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 cobinations

Mismatch repair (MMR)

Nucleotide excision repair (NER)

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]

Base excision repair

Repair enzymes

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.[15-18]

PARP

Poly ADP-ribose chain

Homologous recombination

NHJR

DNA damage
Single-strand DNA break

Double-strand break

Palb b2

DNA-binding chemotherapeutic drug

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]

Mutant BRCA

PARP

Poly ADP-ribose

Unrepaired DNA

Synthetic lethality

Dying cancer cells

Cell death

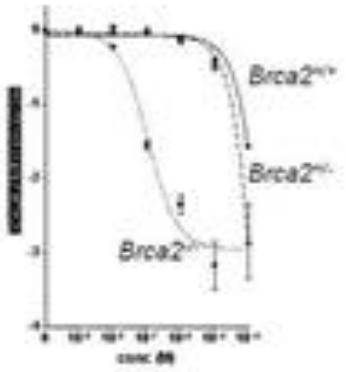
PARP inhibitors: a 10 year history

Olaparib – the full story

2005 Preclinical[1] → Early clinical trials[2,3] (Phase I, IB) → Randomised clinical trials → 2015

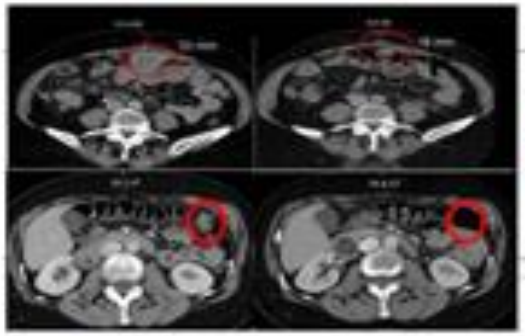
APPROVAL

Exquisite preclinical efficacy of PARPi



Farmer et al. Nature 2005

Phase I trial confirms excellent tolerance and expansion in 50 BRCA patients showed 46% response.

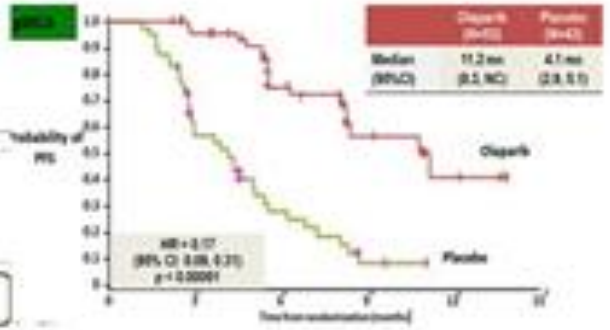


"this is nothing like chemotherapy

Fong P et al. N Engl J Med. 2009; 361, 123-134;
Fong P et al. Ann Oncol 2010; 21, 116-122

Randomised trial (maintenance therapy) showed marked PFS benefit particularly in BMOC

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



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

Study 12 → Study 41 → Study 19

Dose

Single agent maintenance

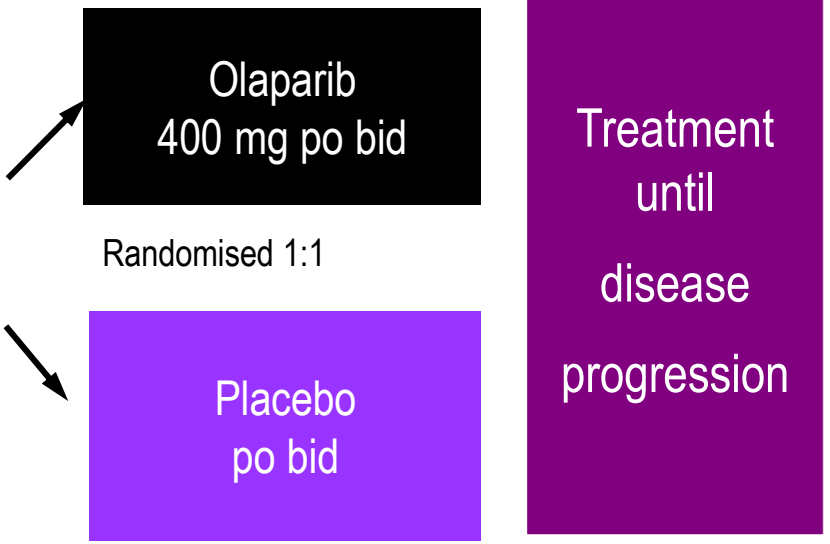
EMA approval

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



Primary end point: PFS

Sept 2008–Feb 2010

bid, twice daily; CA-125, Cancer Antigen 125; CR, complete response; po, orally; PR, partial response.

Ledermann J et al. N Engl J Med 2012;366:1382–1392

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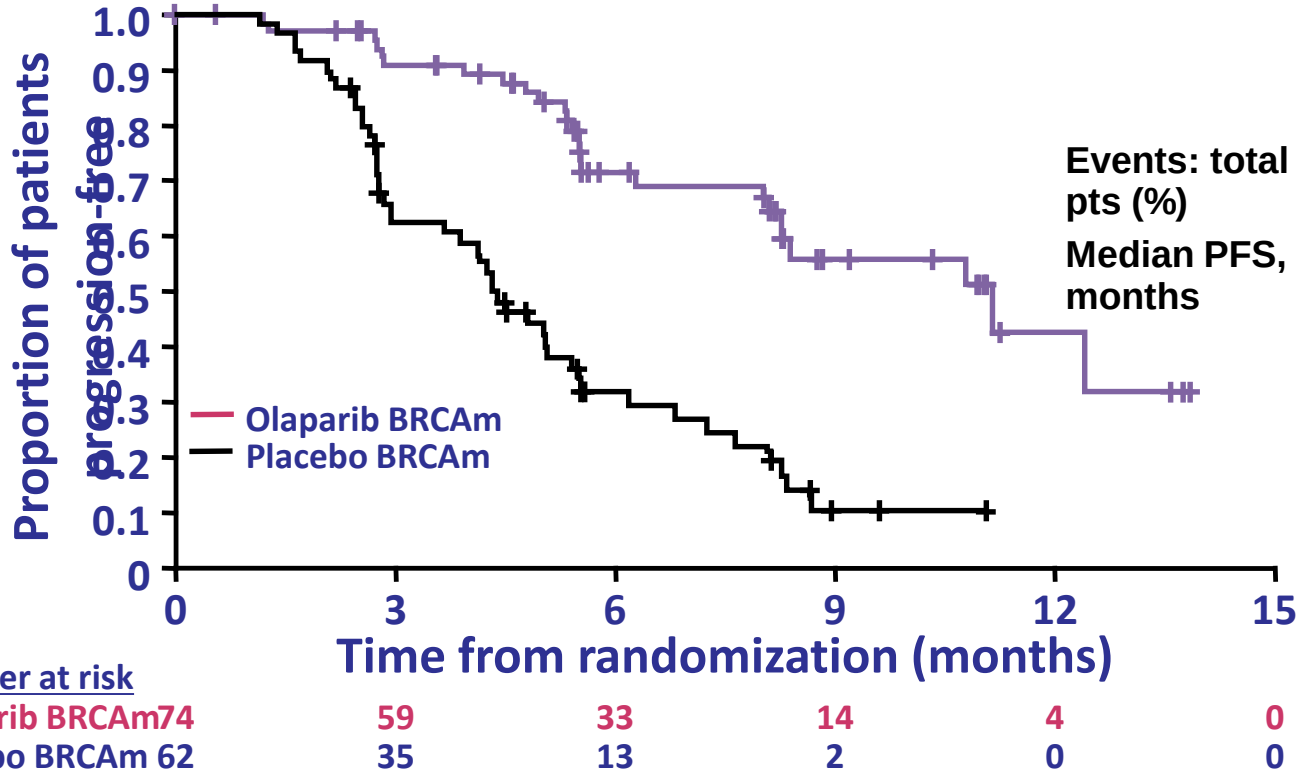
ORIGINAL ARTICLE

