

P3.187: Treatment sequences and outcomes in patients with *ALK/ROS1* advanced non-small cell lung cancer: a nationwide cohort study

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INTRODUCTION

- Current first-line (L1) treatment for patients with advanced non-small cell lung cancer (aNSCLC) with *ALK/ROS1* fusions is based on tyrosine kinase inhibitors (TKI)
- The preferred TKI and the optimal sequence is still up to debate
- 3 to 5% of western patients harbor *ALK/ROS1* fusions
- The French National Health Data System (SNDS) is a database that includes anonymous data of reimbursed claims from insurance plans linked to hospital discharge summaries, the national death registry, and covers 98.8% of the French population
- Using the SNDS, we created a cohort including all patients with aNSCLC in France treated with an *ALK/ROS1* TKI. We describe data sources, inclusion and exclusion criteria, basic descriptive analyses, and treatment sequences.

METHODS

Design

- Retrospective nationwide cohort study

Population

- Inclusion criteria
 - Being older than 18 years old
 - Starting a targeted therapy between 2019 and 2024
 - The therapies of interest were crizotinib, ceritinib, brigatinib, alectinib, lorlatinib
- Exclusion criteria
 - Same-sex twins, because their identifiers are not always unique and therefore a source of errors
 - Outliers with aberrant treatment sequences
 - Melanoma diagnosis, identified the previous year prior to the therapy started
 - Lung surgery (pneumonectomy, lobectomy or segmentectomy) to include only therapies for advanced disease

Statistical analysis

- Time-to-event endpoints were estimated using the Kaplan–Meier estimator
- Overall survival (OS) was defined as the time from treatment start to death or censoring
- Time to next treatment or death (TNTD) was defined as the time from treatment start to new treatment initiation or death or censoring
- The cut-off date for the analysis was September 1, 2025.
- As receiving a TKI was an inclusion criterion, all patients who started with another treatment (chemotherapy or immunotherapy) are subject to immortal time. Thus, we did not describe outcomes of treatments received before TKI
- We compared the 3 L1 *ALK* TKI (alectinib, brigatinib, lorlatinib). We used an univariable Cox proportional hazard model and a multivariable Cox proportional hazard model (sex, age, deprivation index, year of diagnosis).

