113年度台灣婦產科醫學會年會

卵巢癌的治療新趨勢與展望

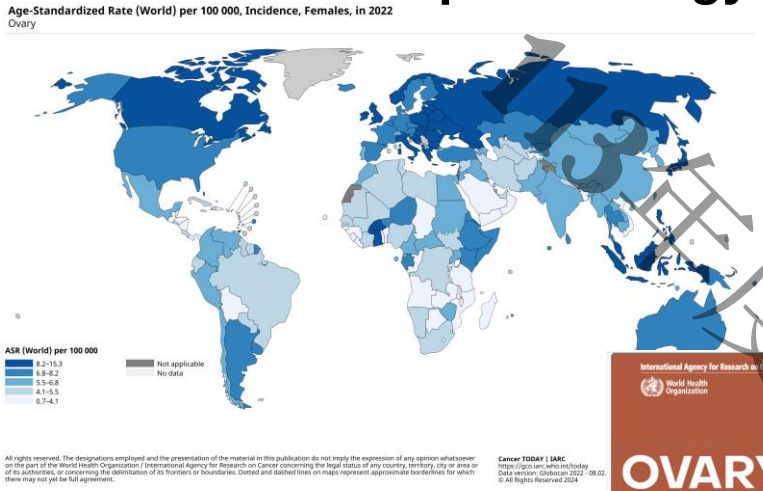
臺大醫院婦產部 江盈澄

台大醫院 NTUH

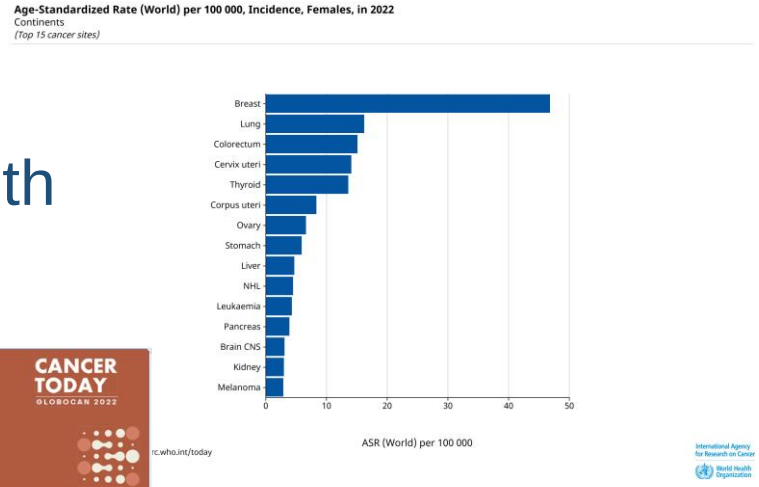
正直誠信．創新卓越．團隊合作．健康尊嚴

Introduction of Epithelial Ovarian Cancer

Epidemiology of Ovarian Cancer-WHO 2022



7th



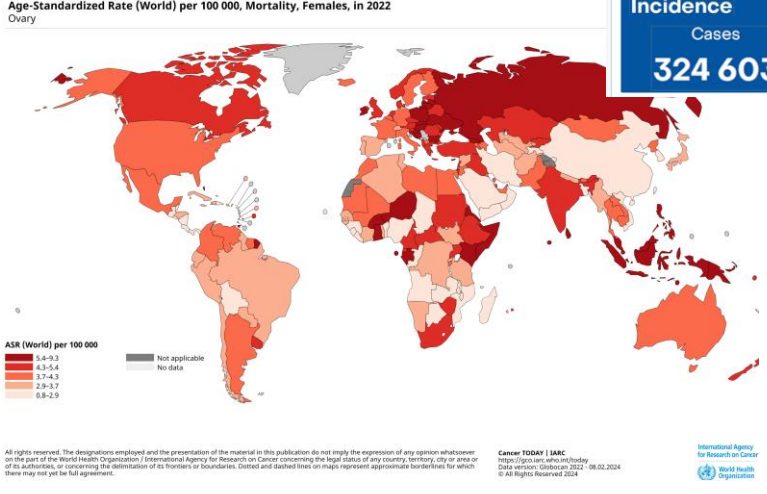
International Agency for Research on Cancer
World Health Organization

GLOBAL CANCER OBSERVATORY

CANCER TODAY
GLOBOCAN 2022

OVARY

Incidence		Mortality	
Cases	ASR (World)	Deaths	ASR (World)
324 603	6.7	206 956	4.0



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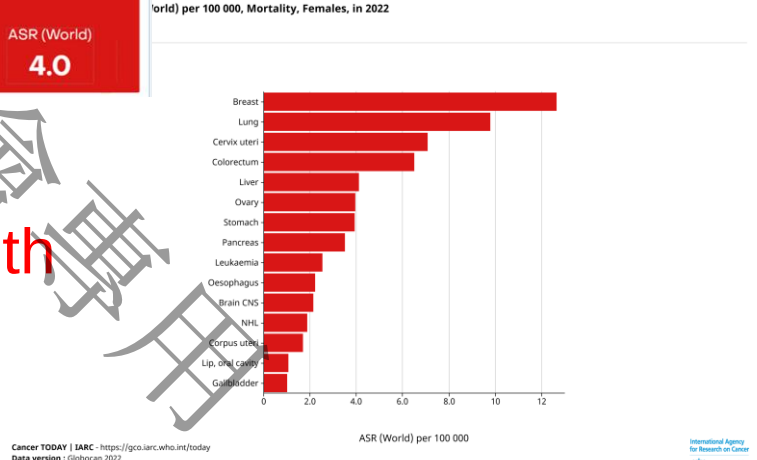
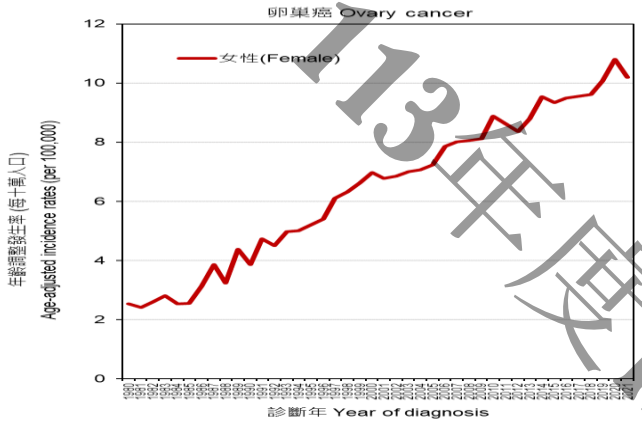


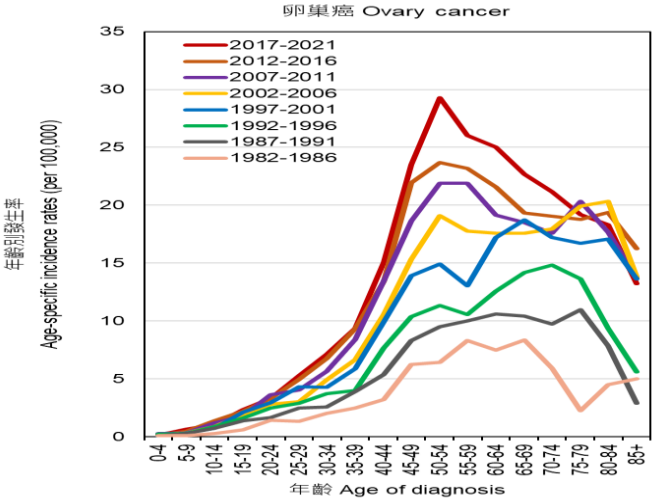
Epidemiology of Ovarian Cancer-Taiwan 2021

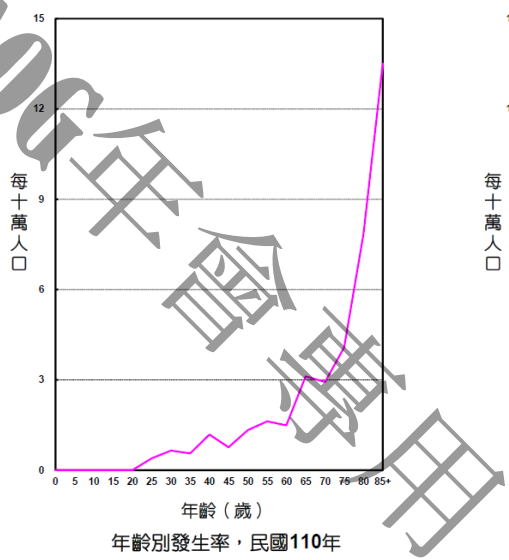


項　目	發生個案 女性
個案數(人)	179
年齡中位數	68
粗率(每10萬人口)	1.52
年齡標準化率[2](每10萬人口)	0.71
年齡標準化率[3](每10萬人口)	0.82

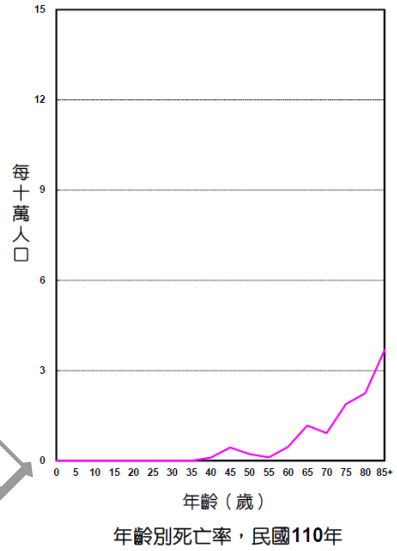
項　目	死亡個案 女性
個案數(人)	47
年齡中位數	72
粗率(每10萬人口)	0.40
年齡標準化率[2](每10萬人口)	0.17
年齡標準化率[3](每10萬人口)	0.19

註：1. 自 96 年癌症登記報告起，惡性淋巴瘤從各部位獨立出來計算發生率，並納入排名。
2. 3.年齡標準化率 [2] 係使用 1976 年世界標準人口為標準人口，年齡標準化率 [3] 係使用 2000 年世界標準人口為標準人口。





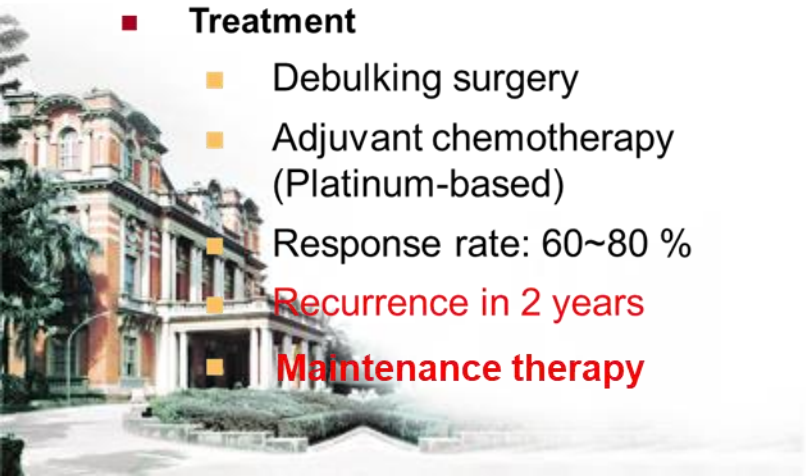
年齡別發生率，民國110年

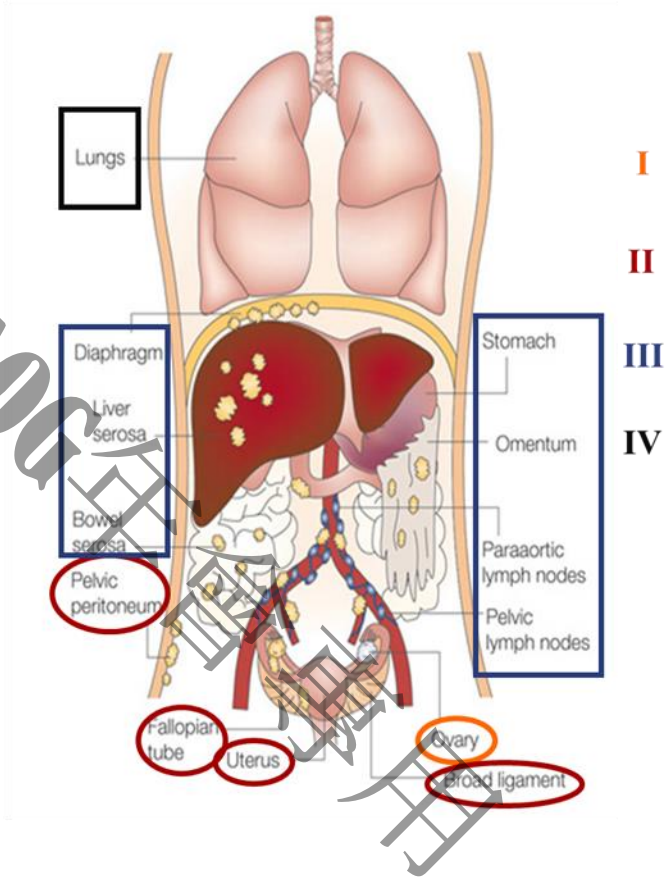


年齡別死亡率，民國110年

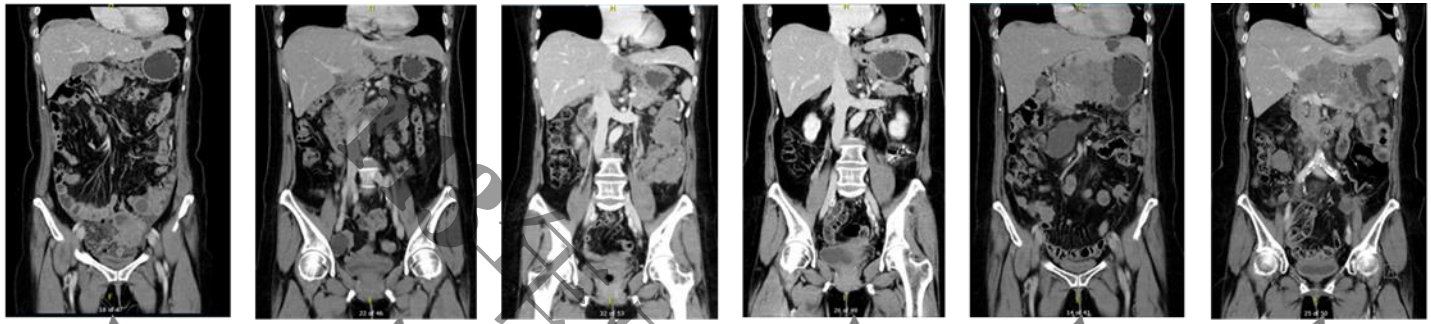
Epithelial Ovarian cancer

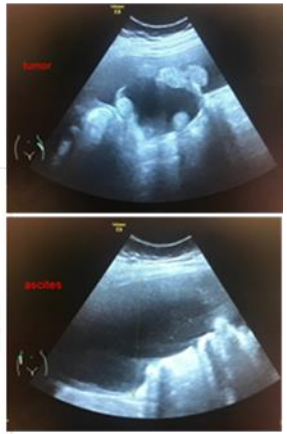
- **Histology**
  - Serous (50~60%)
  - Mucinous (5~10%)
  - Endometrioid (10~15%)
  - Clear cell (10~15%)
- **FIGO stage**
  - Diagnosis at advanced stage
- **Treatment**
  - Debulking surgery
  - Adjuvant chemotherapy (Platinum-based)
  - Response rate: 60~80 %
  - Recurrence in 2 years
  - **Maintenance therapy**

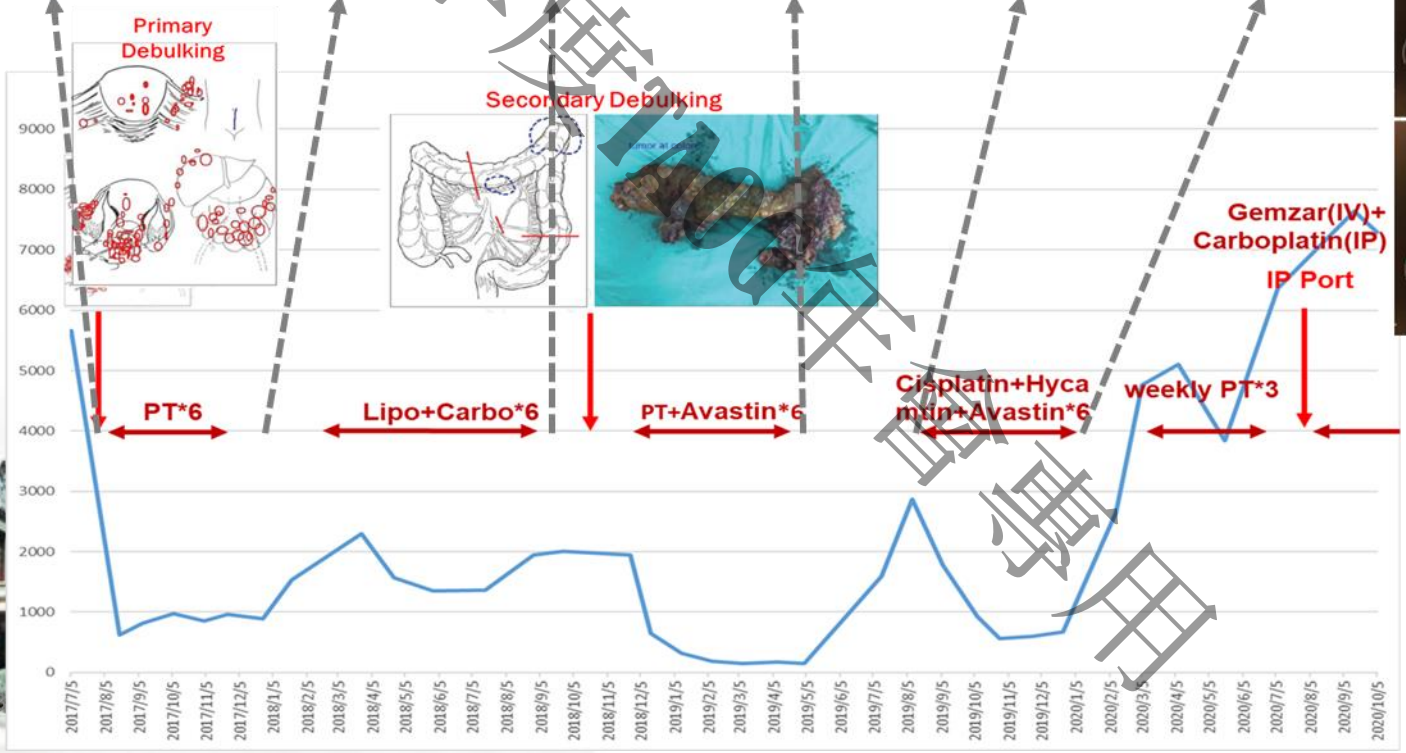




J Clin Oncol 1998; 16:3674-90
Nature Reviews Cancer 2005; 5, 355-366




tumor
ascites


Primary Debulking
Secondary Debulking
PT*6
Lipo+Carbo*6
PT+Avastin*6
Cisplatin+Hycamtin+Avastin*6
weekly PT*3
Gemzar(IV)+ Carboplatin(IP)
IP Port
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2017/7/5
2017/8/5
2017/9/5
2017/10/5
2017/11/5
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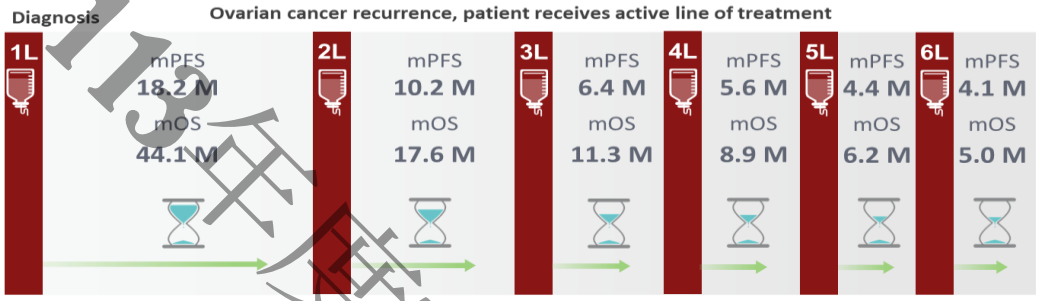
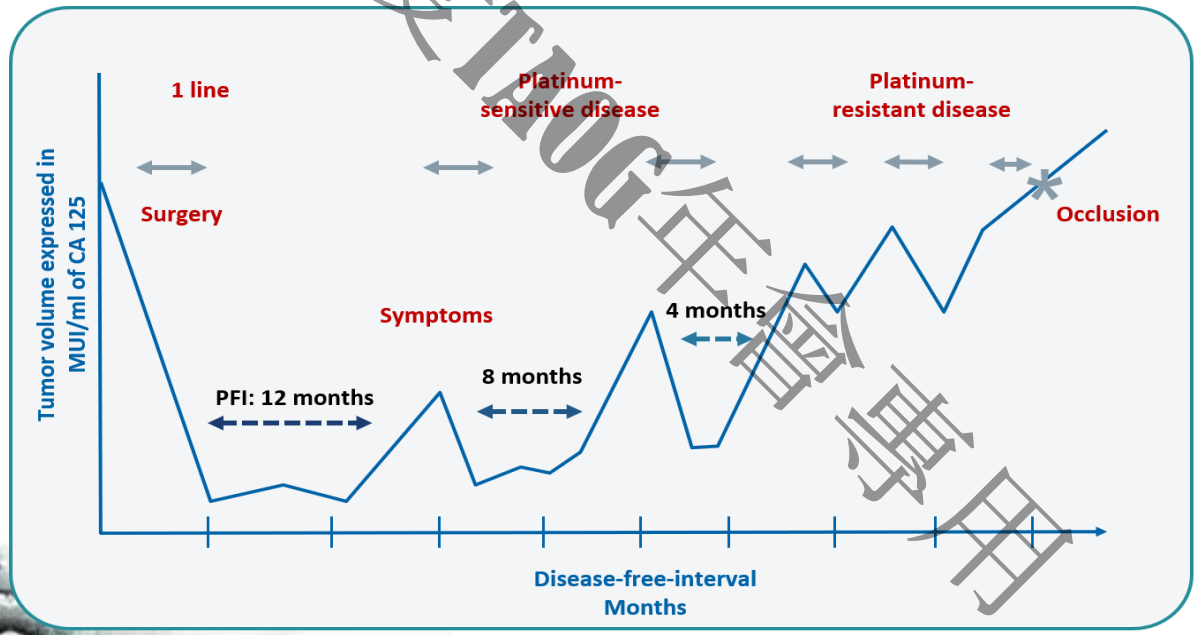
2020/10/5

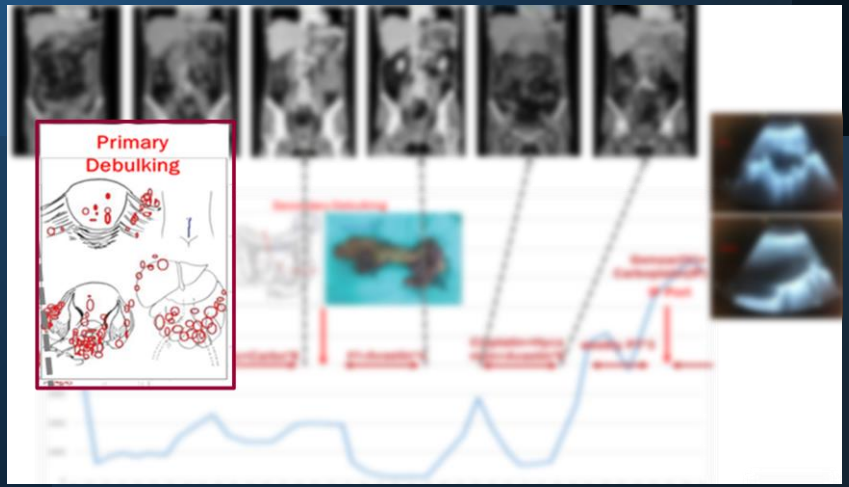
Clinical Courses of Epithelial Ovarian Cancer



