15th CONGRESS on Lung CANCER
MADRID
23&24 November 2023
#15CongressGECP

Fundación GECP lung cancer research

ALK. The optimal sequence of treatments

Luis León

Hospital Clínico de Santiago de Compostela

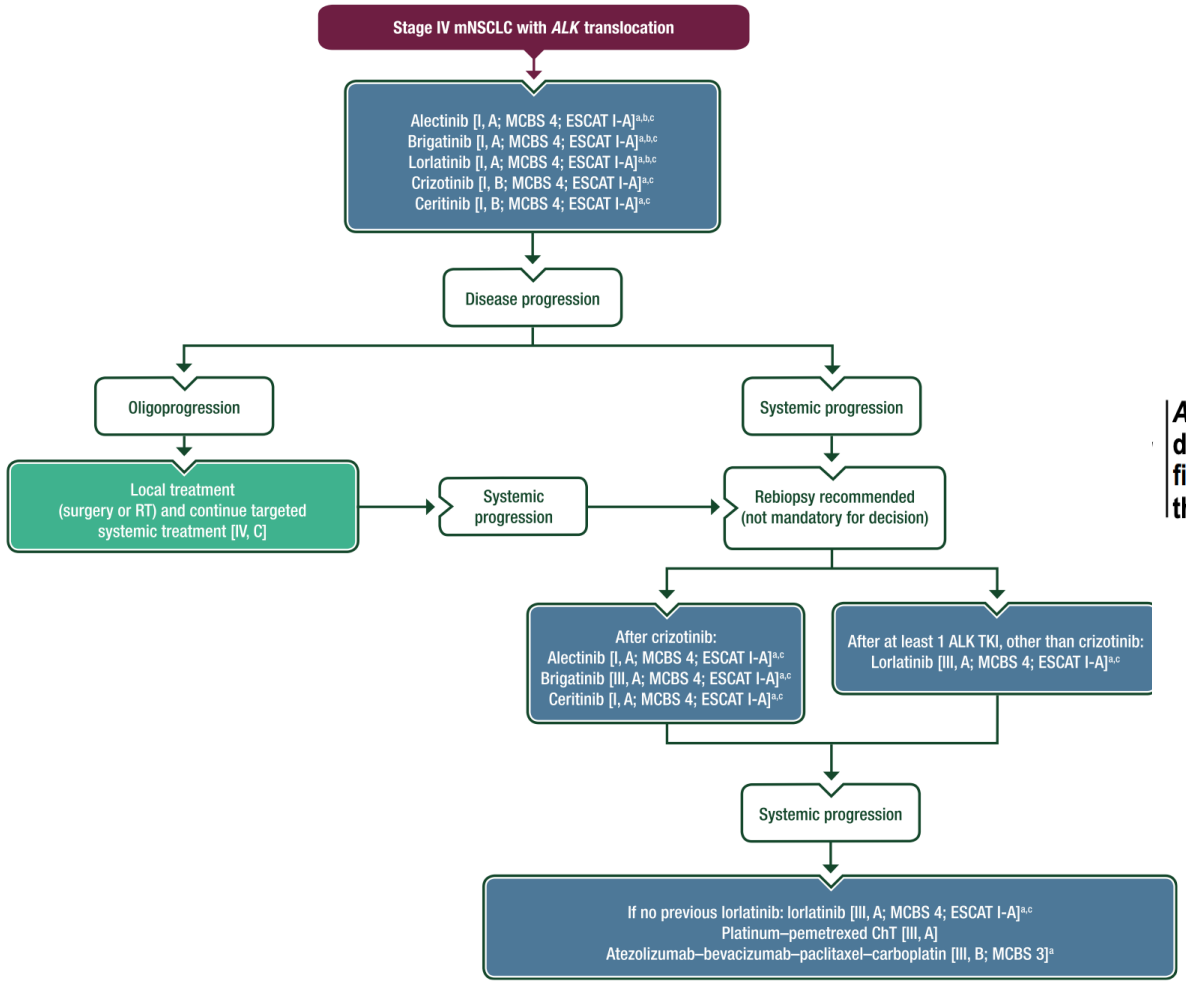
Conflicto de intereses

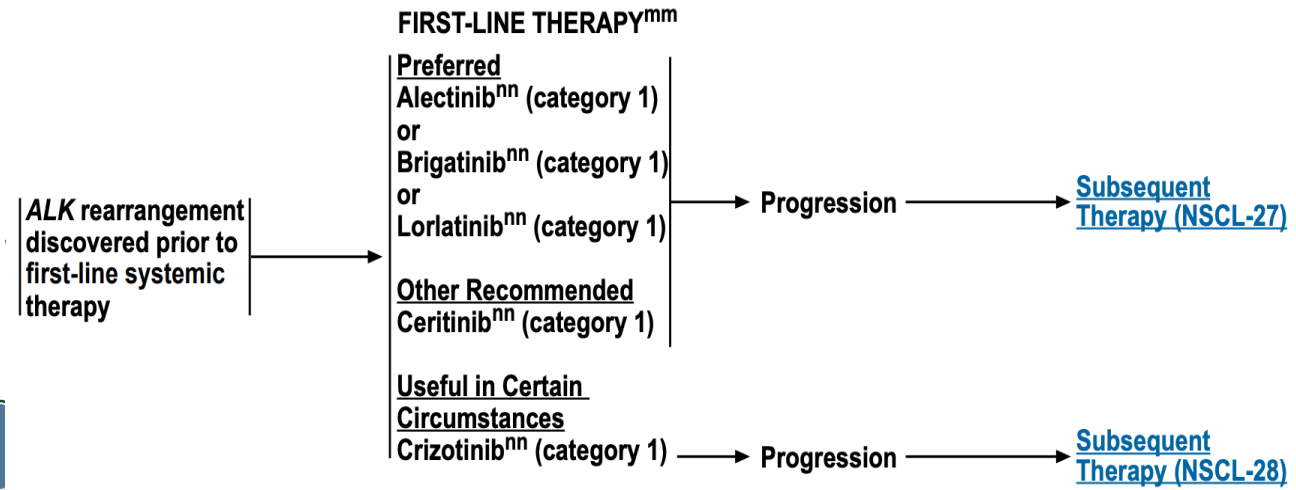
Employment, Consulting, Advisory role or Speaker:

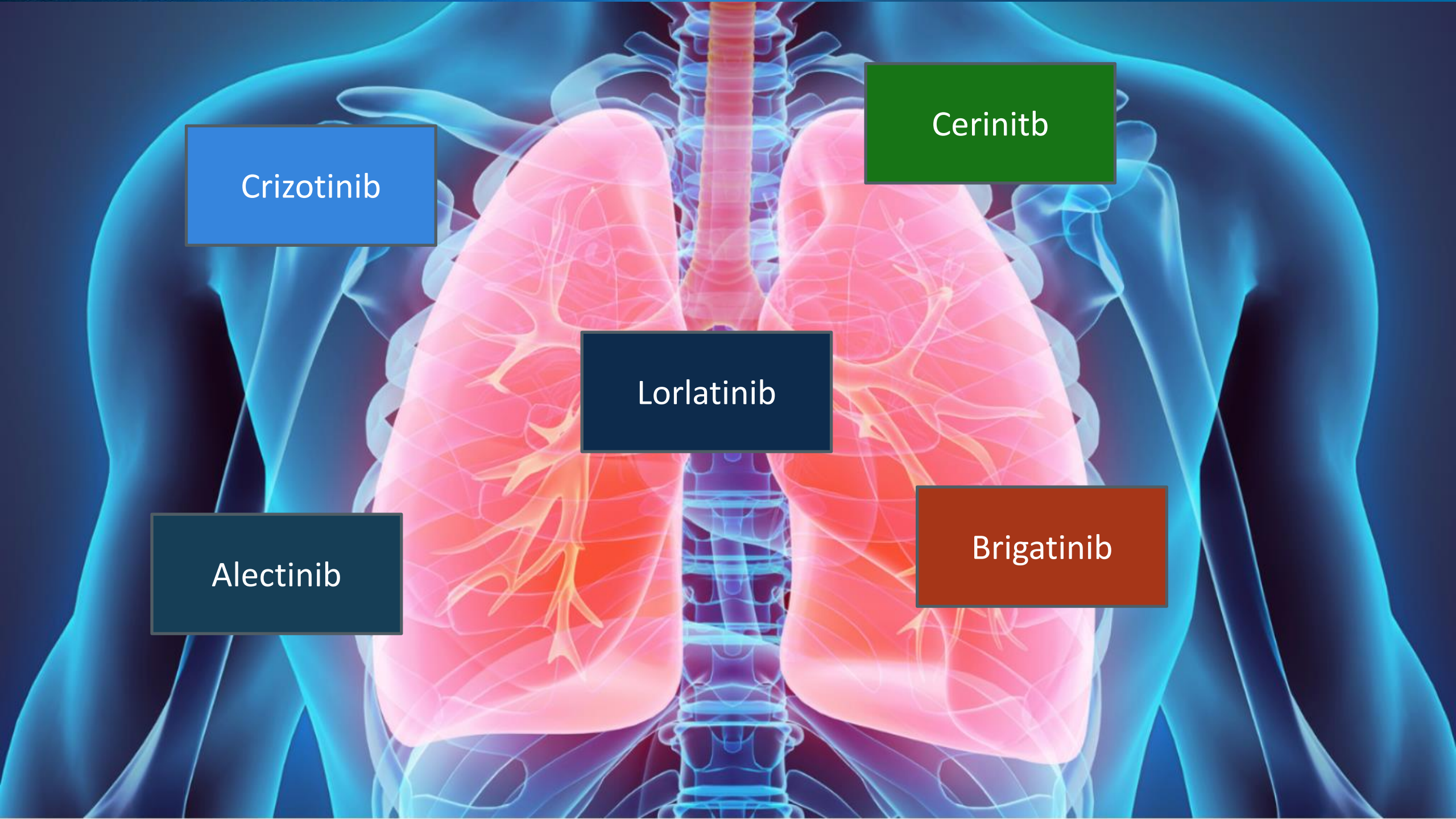
Pfizer, Boheringer, Novartis, Roche, Astra Zeneca, Sanofi, Bristol, Jansen, Pfizer, Astellas, MSD, Ipsen

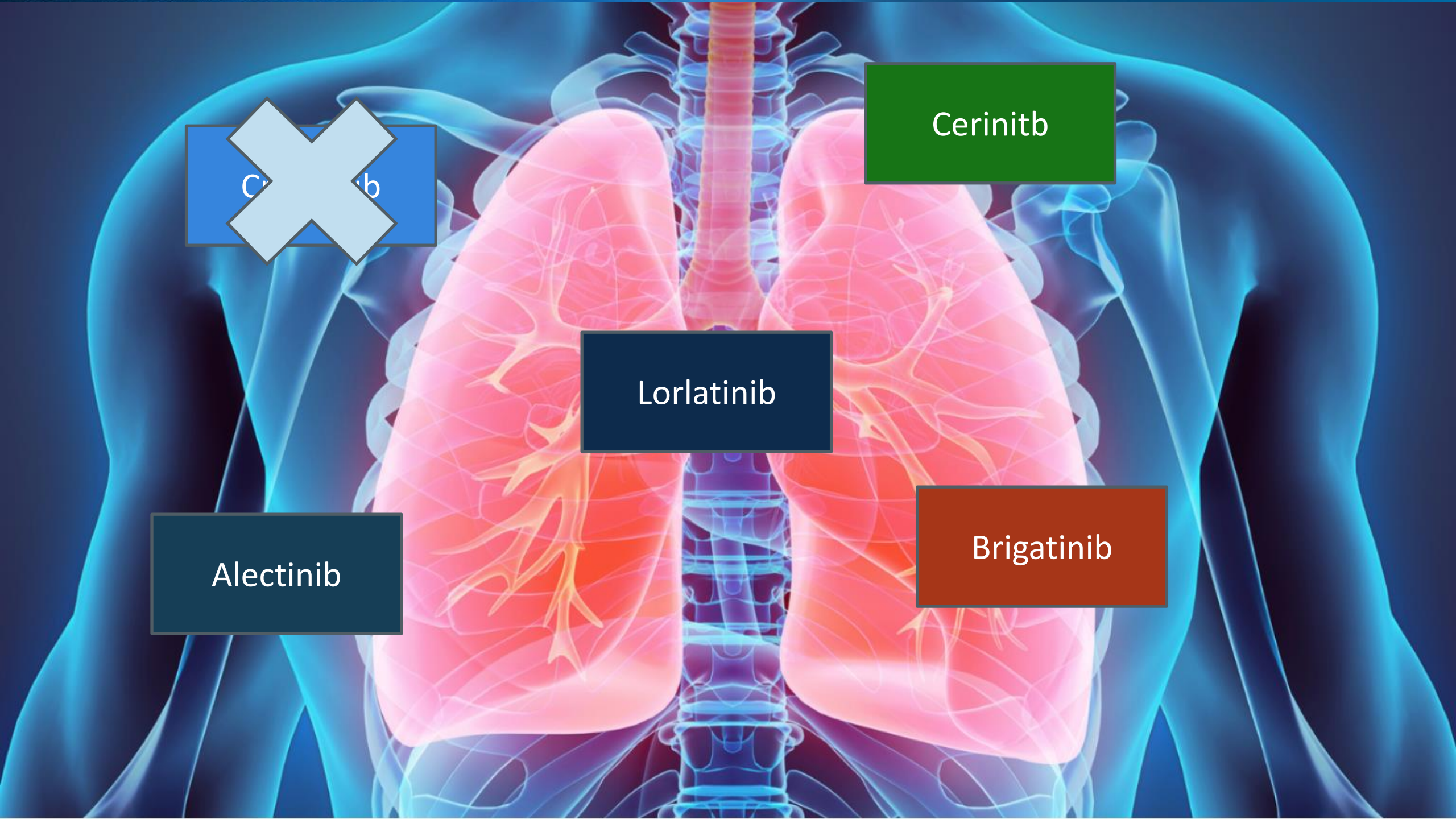
Grant or travel support: MSD, Ipsen, Sanofi, Jansen, Roche

