



**AEPU**  
ASSOCIATION D'ENSEIGNEMENT POST-UNIVERSITAIRE

# Le Mélanome: Les traitements immunologiques et les traitements ciblés

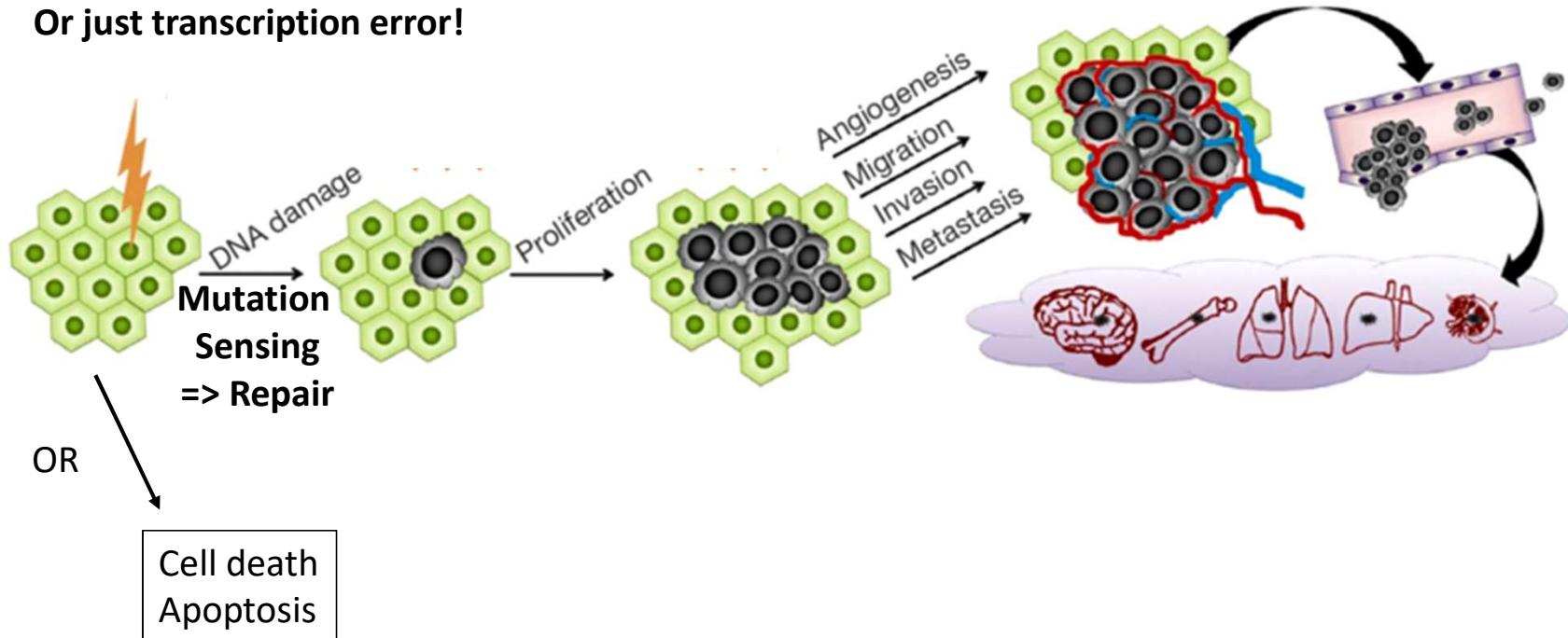
**Dr Guy Berchem MD, PhD**

Oncologue Médical

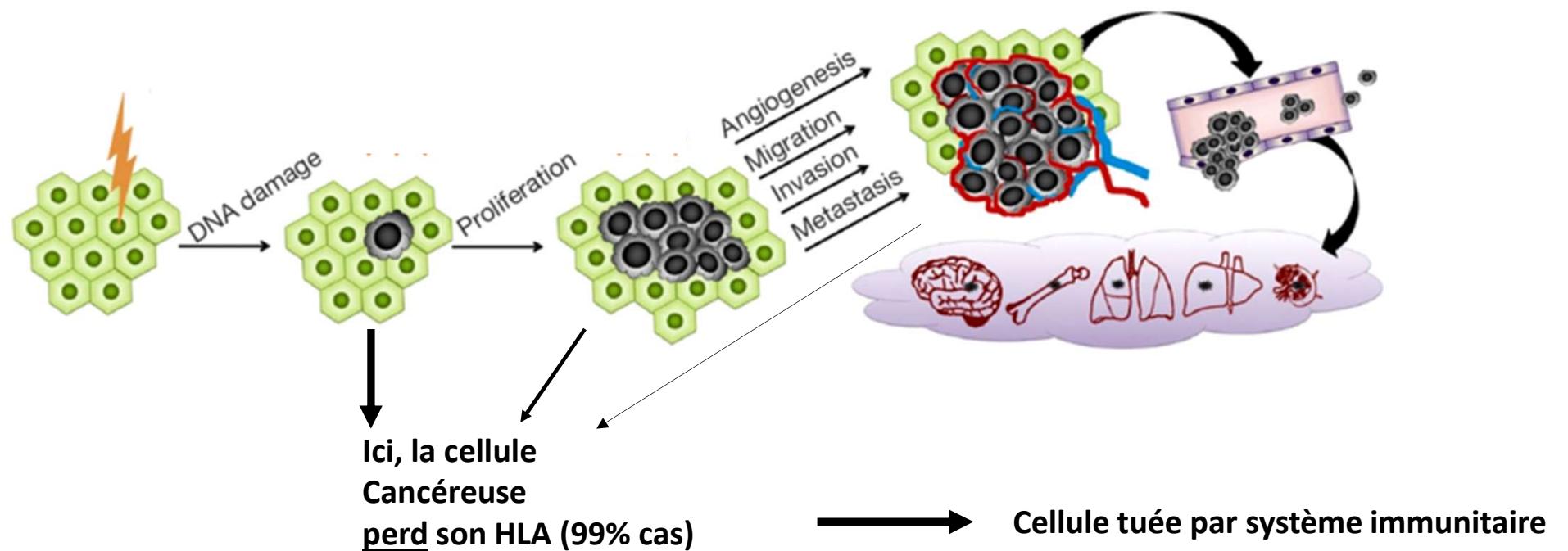
Centre Hospitalier de Luxembourg

# La cellule tumorale d'où vient elle?

Chemical attack  
Irradiation  
Or just transcription error!

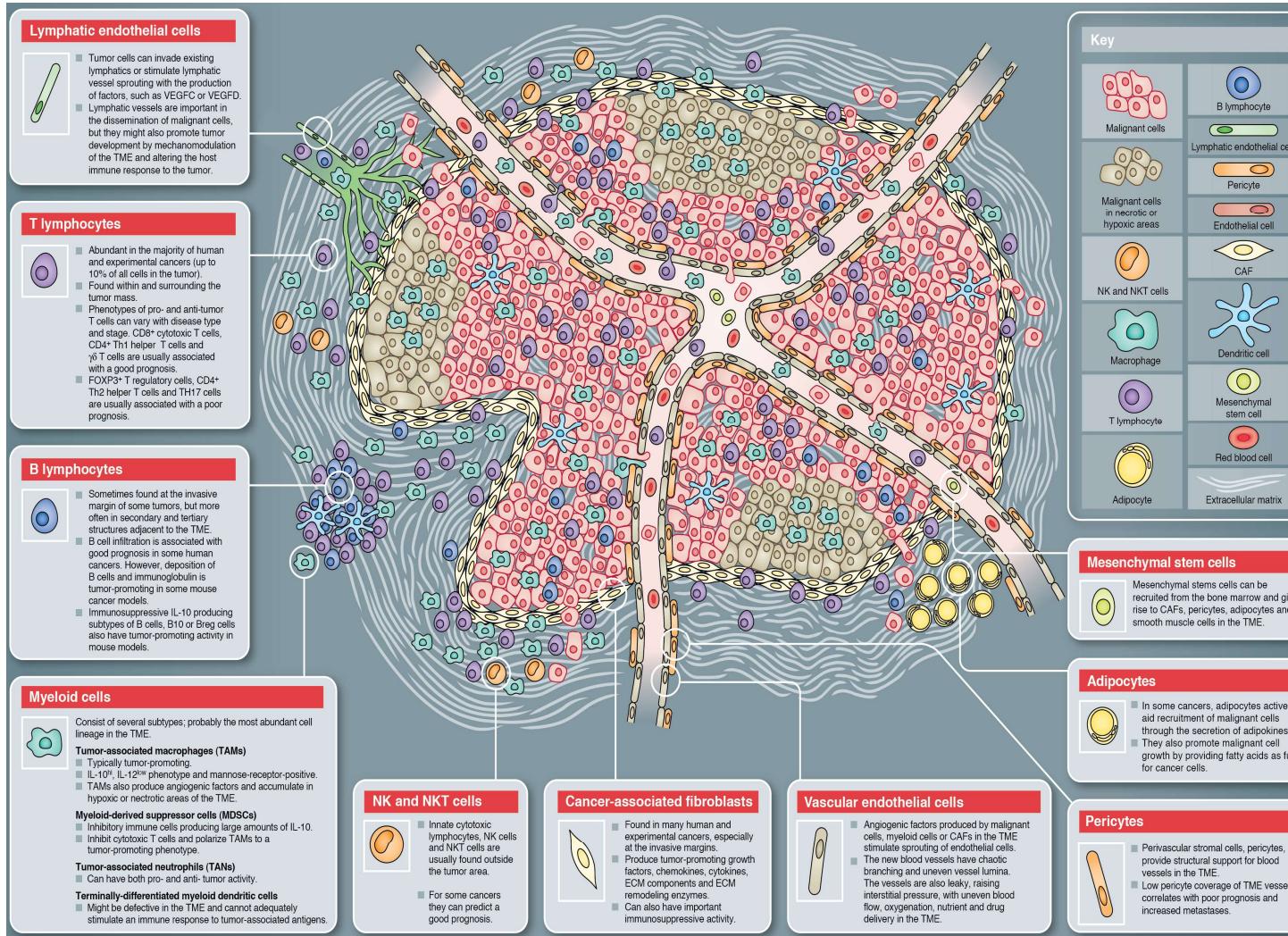


# Le cancer et le système immunitaire...



**Mais maintenant, c'est quoi le système immunitaire dans ce contexte?**

# La complexité du Microenvironnement tumoral



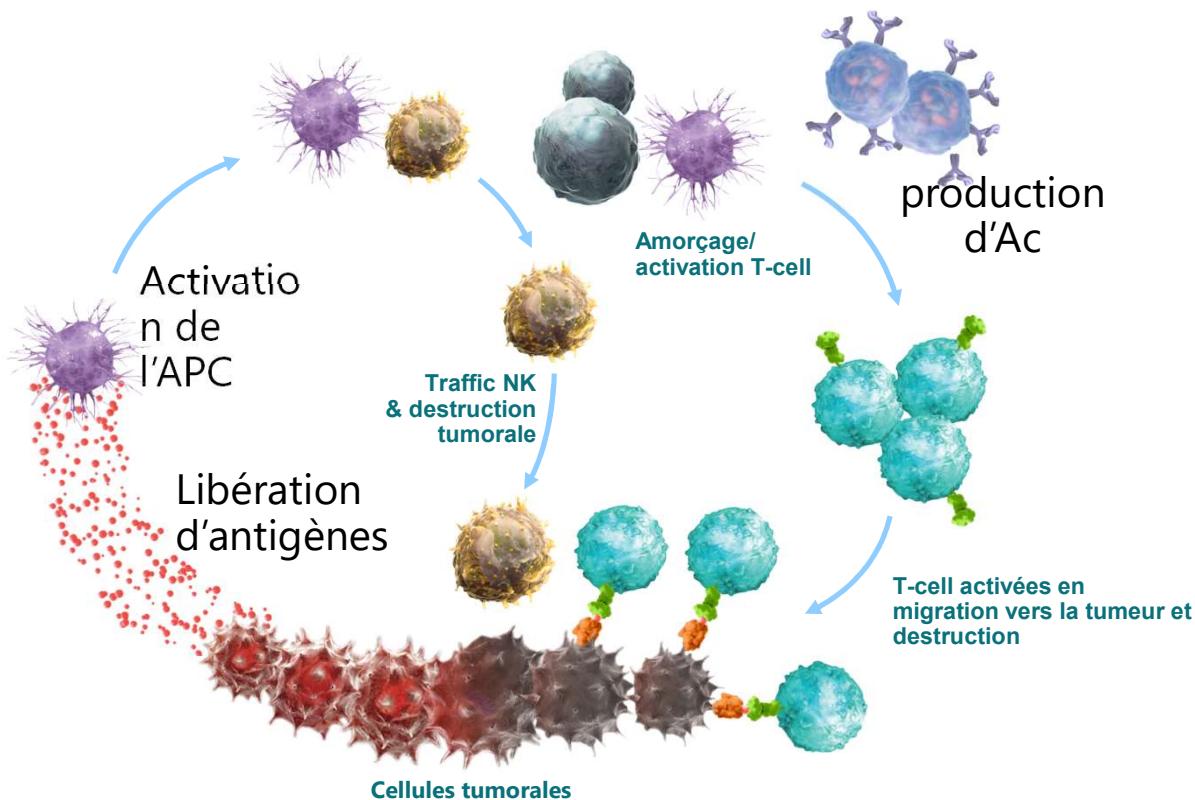
## Cellules qui créent un « climat » immunsupresseur

- T régulateurs (immunosupresseurs)**
- TAN (tumor associated neutrophils)**
- Macrophages (M2, très immunsuppressifs)**
- MDSCs (myeloid derived supp. cells, très immunsuppressifs)**
- TAMs (tumor associated macrophages)**
- CAFs (cancer associated fibroblasts)**
- B régulateurs (autoimmunité)**

Comment toutes ces cellules nous défendent elles contre les infections et le cancer?

## La surveillance immunitaire

Identification et élimination des cellules cancéreuses par le système immunitaire<sup>1-5</sup>



APC, antigen-presenting cell; NK, natural killer.

1. Abbas AK et al. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders;2012.

2. Mellman I et al. *Nature*. 2011;480:480-489.

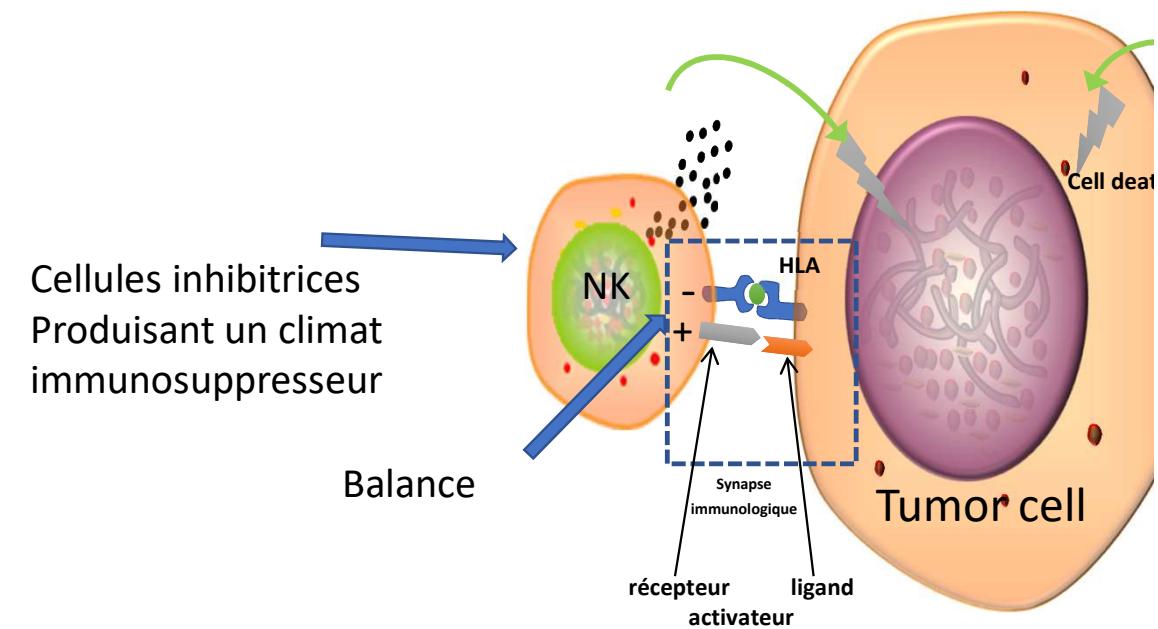
3. Boudreau JE et al. *Mol Ther*. 2011;19(5):841-853.

4. Janeway CA Jr et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001.

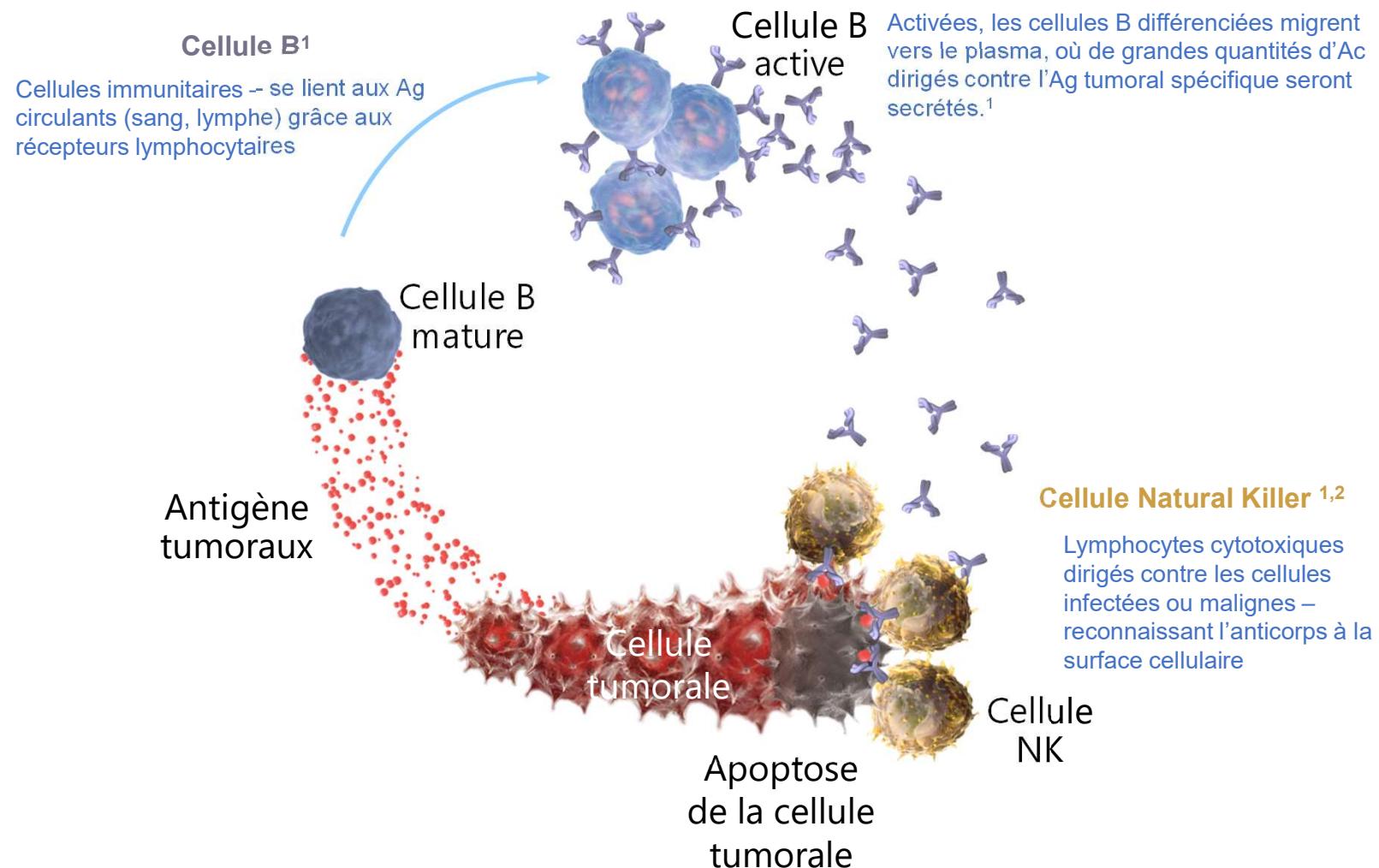
5. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264.

# Coopération entre le système immunitaire inné et adaptatif dans le contrôle des cellules tumorales

## Système immunitaire inné



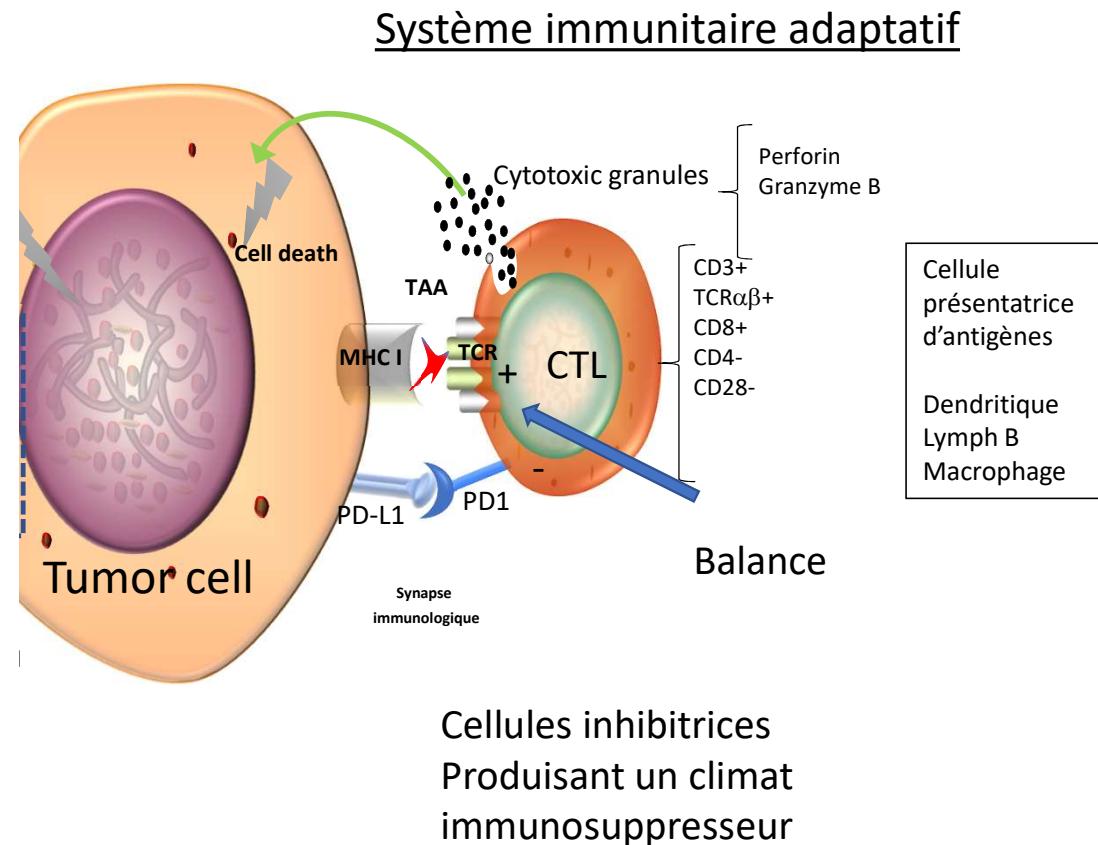
# Cytotoxicité transmise par les lymphocytes B



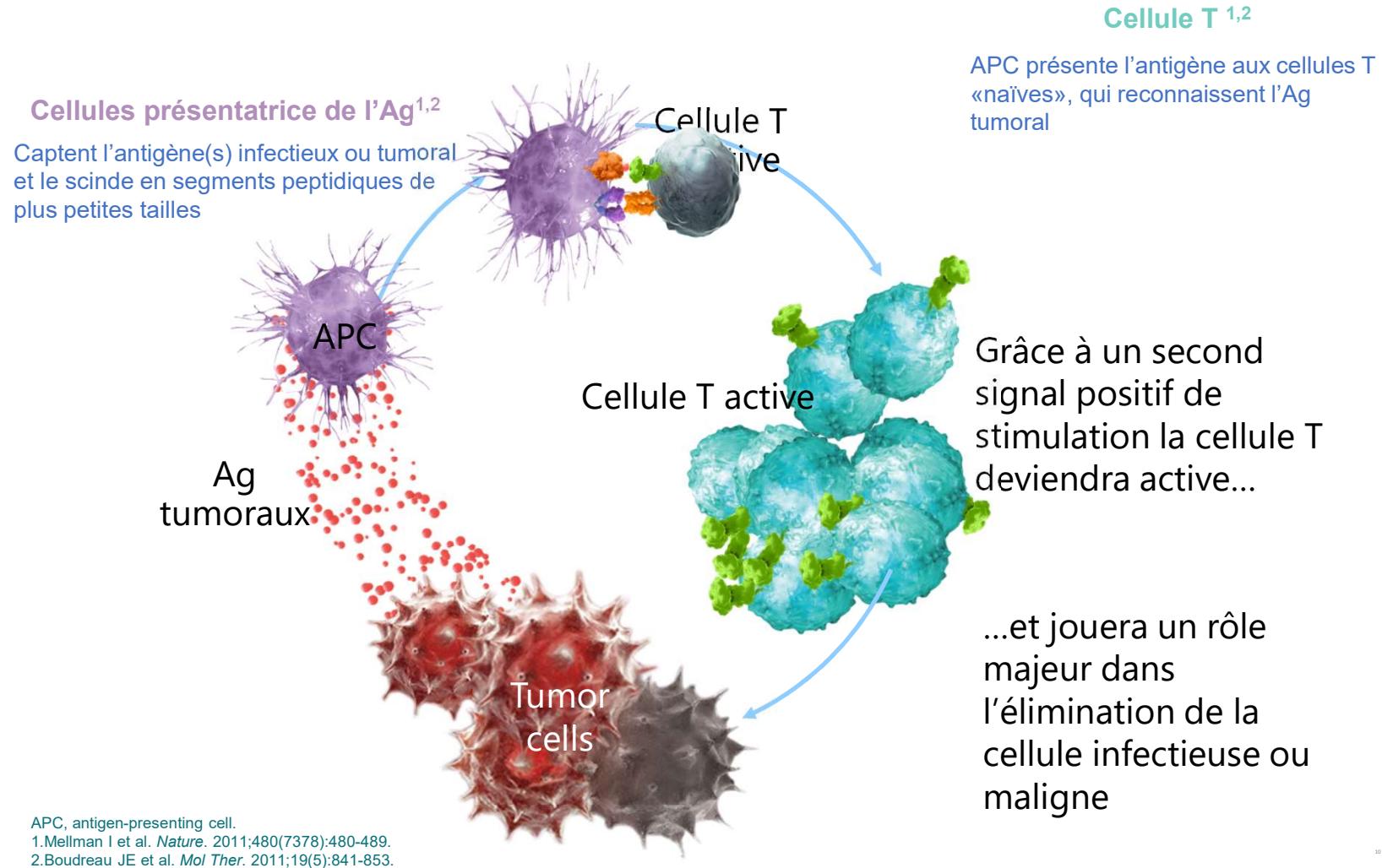
1.Janeway CA Jr et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001.

