Supporting decision making and early prediction of survival for oncology drug development using a pharmacometrics-machine learning based model

Sébastien Benzekry, Mélanie Karlsen, Abdessamad Elkaoutari, René Bruno, Aleš Neubert, François Mercier, Bruno Gomes, Suresh Vatakuti, Peter Curle, Candice Jamois

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(1) COMPO Inria – Inserm, Marseille, France; (2) Genentech-Roche, Marseille, France; (3) Roche pRED, Basel, Switzerland

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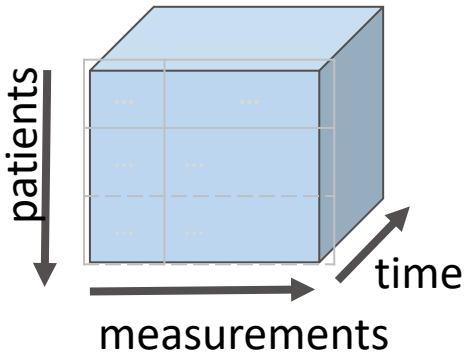
Project Schematic and Objectives

Prediction of overall survival in NSCLC patients treated with atezolizumab

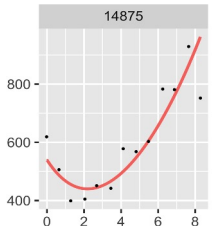
Raw longitudinal data

Tumor Kinetics (TK)

Pharmacodynamic markers (PD)
Albumin, CRP, neutrophils, LDH



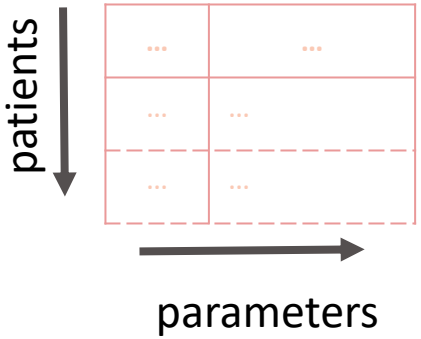
NLME



Model-based individual parameters

TK

PD



Raw baseline data

Clinical characteristics

Genomic and Transcriptomic data

Feature selection

Minimal signature

Clinical characteristics

Genomic and Transcriptomic data

Machine Learning

Outputs

Individual prognosis
- **C-index**
- **12-months survival**

Study level predictions
- **Survival curve**
- **Hazard ratio**

NLME: NonLinear Mixed Effect Modeling; CRP: C-reactive protein; LDH: lactate deshydrogenase

Data for model development (Train set) and external validation (Test set)

Four monotherapy studies of atezolizumab in advanced NSCLC

- **Baseline data**
  - Patients' and disease characteristics
    p = 73 parameters
  - Transcriptomic and mutational data
    p = 58,311 and 395
- **Longitudinal data**
  - Tumor kinetics (TK, SLD)
    5,570/3,065 observations
  - 4 PD markers (CRP, LDH, Albumin and Neutrophils)
    61,296/47,255 observations

Study	Description	N	
FIR GO28625	Phase 2 study for the efficacy and safety of anti-programmed death-ligand 1 (PD-L1) atezolizumab (ATZ) in advanced NSCLC selected by tumor cell (TC) or tumor-infiltrating immune cell (IC) PD-L1 expression	133	Train
POPLAR GO28753	Phase 2 randomised controlled trial (RCT) of ATZ versus docetaxel for patients with previously treated NSCLC (locally advanced or metastatic NSCLC who failed to platinum therapy)	134	
BIRCH GO28754	Phase 2 study of ATZ in patients with PD-L1 positive locally advanced or metastatic NSCLC	595	
Train		**862**	
Test - OAK GO28915	Phase 3 RCT of ATZ versus docetaxel (DTX) in patients with previously treated NSCLC	**553**	Test
Train + Test		**1415**	

NSCLC: Non-Small Cell Lung Cancer; p = number of parameters, N: number of patients treated with atezolizumab (patients from French centers were excluded for legal reasons (N=118); In total, data from 1074 patients from OAK were used as Test set (553 from the ATZ arm, 521 from the DTX arm); PD: Pharmacodynamic; SLD: Sum of the Largest Diameters. CRP: C Reactive Protein; LDH: Lactate Dehydrogenase.

