

## **Plasma gene conversions after 1 cycle abiraterone acetate(AA) for metastatic castration-resistant prostate cancer (mCRPC): a biomarker analysis of a multi-centre, international trial**

**A. Jayaram**<sup>1</sup>, D. Shen<sup>2</sup>, A. Wingate<sup>1</sup>, D. Wetterskog<sup>1</sup>, C. Sternberg<sup>3</sup>, R. Jones<sup>4</sup>, A. Berrutis<sup>5</sup>, F. Lefresne<sup>6</sup>, M. Lahaye<sup>6</sup>, S. Thomas<sup>2</sup>, S. Joshi<sup>7</sup>, M. Gormley<sup>2</sup>, B. Tombal<sup>8</sup>, A. Merseburger<sup>9</sup>, D. Ricci<sup>2</sup>, G. Attard<sup>1</sup>

<sup>1</sup>Treatment Resistance- Department of Oncology, UCL Cancer Institute, London, United Kingdom, <sup>2</sup>Janssen Research and Development, Spring House Pa, AL, United States of America, <sup>3</sup>Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, United States of America, <sup>4</sup>The Beatson West Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom, <sup>5</sup>Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili Hospital, Brescia, Italy, <sup>6</sup>Janssen Research and Development, Beerse, Belgium, <sup>7</sup>HireGenics, Duluth, Ga, AL, United States of America, <sup>8</sup>Institut de Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium, <sup>9</sup>Department Urology, University Hospital Schleswig-Holstein, Campus Lübeck, Lubeck, Germany

### **Background**

A number of genomic alterations detected in plasma DNA have been associated with worse outcome in mCRPC. We hypothesized that patients (pts) who harbored a genomic alteration that decreased after 1 cycle (C) treatment derived clinical benefit and this would distinguish them from truly resistant pts.

### **Methods**

Plasma DNA (128 C1 day (D)1, 134 C2 D1, and 41 progression [PD] from chemotherapy-naïve mCRPC pts in a Phase 2 study of AA (NCT01867710), were subjected to custom targeted-capture NGS. Assay was optimised to detect pathogenic point mutations (PM), deletions and copy number alterations (CNA) in *AR*, *TP53*, *RB1*, *PIK3CA* and *DNA repair deficient genes (DRD)*: *BRCA1*, *BRCA2*, *FANCA*, *ATM*, *CHEK2*, *HDAC2*, *BRIP1*, and *PALB2*. Pts were followed up for overall survival (OS) and radiographic progression-free survival (rPFS) (48 months).

### **Results**

Pts were classified into 4 groups based on whether a gene alteration was detectable (+) or not (-) at C1D1 and C2D1 respectively. At C1D1 49pts (37.5%) had + alterations. Pts who converted from + to - (+/-) had similar outcomes as pts who remained - (-/-) and those that did not convert had worst outcomes (+/+) (Table). In matched C1D1 and PD samples pts with *AR* gain (G) at C1D1 were more *AR* G at PD ( $p < 0.01$ ) while *AR* PM were only detected in PD samples that were *AR* normal (N) at C1D1. DRD + pts at C1D1 were more likely DRD + at PD ( $p < 0.1$ ).

Gene conversion (N)	C2 Conversion (%)	rPFS				OS			
		p	HR	95.0% CI		p	HR	95.0% CI	
<b>C1D1 + vs -</b>		<0.01	2.0	1.23	3.30	<0.01	2.5	1.51	4.27
<b>TP53</b> -/- (85) vs +/- (16) +/(8) vs +/-	60.7	0.23 0.07	1.4 2.2	0.74 0.73	2.77 6.7	0.7 <0.01	1.2 4.2	0.55 1.10	2.51 16.44
<b>AR</b> -/(88) vs +/- (16) +/(7) vs +/-	69.6	0.46 <0.01	1.3 3.3	0.61 0.9	2.7 11.4	0.09 0.07	1.8 2.5	0.79 0.65	3.91 9.84
<b>RB1</b> -/(92) vs +/- (12) +/(6) vs +/-	66.67	0.79 <0.01	1.1 5.7	0.5 1.11	2.4 29.1	0.37 <0.01	1.4 5.6	0.60 0.92	3.27 34.26
<b>DRD</b> -/(96) vs +/- (10) +/(4) vs +/-	73.3	0.85 0.03	0.9 4.4	0.44 0.29	2.0 69.1	1.0 <0.01	1.0 4.7	0.43 0.72	2.36 30.39
<b>PIK3CA</b> +/(100) vs +/- (5) +/(5) vs +/-	50	0.02 0.29	2.7 1.9	0.65 0.51	11.37 6.85	0.06 0.7	2.6 1.3	0.54 0.32	12.33 5.2

## Conclusions

These findings suggest that tracking gene aberrations in plasma DNA could be an early marker of treatment efficacy.

## Funding Acknowledgments

The PCR2023 study was supported by Janssen. A.J. is supported by a Medical Research Council Clinical Research Training Fellowship. G.A. is supported by a Cancer Research UK Advanced Clinician Scientist Fellowship.

