Supplemental Online Content

Xu J, Liu Z, Bai H, et al. Evaluation of clinical outcomes of icotinib in patients with clinically diagnosed advanced lung cancer with *EGFR*-sensitizing variants assessed by circulating tumor DNA testing: a phase 2 nonrandomized clinical trial. *JAMA Oncol*. Published online July 21, 2022. doi:10.1001/jamaoncol.2022.2719

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

The justification of sample size

According to previous literatures, it is estimated that the objective response rate (ORR) of icotinib treatment in treatment-naive advanced non-small-cell lung cancer (NSCLC) patients with *epidermal growth factor receptor* (*EGFR)* sensitive mutation as detected by blood test is approximately 60%, with an allowable error of 10% and a significance level of 0.05%. It is estimated that at least 93 evaluable subjects are needed. Therefore, considering a dropout rate of not more than 20%, at least 117 subjects should be enrolled.

The statistical methods

ORR and disease control rate (DCR) were defined according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 as evaluated by independent review committee, and the 95% Confidence Intervals (CI) for ORR and DCR were estimated by Clopper-pearson method. The median progression-free survival (mPFS), median overall survival (mOS), the median duration of response (mDOR) and the corresponding 95% CIs were analyzed using Kaplan-Meier estimation. The follow-up duration was calculated by reverse Kaplan-Meier estimation. The analyses were conducted from September 9th 2021 to December 31th 2021 using SAS 9.4 (SAS Institute Inc., Cary, NC) software.

The concordance of SuperARMS, ddPCR and NGS

The concordance of the three platforms is the sum of positive concordance and negative concordance among three platforms (SuperARMS[1], ddPCR[2] and NGS[3]). The positive concordance refers to the percentage of cases detected with positive *EGFR* 19Del, L858R, and

T790M by all three platforms among all cases detected, while the negative concordance refers to the percentage of cases detected with negative *EGFR* 19Del, L858R, and T790M by all three platforms among all cases detected.

eTable 1. The Clinical Outcomes Evaluated by Independent Review Committee (N = 116)

Items	
Best response	
CR (n, %)	1 (0.9%)
PR (n, %)	60 (51.7%)
SD (n, %)	37 (31.9%)
PD (n, %)	16 (13.8%)
NE (n, %)	2 (1.7%)
ORR (95% CI)	52.6% (43.1%, 61.9%)
DCR (95% CI)	84.5 % (76.6%, 90.5%)
Median PFS (95% CI)	10.3 (8.3, 12.2)
PFS rate (95% CI)	
1-year	42.2% (33.2%, 51.0%)
2-year	22.4% (15.3%, 30.3%)
3-year	12.2% (6.6%, 19.7%)
Median OS (95% CI)	23.2 (17.7, 28.0)
OS rate (95% CI)	
1-year	75.7% (66.8%, 82.5%)
2-year	48.4% (39.0%, 57.2%)
3-year	30.6% (21.9%, 39.7%)
Median DOR (95% CI)	9.1 (7.3, 11.7)

Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressed disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; CI, confidence interval.

eTable 2. The Treatment-Related Adverse Events of 116 Patients

	N (%)					
TRAE	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**NA**	**Total**
Rash	53 (45.7)	6 (5.2)	0 (0.0)	1 (0.9)	0 (0.0)	60 (51.7)
Fatigue	48 (41.4)	7 (6.0)	3 (2.6)	0 (0.0)	0 (0.0)	58 (50.0)
Diarrhea	33 (28.4)	4 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	37 (31.9)
Pruritus	32 (27.6)	6 (5.2)	2 (1.7)	0 (0.0)	0 (0.0)	40 (34.5)
Dry skin	30 (25.9)	8 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	38 (32.8)
Alopecia	27 (23.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	27 (23.3)
Stomatitis	26 (22.4)	11 (9.5)	1 (0.9)	0 (0.0)	0 (0.0)	38 (32.8)
Hepatic function abnormal	20 (17.2)	2 (1.7)	2 (1.7)	0 (0.0)	0 (0.0)	24 (20.7)
Nausea	16 (13.8)	5 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (18.1)
Dyspnea	12 (10.3)	4 (3.4)	1 (0.9)	0 (0.0)	0 (0.0)	17 (14.7)
Dysphagia	10 (8.6)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (10.3)
White blood cell count decreased	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)
Neutrophil count decreased	2 (1.7)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)
Paronychia	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Anemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Bilirubin increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Blood alkaline phosphatase increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Blood urine present	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Gastrointestinal pain	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Protein urine	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Chronic gastritis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Creatinine increased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Dyspepsia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)

