Supplementary

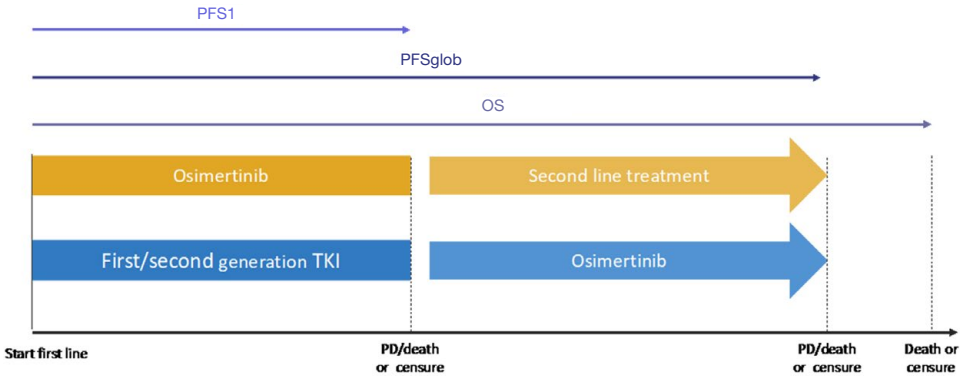

Figure S1 Summary of the study endpoints. PFS1, progression-free survival for first line; PFSglob, progression-free survival of the global strategy; OS, overall survival.

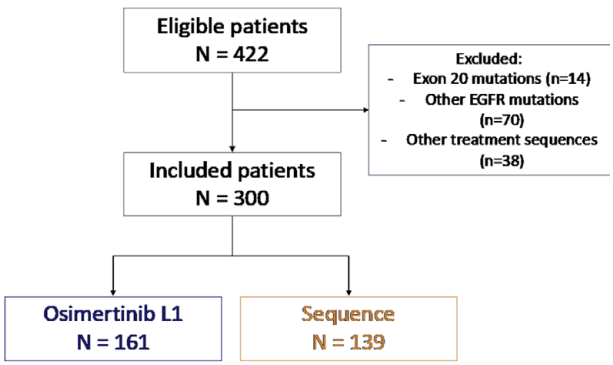

Figure S2 Flowchart of the study.

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Table S1 Patients characteristics in the propensity score population

Characteristics	Whole sample (N=192)	Osimertinib (N=96)	Sequence (N=96)	P
Age, >65 years	95 (49.5%)	45 (46.9%)	50 (52.1%)	0.47
Gender, female	140 (72.9%)	68 (70.8%)	72 (75%)	0.52
Smoking history				0.10
Former	61 (32.4%)	37 (38.9%)	24 (25.8%)	
Never smoker	113 (60.1%)	50 (52.6%)	63 (67.7%)	
Current	14 (7.5%)	8 (8.5%)	6 (6.5%)	
Missing	4	1	3	
TP53 co mutation				0.18
Not done	79 (45.9%)	34 (39.1%)	45 (52.9%)	
Yes	20 (11.6%)	12 (13.8%)	8 (9.4%)	
Missing	20	9	11	
Stage at EGFR TKI start				0.87
IV	174 (93.5%)	88 (94.6%)	86 (92.5%)	
Missing	6	3	3	
N metastatic sites, >3	41 (21.4%)	20 (20.8%)	21 (21.9%)	0.86
Metastatic location				
Liver	24 (12.5%)	12 (12.5%)	12 (12.5%)	>0.99
Pleura	68 (35.8%)	32 (33.3%)	36 (38.3%)	0.47
Lung	100 (52.1%)	49 (51%)	51 (53.1%)	0.77
Bone	98 (51%)	51 (53.1%)	47 (49%)	0.56
CNS	46 (24%)	24 (25%)	22 (22.9%)	0.73
Soft tissue	3 (1.6%)	0 (0%)	3 (3.2%)	0.35
Missing	2	1	1	
Tumour burden, high	67 (34.9%)	35 (36.5%)	32 (33.3%)	0.65
ECOG PS, 2–4	21 (10.9%)	12 (12.5%)	9 (9.4%)	0.49

CNS, central nervous system; high tumour burden, >3 metastatic location and/or CNS involvement; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

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Table S2 Multivariable Cox models for OS, PFSglob and PFS1 (n=225)

Variables	Overall survival		Progression-free survival global strategy		Progression-free survival L1	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, >65 years	1.58 (1.02–2.46)	0.04	1.17 (0.91–1.69)	0.40	1.08 (0.78–1.51)	0.63
Smoking history		0.06		0.06		0.05
Former	0.50 (0.22–1.14)		0.71 (0.31–1.58)		0.65 (0.32–1.32)	
Never	0.39 (0.18–0.87)		0.49 (0.23–1.07)		0.48 (0.24–0.95)	
Number of metastatic sites, >4	1.12 (0.61–2.07)	0.71	1.22 (0.69–2.15)	0.49	1.06 (0.64–1.78)	0.81
Metastatic sites						
Liver	1.50 (0.82–2.74)	0.19	1.41 (0.84–2.38)	0.19	1.44 (0.85–2.42)	0.17
CNS	1.11 (0.66–1.86)	0.70	1.20 (0.76–1.87)	0.43	1.20 (0.81–1.78)	0.37
Soft tissue	3.46 (0.99–12.11)	0.05	3.37 (1.12–10.12)	0.03	4.97 (1.62–15.29)	<0.01
ECOG PS, 2–4	4.01 (2.19–7.37)	<0.001	3.28 (1.86–5.79)	<0.001	2.83 (1.66–4.84)	<0.001
Treatment group, sequence	0.71 (0.44–1.17)	0.18	0.89 (0.59–1.35)	0.59	1.93 (1.34–2.76)	<0.001

CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS1, progression-free survival for first line; PFSglob, progression-free survival of the global strategy.

