Immunothérapies dans les tumeurs solides : l'exemple du mélanome

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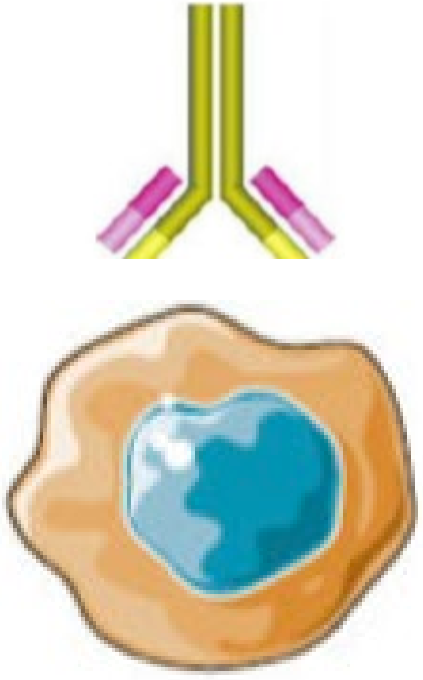
Immunothérapie en oncologie: changement de paradigme

AVANT

Cibler la tumeur

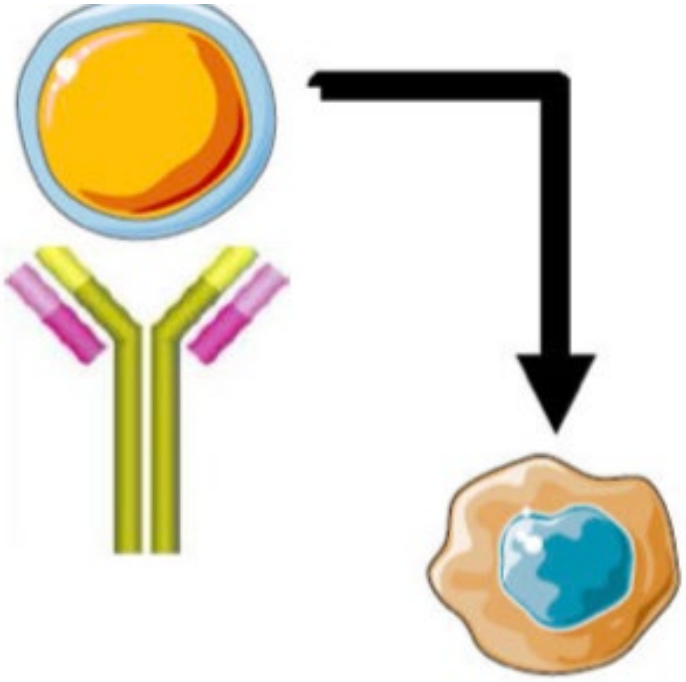


Cellule tumorale

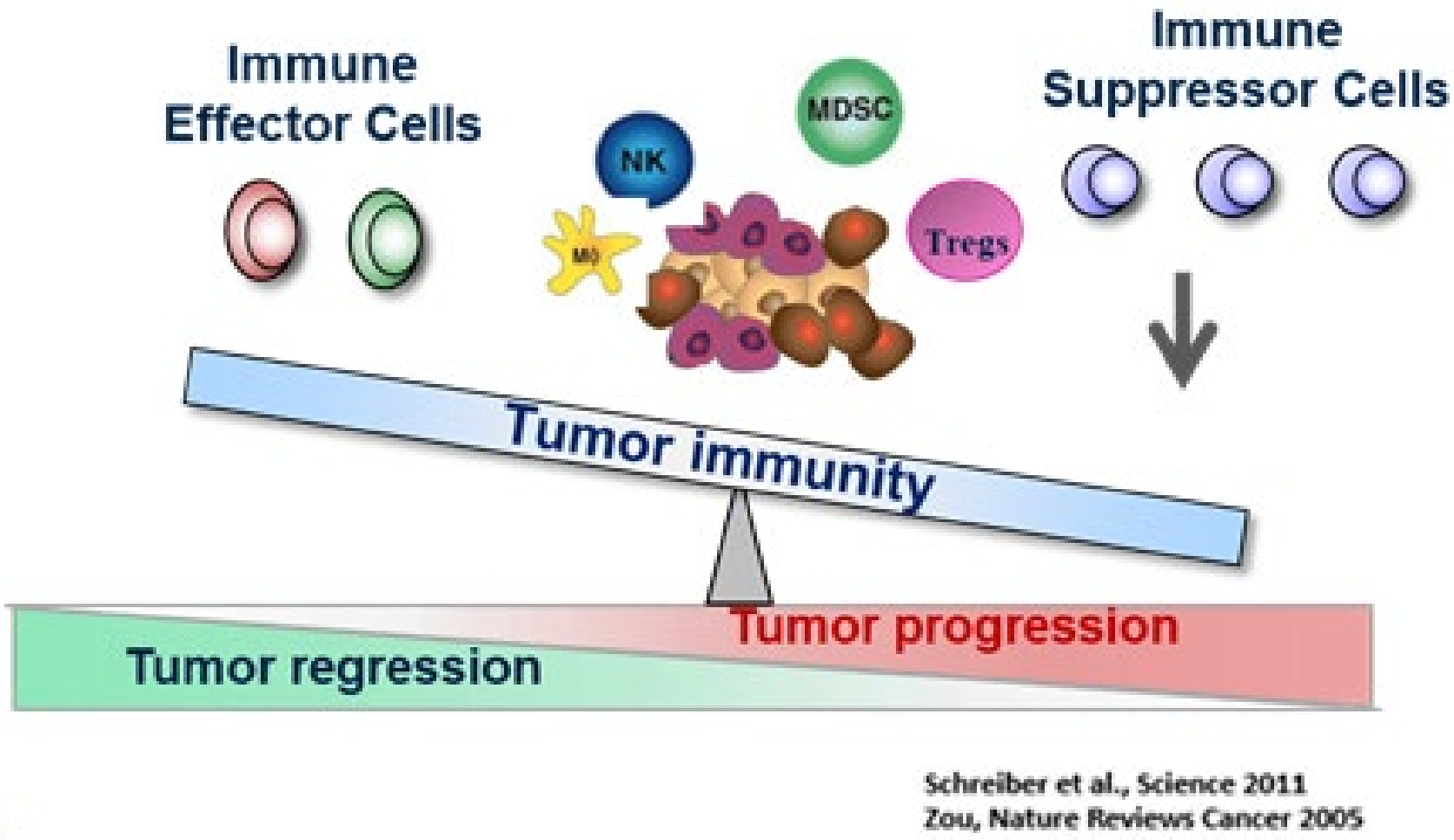
AUJOURD'HUI

Cibler le système immunitaire

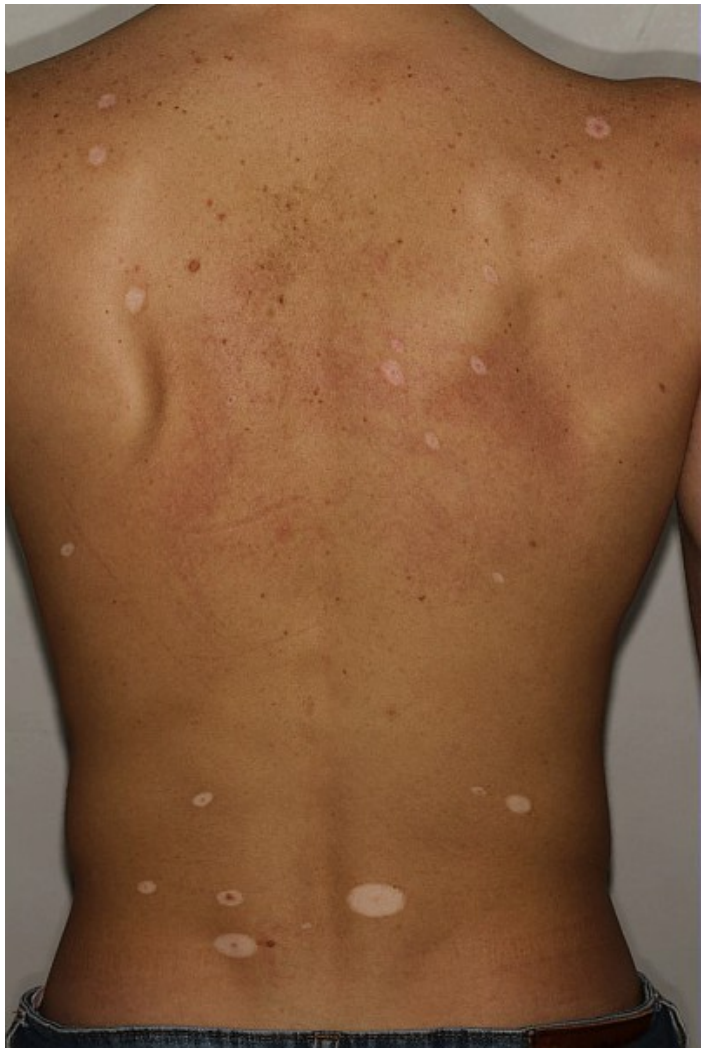
lymphocyte



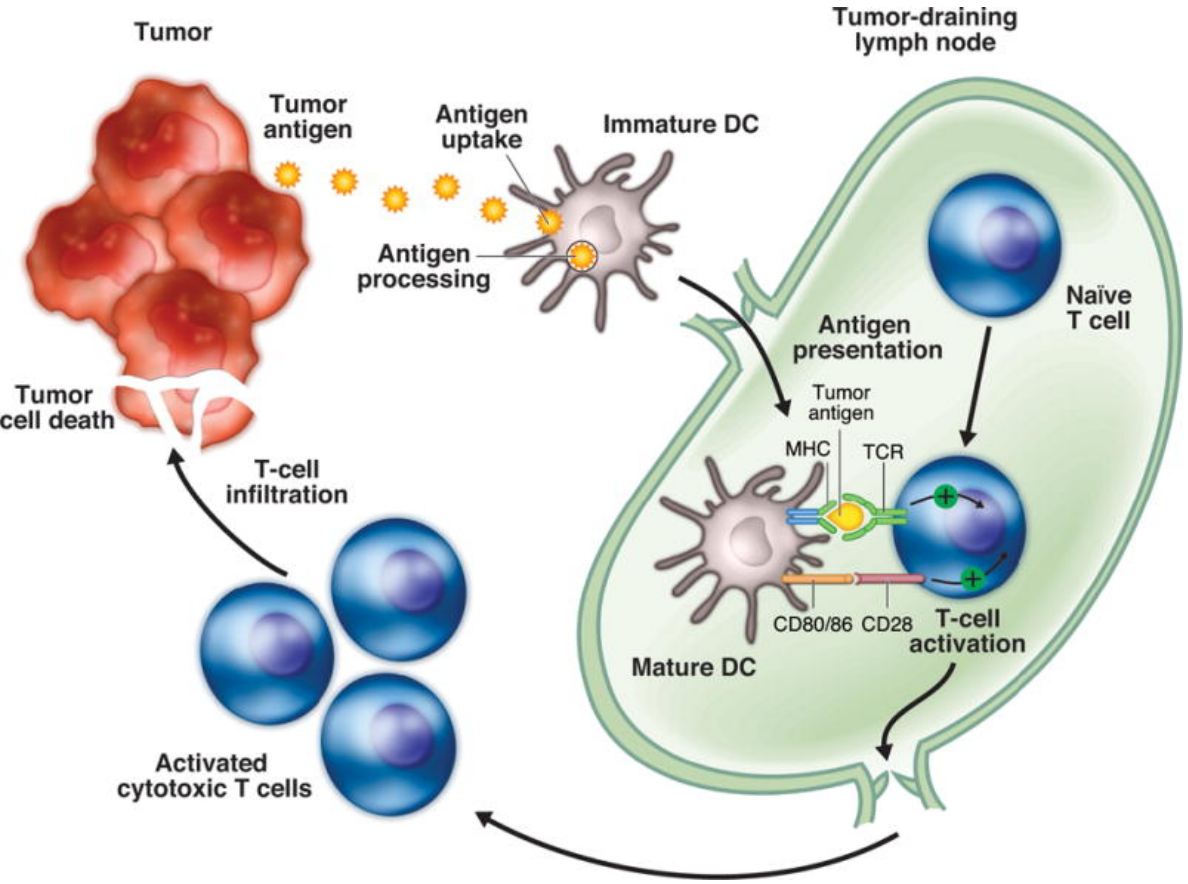
Comment stimuler l'immunité anti-tumorale ?



