

Treatment Innovations in Ovarian Cancer

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Clínica
Universidad
de Navarra



Cancer
Center



Declaration of Interest

Employment: Clinica Universidad de Navarra

Consultant or Advisory: Alkermes, Amgen, AstraZeneca, Clovis, Genmab, GSK, HederaDx, Immunogen, Kartos, Karyopharm, Illumina, Mersana, MSD, Novartis, Novocure, Oncoinvent, PharmaMar, Roche, SOTIO, SUTRO, Seagen, Takeda, Tubulis

Stock Ownership: NO

Research Funding: GSK, Roche, ISCiii, AECC

Speaker: AstraZeneca, Clovis, GSK, Immunogen, Mersana, MSD, Novocure, PharmaMar, Roche, Seagen/Pfizer, Takeda.

Other: GEICO President. ENGOT President (2018-2020).

PI: PRIMA/ENGOT-Ov26/GOG3012 trial

Epidemiology

1 in 70 woman

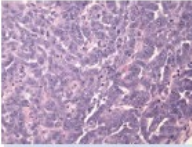
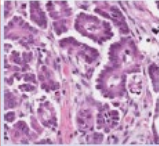
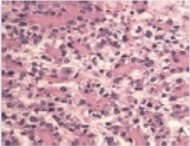
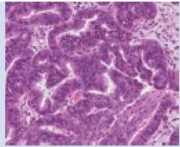
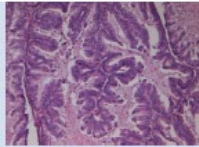
90% after 40 years
30-40% after 65 years

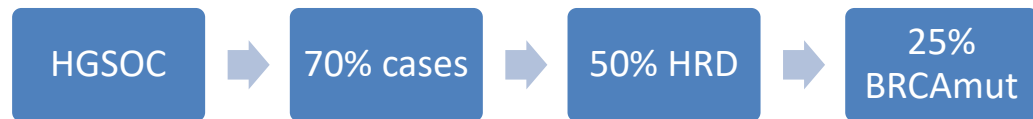
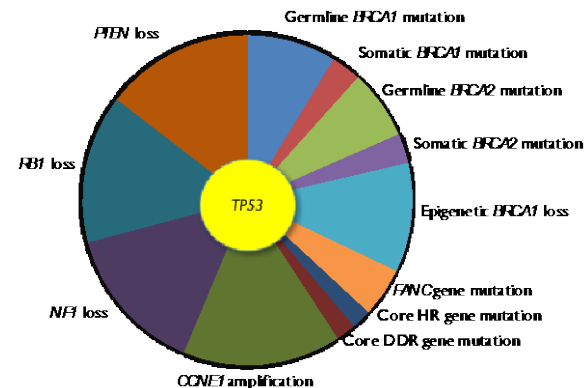
5th cause of death in
woman due to cancer
after lung, breast,
colo-rectal, and
pancreas

1st cause of death due
to gynecological
cancer

80% diagnosed in
advanced stage

Epithelial ovarian cancer is not a single disease: Five subtypes are identified

	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 <i>TP53</i> <i>BRCA1/2</i> HRD 95% TP53mut	CNA low MAPK act. <i>KRAS</i> <i>BRAF</i>	<i>ARID1A</i> PI3K/AKT act. RTK/Ras act. MMR	<i>PI3KCA</i> <i>ARID1A</i> <i>KRAS</i> Wnt/ β -catenin act. <i>PTEN</i>	<i>KRAS</i> <i>HER2</i> amplif.



ESMO Guidelines



SPECIAL ARTICLE

Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

A. González-Martín¹, P. Harter², A. Leary³, D. Lorusso^{4,5}, R. E. Miller^{6,7}, B. Pothuri⁸, I. Ray-Coquard⁹, D. S. P. Tan^{10,11,12,13}, E. Bellet¹⁴, A. Oaknin¹⁵ & J. A. Ledermann¹⁶, on behalf of the ESMO Guidelines Committee*



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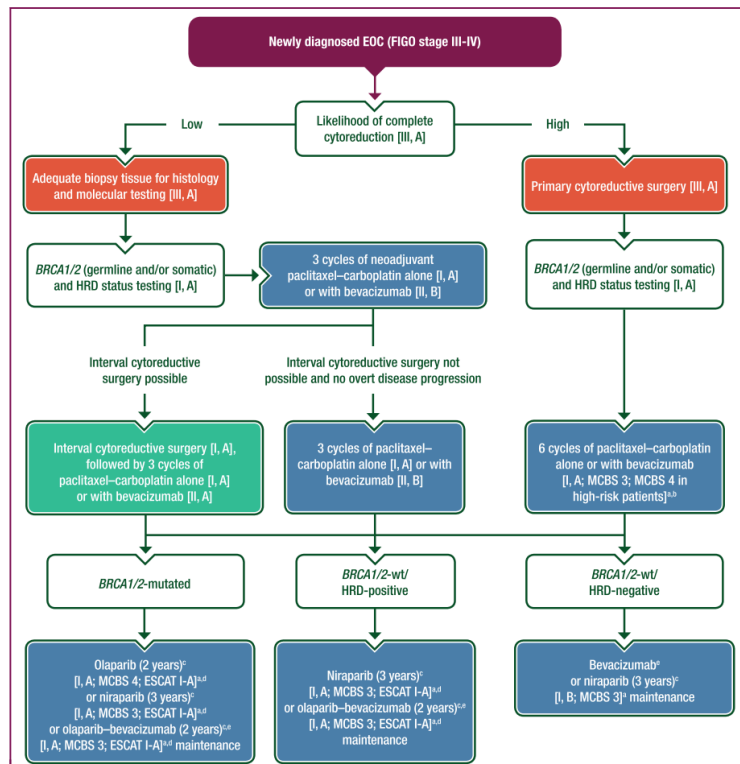


Figure 2. Management of advanced EOC (FIGO stage III-IV).

Surgery

**Chemotherapy
+/- bevacizumab**



**Molecular
Diagnostic**

**PARPi
Maintenance**

ESMO Guidelines

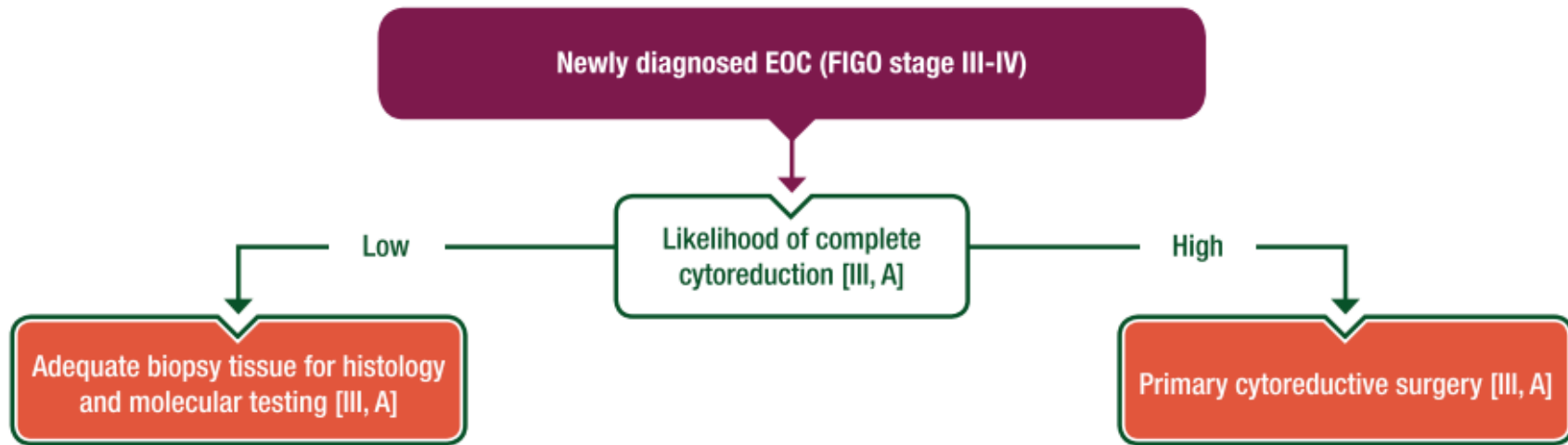
Surgery

Chemotherapy
+/- bevacizumab



Molecular
Diagnostic

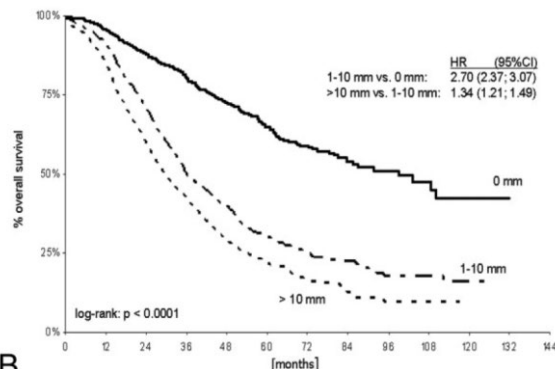
PARPi
Maintenance



Role of Surgery: PCS vs NACT-ICS



**AGO-OVAR OP.7
TRUST
ENGOT-ov33**



B

0 mm	N=1046	996	900	773	596	333	147	70	36	19	8	0	0	E=369
1-10 mm	N= 975	896	669	451	293	157	73	36	18	12	5	0	0	E=463
>10 mm	N=1105	933	650	435	247	116	40	15	6	2	0	0	0	E=629

Du Bois et al. Cancer 2009

**ENGOT model A
Sponsor AGO Study Group**

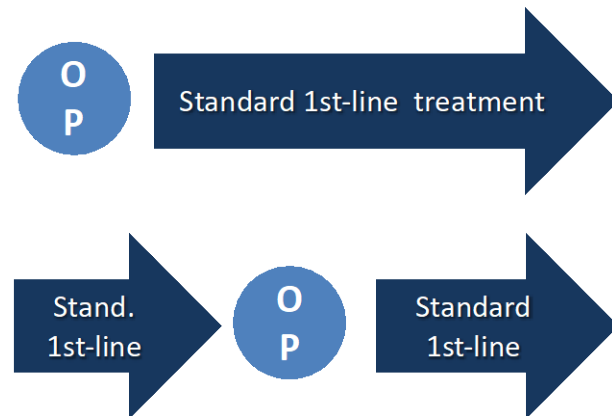
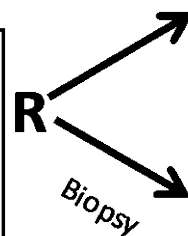
**Pt with ovarian-,
tube- or
peritoneal carcinoma**