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer



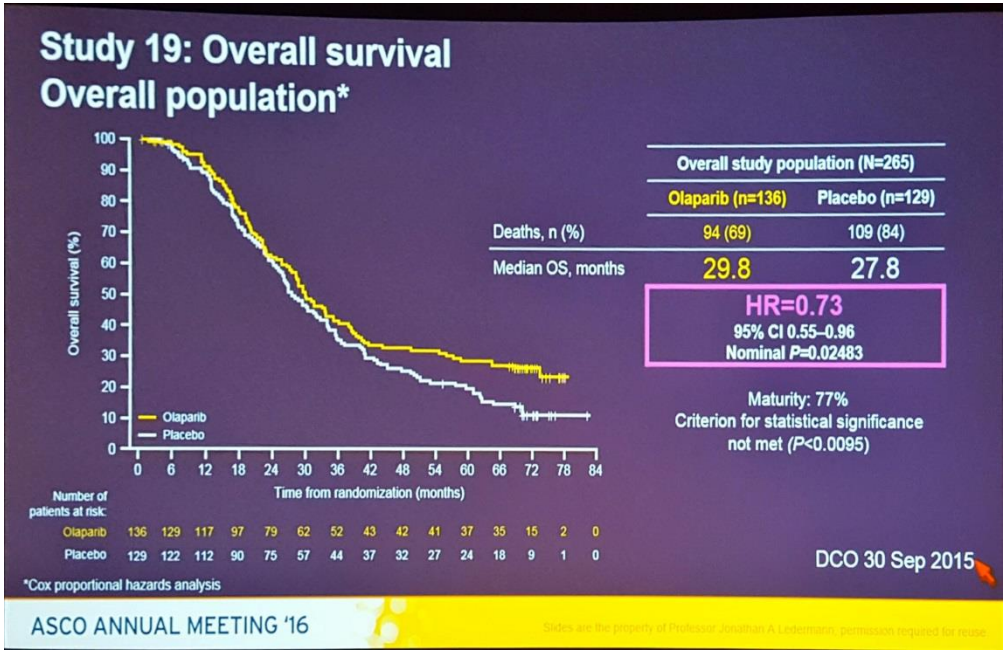
Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

BRCAm (n=136)	
Olaparib	Placebo
Events: total pts (%) 26:74 (35.1)	46:62 (74.2)
Median PFS, months 11.2	4.3

HR=0.18
95% CI (0.11, 0.31);
P<0.00001

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

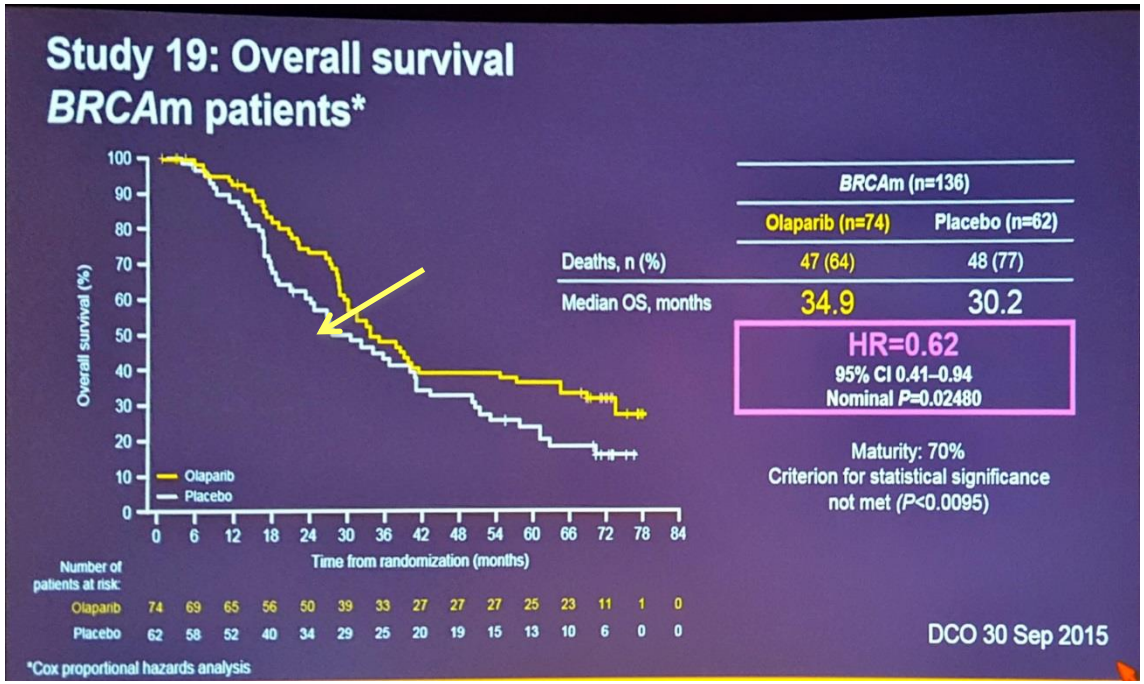
Ledermann J *et al. N Engl J Med* 2012;366:1382–1392



