



P3.205: Second vs Third-Generation EGFR-TKIs as Frontline Treatment for EGFR-Mutant NSCLC: Interim Result from Korean EGFR Registry

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INTRODUCTION

- Although previous clinical trials including FLAURA and LASER 301 have demonstrated the survival benefit over first-generation EGFR-tyrosine kinase inhibitors (TKIs) in EGFR-mutant non-small cell lung cancer (NSCLC), evidence of real-world comparisons between second-generation (2G) and third-generation (3G) EGFR-TKIs as first-line treatment remains limited.
- This study aims to compare the clinical outcomes and safety of 2G and 3G EGFR-TKIs using a robust, large-scale nationwide registry.

METHODS

- Data were derived from the Korean EGFR Registry, a multicenter cohort that retrospectively and prospectively enrolled patients with EGFR-mutant NSCLC across 40 institutions in South Korea (May 2022 – June 2024).
- The data cutoff for this analysis was May 31, 2026.
- Among 1,954 total enrolled patients, we analyzed 1,198 patients with metastatic or recurrent disease treated with either 2G (n=701; afatinib [n=597] or dacomitinib [n=104]) or 3G TKIs (n=497; osimertinib [n=155] or lazertinib [n=342]) as frontline therapy.
- Clinical outcomes assessed were time to treatment failure (TTF), time to discontinuation of TKI (TD-TKI), progression-free survival (PFS), and overall survival (OS).
- Treatment effects were estimated within a **target trial emulation (TTE)** design using **inverse probability of treatment weighting (IPTW)** based on 10 baseline covariates (institution, age, sex, histology, smoking, EGFR subtype, stage, ECOG PS, PD-L1, brain metastasis).
- Sensitivity analyses: unadjusted, 1:1 propensity-score matching (PSM), stabilized and truncated IPTW.

RESULTS

Table 1. Baseline characteristics of the patients

Characteristics	Overall (n=1,198)	2G TKI (n=701)	3G TKI (n=497)	P value
Cohort				
Retrospective	314 (26.2)	276 (39.4)	38 (7.6)	<0.001
Prospective	884 (73.8)	425 (60.6)	459 (92.4)	
Age (years)				
Median (range)	67.6 (30-94)	67.9 (37-92)	67.1 (30-94)	0.193
<70	677 (56.5)	386 (55.1)	291 (58.6)	0.254
≥70	521 (43.5)	315 (44.9)	206 (41.4)	
Sex				
Male	493 (41.2)	297 (42.4)	196 (39.4)	0.339
Female	705 (58.8)	404 (57.6)	301 (60.6)	
Smoking				
Never	742 (62.2)	415 (59.7)	327 (65.8)	0.038
Ever	450 (37.8)	280 (40.3)	170 (34.2)	
Smoking intensity				
<30 pack-years	991 (82.7)	567 (80.9)	424 (85.3)	0.103
≥30 pack-years	195 (16.3)	125 (17.8)	70 (14.1)	
ECOG PS				
<2	987 (82.4)	590 (84.2)	397 (79.9)	0.158
≥2	124 (10.4)	65 (9.3)	59 (11.9)	
Histologic subtypes				
Adenocarcinoma	1152 (96.2)	677 (96.6)	475 (95.6)	0.068
Squamous cell carcinoma	13 (1.1)	10 (1.4)	3 (0.6)	
Differentiation				
Well/moderate	173 (14.4)	88 (12.6)	85 (17.1)	0.061
Poor	133 (11.1)	75 (10.7)	58 (11.7)	
Unknown/undiff./combined	892 (74.5)	538 (76.7)	354 (71.2)	
Stage				
0.670				
III	124 (10.4)	77 (11.0)	47 (9.5)	
IV	942 (78.6)	548 (78.2)	394 (79.3)	
Post-op recurrence before 1L Tx				
Yes (early stage at dx)	187 (15.6)	107 (15.3)	80 (16.1)	0.756
No (stage III/IV at dx)	1011 (84.4)	594 (84.7)	417 (83.9)	
No. of involved organs				
<3	884 (73.8)	542 (77.3)	342 (68.8)	0.001
≥3	314 (26.2)	159 (22.7)	155 (31.2)	
Brain metastasis				
No	740 (61.8)	480 (68.5)	260 (52.3)	<0.001
Yes	458 (38.2)	221 (31.5)	237 (47.7)	
Liver metastasis				
No	1098 (91.7)	643 (91.7)	455 (91.5)	0.998
Yes	100 (8.3)	58 (8.3)	42 (8.5)	
PD-L1 expression				
<1%	472 (39.4)	283 (40.4)	189 (38.0)	0.270
1-49%	176 (14.7)	92 (13.1)	84 (16.9)	
≥50%	443 (37.0)	266 (37.9)	177 (35.6)	
EGFR subtypes				
19del	569 (47.5)	325 (46.4)	244 (49.1)	<0.001
L858R	515 (43.0)	285 (40.7)	230 (46.3)	
Uncommon or compound	114 (9.5)	91 (13.0)	23 (4.6)	
EGFR-TKIs				
Dacomitinib	104 (8.7)	104 (14.8)	0 (0.0)	<0.001
Afatinib	597 (49.8)	597 (85.2)	0 (0.0)	
Osimertinib	155 (12.9)	0 (0.0)	155 (31.2)	
Lazertinib	342 (28.5)	0 (0.0)	342 (68.8)	
Second-line treatment				
Yes	590 (49.2)	411 (58.6)	179 (36.0)	<0.001
No	608 (50.8)	290 (41.4)	318 (64.0)	
Dose modification				
Yes	304 (25.4)	101 (14.4)	203 (40.8)	<0.001
No	893 (74.5)	599 (85.4)	294 (59.2)	

