.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

El puzzle de la primera línea

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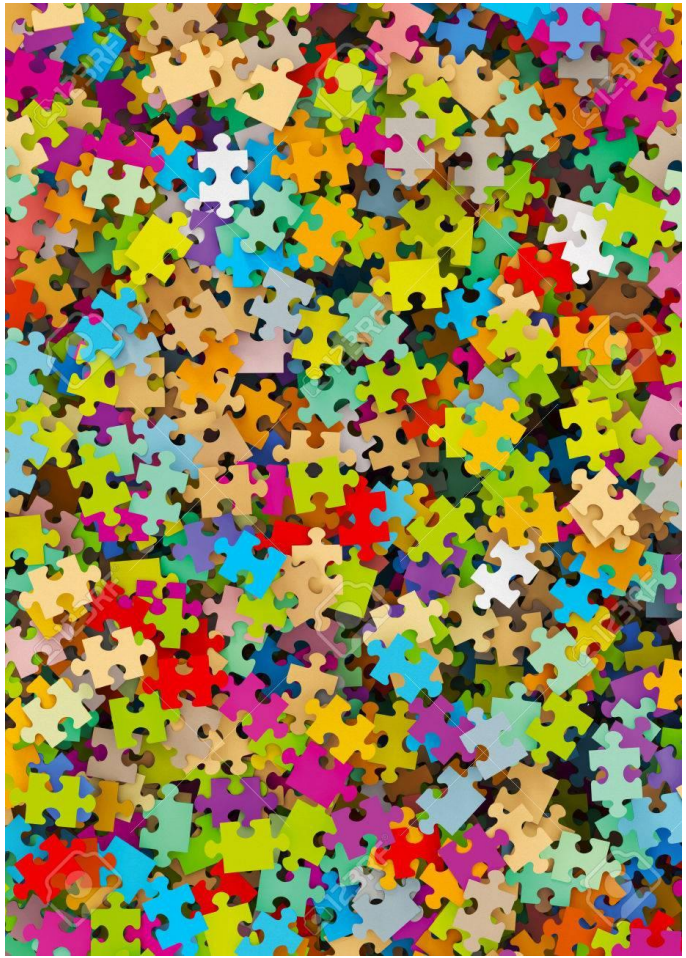
Grupo Español de Investigación en Cáncer de Ovario

CONFLICT OF INTEREST

- I have received fees for different educational or advisory related activities from: Alkermes, Amgen, AstraZeneca, Clovis, Genmab, GSK, HederaDx, Immunogen, Illumina, Mersana, MSD, Novartis, Novocure, Oncoinvent, PharmaMar, Roche, SOTIO, SUTRO, Seagen, Takeda, Tubulis

- Non-financial interest: Chairman of GEICO, Chairman (2018-2020) of ENGOT



Edad y *performance status* (ECOG)
Co-morbilidades
Situación socio-familiar
Valoración pre-quirúrgica (CT vs PET vs laparoscopia)
Capacitación del equipo quirúrgico
Histología
BRCA y HRD
Perfil molecular más allá de HRD (CCNE1, RAD51,…)
Microambiente tumoral
Enfermedad residual tras cirugía primaria
Respuesta a quimioterapia neoadyuvante (RECIST)
Enfermedad residual tras cirugía de intervalo
Complicaciones post-quirúrgicas
Cinética de eliminación de CA-125 (KELIM)
HIPEC
Bevacizumab
PARP inhibitor
Mecanismo de resistencia a platino y PARPi
Efectos secundarios de fármacos
Acceso y reembolso de fármacos….

REAL ACADEMIA ESPAÑOLA

Sinónimo de puzzle : ROMPECABEZAS

Cirugía

Diagnóstico Molecular

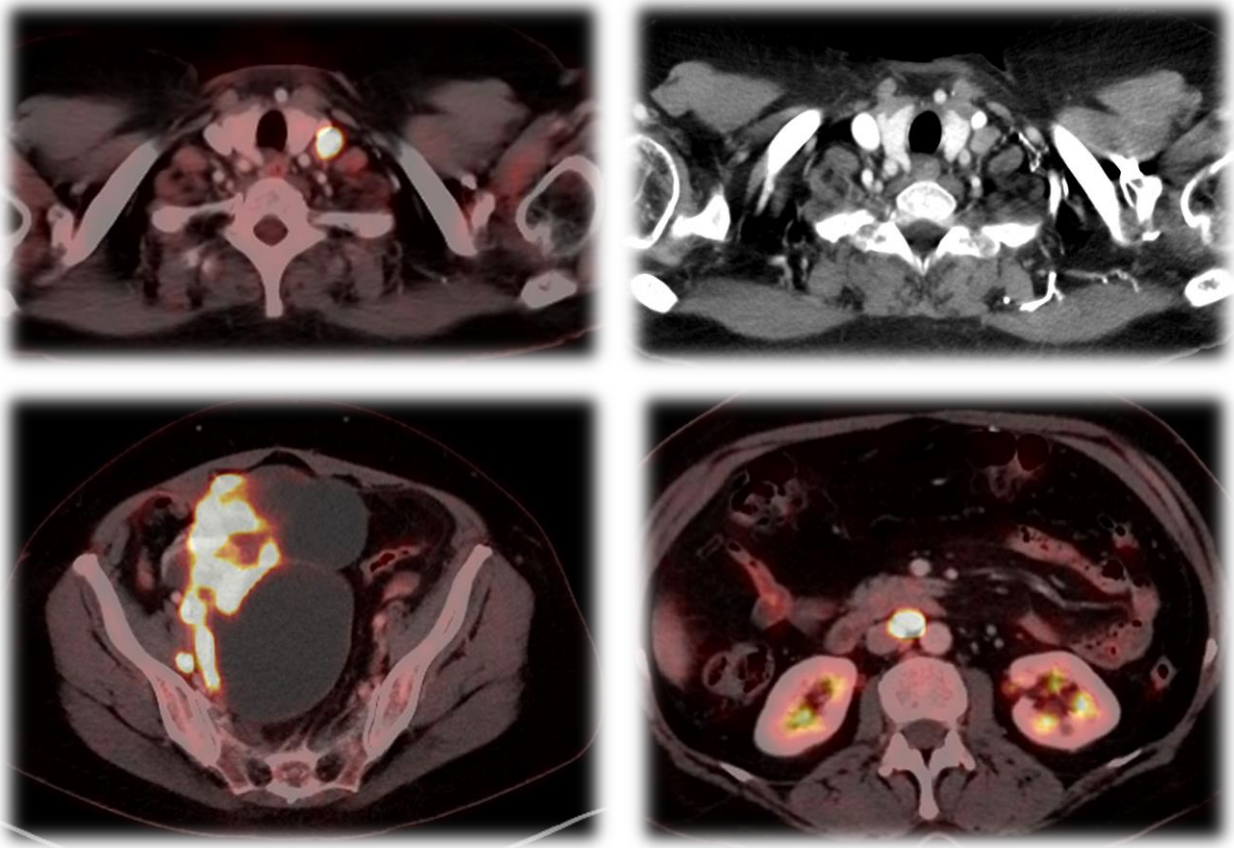
Quimioterapia +/- bevacizumab

Mantenimiento PARPi

DIAGNOSTIC WORKUP

IS NACT THE BEST OPTION FOR THIS PATIENT?

