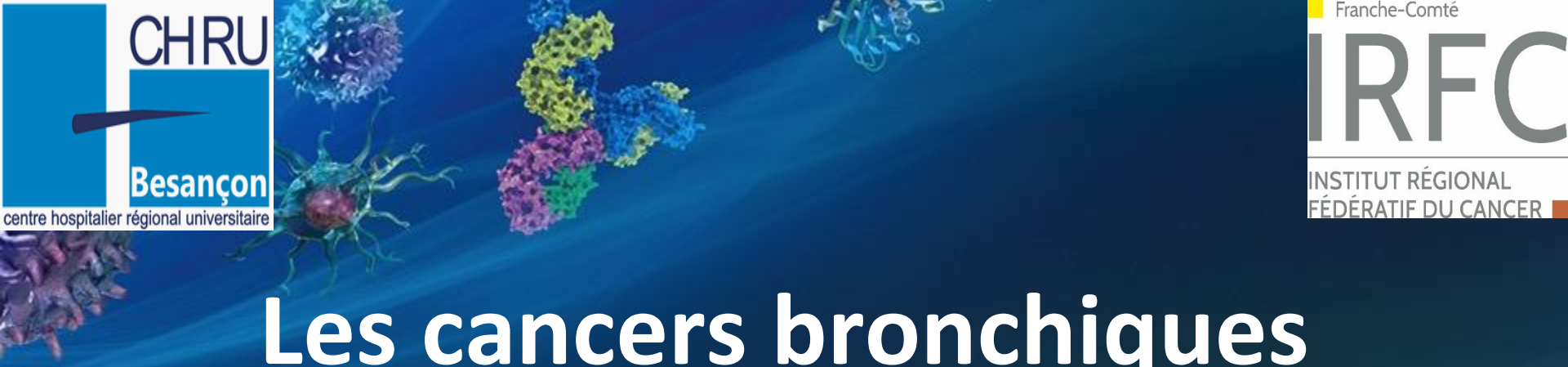
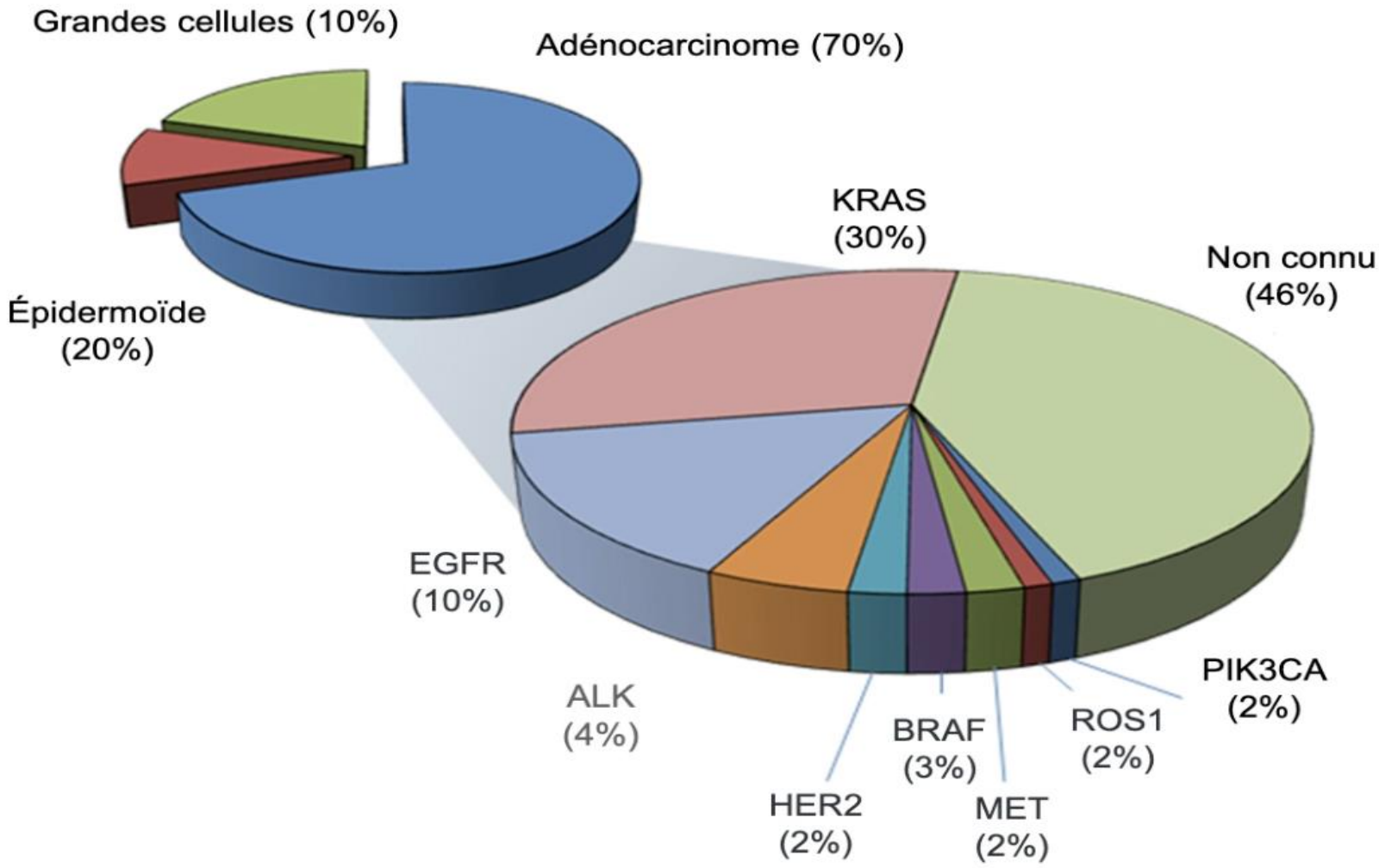


Les cancers bronchiques métastatiques avec une addiction oncogénique

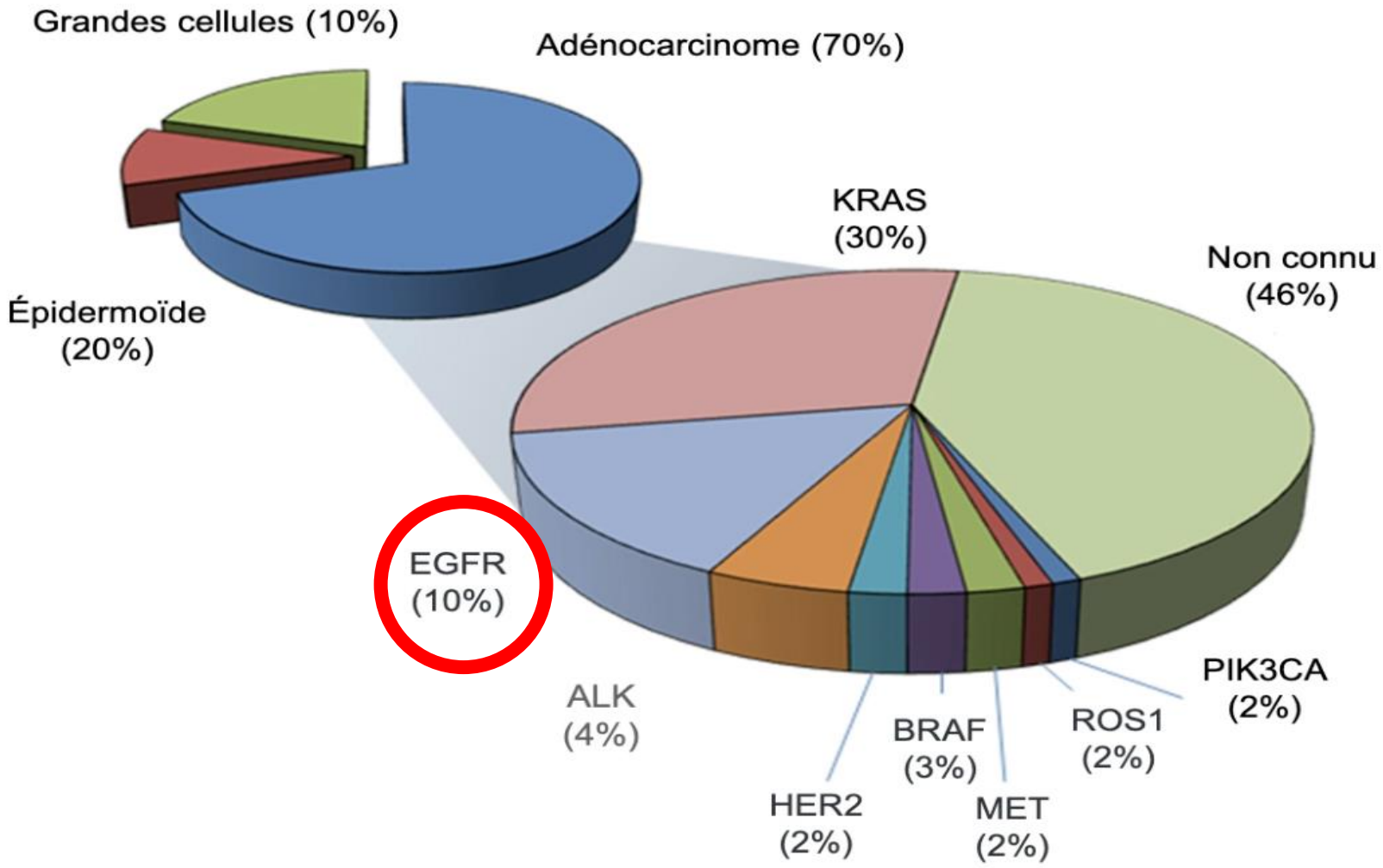
DR ALMOTLAK Hamadi
IRFC
CHRU Besançon

ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



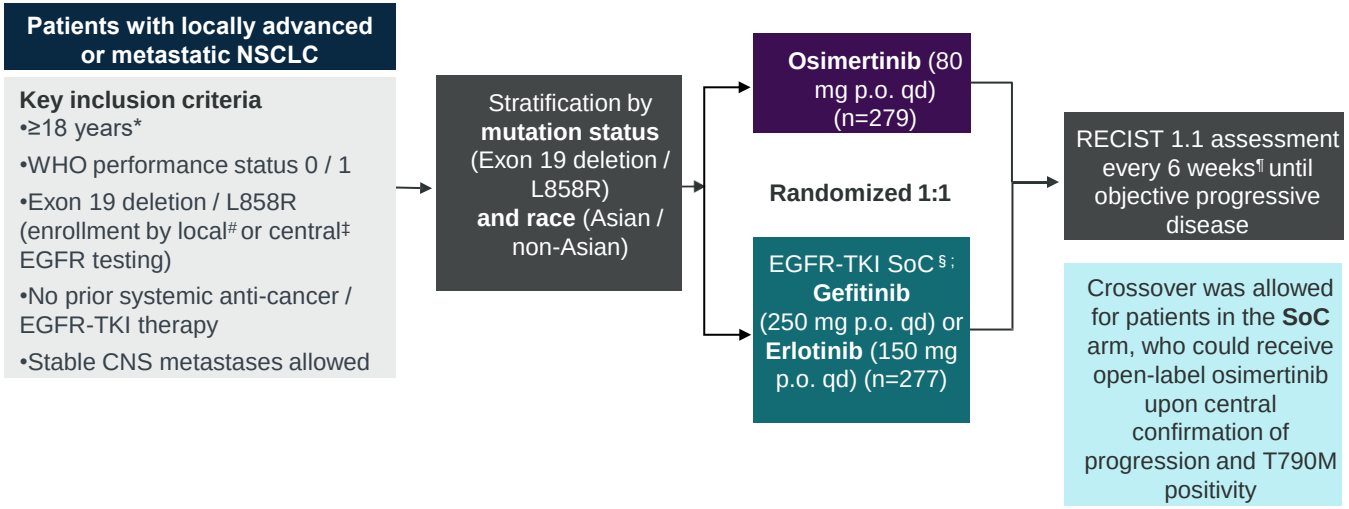
Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

FLAURA:
Phase III, Double-Blind, Randomized Trial of Osimertinib as First-Line Therapy



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

FLAURA data cut-off: 12 June 2017; NCT02296125.

*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

CNS = central nervous system; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PFS = progression-free survival; p.o. = orally; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; qd = once daily; SoC = standard-of-care; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

2 Soria J-C et al. *N Engl J Med.* 2018;378:113-125.

Baseline Characteristics

Characteristic, %	Osimertinib (n=279)	SoC* (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: White / Asian / other[#]	36 / 62 / 1	36 / 62 / 1
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry[‡]	19	23
WHO performance status[§]: 0 / 1	40 / 60	42 / 58
Overall disease classification[¶]: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomization[**]: Exon 19 deletion / L858R	63 / 37	63 / 37

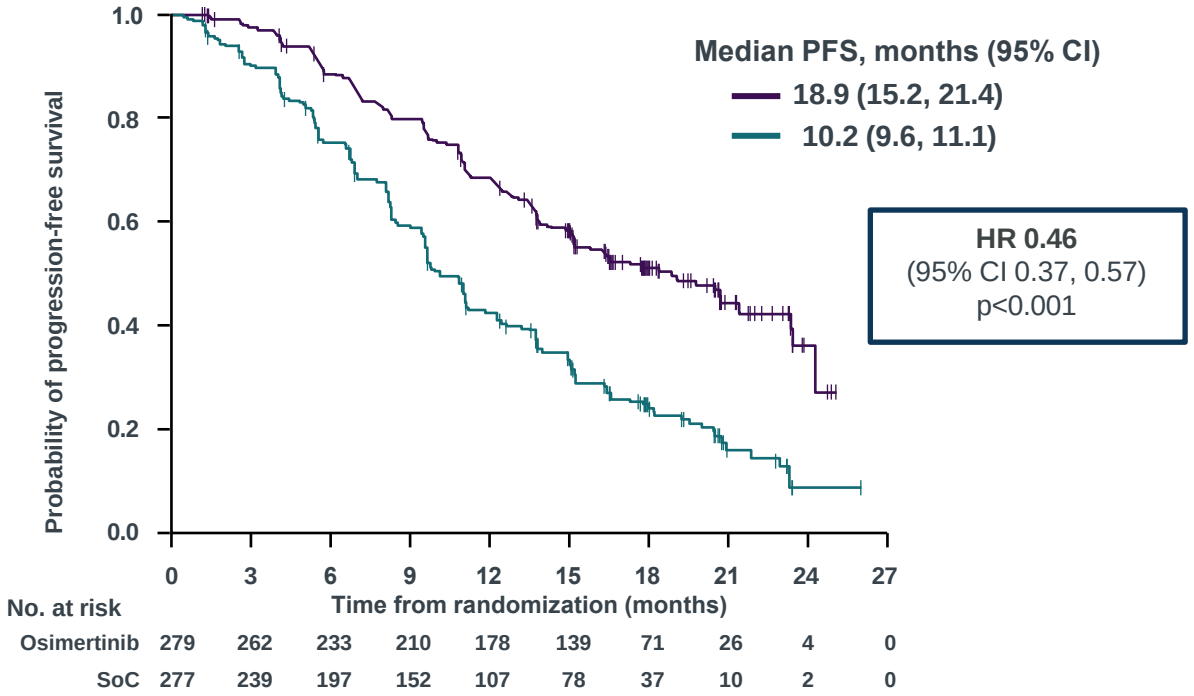
FLAURA data cut-off: 12 June 2017.

*In the SoC arm, 66% of patients received gefitinib and 34% received erlotinib; [#]Including Black or African American and American Indian or Alaska Native. Race was missing for one patient in the osimertinib arm and one patient in the SoC arm; [‡]CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy; [§]WHO performance status was missing for one patient in the SoC arm; [¶]Overall disease classification was missing for one patient in the osimertinib arm; [**]Local or central test.

CNS = central nervous system; EGFR = epidermal growth factor receptor; SoC = standard-of-care; WHO = World Health Organization. Soria J-C et al. *N Engl J Med.* 2018;378:113-125.

Primary Endpoint: PFS by Investigator Assessment

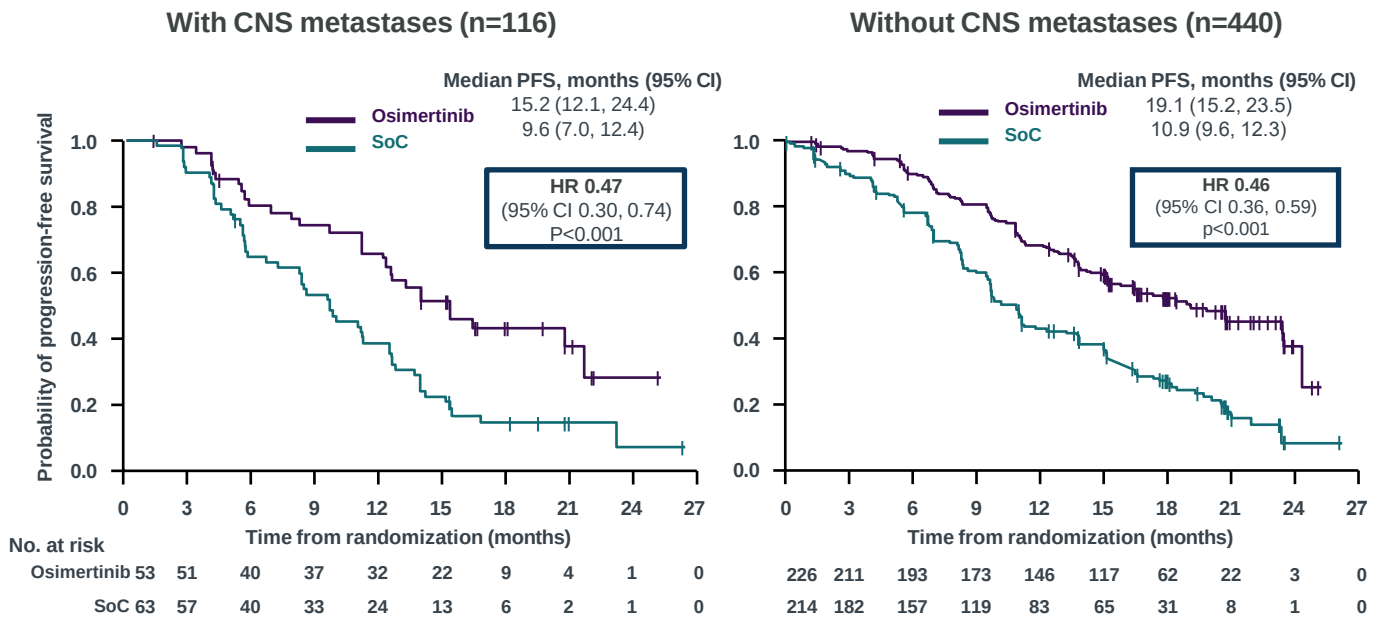
342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



FLAURA data cut-off: 12 June 2017. Tick marks indicate censored data;
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; SoC = standard-of-care; PFS = progression-free survival. Soria J-C et al. *N Engl J Med.* 2018;378:113-125

4

PFS* in Patients With And Without CNS Metastases at Study Entry



- **Across all patients, progression in the CNS occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC**

FLAURA data cut-off: 12 June 2017.
Tick marks indicate censored data; *By Investigator assessment.
CI = confidence interval; CNS = central nervous system; HR = hazard ratio; PFS = progression-free survival; SoC = standard-of-care. Soria J-C et al. *N Engl J Med*. 2018;378:113-125.