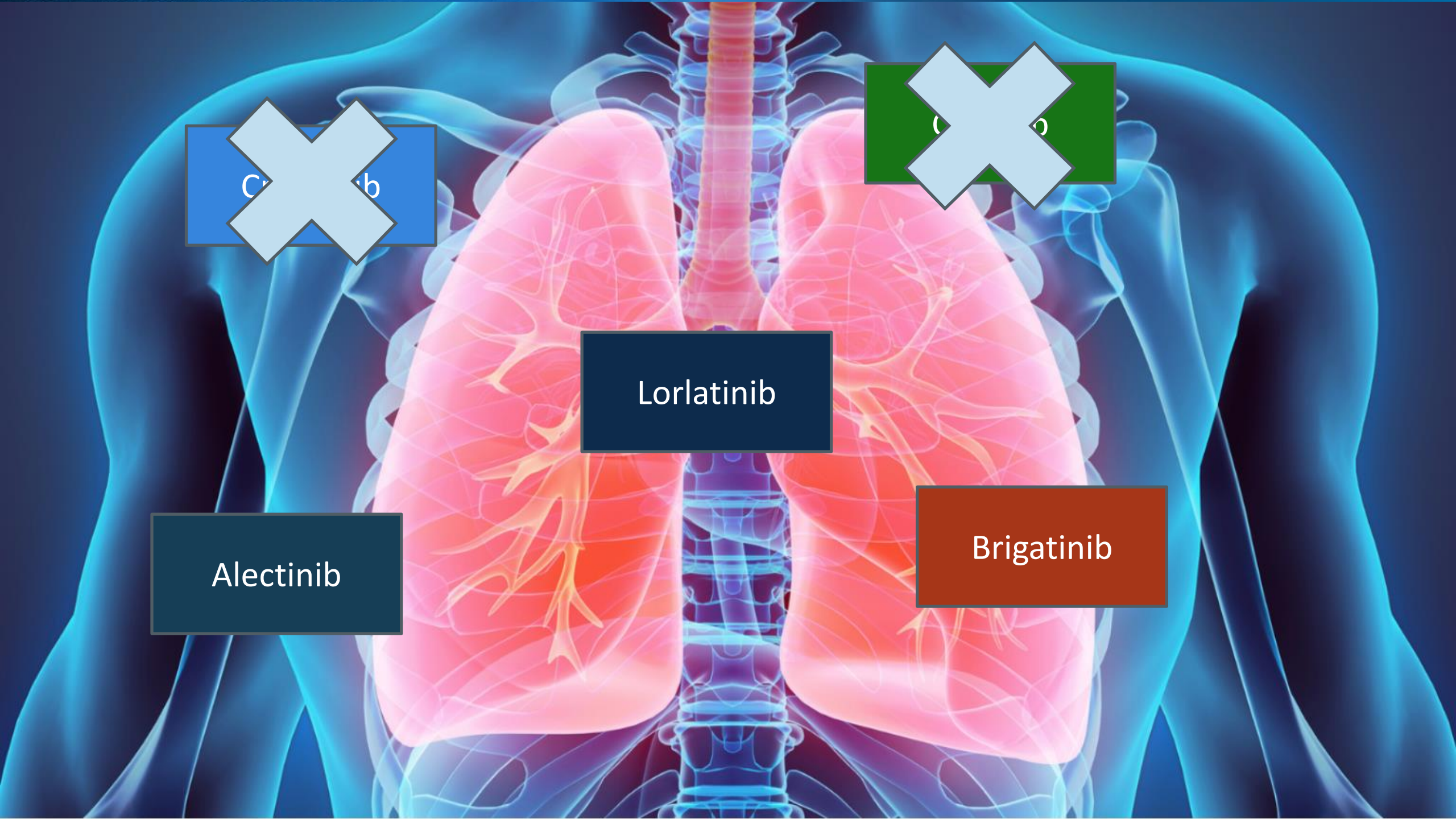
Guías ESMO y NCCN 2023



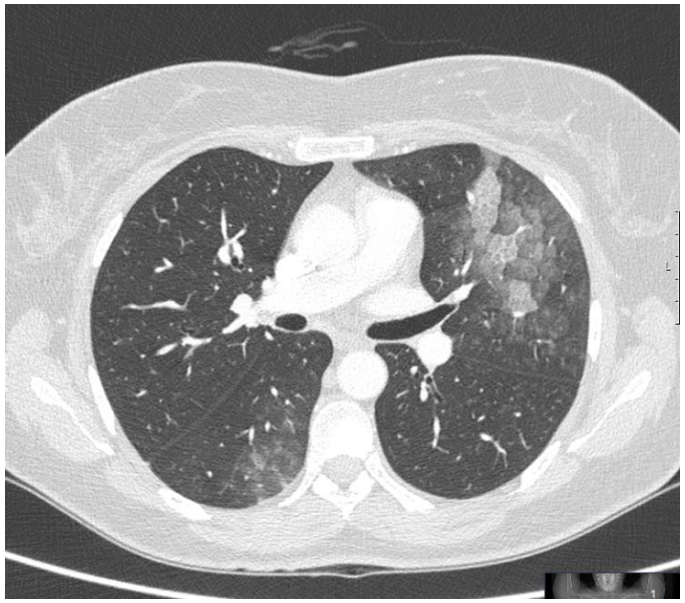


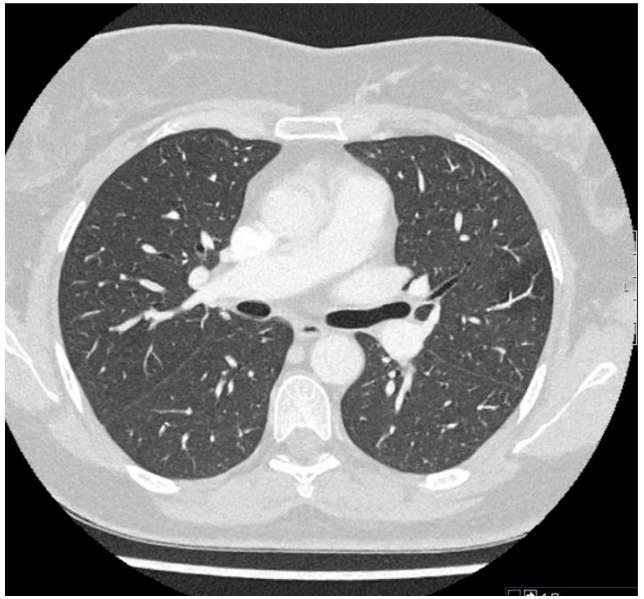

Crizotinib
Cerinitb
Lorlatinib
Alectinib
Brigatinib

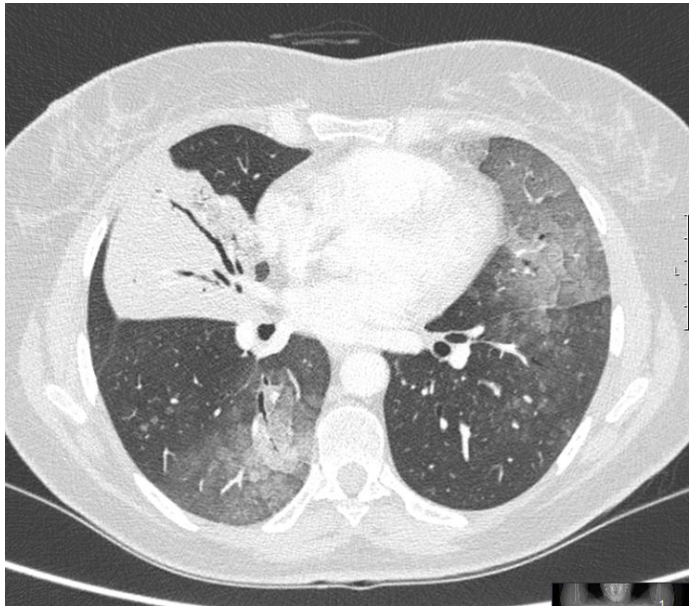

Cerinitb
Lorlatinib
Alectinib
Brigatinib

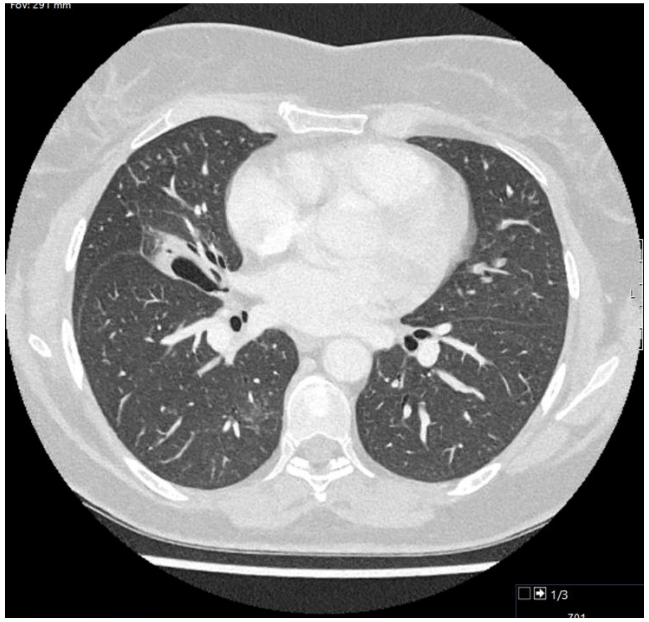

Lorlatinib
Alectinib
Brigatinib

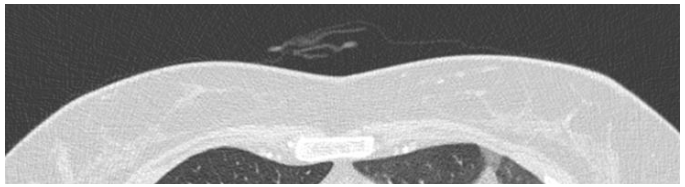
Mujer 51 años,
NSCLC IV
ALK traslocado
Mayo 23

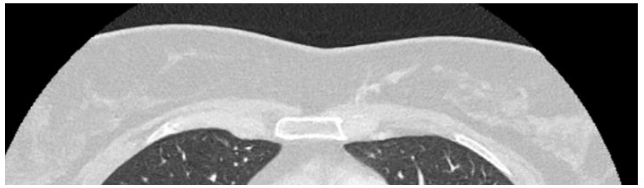












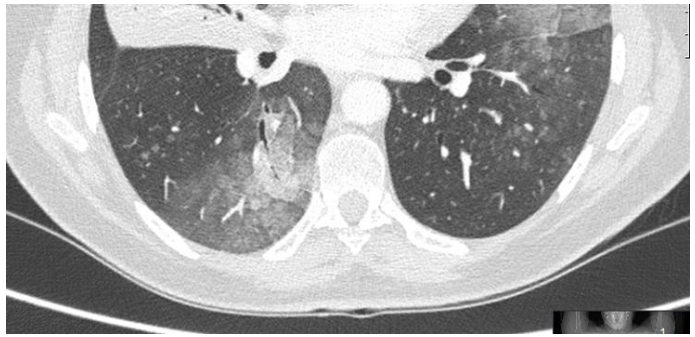
secuencia

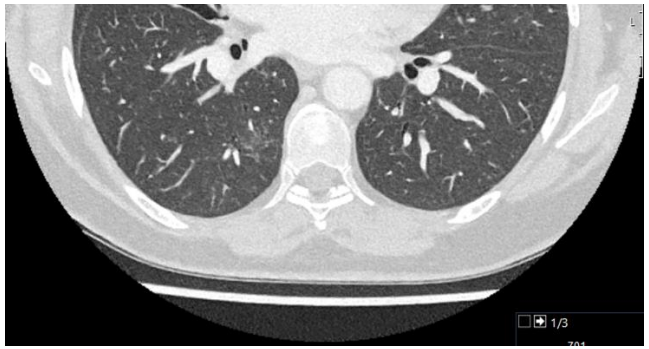
Del lat. *sequentia* 'continuación', de *sequi* 'seguir'.

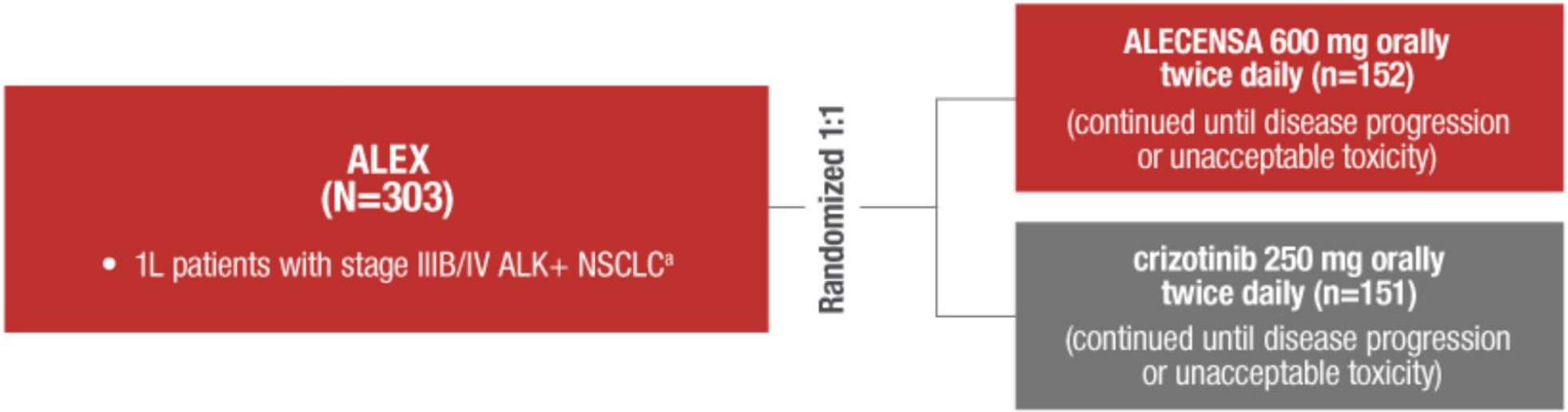
1. f. Continuidad, sucesión ordenada.

2. f. Serie o sucesión de cosas que guardan entre sí cierta relación.

3. f. En una película, plano o serie de planos que constituyen una unidad argumental.







