

Title: Barriers and drivers of treatment intensification in metastatic castration-sensitive prostate cancer

Authors: Stacy Loeb, MD, MSc, PhD (Hon)^{1*}; Neeraj Agarwal, MD^{2*}; Nader El-Chaar, PhD, MSCI³; Laura de Ruiter, PhD, MSc³; Janet Kim, PhD³; Jesse Mack, PharmD³; Betty Thompson, PhD⁴; Sarah Rich-Zendel, PhD⁵; Jay Sheldon, PhD⁵; Jin Su Joo, PhD⁵; Judith Dyson, PhD⁶

*Denotes equal contribution

Affiliations:

¹Department of Urology and Department of Population Health, New York University Langone Health, 227 E 30th St 6th Floor, New York, NY 10016, USA

²Huntsman Cancer Institute, University of Utah, 1950 Cir of Hope Dr, Salt Lake City, UT 84112, USA

³Astellas Pharma Inc., 2375 Waterview Drive, Northbrook, IL 60062, USA

⁴Pfizer Inc., 66 Hudson Blvd E, New York, NY 10001, USA

⁵Throughline Strategy, 55 Eglinton Ave E, Toronto, Ontario, M4P 1G8, Canada

⁶Birmingham City University, Westbourne Road, Edgbaston, Birmingham B15 3TN, UK

Corresponding Author:

Stacy Loeb, MD, MSc PhD (Hon)

Department of Urology and Department of Population Health

New York University Langone Health

227 E 30th St 6th Floor

New York, NY 10016, USA

Tel: 718-261-9100

Email: stacyloeb@gmail.com

Word count: 2973/3000

Key Points

- **Question:** Why is first-line treatment intensification underutilized by US-based urologists and oncologists who treat patients with metastatic castration-sensitive prostate cancer (mCSPC)?
- **Findings:** In the qualitative study, we identified barriers and facilitators underlying first-line treatment intensification for mCSPC, including knowledge, decision processes, and beliefs about consequences. Notable differences exist between urologists and oncologists and the resources they consider helpful for supporting intensification. Cross-specialty tumor boards offer a feasible potential solution for improving treatment intensification uptake in both specialties.
- **Meaning:** Concrete, specialty-tailored tools that address the barriers and capitalize on the facilitators are needed to increase first-line treatment intensification uptake for mCSPC.

Abstract

Importance: Despite evidence of clinical benefits and guidelines recommending first-line treatment intensification for metastatic castration-sensitive prostate cancer, the majority of patients do not receive it.

Objective: The goal of IMPLEMENT was to investigate why first-line treatment intensification is underutilized.

Design: IMPLEMENT was conducted from March 2022–August 2024. The study comprised three phases and used a mixed-methods approach.

Setting: United States

Participants: United States-based urologists and oncologists who were primary treaters for ≥ 1 patient with metastatic castration-sensitive prostate cancer in the past 6 months, had been practicing for 2–35 years, spent $\geq 50\%$ of their time in direct patient care, and were able to provide informed consent. Recruited using purposive sampling.

Interventions: Phase 1: semi-structured interviews based on the Theoretical Domains Framework. Thematic analysis was used to identify barriers and facilitators to treatment intensification. Phase 2: discrete choice experiment to identify priority barriers and helpful resources. Phase 3: co-creation sessions to ideate potential solutions to underutilization based on the findings of the previous phases.

Main Outcomes and Measures: Phase 1: barriers to and facilitators of first-line treatment intensification. Phase 2: perceived helpfulness of potential resources for first-line treatment intensification decisions. Phase 3: potential solutions co-created by urologists and oncologists to increase treatment intensification uptake.

Results: Phases 1–3 of IMPLEMENT included 36, 302, and 14 participants, respectively. In each phase, half of participants were oncologists and half were urologists. In phase 1, five domains had the greatest influence on intensification: Memory, Attention, and Decision Processes; Environmental Context and Resources; Knowledge; Beliefs About Consequences; and Social/Professional Role. Urologists more commonly reported barriers to intensification, while oncologists more commonly reported facilitators. In phase 2, urologists found decision-support tools most helpful, while oncologists preferred post-treatment databases and clinical trial summaries. In phase 3, cross-specialty tumor boards were ranked by both specialties as the best solution to address treatment intensification underutilization.

Conclusions and Relevance: In this qualitative study, the issues underlying treatment intensification underutilization were numerous and multifactorial. The results of IMPLEMENT suggested that the barriers encountered by physicians, and the resources that could help to address them, varied by specialty. All these findings offer insights into physician-supported strategies that could help improve rates of first-line treatment intensification for mCSPC.

