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Sébastien Benzekry, Mélanie Karlsen, Abdessamad Elkaoutari, René Bruno, Aleš Neubert, et al.. Supporting decision making and early prediction of survival for oncology drug development using a pharmacometrics-machine learning based model. PAGE - Population Approach Group Europe, Jun 2022, Ljubljana, Slovenia. hal-03921394

HAL Id: hal-03921394

<https://inria.hal.science/hal-03921394v1>

Submitted on 3 Jan 2023

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

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

Thirtieth PAGE meeting, Ljubljana, Slovenia
30 June 2022

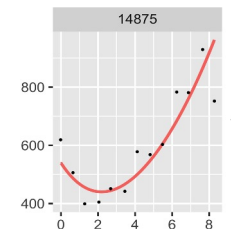
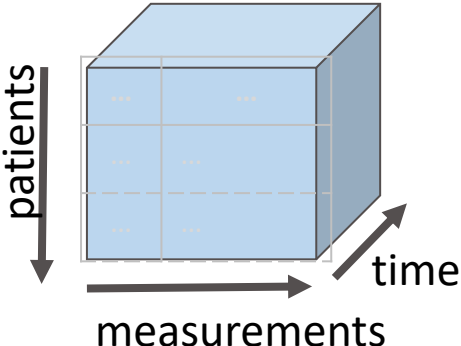
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Raw longitudinal data

Tumor Kinetics (TK)

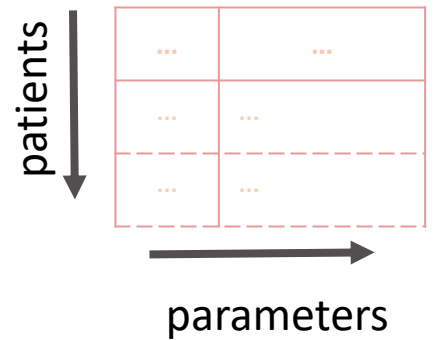
Pharmacodynamic markers (PD)
Albumin, CRP, neutrophils, LDH



Model-based individual parameters

TK

PD



Raw baseline data

Clinical characteristics

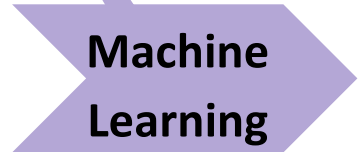
Genomic and Transcriptomic data



Minimal signature

Clinical characteristics

Genomic and Transcriptomic data



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 dehydrogenase

- **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
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
Train + Test		1415

Train

Test

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)

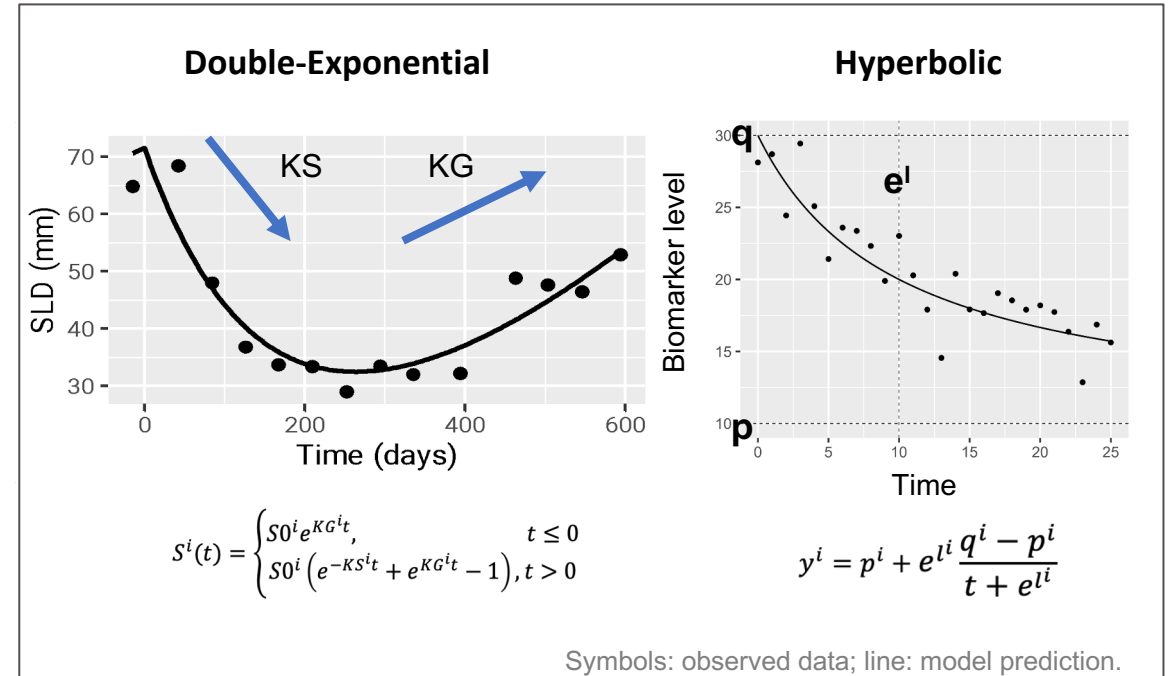
- Tumor kinetics (TK) : **double-exponential** model^{1,2}
- PD time courses : **empirical models**³
 - constant? linear? hyperbolic? double-exponential?
- Statistical Nonlinear Mixed Effect (**NLME**) model
- Observation model : constant (TK) or proportional (PD)

