Phase II randomized trial of afatinib with or without cetuximab as first-line treatment for EGFR mutated non-small cell lung cancer (NSCLC) patients (IFCT-1503 ACE-Lung)

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Background

- EGFR tyrosine kinase inhibitors (TKIs) are active in EGFR-mutant non-small cell lung cancer (NSCLC), however resistance inevitably develops
- The combination of the irreversible ErbB family TKI afatinib and the EGFR monoclonal antibody cetuximab was previously shown to delay acquired resistance to 1st-generation EGFR TKIs
- We hypothesized that front-line afatinib plus cetuximab would delay the development of resistance
- We conducted a randomized trial of afatinib plus cetuximab versus afatinib in treatment-naïve patients with advanced EGFR-mutant NSCLC

Endpoints

- **Primary endpoint: Time to Treatment Failure (TTF) at 9 months**
- Tolerance (NCI-CTC 4.0)
- Progression-free Survival (PFS)
- Overall Survival (OS)

Trial Design

- **Advanced non-squamous NSCLC**
- **Common sensitizing *EGFR* mutations (exon 19 deletion or L858R, G719X, L861Q, S768I mutations, or exon 19 insertions)**
- **Chemotherapy- and TKI-naïve**
- **PS 0-1**
- **Untreated brain metastases allowed**

Randomize 1:1

→ **Afatinib PO 40 mg Daily + Cetuximab IV 500 mg/m² Q2W (6 months)** 1st injection at D15 (250 mg/m²)

→ **Afatinib PO 40mg Daily**

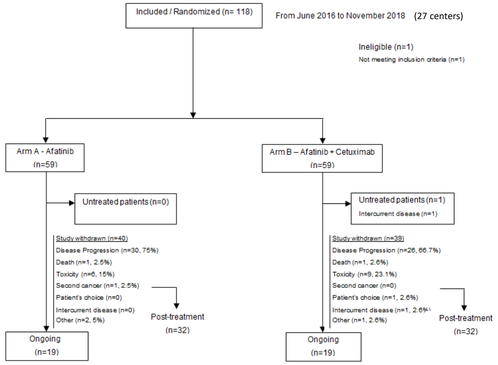
Randomized Phase II study (Fleming one-stage method), with a 5% unilateral alpha risk, and a power of 90% in each of the 2 groups

Statistical hypothesis (85 patients planned in each of the 2 groups):
H0 : p0 (Treatment Failure rate at Month 9) ≤ 50%
H1 : p1 (Treatment Failure rate at Month 9) ≥ 67%

Randomization method: minimization

Stratification factors : centre, mutation EGFR (exon 19 deletion vs L858R mut vs others mutations) and smoking habits (never-smoker (< 100 cig) vs smoker)

Flow-Chart

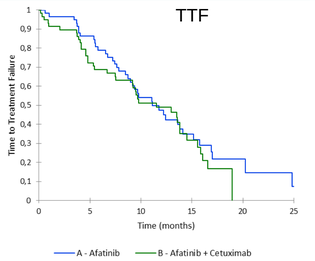


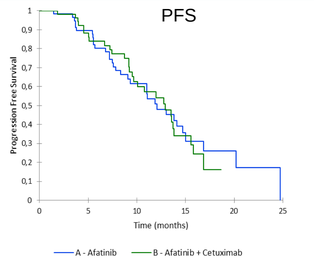
Baseline characteristics

			Afatinib (N=59)	Afatinib + Cetuximab (N=59)
Sex	Female	N (%)	43 (72.9)	41 (69.5)
Age (years)		Median	68.1	63.8
		Range	[34.8-86.2]	[41.7-84.3]
Smoking	No	N (%)	34 (57.6)	33 (55.9)
EGFR mutation	Exon 19 deletions	N (%)	33 (55.9)	30 (50.8)
	Exon 21 L858R mutation	N (%)	23 (39)	24 (40.7)
	Other mutation	N (%)	3 (5.1)	5 (8.5)
PS	0	N (%)	21 (35.6)	22 (37.3)
	1	N (%)	38 (64.4)	36 (61.0)
	2	N (%)	0	1 (1.7)
TNM	Stage III	N (%)	1 (1.7)	3 (5.1)
	Stage IV	N (%)	58 (98.3)	56 (94.9)
Histological Type	Adenocarcinoma	N (%)	57 (96.6)	57 (96.6)
	Others non-squamous NSCLC	N (%)	2 (3.4)	2 (3.4)

Compliance (cetuximab, median-min-max): 12 injections [0-14]

Efficacy (TTF – PFS – Response after 2 cycle)





	Afatinib (N =59)	Afatinib + Cetuximab (N =58)
Event : N (%)	39 (66.1)	39 (67.2)
Median TTF: months [95% CI]	11.1 [8.7-14.1]	11.5 [7.6-13.8]
9-m TTF: % [95% CI]	62.1 [47.9-73.4]	63.2 [49.3-74.2]

