Real-World Outcomes of Sequential Afatinib and Osimertinib Versus Afatinib and Chemotherapy in EGFR-Mutant NSCLC: Taiwan Multicenter GIANT Study

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Table S1. Details of chemotherapeutic regimens among afatinib-chemotherapy patients.

Characteristic	**N = 430**[a]
Chemotherapy*	
Platinum-based chemotherapy	118 (27%)
Non-platinum-based chemotherapy	36 (8.4%)
TKIs ± chemotherapy	32 (7.4%)
Chemotherapy + anti-VEGF	22 (5.1%)
Chemotherapy + immunotherapy	15 (3.5%)
Undefined chemotherapeutic regimen	191 (44%)
Others	16 (3.7%)

[a] n (%)

* Platinum-based chemotherapy included cisplatin/carboplatin with etoposide, pemetrexed, gemcitabine, vinorelbine, paclitaxel, and/or docetaxel. Non-platinum based chemotherapy included pemetrexed, gemcitabine, vinorelbine, or docetaxel. TKIs included gefitinib, erlotinib, capmatinib, and savolitinib. Anti-VEGF included bevacizumab, bevacizumab biosimilar, or Ramucirumab. Immunotherapy included durvalumab, tremelimumab, atezolizumab, pembrolizumab, or nivolumab. Others included radiotherapy with or without chemotherapy, hospital care, trastuzumab, and gefitinib with bevacizumab.

Table S2. T790M test sample type and results after disease progression between the two treatment groups.

Characteristics	**Chemotherapy or other lines (N = 430[a])**	**Osimertinib (N = 303[a])**	**Overall (N = 733[a])**	**p-value[b]**
T790M test after disease progression				<0.001
Positive	39 (17%)	250 (96%)	289 (59%)	
Negative	188 (83%)	10 (3.8%)	198 (41%)	
Unknown/ not done	203	43	246	
T790M sample type				0.9
Tissue	180 (78%)	208 (79%)	388 (78%)	
Liquid	44 (19%)	50 (19%)	94 (19%)	
Both	7 (3.0%)	6 (2.3%)	13 (2.6%)	
Unknown	199	39	238	
T790M test method				0.032
ARMS	121 (68%)	136 (61%)	257 (64%)	
Others	42 (23%)	53 (24%)	95 (24%)	
NGS	14 (7.8%)	35 (16%)	49 (12%)	
De novo T790M	2 (1.1%)	0 (0%)	2 (0.5%)	
Unknown	251	79	330	

[a] n (%)

[b] Pearson's Chi-squared test

Table S3. T790M test results after disease progression between EGFR groups.

Characteristic	Del19 (N = 360[a])	L858R (N = 372[a])	p-value[b]
T790M test after disease progression			0.3
Negative	94 (38%)	103 (43%)	
Positive	153 (62%)	136 (57%)	
Unknown/ not done	113	133	

[a] n (%)

[b] Pearson's Chi-squared test

Table S4. Comparison of patients with and without brain metastasis according to EGFR mutation and treatment group.

	Arm	**Chemotherapy (N = 430[a])**	**Osimertinib (N = 303[a])**	**p-value[b]**
EGFR mutation	Characteristic			
Del19	Brain metastasis	25.6 (21.3, 34.1), N = 73	53.2 (49.8, 67), N = 54	<0.001
	Without brain metastasis	34.1 (31.5, 43.1), N = 142	58.6 (53.5, NA), N = 91	<0.001
L858R	Brain metastasis	27.7 (22.1, 34.4), N = 72	51 (41.4, NA), N = 42	<0.001
	Without brain metastasis	34.5 (31.8, 47.2), N = 143	57.7 (41.2, 69.5), N = 115	<0.001

[a] months; median survival; 95% CI (N)

[b] Log-rank test

Table S5. Baseline characteristics and clinical outcomes of the patients enrolled in the GIANT study and the MARIPOSA-ASIAN and FLAURA-2 trials.

