NEWS RELEASE

Clovis Oncology’s Rubraca® (Rucaparib) as First-Line Maintenance Treatment Improves Progression-Free Survival in Women with Advanced Ovarian Cancer Across Disease Risk Subgroups

9/11/2022

- Subgroup analysis from the Phase 3 ATHENA trial evaluating Rubraca monotherapy versus placebo (ATHENA-MONO) presented in a Mini Oral session at the ESMO Congress 2022
- Results reinforce potential of Rubraca as a first-line maintenance treatment option in a broad population of patients with ovarian cancer irrespective of molecular characteristics, with or without high risk factors for progression

BOULDER, Colo.--(BUSINESS WIRE)-- Clovis Oncology, Inc. (NASDAQ: CLVS), today announced results from a subgroup analysis of data from the monotherapy comparison of the randomized, Phase 3 ATHENA (GOG-3020/ENGOT-ov45) trial (ATHENA-MONO). These data showed that Rubraca as first-line maintenance treatment improved progression-free survival (PFS) versus placebo across disease risk subgroups including surgical outcome, response to first-line chemotherapy, and additional analyses in other subgroups. The data were presented by Rebecca S. Kristeleit, MD, PhD, of Guy's and St. Thomas' NHS Foundation Trust in London and lead ENGOT/NCRI National Cancer Research Institute (https://www.ncri.org.uk/) investigator of the ATHENA trial as a Mini Oral abstract at the European Society of Medical Oncology (ESMO) Congress 2022 in Paris.

“These additional results from the ATHENA-MONO analysis of the Phase 3 ATHENA trial demonstrate that rucaparib should be considered a new first-line maintenance treatment option for women with advanced ovarian cancer,” Dr. Kristeleit said. “In this analysis, rucaparib prolonged progression-free survival for patients with or without high risk factors for progression, irrespective of molecular characteristics, adding to our understanding of the efficacy of rucaparib in the broadest population of patients assessed in a clinical trial for first-line PARP inhibitor monotherapy.”

ATHENA is a double-blind, placebo-controlled, Phase 3 trial of Rubraca in first-line ovarian cancer maintenance
treatment. It has two parts which are statistically independent. The results presented at ESMO are from the ATHENA-MONO part (Rubraca versus placebo), with results from the ATHENA-COMBO part (Rubraca plus nivolumab versus Rubraca) expected in Q1 2023.

“As further demonstrated by the additional data presented at ESMO, the ATHENA-MONO analysis continues to reinforce the potential of Rubraca as a first-line maintenance therapy for women with advanced ovarian cancer,” said Patrick J. Mahaffy, President and CEO of Clovis Oncology. “We remain grateful to the patients who participated in the trial and for the support of the clinical community familiar with these results.”

ATHENA-MONO enrolled 538 women with high-grade ovarian, fallopian tube, or primary peritoneal cancer. The primary efficacy analysis evaluated two prospectively defined molecular subgroups in a step-down manner: 1) homologous recombination deficiency (HRD)-positive (inclusive of BRCAm tumors and BRCAwt/LOH high tumors), and 2) all patients randomized (overall intent-to-treat population [ITT]) in ATHENA-MONO. The following exploratory subgroup analyses are included in the ESMO presentation:

**PFS by Surgical Outcome**

Patients who received Rubraca as maintenance therapy showed benefit regardless of surgical outcome, whether there was complete resection (R0) during cytoreductive surgery or not.

In HRD-positive patients:

- **Patients who had a complete resection following cytoreductive surgery (R0):**
  - Rubraca (n=107), median PFS not yet reached (NR); placebo (n=33), median PFS of 22.1 months
  - Hazard ratio of 0.52 (95% [Confidence Interval] CI: 0.30-0.92)

- **Patients who did not have a complete resection following cytoreductive surgery (non-R0):**
  - Rubraca (n=78), median PFS of 20.3 months; placebo (n=16), median PFS of 9.1 months
  - Hazard ratio of 0.29 (95% CI: 0.15-0.56)

Among the ITT population:

- **Patients who had a complete resection following cytoreductive surgery (R0):**
  - Rubraca (n=263), median PFS of 25.1 months; placebo (n=73), median PFS of 12.0 months
  - Hazard ratio of 0.60 (95% CI: 0.43-0.84)

- **Patients who did not have a complete resection following cytoreductive surgery (non-R0):**
  - Rubraca (n=164), median PFS of 13.9 months; placebo (n=38), median PFS of 6.4 months
  - Hazard ratio of 0.41 (95% CI: 0.27-0.62)
PFS by First-Line Chemotherapy Response

Similarly, patients treated with Rubraca as maintenance therapy showed benefit among all subgroups when evaluated against response per RECIST v1.1 at any time during first-line chemotherapy.

