Maintenance Therapy in OVARIAN CANCER

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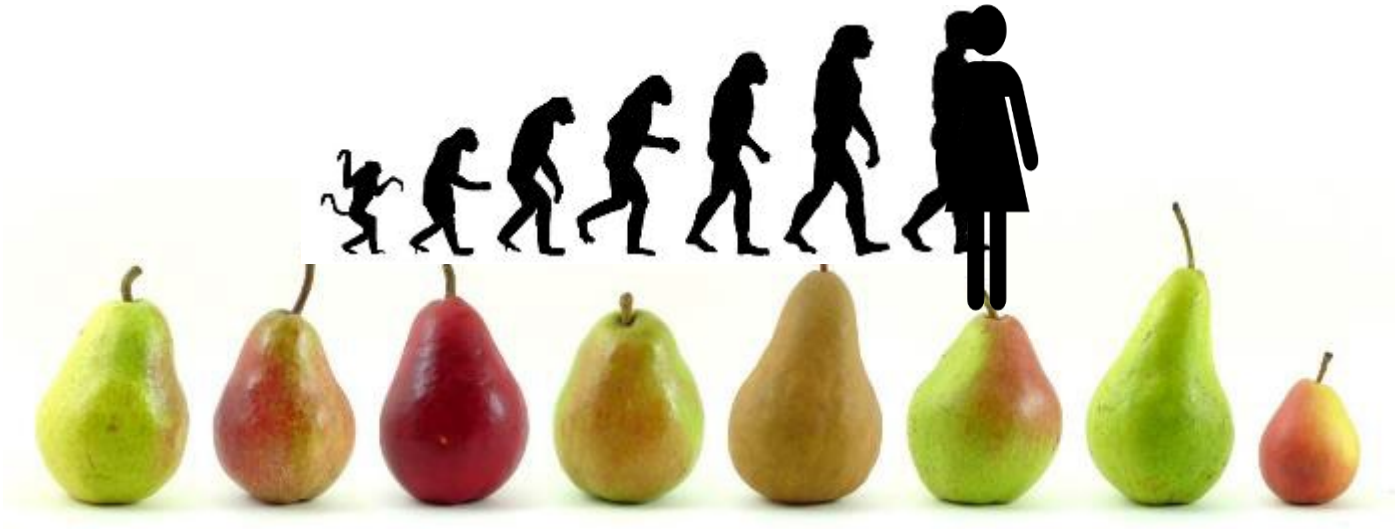
University of Berlin, Germany, Europe one world!

The Evolution in Ovarian Cancer



Surgery

Surgery + Rx

Surgery + Cx

Surgery + Cx+ Maintenance

Stadien I-IVb

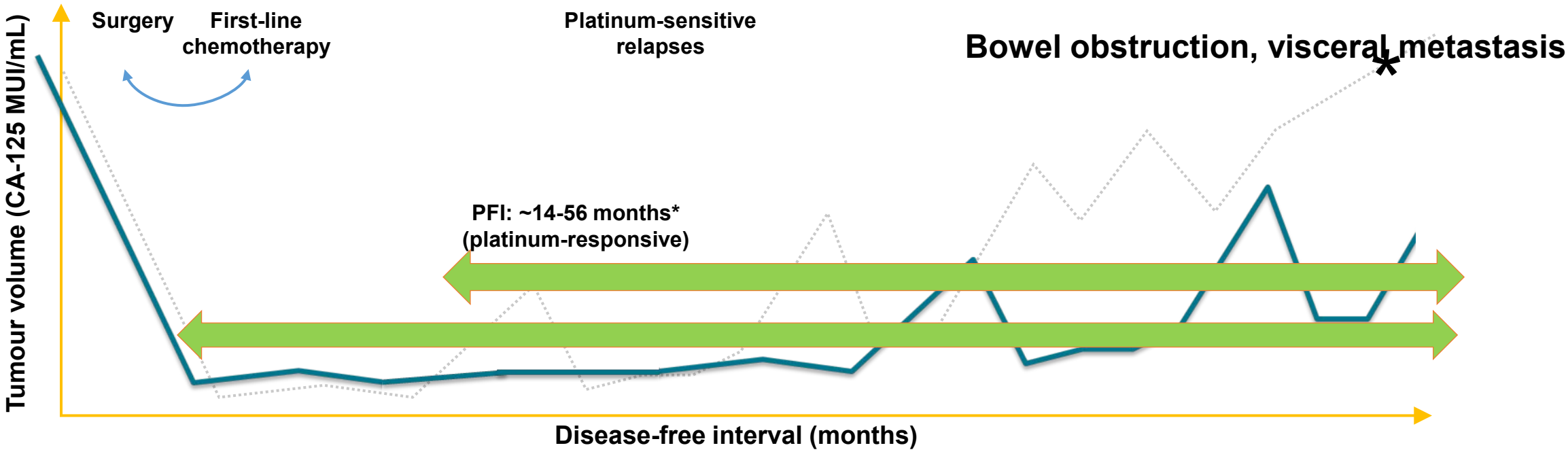
low grade/high grade

BRCA+

HRD

Disease-free intervals decrease with each relapse in advanced ovarian cancer[1]

Ovarian cancer: treatment and recurrence pattern with PARPi maintenance therapy[1-3]



Maintenance therapy with PARPi can lengthen PFI for patients with platinum-sensitive recurrent ovarian cancer[4]

*PFI based on mPFS observed in SOLO1 and PRIMA (overall population).[2,3]

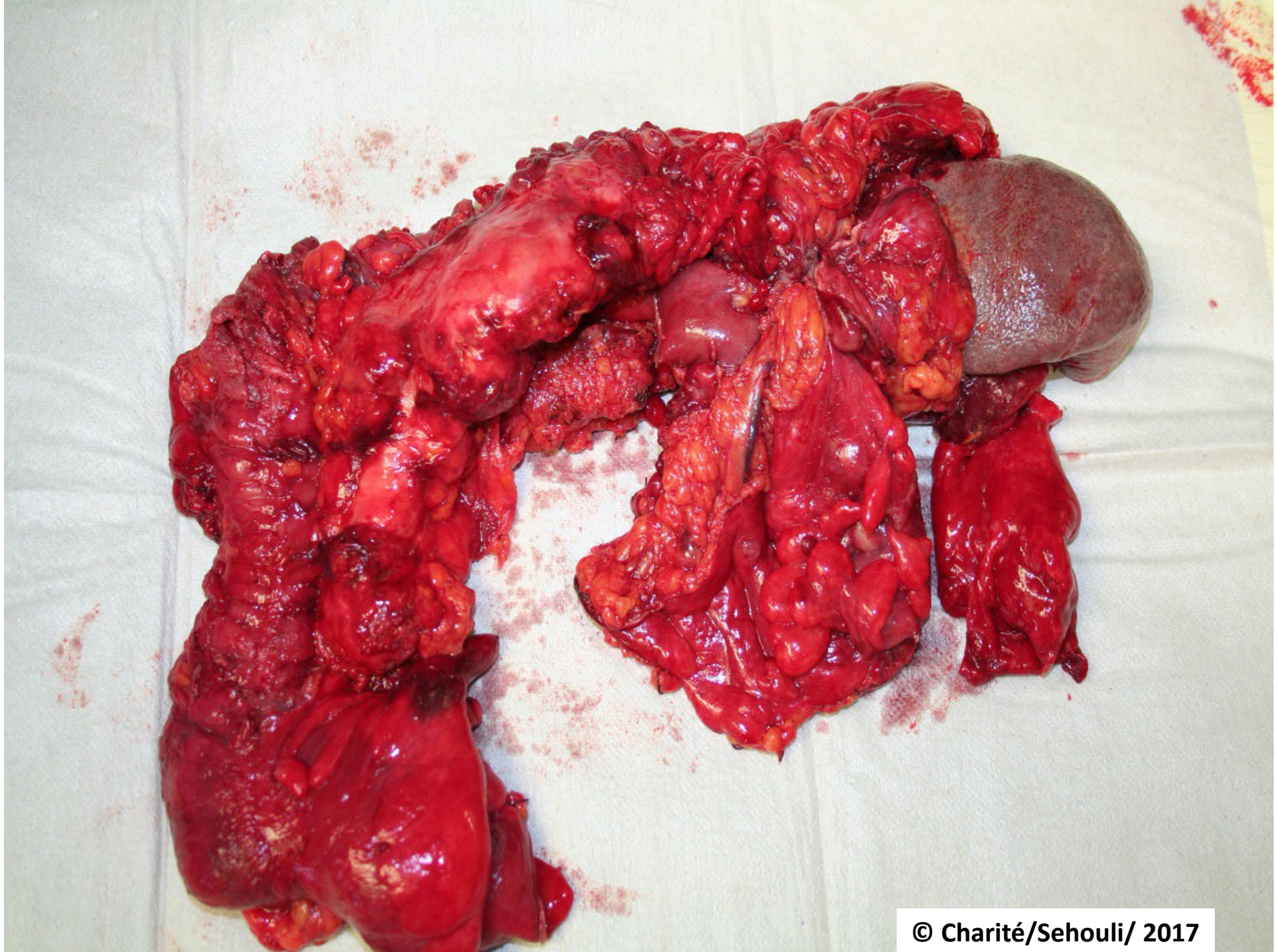
CA-125, cancer antigen 125; mPFS, median progression-free survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval or duration of disease control without chemotherapy.