	GIANT			**MARIPOSA-ASIAN**			**FLAURA-2**		
	Sequential afatinib-chemotherapy (N=430)[a]	**Sequential afatinib-osimertinib (N=303)[a]**	**p-value**	**Amivantamab-lazertinib (N = 250)**	**Osimertinib (N = 251)**	**p-value**	**Osimertinib + chemotherapy (N=279)[a]**	**Osimertinib (N=278)[a]**	**p-value**
Note	1125 cases → 733 cases (2016-2023) included in this table								
Study period	2016-2023			2020-2022			2020-2021		
Sex			0.055						
Male	189 (44%)	112 (37%)		98 (39%)	108 (43%)		106 (38%)	109 (39%)	
Female	241 (56%)	191 (63%)		152 (61%)	143 (57%)		173 (62%)	169 (61%)	
Age (years)	61 (30-89)	63 (29-95)	0.059	63 (range: 35-85)	63 (range: 28-88)		61 (26-83)	62 (30-85)	
Ethnic origin				Region of enrollment					
Asian	-	-		245 (98%)	242 (96%)		179 (64%)	176 (63%)	
Non-Asian	-	-		5 (2%)	9 (4%)		100 (36%)	102 (37%)	
Histology			0.2						
Adenocarcinoma	425 (99%)	302 (100%)		244 (97%)	239 (95%)		275 (99%)	275 (99%)	
Squamous cell carcinoma	1 (0.2%)	1 (0.3%)					0	0	
Adenosquamous carcinoma	-	-		4 (2%)	4 (2%)		2 (1%)	0	
Others	4 (0.9%)	0		2 (1%)	8 (3%)		2 (1%)	3 (1%)	
Disease extent			0.4						
Locally advanced	6 (1%)	1 (0.3%)		-	-		14 (5%)	7 (3%)	
Metastatic	411 (99%)	288 (99.7%)		-	-		265 (95%)	271 (97%)	
Unknown				-	-		0	0	
Baseline ECOG performance status			0.3						
0	106 (25%)	92 (30%)		69 (28%)	84 (33%)		104 (37%)	102 (37%)	

	GIANT			MARIPOSA-ASIAN			FLAURA-2		
	Sequential afatinib-chemotherapy (N=430)[a]	**Sequential afatinib-osimertinib (N=303)[a]**	**p-value**	**Amivantamab-lazertinib (N = 250)**	**Osimertinib (N = 251)**	**p-value**	**Osimertinib + chemotherapy (N=279)[a]**	**Osimertinib (N=278)[a]**	**p-value**
1	303 (70%)	190 (63%)		181 (72%)	167 (67%)		174 (62%)	176 (63%)	
2	21 (4.9%)	20 (6.6%)		0	0		1 (<1%)	0	
Unknown	0	1					0	0	
EGFR mutation			0.6						
Del19	215 (50%)	145 (48%)		138 (55%)	139 (55%)		169 (61%)	168 (60%)	
L858R	215 (50%)	157 (52%)		113 (45%)	112 (45%)		106 (38%)	107 (38%)	
Both Del19 and L858R mutation	-	-		-	-		3 (1%)	1 (<1%)	
Uncommon mutations	-	-		-	-		1 (<1%)	2 (1%)	
Smoking status			0.023						
Never	317 (74%)	245 (81%)		180 (72%)	181 (72%)		-	-	
Current or former	113 (26%)	58 (19%)		70 (28%)	70 (28%)		-	-	
Unknown	-	-		-	-		-	-	
Brain metastasis (yes)	145 (34%)	96 (32%)	0.5	110 (44%)	108 (43%)		116 (42%)	110 (40%)	
Liver metastasis (yes)	48 (13%)	50 (20%)	0.028	-	-		43 (15%)	66 (24%)	
Unknown	67	51		-	-		-	-	
Bone and locomotor-system metastases (yes)	232 (60%)	154 (58%)	0.7	-	-		132 (47%)	142 (51%)	
Unknown	41	39		-	-		-	-	

