Furmonertinib versus gefitinib in treatment-naïve *EGFR* mutated non-small cell lung cancer: a randomized, double-blind, multi-center, phase III study (FURLONG)

Yuankai Shi[*1], Gongyan Chen[2], Xiang Wang[3], Yunpeng Liu[4], Lin Wu[5], Yanrong Hao[6], Chunling Liu[7], Shuyang Zhu[8], Xiaodong Zhang[9], Yuping Li[10], Jiwei Liu[11], Lejie Cao[12], Ying Cheng[13], Hui Zhao[14], Shucai Zhang[15], Aimin Zang[16], Jiuwei Cui[17], Jian Feng[18], Fei Liu[19], Chuan Gu[19]

DR Rajesh Patidar
Associate Professor, SAIMS ,INDORE

Background

- Furmonertinib (AST2818)
  - A novel third-generation EGFR tyrosine-kinase inhibitor that targets both EGFR sensitising mutations and the Thr790Met mutation while sparing wild-type EGFR.
- **Advantages with Furmonertinib**
  - **Encouraging efficacy and good tolerability in** previous phase 1/2 and phase 2b studies of patients with **EGFR Thr790Met-mutated NSCLC**.
  - **Activity in the CNS lesions** of patients with EGFR mutated NSCLC, with an ORR of 66% (95% CI 46–82).
  - **Infrequent adverse events** related to drug action on wild-type EGFR, such as diarrhoea and rashes.
- **Present study compared furmonertinib with gefitinib** as first-line treatments for patients with locally advanced or metastatic EGFR-mutated NSCLC.

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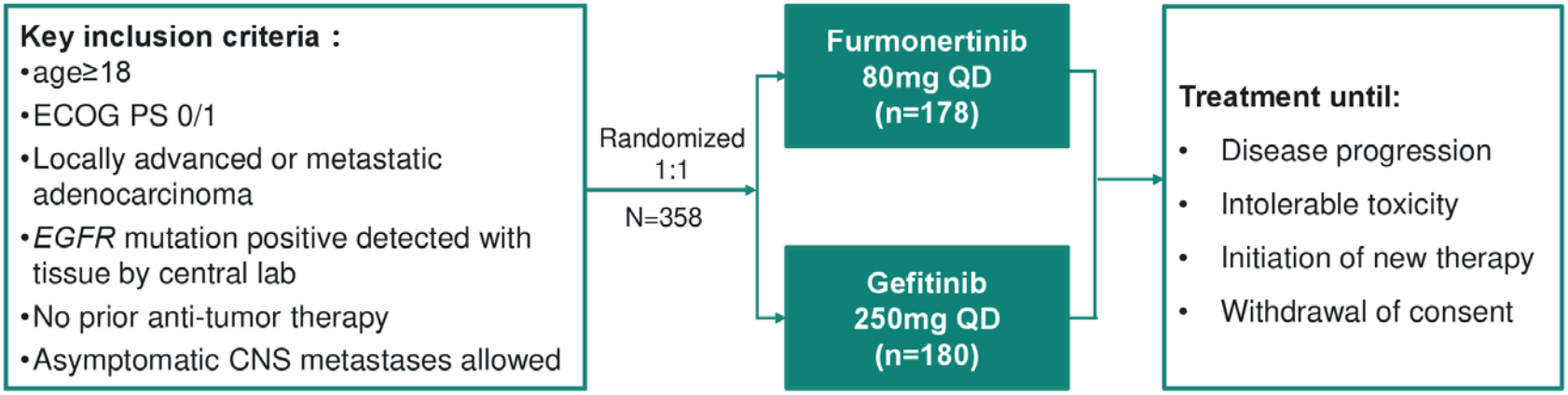
Methods

FURLONG Study Design

A randomized, double-blind, multi-center phase III study conducted in 55 hospitals in mainland China



Stratification factors : *EGFR* mutations (Ex19Del vs L858R) , CNS metastases (yes vs no)

Primary endpoint: PFS (assessed by IRC)

