

P3.188: Treatment sequences and outcomes in patients with *BRAF* 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 *BRAF* mutations is based on tyrosine kinase inhibitors (TKI)
- The preferred TKI and the optimal sequence is still up to debate
- 1 to 2% of western patients harbor *BRAF* mutations
- 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 *BRAF*/MEK 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 dabrafenib, trametinib, encorafenib and binimetinib
- 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 L1 dabrafenib + trametinib vs L2 dabrafenib + trametinib. To limit immortal time bias, we restricted the analysis only to patients who had a L2, ie. dabrafenib + trametinib then L2 versus L1 then dabrafenib + trametinib. 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

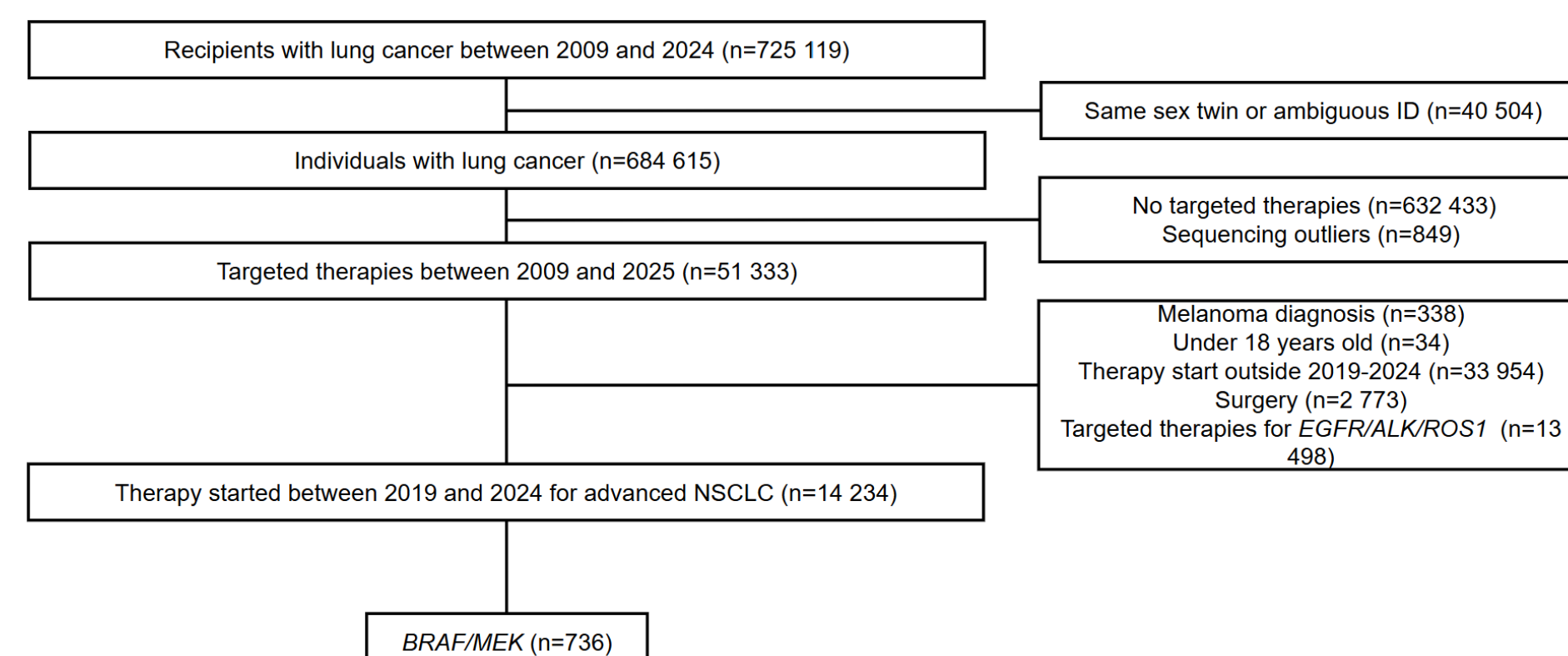


Table 1: Patient's characteristics

	BRAF/MEK (N=736)
Sex	
Female	375 (51.0%)
Male	361 (49.0%)
Age at diagnosis	
Mean (SD)	68.2 (11.0)
Median [Min, Max]	69.1 [34.3, 95.5]
Age category	
(18,50)	43 (5.8%)
(50,60)	137 (18.6%)
(60,70)	208 (28.3%)
(70,80)	246 (33.4%)
(80,107)	102 (13.9%)
Year of diagnosis	
2020-22	378 (51.4%)
2023-24	196 (26.6%)
Before 2019	162 (22.0%)

Table 2: Sequence analysis

