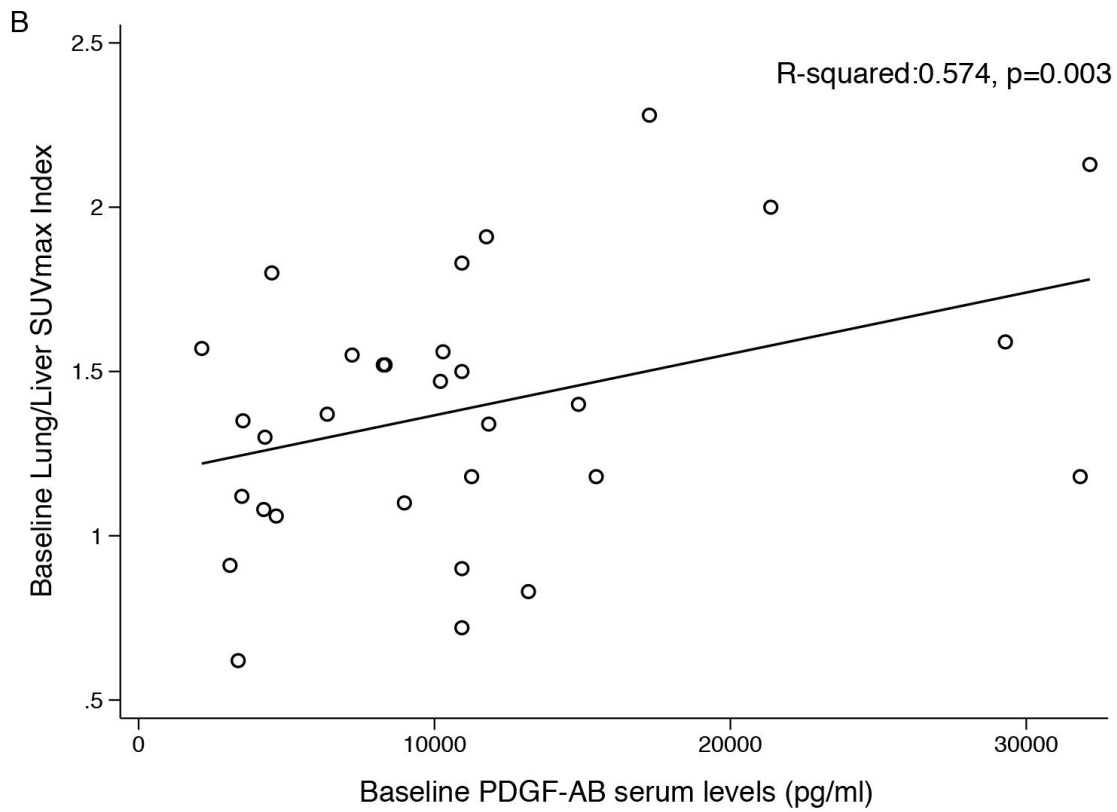
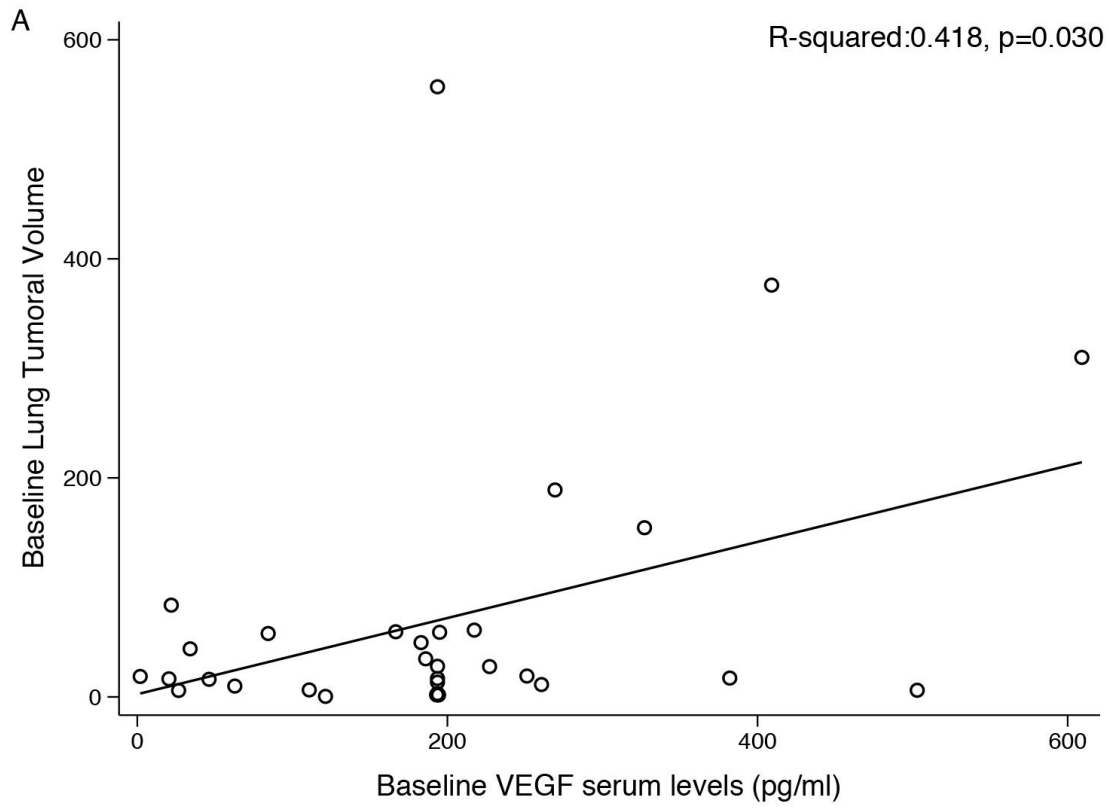


