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

AUTHORS: Sébastien Benzekry (1), Mélanie Karlsen (1), Abdessamad El Kaoutari (1), Suresh Vatakuti (3), Peter Curle (2) and Candice Jamois (3)

AFFILIATIONS:
(1) COMPO (COMPutational pharmacology and clinical Oncology), Inria Sophia Antipolis – Méditerranée and Center for Research on Cancer of Marseille, Inserm U1068, CNRS UMR7258, Institut Paoli-Calmettes, Aix-Marseille University, France
(2) Safety and Early Development Informatics, Pharma Research and Early Development, Roche Innovation Center Basel, Switzerland
(3) Clinical Pharmacometrics, Clinical Pharmacology, Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, Switzerland

BACKGROUND: Pharmacometrics (PMx) and Machine Learning (ML) approaches could help to predict survival based on patients' and disease characteristics and early response to treatment.

METHODS: We developed a predictive algorithm of survival following atezolizumab (ATZ) therapy based on the combination of nonlinear mixed-effects modeling (NLME) and ML. The data consisted of three phase 2 trials (862 patients). Longitudinal data included tumor kinetics (TK, 5,570 data points) and four pharmacodynamic (PD) markers: neutrophils, C-reactive protein (CRP), lactate dehydrogenase (LDH) and albumin (61,296 data points). Baseline data included clinical factors (p = 73 variables), transcriptomic data (p = 58,311 transcripts) and mutation data (p = 395 genes).

RESULTS: The best models were double-exponential (TK, neutrophils, CRP, LDH) and hyperbolic (albumin) models for NLME and a random survival forest for ML. A minimal ML model was derived that contains 11 routine clinical variables (CRP, heart rate, neutrophils-to-lymphocyte ratio, neutrophils, lymphocytes-to-leucocytes ratio, hepatic metastases, ECOG, PDL1, hemoglobin, baseline tumor size and LDH), together with 3 TK and 9 PD model derived parameters obtained from Bayesian estimation. Predictive power was significantly improved when using the PD data compared with models based either on clinical variables or TK parameters for both discrimination (c-index = 0.83 ± 0.02 vs 0.72 ± 0.04 vs 0.72 ± 0.02 in cross-validation, 0.79 vs 0.69 vs 0.70 in test, 1-year AUC = 0.92 ± 0.02 vs 0.80 ± 0.05 vs 0.81 ± 0.05) and calibration metrics.

CONCLUSION: Our novel prediction algorithm was able to predict accurately survival following atezolizumab monotherapy, both at the study and individual levels. External validation of the model is currently ongoing.