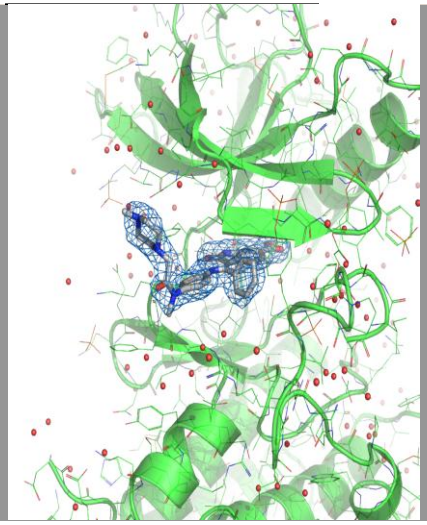


BIBF 1120 (Nintedanib)

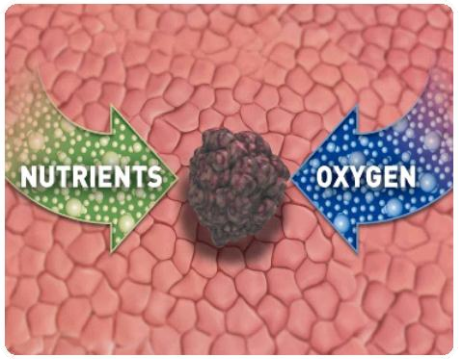
- Nintedanib –
  A triple angiokinase inhibitor for the treatment of cancer

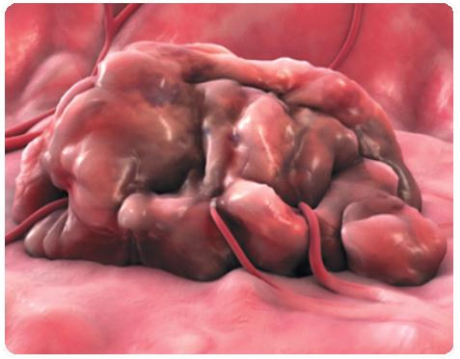
Frank Hilberg, Boehringer Ingelheim RCV

Tumor angiogenesis

Mechanisms and significance

- Angiogenesis, the formation of new blood vessels from pre-existing vasculature
- Triggered by growth factors secreted by hypoxic tumor cells (central role of VEGF clinically validated)
- Essential for tumor growth and metastasis formation
- Therapeutic inhibition should be effective in all solid malignancies
- Target tissue in direct contact with blood, facilitating drug delivery
- Vascular cells less prone to genetic aberrations and the development of drug resistance than tumor cells

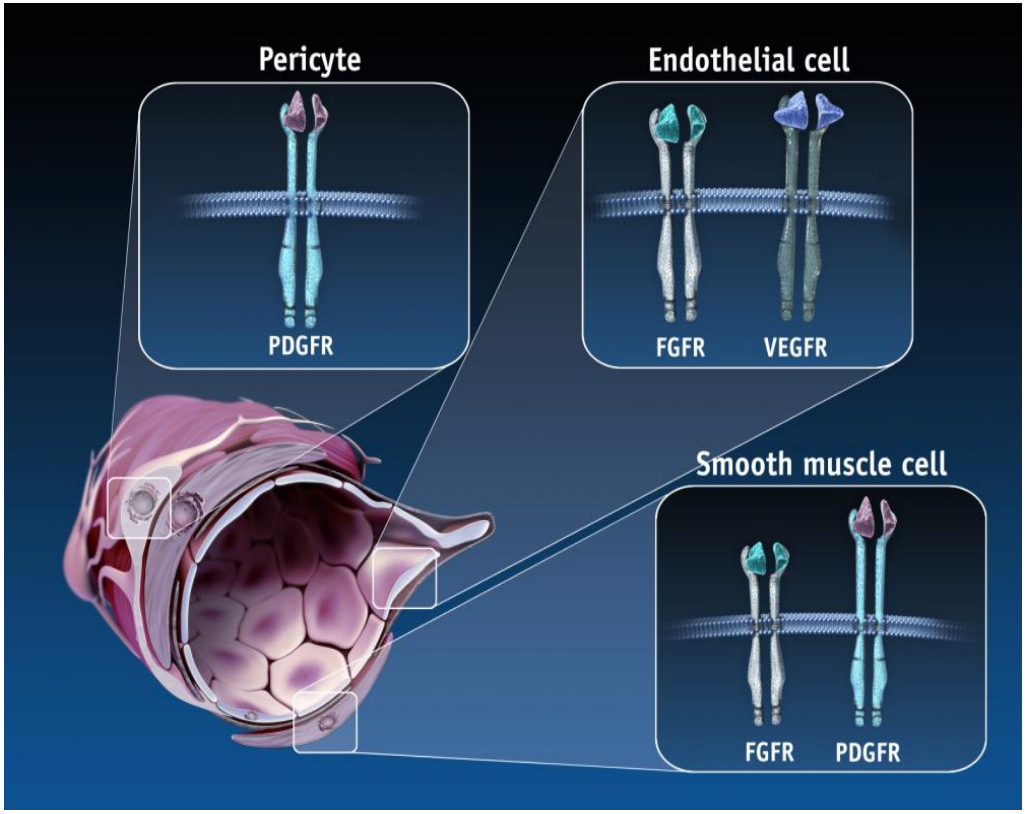




Nintedanib: a triple angiokinase inhibitor

Introducing the triple angiokinase concept

- Nintedanib inhibits all types of three key RTKs involved in angiogenesis*
  - VEGFRs,
  - PDGFRs and
  - FGFRs

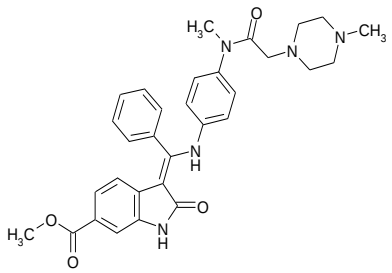


VEGFR=vascular endothelial growth factor receptor; PDGFR=platelet-derived growth factor receptor; FGFR=fibroblast growth factor receptor

*Hilberg F, et al. *Cancer Res* 2008;68:4774–4782; Von Pawel J, et al. Oral presentation at: ESMO/IASLC 1st European Lung Cancer Conference; 23–26 April 2008; Geneva, Switzerland

Nintedanib: triple angiokinase inhibition

Nintedanib inhibits multiple pro-angiogenic receptors



Triple angiokinase profile	VEGFR 1 / 2 / 3	PDGFR α / β	FGFR 1 / 2 / 3
IC_{50} *[nM]*	34 / 21 / 13	59 / 65	69 / 37 / 108

Additionally targeted kinases	Flt-3	Ret	Src, Lck, Lyn
IC_{50} *[nM]*	26	35	156 / 16 / 195

	IGF1R, InsR	EGFR, HER2, CDK1, CDK2, CDK4
IC_{50} *[nM]*	>1000, <10000	>50000

Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib inhibits proliferation of vascular cells

