Mélanome : développements récents…et effets 2aires des traitements

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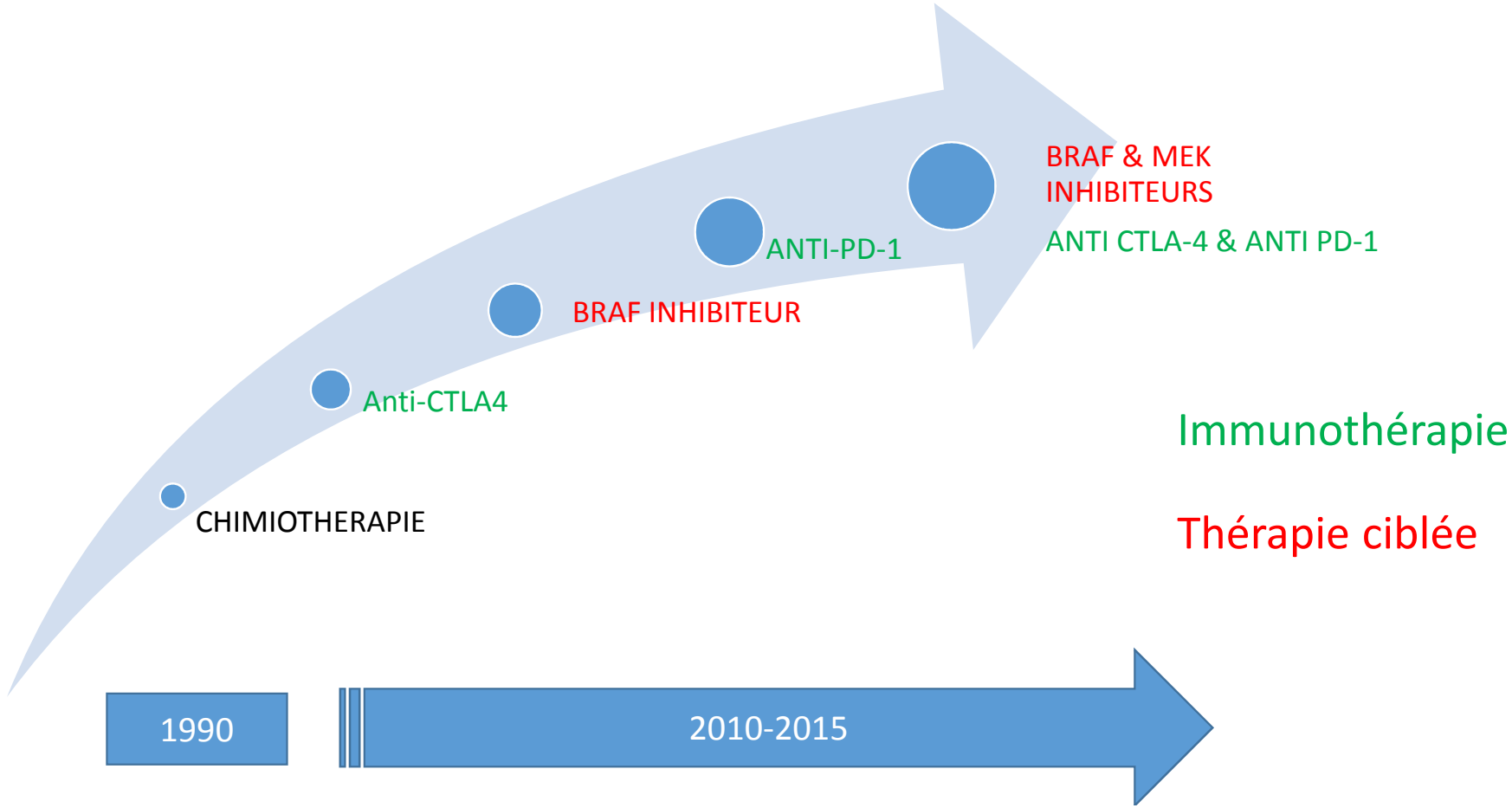
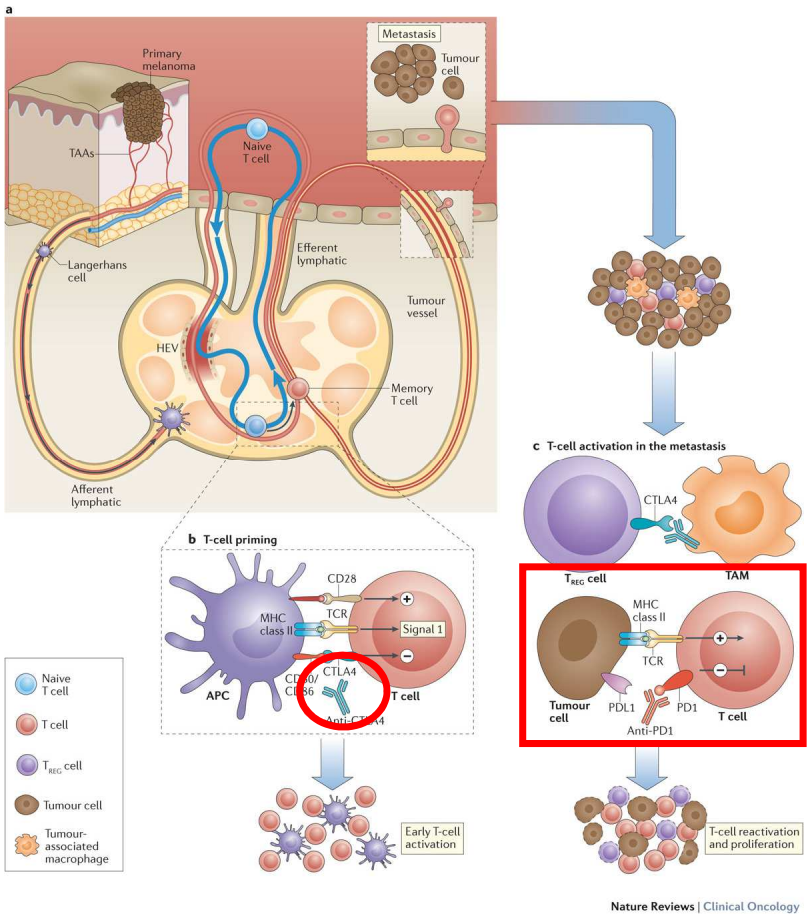
Mélanome métastatique

Survie à 1 an



Immunothérapie

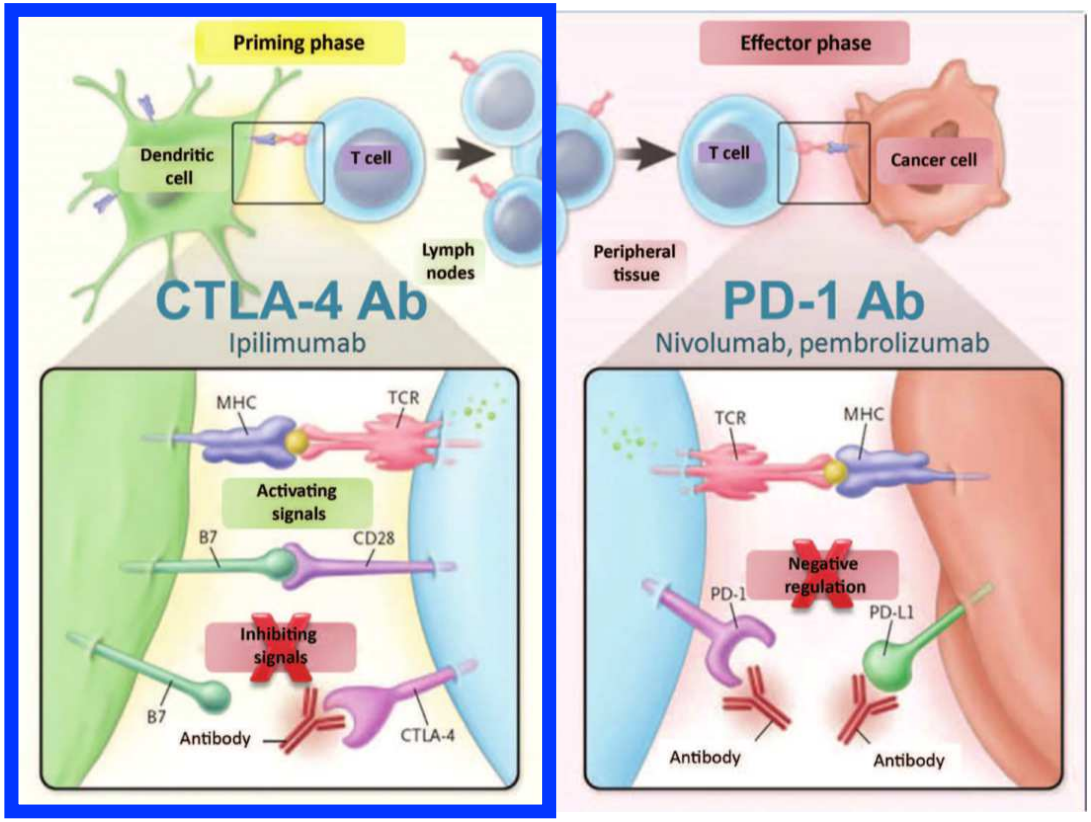
mode d'action



Boutros, C. *et al.* (2016) *Nat. Rev. Clin. Oncol.*

Immunothérapie

anti-CTLA-4

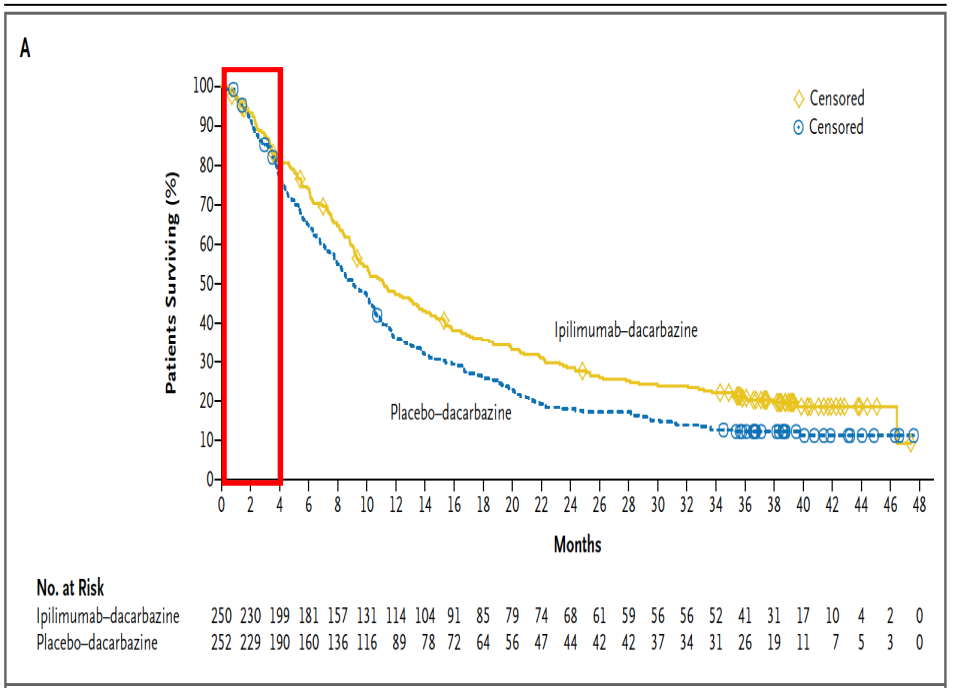


Ribas , A. *et al.* (2012*) NEJM.*

Immunothérapie

Ipilimumab (anti-CTLA4)

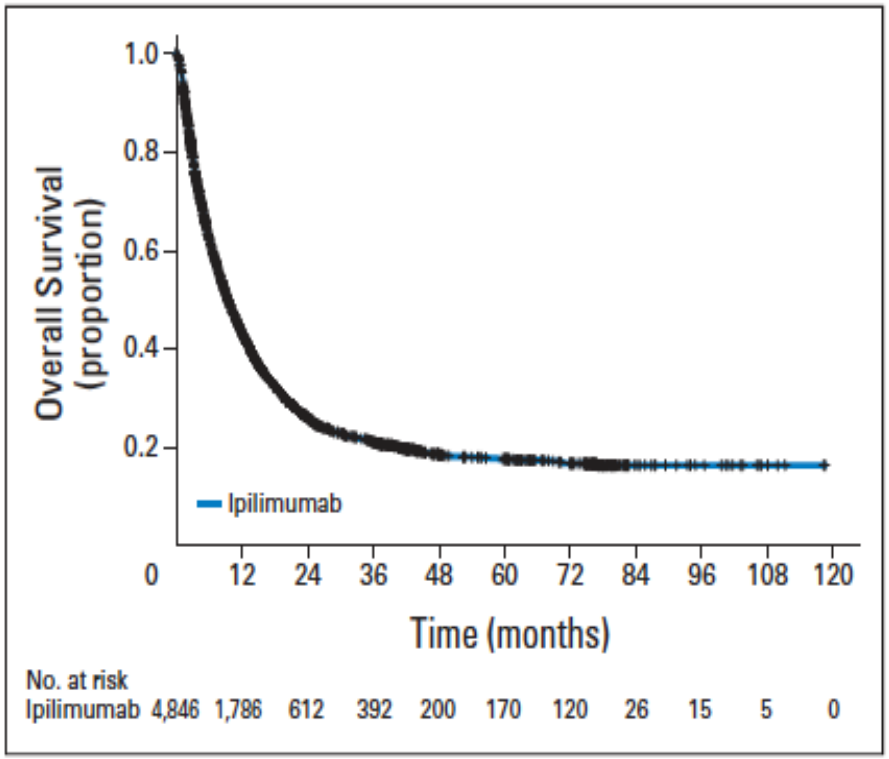
Best overall response — no. (%)*	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease — no. (%)*	45 (18.0)	50 (19.8)
Progressive disease — no. (%)	111 (44.4)	131 (52.0)
Response not evaluated — no. (%)†	56 (22.4)	45 (17.9)