Introduction

For patients with metastatic castration-sensitive prostate cancer (mCSPC; also known as metastatic hormone-sensitive prostate cancer), American Urological Association (AUA) guidelines¹ and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)² recommend treatment intensification (also known as combination therapy³) as a first-line treatment option. Options for treatment intensification include androgen-deprivation therapy (ADT) combined with androgen receptor pathway inhibitors (ARPIs; e.g., abiraterone, apalutamide, darolutamide, enzalutamide), or triplet therapy, which includes ADT with docetaxel and ARPIs.² Compared with ADT alone, treatment intensification has been found to substantially increase overall survival in several randomized controlled trials⁴⁻⁷ and in real-world settings⁸ without decreasing quality of life.⁹ Despite these benefits and clinical recommendations, first-line treatment intensification is underutilized, with less than half of patients with mCSPC in the United States receiving it.⁹⁻¹³ The reasons for this underutilization have not been fully elucidated.

Implementation Science

Implementation science is the study of the translation of research findings into routine clinical practice.¹⁴ It has been used in oncology studies to improve uptake of evidence-based practices, such as screening programs, and to reduce use of practices lacking evidence of clinical benefits.¹⁵

The Theoretical Domains Framework (TDF) is an implementation-science tool developed to better understand why evidence-based practices are often not incorporated sufficiently. It includes 11 domains that can guide the investigation of barriers to and facilitators of the implementation of an evidence-based practice.¹⁶ It is widely used to identify influences on

behavior, design systematic interventions, and facilitate behavior change techniques (BCTs),¹⁷ which are the “active ingredients” in interventions that address specific barriers to target behaviors.

Objectives

The goal of the IMPLEMENT study was to investigate why first-line treatment intensification is underutilized in patients with mCSPC, using a qualitative implementation-science approach combined with a quantitative discrete choice experiment (DCE). The objective of phase 1 was to understand barriers to and facilitators of first-line treatment intensification for mCSPC among urologists and oncologists in the United States, and to identify BCTs that may help to address these factors. Building on phase 1, the objectives of phase 2 were to validate, quantify, and prioritize top determinants of first-line treatment intensification, and to establish which resources physicians consider most helpful to support treatment intensification. Differences between urologists and oncologists were investigated as an exploratory objective in phases 1 and 2.

Drawing on the findings of phases 1 and 2, the objective of phase 3 was to work with healthcare providers (HCPs) to co-create evidence-based interventions that would help support first-line treatment intensification.

Methods

Study Reporting

This study was reported using the Standards for Reporting Qualitative Research checklist (Supplementary Materials).

Ethics

All participants in the IMPLEMENT study provided written informed consent to participate in the study. All aspects of this study were approved by Advarra Institutional Review Board (Pro00066531).

Phase 1

This study built upon and modified a mixed-methods approach that was previously used in a study of localized prostate cancer.¹⁸ Phase 1 was conducted from 2022–2023. We used a qualitative implementation-science design using the TDF (eFigure 1A) and conducted virtual, double-masked, semi-structured interviews with 36 urologists and oncologists in the US who treat patients with mCSPC. Eligible physicians were US-based urologists or oncologists, were primary treaters for ≥ 1 patient with mCSPC in the past 6 months, had been practicing for 2–35 years, spent $\geq 50\%$ of their time in direct patient care, and were able to provide informed consent. Purposive sampling was used to ensure a variety of backgrounds and perspectives were captured. A sample size of ≥ 15 participants per specialist group was targeted for the initial analysis sample, which exceeded the minimum recommended number (i.e., 10).¹⁷ Six participants (17%) with very high levels of first-line treatment intensification (i.e., $>90\%$, referred to as super intensifiers) were included in phase 1. Additional details about participant eligibility, sampling, and saturation testing are provided in the eMethods.

An interview guide was developed based on the TDF and optimized through pilot testing (Supplemental Materials, eMethods). Definitions of the TDF domains are presented in the eMethods.

Phase 2

Phase 2 was conducted in 2023. Key themes from phase 1 advanced to the phase-2 DCE (eFigure 1B, eMethods). Urologists and oncologists ($n = 302$) were recruited independently from

phase 1. A total of 14 super intensifiers (5%) were included in phase 2. Across 12 hypothetical scenarios, respondents saw descriptions of two hypothetical resource sets and selected the set they believed would be most helpful for first-line treatment intensification decisions (eFigure 2). Following the DCE, respondents were asked a series of semantic balance questions intended to better understand how they make treatment decisions, as well as their information preferences to help inform the design of potential interventions (eMethods).

