

IMMUNOTHERAPIE et MELANOME

Anti-CTLA4 / anti-PD1 et toxicité

BIENNALES DE MONACO

3 février 2016

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**GUSTAVE
ROUSSY**
CANCER CAMPUS
GRAND PARIS

The logo graphic for Gustave Roussy consists of several colored lines: an orange line above the 'E' in 'GUSTAVE', a green line below the 'Y' in 'ROUSSY', and a pink line below the 'Y' in 'ROUSSY'. There is also a teal line below the 'S' in 'ROUSSY'.



Epidémiologie

- Exceptionnel avant la puberté
- Pic d'incidence : 40 et 50 ans. Sex-ratio = 1
- 2 % des cancers; Mortalité : 0,6-0,9% des décès par cancer

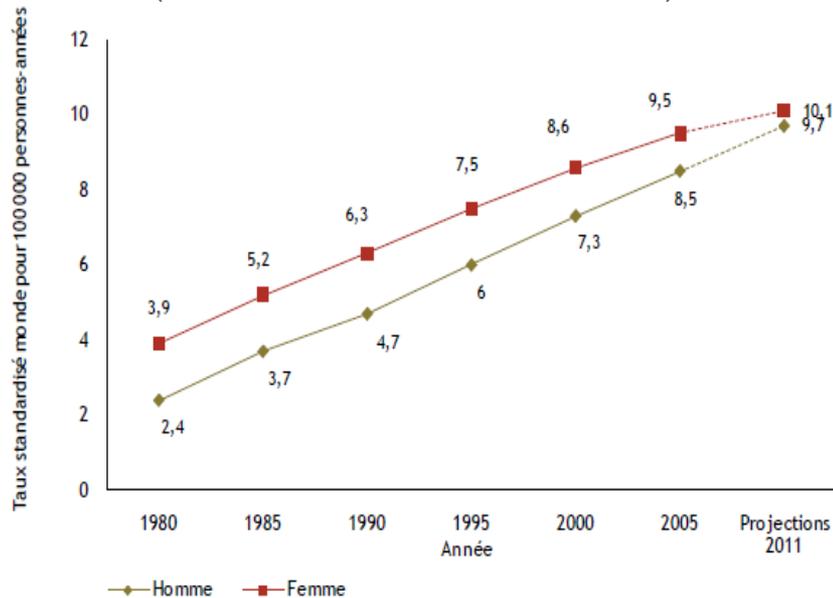
- Survie à 5 ans passée de 50 % à 80 % entre 1950 et 2000 : diagnostic plus précoce

Epidémiologie - France

Incidence

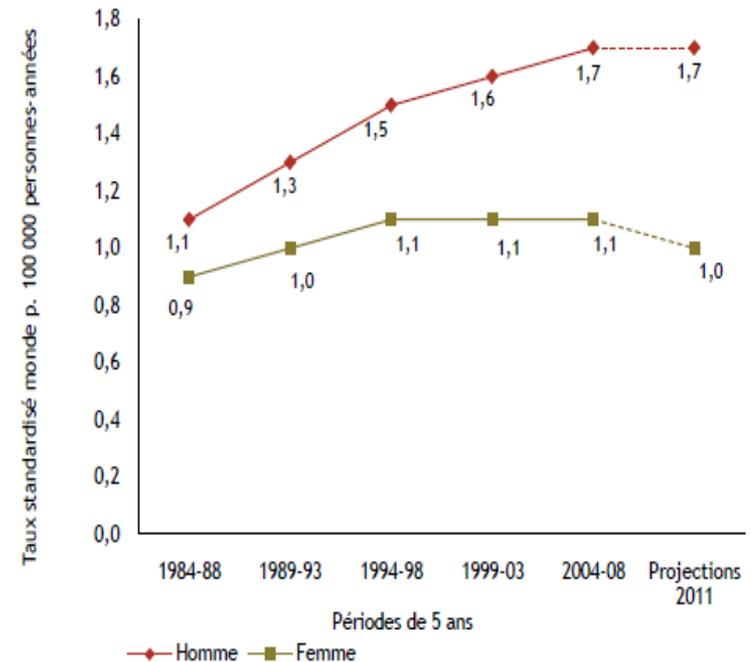
En 2011 : 9 780 nouveaux cas
En 2012 : 11 176 nouveaux cas par an.
(Rapport INCA 2014)

Plus forte augmentation d'incidence
parmi l'ensemble des cancers
(ralentissement récent observé).



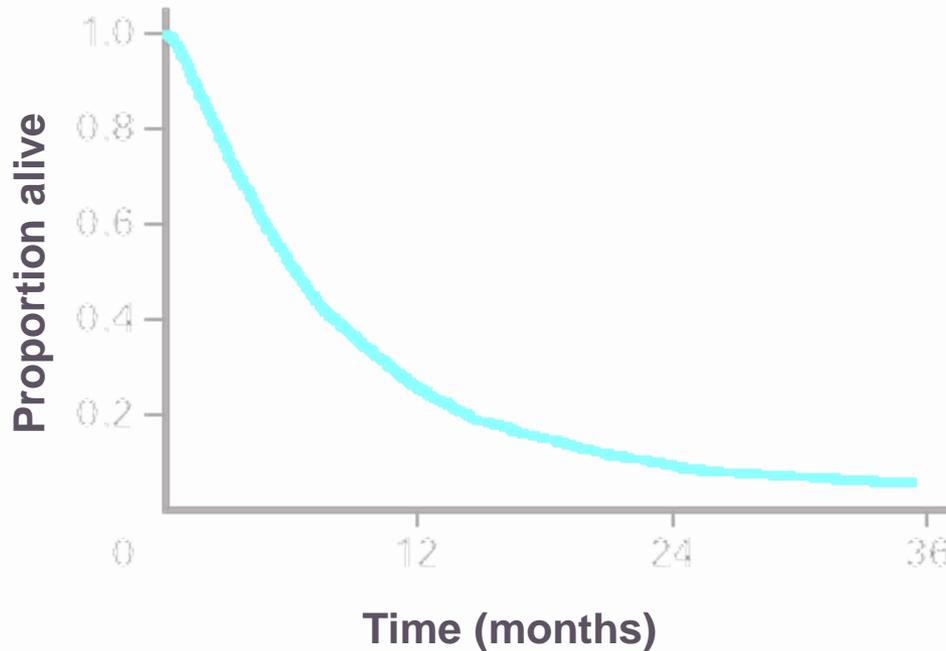
Mortalité

1 620 décès
estimés en 2011



Probabilité de survie en phase métastatique

Overall Survival for Metastatic Melanoma



Adapted from Korn 2008

Données de Survie d'après 42 études de Phase II incluant 2.100 pts stade IV:

- survie globale à 12 mois: 25.5 %,
- médiane de survie: 6.2 mois

1Korn EL et al. J Clin Oncol 2008;26(4):527-34.

2Dummer R, Hauschild A, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii86-8.

3 Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer;46(2):270-83.

Traitement mélanome stade IV - 2010

chimiothérapies cytotoxiques

dacarbazine Déticène®
1000mg/m²/3semaines.

fotémustine Muphoran®

immunothérapies :

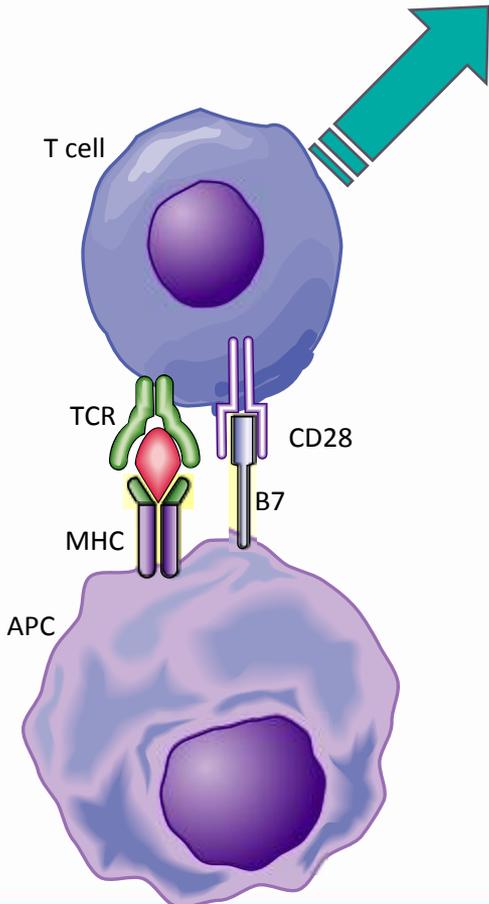
Interleukine - utilisée aux
USA peu en France.

L'ipilimumab = anti CTLA4
(Yervoy®) AMM en 2^oligne

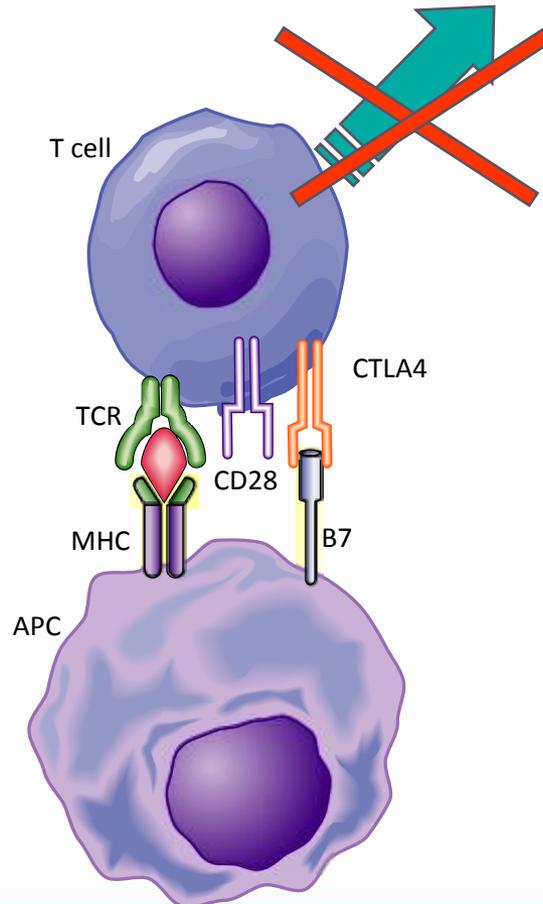
Mécanisme d'action de l'Ipilimumab

Ipilimumab blocks negative signaling from CTLA-4

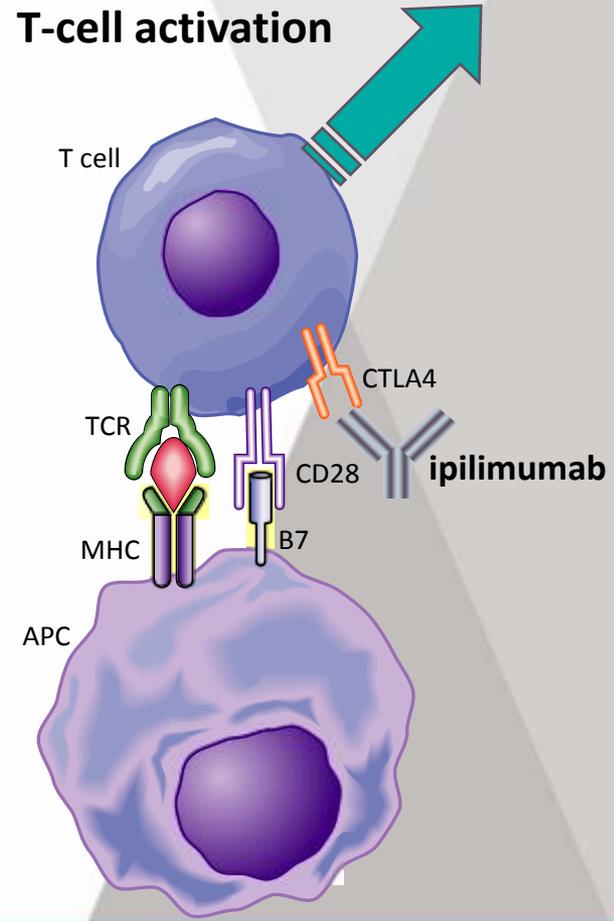
Co-stimulation via CD28:
T-cell activation