RESULTS

Figure 1: Flow chart

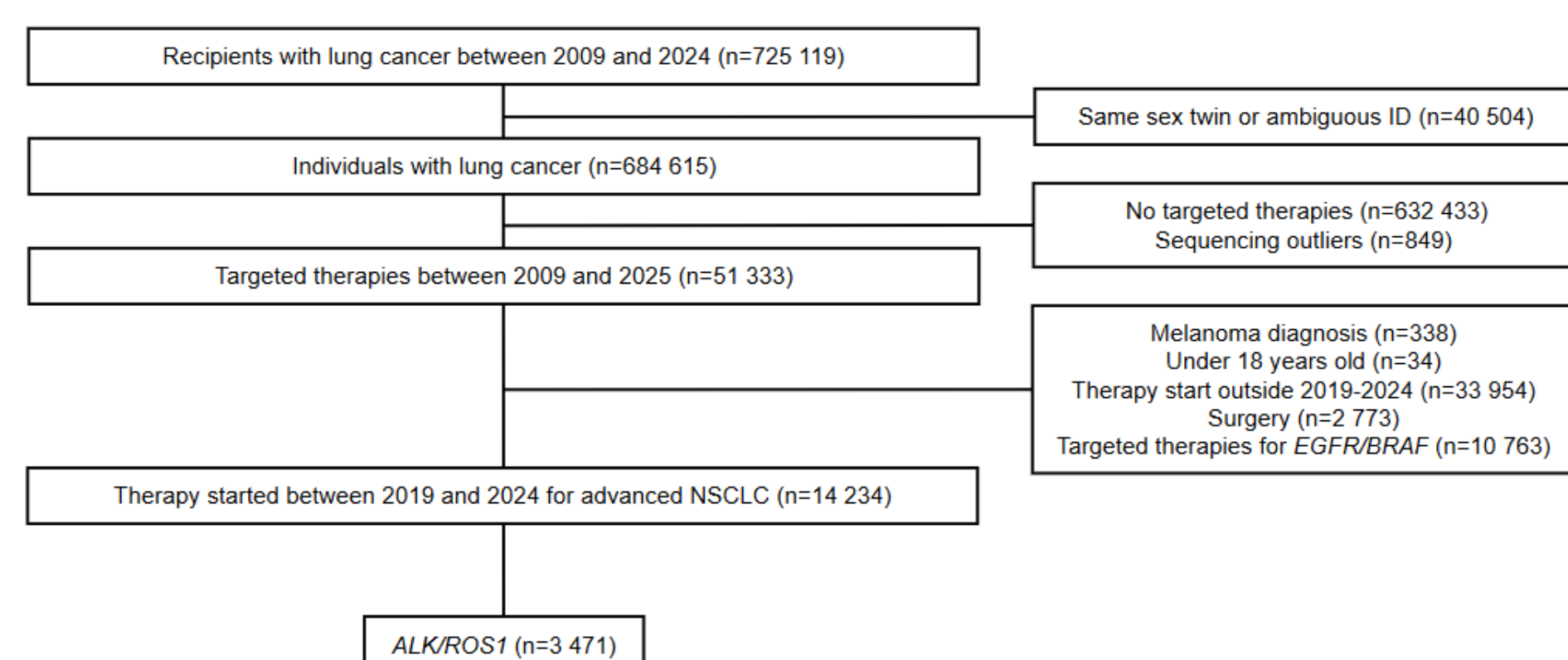


Table 1: Patient's characteristics

	ALK/ROS1 (N=3471)
Sex	
Female	2001 (57.6%)
Male	1470 (42.4%)
Age at diagnosis	
Mean (SD)	65.9 (14.3)
Median [Min, Max]	67.7 [19.1, 101]
Age category	
[18, 50]	517 (14.9%)
[50, 60]	576 (16.6%)
[60, 70]	868 (25.0%)
[70, 80]	930 (26.8%)
[80, 107]	580 (16.7%)
Year of diagnosis	
2020-22	1705 (49.1%)
2023-24	1109 (32.0%)
Before 2019	657 (18.9%)

Table 2: L1 difference analysis

Molecule	Univariable analysis			Multivariable analysis		
	HR	95CI	p-value	HR	95CI	p-value
Overall Survival						
Alectinib				Reference		
Brigatinib	0.87	0.68-1.12	0.29	0.89	0.68-1.16	0.38
Lorlatinib	1.05	0.71-1.54	0.80	1.28	0.85-1.93	0.23
Time to next treatment or death						
Alectinib				Reference		
Brigatinib	1.07	0.90-1.28	0.43	1.04	0.86-1.26	0.67
Lorlatinib	0.99	0.74-1.34	0.99	1.04	0.76-1.44	0.79

