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

Scagliotti GV, Gaafar R, Nowak AK, Nakano T, Van Meerbeeck J, Popat S, Vogelzang NJ, Grosso F, Aboelhassan R, Jakopovic M, Ceresoli GL, Taylor P, Orlandi F, Fennell DA, Novello S, Scherpereel A, Von Wangenheim U, Kim M, Barrueco J and Tsao AS

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Background

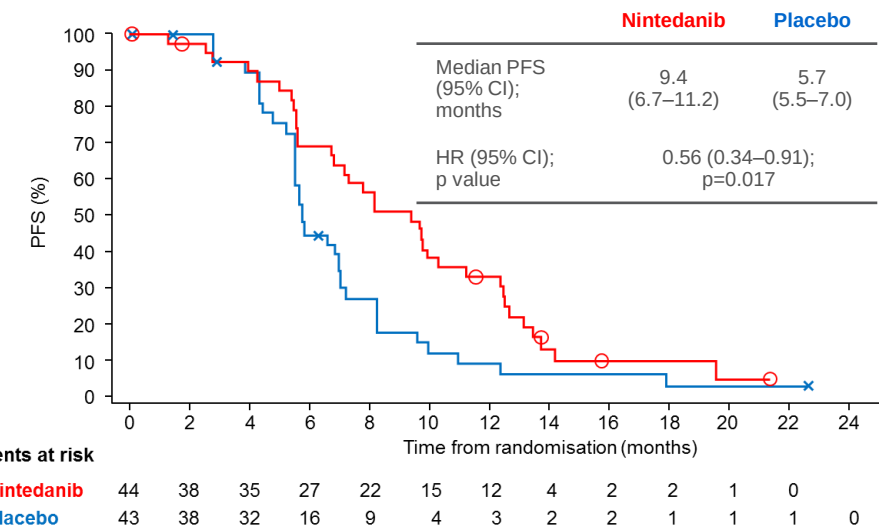
- Malignant pleural mesothelioma (MPM) is an uncommon tumour originating from cells lining the mesothelial surfaces
- Globally, incidence of MPM has risen steadily over the past decade and is predicted to peak in ~2020,[1] although it will continue to increase in many countries[2,3]
- Pemetrexed/cisplatin is the only approved regimen (since 2003), with a median OS of ~1 year[4]
- The Phase III MAPS study showed that bevacizumab (anti-VEGF monoclonal antibody) combined with platinum-based chemotherapy improved both median PFS and OS[5]

1. Bibby AC, et al. Eur Respir Rev 2016;25:472–86; 2. Delgermaa V, et al. Bull World Health Organ 2011;89:716–24; 3. Carbone M, et al. J Thorac Oncol 2016;11:1246–62;
4. Vogelzang NJ, et al. J Clin Oncol 2003;21:2636–44; 5. Zalcman G, et al. Lancet 2016;387:1405–14.

Nintedanib and LUME-Meso Phase II

- Nintedanib is an oral, multikinase inhibitor targeting VEGF receptors 1–3, PDGF receptors α/β, FGF receptors 1–3, and Src and Abl kinase signalling[1,2]
- LUME-Meso Phase II: nintedanib combined with pemetrexed/cisplatin:
  - Improved PFS (HR [95% CI]=0.56 [0.34–0.91])[3]
  - Trend towards improved OS (HR [95% CI]=0.77 [0.46–1.29])[3]
  - Effect particularly evident in patients with epithelioid histology: PFS HR [95% CI]=0.51 [0.30–0.86]; OS HR [95% CI]=0.70 [0.40–1.21])[3]

Phase II PFS (ITT population; primary endpoint*)[4]



*Cut-off date 4 March 2016; 79% PFS events.

1. Awasthi N, Schwarz RE. Onco Targets Ther 2015;8:3691–712; 2. Hilberg F, et al. Cancer Res 2008;68:4774–82; 3. Grosso F, et al. J Clin Oncol 2017;35:3591–600; 4. Grosso F, et al. IASLC 17th World Conference on Lung Cancer. Abstract OA22.02 and presentation.

