Dermatologie

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Traitement adjuvant du mélanome : bénéfice de survie sans métastase à distance dans l'étude Keynote 054 pembrolizumab vs placebo

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

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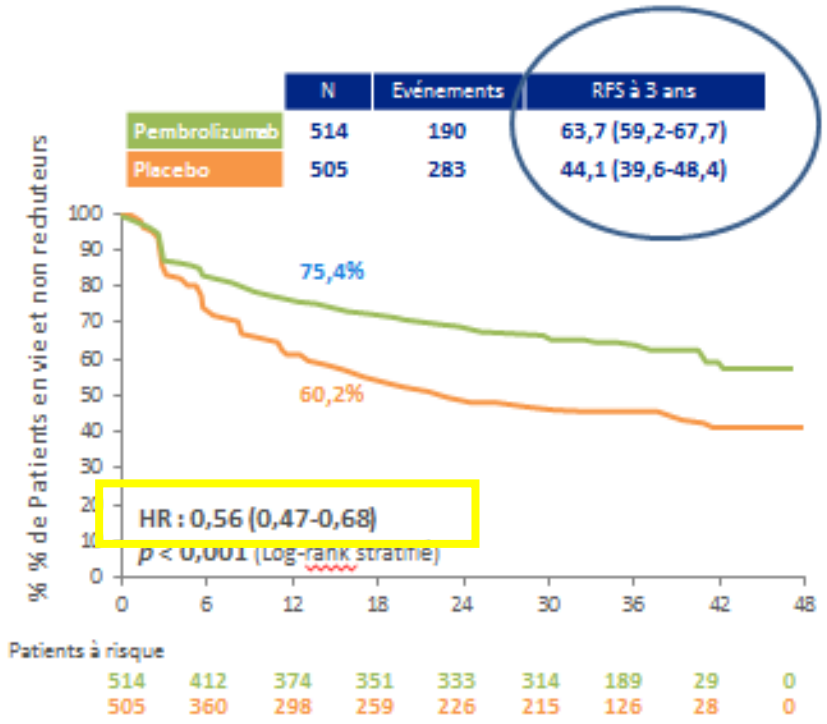
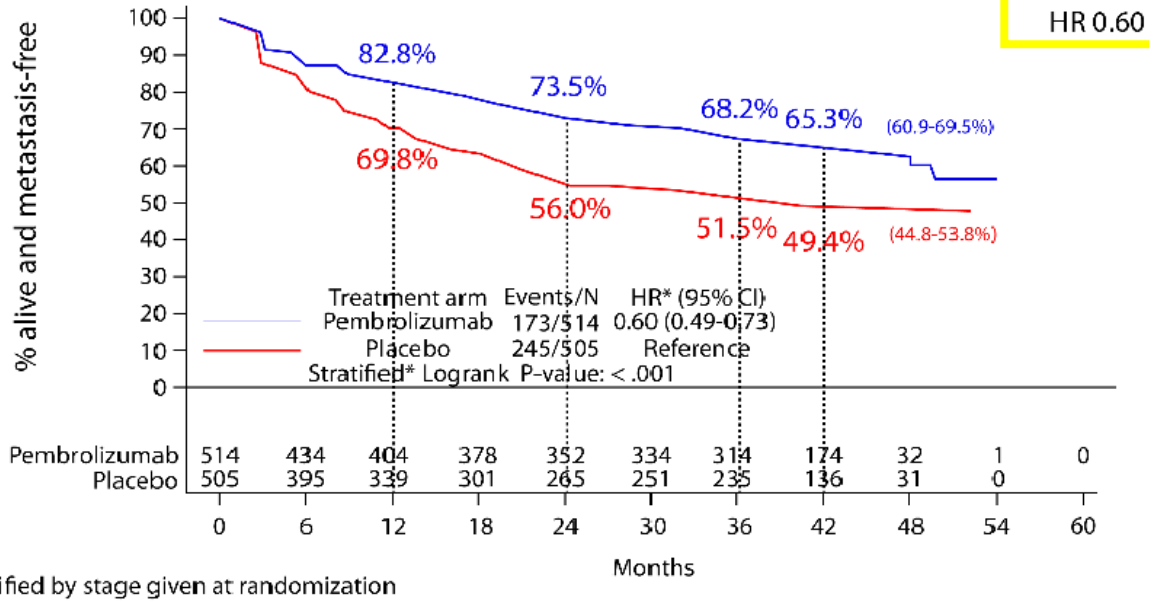
Alexander M. Eggermont *et al.*, ASCO® 2020, Abs #10000