FIGO Stage IIIB- IV

No. Pts.: n = 797 randomized

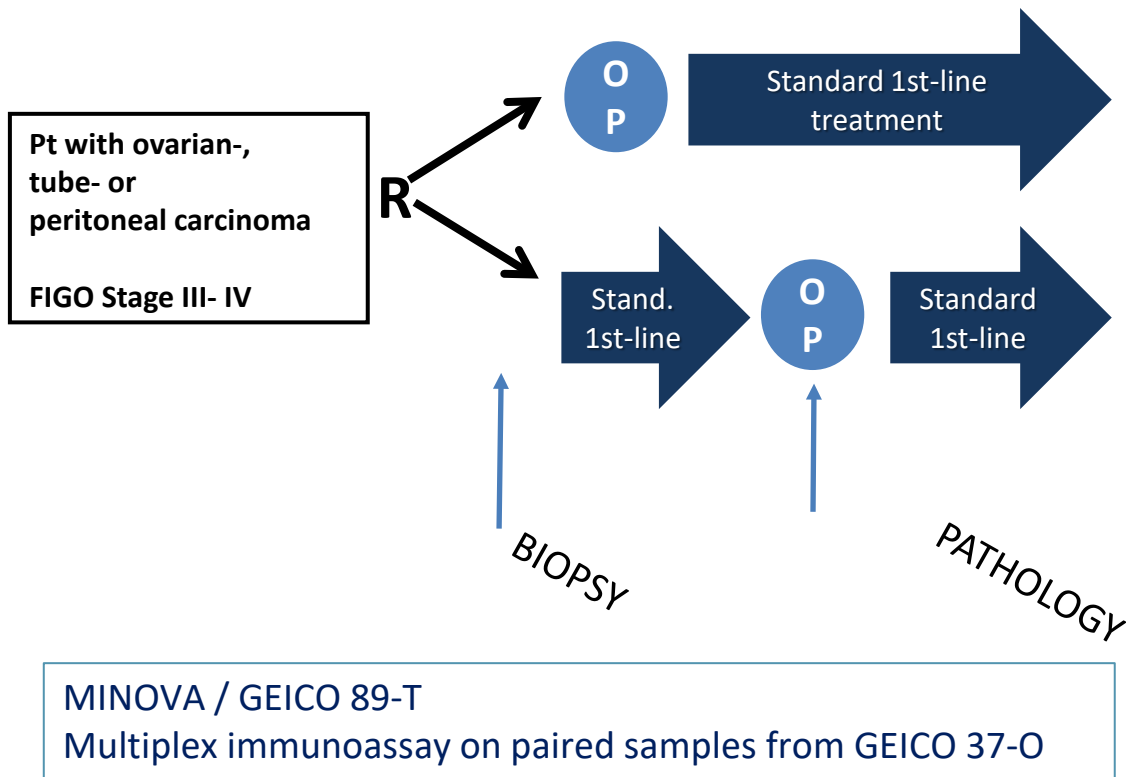
Last Patient In: 07-Jun-2019

Primary OS analysis: ~ 2024

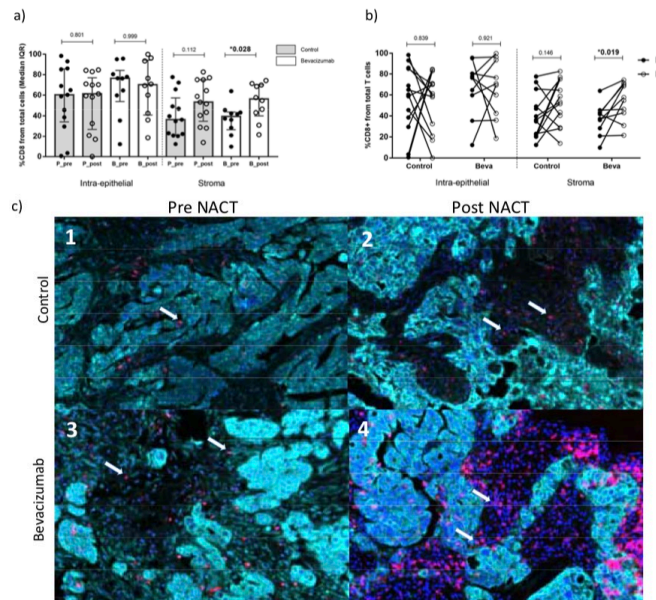


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NACT-IDS is a platform for translational research



Addition of bevacizumab to CP
increased CD8+ T cells,
only in the stroma



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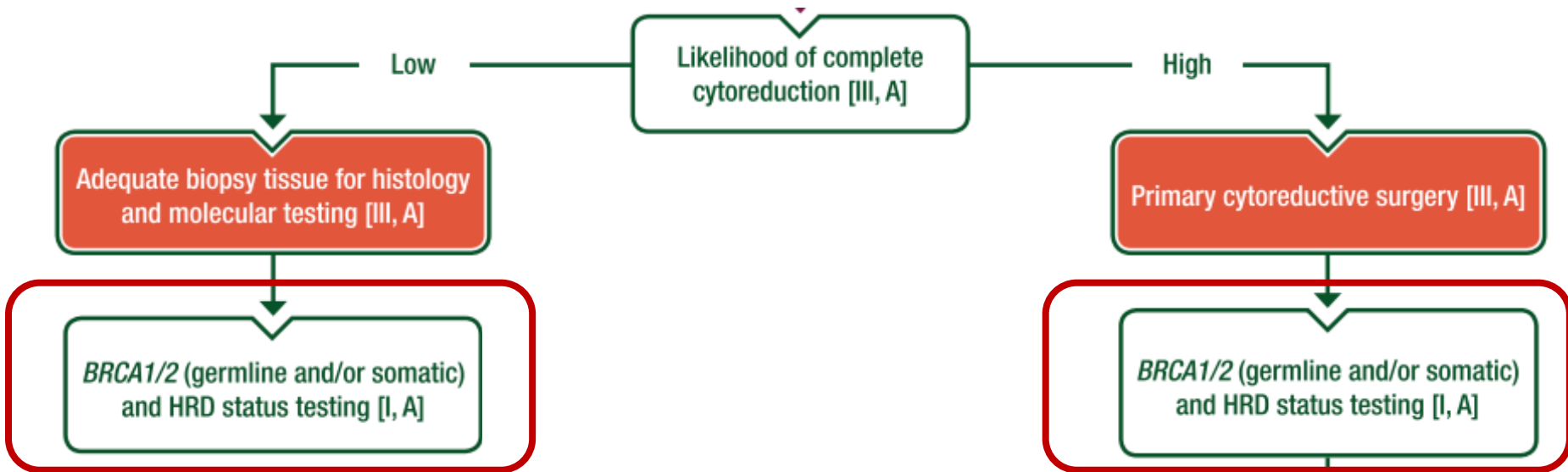
Surgery

Chemotherapy
+/- bevacizumab



Molecular
Diagnostic

PARPi
Maintenance



Biomarkers for Maintenance Selection

HRD Testing

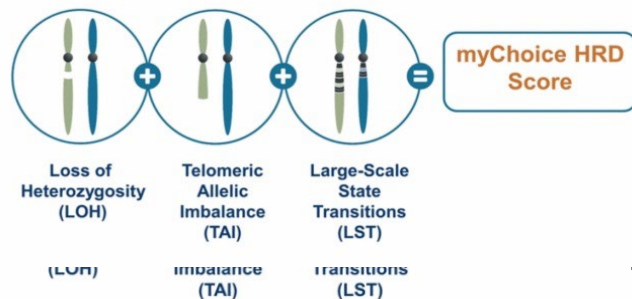
Commercial HRD tests (combinatorial) Myriad myChoice® CDx

Myriad myChoice® CDx (+/- other HRR genes) (gold-standard)

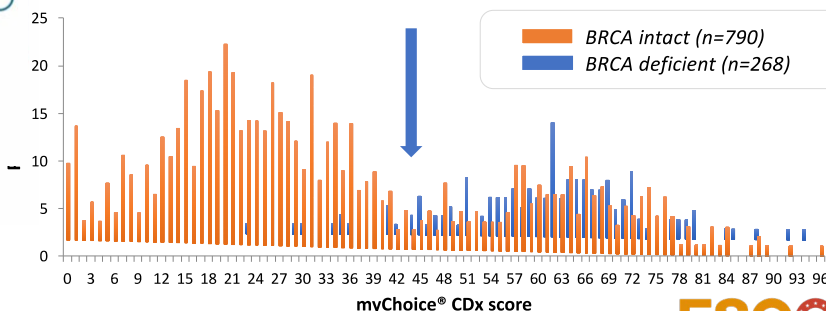
- **BRCA1/2**: pathogenic or probable pathogenic mutation
- **LOH** (15Mb)
- **Telomeric allelic imbalance**
- **Large-scale state transitions** (CNV >10 Mb/3Mb)
- Integration in the Illumina TSO 500 kit

Genomic instability score (GIS) (threshold: 42)

$$LOH + TAI + LST = HRD$$



There is a high-scoring (HRD-positive) and low-scoring (HRD-negative) group represented by the two peaks.



BRCA=breast cancer gene; CDx=companion diagnostic; CNV=copy number variation; GIS=genomic instability score; HRD=homologous recombination deficiency; HRR=homologous recombination repair; LOH=loss of heterozygosity; LST=large-scale state transitions; TAI=telomeric allelic imbalance.

Available at: https://www.dlongwood.com/wp-content/uploads/2021/08/MY_myChoiceCDxPLUS_HRD_OPTIONS_BRO_singPages_EN_06_2021.pdf (last accessed June 2023)



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Stratification Factor
in PRIMA

Pre-planned
exploratory analysis
in PAOLA-1

Biomarkers for Maintenance Selection

HRD Testing: Validation of different platforms with PAOLA-1 samples

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Validation of the Clinical Use of GISCAR, an Academic-developed Genomic Instability Score Predicting Sensitivity to Maintenance Olaparib for Ovarian Cancer

Raphaël Leman^{1,2}, Etienne Muller^{1,2}, Angelina Legros¹, Nicolas Gaudon^{1,2}, Imène Chentil¹, Alexandre Atkinson^{1,2}, Aurèle Tranchant¹, Laurent Castera^{1,2}, Sophie Krieger^{1,2}, Agathe Ricou^{1,2}, Flavie Boulouard^{1,2}, Florence Joly², Romain Boucay⁴, Aurélie Dumont⁴, Noémie Basset^{5,6}, Florence Coulet^{5,6}, Louise-Marie Chevalier^{7,8}, Etienne Rouleau⁹, Katharina Leitner^{10,11}, Antonio González-Martin^{12,13}, Piera Gargiulo^{14,15}, Hans-Joachim Lück^{16,17}, Catherine Genestie¹⁸, the PAOLA-1 investigators, Isabelle Ray-Coquard^{19,20}, Eric Pujade-Lauraine²⁰, and Dominique Vaur^{1,2}

www.nature.com/onc

ARTICLE OPEN

Shallow whole genome sequencing approach to detect Homologous Recombination Deficiency in the PAOLA-1/ENGOT-OV25 phase-III trial

Celine Callens^{1,2}, Manuel Rodriguez^{2,3}, Adrien Briaux¹, Eleonore Frouin⁴, Alexandre Eckhoutte⁵, Eric Pujade-Lauraine², Victor Benoit⁶, Dominica Cernovale⁷, Ivan Biehl⁸, Guillaume Bataillon⁹, Julie Karsan-Tanov⁷, Tristan Berthelot⁷

Original Reports | Biomarkers

Normalized LST Is an Efficient Biomarker for Homologous Recombination Deficiency and Olaparib Response in Ovarian Carcinoma

Yann Christinat, PhD¹, Liza Ho, PhD²; Sophie Clément, PhD²; Catherine Genestie, MD, PhD²; Jalid Sehoul, MD, PhD²; Saverio Cinieri, MD, PhD²; Antonio Gonzalez Martin, MD, PhD²; Ursula Denison, MD²; Keiichi Fujiwara, MD, PhD²; Ignace Vergote, MD, PhD²; Germana Tognon, MD²; Sakari Hietanen, MD, PhD¹; Isabelle Ray-Coquard, MD, PhD¹²; Eric Pujade-Lauraine, MD, PhD¹³; and Thomas A. McKee, MD, PhD¹

DOI: <https://doi.org/10.1200/P0.22.00555>

Cell Reports Medicine

Article

Gilger predicts homologous recombination deficiency and patient response to PARPi treatment from shallow genomic profiles

Christian Pozzorini^{1,20}, Gregoire Andre^{1,20}, Tommaso Coletta^{1,20}, Adrien Buisson², Jonathan Bieler¹, Loïc Ferrer², Rieke Kemper¹, Pierre Santigny^{2,3}, Alexandre Harlé⁴, Davide Vacirca⁴, Massimo Barberis⁵, Pauline Gilson⁴, Cristina Roma⁶, Alexandra Salta⁷, Ewan Smith⁸, Floriane Consales Barras⁹, Lucia Ripol¹, Martin Fritzsche¹⁰, Ana Claudia Marques¹¹, Anjar Alkocli¹², Ray Marin¹³, Nicola Normanno¹⁴, Christoph Grimm¹⁵, Leonhard Müllauer¹⁶, Philipp Harter¹⁷, Sandro Pignata¹⁸, Antonio Gonzalez-Martin^{19,12}, Ursula Denison¹³, Keiichi Fujiwara¹⁴, Ignace Vergote¹⁵, Nicoletta Colombo¹⁶, Adrian Willig¹⁷, Eric Pujade-Lauraine¹⁸, Pierre-Alexandre Just¹⁷, Isabelle Ray-Coquard^{19,20}, and Zhenyu Xu^{21,22}

¹SOPHA GENETICS, La Pléce 12, 1180 Rolle, Switzerland

Oncogene

Check for updates

European Journal of Cancer 188 (2023) 131–139



Original Research

PARP inhibitor predictive value of the Leuven HRD test compared with Myriad MyChoice CDx PLUS HRD on 468 ovarian cancer patients from the PAOLA-1/ENGOT-ov25 trial