Schreiber et al., Science 2011
Zou, Nature Reviews Cancer 2005



Réponse immunitaire adaptative

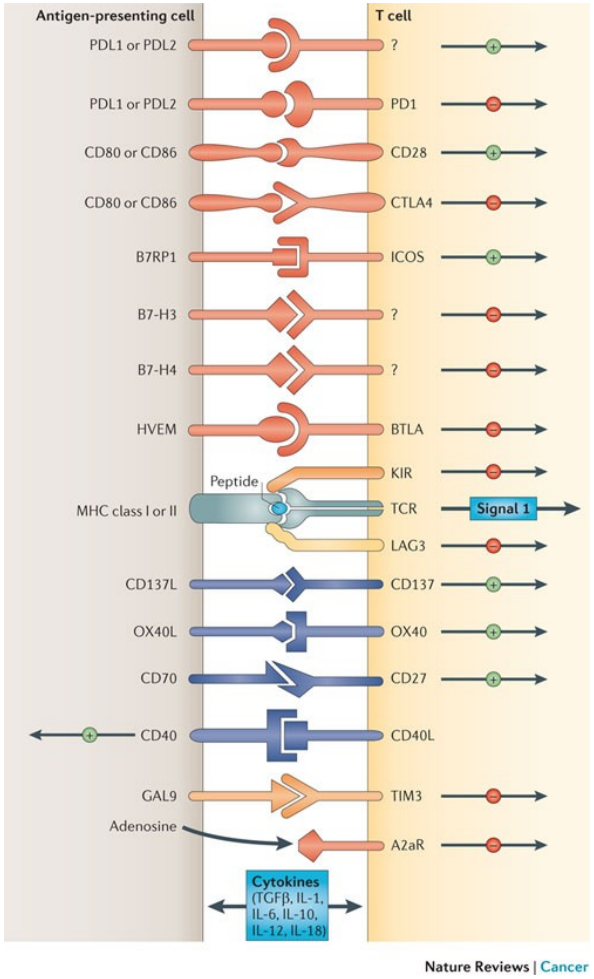


- CDs immature capturent et process les Ag tumoraux
- Migration dans les ganglions
- Présentations Ag dans le cadre du CMH aux LT naïfs
- Activation celles effectrices
- Cette activation nécessite des molécules de co-stimulation (CD80/86, CD28)

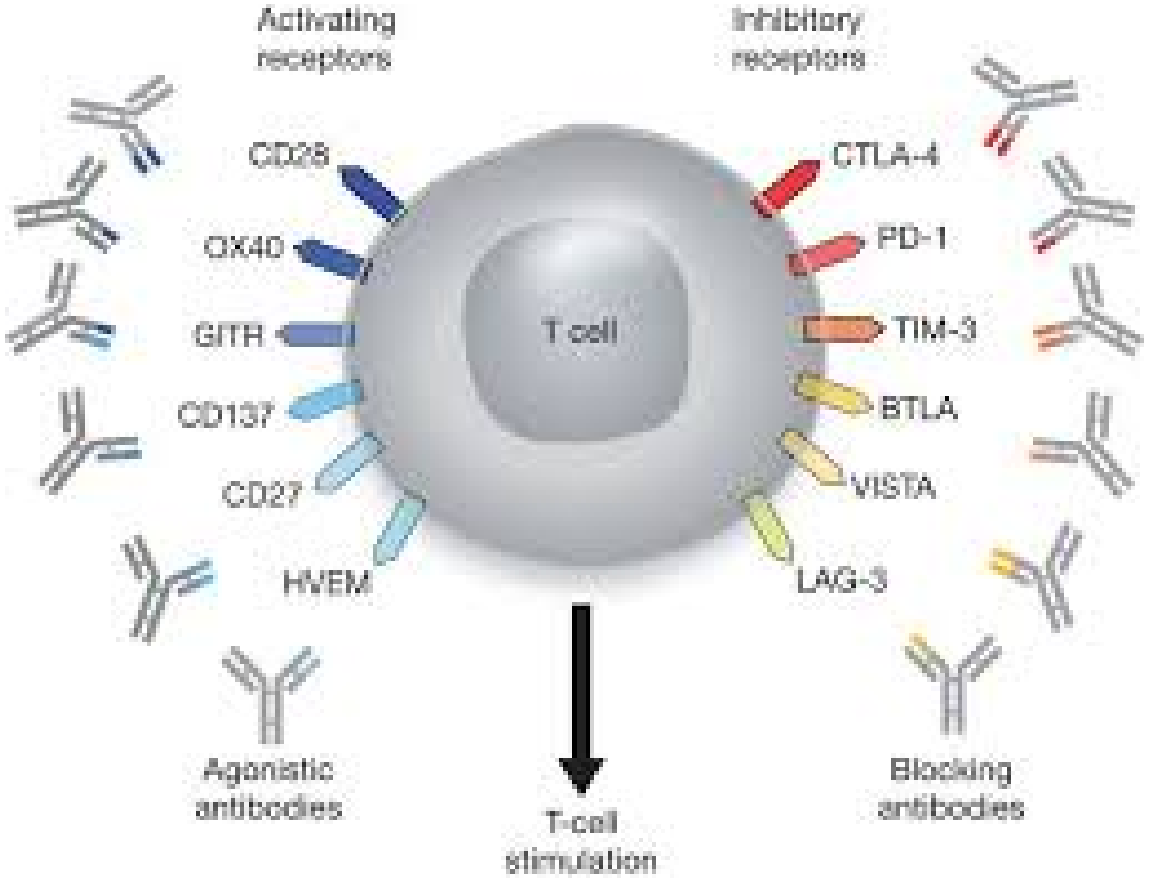
Carbone et al. J Thorac Oncol. 2015

L'activation des T naïfs nécessite un 1er signal via le TCR et des corécepteurs = checkpoint immunitaire

La synapse immunologique



Corécepteurs activateurs et inhibiteurs

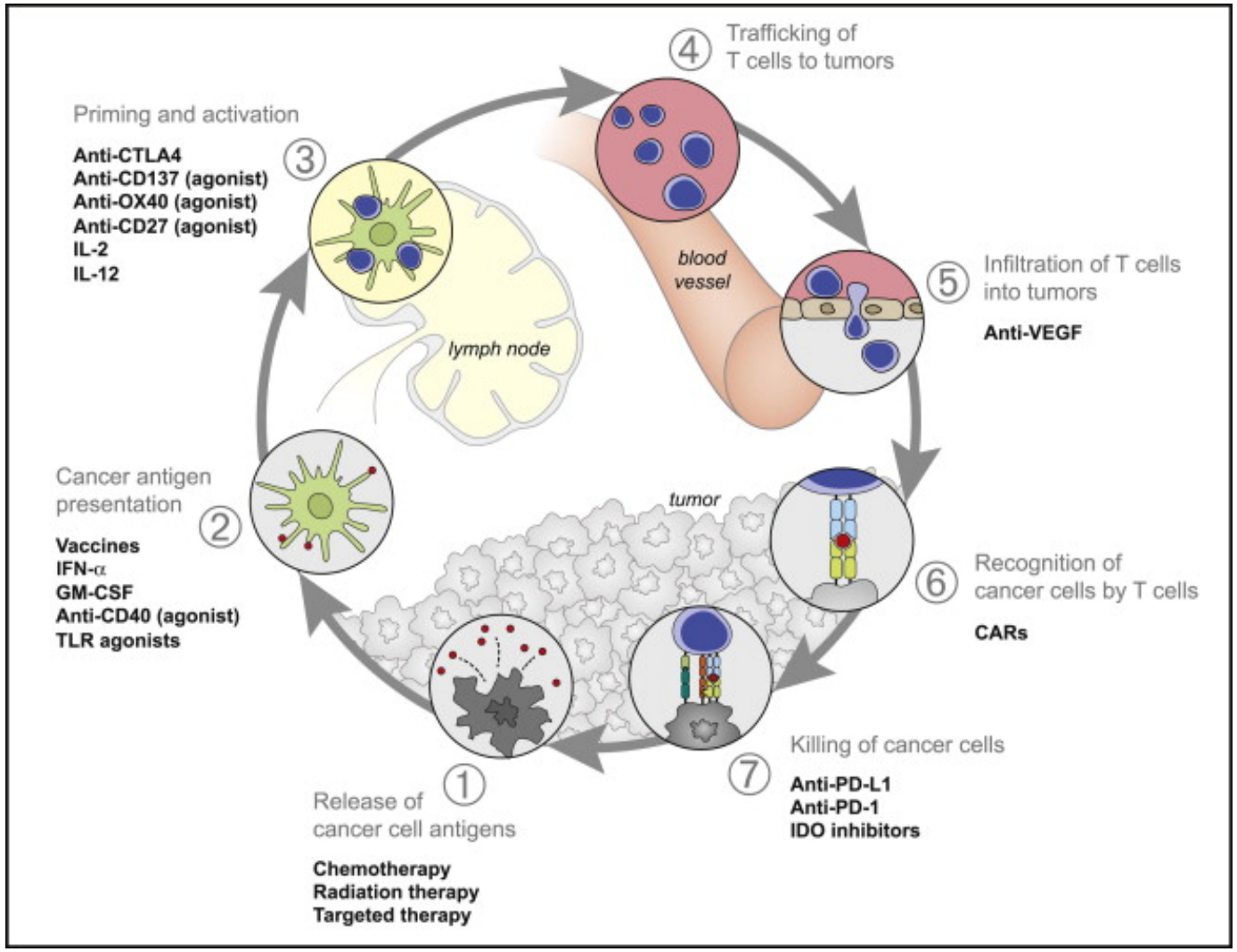


Mellman et al, Nature

Immunité anti-tumorale

- Mort cellulaire immunogène
- Relargage AG tumoraux, signaux danger
- Présentation antigénique
- Activation LT
- Infiltration tumorale par cellules effectrices
- Déplétion cellules immunosuppressives

