Actualités en oncologie thoracique 2024

28 Novembre 2024

Novotel Bordeaux Lac

Dr Nicolas MILHADE

1ère Rencontre de radiothérapie en Nouvelle Aquitaine

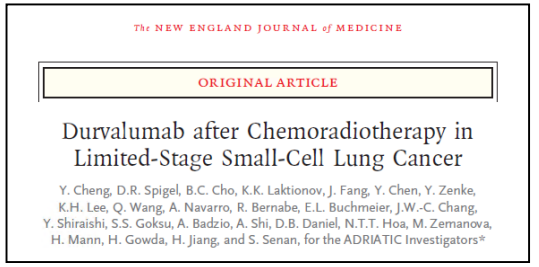
Liens d’intérêts

- Pfizer : congrès
- Astrazeneca et Takeda : board scientifique

Essais qui changent les pratiques

2024 ASCO ANNUAL MEETING

- 1- **ADRIATIC** : CPC stade III RTCT + Durvalumab

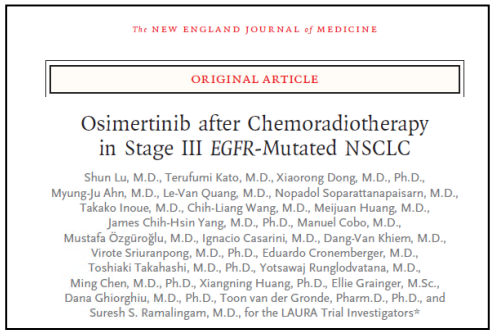

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer

Y. Cheng, D.R. Spigel, B.C. Cho, K.K. Laktionov, J. Fang, Y. Chen, Y. Zenke, K.H. Lee, Q. Wang, A. Navarro, R. Bernabe, E.L. Buchmeier, J.W.-C. Chang, Y. Shiraishi, S.S. Goksu, A. Badzio, A. Shi, D.B. Daniel, N.T.T. Hoa, M. Zemanova, H. Mann, H. Gowda, H. Jiang, and S. Senan, for the ADRIATIC Investigators*

- 2- **LAURA** : EGFR stade III RTCT + Osimertinib

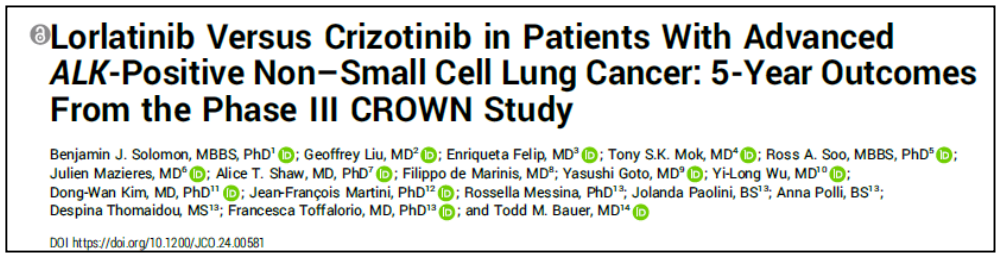

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC

Shun Lu, M.D., Terufumi Kato, M.D., Xiaorong Dong, M.D., Ph.D., Myung-Ju Ahn, M.D., Le-Van Quang, M.D., Nopadol Soparattanapaisarn, M.D., Takako Inoue, M.D., Chih-Liang Wang, M.D., Meijuan Huang, M.D., James Chih-Hsin Yang, M.D., Ph.D., Manuel Cobo, M.D., Mustafa Özgüroğlu, M.D., Ignacio Casarini, M.D., Dang-Van Khiem, M.D., Virote Sriuranpong, M.D., Ph.D., Eduardo Cronemberger, M.D., Toshiaki Takahashi, M.D., Ph.D., Yotsawaj Runglodvatana, M.D., Ming Chen, M.D., Ph.D., Xiangning Huang, Ph.D., Ellie Grainger, M.Sc., Dana Ghiorghiu, M.D., Ph.D., Toon van der Gronde, Pharm.D., Ph.D., and Suresh S. Ramalingam, M.D., for the LAURA Trial Investigators*

- 3- **CROWN** : 1L ALK Lorlatinib à 5 ans


Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

Benjamin J. Solomon, MBBS, PhD[1]; Geoffrey Liu, MD[2]; Enriqueta Felip, MD[3]; Tony S.K. Mok, MD[4]; Ross A. Soo, MBBS, PhD[5]; Julien Mazieres, MD[6]; Alice T. Shaw, MD, PhD[7]; Filippo de Marinis, MD[8]; Yasushi Goto, MD[9]; Yi-Long Wu, MD[10]; Dong-Wan Kim, MD, PhD[11]; Jean-François Martini, PhD[12]; Rossella Messina, PhD[13]; Jolanda Paolini, BS[13]; Anna Polli, BS[13]; Despina Thomaidou, MS[13]; Francesca Toffalorio, MD, PhD[13]; and Todd M. Bauer, MD[14]

DOI https://doi.org/10.1200/JCO.24.00581

ADRIATIC STUDY DESIGN

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization

Spigel et al. Presented at ASCO 2024, Presentation LBA5

BASELINE CHARACTERISTICS

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

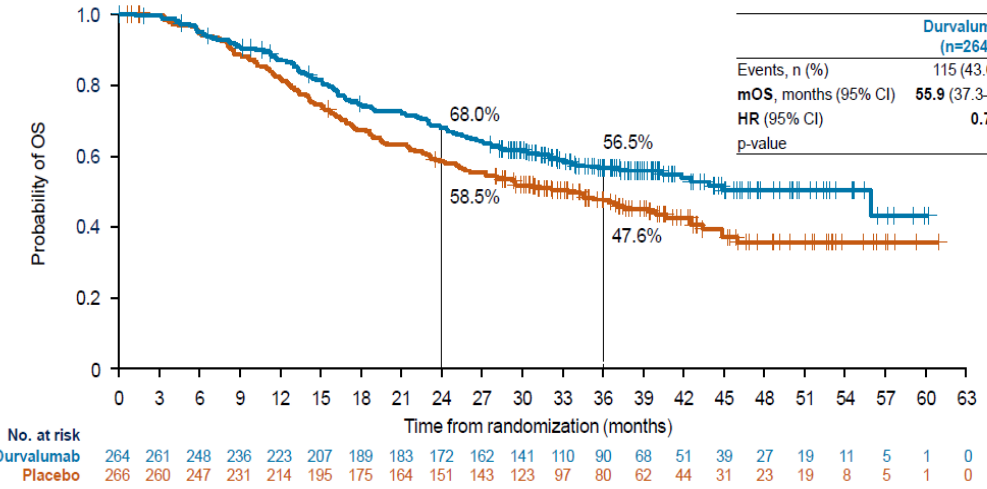
*Based on the first cycle of chemotherapy.
AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response; SD, stable disease.

Spigel et al. Presented at ASCO 2024, Presentation LBA5

Résultats PFS et OS

OVERALL SURVIVAL (DUAL PRIMARY ENDPOINT)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

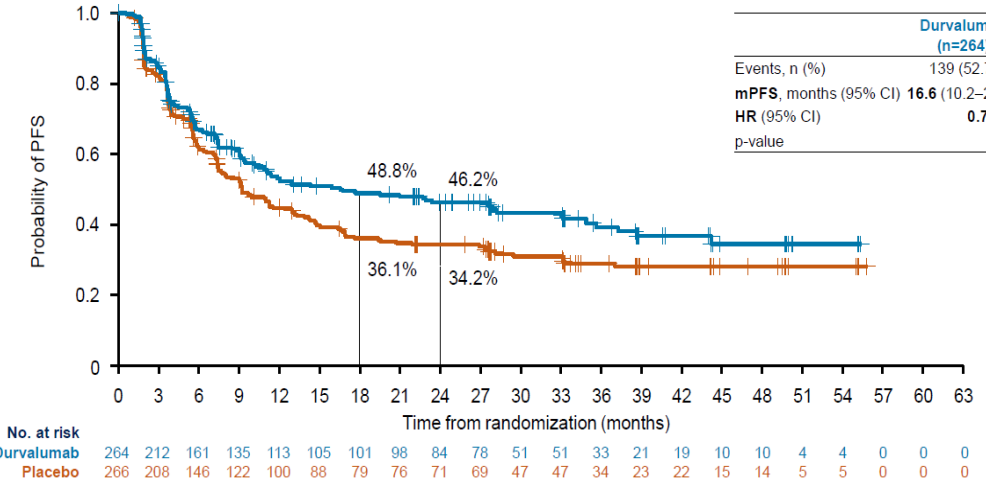
No. at risk																					
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints
CI, confidence interval; mOS, median OS; NE, not estimable.

Spigel et al. Presented at ASCO 2024, Presentation LBA5

PROGRESSION-FREE SURVIVAL* (DUAL PRIMARY ENDPOINT)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																					
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.
PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).
mPFS, median PFS.

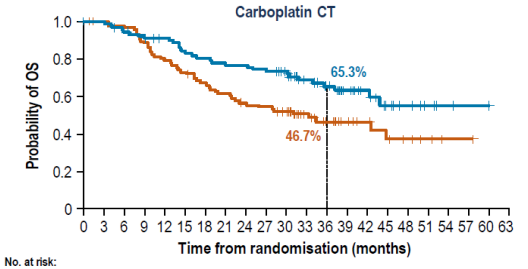
Spigel et al. Presented at ASCO 2024, Presentation LBA5

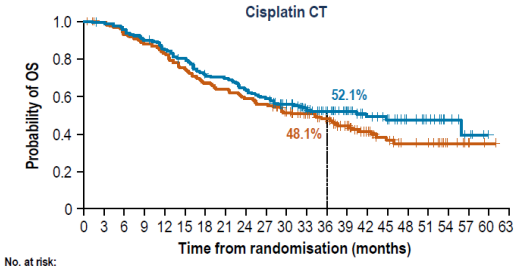
Analyse en sous groupe

BARCELONA 2024 ESMO congress

Carboplatin and cisplatin CT subgroups – OS

	Carboplatin CT		Cisplatin CT		ITT	
	D (n = 91)	P (n = 88)	D (n = 173)	P (n = 178)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (42.5–NE)	33.4 (21.7–NE)	41.9 (27.7–NE)	34.3 (25.4–40.7)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.3	46.7	52.1	48.1	56.5	47.6
HR (95% CI)	0.56 (0.35–0.89)*		0.82 (0.61–1.10)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.55 (0.35–0.87)‡		0.81 (0.60–1.08)‡		–	



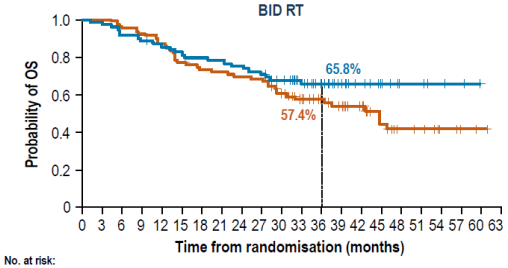


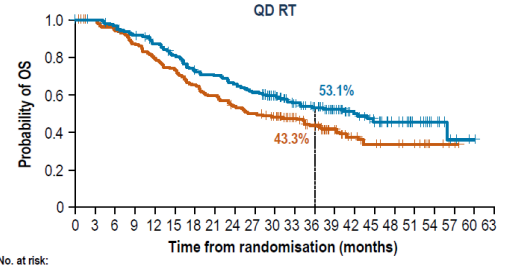
*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.17.

Senan et al. Presented at ESMO meeting 2024, Presentation LBA41

BID and QD RT subgroups – OS

	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (NE–NE)	44.8 (29.4–NE)	41.9 (32.0–NE)	26.1 (21.7–36.8)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.8	57.4	53.1	43.3	56.5	47.6
HR (95% CI)	0.68 (0.40–1.14)*		0.72 (0.55–0.96)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡		–	



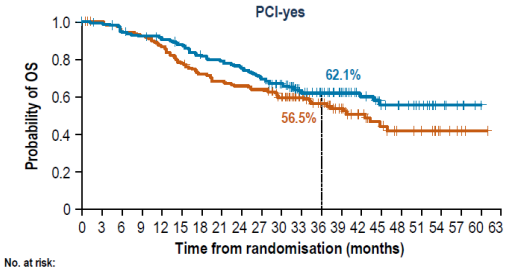


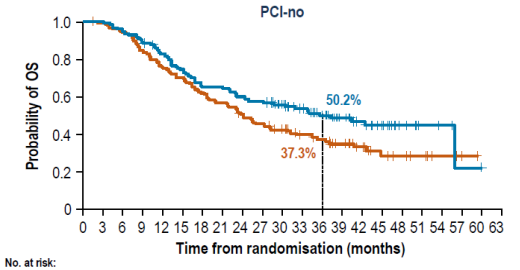
*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.95.

