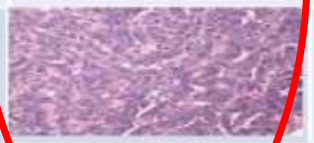
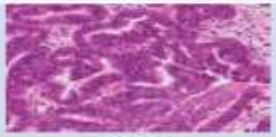
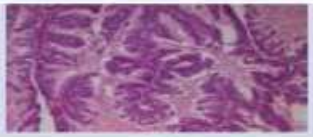
CÁNCER DE OVARIO

Dra. Irene Torres
Oncología Médica HCULB
7 de abril de 2022

Conflictos de interés

- Consultant or Advisory Role: GSK, Pharmamar
- Speaking: Astra Zeneca-MSD, GSK, Clovis
- Registration and attending scientific meetings: Astra Zeneca-MSD, GSK, Clovis.

Entidad heterogénea

	70%	5%	10-15%	10-15%	3%
	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
Pathology					
Molecular features	CNA high *TP53* *BRCA1/2* HRD	CNA low MAPK act. *KRAS* *BRAF*	*ARID1A* PI3K/AKT act. RTK/Ras act. MMR	*PI3KCA* *ARID1A* *KRAS* Wnt/β-catenin act. *PTEN*	*KRAS* *HER2* amplif.
Platinum Chemotherapy	Sensitive	Relatively Resistant	Relatively Resistant	Sensitive	Relatively Resistant

Epidemiología

- 8º tumor más frecuente en la mujer
- 3600 nuevos casos (España)
- 4,7% mortalidad por cáncer en mujeres
- El más letal (50%)
- Supervivencia estimada a 5 años del 40%

  (incluye estadios precoces)

https://seom.org/images/Cifras_del_cancer_en_Espana_2022.pdf

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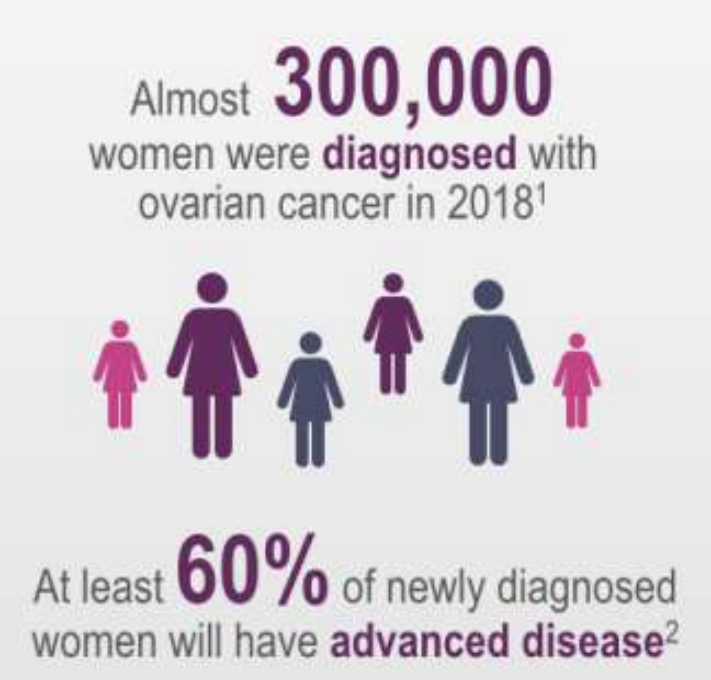
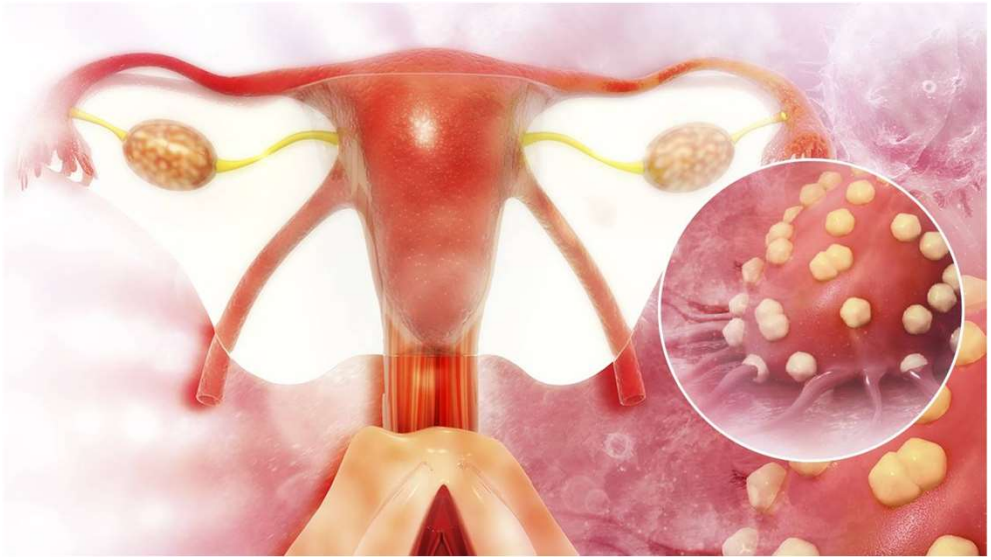
Epidemiología



Diagnóstico: ~ 60 - 70% de las pacientes con enfermedad avanzada.



Torre LA. CA Cancer J Clin 2018

Síntomas

Pérdida de peso

Ascitis

Dolor lumbar

Dolor pélvico/abdominal

Molestias urinarias

Pesadez/ distensión abdominal

Considerar la posibilidad de cáncer de ovario si los síntomas:

- ✓ Son nuevos (comienzo < 1 año)
- ✓ Son persistentes (> 12 días/ mes)

www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

Síntomas

Original Research

Symptoms of Women With High-Risk Early-Stage Ovarian Cancer

John K. Chan, MD, Chunqiao Tian, PhD, Joshua P. Kesterson, MD, Bradley J. Monk, MD, Daniel S. Kapp, MD, Brittany Davidson, MD, Sharon Robertson, MD, Larry J. Copeland, MD, Joan L. Walker, MD, Robert M. Wenham, MD, Yovanni Casablanca, MD, Nick M. Spirtos, MD, Krishnansu S. Tewari, MD, and Jeffrey G. Bell, MD

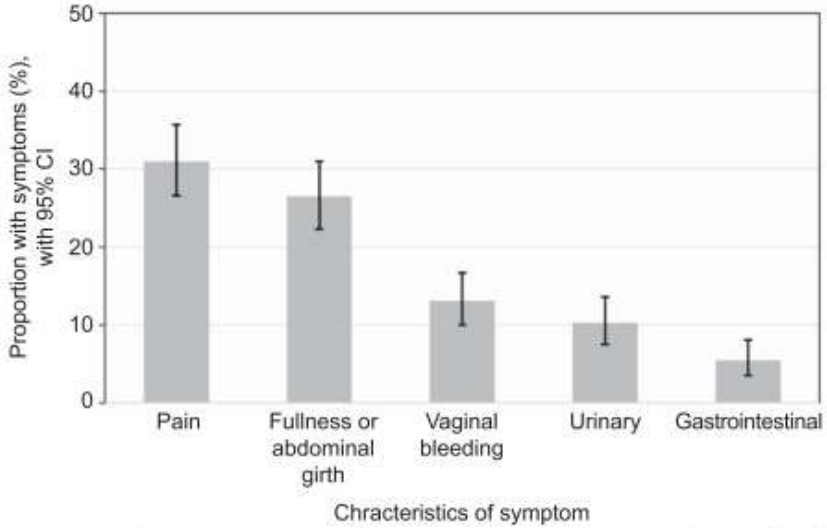


Fig. 1. Characteristics of symptoms associated with high-risk early-stage ovarian cancer.

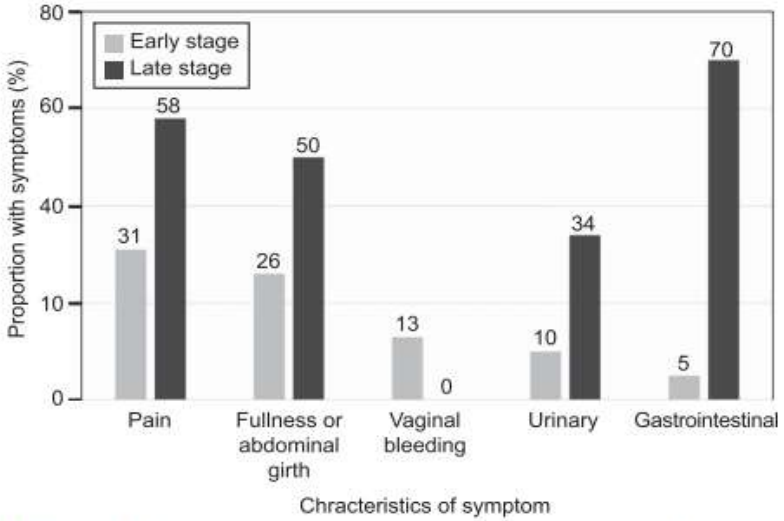
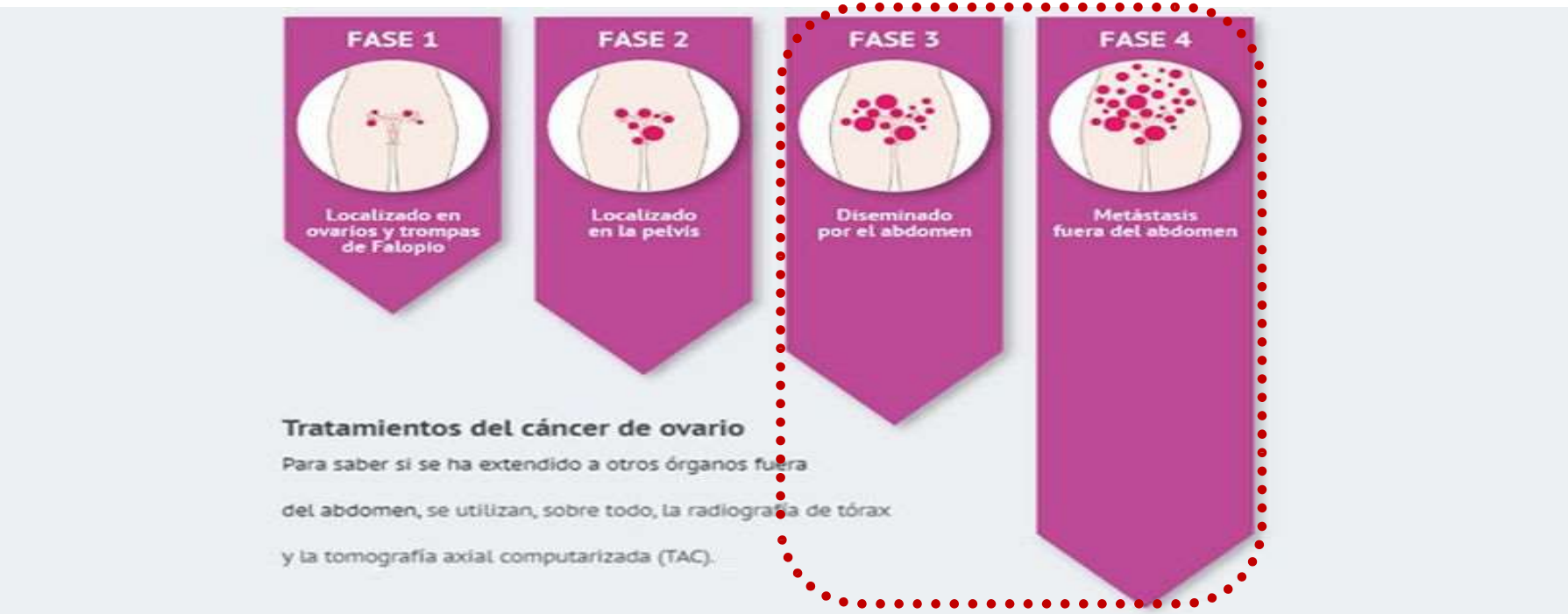


