NINTEDANIB + PEMETREXED/CISPLATIN IN MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Phase II biomarker data from the LUME-Meso study

Nick Pavlakis, Federica Grosso, Nicola Steele, Anna K. Nowak, Silvia Novello, Sanjay Popat, Laurent Greillier, Martin Reck, Thomas Kitzing, Giorgio V Scagliotti

DISCLOSURES

- Financial disclosures for Nick Pavlakis:
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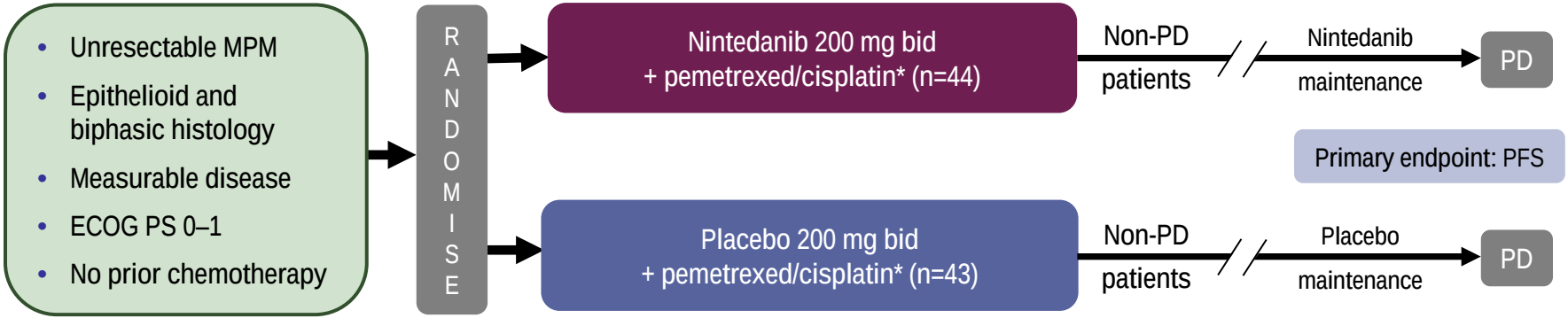
RANDOMISED PHASE II/III LUME-MESO STUDY

Objective and design

- Nintedanib is an oral twice daily triple angiokinase inhibitor of VEGFR1–3, PDGFRα/β and FGFR1–3, as well as Src and Abl kinase signalling[1–3]

Phase II study design:



*Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 iv every 21 days for maximum treatment duration of 6 cycles.
bid, twice daily; ECOG PS, Eastern Co-operative Oncology Group performance status; FGFR, fibroblast growth factor receptor; iv, intravenous; MPM, malignant pleural mesothelioma; PD, progressive disease; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor.

1. Hilberg F, et al. Cancer Res 2008;68:4774–82;
2. Grosso F, et al. J Clin Oncol 2017;35:3591–600;
3. Boehringer Ingelheim. Data on file.

RANDOMISED PHASE II/III LUME-MESO STUDY

Phase II efficacy summary[1]

	ITT population		Population with epithelioid histology	
	Nintedanib (n=44)	Placebo (n=43)	Nintedanib (n=39)	Placebo (n=38)
PFS*				
Median, months	9.4	5.7	9.7	5.7
HR (95% CI)	0.54 (0.33–0.87)		0.49 (0.30–0.82)	
p value	0.010		0.006	
OS				
Median, months	18.3	14.2	20.6	15.2
HR (95% CI)	0.77 (0.46–1.29)		0.70 (0.40–1.21)	
p value	0.319		0.197	