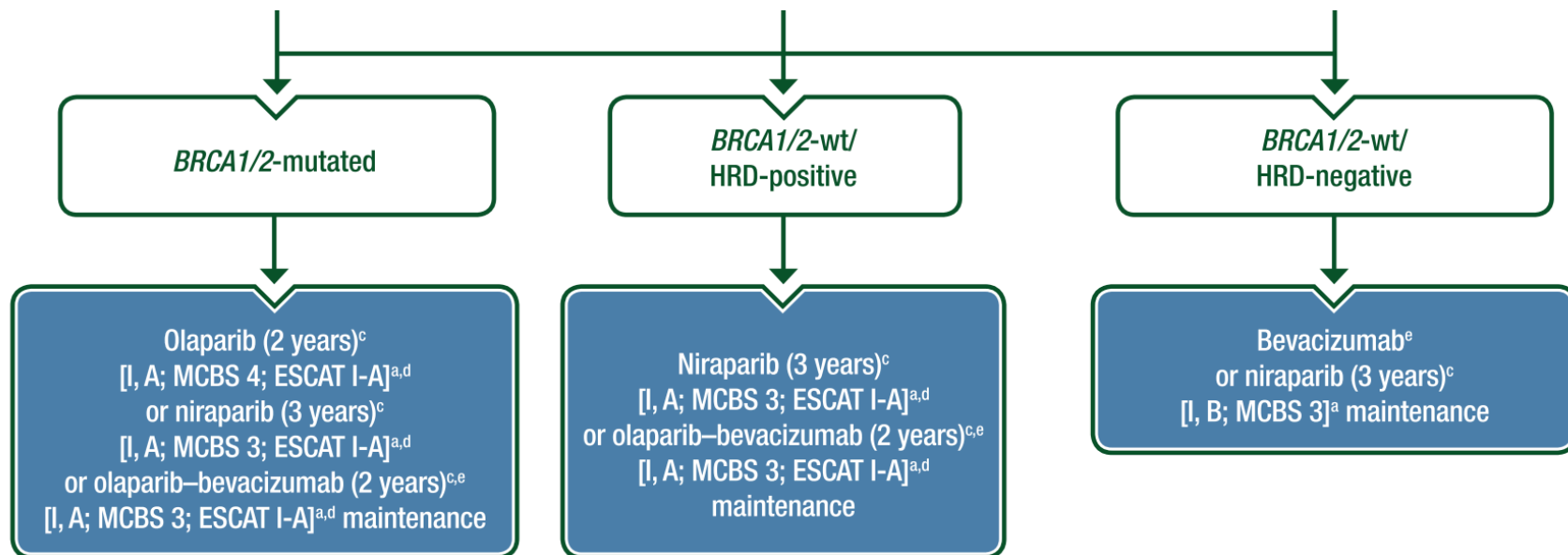
Liselore Loverix^{a,b,1}, Ignace Vergote^{a,1}, Pieter Busschaert^a, Adriaan Vanderstichele^a, Tom Venken^b, Bram Boeckx^b, Philipp Harter^c, Hilde Brems^d, Els Van Nieuwenhuysen^a, Sandro Pignata^e, Thais Baert^a, Antonio Gonzalez-Martin^f, Sileny Han^a, Christian Marth^g, Patrick Neven^a, Nicoletta Colombo^h, Patrick Berteloot^a, Johanna Mäenpääⁱ, Siel Olbrecht^a, Tina Laga^a, Erwin Sablon^b, Isabelle Ray-Coquard^j, Eric Pujade-Lauraine^k, Diether Lambrechts^{b,1}, Toon Van Gorp^{a,*,1}

Maintenance options in first line

SPECIAL ARTICLE

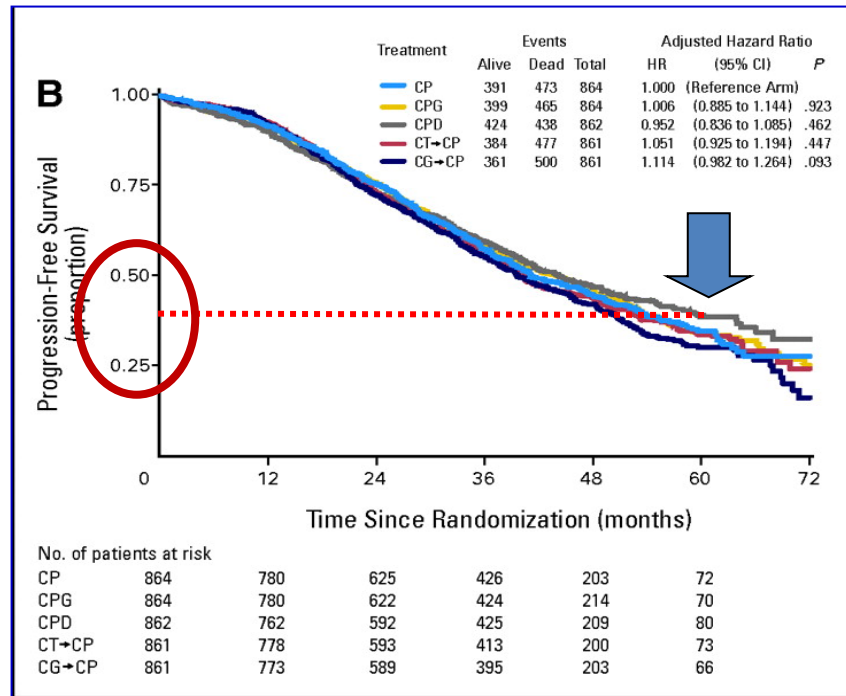
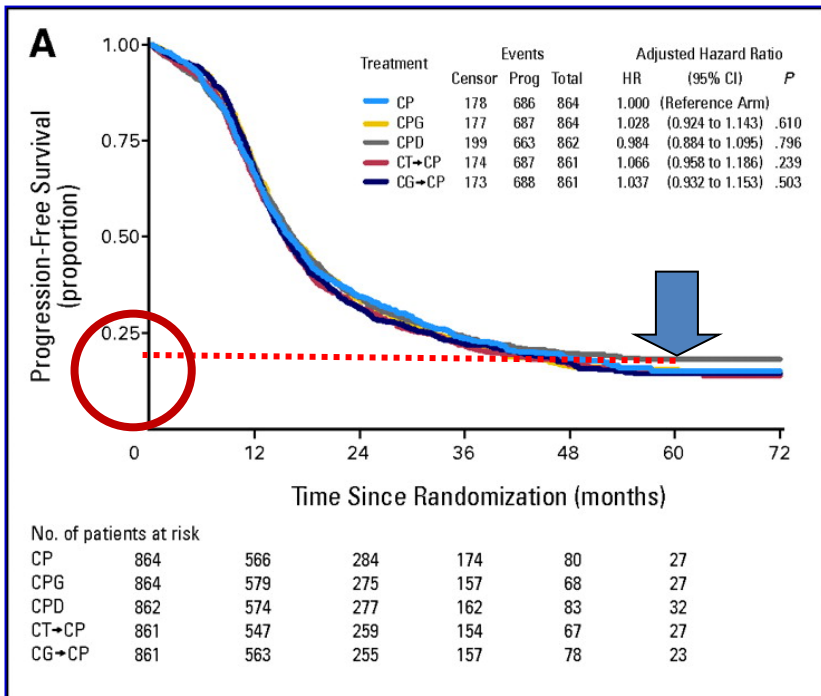
Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

A. González-Martín¹, P. Harter², A. Leary³, D. Lorusso^{4,5}, R. E. Miller^{6,7}, B. Pothuri⁸, I. Ray-Coquard⁹, D. S. P. Tan^{10,11,12,13}, E. Bellet¹⁴, A. Oaknin¹⁵ & J. A. Ledermann¹⁶, on behalf of the ESMO Guidelines Committee^{*}



The outcome of patients with advanced ovarian cancer did not change in the last 2 decades

GOG 182/ICON5: Stage III-IV, PCS, any VRD ($75\% \leq 1 \text{ cm}$)

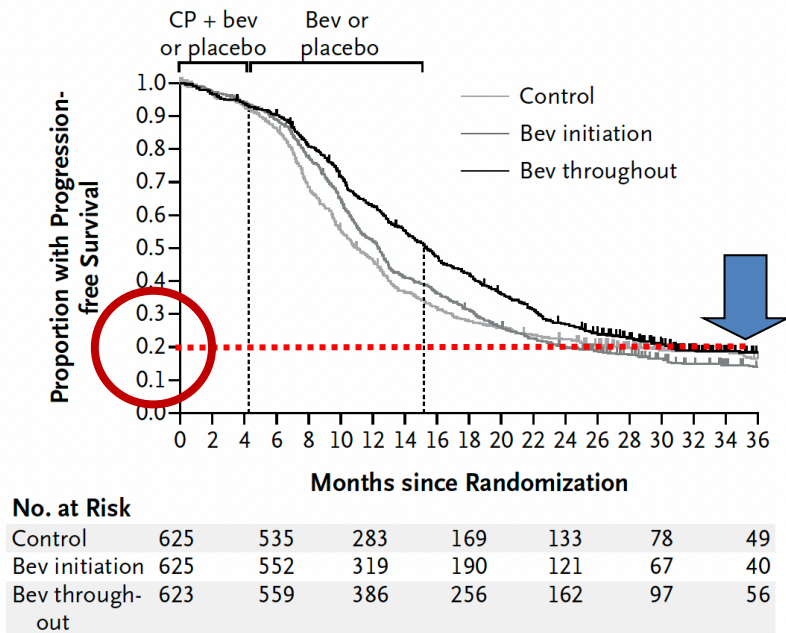


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Even after the introduction of bevacizumab...

