Inhibiteurs de PD1/PDL1 Mécanismes d'action et principales indications

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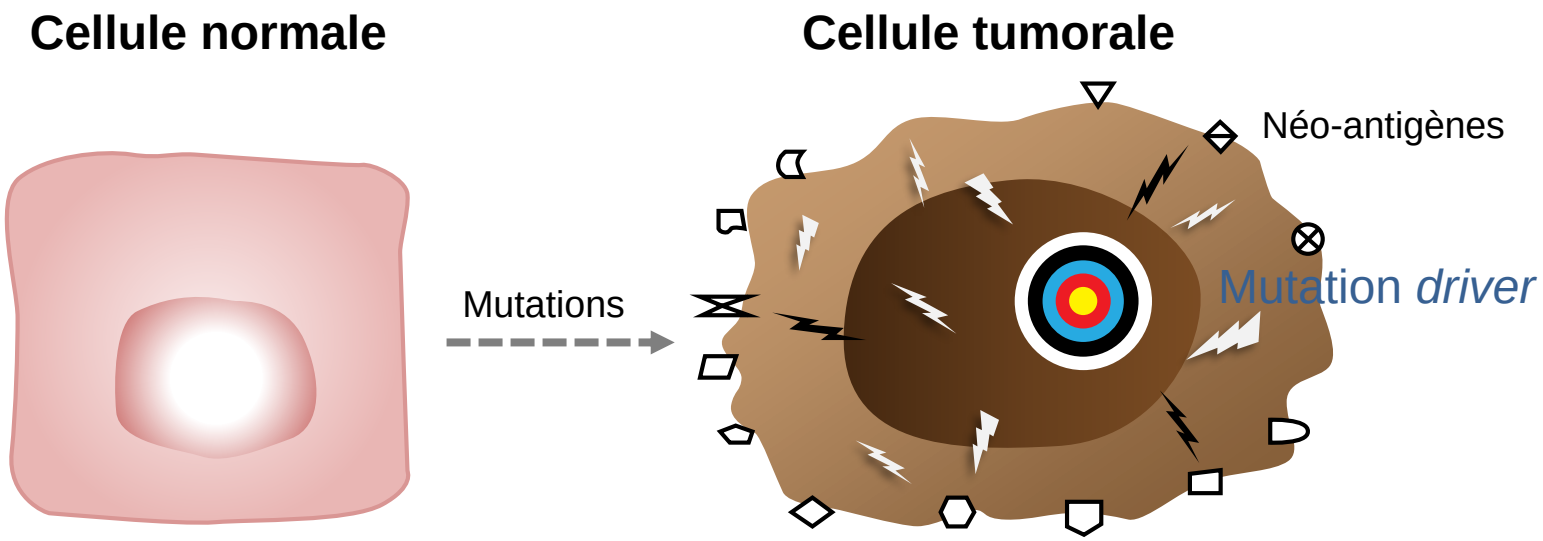
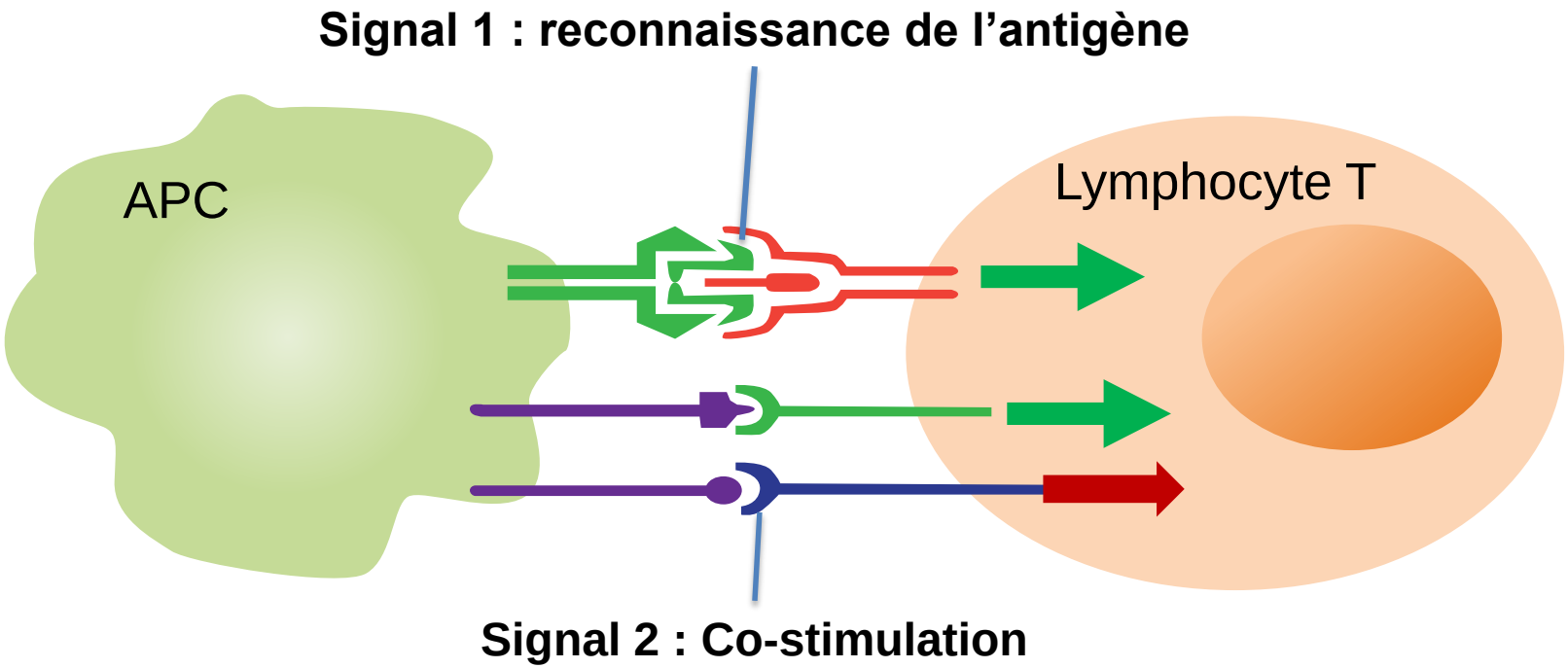
Deux processus d'évolution dans les cancers

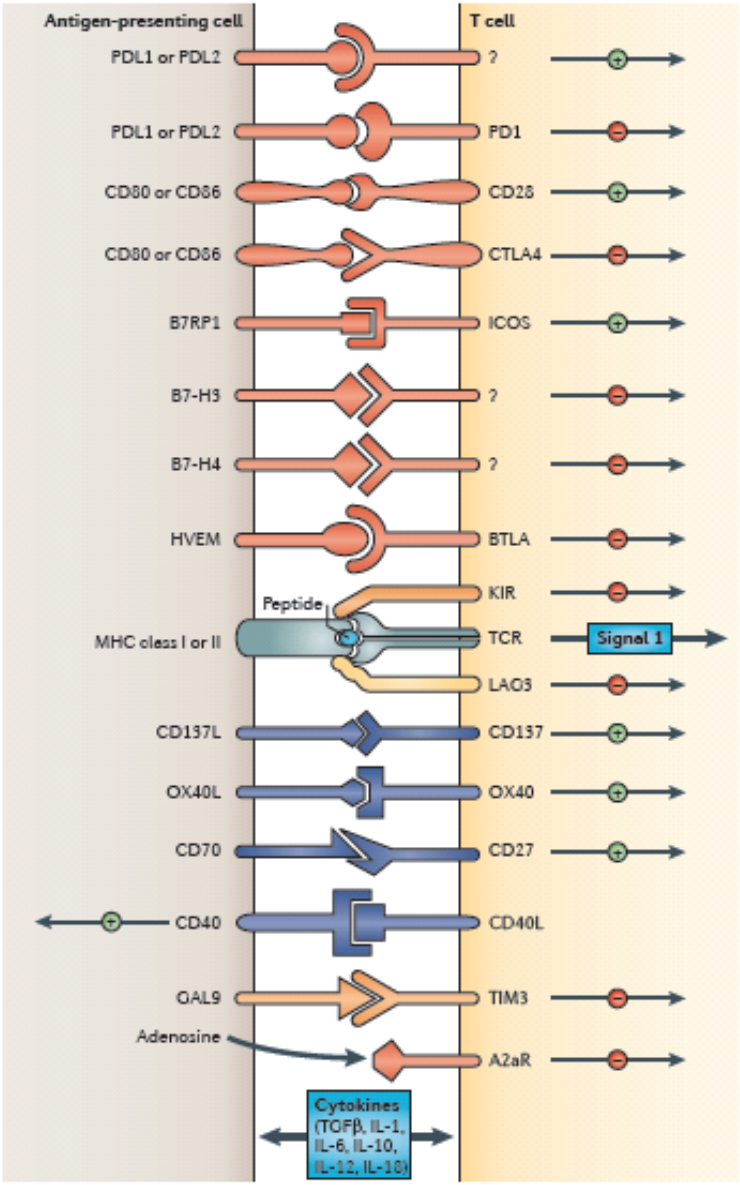
- Mutations de l'ADN
  - rares mutations *driver*
  - nombreuses mutations *passenger*
- Échappement au frein immunitaire : PD-L1, IDO, TGF-b, IL-10, perte de MHC, autres



