Leiden University
Medical Center

Systemische behandelingen bij Ovariumcarcinoom
Chemotherapie, PARP remmers en Immunotherapie

Masterclass Gynecologische Oncologie
2 december 2025

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LEIDEN UNIVERSITY MEDICAL CENTER

Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AstraZeneca		x	x					
Daiichi	x	x						
Eisai		x						
GSK		x						
Lilly		x						
MSD		x						
Novartis		x	x					
Philips			x					

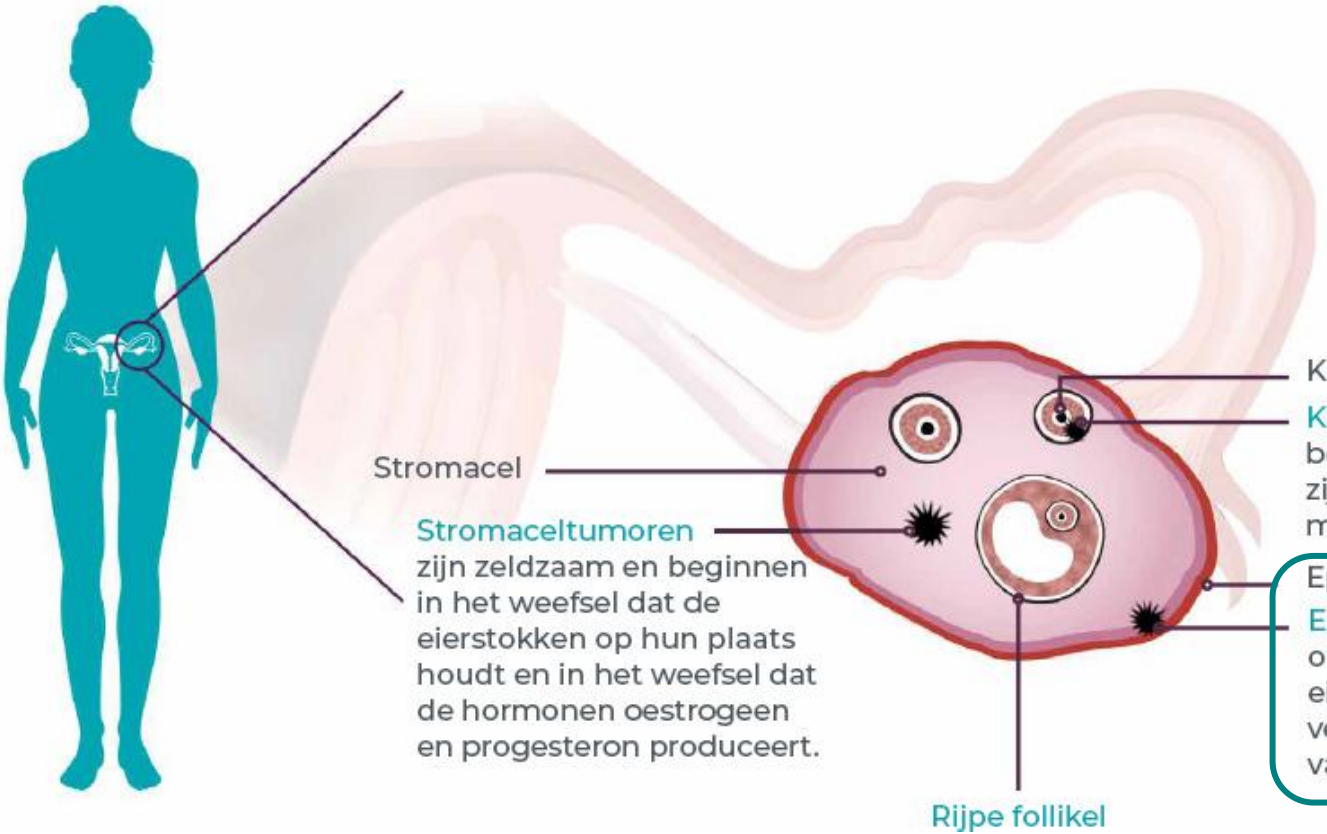
Introduction Ovarian Cancer

- Epidemiology
- Firstline / curative therapy
- PARP inhibition
- HIPEC
- Immunotherapy
- Future perspectives