CTLA-4 blocks co-stimulation:
No T-cell activation



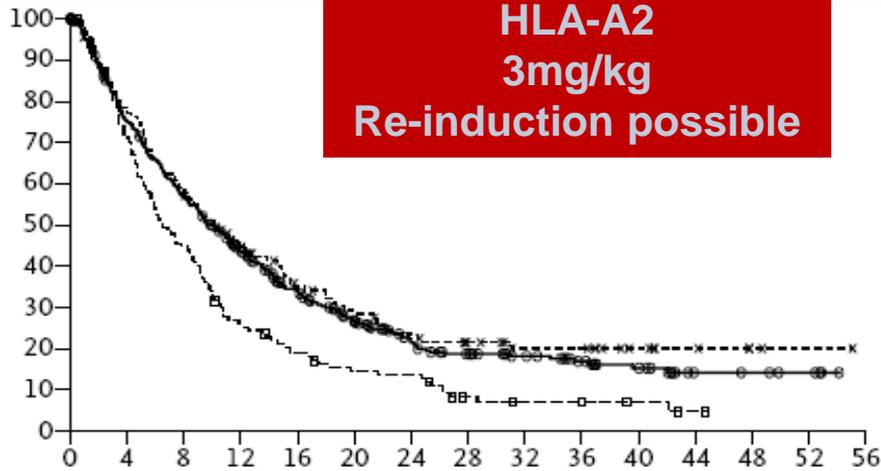
Ipilimumab blocks CTLA-4:
T-cell activation



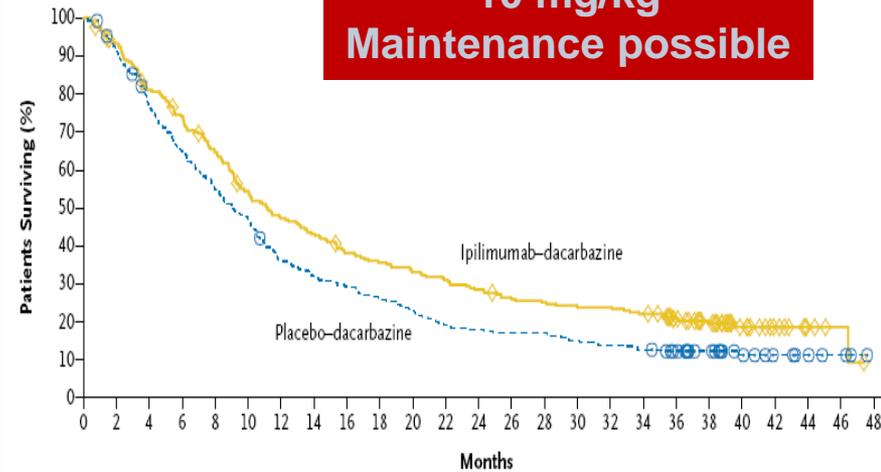
Ipilimumab: essais d'enregistrement

Ipilimumab

**Pre-treated-pts
+/- gp100
HLA-A2
3mg/kg
Re-induction possible**



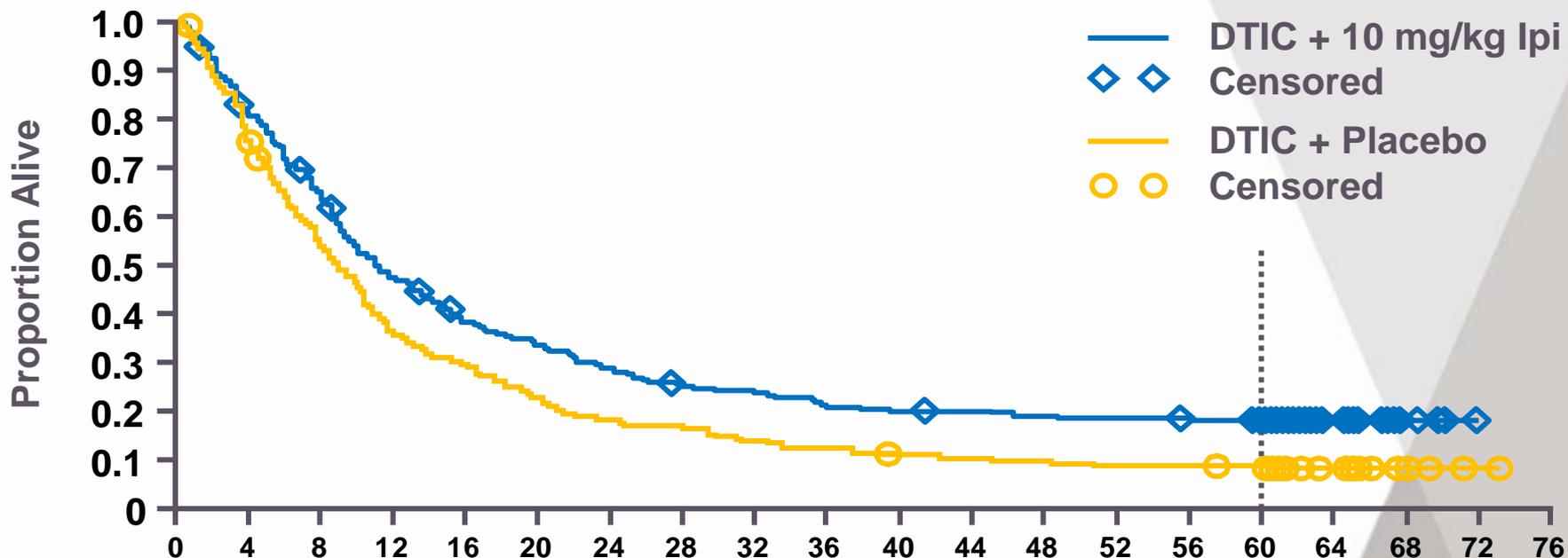
**naive-pts
+ DTIC
10 mg/kg
Maintenance possible**



	1 Year	2 Year
Ipi + gp100 N=403	44%	22%
Ipi + pbo N=137	46%	24%
gp100 + pbo N=136	25%	14%

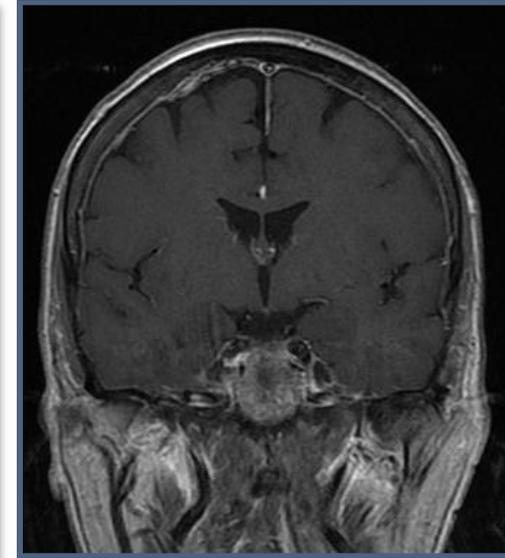
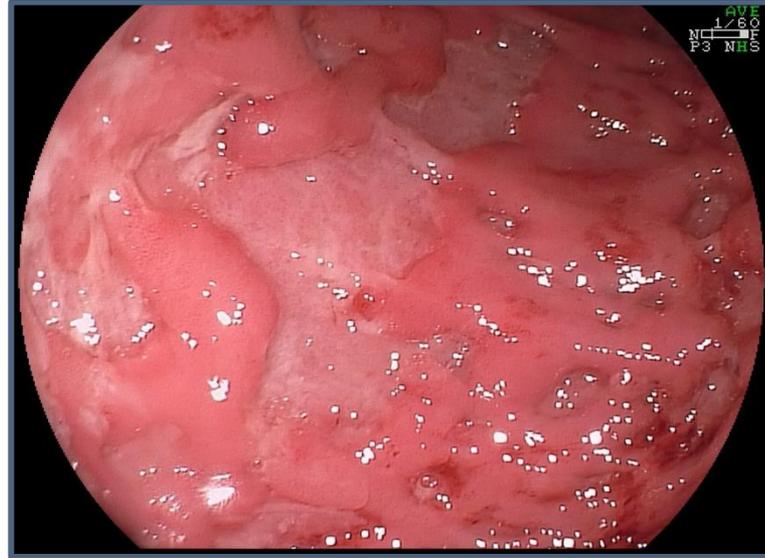
	1 Year	2 Year	3 Year
Ipilimumab+ DTIC N=250	47.3	28.5	20.8
Placebo+ DTIC N=252	36.3	17.9	12.2

Ipilimumab: essai d'enregistrement



Treatment Group	Overall survival rate, % [95% CI]				
	1-year	2-year	3-year	4-year	5-year
Ipi + DTIC (N=250)	47.6 [41.2-53.7]	28.9 [23.3-34.7]	21.3 [16.3-26.6]	19.1 [14.4-24.3]	18.2 [13.6-23.4]
Placebo + DTIC (N=252)	36.4 [30.4-42.4]	17.8 [13.3-22.8]	12.1 [8.4-16.5]	9.7 [6.4-13.7]	8.8 [5.7-12.8]

Toxicité



Grade ^{3/4} AE 3 mg/kg	Drug related	Immune related	AEs (10 mg/kg)	All grade	Grade 3-4,
			Skin	50-70	0-4
Colon	30-45	8-25			
Hepatitis	3-10	3-8			
Endocrinopathy	5-10	1-5			

Traitement mélanome stade IV - 2012

Mutation
BRaf

Pas de mutation
BRaf

thérapies ciblées

mutation BRAF V600 50% MM,

vemurafenib Zelboraf®

Dabrafénib Tafinlar®

réponse tumorale chez 50 % des pts.
résistance secondaire en 7-8mois

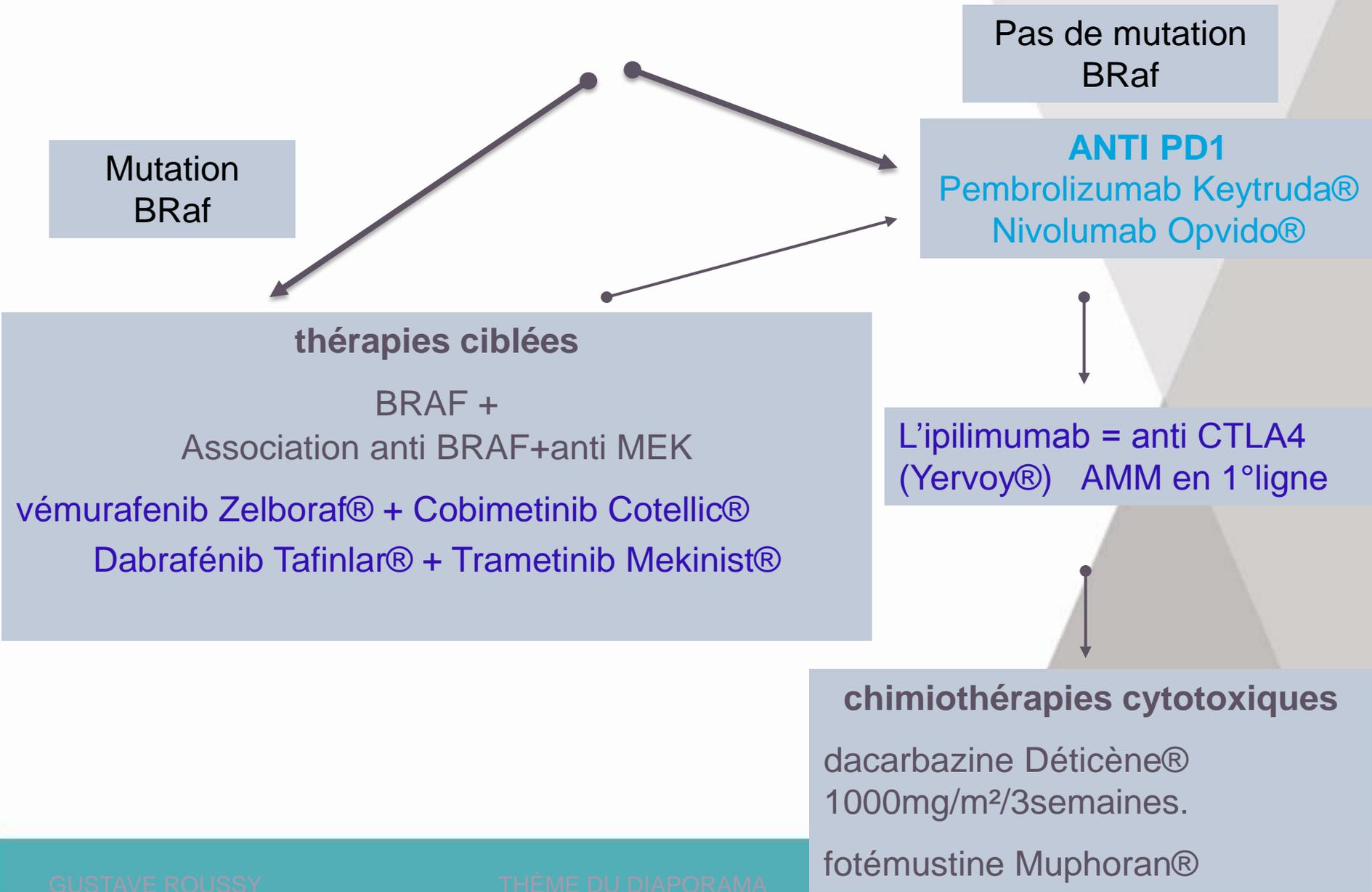
L'ipilimumab = anti CTLA4
(Yervoy®) AMM en 1°ligne

chimiothérapies cytotoxiques

dacarbazine Déticène®
1000mg/m²/3semaines.