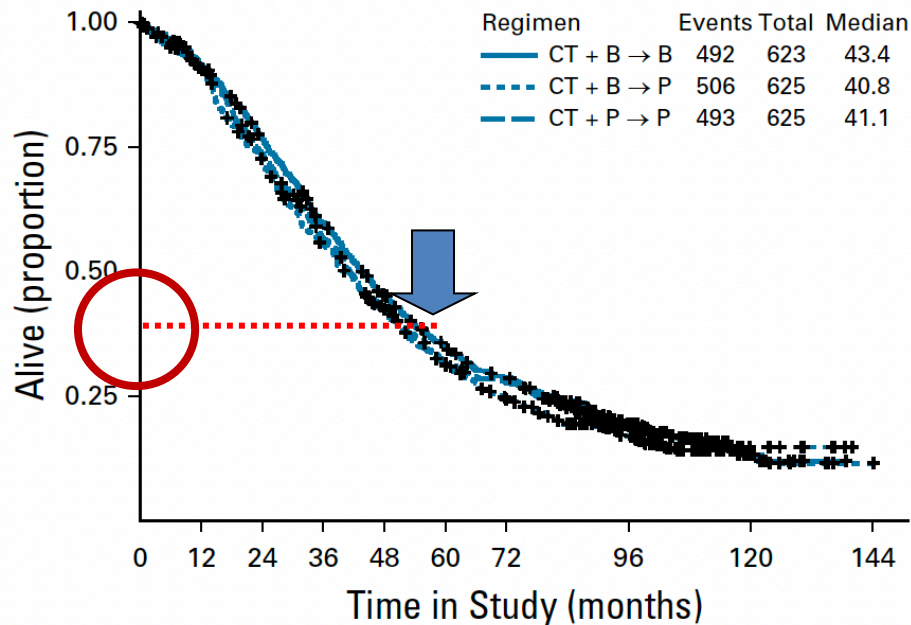
GOG-218: Stage III-IV, PCS, VRD ≥ 1 cm

B Analysis as of August 26, 2011



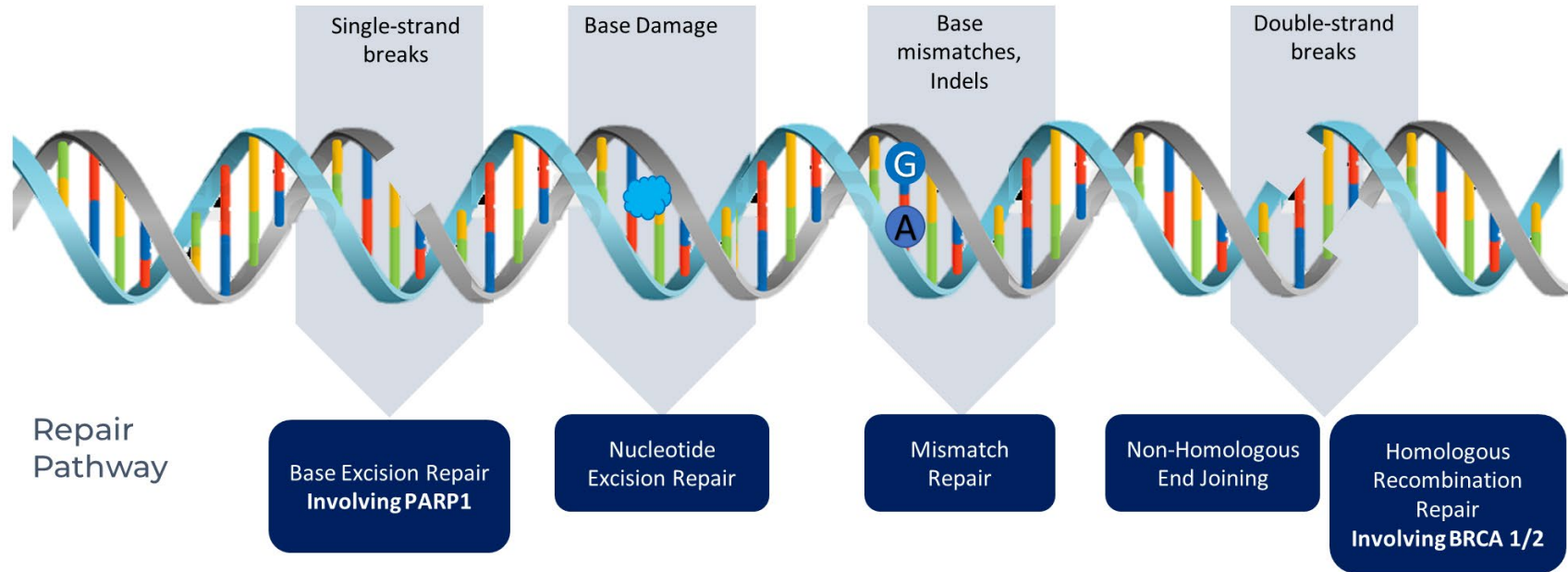
A

Final Protocol-Specified OS

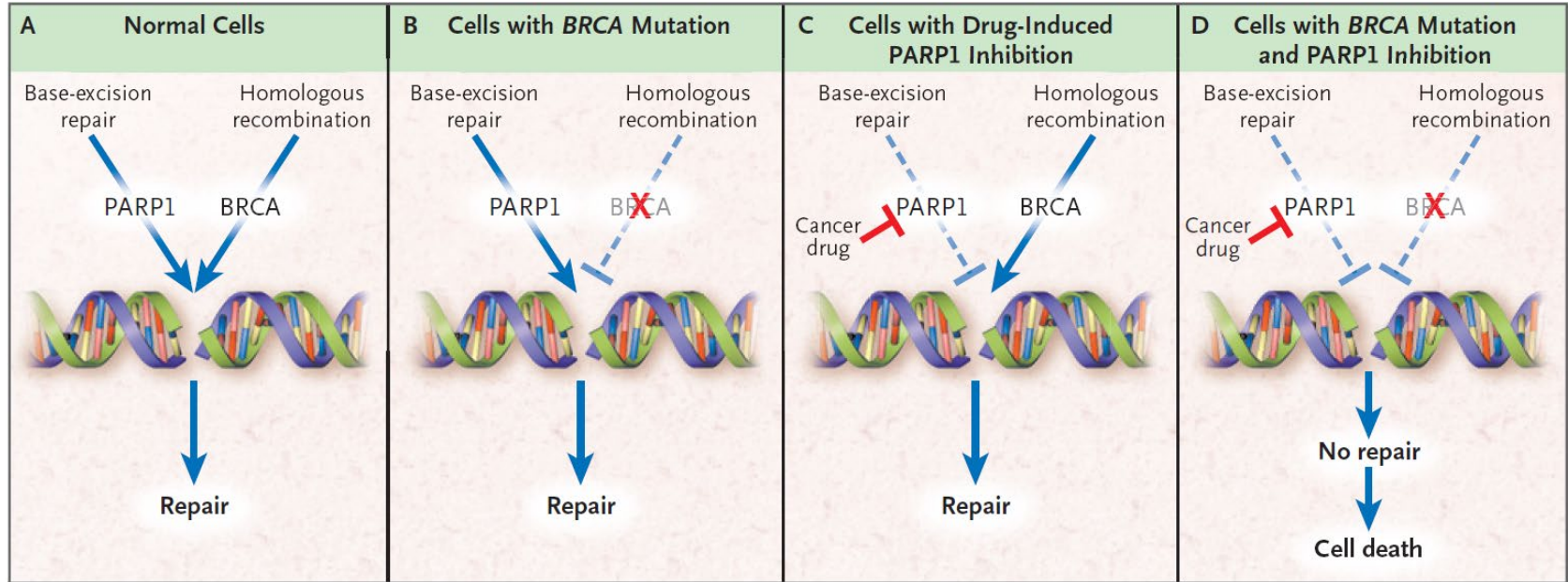


The PARP Inhibition Revolution

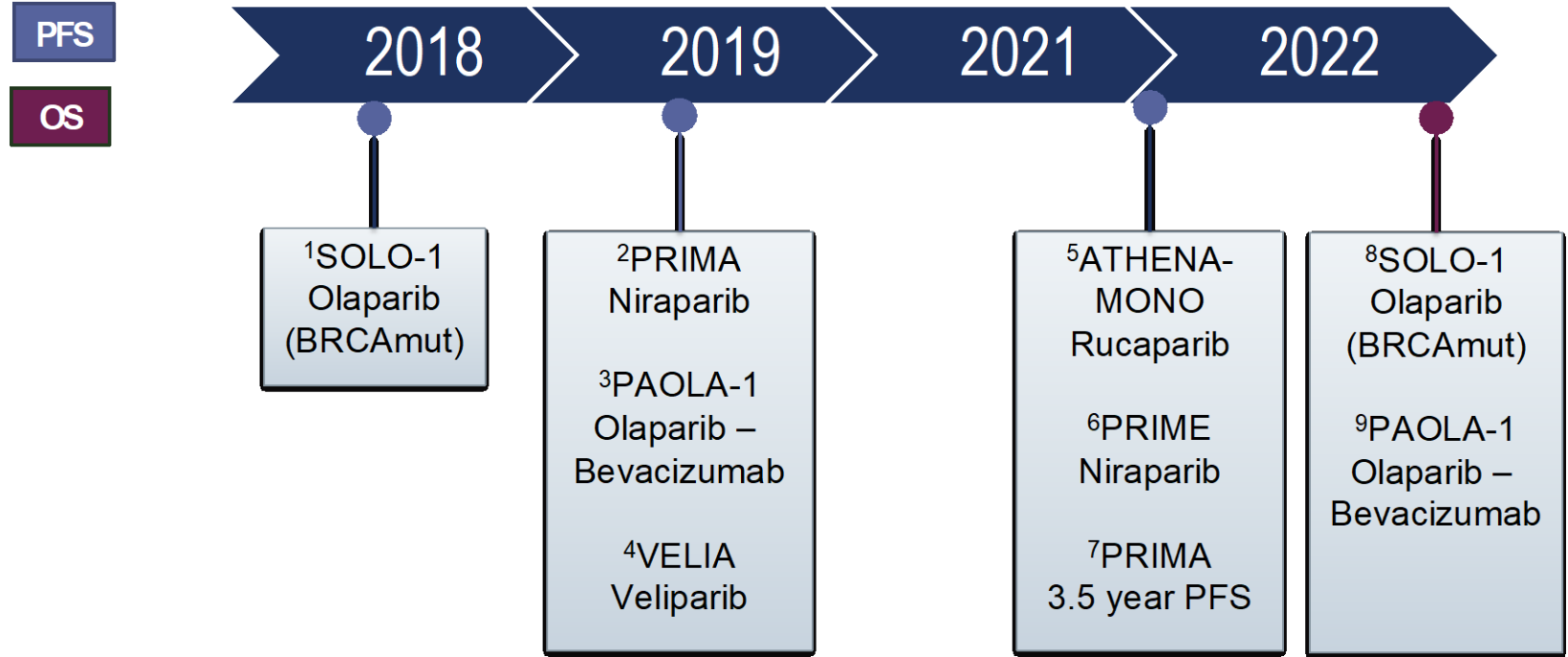
Type of DNA Damage



The PARP Inhibition Revolution

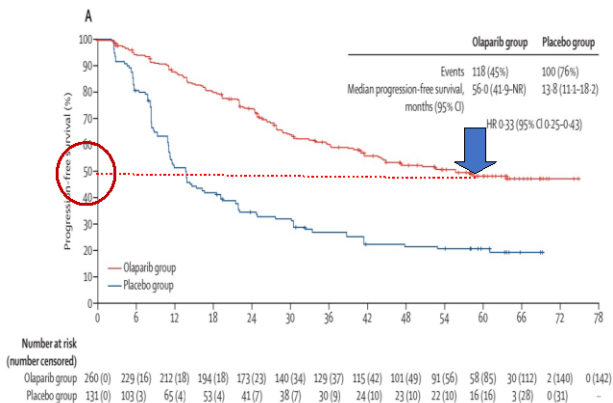


Randomized Trials of PARPi as Maintenance in First Line

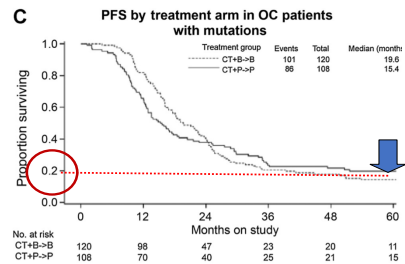
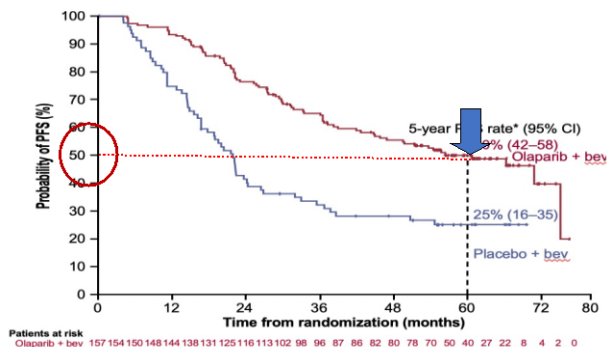


PARPi as maintenance in front line BRCAmut: PFS

SOLO-1

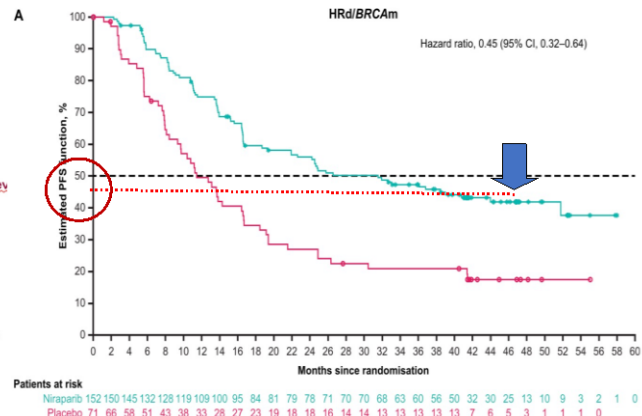


PAOLA-1



Norquist et al. Clin Cancer Res 2017; 24(4); 777-83

PRIMA



Banerjee et al. Lancet Oncol 2021

Gonzalez-Martin et al. ESMO GYN 2023

Gonzalez-Martin et al. Eur J Cancer 2023



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"There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety".