Inhibition of vascular cell proliferation

	HUVEC VEGF	Pericytes PDGF	Smooth muscle cells PDGF
EC_{50} *[nM]*	9	76	55

No direct inhibition of tumor cells with wild type PDGFRs and FGFRs

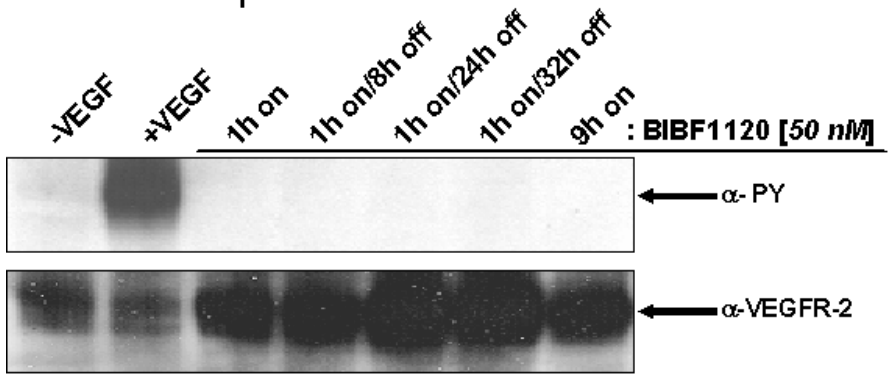
	FaDu (H&N SCC), Calu-6 (NSCLC), HeLa (cervical adeno carcinoma)
EC_{50} *[nM]*	> 3000

Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib: signaling profile

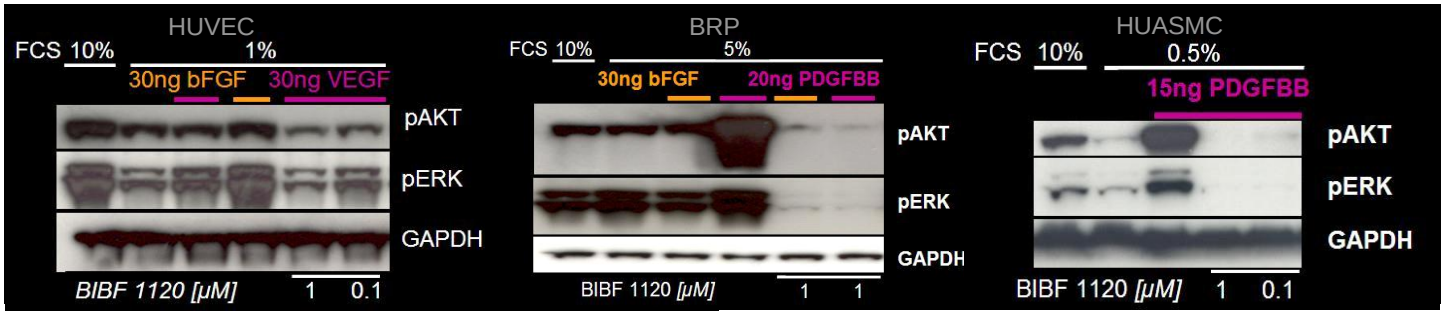
Nintedanib interferes with signaling in vascular cells

- Sustained inhibition of receptor activation



NIH3T3 cells expressing VEGFR-2

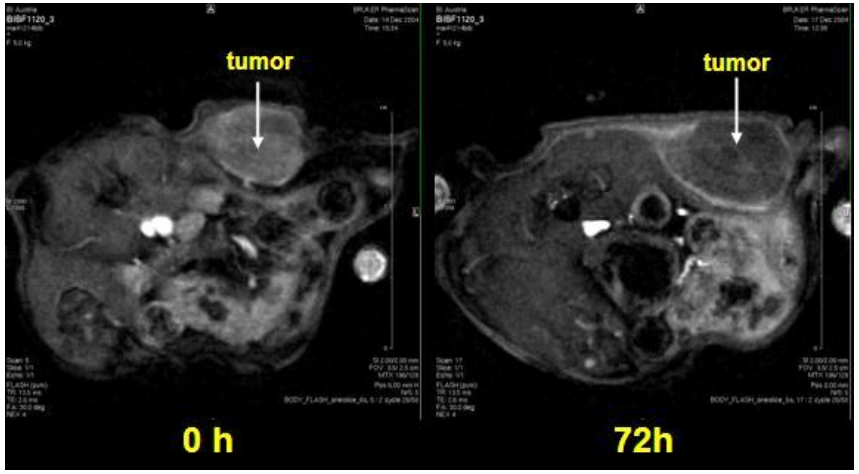
- Inhibition of intracellular signaling in all three vascular cell types

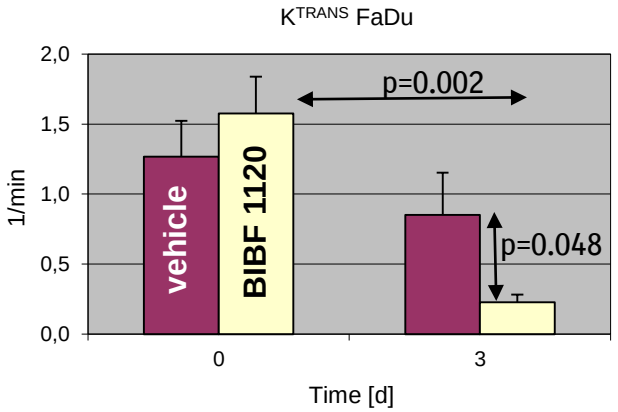


Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib reduces vascular permeability