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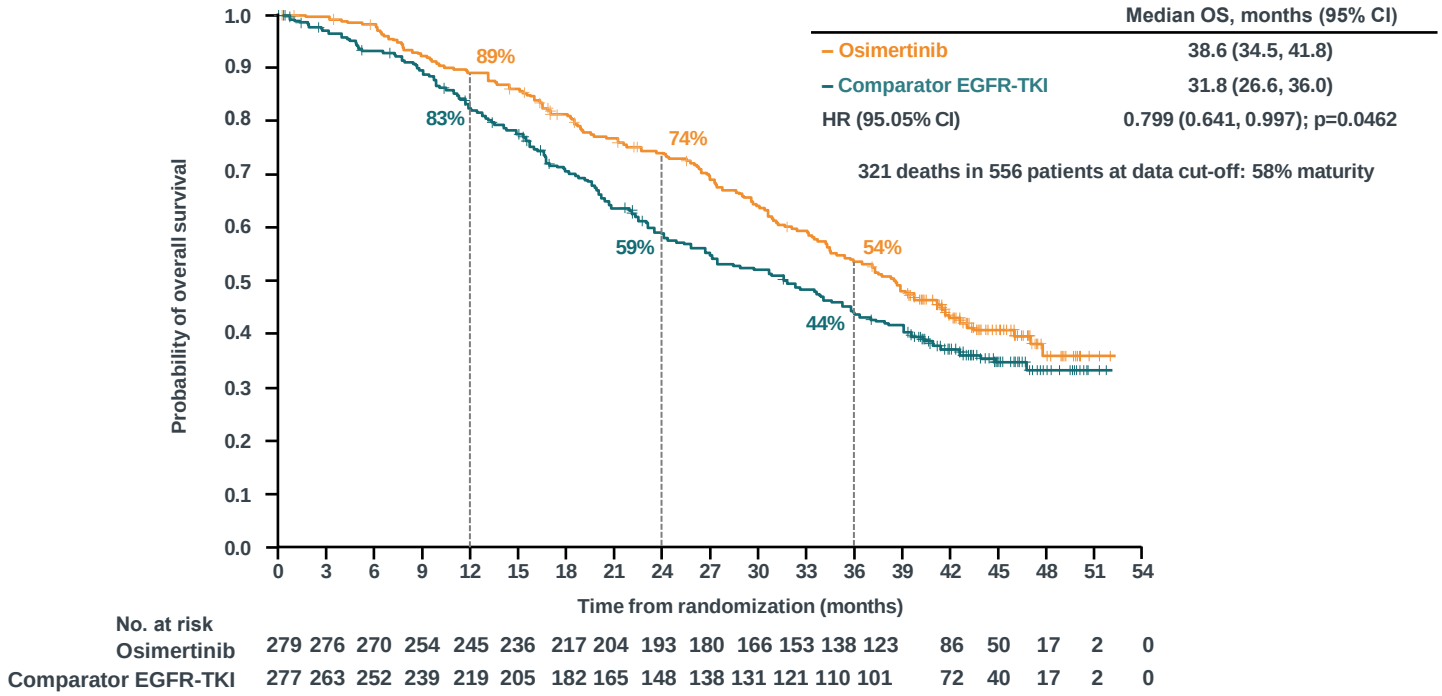
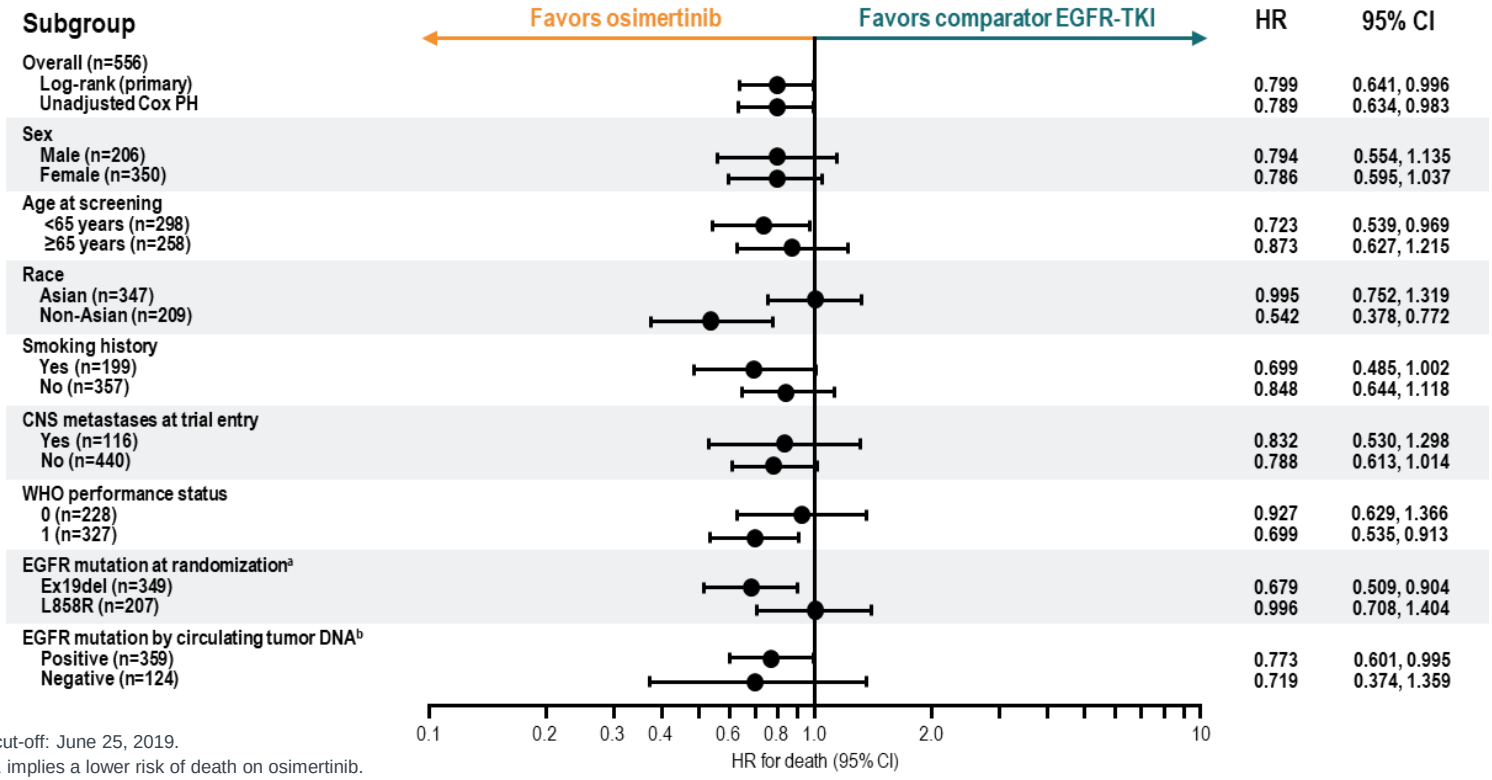
Final Analysis: Overall Survival



FLAURA data cut-off: June 25, 2019.
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required.
CI = confidence interval; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; HR = hazard ratio; OS = overall survival.
9 Ramalingam SS et al. Presented at: European Society for Medical Oncology Congress; September 27 - October 1, 2019; Barcelona, Spain.

OS Across Subgroups



FLAURA data cut-off: June 25, 2019.

Hazard ratio <1 implies a lower risk of death on osimertinib.

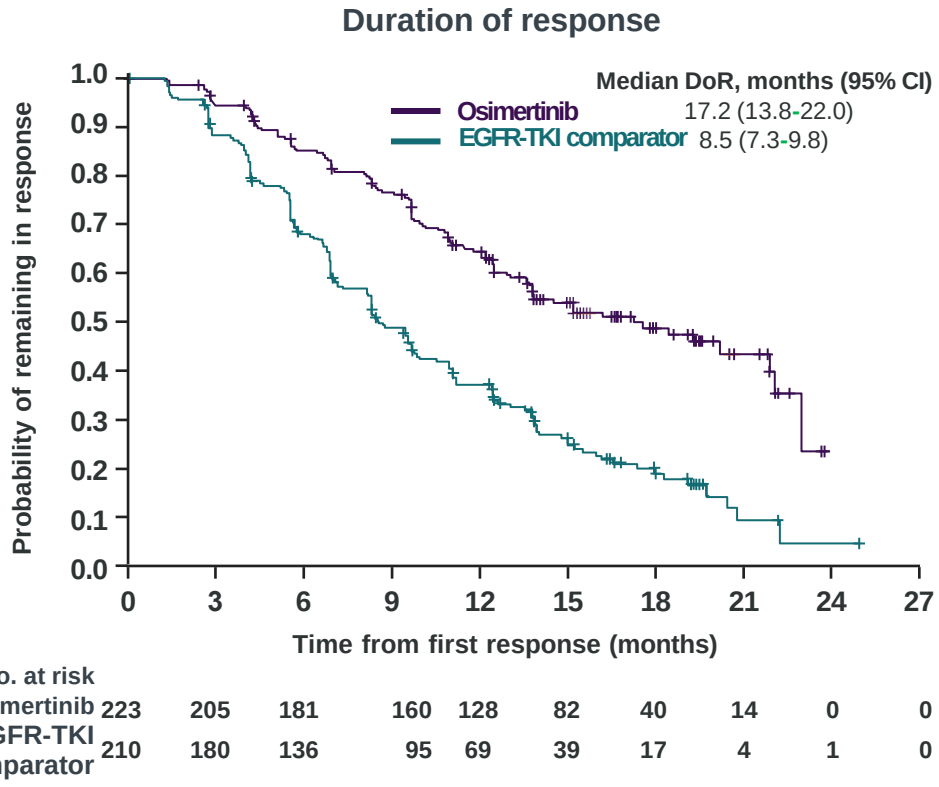
[a]Local or central test; [b]Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm.

CI = confidence interval; CNS = central nervous system; EGFR = epidermal growth factor receptor; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; HR = hazard ratio; OS = overall survival; WHO = World Health Organization.

10 Ramalingam SS et al. Presented at: European Society for Medical Oncology Congress; September 27 - October 1, 2019; Barcelona, Spain.

Objective Response Rate[1,2,a]

	Osimertinib (n=279)	EGFR-TKI comparator (n=277)
ORR (95% CI)	80% (75-85)	76% (70-81)
Odds ratio[b] (95% CI)	1.27 (0.85-1.90); p=0.24	
Complete response,[c] n (%)	7 (3)	4 (1)
Partial response,[c] n (%)	216 (77)	206 (74)
Stable disease ≥6 weeks, n (%)	47 (17)	46 (17)
Progression, n (%)	3 (1)	14 (5)
Not evaluable, n (%)	6 (2)	7 (3)
Duration of response,[d] months, median (95% CI)	17.2 (13.8-22.0)	8.5 (7.3-9.8)
Percent of patients with continued response at:[e]		
12 months, % (95% CI)	64 (58-70)	37 (31-44)
18 months, % (95% CI)	49 (41-56)	19 (13-26)



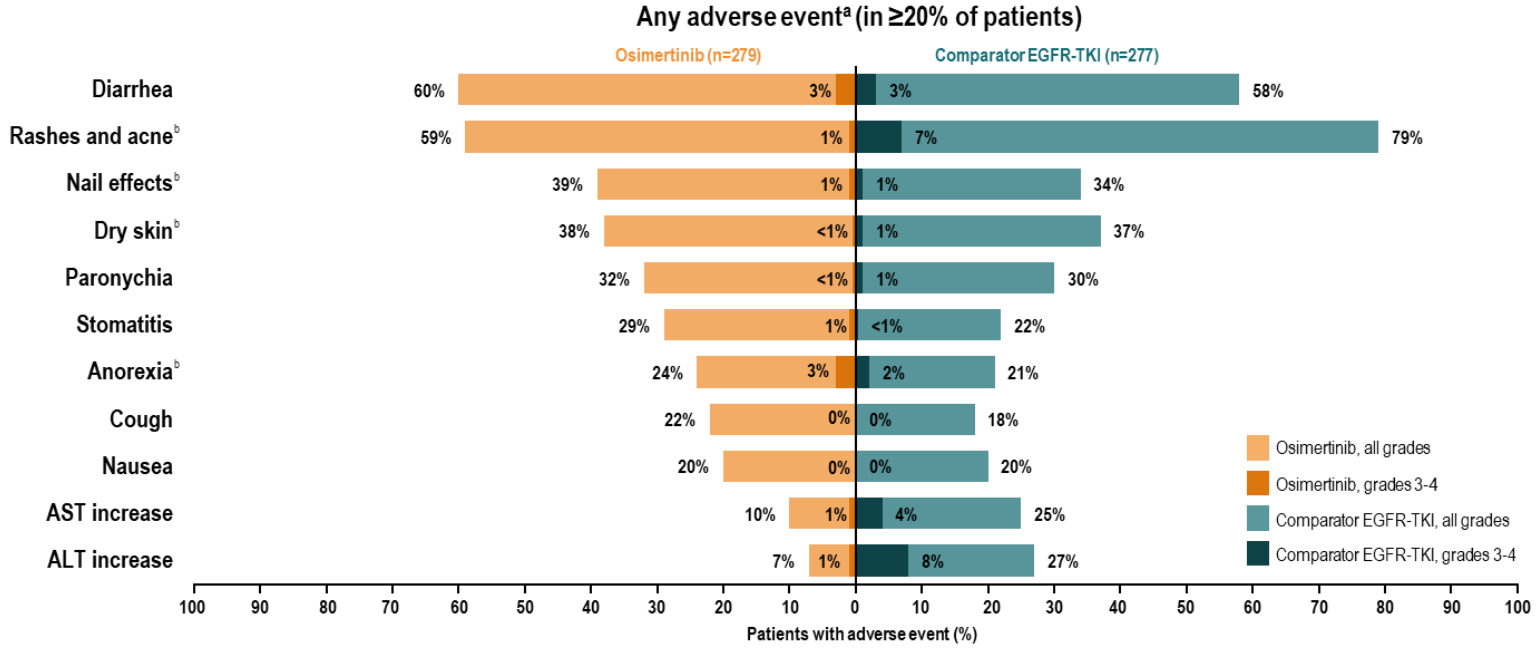
[a]By investigator assessment; [b]Analysis performed using a logistic regression stratified by race (Asian versus Non-Asian) and mutation type (Exon 19 deletion versus L858R); [c]Response did not require confirmation; [d]Calculated with the use of the Kaplan-Meier method from the date of the first documented disease progression or death in the absence of disease progression; [e]Calculated using Kaplan-Meier approach.

DoR = duration of response; EGFR = epidermal growth factor receptor; ORR = objective response rate; TKI = tyrosine kinase inhibitor.

1. Soria J-C et al. *N Engl J Med*. 2018;378:113-125. 2. Ohe Y et al. Presented at: European Society for Medical Oncology Asia Congress; 17-19 November 2017; Singapore

FLAURA Safety Summary

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (**18%**); comparator EGFR-TKI, 79 patients (**29%**)



FLAURA data cut-off: 12 June 2017.

[a]As assessed by the investigator; Patients with multiple events in the same category counted only once in that category; Patients with events in more than one category counted once in each of those categories; [b]Grouped term.

AE = adverse event; AST = aspartate transaminase; ALT = alanine transferase; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor. Ramalingam SS et al. Presented at: European Society for Medical Oncology Congress; September 27 - October 1, 2019; Barcelona, Spain.

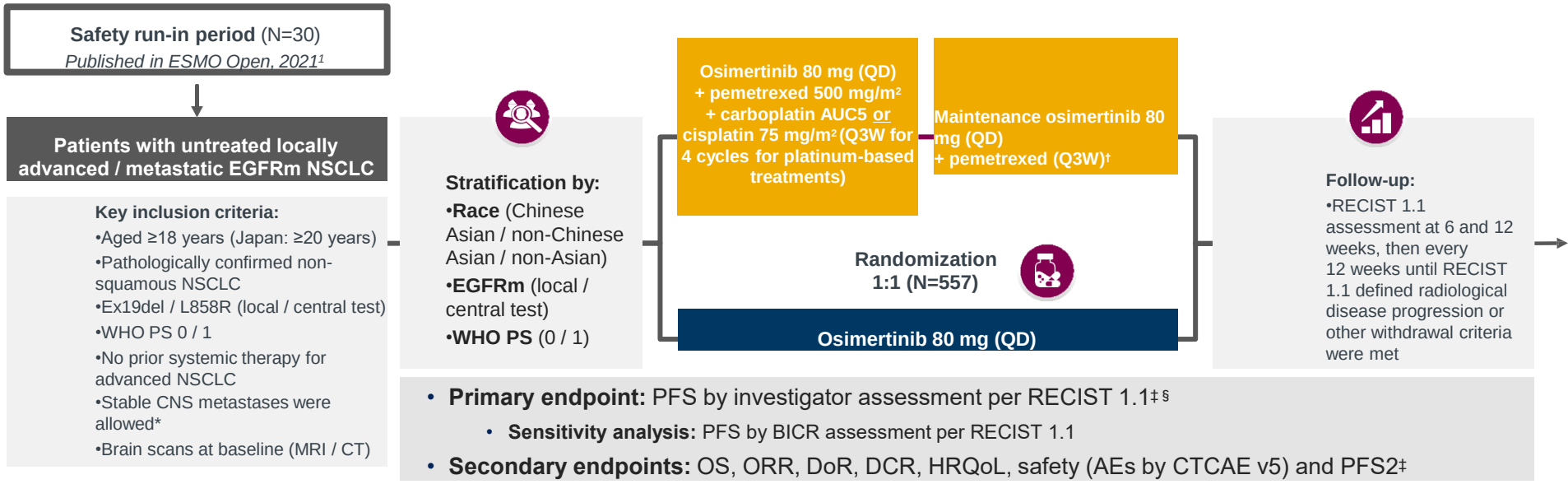
FLAURA: Conclusions

- **Osimertinib resulted in a significant improvement in PFS over EGFR-TKI comparator, median PFS: 18.9 months vs 10.2 months HR, 0.46 (95% CI, 0.37-0.57); p<0.001[1]**
  - Osimertinib demonstrated a consistent PFS benefit across all prespecified subgroups, including in patients with or without CNS metastases and in patients with exon 19 deletion or L858R
  - Increased duration of response (median: 17.2 months vs 8.5 months)
- **FLAURA showed a statistically significant and clinically meaningful improvement in OS with osimertinib[2]**
  - Median OS for patients in the osimertinib arm was extended by 6.8 months
- After three years, 28% of patients in the osimertinib arm and 9% of patients in the comparator EGFR-TKI arm remained on first-line study treatment[2]
- Osimertinib presented a favorable and consistent toxicity profile, despite prolonged exposure[2]

CNS = central nervous system; *EGFR* = epidermal growth factor receptor; *EGFR*m = epidermal growth factor mutation-positive; HR = hazard ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

1. Soria J-C et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:113-125. 2. Ramalingam SS et al. Presented at: European Society for Medical Oncology Congress; September 27 - October 1, 2019; Barcelona, Spain.