1. Fehrenbacher L *et al*. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet (2016)
2. Fehrenbacher L *et al.* Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non–Small Cell Lung Cancer. Journal of Thoracic Oncology (2018)
3. Solange Peters *et al*. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1–Selected Advanced Non–Small-Cell Lung Cancer (BIRCH). JCO (2017)
4. Spigel D.R et al. FIR: Efficacy, Safety, and Biomarker Analysis of a Phase II Open-Label Study of Atezolizumab in PD-L1–Selected Patients With NSCLC. Journal of Thoracic Oncology (2018)

Methodology - Pharmacometric model development

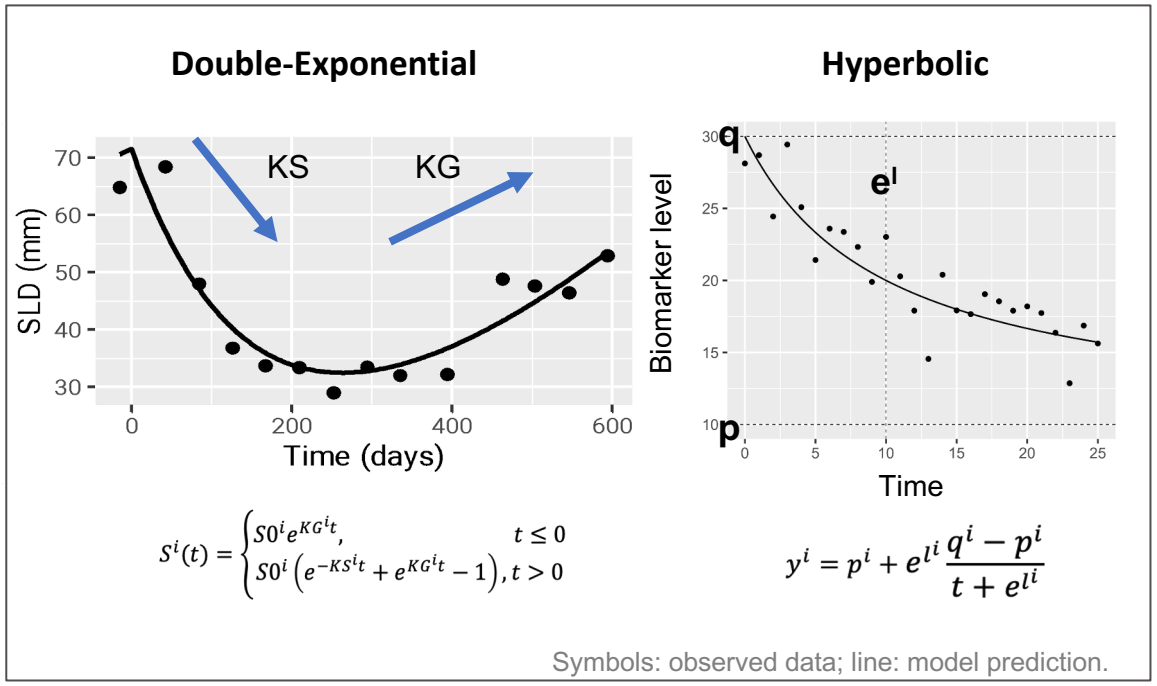
- Tumor kinetics (TK) : double-exponential model[1,2]
- PD time courses : empirical models[3]
  - constant? linear? hyperbolic? double-exponential?
- Statistical Nonlinear Mixed Effect (NLME) model
- Observation model : constant (TK) or proportional (PD)

$$y_j^i = M(t_j^i;\theta^i) + \varepsilon_j^i,\ \varepsilon_j^i \sim \mathcal{N}(0,\sigma_j^i)$$

- Inter-individual

$$\ln(\theta^i) = \ln(\theta_{pop}) + \eta^i,\ \eta^i \sim \mathcal{N}(0,\omega^2)$$

- Population parameters : SAEM algorithm for likelihood maximization
- Individual empirical Bayes estimates (EBEs) from the maximum a posteriori estimator
- Fits performed using the R Monolix2020R1 API



★ Individual TK and PD model parameters = inputs of the Machine Learning (ML) algorithm

★ Model-derived baseline parameters were excluded (baseline markers already in clinical category)

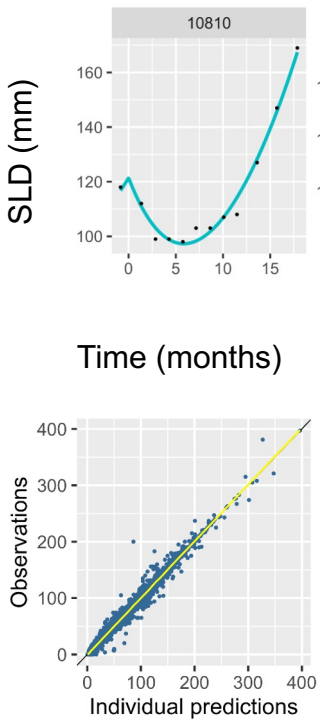
[1]Stein et al., 2008 (PSA), [2]Claret et al. 2018 (SLD, atezolizumab), [3]Gavrilov et al. 2020 (NLR, durvalumab)

NLME modeling of tumor kinetics and PD markers

Is there any kinetic pattern in the PD data?