Molecule	Univariable analysis			Multivariable analysis		
	HR	95CI	p-value	HR	95CI	p-value
BRAF sequence						
Dabrafenib b+Trametinib first				Reference		
Chemotherapy first	1.51	1.01-2.24	0.04	1.40	0.92-2.21	0.11
Immunotherapy first	1.26	0.87-1.83	0.22	1.17	0.79-1.73	0.42

Table 3: Survival outcomes

Molecule	Nu mber	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
In first line									
Dabrafenib b+Trametinib	240	24.6	18.9	67.1	61.3	51.0	44.6	37.7	31.1
								11.7	9.9
								49.5	43.4
								26.6	21.0
								19.7	14.6-26.6
In second line after immunotherapy									
Chemotherapy	75	14.3	10.6	58.1	47.6	34.2	24.5	23.7	14.8
								2.3	1.8
								13.3	7.5
								4.0	1.3
								NA	NA
Dabrafenib b+Trametinib	174	16.8	14.0	61.5	54.4	40.5	33.0	34.2	26.4
								9.5	7.5
								42.0	34.8
								24.7	18.4
								17.9	12.1-26.5
In second line after dabrafenib+trametinib									
Chemotherapy	17	17.7	14.5	76.5	58.7	41.7	22.9	33.4	15.9
								4.6	2.3
								11.8	3.2
								NA	NA
								NA	NA
Immunotherapy	41	13.5	6.0	56.2	42.0	35.3	21.0	26.5	12.3
								2.2	1.4
								26.7	15.3
								23.4	12.7
								NA	NA
Pembrolizumab + pemetrexed	24	NA	36.5	86.2	75.8	75.7	59.1	NA	12.8
								11.0	54.8
								37.3	29.9
								15.4	15.4
								24.9	24.9
									11.7-52.9