Among HRD-positive patients:

- Patients who demonstrated a partial response to first-line chemotherapy:
  - Rubraca (n=33), median PFS of 14.8 months; placebo (n=9), median PFS of 9.1 months
  - Hazard ratio of 0.43 (95% CI: 0.18-1.02)

- Patients who demonstrated a complete response to first-line chemotherapy:
  - Rubraca (n=38), median PFS of 25.8 months; placebo (n=4), median PFS NR
  - Hazard ratio of 0.41 (95% CI: 0.10-1.63)

Among the ITT population:

- Patients who demonstrated a partial response to first-line chemotherapy:
  - Rubraca (n=76), median PFS of 12.2 months; placebo (n=22), median PFS of 6.4 months
  - Hazard ratio of 0.37 (95% CI: 0.21-0.65)

- Patients who demonstrated a complete response to first-line chemotherapy:
  - Rubraca (n=73), median PFS of 15.6 months; placebo (n=11), median PFS of 6.4 months
  - Hazard ratio of 0.48 (95% CI: 0.23-1.03)

Additional Analyses in the ITT Population by Subgroup

Additional analyses in other subgroups based on baseline clinical characteristics, including FIGO stage, timing of surgery, and CA-125 levels, also demonstrated that patients treated with Rubraca experienced a progression-free survival benefit compared to those treated with placebo. Safety was similar between subgroups analyzed.

Dr. Kristeleit’s presentation, as well as other company-sponsored Rubraca data presented at ESMO, can be viewed at the time of presentation at [https://www.clovisoncology.com/pipeline/scientific-presentations/](https://www.clovisoncology.com/pipeline/scientific-presentations/).

Rubraca is not currently approved in the first-line ovarian cancer maintenance setting.

About Rubraca (rucaparib)

Rucaparib is an oral, small molecule inhibitor of PARP1, PARP2 and PARP3 being developed in multiple tumor types,
including ovarian and metastatic castration-resistant prostate cancers, as monotherapy, and in combination with other anti-cancer agents. Exploratory studies in other tumor types are also underway.

Rubraca is an unlicensed medical product outside of the US and Europe.

Rubraca Ovarian Cancer US FDA Approved Indication

Rubraca is indicated for the maintenance treatment of adult women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Select Important Safety Information

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) have occurred in patients treated with Rubraca, and are potentially fatal adverse reactions. In 1,146 treated patients, MDS/AML occurred in 20 patients (1.7%), including those in long term follow-up. Of these, 8 occurred during treatment or during the 28 day safety follow-up (0.7%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 53 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing regimens and/or other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Based on its mechanism of action and findings from animal studies, Rubraca can cause fetal harm when administered to a pregnant woman. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Most common adverse reactions in ARIEL3 (≥ 20%; Grade 1-4) were nausea (76%), fatigue/asthenia (73%), abdominal pain/distention (46%), rash (43%), dysgeusia (40%), anemia (39%), AST/ALT elevation (38%), constipation (37%), vomiting (37%), diarrhea (32%), thrombocytopenia (29%), nasopharyngitis/upper respiratory tract infection (29%), stomatitis (28%), decreased appetite (23%), and neutropenia (20%).

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19.
substrates, which may increase the risk of toxicities of these drugs. Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing frequency of international normalized ratio (INR) monitoring.

Because of the potential for serious adverse reactions in breast-fed children from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the last dose.

Please Click here for full Prescribing Information for Rubraca.

You may also report side effects to Clovis Oncology, Inc. at 1-415-409-7220 (US toll) or 1-844-CLVS-ONC (1-844-258-7662; US toll-free).

Rubraca (rucaparib) European Union (EU) including Northern Ireland, and Great Britain (GB) authorized use and Important Safety Information

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with ≥2 prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.

Efficacy of Rubraca as treatment for relapsed or progressive epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) has not been investigated in patients who have received prior treatment with a PARP inhibitor. Therefore, use in this patient population is not recommended.

