9e ÉDITION

JOURNÉES DU **GFCO 2023**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

Innovations dans le cancer du poumon

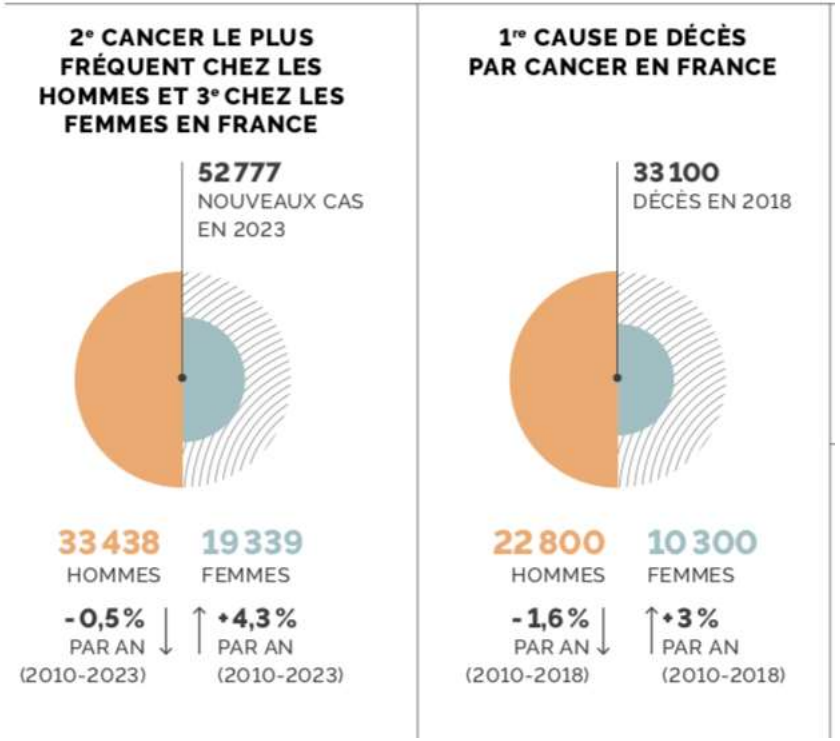
Pr associé Jean-Bernard Auliac

HÔPITAL INTERCOMMUNAL CRÉTEIL

Liens d’intérêt

- Activité de conseil : AstraZeneca, Boerhinger, BMS, Janssen
- Conférences en qualité auditeur : AstraZeneca, Boerhinger, BMS, AMGEN, SANOFI, Takeda, MSD, Janssen
- Congres: BMS, astra zeneca, sanofi, MSD

CBNPC : contexte



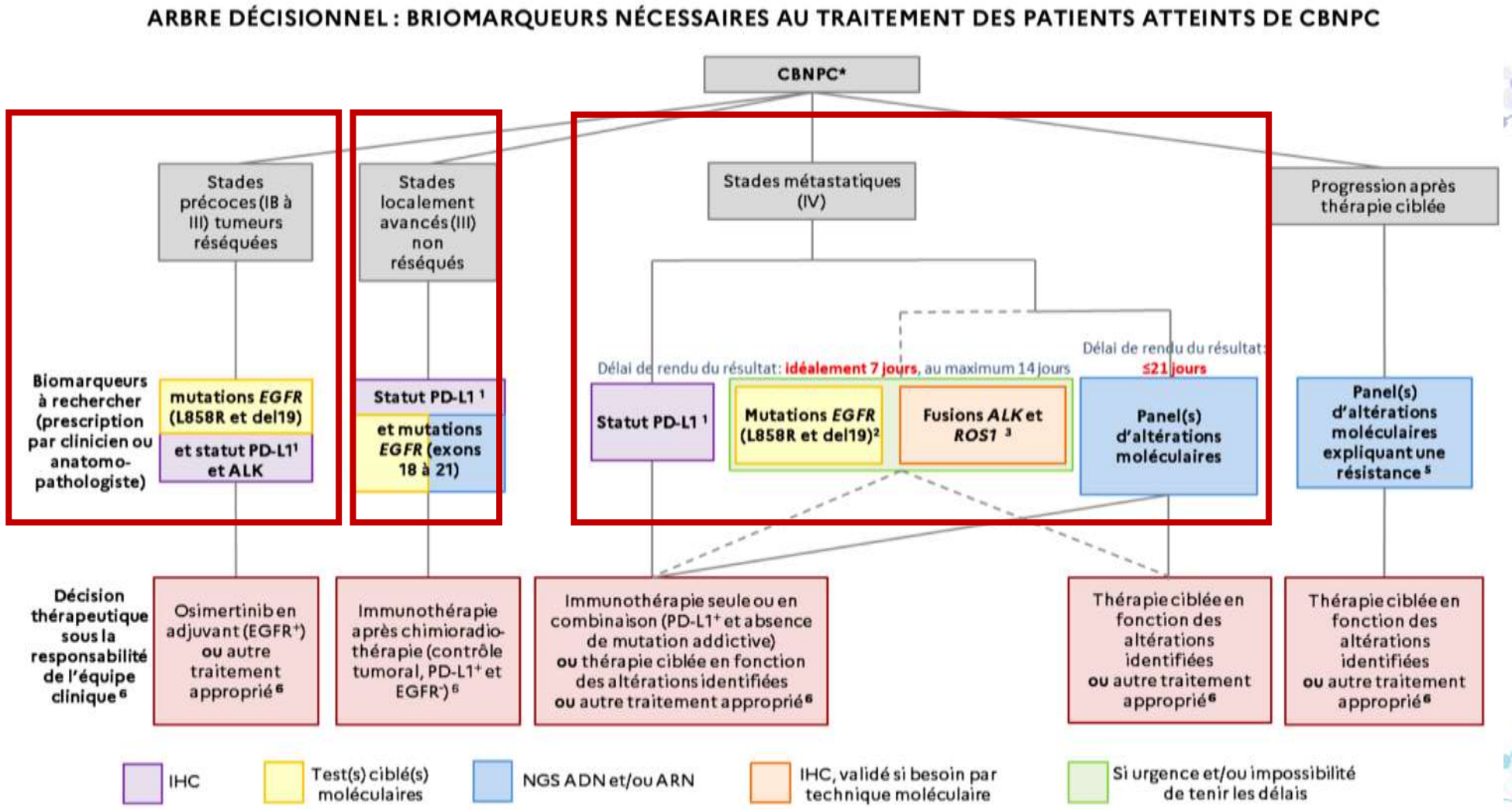
KBP 2020* : répartition des stades au diagnostic des CBPNC :

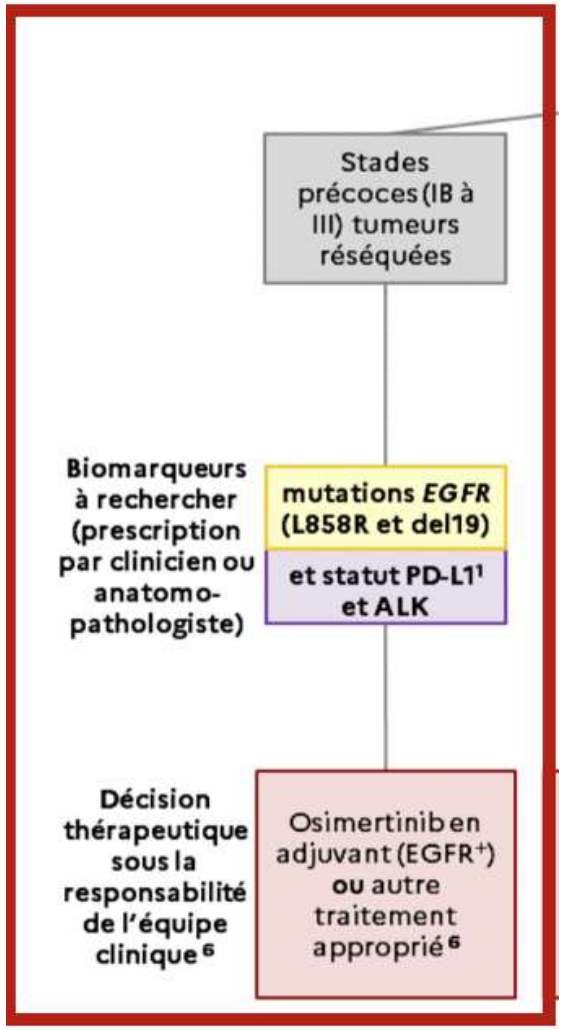
- **Précoce : 21.5%**
- **Localisé : 20.9%**
- **Métastatique : 57.9%**

* Debieuvre d et al :The Lancet Regional Health - Europe 2022;22: 100492

Contexte

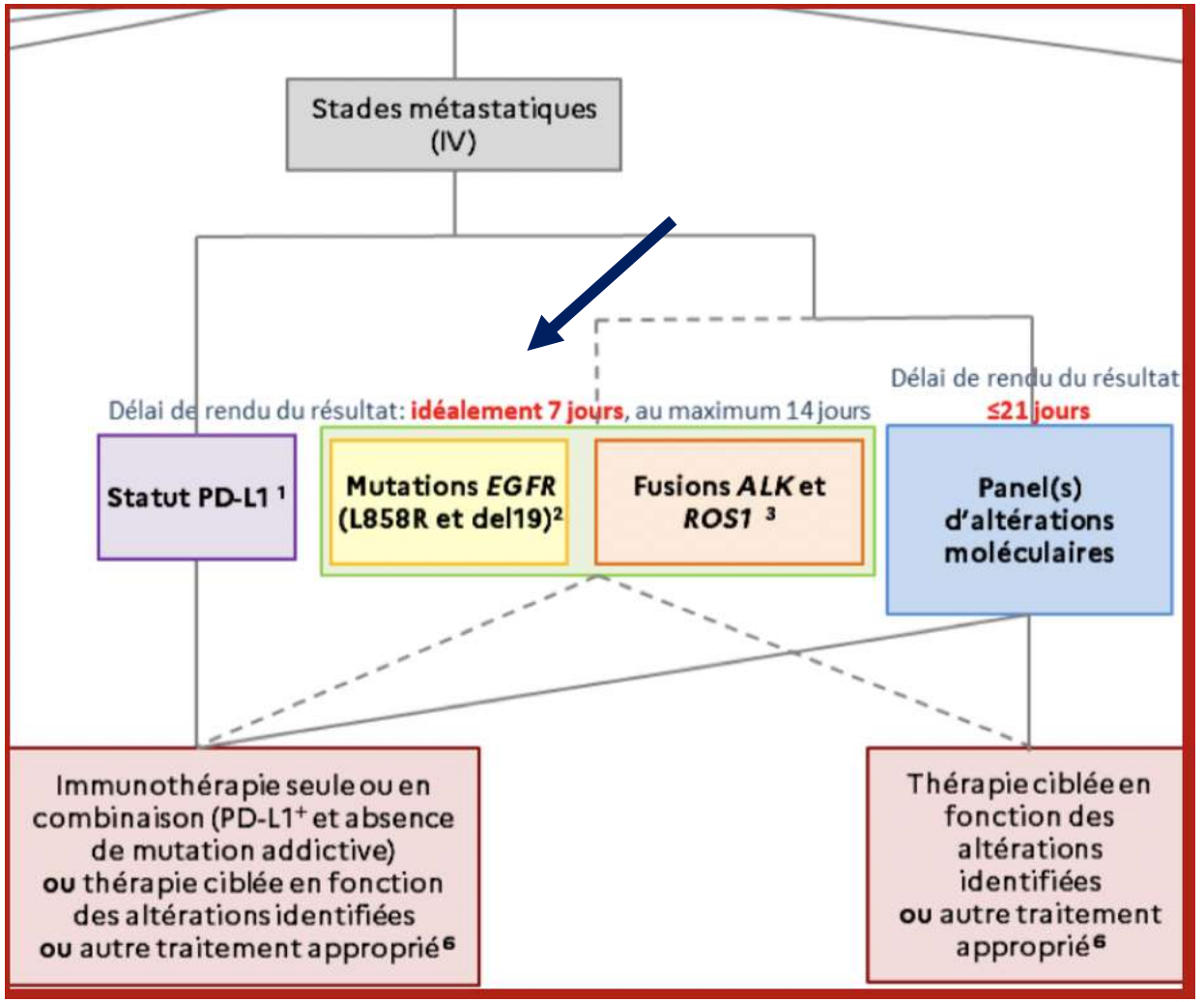
Synthèse
PATIENTS ATTEINTS D'UN CANCER BRONCHIQUE NON À PETITES CELLULES
Indications des tests moléculaires en vue de la prescription de traitements de précision





	TNM8
T1a	≤ 1cm
T1b	>1cm et ≤ 2cm
T1c	> 2cm et <3cm
T2a	> 3 cm mais ≤ 4 cm
T2b	> 4 cm mais ≤ 5 cm
T3	> 5 cm mais ≤ 7 cm OU associée à un(des) nodule(s) tumoral(aux) distinct(s) dans le même lobe, OU envahissant directement la paroi, le nerf phrénique, la plèvre pariétale ou le péricarde pariétal.
T4	> 7 cm OU associée à des nodules tumoraux séparés dans deux lobes différents du même poumon, OU envahissant : -le médiastin, -le cœur ou les gros vaisseaux, -la trachée, ou la carène -le diaphragme, -le nerf récurrent, -l'œsophage, -un(des) corps vertébral(ux)

	N0	N1	N2	N3	M1a-b *Tout N*	M1c *Tout N*
T1a	IA-1	IIB	IIIA	IIIB	IV-A	IV-B
T1b	IA-2	IIB	IIIA	IIIB	IV-A	IV-B
T1c	IA-3	IIB	IIIA	IIIB	IV-A	IV-B
T2a	IB	IIB	IIIA	IIIB	IV-A	IV-B
T2b	IIA	IIB	IIIA	IIIB	IV-A	IV-B
T3	IIB	IIIA	IIIB	IIIC	IV-A	IV-B
T4	IIIA	IIIA	IIIB	IIIC	IV-A	IV-B

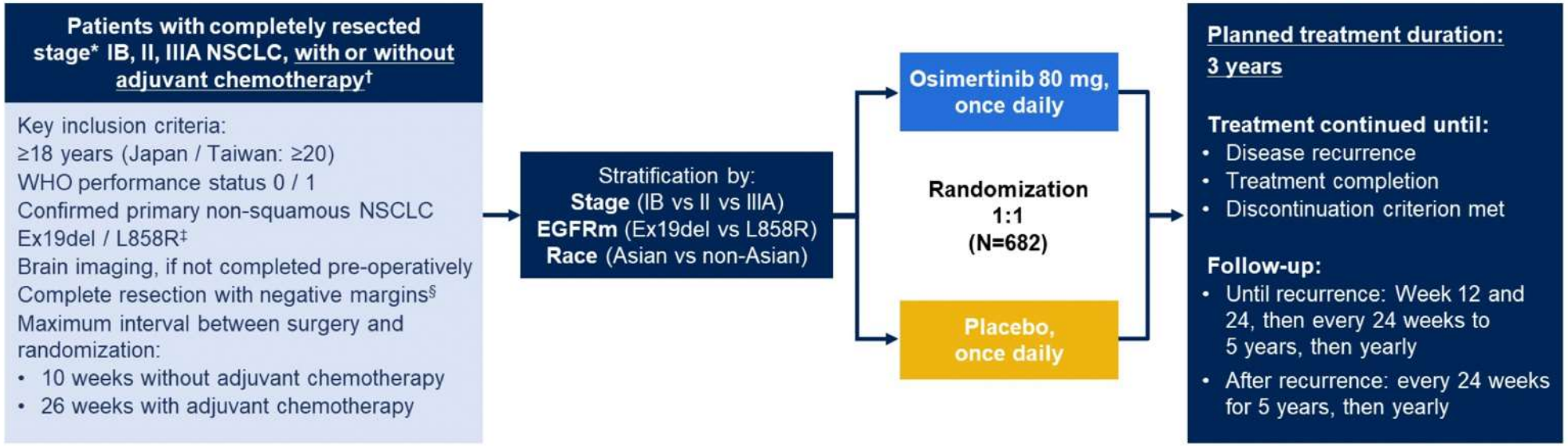

Stades métastatiques (IV)
Délai de rendu du résultat: idéalement 7 jours, au maximum 14 jours
Délai de rendu du résultat ≤21 jours
Statut PD-L1 [1]
Mutations EGFR (L858R et del19)[2]
Fusions ALK et ROS1 [3]
Panel(s) d'altérations moléculaires
Immunothérapie seule ou en combinaison (PD-L1+ et absence de mutation addictive) ou thérapie ciblée en fonction des altérations identifiées ou autre traitement approprié[6]
Thérapie ciblée en fonction des altérations identifiées ou autre traitement approprié[6]

STADE PRÉCOCE RÉSÉCABLE

- **AVEC ADDICTION ONCOGENIQUE**
  - ***EGFR* : ADAURA**
  - ***ALK* : ALINA**
- **SANS ADDICTION ONCOGENIQUE**
  - **Péri-opératoire**

STADE PRÉCOCE *EGFR*+ : étude ADAURA

- **Étude ADAURA**



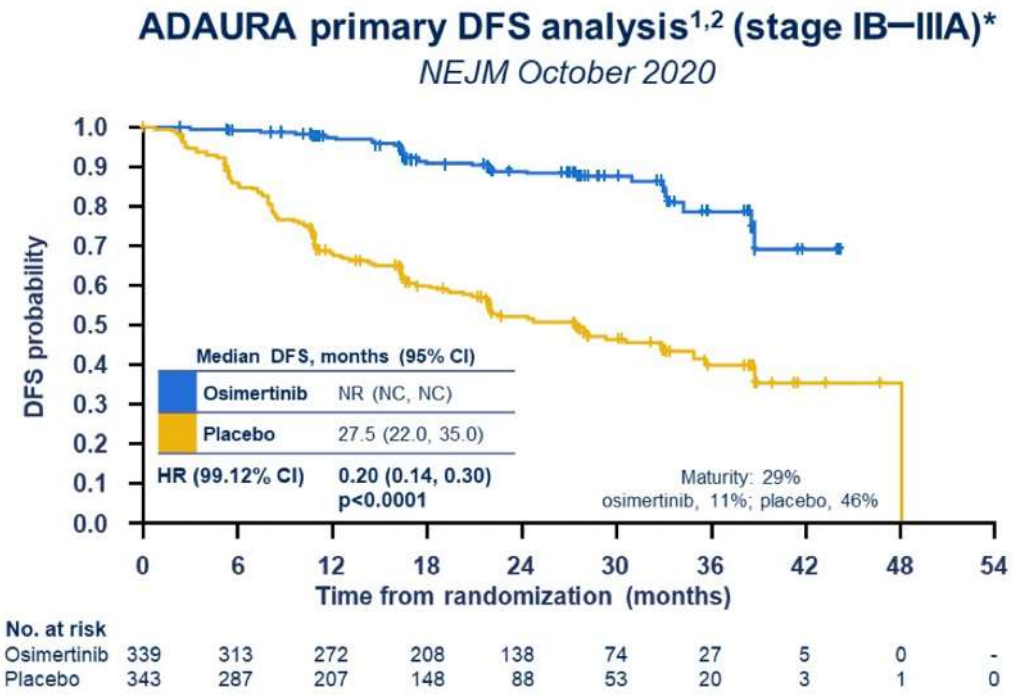
Endpoints

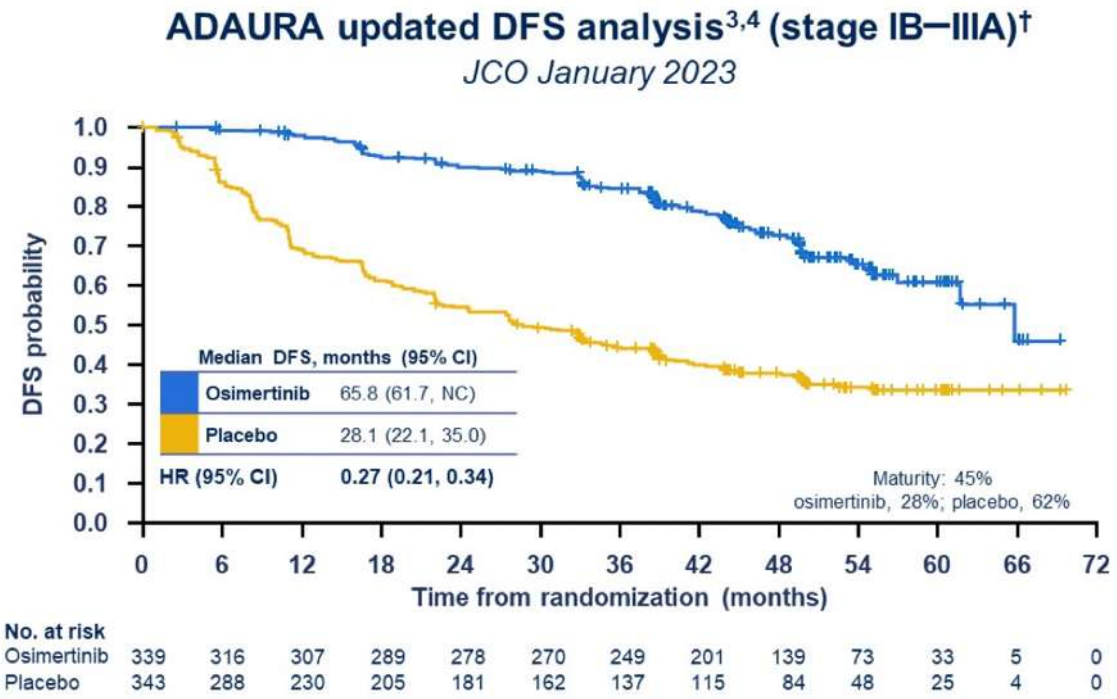
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

Herbst RS et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol. 2023 Apr 1;41(10):1830-1840. doi: 10.1200/JCO.22.02186. Epub 2023 Jan 31. Erratum in: J Clin Oncol. 2023 Aug 1;41(22):3877. PMID: 36720083; PMCID: PMC10082285.

STADE PRÉCOCE *EGFR*+ : étude ADAURA

- **Étude ADAURA**



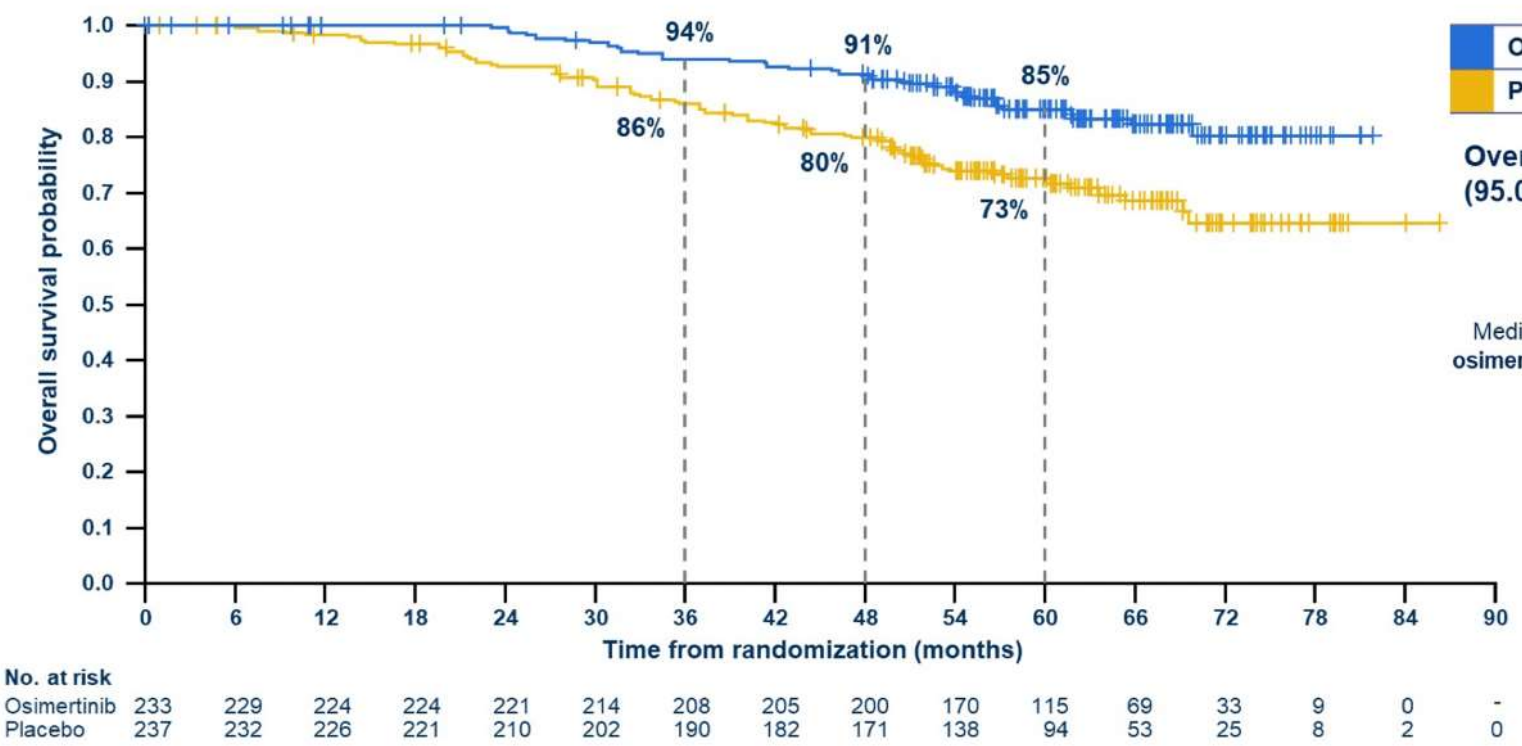


Herbst RS et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol. 2023 Apr 1;41(10):1830-1840. doi: 10.1200/JCO.22.02186. Epub 2023 Jan 31. Erratum in: J Clin Oncol. 2023 Aug 1;41(22):3877. PMID: 36720083; PMCID: PMC10082285.