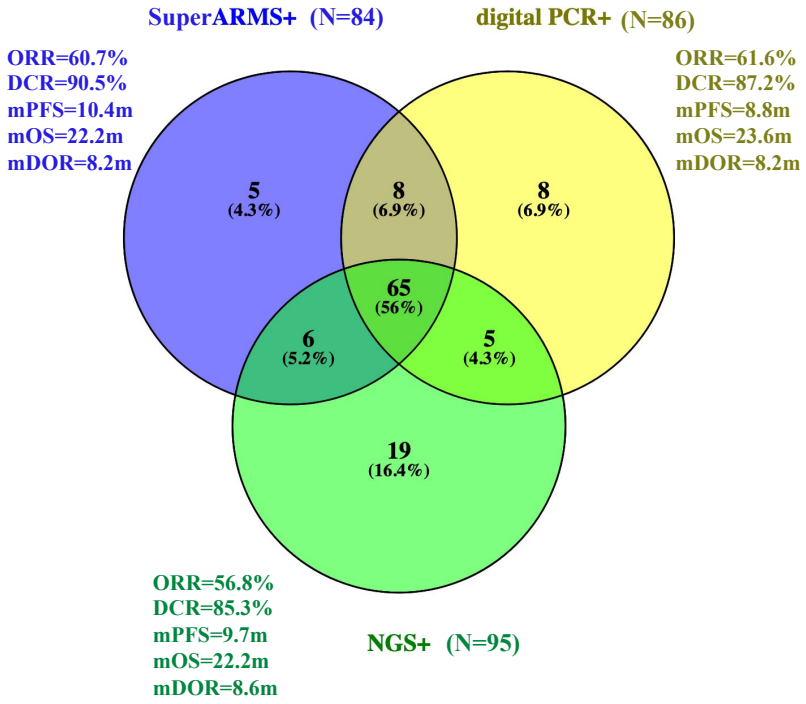
Abbreviations: TRAE, treatment-related adverse event; NA, not applicable.

eTable 3. The Clinical Outcomes of Patients With *EGFR* Variants Detected Using 3 Independent Platforms

SuperARMS	ddPCR	NGS	N	ORR (95%CI) (%)	DCR (95%CI) (%)	mPFS (95%CI) (months)	mOS (95%CI) (months)	mDOR (95%CI) (months)
+			84	60.7 (49.5, 71.2)	90.5 (82.1, 95.8)	10.4 (7.7, 12.4)	22.2 (17.5, 28.0)	8.2 (7.3, 11.7)
	+		86	61.6 (50.5, 71.9)	87.2 (78.3, 93.4)	8.8 (7.2, 12.0)	23.6 (17.7, 28.2)	8.2 (7.3, 11.7)
		+	95	56.8 (46.3, 67.0)	85.3 (76.5, 91.7)	9.7 (7.3, 11.9)	22.2 (17.3, 28.0)	8.6 (6.2, 11.7)
+	+		73	65.8 (53.7, 76.5)	90.4 (81.2, 96.1)	8.6 (7.1, 12.0)	22.2 (17.5, 28.0)	8.2(6.2, 11.7)
+		+	71	64.8 (52.5, 75.8)	91.5 (82.5, 96.8)	10.3 (7.3, 12.0)	21.4 (17.3, 28.0)	8.2 (6.2, 11.3)
	+	+	70	67.1 (54.9, 77.9)	88.6 (78.7, 94.9)	8.5 (7.1, 11.9)	21.8 (17.3, 28.0)	8.2 (6.2, 11.7)
+	+	+	65	67.7 (54.9, 78.8)	90.8 (81.0, 96.5)	8.6 (7.2, 12.0)	21.4 (17.3, 28.0)	8.0 (6.2, 11.3)

Abbreviations: EGFR, epidermal growth factor receptor; SuperARMS, Super-Amplification Refractory Mutation System; ddPCR, digital Polymerase Chain Reaction; NGS, next-generation sequencing; ORR, overall response rate; CI, confidence interval; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; mDOR, median duration of response.

eFigure. Venn Diagram Exhibiting the Distribution and Clinical Outcomes of Patients With *EGFR* Variants Detected Using 3 Independent Platforms



Abbreviations: EGFR, epidermal growth factor receptor; SuperARMS, Super-Amplification Refractory Mutation System; ddPCR, digital Polymerase Chain Reaction; NGS, next-generation sequencing; ORR, overall response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; mDOR, median duration of response.

eReferences.

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