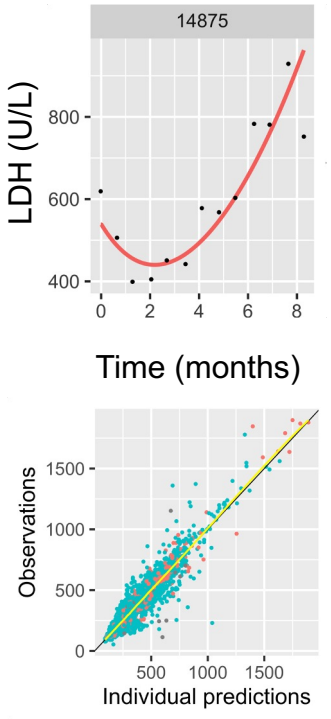
TK

Best Overall Response
CR+PR+SD
PD



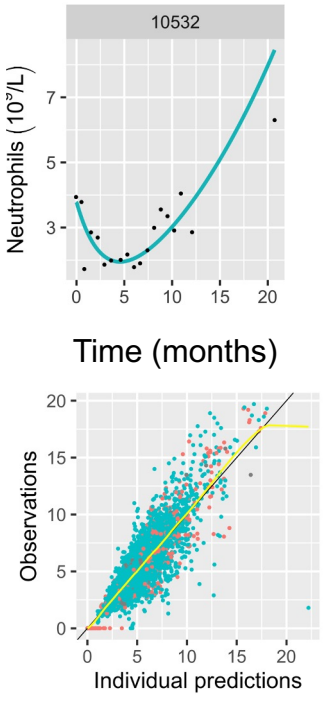
LDH

model	BICc	b
dexp	39,886	0.56
hyperbolic	40,915	0.62
linear	42,462	0.70
constant	42,982	0.74



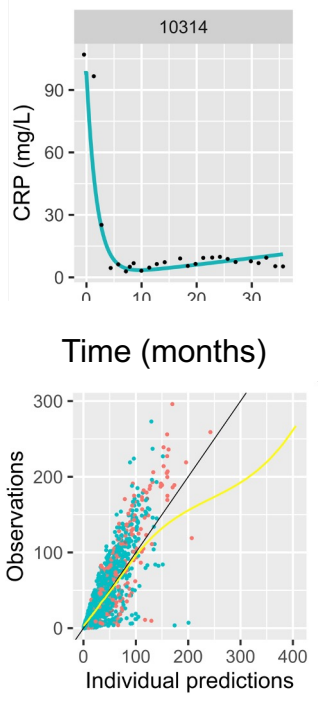
Neutrophils

model	BICc	b
dexp	102,449	0.14
hyperbolic	102,943	0.14
linear	105,193	0.17
constant	106,249	0.18



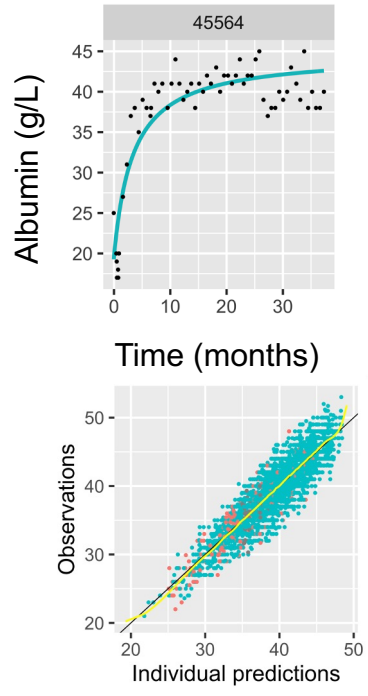
CRP

model	BICc	b
dexp	28,764	0.21
hyperbolic	29,712	0.22
linear	30,020	0.23
constant	31,332	0.25



Albumin

model	BICc	b
hyperbolic	48,007	0.056
dexp	48,395	0.058
linear	49,436	0.063
constant	49,724	0.065



CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, SLD = sum of largest diameters, LDH = lactate deshydrogenase, CRP = C-reactive protein

