Actualités en Oncologie Thoracique

Mardi 21 novembre 2023

Palais de la Bourse - Bordeaux

Sophie Cousin – Institut Bergonié

Les « Actus » de l'ESMO – Soirée Post-ESMO Bordeaux 2023

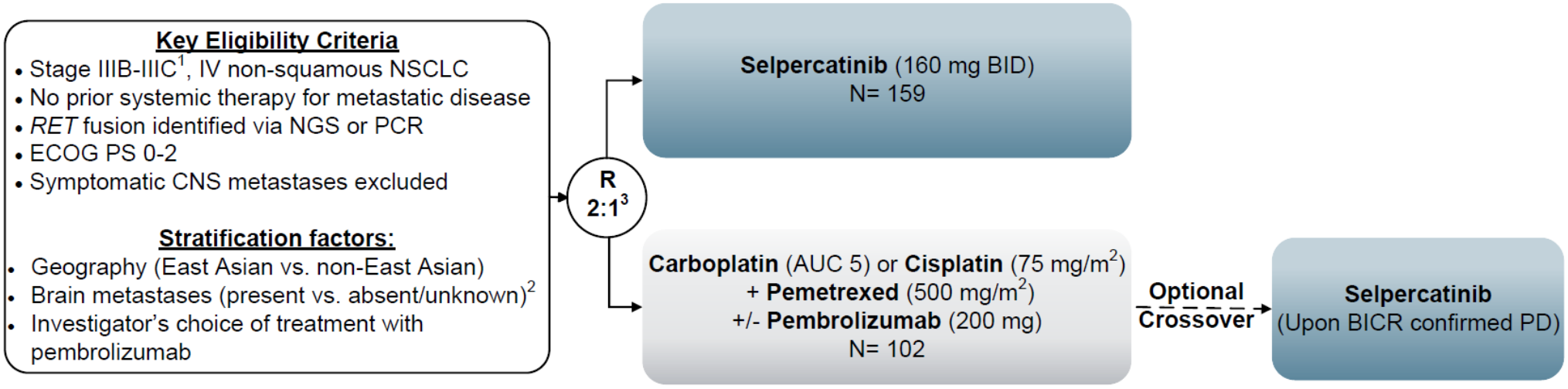
Liens d’intérêts

Boards ou Housing: Astrazeneca, MSD, Abbvie, Bristol Myers Squibb, Sanofi, Novartis, Amgen, Lilly, Takeda, Pfizer

Changements de standard dans le CBNPC de stade avancé ou métastatique

Randomized Phase 3 Study of First line Selpercatinib versus Chemotherapy and Pembrolizumab in RET Fusion positive NSCLC

LIBRETTO-431 (NCT 04194944), phase III randomisée



Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

[1] Not suitable for radical surgery or radiation therapy
[2] Investigator assessed
[3] The initial randomization ratio was 1:1, but amended to 2:1
[4] ITT-Pembrolizumab are patients stratified with investigator intent to receive chemotherapy with pembrolizumab and per protocol had to be at least 80% of the ITT population
[5] Baseline and longitudinal intracranial scans were required for all patients following an amendment. Prior to the amendment, longitudinal intracranial scans were required if patients had known CNS metastases at baseline