Nintedanib inhibits vascular function in human tumor xenografts





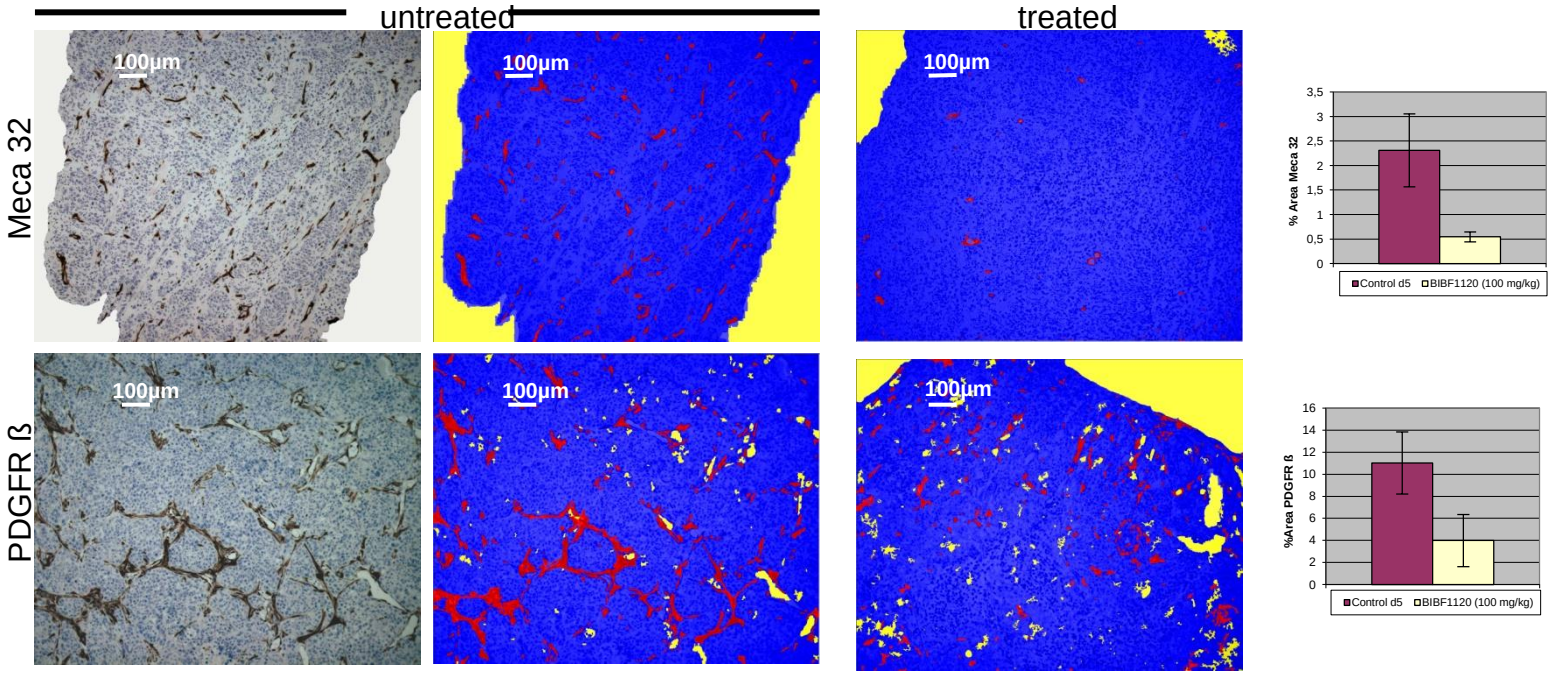
FaDu xenografts, treatment with 100 mg/kg/d
contrast agent signal enhancement 90 sec after bolus

Nintedanib induces rapid changes in tumor perfusion and permeability in FaDu H&NSCC xenografts as measured by DCE-MRI

Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib reduces tumor vessel density and the perivascular cell compartment

IHC analysis of tumor xenografts



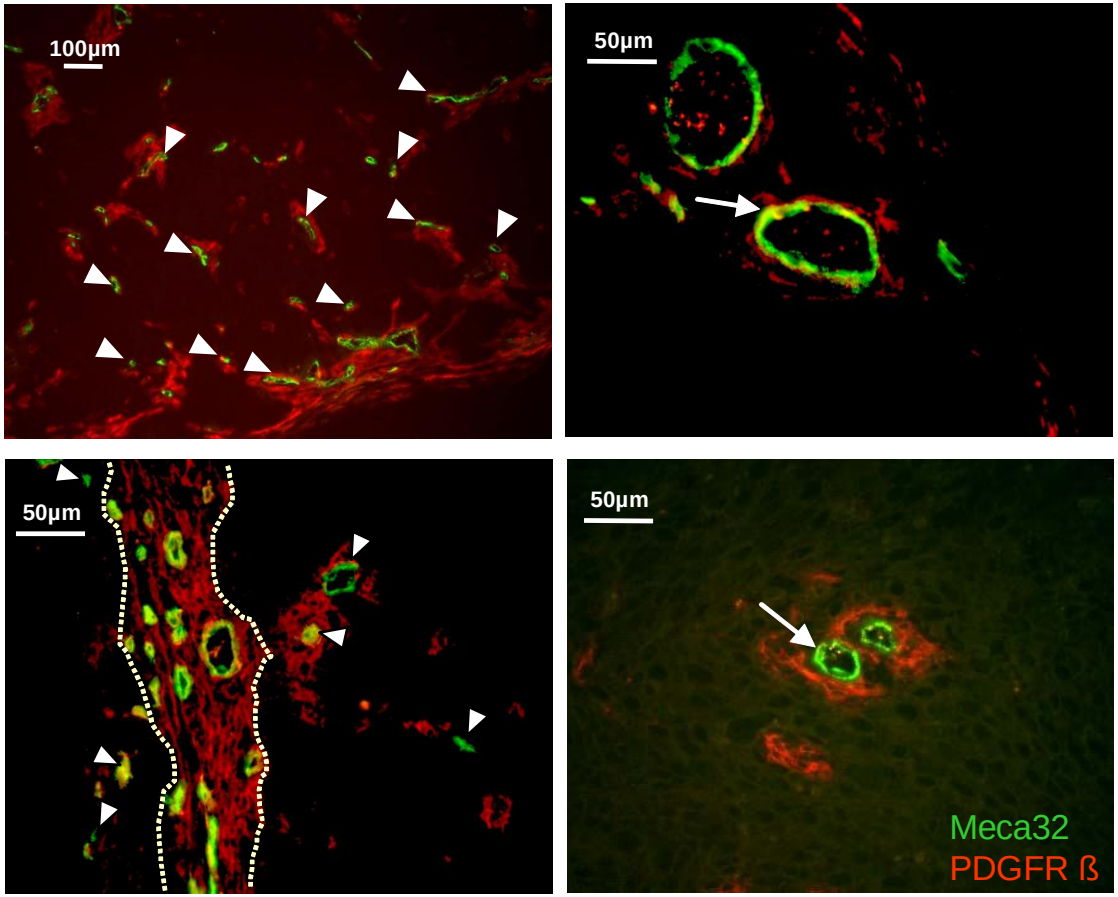
FaDu xenografts, treatment 4 days with 100 mg/kg/d

Nintedanib reduces tumor microvessel density and the number of PDGFRß expressing perivascular cells as measured by IHC

Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib induces changes in tumor vessel architecture