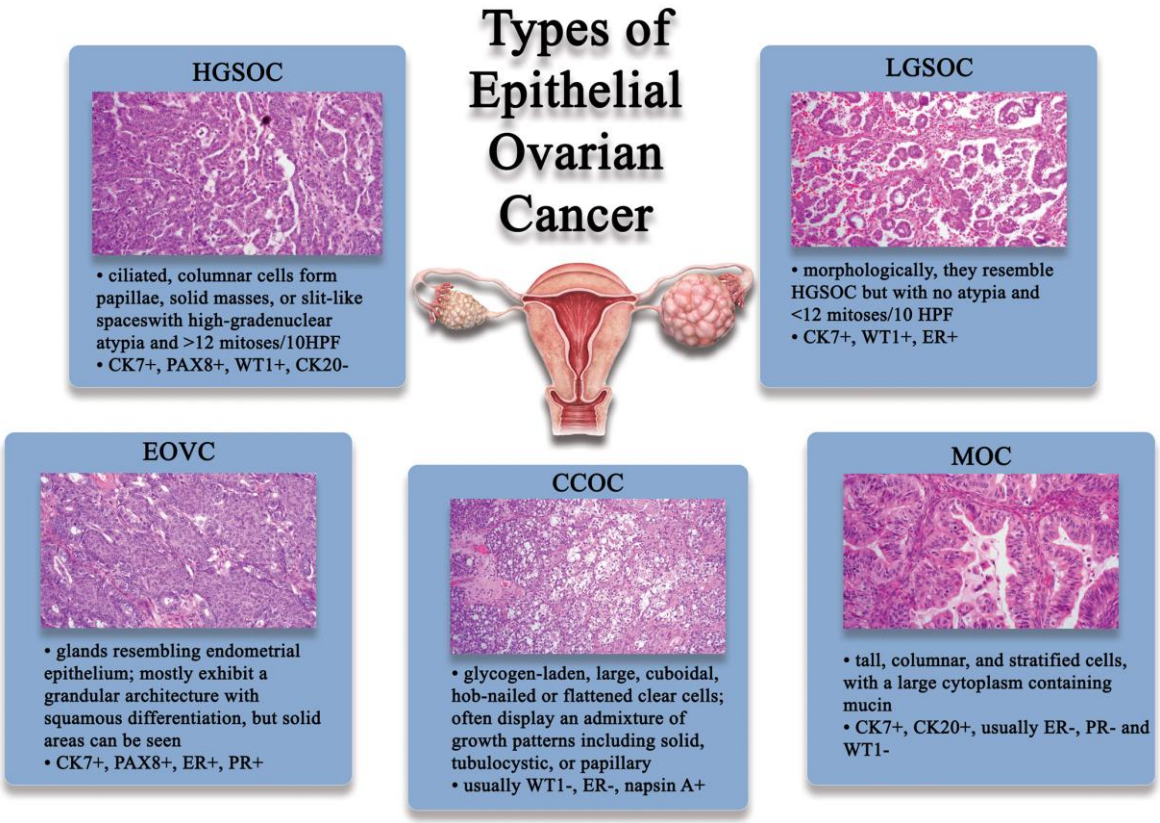
Epidemiology Ovarian Cancer

- De diagnose eierstokkanker in NL in 2021 bij bijna 1.300 vrouwen (NKR)
- 1/85 vrouwen krijgt ovarium carcinoom gedurende haar leven
- 1/100 vrouwen overlijdt aan ovarium carcinoom