Activation des lymphocytes T



ASCO® GU 2016 - D'après Freeman G et al., Renal Cancer Keynote Lecture

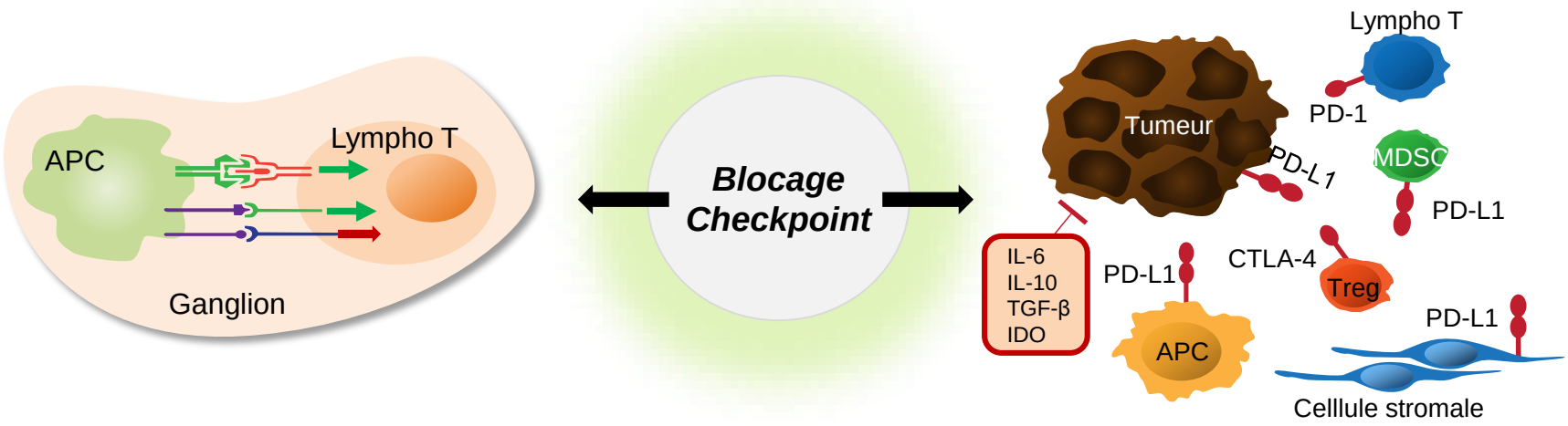


Pardoll, Nat Rev Cancer 2012

Où se situent les *checkpoints* immunologiques?

CTLA-4 dans les ganglions

PD-1 dans la tumeur



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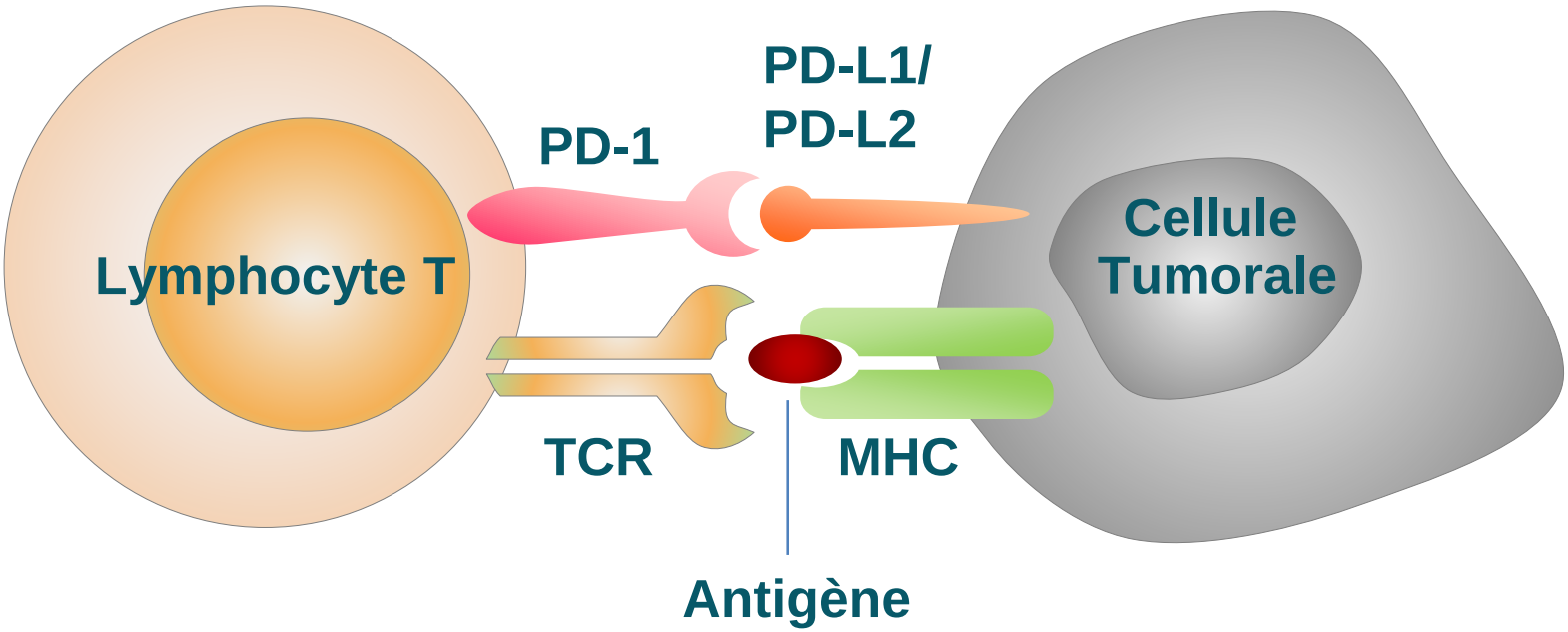
Voie de signalisation PD-1/PD-L1