D OS by treatment arm in OC patients with mutations

Proportion surviving

Months on study

0 12 24 36 48 60

1.0
0.8
0.6
0.4
0.2
0.0

CT+B>B
CT+P>P

Treatment group	Events	Total	Median (months)
CT+B>B	62	120	62.2
CT+P>P	54	108	62.0

No. at risk

Months on study	0	12	24	36	48	60
CT+B>B	120	120	107	81	72	40
CT+P>P	108	105	93	88	66	38

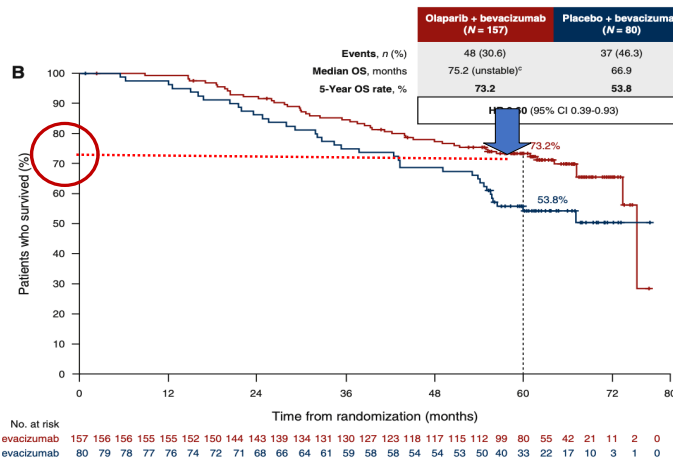
Norquist et al. Clin Cancer Res 2017; 24(4): 777–

83

PAOLA-1 5-year OS



Expected in 2024



Ray-Coquard et al. Ann Oncol 2023

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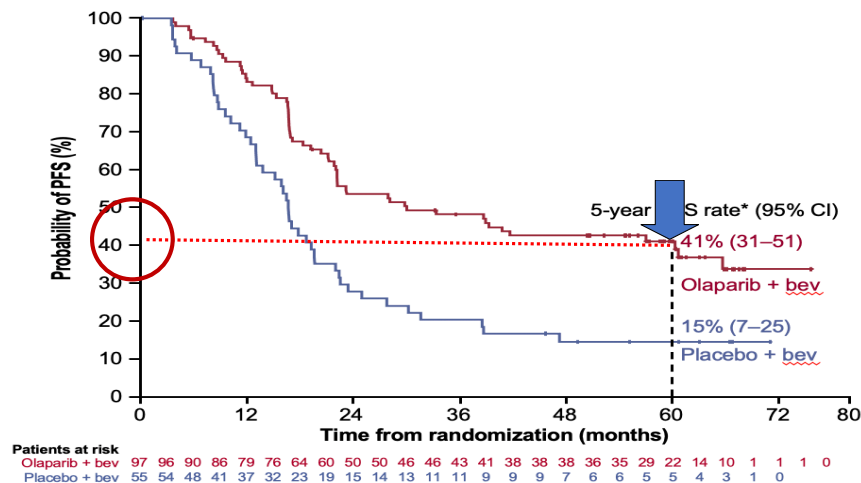
“There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety”.

PARPi as maintenance in front line BRCAwt/HRD-positive: PFS



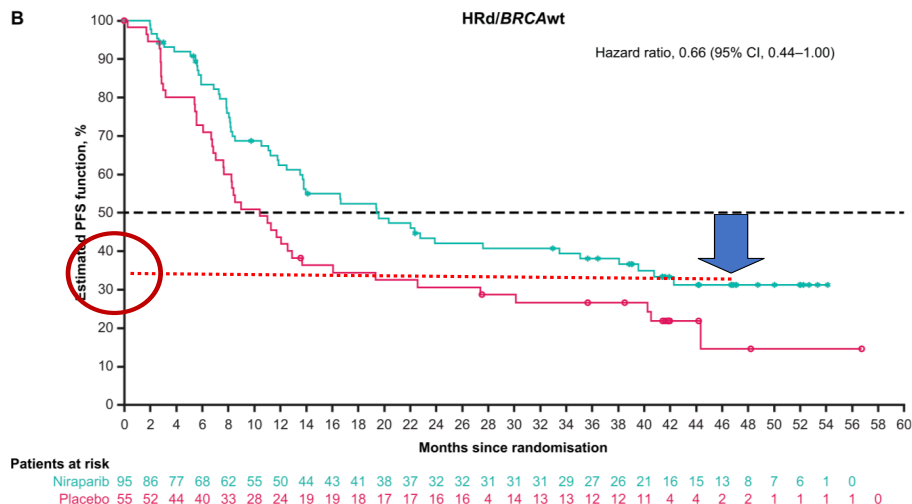
No pre-PARPi data

PAOLA-1



Gonzalez-Martin et al. ESMO GYN 2023

PRIMA



Gonzalez-Martin et al. Eur J Cancer 2023



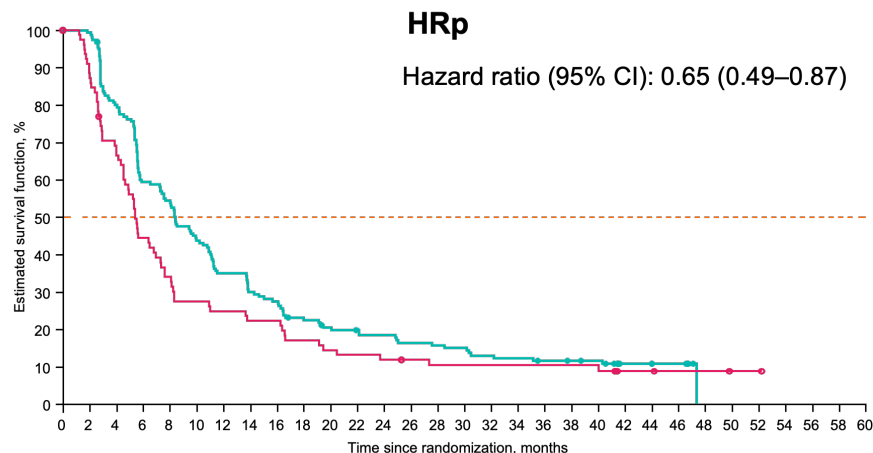
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PARPi as maintenance in front line BRCAwt/HRD-negative: PFS



No pre-PARPi data

PRIMA

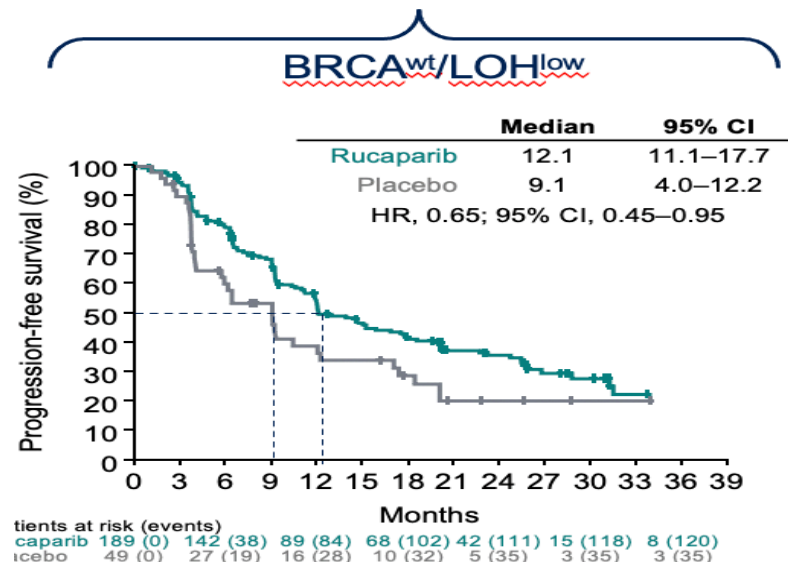


Patients at risk

Rucaparib	169	160	128	95	87	70	56	48	36	31	29	27	24	23	22	19	18	16	15	14	7	7	5	0
Placebo	80	69	53	34	26	21	19	17	13	11	10	9	8	7	7	7	7	7	3	3	2	2	1	0

Gonzalez-Martin et al. Eur J Cancer 2023

ATHENA-MONO



Monk et al. J Clin Oncol 2022.



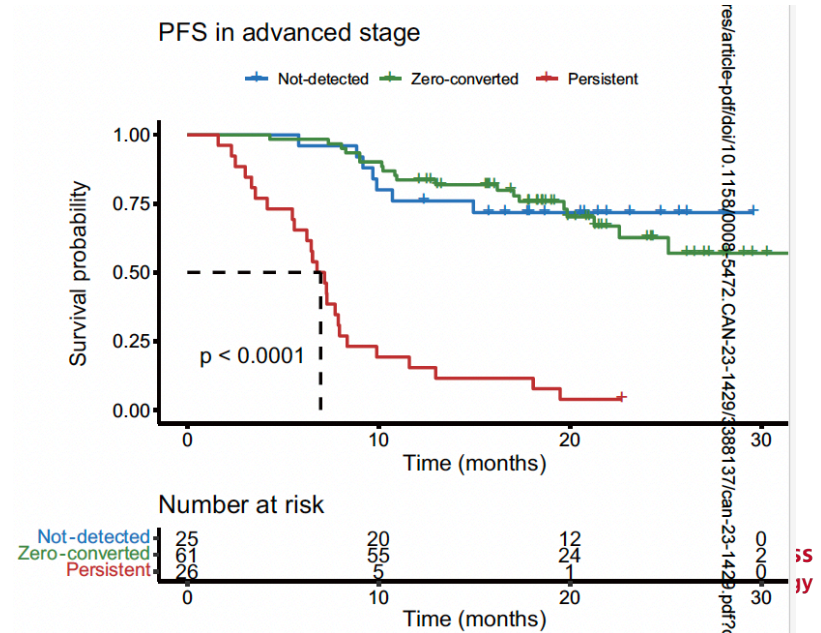
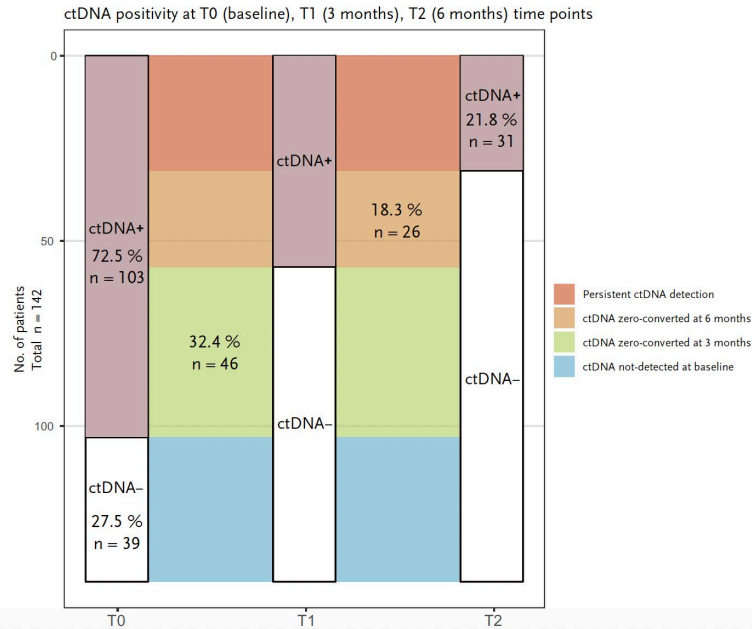
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Future Biomarkers Beyond BRCA/HRD

