Update on PARP inhibitors: opportunities and challenges in cancer therapy

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BRCA mutation and PARP inhibitors

- Mechanism of action
- Clinical activity of PARP-I in ovarian cancer
- Future challenges: biomarkers and combinations
Mechanism of action

Nucleotide excision repair (NER)
Mismatch repair (MMR)

DNA repair mechanisms

Cells protect themselves against DNA damage caused by DNA-binding chemicals, radiation, and other factors by deploying DNA repair mechanisms.15,16

DNA damage
Single-strand DNA break
DNA-binding chemotherapeutic drug

Base excision repair

Poly ADP-ribose chain

Mismatches

NHJR

Nucleotide excision repair (NER)
Mismatch repair (MMR)

Single-strand breaks are repaired via a mechanism called base excision repair, in which PARP enzymes bind to broken DNA and produce poly ADP-ribose chains that help attract other repair enzymes that replace the damaged region with normal DNA.15-16

How PARP inhibitors work in patients with BRCA and other HR deficiencies

Tumor cells that are deficient in HR because of defects in genes such as BRCA1 and BRCA2 can still repair DNA through BER. Preventing BER through PARP inhibition in HR-deficient cells induces cell death.17,19

Synthetic lethality
Unrepaired DNA
Dying cancer cells
Cell death
PARP inhibitors: a 10 year history

Olaparib – the full story

2005 Preclinical
Early clinical trials (Phase I, IB)
Randomised clinical trials

Exquisite preclinical efficacy of PARPi
Phase I trial confirms excellent tolerance and expansion in 50 BRCA patients showed 46% response.
Randomised trial (maintenance therapy) showed marked PFS benefit particularly in BMOC

BRCAm patients derive greater PFS benefit: 7.1 months median PFS improvement

"this is nothing like chemotherapy"

Ledermann et al. NEJM 2012; 366, 1382-92
Ledermann et al. Lancet Oncology 2014

Study 12
Dose
Study 41
Single agent maintenance
Study 19
EMA approval

APPROVAL
Randomised Trial Of Maintenance Olaparib In Platinum-sensitive High-grade Serous Relapsed Ovarian Cancer -‘Study 19’

- Aim: to assess the efficacy and safety of oral olaparib as a maintenance treatment
- Design: randomised, double-blind, placebo-controlled Phase II maintenance study
- 265 patients in 82 investigational sites in 16 countries

Patients:
- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based, to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

Olaparib 400 mg po bid
Randomised 1:1
Placebo po bid

Treatment until disease progression

Primary end point: PFS

Sept 2008–Feb 2010

bid, twice daily; CA-125, Cancer Antigen 125; CR, complete response; po, orally; PR, partial response.
Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

- 82% reduction in risk of disease progression or death with olaparib

**Study 19: Overall survival**

**Overall population**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n=136)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>94 (69)</td>
<td>109 (84)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>29.8</td>
<td>27.8</td>
</tr>
</tbody>
</table>

**Adjusted analysis excluding centres where patients received subsequent PARP inhibitors:**

<table>
<thead>
<tr>
<th>BRCAm patients</th>
<th>Olaparib (n=136)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>47 (84)</td>
<td>48 (77)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>34.9</td>
<td>30.2</td>
</tr>
</tbody>
</table>

**HR 0.52**

95% CI 0.28-0.97

p=0.039

14/62 (22.6%) placebo pts switched to a PARP i
OVERVIEW OF EFFICACY ANALYSES IN PATIENTS WITH A BRCA1/2 MUTATION

**PFS**
- Placebo: 4.3 months
- Olaparib 400 mg bid: 11.2 months
- HR: 0.18 (95% CI 0.10, 0.31), P < 0.0001

**TFST** (Exploratory)
- Placebo: 6.2 months
- Olaparib 400 mg bid: 15.6 months
- HR: 0.33 (95% CI 0.22, 0.50), nominal P < 0.0001

**TTSS** (Exploratory)
- Placebo: 15.2 months
- Olaparib 400 mg bid: 23.8 months
- HR: 0.44 (95% CI 0.29, 0.67), nominal P = 0.00013

**OS**
- Placebo: 31.9 months
- Olaparib 400 mg bid: 34.9 months
- HR: 0.73 (95% CI 0.45, 1.71), P = 0.192

TFST, time from randomisation to first subsequent therapy or death; TSST, time from randomisation to second subsequent therapy or death

Long-term exposure to treatment

- After a median follow-up of 5.9 years, **15 patients (11%)** still received olaparib (8 BRCAm, 7 BRCAwt) and one patient (<1%) still received placebo (BRCAm)

Who are these pts?