Phase 3

Building upon phases 1 and 2, in 2024 we held three co-creation sessions^{23,24} with HCPs (eFigure 1C). Co-creation is a validated implementation-science approach that uses collaboration between intervention designers and users to design effective interventions that support behavior change.²³ A sample size of 6–12 participants is recommended.²⁵ We aimed for the upper range to account for potential dropouts and to ensure enough participants for smaller, interactive groups.

Participants were recruited using purposive sampling using phase 1 inclusion criteria (eMethods). For this phase only, physicians who reported using first-line intensification for >90% of patients were excluded, as they encounter very few barriers. Pseudonyms were used to mask participants' identities from the research team and each other.

Statistical Analyses

All analyses were conducted in R version 4.1.1 and Python version 3.10.

Phase 1

Interviews were transcribed and analyzed using a thematic analysis approach.¹⁹ Deductive coding was used to map data onto TDF domains. Inductive coding was used to group the content within the domains and to develop themes and belief statements. Belief statements

were derived from themes and restructured as barriers, facilitators, or neutral statements if they hindered, drove, or were not associated with treatment intensification behavior, respectively. Three criteria were scored to determine whether each theme was key or peripheral to treatment intensification decisions: the frequency of each theme (high/medium/low); the degree of conflicting beliefs within a theme (i.e., divergence; high/low); and the strength of each theme's impact on intensifying treatment (high/low). Definitions and scoring of these criteria are provided in the eMethods. Themes with the maximum score, and the domains they belonged to, were considered key. Barriers and facilitators within key domains were considered key to treatment intensification behavior. Intercooder agreement was evaluated using Cohen's kappa with a target value of $\kappa = 0.75$. We ultimately achieved $\kappa = 0.77$ after double-coding 10% of the interviews.

Relevant BCTs for each domain were identified using validated taxonomy based on the TDF (eMethods).^{20,21}

Differences in barriers and facilitators between urologists and oncologists were assessed using a percentage point delta analysis, where differences in the frequency of belief statements between subgroups were calculated. Frequency differences of $\geq 20\%$ were considered notable, in accordance with the upper bound of a 90% confidence interval (CI) for the subgroup size.²²

Phase 2

We analyzed DCE responses using a constrained mixed-effects logit model, with physician specialty as a covariate, and calculated a coefficient of helpfulness [CoH] for each resource to identify those with the strongest impact on physicians' decisions (eMethods). To facilitate interpretation, coefficients were transformed to have a minimum value of zero and an average of 1. Therefore, resources with coefficients >1 could be interpreted as offering greater

utility than average. Logit model accuracy was evaluated by comparing the model-predicted most-likely choice and the average actual choice. 95% confidence intervals were calculated from bootstrap sampling. Differences in helpfulness scores between specialties were compared using bootstrap testing of subgroup averages. Differences in information and practice preferences between specialties were evaluated using independent t-tests, while differences in the importance of information sources were evaluated using z-tests between specialties for each source (eMethods). For all analyses, statistical significance was set at 0.05.

Phase 3

The co-creation sessions were designed to ideate solutions based on four of the key domains and their associated BCTs identified in phase 1, as well as the interventions viewed as most helpful in phase 2. The solutions were then rated by participants based on cost-effectiveness, practicality, and acceptability. The five top-rated ideas were further developed. Additional details about the co-creation sessions are presented in the eMethods.

Results

Study Participants

Phases 1–3 included 36, 302, and 14 participants, respectively (**Table 1**). Across all three phases, half of participants were urologists, and half were oncologists. On average, participants had been practicing for approximately 20 years (range 5–35). The majority of participants practiced in non-academic settings.

Phase 1

A total of 17 barriers and 14 facilitators were identified across 10 of the 11 domains assessed (Supplemental Materials). Five key domains were deemed to have the greatest influence

on first-line treatment intensification: Memory, Attention, and Decision Processes; Environmental Context and Resources; Knowledge; Beliefs About Consequences; and Social/Professional Role (eTable 1). Within these five domains, key barriers were knowledge gaps, habit of not intensifying first line, anticipated regret over side effects and losing treatment options for later, cost of treatment intensification, tendency to restrict treatment intensification to high-volume or severe disease, insufficient clinical support, and delayed urologist referral to oncologists. Key facilitators were good knowledge of clinical trial data, habit of intensifying first line, good interdisciplinary collaboration, anticipated regret over losing the best chance at improving survival, administrative support to address cost, and clinical staff to facilitate treatment intensification. Figure 1 shows the associated BCTs known to address the barriers within each TDF domain.