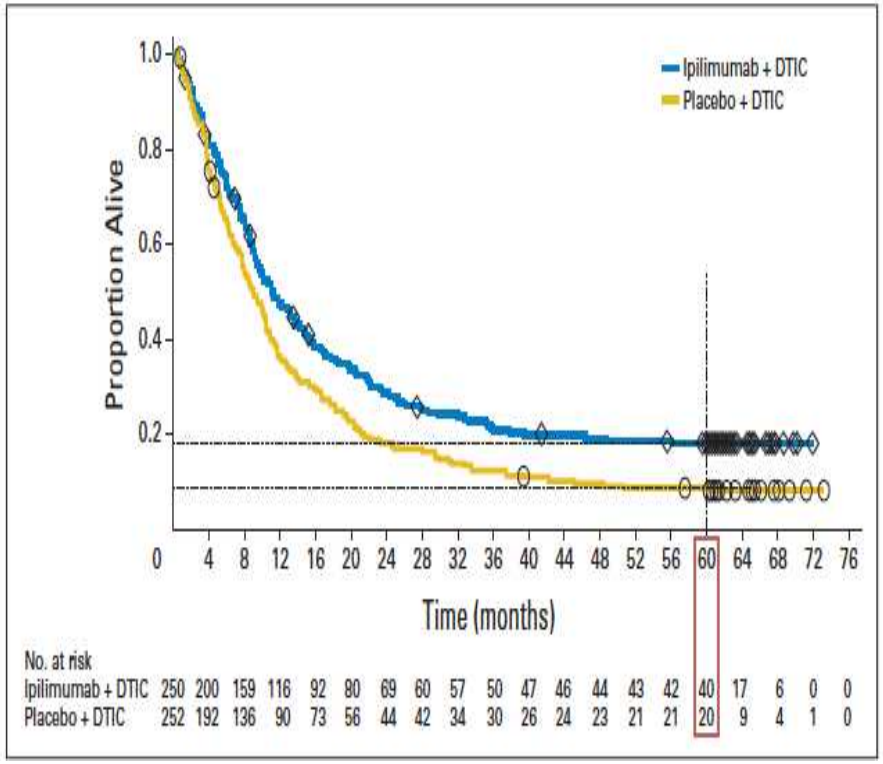


S. Hodi et *al* (2010), *NEJM*
C. Robert et *al* (2011), *NEJM*

Immunothérapie

ipilimumab (anti-CTLA4)





D. Schadendorf et *al* (2015*), JCO*
M. Maio et *al* (2015), *JCO*

Ipilimumab

Effets secondaires immuno-médié

Gastrointestinal[1]

Signs and symptoms such as

- Severe diarrhoea
- Abdominal pain
- Blood in stool
- Bowel perforation
- Peritoneal signs
- Ileus

Liver[1]

Signs such as

- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)

Skin[1]

Symptoms such as

- Pruritus
- Rash

Neurologic[1]

Symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Endocrine[1]

Signs and symptoms such as

- Fatigue
- Headache
- Hypotension
- Visual field defects
- Behavioural changes
- Electrolyte disturbances

Other adverse reactions[1] **including ocular manifestations**

Ipilimumab 10 mg/kg body weight	Any grade	Grade 3–4
Skin, exanthema, pruritus	47–68 %	0–4 %
Gastrointestinal tract, diarrhea, colitis	31–46 %	8–23 %
Inflammatory hepatotoxicity	3–9 %	3–7 %
Hypophysitis	4–6 %	1–5 %

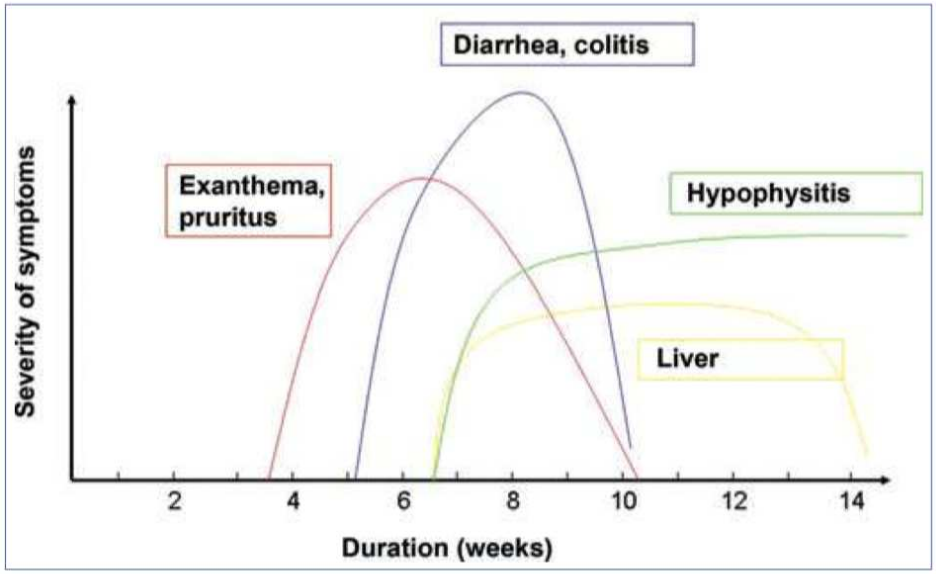
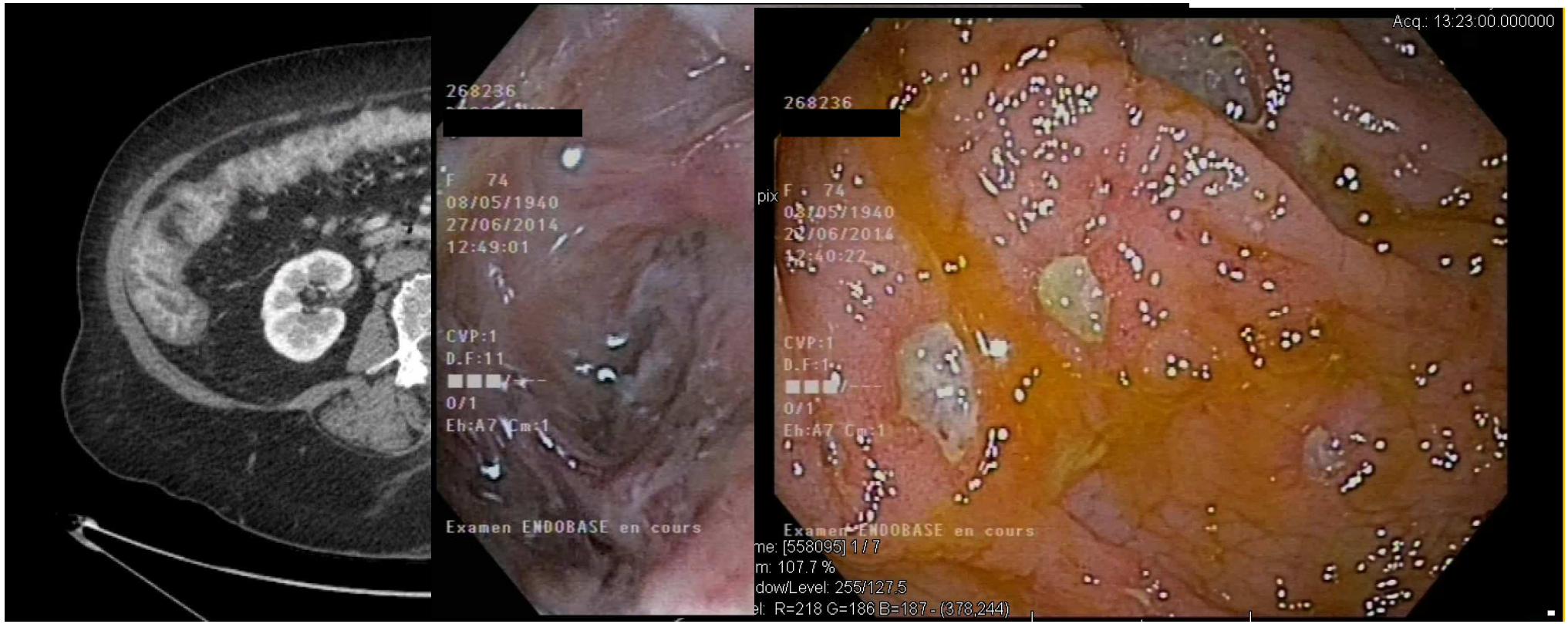


Figure 2: Time course of typical adverse events during a therapy with CTLA-4-antibodies.

K.. K!ahler et *al* (2011), *JDDG*

Ipilimumab

colite



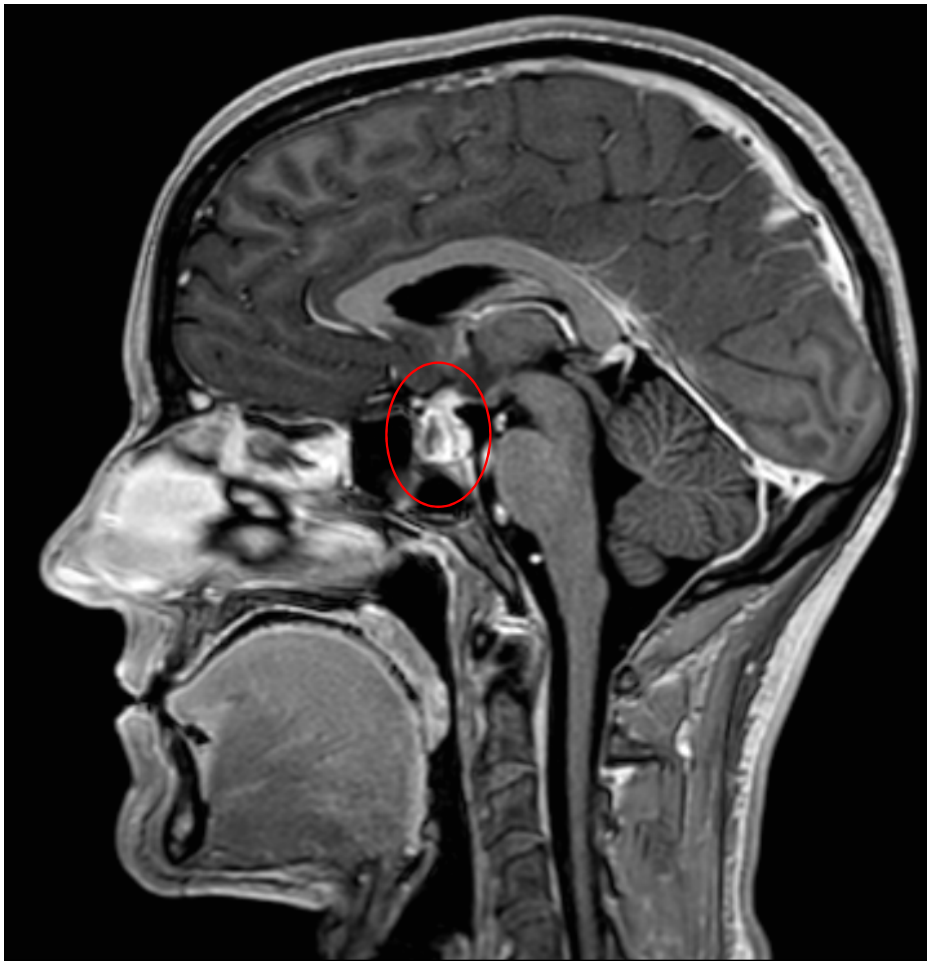
Ipilimumab

hypophysite

voir sous MS-Excel Copier les colonnes choisies pour MS-Word Nombre de colonnes affichées : 6	Unité	Valeurs Réf./Seuil	09/01/2015 15:30:00 OH-INF 09 1603 sgv (*)	09/01/2015 15:25:00 OH-INF 09 1600 sgv (*)	09/01/2015 10:35:00 OH-INF 09 1282 sgv (*)
glucose	mmol/l	4.1 - 6	4.3 [A]		
sodium	mmol/l	136 - 144	122 [A]		123
potassium	mmol/l	3.6 - 4.6	[B]		3.7
chlorures	mmol/l	96 - 107			
urée	mmol/l	2.8 - 7.1	3.4 [A]		3.9
créatinine	µmol/l	35 - 88			59
eGFR (CKD-EPI)	ml/min/1.73m²	> 60			106 [C]

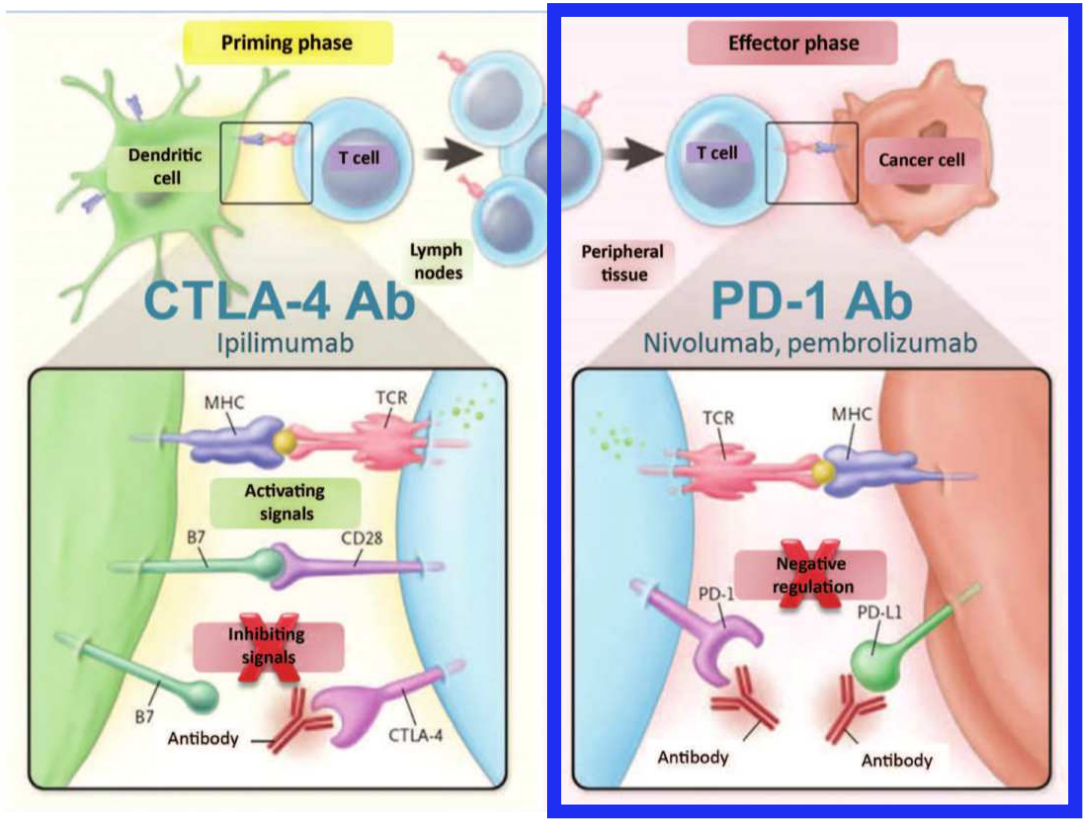
TSH	mUI/l	0.4 - 4	<0.004
T4 libre	pmol/l	10.3 - 23.8	20.1
T3 totale	nmol/l	0.8 - 2.7	1.10