STADE PRÉCOCE *EGFR*+ : étude ADAURA

- **Étude ADAURA**

Overall survival: patients with stage II / IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

RS. Herbst et al., ASCO® 2023, LBA#3

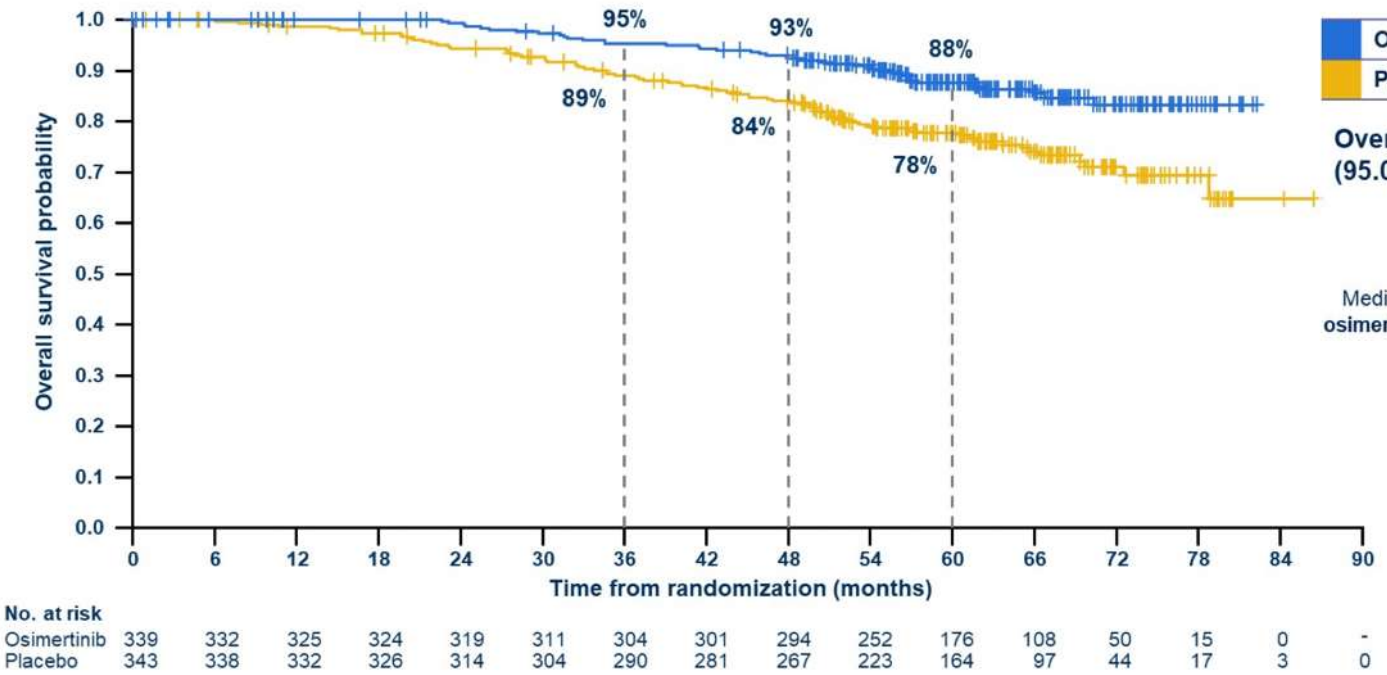
STADE PRÉCOCE *EGFR*+ : étude ADAURA

- **Étude ADAURA**

Overall survival: patients with stage IB / II / IIIA disease

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

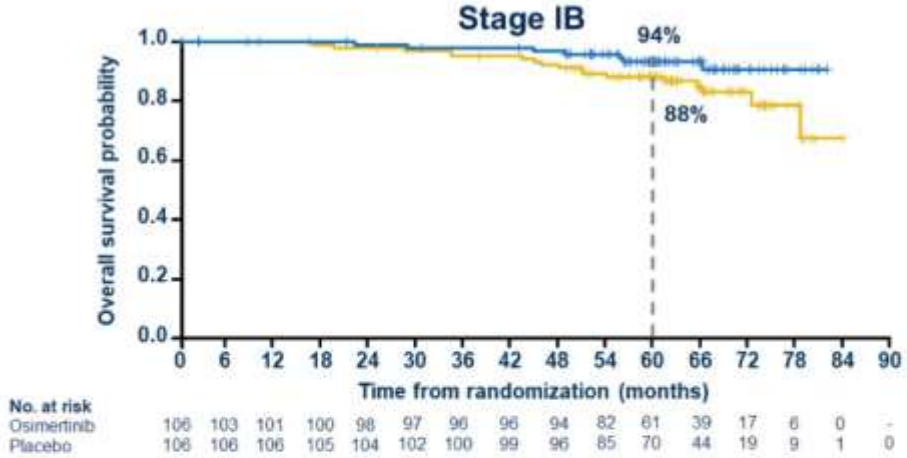
Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

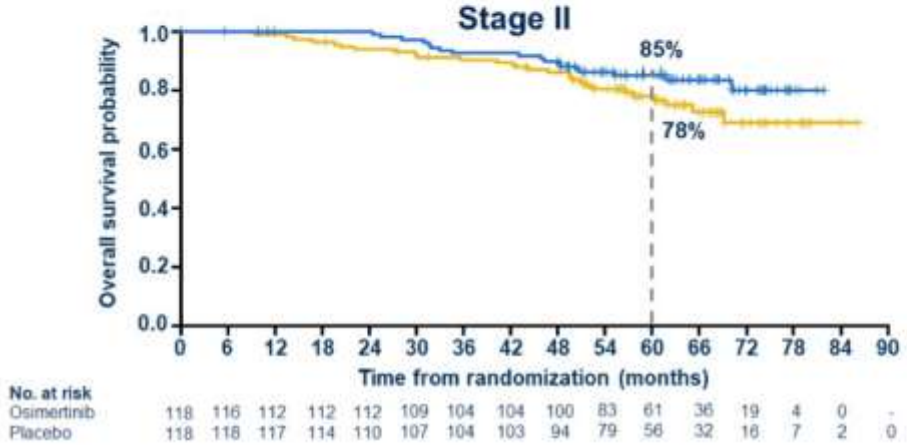
RS. Herbst et al., ASCO® 2023, LBA#3

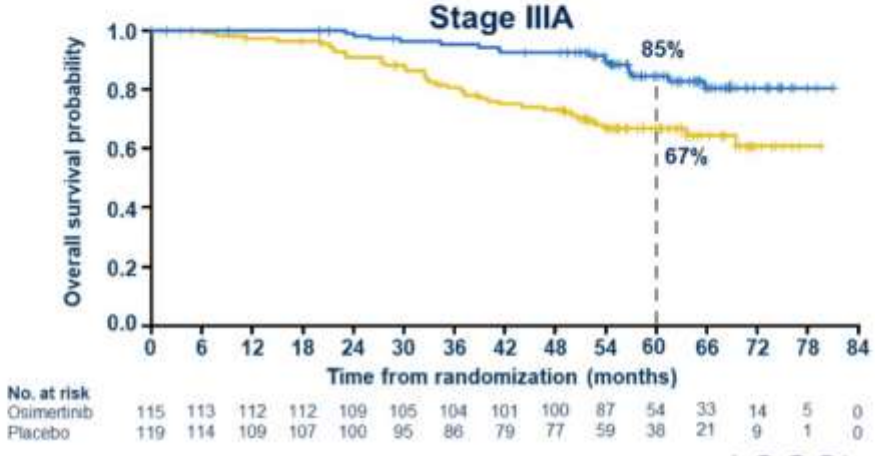
STADE PRÉCOCE *EGFR*+ : étude ADAURA

Overall survival by disease stage



	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	**0.44 (0.17, 1.02)**	**0.63 (0.34, 1.12)**	**0.37 (0.20, 0.64)**





RS. Herbst et al., ASCO® 2023, LBA#3

STADE PRÉCOCE EGFR + : étude ADAURA tolérance :

AE[a]	Osimertinib (n = 337)	Placebo (n = 343)
Any AE	330 (98)	309 (90)
Any AE ≥ grade 3	79 (23)	48 (14)
Any SAE	68 (20)	47 (14)
Any AE with outcome of death[b]	1 (< 1)	2 (1)
Any AE leading to treatment discontinuation	43 (13)	9 (3)
Any AE leading to dose interruption	91 (27)	43 (13)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE causally related to study drug[c]	308 (91)	199 (58)
AE ≥ grade 3 causally related to study drug[c]	36 (11)	7 (2)
SAE causally related to study drug[c]	10 (3)	2 (1)
AE with outcome of death causally related to study drug[c]	0	0
AE leading to treatment discontinuation causally related to study drug[c]	35 (10)	5 (1)

	Osimertinib (n = 337)				Placebo (n = 343)			
Most Common All-Causality AE[a]	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
Diarrhea	159 (47)	114 (34)	36 (11)	9 (3)	70 (20)	55 (16)	14 (4)	1 (< 1)
Paronychia	92 (27)	33 (10)	56 (17)	3 (1)	5 (1)	2 (1)	3 (1)	0
Dry skin	84 (25)	79 (23)	4 (1)	1 (< 1)	23 (7)	19 (6)	4 (1)	0
Pruritus	70 (21)	52 (15)	18 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	66 (20)	45 (13)	21 (6)	0	61 (18)	44 (13)	17 (5)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	15 (4)	11 (3)	4 (1)	0
Upper respiratory tract infection	53 (16)	29 (9)	22 (7)	2 (1)	37 (11)	19 (6)	18 (5)	0
Nasopharyngitis	50 (15)	31 (9)	19 (6)	0	36 (10)	25 (7)	11 (3)	0
Decreased appetite	48 (14)	33 (10)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Dermatitis acneiform	41 (12)	31 (9)	10 (3)	0	16 (5)	12 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	10 (3)	7 (2)	3 (1)	0
Weight decreased	35 (10)	19 (6)	14 (4)	2 (1)	9 (3)	7 (2)	2 (1)	0
Nausea	34 (10)	28 (8)	5 (1)	1 (< 1)	20 (6)	15 (4)	5 (1)	0
Rash	33 (10)	24 (7)	9 (3)	0	12 (3)	10 (3)	2 (1)	0
Arthralgia	23 (7)	18 (5)	5 (1)	0	37 (11)	32 (9)	5 (1)	0
Headache	26 (8)	24 (7)	2 (1)	0	34 (10)	27 (8)	7 (2)	0

RS. Herbst et al., ASCO® 2023, LBA#3

STADE PRÉCOCE : *EGFR*+ en développement

Ongoing osimertinib studies in resectable EGFRm NSCLC

Phase III NeoADAURA study (NCT04351555)

Neoadjuvant osimertinib with or without CT vs CT alone in resectable EGFRm stage II–IIIB N2 NSCLC

Phase III ADAURA2 study (NCT05120349)

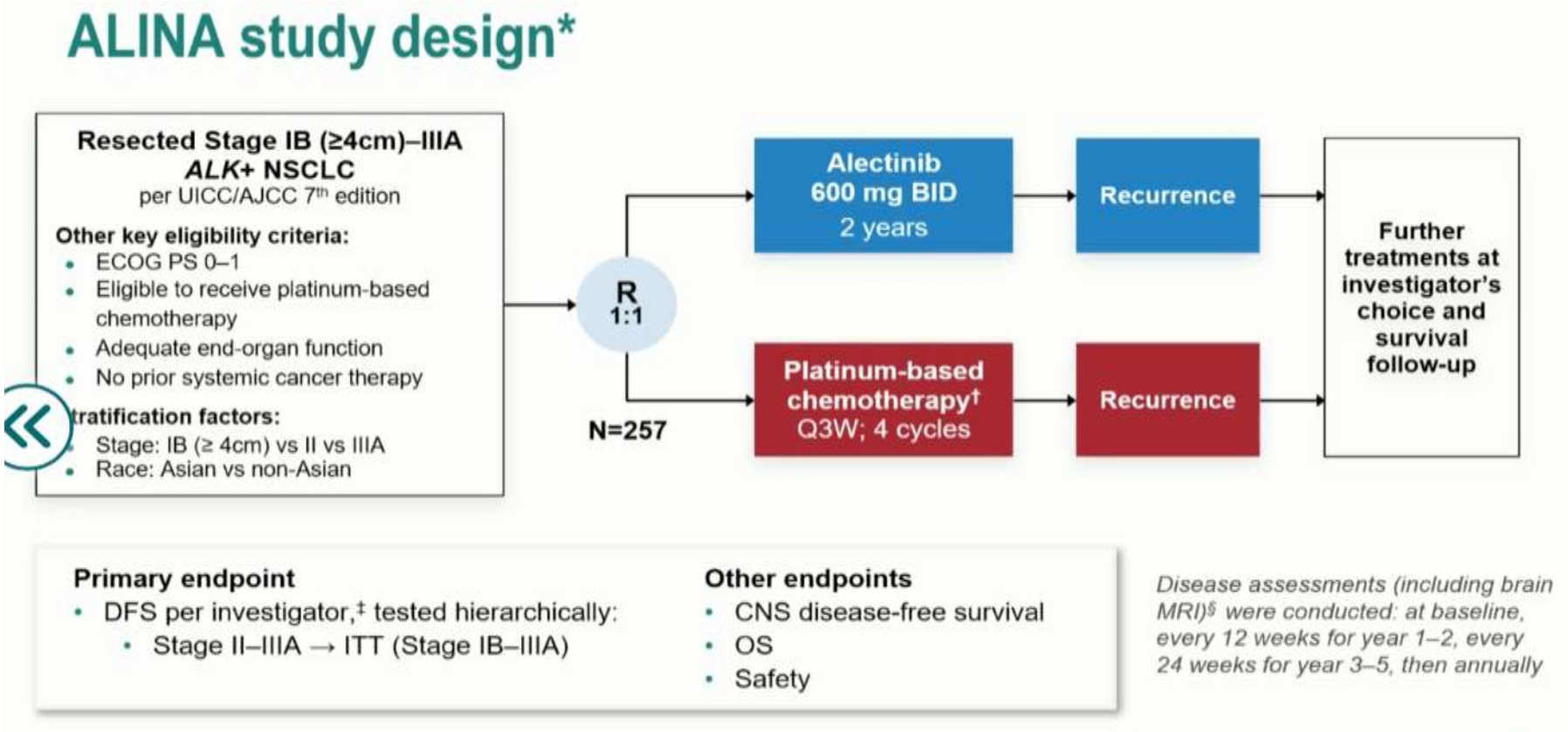
Adjuvant osimertinib vs placebo in resected EGFRm stage IA NSCLC

Phase II TARGET study (NCT05526755)

5-year adjuvant osimertinib in resected EGFRm stage II–IIIB NSCLC

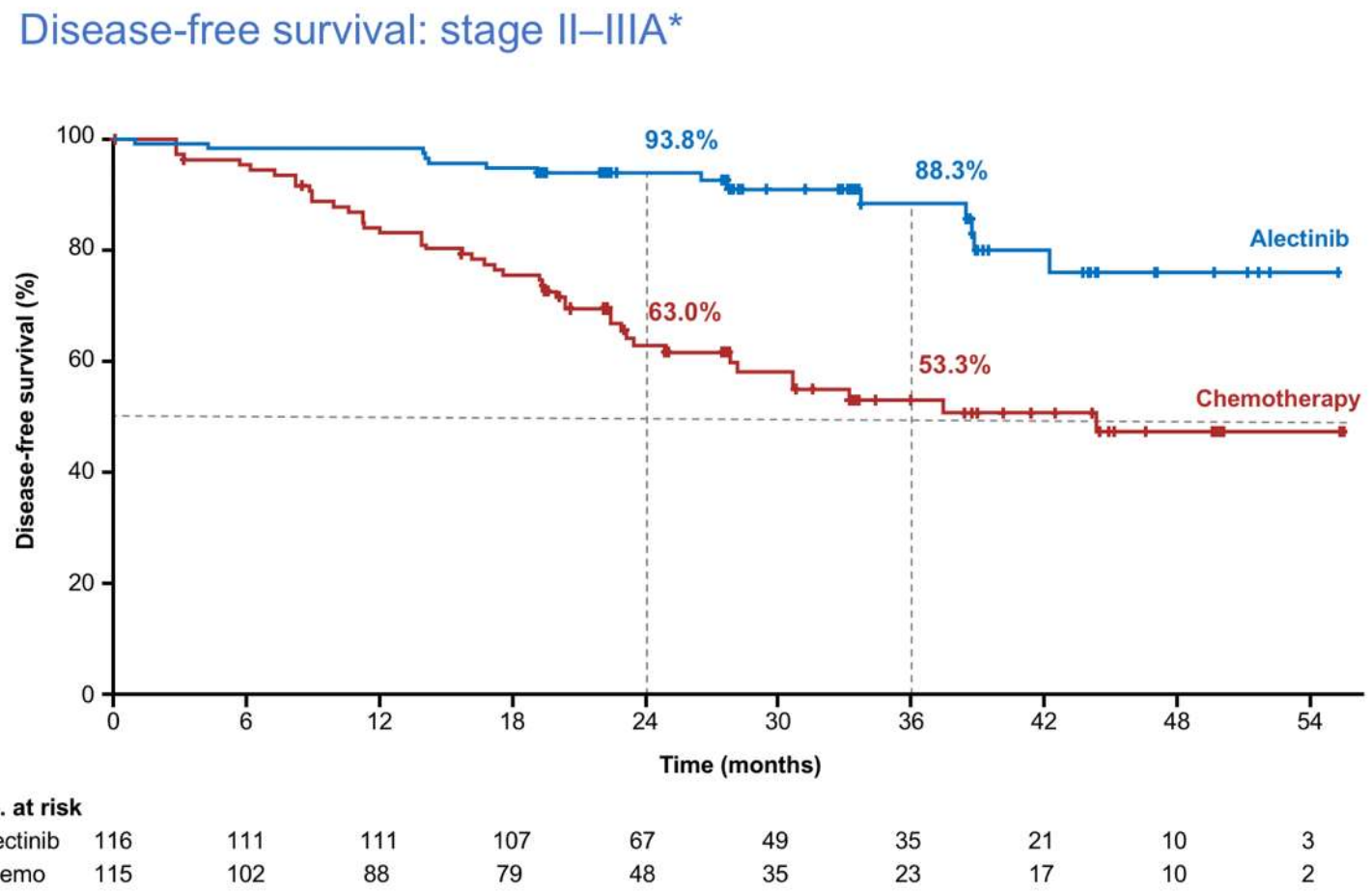
STADE PRÉCOCE *ALK*+ : étude ALINA

- **ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC)**
  - Analyse intermediaire



Solomon BJ, et al. Ann Oncol 2023;34(suppl):Abstr LBA2

STADE PRÉCOCE *ALK*+ : étude ALINA



	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

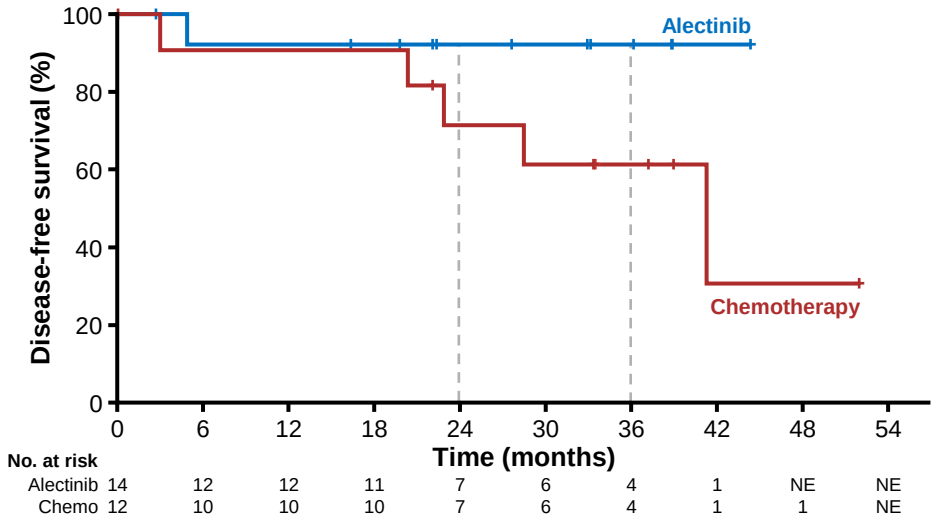
Solomon BJ, et al. Ann Oncol 2023;34(suppl):Abstr LBA2

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

STADE PRÉCOCE *ALK*+ : étude ALINA

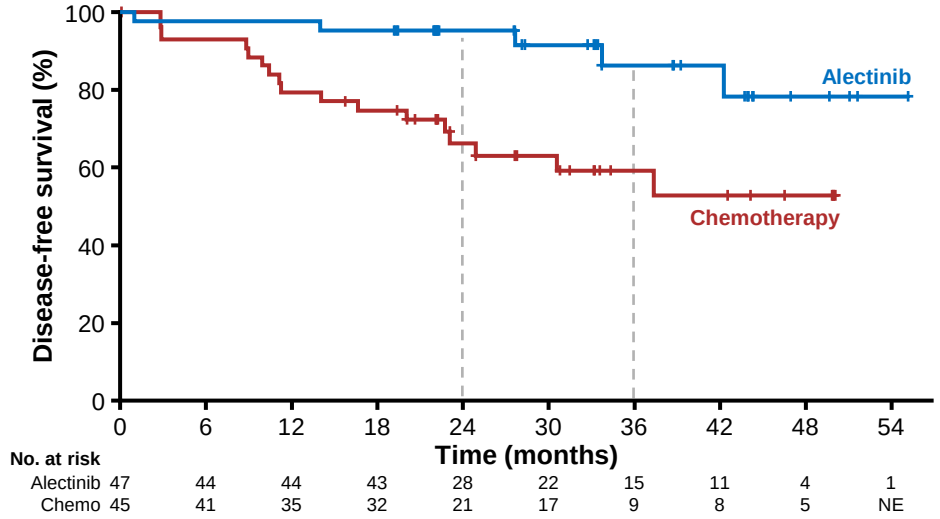
Disease-free survival by stage*

Stage IB

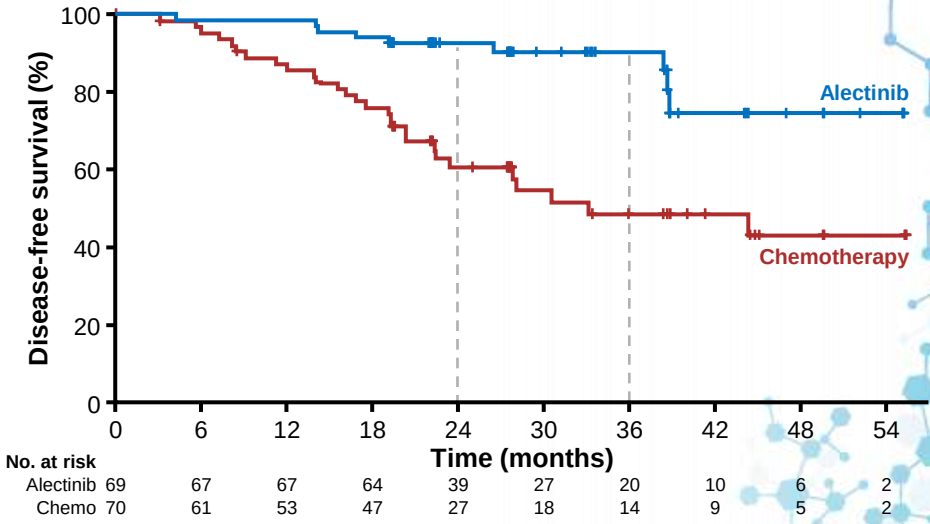


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



Stage IIIA



Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

Solomon BJ, et al. Ann Oncol 2023;34(suppl):Abstr LBA2

STADE PRÉCOCE *ALK*+ : étude ALINA

Disease-free survival subgroup analysis (ITT)

Subgroup		No. of events / patients	DFS HR (95% CI)
All patients		65 / 257	0.24 (0.14–0.43)
Age	<65	43 / 196	0.26 (0.13–0.52)
	≥65	22 / 61	0.24 (0.08–0.71)
Sex	Male	35 / 123	0.26 (0.11–0.60)
	Female	30 / 134	0.22 (0.10–0.50)
Race	Asian	31 / 143	0.36 (0.17–0.79)
	Non-Asian	34 / 114	0.16 (0.06–0.38)
ECOG PS at baseline	0	32 / 137	0.20 (0.09–0.46)
	1	33 / 120	0.31 (0.14–0.69)
Tobacco use history	Never	37 / 154	0.27 (0.13–0.55)
	Current	0 / 8	NE
	Previous	28 / 95	0.22 (0.08–0.57)
Stage*	Stage IB	6 / 26	0.21 (0.02–1.84)
	Stage II	22 / 92	0.24 (0.09–0.65)
	Stage IIIA	37 / 139	0.25 (0.12–0.53)
Regional lymph node status	N0	11 / 39	0.19 (0.04–0.88)
	N1	20 / 88	0.34 (0.13–0.89)
	N2	34 / 130	0.21 (0.09–0.47)

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023

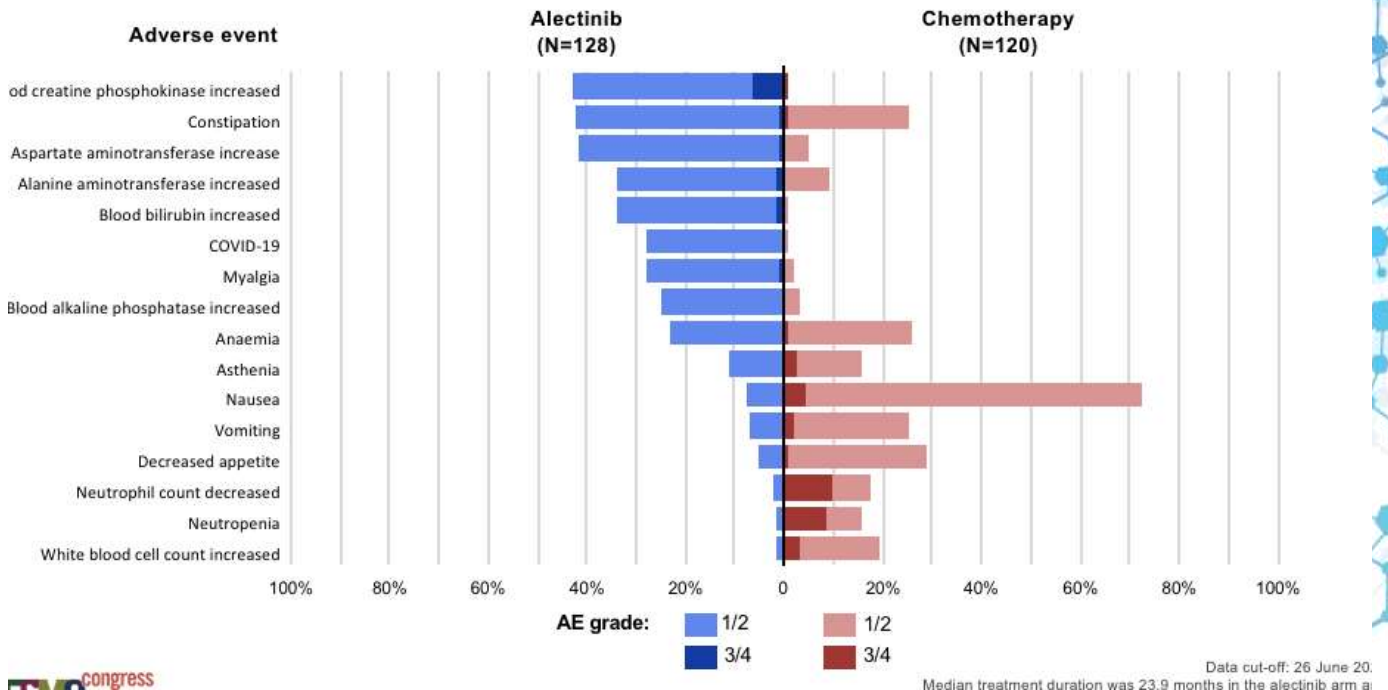
Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

