrolizumab 200 mg
à progression ou jusqu'à 35 cycles

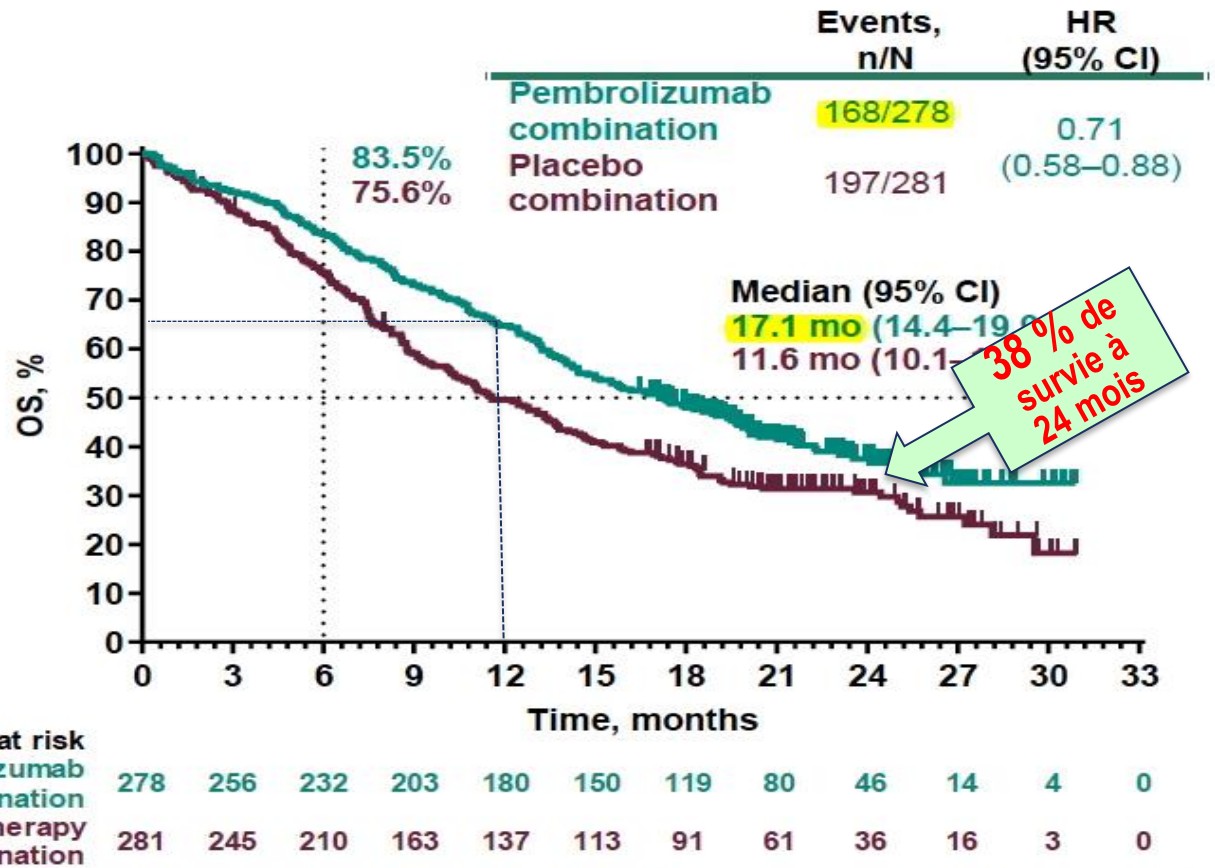
1ère présentation: ASCO 2018 **à 7,8 mois** de suivi médian

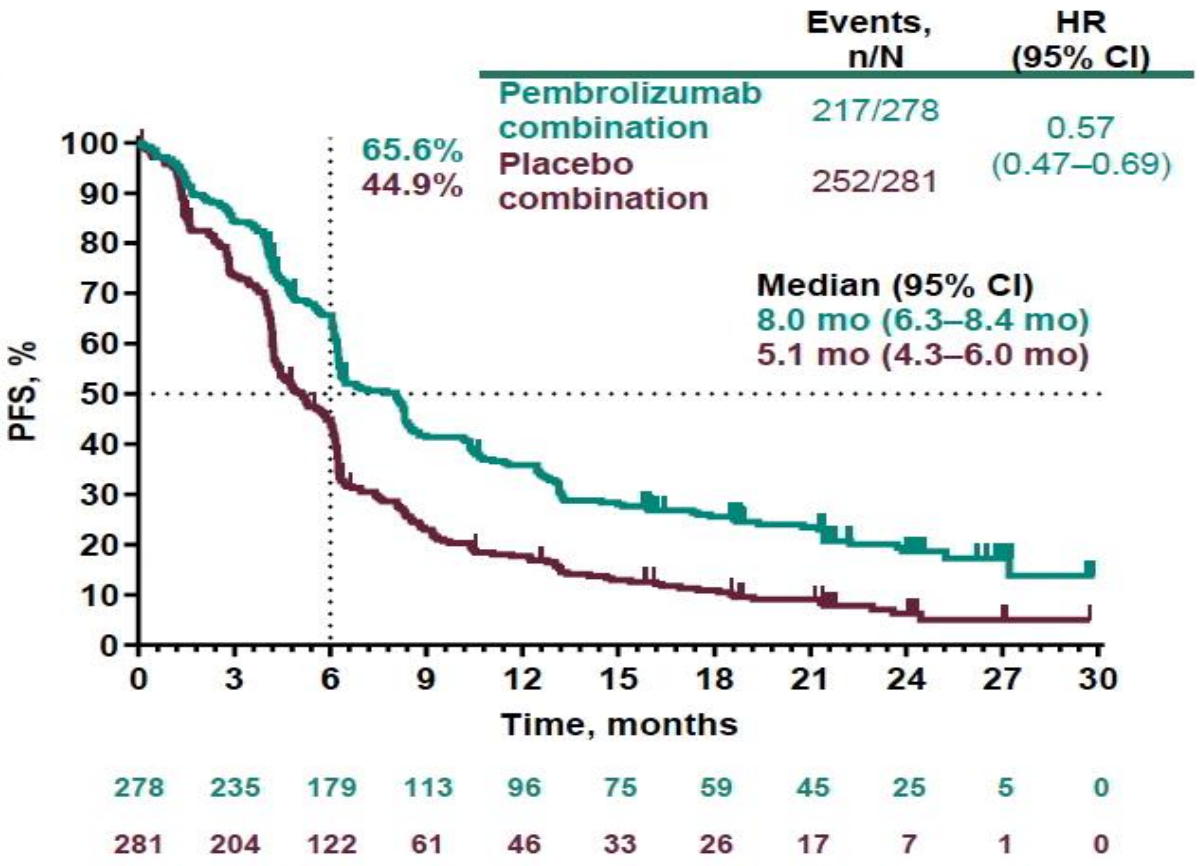
Analyse finale Keynote-407: Paez-Aeres L et al. ESMO 2019

Kaplan-Meier Estimates of OS and PFS[a]

Overall Study Population

Epi





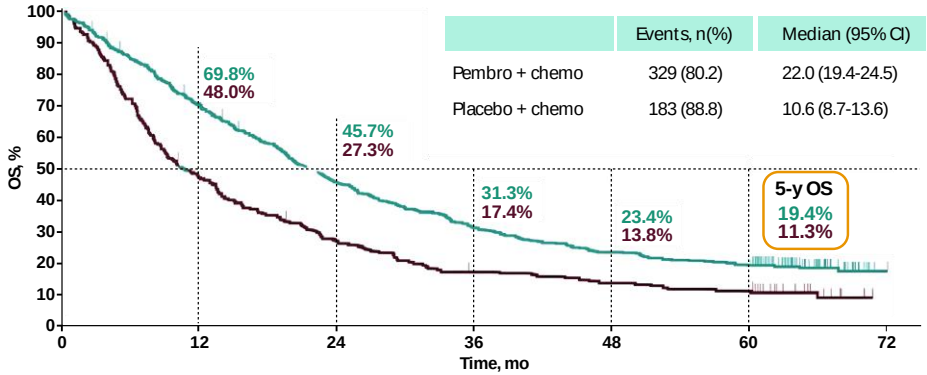
Median (range) follow-up: 14.3 (0.1–31.3) months

[a]Response assessed per RECIST v1.1 by blinded independent central review. Data cutoff date: May 9, 2019.

