Olaparib+bevacizumab is approved as first-line maintenance treatment of advanced homologous recombination deficiency (HRD)-positive ovarian cancer (OC), defined by the presence of a deleterious or suspected deleterious BRCA mutation (BRCAm) and/or genomic instability (evaluated with a United States Food and Drug Administration-approved companion diagnostic). We evaluated the performance of an in-development next-generation sequencing assay, based on Illumina’s RUO TSO 500 content, that identifies variants in tumour tissue and HRD genomic scars (Illumina test). Herein, we report the performances of the in-development Illumina test versus the Myriad myChoice PLUS assay (Myriad test).

Methodology
OC tissue samples were analysed with Illumina (n=227; 40ng DNA) and Myriad tests (n=254; 200ng DNA). Samples that failed QC during the first run using the Illumina test were retested with higher DNA input. Agreement rates for BRCAm, genomic instability score (GIS), and HRD status (includes BRCA and GIS [cutoff, 42]) were analysed. For the overall and the non-BRCAm cohorts, correlation between the continuous GIS of the Illumina and Myriad tests was determined. The analytical sensitivity and specificity of the Illumina-derived GIS to correctly classify genomic instability status as determined by the Myriad test (cutoff, 42) was evaluated using area under the receiver operating characteristic (AUROC).

Results
Agreement rates are reported in the Table. The GIS correlation between the 2 tests was 0.980 (all samples) and 0.975 (non-BRCAm cohort). AUROC was 0.992 (all samples) and 0.988 (non-BRCAm cohort). Prevalence (Illumina and Myriad tests) was 51.0% and 49.2% for overall HRD and 27.6% and 25.5% for BRCAm. Success rates (Illumina and Myriad tests) were 86.8% (197/227) and 94.1% (239/254) (overall HRD), 88.1% (200/227) and 97.6% (248/254) (BRCAm), and 91.2% (207/227) and 94.1% (239/254) (GIS); after re-running the failed samples with the Illumina test, rates were 90.3%, 92.5%, and 93.4%, respectively.

Conclusion
Illumina test and Myriad test HRD, BRCAm, and GIS detection results were in >91% agreement. With both tests, GIS was highly correlated (0.98), and prevalence estimates of HRD and BRCAm rates were similar. Data suggest that a distributable solution such as the Illumina test may replicate the performance of the Myriad myChoice HRD assay.

Abstract 978 Table 1

<table>
<thead>
<tr>
<th></th>
<th>Positive Percentage Agreement, % (95% CI)</th>
<th>Negative Percentage Agreement, % (95% CI)</th>
<th>Overall Percentage Agreement, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRD (positive vs negative) (n=194)</td>
<td>92.3 (85.5-96.1)</td>
<td>90.7 (90.7-96.9)</td>
<td>93.4 (90.1-96.8)</td>
</tr>
<tr>
<td>BRCAm (positive vs negative) (n=187)</td>
<td>92.9 (83.0-97.2)</td>
<td>95.6 (95.0-96.6)</td>
<td>96.9 (93.5-98.8)</td>
</tr>
<tr>
<td>GIS (cutoff vs &gt;42) (n=206)</td>
<td>91.3 (84.2-96.3)</td>
<td>98.0 (93.1-99.5)</td>
<td>94.6 (90.8-97.9)</td>
</tr>
</tbody>
</table>

Introduction/Background

Ovarian cancer (OC) is believed to be one of the most lethal gynaecologic malignancies worldwide. Despite advances in the treatment of OC after the introduction of poly(ADP-ribose) polymerase inhibitors (PARPi) in the frontline setting as maintenance therapy and in the recurrent setting, the 5-year survival rate of high-grade serous ovarian cancer (HGSOC) ranges between 35 and 40%. PARPi exhibit meaningful activity against OC, however resistance to these agents emerges ultimately. Thus, there is a need to develop more effective treatments for OC. Recent reports highlighting increased OC cell reliance on ATR/CHK1 pathway gives hope to overcome PARPi resistance and prolong patient’s survival.

Methodology

The aim of this study was to estimate cytotoxic activity of PARPi (olaparib), the ataxia telangiectasia and Rad-3 related protein (ATR) inhibitor (ATRi, ceralasertib), and the checkpoint kinase 1 (CHK1) inhibitor (CHK1i, MK-8776) alone or in combinations in PEO1 (BRCA2MUT) OC cell line, and in PEO1-derived olaparib-resistant (PEO1-OR) cell line developed by continuous incremental long-term treatment with olaparib. Here, we evaluated the effect of tested drugs on cell survival in respect of metabolic activity by MTT assay and colony forming capacity. We also preliminarily elucidated mechanisms conferring resistance to olaparib in OC cells by assessment of expression of key proteins (ATR, CHK1, PARPi, P-glycoprotein) by western blot analysis. Statistical analyses were performed using Student’s t-test and ANOVA followed by the Tukey’s multiple comparisons post-hoc test.

Results

OC cells are more sensitive to combination of the drugs in comparison with monotherapy with each agent alone. What is more, treatment with single-agent PARPi or combination of PARPi/ATRi or PARPi/CHK1i activates ATR/CHK1 reaction...