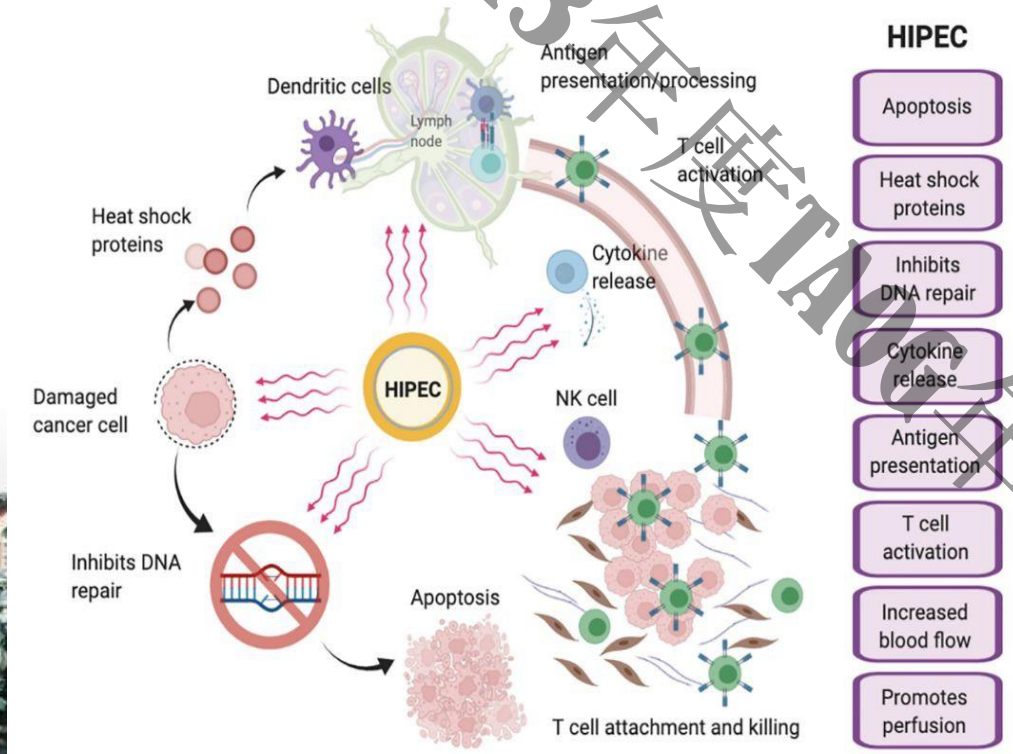


Ann Oncol. 2012;23:2605-2612; Gynecol Oncol Res Pract. 2017;4:13; SpringerPlus. 2016;5:1197

Hyperthermic intraperitoneal chemotherapy in PDS / IDS



Hyperthermic intraperitoneal chemotherapy (HIPEC)



Drug	Molecular weight	Hydrophilic	AUC ratio	Thermal enhance-ment
Taxanes				
Paclitaxel	854 g/mol	No	550–2300	No
Docetaxel	808 g/mol	No	150–500	No
Topoisomerase inhibitors				
Irinotecan	587 g/mol	Yes	38[a]	No
Mitoxantrone	444 g/mol	No	162–230	No
Doxorubicin	544 g/mol	Yes	1109	Yes
Platinum-based agents				
Cisplatin	300 g/mol	Yes	12–22	Yes
Carboplatin	371 g/mol	Yes	15–20	Yes
Oxaliplatin	397 g/mol	Minimal	16	Yes
Antimetabolites				
5-Fluoro-uracil	130 g/mol	Minimal	344	Minimal
Gemcitabine	263 g/mol	Yes	847	Yes
Pemetrexed	427 g/mol	Yes	70	Yes

[a]The AUC-ratio for SN-38, the active metabolite of irinotecan, is approximately 4–15

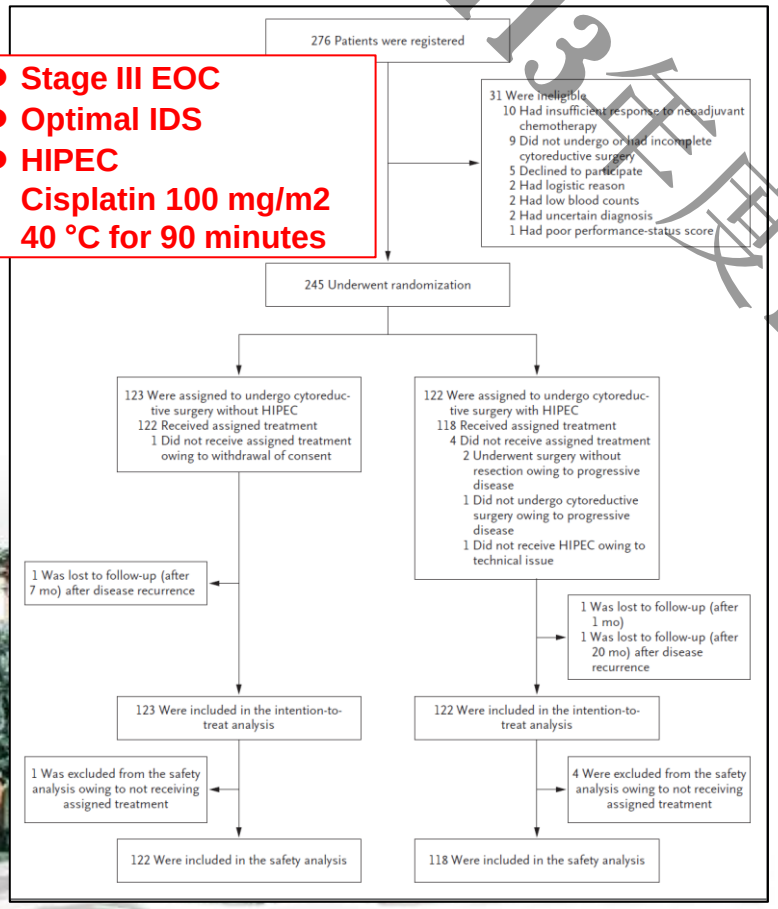
Drugs. 2023 Feb;83(2):159-180.

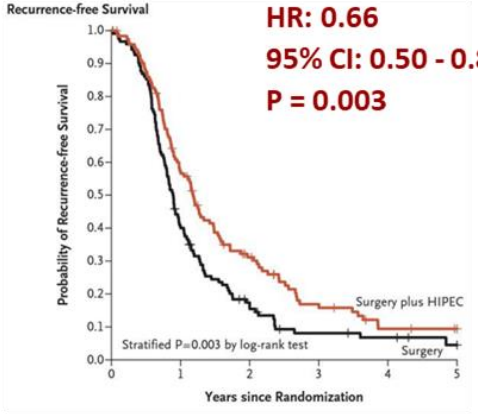
HIPEC in IDS

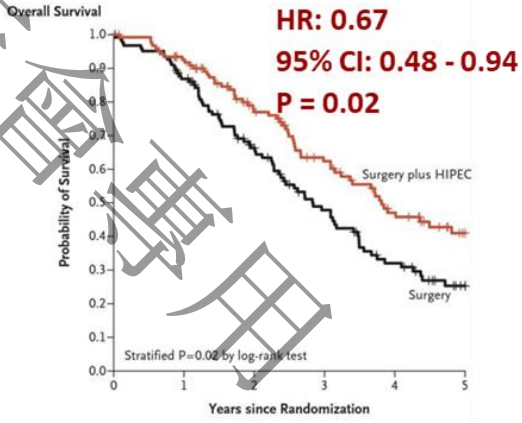
The NEW ENGLAND JOURNAL of MEDICINE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

- **Stage III EOC**
- **Optimal IDS**
- **HIPEC**
  Cisplatin 100 mg/m2
  40 °C for 90 minutes







N Engl J Med. 2018 Jan 18;378(3):230-240.

The NEW ENGLAND JOURNAL of MEDICINE

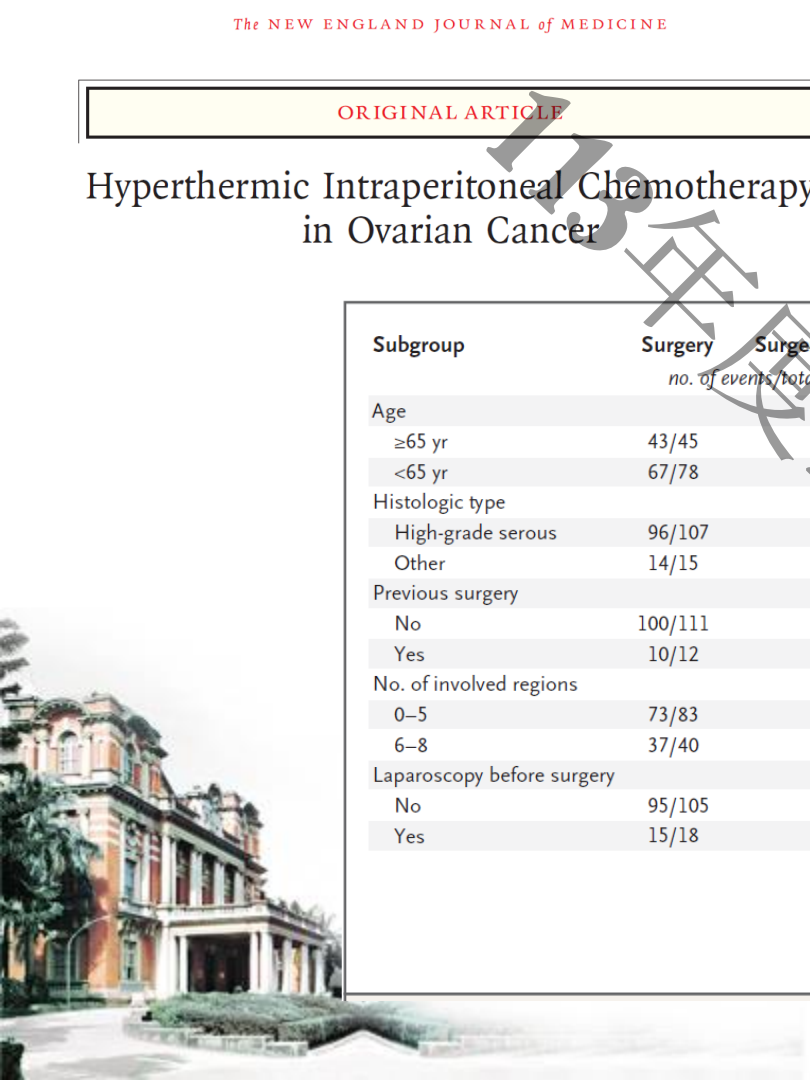
ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

CONCLUSIONS

Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects. (Funded by the Dutch Cancer Society; ClinicalTrials.gov number, NCT00426257; EudraCT number, 2006-003466-34.)

Subgroup	Surgery	Surgery plus HIPEC	Hazard Ratio (99% CI)
	no. of events/total no.		
Age			
≥65 yr	43/45	34/43	0.63 (0.35–1.15)
<65 yr	67/78	65/79	0.72 (0.46–1.12)
Histologic type			
High-grade serous	96/107	91/112	0.69 (0.48–1.02)
Other	14/15	7/9	0.56 (0.17–1.86)
Previous surgery			
No	100/111	90/110	0.71 (0.49–1.03)
Yes	10/12	9/12	0.47 (0.14–1.61)
No. of involved regions			
0–5	73/83	62/83	0.64 (0.41–1.01)
6–8	37/40	37/39	0.66 (0.35–1.23)
Laparoscopy before surgery			
No	95/105	86/103	0.69 (0.47–1.02)
Yes	15/18	13/19	0.61 (0.23–1.63)



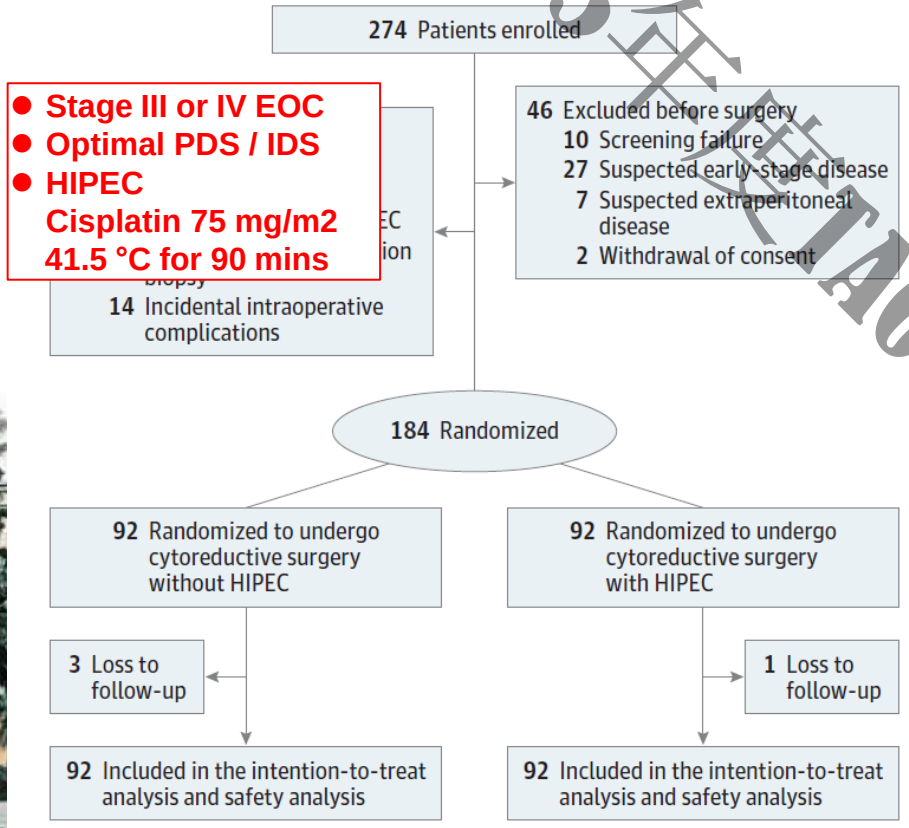
HIPEC in PDS/IDS

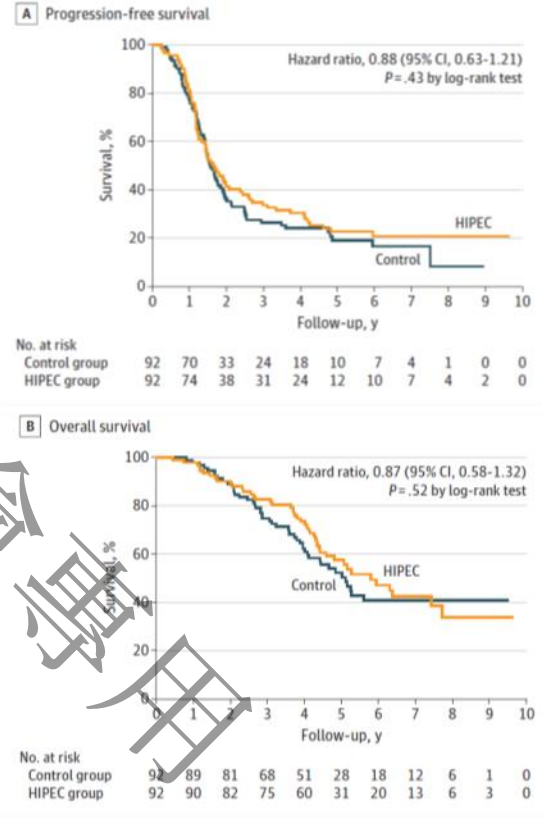
JAMA Surgery | Original Investigation

Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer

A Randomized Clinical Trial

- **Stage III or IV EOC**
- **Optimal PDS / IDS**
- **HIPEC**
  Cisplatin 75 mg/m2
  41.5 °C for 90 mins





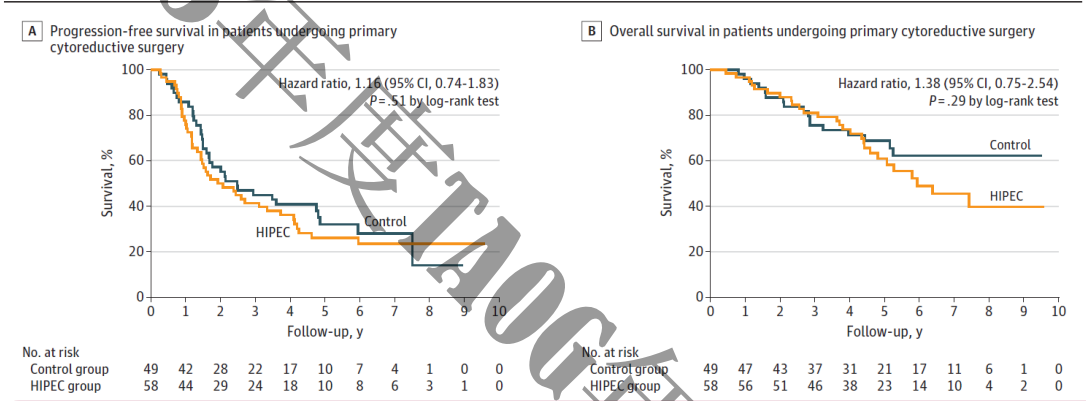
JAMA Surg. 2022 May 1;157(5):374-383.

JAMA Surgery | Original Investigation

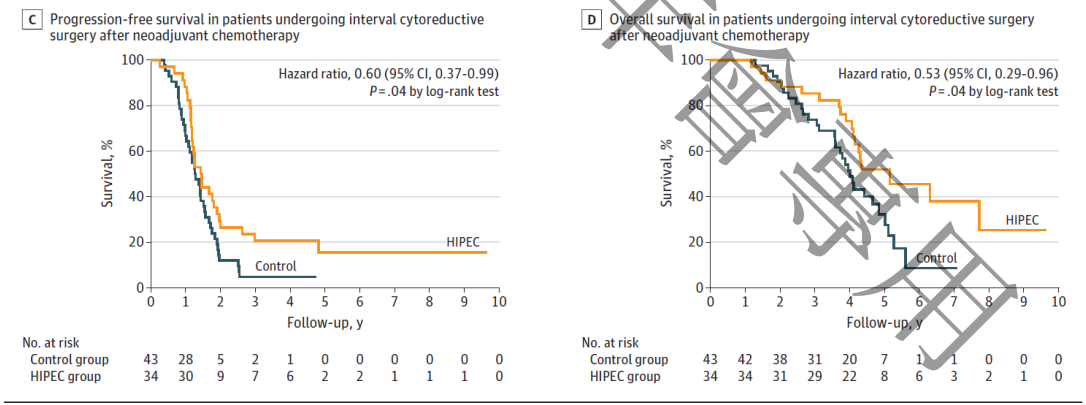
Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer

A Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE The addition of HIPEC to cytoreductive surgery did not improve progression-free and overall survival in patients with advanced epithelial ovarian cancer. Although the results are from a subgroup analysis, the addition of HIPEC to interval cytoreductive surgery provided an improvement of progression-free and overall survival.



PDS



IDS

JAMA Surg. 2022 May 1;157(5):374-383.

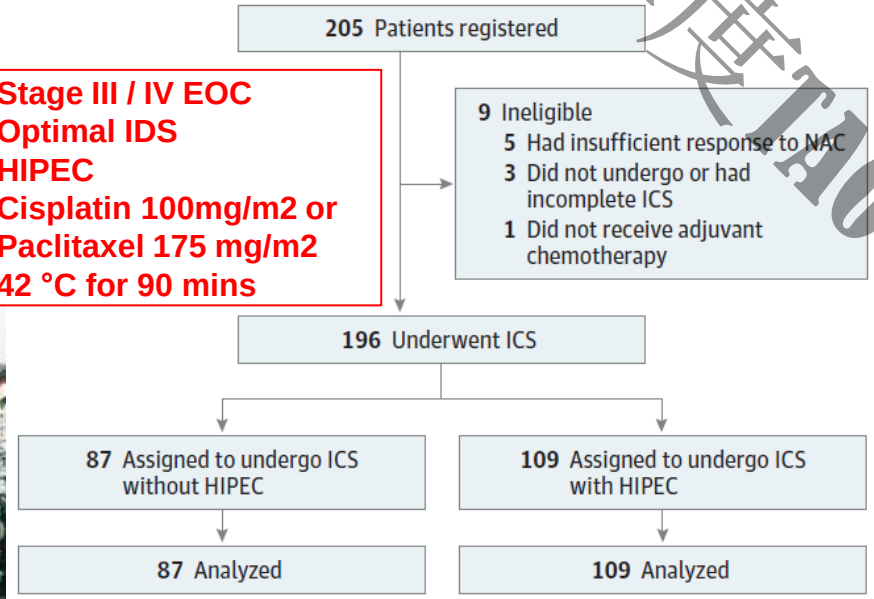
HIPEC in IDS

JAMA Surgery | Original Investigation

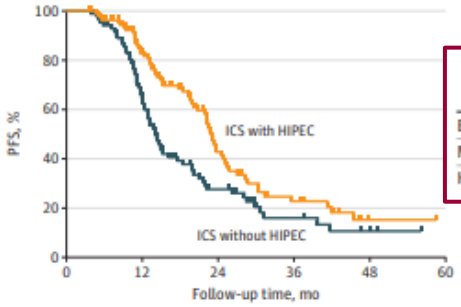
Hyperthermic Intraperitoneal Chemotherapy After Interval Cytoreductive Surgery for Patients With Advanced-Stage Ovarian Cancer Who Had Received Neoadjuvant Chemotherapy

- **Stage III / IV EOC**
- **Optimal IDS**
- **HIPEC**
  Cisplatin 100mg/m2 or
  Paclitaxel 175 mg/m2
  42 °C for 90 mins

Figure 1. Flow Diagram of Patients



A PFS

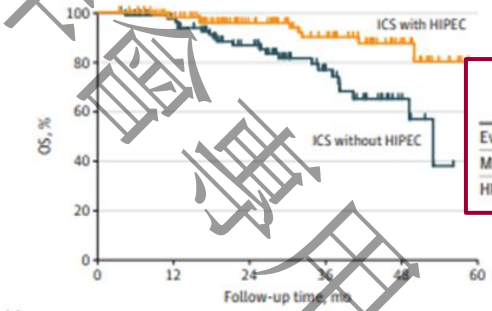


No. at risk

ICS without HIPEC	87	52	19	8	4	0
ICS with HIPEC	109	79	30	13	2	0

	ICS without HIPEC	ICS with HIPEC	Log-rank *P* value
Events	64	64	
Median PFS	14.2 mo	22.9 mo	.005
HR (95% CI)	0.61 (0.43-0.87)		

B OS



No. at risk

ICS without HIPEC	87	77	57	36	10	0
ICS with HIPEC	109	94	65	45	18	0

	ICS without HIPEC	ICS with HIPEC	Log-rank *P* value
Events	21	9	
Median OS	53.0 mo	NR	.002
HR (95% CI)	0.31 (0.14-0.67)		

JAMA Surg. 2023;158(11):1133-1140

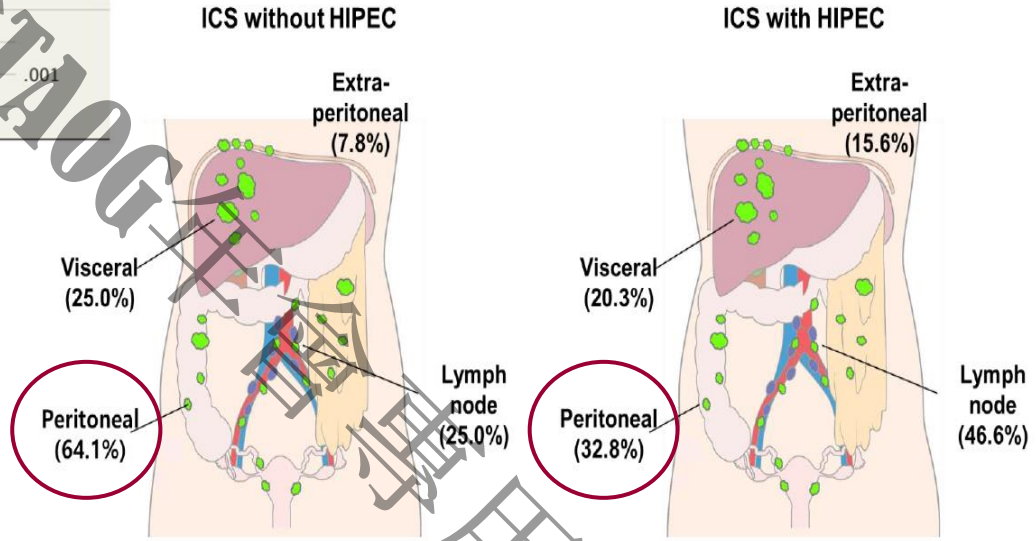
JAMA Surgery | Original Investigation

Hyperthermic Intraperitoneal Chemotherapy After Interval Cytoreductive Surgery for Patients With Advanced-Stage Ovarian Cancer Who Had Received Neoadjuvant Chemotherapy

CONCLUSIONS AND RELEVANCE This study suggests that ICS in conjunction with HIPEC was associated with longer PFS and OS than ICS without HIPEC for patients with advanced-stage ovarian cancer and was not associated with higher rates of postoperative complications. The lower rate of peritoneal recurrence after HIPEC may be associated with improved OS.