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

- Inter-individual

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

- 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)

Is there any kinetic pattern in the PD data?

TK

LDH

Neutrophils

CRP

Albumin

Best Overall Response

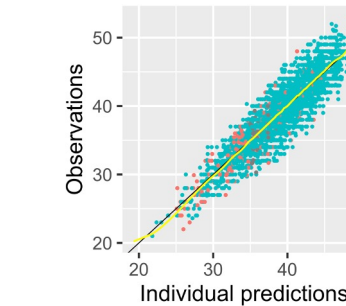
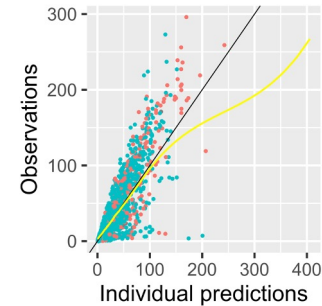
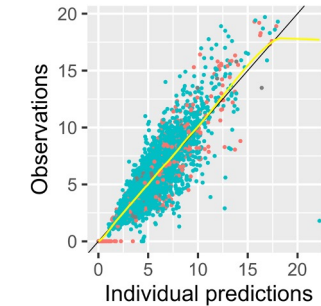
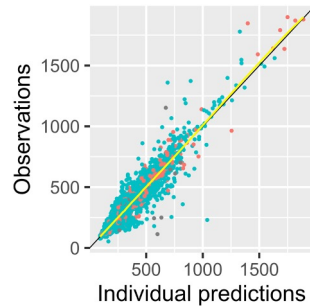
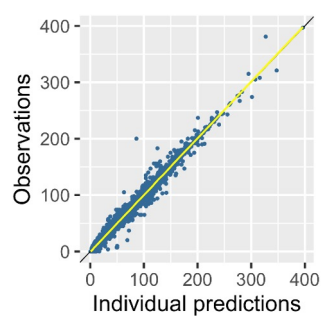
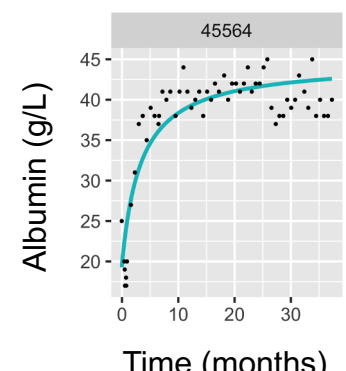
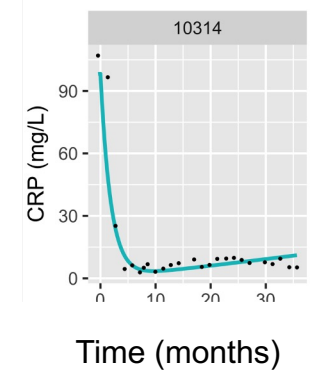
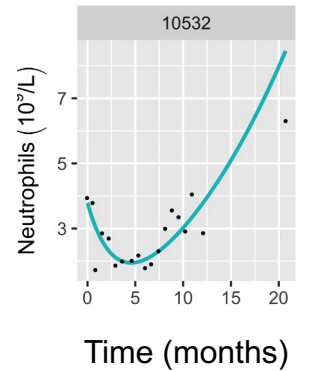
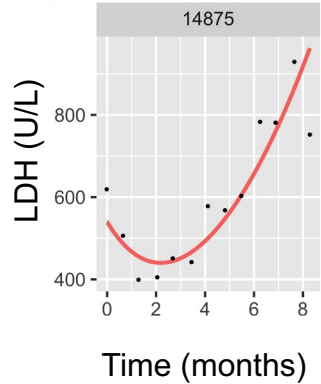
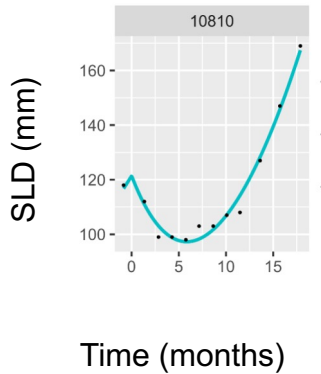
CR+PR+SD
PD