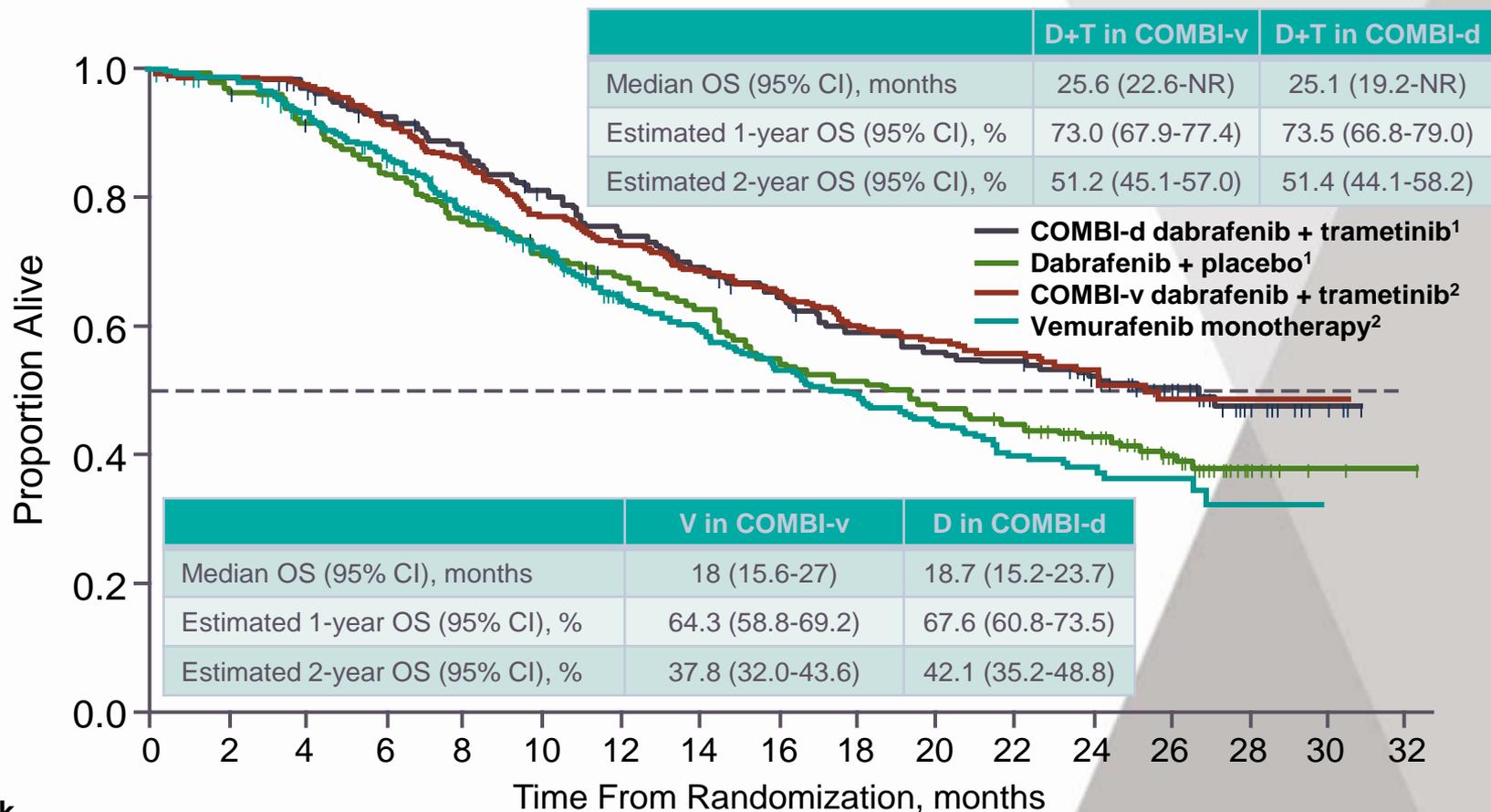
fotémustine Muphoran®

Traitement mélanome stade IV - 2015



Mutation Braf: Braf +/- Mek inhibiteurs

COMBI-v and COMBI-d: Overall Survival Curves



Number at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
COMBI-d D + T ¹	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0
Dabrafenib + placebo ¹	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1
COMBI-v D + T ²	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib ²	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

1. Long GV, et al. *Lancet Oncol.* 2015;386:444-451; 2. Data on file (March 2015 cutoff).

Blocking CTLA-4

- CTLA-4 expressed 24-48 H after AG presentation
- During first AG encounter



Blocking PD-1

- Further AG encounters also
- PD-1 expressed during chronic AG presentation

Blocking CTLA-4

- CTLA-4 expressed 24-48 H after AG presentation
- During first AG encounter
- Ligands expressed on APC in lymphoid organs



Blocking PD-1

- PD-1 expressed during chronic AG presentation
- Further AG encounters also
- Ligand expressed on APC and inflammed tissues and tumors
- Expression of PD-L1 might influence treatment outcome

Blocking CTLA-4

- CTLA-4 expressed 24-48 H after AG presentation
- During first AG encounter



- Ligands expressed on APC in lymphoid organs



- Delayed effect
- Broad T cell repertoire activation
- Wide spectrum of adverse events expected



Blocking PD-1

- PD-1 expressed during chronic AG presentation
- Further AG encounters also

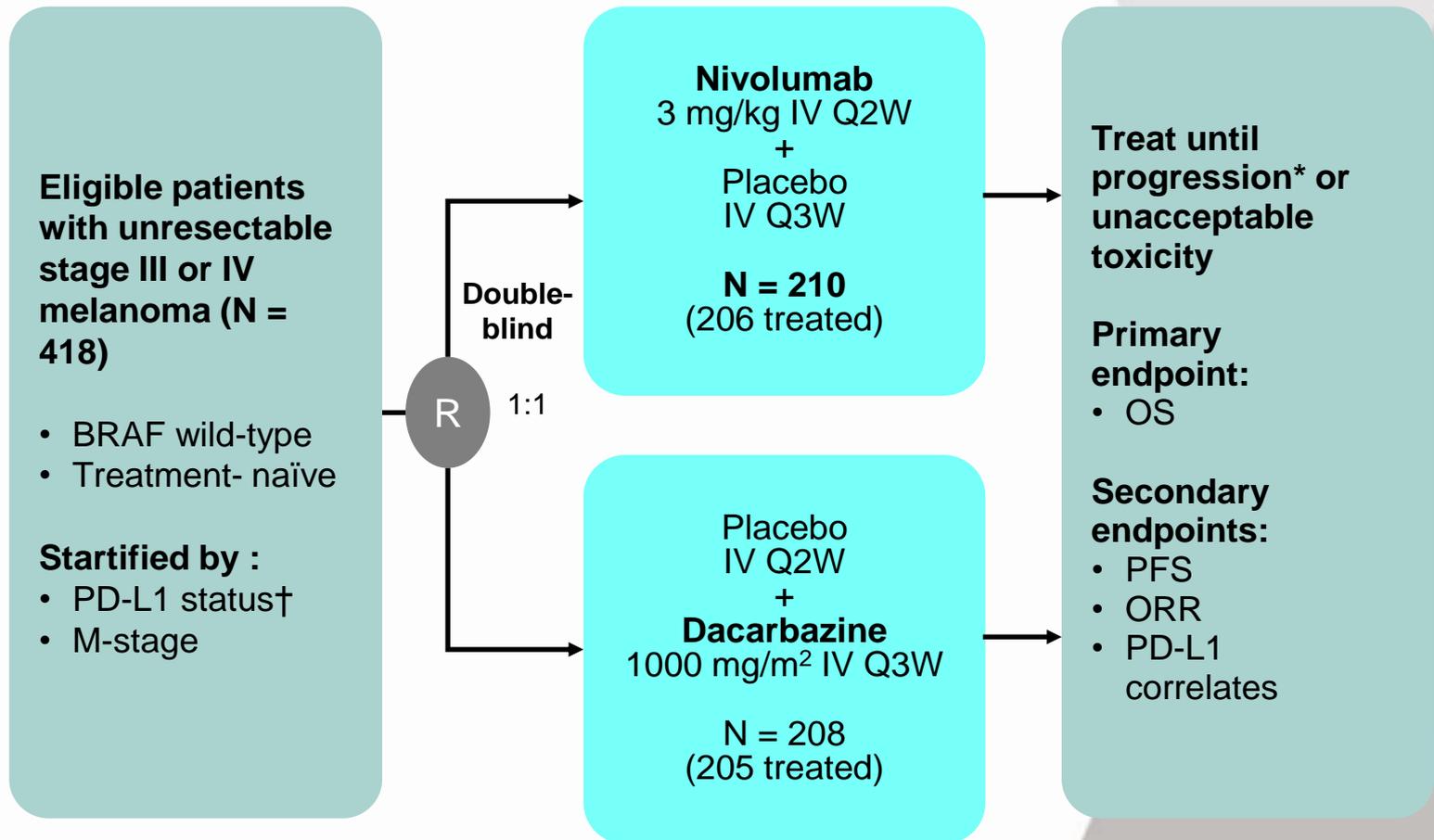
- Ligand expressed in inflamed tissues and tumors
- Expression of PD-L1 might influence treatment outcome

- More rapid effect
- More specific effect on T cells already « on site » or inflammatory context
- Less adverse events expected



Nivolumab

Chekmate 066: Schéma de l'étude



†PD-L1 positive: ≥ 5% tumor cell surface staining.

Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Meilleure réponse globale

	Nivolumab (N = 210)	Dacarbazine (N = 208)
ORR, % (95% CI)	40 % (33–47 %)	14 % (10–19 %)
Best overall response		
Complete response	8 %	1 %
Partial response	32 %	13 %
Stable disease	17 %	22 %
Progressive disease	33 %	49 %
Unable to determine	11 %	15 %

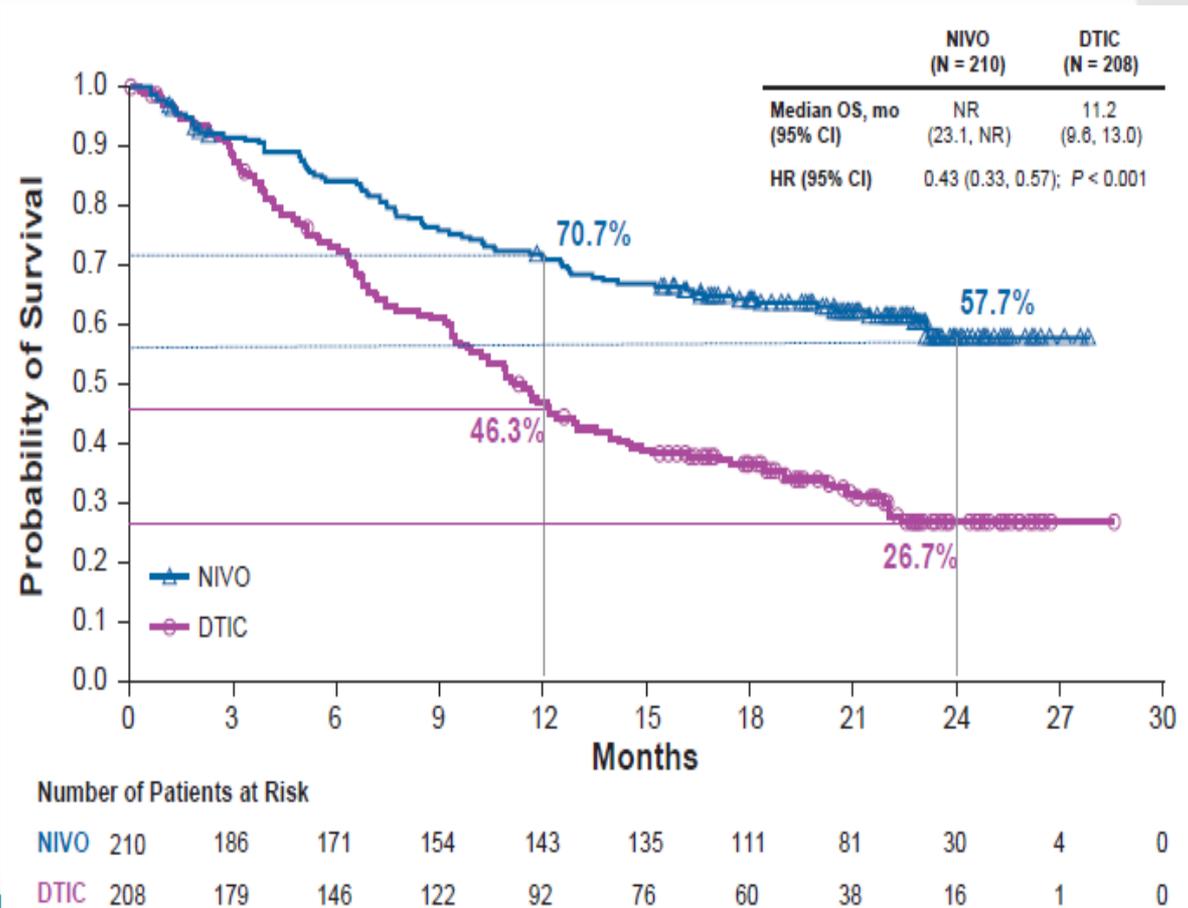
Effets indésirables

	Nivolumab (N = 206)		Dacarbazine (N = 205)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Patients reporting, n (%)				
Drug-related AE	153 (74)	24 (12)	155 (76)	36 (18)
Serious drug-related AE	19 (9)	12 (6)	18 (9)	12 (6)
Drug-related AE leading to discontinuation	5 (2)	4 (2)	7 (3)	5 (2)

There were no deaths related to study drug toxicity in either arm

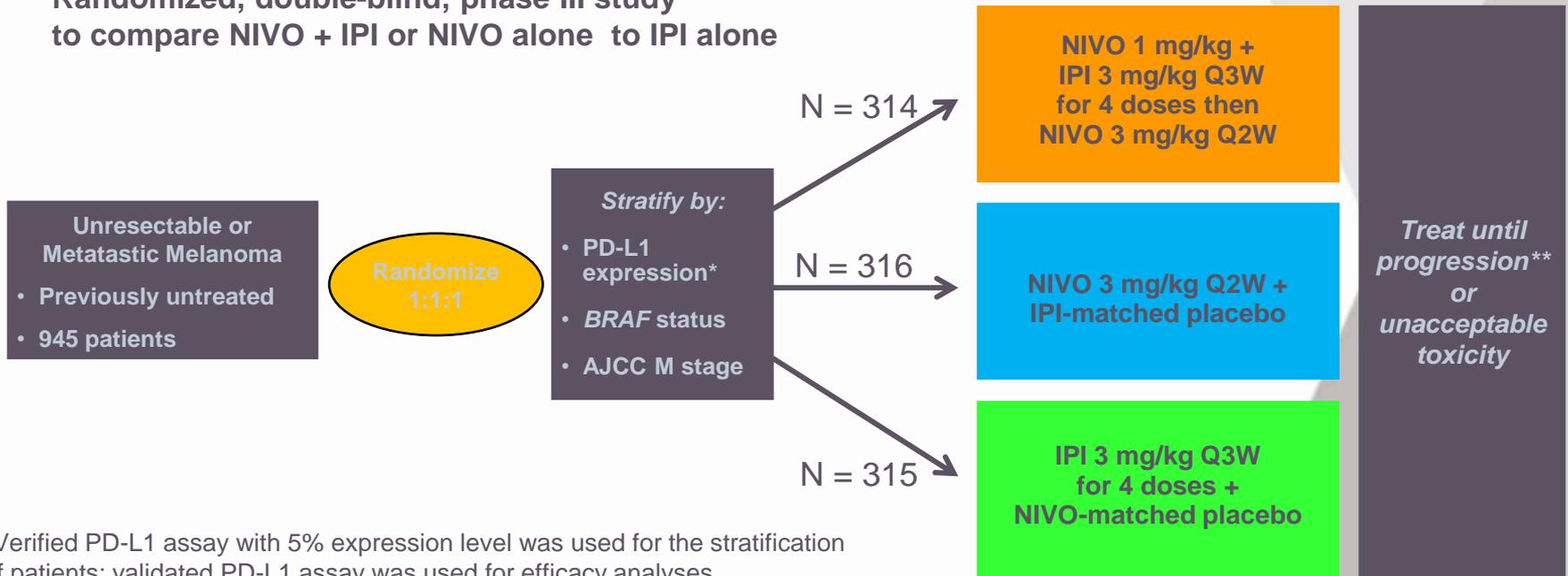
Étude CheckMate 066

- Survie à 2 ans et données actualisées de tolérance chez des patients naïfs de traitement atteints d'un mélanome avancé traités par nivolumab ou dacarbazine



Checkmate 067: Study Design

Randomized, double-blind, phase III study
to compare NIVO + IPI or NIVO alone to IPI alone

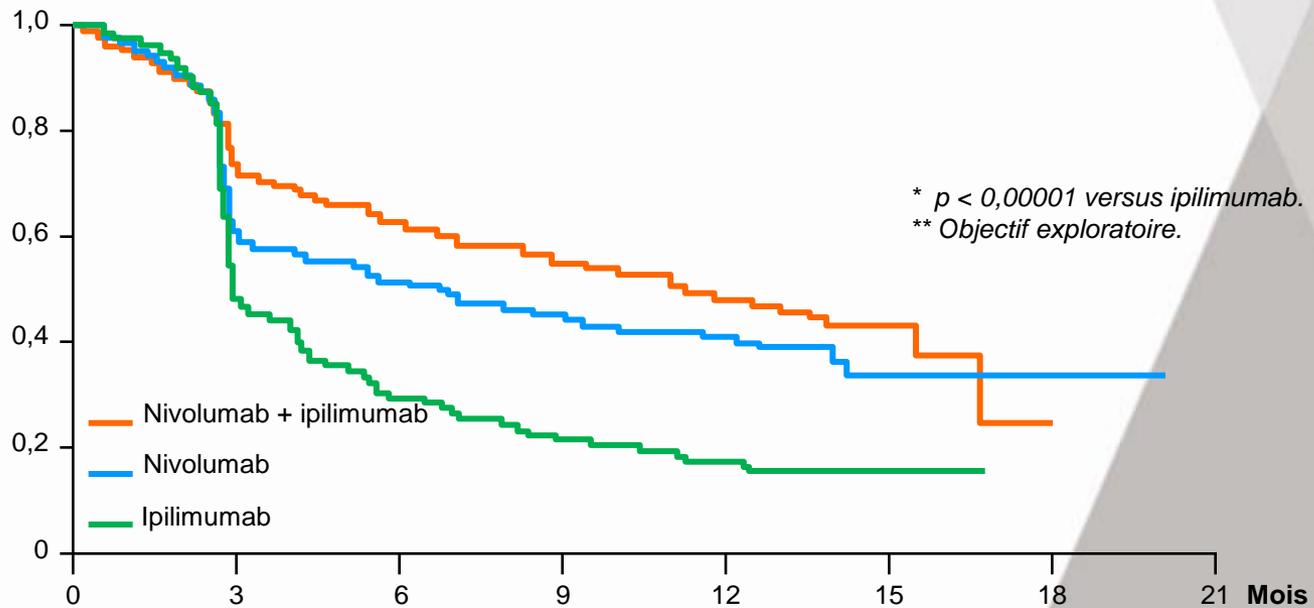


*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Ckeckmate 067: Survie sans progression

	Nivolumab + ipilimumab (n = 314)	Nivolumab (n = 316)	Ipilimumab (n = 315)
SSP médiane, mois (IC ₉₅)	11,5 (8,9-16,7)	6,9 (4,3-9,5)	2,9 (2,8-3,4)
HR (IC _{99,5}) versus ipilimumab	0,42 (0,31-0,57)*	0,57 (0,43-0,76)	-
HR (IC ₉₅) versus nivolumab	0,74 (0,60-0,92)**	-	-



Patients à risque (n)

— Nivolumab + ipilimumab	314	219	173	151	65	11	1	0
— Nivolumab	316	177	147	124	50	9	1	0
— Ipilimumab	315	137	77	54	24	4	0	0

Safety Summary

Patients Reporting Event, %	NIVO + IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- **67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response**

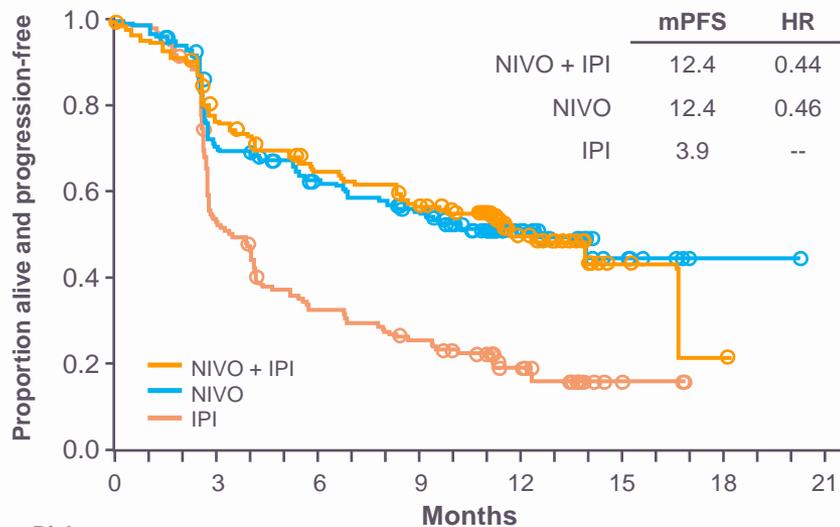
Treatment-Related Select AEs Reported in $\geq 10\%$ of Patients

Patients Reporting Event, %	NIVO + IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	17.6	8.3	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0	4.8	14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve

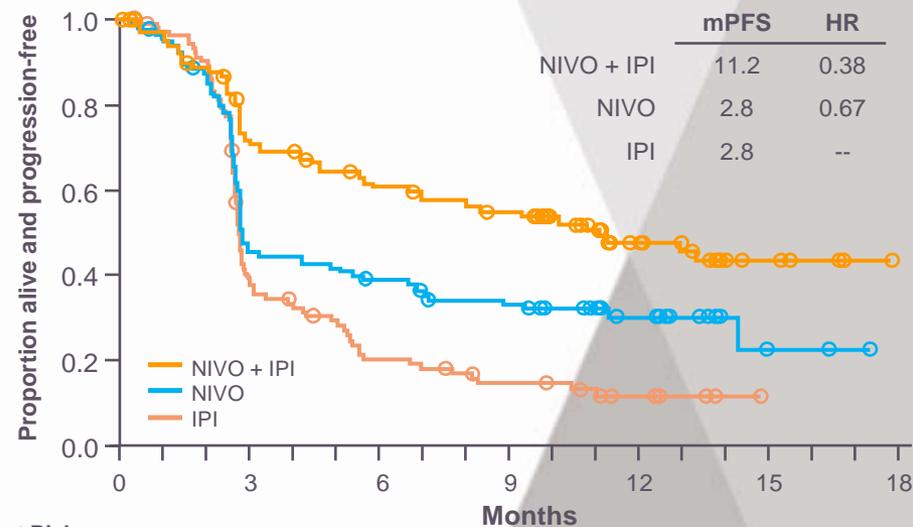
Checkmate 067 : PFS by PD-L1 Expression Level (1%)