UPDATE AT 5 YEARS OF KEYNOTE-189 AND 407

KN-189: Non squamous

OS: ITT Population



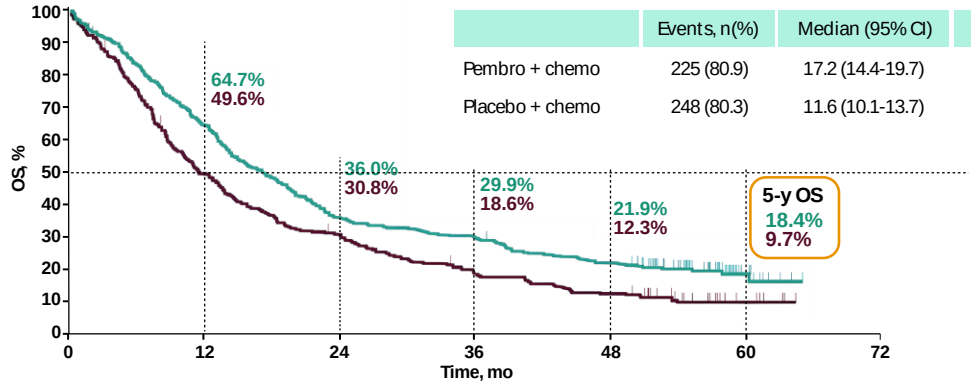
	Events, n(%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.4-24.5)	0.60 (0.50-0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7-13.6)	

No at risk							
Pembro + chemo	410	183	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Pembro + chemo (n=70)	Pembro + chemo (n=128)	Pembro + chemo (n=58)	Pembro + chemo (n=127)	Pembro + chemo (n=63)
OS HR (95% CI)	0.68 (0.49-0.96)		0.65 (0.65-0.90)		0.55 (0.39-0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

KN-407: Squamous

OS: ITT Population



	Events, n(%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4-19.7)	0.71 (0.59-0.85)
Placebo + chemo	248 (80.3)	11.6 (10.1-13.7)	

No at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + chemo (n=73)	Pembro + chemo (n=73)	Pembro + chemo (n=103)	Pembro + chemo (n=104)	Pembro + chemo (n=95)	Pembro + chemo (n=99)
OS HR (95% CI)	0.68 (0.47-0.97)		0.61 (0.45-0.83)		0.83 (0.61-1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

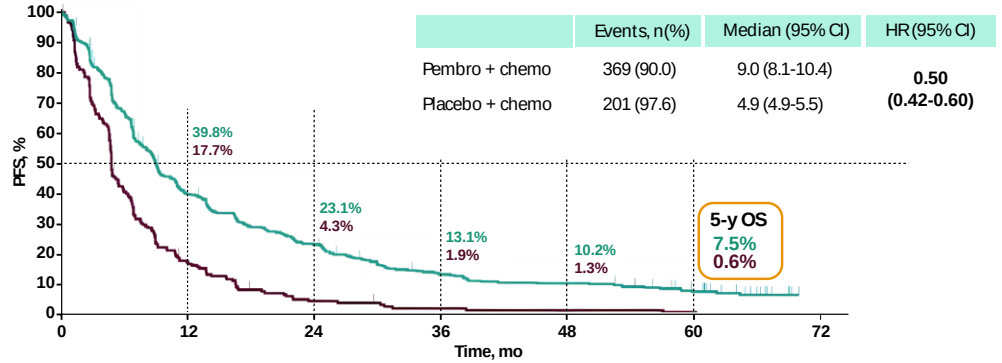
[a]Kaplan-Meier estimate. Data cuto date: February 23, 2022

Garassino et al_ESMO 2022; Novello S et al_ESMO 2022

Update at 5 years of KEYNOTE-189 AND 407

KN-189: Non squamous

PFS[a]: ITT Population



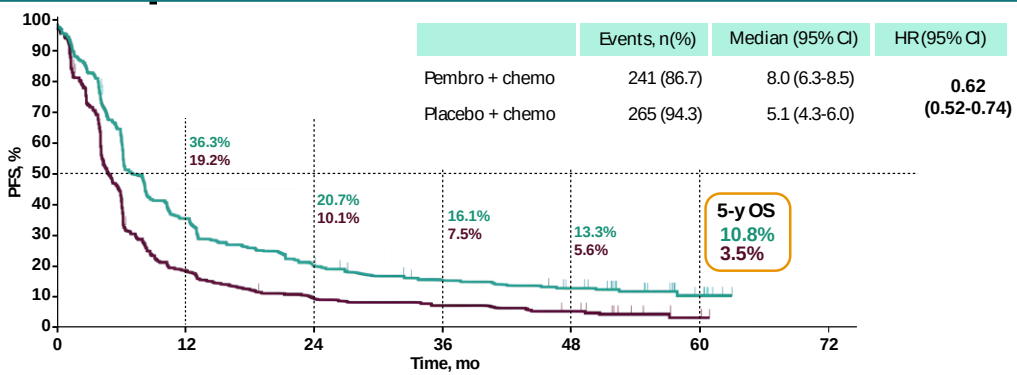
	Events, n(%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	369 (90.0)	9.0 (8.1-10.4)	0.50 (0.42-0.60)
Placebo + chemo	201 (97.6)	4.9 (4.9-5.5)	

No at risk							
Pembro + chemo	410	158	91	49	37	21	0
Placebo + chemo	206	35	8	3	2	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Pembro + chemo (n=70)	Pembro + chemo (n=128)	Pembro + chemo (n=58)	Pembro + chemo (n=127)	Pembro + chemo (n=63)
OS HR (95% CI)	0.35 (0.25-0.49)		0.57 (0.41-0.80)		0.67 (0.49-0.92)	
5-y OS rate,[a] %	12.8	0	6.5	1.9	2.4	0

KN-407: Squamous

PFS[a]: ITT Population



	Events, n(%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	241 (86.7)	8.0 (6.3-8.5)	0.62 (0.52-0.74)
Placebo + chemo	265 (94.3)	5.1 (4.3-6.0)	

No at risk							
Pembro + chemo	278	100	56	40	30	7	0
Placebo + chemo	281	53	27	20	14	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + chemo (n=73)	Pembro + chemo (n=73)	Pembro + chemo (n=103)	Pembro + chemo (n=104)	Pembro + chemo (n=95)	Pembro + chemo (n=99)
OS HR (95% CI)	0.48 (0.33-0.69)		0.60 (0.45-0.81)		0.70 (0.52-0.95)	
5-y OS rate[b], %	15.0	NR	11.8	NR	7.1	6.7

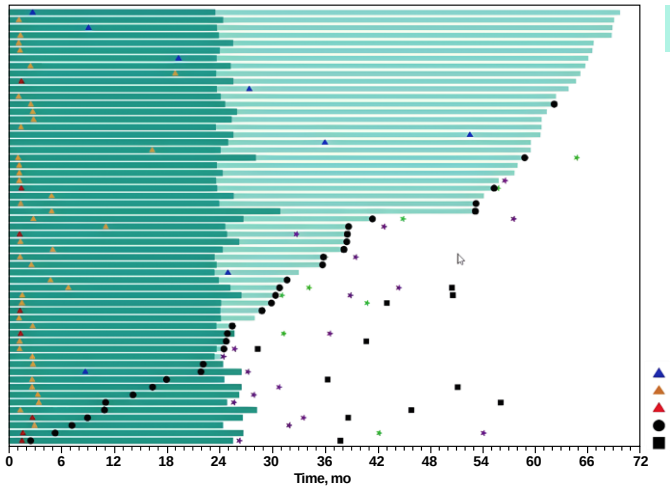
[a]Per RECIST v1.1 by BICR. [b]Kaplan-Meier estimate. Data cuto date: February 23, 2022.

Garassino et al_ESMO 2022; Novello S et al_ESMO 2022

Update at 5 years of KEYNOTE-189 AND 407

KN-189: Non squamous

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

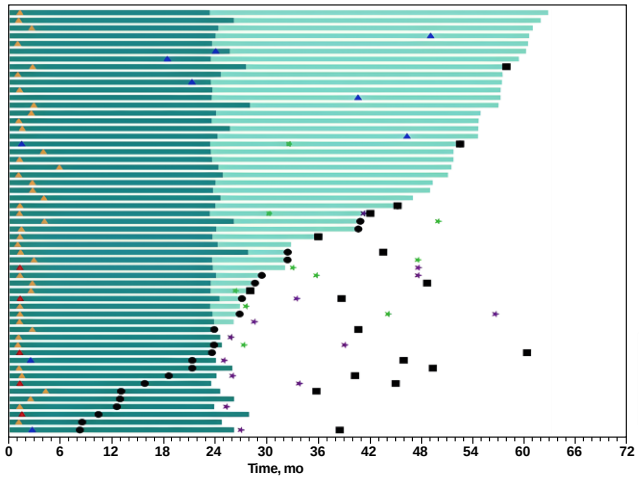


	n = 57
ORR (95% CI),[a] %	86.0 (74.2-93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

57/410 (13,9%) → 35 cycles
72% alive
40% without relapse
83,9% PD-L1≥1%*

KN-407: Squamous

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



	n = 55
ORR (95% CI),[a] %	90.9 (80.0-97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] mo	NR (7.1 to 61.5+)
3-y OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

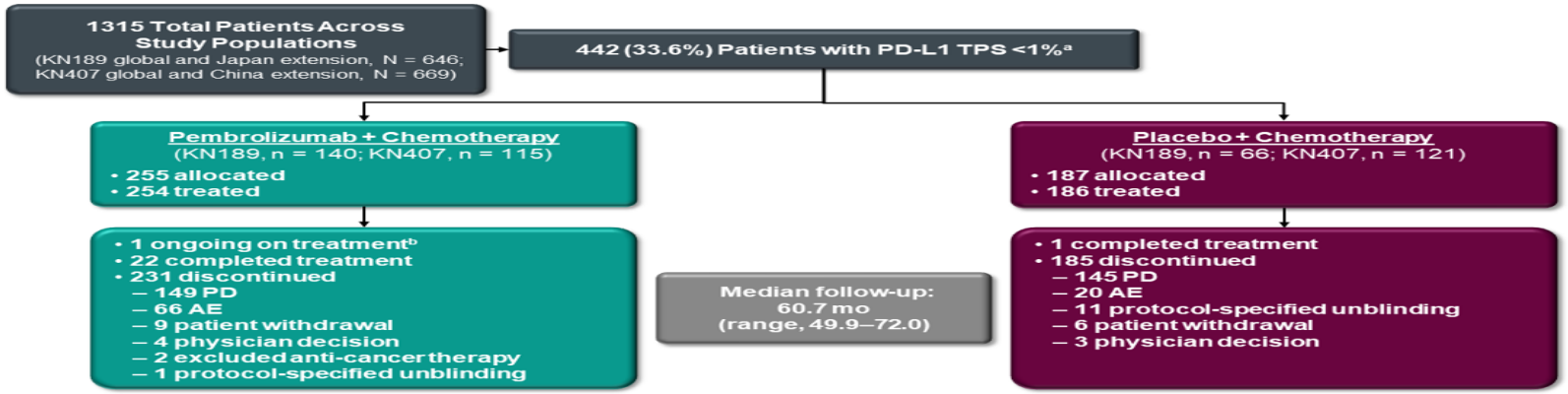
55/278 (19,7%) → 35 cycles
69,5% alive
43% without relapse

