12e colloque
Données de Santé en vie réelle

UNIVOC

Management of patients with advanced non-small cell lung cancer who are alive 2 years after nivolumab initiated in second-line or beyond: contribution of a Machine Learning procedure

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Disclosure Information

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Conflicting interests:

Pr Christos Chouaïd reports consultancy fees from Astra Zeneca, Boehringer Ingelheim, MSD, Pierre Fabre Oncology, Lilly, Roche, Bristol Myers Squibb, and Novartis.

Background and Context (1/2)

- More than 46,000 people were diagnosed with **lung cancer** in France in 2018. [1]
- Lung cancer is frequently diagnosed at an advanced stage with **5-year survival rates** historically that do not exceed 5%. [2]
- **Non-small cell lung cancer (NSCLC)** is the most common histological subtype, accounting for 87% of all cases. [3]
- In phase III clinical trials, **immunotherapies** (PD-1/PD-L1 inhibitors) such as nivolumab, pembrolizumab and atezolizumab showed greater efficacy compared with docetaxel in second-line treatment of advanced NSCLC.
- **Nivolumab is available in France since January 2015**, at first under the Temporary Authorization for Use program (ATU), and then as a marketed drug for locally advanced or metastatic NSCLC patients who have previously received chemotherapy. [4-5]

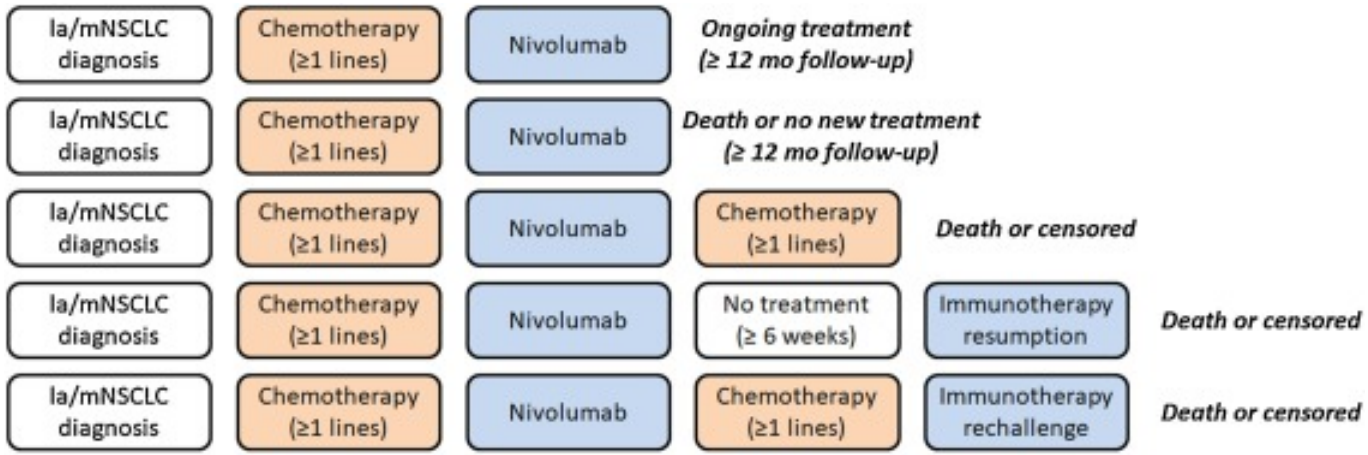
[1] InCa. 2019; [2] Siegel et al. *Cancer J Clin*. 2019; [3] Grapatsas et al. *Oncomed.* 2017; [4] Brahmer et al. *NEJM* 2015; [5] Borghaei et al. *NEJM* 2015

Background and Context (2/2)

- **Post-immunotherapy** data in real-world clinical practice are limited.
- Based on the National hospital database (PMSI), the **UNIVOC study** previously described [1]:
  - The usage of nivolumab in a **large population** of unselected patients with advanced NSCLC in France (>10,000 patients);
  - The clinical interest of subsequent retreatment and **rechallenge with a PD-1 inhibitor** after initial nivolumab discontinuation.