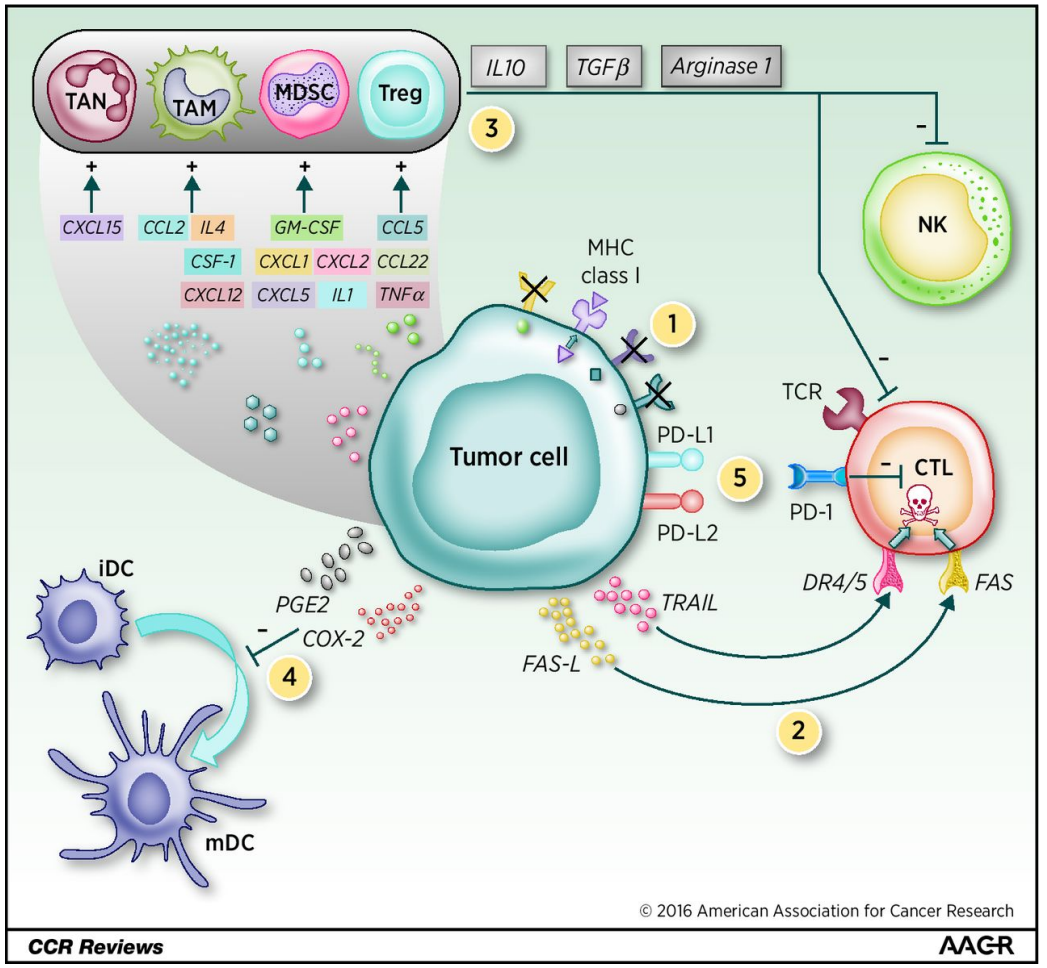
CANCER: cycle immunitaire



Evasion tumorale

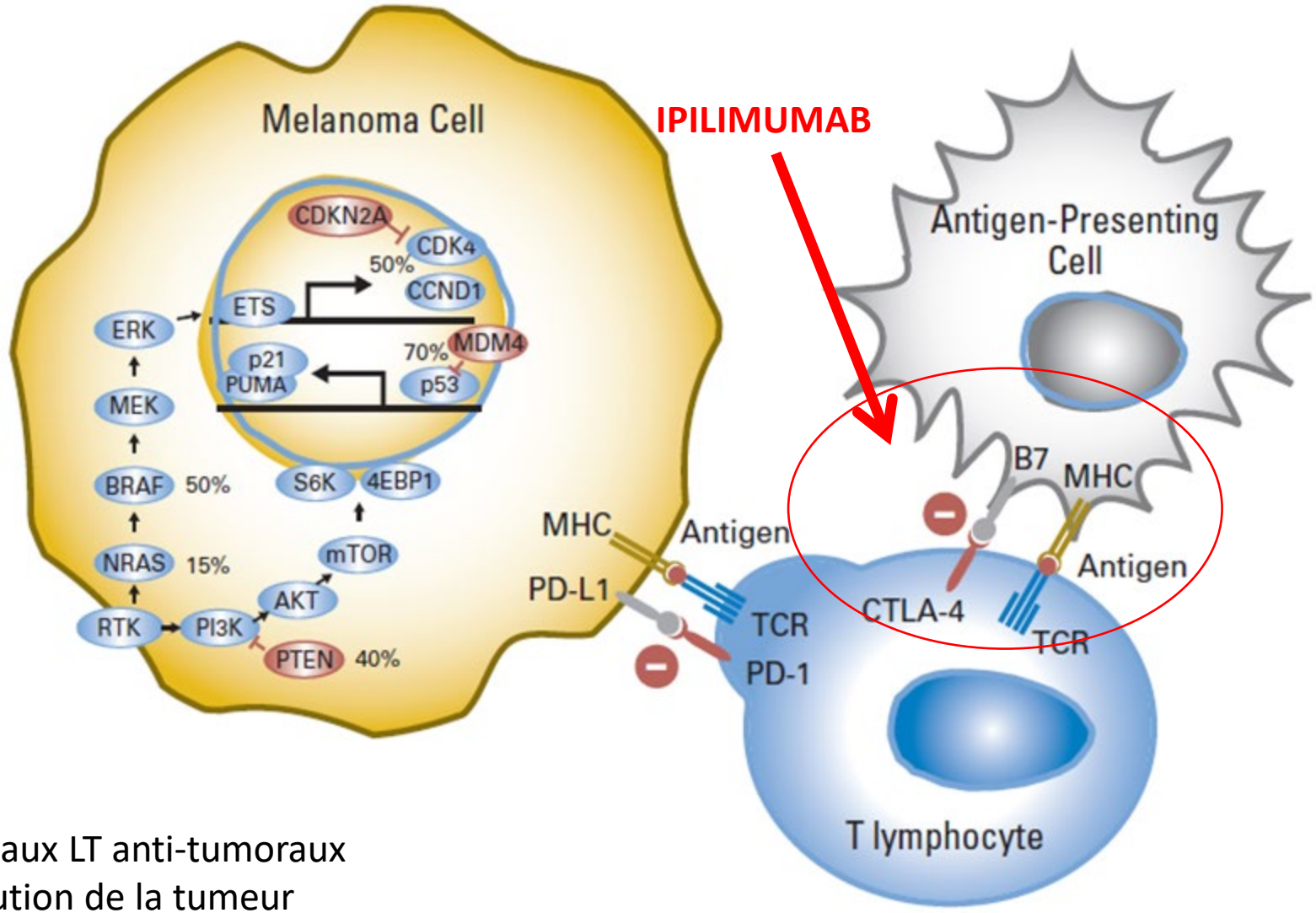
La tumeur a de nombreux mécanismes d'évasion immunologique

- Diminution d'expression du CMH I par la tumeur → moins de présentation antigénique
- Activation de mécanismes immunosuppresseurs FAS → signal de mort/apoptose cellules immunitaires
- Induction de cellules « tolérantes » : Treg, MDSC (cellules myéloïdes suppressives)…
- Relargage de molécules immunosuppressives (Il6, Il10, IDO)



Roman M. Chabanon et al. Clin Cancer Res 2016

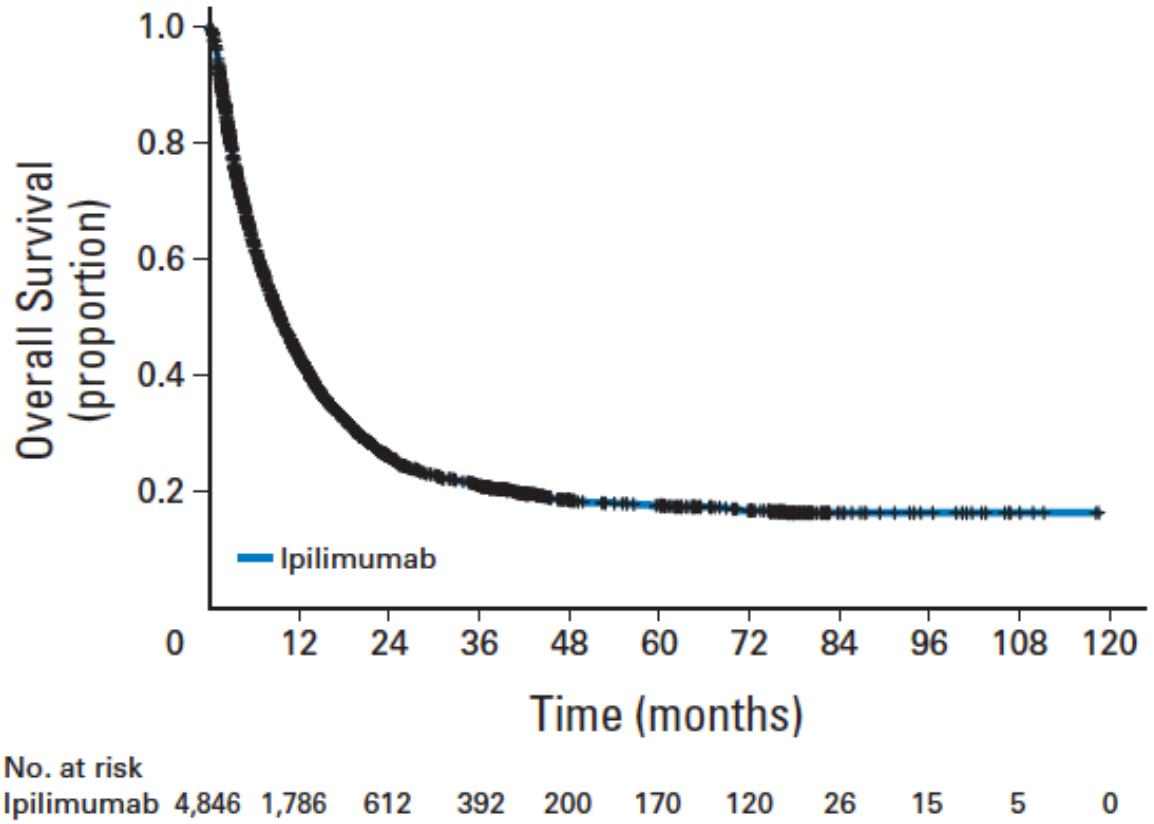
Ipilimumab (anti–CTLA-4)



Induction de nouveaux LT anti-tumoraux
Adaptation à l'évolution de la tumeur
Promotion de LT mémoires
Induction d'expression de PDL1 par la tumeur

Anti-CTLA4 (ipilimumab) et mélanome

1ère immunothérapie à avoir montré un bénéfice en terme de survie

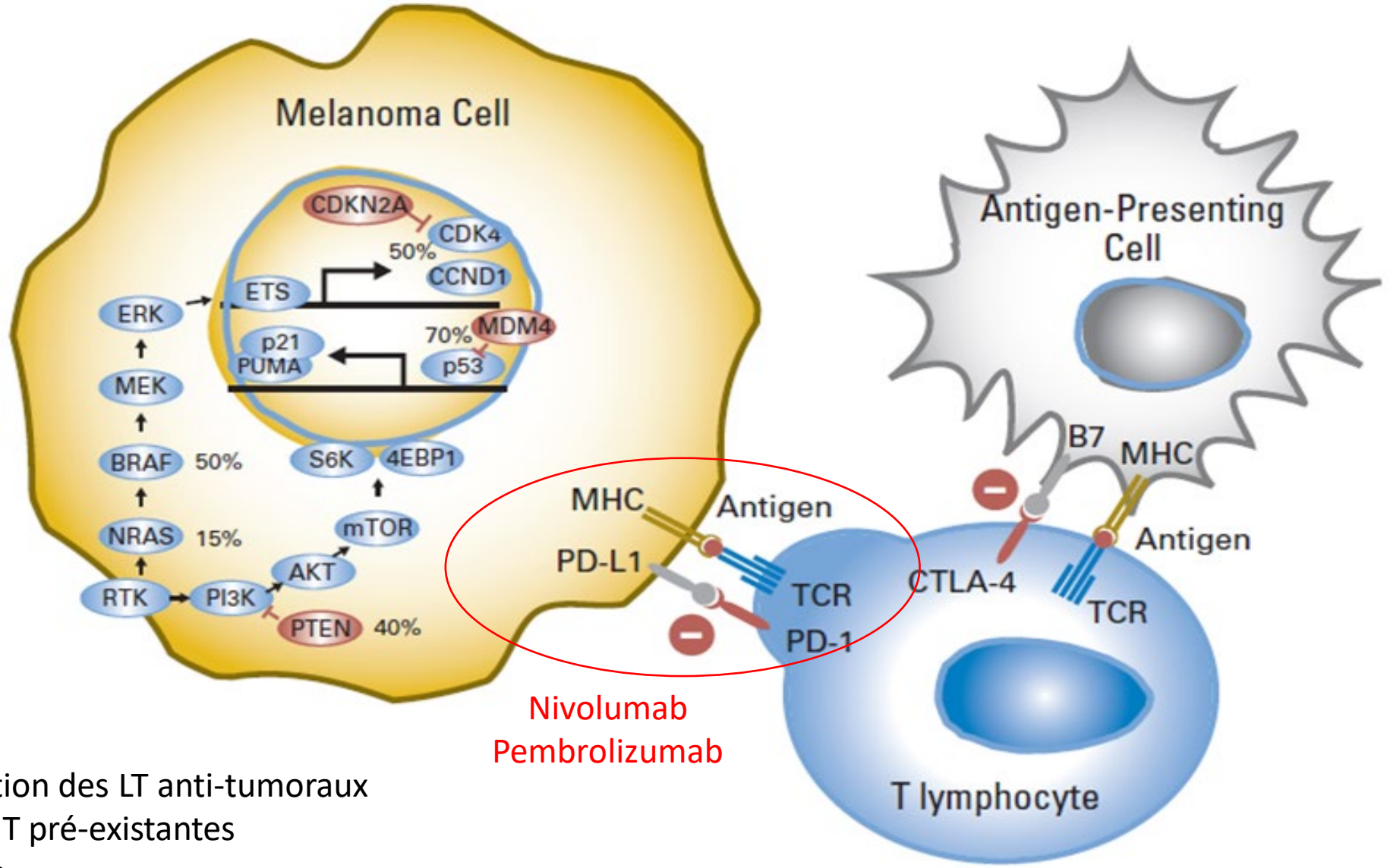


AMM = 3mk/kg toutes les 3 semaines pour 4 perfusions.
Désormais associé au nivolumab en bithérapie

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Schadendorf D et al, J Clin Oncol 2015

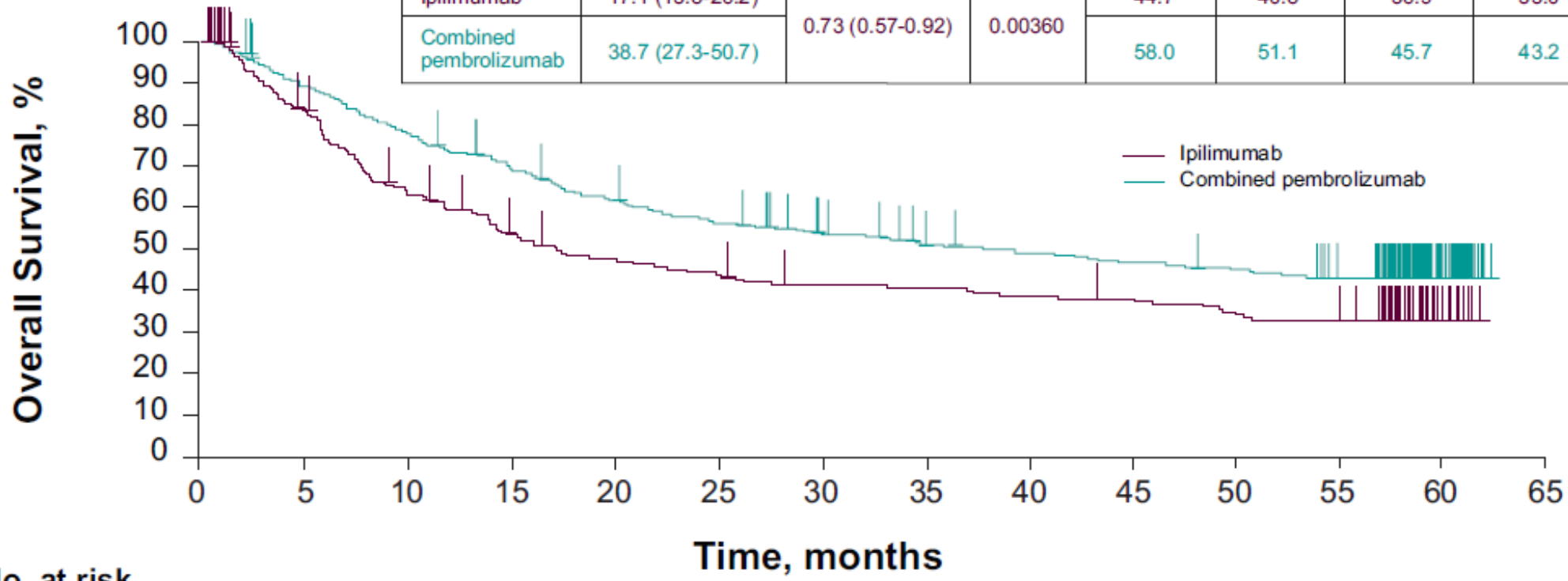
Nivolumab / pembrolizumab (anti–PD-1)