PD-L1 ≥1%*



No. at Risk	Months							
	0	3	6	9	12	15	18	21
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



No. at Risk	Months						
	0	3	6	9	12	15	18
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

MK3475 Pembrolizumab

Étude de cohorte KEYNOTE-001

11	2012												2013								
D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S

Nonrandomized
IPI Naive and IPI Treated
2 Q3W, 10 Q3W, 10 Q2W
N = 135

Randomized
IPI Treated
2 Q3W vs 10 Q3W
N = 173

Randomized
IPI Naive and Treated
10 Q3W vs 10 Q2W
N = 244

This Pooled Analysis
N = 655

Randomized
IPI Naive
2 Q3W vs 10 Q3W
N = 103

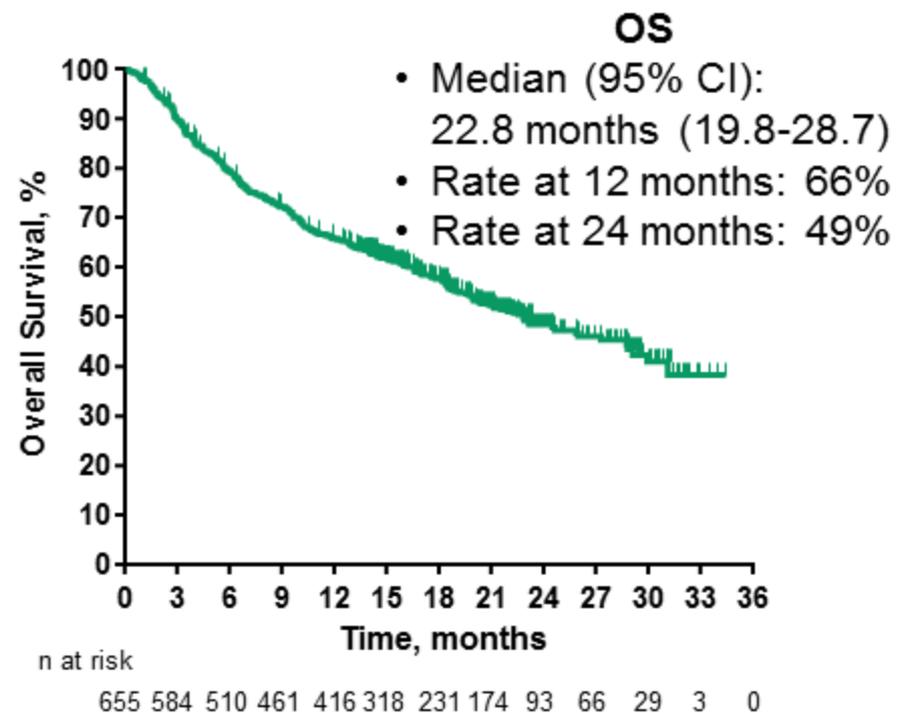
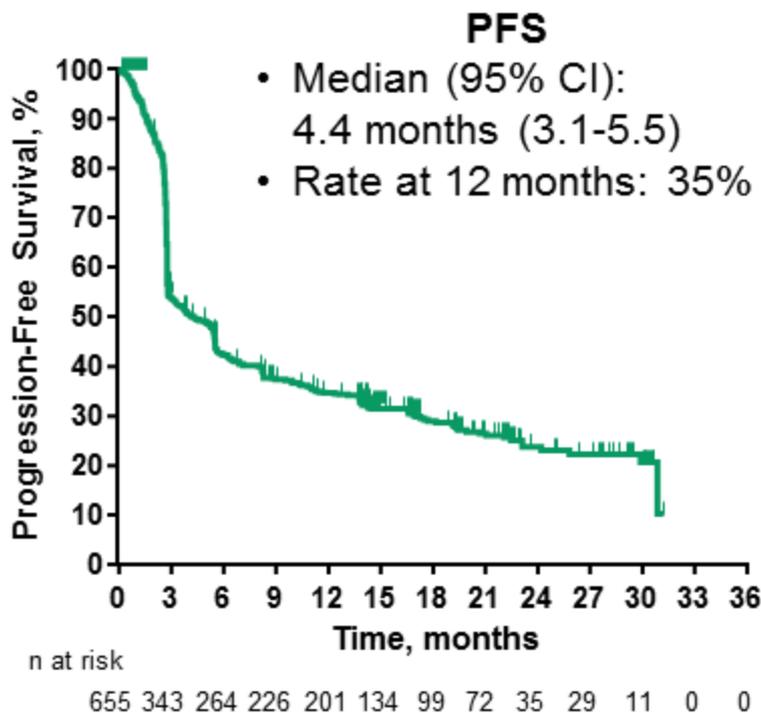
- IPI-T defined as **unequivocal PD** within 6 mo of first IPI dose
- BRAF inhibitor **not required** for *BRAF*-mutant melanoma

- IPI-T defined as **confirmed PD** within 24 wk of last IPI dose; **≥ 2 IPI doses required**
- BRAF inhibitor **required** for IPI-T, but not IPI-N, *BRAF*-mutant melanoma

Keynote 001 : Survie sur l'ensemble de la population

A. Daud. Presented May 30, 2015.

Survival in Total Population



Analysis cut-off date: October 18, 2014.

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual Meeting '15

Keynote 001 : Résumé des effets indésirables

Adverse Event, n (%)	IPI-T (n = 342)	IPI-N (n = 313)	Total (n = 655)
Duration of therapy, mean (range), weeks	31,9 (0,1-116,3)	35,1 (0,1-123,1)	33,4 (0,1-123,1)
No. of doses, median (range)	8 (1-59)	11 (1-58)	10 (1-59)
Any grade treatment related	82 %	85 %	83 %
Grade 3-4 treatment related	14 %	14 %	14 %
Treatment-related death	0 %	0 %	0 %
Discontinuation due to treatment-related AE	4 %	4 %	4 %

- Median duration of follow-up was 15 months (range, 8-29)
- As of data cutoff date, 244 patients (37 %) were still receiving pembrolizumab
 - As of May 2015, ~180 patients (~ 27 %) remain on treatment

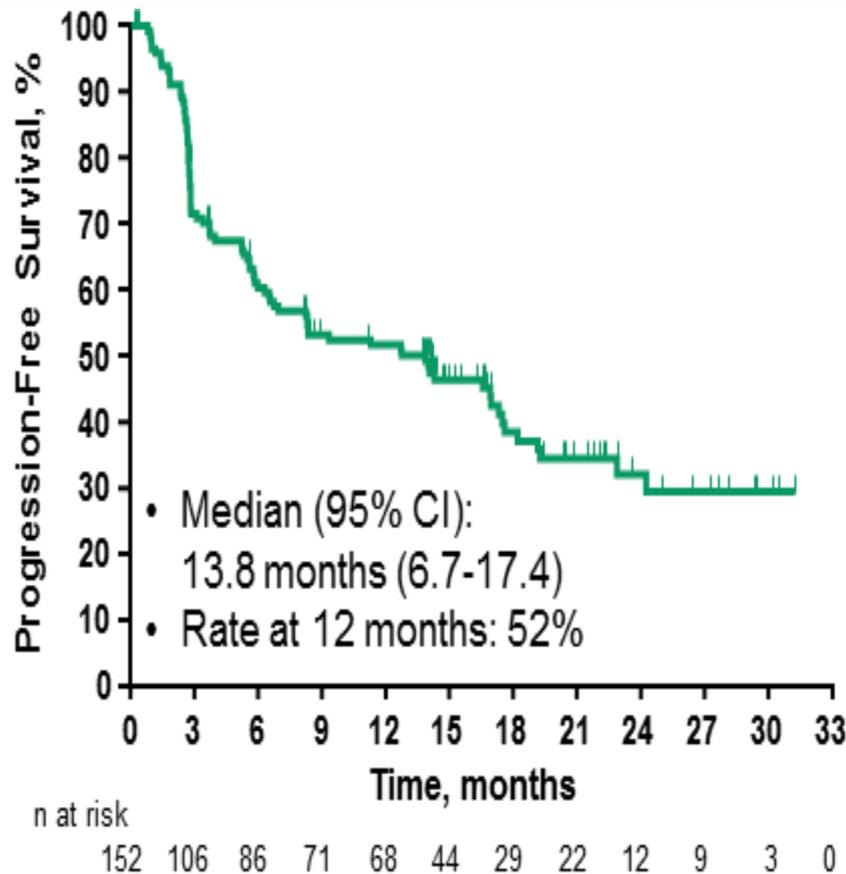
Keynote 001 : Traitement de 1^{ère} ligne : efficacité^a

	Total (N = 133)	BRAF^{v600} Wild Type (n = 109)	BRAF^{v600} Mutant (n = 22)
Complete response, % (95% CI)	13,5 (8,2-20,5)	12,8 (7,2-20,6)	18,2 (5,2-40,3)
ORR, % (95% CI)	45,1 (36,5-54,0)	45,0 (35,4-54,8)	50,0 (28,2-71,8)
DCR, % (95% CI)	60,9 (52,1-69,2)	60,6 (50,7-69,8)	63,6 (40,7-82,8)

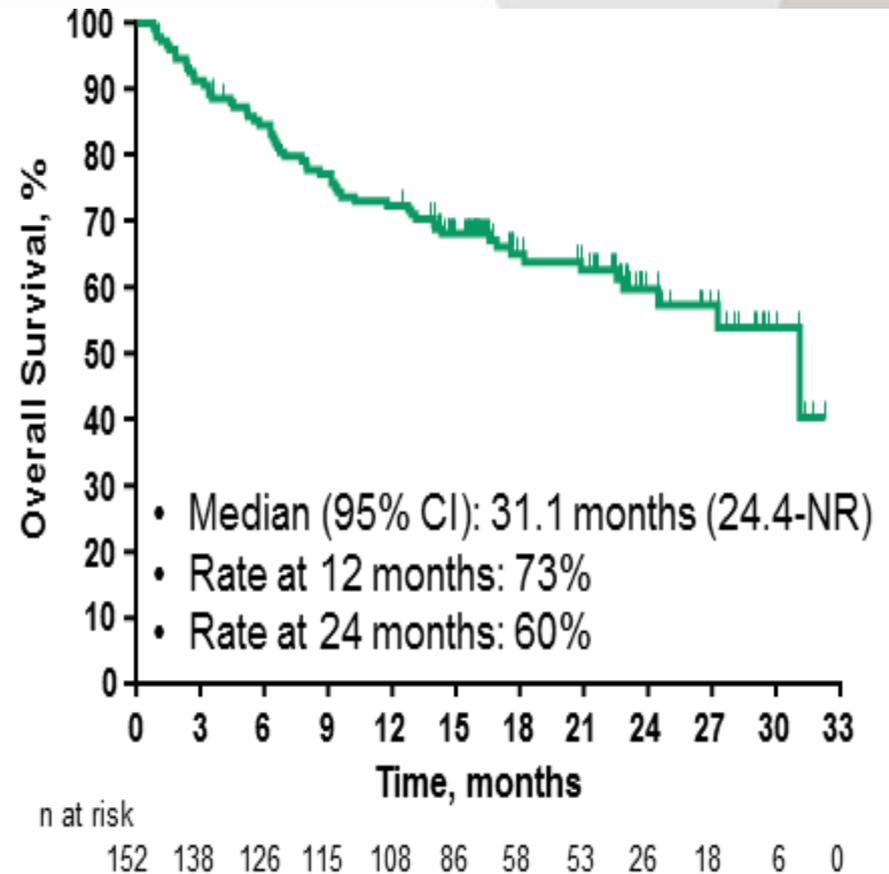
^aExcludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.