Senan et al. Presented at ESMO meeting 2024, Presentation LBA41

PCI-yes and PCI-no subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	





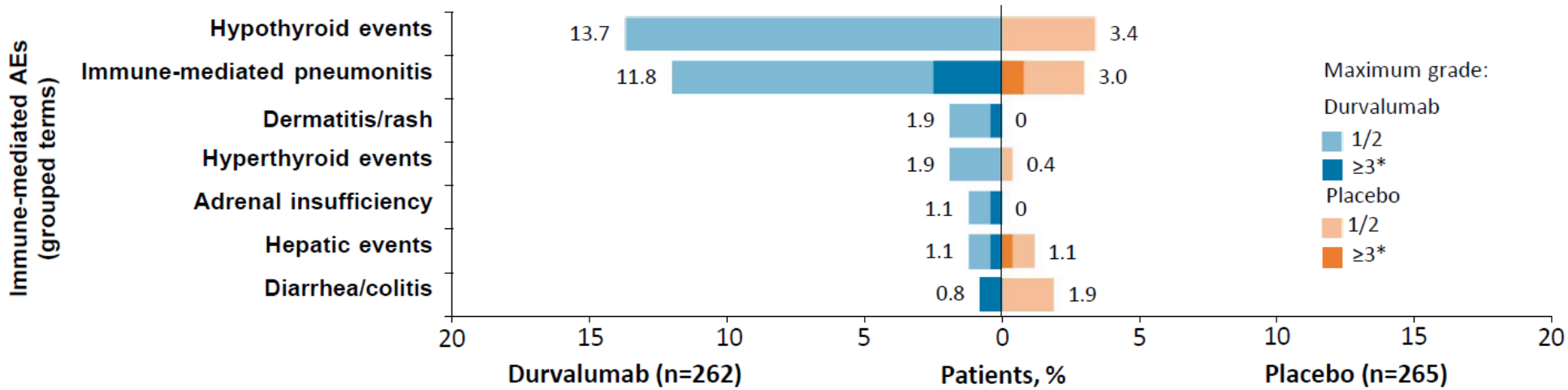
CI, confidence interval; NE, not estimable; NR, not reached; yr, year.

*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.96.

Senan et al. Presented at ESMO meeting 2024, Presentation LBA41

Immune-mediated AEs: summary

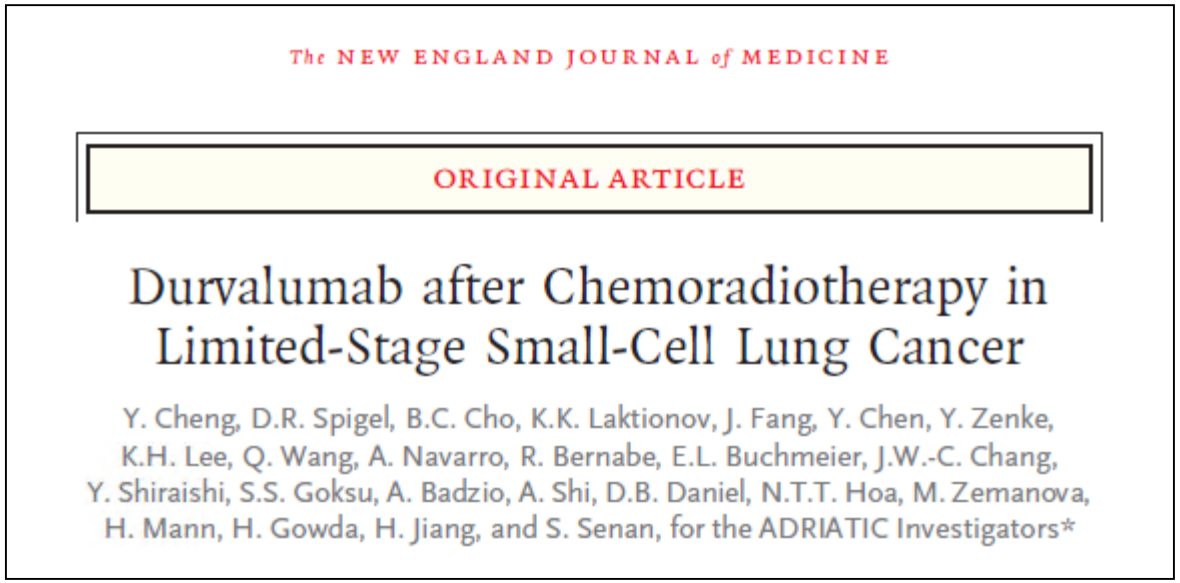
Immune-mediated AEs, %	Durvalumab (n=262)	Placebo (n=265)
Any grade	32.1	10.2
Maximum grade 3/4	5.3	1.5
Serious	9.2	3.0
Leading to death	0.4	0
Leading to treatment discontinuation	7.3	2.6



Events reported in ≥1% of patients in either treatment arm are shown. *All grade ≥3 imAEs were grade 3/4 except one case of grade 5 immune-mediated pneumonitis in the durvalumab arm.

Iyengar et al. Presented at ASTRO meeting 2024, Presentation LBA13

A retenir d'ADRIATIC



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Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer

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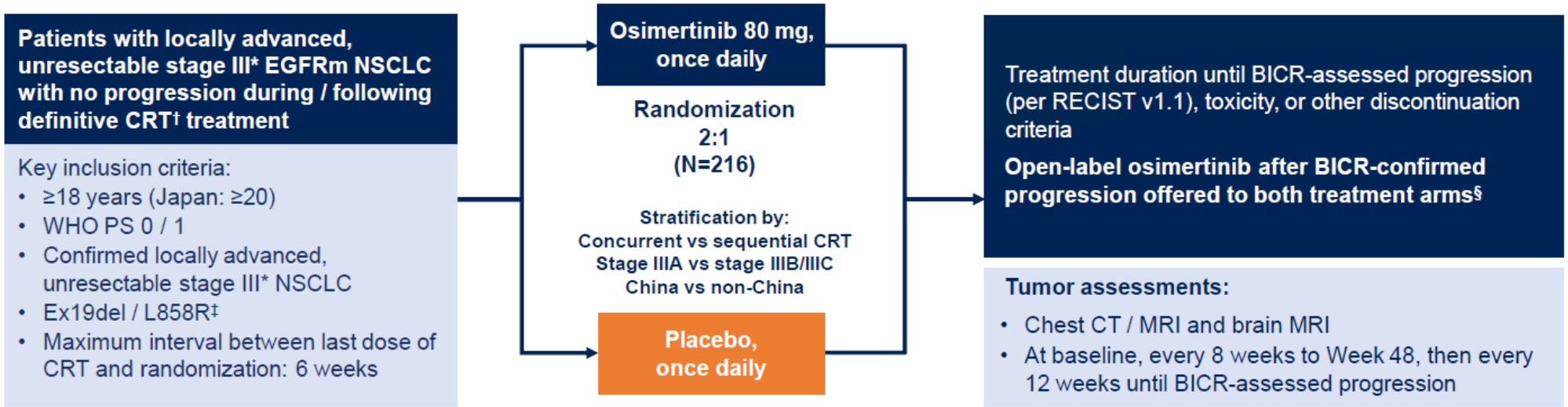
2024 ASCO ANNUAL MEETING

BARCELONA 2024 ESMO congress

ASTRO 2024

Bénéficie en OS et PFS => Nouveau standard pour les CPC stade III non opérables

LAURA PHASE 3 DOUBLE-BLIND STUDY DESIGN



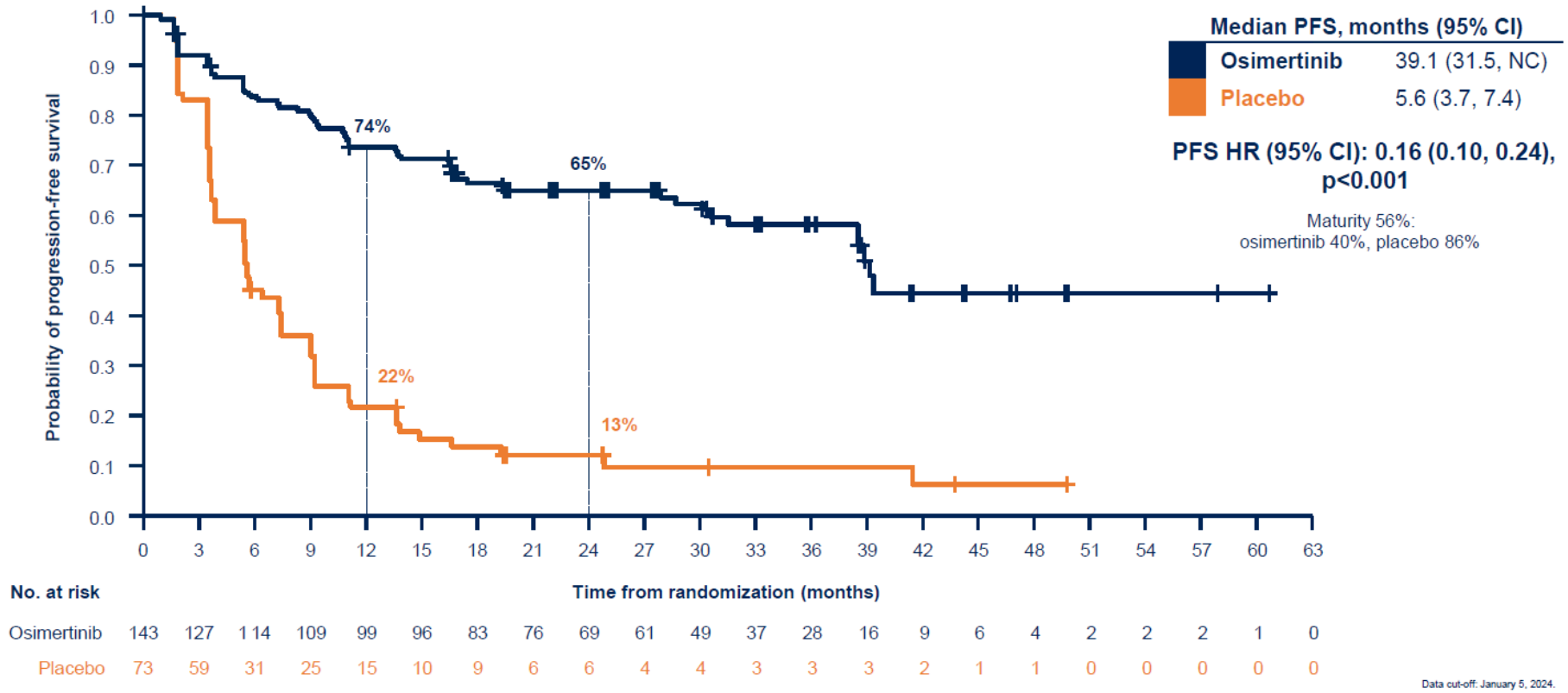
Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