IGF-1	µg/l	94 - 252			118 [D]
estradiol	ng/l				<5 [E]
follitrophine	U/l				4.2 [E]
lutrophine	U/l				1.0 [E]
prolactine	µg/l	4.8 - 23.3			1.0



Immunothérapie

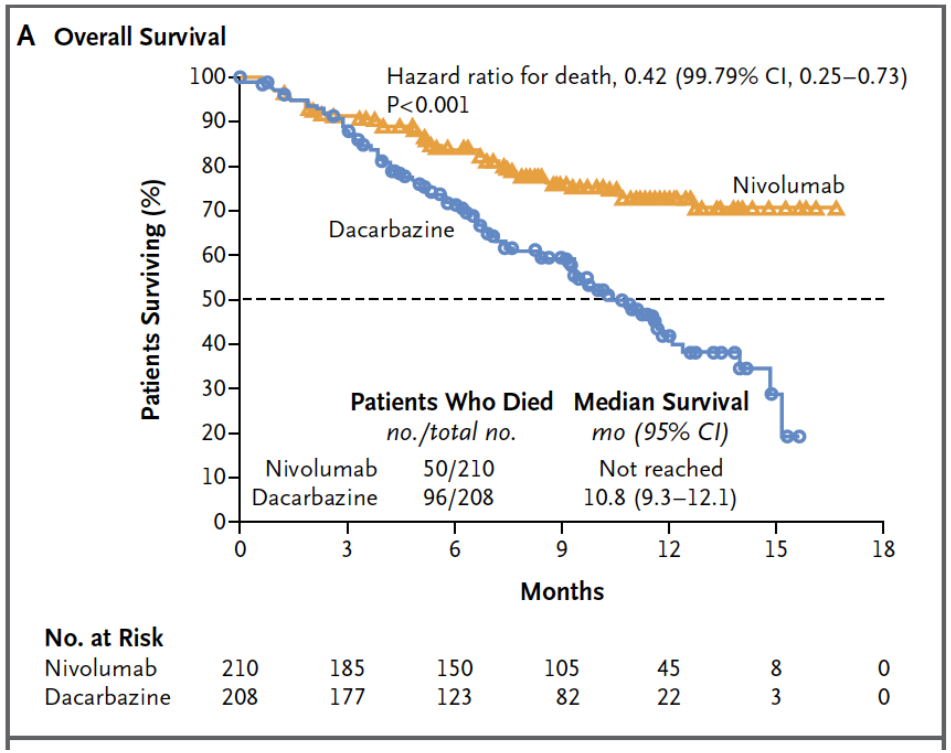
anti PD-1

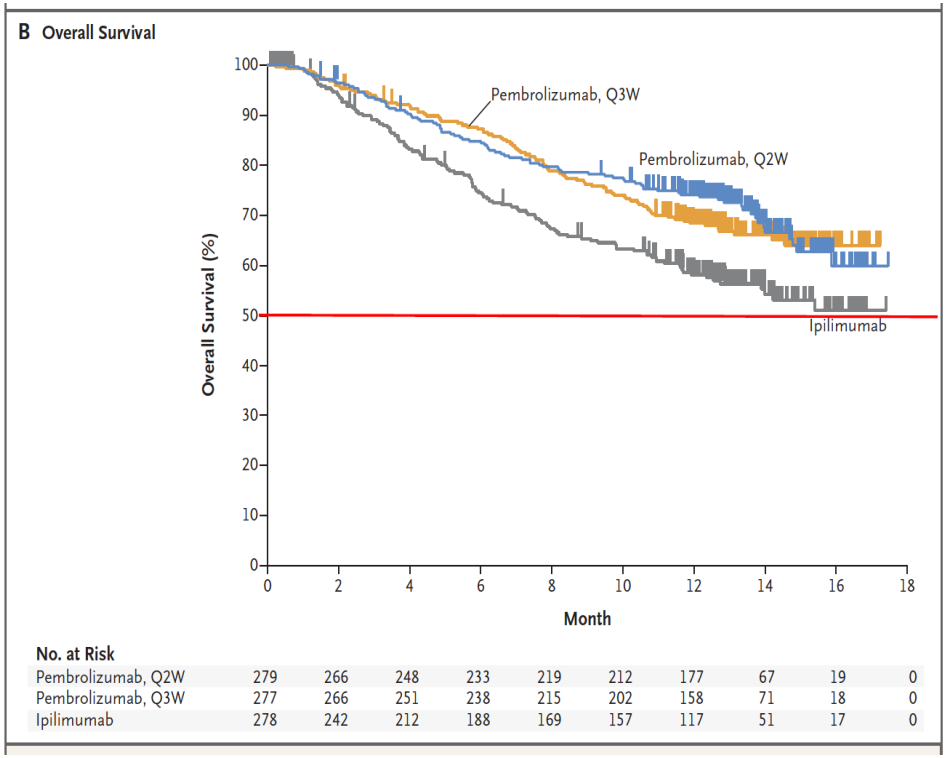


Ribas , A. *et al.* (2012*) NEJM.*

Immunothérapie

anti PD-1





C. Robert et *al*, (2016) *NEJM*

Anti PD-1

effets secondaires immuno-medié

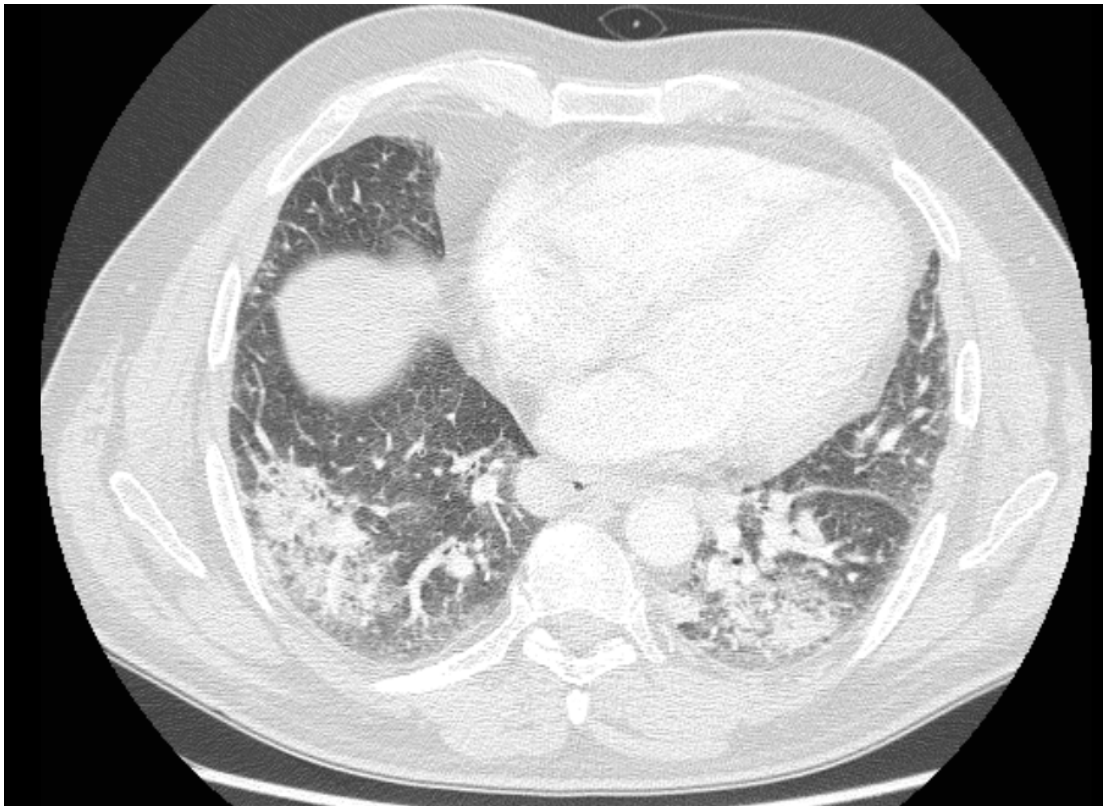
Table 2. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)		Ipilimumab (N=256)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)					
Related to treatment*						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in ≥10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest†						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