Summary warnings and precautions:

Hematological toxicity

During treatment with Rubraca, events of myelosuppression (anemia, neutropenia, thrombocytopenia) may be observed and are typically first observed after 8–10 weeks of treatment with Rubraca. These reactions are manageable with routine medical treatment and/or dose adjustment for more severe cases. Complete blood count testing prior to starting treatment with Rubraca, and monthly thereafter, is advised. Patients should not start Rubraca treatment until they have recovered from hematological toxicities caused by previous chemotherapy.
(CTCAE grade ≥1).

Supportive care and institutional guidelines should be implemented for the management of low blood counts for the treatment of anemia and neutropenia. Rubraca should be interrupted or dose reduced according to Table 1 (see Posology and Method of Administration [4.2] of the Summary of Product Characteristics [SPC]) and blood counts monitored weekly until recovery. If the levels have not recovered to CTCAE grade 1 or better after 4 weeks, the patient should be referred to a hematologist for further investigations.

MDS/AML

MDS/AML, including cases with fatal outcome, have been reported in patients who received Rubraca. The duration of therapy with Rubraca in patients who developed MDS/AML varied from less than 1 month to approximately 28 months.

If MDS/AML is suspected, the patient should be referred to a hematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged hematological toxicity, MDS/AML is confirmed, Rubraca should be discontinued.

Photosensitivity

Photosensitivity has been observed in patients treated with Rubraca. Patients should avoid spending time in direct sunlight because they may burn more easily during Rubraca treatment; when outdoors, patients should wear a hat and protective clothing, and use sunscreen and lip balm with sun protection factor of 50 or greater.

Gastrointestinal toxicities

Gastrointestinal toxicities (nausea and vomiting) are frequently reported with Rubraca and are generally low grade (CTCAE grade 1 or 2) and may be managed with dose reduction (refer to Posology and Method of Administration [4.2], Table 1 of the SPC) or interruption. Antiemetics, such as 5-HT3 antagonists, dexamethasone, aprepitant and fosaprepitant, can be used as treatment for nausea/vomiting and may also be considered for prophylactic (i.e. preventative) use prior to starting Rubraca. It is important to proactively manage these events to avoid prolonged or more severe events of nausea/vomiting which have the potential to lead to complications such as dehydration or hospitalization.

Embryofetal toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and
findings from animal studies. In an animal reproduction study, administration of Rubraca to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 600 mg twice daily (see Preclinical Safety Data [5.3] of the SPC).

Pregnancy/contraception

Pregnant women should be informed of the potential risk to a fetus. Women of reproductive potential should be advised to use effective contraception during treatment and for 6 months following the last dose of Rubraca (see section 4.6 of the SPC). A pregnancy test before initiating treatment is recommended in women of reproductive potential.

Click here to access the current EU SmPC (including for Northern Ireland). Click here to access the current GB SmPC.

Healthcare professionals should report any suspected adverse reactions via their national reporting systems.

About the ATHENA Clinical Trial

ATHENA (GOG 3020/ENGOT-ov45) (NCT03522246) is an international, randomized, double-blind, phase III trial consisting of two separate and fully independently powered study comparisons evaluating Rubraca monotherapy (ATHENA-MONO) and Rubraca in combination with nivolumab (ATHENA-COMBO) as maintenance treatment for patients with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. ATHENA enrolled approximately 1000 patients across 24 countries, all women with newly diagnosed ovarian cancer who responded to their first-line chemotherapy. The trial completed accrual in 2020 and was conducted in association with the Gynecologic Oncology Group (GOG) in the US and the European Network of Gynaecological Oncological Trial groups (ENGOT) in Europe. GOG and ENGOT are the two largest cooperative groups in the US and Europe dedicated to the treatment of gynecological cancers.

ATHENA-MONO is evaluating the benefit of Rubraca monotherapy versus placebo in 538 women in this patient population. The primary efficacy analysis evaluated two prospectively defined molecular sub-groups in a step-down manner: 1) HRD-positive (inclusive of BRCA mutant) tumors, and 2) the intent-to-treat population, or all patients treated in ATHENA-MONO.