Table 3: Survival outcomes

Molecule	Number	Median OS		OS rate at 12 months		OS rate at 24 months		OS rate at 36 months		Median TNTD		TNTD rate at 12 months		TNTD rate at 24 months		TNTD rate at 36 months	
		Estimation (months)	95CI	Estimation (%)	95CI	Estimation (%)	95CI	Estimation (%)	95CI	Estimation (months)	95CI	Estimation (%)	95CI	Estimation (%)	95CI	Estimation (%)	95CI
In first line																	
Alectinib	1347	71.9	59.7-NA	85.1	83.2-87.0	73.7	71.3-76.2	64.6	61.9-67.4	27.1	24.4-31.2	70.1	67.7-72.6	53.0	50.3-55.8	43.7	41.0-46.6
Brigatinib	268	NA	NA	87.9	84.0-91.9	76.9	71.6-82.6	66.0	59.0-73.7	26.9	21.2-31.6	72.5	67.3-78.1	53.8	47.8-60.5	36.4	29.8-44.5
Crizotinib	735	22.6	19.6-25.9	64.1	60.7-67.7	47.6	43.9-51.6	37.1	33.3-41.4	9.1	8.3-10.6	42.5	39.0-46.3	25.9	22.7-29.6	18.2	15.2-21.9
Lorlatinib	139	NA	32.2-NA	85.5	97.4-92.1	73.5	63.0-85.8	55.3	38.1-80.1	32.2	19.6-NA	71.6	64.2-79.8	51.2	39.0-67.2	41.0	24.5-68.8
In second line after alectinib																	
Brigatinib	104	26.5	21.0-NA	72.2	63.9-81.5	54.0	44.6-65.5	38.3	28.0-52.5	7.1	5.0-13.1	40.7	32.2-51.4	20.7	13.9-30.8	18.1	11.6-28.1
Chemotherapy or Immunotherapy based	100	14.3	9.6-23.1	54.8	45.5-65.9	36.6	27.4-48.9	24.6	16.2-37.3	3.3	2.8-4.8	20.8	14.0-30.8	11.2	6.2-20.2	7.2	1.3-15.7
Lorlatinib	379	20.2	15.0-26.7	63.6	58.6-68.9	45.4	39.9-51.6	37.1	31.4-43.9	8.7	9.1-11.6	44.0	39.0-49.6	34.0	29.0-39.8	25.8	20.8-32.1
Other ALK/ROS1 TKI	21	8.1	3.9-27.6	27.1	12.9-57.0	20.4	8.0-51.8	NA	NA	2.6	1.8-11.9	17.2	6.3-47.4	11.5	3.2-41.7	NA	NA
In second line after crizotinib																	
Chemotherapy	97	17.7	11.9-23.0	58.3	48.8-69.7	34.6	25.0-47.6	26.2	17.2-39.9	6.1	4.5-10.8	34.1	25.5-45.7	17.2	10.3-28.8	10.3	4.5-23.6
Immunotherapy	72	13.1	8.5-20.5	51.1	40.3-64.8	33.0	22.7-48.0	NA	NA	6.0	4.3-11.1	32.7	23.1-46.3	20.1	12.1-33.3	NA	NA
Lorlatinib	89	21.6	17.0-36.3	69.6	60.3-80.4	46.9	36.3-60.6	36.6	26.1-51.3	11.7	8.2-23.1	47.6	37.8-60.1	35.7	26.0-49.2	26.2	16.9-40.8
Other ALK/ROS1 TKI	33	NA	23.3-NA	80.9	68.3-95.9	64.7	49.9-83.9	60.9	45.8-81.0	15.2	5.7-27.2	59.2	44.4-79.0	36.2	22.7-57.8	19.2	9.2-40.2
In third line after alectinib then brigatinib																	
Lorlatinib	42	20.1	13.1-NA	72.2	58.9-88.6	35.1	19.8-62.1	NA	NA	5.1	3.0-11.9	30.2	18.5-49.4	15.1	5.9-38.6	NA	NA
Other	24	12.2	6.4-NA	53.9	36.3-80.2	20.5	7.8-54.2	NA	NA	4.2	2.0-10.9	16.0	5.9-43.5	NA	NA	NA	NA

