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## ► To cite this version:

Sébastien Benzekry, Mélanie Karlsen, Célestin Bigarré, Abdessamad El Kaoutari, Bruno Gomes, et al.. Predicting survival and trial outcome in non-small cell lung cancer integrating tumor and blood markers kinetics with machine learning. 2023. hal-04375606

**HAL Id: hal-04375606**

**<https://inria.hal.science/hal-04375606v1>**

Preprint submitted on 5 Jan 2024

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# Predicting survival and trial outcome in non-small cell lung cancer integrating tumor and blood markers kinetics with machine learning

Sébastien Benzekry<sup>1</sup>✉, Mélanie Karlsen<sup>1</sup>, Célestin Bigarré<sup>1</sup>, Abdessamad El Kaoutari<sup>1</sup>, Bruno Gomes<sup>2</sup>, Martin Stern<sup>3</sup>, Ales Neubert<sup>4</sup>, Rene Bruno<sup>5</sup>, François Mercier<sup>6</sup>, Suresh Vatakuti<sup>7</sup>, Peter Curle<sup>8</sup>, Candice Jamois<sup>9</sup>

✉ **For correspondence:**  
sebastien.benzekry@inria.fr

**Present address:** COMPO team, Pharmacy faculty  
27 Bd Jean Moulin  
13385 Marseille, FRANCE

**Data availability:** Qualified researchers may request access to individual patient level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here <https://www.roche.com/innovation/process/clinical-trials/data-sharing/>.

**Funding:** This work was sponsored by the Roche Pharma Research and Early Development (pRED) One-D Modeling and Simulation Digital Initiative. It also benefited from funding from ITMO Cancer AVIESAN and French Institut National du Cancer (grant #19CM148-00)

**Competing interests:** The authors declare the existence of a financial competing interest

<sup>1</sup>COMPUTational pharmacology and clinical Oncology Department, Inria Sophia Antipolis-Méditerranée, Cancer Research Center of Marseille, Inserm UMR1068, CNRS UMR7258, Aix Marseille University UM105, Marseille, France; <sup>2</sup>Pharma Research and Early Development, Early Development Oncology, Roche Innovation Center Basel, Switzerland; <sup>3</sup>Pharma Research and Early Development, Early Development Oncology, Roche Innovation Center Zurich, Switzerland; <sup>4</sup>Pharma Research and Early Development, Data & Analytics, Roche Innovation Center Basel, Switzerland; <sup>5</sup>Modeling and Simulation, Clinical Pharmacology, Genentech Research and Early Development, Marseille France; <sup>6</sup>Modeling and Simulation, Clinical Pharmacology, Genentech Research and Early Development, Roche Innovation Center Basel; <sup>7</sup>Pharma Research and Early Development, Predictive Modeling and Data Analytics, Roche Innovation Center Basel, Switzerland; <sup>8</sup>Inovigate, Basel, Switzerland; <sup>9</sup>Pharma Research and Early Development, Translational PKPD and Clinical Pharmacology, Roche Innovation Center Basel, Switzerland

## Abstract

Existing survival prediction models rely only on baseline or tumor kinetics data and lack machine learning integration. We introduce a novel kinetics-machine learning (kML) model that integrates baseline markers, tumor kinetics and four on-treatment simple blood markers (albumin, CRP, lactate dehydrogenase and neutrophils). Developed for immune-checkpoint inhibition (ICI) in non-small cell lung cancer on three phase 2 trials (533 patients), kML was validated on the two arms of a phase 3 trial (ICI and chemotherapy, 377 and 354 patients). It outperformed the current state-of-the-art for individual predictions with a test set c-index of 0.790, a 12-months survival accuracy of 78.7% and a hazard ratio of 25.2 (95% CI: 10.4 – 61.3,  $p < 0.0001$ ) to identify long-term survivors. Critically, kML predicted the success of the phase 3 trial using only 25 weeks of on-study data (predicted HR = 0.814 (0.64 – 0.994) versus final study HR = 0.778 (0.65 – 0.931)). Our model constitutes a valuable approach to support personalized medicine and drug development.

## 37 Introduction

38 Lung cancer is the leading cause of cancer death worldwide<sup>1</sup>, with non-small cell lung cancer  
39 (NSCLC) being the most prevalent type, representing 80%–85% of case<sup>2</sup>. Immune-checkpoint in-  
40 hibitors (ICI) (e.g., atezolizumab (ATZ)) have led to significant improvements in survival rates for pa-  
41 tients with advanced cancers such as NSCLC<sup>3,4</sup>. However, there is still a large variability in clinical  
42 response and progression eventually occurs in a majority of patients<sup>5</sup>. Additionally, drug devel-  
43 opment in immuno-oncology is highly challenging, with a 95% attrition rate<sup>6</sup>. Current approaches  
44 for go/no-go decisions are based on interim endpoints (e.g., progression-free survival, overall re-  
45 sponse rate) that have often been found to be poor predictors of the primary endpoint of most  
46 clinical trials in oncology, overall survival (OS)<sup>7</sup>. This calls for better surrogate markers at interim  
47 analyses. Altogether, there is a need for better and validated predictive models of OS for both  
48 personalized health care (individual predictions) and drug development (trial predictions).

49 Currently, PDL1 expression is the only routine biomarker used for NSCLC patients<sup>5,8</sup> despite  
50 being controversial<sup>9,10</sup>. Tumor mutational burden<sup>8,11,12</sup> and transcriptomic data<sup>5,13,14</sup> have also  
51 been investigated but did not reach clinical practice. Here we posit that such static and single  
52 marker approach is intrinsically limited and that substantial additional predictive performances  
53 could be gained by: 1) using multi-modal integrative analyses relying on a combination of markers  
54 and machine learning algorithms<sup>5,12,14,15</sup> and 2) including dynamic markers obtained from early  
55 on-treatment data<sup>15,16</sup>. The nonlinear mixed-effects (NLME) modeling approach is well suited for  
56 the latter<sup>17</sup>, and tumor kinetics (TK) model-based metrics have been shown to carry significant  
57 predictive value for OS in oncology, including ATZ monotherapy in advanced NSCLC<sup>18–20</sup>. The first  
58 main novelty of the current study is to establish the predictive value of model-based parameters  
59 of simple blood markers kinetics (BK), in addition to TK.

60 The second main novelty is to apply machine learning (ML) algorithms, increasingly used in  
61 biology and medicine<sup>21</sup> but only rarely for TK-OS modeling<sup>22</sup>, instead of classical survival mod-  
62 els. Extensions of classical ML models to survival data have been proposed (e.g., random survival  
63 forests<sup>23</sup>), but their actual superiority over standard approaches remains controversial<sup>24</sup>. In addi-  
64 tion, most ML studies to date are underpowered due to low sample sizes in both training and test  
65 sets.

66 Here, we coupled the strengths of NLME modeling with ML to derive a predictive model of OS  
67 from baseline and on-treatment data, called kinetics-machine learning (kML, Figure 1A). We lever-  
68 aged large training and test datasets to achieve robust results (Figure 1B). Subsequently, we tested  
69 the operational predictive capabilities of kML in two relevant scenarios: 1) individual prediction of  
70 OS and 2) prediction of the outcome of a phase 3 trial from early on-study data.

## 71 Methods

### 72 Data

73 For both training and external validation (testing) sets, patients from French centers were excluded  
74 for legal reasons ( $N = 118$ , not included in the numbers above). The training set comprised the  
75 FIR (NCT01846416)<sup>25</sup>, POPLAR (NCT01903993)<sup>3</sup> and BIRCH (NCT02031458)<sup>26</sup> phase 2 clinical trials.  
76 The test set was the atezolizumab arm of the OAK phase 3 trial (NCT02008227)<sup>27</sup> for individual pre-  
77 dictions and additionally the docetaxel arm for trial predictions (Supplementary Figure 1). These  
78 studies were conducted in accordance with the Declaration of Helsinki after approval by institu-  
79 tional review boards or independent ethics committees. All patients provided written informed  
80 consent.

81 The outcome considered was overall survival (OS), defined as the time between treatment start  
82 and death or last follow-up, in which case the data was right-censored. The median follow-up was  
83 35.2 months (95%CI:34.5–35.7) in the training set and 26.8 months (95%CI:26.3–27.5) in the test set.

### 84 Preprocessing

## 85 Baseline data

86 The baseline data consisted of 63 variables spanning demographic and biological data, clinical infor-  
87 mation and disease status (see Supplementary Figure 2–4 for a description of the main variables).  
88 PD-L1 expression on tumor cells was measured by immunohistochemistry or quantitative poly-  
89 merase chain reaction, with four possible levels (0: < 1%; 1: ≥ 1%; 2: ≥ 5% and 3: ≥ 50%)<sup>3</sup>. We refer  
90 to the above-mentioned identifiers and references for further details on the other variables. Data  
91 were measured in accordance to the studies principles.

## 92 Tumor and blood markers kinetics (TK and BK)

93 Patients with only one baseline SLD measurement and no SLD measurement during the treatment  
94 period were excluded ( $N = 110$ ). For BK, first time points prior to treatment start were discarded.  
95 Then, four exclusion rules were established to identify anomalous data points: 1) values outside  
96 physiologically possible bounds, 2) duplicates, 3) values that abruptly went to an extreme out-of-  
97 range value between two measurements, 4) only the BK value at the closest time point to treatment  
98 initiation was kept. Eventually, in order to have sufficient data for Bayesian estimation with early  
99 data, patients with less than three observations before cycle 5 were removed. We refer to the  
100 supplementary methods for details.

## 101 Nonlinear mixed-effects modeling

### 102 Population approach

103 Statistical hierarchical nonlinear mixed-effects modeling (NLME) was used to implement a popula-  
104 tion approach<sup>28</sup> for the kinetic data and parameter estimation was conducted using the Monolix  
105 software<sup>29</sup>. Mathematical details are given in the supplementary methods.

### 106 Structural models

107 Following previous work, the TK structural model was assumed to be the sum of two exponen-  
108 tials<sup>19,30</sup>:

$$y_j^i = \begin{cases} y_0^i e^{KG^i t} & t \leq 0 \\ y_0^i (e^{-KS^i t} + e^{KG^i t} - 1) & t > 0 \end{cases}$$

109 where  $t = 0$  corresponds to treatment initiation and  $y_0$ ,  $KG$  and  $KS$  are three parameters, represent-  
110 ing respectively the baseline value, growth and shrinkage rates. This model was also considered  
111 for BK, together with three other models: constant ( $y_j^i = \alpha^i, \forall j$ ), linear ( $y_j^i = \alpha^i + \beta^i t_j^i, \forall j$ ) and hy-  
112 perbolic ( $y_j^i = p^i + \frac{e^{q^i t_j^i} - p^i}{t_j^i + e^{q^i t_j^i}}$ )<sup>31</sup>. Quantitative comparison of goodness-of-fit between models was  
113 assessed using the corrected Bayesian information criterion<sup>32</sup>.

### 114 Identification of individual model-based parameters

115 The population parameters identified on the training set were used to define prior distributions of  
116 the TK and BK model parameters. These “training” priors were used for Bayesian estimation (maxi-  
117 mum a posteriori estimate) of the individual TK and BK model parameters, not only for the training  
118 set but also for the test sets, in order to avoid leakage. To focus on the pure kinetic parameters,  
119 the model-estimated baseline parameters were not kept. We additionally considered the ratio of  
120 the model-predicted value at cycle 3 day 1 to the model-estimated baseline parameter. Altogether,  
121 there were three individual parameters for each marker:  $X_{KG}$ ,  $X_{KS}$  and  $X_{ratio}$  for  $X = \text{TK, CRP, LDH}$   
122 and neutrophils; and  $\text{albumin}_p$ ,  $\text{albumin}_l$  and  $\text{albumin}_{ratio}$  for albumin.

### 123 Truncated data: individual-level

124 Individual-level truncated datasets were derived from the longitudinal TK and BK data by keeping  
125 data only up to: cycle 3 day 1 (C3D1, 1.5 months), C5D1 (3 months) and C10D1 (6.75 months). New  
126 training priors were estimated from each CXD1 training set. The resulting TK and BK truncated  
127 model parameter  $Y$  for marker  $X$  at cycle  $i$  were denoted by  $X_{Y,i}$  (e.g.,  $ldh_{KG,5}$ ).

128 Truncated data: study-level for trial prediction

129 Study-level truncated datasets were defined at the following on-study landmark times  $t$  after study  
130 initiation (first patient recruited):  $t = 10, 25$  and 60 weeks.

131 Only the patients enrolled before this time and their data collected up to  $t$  was used. Note  
132 that here  $t = 0$  corresponds to study initiation and thus patients in these datasets have varying  
133 follow-up duration (from 0 to  $t$ ), in contrast to individual-level truncated datasets.