2.Vesely MD et al. *Annu Rev Immunol*. 2011;29:235-271.

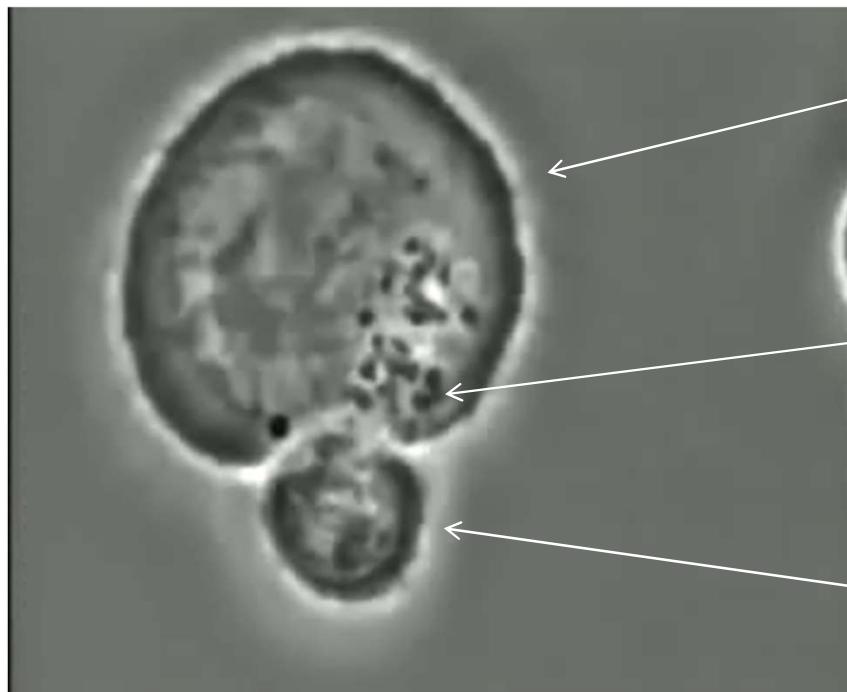
# Coopération entre le système immunitaire inné et adaptatif dans le contrôle des cellules tumorales



# Cytotoxicité transmise par les lymphocytes T



# Cytotoxicité T (CTL)



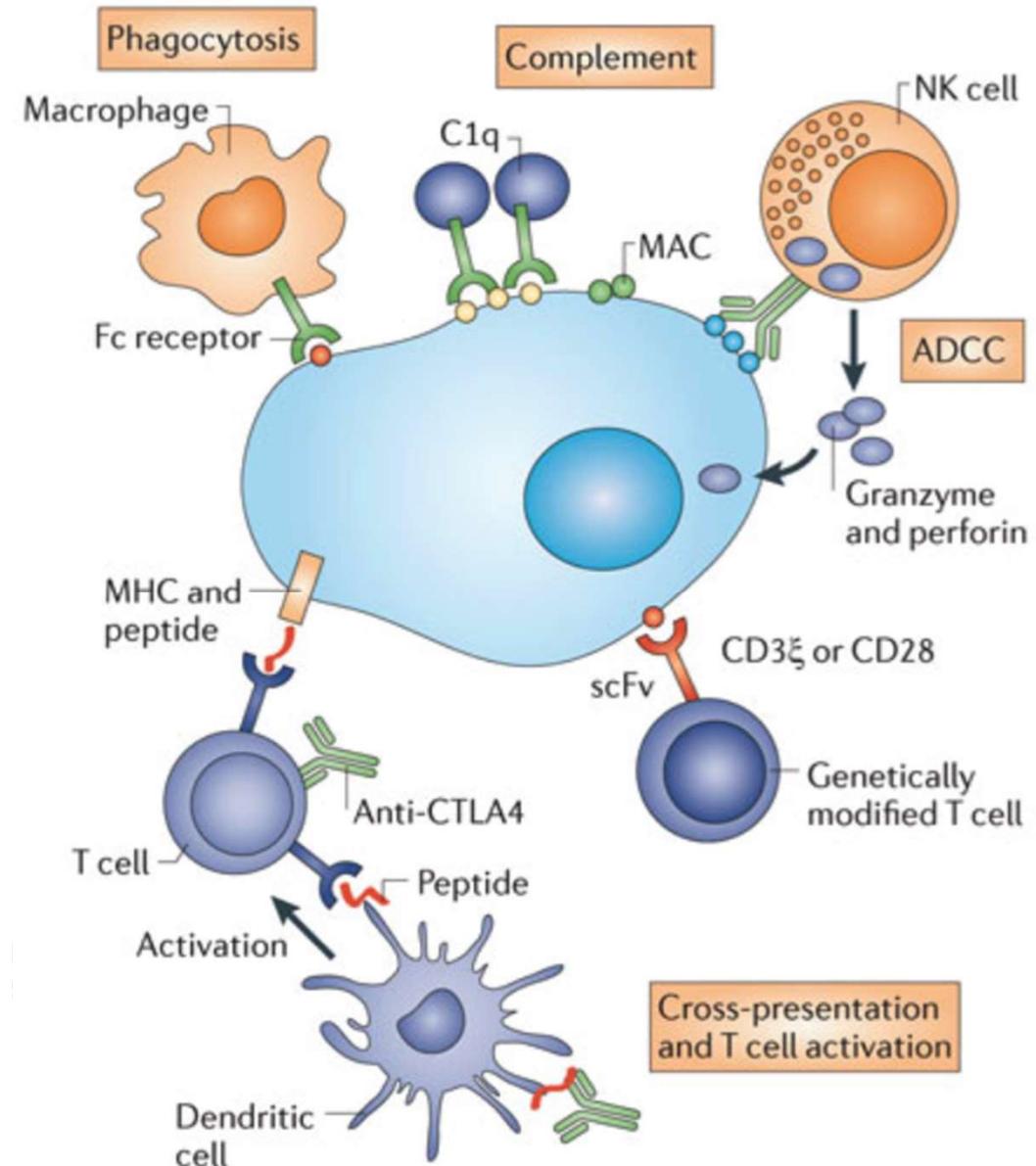
Cellule tumorale

Granule cytotoxique  
avec Perforine et  
Granzyme B

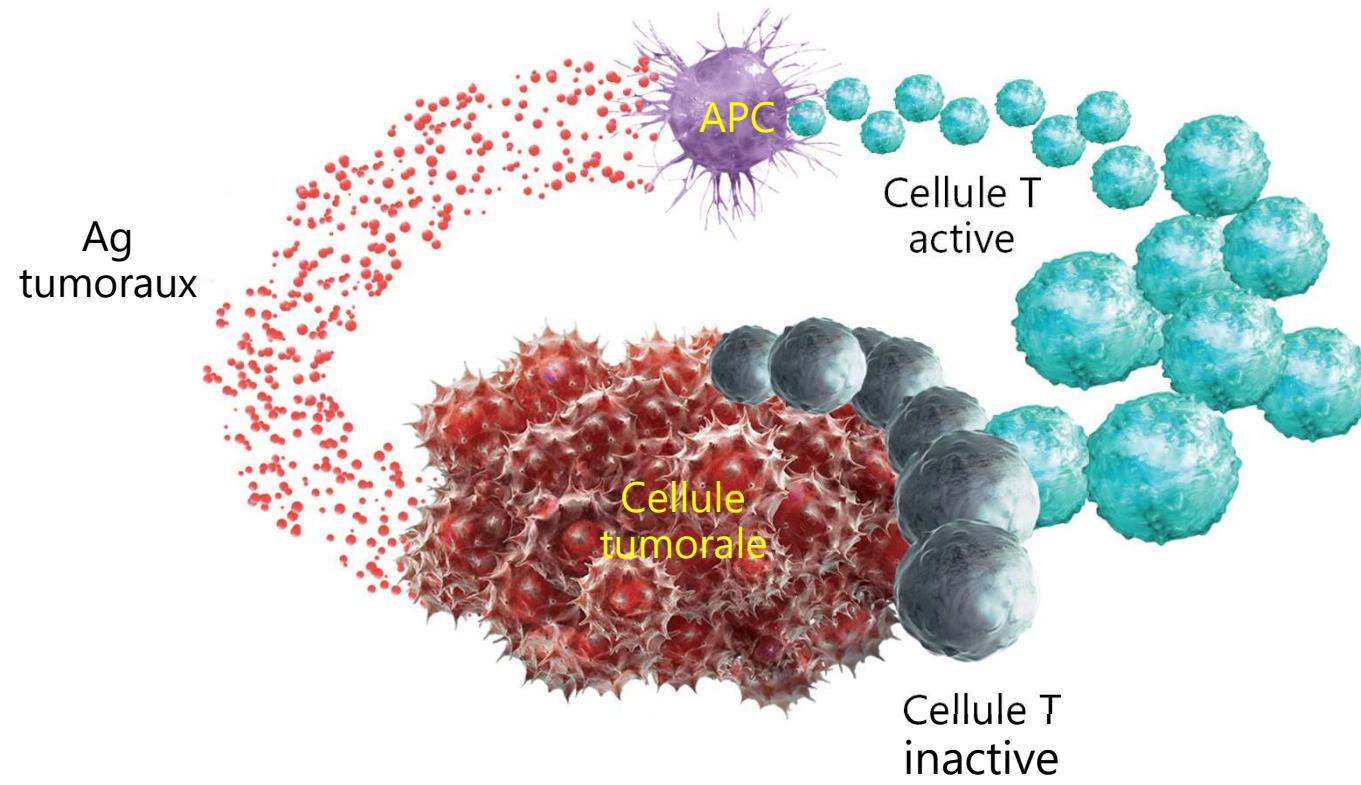
Cellule T

# En résumé:

Moyens du système immunitaire de tuer les cellules tumorales



Mais en réalité cela ne fonctionne plus bien quand la tumeur est installée.



Pourquoi?

APC, antigen-presenting cell.

1.Gajewski TF et al. *Nat Immunol.* 2013;14(10):1014-1022.

2.Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252-264.

3.Vesely MD et al. *Annu Rev Immunol.* 2011;29:235-271.

## Autophagy makes tumor cells resistant to NK cell killing

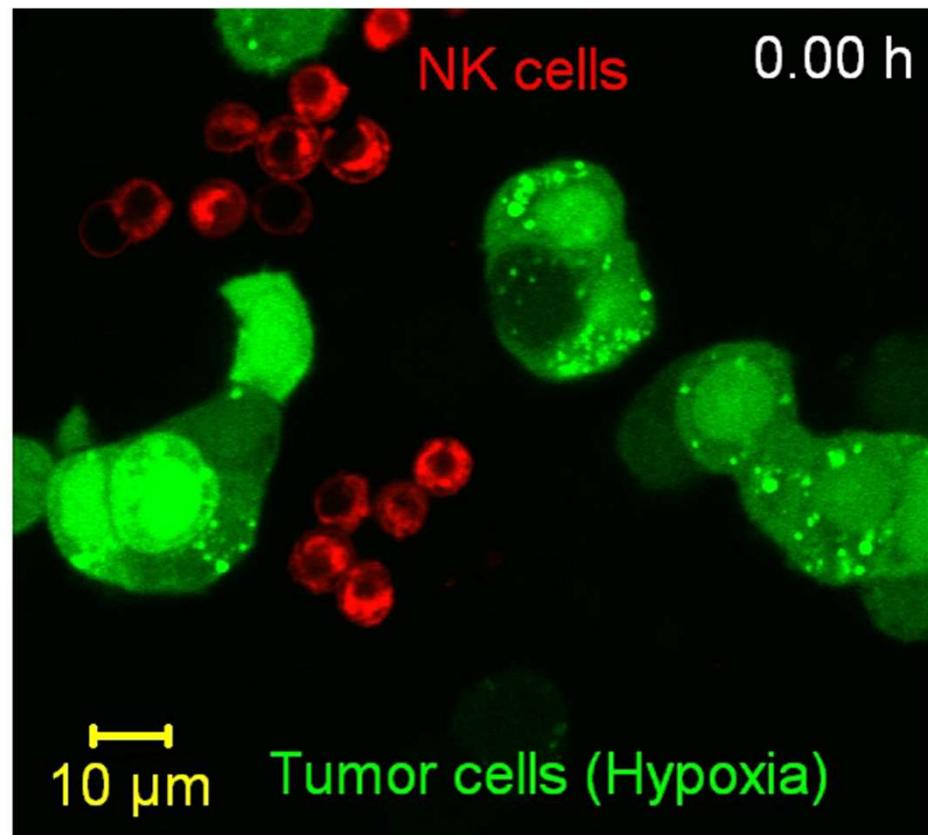
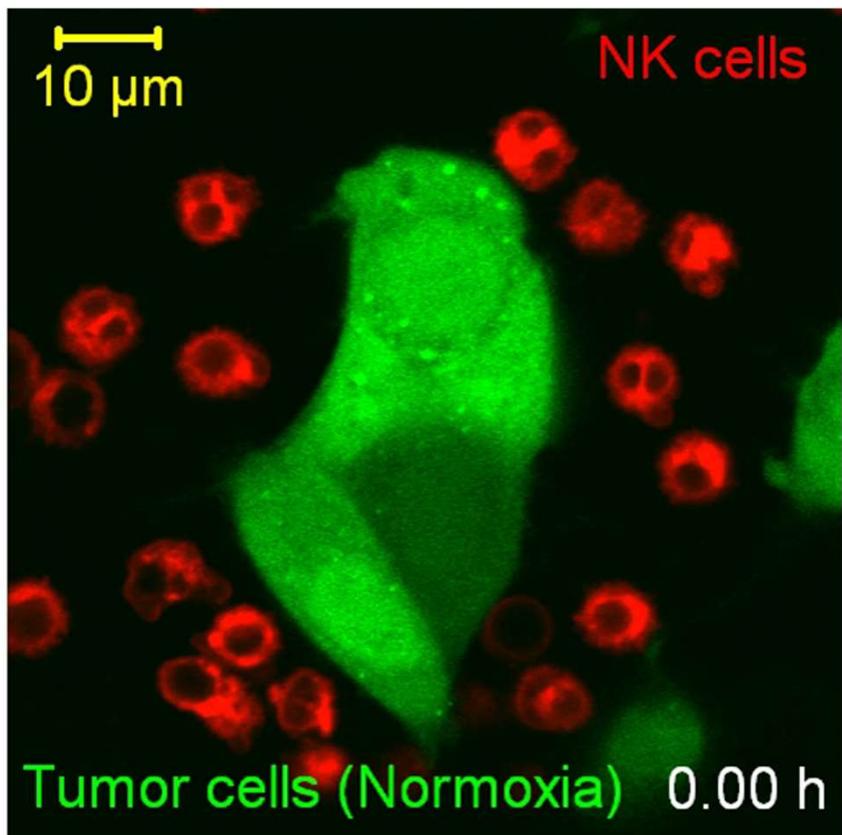
NK cells (PKH26 red)

LC3-GFP

MCF-7

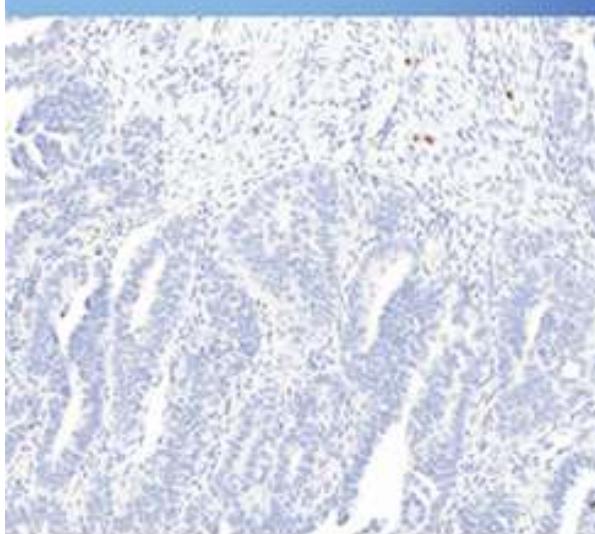
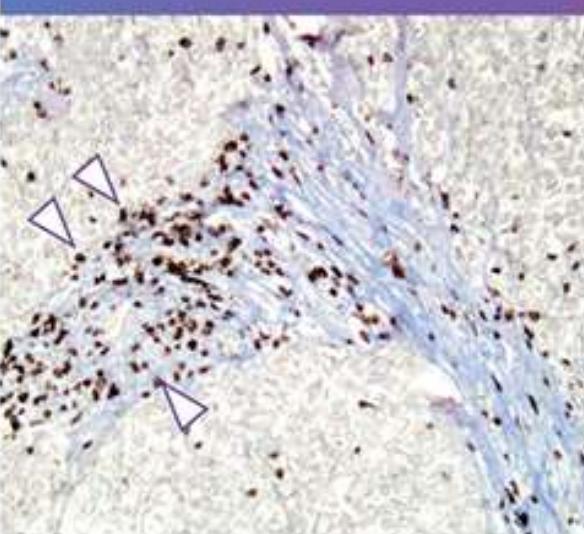
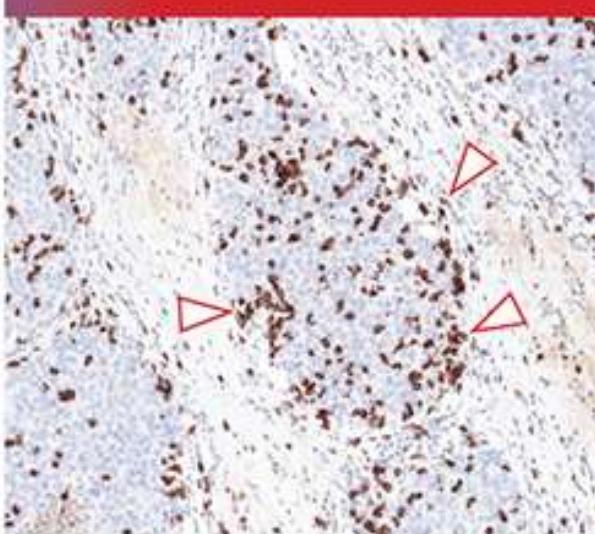
Normoxia

Hypoxia



Baginska, Berchem et al Granzyme B degradation by autophagy decreases tumor cell susceptibility to natural killer-mediated lysis under hypoxia. PNAS 2013

# Trois types d'environnements tumoraux

IMMUNE DESERT	IMMUNE EXCLUDED	INFLAMED
PATTERN OF IMMUNE ACTIVITY		
T cells are absent from the tumour and the tumour microenvironment	T cells have accumulated, but are not efficiently infiltrating the tumour microenvironment*	T cells have infiltrated, but are not functioning properly†
		

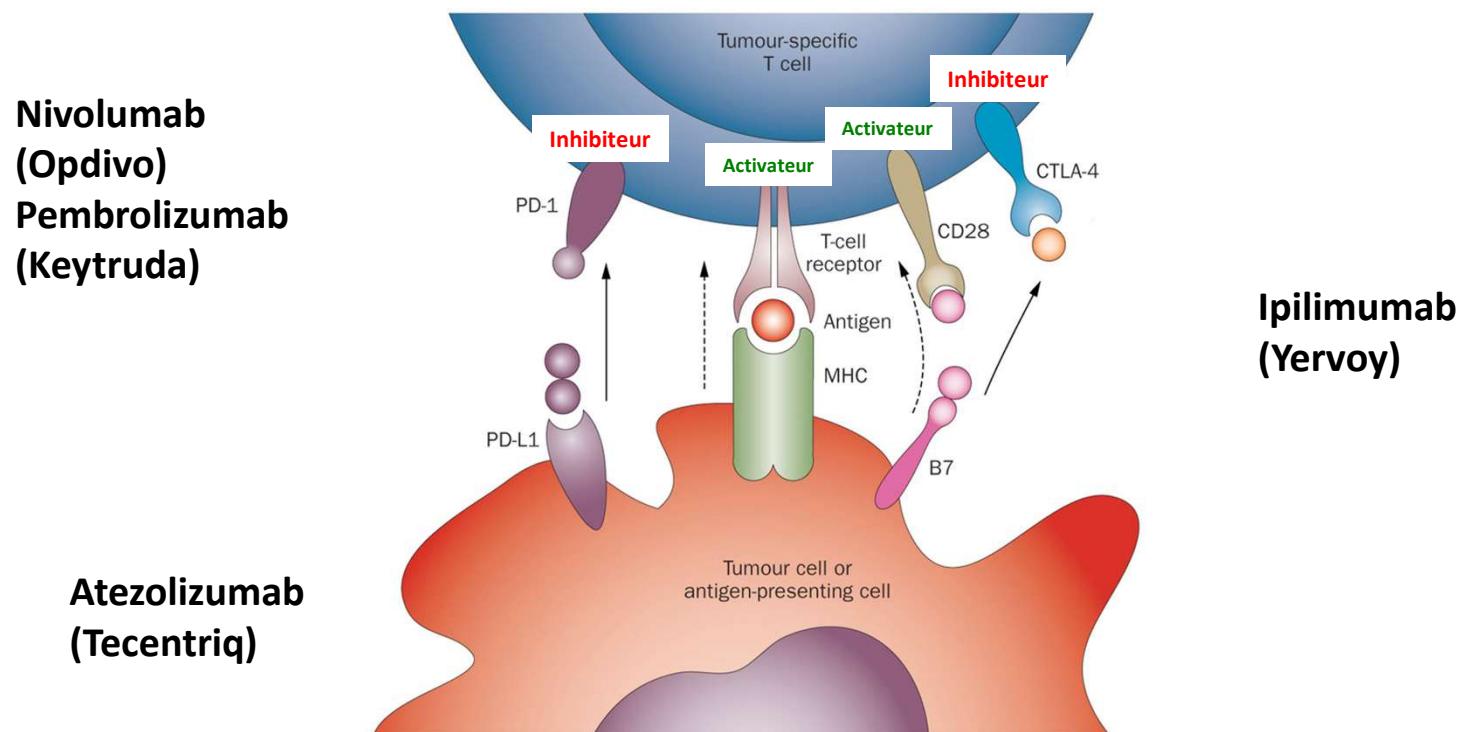
# Comment fonctionnent les nouveaux inhibiteurs des Checkpoint?

Ipilimumab (Yervoy)  
Nivolumab (Opdivo),  
Pembrolizumab (Keytruda)  
Atezolizumab (Tecentriq)

...

Pour que les lymphocytes n'attaquent pas les cellules normales il faut un frein....

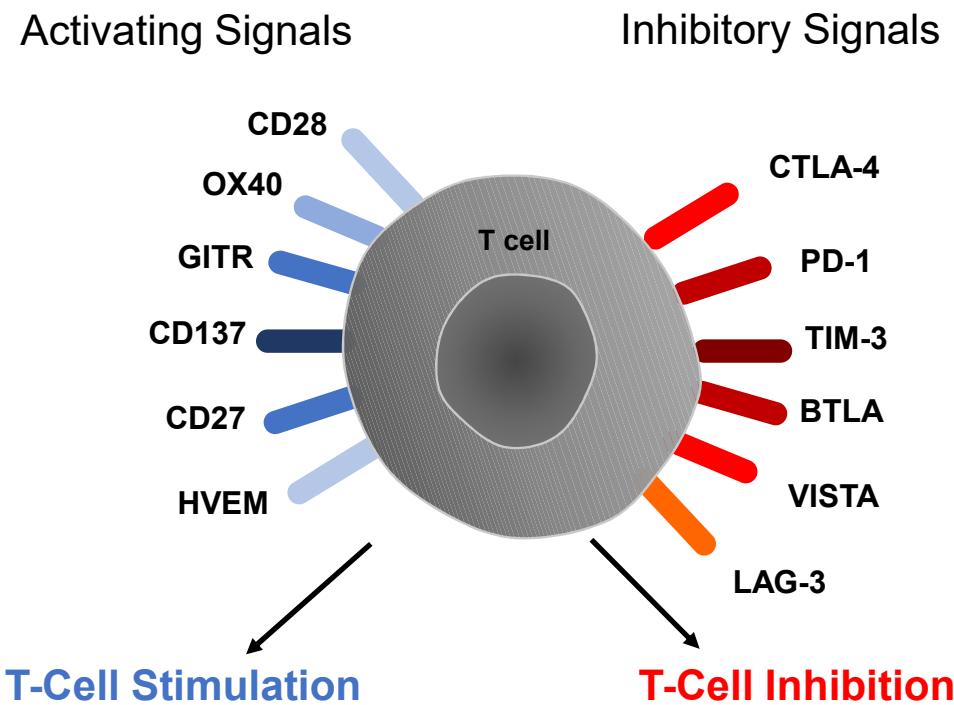
# C'est quoi un Checkpoint?