C. Robert et *al*, (2016) *NEJM*

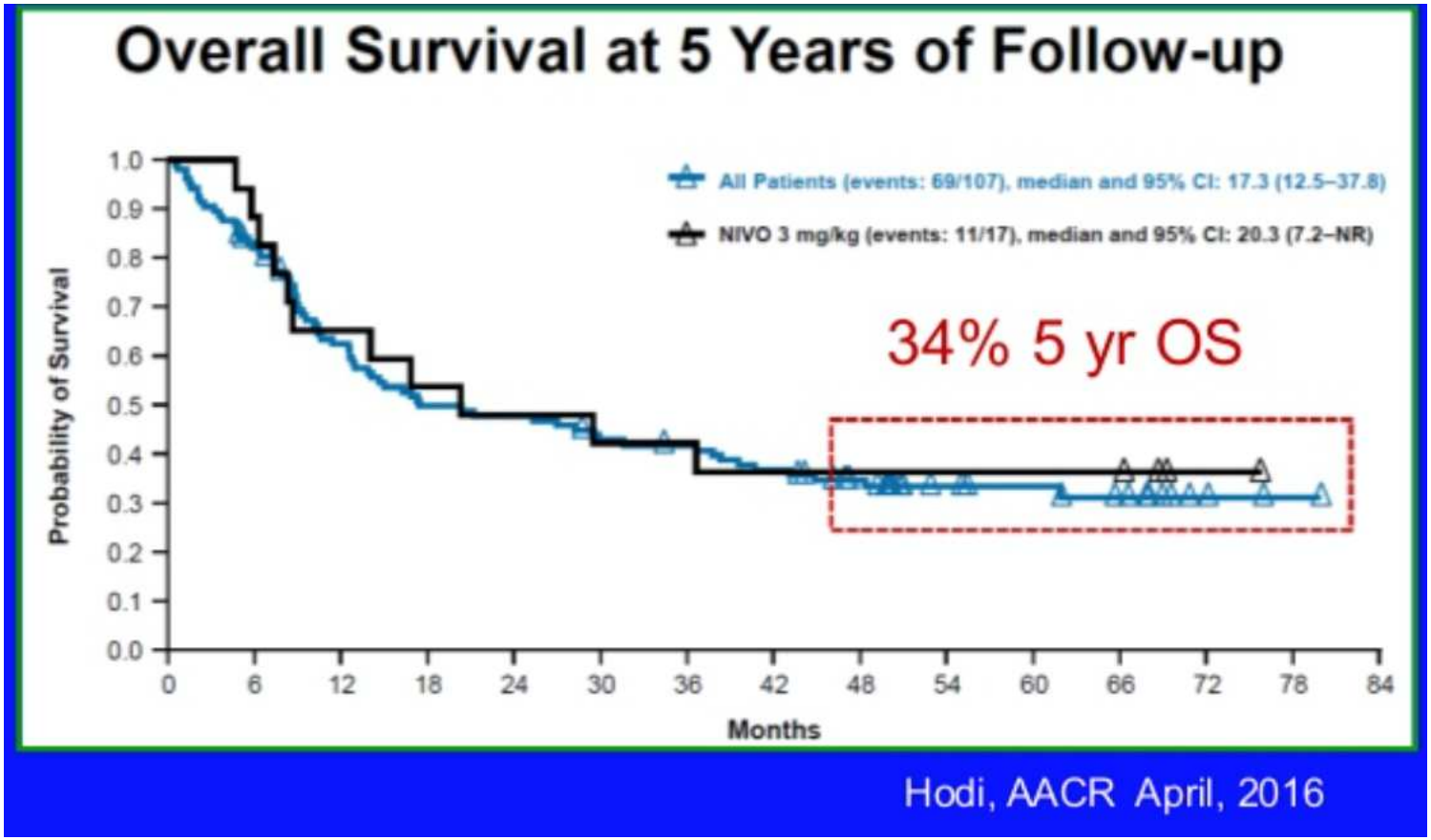
Anti PD-1

pneumopathie



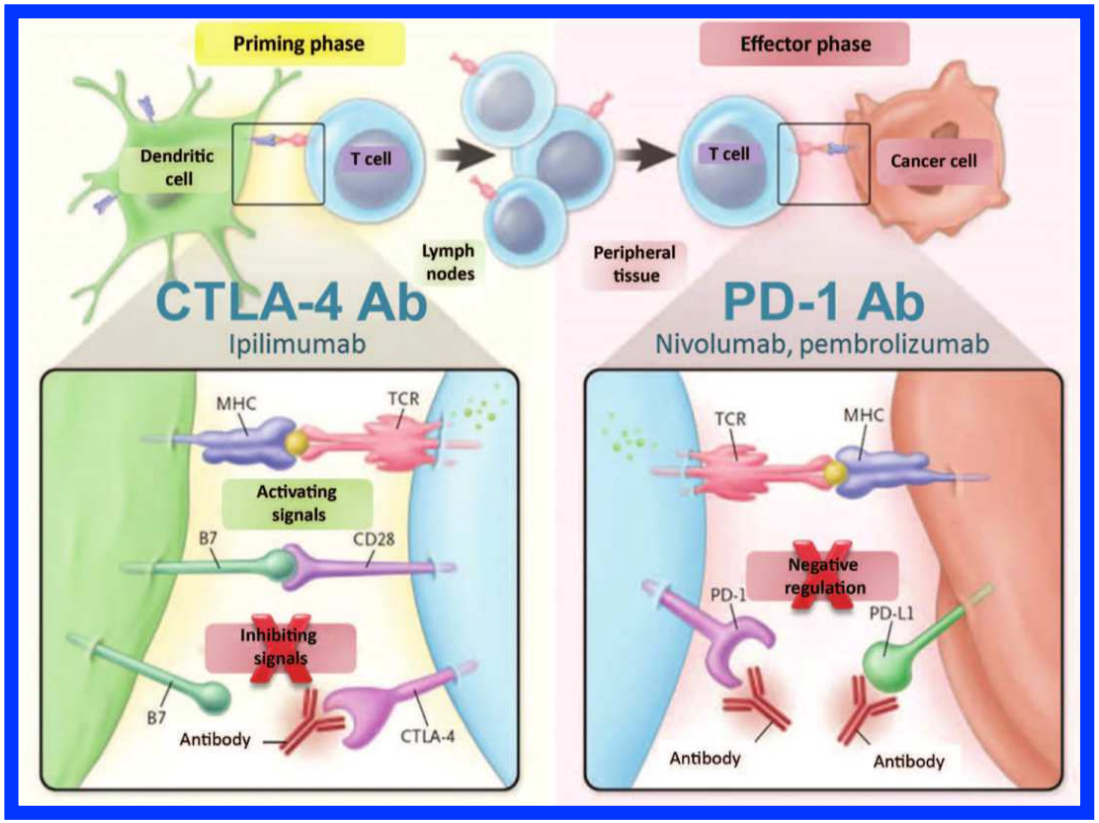
Immunothérapie

anti PD-1



Immunothérapie

combinaison

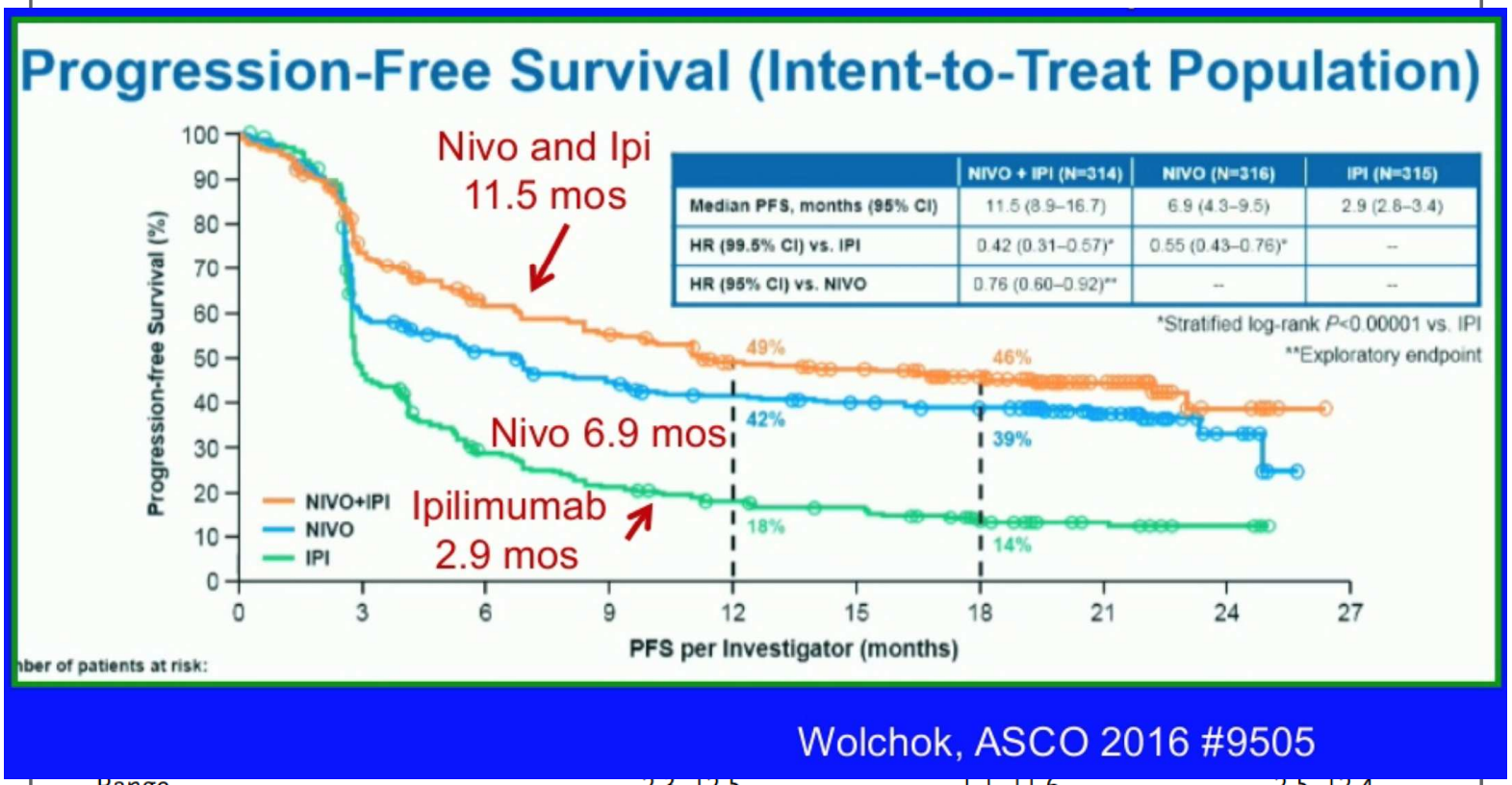


Ribas , A. *et al.* (2012*) NEJM.*

Combinaison anti CTLA4 et PD-1

concomitant

Table 2. Response to Treatment.



Range	2.3–12.5	1.1–11.6	2.5–12.4

J. Larkin et *al* (2016), *NEJM*

Combinaison anti CTLA4 et PD-1

concomitant

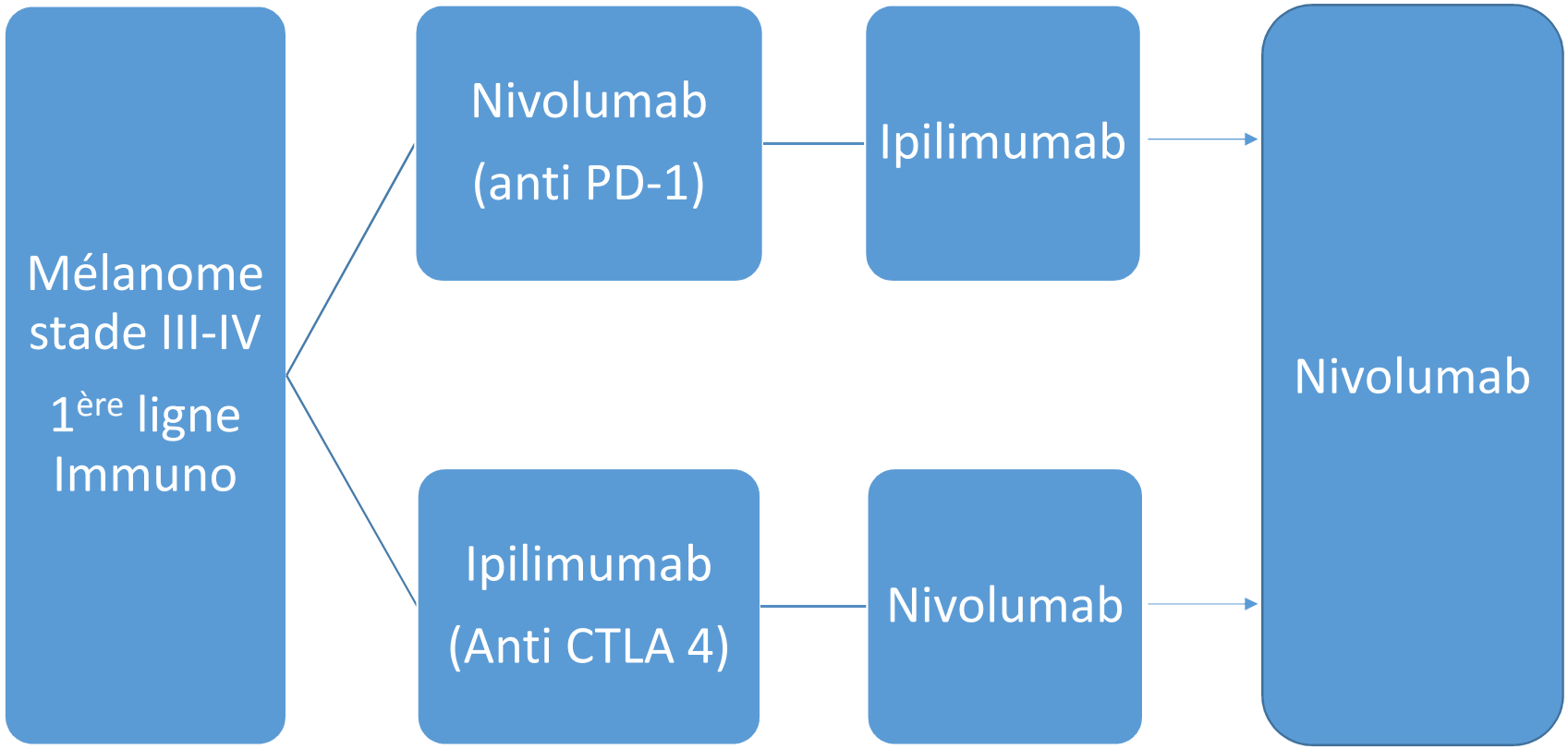
Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

J. Larkin et *al* (2016), *NEJM*

Combinaison anti CTLA4 et PD-1

séquentielle



JS Weber et *al* (2016), *Lancet oncol*

Combinaison anti CTLA4 et PD-1

séquentielle

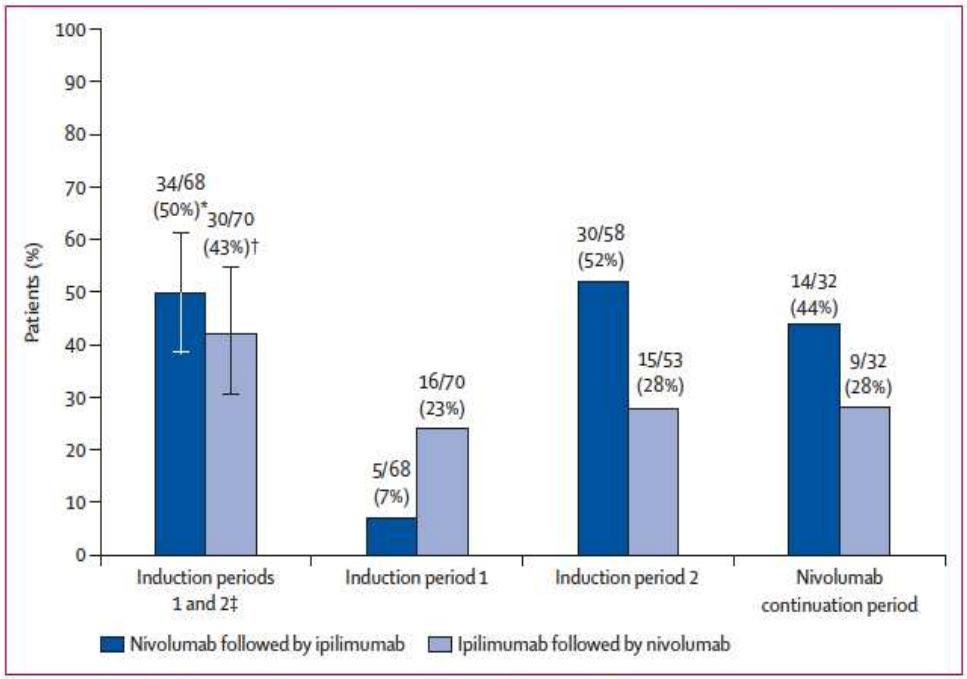
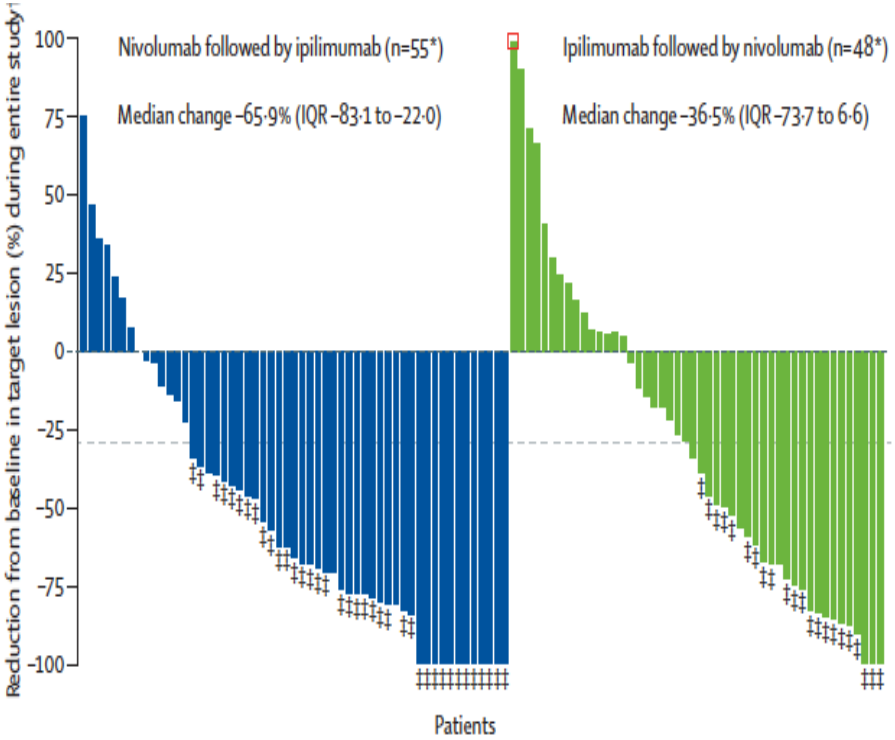


Figure 2: **Treatment-related grade 3–5 adverse events by study period**
No treatment-related deaths were reported during any study period. *95% CI 37·6–62·4%. †95% CI 31·1–55·3%. ‡Adverse events were counted only once for both induction periods. Error bars are 95% CIs.