Supplemental Fig. 1



Supplemental Fig. 2. Scatterplots of the significant correlations among baseline PET/CT parameters measured with ^{68}Ga -DOTA-E-[c(RGDfK)]₂ radiotracer and angiogenic soluble factors.

Supplemental Table 1. General characteristics of patients (N=38)

Variable	% (n/N)
Gender	
Female	65.8 (25/38)
Male	34.2 (13/38)
Age	
Mean \pm SD	58.7 \pm 11.4
\leq 60 yrs	42.1 (16/38)
$>$ 60 yrs	57.9 (22/38)
Tobacco exposure	
Non-smokers	57.9 (22/38)
Smokers	42.1 (16/38)
Tobacco index	
Median (range)	24 (1-102)
Diabetes Mellitus	
Absent	84.2 (32/38)
Present	15.8 (6/38)
Systemic hypertension	
Absent	71.1 (27/38)
Present	28.9 (11/38)
Clinical stage at diagnosis	
II-III	18.4 (7/38)
IV	81.6 (31/38)
Baseline ECOG	
\leq 1	97.4 (37/38)
\geq 2	2.6 (1/38)
Adenocarcinoma histological pattern	
Lepidic	5.3 (2/38)
Papillary	15.8 (6/38)
Acinar	21.1 (8/38)
Solid	10.5 (4/38)
Other/Not specified	47.4 (18/38)
Carcinoembryonic antigen	
Median [Range]	7.3 [0.53 - 1,590.0]
Carcinoembryonic antigen	
\leq 10 pg/mL	52.6 (20/38)
$>$ 10 pg/mL	47.4 (18/38)
1st line therapy scheme	
Cis/Carbo-platin /Taxane	71.1 (27/38)
Cis/Carbo-platin /Pemetrexed	23.7 (9/38)
Cis/Carboplatin/ Gemcitabine	5.6 (2/38)
1st line Overall response rate	47.3 (18/38)
1st line Disease control rate	73.7 (28/38)
2nd line therapy scheme	
Nintedanib/Docetaxel	100 (38/38)
2nd line Overall response rate	7.9 (3/38)
2nd line Disease control rate	47.3 (18/38)

Abbreviations= SD: standard deviation; yrs: years; ECOG: Eastern Cooperative Oncology Group of performance status.

Supplemental Table 2. Characteristics of patients according to disease control rate (DCR) to nintedanib assessed by ⁶⁸Ga-DOTA-E-[c(RGDfK)]² PET/CT

Variable	Disease control rate (CR + PR + SD)		<i>P</i>
	No % (n/N)	Yes % (n/N)	
Gender			
Female	50.0 (12/24)	50.0 (12/24)	0.715*
Male	40.0 (4/10)	60.0 (6/10)	
Age			
≤ 60 yrs	56.3 (9/16)	43.8 (7/16)	0.311
> 60 yrs	38.9 (7/18)	61.1 (11/18)	
Tobacco exposure			
Non-smokers	42.9 (9/21)	57.1 (12/21)	0.533
Smokers	53.8 (7/13)	46.2 (6/13)	
Diabetes Mellitus			
Absent	48.3 (14/29)	51.7 (15/29)	1.000*
Present	40.0 (2/5)	60.0 (3/5)	
Systemic hypertension			
Absent	56.0 (14/25)	44.0 (11/25)	0.125*
Present	22.2 (2/9)	77.8 (7/9)	
Number of metastases			
≤1	30.0 (3/10)	70.0 (7/10)	0.270*
≥2	54.2 (13/24)	45.8 (11/24)	
Histological grade of differentiation†			
Low & Moderate	35.7 (5/9)	64.3 (9/14)	0.527
High	50.0 (2/4)	50.0 (2/4)	
Not specified	56.3 (9/16)	43.8 (7/16)	
Carcinoembryonic antigen			
≤10 pg/mL	61.1 (11/18)	38.9 (7/18)	0.100
>10 pg/mL	31.3 (5/16)	68.8 (11/16)	

Abbreviations= PET/CT: Positron Emission Tomography/Computed Tomography; CR: complete response; PR: partial response; SD: stable disease; yrs: years. p-Value for Chi-Square test and (*) Fisher's exact test.

