

13570

# **Biomarker analysis and updated results from the Phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)**

F. Saad<sup>1</sup>, A.J. Armstrong<sup>2</sup>, A. Thiery-Vuillemin<sup>3</sup>, M. Oya<sup>4</sup>, N.D. Shore<sup>5</sup>, G. Procopio<sup>6</sup>, C. Arslan<sup>7</sup>, N. Mehra<sup>8</sup>, F. Parnis<sup>9</sup>, E. Brown<sup>10</sup>, F. Constans Schlurmann<sup>11</sup>, J.Y. Joung<sup>12</sup>, M. Sugimoto<sup>13</sup>, O. Sartor<sup>14</sup>, Y-Z. Liu<sup>15</sup>, C.H. Poehlein<sup>16</sup>, C. Desai<sup>17</sup>, P.M.D. Del Rosario<sup>17</sup>, N. Clarke<sup>18</sup>

<sup>1</sup> Department of Urology, Centre Hospitalier de l'Université de Montréal/CRCHUM, Université de Montreal, Montreal, QC, Canada, <sup>2</sup> Department of Medicine, Duke Cancer Institute Center, Durham, NC, USA, <sup>3</sup> Medical Oncology Department, CHRU Besançon Hôpital J.Minjoz, Besancon, France, <sup>4</sup> Department of Urology, Keio University School of Medicine, Tokyo, Japan, <sup>5</sup> Surgery and Oncology, Carolina Urologic Research Center, Myrtle Beach, SC, USA, <sup>6</sup> Medical Oncology Department, Istituto Nazionale per Cura Tumori Milano, Milan, Italy, <sup>7</sup> Medical Oncology Department, Izmir Economy University Medical Park Hospital, Karsiyaka, Turkey, <sup>8</sup> Medical Oncology Department, Radboud Universitair Medisch Centrum, Nijmegen, Netherlands, <sup>9</sup> Medical Oncology Department, Ashford Cancer Centre Research, Kurralta Park, SA, Australia, <sup>10</sup> Medical Oncology Department, University Hospital Southampton, Southampton, UK, <sup>11</sup> Medical Oncology Department, Centre Hospitalier de Cornouaille, Quimper, France, <sup>12</sup> Center for Urological Cancer, National Cancer Center, Goyang-si, Republic of Korea, <sup>13</sup> Urology Department, Kagawa University Hospital, Kagawa, Japan, <sup>14</sup> Hematology/Oncology Department, Tulane Cancer Center, New Orleans, LA, USA, <sup>15</sup> Precision Medicine, Oncology R&D, AstraZeneca, Cambridge, UK, <sup>16</sup> Clinical Research, Merck & Co., Inc., Rahway, NJ, USA, <sup>17</sup> Global Medicines Development, Oncology R&D, AstraZeneca, Cambridge, UK <sup>18</sup> Department of Urology, The Christie and Salford Royal NHS Foundation Trusts, Manchester, UK

## **Background**

At the primary analysis of PROpel (NCT03732820; data cut-off [DCO]: 30/07/21), abi + ola significantly prolonged radiographic progression-free survival (rPFS) vs pbo + abi in 1L mCRPC (HR 0.66, 95% CI 0.54–0.81; P<0.0001). Overall survival (OS) trended towards a benefit with abi + ola vs abi + pbo (28.6% maturity; HR 0.86, 95% CI 0.66–1.12). We report biomarker analysis from the primary analysis and updated overall survival and safety data from a planned OS interim analysis (DCO2).

## **Methods**

PROpel is a double-blind, pbo-controlled trial. 796 pts were randomized 1:1 to ola (300 mg twice daily [bid]) or pbo, and abi (1000 mg once daily) + prednisone or prednisolone (5 mg bid), irrespective of homologous recombination repair gene mutation (HRRm) status. The primary endpoint was rPFS by investigator assessment. OS was a key secondary endpoint. Aggregated results from tumour tissue (FoundationOne®CDx) and circulating tumour DNA (FoundationOne®Liquid CDx) tests were used to classify pts HRRm status.

## **Results**

Pts with HRRm, including BRCAm, were balanced between treatment arms and rPFS favoured abi + ola for all biomarker subgroups, including pts with non-HRRm, HRRm and BRCAm status (HR 0.76, 0.50 and 0.23 respectively; Table). Sensitivity analysis of rPFS by blinded independent central review was consistent. At DCO2 (14/03/22) rPFS was consistent with the primary analysis (25.0 vs 16.4 months; HR 0.67, 95% CI 0.56–0.81). A trend towards improved OS with abi + ola vs abi + pbo continued (maturity 40%; HR 0.83; 95% CI 0.66–1.03). Safety and tolerability results remained stable.