Epithelial Ovarian Cancer



Epithelial Ovarian Cancer types

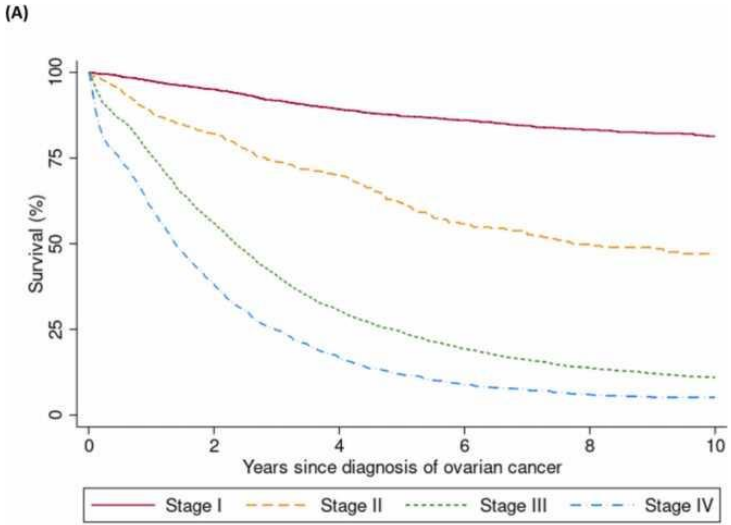


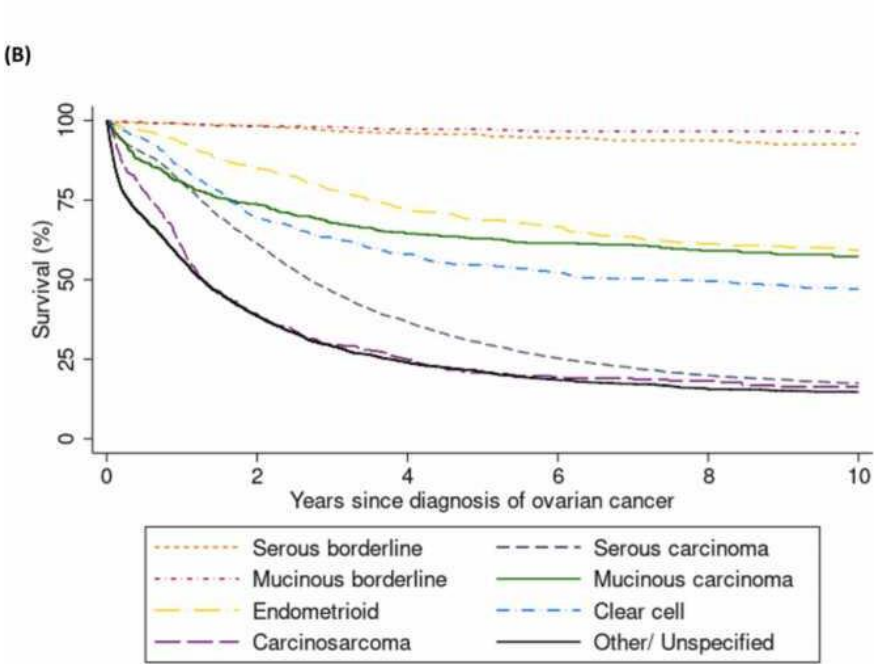
OC – ovarian cancer

- HGSOC – high-grade serous OC
- EOVC – endometrioid OC
- CCOC – clear cell OC
- LGSOC – low-grade serous OC

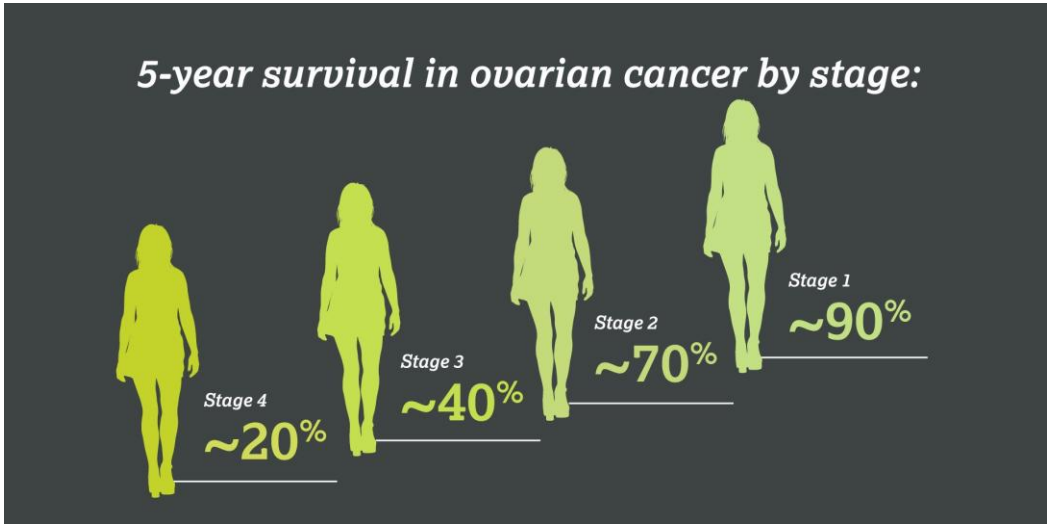
MOC – mucinous OC

Overall survival curves for advanced-stage epithelial ovarian cancer.