WHAT IF YOU DON'T INCLUDE PET IN THE WORKUP?



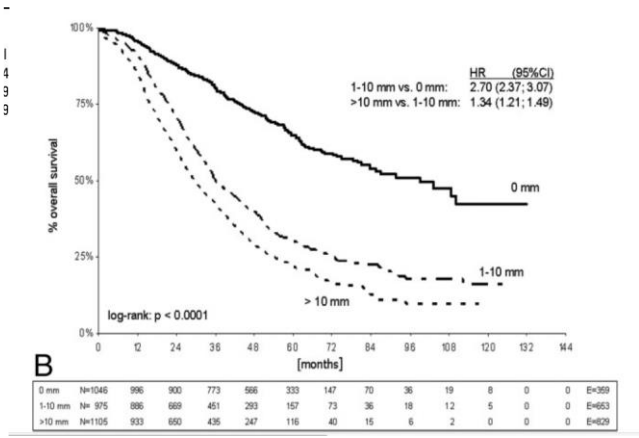
GCIG Sixth Ovarian Cancer Conference on Clinical Research

Statement 1

Selection of patients for neoadjuvant chemotherapy or primary cytoreductive surgery (PCS) (32 of 33 groups approved, one opposed)

PCS after assessment in an expert gynecological oncology unit is preferred. Neoadjuvant chemotherapy followed by interval cytoreductive surgery (ICS) is a valid alternative only if PCS is not feasible.

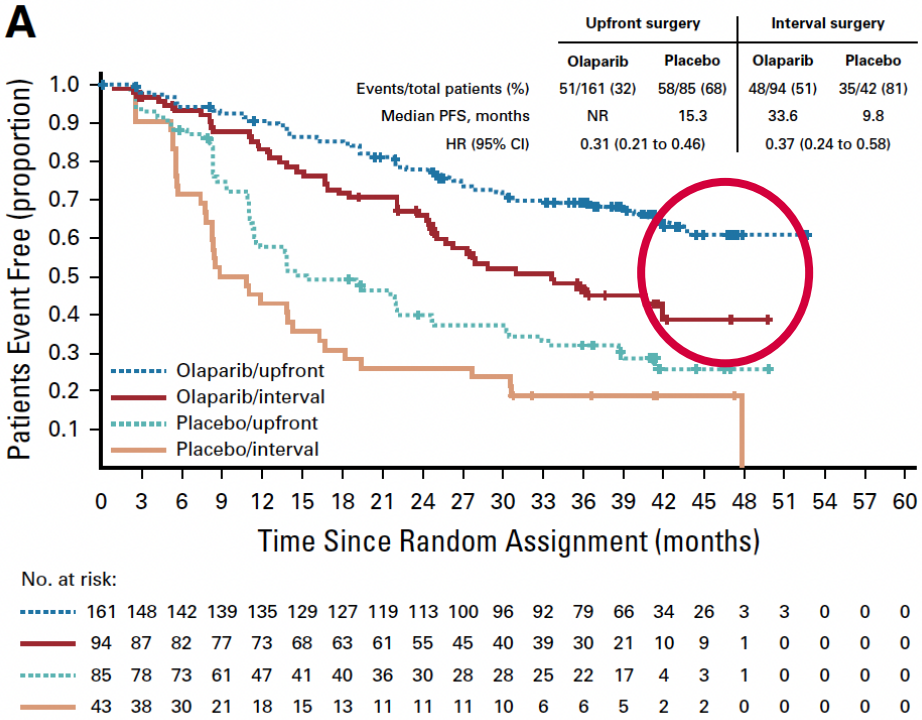
Vergote et al. Lancet Oncol 2022; 23: e374–84

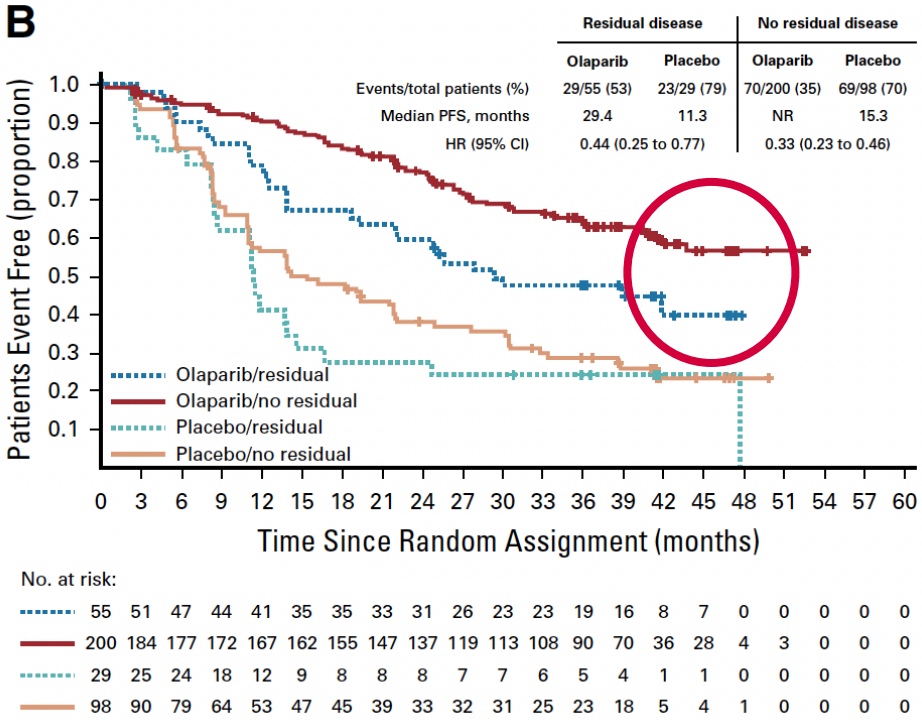


Du Bois et al. Cancer 2009

What is the impact of complete cytoreduction in the era of biological and maintenance therapy?