BASELINE CHARACTERISTICS

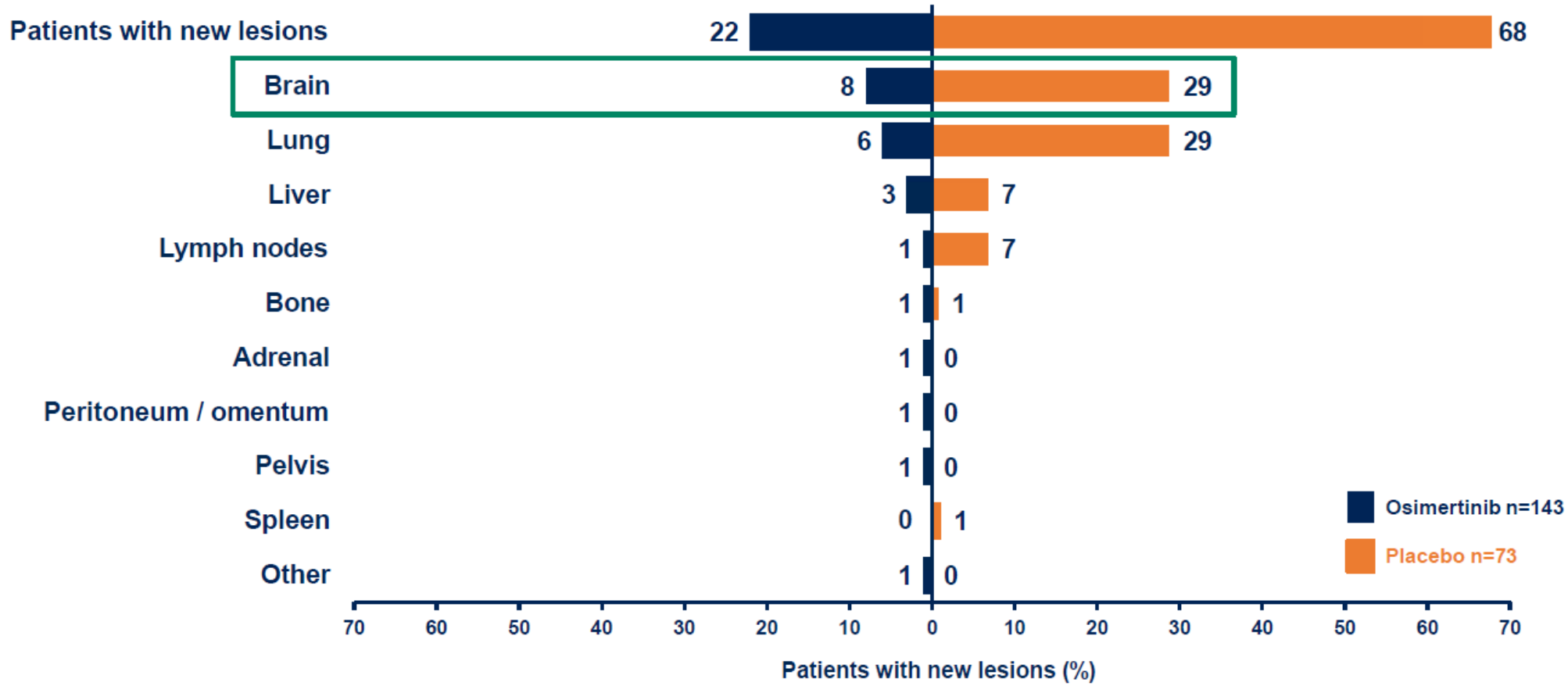
Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomization:* Ex19del / L858R	52 / 48†	59 / 41
Type of CRT: concurrent CRT / sequential CRT	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR:‡ mean (SD), mm	33 (18)	36 (17)
Pre-CRT PET scan: yes / no	55 / 45	45 / 55

PROGRESSION-FREE SURVIVAL BY BICR



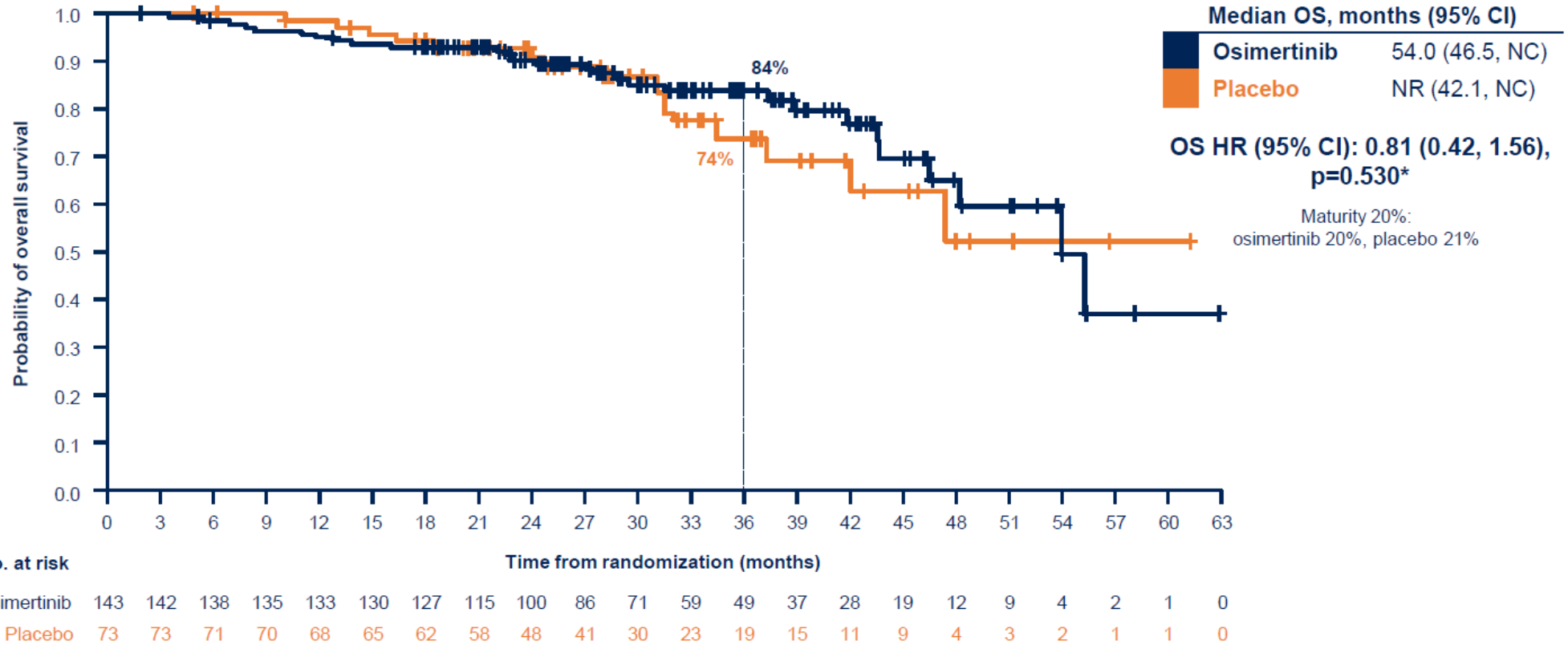
Data cut-off: January 5, 2024.

SITES OF NEW LESIONS BY BICR



INTERIM ANALYSIS OF OVERALL SURVIVAL

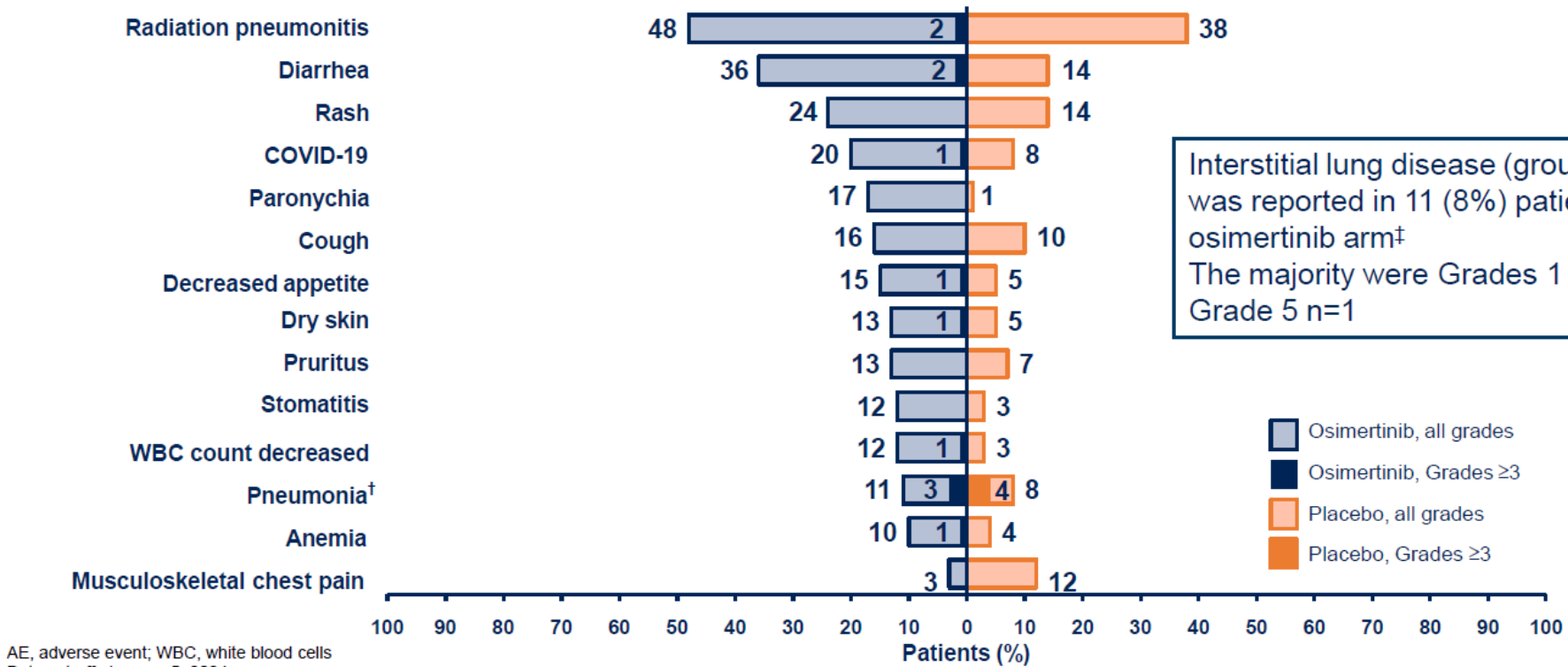
- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

ALL-CAUSALITY ADVERSE EVENTS (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

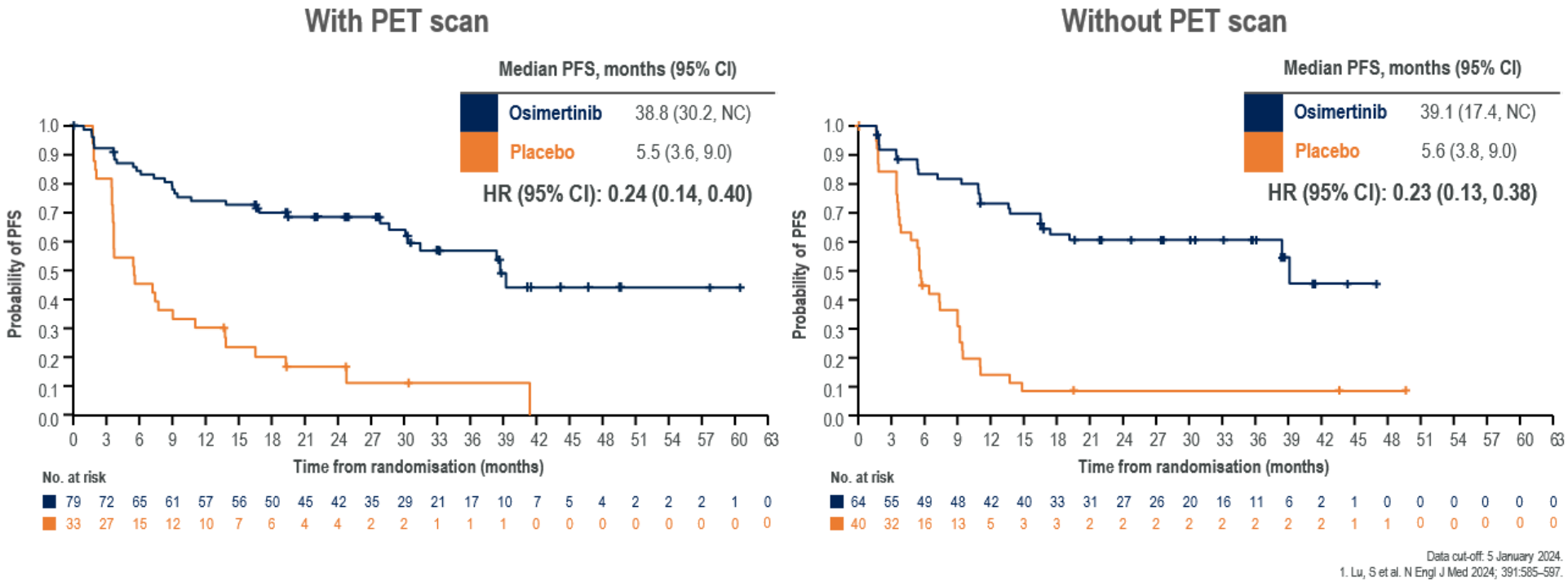
AE, adverse event; WBC, white blood cells
Data cut-off: January 5, 2024.