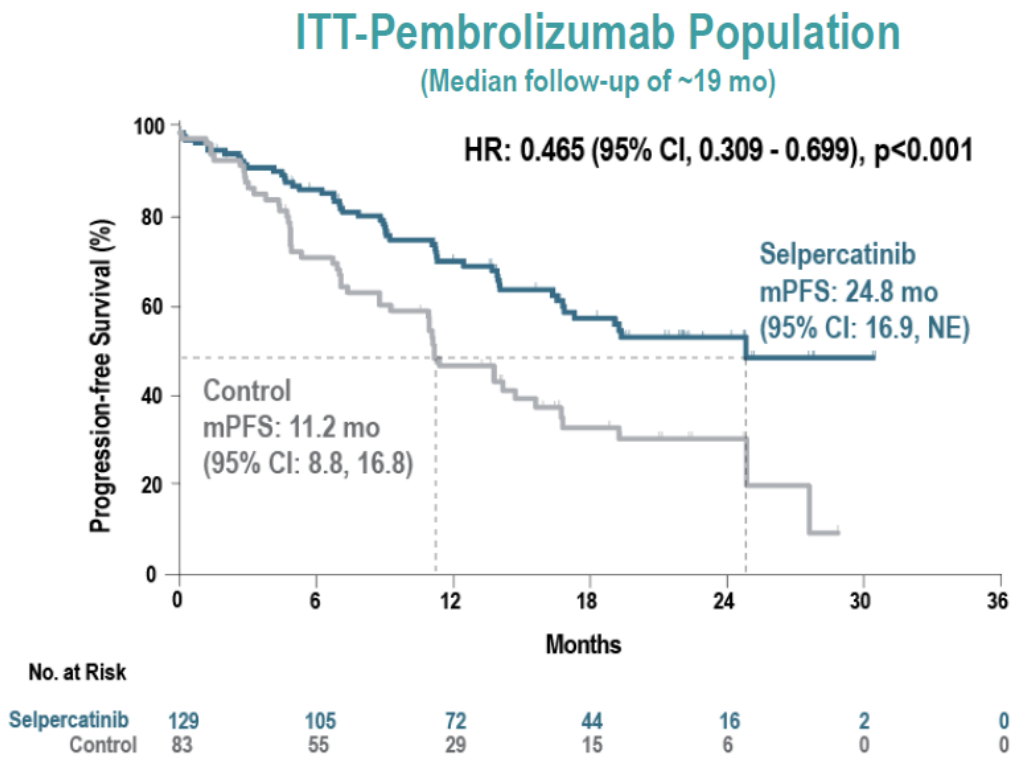
Loong H.H. et al. Abstract LBA4

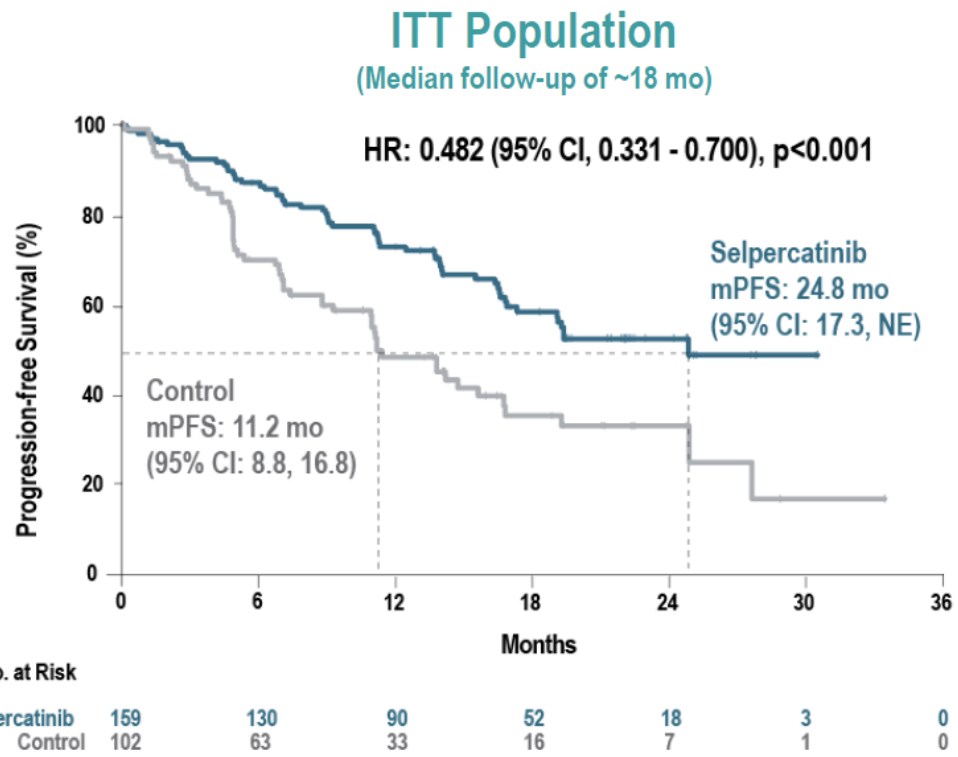
Caractéristiques des patients

Characteristic		Selpercatinib N= 129	Control N= 83
Age, years	Median (range)	60.0 (31-84)	62.0 (31-83)
Sex, no. (%)	Female	65 (50.4)	48 (57.8)
	Male	64 (49.6)	35 (42.2)
Smoking status, no. (%)	Current/Former	44 (34.1)	24 (28.9)
	Never	85 (65.9)	59 (71.1)
Race, no. (%)	Asian	76 (58.9)	41 (51.9)
	White	49 (38.0)	37 (46.8)
	Other	4 (3.2)	1 (1.3)
Region of enrollment, no. (%)	East Asia	75 (58.1)	41 (49.4)
	Non-East Asia	54 (41.9)	42 (50.6)
Disease stage, no. (%)	Stage IIIB/C	7 (5.4)	7 (8.4)
	Stage IV	122 (94.6)	76 (91.6)
ECOG PS, no. (%)	0	45 (34.9)	27 (32.5)
	1	81 (62.8)	52 (62.7)
	2	3 (2.3)	4 (4.8)
Brain metastases, no. (%)	No/Unknown	104 (80.6)	65 (78.3)
	Yes	25 (19.4)	18 (21.7)
PDL-1 expression, no. (%)	Negative	31 (24.0)	12 (14.5)
	Positive (≥1%)	55 (42.6)	39 (47.0)
	Missing	43 (33.3)	32 (38.6)
***RET* fusion partner, no. (%)**	*KIF5B-RET*	54 (41.9)	41 (49.4)
	CCDC6-RET	13 (10.1)	8 (9.6)
	Other	4 (3.1)	3 (3.6)
	Positive (partner undefined)	58 (45.0)	31 (37.3)

Loong H.H. et al. Abstract LBA4

Objectif I: Survie sans progression (par BICR)





The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

Loong H.H. et al. Abstract LBA4

Données de réponse, dont réponse intra crânienne

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

[1] Effective crossover rate: patients who discontinued from control treatment and received a selective RET inhibitor on or off study
[2] In patients with measurable CNS disease at baseline.

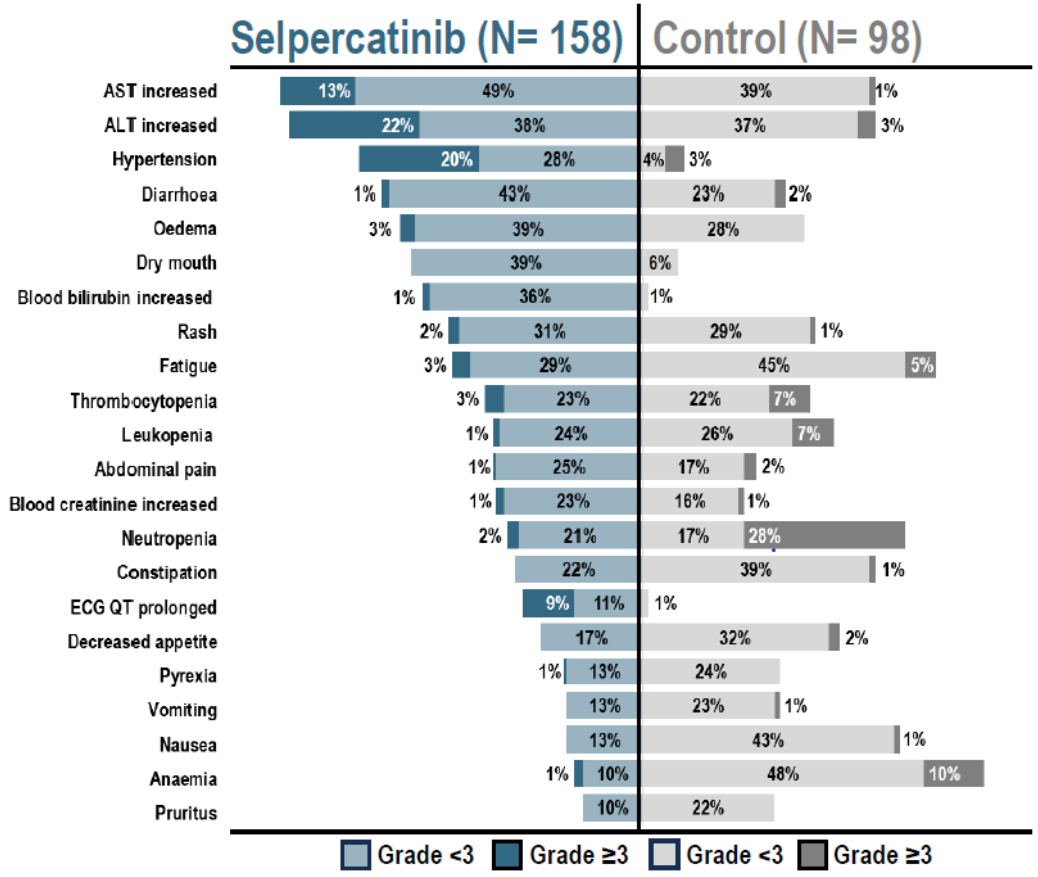
Meilleur taux de réponse selon RECIST 1.1 et réponse plus durable que le bras contrôle

Chez les patients avec de la maladie intra crânienne mesurable:

- Meilleur taux de réponse selon RECIST 1.1
- Meilleure survie sans progression intra crânienne

Loong H.H. et al. Abstract LBA4

Données de tolérance



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

Temps médian sous traitement plus long avec le selpercatinib: 16,7 mois vs 9,8 mois

Profil de tolérance similaire aux études précédentes, gérables avec réduction de dose

	Selpercatinib N= 158	Control N= 98
Median time on treatment, months ± SD	16.7 ± 8.3	9.8 ± 7.2
Any AE, n (%)	158 (100.0)	97 (99.0)
AE Grade ≥3	111 (70.3)	56 (57.1)
Deaths due to AE, n (%)	7 (4.4)	0
Related AE (malnutrition and sudden death)	2 (1.3)	0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to any dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction	81 (51.3)	28 (28.6)

Loong H.H. et al. Abstract LBA4

Conclusion sur Libretto-431

- Supériorité du Selpercartinib vers doublet à base de platine +/- Pembrolizumab
- Excellente efficacité intra crânienne
- Tolérance correcte et gérable

