30 September 2019 15:30 BST

# *Lynparza* more than doubled the time without radiographic disease progression in patients with BRCA1/2- or ATM-mutated metastatic castration-resistant prostate cancer

## *AstraZeneca and MSD's Lynparza reduced the risk of disease progression or death by 51% in men with homologous recombination repair (HRR) gene mutations*

### *First positive Phase III trial testing a targeted treatment in biomarker-selected prostate cancer patients*

AstraZeneca and MSD Inc., Kenilworth, N.J., US (MSD: known as Merck & Co., Inc. inside the US and Canada) today presented detailed results from the Phase III PROfound trial in 387 men with metastatic castration-resistant prostate cancer (mCRPC) who have a mutation in their homologous recombination repair (HRRm) genes and whose disease had progressed on prior treatment with new hormonal agent (NHA) treatments (e.g. abiraterone or enzalutamide).

The trial was designed to analyse men with HRRm genes in two cohorts: the primary endpoint was in those with mutations in BRCA1/2 or ATM genes and then, if *Lynparza* (olaparib) showed clinical benefit, a formal analysis was performed of the overall trial population of men with HRRm genes (BRCA1/2, ATM, CDK12 and 11 other HRRm genes; key secondary endpoint).

Results showed a statistically significant and clinically meaningful improvement with *Lynparza* in the primary endpoint of radiographic progression-free survival (rPFS), improving the time men with BRCA1/2- or ATM-mutated mCRPC lived without disease progression or death to a median of 7.4 months vs. 3.6 months for those treated with abiraterone or enzalutamide. *Lynparza* reduced the risk of disease progression or death by 66% (equal to a hazard ratio of 0.34) for these men.

The trial also met the key secondary endpoint of rPFS in the overall HRRm population, where *Lynparza* reduced the risk of disease progression or death by 51% (equal to a hazard ratio of 0.49) and improved rPFS to a median of 5.8 months vs. 3.5 months for abiraterone or enzalutamide.

The results were presented during the Presidential Symposium at the 2019 European Society of Medical Oncology (ESMO) congress in Barcelona, Spain (Abstract #LBA12_PR).

Results also showed a trend at this interim analysis time point for improvement in overall survival (OS), another key secondary endpoint, in the two groups. *Lynparza* extended OS to 18.5 months vs.15.1 months for abiraterone or enzalutamide in men with BRCA1/2- or ATM-mutated tumours, despite that at this interim analysis 81% of patients on NHA crossed over to *Lynparza* at progression. A similar trend in OS was observed at this interim analysis in the overall HRRm population with a median of 17.5 months' OS for men treated with *Lynparza* vs. 14.3 months for abiraterone or enzalutamide (analysis at 41% data maturity).

José Baselga, Executive Vice President, Oncology R&D, said: "Results from PROfound demonstrate that, in addition to providing substantial benefit as a precision medicine for men with metastatic castration-resistant prostate cancer with BRCA-mutated tumours, *Lynparza* is effective beyond just BRCA in tumours with mutations in other genes associated with homologous recombination repair. PROfound validates the concept of PARP sensitivity across multiple genes associated with homologous recombination repair in this disease and marks the first positive Phase III trial using a molecular biomarker to identify men for targeted

treatment for metastatic castration-resistant prostate cancer. We are working with global health authorities to bring *Lynparza* to these patients as quickly as possible."

Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, MSD Research Laboratories, said: "The results from the Phase III PROfound trial are a testament to MSD and AstraZeneca's lasting commitment to patients with cancer. The trial met the primary endpoint in men with metastatic castration-resistant prostate cancer that progressed on prior hormonal therapy, a notoriously difficult-to-treat disease. The benefit seen in patients beyond just those with BRCA mutations underscores the potential value of genomic testing in prostate cancer."

Maha Hussain, one of the principal investigators of the PROfound trial and Deputy Director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, said: "We have seen advances in the treatment over the last 15 years for men with metastatic castration-resistant prostate cancer. However, to date treatments for this state of disease continue to use 'one size fits all' approaches overlooking the genomic make-up of the tumour and how it could inform treatment decisions to better personalise care and impact outcomes. I am thrilled by the PROfound results and *Lynparza's* clinically meaningful benefit which offers the potential of a molecularly targeted treatment for this patient population with advanced disease. I am confident we are now entering a new era of personalised care and precision medicine for metastatic castration-resistant prostate cancer."