Figure 2: Alluvial plot

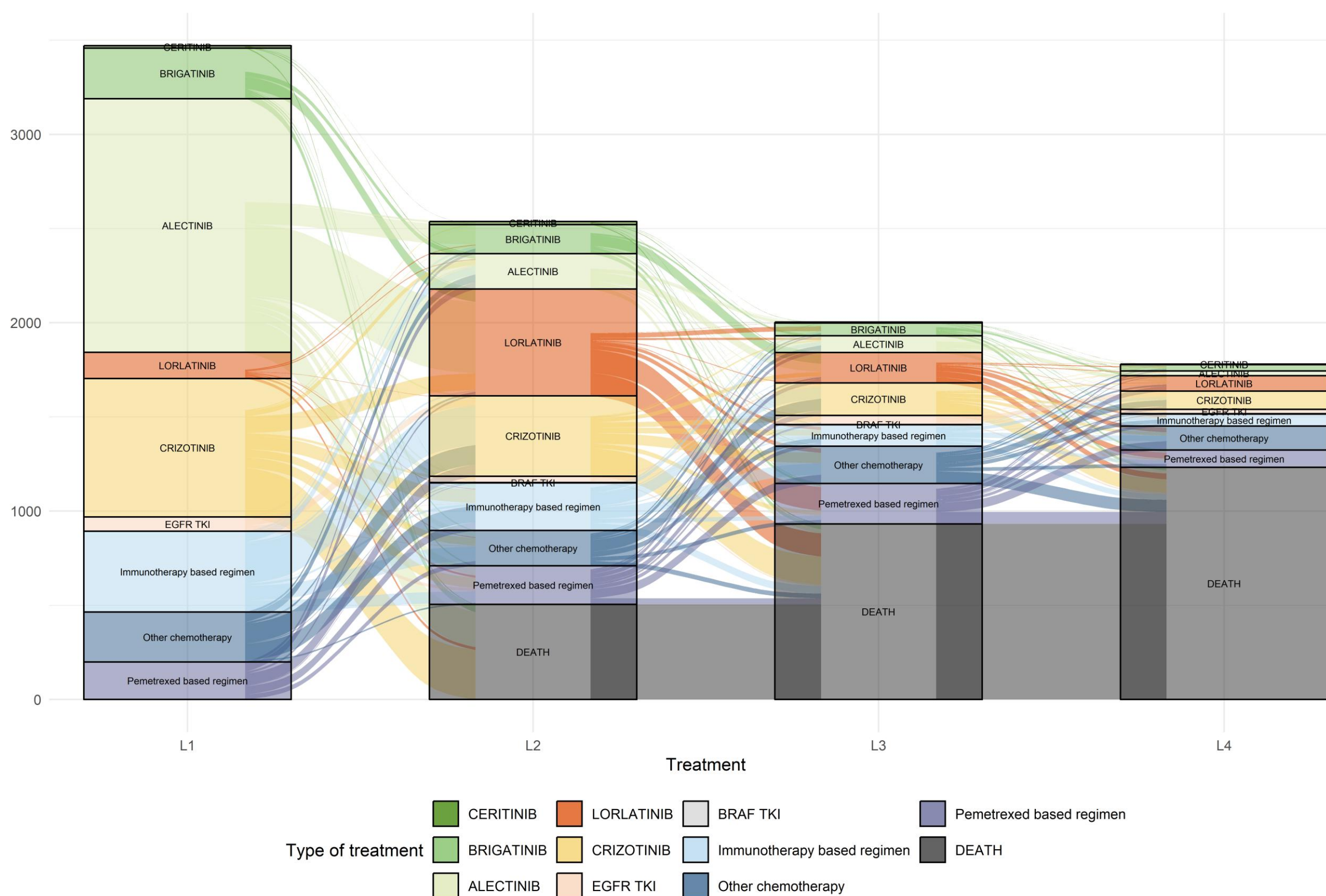
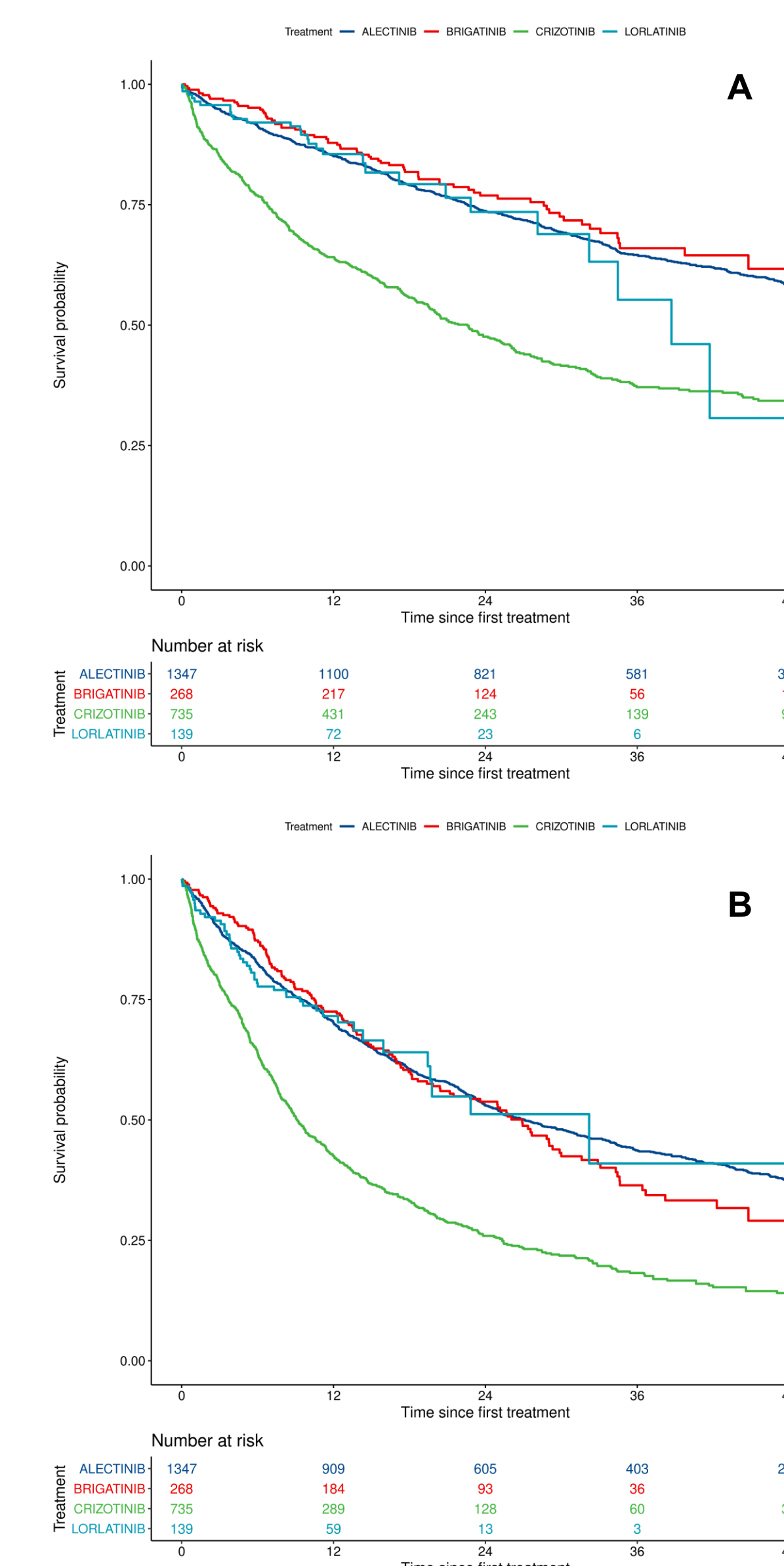