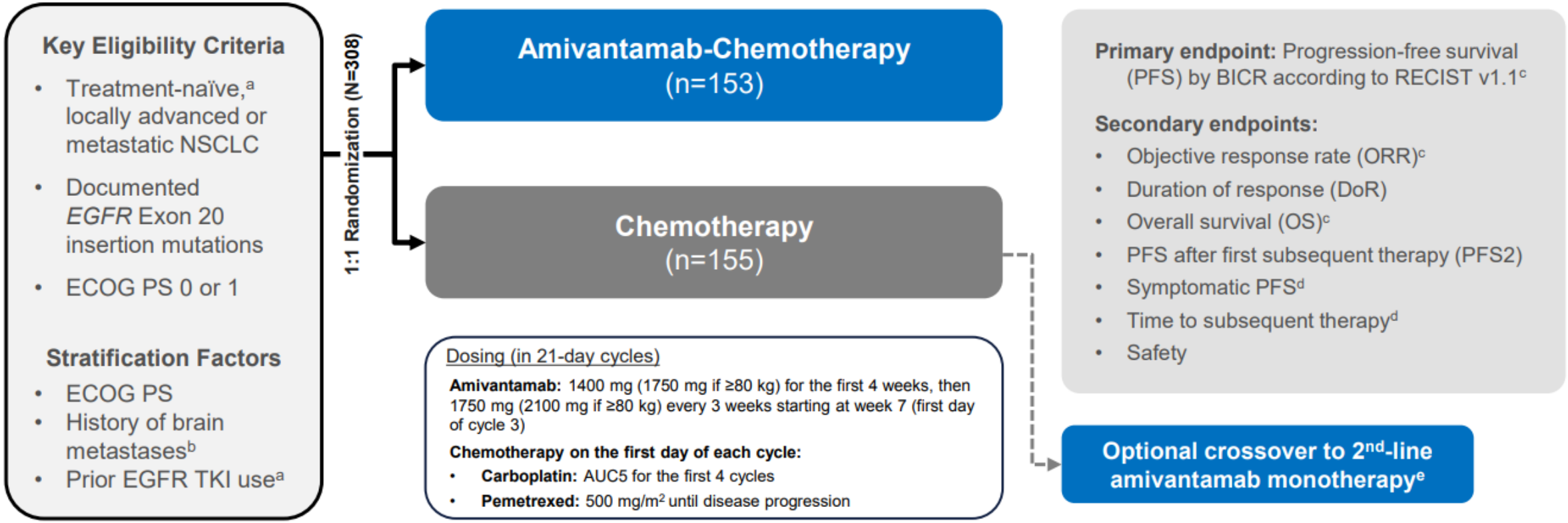
Selpercatinib doit devenir le standard en première ligne chez les patients avec mCBNPC présentant une fusion de RET

IMPORTANCE du testing des fusions de RET au DIAGNOSTIC pour le choix de la 1ere ligne

Loong H.H. et al. Abstract LBA4

Amivantamab Plus Chemotherapy vs Chemotherapy as First-line Treatment in EGFR Exon 20 Insertion–mutated Advanced Non-small Cell Lung Cancer (NSCLC)

PAPILLON, phase III randomisée



Girard N. et al. Abstract LBA5

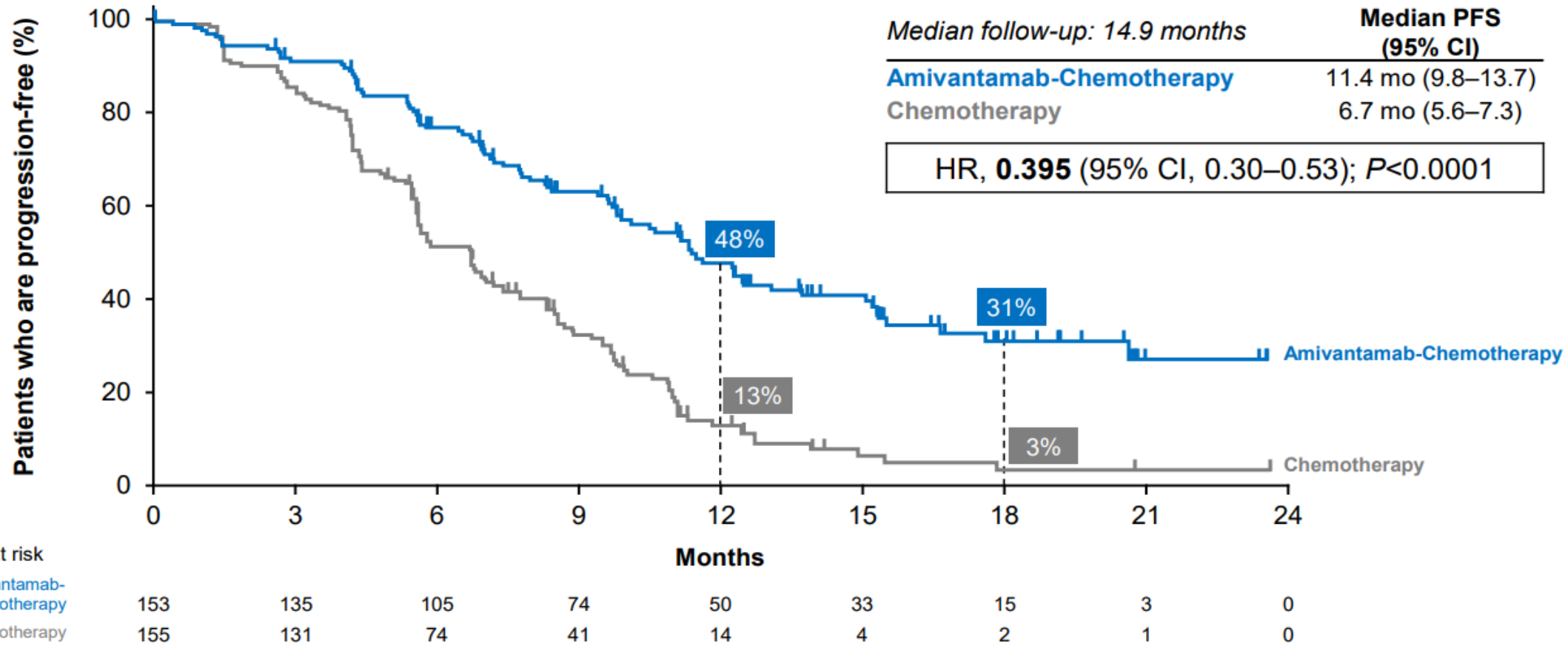
Caractéristiques des patients

Characteristic, n (%)	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Median age, years (range)	61 (27–86)	62 (30–92)
Female / male	85 (56) / 68 (44)	93 (60) / 62 (40)
Race[a]		
Asian	97 (64)	89 (59)
White	49 (32)	60 (39)
Other[b]	5 (3)	3 (2)
ECOG PS 0 / 1	54 (35) / 99 (65)	55 (35) / 100 (65)
History of smoking: yes / no	65 (42) / 88 (58)	64 (41) / 91 (59)
History of brain metastases: yes / no	35 (23) / 118 (77)	36 (23) / 119 (77)
Prior EGFR TKI use: yes[c] / no	1 (1) / 152 (99)	3 (2) / 152 (98)
Histology: adenocarcinoma subtype / other[d]	151 (99) / 2 (1)	153 (99) / 2 (1)

Girard N. et al. Abstract LBA5

Objectif I: survie sans progression

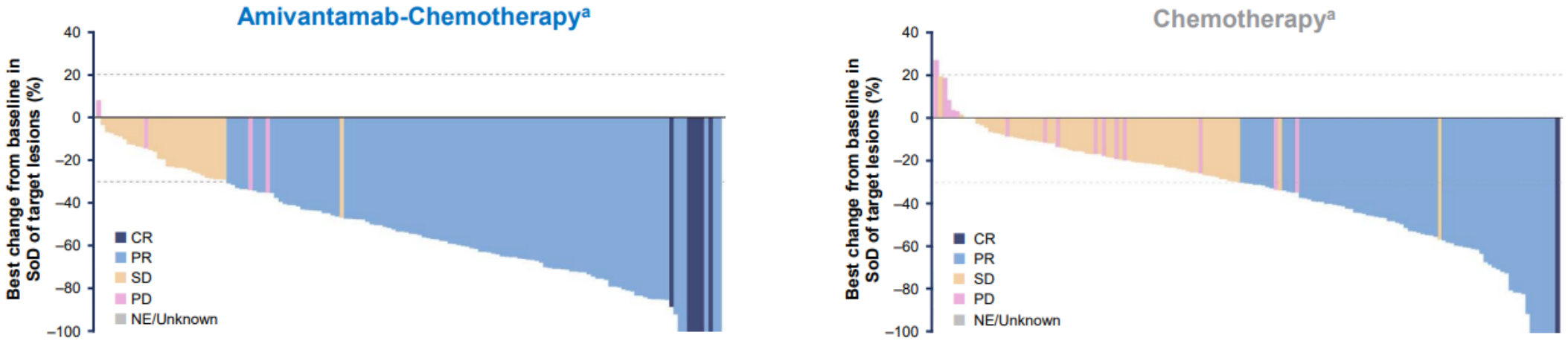
Amivantamab réduit de 60% le risque de progression