*Updated analysis.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

1. Grosso F, et al. J Clin Oncol 2017;35:3591–600.

LUME-MESO PHASE II BIOMARKER ANALYSIS

Methodology

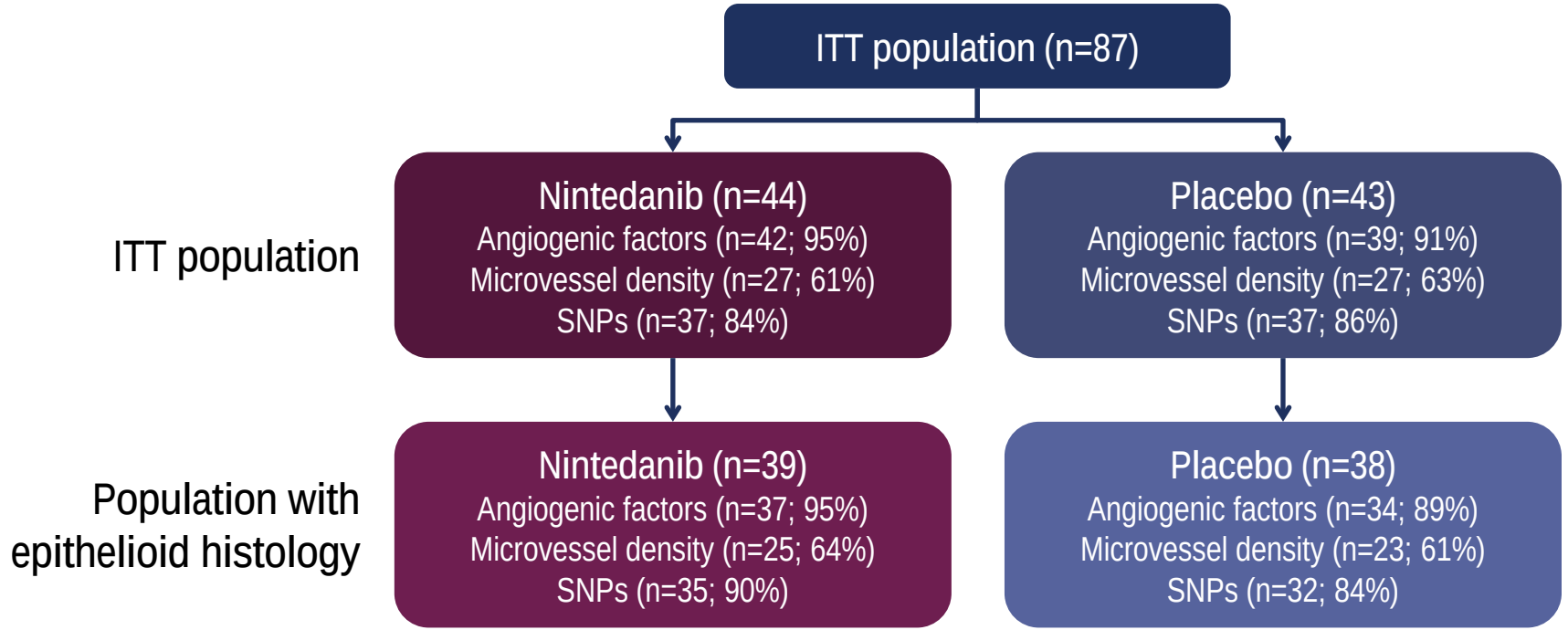
- Biomarkers
  - Baseline plasma levels of 58 angiogenic factors (Human AngiogenesisMAP® panel, Myriad RBM)
  - Microvessel density: Manual and Chalkley counts[1] based on PECAM-1 (CD31) IHC staining of archival biopsy samples
  - Known SNPs in genes for mesothelin (*MSLN*), VEGFR1 (*FLT1*) and VEGFR3 (*FLT4*)
- Statistics
  - Predictive and prognostic analyses performed for OS and PFS
  - Cox regression modelling used for categorical markers
  - p values corrected for multiple testing by FDR adjustment
  - All analyses exploratory and considered hypothesis generating
- This presentation focuses on results for the epithelioid population

FDR, false-discovery rate; IHC, immunohistochemistry; PECAM-1, platelet endothelial cell adhesion molecule; SNP, single-nucleotide polymorphism.