réduction de rechute de 44%

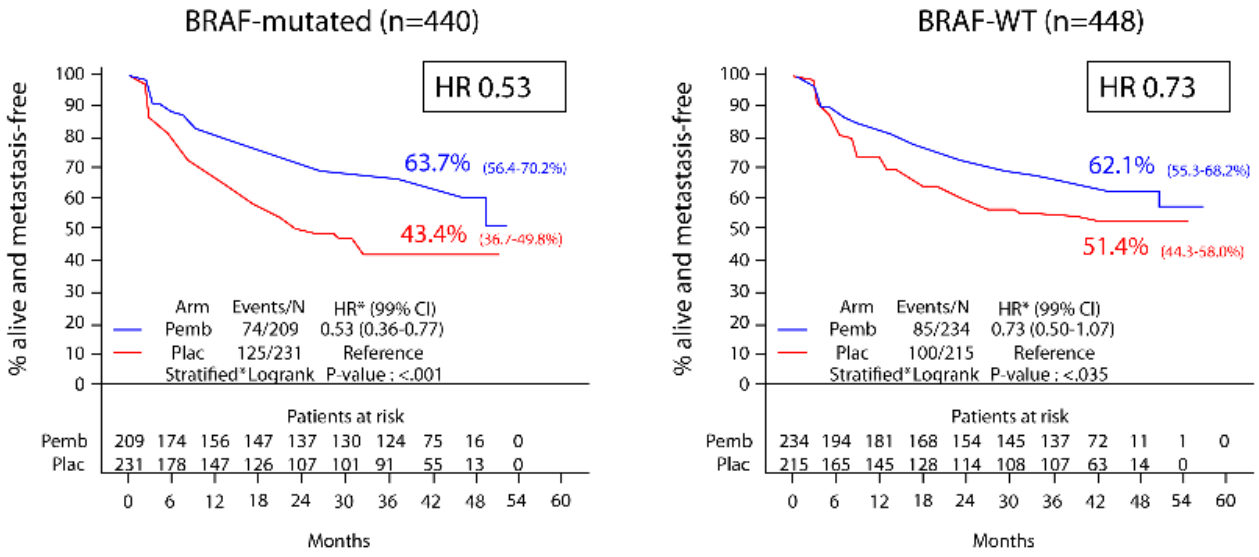
ESMO 2020/ analyse finale de la survie sans métastase à distance avec un suivi médian de 3,5 ans



Diminution du risque de rechute de 40%

Analyse en sous groupes :
HR plus favorable pour les mélanomes mutés BRAF (HR 0,53) que pour les mélanomes WT (HR 0,73)
Charge mutationnelle plus élevée?