FLAURA2 Phase III study design



- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

1. Planchard et al. ESMO Open 2021;6:100271
*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; EGFRm, epidermal growth factor receptor-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate;

OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO PS, World Health Organization performance status

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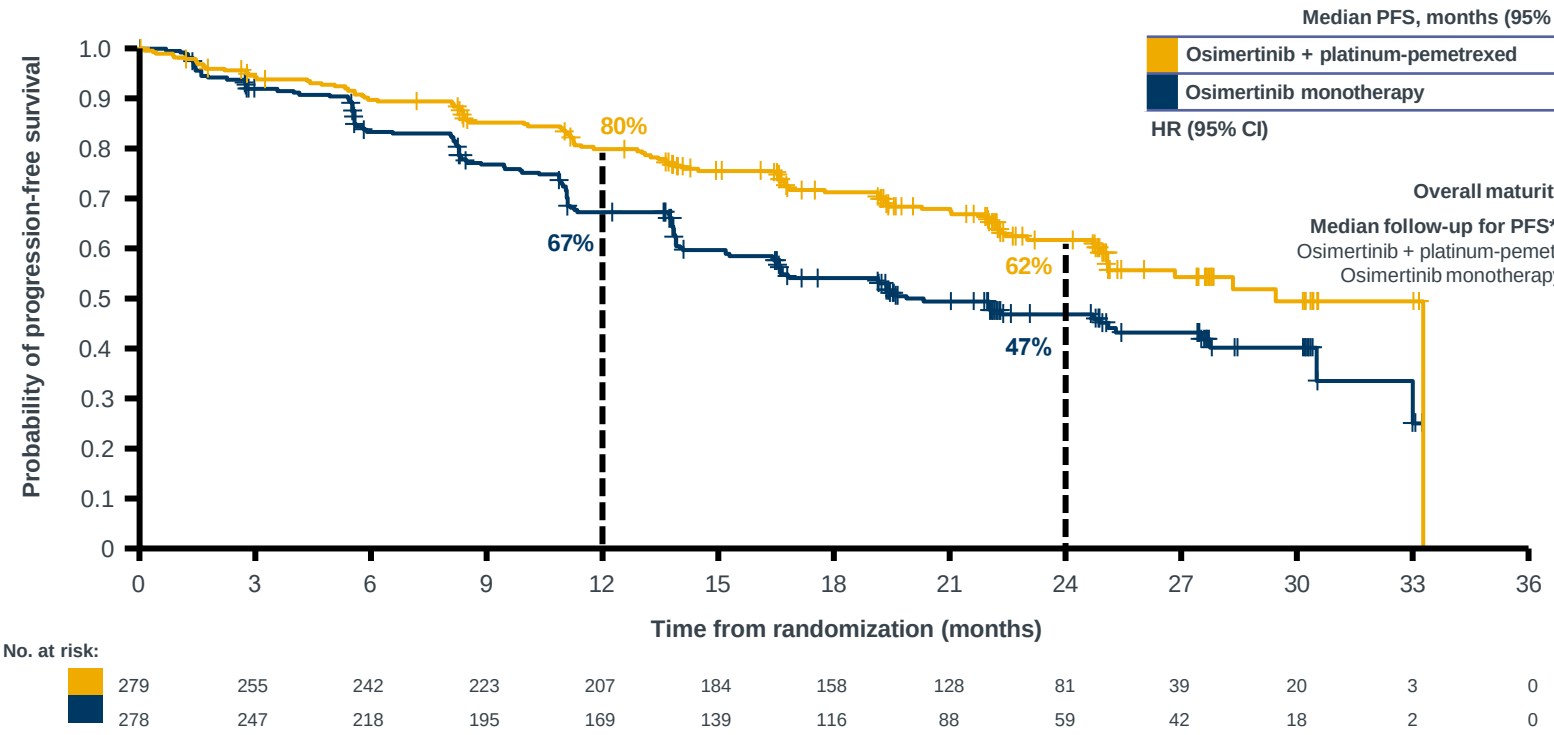
Progression-free survival per BICR

- Median PFS was improved by ~9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Data cut-off: 03 April 2023
*In all patients
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival
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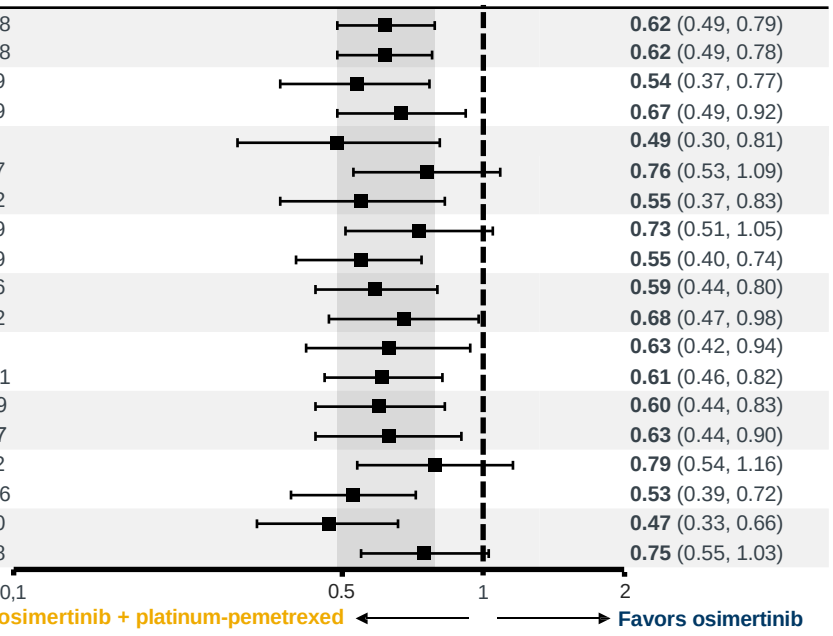
PFS per investigator across subgroups*

- PFS benefit was consistent across all pre-defined subgroups

Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type†	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)



Data cut-off: 03 April 2023

*Two additional subgroups performed to fulfil regulatory requirements for diagnostics are not included: EGFR mutations by central cobas® tissue test and EGFR mutations by central cobas® ctDNA test; †For EGFR mutation type, patients with both Ex19del and L858R were included in the Ex19del group

CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; PFS, progression-free survival; PH, proportional hazard; WHO PS, World Health Organization performance status

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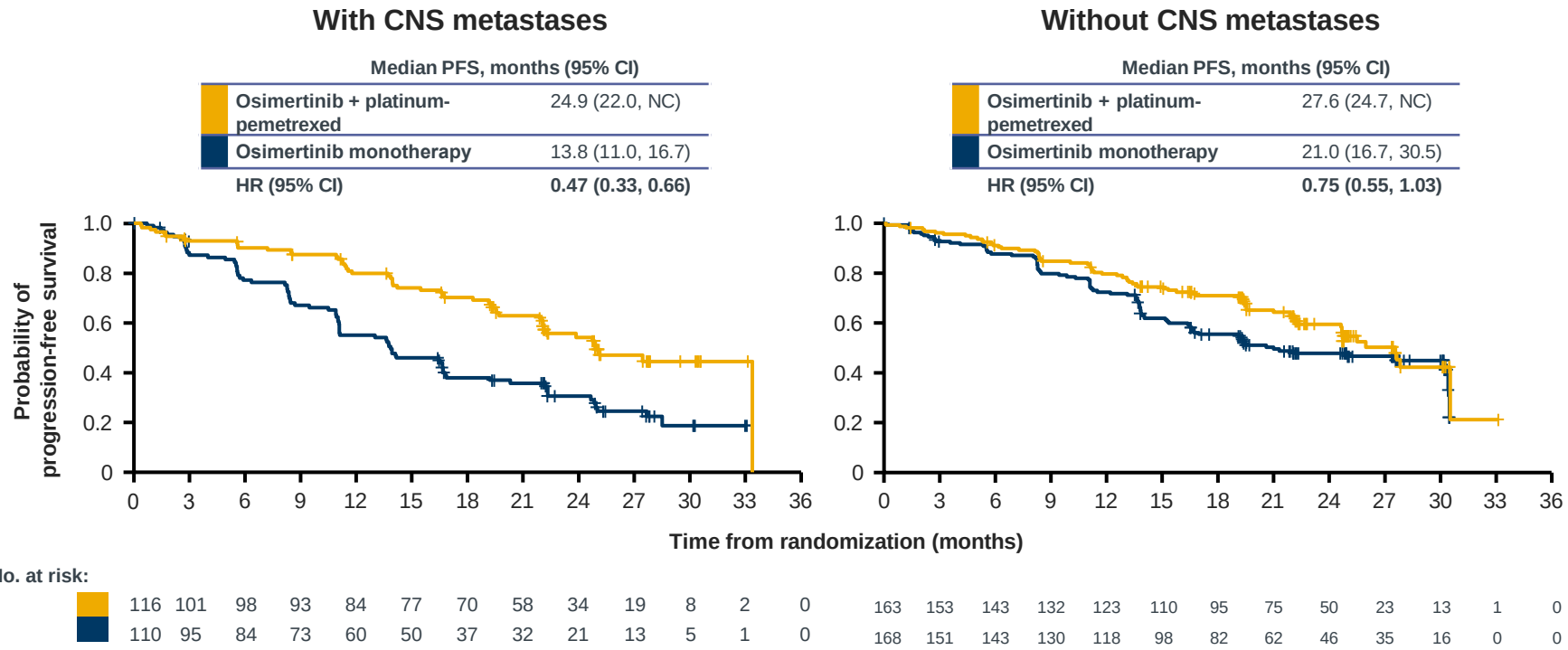
PFS per investigator in patients with / without CNS metastases at baseline*



Data cut-off: 03 April 2023
*CNS metastases determined by the investigator and recorded in the eCRF
CI, confidence interval; CNS, central nervous system; eCRF, electronic case report form; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

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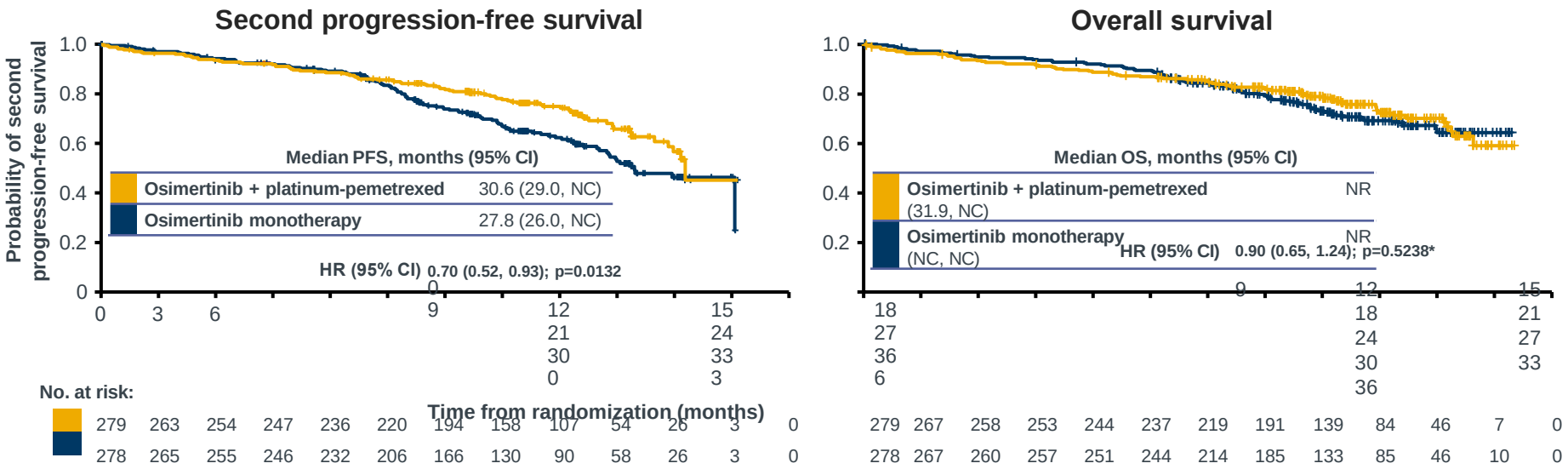
PFS2 and interim analysis of OS



- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

Data cut-off: 03 April 2023
*Significance level is p-value <0.00158 at this interim for OS; †Subsequent anti-cancer treatments included those with a start date after the date of the last dose of study treatment; patients could have received more than one subsequent anti-cancer treatment, and percentages of patients by treatment type are calculated from the number of patients who discontinued randomized study treatment
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

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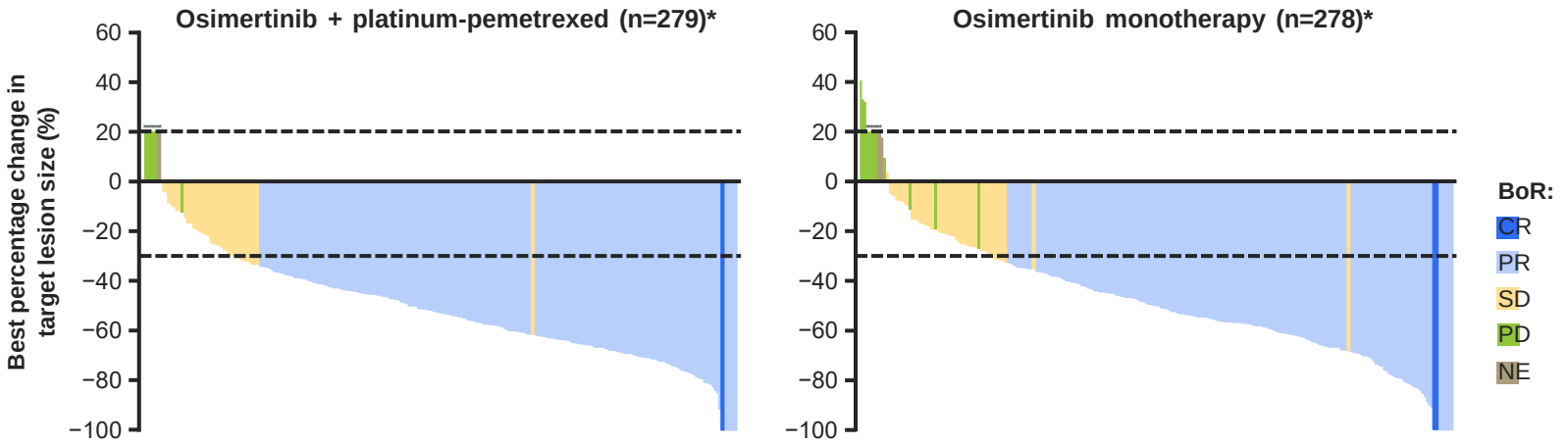
Tumor response per investigator



		Osimertinib monotherapy (n=278)
Median best percentage change in target lesion size, % (range)	-52.6 (-100.0, 20.0)	-50.0 (-100.0, 40.4)
Objective response rate, % (95% CI)	83 (78, 87)	76 (70, 80)
Adjusted odds ratio (95% CI)†		1.61 (1.06, 2.44)
Complete response, n (%) Partial response, n (%) Stable disease ≥35 days, n (%) Progression, n (%)‡	1 (<1) 231 (83) 34 (12) 7 (3)	2 (1) 208 (75) 51 (18) 12 (4)
Median duration of response, months (95% CI)	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)

Data cut-off: 03 April 2023
*Overall, 275 patients from the osimertinib + platinum-pemetrexed arm and 276 from the osimertinib monotherapy arm had best percentage change in target lesion size available, including imputed values – indicated by * on the graphs; best percentage change will be imputed as +20% if it is known that the patient has died, has new lesions / progression of lesions, or has withdrawn due to progressive disease and has no evaluable target lesion data before or at progressive disease; †Performed using a logistic regression stratified by race, WHO PS and tissue test method; ‡Progression or death in the absence of progression; BoR, best overall response; CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; WHO, World Health Organization performance status

Safety summary

- Median total duration of osimertinib exposure was 22.3 months (range 0.1–33.8) in the osimertinib plus platinum-pemetrexed arm and 19.3 months (range
0.1–33.8) in the osimertinib monotherapy arm
- In the osimertinib plus platinum-pemetrexed arm, patients received a median of 12 cycles of pemetrexed (range 1–48) and 211 patients (76%) completed 4 cycles of pemetrexed.
    - In the osimertinib plus platinum-pemetrexed arm, 208 patients (75%) discontinued pemetrexed, mainly due to AEs. The median total exposure time for pemetrexed was 8.28 months (range: 0.7 to 33.8 months).

Patients with AEs, n (%)*	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
AE possibly causally related to treatment†	**269 (97)**	**241 (88)**
Any AE Grade ≥3	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (<1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (<1) / NA / NA
Any serious AE	52 (19)	15 (5)

AE, adverse event; NA, not applicable
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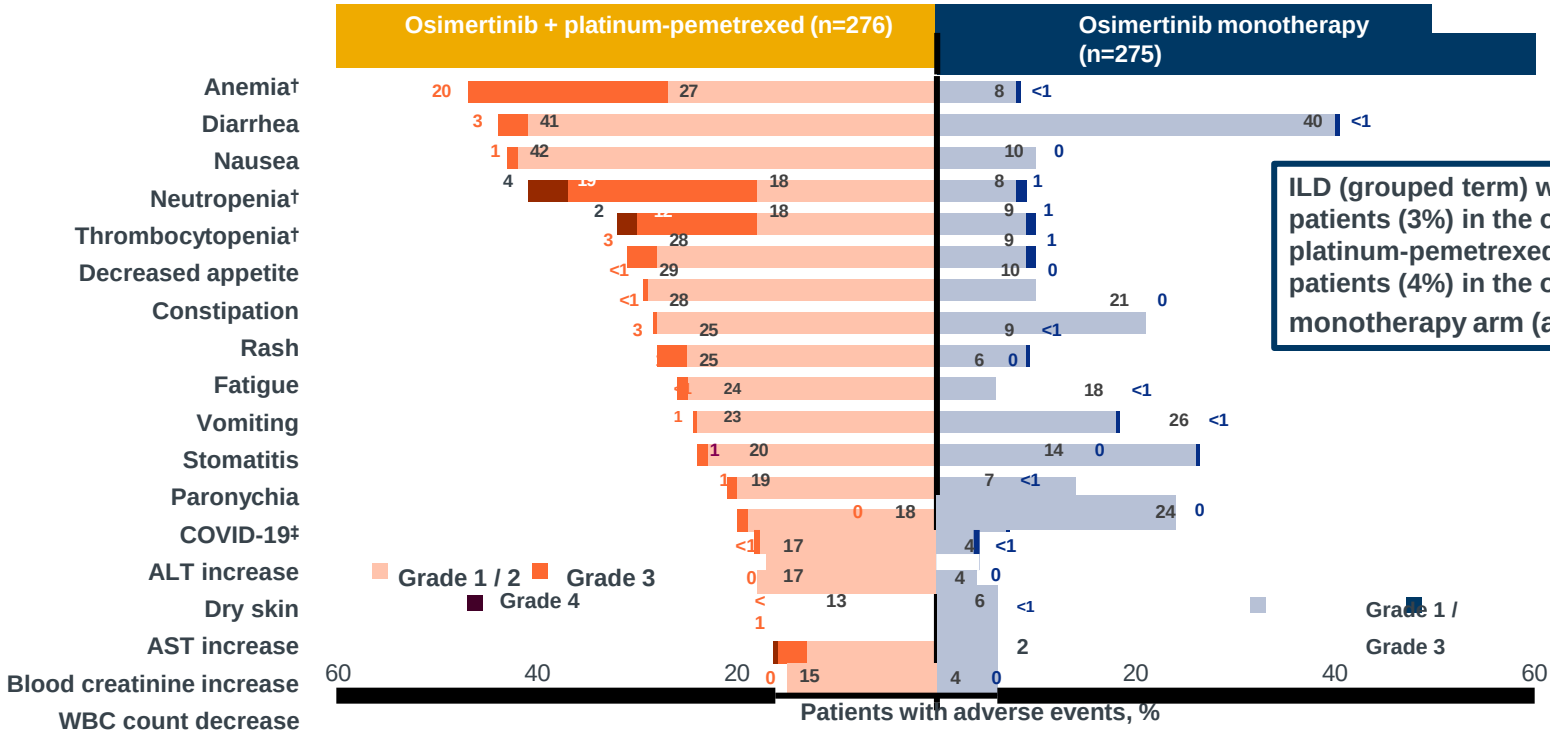
Data cut-off: 03 April 2023
*Percentages calculated and rounded to nearest whole number; †Per investigator assessment

Common adverse events (≥15% of patients)*



ILD (grouped term) was reported in 9 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†

- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Data cut-off: 03 April 2023

*In commonly reported AEs, defined as occurring in >15% of patients in either treatment arm, by MedDRA preferred terms (unless stated as a grouped term of the same medical concepts); †Grouped term: anemia / hemoglobin decreased, thrombocytopenia / platelet count decreased, neutropenia / neutrophil count decreased, and interstitial lung disease / pneumonitis / organizing pneumonitis (by preferred terms); ‡Of common AEs (≥15% of patients), one Grade 5 AE of COVID-19 was reported in the osimertinib plus platinum-pemetrexed arm

