MADRID 2023 ESMO congress

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Réseau Régional de Cancérologie

Les buzz de l'ESMO 2023
Session en vrac

Mardi 21 Novembre 2023

Bordeaux

Dr Daste / Dr Domblides

Randomized Phase 3 Study of Selpercatinib versus Cabozantinib or Vandetanib in Advanced, Kinase Inhibitor-Naïve, *RET*-mutant Medullary Thyroid Cancer

LIBRETTO-531 (NCT04211337)

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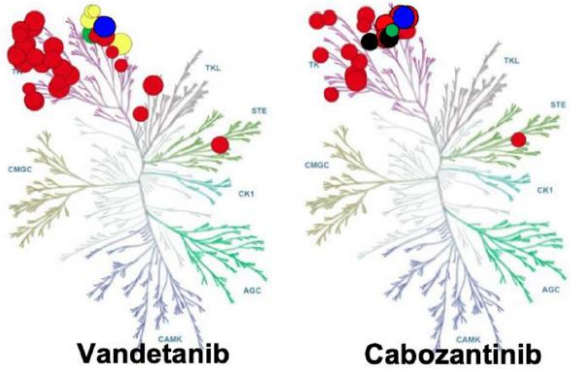
Les carcinomes médullaires de la thyroïde

- 5% des cancers de la thyroïde
- Mutations de RET : 100% des formes héréditaires et 25 à 50% des formes sporadiques
- 90% de mutations de RET en situation de rechute métastatique
- Cabozantinib (ORR 15%) et vandetanib (ORR 45%) indiqués en 1ère ligne



- Mais inhibition de RET limitée et profils de toxicité limitant

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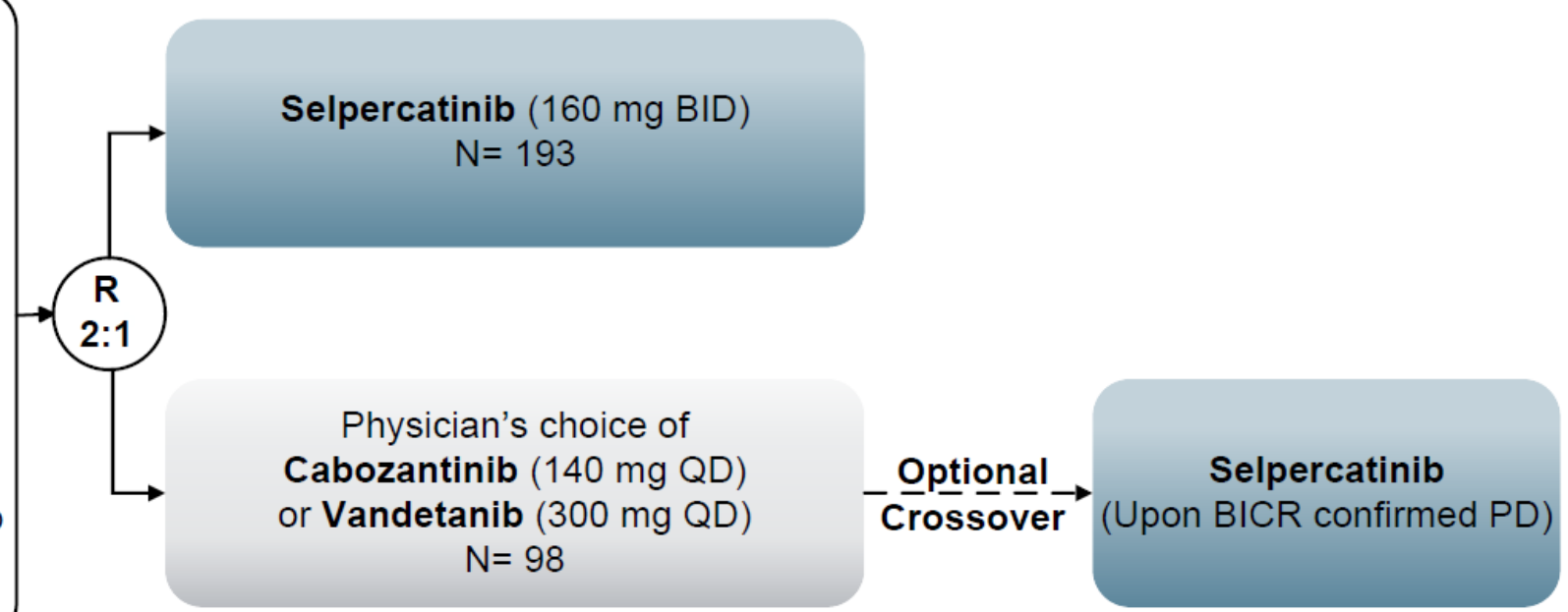
Design de l'étude

Key Eligibility Criteria

- Unresectable locally advanced or metastatic *RET*-mutant MTC
- No prior history of treatment with kinase inhibitors
- Documented RECIST 1.1 PD within 14 months (centrally reviewed)
- *RET* mutation identified via NGS or PCR

Stratification factors

- Mutation status: (M918T vs other)
- Physician's choice of treatment if randomized to control arm, with declared intent before randomization



Primary endpoint: PFS per RECIST 1.1 by BICR

Secondary endpoints:

- **Efficacy** (TFFS[1] by BICR and investigator, PFS by investigator, ORR by BICR and investigator, and OS)
- **Safety**

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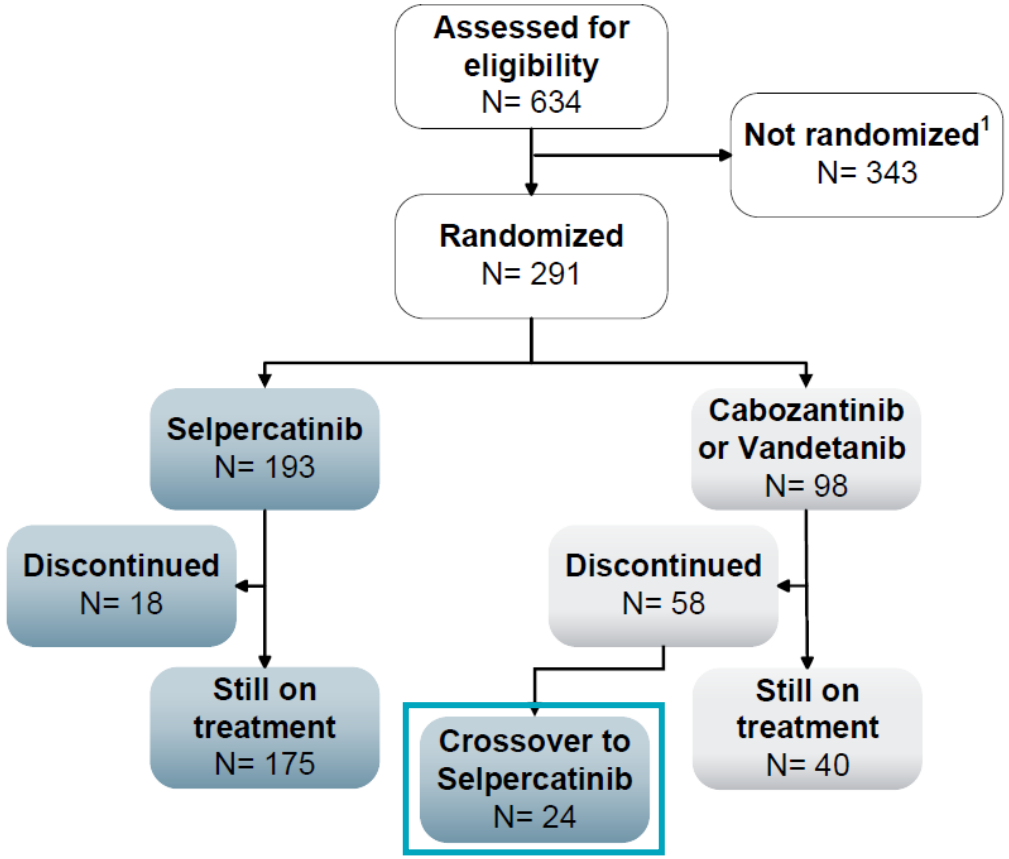
Caractéristiques des patients