Methodology - Machine learning model development

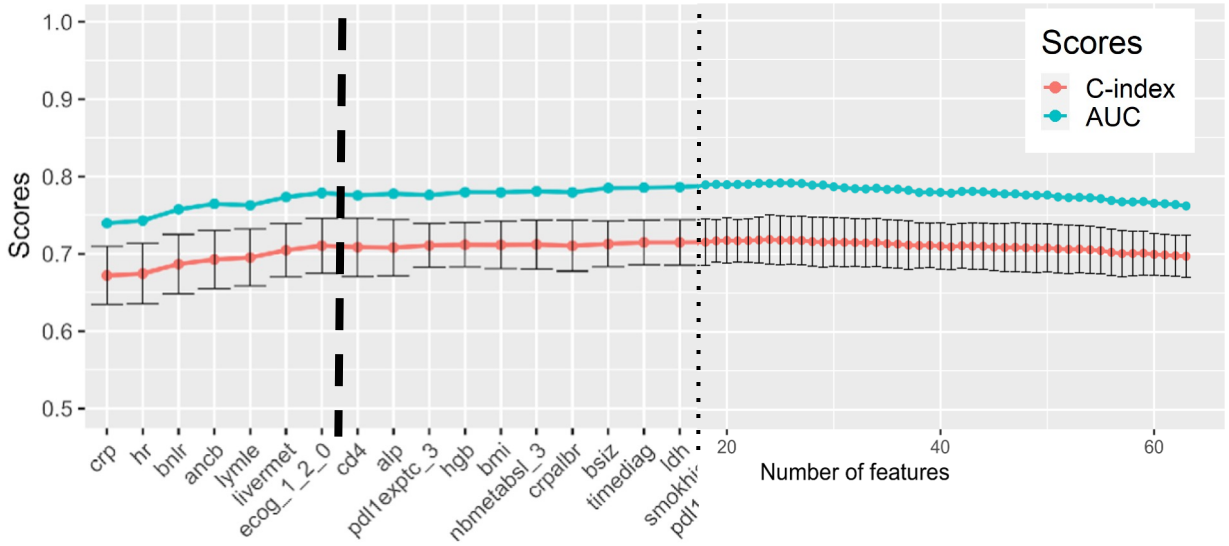
- Preprocess to handle missing data
  Drop zero-variance or >25% NA columns, dummification, NA imputation, scaling
- Dimensionality reduction for FMI and RNAseq data (bootstrap LASSO)
- Features selection:
  - 5 methods: **LASSO**, random survival forest (RSF) importance, Cox-based and stepwise forward/backward
  - 3 strategies : i) all variables, ii) per feature set and iii) pooled selected sets
- 4 survival algorithms tested:
  Cox, Cox and accelerated failure time with gradient boosting and **random survival forest (RSF)**
- Evaluation of machine learning models
  - Model development: 10-fold cross-validation
    C-index, calibration curves and 12-months survival classification metrics
  - Study-level predictions: survival curves, **hazard ratios**

Working principle: need for a **minimal signature** model with limited number of easily measurable variables

Reducing number of features to a minimal signature

Baseline clinical parameters

7 features



- All features sorted using LASSO
- Incremental models with increasing number of features
- Minimal set of features that reaches the plateau

Minimal signature baseline characteristics (p = 11)
CRP
Heart rate
Neutrophils-to-lymphocytes ratio
Neutrophils
Lymphocytes-to-leukocytes ratio
Liver metastases
ECOG (0 vs 1)
PD-L1 (≥ 50% on tumor cells)
Hemoglobin
SLD
Lactate dehydrogenase

7 features

4 features added because of established prognostic/predictive value[1,2,3]

[1]Fangfang Wu *et al*. Prognostic value of baseline hemoglobin-to-red blood cell distribution width ratio in small cell lung cancer: A retrospective analysis. Thoracic Cancer. 2020 Apr; 11(4): 888–897

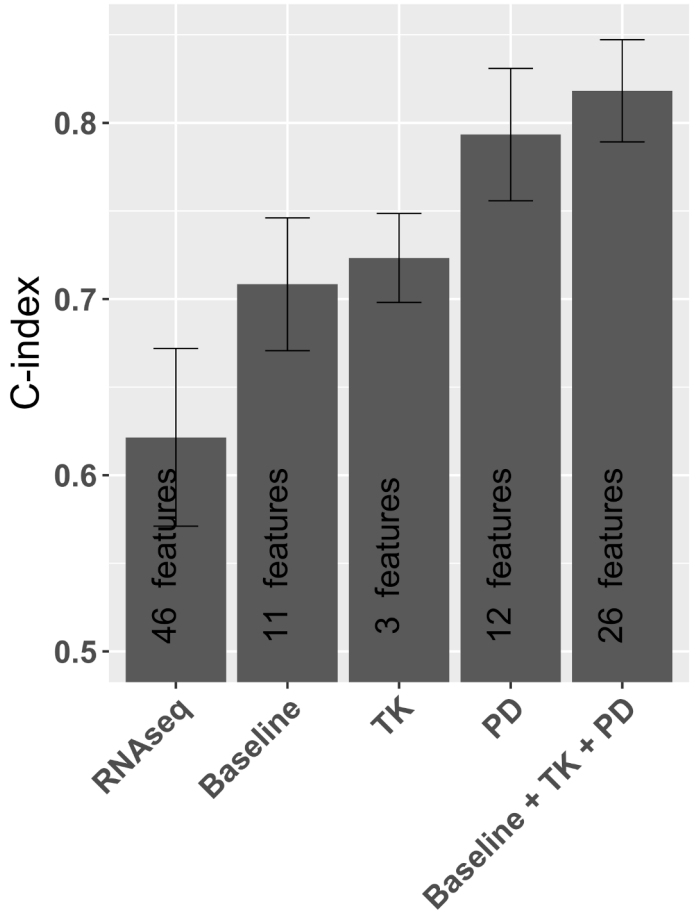
[2]Matthen Mathew, Rachael A. Safyan, Catherine A. Shu. PD-L1 as a biomarker in NSCLC: challenges and future directions - Annals of Translational Medicine. 2017 Vol 5, No 18.