Restauration de l'activation des LT anti-tumoraux
Promotion de réponses T pré-existantes
Production de cytokines

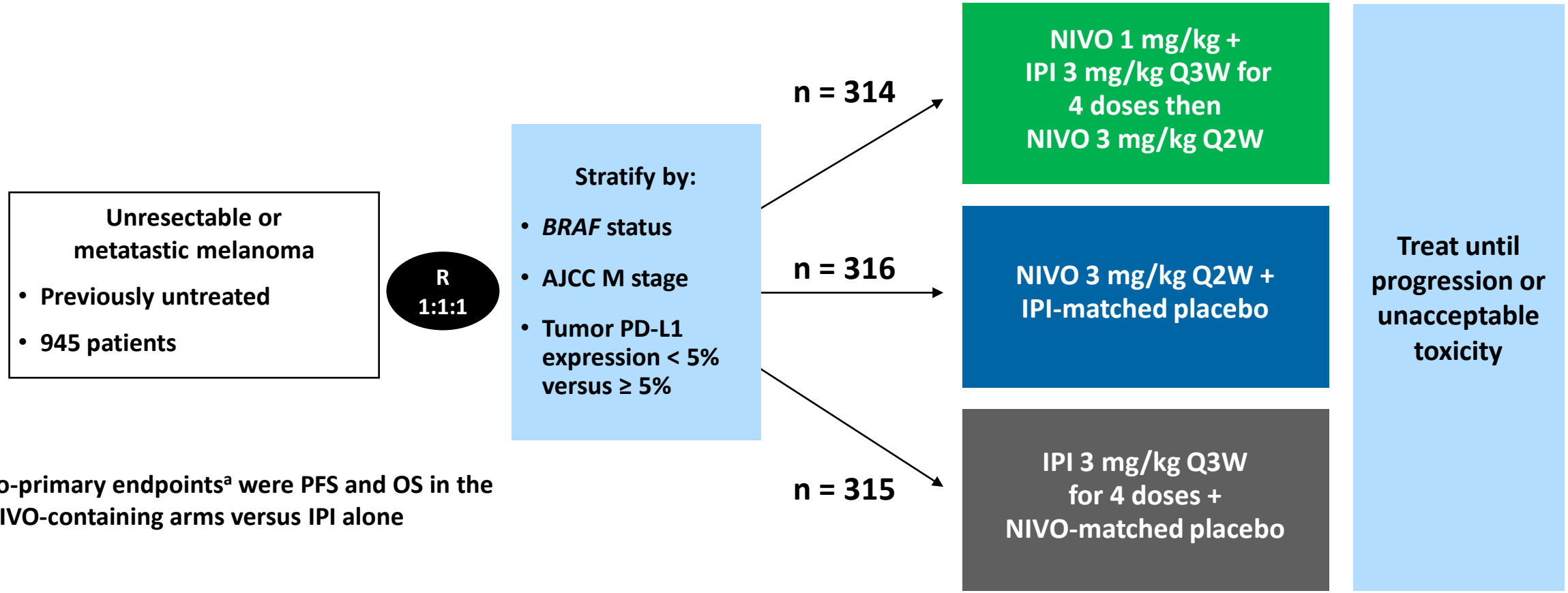
Pembrolizumab : survie globale à 5 ans chez les patients naïfs

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2



No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

CheckMate 067: Study Design



Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

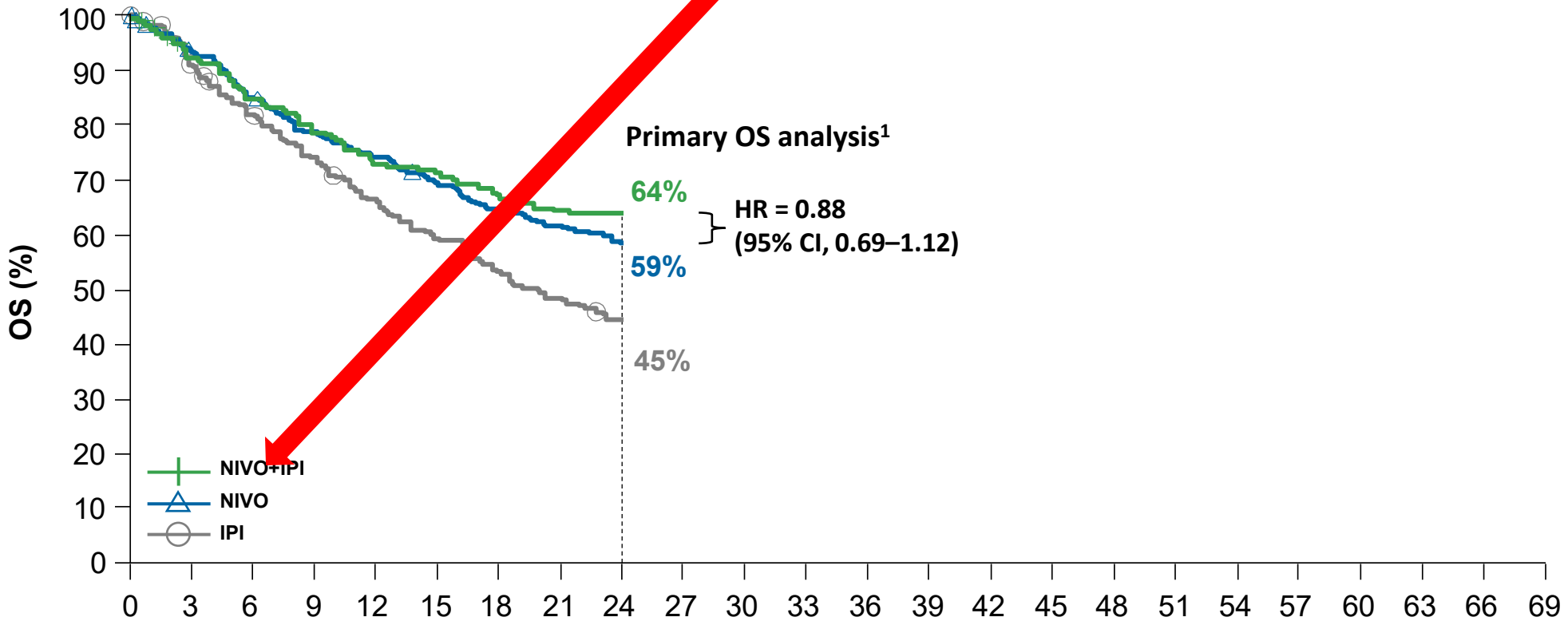
Database lock: July 2, 2019; minimum follow-up of 60 months for all patients

NCT01844505

[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Overall Survival

Taux de réponse chimiothérapie : 15%
Pas de bénéfice en OS

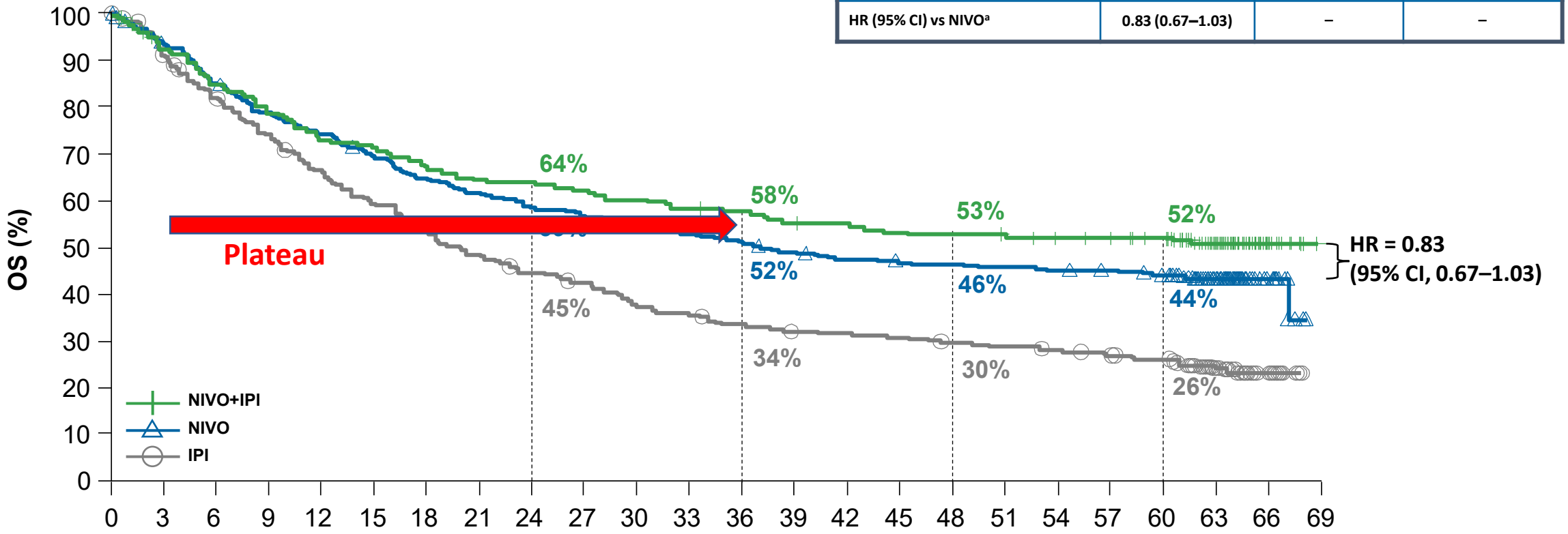


No. at risk																							
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075.

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

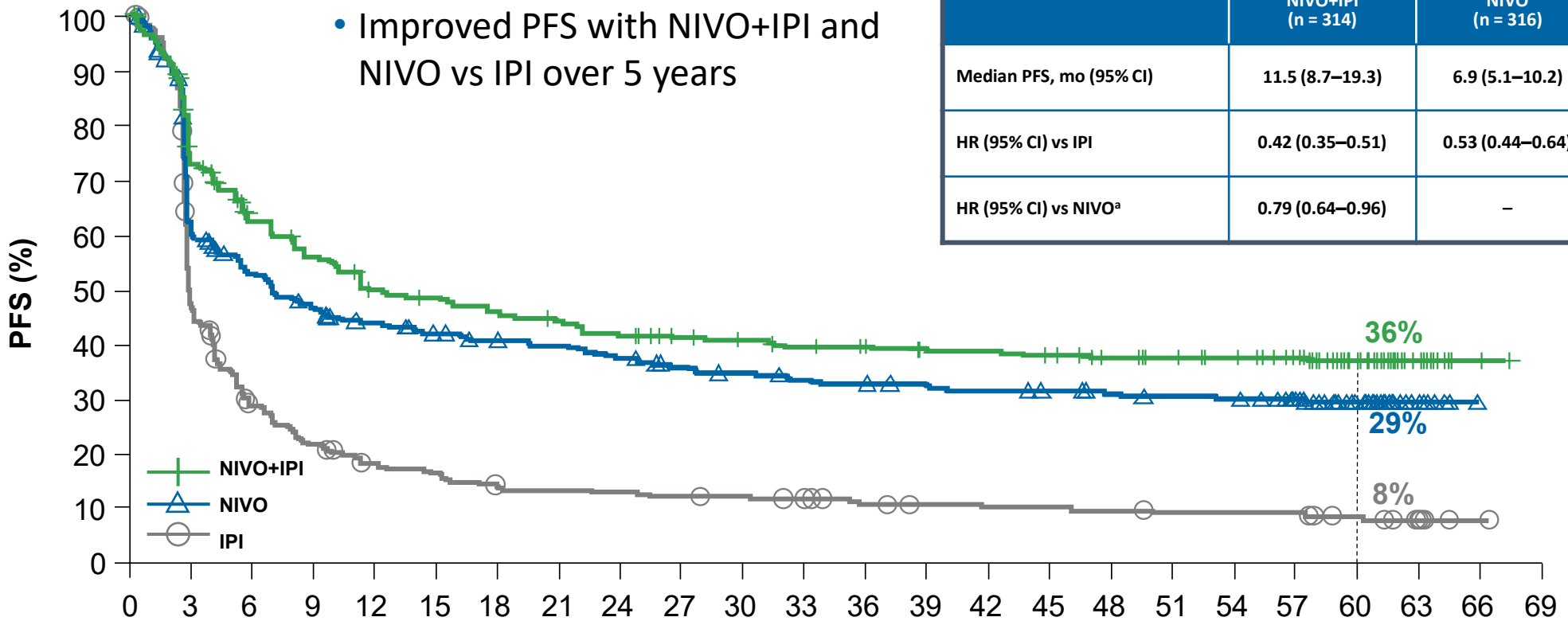


[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Progression-Free Survival

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–



No. at risk

NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

[a]Descriptive analysis.