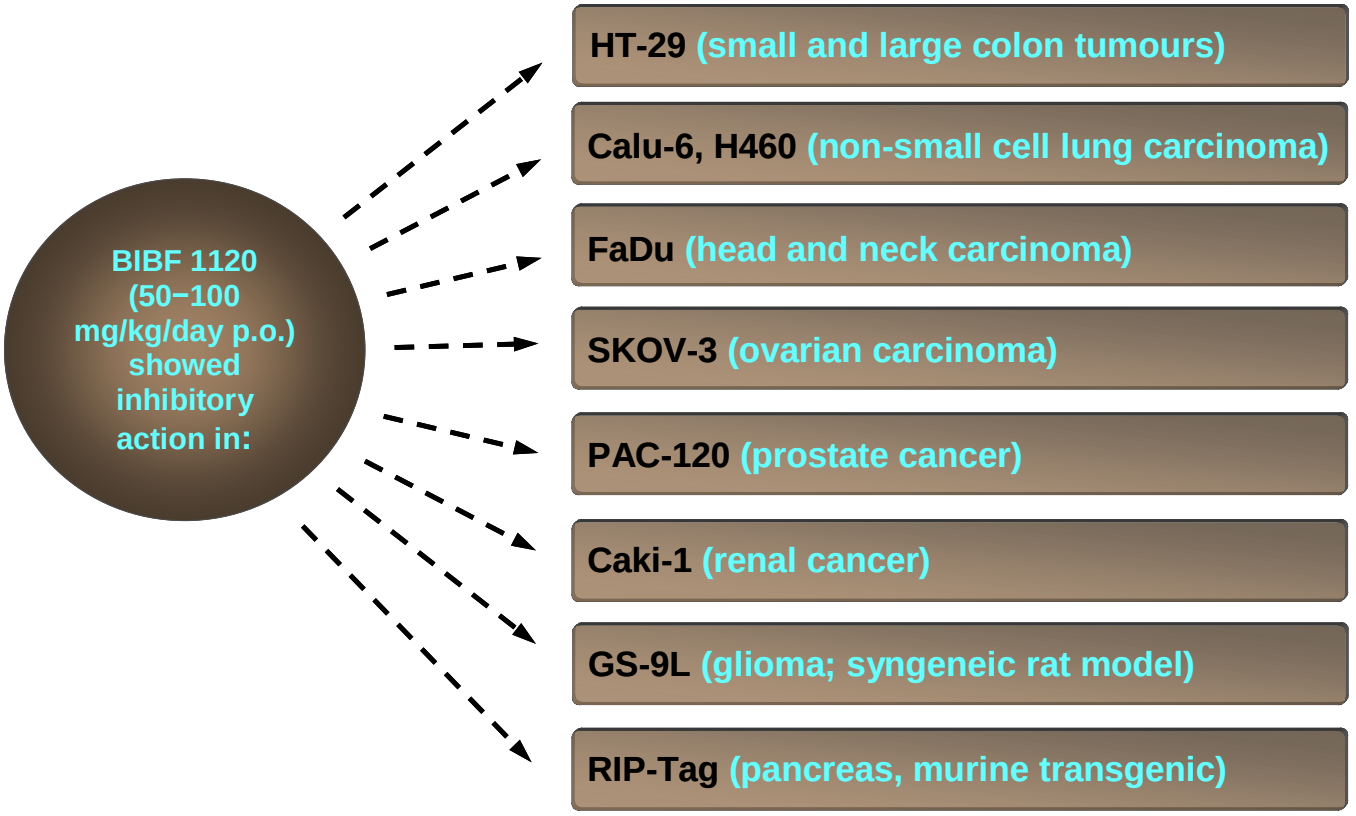
Double immunofluorescence analysis of xenograft sections



Hilberg *et al.* Cancer Res 2008; 68: (12), June 15, 2008.

Nintedanib: anti-tumor activity in xenograft models

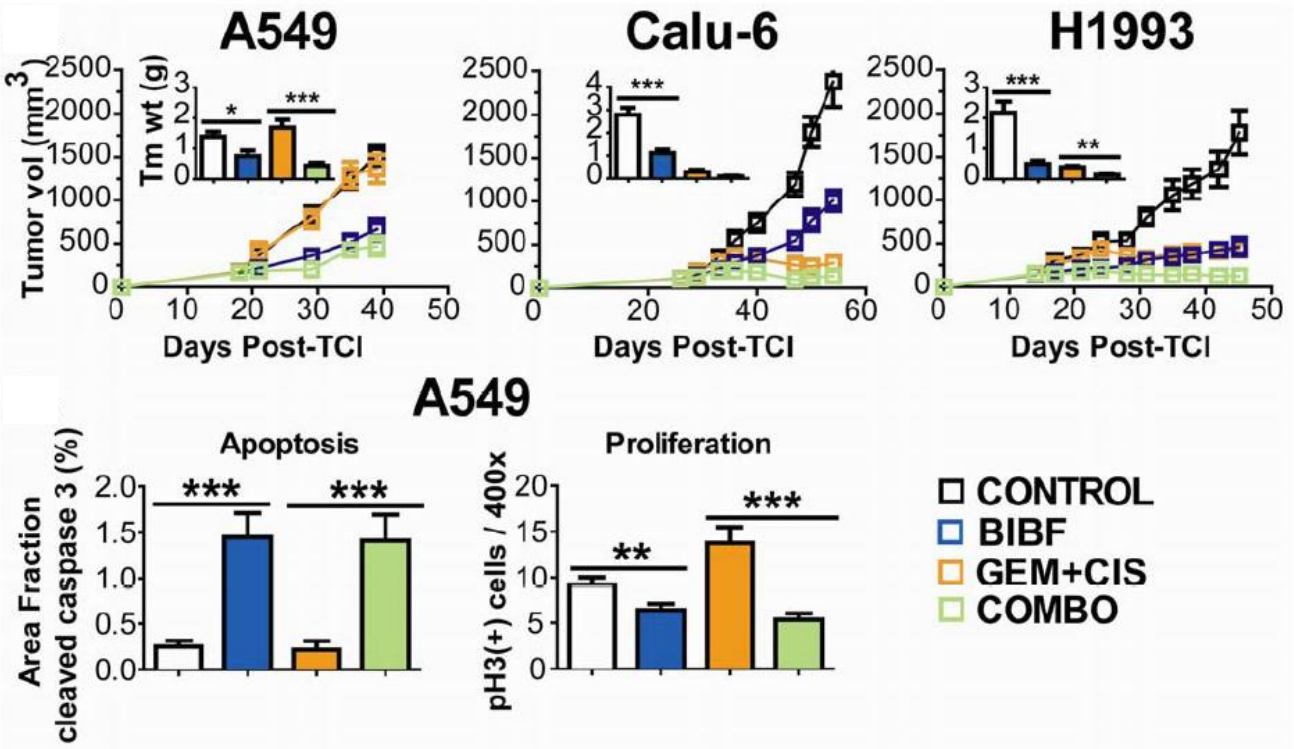
Effective in all preclinical models tested at well tolerated doses



