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Molecular Cancer Therapeutics

Germline Variant in *SLCO2B1* and Response to Abiraterone Acetate Plus Prednisone (AA) in New-onset Metastatic Castration-resistant Prostate Cancer (mCRPC)

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Abstract

There are many treatment options available for men with metastatic castration-resistant prostate cancer (mCRPC). Yet, biomarkers predictive of differential response to treatment are currently unavailable. A recent translational study suggested that *SLCO2B1* genotype could predict response to abiraterone acetate for men with advanced prostate cancer. Here, we investigate whether germline variants in *SLCO2B1* are predictive of response to first-line abiraterone acetate in men with new mCRPC. Clinical data and samples were analyzed from a prospective prostate cancer registry at the University of Utah (Salt Lake City, UT). Genotyping was performed using the Illumina OmniExpress genotyping platform. Primary endpoint was progression-free survival (PFS) on first-line abiraterone acetate in men with mCRPC. We performed a prespecified multivariate Cox regression analysis to assess the independent predictive value of rs12422149 and rs1789693 on PFS on abiraterone acetate. Of 401 men with advanced prostate cancer genotyped, 323 were homozygous wild-type for rs12422149 (80.5%), 74 were heterozygous (18.5%), and 4 were homozygous variant (1.0%). In a multivariate analysis of 79 men treated with first-line abiraterone acetate for mCRPC, men heterozygous for rs12422149 had significantly improved median PFS compared with the homozygous wild-type group (8.9 months vs. 6.3 months; HR, 0.46; 95% confidence interval, 0.23–0.94; $P = 0.03$). No significant difference in median PFS was seen by rs1789693 genotype. In this first clinical validation of translational data reported by Mostaghel and colleagues, germline variant alleles in rs12422149 of *SLCO2B1* are common and predict improved response to first-line abiraterone acetate in men with mCRPC.

Introduction

Prostate cancer is the most common cancer in men in the United States, and metastatic prostate cancer is generally considered an incurable disease (1). Once men are diagnosed with metastatic prostate cancer, the majority will progress to metastatic castration-resistant prostate cancer (mCRPC). Currently, there are six treatments approved for the treatment of mCRPC (abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, radium-223, and sipuleucel-T), and more novel treatments are currently under investigation (2). Moreover, some of the treatments for mCRPC, abiraterone acetate and docetaxel, are now also approved for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC; ref. 3). With so many options available across treatment of metastatic prostate cancer, biomarkers predictive of differential response to treatment are needed and could improve patient selection and outcomes in men with metastatic prostate cancer.

SLCO2B1 encodes transporter proteins that mediate cellular uptake of numerous drugs and hormones, including testosterone, DHEA sulfate, and abiraterone acetate (4–6). Initially, SNPs in *SLCO2B1* were shown to be a validated, predictive biomarker of time to progression on androgen deprivation therapy (ADT) in patients with mHSPC and biochemical recurrence (5, 7, 8). In a more recent translational study, Mostaghel and colleagues found that SNPs in *SLCO2B1* were associated with higher abiraterone acetate levels in prostate tissue and higher rates of pathologic minimal residual disease on prostatectomy (6). These findings suggested that *SLCO2B1* genotype could predict response to abiraterone acetate for patients with metastatic prostate cancer. Herein, we investigate whether variant alleles in rs12422149 and rs1789693 of SLCO2B1 are predictive of improved response to first-line abiraterone acetate for mCRPC.

Materials and Methods

From a prospectively maintained, institutional review board–approved prostate cancer registry at the University of Utah (Salt Lake City, UT), we determined the genotype of *SLCO2B1* SNPs rs12422149 and rs1789693 retrospectively in men with advanced prostate cancer. Genotyping was performed using the Illumina OmniExpress genotyping platform. We then identified men with mCRPC who received first-line abiraterone as standard of care and

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correlated genotype with response to abiraterone. The primary endpoint was progression-free survival (PFS) on first-line abiraterone, defined as two consecutive increases in the PSA level meeting the following criteria: ≥2 ng/mL and ≥25% increase from the nadir, as defined by the prostate cancer working group 2, and/or radiographic or clinical progression. We analyzed PFS using Kaplan–Meier methods. We performed a prespecified multivariate Cox regression analysis to assess the independent predictive value of rs12422149 and rs1789693 on PFS on abiraterone acetate. Genotype and phenotype data are available under a GEO accession number GSE123695.