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Table S3 Subgroups analysis for response and progression-free survival endpoints

Subgroups analysis	Patients (n)	ORR L1	P	PFS L1 18 months	mPFS L1	Log-rank	OS 24 months	mOS	Log-rank	PFS glob 24 months	mPFS glob	Log-rank
CNS involvement												
Osimertinib	66	90.8%		53.5% (41.8–68.4)	18.4 (15.7–33.9)		58.3% (45.8–74.2)	26.4 (20.4–NR)		52.2% (40.1–68.1)	25.6 (17.2–NR)	
Seq osi	35	88.2%	0.73	27.6% (15.8–48.0)	12.0 (10.1–16.9)	<0.0001	79.4% (66.8–94.3)	38.1 (33.0–52.3)	0.10	58.8% (44.3–78.0)	28.7 (19.6–32.9)	0.80
No CNS involvement												
Osimertinib	94	73.6%		52.4% (42.5–64.7)	19.7 (14.3–NR)		65.2% (54.8–77.5)	NR (NR–NR)		57.2% (46.4–70.4)	35.5 (20.5–NR)	
Seq osi	104	86.5%	0.02	53.4% (44.6–64.0)	19.3 (16.1–23.0)	0.30	79.7% (72.3–87.9)	45.8 (41.5–63.2)	0.06	68.3% (59.9–77.8)	37.9 (31.2–43.5)	0.07
Good PS												
Osimertinib	111	80.9%		60.8% (51.7–71.4)	24.2–18.4–NR)		71.1% (61.9–81.7)	NR (NR–NR)		64.3% (54.9–75.4)	35.5 (25.9–NR)	
Seq osi	89	86.4%	0.31	47.7% (38.3–59.4)	17.0 (14.1–20.7)	0.001	80.6% (72.8–89.3)	51.2 (41.2–67.5)	0.20	66.1% (56.9–76.7)	28.3 (24.1–NR)	0.80
Poor PS (≥2)												
Osimertinib	30	85.2%		38.2% (23.0–63.3)	11.17 (4.27–NR)		45.8% (28.7–73)	19.8 (8.5–NR)		40.1% (22.4–71.7)	20.50 (4.76–NR)	
Seq osi	9	88.9%	>0.99	0%	10.97 (4.37–NR)	0.20	29.6% (10.0–87.5)	22.2 (15.7–NR)	>0.99	16.7% (3.1–88.2)	19.61 (8.02–NR)	0.60
Low tumour burden												
Osimertinib	77	71.6%		54.5% (43.7–68.0)	23.3 (14.3–NR)		67.5% (56.3–81.0)	NR (NR–NR)		62.6% (51.5–76.1)	35.5 (23.9–NR)	
Seq osi	89	89.9%	0.003	58.0% (48.5–69.3)	20.4 (17.0–23.7)	0.70	80.9% (73.1–89.5)	53.8 (43.1–68.7)	0.07	71.9% (63.1–81.9)	38.5 (32.4–45.6)	0.05
High tumour burden												
Osimertinib	81	90%		51.2% (40.4–64.8)	18.13 (15.34–33.9)		57.9% (46.5–72.1)	26.4 (20.4–NR)		50.7% (39.5–65.2)	25.6 (17.7–NR)	
Seq osi	47	82.6%	0.23	24.6% (14.7–41.1)	11.79 (9.63–15.9)	<0.0001	78.0% (66.8–91.1)	35.2 (32.0–48.1)	0.10	54.3% (41.5–70.9)	26.1 (19.6–31.2)	>0.99
Liver metastasis												
Osimertinib	23	86.4%		41.7% (24.6–70.9)	15.34 (11.17–NR)		35.2% (18.1–68.3)	19.0 (16.8–NR)		31.6% (15.5–64.4)	17.7 (15.01–NR)	
Seq osi	19	78.9%	0.68	5.6% (1.0–37.3)	9.66 (7.62–14.1)	0.006	56.8% (38.1–84.9)	38.1 (20.1–52.3)	0.50	42.1% (24.8–71.3)	14.8 (12.91–32.9)	0.70
No liver metastasis												
Osimertinib	137	79.9%		54.8% (46.4–64.7)	23.3 (16.2–33.8)		68.2% (59.7–77.9)	NR (26.5–NR)		60.1% (51.2–70.6)	30.1 (25.6–NR)	
Seq osi	119	88.1%	0.07	53.9% (45.6–63.7)	19.3 (16.1–21.6)	0.20	82.9% (76.3–90.0)	51.2 (41.2–63.2)	0.01	70.3% (62.5–79.0)	36.0 (30.8–39.4)	0.02

Data in parentheses are presented as (95% CI). CI, confidence interval; CNS, central nervous system; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

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