MADRID 2023 ESMO congress

LBA66: Afatinib versus chemotherapy for treatment-naïve non-small cell lung cancer with a sensitizing uncommon epidermal growth factor receptor mutation: a phase III study (ACHILLES/TORG1834)

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DECLARATION OF INTERESTS

Presenter: Satoru Miura, Niigata Cancer Center Hospital

Honoraria: Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Eli Lilly, Boehringer-Ingelheim Japan Ono Pharmaceutical, AstraZeneca, Novartis, MSD, Bristol-Myers Squibb, Kyowa Hakko Kirin, Daiichi Sankyo, Nippon Kayaku, AMGEN, Merck, Takeda Pharmaceutical

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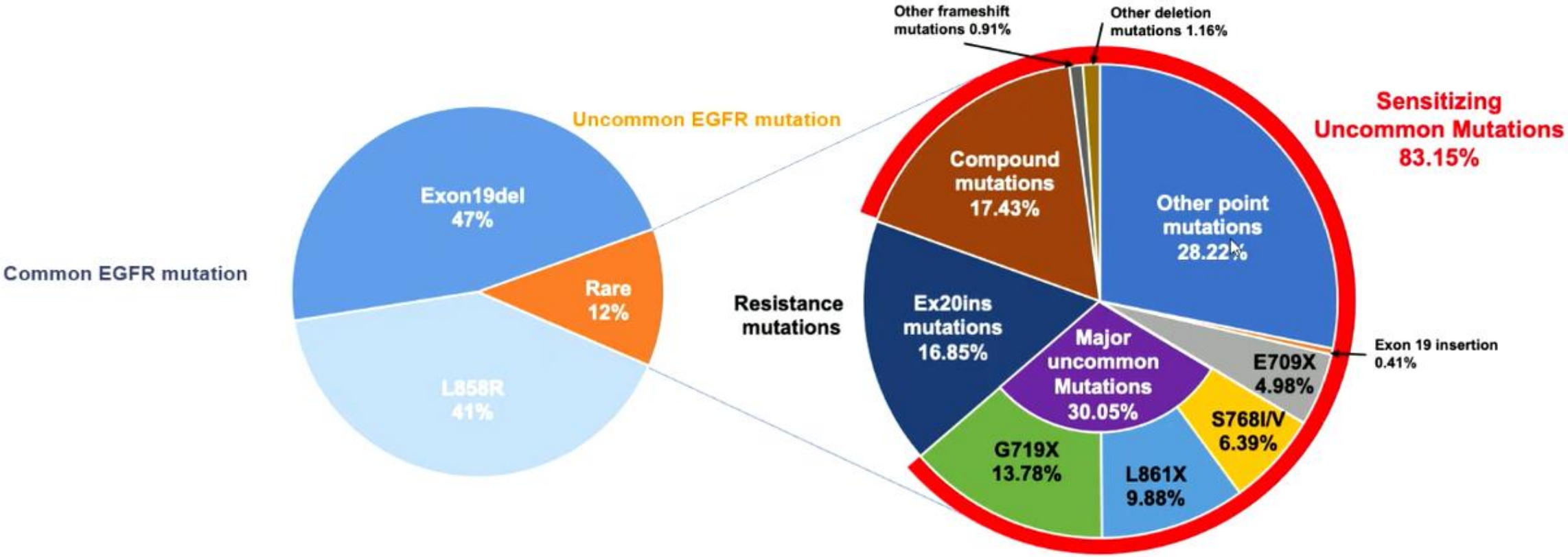
Uncommon/Compound *EGFR* mutations

- The development of gene detection methods has revealed the diversity of *EGFR* mutations.
- We classified uncommon/compound *EGFR* mutations without Exon 20 insertion and de-novo T790M mutation as “sensitizing uncommon mutations”.



Harrison PT et al. *Semin Cancer Biol.* 2020;61:167

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Rationale

- EGFR-tyrosine kinase inhibitor (TKI) based therapy has been the standard treatment for patients with common *EGFR*-positive non-small cell lung cancer (NSCLC) patients.
- No randomized phase III study has been conducted in patients with “sensitizing uncommon mutations”.
- There is no conclusion on whether EGFR-TKI is the optimal initial treatment for this population.

- Afatinib has a broad-range antitumor activity for various *EGFR* mutations.
- Post-hoc combined analysis (LUX-Lung 2, 3, and 6) and retrospective studies have demonstrated promising activities for this population [1-3].