The remaining six domains (Skills; Motivation, Goals, and Priorities; Beliefs About Capabilities; Social Influence; Action Planning; and Emotions) and the barriers and facilitators within them were considered peripheral in their influence on treatment intensification (Figure 1, eTable 1).

Phase 1 Subgroup Analysis: Urologists vs Oncologists

Notable differences were identified between specialties (Figure 2, eResults, eFigures 3A–B). Urologists more commonly reported barriers, including insufficient clinical support and a habit of not intensifying first line. However, they were aided by good interdisciplinary collaboration and their belief in a urologist’s role in treatment intensification. Oncologists were more likely to report facilitators, including anticipated regret over losing the best chance at improving survival and having good clinical support. However, delayed urologist referrals were a barrier to treatment intensification. Both specialties commonly experienced knowledge gaps

and cost of treatment intensification as barriers, and good administrative support as a facilitator (Figure 2).

Phase 2

Logit model accuracy for the DCE was 72%, indicating good accuracy. Urologists tended to find decision-support tools most beneficial (CoH, 3.27; 95% CI, 2.90–3.64), while oncologists tended to prefer post-treatment databases (CoH, 2.58; 95% CI, 2.29–2.89) and clinical trial summaries (CoH, 2.41; 95% CI, 2.13–2.69) (Figure 3). Urologists also found cross-specialty treatment guidelines and databases of post-treatment options to be slightly above average in terms of helpfulness. These differences indicated disparate priority barriers and facilitators between specialties (eTable 2). Tools to reduce administrative burden and information on outcomes of earlier versus later treatment intensification were considered less helpful by both specialties.

Several differences were significant between specialties in terms of information preferences and treatment approaches (eFigure 4). Urologists tended to prefer succinct summaries and clear, direct information. They also tended to follow standardized and individualized treatment approaches equally. Oncologists had no strong preferences regarding succinctness or directness of information, and tended to take a more individualized approach to treatment.

In terms of information sources, urologists showed a significantly greater preference for continuing medical education courses ($P = 0.01$), while oncologists preferred clinical trial summaries ($P < 0.01$) and online medical platforms and forums ($P = 0.04$) (eFigure 5).

Phase 3

Participants suggested 13 potential solutions across four key domains. The five top-rated solutions varied by specialty, but both specialties included ideas associated with the Memory, Attention, and Decision Processes, and the Knowledge domains (Figure 4). The five ideas built out in session 3 were: cross-specialty tumor boards; consolidation of data; journal club; database of post-treatment options; and immersive modular case-based learning. The solutions and their recommended components are described further in eTable 3. Ultimately, cross-specialty tumor boards were ranked by both specialties as the best solution to address underutilization of first-line treatment intensification (Figure 4).

The final logic model illustrates how the proposed solutions address barriers and facilitators from phases 1 and 2. The top-rated solution—cross-specialty tumor boards—addresses all four key domains (eFigure 6) and five peripheral domains (eFigure 7).

Discussion

IMPLEMENT identified clear, data-driven determinants of treatment intensification among practicing US-based urologists and oncologists, and offers evidence-based strategies for improving uptake. Using best practices in implementation science, our phase 1 findings suggest that the issues behind insufficient first-line treatment intensification are numerous and multifactorial. Physicians encounter several key barriers and facilitators that impact both their ability to intensify treatment (Knowledge; Memory, Attention, and Decision Processes; Environmental Context and Resources) and their motivation to do so (Beliefs About Consequences; Social/Professional Role).

One notable finding was the influence of anticipated regret on intensification behaviors (Beliefs About Consequences). If physicians anticipated regretting missing the best chance of

improving survival, they were driven to intensify. If they anticipated regret over losing intensification as a future option, or negatively affecting quality of life, regret was a barrier. Additionally, both specialties encountered obstacles relating to Knowledge, consistent with a recent physician survey study that identified knowledge gaps as a reason against treatment intensification in mCSPC.¹¹ These issues are especially important to address, given previous evidence that patients with mCSPC rely heavily on their physicians' treatment recommendations and prioritize treatments that will extend their survival.²⁶

Differences in the experience of high and low intensifiers were further explored in a sub-analysis of phases 1 and 2 that was recently presented at the American Society of Clinical Oncology – Genitourinary Conference 2025.²⁷ As expected, low intensifiers experienced more barriers than high intensifiers, who encountered more facilitators. Notably, clinical trial summaries were considered very helpful by high intensifiers, whereas low intensifiers found them less helpful, but decision support tools were considered helpful by both.

