IASLC
2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

A Randomized Phase III Trial of Fruquintinib versus Placebo in Patients with Advanced Non-Small Cell Lung Cancer (FALUCA)

Shun Lu
Shanghai Chest Hospital, China

Shun Lu[1], Gongyan Chen[2], Yuping Sun[3], Sanyuan Sun[4], Jianhua Chang[5], Yu Yao[6],Zhendong Chen[7], Feng Ye[8], Junguo Lu[9], Jianhua Shi[10], Jianxing He[11], Xiaoqing Liu[12], Yiping Zhang[13], Zhihua Liu[14], Jian Fang[15], Ying Cheng[16], Chunhong Hu[17], Weidong Mao[18], Yanping Hu[19], Youling Gong[20], Li Shan[21], Zhixiong Yang[22], Yong Song[23], Wei Li[24], Chong Bai[25], Buhai Wang[26], Rui Ma[27], Zhendong Zheng[28],Mingfang Liu[29], Zhijun Jie[30], Lejie Cao[31], Wangjun Liao[32], Hongming Pan[33], Dongning Huang[34], Yuan Chen[35],Jinji Yang[36], Shukui Qin[37], Shenglin Ma[38], Li Liang[39], Zhe Liu[40], Jianying Zhou[41], Min Tao[42], Yijiang Huang[43], Feng Qiu[44], Yunchao Huang[45], Ye Hua[46], Yiping Chen[46] and Weiguo Su[46]

[1]Shanghai Chest Hospital,[2]Affiliated Cancer Hospital of Harbin Medical University,[3]Jinnan Central Hospital,[4]XuZhou Central Hospital,[5]Fudan University Shanghai Cancer Center,[6]The First Affiliated Hospital of Xi'an Jiaotong University,[7]The Second Hospital of Anhui Medical University,[8]The First Affiliated Hospital of Xiamen University,[9]Nantong Tumor Hospital,[10]Linyi Cancer Hospital,[11]The First Affiliated Hospital of Guanzhou Medical University,[12]The 307 Hospital of People's Liberation Army,[13]Zhejiang Cancer Hospital,[14]Jiangxi Cancer Hospital,[15]Beijing Cancer Hospital,[16]Jilin Cancer Hospital,[17]The Second Xiangya Hospital of Central South University,[18]Jiangyin People's Hospital,[19]Hubei Cancer Hospital,[20]West China Hospital of Sichuan University,[21]Xinjiang Cancer Hospital,[22]Affiliated hospital of Guangdong Medical University,[23]General Hospital of the Eastern War Zone of the Chinese People's Liberation Army,[24]The First hospital of Jilin University,[25]Shanghai Changhai Hospital,[26]Northern Jiangsu People's hospital,[27]Liaoning Cancer Hospital,[28]General Hospital of Northern Theater Command,[29]General Hospital of Ningxia Medical University,[30]The Fifth People's Hospital of Shanghai,[31]Anhui Provincial Hospital,[32]Nanfang Hospital of Southern Medical University,[33]Sir Run Run Shaw Hospital Affiliated with School of Medicine, Zhe Jiang University,[34]The Fourth Affiliated Hospital of Guangxi Medical University,[35]Tongji Hospital ,Tongji Medical College of Hust,[36]Guandong provincial people's hospital,[37]Nanjing Chinese Medicine University–Affiliated Bayi Hospital,[38]Hangzhou First People's Hospital,[39]Peking University Third Hospital,[40]Beijing Chest Hospital , Capital Medical University,[41]The First Affiliated Hospital, Zhejiang University,[42]The First Affiliated Hospital of Soochow University,[43]Hainan General Hospital,[44]The First Affiliated Hospital of Nanchang University,[45]Yunnan Cancer Hospital,[46]Hutchison MediPharma, Shanghai, China

Disclosures

Relationship	Commercial Interests
Research support	AstraZeneca, Hutchison, Roche
Speaker fees	AstraZeneca, Roche
Advisor or consultant	AstraZeneca, Boehringer Ingelheim, Hutchison, Roche, Simcere

FALUCA Study Design

- Stage IIIB/IV non-squamous NSCLC
- Failed 2 prior chemotherapy regimens
- EGFR mutation or ALK translocation were permitted if treated with EGFR/ALK-TKIs
- Patients screened n=730
- Randomized N=527