SOLO-1 Trial: Subgroup Analysis





Paul DiSilvestro et al. J Clin Oncol 2020

Cirugía

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer

I. Vergote[1*], A. González-Martín[2,3], I. Ray-Coquard[4], P. Harter[5], N. Colombo[6], P. Pujol[7], D. Lorusso[8], M. R. Mirza[9], B. Brasiuniene[10], R. Madry[11], J. D. Brenton[12], M. G. E. M. Ausems[13], R. Büttner[14] & D. Lambrechts[15], on behalf of the European experts' consensus group[†]

Table 5. Genetic testing in the clinic: consensus statements

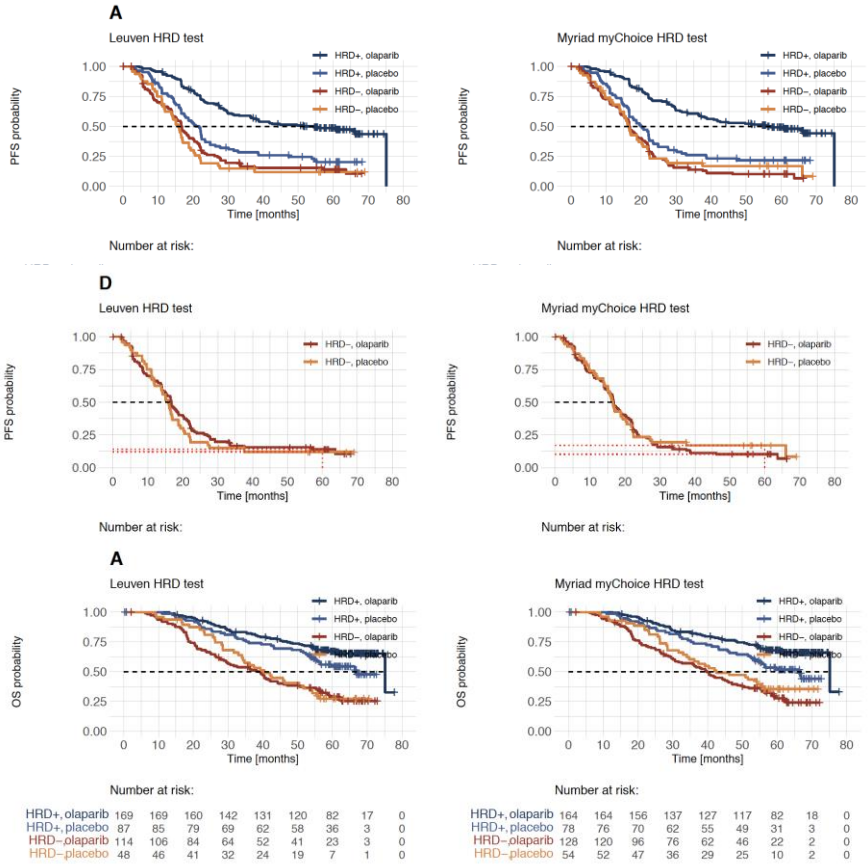
Consensus statements	Level of contributor agreement (%)[a]
Germline and/or tumour *BRCA* status and, if *BRCA* WT, tumour HRR deficiency status should be determined after primary diagnosis and ideally before the end of first-line chemotherapy	97

Ann Oncol. 2022 Mar;33(3):276-287.

HRD TESTING

WHAT WE KNOW

- Quality of sample is crucial
- HRD is Prognostic[1], Predictive of response to platinum[1] and Predictive of response to PARPi[2-3]
- Any gene panel for non-BRCA HRRmut is not predictive[4]
- Correlation of Academic and Industry HRD platforms with Myriad range from 0.85 to 0.96[5]
- Academic platforms have similar predictive value than Myriad[6]



1. Swisher et al. Gyn Oncol 2022 ; 2. Gonzalez-Martin et al. Eur J Cancer 2023; 3. Ray-Coquard et al. NEJM 2019;
4. Pujade. SGO 2021; 5. Weichert et al. ESMO 2022; 6. L. Loverix et al. Eur J Cancer 2023

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WHAT WE DON'T KNOW YET

- Optimal sequence of BRCA testing: Germinal vs Tumour
- Correlation of different platforms for an individual patient
- Real correlation of HRD test result with HRR function
- Implication of other biomarkers (i.e CCNE1)
- Mechanism of primary resistance to PARPi or secondary resistance induced by platinum therapy

1. Swisher et al. Gyn Oncol 2022 ; 2. Gonzalez-Martin et al. Eur J Cancer 2023; 3. Ray-Coquard et al. NEJM 2019;
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PRE-PARPi ERA

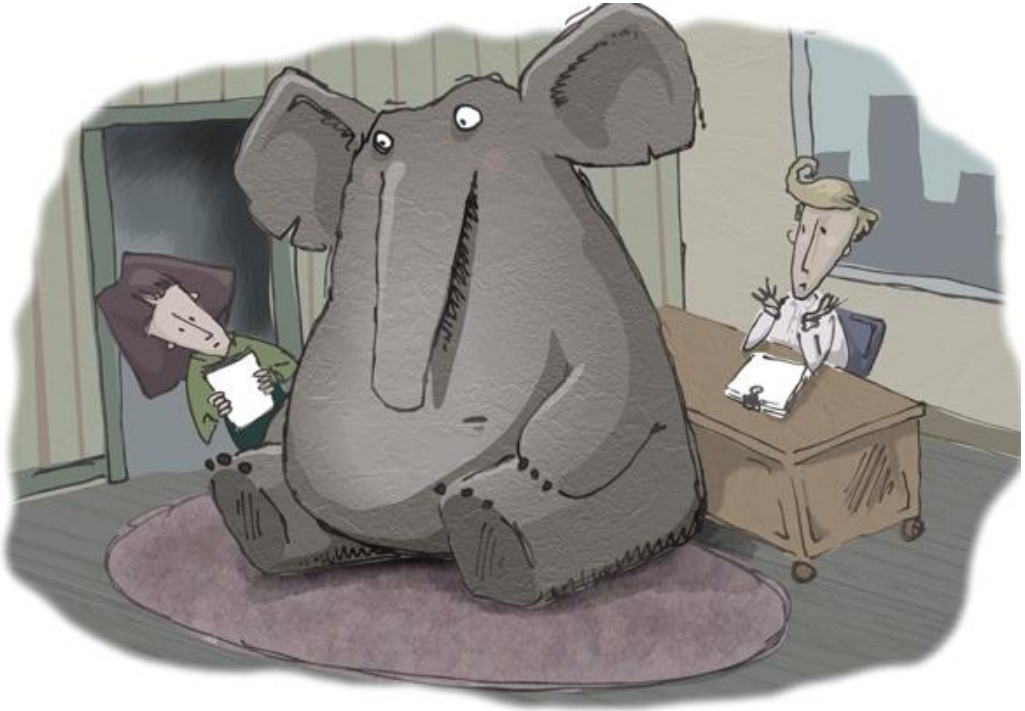
Bevacizumab in front-line

Summary of recommendations	LoE	GoR	Consensus
Bevacizumab (15mg/kg or 7.5 mg/kg every 3 weeks for maximum of 15 months) improves progression-free survival in patients with stage III-IV ovarian cancer and should be considered in addition to carboplatin and paclitaxel	I	A	Yes: 97.5% *(39 voters)* Abstain: 2.5% *(1 voter)*
Bevacizumab in the neoadjuvant setting can be considered although the additional improvement in efficacy is not proven with level I evidence	II	B	Yes: 97.5% *(39 voters)* No: 2.5% *(1 voter)*
Bevacizumab can be safely administered in the neo-adjuvant setting before and after IDS providing the interval between surgery and administration is at least 4-6 weeks	II	B	Yes: 100% *(40 voters)*

Colombo N et al, Ann Oncol 2019 and Int J Gynecol Cancer 2019

Post-PARPi ERA

What to do with bevacizumab in front-line?