- Here, we report the first result of the randomized phase III study, ACHILLES/TORG1834 study, comparing afatinib and chemotherapy, in sensitizing uncommon *EGFR* mutant NSCLC.

1) Yang et al. *Lancet Oncol*. 2015;16:830.
2) Popat et al. *Oncologist*. 2022; 27(4): 255-26
3) Yang et al. *Front Oncol*. 2022; 12: 834704

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Study design ~ACHILLES/TORG1834~

Key inclusion criteria

Locally advanced/metastatic Non-Sq NSCLC
≥20 years
ECOG performance status 0 / 1
Sensitizing uncommon mutation*
No prior systemic anticancer /EGFR-TKI therapy
Stable CNS metastases allowed

Stratification factors
Mutation status (Single vs Compound)
Stage (III/IV vs Recurrence)
CNS metastasis (Yes vs No)
Afatinib dose (30 mg vs 40 mg)

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1 → **Platinum + Pemetrexed ** Until PD (n=36)**

2 → **Afatinib 40mg or 30mg *** Until PD (n=73)**

Clinical trial information: jRCTs031180175

* Uncommon/Compound EGFR mutations without exon 20 insertions and de-novo T790M mutations

** Cisplatin 75 mg/m^2 or carboplatin (AUC 5 or 6) and pemetrexed (500 mg/m^2), followed by pemetrexed maintenance therapy every 3 weeks.

*** A 30 mg dose of afatinib could be selected for elderly/frail patients as a starting dose before randomization

Primary endpoint: Progression free survival (PFS) assessed by investigators

The sample size of 106 was based on 75% power to detect a hazard ratio of 0.6 in PFS with α= 0.05.

The interim analysis regarding PFS was pre-planned upon completion of enrollment.

The analysis adjusted for multiple testing with the Lan-DeMets alpha-spending function, using the O'Brien and Fleming metho

Secondary endpoint :

Safety, Objective response rate (ORR), Disease control rate (DCR), Overall survival (OS), Time to Treatment Failure (TTF)

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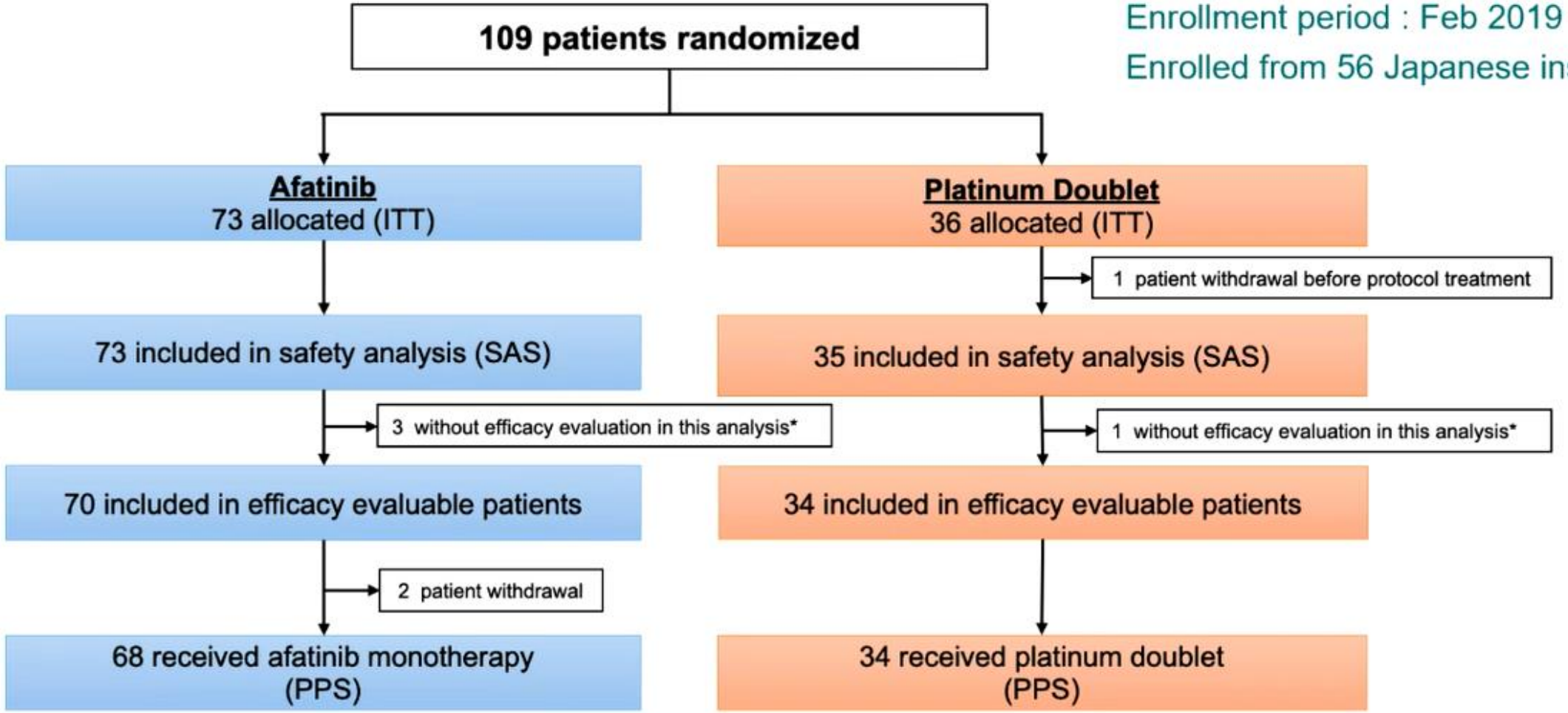
Patient Disposition



