**Development and external validation of a computational approach for early read out of randomized clinical trials in metastatic prostate cancer**

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**Background**: While overall survival (OS) is the gold standard endpoint for clinical trials in metastatic prostate cancer (mPC), it requires years of follow-up. We sought to develop and externally validate a computational model based on short term PSA kinetic data in order to accelerate trial reporting through early predictions of long-term OS outcomes of phase 3 mPC trials.

**Methods:** Longitudinal PSA data were obtained from 7 completed phase 3 mPC trials (TITAN, COU-AA-301, COU-AA-302, LATITUDE, ACIS, MAGNITUDE, and CHAARTED). Using data from the first 4 months on trial, 18 different PSA kinetic variables were developed, including 50% and 90% decline in PSA , PSA=0.1, and PSA=0.2 at 1, 2, 3, and 4 months, and slope and base of the exponential fit of PSA. TITAN, COU-AA-301, and ACIS comprised the test cohort. Data from those trials was used to model OS using a relaxed LASSO approach. The resulting model was applied to 4 validation trials (COU-AA-302, LATITUDE, MAGNITUDE, and CHAARTED) to simulate 1,000 potential outcomes for each trial (after Harden and Kropko). For the CHAARTED trial, a model using only PSA-kinetic data was used for prediction as we did not have all the remaining baseline variables. The distribution of 1,000 simulated Hazard Ratios (HR) for each trial were compared against the actual (reported) HR from each trial.

**Results:** Overall, > 90,000 PSA values were used with a total 6,755 eligible study pts, with ~ 50,000 PSA values and a total 3,938 patients comprised the test cohort. The model identified baseline PSA at treatment, PSA50 at 4 months, and the PSA slope as the most informative predictors of OS. Table 1 below compares the predicted HR from the 1,000 simulations with the reported HR for each validation trial. Figures 2 and 3 show the distribution of the predicted HRs compated to the actual (reported) HR from each trial using the complete model and PSA-only versions of model, respectively. The model correctly predicted the OS outcome using just the first 4 months of PSA data.

**Conclusions:** A computational simulation approach to predict the OS outcome of phase 3 mPC trials based on PSA kinetics from the first 4 months on trial was developed. This model, trained on 3 completed phase 3 trials, correctly predicted OS outcomes in 4 completed validation phase 3 trials with positive and negative outcomes for OS in both hormone sensitive and resistant mPC, and involving AR signaling inhibitors, chemotherapy and a PARP inhibitor. This model is being further validated with additional completed phase 3 trials, and once prospectively validated, has the potential to significantly shorten the follow up required for OS readout from phase 3 trials in mPC.

*Table 1 Predicted vs. actual (reported) HR of each trial*

| Validation Trial | Predicted HR range | Actual HR [95%-CI] |
|---|---|---|
| LATITUDE | 0.46 – 0.87 | 0.66 [0.56 – 0.78] |
| COU-AA-302 | 0.53 – 0.86 | 0.81 [0.70 – 0.93] |