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

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

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

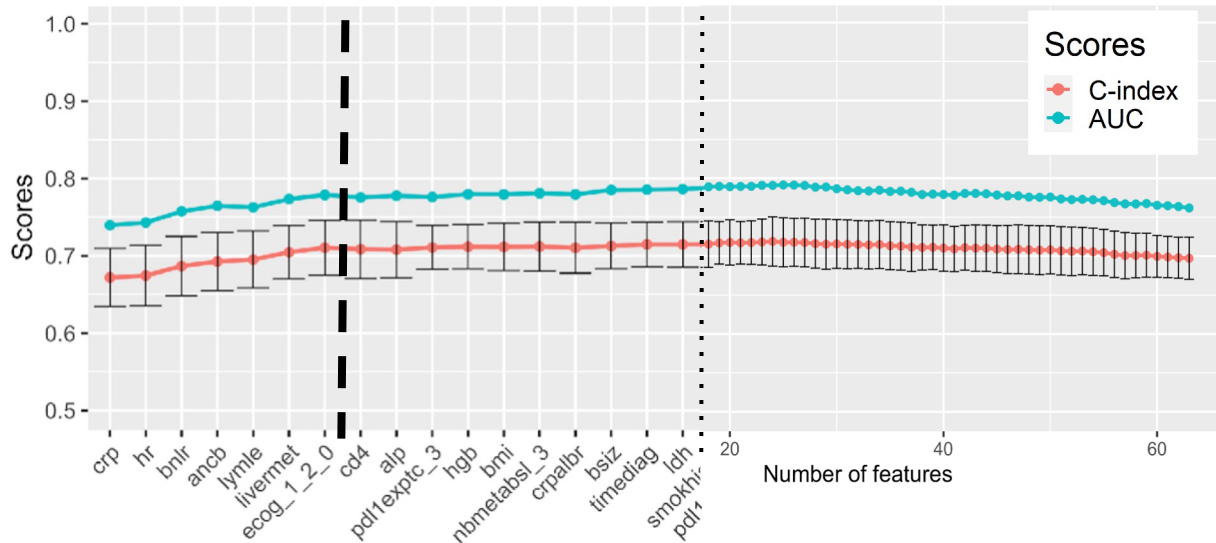
model	BICc	b
hyperbolic	48,007	0.056
dexp	48,395	0.058
linear	49,436	0.063
constant	49,724	0.065



- **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

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}

¹Fangfang 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

²Matthen 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.