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID, coronavirus disease; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell

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Conclusions

- Osimertinib in combination with platinum-pemetrexed has demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy in patients with EGFRm advanced NSCLC (HR: 0.62)
  - **Investigator-assessed median PFS: 25.5 vs 16.7 months (improvement of ~8.8 months)**
  - **BICR-assessed median PFS: 29.4 vs 19.9 months (improvement of ~9.5 months)**
- PFS benefits were consistent across all pre-defined subgroups
- PFS2 and OS data were immature at this interim analysis
- The safety profiles were as expected for each treatment and were manageable with standard medical practice
- Further ongoing analyses include CNS BICR response and progression, patient-reported outcomes, post-progression endpoints, and ctDNA analyses (resistance mechanisms and ctDNA dynamics)

Osimertinib plus platinum-pemetrexed offers a new first-line treatment option for patients with EGFRm advanced NSCLC

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; ctDNA, circulating tumor DNA; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

Professor Pasi Jänne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, USA – Presented at WCLC 2023, Oral communication PL03.13

ACQUIRED RESISTANCE MECHANISMS

Functional groups	Acquired gene alteration, n (%)	FLAURA osimertinib monotherapy (n=109)[1]	FLAURA2 osimertinib monotherapy (n=73)	FLAURA2 osimertinib + platinum-pemetrexed (n=53)*
EGFR mutations	C797S	7 (6)	9 (12)	2 (4)
	Other Uncommon	5 (5)	3 (4)	ND
RTK amplifications	*MET* amplification	17 (16)	10 (14)	5 (9)
	ERRB2 amplification	2 (2)	1 (1)	3 (6)
MAPK / PI3K mutations	*BRAF* V600E	3 (3)	4 (5)	ND
	KRAS mutation	3 (3)	6 (8)	3 (6)
	PIK3CA mutation	6 (6)	6 (8)	2 (4)
	ERBB2 mutation	ND	1 (1)	ND
Cell cycle gene amplifications	*CCND1 / E1* amplification	7 (6)	1 (1)	3 (6)
	CDK4 / 6 amplification	7 (6)	4 (5)	3 (6)
Fusions	*RET*	ND	3 (4)	1 (2)
	BRAF	ND	3 (4)	1 (2)
	ALK	1 (1)	2 (3)	ND
	Other	NR	5 (7)	2 (4)
***RB1* loss (with *TP53*)**		NR	4 (5)	ND
No known resistance alteration detected		NR	36 (49)	40 (75)

Acquired resistance mechanisms were broadly similar across treatment arms

Chee Khoon Lee, MBBS, PhD

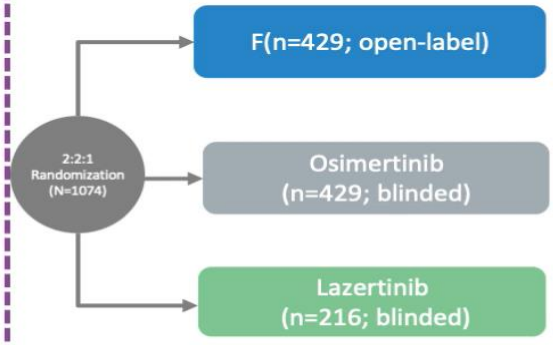
[1]Chmielecki et al. Nat Comm 2023;14:1070
*Includes plasma samples from patients in SR1 (n=7) and randomised parts (n=46) of FLAURA2

MARIPOSA: design de l'étude

Key Eligibility Criteria :
- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors :
- *EGFR* mutation-type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Serial brain MRIs were required for all patient



Primary endpoint of progression-free survival (PFS) by BICR per RECIST v1.1:
- Amivantamab + lazertinib vs osimertinib

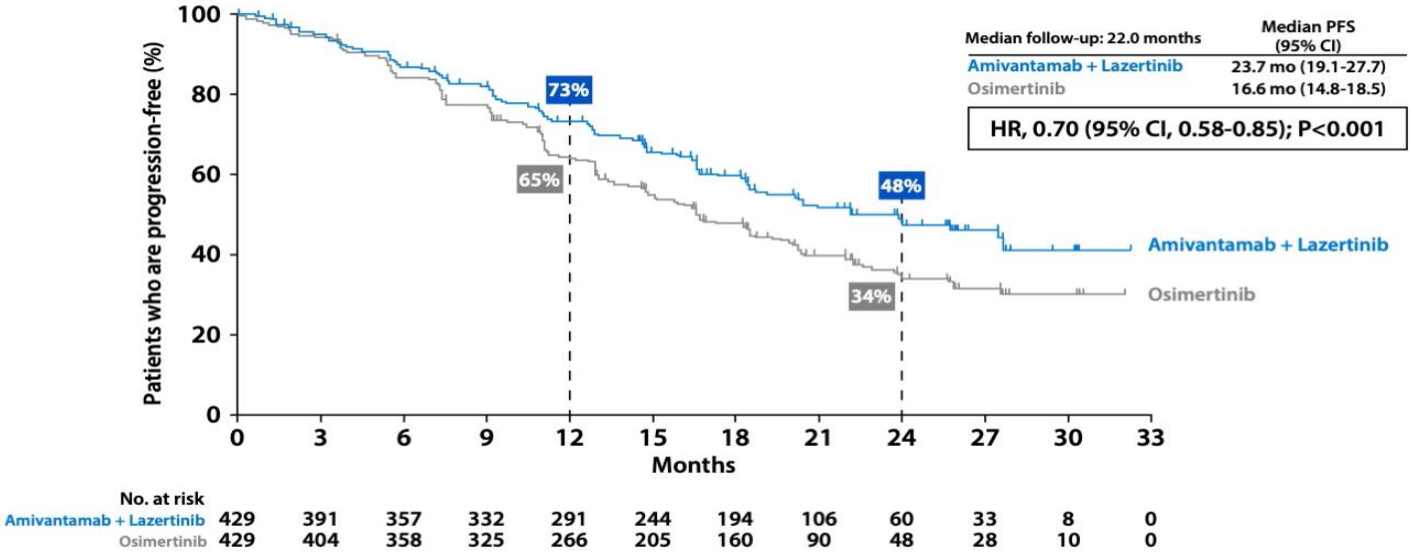
Secondary endpoints of amivantamab + lazertinib vs osimertinib:
- Overall survival (OS)
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS
- Intracranial PFS
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

- Critère de jugement principal: survie sans progression du bras lazertinib amivantamab versus osimertinib selon un comité de relecture

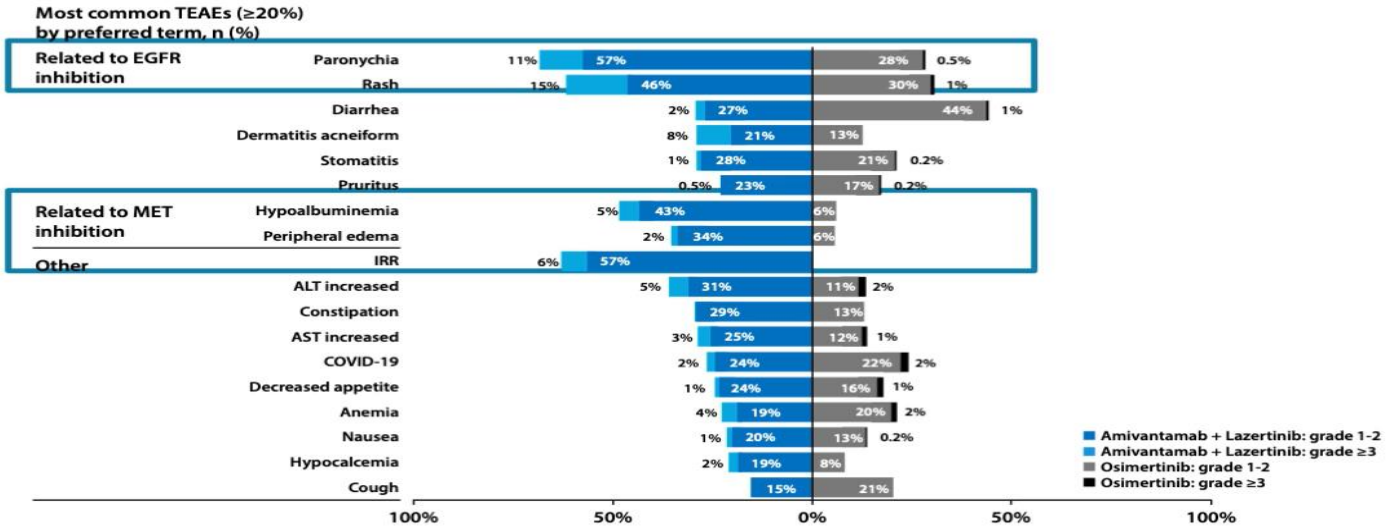
MARIPOSA: Survie sans progression selon le comité de relecture indépendant



- Amélioration de la survie sans progression de 8 mois
- Bénéfice dans tous les sous-groupes

Cho BC et al. #LBA14, ESMO 2023

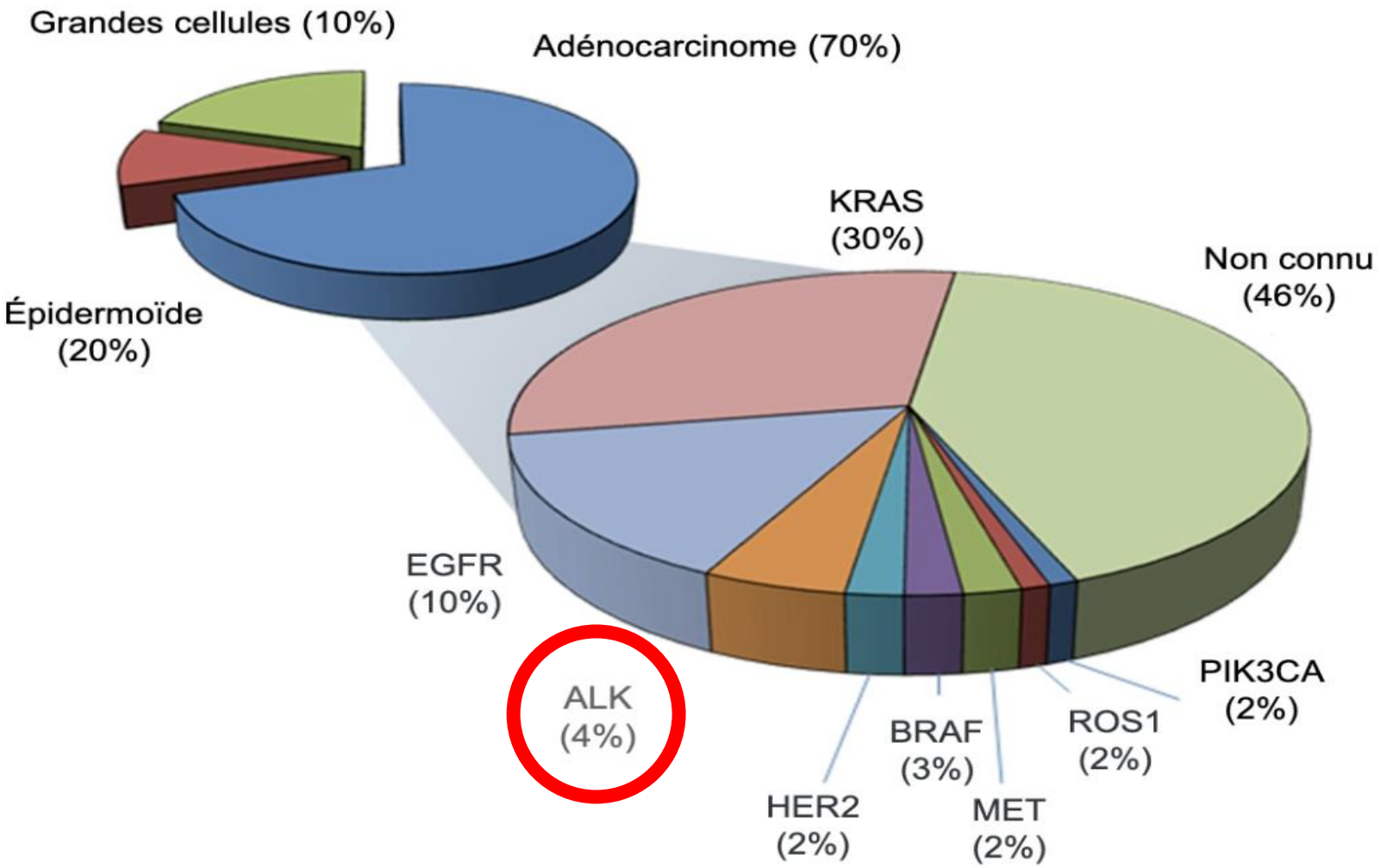
MARIPOSA: profil de tolérance



TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

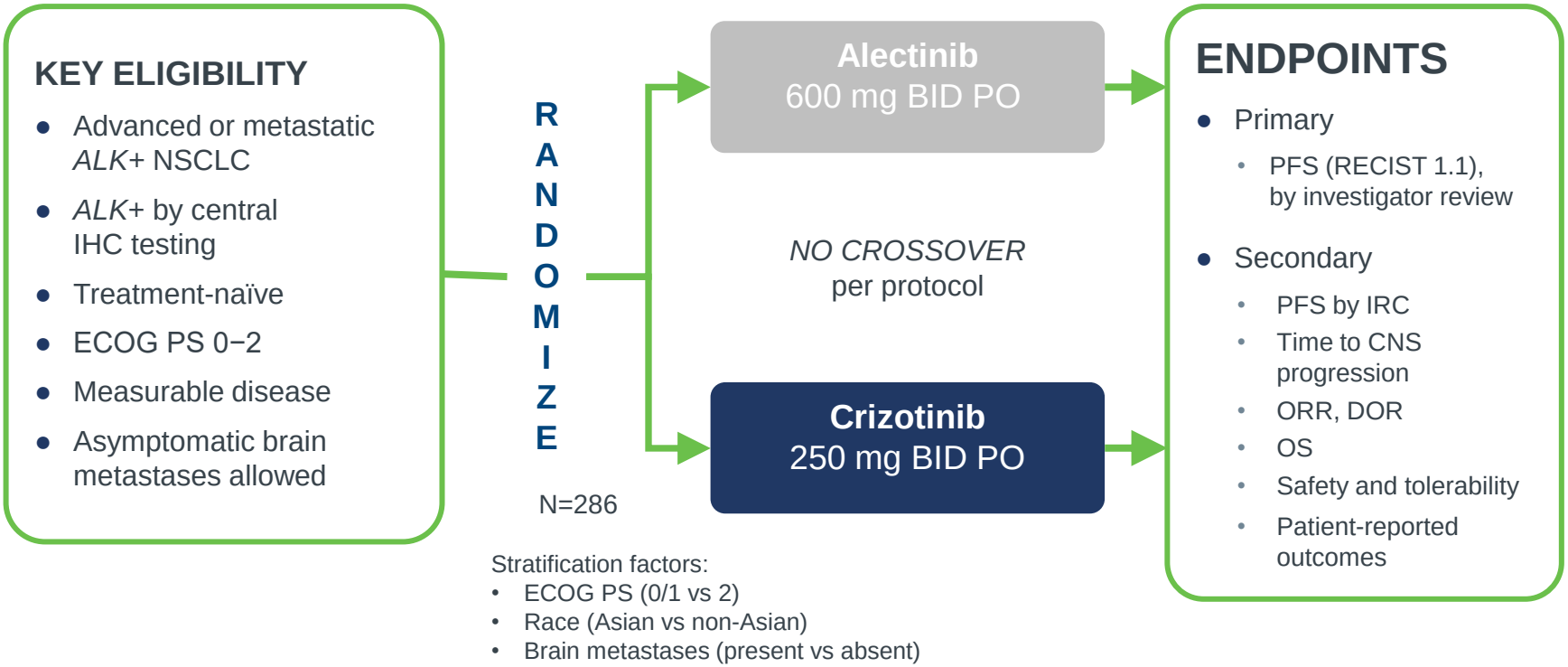
Cho BC et al. #LBA14, ESMO 2023

ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

ALEX: Alectinib as first-line treatment



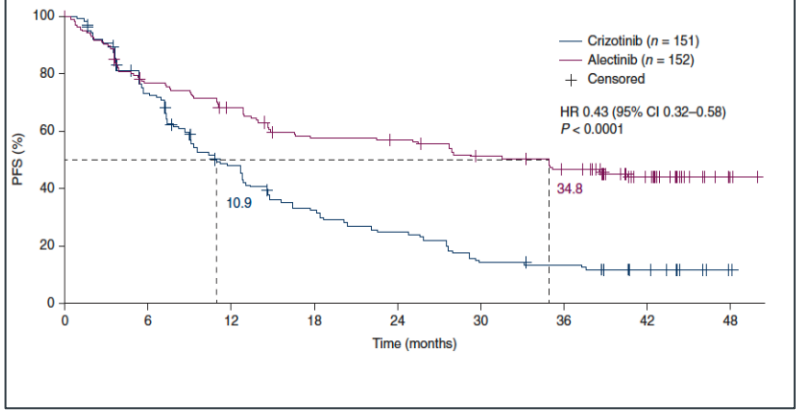
BID, twice daily; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; IRC, independent review committee; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PO, by mouth; PFS, progression-free survival.
*Brigatinib is centrally authorised in the EU after crizotinib failure but not yet marketed in Spain pending pricing and reimbursement approval.

1. Shaw A, et al. Presented at ASCO 2017, Chicago, USA, 2–6 June 2017.
2. Alecensa (alectinib) Summary of Product Characteristics. Last updated September 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf;
3. Xalkori (crizotinib) Summary of Product Characteristics. Last updated February 2018.Available at: https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information_en.pdf (SmPCs accessed August 2019).

Updated ALEX: Alectinib as first-line treatment

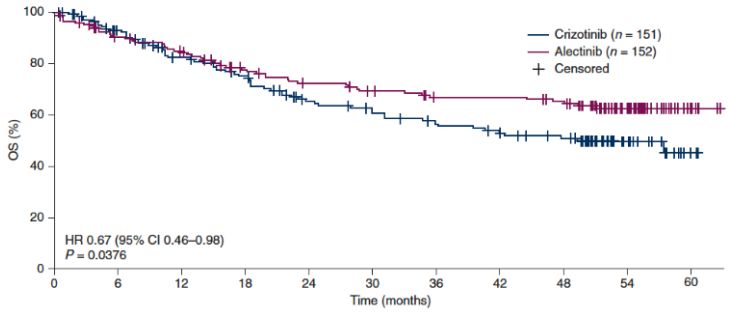
ALEX trial
-NCT02075840
-Phase 3
-No prior chemo

Progression Free Survival



Overall Survival

5-year OS rate: 62.5%



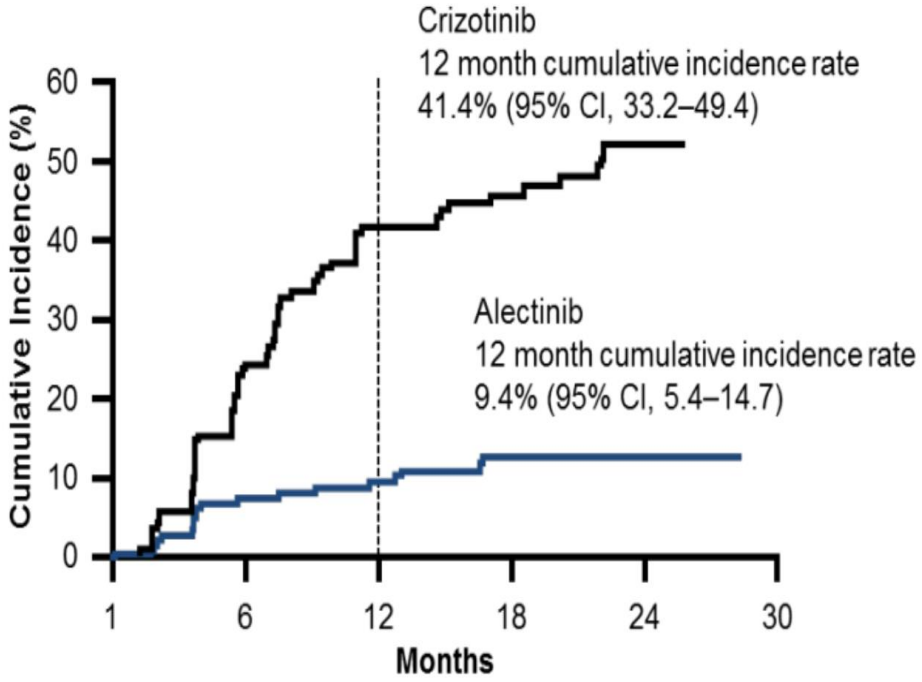
mPFS Alectinib 34.8 months *vs* Crizotinib 10.9 months

For full information about the treatment please refer to local recommendation applicable in your country and prescribing information available on the SmPC

mPFS, median progression free survival; OS, overall survival.