**Summary of results**[i]

| | **Cohort A (BRCA1/2 or ATM)** | | **Cohort A+B**[ii] **(Overall HRRm)** | |
|---|---|---|---|---|
| | *Lynparza* n=162 | pcNHA n=83 | *Lynparza* n=256 | pcNHA n=131 |
| **rPFS** | | | | |
| Median, months | 7.4 | 3.6 | 5.8 | 3.5 |
| % progression-free at 6 months | 59.8 | 22.6 | 49.7 | 23.7 |
| % progression-free at 12 months | 28.1 | 9.4 | 22.1 | 13.5 |
| Hazard ratio (95% CI) | 0.34 (0.25-0.47) | | 0.49 (0.38-0.63) | |
| p-value | <0.0001 | | <0.0001 | |
| **Confirmed ORR** | | | | |
| Patients with response (%) | 33.3 | 2.3 | 21.7 | 4.5 |
| Odds ratio (95% CI) | 20.86 (4.18-379.18) | | 5.93 (2.01-25.40) | |
| p-value | <0.0001 | | 0.0006 (nominal) | |
| **Time to pain progression**[iii] | | | | |
| Median, months | NR | 9.92 | | |
| Hazard ratio (95% CI) | 0.44 (0.22-0.91) | | | |
| p-value | 0.0192 | | | |
| **OS (interim)**[iv] | | | | |
| Median, months | 18.5 | 15.1 | 17.5 | 14.3 |
| Hazard ratio (95% CI) | 0.64 (0.43-0.97) | | 0.67 (0.49-0.93) | |
| p-value | 0.0173 | | 0.0063 (nominal) | |

NR, not reached; ORR, objective response rate; pc, physician's choice

[i] Assessed by blinded independent central review (BICR)

[ii] Cohort B included patients with any 1 of 12 other HRR mutations

[iii] Time to pain progression in Cohort A was a secondary endpoint included in the formal testing hierarchy

[iv] Interim analysis was done at 38% (Cohort A) and 41% (Cohort A+B) data maturity; Alpha spend at interim was 0.01; statistical significance not reached

The safety and tolerability profile of *Lynparza* in the PROfound trial was in line with that observed in prior clinical trials. The most common adverse events (AEs) ≥20% were anaemia (47%), nausea (41%), fatigue/asthenia (41%), decreased appetite (30%) and diarrhoea (21%). Grade 3 or above AEs were anaemia (22%), pulmonary embolism (4%), fatigue/asthenia (3%), vomiting (2%), dyspnoea (2%), urinary tract infection (2%), decreased appetite (1%), diarrhoea (1%) and backpain (1%). 16% of patients on *Lynparza* discontinued treatment due to AEs.

AstraZeneca and MSD are also exploring additional trials in prostate cancer, including the ongoing Phase III PROpel trial, testing *Lynparza* as a 1st-line therapy in mCRPC, in combination with abiraterone.

**About PROfound**
PROfound is a prospective, multicentre, randomised, open-label, Phase III trial testing the efficacy and safety of *Lynparza* versus new hormonal agents (e.g. abiraterone or enzalutamide) in patients with mCRPC who have progressed on prior treatment with new hormonal anticancer treatments and have a qualifying tumour mutation in one of 15 genes involved in the HRR pathway, including among them BRCA1/2, ATM and CDK12.

**About metastatic castration-resistant prostate cancer**
Prostate cancer is the second-most common cancer in men, with an estimated 1.3 million new cases diagnosed worldwide in 2018 and is associated with a significant mortality rate.[1]Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone.[2] mCRPC occurs when prostate cancer grows and spreads to other parts of the body despite the use of androgen-deprivation therapy to block the action of male sex hormones.[2] Approximately 10-20% of men with advanced prostate cancer will develop CRPC within five years, and at least 84% of these will have metastases at the time of CRPC diagnosis.[3]Of men with no metastases at CRPC diagnosis, 33% are likely to develop metastases within two years.[3] Despite an increase in the number of available therapies for men with mCRPC, five-year survival remains low.[3]

**About HRR gene mutations**
HRR is a DNA repair process that allows for high-fidelity, error-free repair of damaged DNA, in the form of double-strand breaks and inter-strand crosslinks (amongst others).[4,5] The inability to properly repair DNA damage leads to genomic instability and contributes to cancer aetiology.[5] Deficiency in HRR leads to a compromised ability to repair damaged DNA, and is a feature of cancer cells that is a target for PARP inhibitors, such as *Lynparza*. PARP inhibitors block DNA damage repair by trapping of PARP bound to DNA single-strand breaks which leads to replication fork stalling causing their collapse and the generation of DNA double-strand breaks which in turn lead to cancer cell death.[4]

**About *Lynparza***
*Lynparza* (olaparib) is a first-in-class PARP inhibitor and the first targeted treatment to block DNA damage response (DDR) in cells/tumours harbouring a deficiency in homologous recombination repair (HRR), such as mutations in BRCA1 and/or BRCA2. Inhibition of PARP with *Lynparza* leads to the trapping of PARP bound to DNA single-strand breaks, stalling of replication forks, their collapse and the generation of DNA double-strand breaks and cancer cell death. *Lynparza* is being tested in a range of PARP-dependent tumour types with defects and dependencies in the DDR pathway.