Table 2. Efficacy outcomes

Variable	Overall	2G TKI (n=701)	3G TKI (n=497)
Ongoing treatment			
300 (25.0)	123 (17.5)	177 (35.6)	
Reason for cessation of Tx			
Progression	574 (63.4)	400 (68.5)	174 (54.2)
Adverse events	126 (13.9)	71 (12.2)	55 (17.1)
Withdrawal of consent	25 (2.8)	11 (1.9)	14 (4.4)
Death	67 (7.4)	35 (6.0)	32 (10.0)
Researchers' decision	113 (12.5)	67 (11.5)	46 (14.3)
Best response			
CR	24 (2.1)	17 (2.5)	7 (1.5)
PR	699 (61.5)	401 (60.0)	298 (63.7)
SD	352 (31.0)	210 (31.4)	142 (30.3)
PD	48 (4.2)	36 (5.4)	12 (2.6)
NE	13 (1.1)	4 (0.6)	9 (1.9)
Objective response rate, %	723 (60.4)	418 (59.6)	305 (61.4)
Disease control rate, %	1075 (89.7)	628 (89.6)	447 (89.9)
Follow-up, months	31.8 (31.0-33.1)	37.3 (36.1-38.5)	26.9 (26.6-27.8)
TOT, months	14.9 (14.0-16.1)	14.3 (13.4-15.6)	16.3 (14.2-18.6)
TTF, months	14.9 (14.1-16.3)	14.3 (13.4-15.6)	16.2 (14.3-18.6)
PFS, months	20.0 (19.1-21.6)	17.9 (16.8-19.7)	24.6 (21.6-30.4)

Table 3. PFS according to clinicopathological parameters

Variable	Median PFS (mo)	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
No. of involved organs					
<3	22.7 (20.9-25.3)	reference		reference	
≥3	14.7 (13.7-17.1)	1.704 (1.439-2.016)	<0.001	1.097 (0.576-2.090)	0.778
Brain metastasis					
No	21.9 (20.0-24.9)	reference		reference	
Yes	17.4 (15.7-19.6)	1.324 (1.130-1.550)	<0.001	1.090 (0.586-2.028)	0.787
Liver metastasis					
No	20.9 (19.6-22.7)	reference		reference	
Yes	11.7 (11.1-14.7)	2.042 (1.588-2.625)	<0.001	1.637 (0.911-2.941)	0.099
PD-L1 expression					
<1%	21.6 (19.6-25.2)	reference		reference	
1-49%	20.0 (18.4-22.1)	1.100 (0.921-1.314)	0.294	0.915 (0.592-1.416)	0.690
≥50%	13.6 (11.4-17.8)	1.603 (1.265-2.031)	<0.001	1.881 (1.063-3.325)	0.030
EGFR subtypes					
19del	22.1 (20.0-26.2)	reference		reference	
L858R	19.2 (17.1-20.9)	1.283 (1.089-1.512)	0.003	1.240 (0.820-1.877)	0.308
Uncommon/co mpound	14.2 (12.0-22.9)	1.499 (1.150-1.953)	0.003	4.403 (2.107-9.203)	<0.001
EGFR-TKIs					
2G	17.9 (16.8-19.7)	reference		reference	
3G	24.6 (21.6-30.4)	0.672 (0.567-0.795)	<0.001	0.533 (0.339-0.837)	0.006
Second-line treatment					
No	NR (53.7-NE)	reference		Not in model	
Yes	13.8 (13.3-14.6)	6.328 (5.230-7.658)	<0.001	Not in model	
Dose modification					
No	20.5 (19.5-22.3)	reference		reference	
Yes	18.8 (16.1-21.8)	1.137 (0.947-1.365)	0.168	0.711 (0.423-1.197)	0.200

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Table 4. Hazard ratio based on method of propensity score analysis