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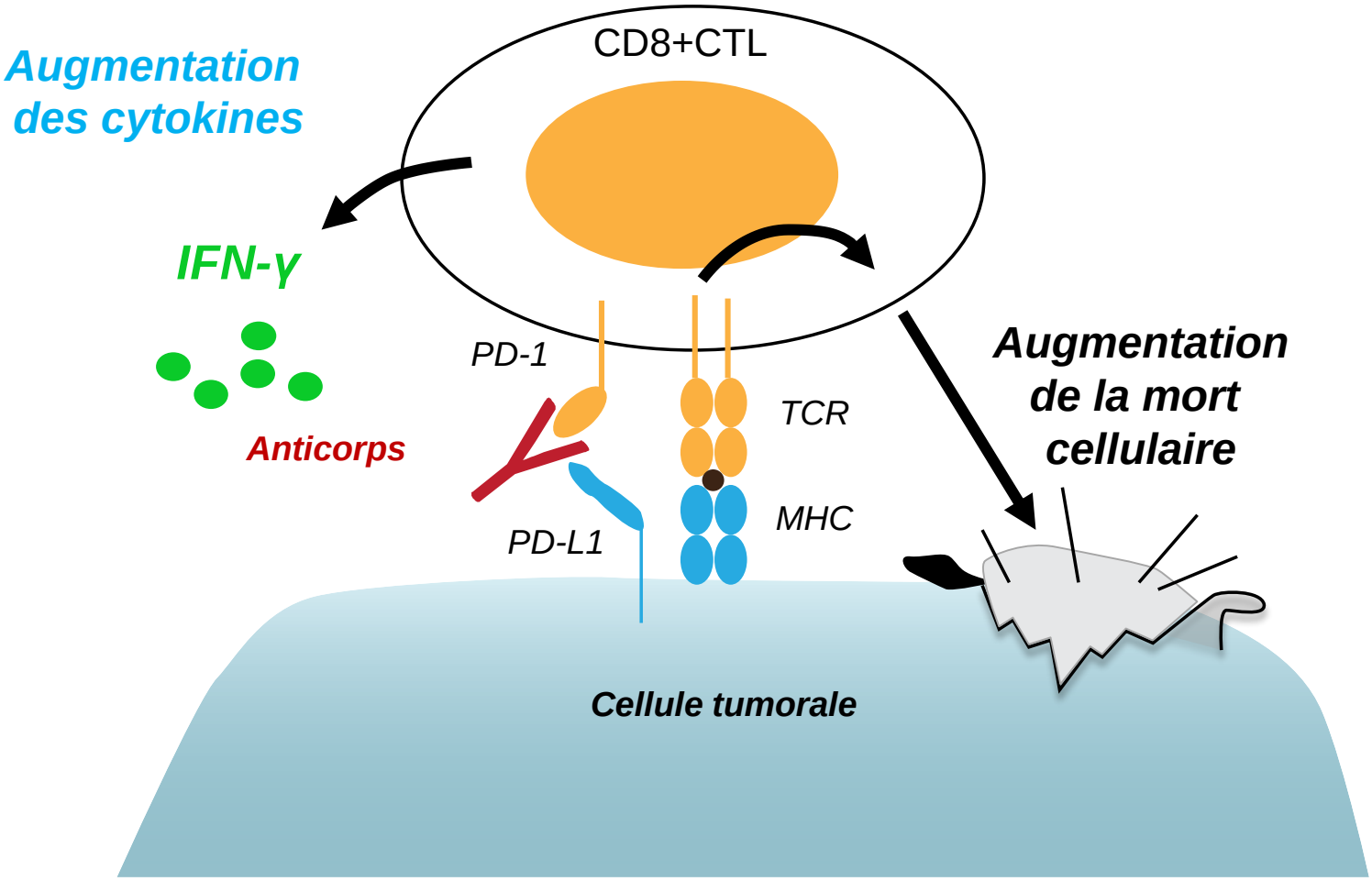
Le blocage de PD-1 ou PD-L1 stimule la réponse immune anti-tumorale

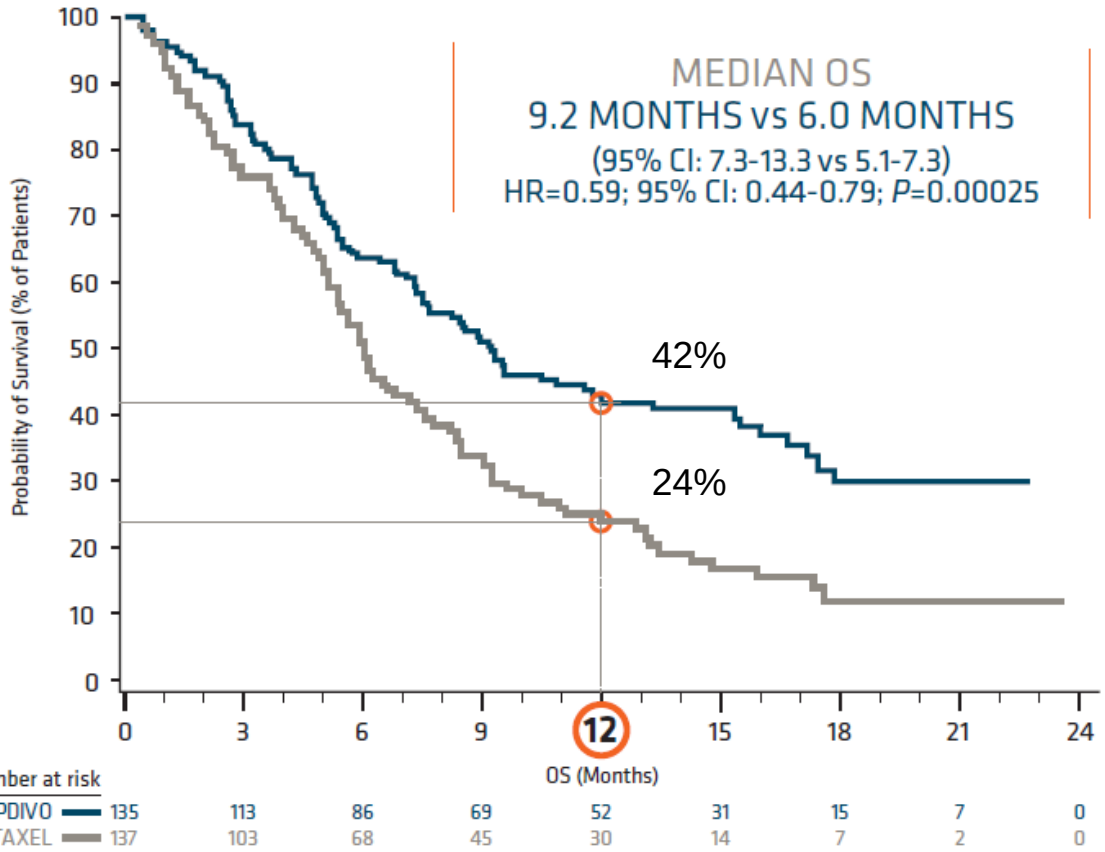


ASCO® GU 2016 - D'après Freeman G et al., Renal Cancer Keynote Lecture

NIVOLUMAB

CheckMate 017 : Essai de phase III
Carcinomes épidermoïdes bronchiques

Overall Survival[1]