Solomon BJ, et al. Ann Oncol 2023;34(suppl):Abstr LBA2

STADE PRÉCOCE *ALK*+ : étude ALINA

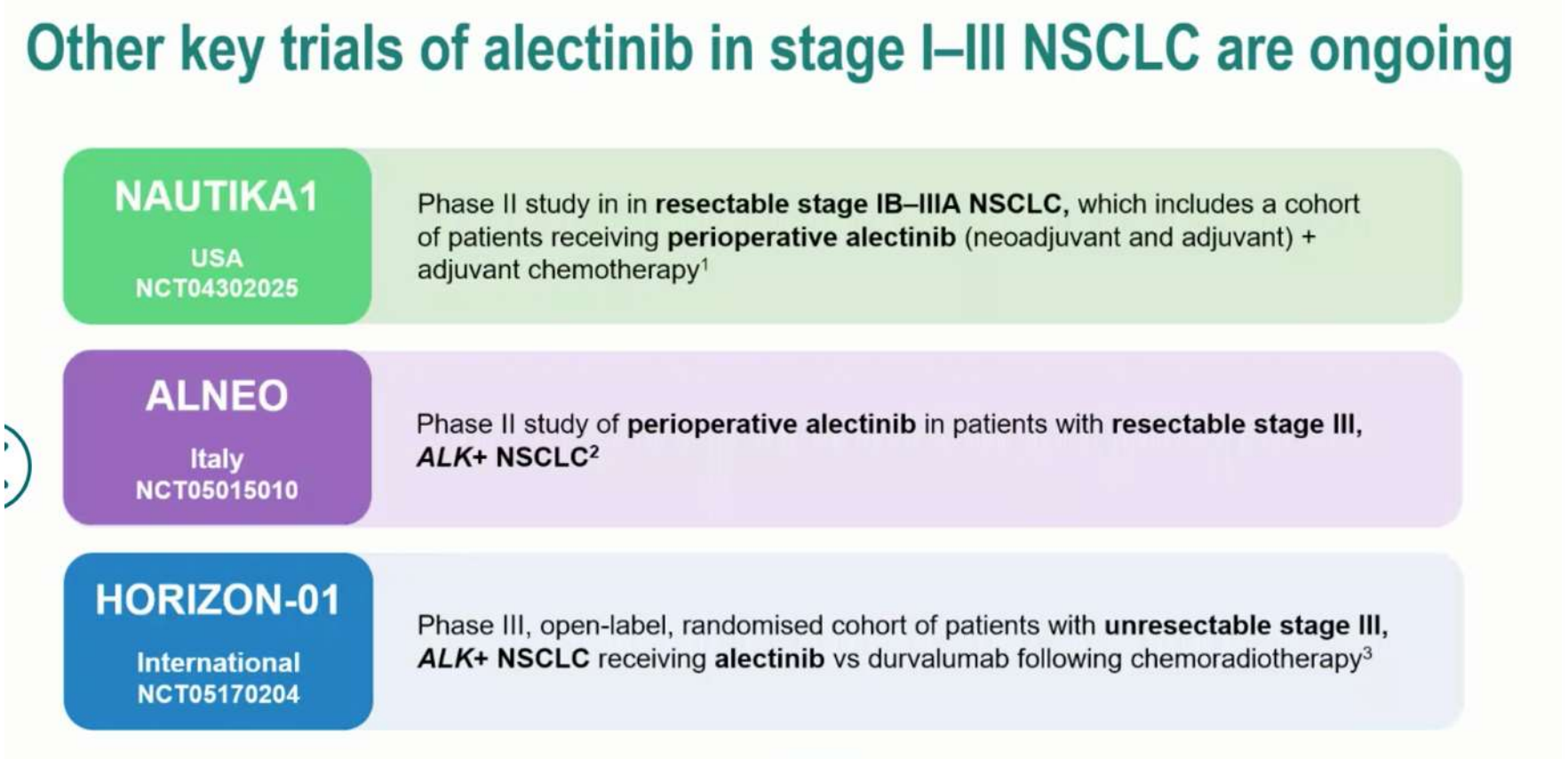
Tolérance

	Alectinib (n=128)	Chemotherapy (n=120)
Median treatment duration	**23.9 months**	**2.1 months**
Patients with any AEs, %	**98**	**93**
Grade 3/4 AEs	30	31
Grade 5 AEs	0	0
Serious AEs	13	8
Treatment-related serious AEs	2	7
AEs leading to dose reduction	26	10
AEs leading to dose interruption	27	18
AEs leading to treatment withdrawal	5	13



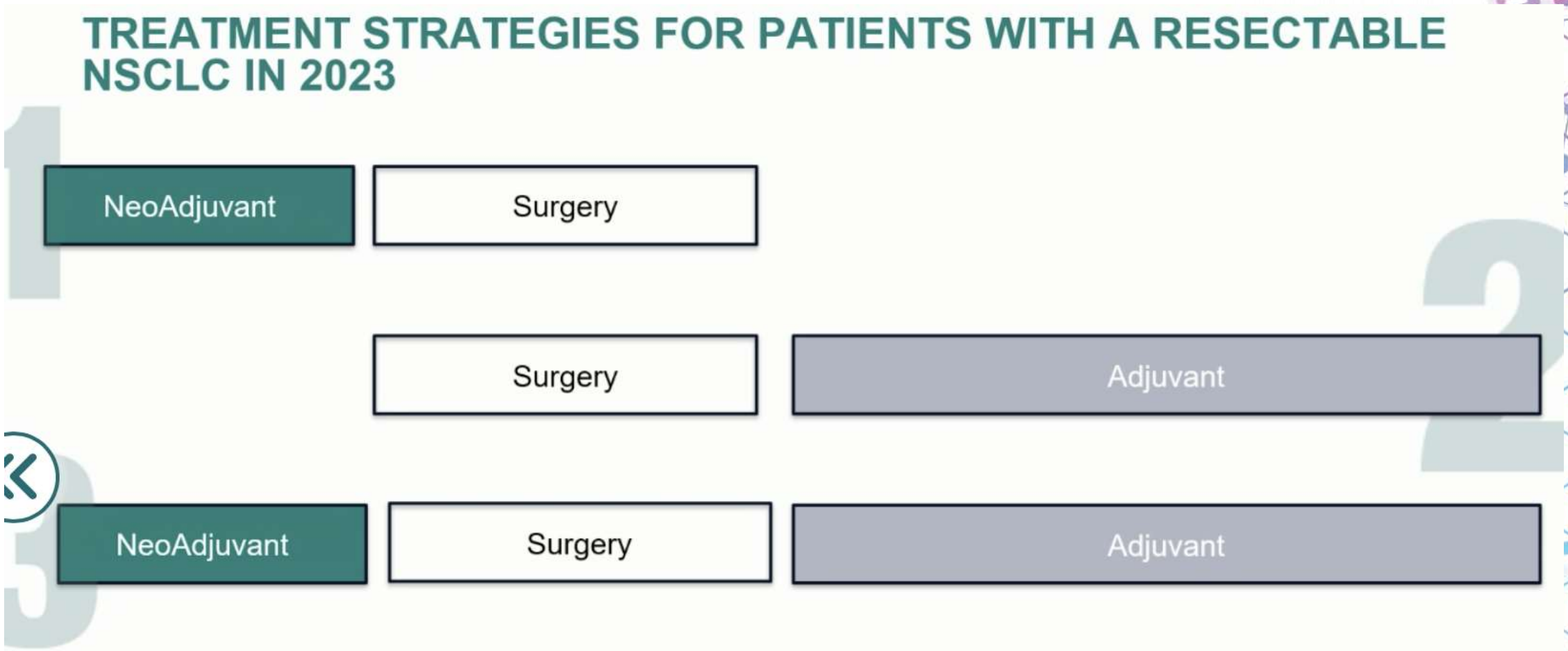
Solomon BJ, et al. Ann Oncol 2023;34(suppl):Abstr LBA2

STADE PRÉCOCE : *ALK*+ en développement



- **STADE PRÉCOCE : RET +**
  - ´Étude de phase III LIBRETTO-432 (selpercatinib)

STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*...



STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*...

Tableau 5 : Principales études de phase III l'association chimiothérapie (CT) immunothérapie en néoadjuvant et +/− en adjuvant.

	Protocole	Nombre de patient	Stade de la maladie	RPC	Survie sans évènement (médiane)	Survie globale (2 ans)
CheckMate-816 *	nivolumab-CT 3 cycles	358	IB/II : 36 % IIIA : 64 %	24 % vs 2,2 %	31,6 (30,2-NR) vs 20,8 (14-26,7)	83 % vs 71 %
KEYNOTE-671 *	pembrolizumab-CT 4 cycles puis pembrolizumab 13 cycles	797	II : 30 % III : 70 % IIIA : 55 % IIIB : 15 %	18,1 % vs 4 %	NR (34,1-NR) vs 17 (14,3 – 22,0)	80,9 % vs 77,6 %
AEGEAN *	durvalumab-CT 4 cycles puis durvalumab en adjuvant 12 cycles	704	II : 28,9 % IIIA : 45,7 % IIIB : 25,1 %	17,2 % vs 4,3 %	NR (31,9-NR) vs 25,9 (18,0-NR)	
Neotorch *	toripalumab-CT 3 cycles puis toripalumab-CT 1 cycle puis toripalumab 13 cycles	404	IIIA : 67 % IIIB : 32 % IIIC : 0.2 % IV : 1 %	24,8 % vs 1 %	NR (NR-NR) vs 15,5 (9,9-NR)	81,2 % vs 74,3 %

*** Hors AMM ; Données non validées par les Autorités de Santé à ce jour**

Cortot a et al . Prise en charge des stades précoces : place des thérapies ciblées en périopératoire Revue des Maladies Respiratoires Actualités (2023) 15, 2S61-2S66

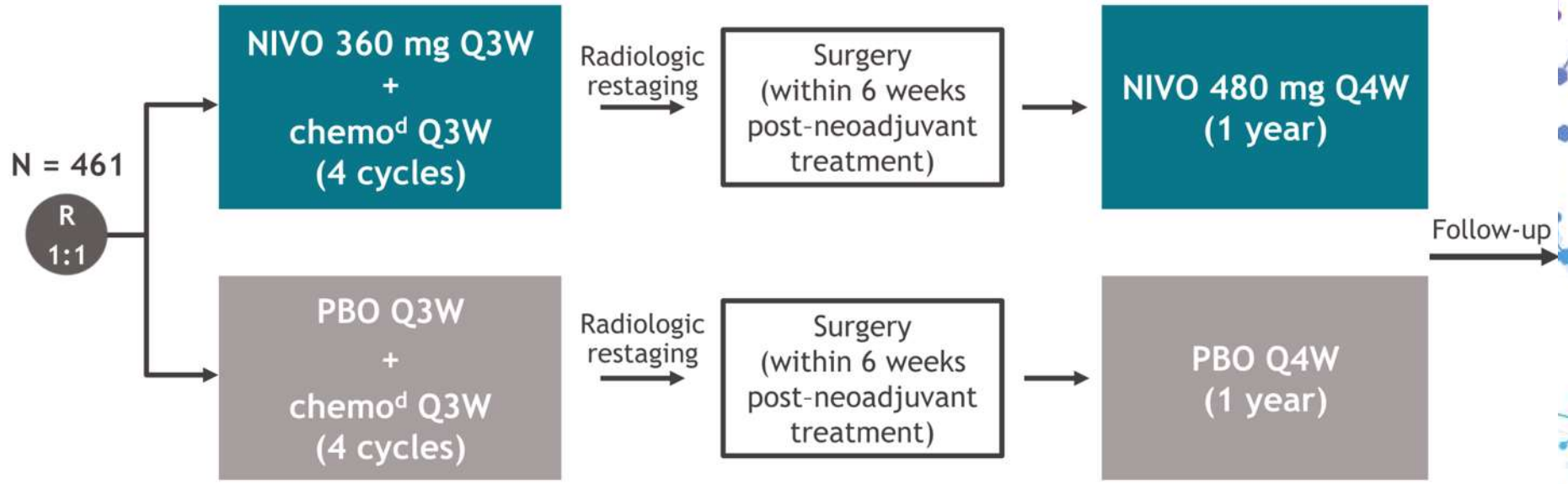
STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*...

CM77T – nivolumab + chimiothérapie néoadjuvante *vs* placebo + chimiothérapie → chirurgie → nivolumab / placebo adjuvante pour des CBNPC résécables de stade II-IIIB

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)



Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

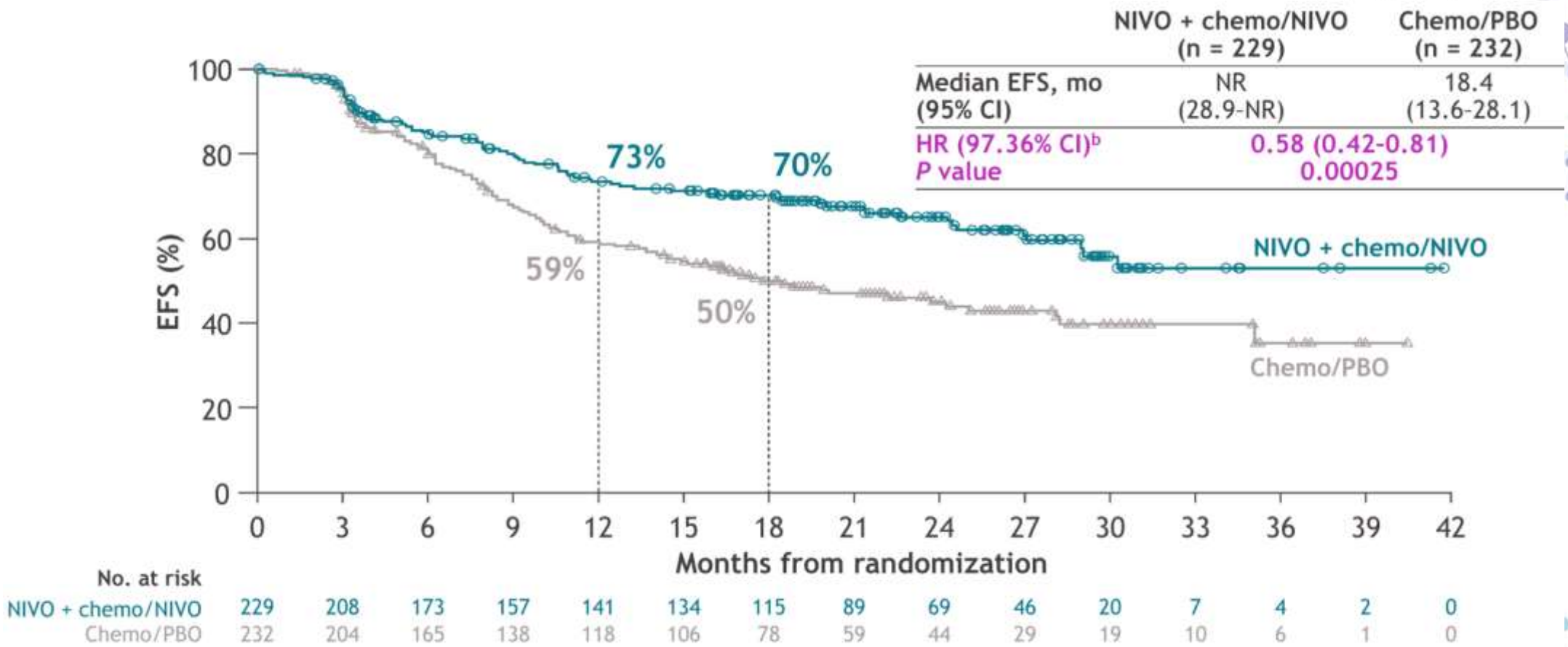
Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Cascone T, et al. Ann Oncol 2023;34(suppl):Abstr LBA1

STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*…

CM77T – survie sans évènement



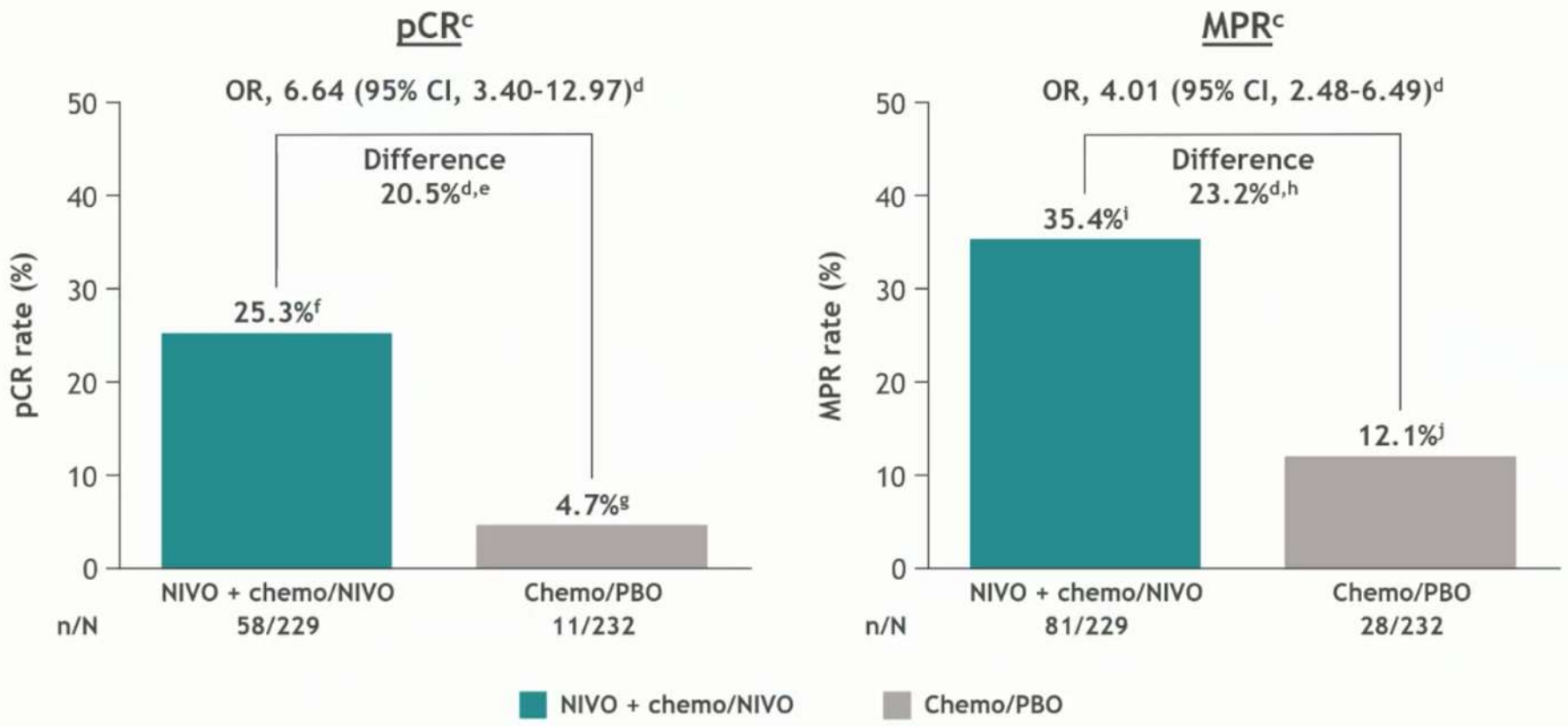
Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Cascone T, et al. Ann Oncol 2023;34(suppl):Abstr LBA1

STADE PRÉCOCE Résécable sans addiction *EGFR, ALK...*

CheckMate 77T: perioperative NIVO in resectable NSCLC

pCR[a] and MPR[b] per BIPR



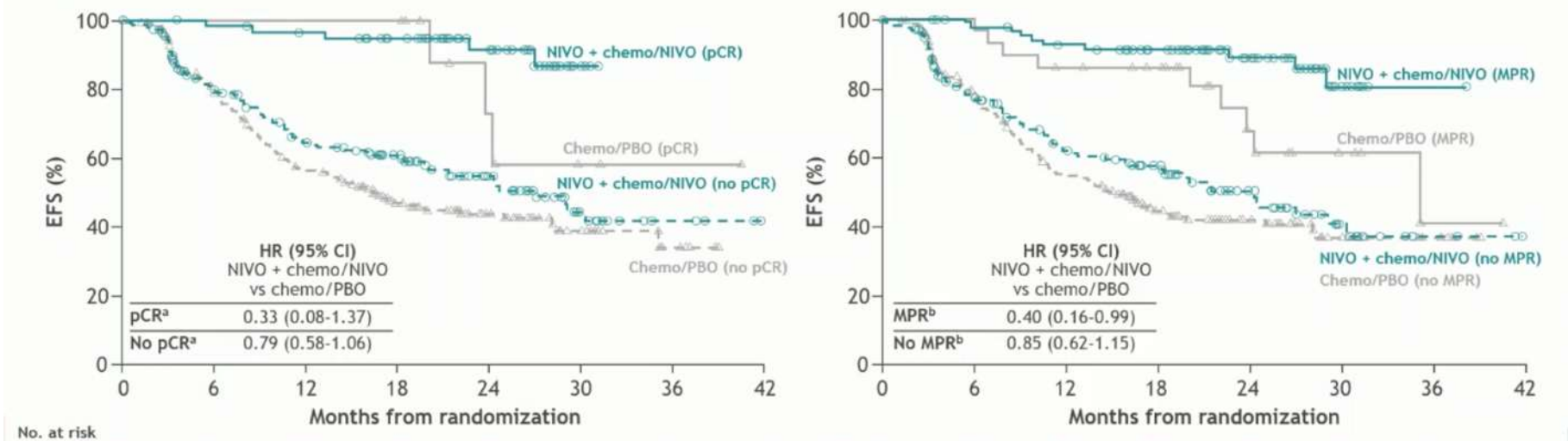
[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [b]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [c]Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-responders. [d]Calculated using the stratified Cochran-Mantel-Haenszel method. [e-j]95% CI: [e]14.3-26.6; [f]19.8-31.5; [g]2.4-8.3; [h]15.8-30.6; [i]29.2-41.9; [j]8.2-17.0. BIPR, blinded independent pathological review.

Cascone T, et al. Ann Oncol 2023;34(suppl):Abstr LBA1

STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*...

CheckMate 77T: perioperative NIVO in resectable NSCLC

Exploratory analysis: EFS by pCR and MPR status



No. at risk

pCR	58	56	53	45	28	4	0	0
pCR	11	11	11	11	5	2	1	0
No pCR	171	117	88	70	41	16	4	0
No pCR	221	154	107	67	39	17	5	0

MPR	81	76	70	59	37	8	1	0
MPR	28	27	23	20	10	5	1	0
No MPR	148	97	71	56	32	12	3	0
No MPR	204	138	95	58	34	14	5	0

Median follow-up (range): 25.4 months (15.7-44.2).
[a]HR (95% CI), 0.14 (0.06-0.35) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.32 (0.10-1.00) in the chemo/PBO arm. [b]HR (95% CI), 0.18 (0.09-0.35) in patients with MPR vs those without in the NIVO + chemo/NIVO arm and 0.40 (0.20-0.78) in the chemo/PBO arm.

Cascone T, et al. Ann Oncol 2023;34(suppl):Abstr LBA1

STADE PRÉCOCE Résécable sans addiction *EGFR*, *ALK*...