Crossover no permitido

PRIMARY ENDPOINT[2]:

- PFS (INV)[b]

ADDITIONAL EFFICACY ENDPOINTS[2]:

- PFS (IRC)[b]
- Time to CNS progression (IRC)[b]
- ORR (IRC)
- DOR (IRC)
- OS (INV)

EXPLORATORY ENDPOINTS[2]:

- CNS ORR in patients with CNS metastases at baseline (IRC)
- CNS DOR in patients with CNS metastases at baseline (IRC)

STRATIFICATION FACTORS[2]:

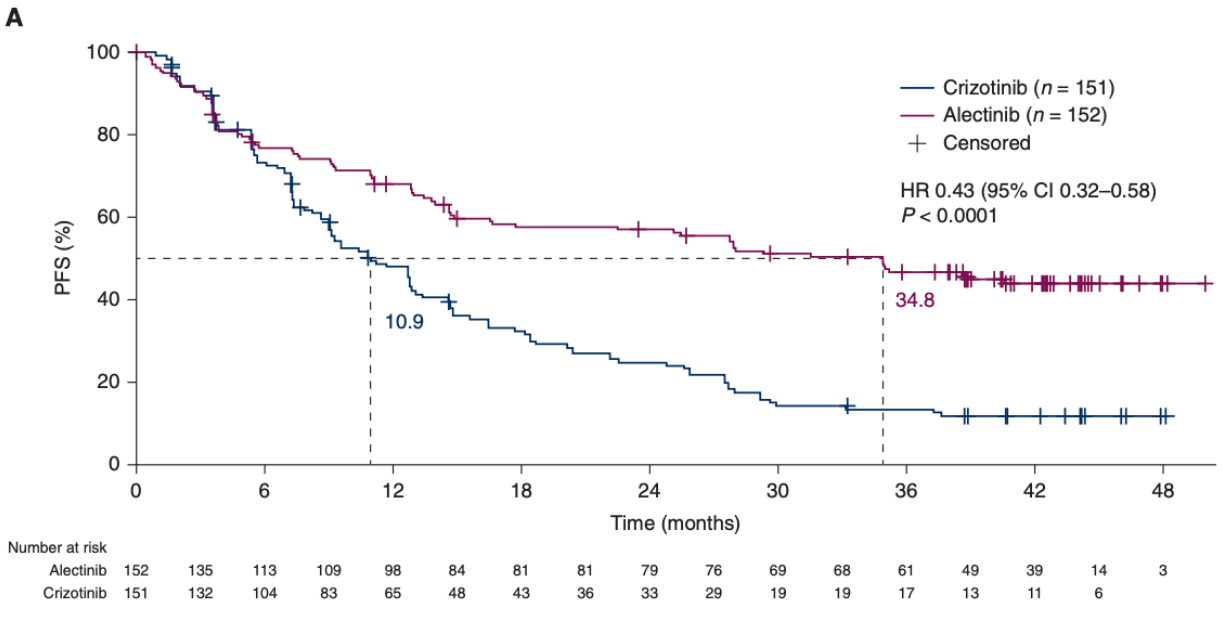
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- CNS metastases at baseline (yes vs no)

[a]Patients were required to have an ECOG PS of 0-2 and ALK+ NSCLC as identified by the VENTANA ALK (D5F3) CDx assay.

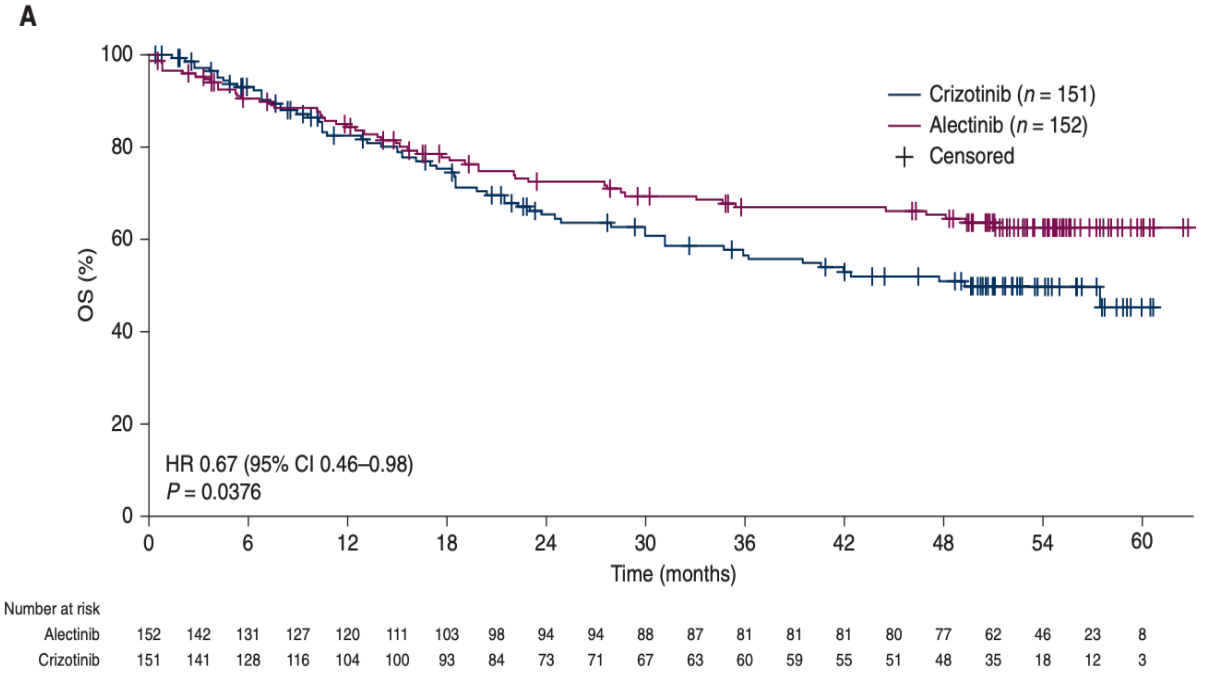
Mok Ann Oncol 2020

ALECTINIB (ALEX)

PFS



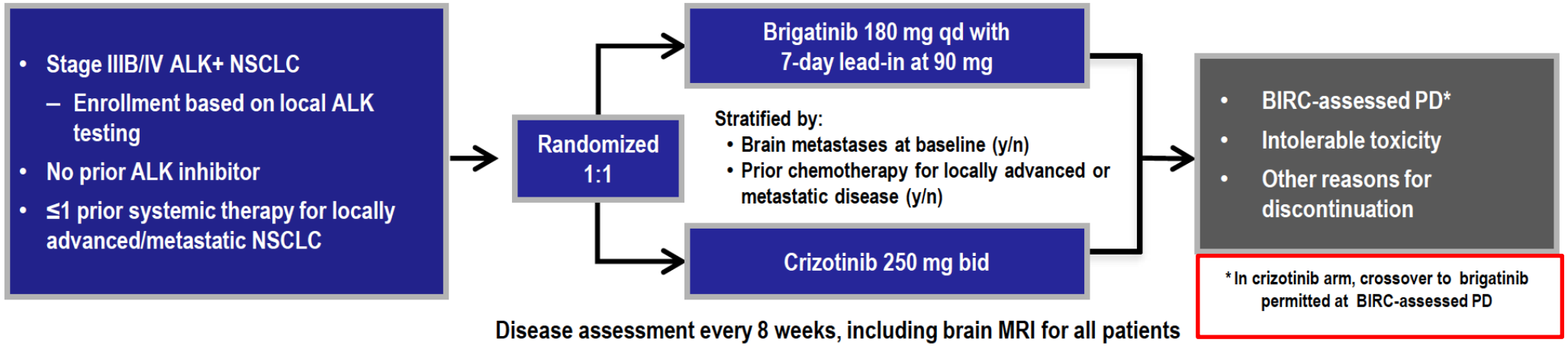
OS



ORR: Alectinib 83 vs Crizotinib 76 %

Mok Ann Oncol 2020

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter Study (NCT02737501); Second Interim Analysis



- Primary endpoint[a]: Blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1
- Key secondary endpoints: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- Statistical considerations: ≈270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

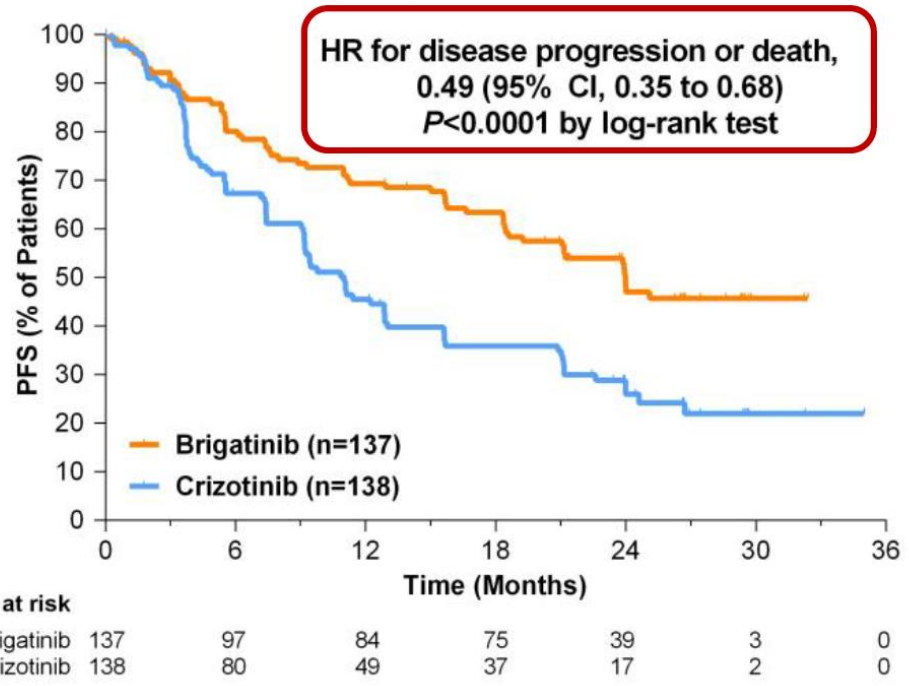
Trial fully accrued in August 2017 (N=275)

[a] Statistical significance for the primary endpoint was achieved at the first interim analysis

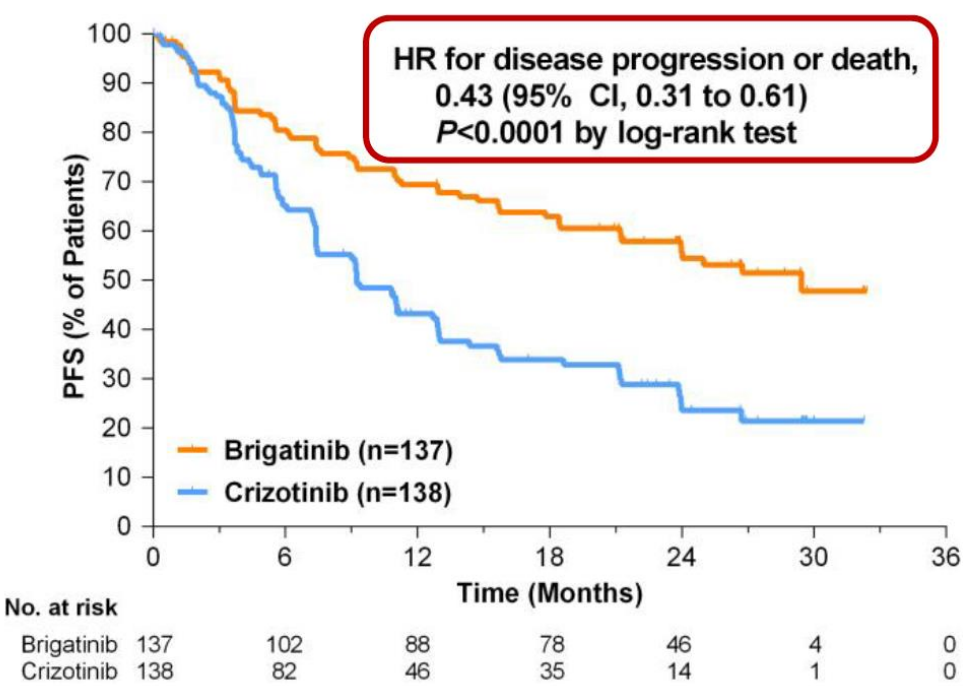
Camidge NEJM 2018

Brigatinib significantly reduced the risk of progression or death by 51% and 57% vs crizotinib, by BIRC and INV respectively

Primary Endpoint: BIRC-Assessed PFS



Investigator-Assessed PFS



Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	63 (46)	24.0 mo (18.5–NR)	48 (39–57)
Crizotinib (n=138)	87 (63)	11.0 mo (9.2–12.9)	26 (18–35)

Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	59 (43)	29.4 mo (21.2–NR)	56 (46–64)
Crizotinib (n=138)	92 (67)	9.2 mo (7.4–12.9)	24 (16–32)

ORR Brigatinib 74 vs Crizotinib 62 %

Camidge NEJM 2018

CROWN: Study Design[1,2]

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*

N=296

1:1 RANDOMIZED

Lorlatinib 100 mg QD (n=149)

Crizotinib 250 mg BID (n=147)

Stratification factors

- Presence of brain metastases (yes vs. no)
- Ethnicity (Asian vs. non-Asian)