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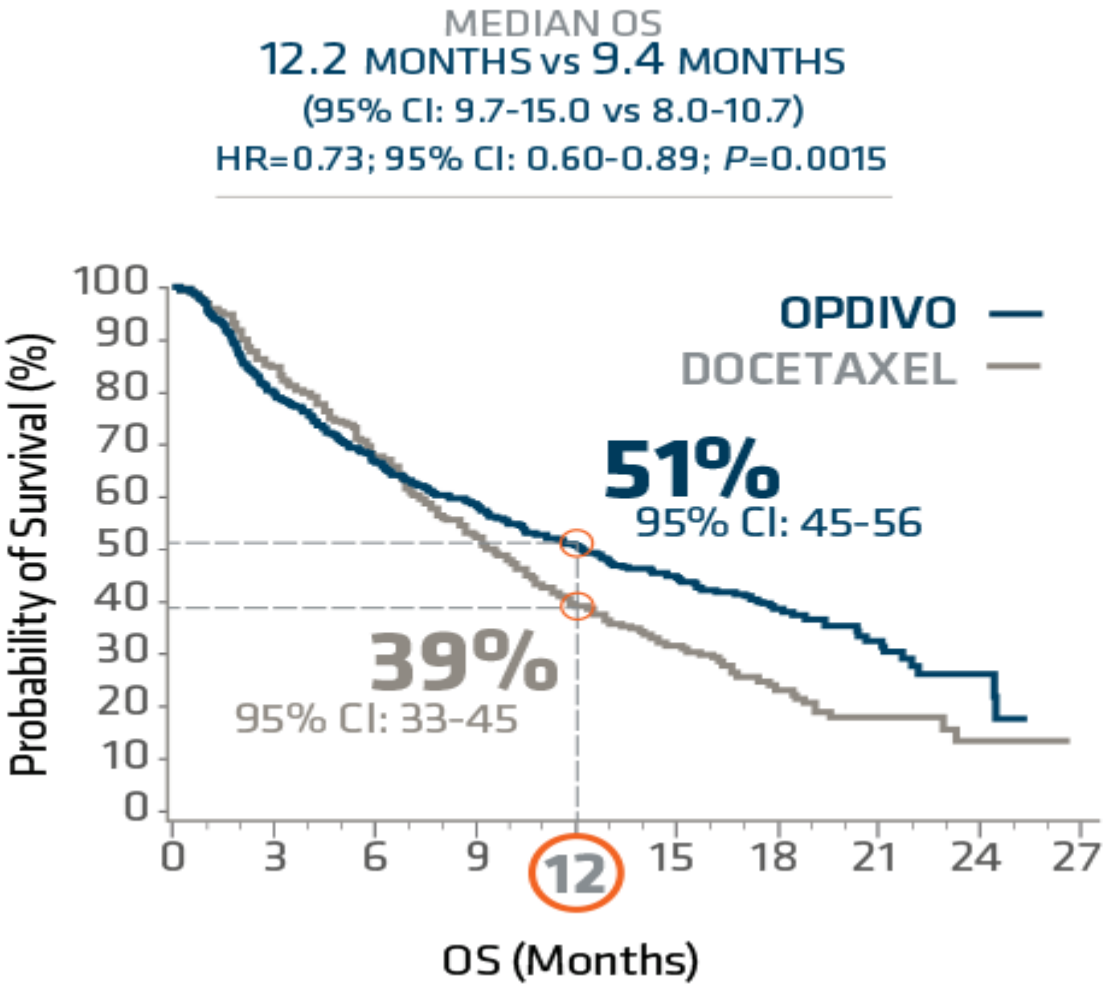
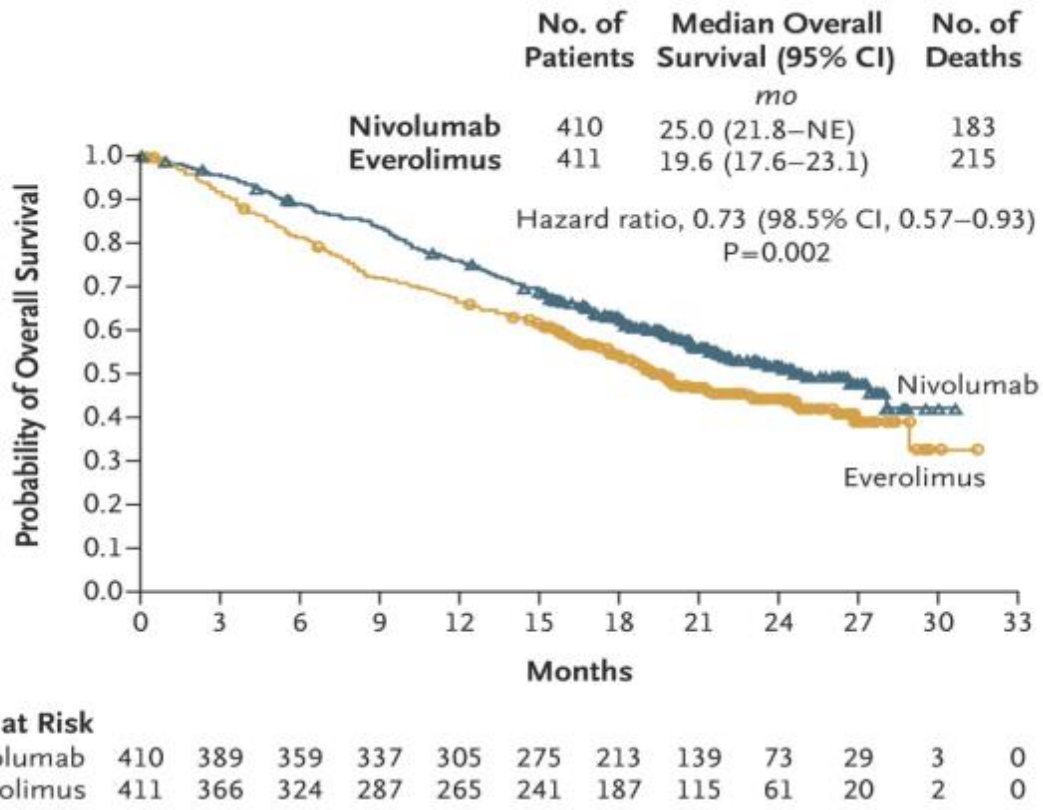
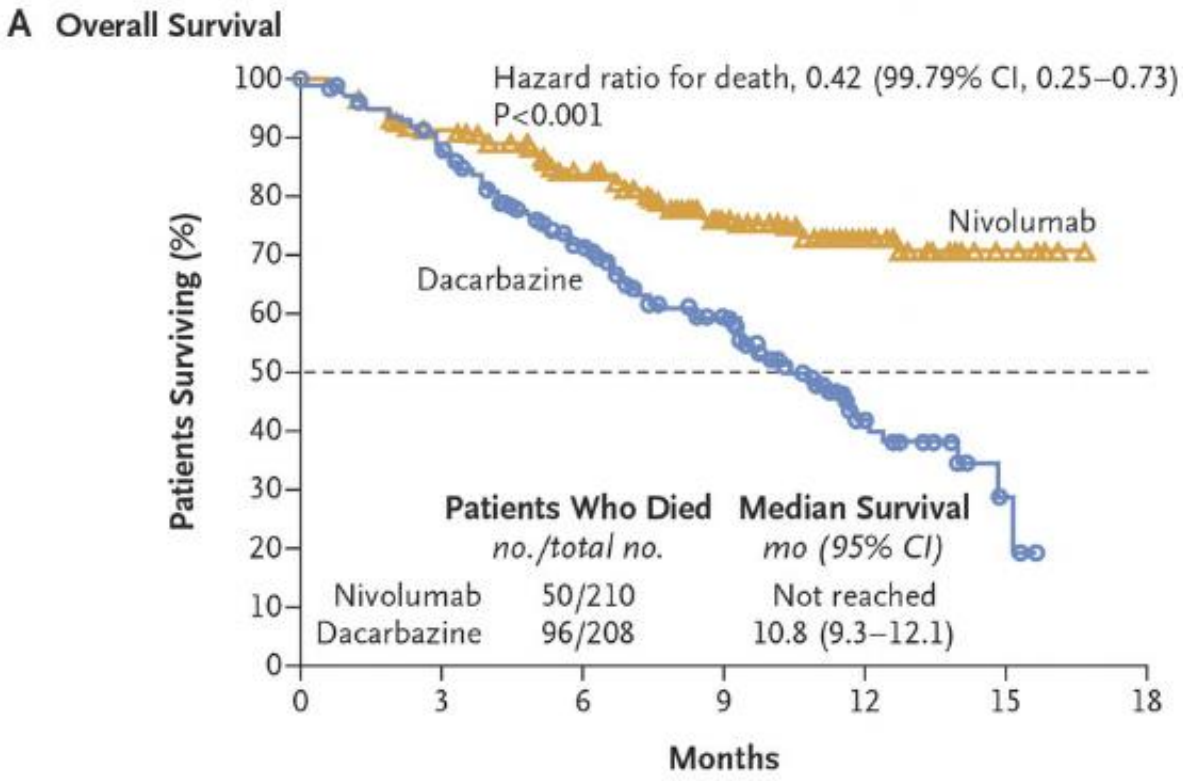
CheckMate 057 : Essai de phase III
K bronchiques non epidermoides



