Characterization of long-term responders to olaparib from study D0810C000019

Lheureux S1, Ledermann J2, Runswick S1, Hodgson D1, Timms K1, Lanchbury J1, Kaye S1, Gourtley C1, Bowtell D1, Kohn E1, Scott C1, Matulonis U1, Panzarella T1, Dougherty B2, Barrett C1, Lai Z1, O Connor M11, Robertson J1, Ho T11, Oza AM1

1Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre Toronto Canada; 2Cancer Institute, University College London, and University College London Hospitals, London, UK; 3AstraZeneca; Macclesfield, Chesire, UK; 4Myriad Genetics, Inc; Salt Lake City, USA; 5The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, UK; 6Edinburgh Cancer Research UK Centre, Edinburgh, UK; 7Peter MacCallum Cancer Centre, Melbourne, Australia; 8National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; 9Royal Melbourne Hospital, Victoria, Australia; 10Dana-Farber Cancer Institute, Boston, Massachusetts, USA; 11AstraZeneca, Wilmington, Delaware, USA.

Presented at ASCO - May 30, 2015

BACKGROUND

Olaparib is the most studied PARP inhibitor

• Olaparib maintenance monotherapy signiﬁcantly prolonged PFS in patients with platinum-sensitive relapsed serous ovarian cancer

• Patients with a BRCA mutation (BRCAm) receive greater treatment beneﬁt

• Non-mutation carriers may also beneﬁt from olaparib therapy

OBJECTIVES

• To clinically, molecularly and genomically characterize the long (>2 years) and short-term (<3 months) responders on olaparib maintenance

• Focus on the pivotal study D0810C000019: Phase II randomised, double blind, study of olaparib in patients with platinum sensitive relapsed serous ovarian cancer following treatment with two or more platinum containing regimens

METHODS

• Retrospective molecular analysis of prospectively collected specimens and data

– Clinical data:

  – Previous lines of chemotherapy, initial stage, platinum free interval

  – Response to platinum chemotherapy according RECIST 1.1 at the time of olaparib maintenance

– Germline BRCA1/2 testing by Myriad Genetics

– Molecular variables from archival tumor samples

  – Myriad Genetics:

    – Homologous Recombination Deficiency (HRD) score (positive ≥42)

  – Foundation Medicine: FoundationOne® panel

– Methylation of BRCA1 by testing by Myriad Genetics

– Ampliﬁed observed in at least 2 pts: Myc (4 pts), CCNE1 (3 pts), MCL1 (3 pts), FGF (3 pts) and KRAS (2 pts)

Results

RESULTS

Patients on olaparib maintenance therapy

1. Complete response vs. mutation in the BRCA1 (n=37): No signiﬁcant associations

2. Partial response vs. mutation in the BRCA1 (n=26): No signiﬁcant associations

3. Complete response at the time of olaparib maintenance (n=37): No signiﬁcant associations

4. HRD status (HRDm) associated with both BRCAm and HRDm: No signiﬁcant associations

5. Pathology review on-going

Patients on placebo maintenance therapy

1. Complete response vs. mutation in the BRCA1 (n=26): No signiﬁcant associations

2. Partial response vs. mutation in the BRCA1 (n=13): No signiﬁcant associations

3. Complete response at the time of olaparib maintenance (n=26): No signiﬁcant associations

4. Patients on placebo Maintenance Therapy: Trend for the presence of TP53 mutation (p=0.051)

Univariate analysis

• Predictive markers of long-term response to olaparib

  – Complete response at the time of olaparib maintenance (p=0.026)

  – HRD status (p=0.026) associated with long term responders

  – Long-term group: trend for the presence of TP53 mutation (p=0.061)

  – Short term responders: 28/29 pts with TP53 mutations (97%)

  – Long-term responders: 27/37 long-term pts had TP53 mutations (97%)

CONCLUSION

• A signiﬁcant numbers of patients with recurrent advanced ovarian cancer have prolonged beneﬁt from olaparib maintenance

• Markers of long-term sensitivity to olaparib maintenance

  – Complete response to platinum-based chemotherapy

  – BRCAm and HRD

  – TP53 needs further investigations

• Methylation of BRCA1 seems to not confer same degree of phenotype

• Prospective evaluation: Olala protocol

Acknowledgements

This research is supported by AstraZeneca

CR: complete response; m, mutation; mths: months; No: number; PR: partial response; pts: patients; TP53: TP53 mutation; Wild type: wild type