Response to Treatment

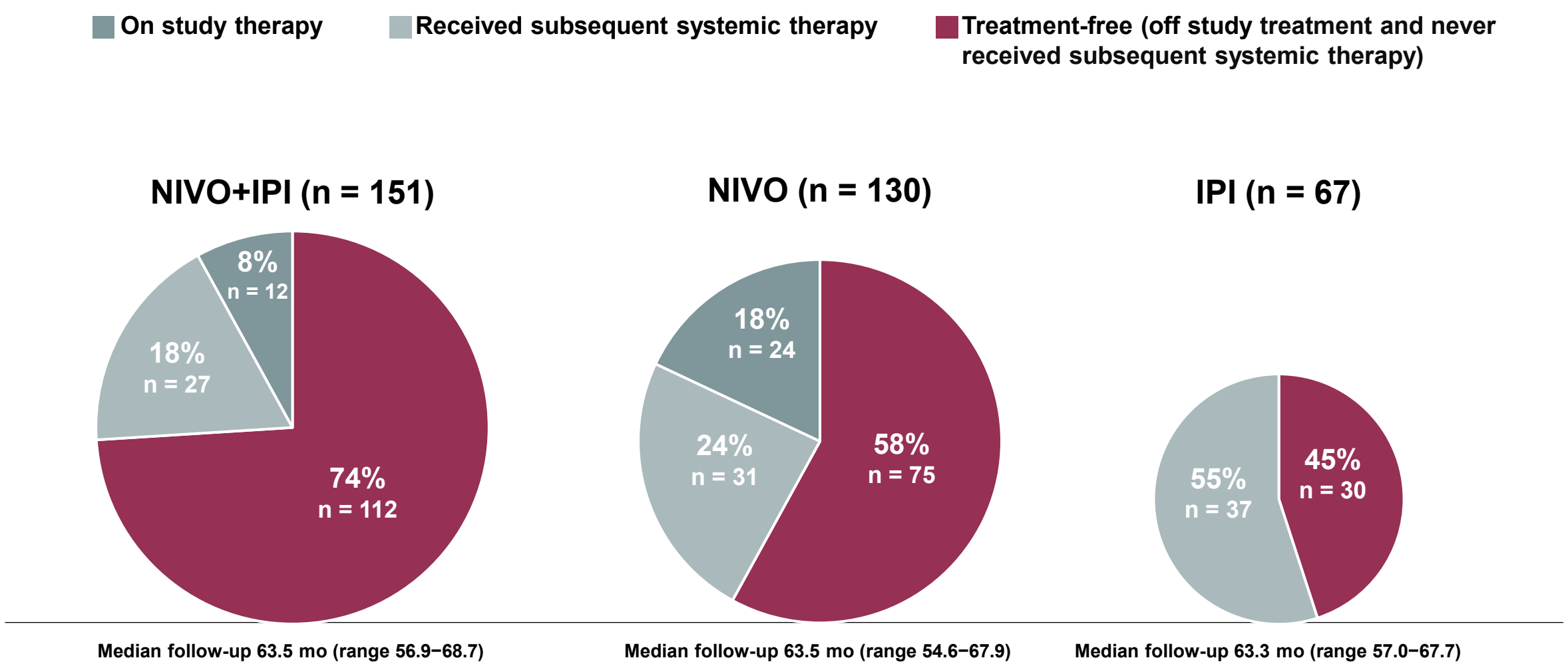
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	58 (53–64)	45 (39–50)	19 (15–24)
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	NR[a]	NR (50.4–NR)	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

- While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]
  - 19%, 21%, and 22% for NIVO+IPI
  - 16%, 18%, and 19% for NIVO
  - 5%, 5%, and 6% for IPI

[a]Although a median was reported at the previous analysis, that estimate was immature and greater than the minimum study follow-up. ITT, intention to treat.

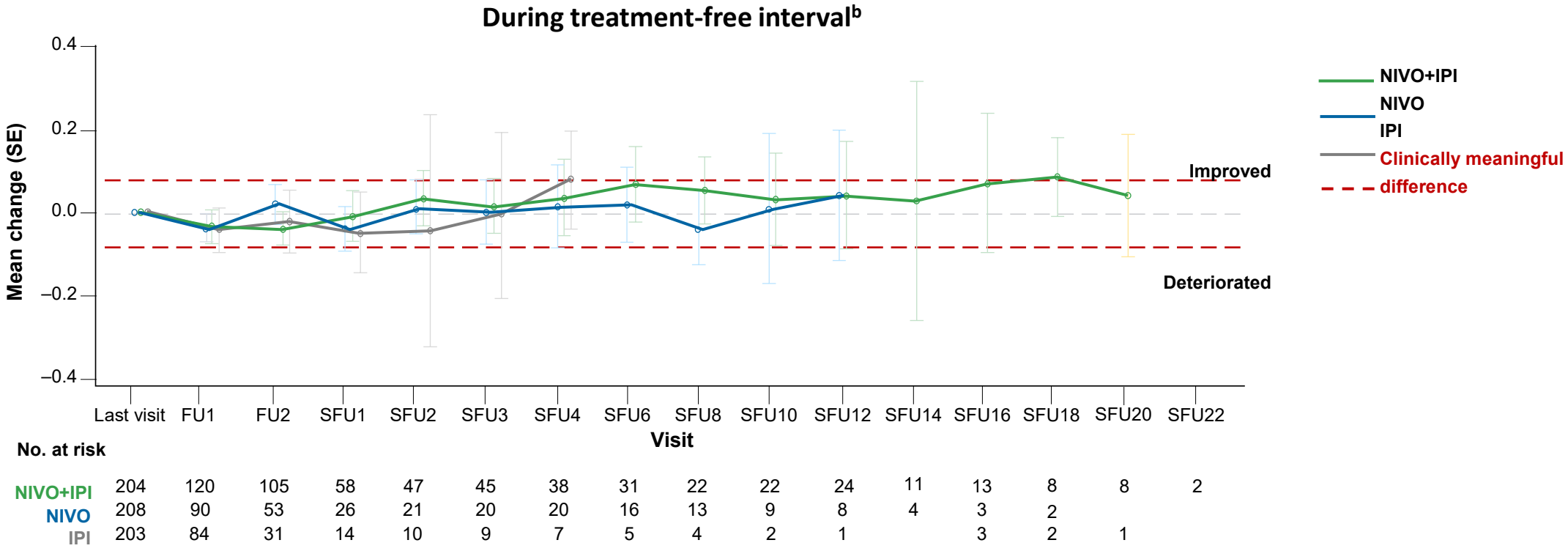
1. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Patients vivants et sans traitement à 5 ans



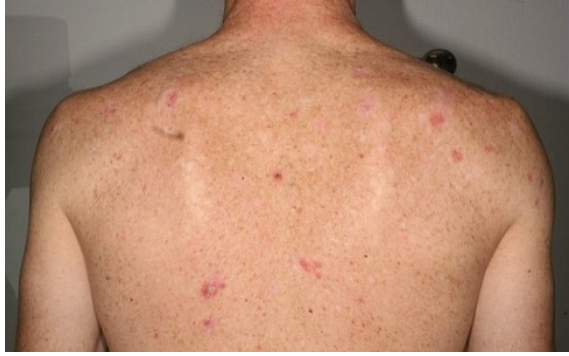
[a]Post-hoc analysis.

Pas d'alteration de la qualité de vie pendant les 5 années de suivi chez les patients traités par nivolumab



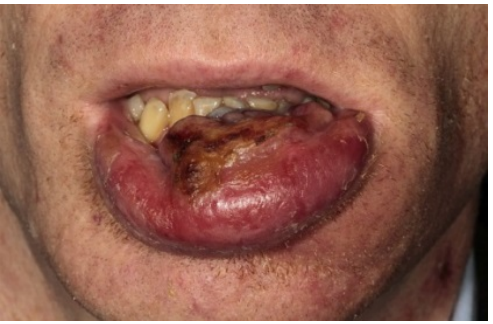
[a]Quality of life assessed by EQ-5D-3L Utility Index; [b]At timepoints with > 5 patients. Pickard AS, et al. *Health Qual Life Outcomes* 2007:5;70.

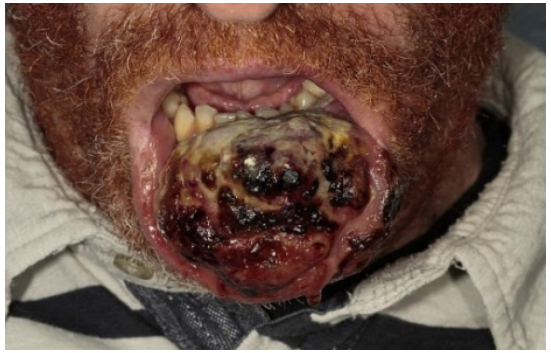
Mr D, 38 ans
Phototype I
ATCD multiples carcinomes cutanés
Notion de mélanome chez la mère

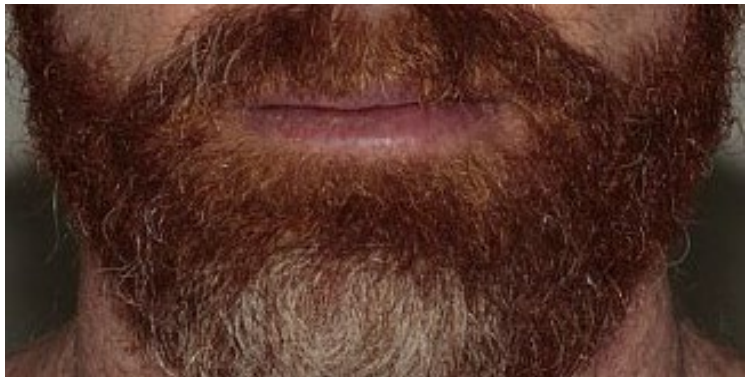


Mélanome muqueux de la lèvre inférieure avec infiltration osseuse au contact du périoste

