Development of a machine learning model to predict overall survival results from randomized clinical trials of patients with metastatic prostate cancer

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Background: Overall survival (OS) remains the gold standard endpoint for clinical trials in metastatic prostate cancer (metPC) yet requires extensive follow-up. We sought to develop a model utilizing short term (≤ 4 months) prostate specific antigen (PSA) kinetic data to predict the OS readout from phase 3 clinical trials, with the goal of accelerating readout time of trials for patients (pts) with metPC.
Methods: Clinical and PSA data were obtained from 7 metPC trials: 6 randomized, double-blind, phase 3 trials (TITAN, COU-AA-301, COU-AA-302, LATITUDE, ACIS, and MAGNITUDE), and one multicenter, phase II trial (GALAHAD). We developed 18 PSA kinetic variables from the first 4 months of enrollment including: 50% decline in PSA (PSA50), 90% decline in PSA, PSA=0.1, and PSA=0.2 within 1, 2, 3, and 4 months; and slope and base of the exponential fit of PSA over the first 4 months on study). To balance pt and disease characteristics, TITAN, COU-AA-301, and ACIS were used to train the intermediate endpoint, with remaining studies held out as an external testing cohort. A random 60/40% split of the pooled pt-level data was performed as a sensitivity analysis. Adaptive least absolute shrinkage and selection operator (aLASSO)-based Cox proportional hazards models were applied to select previously identified prognostic baseline clinical variables with and without PSA kinetic variables most predictive of OS on five-fold cross validation. Performance with and without PSA kinetics was assessed using C-index, integrated Brier score (IBS), and time-dependent area under the receiver operating characteristic curve (tAUC) at 12, 24, 36, and 48 months.
Results: The study included 6,451 pts with median follow-up of 22 months and 85,785 PSA values. aLASSO selected Eastern Cooperative Oncology Group performance status, disease extent, lactate dehydrogenase, albumin, hemoglobin, PSA, and alkaline phosphatase as baseline variables for the prognostic comparator model. In the model including PSA kinetics, aLASSO identified PSA50 at 4 months, PSA0.1 at 1 month, and PSA slope as kinetics providing additional intra-treatment information to improve prediction of OS. The model with PSA kinetics showed improved performance on the test trials: C-index (0.72 vs. 0.66), IBS (0.158 vs. 0.173), and tAUC (0.84, 0.78, 0.78, and 0.76 vs. 0.78, 0.71, 0.69, and 0.65 at times 12, 24, 36, and 48 months, respectively; $p < 0.05$.) Sensitivity analysis using a random split of the pooled pt-level data supported the importance of PSA50 at 4 months and PSA slope.
Conclusions: Data from 6,451 mPC pts enrolled on prospective clinical trials were used to develop a machine learning model which included kinetic PSA data and predicted the long-term OS readout in Phase 3 trials with just the first four months of data. This model will be validated in independent data sets comprised of other completed phase 3 trials.

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