Girard N. et al. Abstract LBA5

Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

Taux de réponse objective (par BICR)



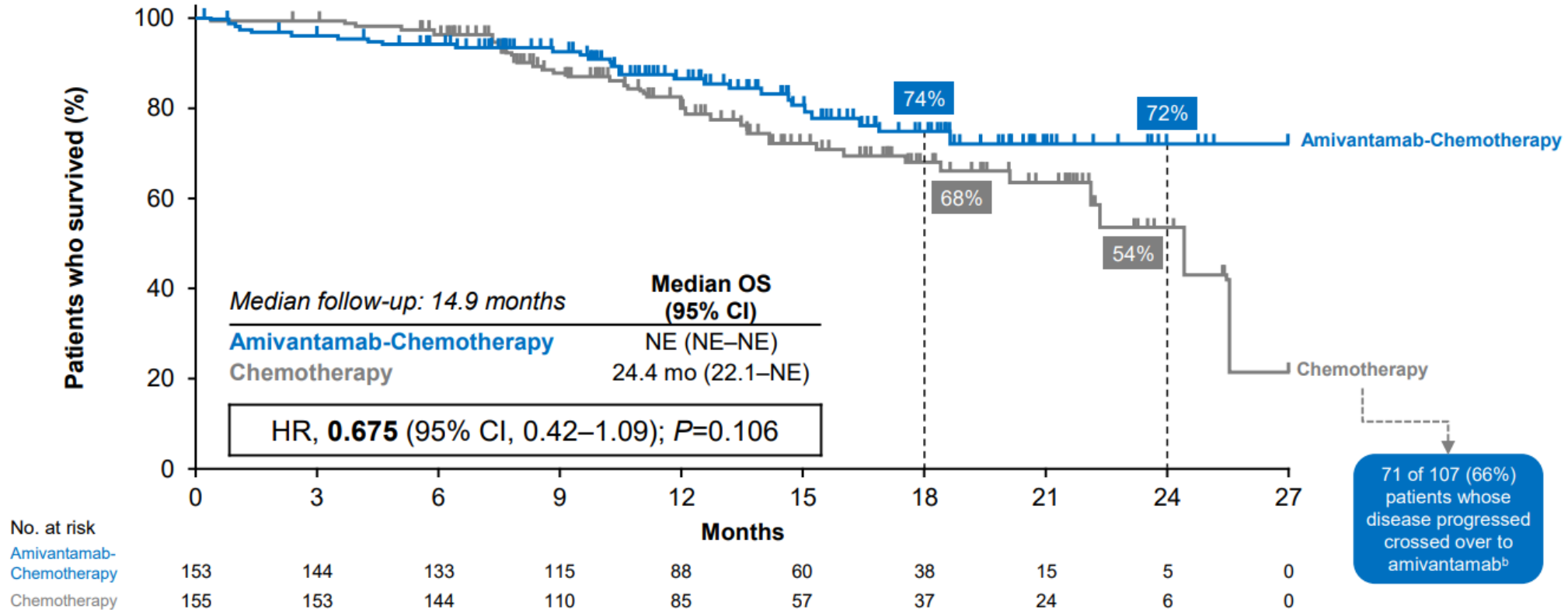
BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)
Median time to response	6.7 wk (range, 5.1–72.5)	11.4 wk (range, 5.1–60.2)

Consistent results with investigator assessment: ORR of 66% vs 43% (OR, 2.6; *P*<0.0001)

Girard N. et al. Abstract LBA5

Données de survie globale (immatures)

Tendance à l'amélioration de la survie globale de 30%



Girard N. et al. Abstract LBA5

Données de tolérance

Treatment-emergent AEs, n (%)	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Any AEs	151 (100)	152 (98)
Grade ≥3 AEs	114 (75)	83 (54)
Serious AEs	56 (37)	48 (31)
AEs leading to death	7 (5)	4 (3)
Any AE leading to treatment:		
Interruptions of any agent	104 (69)	56 (36)
Related interruptions of amivantamab	63 (42)	–
Reductions of any agent	73 (48)	35 (23)
Related reductions of amivantamab	54 (36)	–
Discontinuations of any agent	36 (24)	16 (10)
Related discontinuations of amivantamab	10 (7)	–
Discontinuations of all study agents due to AEs	12 (8)	12 (8)

Arrêt des traitements pour toxicités similaires
Plus de toxicités spécifiques EGFR/MET dans le bras chimio + Amivantamab
Hématotoxicité similaire sauf pour la neutropénie
3% de pneumonie dans le bras chimio + amivantamab

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

Girard N. et al. Abstract LBA5

Conclusion sur PAPILLON

- Amélioration statistiquement significative de la survie sans progression de l'ajout de l'amivantamab à la chimiothérapie
- Amélioration du taux de réponse, de la durée de réponse
- Données de survie globale immature mais une tendance favorable
- Toxicité: pas de signal inattendu.

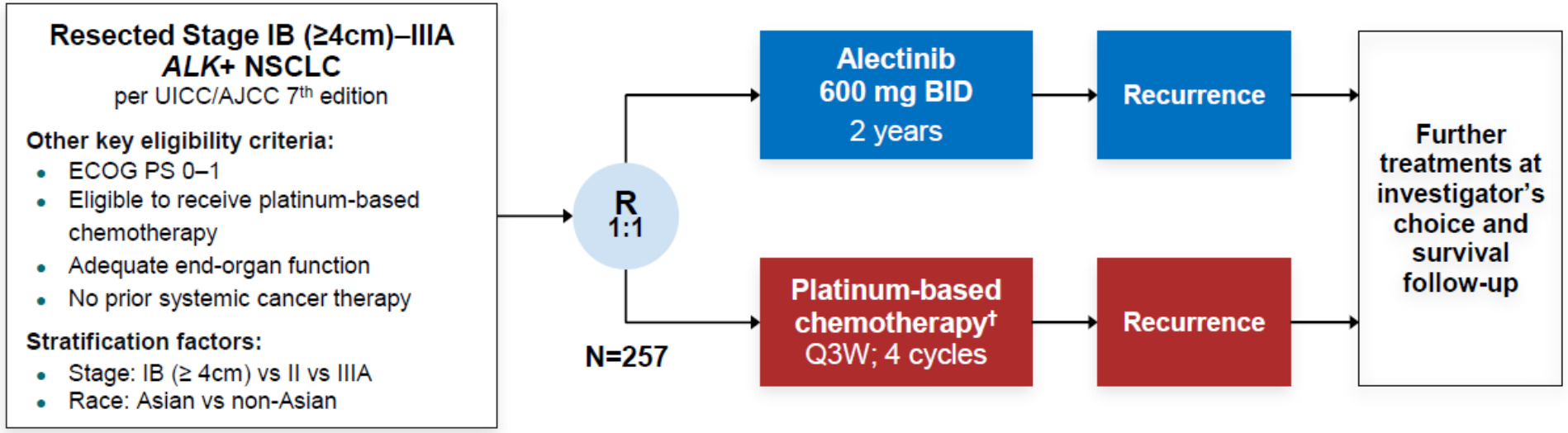
Amivantamab associé à un doublet à base de platine représente le nouveau standard en cas de mCBNPC avec mutation d'insertion de l'exon 20 de l'EGFR