R 2:1

- Fruquintinib 5mg + BSC
  3-weeks-on / 1-week-off (N=354)
- Placebo + BSC
  3-weeks-on / 1-week-off (N=173)

→ Continuous treatment until PD, intolerable toxicity, or withdrawal

Tumor assessment: 4 wks, 8 wks, and every 8 wks

STRATIFICATION FACTORS:
- EGFR status: mutant vs. wild type (EGFR+ must have failed EGFR TKI)
- Prior VEGF inhibitor therapy: yes vs. no

- **Fruquintinib:** a highly selective, potent, oral VEGFR TKI[1].
- Antitumor effect in NSCLC PoC studies both monotherapy[2] and in combos[3], and in mCRC Phase III[4] monotherapy.
- Other VEGF/VEGFR TKIs known to be hampered by safety issues, as monotherapy or particularly in combos[5].

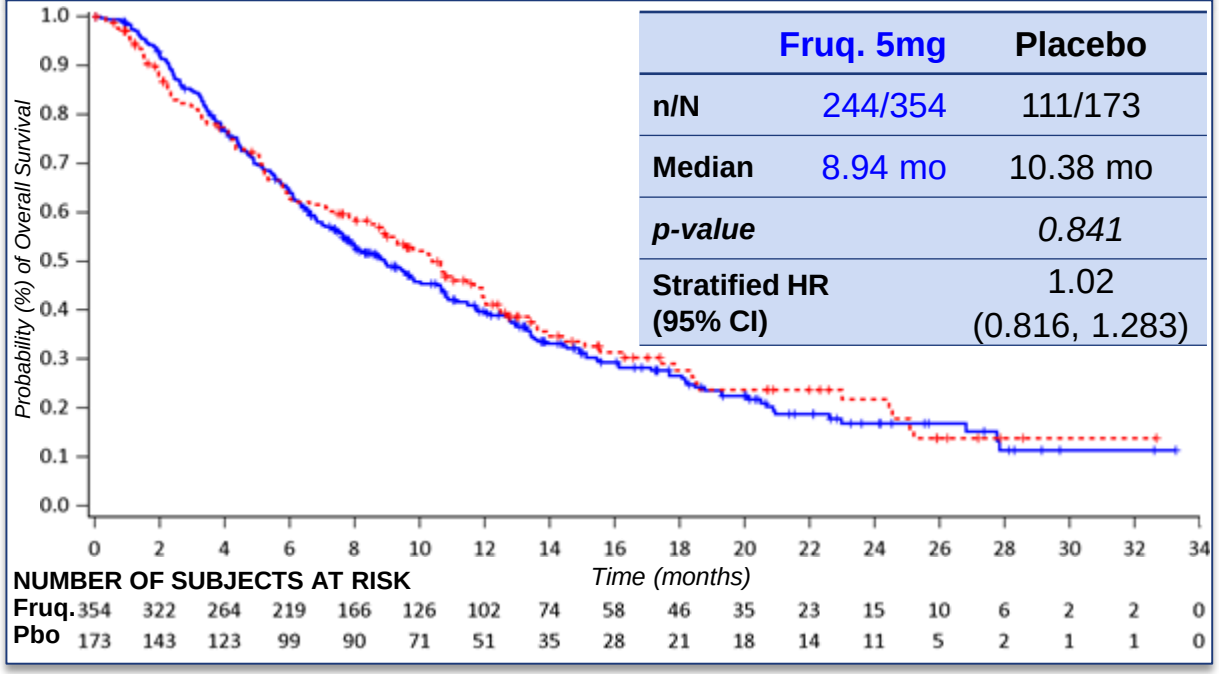
- **Multicenter, randomized, double-blind, placebo-controlled, phase III trial** (NCT02691299)
- **Recruitment:** Dec 2015 to Feb 2018
- **Data cut-off:** 21 Sep 2018
- **PRIMARY ENDPOINTS:** Overall Survival (OS)
- **SECONDARY ENDPOINTS:** PFS, ORR and DCR

Shun Lu, Shanghai Chest Hospital, China

1. Sun et al, *Cancer Biol Ther*. 2014;15(12):1635–45; 2. Lu et al, *J Clin Oncol*. 2018 Apr 20;36(12):1207-1217; 3. Lu et al, *#10907* WCLC 2017; 4. Li et al, *JAMA* 2018 Jun 26;319(24):2486-2496; 5. Seto et al, *Lancet Oncol*. 2014;15(11):1236-44.