# Prix Nobel de Médecine en 2018



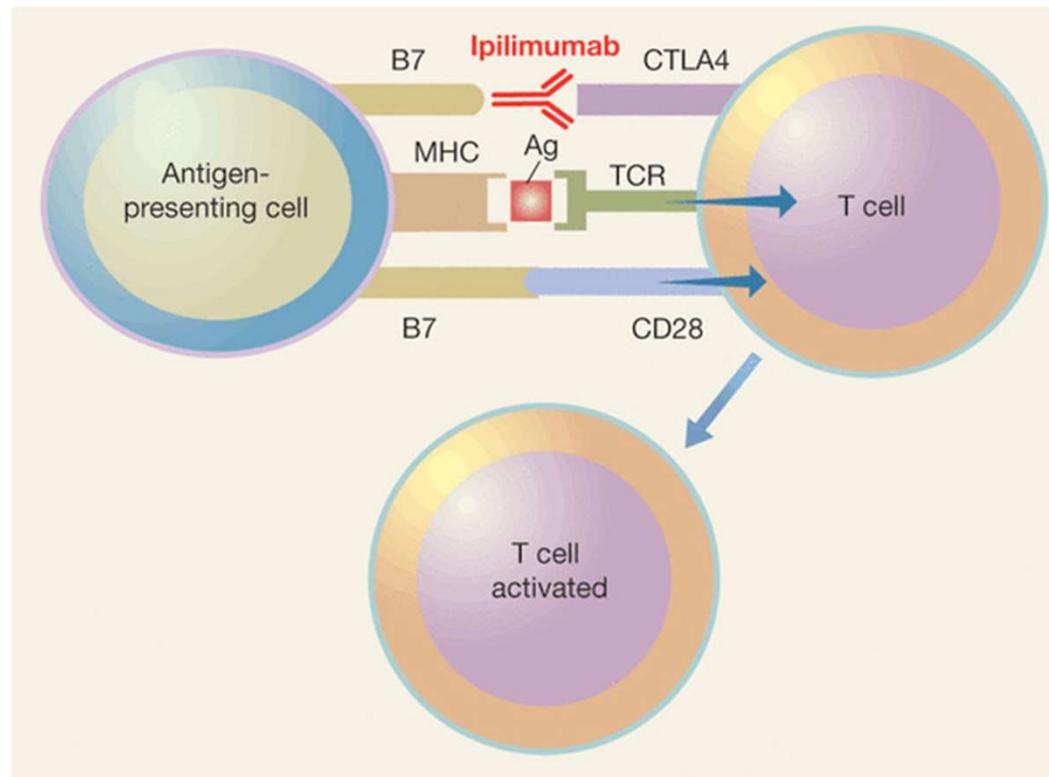
# Other targets to Accelerate or Brake



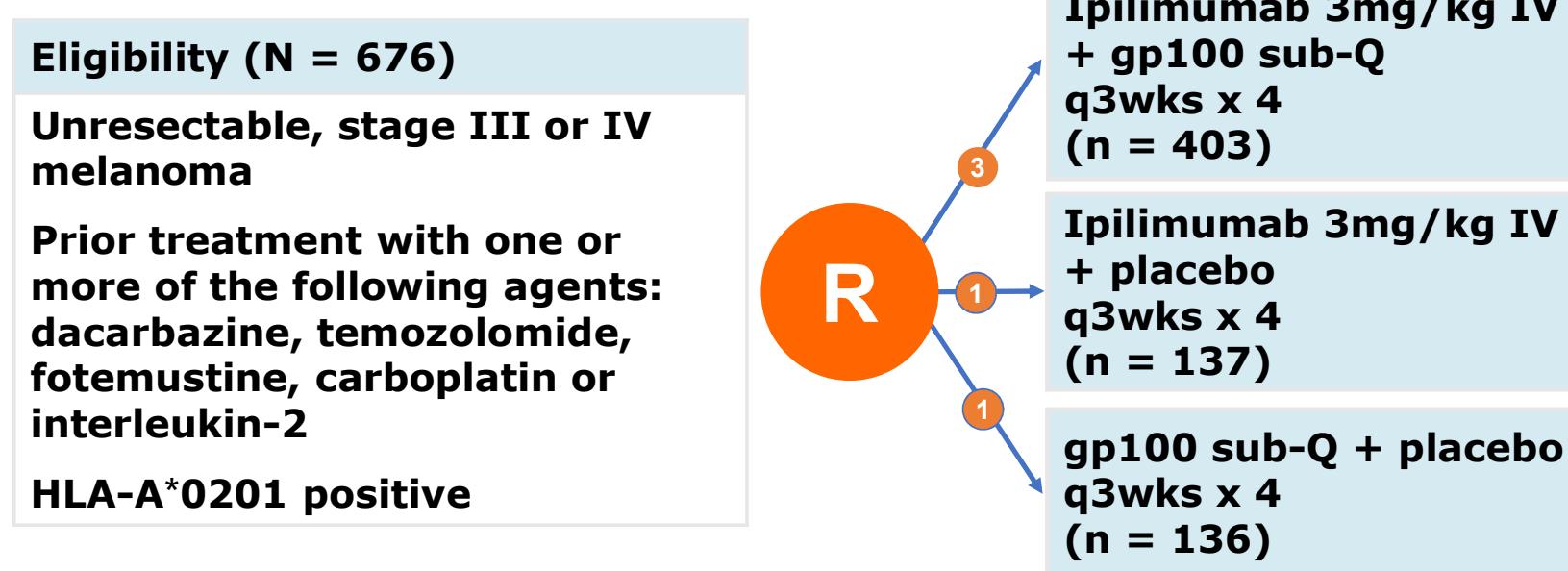
Mellman I, et al. Nature. 2011;480:480-489.

# Ipilimumab (Yervoy) anti CTLA4

- Premier anticorps ciblant une molécule du checkpoint (CTLA4)
- Etudié dans le mélanome



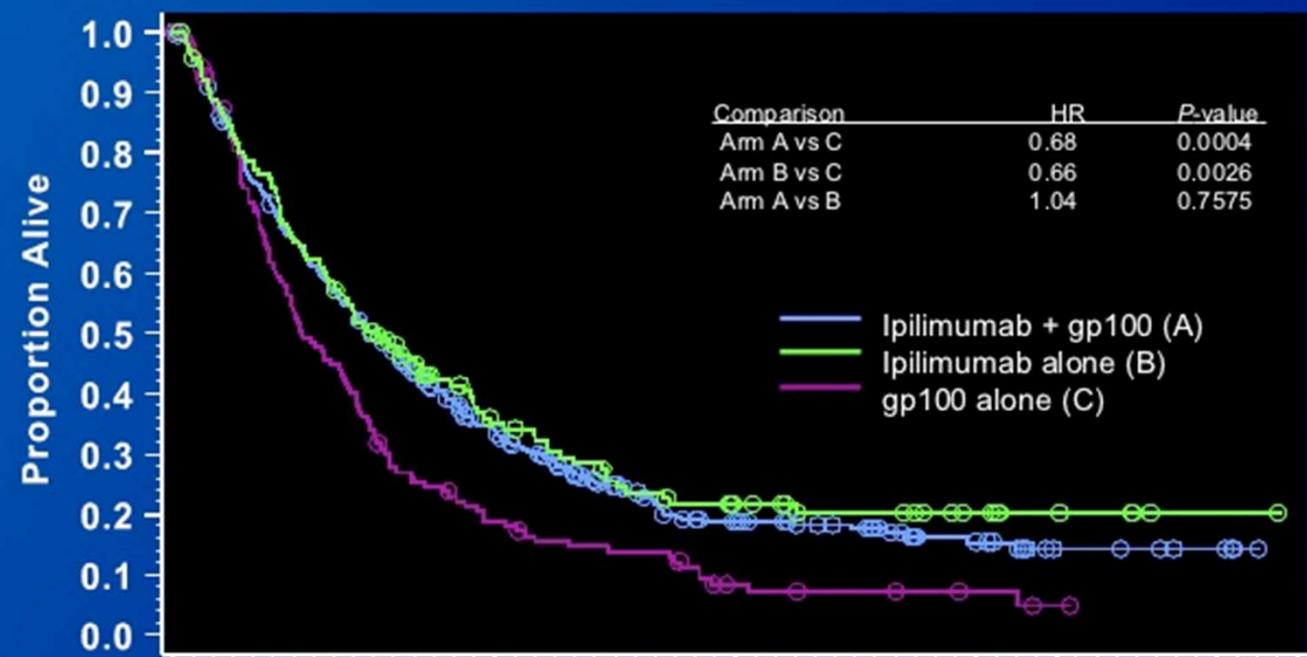
# Ipilimumab (anti CTLA4)



*Patients with stable disease for 3 months after week 12, or a confirmed partial or complete response were offered reinduction with assigned treatment regimen upon disease progression.*

O'Day S et al. Proc ASCO 2010;Abstract 4; Hodi FS et al. Proc ASCO 2010; Abstract 8509; Hodi FS et al. N Engl J Med 2010;[Epub ahead of print].

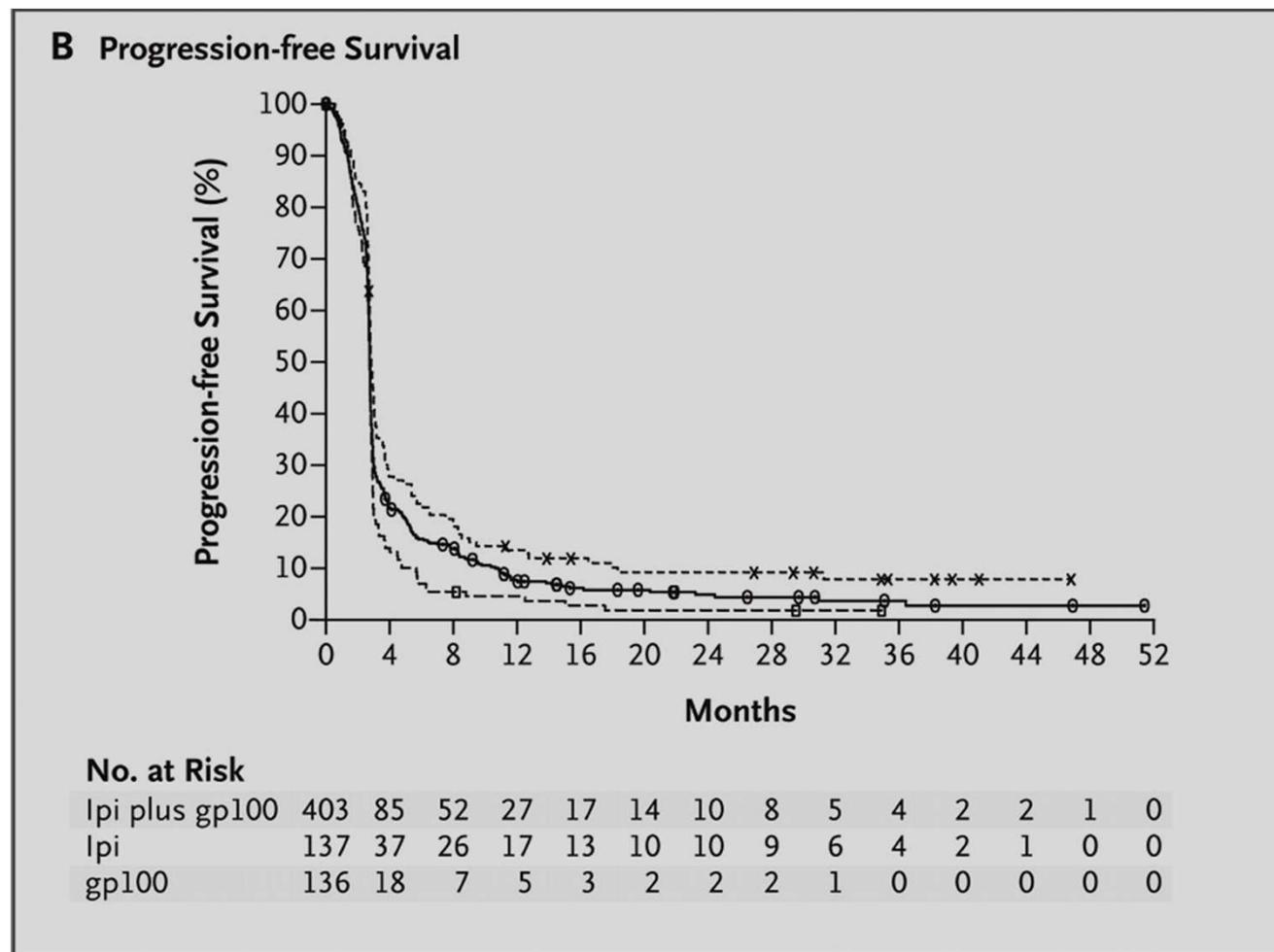
## Ipilimumab in Melanoma: The First “Drug” Ever to Show a Survival Benefit in a Randomized Clinical Trial



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

Hodi et al, 2010.

## Kaplan–Meier Curves for Progression-free Survival



Hodi FS et al. N Engl J Med 2010;363:711-723.

# Survival Data Intent-To-Treat Population

<b>Overall Survival (OS)</b>	<b>Ipilimumab + gp100 (n = 403)</b>	<b>Ipilimumab + placebo (n = 137)</b>	<b>gp100 + placebo (n = 136)</b>
Median OS	10.0 months	10.1 months	6.4 months
Hazard ratio, versus gp100 alone (p-value)	0.68 (<0.001)	0.66 (0.003)	—
2-year OS rate	21.6%	23.5%	13.7%
<b>Progression-Free Survival (PFS)</b>			
Median PFS	2.76 months	2.86 months	2.76 months
PFS rate at week 12	49.1%	57.7%	48.5%

O'Day S et al. *Proc ASCO 2010;Abstract 4*; Hodi FS et al. *Proc ASCO 2010; Abstract 8509*; Hodi FS et al. *N Engl J Med 2010;[Epub ahead of print]*.

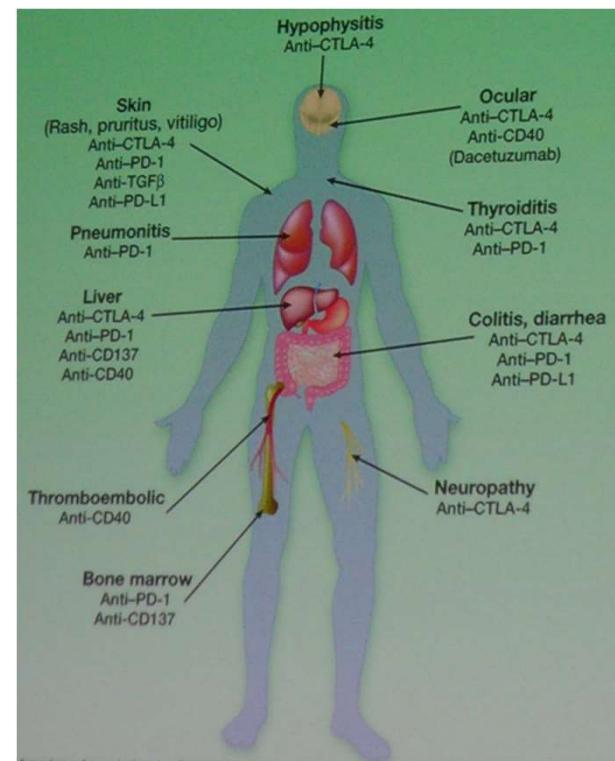
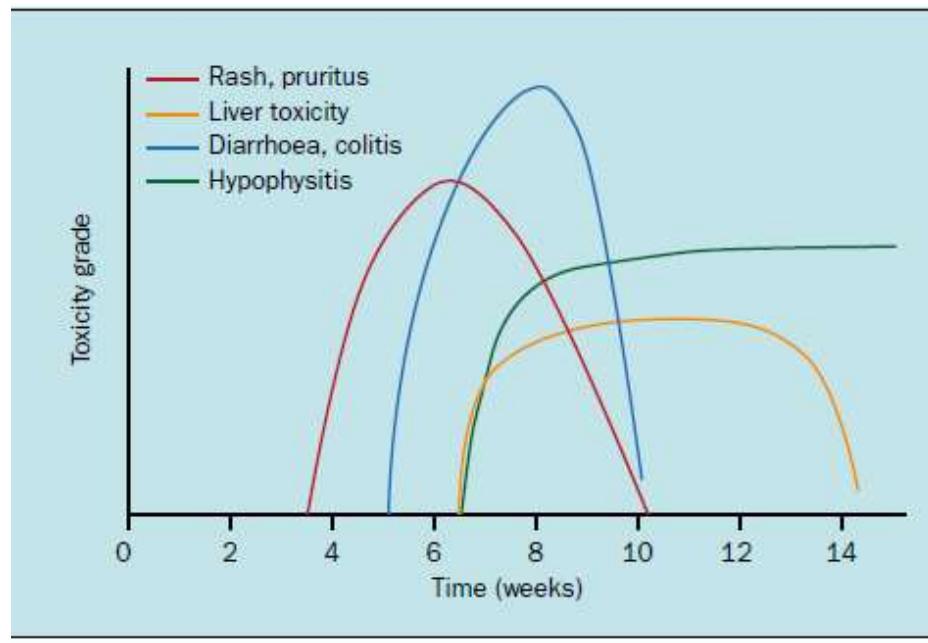
## Select Grade 3/4 Adverse Events

Adverse Event*	Ipilimumab + gp100 (n = 380)		Ipilimumab + placebo (n = 131)		gp100 + placebo (n = 132)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Any drug-related event	16.3%	1.1%	19.1%	3.8%	11.4%	0
Diarrhea	4.2%	0.3%	5.3%	0	0.8%	0
Fatigue	5.0%	0	6.9%	0	3.0%	0
Anemia	2.9%	0	3.1%	0	8.3%	0
Any immune-related event	9.7%	0.5%	12.2%	2.3%	3.0%	0

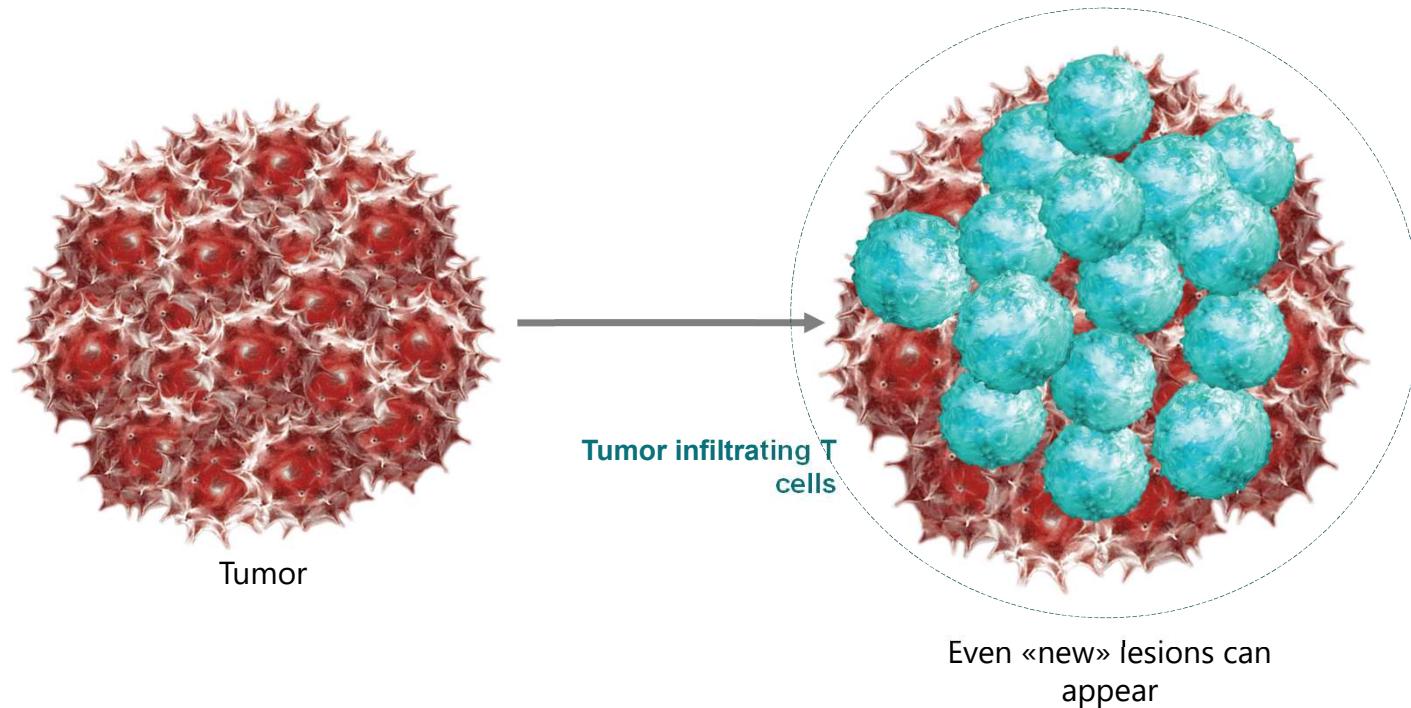
\* Listed adverse events occurred in  $\geq 15\%$  of patients. A total of 14 treatment-related deaths occurred (8 in ipilimumab + gp100 group, 4 in ipilimumab alone group and 2 in the gp100 alone group).

O'Day S et al. *Proc ASCO 2010;Abstract 4*; Hodi FS et al. *Proc ASCO 2010; Abstract 8509*; Hodi FS et al. *N Engl J Med 2010;[Epub ahead of print]*.

# Immunotherapy – autoimmune toxicity



# Pseudo-progression



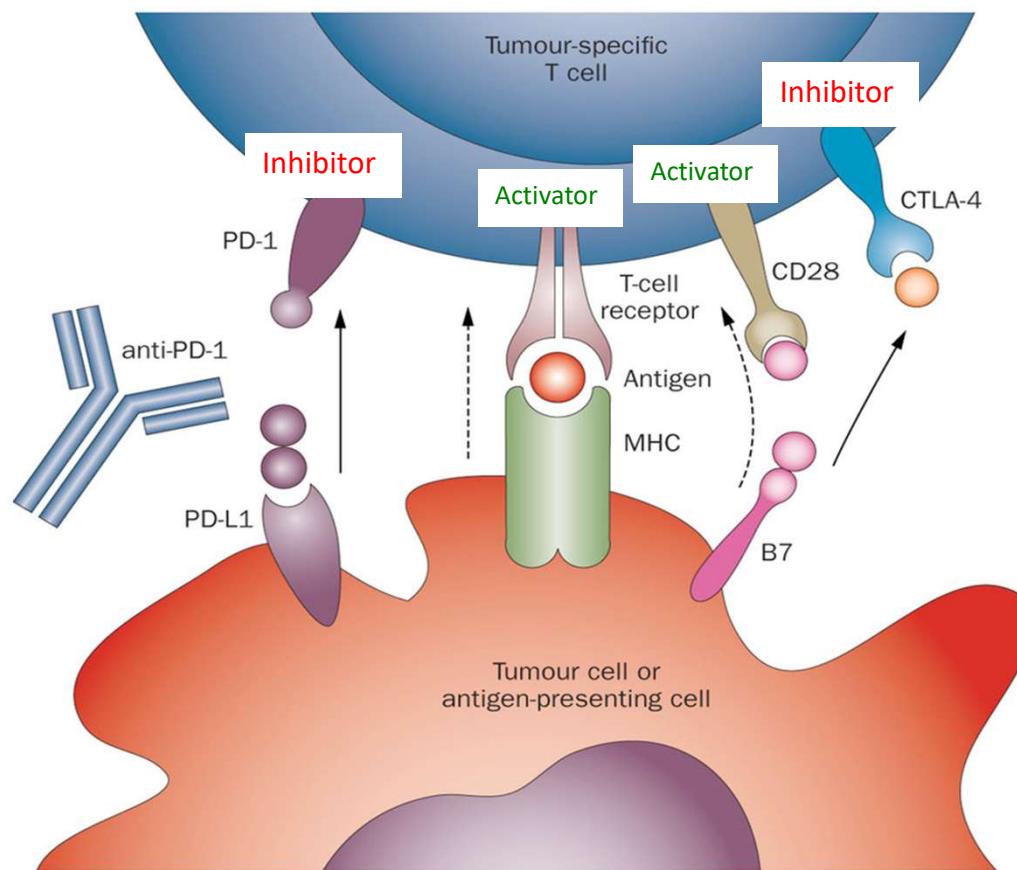
I-O, immuno-oncology.

1.Wolchok JD et al. *Clin Cancer Res.* 2009;15:7412-7420.

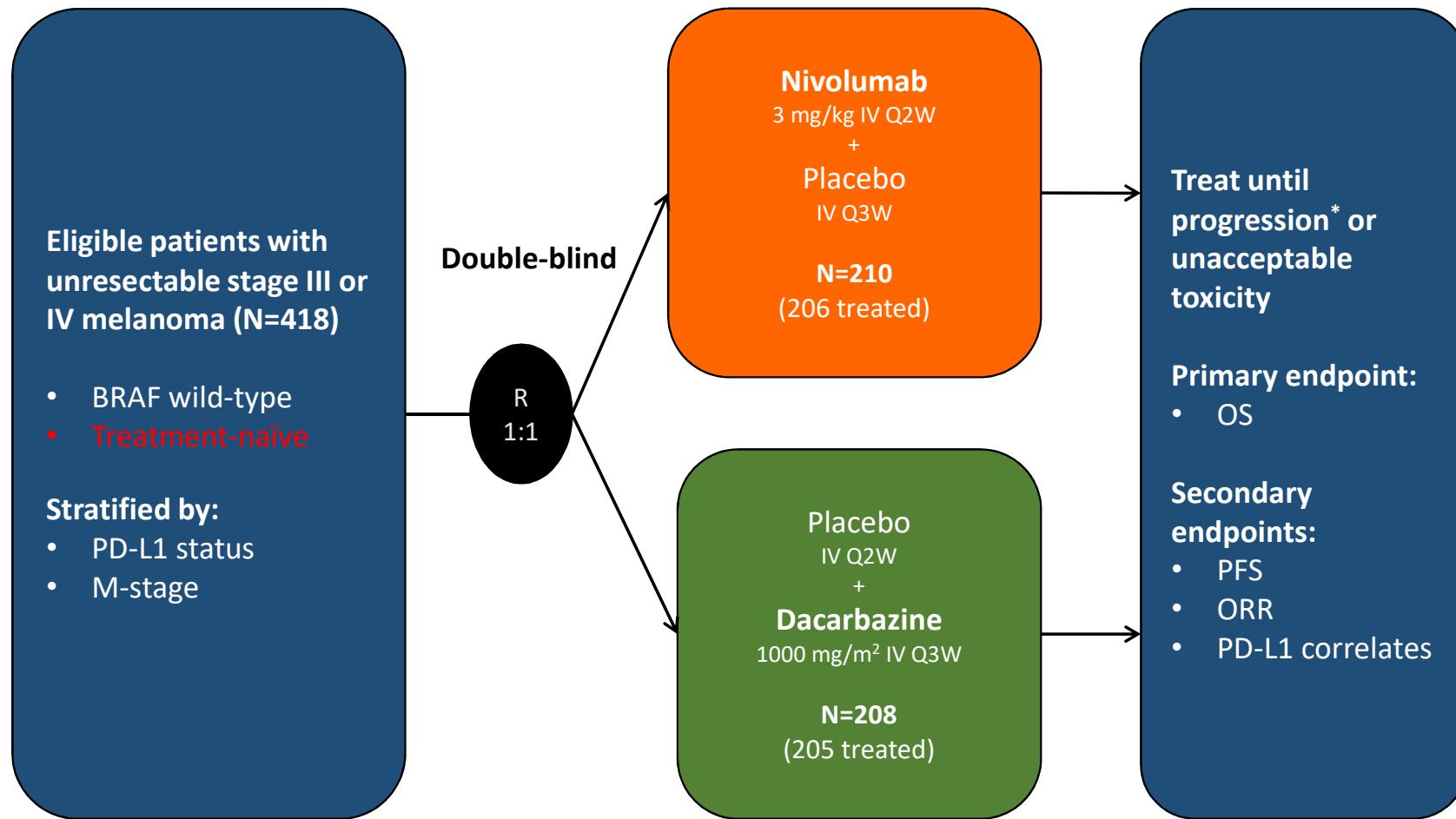
2.Ribas A et al. *Clin Cancer Res.* 2009;15:7116-7118.

