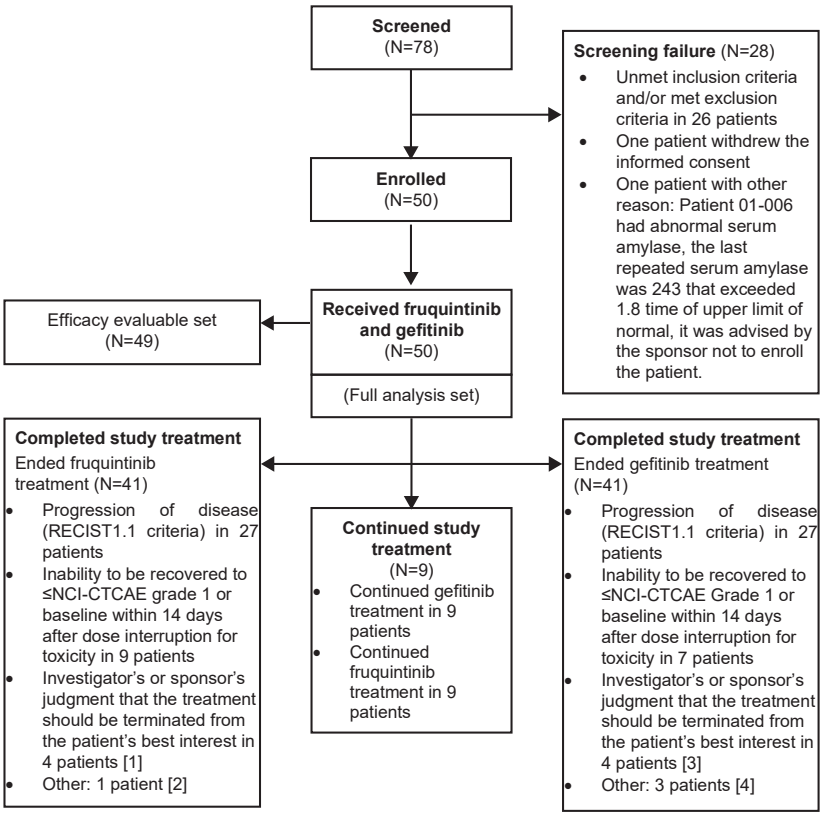

Figure S1 CONSORT diagram. Patient disposition through 28 June 2019. [1], the reason for termination of treatment was recorded as investigator's or sponsor's judgment that the treatment should be terminated for the patient's best interest. Patient 01-014 (date of termination 10 October 2017) experienced a bronchopleural fistula on 9 October 2017, leading to discontinuation of fruquintinib and gefitinib. [2], Patient 02-017 withdrew from the treatment voluntarily after consideration. [3], the reason for termination of treatment was recorded as investigator's or sponsor's judgment that the treatment should be terminated for the patient's best interest. [4], the reason for termination of treatment was recorded as 'other' in Patient 02-013 [voluntary withdrawal for repeated drug-induced liver injury (date of termination 6 February 2018)]; however, the adverse event was recorded as increased glutamic-pyruvate transaminase on October 31, 2017, leading to discontinuation of gefitinib. The reason for termination of treatment was recorded as 'other' in Patient 02-014 (permanent discontinuation of gefitinib for interstitial pneumonia: date of termination 9 April 2018). NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events. Patient 02-017 withdrew from the treatment voluntarily after consideration.

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Table S1 Inclusion and exclusion criteria

Inclusion criteria (all the following conditions had to be met prior to enrollment)

1. Patients understood the study protocol adequately, and voluntarily signed the informed consent form
2. Patients were with histologically and/or cytologically confirmed stage IIIB/IV non-squamous non-small-cell lung cancer (NSCLC) and naïve to the systematic treatment for advanced diseases
3. Presence of epidermal growth factor receptor (EGFR)-sensitive mutation (EGFR exon-19 deletion or exon-21 L858R mutation)
4. Presence of at least one measurable tumor lesion in accordance with RECIST 1.1 criteria [having not received radiotherapy for the lesion, major axis of the lesion ≥10 mm in CT or MRI during baseline screening (minor axis ≥15 mm for lymph node lesion)]
5. Aged 18–75 years
6. Physical performance score (Eastern Cooperative Oncology Group performance status score) 0–1
7. Expected survival >3 months

Exclusion criteria (subjects were excluded from this study if any one of the following criteria were identified)