Characteristic		Selpercatinib (N= 193)	Cabozantinib or Vandetanib (N= 98)
Age — years	Median (range)	56.0 (12 – 79)	53.5 (18 – 84)
Age distribution — n (%)	<18 years	1 (0.5)	0 (0.0)
	≥18 to <65 years	143 (74.1)	72 (73.5)
	≥65 years	49 (25.4)	26 (26.5)
Sex — no. (%)	Male	115 (59.6)	68 (69.4)
	Female	78 (40.4)	30 (30.6)
Race — no. (%)[1]	White	116 (70.7)	52 (66.7)
	Asian	43 (26.2)	24 (30.8)
	Black	5 (3.0)	2 (2.6)
ECOG PS score — no. (%)[2]	0	122 (63.2)	55 (56.1)
	1	70 (36.3)	39 (39.8)
	2	0 (0.0)	3 (3.1)
***RET* mutation — no. (%)**	M918T mutation	121 (62.7)	61 (62.2)
Time from diagnosis to enrollment — mo	Median (Q1-Q3)	42.7 (15.2 - 98.9)	61.6 (20.2 - 141.0)

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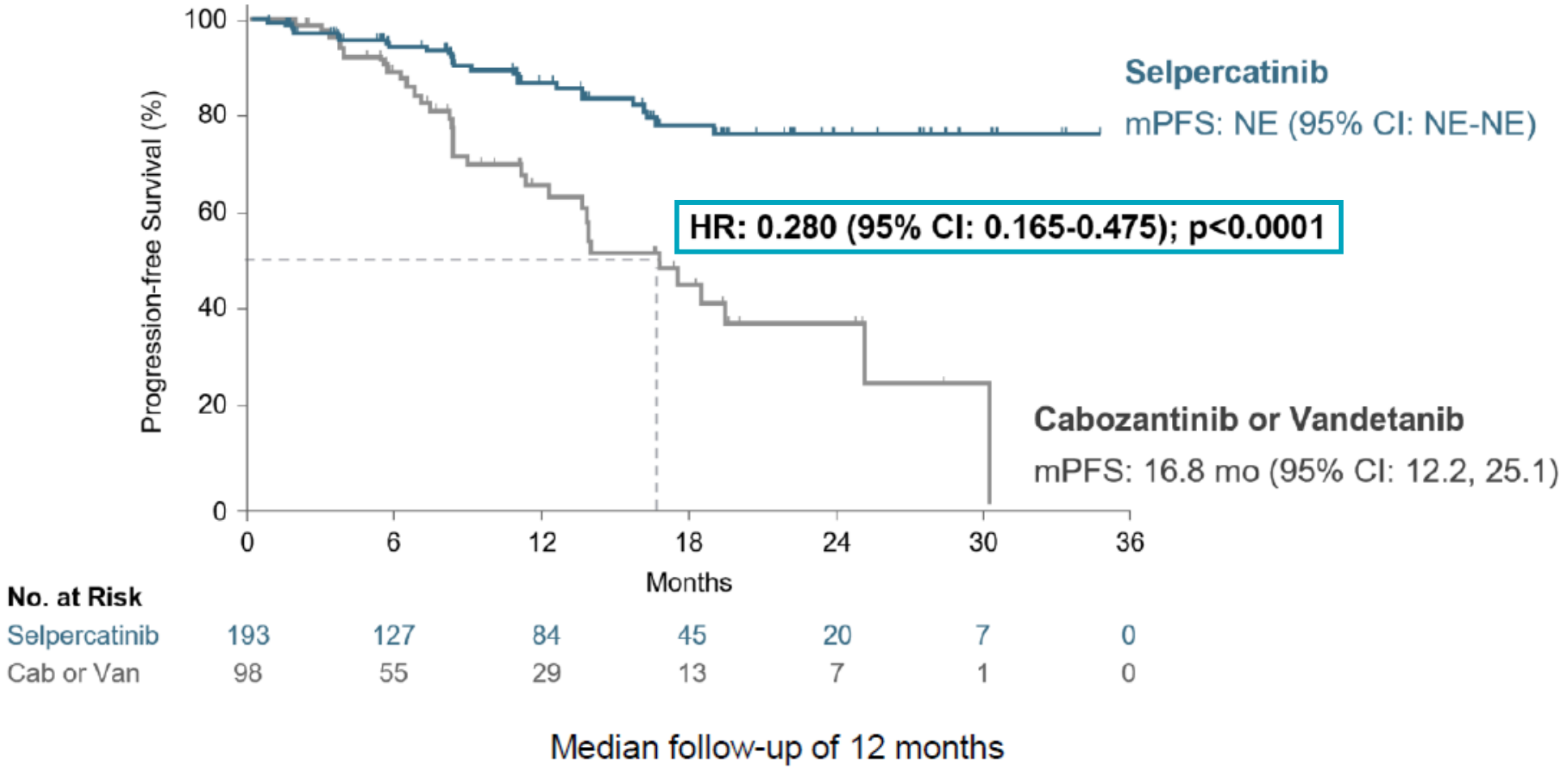
Efficacité du selpercatinib en 1ère ligne