Fig. 4. Ovarian cancer symptoms: early- vs advanced-stage. Data from early-stage disease based on current report, and data from advanced-stage disease from historical report.[8]

Chan JK. *Obstet Gynecol* 2022

Diagnóstico en fases avanzadas

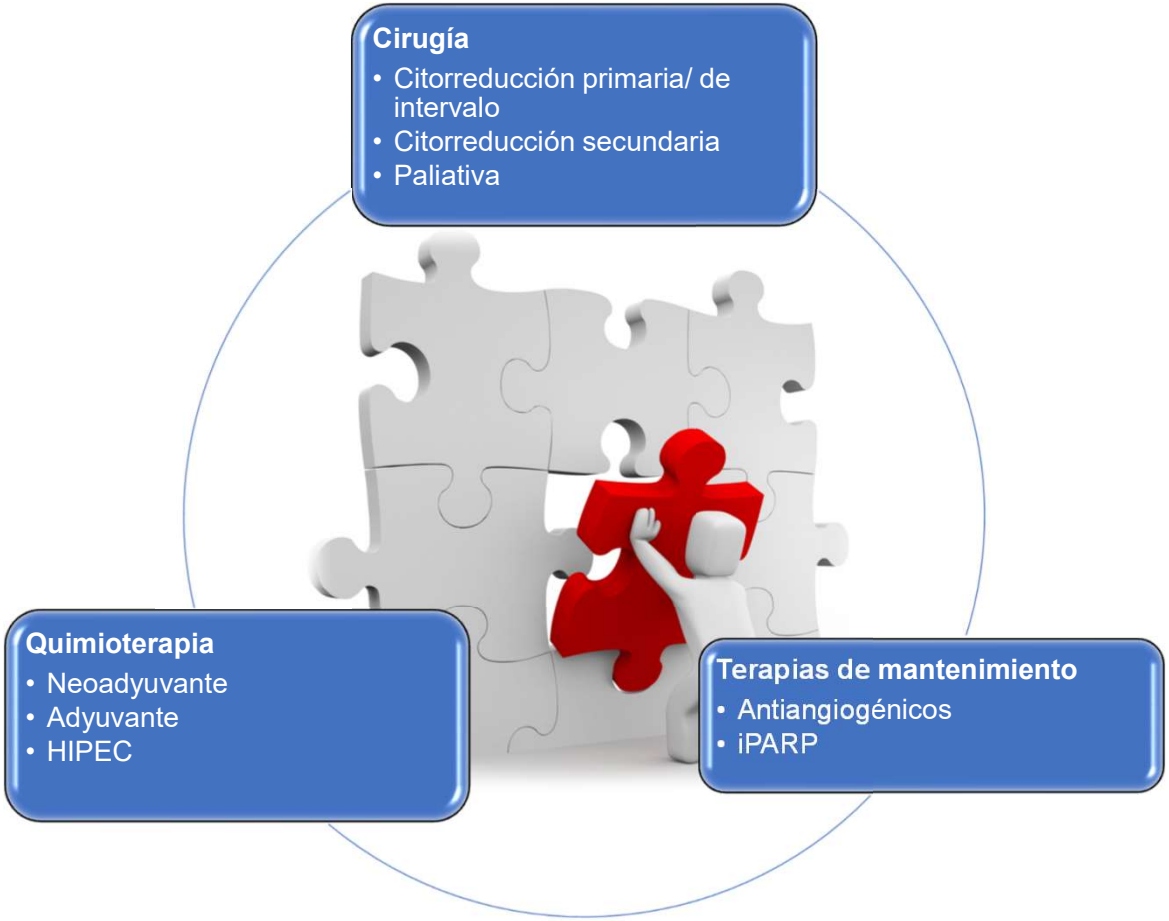
- Síntomas poco específicos.
- Eficacia de programas de *screening* no demostrada en ensayos controlados, aleatorizados y prospectivos.



Tratamiento

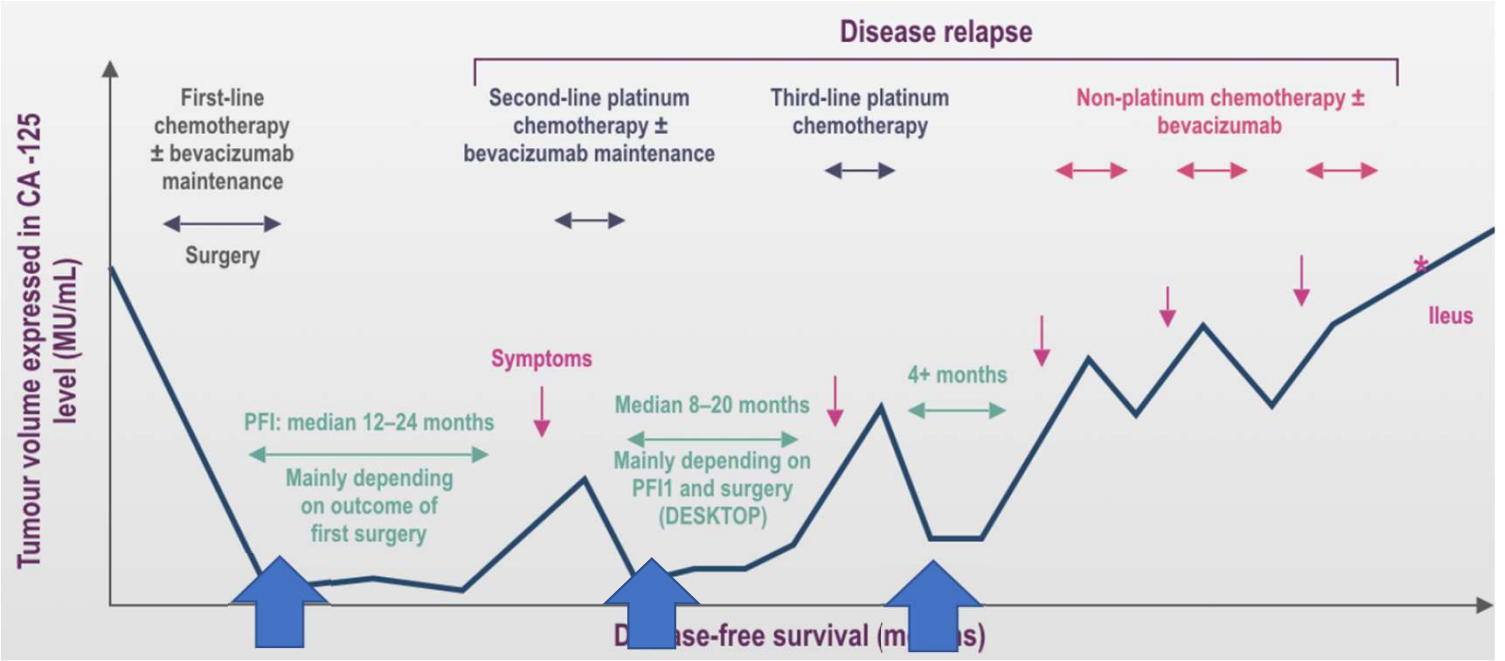
MULTIDISCIPLINAR

Comité Tumores Ginecológicos HCULB



Terapias de mantenimiento

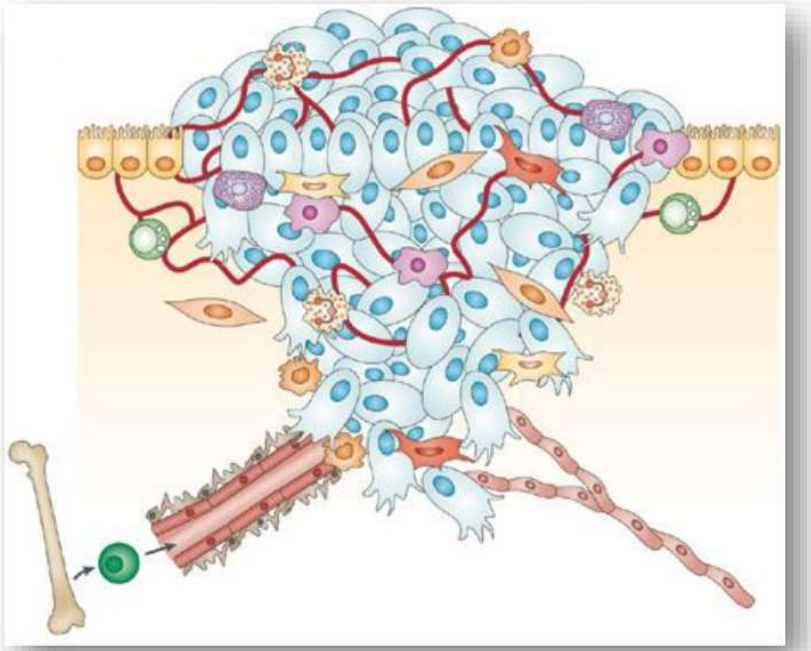
- El CO epitelial avanzado (III-IV FIGO) es una enfermedad agresiva que cursa con múltiples recaídas.
- Se caracteriza por la sensibilidad al platino, aunque ésta va disminuyendo en el tiempo[1].
- El intervalo libre de tratamiento con platino (ILP) es un factor muy importante para predecir la supervivencia.[2]