## Conflicts of Interest

**Anna Wingate:** Research Funding: Janssen (Inst) Travel, Accommodations, Expenses: Janssen

**Alfredo Berruti:** Consulting or Advisory Role: Janssen-Cilag, Astellas Pharma

Speakers' Bureau: Janssen-Cilag Research Funding: Astellas Pharma (Inst), Janssen-Cilag (Inst) Travel, Accommodations, Expenses: Janssen-Cilag, Sanofi

### **Cora N. Sternberg:**

Honoraria: Pfizer, Astellas Pharma, Sanofi, Ipsen, AstraZeneca. Janssen

Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Bayer, Eisai, MSD, Clovis Oncology, Pfizer, Roche, Ipsen, Incyte, AstraZeneca, Sanofi, Merck, Medscape, UroToday

Research Funding: Janssen (Inst), Genentech (Inst), Bayer (Inst), Sanofi (Inst), Medivation (Inst), Exelixis (Inst), Genzyme (Inst), Aragon Pharmaceuticals (Inst), Array BioPharma (Inst), Aveo (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Clovis Oncology (Inst), Eisai (Inst), Genentech (Inst), GlaxoSmithKline (Inst), Eli Lilly (Inst), Incyte (Inst), Merck (Inst), Millennium (Inst), Myovant Sciences (Inst), Nektar (Inst), Pfizer (Inst), Clovis Atlas (Inst)

### **Rob Jones:**

Honoraria: Astellas Pharma, Janssen, AstraZeneca, MSD Oncology, Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Seattle Genetics, Sanofi, Bayer, Genentech, Eusa Pharma, Pharmacyclics

Consulting or Advisory Role: Clovis Oncology

Research Funding: Roche (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), Pfizer (Inst), Novartis (Inst), Exelixis (Inst), Clovis Oncology (Inst)

Travel, Accommodations, Expenses: Ipsen, Bayer, Janssen, Astellas Pharma, MSD Oncology

**Florence Lefresne:**

Employment: Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Honoraria: Johnson & Johnson

Research Funding: Johnson & Johnson

Travel, Accommodations, Expenses: Johnson & Johnson

**Marjolein Lahaye:**

Employment: Janssen-Cilag

Leadership: Janssen-Cilag

Stock and Other Ownership Interests: Janssen-Cilag

Honoraria: Janssen-Cilag

Consulting or Advisory Role: Janssen-Cilag

**Shibu Thomas**

Employment: Janssen Research & Development

Leadership: Janssen Research & Development

Stock and Other Ownership Interests: Janssen Research & Development

Research Funding: Janssen Oncology

Patents, Royalties, Other Intellectual Property: Four patents (Inst)

Travel, Accommodations, Expenses: Janssen Research & Development

**Dong Shen**

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Janssen Research & Development

**Deborah Ricci:**

Employment: Janssen

Stock and Other Ownership Interests: Janssen

Patents, Royalties, Other Intellectual Property: Janssen (Inst)

Travel, Accommodations, Expenses: Janssen

**Michael Gormley:**

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Johnson & Johnson

Patents, Royalties, Other Intellectual Property: I have several patents pending where I am listed as the inventor that have been developed in the course of my work at Janssen Research and Development (Inst)

Travel, Accommodations, Expenses: Janssen Research & Development

**Axel S. Merseburger**

Honoraria: Janssen-Cilag, Astellas Pharma, Ipsen, Roche, Bristol-Myers Squibb, Eisai, Takeda, Pfizer, Novartis

Consulting or Advisory Role: MSD Oncology, Bristol-Myers Squibb, Janssen-Cilag, Astellas Pharma, Ipsen

Speakers' Bureau: Ipsen

Research Funding: Novartis (Inst), AstraZeneca (Inst), Janssen-Cilag (Inst), Bristol-Myers Squibb (Inst), Clovis Oncology (Inst)

Travel, Accommodations, Expenses: Janssen-Cilag, Astellas Pharma, Ipsen

**Bertrand Tombal**

Honoraria: Amgen, Astellas Pharma, Bayer, Ferring, Sanofi, Janssen, Pfizer, Myovant Sciences

Consulting or Advisory Role: Astellas Pharma, Bayer, Ferring, Janssen, Takeda, Steba Biotech, Sanofi

Speakers' Bureau: Amgen, Janssen

Research Funding: Ferring (Inst)

Travel, Accommodations, Expenses: Amgen, Astellas Pharma, Bayer, Ferring, Janssen, Sanofi

**Gerhardt Attard**

Honoraria: Janssen, Astellas Pharma, Janssen (I)

Consulting or Advisory Role: Janssen-Cilag, Veridex, Ventana Medical

Systems, Astellas Pharma, Medivation, Novartis, Millennium, Abbott Laboratories, ESSA, Bayer, Pfizer

Speakers' Bureau: Janssen, Astellas Pharma, Takeda, Sanofi, Ventana Medical Systems

Research Funding: Janssen (Inst), Arno Therapeutics (Inst), Innocrin Pharma (Inst)

Patents, Royalties, Other Intellectual Property: I am on the Institute of Cancer Research Rewards to Inventors list of abiraterone acetate

Travel, Accommodations, Expenses: Janssen, Astellas Pharma,

Medivation, Ventana Medical Systems, Abbott Laboratories, Bayer, ESSA, Janssen (I), Astellas Pharma (I), Pfizer

Other Relationship: Institute of Cancer Research