Note: †according to adenocarcinoma IASLC/ATS/ERS classification.

Supplemental Table 3. ⁶⁸Ga-DOTA-E-[c(RGDfK)]² PET/CT parameters (N=30) according to disease control rate

Variable	Disease Control Rate							<i>P</i>
	Non-responders			Responders				
	Median	Range			Median	Range		
Lung Tumor SUVmax								
Baseline	5.5	1.3	7	0.346	4.3	2	9.2	0.363
Follow-Up	4	2.5	6.6		3.5	1.8	7.8	
%Δ Lung Tumor SUVmax		-27.3				-18.6		
Spleen SUVmax								
Baseline	5	1.6	6.9	0.118	5.8	4.3	8.4	0.255
Follow-Up	5.8	2.4	8.3		5.2	2.8	12.1	
%Δ Spleen SUVmax		16				-10.3		
Liver SUVmax								
Baseline	3.5	1	5	0.753	3.2	2.1	5.5	0.410
Follow-Up	3.3	2	5.9		3.1	1.6	6.5	
%Δ Liver SUVmax		-5.7				-3.1		
Lung Tumor/Spleen SUVmax Index								
Baseline	1	0.4	1.6	0.008	0.8	0.4	1.1	0.806
Follow-Up	0.7	0.4	1.3		0.7	0.5	1.2	
%Δ Lung/Spleen Index		-30				-13		
LungTumor/Liver SUVmax Index								
Baseline	1.5	0.8	2.3	0.074	1.2	0.6	2.1	0.629
Follow-Up	1.2	0.8	2.8		1.3	0.7	1.9	
%Δ Lung/Liver SUVmax Index		-18				6.8		
Lung Tumoral Volume								
Baseline	49.6	0.5	557.1	0.088	17.2	1.8	189	0.005
Follow-Up	35.9	0.3	634.4		10.8	0	180	
%Δ Lung Tumoral Volume		-27.6				-37.2		

Abbreviations= PET/CT: Positron Emission Tomography/Computed Tomography; %Δ: percentage of change; SUV: Standardized Unit Values.

Supplemental Table 4. Association of ⁶⁸Ga-DOTA-E-[c(RGDfK)]₂ PET/CT parameters with baseline and %Δ angiogenic soluble factors

Variable	Baseline FGF		Baseline VEGF		Baseline PDGF-AB	
	r ²	P	r ²	P	r ²	P
PET/CT parameter						
Baseline Lung Tumor SUVmax	-0.219	0.316	0.078	0.719	0.339	0.083
Baseline Spleen SUVmax	-0.062	0.779	-0.080	0.710	0.130	0.520
Baseline Liver SUVmax	-0.110	0.617	0.056	0.793	0.128	0.526
Baseline Lung Tumor/Spleen SUVmax Index	-0.208	0.340	0.167	0.435	0.332	0.091
Baseline Lung Tumor/Liver SUVmax Index	-0.173	0.430	0.041	0.848	0.418	0.030
Baseline Lung Tumoral Volume	0.113	0.607	0.574	0.003	-0.310	0.116

Abbreviations= SUV: Standardized Unit Values; PET/CT: Positron Emission Tomography/Computed Tomography; %Δ: percentage of change; FGF: Fibroblast growth factor; VEGF: Vascular endothelial growth factor; PDGF-AB: Platelet derived growth factor-AB; r²: root-squared.

Supplemental Table 5. Univariate analysis of clinical and ⁶⁸Ga-DOTA-E-[c(RGDfK)]₂ PET/CT factors associated with Progression-free Survival and Overall Survival

