SGO VIRTUAL ANNUAL MEETING ON WOMEN’S CANCER®
Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer

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Disclosures – Dr. Matulonis

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Primary PFS Endpoint: ENGOT-OV16/NOVA Study

- NOVA is a randomized, double-blind, placebo-controlled phase 3 trial of niraparib maintenance treatment for patients with platinum-sensitive recurrent OC.
- Niraparib demonstrated statistically significant improvement in PFS in gBRCAm and non-gBRCAm cohorts¹

Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to platinum-based therapy

- gBRCAm (n=203)
  - 2:1 randomization
    - Niraparib 300 mg QD (n=138)
      - Placebo 300 mg QD (n=65)
      - HR 0.27 (95%CI 0.17 to 0.41, p<0.001)
      - mPFS 21.0 vs. 5.5 months
  - Non-gBRCAm (n=350)
    - 2:1 randomization
      - Niraparib 300 mg QD (n=234)
        - Placebo 300 mg QD (n=116)
        - HR 0.45 (95%CI 0.34 to 0.61, p<0.001)
        - mPFS 9.3 vs. 3.9 months

- Secondary endpoints include safety and exploratory long-term efficacy such as PFS2 and OS which were not statistically powered

Primary data cut-off was June 20, 2016 (median duration of follow up 16.9 months).

¹ Mirza et al. NEJM, 2016;375:2154-64.
Approvals of PARPi for advanced OC

- PARP inhibitors have changed the treatment paradigm for the management of advanced OC

High proportion of patients were withdrawn from the NOVA study after primary results in 2016 and post commercial availability of PARPi

2Lm, second-line maintenance; BRCA, breast cancer gene; CT, chemotherapy; EOC, epithelial ovarian, tubal, or primary peritoneal cancer; EMA, European Medicines Agency; FDA, Food & Drug Administration; g/sBRCAm, germline/somatic BRCA mutant; HGS, high-grade serous; HRd, homologous recombination deficient; PARPi, poly(ADP-ribose)polymerase inhibitor; Pt, platinum.

1. ZEJULA® (niraparib): US prescribing information (Apr 2020); 2. LYNPARZA® (olaparib): US prescribing information (Nov 2020); 3. RUBRACA® (rucaparib): US prescribing information (Oct 2020); 4. ZEJULA® (niraparib): EPAR – Product information - Summary of product characteristics (Nov 2020); 5. LYNPARZA® (olaparib): EPAR – Product information - Summary of product characteristics (Nov 2020); 6. RUBRACA® (rucaparib): EPAR – Product information - Summary of product characteristics (Jan 2021);
Patient Disposition and Survival Status

In the overall population, 28% (155/553) discontinued from study for non-death reasons
  - Imbalances observed due to small sample size in each cohort
  - Early withdrawal of consent limited collection of survival and subsequent therapy data

By final data-lock, survival status could not be retrieved for 49% (76/155) patients:
  - gBRCAm cohort: 14% (19/138) in niraparib group, 14% (9/65) in placebo group
  - Non-gBRCAm cohort: 14% (33/234) in niraparib group, 13% (15/116) in placebo group

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).
Assessment of Missing Subsequent PARPi Therapy

- Cross-over to PARP inhibitor (PARPi) on study was not permitted; however, patients could receive subsequent PARPi after disease progression or withdrawal from study per oncologist’s clinical judgement.

- Due to study discontinuation, post-progression therapy information was not available for 25% (138/553) of patients.

<table>
<thead>
<tr>
<th>Subsequent PARPi treatment received on NOVA</th>
<th>Niraparib (n=138)</th>
<th>Placebo (n=65)</th>
<th>Niraparib (n=234)</th>
<th>Placebo (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>34 (25%)</td>
<td>30 (46%)</td>
<td>15 (6%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>No</td>
<td>68 (49%)</td>
<td>15 (23%)</td>
<td>168 (72%)</td>
<td>70 (60%)</td>
</tr>
<tr>
<td>Missing information</td>
<td>36 (26%)</td>
<td>20 (31%)</td>
<td>51 (22%)</td>
<td>31 (27%)</td>
</tr>
</tbody>
</table>

- Both small sample size and the missing data challenge survival analyses and interpretation.
OS Sensitivity Analyses

- Adjusted OS analysis was conducted, after missing subsequent PARPi therapy data was imputed
- Inverse probability of censoring weighted (IPCW) methodology\(^2,3\) was applied to adjust for subsequent PARPi therapy use

1. 46% on the gBRCAm and 13% in the non-gBRCAm.
2. Ishak et al. Methods for Adjusting for Bias Due to Crossover in Oncology Trials, PharmacoEconomics (2014) 32:533–546
3. NICE DSU TSU 16, Latimer et al. Adjusting survival time estimates in the presence of treatment switching, 2014