| | | |
|---|---|---|
| MAGNITUDE | 0.78 – 1.49 | 1.06 [0.88 – 1.26] |
| CHAARTED | 0.43 – 1.18 | 0.72 [0.59 – 0.89] |

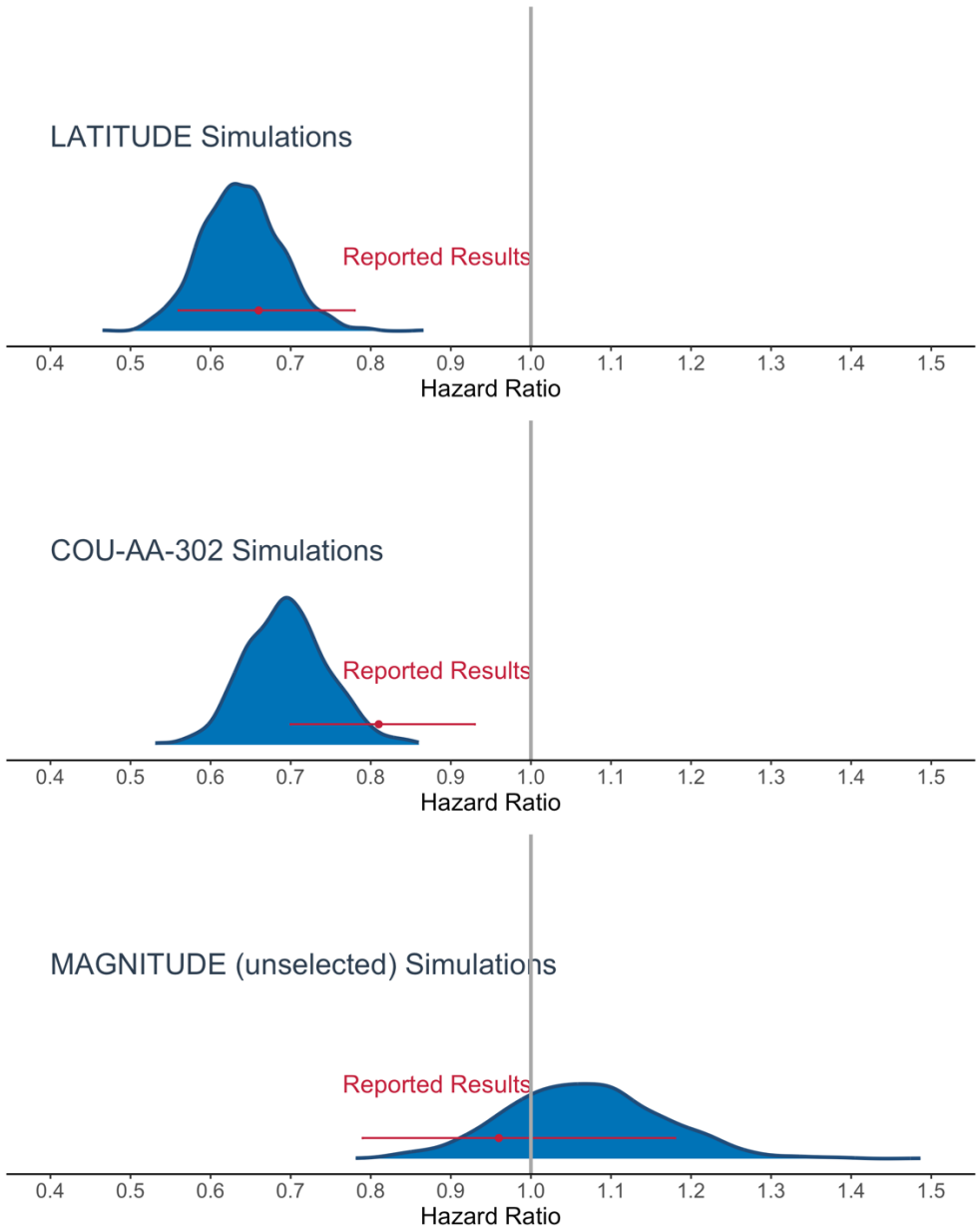


*Figure 1Distribution of model-simulated HRs for Each Trial (blue) compared with actual trial HR and 95%-CI (red). Positive trials would be expected to have all simulations in blue and the actual survival (red) 95% CI error bar to fall completely to the left of a HR of 1.0, whereas negative trials would be expected to have simulations as well as an actual OS 95% CI exceeding a HR of 1.0*

