Genetic Drivers of Quality Of Life in Prostate Cancer - An Evaluation of Genetic Polymorphisms, Patient Reported Outcomes, and Adverse Events in E3805 CHAARTED trial

Daniel Sentana Lledo[1], Xiangying Chu[2], Arjun Gupta[3], Christopher J. Sweeney[4], David F. Jarrard[5], Elizabeth R. Plimack[6], Benjamin A. Gartrell[7], Michael A. Carducci[8], Maha Hussain[9], Jorge A. Garcia[10], David Cella[9], Robert S. DiPaola[11], Alicia K. Morgans[1]

1. Dana-Farber Cancer Institute, Boston, MA. 2. ECOG-ACRIN Biostatistics Center, Boston, MA. 3. University of Minnesota, Minneapolis, MN. 4. South Australian Immunogenomics Cancer Institute/University of Adelaide, SA, Australia. 5. University of Wisconsin, Madison, WI. 6. Fox Chase Cancer Center, Philadelphia, PA. 7. Montefiore Center for Cancer Care, Bronx, NY. 8. Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD. 9. Northwestern University, Chicago, IL. 10. Case Western Comprehensive Cancer Center, Cleveland, OH. 11. University of Kentucky, Lexington, KY.

Funding acknowledgements: This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, UG1CA189859, UG1CA233180, UG1CA233196, UG1CA233234, UG1CA233277, and UG1CA233320. Additional funding from Prostate Cancer Foundation Grant 17CHAL04 and Sanofi.

COI Disclosure Statement: DS on behalf of co-authors states no relevant conflict of interests regarding this work.

Background:

Single nucleotide polymorphisms (SNP) of genes associated with neurotransmitter metabolism have been linked with patients' perception of symptoms derived from cancer treatment. SNP rs4680 of the Carboxy-O-MethylTransferase (COMT) gene results in reduced clearance of dopamine, leading to improved mood and decreased symptoms in non-cancer populations. We previously shared preliminary results of the association between COMT function and quality of life (QOL) in patients with metastatic hormone positive prostate cancer (mHSPC) in the E3805 CHAARTED trial. Here we further define the effect of androgen deprivation therapy (ADT) in QOL of patients with or without COMT rs4680.

Methods:

This pre-planned post-hoc analysis of the E3805 trial (ADT ± docetaxel in men with mHSPC) assessed the effect of COMT wildtype (WT) vs rs4680 in QOL using several patient-reported outcome measurements (PROM), including the Functional Assessment of Cancer Therapy – Prostate (FACT-P), -Fatigue (FACIT-F) and Brief Pain Inventory (BPI). PROMs were collected at baseline, 3, 6, 9 and 12 months. Blood samples for genotyping were collected prior to treatment start. Descriptive statistics characterized QOL over time, while Fisher's exact test, Wilcoxon rank sum test, and mixed effects models were used to evaluate the associations between rs4680 and QOL in each arm.

Results:

550 participants with SNP data (of 790 total) were included in the analysis. There was no independent association of COMT rs4680 with FACT-P, FACIT-F, or BPI scores in all patients during the 12-month period. When accounting for treatment arm, there were no differences seen in QOL in patients with rs4680 treated with ADT+D. However, compared to COMT WT, patients with rs4680 treated with ADT experienced improved QOL at 6 months (128.9 vs 118.5, $p = 0.04$), less pain at 3 months (no pain 70.4% vs 41.5%, $p = 0.01$), and less interference by pain at the 3-month (no interference 76% vs 51.3%, $p = 0.03$), 6-month (75% vs 48.7%, $p = 0.02$), and 9-month timepoints (83.3% vs 52%, $p = 0.02$). There were no difference

in FACIT-F scores in patients with COMT rs4680, nor new trends identified in the top and bottom quartiles of QOL by rs4680.

Conclusions:

Compared to patients with COMT WT, patients with COMT rs4680 experienced less pain and improved global QOL in the months after starting treatment with ADT. This is the first study to show that polymorphisms in genes affecting neurotransmitter metabolism can influence patients' QOL while receiving ADT. Future studies can validate these findings in other prostate cancer populations, and ultimately help incorporate COMT genotyping into decision-making on patient's expected side effects and QOL outcomes.

Table 1. Association between COMT rs4680 and FACT-P

Median (range) FACT-P scores	ADT			ADT+D		
	rs4680*	WT	p-value	rs4680*	WT	p-value
Baseline	130 (43.7, 152)	123.5 (46, 153.9)	0.14	120.1 (58, 148.9)	125.0 (47, 156)	0.15
3-month	127 (81, 155)	123.9 (45, 154)	0.15	117.0 (67, 155)	120.0 (39.6, 150.8)	0.50
6-month	128.9 (82, 151)	118.5 (60, 156)	**0.04**	116.5 (66.4, 153)	121.2 (54, 153)	0.37
9-month	129 (80, 149.7)	122 (29.8, 154.8)	0.15	118.0 (76, 154)	123.0 (40.2, 154.9)	0.52
12-month	121 (70, 149)	120 (56, 156)	0.66	125.0 (54.5, 152)	123.0 (52, 156)	0.92

*rs4680 (0=AA), WT (1=GA, 2=GG)