BRIEF COMMUNICATION

Evaluation of clinical risk stratification to determine benefit from long-term versus short-term androgen deprivation in high-risk localized prostate cancer

Praful Ravi[1]✉, Wanling Xie[1], Silke Gillessen[2], Bertrand Tombal[3], Daniel E. Spratt[4], Paul L. Nguyen[5] and Christopher J. Sweeney[6]

BACKGROUND: Patients treated with RT and long-term androgen deprivation therapy (ltADT) for high-risk localized prostate cancer (HRLPC) with 1 high-risk factor (any of Gleason ≥8, PSA > 20 ng/mL, ≥cT3; "high-risk") have better outcomes than those with 2–3 factors and/or cN1 disease ("very high risk"). We evaluated whether this risk stratification could determine benefit from ltADT versus short-term (stADT).

METHODS: The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) repository of randomized trials was queried to identify eligible patients and trials. The key outcomes of interest were metastasis-free survival (MFS), overall survival (OS), time to metastasis (TTM) and prostate cancer-specific mortality (PCSM). Stratified Cox and Gray's regression were used to obtain the overall treatment effect for outcomes and risk groups, and the Wald interaction test to estimate whether treatment benefit differed by risk group or trial. Heterogeneity of studies was assessed by Cochran's Q and I^2.

RESULTS: 2780 patients from 3 trials were included. Patients with very-high risk disease had greater benefit with ltADT compared to high-risk disease (MFS HR 0.77 [0.68–0.88] vs. 0.89 [0.76–1.03]; TTM 0.61 [0.51–0.74] vs. 0.77 [0.59–0.99]; PCSM 0.71 [0.56–0.90] vs. 0.82 [0.59–1.14]; OS 0.87 [0.76–1.00] vs. 0.93 [0.79–1.08]), but there was no statistically significant difference in treatment effect by risk group (*p*-interaction >0.1). Heterogeneity for treatment effect across trials was low in the very high-risk group and moderate in the high-risk group.

CONCLUSIONS: Clinical risk stratification merits further evaluation in clinical trials to identify which patients with HRLPC may benefit from ltADT versus stADT.

Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-025-00937-0

The addition of androgen deprivation therapy (ADT) to radiotherapy (RT) is a standard-of-care in the treatment of high-risk localized prostate cancer (HRLPC), with extension of ADT beyond 18 months (long-term ADT; ltADT) conferring an 8% metastasis-free survival (MFS) benefit at 10 years compared to short-term ADT (stADT; 3–6 months) [1]. There has been interest in use of biomarkers to predict benefit from ltADT, including a 22-gene genomic classifier (Decipher-GC) [2] and an artificial intelligence (AI)-derived digital pathology biomarker (ArteraAI) [3, 4].

We published a prognostic risk model for patients treated with RT and ltADT for HRLPC from the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) data repository [5]. Patients with 1 National Comprehensive Cancer Network (NCCN) high-risk factor (Gleason ≥8, PSA > 20 ng/mL, ≥cT3 disease) had significantly better MFS and overall survival (OS), and lower rate of prostate cancer-specific mortality (PCSM) compared to those with 2–3 risk factors and/or cN1 disease. We aimed to evaluate whether use of this risk stratification could differentiate benefit from stADT versus ltADT.

The ICECaP individual patient data (IPD) repository of 31 RT-based randomized trials was queried to identify HRLPC patients with HRLPC treated on studies evaluating stADT versus ltADT (Supplementary Fig. 1). The key outcomes of interest were MFS, OS, time to metastasis (TTM) and PCSM, defined as previously reported [5]. ICECaP risk was defined as either "high" (i.e. 1 NCCN risk factor) or "very high" (2–3 risk factors and/or N1).

The overall treatment effect for each outcome and risk group was obtained from stratified Cox regression (MFS, OS) or Gray's regression (TTM, PCSM), adjusted for age and performance status, and stratified by trial and year of randomization (per 5-year increment) using the one-stage model for IPD meta-analysis. The Wald test from the interaction term of the Cox or Gray model estimated whether treatment benefit differed by risk group or trial. A sensitivity analysis based on the two-stage meta-analysis fixed-effect model, weighed by the inverse of variance of individual trial estimate, was also performed; heterogeneity of studies was assessed by Cochran's Q statistics and I^2 following PRISMA-IPD guidelines.