Garassino et al_ESMO 2022; Novello S et al_ESMO 2022; *Rodrigues-Abreu et al_Ann Oncol 2020

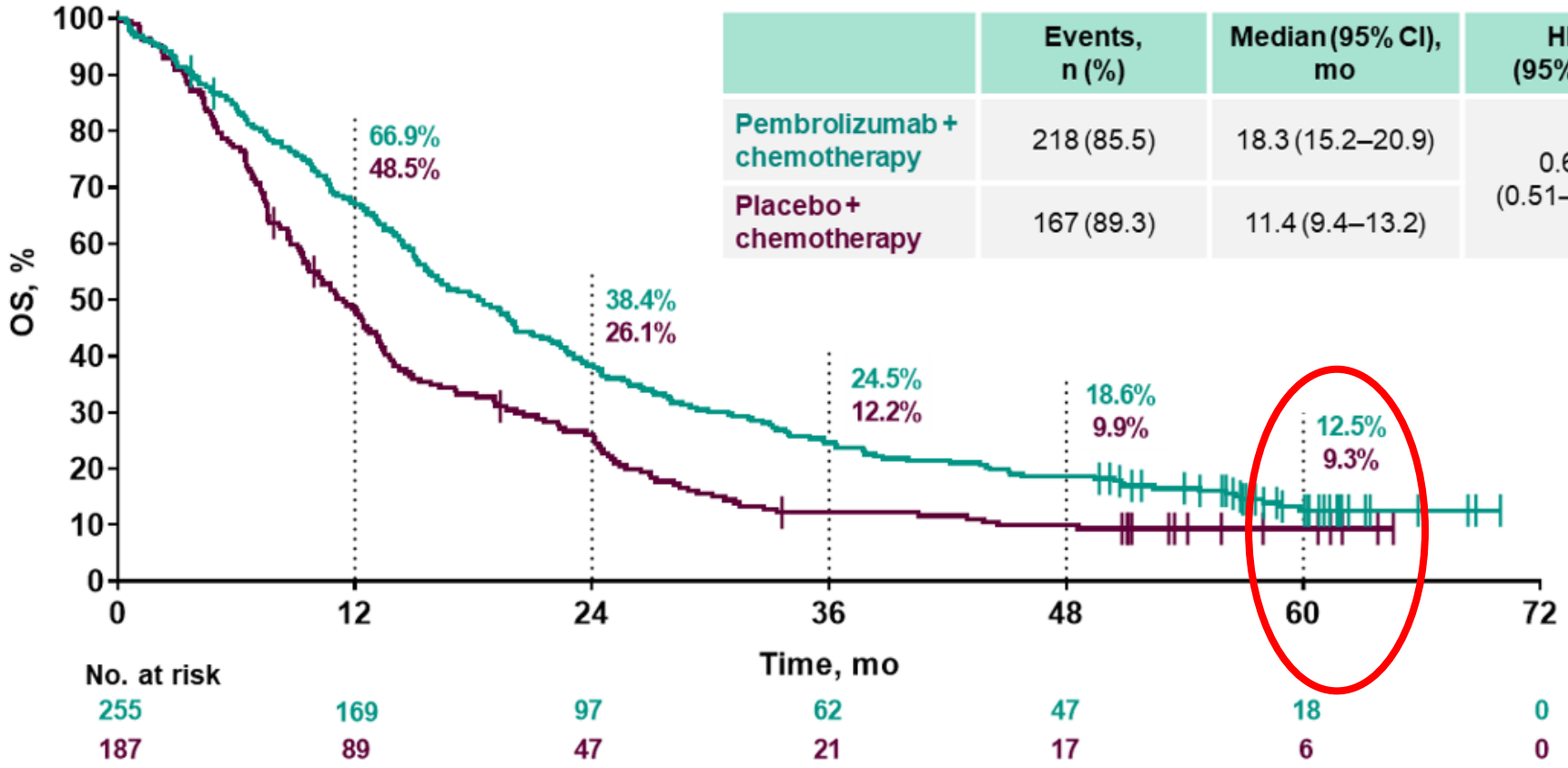
CT AND antiPD(L)1 – PDL1 <1%

Pooled analyses KN 189 AND KN 407

PD-L1<1% - data at 5 years



	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	218 (85.5)	18.3 (15.2–20.9)	0.64 (0.51–0.79)
Placebo + chemotherapy	167 (89.3)	11.4 (9.4–13.2)	

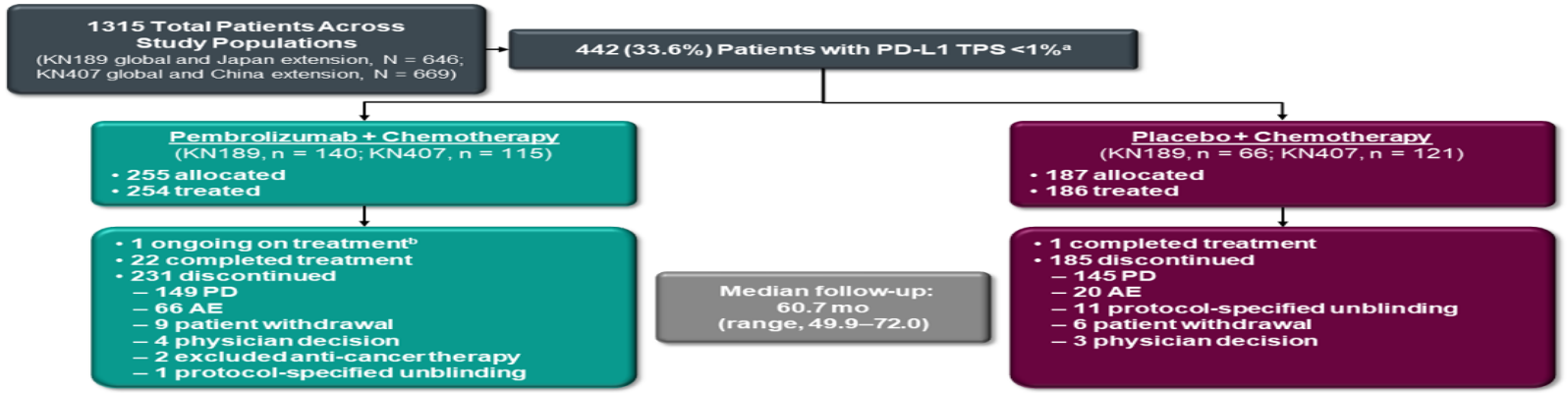


S. Gadgeel et al WCLC 2023

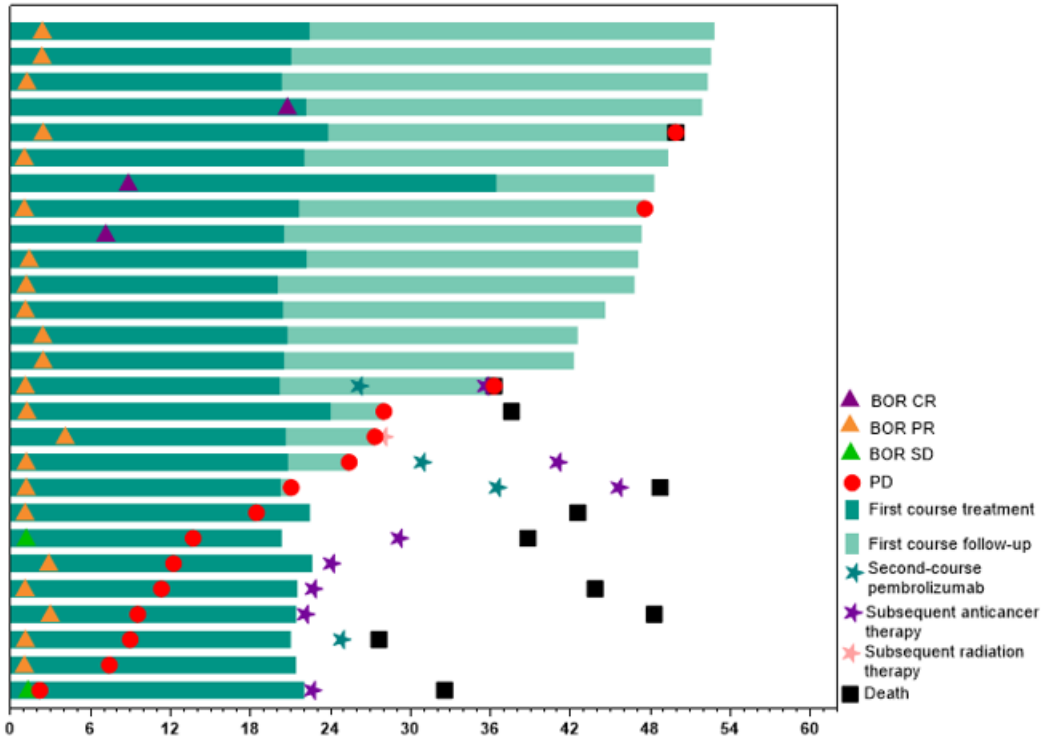
CT AND antiPD(L)1 – PDL1 <1%

Pooled analyses KN 189 AND KN 407

PD-L1<1% - data at 5 years



Group of patients who recieved 2 years of Pembrolizumab



Outcome	Patients who completed 35 cycles[a] n = 27
ORR[b] (95% CI), %	92.6 (75.7–99.1)
Best overall response, n (%)	
Complete response	3 (11.1)
Partial response	22 (81.5)
Stable disease[c]	2 (7.4)
Median DOR (range), mo	55.1 (7.4 to 59.3+)
3-year OS rate after completing 35 cycles, %	56.7
Alive without subsequent therapy or PD, n (%)	12 (44.4)