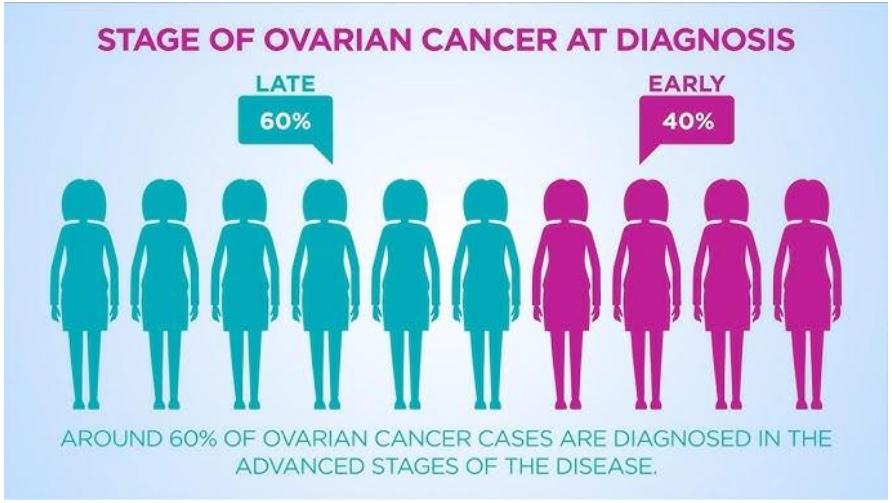


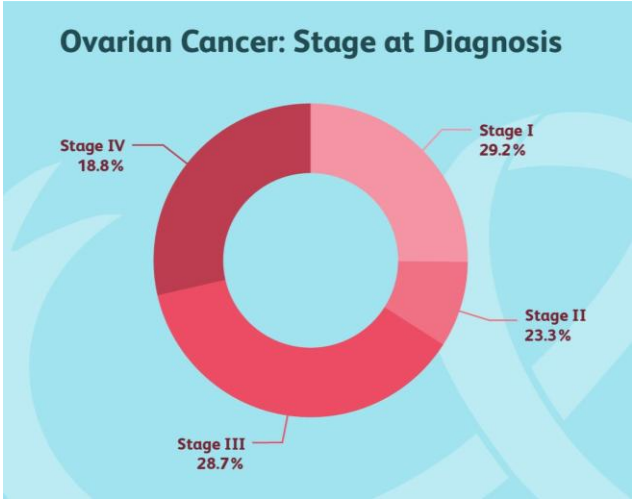
5 year Overall Survival



Filippova, Gyn Oncol 2021

Ovarian Cancer stage at diagnosis





Staging Ovarian Cancer

STAGE I: Tumour confined to ovaries	
IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings
IB	Tumour involves both ovaries otherwise like IA
IC: Tumour limited to 1 or both ovaries	
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumour on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings

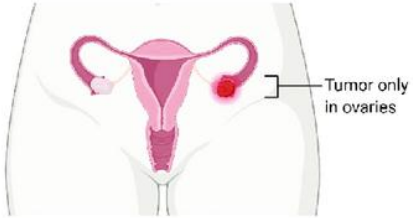
STAGE II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues

STAGE III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		
IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)		
IIIA1	Positive retroperitoneal lymph nodes only	
	IIIA1(i)	Metastasis ≤ 10 mm
	IIIA1 (ii)	Metastasis > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	

STAGE IV: Distant metastasis excluding peritoneal metastasis	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

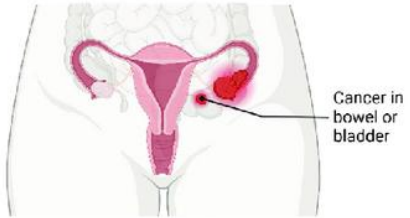
Stage I: Tumor confined to ovaries

IA: Cancer is confined to one ovary
IB: Cancer is in both ovaries
IC: Cancer cells are on the outer surface of the ovary or are spilling from one or both ovaries



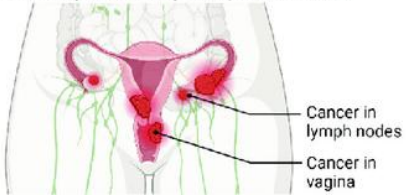
Stage II: Tumor involves one or both ovaries with pelvic extension

IIA: Cancer spreads to fallopian tubes or uterus
IIB: Cancer spreads to other pelvic organs