[1]Dana-Farber Cancer Institute, Boston, MA, USA. [2]Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland. [3]Cliniques Universitaires Saint-Luc, Brussels, Belgium. [4]University Hospitals Siedman Cancer Center, Case Western Reserve University, Cleveland, OH, USA. [5]Brigham & Women's Hospital, Boston, MA, USA. [6]South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia. ✉email: praful_ravi@dfci.harvard.edu

Received: 5 November 2024 Revised: 12 December 2024 Accepted: 3 January 2025
Published online: 08 January 2025

Overall, 2780 patients from 3 trials (EORTC-22961, [6] RTOG-9202, [7] TROG-0304 [8]) were included with a median follow-up of 11 years (IQR 7-19); baseline characteristics of these patients at randomization are shown in Supplementary Table 2. ICECaP risk (high vs. very high) showed good prognostic power across all three trials (Supplementary Fig. 2). The impact of ICECaP risk on MFS, TTM, PCSM and OS for ltADT versus stADT is shown in Supplementary Table 3. Though patients with ICECaP very-high risk disease derived greater benefit with ltADT compared to those with ICECaP high-risk disease (MFS HR 0.77 [0.68–0.88] vs. 0.89 [0.76–1.03]; TTM HR 0.61 [0.51–0.74] vs. 0.77 [0.59–0.99]; PCSM HR 0.71 [0.56–0.90] vs. 0.82 [0.59–1.14]; OS HR 0.87 [0.76–1.00] vs. 0.93 [0.79–1.08]), there was no statistically significant difference in treatment effect by risk group (p-interaction>0.1). Similar results were observed using the two-stage meta-analysis models (Supplementary Table 4).

When evaluated for each of the three included trials, the overall different treatment effects across risk groups were driven largely from the RTOG-9202 study (MFS HR 0.80 vs. 0.98; TTM HR 0.57 vs. 0.96; PCSM HR 0.67 vs. 0.88; OS HR 0.89 vs. 0.87 for very-high vs. high risk; Fig. 1, Supplementary Table 4). Kaplan-Meier and cumulative incidence curves showing MFS and TTM for each study stratified by ICECAP risk are shown in Supplementary Fig. 3. Overall, the heterogeneity for treatment effect across trials was low in the very-high risk population. In contrast, moderate heterogeneity was seen in the high-risk group. A greater treatment benefit for long- versus short-term ADT on MFS and TTM was seen in the EORTC trial compared to the other 2 trials within the high-risk group (p-interaction <0.05, Supplementary Table 4).

In this analysis comprising nearly 3000 patients treated on three randomized trials evaluating ADT duration with RT for HRLPC, clinical risk stratification was able to provide some measure of benefit from ltADT (vs. stADT) in patients with 2-3 NCCN risk factors and/or N1 disease. However, for patients with 1 NCCN risk factor, there was significant heterogeneity in treatment effect across trials with the overall treatment effect driven largely by data from one trial (RTOG-9902) [7].

These findings show that use of routine clinical parameters could have value in selecting which patients with HRLPC need ltADT and who may be well served with stADT. The current NCCN guidelines suggest that Decipher-GC and ArteraAI may be used to aid in risk stratification and selection of patients for ADT [9]. These were both validated as post-hoc analyses of NRG trials, including RTOG-9202. Use of ICECaP risk [5] was able to identify patients who might benefit from ltADT in the RTOG-9202 trial, where median follow-up was 20 years, but not in the EORTC-22961 trial, where median follow-up was 6 years. It is plausible that the impact of non-prostate cancer deaths with longer follow-up could explain this difference, with other potential confounders including heterogeneity in RT dose and field as well as duration of neoadjuvant ADT between trials. Other limitations of this study include the use of suboptimal RT dose by contemporary standards (given the inclusion of only patients treated between 1992 and 2007) and lack of use of PSMA-PET, which is now the standard-of-care for staging HRLPC.

At the very least, our results highlight the need to externally validate biomarkers such as ArteraAI or Decipher-GC and prospectively evaluate their use to guide management. Though our results do not support the routine clinical use of ICECaP risk to guide ADT decisions in HRLPC, they support further evaluation of these in prospective trials and in retrospective analyses of contemporary trials such as DART 01/05 [10]. Furthermore, these easily-available parameters may have particular value to guide decision-making on ADT duration in resource-limited settings.