Figure 2: Alluvial plot

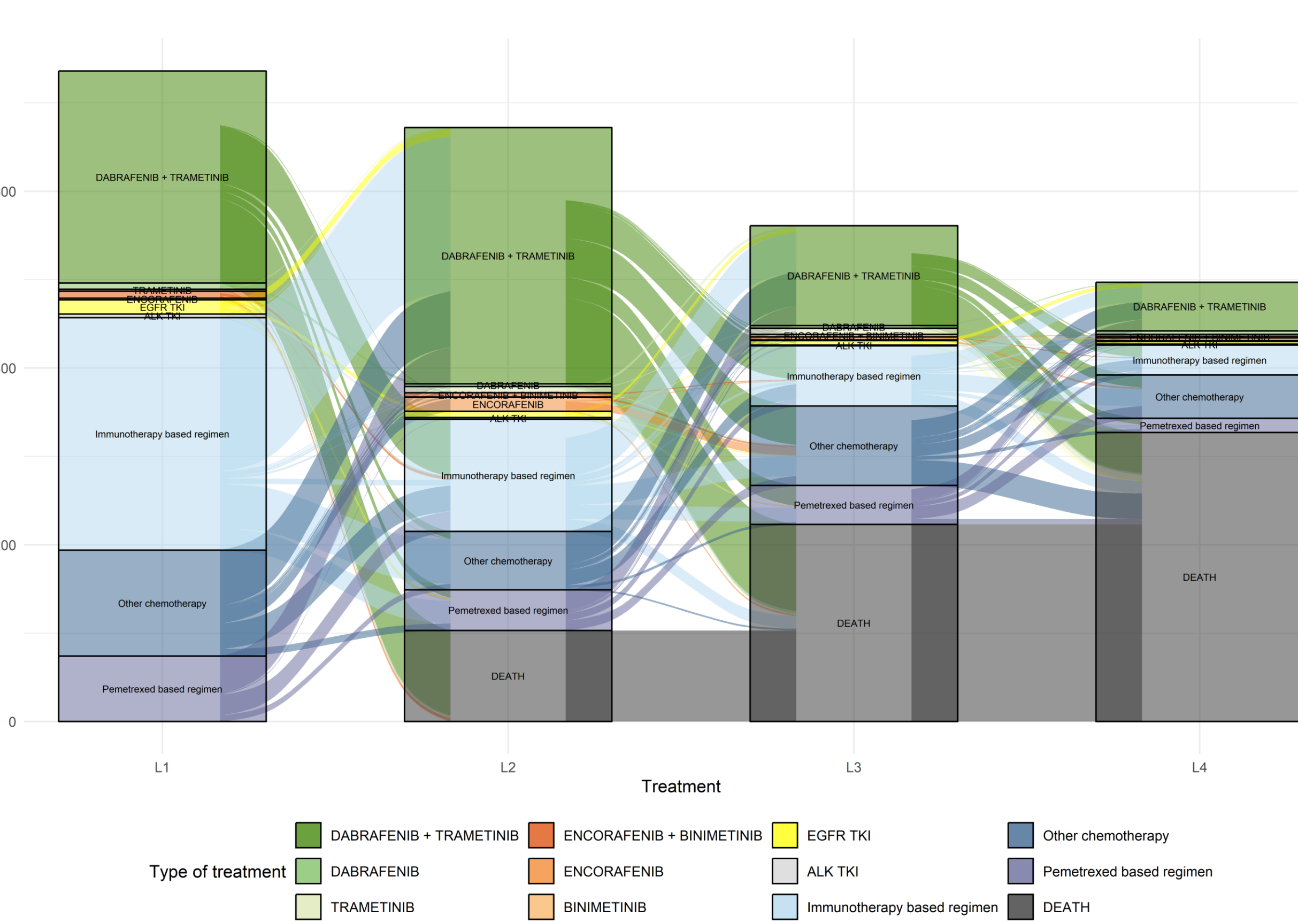


Figure 2: OS (A) and TNTD (B) curve of L1 dabrafenib + trametinib

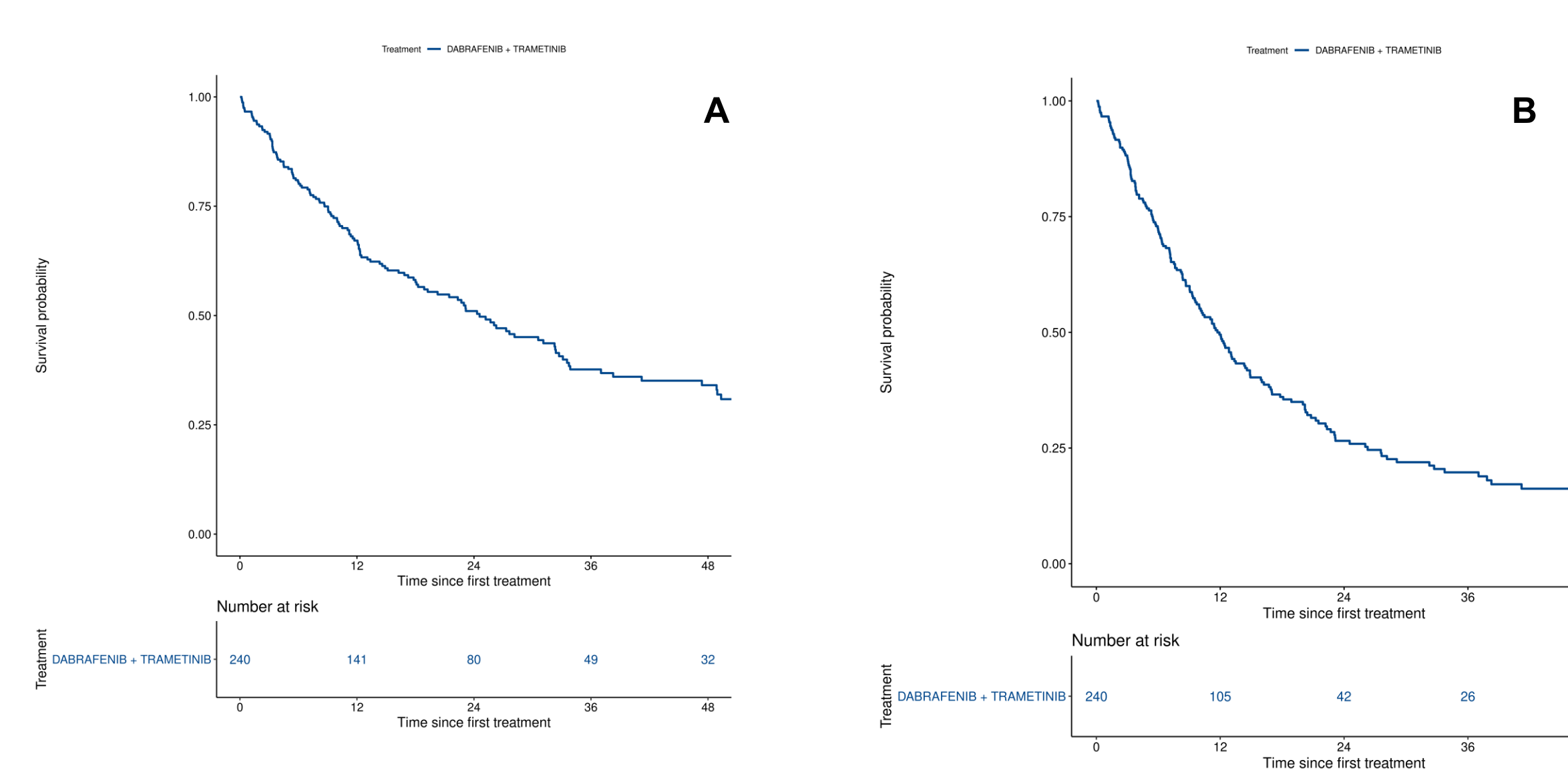
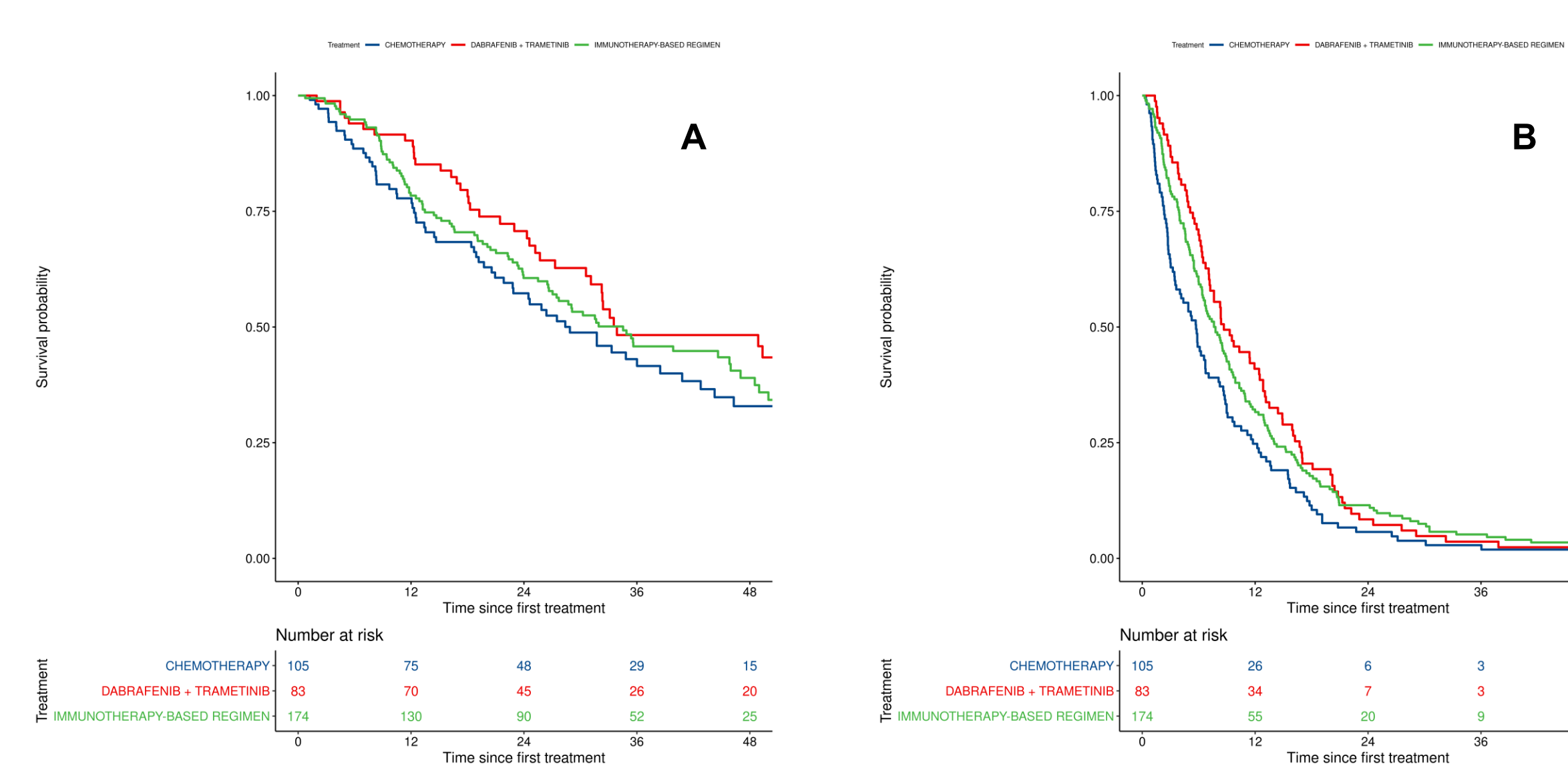


Figure 3: OS (A) and TNTD (B) curves in patients who received at least 2 lines



DISCUSSION

Discussion

- This study is one of the largest real-world cohorts on oncogene addicted aNSCLC
- In clinical trials, the median OS of untreated patients under targeted therapies was 18.2 months with dabrafenib + trametinib¹ and 47.6 months with encorafenib + binimetinib². Our results are somewhere in the middle with 24.6 months and are consistent with other observational studies³.
- The optimal sequence in BRAF disease is still under debate. In an multicentric retrospective cohort of 286 patients with BRAF V600E mutation⁴, immunotherapy with or without chemotherapy was associated with improved OS compared to BRAF/MEK inhibitors. However, in a German retrospective cohort of 205 patients⁵, OS and time-to-treatment failure was identical for patients receiving first-line dabrafenib + trametinib or chemo-immunotherapy. We did not find any difference in OS between these two strategies in our study, but our analysis is limited.

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.
- Furthermore, if a patient dies before receiving a targeted treatment, he cannot be included in this database
- Because we had to restrict the analysis to patients receiving at least 2 lines of treatment, this analysis did not include early deaths

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SCAN ME