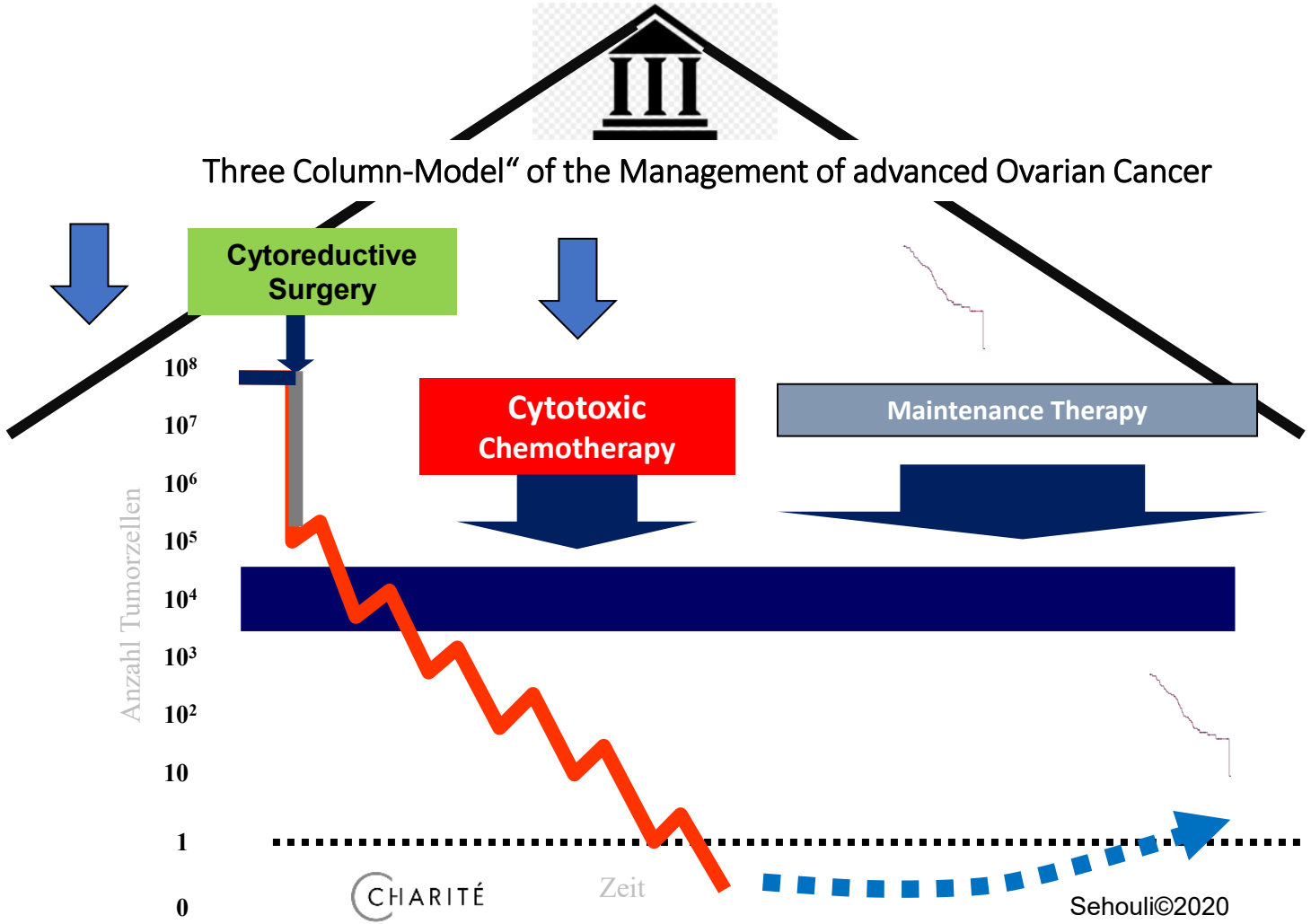
1. Giornelli GH. *Springerplus*. 2016;5(1):1197. doi:10.1186/s40064-016-2660-0 **2.** Banerjee S et al. *Lancet Oncol.* 2021;22(12):1721-1731. **3.** González-Martín A et al. *N Engl J Med.* 2019;381(25):2391-2402. **4.** Wu XH et al. *Ann Oncol*. 2021;32(4):512-521.

Maintenance therapy in ovarian cancer

What do we know?

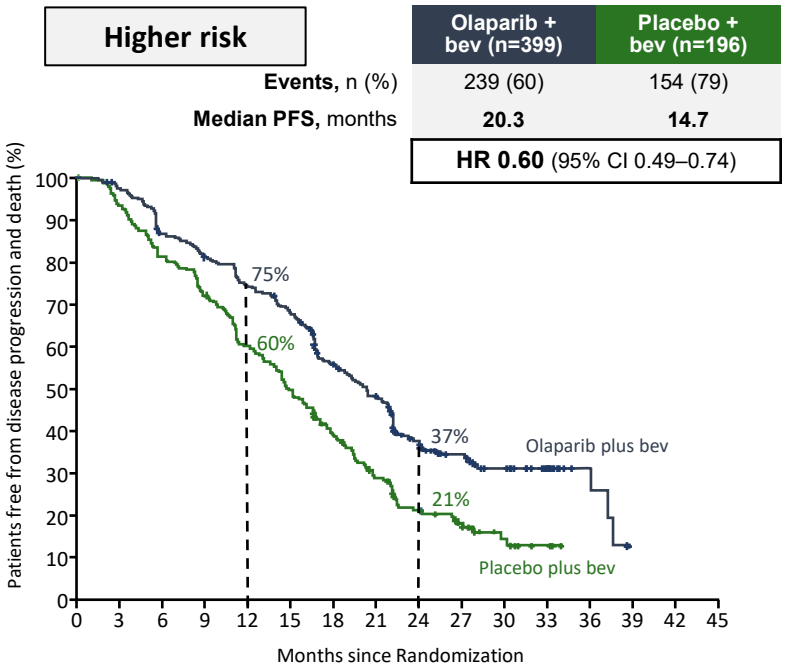
What do we don´t know?





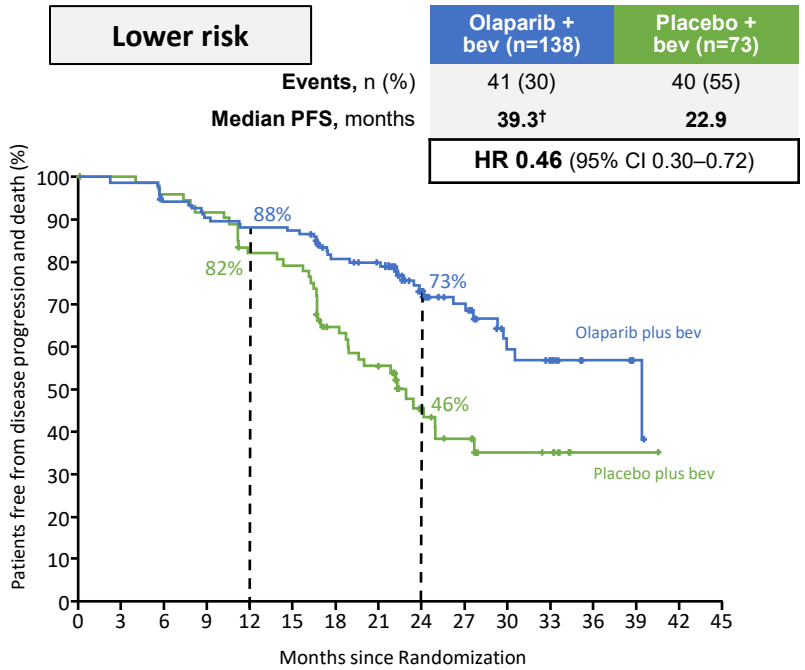
Surgery alone?

PFS by clinical risk*



Number of patients at risk:

Olaparib plus bev	399	381	336	313	287	259	188	153	86	68	31	19	6	0
Placebo plus bev	196	180	157	139	114	95	67	48	31	21	9	4	0	



Number of patients at risk:

Olaparib plus bev	138	132	125	120	116	115	91	87	55	44	24	18	6	3	0
Placebo plus bev	73	72	69	66	58	56	42	35	19	14	6	5	1	1	0

*The median time from the first cycle of chemotherapy to randomization was 7 months. The median duration of follow-up for PFS in higher-risk patients was 22.3 months (olaparib plus bevacizumab) and 24.6 months (placebo plus bevacizumab) and in lower-risk patients was 23.9 months (olaparib plus bevacizumab) and 22.3 months (placebo plus bevacizumab)

†Unstable median due to lack of events

Surgery plus Chemotherapy alone?

What factors influence the treatment decision making process („the Charité-algorhytm“)

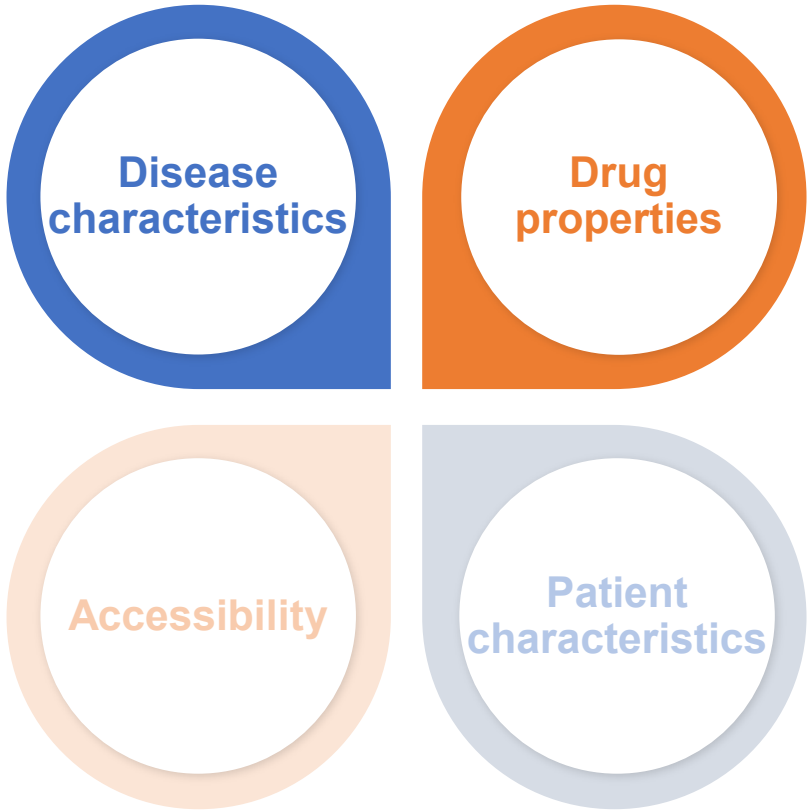
- Current syptoms?, tumor pattern?
- Therapie free and progression free interval? (platinum resistance yes/no, relative or platinumsensitive?)
- Histology (low grade/high grade)
- General and functional status
- Relevant comorbidities? comedication?
- Side effects and complications of previous therapies?
- Ressources to overcome complications?
- Quality and results of the surgical and medical therapies?
- Previous therapy with bevacizumab?
- Tumorbiology (BRCA-Test?)
- Surgery vs. Surgery + medical therapy vs medical therapy vs best supportive care
- Motivation of the patients (preference, attitude)
- Treatment options?
- Study participation?

Treatment decision

CHARITÉ

Optimal first-line maintenance decisions need to consider multiple factors[1-4]

- Clinical characteristics (symptoms, residual tumour)
- Molecular characteristics (biomarker status)
- Histology (low/high grade)

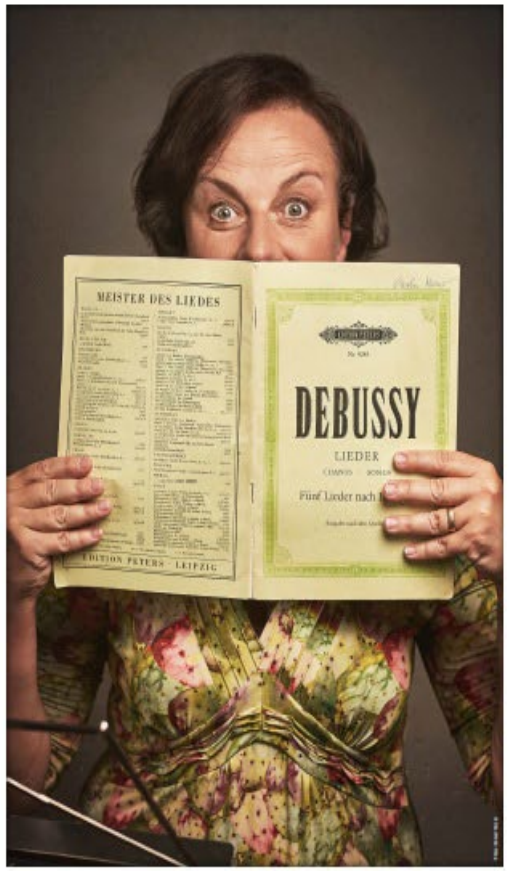


- Safety and efficacy
- Ease of administration
- Individualised dosing
- Drug interactions

- Genetic *BRCA* and HRD testing
- Approvals and indications
- Reimbursement/cost
- Therapy quality/ treatment options

- Overall treatment plan
- Comorbidities
- Patient preference
- Quality of life/ patient-reported outcomes
- General/functional status

„I live“



Carolin Masur

Erstdiagnose Eierstockkrebs: 2005

„Ich habe das große Glück, meine Energie für das Leben und die Musik wiedergefunden zu haben. Dankbar dafür teile ich diese Leidenschaft gern."