In summary, use of ICECaP risk grouping for HRLPC did not identify benefit from ltADT versus stADT in this IPD analysis of 3

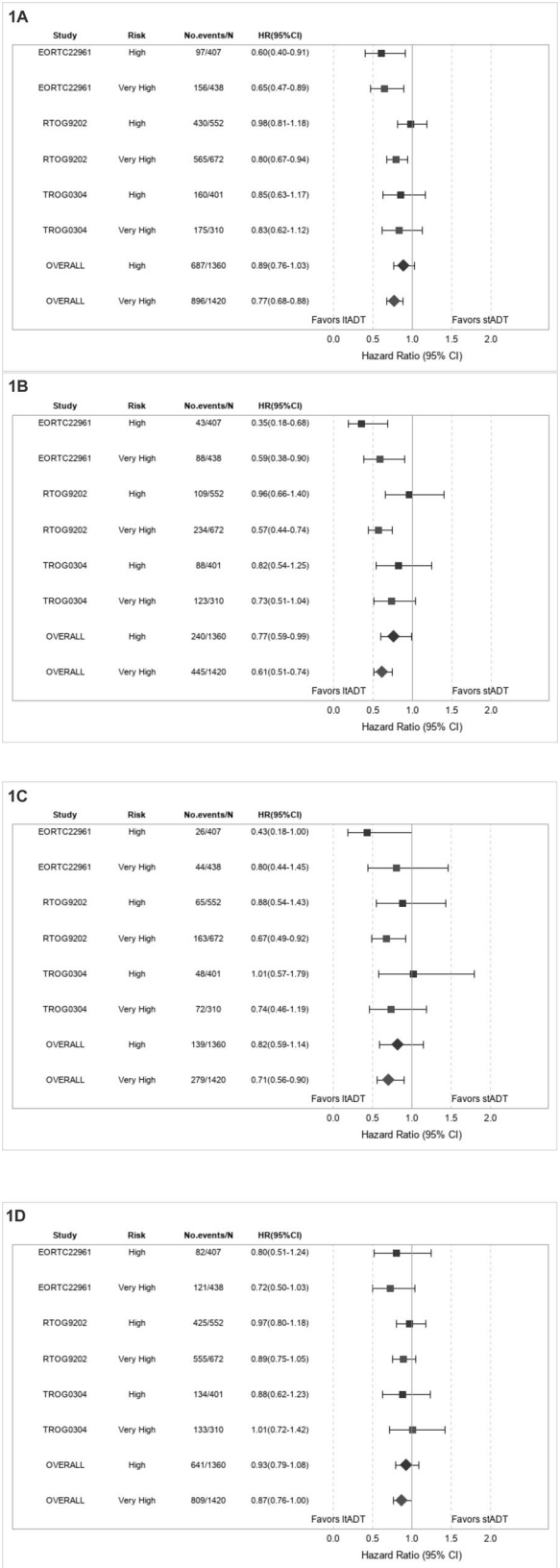

Fig. 1 Forest plots showing the treatment comparison of long- vs. short-term ADT on metastasis-free survival (**A**), time to metastasis (**B**), prostate cancer-specific mortality (**C**) and overall survival (**D**) in subgroups defined by ICECaP risk across all trials and for each trial separately.

trials, with heterogeneous treatment effects seen across trials for the high-risk disease group. Clinical risk grouping merits further evaluation in trials evaluating ADT duration in HRLPC.