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ASCN ANNUAL MEETING '16

Gemelli
<table>
<thead>
<tr>
<th>Qualità dell'evidenza SIGN</th>
<th>Raccomandazione clinica</th>
<th>Forza della raccomandazione clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Nelle pazienti con malattia platino refrattaria/resistente con indicazione alla chemioterapia, è indicato un trattamento monochemioterapico</td>
<td>Positiva forte</td>
</tr>
<tr>
<td>A</td>
<td>Nelle pazienti con malattia platino sensibile è indicato un trattamento con carboplatino e paclitaxel</td>
<td>Positiva forte</td>
</tr>
<tr>
<td>A</td>
<td>Nelle pazienti non candidabili a trattamento standard contenente paclitaxel (ad es. in caso di ipersensibilità) i regimi con carboplatino associato a doxorubicina liposomiale o gemcitabina possono essere proposti come valida alternativa</td>
<td>Positiva debole</td>
</tr>
<tr>
<td>A</td>
<td>Nelle pazienti non pretrattate con bevacizumab, bevacizumab può essere associato alla chemioterapia e continuato come mantenimento</td>
<td>Positiva forte</td>
</tr>
<tr>
<td>B</td>
<td>Nelle pazienti con mutazione di BRCA, olaparib può essere somministrato dopo la chemioterapia e continuato come mantenimento</td>
<td>Positiva forte</td>
</tr>
</tbody>
</table>

..... Recidiva di carcinoma ovarico “platino sensibile” con mutazioni germinali o somatiche di BRCA
SOLO-1 & SOLO 2 Program
BRCAm Population Only

First-line maintenance or maintenance in ‘platinum-sensitive’ setting

Response to platinum-based chemotherapy

Olaparib

Randomization 2:1

Placebo

SOLO-1 344 patients
2 years
PFS/PFS2/OS + QoL

SOLO-2 264 patients
to progression
PFS/PFS2/OS + QoL
Can PARP inhibitors replace platinum-based chemotherapy in platinum-sensitive patients?
Ovarian cancer (193): platinum resistant or not suitable for further platinum therapy, median N. of prior line: 4,3  RR:34%
Olaparib monotherapy for BMOC – the route to registration in the USA

- From the ongoing pooled analysis of almost 300 patients, data on subgroup of 137 patients who received ≥ 3 lines of chemo presented to FDA for accelerated approval.
  - response rate 34%; response duration 7.9m.

Note: approval does not distinguish between platinum-sensitive and platinum resistant BMOC
SINOSSI DEL PROTOCOLLO

Studio di Fase III, in aperto, randomizzato, controllato, multicentrico per valutare l'efficacia e la sicurezza di olaparib in monoterapia rispetto alla chemioterapia ad agente singolo di scelta del medico nel trattamento del cancro dell'ovaio recidivo platino-sensibile in pazienti portatrici delle mutazioni della linea germinale BRCA1/2.

Primary Objectives:
- PFS

Platinum sensitive OC
- 2 recurrence
- Germline BRCA1/2 mutation
411 PTS

Randomization

Olaparib

Chemotherapy Single Agent
BRCA mutation and PARP inhibitors

- Mechanism of action
- Clinical activity of PARP-I in ovarian cancer
- Future challenges: biomarkers
PARP inhibitors in ovarian cancer: current status and future promise

OLAPARIB
NIRAPARIB
RUCAPARIB
VELIPARIB
TALAZOPARIB
Future challenges: Biomarkers

How to identify BRCAAness to extend the benefit of PARPi to most patients with ovarian cancer?