„I live“

Gunda Eigenwillig

Erstdiagnose Eierstockkrebs: 2004 | Rezidiv: 2008

„Ich bin schon immer gern verreist. Das habe ich auch in den vergangenen Jahren beibehalten. Reisen sind für mich Abwechslung vom Alltag und geben Kraft und man bekommt neue Eindrücke."

„I live“

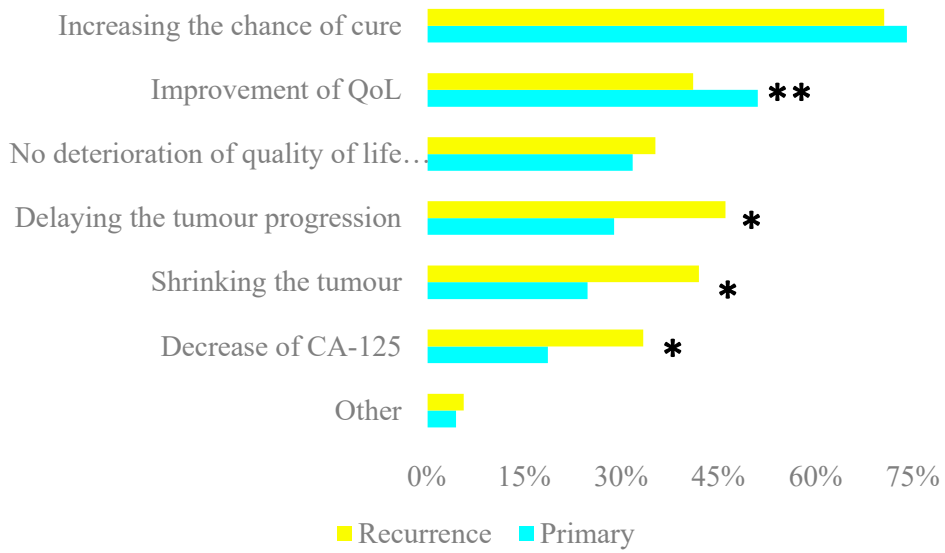
Dorothea Müller

Erstdiagnose Eierstockkrebs: 2003 | Rezidiv: 2006

„Während meiner Erkrankung ließ mich die "pure Lust am Leben" durchhalten, was manchmal wirklich schwer war. Manchmal hat der Mensch auch Glück! Denn vieles liegt außerhalb unseres Machtbereiches."

Results

Primary / Recurrence



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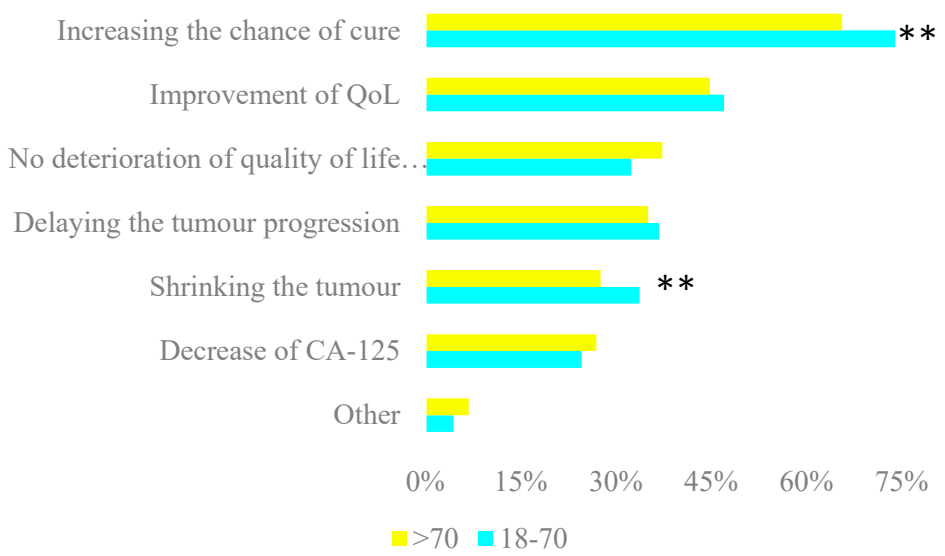


Personal obj[Expectations and preferences of patients with primary and relapsed ovarian cancer to maintenance therapy: A NOGGO/ENGOT-ov22 and GCIG survey (Expression IV).](#)Rohr I, Alavi S, Richter R, Keller M, Chekerov R, Oskay-Özcelik G, Heinrich M, Taskiran C, Joly F, Berger R, du Bois A, Gornjec A, Vergote I, Achimas-Cadariu P, Lorusso D, Maenpaa J, Sehouli J.Int J Gynecol Cancer. 2020

* p <0,001
** p <0,05

What are the goals of the maintenance therapy in ovarian cancer cancer, what is the doctor´s perspective, what the patient´s perspective?

?

- Symptom control
- Response
- QoL
- Cure
- Recurrence Free Survival
- Progression Free Survival
- Time to Subsequent Therapy

QoL in maintenance therapy

- Most of the applied questionaires are not validated for maintenance and non-chemotherapeutical regimens!
- Most toxicities are grade 1/2!
- Impact on daily activities generally not reflected!
- Impact of education, information and best supportive care are generally not reflected!

Maintenance therapy in ovarian cancer

What we don´t know?

Early stage ovarian cancer

Low Grade Ovarian Cancer

Who will not really benefit from the maintenance therapy

Maintenance therapy in ovarian cancer

What do we know?

„Maintenance for high-grade ovarian-, fallopian und peritoneal cancer is a Should Therapy Option!“

Overview of available first-line maintenance therapy options in advanced ovarian cancer (EU and US)*[1-6]

Niraparib[1,2]	Olaparib[3,4]	Olaparib + bevacizumab[3,4]	Bevacizumab†[5,6]
All biomarker subgroups (HRd/*BRCA*m, HRd/*BRCA*wt, and HRp)	*BRCA*m	*BRCA*m or HRd	All comers

*Approvals, indications, prescribing information, and reimbursement status may vary by country. Healthcare professionals must refer to their country's prescribing information/SmPC and local reimbursement information.

†Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for the front-line treatment of adult patients with advanced ovarian cancer.[5]

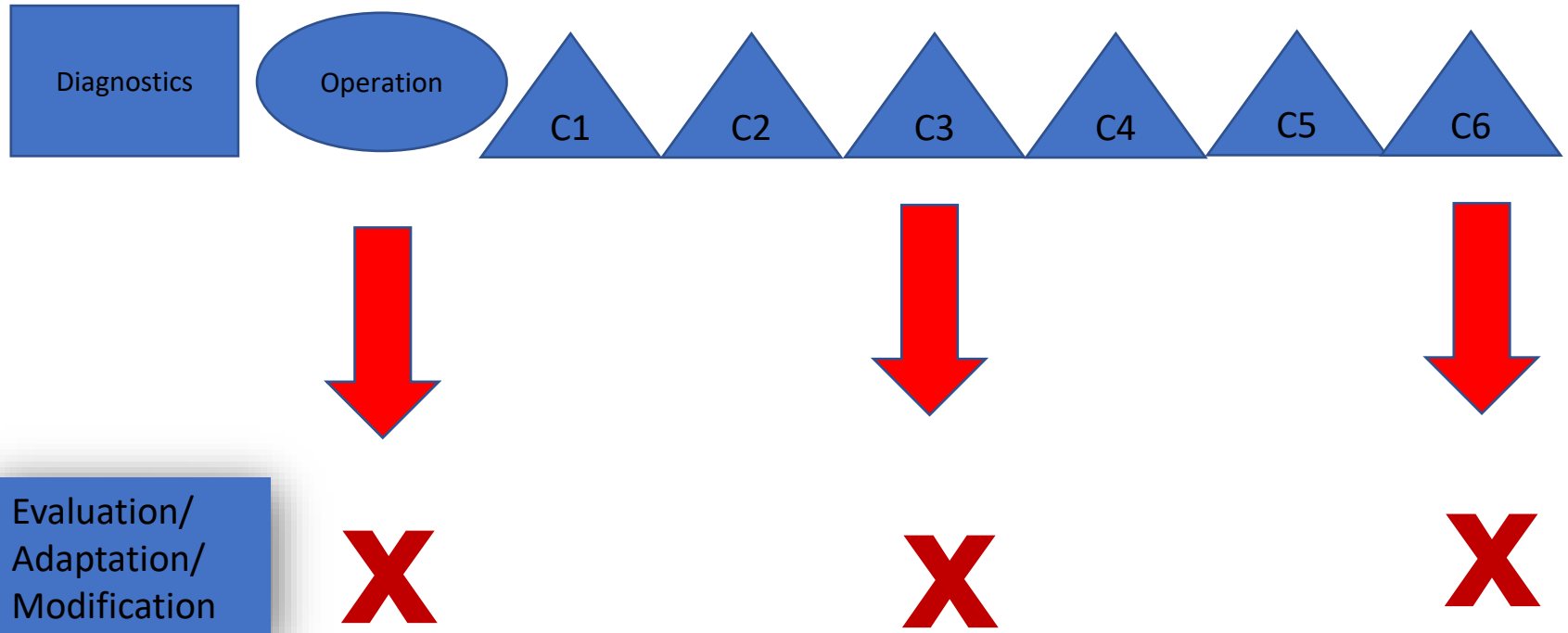
*BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild-type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; SmPC, Summary of Product Characteristics.

1. Niraparib. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Limited; 2021. **2.** Niraparib. Prescribing Information. GlaxoSmithKline; 2021. **3.** Olaparib. Summary of Product Characteristics. AstraZeneca; 2022. **4.** Olaparib. Prescribing Information. AstraZeneca; 2021. **5.** Bevacizumab. Summary of Product Characteristics. Genentech, Inc.; 2022. **6.** Bevacizumab. Prescribing Information. Genentech, Inc.; 2021.

