The Oncologist, 2023, **28**, 642–e561
https://doi.org/10.1093/oncolo/oyad058
Advance access publication 3 May 2023
Clinical Trial Results

Flutamide With or Without PROSTVAC in Non-metastatic Castration Resistant (M0) Prostate Cancer

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Abstract

Background: Before 2018, there was no standard of care for non-metastatic (M0) castration resistant prostate cancer nmCRPC. Androgen receptor antagonists (ARAs) were commonly used sequentially nmCRPC.

Methods: This was a multicenter, randomized clinical trial comparing the ARA flutamide+/−PROSTVAC, a pox viral vaccine targeting PSA that includes T-cell co-stimulatory molecules. Eligible men had negative CT and Tc99 bone scans, and rising PSA on ADT. Previous treatment with ARA was a stratification factor. Patients were also evaluated for antigen-specific immune responses using intracellular cytokine staining.

Results: Thirty-three patients randomized to flutamide and 31 to flutamide+vaccine. The median age was 71.8 and 69.8 years, respectively. The median time to treatment failure after a median potential follow-up of 46.7 months was, 4.5 months (range 2-70) for flutamide alone vs. 6.9 months (2.5-40; $P = .38$) with flutamide+vaccine. Seven patients in each arm had a >50% PSA response. Antigen-specific responses were similar in both arms (58% of patients in flutamide alone and 56% in flutamide+vaccine). The treatments were well tolerated. The most common side effect > grade 2 was injection site reaction seen in 29/31 vaccine patients which were self-limiting.

Conclusion: The combination of flutamide+PROSTVAC did not improve outcomes in men with nmCRPC compared with flutamide alone. (ClinicalTrials.gov Identifier: NCT00450463)

Key words: prostate cancer; immunotherapy; cancer vaccine; anti-androgen therapy.

Lessons Learned

The combination of flutamide+PROSTVAC was well tolerated but did not improve clinical or immunologic outcomes in men with nmCRPC compared with flutamide alone.

Discussion

This clinical trial in non-metastatic castration resistant prostate cancer was based on a previous study that suggested the sequential use of a pox viral-based vaccine with an androgen receptor antagonist could improve clinical outcomes.[1] Although first-generation anti-androgens, such as flutamide, do not have a survival benefit demonstrated in randomized trials, they were frequently used in this prostate cancer population (non-metastatic castration resistant or M0) prior to recent approvals of next generation anti-androgens.[2-4] In this trial, flutamide was chosen because it was less likely to be used in this population of prostate cancer than bicalutamide, potentiating greater accrual. PROSTVAC is a pox viral-based therapeutic cancer vaccine targeting PSA that contains transgeneses for 3 T-cell costimulatory molecules.[5] Since this study was launched, a phase III trial of PROSTVAC failed to demonstrate its ability as a single-agent therapy to improve survival in metastatic castration resistant prostate cancer.[6] More recent studies suggest that PROSTVAC alone without flutamide and androgen deprivation may have a delayed impact on PSA in men with

Received: 28 December 2022; Accepted: 10 February 2023.

a normal testosterone and rising PSA after surgery or radiation (ie, biochemically recurrent prostate cancer).[7]

Previous studies of PROSTVAC have demonstrated the ability to induce immunologic responses, but the findings in this study suggest that PSA-specific T cells were no different between the flutamide + PROSTVAC arm and the flutamide alone arm (56% vs 58%), respectively.[8] Furthermore, there were no differences in clinical outcomes. Emerging data provide possible explanations for the minimal impact of PROSTVAC when added to flutamide, beyond the possibility that PROSTVAC itself is ineffective. It is possible that flutamide has its own immunologic effects that may foster an immune response. This was suggested in a recent trial in biochemically recurrent prostate cancer where a modern anti-androgen, enzalutamide, demonstrated the ability to increase natural killer cells and decrease myeloid derived suppressor cells.[9] A separate study in castration resistant prostate cancer has suggested that targeting the androgen receptor with enzalutamide increased circulating glucocorticoids which may negatively impact the ability of PROSTVAC to activate T cells.[10]

In recent years, more modern anti-androgen therapies, such as enzalutamide, apalutamide, and darolutamide, have demonstrated clinical efficacy in this population of non-metastatic castration resistant prostate cancer.[2-4] In addition, clinical data supporting immune combinations with these agents remain elusive as demonstrated by the recent negative phase III trial of enzalutamide and atezolizumab in metastatic castration resistant prostate cancer.[11] Future studies may require a better understanding of how anti-androgens impact the immune system in order to develop immune combinations with optimal clinical efficacy.

Author disclosures and references available online.