Between specialties, oncologists reported more facilitators than urologists, including having good clinical support and being concerned about missing an opportunity to prolong survival. By contrast, urologists more frequently experienced barriers, including a habit of low intensification and insufficient clinical support. Our findings may explain why previous studies have shown that urologists have lower treatment intensification rates than oncologists.^{28,29} Notably, urologists were encouraged to intensify by a belief in their role in intensification and by good collaboration with oncologists, suggesting that promoting these factors may improve intensification uptake.

Our phase 2 DCE indicated that the perceived helpfulness of resources varies by specialty. Urologists preferred decision-support tools (Memory, Attention, and Decision

Processes), while oncologists preferred resources offering post-treatment options for progression and summaries of clinical trial data (Beliefs About Consequences; Knowledge). These findings suggest that different resources and approaches are needed for each specialty to support treatment intensification; oncologists prefer to be educated on and receive the clinical information needed to make treatment decisions, while urologists prefer to have tools to directly guide and support treatment decision-making.

Of note, the resource considered helpful by both specialties (database of post-treatment options) addresses the theme of anticipated regret. This resource was also considered helpful in our recent sub-analysis of high and low intensifiers and physicians in academic and non-academic settings.²⁷ Conversely, resources seeking to address the domain of Environmental Context and Resources, particularly those addressing associated barriers, like the cost of ARPIs and the administrative burden of accessing them, were considered least helpful. This suggests that efforts to address these barriers may have limited impact without simultaneously tackling educational, cognitive, or psychological barriers physicians face, or that physicians are not confident such resources could be developed.³⁰ The co-creation sessions in phase 3 led to development of five potential solutions to increase uptake of first-line treatment intensification. Of these, cross-specialty tumor boards were identified as the best solution. Although tumor boards are a feature of academic institutions, many community physicians may not have them available at their practices. These physicians would therefore be encouraged to join virtual tumor boards, particularly with the incentive of receiving continued medical education credit and learning from experts in the field. In addition, to address participant concerns about the potential for bias, these boards would be independent from pharmaceutical sponsorship (eTable 3). As this study was conducted among US-based physicians, future research should aim to determine

whether the resources deemed helpful in the US context are also considered helpful elsewhere and by other physicians. In a recent study of Swedish patients with de novo mCSPC, HCP engagement in multidisciplinary conferences was not associated with greater uptake of guideline-concordant treatment intensification practices.³¹ This suggests that the enthusiasm for tumor boards and continuing medical education identified among participants in our study may not be generalizable to the views of other HCPs outside the U.S.. Phase 4 of IMPLEMENT is underway and will involve development and validation of prototypes for cross-specialty virtual tumor boards and consolidated data, another high-ranking solution proposed in phase 3, based on HCP feedback and advice.

Limitations

Although reliability is a potential issue for the qualitative portion of phase 1 of IMPLEMENT, we attempted to mitigate this through intercoder reliability testing. Social desirability bias was also a concern, which was mitigated through double masking in phases 1 and 2, and single masking in phase 3. Although our study included relatively few participants in phases 1 and 3, the sample sizes obtained exceed the minimum requirements for this type of qualitative analysis,^{17,25} and our findings were tested for saturation in phase 1. As physicians were recruited online, there was also potential for selection bias. This was mitigated with purposive sampling and soft recruitment quotas that sought to capture a diverse range of perspectives, which also helped ensure that a large proportion of participants in all three phases were low intensifiers (phase 1: 56%; phase 2: 39%; phase 3: 36%), so reasons for underutilization could be more fully explored. Importantly, high intensifiers also encounter barriers to treatment intensification,³² and their representation in this study allowed us to examine the unique barriers and facilitators they encounter. Despite our use of soft quotas, the

number of female and rural participants was low. Additionally, the study was restricted to US-based oncologists and urologists, limiting the generalizability of our findings. Perspectives from patients, nurses, caregivers, physician assistants, and HCPs from other specialties or jurisdictions may differ.

In phase 2, resource sets were chosen in advance, meaning our results are applicable only to the resource options and descriptions presented in the DCE. Further, given our resource-based approach to the DCE, it is possible participants made their decisions about which resource description they preferred based on the resource itself rather than on its value in helping with treatment intensification decisions. Resource sets were developed based on validated BCTs, strengthening our confidence in the relevance of the resources presented. Similarly, the solutions that were ideated in phase 3 were co-created with low intensifiers, suggesting that the proposed solutions are those that HCPs believe would work for them

In phase 3, solutions that addressed the domain of Environmental Context and Resources were not explored. Future analyses should attempt to investigate this domain.