Réponse complète: 12 % vs 6%

Réponse: 56% vs 31%

JS Weber et *al* (2016), *Lancet oncol*

Combinaison anti CTLA4 et PD-1

séquentielle

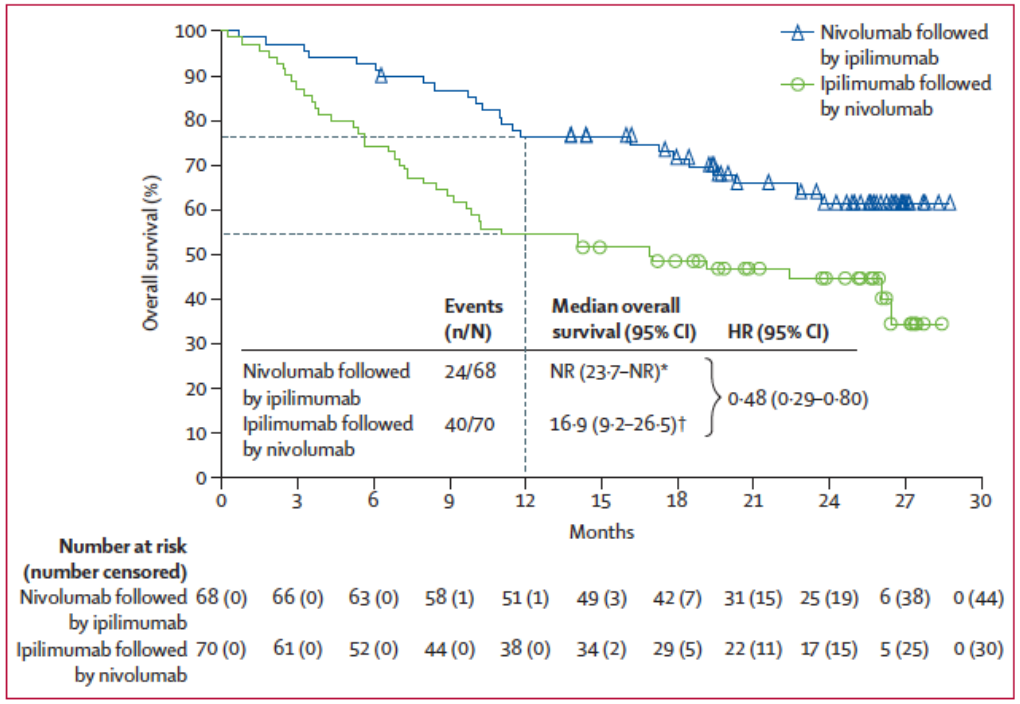


Figure 4: **Overall survival**

HR=hazard ratio. NR=not reached. *Median follow-up in the nivolumab followed by ipilimumab group was 19·8 months (IQR 12·8–25·7). †Median follow-up in the ipilimumab followed by nivolumab group was 14·7 months (5·6–23·9).

JS Weber et *al* (2016), *Lancet oncol*

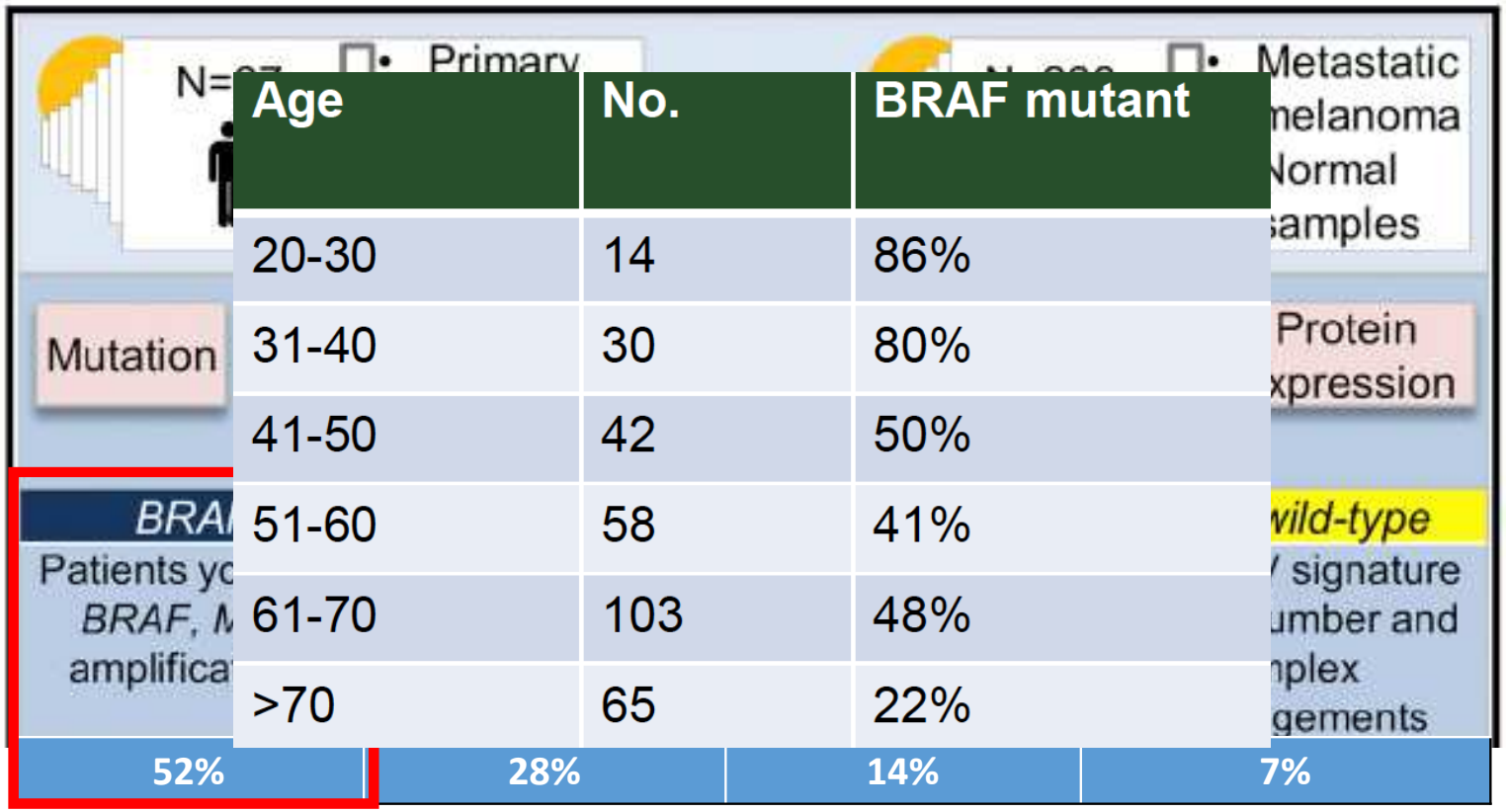
Toxicité immunothérapie

prise en charge

AEOSI (Grade) (acc. NCI CTC v.4)	Examinations *For the detailed laboratory panel please refer to Table 4*	Management *Anti-PD-1 therapy / Methyl-prednisolone or equivalent* [a]	& Follow-up *In case of:* ↗ Improvemen → No change ↘ Worsening
Skin events			
°1		Topical steroid [b]	
°2		Topical steroid [b]	
°3-4	(⊙Skin biopsy)	△ or ■ **1.0-2.0** mg/kg/d	↗ : ●
Diarrhea/Colitis			
°1	Stool test on pathogens	--- [c]	
°2	(⊙ Colonoscopy)	△ **0.5-1.0** mg/kg/d	→ : ■
°3-4	Colonoscopy	■ **1.0-2.0** mg/kg/d	→ / ↘ : Infliximab *Cave!* [d]
Pneumonitis			
°1	Frequent controls [q2-3d]	● ---	
°2	Daily symptom contr.; (⊙ Bronchoscopy)	△ **1.0-2.0** mg/kg/d	↗ : ●
°3-4	Bronchoscopy/biopsy	■ **2.0-4.0** mg/kg/d	→ / ↘ : Immunosuppr. therapy [e]
Endocrine events *Please refer primarily to full-text section for adequate guidance with regard to complex features of AEOSI*			
Asymptomatic °1	Regular controls; (⊙ Imaging)	● ---	
Symptomatic °2	Regular controls; (⊙ Imaging; ⊙ Further diagnostics)	△ (⊙HRT);**1.0-2.0** mg/kg/d	↗ : ● → : Start/maintain HRT
°3-4		△ (⊙HRT); i.v. steroids [g]	↗ : ● Regular controls
Renal events			
°1	Control for signs of renal dysfunction	● ---	
°2	(⊙Renal biopsy); Creatinine [q2-3d]	△ **0.5-1.0** mg/kg/d	↗ : ●
°3-4	(⊙Renal biopsy)	■ **1.0-2.0** mg/kg/d	
Hepatic events			
°1	Control for signs of hepatitis	● ---	
°2	Frequent controls [transaminases]	△ **0.5-1.0** mg/kg/d	↗ : ●
°3-4	Very frequent contr. [q1-2d]; (⊙Biopsy)	■ **1.0-2.0** mg/kg/d	→ / ↘ : Immunosuppr. therapy [e]
Infusion reactions [h]			
°3-4	Vigilant controls/monitoring	■ **2.0-4.0** mg/kg/d or i.v. corticosteroids ≥ antihistamines	

Mélanome

classification génomique

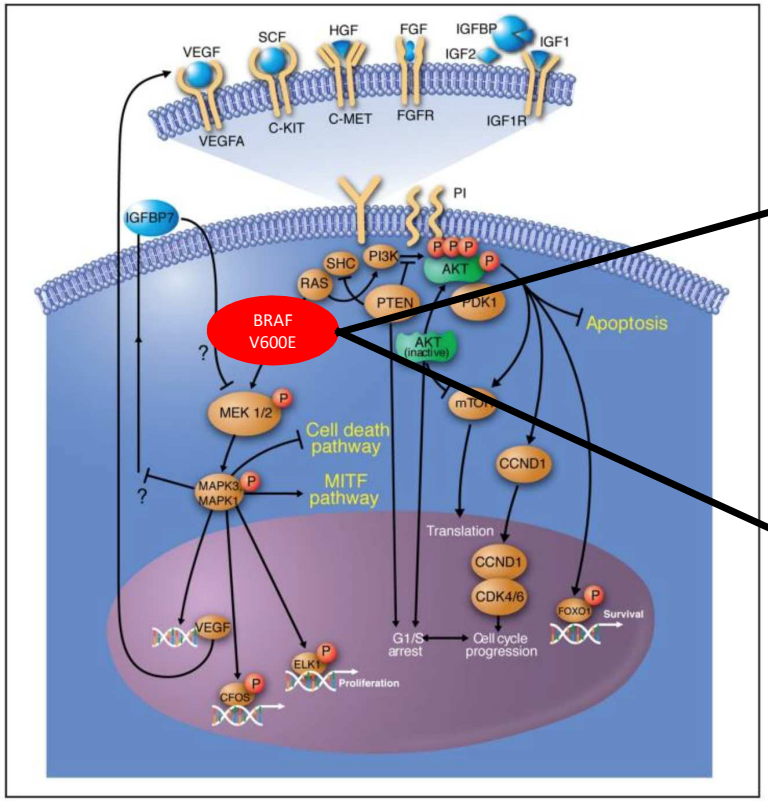


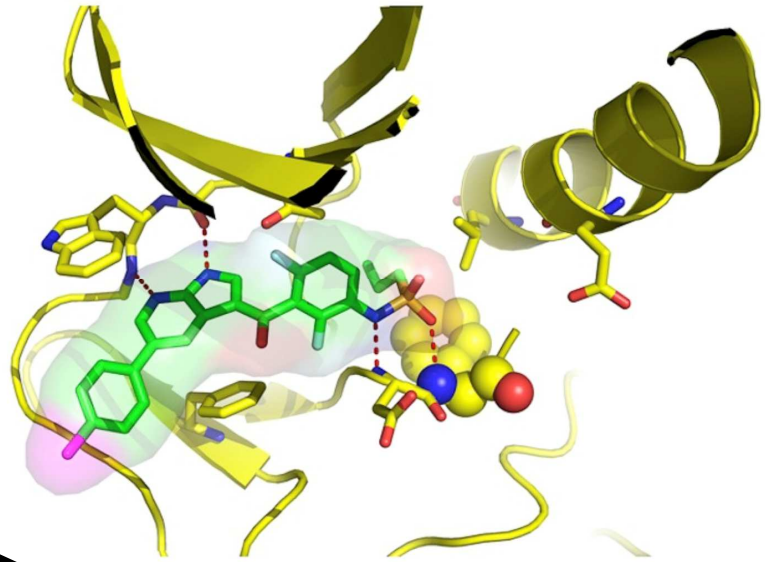
Age	No.	BRAF mutant
20-30	14	86%
31-40	30	80%
41-50	42	50%
51-60	58	41%
61-70	103	48%
>70	65	22%