Secondary endpoints: ORR, DCR, DOR, OS, DepOR, TTP, safety, PROs

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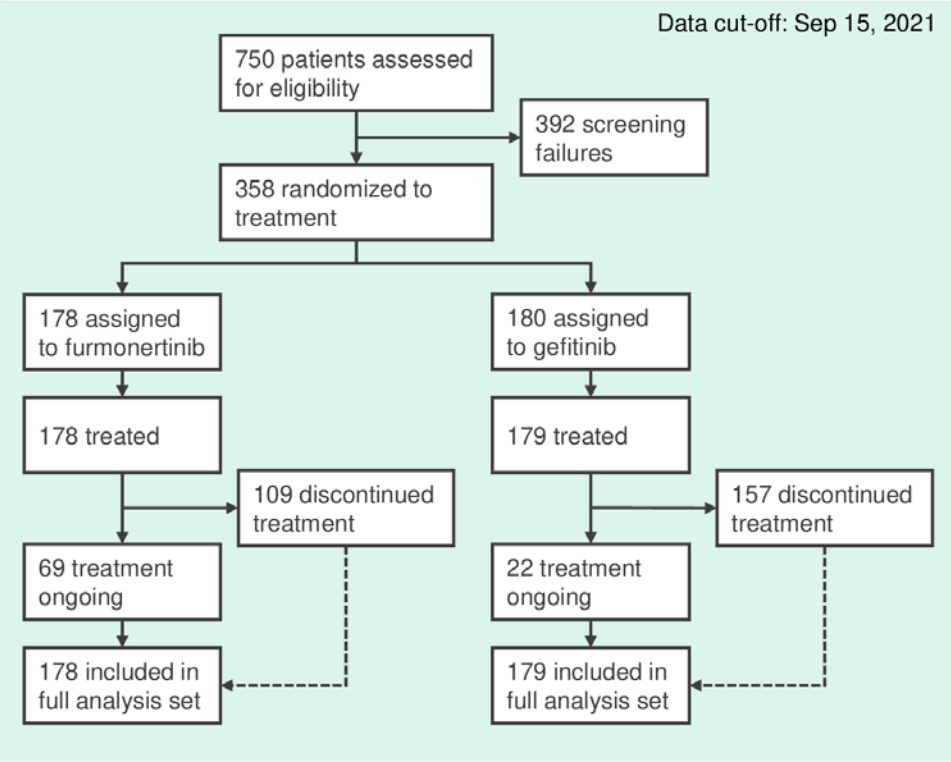
Baseline demographics and Trial Flow

Trial profile & baseline characteristics



Characteristics, data are median (range) or n (%)		Furmonertinib (n=178)	Gefitinib (n=179)
Age	Median	59 (31-81)	60 (32-83)
Sex	Female	116 (65%)	111 (62%)
	Male	62 (35%)	68 (38%)
ECOG PS	0	39 (22%)	28 (16%)
	1	138 (76%)	151 (84%)
	2	1 (1%)	0
EGFR mutation	Ex19Del	91 (51%)	92 (51%)
	L858R	87 (49%)	87 (49%)
Smoking history	Yes	41 (23%)	44 (25%)
	No	137 (77%)	135 (75%)
Disease stage	III	10 (6%)	7 (4%)
	IV	168 (94%)	172 (96%)
CNS metastases	Yes	63 (35%)	58 (32%)
	No	115 (65%)	121 (68%)