Conclusions

The results of the qualitative portion of the IMPLEMENT study indicated that many barriers and facilitators underlie first-line treatment intensification for mCSPC, with notable differences between urologists and oncologists. These differences contributed to variability between specialties in the resources they considered helpful for supporting intensification. Decision-support tools were considered by urologists to be the most helpful resources, whereas oncologists preferred a database of post-treatment options and clinical trial summaries. Finally, through a series of co-creation sessions, we determined that cross-specialty tumor boards offered a promising and feasible potential solution for improving rates of first-line treatment

intensification that would address most TDF domains. All these findings offer insights into concrete, physician-supported resources that could be developed to help improve rates of first-line treatment intensification for mCSPC.

Author Contributions

SL: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

NA: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

NE: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

LDR: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

JK: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

JM: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

BT: analysis of study data; writing – reviewing and editing

SRZ: acquisition of study data; analysis of study data; interpretation of study data; writing – reviewing and editing

JS: substantial contribution to study design; acquisition of study data; analysis of study data; interpretation of study data; writing – reviewing and editing

JSJ: substantial contribution to study design; acquisition of study data; analysis of study data; interpretation of study data; writing – reviewing and editing

JD: substantial contribution to study design; analysis of study data; interpretation of study data; writing – reviewing and editing

Conflicts of Interest

SL: Consulting/Advisory Role: Astellas Pharma, Blue Earth, Doceree, Savor Health. Research funding: Endo.

NA: None to declare.

NE: Employment: Astellas Pharma; Research Funding: Astellas Pharma

LDR: Employment: Astellas Pharma; Research Funding: Astellas Pharma

JK: Employment: Astellas Pharma

JM: Employment: Astellas Pharma

BT: Employment: Pfizer; Stock or Stock Options: Pfizer

SRZ: Consulting/Advisory Role: Astellas Pharma, Lilly

JS: Consulting/Advisory Role: Throughline Strategy

JSJ: None to declare.

JD: Consulting/Advisory Role: Astellas Pharma; Honoraria: Astellas Pharma

Acknowledgments

Support for medical writing, editing, and graphic design was provided by Lindsay Wilson (MSc), Olga Klibanov (PharmD), Nathaniel Grubbs (PhD), and Samila Sakhabuth (BAHons) from IQVIA, funded by the study sponsors.

Funding

This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide. Authors NE, LDR, JK, JM, and BT are employees of Astellas Pharma and were involved in the study design, as well as the acquisition, analysis, and interpretation of the data.

Data Availability Statement

All data generated or analyzed during this study, which support the findings of this study, are included within this article and its supplementary information files. Researchers interested in further analyses not present in the manuscript may contact the corresponding author.

Previous Presentations of Manuscript Information:

The findings of the first three phases of IMPLEMENT have previously been presented as poster and oral presentations at ASCO-GU 2024 (phase 1), AUA 2024 (sub-analysis of phase 1, comparing urologists and oncologists), ASCO 2024 (phase 2), and IHI 2024 (phase 3) and have been covered by the medical media (UroToday, AJMC, Renal & Urology News).

References

1. Lowrance W, Dreicer R, Jarrard DF, et al. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). *J Urol*. Jun 2023;209(6):1082-1090. doi:10.1097/JU.0000000000003452.
2. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer. Version 1.2025*. 2024. December 4, 2024. .
3. Oh WK, Agarwal N, Bryce A, et al. What's in a Name? Why Words Matter in Advanced Prostate Cancer. *European Urology*. 2025/02/01/ 2025;87(2):101-103. doi:<https://doi.org/10.1016/j.eururo.2024.10.017>.
4. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. May 2019;20(5):686-700. doi:10.1016/S1470-2045(19)30082-8.
5. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*. Aug 20 2015;373(8):737-746. doi:10.1056/NEJMoA1503747.
6. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. Mar 19 2016;387(10024):1163-1177. doi:10.1016/S0140-6736(15)01037-5.
7. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med*. Jul 27 2017;377(4):338-351. doi:10.1056/NEJMoA1702900.