1. Fox SB, et al. J Pathol 1995;177:275–83.

LUME-MESO PHASE II BIOMARKER ANALYSIS

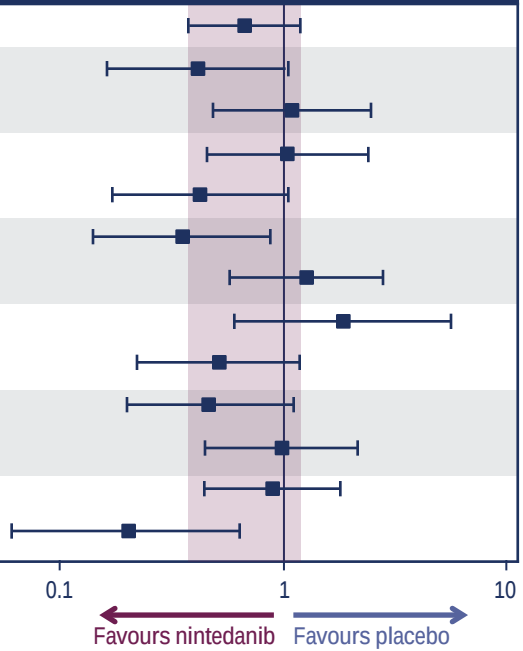
Biomarker-evaluable populations



ANGIOGENIC FACTOR LEVELS AT BASELINE

Predictive analysis of OS (population with epithelioid histology)

Factor*	Subgroup	Events, n/N		HR (95% CI)	Interaction p value	
		Nintedanib	Placebo		Unadjusted	FDR-adjusted
Overall	N/A	23/37	25/34	0.66 (0.37–1.17)	N/A	N/A
ANG-1	<Median	8/17	13/16	0.41 (0.16–1.03)	0.097	0.956
	≥Median	15/19	10/15	1.08 (0.48–2.43)		
CEACAM1	<Median	16/21	9/14	1.03 (0.45–2.36)	0.120	0.956
	≥Median	7/16	16/20	0.42 (0.17–1.04)		
Endoglin	<Median	9/18	12/15	0.35 (0.14–0.86)	0.023	0.720
	≥Median	14/19	13/19	1.25 (0.57–2.73)		
IGFBP-2	<Median	15/24	4/11	1.83 (0.60–5.59)	0.054	0.723
	≥Median	8/13	21/23	0.51 (0.22–1.16)		
PDGF-BB	<Median	11/22	11/13	0.46 (0.20–1.10)	0.179	0.962
	≥Median	12/15	14/21	0.97 (0.44–2.14)		
VEGF-D	<LLOQ	16/26	17/24	0.88 (0.44–1.77)	0.036	0.720
	≥LLOQ	7/11	8/10	0.20 (0.06–0.63)		

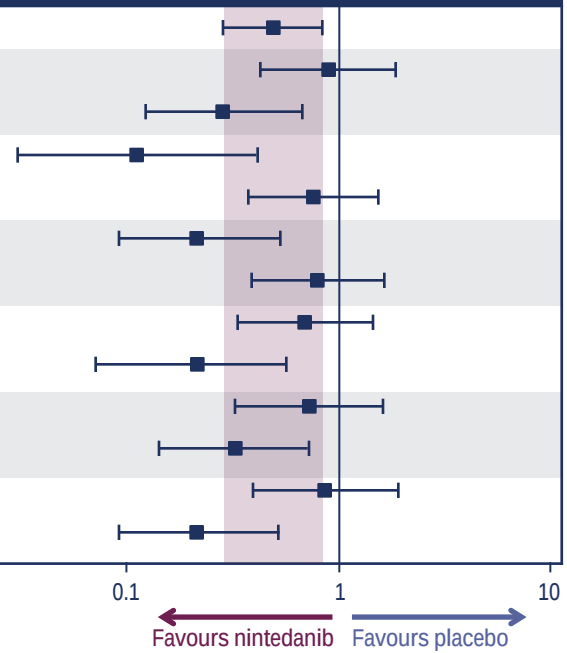


*Factors with lowest unadjusted p values are shown. ANG-1, angiopoietin-1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; IGFBP-2, insulin-like growth factor-binding protein-2; LLOQ, lower limit of quantitation; n, number of events; N, number of patients; N/A, not applicable; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

ANGIOGENIC FACTOR LEVELS AT BASELINE

Predictive analysis of PFS (population with epithelioid histology)