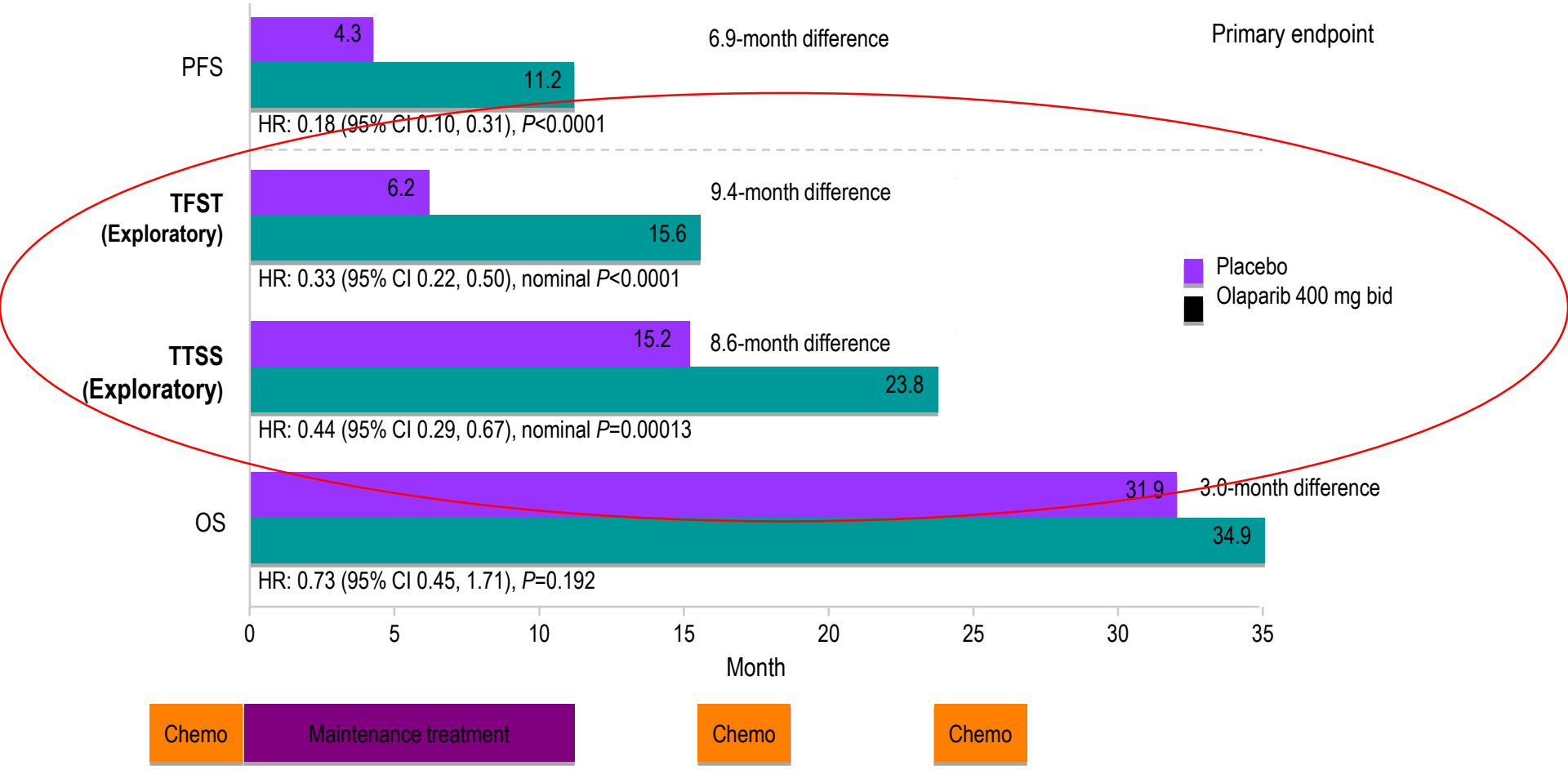
14/62 (22,6%) placebo pts switched to a PARP i

Adjusted analysis excluding centres where patients received subsequent PARP inhibitors:

	BRCAm (n=97)	
	Olaparib	Placebo
Median OS Months	**34.9**	26.6
	HR 0.52 95% CI 0.28-0.97 p=0.039	



OVERVIEW OF EFFICACY ANALYSES IN PATIENTS WITH A *BRCA1/2* MUTATION

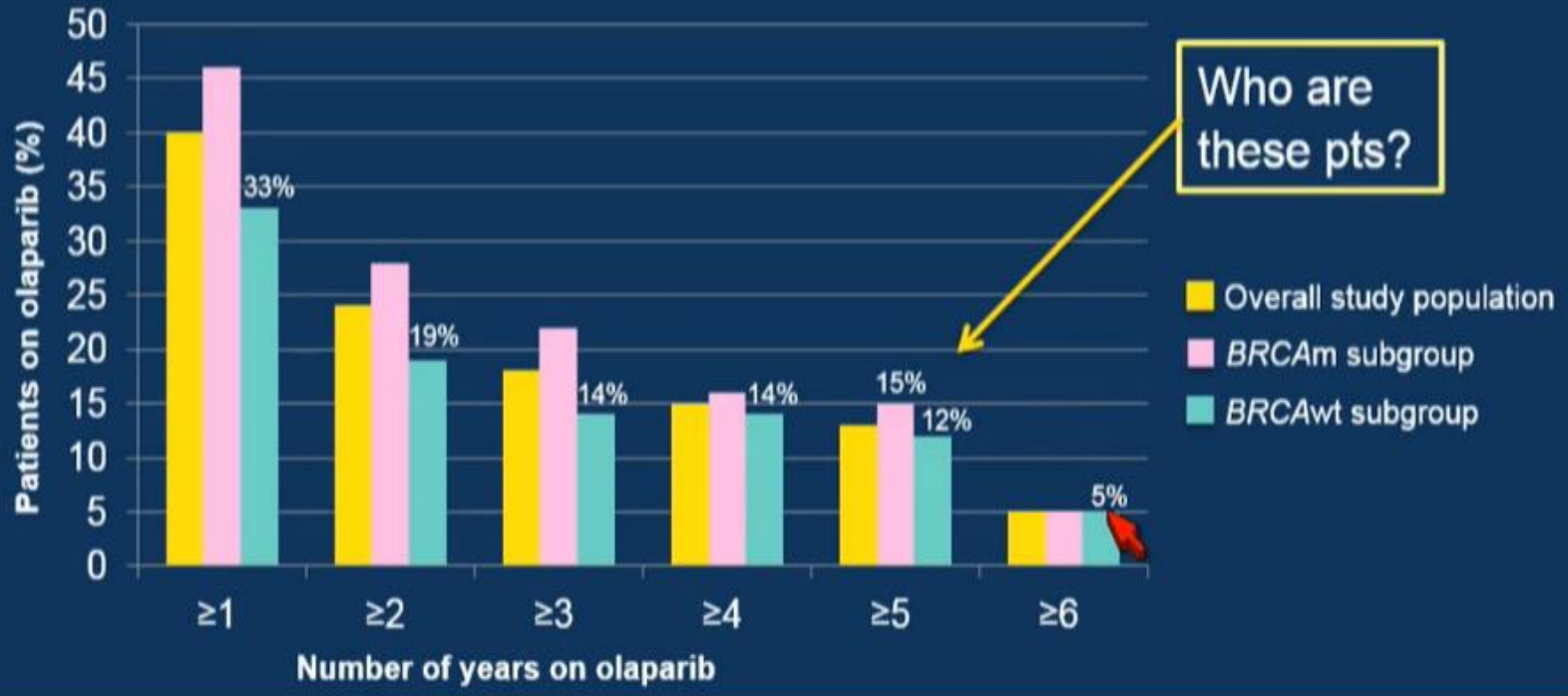


TFST, time from randomisation to first subsequent therapy or death; TSST, time from randomisation to second subsequent therapy or death

Ledermann J et al. Lancet Oncol 2014;15:852–861 (Supplementary Appendix, p 5)