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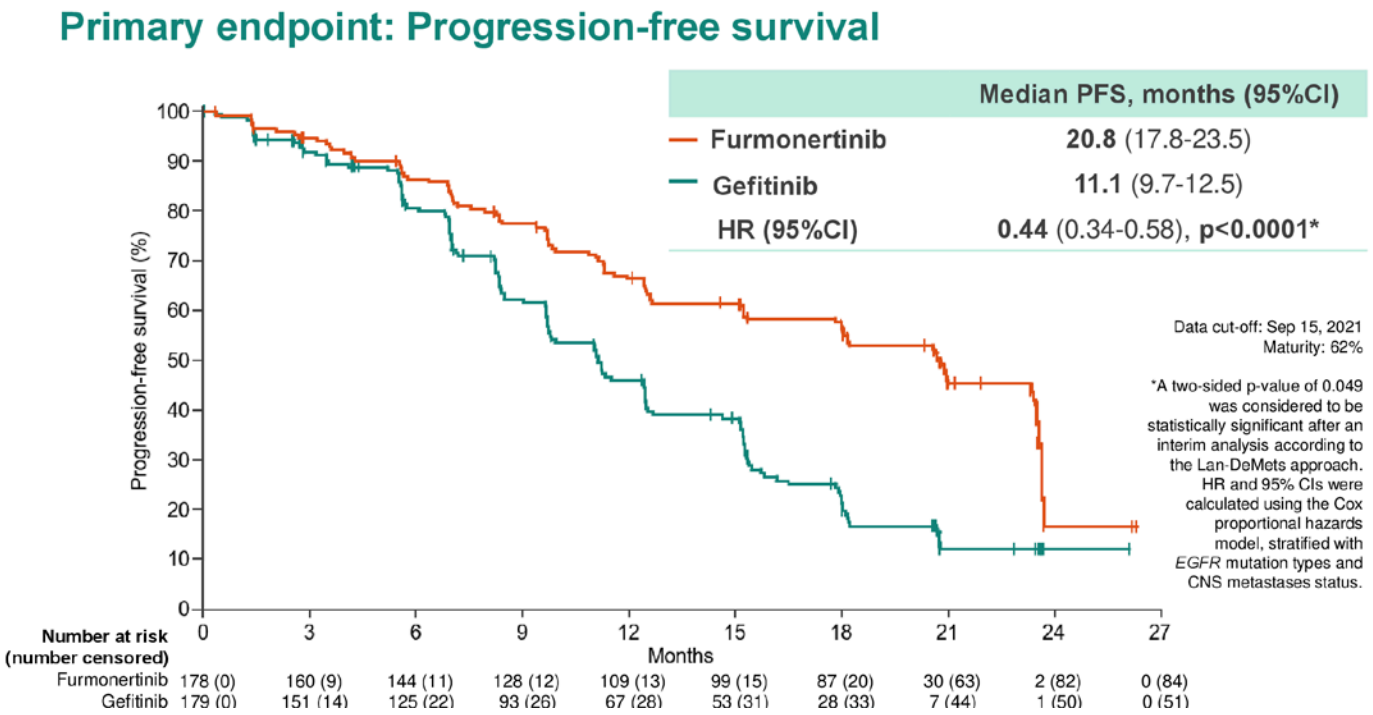
Results

- **Median follow-up**
  - **21·0 months (IQR 18·0–23·5) in the furmonertinib group 11·1 months (9·7–12·5) in the gefitinib group (p<0.0001)**



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Results

- **In subgroup analyses,**
  - **Furmonertinib was associated with longer PFS compared with gefitinib in most prespecified subgroups, including in patients with CNS metastases (p=0.0028)**

PFS subgroup analysis

		Furmonertinib n/N	Gefitinib n/N	HR (95%CI)	p value
Age (years)	<65	60/118	89/114	0.36 (0.26, 0.51)	<0.0001
	≥65	34/60	39/65	0.68 (0.43, 1.09)	0.1088
Sex	Male	33/62	56/68	0.39 (0.25, 0.61)	<0.0001
	Female	61/116	72/111	0.49 (0.35, 0.70)	<0.0001
ECOG PS	0	16/39	23/28	0.33 (0.17, 0.63)	0.0005
	1	78/138	105/151	0.49 (0.36, 0.66)	<0.0001
	2	0/1	0/0	NE (NE, NE)	NE
Smoking history	Yes	24/41	33/44	0.53 (0.30, 0.92)	0.0232
	No	70/127	95/135	0.42 (0.31, 0.58)	<0.0001
EGFR mutation	Ex19del	38/91	60/92	0.35 (0.23, 0.53)	<0.0001
	L858R	56/87	68/87	0.54 (0.37, 0.77)	0.0006
CNS Metastases*	Yes	36/63	42/58	0.50 (0.32, 0.80)	0.0028
	No	56/115	86/121	0.42 (0.30, 0.59)	<0.0001
Overall		94/178	128/179	0.45 (0.34, 0.59)	<0.0001

*CNS metastases were determined from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy, all reported by investigators.
HRs and p values were estimated with unstratified Cox proportional hazards model and unstratified log-rank test.

