Plenaria III

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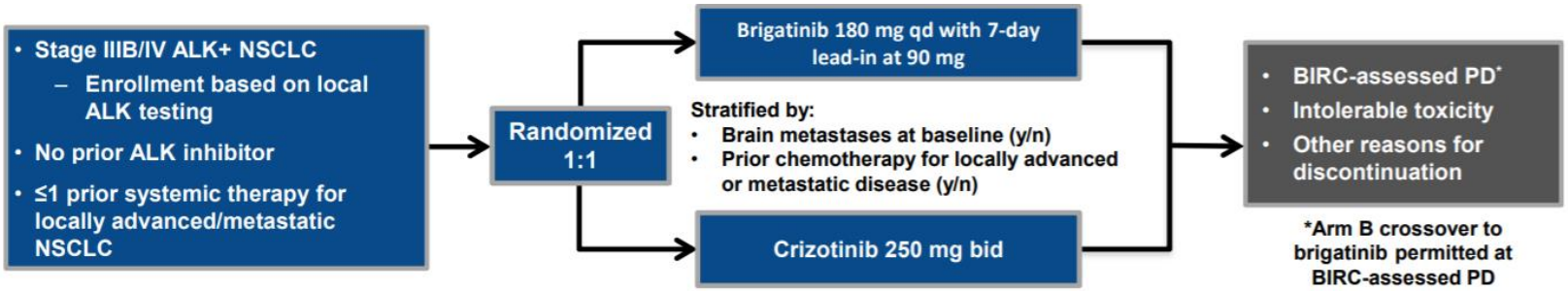
Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

ALTA 1L: Brigatinib vs Crizotinib in 1L ALK+ (Phase 3)

Brigatinib vs Crizotinib in Patients With ALK Inhibitor–Naive Advanced ALK+ NSCLC: First Report of a Phase 3 Trial (ALTA-1L)



Disease assessment every 8 weeks, including brain MRI for all patients

- Primary endpoint: 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)

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Demographics and Baseline Characteristics		Brigatinib n=137	Crizotinib n=138	Total N=275
Median age, y (range)		58 (27–86)	60 (29–89)	59 (27–89)
Sex, %	Female	50	59	55
Race, %	White, Asian, Other	55, 43, 1	62, 36, 2	59, 39, 2
ECOG performance status, %	0, 1, 2	42, 53, 4	43, 52, 4	43, 53, 4
Stage of disease at study entry, %	IIIB, IV	6, 94	9, 91	7, 93
ALK status assessed locally by FDA-approved test, %[a]		90	81	86
Brain metastases at baseline,[b] %		29	30	29
Prior radiotherapy to the brain, %		13	14	13
Prior chemotherapy in the locally advanced or metastatic setting,[c] %		26	27	27

[a]Patients whose ALK+ status was confirmed locally by Vysis FISH or Ventana IHC. [b]As assessed by the investigator. [c]Prior chemotherapy was defined as completion of at least one full cycle of chemotherapy in the locally advanced or metastatic setting.

As of the first interim analysis (data cut off: February 19, 2018):

- **95 patients (69%) in the brigatinib arm and 59 (43%) in the crizotinib arm remained on study treatment**
- **Median (range) follow-up: 11.0 (0–20.0) months and 9.25 (0–20.9) months, respectively**
- **35 patients who discontinued crizotinib due to disease progression crossed over to brigatinib as part of the trial**