Figure 2: OS (A) and TNTD (B) curves in first line



DISCUSSION

Discussion

- This study is one of the largest real-world cohorts on oncogene addicted aNSCLC
- Overall, real-world outcomes are lower than those reported in clinical trials
- In the *ALK/ROS1* cohort, the median OS of 71.9 months with alectinib was lower than in ALEX trial (81.1 months)¹
- Our results are consistent with other real-world studies^{2,3}
- We did not find a survival difference between L1 TKI for *ALK* patients, consistently with a Korean study which did not find any difference in OS or PFS between alectinib and lorlatinib⁴. Another Korean study found that alectinib and brigatinib demonstrated comparable efficacy in aNSCLC⁵

Strengths and limitations

- Because of the large sample size, we were able to estimate outcomes with great power and high confidence
- External validity should be high because we used a nationwide database
- We included patients treated in small centers, with old age and who died early after treatment initiation
- A retrospective study on administrative data can be prone to selection and confounding bias
- Several important prognosis factors are absent from the database, so we were not able to include them
- Molecular profile is absent from the database; thus, we did not have the information on the mutation that led to prescription. For instance, crizotinib may be prescribed for *ROS1*, *ALK* or *MET* alterations
- Furthermore, if a patient dies before receiving a targeted treatment he cannot be included in this database
- SNDS is an insurance claim database, so treatments during clinical trials are not included. Therefore, newly approved treatments such as neladalkib or zidesaminib are not yet available
- Because of a short follow-up, late events for recent drugs like lorlatinib are underrepresented

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