Baseline characteristics

Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Pre-CRT PET scan: yes / no	55 / 45	45 / 55
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomisation:* Ex19del / L858R	52 / 48	59 / 41
Type of CRT: cCRT / sCRT	92 / 8	85 / 15
Best response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR: mean (standard deviation), mm	33 (18)	36 (17)
CNS metastases at baseline per neuroradiologist BICR:† n (%)	14 (10)	5 (7)
CNS metastases at baseline per neuroradiologist BICR† and received pre-CRT PET scan: n (%)	8 (6)	3 (4)

BICR-assessed PFS by pre-CRT PET scan

- Pre-CRT PET-CT staging scans were recommended but not mandatory, since diagnosis of unresectable stage III disease prior to CRT was determined by the investigator per local clinical practice
- PFS benefit with osimertinib vs placebo was consistent with or without pre-CRT staging by PET scan, and consistent with the primary PFS data[1]



Data cut-off: 5 January 2024.

1. Lu, S et al. N Engl J Med 2024; 391:585–597.

A retenir de LAURA

Bénéfice PFS et PFS cérébrale
Pas significatif sur OS mais cross over

- **Surtraitement** des patients guéris par RTCT (ADNc)
- Toxicité d'un TKI qui pourrait être retardé : **QoL**

Discussion RCP et avec le patient

RÉPUBLIQUE FRANÇAISE
HAS HAUTE AUTORITÉ DE SANTÉ | Développer la qualité dans le champ sanitaire, social et médico-social

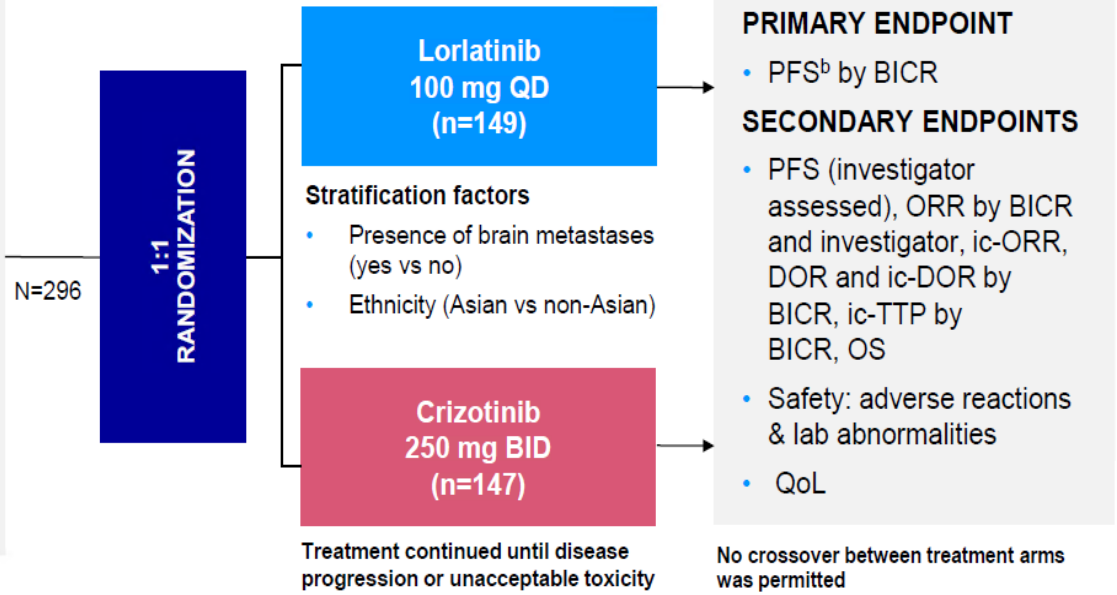
Décision n° 2024.0293/DC/SEM du 17 octobre 2024 du collège de la Haute Autorité de santé portant autorisation d'accès précoce de la spécialité TAGRISSO (osimertinib)

Accès précoce ✓ *AMM à venir*

CROWN: Study Design

KEY ELIGIBILITY CRITERIA

- Stage IIIB/IV ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx
- No prior systemic treatment for metastatic disease
- ECOG PS 0–2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required
- Patients with severe acute or chronic psychiatric conditions were excluded[a]



[a]Including recent (within the past year) or active suicidal ideation or behavior.
[b]Defined as the time from randomization to RECIST-defined progression or death due to any cause.
ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Groups performance status; ic-DOR, intracranial duration of response; ic-ORR, intracranial objective response rate; ic-TTP, intracranial time to tumor progression; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, each day; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number: NCT03052608 (Study B7461006); 1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029.

Recommandations AURA

1ere ligne ALK M+ :

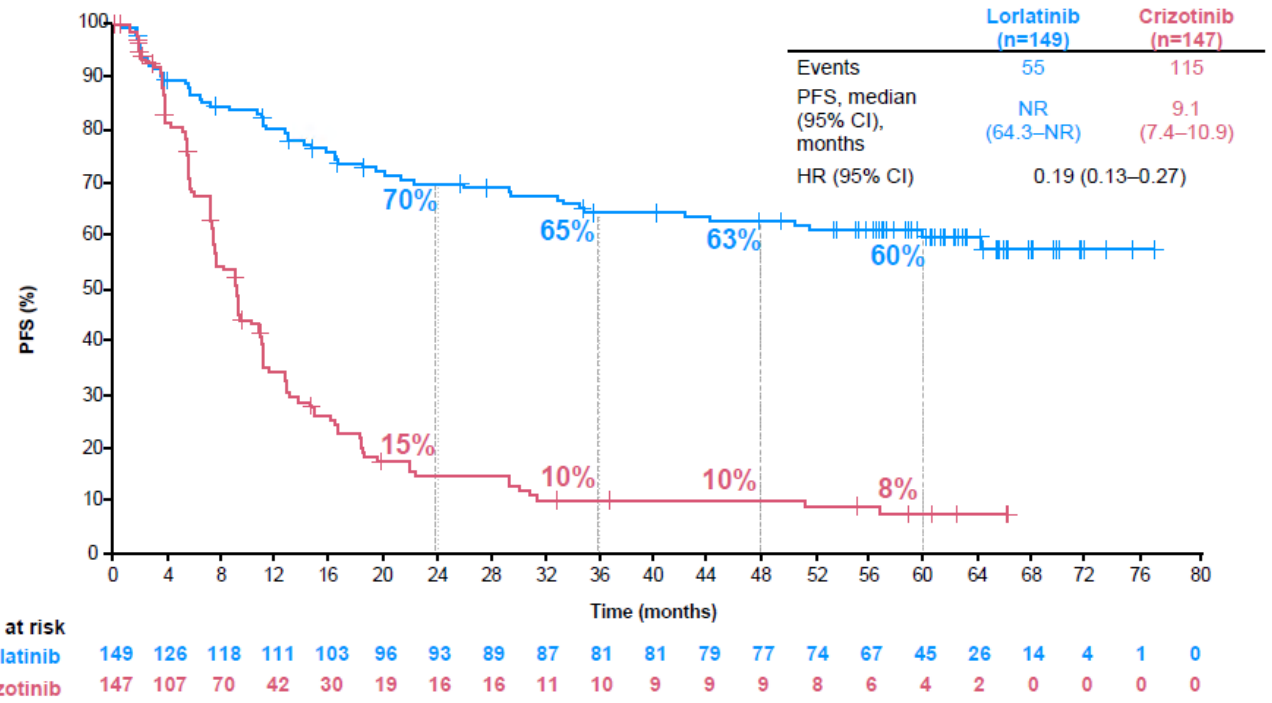
2ème G
- **Alectinib** (ALEX)
- **Brigatinib** (ALTA-1L)

3ème G
- **Lorlatinib** (CROWN)

Etude	Bras	N	Médiane de PFS	HR PFS	Tx PFS 1 an	Tx sans progression cérébrale à 1 an	%G3-5
ALEX Peters, NEJM, 2017 Camidge, JTO, 2019 Mok, ESMO 2019, #3850	Alectinib	152	34,8 (17,7-NE)	0,43 [0,32-0,58]	68,4% [61,0-75,9]	-	45%
	Crizotinib	151	10,9 (9,1-12,9)		48,7% [40,4-56,9]	-	51%
ALTA-1L Camidge, NEJM, 2018 Camidge, JTO, 2021	Brigatinib	137	24,0 (18,5-43,2)	0,48 [0,35-0,66]	67% [56-75]	78% (68-85)	61%
	Crizotinib	138	11,1 (9,1-13,0)		43 [32-53]	61% (50-71)	78%
CROWN Shaw, NEJM, 2020 SolomonB, Lancet Respir Med, 2022	Lorlatinib	149	NR (NR-NR)	0,28 [0,19-0,41]	78% [70-84]	96% (91-98)	72%
	Crizotinib	147	9,3 (7,6-11,1)		39% [40-38]	60% (49-69)	56%

Tableau 8 – Comparaison des essais randomisés comparant lmes ITK en 1ère ligne de CBNPC métastatique avec réarrangement de *ALK*.

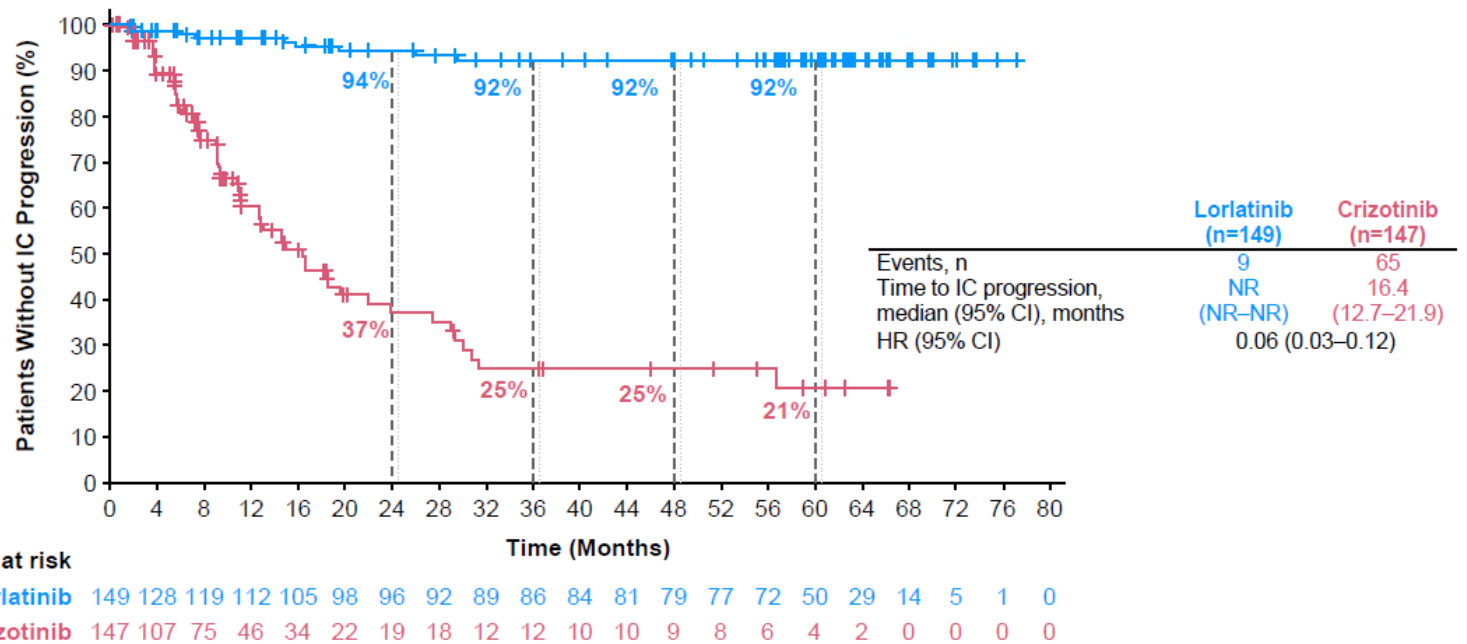
CROWN: PFS by Investigator Assessment (ITT Population)



After 5 years of follow-up, the median progression-free survival with lorlatinib treatment has not been reached, with an investigator-assessed PFS rate of 60%, with only 6 additional PFS events occurring between Year 3 and Year 5.
This PFS benefit, which exceeds 5 years, is the longest reported PFS in advanced NSCLC to date

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by investigator assessment: lorlatinib, 60.2 months; crizotinib, 55.1 months.
CI, confidence interval; HR, hazard ratio; NR, not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival.
Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Time to IC Progression[a] by Investigator Assessment[1] (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR–NR)	16.4 (12.7–21.9)
HR (95% CI)	0.06 (0.03–0.12)	

Lorlatinib delayed intracranial progression versus crizotinib, with no new IC events occurring between Year 3 and Year 5.