## 134 Machine learning

### 135 Data preparation

136 Missing values (1.6% total, maximum 12% in one variable) were imputed with the median for nu-  
137 meric variables and mode for categorical variables, learned on the training set, even when applied  
138 to the test set. All numeric variables were centered and scaled. Means and standard deviations  
139 were learned on the train and carried to the test set.

### 140 Models

141 Model elaboration and development was performed exclusively on the training set, using 10 folds  
142 cross-validation for predictive performances evaluation. Due to censoring in the data, survival  
143 models were used: proportional hazards Cox regression<sup>33</sup>, extreme gradient boosting (XGB) with  
144 either Cox or accelerated failure time (AFT) models<sup>34</sup> and random survival forests (RSF)<sup>23</sup>. Nested  
145 cross-validation with inner bagging in each 10-fold cross-validation outer loop was used to evaluate  
146 the benefit of tuning the hyperparameters<sup>35</sup>. Improvement of the performances was negligible  
147 with hyperparameter tuning (Supplementary Figure 5). Therefore, we used the default values of  
148 the hyperparameters. For the final RSF model: number of trees  $n_{tree} = 500$ , number of variables  
149 to possibly split at each node  $m_{try} = 5$ , minimum size of terminal node  $n_{odesize} = 15$ , number of  
150 random splits for splitting a variable  $n_{split} = 10$ .

### 151 Evaluation

152 Predictive performances were assessed for either discrimination (c-index and classification met-  
153 rics at horizon times  $\tau$ ), calibration (calibration curves) or stratification (dichotomized KM survival  
154 curves). For each individual, the RSF model gives two prediction outputs: a scalar value termed  
155 “mortality” that we will refer to as “ML score”, and time-dependent predicted survival curves<sup>23</sup>. The  
156 former was used to compute the c-index using the `rcorr.cens` function of the `hmisc` R package<sup>36,37</sup>.  
157 For prediction of survival at a horizon time  $\tau$ , we used the latter to compute model-predicted prob-  
158 abilities of death at  $\tau$ . Unless otherwise specified,  $\tau = 12$  months. Survival-adapted metrics of pre-  
159 dictive performance were used for sensitivity, specificity, area under the receiver-operator curve  
160 (ROC AUC) and negative and positive predictive value (NPV and PPV) to account for censoring<sup>38,39</sup>.  
161 For computation of accuracy, censored patients before  $\tau$  were discarded ( $N = 17/396$  in the test  
162 set at 12 months). The optimal cut-points used for individual OS predictions on the test set were  
163 defined as the Kaplan-Meier estimated survival probability in the training set at  $\tau$  (0.257 at 6 months,  
164 0.437 at 12 months, 0.634 at 24 months).

165 For patient stratification (dichotomized KM curves), the ML score was used, with models trained  
166 on the training set and predicted on the test set. In order to assess stratification abilities to capture  
167 the 20% of long-term survivors, cut-points were set at the 20<sup>th</sup> percentiles for each variable/score  
168 evaluated. This cut-point arbitrary definition was also motivated by the aim to ensure fair compar-  
169 ison between multiple parameters on the same data. Significance of differences in KM curves was  
170 established using the logrank test, and hazard ratios were computed using proportional hazards  
171 Cox regression.

### 172 Variable selection and minimal signature

173 Variable selection was performed only for the BSL data. The method was based on two steps: 1)  
174 sorting the variables using least absolute shrinkage and selection operator (LASSO)<sup>40</sup> and 2) build-  
175 ing RSF incremental models including increasing numbers of variables. LASSO sorting was defined

176 as taking the coefficients gradually becoming non-zero during likelihood maximization when the  
177 regularization parameter decreases. The minimal signature was defined as the minimal set of vari-  
178 ables able to achieve a c-index larger than 0.75 and an AUC larger than 0.8, with the addition of 4  
179 well-established prognosis.

#### 180 Survival simulations and computation of predicted HRs

181 For each patient  $i$ , one output of the kML model is a survival curve  $S^i(t)$ . This gives the cumulative  
182 distribution function  $1 - S^i(t)$  of the random variable  $T^i$  of the time to death for patient  $i$ , which  
183 was used to simulate 100 replicates of  $T^i$ . Pooling all patients together, we thus obtained 100 repli-  
184 cates of  $\{T^{i, ATZ}, T^{j, DTX}\}$  for  $i$  and  $j$  being the patient indices within the ATZ and docetaxel arms,  
185 respectively. Each replicate then led to 1) a predicted survival curve in each arm and 2) a Cox pro-  
186 portional hazard HR between the two arms. Taking the mean and the 5<sup>th</sup> and 95<sup>th</sup> percentiles over  
187 all replicates yielded the reported point estimate and corresponding 95% prediction interval. The  
188 same procedure was used for study-truncated data.

#### 189 Data Availability

190 Qualified researchers may request access to individual patient level data through the clinical study  
191 data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are  
192 available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy  
193 on the Sharing of Clinical Information and how to request access to related clinical study docu-  
194 ments, see here <https://www.roche.com/innovation/process/clinical-trials/data-sharing/>.

#### 195 Code availability

196 Algorithms used for data analysis are all publicly available from the indicated libraries and refer-  
197 ences in the Methods section.

## 198 Results

### 199 Data

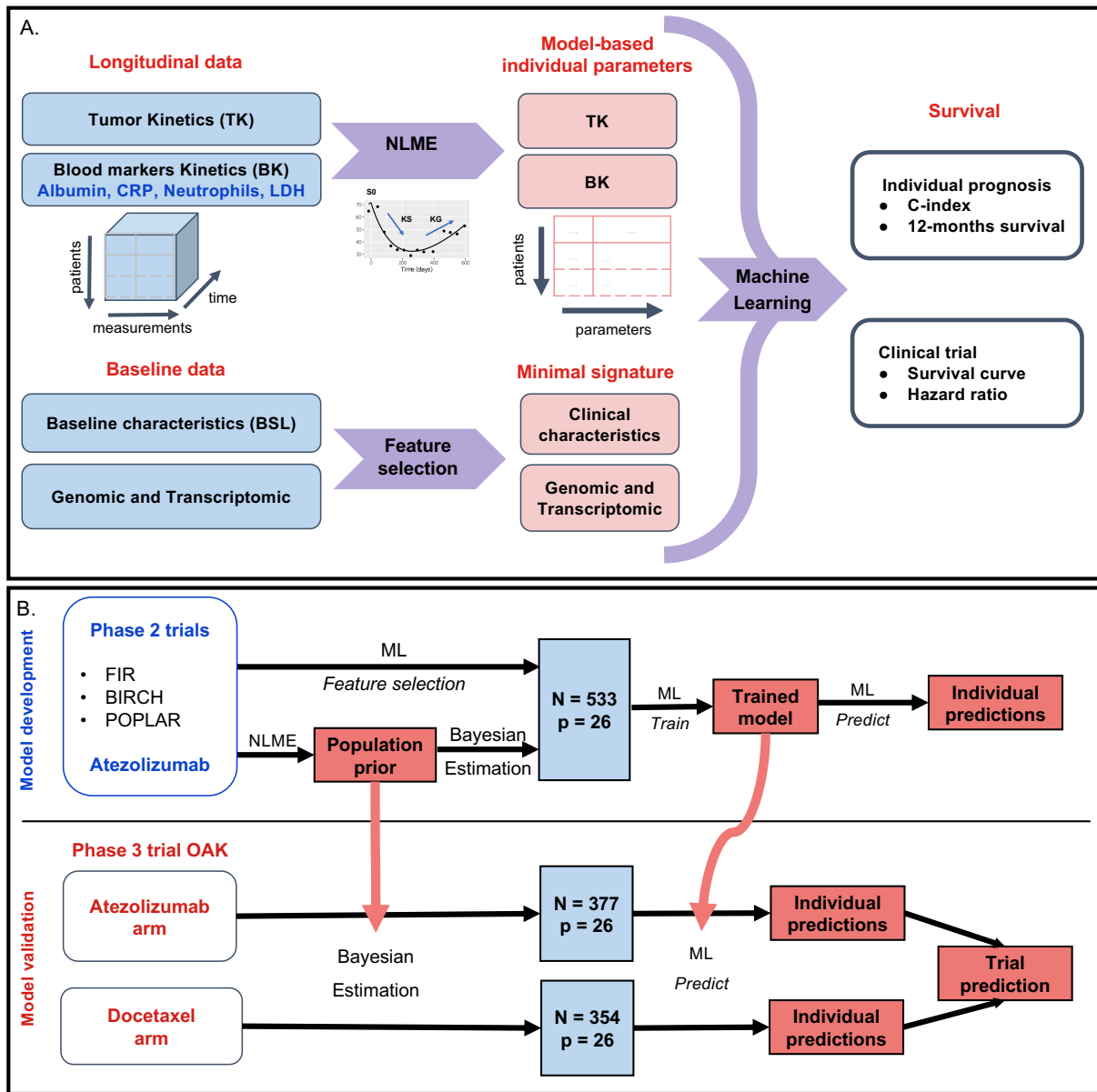
200 The data consisted of advanced NSCLC patients enrolled in ATZ trials ( $N = 1936$ , Figure 1B and  
201 Supplementary Figure 1). Three ATZ phase 2 trials were pooled into a training dataset<sup>3,25,26</sup> ( $N =$   
202  $862$ ). The external validation (test) set comprised data from the ATZ arm ( $N = 553$ ) of the OAK phase  
203 3 trial<sup>27</sup>. For trial outcome prediction the docetaxel arm ( $N = 521$ ) was added as an additional test  
204 set.

205 Variables comprised baseline (pre-treatment) and longitudinal (on-treatment) data (Figure 1A).  
206 The former included: patients and disease characteristics ( $p = 63$  variables, 43 numeric and 20  
207 categorical, denoted BSL) and transcriptomic ("RNAseq",  $p = 58,311$  transcripts) data. The latter  
208 included: longitudinal investigator-assessed sum of largest diameters (SLD) of lesions as per the  
209 RECIST criteria<sup>41</sup>, denoted by tumor kinetics (TK,  $k = 5, 473/3, 015$  time points in the train/test sets, re-  
210 spectively, median 5/4 data points per patient, range 2/2 —24/20); and longitudinal measurements  
211 of four blood markers (albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH) and neu-  
212 trophils), denoted together as blood markers kinetics (BK,  $k = 60, 779/38, 460$  data points, median  
213 11-7-11-11/9-9-9-10 data points per patient, range 3-3-3-3/3-3-3-3 —60-63-63-78/82-47-77-89 for  
214 albumin-CRP-LDH-neutrophils in the train/test sets, respectively).

### 215 Nonlinear mixed-effects modeling (NLME) of longitudinal markers

216 We first developed NLME models for the longitudinal data (Figure 1B). The TK structural model was  
217 the sum of an increasing and a decreasing exponential function (double exponential model)<sup>30</sup>. It  
218 was able to accurately describe the training data with no goodness-of-fit misspecification (Figure  
219 2A and Supplementary Figure 6). Population parameters were estimated with good accuracy (all  
220 relative standard errors smaller than 9%, Table 1).

**Figure 1: Schematic of the kML framework**



**Figure 1. Study schematic** **A.** Baseline and longitudinal data were combined into a machine learning algorithm in order to predict individual survival prognosis. Longitudinal data were modelled using nonlinear mixed-effects modelling, whereas machine learning-based feature selection was applied to the baseline data to derive a minimal signature. Tumor kinetics and biological kinetics parameters were combined with the minimal signature to predict survival. Predictive performances were assessed using survival metrics (c-index and survival at horizon times). **B.** Algorithm used to develop the model on the train data and carry it to the test set for external validation. Each step — preprocess, learning of the Bayesian priors, dimensionality reduction, feature selection, choice, tuning and training of the machine learning algorithm — were calibrated on the training set and then applied to the test set. TK: tumor kinetics; BK: blood markers kinetics; ML: machine learning; NLME: nonlinear mixed-effects modelling

**Table 1.** Parameters from nonlinear mixed-effects modeling of tumor and blood marker kinetics

|                                  | K        |        | CRP      |         | LDH      |         | Neutrophils |         | Albumin               |        |        |
|----------------------------------|----------|--------|----------|---------|----------|---------|-------------|---------|-----------------------|--------|--------|
| $KG_{pop}$ (week <sup>-1</sup> ) | 0.004 92 | (6.80) | 0.008 14 | ( 9.38) | 0.002 38 | (10.48) | 0.004 36    | ( 8.69) | $p_{pop}$ (g/l)       | 29.4   | (3.82) |
| $KG_{pop}$ (week <sup>-1</sup> ) | 0.007 78 | (8.22) | 0.0137   | (14.14) | 0.001 84 | (13.73) | 0.000 987   | (21.16) | $l_{pop}$ (log (day)) | 8.09   | (2.74) |
| $\omega_{KG}$                    | 1.36     | (3.80) | 1.61     | ( 4.25) | 1.55     | ( 5.36) | 1.41        | ( 4.48) | $\omega_p$            | 0.476  | (7.48) |
| $\omega_{KS}$                    | 1.41     | (4.66) | 1.81     | ( 6.29) | 1.92     | ( 5.34) | 2.46        | ( 5.82) | $\omega_l$            | 0.359  | (6.42) |
| error <sup>1</sup>               | 6.82     | (1.15) | 0.559    | ( 1.23) | 0.138    | ( 0.79) | 0.207       | ( 0.82) | error <sup>1</sup>    | 0.0549 | (0.77) |

Parameter value (relative standard error (%)). TK: constant error, others: proportional error. CRP : C-reactive protein; LDH : lactate deshydrogenase.