• Clinical phenotype: high grade serous with repeated response to platinum (study 19)
• Genetic signature
• Genetic scars (LOH, TAI, LST)
• Composite HRD score (genes+scars)
Two Main HRD Genomic Scar Tests Have Been Developed

- Genomic loss of Heterozygosity (LOH)
- Foundation Medicine is developing a test in collaboration with Clovis Oncology that assesses HRD status using an algorithm comprising two elements\(^1,2\)
  - tBRCAm status
  - Genomic LOH (high or low)
- A tumor is defined as HRD negative if it is BRCAwt with low genomic LOH\(^1\)

- Myriad myChoice HRD
- Provides a score based on an assessment of three genomic scars:
  - Loss of heterozygosity (LOH)
  - Telomeric allelic imbalance
  - Large-scale state transitions
- A score \(\geq 42\) (on a scale of 0-100) represents a positive score (loss of DNA repair function), while a score \(<42\) reflects a negative score (intact DNA repair function)\(^3,4\)
- Also tests for tBRCAm

1. Swisher EM et al ASCO 2014 Abstract TPS5619
HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS.

**Hypothesis 1:** Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

**Hypothesis 2:** Ovarian cancer patients who are “Biomarker Negative” (i.e., with low genomic LOH) will not respond to PARPi.

- Foundation Medicine’s NGS-based comprehensive cancer genomic profiling assay sequences BRCA1/2 genes in tumor-derived DNA.
- The assay also sequences single-nucleotide polymorphisms (SNPs).
- SNP analysis identifies and quantifies genomic LOH.

NGS = next-generation sequencing; mut = mutation; wt = wild type.
Primary efficacy analysis: PFS in BRCA\textsuperscript{mut} and BRCA-like versus Biomarker Negative patients

Progression-free survival by HRD molecular subgroup

<table>
<thead>
<tr>
<th>HRD Subgroup</th>
<th>Median PFS, mo (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA\textsuperscript{mut}</td>
<td>9.4 (7.3, Not Reached)</td>
</tr>
<tr>
<td>BRCA-like</td>
<td>7.1 (3.7, 10.8)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>3.7 (3.5, 5.5)</td>
</tr>
</tbody>
</table>

Subgroup Comparison

<table>
<thead>
<tr>
<th>Subgroup Comparison</th>
<th>Hazard Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA\textsuperscript{mut} vs Biomarker Negative</td>
<td>0.47 (0.35, 0.64)</td>
</tr>
<tr>
<td>BRCA-like vs Biomarker Negative</td>
<td>0.61 (0.41, 0.92)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Rucaparib ovarian cancer trials enrolling in 2015

The HRD algorithm will be applied prospectively to two ongoing trials

**ARIEL2 Part 2 (N=300)**
Single arm in HGOC patients who have received ≥3 prior chemotherapy regimens (NCT01891344)

**ARIEL3 (N=540)**
Randomized maintenance study rucaparib vs placebo in HGOC patients who have received ≥2 platinum regimens (NCT01968213)
Myriad Genetic test: 3-Biomarker HRD Score

• An HR deficiency (HRD) score, which is a measure of genome instability, has been developed as the sum of three independent biomarkers:
  – TAI (telomeric-allelic imbalance)$^1$
  – LST (large-scale state transitions)$^2$
  – LOH (loss of heterozygosity)$^3$

• HRD score is calculated from SNP-derived whole genome profiling

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer


This article was published on October 8, 2016, at NEJM.org.
ENGOT-OV16/NOVA Trial

Platinum-Sensitive Recurrent High Grade Serous Ovarian Cancer

Treatment with 4-6 Cycles of Platinum-based Therapy

Response to Platinum Treatment

- gBRCAmut
  - 2:1 Randomization
    - Niraparib 300 mg once daily
    - Placebo
  - Treat until Progression of Disease

- Non-gBRCAmut
  - 2:1 Randomization
    - Niraparib 300 mg once daily
    - Placebo
  - Treat until Progression of Disease