23/11/2016 15/12/16 24/03/17

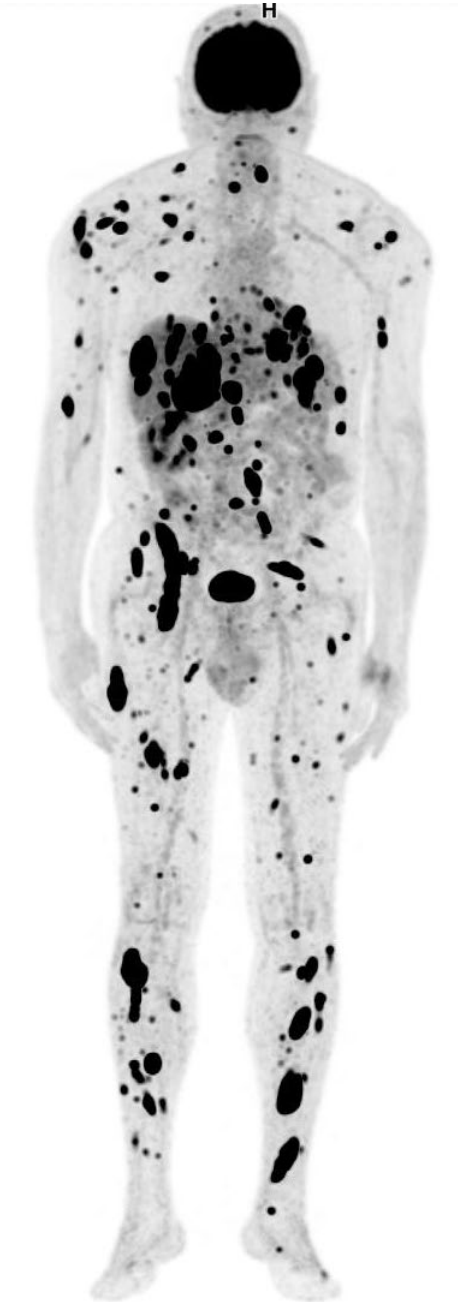




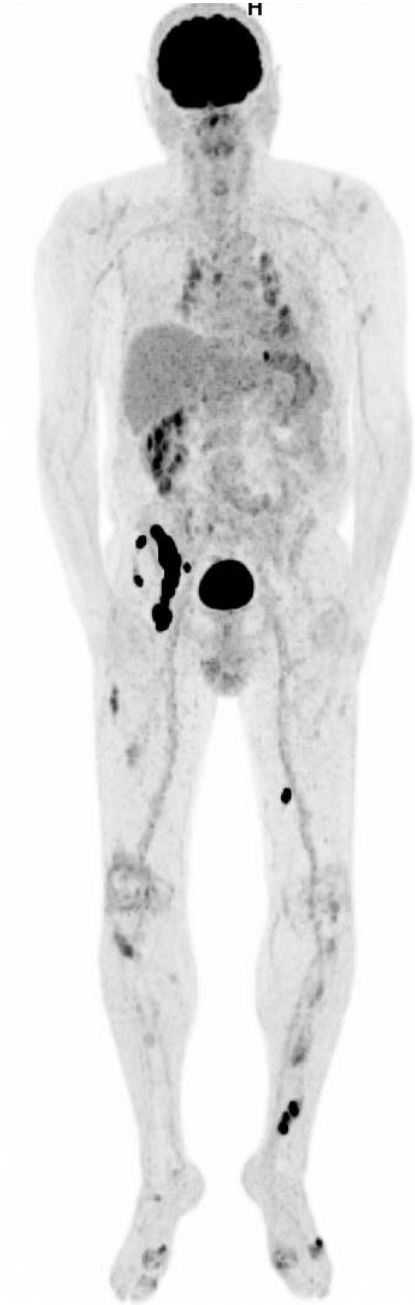


BRAFsauvage

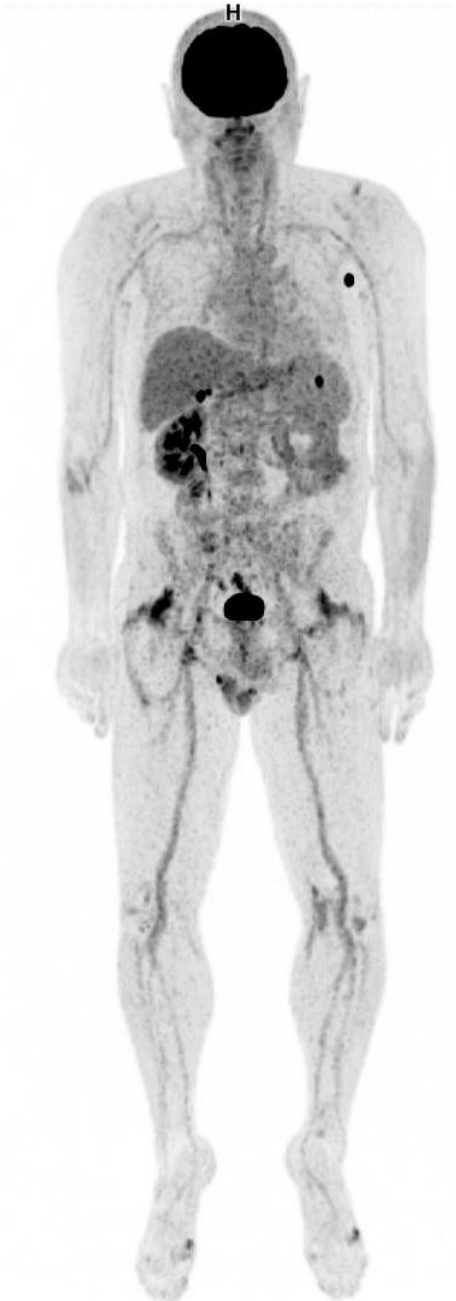
Inclusion dans le protole BMS 401
ipilimumab+ nivolumab C1J1 le 16/12/2016



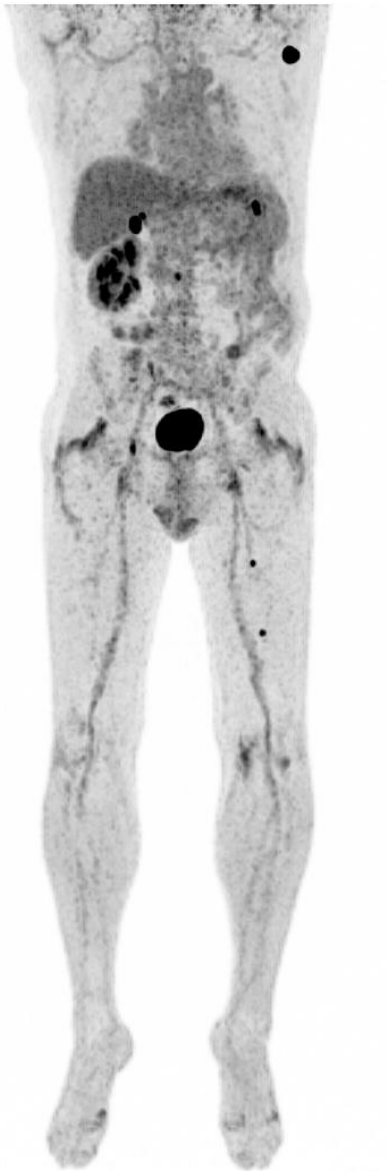
Avant le traitement



A 3 mois de traitement



A 8 mois de traitement



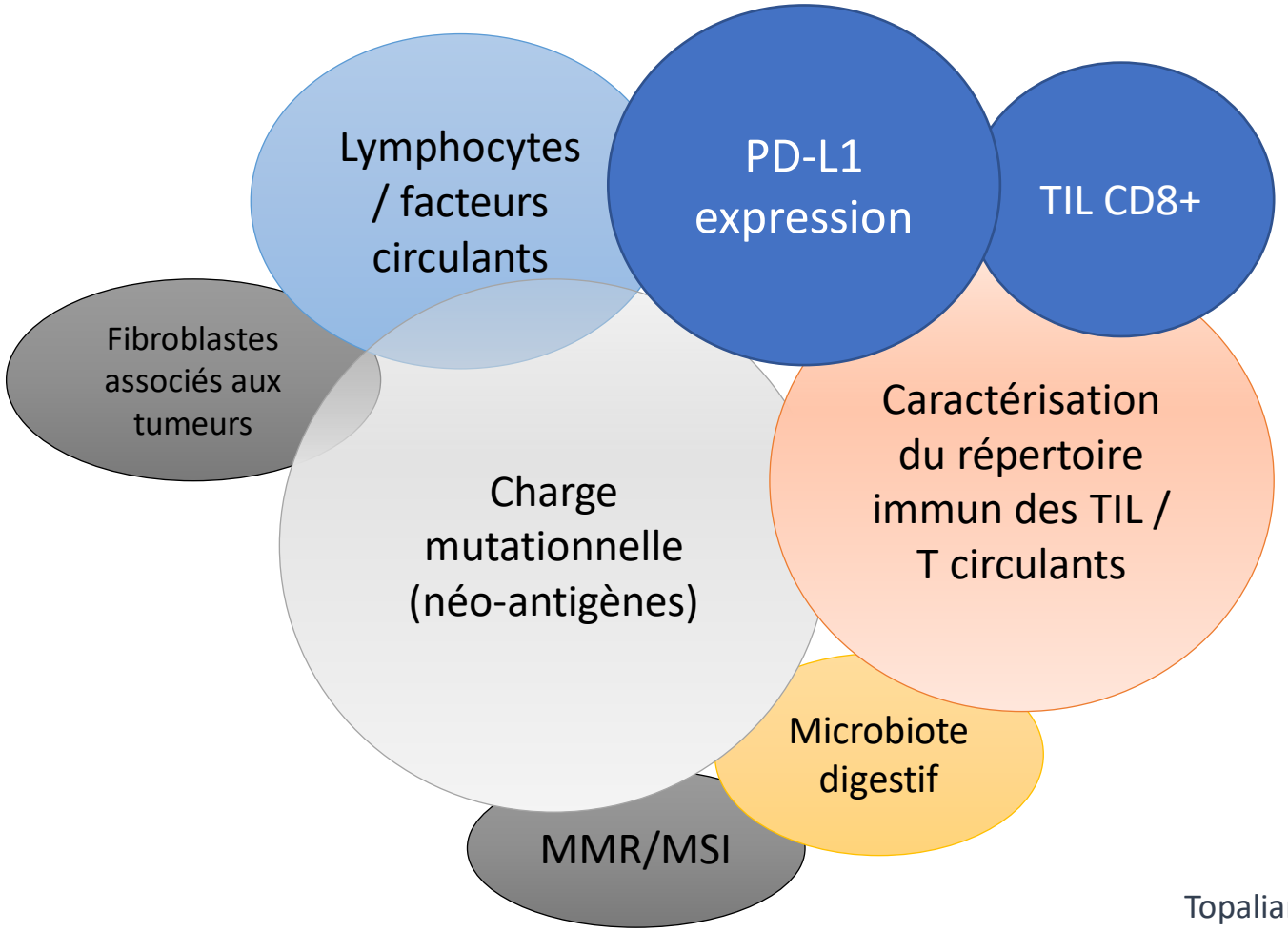
A 11 mois

- Des patients métastatiques en vie à plus de 5 ans
- Parfois sans traitement
- Une qualité de vie préservée
- Des réponses sur les métastases cérébrales

Mais…

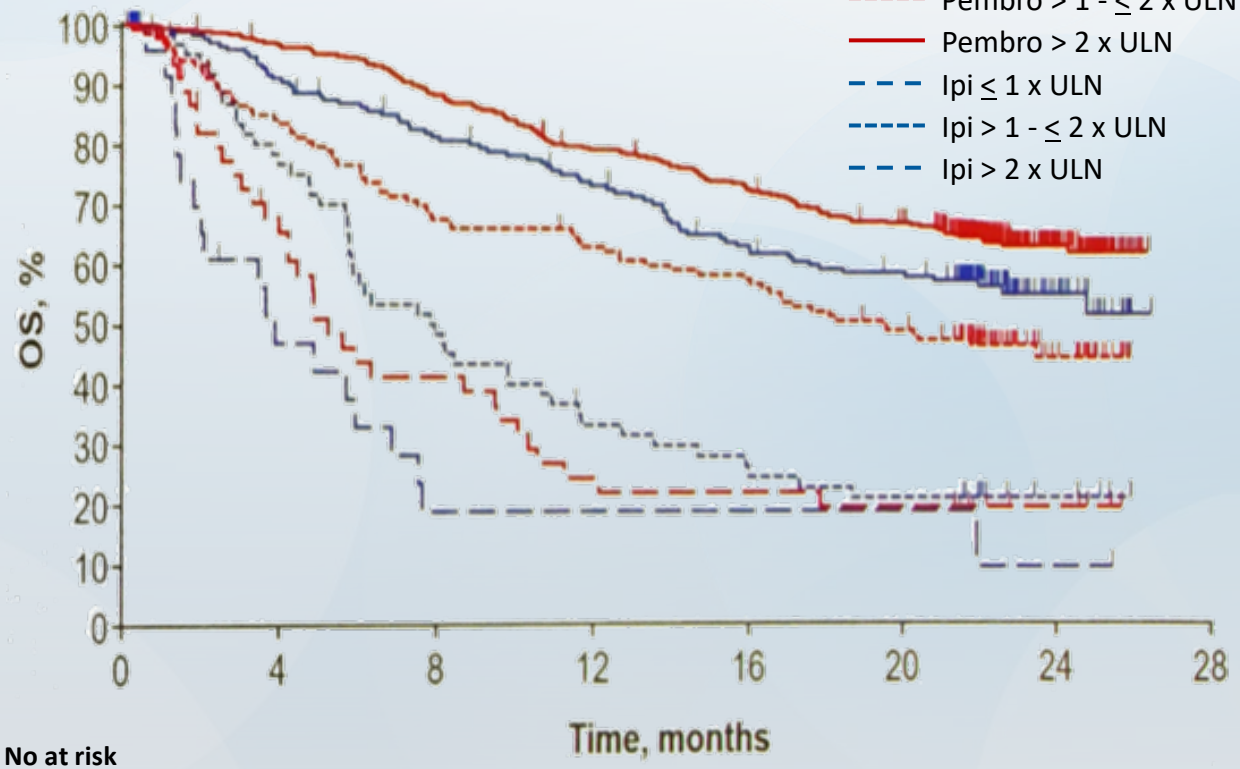
- Des survie sans progression parfois limitées
- Des réponses parfois dissociées
- Des effets indésirables parfois irréversibles

Biomarqueurs prédictifs des immunothérapies



Topalian et al, Nat Rev Cancer 2016
Gros et al , Nat Med 2016
Friedman et al, Curr Oncol Rep 2016

KEYNOTE 006 : OVERALL SURVIVAL ACCORDING LDH LEVEL



	Median (95% CI), mo
Pembro < 1 x ULN	NR (NR-NR)
Pembro > 1 - ≤ 2 x ULN	19,5 (14,7-NR)
Pembro > 2 x ULN	5,3 (4,0-9,5)
Ipi ≤ 1 x ULN	NR (20,8-NR)
Ipi > 1 - ≤ 2 x ULN	8,0 (5,8-10,9)
Ipi > 2 x ULN	3,9 (1,8-6,9)