Mok T, et al. Ann Oncol 2020;31:1056–1064.

Figure 4: Cumulative Incidence of CNS Progression in the Phase 3 ALEX Study[1]



The cumulative incidence of CNS progression in patients with and without CNS metastases and prior and no prior radiation is shown in Table 3.

Mok T, et al. Ann Oncol 2020;31:1056–1064.

Figure 4: Cumulative Incidence of CNS Progression in the Phase 3 ALEX Study[1]

Table 5: Adverse Events, ≥10% Difference Between Treatment Arms in the Phase 3 ALEX Study[1]

Adverse Events, n (%)	Alecensa (n=152)		Crizotinib (n=151)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Anemia	30 (20)	7 (5)	7 (5)	1 (1)
Peripheral Edema	26 (17)	0	42 (28)	1 (1)
Myalgia	24 (16)	0	3 (2)	0
Increased ALT	23 (15)	7 (5)	45 (30)	22 (15)
Increased blood bilirubin	23 (15)	3 (2)	2 (1)	0
Nausea	21 (14)	1 (1)	72 (48)	5 (3)
Increased AST	21 (14)	8 (5)	37 (25)	16 (11)
Diarrhea	18 (12)	0	68 (45)	3 (2)
Increased weight	15 (10)	1 (1)	0	0
Vomiting	11 (7)	0	58 (38)	5 (3)
Dysgeusia	4 (3)	0	29 (19)	0
Visual impairment	2 (1)	0	8 (12)	0

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase.

ÉTUDE ALTA-1L

MÉTHODOLOGIE[3]

Critère d'évaluation principal

Survie sans progression (SSP) évaluée en aveugle par un comité de revue indépendant (CRI) selon les critères RECIST v1.1

Principaux critères d'évaluation secondaires

- Taux de réponse objective (TRO) confirmée, évaluée par le CRI*
- Durée de la réponse (DR), évaluée par le CRI
- Taux de réponse objective intracrânienne (TROic) confirmée, évaluée par le CRI*
- Durée de réponse intracrânienne
- Survie sans progression intracrânienne (SSPic)**, évaluée par le CRI*
- Survie globale (SG)*
- Délai jusqu'à la réponse, évalué par le CRI
- Qualité de vie : variation du score d'état de santé global et de qualité de vie par rapport à l'inclusion
- Tolérance

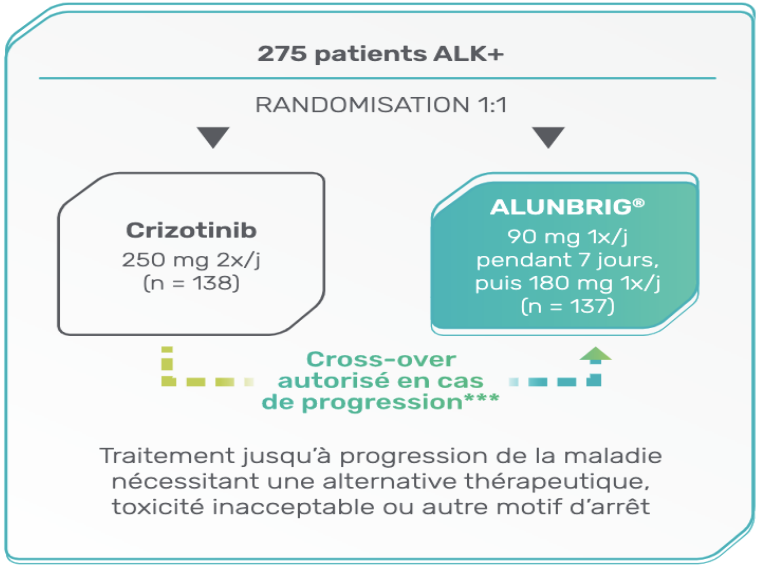
Deux analyses intermédiaires ont été planifiées à 50 % et à 75 % de la survenue totale des évènements attendus (progression ou décès)

* Ces 4 critères secondaires (TRO, TROic, SSPic, SG) ont fait l'objet d'une analyse hiérarchique séquentielle.

** Définie par la durée entre la date de randomisation et la date de progression intracrânienne, de décès ou de radiothérapie pour le traitement d'une métastase cérébrale chez les patients ayant des métastases cérébrales à l'inclusion.

Médiane de suivi : ALUNBRIG® : 40,4 mois et crizotinib : 15,2 mois

Design de l'étude



Stratification selon :

- La présence de métastases cérébrales (présence *vs* absence)
- L'administration antérieure d'une chimiothérapie dans un contexte de maladie localement avancée ou métastatique (oui *vs* non)

*** 10 jours de wash-out avant admission dans le bras ALUNBRIG®.

ÉTUDE ALTA-1L

RÉSULTATS D'EFFICACITÉ[3]

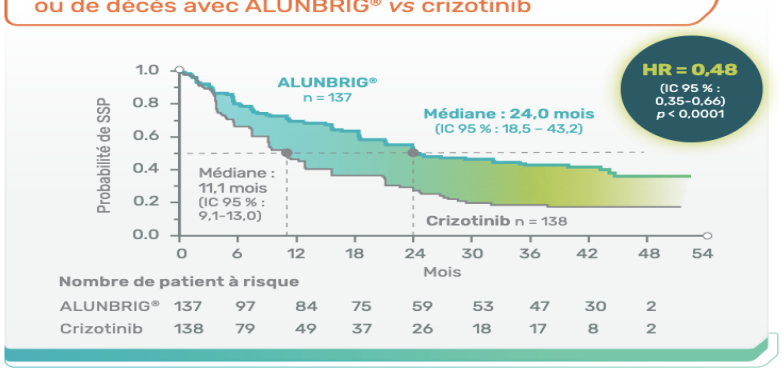
POPULATION EN ITT (n = 275)

Critère principal

Survie sans progression

(évaluation en aveugle par le comité de revue indépendant)

Réduction significative de 52 % du risque de progression ou de décès avec ALUNBRIG® *vs* crizotinib



Durée médiane de suivi : **40,4 mois (0 - 52,4) pour le bras ALUNBRIG®** et 15,2 mois (0,1 – 51,7) pour le bras crizotinib

Durée médiane de traitement : **34,9 mois (0,1 - 52,4) pour le bras ALUNBRIG®** et 9,3 mois (0,1 - 51,5) pour le bras crizotinib

SSP médiane évaluée par l'investigateur : **30,8 mois (IC 95 % : 21,3 – 40,6) pour le bras ALUNBRIG®** et 9,2 mois (IC 95 % : 7,4 – 12,7) pour le bras crizotinib ; HR = 0,43 (IC 95 % : 0,31–0,58), p<0,0001

Survenue d'un évènement (progression, décès ou radiothérapie palliative) chez 53 % des patients traités par ALUNBRIG® et 67 % des patients traités par crizotinib

Une réduction de 75 % du risque de progression ou de décès avec ALUNBRIG® *vs* crizotinib chez les patients avec métastases cérébrales à l'inclusion*
(bras ALUNBRIG® : n = 40 ; bras crizotinib : n = 41 ; HR = 0,25 ; IC 95 % : 0,14–0,46)

Critères secondaires

Taux de réponse objective confirmée

(évaluation par le comité de revue indépendant)

	ALUNBRIG® (n = 137)	Crizotinib (n = 138)
N. de patients	137	138
Taux de réponse objective confirmée, % (n)	74 % (102) (IC 95 % : 66-82)	62 % (86) (IC 95 % : 54-70)
OR (IC 95 %)	1,74 (1,04-2,91) p = 0,0330	
Réponse complète, % (n)	24 % (33)	13 % (18)
Réponse partielle, % (n)	50 % (69)	49 % (68)

Le taux de réponse objective confirmée n'étant pas significatif à la 1ère analyse intermédiaire, tous les critères secondaires suivants sont présentés à titre exploratoire.

Durée médiane de réponse confirmée

(évaluation par le comité de revue indépendant ; résultat présenté à titre exploratoire)

ALUNBRIG®
33,2 mois
(IC 95 % : 22,1-NA)

Crizotinib
13,8 mois
(IC 95 % : 10,4–22,1)

NA : non atteint ; ITT : intention de traiter ; OR : odds ratio.
* Métastases cérébrales à l'inclusion évaluées par l'investigateur.
# Médiane de suivi : ALUNBRIG® : 40,4 mois et crizotinib : 15,2 mois.

ÉTUDE ALTA-1L

RÉSULTATS D'EFFICACITÉ [3,4]

POPULATION EN ITT (n = 275)

Analyse Finale ALTA-1L Suivi médian >3 ans*

Critère secondaire
(résultat présenté à titre exploratoire)

Survie globale

ALUNBRIG® : non atteinte (IC 95 % : NA–NA)
Crizotinib : non atteinte (IC 95 % : NA–NA)
HR = 0,81 (IC 95 % : 0,53 – 1,22) ; p = 0,331

Selon l'analyse de sensibilité, le hazard ratio de la survie globale, après ajustement sur l'effet du cross-over, était de 0,54 (IC 95 % : 0,31–0,92, p = 0,023) par la méthode MSM, et de 0,50 (IC 95 % : 0,28–0,87 ; p = 0,014) par la méthode IPCW.

Délai jusqu'à la réponse chez les patients répondeurs
(évaluation par le comité de revue indépendant)

ALUNBRIG® (n = 137)
Patients répondeurs : n = 102
Délai jusqu'à la réponse (médiane) : **1,84 mois**
(IC 95 % : 1,84–1,87)

Crizotinib (n = 138)
Patients répondeurs : n = 86
Délai jusqu'à la réponse (médiane) : 1,87 mois
(IC 95 % : 1,84–1,87)

IPCW : Inverse probability of censoring weighting ; ITT : intention de traiter ; MSM : Marginal structural approach ; NA : non atteint ; NE : non évaluable.
* Médiane de suivi : ALUNBRIG® : 40,4 mois et crizotinib : 15,2 mois.

RÉSULTATS D'EFFICACITÉ INTRACRÂNIENNE [3]

PATIENTS AVEC MÉTASTASES MESURABLES À L'INCLUSION (n = 41)

Critères secondaires
(résultats présentés à titre exploratoire)

Taux de réponse objective intracrânienne confirmée
(évaluation par le comité de revue indépendant)

	ALUNBRIG® (n = 18)	Crizotinib (n = 23)
Taux de réponse objective intracrânienne, % (n)	78 % (14) (IC 95 % : 52 - 94)	26 % (6) (IC 95 % : 10 - 48)
OR (IC 95 %)	11,67 (2,15 - 63,27) p = 0,0014	
Réponse complète, % (n)	28 % (5)	0
Réponse partielle, % (n)	50 % (9)	26 % (6)

Durée médiane de réponse intracrânienne chez les patients répondeurs
(évaluation par le comité de revue indépendant)

ALUNBRIG®
27,9 mois
(IC 95 % : 5,7–NE)

Crizotinib
9,2 mois
(IC 95 % : 3,9–NE)

ÉTUDE ALTA-1L

RÉSULTATS DE QUALITÉ DE VIE[3]

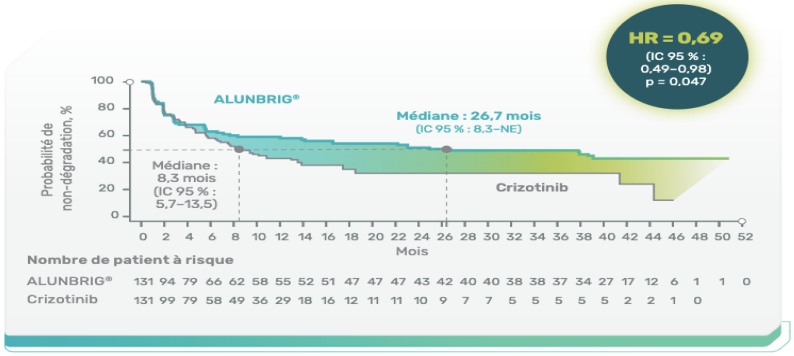
POPULATION PRO-ITT (n = 262)

Critères secondaires

(résultats présentés à titre exploratoire)

Délai avant la dégradation du score de qualité de vie*

(données rapportées par les patients, questionnaire EORTC QLQ-C30)



Délai avant la dégradation du score de qualité de vie globale et des scores de symptômes

Qualité de vie globale et scores fonctionnels	Hazard Ratio (IC 95 %)
Etat de santé global	0,69 (0,49–0,98)
Fonctionnement physique	0,69 (0,49–0,98)
Fonctionnement quotidien	0,85 (0,62–1,18)
Fonctionnement émotionnel	0,54 (0,38–0,79)
Fonctionnement cognitif	0,76 (0,56–1,04)
Fonctionnement social	0,57 (0,40–0,81)

Scores des symptômes	Hazard Ratio (IC 95%)
Fatigue	0,69 (0,50–0,96)
Nausées et vomissements	0,57 (0,41–0,78)
Douleur	0,84 (0,61–1,17)
Dyspnée	0,91 (0,63–1,33)
Insomnie	0,95 (0,64–1,40)
Perte d'appétit	0,60 (0,42–0,87)
Constipation	0,53 (0,38–0,74)
Diarrhée	1,01 (0,76–1,36)

EORTC : European Organization for Research and Treatment of Cancer Quality of Life Questionnaire ; PRO-ITT : résultat rapporté par les patients – intention de traiter.

* Un changement ≥ 10 points a été défini comme la détérioration minimale cliniquement significative. Le délai d'aggravation était défini comme le temps écoulé entre la date de randomisation et la date la plus ancienne à laquelle le score du patient a subi une détérioration ≥ 10 points par rapport à la valeur initiale.

Médiane de suivi : ALUNBRIG® : 40,4 mois et crizotinib : 15,2 mois

ÉTUDE ALTA-1L

TOLÉRANCE[3]

POPULATION EN ITT (n = 275)

Effets indésirables rapportés chez ≥ 5 % des patients, tous grades confondus (suite)

Effets indésirables, n(%)	ALUNBRIG® (n = 136)	Crizotinib (n = 137)
Rhinorrhée	7 (5)	5 (4)
Hyperkaliémie	7 (5)	3 (2)
Malaise	7 (5)	3 (2)
Hypokaliémie	7 (5)	1 (1)
Hypercholestérolémie	7 (5)	0
Syndrome grippal	6 (4)	11 (8)
Dysgueusie	5 (4)	20 (15)
Dépression	5 (4)	8 (6)
Augmentation de la GT	5 (4)	8 (6)
Œdème périphérique	5 (4)	8 (6)
Epanchement pleural	4 (3)	10 (7)
Douleur osseuse	4 (3)	7 (5)
Diminution du taux de neutrophiles	3 (2)	14 (10)
Dysphagie	3 (2)	12 (9)
Hypocalcémie	3 (2)	11 (8)
Hypotension	3 (2)	10 (7)
Hypoesthésie	3 (2)	9 (7)
Embolie pulmonaire	3 (2)	8 (6)
Troubles du goût	3 (2)	8 (6)
Photopsie	1 (1)	29 (21)
Déficience visuelle	1 (1)	23 (17)
Reflux gastro-œsophagien	1 (1)	16 (12)
Hypoalbuminémie	1 (1)	11 (8)
Thrombose veineuse profonde	0	9 (7)

Effets indésirables de grade ≥ 3 rapportés chez ≥ 2 % des patients de l'un des groupes (suite)

Effets indésirables, n(%)	ALUNBRIG® (n = 136)	Crizotinib (n = 137)
Augmentation du taux de CPK[a]	36 (26)	2 (1)
Augmentation du taux de lipase[b]	21 (15)	11 (8)
Hypertension	19 (14)	6 (4)
Augmentation du taux d'amylase[b]	8 (6)	2 (1)
Pneumonie	7 (5)	5 (4)
Augmentation du taux d'ALAT	6 (4)	14 (10)
Augmentation du taux d'ASAT	6 (4)	9 (7)
Progression des néoplasmes	4 (3)	4 (3)
Anémie	4 (3)	1 (1)
Augmentation du taux de phosphatase alkaline	4 (3)	1 (1)
Dyspnée	3 (2)	6 (4)
Embolie pulmonaire	3 (2)	5 (4)
Diarrhée	3 (2)	4 (3)
Nausée	3 (2)	4 (3)
Hypophosphatémie	3 (2)	3 (2)
Augmentation du taux de Gamma-GT	3 (2)	3 (2)
Maux de tête	3 (2)	0
Neutropénie	2 (1)	4 (3)
Epanchement pleural	2 (1)	3 (2)
Vomissements	2 (1)	3 (2)
Diminution du taux de neutrophiles	1 (1)	7 (5)
Diminution de l'appétit	1 (1)	4 (3)
Infection urinaire	1 (1)	3 (2)
Douleur abdominale haute	1 (1)	3 (2)
Douleur thoracique non-cardiaque	0	3 (2)

ALAT : Alanine aminotransférase ; ASAT : aspartate aminotransférase ; CPK : créatine phosphokinase ; Gamma-GT : Gamma-glutamyl transférase ; ITT : intention de traiter

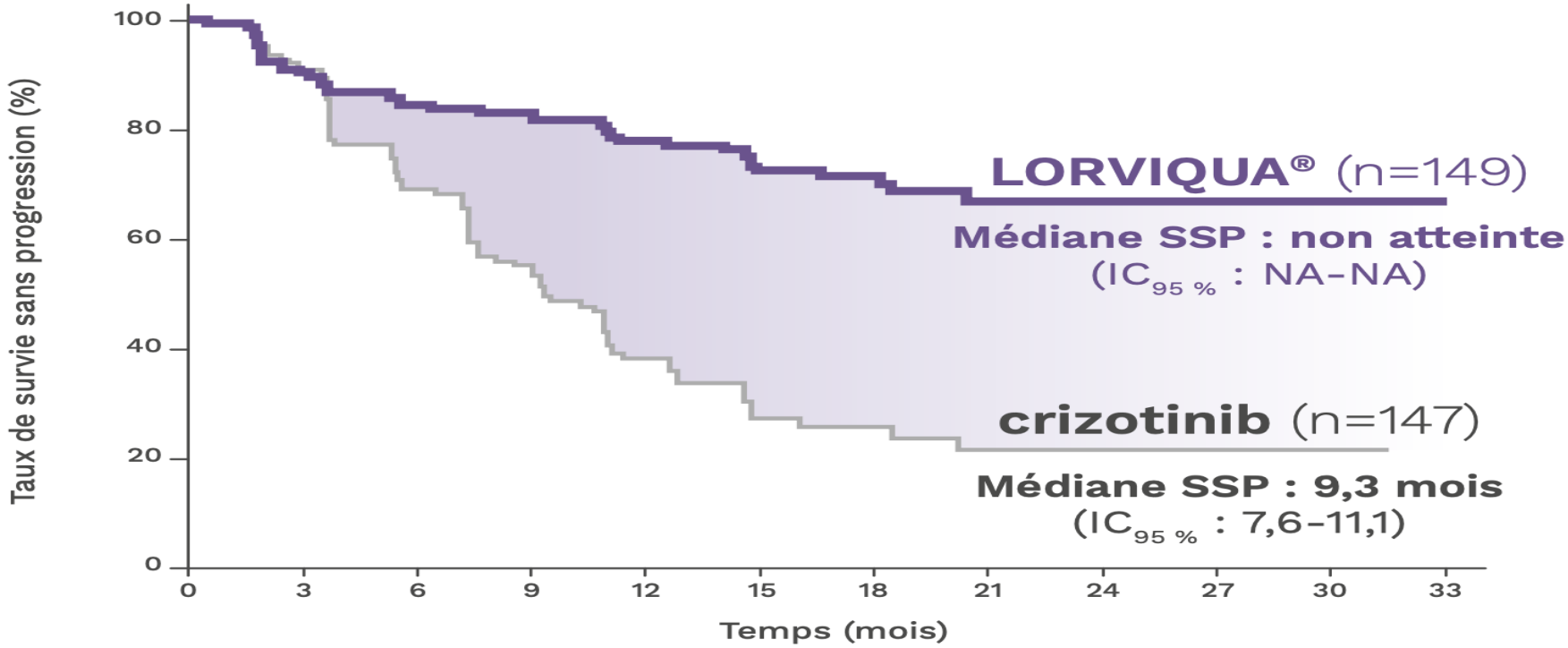
[a] Des myalgies ont été rapportées chez 14 (10 %) et 11 (8 %) patients dans les bras ALUNBRIG® et crizotinib, respectivement. Des douleurs musculo-squelettiques ont été signalées chez 15 (11 %) et 11 (8 %) patients, respectivement. Aucune myalgie ou douleur musculo-squelettique de grade ≥ 3 n'a été signalée dans les deux bras. [b] Aucun cas de pancréatite clinique n'a été signalé dans les deux bras.