553 pts
203 pts
350 pts
## Patient Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>gBRCAmut</th>
<th>Non-gBRCAmut</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Niraparib</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=138)</td>
<td>(N=65)</td>
</tr>
<tr>
<td>Age - years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>57.0 (36, 83)</td>
<td>58.0 (38, 73)</td>
</tr>
<tr>
<td>Region – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA and Canada</td>
<td>53 (38.4)</td>
<td>28 (43.1)</td>
</tr>
<tr>
<td>Europe and Israel</td>
<td>85 (61.6)</td>
<td>37 (56.9)</td>
</tr>
<tr>
<td>ECOG performance status – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>91 (65.9)</td>
<td>48 (73.8)</td>
</tr>
<tr>
<td>1</td>
<td>47 (34.1)</td>
<td>17 (26.2)</td>
</tr>
<tr>
<td>Primary tumor site – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>122 (88.4)</td>
<td>53 (81.5)</td>
</tr>
<tr>
<td>Primary peritoneal</td>
<td>7 (5.1)</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>9 (6.5)</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Lines of previous chemotherapy – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>70 (50.7)</td>
<td>30 (46.2)</td>
</tr>
<tr>
<td>≥3</td>
<td>67 (48.6)</td>
<td>35 (53.8)</td>
</tr>
</tbody>
</table>

*One patient received one line of prior therapy.*
### Prospective Stratification Factors for Randomization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>gBRCAmut</th>
<th></th>
<th>Non-gBRCAmut</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Niraparib (N=138)</td>
<td>Placebo (N=65)</td>
<td>Niraparib (N=234)</td>
<td>Placebo (N=116)</td>
</tr>
<tr>
<td>Time to progression after penultimate platinum therapy — no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 to &lt;12 months</td>
<td>54 (39.1)</td>
<td>26 (40.0)</td>
<td>90 (38.5)</td>
<td>44 (37.9)</td>
</tr>
<tr>
<td>≥12 months</td>
<td>84 (60.9)</td>
<td>39 (60.0)</td>
<td>144 (61.5)</td>
<td>72 (62.1)</td>
</tr>
<tr>
<td>Best response to most recent platinum therapy — no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>71 (51.4)</td>
<td>33 (50.8)</td>
<td>117 (50.0)</td>
<td>60 (51.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>67 (48.6)</td>
<td>32 (49.2)</td>
<td>117 (50.0)</td>
<td>56 (48.3)</td>
</tr>
<tr>
<td>Prior bevacizumab use — no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (23.9)</td>
<td>17 (26.2)</td>
<td>62 (26.5)</td>
<td>30 (25.9)</td>
</tr>
<tr>
<td>No</td>
<td>105 (76.1)</td>
<td>48 (73.8)</td>
<td>172 (73.5)</td>
<td>86 (74.1)</td>
</tr>
</tbody>
</table>
NOVA: Niraparib is active in both mutated and non mutated patients

gBRCA mut
21 vs 5.5 months (HR 0.27)

gBRCA wt
9.3 vs 3.9 months (HR 0.45)
NOVA: in BRCA wt patients Niraparib is particularly active in HRD positive

- gBRCA wt - HRD positive: 12.9 vs 3.8 months (HR 0.38)
- All gBRCA wt: 9.3 vs 3.9 months (HR 0.45)
## Treatment-emergent Grade 3/4 Adverse Events Occurring in ≥5% of Patients

<table>
<thead>
<tr>
<th>Event — no. (%)</th>
<th>Niraparib (N=367)</th>
<th>Placebo (N=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia*</td>
<td>124 (33.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Anemia*</td>
<td>93 (25.3)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>72 (19.6)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>30 (8.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (8.2)</td>
<td>4 (2.2)</td>
</tr>
</tbody>
</table>

MDS/AML occurred in 5 of 367 (1.4%) in patients who received niraparib and 2 of 179 (1.1%) in patients who received placebo.

*There were no Grade 5 events.