A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.

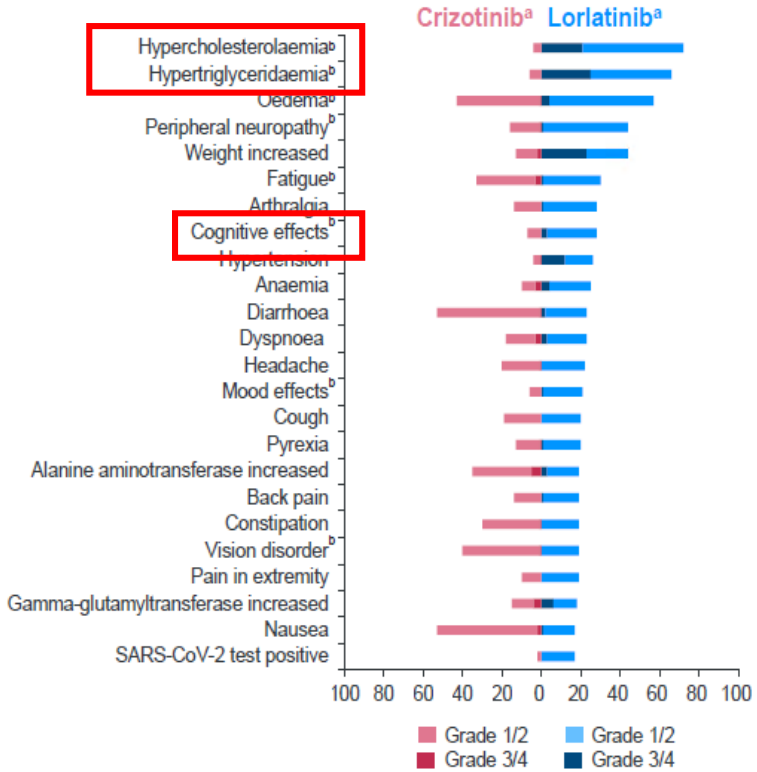
[a]Time to CNS progression was defined as the time from randomization to the first objective progression of CNS disease (either new brain metastases or progression of existing brain metastases). Tumour assessments, including brain magnetic resonance imaging, have been performed every 8 weeks in all patients throughout the study. The secondary endpoint of intracranial time to progression was not part of the statistical testing hierarchy.[1,2]

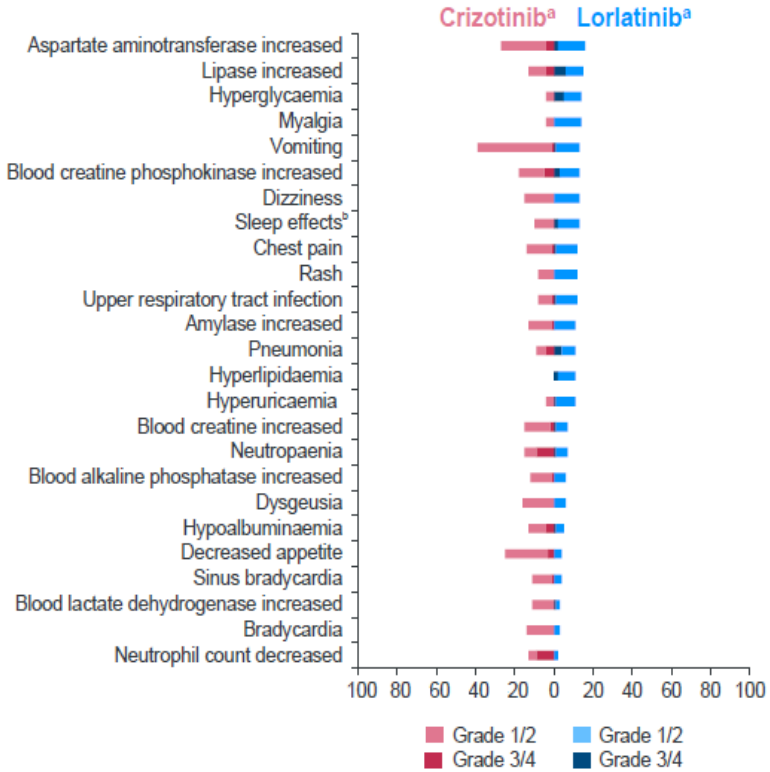
Data cutoff: October 31, 2023. Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.

CI, confidence interval; HR, hazard ratio; IC, intracranial; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018–2029.

Event, n (%)	Lorlatinib (n=149)	Crizotinib (n=142)
All-causalities AEs		
Any-grade AE	149 (100)	140 (99)
Grade 3/4 AE	115 (77)	81 (57)
Death	14 (9)	7 (5)
Any serious AE	65 (44)	45 (32)
AEs leading to temporary discontinuations	92 (62)	68 (48)
AEs leading to dose reduction	34 (23)	21 (15)
AEs leading to permanent treatment discontinuation	16 (11)	15 (11)
TRAEs		
Any-grade AE	145 (97)	133 (94)
Grade 3/4 AE	99 (66)	55 (39)
Death	2 (1)	0
Any serious AE	14 (9)	9 (6)
AEs leading to temporary discontinuations	58 (39)	51 (36)
AEs leading to dose reduction	31 (21)	19 (13)
AEs leading to permanent treatment discontinuation	8 (5)	8 (6)





The most common grade 3 and 4 adverse events in the lorlatinib-treated group were hypertriglyceridaemia (24.8%), increased weight (22.8%), hypercholesterolaemia (21.5%), and hypertension (12.1%)[1,2]

	Lorlatinib (n=149)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any CNS adverse events	58 (39)	34 (23)	16 (11)	8 (5)	0
Cognitive effects	38 (26)	23 (15)	10 (7)	5 (3)	0
Mood effects	26 (17)	14 (9)	10 (7)	2 (1)	0
Speech effects	8 (5)	6 (4)	1 (1)	1 (1)	0
Psychotic effects	7 (5)	5 (3)	1 (1)	1 (1)	0

Data are n (%).
Cognitive effects were any event from cognitive and attention disorders and disturbances, or deliria (including confusion), or mental impairment disorders.
Mood effects were any event from anxiety disorders and symptoms, or depressed mood disorders and disturbances, or manic and bipolar mood disorders and disturbances, or mood disorders and disturbances NEC, or personality disorders and disturbances in behaviour.
Speech effects were any event from speech and language abnormalities.
Psychotic effects were any event from narrow psychosis and psychotic disorders or PT of psychotic symptom.

A retenir de CROWN

- mPFS non atteinte à 5 ans
- Efficacité cérébrale +++
- Attention au profil de toxicité cardiaque et neurocognitive

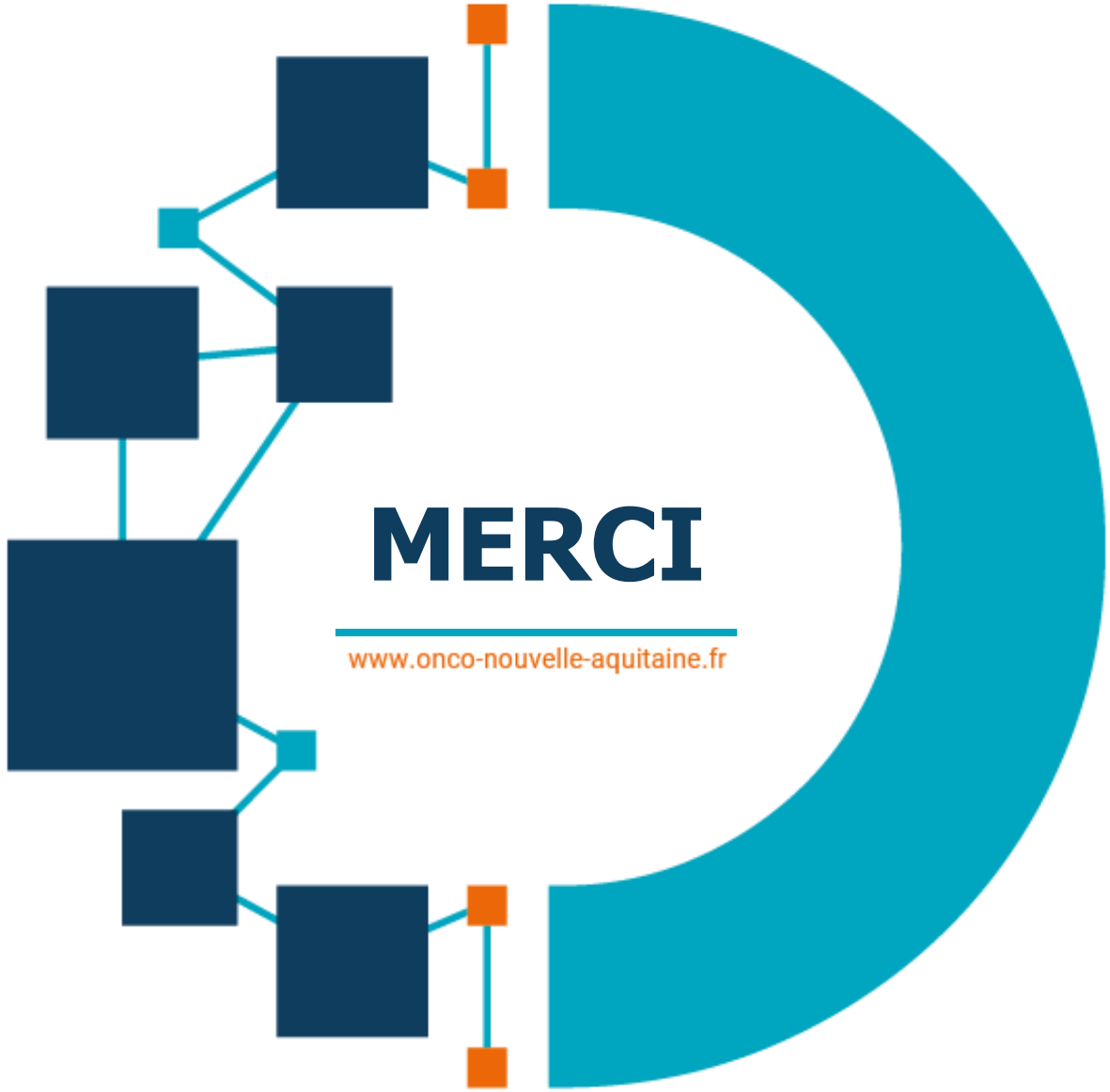
1 ère intention 1L ALK si pas de contre indication

TAKE HOME MESSAGE

1- ADRIATIC : DURVALUMAB en adjuvant pour les CPC stade III après RTCT AMM à venir

2- LAURA : OSIMERTINIB en adjuvant EGFR muté stade III après RTCT bénéfice en PFS, AMM à venir : Discussion au cas par cas

3- CROWN : 1ère ligne ALK : LORLATINIB en 1ère intention en l'absence de contre indication