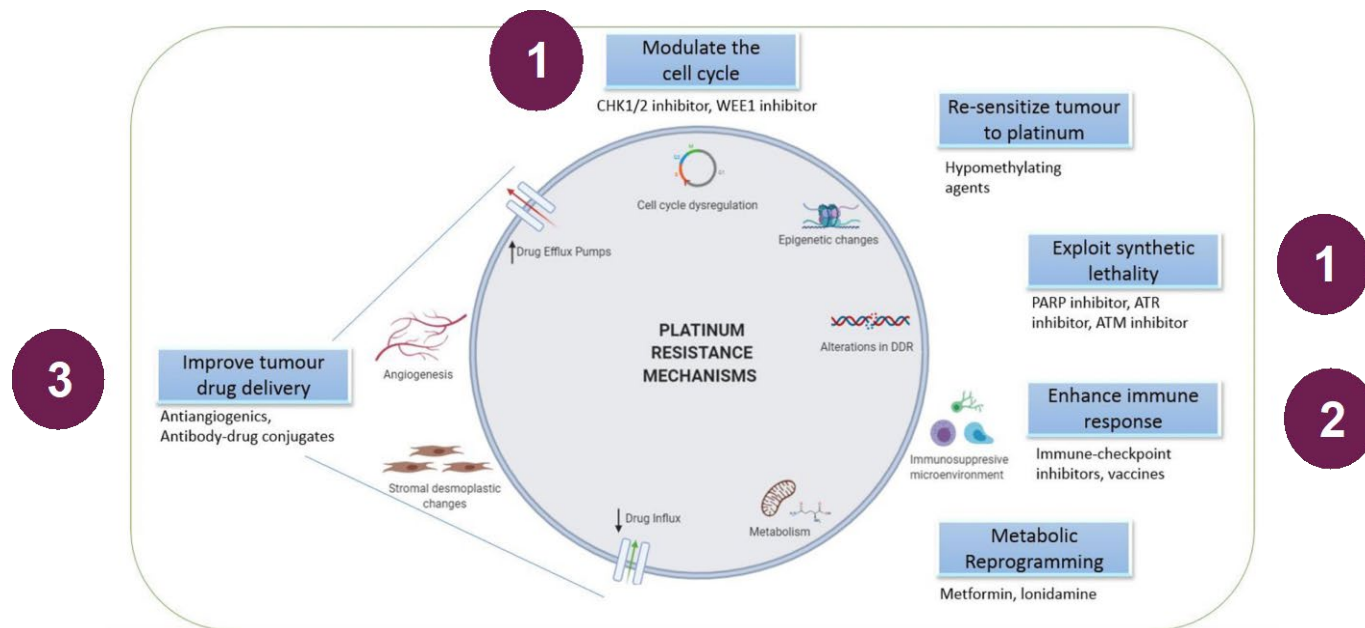
ctDNA

296 patients (EOC & BOT/Benign)
Samples collected at diagnosis or surgery

Disease monitoring with serial ctDNA collected at 3 monthly intervals
NGS: TP53, BRCA1, BRCA2, ARID1A, CCNE1, KRAS, MYC, PIK3CA, PTEN

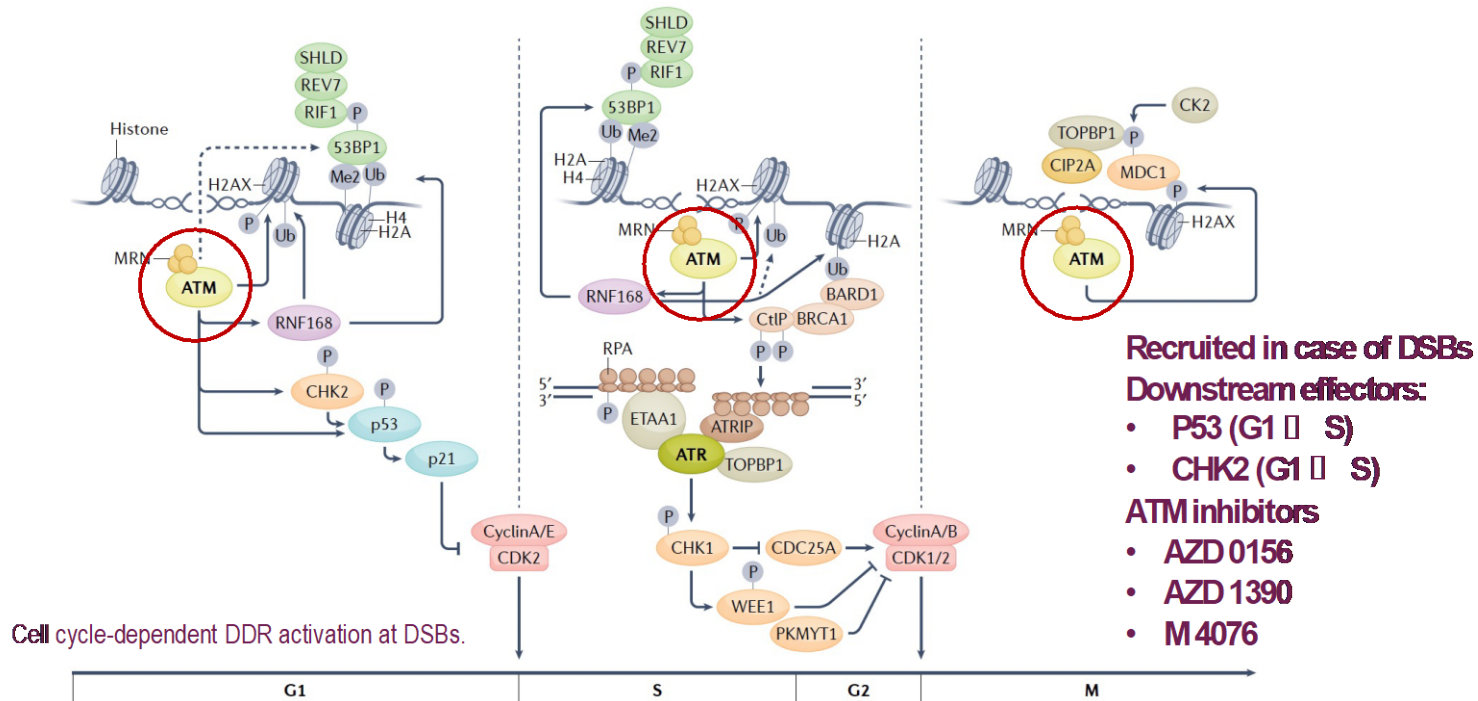


Novel Therapies in Ovarian Cancer



Adapted from McMullen et al. Seminars in Cancer Biology 2021

TARGETING other DDR KINASES: ATM



Cell cycle-dependent DDR activation at DSBs.

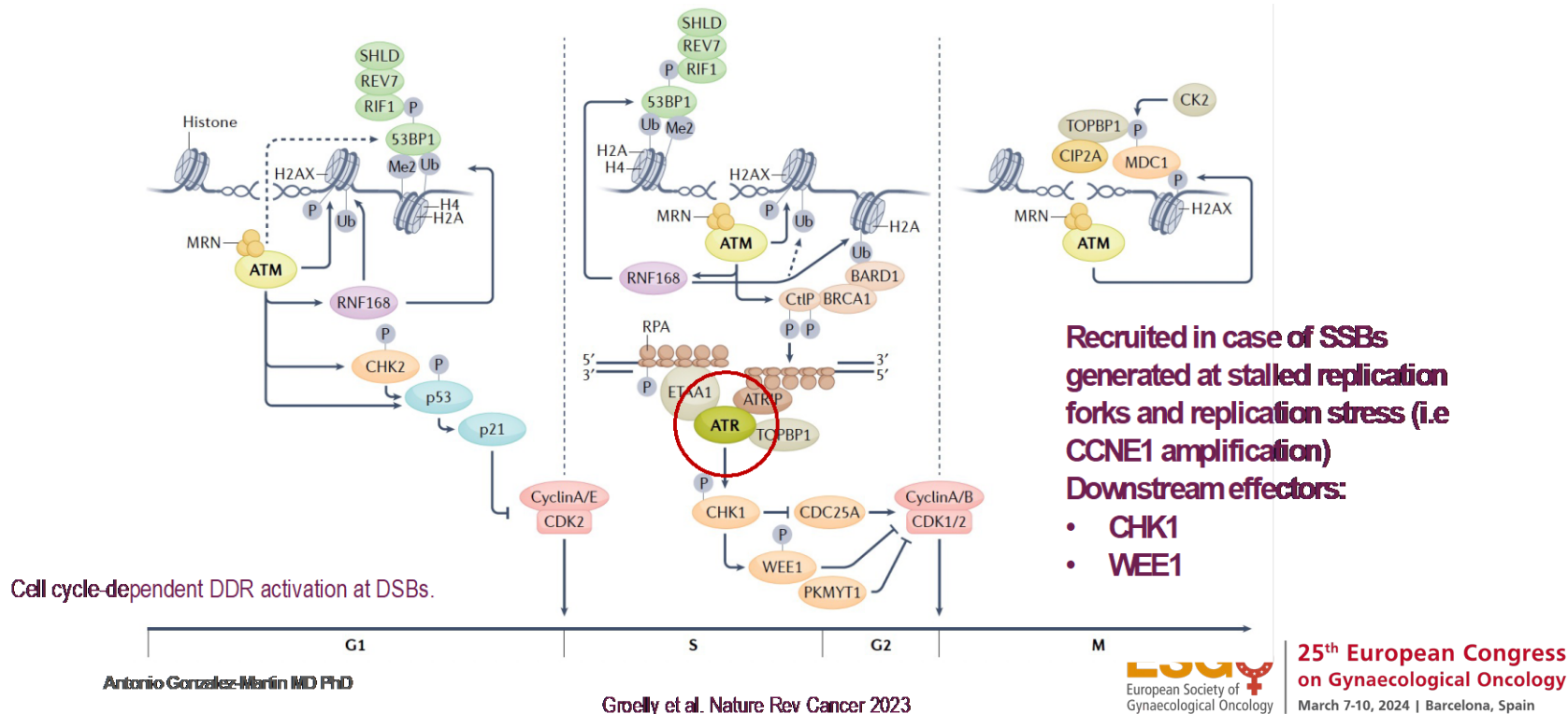
Antonio Gonzalez-Martin MD PhD

Groelly et al. Nature Rev Cancer 2023

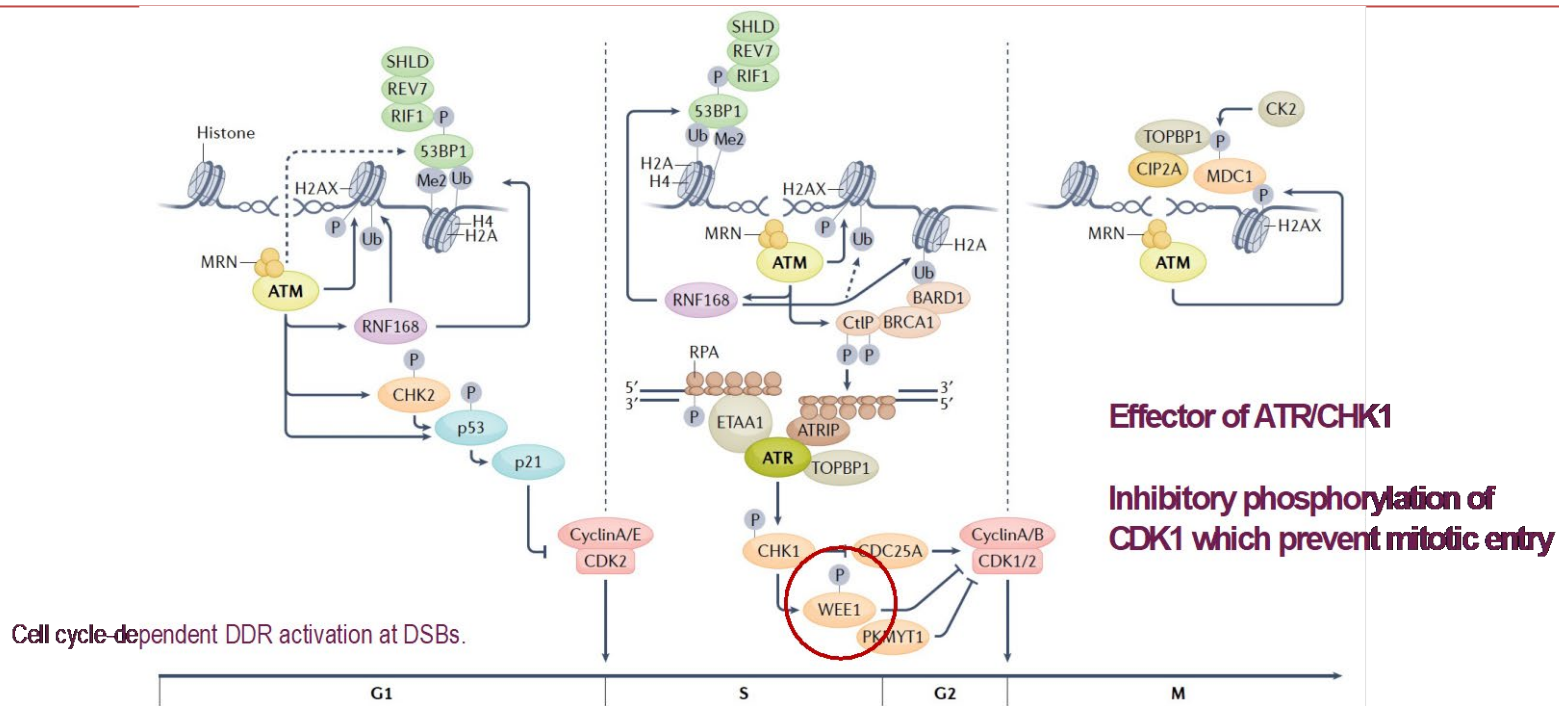
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TARGETING other DDR KINASES: ATR