CheckMate 025 : Essai de phase III
Carcinome rénal à cellules claires



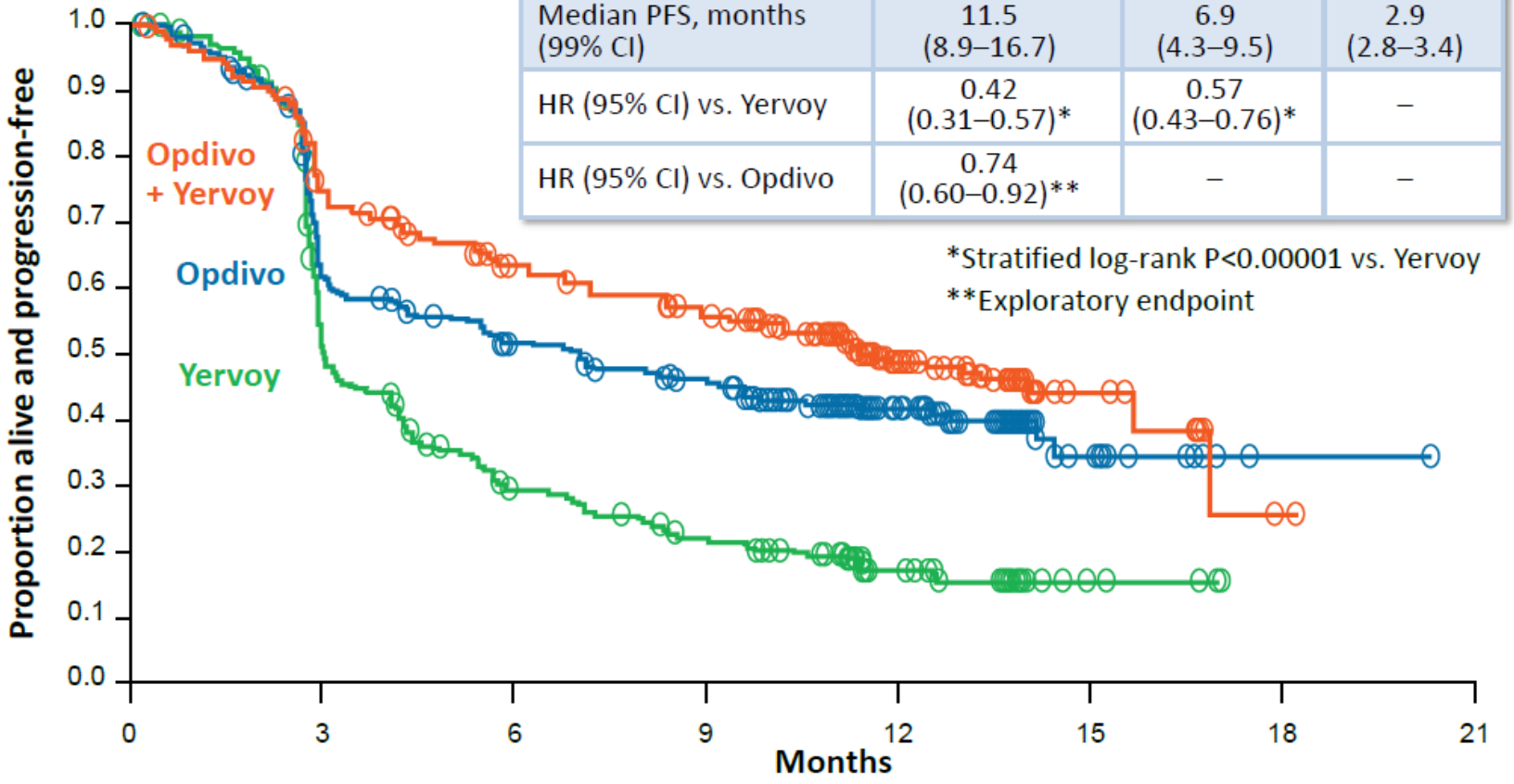
Keynote 066 : Essai de phase III Mélanome en 1ere ligne



NIVOLUMAB
+
IPILIMUMAB

CheckMate 067 : Essai de phase III
1ère Ligne mélanome métastatique

	Opdivo + Yervoy (N=314)	Opdivo (N=316)	Yervoy (N=315)
Median PFS, months (99% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (95% CI) vs. Yervoy	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	–
HR (95% CI) vs. Opdivo	0.74 (0.60–0.92)**	–	–