Treatment continued until disease progression or unacceptable toxicity

Primary Endpoint

- PFS† by BICR

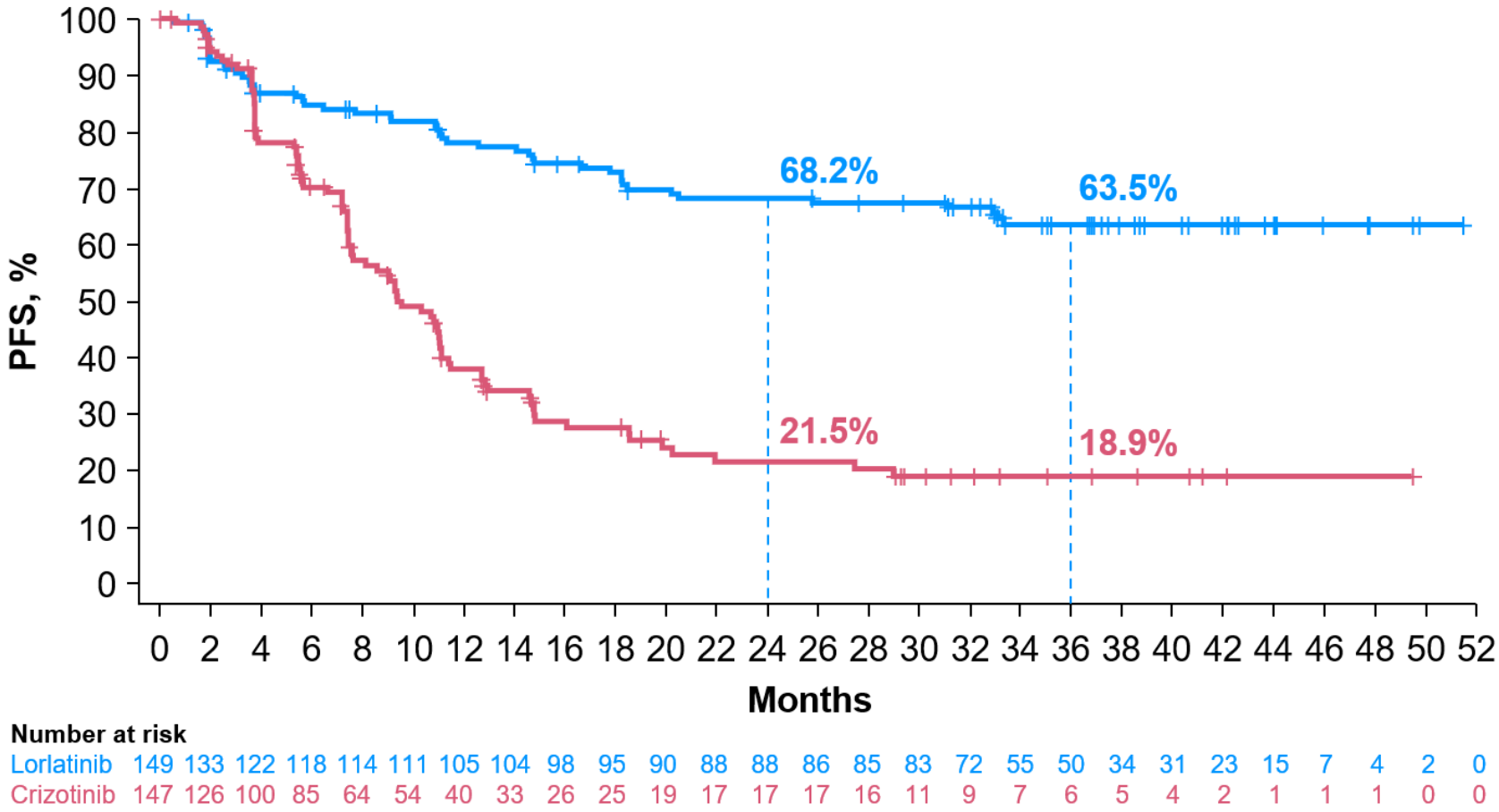
Secondary Endpoints

- PFS (investigator assessed), ORR by BICR and investigator, ic-ORR, DOR and ic-DOR by BICR, ic-TTP by BICR, OS
- Safety: adverse reactions & lab abnormalities
- QoL

No crossover between treatment arms was permitted

Shaw NEJM 2021

CROWN Primary Endpoint: PFS by BICR (long-term follow up, ITT population)



Number at risk

Lorlatinib	149	133	122	118	114	111	105	104	98	95	90	88	88	86	85	83	72	55	50	34	31	23	15	7	4	2	0
Crizotinib	147	126	100	85	64	54	40	33	26	25	19	17	17	17	16	11	9	7	6	5	4	2	1	1	1	0	0

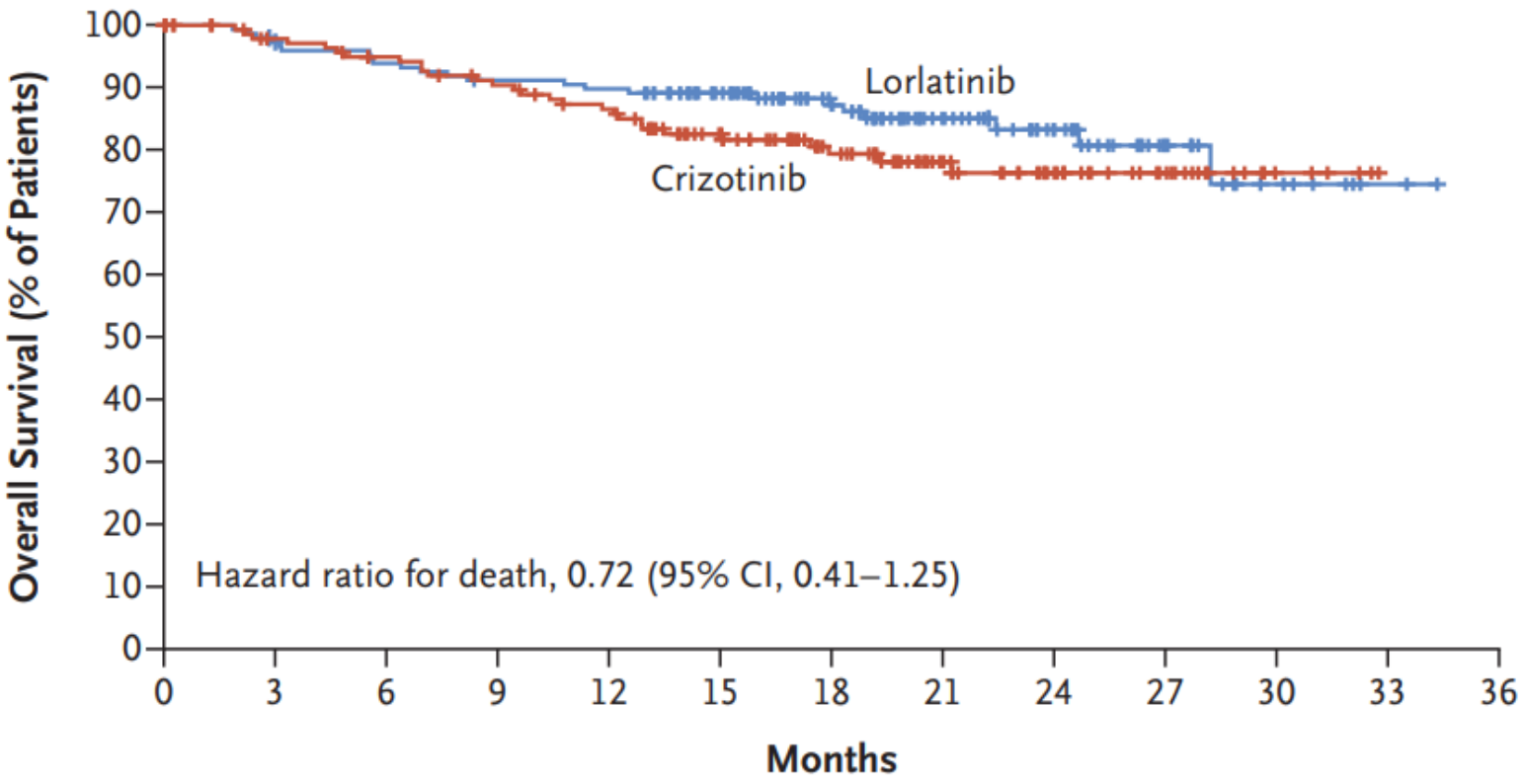
	Lorlatinib (n = 149)	Crizotinib (n = 147)
Events	49	92
PFS, median (95% CI), months	NR (NR–NR)	9.3 (7.6–11.1)
HR (95% CI)	0.27 (0.184–0.388)	

- PFS as assessed by the investigators was also longer with lorlatinib than crizotinib
  - Median PFS was NR (95% CI, NR-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9 months) with crizotinib (HR, 0.19; 95% CI, 0.131-0.274)

Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by BICR: lorlatinib, 36.7 months; crizotinib, 29.3 months.
BICR, blinded independent central review; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

Solomon AACR 2022

Overall Survival



No. at Risk

Lorlatinib	149	148	141	138	135	133	131	122	101	85	63	50	38	27	13	8	4	1	0
Crizotinib	147	139	133	127	122	116	111	97	85	68	55	40	31	22	12	5	3	0	0

Solomon Lancet Respir Med 2022

Table 1 Systemic Response of Next-generation ALK Inhibitors

	Alectinib	**Brigatinib**	**Ceritinib**	**Lorlatinib**
Clinical trial	ALEX[9,18]	ALTA-1L[17,22]	ASCEND-4[16]	CROWN[11]
OR (%) (95% CI)	82.9 (76.0–88.5)	74 (66–81)	72.5 (65.5–78.7)	76 (68–83)
Median DOR (months) (95% CI)	NE (NE)	33.2 (22.1 – NE)	23.9 (16.6 – NE)	NE (NE – NE)
Median PFS by ICR (months) (95% CI)	25.7 (19.9 – NE)	24.0 (18.5–43.2)*	16.6 (12.6–27.2)*	NE (NE – NE)*
Median PFS by IR (months) (95% CI)	34.8 (17.7 – NE)*	30.8 (21.3–40.6)	16.8 (13.5–25.2)	NE (NE – NE)
HR for disease progression or death (95% CI)	0.47 (0.34–0.65)	0.48 (0.35–0.66)	0.55 (0.42–0.73)	0.28 (0.19–0.41)
OS rates (%) (95% CI)	5-year OS rate 62.5% (54.3–70.8)	3 year-OS probability 71% (62–78)	2 year-OS probability 70.6% (62.2–77.5)	NA
Median OS, HR (95% CI)	0.67 (0.46–0.98)	0.81 (0.53–1.22)	0.73 (0.50–1.08)	0.72 (0.41–1.25)

Note: *Primary end point of the study.

Abbreviations: ICR, independent central review; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IR, investigator review; NA, no available data; NE, not estimable; OR, overall response; OS, overall survival; PFS, progression-free survival.

Pacientes con NSCLC ALK traslocado y metástasis SNC

Substance	Intracranial overall response rate*	Intracranial complete response rate*	Intracranial duration of response >12 months	Study
Alectinib	**81 %**	**38 %**	**59 %**	**ALEX[1,9] (asympt.)**
Brigatinib	**78 %**	**28 %**	**-**	**ALTA-1L[2] (asympt.)**
Lorlatinib	**82 %**	**71 %**	**79 %**	**CROWN[4,10] (asympt.)**
Crizotinib	20–50 %	~10 %	-	ALEX[1], ALTA-1L[2], CROWN[4]
Chemotherapy	20–30 %	~10 %	-	ASCEND4[3], AURA3[5]
Radiotherapy	60 %	<5 %	-	Various series[6,7]

*BICR-assessed, measurable CNS metastases.

Patients with prior radiotherapy (% of patients with brain metastases): ALEX: 39 %, ALTA-1L: 46 %, CROWN: 24 %.

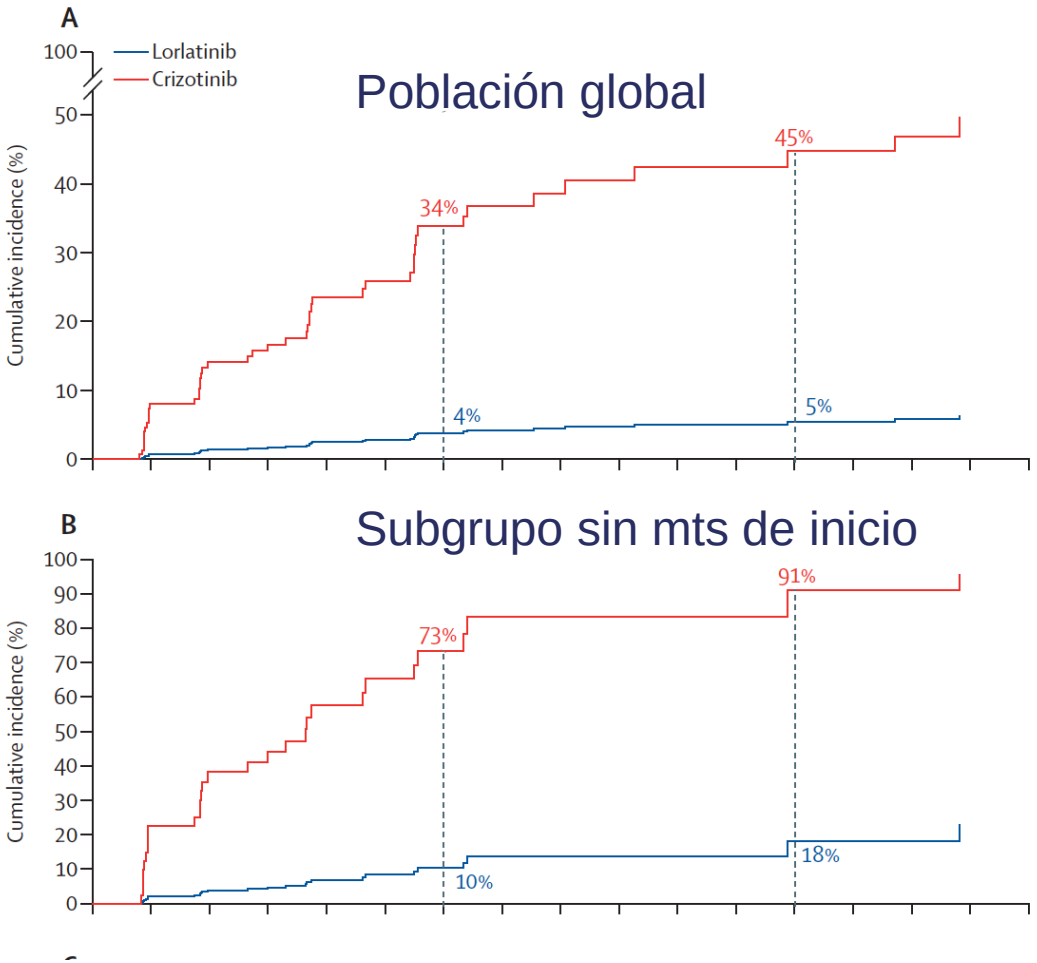
Pacientes con NSCLC ALK traslocado y metástasis SNC