# Anti PD1

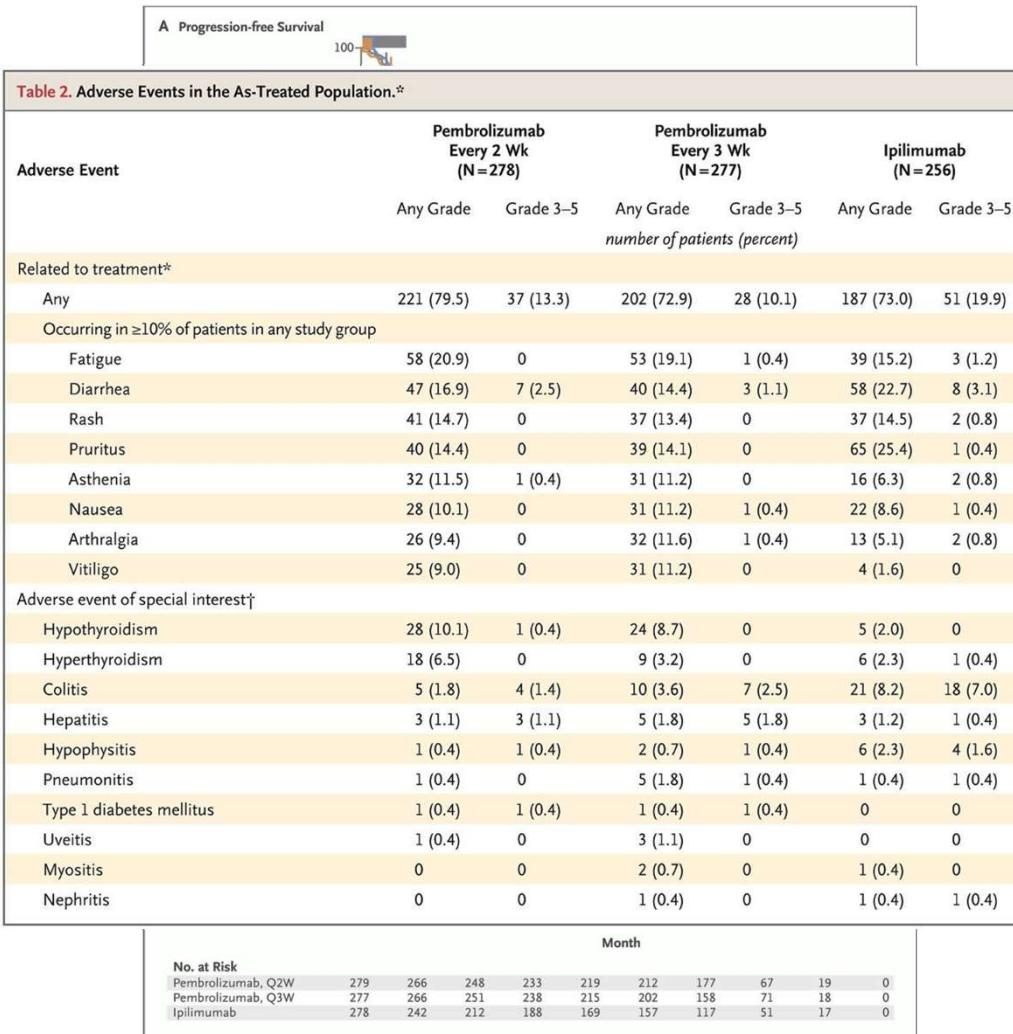
- Pembrolizumab and Nivolumab



# Pembrolizumab and Nivolumab 2<sup>nd</sup> & 1<sup>st</sup> line



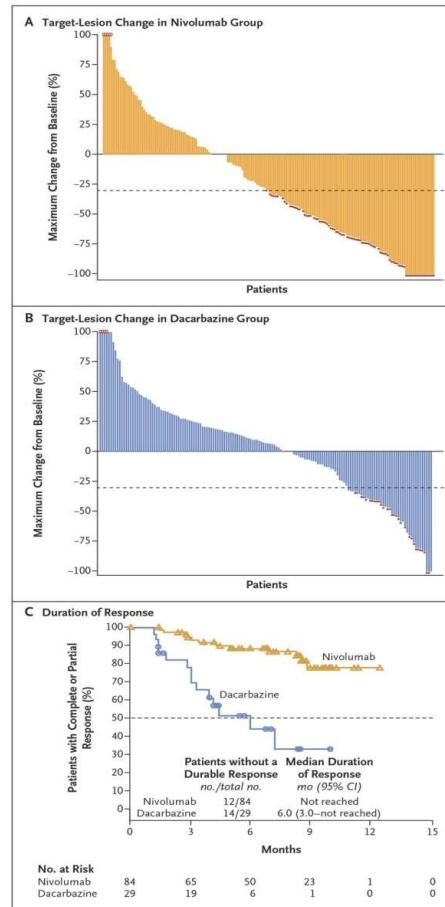
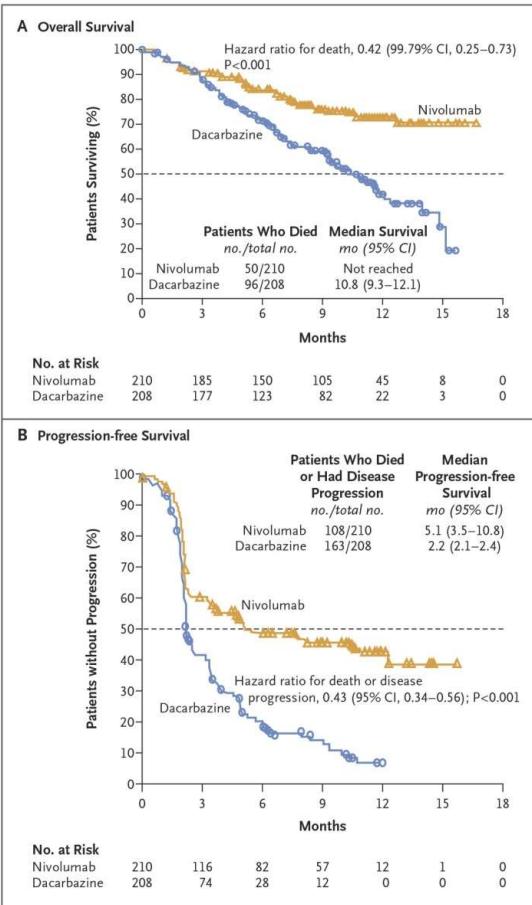
# Pembro 2<sup>nd</sup> line OS and safety



**Pembrolizumab is clearly superior in PFS as well as in OS to ipilimumab**

**!!! Much less side effects**

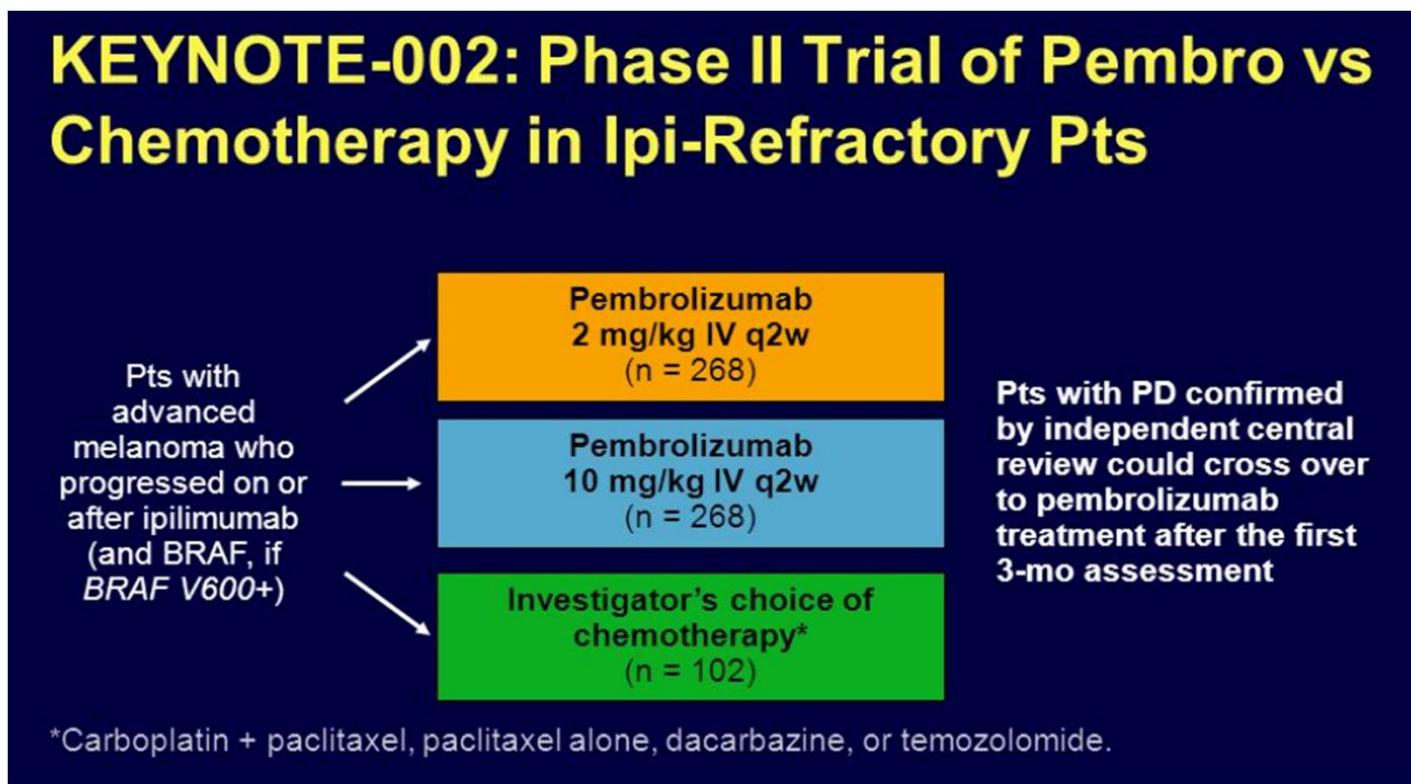
# Nivolumab 1<sup>st</sup> line



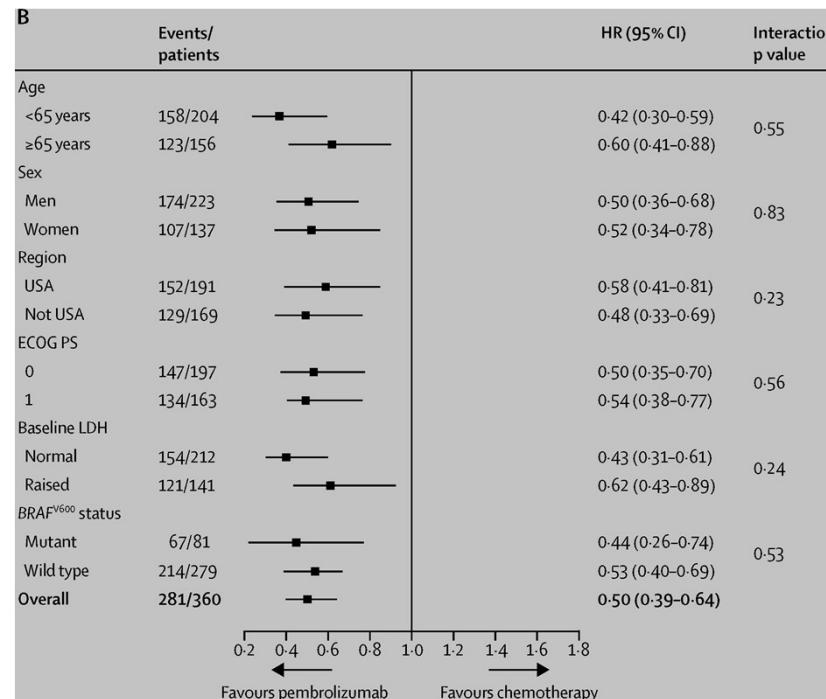
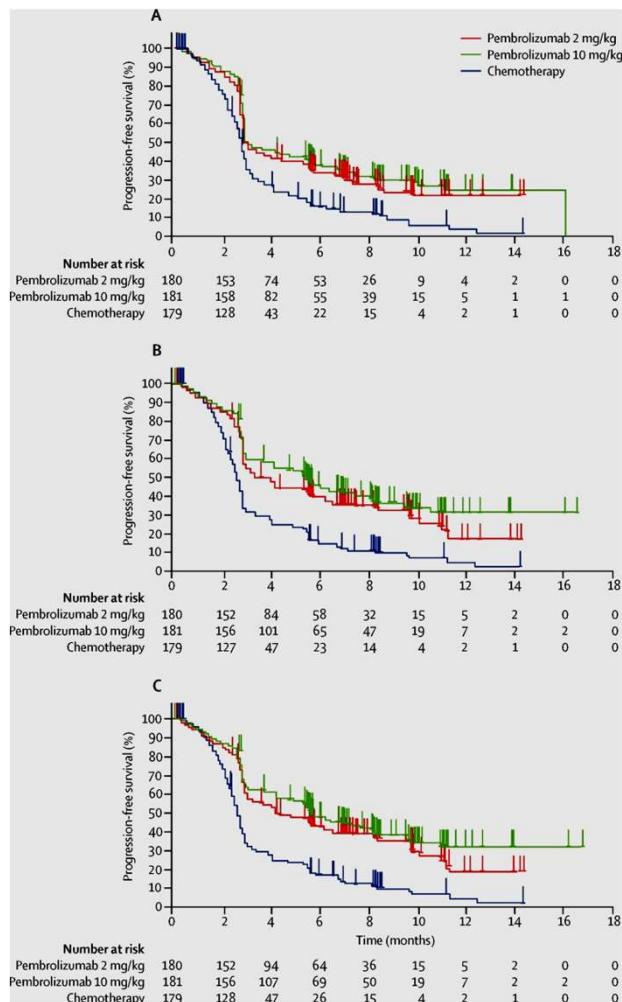
	Nivolumab (N=210)	Dacarbazine (N=208)
ORR, % (95% CI)	40%	14%
<b>Overall response</b>		
CR	8%	1%
PR	32%	13%
SD	17%	22%
PD	33%	49%

Less toxicity than chemo !

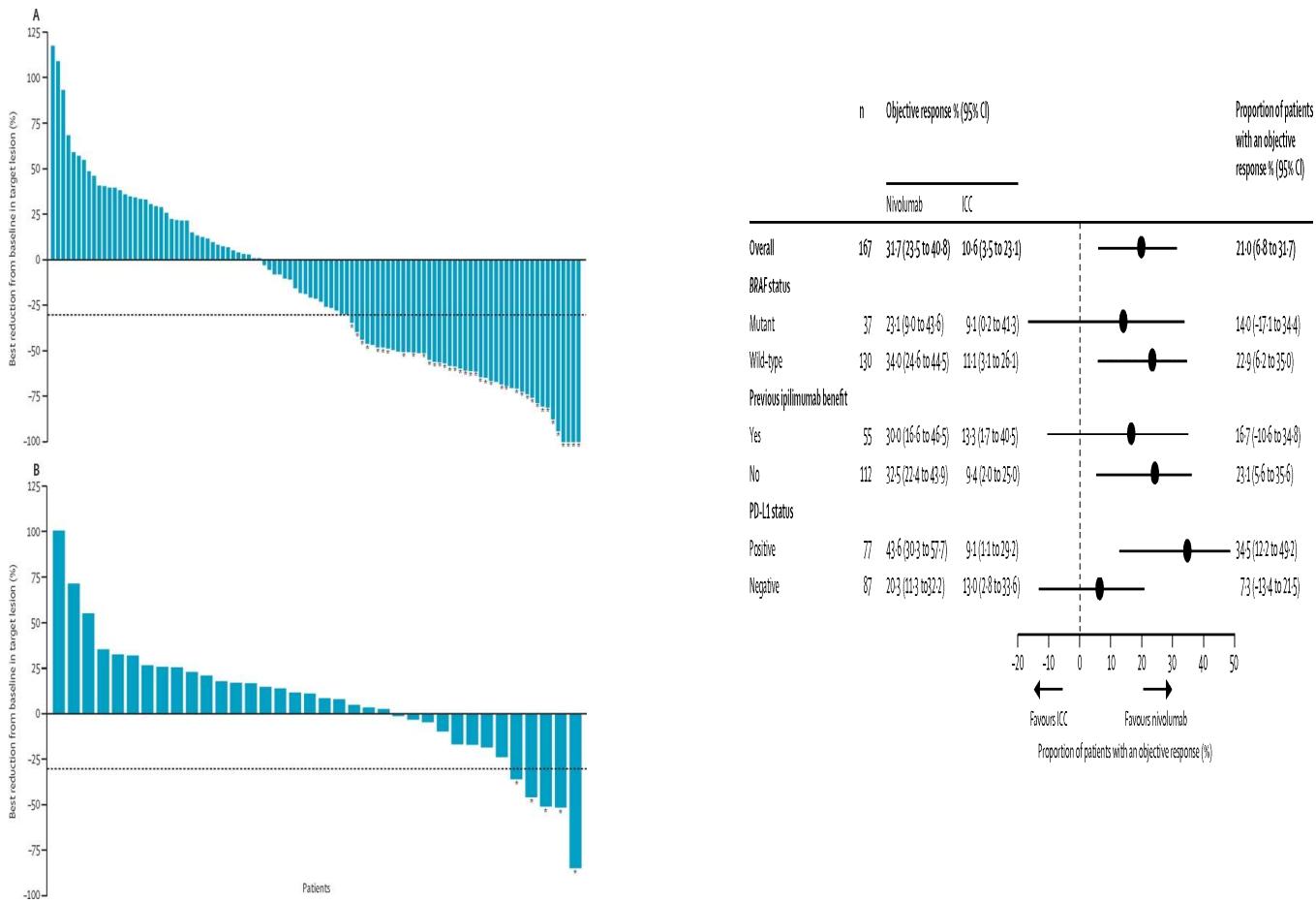
# Pembrolizumab versus chemotherapy for ipilimumab-refractory melanoma



# Survival and subgroups

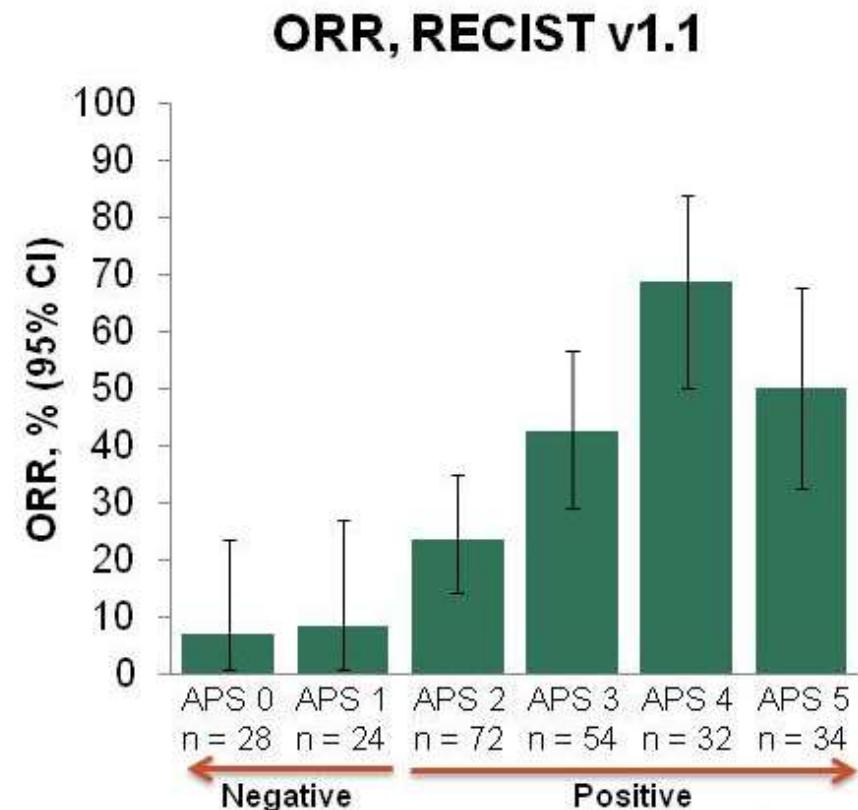
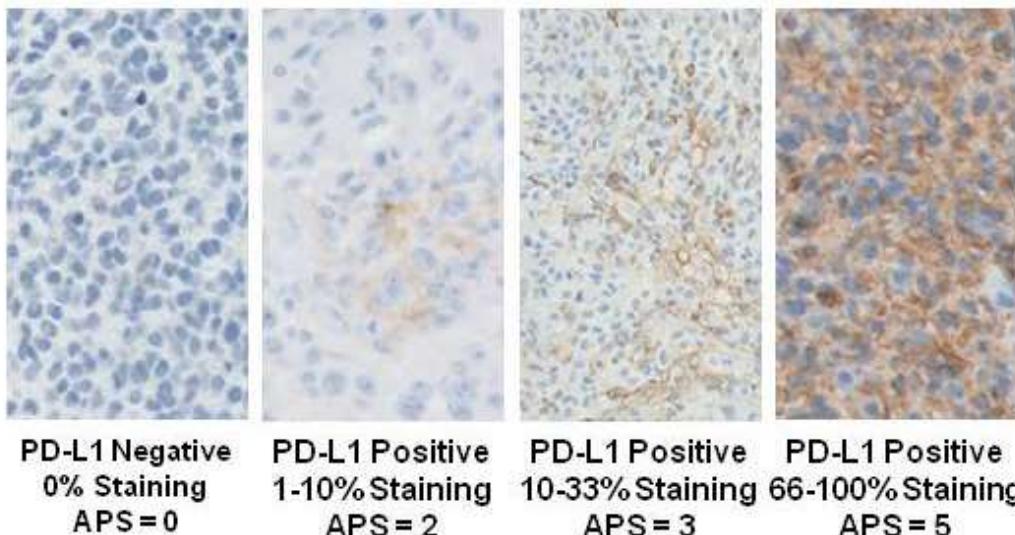


# Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment CheckMate 037: phase 3



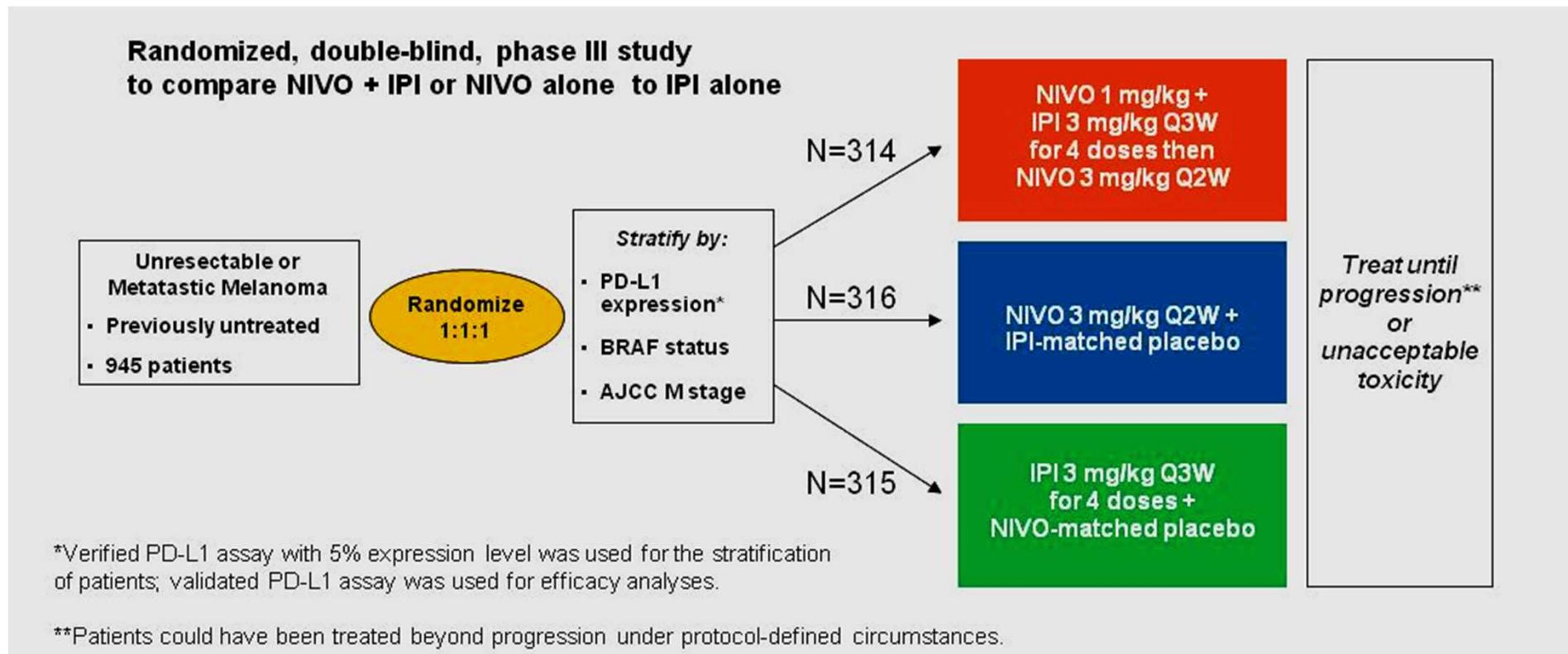
## PD-L1 Expression and Relationship With Response

- Among first 411 patients enrolled, 67% evaluable for PD-L1 status
- Correlation between PD-L1 expression and ORR ( $P < 0.0001$ )



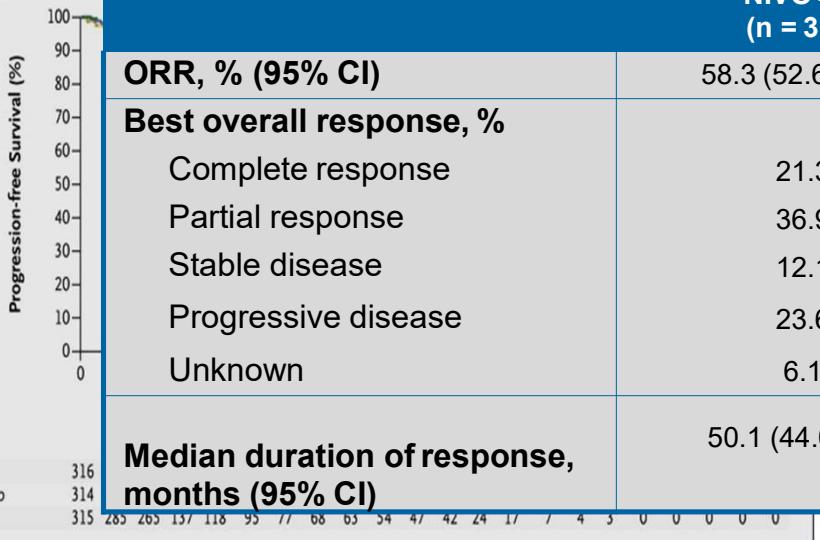
# Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

## CheckMate 067: Study Design

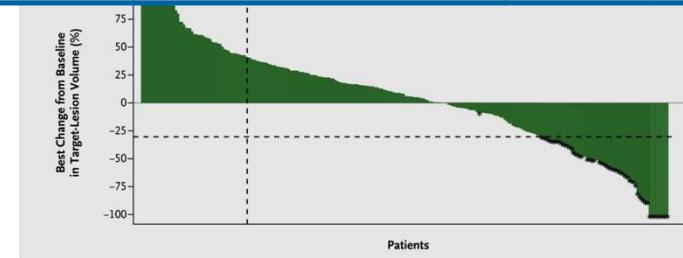


# Survival & Responses

A Intention-to-Treat Population		NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Progression-free Survival (%)		58.3 (52.6, 63.8)	44.6 (39.1, 50.3)	19.0 (14.9, 23.8)
<b>ORR, % (95% CI)</b>				
Complete response	21.3	17.7	5.1	
Partial response	36.9	26.9	14.0	
Stable disease	12.1	9.5	21.6	
Progressive disease	23.6	38.3	50.5	
Unknown	6.1	7.6	8.9	
<b>Median duration of response, months (95% CI)</b>	50.1 (44.0, NR)	NR (45.7, NR)	14.4 (8.3, NR)	
No. at Risk				
Nivolumab	316			
Nivolumab plus ipilimumab	314			
Ipilimumab	315			



The figure shows a Kaplan-Meier survival plot for progression-free survival. The y-axis represents the percentage of patients (0-100) and the x-axis represents time in months (0-5). The NIVO+IPI group (blue line) shows the highest survival probability, followed by the NIVO group (green line), and the IPI group (red line) shows the lowest survival probability.