LUME-Meso Phase III study design

Patients with histologically confirmed, unresected epithelioid MPM

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

RANDOMISE

N=458
Randomised 1:1

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

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

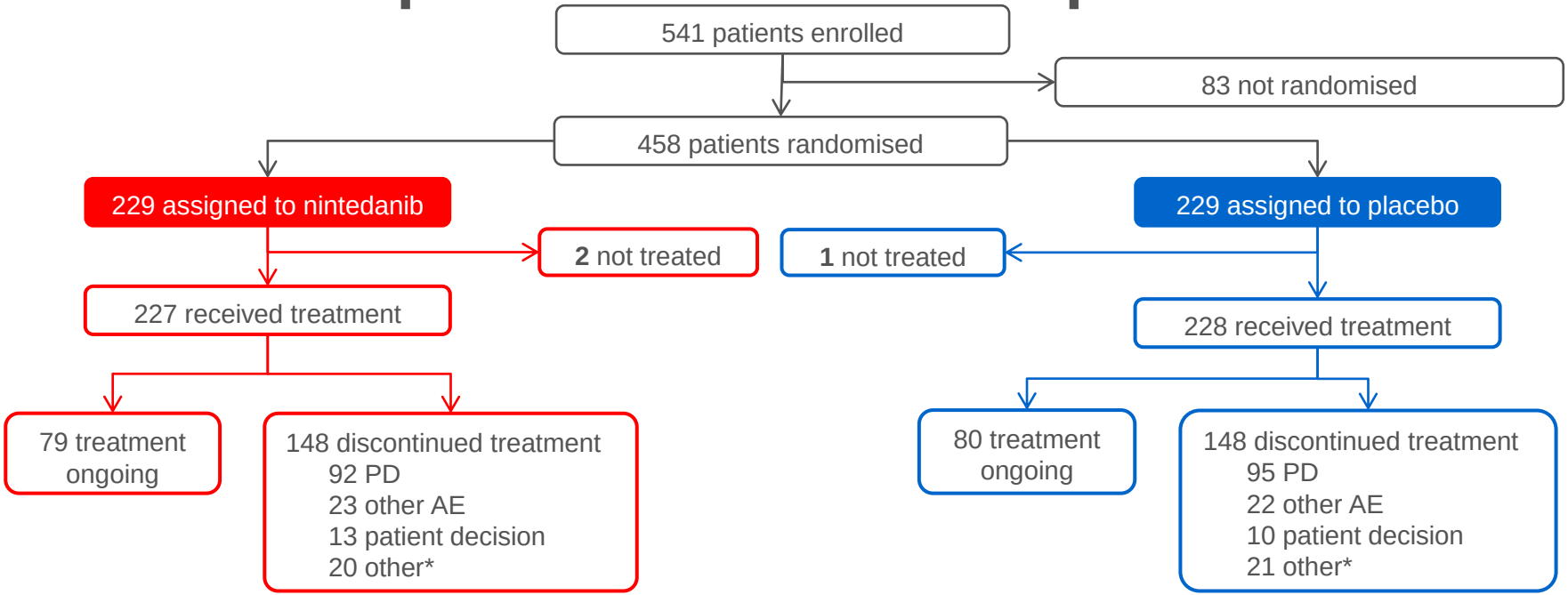
Primary endpoint: PFS¶
Key secondary endpoint: OS

*On Days 2–21; §500 mg/m^2/75 mg/m^2 i.v. every 21 days. Maximum treatment duration: 6 cycles;
¶By investigator assessment according to mRECIST. A sensitivity analysis was done for PFS by central independent review.

Statistical assumptions (per protocol)

- **PFS**
  - 90% power to detect a HR of 0.63
  - Expected absolute median PFS improvement: 6.0 versus 9.5 months
  - Tested at a one-sided alpha level of 0.025 using a log-rank test
- **OS**
  - 80% power to detect a HR of 0.71
  - Assumed treatment effect median OS improvement: 14.5 versus 20.3 months
  - Interim OS analysis at the time of the primary PFS analysis: tested using a log-rank test with an interim alpha according to an O'Brien–Fleming alpha-spending function (overall one-sided alpha 0.025)