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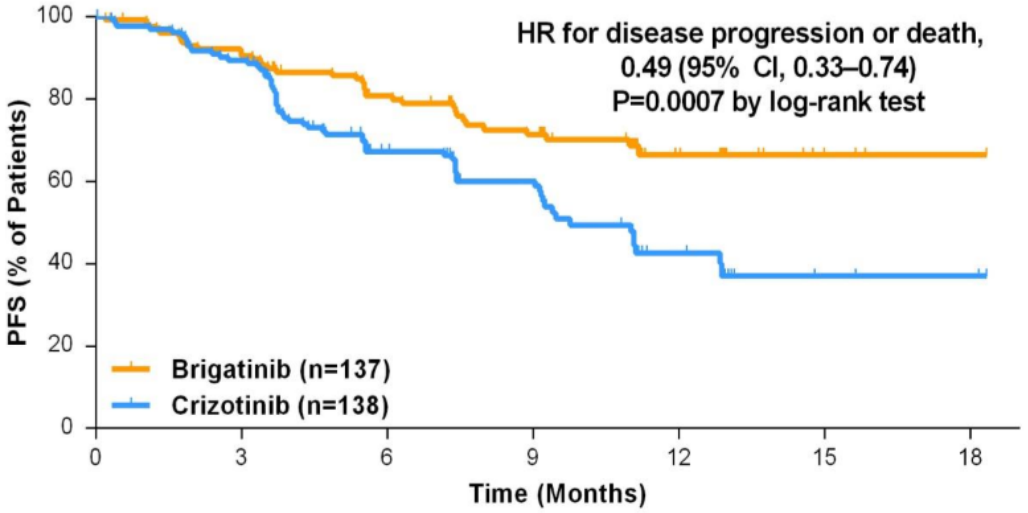
Primary Endpoint: BIRC-Assessed PFS

Brigatinib met the prespecified threshold for statistical superiority vs crizotinib



Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

- Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank P=0.0001)
- 1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)

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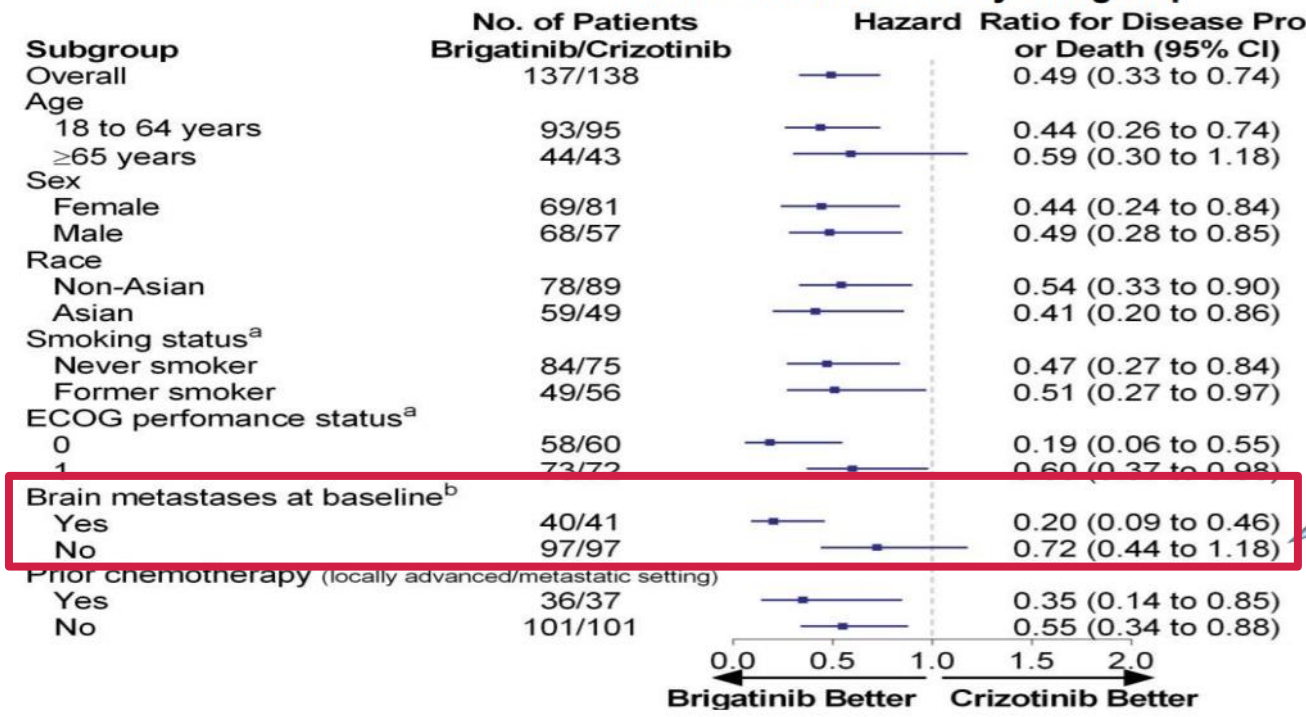
BIRC-Assessed PFS by Subgroup