	GIANT			MARIPOSA-ASIAN			FLAURA-2		
	Sequential afatinib-chemotherapy (N=430)[a]	**Sequential afatinib-osimertinib (N=303)[a]**	**p-value**	**Amivantamab-lazertinib (N = 250)**	**Osimertinib (N = 251)**	**p-value**	**Osimertinib + chemotherapy (N=279)[a]**	**Osimertinib (N=278)[a]**	**p-value**
Follow-up duration (months; median)	28 (IQR: 17, 43)	44 (IQR: 29, 60)	<0.001	22.5			19.5 (range: 0- 33.3) Updated*: Osi+CTx 51.2 (range: 0.2- 60.4) Osi mono 51.3 (range: 0.1- 60.1)		
OS (months; median survival; 95% CI) (N)	For 1125 cases: 39.4 (37.2, 43.2)		<0.001	NA (NA, NA) (250)	NA (NA, NA) (251)	0.38	Updated*: 47.5 (41, NA)	Updated*: 37.6 (33.2, 43.2)	
	32.3 (30.3, 34.5) (430)	55 (53.2, 66.4) (303)							
OS- Del19 (months; median survival; 95% CI) (N)	31.6 (28.6, 38.1) (215)	54.2 (53.5, 71.2) (145)	0.0014	-	-		-	-	
OS- L858R (months; median survival; 95% CI) (N)	32.7 (30.2, 35.6) (215)	55.2 (43.3, 69.4) (157)	0.0012	-	-		-	-	
Hazard ratio for OS (95% CI)	-	Adjusted HR: 0.43 (0.35, 0.52)	<0.001	0.84 (0.58, 1.23)	-	0.38	Updated*: 0.77 (0.61, 0.96)	-	**0.02**

[a] Median (IQR) or n (%) unless otherwise specified.

* Recently released unpublished data provided by the study investigators.