CM77T – survie sans évènement : analyses en sous-groupes

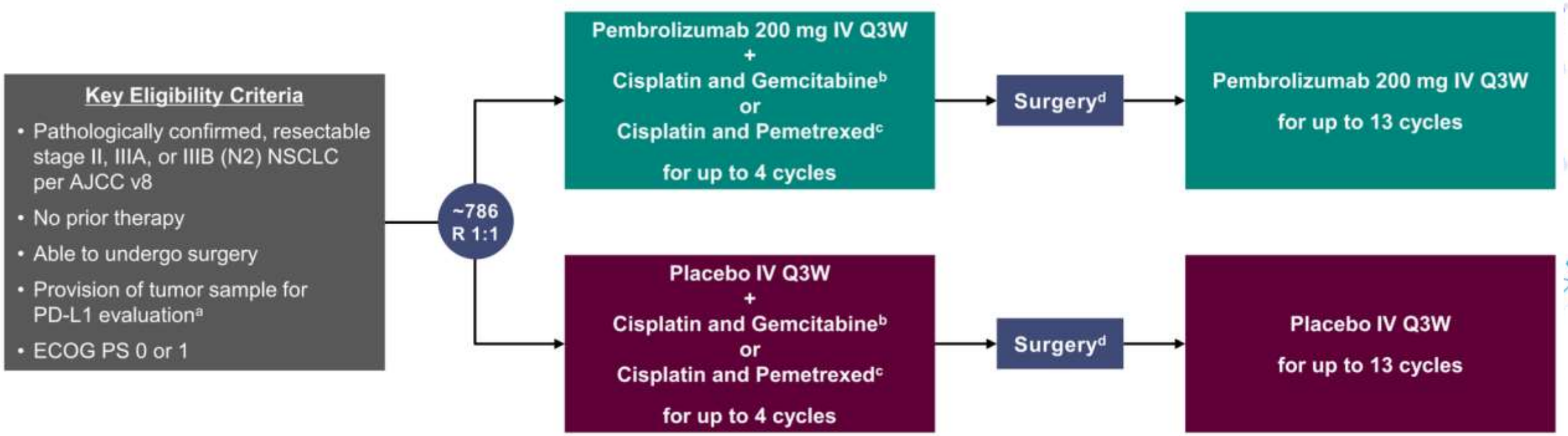
	Median EFS,[a] mo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
Overall (N = 461)	NR	18.4		0.59 (0.44-0.79)
< 65 years (n = 202)	NR	16.7		0.55 (0.36-0.85)
≥ 65 years (n = 259)	NR	20.1		0.61 (0.41-0.91)
Male (n = 327)	NR	16.7		0.53 (0.37-0.75)
Female (n = 134)	30.2	18.8		0.71 (0.41-1.20)
North America (n = 44)	30.2	9.4		0.59 (0.25-1.38)
Europe (n = 250)	NR	23.7		0.61 (0.40-0.92)
Asia (n = 115)	NR	13.9		0.47 (0.26-0.86)
ECOG PS 0 (n = 288)	NR	20.1		0.57 (0.39-0.83)
ECOG PS 1 (n = 173)	29.0	17.3		0.61 (0.39-0.97)
Stage II (n = 162)	NR	NR		0.81 (0.46-1.43)
Stage III (n = 297)	30.2	13.4		0.51 (0.36-0.72)
N0 (n = 167)[b]	NR	NR		0.80 (0.48-1.32)
N1 (n = 108)[b]	NR	28.1		0.58 (0.29-1.16)
N2 (n = 182)[b,c]	30.2	10.0		0.46 (0.30-0.70)
Single-station (n = 112)	30.2	10.0		0.49 (0.29-0.84)
Multi-station (n = 69)	NR	10.0		0.43 (0.21-0.88)
Squamous (n = 234)	NR	17.0		0.46 (0.30-0.72)
Non-squamous (n = 227)	28.9	18.4		0.72 (0.49-1.07)
Current/former smoker (n = 417)	NR	17.0		0.54 (0.40-0.74)
Never smoker (n = 44)	19.7	25.0		1.32 (0.54-3.20)
PD-L1 < 1% (n = 186)[d]	29.0	19.8		0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8		0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	30.2	28.1		0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0		0.26 (0.12-0.55)
Cisplatin (n = 97)	27.0	15.8		0.61 (0.35-1.08)
Carboplatin (n = 347)	NR	17.3		0.53 (0.37-0.75)

Median follow-up (range): 25.4 months (15.7-44.2).
[a]Per BICR. [b]Nodal status was N3 in 4 patients. [c]N2 subcategory was not reported in 1 patient.Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression (median 10% across both arms).

Cascone et al, ESMO 2023

STADE PRÉCOCE Résécable sans addiction *EGFR, ALK...*

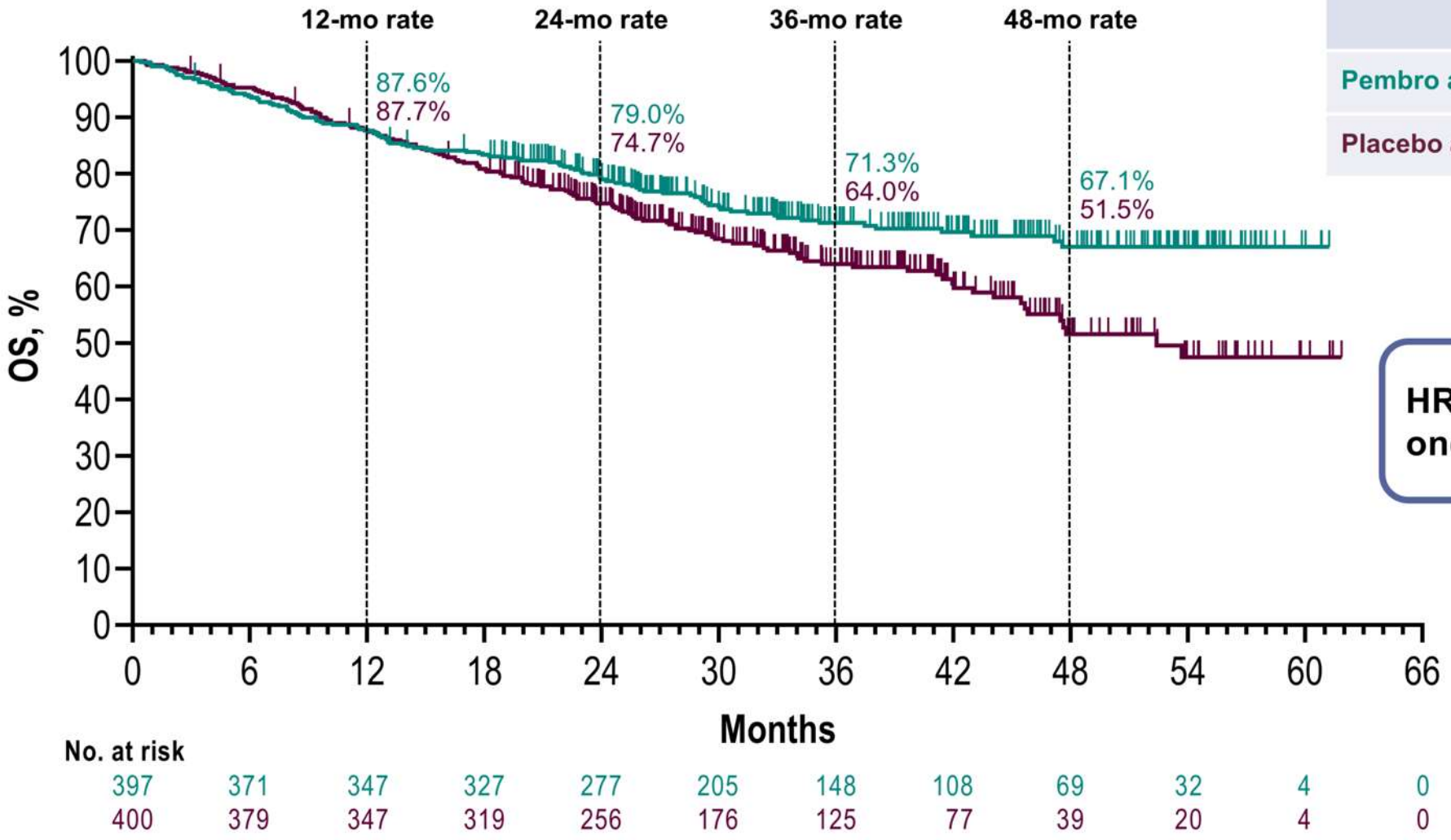
KN671 – Pembrolizumab péri-opératoire pour des CBNPC résécables



Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Spicer JD, et al. Ann Oncol 2023;34(suppl):Abstr LBA56

KN671 – survie globale



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Spicer JD, et al. Ann Oncol 2023;34(suppl):Abstr LBA56

KN671 – survie globale : analyses en sous-groupes

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Age			
<65 y	54/221	82/214	0.57 (0.40-0.80)
≥65 y	56/176	62/186	0.96 (0.67-1.38)
Sex			
Female	21/118	30/116	0.69 (0.39-1.20)
Male	89/279	114/284	0.73 (0.55-0.96)
Race			
White	73/250	97/239	0.66 (0.49-0.90)
All others	34/134	39/145	0.93 (0.59-1.48)
Geographic region			
East Asia	32/123	30/121	1.05 (0.64-1.73)
Not east Asia	78/274	114/279	0.63 (0.48-0.85)
Smoking status			
Current	31/96	48/103	0.59 (0.38-0.93)
Former	69/247	87/250	0.76 (0.56-1.05)
Never	10/54	9/47	1.00 (0.41-2.46)
Histology			
Nonsquamous	49/226	64/227	0.73 (0.50-1.06)
Squamous	61/171	80/173	0.71 (0.51-0.99)

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Clinical stage			
II	26/118	39/121	0.67 (0.41-1.10)
IIIA	62/217	79/224	0.74 (0.53-1.03)
IIIB	22/62	26/55	0.69 (0.39-1.22)
N status			
cN0	40/148	52/142	0.70 (0.46-1.06)
cN1	21/81	24/71	0.74 (0.41-1.33)
cN2	49/168	68/187	0.74 (0.52-1.07)
PD-L1 TPS			
≥50%	23/132	39/134	0.55 (0.33-0.92)
1-49%	35/127	44/115	0.69 (0.44-1.07)
<1%	52/138	61/151	0.91 (0.63-1.32)
***EGFR* mutation**			
No	20/111	33/124	0.64 (0.37-1.11)
Yes	1/14	5/19	0.24 (0.03-2.03)
Unknown	89/272	106/257	0.75 (0.56-0.99)
***ALK* translocation**			
No	22/104	38/132	0.70 (0.41-1.18)
Unknown	87/281	105/259	0.72 (0.54-0.96)

Spicer JD, et al. Ann Oncol 2023;34(suppl):Abstr LBA56

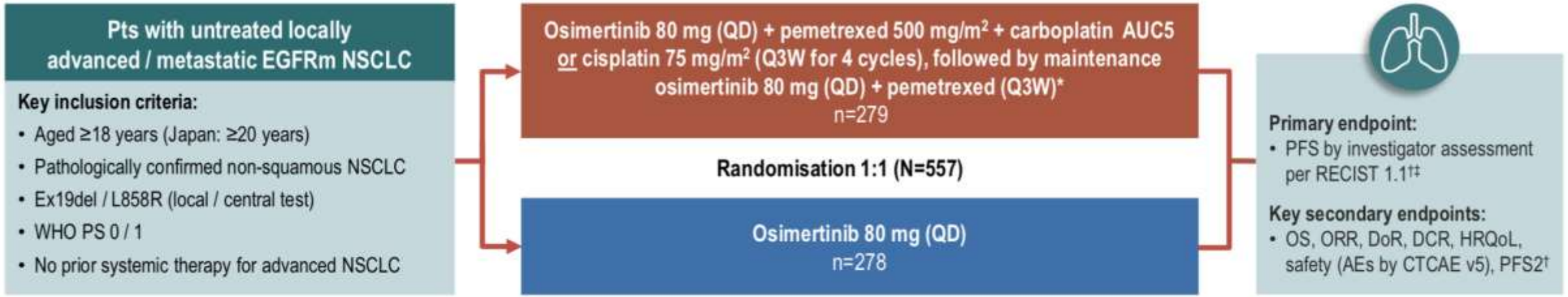
Stade IV

- ***EGFR*+ (exon del19- exon 21 L 858R)**
  - FLAURA 2
  - MARIPOSA
  - MARIPOSA 2
- ***EGFR* UNCOMMON**
  - PAPILLON
  - ACHYLLE
- ***RET***
  - LIBRETO
- ***KRAS* G12C: SCARLET**
- **SANS ADDICTION : TROPION**
- **BIOPSIE LIQUIDE: LIBELULE**

STADE MÉTASTATIQUE : *EGFR*+ (exon del19- exon 21 L 858R)

- **Étude Flaura 2**

FLAURA2 PHASE III STUDY

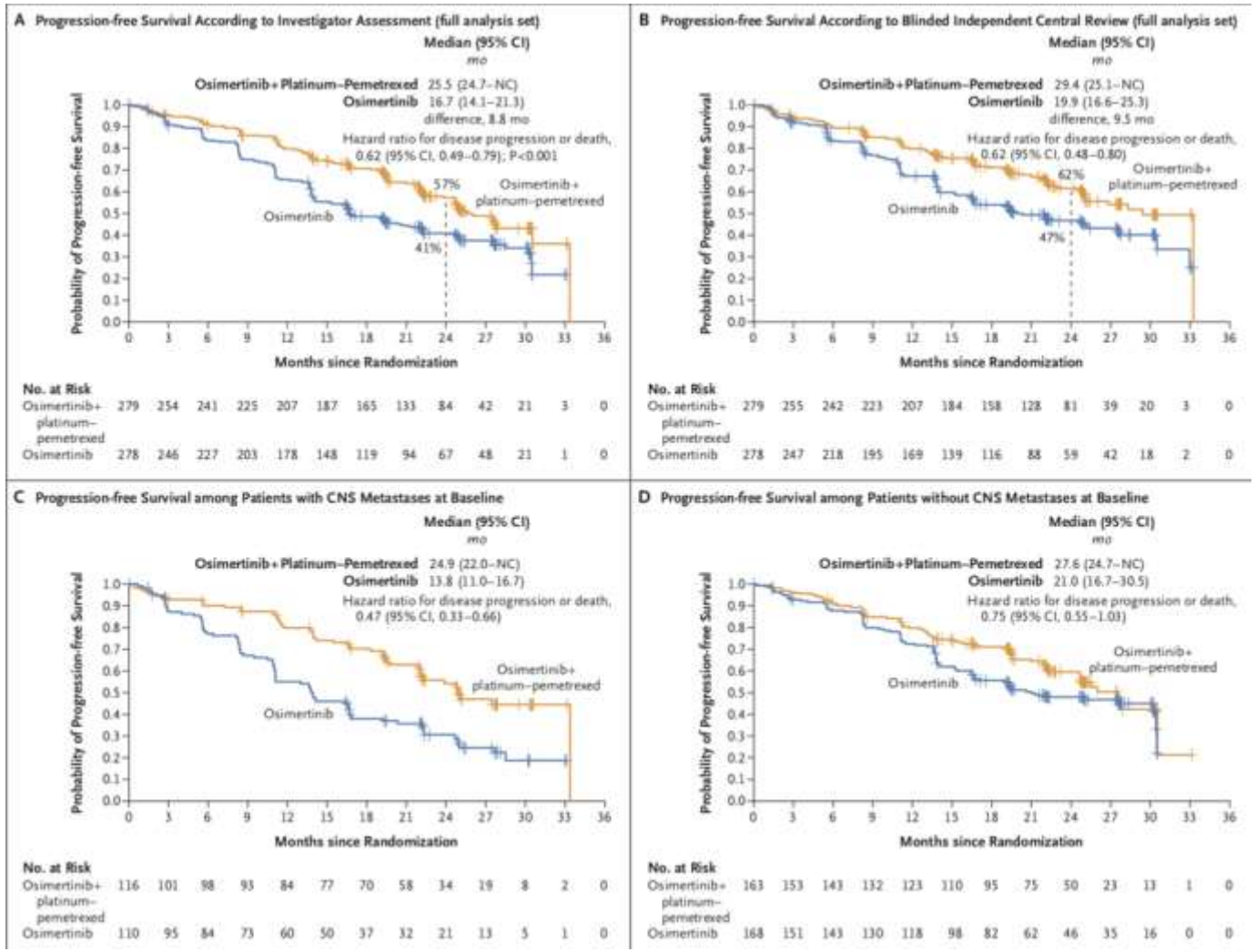


Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, Sugawara S, Yu Y, Fan Y, Geater SL, Laktionov K, Lee CK, Valdiviezo N, Ahmed S, Maurel JM, Andrasina I, Goldman J, Ghiorghiu D, Rukazenkov Y, Todd A, Kobayashi K; FLAURA2 Investigators. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 8. doi: 10.1056/NEJMoa2306434. Epub ahead of print. PMID: 37937763.

STADE MÉTASTATIQUE : *EGFR*+ (exon del19- exon 21 L 858R)

- **Étude Flaura 2**



Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, Sugawara S, Yu Y, Fan Y, Geater SL, Laktionov K, Lee CK, Valdiviezo N, Ahmed S, Maurel JM, Andrasina I, Goldman J, Ghiorghiu D, Rukazenkov Y, Todd A, Kobayashi K; FLAURA2 Investigators. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 8. doi: 10.1056/NEJMoa2306434. Epub ahead of print. PMID: 37937763.

STADE MÉTASTATIQUE : *EGFR*+ (exon del19- exon 21 L 858R)
Tolérance

Table 3. Adverse Events.*

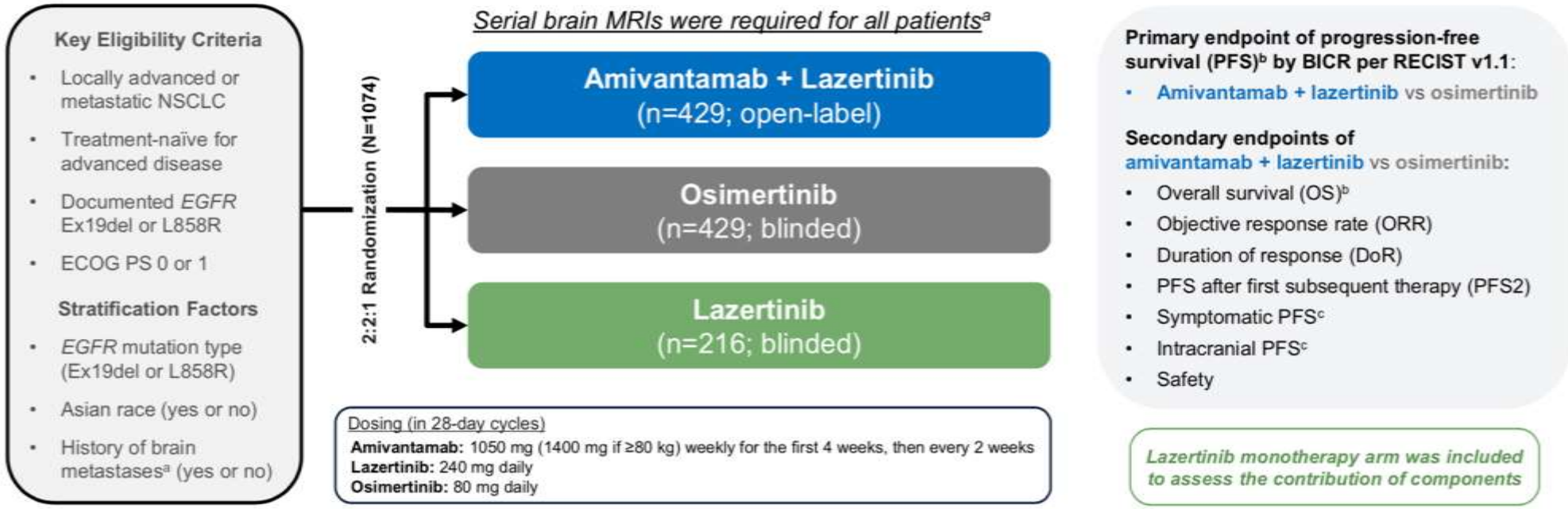
Event	Osimertinib + Platinum–Pemetrexed (N = 276)					Osimertinib Monotherapy (N = 275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, Sugawara S, Yu Y, Fan Y, Geater SL, Laktionov K, Lee CK, Valdiviezo N, Ahmed S, Maurel JM, Andrasina I, Goldman J, Ghiorghiu D, Rukazenkov Y, Todd A, Kobayashi K; FLAURA2 Investigators. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 8. doi: 10.1056/NEJMoa2306434. Epub ahead of print. PMID: 37937763.

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**

MARIPOSA: Phase 3 Study Design

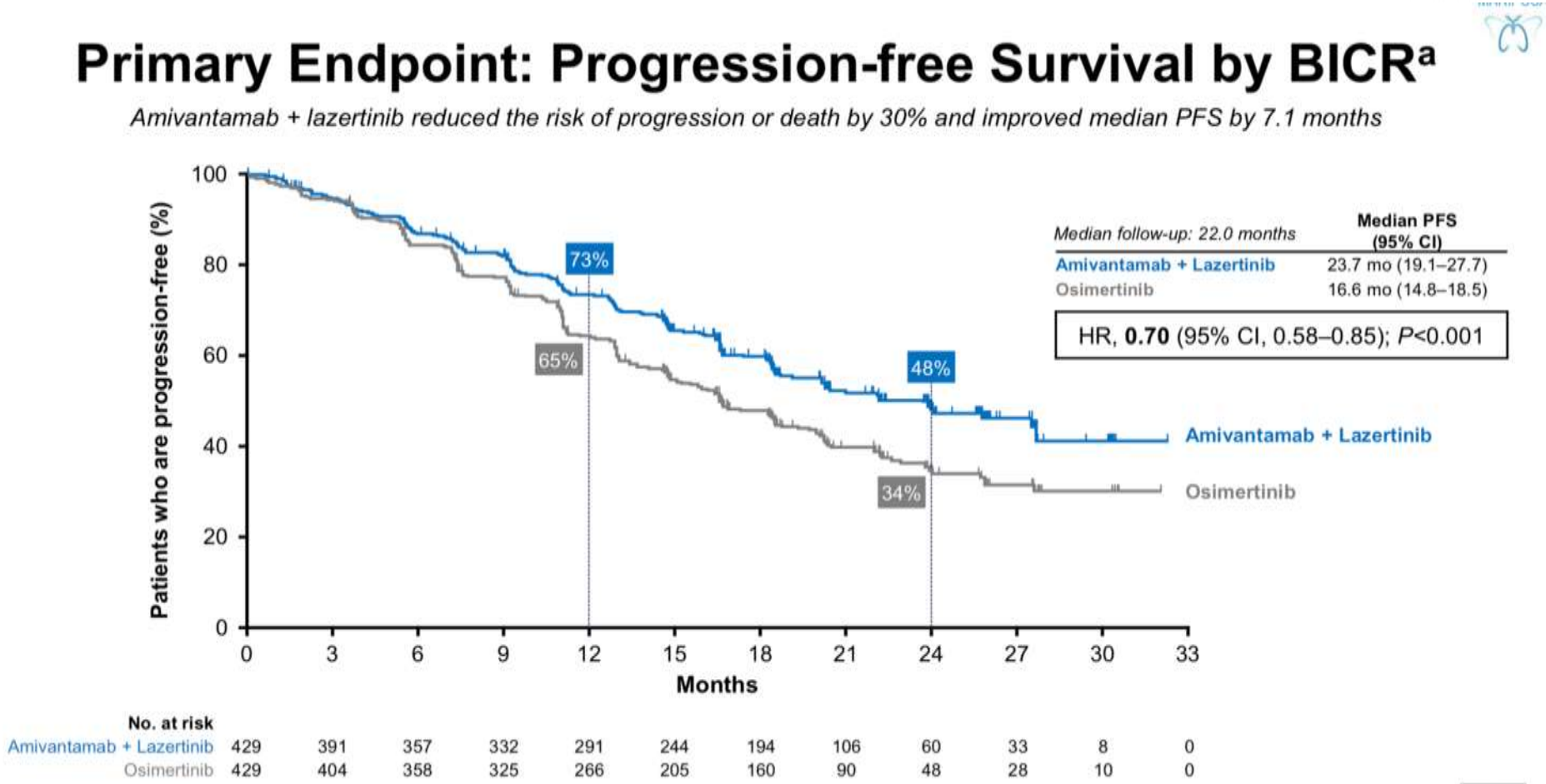


Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Cho BC, et al. Ann Oncol 2023;34(suppl):Abstr LBA14

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**

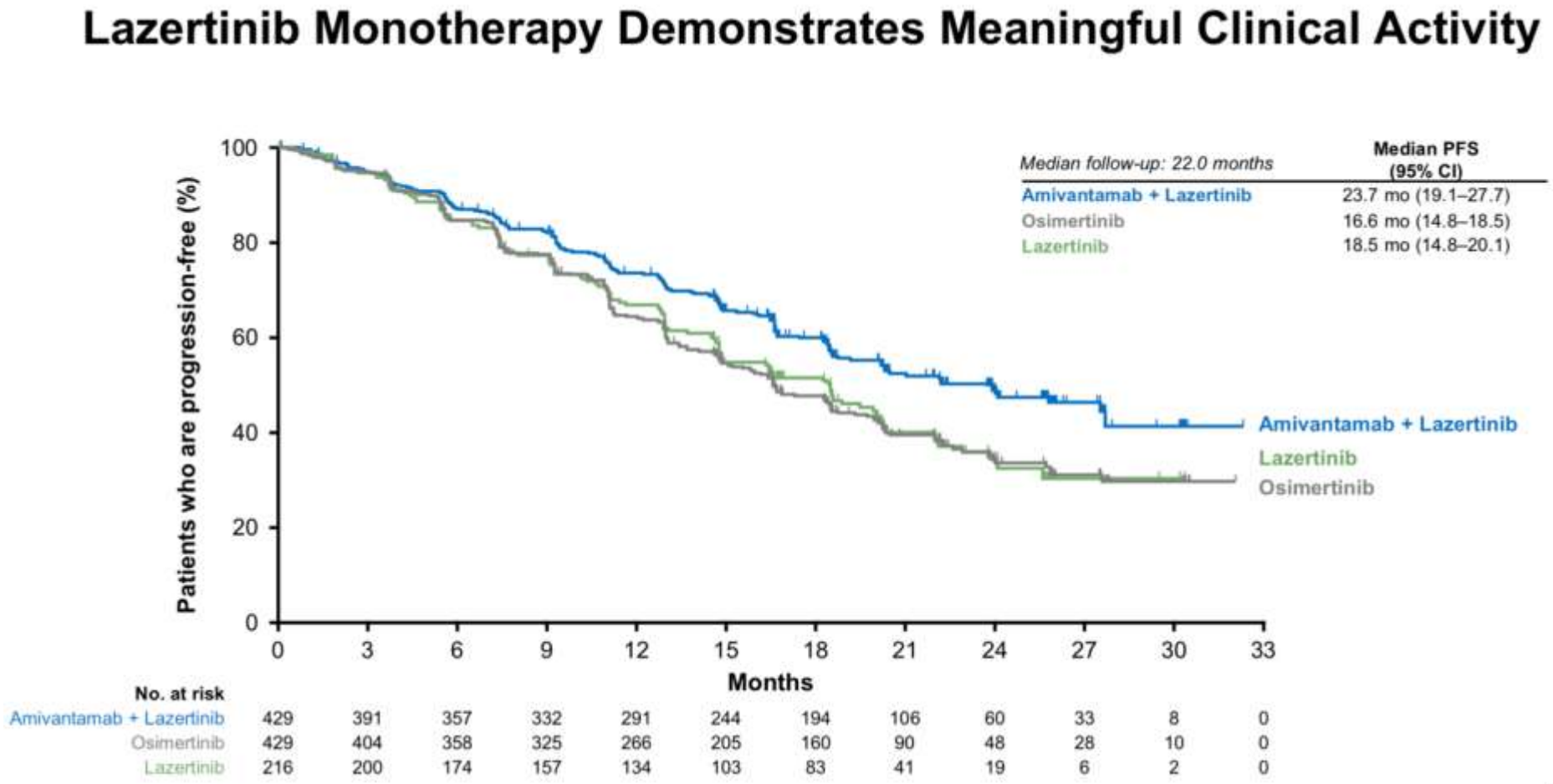


Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Cho BC, et al. Ann Oncol 2023;34(suppl):Abstr LBA14