S. Gadgeel et al WCLC 2023

Combo chemotherapy with antiPD(L)1 in L1

ICIs	Trial	Population	Primary Endpoint	ORR	PFS	OS	5y-ORR	5y-PFS	5y-OS
Atezolizumab plus Bevacizumab plus CT	IMpower150	Any PD-L1 and Non-squamous histology	PFS and OS	63.5% (ABCP) vs. 48.0% (BCP)	8.3 vs. 6.8 months ABCP vs. BCP HR 0.62 (95% CI 0.52–0.74)	19.5 vs. 14.7 months ABCP vs. BCP: HR 0.78 (95% CI 0.64–0.96)		8.4 vs. 6.8 months ABCP vs. BCP HR 0.57 (95% CI 0.48–0.67)	19.5 vs. 14.7 months HR 0.80 (95% CI 0.67–0.95)
Atezolizumab plus platinum plus paclitaxel/nab paclitaxel	IMpower130	Any PD-L1 and Non-squamous histology	PFS and OS	49.2% vs. 31.9%	7.0 versus 5.5 months (HR 0.64; 95% CI 0.54–0.77)	18.6 versus 13.9 months (HR 0.79; 95% CI 0·64–0·98)	-	-	-
Atezolizumab plus platinum plus paclitaxel/nab paclitaxel	IMpower131	Any PD-L1 and squamous histology	PFS and OS	49.4% vs. 41.3%	6.3 vs. 5.6 months HR 0.71 (95% CI 0.60–0.85)	14.2 versus 13.5 months (HR 0.88; 95% CI 0.73–1.05)	-	-	-
Atezolizumab plus platinum plus pemetrexed	IMpower132	Any PD-L1 and Non-squamous histology	PFS and OS	47% vs. 32%	7.6 versus 5.2 months; HR 0.60, 95% CI 0.49–0.72	18.1 versus 13.6 months; HR 0.81, 95% CI 0.64–1.03	-	-	17.5 vs. 13.6 months *; HR 0.86 (0.71–1.06)
Cemiplimab plus platinum-doublet chemotherapy	EMPOWER-Lung 3	Any PD-L1; squamous and Non-squamous histology	OS	43.3% vs. 22.7%	8.2 vs. 5.0 months HR = 0.56; 95% CI, 0.44–0.70	21.9 vs. 13.9 months; HR 0.71; 95% CI, 0.53–0.93	43.6% versus 22.1%	8.2 months versus 5.5 months (HR 0.55, 95% CI 0.44–0.68	21.1 versus 12.9 months; HR 0.65, 95% CI 0.51–0.82
Nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy	CheckMate 9LA	Any PD-L1; squamous and Non-squamous histology	OS	37.7% vs. 25.1%	6.8 vs. 5.0 months HR 0.70 [97·48% CI 0.57–0.86	14.1 versus 10.7 months; HR 0.69; 96.71% CI 0.55–0.87	38% vs. 25% *	6.4 versus 5.3 months *	15.8 versus 11 months *; HR 0.74, 95% CI 0.62–0.87
Pembrolizumab plus platinum (carboplatin or cisplatin) plus pemetrexed	KEYNOTE-189	Any PD-L1 and Non-squamous histology	PFS and OS	47.6% vs. 18.9%	8.8 vs. 4.9 months HR 0.52 (95% CI 0.43–0.64)	NR vs. 11.3 months; HR 0.49; 95% CI 0.38–0.64	48.3% vs. 19.9%	9.0 versus 4.9 months; HR 0.5; 95% CI 0.42–0.60	22.0 versus 10.6 months; HR 0.6; 95% CI 0.50–0.72
Pembrolizumab plus platinum (carboplatin or cisplatin) plus Paclitaxel or nab-paclitaxel	KEYNOTE-407	Any PD-L1 and squamous histology	PFS and OS	57.9% vs. 38.4%	6.4 versus 4.8 months; HR 56; 95% CI 0.45–0.70	15.9 months and 11.3 months HR 0.64; 95% CI 0.49–0.85	66.2% vs. 38.8%	8 versus 5.1 months; HR 0.62; CI 0.52–0.74	17.2 versus 11.6 months HR 0.71; 95% CI 0.59–0.85
Tremelimumab plus durvalumab plus CT	POSEIDON	Any PD-L1; squamous and Non-squamous histology	PFS and OS	46.3% vs. 33.4%	6.2 v 4.8 months; HR 0.72; 95% CI 0.60–0.86	14.0 versus 11.7 months; HR 0.77; 95% CI 0.65–0.92	-	-	-

Roque, K. *et al.* Update in Immunotherapy for Advanced Non-Small Cell Lung Cancer: Optimizing Treatment Sequencing and Identifying the Best Choices. *Cancers* **15**, 4547 (2023).

New AMM combo 2023

EMPOWER-Lung 3

Key eligibility criteria
- Treatment-naive advanced NSCLC (squamous and non-squamous histology; Stage IIIb/c, IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* aberrations
- ECOG performance status 0 or 1
- Treated, clinically stable CNS metastases

Stratification factors
- PD-L1 expression: ≥50% vs 1–49% vs <1%
- Histology: squamous vs non-squamous