Girard N. et al. Abstract LBA5

Affaire à suivre

Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ NSCLC

ALINA, phase III randomisée



Primary endpoint

- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints

- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

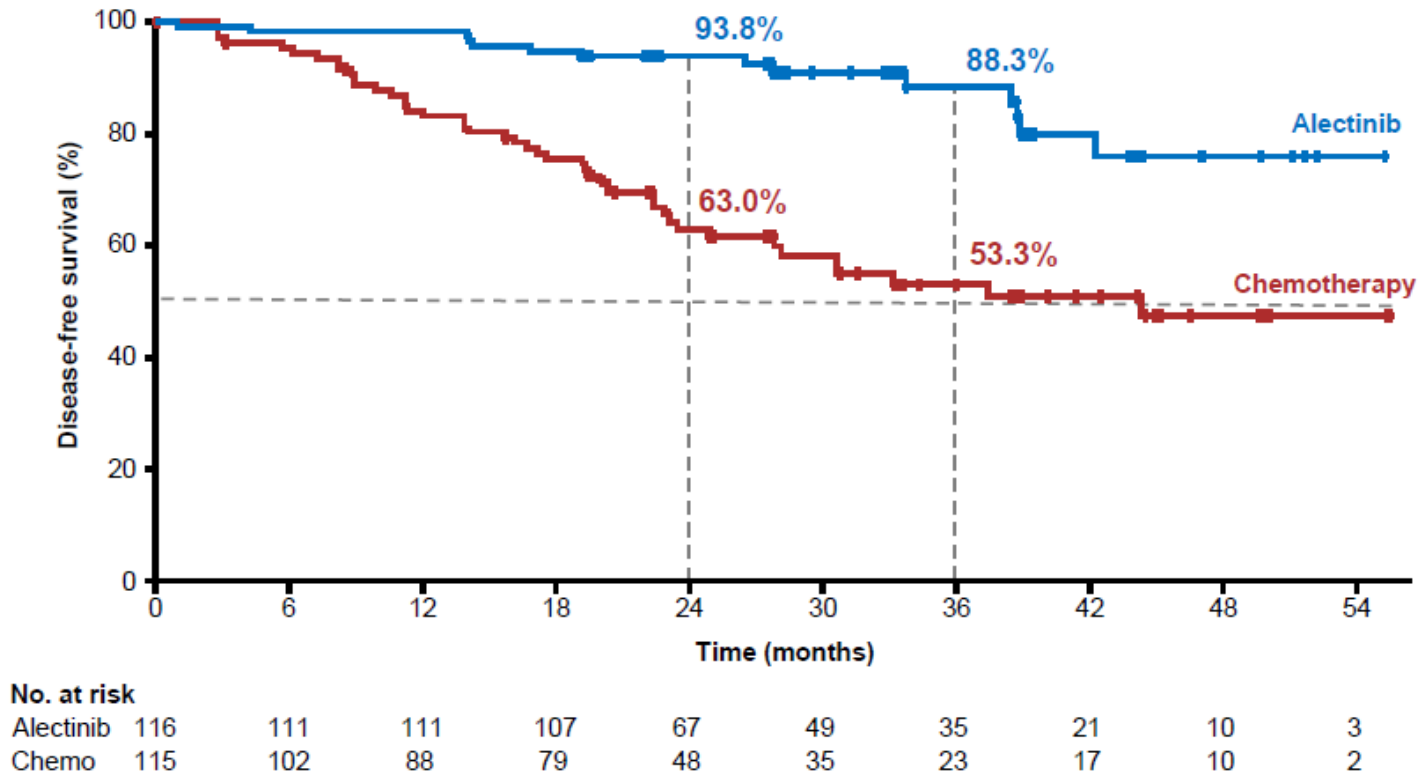
Solomon B et al. Abstract LBA2

Caractéristiques des patients

Characteristic	Alectinib (n=130)	Chemotherapy (n=127)
Median age <65 / ≥65 years, %	54 years 79 / 21	57 years 73 / 27
Sex: female / male, %	58 / 42	46 / 54
Smoking status: never / former / current, %	65 / 32 / 4	55 / 43 / 2
Race: Asian / non-Asian, %	55 / 45	56 / 44
ECOG PS: 0 / 1, %	55 / 45	51 / 49
Stage at diagnosis*: IB / II / IIIA, %	11 / 36 / 53	9 / 35 / 55
Nodal status: N0 / N1 / N2, %	16 / 35 / 49	14 / 34 / 52
Histology: squamous / non-squamous, %	5 / 95	2 / 98
Surgical procedure: Lobectomy / Other‡, %	97 / 3	92 / 8

Solomon B et al. Abstract LBA2

Survie sans maladie: stade II - IIIA

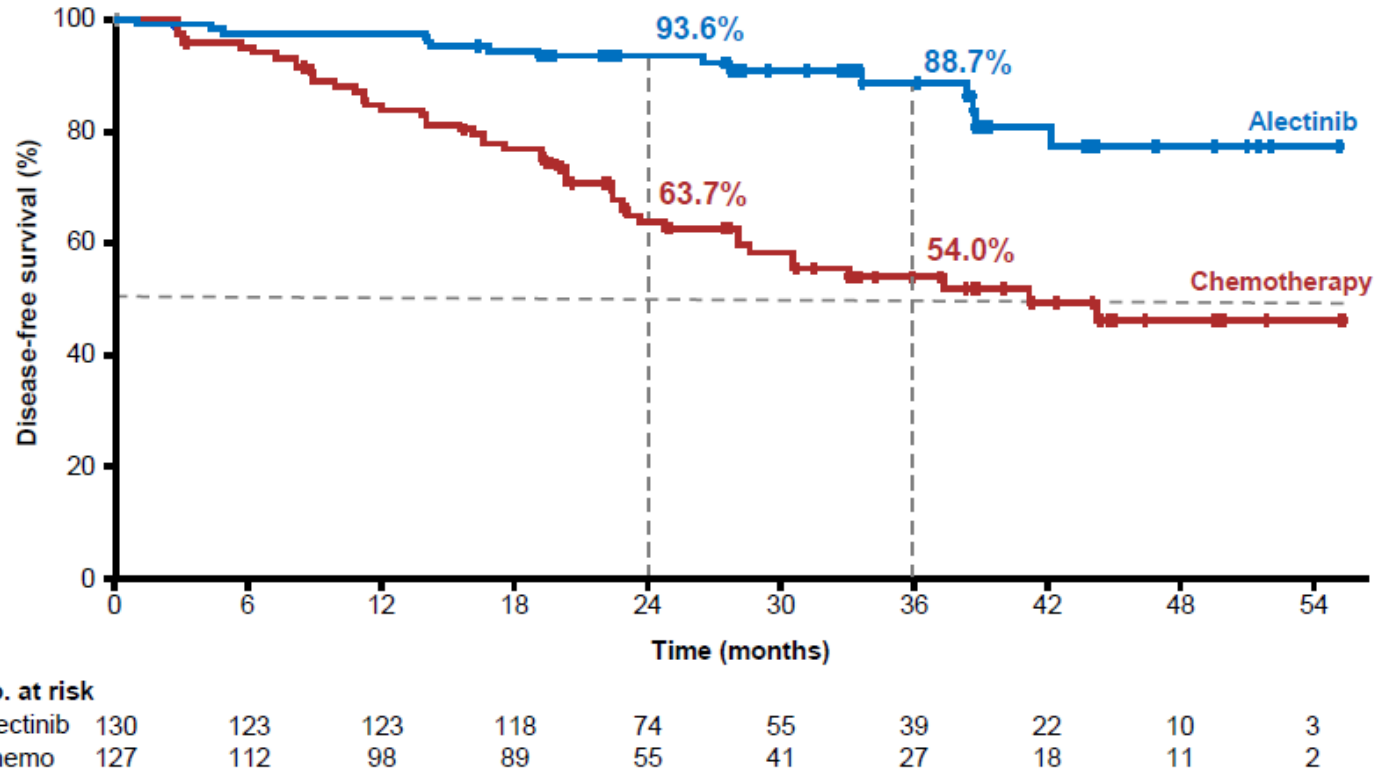


	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Solomon B et al. Abstract LBA2