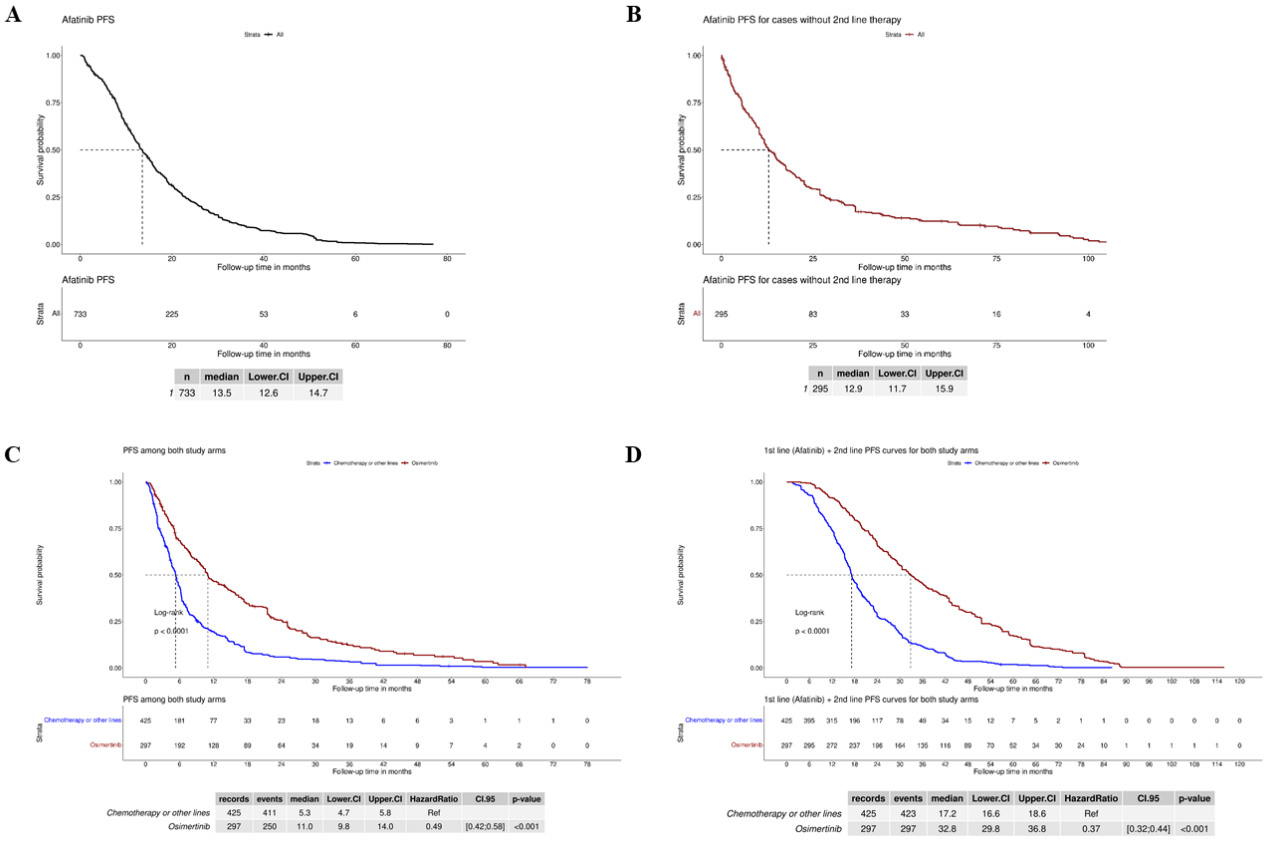


Figure S1. Kaplan–Meier curves for PFS among the patients enrolled in the GIANT study: (A) PFS of first-line afatinib for the study cohort, (B) PFS of first-line afatinib for patients not receiving a second-line therapy (excluded from the GIANT cohort), (C) second-line PFS (PFS-2) for osimertinib and chemotherapy groups, and (D) combined first-line and second-line PFS for afatinib-osimertinib and afatinib-chemotherapy groups.