Factor*	Subgroup	Events, n/N		HR (95% CI)	Interaction p value	
		Nintedanib	Placebo		Unadjusted	FDR-adjusted
Overall	N/A	30/37	28/34	0.48 (0.28–0.82)	N/A	N/A
6Ckine	<Median	13/18	17/17	0.88 (0.42–1.84)	0.052	0.487
	≥Median	17/19	11/17	0.28 (0.12–0.66)		
EGFR	<Median	14/17	12/15	0.11 (0.03–0.41)	0.026	0.487
	≥Median	16/20	16/19	0.75 (0.37–1.52)		
Endoglin	<Median	14/18	13/15	0.21 (0.09–0.52)	0.061	0.487
	≥Median	16/19	15/19	0.78 (0.38–1.61)		
ICAM-1	<Median	15/20	14/15	0.68 (0.33–1.42)	0.045	0.487
	≥Median	15/17	14/19	0.21 (0.07–0.56)		
MCP-1	<Median	16/20	11/12	0.72 (0.32–1.60)	0.088	0.584
	≥Median	14/17	17/22	0.32 (0.14–0.71)		
SDF-1	<Median	11/16	16/19	0.85 (0.39–1.87)	0.008	0.305
	≥Median	19/21	12/15	0.21 (0.09–0.51)		

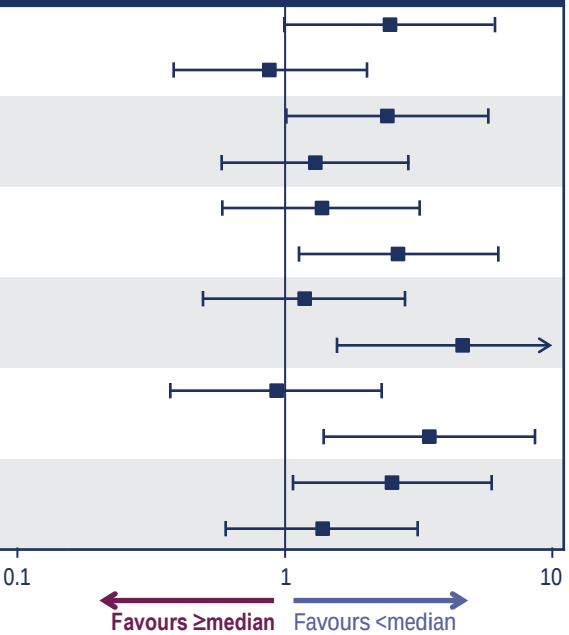


*Factors with lowest unadjusted p values are shown.
EGFR, epidermal growth factor receptor; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemotactic protein-1; SDF-1, stromal cell-derived factor.

ANGIOGENIC FACTOR LEVELS AT BASELINE

Prognostic analysis of OS (population with epithelioid histology)

Factor*	Arm	Events, n/N		HR (95% CI)	Interaction p value	
		≥Median	<Median		Unadjusted	FDR-adjusted
ANG-1	Nintedanib	15/19	8/17	2.44 (0.99–6.02)	0.046	0.352
	Placebo	10/15	13/16	0.87 (0.38–2.02)	0.749	0.810
CRP	Nintedanib	13/18	10/19	2.39 (1.01–5.68)	0.042	0.352
	Placebo	14/19	11/15	1.29 (0.58–2.87)	0.527	0.810
ICAM-1	Nintedanib	12/17	11/20	1.36 (0.58–3.15)	0.479	0.721
	Placebo	15/19	10/15	2.63 (1.11–6.22)	0.023	0.302
IGFBP-2	Nintedanib	8/13	15/24	1.17 (0.49–2.79)	0.732	0.905
	Placebo	21/23	4/11	4.59 (1.55–13.60)	0.003	0.101
VEGF-D**	Nintedanib	7/11	16/26	0.92 (0.37–2.27)	0.860	0.905
	Placebo	8/10	17/24	3.43 (1.38–8.54)	0.005	0.101
VEGFR3	Nintedanib	13/16	10/21	2.50 (1.07–5.88)	0.030	0.352
	Placebo	16/20	9/14	1.37 (0.60–3.12)	0.455	0.810