Table 3. Sites of Recurrence[a]

Variable	ICS without HIPEC (n = 87)	ICS with HIPEC (n = 109)	*P* value
Patients with recurrence, No. (%)	64 (73.6)	64 (58.7)	<.001
Recurrence site, No./total No. (%)			
Intraperitoneal	41/64 (64.1)	21/64 (32.8)	
Extraperitoneal	5/64 (7.8)	10/64 (15.6)	
Visceral metastasis	6/64 (9.4)	13/64 (20.3)	.001
Lymph node	16/64 (25.0)	30/64 (46.9)	



Side effects of HIPEC

PeerJ. 2023; 11: e15277.

Risk factors of acute renal impairment after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Conclusions: Identifying the risk factors of post-HIPEC creatinine increased can help to improve patient selection, a dose of HIPEC regimens modification and perioperative care. We also identified the detrimental renal effect of peritoneal dialysis solution as HIPEC perfusate. More prospective studies are warranted to confirm these findings.

Table 1. Demographic and clinical data of the patients who underwent CRS/HIPEC.

Characteristic	All ($n=169$)	ARI Group ($n=21$)	Non-ARI Group ($n=148$)	p-value
Previous systemic therapy				0.021*
Never	53 (31.4%)	4 (19.0%)	49 (33.1%)	
1st line	57 (33.7%)	4 (19.0%)	53 (35.8%)	
2nd lines or more	59 (34.9%)	13 (61.9%)	46 (31.1%)	
Previous chemotherapy				0.007*
Platinum based	61 (36.1%)	14 (66.7%)	47 (31.8%)	
Others	54 (32.0%)	4 (19.0%)	50 (33.8%)	
Never received chemotherapy	54 (32.0%)	3 (14.3%)	51 (34.5%)	
Cancer				0.04*
Colorectal	54 (32.0%)	5 (23.8%)	49 (33.1%)	
Ovary	60 (35.5%)	13 (61.9%)	47 (31.8%)	
Gastric	30 (17.8%)	1 (4.8%)	29 (19.6%)	
Mesothelioma	2 (1.2%)	1 (4.8%)	1 (0.7%)	
Pseudomyxoma peritonei	16 (9.5%)	1 (4.8%)	15 (10.1%)	
Others	7 (4.1%)	0 (0%)	7 (4.7%)	
HIPEC regimen				0.004*
Cisplatin	71 (42.0%)	15 (71.4%)	56 (37.8%)	
Non-cisplatin	98 (58.0%)	6 (28.6%)	92 (62.2%)	

Table 4. Analysis of risk factors for the occurrence of ARI using multiple logistic regression models.

	Adjusted OR (95% CI)	p-value
Age (years)		
≥55	2.54 (0.86, 7.49)	0.091
<55	1	
Sex		
Female	1.42 (0.42, 4.84)	0.573
Male	1	
HIPEC regimen		
Cisplatin	11.38 (3.07, 42.13)	<0.001*
Non-cisplatin	1	
HIPEC perfusate		
Peritoneal dialysis solution	7.07 (2.06, 24.26)	0.002*
Normal saline-based solution	1	

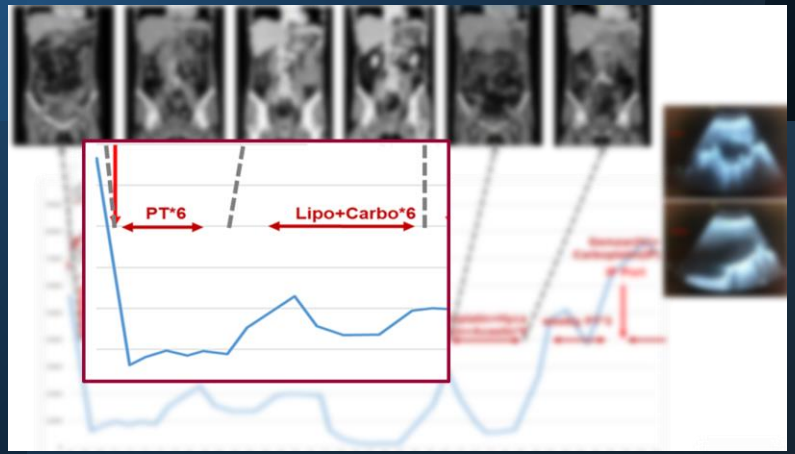
ARI: acute renal impairment; OR: odds ratio; CI: confidence interval; HIPEC: hyperthermic intraperitoneal chemotherapy.
*p-value <0.05 was considered to be statistically significant.

Int J Hyperthermia. 2020;37(1):1279-1286.

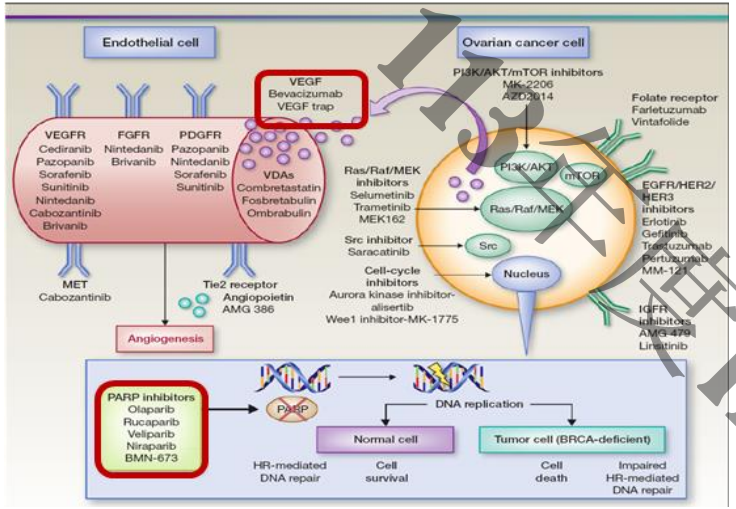
Summary

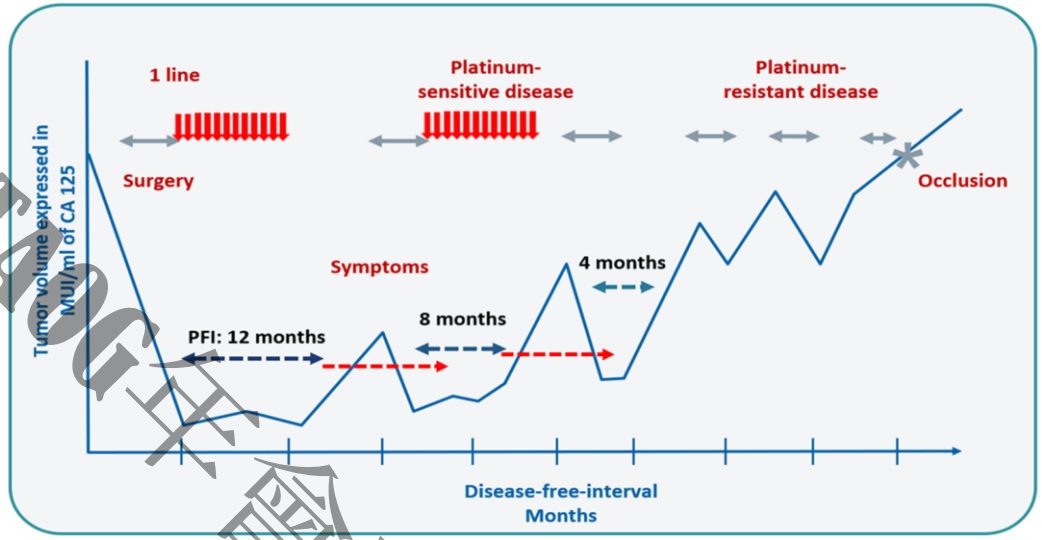
- HIPEC in in advanced stage EOC s/p IDS: survival benefit
- HIPEC in advanced stage EOC s/p PCS: no sufficient evidence
- Multidisciplinary teamwork decreases complication
- Cisplatin regimen and Peritoneal dialysis solution are risk factor of AKI in Post - HIPEC surgery

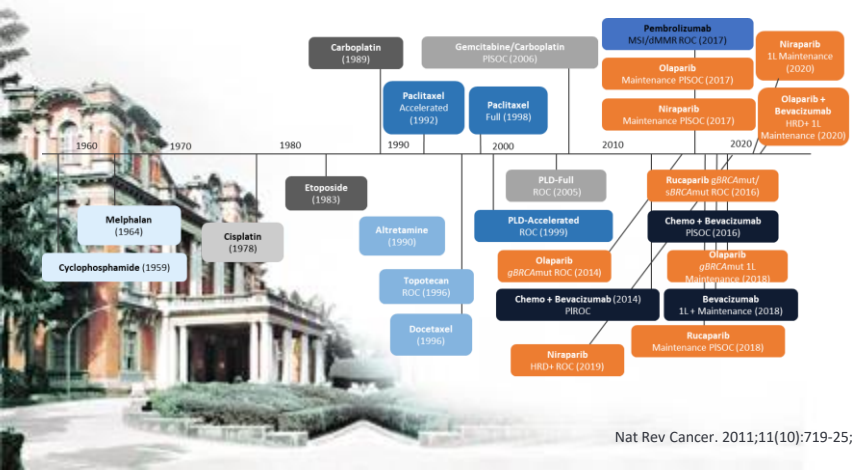
Maintenance Therapy in Epithelial Ovarian Cancer - Bevacizumab



Maintenance Therapy is the Standard Care of EOC in Front-line







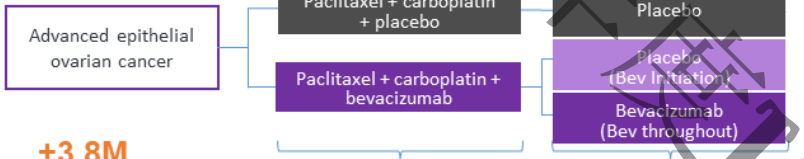
Bevacizumab

PARP inhibitors

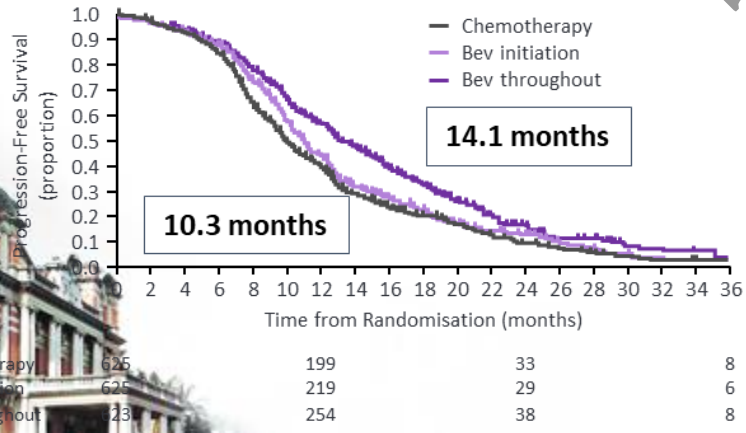
Nat Rev Cancer. 2011;11(10):719-25; Clin Cancer Res 2013; 19(5); 961–8; Br J Cancer. 2015;113 Suppl 1:S10-6; Ann Oncol. 2016;27 Suppl 1:i33-i39; Gynecol Oncol. 2016;142(3):588-96; Gynecol Oncol. 2019;152(2):416-425.; Cancer. 2019;125 Suppl 24:4582-4586. clinicaloptions.com

First-Line Bevacizumab: Progression-Free Survival

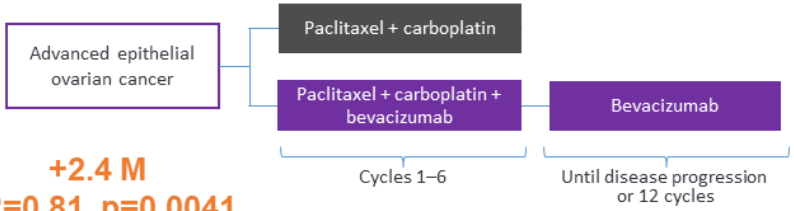
GOG 218[1]



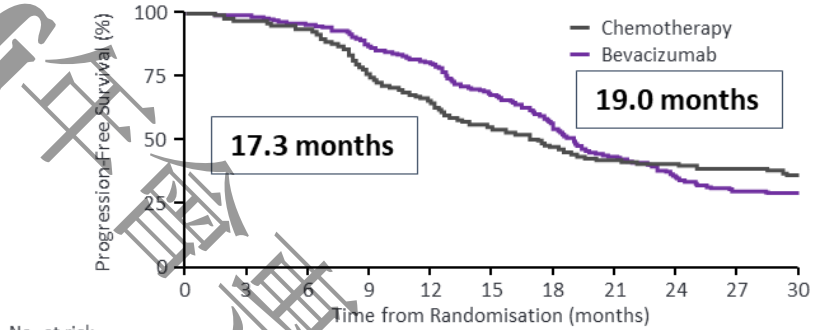
+3.8M
HR: 0.717, p<0.001



ICON7[2]



+2.4 M
HR=0.81, p=0.0041

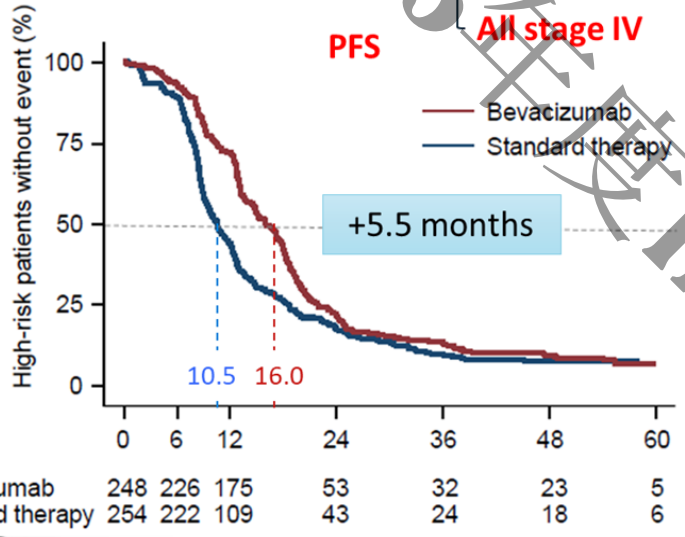


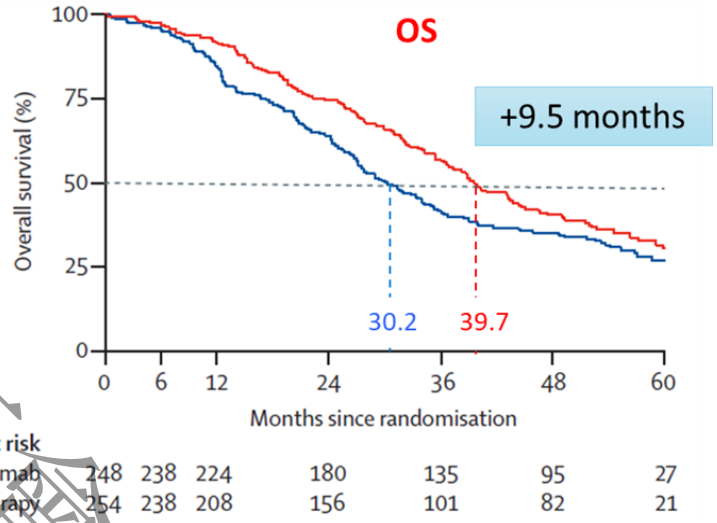
1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. 2. Perren TJ et al. *N Engl J Med.* 2011;365(26):2484-2496.

Overall Survival Benefits of Maintenance Bevacizumab
ICON7: "High risk" population

Stage III-no surgery, suboptimal debulking (>1 cm)

All stage IV





	Standard (n=254)	Bev (n=248)
Mean median PFS (months; 95% CI)	10.5 (9.3-12.0)	16.0 (14.2-17.8)
HR (95% CI)	0.73 (0.61-0.88)	
p value	<0.0001	

	Standard (n=254)	Bev (n=248)
Mean median OS (months; 95% CI)	30.2 (27.0-34.3)	39.7 (36.0-44.2)
HR (95% CI)	0.78 (0.63-0.97)	
p value	0.03	

Oza AM, et al. Lancet Oncol 2015

CA-125 ELIMination Rate Constant K (KELIM)

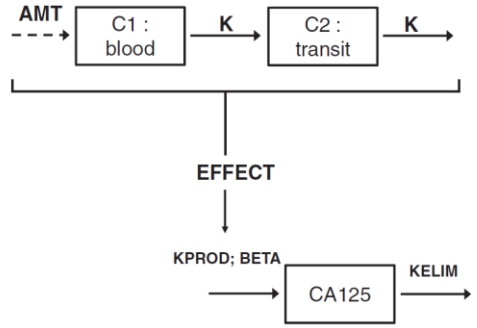
The strong prognostic value of KELIM, a model-based parameter from CA 125 kinetics in ovarian cancer: Data from CALYPSO trial (a GINECO-GCIG study)

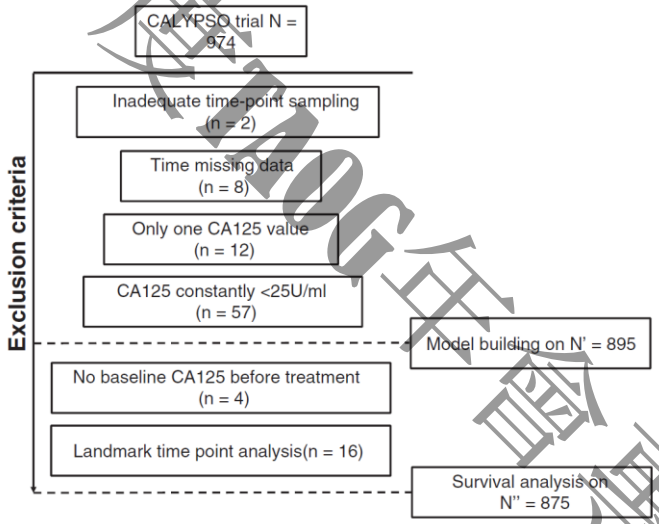
$$\frac{dC1}{dt} = -K \times C1 \quad (1)$$

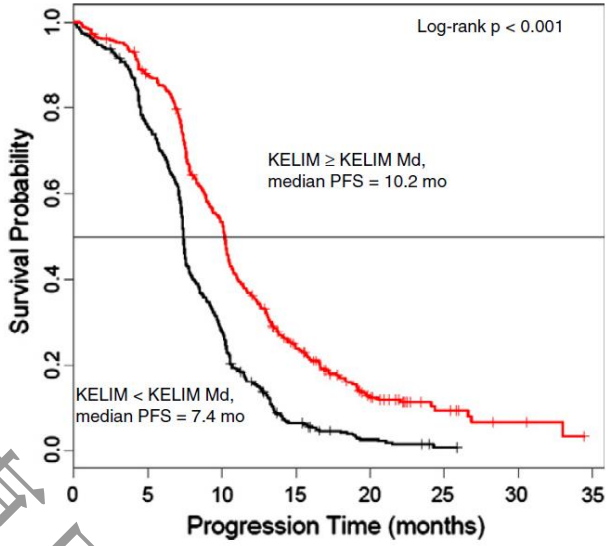
$$\frac{dC2}{dt} = K \times C1 - K \times C2 \quad (2)$$

$$\frac{dCA125}{dt} = KPROD \times e^{BETA \times time} \times EFFECT - KELIM \times CA125 \quad (3)$$

$$EFFECT = 1 - \frac{C2}{A50 + C2} \epsilon [0; 1] \quad (4)$$







B. You et al. / Gynecologic Oncology 130 (2013) 289–294

Biomarker Kinetics
Is it a favorable decrease?

Presentation | PSA | hCG | CA-125 neo-adjuvant | CA-125 adjuvant | Publications | Authors | Contact | Terms of use

Neo-adjuvant chemotherapy page

Modeled CA-125 KELIM in patients with stage III-IV high grade serous ovarian carcinomas treated with first line neo-adjuvant chemotherapy

For patients with stage III or IV high grade serous ovarian carcinomas treated with neoadjuvant platinum-based chemotherapy (with 3 weekly-cycles carboplatin + paclitaxel).

CA125 KELIM is calculated on the data of individual patients for information purpose only. The authors of the site do not take any responsability or endorse treatment decision. For scientific studies ≥ 2 patients, the website team should be contacted at biomarkers.kinetics@univ-lyon1.fr

CA-125 KELIM is calculated for information purpose only . The authors of this site do not take any responsability or endorse treatment decision.

Patient information

Patient Identification Code: 69007

Chemotherapy

2021-11-08
2021-11-19
2021-12-20
2022-01-10

Dates of chemotherapy

CA-125 measured (UI/ml)

Note: enter CA-125 concentration measured just before the onset of chemotherapy

dates and values of CA-125

2021-11-08	500
2021-11-19	200
2021-12-20	100
2022-01-10	50

Reset

"Compute" button

Compute

Value of KELIM "Standardized KELIM = 0.885"

CA-125 KELIM

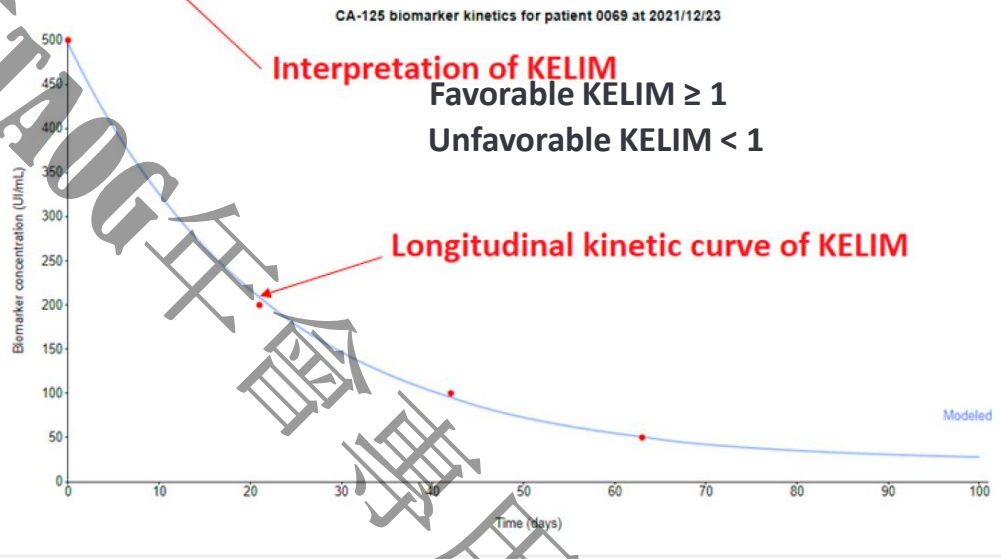
Standardized KELIM = 0.885 Standardized CA-125 elimination rate *(unitless)*

Favorable KELIM	≥ 1 associated with high tumor primary chemosensitivity, and better prognosis
Unfavorable KELIM	< 1 associated with poor tumor primary chemosensitivity, and worse prognosis

Interpretation of KELIM

Favorable KELIM ≥ 1

Unfavorable KELIM < 1

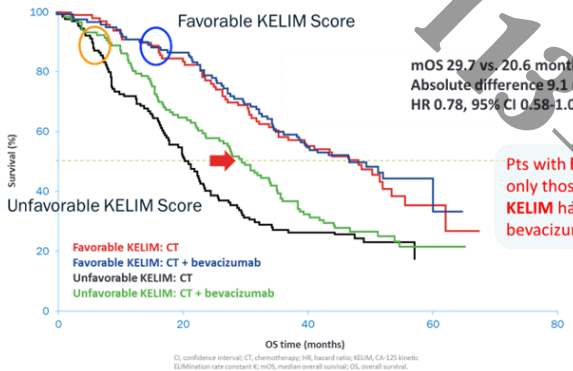


Longitudinal kinetic curve of KELIM

https://www.biomarker-kinetics.org/CA-125

https://www.biomarker-kinetics.org/CA-125-neo

Predictive value of KELIM regarding benefit from bevacizumab
"High risk" population in ICON-7 (initial study)



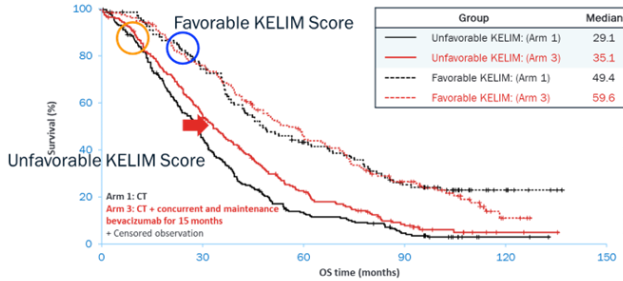
mOS 29.7 vs. 20.6 months
Absolute difference 9.1 months
HR 0.78, 95% CI 0.58-1.04

Pts with **high-risk diseases**: only those with **unfavorable KELIM** had OS benefit from bevacizumab

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; KELIM, CA-125 kinetic ELIMination rate constant K; mOS, median overall survival; OS, overall survival.