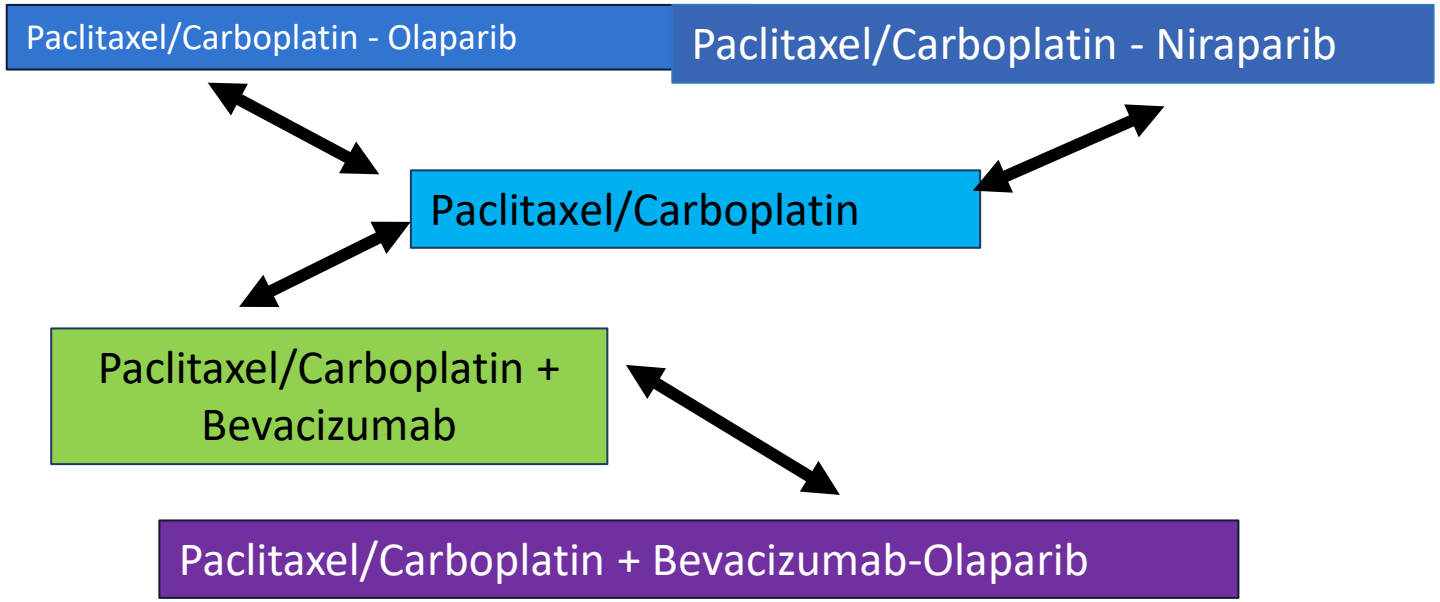
Das Charité-RECALL-KONZEPT

11th International Charité Mayo Conference

Evaluation: Efficacy/Toxicity/QoL



Therapy options



Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1

Susana Banerjee,[1] Kathleen Moore,[2] Nicoletta Colombo,[3] Giovanni Scambia,[4] Byoung-Gie Kim,[5] Ana Oaknin,[6] Michael Friedlander,[7] Alla Lisyanskaya,[8] Anne Floquet,[9] Alexandra Leary,[10] Gabe S Sonke,[11] Charlie Gourley,[12] Amit Oza,[13] Antonio González-Martín,[14] Carol Aghajanian,[15] William Bradley,[16] Eileen Holmes,[17] Elizabeth S Lowe,[18] Paul DiSilvestro[19]

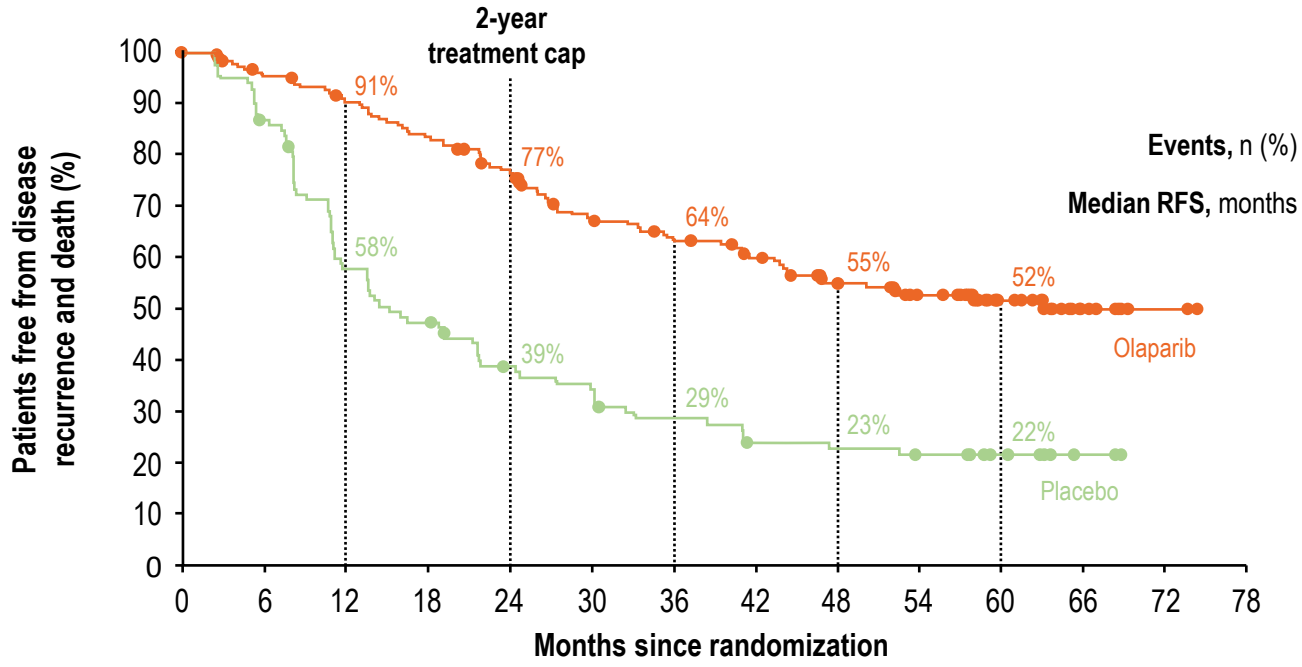
[1]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [2]Stephenson Oklahoma Cancer Center, Oklahoma City, OK, USA; [3]University of Milan-Bicocca and Istituto Europeo di Oncologia, Milan, Italy; [4]Università Cattolica del Sacro Cuore-Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; [8]St Petersburg City Oncology Dispensary, St Petersburg, Russia; [9]Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, France; [10]Institut Gustave-Roussy, Villejuif, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, France; [11]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [12]Cancer Research UK Edinburgh Centre, University of Edinburgh, Edinburgh, UK; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Clínica Universidad de Navarra, Madrid, Spain; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA; [17]AstraZeneca, Cambridge, UK; [18]AstraZeneca, Gaithersburg, MD, USA; [19]Women & Infants Hospital, Providence, RI, USA

Conducted in partnership with the Gynecologic Oncology Group (GOG-3004)

ClinicalTrials.gov identifier: NCT01844986. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Mobile-friendly infographic

Recurrence-free survival in patients who achieved complete response to chemotherapy



No. at risk

Olaparib	189	169	159	147	132	107	99	89	75	66	42	19	2	0
Placebo	101	85	56	46	35	32	25	20	19	18	12	2	0	

	Olaparib (N=189)	Placebo (N=101)
Events, n (%)	79 (42)	74 (73)
Median RFS, months	**NR**	**15.3**
HR 0.37 (95% CI 0.27–0.52)		

Recurrence-free survival

defined *post hoc* as time from randomization to disease recurrence* or death for patients in complete response† to platinum-based chemotherapy at baseline

*New lesions by imaging; †Based on electronic case report form data
RFS, recurrence-free survival

73% and 77% of olaparib- and placebo-arm patients, respectively, were in CR at baseline. Investigator-assessed by modified RECIST v1.1. DCO: 5 March 2020

Final overall survival results from the Phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer

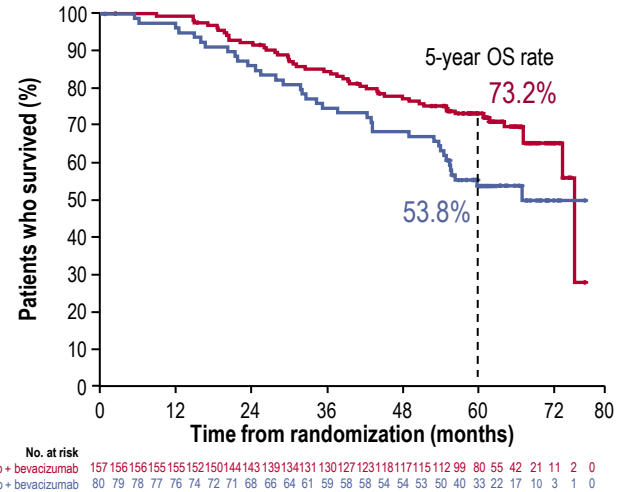
Isabelle Ray-Coquard,[1] Alexandra Leary,[2] Sandro Pignata,[3] Claire Cropet,[4] Antonio González-Martín,[5] Gerhard Bogner,[6] Hiroyuki Yoshida,[7] Ignace Vergote,[8] Nicoletta Colombo,[9] Johanna Mäenpää,[10] Frédéric Selle,[11] Barbara Schmalfeldt,[12] Giovanni Scambia,[13] Eva Maria Guerra Alia,[14] Claudia Lefeuvre-Plesse,[15] Antje Belau,[16] Alain Lortholary,[17] Martina Gropp-Meier,[18] Eric Pujade-Lauraine,[19] Philipp Harter[20]

[1]Centre Léon BERARD, Lyon, and GINECO, France; [2]Institut Gustave Roussy, Villejuif, and GINECO, France; [3]Istituto Nazionale Tumori 'Fondazione G Pascale', IRCCS, Napoli, and MITO, Italy; [4]Centre Léon BERARD, Lyon,, France; [5]Clínica Universidad de Navarra, Madrid, and GEICO, Spain; [6]Paracelsus Medical University Salzburg, Salzburg, and AGO Au, Austria; [7]Saitama Medical University International Medical Center, Saitama, and GOTIC, Japan; [8]Leuven Cancer Institute, Leuven, and BGOG, Belgium; [9]European Institute of Oncology, Milan, and MANGO, Italy; [10]Tampere University and University Hospital, Tampere, and NSGO, Finland; [11]Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, and GINECO, France; [12]Universitätsklinikum Hamburg-Eppendorf, Hamburg, and AGO, Germany; [13]Università Cattolica del Sacro Cuore di Roma, Rome, and MITO, Italy; [14]Hospital Universitario Ramón y Cajal, Madrid, and GEICO, Spain; [15]Centre Eugène Marquis, Rennes, and GINECO, France; [16]Universitätsmedizin Greifswald, Frauenklinik & Frauenarztpraxis, Greifswald, and AGO, Germany; [17]Hopital privé du Confluent, Nantes, and GINECO, France; [18]Onkologie Ravensburg, Ravensburg, and AGO, Germany; [19]ARCAGY Research, Paris, France; [20]Kliniken Essen-Mitte, Essen, and AGO, Germany

ClinicalTrials.gov identifier: NCT02477644 | This study was sponsored by ARCAGY Research.