221 To analyze the BK data, we first investigated whether significant kinetic patterns could be ob-  
 222 served beyond random noise (due to, e.g., measurement errors, see raw data in Supplementary  
 223 Figures 7–10). The latter was considered as the null hypothesis, described by a constant model.  
 224 It was tested against three alternative empiric models: linear, hyperbolic (monotonous but non-  
 225 linear and saturating) and double-exponential (nonlinear and non-monotonous). For all four BKs,  
 226 we found significant kinetics compared with the constant model, as shown by lower corrected  
 227 Bayesian information criterion and relative error between model fits and data (Supplementary Fig-  
 228 ure 11). The best descriptive models were hyperbolic for albumin and double-exponential for the  
 229 other BKs. Individual fits to patient kinetics with the best models showed substantial descriptive  
 230 power (Figure 2A), which was confirmed by data versus model fits plots (Supplementary Figures  
 231 12–15). Parametric identifiability of population parameters was excellent for all models (Table 1).

232 We further assessed the stratification value of the individual model-based kinetic marker for  
 233 OS prognosis (Figure 2B). The TK parameter  $KG$  (growth rate) exhibited good stratifying ability  
 234 (HR = 4.39 (2.8–6.89)), which was similar to the  $CRP_{KG}$  parameter (HR = 4.37 (2.76–6.91)). Ranked  
 235 by HR importance; (controlled by the 20<sup>th</sup> percentile definition of the cut-point, see methods), the  
 236 following four best parameters were albumin<sub>p</sub> (HR = 3.17 (2.11–4.78)), neutrophils<sub>KG</sub> (HR = 3.07  
 237 (2.04–4.63)), neutrophils<sub>KS</sub> (HR = 2.33 (1.6–3.39)) and TK<sub>KS</sub> (HR = 2.02 (1.42–2.89)). All kinetic param-  
 238 eters carried substantial prognostic power ( $p < 0.0001$ , log rank test).

239 For TK and BKs we complemented the initial model parameters with an additional metric that  
 240 was considered valuable for early prediction: the model-predicted ratio of change over baseline at  
 241 cycle 3 day 1.

### 242 Survival prediction using kinetics-machine learning (kML): model development

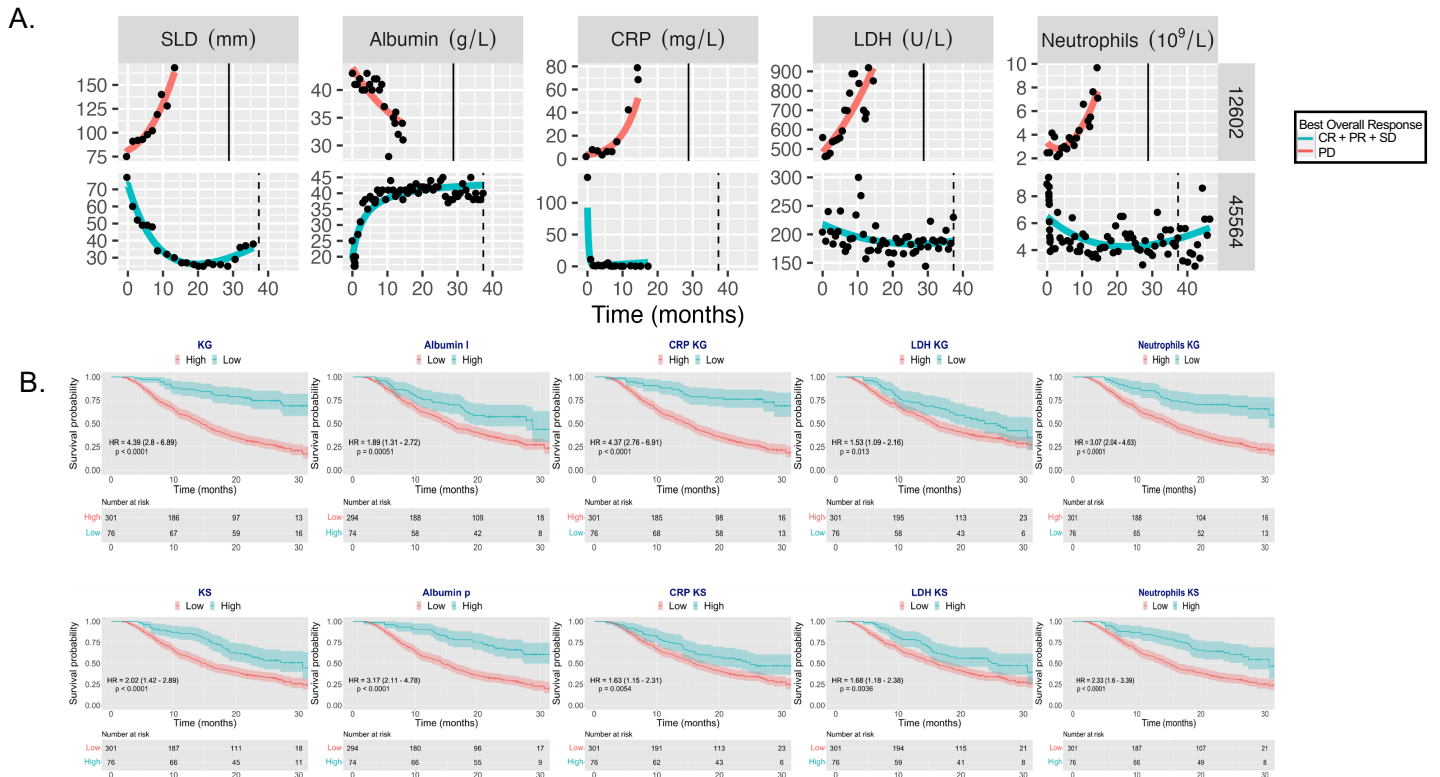
243 Four feature sets resulted from the analysis above: BSL, RNAseq, TK and BK (Figure 1A). The devel-  
 244 opment of a kinetics-machine learning (kML) comprised two main steps: choice of the algorithm  
 245 and derivation of a minimal signature (Figure 1B). The first was achieved by benchmarking four  
 246 models that used all variables ( $p = 119$ ,  $N = 553$ ). The random survival forest (RSF) model found  
 247 to exhibit the best performances (Supplementary Figure 5) and was thus selected. Notably, we  
 248 found significantly better predictive performances of RSF over a classical Cox proportional hazard  
 249 regression model ( $p = 0.0006$ ).

250 Feature selection on BSL variables was performed building incremental RSF models based on  
 251 LASSO importance-sorted variables (Figure 3A). The model using all of them achieved the best  
 252 score. Nevertheless, keeping in mind the objective to ultimately support decision making and pa-  
 253 tient stratification, a minimal (11 features), near-optimal, set of BSL variables was selected and  
 254 denoted mBSL. It was defined as the first seven variables reaching the plateau (CRP, heart rate, neu-  
 255 trophils to lymphocytes ratio, neutrophils, lymphocytes to leukocytes ratio, liver metastases and  
 256 ECOG score), complemented with four variables with established prognostic or predictive value  
 257 and available in routine care: PD-L1 expression (50% cut-off)<sup>3</sup>, hemoglobin<sup>42</sup>, SLD<sup>22</sup> and LDH<sup>43,44</sup>.

258 Applying stringent criteria to the RNAseq data (see supplementary methods), we selected 167  
 259 transcripts as candidates for final variable selection using Bolasso regression model to identify the



## Figure 2: Goodness-of-fit metrics and plots of dynamic BK models



**Figure 2. Goodness-of-fit metrics and plots of dynamic BK models** **A.** Representative individual fits for the TK and BK best empirical models showing non-trivial kinetic parameters well captured by the dynamic models. Survival is indicated by a vertical line (solid = death, dashed = censored). **B.** Stratified Kaplan-Meier curves at the 20<sup>th</sup> percentile level on the test set, for TK and BK model-based parameters. Missing values were removed in this univariable analysis, explaining the difference of initial number of patients for albumin that had 9 patients in this case. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

**Table 2.** Contingency table for OS prediction at 12 months

|       |           | TRUTH       |             |             |
|-------|-----------|-------------|-------------|-------------|
|       |           | Alive (0)   | dead (1)    | Total       |
| MODEL | Alive (-) | 182         | 30          | 212 (58.7%) |
|       | Dead (+)  | 48          | 101         | 149 (41.3%) |
|       | Total     | 230 (63.7%) | 131 (36.3%) | 361         |

Note: 16/377 censored patients with survival time  $\leq 12$  months removed for computation of accuracy. sensitivity, specificity, PPV and NPV don't correspond exactly to the numbers because they are computed from KM estimate, thus adjusting for censoring bias.

260 optimal set of predictors<sup>45</sup>. Finally, we ended up with 52 RNAseq variables that corresponded to  
 261 the highest average c-index of 0.64.

262 We then compared the cross-validated c-index of each feature set on the train data (Figure  
 263 3B). Because of negligible discrimination performances ( $c\text{-index} = 0.62 \pm 0.050$ ) and non-systematic  
 264 availability of those data, the RNAseq set was removed from the model. The selected set of clinical  
 265 data at baseline (mBSL) exhibited moderate discrimination performances ( $c\text{-index} = 0.710 \pm 0.038$ ),  
 266 which was slightly outperformed by the TK set ( $c\text{-index} = 0.723 \pm 0.025$ ). Interestingly, the BK set  
 267 significantly outperformed both baseline clinical and TK ( $c\text{-index} = 0.793 \pm 0.038$ ,  $p = 0.0004$  and  $0.0005$   
 268 respectively, Student's t-test). Jointly, mBSL, TK and BK performed significantly better than any  
 269 feature set alone ( $c\text{-index} = 0.824 \pm 0.050$ ,  $p = 0.00007$ ,  $0.0002$  and  $0.055$ ), as well as any combination  
 270 of two sets among the three (mBSL + TK:  $c\text{-index} = 0.77 \pm 0.026$ , mBSL + BK:  $c\text{-index} = 0.81 \pm 0.027$ ,  
 271 TK + BK:  $c\text{-index} = 0.80 \pm 0.049$ ). The resulting model combining mBSL, TK and BK was denoted kML  
 272 (kinetics-machine learning).

273 During cross-validation on the training set, kML exhibited excellent predictive performances  
 274 across multiple metrics, with minimal between-folds variability ( $AUC = 0.919 \pm 0.056$ ,  $accuracy =$   
 275  $0.873 \pm 0.052$ , Figure 3C).