8. Parrish J, Polascik T, Hong A, et al. Real-world (RW) survival and outcomes with androgen receptor pathway inhibitor (ARPI) –doublet therapy in patients (pts) with de novo metastatic castration-sensitive prostate cancer (mCSPC). *Journal of Clinical Oncology*. 2024;42(4)(suppl).
9. Wasim S, Park J, Nam S, Kim J. Review of Current Treatment Intensification Strategies for Prostate Cancer Patients. *Cancers (Basel)*. Nov 28 2023;15(23):5615. doi:10.3390/cancers15235615.
10. Swami U, Hong A, El-Chaar NN, et al. Underutilization of standard of care (SOC) treatment intensification in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) by specialty. *Journal of Clinical Oncology*. 2022;40(6_suppl):183. doi:10.1200/JCO.2022.40.6_suppl.183.
11. Agarwal N, George DJ, Klaassen Z, et al. Physician Reasons for or Against Treatment Intensification in Patients With Metastatic Prostate Cancer. *JAMA Network Open*. 2024;7(12):e2448707-e2448707. doi:10.1001/jamanetworkopen.2024.48707.
12. Wallis CJD, Malone S, Cagiannos I, et al. Real-World Use of Androgen-Deprivation Therapy: Intensification Among Older Canadian Men With de Novo Metastatic Prostate Cancer. *JNCI Cancer Spectr*. Dec 2021;5(6):pkab082. doi:10.1093/jncics/pkab082.
13. Wallis CJ, Satkunasivam R, Nguyen D-D, et al. Understanding variation in treatment intensification for de novo metastatic castration-sensitive prostate cancer (mCSPC): A population-based cohort study. *Journal of Clinical Oncology*. 2024;42(4)(suppl):1. doi:10.1200/JCO.2024.42.4_suppl.6.

14. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychol.* Sep 16 2015;3(1):32. doi:10.1186/s40359-015-0089-9.
15. Check DK, Zullig LL, Davis MM, et al. Improvement Science and Implementation Science in Cancer Care: Identifying Areas of Synergy and Opportunities for Further Integration. *J Gen Intern Med.* Jan 2021;36(1):186-195. doi:10.1007/s11606-020-06138-w.
16. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care.* Feb 2005;14(1):26-33. doi:10.1136/qshc.2004.011155.
17. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implement Sci.* Jun 21 2017;12(1):77. doi:10.1186/s13012-017-0605-9.
18. Skolarus TA, Hawley ST, Wittmann DA, et al. De-implementation of low value castration for men with prostate cancer: protocol for a theory-based, mixed methods approach to minimizing low value androgen deprivation therapy (DeADT). *Implement Sci.* Nov 29 2018;13(1):144. doi:10.1186/s13012-018-0833-7.
19. Clarke V, Braun V. Thematic analysis. *The Journal of Positive Psychology.* 2017/05/04 2017;12(3):297-298. doi:10.1080/17439760.2016.1262613.
20. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med.* Aug 2013;46(1):81-95. doi:10.1007/s12160-013-9486-6.

21. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Applied psychology*. 2008;57(4):660-680. .
22. Wallis S. Binomial Confidence Intervals and Contingency Tests: Mathematical Fundamentals and the Evaluation of Alternative Methods. *Journal of Quantitative Linguistics*. 2013/08/01 2013;20(3):178-208. doi:10.1080/09296174.2013.799918.
23. Taylor N, Lawton R, Slater B, Foy R. The demonstration of a theory-based approach to the design of localized patient safety interventions. *Implement Sci*. Oct 16 2013;8:123. doi:10.1186/1748-5908-8-123.
24. Dyson J, Onukwugha F, Howlett H, Combe K, Catterick M, Smith L. Midwives and service users' perspectives on implementing a dialogue about alcohol use in antenatal care: A qualitative study. *J Adv Nurs*. Aug 2023;79(8):2955-2966. doi:10.1111/jan.15622.
25. Leask CF, Sandlund M, Skelton DA, et al. Framework, principles and recommendations for utilising participatory methodologies in the co-creation and evaluation of public health interventions. *Res Involv Engagem*. 2019;5:2. doi:10.1186/s40900-018-0136-9.
26. Oswald LB, Schumacher FA, Gonzalez BD, Moses KA, Penson DF, Morgans AK. What Do Men with Metastatic Prostate Cancer Consider When Making Treatment Decisions? A Mixed-methods Study. *Patient Prefer Adherence*. 2020;14:1949-1959. doi:10.2147/PPA.S271620.
27. Agarwal N, Loeb S, El-Chaar NN, et al. Barriers to and facilitators of first-line treatment intensification (TI) in metastatic castration-sensitive prostate cancer (mCSPC) by practice setting and intensification frequency: A sub-analysis of IMPLEMENT. *Journal of Clinical Oncology*. 2025;43(5_suppl):48-48. doi:10.1200/JCO.2025.43.5_suppl.48.