R 2:1

Arm A
Cemiplimab 350 mg Q3W + platinum-doublet chemotherapy Q3W for 4 cycles

Arm B
Placebo Q3W + platinum-doublet chemotherapy Q3W for 4 cycles

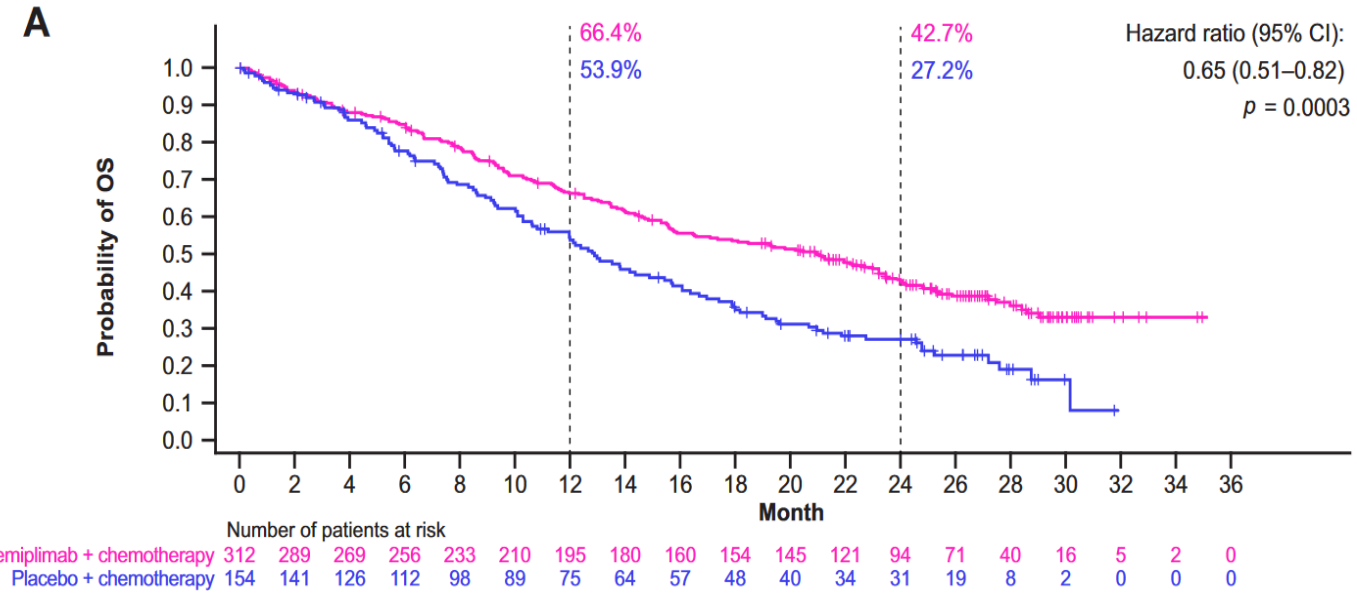
Progressive disease or 108 weeks

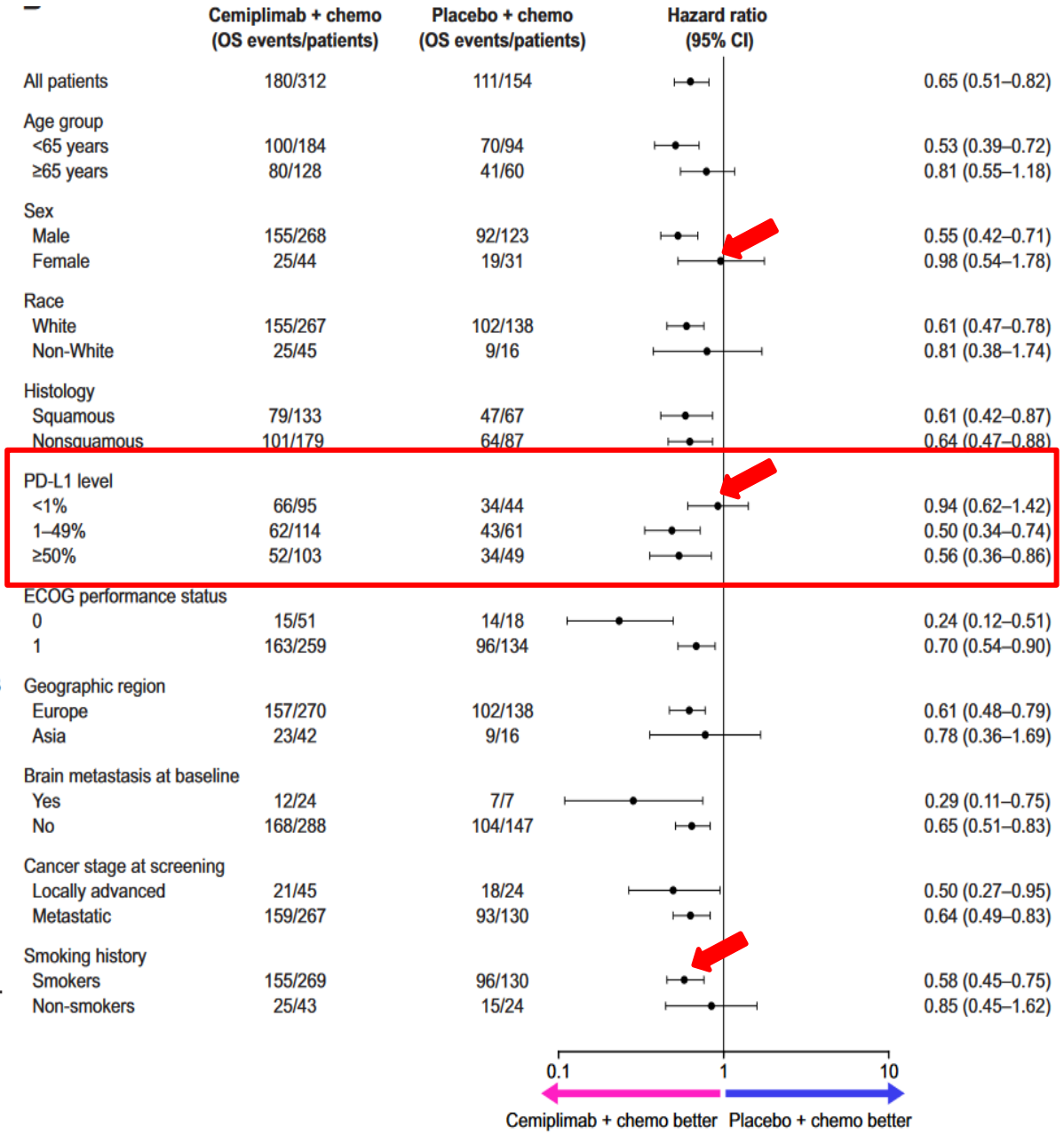
Progressive disease or 108 weeks

Follow-up

N=466

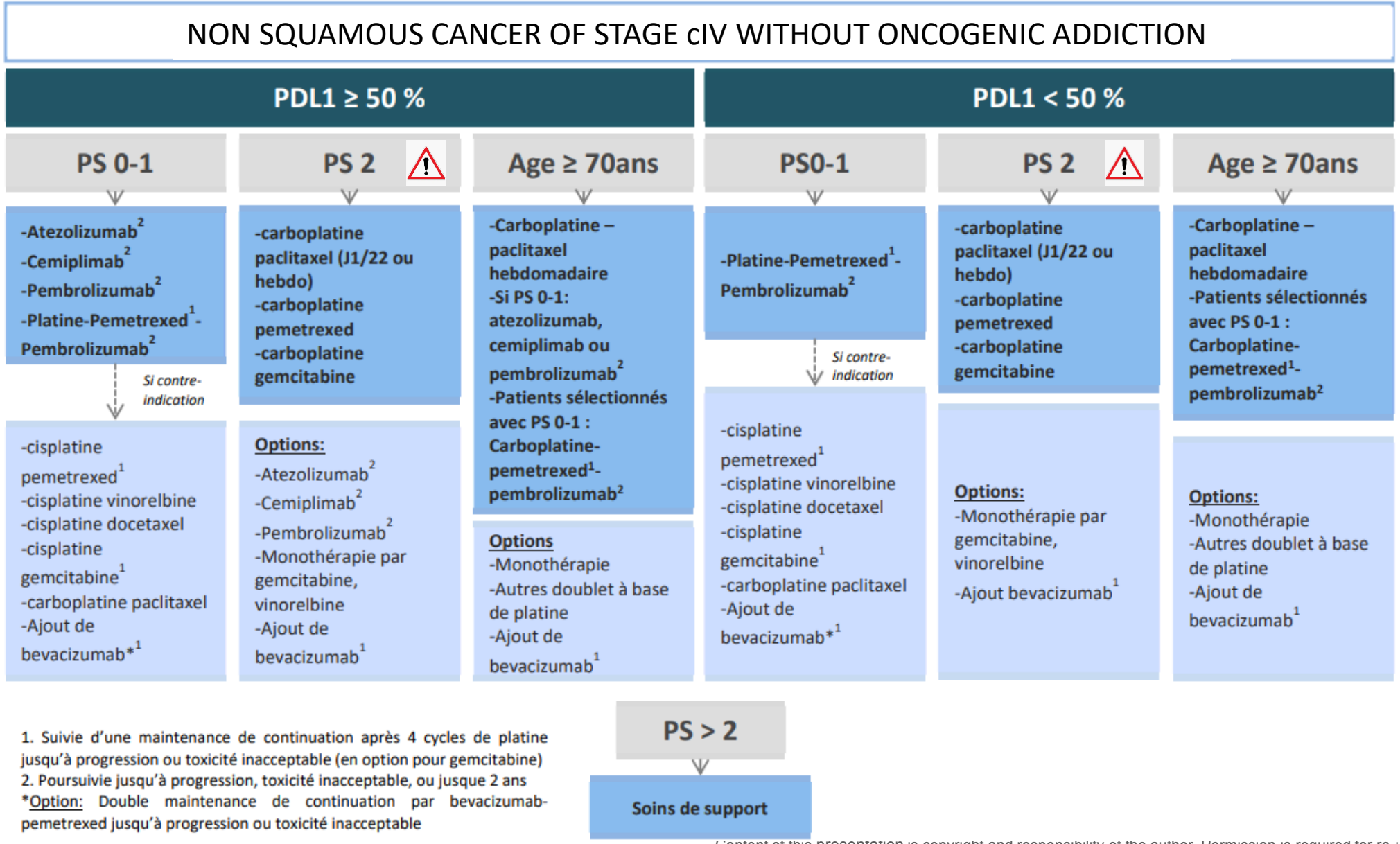
Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PROs





Makharadze, T. et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial. Journal of Thoracic Oncology 18, 755–768 (2023).

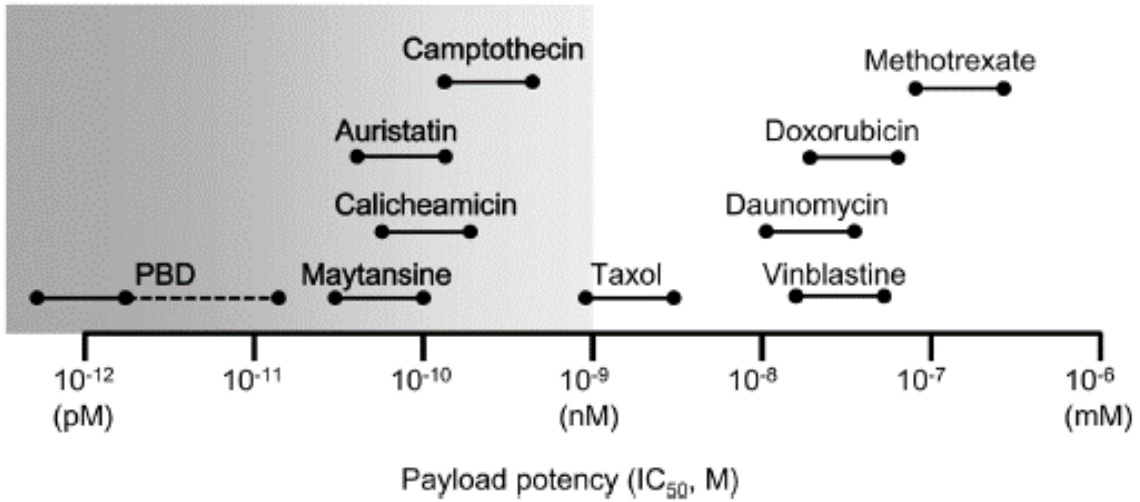
Modality OF 1ST LINE OF ADVANCED NSCLC IN 2023