1. You B, et al. Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2022. 2. Colomban O, et al. JNCI Cancer Spectr 2020;4:pkaa026.

Predictive value of KELIM regarding benefit from bevacizumab
"High risk" population in GOG-0218 (external validation study)



Group	Median	Log-rank	HR (CI)
Unfavorable KELIM: (Arm 1)	29.1	0.023	REF
Unfavorable KELIM: (Arm 3)	35.1		0.79 (0.65, 0.97)
Favorable KELIM: (Arm 1)	49.4	0.748	REF
Favorable KELIM: (Arm 3)	59.6		1.05 (0.79, 1.39)

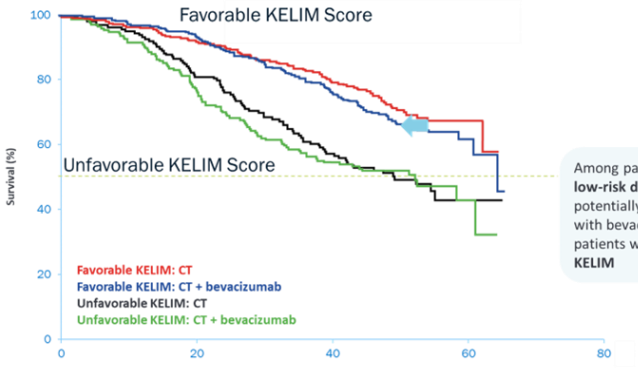
Unfavorable KELIM (Arm 1)	232	108	36	16	2	0
Unfavorable KELIM (Arm 3)	206	117	48	18	2	0
Favorable KELIM (Arm 1)	122	89	51	28	7	0
Favorable KELIM (Arm 3)	151	114	67	36	3	0

Among patients with **high-risk diseases**, only those with **unfavorable KELIM** had OS benefit from bevacizumab

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; KELIM, CA-125 kinetic ELIMination rate constant K; mOS, median overall survival; OS, overall survival.

1. You B, et al. Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2022. 2. Colomban O, et al. JNCI Cancer Spectr 2020;4:pkaa026.

Predictive value of KELIM regarding benefit from bevacizumab
"Low risk" population in ICON-7 (initial study)

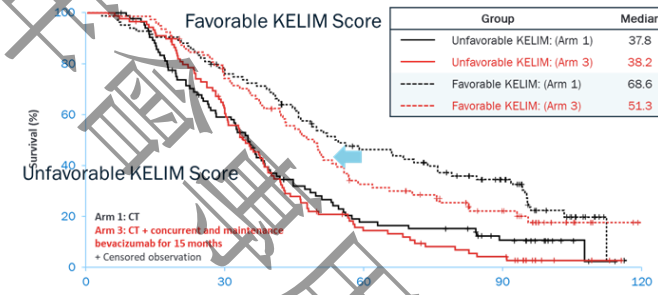


Among patients with **low-risk diseases**, potentially lower OS with bevacizumab in patients with **favorable KELIM**

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; KELIM, CA-125 kinetic ELIMination rate constant K; mOS, median overall survival; OS, overall survival.

1. You B, et al. Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2022. 2. Colomban O, et al. JNCI Cancer Spectr 2020;4:pkaa026.

Predictive value of KELIM regarding benefit from bevacizumab
"Low risk" population in GOG-0218 (external validation study)



Group	Median	Log-rank	HR (CI)
Unfavorable KELIM: (Arm 1)	37.8	0.0002	REF
Unfavorable KELIM: (Arm 3)	38.2		1.08 (0.79, 1.48)
Favorable KELIM: (Arm 1)	68.6		REF
Favorable KELIM: (Arm 3)	51.3		1.18 (0.83, 1.69)

Unfavorable KELIM (Arm 1)	98	60	25	14	0
Unfavorable KELIM (Arm 3)	102	65	23	14	0
Favorable KELIM (Arm 1)	96	74	47	30	0
Favorable KELIM (Arm 3)	90	67	34	20	0

Among patients with **low-risk diseases**, potentially lower PFS with bevacizumab in patients with **favorable KELIM**

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; KELIM, CA-125 kinetic ELIMination rate constant K; mOS, median overall survival; OS, overall survival.

1. You B, et al. Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2022. 2. Colomban O, et al. JNCI Cancer Spectr 2020;4:pkaa026.

Maintenance Bevacizumab Therapy in EOC
Overall Survival Benefits

- **High risk population**
  - **All Stage IV**
  - **Stage III: no surgery or suboptimal debulking**
  - **Unfavorable KELIM**
  - **No other validated guiding biomarkers at present**

Bevacizumab contraindications

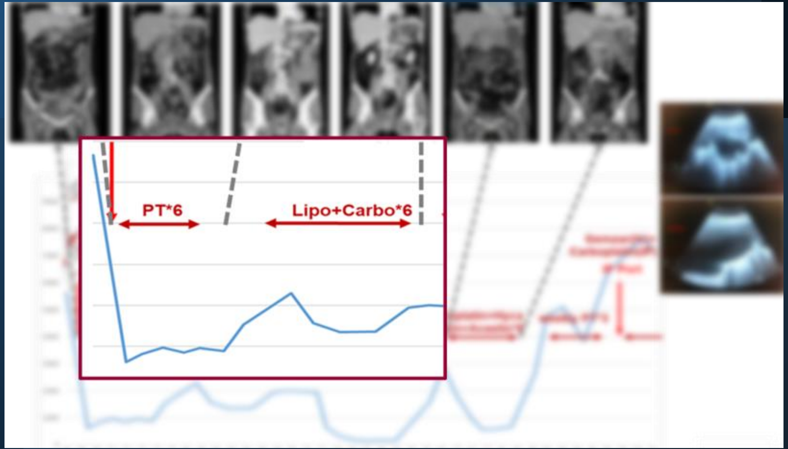
- Hypersensitivity to drug
- Surgery, major within 28 days
- **Unhealed surgical wounds**
- **Severe hemorrhage**
- **Recent hemoptysis**
- **GI perforation**
- **Uncontrolled hypertension**
- **Severe/arterial thromboembolism**

Bevacizumab cautions

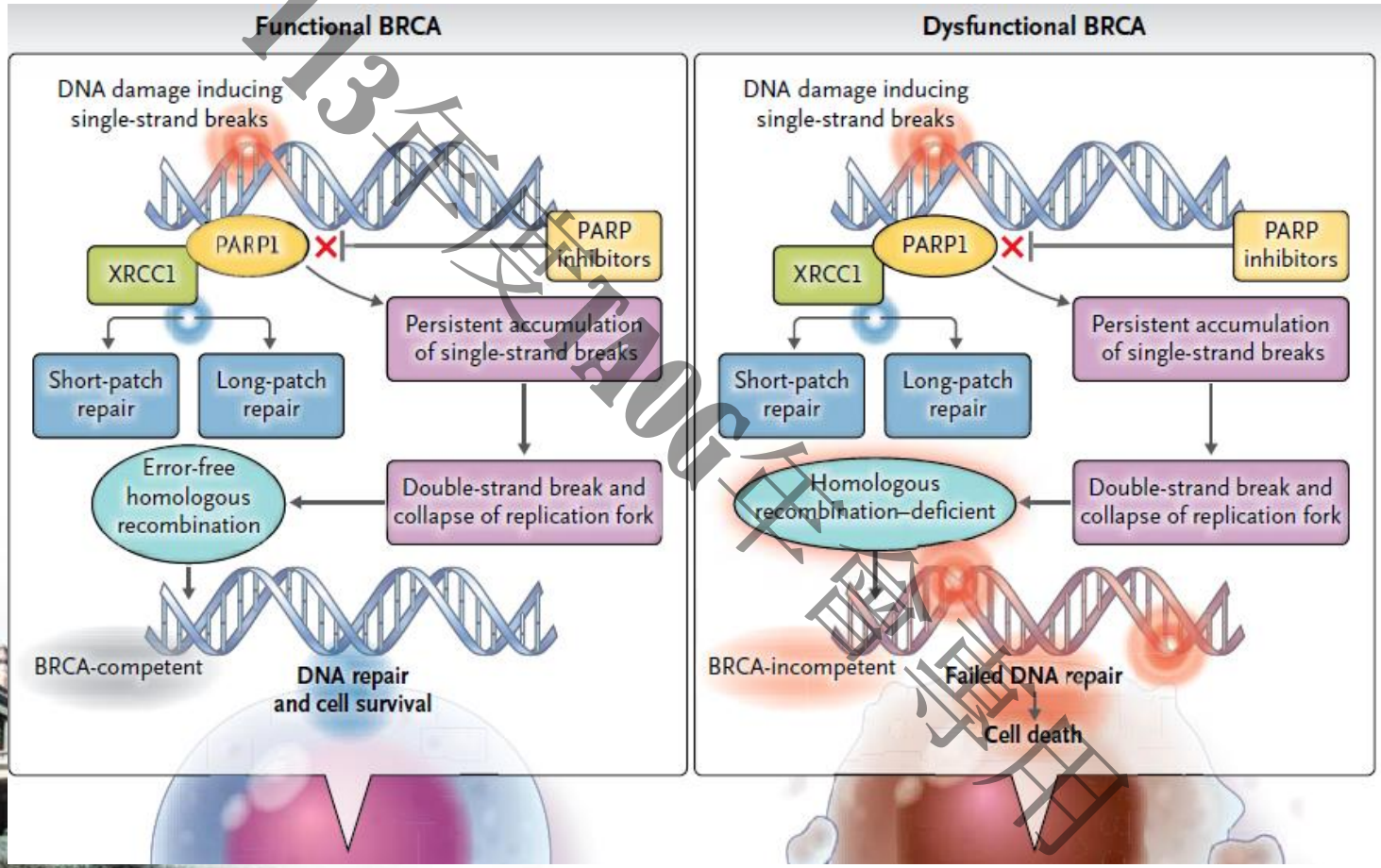
- Congestive heart failure
- Concurrent or past anthracycline use
- Proteinuria
- Thromboembolism history
- elderly patients

Gourley C, et al. *J Clin Oncol*. 2014;32(15 suppl): Abstract 5502.
Kommos et al. *Cancer Clinical Research*. 2017;23(14):3794-3801.
Kommos et al. ASCO 2018
Bais C, et al. *J Natl Cancer Inst*. 2017;109(11):djx066.

Maintenance Therapy in Epithelial Ovarian Cancer - PARP inhibitors



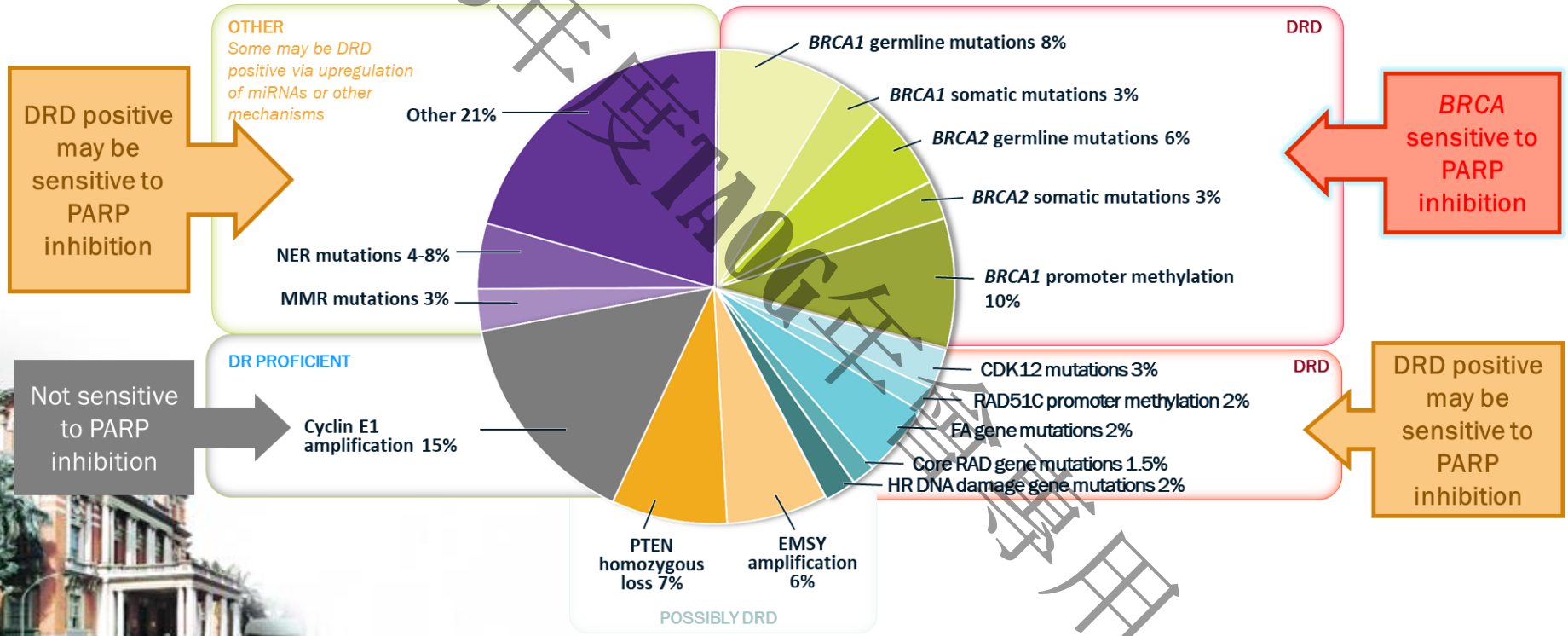
Synthetic Lethality



N Engl J Med 2014; 371:1725-1735

Gene Mutation in High Grade Serous EOC (TCGA)

A subset of ovarian tumors may exhibit DRD in the absence of *BRCA1/2* mutations



CDK12, cyclin dependent kinase 12; EMSY, BRCA2-interacting transcriptional repressor; FA, Fanconi anemia; MMR, mismatch repair; miRNA, micro messenger ribonucleic acid; NER, nucleotide excision repair; PTEN, phosphatase and tensin homolog.

Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-1154.

SOLO1

N Engl J Med 2018; 379: 2495-505

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

- Stage III / IV HGS/E EOC
- BRCA1/2 mutation
- CR/PR after platinum-based chemotherapy

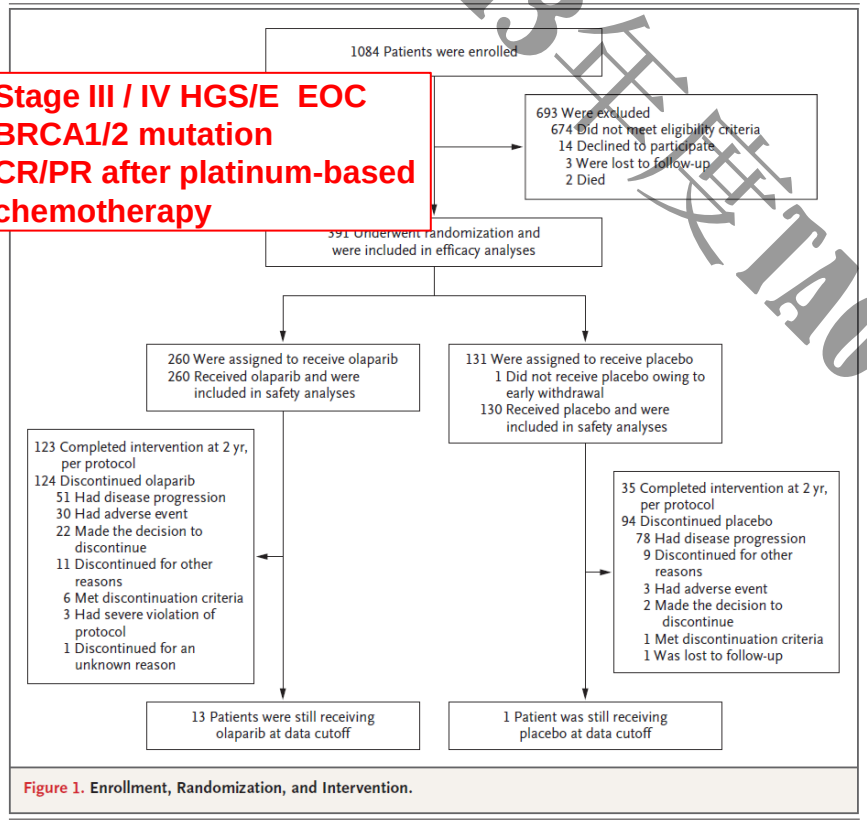
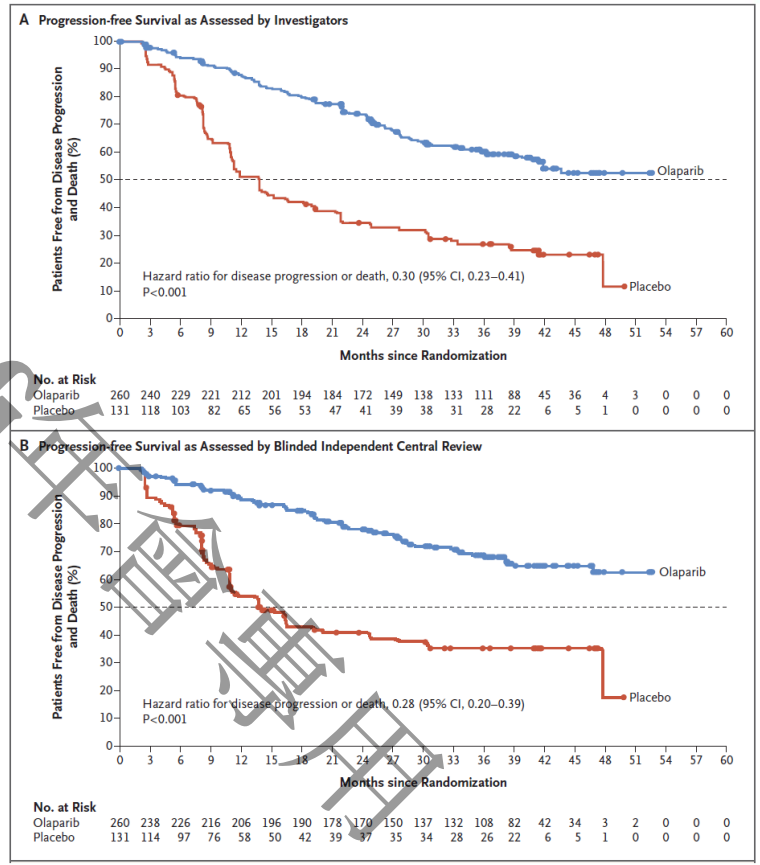


Figure 1. Enrollment, Randomization, and Intervention.



N Engl J Med 2018; 379: 2495-505

O Olaparib

SOLO1

N Engl J Med 2018; 379: 2495-505

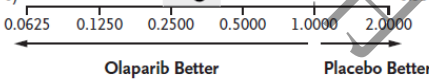
ORIGINAL ARTICLE

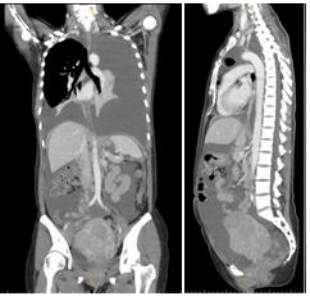
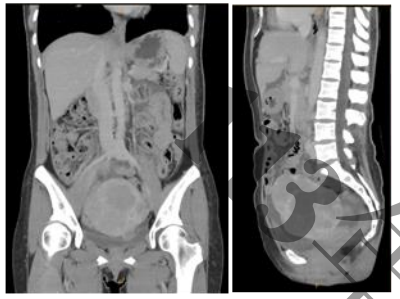
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

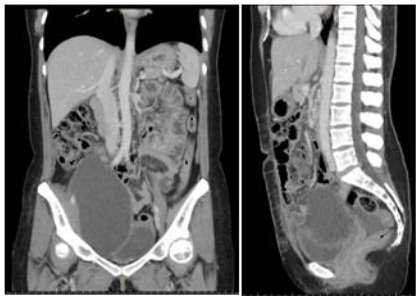
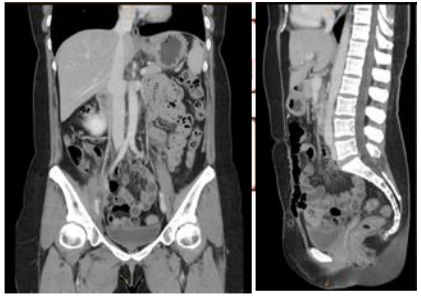
CONCLUSIONS

The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. (Funded by AstraZeneca and Merck; SOLO1 ClinicalTrials.gov number, NCT01844986.)