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**

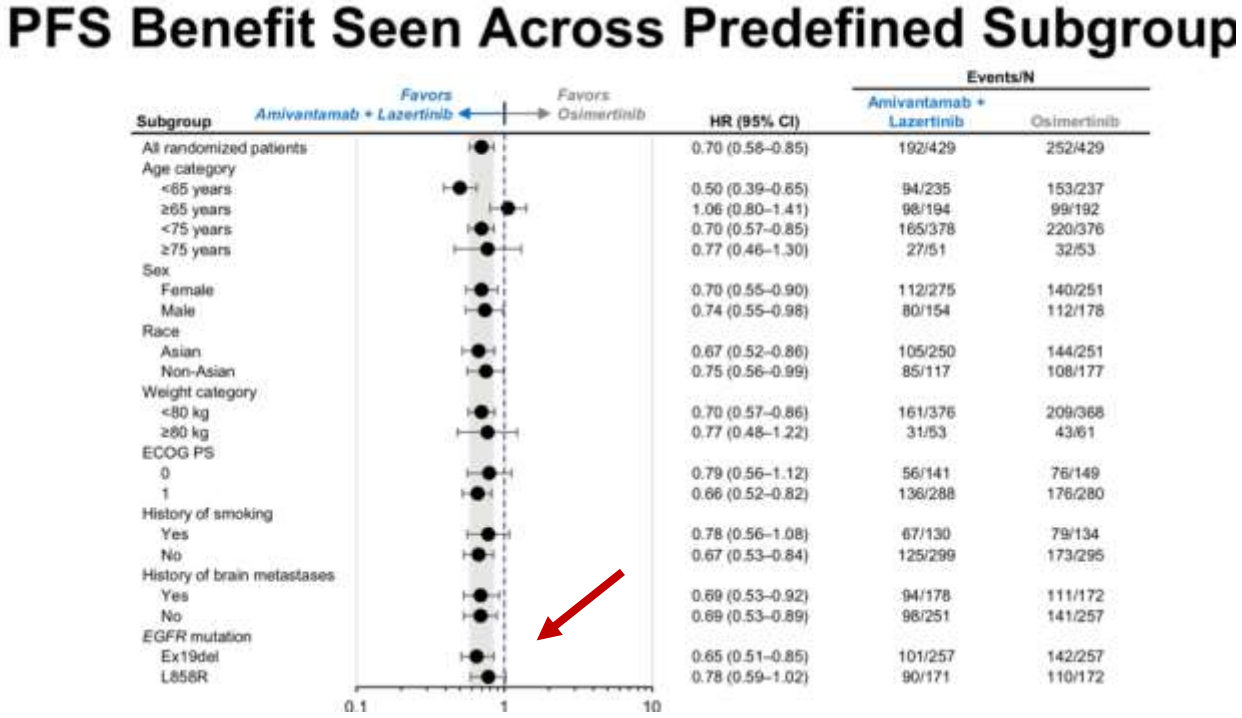


Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Cho BC, et al. Ann Oncol 2023;34(suppl):Abstr LBA14

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**



BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK	21 (5)	11 (3)
Ongoing responses	209 of 336 (62%)	151 of 314 (48%)

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**

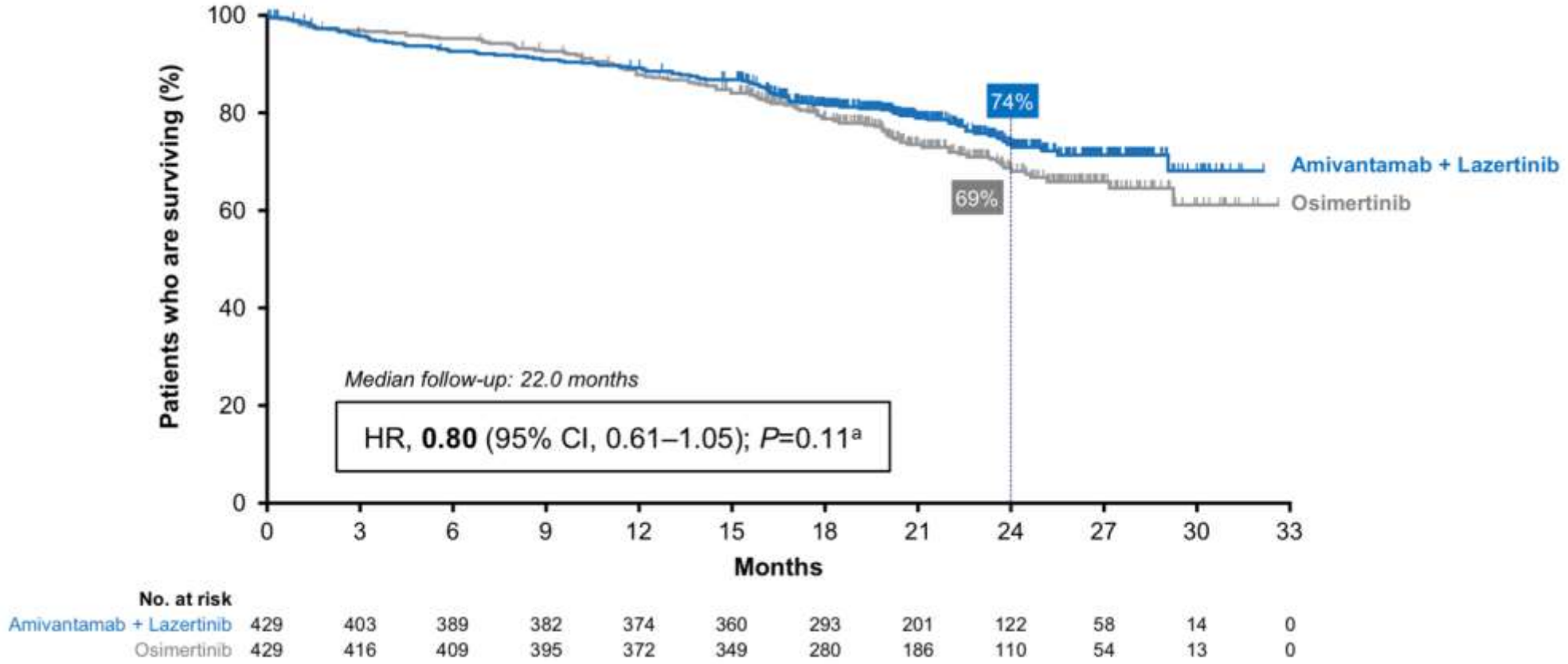
AEs, %	Amivantamab + lazertinib (n=421)		Osimertinib (n=428)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Related to EGFR inhibition	**57**	**11**	**28**	**0.5**
Paronychia	**46**	**15**	**30**	**1**
Rash	**27**	**2**	**44**	**1**
Diarrhea	**21**	**8**	**13**	**0**
Stomatitis	**28**	**1**	**21**	**0.2**
Pruritus	**23**	**0.5**	**17**	**0.2**
Related to MET inhibition				
Hypoalbuminemia	**43**	**5**	**6**	**0**
Peripheral edema	**34**	**2**	**6**	**0**

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

Cho BC, et al. Ann Oncol 2023;34(suppl):Abstr LBA14

STADE MÉTASTATIQUE : *EGFR*+
(exon del19- exon 21 L 858R)

- **Étude Mariposa**

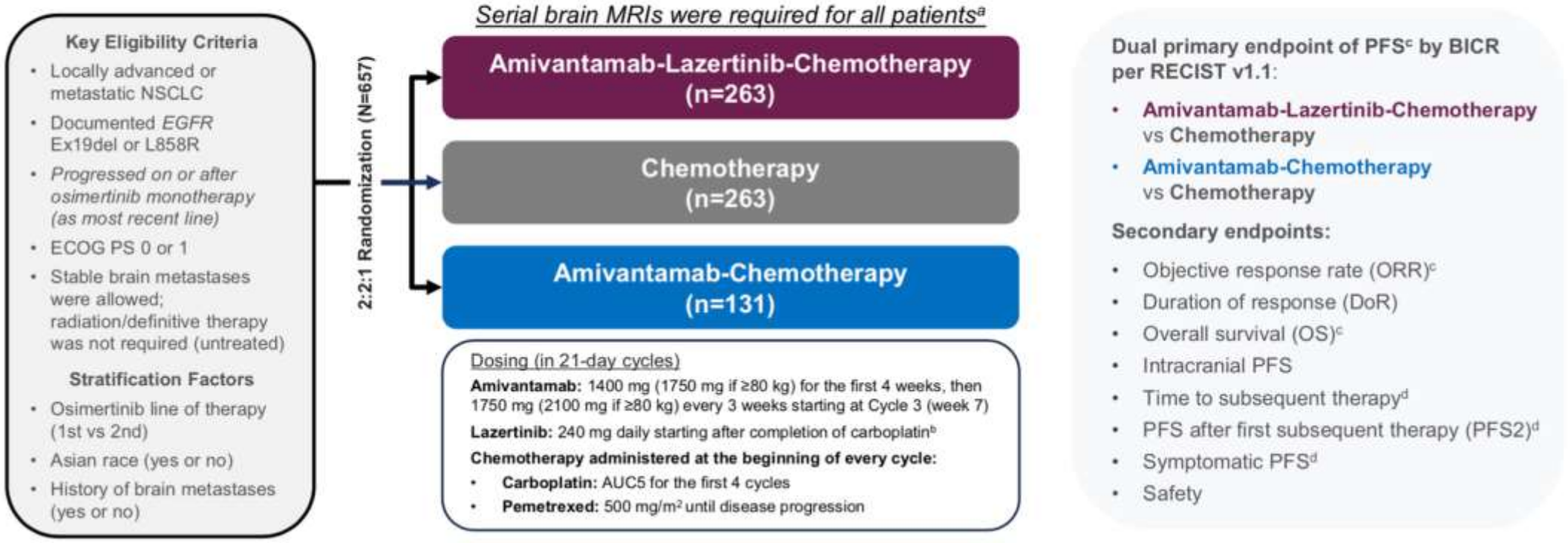


Cho BC, et al. Ann Oncol 2023;34(suppl):Abstr LBA14

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

STADE MÉTASTATIQUE *EGFR* post osimertinib

MARIPOSA-2: Phase 3 Study Design



The amivantamab + lazertinib + chemotherapy regimen was modified to start lazertinib after carboplatin completion due to hematologic toxicities

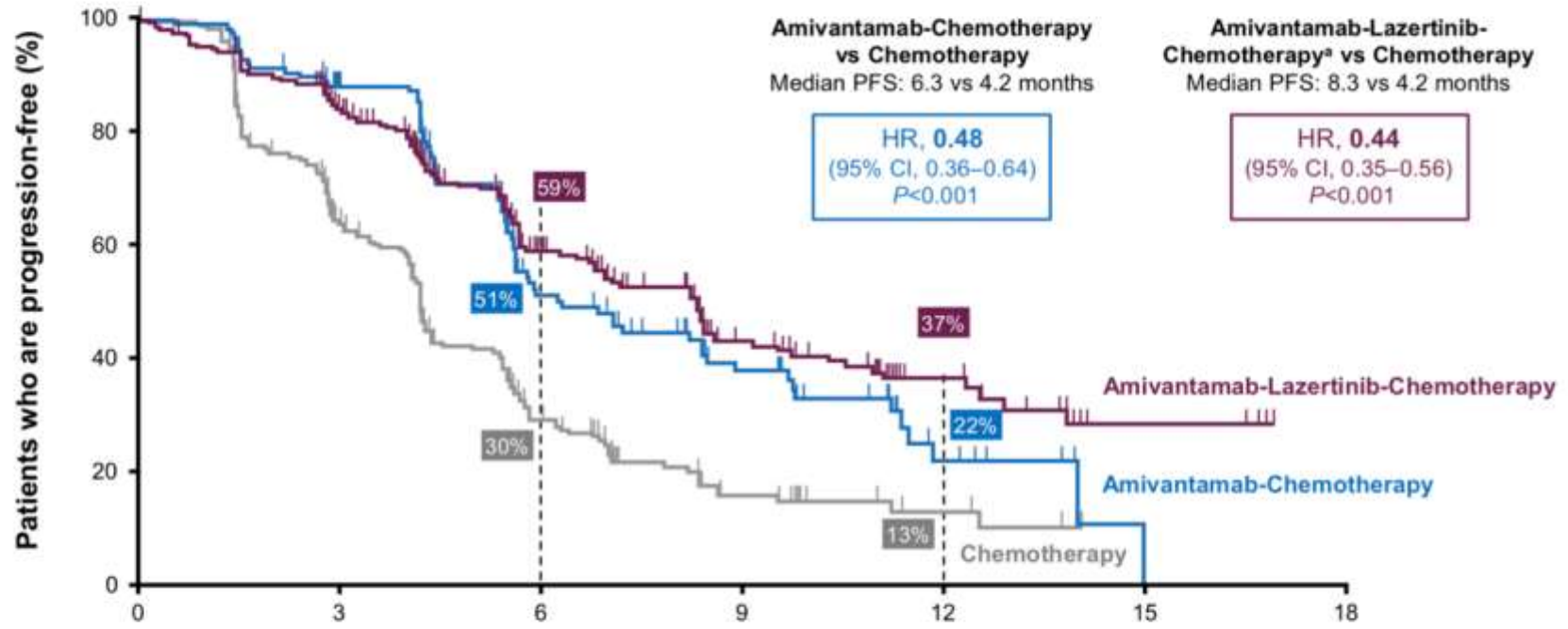
Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Passaro A, et al. Ann Oncol 2023;34(suppl):Abstr LBA15

STADE MÉTASTATIQUE *EGFR* post osimertinib

Primary Endpoint: Progression-free Survival by BICR

At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively



No. at risk							
Amivantamab-Chemotherapy	131	99	49	27	7	0	0
Amivantamab-Lazertinib-Chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

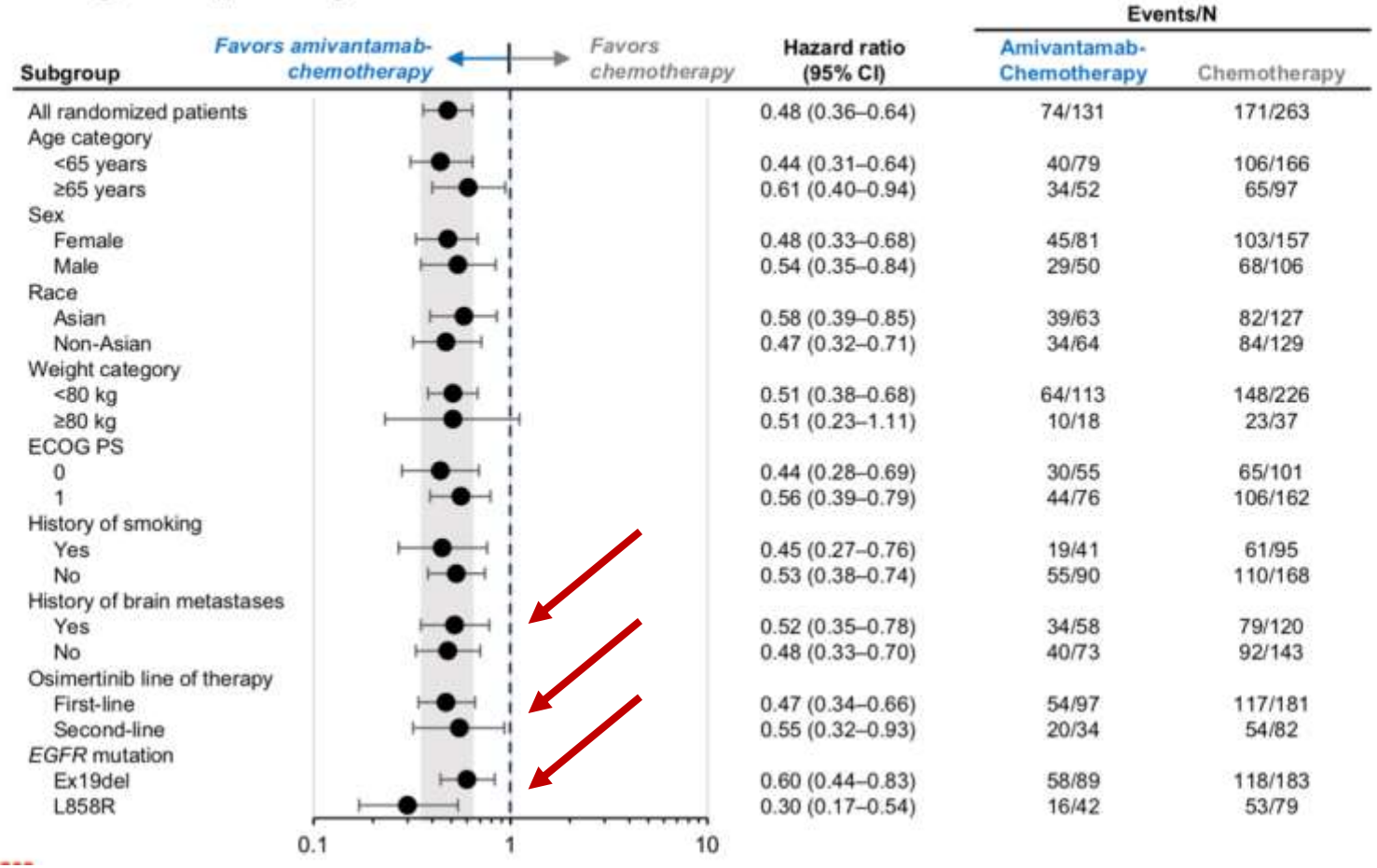
Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])

Passaro A, et al. Ann Oncol 2023;34(suppl):Abstr LBA15

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

STADE MÉTASTATIQUE *EGFR* post osimertinib

Consistent PFS Benefit of Amivantamab-Chemotherapy Across Subgroups by BICR



Subgroup	Hazard ratio (95% CI)	Events/N: Amivantamab-Chemotherapy	Events/N: Chemotherapy
All randomized patients	0.48 (0.36–0.64)	74/131	171/263
Age category			
<65 years	0.44 (0.31–0.64)	40/79	106/166
≥65 years	0.61 (0.40–0.94)	34/52	65/97
Sex			
Female	0.48 (0.33–0.68)	45/81	103/157
Male	0.54 (0.35–0.84)	29/50	68/106
Race			
Asian	0.58 (0.39–0.85)	39/63	82/127
Non-Asian	0.47 (0.32–0.71)	34/64	84/129
Weight category			
<80 kg	0.51 (0.38–0.68)	64/113	148/226
≥80 kg	0.51 (0.23–1.11)	10/18	23/37
ECOG PS			
0	0.44 (0.28–0.69)	30/55	65/101
1	0.56 (0.39–0.79)	44/76	106/162
History of smoking			
Yes	0.45 (0.27–0.76)	19/41	61/95
No	0.53 (0.38–0.74)	55/90	110/168
History of brain metastases			
Yes	0.52 (0.35–0.78)	34/58	79/120
No	0.48 (0.33–0.70)	40/73	92/143
Osimertinib line of therapy			
First-line	0.47 (0.34–0.66)	54/97	117/181
Second-line	0.55 (0.32–0.93)	20/34	54/82
EGFR mutation			
Ex19del	0.60 (0.44–0.83)	58/89	118/183
L858R	0.30 (0.17–0.54)	16/42	53/79

Passaro A, et al. Ann Oncol 2023;34(suppl):Abstr LBA15

STADE MÉTASTATIQUE *EGFR* post osimertinib

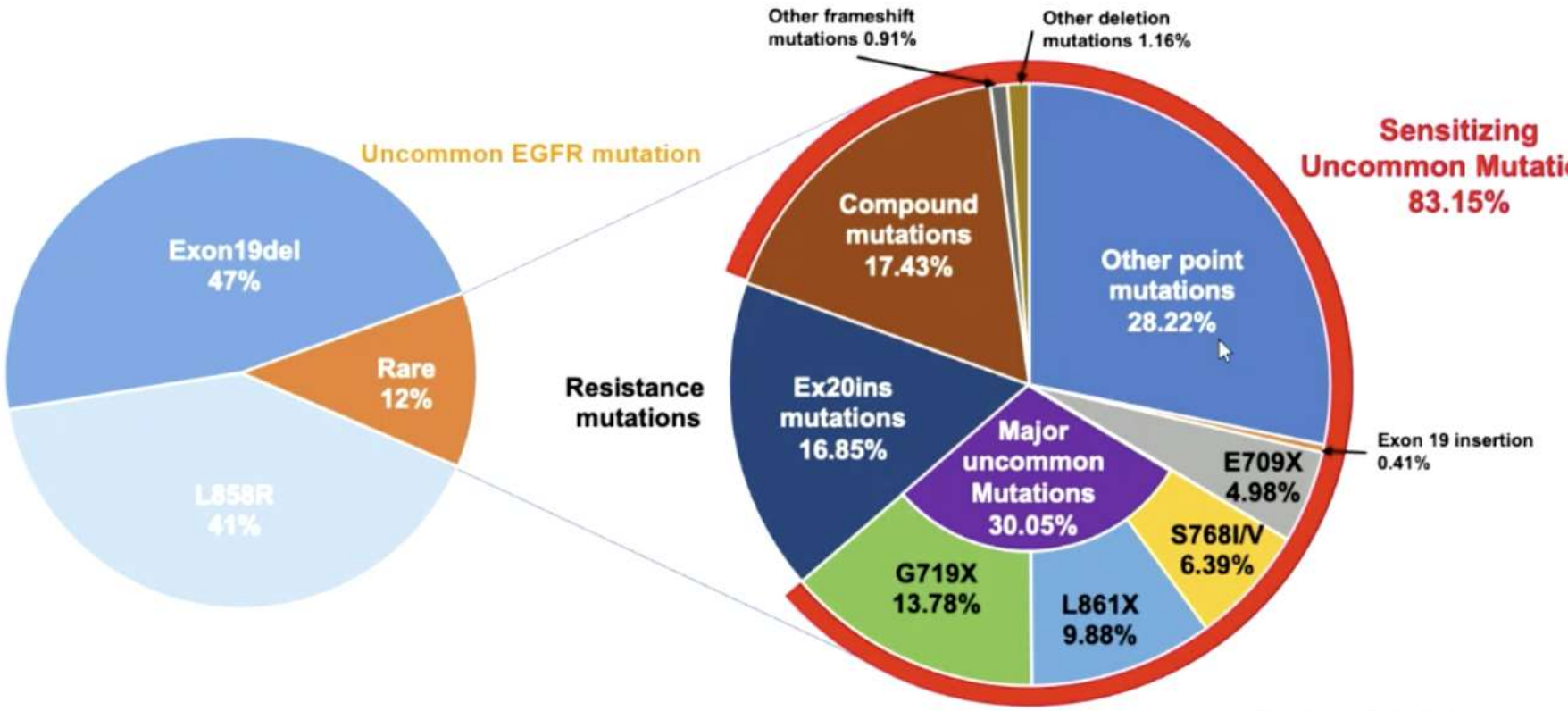
BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=130)	Amivantamab-Lazertinib-Chemotherapy[a] (n=263)
Treatment duration, median (range)	3.7 months (0–15.9)	6.3 months (0–14.7)	5.7 months (0.1–18.6)
No. of chemotherapy cycles, median (range)			
Carboplatin	4 (1–5)	4 (1–4)	4 (1–4)
Pemetrexed	6 (1–23)	9 (1–22)	7 (1–25)

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)
AEs leading to death	3 (1)	3 (2)	14 (5)
Any AE leading to treatment:			
Interruptions of any agent	81 (33)	84 (65)	202 (77)
Reductions of any agent	37 (15)	53 (41)	171 (65)
Discontinuations of any agent	9 (4)	24 (18)	90 (34)
Discontinuations of all agents due to AE	10 (4)	14 (11)	38 (14)