# Adverse events:

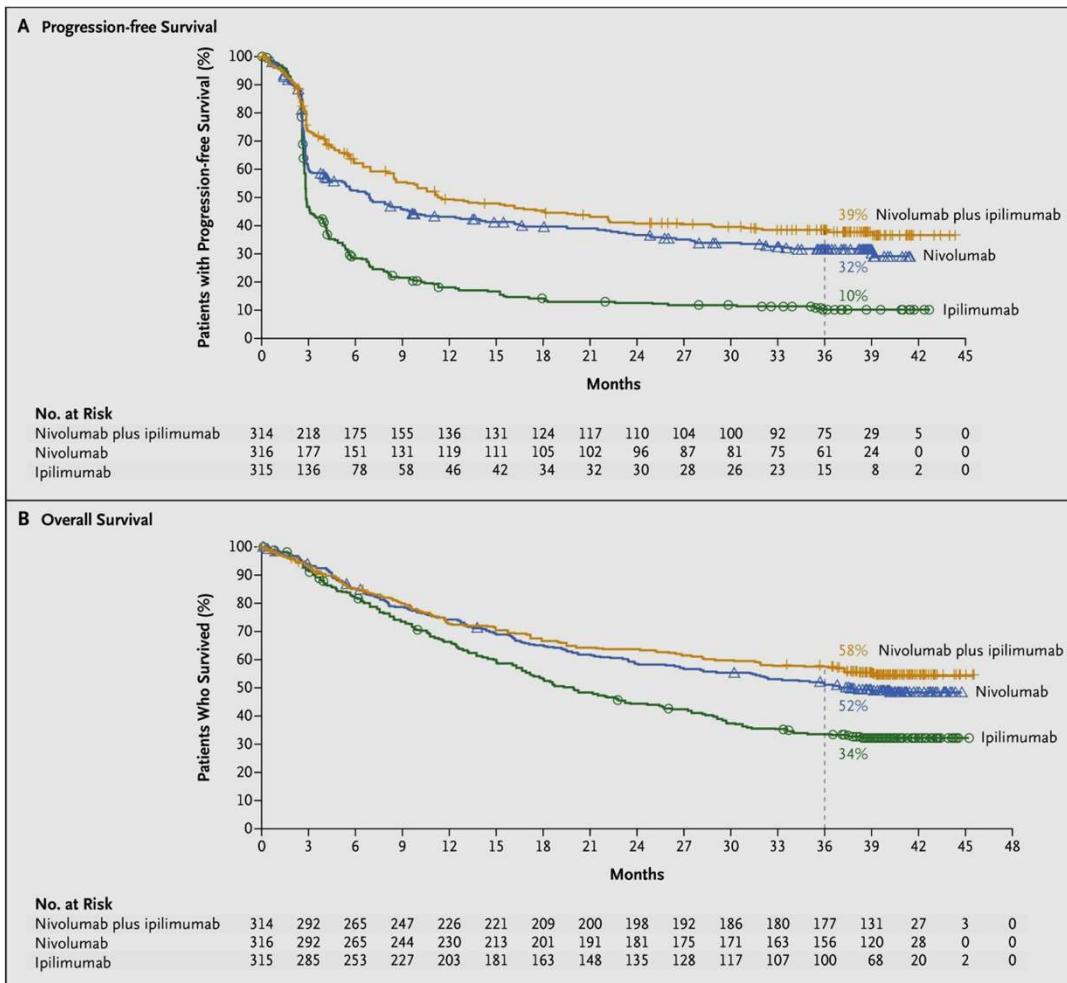
**Table 3.** Adverse Events.\*

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
<i>number of patients with event (percent)</i>						
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)

## Conclusion

The combination of a CTLA-4 blocker and a PD-1 blocker produced responses in more than **60%** of previously untreated patients with *BRAF* wild-type advanced melanoma, including complete responses in more than 20% of these patients.

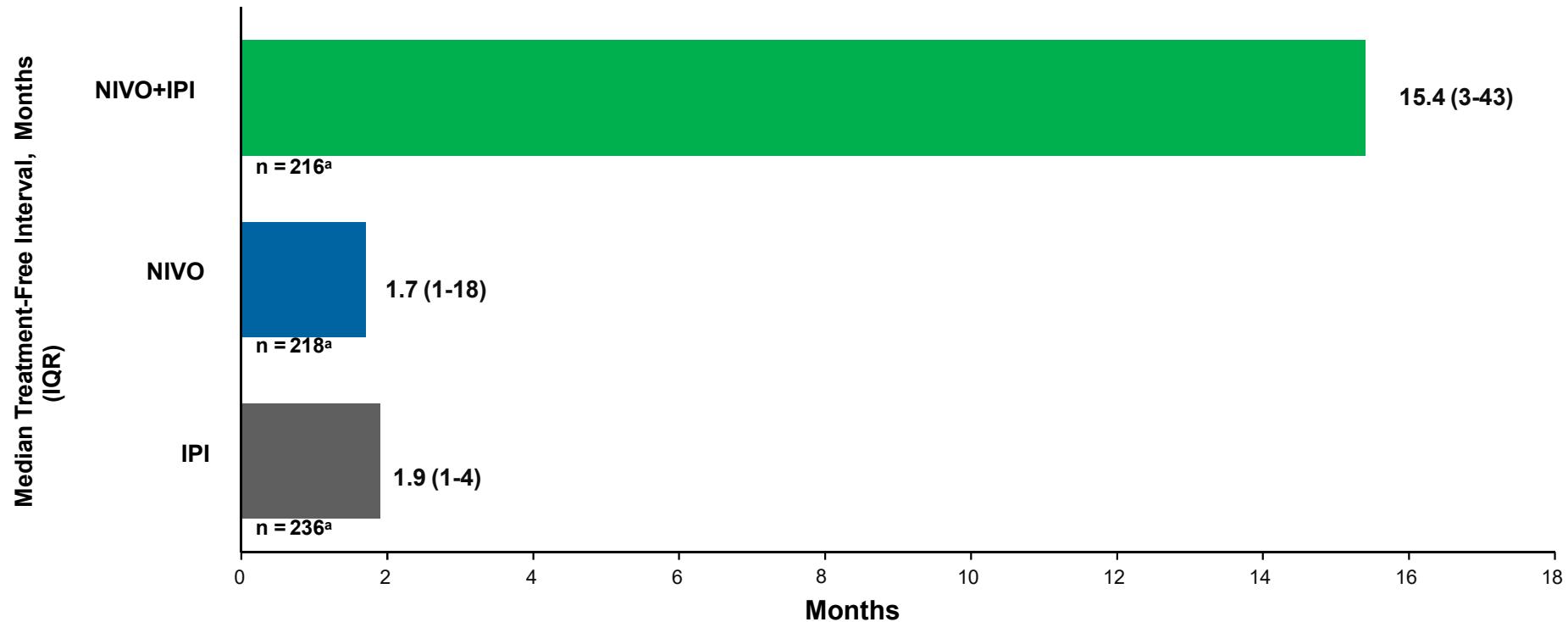
# Long term results (combination)



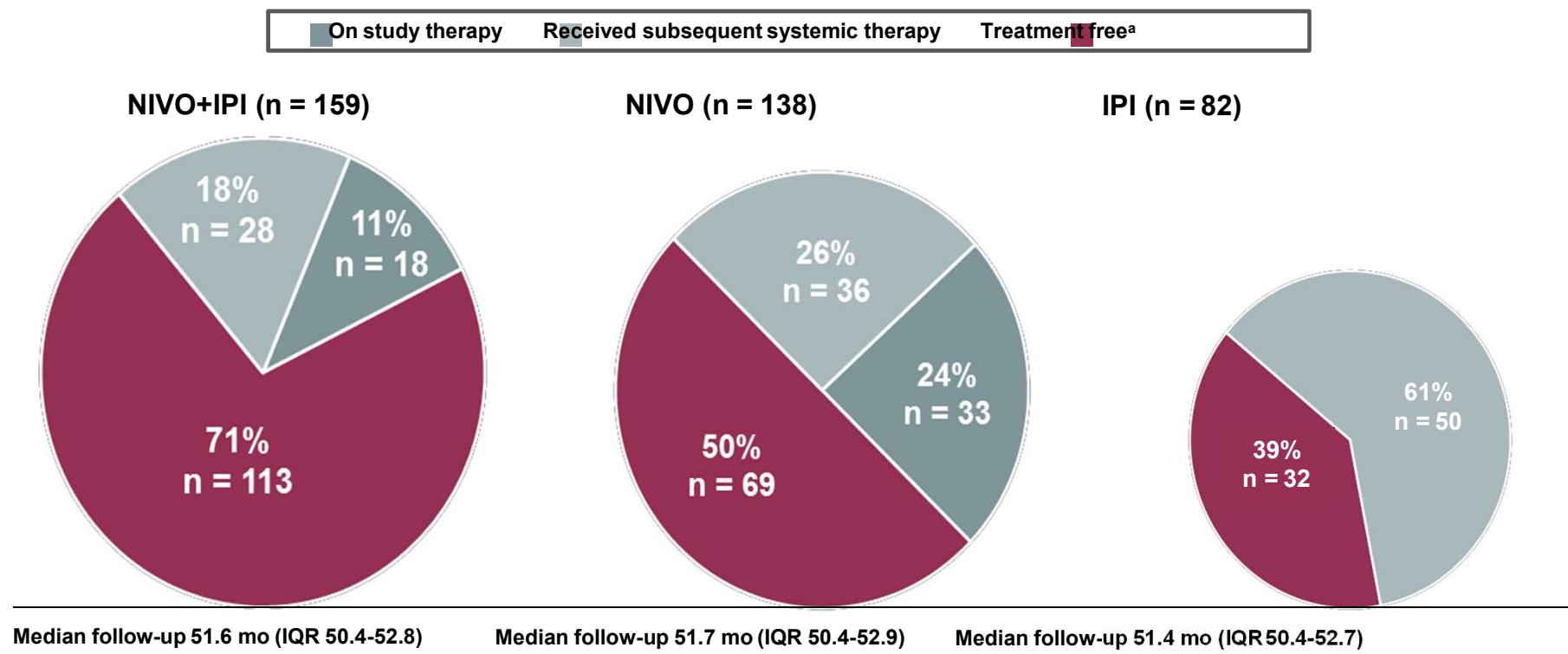
**La différence entre nivolumab monotherapie et Ipi nivo est statistiquement significative en OS et PFS, mais est-ce que la différence vaut la toxicité...?**

# Treatment-Free Interval at 4 Years in Patients Who Discontinued Study Therapy

Stop for toxicity!!!



# Patients Alive at 4 Years



- At the time of the 4-year follow-up, 71% of patients in the NIVO+IPI group were treatment free, which is increased from that observed at the 3-year follow-up (67%; 114/170)

## Is another dosing schedule less toxic?

### CHECKMATE 511: Phase 3b/4 Study of Two Dosing Regimens of Nivolumab in Combination with Ipilimumab in Advanced Melanoma

Previously untreated Advanced Melanoma  
Randomised 1:1

NIVO 1 mg/kg + IPI 3 mg/kg  
Q3W  
4 doses (N=178)

vs

NIVO 3 mg/kg + IPI 1 mg/kg  
Q3W  
4 doses (N=180)

6 weeks

NIVO flat dose 480 mg  
Q4W

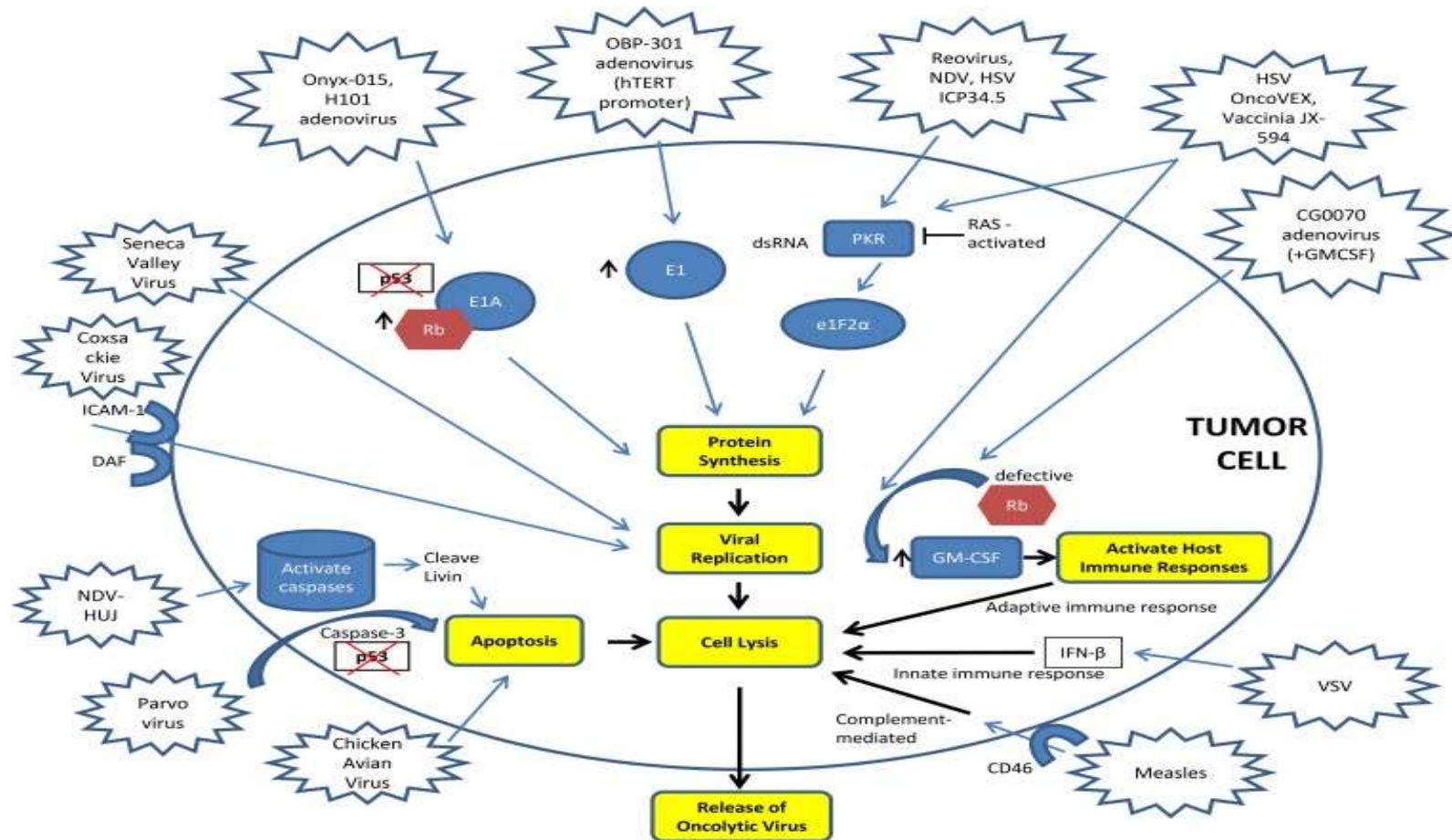
6 weeks

NIVO flat dose 480 mg  
Q4W

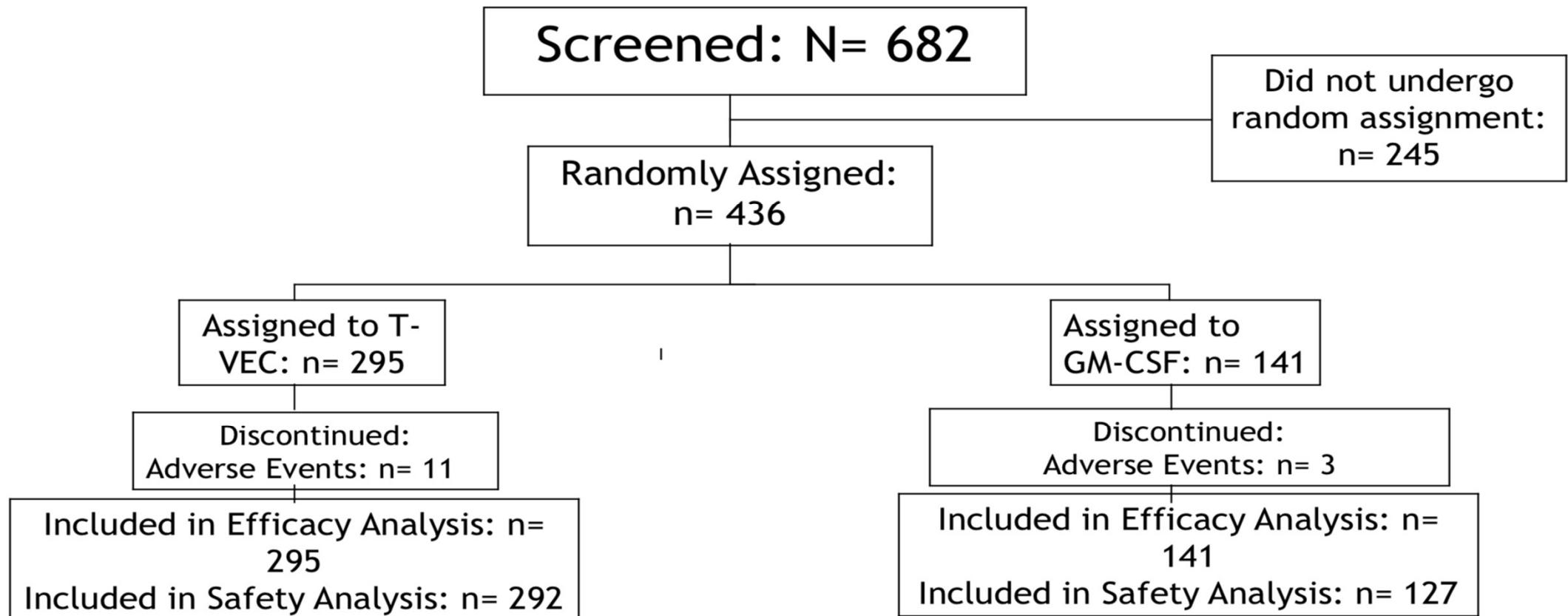
Primary Endpoint - Compare incidence of treatment-related grade 3-5 AEs

Secondary Endpoints (not powered to compare) - ORR (RECIST v1.1), PFS and OS

# Oncolytic viruses



# IMLYGIC® (talimogene laherparepvec, T-Vec)



(Andtbacka R H.I. et. al.. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol.* 2015 Sep 1; 33(25): 2780-2788, Figure 1

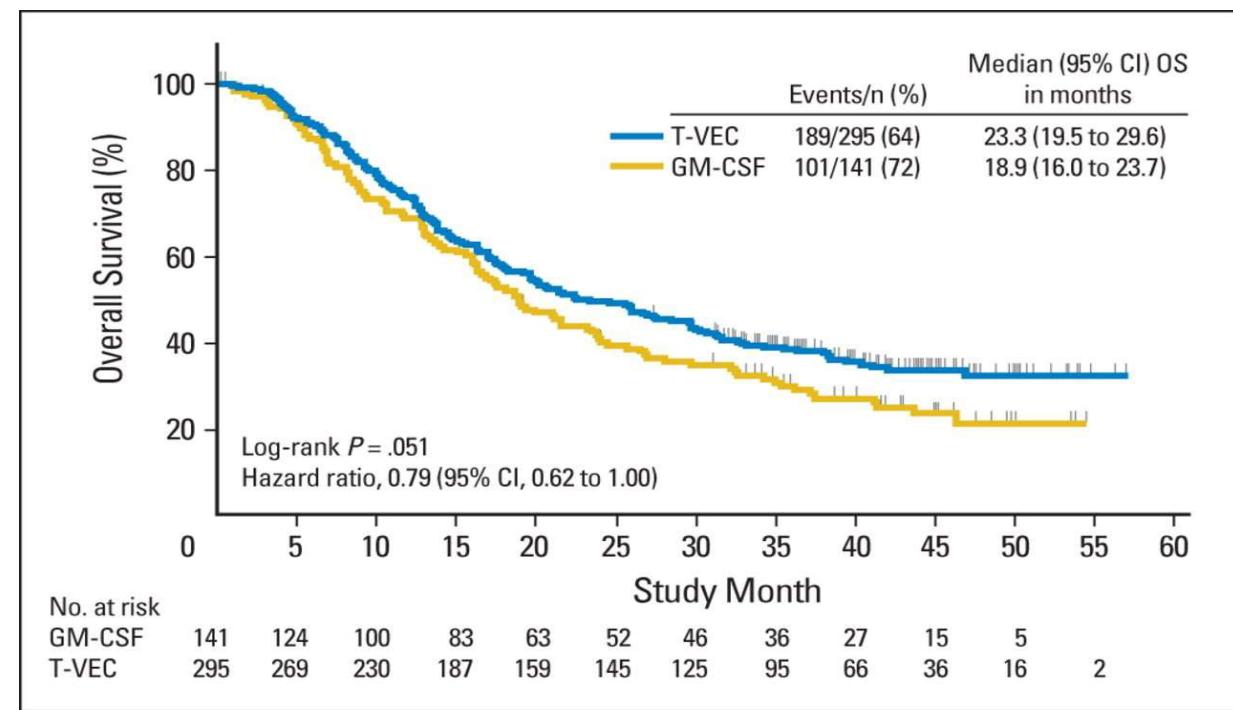
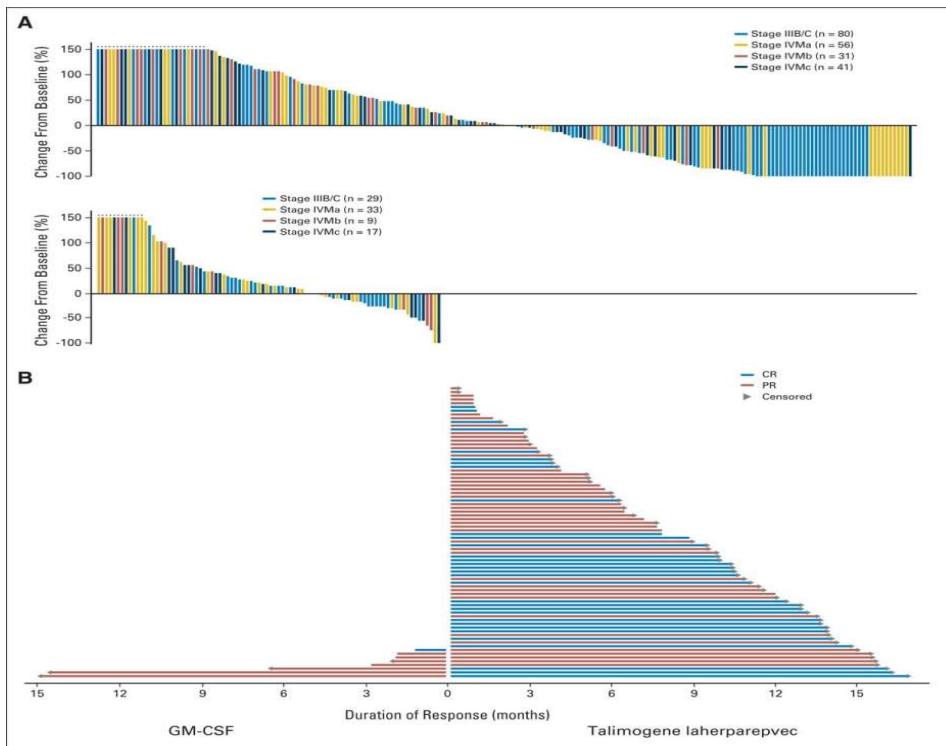
Andtbacka R.H.I., Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol.* 2015;33:2780-2788

