Roche

A Dynamic and Machine Learning-powered Clinical Decision Support System to Enhance Patient Management: an Example from Atezolizumab in Non Small Cell Lung Cancer Patients

Anna Fochesato[1], François Mercier[2], Karla Diaz-Ordaz[3], Candice Jamois[1]

[1]Translational PKPD and Clinical Pharmacology,Roche Innovation Center Basel, Switzerland
[2]Genentech Clinical Pharmacology, Roche Innovation Center Basel, Switzerland
[3]Department of Statistical Sciences, University College London, UK

Thessaloniki, June 5th 2025 | 33rd PAGE Meeting

Background & Objective

Supporting Cancer Immunotherapy Landscape

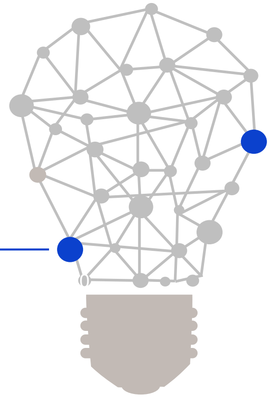
In cancer immunotherapy, clinical teams quickly move to combination trials as an attempt to improve treatment response rates. This results in a plethora of combinational studies run by pharmaceutical companies.

Early readouts of peripheral pharmacodynamic (PD) biomarkers could supplement tumor assessments toward an early understanding of the disease state and a better decision-making on patient management and study prioritization.

Leveraging retrospective data on single immuno-agent, can we…

1 PRECISION MEDICINE

… predict long-term survival outcome for patients enrolled in combination trials to inform their management?



DRUG DEVELOPMENT 2

… predict if a new molecular entity given as a combination is likely to outperform the monotherapy?

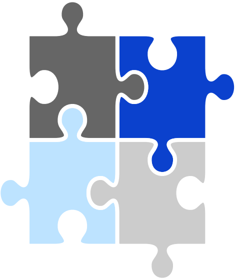
Clinical Trials

Full Data Overview: from Single Agent studies to Ongoing Combinations

DEVELOPMENT	VALIDATION	APPLICATION
2 years of longitudinal data	6/12/24 weeks of longitudinal data	6/12/24 weeks of longitudinal data
Pooled Phase II atezolizumab (ATZ) studies (i) BIRCH (ii) FIR (iii) POPLAR	OAK Phase III ATZ study	**(i)** ATZ + Carboplatin + Paclitaxel **(ii)** ATZ + Carboplatin + nab-Paclitaxel **(iii)** ATZ + Bevacizumab + Carboplatin + Paclitaxel * Note: same ATZ dosing regimen as in development

Covariates

SOCIAL/DEMOGRAPHIC



LONGITUDINAL BIOMARKERS
sum of longest diameters + neutrophils, albumin, lactate dehydrogenase

LABORATORY VALUES

TUMOR CHARACTERISTICS

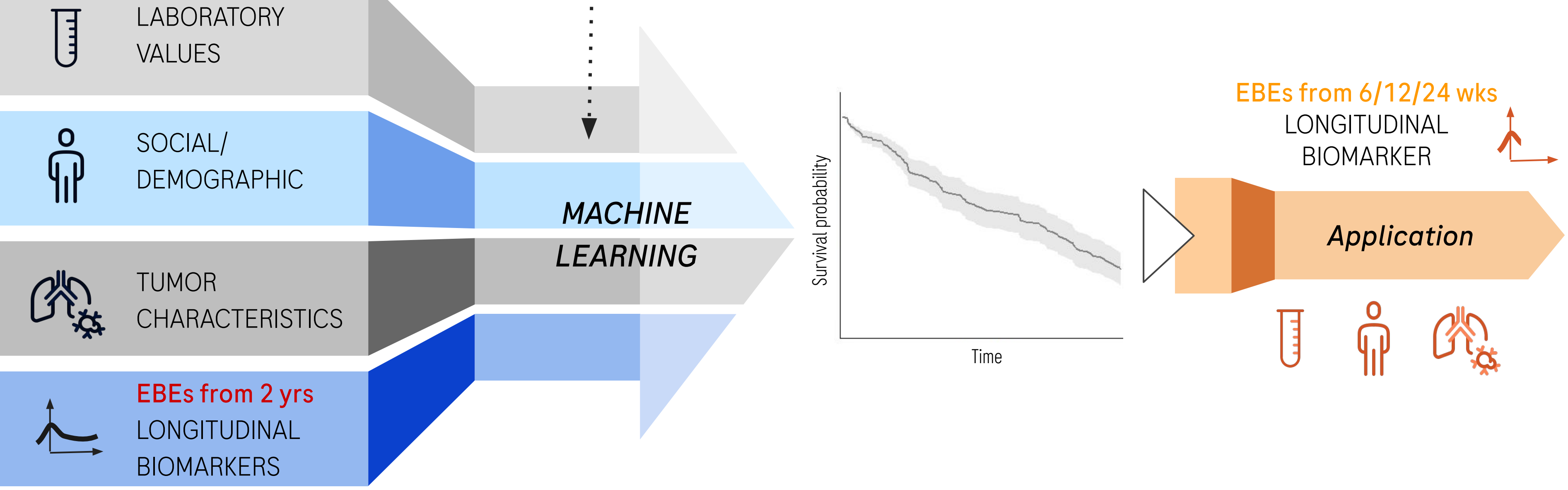
BIRCH = NCT02031458; FIR = NCT01846416; POPLAR = NCT01903993; OAK = NCT02008227; IMpower131 = NCT02367794; IMpower150 = NCT02366143; NSCLC = non-small cell lung cancer