REFERENCES

1. Kishan AU, Sun Y, Hartman H, Pisansky TM, Bolla M, Neven A, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol. 2022;23:304–16.
2. Nguyen PL, Huang HR, Spratt DE, Davicioni E, Sandler HM, Shipley WU, et al. Analysis of a Biopsy-Based Genomic Classifier in High-Risk Prostate Cancer: Meta-Analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 Phase 3 Randomized Trials. Int J Radiat Oncol Biol Phys. 2023;116:521–9.
3. Armstrong AJ, Liu VYT, Selvaraju RR, Chen E, Simko J, DeVries S, et al. Development and validation of an AI-derived digital pathology-based biomarker to predict benefit of long-term androgen deprivation therapy with radiotherapy in men with localized high-risk prostate cancer across multiple phase III NRG/RTOG trials. J Clin Oncol. 2023;41. https://doi.org/10.1200/JCO.2023.41.16_suppl.5001.
4. Spratt DE, Tang S, Sun Y, Huang HC, Chen E, Mohamad O, et al. Artificial Intelligence Predictive Model for Hormone Therapy Use in Prostate Cancer. NEJM Evid. 2023;2:EVIDoa2300023.
5. Ravi P, Xie W, Buyse M, Halabi S, Kantoff PW, Sartor O, et al. Refining Risk Stratification of High-risk and Locoregional Prostate Cancer: A Pooled Analysis of Randomized Trials. Eur Urol. 2024. https://pubmed.ncbi.nlm.nih.gov/38777647/.
6. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, et al. Duration of androgen suppression in the treatment of prostate cancer. N. Engl J Med. 2009;360:2516–27.
7. Lawton CAF, Lin X, Hanks GE, Lepor H, Grignon DJ, Brereton HD, et al. Duration of Androgen Deprivation in Locally Advanced Prostate Cancer: Long-Term Update of NRG Oncology RTOG 9202. Int J Radiat Oncol Biol Phys. 2017;98:296–303.
8. Denham JW, Joseph D, Lamb DS, Spry NA, Duchesne G, Matthews J, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. Lancet Oncol. 2019;20:267–81.
9. Schaeffer EM, Srinivas S, Adra N, An Y, Bitting R, Chapin B, et al. NCCN Guidelines(R) Insights: Prostate Cancer, Version 3.2024. J Natl Compr Canc Netw. 2024;22:140–50.
10. Zapatero A, Guerrero A, Maldonado X, Alvarez A, San-Segundo CG, Rodriguez MAC, et al. High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase 3 randomised, controlled trial. Lancet Oncol. 2022;23:671–81.

AUTHOR CONTRIBUTIONS

Conceptualization—PR, WX, CJS; Statistical analysis—WX, Provision of study materials—SG, BT, DES, PLN; Writing (original draft)—PR, WX; Writing (review)—all authors; Funding acquisition—CJS.

FUNDING

Funded by the Prostate Cancer Foundation Challenge Award, and grants from Astellas Pharma, Pfizer, Janssen Pharmaceuticals, Millennium Pharmaceuticals, Sotio, Bayer, Dendreon and Sanofi.

COMPETING INTERESTS

PR—Research funding to institution from Bayer, Lilly, Telix, Blue Earth Diagnostics, Lantheus, Novartis, Advisory board - Bayer; WX—Consulting Role: Convergent Therapeutics, PCCTC; SG—Personal honoraria for participation in *advisory boards* from Amgen, MSD; *other honoraria* from Radio-televisione Svizzera Italiana (RSI), German-speaking European School of Oncology (DESO); *invited speaker* for ESMO, Swiss group for Clinical Cancer Research (SAKK), Swiss Academy of Multidisciplinary oncology (SAMO), Orikata academy research group, *Speaker's bureau* for Janssen Cilag; *travel grant* from ProteoMEdiX and AstraZeneca; Institutional honoraria for participation in *advisory boards or in Independent Data Monitoring Committees and Steering Committees* from AAA International, Amgen, AstraZeneca, Astellas Pharma, Bayer, Bristol-Myers Squibb, DAIICHI Sankyo, Janssen, Modra Pharmaceuticals, MSD, Myriad Genetic, Novartis, Orion, Pfizer, Roche, Telixpharma, Tolermo Pharmaceutcials; *invited speaker* for Swiss group for Clinical Cancer Research (SAKK), Cold Spring Harbor Laboratory, ASCO GU; *other honoraria* from PeerVoice, Silvio Grasso Consulting, WebMD-Medscape; Patent royalties and other intellectual property for a research method for biomarker WO2009138392; DES—Personal fees: Astellas, AstraZeneca, Bayer, Boston Scientific, GSK, Janssen, Novartis, Pfizer; PLN—research funding paid to institution: Janssen, Astellas, Bayer; Consulting: Boston Scientific, Janssen, Bayer, Novartis, Nanocan; Stock or Other Ownership: Nanocan, Stratagen Bio, Reversal Therapeutics; CJS—research funding paid to institution by Janssen, Astellas, Sanofi, Bayer; Patents, Consulting, or Advisory Role: Sanofi, Janssen, Astellas, Bayer, Genentech/Roche, Pfizer, Lilly; Hengrui; CellCentric, PointBiopharma; Royalties and other Intellectual Property: Parthenolide (Indiana University); dimethylamino parthenolide (Leuchemix); Exelixis: Abiraterone plus cabozantinib combination; FRAS1 SNP and tristetraprolin as biomarkers of lethal prostate cancer; Stock or Other Ownership: Leuchemix. All other authors declare to relevant conflicts.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41391-025-00937-0.

Correspondence and requests for materials should be addressed to Praful Ravi.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.