Substance	Intracranial overall response rate*	Intracranial complete response rate*	Intracranial duration of response >12 months	Study
Alectinib	**81 %**	**38 %**	**59 %**	**ALEX[1,9] (asympt.)**
Brigatinib	**78 %**	**28 %**	**-**	**ALTA-1L[2] (asympt.)**
Lorlatinib	**82 %**	**71 %**	**79 %**	**CROWN[4,10] (asympt.)**
Crizotinib	20–50 %	~10 %	-	ALEX[1], ALTA-1L[2], CROWN[4]
Chemotherapy	20–30 %	~10 %	-	ASCEND4[3], AURA3[5]
Radiotherapy	60 %	<5 %	-	Various series[6,7]

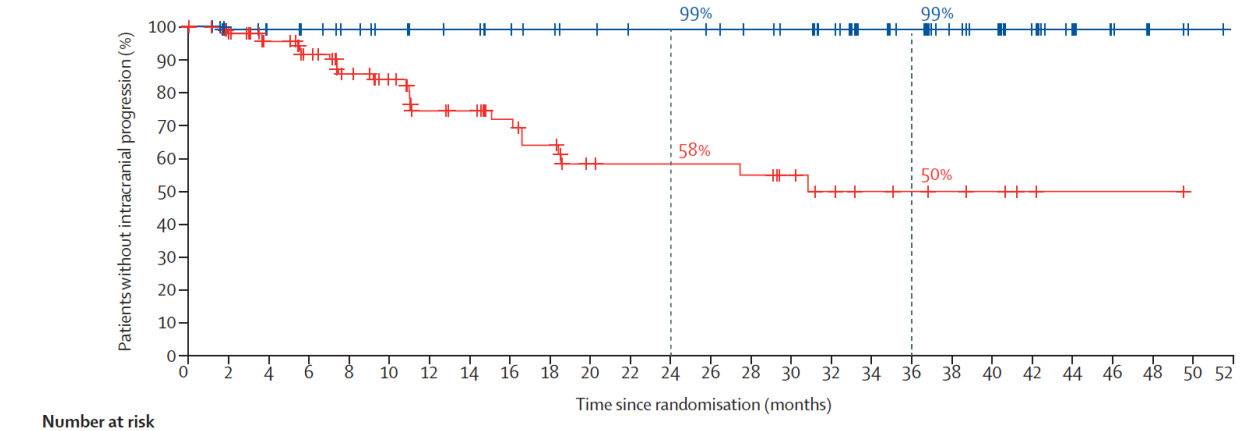
*BICR-assessed, measurable CNS metastases.

Patients with prior radiotherapy (% of patients with brain metastases): ALEX: 39 %, ALTA-1L: 46 %, CROWN: 24 %.

Actividad SNC de Lorlatinib



Supervivencia libre PD SNC en pts sin mts de inicio



Number at risk (number censored)

Lorlatinib	112	99	96	93	90	87	85	84	81	79	76	74	74	73	71	69	61	49	44	31	27	20	13	7	3	1	0
	(0)	(12)	(15)	(18)	(21)	(24)	(26)	(27)	(30)	(32)	(35)	(37)	(37)	(38)	(40)	(42)	(50)	(62)	(67)	(80)	(84)	(91)	(98)	(104)	(108)	(110)	(111)
Crizotinib	108	89	76	67	54	47	36	34	28	24	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0
	(0)	(17)	(28)	(34)	(43)	(49)	(55)	(57)	(62)	(63)	(67)	(68)	(68)	(68)	(68)	(72)	(74)	(76)	(77)	(78)	(79)	(81)	(82)	(82)	(82)	(83)	..

Solomon Lancet Respir Med 2022

Safety and Toxicity Profiles

Drug (dose)	Serious TRAEs	TRAE leading to dose reduction (% pts)	TRAE leading to drug discontinuation (% pts)	TRAEs more common in study drug vs. crizotinib	Ref.
Lorlatinib (100mg po / day)	Lorlatinib = 34% Crizotinib = 27%	Lorlatinib = 49% Crizotinib = 47%	Lorlatinib = 7% Crizotinib = 9%	Hypercholesterolemia Hypertriglyceridemia Weight increase Peripheral Neuropathy Cognitive Effects	Solomon B, et. al. ESMO 2020, 09.19/2020, LBA2
Alectinib (600mg po twice/day)	Alectinib = 28% Crizotinib = 29%	Alectinib = 16% Crizotinib = 21%	Alectinib = 11% Crizotinib = 13%	Anemia Myalgia Increased Bilirubin Increased weight Musculoskeletal pain Photosensitivity reaction	Initial Publication: Peters et al. *NEJM* 377;9 08/31/2017
Brigatinib (90mg po / day x 7 days, then 180mg po / day)	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 12% Crizotinib = 9%	Increased CK Cough Hypertension Increased Lipase Early onset ILD/pneumonitis	Initial Publication: Camidge et al. *NEJM* 379;21 11/22/2018
Ensartinib (225 mg po / day)	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 9% Crizotinib = 7%	Rash -- all grade ~70%, grade 1/2 ~60% Pruritis Pyrexia	Horn L et al. IASLC WCLC 08/08/2020

PO, by mouth, TRAE, treatment related adverse event

Lovly, presented at ESMO Virtual Congress 2020, 19 Sept 2020 – 21 Sept 2020.

Safety and Toxicity Profiles

Drug (dose)	Serious TRAEs	TRAE leading to dose reduction (% pts)	TRAE leading to drug discontinuation (% pts)	TRAEs more common in study drug vs. crizotinib	Ref.
Lorlatinib (100mg po / day)	Lorlatinib = 34% Crizotinib = 27%	Lorlatinib = 49% Crizotinib = 47%	Lorlatinib = 7% Crizotinib = 9%	Hypercholesterolemia Hypertriglyceridemia Weight increase Peripheral Neuropathy Cognitive Effects	Solomon B, et. al. ESMO 2020, 09.19/2020, LBA2
Alectinib (600mg po twice/day)	Alectinib = 28% Crizotinib = 29%	Alectinib = 16% Crizotinib = 21%	Alectinib = 11% Crizotinib = 13%	Anemia Myalgia Increased Bilirubin Increased weight Musculoskeletal pain Photosensitivity reaction	Initial Publication: Peters et al. *NEJM* 377;9 08/31/2017
Brigatinib (90mg po / day x 7 days, then 180mg po / day)	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 12% Crizotinib = 9%	Increased CK Cough Hypertension Increased Lipase Early onset ILD/pneumonitis	Initial Publication: Camidge et al. *NEJM* 379;21 11/22/2018
Ensartinib (225 mg po / day)	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 9% Crizotinib = 7%	Rash -- all grade ~70%, grade 1/2 ~60% Pruritis Pyrexia	Horn L et al. IASLC WCLC 08/08/2020

PO, by mouth, TRAE, treatment related adverse event

Lovly, presented at ESMO Virtual Congress 2020, 19 Sept 2020 – 21 Sept 2020.

Safety and Toxicity Profiles

Drug (dose)	Serious TRAEs	TRAE leading to dose reduction (% pts)	TRAE leading to drug discontinuation (% pts)	TRAEs more common in study drug vs. crizotinib	Ref.
Lorlatinib (100mg po / day)	Lorlatinib = 34% Crizotinib = 27%	Lorlatinib = 49% Crizotinib = 47%	Lorlatinib = 7% Crizotinib = 9%	Hypercholesterolemia Hypertriglyceridemia Weight increase Peripheral Neuropathy Cognitive Effects	Solomon B, et. al. ESMO 2020, 09.19/2020, LBA2
Alectinib (600mg po twice/day)	Alectinib = 28% Crizotinib = 29%	Alectinib = 16% Crizotinib = 21%	Alectinib = 11% Crizotinib = 13%	Anemia Myalgia Increased Bilirubin Increased weight Musculoskeletal pain Photosensitivity reaction	Initial Publication: Peters et al. *NEJM* 377;9 08/31/2017
Brigatinib (90mg po / day x 7 days, then 180mg po / day)	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 12% Crizotinib = 9%	Increased CK Cough Hypertension Increased Lipase Early onset ILD/pneumonitis	Initial Publication: Camidge et al. *NEJM* 379;21 11/22/2018
Ensartinib (225 mg po / day)	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 9% Crizotinib = 7%	Rash -- all grade ~70%, grade 1/2 ~60% Pruritis Pyrexia	Horn L et al. IASLC WCLC 08/08/2020

PO, by mouth, TRAE, treatment related adverse event

Lovly, presented at ESMO Virtual Congress 2020, 19 Sept 2020 – 21 Sept 2020.

Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival

Margret Merino, MD[1]; Yvette Kasamon, MD[1]; Marc Theoret, MD[1,2]; Richard Pazdur, MD[1,2]; Paul Kluetz, MD[1,2]; and Nicole Gormley, MD[1]

TABLE 2. Key Considerations for Early End Point and OS Analysis in Oncology Trials

Consideration
Toxicity
Greater attention to dose optimization is needed to minimize toxicity while maximizing efficacy. This has the potential to result in a more favorable benefit-risk profile.
Adequate capture of information on subsequent therapy and long-term safety outcomes is important to assess the overall benefit risk.
OS analysis
Clinical trial design and statistical analysis plans should consider the amount of OS information that will be available at the time of early end point analysis.
If OS is not the primary efficacy end point, when feasible, OS should be included as a key secondary end point.
When OS is not the primary or key secondary efficacy end point, OS information should be provided to assess the potential for harm.
Trials should provide for adequate OS follow-up and analysis.
Subgroup considerations
Consider biomarker predictiveness and mechanism of action in the trial design, sample size, and prespecified analyses.
Clinical trials should include an adequate number of patients, including relevant subpopulations to evaluate both early end points and OS.

Progression-Free Survival Should Not Be Used as a Primary End Point for Registration of Anticancer Drugs

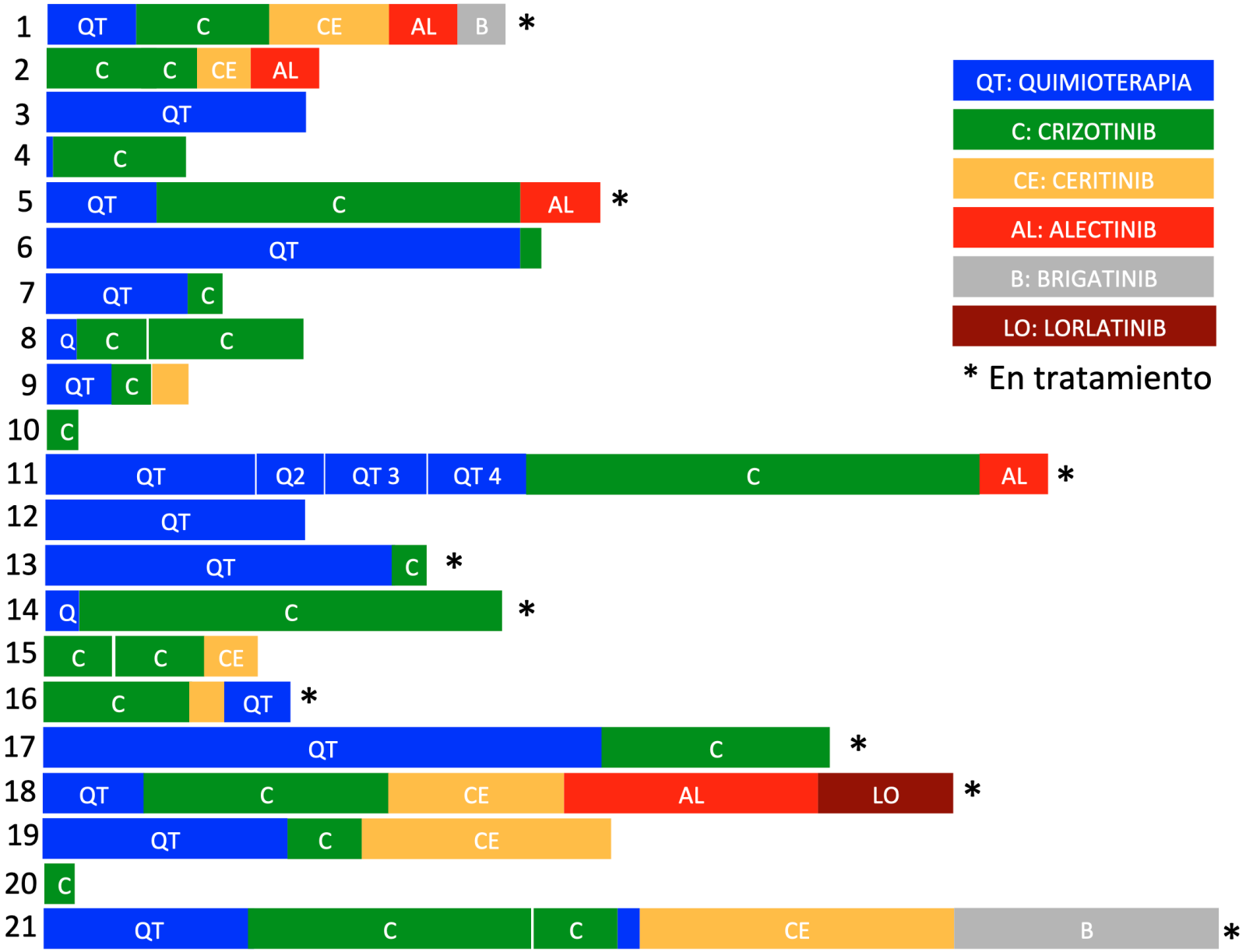
Christopher M. Booth, MD[1,2,3]; Elizabeth A. Eisenhauer, MD[2]; Bishal Gyawali, MD, PhD[1,2,3]; and Ian F. Tannock, MD, PhD[4]

TABLE 1. Reasons Why PFS Is an Inappropriate Primary End Point in Most Trials Evaluating Anticancer Drugs