Technical Snapshot

Bridging Pharmacometrics and Machine Learning

Landmark approach for dynamic predictions

1. only patients who survived till the landmark are eligible
2. baseline shifted to the landmark



EBEs = Empirical Bayes Estimates

Modeling choices

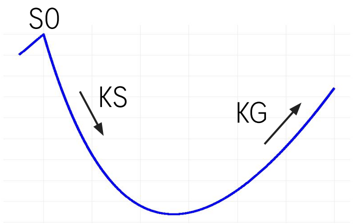
Pharmacometric and Machine Learning models

PMx IN DEVELOPMENT

SLD | LDH | NEUTROPHILS

STEIN MODEL

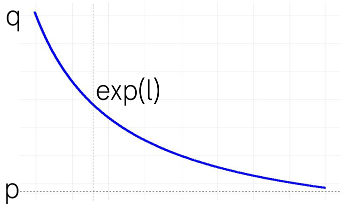
$$f(t) = \begin{cases} S0 * \left(e^{KG * t}\right) & t < 0 \\ S0 * \left(e^{KG * t} + e^{-KS * t} - 1\right) & t \geq 0 \end{cases}$$



ALBUMIN

HYPERBOLIC FUNCTION

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



PMx IN APPLICATION

Bayesian feedback approach for the EBEs on landmark data

6-week observations	Min	Max
# obs. TK	1	4
# obs. LDH	2	9
# obs. NEUTROPHILS	1	6
# obs. ALBUMIN	1	7

SLD = Sum of Longest Diameters; LDH = lactate dehydrogenase

Modeling choices

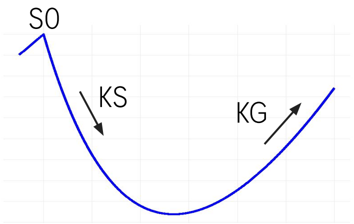
Pharmacometric and Machine Learning models

PMx IN DEVELOPMENT

SLD | LDH | NEUTROPHILS

STEIN MODEL

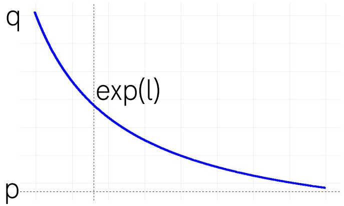
$$f(t) = \begin{cases} S0 * \left(e^{KG*t}\right) & t < 0 \\ S0 * \left(e^{KG*t} + e^{-KS*t} - 1\right) & t \geq 0 \end{cases}$$



ALBUMIN

HYPERBOLIC FUNCTION

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



PMx IN APPLICATION

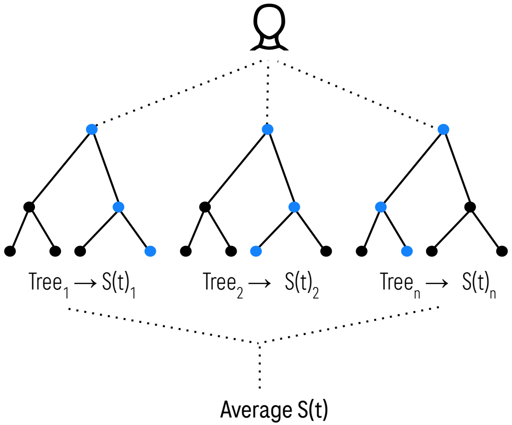
Bayesian feedback approach for the EBEs on landmark data

6-week observations	Min	Max
# obs. TK	1	4
# obs. LDH	2	9
# obs. NEUTROPHILS	1	6
# obs. ALBUMIN	1	7

ML IN DEVELOPMENT

RANDOM SURVIVAL FOREST

Ensemble method that averages cumulative hazard functions from survival tree predictors trained on a bootstrap data sample



SLD = Sum of Longest Diameters; LDH = lactate dehydrogenase

Trust for High-Risk Context-of-Use

Incorporating predictive uncertainty quantification

CONFIDENCE

Inductive conformal prediction (ICP) to equip predictions with uncertainty quantification

Instead of point estimates, ICP outputs a set of possible labels - for us, {Alive}, {Death}, {Multiple}, {Empty} - that are likely to contain the true label with a user-defined confidence.