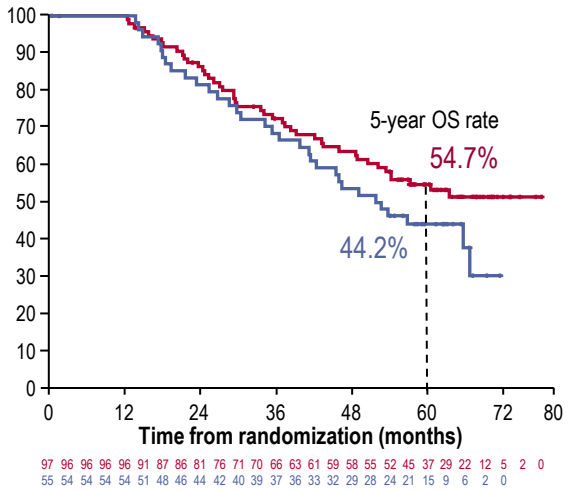
OS subgroup analysis by BRCAm and HRD status

BRCAm*



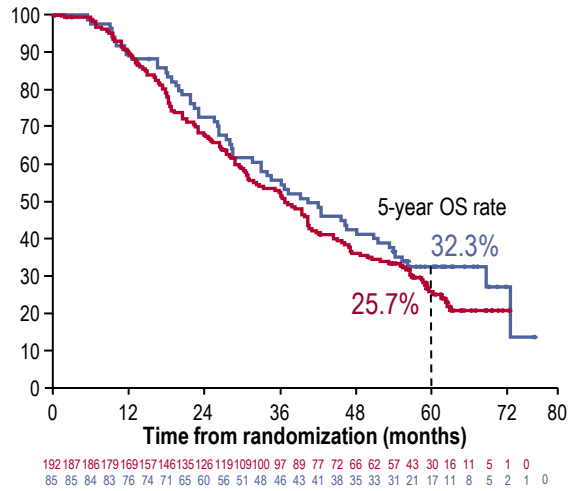
	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

HRD positive‡ excluding BRCAm



Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
44 (45.4)	32 (58.2)
NR	52.0
54.7	**44.2**
9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)	

HRD negative†

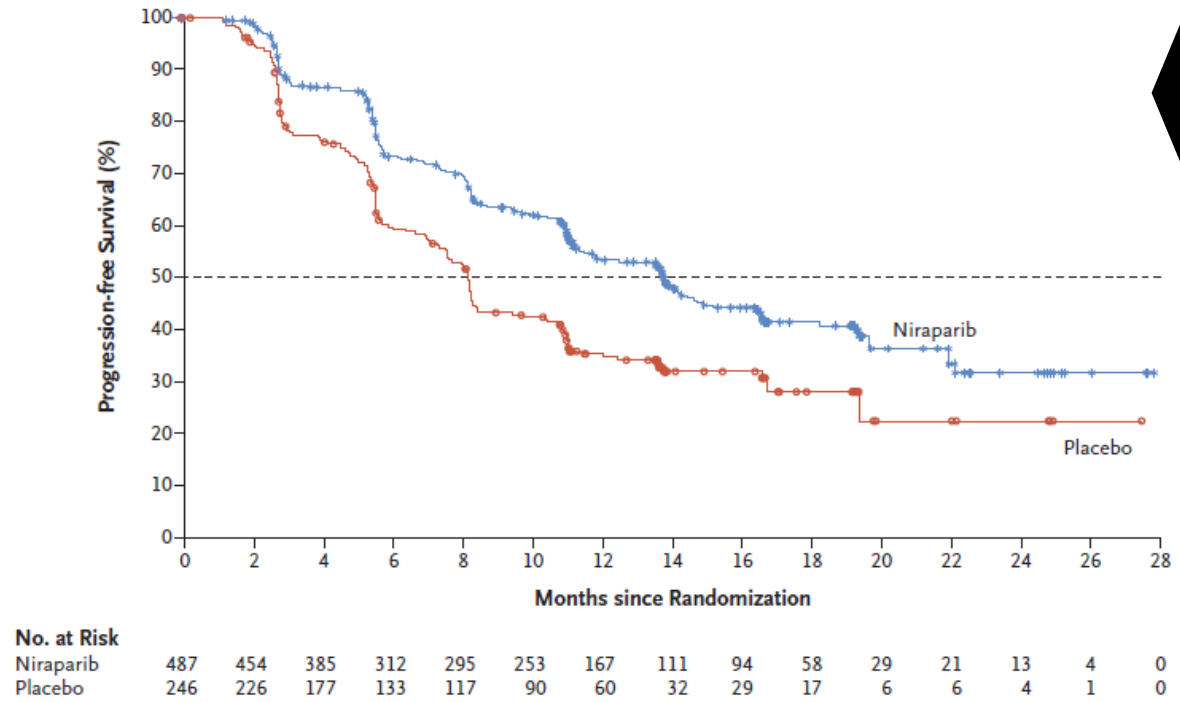


Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
140 (72.9)	58 (68.2)
36.8	40.4
25.7	**32.3**
46 (24.0)	34 (40.0)
HR 1.19 (95% CI 0.88–1.63)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

Primary Endpoint: PFS in the Overall Population

Niraparib significantly reduced the risk of progression or death by 38% in the overall PRIMA population of women with newly diagnosed advanced ovarian cancer



HR (95% CI) for disease progression or death: 0.62 (0.50–0.76; P<0.001)

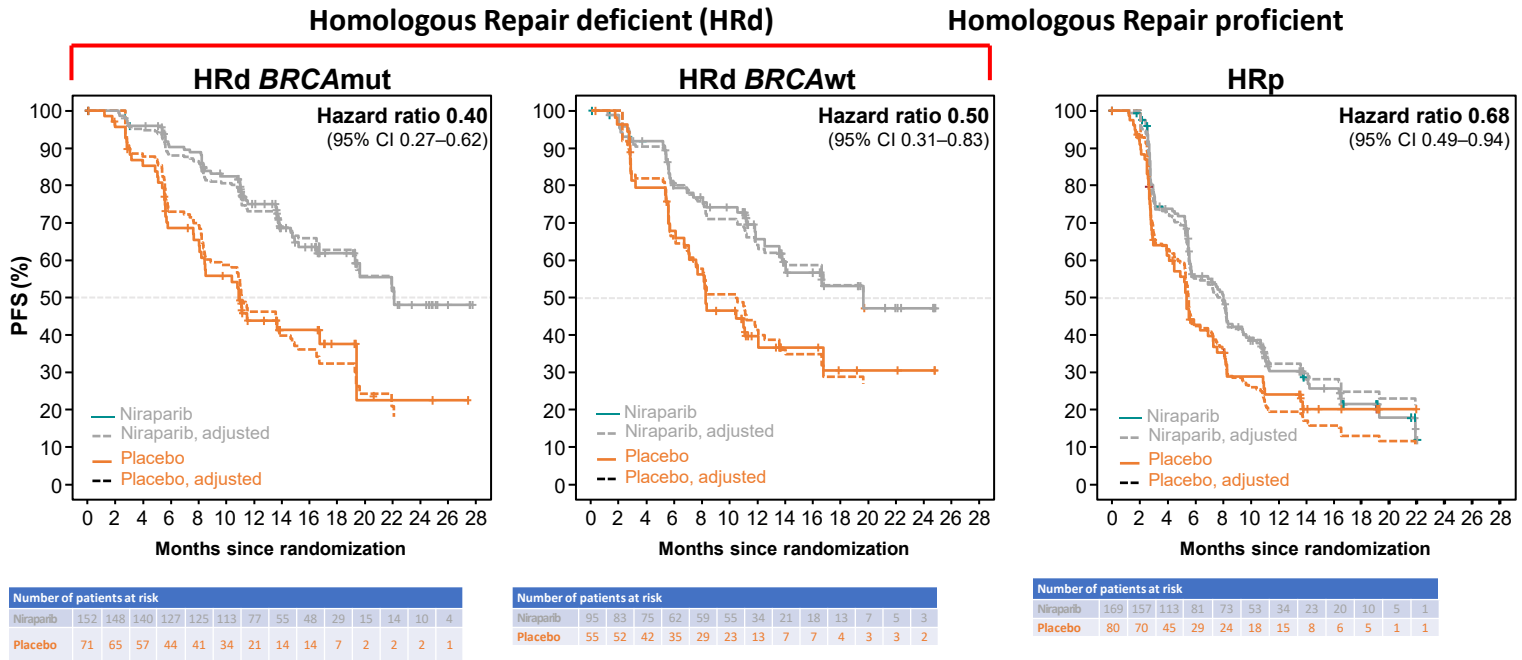
	Niraparib (n = 487)	Placebo (n = 246)
Median PFS		
months (95% CI)	13.8 (11.5 – 14.9)	8.2 (7.3 – 8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

- CI = confidence interval; HR = hazard ratio; PD = progressive disease; PFS = progression-free survival
- Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

PFS Benefit in HRd and HRp Subgroups*

Niraparib reduced the risk of progression or death regardless of *BRCA* status and HR-deficiency or HR-proficiency

Adjusted (dashed lines) and unadjusted (solid lines) Kaplan-Meier graphs for all subgroups



* by blinded independent central review (BICR)

HRd *BRCA*wt population represents all HRd patients who are not *BRCA*mut.; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient;mut, mutant; PFS, progression-free survival; wt, wild-type.

Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCA and homologous recombination status: PRIMA/ENGOT-OV26/GOG-3012 study; **B.J. Monk and A. Gonzalez Martin**, SGO 2020, abstract 31 (Webinar 2, streamed on 29th April 2020)

Key Questions for th use of maintenance therapies?

- What is the best patients population of longterm survivor for maintenance therapy?
- Who will not benefit from a maintenance strategy?
- How to create evidence for the benefit from the patient´s perspective and the society perspective?