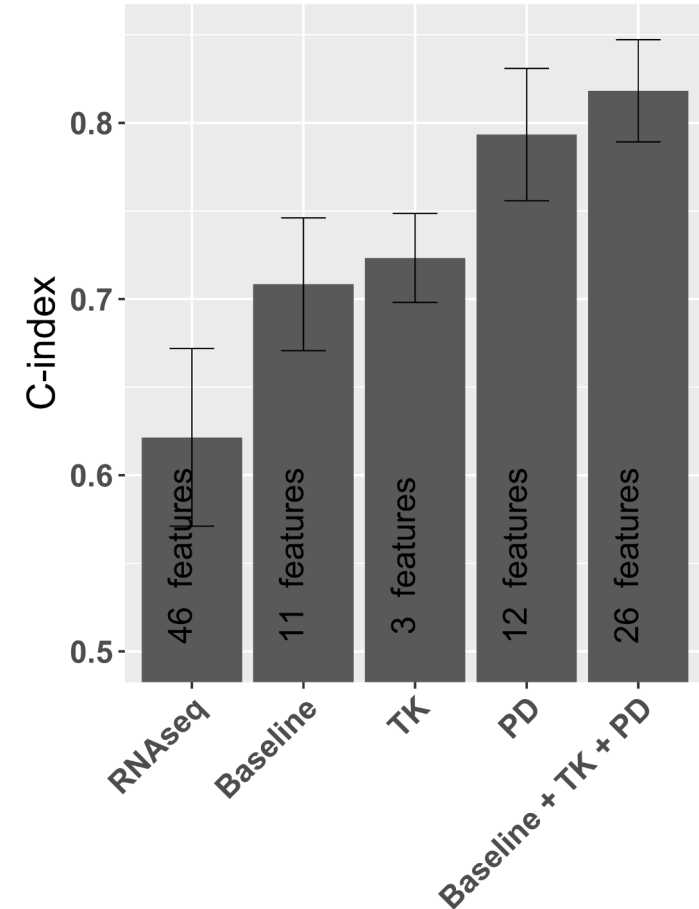
³Bernhard C D. *et al.* Long-term Survival Is Linked to Serum LDH and Partly to Tumour LDH-5 in NSCLC. *Anticancer Research* April 2010, 30 (4) 1347-1351.

Inria 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)

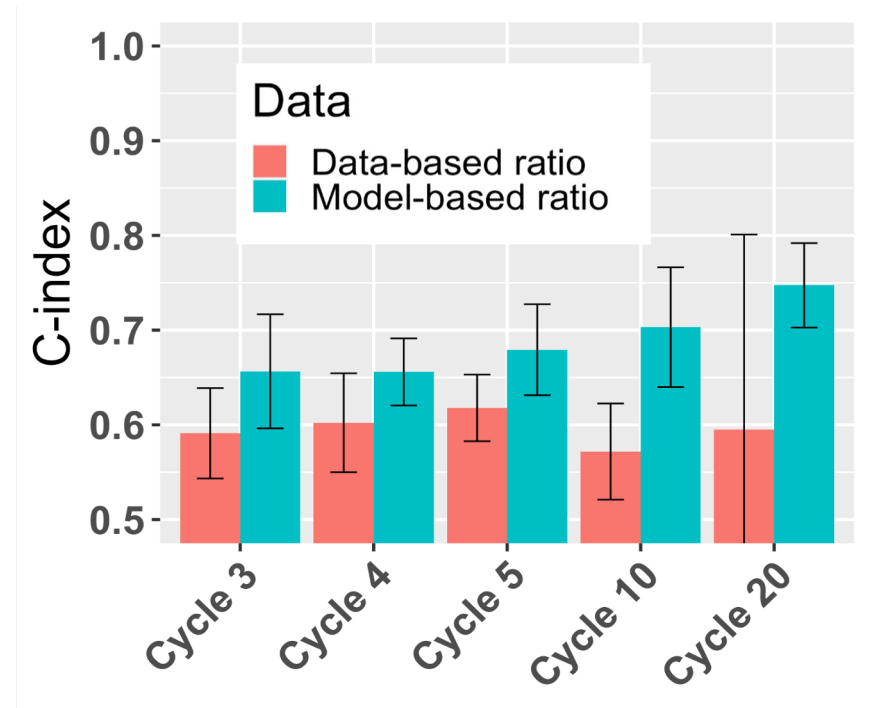
➤ A pooled model of 26 features has **very good predictive metrics**