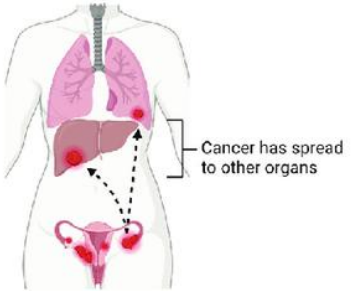
Stage III: Tumor involves one or both ovaries with spread to peritoneum outside of the pelvis and/or metastasis to retroperitoneal lymph nodes

IIIA: Cancer spreads to upper abdomen or lymph nodes, microscopically visible only
IIIB: Cancer spreads beyond pelvis < 2cm
IIIC: Cancer spreads beyond pelvis > 2cm



Stage IV: Distant metastasis

IVA: Cancer spreads to fluid around lungs
IVB: Cancer spreads to inside lungs, liver, spleen



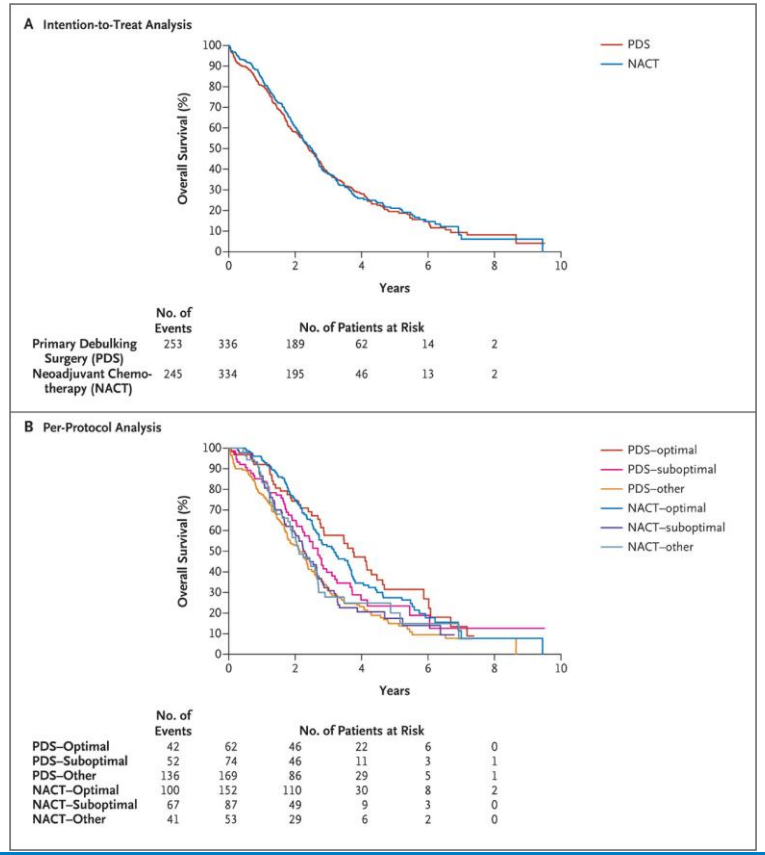
Ovarian Cancer Symptoms

First-line therapy (curative intent)

Surgery with maximum cytoreduction effort <1cm residual disease

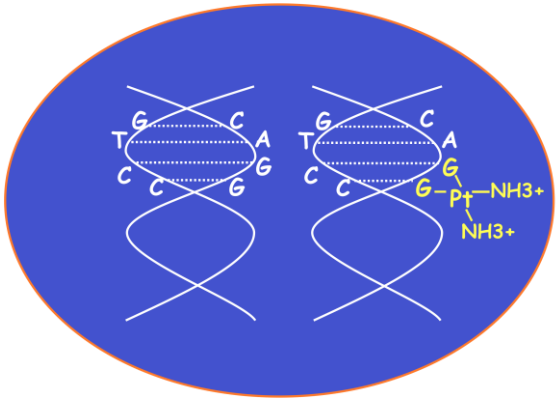
Chemotherapy +/- PARP inhibition (Carboplatin + Paclitaxel)

Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

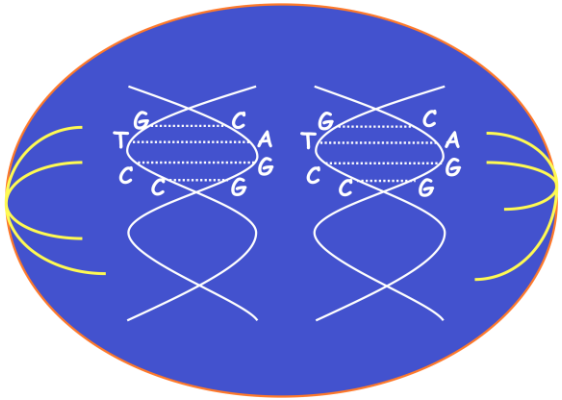


Vergote, NEJM, 2010

Chemotherapy

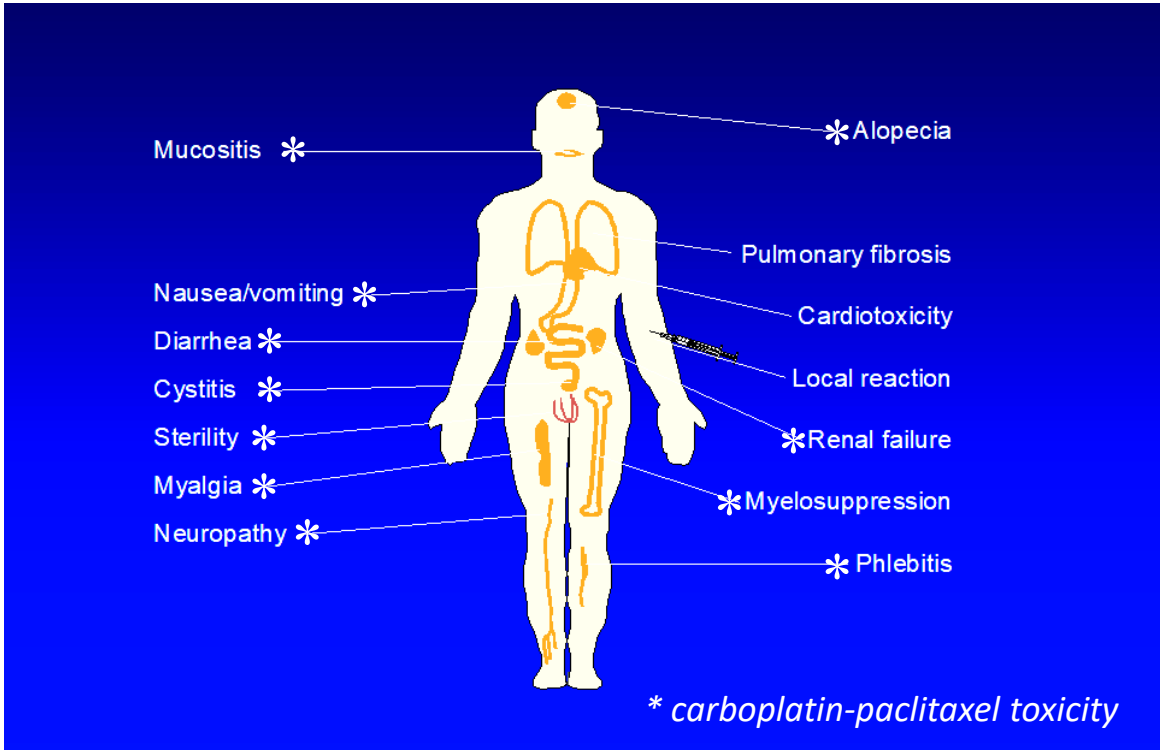


Platinum
Carboplatin



Taxane
Paclitaxel

Toxicity


Mucositis *
Nausea/vomiting *
Diarrhea *
Cystitis *
Sterility *
Myalgia *
Neuropathy *
*Alopecia
Pulmonary fibrosis
Cardiotoxicity
Local reaction
*Renal failure
*Myelosuppression
*Phlebitis
* carboplatin-paclitaxel toxicity