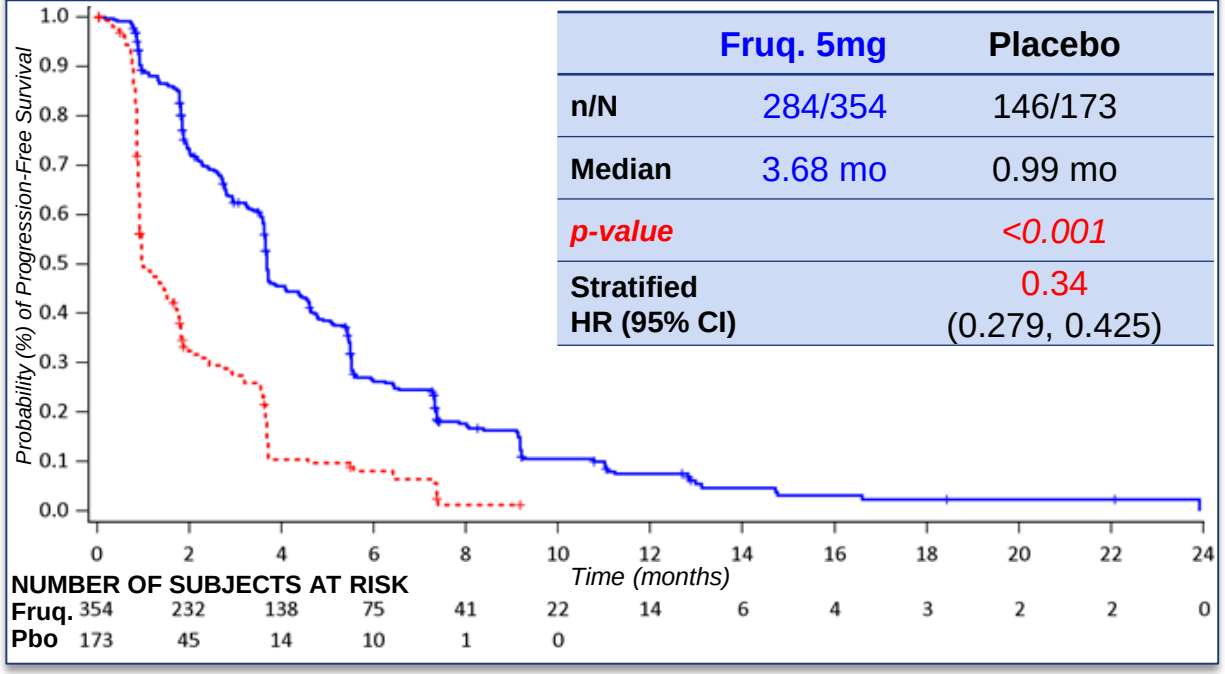
Primary (OS) & Secondary (PFS, ORR & DCR) Endpoints – ITT Set

OVERALL SURVIVAL BY TREATMENT GROUP – Intention-to-Treat Set



	Fruq. 5mg	Placebo
n/N	244/354	111/173
Median	8.94 mo	10.38 mo
p-value		*0.841*
Stratified HR (95% CI)		1.02 (0.816, 1.283)