-- Observed Events
  - Missing subsequent PARPi data
    - About 28% of the placebo patients in NOVA
  - Switching to PARPi
    - About 25% of placebo patients with confirmed receipt of subsequent PARPi\(^1\)

-- Step 1
  - Confounded Placebo Arm
  - Adjustment for missingness
    - Impute synthetic probability and date of PARPi cross-over among placebo patients with missing information

-- Step 2
  - Adjustment for switching
    - Apply IPCW adjustment on the simulated dataset
PFS2: non-g*BRCAm and g*BRCAm Cohorts

- Benefit of niraparib extends beyond first progression based on updated analysis

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).
PFS2 was measured from time of randomization to progression on subsequent chemotherapy.
OS: Non-gBRCAmut Cohort

- At the time of the final analysis, average follow up time was 5.6 years
- Based on adjusted analysis for subsequent PARPi therapy, no difference in survival observed

Final data cut-off was Oct 1, 2020

Given evidence of non-proportional hazards, RMST analysis was conducted in ITT population to estimate the difference in restricted mean values (area under the curve).

- **up to 24 months:** 20.6 months in placebo vs 21.3 months niraparib ($\Delta$ of 0.7, 95% CI: -0.5, 1.9)
- **up to 72 months:** 39.1 months in placebo vs 38.5 months in niraparib ($\Delta$ of -0.7, 95% CI: -6.0, 4.7)
OS: gBRCAmut Cohort

- At the time of the final analysis, average follow up time was 5.6 years
- Adjusted analysis indicates a trend for improved survival with niraparib maintenance with a HR 0.66 and increased mOS by 9.7 months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo, IPCW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>138</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>46</td>
</tr>
</tbody>
</table>

HR (95%CI): 0.93 (0.633–1.355)
Median OS
Niraparib 43.6 months
Placebo 41.6 months

HR, IPCW (95%CI): 0.66 (0.44–0.99)
Median OS
Niraparib 43.8 months (36.4–56.2)
Placebo, IPCW 34.1 months (27.6–53.0)

Final data cut-off was Oct 1, 2020
Long-term Safety: Grade ≥3 Adverse Events

- Hematologic TEAEs primarily occurred in the first year of niraparib treatment
- Incidence of grade ≥3 thrombocytopenia decreased from 33.8% to 2.8%, anemia decreased from 25.6% to 0.7%, and neutropenia decreased from 19.3% to 2.1% from year 1 to year 2–3, respectively
- 49 (13%) patients remained on niraparib vs. 9 (5%) on placebo for more than 3 years

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Niraparib Arm</th>
<th>Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (N=367)</td>
<td>Year 1 (n=367)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>131 (35.7)</td>
<td>124 (33.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>99 (27.0)</td>
<td>94 (25.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>76 (20.7)</td>
<td>71 (19.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (9.8)</td>
<td>32 (8.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (8.4)</td>
<td>30 (8.2)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>30 (8.2)</td>
<td>24 (6.5)</td>
</tr>
</tbody>
</table>

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).

The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. The category of fatigue includes reports of fatigue, asthenia, malaise. The category of anemia includes reports of anemia and decreased hemoglobin count. The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia. The category of GI disorders includes constipation, diarrhea, nausea, vomiting, abdominal pain.
Summary of MDS/AML

- At the time of the primary analysis, incidence of MDS/AML was 1.4% (5/367) in the niraparib arm vs 1.1% (2/179) in the placebo arm.

- With long term follow up and administration of subsequent therapies, 3.5% (13/367) of patients in the niraparib arm vs. 1.7% (3/179) in the placebo arm developed MDS/AML.

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Niraparib Arm</th>
<th>Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N=367)</td>
<td>gBRCAm n=136</td>
</tr>
<tr>
<td>MDS/AML All</td>
<td>13* (3.5)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>TEAE (treatment)</td>
<td>9 (2.5)</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>TEAE (follow-up)</td>
<td>4 (1.1)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).

*Total 16 events of MDS/AML reported in 13 patients treated with niraparib; 1 patient had MDS then AML; 1 patient had MDS grade 1, MDS grade 4, then AML.

Final NOVA Analysis In Platinum-sensitive Recurrent Ovarian Cancer

- Clinical benefit of niraparib was demonstrated in the primary PFS analysis in non-\(gBRCA\)m and \(gBRCA\)m patients

- Final PFS2 analysis indicates benefit of niraparib maintenance therapy extends beyond first progression

- OS was a secondary endpoint and not statistically powered in the NOVA study
  - Interpretation is challenged by a high rate of subsequent PARPi use and missing data
  - No difference in survival was observed in non-\(gBRCA\)m patients
  - Trend towards improved survival was observed in \(gBRCA\)m patients based on the adjusted analyses, with 9.7 months increase in survival

- Long term safety analysis supports use of niraparib for maintenance treatment
  - Hematologic adverse events decreased after first year of maintenance
Acknowledgments

We thank the 553 patients and their families for participating in this trial

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