

INTRODUCTION

- Over the past two decades, lung cancer incidence has declined alongside reduced tobacco use; however, this trend has not been uniform, particularly among younger adults, women, and patients with no smoking history.
- The clinical characteristics, treatment patterns, and real-world outcomes of young-onset NSCLC remain incompletely characterized.
- We evaluated first-line treatment patterns and outcomes among patients with young-onset NSCLC using a large real-world clinicogenomic dataset.

METHODS

- The Tempus Lens platform was used to identify patients diagnosed with NSCLC on or after January 1, 2016.
- Eligible patients underwent Tempus xT (DNA, 648 genes) and xR (RNA, whole transcriptome) sequencing. Tumor purity was required to be $\geq 30\%$, and samples were collected anytime before or up to 15 days after first-line (1L) therapy initiation.
- Young-onset NSCLC was defined as diagnosis at ≤ 50 years and average-onset NSCLC as diagnosis at > 50 years. *KRAS* and *ERBB2* were excluded from actionable alterations as they were not targetable in the 1L setting at the time of data collection.
- Real-world overall survival (rwOS) and time to next treatment (rwTTNT) were measured from 1L initiation to death/next line start or loss to follow-up, respectively.
- Median rwOS or rwTTNT (in months) was estimated using Kaplan–Meier methods, log-rank tests, and weighted Cox models reported as average hazard ratios (aHR).

DISCUSSION AND CONCLUSION

- Median rwOS was longer in patients with young-onset disease, actionable alterations, TKI treatment, and never smokers.
- Median rwTTNT was longer for younger patients and those with actionable alterations.
- Our data emphasize the importance of individualized prognostication in NSCLC tailored to age of onset, treatment, smoking status, and genomic alterations.
- Future trials should incorporate and report young-onset patients as a clinically relevant subgroup.

RESULTS

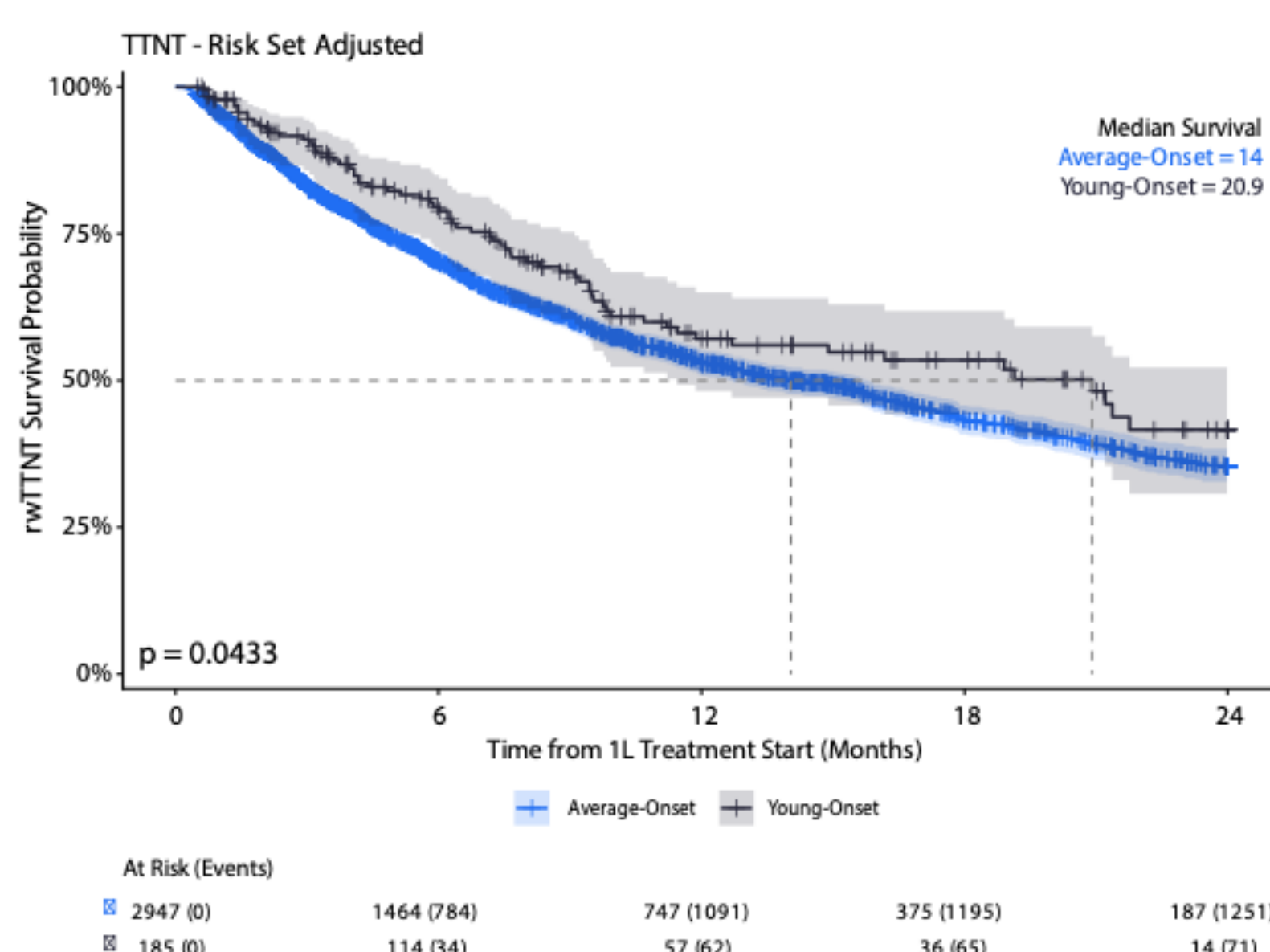
Table 1: Patient and Clinical Characteristics by Age at Onset