Survie sans maladie, population en intention de traiter (stade Ib – IIIA)



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

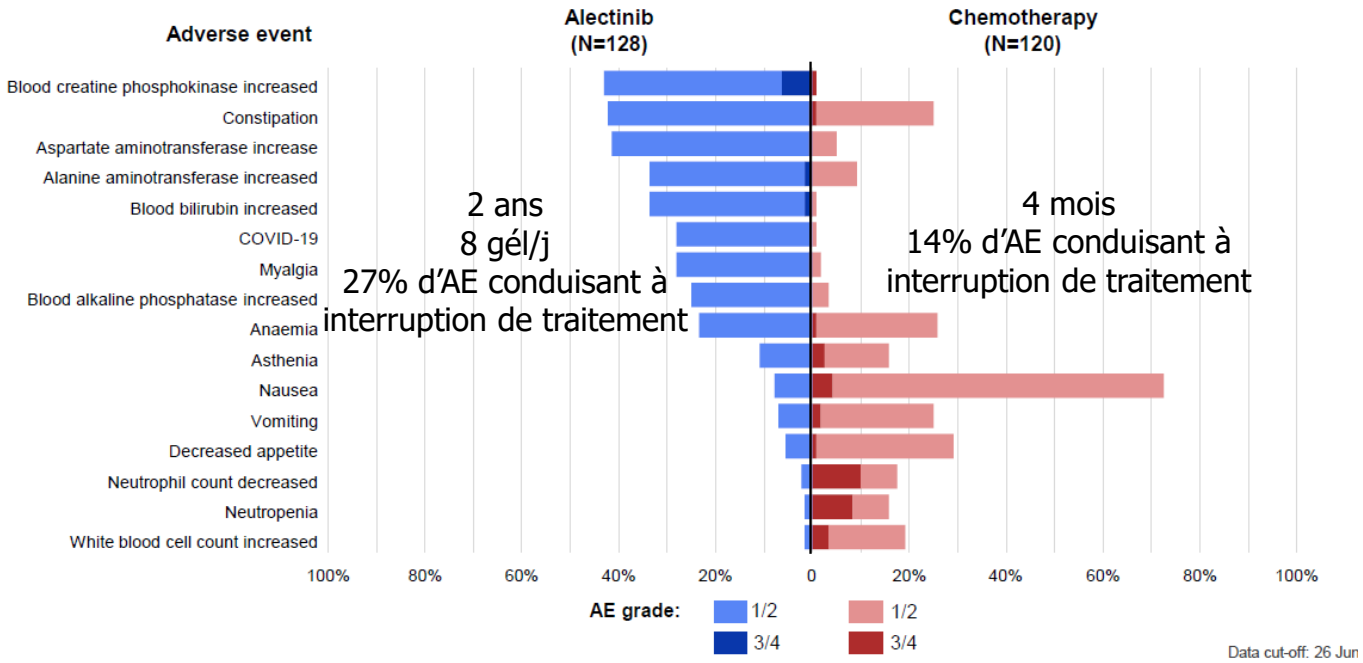
At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

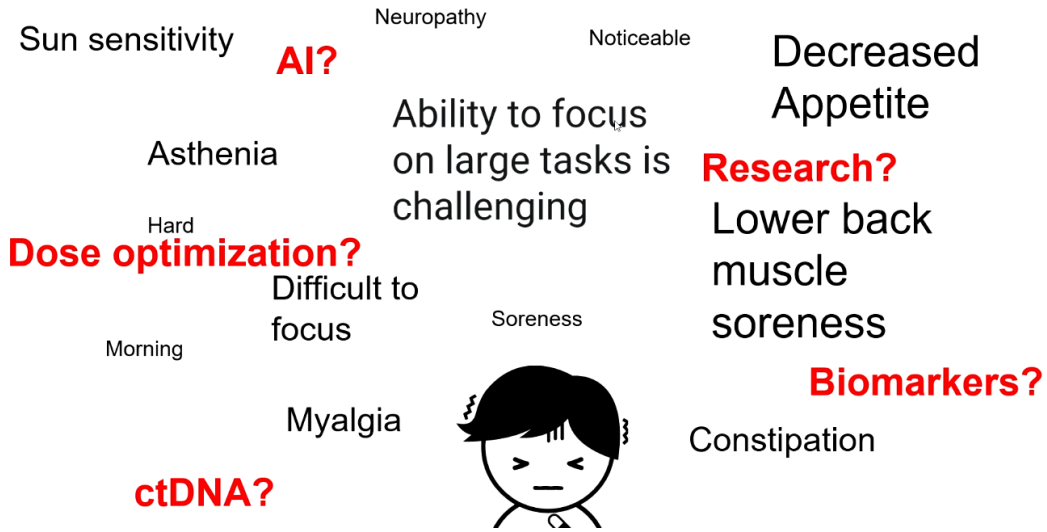
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Solomon B et al. Abstract LBA2