Data cut-off: Sep 15, 2021

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Results

- **In patients with CNS metastases,**
  - Median investigator-assessed progression free survival
    - 18·0 months (95% CI 12·4–23·3) with furmonertinib and
    - 12·4 months (8·3–15·1) with gefitinib.
- **According to Independent review centre (IRC) assessment**
  - Among patients with an OR,
    - 77 (49%) of 158 in the furmonertinib group progressed or died and
    - 107 (71%) of 151 in the gefitinib group progressed or died.
  - **Duration of response** was significantly longer with furmonertinib than with gefitinib
    - (19·7 months vs 11·0 months, p<0.0001)
  - **Rate of disease control**
    - 96% with furmonertinib and 93% with gefitinib (p=0·36).
  - **Median best percentage change in target lesion size** (depth of response) from baseline
    - –61·1% with furmonertinib and –55·9% with gefitinib (p=0·085)

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Results

Summary of secondary endpoints

Endpoint	Furmonertinib n=178	Gefitinib n=179	OR / HR	p-value
ORR (95%CI)	89% (83-93)	84% (78-89)	1.50 (0.80-2.83)	0.2078
DCR (95%CI)	96% (91-98)	93% (89-97)	1.56 (0.61-3.98)	0.3551
DOR, median (95%CI)	19.7 months (16.8-22.1)	10.5 months (8.5-11.3)	0.39 (0.29-0.52)	**<0.0001**
DepOR, median (range)	61.1% (-61.1, 91.4)	55.9% (-56.0, 100)	-	0.0852
TTP, median (95%CI)	20.9 months (18.0-23.5)	11.2 months (9.7-12.5)	0.41 (0.31-0.55)	**<0.0001**
OS*, median (95%CI)	NR	NR	0.94 (0.65-1.36)	0.7446

*In the gefitinib group, 43% patients had received third-generation EGFR-TKIs after progression. All the endpoints above were assessed by IRC (independent review center) excluding OS. Maturity of OS was 32%. ORR: objective response rate; DCR: disease control rate; DOR: duration of response; OS: overall survival; DepOR: depth of response; TTP: time to progression; NR: not reached; HR: hazard ratio. OR: odds ratio.

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Results - Safety

- **TRAEs of a grade 3 or more were reported in 20 (11%) patients in the furmonertinib group and in 32 (18%) patients in the gefitinib group.**
- **TRSAEs were reported in ten (6%) patients who received furmonertinib and in 11 (6%) patients who received gefitinib.**
- **Most common TRSAEs** were
  - elevated alanine aminotransferase (four [2%] patients in the furmonertinib group; three [2%] patients in the gefitinib group) and
  - elevated aspartate aminotransferase (three [2%] patients in the furmonertinib group; four [2%] patients in the gefitinib group; appendix 2 pp 11–12

Median duration of exposure: 18.3 months with furmonertinib and 11.2 months with gefitinib

Treatment-emergent adverse events (TEAEs)

	Furmonertinib (n=178)	Gefitinib (n=179)
Any AE	178 (100%)	177 (99%)
Grade ≥3 AE	62 (35%)	60 (34%)
SAE	44 (25%)	29 (16%)
Dose interruption	27 (15%)	34 (19%)
Dose reduction	5 (3%)	6 (3%)
Discontinuation	11 (6%)	7 (4%)
AE with outcome of death	10 (6%)	3 (2%)

Treatment-related adverse events (TRAEs)

	Furmonertinib (n=178)	Gefitinib (n=179)
Any TRAE	160 (90%)	170 (95%)
Grade ≥3 TRAE	**20 (11%)**	**32 (18%)**
TRSAE	10 (6%)	11 (6%)
Dose interruption	24 (13%)	28 (16%)
Dose reduction	5 (3%)	NA*
Discontinuation	6 (3%)	4 (2%)
TRAE with outcome of death	0	0

*6 patients (3%) had dose reduction in the gefitinib group, but only furmonertinib placebo was reduced because dose reduction of gefitinib was not allowed according to the prescribing information of gefitinib. TRAE: treatment-related adverse event; TEAE: treatment-emergent adverse event; AE: adverse event. TRSAE: treatment-related serious