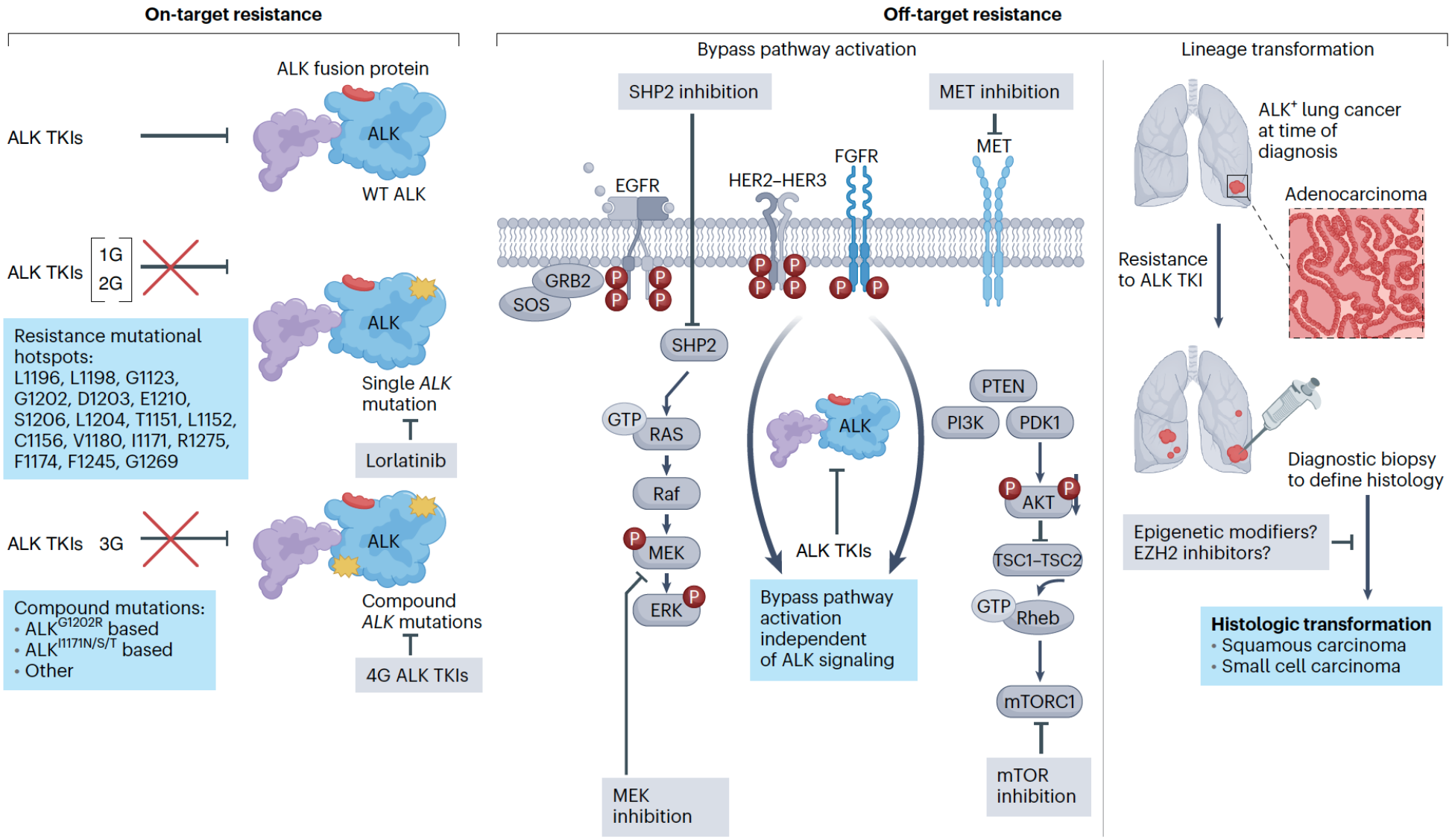
Improvement in PFS is seldom a surrogate for, nor reliably predictive of, improvement in OS
Improvement in PFS is not a surrogate for, nor predictive of, improvement in QoL
PFS does not recognize that the balance between benefit and harm depends not only on changes in tumor size but also on toxicity
PFS measurement and comparisons are subject to error and bias because of
Timing of assessment
Measurement error in assessing tumor progression
Informative censoring because of uneven dropout between groups in an RCT
Improvement in PFS is widely misunderstood by patients and the public to imply improvement in survival

Booth JCO 2023; Merino JCO 2023

Hospital Clínico
Santiago, 2018



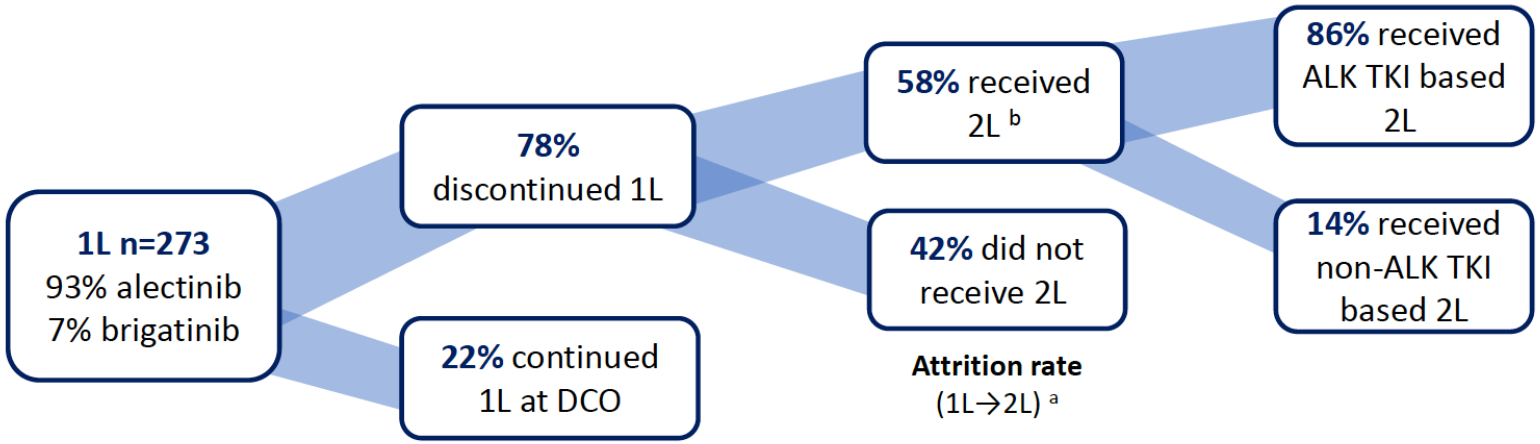
ALK-positive lung cancer: a moving target



Schneider Lancet Nature 2023

89.062 Pacientes en el base de datos Flatiron NSCLC

Results: 42% of patients who discontinued 1L did not receive 2L



2L (n=124)
Lorlatinib (n=65, 52%)
Brigatinib (n=17, 14%)
Other (n=42, 34%)

- Alectinib followed by lorlatinib was the most common sequence
- 36% of patients discontinued their 1L treatment within 12 months

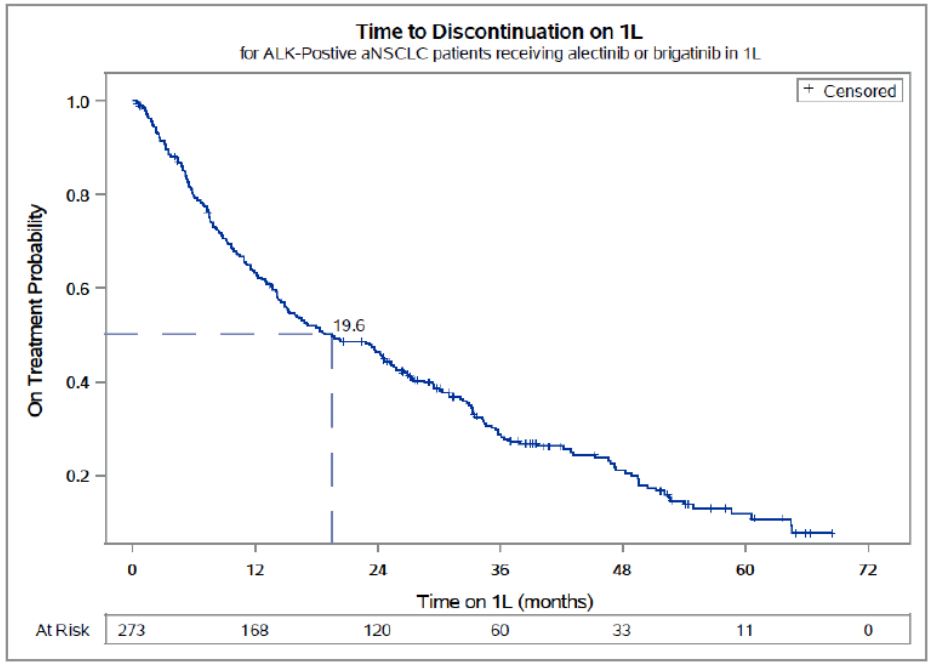
ALK Test Type, (%)	
Fluorescence in situ (FISH)	145 (53)
Immunohistochemistry screening (IHC)	27 (10)
Next Generation Sequencing (NGS)	89 (33)
Other, unknown	12 (4)

Bauman WLCL 2023

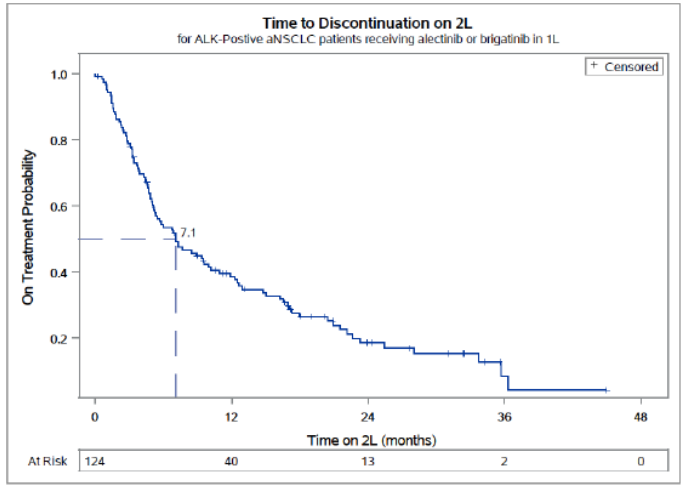
89.062 Pacientes en el base de datos Flatiron NSCLC

Results: Decreased effectiveness in 2L vs 1L

Median (95% CI) TTD **1L**: 19.6 (15.1-25.1) months



Median (95% CI) TTD **2L**: 7.1 (5.2-10.2) months



2L (n=124)	
Stratification	**Median TTD (95%CI)**
ALK TKI- based (n=107)	8.9 (6.7-12.5)
Non-ALK TKI based (n=17)	4.6 (3.2-5.2)

Bauman WLCL 2023

CROWN: First Subsequent Systemic Anticancer Therapies (long-term follow up)

	Lorlatinib	Crizotinib
≥1 Subsequent therapy, n/N (%)	**33/149 (22.1)**	**103/147 (70.1)**
First subsequent therapy, n	**33**	**103**
ALK TKI, n/N (%)	21/33 (63.6)	96/103 (93.2)
Alectinib	12/21 (57.1)	65/96 (67.7)
Crizotinib	4/21 (19.0)	5/96 (5.2)
Ceritinib	3/21 (14.3)	3/96 (3.1)
Brigatinib	1/21 (4.8)	20/96 (20.8)
Lorlatinib	1/21 (4.8)	3/96 (3.1)
Chemotherapy ± anti-angiogenic drugs, n/N (%)	11/33 (33.3)	3/103 (2.9)
Chemotherapy/immunotherapy, n/N (%)	1/33 (3.0)	0
Other, n/N (%)	0	4/103 (3.9)
Duration of first subsequent systemic anticancer therapy, median (IQR), months	**9.6 (2.9–18.1)**	**13.3 (4.8–21.2)**
ALK TKIs as first subsequent therapy	9.6 (2.8–19.3)	14.0 (6.5–21.8)
Non-ALK TKIs* as first subsequent therapy	10.4 (3.4–15.1)	1.0 (0.8–1.8)

Tras recaída a Lorlatinib 1L, en el estudio CROWN, alrededor de un 30% de pacientes alcanzó respuesta objetiva con un ALK TKI alternativo

Bauman WLCL 2023

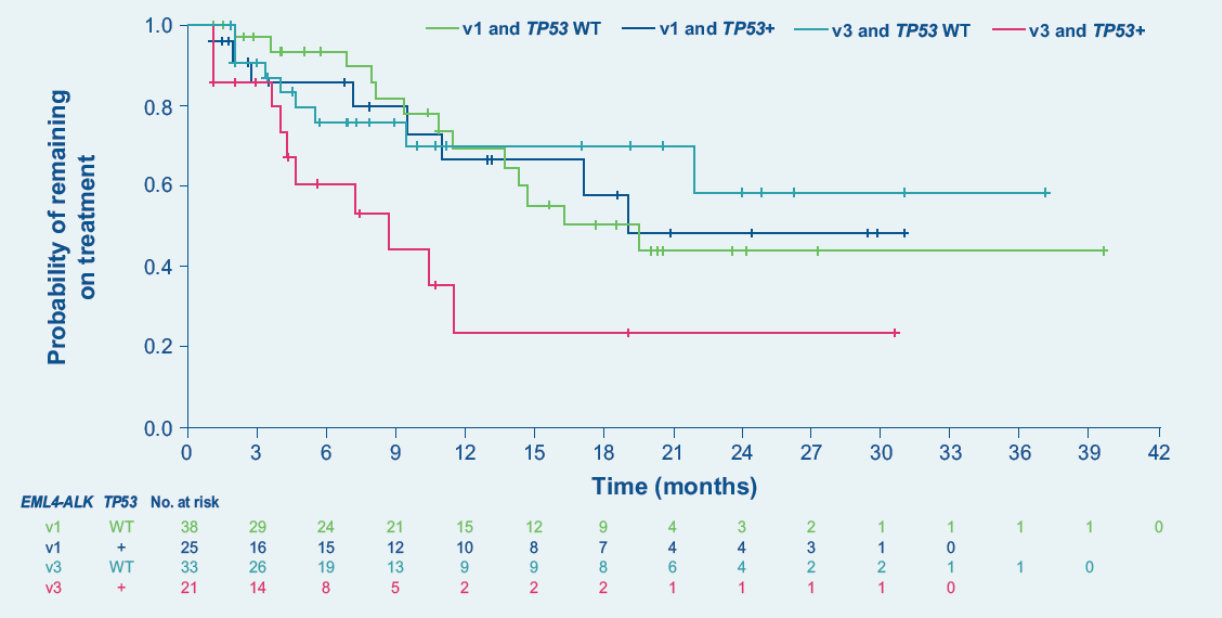
Plasma Genotyping From the CROWN, ALTA-1L, and ALEX Trials: Can We Speak With One Voice on What to Test, How to Test, When to Test, and for What Purpose?