1. Prior systematic treatment for advanced lung cancer (e.g., chemotherapy, targeted therapy); participation in and administration of the drug in other clinical trials within 4 weeks prior to the first dose of the investigational product; having received biotherapy or immunotherapy within 4 weeks prior to the study treatment; having received the traditional Chinese medicine with antitumor activity within 1 week prior to the study treatment
2. Recurrence or metastasis occurred during or within 1 year after completion of neoadjuvant/adjuvant chemotherapy (if applicable)
3. Received palliative radiotherapy within 1 week prior to the study treatment; proportion of bone marrow >30% at the site receiving radiotherapy within 4 weeks prior to study treatment, or having received radical/extensive radiation therapy (if applicable); brachytherapy within 60 days prior to the first dose of investigational product (e.g., particle implantation)
4. Prior treatment with tyrosine kinase inhibitor (TKI) or monoclonal antibody against EGFR
5. Prior treatment with TKI or monoclonal antibody against vascular endothelial growth factor (VEGF) and/or VEGF receptor
6. Known T790M mutation
7. Received potent inhibitor and/or inducer of cytochrome P450 3A4 (CYP3A4) within 2 weeks prior to the treatment of investigational product
8. Received P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate within 2 weeks prior to the treatment of investigational product
9. Major surgery or large invasive procedure within 60 days prior to the first dose of investigational product; or incomplete recovery from prior surgery/procedure (if applicable)
10. Presence of active brain metastasis prior to the study (no prior radiation to brain or stable of clinical symptoms <4 weeks after brain radiotherapy or having clinical symptoms)
11. Radiological evidence showing tumor invasion to or encompassing major vessels of lungs (e.g., pulmonary artery, superior vena cava)
12. Prior interstitial lung disease, or drug-induced interstitial disease, or radiation pneumonitis requiring hormone therapy, or any active interstitial lung disease with clinical evidence; pulmonary insufficiency requiring oxygen inhalation (judgment criteria: clinical examination or arterial partial pressure of oxygen <70 mmHg
13. Dysphagia or known drug absorption disorder; refractory nausea/vomiting; any serious disease or infection affecting absorption of investigational product, for example, environment-related frequent diarrhea
14. Serious ocular disease (≥ CTCAE grade 2), including but not limited to ulcerative conjunctivitis, ulcerative keratitis, corneal erosion
15. Clinically uncontrolled active infection, including but not limited to acute pneumonia
16. Known history of significant hepatic disease, including but not limited to hepatitis B virus (HBV) infection and positive HBV DNA (≥1×10^4 /mL or ≥2,000 IU/mL); known hepatitis C virus (HCV) infection and positive HCV RNA, or liver cirrhosis
17. Known HIV infection

Table S1 (*continued*)

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Table S1 (*continued*)

18. Currently active duodenal ulcer, ulcerative colitis, intestinal obstruction or other conditions as judged by investigators to possibly cause gastrointestinal hemorrhage or perforation; prior history of intestinal perforation or fistula
19. Other malignant tumors in the past 5 years, except the basal cell carcinoma of skin or cervical carcinoma *in situ* that has received curative therapy
20. Subjects will be excluded for the following conditions
    a. Absolute neutrophil count 9/L, or platelet 9/L, or hemoglobin <9 g/dL in the laboratory examination within 1 week prior to the first dose of investigational product
    s. Serum total bilirubin exceeding upper limits of normal (ULN), or alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) exceeding 1.5 times the ULN (based on the normal value at the clinical study center); ALT or AST exceeding 3 times the ULN for the patients with hepatic metastasis
    d. Presence of clinically significant electrolyte abnormality
    f. Serum creatinine exceeding 1.5 times the ULN (based on the normal value at the clinical study center) or creatinine clearance lower than 60 mL/min
    g. Calculation formula for creatinine clearance rate (Ccr) = (140 – age) × weight (kg)/ [72 × Scr (mg/dl)], or Ccr = [(140 – age) × weight (kg)] × 1.23/ [Scr (μmol/L)], the unit of creatinine should be noted in the calculation of Ccr, the result calculated × 0.85 for women
    h. Urine protein 2+ or above, or 24-hour urine protein quantitation ≥1.0 g/24 h
    j. Activated partial thromboplastin time exceeding 1.5 times the ULN (based on the normal value at the clinical study center) or international normalized ratio >1.5
    h. Uncontrollable hypertension, i.e., systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after drug therapy
    i. Cardiac function assessment: left ventricular ejection fraction <50% (by echocardiogram) moderate or above mitral or tricuspid insufficiency
    j. Acute myocardial infarction, serious/unstable angina pectoris or coronary artery bypass grafting within 6 months prior to the first dose of investigational product; or New York Heart Association grade 2 or above cardiac insufficiency
    k. Stroke event and/or transient ischemic attack within 12 months prior to the first dose of investigational product
    l. Mean QT interval (QTc) corrected using Fridericia formula >470 msec on 12-lead electrocardiogram (ECG) (at least two measurements); calculation formula: QTcF = QTc (Fridericia) = QT/(RR/1000)1/3
21. History of arterial thrombosis or deep venous thrombosis within 6 months prior to the first dose of investigational product, or evidence or history of thrombotic or hemorrhagic tendency within 2 months prior to enrollment (e.g., ≥3 cm hepatic hemangioma), regardless of severity; history of hemoptysis (defined as blood loss >2.5 mL, and blood appearing bright red) within 1 month prior to enrollment
22. Current (within 10 days prior to the first dose of investigational product) use of thrombolytic therapy or therapeutic use of anticoagulant (except preventive use of anticoagulants)
23. Incomplete recovery of serious ulcer or fracture at skin wound, site of trauma or mucosa
24. Pregnant or lactating women or positive pregnancy test for females of childbearing potential prior to the first dose (if applicable)
25. Patients who have childing-bearing potential but are not willing to use contraceptive measures, or whose sex partners who are not willing to use contraceptive measures
26. Presence of any clinical or laboratory abnormality regarded inappropriate to participate in this clinical study, as considered by investigators
27. Presence of serious psychological or mental abnormality, poor compliance with participation in this clinical study as evaluated
28. Serious allergic reaction to the active substance of fruquintinib and/or gefitinib and/or any excipient in the investigational product