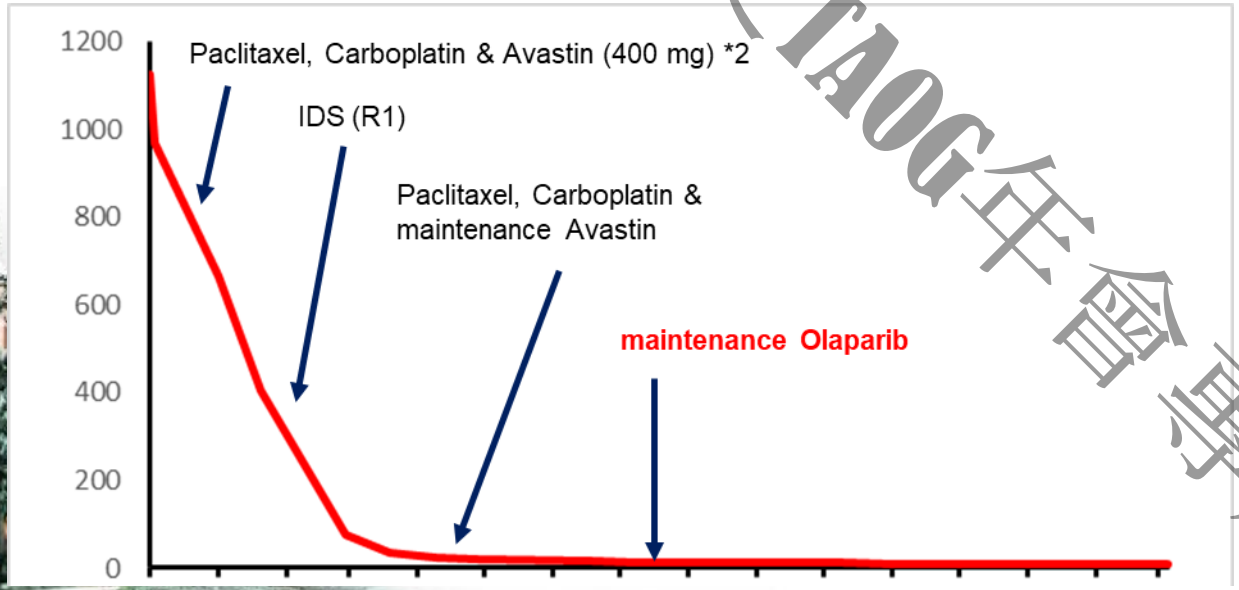
Subgroup	Olaparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	102/260 (39)	96/131 (73)	0.30 (0.23–0.41)
Clinical response after chemotherapy			
Complete response	73/213 (34)	73/107 (68)	0.35 (0.26–0.49)
Partial response	29/47 (62)	23/24 (96)	0.19 (0.11–0.34)
ECOG performance status at baseline			
Normal activity	75/200 (38)	76/105 (72)	0.33 (0.24–0.46)
Restricted activity	27/60 (45)	20/25 (80)	0.38 (0.21–0.68)
CA-125 level at baseline			
≤ULN	92/247 (37)	89/123 (72)	0.34 (0.25–0.46)
>ULN	10/13 (77)	7/7 (100)	NC
Germline *BRCA* mutation according to testing at Myriad			
BRCA1	84/188 (45)	69/91 (76)	0.40 (0.29–0.56)
BRCA2	15/62 (24)	26/39 (67)	0.20 (0.10–0.38)
BRCA1 and *BRCA2*	0/3	0/0	NC
None	3/7 (43)	1/1 (100)	NC
Age at baseline			
<65 yr	85/225 (38)	82/112 (73)	0.33 (0.24–0.45)
≥65 yr	17/35 (49)	14/19 (74)	0.45 (0.22–0.92)
International FIGO stage at initial diagnosis			
Stage III	83/220 (38)	79/105 (75)	0.32 (0.24–0.44)
Stage IV	19/40 (48)	17/26 (65)	0.49 (0.25–0.94)
Presence of residual macroscopic disease after debulking surgery performed before trial entry			
Yes	29/55 (53)	23/29 (79)	0.44 (0.25–0.77)
No	70/200 (35)	69/98 (70)	0.33 (0.23–0.46)



Ovarian high grade serous carcinoma, FIGO stage IVA
63 y/o



【Result】

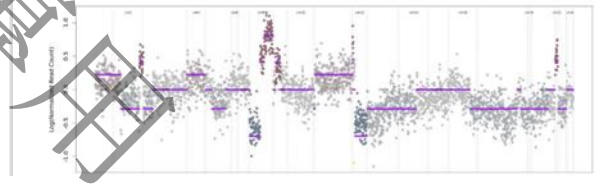
1. Nonsynonymous SNV and small indel

Pathogenic / likely pathogenic variants

BRCA2:NM_000059:exon11:c.3680_3681del:p.L1227fs

TP53:NM_000546:exon5:c.422dupG:p.C141fs

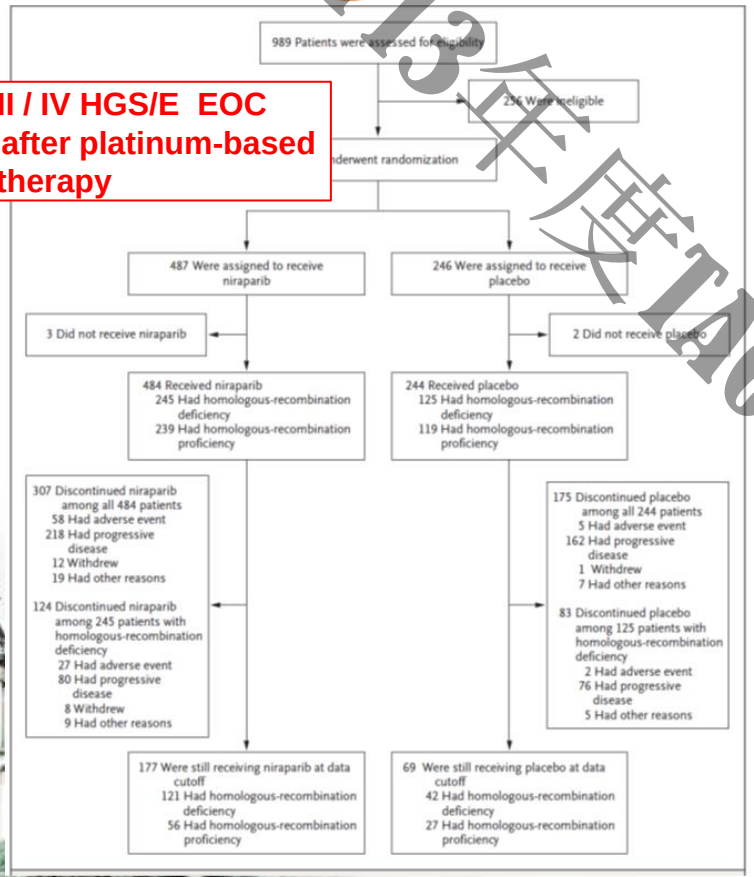
chr2	215593503	215674377	Gain	copy=3	*BARD1*
chr8	15967635	31030550	Loss	copy=1	*MSR1,WRN*
chr8	90947773	90994989	Gain	copy=3	*NBN*
chr8	90996727	145742018	Gain	copy=4.5	*NBN,EXT1,RECQL4*
chr8	145742057	145743014	Gain	copy=3.5	*RECQL4*
chr9	21968324	97873938	Gain	copy=3	*CDKN2A,FANCG,FANCC*
chr12	12870880	58144547	Gain	copy=3	*CDKN1B,CDK4*
chr12	133201347	133263932	Loss	copy=1	*POLE*
chr21	36164511	36421130	Gain	copy=3	*RUNX1*



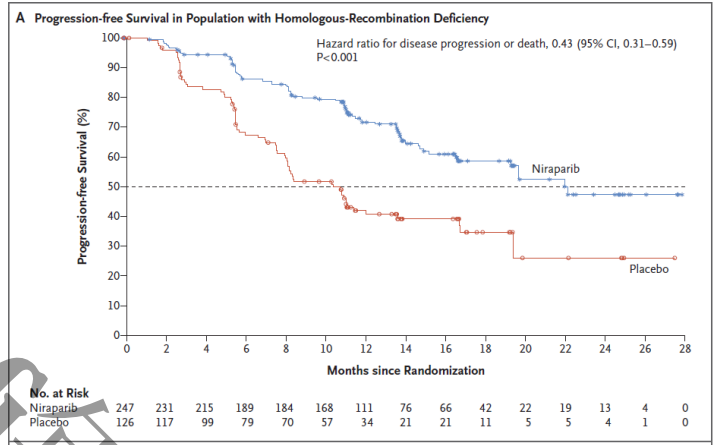
PRIMA

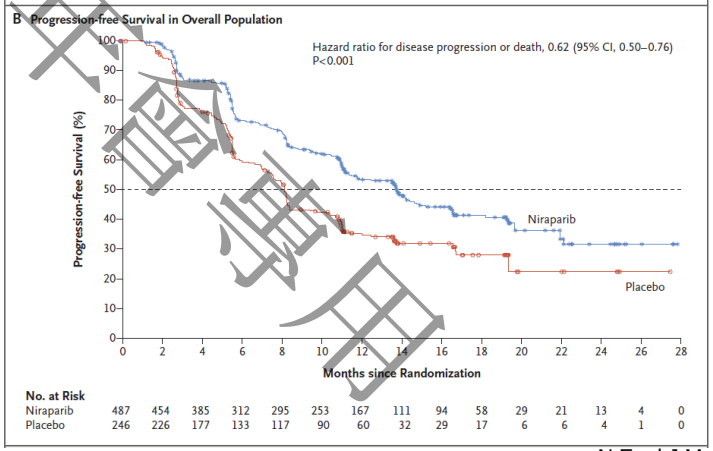
N Engl J Med 2019; 381:2391-402

- Stage III / IV HGS/E EOC
- CR/PR after platinum-based chemotherapy



Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer





N Engl J Med 2019; 381:2391-402

PRIMA

N Engl J Med 2019; 381:2391-402

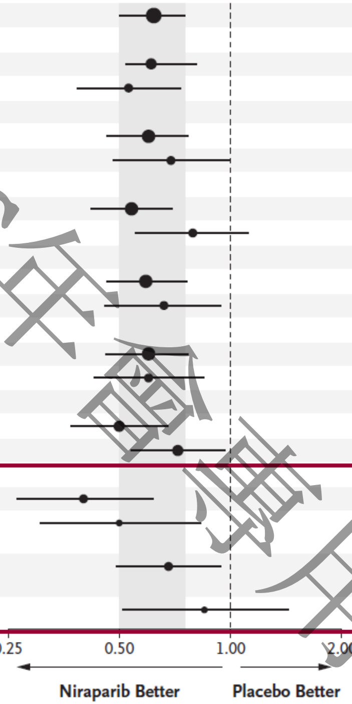
ORIGINAL ARTICLE

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

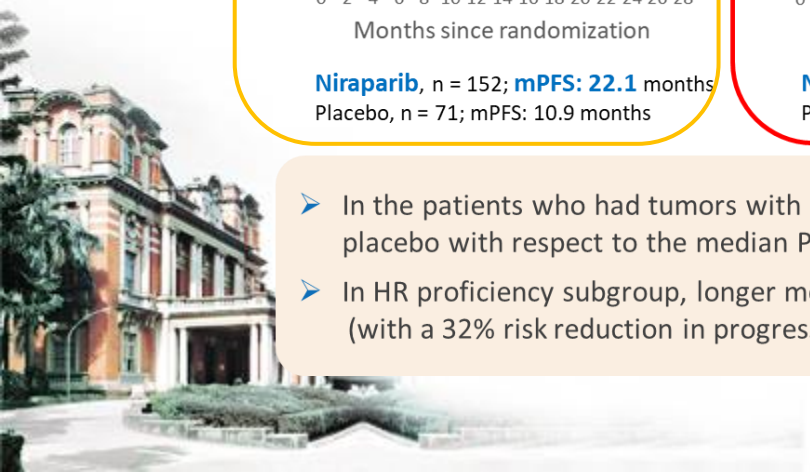
CONCLUSIONS

Among patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy, those who received niraparib had significantly longer progression-free survival than those who received placebo, regardless of the presence or absence of homologous-recombination deficiency. (Funded by GlaxoSmithKline; PRIMA/ENGOT-OV26/GOG-3012 ClinicalTrials.gov number, NCT02655016.)

Subgroup	Niraparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	232/487 (47.6)	155/246 (63.0)	0.62 (0.50–0.76)
Age			
<65 yr	136/297 (45.8)	86/147 (58.5)	0.61 (0.47–0.81)
≥65 yr	96/190 (50.5)	69/99 (69.7)	0.53 (0.38–0.74)
ECOG score			
0	146/337 (43.3)	107/174 (61.5)	0.60 (0.46–0.77)
1	86/150 (57.3)	48/72 (66.7)	0.69 (0.48–1.00)
Stage of disease at initial diagnosis			
III	143/318 (45.0)	103/158 (65.2)	0.54 (0.42–0.70)
IV	89/169 (52.7)	52/88 (59.1)	0.79 (0.55–1.12)
Neoadjuvant chemotherapy			
Yes	151/322 (46.9)	107/167 (64.1)	0.59 (0.46–0.76)
No	81/165 (49.1)	48/79 (60.8)	0.66 (0.46–0.94)
Best response to platinum therapy			
Complete response	146/337 (43.3)	100/172 (58.1)	0.60 (0.46–0.77)
Partial response	86/150 (57.3)	55/74 (74.3)	0.60 (0.43–0.85)
Geographic region			
North America	104/218 (47.7)	82/115 (71.3)	0.50 (0.37–0.68)
All other regions	128/269 (47.6)	73/131 (55.7)	0.72 (0.54–0.96)
Homologous-recombination status			
BRCA mutation	49/152 (32.2)	40/71 (56.3)	0.40 (0.27–0.62)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)	0.50 (0.31–0.83)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)	0.68 (0.49–0.94)
Not determined	40/71 (56.3)	26/40 (65.0)	0.85 (0.51–1.43)

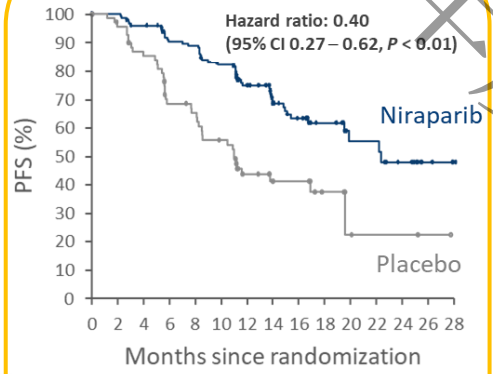


PRIMA: PFS by BRCA/HRD status



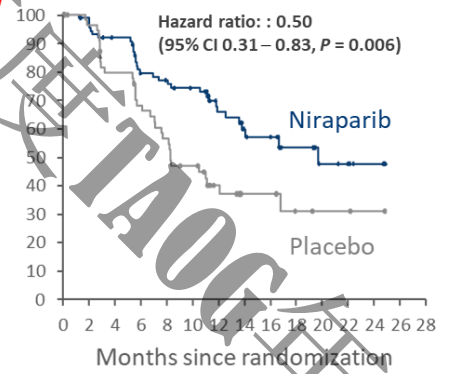
HR deficient

*BRCA*mut



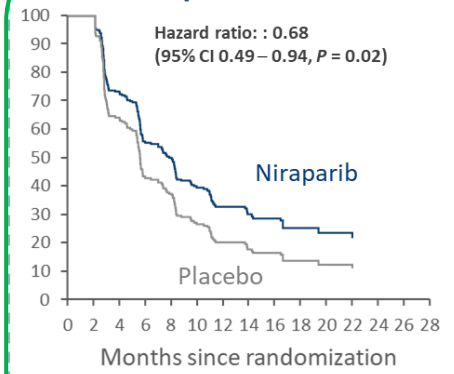
Niraparib, n = 152; **mPFS: 22.1** months
Placebo, n = 71; mPFS: 10.9 months

*BRCA*wt



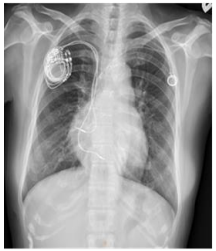
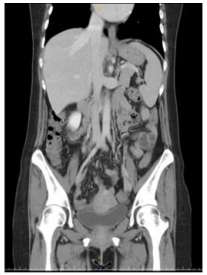
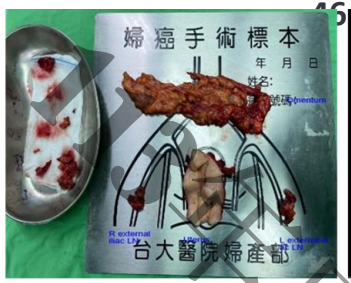
Niraparib, n = 95; **mPFS: 19.6** months
Placebo, n = 55; mPFS: 8.2 months

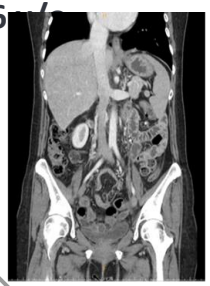
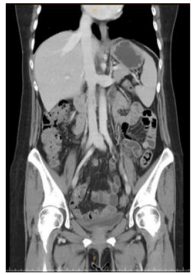
HR proficient



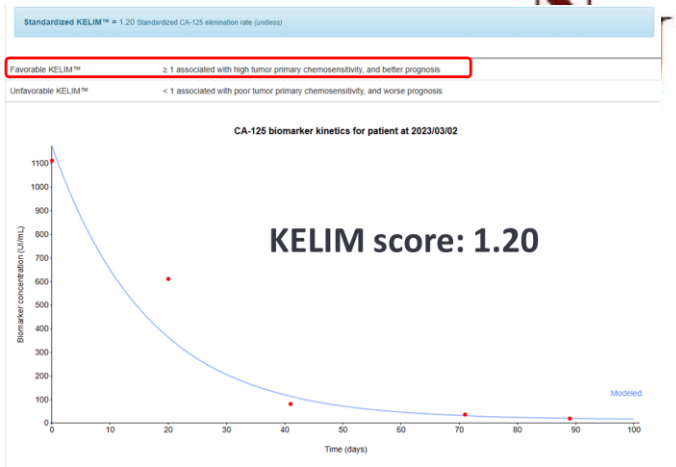
Niraparib, n = 169; **mPFS: 8.1** months
Placebo, n = 80; mPFS: 5.4 months

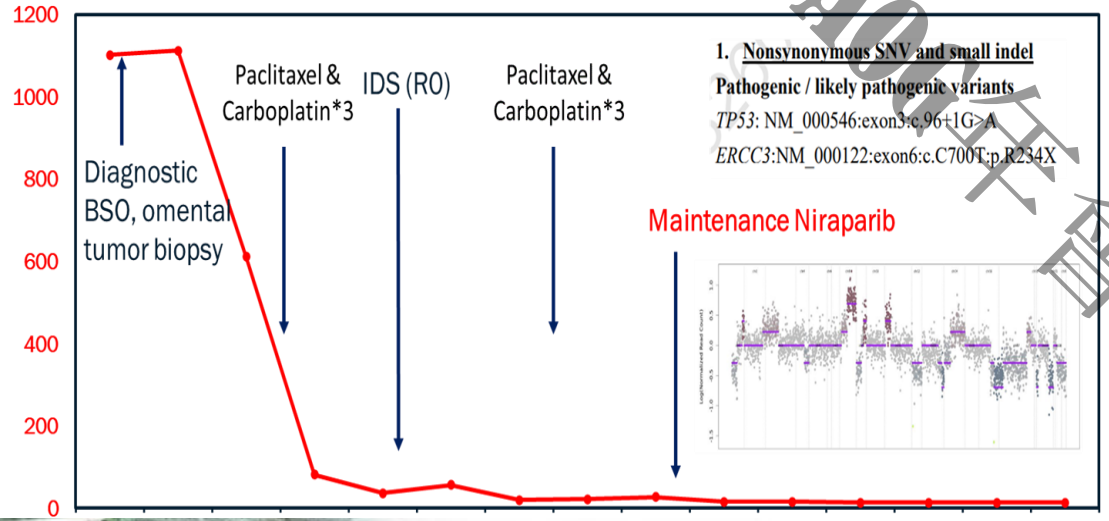
- In the patients who had tumors with **HR deficient**, niraparib provided a **significant clinical benefit** over placebo with respect to the median PFS both in patients with and without *BRCA*mut.
- In HR proficiency subgroup, longer median PFS with niraparib group than with placebo. (with a 32% risk reduction in progression or death)

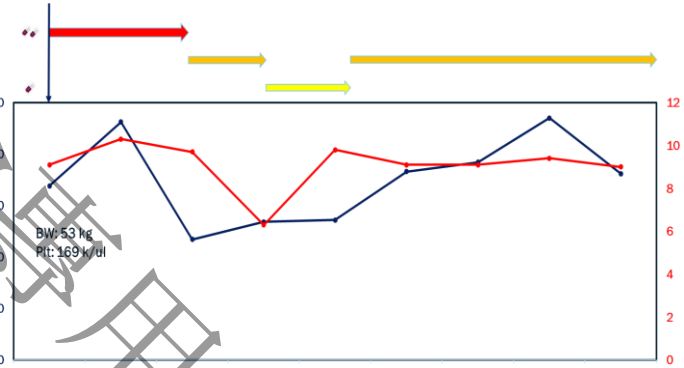




Ovarian high grade serous carcinoma, FIGO stage IIIC
46 y/o







Olaparib

PAOLA-1

N Engl J Med 2019; 381:2416-28

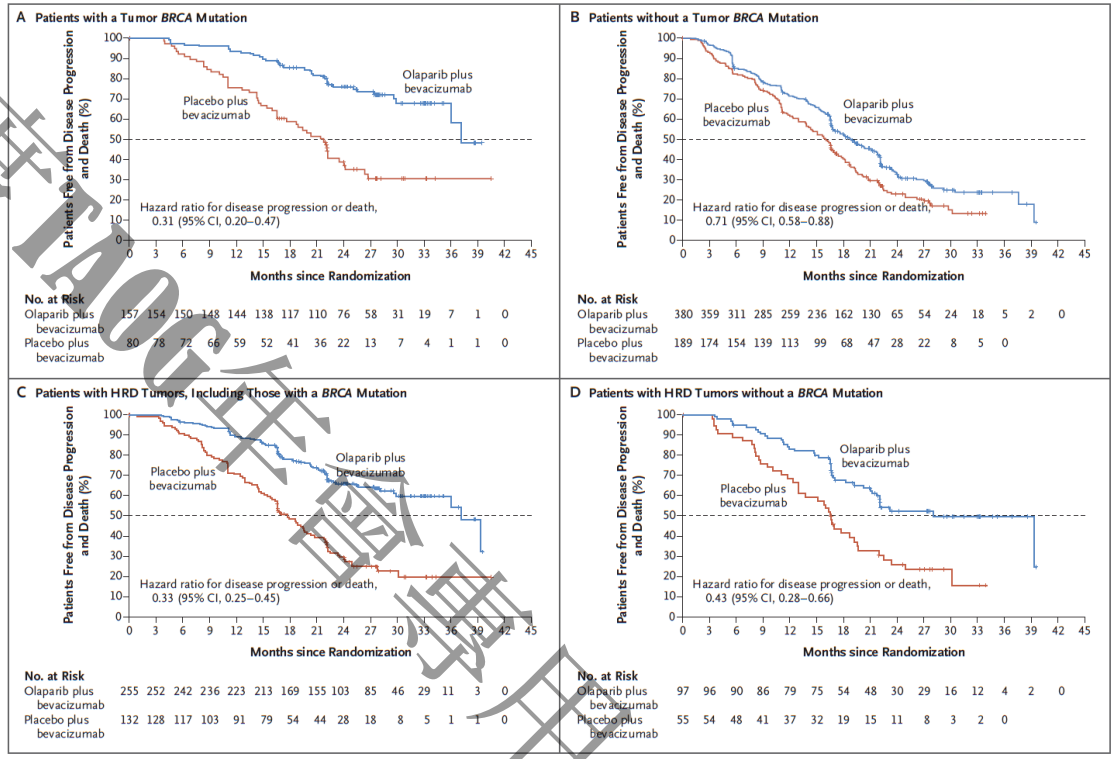
ORIGINAL ARTICLE

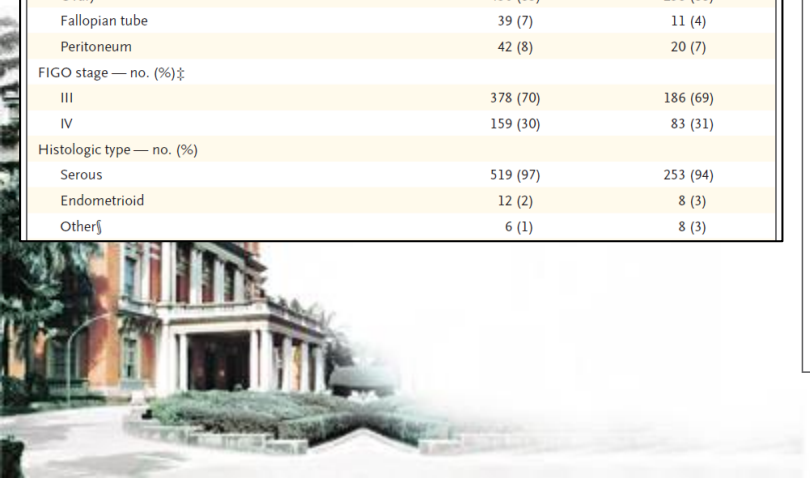
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

- **Stage III / IV HGS/E EOC**
- **CR/PR after platinum-based chemotherapy**

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Olaparib plus Bevacizumab (N=537)	Placebo plus Bevacizumab (N=269)
Median age (range) — yr	61.0 (32.0–87.0)	60.0 (26.0–85.0)
ECOG performance status — no. (%)†		
0	378 (70)	189 (70)
1	153 (28)	76 (28)
Missing data	6 (1)	4 (1)
Primary tumor location — no. (%)		
Ovary	456 (85)	238 (88)
Fallopian tube	39 (7)	11 (4)
Peritoneum	42 (8)	20 (7)
FIGO stage — no. (%)‡		
III	378 (70)	186 (69)
IV	159 (30)	83 (31)
Histologic type — no. (%)		
Serous	519 (97)	253 (94)
Endometrioid	12 (2)	8 (3)
Other§	6 (1)	8 (3)





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Olaparib

PAOLA-1

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ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

CONCLUSIONS

In patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without a *BRCA* mutation. (Funded by ARCAGY Research and others; PAOLA-1 ClinicalTrials.gov number, NCT02477644.)

