

Supplementary Data

Patient characteristics

From 2010 to 2018, 176 patients admitted to the ICU with MV use and the diagnosis of NSCLC, and who were treated with EGFR-TKI, were enrolled. Fifty-one patients were excluded due to a lack of documentation of EGFR mutation status. Another 62 patients were excluded because of previous use of chemotherapy or other TKIs. Finally, 63 patients who received EGFR-TKIs as first-line therapy for lung cancer, and among whom 35 harbored a sensitizing EGFR mutation and 28 did not, were included. The median age of the patients was 73 years, 60% of the patients were female, and 68% were never-smokers. In terms of comorbidities, 11% of the patients had coronary artery disease or heart failure, and 21% had COPD. The major reason for ICU admission and MV use was pneumonia (87%). Most of the patients (61 of 63, 97%) were diagnosed with adenocarcinoma, and 2 patients had sarcomatoid carcinoma. All of the patients had stage 4 lung cancer, according to the American Joint Committee on Cancer 7th edition, and 19% had brain metastases. The mutation subtypes of the 35 (57%) patients who had a sensitizing EGFR mutation were as follows: L858R: 15 (42.8%), exon 19 deletion: 14 (40%), and uncommon mutation: 6 (17.1%). There was no significant difference between EGFR-mutant and wild-type cases, except patients with an EGFR mutation had a higher APACHE II score (EGFR wild-type versus EGFR-mutant: 20 versus 25 points, p -value = 0.002)

Table S1. Demographic data of EGFR-TKI-treated NSCLC patients who were admitted to the ICU and received mechanical ventilation.

	All ($n = 63$)		EGFR Wild-type ($n = 28$)		EGFR mutation ($n = 35$)		p value
Gender (Male)	25	40%	13	46%	12	34%	0.328
Age (median, range)	73 (63–80)		73 (56–84)		73 (67–79)		0.793
Smokers (n , %)	20	32%	12	43%	8	23%	0.248
APACHE II score	23 (18–27)		20 (15–25)		25 (22–28)		0.002
Stage IV (n , %)	61	97%	27	96%	34	97%	0.872
Interval between cancer diagnosis and ICU admission (days)	17 (0–376)		5 (0–45)		134 (6–546)		0.003
Histology							
Adenocarcinoma (22 with histological subclassification)	61	97%	27	96%	34	97%	0.872
Acinar	10/22	45.5%	4/10	40%	6/12	50%	0.658
Papillary	5/22	22.7%	3/10	30%	2/12	16.7%	0.481
Solid	3/22	13.6%	2/10	20%	1/12	8.3%	0.451
Mucinous	2/22	9.1%	2/10	20%	0/12	0%	0.899
Poorly-differentiated	2/22	9.1%	0/10	0%	2/12	16.7%	0.193
Sarcomatoid carcinoma	2	3%	1	4%	1	3%	0.872
Comorbidity							
DM	20	32%	8	29%	12	34%	0.628
HTN	25	40%	9	32%	16	46%	0.274
COPD	13	21%	7	25%	6	17%	0.444
CAD/HF	7	11%	4	14%	3	9%	0.473
CKD	4	6%	1	4%	3	9%	0.419
Reason for ICU admission							
Pneumonia	55	87%	27	96%	28	80%	0.145
Shock	9	14%	3	11%	6	17%	0.469
Cardiac-related	3	5%	2	7%	1	3%	0.427
Neurological deficit	3	5%	0	0%	3	9%	0.112
Operation	2	3%	1	4%	1	3%	0.767
Type of EGFR mutation							

L858R	15	43%					
Deletion 19	14	40%					
Uncommon	6	17%					
Metastatic site							
Lung-to-lung	39	62%	19	68%	20	57%	0.384
Pleura	41	65%	16	57%	25	71%	0.237
Pericardial effusion	7	11%	3	11%	4	11%	0.929
Bone	32	51%	15	54%	17	49%	0.693
Brain	12	19%	4	14%	8	23%	0.389
Liver	12	19%	4	14%	8	23%	0.389

Acronyms: APACHE II= Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scoring System, DM= diabetes mellitus, HTN= hypertension, COPD= chronic obstructive pulmonary disease, CAD/HF= coronary artery disease or heart failure, CKD= chronic kidney disease

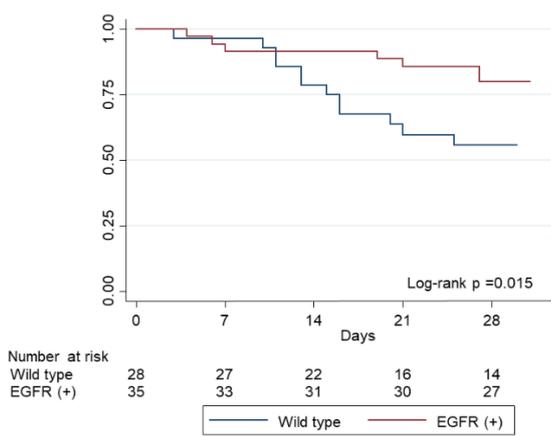
Clinical Outcomes of all TKI-treated patients in ICU