MERCI
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ADRIATIC

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Durvalumab (N=264)	Placebo (N=266)
Median age (range) — yr	62 (28–84)	62 (28–79)
Male sex — no. (%)	178 (67.4)	188 (70.7)
Race — no. (%)†		
White	130 (49.2)	137 (51.5)
Asian	131 (49.6)	121 (45.5)
Black	1 (0.4)	3 (1.1)
Other	2 (0.8)	5 (1.9)
Geographic region — no. (%)‡		
Asia	129 (48.9)	120 (45.1)
Europe	94 (35.6)	112 (42.1)
North or South America	41 (15.5)	34 (12.8)
WHO performance-status score — no. (%)§		
0	132 (50.0)	126 (47.4)
1	132 (50.0)	140 (52.6)
Former or current smoker — no. (%)	241 (91.3)	240 (90.2)
Tumor–node–metastasis stage at diagnosis — no. (%)¶		
I or II	33 (12.5)	34 (12.8)
III	231 (87.5)	232 (87.2)
Previous concurrent chemoradiotherapy — no. (%)		
Chemotherapy regimen in first cycle		
Cisplatin–etoposide	173 (65.5)	178 (66.9)
Carboplatin–etoposide	91 (34.5)	88 (33.1)
Radiotherapy fractionation schedule		
Once daily	195 (73.9)	187 (70.3)
Twice daily	69 (26.1)	79 (29.7)
Best response		
Complete response	31 (11.7)	34 (12.8)
Partial response	191 (72.3)	200 (75.2)
Stable disease	42 (15.9)	32 (12.0)
Time from end of previous concurrent chemoradiotherapy to randomization — no. (%)		
<14 days	32 (12.1)	32 (12.0)
14 to <28 days	79 (29.9)	80 (30.1)
≥28 days	153 (58.0)	154 (57.9)
Receipt of prophylactic cranial irradiation before randomization — no. (%)¶	142 (53.8)	143 (53.8)

Bénéfice RT + CT

Role of thoracic RT in limited SCLC

Meta-analysis: 13 studies (2 140 pts) comparing CT-RT to CT alone :

↗ 5% 3-yr survival by combining TRT to CT

(10% with CT, 15 % with CT-RT)

- **No difference between**
  - **RT early or RT administered late**
  - **Sequential, alternating or Concomitant CTRT regimen**
- **Benefit of CT-RT, observed mostly in younger pts < 55**

3-yr Survival : 9% (CT) and 17 % (CT-RT)

Pignon et al, NEJM 1992, 327

BID vs QD

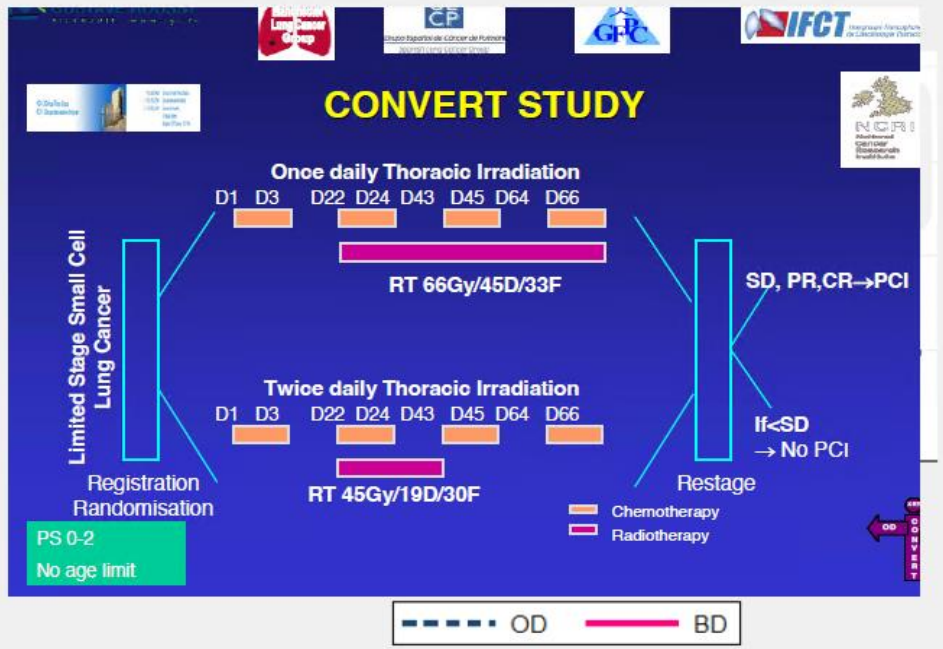
Concurrent CT-RT : Conventional versus Hyperfractionated Accelerated TRT with 4 EP

	1.8 Gy/d OD	1.5 GyX2/d BID	
Results :	**RT(45Gy/5wks)**	**HFART(45Gy/3wks)**	**p**
CRR	49 %	56 %	ns
ORR	87 %	87 %	
MST	19 m	23 m	
2-5-Year S	41%/16 %	47 %/26%	0.04
2-Year DFS	24 %	29 %	0,10
LR	**52 %**	**36 %**	**0.06**
LR + Dist R	23%	6%	0.01

Turrisi et al, NEJM 1999

Bénéfice en mOS à 5 ans 26% vs 16% + d'oesophagites grade ¾
Meilleur control local

What is the Optimal RT dose in SCLC?



Primary objective-survival at 2 years
Trial hypothesis
- **Expected survival BD arm 44%**
- **Projected survival OD arm 56%**

Median FU: 45 months,
Median GTV=80-85cc
PET/CT staging in 57% pts

Overall survival (n=543)	BD	OD	Log-rank
Median (Mo)	30 (24-34)	25 (21-31)	p=0.15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	
5-year	34%(27–41)	31%(25–37)	

Faivre-Finn ASCO 2016; Lancet Oncol 2017

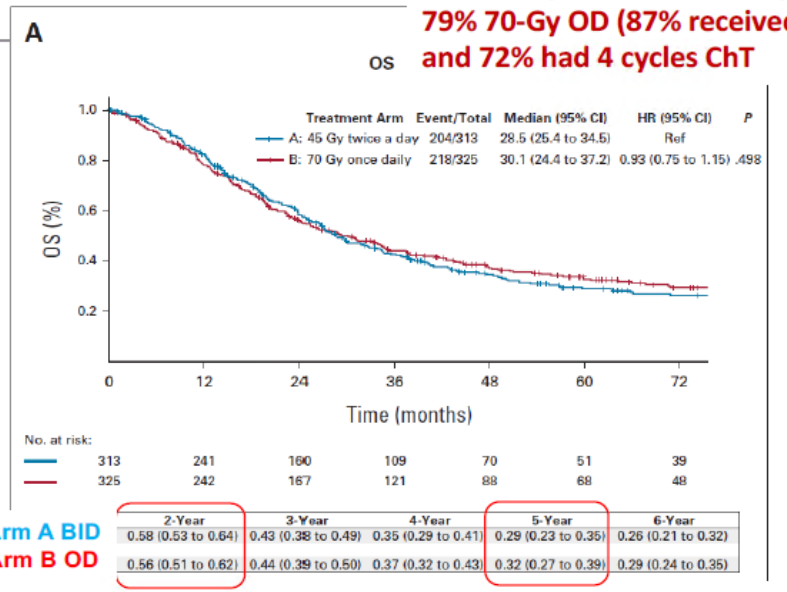
High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

TRT started cc with D1 or D21 of ChT
92% 45-Gy BID and 80% 4 cycles ChT
79% 70-Gy OD (87% received>60 Gy), and 72% had 4 cycles ChT

OS (n=638)	BD	OD	Log-rank
Median (Mo)	28,5	30,1	p=0.498
2-year	58% (53-64)	56% (51-62)	
3-year	43% (38-49)	44% (39-50)	
5-year	29%(23–35)	32%(27–39)	

Although the study does not definitively define the most ideal dose fractionation schedule
Survival rates similar in the OD (5yr rate 32%) and BID (5yr rate 29%) regimen.



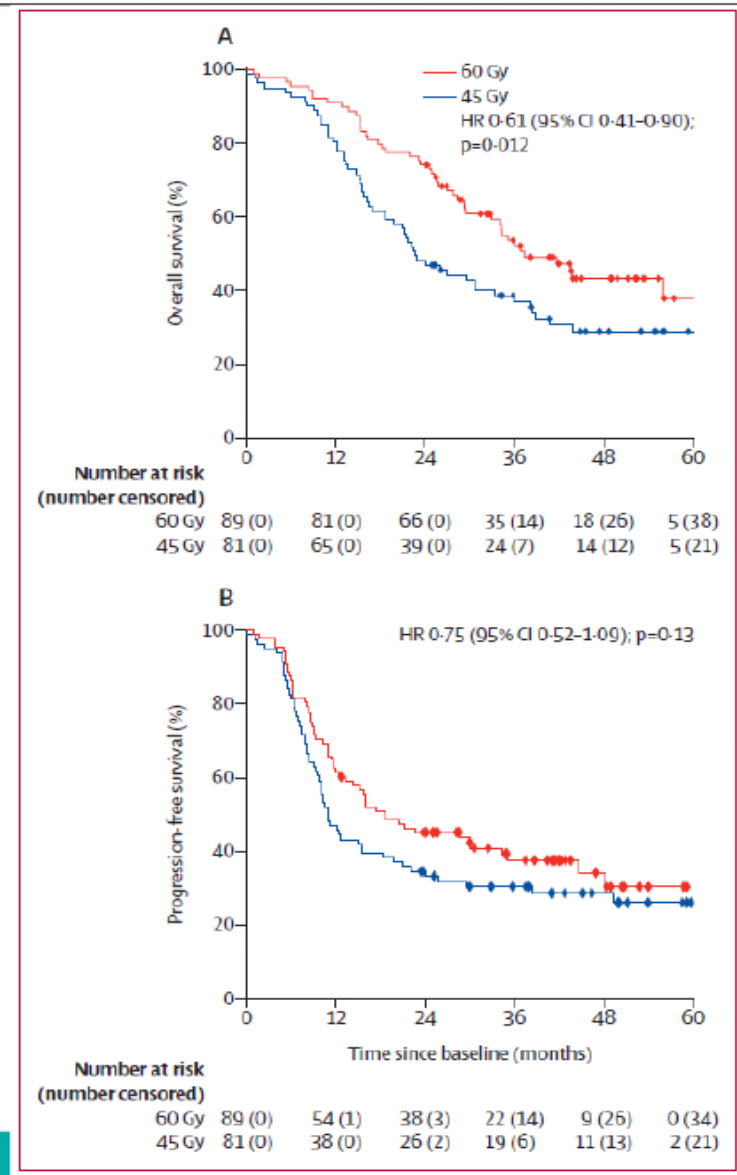
	2-Year	3-Year	4-Year	5-Year	6-Year
Arm A BID	0.58 (0.53 to 0.64)	0.43 (0.38 to 0.49)	0.35 (0.29 to 0.41)	0.29 (0.23 to 0.35)	0.26 (0.21 to 0.32)
Arm B OD	0.56 (0.51 to 0.62)	0.44 (0.39 to 0.50)	0.37 (0.32 to 0.43)	0.32 (0.27 to 0.39)	0.29 (0.24 to 0.35)

Although 45-Gy twice-daily RT remains the SOC, this study as well as CONVERT provide the most robust information available to help guide the choice of thoracic radiotherapy regimen for pts with LD SCLC

Bogart et al JCO 2023

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

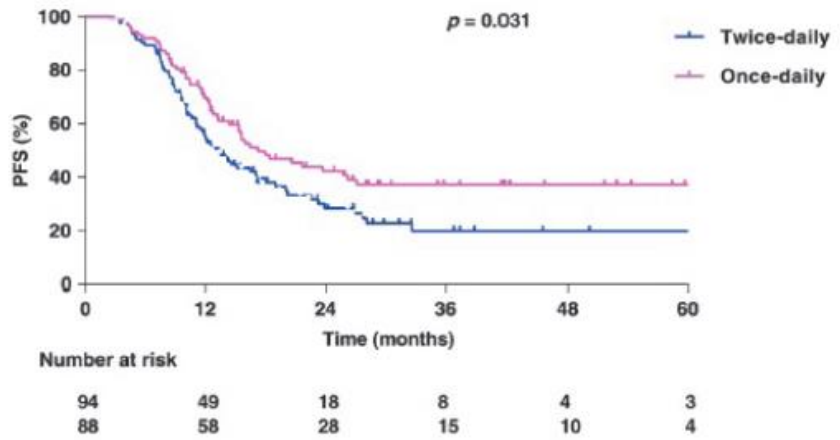
- **170 patients randomized between July 2014 and June 2018.**
- **4 cycles of CDDP 75 mg/m² or carboplatin AUC 5-6 day 1 and etoposide 100 mg/m² on days 1 to 3 every three weeks.**
  - HFRT 60 Gy in 40 fractions (n = 89), ten fractions per week.
  - HFRT 45 Gy in 30 fractions (n = 81), ten fractions per week.
- **RT to primary tumor and Nodes identified in PET-CT, starting 20-28 days after C1. Patients with response received PCI (25 to 30 Gy)- 85% had PCI**
- **Primary endpoint : 2 yr OS**
  - 2 yr OS=74.2% (60 Gy group) vs 48.1% (45 Gy group)
  - (OR = 3.09; CI 95% = 1.62-5.89; P = 0.0005).
  - MST: 37.2 vs 22.6 months (HR = 0.61; CI 95% = 0.41–0.90; P = 0.012).
- **OR rate: 77.5% versus 76.5% of patients (P = 0.88),**
- **CR rate: 18.0% versus 21.0%.**
- **Relapse in the RT field: 21% versus 35% pts (P = 0.054).**
- **Most common gr 3-4 AE: neutropenia in 72 pts [81%] vs 62 [81%], neutropenic infections, thrombocytopenia, anaemia oesophagitis :19 [21%] vs 14 [18%].**