Limits of treatment sequences analysis:

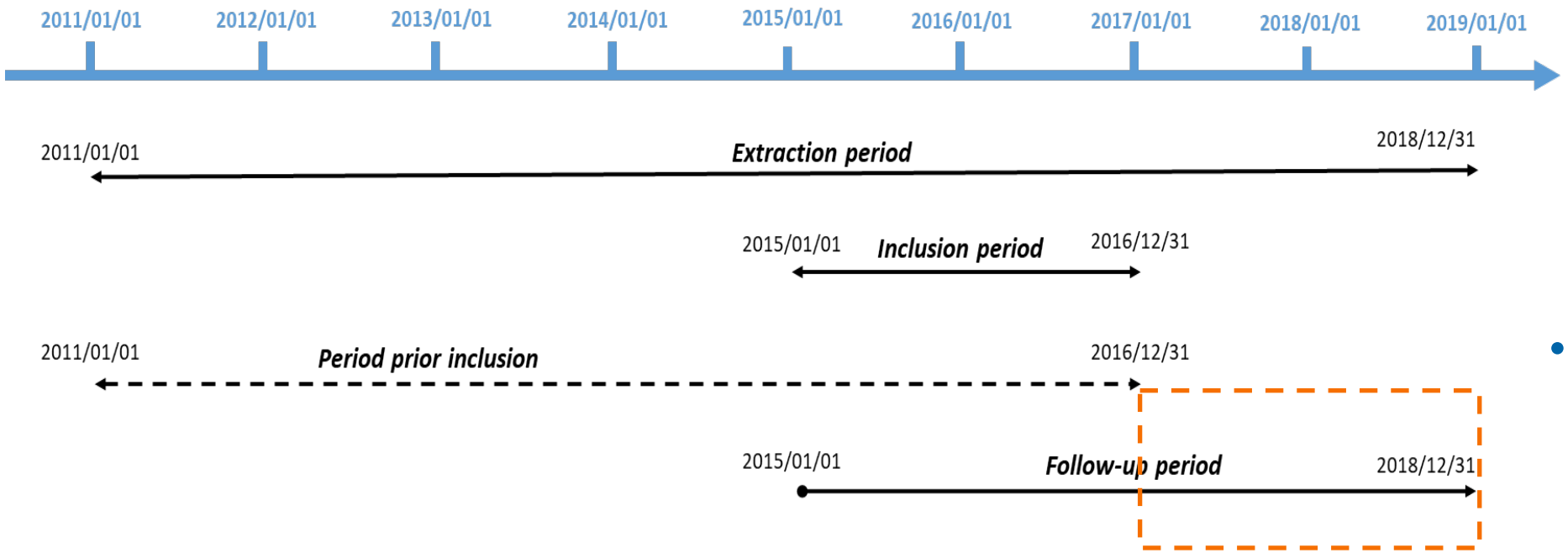
- Pre-defined
- Simplistic
- Not time-dependent