Enrollment period : Feb 2019 – Feb 2023

Enrolled from 56 Japanese institutions

* Patients for whom an initial efficacy evaluation (6 weeks) was not performed at the cut-off date.

ITT: Intention-to-Treat
SAS: Safety analysis set
PPS: Per-protocol set

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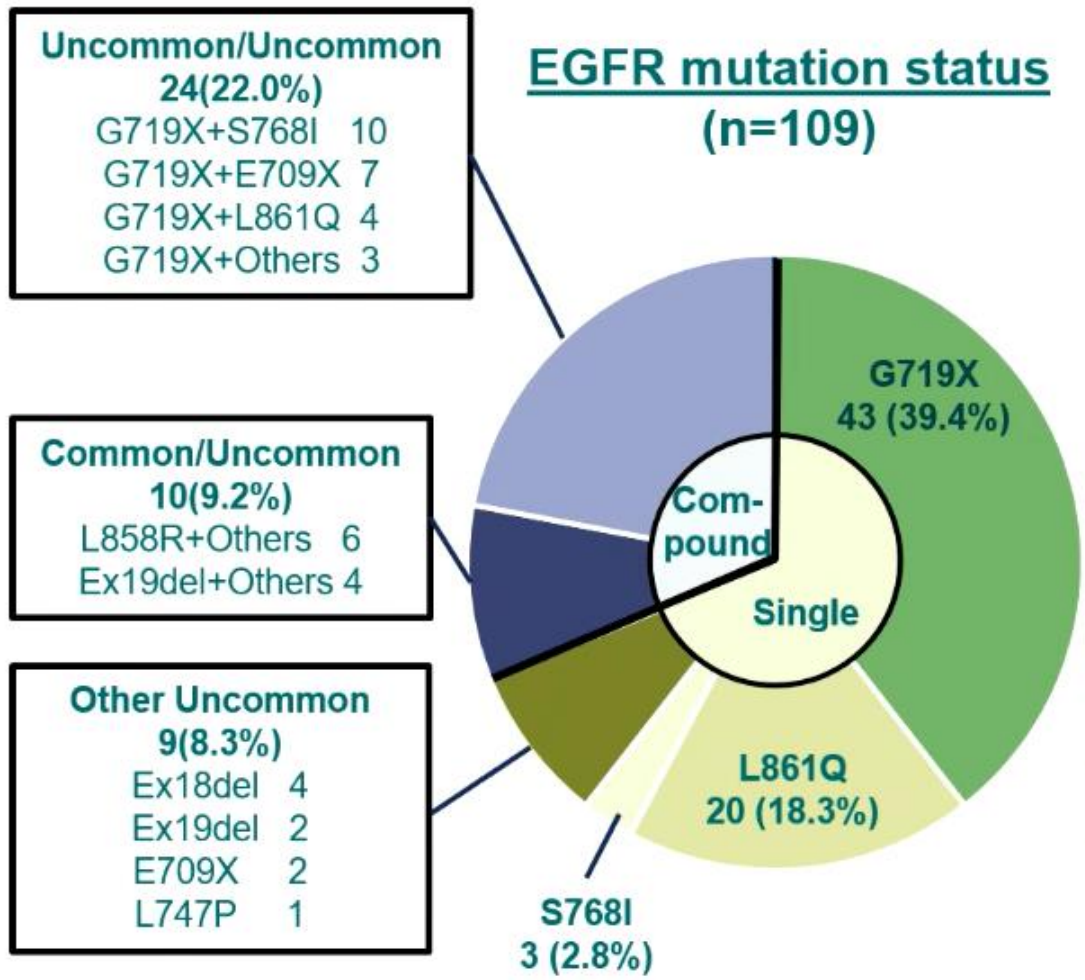
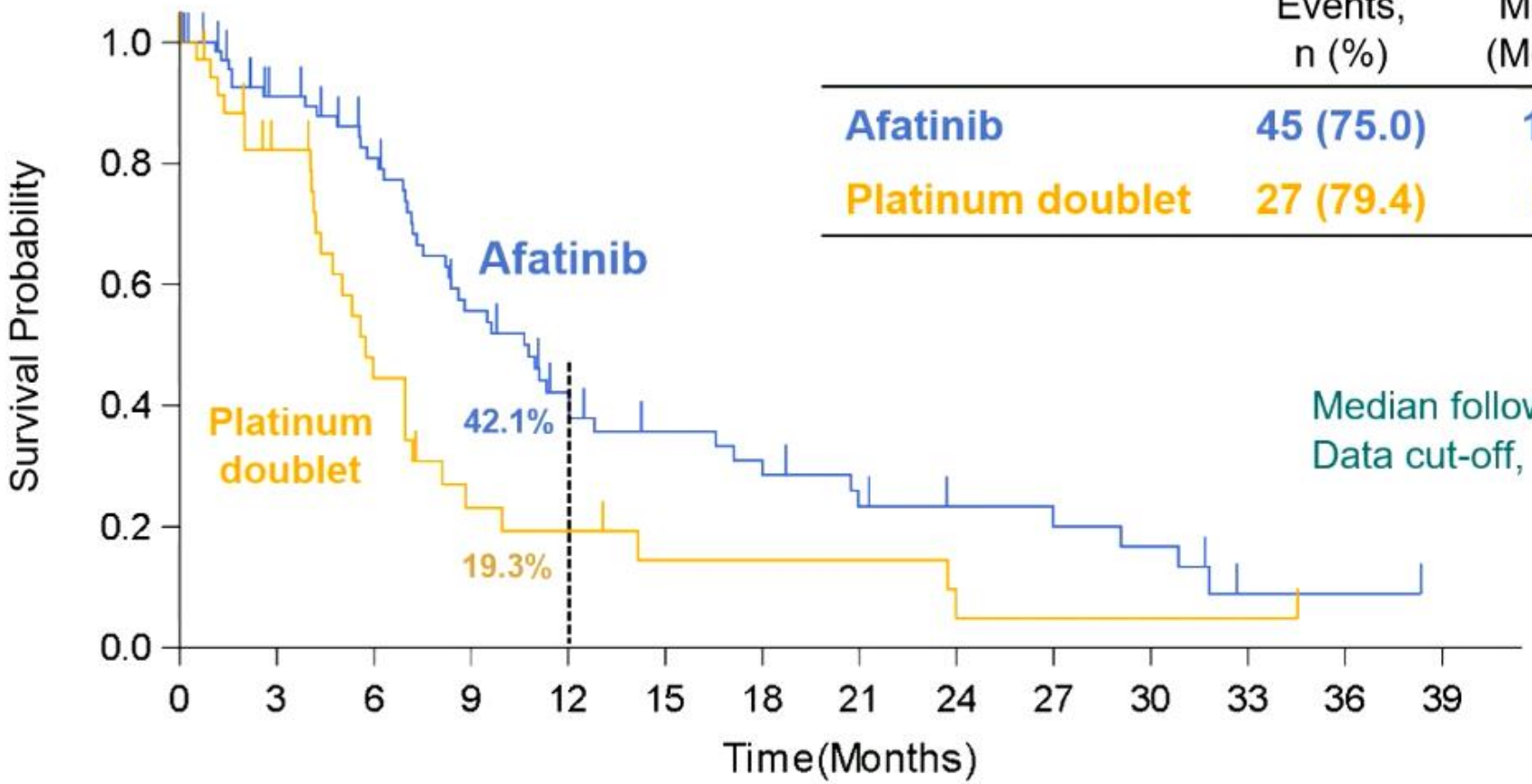
Demographics and Baseline Characteristics