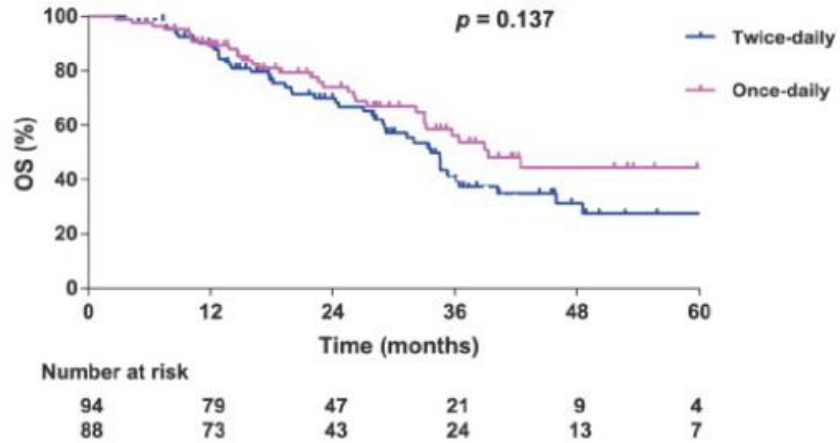
Gronberg et al, TLO 2021

Hypofractionated accelerated high-dose TRT

65 Gy/26 fr of 2.5 Gy



	Median PFS	2-year PFS
QD 65 Gy/26 fractions	17.2 months	42.3%
BID 45 Gy	13.4 months	28.4%



	Median OS	2-year OS
QD 65Gy/26 fractions	39.3 months	74.2%
BID 45 Gy	33.6 months	69.9%

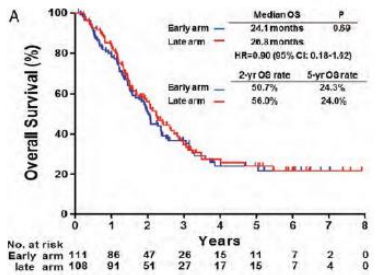
Qiu et al, IJROBP 2021

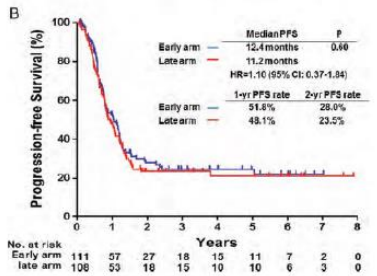
Qiu et al. Moderately Hypofractionated Once-daily Compared with BID TRT Concurrently with Etoposide and Cisplatin in LS SCLC: a Multi-center, Phase II, RCT. Int J Radiat Oncol Biol Phys (2021)

Timing de la RT ?

Phase III trial of concurrent TRT with either 1st- or 3rd-cycle chemotherapy for LD-SCLC

- Patients with LD-SCLC received 4 cycles of etoposide plus cisplatin every 21 days.
- Patients were randomly assigned to receive TRT (51.5 Gy /25 fr of 2.1 Gy) cc with first cycle (early TRT) or the third cycle (late TRT) of ChT



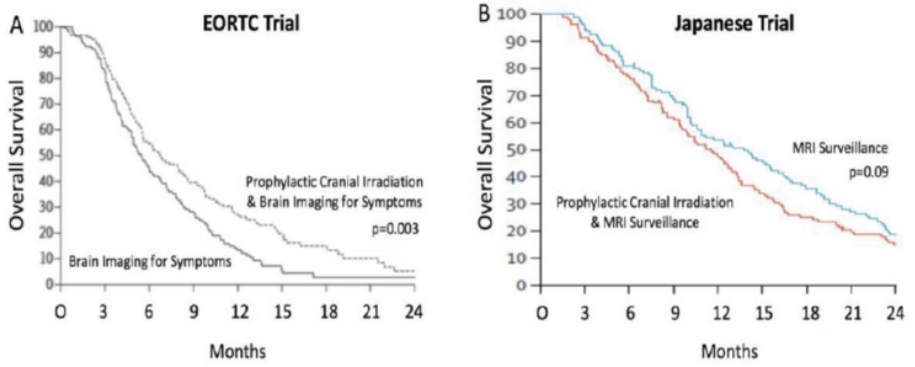


- Primary end point = CR rate.
- Results: 222 pts randomized. Late TRT : not inferior to early TRT in terms of CR rate (early versus late; 36.0% versus 38.0%).
- OS [median, 24.1 versus 26.8 mo; | | 2-yr OS rate | 5-yr OS rate | | |
  | --- | --- | --- | --- | --- |
  | Early arm | 50.7% | 24.3% |] | NS |
  | Late arm | 56.0% | 24.0% | | |
- PFS (median, 12.4 versus 11.2 mo; | | 1-yr PFS rate | 2-yr PFS rate | | |
  | --- | --- | --- | --- | --- |
  | Early arm | 51.8% | 28.0% |] | NS |
  | Late arm | 48.1% | 23.5% | | |
- No statistical difference in the pattern of treatment failures.
- Neutropenic fever in early TRT arm > late TRT arm (21.6% versus 10.2%; P = 0.02).
- Conclusion: In LD-SCLC treatment, TRT starting in the third cycle of ChT seemed to be non-inferior to early TRT, and had a more favorable profile with regard to neutropenic fever.

Sun et al; Ann Oncol 2013

Primalung : Rationnel

- **Irradiation prophylactique cérébrale chez les CPPC-SL:**
  - La plupart des essais des années 1970 à 1990 ont montré une incidence réduite des métastases cérébrales après IPC et de meilleurs résultats chez les patients ayant un bon état de performance.
  - Une large méta-analyse a montré:
    - Un bénéfice de 5% pour la survie à 3 ans pour les patients recevant l'IPC.
    - Un taux cumulatif de métastases cérébrales à 3 ans de 59% pour les patients dans le bras contrôle et de 33% pour les patients recevant l'IPC.
- **Irradiation prophylactique cérébrale chez les CPPC-SE:**
  - L'IPC diminue l'incidence des métastases cérébrales symptomatiques
  - L'effet sur la survie globale est controversée.

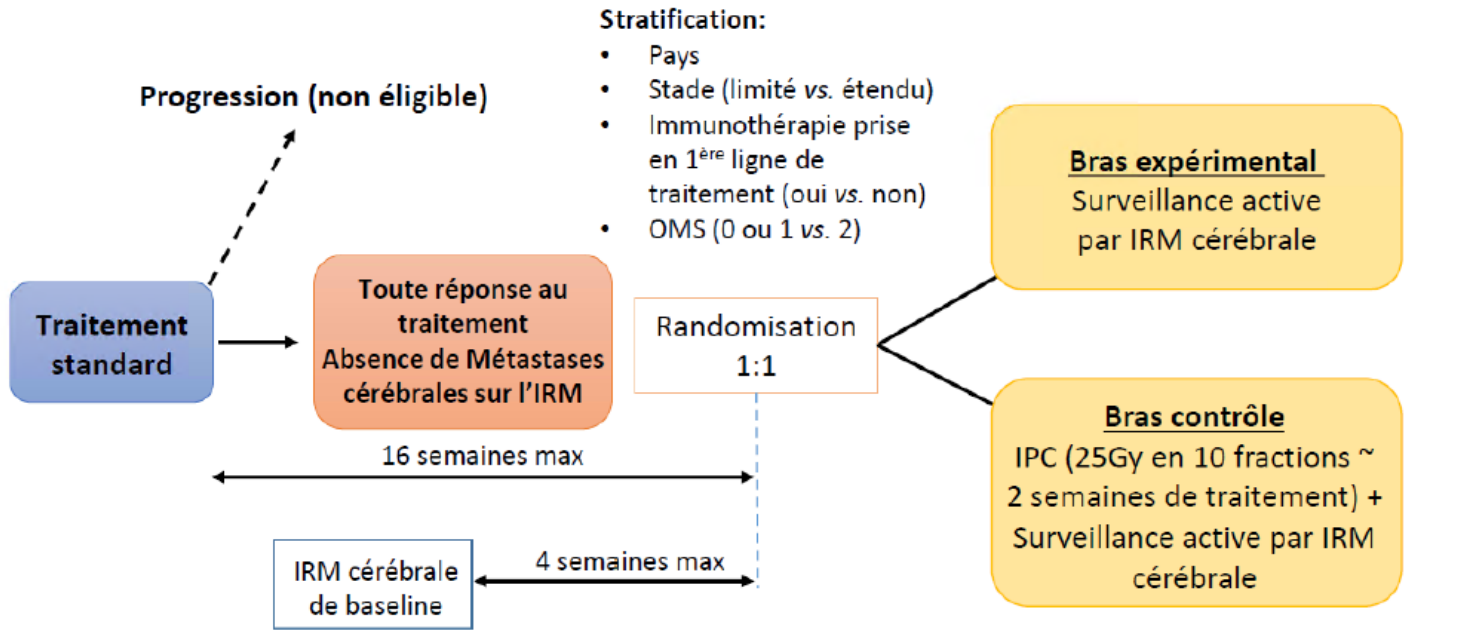


- Utilisation de l'IPC en systématique est remise en question:
  - Neurotoxicités fréquentes de l'IPC qui peuvent être permanentes
  - Manque d'impact sur la survie positif pour les CPPC-SE et la possibilité d'effectuer une surveillance active par IRM cérébrale : détection des métastases cérébrales augmentée avec l'IRM *versus* scanner (24% vs 10%)
  - Interactions entre anti-PD-L1 et IPC non connues

DESIGN DE L'ESSAI

Etude de phase III, multicentrique, randomisée , internationale ouverte

Indication: Patients atteints d'un cancer du poumon à petites cellules de stades limités (CPPC-SL): stades I à III ou de stades étendus (CPPC-SE) stade IV, sans métastases cérébrales et en absence de progression après avoir reçu le traitement initial standard pour la pathologie.

