# News Release

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## *Lynparza* in combination with bevacizumab, and as a monotherapy, demonstrates clinically meaningful survival benefit in 1st-line advanced ovarian cancer across two Phase III trials

***Landmark 5-year follow-up of PAOLA-1 Phase III trial demonstrated Lynparza plus bevacizumab meaningfully extended survival with 65.5% of HRD-positive patients surviving 5 years vs. 48.4% treated with bevacizumab and placebo***

***SOLO-1 Phase III trial demonstrated 67% of advanced ovarian cancer patients with BRCA mutations treated with Lynparza were alive at 7 years vs. 47% on placebo***

Positive long-term follow-up results from the PAOLA-1 and SOLO-1 Phase III trials of AstraZeneca and MSD's *Lynparza* (olaparib) with or without bevacizumab demonstrated clinically meaningful improvements in overall survival (OS). Further results showed class-leading progression-free survival (PFS) in combination with bevacizumab for homologous recombination deficiency (HRD)-positive patients, versus active comparator, bevacizumab, and as monotherapy for patients with BRCA mutations, versus placebo, respectively.

Both trials which were conducted in biomarker-selected, newly diagnosed patients with advanced ovarian cancer in the 1st-line maintenance setting also demonstrated a consistent safety profile.[1,2]

The results for PAOLA-1 (Abstract #LBA29) and SOLO-1 (Abstract #517O) were presented on 9 September at the 2022 European Society of Medical Oncology (ESMO) and SOLO-1 results were published in *Journal of Clinical Oncology*.

Ovarian cancer is one of the most common gynaecologic cancers, with a poor prognosis and a high mortality rate.[3] Over two thirds of patients are diagnosed with advanced disease, and approximately 50-70% of these patients die within five years.[4,5] Up to one in five women with advanced ovarian cancer have a BRCA mutation, and roughly half of women have HRD-positive tumours (which includes those with a BRCA mutation).[6-8]

Professor Isabelle Ray-Coquard, principal investigator from the PAOLA-1 trial and President of the Gineco group, said: "For women facing an advanced ovarian cancer diagnosis who are HRD-positive, a targeted treatment in the 1st-line maintenance setting is critical to helping them live longer. These latest results at the five-year landmark demonstrate that olaparib with bevacizumab reduces the risk of death by 38% in HRD-positive patients compared to bevacizumab alone, further reinforcing the clinically meaningful long-term survival benefit of this combination. This should be promising news for both clinicians and patients, as we see these additional data show that this combination may allow patients more time with family and loved ones. These results also highlight the importance of biomarker testing as part of a precision medicine approach to guide treatment decisions in ovarian cancer patients."

Professor Paul DiSilvestro, investigator from the SOLO-1 trial and Director of the Program in Women's Oncology at Women and Infants Hospital in Providence, Rhode Island, said: "The long-term results from SOLO-1 confirm that olaparib continues to elicit a clinically meaningful improvement in overall survival in the 1st-line maintenance setting for more than seven years. Achieving long-term survival for patients with newly diagnosed advanced ovarian cancer is critical because the 1st-line setting offers the greatest potential to impact patient survival."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "Historically the five year survival rate of newly diagnosed patients with advanced ovarian cancer is 30-50%. In that context, it is phenomenal to share the long term overall survival data from both PAOLA-1 and SOLO-1, with two out of three patients still alive in these trials. We continue to believe in *Lynparza's* ability to help biomarker-selected patients with advanced ovarian cancer to achieve better outcomes."

Dr Eliav Barr, Senior Vice President, Head of Global Clinical Development and Chief Medical Officer, MSD Research Laboratories, said: "These latest data from the PAOLA-1 and SOLO-1 trials further highlight the importance of HRD testing, including for BRCA1/2 mutations, for all newly diagnosed advanced ovarian cancer patients at the point of diagnosis. Maintenance therapy with *Lynparza* may provide certain patients with HRD-positive and/or BRCA-mutated advanced ovarian cancer the opportunity to live longer."

**Updated results from the PAOLA-1 Phase III trial**

Updated results from the PAOLA-1 Phase III trial demonstrate that *Lynparza* plus bevacizumab increased median overall survival to 56.5 months versus 51.6 months with bevacizumab alone, in patients with newly diagnosed advanced ovarian cancer irrespective of HRD status. This increase was not statistically significant.

In HRD-positive patients, *Lynparza* plus bevacizumab provided a clinically meaningful improvement in overall survival, reducing the risk of death by 38% versus bevacizumab (based on a HR of 0.62; 95% CI 0.45-0.85) despite PAOLA-1 having 30% Stage IV patients. 65.5% of patients treated with *Lynparza* plus bevacizumab were still alive at five years versus 48.4% of those treated with bevacizumab alone. *Lynparza* plus bevacizumab also improved median PFS to almost four years (46.8 months) versus 17.6 months with bevacizumab plus placebo and 46.1% of patients treated with *Lynparza* plus bevacizumab remain progression free at five years versus 19.2% of patients treated with bevacizumab alone. The safety and tolerability profile of *Lynparza* in this trial was in line with that observed in prior clinical trials, with no new safety signals.