CT, computerized tomography; MRI, magnetic resonance imaging CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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Table S2 Exposure to investigational treatment (FAS)

Parameters	Fruquintinib [4 mg QD (Cycle1†) then 5 mg] + Gefitinib 250 mg QD (N=26)		Fruquintinib (4 mg QD) + Gefitinib 250 mg QD (N=24)		Total (N=50)	
	Fruquintinib	Gefitinib	Fruquintinib	Gefitinib	Fruquintinib	Gefitinib
Median duration of exposure (months)‡	12.8	12.8	13.3	13.3	12.9	12.9
Range (min–max)	2.5–28.1	2.3–28.1	0.5–19.3	0.5–19.3	0.5–28.1	0.5–28.1
Mean RDI§, n (%)	0.78 (0.183)	0.96 (0.075)	0.82 (0.153)	0.97 (0.042)	0.80 (0.168)	0.97 (0.061)

†, Cycle 1 was 4 weeks duration; ‡, duration of exposure to fruquintinib (months) = (end date of fruquintinib therapy – date of the first dose of fruquintinib + 1)/30.4375. Duration of exposure included the time for dose interruption. Duration of exposure to gefitinib (months) = (date of the last dose of gefitinib – date of the first dose of gefitinib +1)/30.4375. Duration of exposure included the time for dose interruption. §, relative dose intensity (RDI) = dose intensity/planned dose intensity. FAS, full analysis set; qd, once daily.

Table S3 Summary of AEs leading to discontinuation and dose adjustment, SAEs and AEs leading to death—FAS

Parameters	Fruquintinib [4 mg qd (Cycle 1†) then 5 mg] + gefitinib 250 mg qd (N=26), n (%)	Fruquintinib (4 mg qd) + gefitinib 250 mg qd (N=24), n (%)	Total (N=50), n (%)
AEs leading to discontinuation of fruquintinib	6 (23.1)	4 (16.7)	10 (20.0)
AEs leading to adjustment of fruquintinib dose‡	20 (76.9)	17 (70.8)	37 (74.0)
AEs leading to discontinuation of gefitinib	6 (23.1)	4 (16.7)	10 (20.0)
AEs leading to interruption of gefitinib dose§	15 (57.7)	15 (62.5)	30 (60.0)
SAEs	6 (23.1)	3 (12.5)	9 (18.0)
AE leading to death‖	3 (11.5)	0	3 (6.0)

†, Cycle 1 was 4 weeks duration; ‡, dose adjustment included dose interruption and reduction. The adverse events (AEs) leading to dose adjustment did not include the AEs leading to discontinuation of the study treatments however, dose interruption for an AE was recorded in the drug record form for the four patients; §, the AEs leading to dose interruption did not include the AEs leading to discontinuation of the study treatments however, dose interruption for an AE was recorded in the drug record form for the four patients; ‖, patient 01-013 received treatment for 257 days, and died (AE term: acute cerebral infarction) 20 days after the last dose of study treatment; Patient 01-014 received the treatment for 109 days, and died (AE term: death) from progression of disease 26 days after the last dose of study treatment; Patient 01-024 received the treatment for 104 days, and died (AE term: death) of unknown cause 19 days after the last dose of study treatment. Investigators concluded that three deaths as possibly unrelated to fruquintinib and gefitinib. AE, adverse event; qd, once daily; SAE, serious adverse event.