Passaro A, et al. Ann Oncol 2023;34(suppl):Abstr LBA15

STADE MÉTASTATIQUE *EGFR* uncommon



Harrison PT et al. *Semin Cancer Biol*. 2020;61:167

EGFR Exon 20

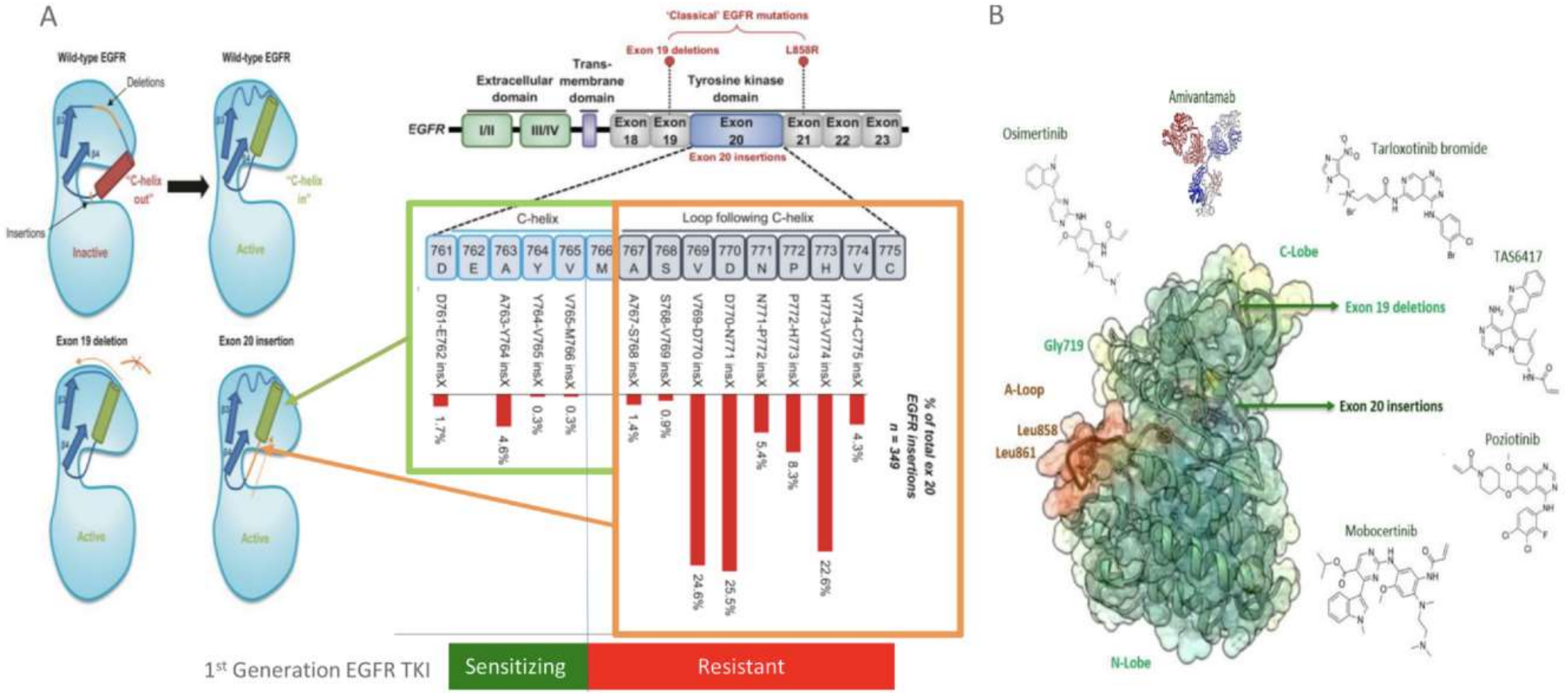
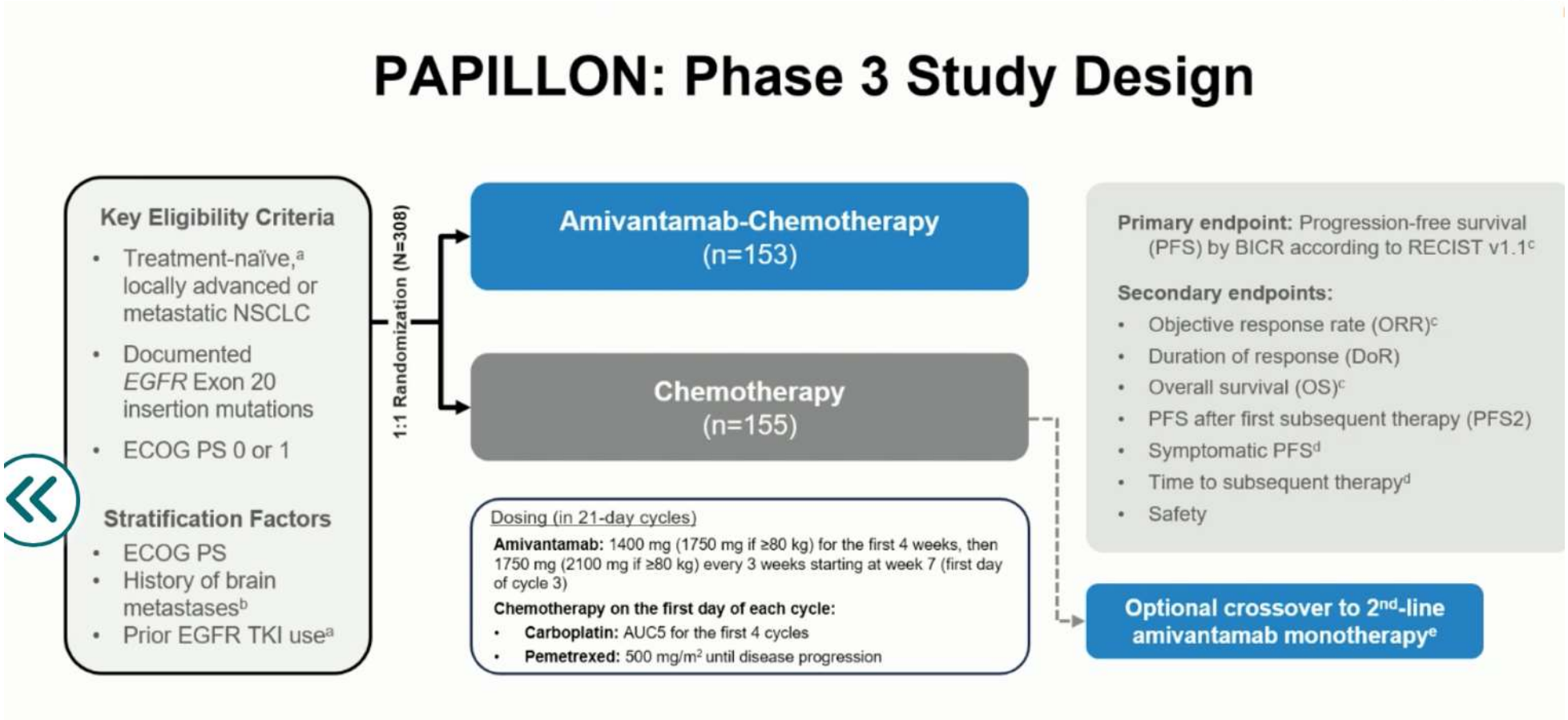


Fig. 2. A) Impact of deletions and insertions on *EGFR* activation, and incidence of *EGFR* exon 20 insertions variants in NSCLC. (modified from Vyse et al. - Signal Transduct Target Ther. 2019); **B)** Potential treatment strategies in *EGFR* exon 20 insertions lung tumors.

Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105.

STADE MÉTASTATIQUE *EGFR* exon 20

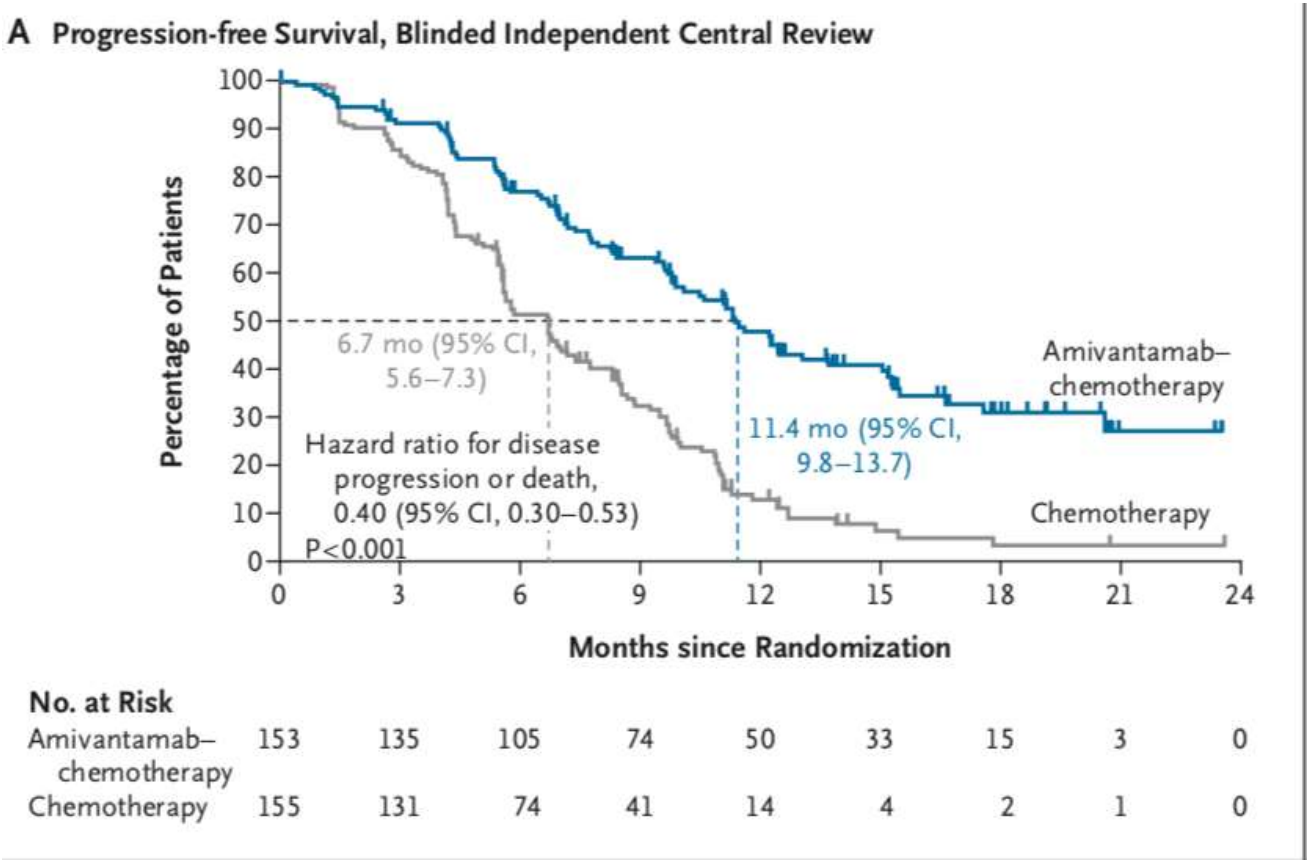
- **Étude Papillon**



Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Zhou C,et al ; PAPILLON Investigators. Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions. N Engl J Med. 2023 Oct 21.

STADE MÉTASTATIQUE *EGFR* exon 20



BICR-assessed response[a]	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)

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Zhou C,et al ; PAPILLON Investigators. Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions. N Engl J Med. 2023 Oct 21.

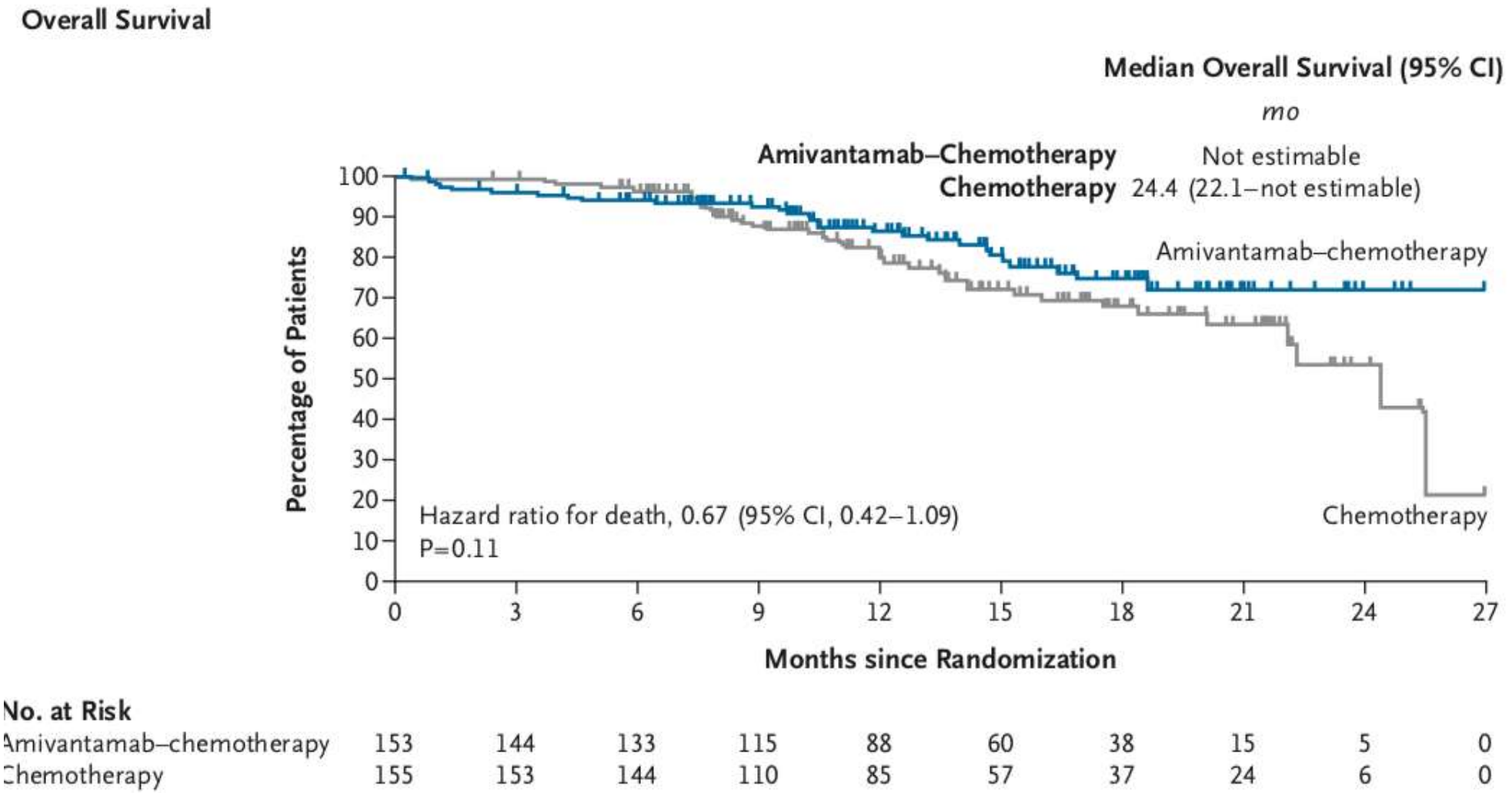
STADE MÉTASTATIQUE *EGFR* exon 20

Table 3. Adverse Events.*

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any event	151 (100)	114 (75)	152 (98)	83 (54)
Any serious event	56 (37)		48 (31)	
Any event resulting in death	7 (5)		4 (3)	
Any event leading to interruption of any agent	104 (69)		56 (36)	
Interruption in dose of amivantamab				
Any	97 (64)			
Related to amivantamab†	63 (42)			
Any event leading to reduction of any agent	73 (48)		35 (23)	
Reduction in dose of amivantamab				
Any	54 (36)			
Related to amivantamab†	54 (36)			
Any event leading to discontinuation of any agent	36 (24)		16 (10)	
Discontinuation of amivantamab				
Any	17 (11)			
Related to amivantamab†	10 (7)			
Discontinuation of all agents because of adverse events‡	12 (8)		12 (8)	

Zhou C,et al ; PAPILLON Investigators. Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions. N Engl J Med. 2023 Oct 21.

STADE MÉTASTATIQUE *EGFR* exon 20



Zhou C,et al ; PAPILLON Investigators. Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions. N Engl J Med. 2023 Oct 21.

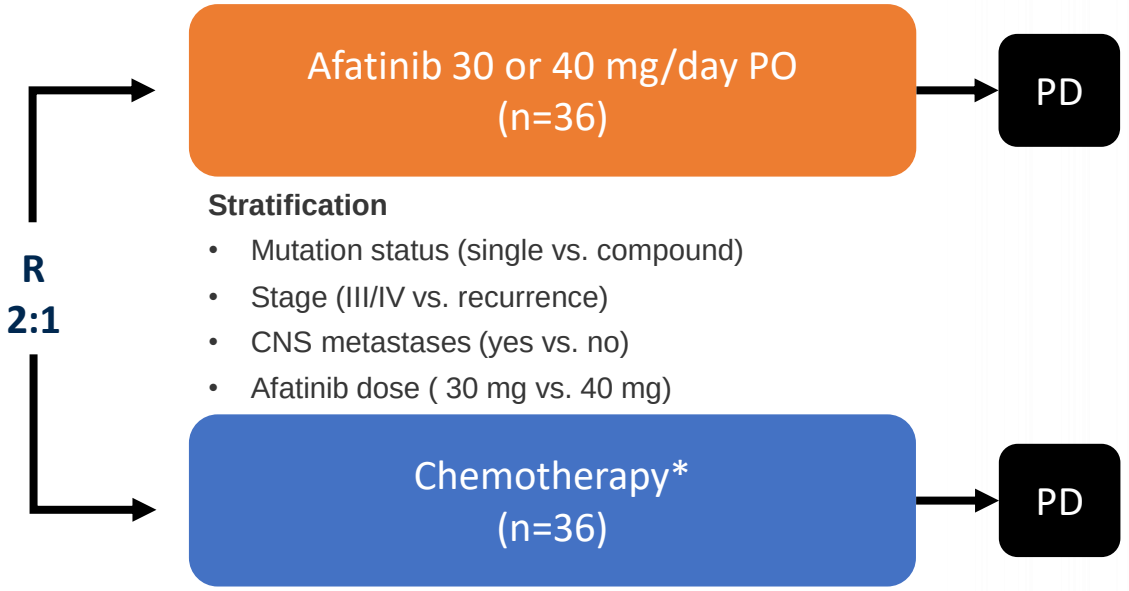
STADE MÉTASTATIQUE *EGFR* uncommon

Étude Achille

Key patient inclusion criteria

- Locally advanced or metastatic nonsquamous NSCLC
- Sensitizing uncommon EGFR mutations
- No prior therapy
- ECOG PS 0–1

(n=109)



Primary endpoint

- PFS (investigator assessed)

Secondary endpoints

- ORR, DCR, OS, TTF, safety

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

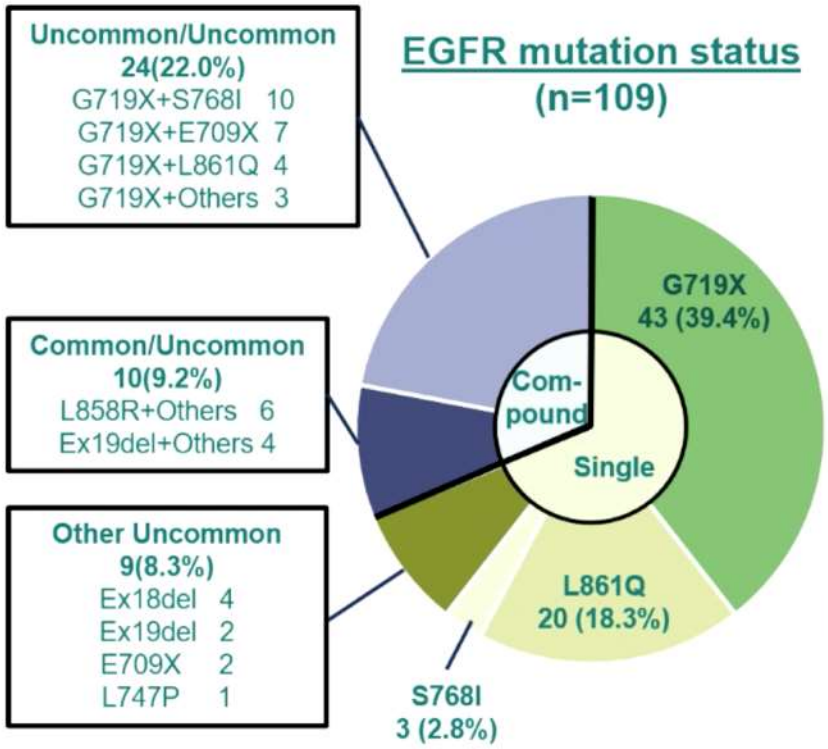
Miura S, et al. Ann Oncol 2023;34(suppl):Abstr LBA66

STADE MÉTASTATIQUE *EGFR* uncommon

- **Étude Achille**

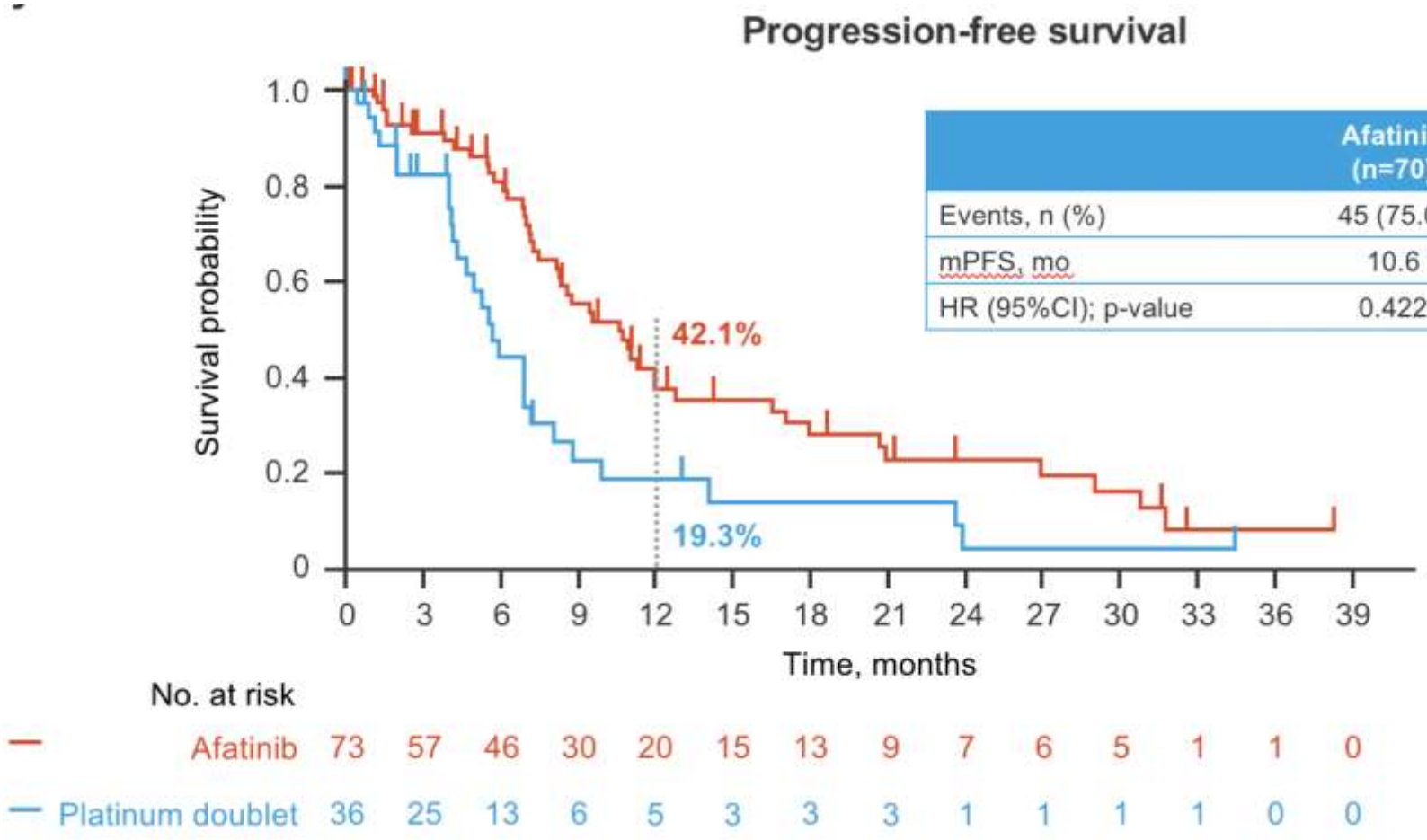
Demographics and Baseline Characteristics

Characteristics		Afatinib (n=73)		Platinum Doublet (n=36)	
Age	Median (range)	71.0	(49-83)	66.5	(42-77)
	≥ 75 years old	19	(26.0%)	5	(13.9%)
Gender	Male	32	(43.8%)	16	(44.4%)
	Female	41	(56.2%)	20	(55.6%)
ECOG performance status	0	32	(43.8%)	16	(44.4%)
	1	41	(56.2%)	20	(55.6%)
Smoking status	Never	38	(52.1%)	13	(36.2%)
	Current	8	(11.0%)	6	(16.7%)
	Former	27	(37.0%)	17	(47.2%)
Stage*	III/IV	55	(75.3%)	29	(80.6%)
	Recurrence	18	(24.7%)	7	(19.4%)
EGFR mutation status*	Single	50	(68.5%)	25	(69.4%)
	Compound	23	(31.5%)	11	(30.6%)
CNS metastasis*	No	50	(68.5%)	25	(69.4%)
	Yes	23	(31.5%)	11	(30.6%)
Afatinib starting dose*	30 mg	37	(50.7%)	19	(52.8%)
	40 mg	36	(49.3%)	17	(47.2%)



Miura S, et al. Ann Oncol 2023;34(suppl):Abstr LBA66

STADE MÉTASTATIQUE *EGFR* uncommon



	Afatinib (n=70)	Platinum doublet (n=34)
Events, n (%)	45 (75.0)	27 (79.4)
mPFS, mo	10.6	5.7
HR (95%CI); p-value	0.422 (0.256, 0.694); 0.0007	

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Miura S, et al. Ann Oncol 2023;34(suppl):Abstr LBA66

STADE MÉTASTATIQUE *RET*+

- **Étude LIBRETTO 431**

Key patient inclusion criteria

- NSCLC
- RET fusion-positive
- ECOG PS 0–2

(n=261)

R 2:1

Selpercatinib 160 mg BID (n=159)

Stratification

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)
- Investigator's choice of treatment with pembrolizumab

Chemotherapy[b] ± pembrolizumab (n=102)

Selpercatinib

Primary endpoint

- PFS (BICR)

Secondary endpoints

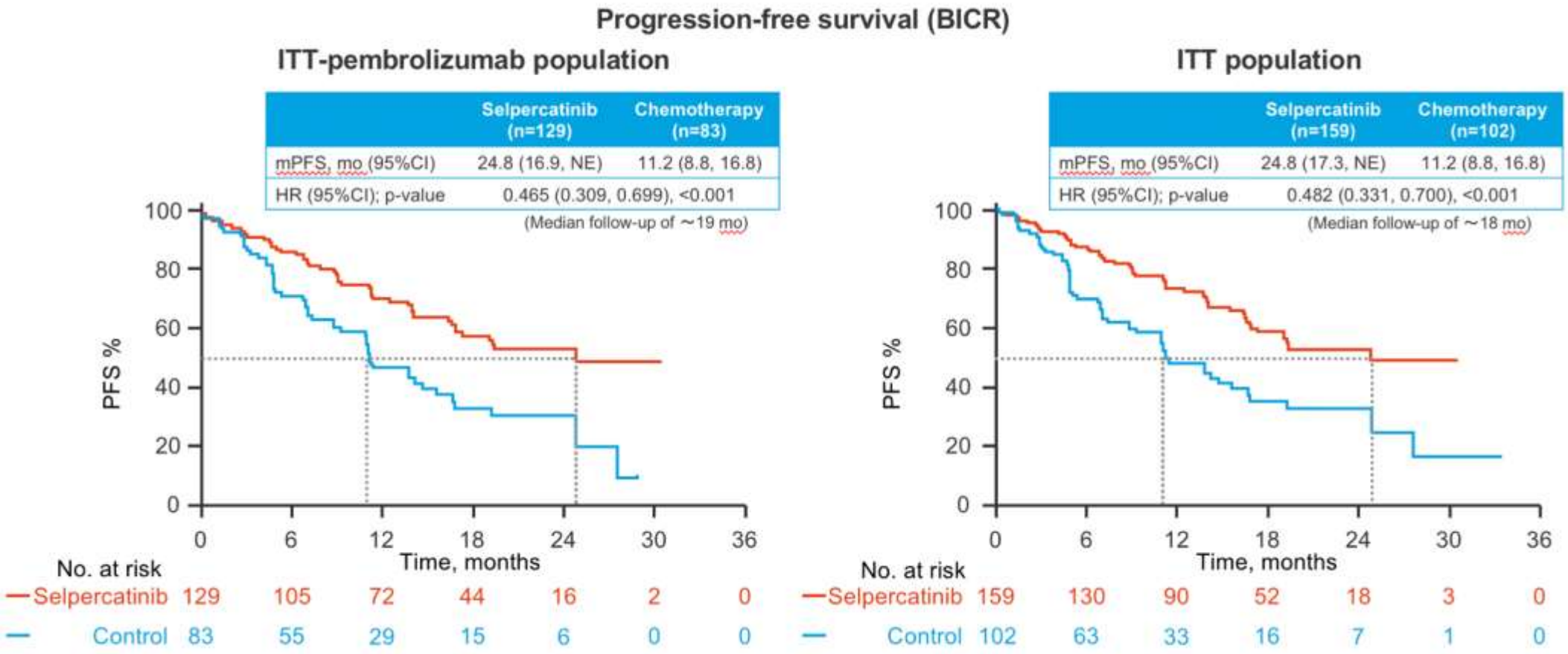
- OS, ORR, DoR, PROs, safety

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, Novello S, Han B, Zhou J, Ardizzoni A, Mak MP, Santini FC, Elamin YY, Drilon A, Wolf J, Payakachat N, Uh MK, Rajakumar D, Han H, Puri T, Soldatenkova V, Lin AB, Lin BK, Goto K; LIBRETTO-431 Trial Investigators. First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion-Positive NSCLC. N Engl J Med. 2023 Oct 21. doi: 10.1056/NEJMoa2309457. Epub ahead of print. PMID: 37870973.