At this first interim analysis, PFS dataset more mature in patients with baseline CNS disease, particularly for crizotinib arm, which was driven by CNS events

<u>% with PFS events, Crizotinib vs Brigatinib:</u>

- **Overall: 46% vs 26%**
- Baseline CNS disease: 59% vs 20%[c]
- No Baseline CNS disease: 40% vs 29%[d]

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Systemic Objective Response[a] (ITT Population)

	Brigatinib n=137	Crizotinib n=138	OR (95% CI)
Confirmed ORR, % (95% CI)	71 (62–78)	60 (51–68)	1.59 (0.96–2.62) P=0.0678
Confirmed CR, %	4	5	
Confirmed PR, %	67	55	
ORR at ≥1 assessment, % (95% CI)	76 (68–83)	73 (65–80)	1.13 (0.66–1.97) P=0.6512
CR, %	7	8	
PR, %	69	65	
Median DoR in confirmed responders, mo (95% CI)	NR (NR–NR)	11.1 (9.2–NR)	
12-month probability of maintaining response, % (95% CI)	75 (63–83)	41 (26–54)	

[a]Assessed by the BIRC.

Intracranial Objective Response[a] in Patients with Brain Metastases at Baseline

Measurable[b] brain metastases at baseline	Brigatinib n=18	Crizotinib n=21	OR (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05) P=0.0028
CR, %	11	0	
PR, %	67	29	
Intracranial ORR at ≥1 assessment, % (95% CI)	83 (59–96)	33 (15–57)	9.29 (1.88–45.85) P=0.0023
Any brain metastases at baseline	**n=43**	**n=47**	
Confirmed intracranial ORR, % (95% CI)	67 (51–81)	17 (8–31)	13.00 (4.38–38.61) P<0.0001
CR, %	37	4	
PR, %	30	13	
Intracranial ORR at ≥1 assessment, % (95% CI)	79 (64–90)	23 (12–38)	16.30 (5.32–49.92) P<0.0001

[a]Assessed by the BIRC.
[b]≥10 mm in diameter.