TARGETING other DDR KINASES: Wee1



Antonio Gonzalez-Martin MD PhD

Groelly et al. Nature Rev Cancer 2023

ESGO
European Society of
Gynaecological Oncology

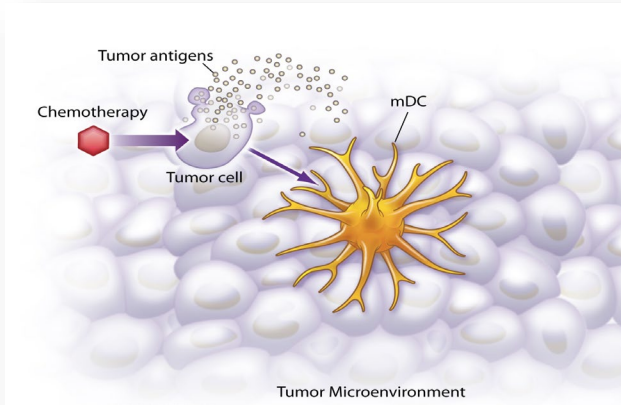
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Check-point inhibitors in ovarian cancer

- KN-100 demonstrated limited ORR with Pembrolizumab in more than 350 patients with recurrent OC regardless of PD-L1 (ORR 8% if CPS > 1; ORR 13.8% if CPS > 10)¹

Combination with Chemo

Immunogenic cell death



Combination with Bevacizumab

Immunosuppressive effect of VEGF

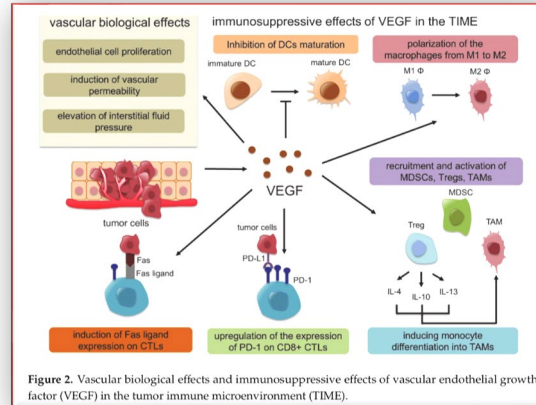
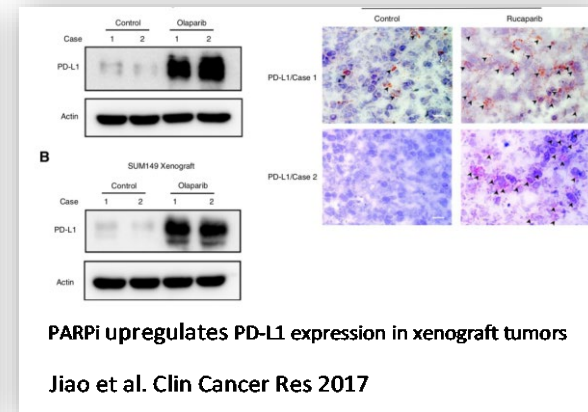


Figure 2. Vascular biological effects and immunosuppressive effects of vascular endothelial growth factor (VEGF) in the tumor immune microenvironment (TIME).

Combination with PARPi

Synergy based on PD-L1 upregulation



PARPi upregulates PD-L1 expression in xenograft tumors

Jiao et al. Clin Cancer Res 2017

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on Gynaecological Oncology
March 7-10, 2024 | Barcelona, Spain

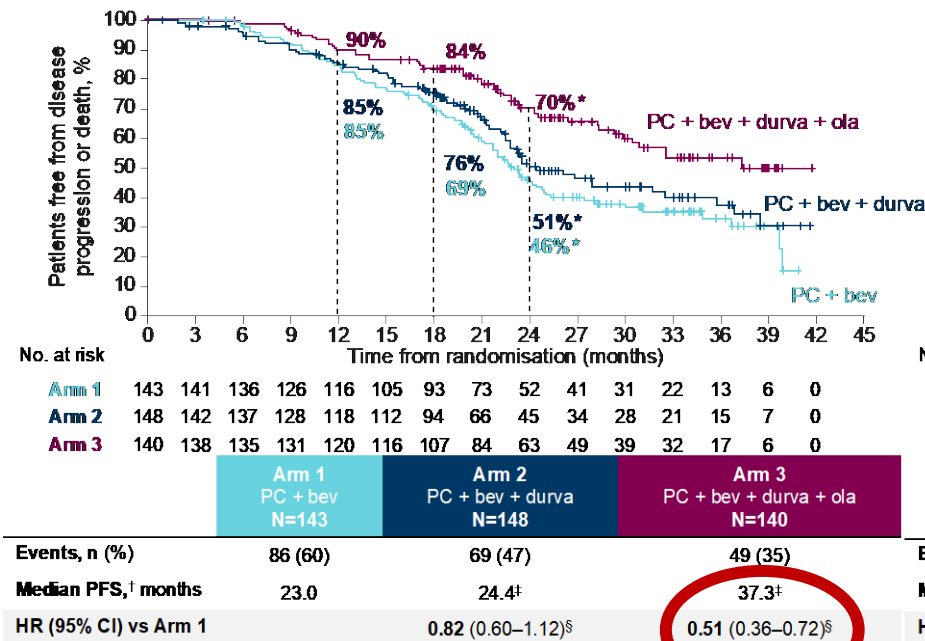
Check-point inhibitors in ovarian cancer

		Chemo ± CPI	Chemo + Bev ± CPI	Chem + PARPi ± CPI	Chemo + Bev ± PARPi ± CPI	Chemo + PARPi ± Bev ± CPI	Chemo ± Bev ± PARPi ± CPI
Presented	1L	JAVELIN ¹ 100	IMAGYN050 ³		DUO-O ENGOT-Ov46		
	PSOC		ATALANTE ⁴	ANITA ⁵ ENGOT-Ov41			
	PROC	JAVELIN ² 200					
Not-Presented	1L			ATHENA Combo		FIRST ENGOT-Ov44	KEYLINK-01 ENGOT-Ov43
	PSOC						
	PROC		AGO OVAR 2.29				

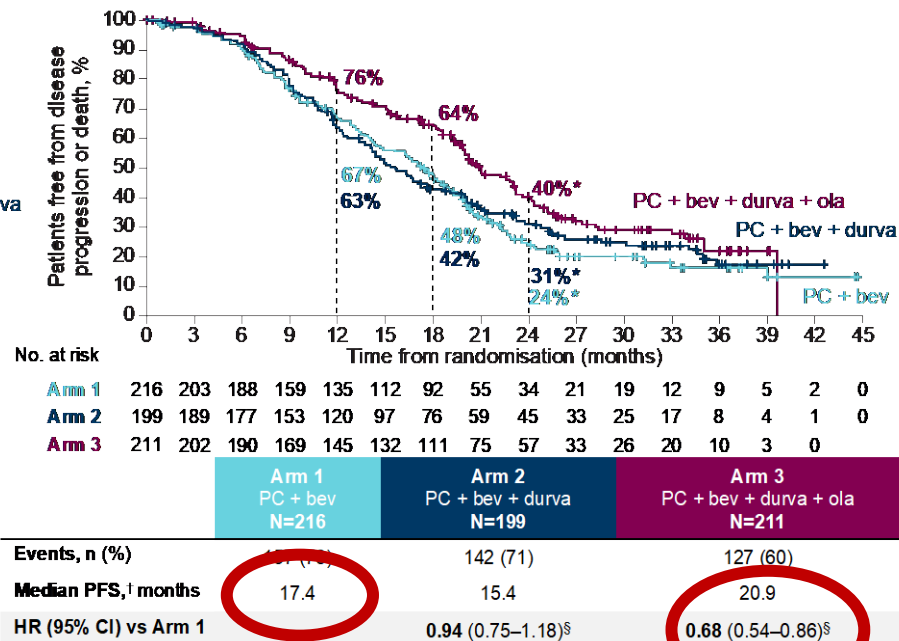
1L: First line; PSOC: Platinum-sensitive ovarian cancer; PROC: Platinum-resistant ovarian cancer

DUO-O / ENGOT-ov46 / GOG-3025: Exploratory Endpoint

Non-tBRCAm HRD positive



HRD negative



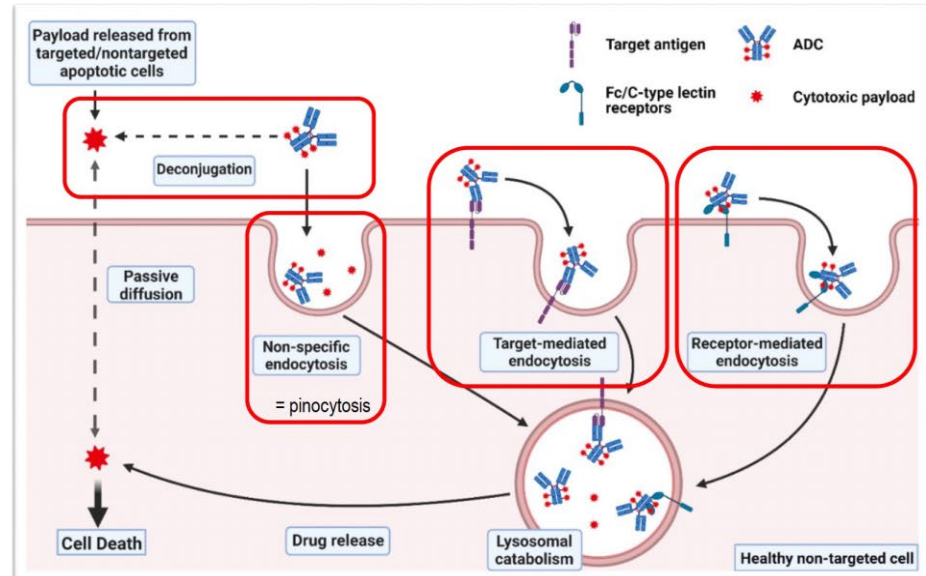
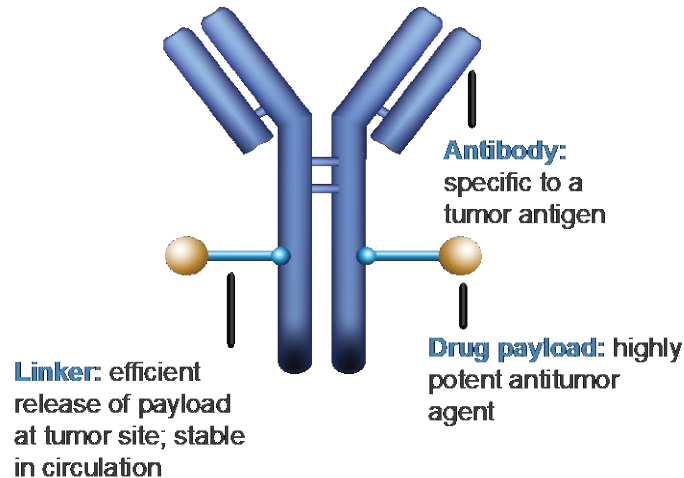
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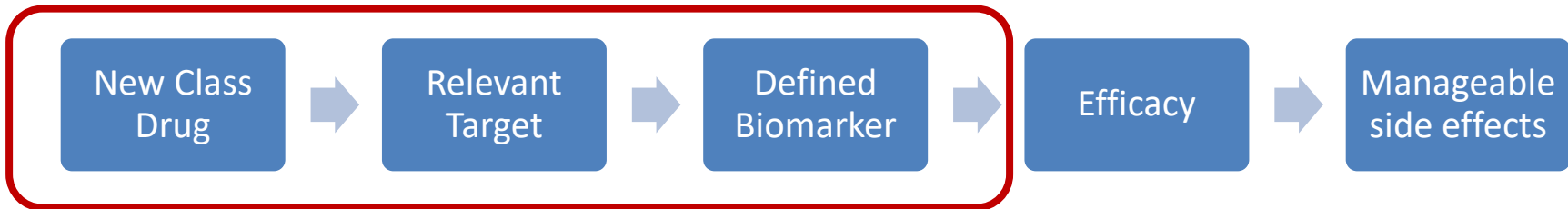
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Anti-body Drug Conjugate

ADCs are designed to ideally enhance antitumor activity and minimize off-target side effects by selectively delivering a high drug payload to tumor cells



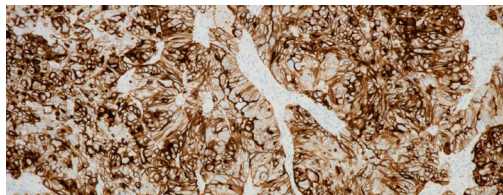
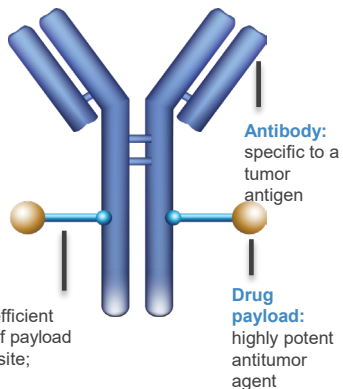
What makes mirvetuximab a practice-changing drug and a milestone in OC?