1. Giornelli GH. Springer Plus 2016. 2. Tomao F. Cancer 2017

Mantenimiento

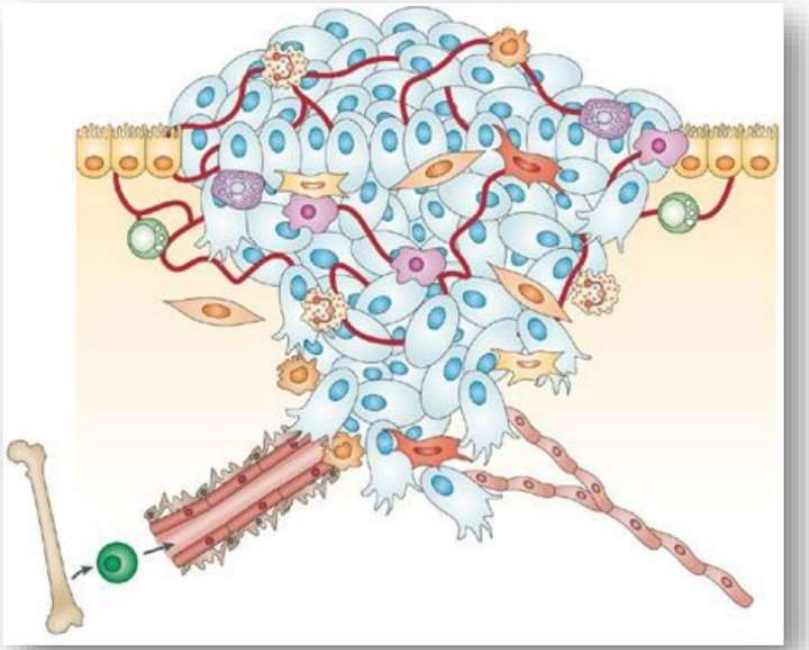
Anti-angiogenesis



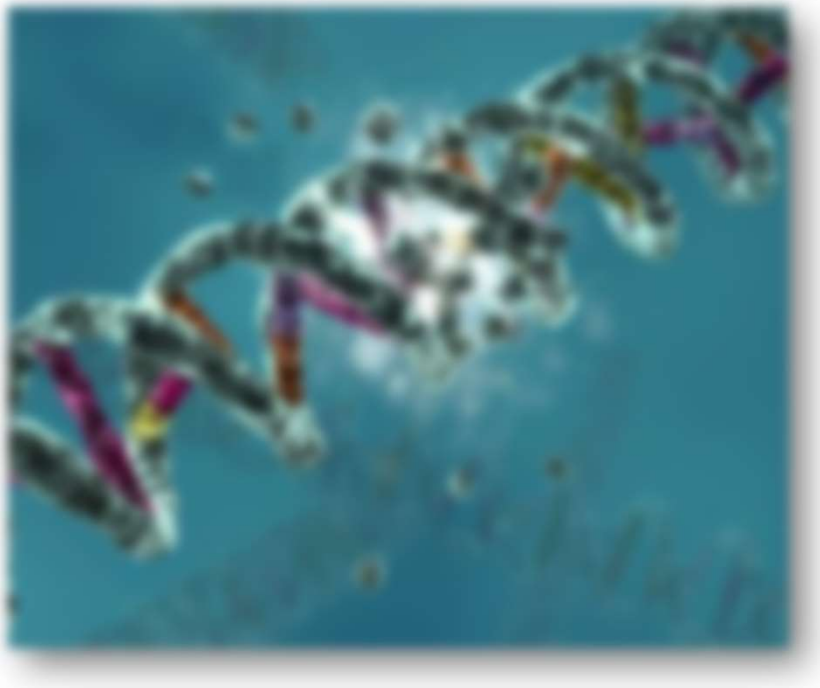
PARPi

Mantenimiento

Anti-angiogenesis

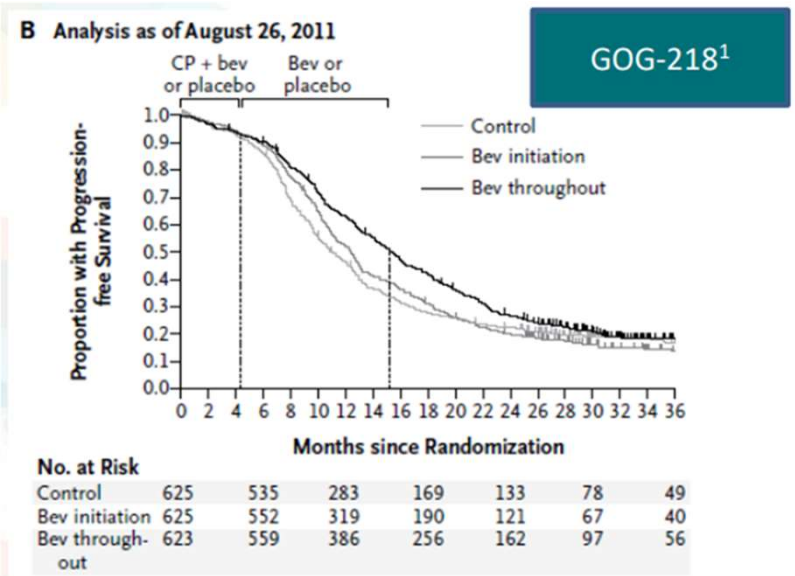


PARPi



Antiangiogénesis. Bevacizumab 1L

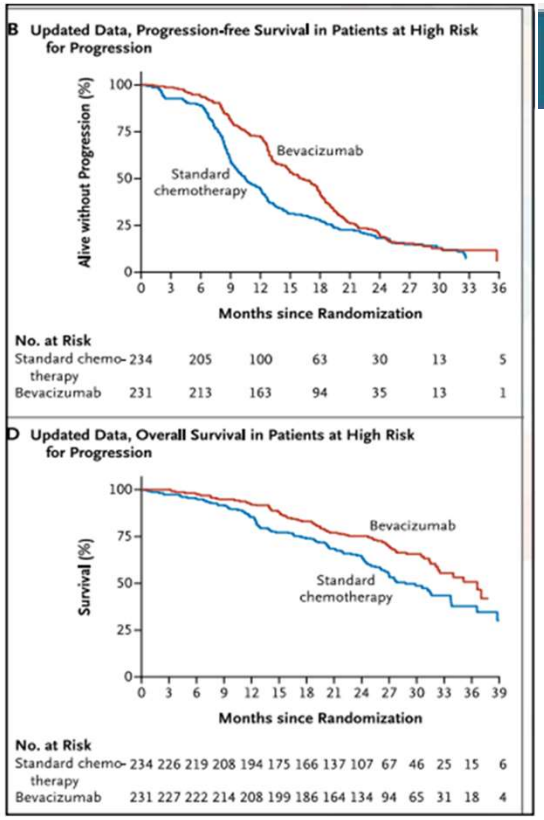
GOG-218[1]



Stage III RT >0cm PDS
Stage IV PDS
Stage III&IV not operated

PFS: Bev vs Control: HR: 0.770
(0.681- 0.870) p<0.001

ICON-7[2]



Stage I-IV all situations.

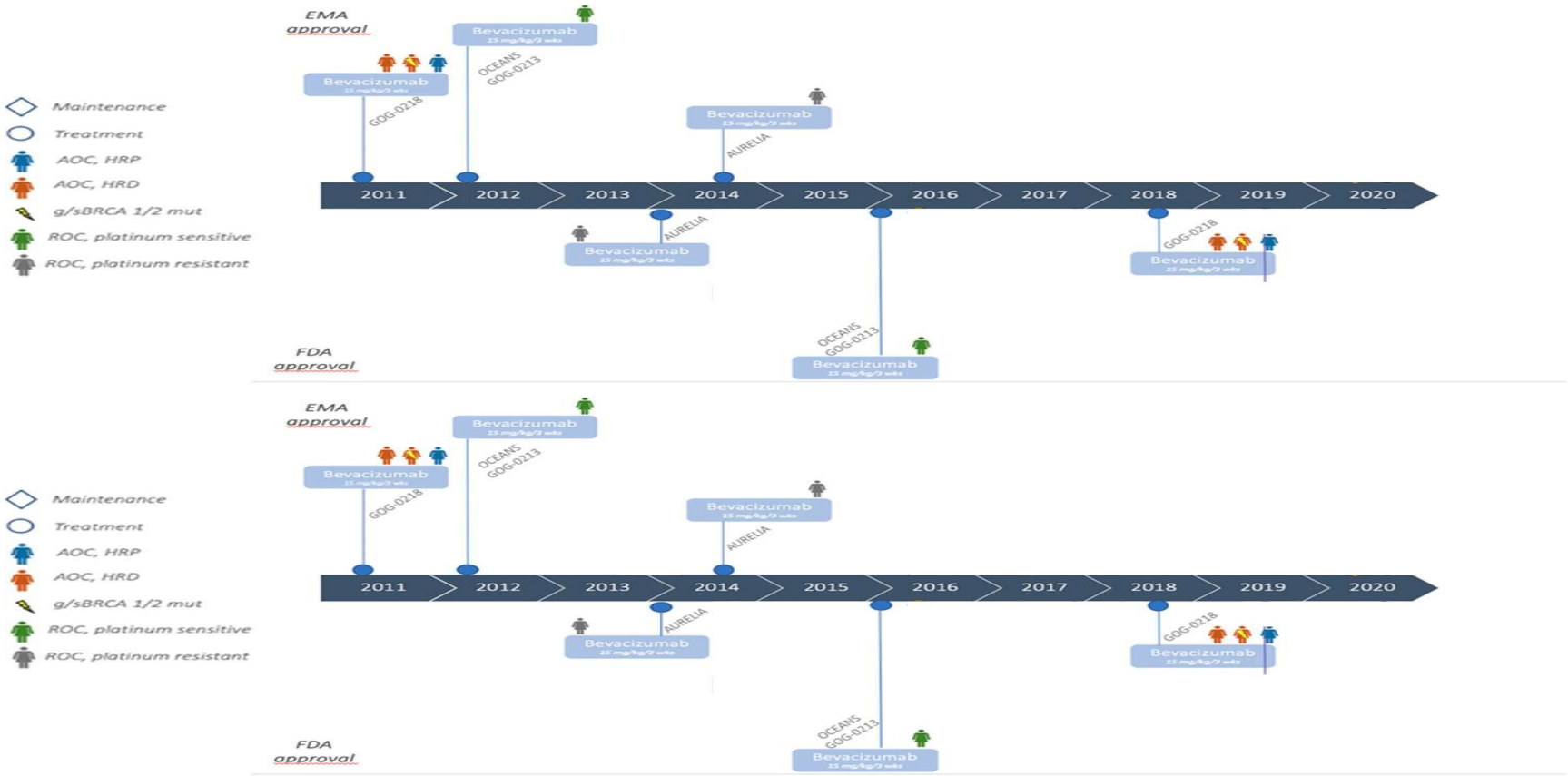
High risk group OS:

Bev vs Control: HR: 0.78

(0.63- 0.97) p< 0.03

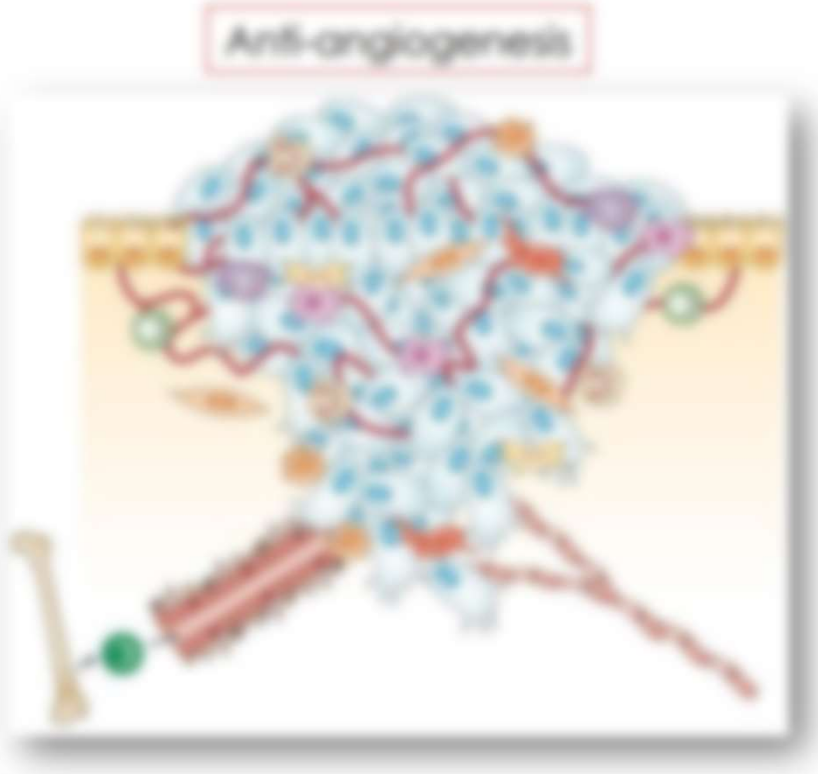
[1]Burguer RA, et al. NEJM 2011
[2]Oza AM, et al. Lancet Oncol 2015

Antiangiogénesis. Bevacizumab

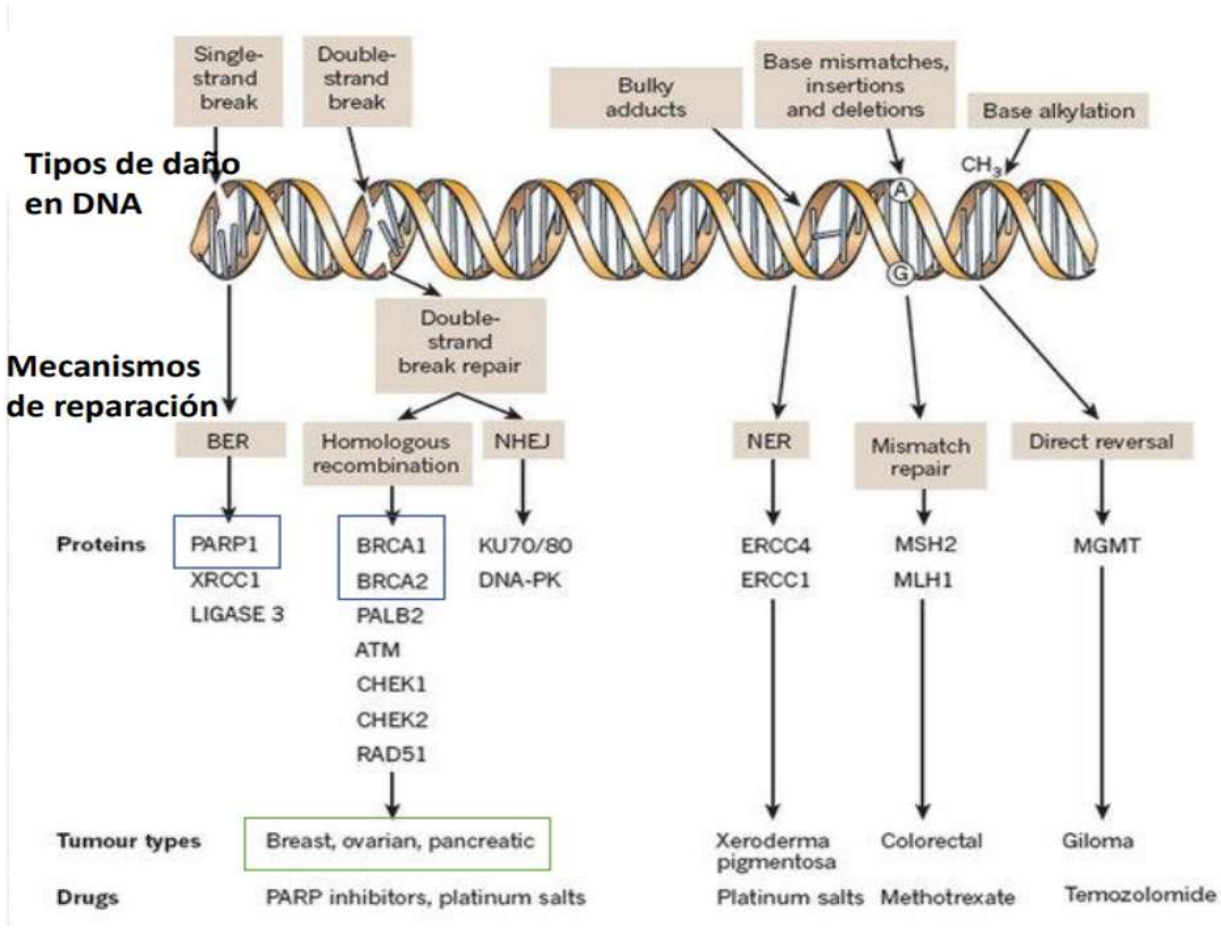


Nero C. Cancers 2021

Mantenimiento



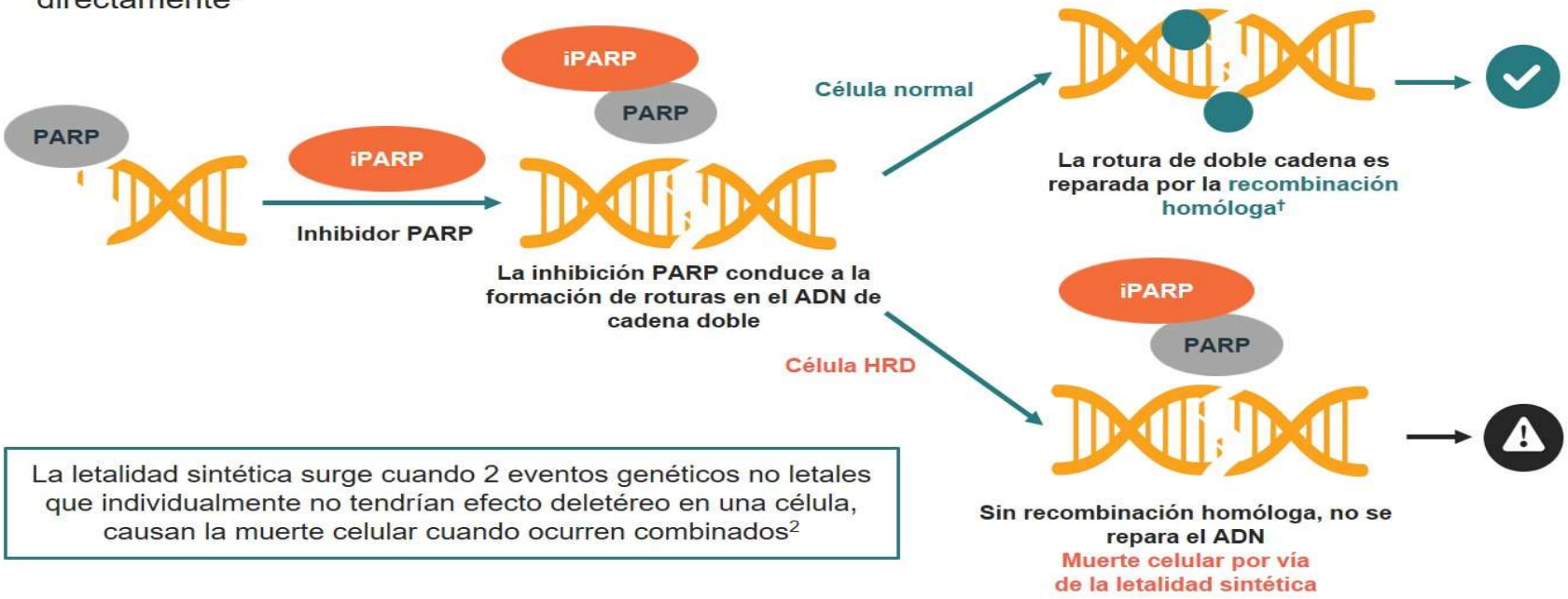
iPARP: Mecanismo de acción



Lord CJ, Ashworth A. Nature 2012

iPARP: Mecanismo de acción

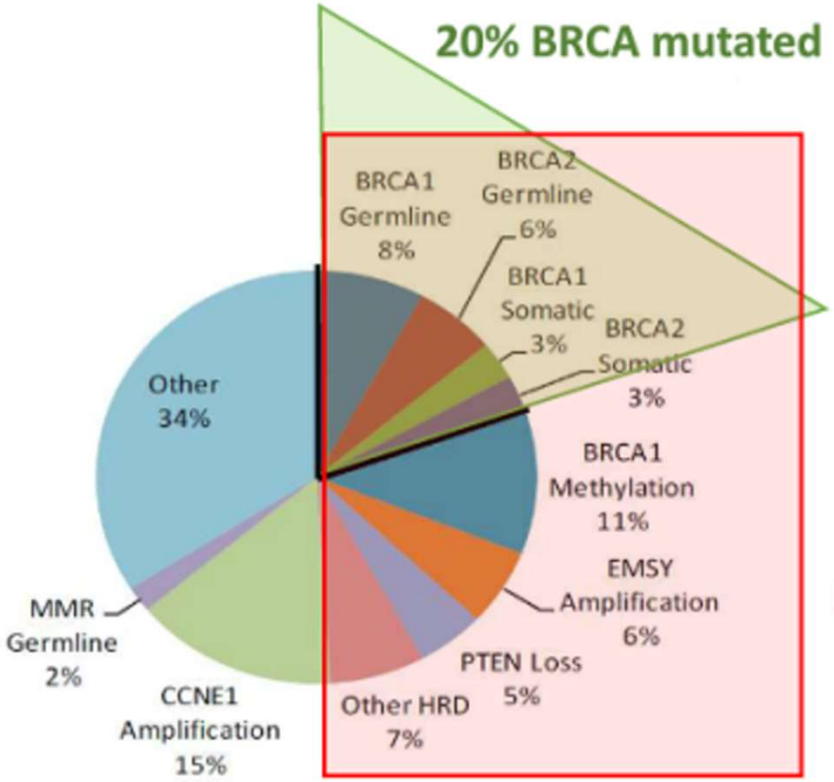
- La inhibición de PARP aumenta la prevalencia de lesiones sin reparar del ADN, conduciendo al colapso del ADN y apoptosis[1]
- A diferencia de la quimioterapia tradicional, los inhibidores de PARP no causan daño al ADN directamente[1]



La letalidad sintética surge cuando 2 eventos genéticos no letales que individualmente no tendrían efecto deletéreo en una célula, causan la muerte celular cuando ocurren combinados[2]