Comparison of predictive performance

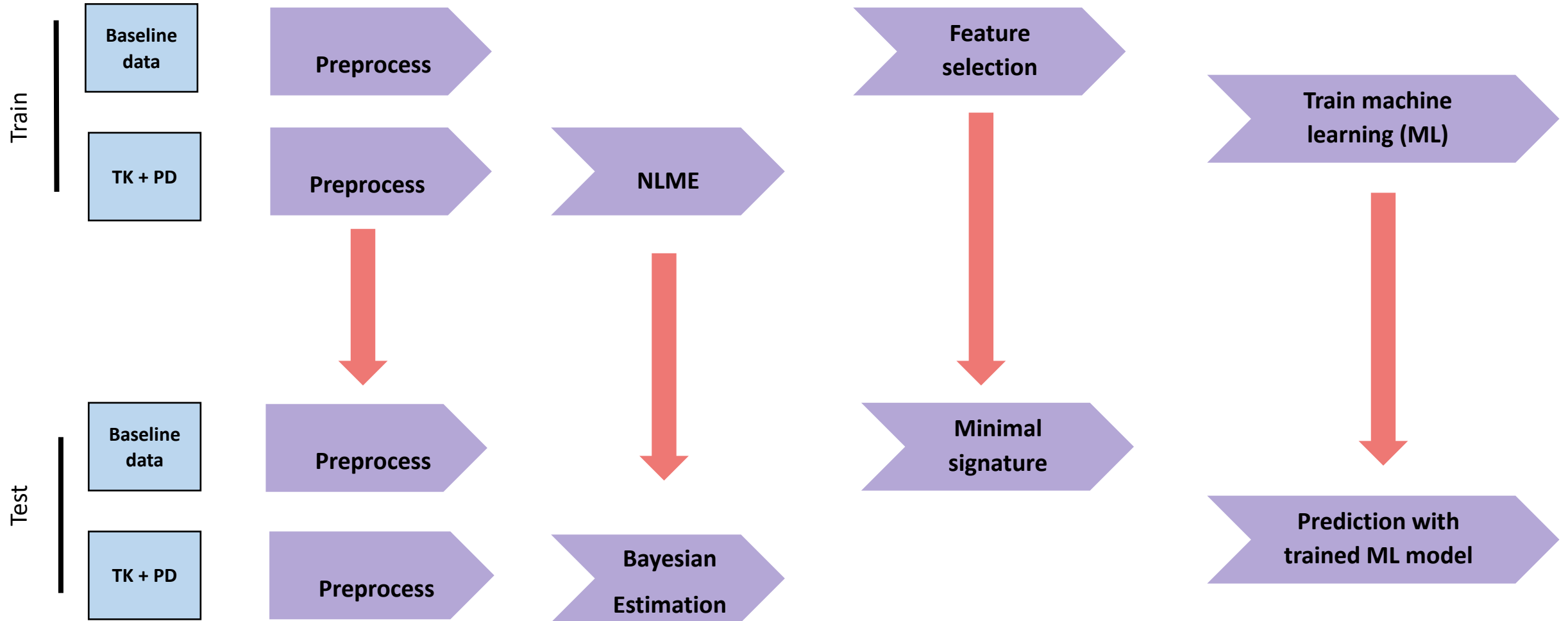
- Using SLD, CRP, Albumin, Neutrophils and LDH parameters
- Several cycle landmark times were used (Cycle 3 to Cycle 20)
- ML model learned from the train set truncated at Cycle X
- For all landmarks, the predictive power of the **data-based** versus **model-based** ratio from baseline at Cycle X pre-dose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