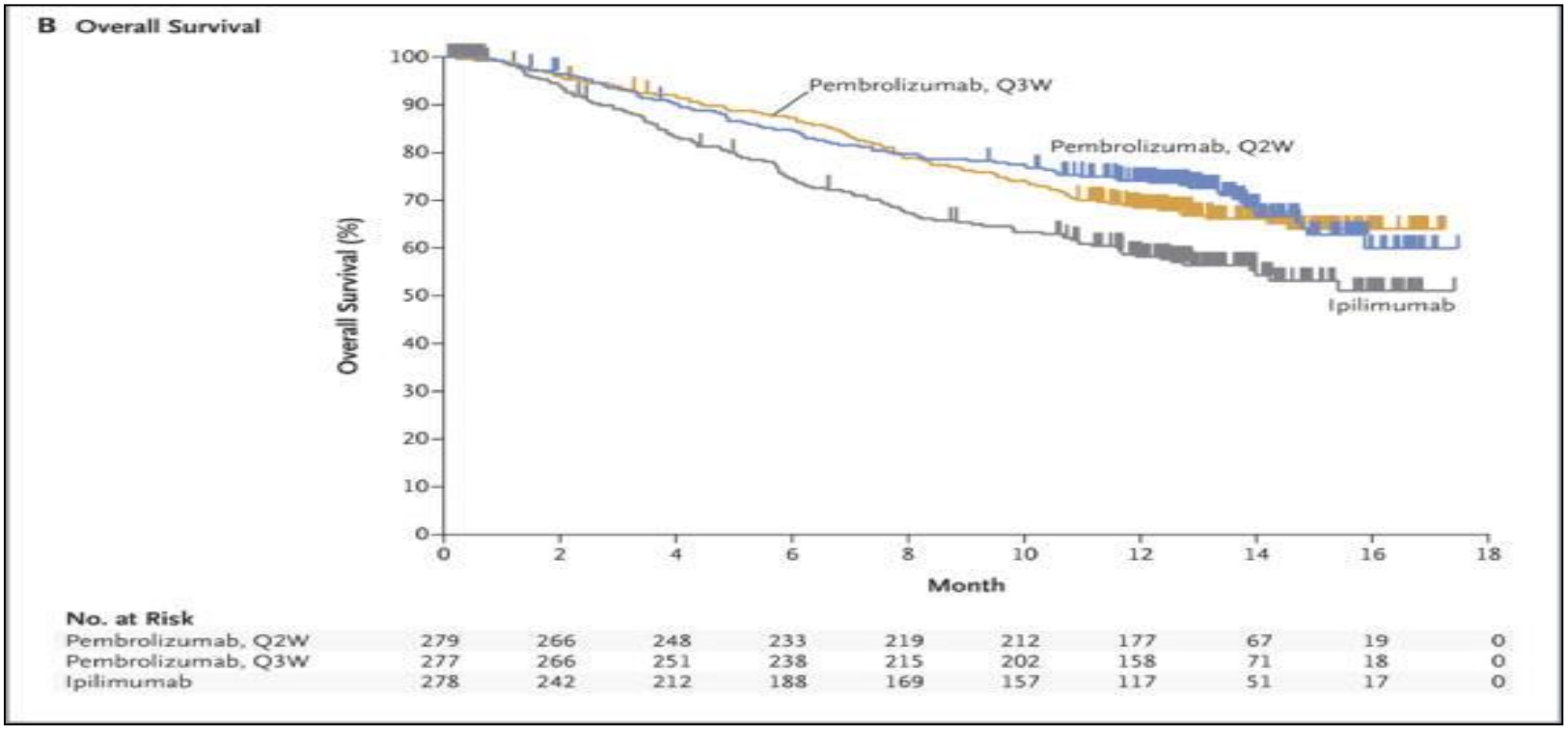


*Stratified log-rank P<0.00001 vs. Yervoy

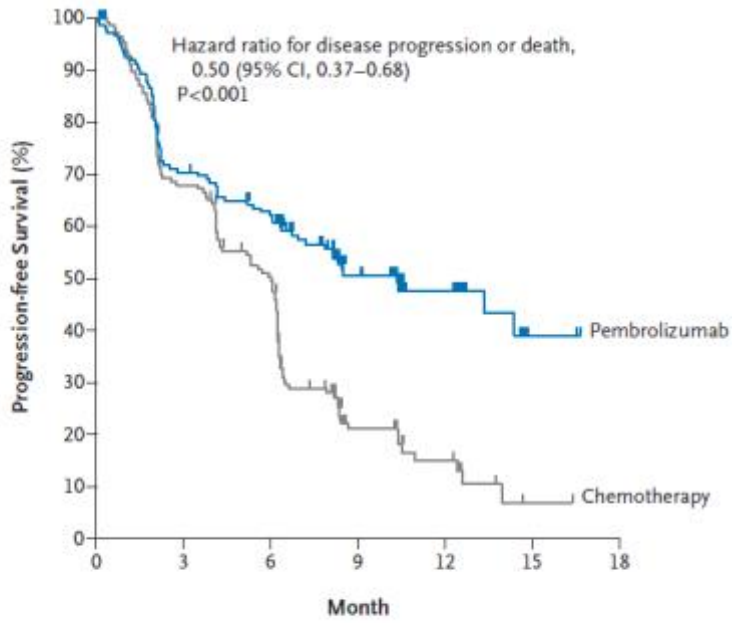
**Exploratory endpoint

PEMBROLIZUMAB

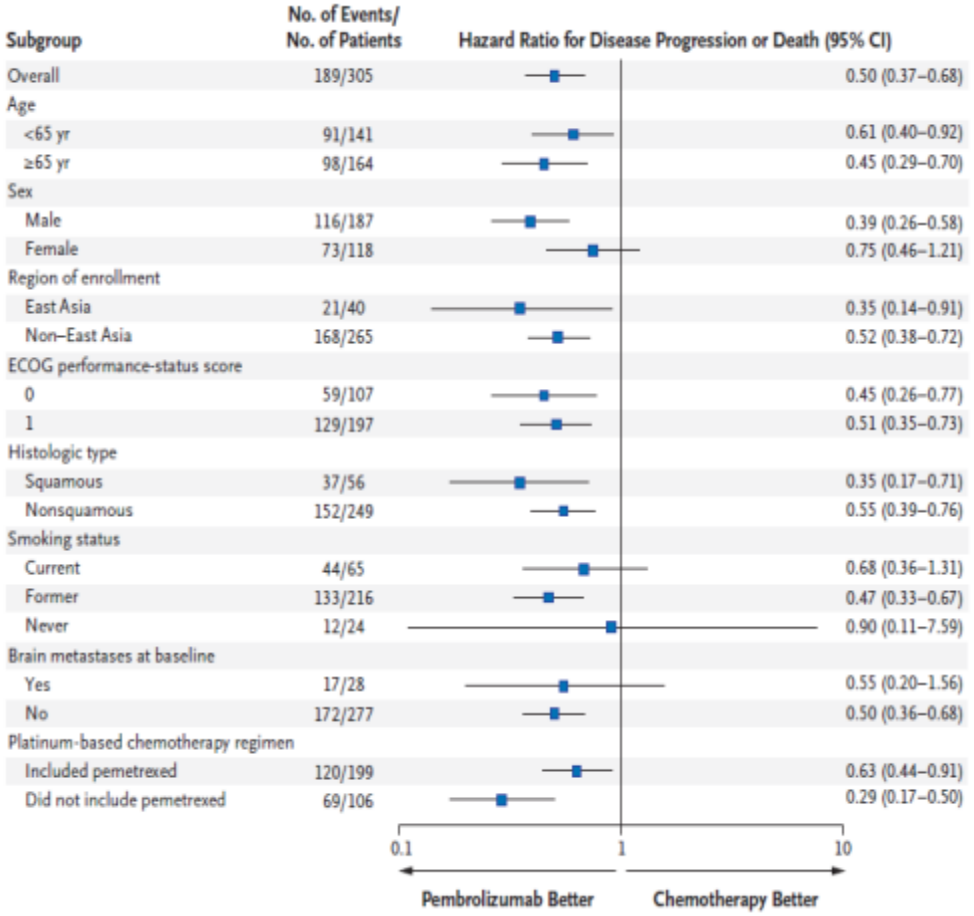
Keynote 006 : Essai de phase III
Mélanome avancé ou métastatique



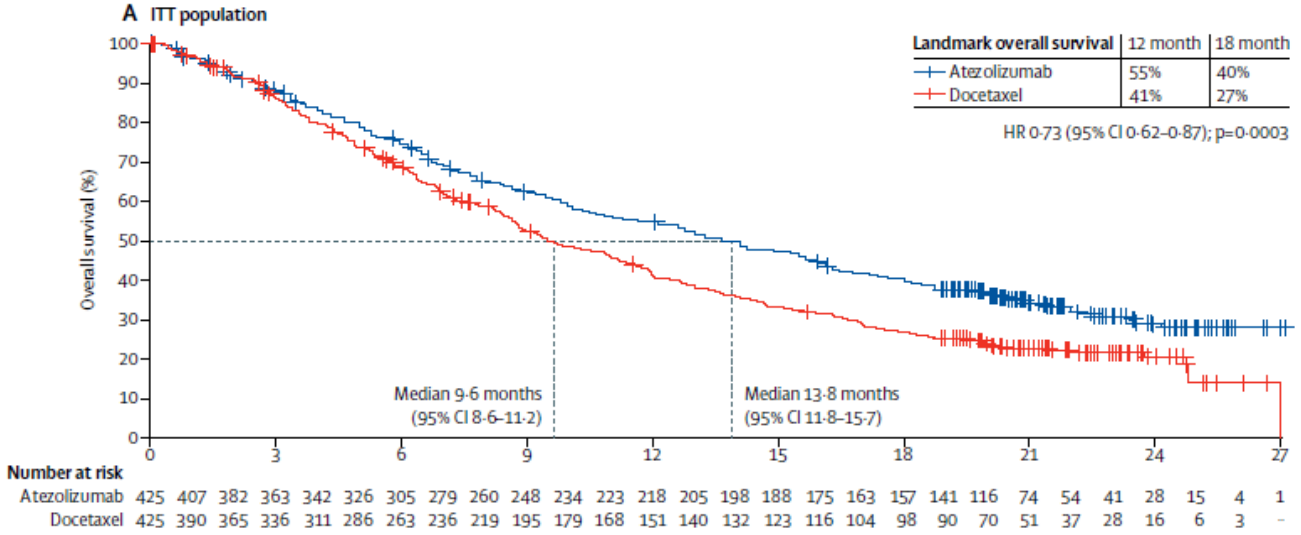
Keynote 024 : Essai de phase III CNPC



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

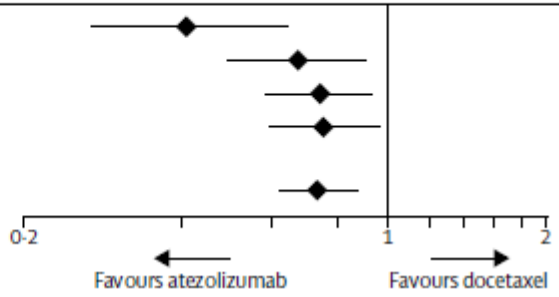


Atezolizumab et CPNPC, ph III
OAK trial



F

	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73 (0·62–0·87)