Akbani et *al* (2016), *Cell*
G. Long et *al* (2011), ASCO abstract 8507

Mutation BRAF

mode d'action

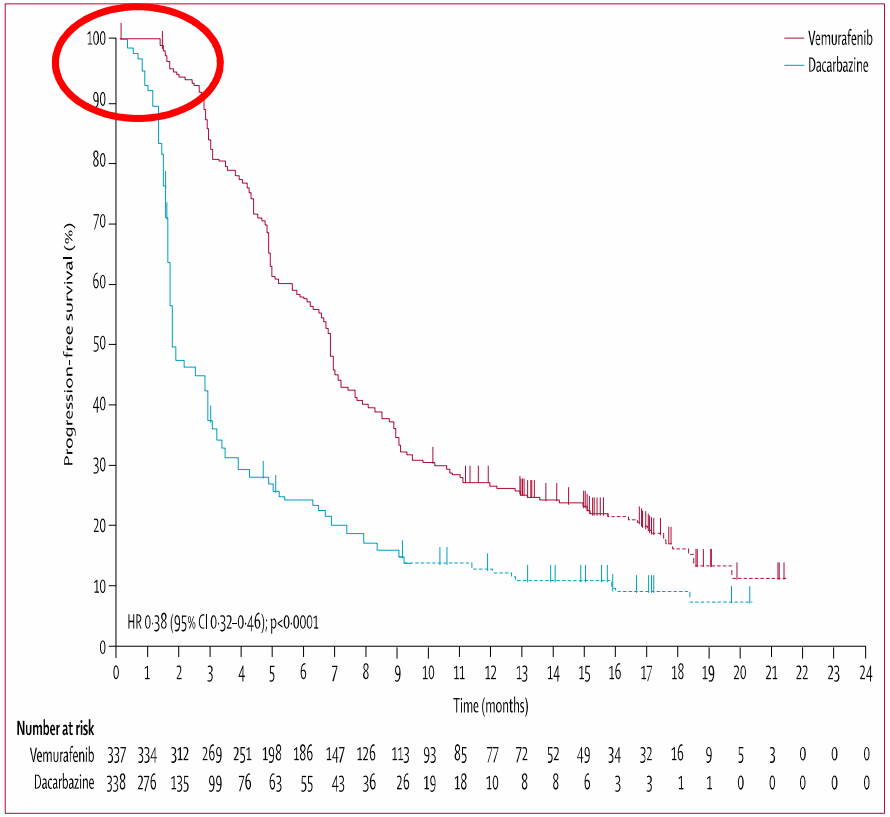


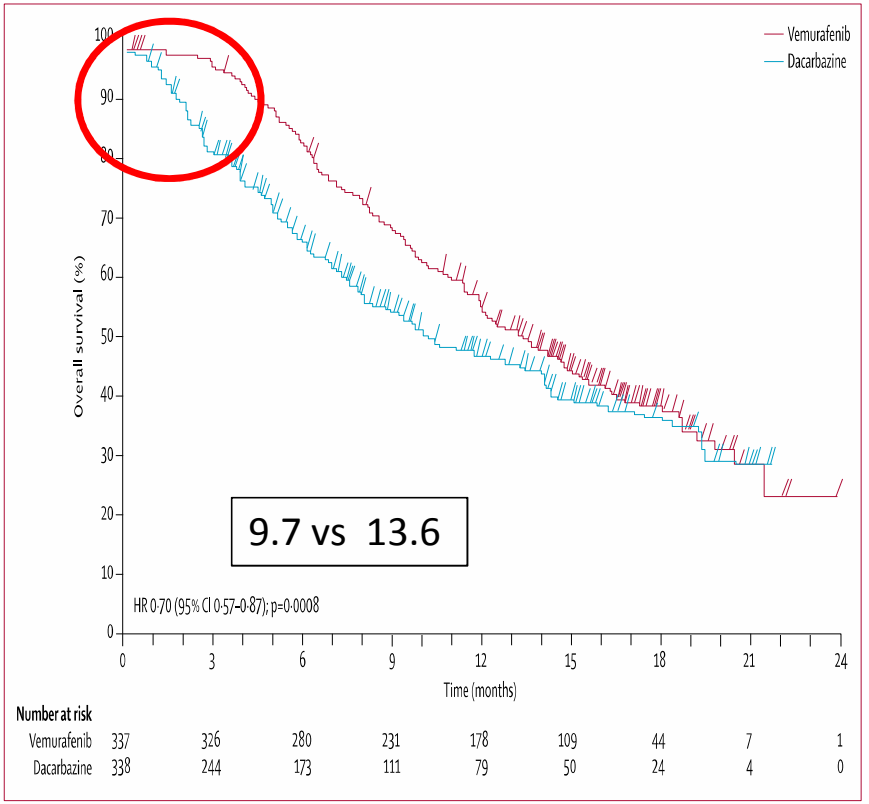


Sekulic et *al (2008)*, Mayo Clin Proc
Energy.gov/Plexxikon Inc

Inhibiteurs BRAF

Progression & Survie

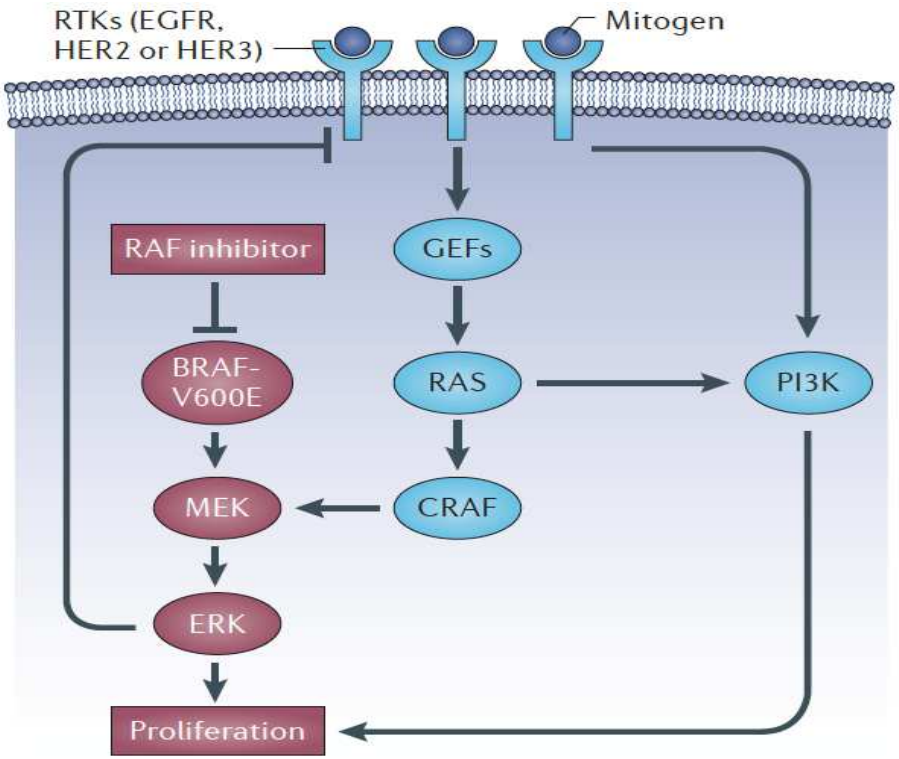


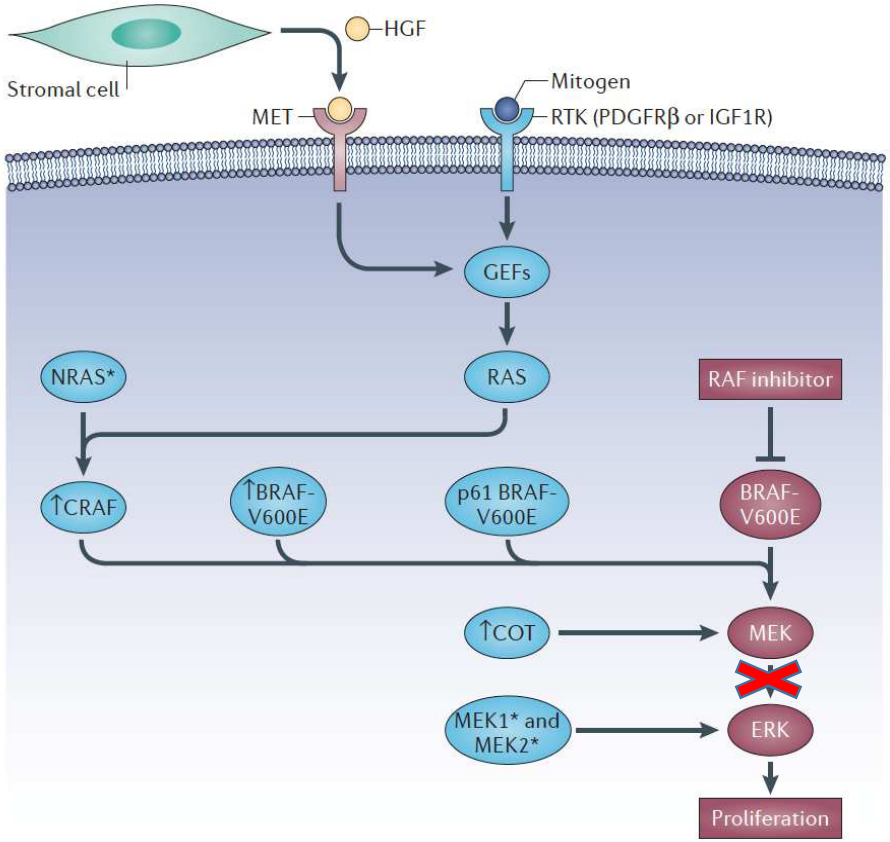


G.A. McArthur, et *al (2014), Lancet Oncol*

Inhibiteurs BRAF

Mode de résistance

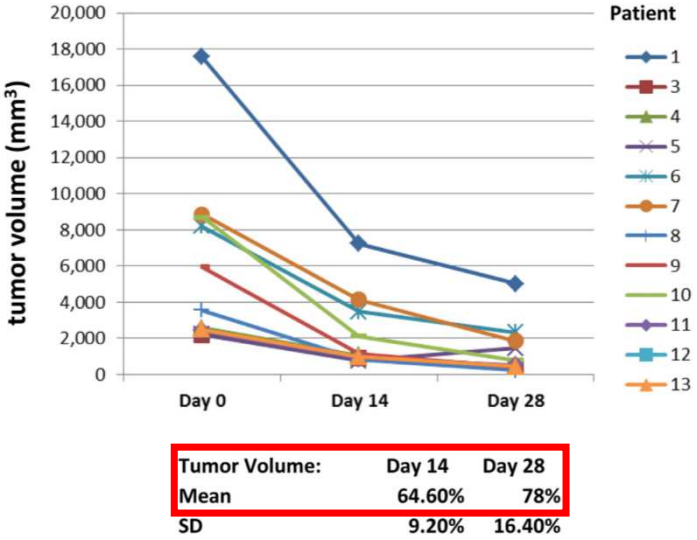




M. Holderfield et *al (2014), Nature Reviews Cancer*

Inhibiteurs BRAF/MEK

Effets



Tumor Volume:	Day 14	Day 28
Mean	64.60%	78%
SD	9.20%	16.40%

Figure 1. Tumor volumes decreased during therapy. Tumor volume at baseline, day 14, and days 28 to 30. Tumor volume is expressed in mm^3 with the exception of patient 7, where volume is expressed in $mm^3 \times 10^2$.