### 276 External validation

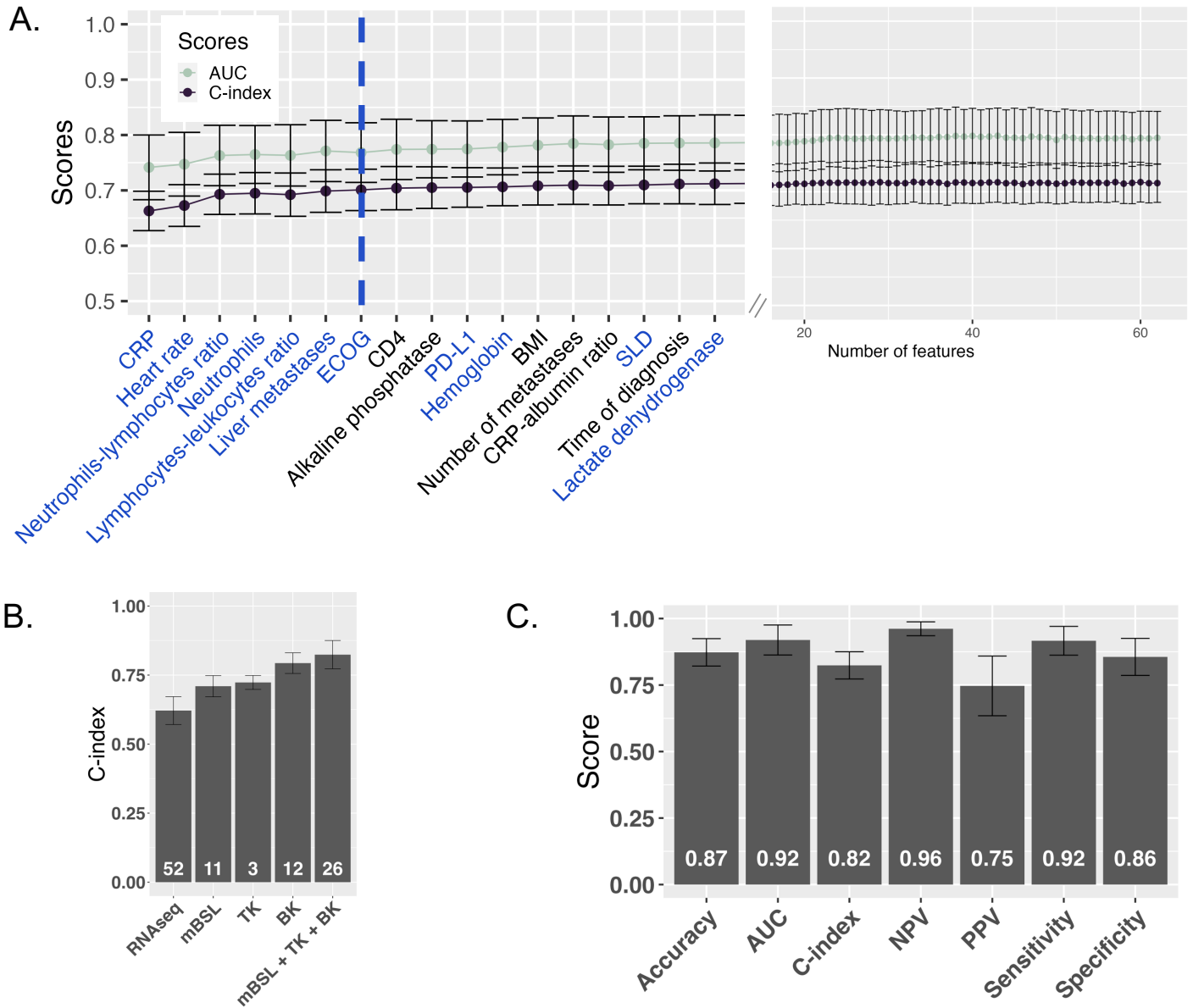
277 The predictive performance of the final kML model (mBSL, TK and BK) was assessed on the ATZ  
 278 test set (377 patients). At the population level, the model-predicted survival curve was in excellent  
 279 agreement with the observed data (Figure 4A). Notably, the prediction interval from the model  
 280 was narrow, indicating high precision. At the individual level, consistent with the cross-validation  
 281 results, substantial discrimination performances were observed ( $c\text{-index} = 0.790$ , accuracy and AUC  
 282 for 12-months survival probability 0.787 and 0.874, respectively, Figure 4B). All classification metrics  
 283 for prediction of survival at 12 months were high ( $\geq 0.78$ ), except PPV, indicating worse ability to  
 284 predict death than survival. Although smaller, they were similar to the cross-validation results.

285 In addition, calibration curves revealed good performance, at multiple horizon times (Figure  
 286 4C). Model-predicted probabilities were concordant with the observed KM estimates of the survival  
 287 probabilities, over the entire range of the binned predicted probabilities. This is further illustrated  
 288 by the contingency Table 2. For instance, among 212 patients predicted to be alive at 12 months,  
 289 182 (85.8%) were actually alive. Predictive AUC was good at other horizon times (0.846 and 0.910 at  
 290 6 and 24 months, respectively, Supplementary Figure 16). However, PPV and sensitivity were very  
 291 low at 6 months.

292 Notably, the kML mortality score derived from the model and learned on the training set was  
 293 able to accurately stratify OS in the test set ( $HR = 25.2$  (10.4–61.3),  $p < 0.0001$ , Figure 4D), indicat-  
 294 ing excellent ability to identify the 20% of long-term survivors. It outperformed all single kinetic  
 295 markers (Figure 2C).

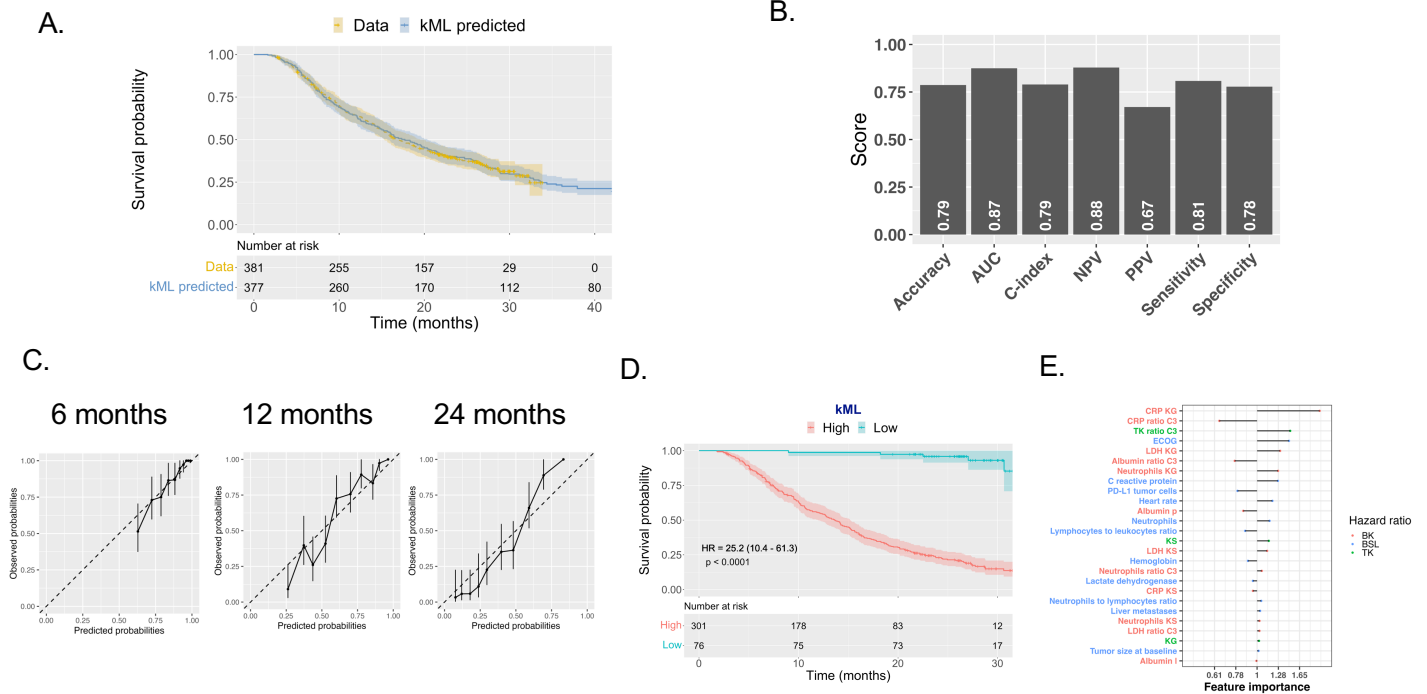
296 Variables importance was assessed by running a post-hoc multivariable Cox regression (Figure

### Figure 3: Minimal baseline (mBSL) signature and kinetics-ML (kML) model



**Figure 3. Minimal baseline (mBSL) signature and kinetics-ML (kML) model** **A.** Cross-validated (CV) performance scores on the training set (c-index and AUC, mean  $\pm$  standard deviation) for incremental random survival forest (RSF) models using an increasing number of baseline clinical and biological variables sorted by LASSO importance. The dashed blue line shows the minimal number of variables reaching the plateau. Blue-colored variables correspond to the minimal clinical signature (mBSL). **B.** Comparative CV c-indices of RSF models based either on RNAseq, mBSL, TK, BK and mBSL + TK + BK (final model, kML) variables showing increased predictive performances over baseline when using model-based parameters of kinetic markers. Numbers on the bars indicate the number of variables. **C.** CV performances of the kML model for discrimination (c-index) and classification (survival prediction at 12-months OS).

## Figure 4: Predictive performances of kML on the ATZ test set



**Figure 4. Predictive performances of kML on the ATZ test set** **A.** Comparison of the population-level survival curves between the data (KM estimator) and the model prediction. **B.** Scores of discrimination metrics. Classification metrics were computed for prediction of OS at 12 months. **C.** Calibration curves at 6, 12 and 24 months, showing the observed survival probabilities (with KM 95% confidence interval) versus the predicted ones in 10 bins corresponding to the model-predicted survival probability deciles. Dashed line is the identity. **D.** Dichotomized KM survival curves based on the ML model-predicted score (high versus low), at the 20<sup>th</sup> percentile cut-off. **E.** Variables importance (multivariable hazard ratios) in the full time-course kML model.

297 4F). Interestingly, the top two variables were BKs (CRP<sub>KG</sub> and CRP ratio C3). In addition, TK and BK made up for six out of the seven top important features and were found more important than PD-L1.

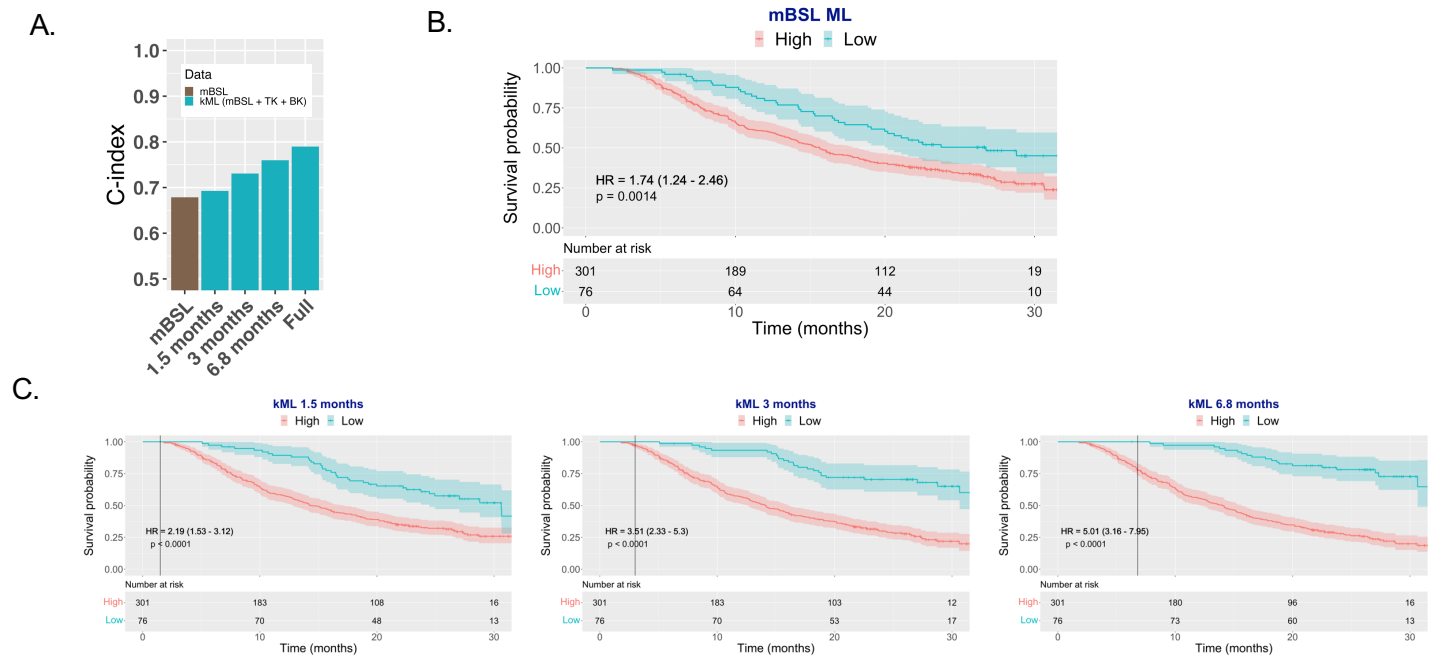
298  
299  
300 Given the large sample size of our data, we further assessed the model performances when  
301 trained on smaller data sets (Supplementary Figure 17). The learning curve revealed that ap-  
302 proximately 200 patients were necessary to reach similar performance to the ones obtained with  
303 the full training set ( $N = 533$ ), for both cross-validation and external validation on the test set  
304 ( $c\text{-index} = 0.82 \pm 0.056$  vs  $c\text{-index} = 0.82 \pm 0.050$  in cross-validation, 0.78 vs 0.79 on the test set, models  
305 trained with 200 vs 533 patients, respectively). Trained with only 60 patients, kML reached already  
306 good performances ( $c\text{-index} = 0.76 \pm 0.15$  and 0.74 in cross-validation and test, respectively).

307 Together, these results demonstrate important predictive performances of overall survival fol-  
308 lowing ATZ treatment using the kML model.