Keynote 001: Survie sans progression et survie globale chez des patients naïfs de traitement (n = 152^a)

PFS



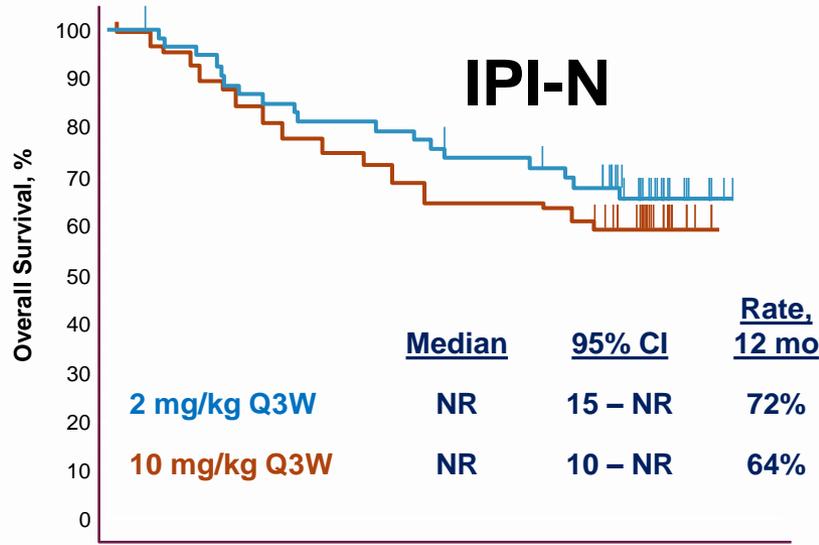
OS



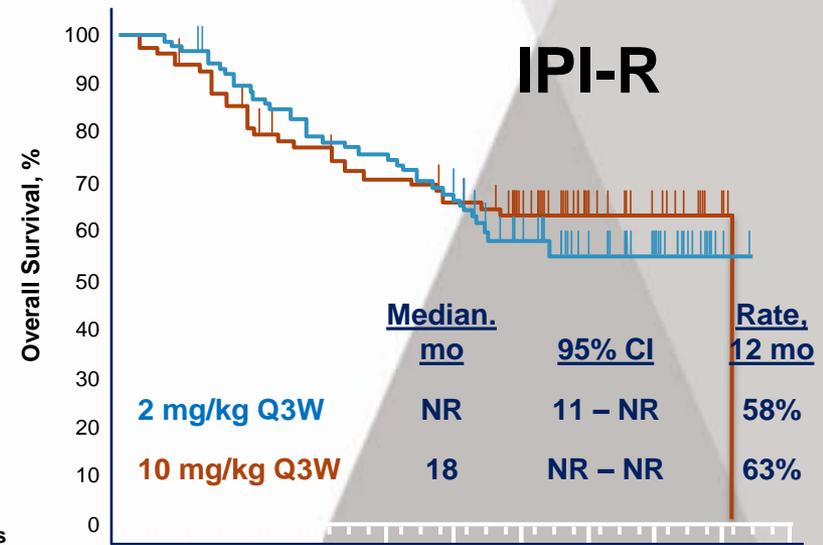
^aExcludes patients with ocular melanoma.
Analysis cut-off date: Octobre 18, 2014.

Keynote 001 : Activité antitumorale

	IPI-N			IPI-R		
	2 mg/kg Q3W	10 mg/kg Q3W	P	2 mg/kg Q3W	10 mg/kg Q3W	P
RECIST v1.1 ^a (independent central review)	n = 45	n = 47		n = 81	n = 76	
CR, % (95% CI)	4 (0-15)	4 (0-14)	—	1 (0-7)	1 (0-7)	—
ORR, % (95% CI)	33 (20-49)	40 (26-56)	0.4835	26 (17-37)	26 (17-38)	0.9558
DCR, % (95% CI)	49 (34-64)	55 (40-70)	0.5393	51 (39-62)	50 (38-62)	0.9386



n at risk	0	2	4	6	8	10	12	14	16	18	20
2 mg/kg Q3W	51	48	43	40	39	36	35	31	17	3	0
10 mg/kg Q3W	52	49	44	40	37	33	33	32	16	2	0

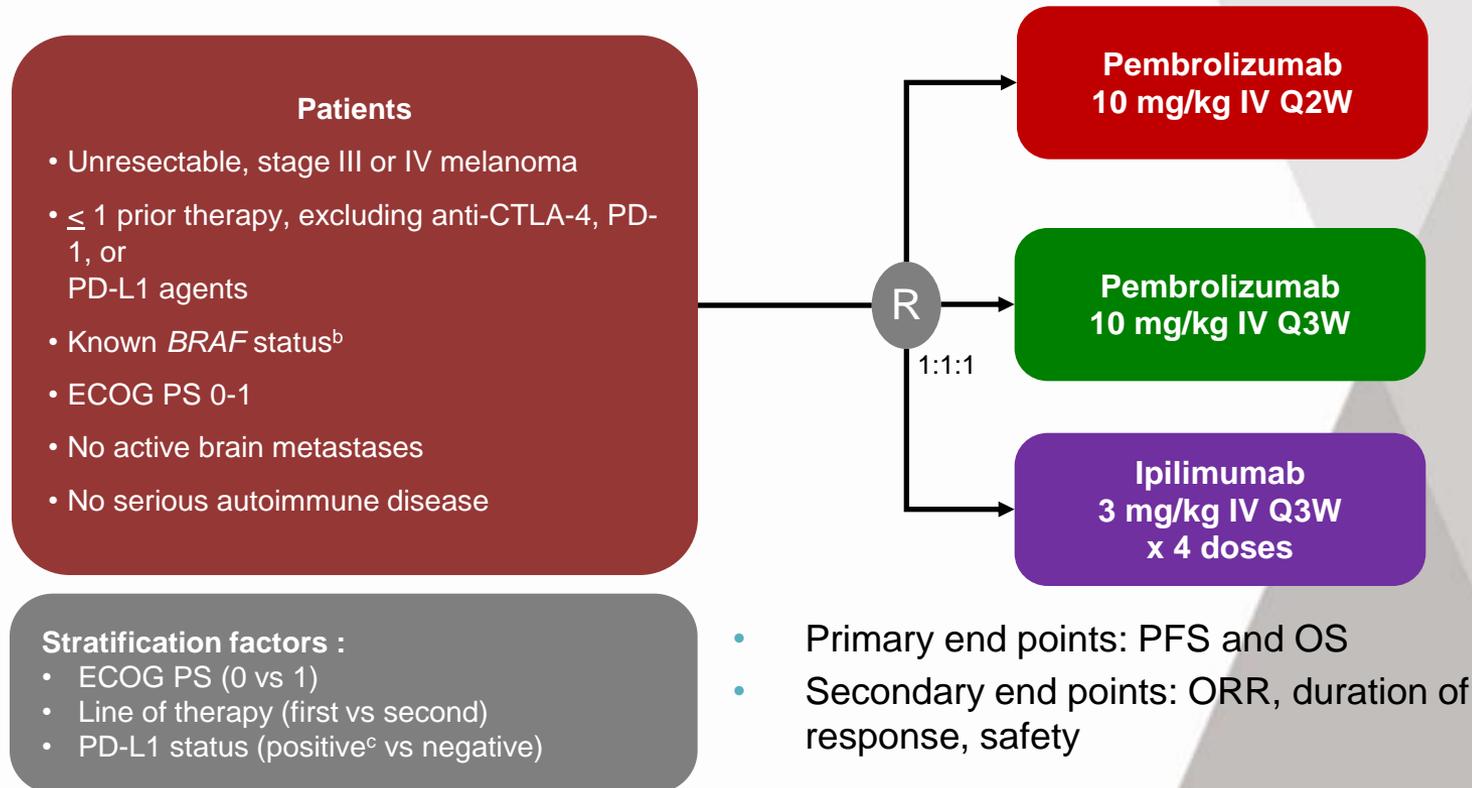


n at risk	0	2	4	6	8	10	12	14	16	18	20
2 mg/kg Q3W	89	86	76	69	66	57	42	29	16	1	0
10 mg/kg Q3W	84	78	65	61	55	50	37	18	12	1	0

^aAssessed in patients with measurable disease at baseline per independent central review.
 Median duration of follow-up: 12 months for IPI-N, 8 months for IPI-R. Analysis cut-off date: October 18, 2013.

Étude KEYNOTE-006 (NCT01866319)

- Étude internationale^a, randomisée, de phase III



^aPatients enrolled from 83 sites in 16 countries.

^bPrior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

^cDefined as membranous PD-L1 expression in $>1\%$ of tumor cells as assessed by IHC using the 22C3 antibody.

Keynote 006 : Réponse tumorale

2^{ème} analyse intermédiaire

	Pembrolizumab Q2W n = 279	Pembrolizumab Q3W n = 277	Ipilimumab n = 278
ORR, % (95% CI)	36,2 (30,6-42,1) P = 0.00003	36,1 (30,4-42,1) P = 0.00001	12,9 (9,2-17,5)
Best overall response, n (%)			
Complete response	23 (8,2)	28 (10,1)	7 (2,5)
Partial response	78 (28,0)	72 (26,0)	29 (10,4)
Stable disease	31 (11,1)	31 (11,2)	43 (15,5)
Non-CR/non-PD ^a	12 (4,3)	14 (5,1)	10 (3,6)
Progressive disease	108 (38,7)	114 (41,2)	137 (49,3)
Not evaluable ^b	19 (6,8)	15 (5,4)	50 (18,0)
No assessment ^c	8 (2,9)	3 (1,1)	2 (0,7)
Ongoing responses, n (%)	82 (81,2)	80 (80,0)	29 (80,6)
Duration of response, median (range), days	Not reached (29+ to 429+)	Not reached (43+ to 424+)	Not reached (33+ to 418+)

CI = confidence interval; CR = complete response; ORR = overall response rate; PD = progressive disease; Q2W = every 2 weeks; Q3W = every 3 weeks. ^aPatients without measurable disease per central review at baseline who did not experience complete response or disease progression.

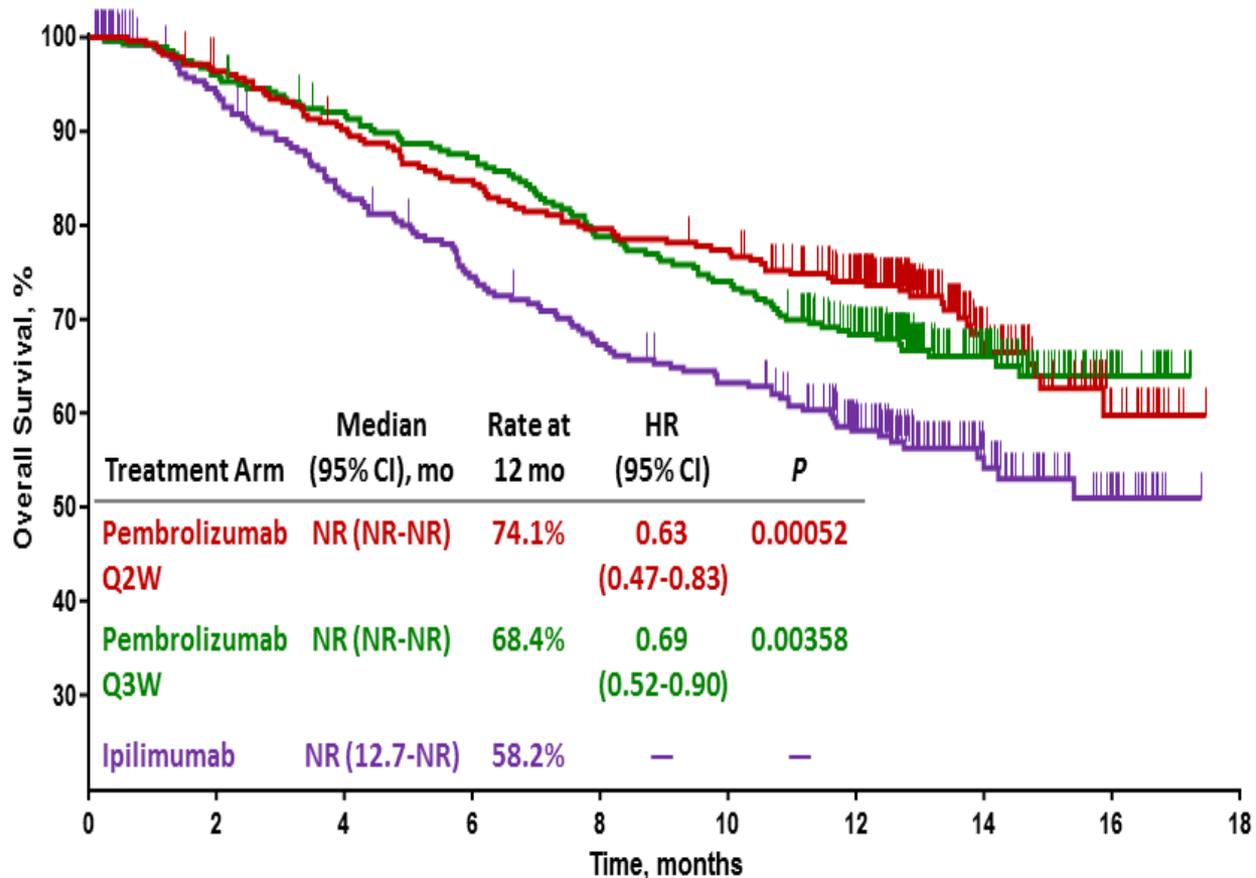
^bTarget lesion not captured by postbaseline scans or in whom a target lesion was surgically removed.