We set confidence level to 85%
→ ~ 72% patients on average deemed evaluable

ATZ + CP = Atezolizumab + Carboplatin + Paclitaxel; ATZ + BCP = Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel;
ATZ + CnP = Atezolizumab + Carboplatin + nab-Paclitaxel

Trust for High-Risk Context-of-Use

Incorporating predictive uncertainty quantification

CONFIDENCE

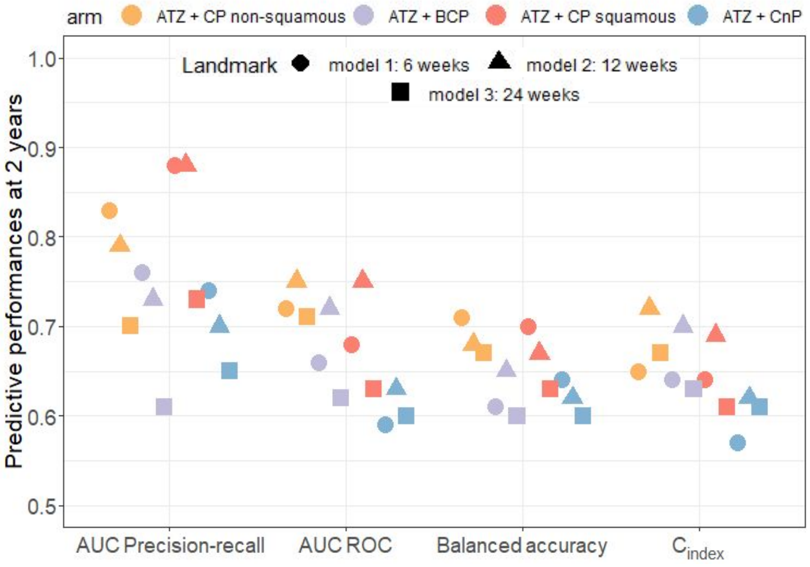
Inductive conformal prediction (ICP) to equip predictions with uncertainty quantification

Instead of point estimates, ICP outputs a set of possible labels - for us, {Alive}, {Death}, {Multiple}, {Empty} - that are likely to contain the true label with a user-defined confidence.