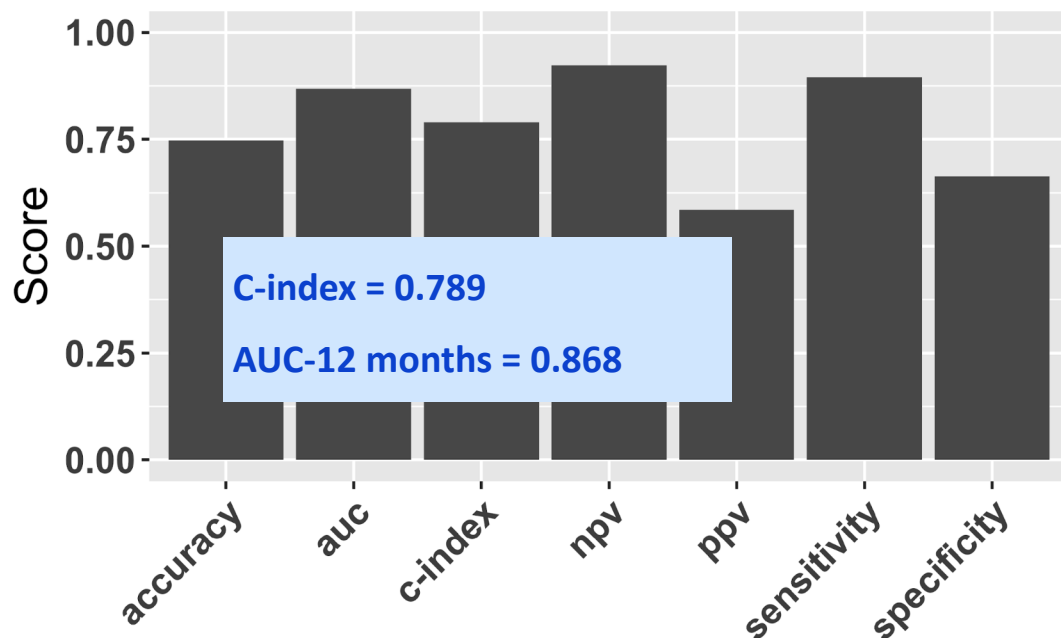
Cross-validation c-indices for **model- and **observed-** based ratio to baseline**



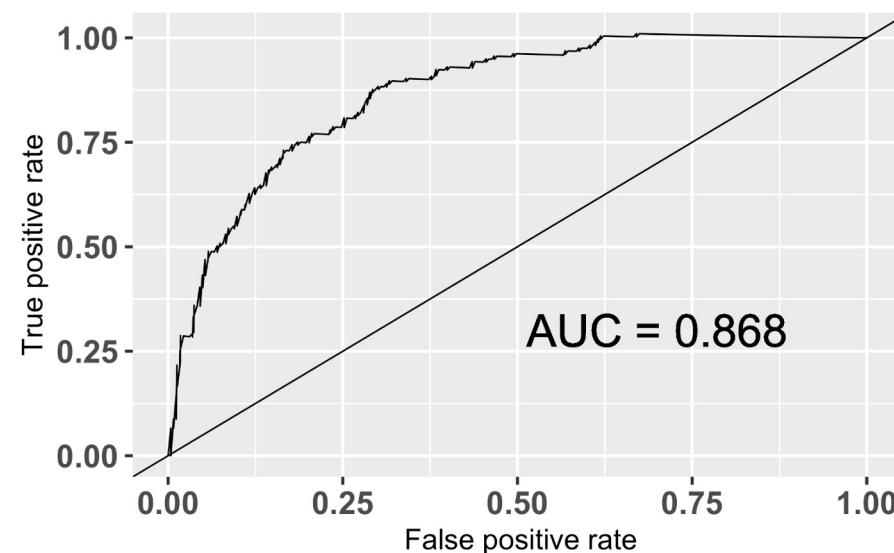
Note: 10-fold cross-validation on FIR, BIRCH and POPLAR (train data set). Only relative change from baseline used as model metric. Other model-based parameters ignored here for fair comparison



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

PDL1¹ : AUC = 0.65

RoPro²:

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.