28. Swami U, Hong A, El-Chaar NN, et al. The Role of Physician Specialty in the Underutilization of Standard-of-Care Treatment Intensification in Patients With Metastatic Castration-sensitive Prostate Cancer. *J Urol*. Jun 2023;209(6):1120-1131. doi:10.1097/JU.0000000000003370.
29. Heath EI, Dyson GE, Cackowski FC, Hafron J, Powell I. Treatment Intensification Patterns and Utilization in Patients with Metastatic Castration-Sensitive Prostate Cancer. *Clinical Genitourinary Cancer*. 2022;20(6):524-532. doi:10.1016/j.clgc.2022.06.017.
30. Panagioti M, Panagopoulou E, Bower P, et al. Controlled Interventions to Reduce Burnout in Physicians: A Systematic Review and Meta-analysis. *JAMA Intern Med*. Feb 1 2017;177(2):195-205. doi:10.1001/jamainternmed.2016.7674.
31. Gedeberg R, Sandin F, Thellenberg-Karlsson C, Styrke J, Franck Lissbrant I, Garmo H, Stattin P. Uptake of doublet therapy for de novo metastatic castration sensitive prostate cancer: a population-based drug utilisation study in Sweden. *Scand J Urol*. Nov 10 2023;58doi:10.2340/sju.v58.9572.
32. Agarwal N, Loeb S, El-Chaar N, et al. Barriers to and facilitators of first-line treatment intensification (TI) in metastatic castration-sensitive prostate cancer (mCSPC) by practice setting and intensification frequency: A sub-analysis of IMPLEMENT. *Journal of Clinical Oncology*. 2025;43(5)(Suppl).

Figure Legend

Figure 1. Barriers to and facilitators of first-line treatment intensification and associated behavior change techniques

NA, not applicable

Figure 2. Barriers to and facilitators of treatment intensification by specialty

^aBarriers and facilitators experienced by $\geq 50\%$ of urologists and oncologists and not notably different between specialties (i.e., difference between specialties $< 20\%$)

^bFrequency difference between specialties $\geq 20\%$

^cPeripheral barrier or facilitator

Figure 3. Coefficient of helpfulness for decision-making related to intensification by specialty

CI: confidence interval; mCSPC: metastatic castration-sensitive prostate cancer.

Figure 4. Proposed solution and ratings by specialty

Table 1

	Phase 1			Phase 2			Phase 3		
	Urologists n = 18	Oncologists n = 18	Total N = 36	Urologists (n = 151)	Oncologists (n = 151)	Total (N = 302)	Urologists (n = 7)	Oncologists (n = 7)	Total (N = 14) ^a
Years in practice, average (range)	21 (9–34)	16 (5–30)	19 (5–34)	19 (5–35)	17 (4–30)	18 (4–35)	22 (12–35)	17 (8–30)	20 (8–35)
Sex, n (%)									
Male	18 (100)	15 (83)	33 (92)	140 (93)	113 (75)	253 (84)	7 (100)	5 (71)	12 (86)
Female	0 (0)	3 (17)	3 (8)	7 (5)	30 (20)	37 (12)	0 (0)	2 (29)	2 (14)
Intensification Status, n (%)									
High intensifier	6 (33)	10 (56)	16 (44)	74 (49)	110 (73)	184 (61)	4 (57)	5 (71)	9 (64)
Low intensifier	12 (67)	8 (44)	20 (56)	77 (51)	41 (27)	118 (39)	3 (43)	2 (29)	5 (36)
Intensification Rate, median (IQR)	–	–	50% (20%, 75%)	–	–	65% (40%, 85%)	–	–	58% (50%, 65%)
Setting, n (%)									
Academic	5 (28)	9 (50)	14 (39)	36 (24)	45 (30)	81 (27)	3 (43)	3 (43)	6 (43)
Non-academic	13 (72)	9 (50)	22 (61)	115 (76)	106 (70)	221 (73)	4 (57)	4 (57)	8 (57)
Location, n (%)									
Urban/suburban	14 (78)	17 (94)	31 (86)	133 (88)	139 (92)	272 (90)	6 (86)	6 (86)	12 (86)
Rural	4 (22)	1 (6)	5 (14)	18 (12)	12 (8)	30 (10)	1 (14)	1 (14)	2 (14)
Region, n (%)									
Northeast	6 (33)	8 (44)	14 (39)	45 (30)	38 (25)	83 (27)	3 (43)	3 (43)	6 (43)
South	5 (28)	3 (17)	8 (22)	40 (26)	55 (36)	95 (31)	2 (29)	1 (14)	3 (21)
Midwest	1 (6)	5 (28)	6 (17)	37 (25)	25 (17)	62 (21)	2 (29)	1 (14)	3 (21)
West	6 (33)	2 (11)	8 (22)	29 (19)	33 (22)	62 (21)	0	2 (29)	2 (14)

^a11 participants attended all three sessions, 3 participants attended sessions 2 and 3 only

IQR: interquartile range