Role of bevacizumab in patients with HRD-positive tumors (BRCA-mut or BRCAwt)?

How to manage patients with HRD-negative tumors? PARPi vs BEV

Biomarkers for bevacizumab and PARPi (beyond HRD)

Bevacizumab

1. CD31 (MVD) & tVEGF
2. IL6 in plasma
3. Visceral fat density (VFD)
4. high c-MET/VEGFR-2 co-localisation
5. Low VEGF-A165b expression
6. TCGA proliferative and mesenchymal molecular subtypes

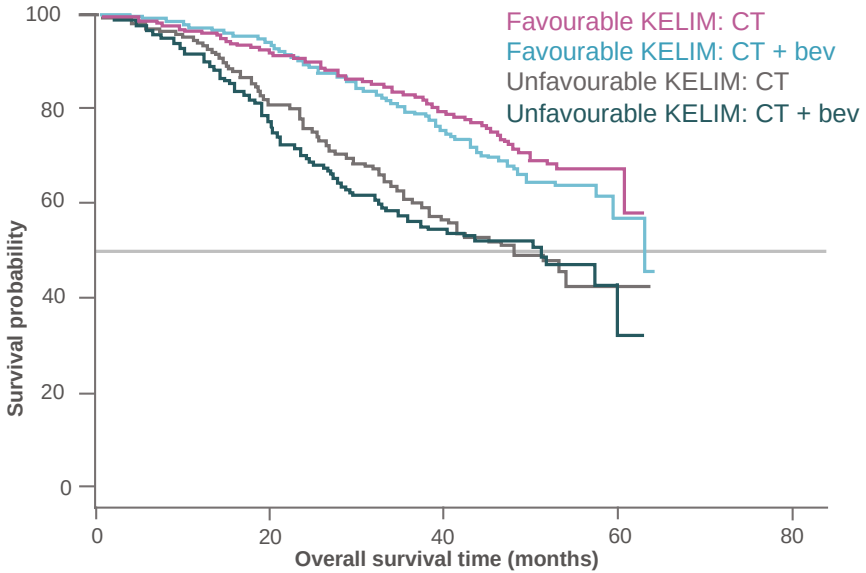
Niraparib

- Response to platinum-based 1L chemotherapy

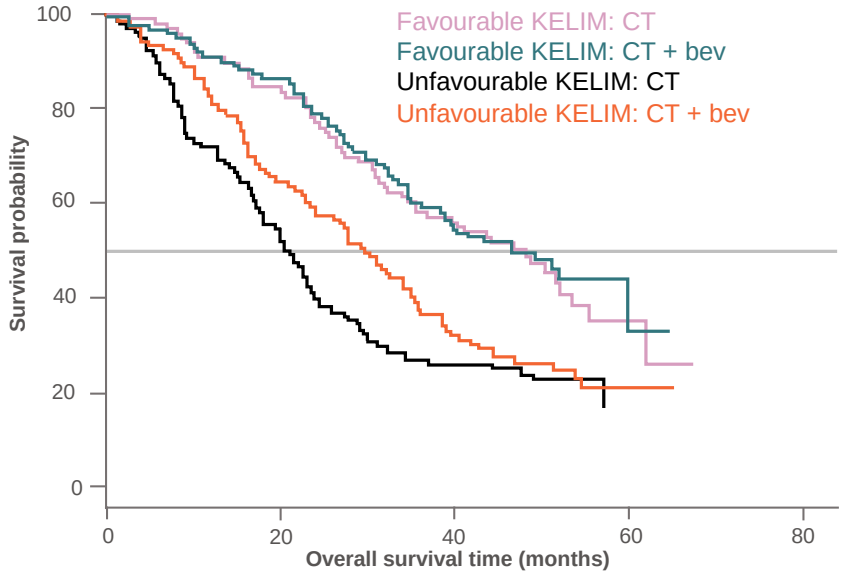
1. Bais C et al. J Natl Cancer Inst. 2017 Nov 1;109(11):djx066. doi: 10.1093/jnci/djx066 (GOG-218)
2. Alvarez Secord et al. Clin Cancer Res. 2020 Mar 15;26(6):1288-1296. doi: 10.1158/1078-0432.CCR-19-0226. (GOG-218)
3. Buechel et al. Gynecol Oncol. 2021 May;161(2):382-388. doi: 10.1016/j.ygyno.2021.02.032. (GOG-218)
4. Morgan R et al. BMC Med. 2022 Feb 11;20(1):59. doi: 10.1186/s12916-022-02270-y. (ICON-7)
5. Wimberger et al. Clin Cancer Res. 2022 Aug 24:CCR-22-1326. doi: 10.1158/1078-0432.CCR-22-1326. (ICON-7)
6. Kommos et al. Clin Cancer Res. 2017 Jul 15;23(14):3794-3801. doi: 10.1158/1078-0432.CCR-16-2196 (ICON-7)

KELIM & bevacizumab benefit in ICON-7

OS in patients with low-risk disease



OS in patients with high-risk disease



Unfavorable KELIM	<1.0
Favorable KELIM	≥1.0

Chemosensitivity, as assessed by KELIM, may be a complementary covariate to consider for decision-making about bevacizumab prescription. Approximately 47% of high-risk patients may not derive survival benefit from the addition of bevacizumab, however, the remaining 53% patients with poorly chemo-sensitive diseases may achieve the maximum survival gain of approximately 9 months.