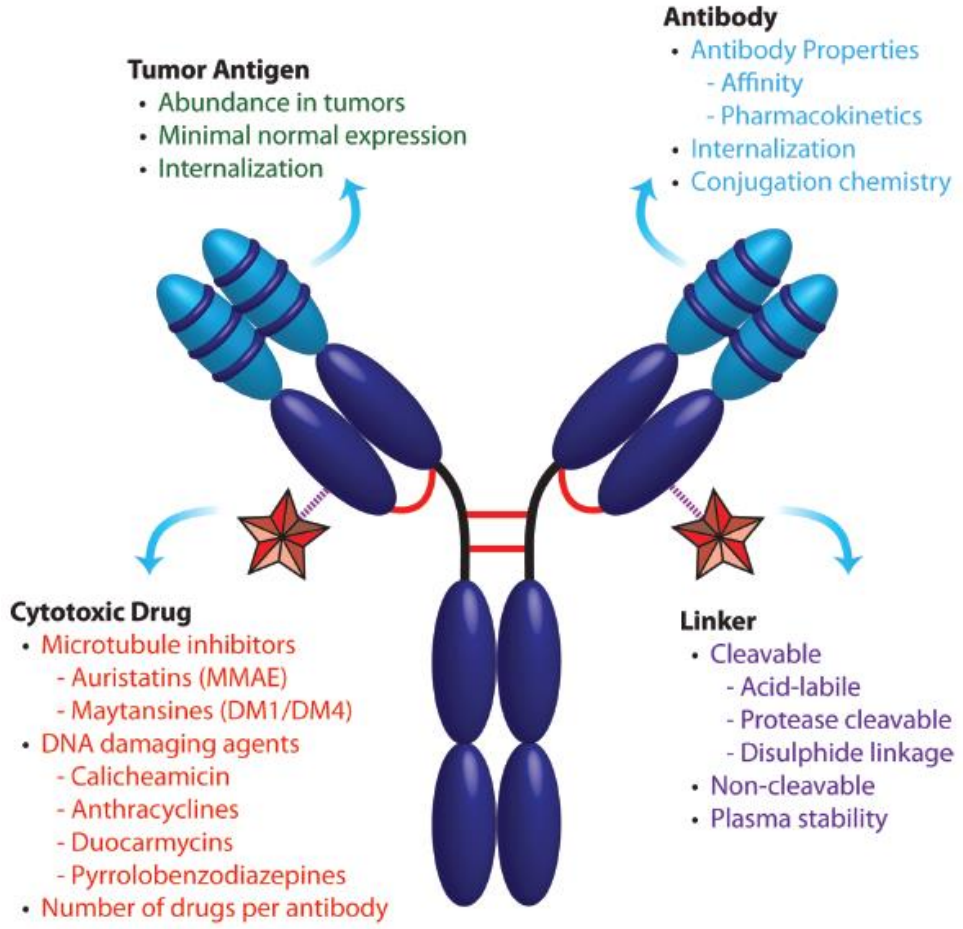


Couraud, S. et al. Référentiel sur le cancer bronchique non à petites-cellules : actualisation 2023. ARISTOT Accessible sur http://referentiels-aristot.com/, 94 (2023).

PERSPECTIVES

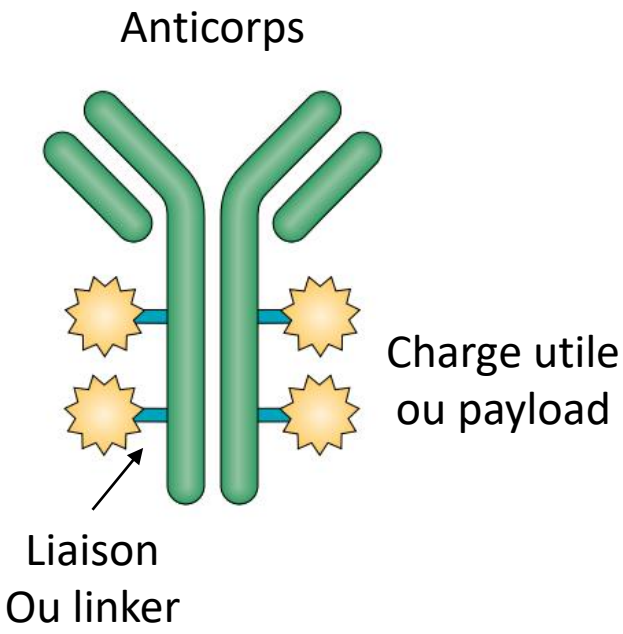
ADC

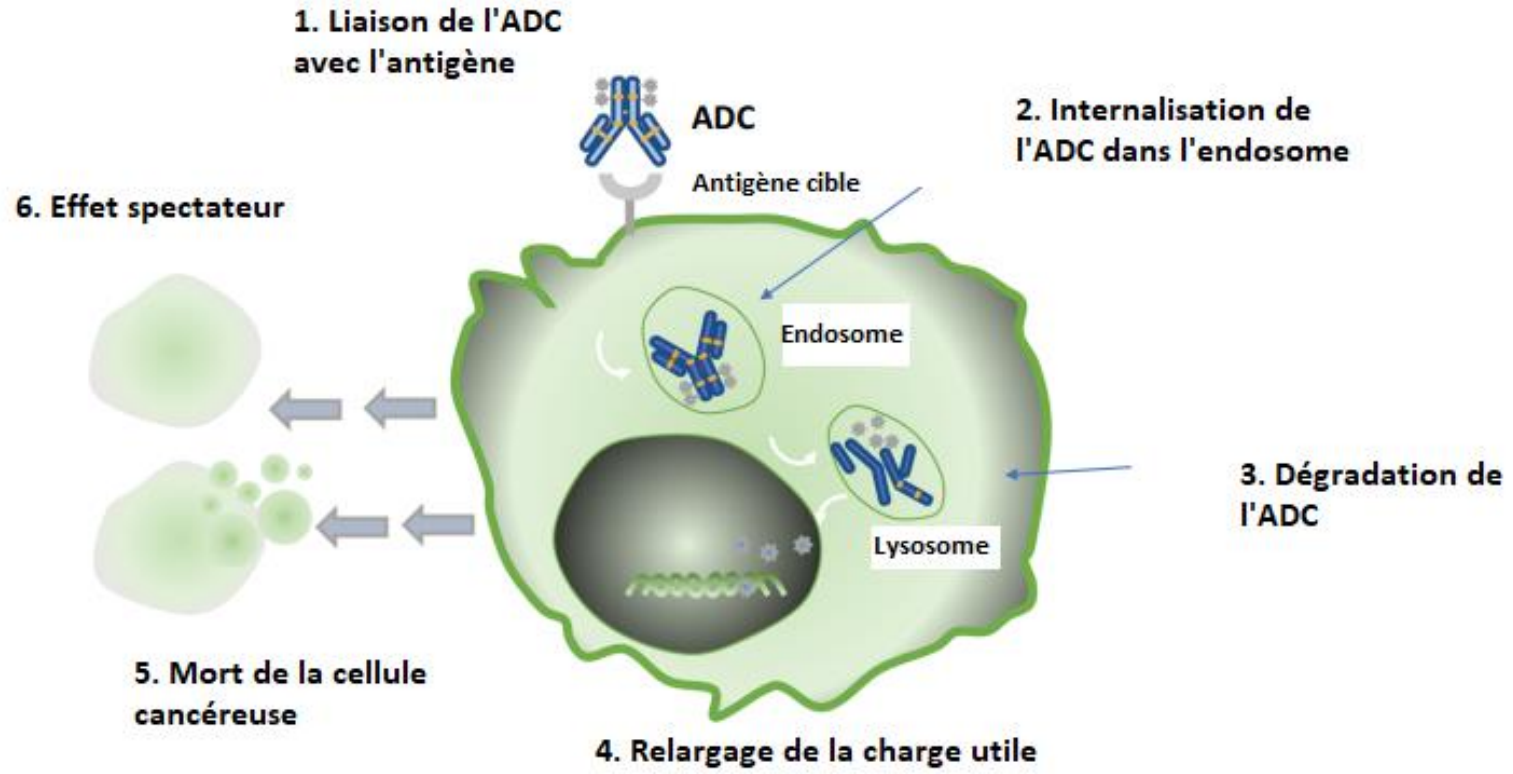




Nakada, Chem. Pharm. Bull. 67, 173–185 (2019); Panowski et al, mAbs 2014, 6: 34–45

ADC ANTIBODY DRUG CONJUGATED

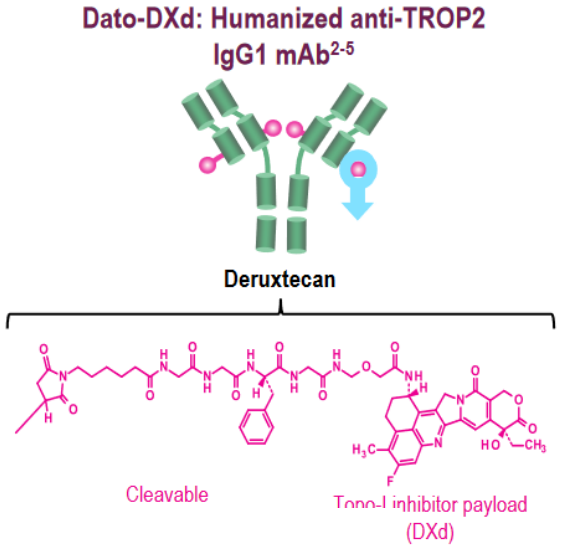




Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

LBA 12 – TROPION-LUNG01 DATOPOTAMAB DERUXTECAN (DATO-DXD) VS DOCETAXEL IN ADVANCED NSCLC

- Phase 3 randomized in open



Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m² Q3W
(N=305)