Median follow-up of 12 months

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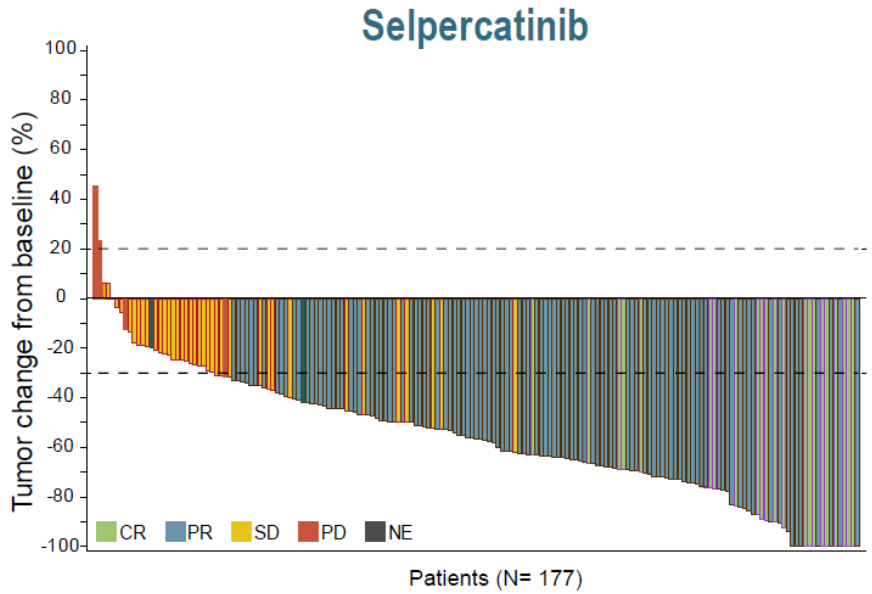
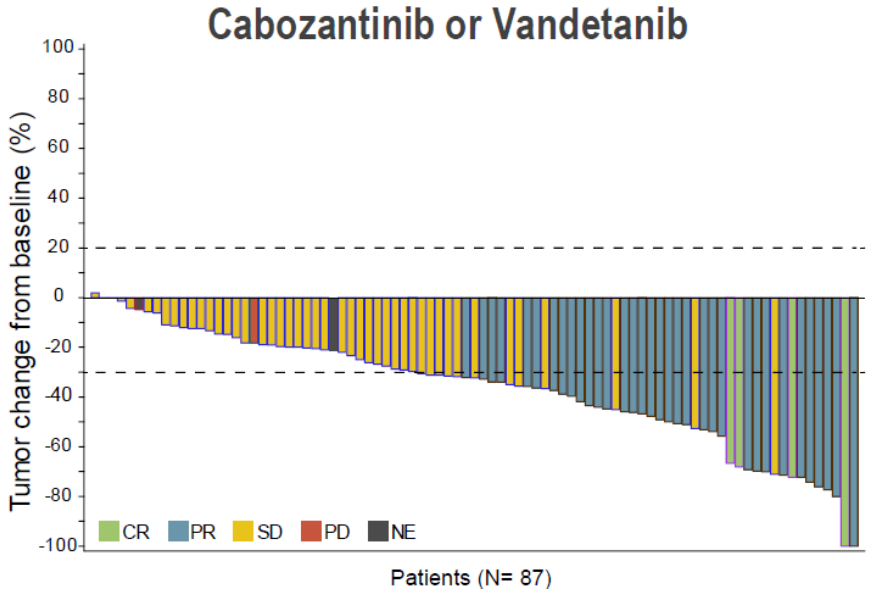
Efficacité du selpercatinib

Outcomes	Selpercatinib (N= 193)	Cabozantinib or Vandetanib (N= 98)
ORR, % (95% CI)[1]	69.4 (62.4, 75.8)	38.8 (29.1, 49.2)
Best overall response, no. (%)		
Complete response	23 (11.9)	4 (4.1)
Partial response	111 (57.5)	34 (34.7)
Median DOR, mo (95% CI)	NE (NE, NE)	16.6 (10.4, NE)





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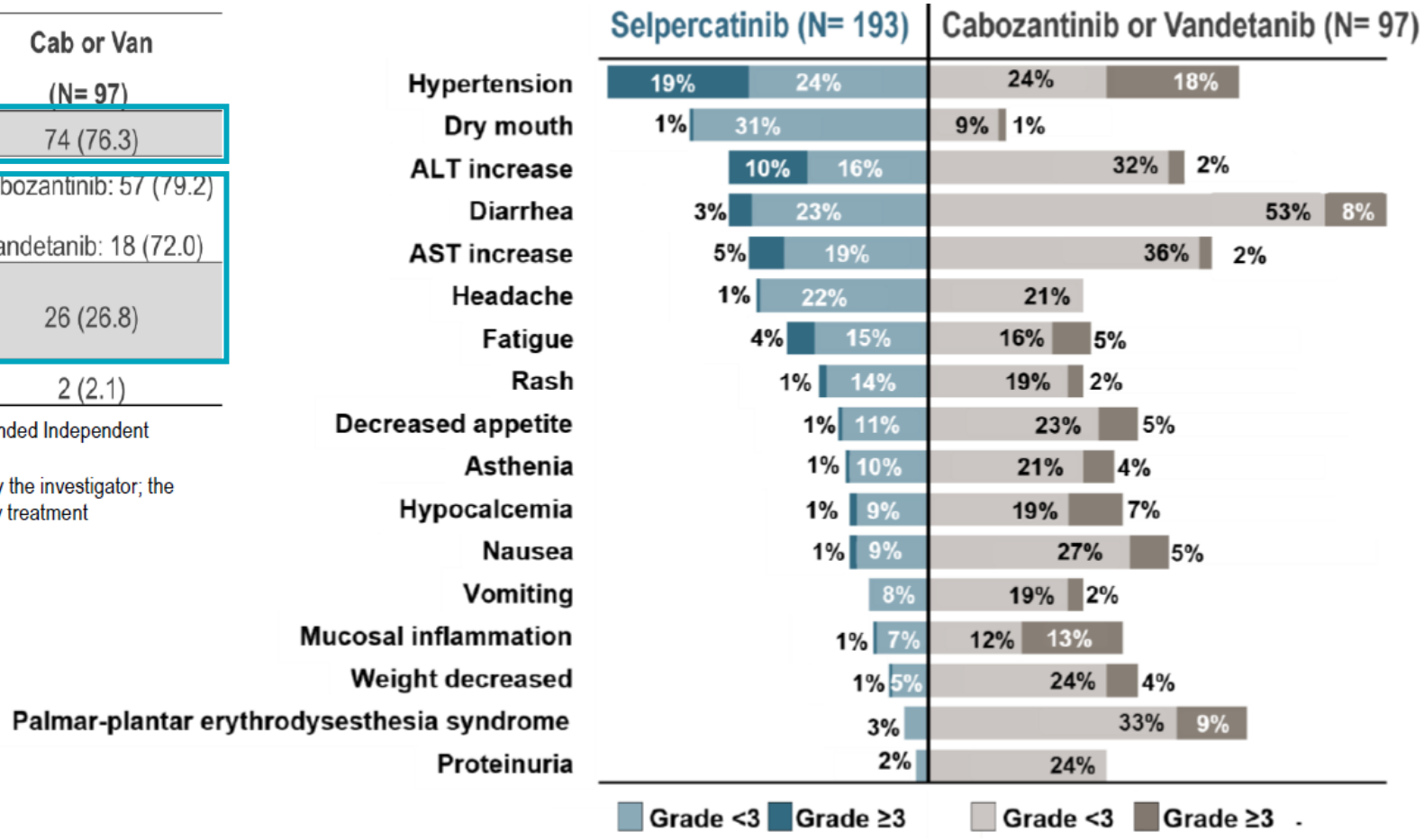
Profil de toxicité