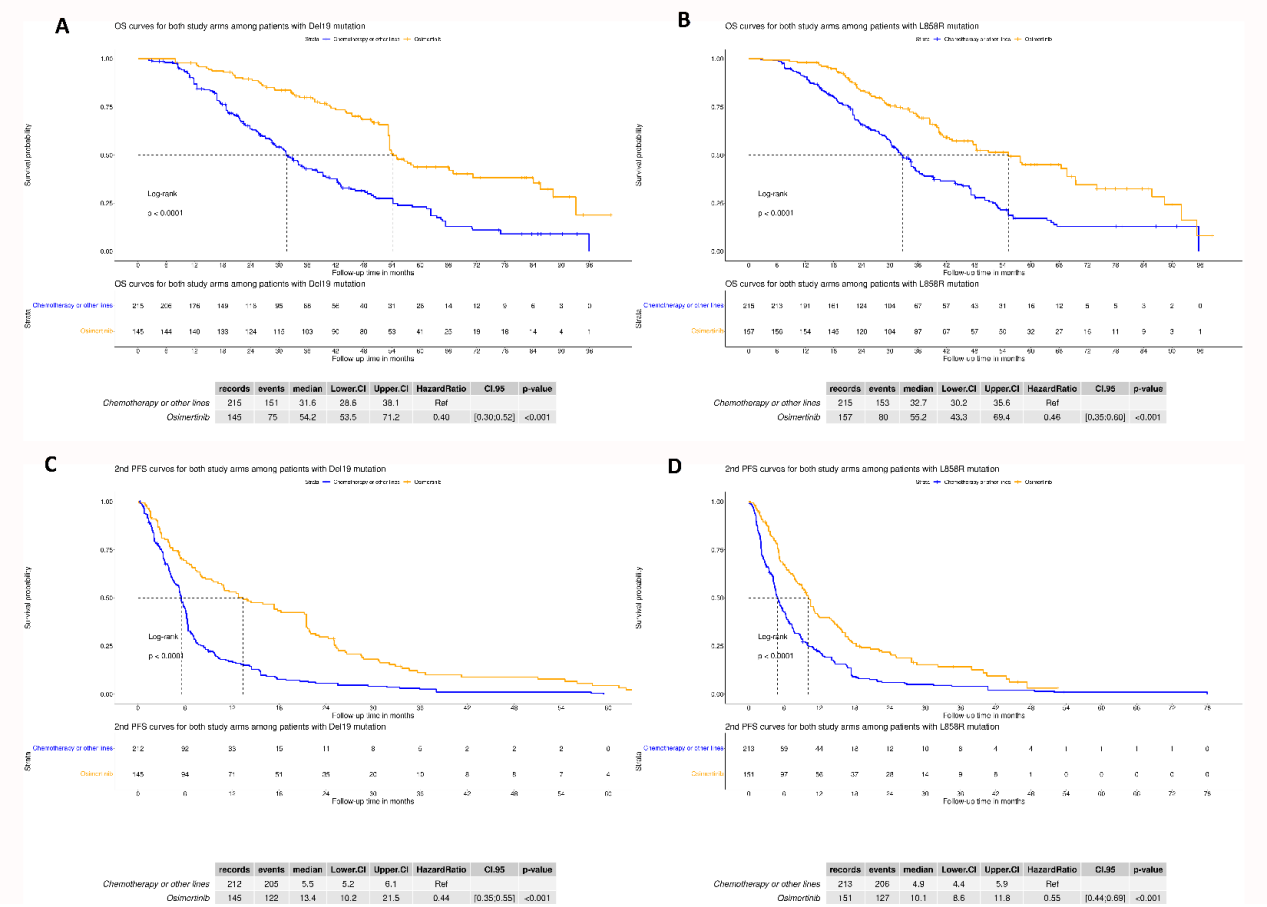
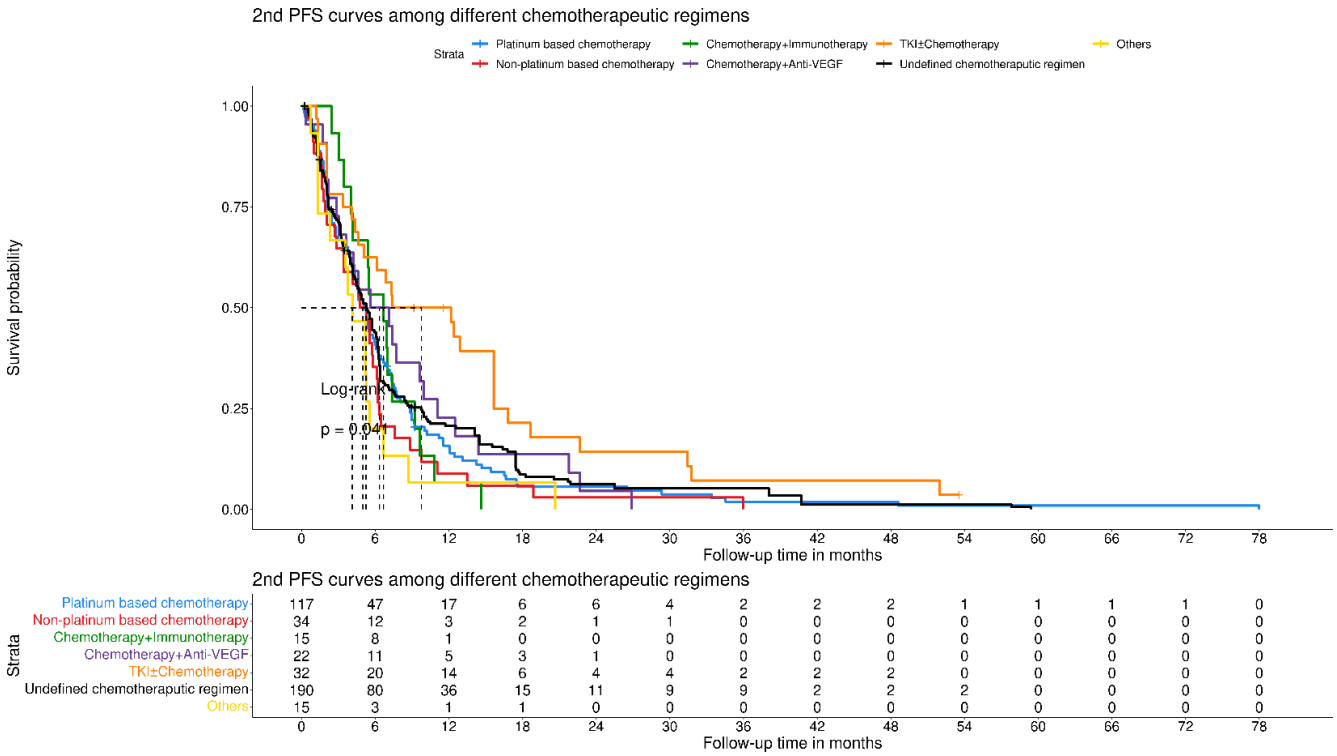