[#] Médiane de suivi : ALUNBRIG® : 40,4 mois et crizotinib : 15,2 mois

ÉTUDE DE PHASE III DE LORVIQUA®
EN 1re LIGNE CHEZ L'ADULTE ATTEINT DU CPNPC AVANCÉ ALK+ (ÉTUDE CROWN)

Hazard ratio : 0,28 ($IC_{95\ \%}$: 0,19–0,41) ; p < 0,001

72 % **Réduction** statistiquement significative du risque de progression ou de décès *versus* crizotinib



Nombre de patients à risque

LORVIQUA®	**149**	**129**	**118**	**113**	**105**	**73**	**59**	**33**	**20**	**11**	**4**	**2**
crizotinib	147	120	84	62	39	19	16	8	4	2	1	0

Critères secondaires [4] : TAUX DE RÉPONSE OBJECTIVE (TRO)

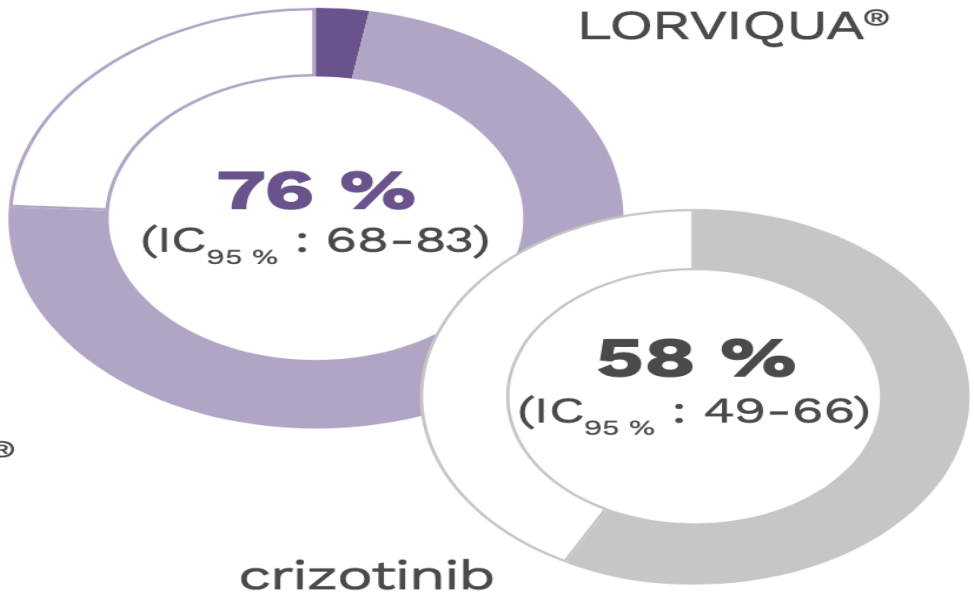
Évaluation «en aveugle» par le **comité de surveillance indépendant** (BICR) dans la population en ITT

TRO LORVIQUA® (n=149)
- **Réponse complète (3 %)**
- Réponse partielle (73 %)

TRO crizotinib (n=147)
- **Réponse complète (0 %)**
- Réponse partielle (58 %)

Durée médiane de réponse :
non atteinte pour LORVIQUA® (NA-NA) *versus* 11 mois (9,0-12,9) avec crizotinib

Durée de réponse ≥ 12 mois :
70 % avec LORVIQUA® *versus* 27 % avec crizotinib



Odds ratio : 2,25 %
($IC_{95\ \%}$: 1,35-3,89)

TAUX DE RÉPONSE OBJECTIVE INTRACRÂNIENNE

Patients avec métastases cérébrales mesurables et non mesurables à l'inclusion

	LORVIQUA® (n=38)	Crizotinib (n=40)
Répondeurs, n (%)	24 (65)	7 (18)
($IC_{95\ \%}$)	(48-80)	(8-34)
Odds ratio ($IC_{95\ \%}$)	8,98 (2,67-29,79)	
Réponse complète, n (%)	22 (59)	5 (13)
Durée de réponse médiane, mois ($IC_{95\ \%}$)	NA (NA - NA)	9,4 (6,0-11,1)

ÉTUDE DE PHASE III DE LORVIQUA®
EN 1re LIGNE CHEZ L'ADULTE ATTEINT DU CPNPC AVANCÉ ALK+ (ÉTUDE CROWN)

Événements	LORVIQUA® (n=149)					crizotinib (n=142)			
	Tout grade	Grade 1	Grade 2	Grade 3	Grade 4	Tout grade	Grade 1	Grade 2	Grade 3	Grade 4
	NOMBRE DE PATIENTS (%)									
Événements indésirables	**149 (100)**	3 (2)	23 (15)	94 (63)	19 (13)	**140 (99)**	8 (6)	44 (31)	69 (49)	12 (8)
Hypercholestérolémie †	**108 (72)**	24 (16)	55 (37)	27 (18)	2 (1)	**5 (4)**	5 (4)	0	0	0
Hypertriglycéridemie †	**99 (66)**	29 (19)	36 (24)	23 (15)	11 (7)	**8 (6)**	5 (4)	3 (2)	0	0
Œdème †	**83 (56)**	55 (37)	22 (15)	6 (4)	0	**61 (43)**	40 (28)	19 (13)	2 (1)	0
Prise de poids	**65 (44)**	10 (7)	25 (17)	30 (20)	0	**18 (13)**	5 (4)	10 (7)	3 (2)	0
Neuropathie périphérique †	**60 (40)**	42 (28)	16 (11)	2 (1)	0	**21 (15)**	18 (13)	2 (1)	1 (1)	0
Arthralgie	**39 (26)**	31 (21)	7 (5)	1 (1)	0	**20 (14)**	14 (10)	6 (4)	0	0
Effets cognitifs †	**38 (26)**	23 (15)	10 (7)	5 (3)	0	**9 (6)**	8 (6)	1 (1)	0	0
Anémie	**33 (22)**	15 (10)	13 (9)	5 (3)	0	**13 (9)**	4 (3)	5 (4)	4 (3)	0
Diarrhées	**33 (22)**	22 (15)	9 (6)	2 (1)	0	**75 (53)**	67 (47)	7 (5)	1 (1)	0
Hypertension	**33 (22)**	1 (1)	15 (10)	17 (11)	0	**4 (3)**	0	3 (2)	1 (1)	0
Constipation	**29 (19)**	27 (18)	2 (1)	**0**	0	**43 (30)**	31 (22)	11 (8)	1 (1)	0
Trouble visuel †	**28 (19)**	26 (17)	2 (1)	**0**	0	**56 (39)**	54 (38)	1 (1)	1 (1)	0
Augmentation du taux ALT †	**27 (18)**	23 (15)	0	4 (3)	0	**49 (35)**	27 (19)	16 (11)	5 (4)	1 (1)
Effets sur l'humeur	**26 (17)**	14 (9)	10 (7)	2 (1)	0	**9 (6)**	5 (4)	4 (3)	0	0
Nausées	**23 (15)**	22 (15)	0	1 (1)	0	**75 (53)**	57 (40)	15 (11)	3 (2)	0
Augmentation du taux de AST †	**22 (15)**	18 (12)	1 (1)	3 (2)	0	**39 (27)**	30 (21)	4 (3)	5 (4)	0
Vomissements	**20 (13)**	17 (11)	2 (1)	1 (1)	0	**56 (39)**	43 (30)	11 (8)	2 (1)	0
Hyperlipidémie	**16 (11)**	6 (4)	7 (5)	2 (1)	1 (1)	**0**	0	0	0	0
Dysgueusie	**9 (6)**	9 (6)	0	**0**	0	**23 (16)**	20 (14)	3 (2)	0	0
Perte d'appétit	**6 (4)**	4 (3)	2 (1)	**0**	0	**35 (25)**	23 (16)	8 (6)	4 (3)	0
Bradycardie	**3 (2)**	3 (2)	0	**0**	0	**20 (14)**	16 (11)	4 (3)	0	0

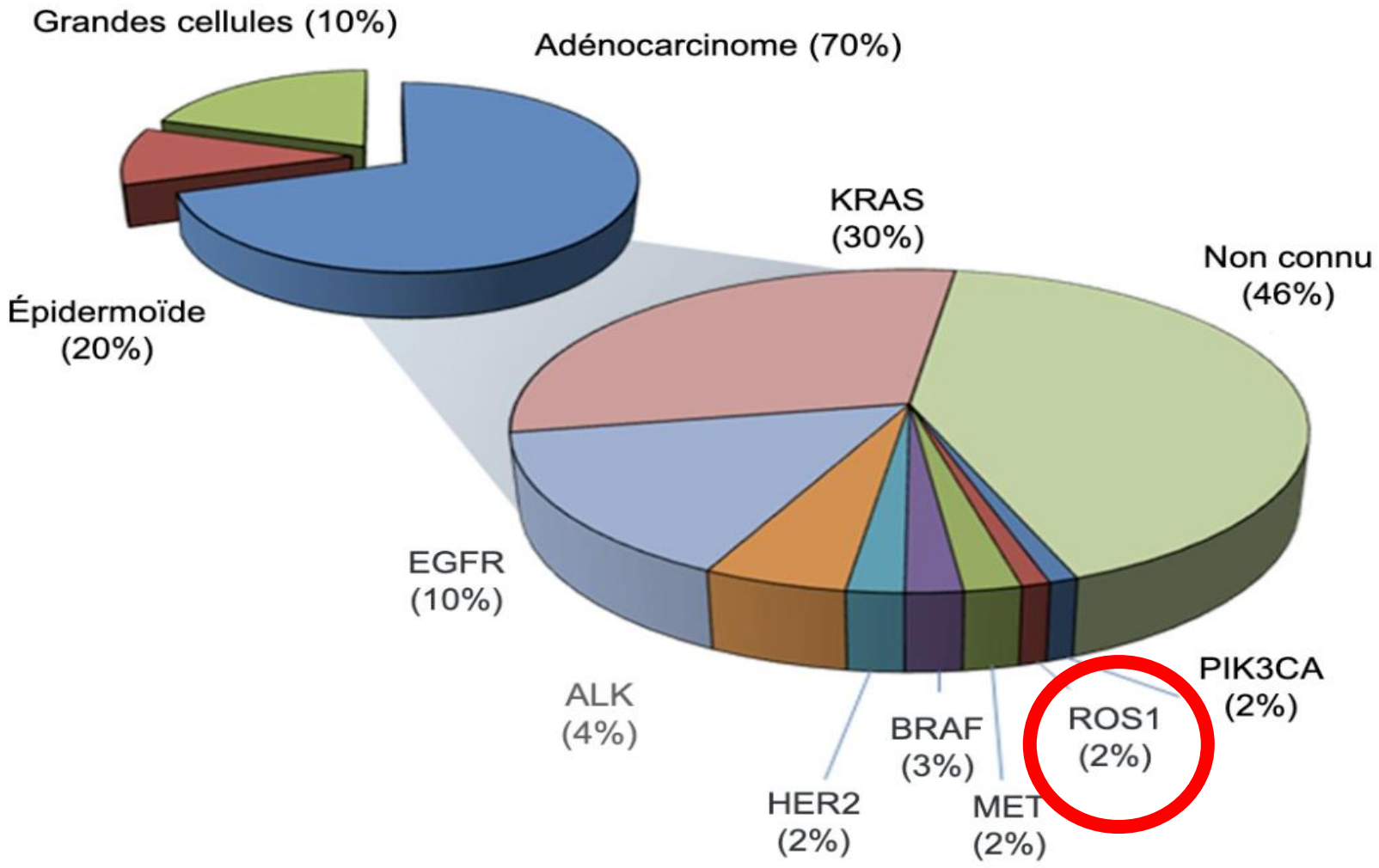
Résumé Anti ALK

CBPNPC avancé avec translocation ALK

Etude	ALTA-1L[1] (%)		ALEX[2]		CROWN[3]	
	Brigatinib (n=137)	Crizotinib (n=138)	Alectinib (n=152)	Crizotinib (n=151)	Lorlatinib (n=147)	Crizotinib (n=149)
PFS (mois)	30,8	9,2	34,8	10,9	NR	9,3
HR (95%CI)	0,43 (0,31 – 0,58)		0,43 (0,32 – 0,58)		0,27 (0,18 – 0,39)	
Taux de PFS-6 mois, %	43	19	46,4	13,5	64	19
Durée médiane de suivi	40,4	15,2	37,8	23,0	36,7	29,3

Camidge DR, et al; J Thorac Oncol 2021; Mok T, et al. Ann Oncol 2020; Solomon BJ, et al. Lancet Resp Med 2023

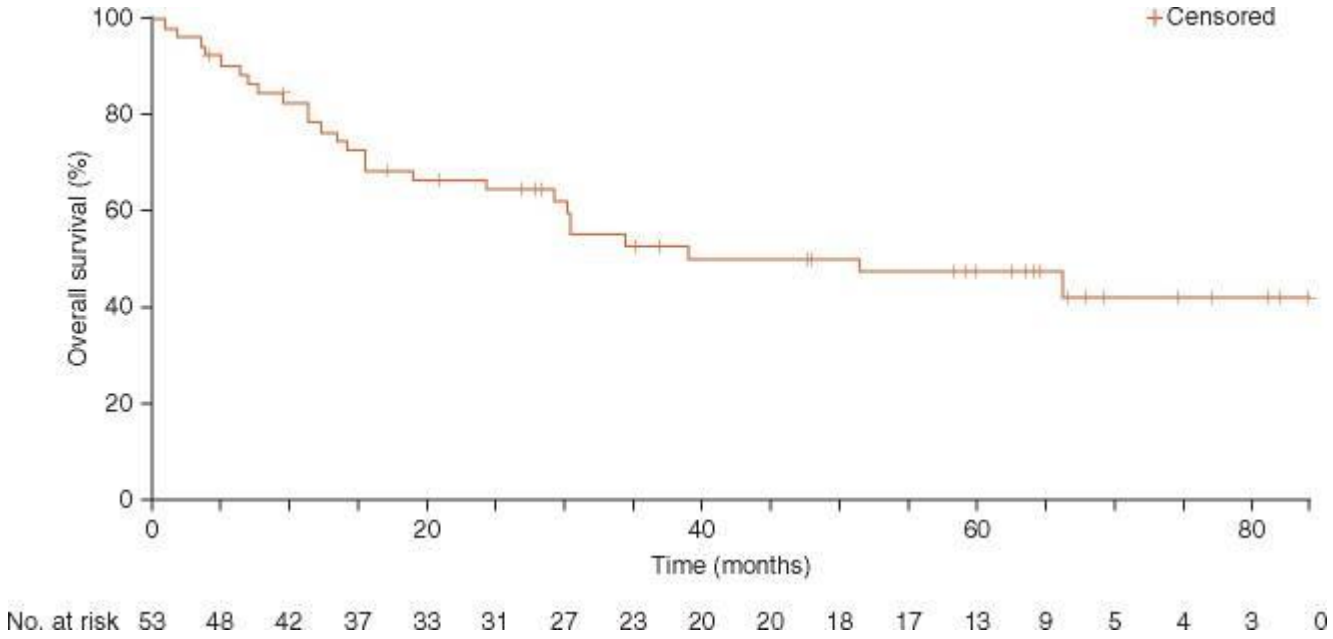
ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



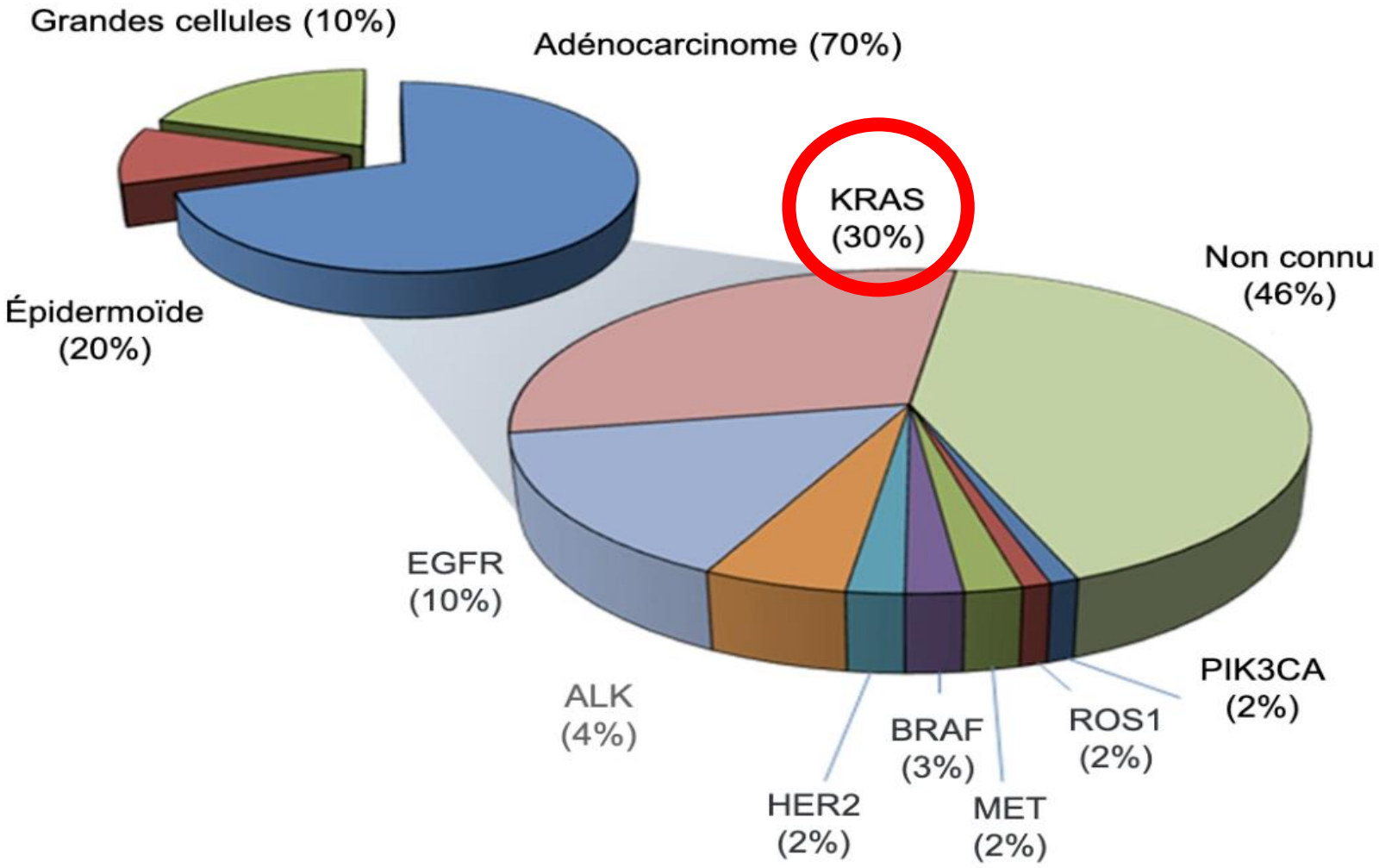
Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001