*Thrombocytopenia=thrombocytopenia and decreased platelet count. No grade 3 or 4 bleeding events were associated with thrombocytopenia;  
*Anemia=anemia and decreased hemoglobin counts;  
*Neutropenia=neutropenia, decreased neutrophil count, and febrile neutropenia;  
*Fatigue=fatigue, asthenia, malaise, and lethargy.
Conclusions

- Niraparib significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer, regardless of BRCA mutation or HRD status
  - gBRCAmut: HR 0.27
  - Non-gBRCAmut: HR 0.45
  - Non-gBRCAmut HRD-positive: HR 0.38
  - Non-gBRCAmut HRD-negative (exploratory): HR 0.58

- Hematologic lab abnormalities were the most common side effects, managed with dose adjustments. The majority of patients remained on treatment until disease progression

- No detrimental effect in quality of life was observed with niraparib

- These landmark results warrant niraparib maintenance therapy to whole study population
NOVA: Niraparib prolongs PFS in mutated and non mutated patients

- This is an extraordinary result that will determine a change in clinical practice, opening the way of PARP inhibition to BRCA non mutated patients.

- This is the first definitive demonstration from a phase 3 trial that not only gBRCA patients benefit from a PARP inhibitor and that we can select by an HRD test the non mutated patients that are likely to benefit more from PARP inhibition.
Other trials have suggested activity for PARP in wt patients

**Olaparib**

<table>
<thead>
<tr>
<th>STUDY 19</th>
<th>HRD subgroup</th>
<th>Median PFS(^1,2) mo (90% CI)</th>
<th>Median PFS(^1,2) mo (90% CI)</th>
<th>HR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Olaparib</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>8.4 (7.4 -11.5)</td>
<td>4.8 (3.0-5.4)</td>
<td>HR=0.35 (0.25 -0.49); p&lt;0.0001</td>
</tr>
<tr>
<td>gBRCA mut</td>
<td></td>
<td>11.2 (8.3 -NC)</td>
<td>4.3  (3.0-5.4)</td>
<td>HR 0.18 (0.10 -0.31); p&lt;0.0001</td>
</tr>
<tr>
<td>gBRCA wt</td>
<td></td>
<td>7.4  (5.5 -10.3)</td>
<td>5.5  (3.7-5.6)</td>
<td>HR 0.54(0.34 -0.85); p=0.0075</td>
</tr>
</tbody>
</table>


ENGOT-OV18/NOVA Trial discussed by Sandro Pignata
Who are the patients treated with Niraparib in NOVA?

- 60% with platinum free interval of more than 1 year
- All responding to platinum (51% complete responders)
- Around 30% with more than 3 previous chemotherapy lines

This population is enriched of patients highly sensitive to platinum

These are the best candidates for PARP inhibition
Why do some HRD negative cases respond to platinum and to Niraparib? Are there other impaired non HRD mechanisms of DNA repair?

- BER (Base excision Repair)
- NER (nucleotide Ex.Rep)
- NHEJ (non Homologus end Joining)

All related to response to platinum

- PARP inhibitors inhibit PARP-1, but also PARP2 that have different functions (i.e. PARP2 is involved in DNA repair through NER)
There are some (many) "exceptional" responders

- An high proportion of patients remains on treatment for a very long time
- We are not able to identify these patients (other biomarkers needed??)
- For "exceptional responders" the natural history of the disease is changed
Perspectives for PARP INHIBITION

✓ PARP in first line (SOLO 1: Olaparib, PRIMA: Niraparib)

✓ Combination with antiangiogenesis (PAOLA-1: Olaparib; AVANOVA: Niraparib, ICON-9: cediranib-Olaparib)

✓ Single agent PARP (QUADRA: Niraparib; SOLO 3: Olaparib; ARIEL4: Rucaparib)

✓ Combinations: Olaparib + immuno check point inhibitors

✓ Resistant disease: Wee-1 inhibitors + Olaparib (phase 1)
Oreo Study design: Olaparib Rechallenge

OC in RELAPSE
- Previous treatment with consecutive PARPi ≥ 6 months

Randomization
- 2:1
- OLAPARIB tablets*
- Placebo

Double-blind phase IIIb study design

*300mg bid or last tolerable dose
Olaparib and PD1 Checkpoint inhibitor- Durvalumab

Durable long term response with D+O

Figure 1. RECIST Response Spidergram of D+O. A majority of pts had durable response with D+O and 1 BRCA wild type OvCa pt (DL1) had PR. 6 pts are still on treatment (+).

Lee Jung-Min et al ASCO 2016
...And that, in simple terms, is how you increase your ranking on search engines.”