Patient disposition and follow-up



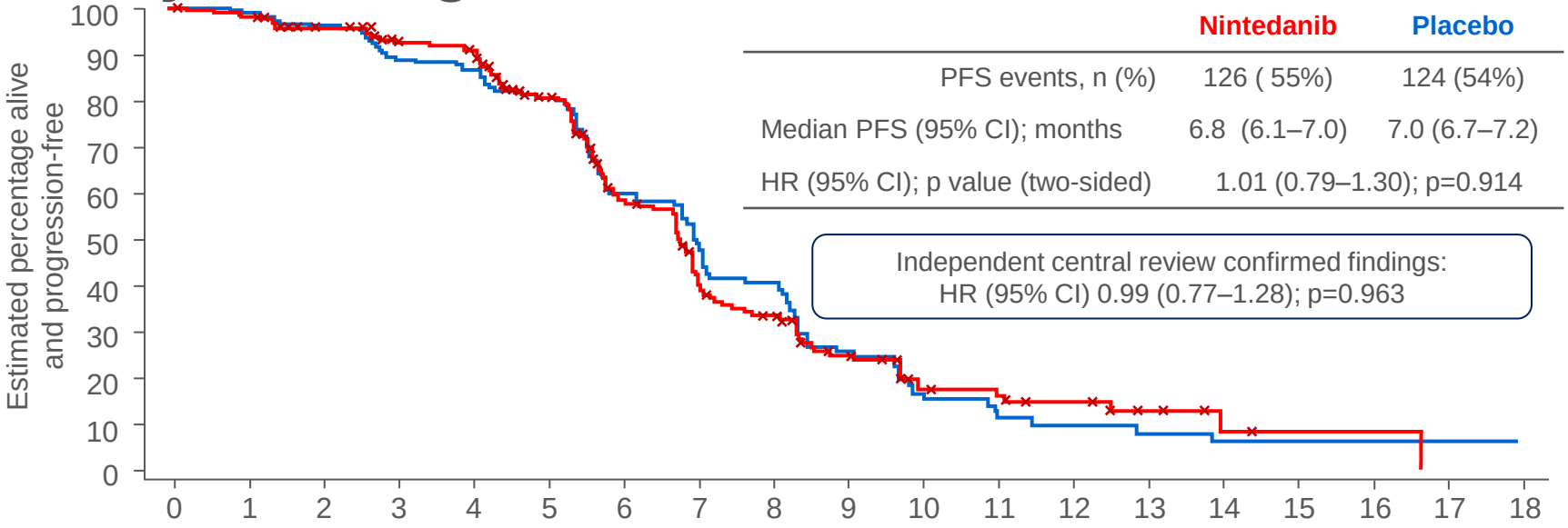
- Median duration of follow-up was: nintedanib, 9.2 months (IQR: 5.2–13.1); placebo, 9.7 months (IQR 5.4–13.9)

*'Other' includes worsening or AE of underlying cancer disease, completed according to protocol, protocol non-compliance, lost to follow-up, and other.

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)

PFS by investigator assessment



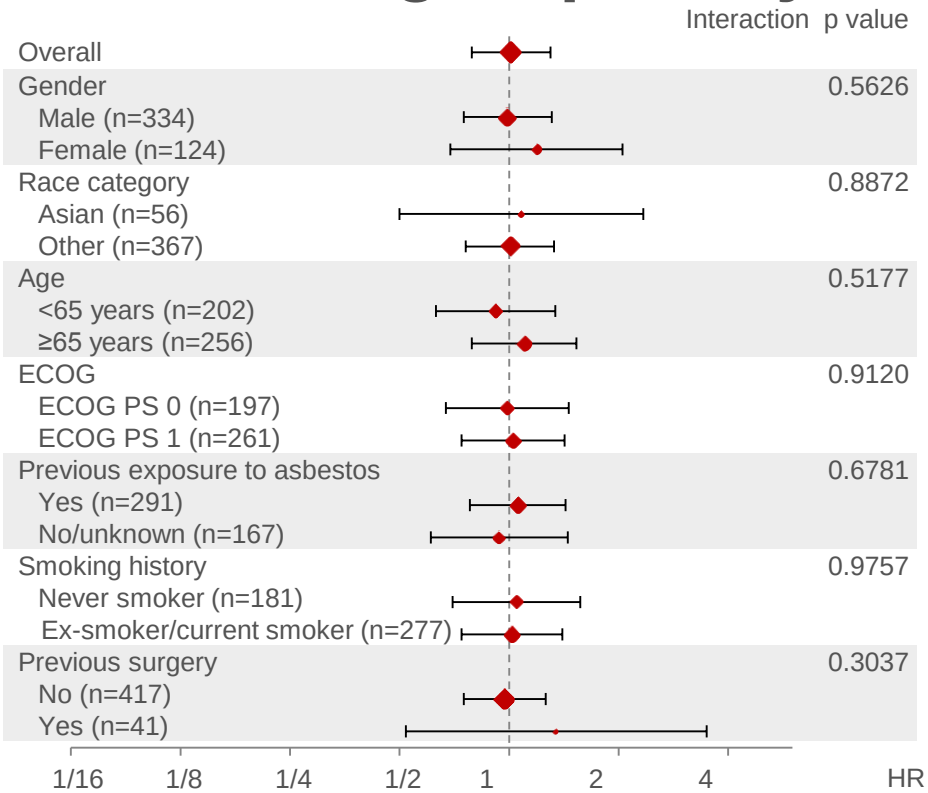
	Nintedanib	Placebo
PFS events, n (%)	126 (55%)	124 (54%)
Median PFS (95% CI); months	6.8 (6.1–7.0)	7.0 (6.7–7.2)
HR (95% CI); p value (two-sided)	1.01 (0.79–1.30); p=0.914	