We set confidence level to 85%
→ ~ 72% patients on average deemed evaluable

ACCURACY

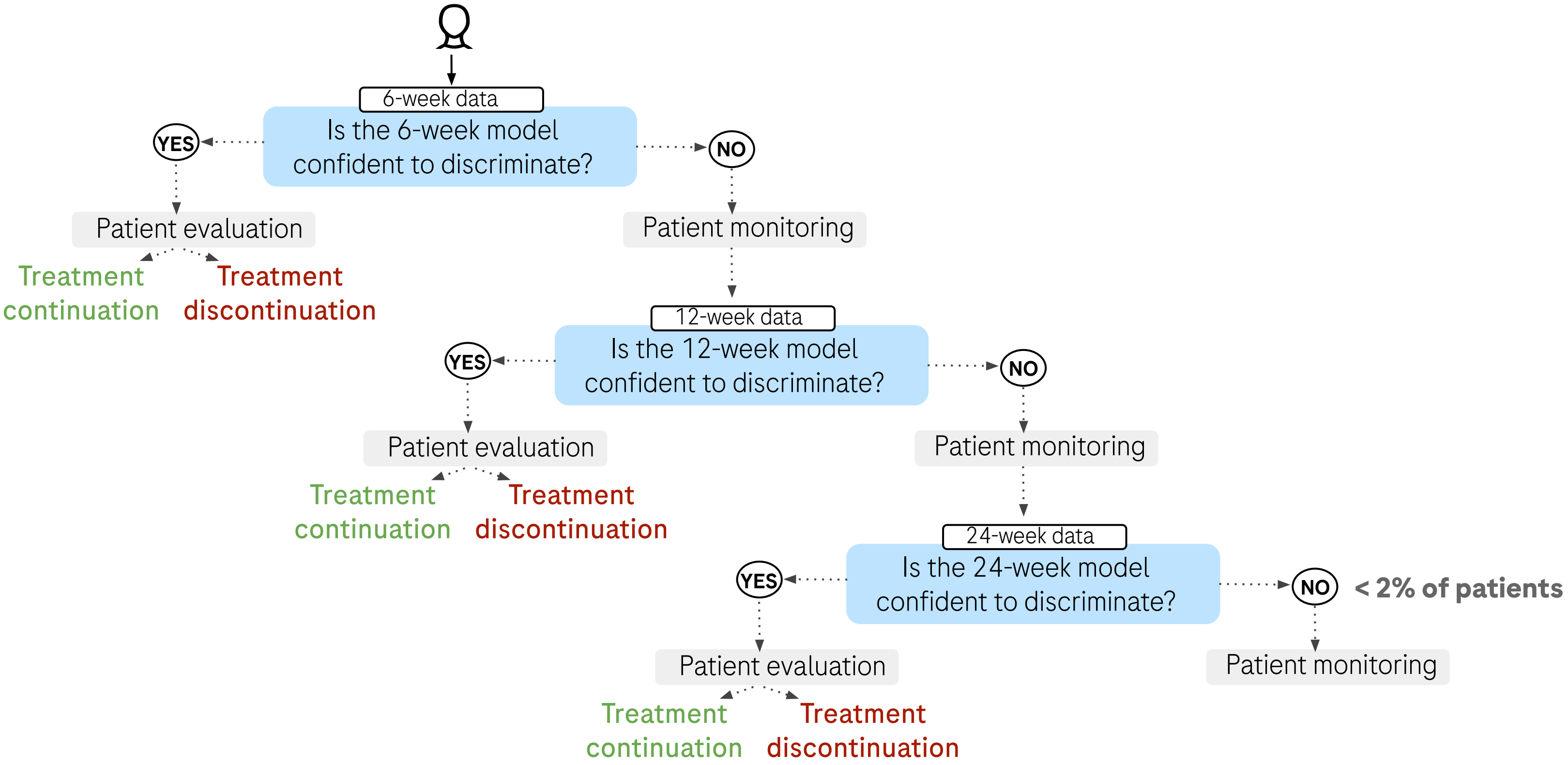
Competitive performances were obtained, holding promises for high-risk applications



ATZ + CP = Atezolizumab + Carboplatin + Paclitaxel; ATZ + BCP = Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel; ATZ + CnP = Atezolizumab + Carboplatin + nab-Paclitaxel

Precision Medicine Decision Tree

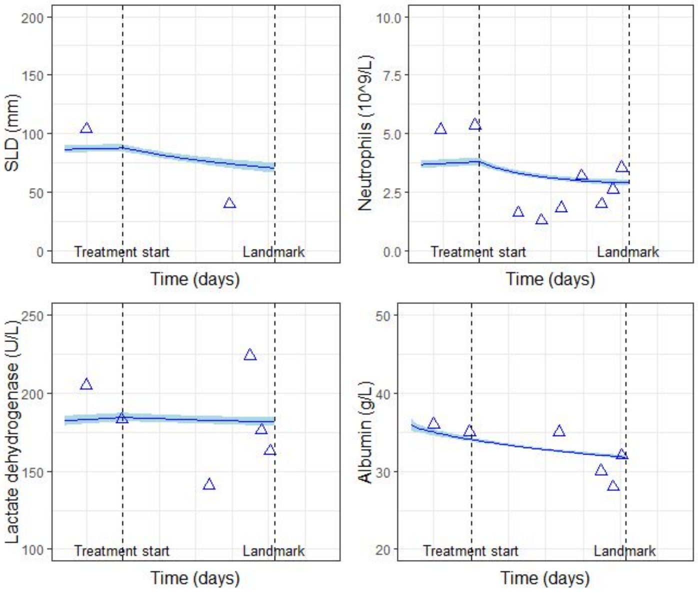
A Clinical Decision Support to assist Oncologists on Patient Management



Case Example at Individual Level

Evaluation vs Monitoring

with 6 weeks data
(at least one CT scan post baseline)