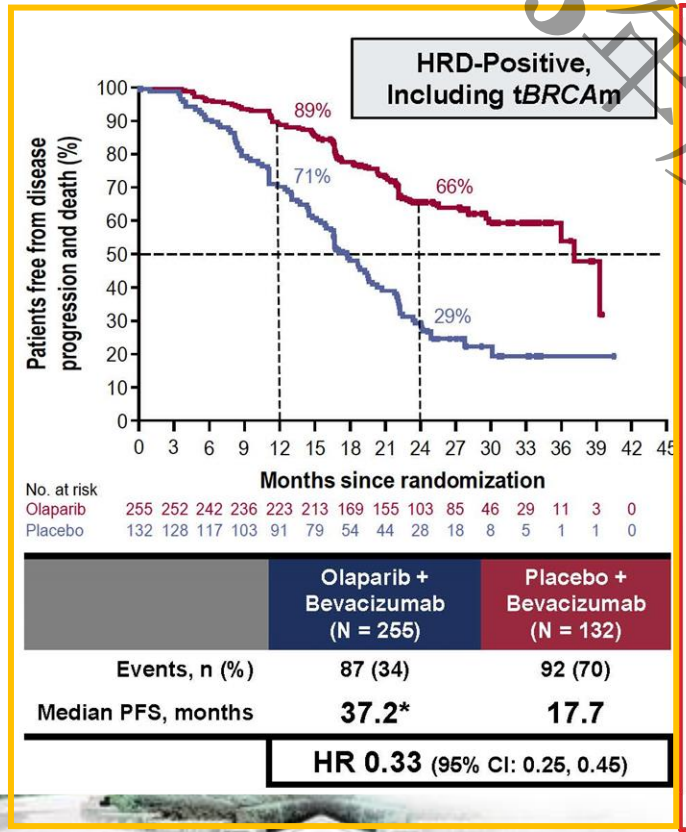
Subgroup	Olaparib plus Bevacizumab	Placebo plus Bevacizumab	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	280/537 (52)	194/269 (72)	0.59 (0.49–0.72)
Age			
<65 yr	171/332 (52)	126/182 (69)	0.61 (0.49–0.77)
≥65 yr	109/205 (53)	68/87 (78)	0.55 (0.41–0.75)
FIGO stage			
III	184/378 (49)	125/186 (67)	0.64 (0.51–0.80)
IV	96/159 (60)	69/83 (83)	0.49 (0.36–0.67)
ECOG performance status at baseline			
0	193/378 (51)	132/189 (70)	0.63 (0.50–0.78)
1	85/153 (56)	61/76 (80)	0.51 (0.37–0.71)
First-line treatment outcome at screening			
NED with complete macroscopic resection at initial cytoreductive surgery	49/158 (31)	46/83 (55)	0.46 (0.31–0.69)
NED or CR with complete macroscopic resection at interval cytoreductive surgery	80/158 (51)	56/75 (75)	0.57 (0.41–0.81)
NED or CR in patients with incomplete resection or no cytoreductive surgery	44/79 (56)	32/36 (89)	0.36 (0.23–0.58)
PR	101/134 (75)	58/73 (79)	0.85 (0.61–1.18)
Cytoreductive surgery outcome			
Cytoreductive surgery with no residual macroscopic disease	135/323 (42)	104/160 (65)	0.54 (0.42–0.71)
Cytoreductive surgery with residual macroscopic disease	113/176 (64)	71/88 (81)	0.63 (0.47–0.85)
No cytoreductive surgery	32/38 (84)	19/21 (90)	0.56 (0.32–1.01)
Timing of cytoreductive surgery			
Upfront	116/271 (43)	92/138 (67)	0.52 (0.40–0.69)
Interval	132/228 (58)	83/110 (75)	0.66 (0.50–0.87)
No cytoreductive surgery	32/38 (84)	19/21 (90)	0.57 (0.32–1.02)
Response to first-line chemotherapy			
NED	119/290 (41)	92/141 (65)	0.53 (0.40–0.70)
CR	54/106 (51)	42/53 (79)	0.44 (0.29–0.66)
PR	107/141 (76)	60/75 (80)	0.86 (0.63–1.19)
CA-125 value			
≤ULN	220/463 (48)	163/234 (70)	0.55 (0.45–0.68)
>ULN	60/74 (81)	30/34 (88)	0.72 (0.47–1.13)
Tumor *BRCA* mutation status			
BRCA mutation	41/157 (26)	49/80 (61)	0.31 (0.20–0.47)
No *BRCA* mutation or unknown	239/380 (63)	145/189 (77)	0.71 (0.58–0.88)
Tumor HRD status			
Positive	87/255 (34)	92/132 (70)	0.33 (0.25–0.45)
Negative	145/192 (76)	66/85 (78)	1.00 (0.75–1.35)
Negative or unknown	193/282 (68)	102/137 (74)	0.92 (0.72–1.17)
Unknown	48/90 (53)	36/52 (69)	0.71 (0.46–1.10)

0.2 0.5 1.0 2.0

← Olaparib plus Bevacizumab Better | Placebo plus Bevacizumab Better →

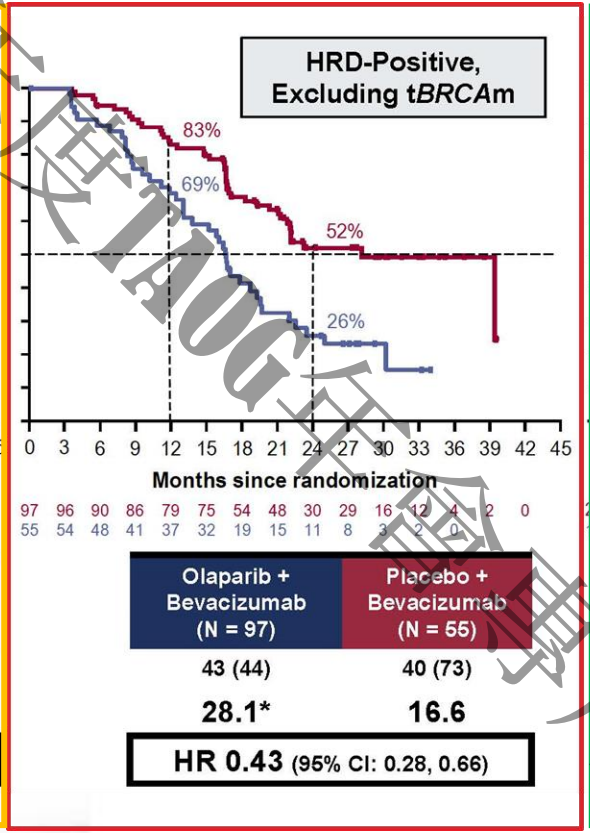
N Engl J Med 2019; 381:2416-28

PAOLA-1: PFS by BRCA/HRD status



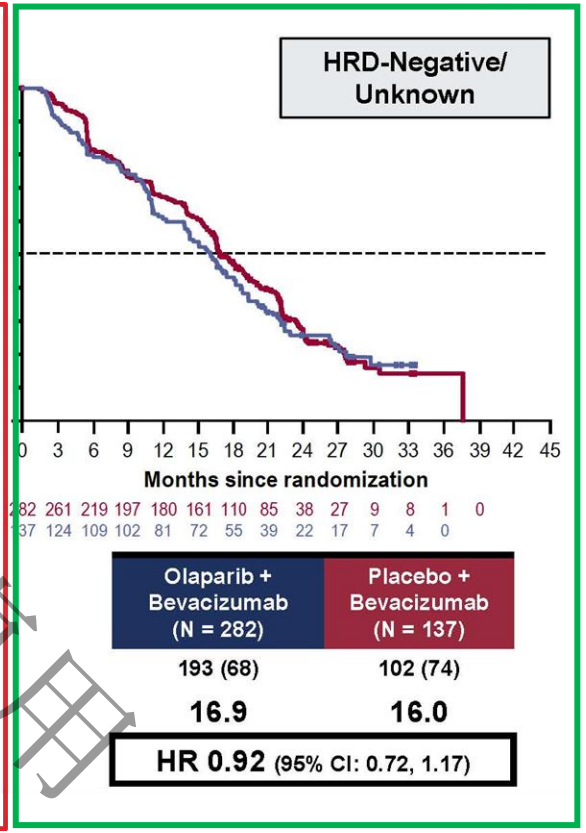
	Olaparib + Bevacizumab (N = 255)	Placebo + Bevacizumab (N = 132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2*	17.7

HR 0.33 (95% CI: 0.25, 0.45)



	Olaparib + Bevacizumab (N = 97)	Placebo + Bevacizumab (N = 55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1*	16.6

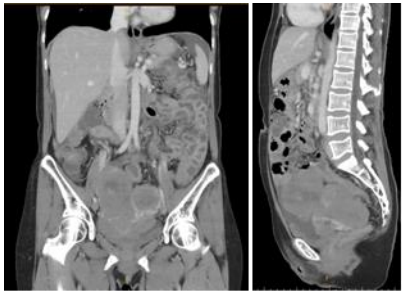
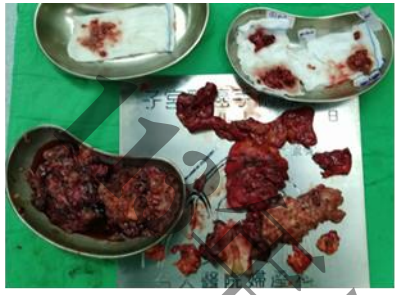
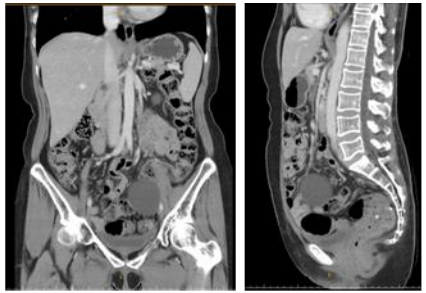
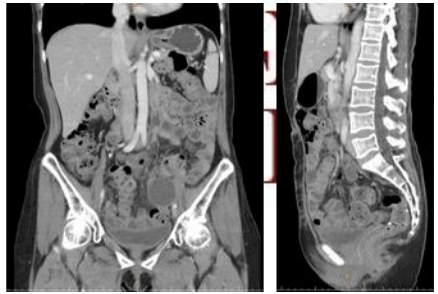
HR 0.43 (95% CI: 0.28, 0.66)



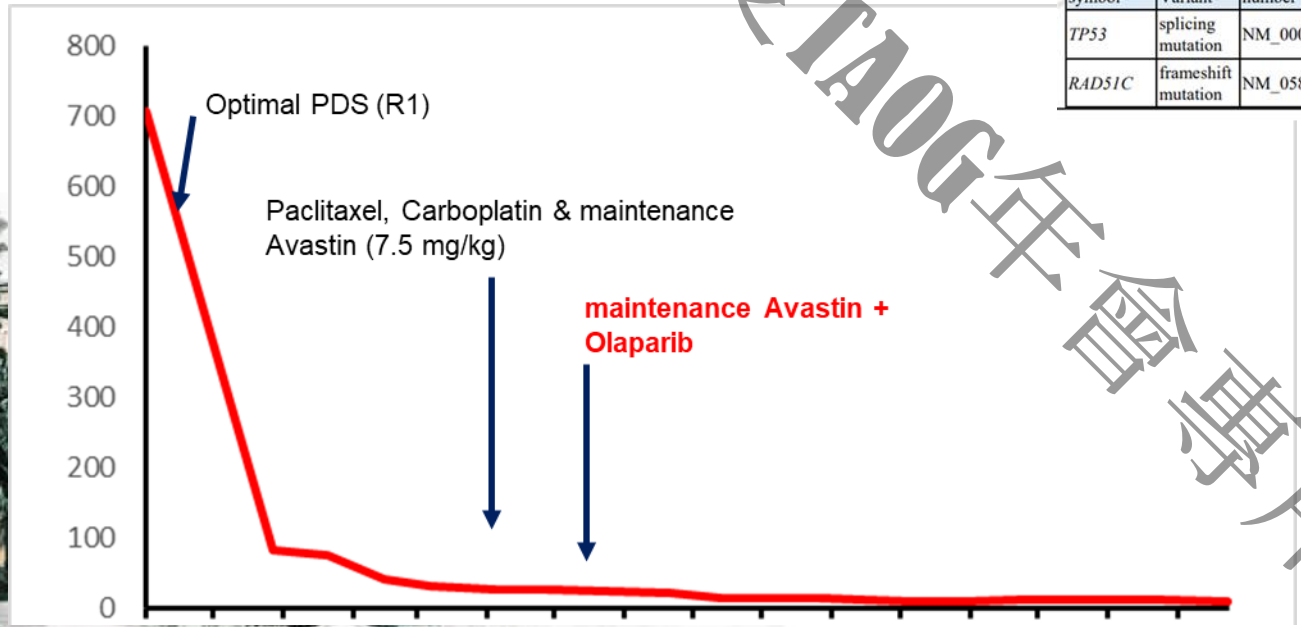
	Olaparib + Bevacizumab (N = 282)	Placebo + Bevacizumab (N = 137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	16.9	16.0

HR 0.92 (95% CI: 0.72, 1.17)

N Engl J Med 2019; 381:2416-2428

Ovarian high grade serous carcinoma, stage IIIC
56 y/o



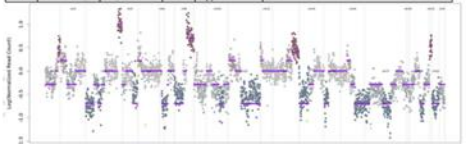
1. Nonsynonymous SNV and small indel

Pathogenic / likely pathogenic variants

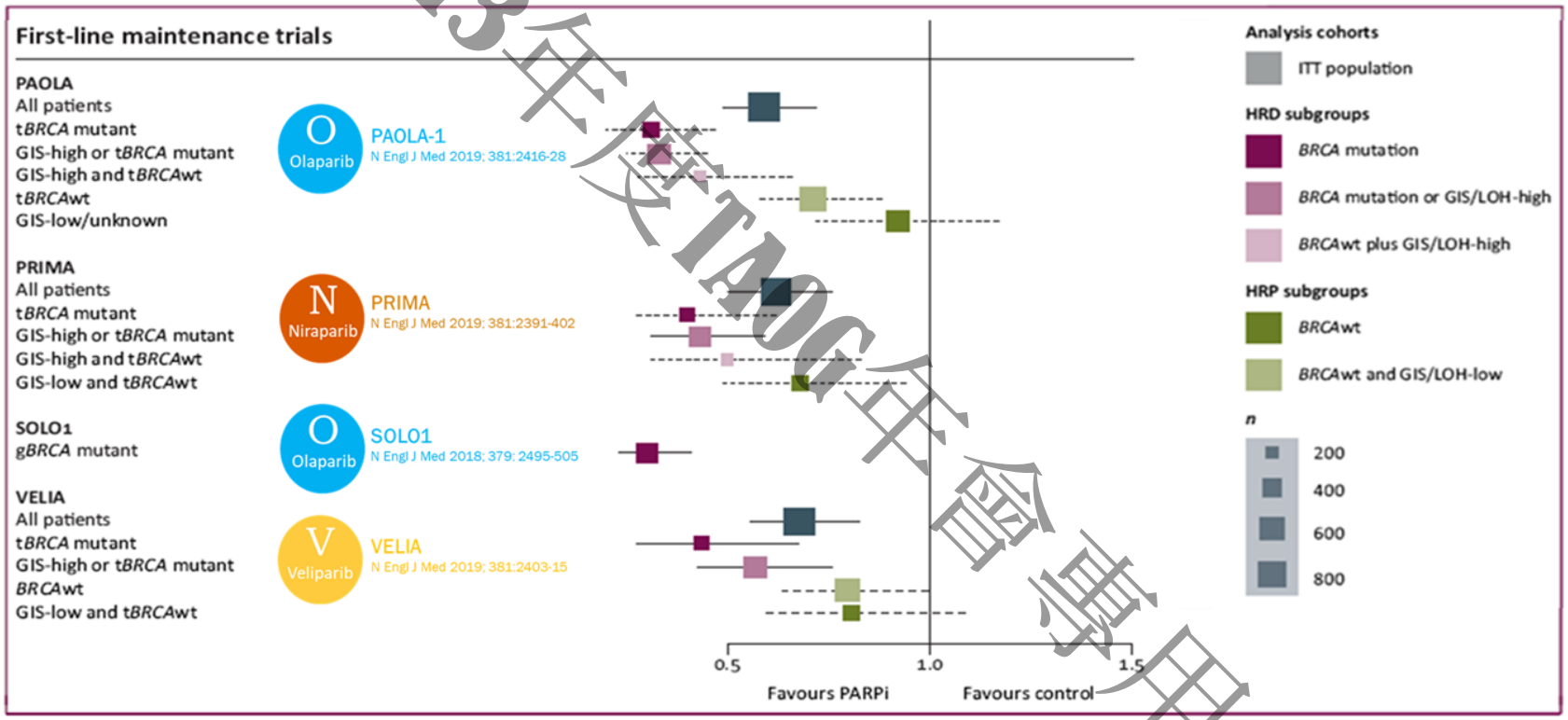
Gene symbol	Type of Variant	Accession number	cDNA	Protein	dbSNP150	Mutation frequency	Clinical significance
TP53	splicing mutation	NM_000546	c.375+2_375+16del		.	0.73	likely pathogenic
RAD51C	frameshift mutation	NM_058216	c.394dupA	p.T132fs	*rs730881940*	0.83	Pathogenic

2. Copy number variation

Chr	Start	End	Type	Copy number	Gene
chr1	241661194	241683006	Gain	copy=3	*FH*
chr2	29416153	29416830	Gain	copy=3	*ALK*
chr3	10070332	10191562	Loss	copy=1	*FANCD2,VHL*
chr3	37042461	52436374	Loss	copy=1	*MLH1,BAP1*
chr3	178916694	178952190	Gain	copy=5.5	*PIK3CA*
chr4	169433575	169847545	Loss	copy=1	*PALLD*
chr6	35434011	43582275	Loss	copy=1	*FANCE,POLH*
chr7	6017256	6043668	Loss	copy=1	*PMS2*
chr8	15967635	31030550	Loss	copy=1	*MSR1,WRN*
chr8	118812059	145742018	Gain	copy=4.5	*EXT1,RECQL4*
chr8	145742057	145743014	Gain	copy=3	*RECQL4*
chr10	73862768	88683375	Loss	copy=1	*ASCC1,BMPR1A*
chr11	64577457	108122750	Loss	copy=1	*MEN1,MRE11,ATM*
chr11	108123523	108150304	Loss	copy=1	*ATM*
chr11	108151802	125525232	Loss	copy=1	*ATM,SDHD,CHEK1*
chr13	49051574	108863437	Gain	copy=3	*RB1,BIVM-ERCC5,LIG4*
chr14	45609928	45644469	Loss	copy=1	*FANCM*
chr14	45644648	68353900	Loss	copy=1	*FANCM,RAD51B*
chr15	40457405	40491832	Loss	copy=1	*BUB1B*
chr15	40492542	40512996	Loss	copy=1	*BUB1B*
chr16	68771247	89883011	Loss	copy=1	*CDH1,FANCA*
chr17	7572937	17131303	Loss	copy=1	*TP53,FLCN*
chr17	33430447	41251902	Loss	copy=1	*RAD51L3-RFFL,BRCA1*
chr17	41256166	41258481	Loss	copy=0.5	*BRCA1*
chr19	33793120	45873555	Loss	copy=1	*CEBPA,ERCC2*
chr21	36164511	36421130	Gain	copy=3.5	*RUNX1*
chr22	24129412	30000088	Loss	copy=1	*SMARCB1,CHEK2,NF2*
chr22	30000145	30090945	Loss	copy=1	*NF2*

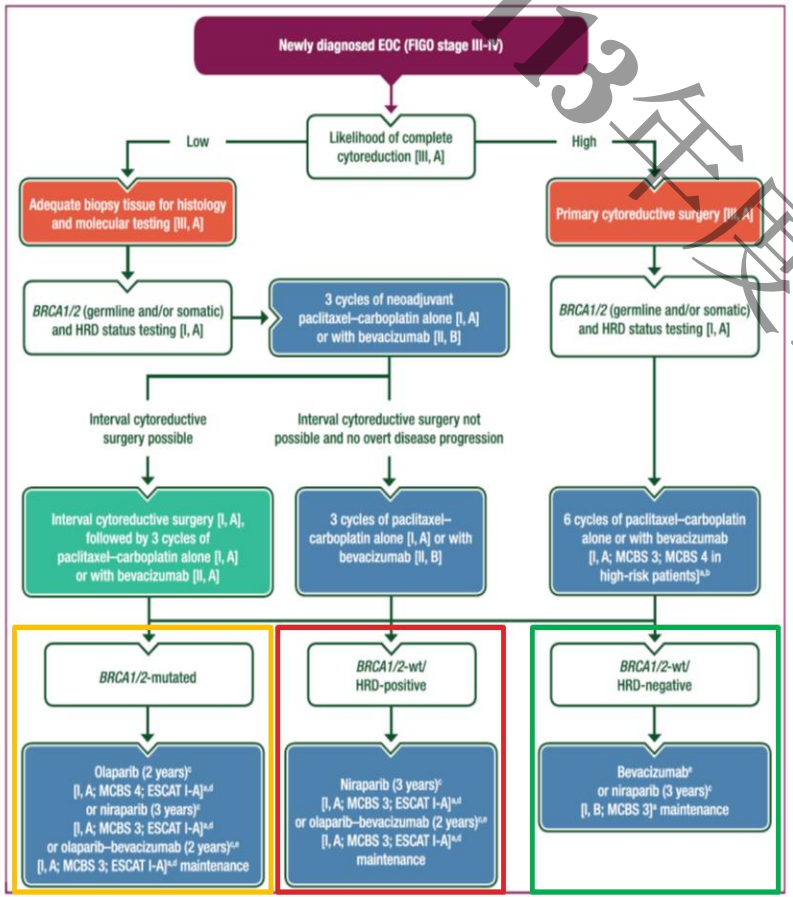


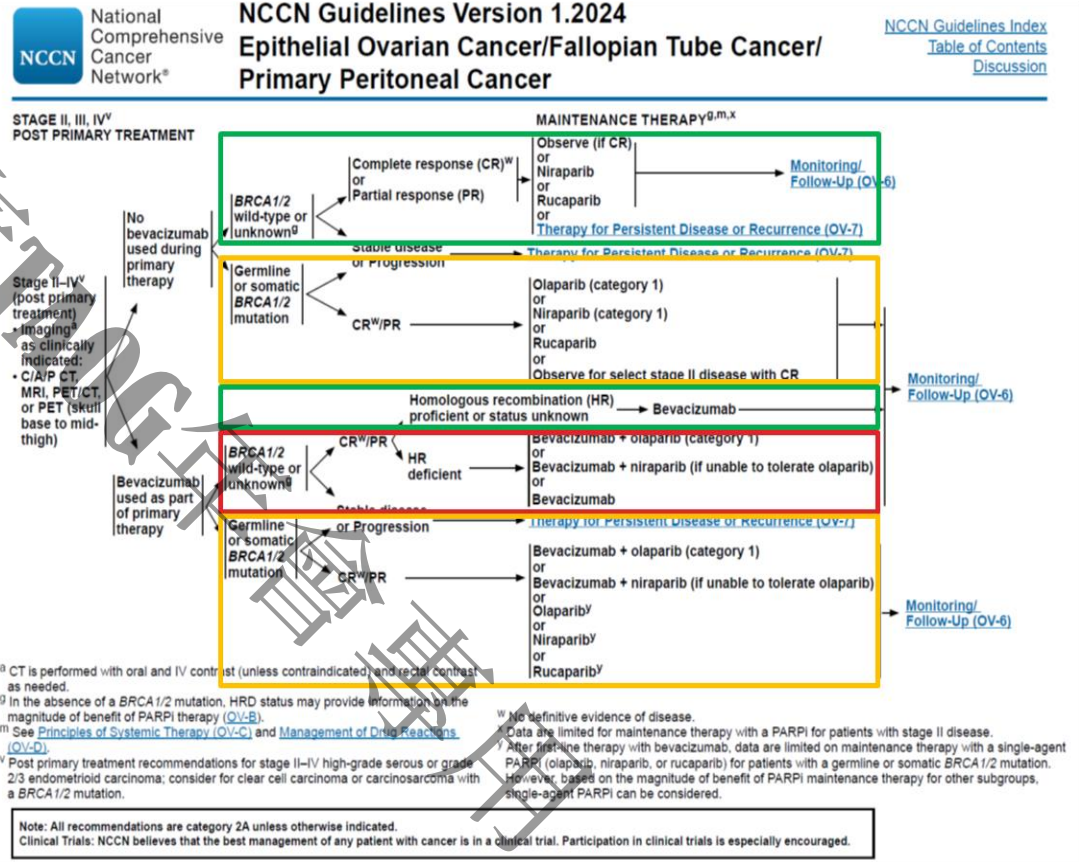
Newly Diagnosed Advanced EOC



Ann Oncol 2020 (12)1606-1622

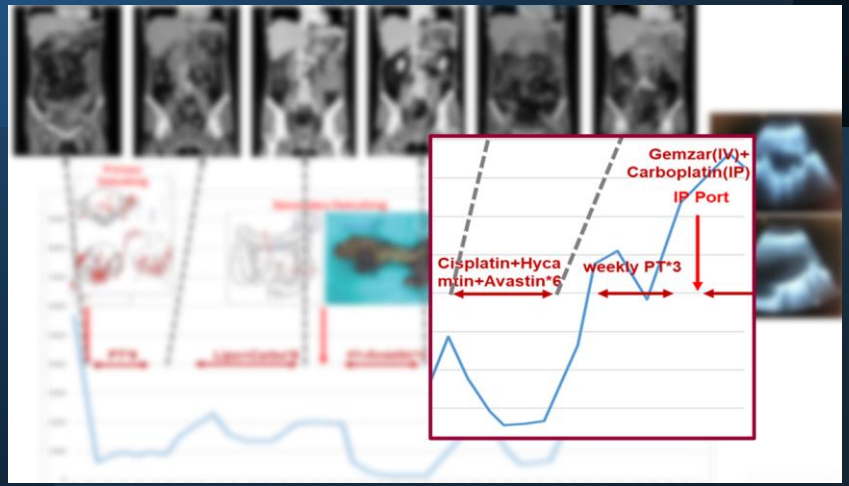
Maintenance Therapy in Epithelial Ovarian Cancer