Nintedanib with chemotherapy in NSCLC

Nintedanib alone and in combination induces apoptosis and inhibits proliferation

A549, Calu-6 and H1993 are poor responders to bevacizumab



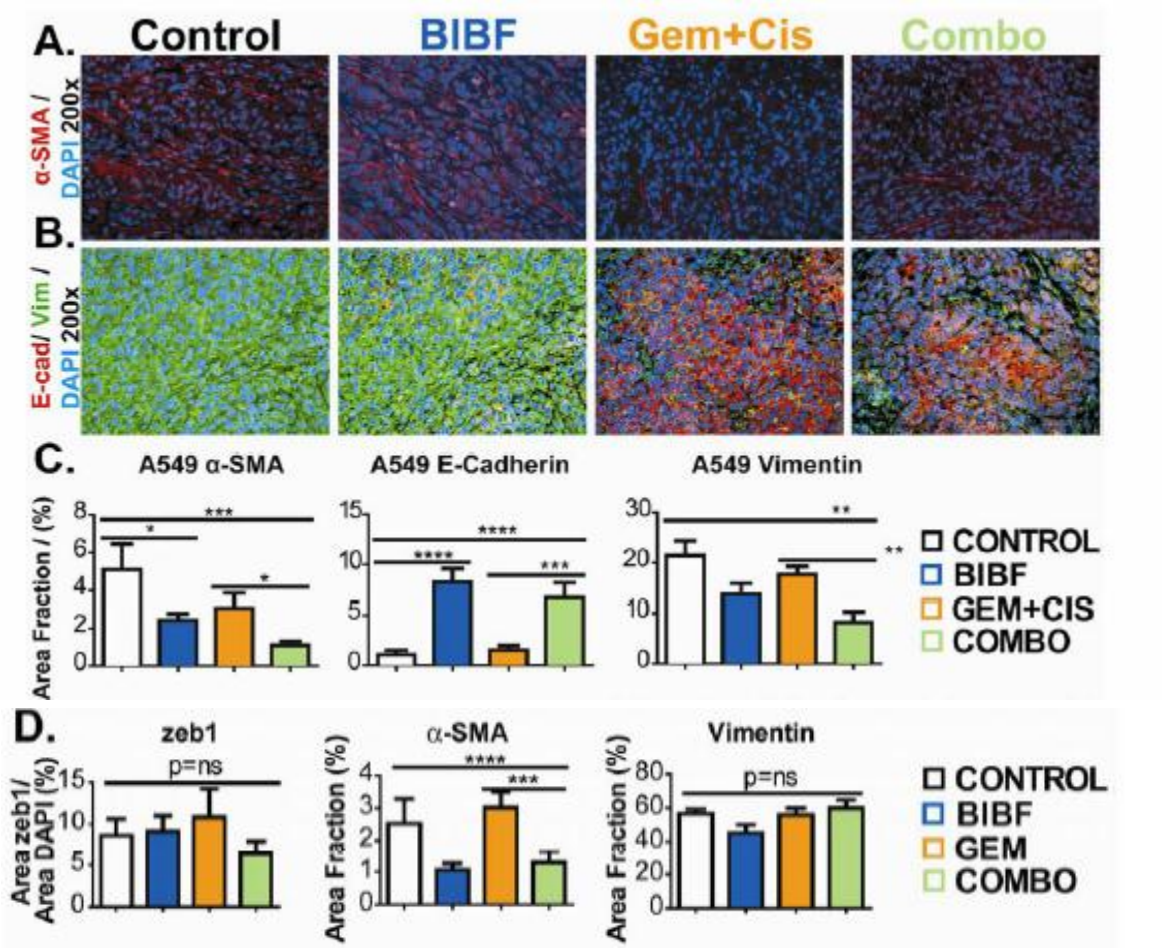
Cenik et al., Mol Cancer Ther; 12(6) June 2013

Nintedanib does not drive an invasive phenotype

Nintedanib treatment does not elevate EMT markers

A549

MIA PaCa-2



Cenik et al., Mol Cancer Ther; 12(6) June 2013

LUME-Lung 1: Basic study design

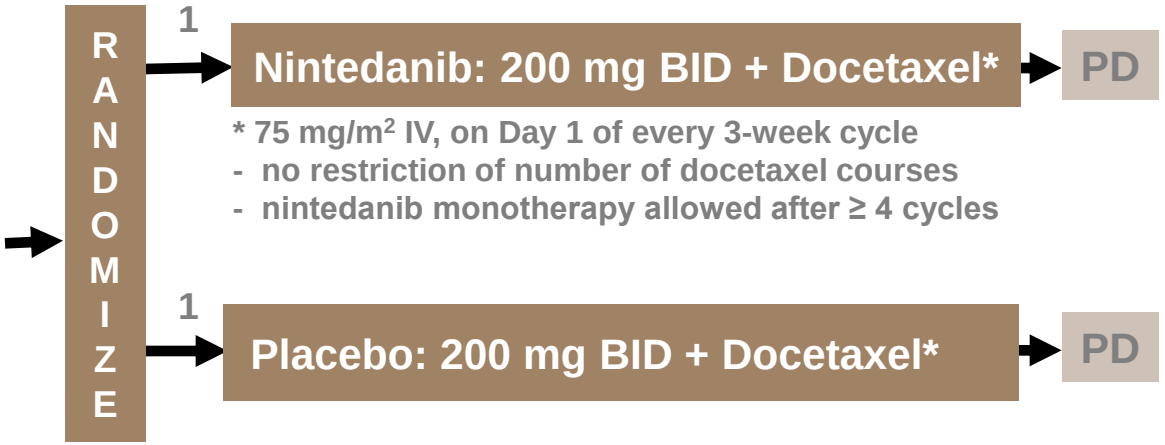
Pivotal study conducted in Europe, Asia and South Africa

Key inclusion criteria

- Stage IIIB/IV NSCLC patients
- All histologies
- Progressing after one prior first-line regimen
- ≥1 measurable, non-irradiated target lesion
- ECOG PS 0 or 1

Key exclusion criteria

- Prior VEGFR inhibitors (except bevacizumab) or docetaxel
- Active brain metastases



Stratification for:
- ECOG performance score (0 vs. 1)
- Prior bevacizumab therapy (yes vs. no)
- Tumour histology (squamous vs. non-squamous)
- Brain metastasis at baseline (yes vs. no)

Primary Endpoint: PFS by independent review (6 weeks CT-schedule)
Secondary Endpoints: OS, PFS investigator, ORR, DCR, HRQOL

Principal investigator: PD Dr M. Reck, German
TCM, Boehringer Ingelheim: Drs. G. Hanft/M. Müller/I. Voccia
PAREXEL: Dr. P. van Vlieberghe

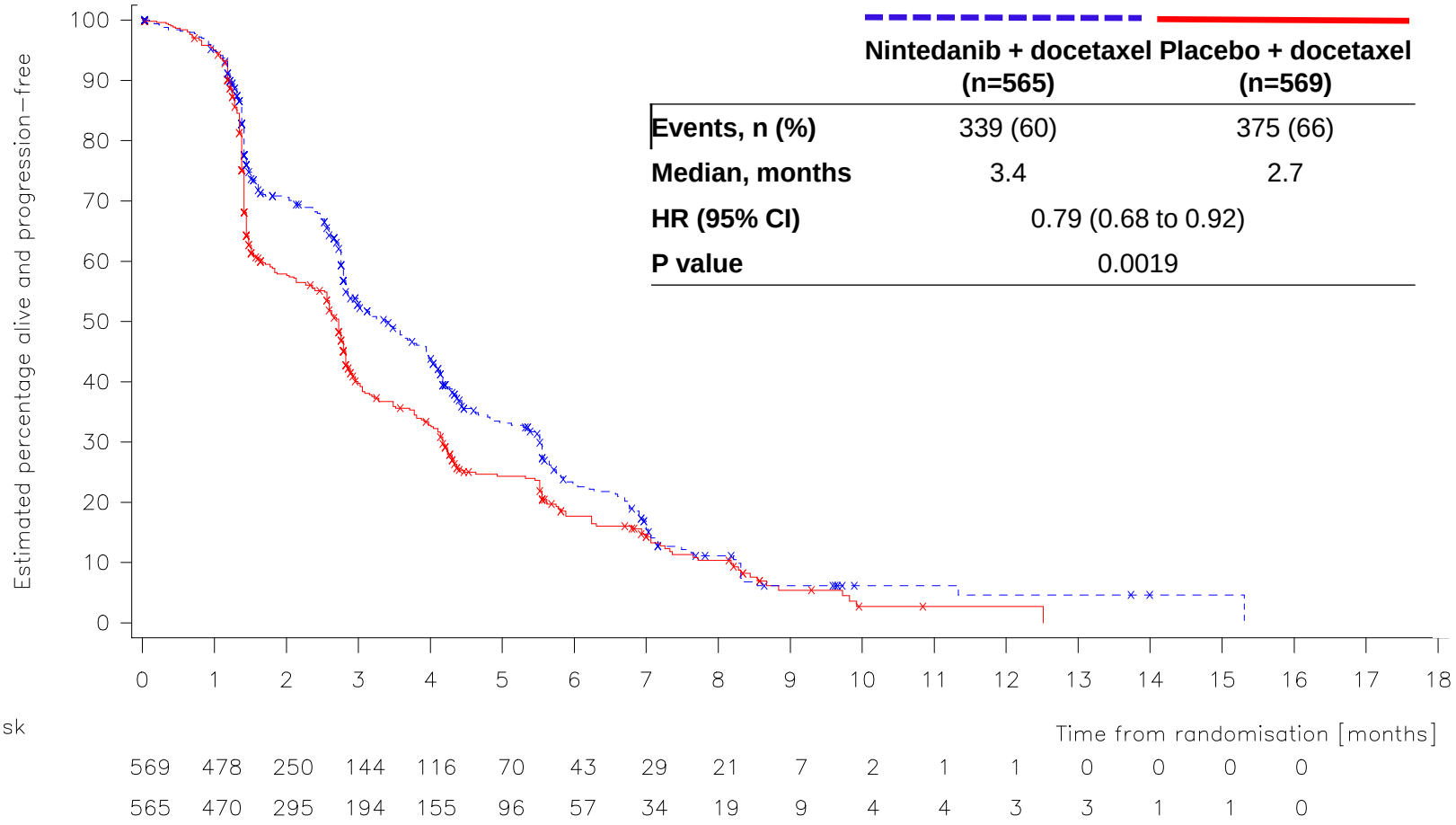
Reck M. et al, Lancet Oncol. 2014 Feb;15(2):143-55.