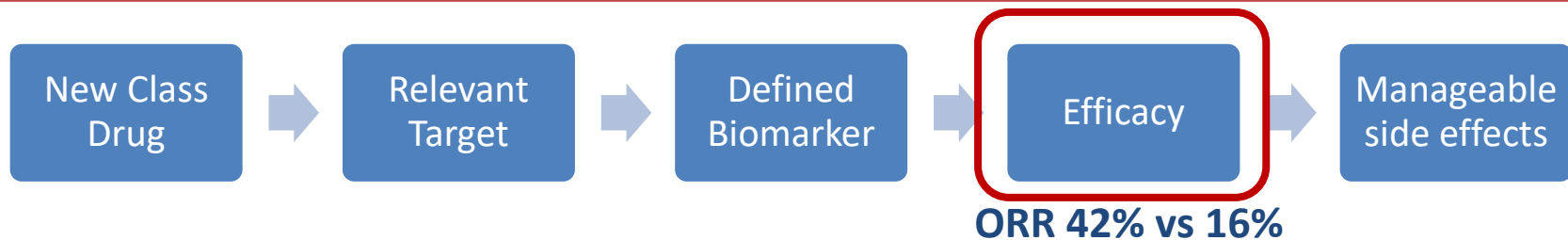
ADC

Folate Receptor- α
(60-100%)

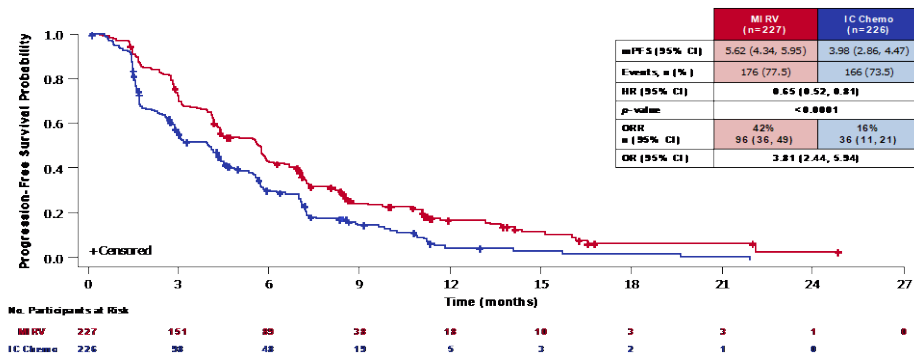
FR α high is defined as > 75% of tumor cells staining with 2+ or 3+ intensity by VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (~ 35% of HGSOC)



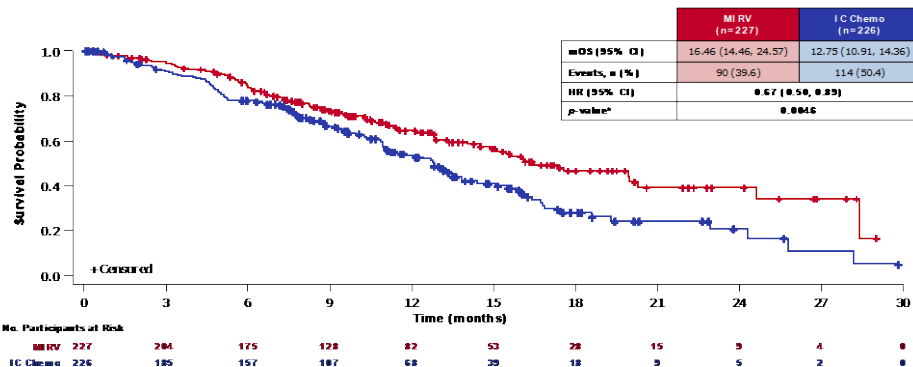
What makes mirvetuximab a practice-changing drug and a milestone in OC?



Progression-Free Survival and Objective Response Rate by Investigator

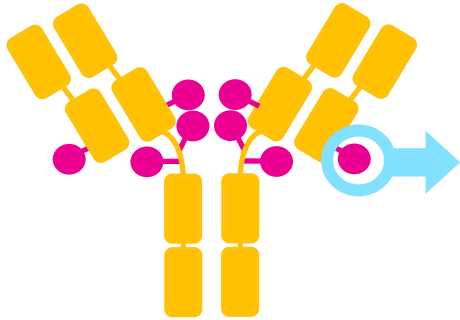


Key Secondary Endpoint: Overall Survival

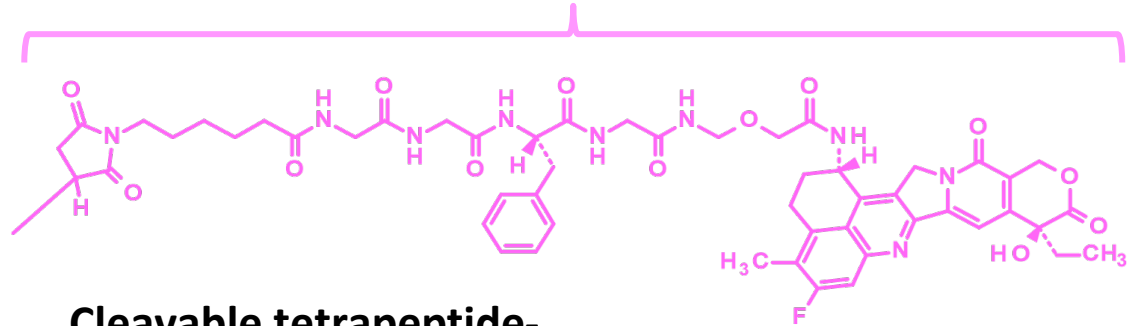


Trastuzumab Deruxtecan

Human anti-HER2
IgG1 mAb



Deruxtecan

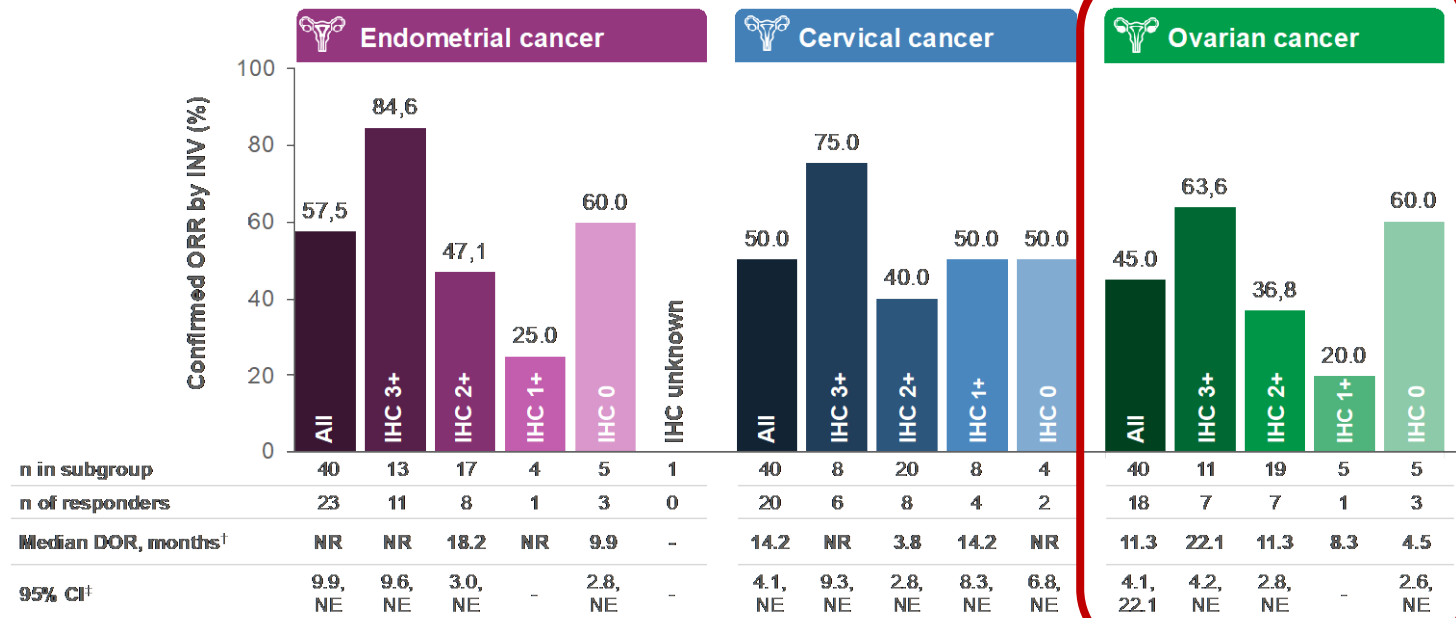


Cleavable tetrapeptide-
based linker

Topoisomerase I
inhibitor payload
(DXd)

DESTINY-Pantumor-02

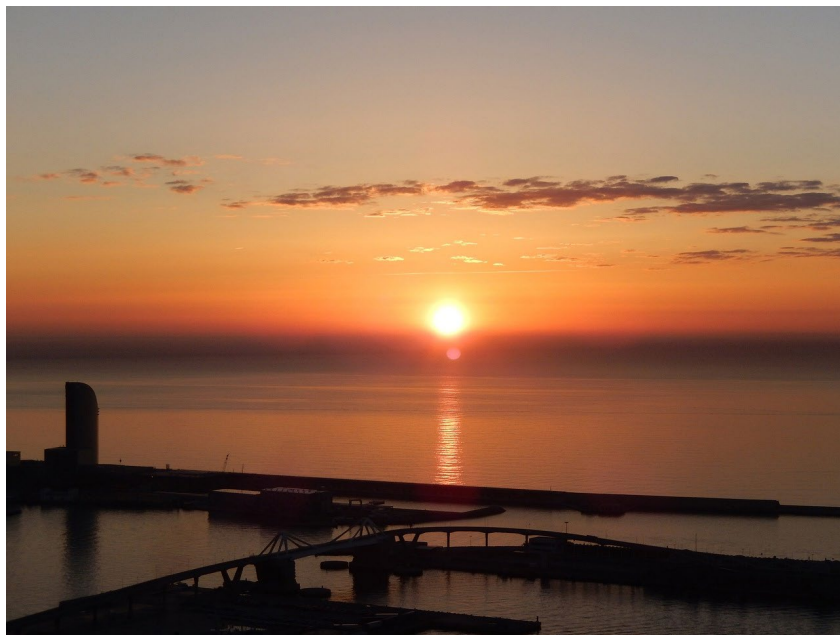
ORR and DOR (INV)*



HER2 status by central testing.

*Similar ORR and DOR results were reported by retrospective independent central review; [†]Median DOR reported for patients with a confirmed an objective response only; [‡]95% CI not shown where n < 4 responses. CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; NE, not evaluable; NR, not reached; ORR, objective response rate.

Congress
al Oncology
elona, Spain



PARP inhibitors have already
changed the natural history of
advanced ovarian cancer

New promising drugs are in the
horizon for continuing the
change

Thank you