[3]Bernhard C D. *et al.* Long-term Survival Is Linked to Serum LDH and Partly to Tumour LDH-5 in NSCLC. Anticancer Research April 2010, 30 (4) 1347-1351.

Prediction metrics by features category

- Each feature set exhibits differential predictive power
- RNAseq has low individual predictive power.
  ⇒ discarded
- Model-based dynamic features (TK, PD) outperform baseline clinical features, with much less variables
- Model-based PD outperforms TK metrics

Cross-validated C-indices by features category



From 10-fold cross-validation on FIR, BIRCH and POPLAR (train data set, N=559)

➢ A pooled model of 26 features has very good predictive metrics

26 features: baseline patient and disease characteristics ('clinical features', 11 features); TK metrics (3 features); PD model derived metrics for LDH, CRP, neutrophils, albumin (12 features)

Model-based metrics features are more informative than observed data

Comparison of predictive performance

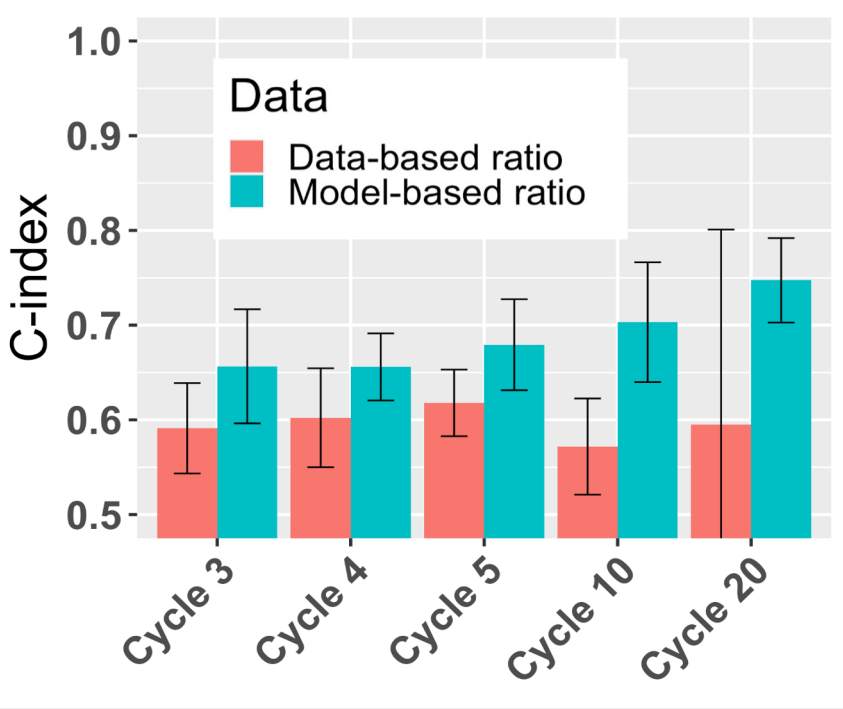
- Using SLD, CRP, Albumin, Neutrophils and LDH parameters
- Several cycle landmark times were used (Cycle 3 to Cycle 20)
- ML model learned from the train set truncated at Cycle X
- For all landmarks, the predictive power of the data-based versus model-based ratio from baseline at Cycle X pre-dose is compared

➢ Model-based metrics clearly have both better predictive power and narrower uncertainty

➢ This illustrates how dynamic modeling allows to capture the kinetics and correct for intra-individual stochasticity (noise)