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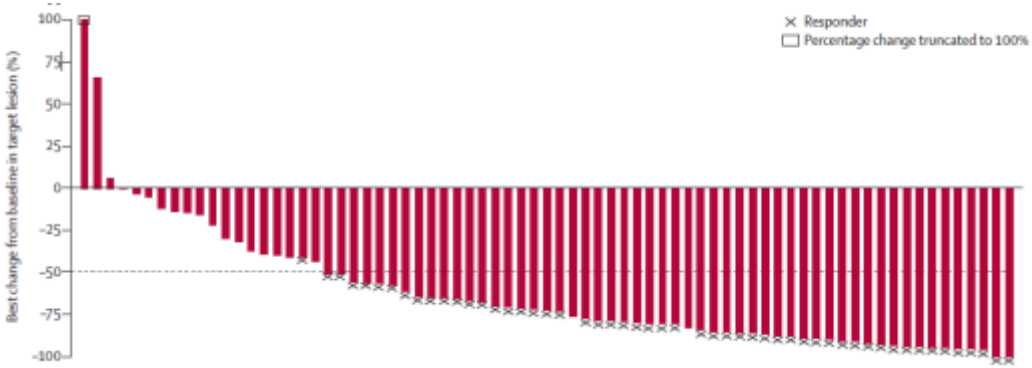
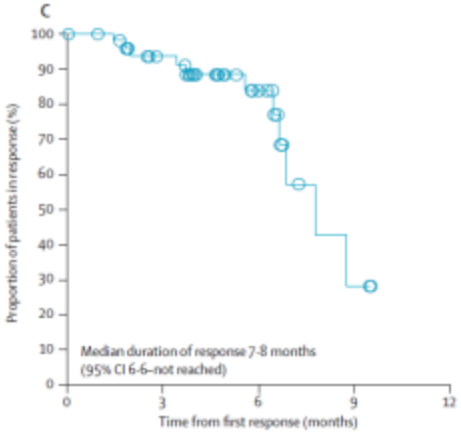
AMM actuelles des inhibiteurs de PD1/PD-L1

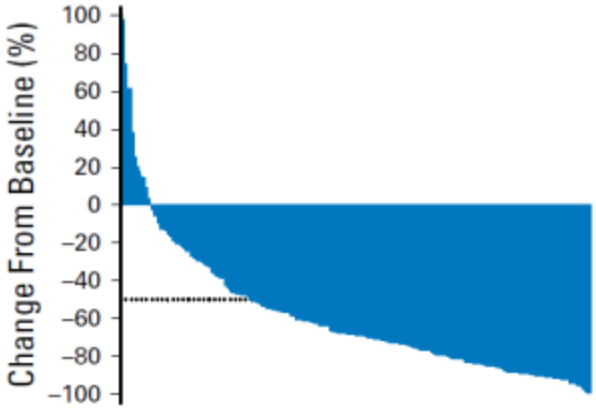
AMM en 2017

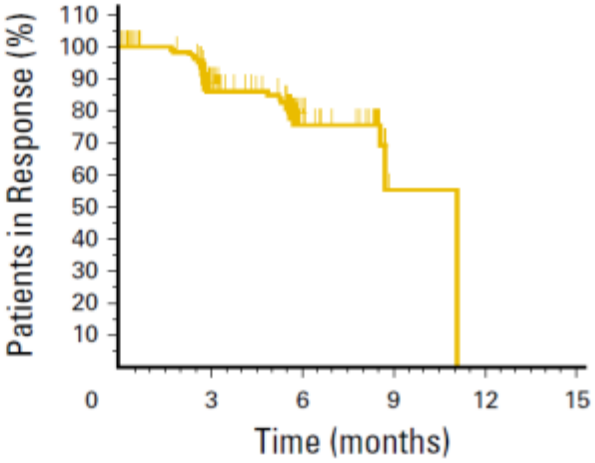
- Nivolumab (OPDIVO)
  - Mélanome métastatique en 1ère ligne, seul ou en association à l'Ipilimumab
  - CPNPC en rechute après platine
  - Cancer du rein après anti-angiogéniques
  - M Hodgkin après autogreffe
- Pembrolizumab (KEYTRUDA)
  - Mélanome métastatique en monothérapie
  - CPNPC en 2ème ligne si PD-L1 > 1%
  - CPNPC en 1ère ligne si PD-L1 > 50%
  - MH après autogreffe
- Atezolizumab (TECENTRIQ)
  - CPNPC en 2ème ligne (FDA)