Jii Bum Lee, MD,[a] Sai-Hong Ignatius Ou, MD, PhD[b,*]

Trial	CROWN (n = 293)[9,12]		ALTA-1L (n = 275)[8]	ALEX (n = 303)[6,7]
Authors	Soo et al.[9]	Bearz et al.[12]	Camidge et al.[8]	Dziadziuszko et al.[6] Camidge et al.[7]
ALK TKI (with plasma samples)	Lorlatinib (n = 134)		Brigatinib (n = 123)	Alectinib (n = 137)
Comparator (with plasma samples)	Crizotinib (n = 129)		Crizotinib (n = 127)	Crizotinib (n = 139)
NGS platform	Guardant360 v2.11 (Guardant Health) (plasma) Guardant360 v2.13 (Guardant Health) (tissue)		ctDx Lung NGS panel (Resolution Bioscience, Kirkland, WA)	FoundationACT (Foundation Medicine Inc.)
Genes analyzed (n)	74		38	62 (6 fusions)
Time points analyzed	Baseline, week 4, week 24, EOT	Baseline	Baseline, cycle 3 and d 2, EOT	Baseline
Purpose of test	1. ctDNA as a prognostic biomarker 2. ctDNA as a response monitor	1. ctDNA as a prognostic biomarker 2. *EML4-ALK* variants and *TP53* mutations as biomarkers for ORR and PFS	Prognostic biomarker, monitoring tool; *EML4-ALK* variants and *TP53* mutations as biomarkers for ORR and PFS	1. Bassline median cfDNA, ctDNA, *EML4-ALK* variants, and *TP53* mutations as biomarkers for ORR and PFS.
Plasma genotyping	ctDNA	*ALK* fusions, TP53	*ALK* fusion, *TP53*	cfDNA, ctDNA, *ALK* fusions, *TP53*

NSCLC avanzado/mts con fusión ALK x Guardant 360 (n=496)

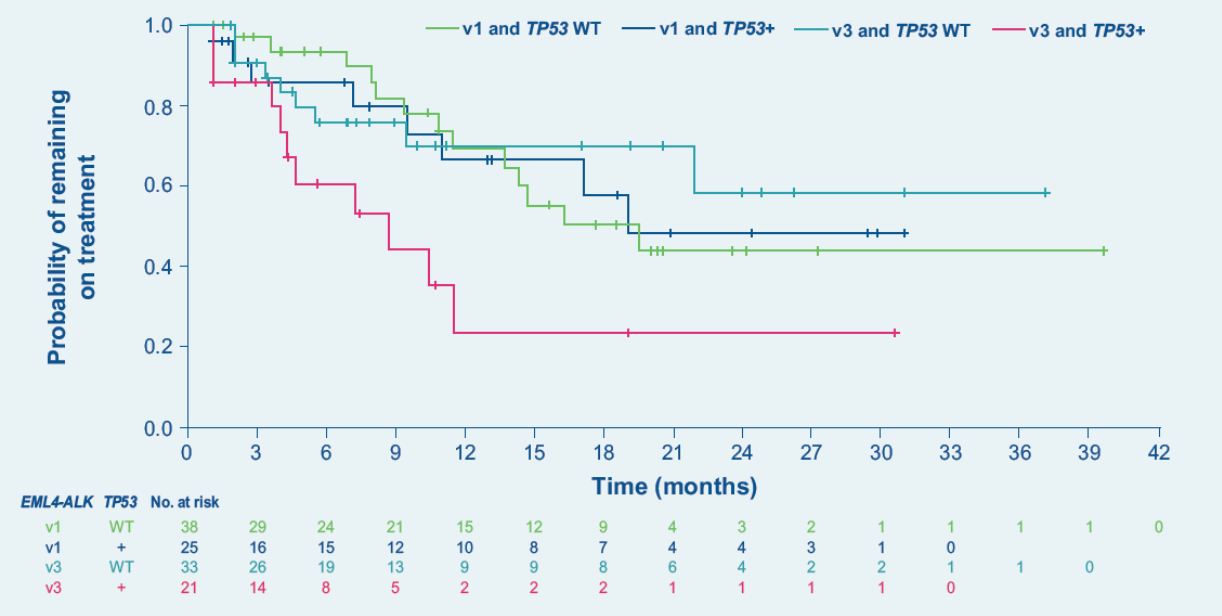
Guardant 360 realizado antes 1L ALK TKI (n=164) Alectinib (147); Brigatinib (7); Lorlatinib (8); Ceritinib (2)



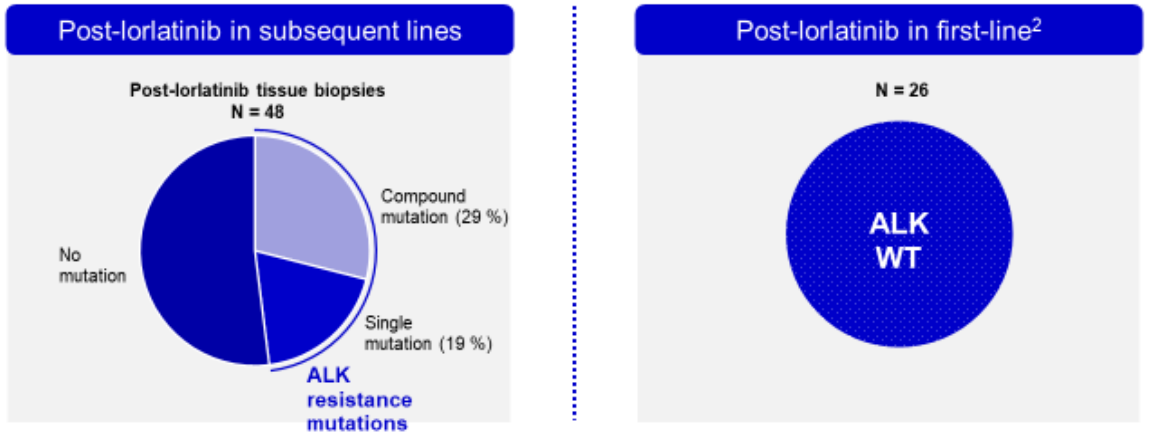
Parihk ASCO 2023; Felip ESMO 2022.

NSCLC avanzado/mts con fusión ALK x Guardant 360 (n=496)

Guardant 360 realizado antes 1L ALK TKI (n=164) Alectinib (147); Brigatinib (7); Lorlatinib (8); Ceritinib (2)



Lorlatinib Resistance Spectrum in 1L Differs From the One in Later Lines: No ALK Resistance Mutations in the CROWN Study so far

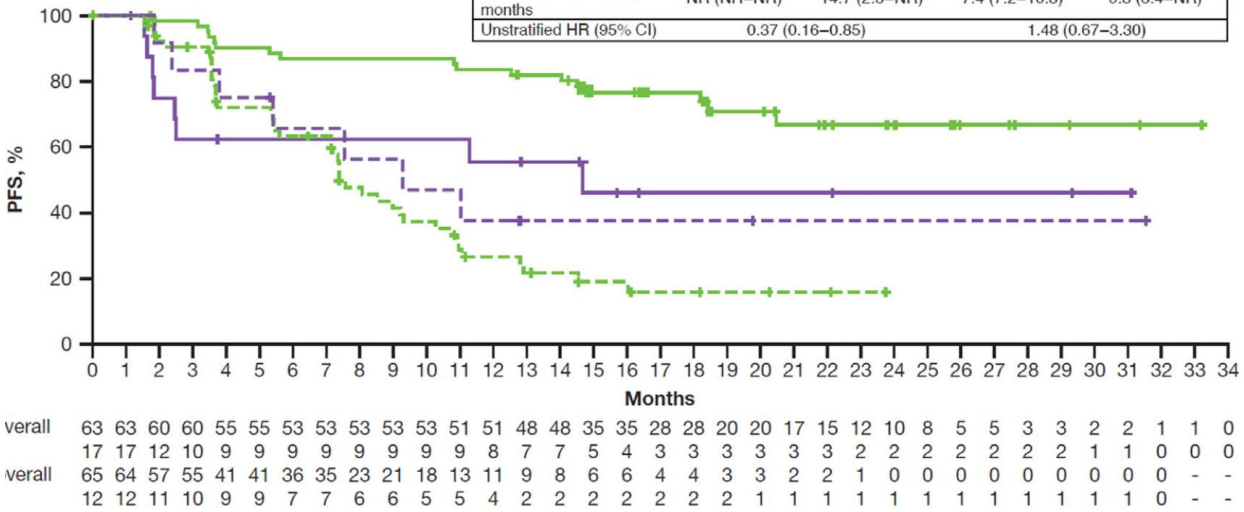


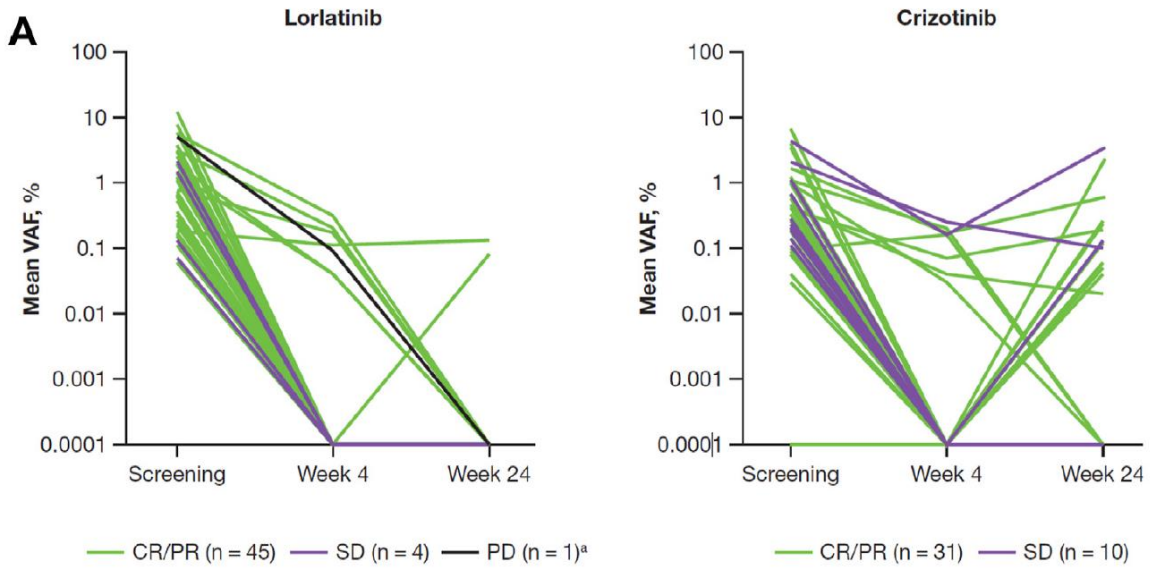
Parihk ASCO 2023; Felip ESMO 2022.

Early circulating tumor DNA dynamics and efficacy of lorlatinib in patients with treatment-Naive advanced, ALK-Positive NSCLC

ctDNA

	Lorlatinib		Crizotinib	
	MR overall (n = 63)	MNR (n = 17)	MR overall (n = 65)	MNR (n = 12)
Events, n	17	8	44	7
Median PFS (95% CI), months	NR (NR–NR)	14.7 (2.5–NR)	7.4 (7.2–10.3)	9.3 (5.4–NR)
Unstratified HR (95% CI)	0.37 (0.16–0.85)		1.48 (0.67–3.30)	





Niveles ctDNA basal y respuesta a 4 sem se correlacionan con mejor pronóstico

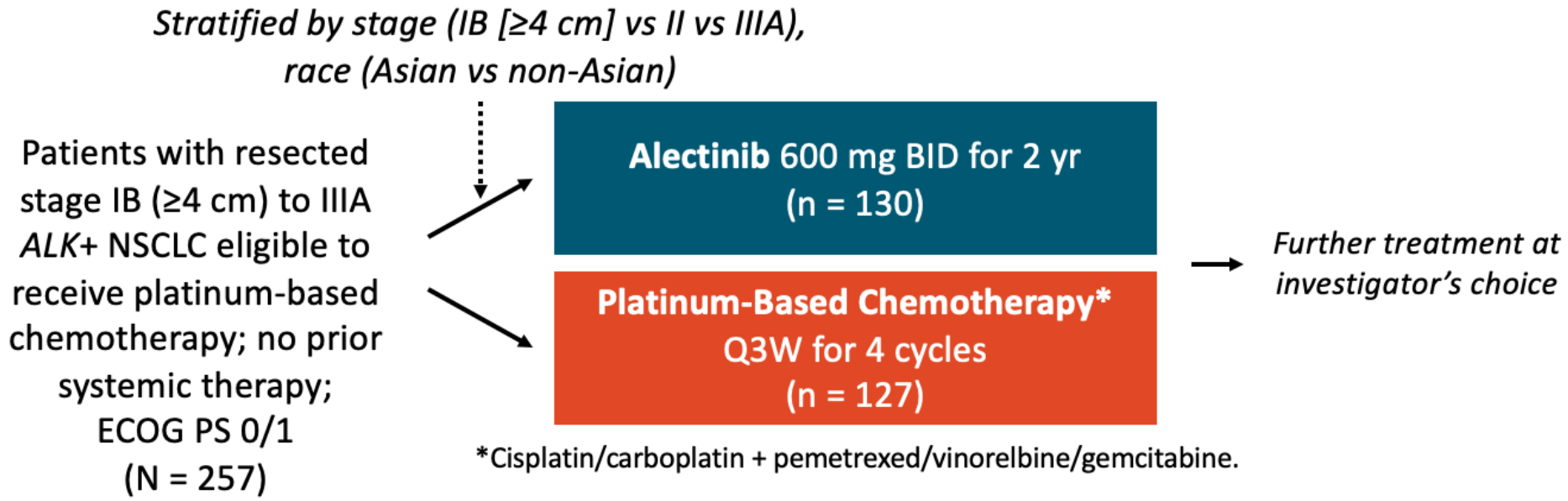
¿La determinación a 4 sem puede servir para establecer estrategia?