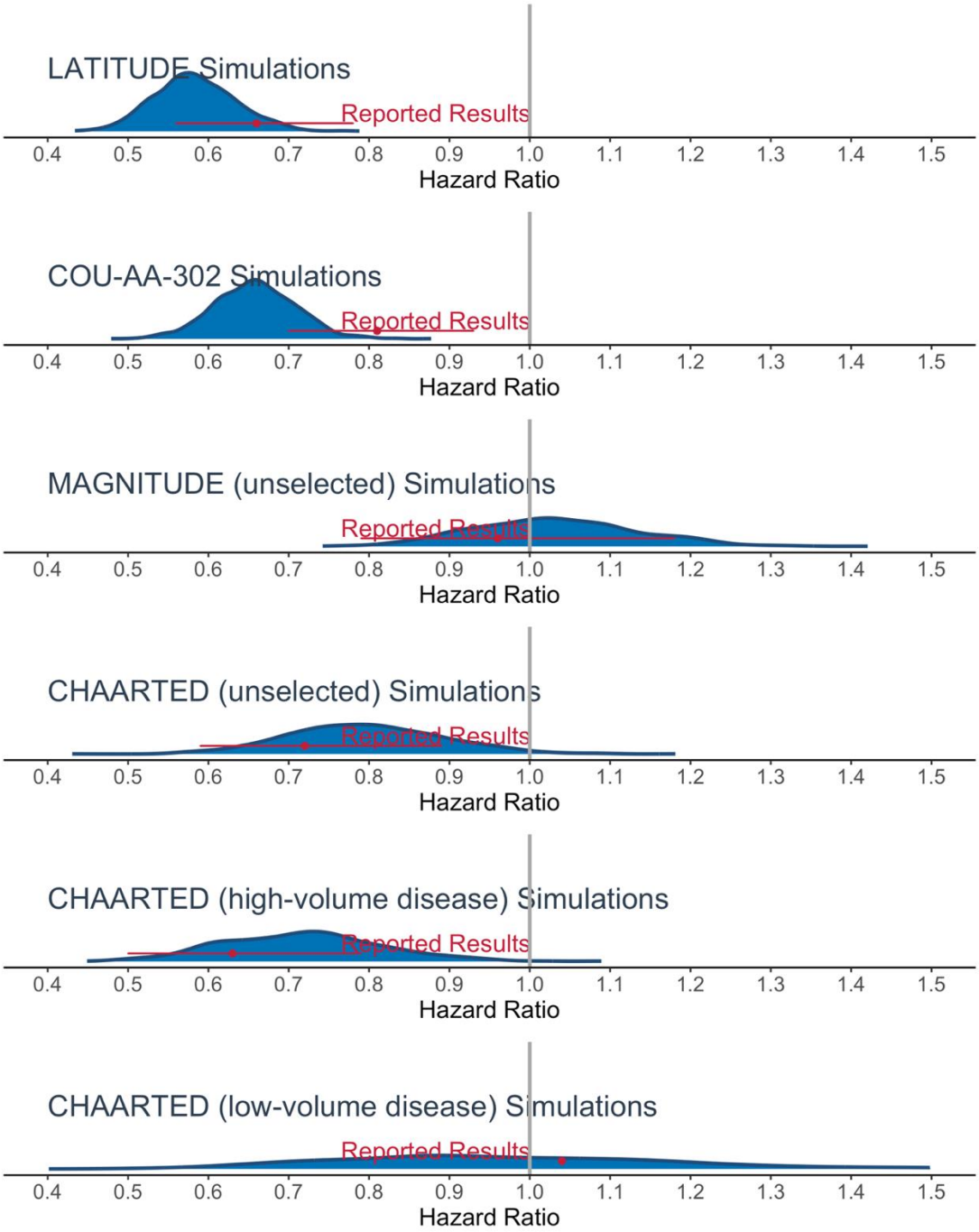


*Figure 2 Distribution of trial outcome simulation using PSA-only model. Note for patients with low-volume disease, curves extend beyond limits of the graph*

Funding Acknowledgement: PCF-Janssen Special Challenge Award 22CHAS02
Conflicts of Interest:
Li Zhang:
- Consulting or Advisory Role: Samay Inc.
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Rahul Aggarwal:
- Consulting or Advisory Role: Pfizer, Merck, Amgen, Alessa Therapeutics, Exelixis, Bayer, Tersera, BioXcel Therapeutics, Janssen, Novartis, AstraZeneca, Boxer Capital, EcoR1 Capital, PCCTC, MJH Life Sciences, Flare Therapeutics, Research to Practice, Guidepoint Inc, Slingshot Insights, Harpoon therapeutics, Washington Research Foundation, Curio Science
- Travel, Accomodations, Expenses: DAVA Oncology
- Expert Testimony: University of Utah Health
- Research Funding: Zenith Epigenetics, Novartis, Xynomic Pharma, Janssen, Merck, Amgen, AstraZeneca

Meera Reddy Chappidi:
- Employment: Horizon Therapeutics (Immediate Family Member)
- Stock and Other Ownership Interests (Immediate Family Member)

Christopher Sweeney:
- Consulting or Advisory Role: Janssen Biotech, Astellas Pharma, Bayer, Genentech/Roche, AstraZeneca, Pfizer, Lilly, POINT Biopharma, Cadence Pharma, CellCentric
- Patents, Royalties, Other Intellectual Property: Leuchemix, Parthenolide, Dimethylaminoparthenolide. Exelixis: Abiraterone plus cabozantinib combination
- Research Funding: Janssen Biotech, Astellas Pharma, Sanofi, Bayer, Dendreon, Pfizer

Yu-Hui Chen:
- Employment: Ribonaut Therapeutics (Immediate Family Member)

Michael A Carducci:
- Consulting or Advisory Role: Pfizer, Acrivon Therapeutics, AstraZeneca, Sanofi
- Honoraria: Remedica
- Research Funding: Pfizer, Arcus Biosciences, Merck, Celgene/Bristol-Myers-Squibb

Hari Singhal:
- Stock and Other Ownership: Johnson & Johnson

Ke Zhang:
- Employment: Janssen Research & Development
- Stock and Other Ownership: Johnson & Johnson
- Research Funding: Janssen Research & Development
- Travel, Accomodations, Expenses: Janssen Research & Development

Joel Greshock:
- Employment: Johnson & Johnson/Janssen

Jinhui Li:
- Employment: Janssen Research & Development
- Stock and Other Ownership: Johnson & Johnson

Margaret Yu:
- Employment: Johnson & Johnson/Janssen
- Stock and Other Ownership: Johnson & Johnson/Janssen

- Patents, Royalties, Other Intellectual Property: Invention patent for invention of apalutamide for the treatment of patients with non-
- metastatic castration resistant prostate cancer
- Travel, Accomodations, Expenses: J&J IM

Eric Small:

- Stock and Other Ownership Interests: Fortis, Teon Therapeutics

Julian Hong:

- Research Funding: Roche