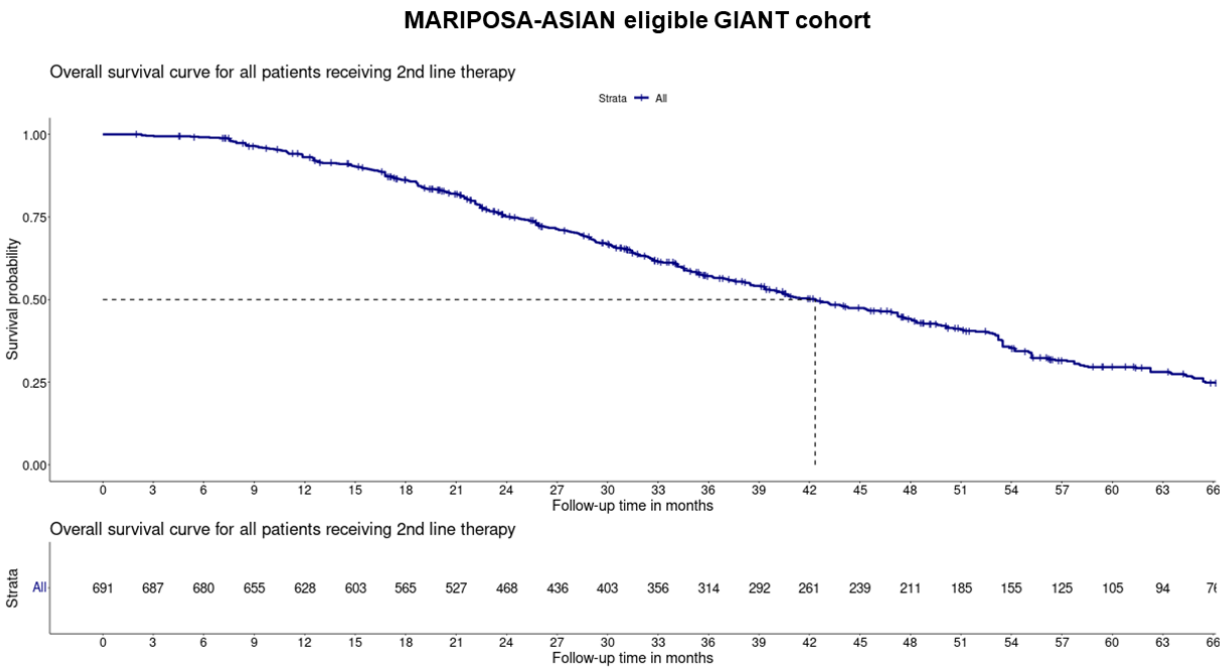