ESGO European Society of Gynaecological Oncology
23rd European Congress on Gynaecological Oncology
Oct 27-30, 2022 | Berlin, Germany

Validation Study of the "NOGGO-GIS ASSAY" based on ovarian cancer samples from the first-line PAOLA-1/ENGOT-ov25 phase-III trial

Eva-Maria Willing[1], Claudia Vollbrecht[2,3], Christine Voessing[1], Peggy Weist[1], Simon Schallenberg[2], Balazs Jori[1], Markus Tiemann[1], Guillaume Bataillon[4], Philipp Harter[5], Sandro Pignata[6], Antonio Gonzales Martin[7,8], Ignace Vergote[9], Nicoletta Colombo[10], Christian Marth[11], Tobias Berg[1], Bettina Kah[1], Johanna Herbst[1], Trine Jakobi Noettrup[12], Markus Falk[1], Kathrin Arndt[1], Isabelle Ray-Coquard[13,14], Andreas Polten[15], Robert Bernstein[1], Franziska Selzam[1], Judith Pirngruber[1], Stefanie Schmidt[1], Michael Hummel[2,3], Jalid Sehouli[16,3], David Horst[2], Elena Ioana Braicu[16,3,14], Eric Pujade Lauraine[14], Katharina Tiemann[1,3], Lukas C Heukamp[1,3]

Assay requirements

NOGGO GIS Assay V1

- genomic instability / HRD
- part of modular wet-lab and bioinformatics workflow with adjustable content
- BRCA1 and BRCA2 mutations including large deletions
- covers all exons of HRR Genes (RAD51, PALB etc.)
- reliable detection of LOH for tumour suppressor genes
- detection of therapeutically relevant driver mutations for HRD negative patients
  - HER2 amp, KRAS, BRAF, PIK3CA, EGFR etc.
- reliable detection on minimum of 40ng of DNA from a single FFPE tumour sample
- robust chemistry with low failure rate

NOGGO GIS Assay V1

57 genes, approx. 20.000 SNP loci and a total size of 2.9Mb

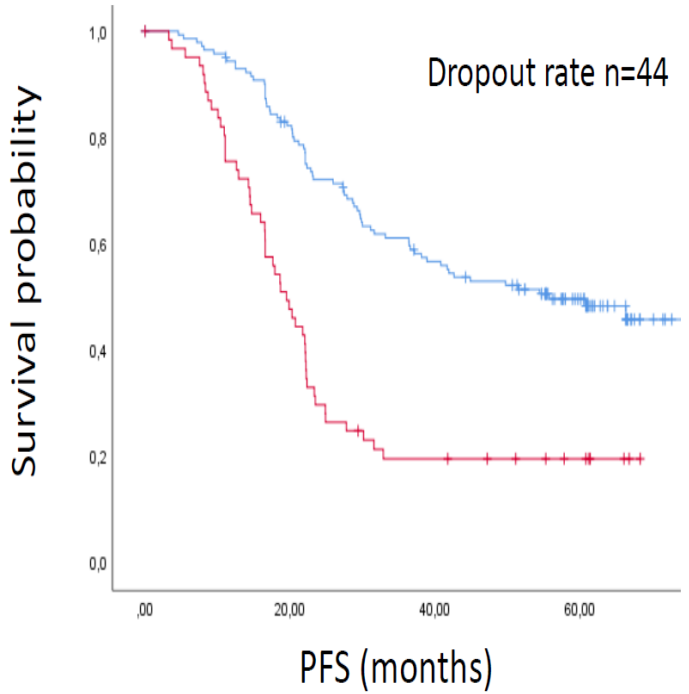
ABRAXAS1	BRIP*	FANCC*	MRE11A*	RAD51B*
APC	BUB1B	FANCD2*	MSH2	RAD51C*
AR	CDH1	FANCE*	MSH6	RAD51D*
ARID1A*	CDK12*	FANCF*	NBN*	RAD52*
ATM*	CHEK1*	FANCG	**NRAS**	RAD54L*
ATR*	CHEK2*	FANCI*	PALB2*	RPA1*
ATRX	CTNNB1	FANCL*	**PIK3CA**	STK11
BARD1*	**EGFR**	FANCM*	PMS2	TP53
BLM*	EMSY*	HDAC2*	PPP2A2R	XRCC2*
BRAF	**ERBB2**	HOXB3	PTEN	
BRCA1*	ESR1	**KRAS**	RAD50*	
BRCA2*	FANCA*	MLH1*	RAD51*	

*HRR-Genes; Bold: tumor driver genes

- Covers BRCA1/BRCA2 and ~ 30 genes associated to HRR pathway plus some typical cancer associated genes (3x enrichment)
- Covers > 20.000 SNP positions for genomic instability status (Agilent CNV backbone, 1x enrichment)

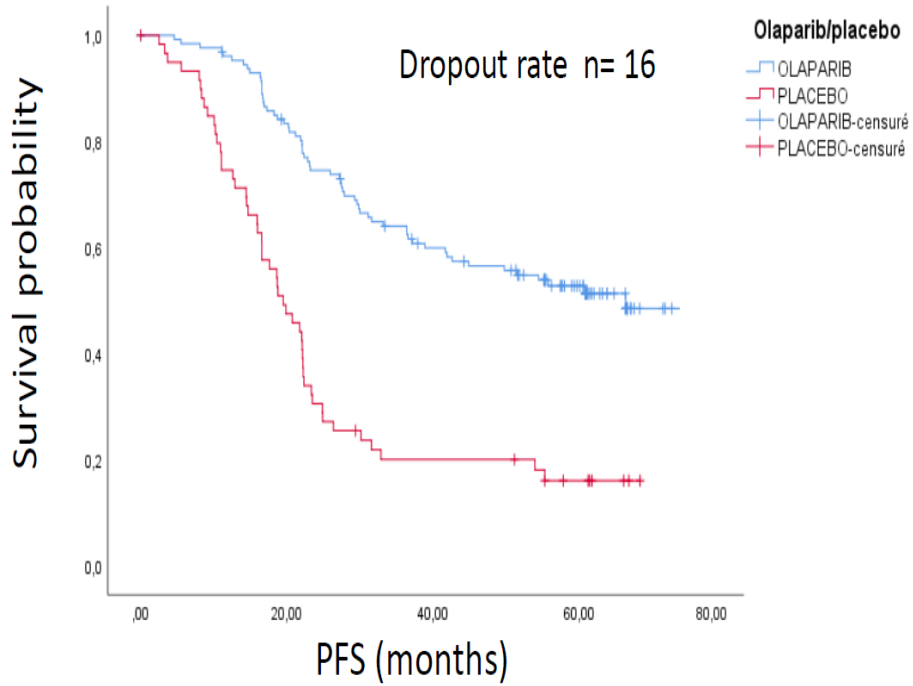
PFS HRD+ (Olaparib+Bev. vs. Bev.)