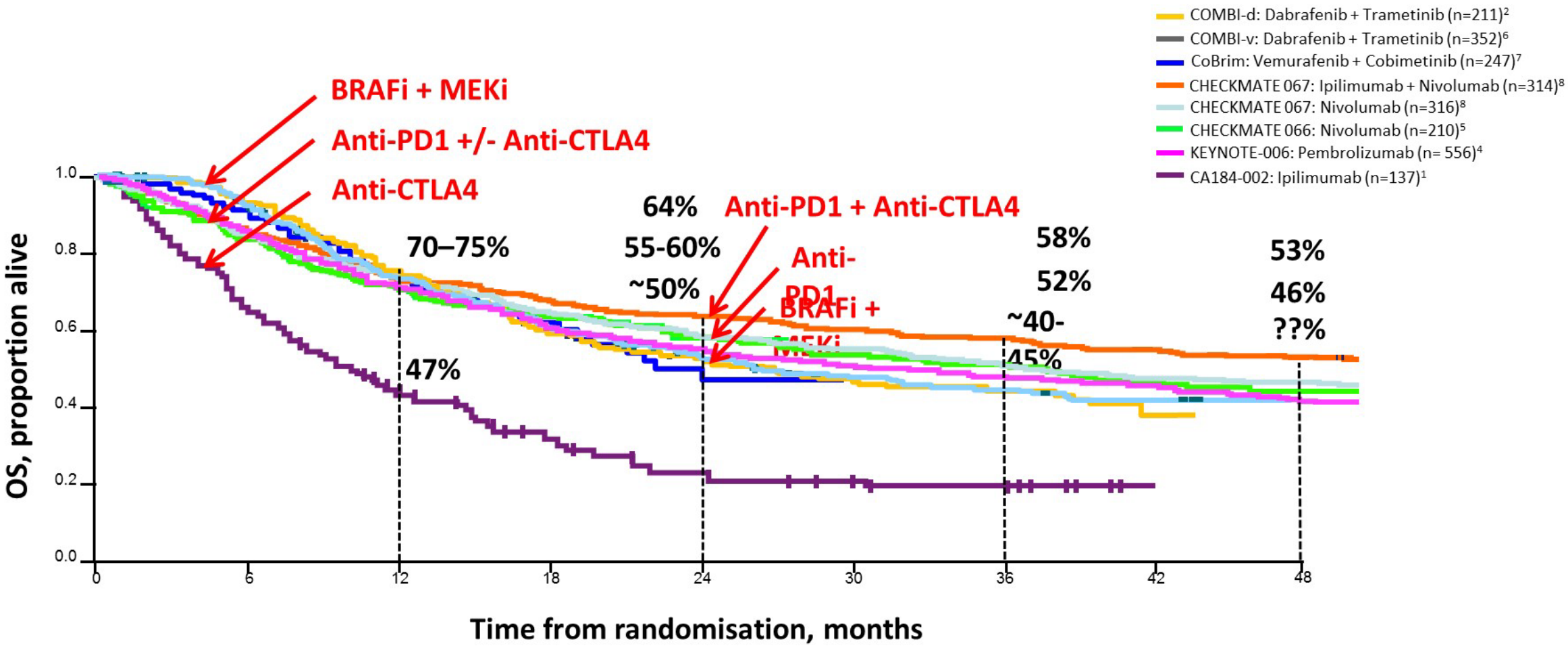
No at risk

369	355	324	288	262	237	64	0
134	111	89	82	75	63	18	0
45	28	17	10	9	8	4	0
178	152	133	118	100	91	23	0
66	46	29	19	15	12	4	0
25	10	4	4	4	4	1	0

Data cut-off date: Dec 3, 2015

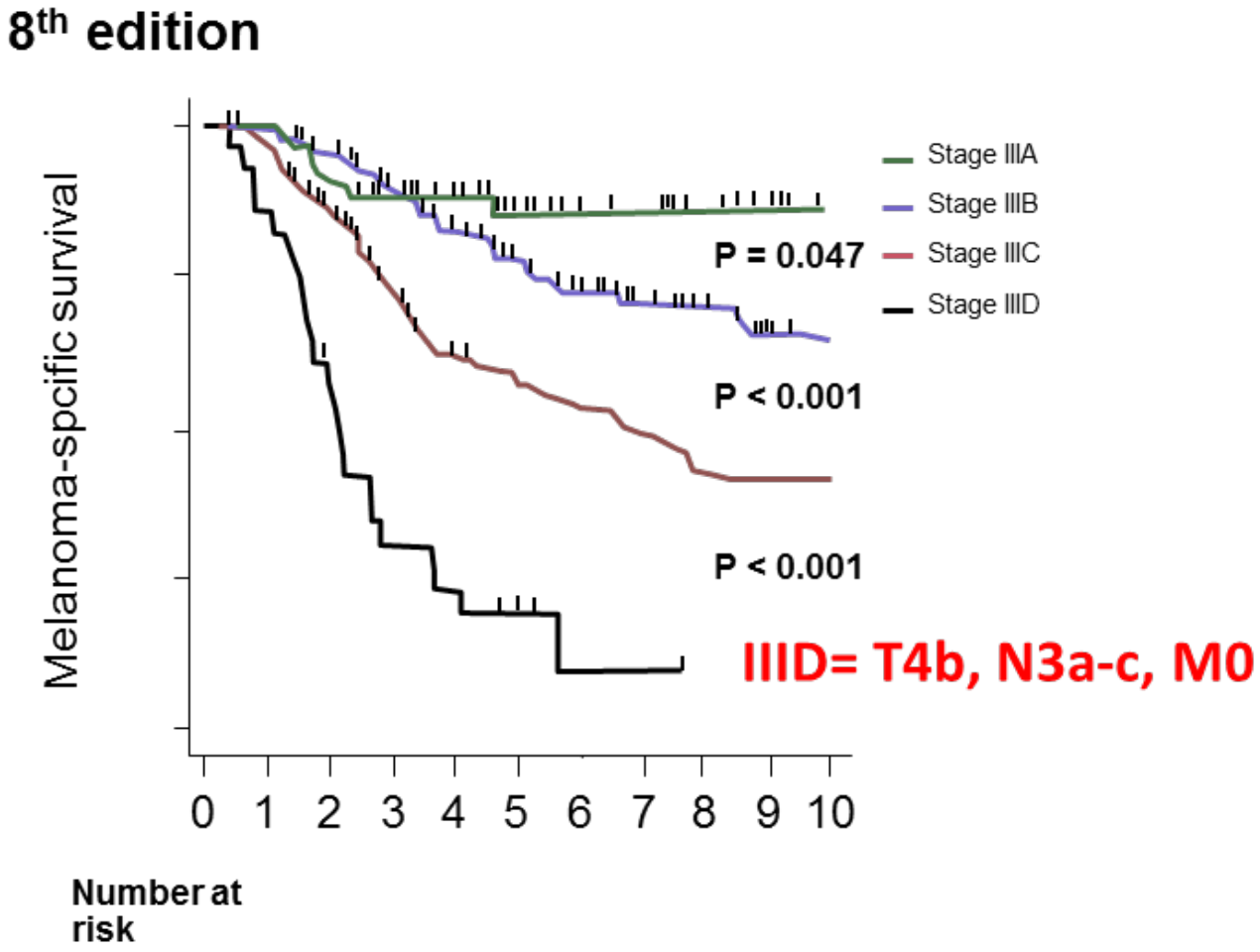
Long et al. ECCO 2017

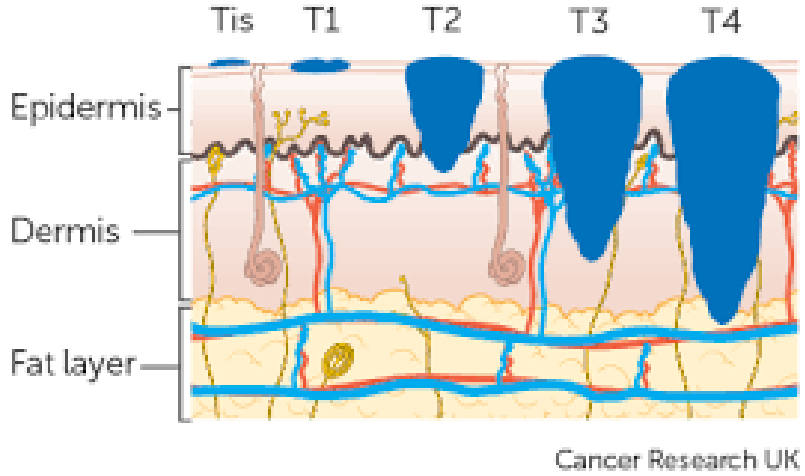
Background: Overall Survival in Melanoma



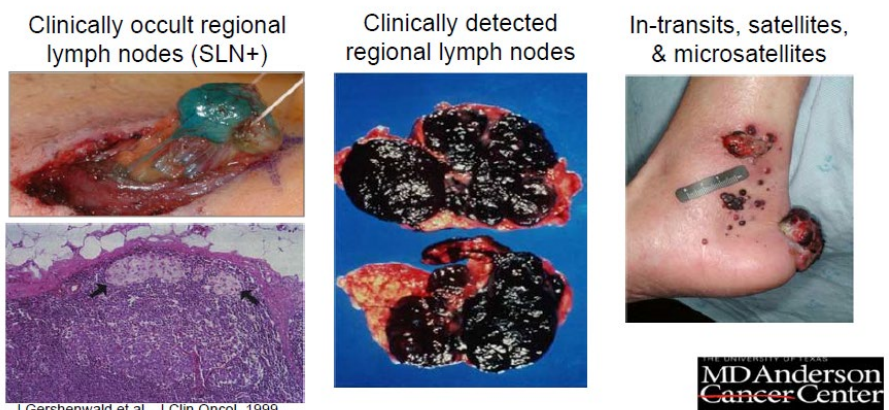
Slide courtesy: Georgina V Long, Melanoma Institute Australia