Effect — no. (%)	Selpercatinib (N= 193)	Cab or Van (N= 97)
Grade ≥ 3 TEAEs	102 (52.8)	74 (76.3)
Dose reduction due to AE	75 (38.9)	Cabozantinib: 57 (79.2) Vandetanib: 18 (72.0)
Permanent discontinuation[1]	9 (4.7)	26 (26.8)
Death due to AE	4 (2.1)[2]	2 (2.1)

[1] Adjudicated centrally and retrospectively by a blinded Independent Review Committee

[2] For one patient, relationship was not assigned by the investigator; the other 3 events were deemed not related to study treatment



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En conclusion

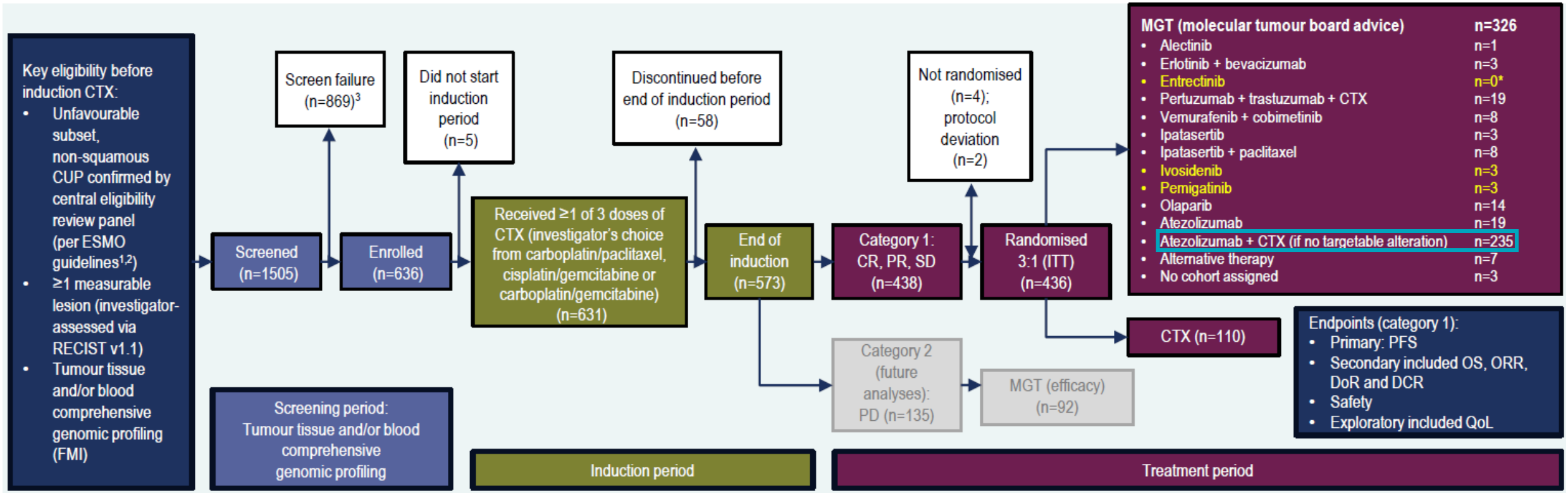
- Meilleure efficacité du selpercatinib comparé au cabozantinib ou vandétanib
- Données de survie globale non matures (suivi de 12 mois) → nécessité d'un suivi plus long
- Profil de toxicité plus favorable, moins de pauses thérapeutiques et de diminutions de posologie
- Nécessité de mieux comprendre les mécanismes de résistance sous selpercatinib

Primary analysis of efficacy and safety in the CUPISCO trial: A randomised, global study of targeted therapy or cancer immunotherapy guided by comprehensive genomic profiling (CGP) vs platinum-based chemotherapy (CTX) in newly diagnosed, unfavourable cancer of unknown primary (CUP)

Linda Mileshkin,[1] Tilmann Bochtler,[2] Chantal Pauli,[3] Gonzalo Durán-Pacheco,[4] Cagatay Arslan,[5] Frédéric Bigot,[6] Nasséra Chalabi,[4] Natalie Cook,[7] Antoine Italiano,[8] Ferran Losa,[9] Juliana Janoski de Menezes,[10] Chantal Michaud,[4] Mustafa Özgüroğlu,[11] Roberto A. Pazo-Cid,[12] Jeffrey S. Ross,[13] Kai-Keen Shiu,[14] Michael Stahl,[15] Marlene Thomas,[4] Holger Moch[3] and Alwin Krämer[16]

Design de l'étude CUPISCO

- Comparaison d'une stratégie guidée par la biologie moléculaire (via une RCP moléculaire) versus une chimiothérapie à base de sel de platine chez les patients contrôlés après un traitement d'induction



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Design de l'étude CUPISCO

CUPISCO molecular tumour board charter				
Rank	**Molecular target based on FMI report**	**VAF**	**Potential corresponding CUPISCO MGT cohort**	
1	Fusion events or rearrangement (*ALK*, *RET*, *ROS1*, *NTRK*)	**Need to be considered** *Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration recognising that tumour fraction and tumour ploidy of samples may vary*	Alectinib (*ALK*, *RET*) or entrectinib (*NTRK*, *ROS1*)	**Consideration of other treatment option cohort instead of CUPISCO MGT cohort**
2	Microsatellite instability high		Atezolizumab monotherapy	
3	*EGFR* alterations (in context of *RAS* wildtype)		Erlotinib + bevacizumab	
4	*BRAF V600E* and *K601E* alterations		Cobimetinib + vemurafenib	
5	*ERBB2* amplifications/alterations		Trastuzumab + pertuzumab + CTX	
6	*BRCA1*/*BRCA2* alterations, *PALB2* and *RAD51B*/*C*/*D* gLOH* (FMI score 20 or above)		Olaparaib	
7	*FGFR1*, *FGFR2* and *FGFR3* alterations		Pemigatinib	
8	TMB-high ≥16 mut/Mb (in the absence of markers of resistance to immune checkpoint blockage or cancer immunotherapies, such as *STK11* alterations or *MDM2* amplifications)		Atezolizumab monotherapy	
9	*PIK3CA*/*AKT1*/*PTEN* alterations		Ipatasertib + chemotherapy	
10	*IDH1 R132* alterations		Ivosidenib	
11	*PTCH1*/*SMO* alterations		Vismodegib (not available in Japan)	
12	*ERBB3* alterations		Trastuzumab + pertuzumab + CTX	
13	TMB-low and/or no actionable alteration (<16mut/Mb)		Atezolizumab + CTX	