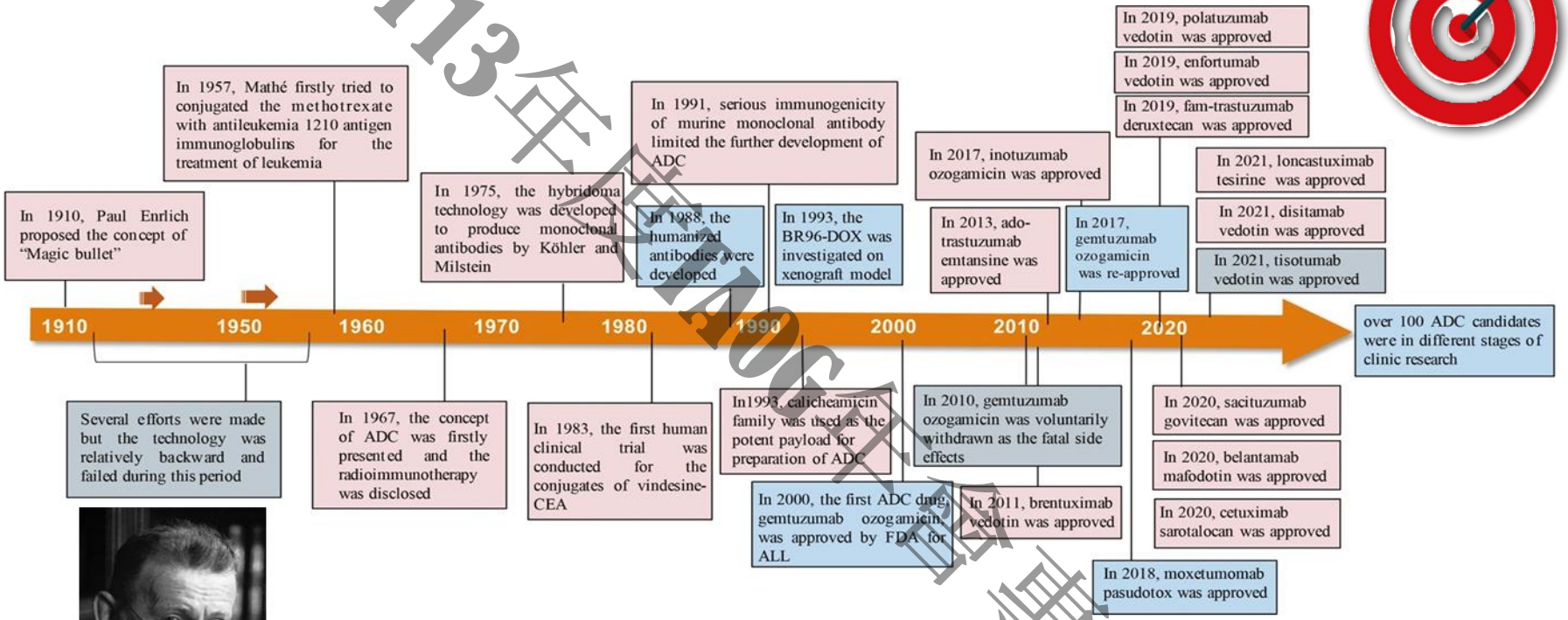


NCCN Guidelines Version 1.2024
Ann Oncol. 2023 Oct;34(10):833-848

New promising Therapy in Epithelial Ovarian Cancer - ADC



Magic Bullets



AS EARLY AS THE BEGINNING OF 20TH CENTURY, PAUL EHRLICH FIRST PROPOSED THE CONCEPT OF "MAGIC BULLETS"

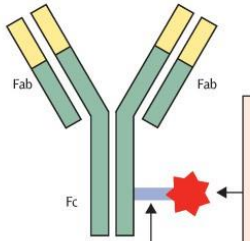
Paul Ehrlich was a Nobel Prize-winning German physician and scientist who worked in the fields of hematology, immunology, and antimicrobial chemotherapy. Among his foremost achievements were finding a cure for syphilis in 1909 and inventing the precursor technique to Gram staining bacteria.

Fu, Z., Li, S., Han, S. *et al.* Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Sig Transduct Target Ther* **7**, 93 (2022). https://doi.org/10.1038/s41392-022-00947-7

Antibody-Drug Conjugates (ADCs)

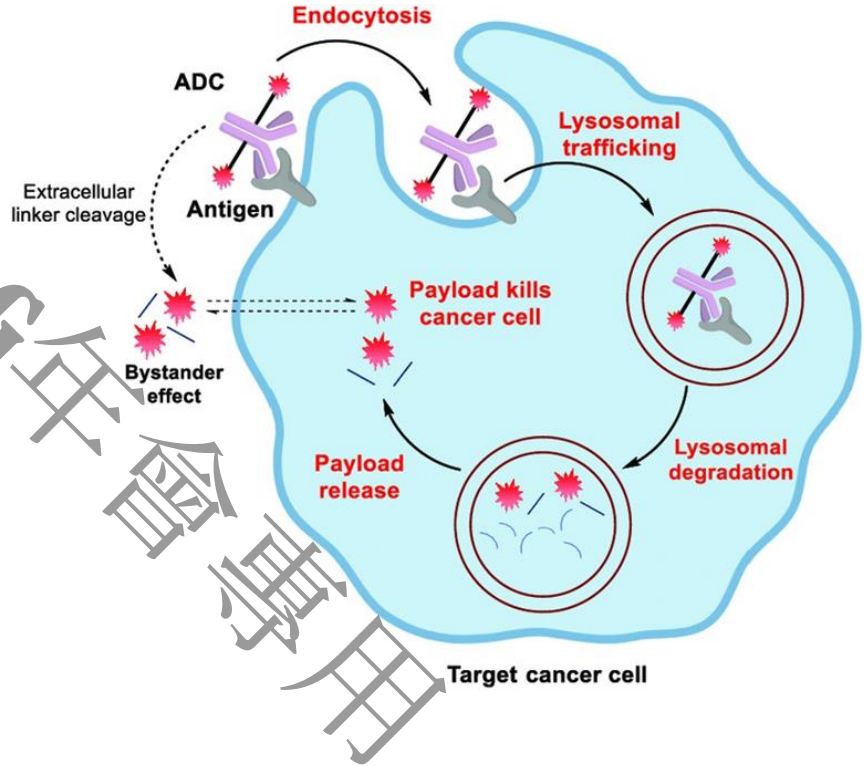
Antigen
- High homogeneous expression on tumour
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumour antigen
- Chimeric or humanised to decrease immunogenicity
- Long half-life and high molecular weight



Cytotoxic payload
- Highly potent agents—IC50 in subnanomolar range:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (monomethyl auristatin E or monomethyl auristatin F)
- Optimal DAR

Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at non-target tissue
- Efficient linker technology
  - Cleavable versus non-cleavable
- Site of conjugation
  - DAR affects drug distribution and pharmacokinetics



Chau CH, Steeg PS, Figg WD. Antibody-drug conjugates for cancer. Lancet. 2019 Aug 31;394(10200):793-804.

ADCs in gynecological malignancies

ADC	Target	Antibody	Linker	Payload
Mirvetuximab soravtansine	FRα	IgG1-kappa	Cleavable	DM4
MORAb-202	FRα	IgG1-kappa (farletuzumab)	Cleavable	Eribulin
Anetumab ravtansine	Mesothelin	IgG1-lambda	Cleavable	DM4
Tisotumab vedotin	Tissue factor	IgG1-kappa	Cleavable	MMAE
Lifastuzumab vedotin	NaPi2B	IgG1	Cleavable	MMAE
Trastuzumab emtansine (T-DM1)	HER2	IgG1	Non cleavable	DM1
Trastuzumab duocarmazine (SYD985)	HER2	IgG1	Cleavable	Duocarmicyn
Trastuzumab deruxtecan (T-DXd)	HER2	IgG1	Cleavable	Topoisomerase 1 inhibitor
Sacituzumab govitecan	Trop2	IgG1-kappa	Cleavable	SN38

Table 2
Select ADCs under clinical investigation in gynecologic malignancies.

Target	ADC	Study	Patient Population	Estimated Primary Completion Date
B7-H4	XMT-1660	Phase I NCT05377996	Recurrent, advanced, or metastatic tumors, including ovarian, peritoneal, Fallopian tube, and endometrial cancer	January 2025
	AZD8205	Phase I/II NCT05123482	Advanced or metastatic solid malignancies, including serous ovarian cancer and endometrial cancer	May 2025
	SGN-B7H4V	Phase I NCT05194072	Unresectable, locally advanced or metastatic solid tumors, including ovarian, peritoneal, fallopian tube, and endometrial cancer	June 2025
FRα	STRO-002	Phase I NCT03748186	Relapsed and/or progressive high-grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer	August 2022
	STRO-002	Phase I NCT05200364	With bevacizumab in relapsed and/or progressive high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer	December 2023
	Mirvetuximab soravtansine (Mirv)	Phase II NCT03835819	With pembrolizumab in patients with FRα-positive microsatellite stable recurrent or persistent endometrial cancer	October 2023
		Phase II NCT04606914	With carboplatin in first-line treatment of patients receiving neoadjuvant chemotherapy with advanced-stage high-grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer who are FRα-positive	May 2023
		Phase II NCT05456685	With carboplatin in FRα-positive, recurrent platinum sensitive, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer following 1 prior line of platinum-based chemotherapy	June 2024
		Phase II PICCOLO NCT05041257	FRα-positive, platinum-sensitive, high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer	May 2023
		Phase III MIRASOL NCT04209855	Vs investigator's choice of chemotherapy in FRα-positive, platinum-resistant, high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer	December 2022
		Phase III GLORIOSA NCT05445778	With bevacizumab vs bevacizumab alone as maintenance in FRα-positive, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer	March 2027
	Farletuzumab ecteribulin (MORAb-202)	Phase I/II NCT04300556	Platinum-resistant advanced, recurrent or metastatic endometrial cancer Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	March 2025
HER2	Trastuzumab duocarmazine (SYD985)	Phase II NCT04205630	HER2-expressing recurrent, advanced or metastatic endometrial carcinoma	December 2022
	Trastuzumab deruxtecan (T-DXd)	Phase I NCT04585958	With olaparib in HER2-expressing advanced cancers or endometrial cancer	January 2023
HER2 Trop-2	Trastuzumab deruxtecan (T-DXd) Datopotamab deruxtecan (Dato-DXd)	Phase I/II PETRA NCT04644068	With AZD5305 PARP inhibitor in ovarian, cervical, and endometrial cancers	July 2025
Mesothelin	Anetumab ravtansine	Phase II NCT02587311	With bevacizumab vs bevacizumab + paclitaxel in platinum-resistant or platinum refractory high-grade serous endometrioid, ovarian, fallopian tube, or primary peritoneal cancer	October 2023
NaPi2b	Upifitamab rilsodotin (UpRi)	Phase I ORIGRADE NCT04907968	With carboplatin in platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer	November 2024
		Phase II UPLIFT NCT03319628	Platinum-resistant metastatic or recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer	April 2023
		Phase III UP-NEXT NCT05329545	In platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer expressing high levels of NaPi2b	September 2024
Trop-2	Sacituzumab govitecan (IMMU-132)	Phase II NCT04251416	Persistent or recurrent endometrial carcinoma that progressed after prior platinum-based chemotherapy or is platinum-refractory with elevated Trop-2 expression	February 2024
	SKB264	Phase I/II NCT04152499	Locally advanced unresectable/metastatic solid tumors including epithelial ovarian cancer refractory to available standard therapies	November 2024

Explor Target Antitumor Ther. 2022;3:149–71
Cancer Treatment Reviews 116 (2023) 102546

Table 1
ADCs currently approved in oncology in the United States and the European Union.

ADC	Target Antigen	mAb	Linker	Payload	Indication	Approval
Tisotumab vedotin (Tivdak®)	Tissue factor	IgG1	Val-Cit	MMAE	Recurrent or metastatic cervical cancer	FDA: September 2021
Brentuximab vedotin (Adcetris®)	CD30	Chimeric IgG1	Val-Cit	MMAE	Relapsed/refractory and previously untreated stage III/IV Hodgkin lymphoma Relapsed/refractory and untreated systemic anaplastic large cell lymphoma	FDA: August 2011 EMA: October 2012
Trastuzumab emtansine (Kadcyla®)	HER2	IgG1k	MCC	DM1	Metastatic HER2-positive breast cancer	FDA: February 2013 EMA: November 2013
Inotuzumab ozogamicin (Besponsa®)	CD22	IgG4	Cleavable acid-labile acetyl butyrate	Calicheamicin	Relapsed/refractory B-cell acute lymphoblastic lymphoma	FDA: August 2017 EMA: June 2017
Gemtuzumab ozogamicin (Mylotarg®)	CD33	IgG4 k	Cleavable acid-labile acetyl butyrate	Calicheamicin	CD33-positive acute myeloid leukemia	FDA: September 2017 EMA: April 2018
Polatuzumab vedotin (Polivy®)	CD79b	IgG1	Val-Cit	MMAE	Diffuse large B-cell lymphoma	FDA: June 2019 EMA: January 2020
Enfortumab vedotin (Padcev®)	Nectin-4	IgG1 k	Val-Cit	MMAE	Locally advanced/metastatic urothelial cancer	FDA: December 2019 EMA: April 2022
Trastuzumab deruxtecan (Enhertu®)	HER2	IgG1	Maleimide–GGFG	DXd	Unresectable/metastatic HER2-positive and HER2-low breast cancer; unresectable/metastatic non-small cell lung cancer	FDA: December 2019 EMA: January 2021
Sacituzumab govitecan (Trodelvy®)	Trop-2	IgG1 k	CL2A	SN-38	Unresectable/metastatic triple negative breast cancer	FDA: April 2020 EMA: November 2021
Belantamab mafodotin (Blenrep®)	BCMA	IgG1	MC	MMAF	Relapsed or refractory multiple myeloma	FDA: August 2020 then withdrawn[a] EMA: August 2020
Loncastuximab tesirine (Zynlonta®)	CD19	IgG1 k	Val-Ala	SG3199/PBD dimer	Relapsed/refractory large B-cell lymphoma; diffuse large B-cell lymphoma	FDA: April 2021
Mirvetuximab soravtansine (Elahere™)	FRα	IgG1	Sulfo-SPDB cleavable linker	DM4	FRα-positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	FDA: November 2022

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

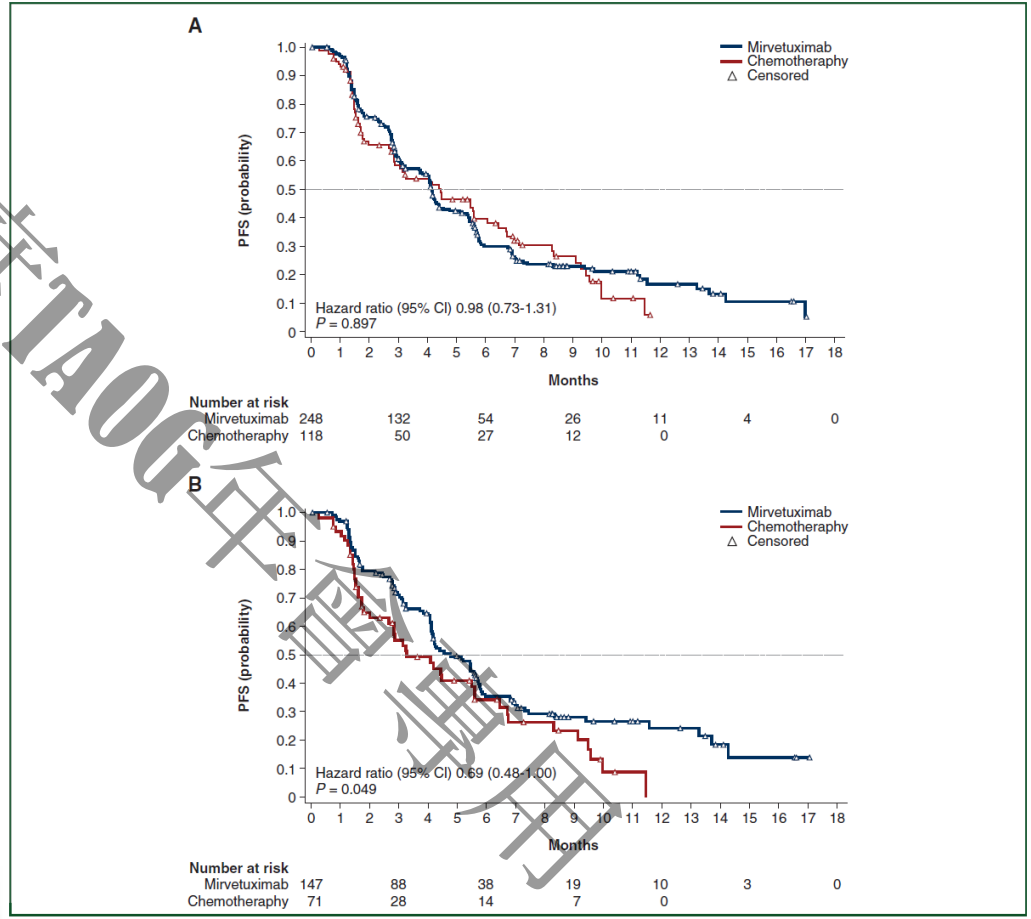
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I

Table 1. Baseline characteristics in the intention-to-treat population

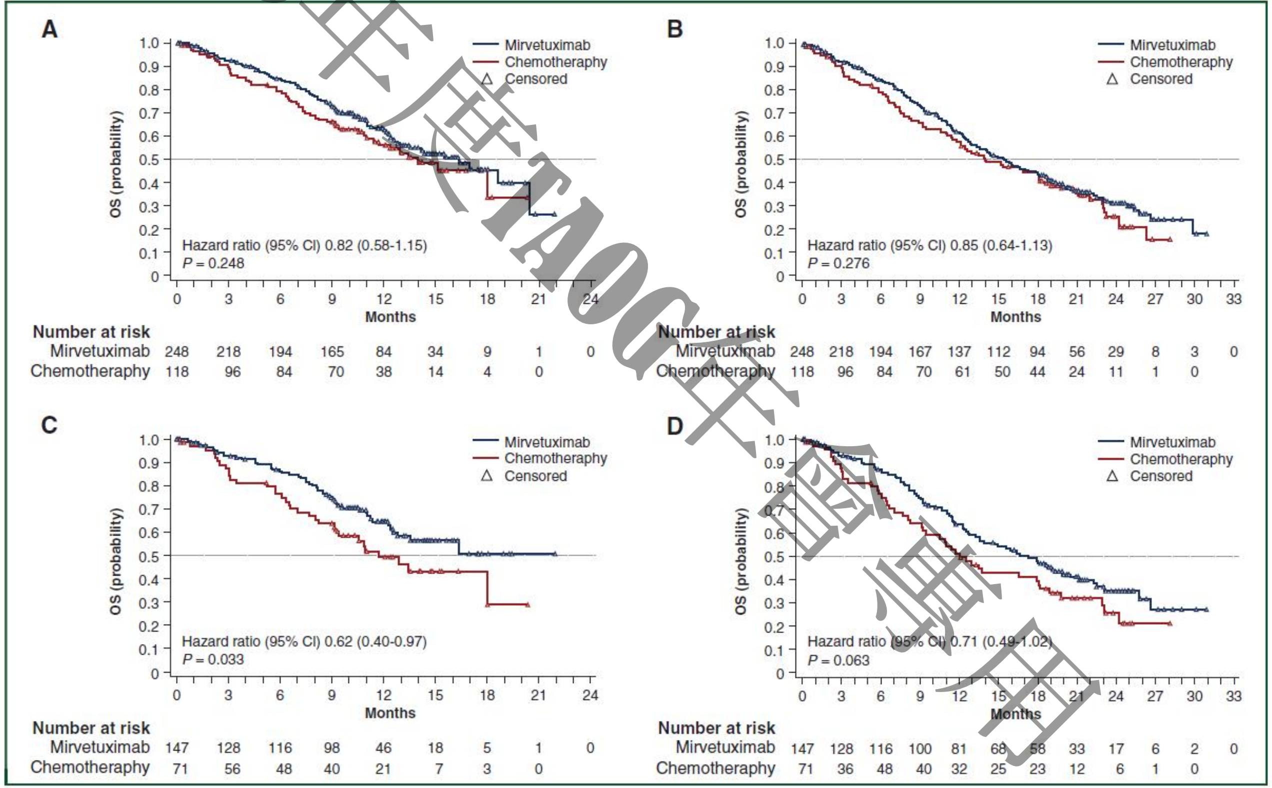
Characteristic	Mirvetuximab soravtansine (n = 248)	IC chemotherapy (n = 118)
Age, years		
Median	64	64
Range	34-89	31-86
Primary cancer diagnosis		
Epithelial ovarian cancer	207 (83.5)	105 (89.0)
Fallopian tube cancer	14 (5.6)	5 (4.2)
Primary peritoneal cancer	27 (10.9)	8 (6.8)
EOC Histology		
High-grade serous	245 (98.8)	114 (96.6)
Endometrioid	0	1 (0.8)
Serous adenocarcinoma	2 (0.8)	3 (2.5)
Mixed serous and carcinoma	1 (0.4)	0
ECOG PS[a]		
0	141 (56.9)	60 (50.8)
1	106 (42.7)	57 (48.3)
No. of prior systemic therapies[b]		
1 or 2	159 (64.1)	74 (62.7)
3	86 (34.7)	43 (36.4)
FRα expression[c]		
High	147 (59.3)	71 (60.2)
Medium	101 (40.7)	46 (39.0)
Prior exposure		
Paclitaxel	238 (96.0)	113 (95.8)
Bevacizumab	121 (48.8)	55 (46.6)
PARP inhibitor	44 (17.7)	19 (16.1)



Ann Oncol. 2021 Jun;32(6):757-765.

Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I

Conclusions: In patients with platinum-resistant EOC, MIRV did not result in a significant improvement in PFS compared with chemotherapy. Secondary endpoints consistently favored MIRV, particularly in patients with high FRα expression. MIRV showed a differentiated and more manageable safety profile than chemotherapy.



Ann Oncol. 2021 Jun;32(6):757-765.