Colomban O et al. JNCI Cancer Spectr. 2020;4(3):pkaa026. doi:10.1093/jncics/pkaa026

KELIM & bevacizumab benefit in GOG-218

FIGO stage IV and Stage III with VRD > 1 cm after PCS

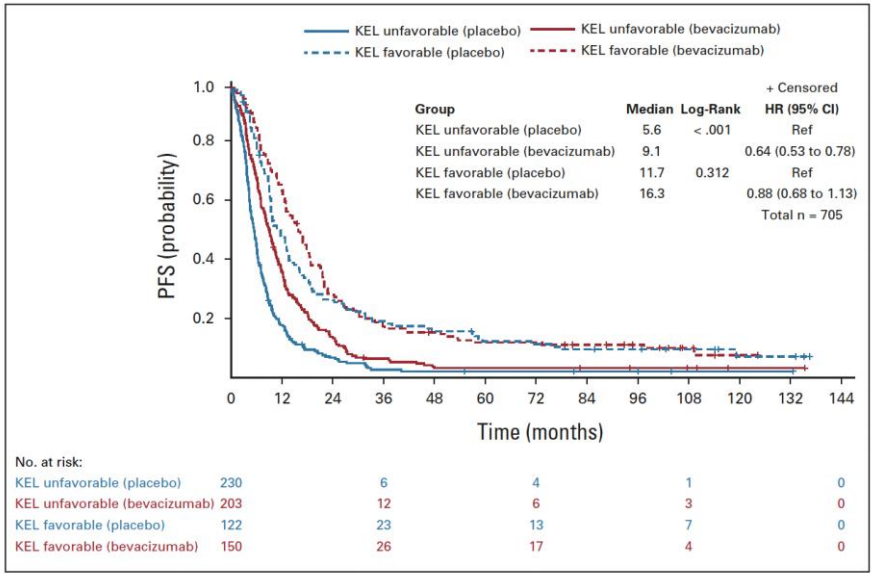


FIG 3. Kaplan-Meier curves of the PFS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

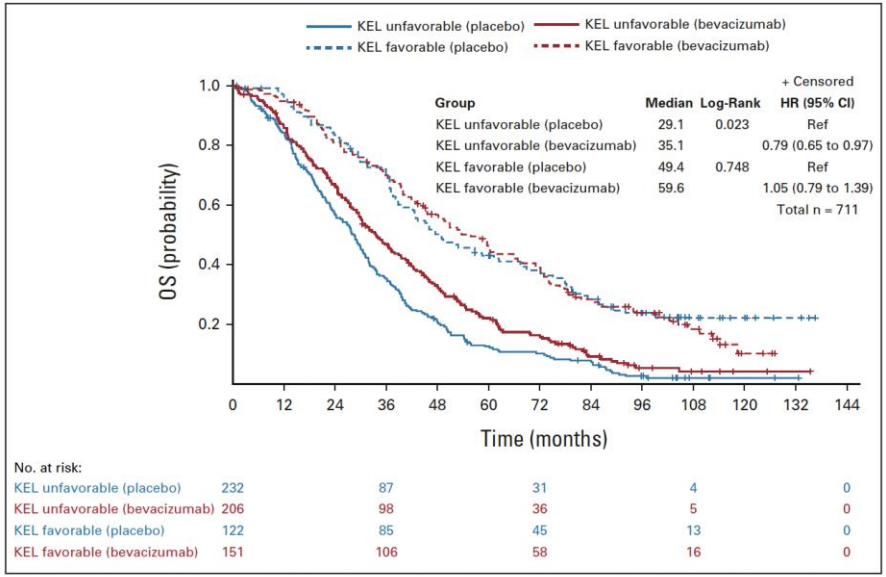


FIG 4. Kaplan-Meier curves of the OS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); OS, overall survival; PFS, progression-free survival; Ref, reference.

You et al. J Clin Oncol 2022 , Oct 17:JCO2201207. doi: 10.1200/JCO.22.01207

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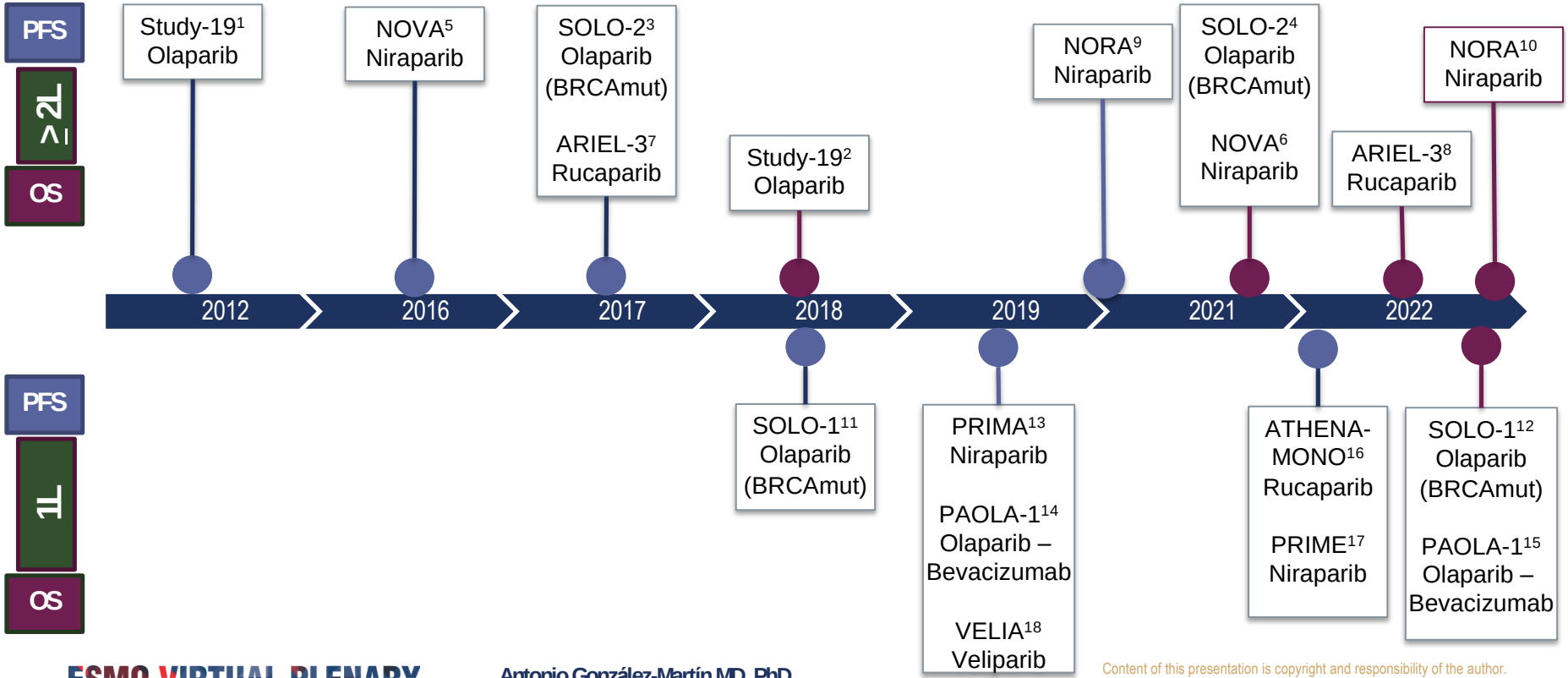
PARPi