Characteristic, n (%)	Average-onset N = 3,283	Young-onset N = 200	P value ¹
Sex			>0.9
Male	1,729 (53)	106 (53)	
Female	1,554 (47)	94 (47)	
Race			0.002
White	2,355 (72)	122 (61)	
Non-White	551 (17)	52 (26)	
Unknown	377 (11)	26 (13)	
Ethnicity			0.016
Hispanic or Latino	120 (3.7)	15 (7.5)	
Not Hispanic or Latino	2,355 (72)	132 (66)	
Unknown	808 (25)	53 (27)	
Histology			0.002
Non-squamous	2,293 (70)	161 (81)	
Squamous	833 (25)	29 (15)	
NOS	157 (4.8)	10 (5.0)	
Smoking status			<0.001
No smoking history	384 (12)	54 (27)	
Former smoking	1,064 (32)	53 (27)	
Current smoking	705 (21)	37 (19)	
Unknown	1,130 (34)	56 (28)	
NCCN-actionable alteration*	669 (20)	81 (41)	<0.001
First-line treatment			—
Chemo + IO	1,722 (52)	91 (46)	
TKI	440 (13)	48 (24)	
Chemotherapy	430 (13)	31 (16)	
IO	502 (15)	7 (3.5)	
Chemo + TKI	49 (1.5)	10 (5.0)	
Other	138 (4.2)	12 (6.0)	

**KRAS* and *ERBB2* were excluded from actionable alterations as they were not targetable in the 1L setting at the time of data collection. ¹P-values calculated using Pearson's Chi-squared test, Fisher's exact test, and Wilcoxon rank sum test

- Among young-onset patients, **TKI treatment was associated with the longest median rwOS** compared with chemoimmunotherapy and chemotherapy (**38.9 vs 21.6 vs 17.1 months**; $p=0.007$; Figure 3). A similar pattern was observed in average-onset patients (**26.5 vs 18.9 vs 11.5 months**; $p<0.001$).
- Patients with **no smoking history had longer median rwOS** than former or current smokers overall (**24.7 vs 20.2 vs 16.9 months**; $p<0.001$). Among young-onset patients, median rwOS was numerically longer in never smokers and former smokers (**36.2 vs 35.7 vs 21.7 months**; $p=0.25$; Figure 4).
- Young-onset disease was independently associated with improved rwOS** (aHR **0.66**, 95% CI **0.53–0.83**; $p<0.001$) after adjustment for smoking status, germline and actionable alterations, race, ethnicity, sex, histology, and 1L treatment (Figure 5).

Figure 1: Kaplan–Meier curve of rwTTNT in young-versus average-onset NSCLC



- Young-onset patients had longer outcomes** than average-onset patients, with median rwTTNT of **20.9 vs 14.0 months** ($p=0.04$; Figure 1) and median rwOS of **33.5 vs 18.9 months** ($p<0.001$; Figure 2).
- Actionable alterations were associated with improved outcomes** across all ages, with median rwTTNT **20.4 vs 12.7 months** and median rwOS **29.9 vs 17.2 months** (both $p<0.001$).