“High” FRα tumor expression:

VENTANA FOLR1 (FOLR1-2.1) RxDx assay

≥75% of viable tumor cells with moderate [2+] or strong [3+] staining intensity

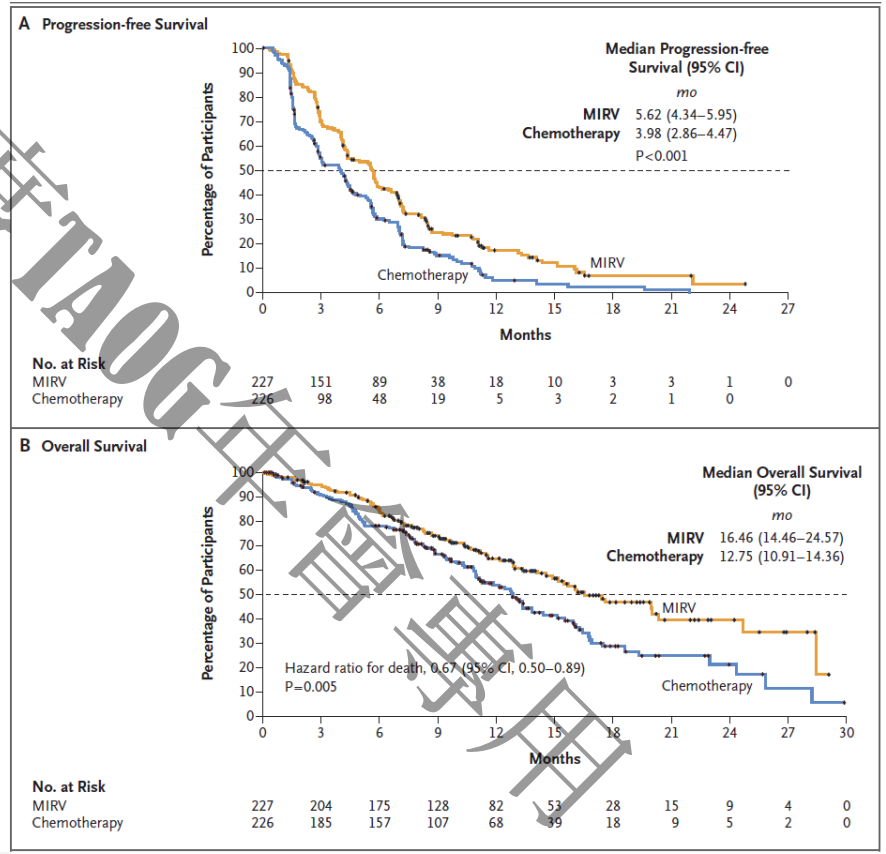
The NEW ENGLAND JOURNAL of MEDICINE

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

MIRASOL trial

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	MIRV (N=227)	Chemotherapy (N=226)
Age		
Median (range) — yr	64 (32–88)	62 (23–87)
≥65 yr — no. (%)	107 (47.1)	92 (40.7)
Primary cancer diagnosis — no. (%)		
Epithelial ovarian cancer	182 (80.2)	182 (80.5)
Fallopian tube cancer	27 (11.9)	23 (10.2)
Primary peritoneal cancer	16 (7.0)	20 (8.8)
Other	2 (0.9)	1 (0.4)
Stage at initial diagnosis — no. (%)‡		
IA or IIA	7 (3.1)	1 (0.4)
IIB or IIC	2 (0.9)	8 (3.5)
IIIA	14 (6.2)	16 (7.1)
IIIB	16 (7.0)	11 (4.9)
IIIC	107 (47.1)	120 (53.1)
IV	76 (33.5)	65 (28.8)
Missing data	5 (2.2)	5 (2.2)
BRCA mutation — no. (%)		
BRCA1 positive	24 (10.6)	29 (12.8)
BRCA2 positive	9 (4.0)	7 (3.1)
Negative or unknown	198 (87.2)	190 (84.1)
Previous lines of systemic therapy		
1	29 (12.8)	34 (15.0)
2	90 (39.6)	88 (38.9)
3	108 (47.6)	104 (46.0)
Previous exposure — no. (%)		
Bevacizumab	138 (60.8)	143 (63.3)
PARP inhibitor	124 (54.6)	127 (56.2)
Taxane	227 (100)	224 (99.1)
Doxorubicin or pegylated liposomal doxorubicin	130 (57.3)	133 (58.8)
Topotecan	1 (0.4)	2 (0.9)
Primary platinum-free interval — no. (%)¶		
≤12 mo	146 (64.3)	142 (62.8)
>12 mo	80 (35.2)	84 (37.2)
Missing data	1 (0.4)	0
Platinum-free interval — no. (%)‖		
≤3 mo	88 (38.8)	99 (43.8)
>3 to ≤6 mo	138 (60.8)	124 (54.9)
>6 mo	1 (0.4)	3 (1.3)



N Engl J Med 2023;389:2162-74.

The NEW ENGLAND JOURNAL of MEDICINE

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

MIRASOL trial

CONCLUSIONS

Among participants with platinum-resistant, FRα-positive ovarian cancer, treatment with MIRV showed a significant benefit over chemotherapy with respect to progression-free and overall survival and objective response. (Funded by ImmunoGen; MIRASOL ClinicalTrials.gov number, NCT04209855.)

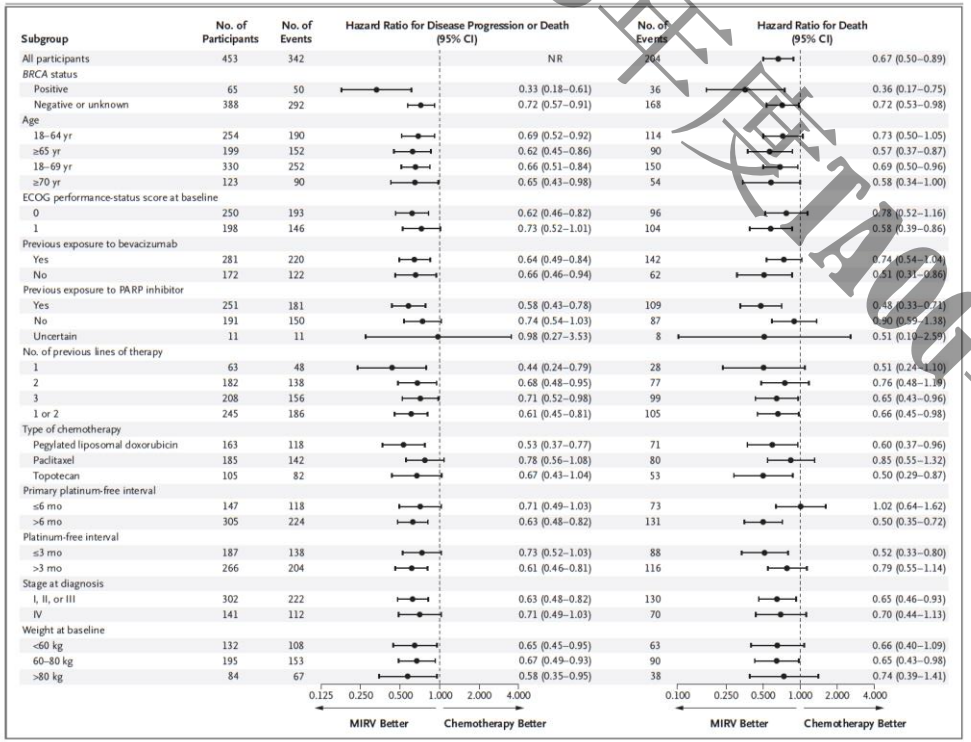


Table 3. Adverse Events That Occurred during the Treatment Period in the Safety Population.*

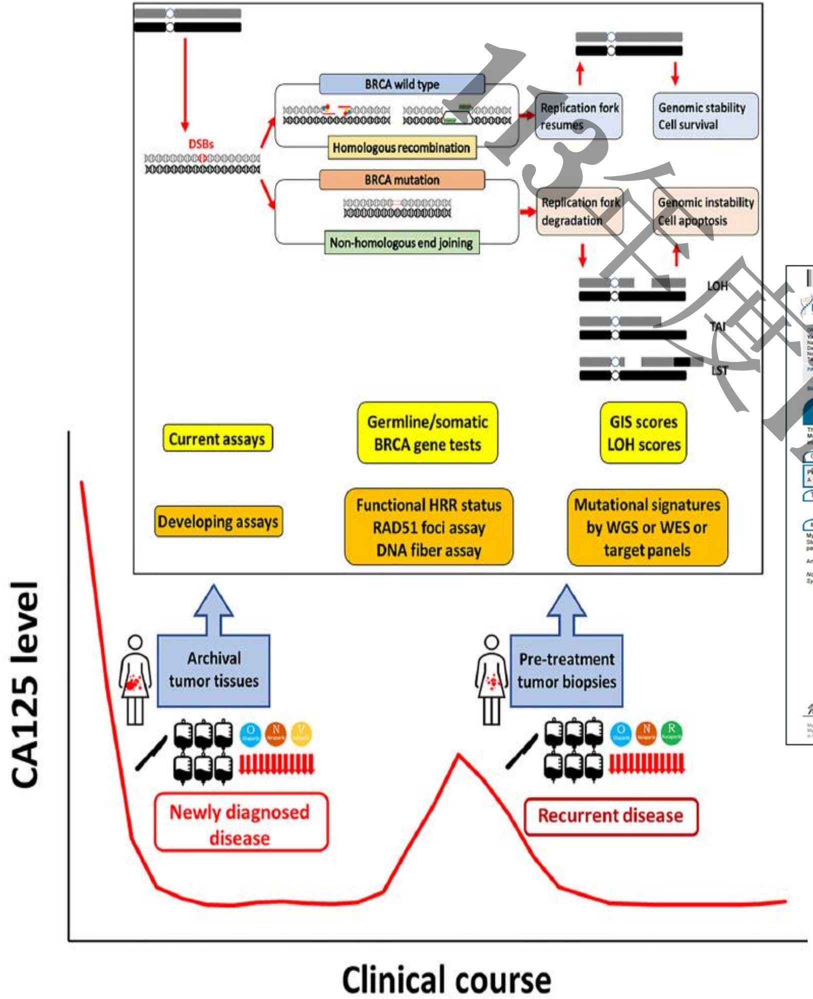
Adverse Event	MIRV (N=218)		Chemotherapy (N=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of participants (percent)			
Any adverse event	210 (96.3)	91 (41.7)	194 (93.7)	112 (54.1)
Any treatment-related adverse event	188 (86.2)	53 (24.3)	167 (80.7)	77 (37.2)
Serious adverse event	52 (23.9)	44 (20.2)	68 (32.9)	59 (28.5)
Serious treatment-related adverse event	20 (9.2)	16 (7.3)	16 (7.7)	16 (7.7)
Adverse event leading to dose reduction	74 (33.9)	—	50 (24.2)	—
Adverse event leading to dose delay or hold	117 (53.7)	—	111 (53.6)	—
Adverse event leading to dose discontinuation	20 (9.2)	—	33 (15.9)	—
Adverse event leading to death	5 (2.3)	—	5 (2.4)	—
Treatment-related adverse event leading to death	1 (0.5)	—	1 (0.5)	—
Adverse events occurring in ≥20% of participants in a trial group				
Blurred vision	89 (40.8)	17 (7.8)	5 (2.4)	0
Keratopathy	70 (32.1)	20 (9.2)	0	0
Abdominal pain	66 (30.3)	6 (2.8)	31 (15.0)	3 (1.4)
Fatigue	66 (30.3)	5 (2.3)	52 (25.1)	11 (5.3)
Diarrhea	64 (29.4)	3 (1.4)	36 (17.4)	1 (0.5)
Dry eye	61 (28.0)	7 (3.2)	5 (2.4)	0
Constipation	59 (27.1)	0	40 (19.3)	2 (1.0)
Nausea	58 (26.6)	4 (1.8)	60 (29.0)	4 (1.9)
Peripheral neuropathy	47 (21.6)	3 (1.4)	30 (14.5)	4 (1.9)
Neutropenia	24 (11.0)	2 (0.9)	59 (28.5)	36 (17.4)
Anemia	21 (9.6)	2 (0.9)	71 (34.3)	21 (10.1)

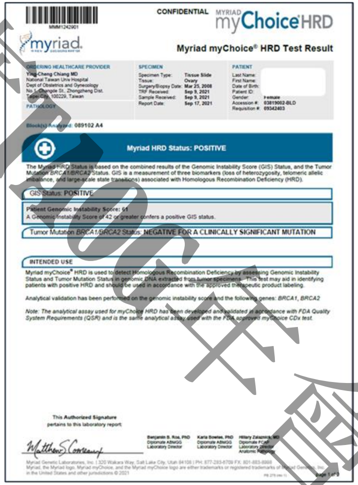
N Engl J Med 2023;389:2162-74.

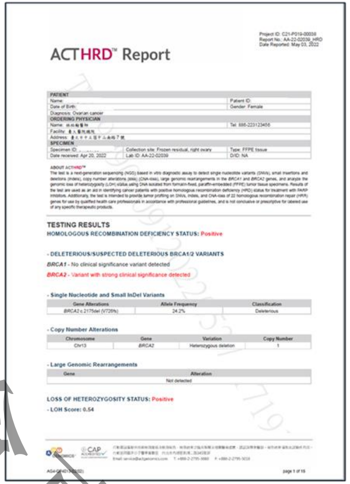
Summary

- ADCs deliver potent cytotoxic drugs directly to cancer cells, limiting systemic toxicity
- Evolving ADC landscape in gynecologic cancers shows potential for improved outcomes
- Mirvetuximab soravtansine (MIRV): FRα-positive platinum resistant epithelial ovarian cancer

Unmet Needs and Challenges

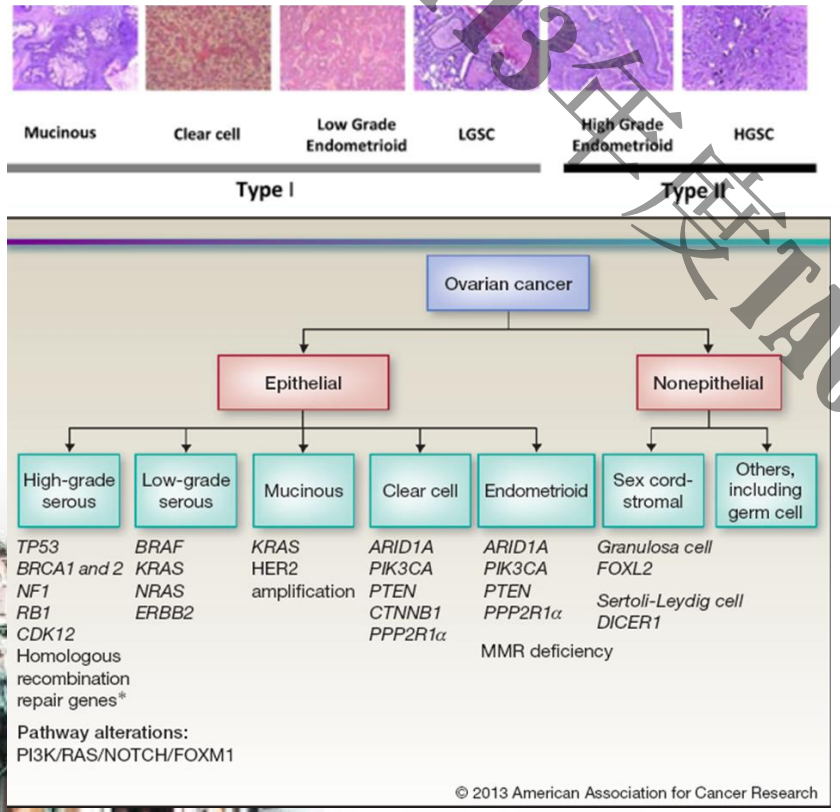


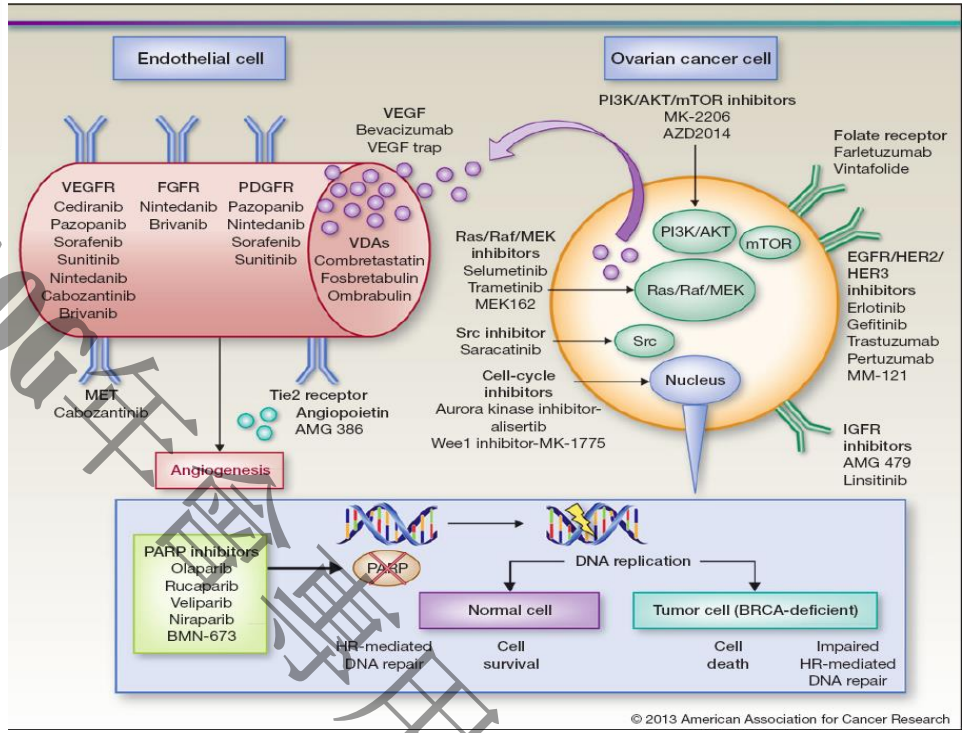




Front Oncol. 2021 Oct 14;11:675972.

Molecular Pathogenesis





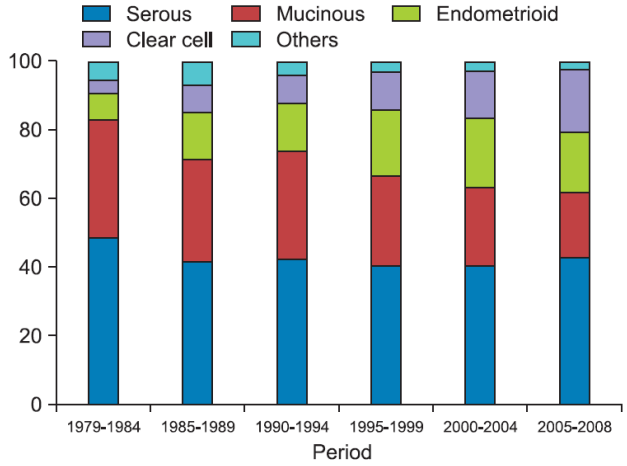
Nat Rev Cancer. 2011;11(10):719-25

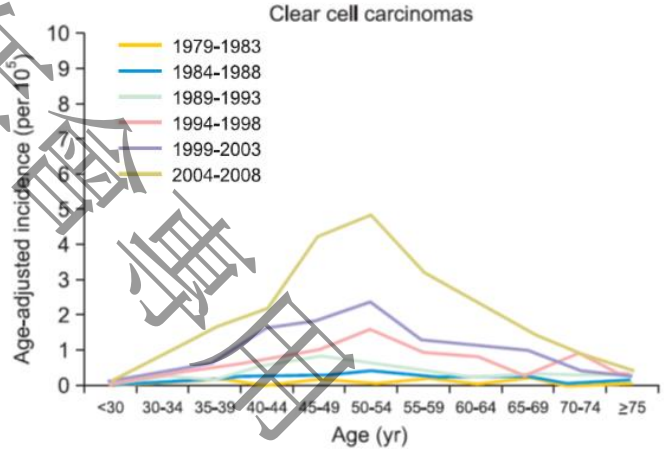
Original Article
J Gynecol Oncol Vol. 24, No. 4:342-351
http://dx.doi.org/10.3802/jgo.2013.24.4.342
pISSN 2005-0380
eISSN 2005-0399
Journal of Gynecologic Oncology
jgo

Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan

組織形態	女性 個案數	各形態百分比	細胞或病理證實數	細胞或病理證實百分比
漿液性腺癌	629	35.08	629	100.00
高惡性度(High-grade)漿液性腺癌	534	29.78	534	100.00
低惡性度(Low-grade)漿液性腺癌	33	1.84	33	100.00
其他	62	3.46	62	100.00
黏液性腺癌	152	8.48	150	98.68
子宮內膜樣癌	284	15.84	284	100.00
明亮細胞癌	337	18.80	337	100.00
混合細胞腺癌	52	2.90	52	100.00
非特定腺癌	73	4.07	73	100.00
生殖細胞瘤	69	3.85	69	100.00
性索間質腫瘤	65	3.63	63	96.92
其他特定上皮癌	36	2.01	36	100.00
非特定上皮癌	48	2.68	41	85.42
惡性肉瘤	10	0.56	10	100.00
其他惡性腫瘤	2	0.11	2	100.00
惡性腫瘤，組織形態不明	36	2.01	4	11.11
惡性淋巴瘤 [1]	3	-	3	100.00
總計 [2]	1,793	100.00	1,750	97.60

註：1. 自96年癌症登記報告起，惡性淋巴瘤（ICD-O-3 M-CODE請見p.496附錄五）從各部位獨立出來計算發生率，並納入排名。
2. 個案數的總計不包含惡性淋巴瘤個案數。



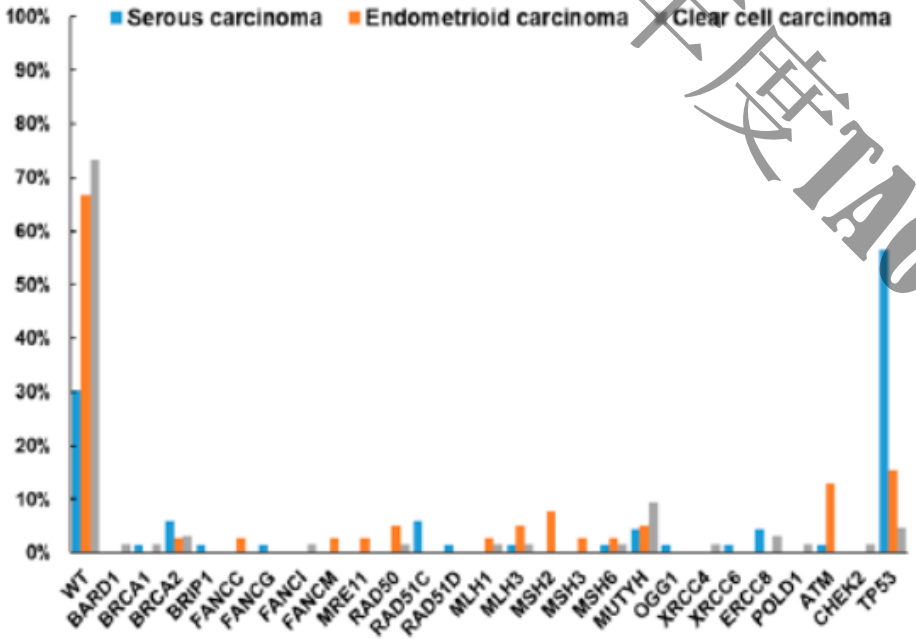


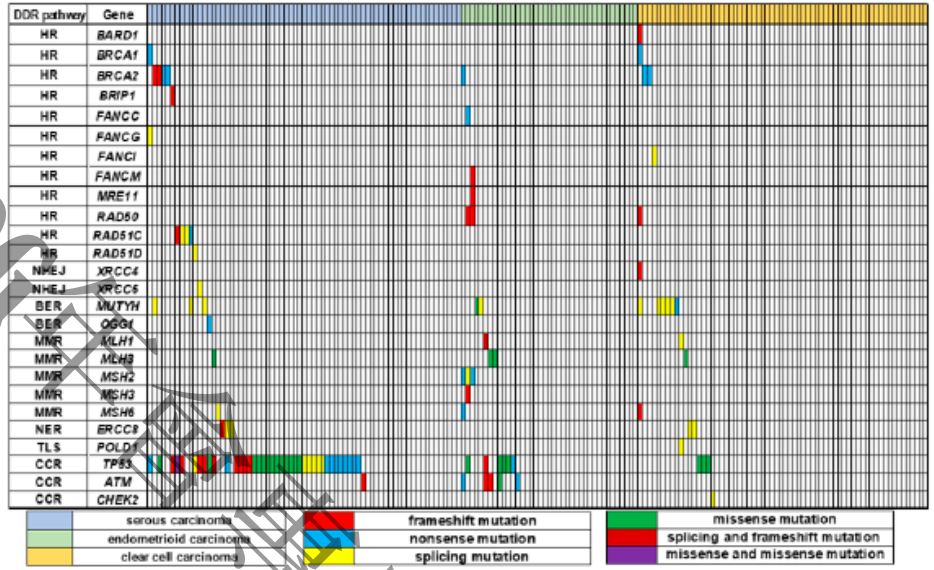
biomedicines

MDPI

Article

A DNA Damage Response Gene Panel for Different Histologic Types of Epithelial Ovarian Carcinomas and Their Outcomes





Take Home Message

Patient
- Age
- Performance status (ECOG)
- Co-morbidities
- Expectations
- Desires and own vision of life
- Caregivers' availability and support

- IDS + HIPEC
- Maintenance therapy: Bevacizumab / PARPi
- ADC: Mirvetuximab soravtansine (MIRV)

Tumour
- Histology
- BRCA and HRD status
- Other Genomics (CCNE1, RAD51,…)
- Tumour microenvironment
- Mechanisms of resistance to platinum and/or PARPi

Surgery and structure
- Pre-surgical assessment (CT vs PET vs laparoscopy)
- Skills of the surgical team (level of specialization)
- Residual tumour after PCS or ICS
- Surgical complications

- Health Insurance
- Financial Toxicity
- Family & Social Support

Systemic therapy
- Response to chemo (RECIST)
- CA-125 kinetic of elimination (KELIM)
- PARPi +/- bevacizumab
- Safety & profile of drugs
- Access and reimbursement

Thank you for your attention