RANDOMIZED CLINICAL TRIALS WITH PARP INHIBITOR AS MAINTENANCE



Antonio González-Martín MD, PhD

1. Ledermann. NEJM 2012; 2. Friedlander. Br J Cancer 2018.; 3. Pujade. Lancet Oncol 2017; 4. Poveda. Lancet Oncol 2021; 5. Mirza. NEJM 2016;6. Matulonis. SGO 2021; 7. Coleman. Lancet 2017 ; 8. Coleman. ESGO 2022; 9. Wu. Ann Oncol 2021; 10. Mirza. ESMO Virtual Plenary 2022
11. Moore. NEJM 2028; 12. DiSilvestro. JCO 2022; 13. Gonzalez-Martin. NEJM 2019; 14. Ray-Coquard NEJM 2019; 15. Ray-Coquard. ESMO 2022.; 16. Monk. JCO 2022; 17. Li. SGO 2022; 19. Coleman. NEJM 2019

Magnitude of benefit with PARPi is related to biomarker
Even patients with HRp (HRD-) benefit from PARPi

	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]	ATHENA-MONO[4]	PRIME[5]
PARPi	Olaparib	Niraparib	Olaparib + Bev	Rucaparib	Niraparib
Control	Placebo	Placebo	Bevacizumab	Placebo	Placebo
Population	BRCAmut	All comers	All comers	All comers	All comers (Chinese)
HRD test	NA	MyChoice	MyChoice	Foundation-One	BGI
BRCAmut	0.33 (0.25–0.43)	0.40* (0.27–0.62)	0.31* (0.20–0.47)	0.31* (0.20–0.47)	0.40* (0.23-0.68)
BRCAwt/HRD+	-	0.50* (0.31-0.83)	0.43* (0.28-0.66)	0.58* (0.33-1.01)	0.58* (0.36-0.93)
BRCAwt/HRD-	-	0.68* (0.49-0.94)	0.92* (0.72-1.17)	0.65* (0.45-0.95)	0.41* (0.25-0.65)

+++
++
+

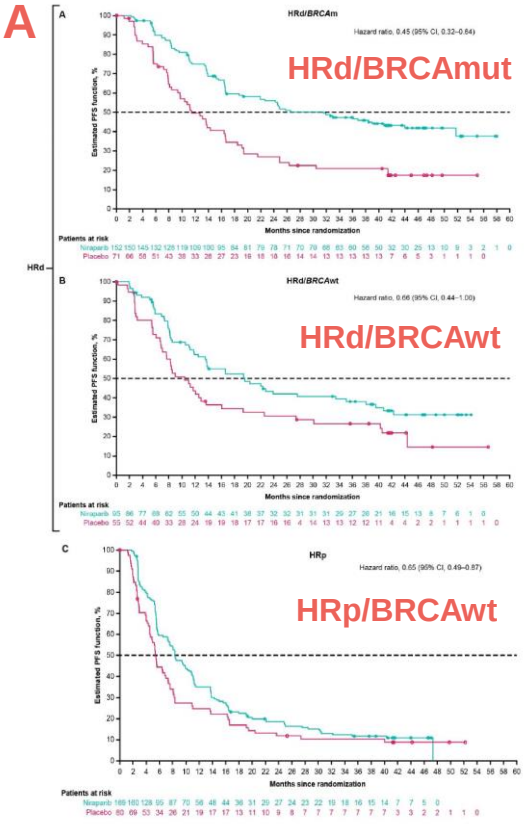
*exploratory

The aim of the table is not the cross-trial comparison

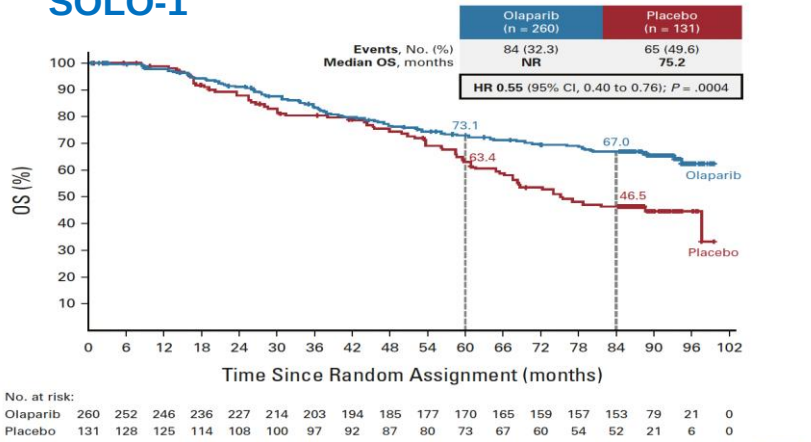
1. Moore. NEJM 2018; 2. Gonzalez-Martin. NEJM 20193; 3. Ray-Coquard. NEJM 2019;
4. Monk. J Clin Oncol 2022; 5. Li.SGO 2022