PAOLA1 trial assay



p-value	HR	95,0% CI for HR		n
0.000	**0.352**	0.243	0.510	383

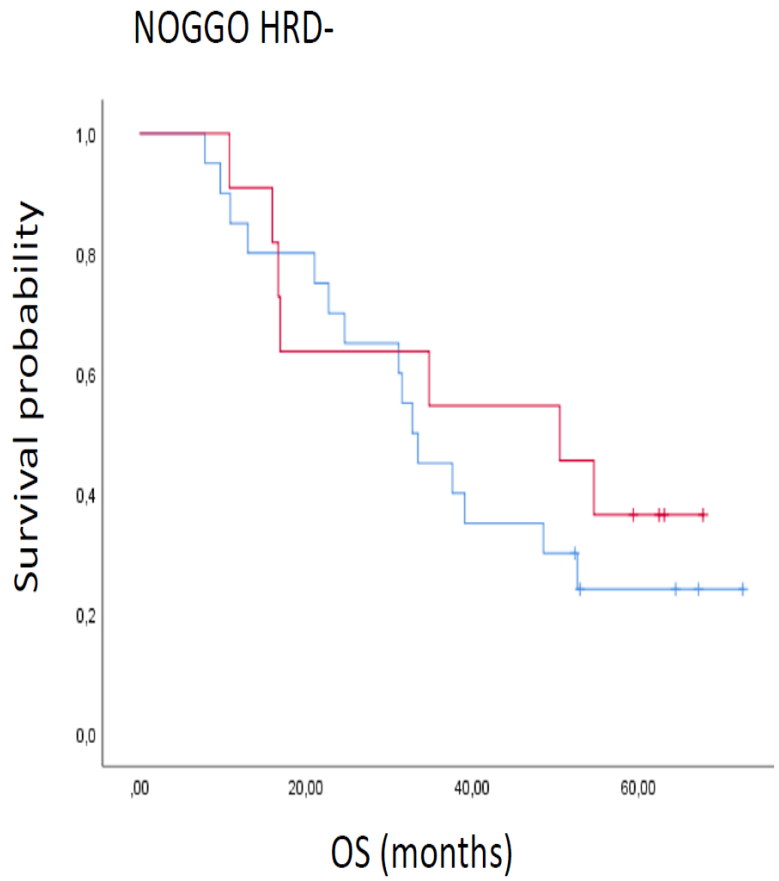
NOGGO GIS Assay V1

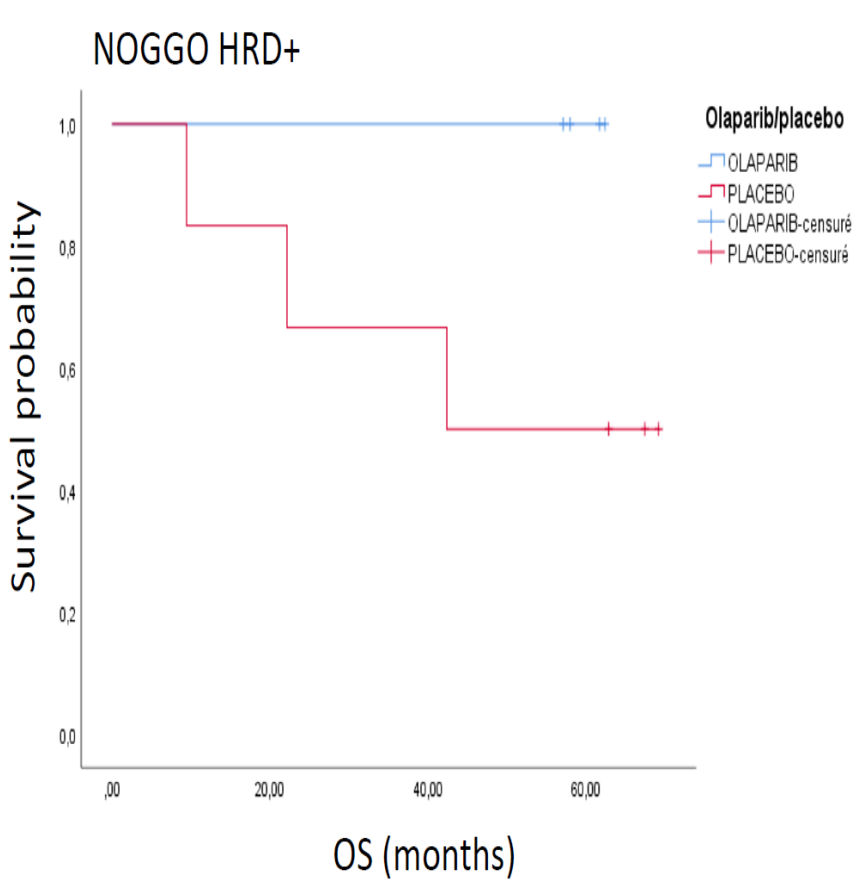


p-value	HR	95,0% CI for HR		n
0.000	**0.310**	0.211	0.456	383

OS for patients with unknown HRD status n=44

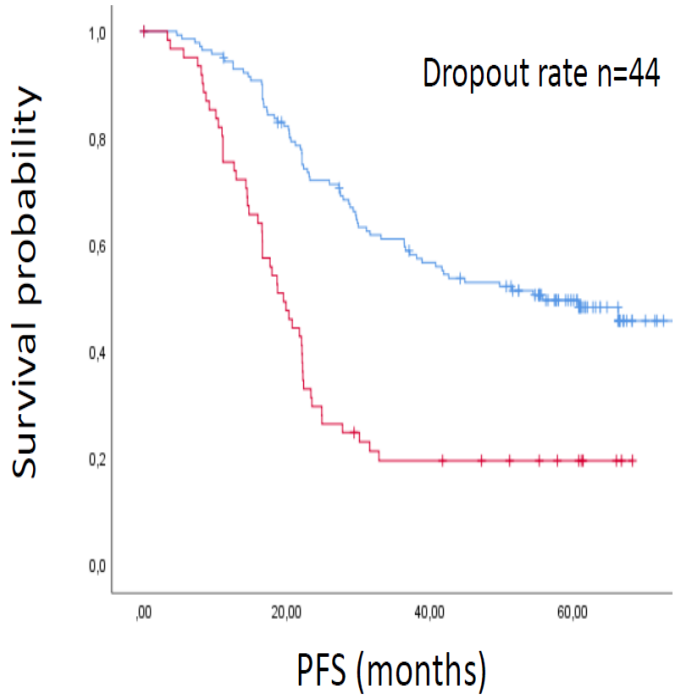
NOGGO GIS Assay V1 results of trial assay drop out cases





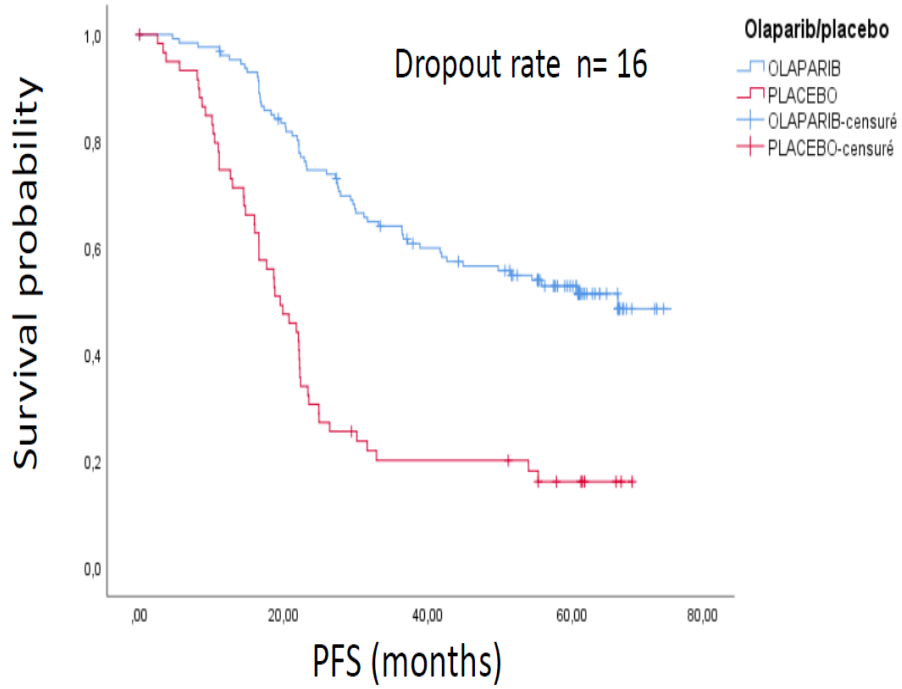
PFS HRD+ (Olaparib+Bev. vs. Bev.)

PAOLA1 trial assay



p-value	HR	95,0% CI for HR		n
0.000	**0.352**	0.243	0.510	383

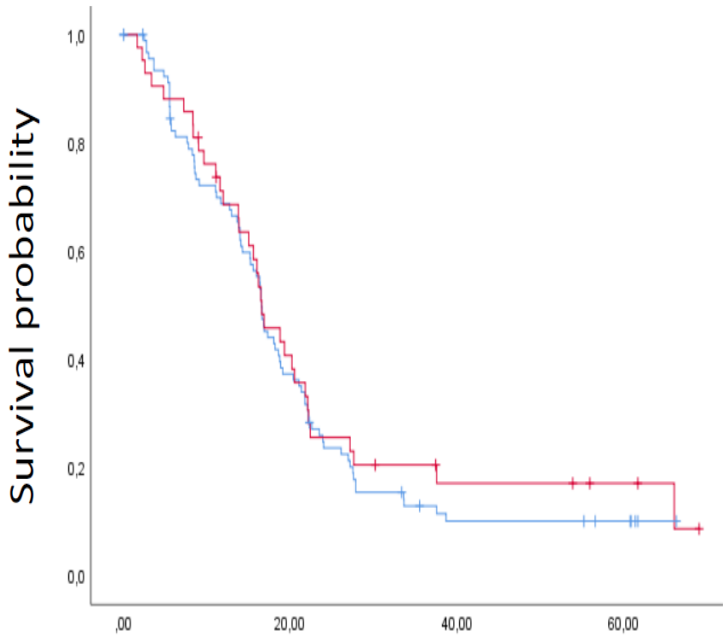
NOGGO GIS Assay V1



p-value	HR	95,0% CI for HR		n
0.000	**0.310**	0.211	0.456	383

PFS HRD- (Olaparib+Bev. vs. Bev.)

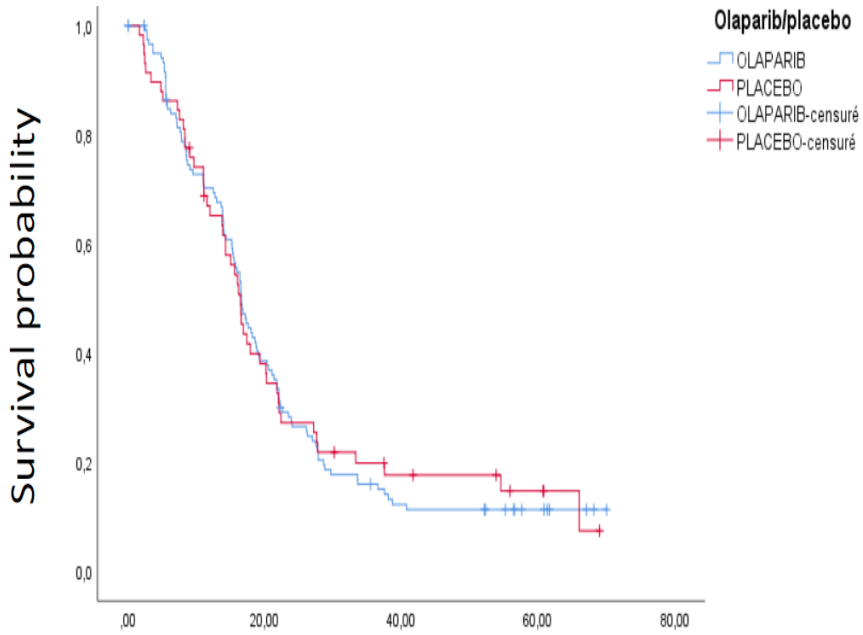
PAOLA1 trial assay



PFS (months)

p-value	HR	95,0% CI for HR		n
0.560	**1.128**	0.753	1.688	383

NOGGO GIS Assay V1



PFS (months)

p-value	HR	95,0% CI for HR		n
0.897	**1.023**	0.726	1.441	383

NOGGO GIS V1 assay Summary

- low failure rate due to low DNA input and bioinformatics (44 vs 16)
- based on robust Agilent HS2 Hybrid Capture NGS chemistry with Illumina sequencing
- GIS determination only requires SNP backbone
- similar PFS and OS data compared to Myriad MyChoice DX
- based on PureCN and software made available on GIT HUB
- sample processing at HP-Hamburg or locally as LDT
- full implementation will be offered by Agilent

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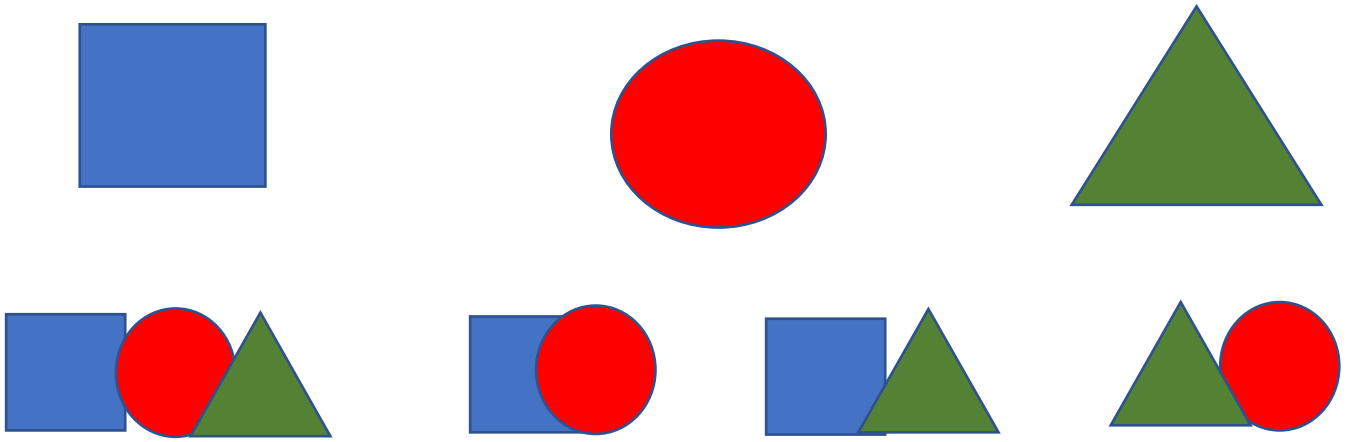
ESGO European Society of Gynaecological Oncology
23rd European Congress on Gynaecological Oncology
Oct 27-30, 2022 | Berlin, Germany
Institut für Hämatopathologie Hamburg
NOGGO e.V. Forschung – Fortbildung – Fortschritt

PARP-Therapy!
What, When How?