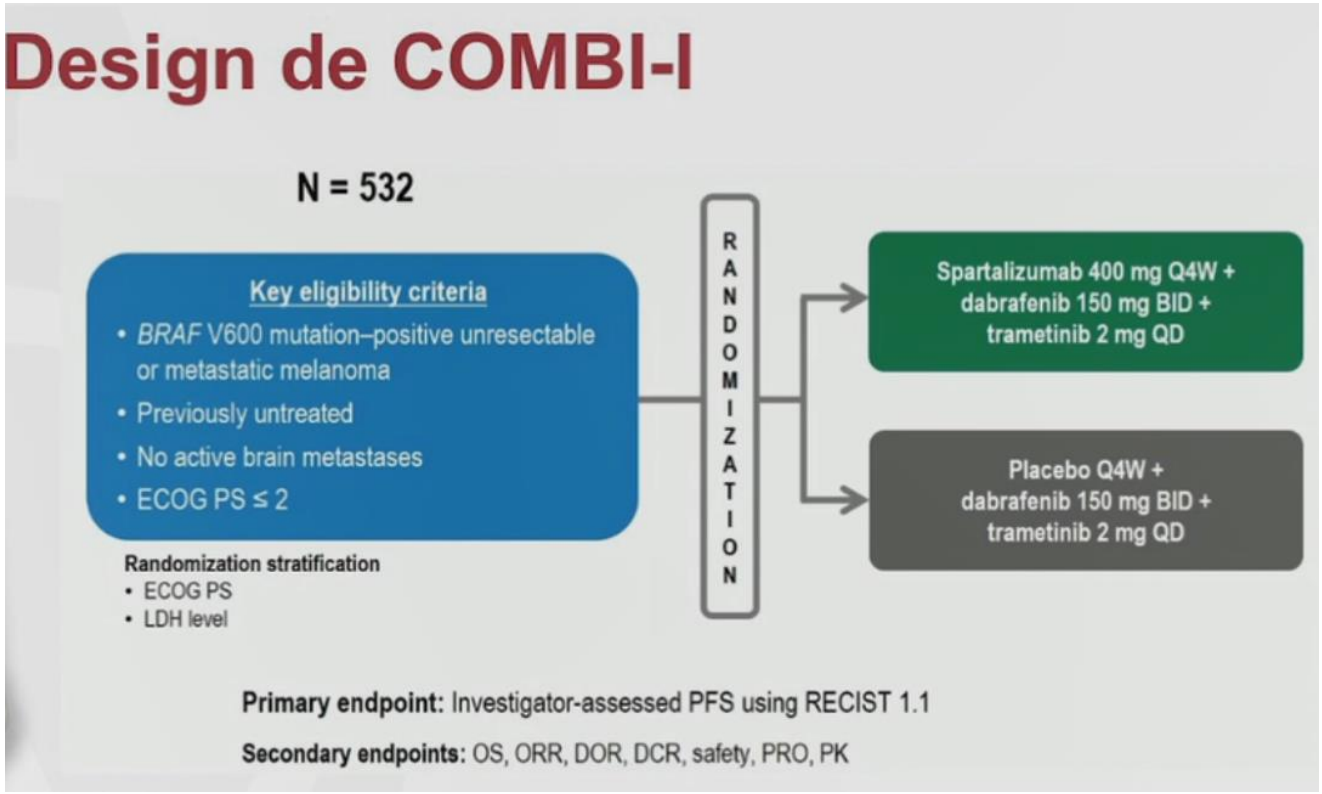
Le bénéfice de survie sans rechute est maintenu à 3,5 ans de suivi



*Stratified by stage given at randomization

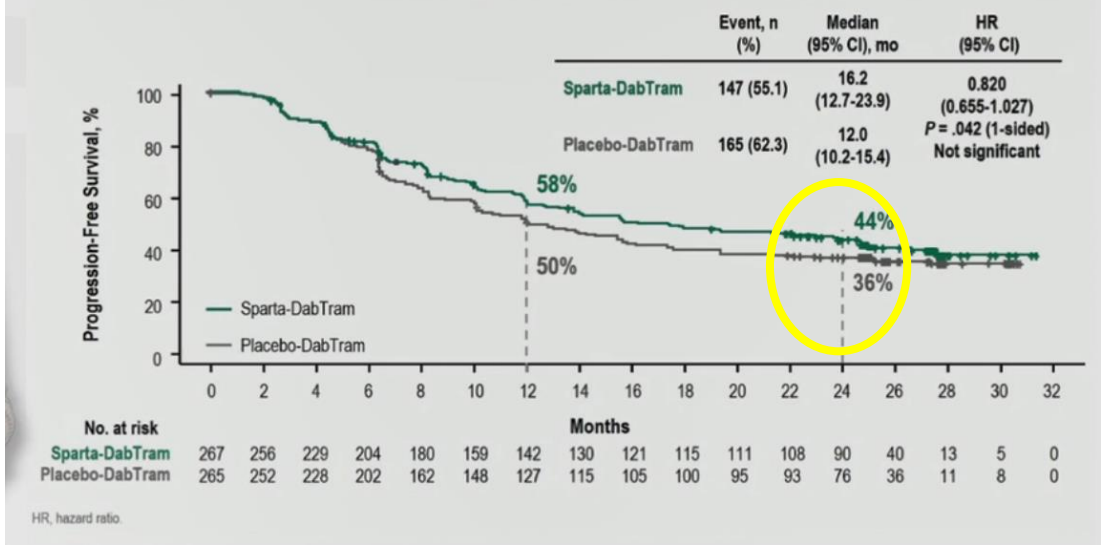
Mélanome métastatique : spartalizumab + dabrafenib et trametinib en 1ère ligne - Étude COMBI-i (analyse intermédiaire à 2 ans)