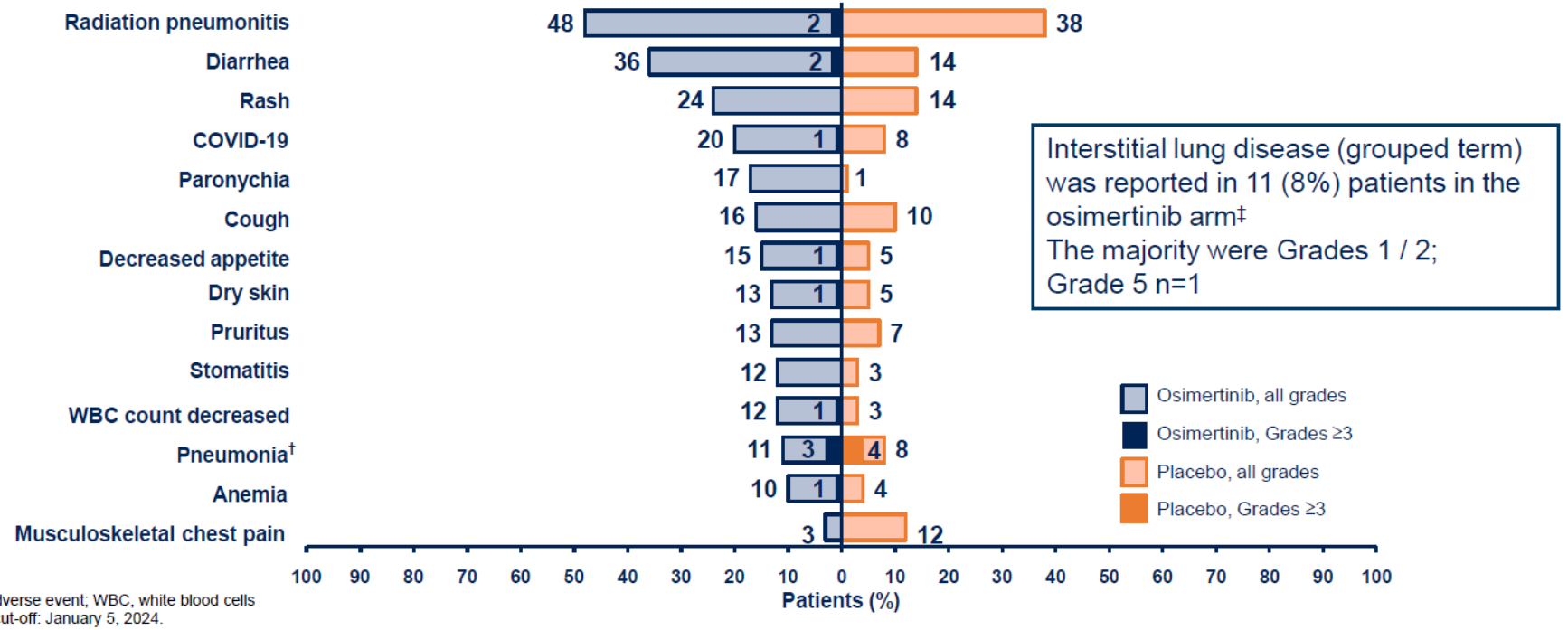


Pour les deux bras:

- **IRM cérébrale et évaluation clinique** tous les 3 mois pendant 1 an puis tous les 6 mois jusqu'à 24 mois à partir de la date de randomisation (3, 6, 9, 12, 18 et 24 mois)

ALL-CAUSALITY ADVERSE EVENTS (≥10%)*

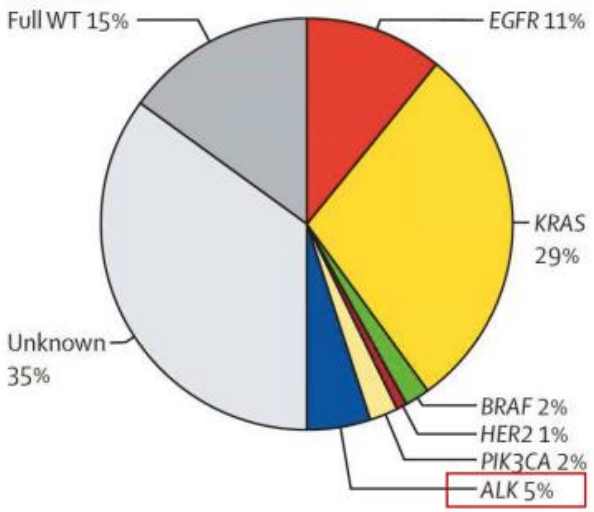
- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

AE, adverse event; WBC, white blood cells
Data cut-off: January 5, 2024.

Incidence MC 38 % au diagnostic



5% des CBNPC

sex ratio

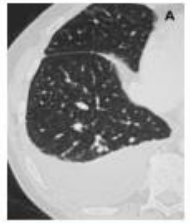
♀ 55-60%

♂ 40-45%

Jeune

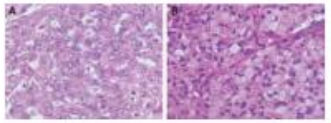
≈ 55-58 ans

Atteinte des séreuses et ganglionnaires

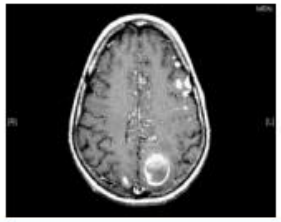


Non-fumeur 55-60% des cas

Adénocarcinomes 90-95%



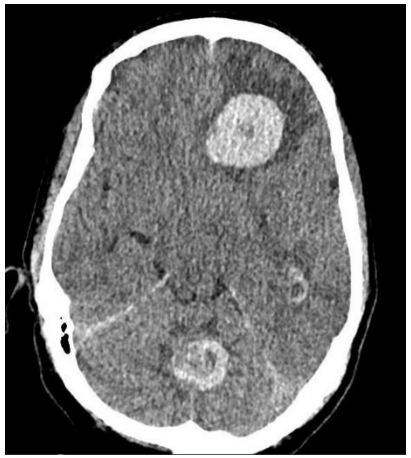
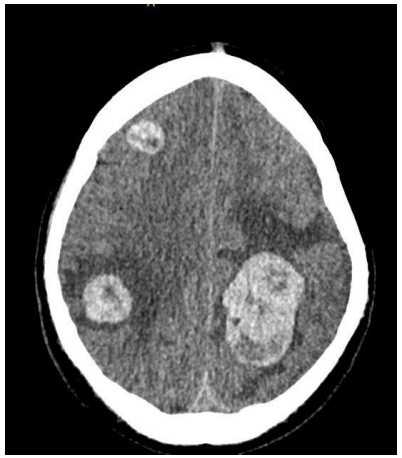
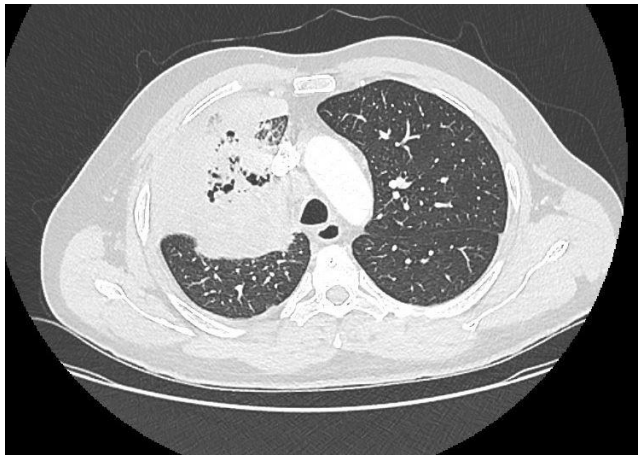
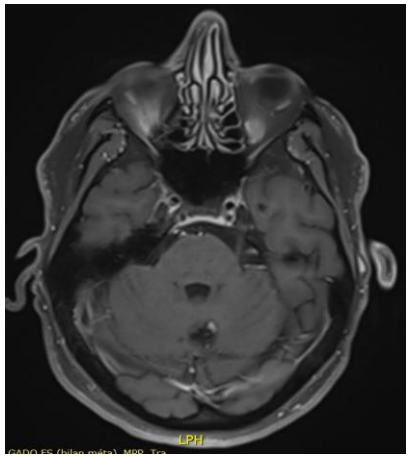
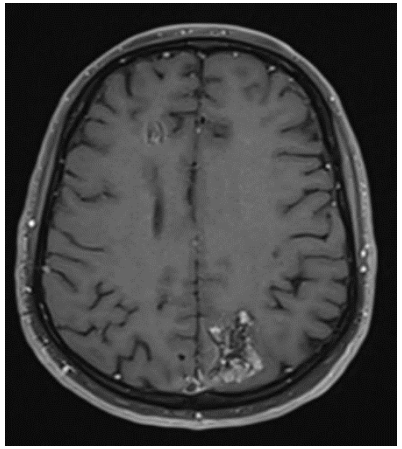
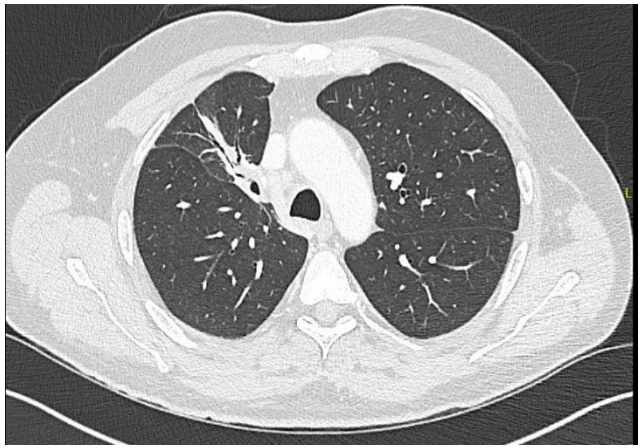
Métastases cérébrales



Barlesi et al. Lancet. 2016 Apr 2;387(10026):1415-1426.

Diagnostic patient OMS 4 début de sédation

Imagerie à 6 mois

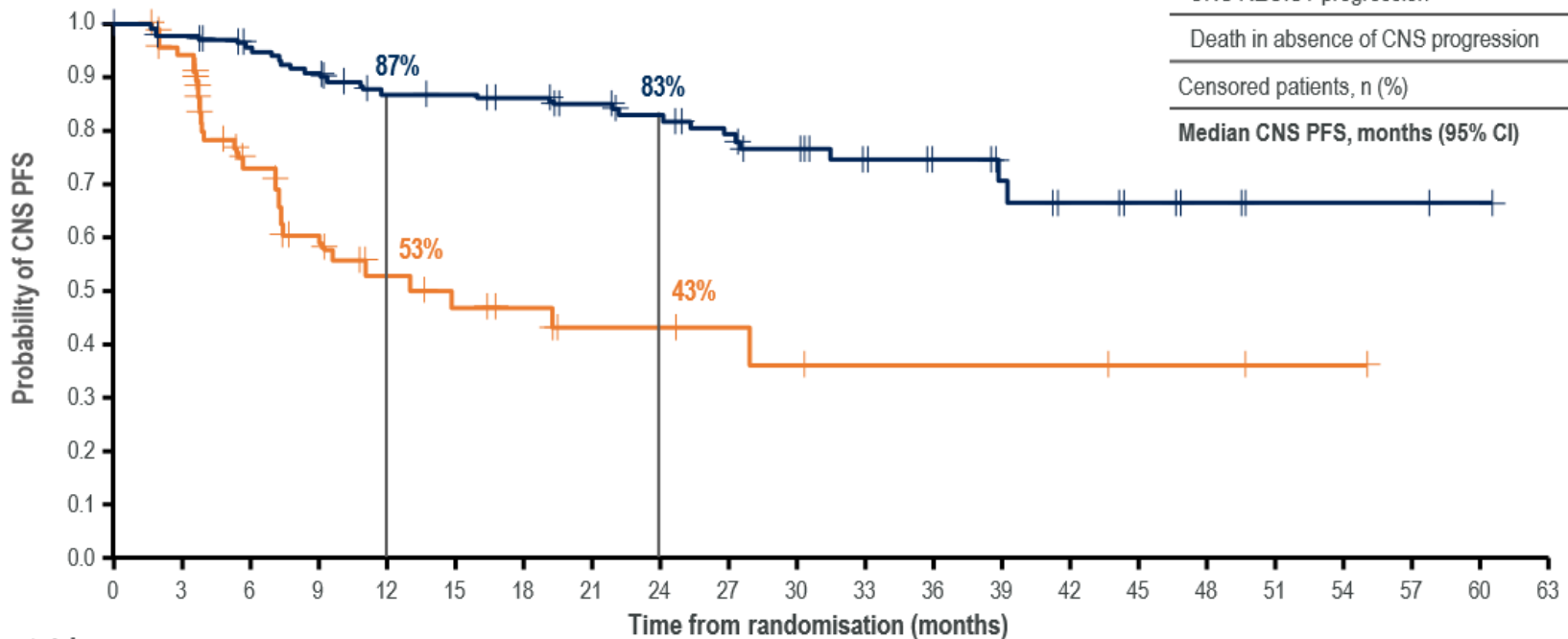







Traitement locaux (RT stéréo) à différer

CNS progression-free survival by neuroradiologist BICR*

- Reduced risk of CNS progression or death with osimertinib vs placebo

	Osimertinib (n=143)	Placebo (n=73)
Total CNS PFS events, n (%)†	29 (20)	30 (41)
CNS RECIST progression‡	18 (13)	26 (36)
Death in absence of CNS progression	11 (8)	4 (5)
Censored patients, n (%)	114 (80)	43 (59)
Median CNS PFS, months (95% CI)	**NR (NC, NC)**	**14.9 (7.4, NC)**



HR: 0.17 (0.09, 0.32), p<0.001 (nominal)

No. at risk

Osimertinib	143	130	121	115	105	104	94	84	74	63	49	37	28	17	9	6	4	2	2	2	1	0
Placebo	73	63	36	26	19	16	12	8	8	6	5	3	3	3	3	2	2	1	1	0	0	0

Data cut-off: 5 January 2024.