^cNo postbaseline scan performed or was not able to be evaluated.

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Keynote 006: Survie globale

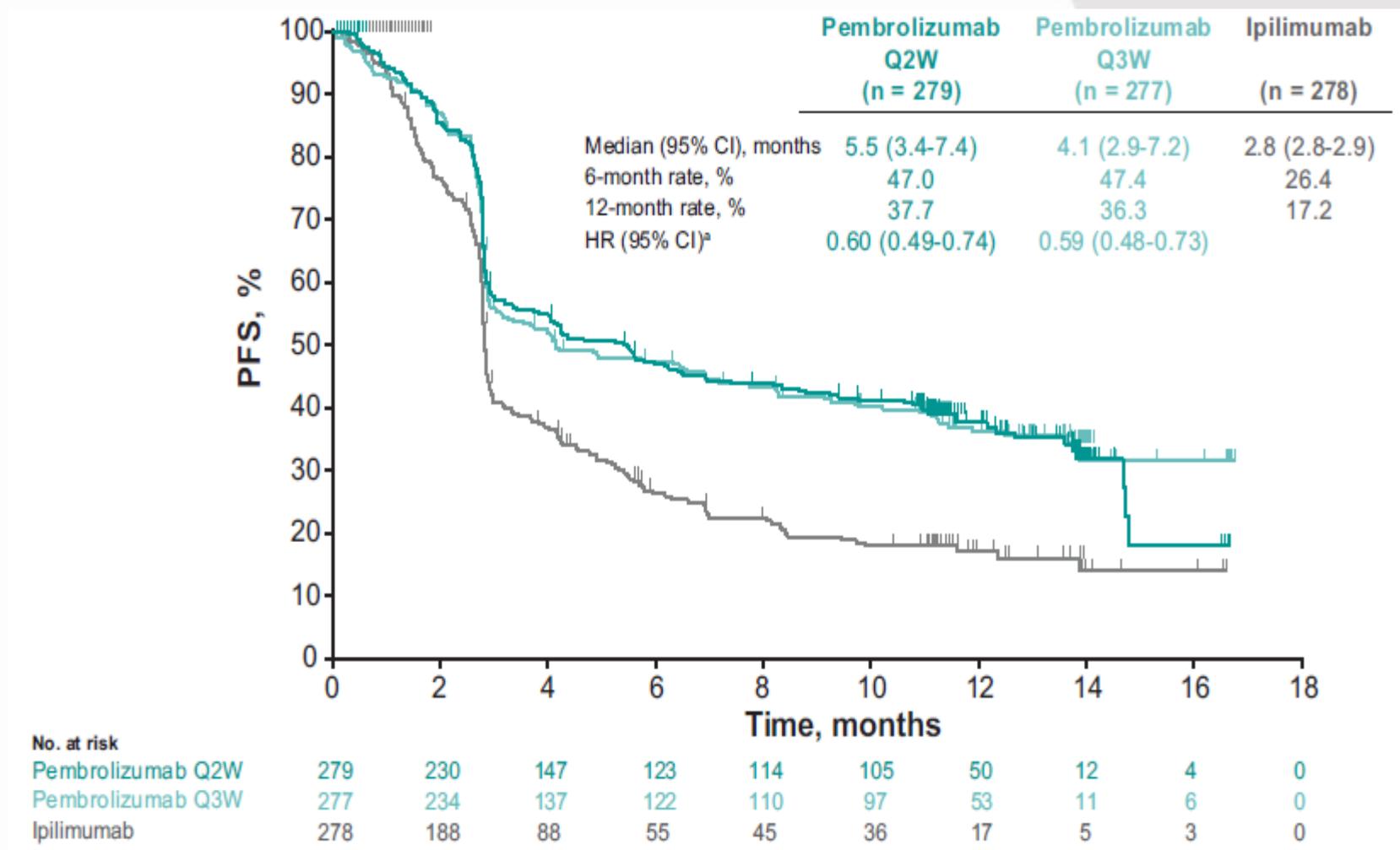
2^{ème} analyse intermédiaire



No. at risk	0	2	4	6	8	10	12	14	16	18
279	266	248	233	219	212	177	67	19	0	0
277	266	251	238	215	202	158	71	18	0	0
278	242	212	188	169	157	117	51	17	0	0

Keynote 006: Survie sans progression

2^{ème} analyse intermédiaire



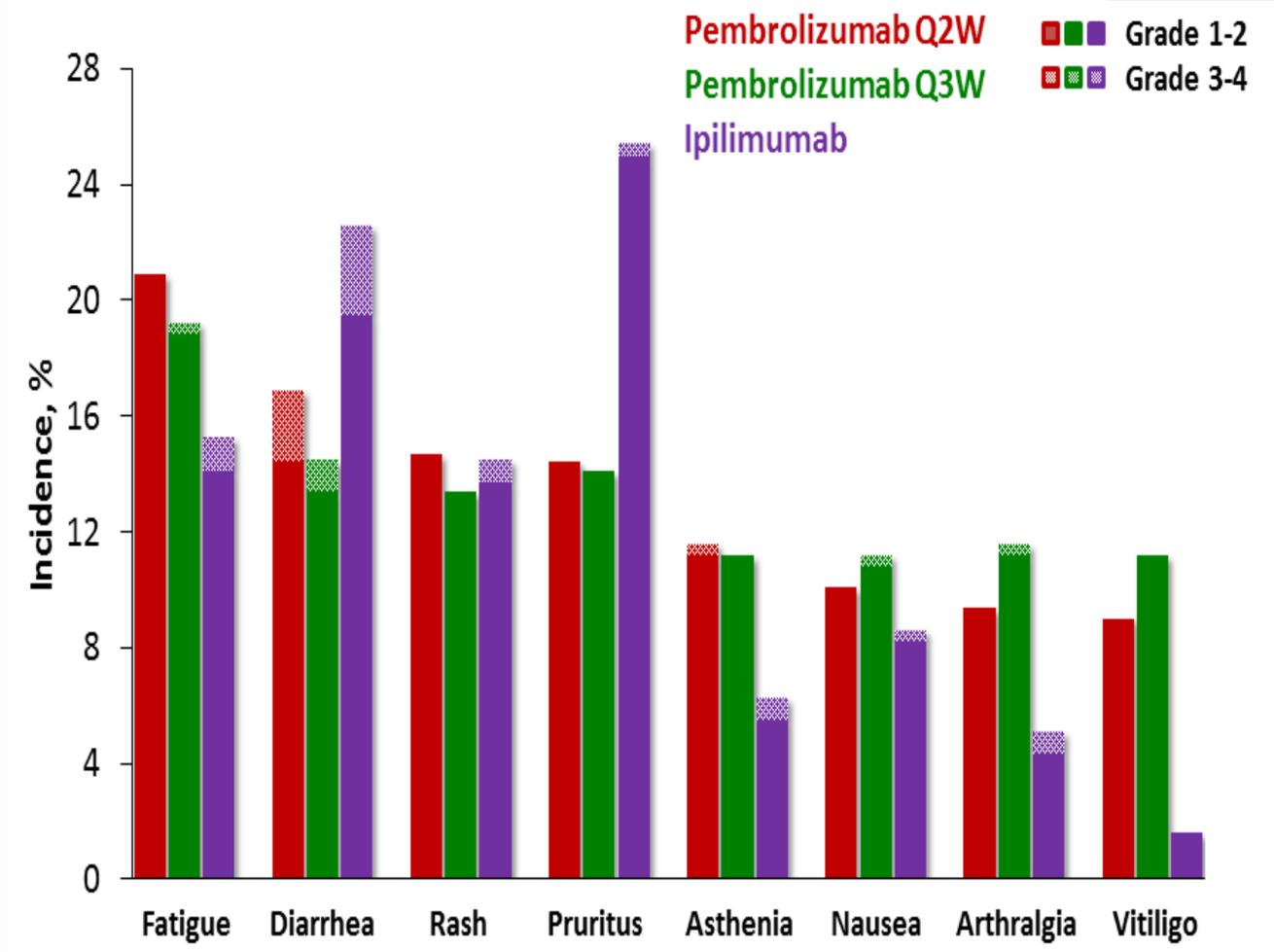
CI = confidence interval; HR = hazard ratio; PFS = progression-free survival, Q2W = every 2 weeks; Q3W = every 3 weeks.

^aComparison of pembrolizumab versus ipilimumab assessed by the stratified log-rank test.

Schachter et al. Poster SMR 2015

Keynote 006, Effets indésirables (incidence $\geq 10\%$)

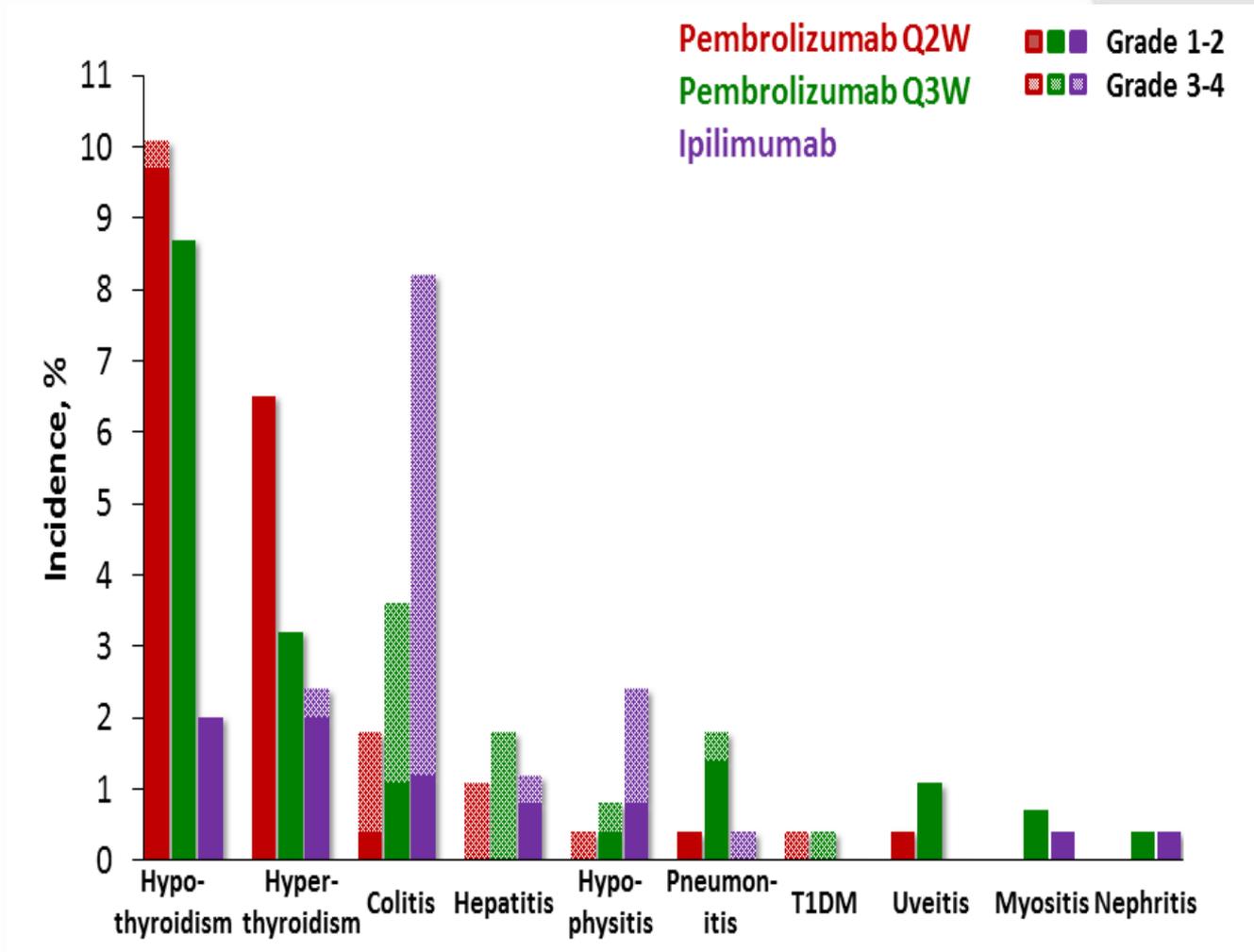
1^{ère} analyse intermédiaire



^aIncidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.