1. Farmer H et al. Nature. 2005; 2. Dedes KJ et al. Cell Cycle. 2011; 3. Lord CJ et al. Nat Rev Cancer. 2016.

Mutaciones BRCA y HRD



Determinación de mutaciones somáticas y germinales de BRCA

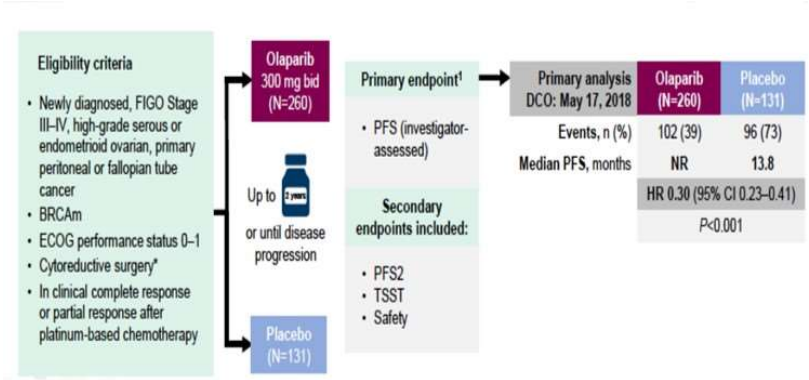
50% HRD

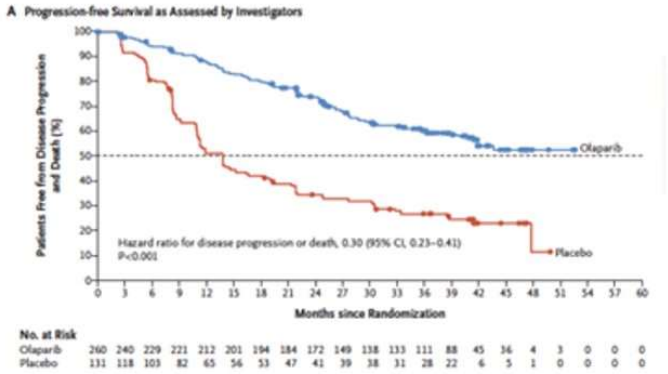
Métodos de determinación de la inestabilidad genómica

The Cancer Genome Atlas Research Network. Nature, 2011:474;609-615

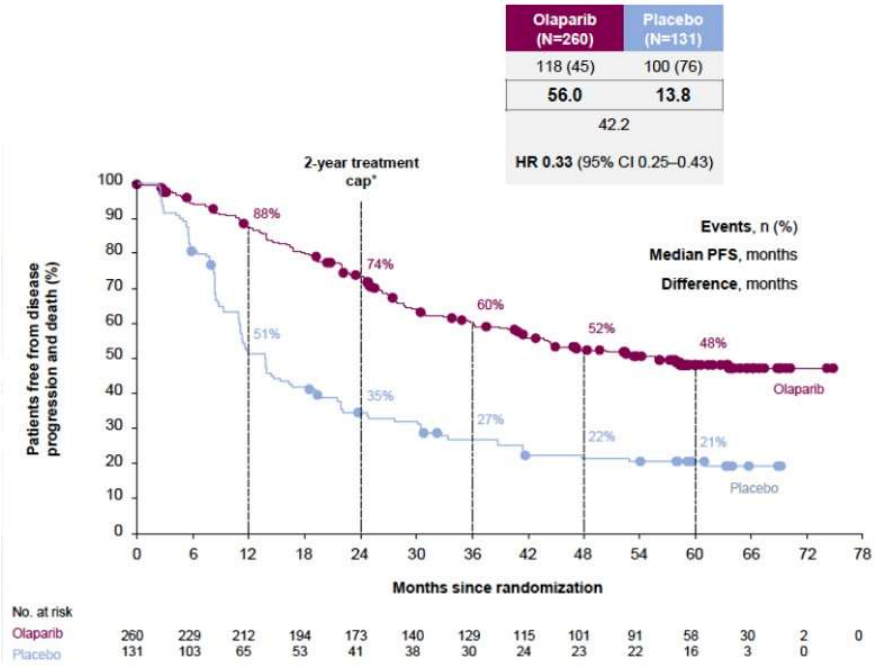
BRCA mutadas. Olaparib

SOLO-1





Moore K, et al. NEJM 2018



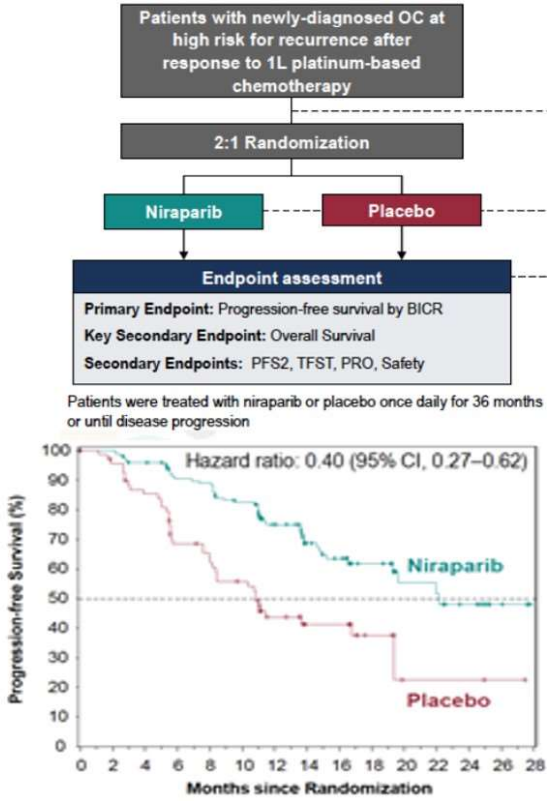
Banerjee et al. ESMO 2020

BRCA mutadas

PRIMA

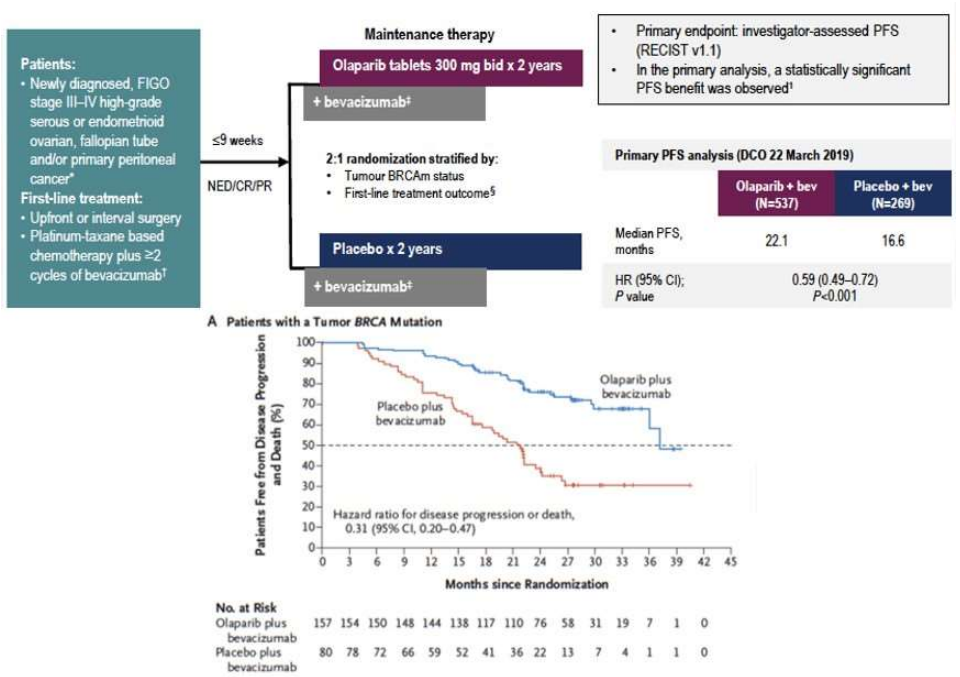
30% of patients included BRCAmut.

PFS in BRCA:
22.1 vs 10.9 months



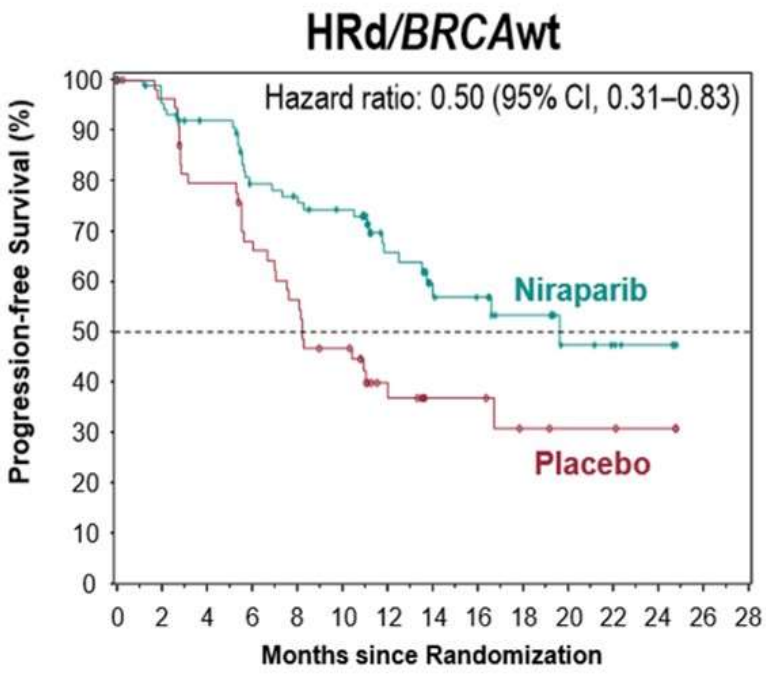
González A. NEJM 2019

PAOLA-1



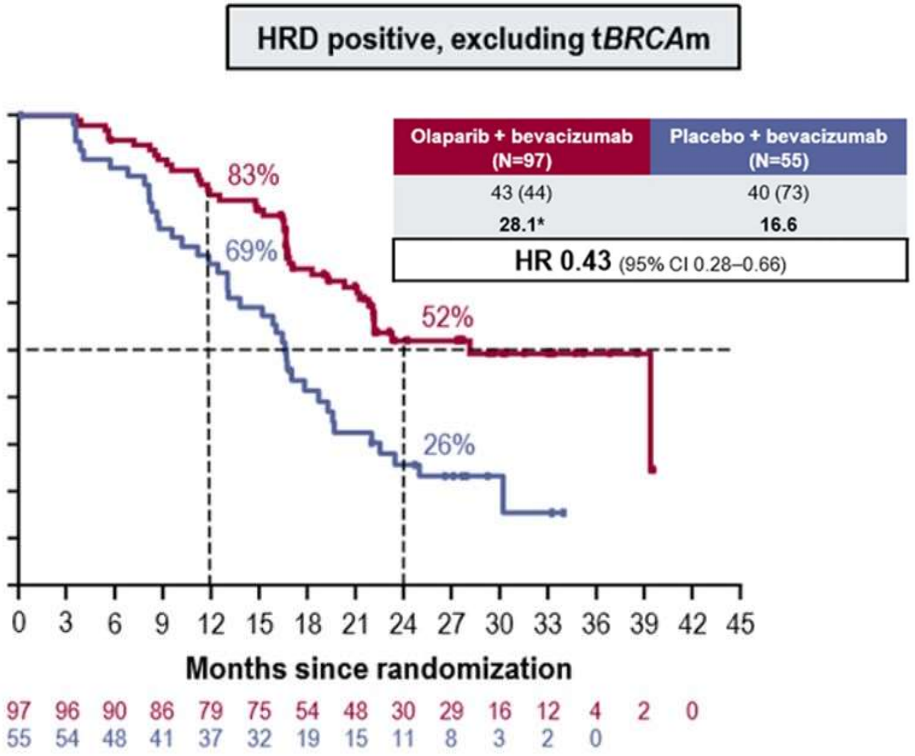
Ray-Coquard I, et al. NEJM 2019

HRD (excluye BRCAmut)