Toxicités et réflexion

Toxicités survenant chez > 15% des patients



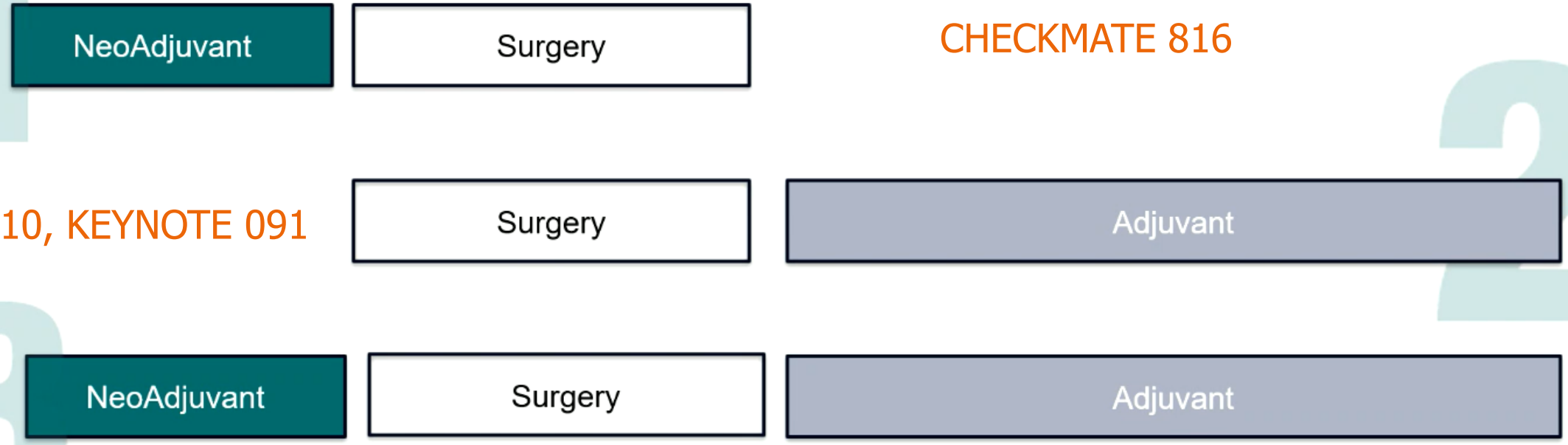


Solomon B et al. Abstract LBA2; Garassino M et al. Discussion

Le péri opératoire en l'absence d'addiction oncogénique

Stratégies péri opératoires

TREATMENT STRATEGIES FOR PATIENTS WITH A RESECTABLE NSCLC IN 2023



CHECKMATE 816

Impower 010, KEYNOTE 091

KEYNOTE 671, AEGEAN, NEOTORCH, CHECKMATE 77T

Garassino M et al Presidential 1 discussion

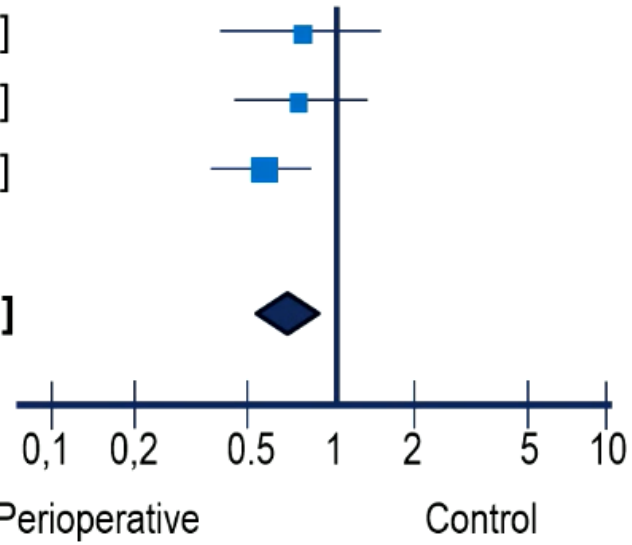
Doit on traiter avec de l'IO péri opératoire les stades II?

OUI

Study or Subgroup	Perioperative Immunothery Events	Total	Placebo Events	Total	Hazard Ratio Exp [(O-E) / V], Fixed, 95% CI
77T	22	81	26	81	0.81 [0.46, 1.43]
Aegean	21	104	27	110	0.76 [0.43, 1.34]
Keynote671	37	118	62	121	0.59 [0.40, 0.88]
Total (95% CI)		**303**		**312**	**0.68 [0.51, 0.90]**
Total events	80		115		

Heterogeneity: $Chi^2 = 1.01$, df = 2 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.70 (P = 0.007)



Garassino M et al Presidential 1 discussion

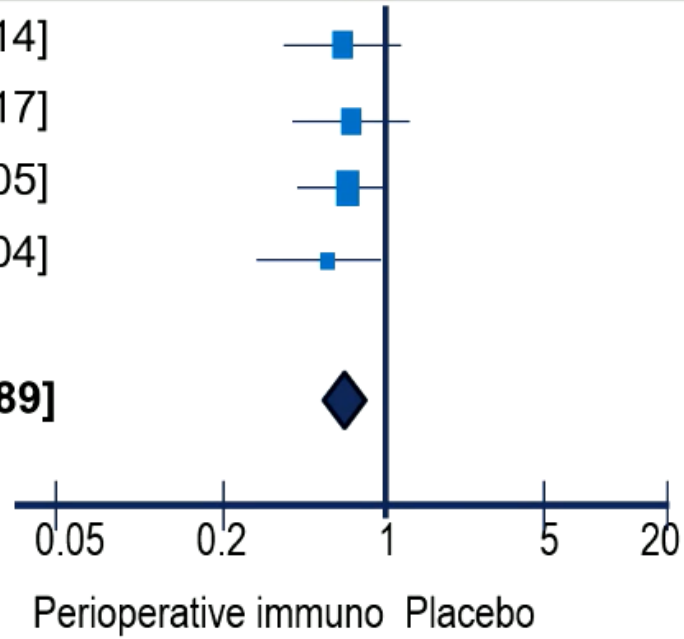
Doit on traiter les patients dont la tumeur est PD-L1 négatif?

OUI

Study or Subgroup	Events	Total	Placebo Events	Total	Hazard Ratio Exp [(O-E) / V], Fixed, 95% CI
77T	33	93	44	93	0.73 [0.47, 1.14]
Aegean	35	122	46	125	0.76 [0.49, 1.17]
Keynote 671	58	138	77	151	0.75 [0.54, 1.05]
Neotorch	17	69	30	70	0.59 [0.33, 1.04]
Total (95% CI)		**422**		**439**	**0.72 [0.58- 0.89]**
Total events	143		197		

Heterogeneity: $Chi^2 = 0.59$, df = 3 (P = 0.90); $I^2 = 0\%$

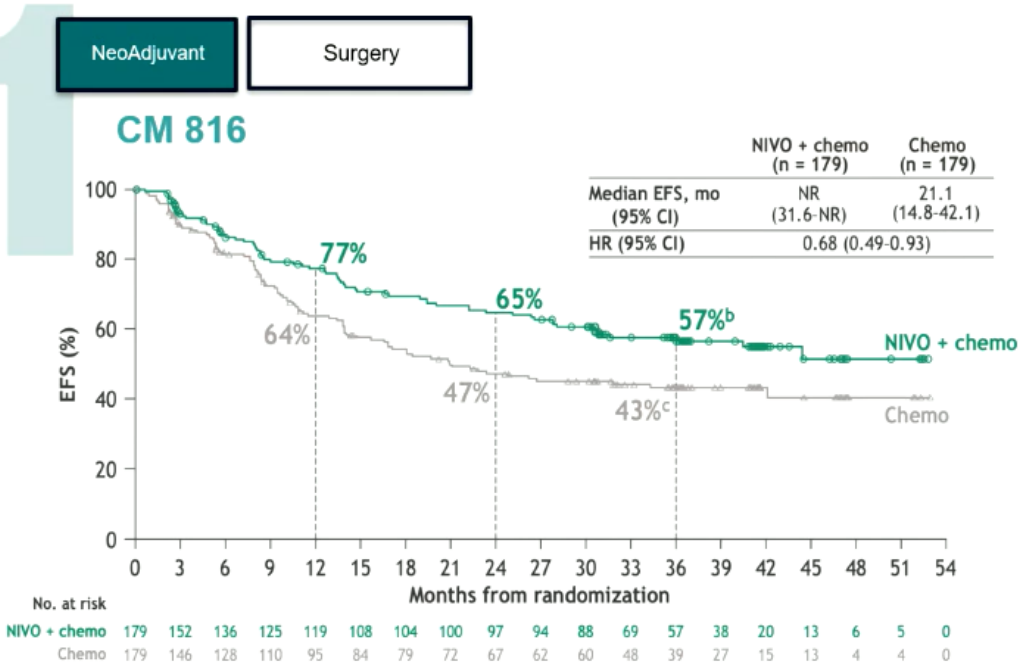
Test for overall effect: Z = 2.99 (P = 0.003)