Trial Information	
Disease	Prostate cancer
Stage of disease/treatment	Non-metastatic, castration resistant prostate cancer
Prior therapy	Previous anti-androgen was allowed, androgen deprivation therapy was required.
Type of study	Randomized phase II
Primary endpoint	Time to treatment failure
Secondary endpoints	Immune responses PSA responses
Investigator's analysis	Inactive because results did not meet primary endpoint

Drug Information				
multi-arm	**Arm 1—flutamide alone**	**Arm 2—flutamide and PROSTVAC-V/PROSTVAC-F**		
Generic/working name	Flutamide	Flutamide	PROSTVAC-V	PROSTVAC-F
Company name	Schering Plough	Schering Plough	Bavarian Nordic	Bavarian Nordic
Drug class	Anti-androgen	Anti-androgen	Cancer vaccine	Cancer vaccine
Dose	250	250	2×10^8	1×10^9
Unit	mg	Mg	Plaque forming units	Plaque forming units
Route	Oral	Oral	SC	SC
Schedule of administration	Every 8 hours	Every 8 hours	Initial dose only	Every 28 days after PROSTVAC-V

Patient Characteristics	Cohort name: flutamide alone
Number of patients, male	33
Number of patients, female	0
Stage	Non-metastatic castration resistant prostate cancer
Age: median	71.8 years
Performance status: ECOG	0: 33 1: 0 2: 0 3: 0 4: 0

Patient Characteristics	Cohort name: flutamide + PROSTVAC
Number of patients, male	31
Number of patients, female	0
Stage	Non-metastatic castration resistant prostate cancer
Age: median	69.8 years
Performance status: ECOG	0: 31 1: 0 2: 0 3: 0 4: 0

Primary Assessment Method

The patients had no evidence of metastatic disease at enrollment so RECIST was not used to assess responses. Thirty-three patients randomized to flutamide and 31 to flutamide+vaccine. The median age was 71.8 and 69.8 years, respectively. The median time to treatment failure after a median potential follow-up of 46.7 months was, 4.5 months (range 2-70) for flutamide alone vs. 6.9 months (2.5-40; P = .38) with flutamide+vaccine. Seven patients in each arm had a >50% PSA response. Antigen-specific responses were similar in both arms (58% of patients in flutamide alone and 56% in flutamide+vaccine). The treatments were well tolerated. The most common side effect > grade 2 was injection site reaction seen in 29/31 vaccine patients which were self-limiting.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's assessment	Inactive because results did not meet primary endpoint

This clinical trial in non-metastatic castration resistant prostate cancer was based on a previous study that suggested the sequential use of a pox viral-based vaccine with an androgen receptor antagonist could improve clinical outcomes.[1] Although first generation anti-androgens such as flutamide do not have a survival benefit demonstrated in randomized trials, they were frequently used in this prostate cancer population (non-metastatic castration resistant or M0) prior to recent approvals of next generation anti-androgens.[2-4] In this trial flutamide was chosen because it was less likely to be used in this population of prostate cancer than bicalutamide, potentiating greater accrual. PROSTVAC is a pox viral-based therapeutic cancer vaccine targeting PSA that contains transgeneses for 3 T-cell costimulatory molecules.[5] Since this study was launched, a phase III trial of PROSTVAC failed to demonstrate its ability as a single agent therapy to improve survival in metastatic castration resistant prostate cancer.[6] More recent studies suggest that PROSTVAC alone without flutamide and androgen deprivation may have a delayed impact on PSA in men with a normal testosterone and rising PSA after surgery or radiation (ie, biochemically recurrent prostate cancer).[7]

Previous studies of PROSTVAC have demonstrated the ability to induce immunologic responses, but the findings in this study suggest that PSA-specific T cells were no different between the flutamide + PROSTVAC arm and the flutamide alone arm (56% vs 58%), respectively.[8] Furthermore, there were no differences in clinical outcomes. Emerging data provides possible explanations for the minimal impact of PROSTVAC when added to flutamide, beyond the possibility that PROSTVAC itself is ineffective. It is possible that flutamide has its own immunologic effects that may foster an immune response. This was suggested in a recent trial in biochemically recurrent prostate cancer where a modern anti-androgen, enzalutamide, demonstrated the ability to increase natural killer cells and decrease myeloid derived suppressor cells.[9] A separate study in castration resistant prostate cancer has suggested that targeting the androgen receptor with enzalutamide increased circulating glucocorticoids which may negatively impact the ability of PROSTVAC to activate T cells.[10]

In recent years, more modern anti-androgen therapies such as enzalutamide, apalutamide, and darolutamide have demonstrated clinical efficacy in this population of non-metastatic castration resistant prostate cancer.[2-4] In addition, clinical data supporting immune combinations with these agents remains elusive as demonstrated by the recent negative phase III trial of enzalutamide and atezolizumab in metastatic castration resistant prostate cancer.[11] Future studies may require a better understanding of how anti-androgens impact the immune system in order to develop immune combinations with optimal clinical efficacy.

Funding

This study was sponsored by the National Cancer Institute. Prostvac was provided under a Cooperative Research and Development Agreement with Bavarian Nordic.

Conflict of Interest

Elizabeth Plimack reported advisory/consulting relationship with Astellas AstraZeneca Aveo BMS EMD Serono Exelixis IMV Merck Pfizer Regeneron Seattle Genetics Signatera Reserach: Genentech, Merck, and BMS. Tina Mayer reported consulting relationships with Aptitude Health, Exelexis, Impact Network, and ICON Clinical Research for AstraZeneca study, editorial compensation from Pfizer, and research funding from Merck and Sotio. The other authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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