Stade III : mauvais pronostique

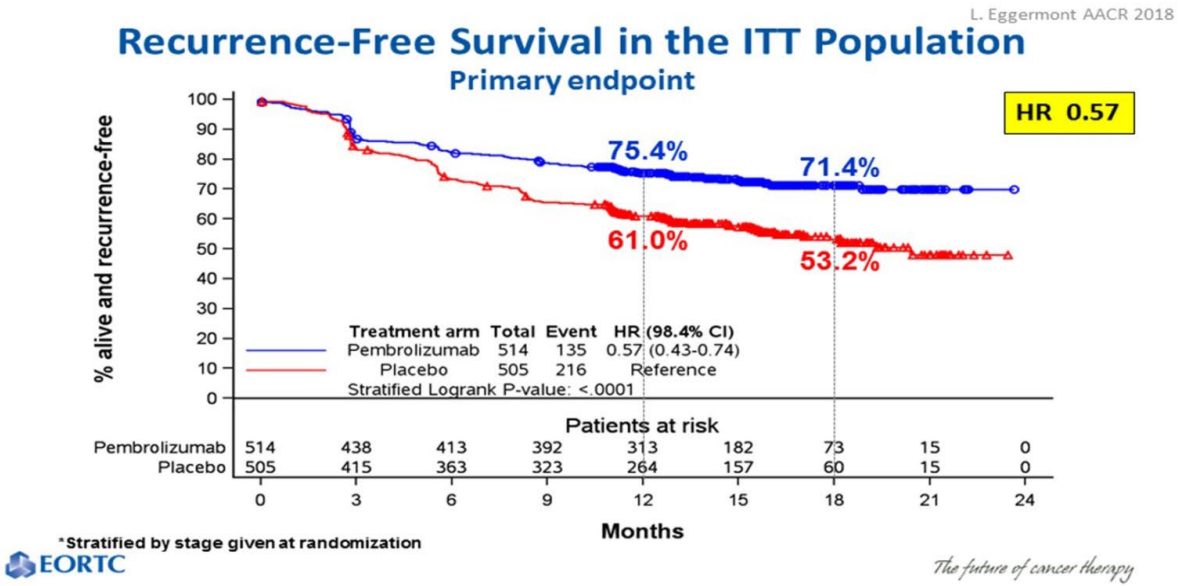


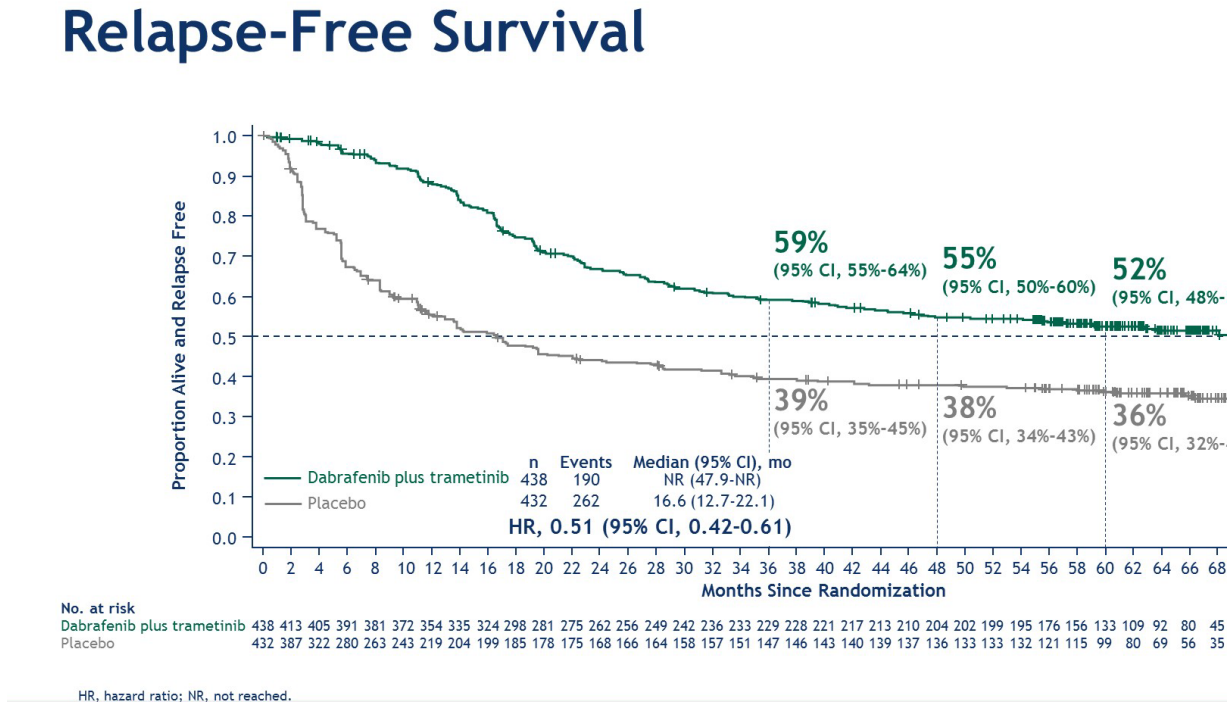


AJCC N Category Criteria

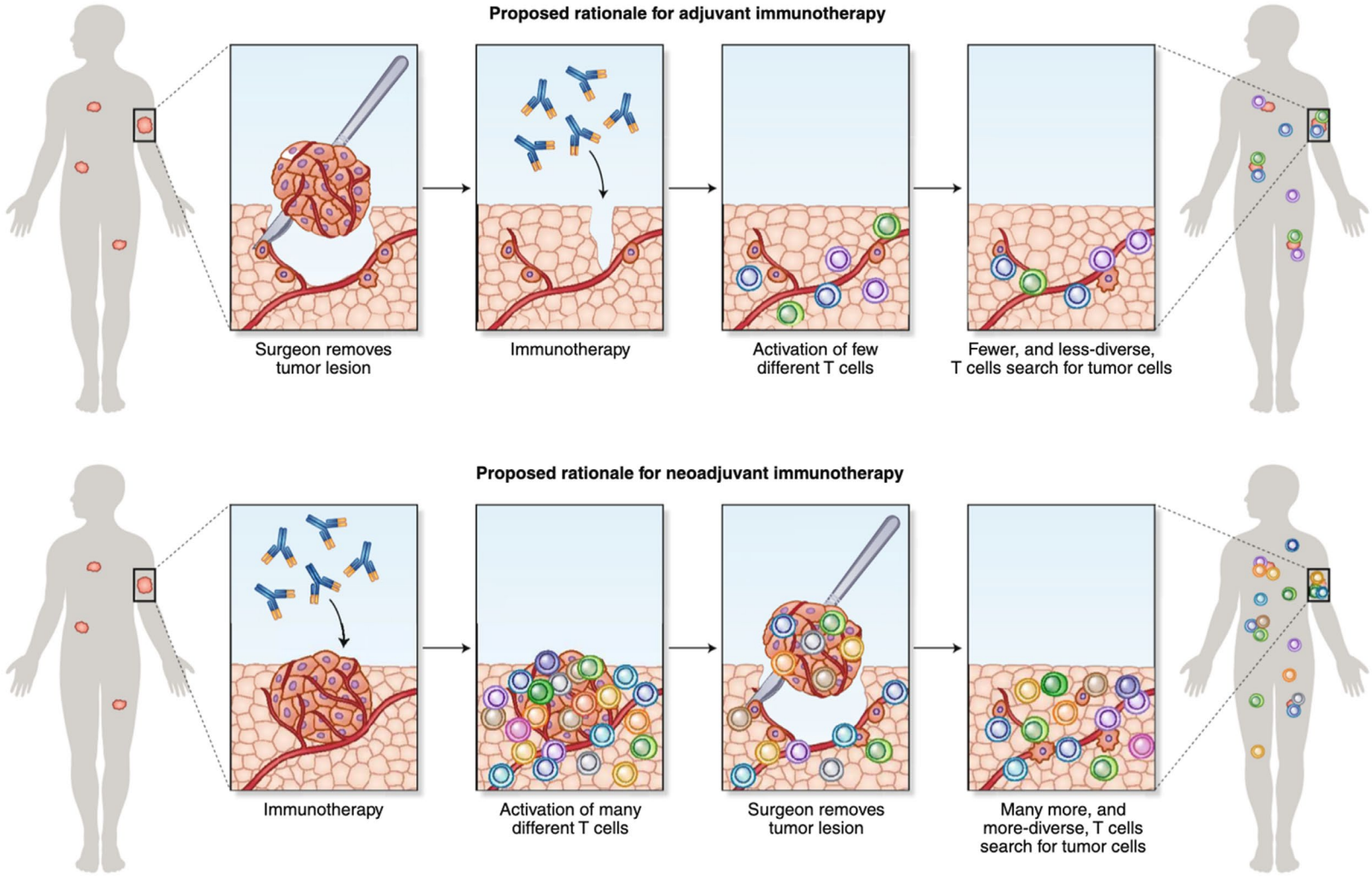


Traitements adjuvants du mélanome : traiter la maladie micrométastatique





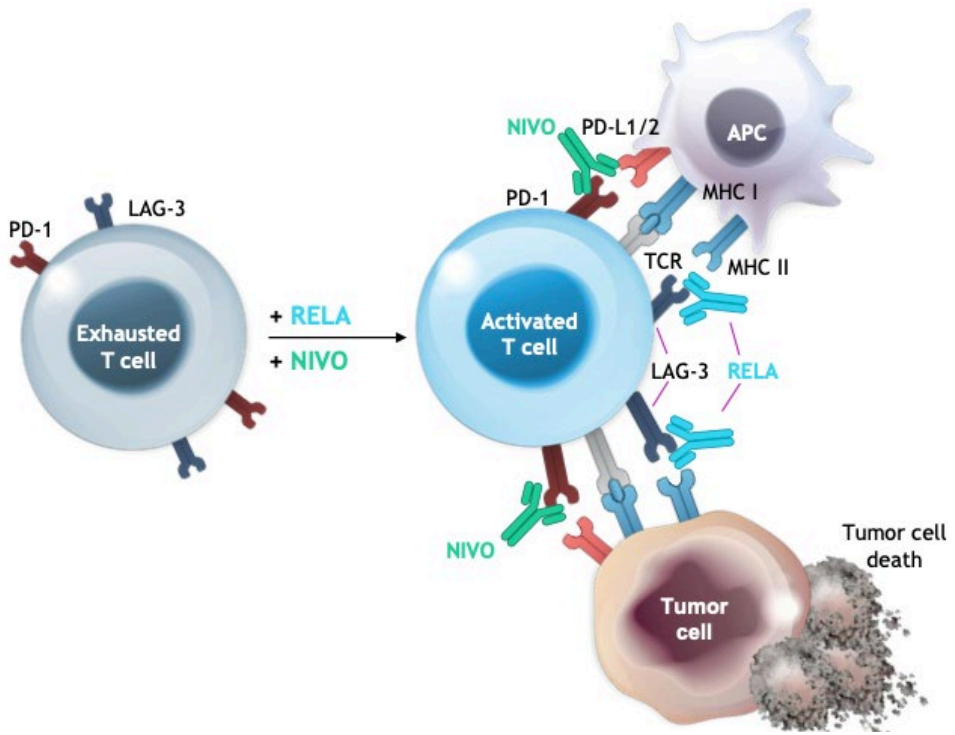
Neoadjuvant superior to adjuvant immunotherapy



Versluis, Long, and Blank
Nat Med 2020

2021 ASCO ANNUAL MEETING

Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)



Study design

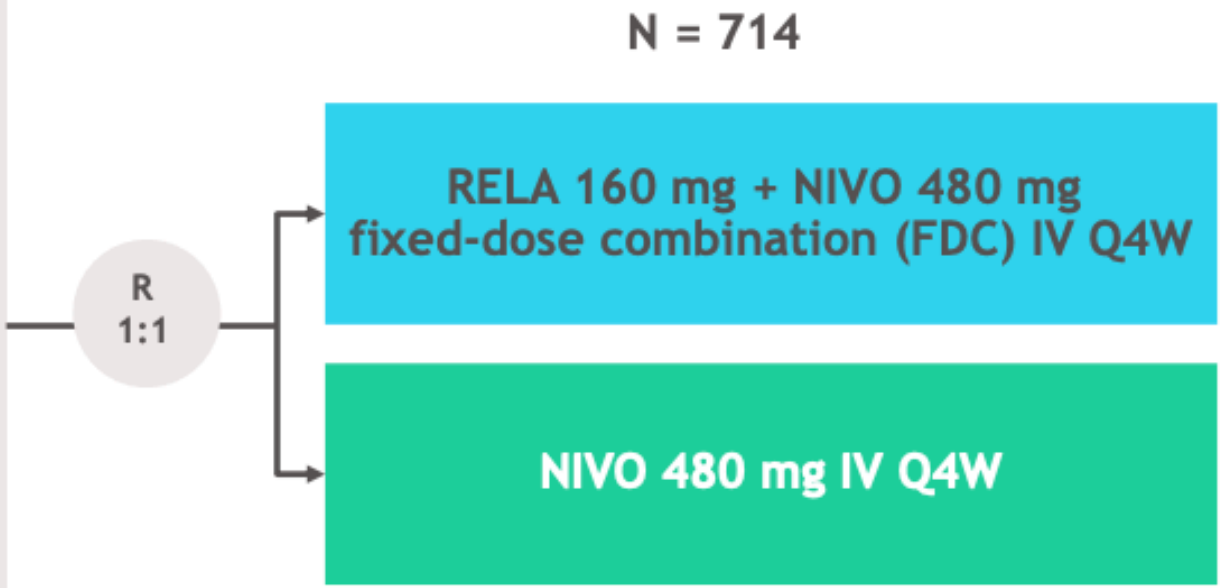
- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria

- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

Stratification factors

- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



Primary endpoint

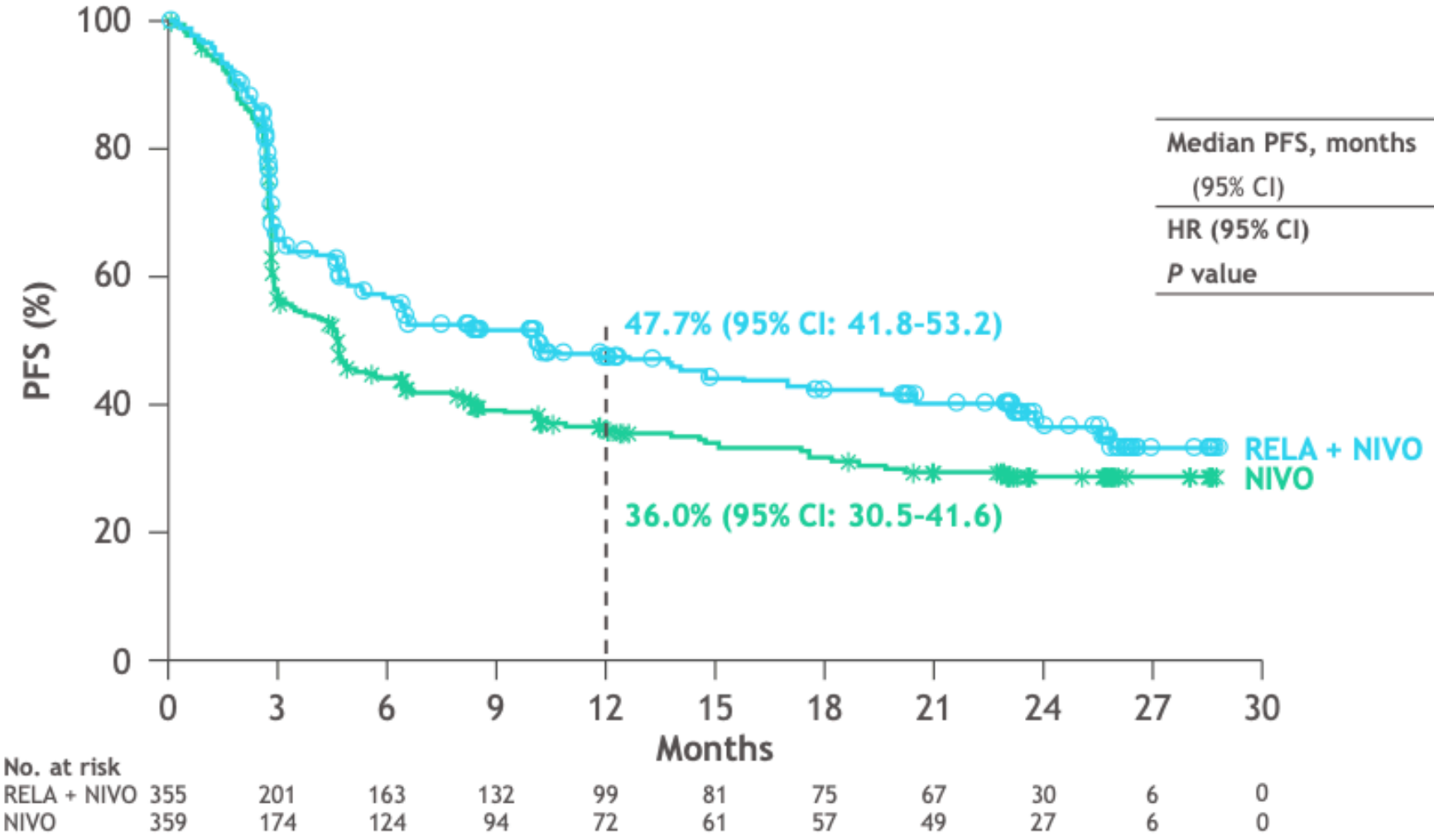
- PFS by BICR[d]

Secondary endpoints

- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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