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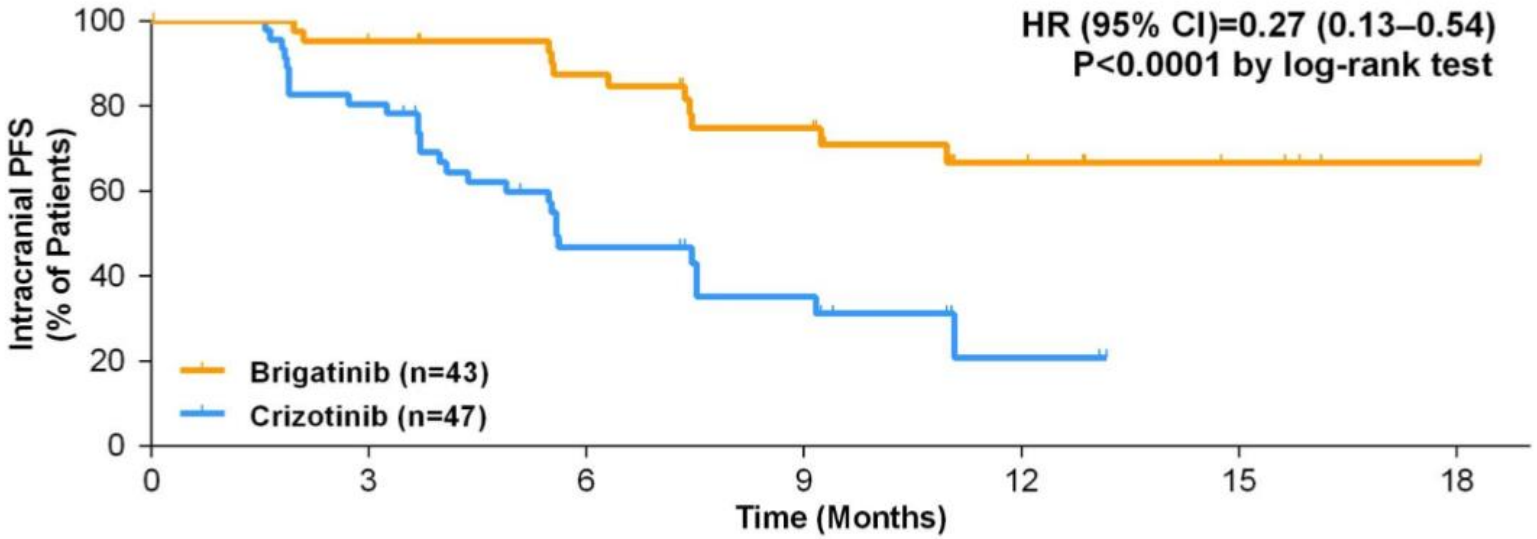
Intracranial PFS in Patients With Any Brain Metastases at Baseline



Treatment	Median Intracranial PFS (95% CI)	1-Year PFS Probability, % (95% CI)
Brigatinib (n=43)	NR (11.0–NR)	67 (47–80)
Crizotinib (n=47)	5.6 months (4.1–9.2)	21 (6–42)

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TRAEs in >20% of pts

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	49	1	55	2
Increased blood CPK	39	16	15	1
Nausea	26	1	56	3
Cough	25	0	16	0
Increased AST	23	1	25	6
Hypertension	23	10	7	3
Increased ALT	19	1	32	9
Increased lipase	19	13	12	5
Vomiting	18	1	39	2
Constipation	15	0	42	1
Increased amylase	14	5	7	1
Pruritus	13	1	4	1
Rash	10	0	2	0
Decreased appetite	7	1	20	3
Dermatitis acneiform	7	0	1	0
Dermatitis acneiform	7	0	1	0

- ILD/pneumonitis similar in both arms (brigatinib 4%; crizotinib 2%)
- Early onset ILD/pneumonitis with brigatinib 3% (none with crizo)
- Dose reduction similar (29%/21%); discontinuation (12%/9%)
- Cause of dose reduction with briga→ lab abnormalities (CPK, lipase, amylase, AST, HTA, pneumonitis, rash)
- No pancreatitis, no difference in myalgia among both arms

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ALTA 1L: Brigatinib vs Crizotinib in 1L ALK+ (Phase 3)

Brigatinib becomes a novel standard of care in 1L ALK+ advanced NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer

D.R. Camidge, H.R. Kim, M.-J. Ahn, J.C.-H. Yang, J.-Y. Han, J.-S. Lee, M.J. Hochmair, J.Y.-C. Li, G.-C. Chang, K.H. Lee, C. Gridelli, A. Delmonte, R. Garcia Campelo, D.-W. Kim, A. Bearz, F. Griesinger, A. Morabito, E. Felip, R. Califano, S. Ghosh, A. Spira, S.N. Gettinger, M. Tiseo, N. Gupta, J. Haney, D. Kerstein, and S. Popat

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IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG #WCLC2018

Nintedanib + pemetrexed/cisplatin in patients with unresectable MPM: Phase III results from the LUME-Meso trial