PARP Antiangiogenese Checkpoint



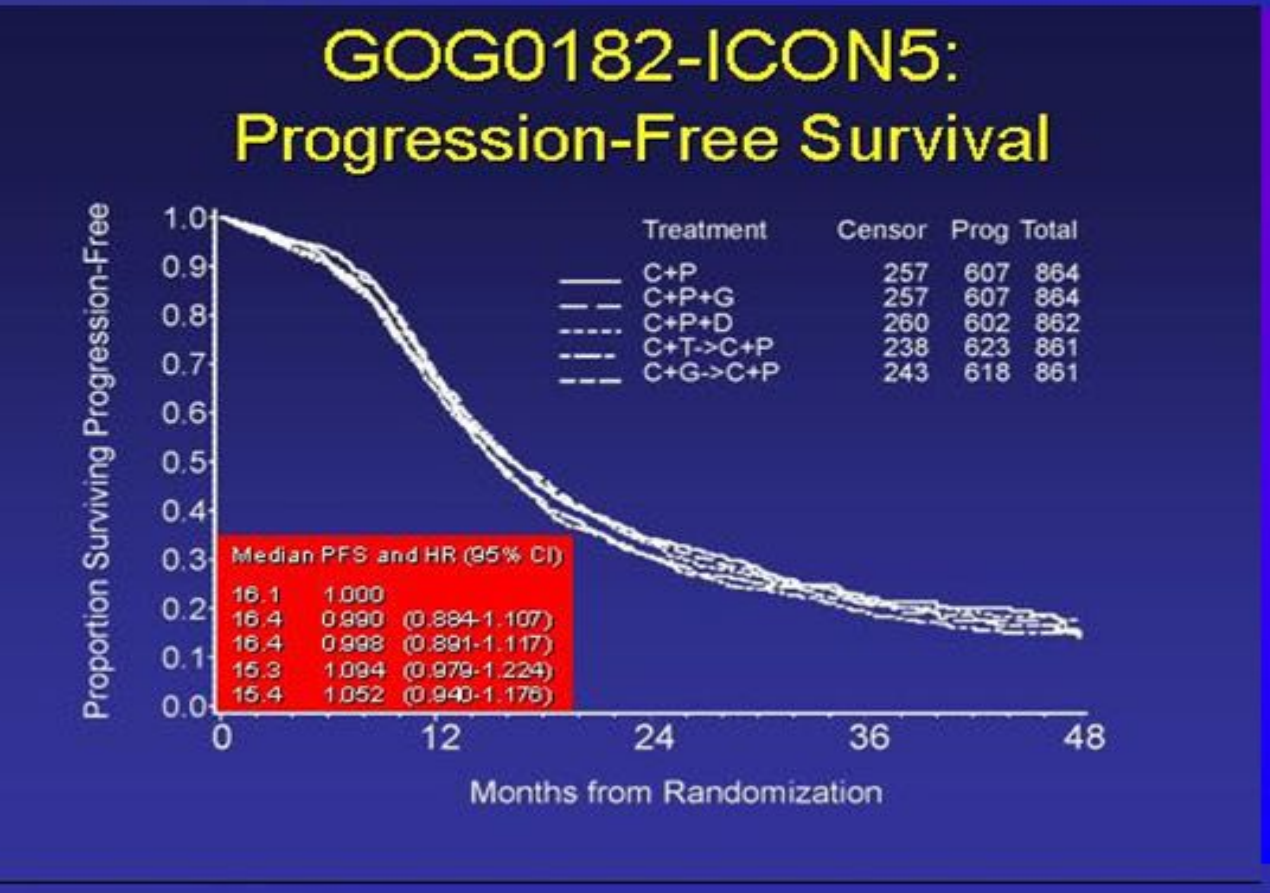
GOG-182 (ICON 5)

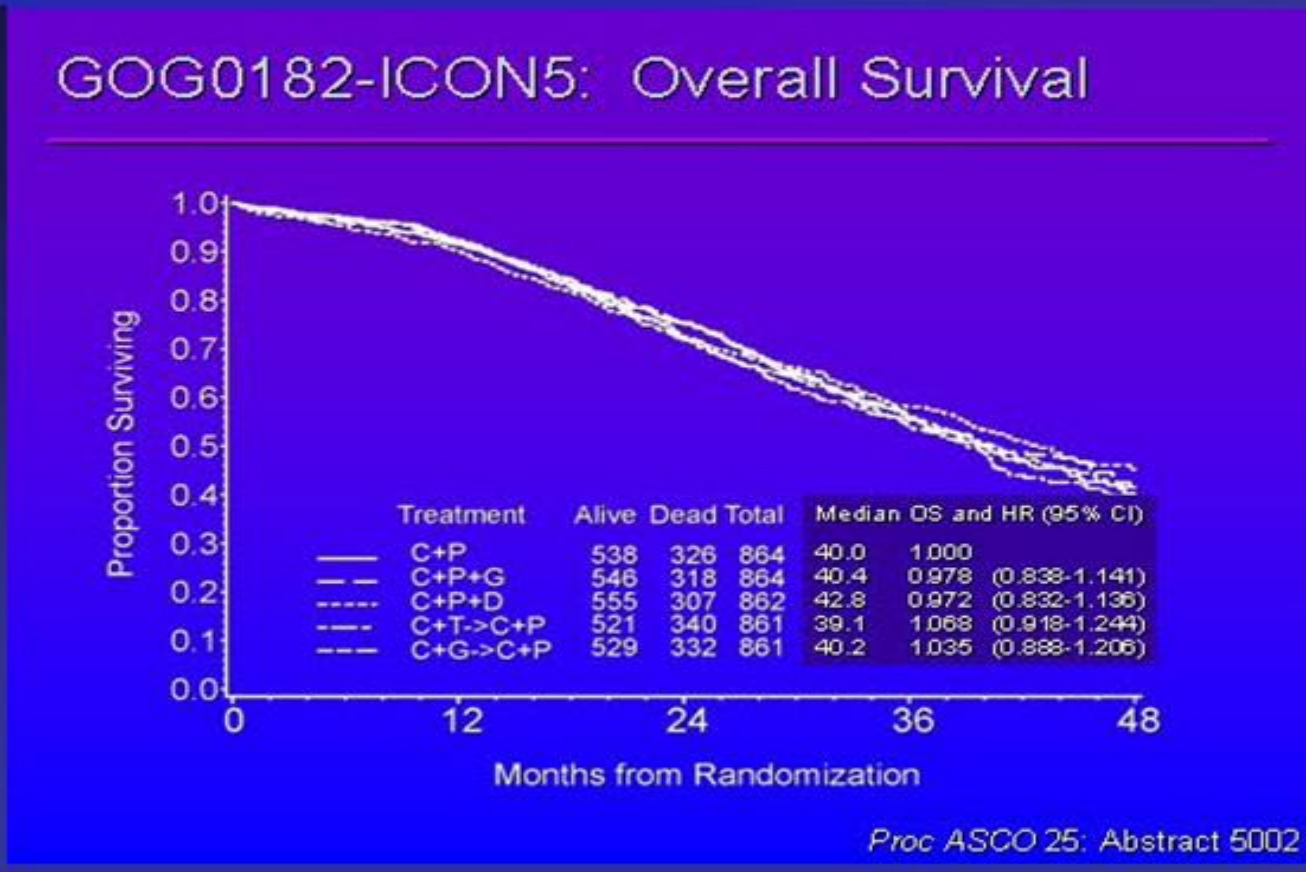
Ovarian Cancer III/IV

- Carboplatin-paclitaxel x 8 *OR* Carboplatin x 8 — Control arm selected by institution
- Carboplatin-gemcitabine x 4 → Carboplatin-paclitaxel x 4
- Carboplatin-Doxil™-paclitaxel x 8
- Carboplatin-topotecan x 4 → Carboplatin-paclitaxel x 4
- Carboplatin-paclitaxel-gemcitabine x 8

GOG 182- ICON 5 Trial

„Maybe we can learn from history!“





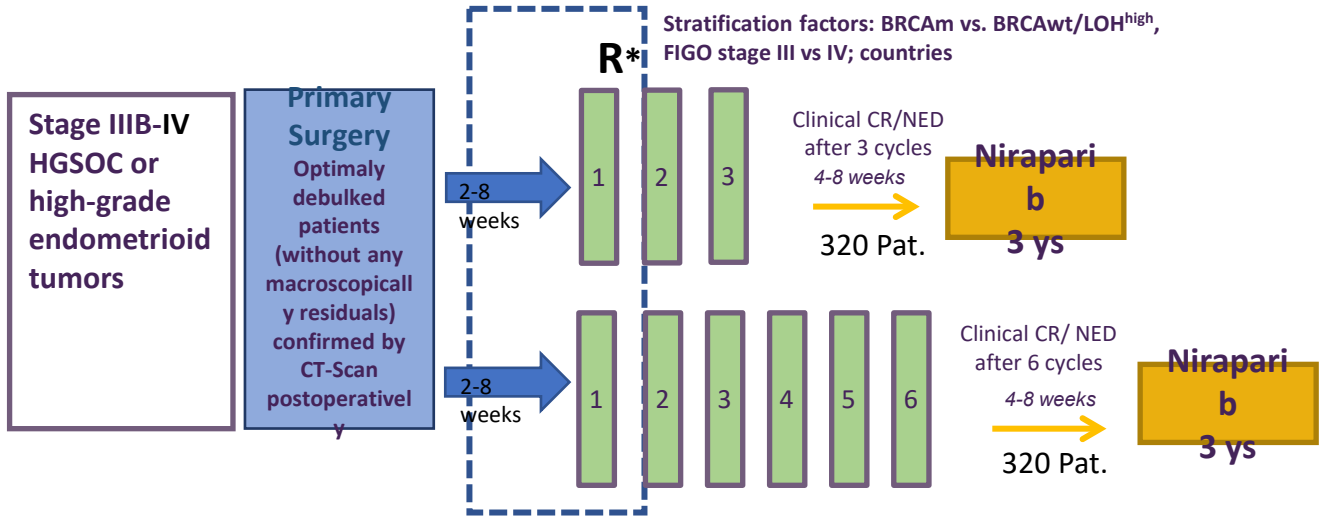
Proc ASCO 25: Abstract 5002

Bookman MA, ASCO 2006

NOGGO-ov53/ ENGOT-ov62

N-Plus

A Phase III randomized, open label study of NiraParib maintenance after Carboplatin and Paclitaxel in optimaLly debUlked advanced HRDpositive high-grade ovarian cancer patientS in first line therapy



Key Inclusion Criteria:

- FIGO Stage III--IV high-grade ovarian cancer (all histological types, except mucinous histology)
- Complete primary debulked patients (without any macroscopically residuals), confirmed by CT-Scan postoperatively

Primary Endpoint:

Recurrence free survival

Secondary Endpoints:

- OS
- TFST, TWIST
- PFS2, PROs, safety, cost effectiveness

* DEcrEaSing ChemotherApy in optimaLly debulked OvArian Cancer IniTiativE

NSGO

NOGGO e.v.
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie e.V.

GOG FOUNDATION®
Transforming the standard of care™

ENGOT
European Network of Gynaecological Oncology Trials groups

GCIG
GYNECOLOGIC CANCER INTERGROUP

+++ SAVE THE DATE +++ SAVE THE DATE +++

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

MAYO CLINIC

12th International Charité Mayo Conference

Global Perspectives and Future Directions in Women's Cancer

April 26–29, 2023
Berlin, Germany