LET'S WORK
ONCOLOGY FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim

LUME Lung 1: Primary endpoint met: Independently reviewed PFS for all patients

All patients, n=1134



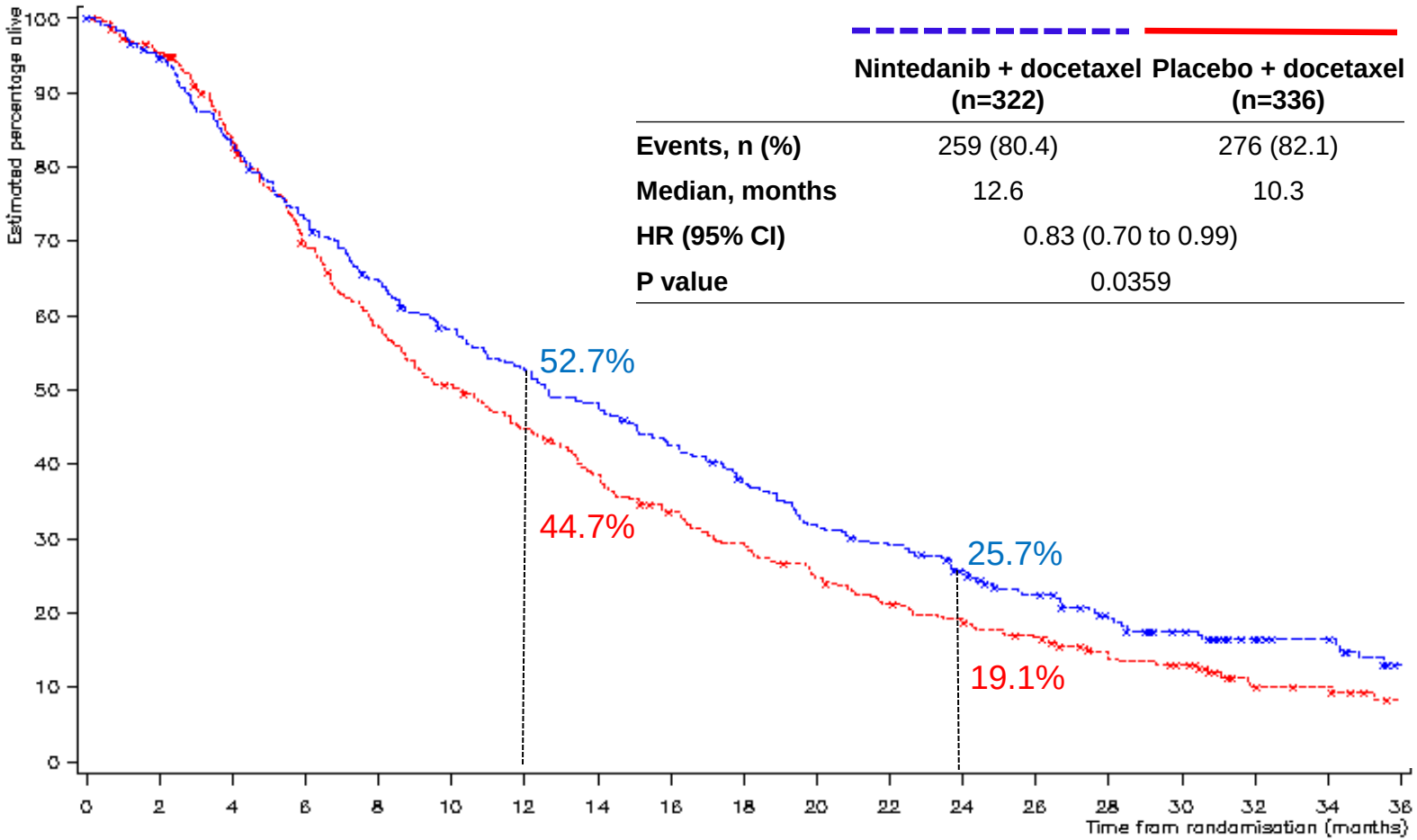
	Nintedanib + docetaxel (n=565)	Placebo + docetaxel (n=569)
Events, n (%)	339 (60)	375 (66)
Median, months	3.4	2.7
HR (95% CI)	0.79 (0.68 to 0.92)	
P value	0.0019	

- **Study met the primary endpoint of independently reviewed PFS for all patients with a HR of 0.79 (95% CI: 0.68–0.92)**
- **Adenocarcinoma patients: HR of 0.77 (95% CI: 0.62 to 0.96),**
- **Squamous cell cancer patients HR of 0.77 (95% CI: 0.62 to 0.96).**

Reck M. et al, Lancet Oncol. 2014 Feb;15(2):143-55.