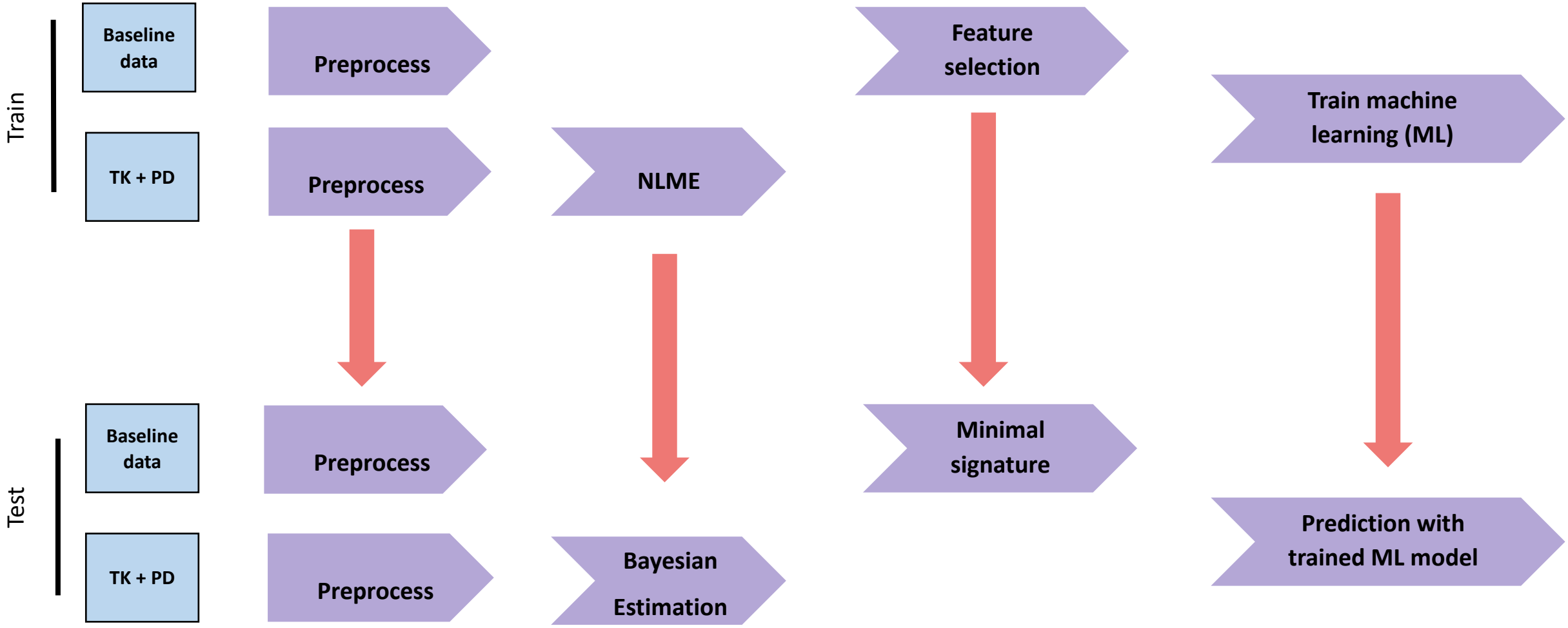
➢ Model-based ratio from baseline is more predictive with increasing number of cycles

Cross -validation c-indices for model- and observed- based ratio to baseline



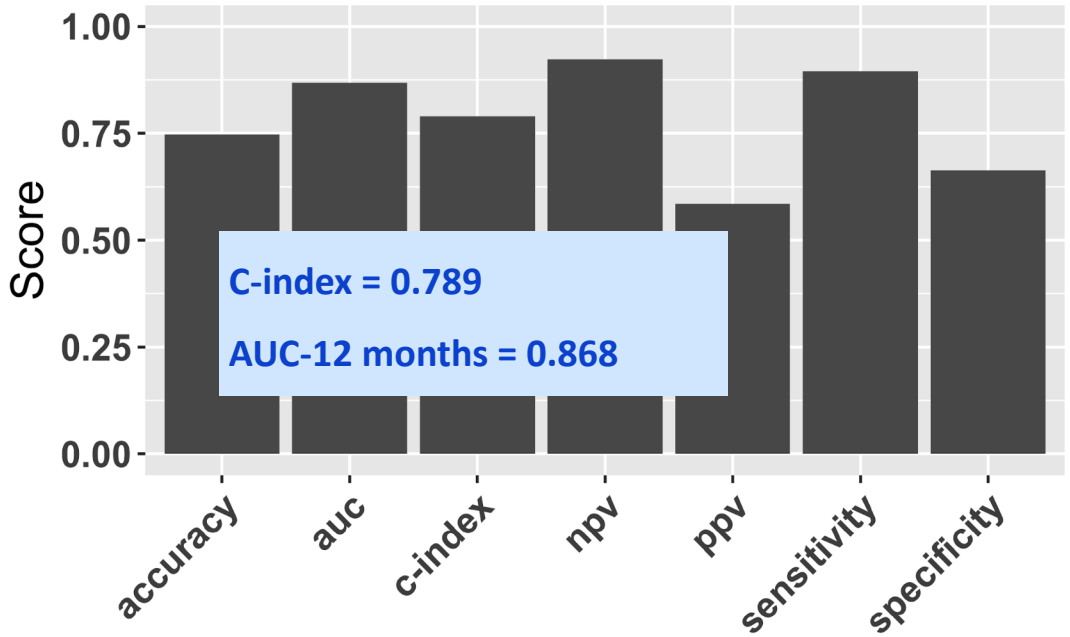
Note: 10-fold cross-validation on FIR, BIRCH and POPLAR (train data set). Only relative change from baseline used as model metric. Other model-based parameters ignored here for fair comparison

