

Treatment sequences of patients surviving at least two years after initiation of nivolumab in previously treated advanced non-small cell lung cancer (aNSCLC): contribution of time-sequence K-clustering analysis

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Introduction

- More than 46,000 people were diagnosed with lung cancer in France in 2018¹. Lung cancer is frequently diagnosed at an advanced stage, with 5-year survival rates historically not exceeding 5%^{2,3}. Non-small cell lung cancer (NSCLC) is the most common histological subtype, accounting for 87% of all cases. In phase III clinical trials, immunotherapies (PD-1/PD-L1 inhibitors) such as nivolumab, pembrolizumab and atezolizumab showed greater efficacy compared to docetaxel in second-line treatment of advanced NSCLC⁴⁻⁶.
- Nivolumab has been available in France since January 2015, at first under the Temporary Authorisation for Use programme (ATU), and then as a marketed drug for locally advanced or metastatic NSCLC patients previously treated with chemotherapy^{7,8}.

UNIVOC background

UNIVOC is a cohort of 10,452 patients including all patients with aNSCLC who had started treatment with nivolumab within two years of its availability in France, identified through the hospital database (Programme de Médicalisation des Systèmes d'Information, PMSI).

The UNIVOC study previously described

- The outcomes of subsequent retreatment and rechallenge with a PD-1 inhibitor after nivolumab discontinuation⁹.
- The long-term overall survival of patients treated with immunotherapy including special populations¹⁰.

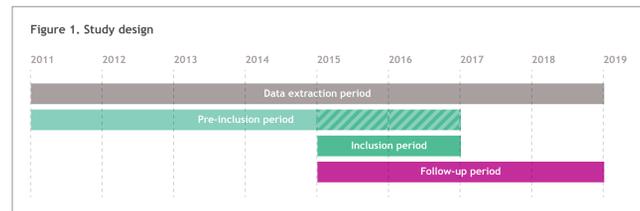
Study rationale

- Long-term management (≥ 2 years of treatment initiation) of patients with aNSCLC treated by nivolumab is poorly documented.
- Treatment sequences analyses are usually pre-defined, simplistic and not time-dependent.
- Post-immunotherapy data in real-world clinical practice are limited and the heterogeneity of practices makes the analysis of treatment sequences complex. Thus, machine learning and innovative algorithmic approaches are relevant.

Study objectives

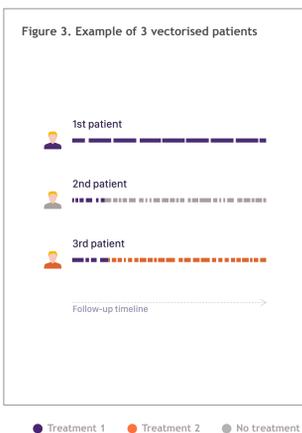
- To describe treatment sequences.
- To identify clusters of patients presenting similar treatment sequences.
- To determine patients' profile from each cluster.

Methods



Study design

Univoc consists in a retrospective a retrospective cohort of all NSCLC patients in the PMSI database (ICD-10 code: C34*), who had received at least one line of platinum-based chemotherapy and started nivolumab in 2015 or 2016. Patients alive two years after initiating nivolumab were identified. Patients were followed until December 2018 (Figure 1).



Analyses

- The analyses used machine learning techniques (Figure 2).
- The clustering technique was the Time sequence Analysis through K-clustering (TAK). It allowed us to model each patient's pathway as a vector and search for common sequences and clustering of similar trajectories (Figure 3). Thus, TAK offered one image with all the information.
- Clinical characteristics of patients within the different clusters were analysed. Characteristics such as age, gender, histology, previous treatment (radiotherapy, surgery), and hospital type were analysed via a pairwise multinomial logistic regression.
- Therapeutic options were: immunotherapies (including nivolumab and pembrolizumab), chemotherapy anti-VEGF therapy (including pemetrexed, bevacizumab and others) and treatment-free interval. For each cluster, cumulative median durations (CMD) of therapeutic options were calculated, and patients characteristics were described (sociodemographic, previous therapeutic management care and comorbidities).

Results

Treatment sequences and TAK algorithm application

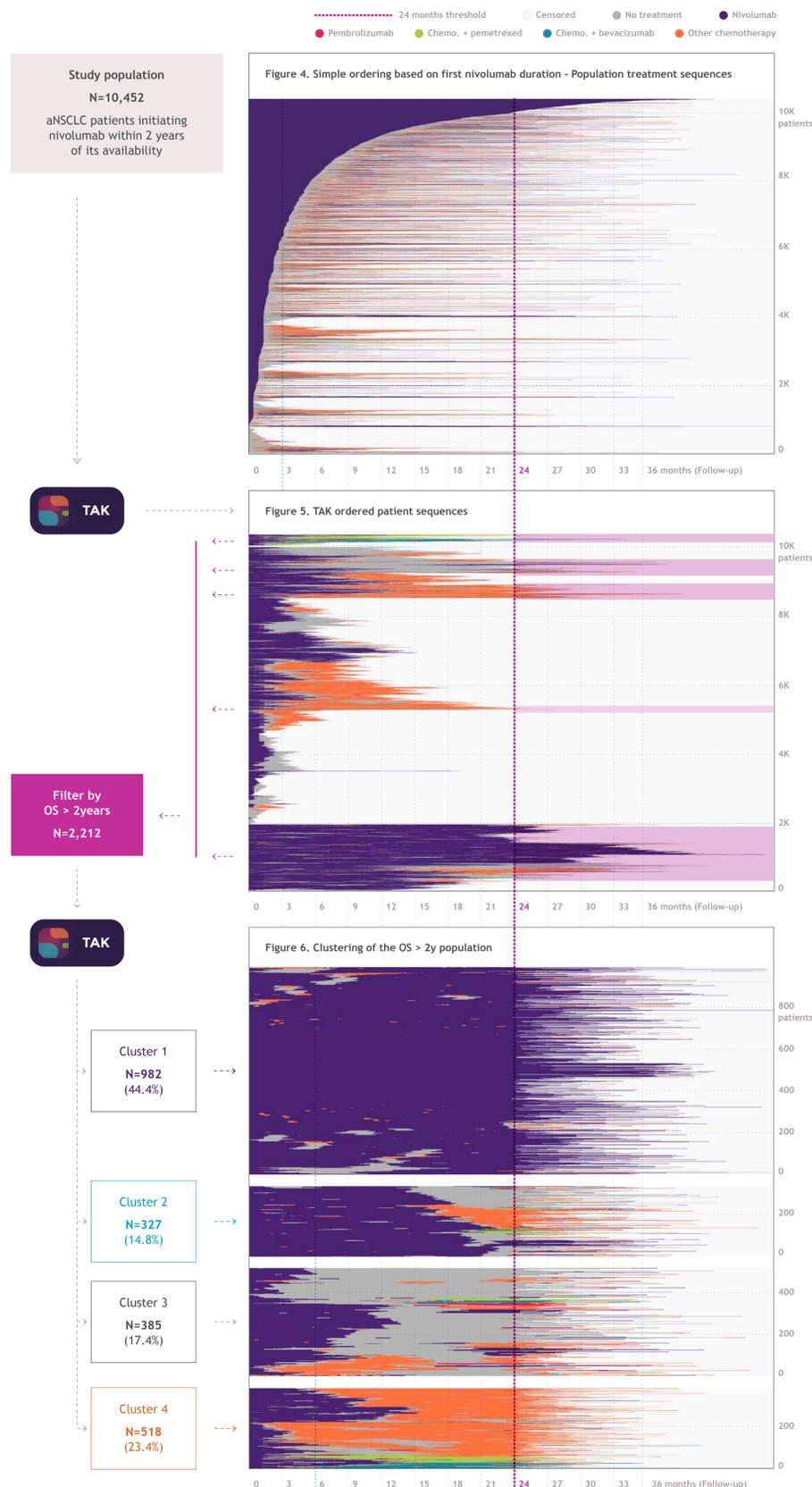
- Figure 4 presents a simple ordering of patient treatment sequences according to initial nivolumab treatment duration. This presentation lacked readability of the figure due to the number of patients (N>10,000). Heterogeneity of treatment sequences and patient outcomes following similar nivolumab treatment duration were high. Thus, no obvious additional assumption could be made for further classification.
- TAK algorithm application revealed the different survival times depending on the treatment sequences (Figure 5).

TAK reapplied to treatment sequences allowed us to flag 4 different clusters within the population of 2,212 patients still alive 2 years after nivolumab treatment (Figure 6).

- Cluster 1** gathered patients with nivolumab as the main treatment over the first 24 months, received almost continuously with a cumulative median duration (CMD) of 21.0 months. Grey/orange spots indicate retreatment/rechallenge with nivolumab*.
- Cluster 2** gathered patients with nivolumab as the main treatment (CMD: 16.5 months) followed by a short chemotherapy (CMD: 2.5 months) and/or a therapeutic break (CMD: 5.3 months).
- Cluster 3** gathered patients with short nivolumab treatment (CMD: 6.4 months) followed by a long therapeutic break (CMD: 14.4 months) with or without chemotherapy.
- Cluster 4** gathered patients with short nivolumab treatment (CMD: 5.5 months) followed by one or several lines of chemotherapy (CMD: 9.5 months).

After comparison of cluster 1 with all other ones, no association with hospital type, histology, or comorbidities could be identified. However, **cluster 1** population was associated with younger patients (<60 years old) with recent lung cancer history (<1 year). Patients also had more brain metastases (except vs **cluster 2**) and more history of radiotherapy. Finally, fewer patients had been treated with surgery since the beginning of their cancer care.

* Nivolumab treatment performed a second or subsequent time after grey/orange spots



Conclusion

Using a large sample of NSCLC patients still alive 2 years after nivolumab initiation, the Machine Learning approach enabled us classifying patients with similar treatment sequences and to identify 4 clusters of patients with distinct care features who as long-term survivors:

- Received nivolumab almost continuously (**Cluster 1**);
- Received nivolumab for a long time but discontinued nivolumab treatment (**Cluster 2**);
- Discontinued nivolumab early and had no subsequent systemic treatment (**Cluster 3**);
- Discontinued nivolumab early and then started a subsequent chemotherapy (**Cluster 4**);

Patients in **Cluster 1** appeared to be particularly different from other clusters. An in-depth study of their clinical profile could provide a better understanding of their specificities.

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Disclosure

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Conflicting interests

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