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Table S4 Adverse events of special interest (incidence in ≥20% of all patients) summarized by preferred term—FAS

AESI category/preferred term	Fruquintinib [4 mg qd (Cycle 1[†]) then 5 mg] + gefitinib qd (N=26), n (%)		Fruquintinib (4 mg qd) + gefitinib qd (N=24), n (%)		Total (N=50), n (%)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any (AESI)[‡] specified in the protocol	26 (100.0)	13 (50.0)	24 (100.0)	8 (33.3)	50 (100.0)	21 (42.0)
Hepatotoxicity[§]	25 (96.2)	10 (38.5)	20 (83.3)	3 (12.5)	45 (90.0)	13 (26.0)
Aspartate aminotransferase increased	23 (88.5)	4 (15.4)	19 (79.2)	1 (4.2)	42 (84.0)	5 (10.0)
Alanine aminotransferase increased	22 (84.6)	9 (34.6)	19 (79.2)	2 (8.3)	41 (82.0)	11 (22.0)
Bilirubin conjugated increased	14 (53.8)	1 (3.8)	8 (33.3)	1 (4.2)	22 (44.0)	2 (4.0)
Blood bilirubin increased	10 (38.5)	0	5 (20.8)	0	15 (30.0)	0
Gamma-glutamyltransferase increased	5 (19.2)	2 (7.7)	7 (29.2)	1 (4.2)	12 (24.0)	3 (6.0)
Thyroid dysfunction	25 (96.2)	0	19 (79.2)	0	44 (88.0)	0
Blood thyroid stimulating hormone increased	23 (88.5)	0	14 (58.3)	0	37 (74.0)	0
Hyperthyroidism	8 (30.8)	0	10 (41.7)	0	18 (36.0)	0
Proteinuria	18 (69.2)	3 (11.5)	20 (83.3)	1 (4.2)	38 (76.0)	4 (8.0)
Proteinuria	18 (69.2)	3 (11.5)	20 (83.3)	1 (4.2)	38 (76.0)	4 (8.0)
Skin toxicity	19 (73.1)	1 (3.8)	14 (58.3)	3 (12.5)	33 (66.0)	4 (8.0)
Palmar-plantar erythrodysesthesia syndrome	11 (42.3)	0	6 (25.0)	0	17 (34.0)	0
Dermatitis acneiform	8 (30.8)	0	6 (25.0)	0	14 (28.0)	0
Rash	5 (19.2)	0	5 (20.8)	1 (4.2)	10 (20.0)	1 (2.0)
Hemorrhage	15 (57.7)	0	16 (66.7)	0	31 (62.0)	0
Upper gastrointestinal hemorrhage	9 (34.6)	0	9 (37.5)	0	18 (36.0)	0
Hypertension	9 (34.6)	2 (7.7)	6 (25.0)	1 (4.2)	15 (30.0)	3 (6.0)
Hypertension	5 (19.2)	1 (3.8)	6 (25.0)	1 (4.2)	11 (22.0)	2 (4.0)

[†], Cycle 1 was 4 weeks duration; [‡], adverse event of special interest (AESIs) specified in the protocol were determined in accordance with standardized MedDRA Query (SMQ) terms. In case the same adverse event occurred multiple times for the same patient, the event could only be counted once in calculation by the same AESI category and preferred term for the patient; [§], hepatotoxicity was defined as transaminase abnormal, hepatic function abnormal or liver injury. FAS, full analysis set; qd, once daily.

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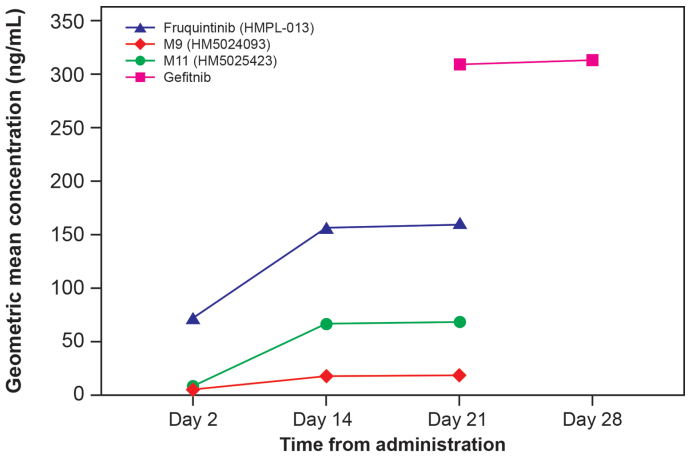

Figure S2 Geometric mean plasma concentrations (ng/mL) of study treatments over Cycle 1. Mean plasma concentrations of fruquintinib (HMPL-013) (4 mg), and its metabolites M11 (HM5025423) and M9 (HM5024093), taken at Day 2, 14, and 21 of Cycle 1. Mean plasma concentrations of gefitinib (250 mg) taken at Day 21 and 28 of Cycle 1.

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