### 309 Application to individual survival prognosis from early on-treatment data

310 Results above required full on-treatment time-course data to compute TK and BK markers, thus  
311 cannot be used to make early predictions. To investigate the operational applicability of our method-  
312 ology, data from the test set were truncated at the beginning of treatment cycles number 3, 5 and  
313 10, respectively corresponding to 1.5, 3 and 6.75 months. We found that integrating longer on-  
314 treatment data in kML, the predictive performances steadily increased (Figure 5A and Supplemen-  
315 tary Figure 18). Using the baseline variables only (mBSL), the stratification ability was significant  
316 but moderate (HR = 1.74 (1.24 - 2.46),  $p = 0.0014$ , Figure 5B). In contrast, kML exhibited increasing  
317 stratification ability from data at 1.5 months (HR = 2.19 (1.53 - 3.12),  $p < 0.0001$ ), 3 months (HR = 3.51

## Figure 5: Individual-level predictions of kML from cycle-truncated data



**Figure 5. Predictive value of kML from cycle-truncated data** **A.** Predictive power (c-index) of ML models using baseline (BSL) or truncated data at 1.5, 3 and 6.8 months as well as the full time-course. **B.** Stratified KM survival curves using a RSF model trained on the minimal baseline (mBSL) variables. **C.** Stratified KM survival curves using kML from 1.5 months (2 cycles), 3 months (4 cycles) and 6.8 months (9 cycles) truncated data. Truncation time is indicated by the vertical line.

TK: tumor kinetics; BK: biological kinetics; LDH: lactate dehydrogenase; CRP: C-reactive protein.

318 (2.33 – 5.3),  $p < 0.0001$ ) and 6.8 months (HR = 5.01 (3.16 – 7.95),  $p < 0.0001$ ), see Figure 5C.

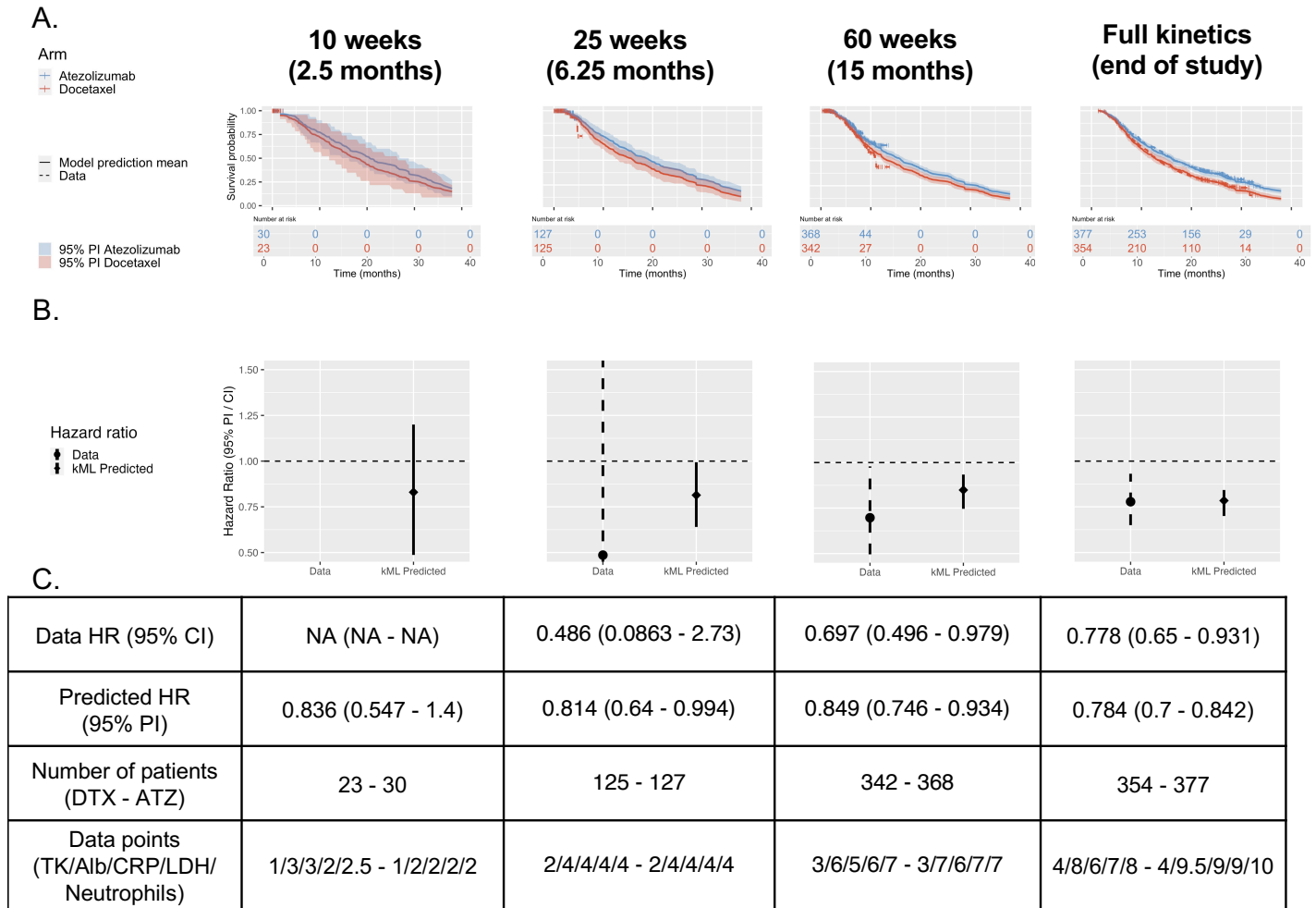
319 Further investigation of the predictive performances of individual kinetic markers revealed  
 320 that TK parameters were the most informative at 6 weeks (1.5 months, first imaging assessment).  
 321 Adding BKs to TKs brought additional predictive value starting at 3 months, and BKs outperformed  
 322 TK from 6.75 months on (Supplementary Figure 19A). Among BKs, neutrophils kinetics appeared to  
 323 be the most predictive, followed by CRP, albumin and LDH. However, the combined BK signature  
 324 outperformed each individual BK, indicating that their collective predictive capabilities were not  
 325 driven by any single biomarker alone.

326 Interestingly, the most important variable at 1.5 months was a kinetic one, TK ratio C3 with  
 327 following variables being from mBSL (e.g., liver metastases, PDL1 and ECOG). When more on-  
 328 treatment variables become available, this shifted to TK and BK (TK ratio C3, TK<sub>KS</sub>, TK<sub>KG</sub>, CRP<sub>KG</sub>,  
 329 LDH<sub>KG</sub>), see Supplementary Figure 19B.

### 330 Application to clinical trial outcome prediction from early on-study data

331 The kML model can also be applied for the prediction of the outcome of a clinical trial (survival  
 332 curves and associated hazard ratio), from early on-study data. We performed on-study runca-  
 333 tions on the test set based on a number of weeks after the date of the first patient recruited (see  
 334 methods). Here, we applied the model to predict not only patients receiving ATZ, but also doc-  
 335 etaxel (Figure 1B). Predictions of the kML model applied to each arm yielded very accurate results  
 336 when using data from the entire study (predicted HR = 0.784 (0.7 – 0.842)), versus data HR = 0.778  
 337 (0.65 – 0.931), Figure 6A–B). Notably, the model prediction intervals were narrower than the data  
 338 Kaplan-Meier confidence intervals, probably because the kML-trained model incorporates the in-  
 339 formation from the three phase 2 trials. Using only early data, the model was already able to detect

**Figure 6: Use of kML for early prediction of the outcome of a clinical trial**



**Figure 6. Use of kML for early-prediction of the outcome of a clinical trial** **A.** Survival curves model-based predictions and prediction intervals versus actual data from on-study data at multiple horizon times after study initiation. Note that the model is able to predict full survival curves even if based on early kinetics. **B.** Compared data and kML-predicted hazard ratios. **C.** Description of hazard ratios, number of patients and number of data points available in each arm, at the landmark on-study time points. PI: prediction interval, CI: confidence interval, DTX: docetaxel arm, ATZ: atezolizumab arm.

340 a (non-significant) tendency at 10 weeks, with only 23 and 30 patients in each arm, and very short  
 341 follow-up. Starting from data available at 25 weeks (6.25 months), the model correctly predicted  
 342 a positive outcome of the study, with a 95% prediction interval of the HR below 1. Of note, the  
 343 available data at this time (dashed lines, Figure 6A and red HR CIs in Figure 6B) was far from being  
 344 conclusive. The model prediction was stable from 25 weeks on whereas the OS data only exhib-  
 345 ited significant HR starting from 60 weeks and required more than 300 patients in each arm to be  
 346 conclusive.

### 347 Discussion

348 Blood markers from hematology and biochemistry are routinely collected during clinical care or  
 349 drug trials. They are cost-effective and easily obtained both before and during treatment. There  
 350 is limited exploration regarding the predictive capabilities of the kinetics of such data. Combining  
 351 BSL variables with on-treatment data (TK and BK), we addressed this question using a novel hy-  
 352 brid NLME-ML methodology. The resulted kML model demonstrated excellent predictive perfor-

353 mances for OS in two aspects: 1) patient-level predictions (discrimination, calibration and patient  
354 stratification) and 2) trial-level predictions. The kML model outperformed current state-of-the-art  
355 methods based on either baseline or on-treatment data alone, utilizing only routine clinical infor-  
356 mation, with a c-index of 0.79 and an accuracy of 78% for prediction of 12-month survival, on the  
357 test dataset. Overall, kML incorporates 26 features, out of which 15 features require monitoring  
358 five quantities over time (tumor size, albumin, CRP, LDH and neutrophils).

359 Regarding baseline markers, the predictive value of PD-L1 expression, commonly used in clinical  
360 care, is controversial<sup>9,10</sup>. Previous studies reported an AUC for durable response of 0.601 and  
361 a PFS HR of 1.90 (PD-L1  $\geq 1\%$  vs 0%)<sup>8</sup>. Baseline tumor mutational burden showed similar predic-  
362 tive value initially (AUC = 0.646)<sup>11</sup>, but led to disappointing results in a recent prospective study<sup>46</sup>.  
363 Baseline blood counts were previously reported to predict overall survival<sup>43,47-49</sup> and treatment  
364 response (AUC = 0.74)<sup>42</sup>. The ROPRO score, derived from a large pan-cancer cohort and incorpo-  
365 rating baseline clinical and biological data (27 variables) achieved a c-index of 0.69 and a 3-months  
366 AUC of 0.743 for prediction of survival in the OAK clinical trial<sup>50</sup>. Here, we confirmed these find-  
367 ings and established a minimal signature of such data composed of only 11 variables (CRP, heart  
368 rate, neutrophils to lymphocytes ratio, neutrophils, lymphocytes to leukocytes ratio, liver metas-  
369 tases, ECOG, PD-L1  $\geq 50\%$ , hemoglobin, SLD and LDH), yet with similar predictive performances  
370 (*c-index* = 0.678) and significant stratification ability (*HR* = 1.74, *p* = 0.0014). Altogether, our kML  
371 model demonstrated substantially better predictive performances than these baseline models.

372 We further confirmed the established predictive value of TK model-based parameters<sup>19,20</sup>. Blood-  
373 or serum-derived longitudinal markers kinetics have to date rarely been modeled. Gavrilov et al.  
374 proposed to model NLR kinetics and demonstrated improved OS predictions over TK alone<sup>31</sup>. Here  
375 we extended to four BKs: albumin, CRP, LDH and neutrophils. This choice was not only motivated  
376 by observed statistical associations, but also from biological considerations. Albumin is associated  
377 with nutritional status (cachexic state) and is known to evolve with time in responders. CRP is a  
378 marker of systemic inflammation<sup>44</sup>. Increased CRP, decreased albumin level, and increased CR-  
379 P/albumin ratio have been reported to be associated with poor survival<sup>51</sup>. Neutrophils play a role  
380 in inflammation by promoting a favorable microenvironment for cancer cell growth and spread,  
381 and activation of carcinogenic signaling pathways<sup>52</sup>. Elevated LDH levels are a marker of cancer  
382 cells turnover rate, and LDH has a potential role for prediction of potential invisible metastases<sup>44</sup>.  
383 We found that all these markers had non-trivial on-treatment kinetics. However, data fits were not  
384 perfect, possibly due to the simplicity and empiric nature of the models we used. Further mecha-  
385 nistic modeling of the joint kinetics of BKs and TK could bring relevant biological information and  
386 yield more accurate predictive parameters. We found that all four BKs were contributive to the  
387 model and that, combined, they outperformed TK performances.

388 We analyzed the RNAseq data using standard methods and found only negligible predictive  
389 performances. Such result could be explained by the fact that the tissue of origin that was used  
390 was heterogeneous across the patients (primary tumor or metastasis), was limited to a local area  
391 of the tumor, and could come from tissue sampled long before treatment initiation. Given that  
392 our main objective was to derive a predictive model from markers available in routine practice, we  
393 excluded it from our minimal signature. A refined analysis, especially focusing on immune-based  
394 signatures, could improve our results<sup>5</sup>.