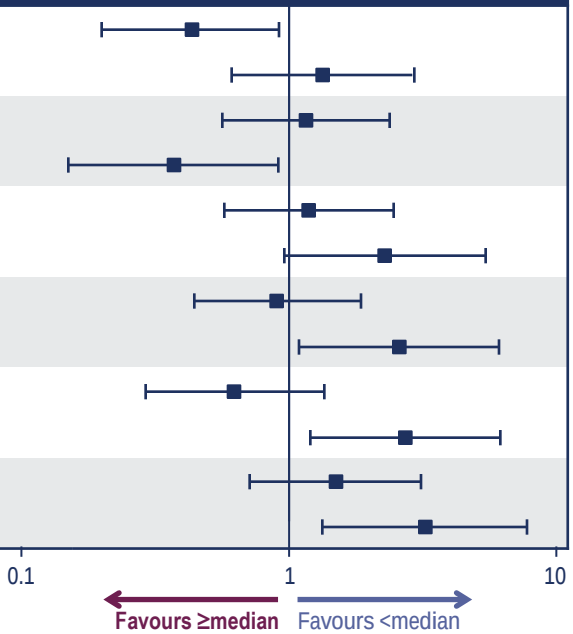


*Factors with lowest unadjusted p values in either arm are shown.
**Lower level of quantitation used as the cut-point.
CRP, C-reactive protein.

ANGIOGENIC FACTOR LEVELS AT BASELINE

Prognostic analysis of PFS (population with epithelioid histology)

Factor*	Arm	Events, n/N		HR (95% CI)	Interaction p value	
		≥Median	<Median		Unadjusted	FDR-adjusted
6Ckine	Nintedanib	17/19	13/18	0.43 (0.20–0.91)	0.025	0.793
	Placebo	11/17	17/17	1.33 (0.61–2.89)	0.468	0.993
EGFR	Nintedanib	16/20	14/17	1.15 (0.56–2.36)	0.713	0.904
	Placebo	16/19	12/15	0.37 (0.15–0.91)	0.026	0.270
Hepsin	Nintedanib	13/16	17/21	1.18 (0.57–2.45)	0.648	0.904
	Placebo	17/20	11/14	2.27 (0.95–5.41)	0.059	0.472
ICAM-1	Nintedanib	15/17	15/20	0.90 (0.44–1.85)	0.769	0.904
	Placebo	14/19	14/15	2.56 (1.08–6.04)	0.027	0.270
SDF-1	Nintedanib	19/21	11/16	0.62 (0.29–1.34)	0.218	0.793
	Placebo	12/15	16/19	2.70 (1.19–6.10)	0.013	0.267
uPAR	Nintedanib	14/15	16/22	1.48 (0.71–3.08)	0.294	0.903
	Placebo	17/21	11/13	3.19 (1.33–7.67)	0.007	0.267

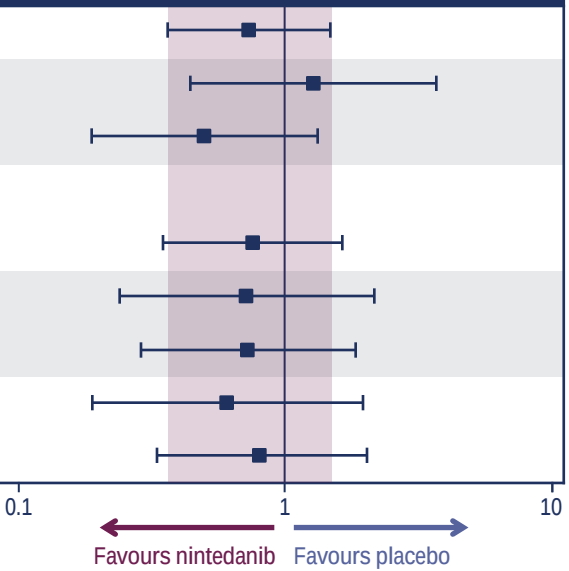


*Factors with lowest unadjusted p values in either arm are shown.
uPAR, urokinase-type plasminogen activator receptor.

MVD

Predictive analysis of OS (population with epithelioid histology)

MVD count (measure*)	Subgroup	Events, n/N		HR (95% CI)	Interaction p value	
		Nintedanib	Placebo		Unadjusted	FDR-adjusted
Total	N/A	16/25	17/23	0.73 (0.36–1.47)	N/A	N/A
Chalkley (average)	<Median	7/9	8/12	1.27 (0.44–3.66)	0.189	0.567
	≥Median	9/16	9/11	0.50 (0.19–1.31)		
Chalkley (highest)	<Median	2/4	3/4	N/C**	N/C**	N/C**
	≥Median	14/21	14/19	0.76 (0.35–1.63)		
Manual (average)	<Median	6/12	8/12	0.71 (0.24–2.13)	0.976	0.976
	≥Median	10/13	9/11	0.72 (0.29–1.82)		
Manual (highest)	<Median	5/11	8/12	0.61 (0.19–1.94)	0.699	0.976
	≥Median	11/14	9/11	0.81 (0.33–2.00)		