Results

Of the 401 men with advanced prostate cancer and *SLCO2B1* rs12422149 genotyping available, 323 were homozygous wild-type (GG, 80.5%), 74 men were heterozygous (AG, 18.5%), and 4 men were homozygous variant (AA, 1.0%). Among the 79 men treated with first-line abiraterone acetate for mCRPC, no significant difference in baseline characteristics was seen by rs12422149 genotype (Table 1). In a multivariate analysis, men heterozygous for rs12422149 had significantly improved median PFS on first-line abiraterone acetate compared with the homozygous wild-type group [8.9 months vs. 6.3 months; HR, 0.46; 95% confidence interval (CI), 0.23–0.94, $P = 0.03$; Table 1; Fig. 1]. Among men treated with first-line abiraterone acetate, none were homozygous variant for rs12422149.

Of the 398 men with advanced prostate cancer and *SLCO2B1* rs1789693 genotyping available, 174 were homozygous wild-type (TT, 43.7%), 170 were heterozygous (AT, 42.7%), and 54 were homozygous variant (AA, 13.6%). Among the 79 men treated with first-line abiraterone acetate, no significant difference in baseline characteristics was seen by rs1789693 genotype (Table 2). Furthermore, in a multivariate analysis, no significant difference in median PFS was seen by rs1789693 genotype (Table 2; Fig. 2).

Table 1. Baseline characteristics by *SLCO2B1* rs12422149 genotype and response to abiraterone acetate

	rs12422149 GG ($n = 63$)	rs12422149 AG ($n = 16$)	rs12422149 AA ($n = 0$)	P^a
log PSA at abiraterone initiation	3.22 (1.47)	3.60 (1.40)	NA	0.36
Gleason grade				0.35
4	2 (3%)	0	0	
5–6	4 (6%)	3 (19%)	0	
7	14 (22%)	2 (12%)	0	
8–10	43 (69%)	11 (69%)	0	
Cox regression results				
Median PFS (months)	6.3	8.9	N/A	
Hazard ratio	1.0	0.462 ($P = 0.034$)	N/A	
95% CI	N/A	0.23–0.94	N/A	

[a]*P* values are comparisons across the two observed genotypes.

Discussion

Currently, many treatment options exist for men with mCRPC. Despite the widespread availability of germline and somatic next-generation sequencing, predictive biomarkers are not routinely used to optimize treatment selection in metastatic prostate cancer. Here, we report the first clinical validation showing that germline variant alleles in rs12422149 of *SLCO2B1* predict improved response to first-line abiraterone acetate for mCRPC. Furthermore, we demonstrate that variant alleles in rs12422149 are present in about 20% of men with advanced prostate cancer. These findings could significantly improve treatment selection for men with mCRPC, and may even have the potential to help guide treatment selection between docetaxel and abiraterone for men with mHSPC. While our findings require independent validation, there is translational evidence to support our findings, which makes *SLCO2B1* a promising biomarker for response to abiraterone acetate in advanced prostate cancer.