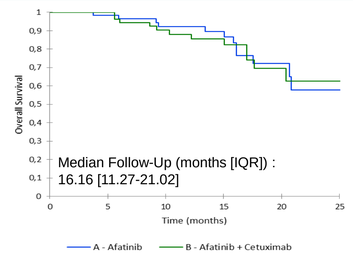
	Afatinib (N =59)	Afatinib + Cetuximab (N =58)
Event : N (%)	33 (55.9)	29 (50.0)
Median PFS: months [95% CI]	12.1 [9.1-15.0]	12.9 [9.5-13.8]
9-m PFS: % [95% CI]	66.2 [51.7-77.3]	74.9 [59.9-84.9]

Response after 2 cycle of treatment		A - Afatinib (N =59)	B - Afatinib + Cetuximab (N =58)
Objective Response Rate	N (%)	41 (69.5)	38 (65.5)
Disease Control Rate	N (%)	57 (96.6)	54 (93.1)
Progression disease / Not done or not evaluable	N (%)	0 (0) / 2 (3.4)	1 (1.7) / 3 (5.2)

Treatment-related Adverse Events (TRAEs)

Adverse events (maximal grade)	Afatinib (N=59)			Afatinib + Cetuximab (N=58)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Grade Max	59 (100%)	22 (37.3%)	3 (5.1%)	57 (98.3%)	30 (51.7%)	0 (0%)
Diarrhoea	55 (93.2%)	9 (15.3%)	2 (3.4%)	51 (87.9%)	7 (12.1%)	0 (0%)
Rash	27 (45.8%)	2 (3.4%)	0 (0%)	41 (70.7%)	1 (1.7%)	0 (0%)
Dry skin	21 (35.6%)	0 (0%)	0 (0%)	35 (60.3%)	1 (1.7%)	0 (0%)
Paronychia	24 (40.7%)	1 (1.7%)	1 (1.7%)	29 (50%)	2 (3.4%)	0 (0%)
Skin fissures	19 (32.2%)	0 (0%)	0 (0%)	32 (55.2%)	1 (1.7%)	0 (0%)
Asthenia	12 (20.3%)	0 (0%)	0 (0%)	24 (41.4%)	4 (6.9%)	0 (0%)
Nausea	19 (32.2%)	1 (1.7%)	0 (0%)	16 (27.6%)	0 (0%)	0 (0%)
Stomatitis	14 (23.7%)	2 (3.4%)	0 (0%)	21 (36.2%)	5 (8.6%)	0 (0%)
Acne	15 (25.4%)	0 (0%)	0 (0%)	19 (32.8%)	2 (3.4%)	0 (0%)
Dermatitis acneiform	7 (11.9%)	1 (1.7%)	0 (0%)	22 (37.9%)	4 (6.9%)	0 (0%)
Aphthous ulcer	14 (23.7%)	1 (1.7%)	0 (0%)	12 (20.7%)	0 (0%)	0 (0%)
Folliculitis	13 (22%)	3 (5.1%)	0 (0%)	12 (20.7%)	7 (12.1%)	0 (0%)
Erythema	11 (18.6%)	0 (0%)	0 (0%)	13 (22.4%)	0 (0%)	0 (0%)
Vomiting	12 (20.3%)	2 (3.4%)	1 (1.7%)	9 (15.5%)	0 (0%)	0 (0%)
Pruritus	4 (6.8%)	1 (1.7%)	0 (0%)	16 (27.6%)	0 (0%)	0 (0%)
Hypertrichosis	3 (5.1%)	0 (0%)	0 (0%)	14 (24.1%)	0 (0%)	0 (0%)
Alanine aminotransferase increased	3 (5.1%)	0 (0%)	0 (0%)	12 (20.7%)	0 (0%)	0 (0%)

Efficacy (OS)



	Afatinib (N =59)	Afatinib + Cetuximab (N =58)
Event : N (%)	12 (20.3)	12 (20.7)
Median OS: months [95% CI]	NR [20.7-NR]	NR [20.4-NR]
12-m OS: % [95% CI]	92.3 [80.6-97.0]	88.0 [75.2-94.5]

Biomarkers

			Afatinib (N=42)	Afatinib + Cetuximab (N=36)	Total (N=78)	pvalue
Circulating tumour DNA at diagnosis	Negative	N (%)	10 (24.4)	7 (20.0)	17 (22.4)	0.65
	Positive	N (%)	31 (75.6)	28 (80.0)	59 (77.6)	
Variant allele frequency (%)		N	41	35	76	0.59
		Nmiss	1	1	2	
		Mean ± SD	8.76 ± 13.02	13.43 ± 22.66	10.91 ± 18.13	
		Median	1.58	3.13	2.48	
		Range	[0.0-52.8]	[0.0-91.0]	[0.0-91.0]	
T790M mutation detected at progression	Negative	N (%)	7 (53.8)	8 (100.0)	15 (71.4)	0.046
	Positive	N (%)	6 (46.2)	0	6 (28.6)	

Conclusions

- Efficacy of afatinib+cetuximab was similar to that of afatinib alone
- Tolerance of afatinib+cetuximab was manageable
- These results don't support further evaluation of this combination in this setting.
- Biological exploratory analysis are ongoing in order to identify predictive biomarkers

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