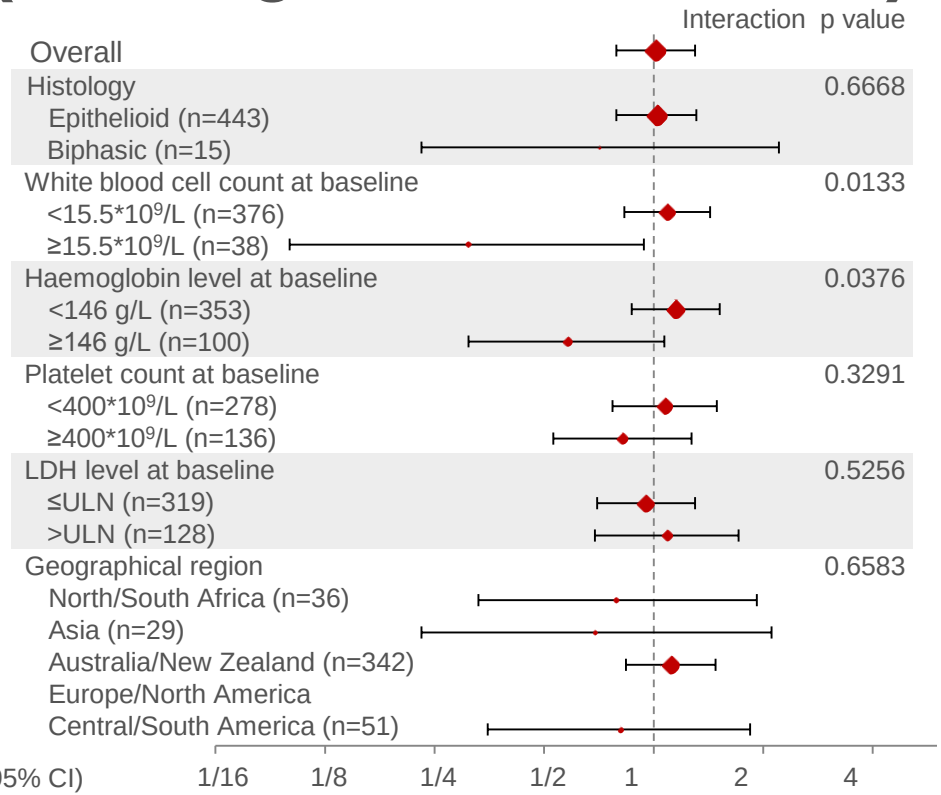
Independent central review confirmed findings:
HR (95% CI) 0.99 (0.77–1.28); p=0.963

Patients 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

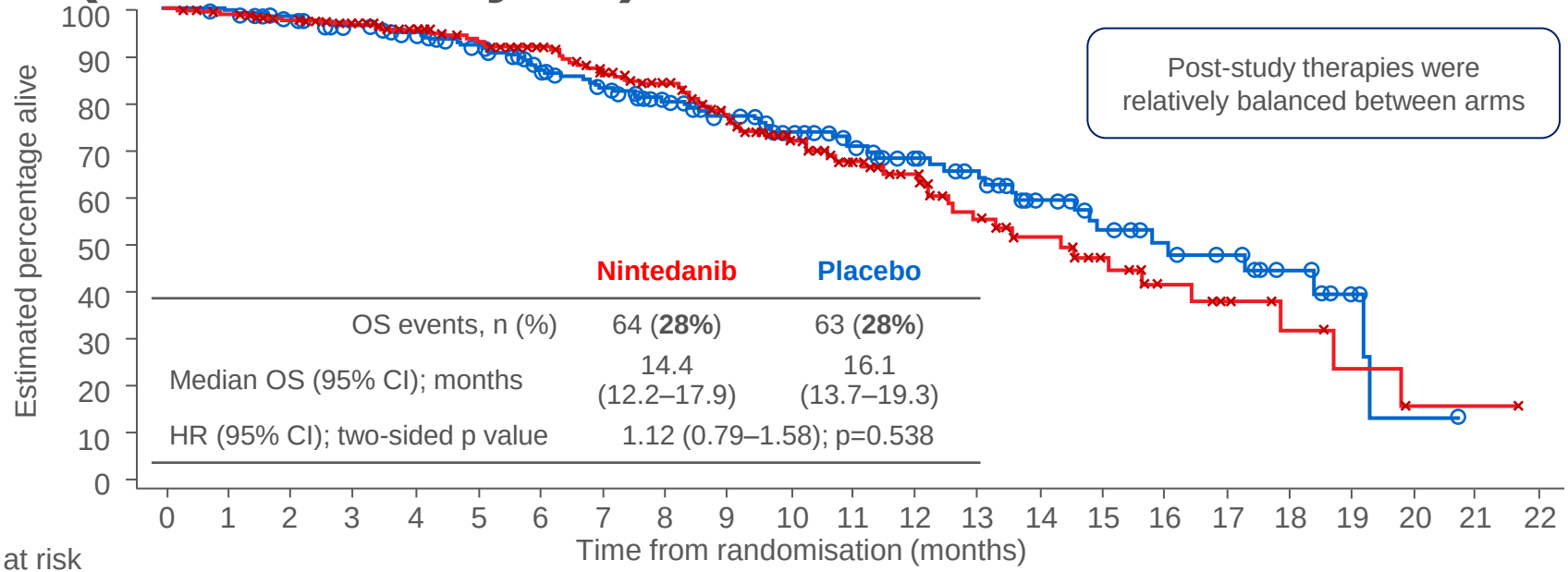
PFS subgroup analysis (investigator assessment)





