

Real-World Toxicity of Contemporary Systemic Treatment for Metastatic Hormone-Sensitive Prostate Cancer: Large-Scale Analysis Using the PIONEER Platform

Pawel Rajwa^{1,2,3}, Andrei Kiselev^{4,5}, Ayman Hijazy⁶, Angelika Borkowetz^{7,8}, Thomas Abbott⁴, Andrea Alberti⁹, Katharina Beyer¹⁰, Anders Bjartell¹¹, James T. Brash¹², Andrew Chilelli¹³, Eleanor Davies¹², Bertrand De Meulder^{4,5}, Tamas Fazekas^{3,14}, Asieh Golozar^{15,16}, Andreas Josefsson¹⁷, Raivo Kolde¹⁸, Daniel Kotik^{19,20}, Michael S. Leapman²¹, Marcin Miszczyk^{3,22}, Rossella Nicoletti⁹, Peter Prinsen²³, Sebastiaan Remmers¹⁰, Maria J. Ribal²⁴, Juan Gómez Rivas²⁵, Lara Rodriguez-Sanchez²⁶, Monique J. Roobol¹⁰, Emma Smith²⁷, Robert Snijder¹³, Carl Steinbeisser²⁸, Hein V. Stroomberg^{29,30}, Giorgio Gandaglia³¹, Philip Cornford³², Susan Evans-Axelsson^{4,33}, Peter-Paul M. Willemse³⁵, Veeru Kasivisvanathan¹, James N'Dow³⁴ on behalf of the PIONEER Consortium

Affiliations: 1 Division of Surgery and Interventional Sciences, University College London and University College London Hospital, London, UK; 2 Department of Urology, Medical University of Silesia, Zabrze, Poland; 3 Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 4 European Association of Urology, Nijmegen, The Netherlands; 5 BDM Consulting, Larajasse, France; 6 Association EISBM, Vourles, France; 7 Department of Urology, University Hospital, University of Rostock, Rostock, Germany; 8 Department of Urology, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; 9 Unit of Urological Robotic Surgery and Renal Transplantation, University of Florence, Careggi Hospital, Florence, Italy; 10 Department of Urology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; 11 Department of Translational Medicine, Lund University, Lund, Sweden; 12 IQVIA, Real World Solutions, Brighton, UK; 13 Astellas Pharma Europe Ltd., Surrey, UK; 14 Department of Urology, Semmelweis University, Budapest, Hungary; 15 Odysseus Data Services, New York, NY, USA; 16 OHDSI Center, Northeastern University, Boston, MA, USA; 17 Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 18 Institute of Computer Science, University of Tartu, Tartu, Estonia; 19 Center for Advanced Systems Understanding, Görlitz, Germany; 20 Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany; 21 Department of Urology, Yale School of Medicine, New Haven, CT, USA; 22 Collegium Medicum - Faculty of Medicine, WSB University, Dąbrowa Górnicza, Poland; 23 Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; 24 Uro-Oncology Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain; 25 Department of Urology, Hospital Clinico San Carlos, Madrid, Spain; 26 Department of Urology, Institut Mutualiste Montsouris, Paris, France; 27 Guidelines Office, European Association of Urology, Arnhem, The Netherlands; 28 Collaborate Project Management, Munich, Germany; 29 Copenhagen Prostate Cancer Center, Department of Urology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; 30 Biotech Research & Innovation Centre (BRIC), University of Copenhagen, Copenhagen, Denmark; 31 Division of Oncology/Unit of Urology, Soldera Prostate Cancer Lab, URI, IRCCS San Raffaele Scientific Institute, Milan, Italy; 32 Liverpool University Hospitals NHS Trust, Liverpool, UK; 33 Bayer AG, Berlin, Germany; 34 Academic Urology Unit, University of Aberdeen, Aberdeen, UK; 35 Department of Urology, Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands.

Background: Treatment intensification has improved outcomes for metastatic hormone-sensitive prostate cancer (mHSPC), but the toxicity burden of contemporary doublet and triplet regimens in routine practice remains incompletely characterized. We evaluated a broad spectrum of clinically relevant adverse events (AEs) across large, heterogeneous real-world populations.

Methods: We used the big-data platform to analyze six real-world databases standardized to the Observational Medical Outcomes Partnership Common Data Model. Men with mHSPC were classified by initial systemic treatment as androgen-deprivation therapy (ADT) alone, ADT plus an androgen-receptor pathway inhibitor (ARPI), ADT plus docetaxel, or ADT plus ARPI plus docetaxel. Twenty-one prespecified AEs were evaluated. Incidence rates were estimated per 1,000 person-years, with Kaplan-Meier estimates for time to first event and mean cumulative functions for recurrent episodic events. Analyses were stratified by treatment and database.

Results: The available dataset included 104,669 men: 65,603 receiving ADT alone, 14,207 ADT+ARPI, 21,030 ADT+docetaxel, and 3,829 triplet therapy. Marked between-database heterogeneity was observed. In OpenClaims, hospitalization incidence was 576.8, 446.7, 609.5, and 521.2 per 1,000 person-years for ADT, ADT+ARPI, ADT+docetaxel, and triplet therapy, respectively. Bone-marrow suppression was particularly frequent with docetaxel-containing regimens, reaching 577.2 per 1,000 person-years for ADT+docetaxel in OpenClaims and 1,775.9 per 1,000 person-years for triplet therapy in MarketScan. Gastrointestinal toxicity with triplet therapy ranged from 230.0 to 1,128.6 per 1,000 person-years across available databases. At 3 years in Pharmetrics Plus, hospitalization-free survival was 49.8% with ADT, 43.3% with ADT+ARPI, 42.9% with ADT+docetaxel, and 30.0% with triplet therapy; corresponding bone-marrow-suppression-free survival was 73.8%, 68.5%, 39.5%, and 26.7%. Cardiovascular and thromboembolic events remained clinically relevant across treatment groups.

Conclusions: In this large real-world mHSPC analysis, clinically important AEs were common and varied substantially across treatments and data sources. The high burden of hospitalization, marrow suppression, gastrointestinal toxicity, and other treatment-related events highlights the need to integrate baseline comorbidity, toxicity surveillance, and supportive care into treatment selection and monitoring. Cross-database heterogeneity should be considered when translating real-world toxicity estimates into clinical practice.

Funding Acknowledgements: P. Rajwa is supported by a Prostate Cancer Foundation Young Investigator Award and John Black Charitable Foundation (25YOUN05). PIONEER and EHDEN were funded by IMI2 (grants 777492 and 806968), with support from EU Horizon 2020 and EFPIA.

Conflicts of Interest Disclosure Statement: P. Rajwa: consultant/speaker for Janssen, Astellas, Ferring, and Bayer; A. Borkowetz: consultant/speaker for Johnson & Johnson, Astellas, Merck, Bayer, MSD, AstraZeneca, and Ipsen; T. Fazekas: consultant/speaker for Johnson & Johnson, Astellas, and AstraZeneca; A. Bjartell: consultant/advisor for Astellas, Bayer, and Pfizer; leadership roles and stock interests in Glactone Pharma and LIDDS Pharma; lecture honoraria from Accord, Astellas, AstraZeneca, Bayer, Ipsen, Janssen, and Merck; trial participation with Astellas, Ferring, and Janssen; stock in WntResearch; H.V. Stroomberg: travel/speaking fees from MSD Denmark and project support from Pfizer Denmark, outside this work.