Method	N	HR (95% CI) – TD-TKI	p	N	HR (95% CI) – OS	p
IPTW	1193	0.944 (0.749-1.190)	0.627	1193	1.245 (0.943-1.643)	0.122
Sensitivity analysis						
Unadjusted	1193	1.033 (0.890-1.199)	0.670	1193	1.514 (1.233-1.860)	<0.001
Matching (1:1)	739	1.014 (0.840-1.223)	0.886	739	1.398 (1.075-1.818)	0.012
Stabilized IPTW	1193	0.947 (0.750-1.196)	0.649	1193	1.255 (0.949-1.660)	0.111
Truncated IPTW	1193	1.005 (0.843-1.197)	0.959	1193	1.333 (1.054-1.684)	0.016
Sensitivity analysis						
IPTW	1194	0.712 (0.568-0.892)	0.003	1193	0.566 (0.433-0.740)	<0.001
Sensitivity analysis						
Unadjusted	1194	0.807 (0.700-0.929)	0.003	1193	0.672 (0.567-0.796)	<0.001
Matching (1:1)	740	0.795 (0.666-0.948)	0.011	739	0.627 (0.505-0.779)	<0.001
Stabilized IPTW	1194	0.712 (0.567-0.894)	0.004	1193	0.567 (0.433-0.742)	<0.001
Truncated IPTW	1194	0.763 (0.644-0.904)	0.002	1193	0.599 (0.489-0.734)	<0.001

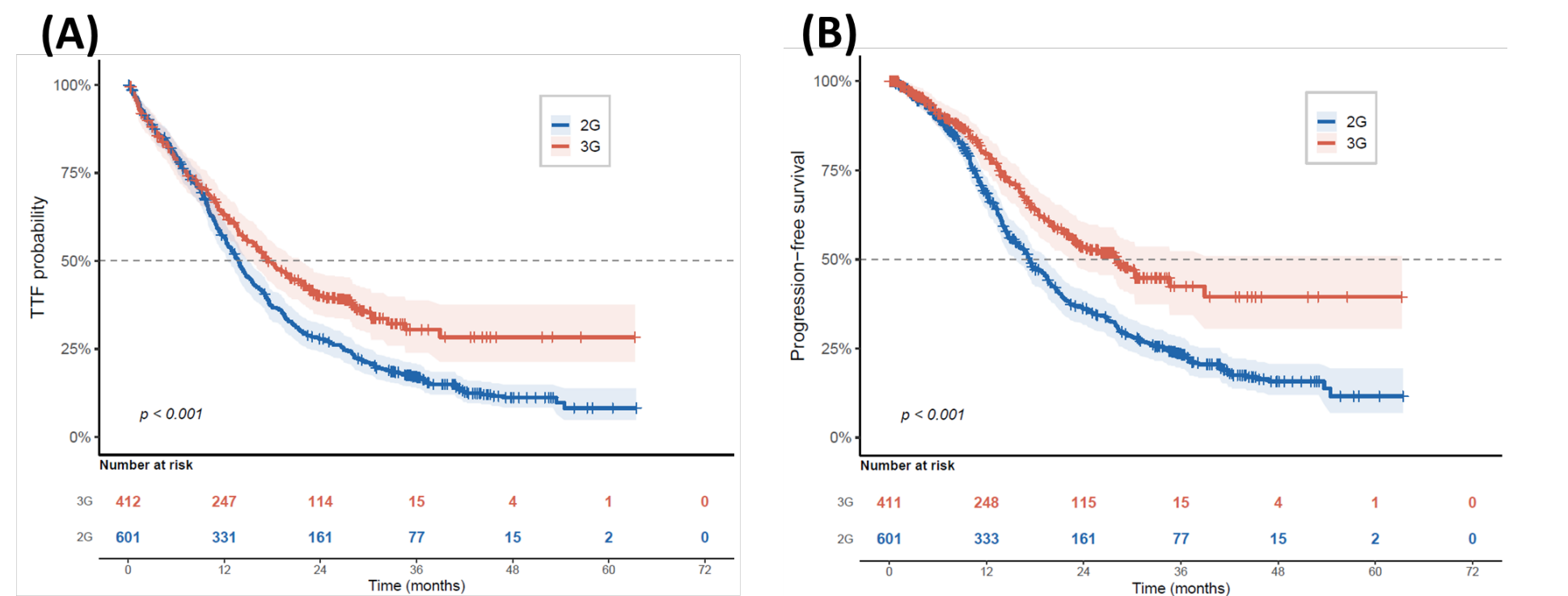


Figure 1. Kaplan-Meier Curves for (A) TTF and (B) PFS (ITT, IPTW)

DISCUSSION AND CONCLUSION

- In this large real-world cohort of 1,198 patients with EGFR-mutant NSCLC applying a target trial emulation framework with IPTW adjustment, frontline 2G- and 3G-TKIs showed similar ORR and DCR, but 3G-TKIs were associated with significantly longer TTF and PFS.
- Time to TKI discontinuation (TD-TKI) did not differ significantly between the two groups in the primary IPTW analysis.
- To the best of our knowledge, this is one of the largest real-world cohorts to directly compare 2G- and 3G-EGFR-TKIs as first-line treatment using a target trial emulation framework.
- However, given the significantly shorter follow-up duration in the 3G group compared with the 2G group (26.9 vs 37.3 months, p<0.001), the OS data remain immature and are not yet reliably interpretable at this stage.
- Longer-term follow-up is needed to clarify the survival implications of frontline TKI selection and optimal 2G-to-3G sequencing strategies.

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