Long-term exposure to treatment

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



Ovarian Cancer: therapy

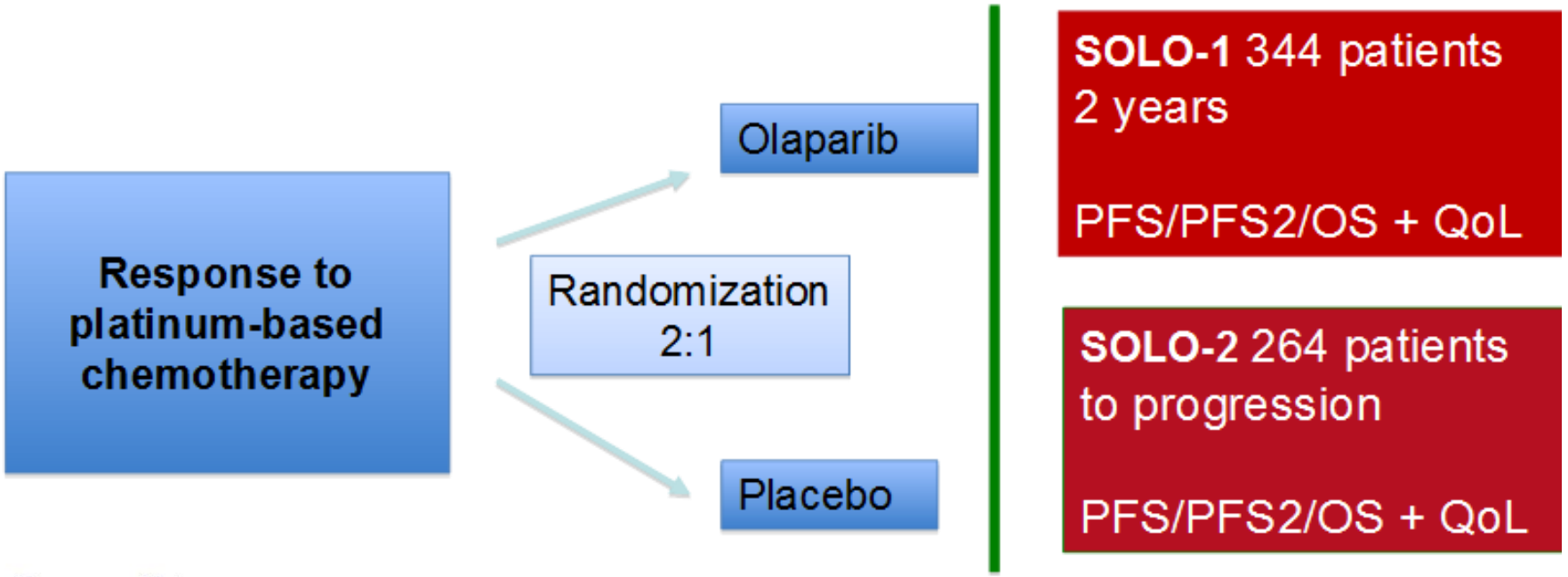
Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pazienti con malattia platino refrattaria/resistente con indicazione alla chemioterapia, è indicato un trattamento monochemioterapico	**Positiva forte**
A	Nelle pazienti con malattia platino sensibile è indicato un trattamento con carboplatino e paclitaxel	**Positiva forte**
A	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	**Positiva debole**
A	Nelle pazienti non pretrattate con bevacizumab, bevacizumab può essere associato alla chemioterapia e continuato come mantenimento	**Positiva forte**
B	Nelle pazienti con mutazione di BRCA, olaparib può essere somministrato dopo la chemioterapia e continuato come mantenimento	**Positiva forte**

Linee Guida, Edizione 2016

….. Recidiva di carcinoma ovarico "platino sensibile" con mutazioni germinali o somatiche di BRCA

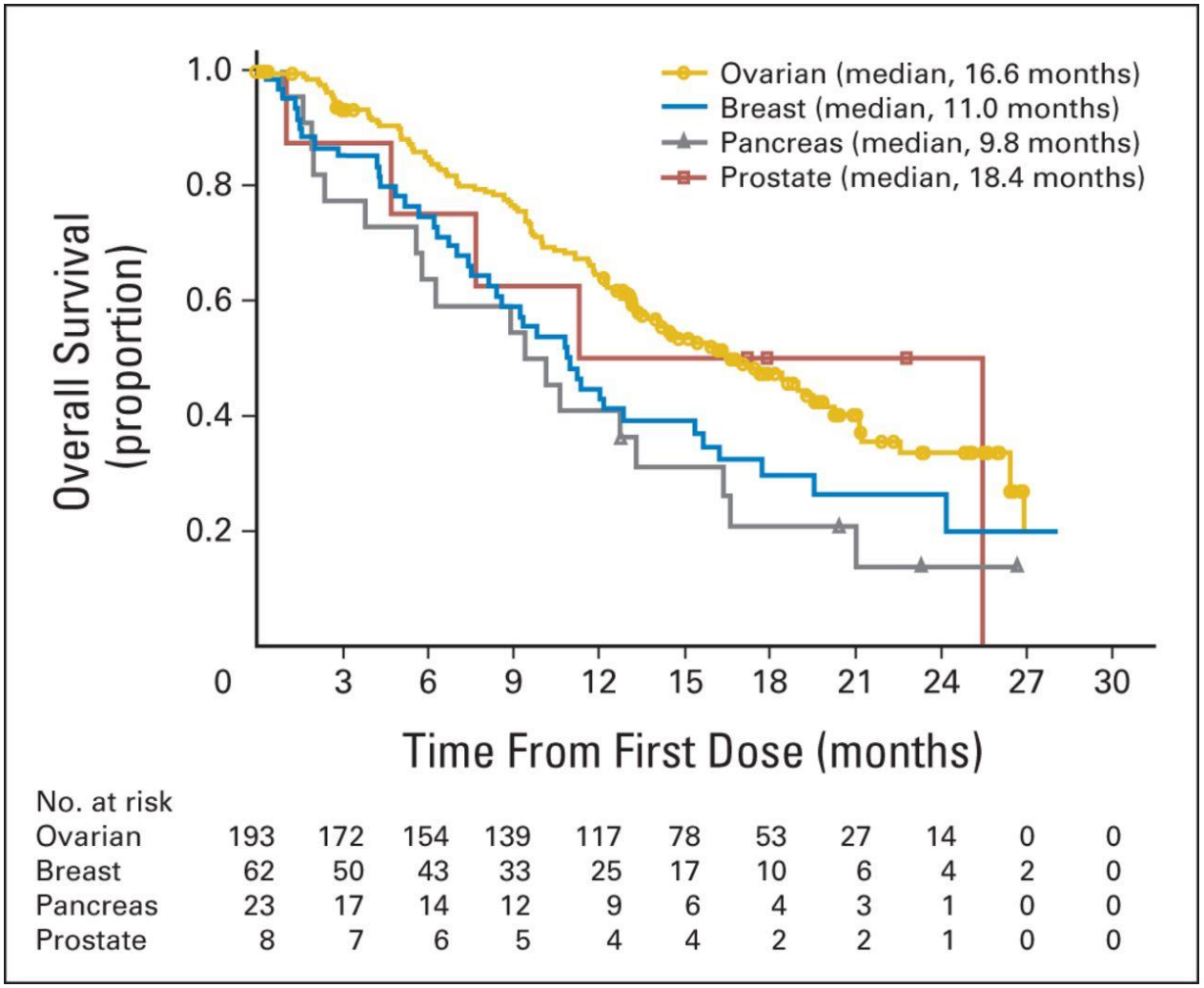
SOLO-1 & SOLO 2 Program
BRCAm Population Only

First-line maintenance or maintenance in 'platinum-sensitive' setting



Can PARP inhibitors replace platinum-based chemotherapy in platinum-sensitive patients?

Olaparib monotherapy Overall survival.



Ovarian cancer (193): platinum resistant or not suitable for further platinum therapy, median N. of prior line: 4,3 RR:34%

Gemelli

Bella Kaufman et al. JCO 2015;33:244-250

JOURNAL OF CLINICAL ONCOLOGY ASCO

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.