- Essai de phase 2 et 3: la combinaison antiPD1 et thérapies ciblées améliore la survie sans progression
- Pourcentage élevé de réponses durables



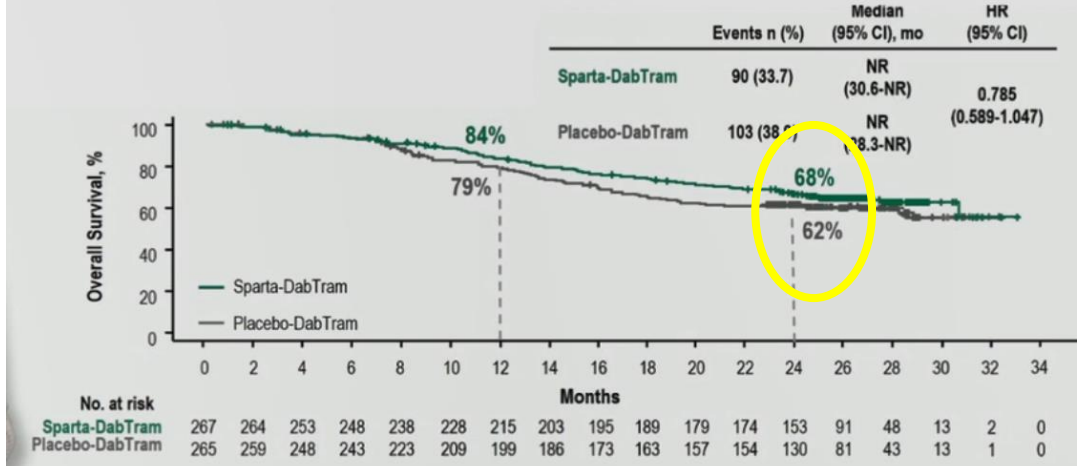
Analyse statistique:
OS: critère secondaire
Analysée que si PFS significative

Survie sans progression



HR, hazard ratio.

Survie globale



- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

NR, not reached.

Patients, n (%)	Sparta-DabTram n = 267		Placebo-DabTram n = 264	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any AE	265 (99.3)	188 (70.4)	256 (97.0)	151 (57.2)
Treatment related	263 (98.5)	146 (54.7)	231 (87.5)	88 (33.3)
Serious AEs	138 (51.7)	91 (34.1)	110 (41.7)	76 (28.8)
Treatment related	106 (39.7)	62 (23.2)	53 (20.1)	29 (11.0)
AEs leading to discontinuation of ≥ 1 study drug	97 (36.3)	58 (21.7)	47 (17.8)	27 (10.2)
Treatment related	85 (31.8)	48 (18.0)	38 (14.4)	19 (7.2)
AEs leading to discontinuation of all 3 study drugs[a]	42 (15.7)	24 (9.0)	24 (9.1)	15 (5.7)
Treatment related	33 (12.4)	16 (6.0)	21 (8.0)	12 (4.5)
AEs leading to dose interruption/adjustment	235 (88.0)	131 (49.1)	192 (72.7)	97 (36.7)
AEs requiring additional therapy	255 (95.5)	118 (44.2)	223 (84.5)	88 (33.3)

AE, adverse event.
[a] Data reported include patients that discontinued all 3 drugs due to the same AE, regardless of the grade or the order of discontinuation.