Benefit with PARPi is sustained and prolongs OS in BRCA and HRD

PRIMA

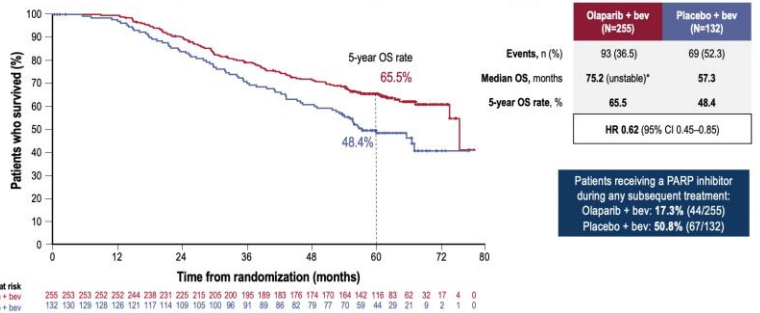


SOLO-1

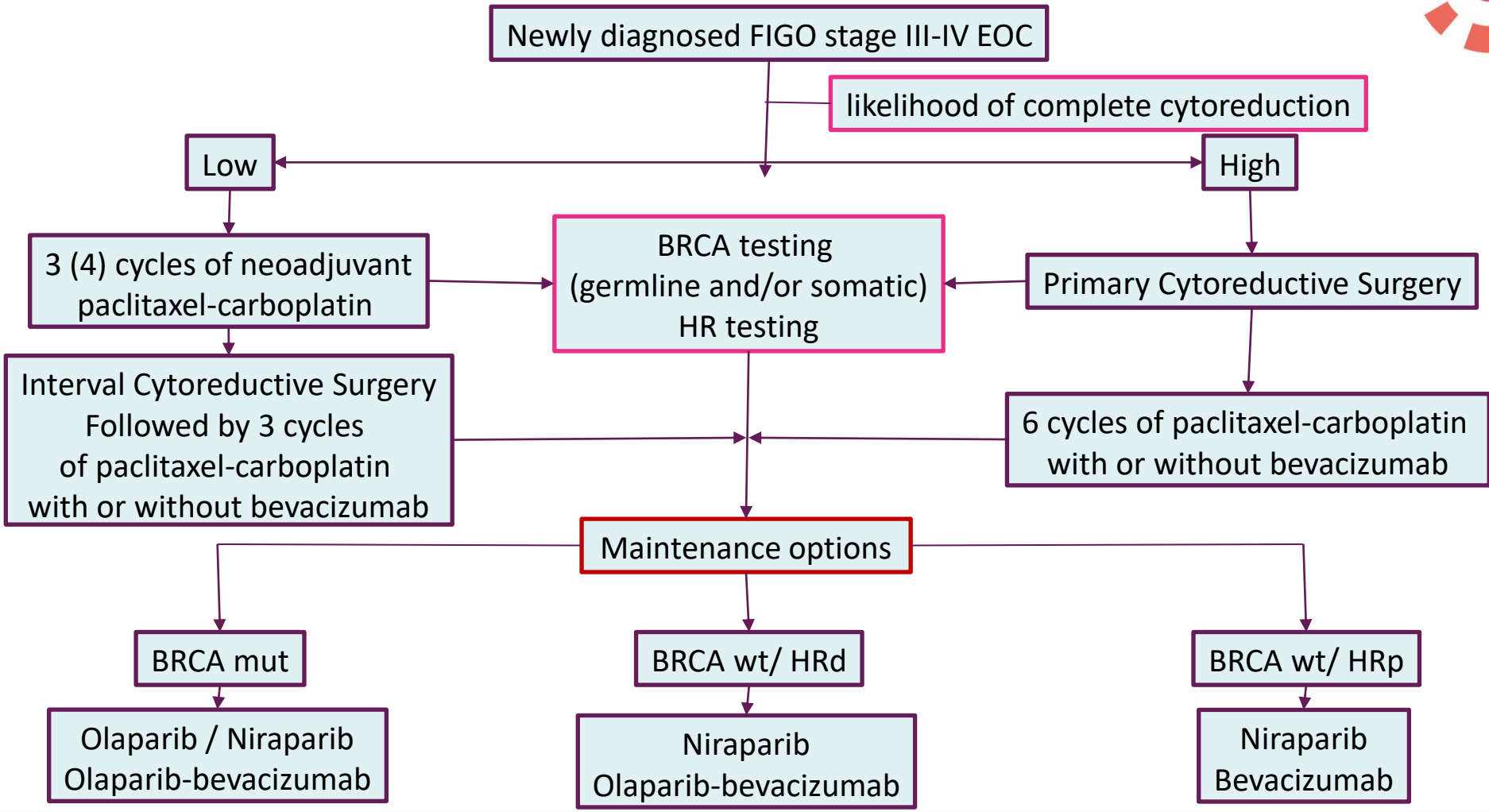


PAOLA-1

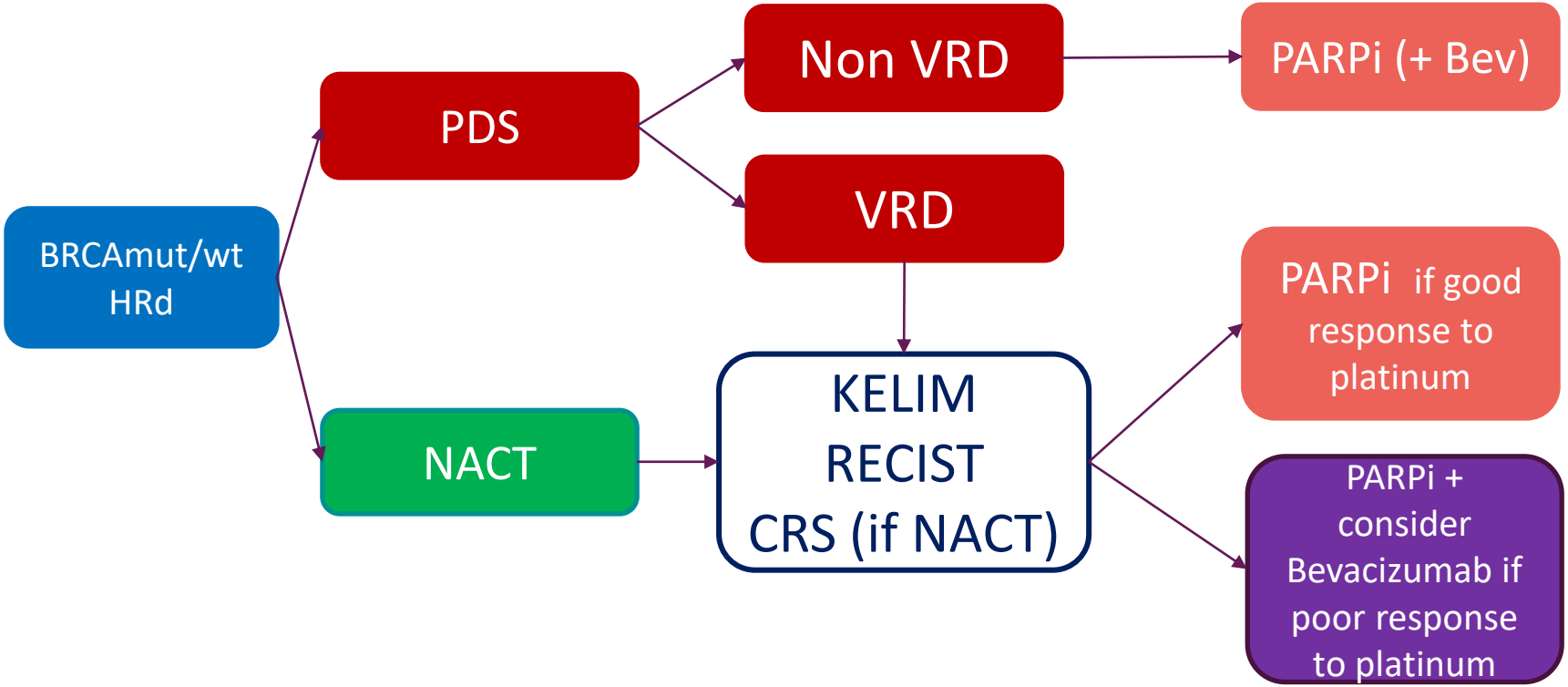
OS was prolonged in the HRD-positive subgroup