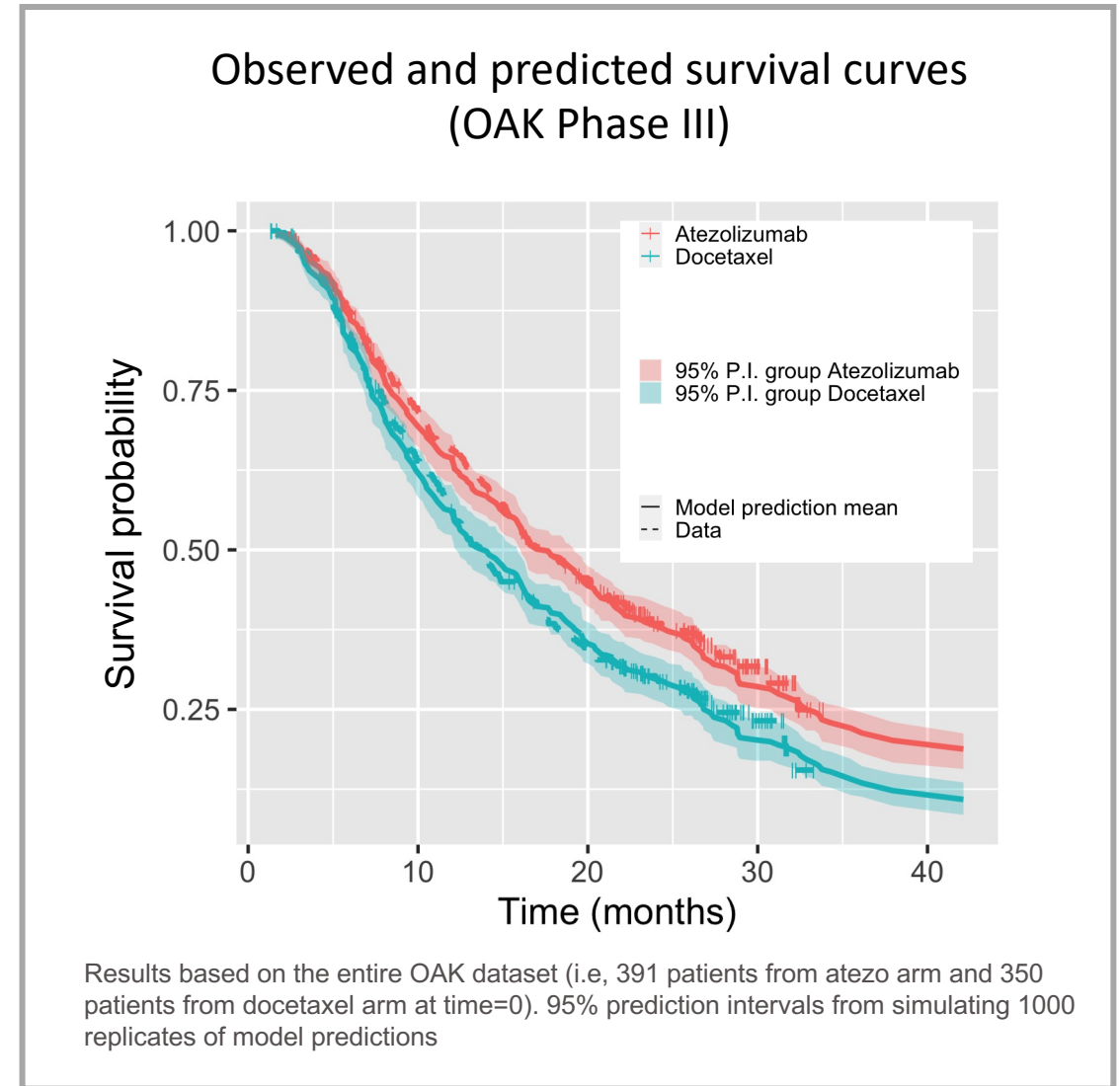
² Becker, T. et al. An enhanced prognostic score for overall survival of patients with cancer derived from a large real-world cohort. Ann Oncol 31, 1561-1568 (2020).

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

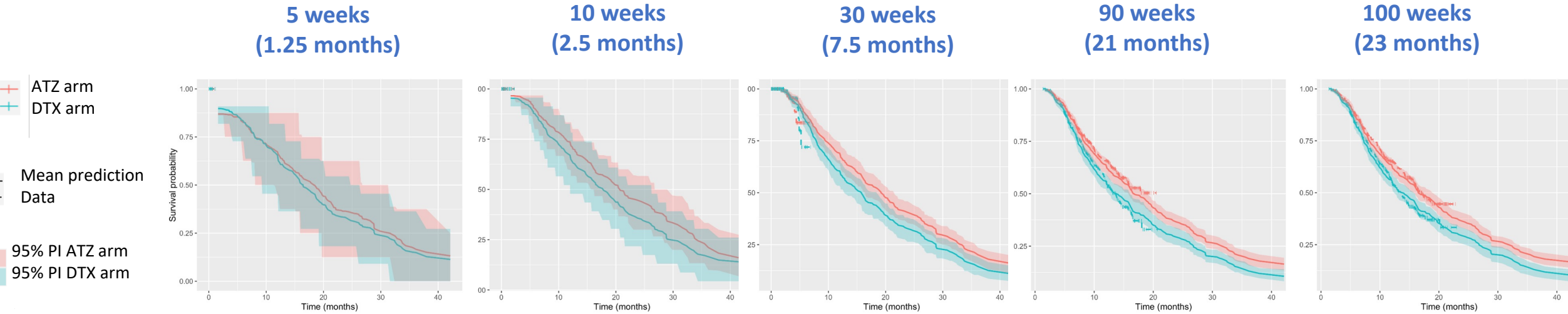
- The model **predicted well** survival curves of ATZ and control arm (docetaxel) from OAK
- The model was able to **predict ATZ survival benefit** over chemotherapy in OAK (HR < 1 with good match between observed and predicted HR)