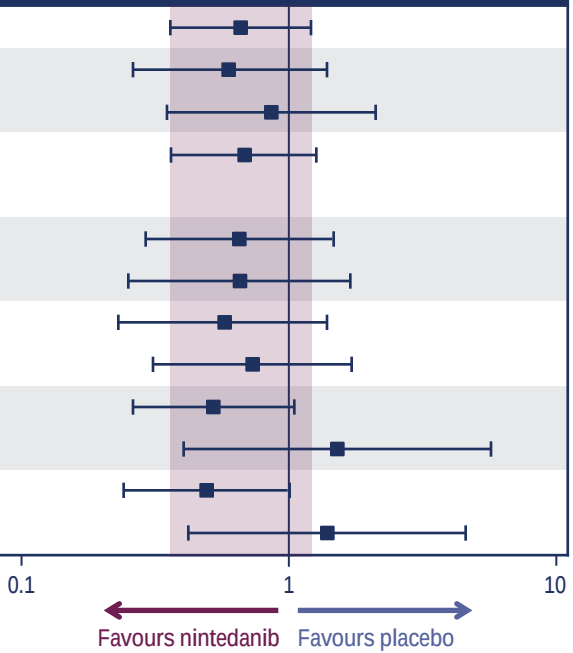


*Average and highest counts from three MVD 'hotspots' per sample.
**N/C due to large number of patients with values at the median.
MVD, microvessel density; N/C, not calculable.

GENETIC VARIANTS

Predictive analysis of OS (population with epithelioid histology)

Gene (SNP)	Genotype	Events, n/N		HR (95% CI)	Interaction p value	
		Nintedanib	Placebo		Unadjusted	FDR-adjusted
Total	N/A	21/35	22/32	0.66 (0.36–1.20)	N/A	N/A
MSLN (rs3764247)	A/A	13/23	10/16	0.59 (0.26–1.38)	0.586	0.926
	A/C or C/C	8/12	12/16	0.85 (0.35–2.08)		
MSLN (rs74002893)	C/C	20/33	21/31	0.68 (0.36–1.26)	N/C	N/C
	C/T*	1/2	1/1	N/C		
FLT1 (rs7993418)	A/A	13/21	12/19	0.65 (0.29–1.46)	0.926	0.926
	A/G or G/G	8/14	10/13	0.65 (0.25–1.68)		
FLT1 (rs9582036)	A/A	10/16	11/15	0.57 (0.23–1.38)	0.783	0.926
	A/C or C/C	11/19	11/17	0.73 (0.31–1.70)		
FLT4 (rs307821)	G/G	16/28	18/25	0.52 (0.26–1.04)	0.140	0.350
	G/T or T/T	5/7	4/7	1.50 (0.40–5.65)		
FLT4 (rs307826)	A/A	14/25	17/21	0.49 (0.24–1.00)	0.117	0.350
	A/G or G/G	7/10	5/11	1.38 (0.42–4.53)		

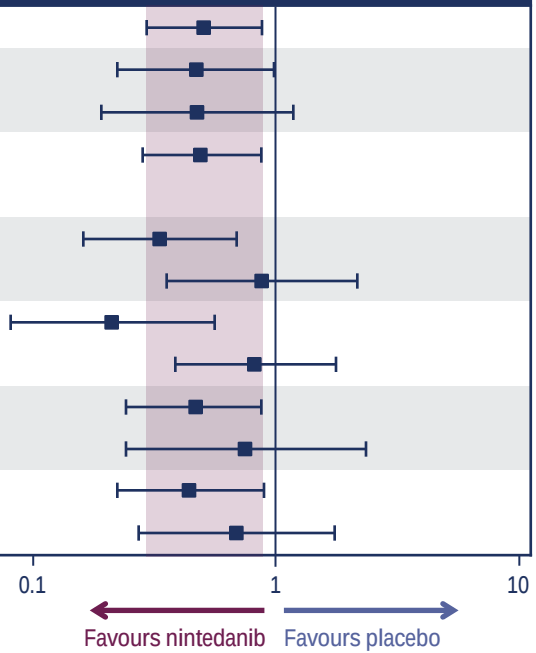


*No patients had genotype T/T at *MSLN* rs74002893.