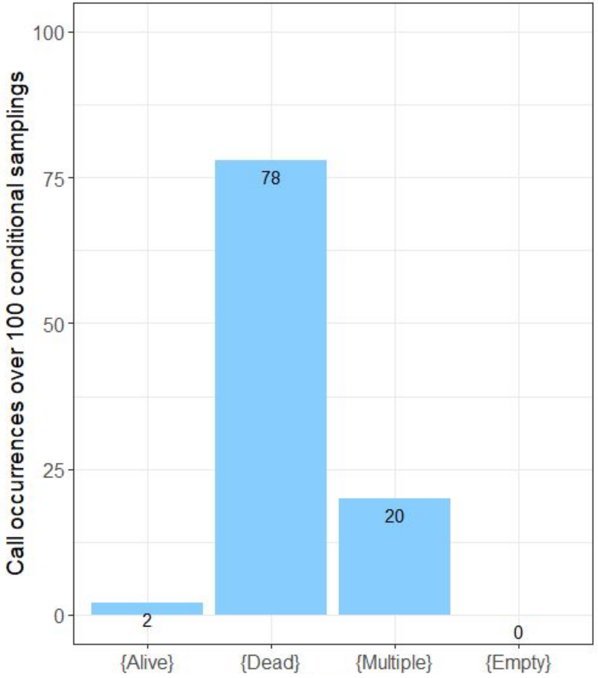
Uncertainty into decision-making

BSL par1	BSL par2	NLME par1	NLME par2
76	3.45	0.01	0.2
76	3.45	0.015	0.22
76	3.45	0.04	0.28

Same baseline covariates

Samplings from Individual conditional distribution

Individual conditional dataset with 100 plausible covariate sets



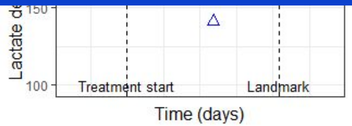
SLD = Sum of Longest Diameters; BSL = baseline; NLME = non-linear mixed effects

Case Example at Individual Level

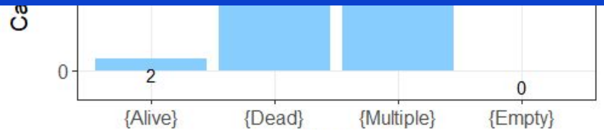
Providing a therapeutic recommendation

with 6 weeks data

PATIENT EVALUATION → **TREATMENT DISCONTINUATION/ADJUSTMENT**



Individual conditional dataset with 100 plausible covariate sets

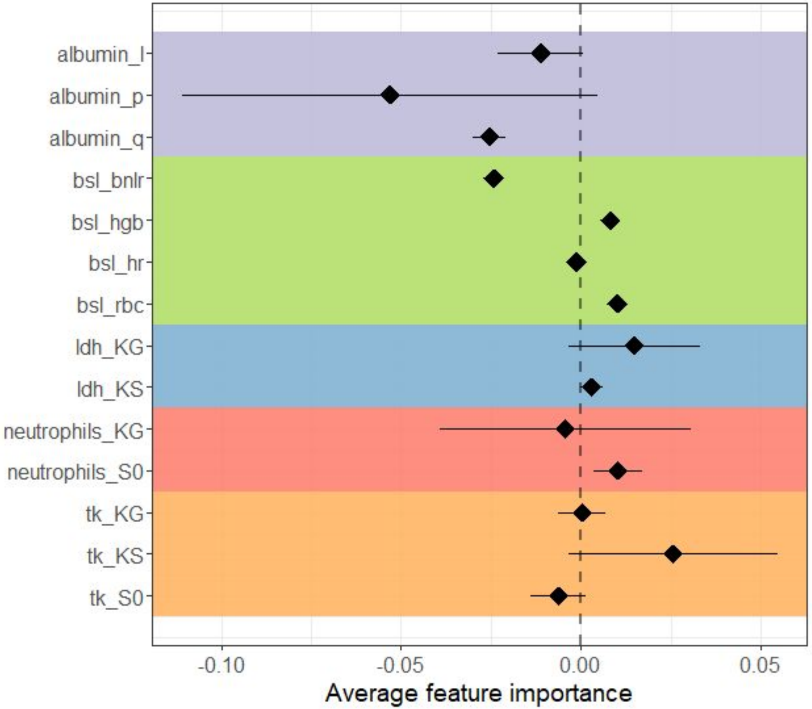


SLD = Sum of Longest Diameters

Case Example at Individual Level

Individual Risk-Factor Analysis

What can we learn from Patient A signature ?