395 Machine learning models, although increasingly used in pharmacological studies —including  
396 recently for TK-OS modeling and variable selection<sup>22,53</sup> —have yet rarely been rigorously compared  
397 to classical statistical models<sup>24</sup>. Here, such comparison revealed significantly better performance  
398 of the nonlinear random survival forest RSF model compared to the linear proportional hazards  
399 Cox model. In our approach, we did not use the propagation of standard statistical quantification  
400 of the parameters' estimates uncertainty to evaluate the accuracy of the model predictions. Rather,  
401 we relied on the RSF-outputted individual survival curves to sample virtual individuals and compute  
402 prediction intervals.

403 A drawback of classical TK-OS studies is that they make use of the full observed kinetics to

404 predict overall survival, which can lead to time-dependent covariate bias<sup>54</sup> and limit their practical  
405 applicability at bedside. We used individual-truncated data sets and found that kML was already  
406 improving predictions over mBSL using data at 1.5 months, which corresponds to the first imag-  
407 ing assessment of the treatment effect. At later times, stratification abilities increased to highly  
408 significant levels (e.g.,  $HR = 5$  at 6.8 months).

409 A strength of our study is that we relied on well-curated data with high number of patients from  
410 clinical trials. However, when extrapolating to other settings — earlier trial phases, real-world data  
411 — limited number of patients might be available. Yet, we found that using only 60 patients to train  
412 kML was sufficient to reach near-optimal performances.

413 Not only kML has value for personalized health care, but it also revealed useful for prediction  
414 of a phase 3 trial using early on-study data. Our model was able to predict the study's positive  
415 outcome with data at  $\sim 6$  months, versus 10 months using TK only<sup>19</sup>. Relying on the data alone,  
416 such positive outcome was only detectable at 15 months. These results could have important im-  
417 plications for drug development as they could inform earlier on go/no-go decisions. Consequently,  
418 this could allow to detect futility more easily and more rapidly during clinical trials, allowing to  
419 avoid treating patients with an inefficient investigational treatment and to reassign funds and en-  
420 ergy to other researches. Of note, in a recent evaluation based on resampling the first-line NSCLC  
421 ATZ study IMpower150 to mimic small, short follow up early Phase Ib studies, TK model-based  
422 metrics had better operating characteristics to predict Phase III success compared with RECIST  
423 endpoints ORR and PFS<sup>55</sup>. Extension of such results with the addition of BKs is thus a promising  
424 line of research. In addition, kML, trained on ATZ data, yielded excellent predictive abilities for the  
425 docetaxel (control) arm. This suggests that the relationships between TK / BK and OS might be  
426 drug-independent. In turn, this opens future perspectives in terms of testing kML on drugs with  
427 different mechanism of action, or combinations.

428 Further avenues of research comprise the development of integrative models from advanced  
429 multi-modal data such as the one collected during the PIONeeR clinical study (NCT03833440)<sup>56,57</sup>  
430 that include quantitative image analysis from multiplex immune-histochemistry, genomic and tran-  
431 scriptomic data, biological and clinical markers. In addition, mechanistic modeling of quantitative  
432 and physiologically meaningful longitudinal data (immune-monitoring, vasculo-monitoring, circu-  
433 lating DNA<sup>12,58-60</sup>, soluble factors<sup>61</sup>, pharmacokinetics, TK and a large number of BKs from either  
434 hematology or biochemistry) paves the way to an improved understanding and prediction of mech-  
435 anisms of relapse to ICI<sup>62</sup>. Furthermore, the predictive abilities of kML — at the both individual and  
436 study levels — should be evaluated in model-based prospective trials<sup>63</sup>.

437 In conclusion, our study shows that integrating model-based on-treatment dynamic data from  
438 routine biological markers shows great promise for both personalized health care and early pre-  
439 diction of the outcome of clinical trials during drug development.

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| Study                         | Description   | Population  | N           |
|-------------------------------|---|---|-------------|
| <b>FIR<br/>GO28625</b>        | Phase 2 study for the efficacy and safety of ATZ in advanced NSCLC                  | PD-L1 positive locally advanced or metastatic NSCLC (lines 1 and 2+)      | 133         |
| <b>POPLAR<br/>GO28753</b>     | Phase 2 randomised controlled trial of ATZ versus docetaxel in NSCLC                | Locally advanced or metastatic NSCLC who failed platinum therapy (line 2) | 134         |
| <b>BIRCH<br/>GO28754</b>      | Phase 2 study of ATZ in advanced or metastatic NSCLC                                | Locally advanced or metastatic NSCLC (lines 1, 2 or 3)                    | 595         |
| <b>Train</b>                  |   |   | <b>862</b>  |
| <b>Test - OAK<br/>GO28915</b> | Phase 3 RCT of ATZ versus docetaxel (DTX) in patients with previously treated NSCLC | Stage IIIb or IV, previously chemo treated                                | <b>553</b>  |
| <b>Train + Test</b>           |   |   | <b>1415</b> |

Four monotherapy studies of atezolizumab in advanced NSCLC. 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.

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**Supplementary Figure 1. Train and test data sets**

| Characteristic             | Total, N = 1415 <sup>1</sup> | FIR, N = 133 <sup>1</sup> | POPLAR, N = 134 <sup>1</sup> | BIRCH, N = 595 <sup>1</sup> | OAK, N = 553 <sup>1</sup> | p-value <sup>2</sup> |
|----------------------------|------------------------------|---------------------------|------------------------------|-----------------------------|---------------------------|----------------------|
| Age                        | 64 (57, 70)                  | 67 (60, 73)               | 62 (55, 69)                  | 65 (57, 71)                 | 64 (57, 70)               | <0.001               |
| Sex                        |                              |                           |                              |                             |                           | 0.3                  |
| Female                     | 568 (40%)                    | 57 (43%)                  | 47 (35%)                     | 251 (42%)                   | 213 (39%)                 |                      |
| Male                       | 847 (60%)                    | 76 (57%)                  | 87 (65%)                     | 344 (58%)                   | 340 (61%)                 |                      |
| Weight                     | 72 (61, 82)                  | 70 (60, 83)               | 73 (63, 84)                  | 72 (61, 82)                 | 71 (60, 82)               | 0.3                  |
| BMI                        | 24.9 (22.1, 28.1)            | 24.8 (21.9, 27.6)         | 25.2 (22.8, 28.7)            | 25.0 (22.1, 28.2)           | 24.7 (22.0, 28.1)         | 0.4                  |
| Unknown                    | 65                           | 8                         | 5                            | 30                          | 22                        |                      |
| Race                       |                              |                           |                              |                             |                           | <0.001               |
| Asian                      | 228 (16%)                    | 6 (4.5%)                  | 23 (17%)                     | 77 (13%)                    | 122 (22%)                 |                      |
| Others, unknown or missing | 73 (5.2%)                    | 9 (6.8%)                  | 9 (6.7%)                     | 23 (3.9%)                   | 32 (5.8%)                 |                      |
| White                      | 1,114 (79%)                  | 118 (89%)                 | 102 (76%)                    | 495 (83%)                   | 399 (72%)                 |                      |
| Smoking history            |                              |                           |                              |                             |                           | 0.13                 |
| Current                    | 171 (12%)                    | 18 (14%)                  | 22 (16%)                     | 60 (10%)                    | 71 (13%)                  |                      |
| Never                      | 248 (18%)                    | 16 (12%)                  | 27 (20%)                     | 102 (17%)                   | 103 (19%)                 |                      |
| Previous                   | 996 (70%)                    | 99 (74%)                  | 85 (63%)                     | 433 (73%)                   | 379 (69%)                 |                      |

| Characteristic          | Total, N = 1415 <sup>1</sup> | FIR, N = 133 <sup>1</sup> | POPLAR, N = 134 <sup>1</sup> | BIRCH, N = 595 <sup>1</sup> | OAK, N = 553 <sup>1</sup> | p-value <sup>2</sup> |
|-------------------------|------------------------------|---------------------------|------------------------------|-----------------------------|---------------------------|----------------------|
| Heart rate              | 81 (71, 92)                  | 80 (70, 94)               | 84 (74, 96)                  | 80 (70, 90)                 | 81 (72, 93)               | 0.049                |
| Systolic blood pressure | 122 (111, 133)               | 122 (113, 132)            | 122 (112, 131)               | 120 (110, 133)              | 123 (113, 135)            | 0.13                 |

<sup>1</sup>Median (IQR); n (%)

<sup>2</sup>Kruskal-Wallis rank sum test; Pearson's Chi-squared test

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**Supplementary Figure 2. Patient characteristics: demographics and clinics**

| Characteristic              | Total, N = 1415 <sup>1</sup> | FIR, N = 133 <sup>1</sup> | POPLAR, N = 134 <sup>1</sup> | BIRCH, N = 595 <sup>1</sup> | OAK, N = 553 <sup>1</sup> | p-value <sup>2</sup> |
|-----------------------------|------------------------------|---------------------------|------------------------------|-----------------------------|---------------------------|----------------------|
| <b>Disease type</b>         |                              |                           |                              |                             |                           | 0.4                  |
| Locally advanced            | 77 (5.4%)                    | 3 (2.3%)                  | 8 (6.0%)                     | 32 (5.4%)                   | 34 (6.1%)                 |                      |
| Metastatic                  | 1,338 (95%)                  | 130 (98%)                 | 126 (94%)                    | 563 (95%)                   | 519 (94%)                 |                      |
| <b>Line</b>                 |                              |                           |                              |                             |                           | <0.001               |
| ≥2                          | 1,255 (89%)                  | 102 (77%)                 | 134 (100%)                   | 466 (78%)                   | 553 (100%)                |                      |
| 1                           | 160 (11%)                    | 31 (23%)                  | 0 (0%)                       | 129 (22%)                   | 0 (0%)                    |                      |
| <b>Histology</b>            |                              |                           |                              |                             |                           | <0.001               |
| Non-squamous                | 1,016 (74%)                  | 95 (100%)                 | 87 (65%)                     | 427 (72%)                   | 407 (74%)                 |                      |
| Squamous                    | 361 (26%)                    | 0 (0%)                    | 47 (35%)                     | 168 (28%)                   | 146 (26%)                 |                      |
| Unknown                     | 38                           | 38                        | 0                            | 0                           | 0                         |                      |
| <b>Stage</b>                |                              |                           |                              |                             |                           | <0.001               |
| I                           | 123 (8.9%)                   | 11 (8.7%)                 | 4 (3.0%)                     | 73 (12%)                    | 35 (6.5%)                 |                      |
| II                          | 140 (10%)                    | 11 (8.7%)                 | 9 (6.8%)                     | 73 (12%)                    | 47 (8.7%)                 |                      |
| III                         | 367 (27%)                    | 30 (24%)                  | 37 (28%)                     | 165 (28%)                   | 135 (25%)                 |                      |
| IV                          | 753 (54%)                    | 75 (59%)                  | 82 (62%)                     | 273 (47%)                   | 323 (60%)                 |                      |
| Unknown                     | 32                           | 6                         | 2                            | 11                          | 13                        |                      |
| <b>Number of metastases</b> |                              |                           |                              |                             |                           | 0.4                  |
| 1                           | 386 (28%)                    | 35 (27%)                  | 34 (26%)                     | 158 (27%)                   | 159 (29%)                 |                      |
| 2                           | 655 (48%)                    | 55 (42%)                  | 61 (47%)                     | 289 (50%)                   | 250 (46%)                 |                      |
| 3                           | 334 (24%)                    | 41 (31%)                  | 34 (26%)                     | 128 (22%)                   | 131 (24%)                 |                      |
| Unknown                     | 40                           | 2                         | 5                            | 20                          | 13                        |                      |
| <b>Liver metastases</b>     | 272 (19%)                    | 29 (22%)                  | 33 (25%)                     | 105 (18%)                   | 105 (19%)                 | 0.3                  |
| <b>Number of met. loc.</b>  |                              |                           |                              |                             |                           | 0.3                  |
| Four sites                  | 70 (4.9%)                    | 13 (9.8%)                 | 6 (4.5%)                     | 27 (4.5%)                   | 24 (4.3%)                 |                      |
| One site                    | 426 (30%)                    | 37 (28%)                  | 39 (29%)                     | 178 (30%)                   | 172 (31%)                 |                      |
| Three sites                 | 264 (19%)                    | 28 (21%)                  | 28 (21%)                     | 101 (17%)                   | 107 (19%)                 |                      |
| Two sites                   | 655 (46%)                    | 55 (41%)                  | 61 (46%)                     | 289 (49%)                   | 250 (45%)                 |                      |
| Tumor size                  | 59 (43, 95)                  | 59 (57, 59)               | 70 (43, 107)                 | 60 (37, 96)                 | 70 (43, 102)              | 0.001                |

<sup>1</sup>n (%); Median (IQR)