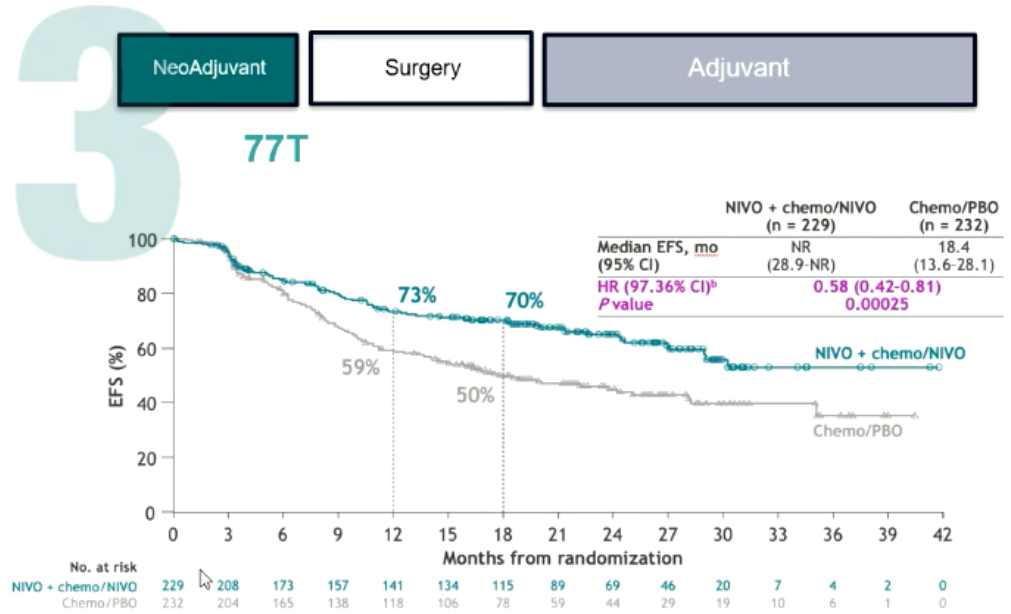


Garassino M et al Presidential 1 discussion

Est-ce que le péri opératoire est supérieur au néo adjuvant?

NC





- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

HR 0.68 (0.49-0.93)

HR 0.58 (0.42-0.81)

Garassino M et al Presidential 1 discussion

CONCLUSION

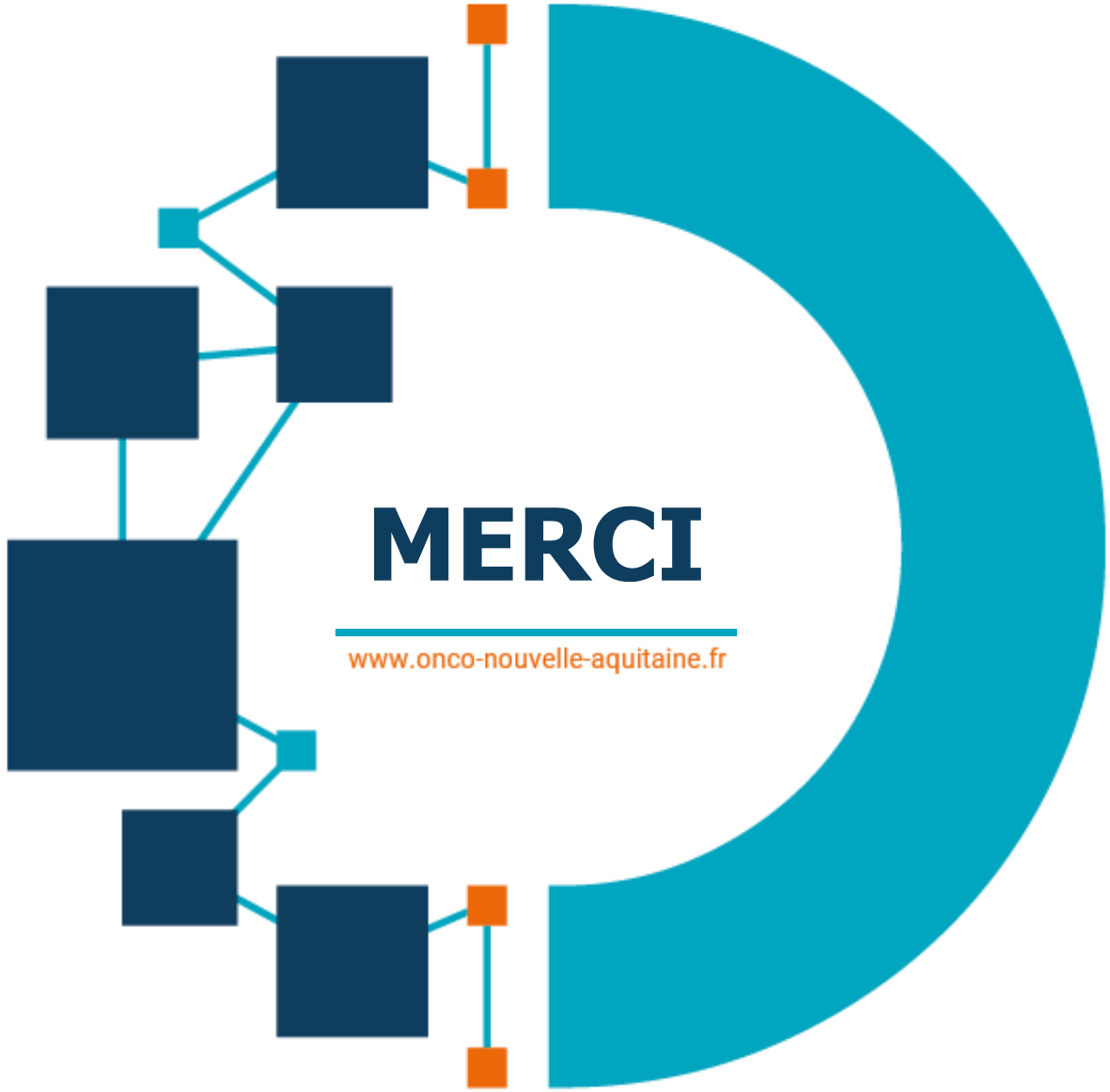
IMPORTANCE du testing des fusions de RET au DIAGNOSTIC pour le choix de la 1ere ligne:

nouveau standard avec le selpercatinib

Nouveau standard en première ligne du mCBNPC avec mutation d'insertion de l'exon 20: amivantamab + chimio

WAIT AND SEE pour alectinib en adjuvant

Toujours plus de données en péri opératoire


MERCI
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Amivantamab et mutations communes de l'EGFR

MARIPOSA

Titre: **Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in *EGFR*-mutated Advanced NSCLC**

Objectif I: Survie sans progression (BICR)

Résultats:

- HR: **0.70** (95% CI, 0.58–0.85); *P*<0.001(23,7 vs16,6 mois)
- ORR: 86 vs 85%
- Durée médiane de réponse: 25,8 vs 16,8 mois

TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)

MARIPOSA2

Titre: **Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy in *EGFR*-mutated, Advanced NSCLC After Progression on Osimertinib**

Objectif I: Survie sans progression (SSP) des 2 bras expérimentaux (BICR)

Résultats:

- Ami + chimio vs chimio: HR= **0,48** (IC95%: 0.36–0.64, *P*<0.001)
- Ami + lazertinib + chimio vs chimio: HR= **0,44** (IC95%: (IC95%: 0.35–0.56, *P*<0.001)
- Taux de réponse objective: 36% vs 64% (bi) vs 63% (tri)
- SSP intracrânienne: statistiquement meilleure avec bithérapie (HR:0.55) ou triplette (HR: 0,58)

TEAE, n (%)	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=130)	Amivantamab-Lazertinib-Chemotherapy[a] (n=263)
Any AEs	227 (93)	130 (100)	263 (100)
Grade ≥3 AEs	117 (48)	94 (72)	242 (92)
Serious AEs	49 (20)	42 (32)	137 (52)

Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy[a] (n=263)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)

Cho BC et al. Abstract LBA14; Passaro A et al. Abstract LBA15