## **Conclusions**

Meaningful rPFS improvement of ≥5 months was observed with abi + ola vs abi + pbo in all assessed biomarker subgroups. Updated results show a continuing trend towards improved OS and support a superior clinical benefit with abi + ola vs abi + pbo as 1L therapy for pts with mCRPC. Table: 13570

### **Biomarker subgroup analyses**

|                | Abi + ola (N=399) |            |                      | Abi + pbo (N=397) |            |                      | HR (95% CI)      |
|----------------|-------------------|------------|----------------------|-------------------|------------|----------------------|------------------|
|                | n                 | Events (%) | Median rPFS (months) | n                 | Events (%) | Median rPFS (months) |                  |
| ITT population | 399               | 168 (42)   | 24.8                 | 397               | 226 (57)   | 16.6                 | 0.66 (0.54–0.81) |

|           | Abi + ola (N=399) |            |                      | Abi + pbo (N=397) |            |                      | HR (95% CI)      |
|-----------|-------------------|------------|----------------------|-------------------|------------|----------------------|------------------|
|           | n                 | Events (%) | Median rPFS (months) | n                 | Events (%) | Median rPFS (months) |                  |
| Non-HRRm  | 279               | 119 (43)   | 24.1                 | 273               | 149 (55)   | 19.0                 | 0.76 (0.60–0.97) |
| HRRm*     | 111               | 43 (39)    | NR                   | 115               | 73 (64)    | 13.9                 | 0.50 (0.34–0.73) |
| Non-BRCAm | 343               | 148 (43)   | 24.1                 | 350               | 194 (55)   | 19.0                 | 0.76 (0.61–0.94) |
| BRCAm†    | 47                | 14 (30)    | NR                   | 38                | 28 (74)    | 8.4                  | 0.23 (0.12–0.43) |

\*Genes assessed were *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*†*BRCA1* and/or *BRCA2*ITT, intention-to-treat, NR, not reachedHRRm unknown pts (n=18) were excluded from the analysis.

### Clinical trial identification

NCT03732820.

### Editorial acknowledgement

Medical writing support was provided by Kirstin Spence, PhD, at Mudskipper Business Ltd., funded by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

### Legal entity responsible for the study

AstraZeneca.