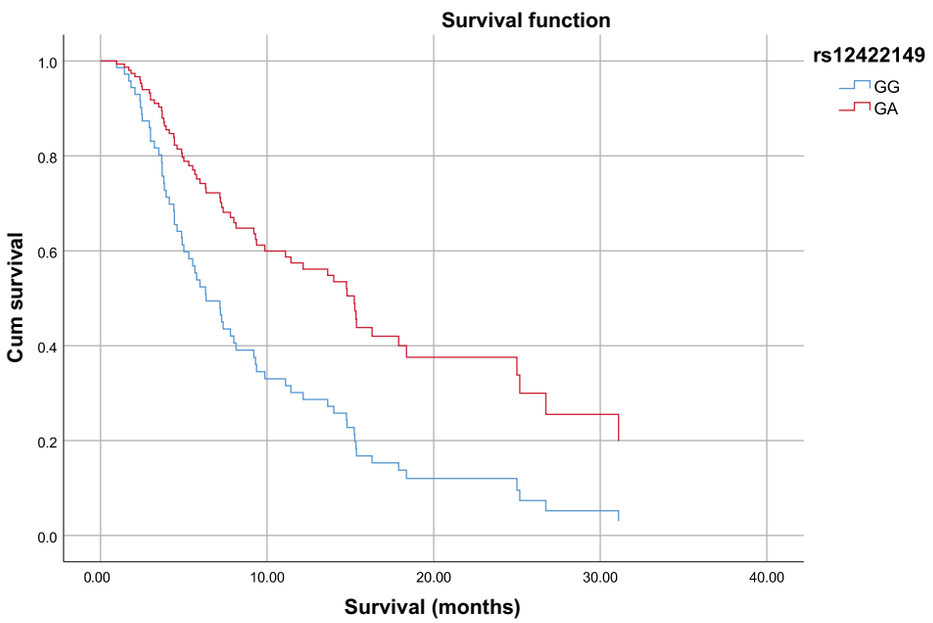

Figure 1.
PFS on first-line abiraterone acetate by *SLCO2B1* rs12422149 genotype. The figure shows that men with mCRPC who are heterozygous (AG) for rs12422149 have improved PFS on first-line abiraterone acetate compared with men who are homozygous wild-type (GG) for rs12422149.

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Table 2. Baseline characteristics by *SLCO2B1 rs*1789693 genotype and response to abiraterone acetate

	***rs*1789693 AA (*n* = 34)**	***rs*1789693 AT (*n* = 38)**	***rs*1789693 TT (*n* = 7)**	***P*[a]**
log PSA at abiraterone initiation	2.94 (1.61)	3.70 (1.31)	2.89 (0.82)	0.065
Gleason grade				0.37
4	0 (0%)	2 (5%)	0 (0%)	
5–6	5 (15%)	1 (3%)	1 (14%)	
7	5 (15%)	9 (24%)	2 (28%)	
8–10	24 (70%)	26 (68%)	4 (57%)	
Cox regression results				
Median PFS (months)	5.65	6.93	13.63	
Hazard ratio	1.0	1.10 ($P = 0.75$)	0.77 ($P = 0.59$)	
95% CI	N/A	0.63–1.91	0.29–2.01	

[a]*P* values are comparisons across the three genotypes.

Translational research by Mostaghel and colleagues led to our hypothesis that germline variant alleles in *SLCO2B1* SNPs could predict response to first-line abiraterone acetate in mCRPC (6). In their study, Mostaghel and colleagues evaluated the effect of *SLCO2B1* genotype on tissue abiraterone acetate levels in a cohort of men with intermediate- or high-risk localized prostate cancer randomized to neoadjuvant ADT or neoadjuvant ADT plus abiraterone acetate. They found that the AA/AG genotypes of rs12422149 were associated with higher mean tissue abiraterone acetate levels than the GG genotype (258 pg/mg vs. 99 pg/mg; $P = 0.03$). The authors also showed that higher tissue abiraterone acetate levels were associated with improved PSA and pathologic response after radical prostatectomy. Thus, we hypothesized that the AG genotype of rs12422149 would predict improved response to first-line abiraterone acetate because these men have higher tissue abiraterone acetate levels, and our results confirmed this hypothesis. Compared with localized prostate cancer, castration-resistant prostate cancer (CRPC) has increased expression of CYP17A1. This suggests that in men with CRPC the *SLCO2B1* genotype will have a more profound effect on response to abiraterone acetate than was previously observed in localized disease.

While our findings on rs12422149 are consistent with Mostaghel and colleagues' previous study, we could not confirm their observations for rs1789693 of *SLCO2B1*. In their study, the TT/AT genotype of rs1789693 was associated with lower tissue abiraterone acetate levels (59 pg/mg vs. 172 pg/mg; $P = 0.0008$). Thus, we hypothesized that the TT/AT genotype of rs1789693 would predict inferior response to abiraterone acetate. However, we did not observe a significant difference in response to abiraterone acetate based upon rs1789693 genotype.

SLCO2B1 has also been evaluated in other settings of advanced prostate cancer. Statins are a well-known substrate for *SLCO2B1*. An early study demonstrated that statins could competitively inhibit *SLCO2B1* (9). Thus, many hypothesized that statins could interfere with abiraterone acetate efficacy because both drugs are transported by *SLCO2B1*. However, a multi-institutional, retrospective study by Harsman and colleagues showed that statins do not interfere with abiraterone acetate efficacy (10). In addition to its previously discussed roles, the SNP rs12422149 of *SLCO2B1* is a validated, predictive biomarker of response to ADT for biochemically recurrent and mHSPC (Table 3; refs. 5, 7, 8). Because rs12422149 of *SLCO2B1* is predictive of response to ADT and abiraterone acetate without matched controls, it is possible that