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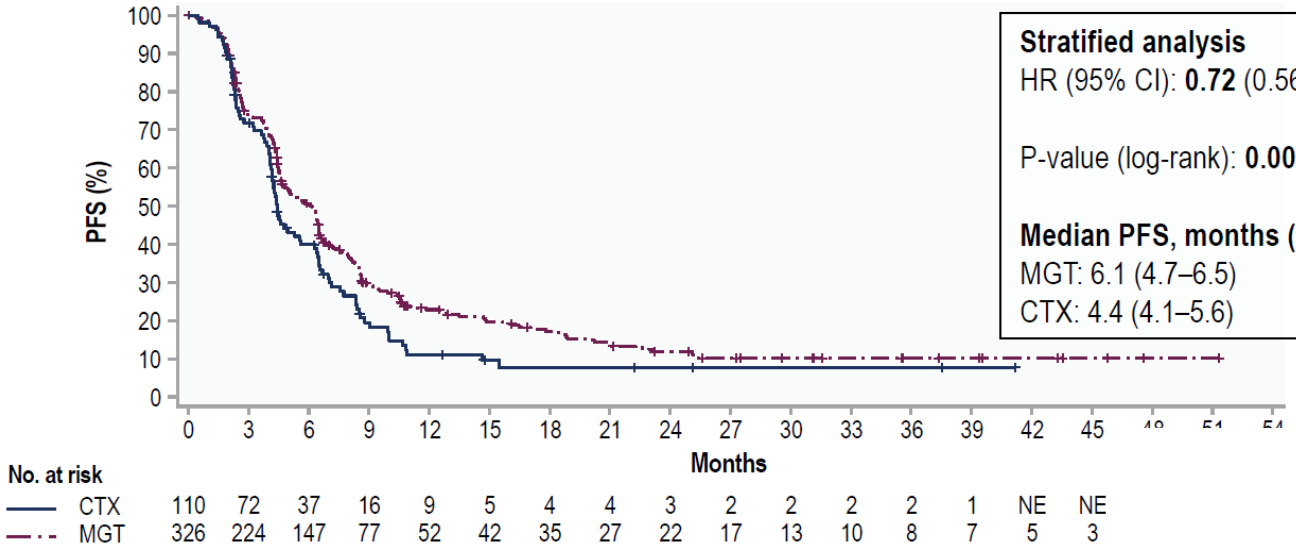
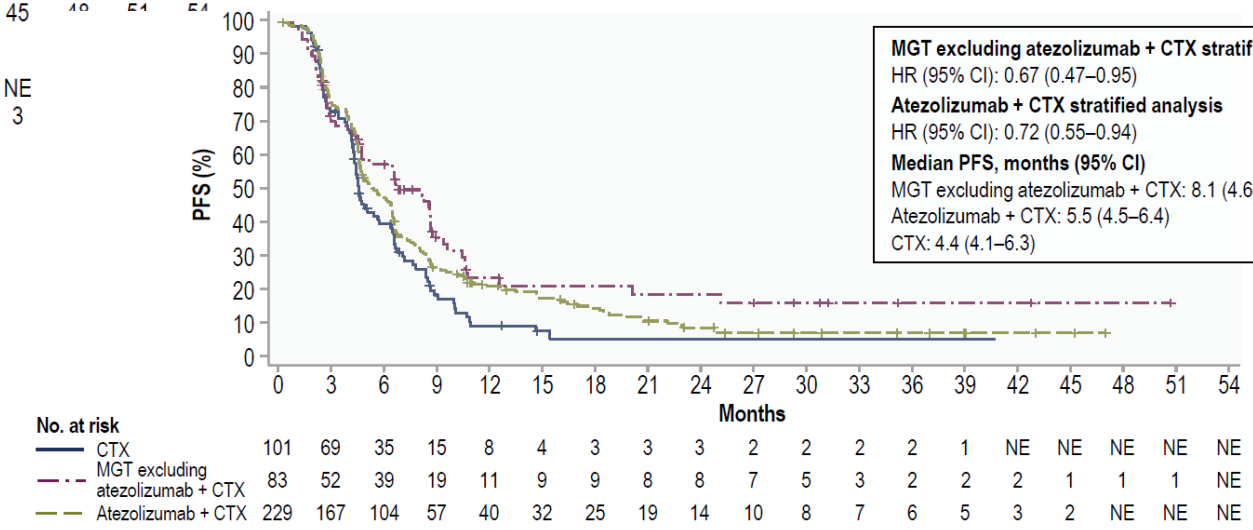
Résultats chez les patients contrôlés après CT



Stratified analysis
HR (95% CI): **0.72** (0.56–0.92)

P-value (log-rank): **0.0079**

Median PFS, months (95% CI)
MGT: 6.1 (4.7–6.5)
CTX: 4.4 (4.1–5.6)



MGT excluding atezolizumab + CTX stratified analysis
HR (95% CI): 0.67 (0.47–0.95)
Atezolizumab + CTX stratified analysis
HR (95% CI): 0.72 (0.55–0.94)
Median PFS, months (95% CI)
MGT excluding atezolizumab + CTX: 8.1 (4.6–8.7)
Atezolizumab + CTX: 5.5 (4.5–6.4)
CTX: 4.4 (4.1–6.3)

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Résultats chez les patients contrôlés après CT

	MGT (n=326)	CTX (n=110)
Best confirmed ORR, n (%)*	17.8 (13.8–22.4)	8.2 (3.8–15.0)
Difference, % (95% CI)	9.6 (2.4–16.8)	
Median DoR, months (range)	16.4 (8.1–NE)	NE (4.1–NE)
HR (95% CI)	0.95 (0.33–2.72)	
DCR, n (%)	64.7 (59.3–69.9)	60.0 (50.2–69.2)
Difference, % (95% CI)	4.7 (–6.4–15.9)	
QoL **Median time to deterioration in EQ-5D-5L VAS scores, months (range)**	5.9 (3.9–8.8)	6.6 (4.6–31.0)
HR (95% CI)	1.14 (0.78–1.65)	
Median time to deterioration in FACT-G total scores, months (range)	10.0 (7.4–12.9)	14.7 (5.8–NE)
HR (95% CI)	1.09 (0.73–1.63)	

Trend to improvement in median OS (data immature):

- 14.7 months (95% CI 13.3–17.3) with MGT vs 11.0 months (9.7–15.4) with CTX
- HR 0.82 (95% CI 0.62–1.09); *P*=0.1779