LUME Lung 1:
Key secondary endpoint Overall Survival

Adenocarcinoma patients (N=658)



	Nintedanib + docetaxel (n=322)	Placebo + docetaxel (n=336)
Events, n (%)	259 (80.4)	276 (82.1)
Median, months	12.6	10.3
HR (95% CI)	0.83 (0.70 to 0.99)	
P value	0.0359	

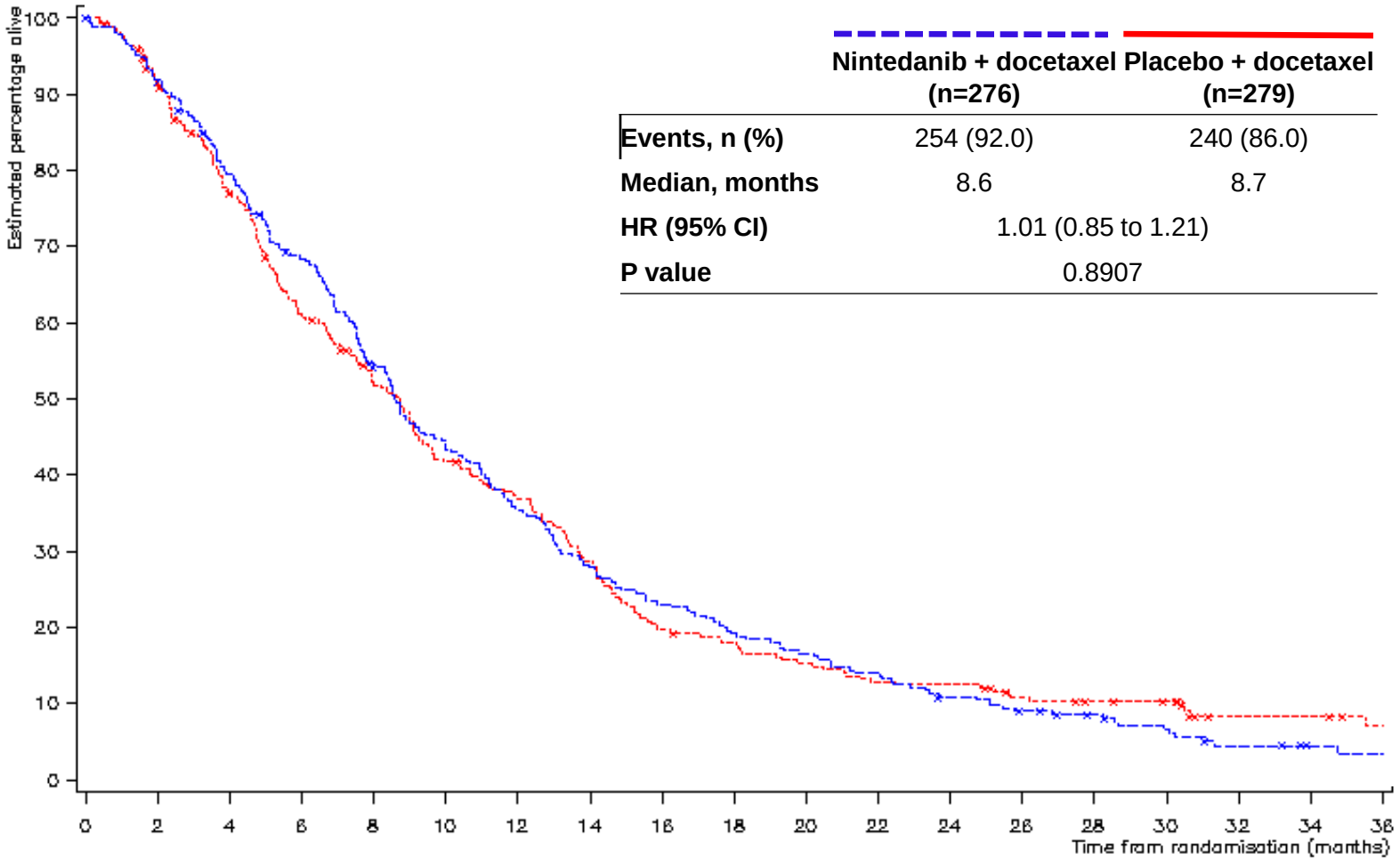
- **Study met the key secondary endpoint of OS in adenocarcinoma patients.**
- **Nintedanib significantly prolonged OS for all adenocarcinoma patients (n=658) with a HR of 0.83 (95% CI: 0.70–0.99) and a median OS improvement of 2.3 months (10.3 vs. 12.6 months, p=0.0359).**
- **Subsequent therapies were balanced between the two arms.**

-

Reck M. et al, Lancet Oncol. 2014 Feb;15(2):143-55.

LUME Lung 1: OS for squamous cell cancer patients

Squamous cell cancer patients, n=555

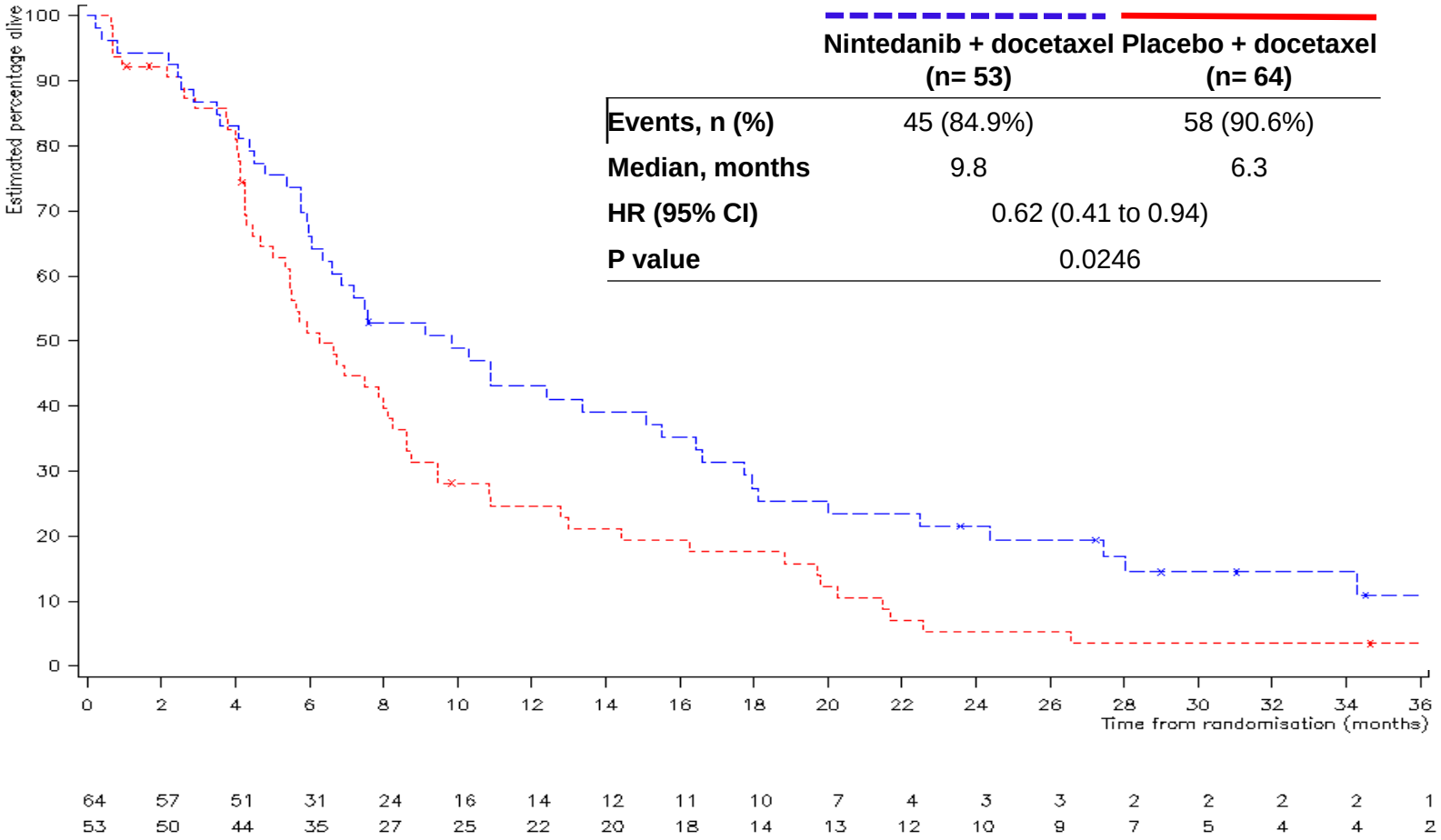


	Nintedanib + docetaxel (n=276)	Placebo + docetaxel (n=279)
Events, n (%)	254 (92.0)	240 (86.0)
Median, months	8.6	8.7
HR (95% CI)	1.01 (0.85 to 1.21)	
P value	0.8907	