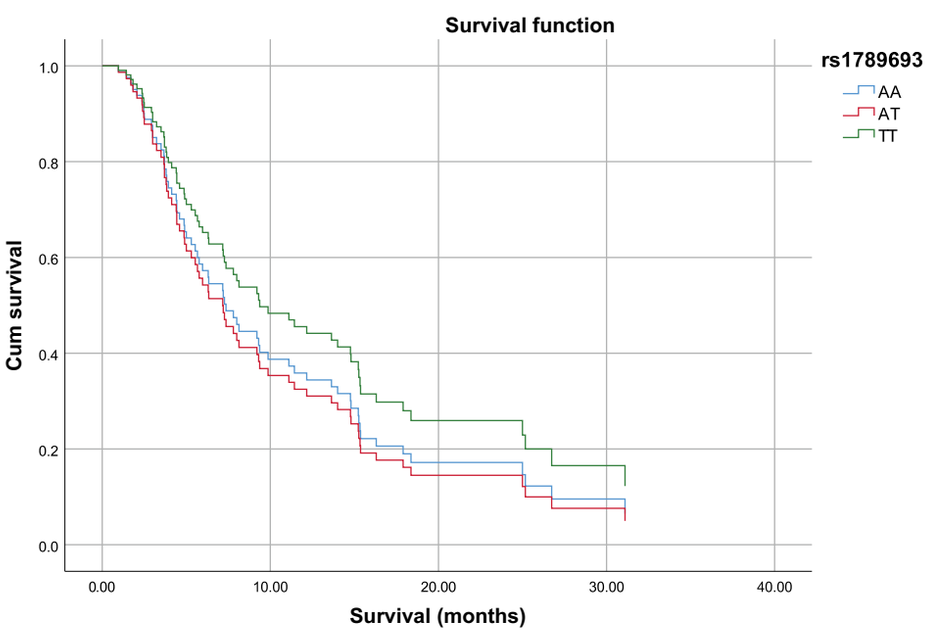

Figure 2.
PFS on first-line abiraterone acetate by *SLCO2B1* rs1789693 genotype. The figure shows that PFS on first-line abiraterone acetate does not significantly differ by *SLCO2B1* rs1789693 genotype.

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Table 3. *SLCO2B1* rs12422149 genotype and response to ADT

Population	Tx	Clinical outcome	Result	HR	*P*
mHSPC + BR	ADT	TTP	21 m for GG vs. 32 m for AA/AG	1.40	0.018
mHSPC + BR	ADT	TTP	20 m for GG vs. 27 m for AA/AG	1.31	0.049
mHSPC + BR	ADT	TTP	10 m for GG vs. 17 m for AA/AG	N/A	0.028

Abbreviations: BR, biochemical recurrence; Tx, treatment.

SLCO2B1 is a prognostic biomarker of improved outcomes in metastatic prostate cancer. Germline DNA testing for men with metastatic prostate cancer is becoming more prevalent, and approximately 1 of every 5 men with advanced prostate has germline variant alleles in rs12422149 of *SLCO2B1*, which have the potential to guide treatment selection in mHSPC and mCRPC. For these reasons, independent and prospective validation of germline variant alleles in rs12422149 of *SLCO2B1* is feasible and necessary. Future studies are needed to determine the role of rs12422149 of *SLCO2B1* in management of metastatic prostate cancer and include a validation cohort with matched controls and randomized clinical trials in patients treated with abiraterone acetate.

Limitations of this study include its retrospective design, small study population, and lack of correlative abiraterone acetate tissue levels. Strengths of this study include the uniform patient population receiving first-line treatment for mCRPC and previous translational research providing rationale for the observed effects of germline variants in rs12422149 of *SLCO2B1*.

Conclusion

In this first clinical validation of translational data reported by Mostaghel and colleagues, germline variant alleles in rs12422149 of *SLCO2B1* are common and predict improved response to first-line abiraterone acetate in men with mCRPC. These findings have the potential to guide treatment selection for mCRPC, but they require independent validation first.

Disclosure of Potential Conflicts of Interest

A. Poole is a consultant/advisory board member for Novartis. N. Agarwal is a consultant/advisory board member for Pfizer, Novartis, Astellas, Eli Lilly, Bayer, Merck, Genentech, Eisai, Exelixis, Clovis, EMD Serono, BMS, and AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.W. Hahn, R.H. Nussenzveig, J.M. Farnham, R.A. Stephenson, B.L. Maughan, N. Agarwal
Writing, review, and/or revision of the manuscript: A.W. Hahn, D.M. Gill, R.H. Nussenzveig, S. Wilson, J.M. Farnham, R.A. Stephenson, B.L. Maughan, N. Agarwal
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Study supervision: L.A. Cannon-Albright, N. Agarwal

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