Fusiones y/o variantes en ALK

Soo Jto 2023

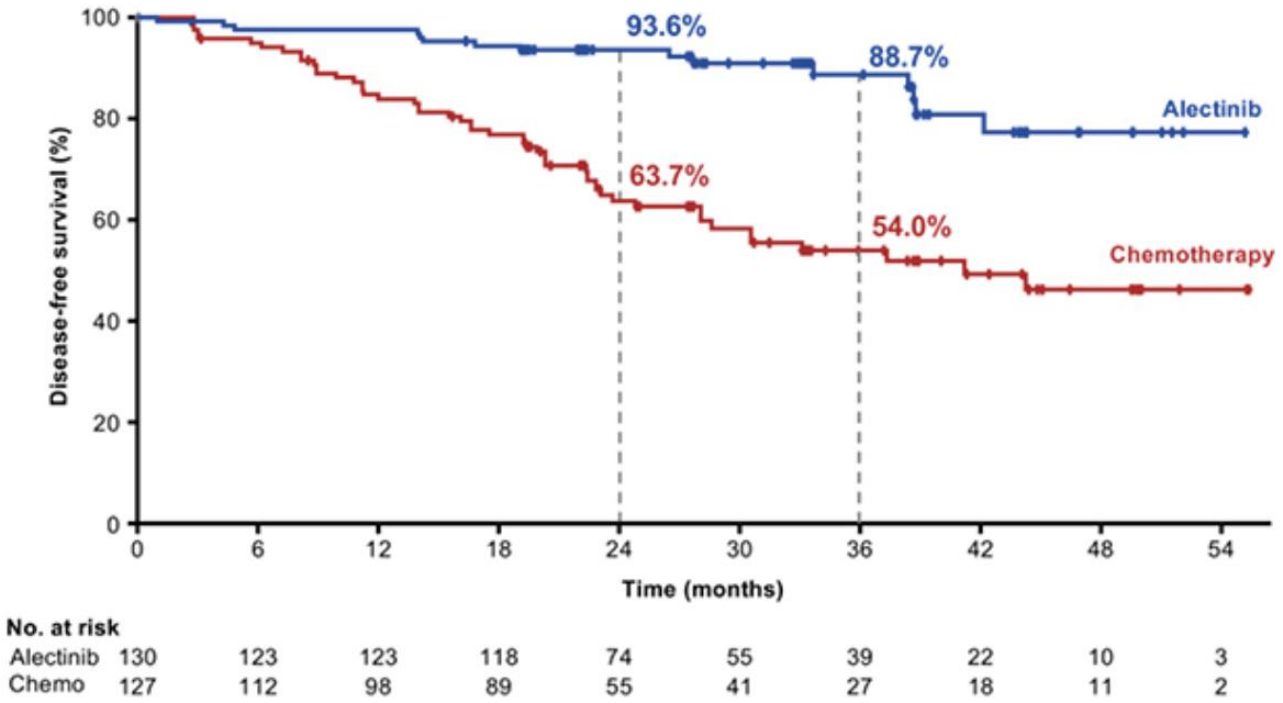
ALINA: Study Design

- International, randomized, open-label phase III trial



- **Primary endpoint:** DFS per investigator (hierarchical: stage II-IIIA; then stage IB-IIIA [ITT population])
- **Secondary endpoints:** CNS DFS, OS, safety

Disease-free survival: ITT (stage IB-IIIA)*



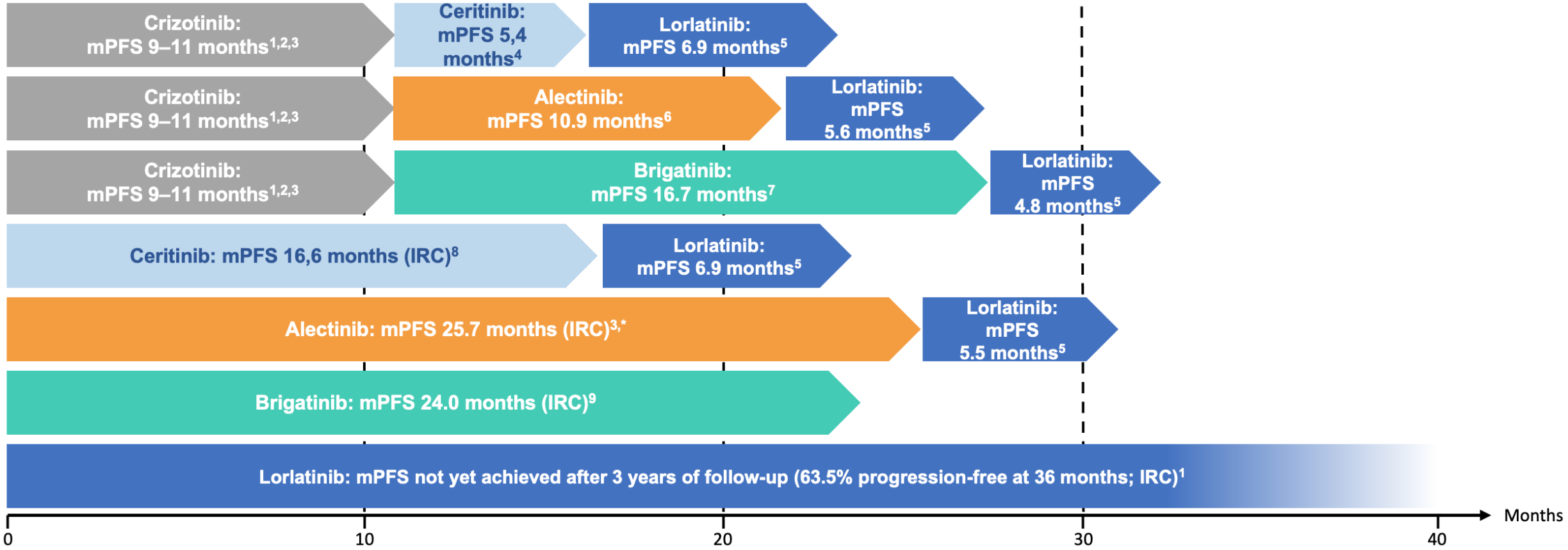
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p‡<0.0001	

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

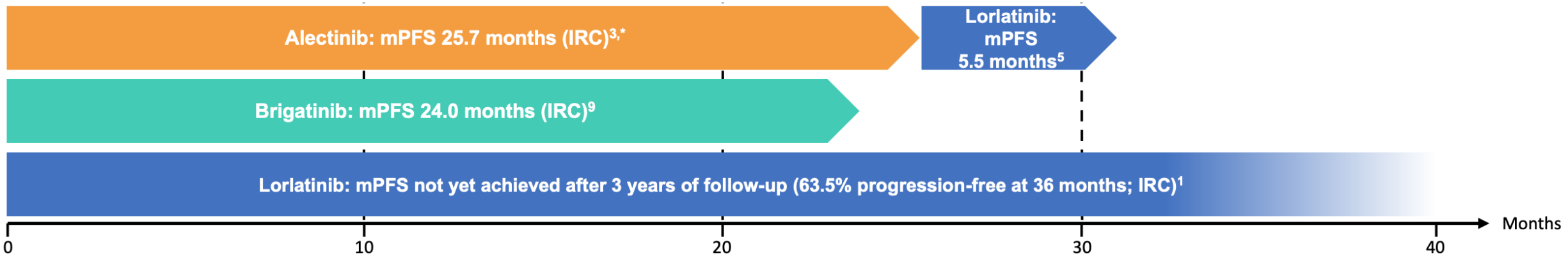
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023; *Per UICC/AJCC 7th edition; ‡Stratified log rank; §2 events in the alectinib arm, 4 events in the chemo arm; one patient in chemo died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first.

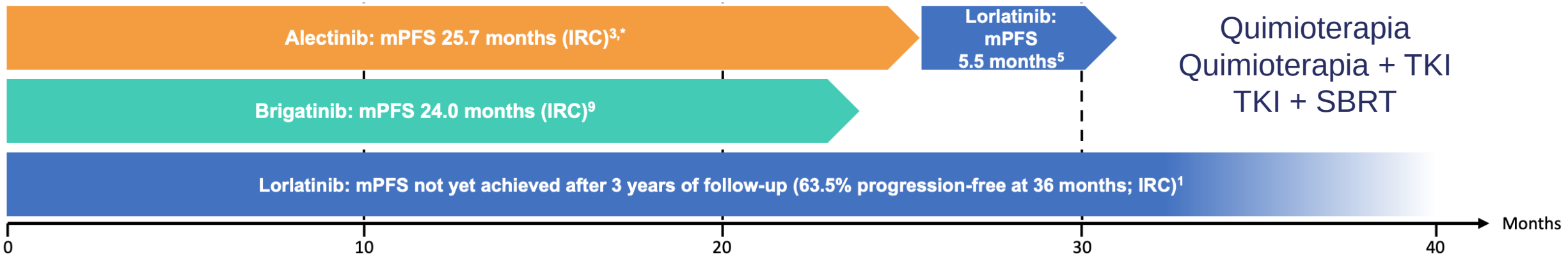
Solomon ESMO 23



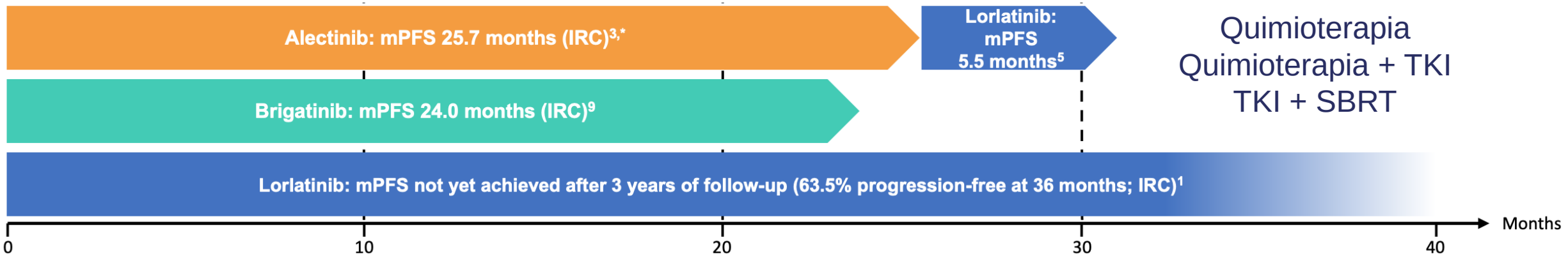
Cross-trial comparisons have clear limitations and are not permitted. These are only summary presentations of published data, not direct comparisons. * Median PFS according to independent, blinded assessment was reported in the ALEX study only from the first data cut. |
References: 1. Solomon BJ et al AACR 2022 Poster CT223. 2. Solomon BJ et al. J Clin Oncol 2018;36: 2251-2258. 3. Mok T et al. Ann Oncol 2020;31(8):1056-1064. 4. Shaw AT et al. Lancet Oncol. 2017;18(7):874-886. 5. Felip E et al. Ann Oncol 2021;32(5):620-630. 6. Wolf J et al. ESMO Open. 2022;7(1):100333. 7. Gettinger SN et al. J Clin Oncol 2021;39:9071-9071. 8. Soria J-C et al. Lancet. 2017; 389(10072): 917-929. 9. Camidge DR et al. J Clin Oncol 2020; 38(31): 3592-3603..



Cross-trial comparisons have clear limitations and are not permitted. These are only summary presentations of published data, not direct comparisons. * Median PFS according to independent, blinded assessment was reported in the ALEX study only from the first data cut. |
References: 1. Solomon BJ et al AACR 2022 Poster CT223. 2. Solomon BJ et al. J Clin Oncol 2018;36: 2251-2258. 3. Mok T et al. Ann Oncol 2020;31(8):1056-1064. 4. Shaw AT et al. Lancet Oncol. 2017;18(7):874-886. 5. Felip E et al. Ann Oncol 2021;32(5):620-630. 6. Wolf J et al. ESMO Open. 2022;7(1):100333. 7. Gettinger SN et al. J Clin Oncol 2021;39:9071-9071. 8. Soria J-C et al. Lancet. 2017; 389(10072): 917-929. 9. Camidge DR et al. J Clin Oncol 2020; 38(31): 3592-3603..



Cross-trial comparisons have clear limitations and are not permitted. These are only summary presentations of published data, not direct comparisons. * Median PFS according to independent, blinded assessment was reported in the ALEX study only from the first data cut. |
References: 1. Solomon BJ et al AACR 2022 Poster CT223. 2. Solomon BJ et al. J Clin Oncol 2018;36: 2251-2258. 3. Mok T et al. Ann Oncol 2020;31(8):1056-1064. 4. Shaw AT et al. Lancet Oncol. 2017;18(7):874-886. 5. Felip E et al. Ann Oncol 2021;32(5):620-630. 6. Wolf J et al. ESMO Open. 2022;7(1):100333. 7. Gettinger SN et al. J Clin Oncol 2021;39:9071-9071. 8. Soria J-C et al. Lancet. 2017; 389(10072): 917-929. 9. Camidge DR et al. J Clin Oncol 2020; 38(31): 3592-3603..



Quimioterapia
Quimioterapia + TKI
TKI + SBRT

Integrando la caracterización molecular

Cross-trial comparisons have clear limitations and are not permitted. These are only summary presentations of published data, not direct comparisons. * Median PFS according to independent, blinded assessment was reported in the ALEX study only from the first data cut. | References: 1. Solomon BJ et al AACR 2022 Poster CT223. 2. Solomon BJ et al. J Clin Oncol 2018;36: 2251-2258. 3. Mok T et al. Ann Oncol 2020;31(8):1056-1064. 4. Shaw AT et al. Lancet Oncol. 2017;18(7):874-886. 5. Felip E et al. Ann Oncol 2021;32(5):620-630. 6. Wolf J et al. ESMO Open. 2022;7(1):100333. 7. Gettinger SN et al. J Clin Oncol 2021;39:9071-9071. 8. Soria J-C et al. Lancet. 2017; 389(10072): 917-929. 9. Camidge DR et al. J Clin Oncol 2020; 38(31): 3592-3603..


15th
MADRID
CONGRESS
on Lung CANCER
23&24
November 2023
#15CongressGECP
Fundación
GECP
lung cancer
research
Muchas Gracias