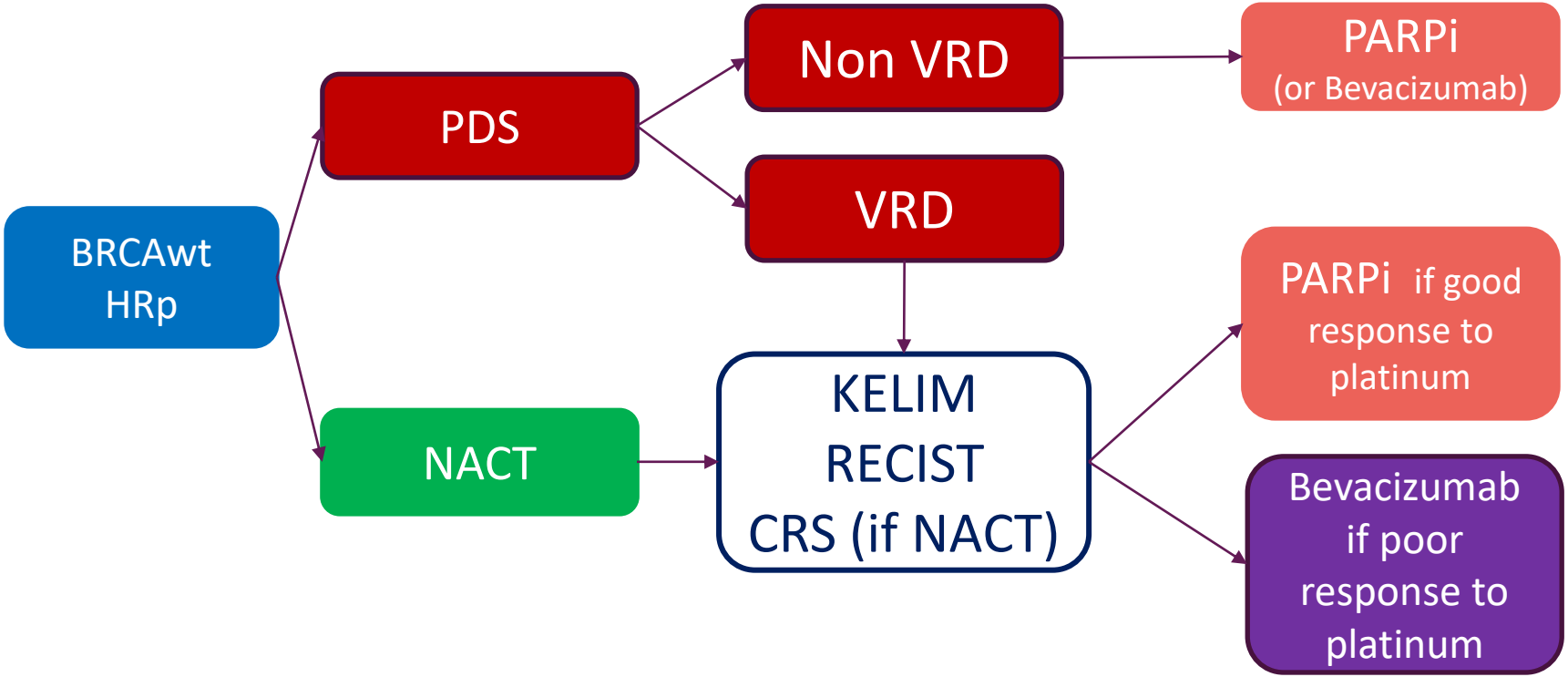
1. Gonzalez-Martin. Eur J Cancer 2023; 2. DiSilvestro et al. J Clin Oncol 2023; 3. Ray-Coquard. Ann Oncol 2023

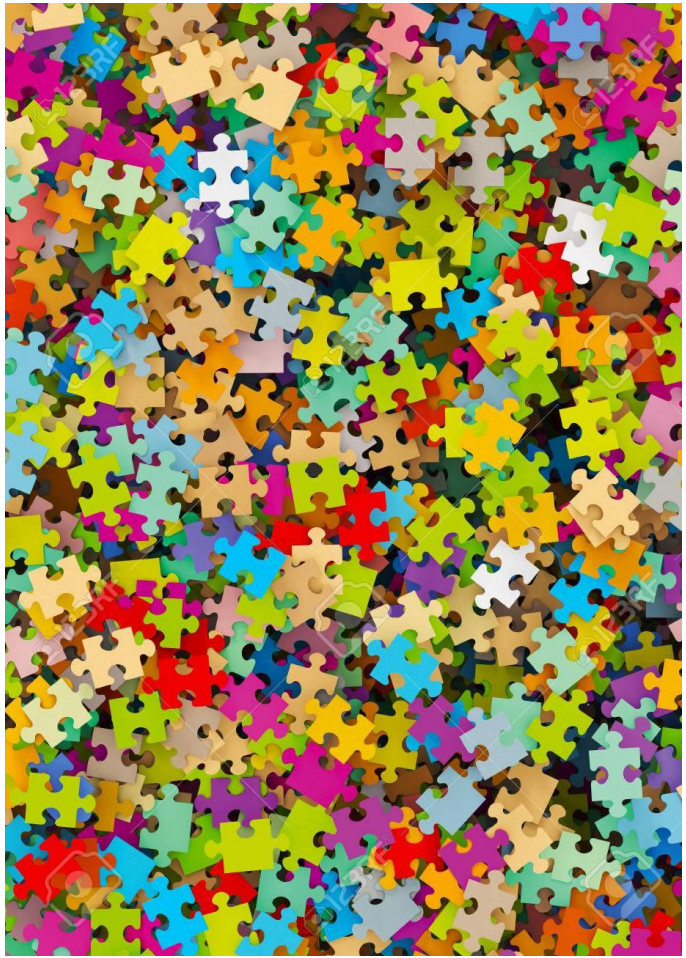

Newly diagnosed FIGO stage III-IV EOC
likelihood of complete cytoreduction
Low
High
3 (4) cycles of neoadjuvant paclitaxel-carboplatin
BRCA testing (germline and/or somatic) HR testing
Primary Cytoreductive Surgery
Interval Cytoreductive Surgery Followed by 3 cycles of paclitaxel-carboplatin with or without bevacizumab
6 cycles of paclitaxel-carboplatin with or without bevacizumab
Maintenance options
BRCA mut
BRCA wt/ HRd
BRCA wt/ HRp
Olaparib / Niraparib Olaparib-bevacizumab
Niraparib Olaparib-bevacizumab
Niraparib Bevacizumab

How to chose maintenance for patients in first-line if HR-deficient ?



How to chose maintenance for patients in first-line if BRCAwt/HRproficient ?





Muchas Gracias!