# Métastase en transit

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# RR & Overall Survival



# Take home messages



L'inhibition de PD-1 en première ligne est supérieure à la chimiothérapie (DTIC) et à l'inhibition de CTLA-4



L'inhibition de PD-1 est efficace en 2ème ligne après inhibition CTLA-4 préalable



Les inhibiteurs PD1 sont généralement bien tolérés et sont devenus le standard en 1ère et en 2ème ligne dans le mélanome généralisé



La combinaison de anti PD-1 et anti CTLA-4 est un standard chez des patients sélectionnés (EG bon, PD-L1 neg?...) 4 yr OS 53%

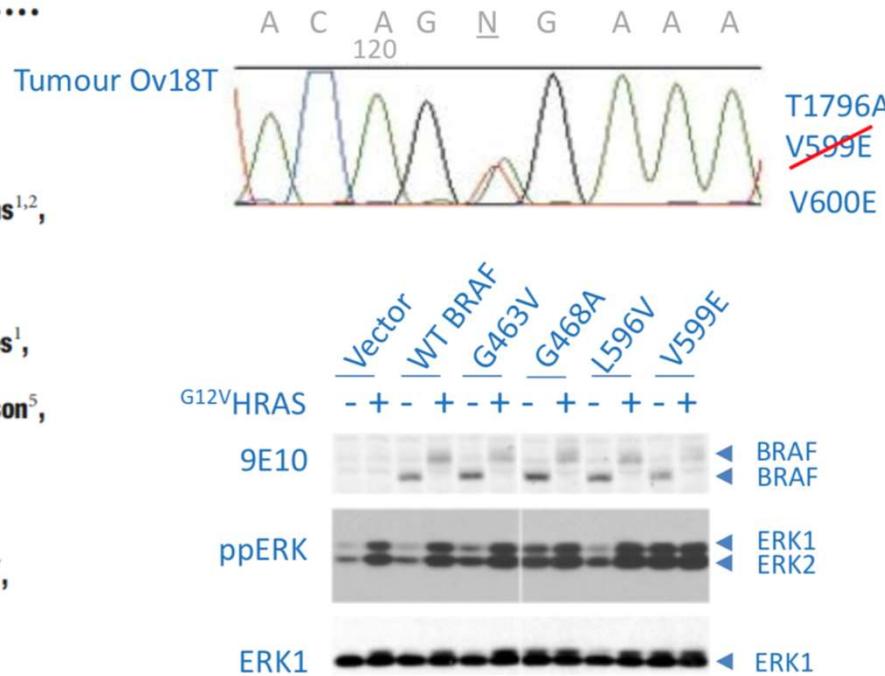


TVEC – Effet sur métastases en transit, avec bystander effect

# BRAF mutation in melanoma

## Mutations of the *BRAF* gene in human cancer

Helen Davies<sup>1,2</sup>, Graham R. Bignell<sup>1,2</sup>, Charles Cox<sup>1,2</sup>, Philip Stephens<sup>1,2</sup>, Sarah Edkins<sup>1</sup>, Sheila Clegg<sup>1</sup>, Jon Teague<sup>1</sup>, Hayley Woffendin<sup>1</sup>, Mathew J. Garnett<sup>3</sup>, William Bottomley<sup>1</sup>, Neil Davis<sup>1</sup>, Ed Dicks<sup>1</sup>, Rebecca Ewing<sup>1</sup>, Yvonne Floyd<sup>1</sup>, Kristian Gray<sup>1</sup>, Sarah Hall<sup>1</sup>, Rachel Hawes<sup>1</sup>, Jaime Hughes<sup>1</sup>, Vivian Kosmidou<sup>1</sup>, Andrew Menzies<sup>1</sup>, Catherine Mould<sup>1</sup>, Adrian Parker<sup>1</sup>, Claire Stevens<sup>1</sup>, Stephen Watt<sup>1</sup>, Steven Hooper<sup>3</sup>, Rebecca Wilson<sup>3</sup>, Hiran Jayatilake<sup>4</sup>, Barry A. Gusterson<sup>5</sup>, Colin Cooper<sup>6</sup>, Janet Shipley<sup>6</sup>, Darren Hargrave<sup>7</sup>, Katherine Pritchard-Jones<sup>7</sup>, Norman Maitland<sup>8</sup>, Georgia Chenevix-Trench<sup>9</sup>, Gregory J. Riggins<sup>10</sup>, Darell D. Bigner<sup>10</sup>, Giuseppe Palmieri<sup>11</sup>, Antonio Cossu<sup>12</sup>, Adrienne Flanagan<sup>13</sup>, Andrew Nicholson<sup>14</sup>, Judy W. C. Ho<sup>15</sup>, Suet Y. Leung<sup>16</sup>, Siu T. Yuen<sup>16</sup>, Barbara L. Weber<sup>17</sup>, Hilliard F. Seigler<sup>18</sup>, Timothy L. Darrow<sup>18</sup>, Hugh Paterson<sup>3</sup>, Richard Marais<sup>3</sup>, Christopher J. Marshall<sup>3</sup>, Richard Wooster<sup>1,6</sup>, Michael R. Stratton<sup>1,4</sup> & P. Andrew Futreal<sup>1</sup>



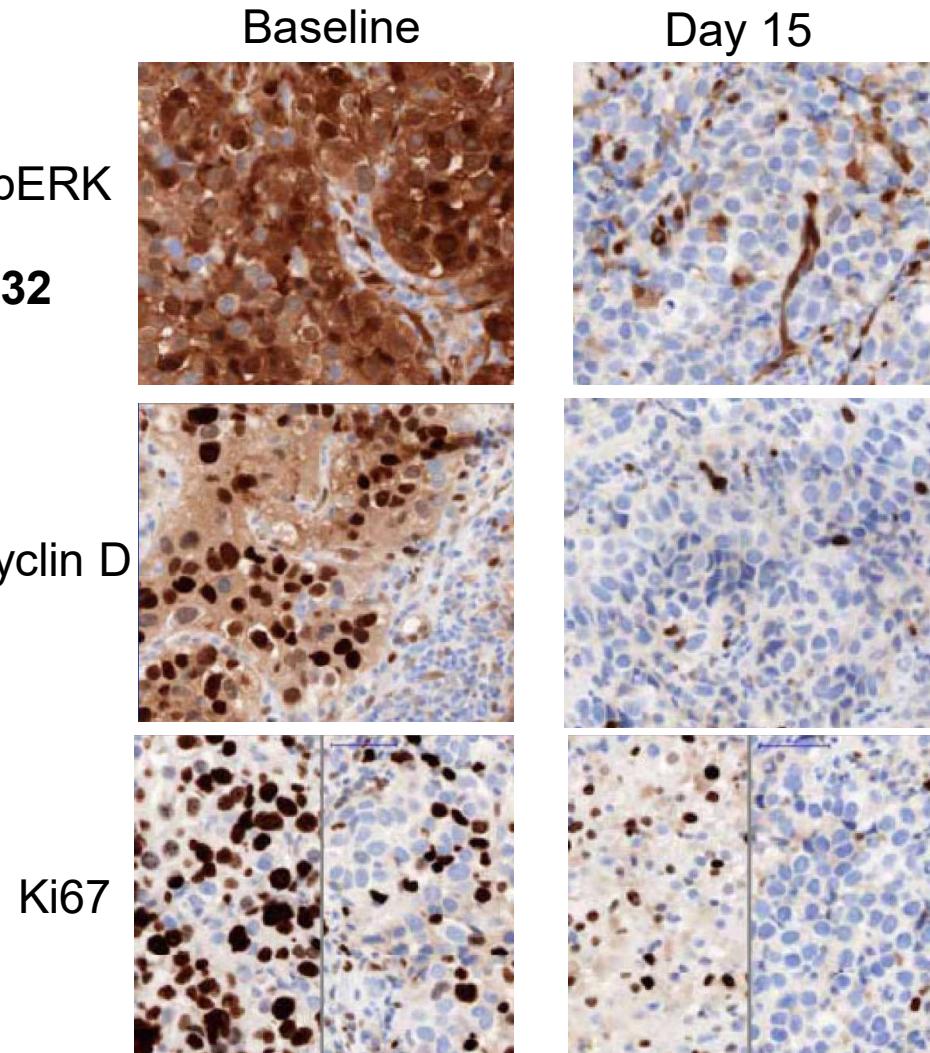
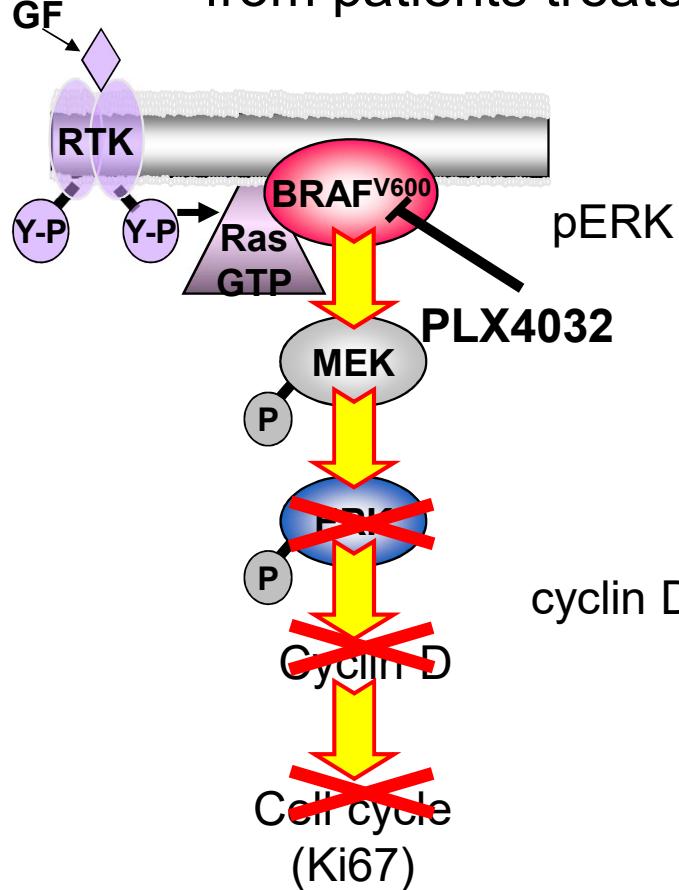
Environ 40%  
des mélanomes  
sont BRAF mutés

BRAF mutations		Cancer cell lines								Primary tumours						
Nucleotide	Amino acid	(1) Mel.	(2) Colo. ca	(3) Glioma	(4) Lung ca.	(5) Sarcoma	(6) Breast	(7) Ovarian	(8) Other	(1) Mel. STC	(2) Mel.	(3) Colo. ca	(4) Ovarian	(5) Sarcoma	(6) Other	Total
T1796A	V599E	19	5	4		5	1		1	11	5	2	3	1	0	57
TG1796-97AT	V599D	1														1
	Total	20	7	4	4	5	1	1	1	12	6	4	5	1	0	71
No. samples screened		34	40	38	131	59	45	26	172	15	9	22	35	182	104	923
Percent (%)		59	18	11	3	9	2	4	0.6	80	67	12	14	0.5	0	8

Mel.=melanoma; Colo.=colorectal; Ca.=cancer; STC=soft tissue cancer.

Davies H, et al. Nature 2002;417:494–54.

# Inhibition of MAPK signaling in biopsies of BRAF<sup>V600</sup> melanoma from patients treated with vemurafenib (PLX4032)



# Tumor Response to Vemurafenib

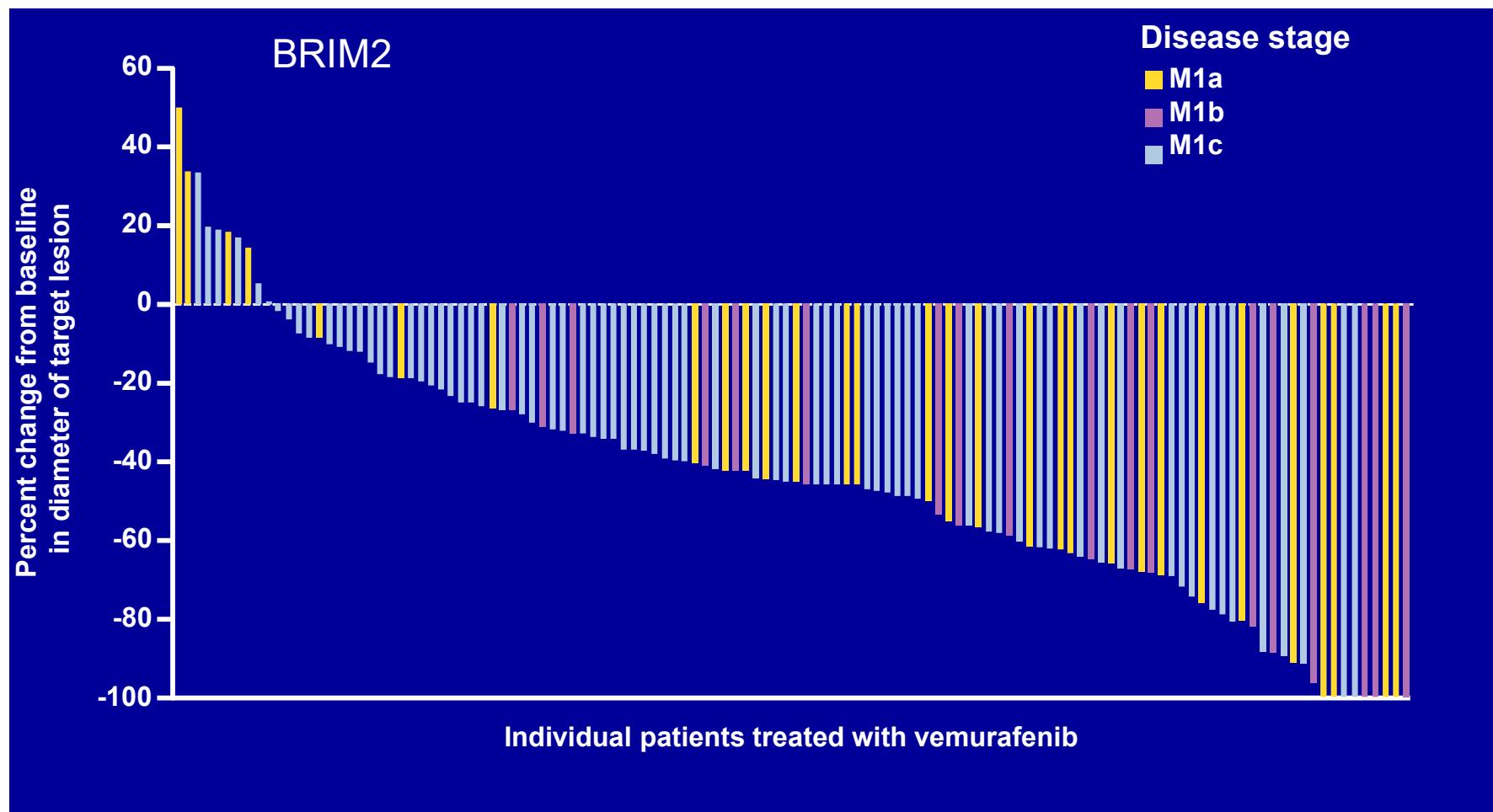
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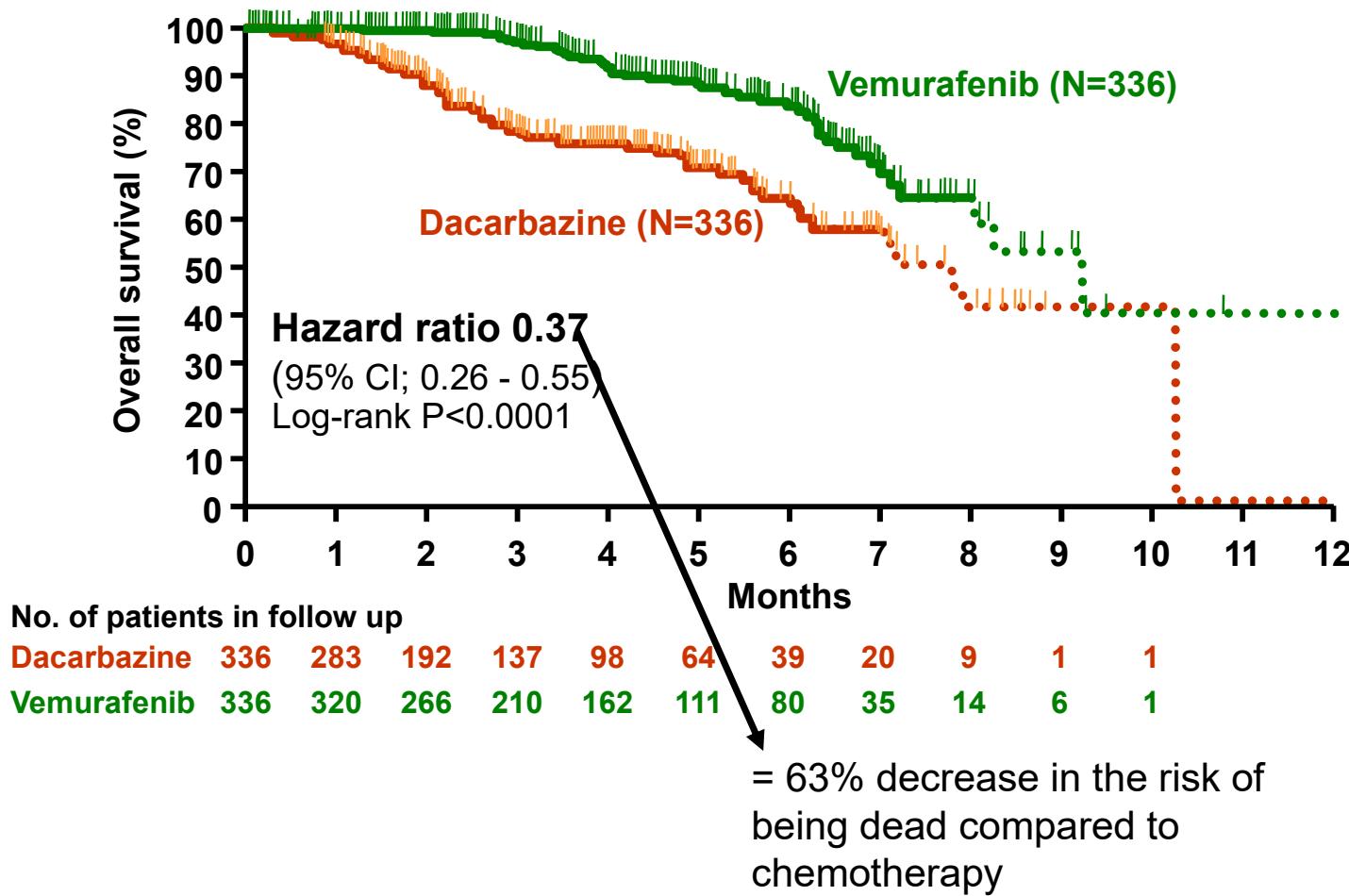
T 3 mo



# Melanoma tumor responses with vemurafenib: BRIM2 study (132 patients)



# Overall survival



Chapman *et al.* NEJM 2011

# BRIM2: Toxicities with vemurafenib

**Includes AEs reported in ≥20 patients**

	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Overall</b>	<b>130 (99)</b>	<b>79 (60)</b>	<b>5 (4)†</b>
<b>Arthralgia</b>	<b>78 (59)</b>	<b>8 (6)</b>	—
<b>Rash</b>	<b>69 (52)</b>	<b>9 (7)</b>	—
<b>Photosensitivity reaction</b>	<b>69 (52)</b>	<b>4 (3)</b>	—
<b>Fatigue</b>	<b>56 (42)</b>	<b>2 (2)</b>	—
<b>Alopecia</b>	<b>48 (36 )</b>	—	—
<b>Pruritus</b>	<b>38 (29)</b>	<b>3 (2)</b>	—
<b>Skin papilloma</b>	<b>38 (29)</b>	—	—
Tumeurs spinocellulaires de la peau	cuSCC / KA‡	34 (26)	34 (26)
	<b>Nausea</b>	<b>30 (23)</b>	<b>2 (2)</b>
	<b>Elevated liver enzymes</b>	<b>23 (17)</b>	<b>8 (6) §</b>
			<b>4 (3)¶</b>

†One patient with 2 grade 4 AEs

‡Cases of cuSCC/KA were generally managed with simple excision and did not generally require dose modification

§ Managed with dose reduction; one removed from study

¶Led to discontinuation of therapy

# CuSCC/KA in Patients Treated with Vemurafenib

		Initial series	Validation set	Total
Gender	Female	3	2	5
	Male	8	10	18
Age	Mean	60	66	60
	Range	44-83	46-84	44-84
Number of Reported cuSCC/KA Events	Mean	2	4	3
	Range	1-6	1-10	1-10
Time to First cuSCC/KA (weeks)	Mean	9	11	10
HRAS	G12D, G13D, G13V, Q61K, Q61L, Q61R	12/21	4/14	21/35 (60%)
KRAS	G12C, G12D	1/21*	4/14	
NRAS	G12D	1/21*	0/14	
TP53	P278S, R196X	2/18	NA	2/18 (11%)

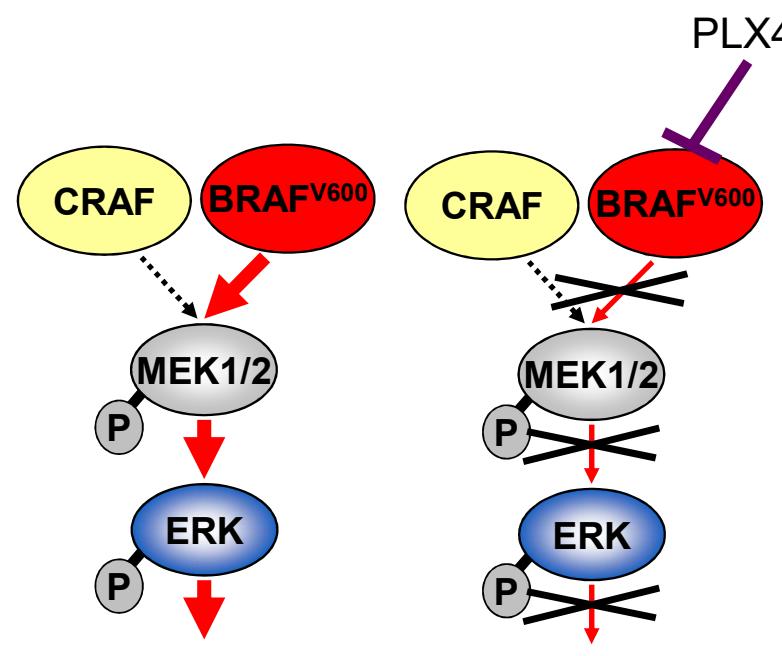
Most prevalent = *HRAS*<sup>Q61L</sup>

\*Co-incident with HRAS mutations in the same lesion

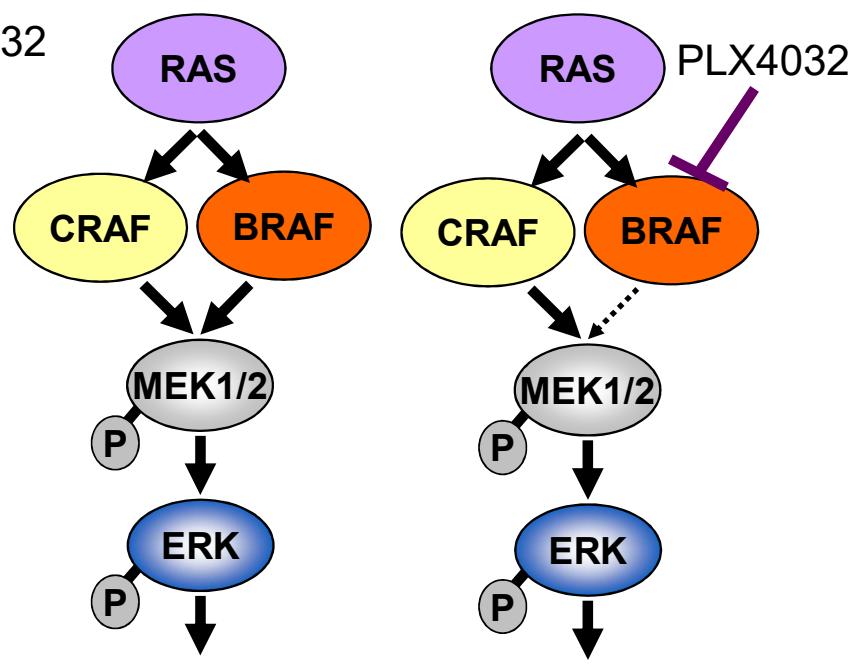
Su, Viros et al. RAS Mutations in Cutaneous Squamous Cell Carcinomas with BRAF Inhibitors. NEJM Jan 19, 2012