Characteristics		Afatinib (n=73)		Platinum Doublet (n=36)	
Age	Median (range)	71.0	(49-83)	66.5	(42-77)
	≥ 75 years old	19	(26.0%)	5	(13.9%)
Gender	Male	32	(43.8%)	16	(44.4%)
	Female	41	(56.2%)	20	(55.6%)
ECOG performance status	0	32	(43.8%)	16	(44.4%)
	1	41	(56.2%)	20	(55.6%)
Smoking status	Never	38	(52.1%)	13	(36.2%)
	Current	8	(11.0%)	6	(16.7%)
	Former	27	(37.0%)	17	(47.2%)
Stage*	III/IV	55	(75.3%)	29	(80.6%)
	Recurrence	18	(24.7%)	7	(19.4%)
EGFR mutation status*	Single	50	(68.5%)	25	(69.4%)
	Compound	23	(31.5%)	11	(30.6%)
CNS metastasis*	No	50	(68.5%)	25	(69.4%)
	Yes	23	(31.5%)	11	(30.6%)
Afatinib starting dose*	30 mg	37	(50.7%)	19	(52.8%)
	40 mg	36	(49.3%)	17	(47.2%)



* Stratification factor

Primary endpoint: Progression-Free Survival



	Events, n (%)	Median (Months)	HR (95% CI)	*p* value
Afatinib	45 (75.0)	10.6	0.422 (0.256-0.694)	0.0007
Platinum doublet	27 (79.4)	5.7		

***Efficacy boundary, p=0.0304**

Median follow-up: 12.5 months (range, 0–43.5)
Data cut-off, 28 Feb 2023

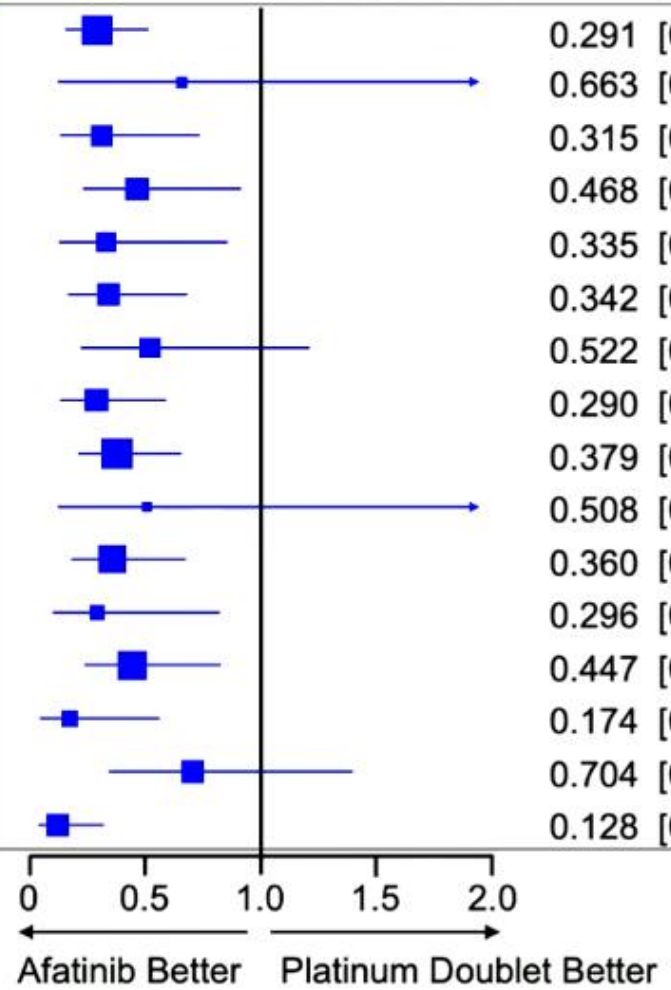
Number at risk

Afatinib	73	57	46	30	20	15	13	9	7	6	5	1	1	0
Platinum Doublet	36	25	13	6	5	3	3	3	1	1	1	1	0	0