Anti PD-1 et Maladie de Hodgkin



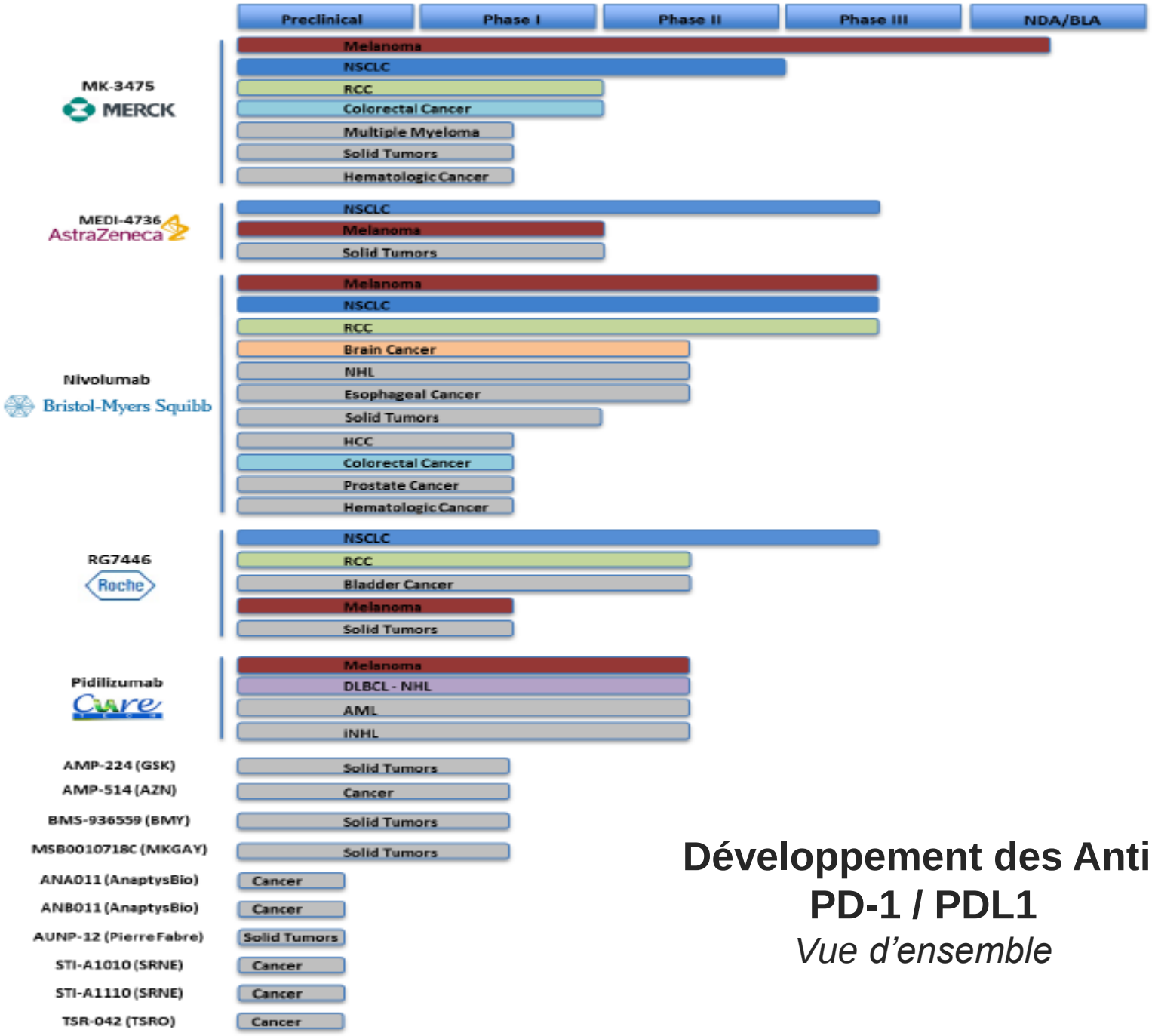






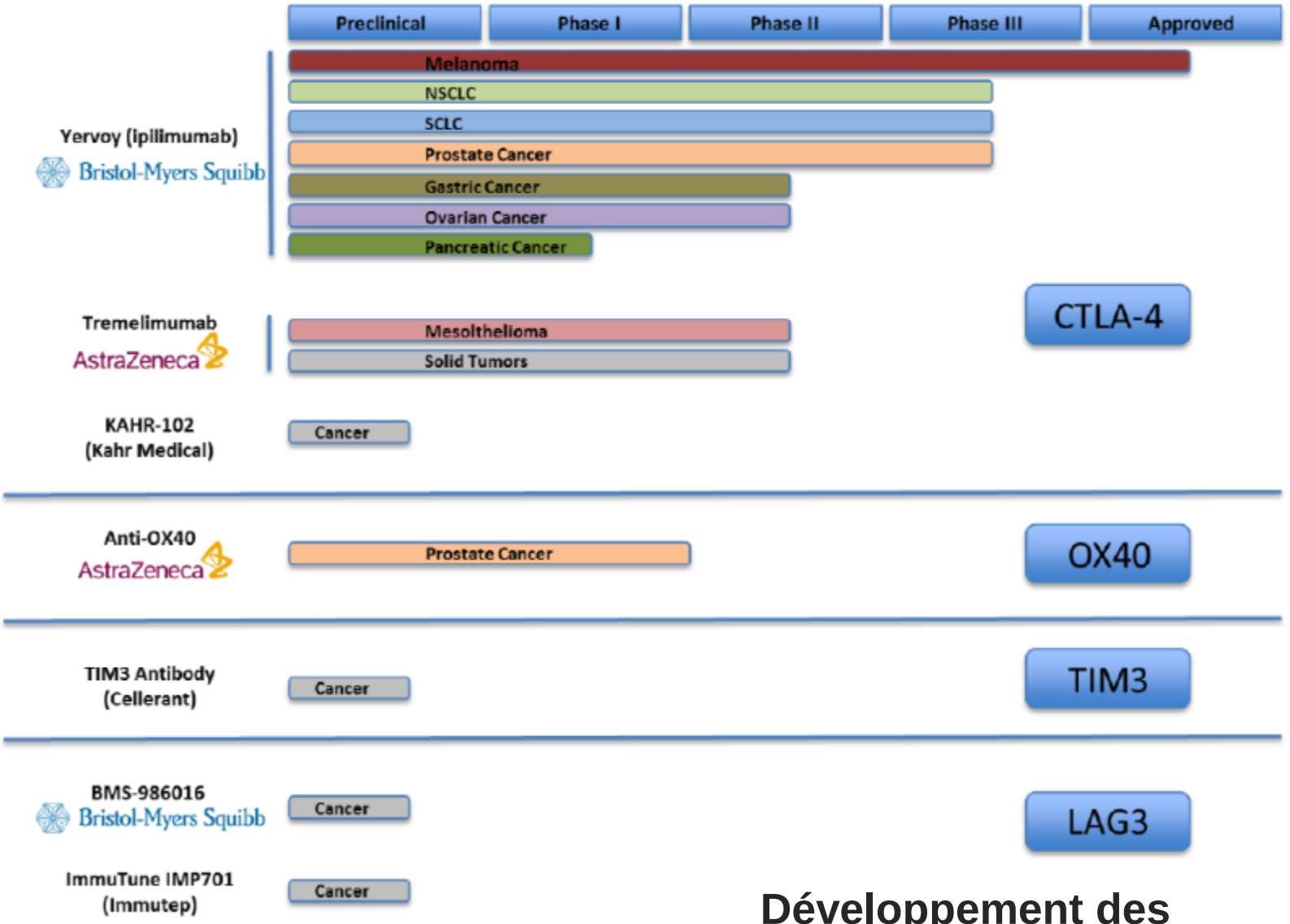
Anas Y, *Lancet Oncol* 2016
Chen R, *J Clin Oncol* 2017

Vue d’ensemble du développement des immunothérapies



Développement des Anti-PD-1 / PDL1

Vue d'ensemble



Développement des CTLA-4, TIM3, et LAG3 checkpoint inhibitors

Vue d'ensemble

Futures indications

- Mesotheliome,
- Cancers urothéliaux,
- Gyneco : col – ovaire
- Cancers du sein triple-négatif
- …

Adverse Events

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer (CheckMate 057)

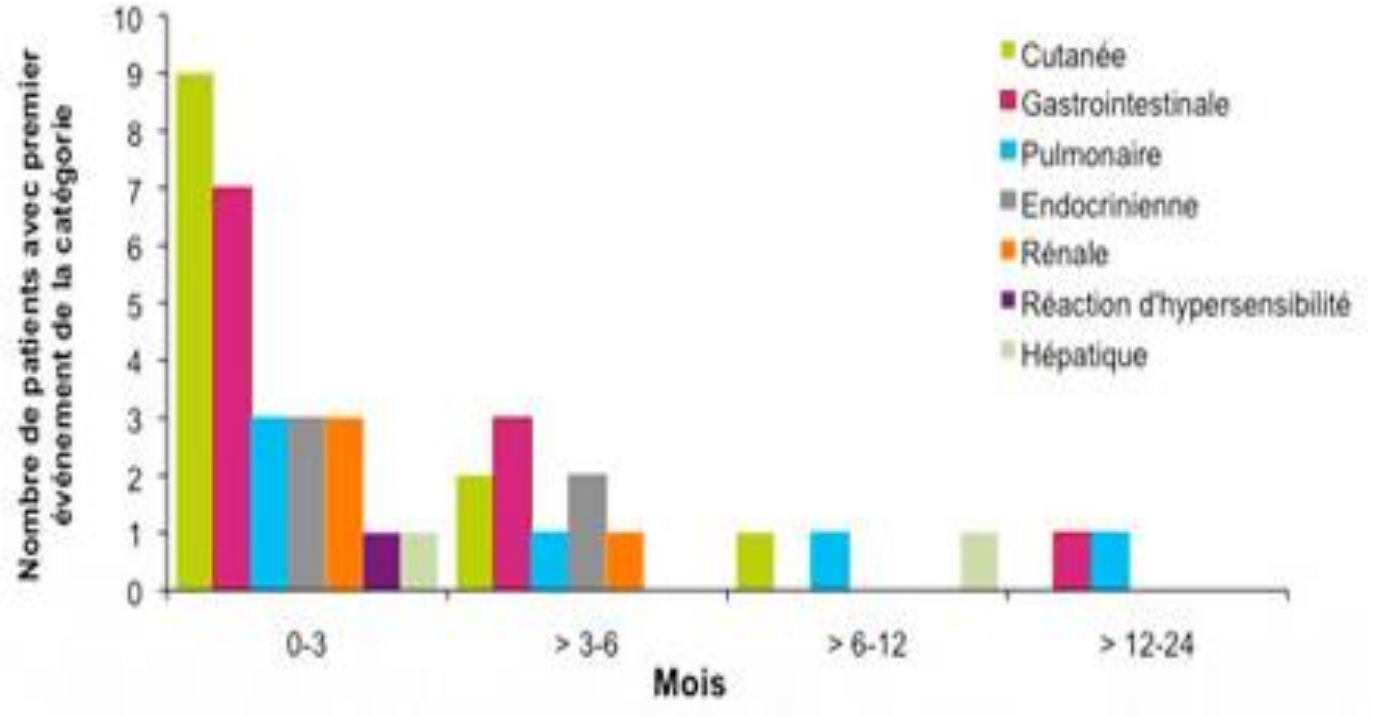
Table 3. Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

Event	Nivolumab (N = 287)		Docetaxel (N = 268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

* Data are based on a March 18, 2015, database lock. Safety analyses included all the patients who received at least one dose of study drug. Some patients had more than one adverse event. No treatment-related grade 5 events (deaths) were reported at the time of the database lock. The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock. A treatment-related death of a patient in the docetaxel group, which occurred before the database lock, was reported as grade 4 febrile neutropenia.

CheckMate 017
La plupart des toxicités apparaissent dans les 3 premiers mois de traitement

Communication orale



Données de qualité de vie (QDV) des patients inclus dans l'essai CheckMate 017
Evolution du score LCSS

Communication orale