## Differential effects of BRAF inhibition in *BRAF<sup>V600</sup>* mutant melanoma and BRAF wild type cells

*BRAF<sup>V600</sup>* mutant melanoma

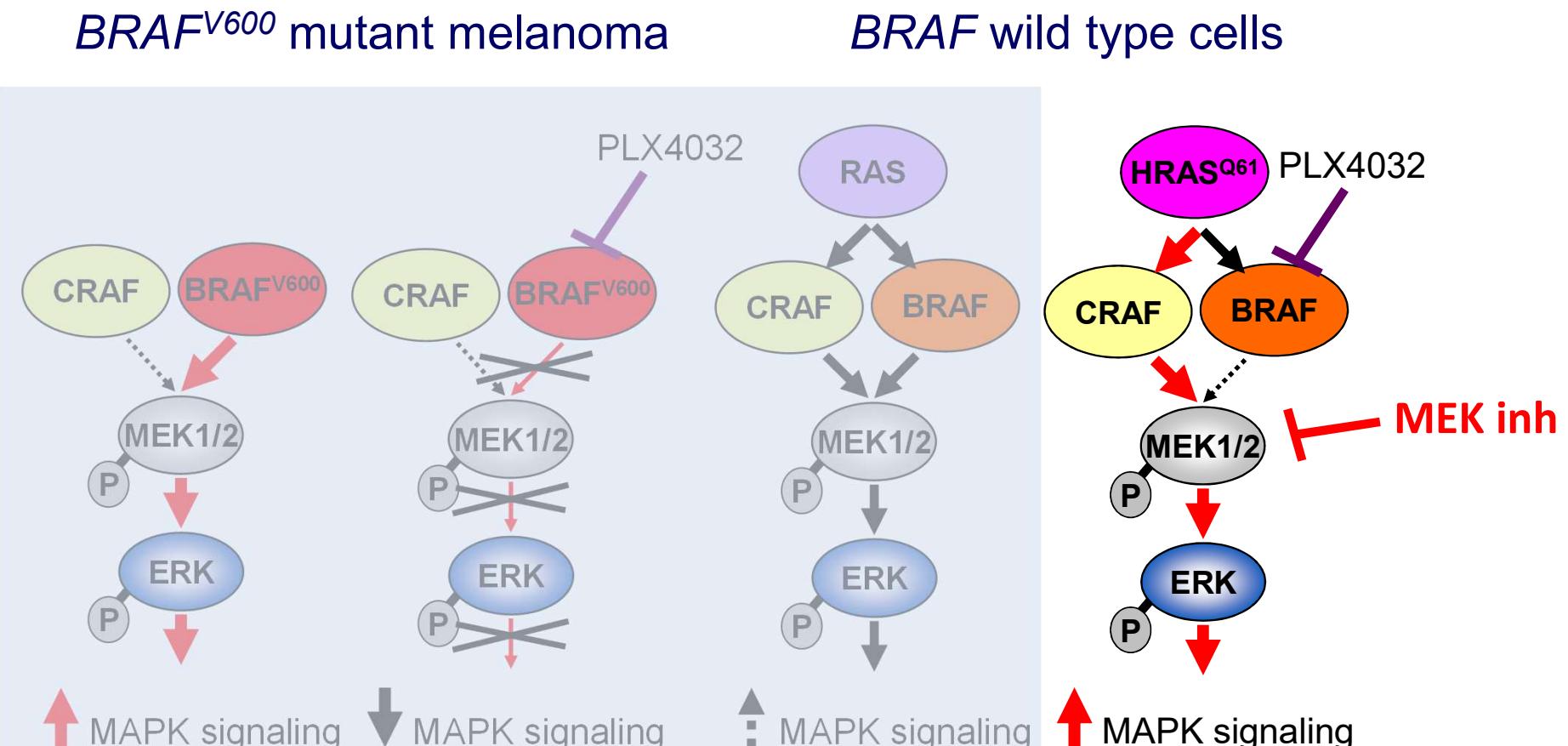


*BRAF* wild type cells



Hatzivassiliou *et al.* Nature 2010,  
Heidorn *et al.* Cell 2010, Poulikakos *et al.* Nature 2010

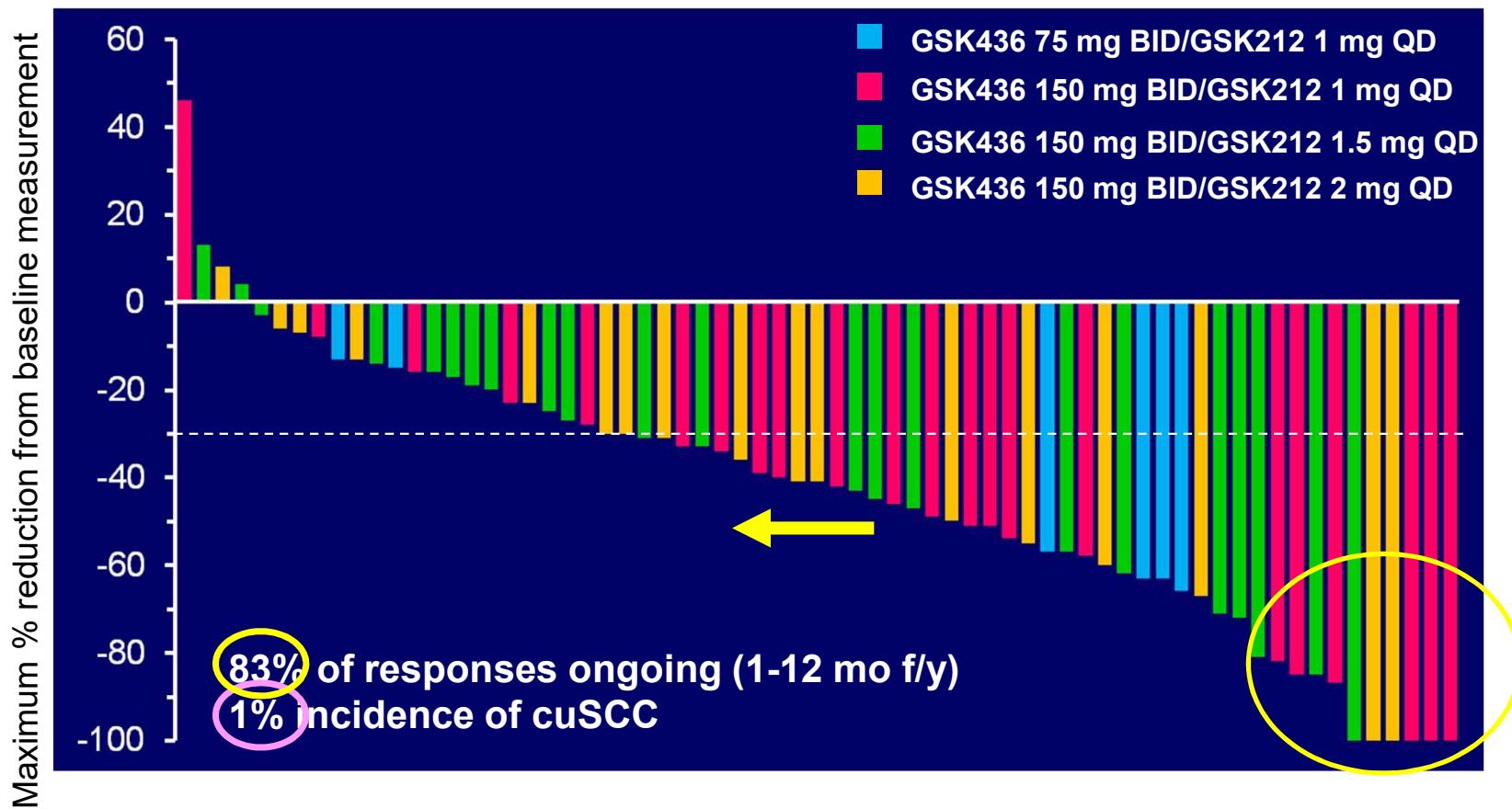
# Paradoxical MAPK activation in HRAS mutant cuSCC/KAs



Hatzivassiliou *et al.* Nature 2010,  
Heidorn *et al.* Cell 2010, Poulikakos *et al.* Nature 2010

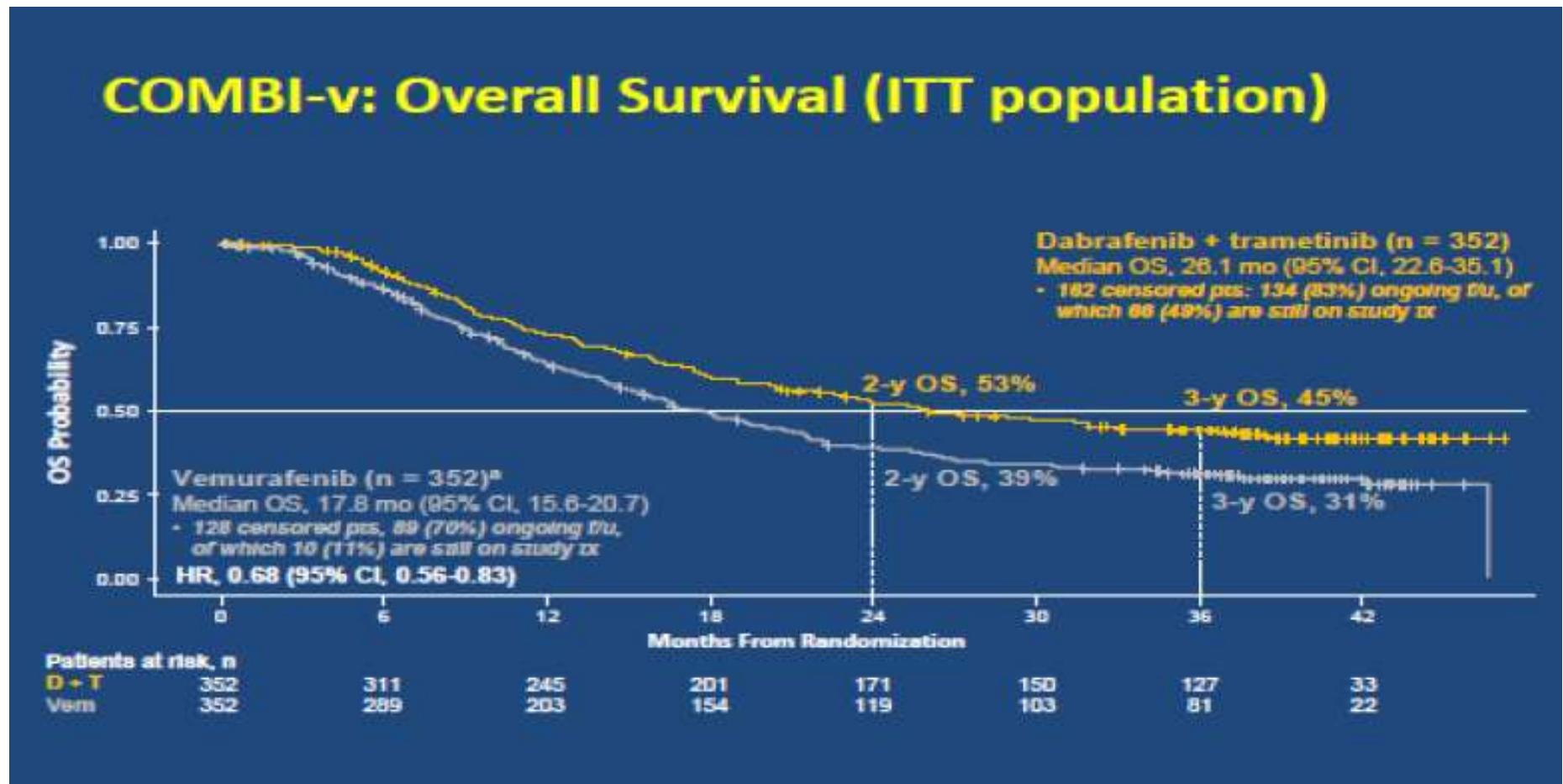
**Paradoxical MAPK activation  
with RAF inhibitors**

## GSK BRAFi+MEKi phase 1: A new paradigm in combination targeted therapy drug development



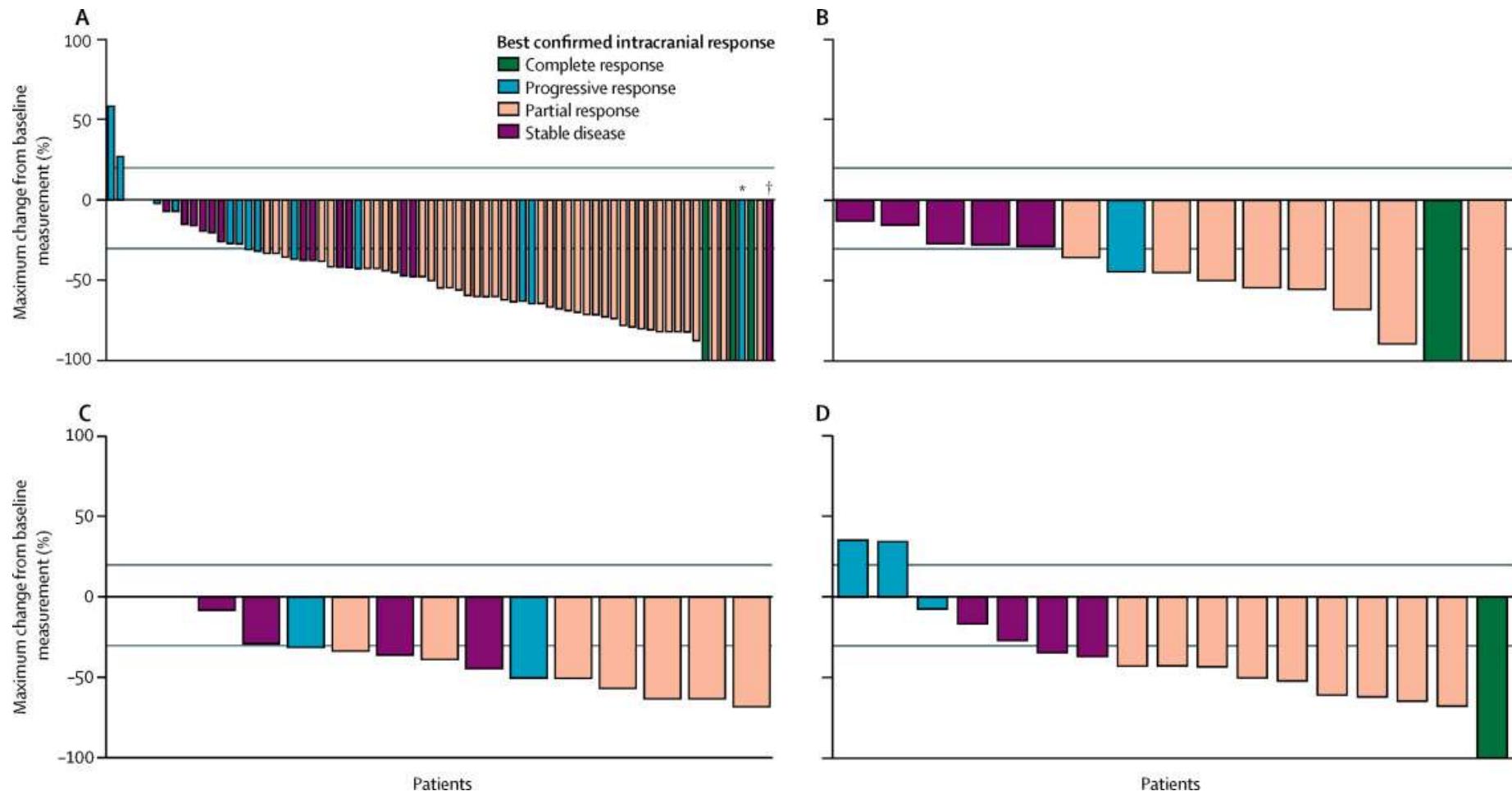
ASCO 2011, abstract #8503: Infante, J. R., G. S. Falchook, D. P. Lawrence, J. S. Weber, R. F. Kefford, J. C. Bendell, R. Kurzrock, G. Shapiro, R. R. Kudchadkar, G. V. Long, H. A. Burris, K. B. Kim, A. Clements, S. Peng, B. Yi, A. J. Allred, D. Ouellet, K. Patel, P. F. Lebowitz, and K. T. Flaherty.

# COMBI OS



Long GV et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/ K-mutant melanoma: long-term survival and safety analysis of a phase 3 study AnnalsofOncology 28: 1631–1639, 2017

# Activity of Dabrafenib + Trametinib on brain mets



Davies MA et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017 Jul;18(7):863-873.

# Take home messages



Environ 40% des mélanomes sont BRAF V600 mutés



L'inhibition BRAF V600 est extrêmement efficace dans les mélanomes BRAF mutés



En monothérapie, les inhibiteurs de BRAF induisent des Spinocellulaires de la peau chez les patients avec mutations de RAS



Les traitements anti BRAF sont extrêmement efficaces sur les métastases cérébrales



La combinaison anti BRAF et anti MEK est maintenant un standard en première ligne chez les patients BRAF mutés

Qu'en est-il en adjuvant?

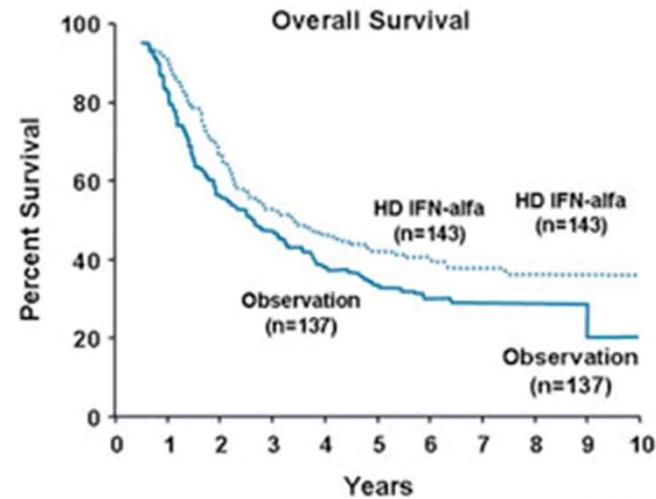
Immunotherapy

BRAF TKIs

# Melanoma (adjuvant treatment)

- High dose IFNa trials
- ECOG 1684
- > IIb – IV resected
- IFNa treatment 20 million units/m<sup>2</sup> five days per week for 4 weeks followed by 10 million units/m<sup>2</sup> subcutaneously three times weekly for an additional 11 months.

## Adjuvant Interferon Alfa-2b: ECOG 1684 Overall Survival



Kirkwood JM, et al. *J Clin Oncol*. 1996;14:7-17.

**Medscape**

This was the only ever really positive study for this regimen...

Ifn alpha thus got FDA approval

But every following study failed to show a survival advantage.

# Melanoma (adjuvant treatment)

- **Low dose SC IFNa**

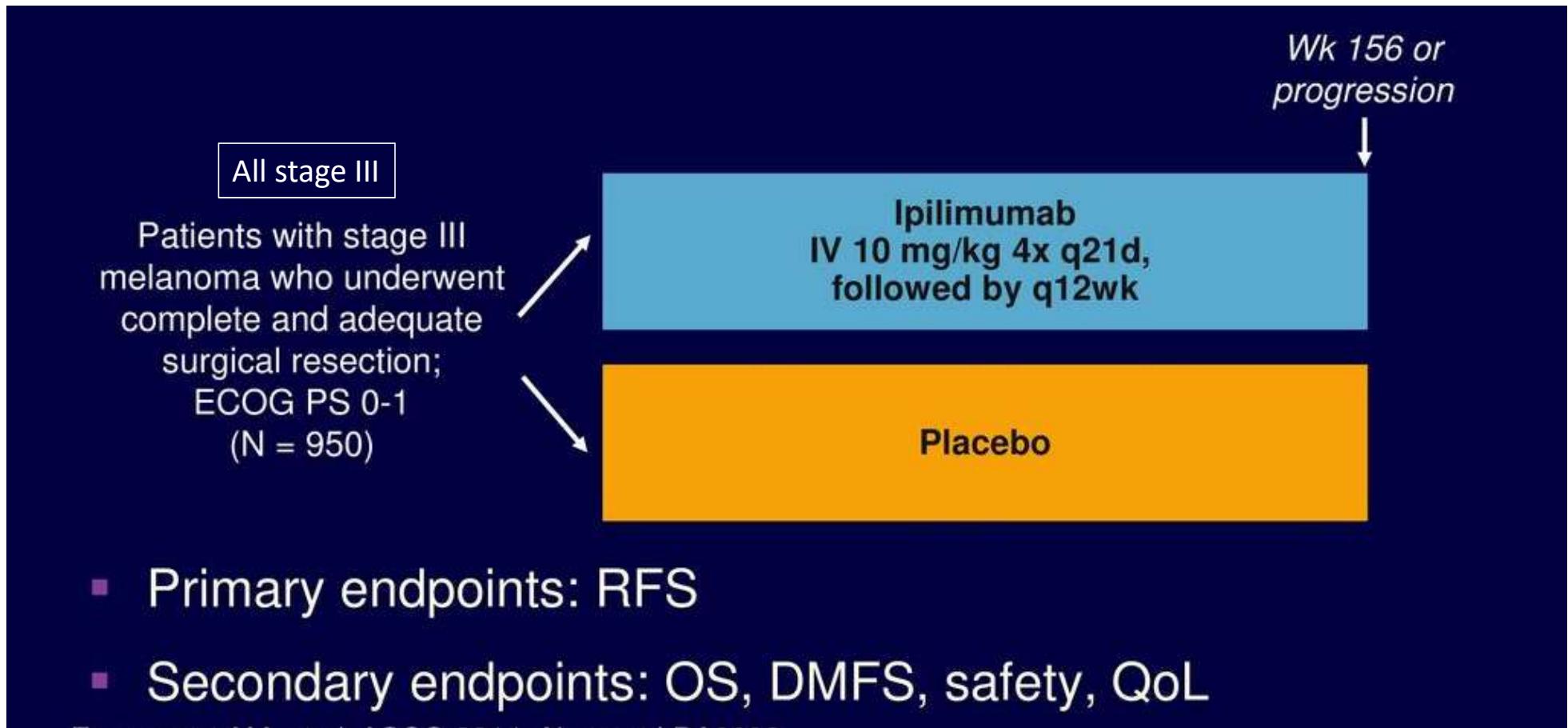
- The use of low or intermediate doses of IFNa and the use of pegylated IFN never showed superior results to high-dose IFNa in terms of overall survival<sup>1, 2</sup>

- **Biochemotherapy**

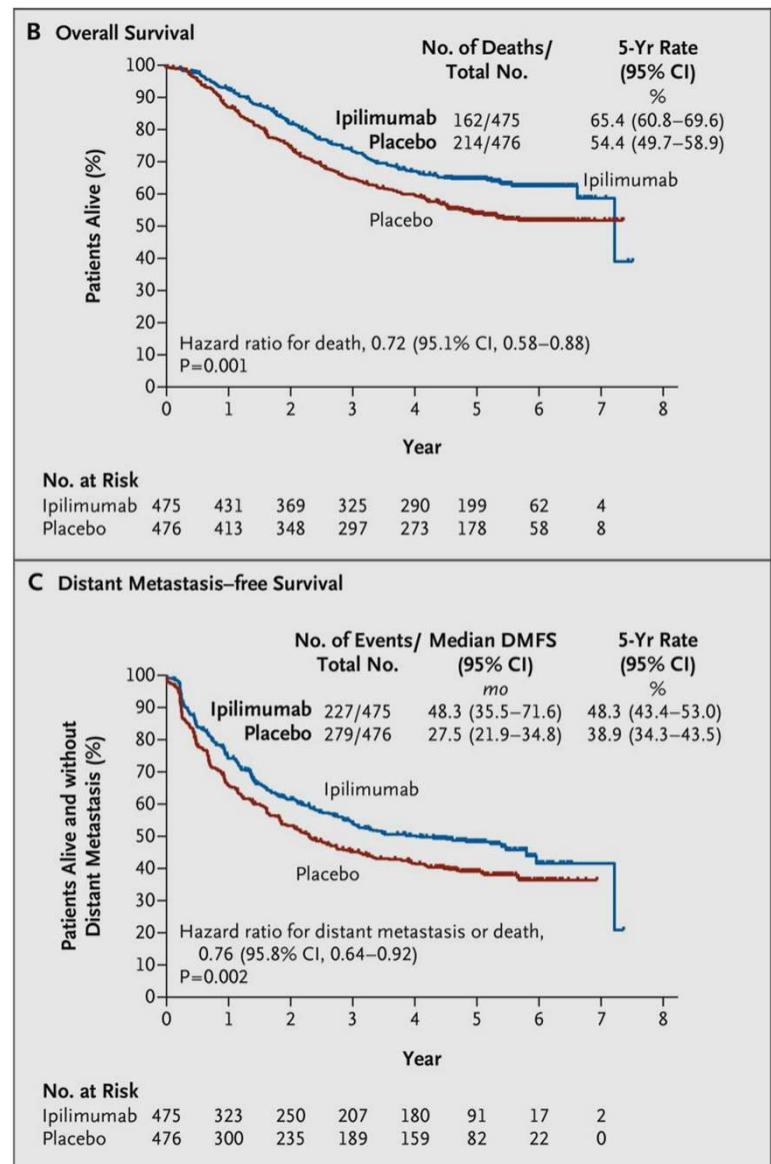
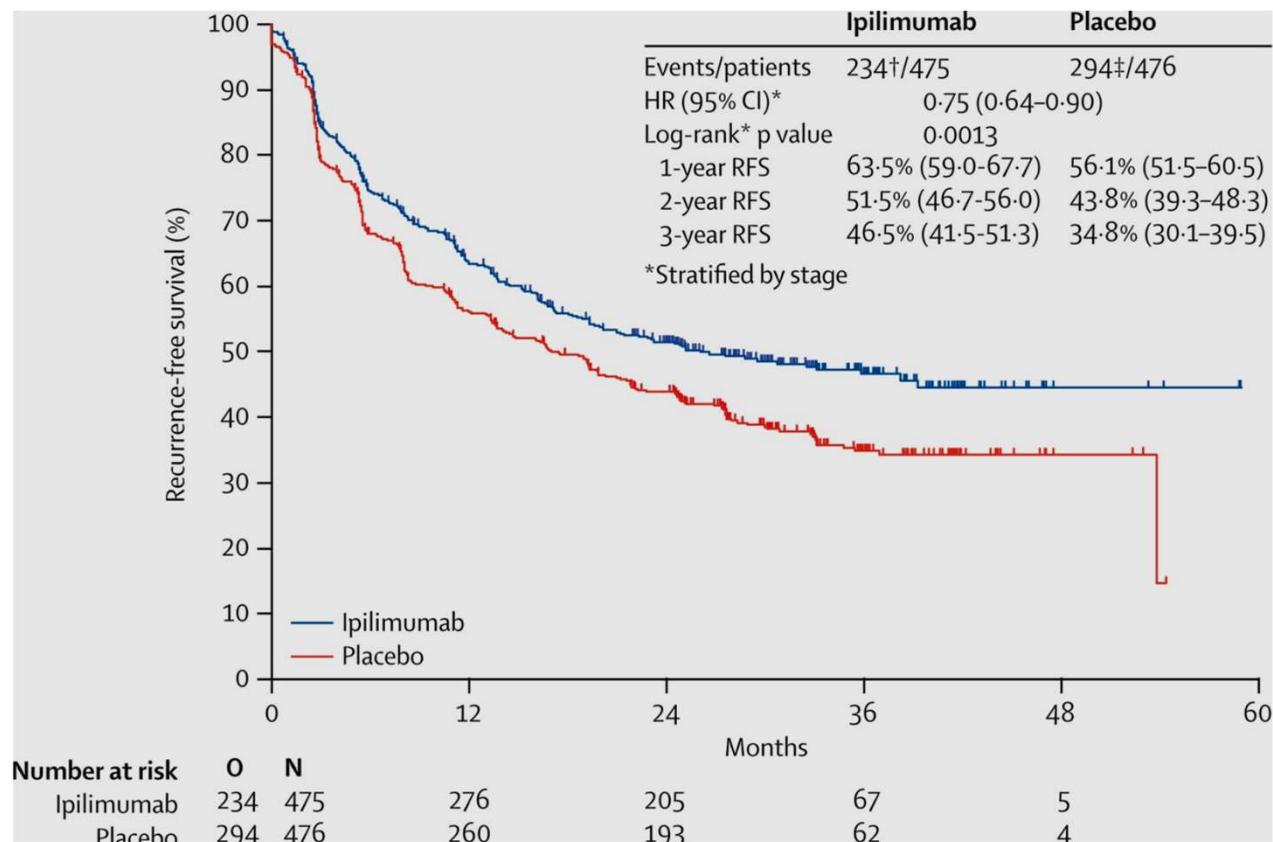
- Intensive biochemotherapy was evaluated as an alternative to high dose IFNa in a phase III cooperative group trial (S0008) with 432 patients with high risk melanoma to either three cycles of DDP, VBL, DTIC, IL-2, and IFNa or to high dose IFNa for one year. No survival advantage<sup>3</sup>