Most of the patients were treated with a first- or second-generation EGFR-TKI (gefitinib: 39, erlotinib: 22, and afatinib: 1). Only 1 patient received osimertinib treatment in the ICU. The median duration for the use of EGFR-TKIs in the ICU was 17 vs 8 days ($p = 0.001$) for patients with and without a sensitizing EGFR mutation. The 28-day ICU survival rate in patients with and without mutant EGFR was 77% and 50% ($p = 0.025$), respectively, with significant difference revealed by log rank test ($p = 0.015$). The median survival time for the whole cohort, EGFR-mutant, and EGFR wild-type patients was 52, 67, and 28 days, respectively. The Kaplan-Meier plotting of 28-day, 90-day, and overall survival is shown in Figures 2A, 2B and 2C. The log rank test showed significantly better 28-day, 90-day and overall survival with a p value of 0.015, 0.010, and 0.001, respectively. In addition, 35% of the patients were successfully weaned from MV. The successful weaning rate was higher among EGFR-mutant cases, (EGFR-mutant versus wild-type: 43% versus 25%, $p = 0.14$); however, the Kaplan-Meier method did not show a significant difference in ventilator-free survival, with a log-rank p value of 0.949 (Figure 2D). The clinical outcomes were summarized in Table S2.

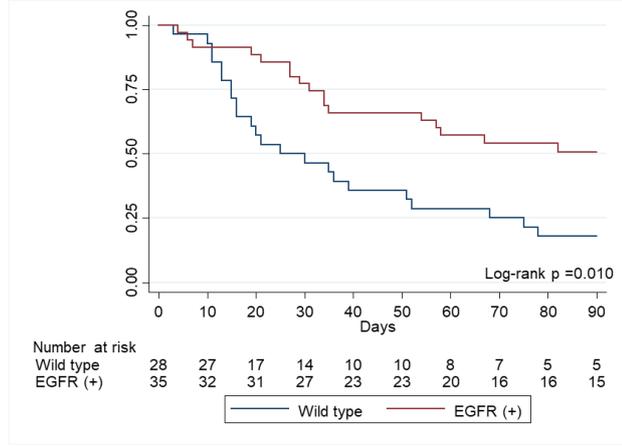
Table S2. Treatment outcomes relevant to EGFR-TKIs.

	All ($n = 63$)		Wild-type ($n = 28$)		EGFR + ($n = 35$)		p value
EGFR-TKI							
Gefitinib	39	62%	17	61%	22	63%	0.001
Erlotinib	22	35%	11	39%	11	31%	
Afatinib	1	2%	0	0%	1	3%	
Osimertinib	1	1%	0	0%	1	3%	
EGFR-TKI treatment duration							
Before ICU (days)	0 (-6–129)		-4 (-8–12)		52 (-4–487)		0.005
During ICU (days)	11 (7–21)		8 (4–11)		17 (10–27)		0.001
TKI adverse events							
Interstitial pneumonitis ($n, \%$)	5	8%	3	11%	2	6%	0.338
Diarrhea ($n, \%$)	4	6%	2	7%	2	6%	0.974
Hepatitis ($n, \%$)	1	2%	0	0%	1	3%	0.367
Skin toxicity ($n, \%$)	4	6%	0	0%	4	11%	0.181
Outcome							
ICU 28-day-survival rate	41	65%	14	50%	27	77%	0.025
Overall survival (days)	52 (20–151)		28 (15–72)		67 (31–320)		0.005
Successful weaning from ventilator ($n, \%$)	22	35%	7	25%	15	43%	0.140

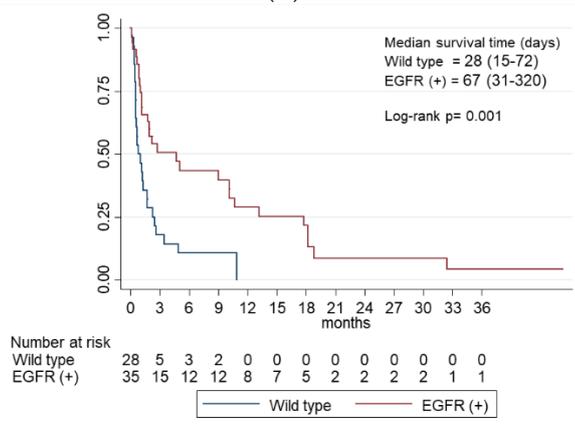
Acronyms: EGFR = epidermal growth factor receptor, ICU = intensive care unit, TKI = tyrosine kinase inhibitor



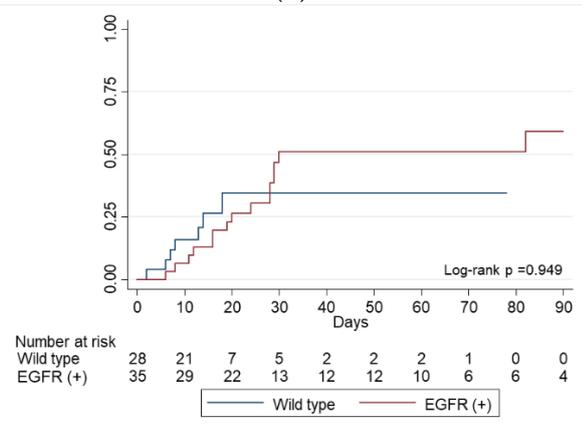
(A)



(B)



(C)



(D)

Figure S1. Survival and rate of successful weaning from mechanical ventilation of lung cancer patients receiving EGFR-TKIs in the ICU. (A) 28-day ICU survival. (B) 90-day survival. (C) Overall survival. (D) Cumulative incidence of patients with successful weaning from mechanical ventilators. Acronyms: EGFR = epidermal growth factor receptor, ICU= intensive care unit, TKI= tyrosine kinase inhibitor.