<sup>2</sup>Pearson's Chi-squared test; Kruskal-Wallis rank sum test

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### Supplementary Figure 3. Patient characteristics: disease

| Characteristic            | Total, N = 1415 <sup>1</sup> | FIR, N = 133 <sup>1</sup> | POPLAR, N = 134 <sup>1</sup> | BIRCH, N = 595 <sup>1</sup> | OAK, N = 553 <sup>1</sup> | p-value <sup>2</sup> |
|---------------------------|------------------------------|---------------------------|------------------------------|-----------------------------|---------------------------|----------------------|
| <b>PD-L1 tumor cells</b>  |                              |                           |                              |                             |                           | <0.001               |
| 0                         | 606 (43%)                    | 4 (3.0%)                  | 40 (30%)                     | 212 (36%)                   | 350 (64%)                 |                      |
| 1                         | 209 (15%)                    | 21 (16%)                  | 56 (42%)                     | 69 (12%)                    | 63 (11%)                  |                      |
| 2                         | 381 (27%)                    | 105 (79%)                 | 37 (28%)                     | 160 (27%)                   | 79 (14%)                  |                      |
| 3                         | 217 (15%)                    | 3 (2.3%)                  | 1 (0.7%)                     | 154 (26%)                   | 59 (11%)                  |                      |
| Unknown                   | 2                            | 0                         | 0                            | 0                           | 2                         |                      |
| <b>PD-L1 immune cells</b> |                              |                           |                              |                             |                           | <0.001               |
| 0                         | 252 (18%)                    | 3 (2.3%)                  | 40 (30%)                     | 16 (2.7%)                   | 193 (35%)                 |                      |
| 1                         | 398 (28%)                    | 5 (3.8%)                  | 56 (42%)                     | 122 (21%)                   | 215 (39%)                 |                      |
| 2                         | 439 (31%)                    | 25 (19%)                  | 19 (14%)                     | 297 (50%)                   | 98 (18%)                  |                      |
| 3                         | 322 (23%)                    | 99 (75%)                  | 19 (14%)                     | 159 (27%)                   | 45 (8.2%)                 |                      |
| Unknown                   | 4                            | 1                         | 0                            | 1                           | 2                         |                      |
| <b>ECOG</b>               |                              |                           |                              |                             |                           | 0.6                  |
| Status 0                  | 505 (36%)                    | 42 (32%)                  | 44 (33%)                     | 215 (36%)                   | 204 (37%)                 |                      |
| Status 1 or 2             | 909 (64%)                    | 90 (68%)                  | 90 (67%)                     | 380 (64%)                   | 349 (63%)                 |                      |
| Unknown                   | 1                            | 1                         | 0                            | 0                           | 0                         |                      |

<sup>1</sup>n (%)

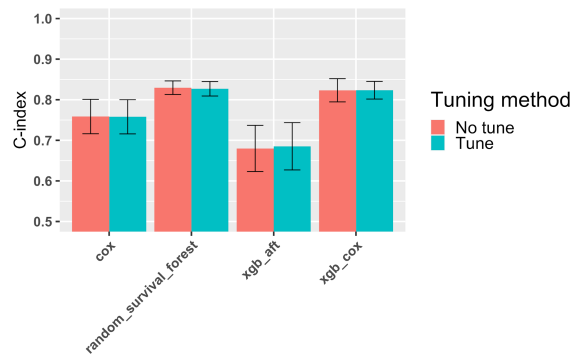
<sup>2</sup>Pearson's Chi-squared test

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### Supplementary Figure 4. Patient characteristics: PD-L1 and ECOG

Comparative cross-validated predictive performances of the survival ML models.



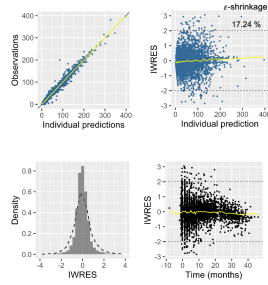
Note: 10-fold cross-validation on FIR, BIRCH and POPLAR (train data set) – performances using all features

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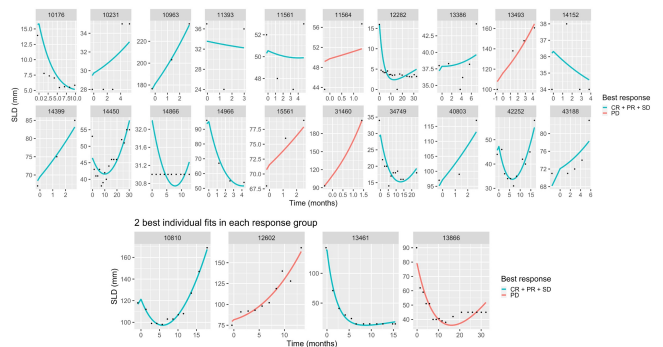
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Supplementary Figure 5. Comparison of ML algorithms and tuning methods

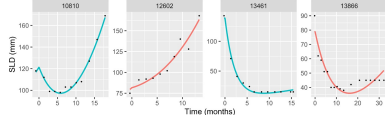
Individual goodness-of-fit (GOF) plots



20 randomly selected individual fits



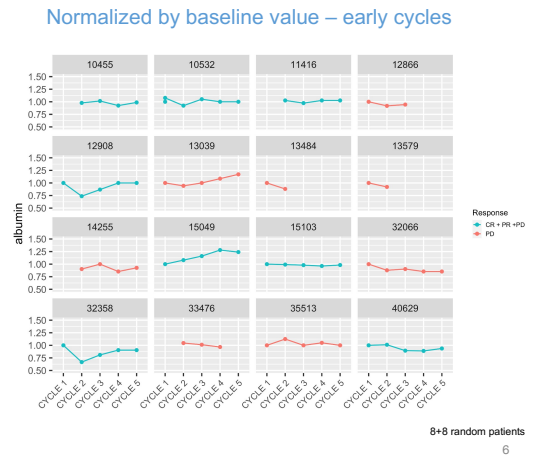
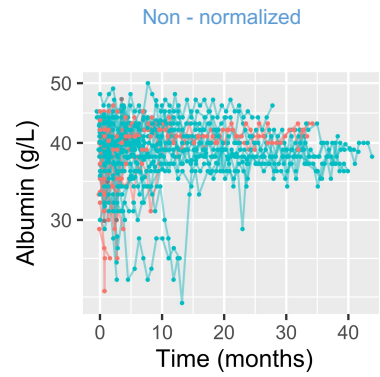
2 best individual fits in each response group



Goodness-of-fit quantitatively assessed with residuals-based metric (see methods)

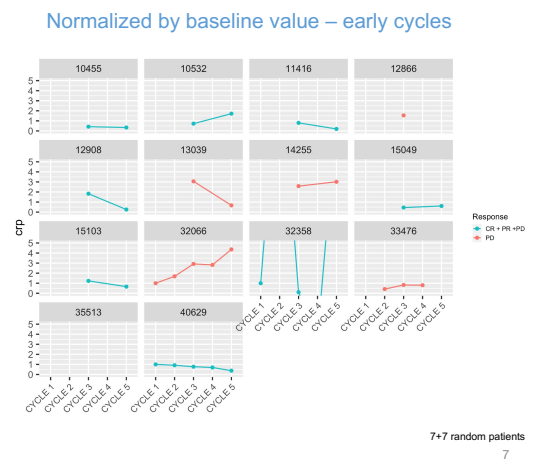
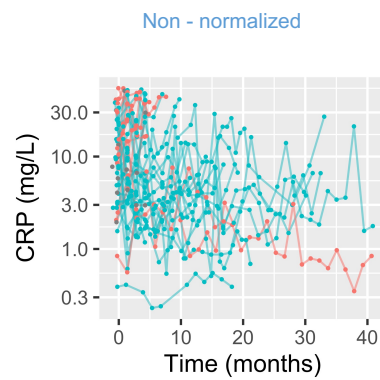
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Supplementary Figure 6. TK modeling goodness-of-fit



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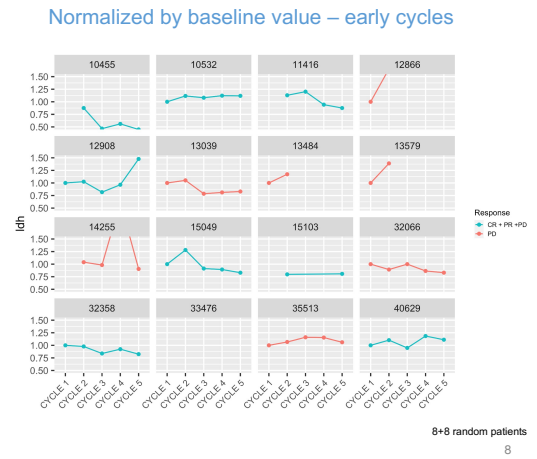
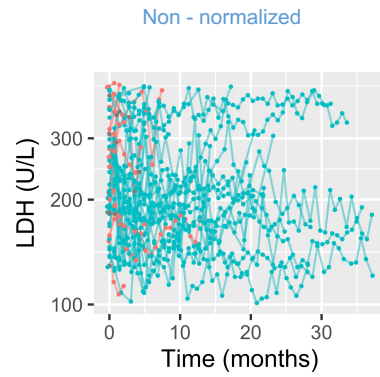
Supplementary Figure 7. Examples of longitudinal kinetics: Albumin



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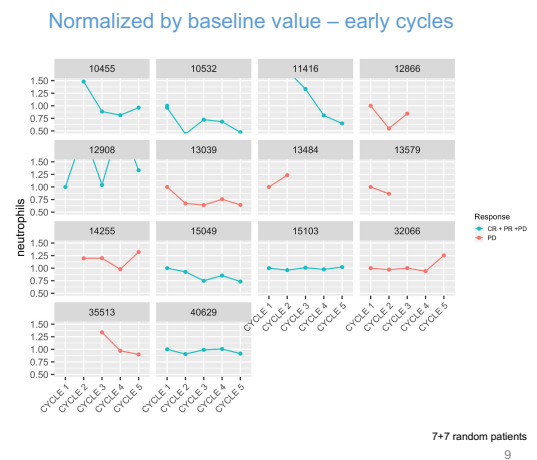
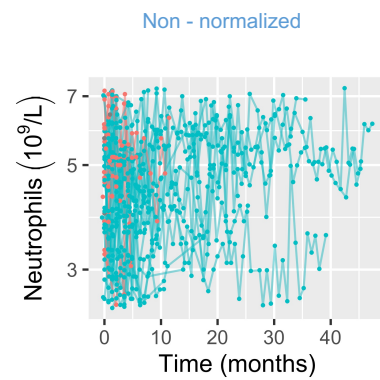
Supplementary Figure 8. Examples of longitudinal kinetics: CRP





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Supplementary Figure 9. Examples of longitudinal kinetics: LDH



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Supplementary Figure 10. Examples of longitudinal kinetics: Neutrophils

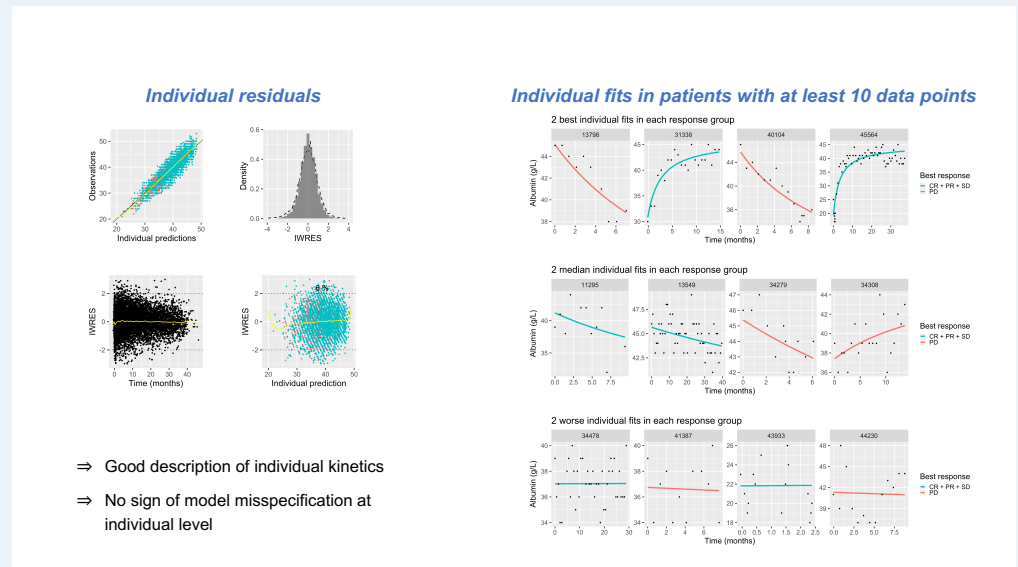
| Model              | Albumin       |              | CRP           |             | LDH           |             | Neutrophils    |             |
|--------------------|---------------|--------------|---------------|-------------|---------------|-------------|----------------|-------------|
|                    | BICc          | b            | BICc          | b           | BICc          | b           | BICc           | b           |
| Double-exponential | 48,395        | 0.058        | <b>28,764</b> | <b>0.21</b> | <b>39,886</b> | <b>0.56</b> | <b>102,449</b> | <b>0.14</b> |
| Hyperbolic         | <b>48,007</b> | <b>0.056</b> | 29,712        | 0.22        | 40,915        | 0.62        | 102,943        | 0.14        |
| Linear             | 49,436        | 0.063        | 30,020        | 0.23        | 42,462        | 0.70        | 105,193        | 0.17        |
| Constant           | 49,724        | 0.065        | 31,332        | 0.25        | 42,982        | 0.74        | 106,249        | 0.18        |