Figure S2. Kaplan-Meier survival curves of treatment groups stratified by EGFR: (A) OS of Del19 patients, (B) OS of L858R patients, (C) PFS-2 of Del19 patients, and (D) PFS-2 of L858R patients.



	records	events	median	Lower.CI	Upper.CI	HazardRatio	CI.95	p-value
Platinum based chemotherapy	117	114	5.2	4.3	6.1	Ref		
Non-platinum based chemotherapy	34	34	5.0	3.4	6.2	1.23	[0.84;1.81]	0.28255
Chemotherapy+Immunotherapy	15	15	6.7	4.2	9.6	1.01	[0.59;1.73]	0.97905
Chemotherapy+Anti-VEGF	22	22	6.3	3.6	11.1	0.86	[0.55;1.37]	0.53302
TKI±Chemotherapy	32	29	9.8	5.1	15.7	0.58	[0.38;0.87]	0.00827
Undefined chemotheraputic regimen	190	182	5.3	4.4	6.2	0.93	[0.74;1.18]	0.55569
Others	15	15	4.1	2.3	6.7	1.46	[0.85;2.51]	0.16843

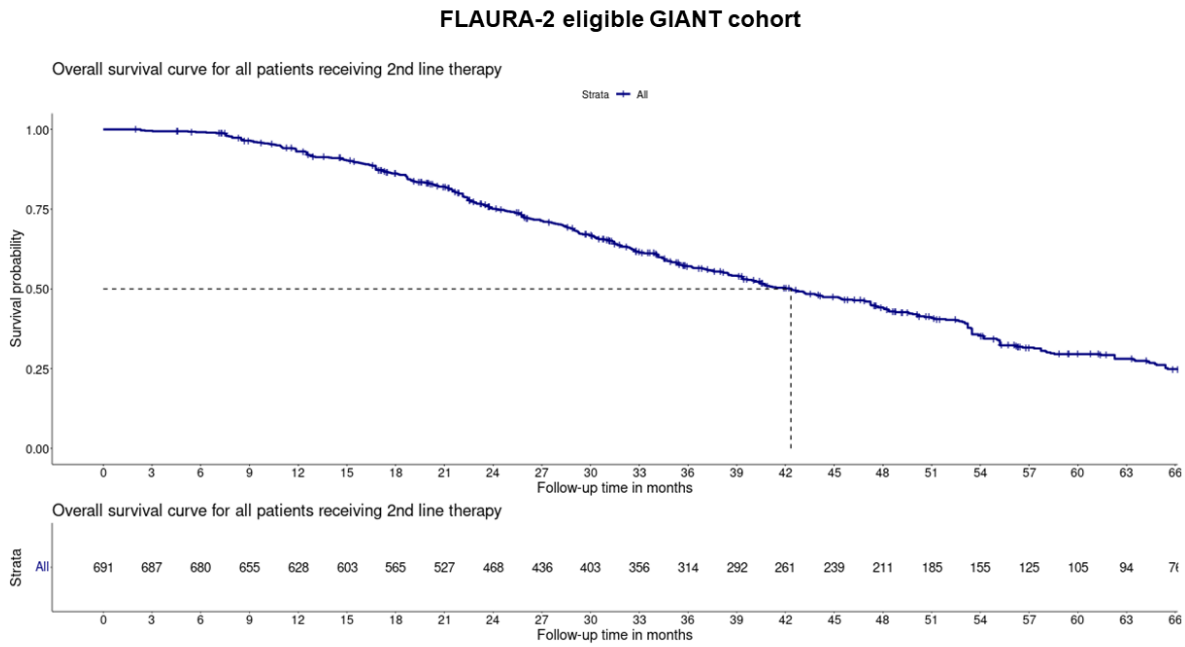
Figure S3. Kaplan–Meier curves for second-line PFS (PFS-2) of the afatinib-chemotherapy group stratified by the chemotherapeutic regimens.



	n	median	Lower.CI	Upper.CI
1	691	42.3	39.3	47.2

Characteristic	12-month OS% (95% CI)	24-month OS% (95% CI)	36-month OS% (95% CI)
Overall	93% (91%, 95%)	75% (72%, 78%)	57% (53%, 61%)

Figure S4. Kaplan–Meier OS curves for MARIPOSA-ASIAN-eligible GIANT patient cohort.



	n	median	Lower.CI	Upper.CI
1	691	42.3	39.3	47.2

Characteristic	12-month OS% (95% CI)	24-month OS% (95% CI)	36-month OS% (95% CI)
Overall	93% (91%, 95%)	75% (72%, 78%)	57% (53%, 61%)

Figure S5. Kaplan–Meier OS curves for FLAURA2-eligible GIANT patient cohort.