Patients with histologically confirmed, unresected epithelioid MPM

- Life expectancy of ≥3 months
- No previous systemic chemotherapy for MPM

RANDOMISE

Nintedanib: 200 mg bid* + pemetrexed/cisplatin§ → Non-PD patients → Nintedanib maintenance → PD

N=458
Randomised 1:1

Placebo: 200 mg bid* + pemetrexed/cisplatin§ → Non-PD patients → Placebo maintenance → PD

- Enrolment: April 2016 to January 2018
- ~120 centres, 27 countries
- Clinical trial identifier: NCT01907100

Selected endpoints

Primary endpoint: PFS¶
Key secondary endpoint: OS

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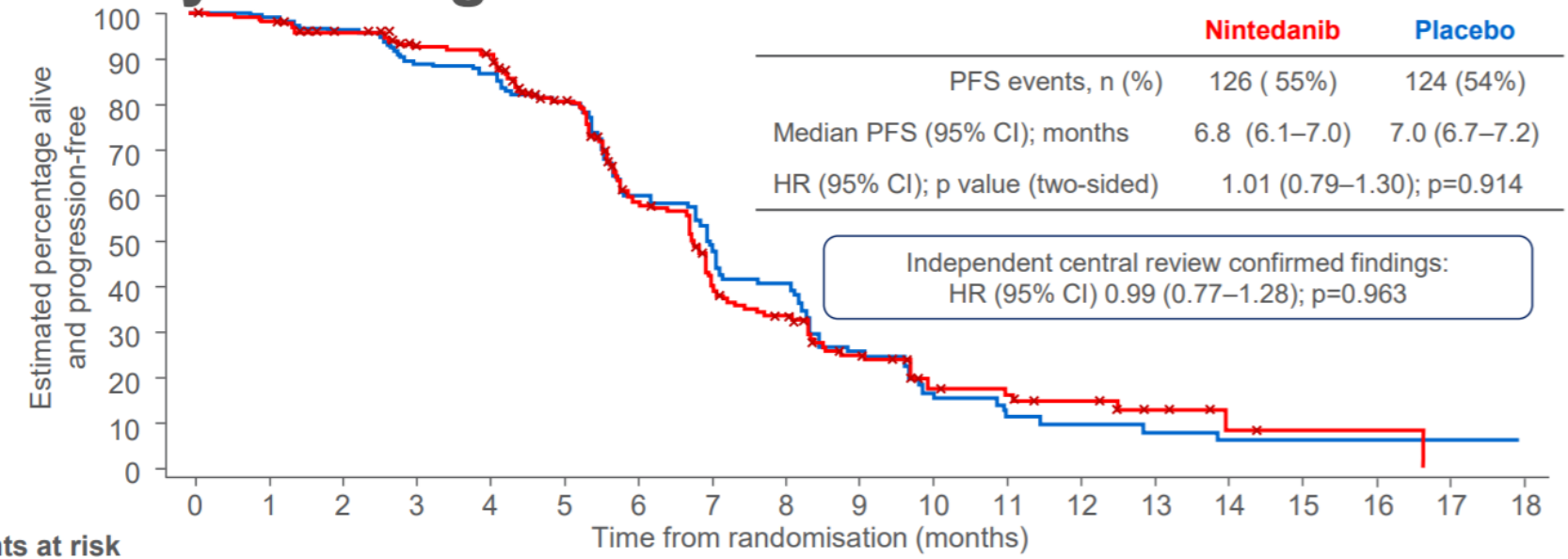
LUME-MESO trial (Phase 3)