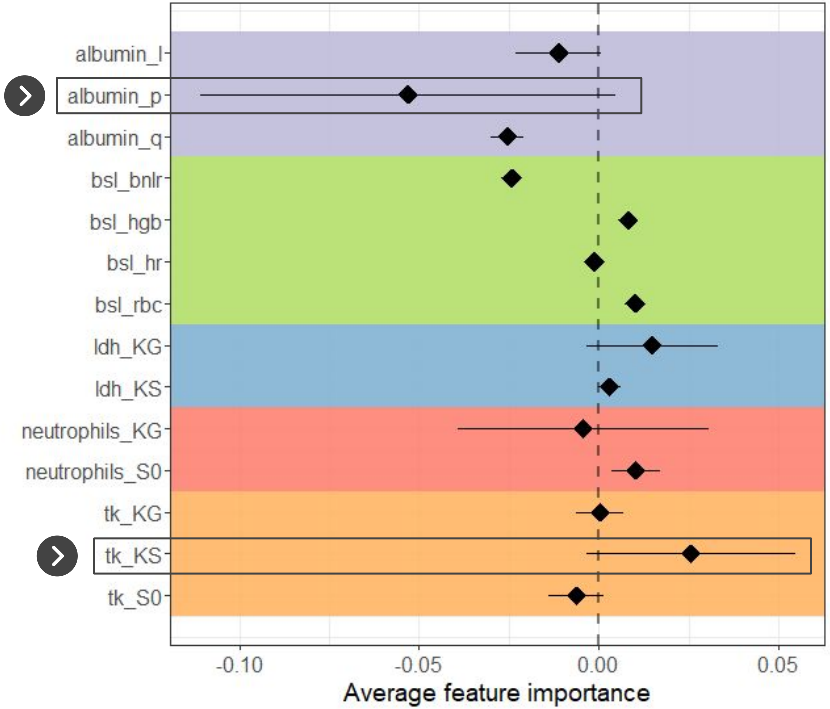
- Average importance: *absolute magnitude*
- Directionality of the impact: *sign*

bsl = baseline, bnlr = baseline neutrophils-to-lymphocyte ratio, hgb = hemoglobin, hr = heart rate, rbc = red blood cells, ldh = lactate dehydrogenase, tk = tumor kinetic, KS = shrinkage rate, KG = regrowth rate, S0 = magnitude at t=0

Case Example at Individual Level

Individual Risk-Factor Analysis

What can we learn from Patient A signature ?



- Average importance: *absolute magnitude*
- Directionality of the impact: *sign*

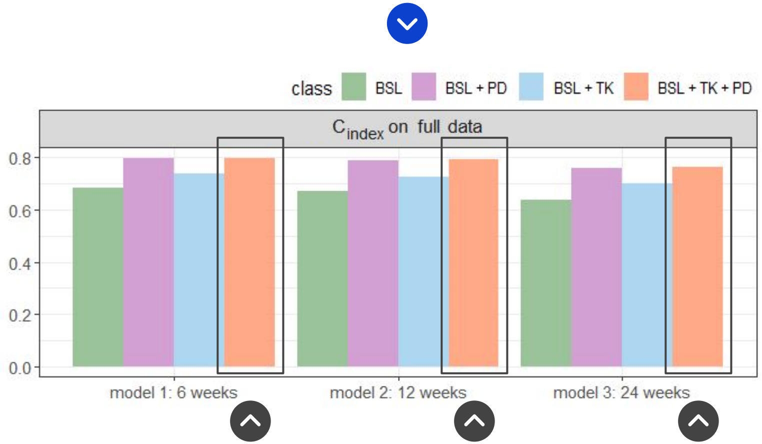
Globally, major driving covariates for our patient's survival outcome were the tumor shrinkage parameter and the albumin lower plateau

bsl = baseline, bnlr = baseline neutrophils-to-lymphocyte ratio, hgb = hemoglobin, hr = heart rate, rbc = red blood cells, ldh = lactate dehydrogenase, tk = tumor kinetic, KS = shrinkage rate, KG = regrowth rate, S0 = magnitude at t=0

Predictive & Prognostic Covariates

The Key Role of PD Biomarkers

Peripheral PD biomarker readouts bring additional predictive value on top of tumor kinetics and baseline covariates