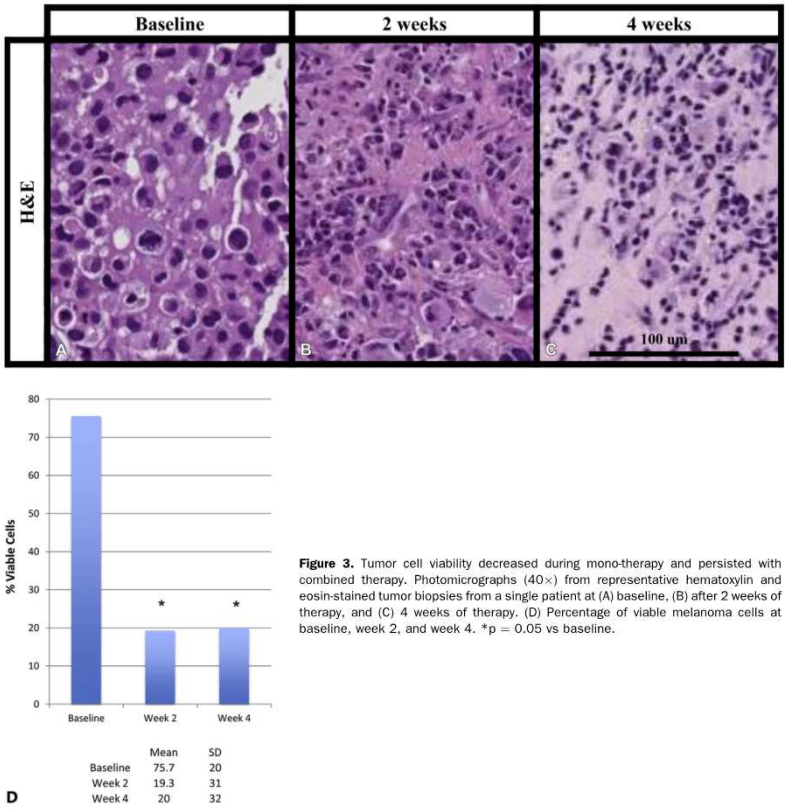
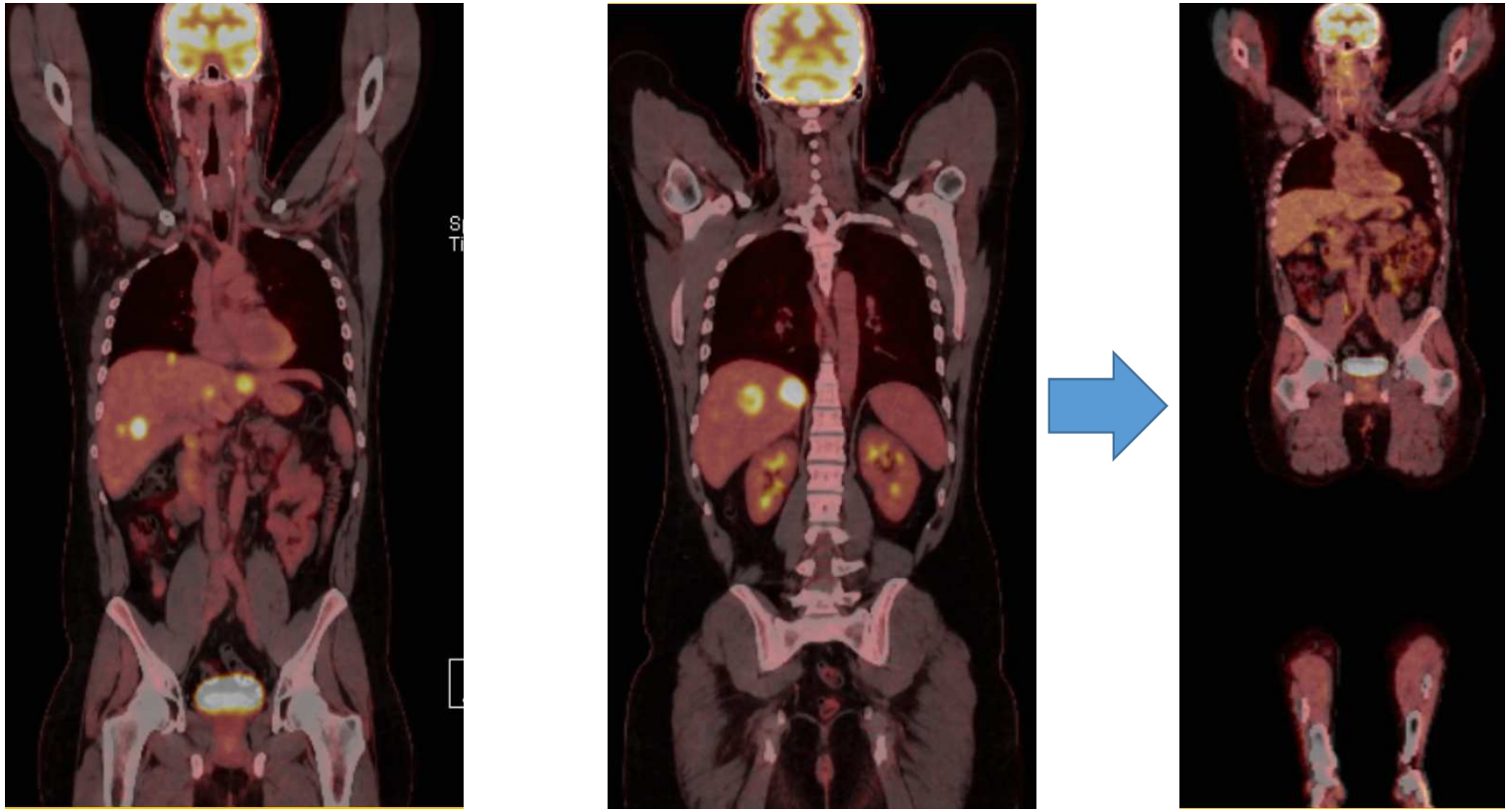


Figure 3. Tumor cell viability decreased during mono-therapy and persisted with combined therapy. Photomicrographs (40×) from representative hematoxylin and eosin-stained tumor biopsies from a single patient at (A) baseline, (B) after 2 weeks of therapy, and (C) 4 weeks of therapy. (D) Percentage of viable melanoma cells at baseline, week 2, and week 4. *p = 0.05 vs baseline.

A.S. Johnson, et *al* (2015), *J Am Coll Surg*

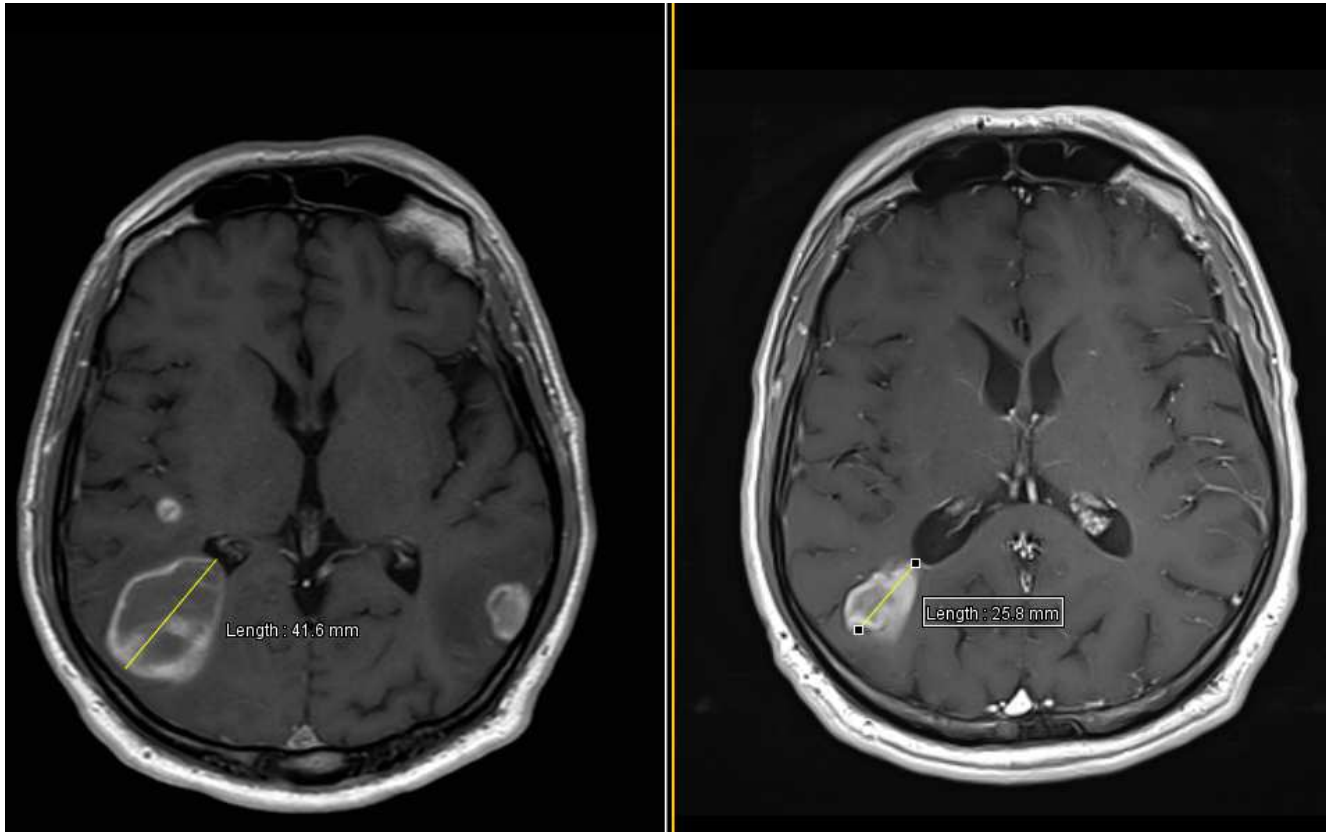
Inhibiteurs BRAF/MEK

Effets



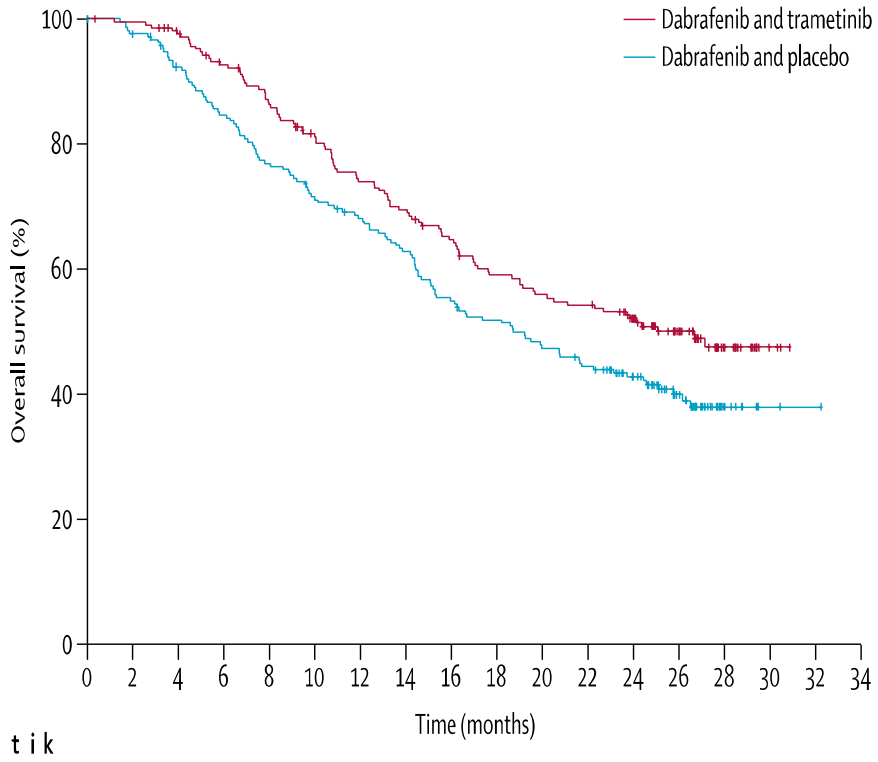
Inhibiteurs BRAF/MEK

Effets



Association BRAF et MEK inhibiteurs

Survie globale



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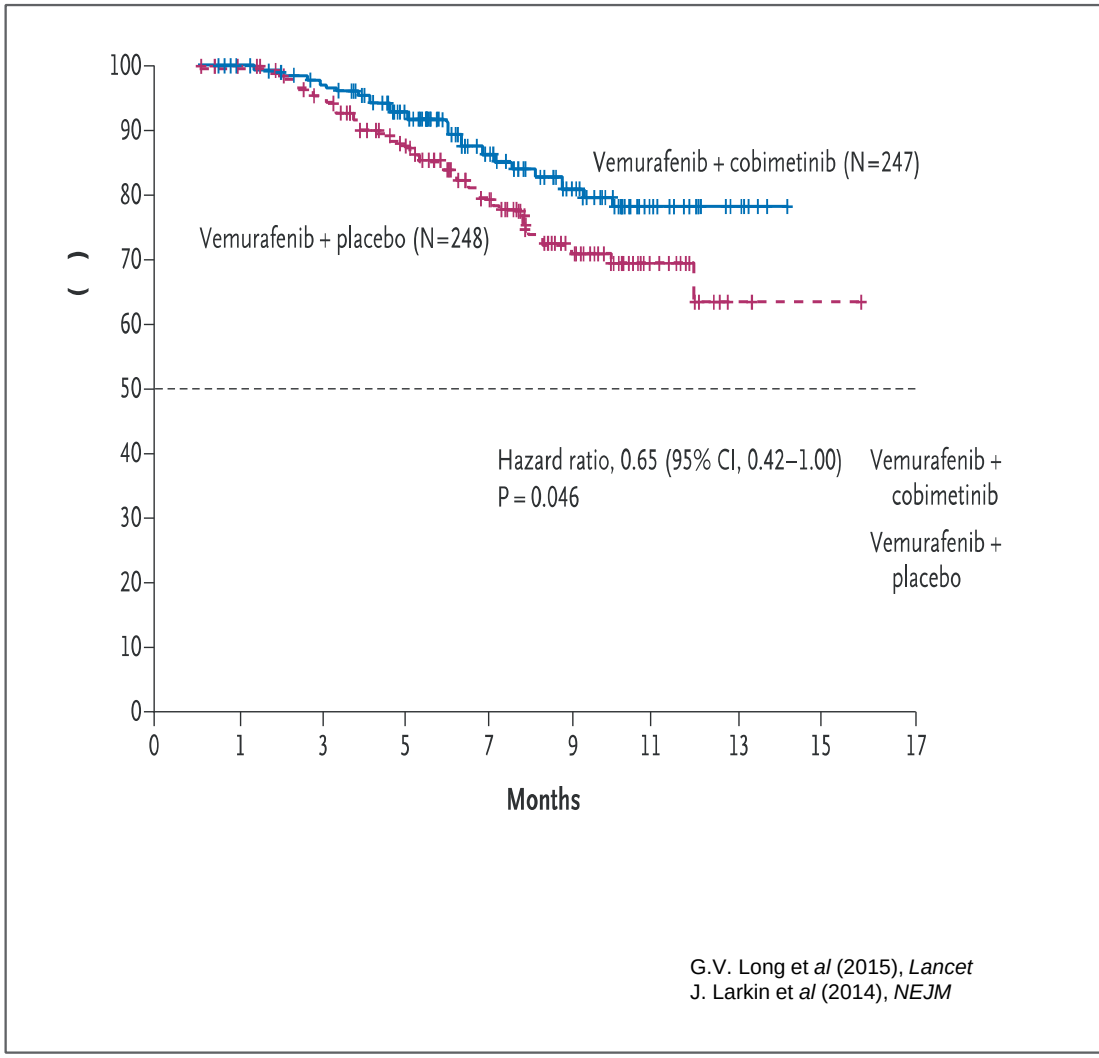