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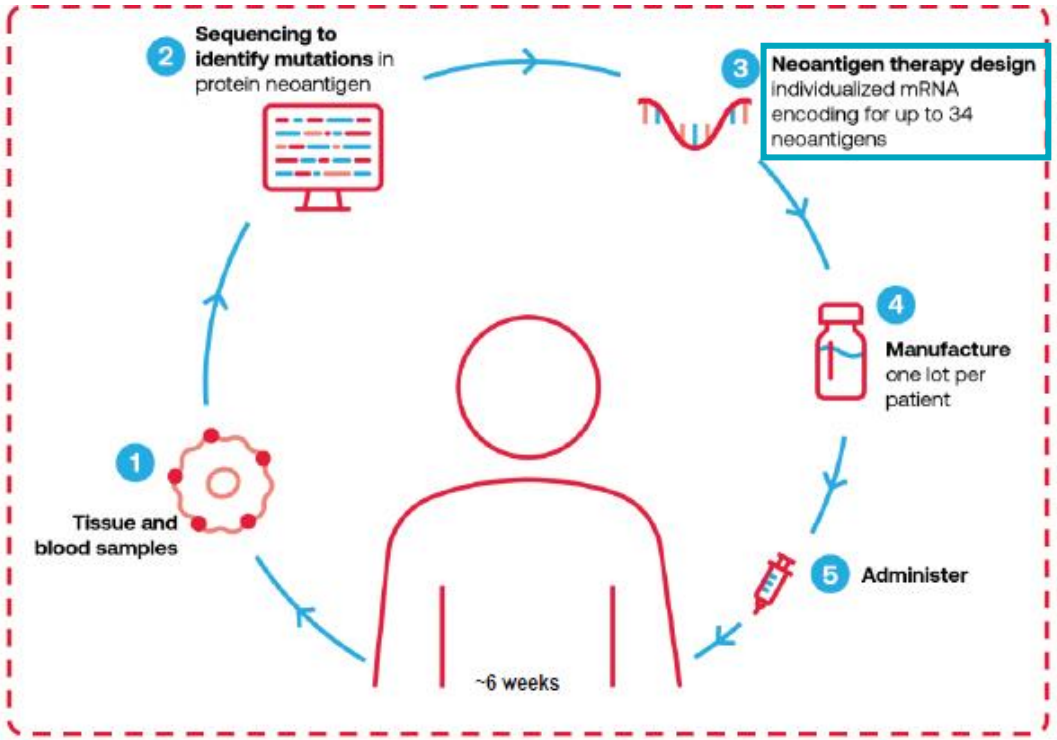
En conclusion

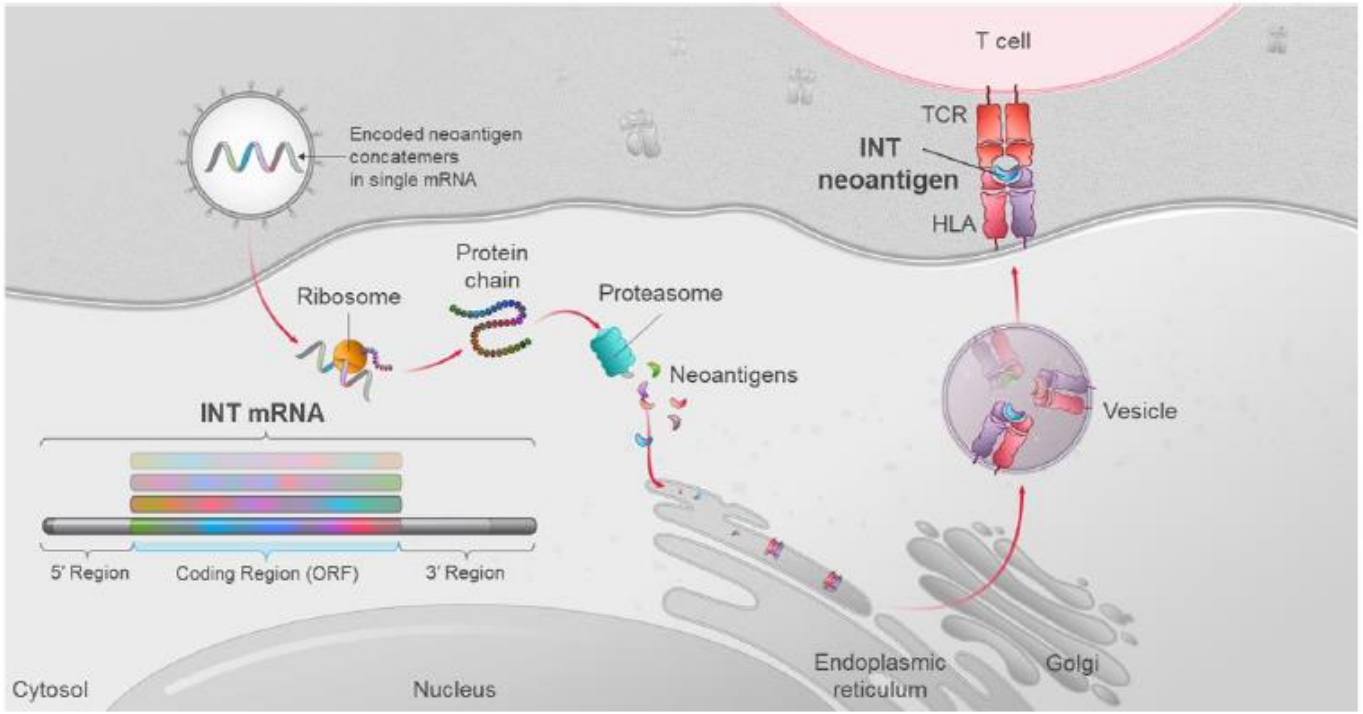
- Amélioration de la SSP avec une thérapie ciblée par rapport à une chimiothérapie +/- immunothérapie en l'absence d'anomalie moléculaire
- Données de survie globale encore immature (suivi médian 24,1 mois)
- Profil de toxicité rassurant
- Impact positif de la thérapie guidée par la biologie moléculaire
- Intérêt de réaliser dès que possible une biopsie tissulaire et/ou liquide pour analyses moléculaires +/- larges

mRNA-4157 (V940) individualized neoantigen therapy + pembrolizumab versus pembrolizumab in high-risk resected melanoma: clinical efficacy and correlates of response

Jeffrey S. Weber,[1] Adnan Khattak,[2] Matteo S. Carlino,[3] Ryan J. Sullivan,[4] Jason J. Luke,[5] Tarek Meniawy,[6] Matthew H. Taylor,[7] George Ansstas,[8] Kevin B. Kim,[9] Meredith McKean,[10] Mark B. Faries,[11] Thuy Tran,[12] C. Lance Cowey,[13] Andrew L. Pecora,[14] Theresa M. Medina,[15] Victoria Atkinson,[16] Geoffrey T. Gibney,[17] Elizabeth I. Buchbinder,[18] Robert S. Meehan,[19] Moderna Author Group,[19] Georgina V. Long[20]