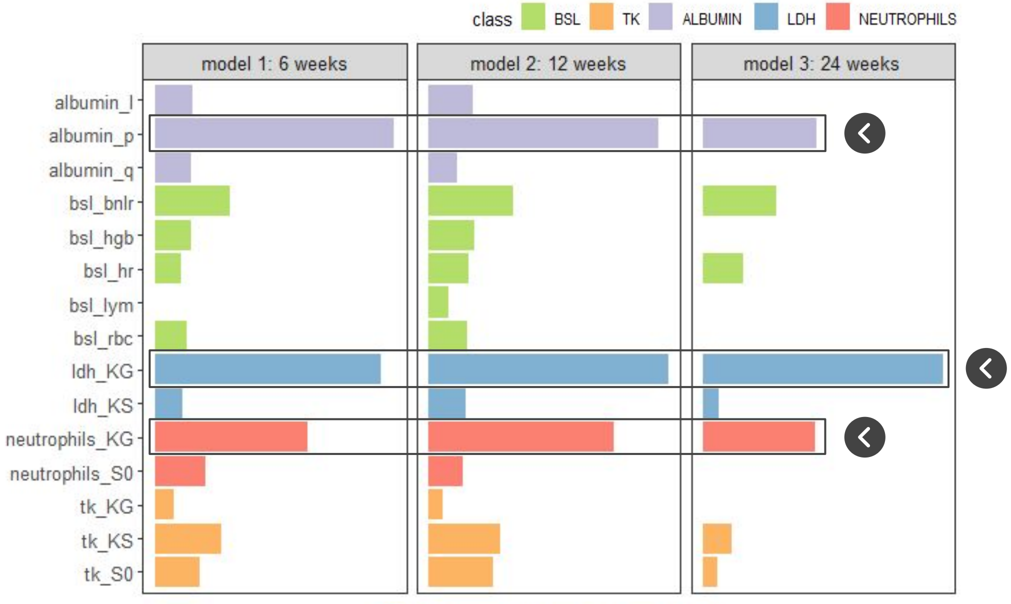


BSL= baseline; TK = tumor kinetics, PD = pharmacodynamic

Predictive & Prognostic Covariates

The Key Role of PD Biomarkers

Peripheral PD biomarker readouts bring additional predictive value on top of tumor kinetics and baseline covariates



Relative importance of the key covariates

BSL/bsl = baseline; TK/tk = tumor kinetics, PD = pharmacodynamic, bnlr = baseline neutrophils-to-lymphocyte ratio, hgb = hemoglobin, hr = heart rate, rbc = red blood cells, ldh = lactate dehydrogenase, KS = shrinkage rate, KG = regrowth rate, S0 = magnitude at t=0

Predictive & Prognostic Covariates

The Key Role of PD Biomarkers

Peripheral PD biomarker readouts bring additional predictive value on top of tumor kinetics and baseline covariates

15 covariates only from <10 clinical quantities

Relative importance of the key covariates

BSL/bsl = baseline; TK/tk = tumor kinetics, PD = pharmacodynamic, bnlr = baseline neutrophils-to-lymphocyte ratio, hgb = hemoglobin, hr = heart rate, rbc = red blood cells, ldh = lactate dehydrogenase, KS = shrinkage rate, KG = regrowth rate, S0 = magnitude at t=0

Individuals Aggregation toward Study-level Insights

Mitigating confounders for causal treatment effect

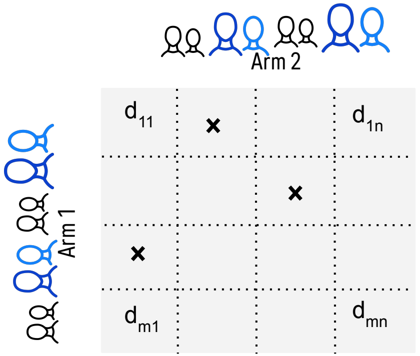
Clinical development teams are interested in *Mono vs Combo* and *Combo 1 vs Combo 2* scenarios.

To predict causal treatment effect in these (likely) non-randomized scenarios, baseline confounders (ONLY) must be mitigated.

MATCHING ANALYSIS STRATEGY

Matching patients with their “twins” of the other arm
→ propensity score matching analysis

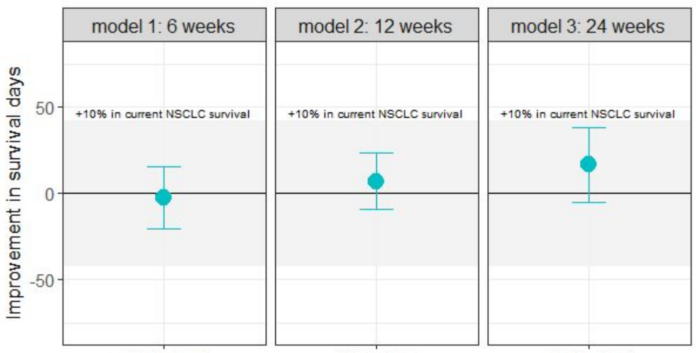
- ↑ Clinical meaning and Obs. vs Pred. feasible
- ↓ (Limited) baseline discrepancies still present