[1] Giaj Levra M, Cotté FE, Corre R et al. *Lung Cancer* 2019, 140:99–106

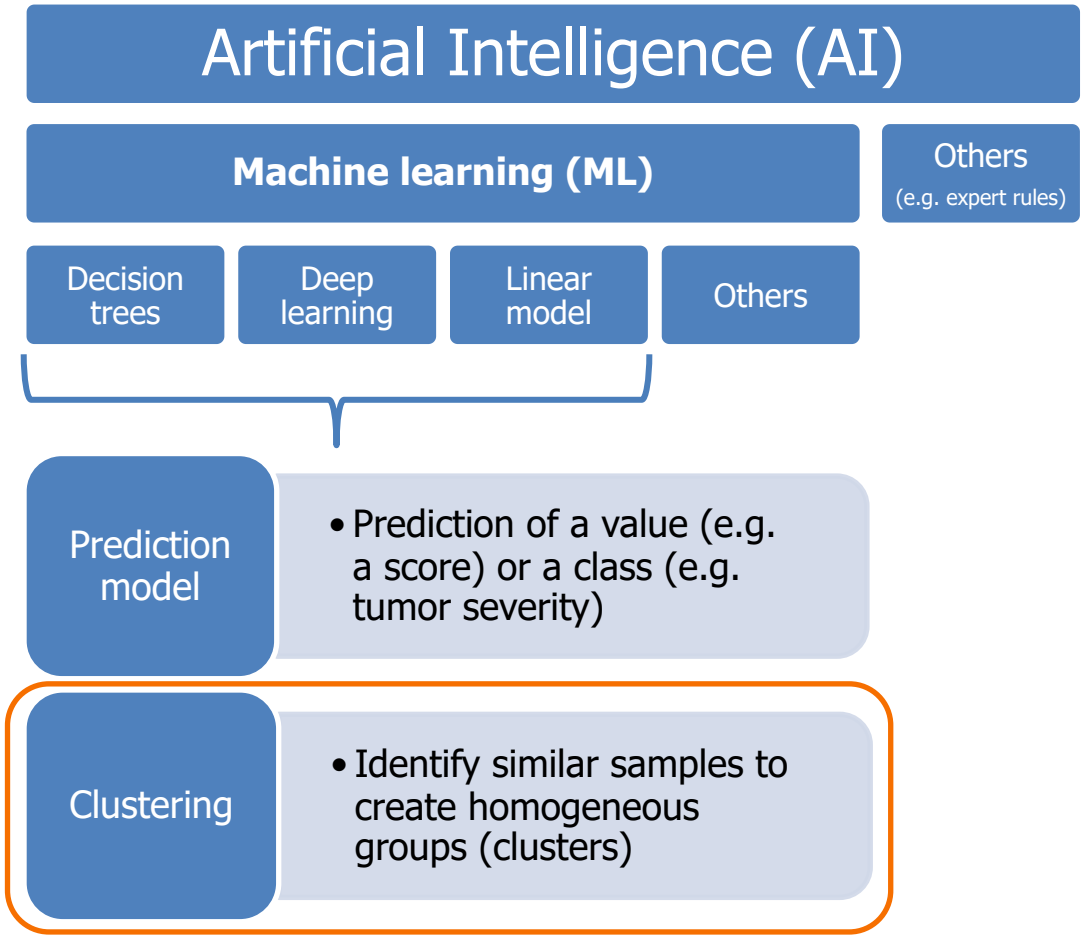
Methods (1/2) – Population

- A **retrospective cohort** of all NSCLC patients in the PMSI database (ICD code: C34*), who had received at least one line of platinum-based chemotherapy and started nivolumab in 2015 or 2016 were followed until December 2018 (N = 10,452)



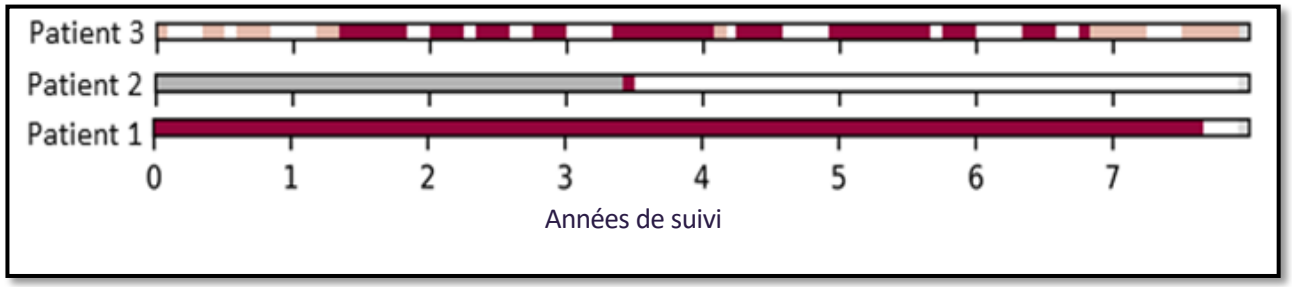
- **Selection** of patients alive 2 years after nivolumab initiation (N = 2,212)

Methods (2/2) – Analyses



Use of the *Time sequence Analysis through K-clustering* (TAK)

- To model each patient and their pathway as a **vector**
- Search for common sequences and **clustering of similar trajectories**
- The TAK offers one **image** with all the information

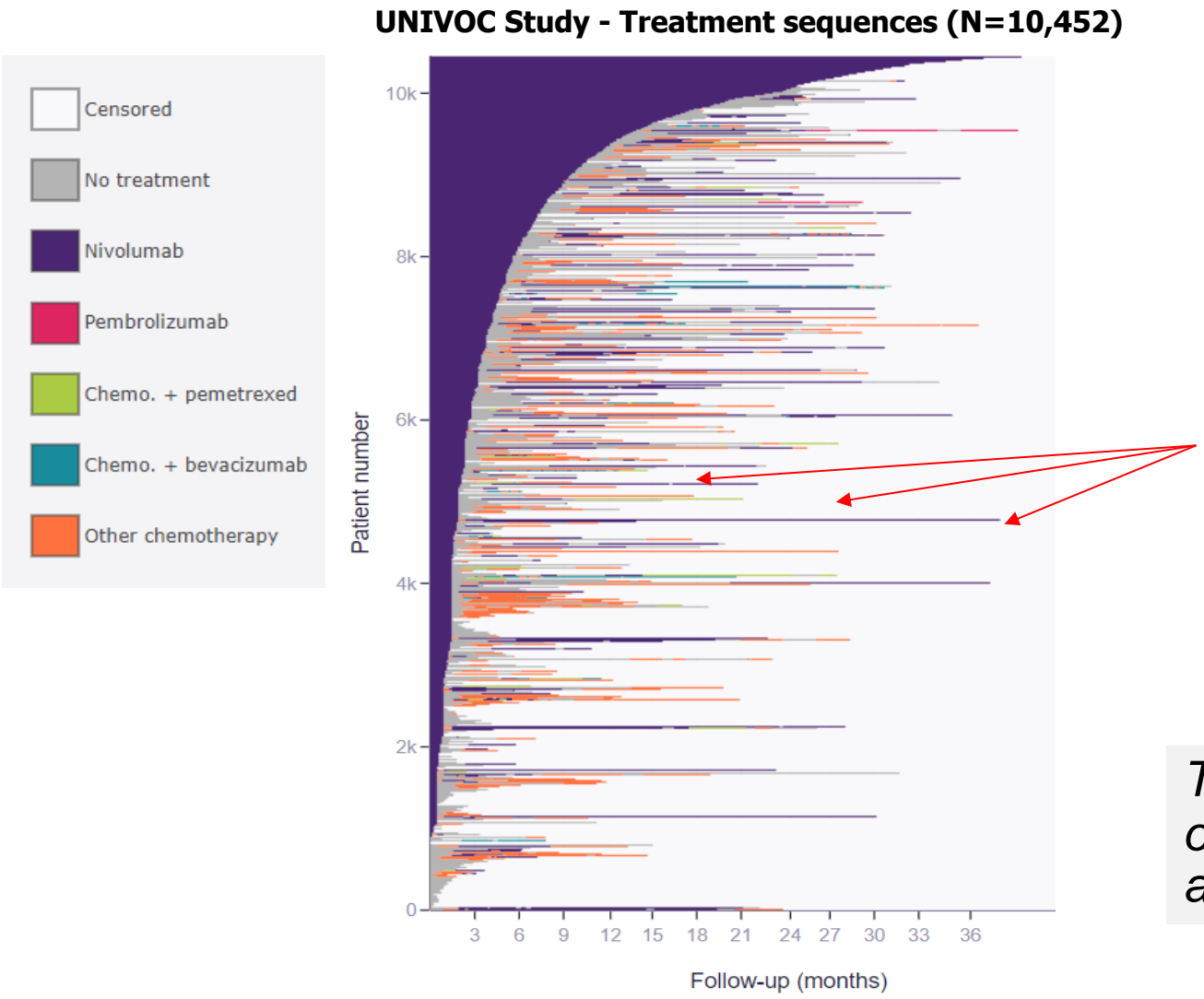


Exemple of 3 vectorised patients

Clusters: exploration of clinical characteristics of patients

- Age, gender, histology, metastases location, cancer history, comorbidities, previous treatment (radiotherapy, surgery), hospital type (CH, CHU, CLCC, others)
- **Pairwise multinomial logistic regression**

Results (1/5) – Treatment sequences in overall population (N=10,452)



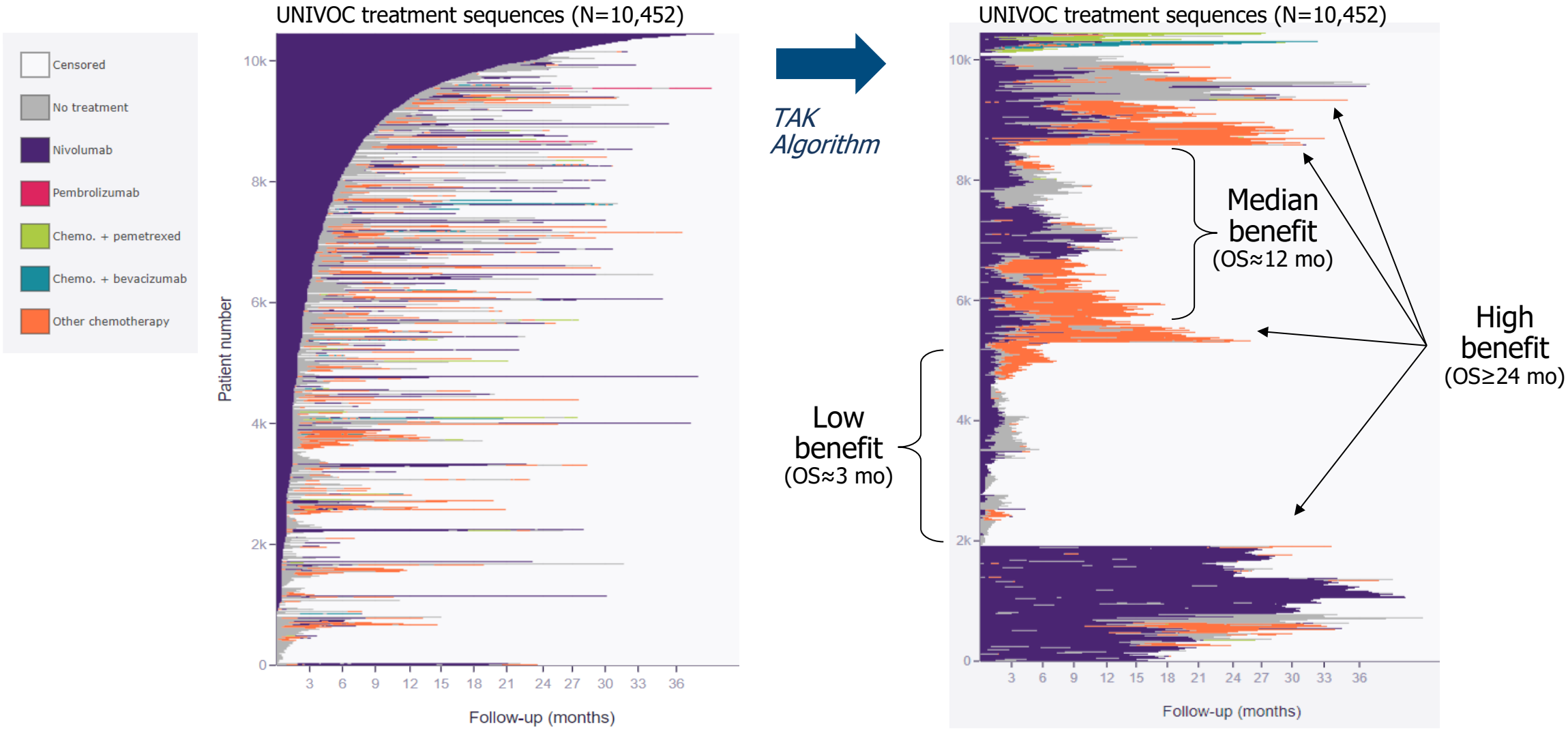
Simple ordering according initial nivolumab treatment duration

Limits:

- Lack of readability of the figure due to number of patients (N>10,000)
- High heterogeneity of sequences and benefit within patients presenting similar nivolumab treatment duration
- No obvious additional assumption for further classification

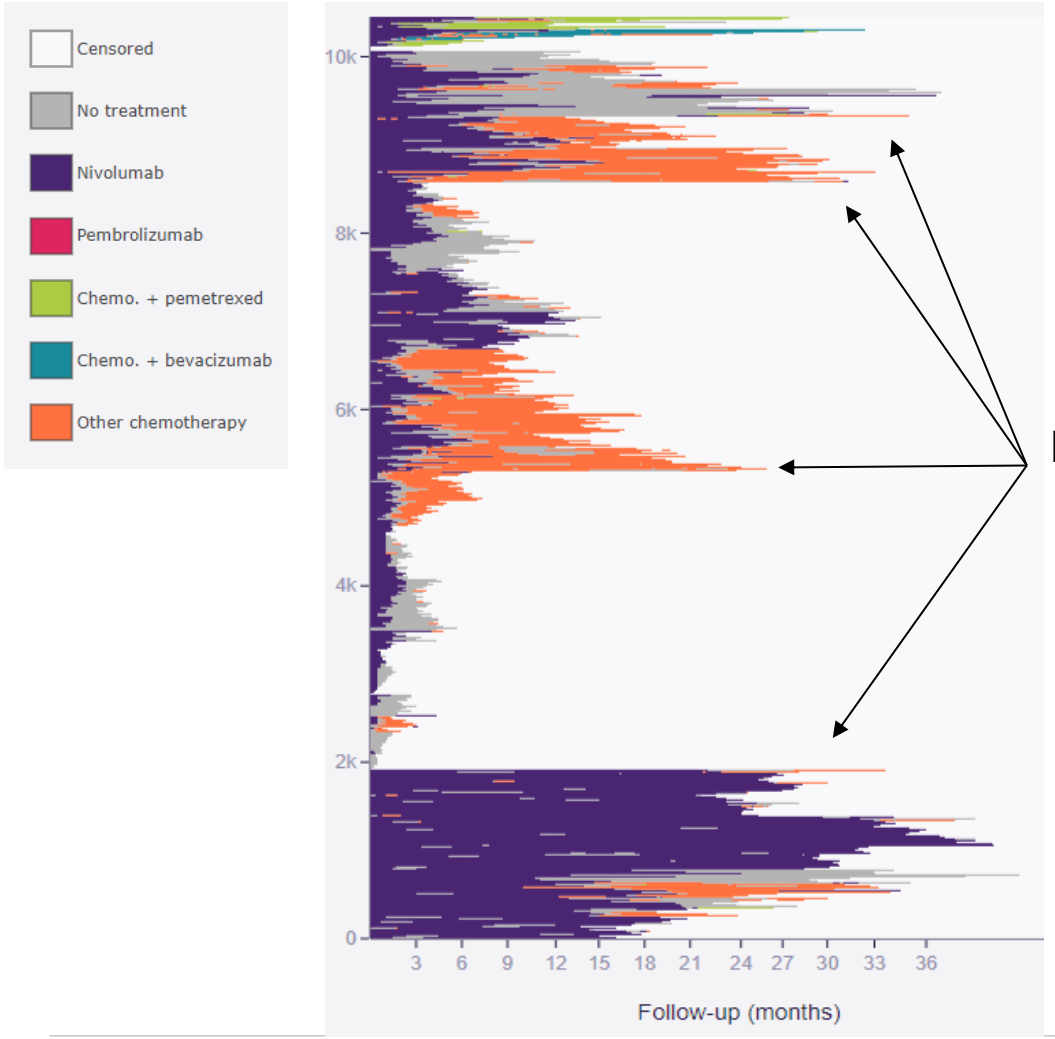
The heterogeneity of practices makes the analysis of ***treatment sequences*** *complex but* ~~*and also*~~ *appropriate for a* ***machine learning approach****.*

Results (2/5) – TAK applied on overall population (N=10,452)



Results (3/5) – Clustering in 2-year survivor population (N=2212)

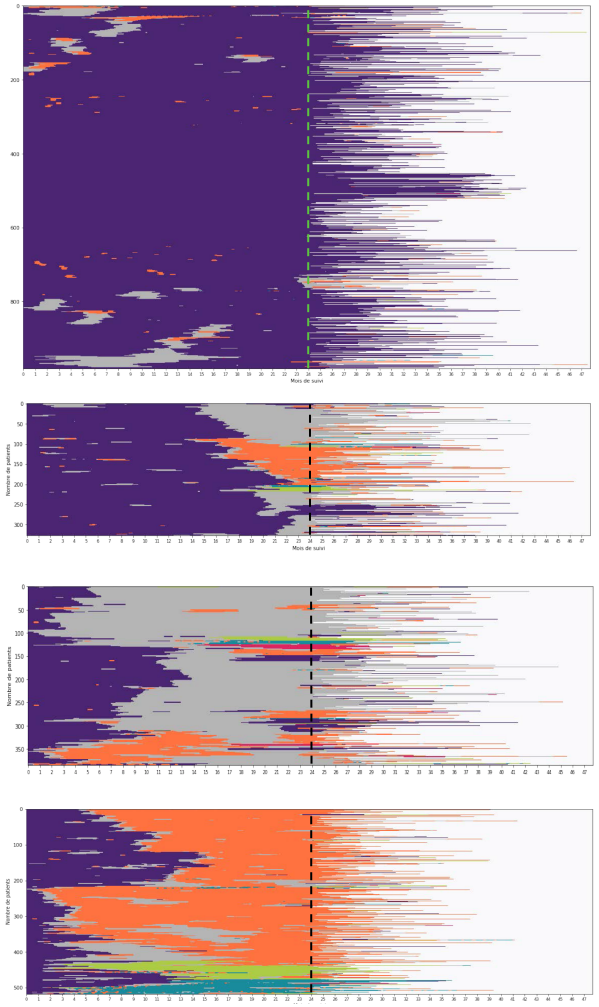
UNIVOC treatment sequences (N=10,452)



Patient selection (alive at 2 years) and clustering

High benefit
(OS ≥ 2 years)

UNIVOC treatment sequences (N=2212)



<u>Cluster 1</u>: N = 982 (44.4%)

<u>Cluster 2</u>: N = 327 (14.8%)

<u>Cluster 3</u>: N = 385 (17.4%)

<u>Cluster 4</u>: N = 518 (23.4%)

→ Cluster initially divided in 2 clusters by type of CT

Results (4/5) – 4 clusters of patients

Cluster 1:

- Nivolumab as the main treatment over the 24 first months, received almost continuously with a **cumulative median duration (CMD)** of 21.0 mo.
- Grey/orange spots indicate retreatment/rechallenge with nivolumab

Cluster 2:

- 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)

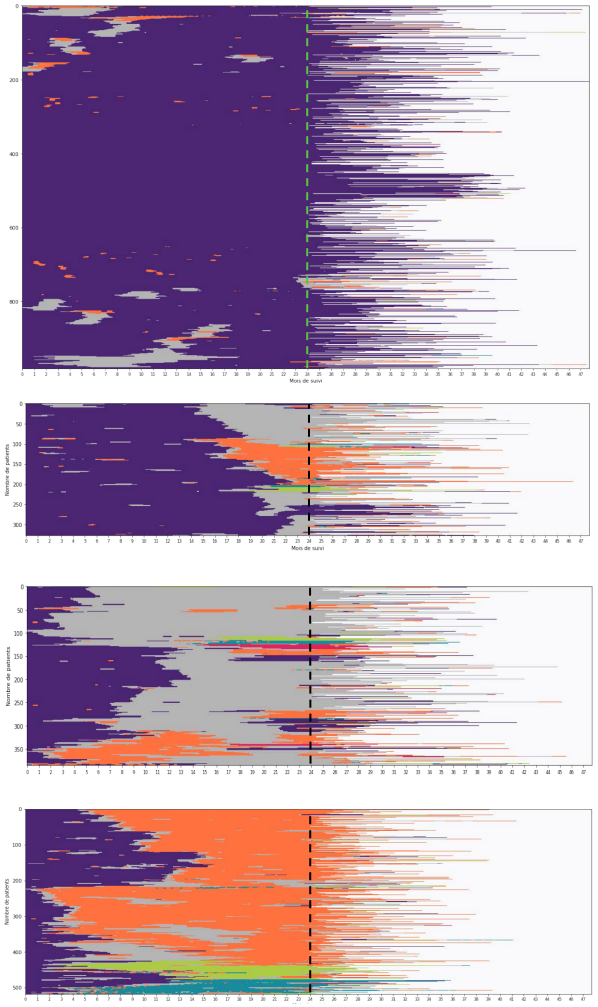
Cluster 3:

- Short treatment with nivolumab (CMD: 6.4 months) followed by a long therapeutic break (CMD: 14.4 months) +/- chemo

Cluster 4:

- Short treatment with nivolumab (CMD: 5.5 months) followed by one or several lines of chemotherapy (CMD: 9.5 months).

UNIVOC treatment sequences (N=2,212)



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Cluster 3: N = 385 (17.4%)

Cluster 4: N = 518 (23.4%)

→ Cluster initially divided in 2 clusters by type of CT

Results (5/5) – Characteristics of Cluster 1

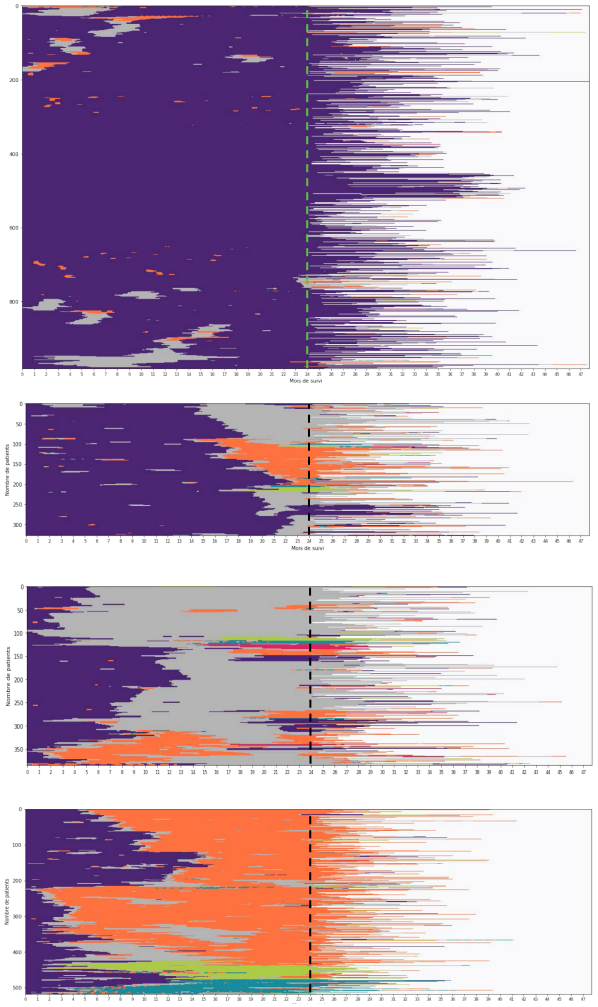
Cluster 1:

- Nivolumab as the main treatment over the 24 first months, received almost continuously with a **cumulative median duration (CMD)** of 21.0 mo.
- Grey/orange spots indicate **retreatment/rechallenge** with nivolumab

Cluster 1 vs
- Cluster 2
- Cluster 3
- Cluster 4

- No association with hospital type, histology or comorbidities
- Association with
  - Younger patients (<60 years old) with recent lung cancer history (<1 year)
  - More cerebral metastases (except vs. Cluster 2)
  - More history of radiotherapy
  - Less history of surgery

UNIVOC treatment sequences (N=2,212)



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Conclusions

- Using a large sample of NSCLC patients surviving 2 years after the initiation of nivolumab, the *Machine Learning* approach enabled to classify patients with **homogeneous treatment sequences** and to identify **4 clusters** of patients with different features of care:
  - Long-term survivors who received almost continuously nivolumab (**cluster 1**);
  - Long-term survivors who received nivolumab for a long time but who discontinued (**cluster 2**);
  - Long-term survivors who discontinued nivolumab early and with no subsequent systemic treatment (**cluster 3**);
  - Long-term survivors who discontinued nivolumab early and then started a subsequent chemotherapy (**cluster 4**);
- **Patients in Cluster 1** appeared to be particularly different from the other clusters. An in-depth study of their clinical profile could provide a better understanding of their management.