HR: Hazard ratio
CI: Confidential Interval

PFS across subgroup analysis

Subgroup		Afatinib No. of Events/Patients	Platinum Doublet No. of Events/Patients	Hazard Ratio for Disease Progression or Death [95%CI]
Age	< 75 years	31/54	25/31	0.291 [0.162,0.523]
	≥ 75 years	14/19	2/5	0.663 [0.128,3.447]
Gender	Male	19/32	11/16	0.315 [0.133,0.744]
	Female	26/41	16/20	0.468 [0.237,0.925]
ECOG	0	16/32	9/16	0.335 [0.130,0.864]
	1	29/41	18/20	0.342 [0.171,0.683]
Smoking status	Never	24/38	10/13	0.522 [0.223,1.219]
	Current / Former	21/35	17/23	0.290 [0.140,0.600]
Stage	Ⅲ/Ⅳ	39/58	23/29	0.379 [0.218,0.658]
	Recurrence	6/15	4/7	0.508 [0.125,2.063]
EGFR mutation status	Single mutation	35/50	18/25	0.360 [0.190,0.680]
	Compound mutation	10/23	9/11	0.296 [0.105,0.831]
CNS metastasis	No	31/50	17/25	0.447 [0.240,0.835]
	Yes	14/23	10/11	0.174 [0.054,0.565]
Afatinib dose	30 mg/day	25/37	14/19	0.704 [0.352,1.406]
	40 mg/day	20/36	13/17	0.128 [0.050,0.327]



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Antitumor activity in efficacy evaluable patients

	Afatinib (n=70)	Platinum Doublet (n=34)
Median treatment course, n (range)	10.0 (0–52)	7.0 (1–35)
Response, n(%)		
CR	2 (2.9 %)	0 (0.0 %)
PR	41 (58.5 %)	16 (47.1 %)
SD	15 (21.4 %)	12 (35.3 %)
PD	6 (11.4 %)	4 (11.8 %)
NE	6 (11.4 %)	2 (5.9 %)
Objective response rate, n(%)	**43 (61.4 %)**	**16 (47.1 %)**
95% Confidential Interval	(49.0–72.8)	(29.8–64.9)
p-value	0.2069	
Disease control rate, n(%)	**58 (82.9 %)**	**28 (82.4 %)**

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Safety Summary

Adverse event	Afatinib (n=73)				Platinum Doublet (n=35)			
	All	(%)	Gr≥3	(%)	All	(%)	Gr≥3	(%)
All events	71	(97.3)	32	(43.8)	32	(91.4)	13	(37.1)
Diarrhea	60	(82.2)	16	(21.9)	4	(11.4)	0	(0)
Paronychia	43	(58.9)	5	(6.8)	0	(0)	0	(0)
Rash	41	(58.9)	1	(1.4)	1	(2.9)	0	(0)
Mucositis	40	(58.9)	6	(8.2)	3	(8.6)	0	(0)
Appetite loss	17	(23.3)	5	(6.8)	15	(42.9)	1	(2.9)
Nausea	17	(23.3)	3	(4.1)	12	(34.3)	3	(8.6)
Neutropenia	0	(0)	0	(0)	9	(25.7)	4	(11.5)
Anemia	4	(5.5)	2	(2.7)	9	(25.7)	3	(8.6)
Thrombocytopenia	0	(0)	0	(0)	6	(17.1)	5	(14.3)
Pneumonitis	2	(2.7)	1	(1.4)*	2	(5.7)	1	(2.9)

* One treatment-related death due to pneumonitis occurred in the afatinib arm

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Conclusion

- The ACHILLES/TORG1834 study is the first randomized phase III study comparing afatinib with platinum-doublet chemotherapy in patients with treatment-naïve non-squamous NSCLC with sensitizing uncommon *EGFR* mutations.

- Afatinib significantly improved progression-free survival over platinum doublet chemotherapy with a HR of 0.422 in the first-line treatment of this population, thus meeting the primary endpoint.

- The safety profile in the afatinib arm was consistent compared to previous reports, and no new safety signal was observed.

- The ACHILLES/TORG1834 study confirmed that afatinib is the standard treatment for patients with treatment-naïve non-squamous NSCLC with sensitizing uncommon *EGFR* mutations.

- Additional data with overall survival, response according to detailed mutation status, and post-progression treatment profiles will eventually be available.

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