Methodology - From Train to Test

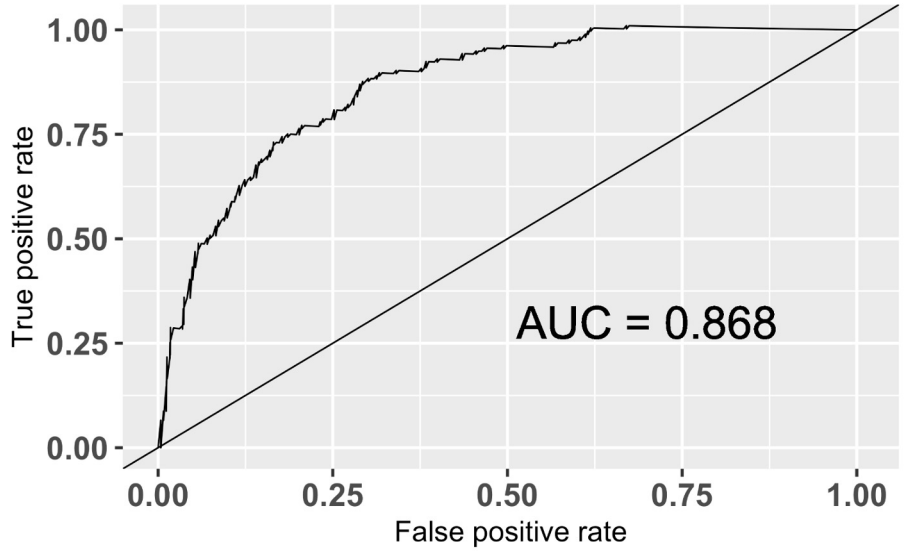


Performance metrics on test set (OAK)

Performance metrics for minimal signature model prediction



Prediction of 12-months survival



Results presented are based on full test set and are prone to immortal time bias

PDL1[1] : AUC = 0.65

RoPro[2]: c-index = 0.69

AUC-3 months = 0.817

Train: 559 patients. Test: 396 patients. Performance metrics using full Test set (N= 391 patients). All metrics are computed at 12 months. Positive (1)= death, negative (0)= Alive; NPV: negative predictive value (NPV=TN/ (FN+TN); TN=true negative; FN=false negative; PPV: positive predictive value (PPV=TP/(TP+FP); TP= true positive; FP = False positive. To compute accuracy, censored patients were excluded (i.e., 17/396 patient at 12 months)

[1] Rizvi, H. et al., J Clin Oncol Molecular Determinants of Response to Anti–Programmed Cell Death (PD)-1 and Anti–Programmed Death-Ligand 1 (PD-L1) Blockade in Patients with Non–Small-Cell Lung Cancer Profiled with Targeted Next-Generation Sequencing. J. Clin. Oncol. 2018, 36, 633–641.

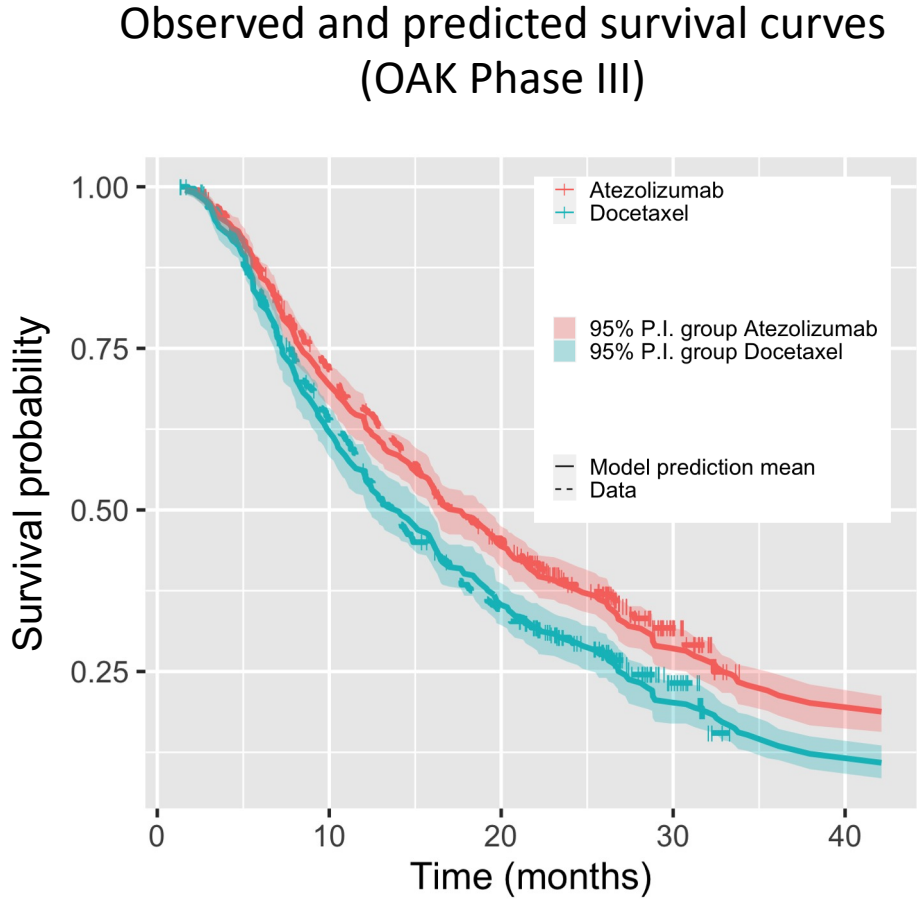
[2] Becker, T. et al. An enhanced prognostic score for overall survival of patients with cancer derived from a large real-world cohort. Ann Oncol 31, 1561–1568 (2020).