### Funding

AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

### Disclosure

F. Saad: Financial Interests, Personal, Other, Honoraria: AbbVie; Advanced Accelerator Applications; Astellas Pharma; AstraZeneca; Bayer; BMS; Janssen Oncology; Knight Therapeutics; Merck; Myovant Sciences; Novartis; Pfizer; Sanofi; Financial Interests, Personal, Advisory Role: AbbVie; Advanced Accelerator Applications; Astellas Pharma; AstraZeneca/MedImmune; Bayer; Janssen Oncology; Knight Therapeutics; Myovant Sciences; Novartis; Pfizer; Sanofi; Financial Interests, Institutional, Funding: Advanced Accelerator Applications (Inst); Astellas Pharma (Inst); AstraZeneca (Inst); Bayer (Inst); Bristol Myers Squibb (Inst); Janssen Oncology (Inst); Merck (Inst); Novartis (Inst); Pfizer (Inst); Sanofi (Inst). A.J. Armstrong: Financial Interests, Personal, Advisory Role: Janssen; Novartis; Myovant Sciences; Bayer; Exelixis; Dendreon; Merck; GoodRx; AstraZeneca; FORMA Therapeutics; Astellas Scientific and Medical Affairs Inc.; Pfizer; Bristol Myers Squibb; Exelixis; Financial Interests, Institutional, Funding: Gilead Sciences (Inst); Roche/Genentech (Inst); Bristol Myers Squibb (Inst); AstraZeneca (Inst); FORMA Therapeutics (Inst); Astellas Pharma (Inst); Constellation Pharmaceuticals (Inst); Dendreon (Inst); Pfizer (Inst); Amgen (Inst); Novartis (Inst); Janssen; Financial Interests, Institutional, Royalties: Circulating Tumor Cell Novel Capture Technology (Inst); Financial Interests, Personal, Other, Travel/accommodation: Astellas Scientific and Medical Affairs Inc. A. Thiery-Vuillemin: Financial Interests, Personal, Advisory Board, & public speaking: Pfizer, AstraZeneca, Janssen, Ipsen, Bristol Myers Squibb; Financial Interests, Personal, Advisory Board: Sanofi, Novartis, Roche/Genentech, MSD, Astellas Pharma; Financial Interests, Institutional, Funding: Pfizer, Ipsen, Bayer; Financial Interests, Institutional, Invited Speaker: Pfizer, AstraZeneca, Sanofi, JNJ, Novartis, Ipsen, Roche, BMS, MSD, Astellas Pharma, excelixis, UNICANCER / GETUG, Incyte; Financial Interests, Invited Speaker: AstraZeneca, Novartis, BMS; Non-Financial Interests, Member: ASCO, GETUG; Other, Travel, Accommodations: Roche, MSD, JNJ, BMS, AstraZeneca, Pfizer, Astellas Pharma, Ipsen. M. Oya: Financial Interests, Personal, Other, Honoraria: Ayer; Bristol Myers Squibb; Novartis; Ono Pharmaceutical; Pfizer; AstraZeneca, Astellas and Takeda; Financial Interests, Personal, Advisory Role: Bayer; Financial Interests, Personal, Funding: Novartis; Pfizer. N.D. Shore: Financial Interests, Personal, Advisory Role, Consultant/Independent Contractor: AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boston Scientific, Clarity, Clovis Oncology, Cold Genesys, Dendreon, Exact Imaging, Exact Sciences, FerGene, Foundation Medicine, Genesis Care, Invitae, Janssen, Lantheus, Lilly, MDxhealth, Merck, Myovant. G. Procopio: Financial Interests, Personal, Advisory Board, consultant fees: Astellas, AstraZeneca, Bayer, BMS, Janssen, Ipsen, Merck, MSD, Novartis, Pfizer; Financial Interests, Institutional, Research Grant, research Funding for No Profit Clinical Trial: Ipsen. C. Arslan: Financial Interests, Personal, Advisory Role: Amgen, AstraZeneca, Bristol Myers Squib, Janssen, Novartis, Pfizer, Teva; Financial Interests, Personal, Speaker’s Bureau: Amgen, AstraZeneca, Bristol Myers Squib, Janssen, Novartis, Pfizer, Teva; Financial Interests, Institutional, Funding: Amgen (Inst), AstraZeneca (Inst), Bristol Myers Squib (Inst), Incyte (Inst), Janssen (Inst), Henlius (Inst), Merck (Inst), Yuhan (Inst), Lilly (Inst), Novartis (Inst), Roche (Inst); Financial Interests, Personal, Other, Travel: Amgen, Astra Zeneca, Bristol Myers Squib, Janssen, Merck, Novartis, Pfizer, Teva. N. Mehra: Financial Interests, Personal, Advisory Board: Pfizer, Roche, MSD, AstraZeneca, Astellas, JNJ; Financial Interests, Institutional, Advisory Board: Janssen; Financial Interests, Institutional, Funding: Astellas, Pfizer; Financial Interests, Personal and Institutional, Funding: Janssen; Financial Interests, Institutional, Invited Speaker: BMS, Janssen, BMS; Financial Interests, Institutional, Research Grant: AstraZeneca, BMS; Non-Financial Interests, Leadership Role, Head of the Prostate Cancer Working group: Dutch Uro-Oncology Study Group; Non-Financial Interests, Principal Investigator, Co-PI: Prospective Bladder Cancer Infrastructure (Netherlands); Non-Financial Interests, Leadership Role: Castration-resistant Prostate Cancer Registry. F.

Parnis: Financial Interests, Personal, Advisory Role: Ipsen; Janssen Oncology; Merck Serono. F. Constans Schlurmann: Financial Interests, Personal, Other, Honoraria: AAA, AstraZeneca; Astellas; Bayer; BMS; Janssen; MSD, Pfizer; Financial Interests, Personal, Advisory Role: AAA, AstraZeneca; Astellas; Bayer; BMS; Janssen; MSD, Pfizer; Financial Interests, Personal, Other, Travel: AAA, AstraZeneca; Astellas; Bayer; BMS; Janssen; MSD, Pfizer. M. Sugimoto: Financial Interests, Personal and Institutional, Funding, Honoraria; travel expenses: Janssen Pharmaceutical, AstraZeneca; Financial Interests, Personal, Other, Honoraria: Takeda Pharmaceutical; Financial Interests, Personal and Institutional, Funding, Honoraria, travel, accommodation and expenses: Astellas Pharma; Financial Interests, Personal, Funding, Travel expenses: BMS; Financial Interests, Personal and Institutional, Funding, Travel expenses: MSD; Financial Interests, Institutional, Funding: Pfizer; Financial Interests, Personal, Other, Travel expenses: Bayer. O. Sartor: Financial Interests, Personal, Advisory Role: Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Meunchen, Janss; Financial Interests, Personal, Research Grant: Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics, Tenebio. Y. Liu, C. Desai, P.M.D. Del Rosario: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. Poehlein, C.H. Poehlein: Financial Interests, Personal, Full or part-time Employment: Merck & Co., Inc. N. Clarke: Financial Interests, Personal, Other, Honoraria: Janssen; Bayer; AstraZeneca; Financial Interests, Personal, Advisory Role: AstraZeneca; Financial Interests, Personal, Other, Consulting: AstraZeneca. All other authors have declared no conflicts of interest.