Baseline demographics and disease characteristics

Characteristic		Nintedanib (n=229)	Placebo (n=229)
Age; median (interquartile range; years)		66 (58–70)	66 (58–70)
Sex; n (%)	Male	165 (72)	169 (74)
ECOG PS; n (%)	0	99 (43)	98 (43)
	1	130 (57)	131 (57)
Smoking status; n (%)	Never smoker	92 (40)	89 (39)
	Ex-smoker	113 (49)	122 (53)
Previous exposure to asbestos; n (%)	Yes	141 (62)	150 (66)
	No	68 (30)	53 (23)
	Unknown	20 (9)	26 (11)
Tumour stage at screening (UICC/AJCC); n (%)	I	12 (5)	15 (7)
	II	15 (7)	17 (7)
	III	89 (39)	90 (39)
	IV	113 (49)	105 (46)
	Missing	0	2 (<1%)
Previous surgery (pleurectomy/decortication/extrapleural pneumonectomy); n (%)		16 (7)	16 (7)
Time since first histologic diagnosis; median (interquartile range; months)		1.3 (0.9–2.0)	1.2 (0.8–1.8)

LUME-MESO trial (Phase 3)

PFS by investigator assessment



	Nintedanib	Placebo
PFS events, n (%)	126 (55%)	124 (54%)
Median PFS (95% CI); months	6.8 (6.1–7.0)	7.0 (6.7–7.2)
HR (95% CI); p value (two-sided)	1.01 (0.79–1.30); p=0.914	

Independent central review confirmed findings:
HR (95% CI) 0.99 (0.77–1.28); p=0.963

ents at risk																			
Nintedanib	229	213	190	162	158	129	86	57	44	28	15	13	9	5	2	1	1	0	
Placebo	229	216	190	163	152	126	86	62	49	26	14	9	6	5	4	3	2	2	0

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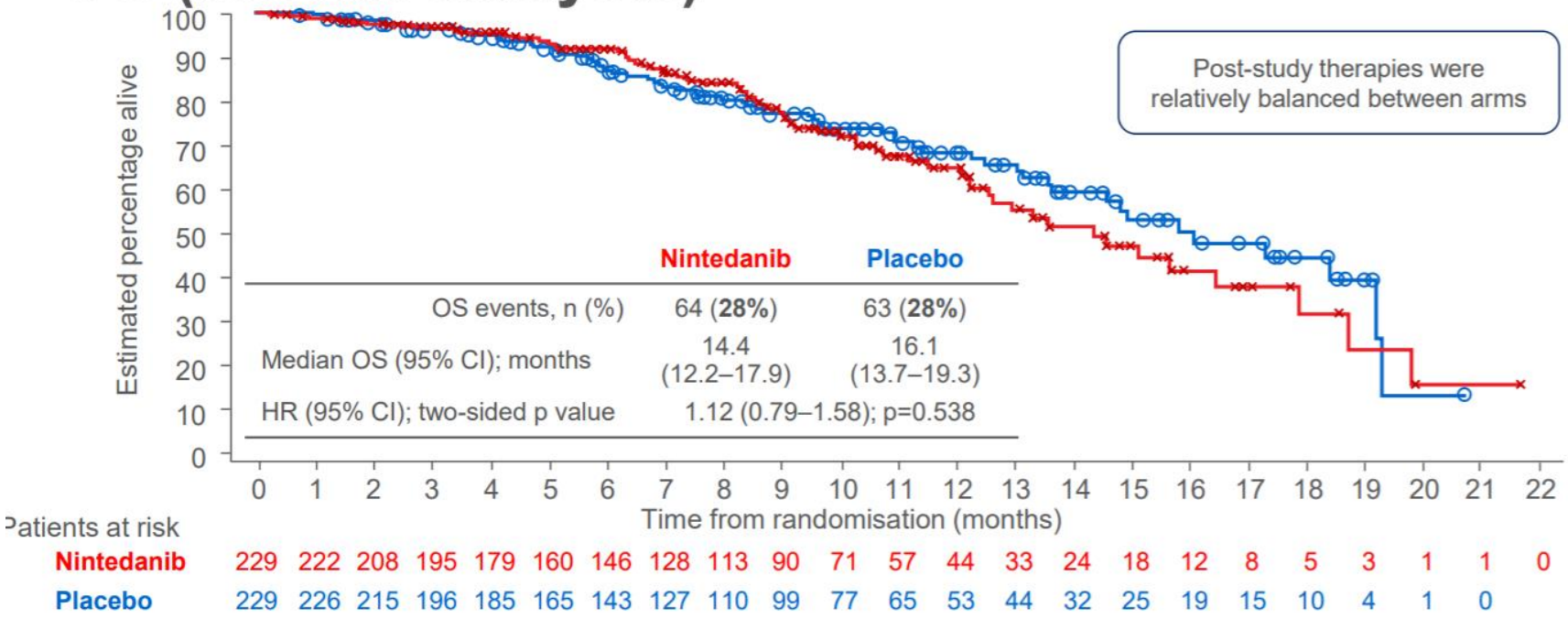
LUME-MESO trial (Phase 3)