FDA News Release

FDA approves Lynparza to treat advanced ovarian cancer

First LDT companion diagnostic test also approved to identify appropriate patients

For Immediate Release December 19, 2014

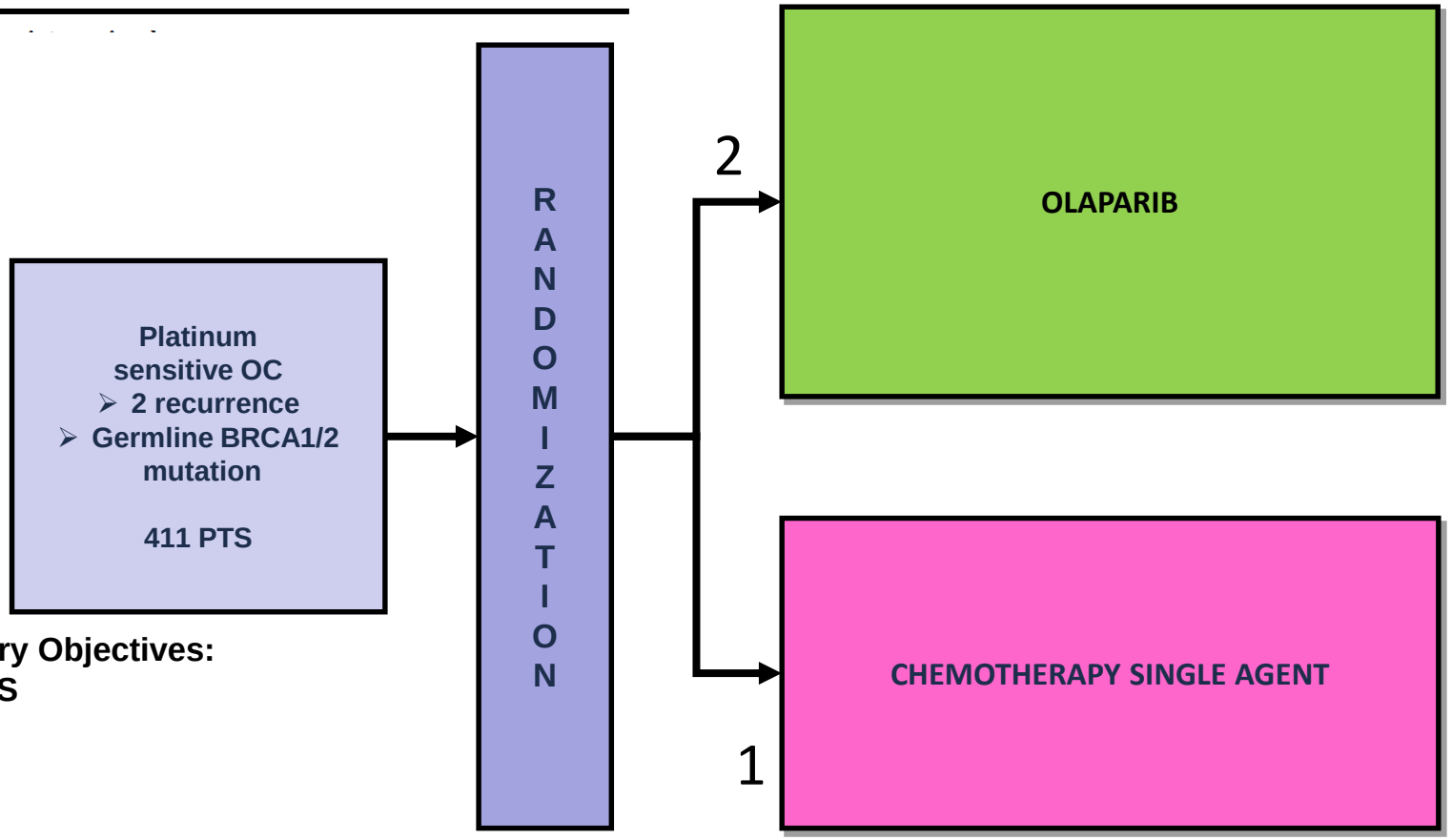
Matulonis et al, SGO 2015		
Plat sens	35/74	47% resp
Plat resi	31/115	27% resp

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

AstraZeneca

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**

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

Future challenges: Biomarkers

How to identify BRCAness 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)**

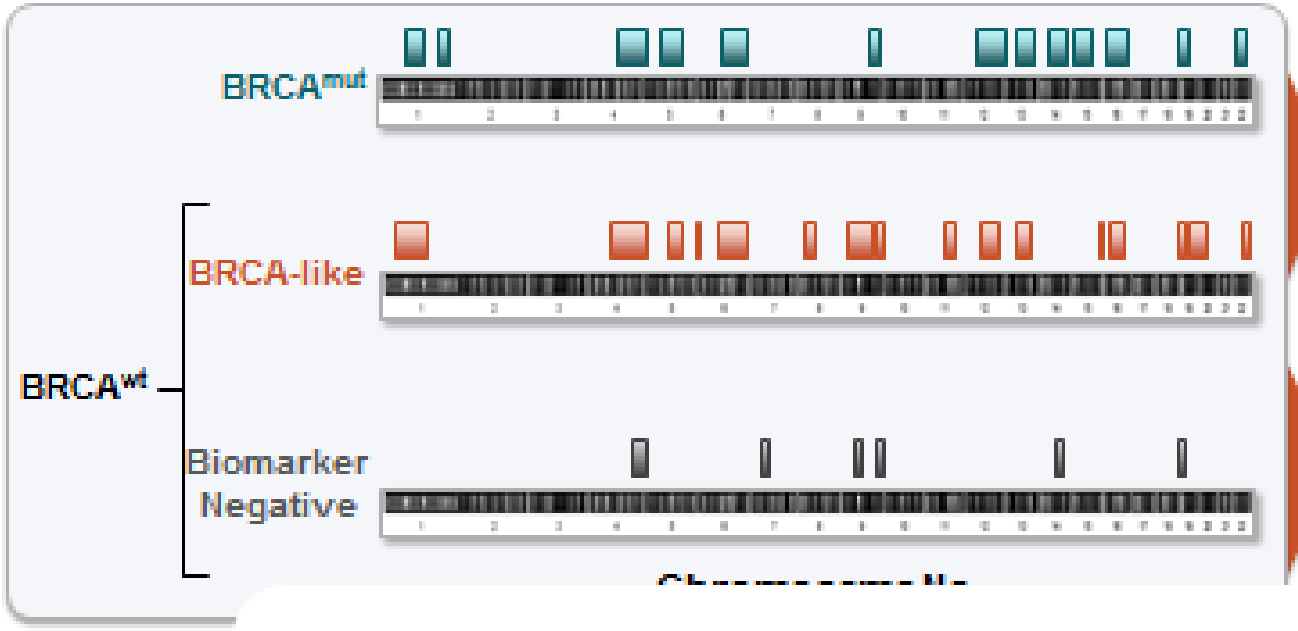
Two Main HRD Genomic Scar Tests Have Been Developed

- **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 ≥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 t*BRCA*m

1. Swisher EM et al ASCO 2014 Abstract TPS5619
2.http://investors.foundationmedicine.com/releasedetail.cfm?releaseid=883986
3.http://investor.myriad.com/releasedetail.cfm?releaseid=915453
4. Mills et al, SGO 2016

HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS



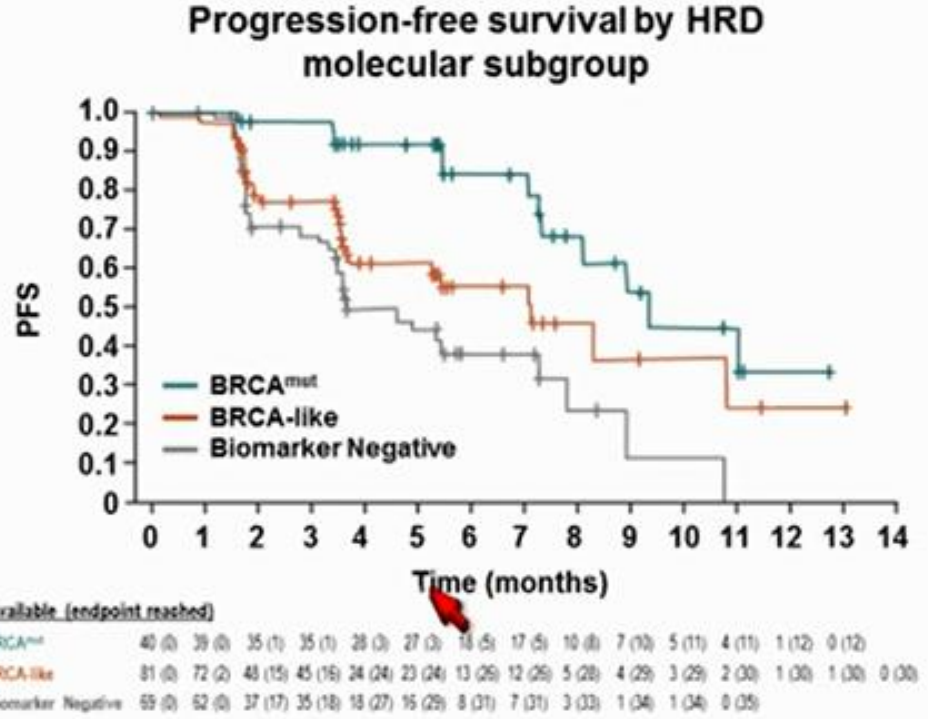
Hypothesis 1: Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

Hypothesis 2: Ovarian cancer patients who are "Biomarker Negative" (ie, with low genomic LOH) will not respond to

- 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^{mut} and BRCA-like versus Biomarker Negative patients



HRD Subgroup	Median PFS, mo (90% CI)
BRCA^{mut}	9.4 (7.3, Not Reached)
BRCA-like	7.1 (3.7, 10.8)
Biomarker Negative	3.7 (3.5, 5.5)

Subgroup Comparison	Hazard Ratio (90% CI)
BRCA^{mut} vs Biomarker Negative	0.47 (0.35, 0.64)
BRCA-like vs Biomarker Negative	0.61 (0.41, 0.92)

CI=confidence interval

PRESENTED AT: ASCO Annual '15 Meeting

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)

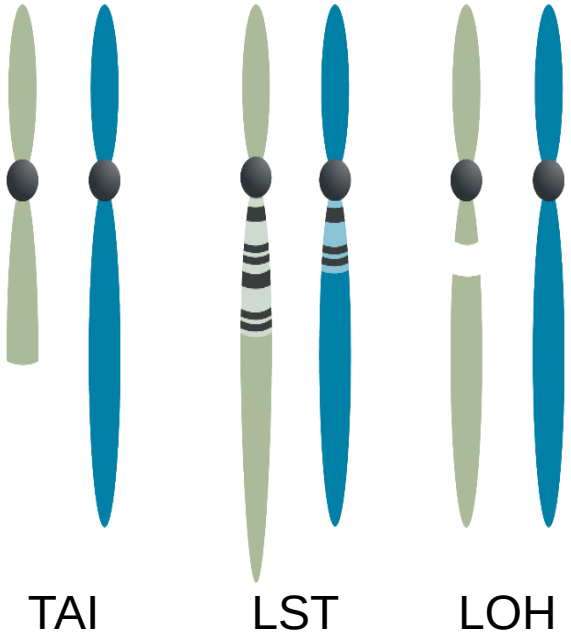
ARIEL3 (N=540)

Randomized maintenance study rucaparib vs placebo in HGOC patients who have received ≥2 platinum regimens (NCT01968213)

PRESENTED AT: ASCO Annual '15 Meeting

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

1. Birbak NJ, et al. *Cancer Discovery*. 2012; 2:366.
2. Popova T, et al. *Cancer Research*. 2012; 72:5454.
3. Abkevich V, et al. *Br J Cancer*. 2012; 107(10):1776.

The NEW ENGLAND JOURNAL of MEDICINE

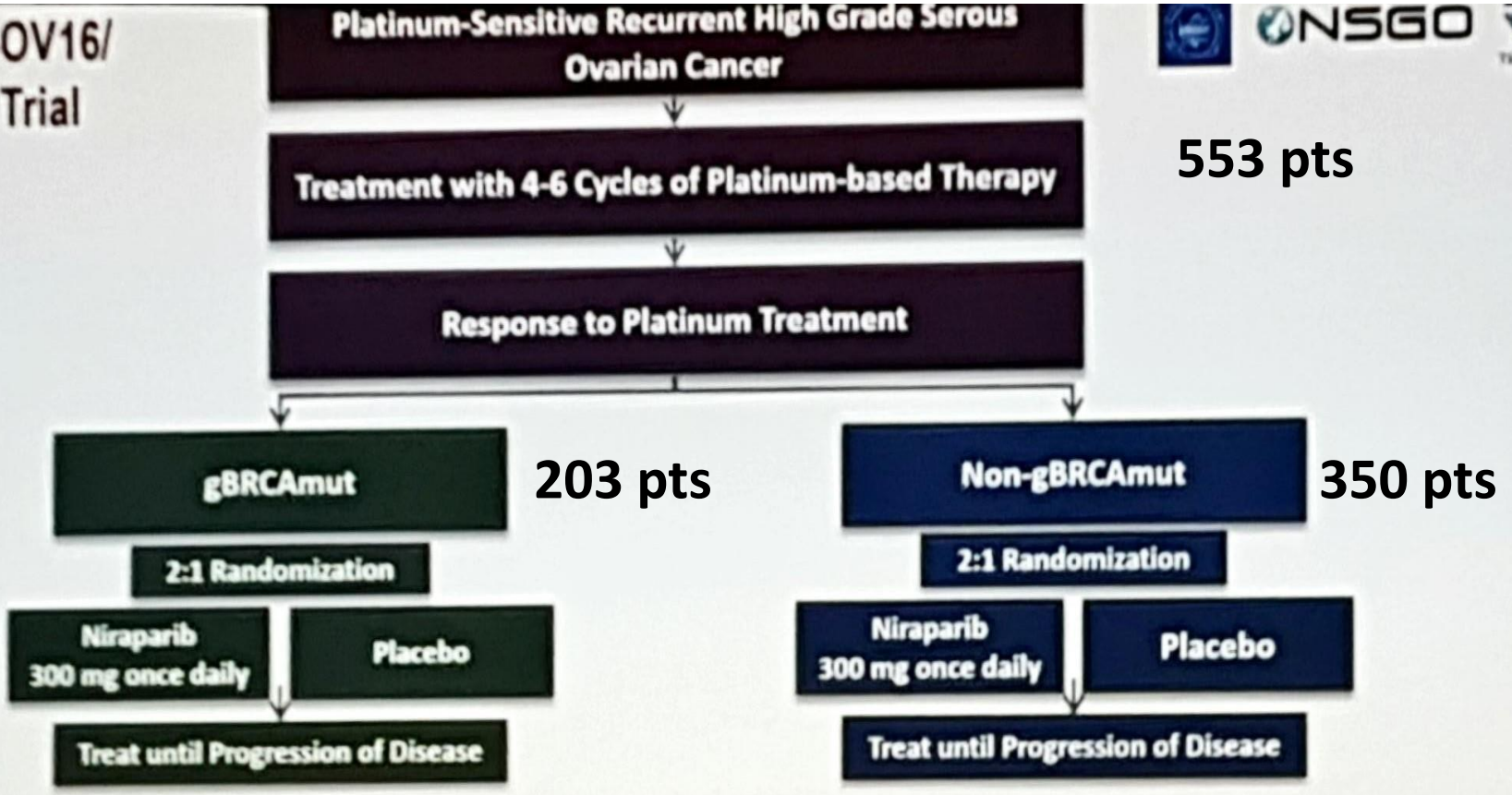
ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

This article was published on October 8, 2016, at NEJM.org.

