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. Jayaram1, D. Shen2, A. Wingate1, D. Wetterskog1, C. Sternberg1, R. Jones4, A. Berruti5, F. Lefresne6, M. Lahaye6, S. Thomas2, S. Joshi7, M. Gormley2, B. Tombal8, A. Merseburger9, D. Ricci2, G. Attard1

1Treatment Resistance- Department of Oncology, UCL Cancer Institute, London, United Kingdom, 2Janssen Research and Development, Spring House Pa, AL, United States of America, 3England Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, United States of America, 4The Beatson West Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom, 5Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili Hospital, Brescia, Italy, 6Janssen Research and Development, Beerse, Belgium, 7HireGenics, Duluth, Ga, AL, United States of America, 8Institut de Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium, 9Department 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 (+/+). 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=0.01).
<table>
<thead>
<tr>
<th>Gene conversion (N)</th>
<th>C2 Conversion (%)</th>
<th>rPFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1D1 + vs -</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-/- (85) vs +/- (16)</td>
<td>60.7</td>
<td>0.23</td>
<td>1.4</td>
</tr>
<tr>
<td>+/+(8) vs +/-</td>
<td>0.07</td>
<td>2.2</td>
<td>0.73</td>
</tr>
<tr>
<td>AR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-/- (88) vs +/- (16)</td>
<td>69.6</td>
<td>0.46</td>
<td>1.3</td>
</tr>
<tr>
<td>+/- (7) vs +/-</td>
<td>&lt;0.01</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>RB1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-/- (92) vs +/- (12)</td>
<td>66.67</td>
<td>0.79</td>
<td>1.1</td>
</tr>
<tr>
<td>+/- (6) vs +/-</td>
<td>&lt;0.01</td>
<td>5.7</td>
<td>1.11</td>
</tr>
<tr>
<td>DRD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-/- (96) vs +/- (10)</td>
<td>73.3</td>
<td>0.85</td>
<td>0.9</td>
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<tr>
<td>+/- (4) vs +/-</td>
<td>0.03</td>
<td>4.4</td>
<td>0.29</td>
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<tr>
<td>PIK3CA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+/- (100) vs +/- (5)</td>
<td>50</td>
<td>0.02</td>
<td>2.7</td>
</tr>
<tr>
<td>+/- (5) vs +/-</td>
<td>0.29</td>
<td>1.9</td>
<td>0.51</td>
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</tbody>
</table>

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

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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:
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Florence Lefresne:
Employment: Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Honouraria: 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

Honouraria: 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
Honouraria: 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

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

Bertrand Tombal
Honouraria: 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
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