PRIMA

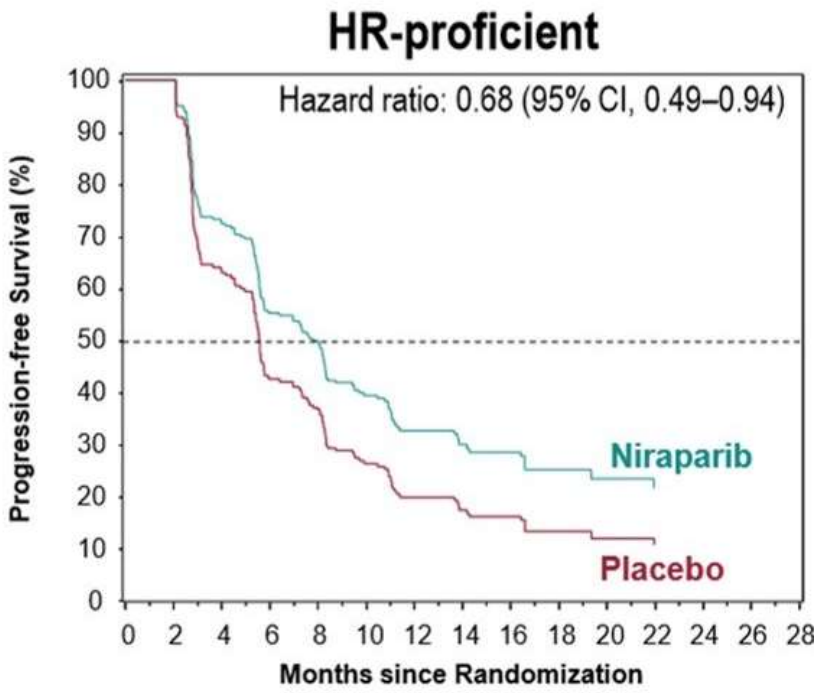
González A. NEJM 2019



PAOLA-1

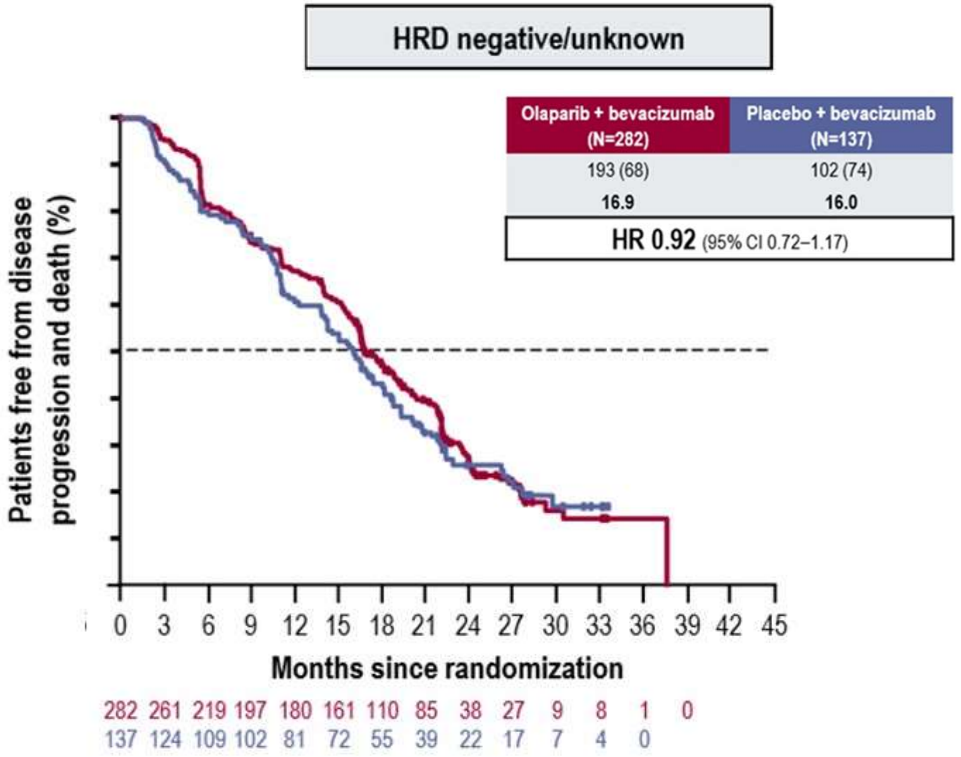
Ray-Coquard I, et al. NEJM 2019

Sin mutaciones: HRp/ BRCA wt



PRIMA

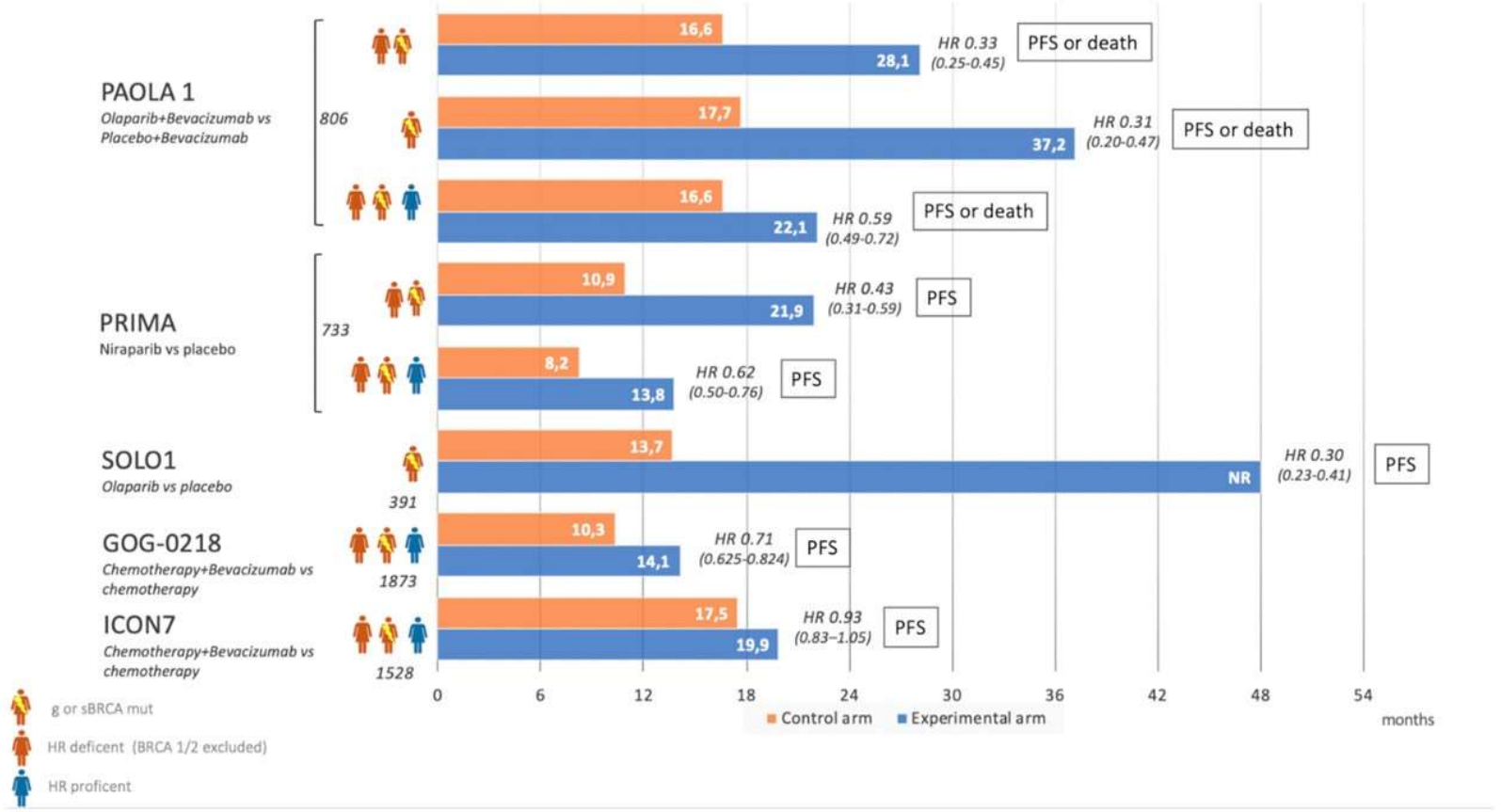
González A. NEJM 2019



PAOLA-1

Ray-Coquard I, et al. NEJM 2019

1ªL mantenimiento

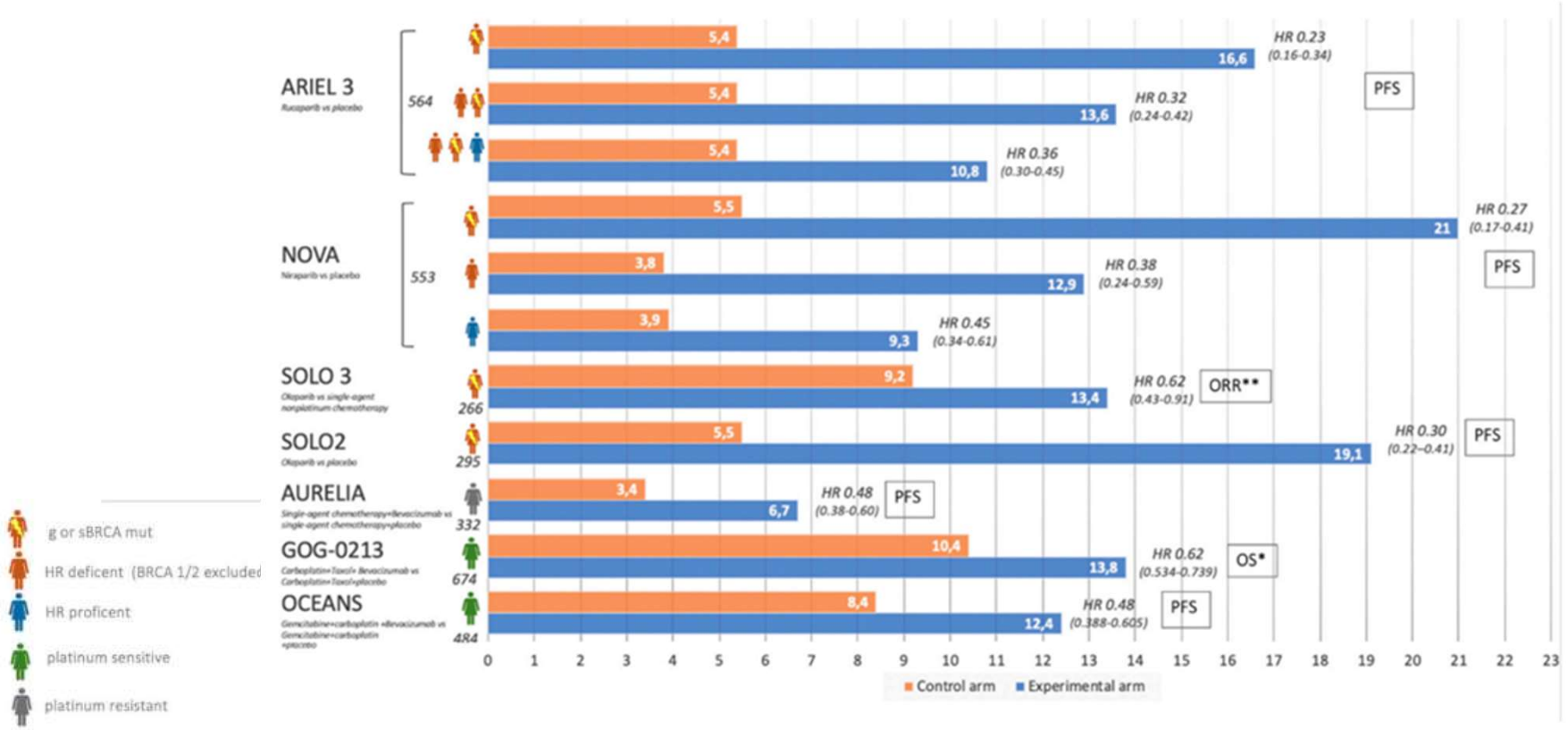


Nero C. Cancers 2021

1ªL mantenimiento

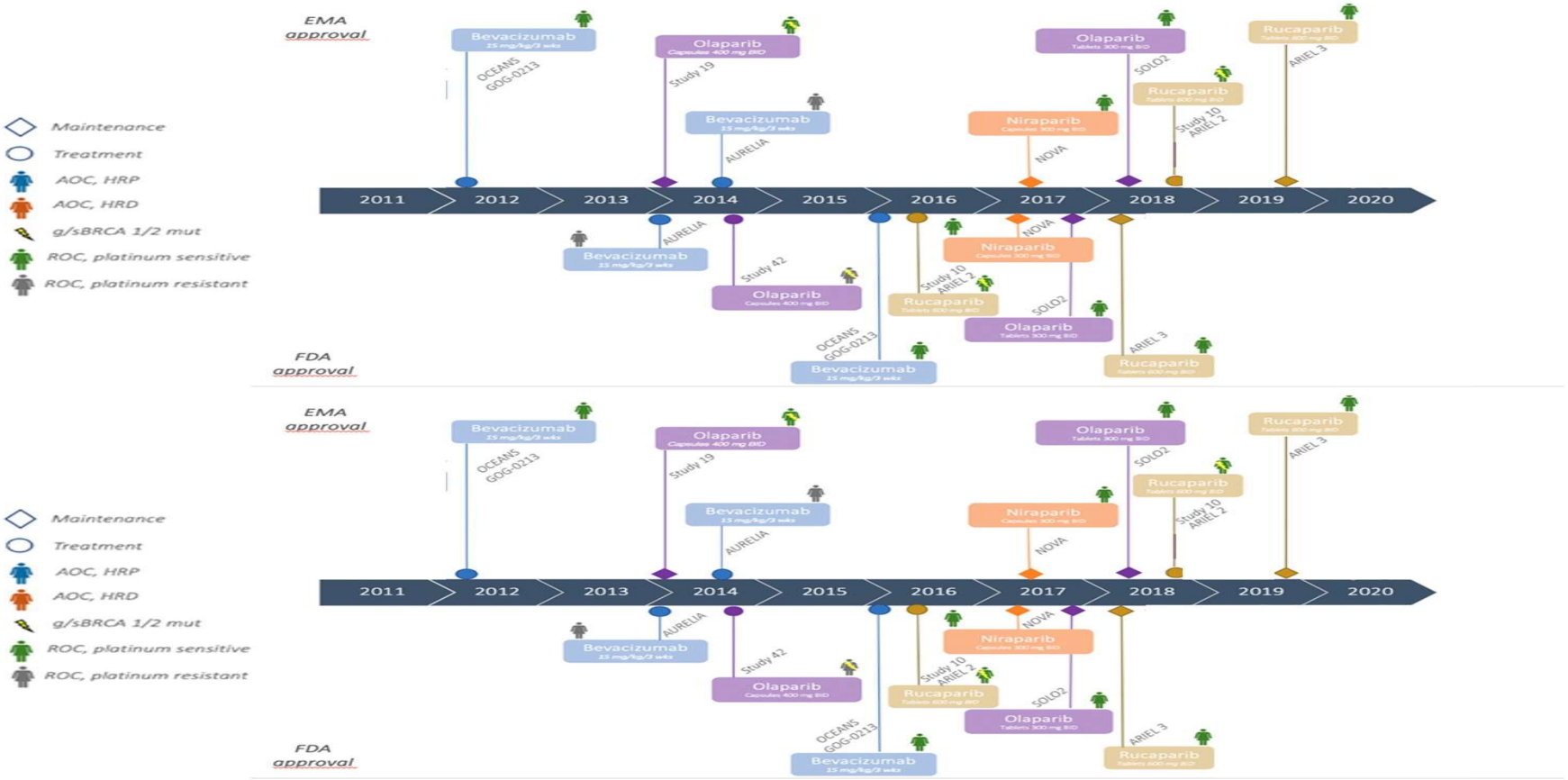
Nero C. Cancers 2021

Líneas sucesivas



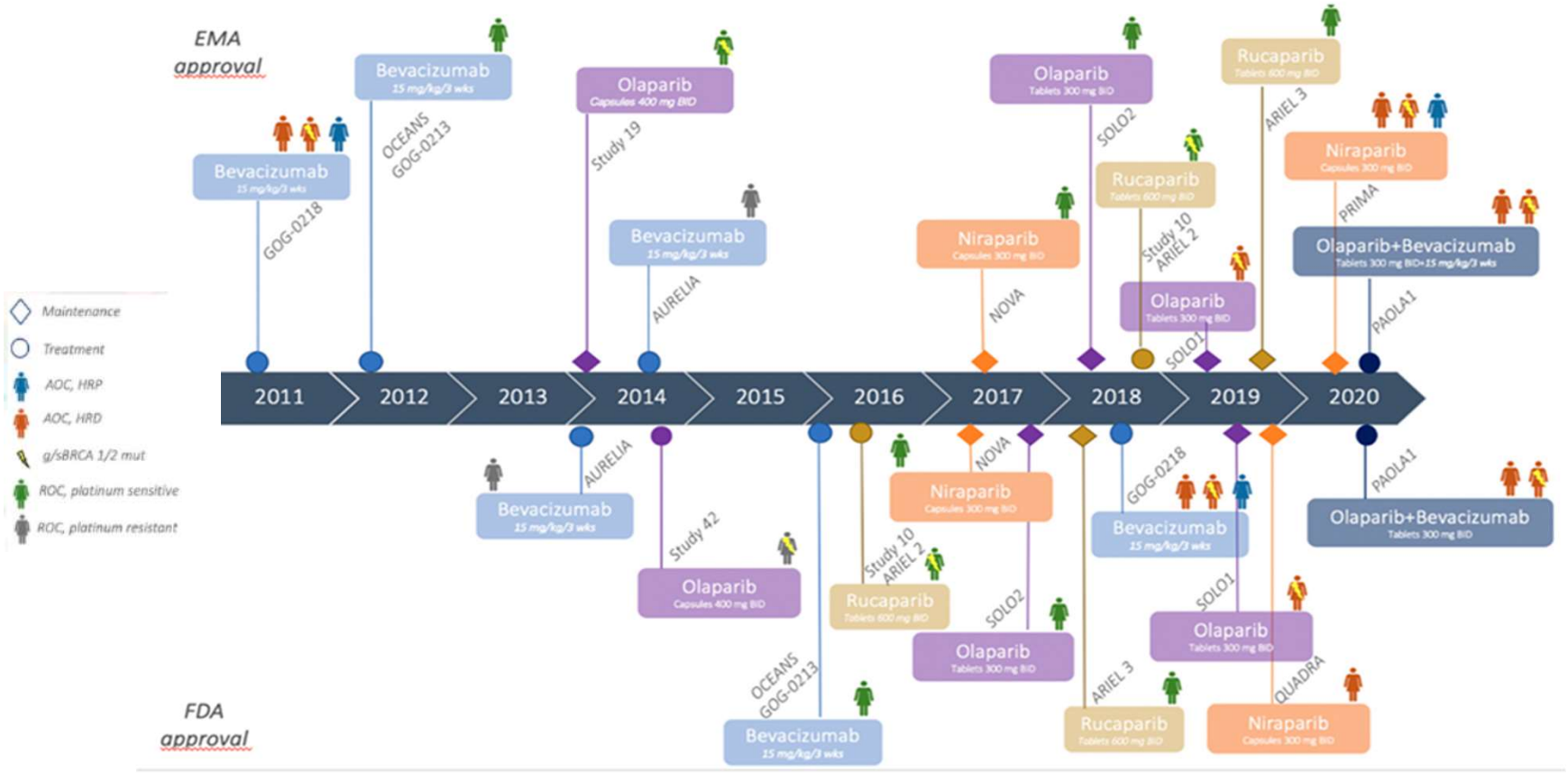
Nero C. Cancers 2021

Líneas sucesivas



Nero C. Cancers 2021

Opciones terapéuticas



Nero C. Cancers 2021

Toxicidades

ADVERSE EVENTS	PRIMA[1] (Niraparib)		PAOLA-1[2] (Olaparib + bevacizumab)		SOLO – 1[3] (Olaparib)	
	Any grade (%)	Grade ≥ 3 (%)	Any grade (%)	Grade ≥ 3 (%)	Any grade (%)	Grade ≥ 3 (%)
Nausea	57	1	53	2	77	1
Fatigue	35	2	53	5	63	4
Vomiting	22	1	22	1	40	<1
Diarrhea	19	1	18	2	34	3
Constipation	39	<1	10	<1	28	<1
Anemia	63	31	41	17	39	22
Thrombocytopenia	46	29	8	2	11	<1
Neutropenia	26	13	18	6	23	8
Lymphopenia	NR	NR	24	7	NR	NR
Insomnia	25	1	NR	NR	NR	NR
Headache	26	<1	14	<1	23	<1
Alopecia	NR	NR	NR	NR	NR	NR
Hypertension	17	6	46	19	NR	NR
Arthralgia	18	<1	22	1	25	<1
Urinary tract infection	NR	NR	15	<1	11	<1