The ATHENA-COMBO portion of the trial, anticipated to readout in Q1 2023, is evaluating the magnitude of benefit of adding Opdivo (nivolumab) to Rubraca monotherapy in the ovarian cancer first-line maintenance treatment setting. ATHENA-COMBO is anticipated to be the first Phase 3 dataset to readout evaluating the combination of a PARP inhibitor and an immune checkpoint inhibitor as maintenance treatment following completion and response...
About Ovarian Cancer

Ovarian cancer is the eighth leading cause of cancer-related death among women worldwide. In 2020, GLOBOCAN estimated 314,000 women received a new diagnosis of ovarian cancer and approximately 207,200 women died from ovarian cancer. According to the American Cancer Society, an estimated more than 19,000 women will be diagnosed with ovarian cancer in the United States and there will be an estimated nearly 13,000 deaths from ovarian cancer in 2022. According to GLOBOCAN, an estimated 66,000 women in Europe are diagnosed each year with ovarian cancer, and ovarian cancer is among those cancers with the highest rate of deaths. According to the NIH National Cancer Institute, more than 75% of women are diagnosed with ovarian cancer at an advanced stage.

Despite recent advances in the therapeutic landscape of newly diagnosed ovarian cancer, advanced ovarian cancer is still considered incurable for the majority of patients, and the optimal treatment strategy has yet to be determined. Although most respond initially to this treatment, 80% of patients with advanced ovarian cancer will have a recurrence and require subsequent therapies.

About Biomarkers in Ovarian Cancer

In the high-grade epithelial ovarian cancer setting, a patient’s tumor can be classified based on the genetic biomarker status: those with homologous recombination deficiencies, or HRD-positive, include those with a mutation of the BRCA gene (BRCAm), inclusive of germline and somatic mutations of BRCA, which represent approximately 25 percent of patients; and those with a range of genetic abnormalities other than BRCAm, which result in other homologous recombination deficiencies that represent an additional estimated 25 percent of patients (HRD-positive, BRCAwt); in addition, those whose test results show no deficiencies in homologous recombination repair (HRD-negative) represent the remaining approximate 50 percent of patients.

About Clovis Oncology

Clovis Oncology, Inc. is a biopharmaceutical company focused on acquiring, developing, and commercializing innovative anti-cancer agents in the US, Europe, and additional international markets. Clovis Oncology targets development programs at specific subsets of cancer populations, and simultaneously develops, with partners, for those indications that require them, diagnostic tools intended to direct a compound in development to the population that is most likely to benefit from its use. Clovis Oncology is headquartered in Boulder, Colorado, with additional office locations in the US and Europe. Please visit www.clovisoncology.com for more information.

To the extent that statements contained in this press release are not descriptions of historical facts regarding Clovis
Oncology, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Examples of forward-looking statements contained in this press release include, among others, statements regarding our expectations concerning future regulatory activities, expectations for submission of regulatory filings and review of those submission by regulatory authorities, our plans to present final or interim data on ongoing clinical trials, our plans to submit additional data to, or meet with, the FDA with respect to the status of or plans for ongoing or planned trials, the timing and pace of commencement of enrollment in and conduct of our clinical trials, the potential results of such clinical trials and the potential for marketing authorizations for new indications, our expectations regarding the suitability of Rubraca, and our plans to develop or seek approval for Rubraca in additional indications and tumor types. Such forward-looking statements involve substantial risks and uncertainties that could cause our future results, performance or achievements to differ significantly from that expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in our clinical development programs for our drug candidates and those of our partners, whether future study results will be consistent with study findings to date, the timing of availability of data from our clinical trials and the initiation, enrollment, timing and results of our planned clinical trials and the corresponding development pathways, effectiveness and suitability of diagnostic tests, the risk that final results of ongoing trials may differ from initial or interim results as a result of factors such as final results from a larger patient population may be different from initial or interim results from a smaller patient population, the risk that additional pre-clinical or clinical studies may not support further development in certain additional indications or tumor types, and actions by the FDA, the EMA or other regulatory authorities regarding data required to support drug applications and whether to approve drug applications and the timing and scope of any approvals. Clovis Oncology does not undertake to update or revise any forward-looking statements. A further description of risks and uncertainties can be found in Clovis Oncology's filings with the Securities and Exchange Commission, including its Annual Report on Form 10-K and its reports on Form 10-Q and Form 8-K.

i Monk BJ et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer. 2021;0:1–6.


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Source: Clovis Oncology, Inc.