PROGRESSION FREE SURVIVAL BY TREATMENT GROUP – Intention-to-Treat Set



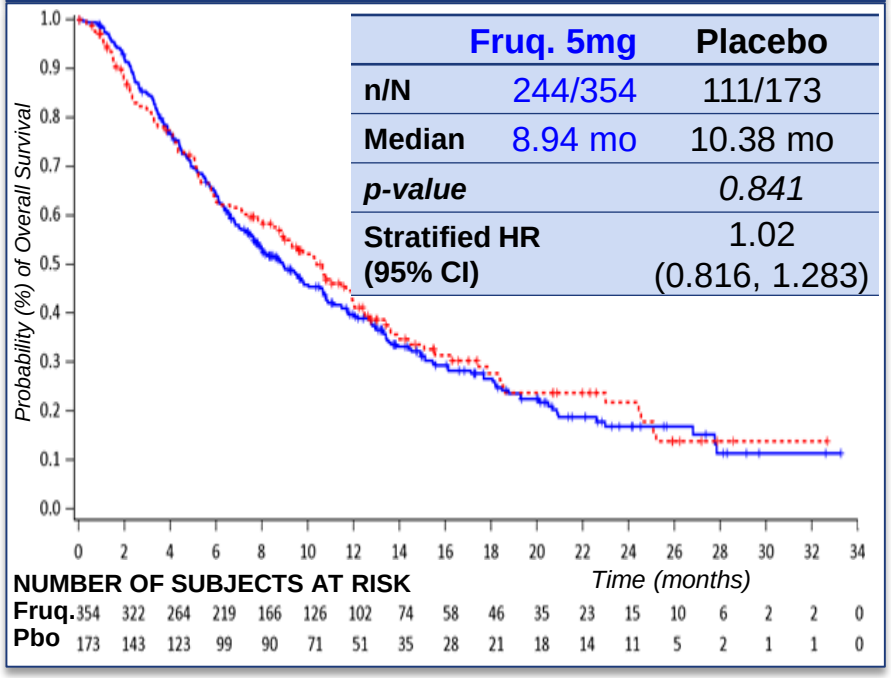
	Fruq. 5mg	Placebo
n/N	284/354	146/173
Median	3.68 mo	0.99 mo
p-value		*<0.001*
Stratified HR (95% CI)		0.34 (0.279, 0.425)

TUMOR ASSESSMENT	Fruquintinib, n (%)	Placebo, n (%)
Objective Response Rate (ORR)	49 (13.8)	1 (0.6)
	p<0.001	
Disease Control Rate (DCR)	236 (66.7)	43 (24.9)
	p<0.001	

- **Fruquintinib failed to meet the primary efficacy endpoint of OS.**
- **Fruquintinib *met all* secondary efficacy endpoints.**

Overall Survival: Post-hoc sensitivity analysis of subsequent ATTs*

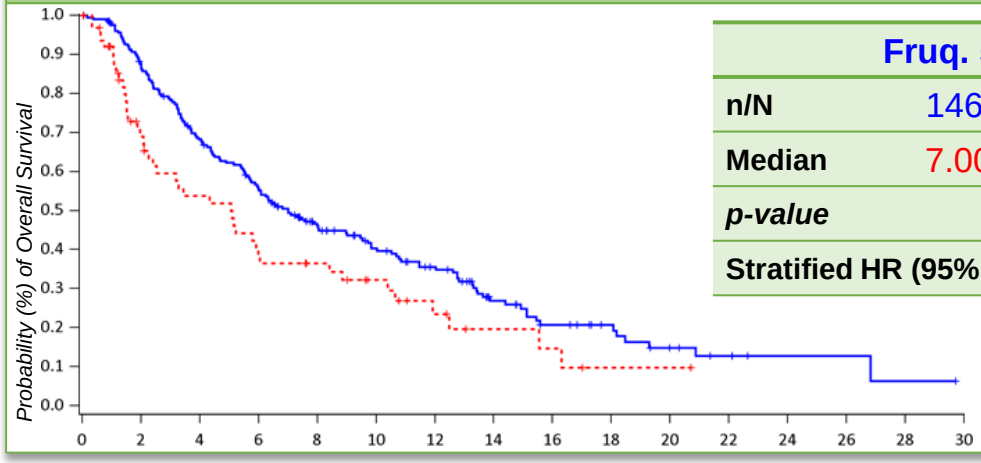
OVERALL SURVIVAL BY TREATMENT GROUP – Intention-to-Treat Set



	Fruq. 5mg	Placebo
n/N	244/354	111/173
Median	8.94 mo	10.38 mo
p-value		*0.841*
Stratified HR (95% CI)		1.02 (0.816, 1.283)