ENGOT-OV16/ NOVA Trial



Patient Demographics & Baseline Characteristics

Characteristic	gBRCAmut		Non-gBRCAmut	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Age - years				
Median (min, max)	57.0 (36, 83)	58.0 (38, 73)	63.0 (33, 84)	60.5 (34, 82)
Region – n (%)				
USA and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
ECOG performance status – n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumor site – n (%)				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Lines of previous chemotherapy – n (%)				
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

*One patient received one line of prior therapy.

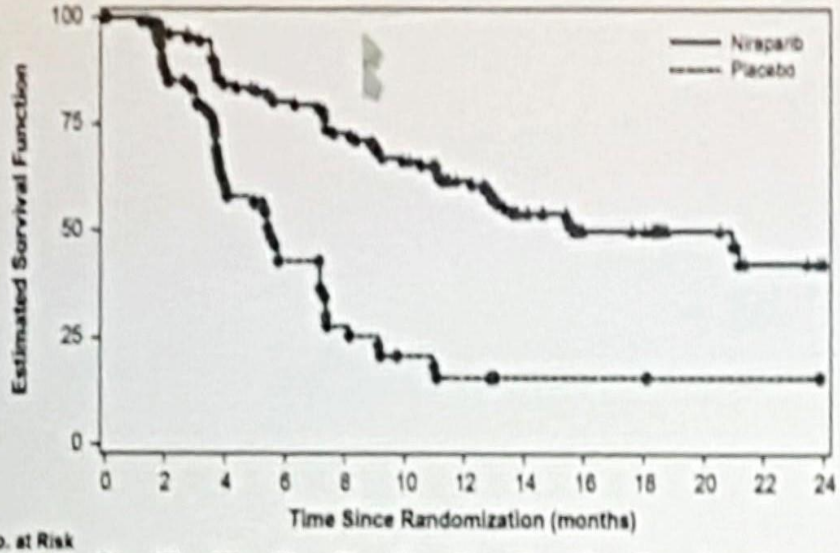
Prospective Stratification Factors for Randomization

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

NOVA: Niraparib is active in both mutated and non mutated patients

gBRCA mut

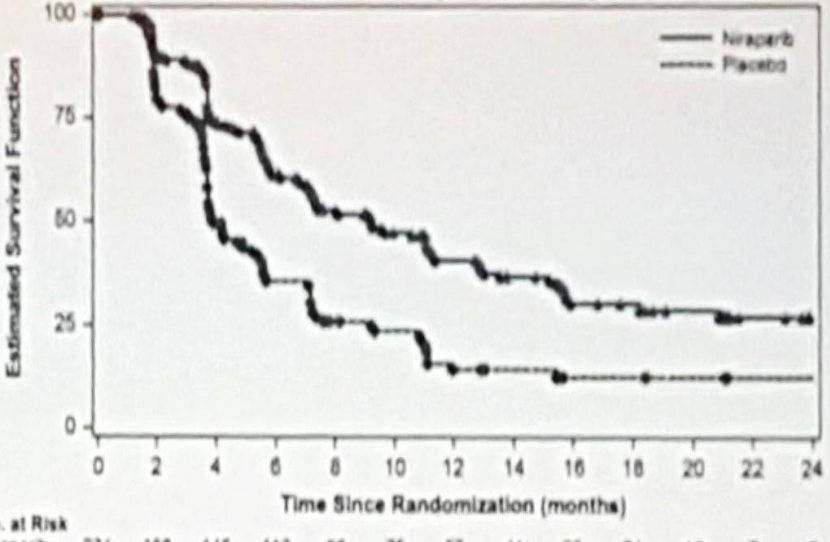
21 *vs* 5.5 months (HR 0.27)



No. at Risk													
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

gBRCA wt

9.3 *vs* 3.9 months (HR 0.45)

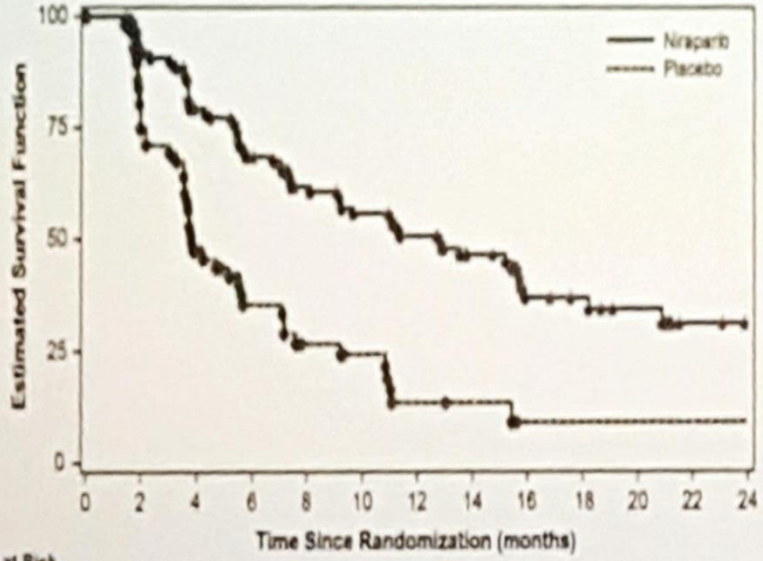


No. at Risk													
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1

NOVA: in BRCA wt patients Niraparib is particularly active in HRD positive

gBRCA wt - HRD positive

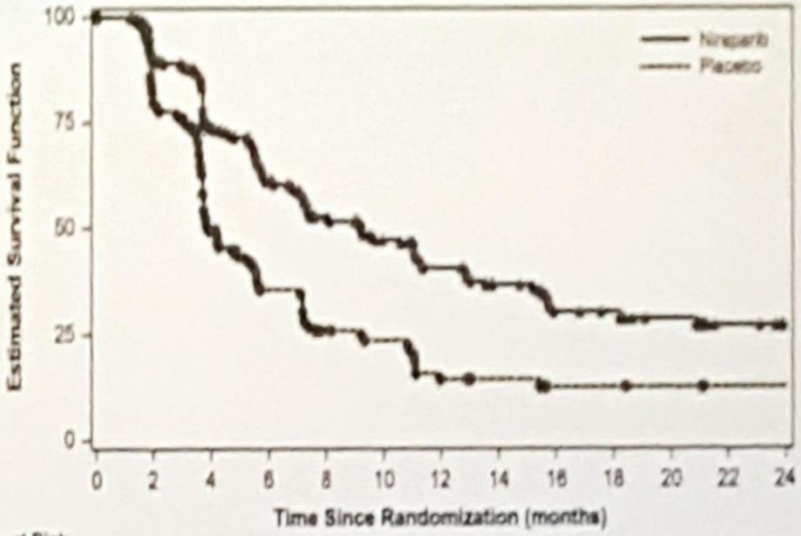
12.9 *vs* 3.8 months (HR 0.38)



No. at Risk													
Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

All gBRCA wt

9.3 *vs* 3.9 months (HR 0.45)



No. at Risk													
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	86	52	33	23	19	10	8	4	4	3	1	1

Treatment-emergent Grade 3/4 Adverse Events Occurring in ≥5% of Patients

Event — no. (%)	Niraparib (N=367)	Placebo (N=179)
Thrombocytopenia[a]	124 (33.8)	1 (0.6)
Anemia[b]	93 (25.3)	0
Neutropenia[c]	72 (19.6)	3 (1.7)
Fatigue[d]	30 (8.2)	1 (0.6)
Hypertension	30 (8.2)	4 (2.2)

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.