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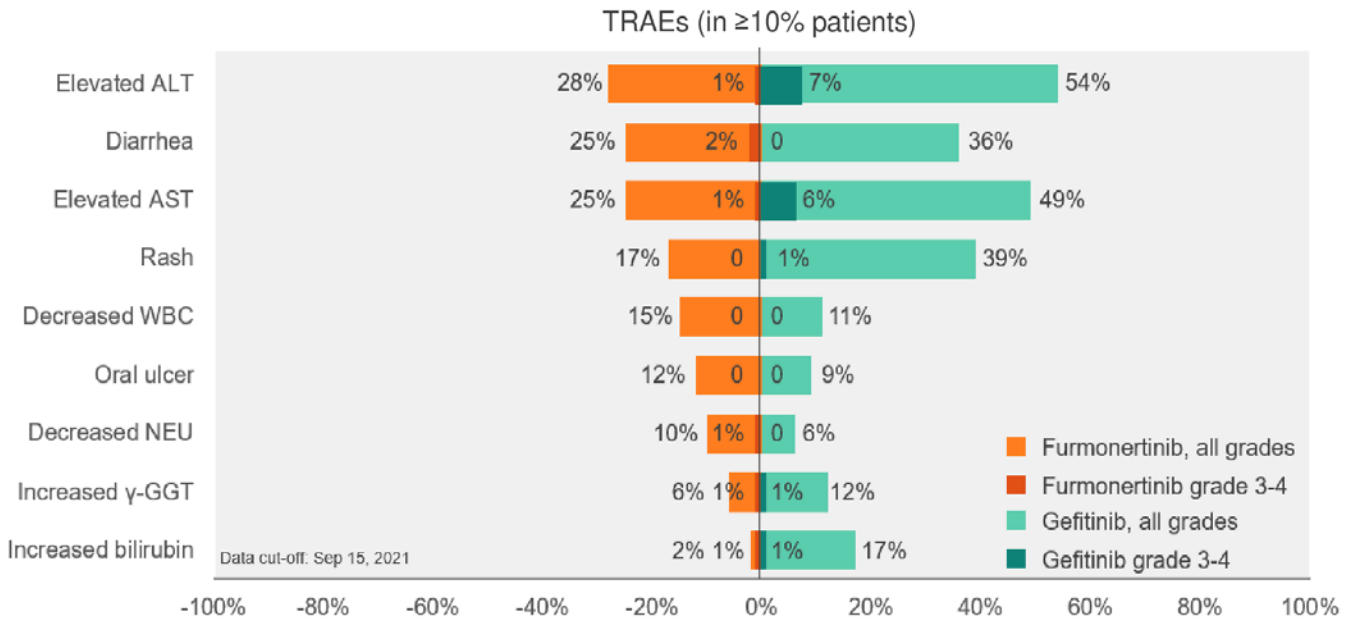
Results - Safety

The most frequent treatment-related adverse events

Median duration of exposure: 18.3 months with furmonertinib and 11.2 months with gefitinib



AEs of interest:

- interstitial lung disease (ILD) was recorded in 1 patient in each group (grade 1 in furmonertinib group, grade 2 in gefitinib group)
- QT prolongation was recorded in 9% and 7% patients in furmonertinib group and gefitinib group, respectively.

Treatment-related adverse events were judged by investigators. Treatment-related adverse events of ≥10% in either group are listed. ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell count; NEU: neutrophil count; GGT: glutamyltransferase. TRAE: treatment-related adverse events/.

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Conclusions

- In this randomized, double-blind, phase III FURLONG study, furmonertinib was associated with a significant longer PFS compared with gefitinib in untreated *EGFR* mutated NSCLC (20.8 vs 11.1 months, HR 0.44). This benefit is consistent across prespecified subgroups.

- Despite a longer duration of exposure, furmonertinib showed an overall favorable safety profile versus gefitinib, with relatively lower frequency of grade ≥3 TRAEs (11% vs 18%), diarrhea, rash and liver abnormalities.

- These results suggest that furmonertinib is a potential preferred first-line therapy in *EGFR* mutated Chinese NSCLC patients compared with gefitinib.

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THANKS !