1. Eggermont AM, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. Lancet. 2005;366(9492):1189.
2. Hauschild A, et al. Efficacy of low-dose interferon {alpha}2a 18 versus 60 months of treatment in patients with primary melanoma of  $\geq 1.5$  mm tumor thickness: results of a randomized phase III DeCOG trial. J Clin Oncol. 2010;28(5):841
3. Eggermont AM, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet. 2008;372(9633):117

# Anti CTLA4 immunotherapy



# EFFICACITE



# Immune-Related Adverse Events

**Table 3.** Immune-Related Adverse Events.\*

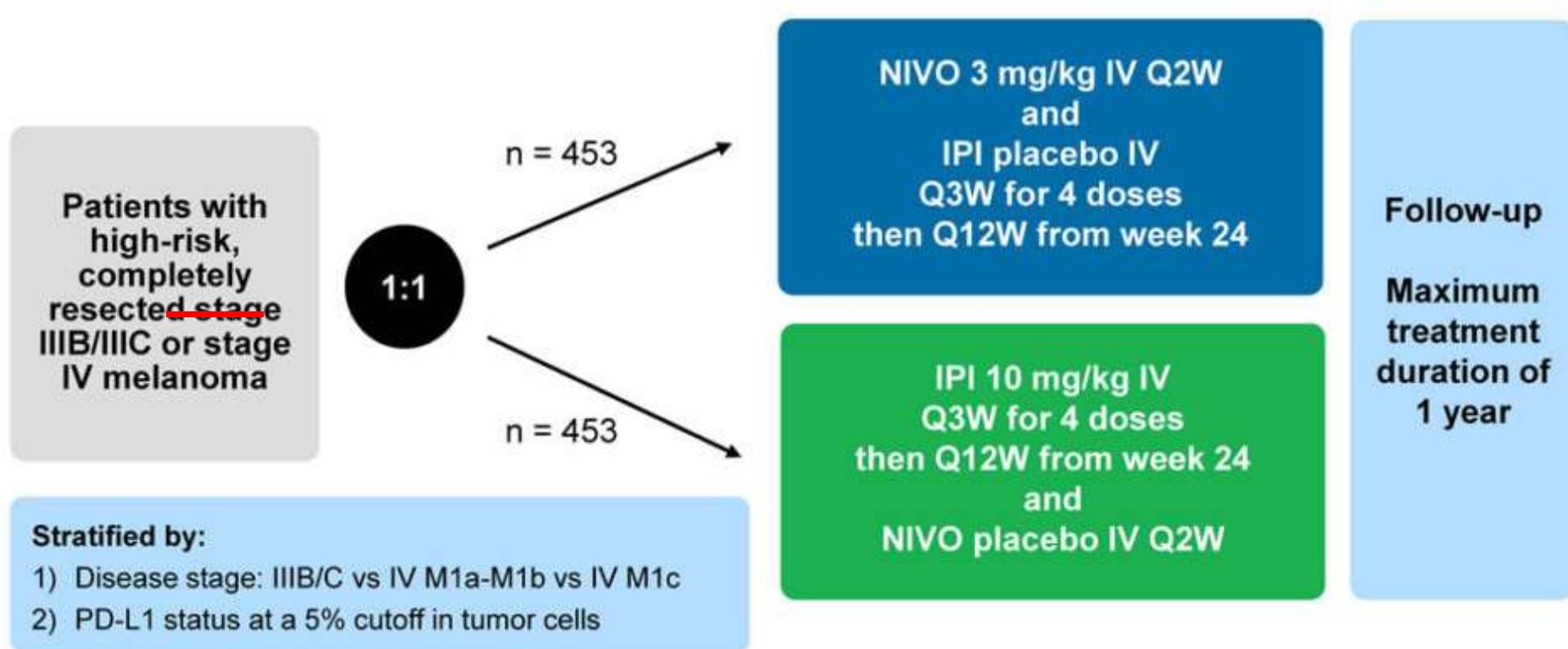
Event	Ipilimumab (N=471)			Placebo (N=474)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 4	Grade 5
Any immune-related adverse event	426 (90.4)	169 (35.9)	27 (5.7)	274 (57.8)	10 (2.1)	0 (0.2)
Any dermatologic event	298 (63.3)	20 (4.2)	0 (0.0)	130 (27.4)	0 (0.0)	0 (0.0)
Rash	161 (34.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any gastrointestinal event†	217 (45.9)	13 (2.7)	3 (0.6)	130 (27.4)	3 (0.6)	1 (0.2)
Diarrhea	113 (23.9)	1 (0.2)	0 (0.0)	80 (16.9)	2 (0.4)	0 (0.0)
Colitis	10 (2.1)	0 (0.0)	0 (0.0)	7 (1.5)	1 (0.2)	1 (0.2)
Any endocrine event‡	10 (2.1)	0 (0.0)	0 (0.0)	38 (8.0)	1 (0.2)	0 (0.0)
Hypophysitis	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Any hepatic event§	13 (2.8)	0 (0.0)	0 (0.0)	20 (4.2)	1 (0.2)	0 (0.0)
Increase in liver enzymes levels	14 (3.0)	6 (1.3)	0 (0.0)	18 (3.8)	0 (0.0)	0 (0.0)
Any neurologic event	21 (4.5)	5 (1.1)	4 (0.8)	9 (1.9)	0 (0.0)	0 (0.0)
Other‡	111 (23.6)	34 (7.2)	2 (0.4)	23 (4.9)	8 (1.7)	0 (0.0)

In Oct 2015 the FDA approval of ipilimumab (Yervoy) in stage III melanoma to include adjuvant treatment of patients with lymph nodes >1 mm who have undergone total lymphadenectomy, including complete resection.

Eggermont AM et al. Lancet Oncol. 2015;16(5):522-530

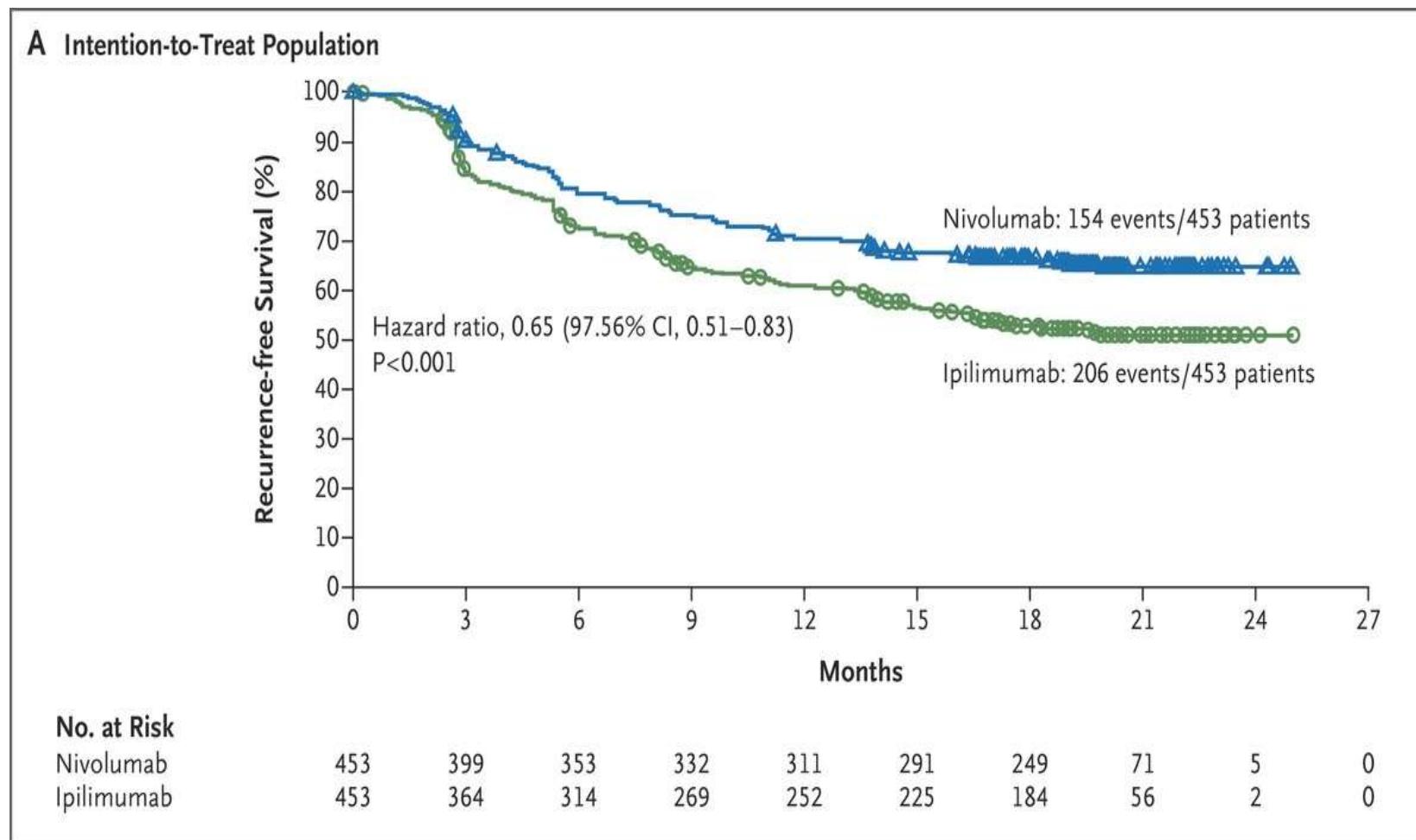
Eggermont AM et al. N Engl J Med 2016;375:1845-1855

# Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma



**Enrollment period:** March 30, 2015 to November 30, 2015

# EFFICACITE



**RFS 12 mois de 70% !!!**

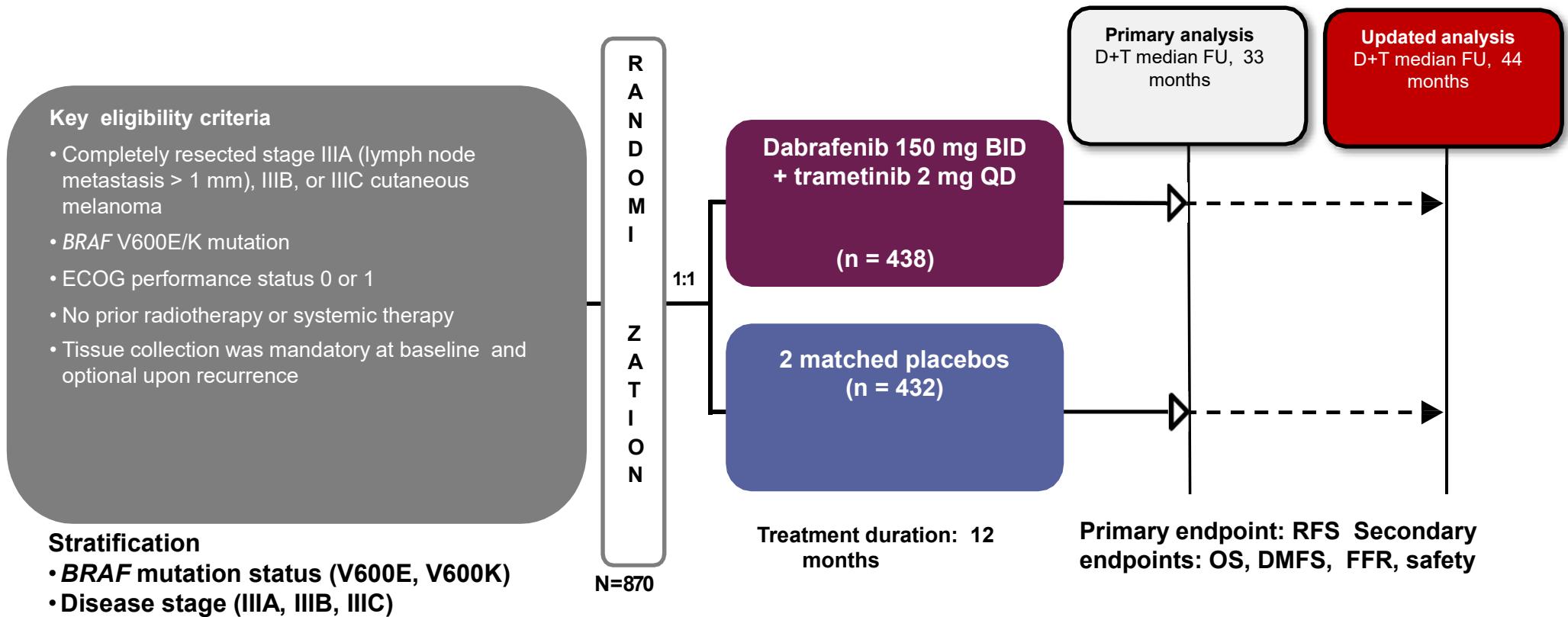
Weber J et al. N Engl J Med ;377:1824-1835

# Qu'en est-il en adjuvant?

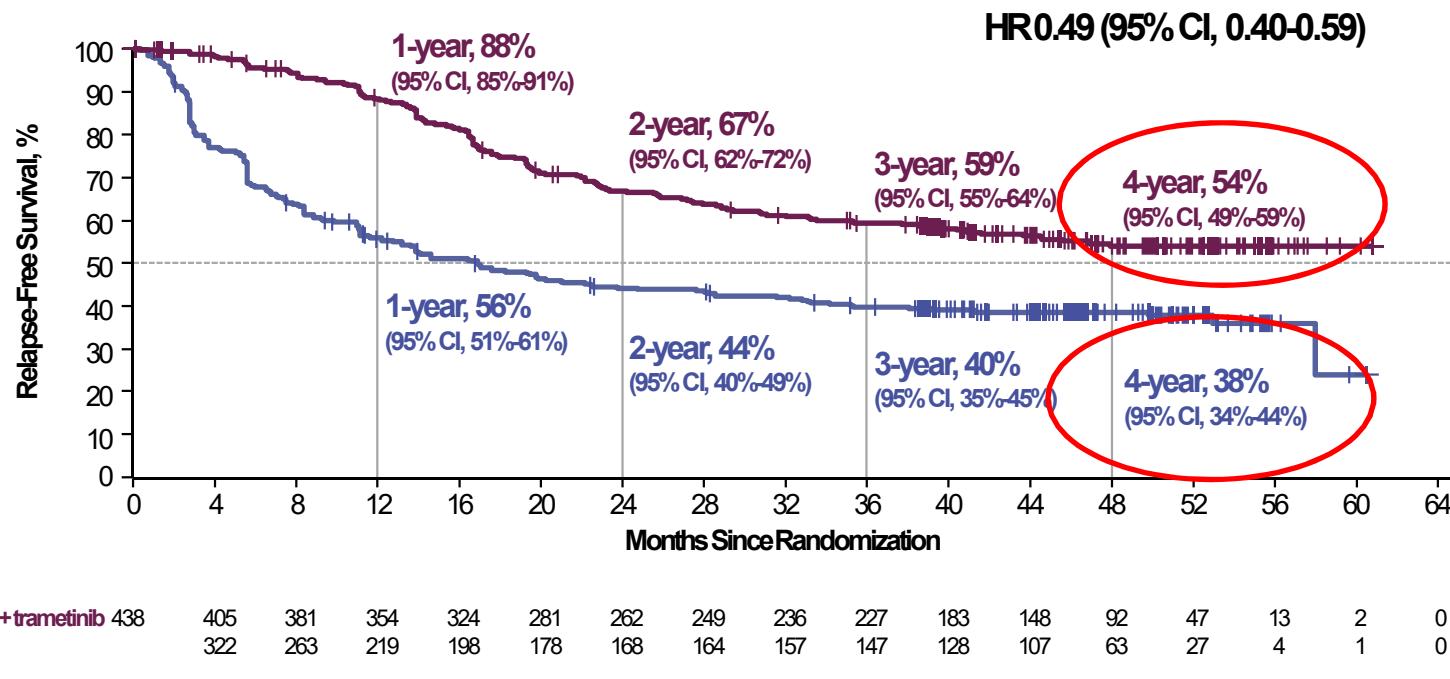
Immunotherapy

BRAF TKIs

# COMBI-AD: STUDY DESIGN

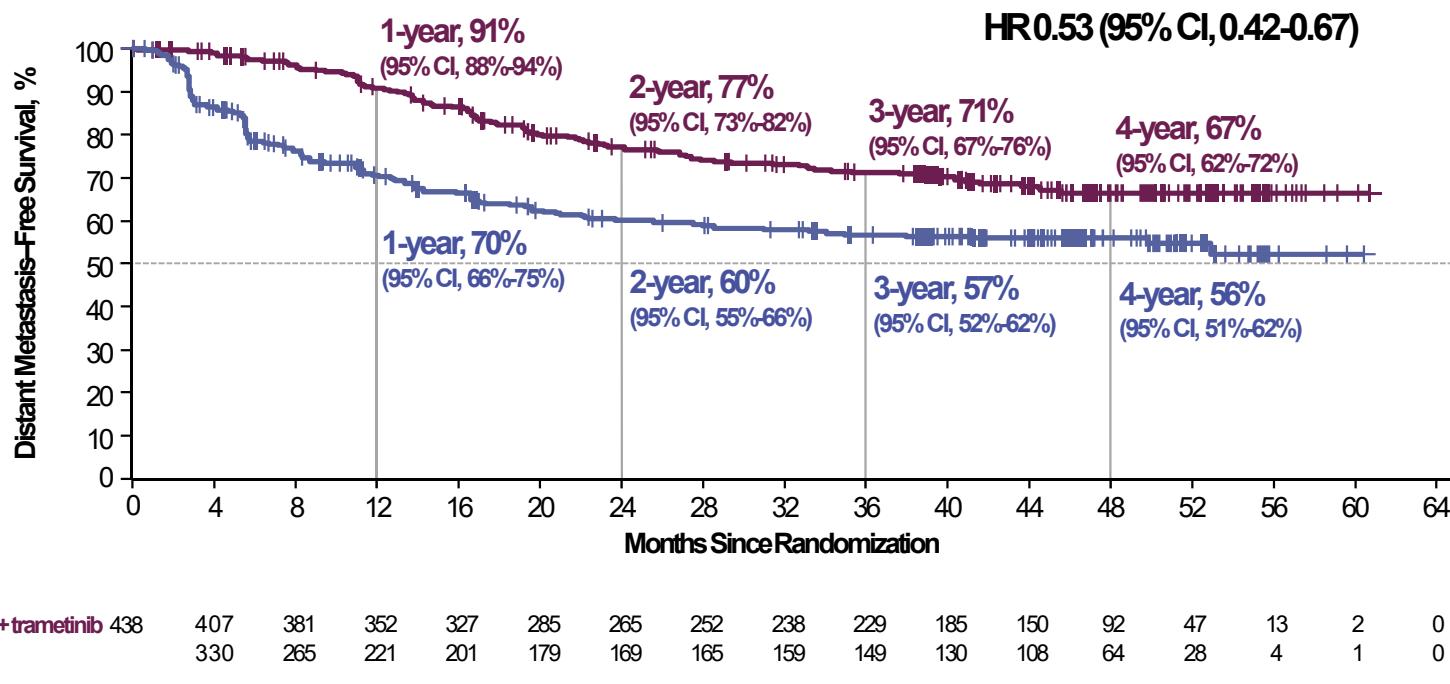


# RELAPSE-FREE SURVIVAL 4 years



PRESENTED BY GV LONG AT ESMO 2018

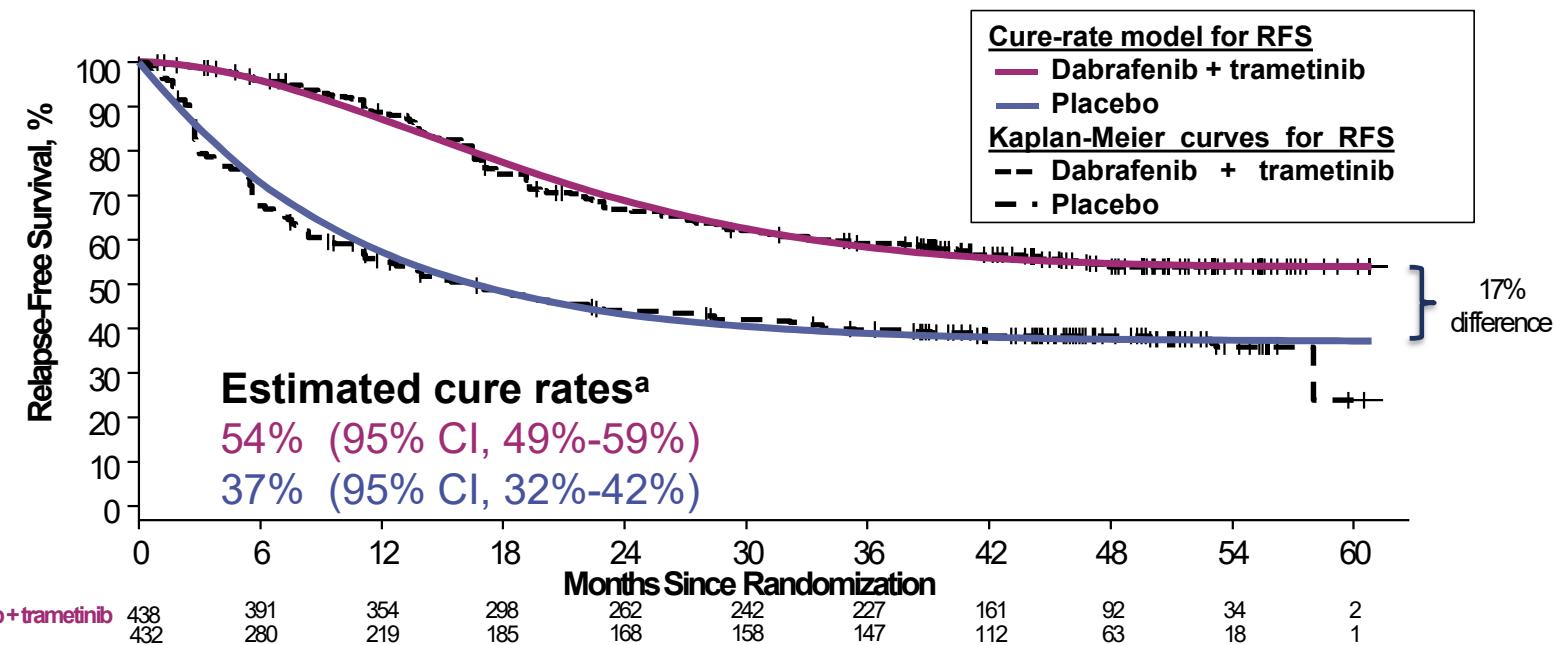
# DISTANT METASTASIS-FREE SURVIVAL



PRESENTED BY GV LONG AT ESMO 2018

# CURE-RATE MODEL RESULTS

A higher proportion of patients are estimated to be relapse-free long term with D+T vs placebo



<sup>a</sup>Proportion of patients expected to remain relapse-free long term.

PRESENTED BY GV LONGA AT ESMO 2018

# Take Home Messages



**En adjuvant, dans les stades 3 réséqués, l'Ipilimumab (anti CTLA-4) augmente la survie mais est très toxique**



**En adjuvant, dans les stades 3 (b,c) réséqués, l'immunothérapie par anti PD-1 est un standard de traitement (RFS 12 mois de 70%) et est nettement moins toxique que l'Ipilimumab**



**Chez les patients BRAF V600 mutés, stade 3 un traitement par association anti BRAF et anti MEK augmente la survie de 17% et est un standard dans ces patients**



**De nouveaux inhibiteurs BRAF sont en développement**



**Des études associant immunothérapie et TKIs anti BRAF sont en cours**



Société Luxembourgeoise d'Oncologie



Merci beaucoup !