[a]Thrombocytopenia=thrombocytopenia and decreased platelet count. No grade 3 or 4 bleeding events were associated with thrombocytopenia; [b]Anemia=anemia and decreased hemoglobin counts; [c]Neutropenia=neutropenia, decreased neutrophil count, and febrile neutropenia; [d]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

STUDY 19	HRD subgroup [2]	Median PFS [1,2] mo (90% CI)	Median PFS [1,2] mo (90% CI)	HR (90% CI)
		Olaparib	Placebo	
	All patients	8.4 (7.4 -11.5)	4.8 (3.0–5.4)	HR=0.35 (0·25–0·49); *p*<0.0001
	gBRCA mut	11.2 (8.3 -NC)	4.3 (3.0–5.4)	HR 0.18 (0.10–0.31); *p*<0.0001
	gBRCA wt	7.4 (5.5 - 10.3)	5.5 (3.7–5.6)	HR 0.54(0.34–0.85); *p*=0.0075

[1] Ledermann J *et al. New Engl J Med* 2012;366:1382–1392; [2] Ledermann J *et al. Lancet Oncol* 2014;15:852–861

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)

Yelamos J et al Am J Cancer Res 2011

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**

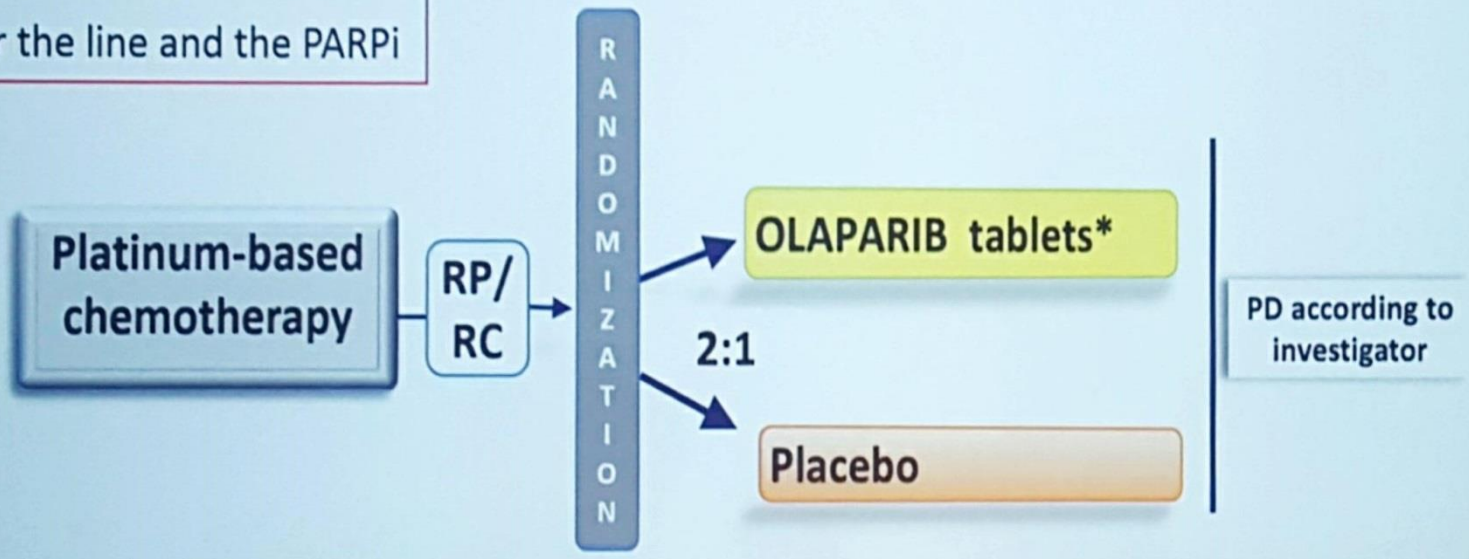
Perspectives for PARP INHIBITION

- 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
- Whatever the line and the PARPi



Double-blind phase IIIb study design

*300mg bid or last tolerable dose

Olaparib and PD1 Checkpoint inhibitor- Durvalumab

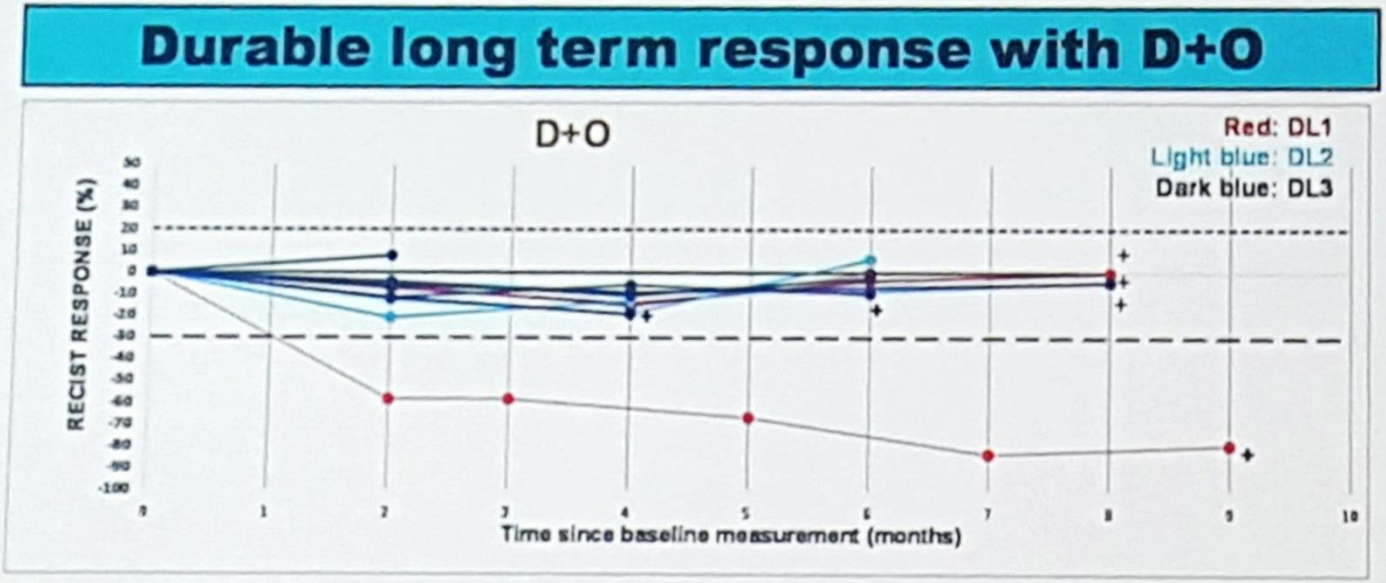


Figure 1. RECIST Response Spidergram of D+O. A majority of pts had durable response with D+O and 1 BRCA wild type OvCa pt (DL1) had PR. 6 pts are still on treatment (+).

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Lee Jung-Min et al ASCO 2016

Thank you

...And that, in simple terms, is how you increase your ranking on search engines."