Corrected Bayesian Information Criterion (BICc) for four empirical kinetic models of BK. b : standard deviation of the proportional error model

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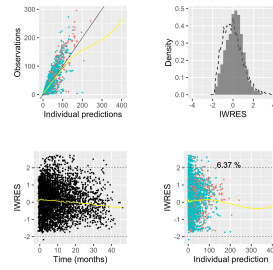
Supplementary Figure 11. Goodness-of-fit metrics of dynamic BK models



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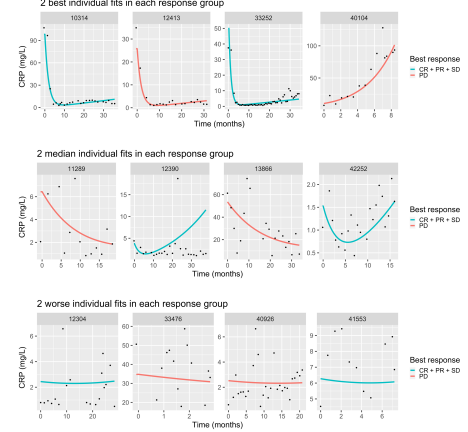
Supplementary Figure 12. Albumin: hyperbolic individual fits

### Individual residuals



- ⇒ Globally, several individuals not adequately fitted
- ⇒ Nevertheless, some patients have very accurate fits
- ⇒ Some trend of the model to underestimation
- ⇒ Distribution of IWRES remains close to gaussian

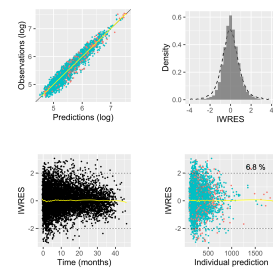
### Individual fits in patients with at least 10 data points



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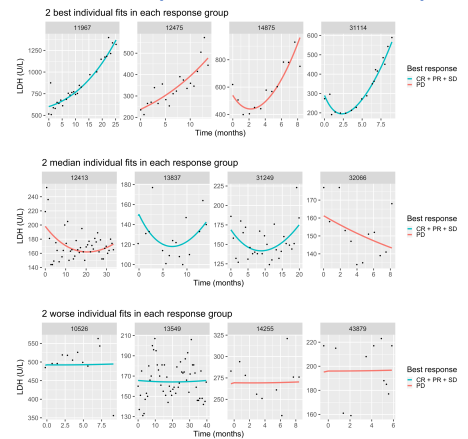
Supplementary Figure 13. CRP: dexp individual fits

### Individual residuals



- ⇒ Very good description of individual kinetics
- ⇒ No sign of model misspecification at individual level

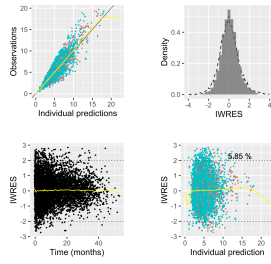
### Individual fits in patients with at least 10 data points



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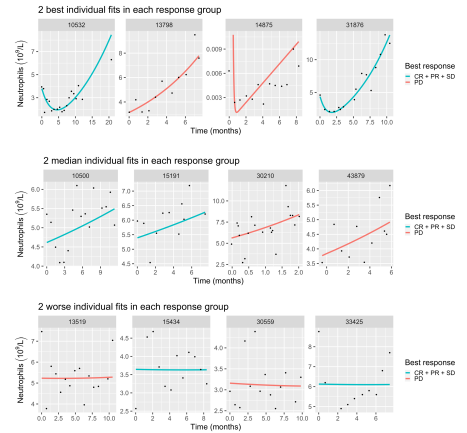
Supplementary Figure 14. LDH: dexp individual fits

### Individual residuals



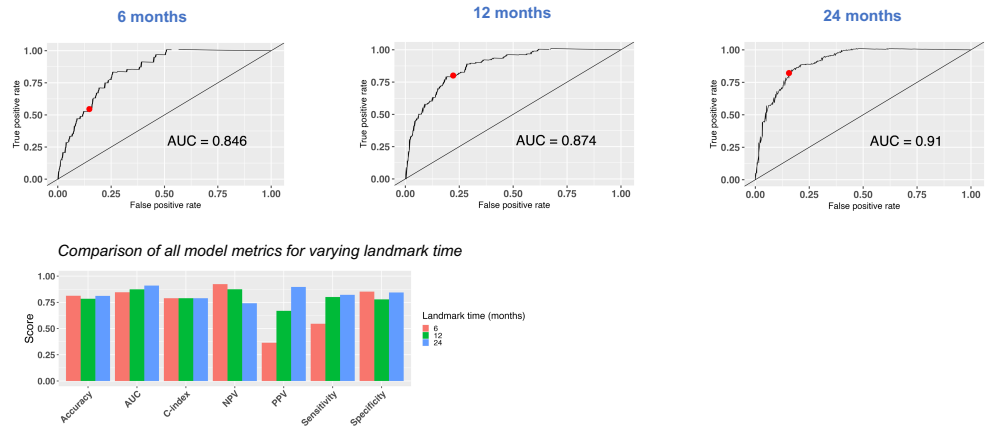
- ⇒ Moderate description of individual kinetics
- ⇒ No major sign of model misspecification at individual level

### Individual fits in patients with at least 10 data points



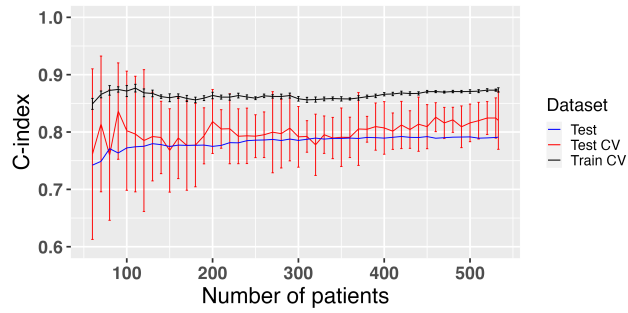
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Supplementary Figure 15. Neutrophils: dexp individual fits



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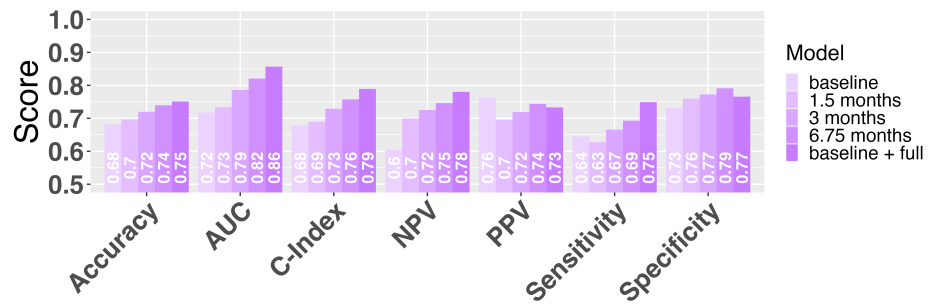
Supplementary Figure 16. ROC curves for variables landmark times (test set - OAK)



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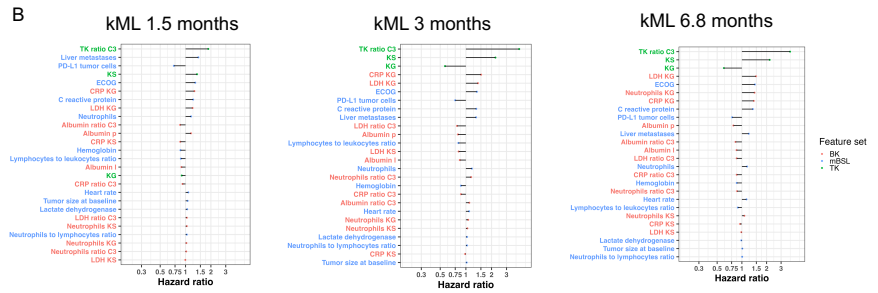
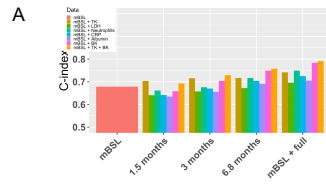
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Supplementary Figure 17. Learning curve



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Supplementary Figure 18. Additional value of NLME to baseline for multiple metrics



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**Supplementary Figure 19. kML models using only single kinetic markers**

### 691 Dimensionality reduction for RNAseq

692 Initial expression data from RNAseq consisted of 715 patients and 58,311 transcripts. The  
 693 first step of data filtering removed all transcripts with less than 10 read counts for all pa-  
 694 tients, then selected genes with highest variability between patients (top 15,000 transcripts  
 695 most variable). Then, data were normalized using upper quartile normalization which con-  
 696 sisted in dividing each read count by the 75<sup>th</sup> percentile of the read counts of the corre-  
 697 sponding sample and the final expression values were  $\log_2$  transformed. Subsequently, a  
 698 univariable Cox regression model was employed to statistically assess the correlations be-  
 699 tween the expression levels of the transcripts and overall survival. Bonferroni correction  
 700 was used to adjust p-values from multiple univariate tests. This step was performed using  
 701 the `RegPara11e1` R package. We selected transcripts with high predictive values using follow-  
 702 ing criteria: adjusted log rank  $< 0.01$  and HR  $< 0.85$  or HR  $> 1.2$ . The remaining transcripts  
 703 were used to perform a bootstrap Lasso Cox regression with cross-validation using mainly  
 704 the `glmnet` R package. Finally, the smallest number of transcripts with best predictive model  
 705 (highest C-index) was selected for further analysis.

### 706 Rules for BK processing

- 707 1. Observations outside lower (LB) and upper (UB) physiological bounds were discarded  
 708 using the following values, determined from discussion with a clinical oncologist: al-  
 709 bumin, LB =  $10 \text{ g L}^{-1}$ , UB =  $100 \text{ g L}^{-1}$ ; CRP, no LB, UB =  $300 \text{ mg L}^{-1}$ ; LDH, LB =  $50 \text{ U/L}$ ,  
 710 UB =  $2000 \text{ U/L}$ ; neutrophils, no LB, UB = 20.
- 711 2. For duplicates, the first one recorded was kept.
- 712 3. Denoting  $BK_n$  the value of the a "BK" at time  $t_n$  for a given patient, we excluded values  
 713 such that:  $BK_n \notin (BK_{n-1}, BK_{n+1})$  AND  $|BK_n - BK_{n-1}| > 3 \times sd_{BK}$  AND  $|BK_n - BK_{n+1}| >$   
 714  $3 \times sd_{BK}$ , where  $sd_{BK}$  is the standard deviation of  $\{BK_n\}_n$ , i.e. all time points for this  
 715 patient.
- 716 4. The BK value at the closest time point to treatment initiation was kept, provided this  
 717 time point was no more than 40 days before or 10 days after treatment initiation (oth-  
 718 erwise, patient was disregarded).

### 720 Nonlinear mixed-effects modeling

721 Denoting by  $\mathcal{M}(t; \theta)$  a structural dynamic model that depends on time  $t$  and a set of pa-  
 722 rameters  $\theta$ , longitudinal observations  $y_j^i$  in patient  $i$  at time  $t_j^i$  were assumed to follow the  
 723 observation model

$$724 y_j^i = \mathcal{M}(t_j^i; \theta^i) + \epsilon_j^i,$$

725 where  $\epsilon_j^i \sim \mathcal{N}(0, \sigma_j^i)$  is the gaussian-distributed error model. The latter was either constant  
 726 ( $\sigma_j^i = a, \forall i, j$ ) for TK or proportional ( $\sigma_j^i = b \mathcal{M}(t_j^i; \theta^i), \forall i, j$ ) for BK. To describe inter-individual  
 727 variability, individual parameters  $\theta^i$  were assumed to follow log-normal distributions:

$$728 \ln(\theta^i) = \ln(\theta_{pop}) + \eta^i, \quad \eta^i \sim \mathcal{N}(0, \omega^2)$$

729 with population-level parameters  $\theta_{pop}$  and  $\omega$ . Estimation of these was performed using the  
 730 stochastic approximation of expectation maximization algorithm implemented in the Mono-  
 731 lix software.  
 732  
 733  
 734