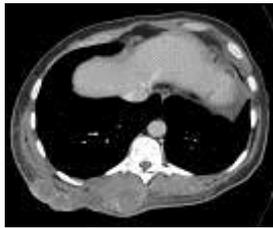
Keynote 006: Effets indésirables présentant un intérêt particulier

1^{ère} analyse intermédiaire



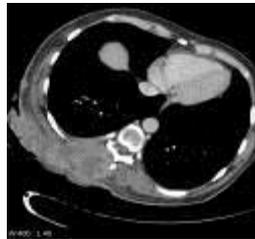
^aIncidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.

Quel est le rationnel de création des critères irRC?



Screening

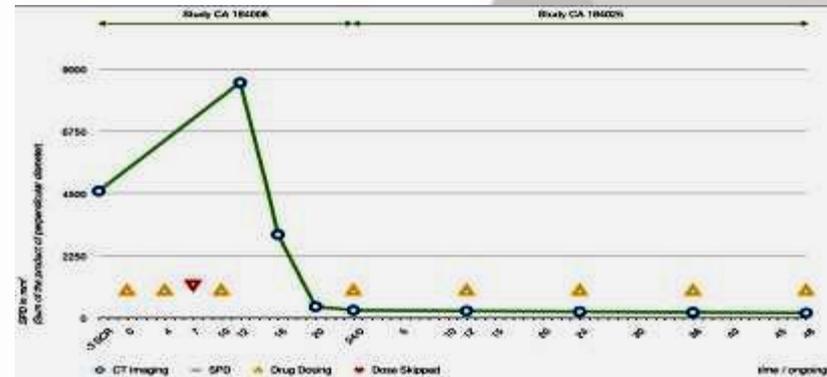
Week 96
Durable & ongoing response
without signs of IRAEs



Week 12
Progression initiale



Week 16
Réponse partielle



Courtesy of K. Harmankaya, Vienna

Baseline :
November 2012



December 2012



January 2013



February 2013



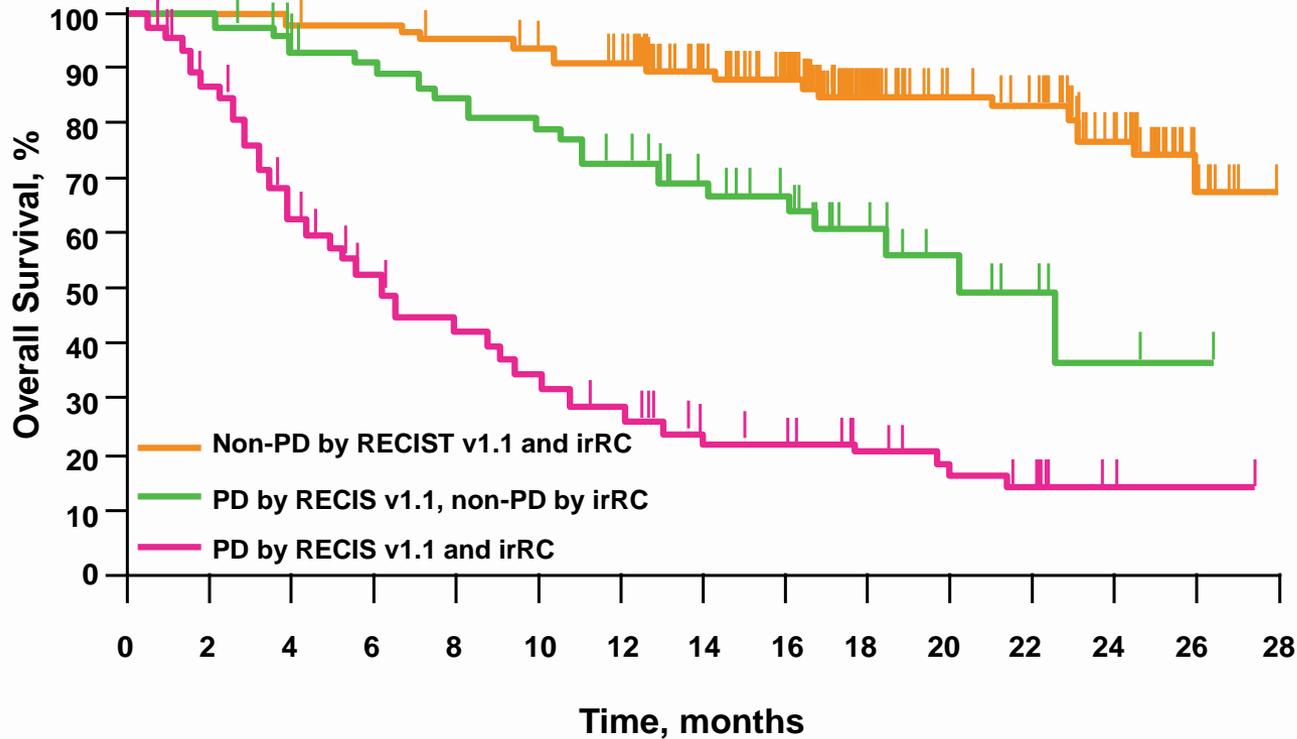
March 2013



July 2013



Kaplan-Meier Estimates of OS Based on Response per RECIST v1.1 and irRC^a



Median, mo	95% CI	Rate, 24 mo
NR	25.9-NR	78%
20.2	15.9-NR	37%
6.4	5.1-8.4	14%

215	215	213	210	206	197	192	159	136	79	60	55	31	8	0
57	56	50	46	44	41	37	28	22	13	9	6	3	2	1
139	116	84	66	54	42	33	23	20	15	10	8	1	1	0

^aAssessed per central review.

Analysis cut-off date: April 18, 2014.

Quel est le rationnel de création des critères irRC?

- **Dans le mélanome, pseudo-progression concernerait 7.2% des patients sous pembrolizumab**
 - À la 1^{ère} évaluation: 3.6% (7/192)
 - Après la 1^{ère} evaluation: 3.6% (7/192)
 - **Au moins 9.5% sous ipilimumab**
- **Des critères d'évaluation spécifiques ont été proposés afin de ne pas passer à côté de ces réponses retardées à l'immunothérapie**

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok, Axel Hoos, Steven O'Day, et al.

Clin Cancer Res 2009;15:7412-7420. Published OnlineFirst November 24, 2009.

Gestion des toxicités liées à l'immunité



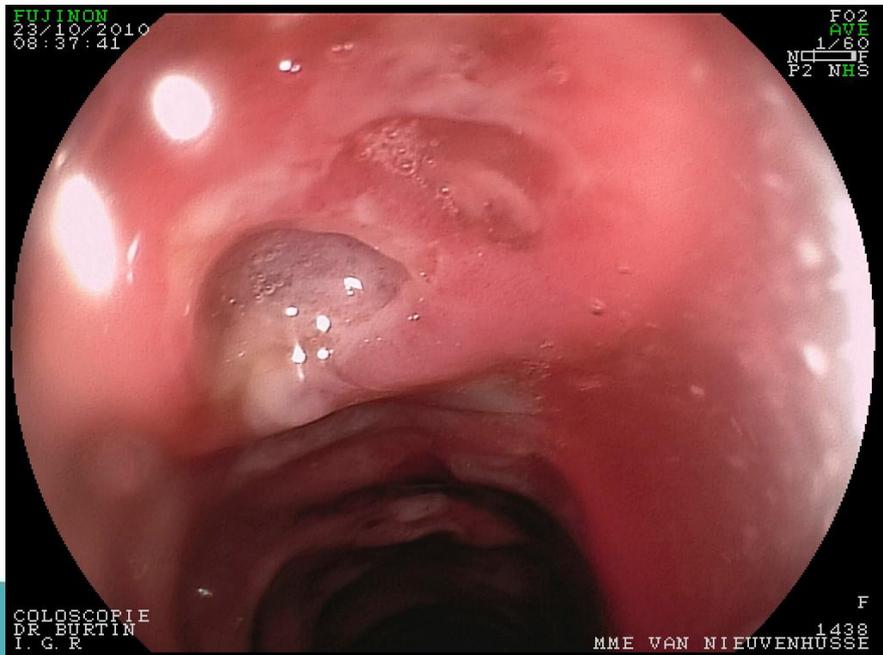
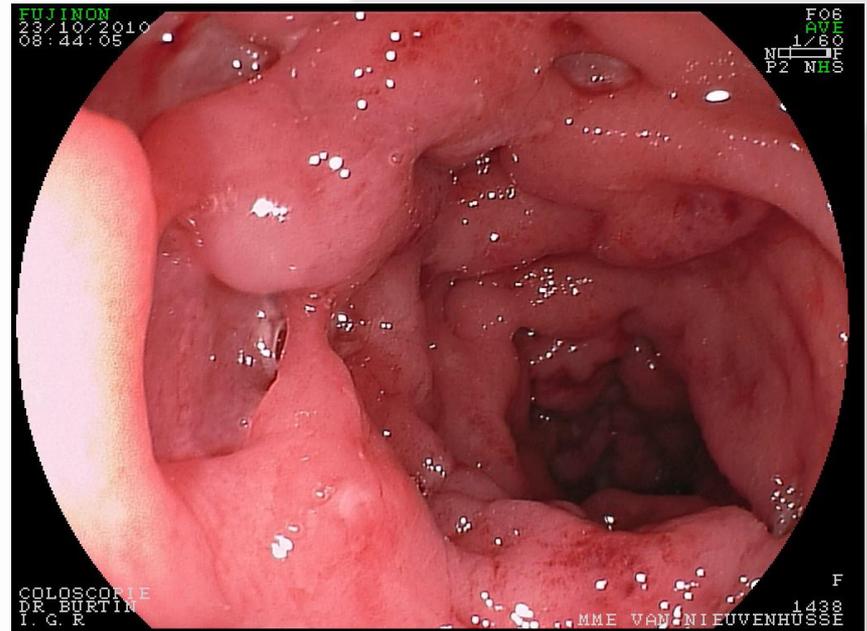
Gestion des IrAE en pratique

- Toxicité cutanée

Grade 1-2:

- émollients
- anti H1
- dermocorticoïdes : diprosone crème
1 fois par jour le soir

Grade 3: avis dermatologue



Gestion des IrAE en pratique

- **Toxicité colique**

Grade 1-2:

- hydratation
- anti-diarrhéiques

Grade 3: avis gastro + endoscopie

- corticoïdes
- Remicade® infliximab

Gestion des IrAE en pratique

- **Toxicité endocrinienne**

Hypothyroïdie : substitution

Hyperthyroïdie :

- **abstention**
- **néomercazole (grade 2)**
- **corticoïdes à discuter (grade 3)**

Hypophysite : substitution

Gestion des IrAE en pratique

- Toxicité hépatique - rénale

Grade 1-2:

- arrêt des traitements hépatotoxiques et néphrotoxiques

Grade 3:

- biopsie
- corticoïdes fortes doses, décroissance très lente
- cellcept® mycophénolate mofétil

Metastatic Melanoma

Targeted therapies / immunotherapy

Drug	RR	PFS	OS (months)	% OS 1 year	% OS 2 years	Gr ^{3/4} AE
Ipi (3)	11	2.8	11	58	24	23
Nivo	32	3.7	17.3	71	57	14
Pembro	34	5.5	NR	73	60	14
Nivo + Ipi	40		NR	85	79	62
BRAF-I	55	7-8.8	18	60	43	36
BRAF-I + MEK-I	67	9.3	25	73	51	35