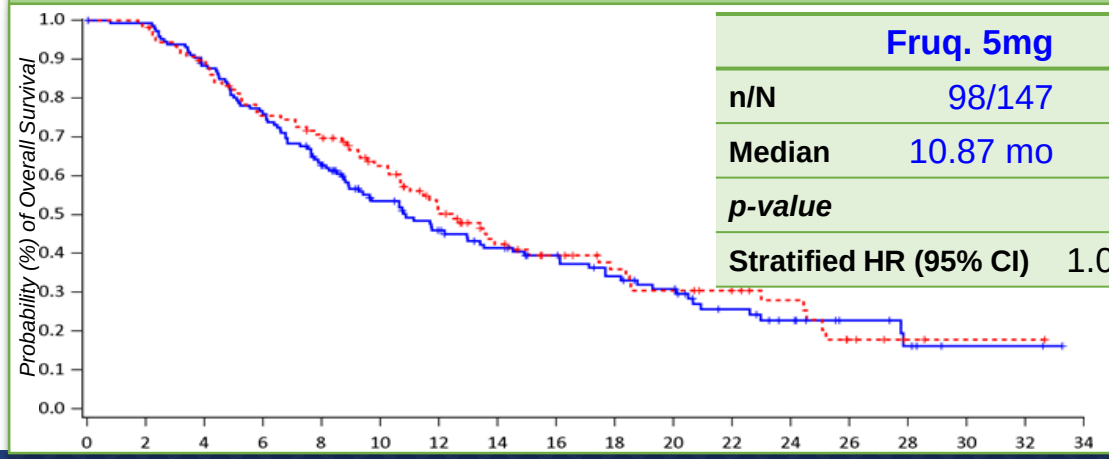
POST-HOC ANALYSIS

Patients *without* subsequent Anti-tumor Treatment (ATT*): SIGNIFICANT OS BENEFIT IN FRUQUINTINIB GROUP



	Fruq. 5mg	Placebo
n/N	146/207	43/65
Median	7.00 mo	5.06 mo
p-value		*0.010*
Stratified HR (95% CI)		0.64 (0.453, 0.903)

Patients *with* subsequent Anti-tumor Treatment (ATT*): EXTENDED OS BENEFIT IN BOTH GROUPS



	Fruq. 5mg	Placebo
n/N	98/147	68/108
Median	10.87 mo	12.45 mo
p-value		*0.767*
Stratified HR (95% CI)		1.05 (0.765, 1.437)

***ATTs (ANTI-TUMOR TREATMENTS), FRUQUINTINIB VS. PLACEBO**

- **Chemotherapy:** 29.7% vs. 53.8%
- **Targeted therapies (Anti-VEGF/VEGFR, and/or anti-EGFR):** 20.9% vs. 31.2%
- **AZD9291 and anlotinib approved in China in** 2017

Treatment-Emergent Adverse Events (Safety Set)

	Fruquintinib (N=353) n (%)	Placebo (N=170) n (%)
Any Grade	347 (98.3%)	149 (87.6%)
Grade 3 or above	216 (61.2%)	47 (27.6%)
SAEs	104 (29.5%)	32 (18.8%)
Leading to:		
Dose interruption	61 (17.3%)	7 (4.1%)
Dose reduction	85 (24.1%)	2 (1.2%)
Dose interruption or reduction	133 (37.7%)	8 (4.7%)
Treatment discontinuation	37 (10.5%)	9 (5.3%)

≥ Grade 3 TEAEs (incidence ≥1%):	Fruquintinib (N=353) n (%)	Placebo (N=170) n (%)
Hypertension	74 (21.0%)	5 (2.9%)
Hand-foot syndrome (HFS)	39 (11.0%)	0
Hyponatremia	14 (4.0%)	3 (1.8%)
Decreased appetite	12 (3.4%)	2 (1.2%)
Weight decreased	6 (1.7%)	0
Proteinuria	5 (1.4%)	0
Stomatitis	4 (1.1%)	0
Nausea	0	2 (1.2%)

Key Points

- **Fruquintinib failed to meet primary efficacy endpoint of OS due to subsequent anti-tumor treatments after disease progression.**
  - Anti-tumor therapies after disease progression greatly reduced OS benefits in the ITT population:
    - Higher percentage of patients in placebo group received subsequent treatments.
    - Subsequent treatments provided substantial OS benefit to patients in both groups.

- **Fruquintinib met all secondary efficacy endpoints** *(all p<0.001)*.
  - PFS (3.68 vs. 0.99 months, HR=0.34) ORR (13.8% vs. 0.6%) DCR (66.7% vs. 24.9%)

- **Fruquintinib demonstrated a good safety profile consistent with expectations.**
  - Most Grade 3 or above TEAEs were target-related and clinically manageable, such as hypertension and HFS.