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

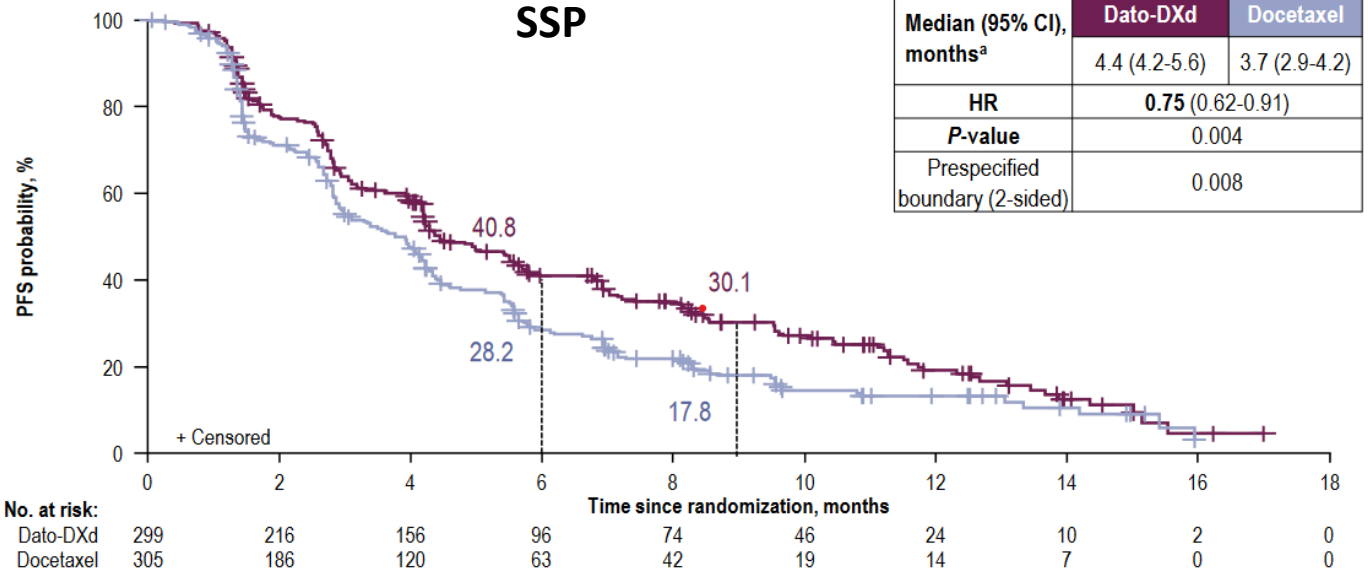
- ORR by BICR
- DOR by BICR
- Safety

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION LUNG01 – PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL IN ITT

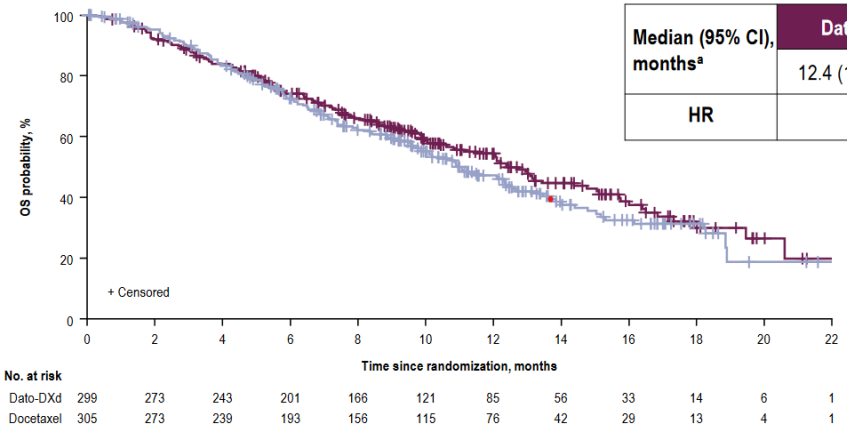
SSP



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

SG immature



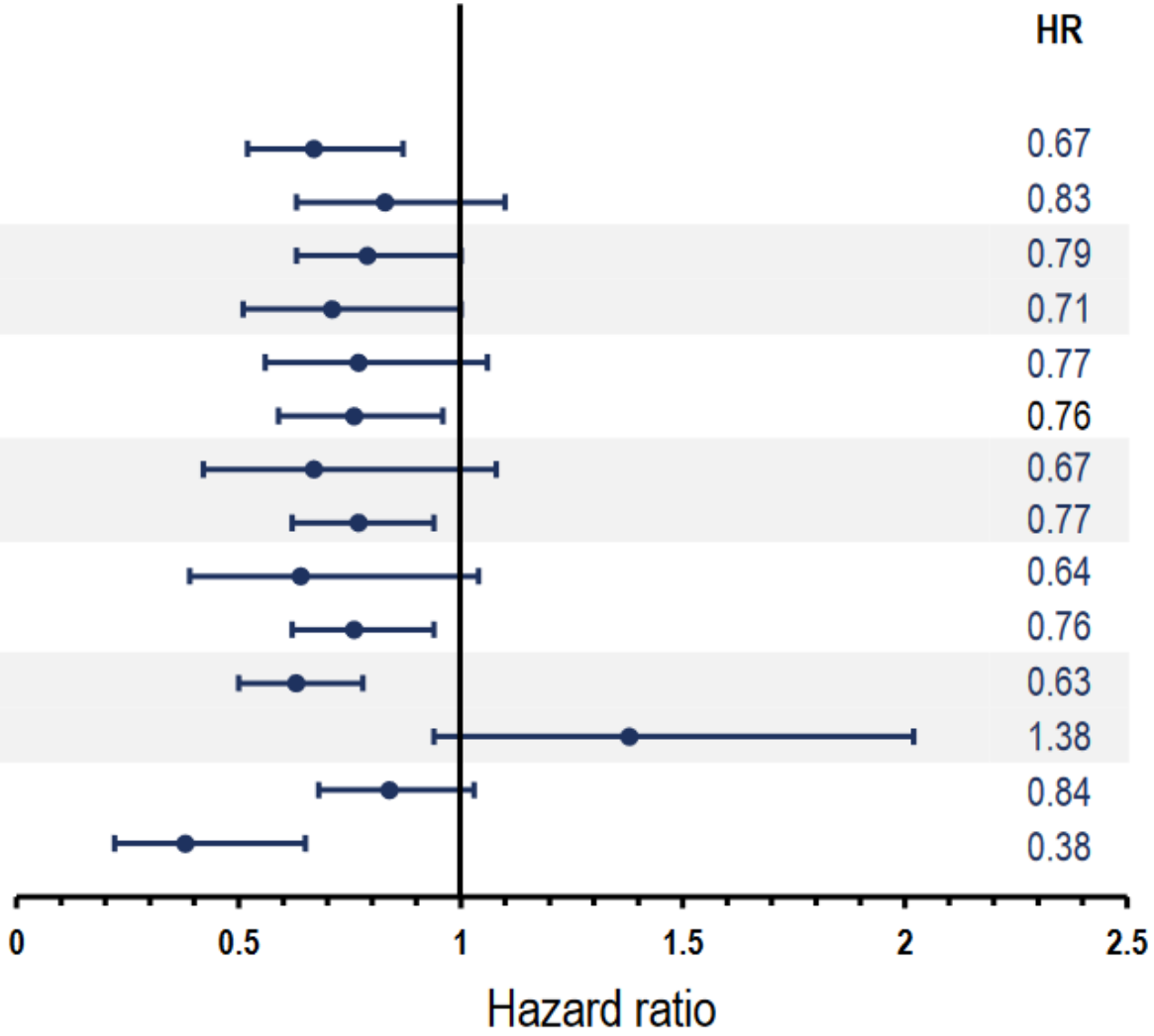
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%.**

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION LUNG01 – PFS IN SUB-GROUPS

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38

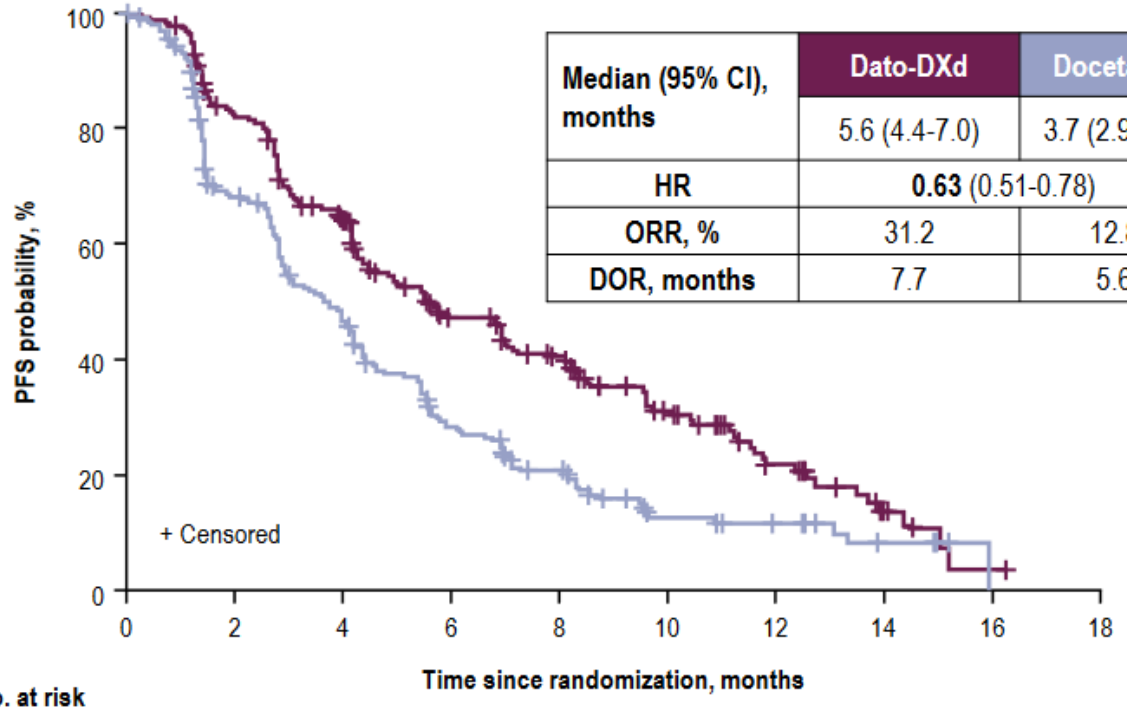


Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION LUNG01 – SSP IN SUB-GROUPS

Non-squamous
(with and without AGAs)

Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

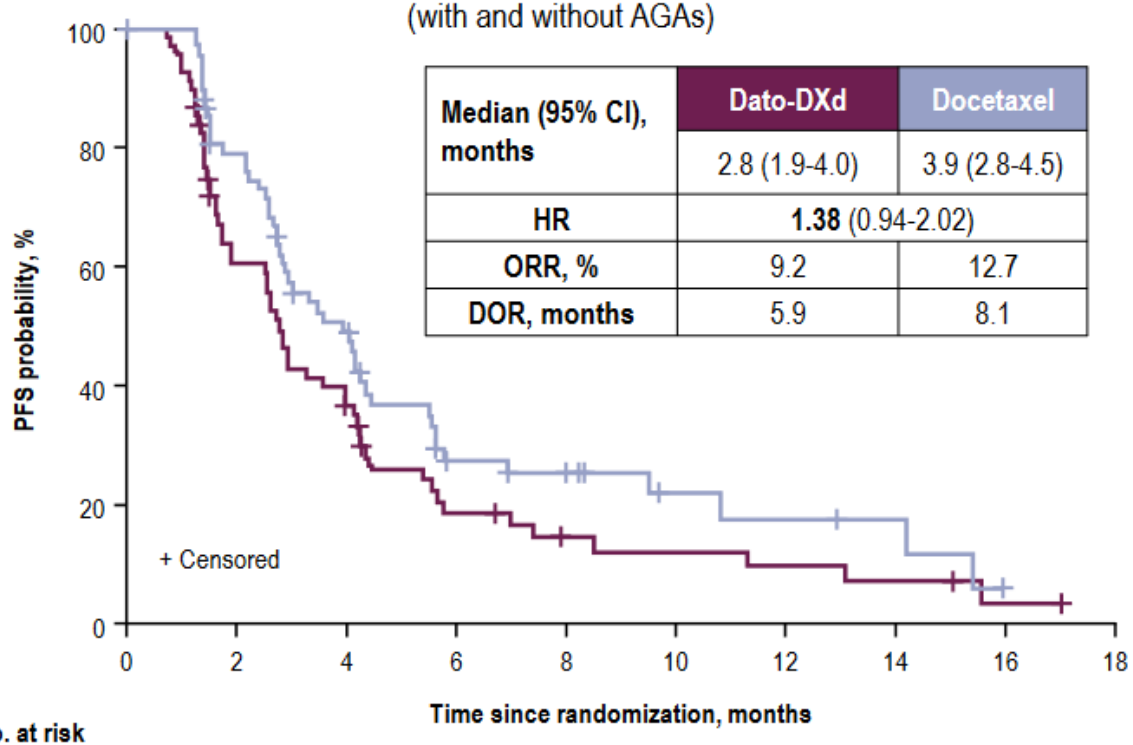


No. at risk

Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous
(with and without AGAs)

Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1



No. at risk

Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION LUNG01 – TOLERANCE

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[a]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

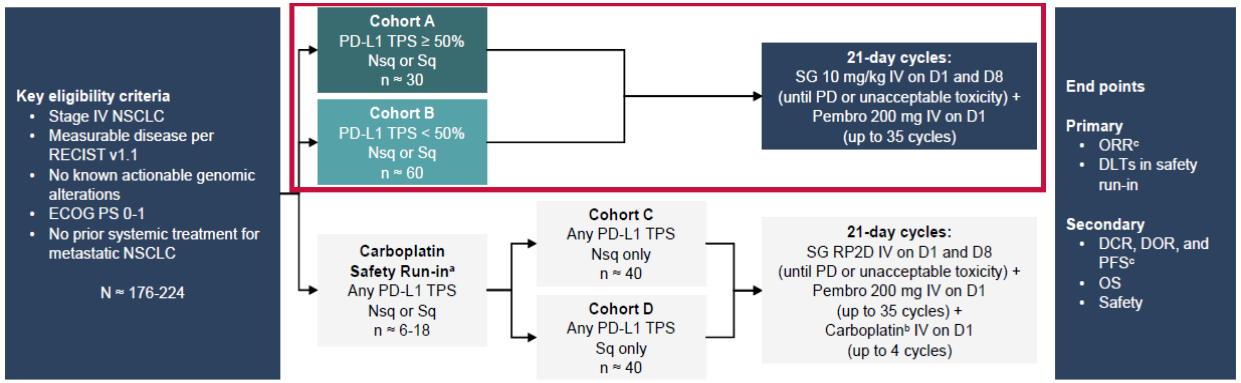
AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

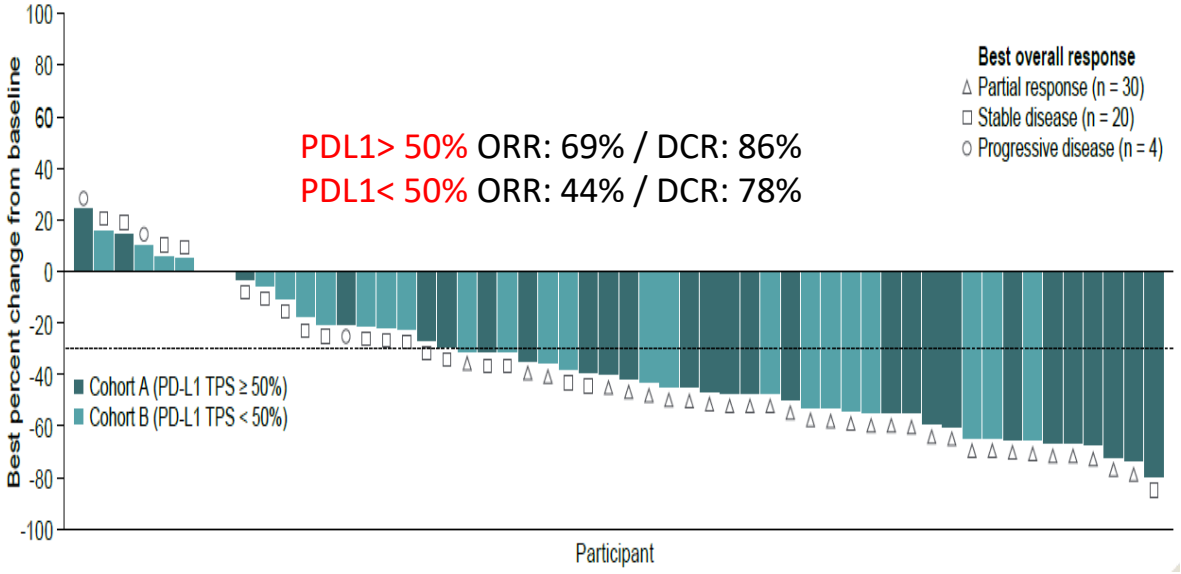
Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

NEW ASSOCIATIONS…

EVOKE 02 Study

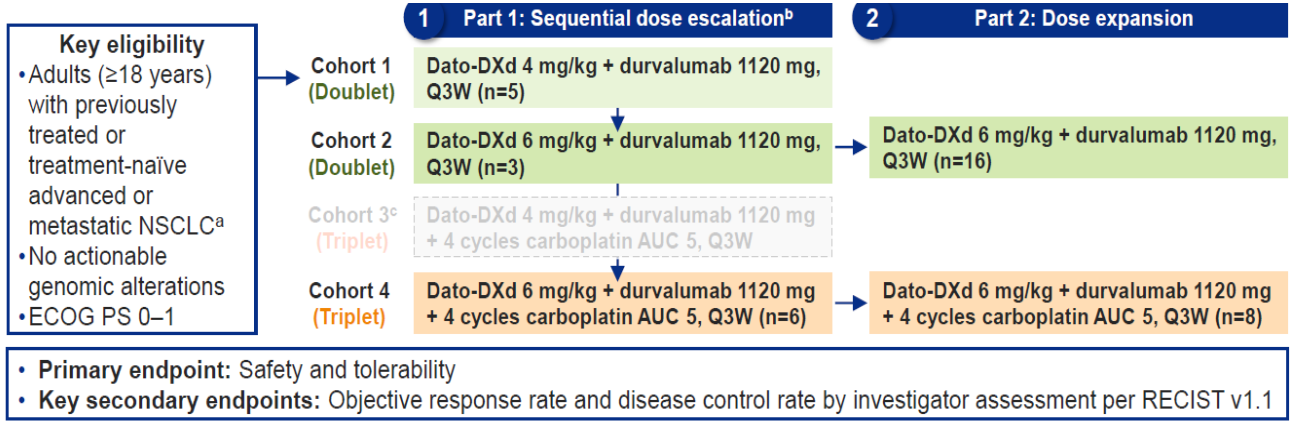
Sacituzumab Govitecan + Pembrolizumab





TROPION Lung04

Datopotamab Deruxtecan + Durvalumab +/-Carboplatin



Response	Cohort 2 (doublet) (n=14)	Cohort 4 (triplet) (n=13)
cORR, n (%) [95%CI]	7 (50.0) [23.0, 77.0]	10 (76.9) [46.2, 95.0]
BOR, n (%)		
PR	7 (50.0)	10 (76.9)
SD	6 (42.9)	2 (15.4)
PD	1 (7.1)	1 (7.7)
DCR, n (%) [95%CI]	13 (92.9) [66.1, 99.8]	12 (92.3) [64.0, 99.8]

Cho BC, et al. J Thorac Oncol 2023;18(suppl 9):Abstr OA05.04 ; Papadopoulos KP, et al. J Thorac Oncol 2023;18(suppl 9):Abstr OA05.06

BEYOND TRIALS: PATIENT BEYOND CLINICAL TRIAL

- General
- Age
- Brain metastasis
- Other metastasis (threatening)
- Symptoms
- Time for evolution
- Sides effects/ Toxicity
- Comorbidity/ Previous treatment
- Comedications (ATB, corticoids, other)

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

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