Objectif principal (SSP) non atteint
(16 mois bras triplet vs 12 mois bras Dab + Tram)

Mélanome métastatique :IO et thérapies ciblée en séquentiel: phase 2 en 1ère ligne

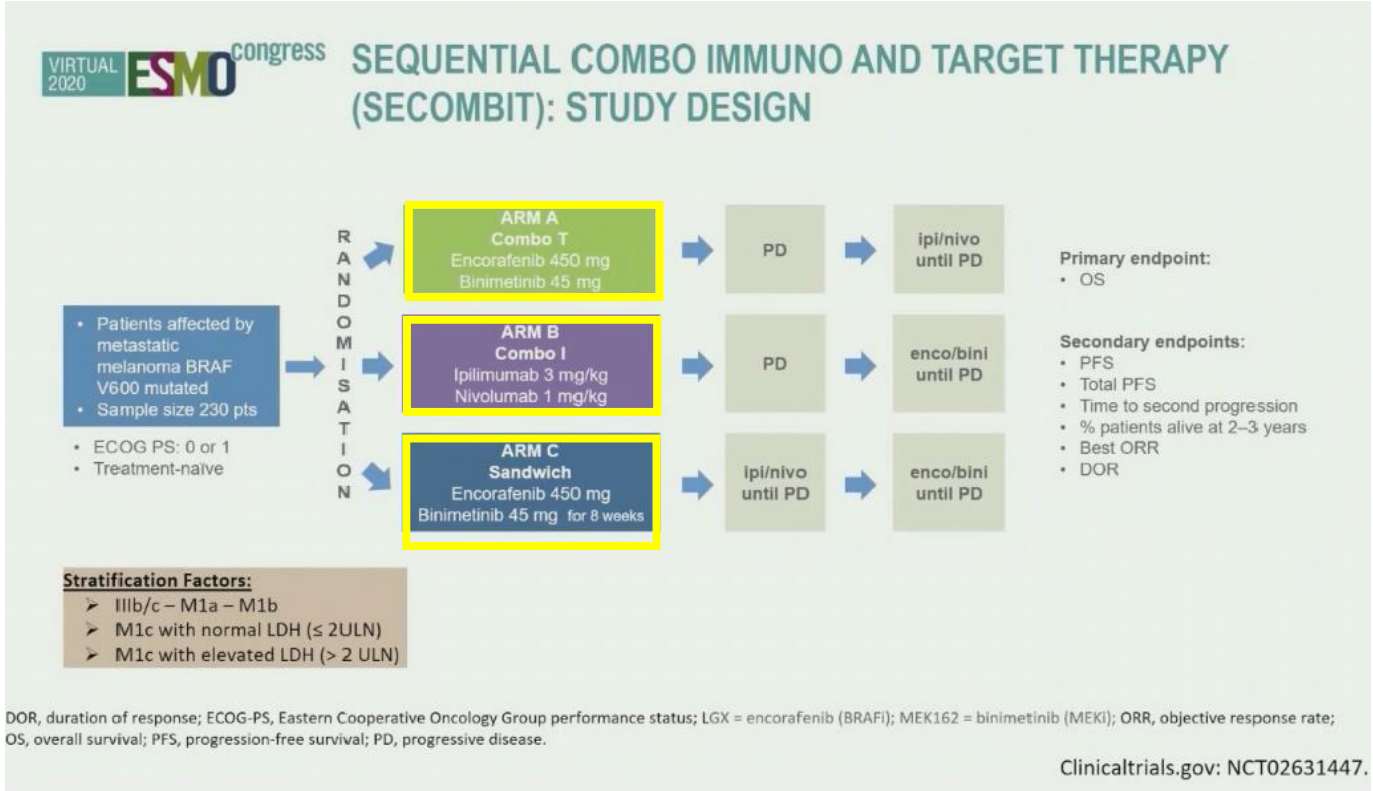
Ascierto PA,[1] Mandalà M,[2] Ferrucci PF,[3] Rutkowski P,[4] Guidoboni M,[5] Arance AM,[6] Ferraresi V[7], Maiello E,[8] Guida M,[9] Del Vecchio M,[10] Fierro MT,[11] Queirolo P,[3-12] Lebbè C,[13] Helgadottir H,[14] Melero I,[15] Palmieri G,[16] Giannarelli D,[17] Grimaldi AM,[1] Dummer R,[18*] Chiarion Sileni V,[19*].