STADE MÉTASTATIQUE *RET*+

- **Étude LIBRETTO 431**



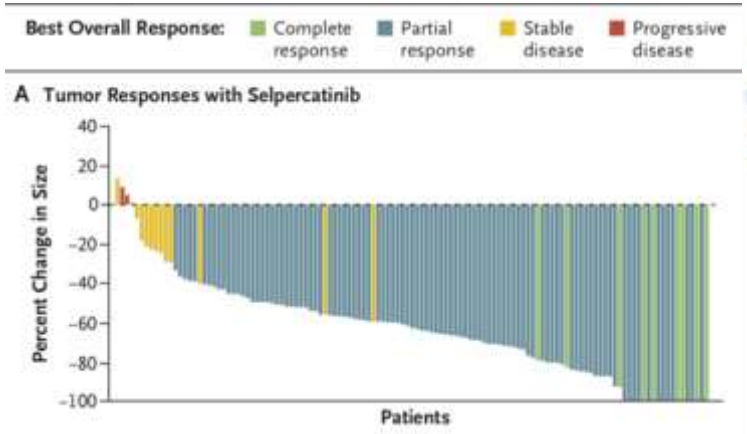
Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, Novello S, Han B, Zhou J, Ardizzoni A, Mak MP, Santini FC, Elamin YY, Drilon A, Wolf J, Payakachat N, Uh MK, Rajakumar D, Han H, Puri T, Soldatenkova V, Lin AB, Lin BK, Goto K; LIBRETTO-431 Trial Investigators. First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion-Positive NSCLC. N Engl J Med. 2023 Oct 21. doi: 10.1056/NEJMoa2309457. Epub ahead of print. PMID: 37870973.

STADE MÉTASTATIQUE *RET*+

Table 2. Summary of End Points Assessed by Blinded Independent Central Review.*

End Point	Intention-to-Treat–Pembrolizumab Population		Overall Intention-to-Treat Population	
	Selpercatinib (N=129)	Control (N=83)	Selpercatinib (N=159)	Control (N=102)
Progression-free survival — mo				
Median progression-free survival (95% CI)	24.8 (16.9–NE)	11.2 (8.8–16.8)	24.8 (17.3–NE)	11.2 (8.8–16.8)
Median duration of follow-up (95% CI)	19.4 (16.7–19.7)	18.9 (14.2–22.3)	19.4 (16.7–19.6)	16.5 (13.6–21.0)
Objective response (95% CI) — % of patients	84 (76–90)	65 (54–75)	84 (77–89)	63 (53–72)
Best overall response — no. (%)				
Complete response	9 (7)	5 (6)	12 (8)	5 (5)
Partial response	99 (77)	49 (59)	121 (76)	59 (58)
Stable disease	14 (11)	20 (24)	17 (11)	26 (25)
Progressive disease	2 (2)	5 (6)	2 (1)	7 (7)
Not evaluable	5 (4)	4 (5)	7 (4)	5 (5)
Duration of response				
Patients with a response — no.	108	54	133	64
Patients with a response and censored data — no. (%)	74 (69)	25 (46)	43 (32)	31 (48)
Median duration of response (95% CI) — mo	24.2 (17.9–NE)	11.5 (9.7–23.3)	24.2 (17.9–NE)	12.0 (9.7–23.3)
Median duration of follow-up (95% CI) — mo	18.0 (16.5–19.5)	14.6 (11.2–19.8)	17.9 (15.7–18.7)	12.7 (11.1–16.6)



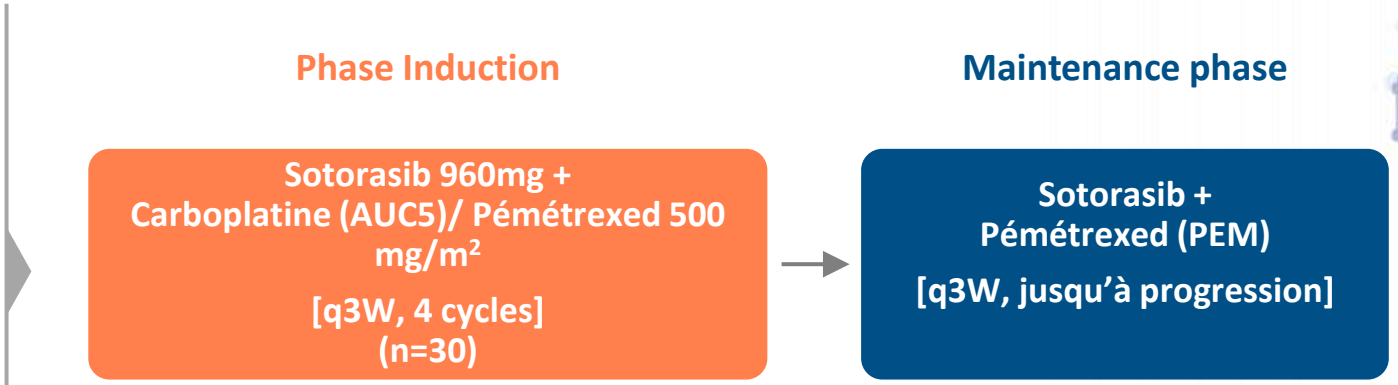
Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, Novello S, Han B, Zhou J, Ardizzoni A, Mak MP, Santini FC, Elamin YY, Drilon A, Wolf J, Payakachat N, Uh MK, Rajakumar D, Han H, Puri T, Soldatenkova V, Lin AB, Lin BK, Goto K; LIBRETTO-431 Trial Investigators. First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion-Positive NSCLC. N Engl J Med. 2023 Oct 21. doi: 10.1056/NEJMoa2309457. Epub ahead of print. PMID: 37870973.

KRAS G12C

Essai de phase II mono-bras évaluant l'association sotorasib et carboplatine-pemetrexed en 1ère ligne de traitement de CBNPC non-épidermoïde *KRAS G12C*

Critères d'inclusion

- CBNPC avancé non-épidermoïde, avec mutation KRAS G12C
- Naïf de chimiothérapie et de KRAS inhibiteur
- Avec lesion mesurable
- ECOG PS 0-1
- Métastases cérébrales asymptomatiques incluables



Critère principal :
Taux de réponse objective par comité indépendant (BICR)

Critères secondaires :
Taux de contrôle de la maladie (DCR), Survie sans progression (SSP), durée de réponse (DOR), Survie globale (SG) et tolérance

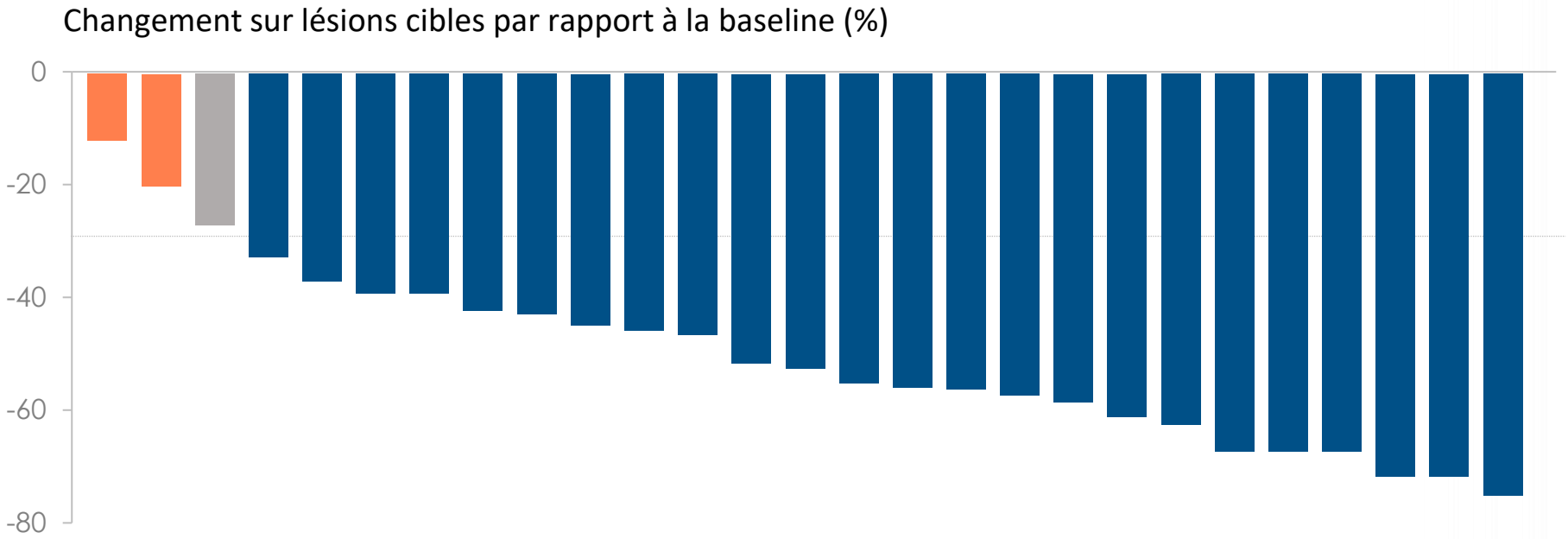
Recherche Translationnelle :
Analyse NGS (tissue et plasma [à baseline, 3 semaines et progression])

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

H. Akamatsu et al., ASCO® 2023, Abs. #9006

KRAS G12C

Taux de Réponse Objective revu par un comité indépendant



ORR 88,9% (IC80% 76,9-95,8%, IC95% 70,8-97,6%)

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

H. Akamatsu et al., ASCO® 2023, Abs. #9006

BRAF V600E

Étude PHAROS

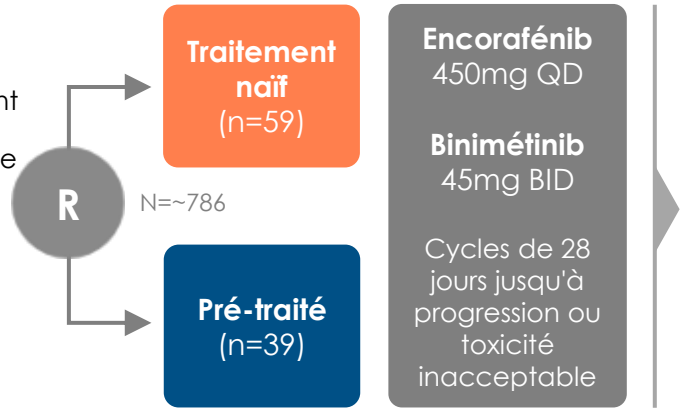
Encorafénib et binimétinib chez des patients avec CBNPC *BRAF*^{V600E} métastatique

Principaux critères d'éligibilité

- CBNPC métastatique muté *BRAF* ^{V600E}
- ECOG performance status 0 ou 1
- Pas de mutation de l'*EGFR*, de fusion *ALK* ou de réarrangement *ROS1*
- Pas plus d'une ligne de traitement antérieure dans un contexte avancé
- Pas de traitement antérieur avec un inhibiteur de *BRAF* ou de *MEK*
- Pas de métastases cérébrales symptomatiques

BRAF mutation testing

- Déterminé localement par un test PCR ou NGS ; envoyé au laboratoire central.
- Le liquide pleural, les tissus frais et archivés et l'aspiration à l'aiguille fine sont acceptables.



Objectif principal

- ORR selon IRR

Objectifs secondaires

- ORR selon investigateur
- DOR, DCR, SSP et TTR (selon IRR et investigateur)
- SG
- Tolérance

Critères d'évaluation exploratoires

Analyses des biomarqueurs et de la pharmacocinétique

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

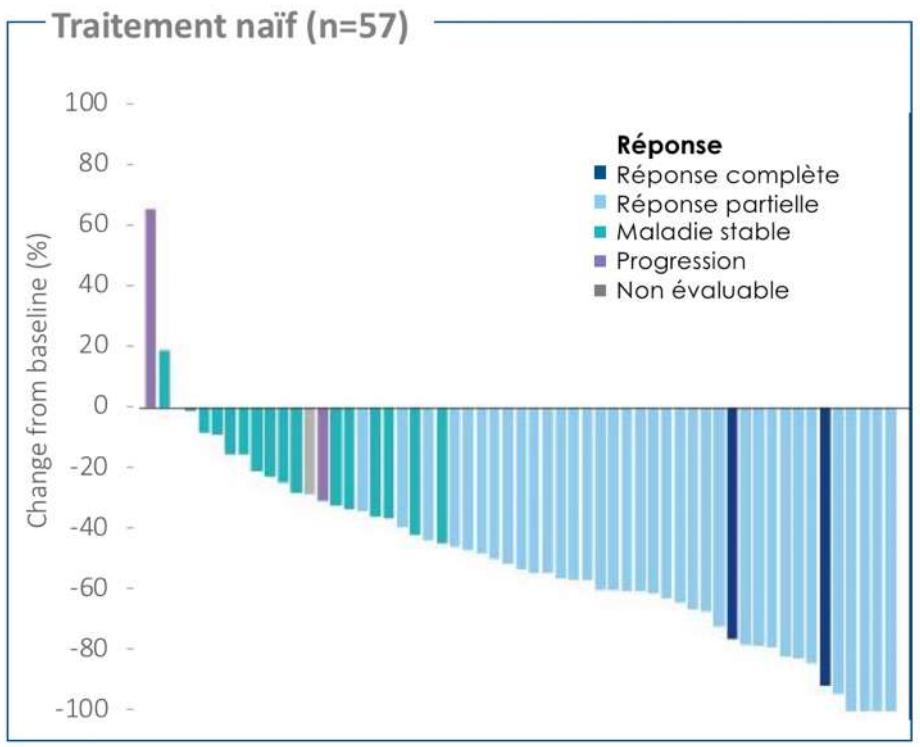
GJ. Riely et al., ASCO® 2023, Abs. #9018

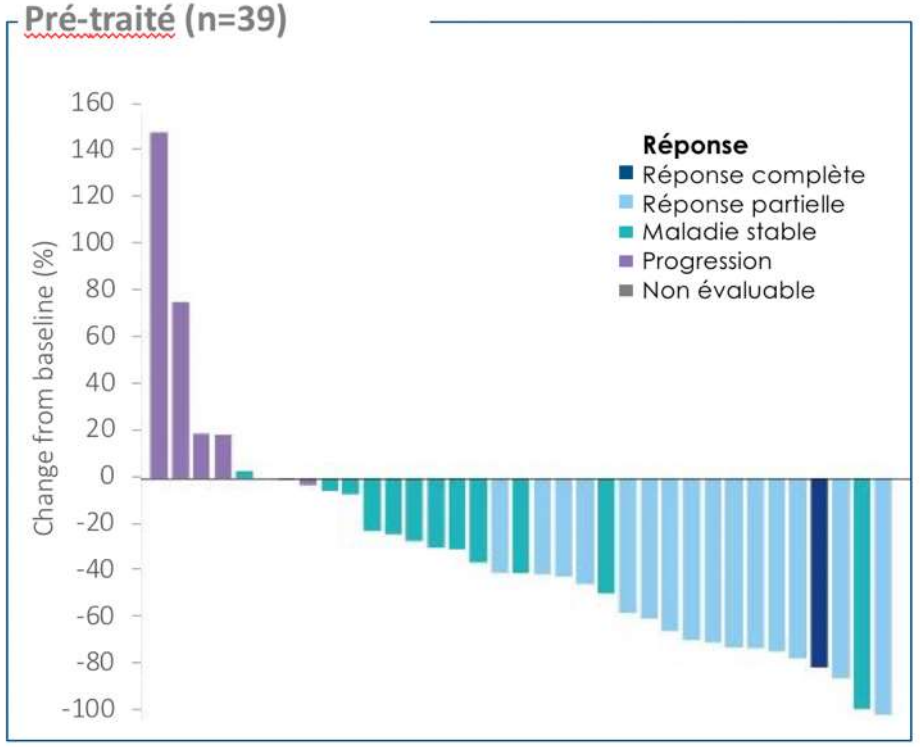
BRAF V600E

Étude PHAROS

Encorafénib et binimétinib chez des patients avec CBNPC *BRAF*^{V600E} métastatique

	Traitement naïf n=59	Pré-traité n=39
Taux de réponse objectif (IC95%I), %	**75 (62-85)**	**46 (30-63)**





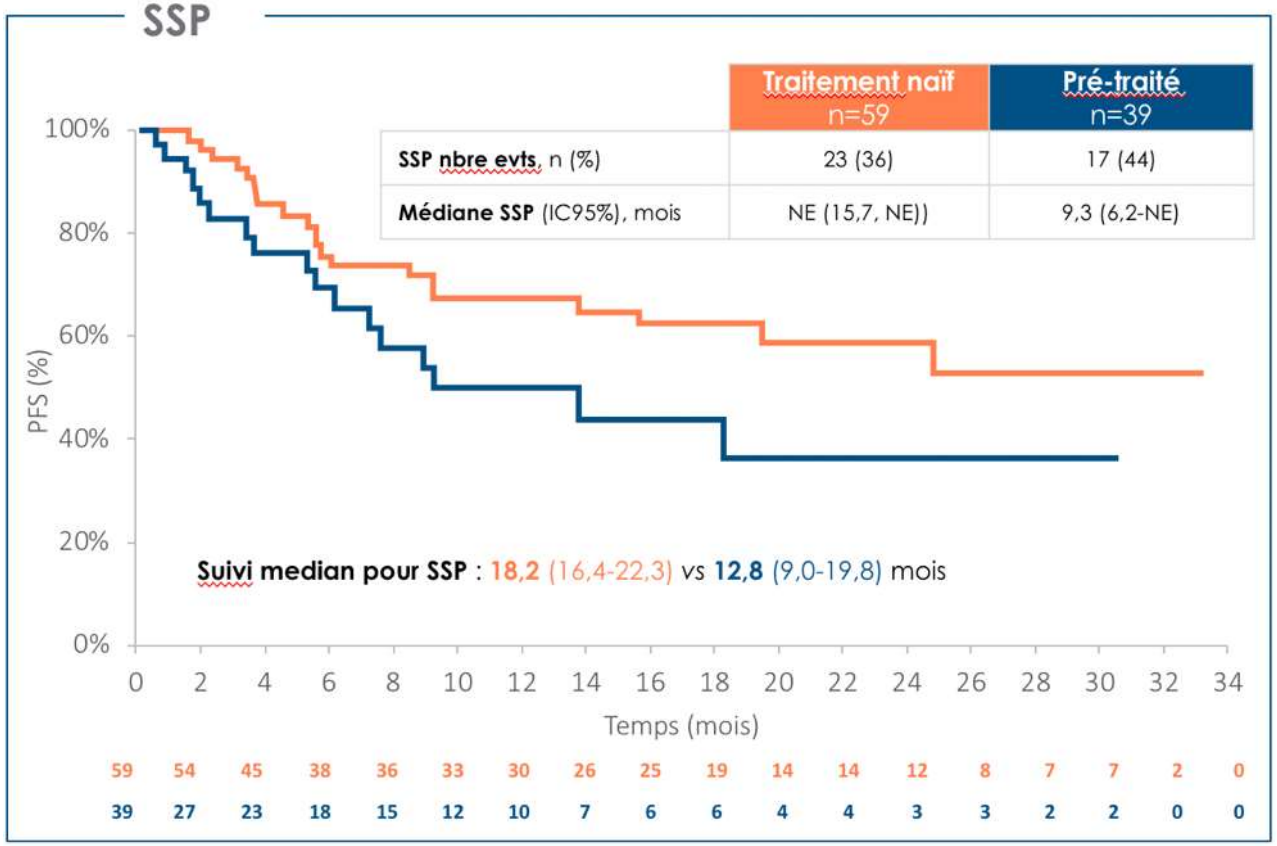
Hors AMM ; Données non validées par les Autorités de Santé à ce jour

GJ. Riely et al., ASCO® 2023, Abs. #9018

BRAF V600E

- **Étude PHAROS**

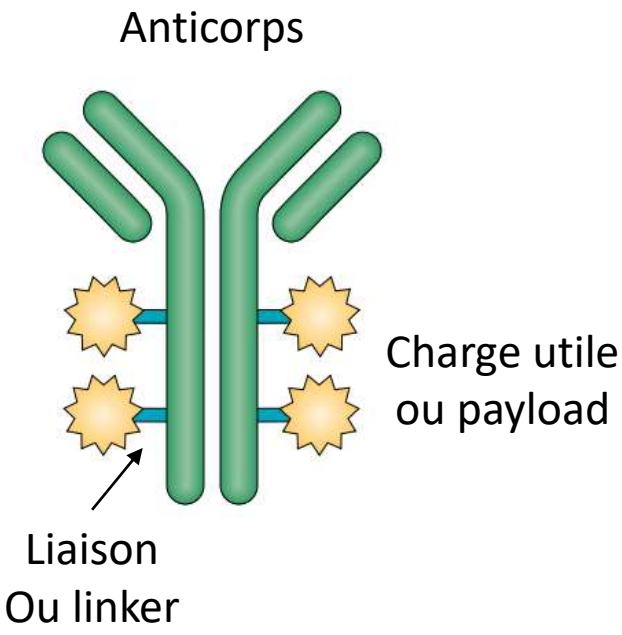
  Encorafénib et binimétinib chez des patients avec CBNPC *BRAF*^{V600E} métastatique

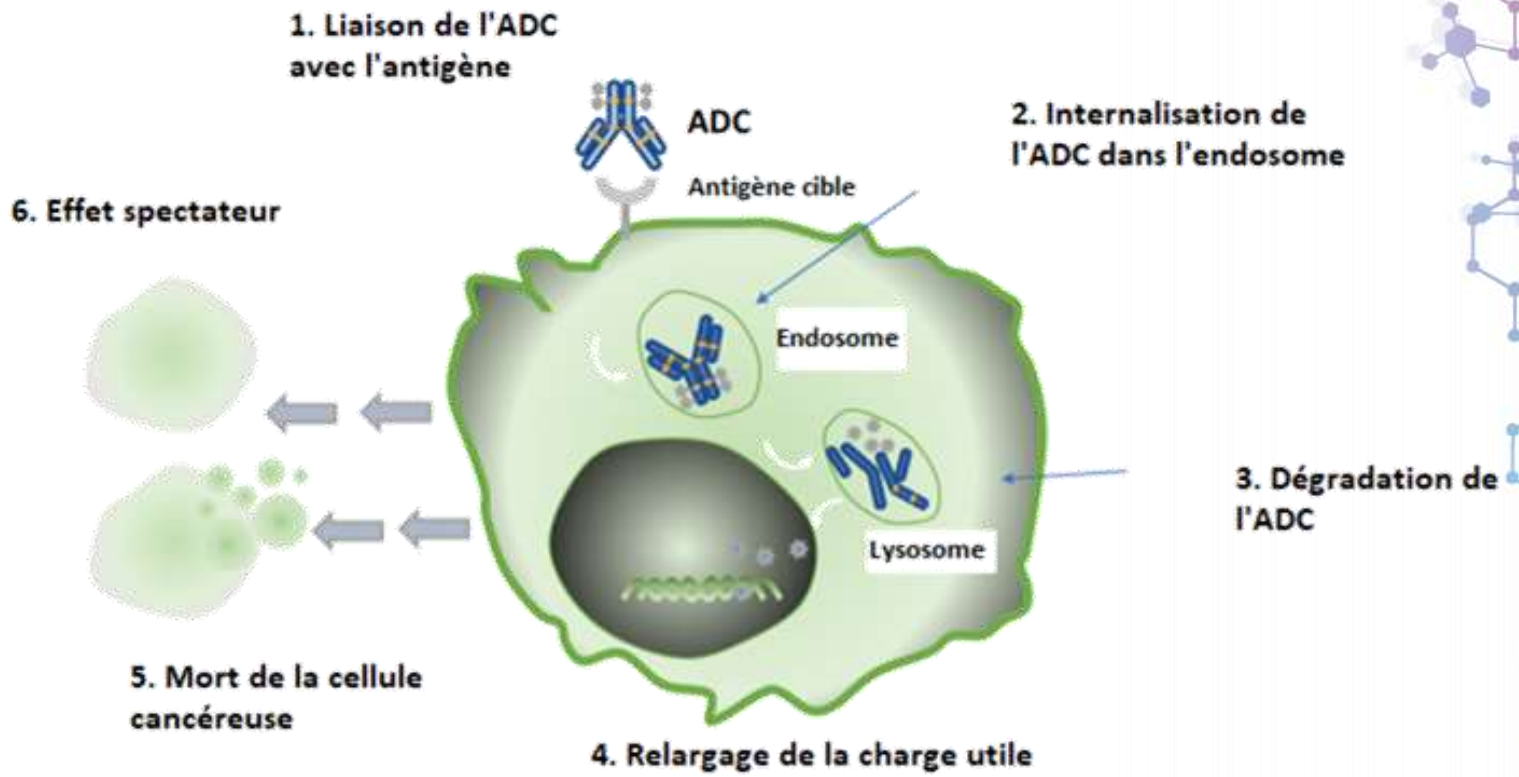


Hors AMM ; Données non validées par les Autorités de Santé à ce jour

GJ. Riely et al., ASCO® 2023, Abs. #9018

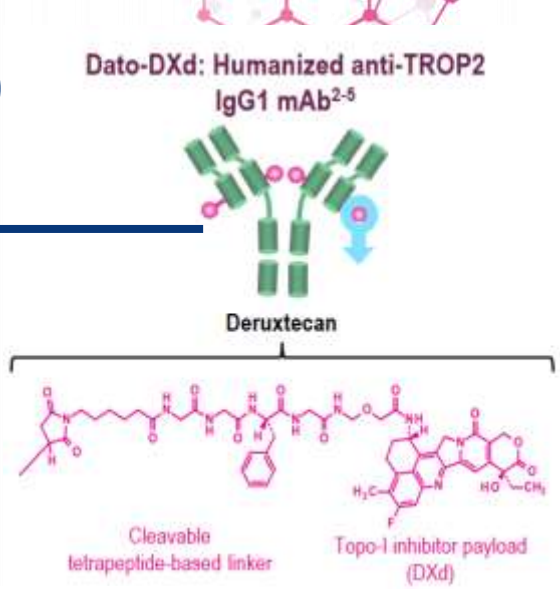
ADC Antibody Drug Conjugated ou anticorps conjugué





Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung01 Datopotamab deruxtecan (Dato-DXd) *vs* docetaxel chez CBNPC avancés/méta pré-traités



- **Phase 3 randomisée en ouvert**

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m² Q3W
(N=305)

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Dual Primary Endpoints
- PFS by BICR
- OS

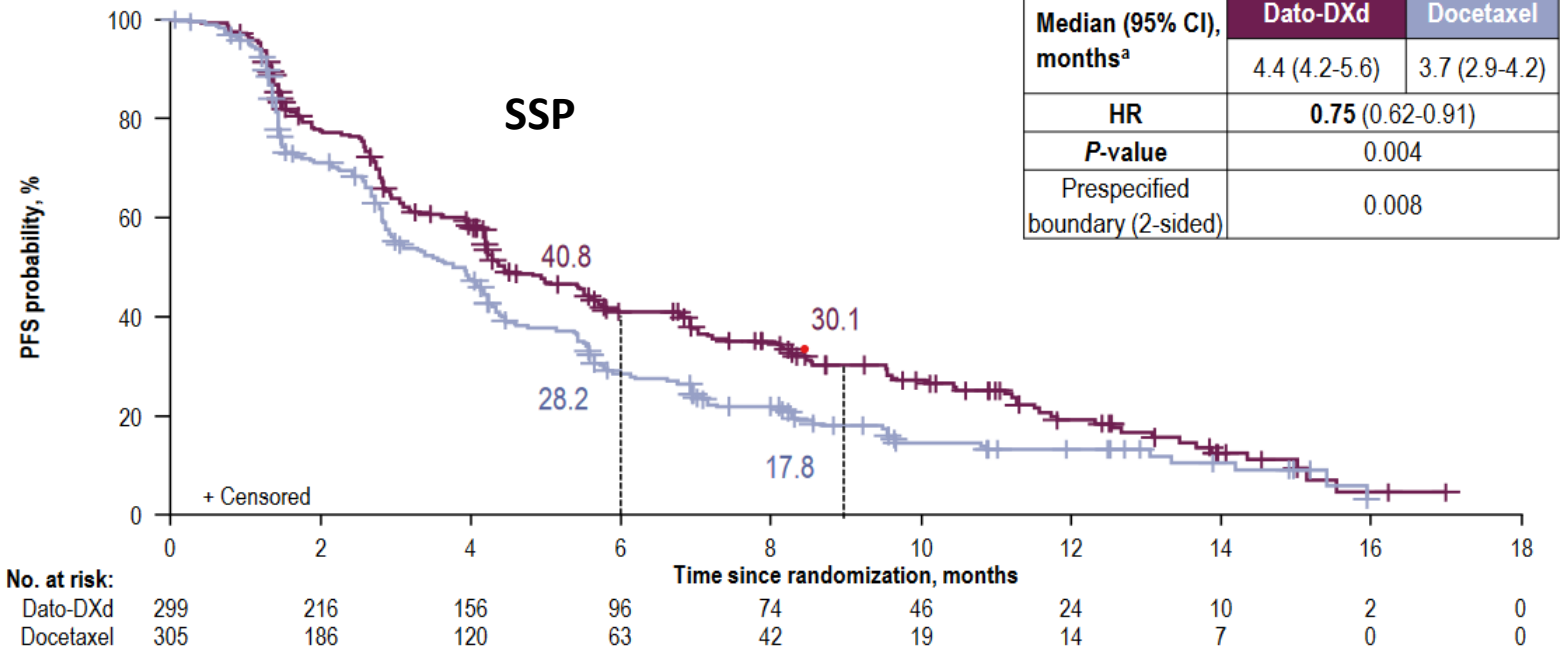
Secondary Endpoints
- ORR by BICR
- DOR by BICR
- Safety

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung01
Survie sans progression et survie globale en ITT

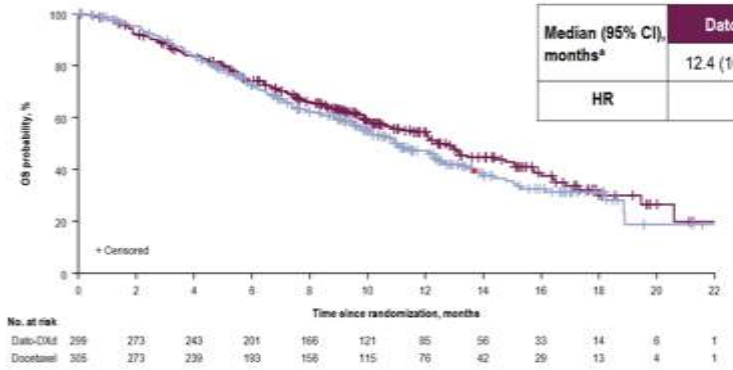
SSP



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

SG immature



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

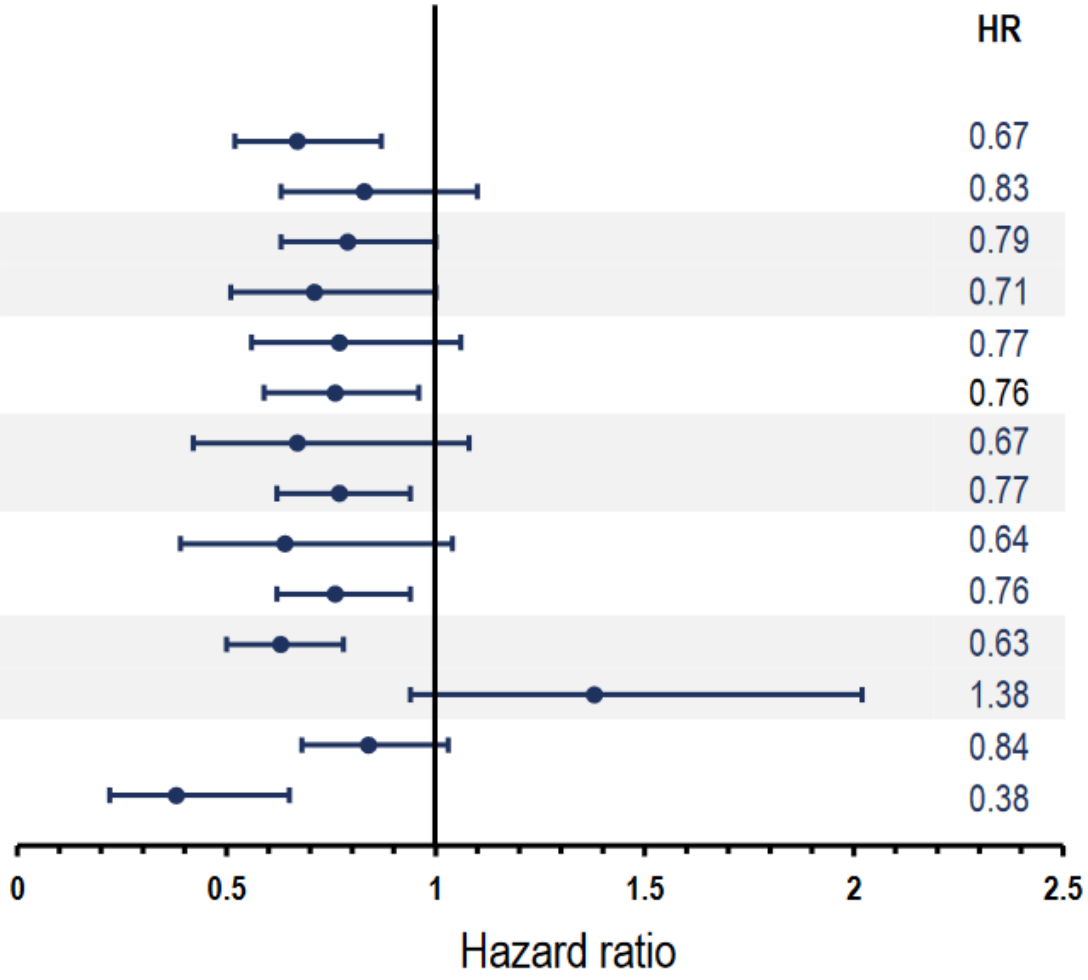
Information fraction at interim analysis (events/total events required): **74%**.

Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung01
SSP en sous-groupes

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38

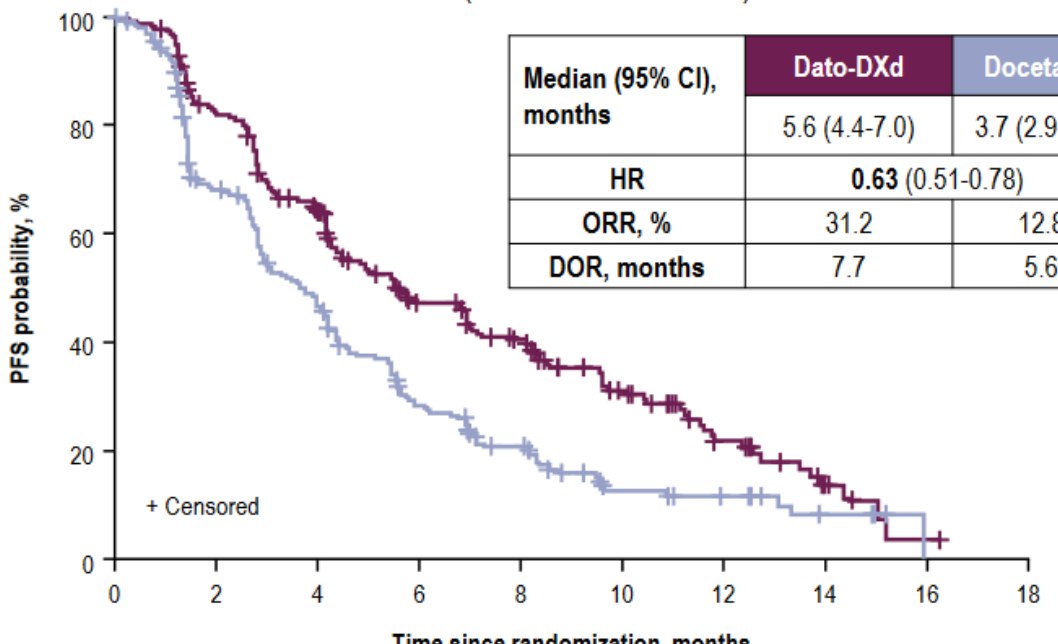


Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung01
SSP en sous-groupes

Non-squamous
(with and without AGAs)

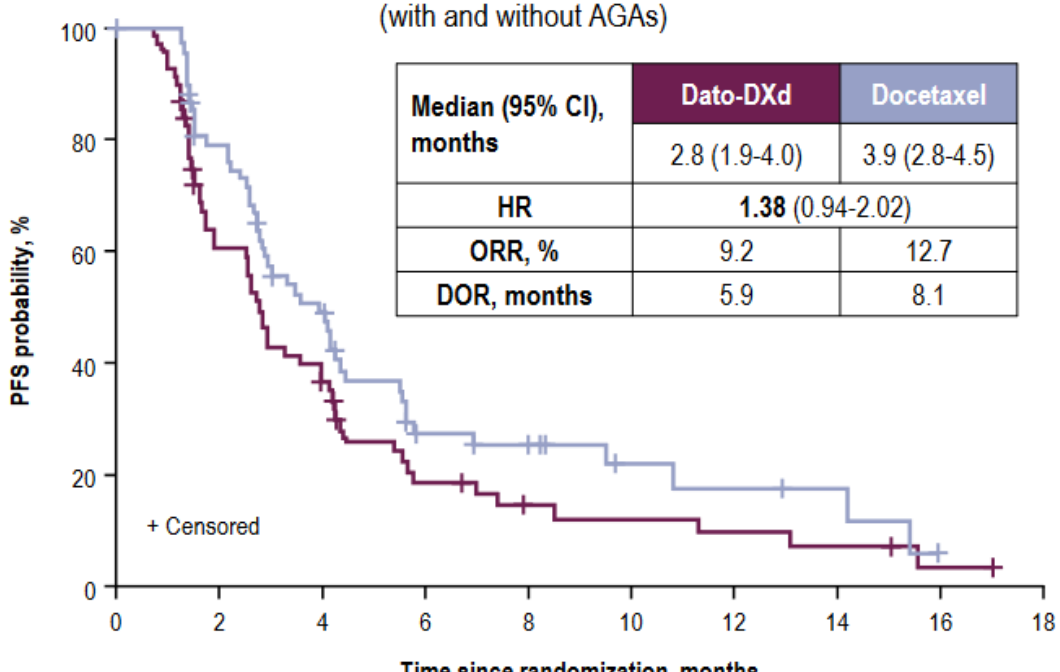
Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6



No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous
(with and without AGAs)

Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1



No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung01
Tolérance

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[a]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

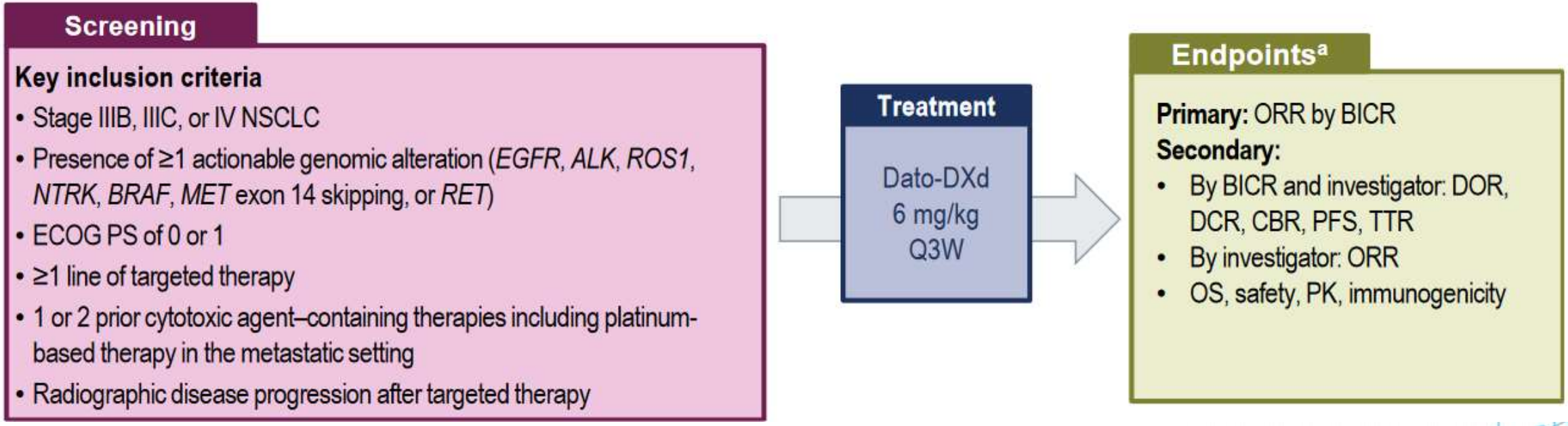
AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

Lisberg AE, et al. Ann Oncol 2023;34(suppl):Abstr LBA12

TROPION-Lung05

Datopotamab deruxtecan (Dato-DXd) chez les CBNPC avec addiction oncogénique pré-traités

- **Essai de phase 2 mono-bras**



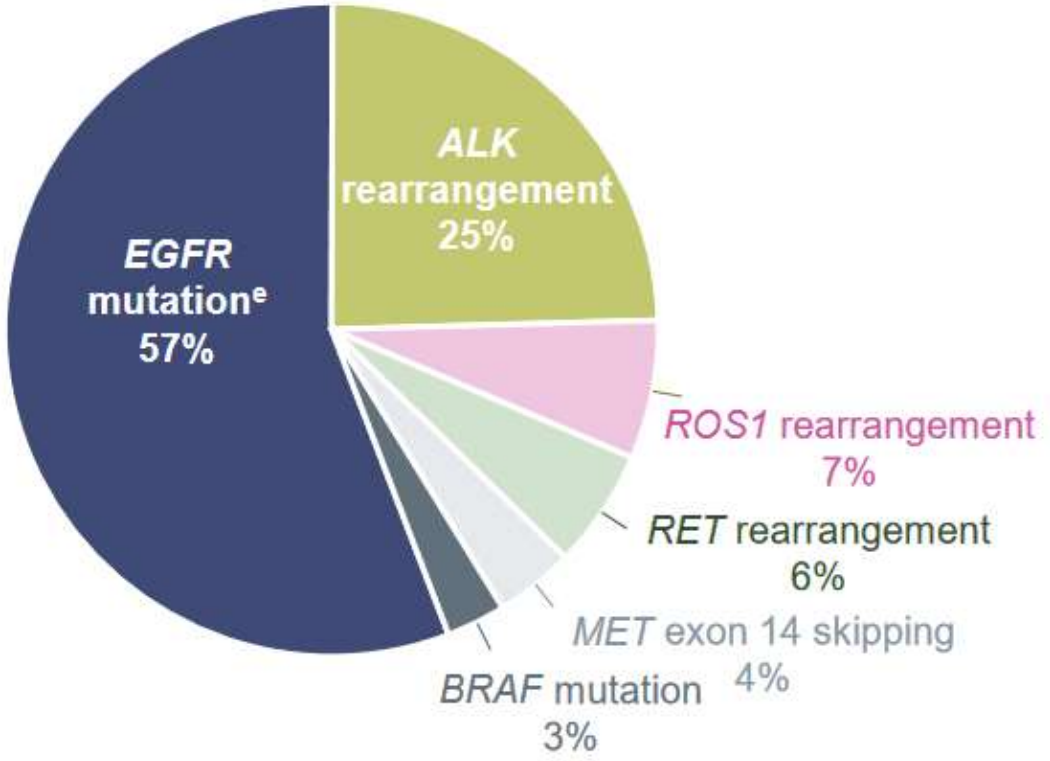
Hors AMM ; Données non validées par les Autorités de Santé à ce jour

Paz-Ares L, et al. Ann Oncol 2023;34(suppl):Abstr 1314MO

TROPION-Lung05
Caractéristiques des 137 patients inclus

- **Essai de phase 2 mono-bras**

Prior lines of therapy, n (%)	137 (100)
≥3 prior lines of therapy for adv/met disease	98 (72)
Prior platinum chemotherapy	137 (100)
Prior anti–PD-1/anti–PD-L1 immunotherapy	49 (36)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)



Paz-Ares L, et al. Ann Oncol 2023;34(suppl):Abstr 1314MO

TROPION-Lung05
Tolérance

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

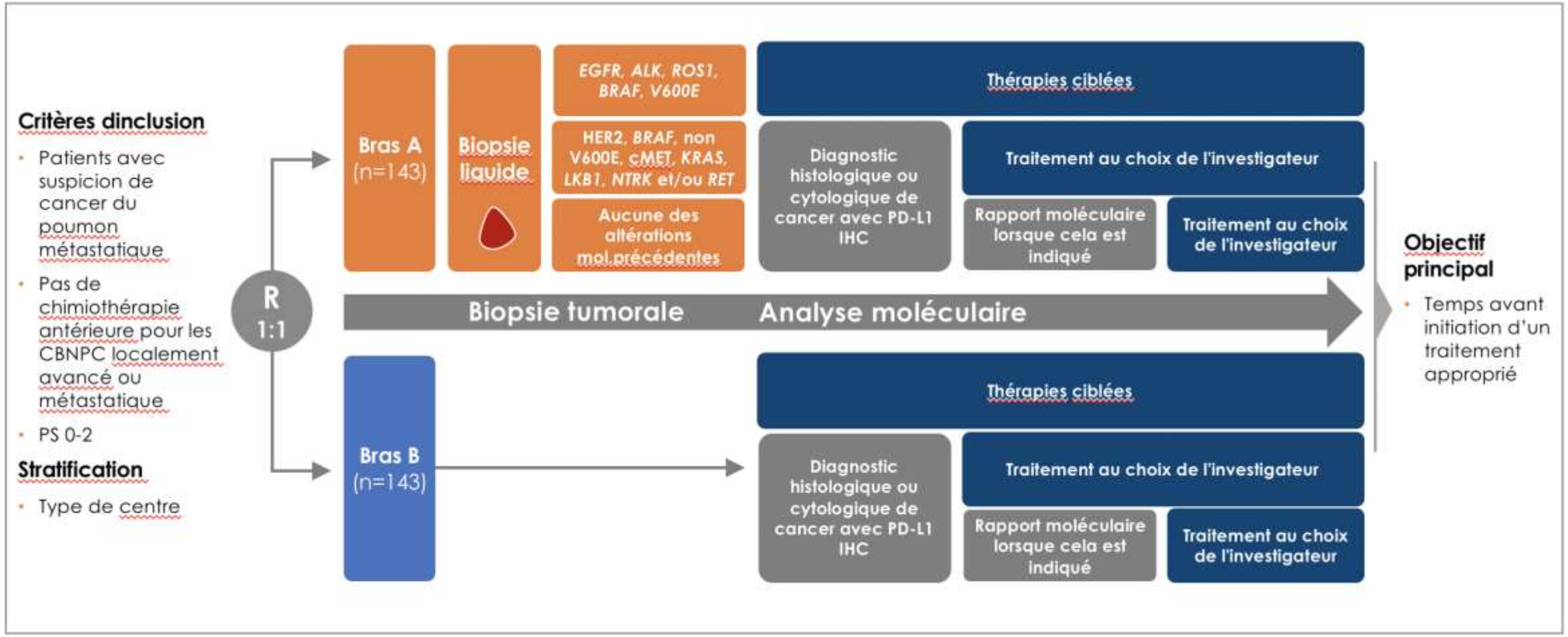
- **47% d'EI de grade ≥ 3**
- **29% d'EI liés au traitement de grade ≥ 3**

Événements indésirables d'intérêt

n (%)	Total	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (66)	45 (33)	30 (22)	15 (11)
Ocular surface toxicity[e]	36 (26)	26 (19)	7 (5)	3 (2)[f]
IRR	22 (16)	15 (11)	7 (5)	0
Adjudicated drug-related ILD	5 (4)	1 (1)	3 (2)	1 (1)[g]

Paz-Ares L, et al. Ann Oncol 2023;34(suppl):Abstr 1314MO

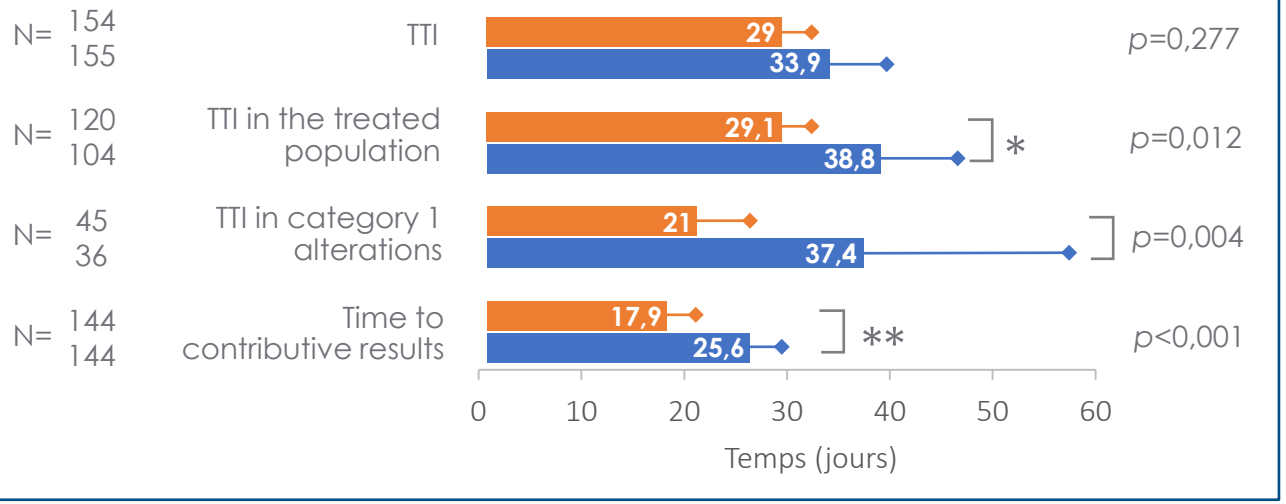
Essai randomisé de phase III évaluant la pertinence clinique d'une biopsie liquide précoce chez des patients avec suspicion de cancer bronchique métastatique : Étude LIBELULE



A. Swalduz et al., ASCO ® 2023, Abs. #9019

Étude LIBELULE

- Temps avant initiation du traitement



- Temps médian avant initiation du traitement
  - **29** jours (IC95% 25,9-32,1) dans bras A *vs* **33,9** (IC95% 28,4-39,5) dans bras B
  - **Il était de 9,7 jours plus court dans le bras A pour ceux ayant eu un traitement systémique, 16,4 jours plus court pour la catégorie 1 (addiction ciblable dès L1)**
  - **Temps avant résultats d'une analyse génomique contributive réduite de 7,7 jours**
  - **Réduction de moitié de la proportion de patients débutant un traitement sans résultats de biologie moléculaire (7,4% bras A *vs* 13,3% bras B)**

A. Swalduz et al., ASCO ® 2023, Abs. #9019

Merci de votre attention

9e ÉDITION

JOURNÉES DU **GFCO 2023**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO