Pharmacometrics modeling coupled with machine learning for early prediction of survival following atezolizumab monotherapy in non-small cell lung cancer

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BACKGROUND

- Treatment of advanced non-small cell lung cancer by atezolizumab-based therapy
- Prediction of survival from baseline or early on-treatment data could
  - guide treatment decision during **drug development**
  - inform **personalized** health care
- Current predictive biomarker: programmed death-ligand 1 (PD-L1)[1]
- State of the art from **baseline** clinical and biological data: ROPRO score[2]
- Predictive value of transcriptomic and mutation data is unclear
- **Tumor kinetics (TK)** model parameter growth rate (KG) has important predictive power of hazard ratio (HR)[3]
- Predictive value of kinetics of **pharmacodynamic biomarkers** is unclear

OBJECTIVE

To provide a digital **decision-enabling tool** by predicting **overall survival** based on early tumor size and longitudinal PD biomarker data using the strengths of ~~pharmacometrics~~ (PHMx) and machine learning (ML)

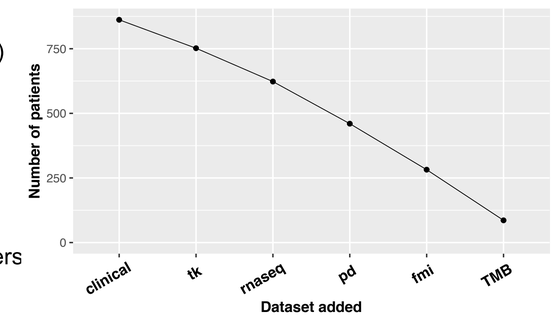
STUDIES, PATIENTS AND DATA

Studies	Study Description	Population	Patients treated with atezolizumab
FIR GO28625	Phase 2 study that evaluated the efficacy and safety of anti-programmed death-ligand 1 (PD-L1) atezolizumab in advanced NSCLC selected by tumor cell (TC) or tumor-infiltrating immune cell (IC) PD-L1 expression	PD-L1 positive locally advanced or metastatic NSCLC (lines 1 and 2+)	133
POPLAR GO28753	Phase 2 randomised controlled trial (RCT) of atezolizumab versus docetaxel for patients with previously treated NSCLC	Locally advanced or metastatic NSCLC who failed platinum therapy	134
BIRCH GO28754	Phase 2 Study of Atezolizumab in participants with PD-L1 positive locally advanced or metastatic NSCLC	Locally advanced or metastatic NSCLC (lines 1, 2 or 3)	595
Total			862

5 sources of data:

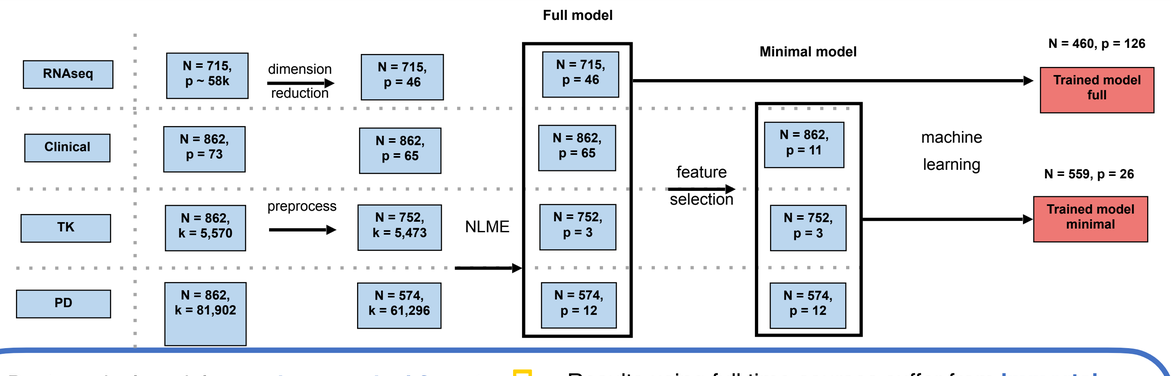
- **Baseline**
  - **clinical** and biological characteristics (73 variables)
  - **RNAseq** (~ 58k variables)
  - **FMI** (mutation data on 395 genes)
  - Tumor mutational burden (TMB)
- **Longitudinal**
  - **kinetics of tumor size** (TK, sum of largest diameters
  - **kinetics** of 4 **pharmacodynamic markers** (PD): albumin, C-reactive protein (CRP), lactate deshydrogenase (LDH), neutrophils

Number of patients with data available for each dataset



➡ FMI and TMB disregarded because they would have highly reduced the number of patients

METHODS



- Best survival model = **random survival forest**
- Multiple methods of **feature selection** were assessed
- Evaluation of performances with 10-fold **cross-validation**

- Results using full time courses suffer from **immortal time bias**

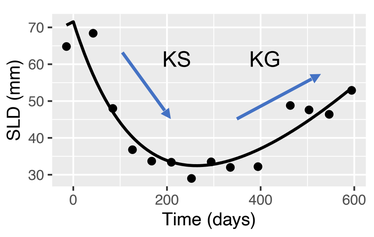
➡ We used **truncated data sets**

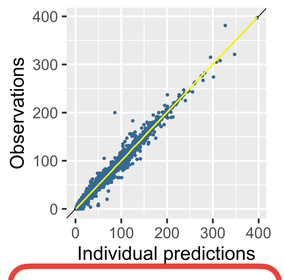
- At cycles 3, 5 and 10 pre-dose
- i.e. after 6, 12 and 27 weeks of treatment

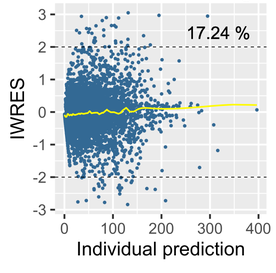
RESULTS : NONLINEAR MIXED-EFFECTS MODELING (NLME)

Tumor kinetics

$$S(t) = S_0\left(e^{-KS\cdot t} + e^{KG\cdot t} - 1\right)$$

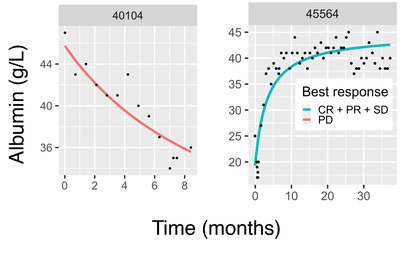


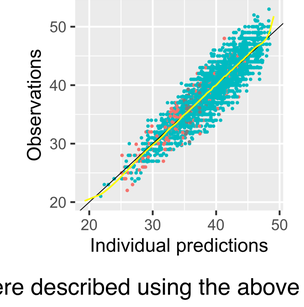


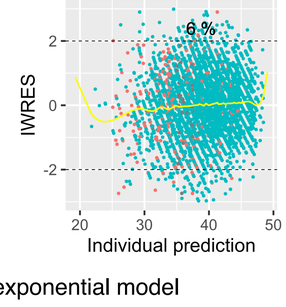


Albumin kinetics

$$y(t) = p + e^{l}\frac{q-p}{t+e^{l}}$$





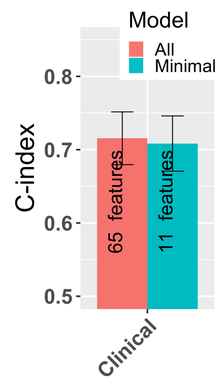


$\mathcal{E}$-shrinkage

CRP, LDH and neutrophils kinetics were described using the above double-exponential model

RESULTS MACHINE LEARNING : FULL TIME COURSE

Minimal clinical signature
C-reactive protein
Heart rate
Neutrophils-to-lymphocytes ratio
Neutrophils
Lymphocytes-to-leukocytes ratio
Liver metastases
ECOG (0 vs 1)
PDL1 (≥ 50%)
Hemoglobin
Baseline sum of longest diameters
Lactate deshydrogenase

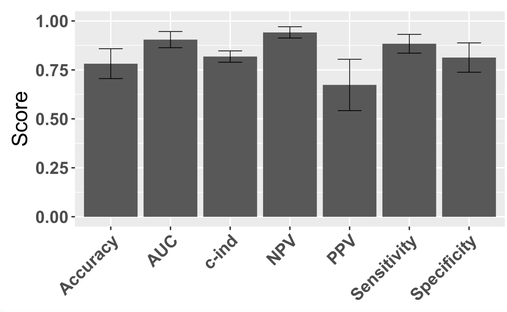


➡ A **minimal signature** achieves (almost) the same performances as the full model

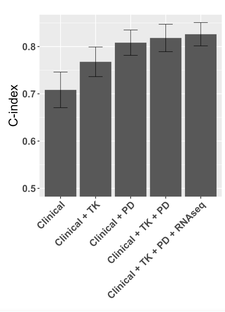
➡ **RNAseq** only brings **negligible** additional predictive power ⇒ dropped in the final model

➡ **Substantial predictive power**, except for PPV (ability to predict death, 67.3 % ± 13.1)

Evaluation of all predictive metrics in cross-validation

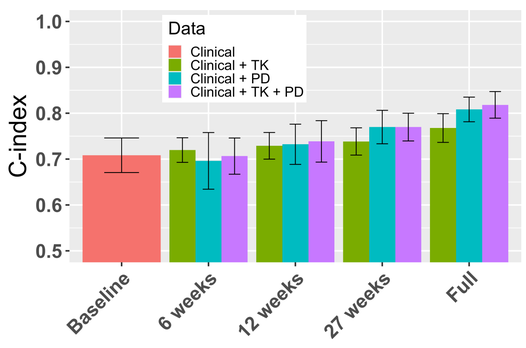


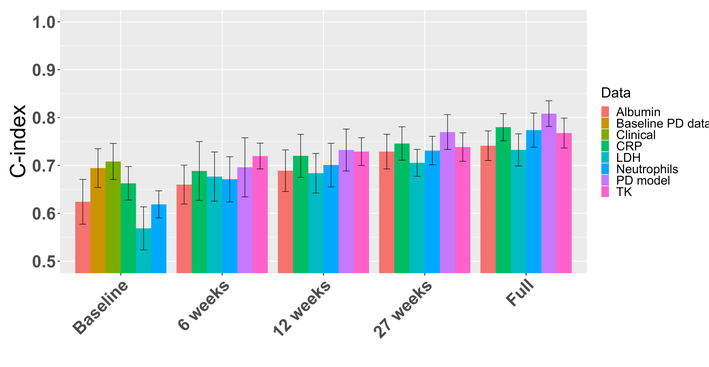
C-index as a function of feature sets



Positive (1) = death,
Negative (0) = alive
All classification metrics computed for survival at 12 months

RESULTS MACHINE LEARNING : TRUNCATED TIME COURSE





- At least **4 completed cycles** of treatment (≥ 12 weeks) of data are required to achieve substantial individual predictive power
- PD model derived metrics are more informative of individual survival than TK metrics from 12 weeks onwards
- Best individual kinetic markers : **CRP and neutrophils**

DISCUSSION

Conclusion

- The **combination of NLME and ML** allowed to take the best of the two approaches in order to predict individual survival
  - NLME for **longitudinal TK and PD** data
  - ML to build **multivariable** models from a large number of features
- A model was established based on a 26 features **minimal signature**: 11 baseline clinical features + longitudinal TK (3 variables) + longitudinal PD (12 variables)
- **C-index = 0.818 ± 0.029, AUC = 0.905 ± 0.0414**
- RNAseq data did not yield substantial predictive power

Perspectives

- **External validation** on the phase 3 OAK trial
- Prediction of study-level overall survival in multiple arms, from early on-study data

1 Shukuya, T. & Carbone, D. P. Predictive Markers for the Efficacy of Anti–PD-1/PD-L1 Antibodies in Lung Cancer. Journal of Thoracic Oncology 11, 976–988 (2016).
2 Becker, T. et al. An enhanced prognostic score for overall survival of patients with cancer derived from a large real-world cohort. Ann Oncol 31, 1561–1568 (2020).
3 Claret, L. et al. A Model of Overall Survival Predicts Treatment Outcomes with Atezolizumab versus Chemotherapy in Non-Small Cell Lung Cancer Based on Early Tumor Kinetics. Clin Cancer Res 24, 3292–3298 (2018).