OS (interim analysis)



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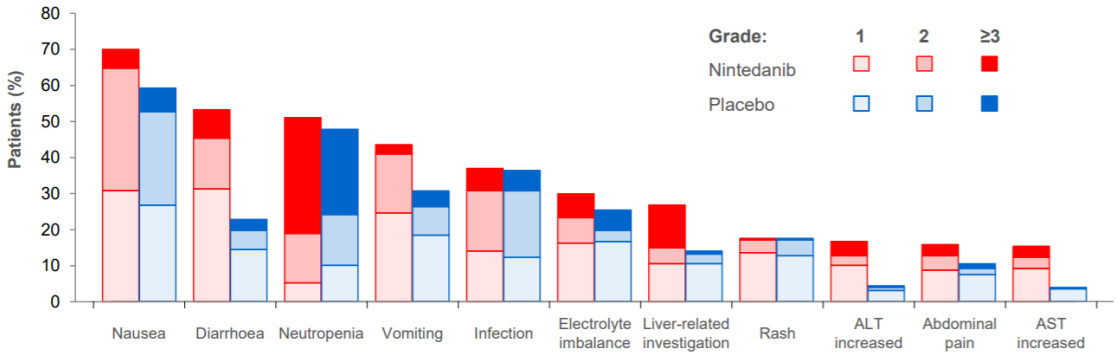
LUME-MESO trial (Phase 3)

Treatment exposure

N (%)			Nintedanib	Placebo
Nintedanib/placebo	Duration of treatment in months; median (range)		5.3 (0.1–19.9)	5.1 (0.1–20.8)
	Dose intensity, percentage; mean (SD)		95.3 (11.5)	98.1 (6.5)
	Dose reductions; n (%):	1	51 (22.5)	17 (7.5)
		2	16 (7.0)	5 (2.2)
Pemetrexed	Number of pemetrexed courses; median (mean)		5.00 (4.7)	6.00 (4.8)
	Dose intensity, percentage; mean (SD)		96.4 (7.4)	98.5 (5.7)
	Dose reductions; n (%):	1	49 (21.6)	17 (7.5)
		2	4 (1.8)	3 (1.3)
Cisplatin	Number of cisplatin courses; median (mean)		5.00 (4.7)	6.00 (4.6)
	Dose intensity, percentage; mean (SD)		96.2 (7.1)	97.9 (6.3)
	Dose reductions; n (%):	1	55 (24.2)	29 (12.7)
		2	2 (0.9)	2 (0.9)
AEs leading to trial discontinuation; n (%)			25 (11.0)	22 (9.6)

Overall frequency of AEs (group term)

AEs of any grade occurring more commonly with nintedanib and in ≥15% of patients



Quality of life was not adversely impacted by the addition of nintedanib to chemotherapy

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Conclusions

- **Primary endpoint of LUME-Meso Phase III was not met**
  - No difference in PFS by investigator assessment (HR=1.01); this was confirmed by independent central review
- **Key secondary endpoint, OS, as well as other endpoints, also showed no difference between treatment groups**
- **Phase III results did not confirm the Phase II findings**
  - The study has been discontinued per protocol
- **Safety profile manageable and consistent with previous nintedanib studies**