After a median follow-up of 62.6 months, median OS was 51.4 months

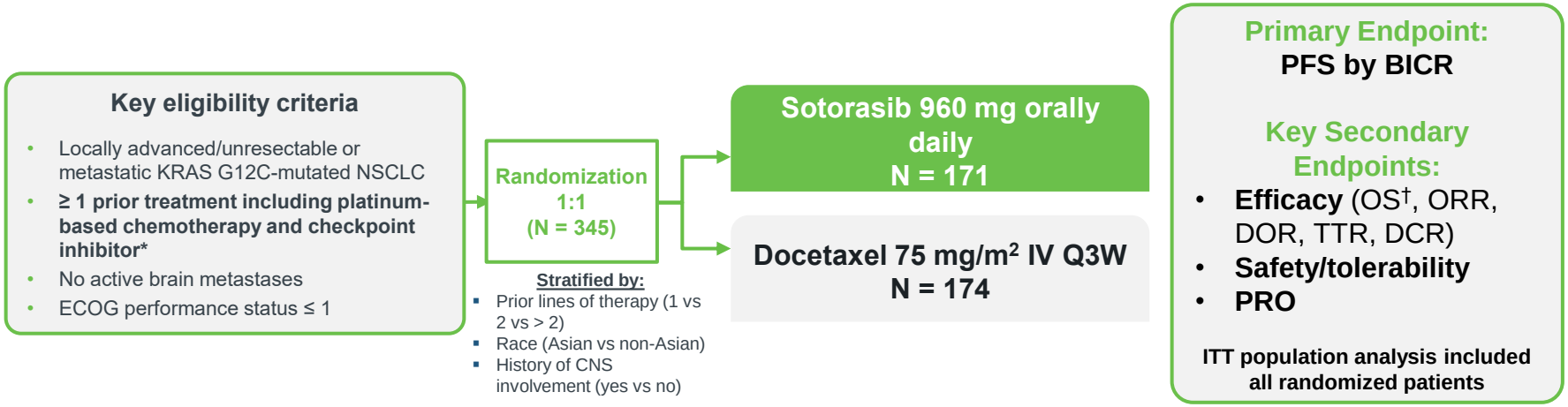


ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

CodeBreaK 200: Phase 3 Study Design



Per regulatory feedback following the observed clinical benefits of sotorasib in the CodeBreaK 100 phase 2 trial:
- The protocol was amended to reduce planned enrollment from 650 to ~330 patients, to limit the overall number of patients treated with docetaxel
- Crossover from docetaxel to sotorasib was permitted upon disease progression

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

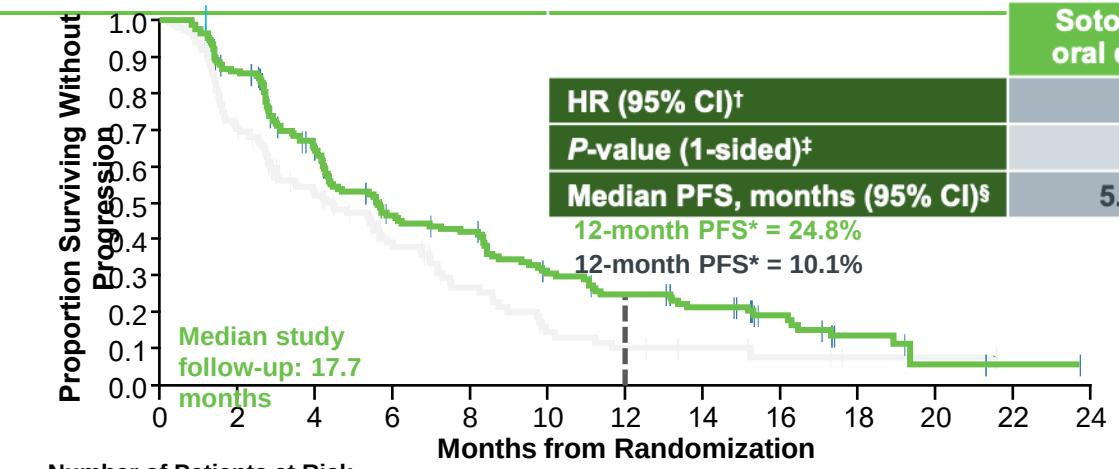
NCT04303780; EudraCT: 2019-003582-18.

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval. †Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

BICR, blinded independent central review; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcomes; Q3W, every 3 weeks; TTR, time to response.

De Langen AJ, et al. *Lancet*. 2023. Epub ahead of print.

Phase 3 Study Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.0017	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

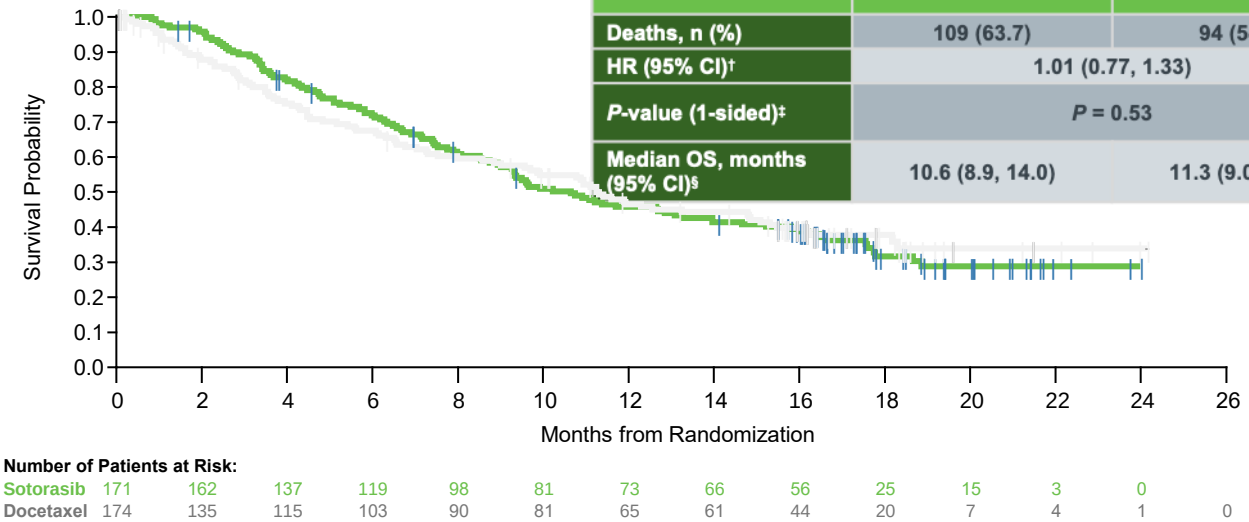
CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population. †HR and 95% CIs estimated using a stratified Cox proportional hazards model. ‡*P*-value calculated using a stratified log-rank test. §Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

BICR, blinded independent central review; HR, hazard ratio; IV, intravenous; PFS, progression-free survival; Q3W, every 3 weeks.

De Langen AJ, et al. *Lancet*. 2023. Epub ahead of print.

Phase 3 Study: OS: Sotorasib versus Docetaxel*



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

List of Subsequent Anti-cancer Treatment

Categories	Sotorasib (N = 171) n (%)	Docetaxel (N = 174) n (%)
Any subsequent anti-cancer therapy including crossover	62 (36.3)	73 (42.0)
Chemotherapy	36 (21.1)	21 (12.1)
$KRAS^{G12C}$ inhibitor	6 (3.5)	59 (33.9)
Immunotherapy	16 (9.4)	10 (5.7)
Checkpoint inhibitor	14 (8.2)	10 (5.7)
Other	25 (14.6)	18 (10.3)

*OS rates estimated using Kaplan-Meier method; ITT population. †HR and 95% CIs estimated using a stratified Cox proportional hazards model. ‡ *P*-value calculated using a stratified log-rank test. §Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation. **Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression.

CI, confidence interval; ITT, intent to treat; IV, intravenous; KRAS, Kirsten rat sarcoma virus; HR, hazard ratio; IO, immuno-oncology therapy; OS, overall survival; Q3W, every 3 weeks; TTR, time to response.

De Langen AJ, et al. *Lancet*. 2023. Epub ahead of print.

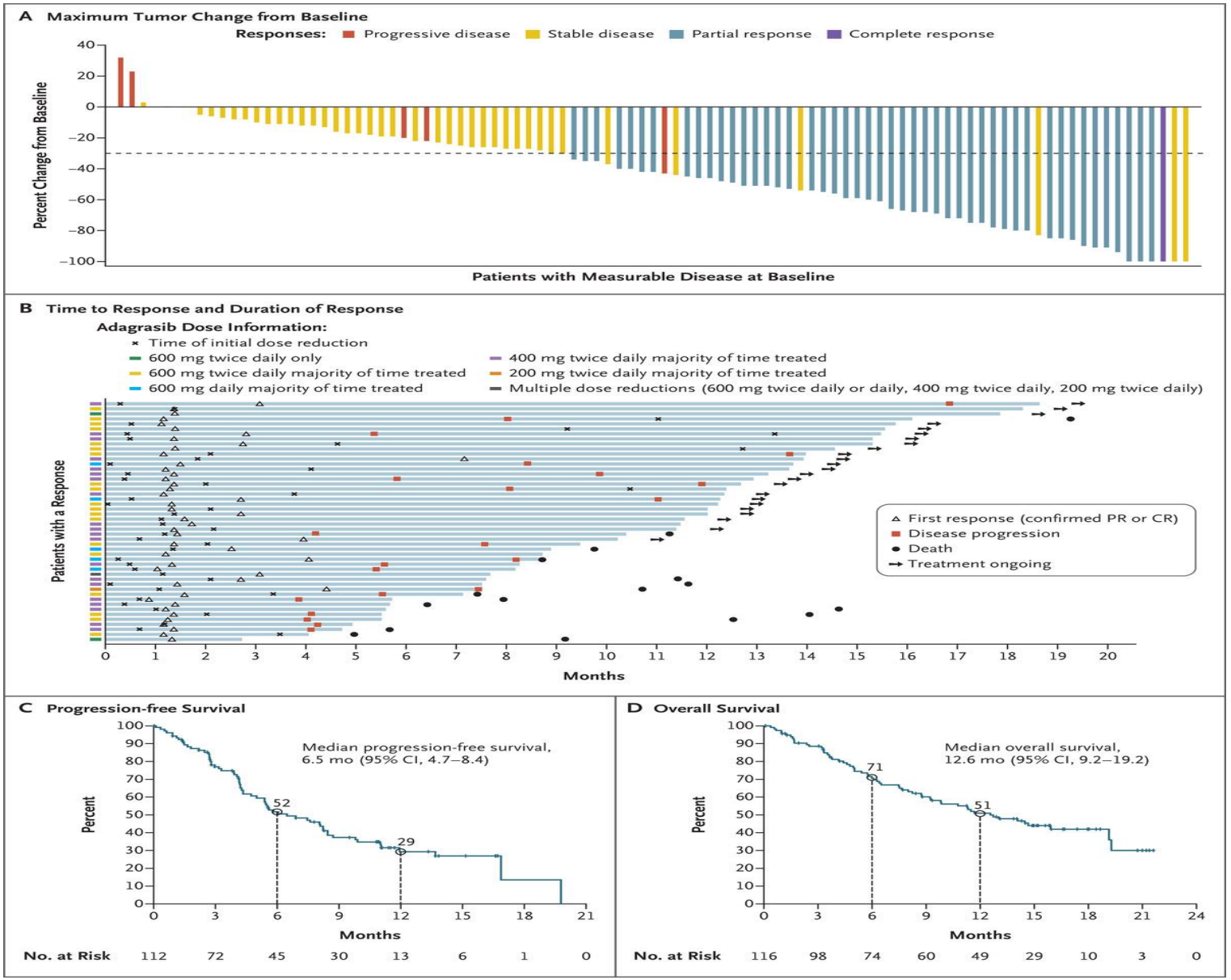
Phase 3 Study: Most Common TRAEs*

	Sotorasib 960 mg oral daily (N = 169)		Docetaxel 75 mg/m^2 IV Q3W (N = 151)	
	Any Grade, n (%)	Grade ≥ 3, n (%)	Any Grade, n (%)	Grade ≥ 3, n (%)
TRAEs	119 (70)	56 (33)	130 (86)	61 (40)
Diarrhea	57 (34)	20 (12)	28 (19)	3 (2)
Fatigue	11 (7)	1 (1)	38 (25)	9 (6)
Alopecia	2 (1)	0	31 (21)	0
Nausea	24 (14)	2 (1)	30 (20)	1 (1)
Anemia	5 (3)	1 (0)	27 (18)	5 (3)
ALT increased	17 (10)	13 (8)	0	0
AST increased	17 (10)	9 (5)	0	0
Neutropenia	2 (1)	0	20 (13)	18 (12)
Febrile neutropenia	0	0	8 (5)	8 (5)

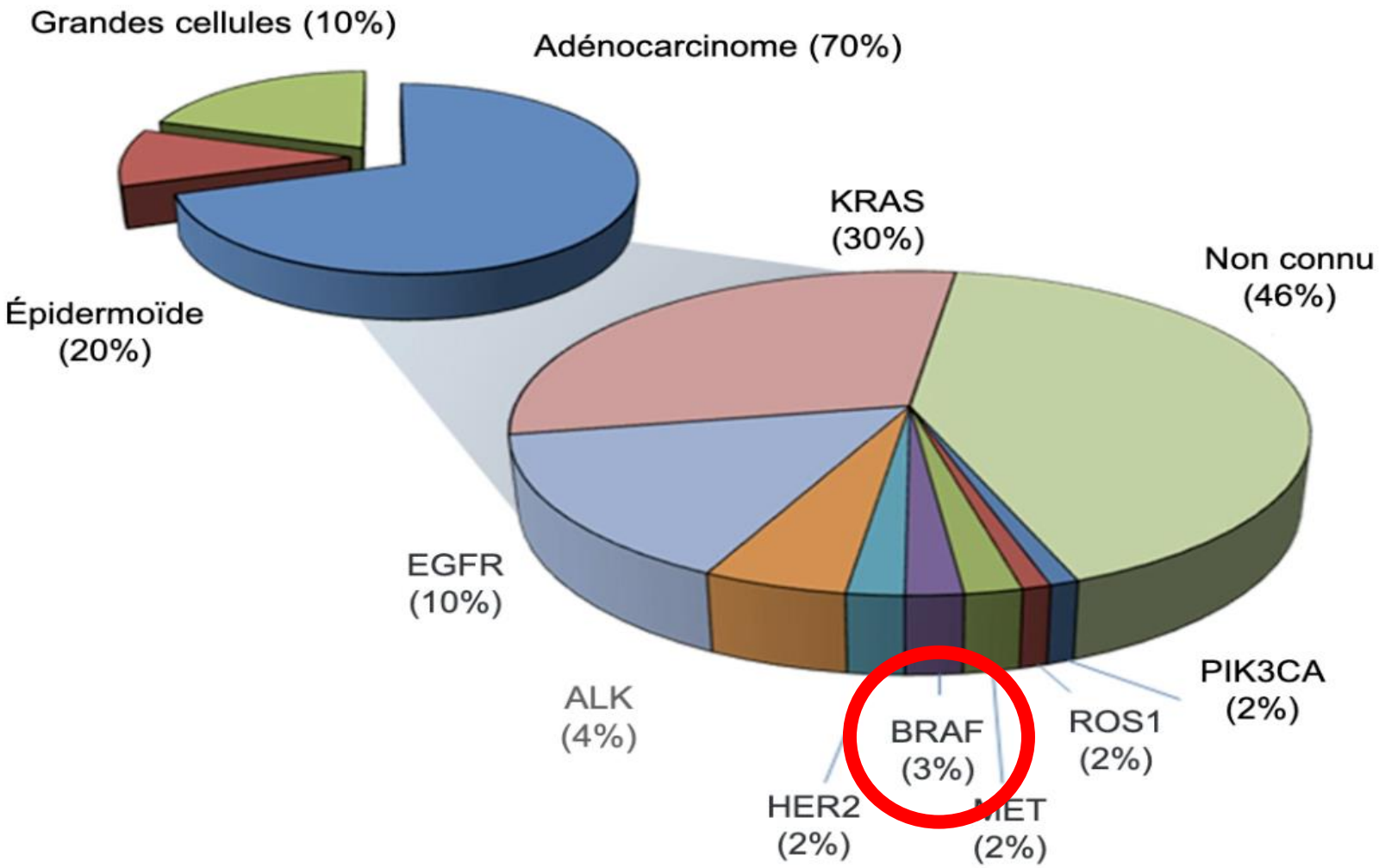
Most common Grade ≥ 3 TRAEs with sotorasib were diarrhea and elevated liver enzymes, and with docetaxel were neutropenia, fatigue, and febrile neutropenia

*Incidence per arm: any grade TRAE > 15%; grade ≥ 3 TRAEs > 5%.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; TRAE, treatment-related adverse event as per investigator.
De Langen AJ, et al. *Lancet*. 2023. Epub ahead of print.

Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation



ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

Résumé des résultats de l'étude pivot

Critères d'évaluation Selon l'investigateur	Cohorte A[1] Dabrafenib Monotherapie N=78 patients	Cohorte B[2] Dabrafenib + Trametinib ≥2L n=57 patients	Cohorte C[2] Dabrafenib + Trametinib 1L N=36 patients
Temps de Suivi médian	**10,7 mois**	**16,6 mois**	**16,3 mois**
Réponse objective IC à 95%	**33%** 23-45	**39 (68,4%)** [58,4,80;1]	**23 (63,9%)** [46,2-79,2]
Durée médiane de la réponse IC à 95%	**9,6 mois** 5,4-15,2	**9,8 mois** [6,9-18,3]	**10,2 mois** [8.3–15.2]
Survie sans progression médiane IC à 95 %	**5,5 mois** 3,4-7,3	**10,2 mois** [6,9-16,7]	**10,8 mois** [7,0-14,5]
Survie globale médiane @12, 24, 36, 48 mois	**12,7 mois** 7,3-16,3	**18,2 mois** OS @1 an : 66% OS @2 ans: 41% OS @3 ans: 33% OS @4 ans: 26% **OS @5 ans: 19%**	**17,3 mois** OS @1 an: 74% OS @2 ans: 49% OS @3 ans : 40% OS @4 ans: 34% **OS @5 ans: 22 %**

1. Planchard D et al. Lancet Oncol;2016;May;17(5):642-50
2. David Planchard et al. **J Thorac Oncol**. 2022 Jan;17(1):103-115

Tolérance

Durée moyenne de traitement 10,55 mois

	dabrafenib	trametinib	
Réduction de doses	48%	32%	Majorité des patients : une seule réduction de dose
Interruption de dose	77 %	71 %	46% ont 3 interruptions ou plus pour D et 30 % pour T

Planchard et al. **J Thorac Oncol**. 2022 Jan;17(1):103-115

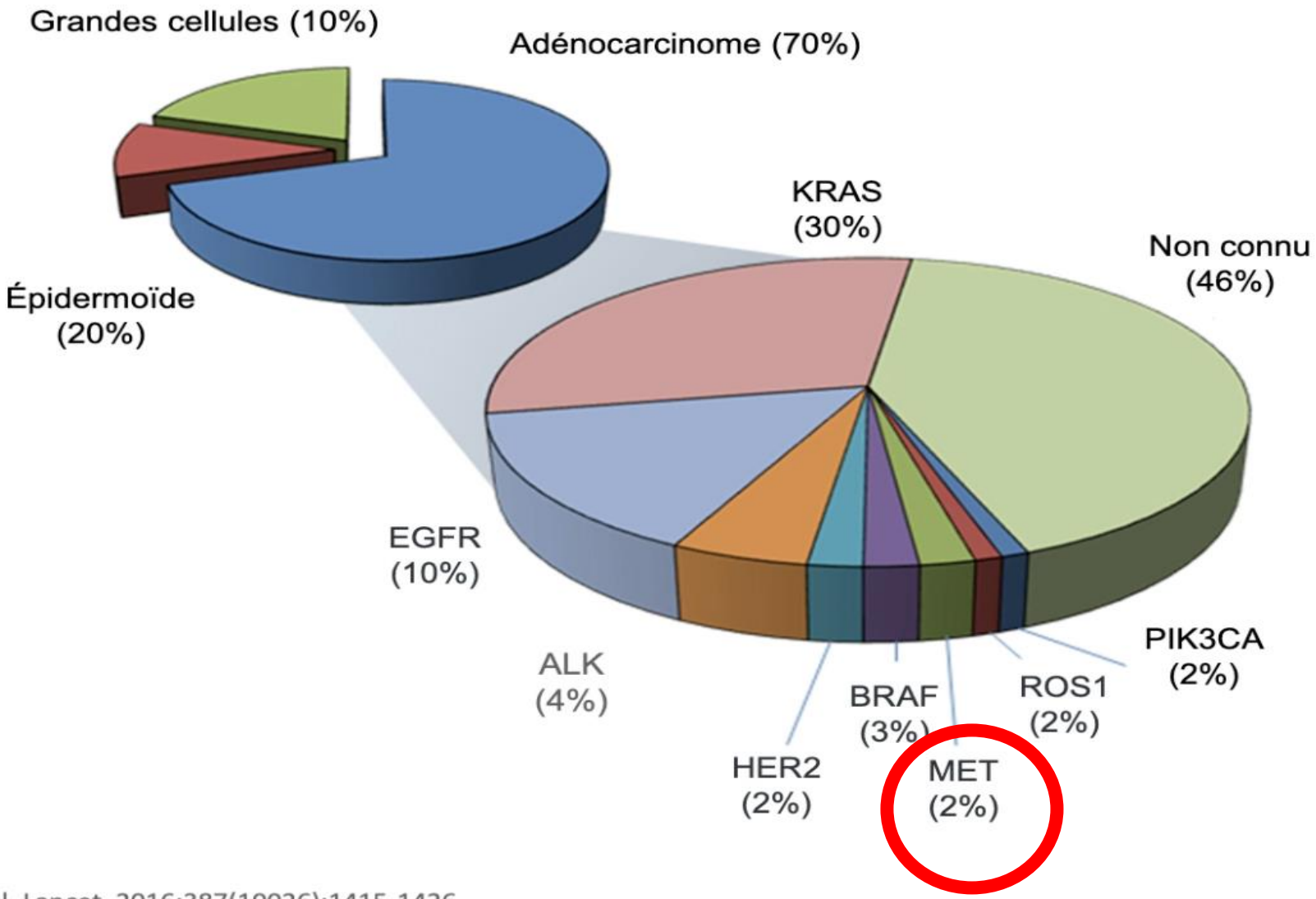
« Le profil de tolérance de l'association Dabrafenib Trametinib dans le CBNPC est similaire à celui observé dans le traitement du mélanome » pas de nouveau signal après 5 ans de suivi.

Table 3. Adverse Events in Patients Receiving Dabrafenib + Trametinib (all grade incidence ≥ 20%)

Adverse Event, n (%)	All Grade	Grade 3	Grade 4
Pyrexia	52 (56)	6 (6)	0
Nausea	46 51	0	0
Vomiting	38 (41)	3 (3)	0
Dry skin	36 (39)	1 (1)	0
Oedema peripheral	35 (38)	0	0
Diarrhoea	34 (37)	2 (2)	0
Decreased appetite	31 (33)	0	0
Cough	29 (31)	0	0
Asthenia	27 (29)	4 (4)	0
Fatigue	26 (28)	3 (3)	0
Chills	25 (27)	0	0
Rash	24 (26)	1 (1)	0
Dyspnoea	24 (26)	6 (6)	0
Arthralgia	21 (23)	1 (1)	0

11 David Planchard et al. **J Thorac Oncol**. 2022 Jan;17(1):103-115

ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.

MET

GEOMETRY mono-1: Efficacy of Capmatinib for NSCLC With *MET* Exon 14-Skipping Mutations

Capmatinib Efficacy in Treatment-Naïve Patients	Overall Response, % (95% CI)	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
Cohort 5b (n = 28)	67.9 (47.6-84.1)	12.4 (8.2-23.4)	20.8 (12.4-NE)
Cohort 7 (n = 32)	68.8 (50.0-83.9)	12.5 (6.9-20.5)	Not mature
All patients (N = 60)	68.3 (55.0-79.7)	12.5 (8.3-18.0)	25.5 (15.2-NE)

VISION: Efficacy of Tepotinib for NSCLC With *MET* Exon 14-Skipping Mutations

Tepotinib Efficacy	ORR, % (95% CI)	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
Treatment-naïve,[a] % (95% CI)	54.0 (45.3-62.6)	10.4 (8.4-15.3)	17.6 (13.4-29.7)
Previously treated,[b] % (95% CI)	44.2 (35.8-52.9)	11.0 (8.2-12.4)	19.9 (15.8-22.3)

EGFR Exon 20 INSERTIONS: TARGETED THERAPIES

Pour la détection du saut de l'exon 14 (exon 14 skipping) de *MET*

POZIOTINIB:
ZENITH20 phase 2 trial

- 115 patients
- **Response rate by BIRC: 15%** (95%CI 9-23%)
- **mPFS: 5.5 mo** (95% CI, 0-13.1)
- **Grade ≥3 TRAE: 30%**
- AEs leading to discontinuation: ?

Socinski et al. LBA60. ESMO 2020
Cornelissen. MA11.04. WCLC 2020

MOBOCERTINIB:
Phase ½ and EXCLAIM cohorts

- 114 and 96 patients
- Response rate per IRC: 23/26% (95%CI 15-33/19-35%)
- mPFS: 7.3 mo (95% CI, 5.5-10.2)
- Grade ≥3 TRAE: 30%
- AEs to discontinuation: 17/10%

Ramalingam et al. OA04.03. WCLC 2020

AMIVANTAMAB:
CHRYSALIS PHASE 1 trial

- 81 patients
- **Response rate by BIRC: 40%** (95%CI 29-51%)
- **mPFS: 8.3 mo** (95% CI, 6.5-10.9)
- **Grade ≥3 TRAE: 16%**
- AEs to discontinuation: 4%

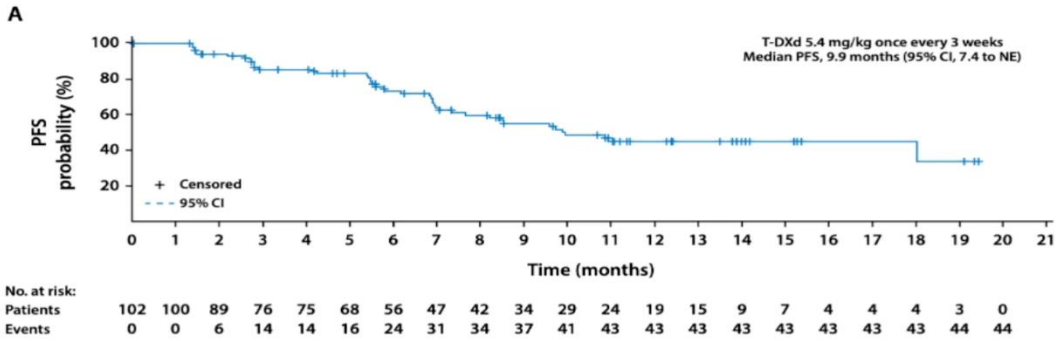
Sabari et al. OA04.04. WCLC 2020

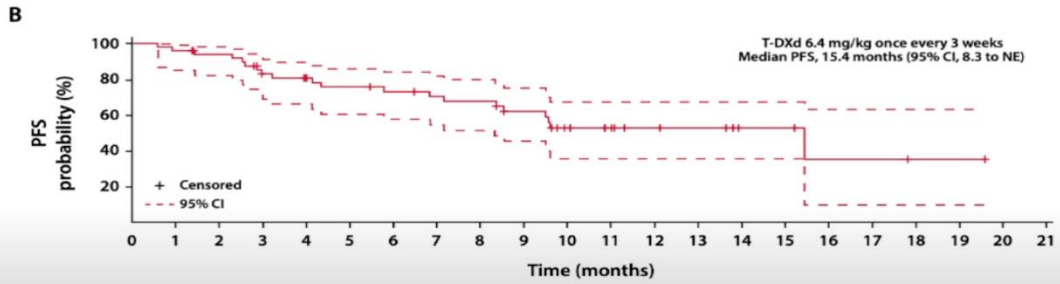
CBPNPC avancé avec insertion exon 20 EGFR

Compound	Trial	N	PFS HR (CI 95%) BIRC-assessed	Median PFS (Mo.)	ORR (%)	Median DoR (mo.)
Mobocertinib	Phase III EXCLAIM-2 Mobocertinib 160mg/d vs. Platinum – pemetrexed and pemetrexed maintenance	179 vs. 175	1.04 (0.77–1.39)	9.6 vs. 9.6	32 vs. 40	12.4 vs. 8.4
Amivantamab	Phase III PAPILLON Amivantamab – platinum – pemetrexed and Amivantamab – pemetrexed maintenance vs. Platinum – pemetrexed and pemetrexed maintenance	153 vs. 155	0.395 (0.30–0.53)	11.4 vs. 6.7	73 vs. 47	9.7 vs. 4.4
Sunvozertinib	Phase I/II WU-KONG1 (NCT03974022) / WU- KONG15 (NCT05559645)	28	NA	10.2(200mg/d) 12.4(300mg/d)	78.6	NR
Furmonertinib	Phase I (240mg/d)	28	NA	NR	79	15.2
YK029A	Phase I	28	NA	9.3	73	7.5

Janne et al. ESMO ASIA 2023; Yang et al. ESMO 2023; Girard et al. ESMO 2023; Han et al. WCLC 2023; Duan et al. JTO 2023

CBPNPC avancé avec mutation HER2 : trastuzumab deruxtecan





Goto et al. JCO 2023

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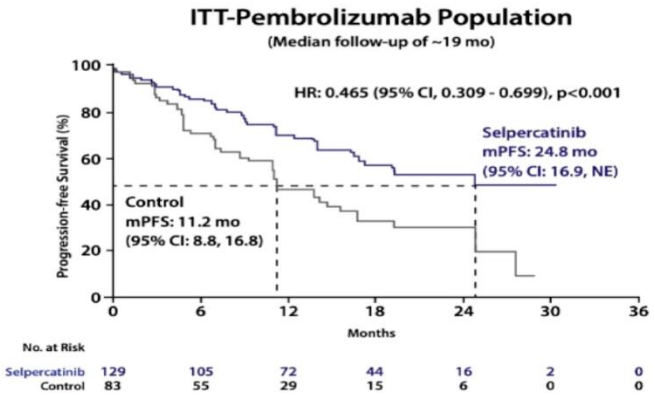
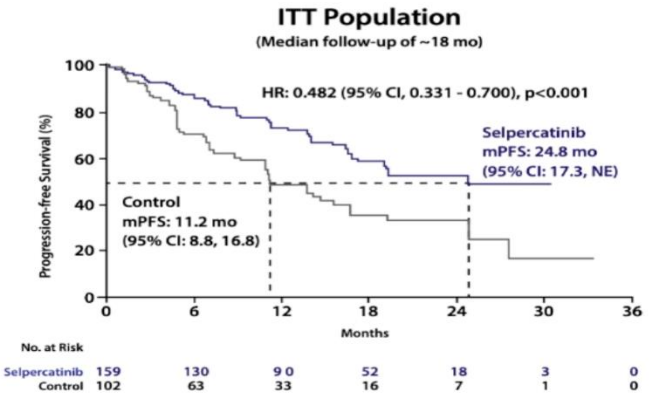
CBPNPC avec fusion RET : essai de phase III - LIBRETTO-431

- ITK-RET Serpercatinib : nouveau standard en première ligne





Loong et al. ESMO 2023

réponse objective 84%

État de lieux en France ??!!

Exemple du CBPNPC stade IV

- Au stade métastatique, 10 altérations moléculaires ont été identifiées par l'ESMO comme devant être connues car ciblables

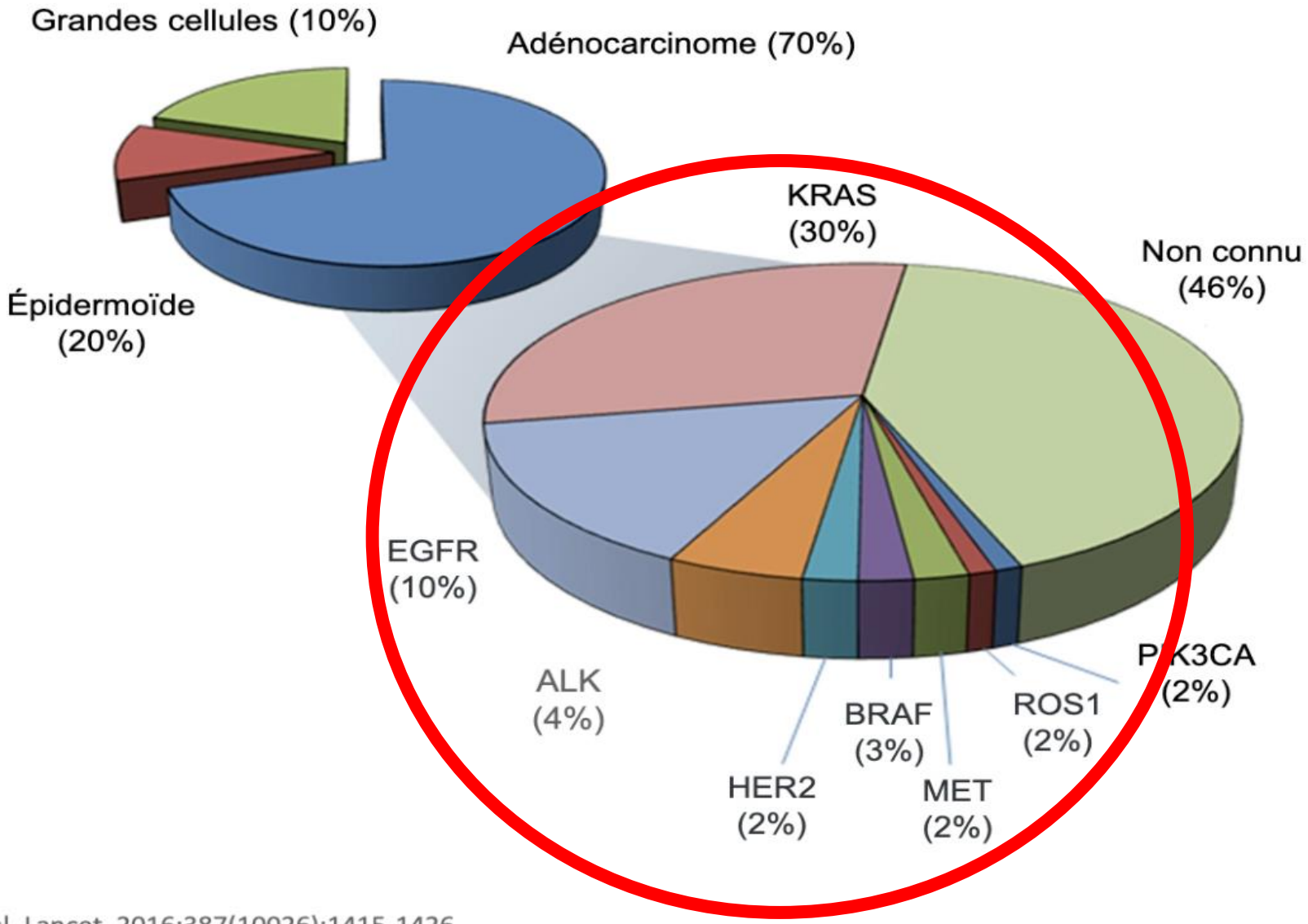
Altérations moléculaires	Lignes de traitement	Thérapeutique ciblée disponible en France
EGFR	1	
ALK	1	
ROS	1	
BRAF	1 ou 2	
RET	1	
NTRK	> 1	
HER2	> 1	
EGFR ins exon 20 (1)	> 1	
Met exon 14	1 ou 2	
KRASG12C (2)	> 1	

oui

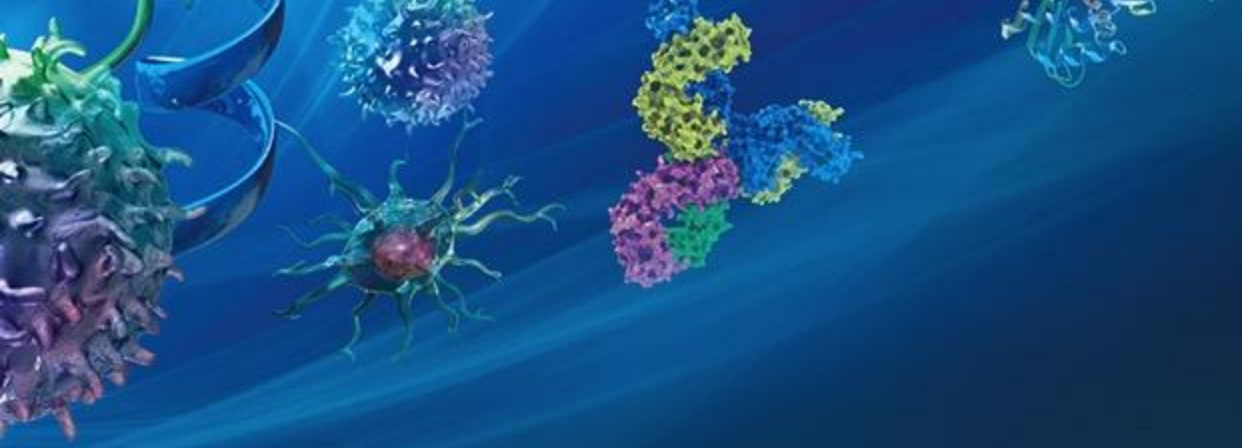
non

(1) Amivantamab, ASMR 5; (2) Sotorasib initialement disponible puis retiré

ALTÉRATIONS MOLÉCULAIRES DANS LE CBNPC



Barlesi F, et al. Lancet. 2016;387(10026):1415-1426.



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