[1]González A. NEJM 2019. [2]Ray-Coquard I. NEJM 2019. [3]Moore K. NEJM 2018

Interacciones

Absorption, distribution, metabolism, and excretion of poly (ADP-ribose) polymerase (PARP) inhibitors

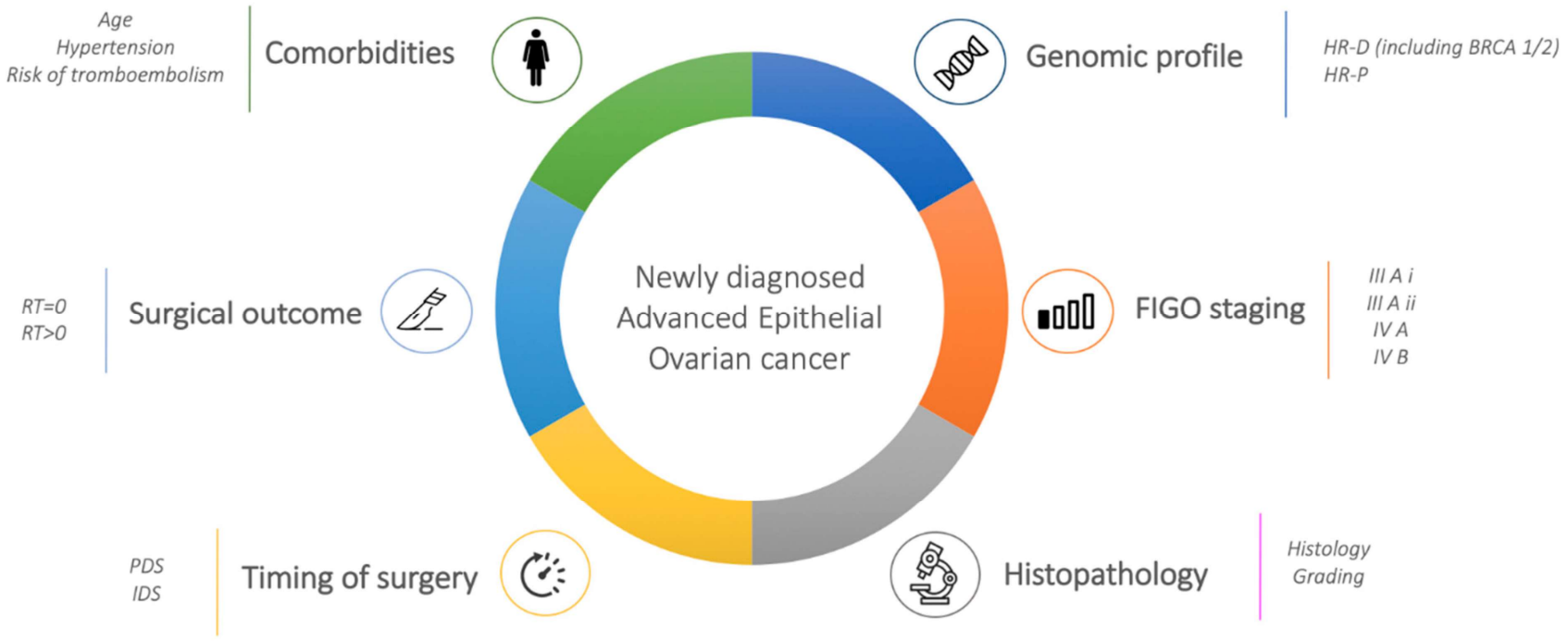
	Enzymes used for metabolism	Effect of PARP inhibitors on other drugs	Effect of other drugs on PARP inhibitors	Effect on renal and hepatic uptake transporters	Pharmacokinetics	Effect with food
Rucaparib[14,27,28]	Is metabolised predominantly by CYP2D6, and by CYP1A2 and CYP3A4 to a lesser extent	Reversibly inhibits CYP1A2, CYP2C19,CYP2C9, and CYP3A; increased area under the curve (ie, total drug exposure overtime) of caffeine, midazolam, warfarin, omeprazole, and digoxin *[29]	No known clinically significant effect	Inhibits MATE1 and MATE2-K (potent effect), and 0CT1 (moderate effect)	Mean half-life=17 h; median time to maximal concentration=1·9 h	Coadministration of a high-fat meal delayed Tmax by 2·5 h and increased area under the curve by 38%, although between-subject variability of the area under the curve and maximum concentration were the same in high-fat intake and fasting groups
Olaparib[30–32]	Is metabolised primarily by CYP3A4	Induces CYP2B6 and inhibits CYP3A †[31]	CYP3A inhibitors increased area under the curve (ie, total drug exposure overtime) in 170% (strong effect) or 121% (moderate effect); CYP3A inducers decreased area under the curve in 87% (strong effect) or 60% (moderate effect)	Inhibits 0ATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2-K	Mean half-life=14·9 h (tablet) or 11·9 hours (capsule); median time to maximal concentration=1·5 h	Coadministration of a high-fat meal delayedTmax by 2·5 h but did not alter the extent of olaparib absorption
Niraparib[24,33,34]	Is metabolised by carboxylesterase-catalysed amide hydrolysis (primarily hepatic metabolism)	Has negligible effect on CYP450 enzymes †[33]	No formal drug interaction studies have been performed with niraparib	No known interaction with the major hepatic or renal transporters	Mean half-life=~36 h; median time to maximal concentration=3 h	Coadministration of a high-fat meal did not affect the pharmacokinetics

*Data from clinical studies.

†Data from in vitro studies only.

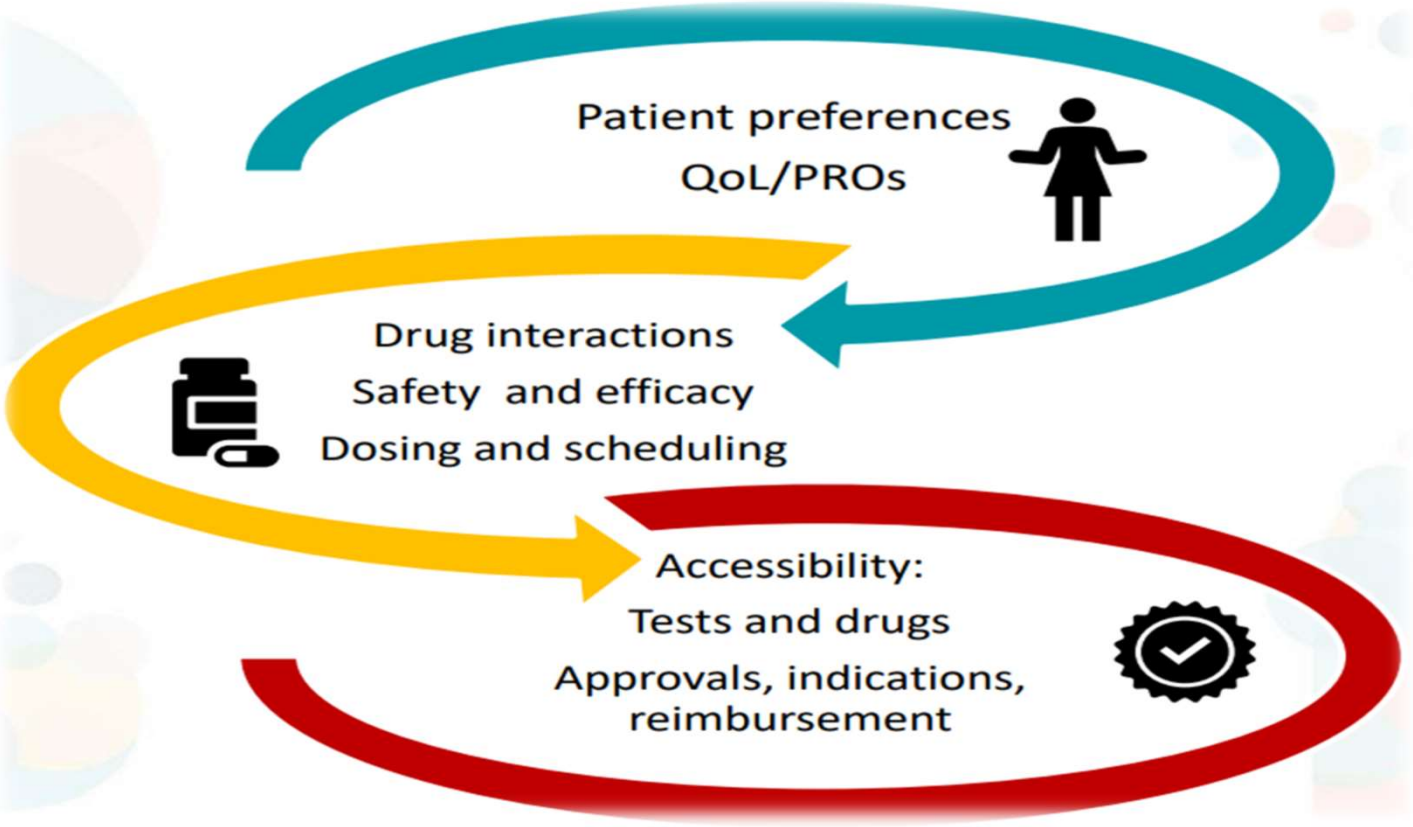
LaFargue CJ. Lancet Oncol 2019

Tratamiento



Nero C. Cancers 2021

Mantenimiento



Conclusiones

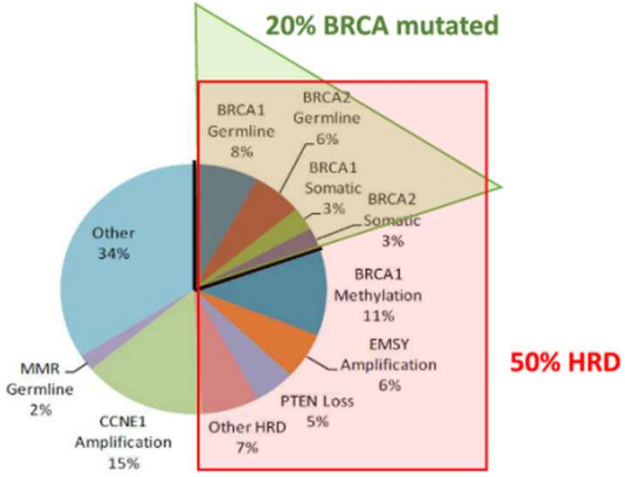
*Take home message

Carcinoma seroso de alto grado de ovario

- Síntomas inespecíficos ⚠️
- Diagnóstico en estadios avanzados.
- Cáncer ginecológico de mayor mortalidad. 🎗️

Terapias dirigidas: iPARP.

- Conocer estado mutacional BRCA1/BRCA2, HRD. ⚠️
- **iPARP 1L:**
  - **BRCA mut**: Remisiones prolongadas …¿curación?
  - **HRD:** Remisiones prolongadas
  - **HRp:** *¿mejor opción* vs antiangiogénicos?
- Líneas sucesivas, también son una opción.
- Toxicidad aceptable y manejable. 👍



CÁNCER DE OVARIO

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