HR (95% CI)

OS (interim analysis)



Patients at risk

Nintedanib	229	222	208	195	179	160	146	128	113	90	71	57	44	33	24	18	12	8	5	3	1	1	0
Placebo	229	226	215	196	185	165	143	127	110	99	77	65	53	44	32	25	19	15	10	4	1	0	

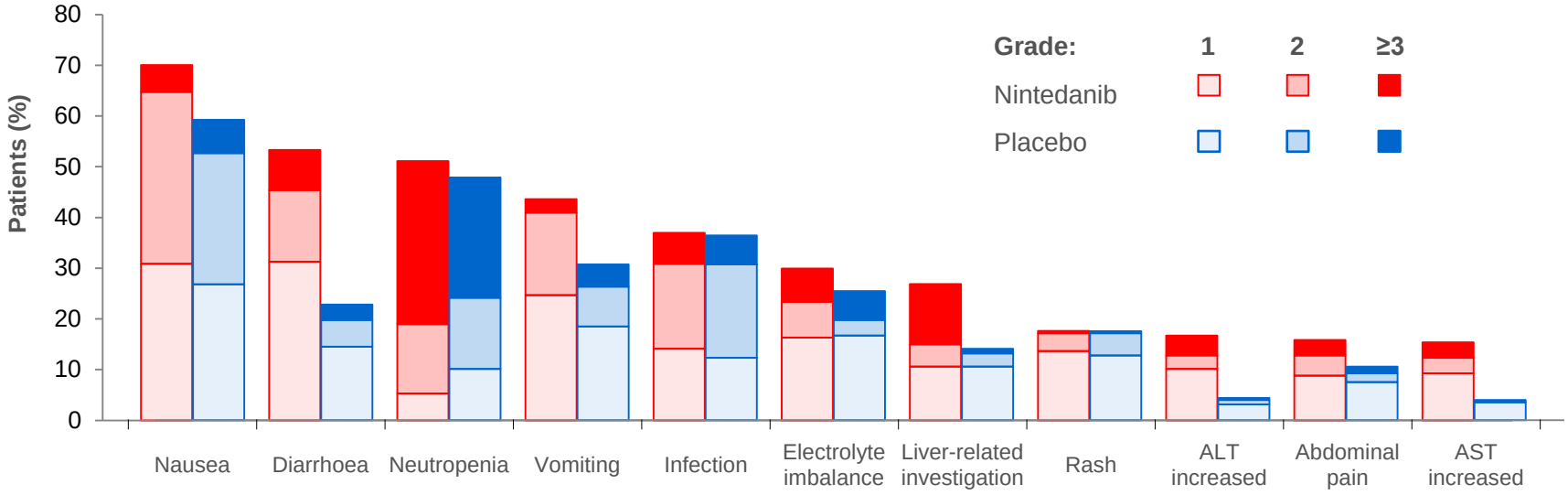
Median duration of follow up: 9.2 months in the nintedanib group and 9.7 months in the placebo group.

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 2	51 (22.5) 16 (7.0)	17 (7.5) 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 2	49 (21.6) 4 (1.8)	17 (7.5) 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 2	55 (24.2) 2 (0.9)	29 (12.7) 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

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**

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