G.V. Long et *al* (2015), *Lancet*
J. Larkin et *al* (2014), *NEJM*

Dabrafenib / Trametinib

Effets secondaires

	Dabrafenib and trametinib (n=209)			Dabrafenib and placebo (n=211)		
	Any grade	Grade 2	Grade 3	Any grade	Grade 2	Grade 3
Events occurring in ≥10% of patients						
Any	181 (87%)	67 (32%)	66 (32%)	189 (90%)	69 (33%)	63 (30%)
Pyrexia*	108 (52%)	47 (22%)	15 (7%)	52 (25%)	21 (10%)	4 (2%)
Chills	58 (28%)	13 (6%)	0	29 (14%)	5 (2%)	1 (<1%)
Fatigue	56 (27%)	20 (10%)	4 (2%)	59 (28%)	21 (10%)	2 (<1%)
Rash	50 (24%)	7 (3%)	0	42 (20%)	5 (2%)	1 (<1%)
Nausea	41 (20%)	8 (4%%)	0	31 (15%)	3 (1%)	1 (<1%)
Headache	39 (19%)	6 (3%)	0	35 (17%)	11 (5%)	0
Diarrhoea	38 (18%)	6 (3%)	1 (<1%)	19 (9%)	3 (1%)	2 (1%)
Arthralgia	34 (16%)	6 (3%)	1 (<1%)	49 (23%)	17 (8%)	0
Vomiting	30 (14%)	5 (2%)	1 (<1%)	20 (9%)	1 (<1%)	1 (<1%)
Aspartate aminotransferase increased	22 (11%)	4 (2%)	6 (3%)	6 (3%)	1 (<1%)	1 (<1%)
Oedema peripheral	22 (11%)	3 (1%)	2 (1%)	4 (2%)	0	0
Alanine aminotransferase increased	20 (10%)	6 (3%)	4 (2%)	7 (3%)	2 (1%)	0
Dry skin	19 (9%)	0	0	29 (14%)	3 (1%)	0
Pruritus	15 (7%)	3 (1%)	0	23 (11%)	3 (1%)	0
Hyperkeratosis	13 (6%)	0	0	70 (33%)	13 (6%)	1 (<1%)
Hand-foot syndrome†	13 (6%)	3 (1%)	1 (<1%)	57 (27%)	17 (8%)	1 (<1%)
Alopecia	10 (5%)	0	0	55 (26%)	5 (2%)	0
Skin papilloma	3 (1%)	0	0	39 (18%)	6 (3%)	0
Adverse events of interest occurring in <10% of patients						
Dermatitis acneiform	17 (8%)	4 (2%)	0	7 (3%)	3 (1%)	0
Bleeding events‡	13 (6%)	0	1 (<1%)	9 (4%)	2 (1%)	1 (<1%)
Ejection fraction decreased	9 (4%)	6 (3%)	3 (1%)	7 (3%)	3 (1%)	4 (2%)
cuSCC§	6 (3%)	0	6 (3%)	20 (9%)	0	20 (9%)
Vision blurred	4 (2%)	1 (<1%)	0	4 (2%)	0	0
Non-cutaneous malignancies¶	2 (1%)	1 (<1%)	1 (<1%)	4 (2%)	0	4 (2%)
Chorioretinopathy	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
New primary melanoma	1 (<1%)	0	1 (<1%)	4 (2%)	2 (1%)	1 (<1%)

G.V. Long et *al* (2015), *Lancet*

Vemurafenib/Cobimetinib

Effets secondaires

Table 3. Common Adverse Events.*

Adverse Event	Vemurafenib and Placebo (N=239)				Vemurafenib and Cobimetinib (N=254)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)							
Any adverse event	21 (9)	70 (29)	117 (49)	22 (9)	19 (7)	66 (26)	125 (49)	34 (13)
Most common adverse events†								
Diarrhea	51 (21)	16 (7)	0	0	99 (39)	29 (11)	16 (6)	0
Nausea	43 (18)	12 (5)	2 (1)	0	75 (30)	22 (9)	2 (1)	0
Vomiting	21 (9)	6 (3)	2 (1)	0	41 (16)	10 (4)	3 (1)	0
Rash	46 (19)	27 (11)	12 (5)	0	55 (22)	29 (11)	13 (5)	2 (1)
Photosensitivity reaction	25 (10)	12 (5)	0	0	48 (19)	18 (7)	6 (2)	0
Hyperkeratosis	49 (21)	14 (6)	5 (2)	0	23 (9)	3 (1)	0	0
Fatigue	42 (18)	24 (10)	7 (3)	0	48 (19)	24 (9)	9 (4)	0
Pyrexia	43 (18)	10 (4)	0	0	49 (19)	13 (5)	4 (2)	0
Arthralgia	53 (22)	31 (13)	12 (5)	0	54 (21)	23 (9)	6 (2)	0
Alopecia	55 (23)	14 (6)	1 (<1)	0	33 (13)	1 (<1)	1 (<1)	0
Increased alanine aminotransferase	17 (7)	11 (5)	14 (6)	1 (<1)	16 (6)	15 (6)	28 (11)	1 (<1)
Increased aspartate aminotransferase	15 (6)	10 (4)	4 (2)	1 (<1)	17 (7)	18 (7)	21 (8)	0
Increased creatine kinase	6 (3)	1 (<1)	0	0	23 (9)	27 (11)	17 (7)	9 (4)
Selected adverse events								
Cutaneous squamous-cell carcinoma	0	0	27 (11)	0	0	1 (<1)	6 (2)	0
Keratoacanthoma	1 (<1)	1 (<1)	18 (8)	0	0	0	2 (1)	0
Chorioretinopathy	1 (<1)	0	0	0	17 (7)	12 (5)	1 (<1)	0
Retinal detachment	0	0	0	0	9 (4)	6 (2)	5 (2)	1 (<1)
Decreased ejection fraction	0	4 (2)	3 (1)	0	2 (1)	14 (6)	3 (1)	0
QT-interval prolongation	8 (3)	2 (1)	3 (1)	0	6 (2)	2 (1)	1 (<1)	0

J. Larkin et *al* (2014), *NEJM*

BRAF/MEK inhibiteurs

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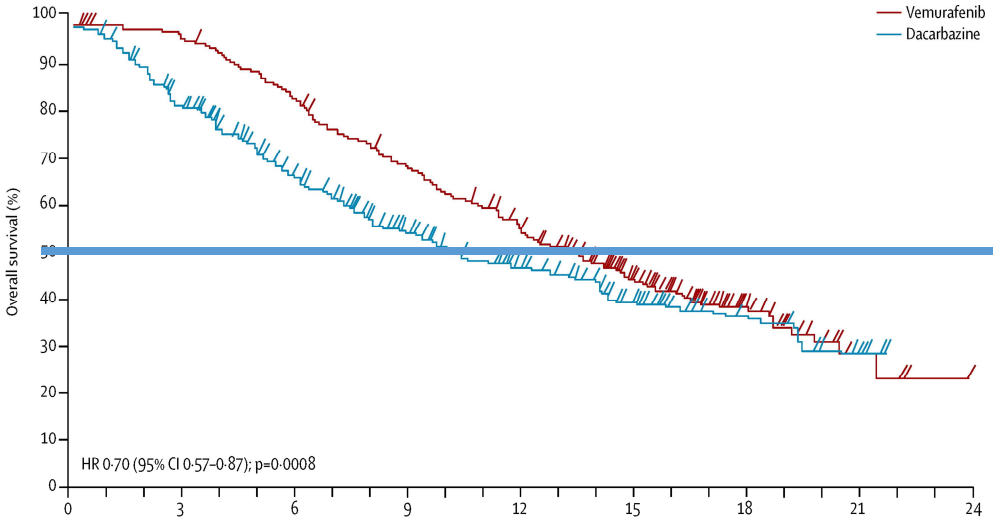
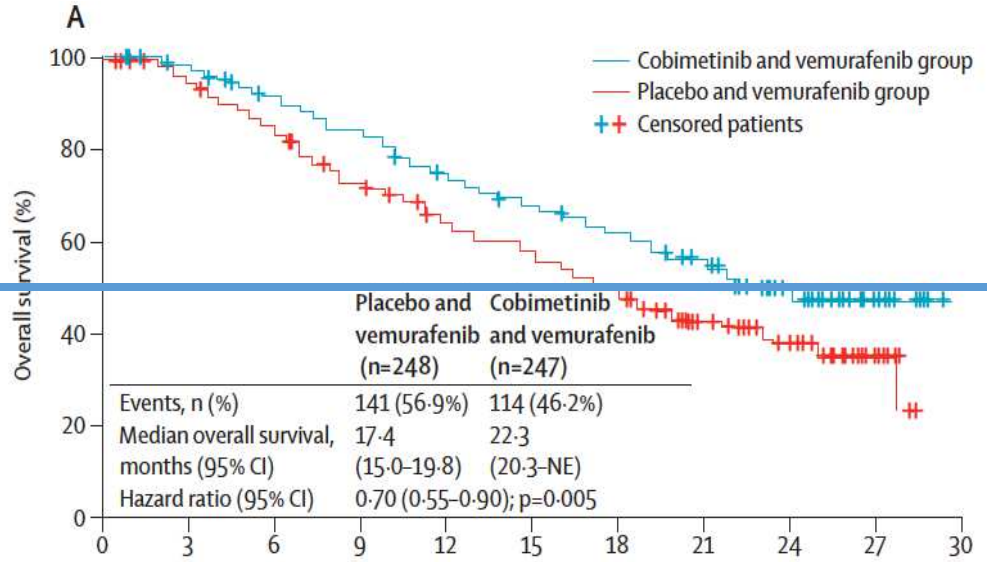




10 mois → 15 mois → 22 mois

P. Ascierto.*et al.* (2016) *Lancet Oncol*

Association TKI/immunothérapie

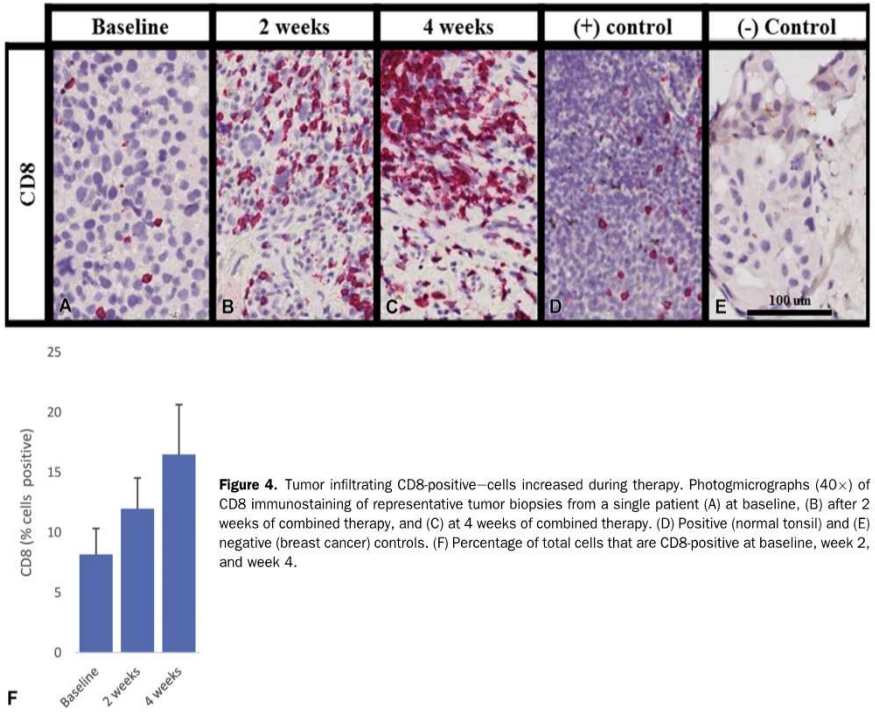
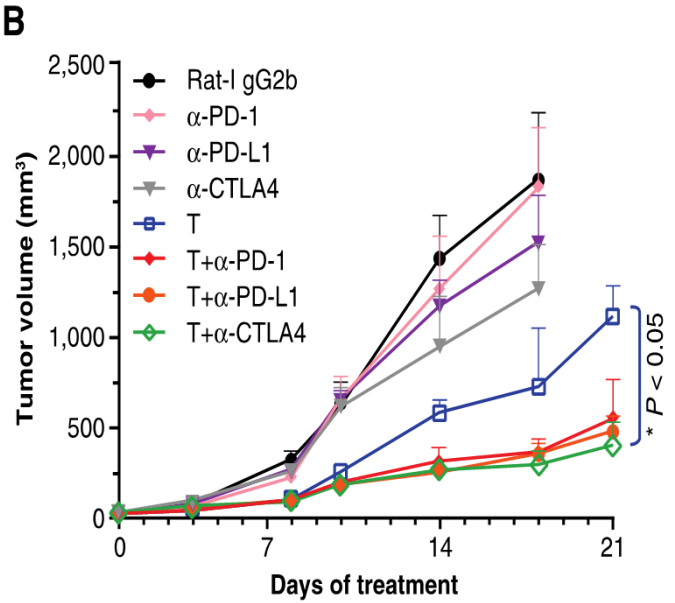


Figure 4. Tumor infiltrating CD8-positive–cells increased during therapy. Photogmicrographs (40×) of CD8 immunostaining of representative tumor biopsies from a single patient (A) at baseline, (B) after 2 weeks of combined therapy, and (C) at 4 weeks of combined therapy. (D) Positive (normal tonsil) and (E) negative (breast cancer) controls. (F) Percentage of total cells that are CD8-positive at baseline, week 2, and week 4.



A.S. Johnson, et *al* (2015) *J Am Coll Surg*
L. Liu et *al* (2015), *Clinical Cancer Research*

Messages

thérapie ciblée

- Thérapie ciblée seulement pour 50% des patients
- Taux de réponse élevé
- Action rapide
- Effet probablement moins long
- Toxicité limitée

Messages

immunothérapie

- Tous les patients peuvent bénéficier d'une immunothérapie
- Apparition d'un effet après 3 mois
- Durée de réponse longue
- Toxicités atypiques et parfois sévères
- En cas de suspicion de toxicité → avis oncologique
- Prise en charge rapide des toxicités