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**



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



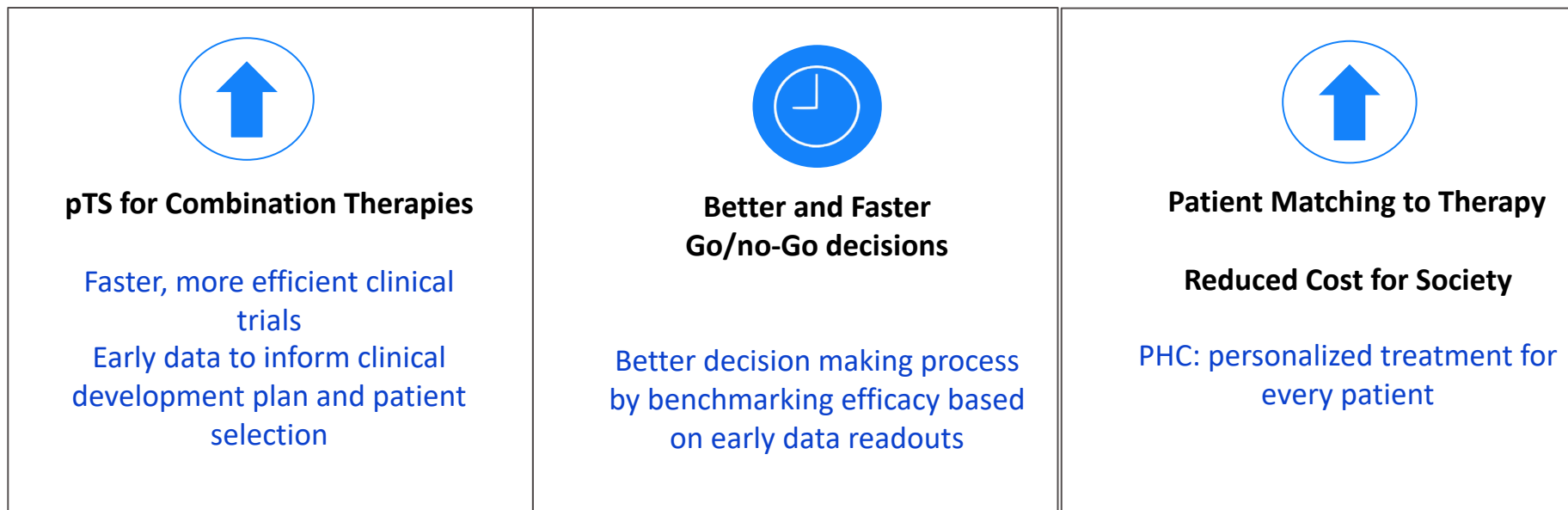
Data HR (95% CI)	NA (NA - NA)	NA (NA - NA)	1.04 (0.386 - 2.79)	0.708 (0.564 - 0.887)	0.748 (0.606 - 0.922)
Predicted HR (95% PI)	0.923 (0.369 - 2.5)	0.836 (0.547 - 1.4)	0.802 (0.655 - 0.907)	0.809 (0.746 - 0.903)	0.798 (0.715 - 0.89)
Number of patients (DTX - ATZ)	11 - 8	23 - 30	163 - 183	352 - 386	352 - 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 ($\geq 50\%$ 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;



Doing now what patients need next