Figure 3: rwOS by 1L treatment in young-onset NSCLC

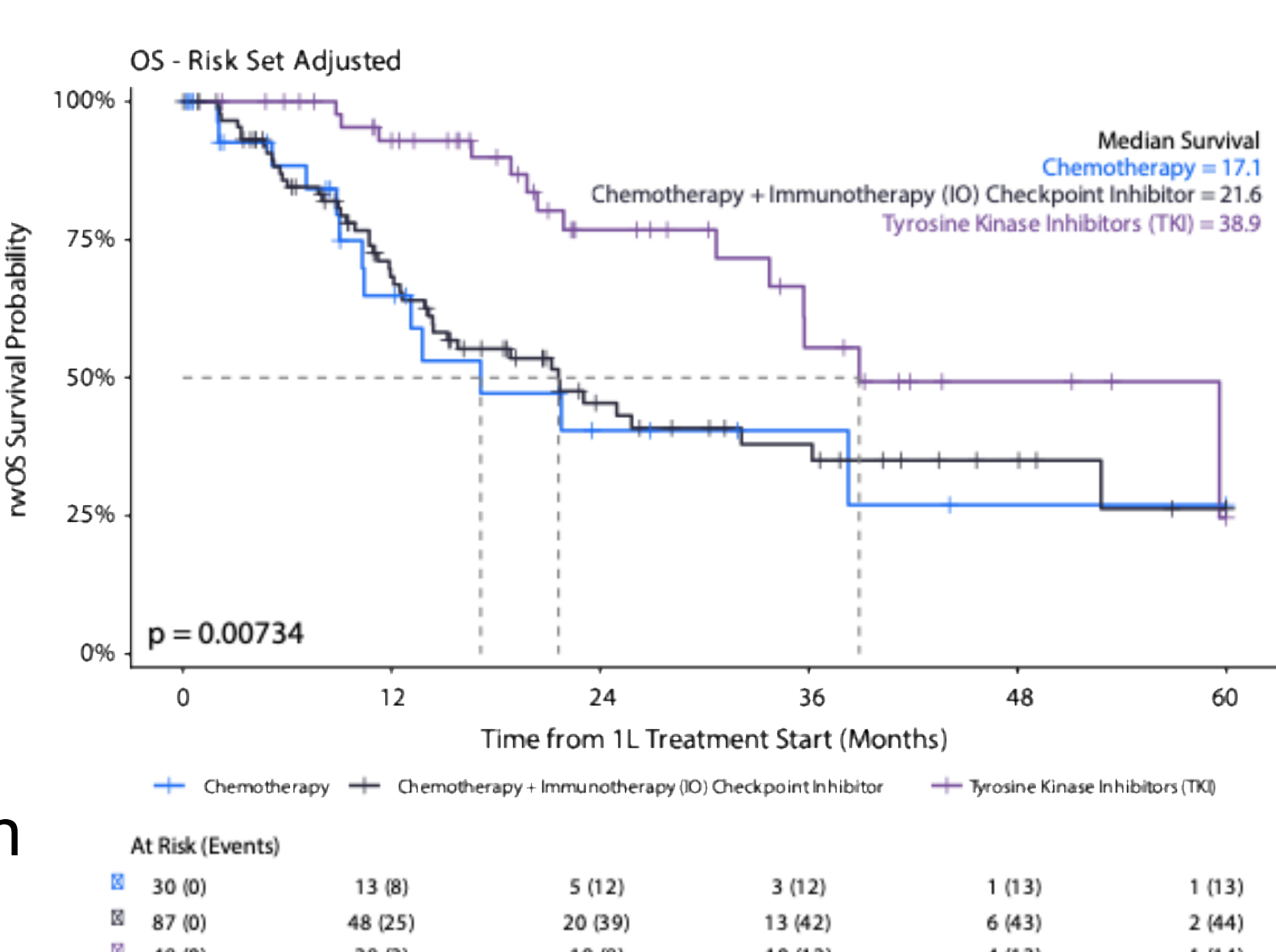


Figure 4: rwOS by smoking status in young-onset NSCLC

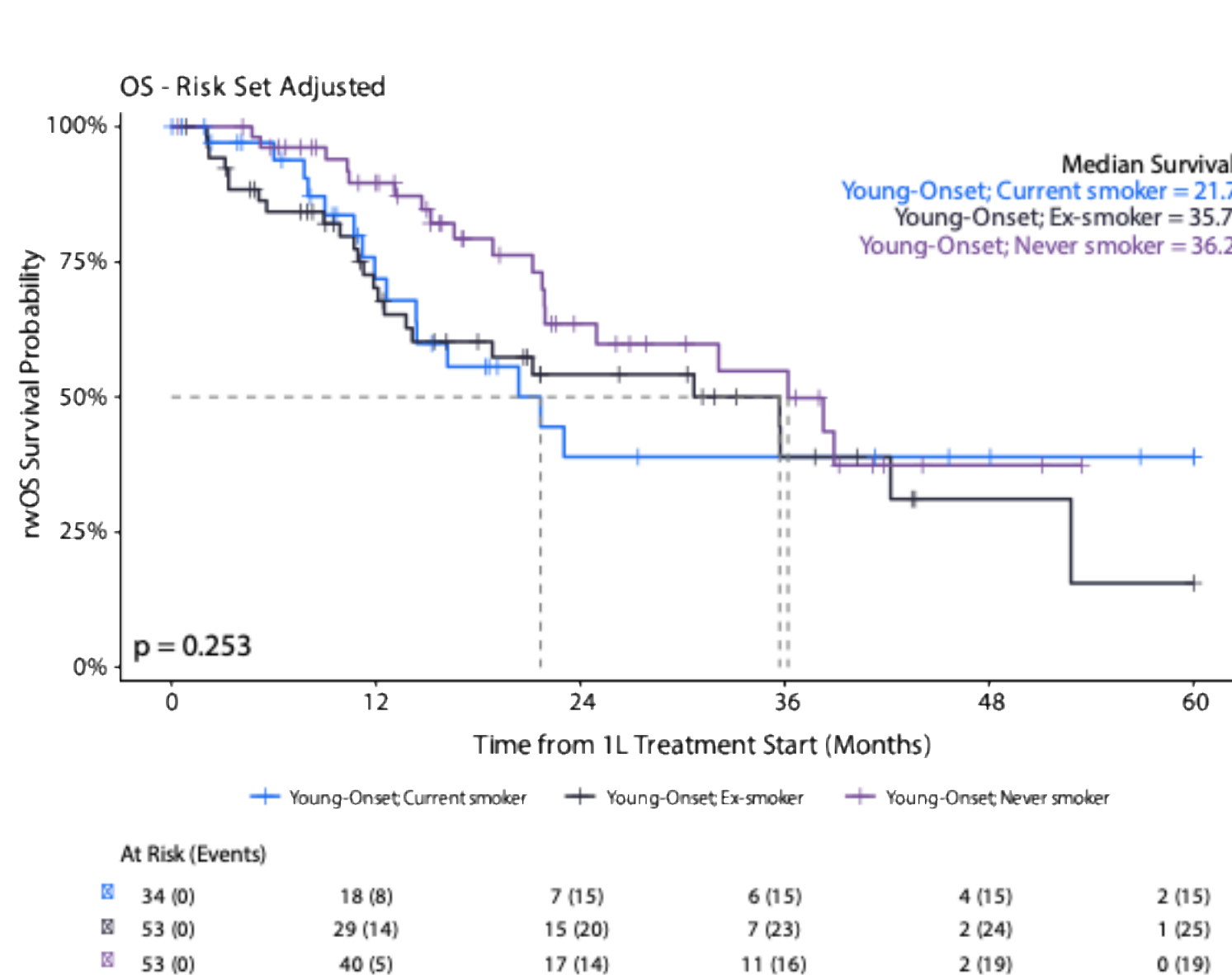


Figure 5: Weighted Cox model for overall survival

Characteristic	N, (%) of patients	HR (95% CI)	p-value
Age at onset			
Average-onset (Ref)	3,283 (54.3%)	Reference	-
Young-onset	200 (40.0%)	0.66 (0.53–0.83)	<0.001
Smoking status at diagnosis			
Current smoker (Ref)	742 (58.4%)	Reference	-
Ex-smoker	1,117 (51.9%)	0.87 (0.76–0.98)	0.028
No smoking history	438 (47.0%)	0.89 (0.74–1.07)	0.212
Actionable alteration*			
No (Ref)	2,650 (57.1%)	Reference	-
Yes	833 (43.3%)	0.64 (0.54–0.77)	<0.001
Race			
Non-White (Ref)	603 (47.4%)	Reference	-
White	2,477 (56.2%)	1.26 (1.10–1.43)	<0.001
Ethnicity			
Hispanic or Latino (Ref)	135 (34.1%)	Reference	-
Not Hispanic or Latino	2,487 (53.5%)	1.48 (1.10–1.99)	0.011
Sex			
Female (Ref)	1,448 (51.4%)	Reference	-
Male	1,835 (56.0%)	1.12 (1.02–1.23)	0.023
Histology at diagnosis			
Non-squamous (Ref)	2,454 (52.0%)	Reference	-
Squamous	862 (57.4%)	1.07 (0.95–1.19)	0.266
1L therapy			
Chemotherapy (Ref)	461 (59.0%)	Reference	-
Chemo + IO	1,813 (54.3%)	0.61 (0.53–0.71)	<0.001
Chemo + TKI	59 (23.7%)	0.53 (0.31–0.91)	0.020
IO	509 (58.2%)	0.71 (0.59–0.85)	<0.001
TKI	488 (45.5%)	0.71 (0.57–0.88)	0.002

*Actionable alterations defined according to NCCN criteria, excluding *KRAS* and *ERBB2*.