The minimal signature model reproduced retrospectively the survival curves of atezolizumab and control arm in the OAK phase III trial

- The model predicted well survival curves of ATZ and control arm (docetaxel) from OAK
- The model was able to predict ATZ survival benefit over chemotherapy in OAK (HR < 1 with good match between observed and predicted HR)

Observed HR (95%CI)	D-Light Prediction HR (95%PI)
0.765 (0.64 - 0.913)	0.765 (0.692-0.829)

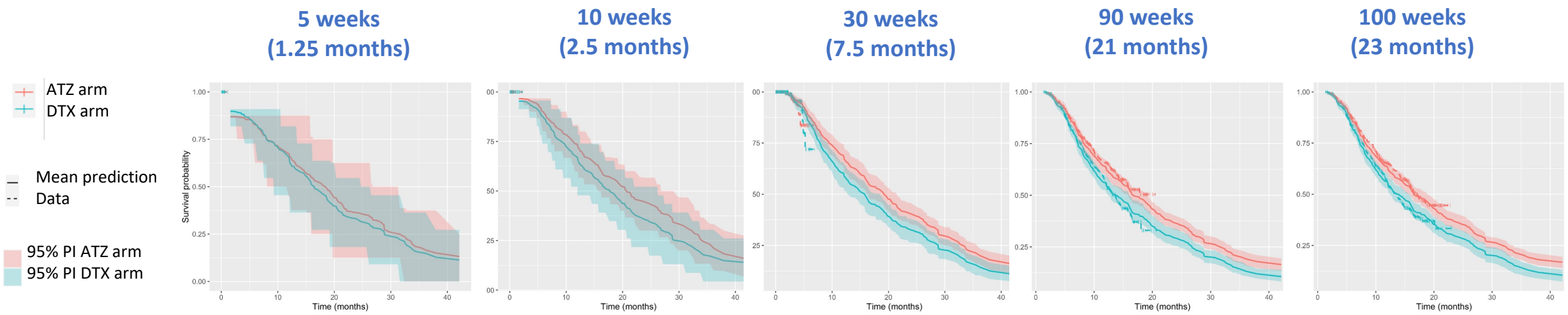
- The relationship between TK and PD metrics and survival is not drug specific



Results based on the entire OAK dataset (i.e, 391 patients from atezo arm and 350 patients from docetaxel arm at time=0). 95% prediction intervals from simulating 1000 replicates of model predictions

Results are prone to Immortal Time bias

The minimal signature model predicts OS benefit for atezolizumab over docetaxel in OAK 7.5 months after first patient randomized



Data HR (95% CI)	NA (NA - NA)	NA (NA - NA)	1.04 (0.386 - 2.79)	0.708 (0.564 - 0.887)	0.748 (0.606 - 0.922)
Predicted HR (95% PI)	0.923 (0.369 - 2.5)	0.836 (0.547 - 1.4)	0.802 (0.655 - 0.907)	0.809 (0.746 - 0.903)	0.798 (0.715 - 0.89)
Number of patients (DTX - ATZ)	11 - 8	23 - 30	163 - 183	352 - 386	352 - 386
Median nb of data points (TK/Alb/CRP/LDH/ Neutrophils)	1/2/2/2/2 - 1/2/1/2/1	1/3/3/2/2.5 - 1/2/2/2/2	2/4/4/4/5 - 2/4/4/4/4	4/8/6/7/8 - 4/10/9/9/10	4/8/6/7/8 - 4/10/9/9/10

Truncation of data is based on the randomization date of the first patient treated in OAK (e.g. at 5 weeks after randomization, 12 patients received atezolizumab (ATZ), 11 docetaxel (DTX); and median TK data points were 2 and 1 for docetaxel and atezo arms respectively)

Summary and applications for early drug development

- A minimal signature NLME-ML model of 26 features (clinical, TK and PD model features)
  - Baseline: CRP, Heart rate, Neutrophils-to-lymphocytes ratio, Neutrophils, Lymphocytes-to-leukocytes ratio, Liver metastases, ECOG (0 vs 1), PD-L1 (≥ 50% on tumor cells), Hemoglobin, SLD, LDH
  - Longitudinal: tumor kinetics (SLD), albumin, CRP, LDH, neutrophils
- Analysis (preprocess, feature selection, CV, train, predict) fully automated in a R package (> 12,000 lines of code)
- Could be applied to early phase data to assess the decision to move an asset to a later phase of development
- Potential extrapolation to other drugs within the same disease setting;

pTS for Combination Therapies

Faster, more efficient clinical trials
Early data to inform clinical development plan and patient selection

Better and Faster Go/no-Go decisions

Better decision making process by benchmarking efficacy based on early data readouts

Patient Matching to Therapy

Reduced Cost for Society

PHC: personalized treatment for every patient

ML: Machine Learning; TK : Tumor Kinetics; PD: Pharmacodynamic; CRP: C-reactive protein, LDH: lactate deshydrogenase; pTS: Probability of Technical Success; PHC: Personalized Healthcare

Doing now what patients need next