Avec les IO et les thérapies ciblées: plus de 50% des patients ont un bénéfice à long terme

Pas de consensus sur les « bonnes » séquences thérapeutiques chez les patients mutés BRAF

Données d'études rétrospectives uniquement

Médiane suivi 17 mois



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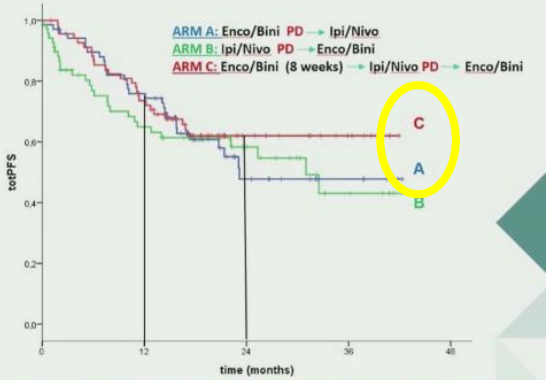
	Arm A (n. 69)	Arm B (n. 71)	Arm C (n. 69)
Response Rate, %*	82.6	45.1	78.3

PFS



24-month total PFS

	Arm A	Arm B	Arm C
N of events (%)	39 (56.5)	41 (57.7)	41 (59.4)
mPFS, months (95% CI)	15.8 (9.5-22.2)	7.2 (3.2-11.3)	11.4 (7.2-15.5)
1y PFS % (95% CI)	60 (48-72)	43 (31-55)	46 (34-58)
2y PFS % (95% CI)	35 (21-49)	38 (26-50)	39 (27-51)

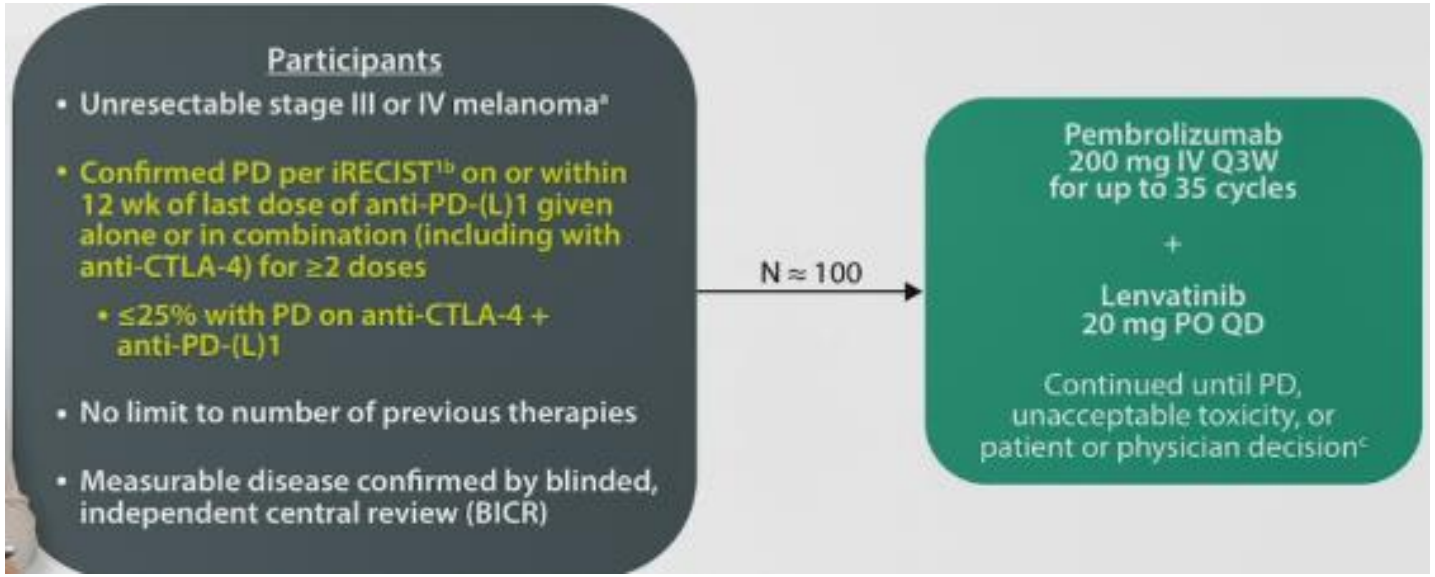
	ARM A (n = 69)		ARM B (n = 71)		ARM C (n = 69)	
Patients reporting event	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any Adverse Event n, (%)	63 (91)	34 (49)	68 (96)	52 (73)	58 (84)	35 (51)
Treatment-related AE, n, (%)	**53 (77)**	**19 (28)**	**59 (83)**	**38 (54)**	**56 (81)**	**22 (32)**
Treatment-related AE leading to discontinuation, n, (%)	7 (10)		8 (11)		3 (4)	