**Updated results from the SOLO-1 Phase III trial**

Updated results from the SOLO-1 Phase III trial demonstrate that *Lynparza* provided a clinically meaningful improvement in overall survival (OS) versus placebo in patients with BRCA-mutated (BRCAm) newly diagnosed advanced ovarian cancer, reducing the risk of death by 45% (based on an HR of 0.55; 95% CI 0.40-0.76; nominal p=0.0004 [not statistically significant]). Median OS was still not reached with *Lynparza* versus 75.2 months with placebo. At the seven-year descriptive OS analysis, 67% of *Lynparza* patients were alive versus 47%

of placebo patients (44% of whom had a subsequent PARP inhibitor) and 45% of *Lynparza* patients versus 21% of placebo patients were alive and had not received a first subsequent treatment.

Additional data showed median time to first subsequent therapy was 64 months with *Lynparza* versus 15.1 months with placebo. The safety and tolerability profile of *Lynparza* in this trial was in line with that observed in prior clinical trials, with no new safety signals.

**Summary of results**

| **PAOLA-1** | | |
|---|---|---|
| | ***Lynparza* + bevacizumab** (n=537) | **Placebo + bevacizumab** (n=269) |
| **OS[1]** | | |
| Number of patients with events (%) | 288 (53.6) | 158 (58.7) |
| Median OS (in months) | 56.5 | 51.6 |
| HR (95% CI)<br>p-value | 0.92 (0.76,1.12)<br>0.4118 | |
| **OS by HRD status[2]** | | |
| **HRD positive (including tBRCAm)** | | |
| Number of patients randomised | 255 | 132 |
| Number of patients with events (%) | 93 (36.5) | 69 (52.3) |
| Median (in months) | 75.2 | 57.3 |
| HR (95% CI) | 0.62 (0.45, 0.85) | |
| **HRD positive (excluding tBRCAm)** | | |
| Number of patients randomised | 97 | 55 |
| Number of patients with events (%) | 44 (45.4) | 32 (58.2) |
| Median (in months) | Not reached | 52.0 |
| HR (95% CI) | 0.71 (0.45, 1.13) | |
| **BRCAm** | | |
| Number of patients randomised | 157 | 80 |
| Number of patients with events (%) | 48 (30.6) | 37 (46.3) |
| Median (in months) | 75.2 | 66.9 |
| HR (95% CI) | 0.60 (0.39, 0.93) | |
| **HRD negative** | | |
| Number of patients randomised | 192 | 85 |
| Number of patients with events (%) | 140 (72.9) | 58 (68.2) |
| Median (95% CI) (in months) | 36.8 | 40.4 |
| HR (95% CI) | 1.19 (0.88, 1.63) | |
| **PFS[3] by HRD status[2]** | | |
| **HRD positive (including tBRCAm)** | | |
| Number of patients randomised | 255 | 132 |
| Number of patients with events (%) | 136 (53.3) | 104 (78.8) |

| | | |
|---|---|---|
| Median (in months) | 46.8 | 17.6 |
| HR (95% CI) | 0.41 (0.32, 0.54) | |

| **SOLO-1** | | |
|---|---|---|
| | ***Lynparza*** (n=260) | **Placebo** (n=131) |
| **OS[4]** | | |
| Number of patients with events (%) | 84 (32.2) | 65 (49.6) |
| Median OS (in months) | Not reached | 75.2 |
| HR (95% CI)<br>p-value[5] | 0.55 (0.40, 0.76)<br>0.0004 | |
| **Time to first subsequent therapy** | | |
| Number of patients with events (%) | 135 (51.9) | 98 (74.8) |
| Median (95% CI) (in months) | 64.0 | 15.1 |
| HR (95% CI) | 0.37 (0.28–0.48) | |
| **Time to second subsequent therapy** | | |
| Number of patients with events (%) | 110 (42.3) | 80 (61.1) |
| Median (95% CI) (in months) | 93.2 | 40.7 |
| HR (95% CI) | 0.5 (0.37, 0.67) | |

1. OS analysis was done at 56% maturity (448 events in 797 patients) and boundary for significance 0.0001; statistical significance not reached.
2. Exploratory subgroup analysis by HRD status. The HRD status of patients in PAOLA-1 was determined from post-randomisation testing of tumour samples using the Myriad myChoice HRD plus test
3. Investigator-assessed PFS (RECIST 1.1)
4. OS analysis was done at 38.1% maturity (149 events in 391 patients) and boundary for significance 0.01; statistical significance not reached. Survival follow up continues and further analyses were planned.
5. P<0.0001 required to declare statistical significance

*Lynparza* is approved as maintenance treatment of platinum-sensitive relapsed ovarian cancer and as both monotherapy and in combination with bevacizumab for the 1st-line maintenance treatment of BRCA-mutated (BRCAm) and HRD-positive advanced ovarian cancer, respectively.