Support to Drug Development decision-making

Individual Contribution Packages and Ungating of Combinations' Next Phases

Mono versus Combo

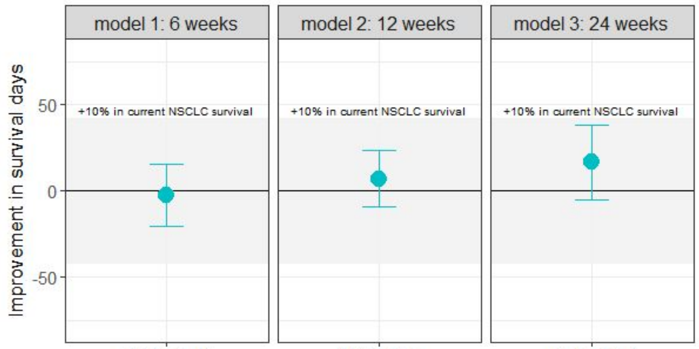


Trends suggest an increase contribution of the combination partner on top of atezolizumab backbone as data matures

Support to Drug Development decision-making

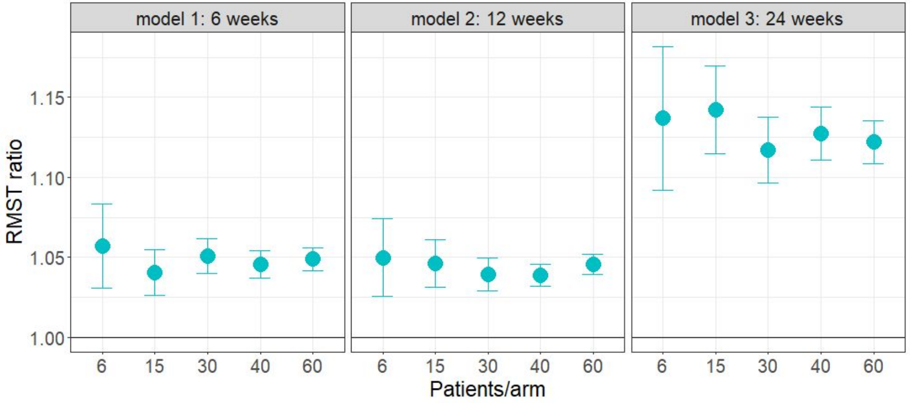
Individual Contribution Packages and Ungating of Combinations' Next Phases

Mono versus Combo



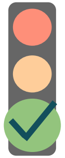
Trends suggest an increase contribution of the combination partner on top of atezolizumab backbone as data matures

Combo 1 versus Combo 2



RESTRICTED MEAN SURVIVAL TIME (RMST) $= \int_{\text{Landmark}}^{\text{Horizon}} S(t)\,dt \longrightarrow$

RMST ratio >> 1, the better



*Note: in alignment with study results

Reflections & Conclusions

Take-home messages

1

2

3

Early on-treatment trends of neutrophils, albumin, and LDH complement anti-tumor response

Early on-treatment PD + anti-tumor trends CAN separate curves well enough to inform decision-making on ungating next development phase for a combination and supporting of regulatory individual contribution data package

As per FDA M15[1] and AI/ML[2] guidelines, ANY model should meet explainability, predictivity, and trustability criteria

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m15-general-principles-model-informed-drug-development

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological

Ongoing work

Limits and Project Extension

1

ACKNOWLEDGE CURRENT LIMITATIONS

- Safety is not explicitly taken into account towards a full risk-benefit assessment
- Working assumptions on data trimming are not challenged in terms of performances
- Generalization to studies with different MoA might benefit from different PD biomarkers

2

OVERCOME SOME OF THEM

- Include more specific efficacy biomarkers (ctDNA) and introduce other safety biomarkers (platelets)
- Extend the framework to meet PoC's interim analysis scenarios, *i.e.*, patients contribute with different number of observations depending on the randomization date

MoA = mechanism of action; PoC = proof of concept

Acknowledgement

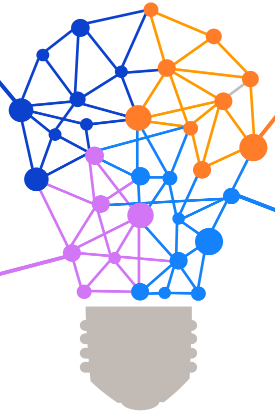
The D-Light Team

Project Core Team

Candice Jamois
Francois Mercier

Roche Academic Partner

Karla Diaz-Ordaz, UCL



Project Consultant

Philippe Pierrillas
Francesco Brizzi
Sebastien Jolivet

Roche Advisory Board

Ales Neubert
Andreas Roller
Astrid Kiermaier
Ken Wang
Bruno Gomes
Sophie Keufer-Le Gall
Sherri Dudal
Ulrich Beyer

Doing now what patients need next