Survie sans progression totale:
tendance pour la séquence ITK courte durée
puis double immunothérapie
puis reprise ITK
Nécessite données de suivi plus matures

Mélanome en progression sous anti-PD1 : lenvatinib + pembrolizumab en rattrapage

Ana Arance,[1] Steven J. O'Day,[2] Luis de la Cruz Merino,[3] Teresa M. Petrella,[4] Rahima Jamal,[5] Lars Ny,[6] Ana Carneiro,[7] Alfonso Berrocal,[8] Ivan Márquez-Rodas,[9] Anna Spreafico,[10] Victoria Atkinson,[11] Fernanda Costa Svedman,[12] Alan D. Smith,[13] Ke Chen,[14] Scott J. Diede,[14] Clemens Krepler,[14] Georgina V. Long[15]

- Problématique des résistances primaires ou secondaires/antiOD1
- Lenvatinib cible plusieurs tyrosines kinases: PDGFR, VEGFR, KIT, FGFR
- Pembrolizumab + lenvatinib: potentialise le pembrolizumab (JCO 2019)



Characteristic, n (%)	N = 103
Age, median (range)	63 y (21-85)
Males	55 (53.4%)
ECOG PS 1	41 (39.8%)
LDH > ULN	57 (55.3%)
≥2 x ULN	21 (20.4%)
Brain metastasis (history of or current)	15 (14.6%)
Sum of target lesions, median (range)	100 mm (11-530)

Characteristic, n (%)	N = 103
$BRAF^{V600}$ mutation	38 (36.9%)
PD-L1 positive[a]	66 (64.1%)
Metastatic stage at enrollment	
M0	7 (6.8%)
M1a	15 (14.6%)
M1b	12 (11.7%)
M1c	57 (55.3%)
M1d	12 (11.7%)

Treatment, n (%)	N = 103
Any adjuvant therapy	34 (33.0%)
Any immunotherapy	29 (28.2%)
BRAF ± MEK inhibitor	2 (1.9%)[a]
Any immunotherapy for metastatic disease	94 (91.3%)
BRAF ± MEK inhibitor for metastatic disease	32 (31.1%)[a]
PD on prior anti-CTLA-4 + anti-PD-(L)1	29 (28.2%)

Treatment, n (%)	N = 103
Prior lines of therapy across all stages	
1	40 (38.8%)
2	24 (23.3%)
3	19 (18.4%)
4	8 (7.8%)
≥5	12 (11.7%)