*Lynparza* is currently approved in 64 countries, including those in the EU, for the maintenance treatment of platinum-sensitive relapsed ovarian cancer, regardless of BRCA status. It is approved in the US, the EU, Japan and several other countries as 1st-line maintenance treatment of BRCA-mutated advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in 43 countries, including the US and Japan, for germline

BRCA-mutated, HER2-negative, metastatic breast cancer, previously treated with chemotherapy; in the EU, this includes locally-advanced breast cancer. Regulatory reviews are underway in other jurisdictions for ovarian, breast and pancreatic cancers.

*Lynparza*, which is being jointly developed and commercialised by AstraZeneca and MSD, is approved for advanced ovarian cancer and metastatic breast cancer and has been used in over 25,000 patients worldwide. *Lynparza* has the broadest and most advanced clinical trial development programme of any PARP inhibitor, and AstraZeneca and MSD are working together to understand how it may affect multiple PARP-dependent tumours as a monotherapy and in combination across multiple cancer types. *Lynparza* is the foundation of AstraZeneca's industry-leading portfolio of potential new medicines targeting DDR mechanisms in cancer cells.

**About the AstraZeneca and MSD strategic oncology collaboration**
In July 2017, AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, US, known as MSD outside the United States and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialise *Lynparza*, the world's first PARP inhibitor, and potential new medicine selumetinib, a MEK inhibitor, for multiple cancer types. Working together, the companies will develop *Lynparza* and selumetinib in combination with other potential new medicines and as monotherapies. Independently, the companies will develop *Lynparza* and selumetinib in combination with their respective PD-L1 and PD-1 medicines.

**About AstraZeneca in Oncology**
AstraZeneca has a deep-rooted heritage in Oncology and offers a quickly-growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With at least six new medicines to be launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, we are committed to advance Oncology as one of AstraZeneca's four Growth Platforms focused on lung, ovarian, breast and blood cancers. In addition to our core capabilities, we actively pursue innovative partnerships and investments that accelerate the delivery of our strategy, as illustrated by our investment in Acerta Pharma in haematology.

By harnessing the power of four scientific platforms - Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response and Antibody Drug Conjugates - and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment and one day eliminate cancer as a cause of death.

**About AstraZeneca**
AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal and Metabolism (CVRM), and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow us on Twitter @AstraZeneca.


**Media Relations**

| | | |
|---|---|---|
| Gonzalo Viña | | +44 203 749 5916 |
| Rob Skelding | Oncology | +44 203 749 5821 |
| Rebecca Einhorn | Oncology | +1 301 518 4122 |
| Matt Kent | BioPharmaceuticals | +44 203 749 5906 |
| Jennifer Hursit | Other | +44 203 749 5762 |

| | | |
|---|---|---|
| Christina Malmberg Hägerstrand | Sweden | +46 8 552 53 106 |
| Michele Meixell | US | +1 302 885 2677 |

**Investor Relations**

| | | |
|---|---|---|
| Thomas Kudsk Larsen | | +44 203 749 5712 |
| Henry Wheeler | Oncology | +44 203 749 5797 |
| Christer Gruvris | BioPharmaceuticals (CV, metabolism) | +44 203 749 5711 |
| Nick Stone | BioPharmaceuticals (respiratory, renal) | +44 203 749 5716 |
| Josie Afolabi | Other medicines | +44 203 749 5631 |
| Craig Marks | Finance, fixed income | +44 7881 615 764 |
| Jennifer Kretzmann | Corporate access, retail investors | +44 203 749 5824 |
| US toll-free | | +1 866 381 72 77 |

**References**

1. Bray, F., Ferlay, et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: *A Cancer Journal for Clinicians*, 68(6), pp.394-424.
2. Cancer.Net. (2019). Treatment of metastatic castration-resistant prostate cancer. https://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer [Accessed September 2019].
3. Cancer.Net. (2019). Prostate Cancer - Statistics. Available at: www.cancer.net/cancer-types/prostate-cancer/statistics [Accessed September 2019].
4. Li, X. and Heyer, W. (2008). Homologous recombination in DNA repair and DNA damage tolerance. *Cell Research*, 18(1), pp.99-113.
5. Ledermann, J., Drew, Y. and Kristeleit, R. (2016). Homologous recombination deficiency and ovarian cancer. *European Journal of Cancer*, 60, pp.49-58.

**Adrian Kemp**
**Company Secretary**
**AstraZeneca PLC**