GENETIC VARIANTS

Predictive analysis of PFS (population with epithelioid histology)

Gene (SNP)	Genotype	Events, n/N		HR (95% CI)	Interaction p value	
		Nintedanib	Placebo		Unadjusted	FDR-adjusted
Total	N/A	28/35	26/32	0.50 (0.29–0.87)	N/A	N/A
MSLN (rs3764247)	A/A	20/23	13/16	0.46 (0.22–0.98)	0.853	0.853
	A/C or C/C	8/12	13/16	0.47 (0.19–1.16)		
MSLN (rs74002893)	C/C	26/33	26/31	0.49 (0.28–0.86)	N/C	N/C
	C/T*	2/2	0/1	N/C		
FLT1 (rs7993418)	A/A	18/21	16/19	0.33 (0.16–0.68)	0.218	0.546
	A/G or G/G	10/14	1013	0.86 (0.35–2.13)		
FLT1 (rs9582036)	A/A	13/16	13/15	0.21 (0.08–0.55)	0.066	0.328
	A/C or C/C	15/19	13/17	0.81 (0.38–1.74)		
FLT4 (rs307821)	G/G	21/28	20/25	0.46 (0.24–0.86)	0.616	0.770
	G/T or T/T	7/7	6/7	0.74 (0.24–2.32)		
FLT4 (rs307826)	A/A	18/25	17/21	0.44 (0.22–0.88)	0.410	0.683
	A/G or G/G	10/10	9/11	0.68 (0.27–1.73)		

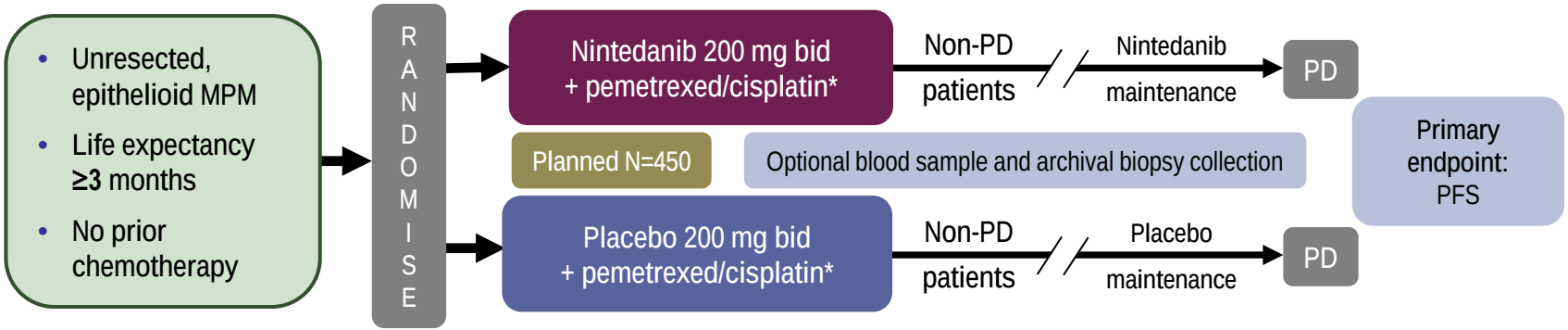


*No patients had genotype T/T at *MSLN* rs74002893.

LUME-MESO PHASE II BIOMARKER ANALYSIS

Conclusions and future directions

- No biomarkers showed clear association with nintedanib benefit
- There were potential signals for greater treatment effect in patients with low plasma endoglin and major homozygous *FLT1* and *FLT4* genotypes
- Analyses were limited by small sample size; none were significant after FDR adjustment
- These findings will be evaluated further in the Phase III part of the study:[1]



*Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 iv every 21 days for maximum treatment duration of 6 cycles.

1. Scagliotti GV, et al. Clin Lung Cancer 2017;18:589–93.

LUME-MESO PHASE II BIOMARKER ANALYSIS

Acknowledgments

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