Le vaccin mRNA-4157





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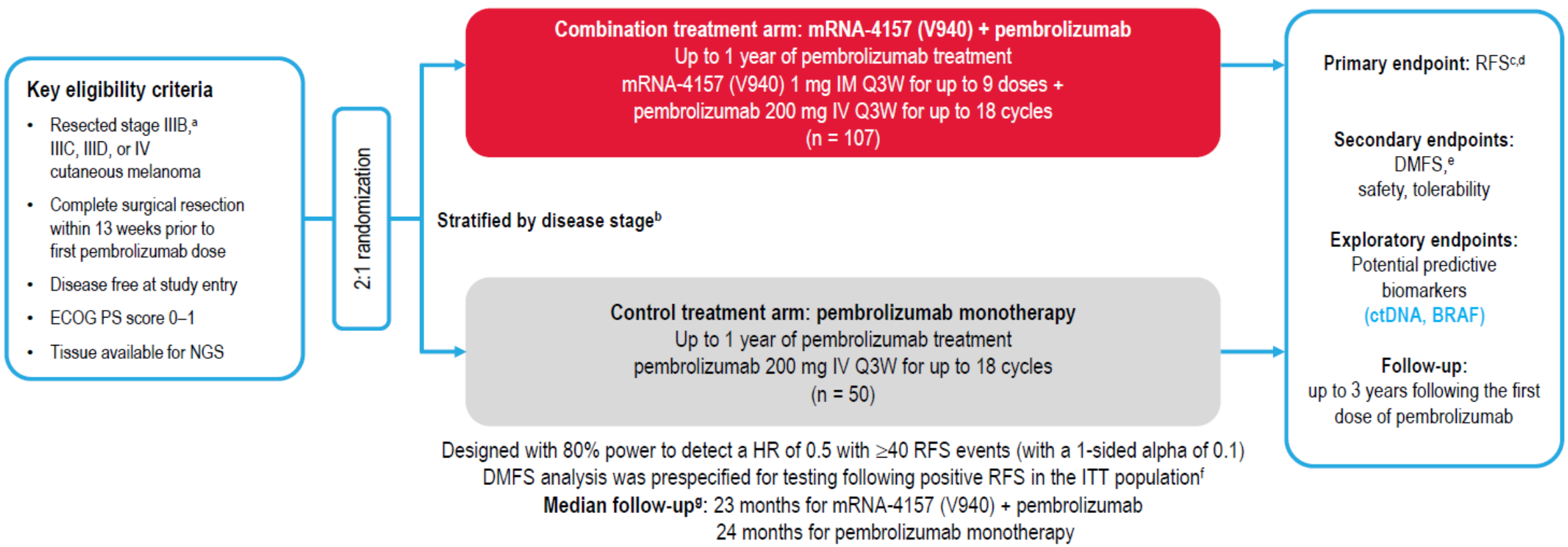
Design de l'étude de phase 2



Designed with 80% power to detect a HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

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Tolérance de la vaccination

	mRNA-4157 (V940) + pembrolizumab (n = 104)		pembrolizumab (n = 50)	
Event, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	104 (100.0)	36 (34.6)	47 (94.0)	18 (36.0)
Any treatment-related AE	104 (100.0)	26 (25.0)	41 (82.0)	9 (18.0)
Serious AE[a]	**15 (14.4)**	**13 (12.5)**	**5 (10.0)**	**4 (8.0)**
Most frequently occurring TEAEs (≥15%) by decreasing frequency				
Any	104 (100)		47 (94.0)	
Fatigue	87 (83.7)		27 (54.0)	
Injection-site pain	59 (56.7)		1 (2.0)	
Chills	54 (51.9)		3 (6.0)	
Pyrexia	54 (51.9)		3 (6.0)	
Headache	48 (46.2)		12 (24.0)	
Diarrhoea	44 (42.3)		10 (20.0)	
Nausea	44 (42.3)		9 (18.0)	
Influenza-like illness	35 (33.7)		1 (2.0)	
Pruritus	34 (32.7)		14 (28.0)	
Injection-site erythema	33 (31.7)		0 (0.0)	
Arthralgia	30 (28.8)		13 (26.0)	
Decreased appetite	27 (26.0)		5 (10.0)	
Myalgia	27 (26.0)		3 (6.0)	
Hypothyroidism	21 (20.2)		8 (16.0)	
Cough	17 (16.3)		5 (10.0)	
Rash maculo-popular	17 (16.3)		6 (12.0)	
Vomiting	17 (16.3)		3 (6.0)	

Immune-mediated AEs	**mRNA-4157 (V940) + pembrolizumab (n = 104)**		**pembrolizumab (n = 50)**	
Event, n (%)	**Any grade**	**Grade ≥3[a]**	**Any grade**	**Grade ≥3[b]**
Any	**37 (35.6)**	**11 (10.6)**	**18 (36.0)**	**7 (14.0)**