Variable	Progression-free Survival			Overall Survival		
	Median	95% CI	<i>P</i>	Median	95% CI	<i>P</i>
Overall	3.7	[2.04 - 5.38]		NR	NR	
Gender						
Female	3.7	[1.01 - 6.34]	0.666	NR	NR	0.726
Male	5.6	[2.24 - 8.98]		NR	NR	
Age						
<60 yrs	3.4	[1.84 - 4.92]	0.307	NR	NR	0.265
>60 yrs	5.6	[2.43 - 8.79]		NR	NR	
Tobacco exposure						
Non-smokers	3.7	[1.16 - 6.19]	0.414	NR	NR	0.038*
Smokers	5.3	[0.64 - 6.77]		NR	NR	
Diabetes Mellitus						
Absent	3.7	[2.18 - 5.17]	0.555	NR	NR	0.985
Present	5.3	[0.00 - 13.59]		NR	NR	
Systemic hypertension						
Absent	3.4	[1.73 - 5.03]	0.023	NR	NR	0.118
Present	6.4	[5.54 - 7.20]		NR	NR	
Clinical stage at diagnosis						
II-III	3.4	[0.00 - 7.34]	0.412	NR	NR	0.734
IV	3.7	[1.37 - 6.04]		NR	NR	
Baseline ECOG						
≤1	3.7	[2.05 - 5.30]	0.431	NR	NR	0.488
≥2	NR	[NR]		NR	NR	
Carcinoembryonic antigen						
≤10 pg/mL	3.7	[1.98-5.37]	0.629	NR	NR	0.972
>10 pg/mL	5.6	[2.29 - 8.94]		NR	NR	
Baseline Lung Tumor SUVmax						
<4.3	4.7	[0.09 - 9.37]	0.600	7.1	NR	0.170
≥4.3	3.7	[3.15 - 4.20]		NR	NR	
%Δ Lung Tumor SUVmax						
< - 18.6	2.0	[1.46 - 2.61]	0.120*	7.1	[0.0 - 14.7]	0.016
≥ - 18.6	3.7	[2.24 - 5.17]		NR	NR	
Baseline Spleen SUVmax						
<5	4.7	[2.30 - 7.15]	0.618	NR	NR	0.888
≥5	3.6	[2.25 - 4.90]		NR	NR	
%Δ Spleen SUVmax						
< 16.0	4.7	[0.73 - 8.72]	0.790	NR	NR	0.603
≥ 16.0	3.6	[2.39 - 4.77]		NR	NR	
Baseline Liver SUVmax						
<3.2	4.7	[0.44 - 9.01]	0.673	NR	NR	0.697
≥3.2	3.7	[2.11 - 5.24]		NR	NR	
%Δ Liver SUVmax			0.858*			0.069*

< 3.5	4.7	[0.69-8.77]		NR	NR	
≥ 3.5	3.6	[2.27 - 4.88]		NR	NR	
Baseline Lung Tumor/Spleen SUVmax Index						
<0.8	2.8	[0.87 - 4.71]	0.460	4.6	[1.4 - 7.7]	0.022
≥0.8	3.7	[1.37 - 6.04]		NR	NR	
%Δ Lung Tumor/Spleen SUVmax Index						
< - 12.5	2.8	[0.33 - 5.24]	0.409*	7.8	[5.9 - 9.8]	0.043
≥ -12.5	4.7	[2.52 - 6.93]		NR	NR	
Baseline Lung Tumor/Liver SUVmax Index						
<1.4	2.3	[0.00 - 5.34]	0.464*	NR	NR	0.486
≥1.4	3.7	[3.12 - 4.30]		NR	NR	
%Δ Lung Tumor/Liver SUVmax Index						
< -14.2	3.7	[1.77 - 5.58]	0.308	NR	NR	0.343
≥ -14.2	3.7	[1.55 - 5.87]		NR	NR	
Baseline Lung Tumoral Volume						
<19.1	2.1	[1.66 - 2.61]	0.007	NR	NR	0.459
≥19.1	6.4	[2.12 - 10.62]		NR	NR	
%Δ Lung Tumoral Volume						
< -37.7	3.7	[2.32 - 5.03]	0.365	NR	NR	0.378
≥ -37.7	2.8	[0.67 - 4.91]		NR	NR	

Abbreviations: CI: Confidence interval; yrs:years, ECOG PS: European Clinical Oncological Group performance status; SUV: Standardized Unit Values; %Δ: percentage of change. Notes (*) Breslow test.

Supplemental Table 6. Multivariate analysis of clinical and ⁶⁸Ga-DOTA-E-[c(RGDfK)]² PET/CT factors associated with Progression-free Survival and Overall Survival

Variable	Progression-free Survival		Overall Survival	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Gender			0.9 (0.27 - 3.53)	0.979
Age			1.4 (0.55 - 3.67)	0.455
Tobacco exposure			2.3 (0.68 - 7.95)	0.176
Systemic hypertension	0.2 (0.07 - 0.80)	0.021		
%Δ Lung Tumor SUVmax			3.1 (1.0 - 9.8)	0.048
Baseline Spleen SUVmax	0.4 (0.14 - 1.09)	0.074		
Baseline Lung Tumoral Volume	0.4 (0.17 - 1.08)	0.075		

Abbreviations= PET/CT: Positron Emission Tomography/Computed Tomography; CI: Confidence Interval; %Δ: percentage of change; SUV: Standardized Unit Values.