Objectif principal: ORR
Ob secondaires: DOR, PFR, OS

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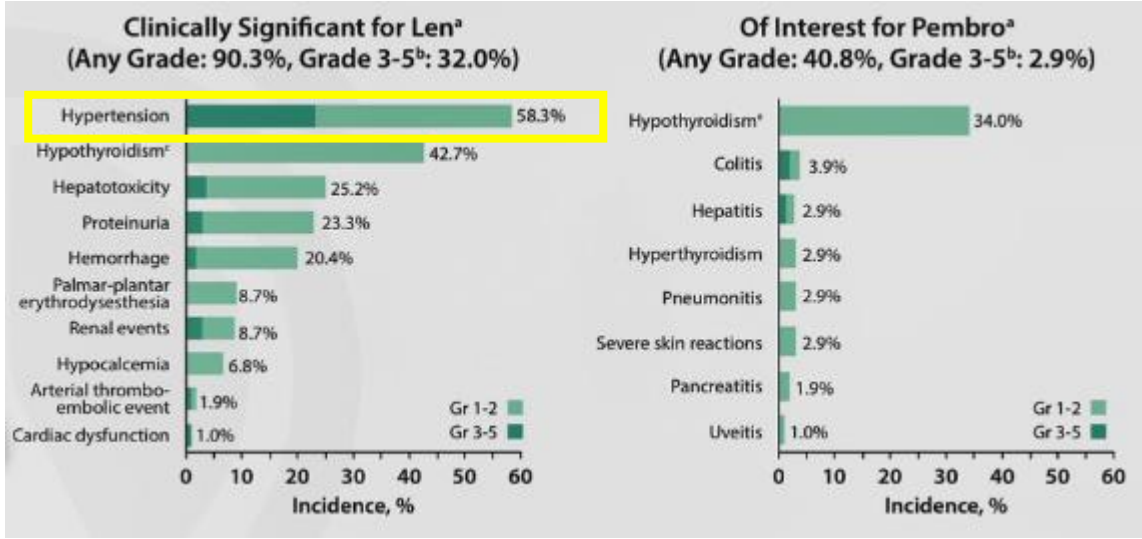
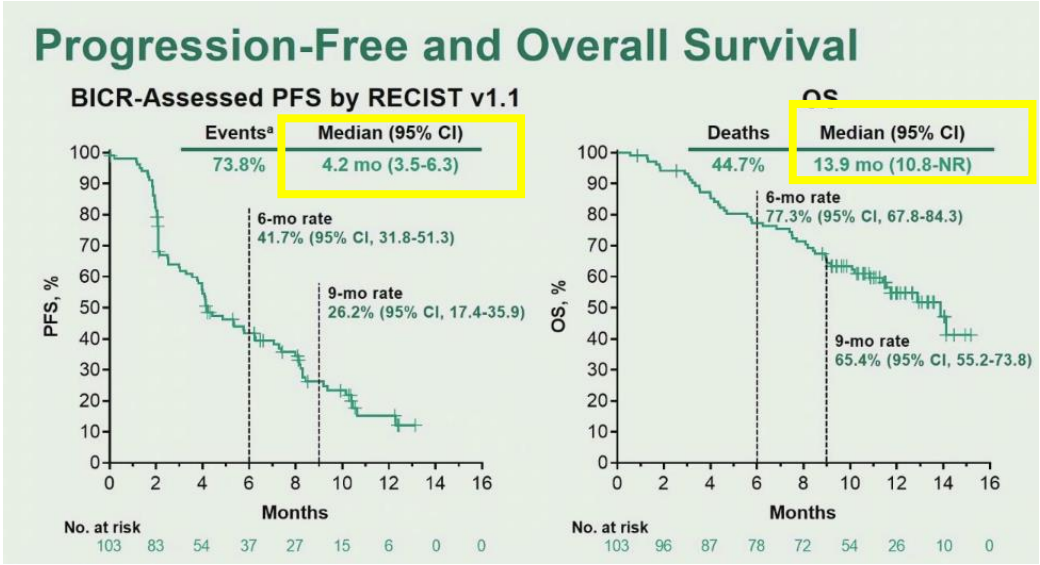
	Total Population N = 103
ORR, % (95% CI)	21.4% (13.9-30.5)
DCR, % (95% CI)	65.0% (55.0-74.2)
Best overall response, n (%)	
CR	2 (1.9%)
PR	20 (19.4%)
SD	45 (43.7%)
PD	31 (30.1%)
Not assessed[a]	5 (4.9%)

		PD on Prior Anti-CTLA-4 + Anti-PD-(L)1	
	Total Population N = 103	Yes n = 29	No n = 74
ORR, % (95% CI)	21.4% (13.9-30.5)	31.0% (15.3-50.8))	17.6% (9.7-28.2)
DCR, % (95% CI)	65.0% (55.0-74.2)	62.1% (42.3-79.3)	66.2% (54.3-76.8)
Best overall response, n (%)			
CR	2 (1.9%)	1 (3.4%)	1 (1.4%)
PR	20 (19.4%)	8 (27.6%)	12 (16.2%)
SD	45 (43.7%)	9 (31.0%)	36 (48.6%)
PD	31 (30.1%)	10 (34.5%)	21 (28.4%)
Not assessed[a]	5 (4.9%)	1 (3.4%)	4 (5.4%)





Activité anti-tumorale prometteuse
21% de réponse
31% patients préalablement traités par ipi+nivo
Tolérance acceptable