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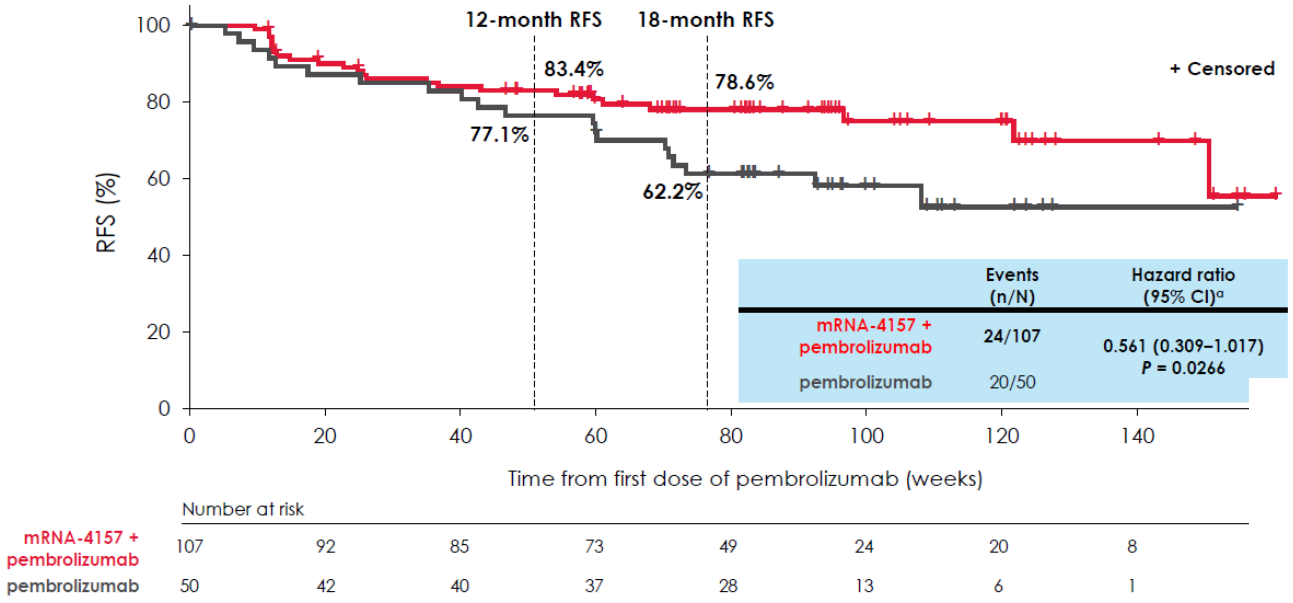
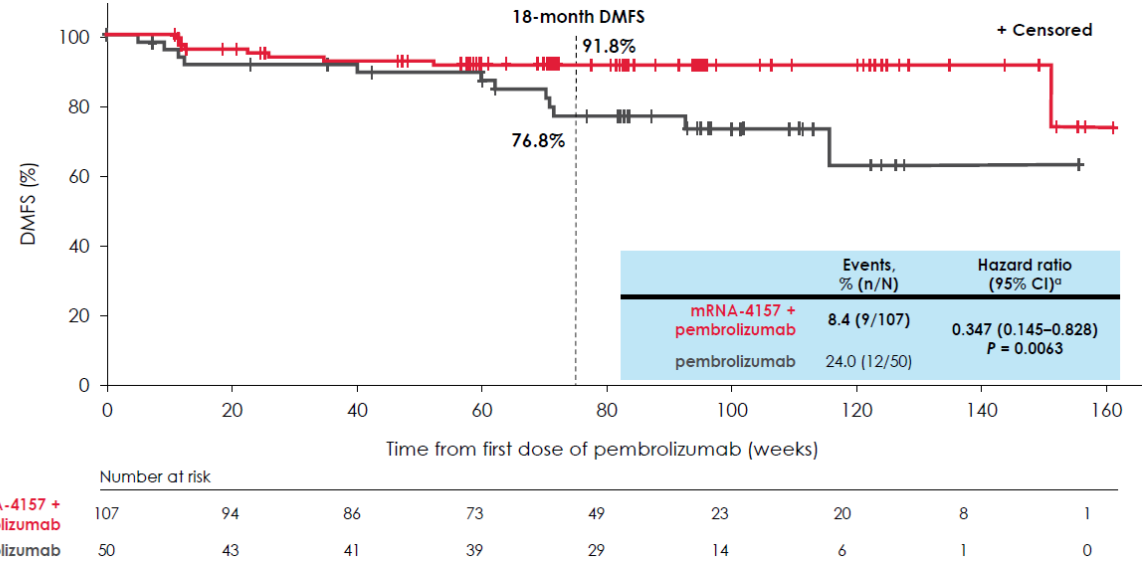
Apport de la vaccination en termes d'efficacité





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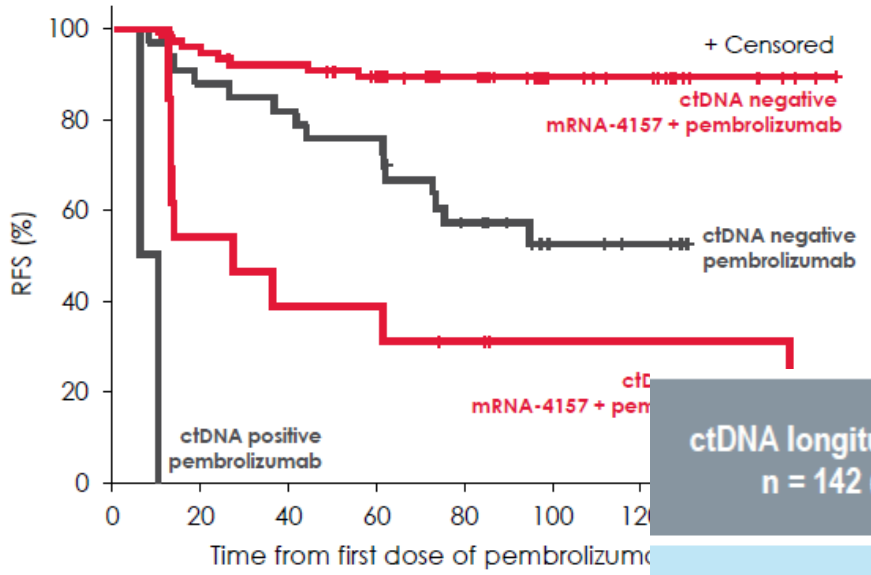
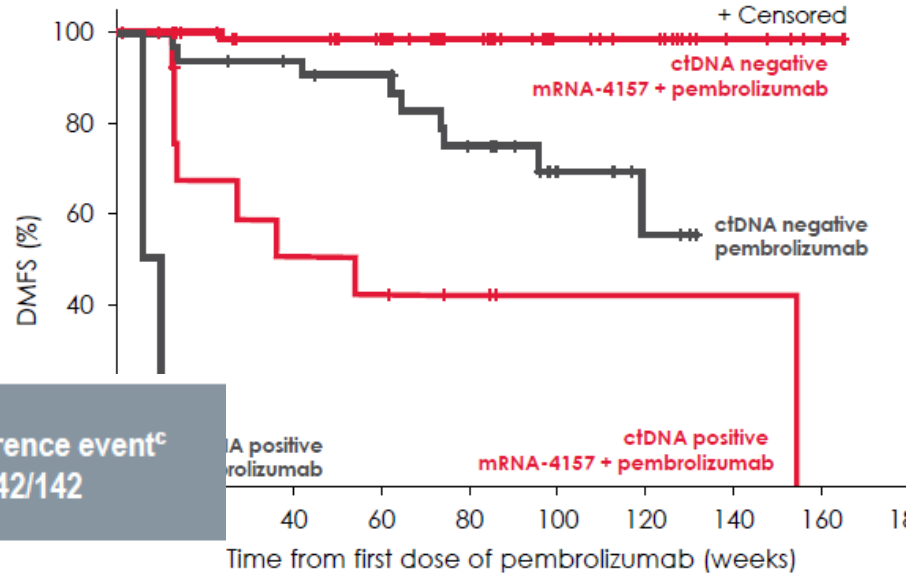
Impact du monitoring par ctDNA

RFS in patients with high-risk melanoma by baseline ctDNA status



DMFS in patients with high-risk melanoma by baseline ctDNA status



ctDNA longitudinal pattern n = 142 (101+41)	Recurrence event[c] 42/142
ctDNA negative pattern n = 112 (79+33)	19/112 (17%)
ctDNA positive MR n = 14 (12+2)	8/14 (57%)
ctDNA positive MNR n = 16 (10+6)	15/16 (94%)

Weber JS. et al. ESMO 2023;LBA49

En conclusion

- Amélioration de la survie sans rechute et la survie sans métastases
- Profil de tolérance correct
- ctDNA à la baseline = facteur pronostic → sélection des patients nécessitant une stratégie plus « agressive » ?
- Corrélation entre l'évolution du ctDNA et le pronostique des patients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