- **There was no detrimental effect of nintedanib + docetaxel for squamous cell cancer patients. There was no OS improvement (HR of 1.01 (95%CI: 0.85-1.21, p=0.8908)**
- **Pre-specified sensitivity analysis with sum of longest diameter and strata; HR 0.92 (95%CI: 0.77-1.10, p=0.3649).**

LUME-Lung 1: OS for adenocarcinoma patients who had as best response PD in 1st line therapy

Exploratory analysis



	Nintedanib + docetaxel (n= 53)	Placebo + docetaxel (n= 64)
Events, n (%)	45 (84.9%)	58 (90.6%)
Median, months	9.8	6.3
HR (95% CI)	0.62 (0.41 to 0.94)	
P value	0.0246	

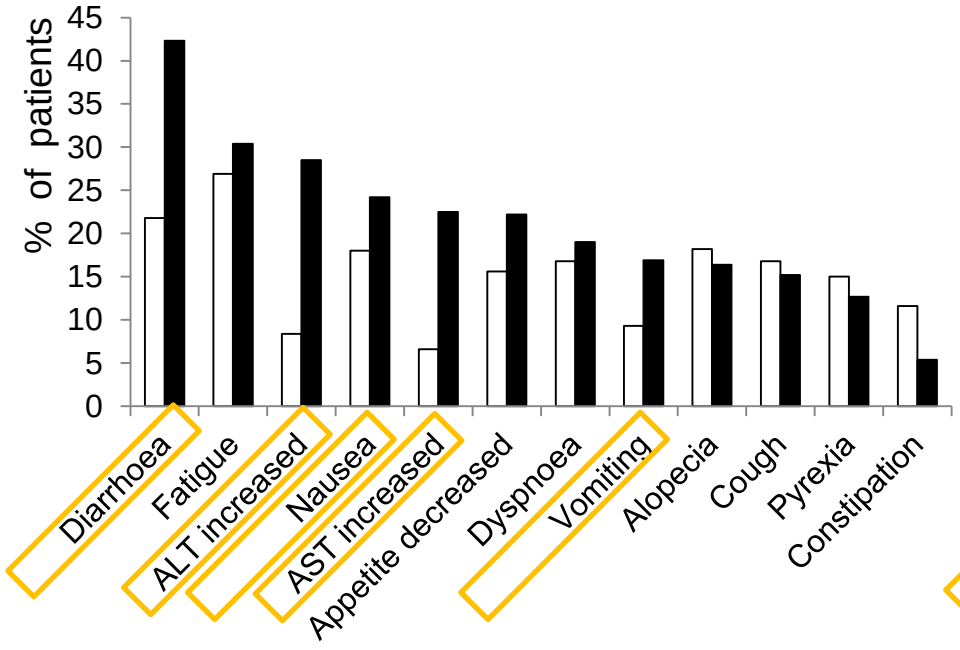
Reck M. et al, Lancet Oncol. 2014 Feb;15(2):143-55.

Boehringer Ingelheim

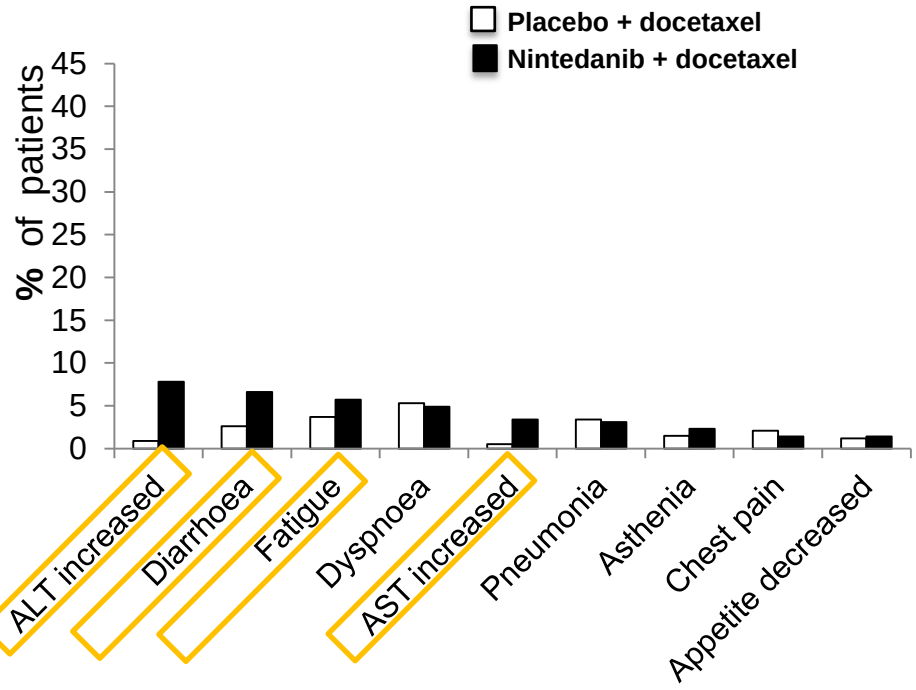
LUME-Lung 1:
non-haematological AEs, all Grades and Grade ≥ 3

All treated patients

All CTCAE Grades (%), > 10%



CTCAE Grades 3–5 (%), ≥ 1%



- **Numbers are confounded due to longer observation period in nintedanib arm**
- **The safety profile of nintedanib was consistent with previous studies of nintedanib with gastrointestinal adverse events and reversible liver enzyme elevations.**
- **The most frequent Grade 3-5 reactions on the nintedanib arm with a ≥3% increased incidence were diarrhea (6.6 vs 2.6%) and ALT elevation (7.8 vs 0.9%).**

Nintedanib (BIBF 1120): Summary

Nintedanib (BIBF 1120)

- is a potent triple angiokinase inhibitor *in vitro* and *in vivo*
- treatment does not drive an invasive phenotype
- has direct anti-tumor activity when tumors are driven by nintedanib targets
- provides PFS and OS advantage to 2nd line NSCLC patients
- manageable AEs

- Acknowledgements:

- BI research and development teams
- Drs. Gerber & Brekken, UT Southwestern, Texas
- Patients and families