## Notes

### Ovarian cancer

Ovarian cancer is the eighth most common cancer in women worldwide.[9] There were more than 313,000 new cases of ovarian cancer in 2020, and over 207,000 deaths. The 5-year survival rate of newly diagnosed advanced ovarian cancer patients has typically been 30-50%.[4,5] Roughly half of women with advanced ovarian cancer have homologous recombination deficiency (HRD)-positive tumours including those with a BRCA mutation and up to one in five women have a BRCA mutation.[6-8] The primary aim of 1st-line treatment is to delay disease progression for as long as possible with the intent to achieve long-term remission.[10-12]

**PAOLA-1**

PAOLA-1 is a double-blinded Phase III trial testing the efficacy and safety of *Lynparza* added to standard-of-care bevacizumab versus bevacizumab alone, as a 1st-line maintenance treatment for newly diagnosed advanced FIGO Stage III-IV high-grade serous or endometroid ovarian, fallopian tube, or peritoneal cancer patients who had a complete or partial response to 1st-line treatment with platinum-based chemotherapy and bevacizumab. AstraZeneca and MSD announced in August 2019 that the trial met its primary endpoint of PFS in the overall trial population.

PAOLA-1 is an ENGOT (European Network of Gynaecological Oncological Trial groups) trial, sponsored by ARCAGY Research (Association de Recherche sur les CAncers dont GYnécologiques) on behalf of GINECO (Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein). ARCAGY-GINECO is an academic group specialising in clinical and translational research in patients' cancers and a member of the GCIG (Gynecologic Cancer InterGroup).

**SOLO-1**

SOLO-1 is a Phase III randomised, double-blinded, placebo-controlled, multicentre trial to evaluate the efficacy and safety of *Lynparza* tablets (300 mg twice daily) as maintenance monotherapy compared with placebo, in newly-diagnosed patients with advanced BRCAm ovarian cancer following platinum-based chemotherapy. The trial randomised 391 patients with a deleterious or suspected deleterious BRCA1 or BRCA2 mutation who were in clinical complete or partial response following platinum-based chemotherapy. Patients were randomised (2:1) to receive *Lynparza* or placebo for up to two years or until disease progression (at the investigator's discretion). The primary endpoint was PFS and key secondary endpoints included time to second disease progression or death, time to first subsequent treatment and overall survival. AstraZeneca and MSD announced in June 2018 that the trial met its primary endpoint of PFS in the overall trial population.

**BRCA**

BRCA1 and BRCA2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role maintaining the genetic stability of cells.[13] When either of these genes is mutated or altered such that its protein product either is not made or does not function correctly, DNA damage may not be repaired properly, and cells become unstable. As a result, cells are more likely to develop additional alterations that can lead to cancer. Cancers with BRCA mutations are more likely to be sensitive to PARP inhibitors including *Lynparza*.[13-16]

**Homologous recombination deficiency**

HRD, which defines a subgroup of ovarian cancer, encompasses a wide range of genetic abnormalities, including BRCA mutations and beyond. As with BRCA gene mutations, HRD interferes with normal cell DNA repair mechanisms and confers sensitivity to PARP inhibitors including *Lynparza*.[2]

***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 those with mutations in BRCA1 and/or BRCA2, or those where deficiency is induced by other agents (such as new hormonal agents – NHAs).

Inhibition of PARP proteins 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 currently approved in a number of countries across multiple tumour types including maintenance treatment of platinum-sensitive relapsed ovarian cancer and as both monotherapy and in combination with bevacizumab for the 1st-line maintenance treatment of BRCA-mutated (BRCAm) and homologous recombination repair deficient (HRD)-positive advanced ovarian cancer, respectively; for gBRCAm, HER2-negative metastatic breast cancer (in the EU and Japan this includes locally advanced breast cancer); for gBRCAm, HER2-negative high-risk early breast cancer (in Japan this includes all BRCAm HER2-negative high-risk early breast cancer); for gBRCAm metastatic pancreatic cancer; and HRR gene-mutated metastatic castration-resistant prostate cancer (BRCAm only in the EU and Japan).

*Lynparza*, which is being jointly developed and commercialised by AstraZeneca and MSD, is the foundation of AstraZeneca's industry-leading portfolio of potential new medicines targeting DDR mechanisms in cancer cells.

**The AstraZeneca and MSD strategic oncology collaboration**

In July 2017, AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, US, known as MSD outside the US and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialise *Lynparza*, the world’s first PARP inhibitor, and *Koselugo* (selumetinib), a mitogen-activated protein kinase (MEK) inhibitor, for multiple cancer types.

Working together, the companies will develop *Lynparza* and *Koselugo* in combination with other potential new medicines and as monotherapies. The companies will develop *Lynparza* and *Koselugo* in combination with their respective PD-L1 and PD-1 medicines independently.

**AstraZeneca in oncology**

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

**AstraZeneca**

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

**Contacts**

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