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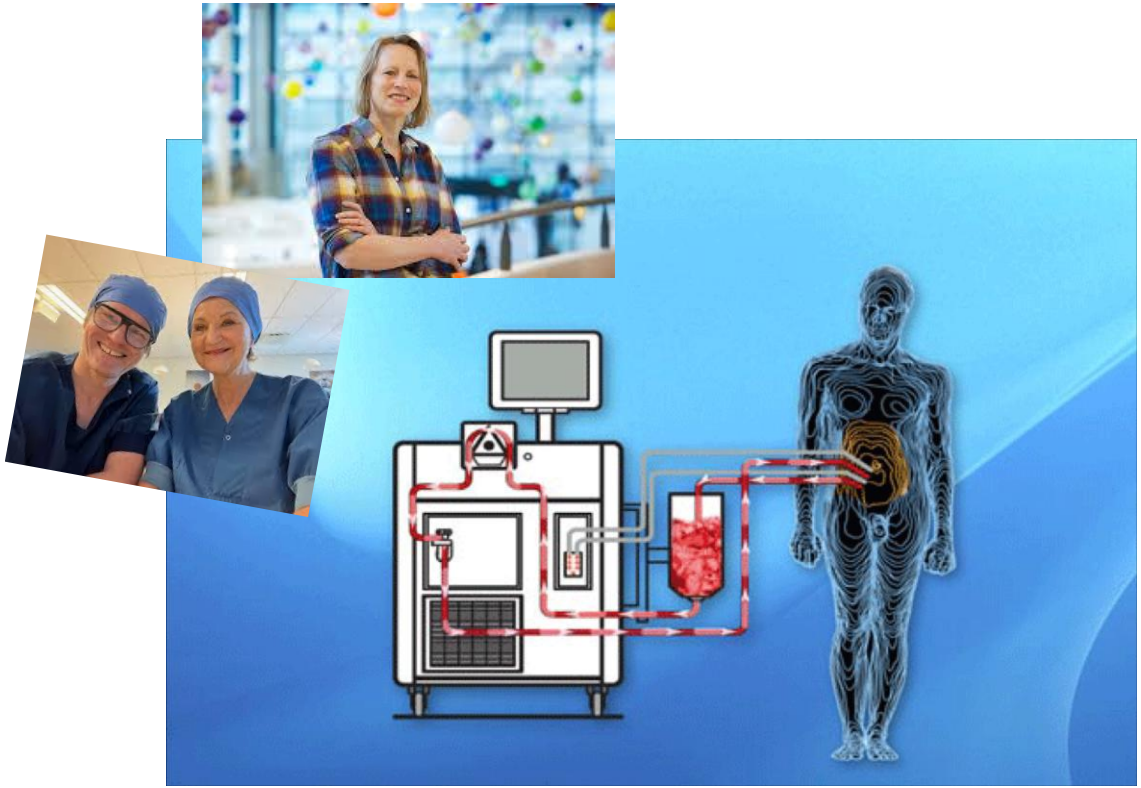
HIPEC

OVHIPEC Hyperthermic intraperitoneal chemotherapy (HIPEC) in Ovarian Cancer



- Cisplatin

100mg/m_2

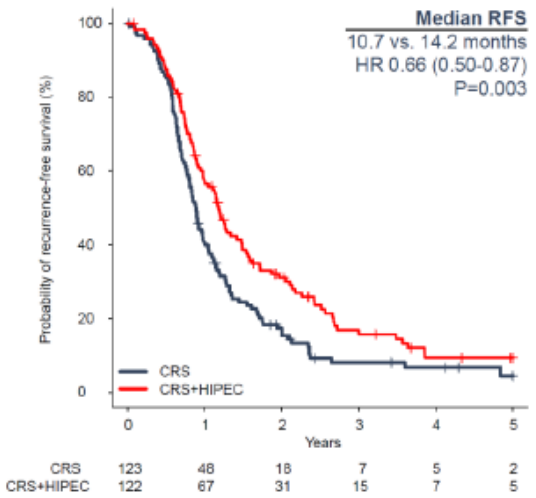
- 40 - 41$_o$ C

- 90 minuten perfusie

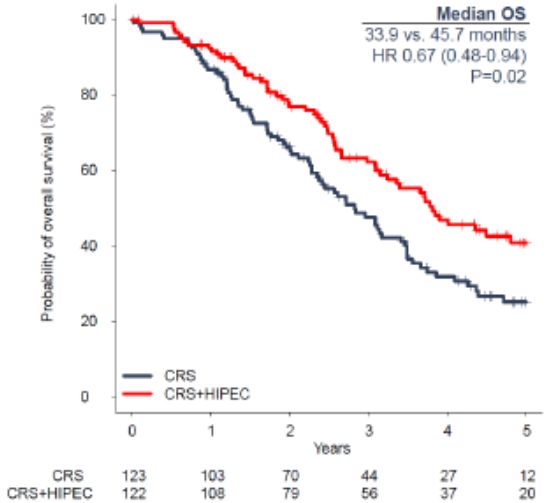
OVHIPEC

HIPEC geeft overlevingswinst (bijna 12 mnd)

Recurrence-free survival

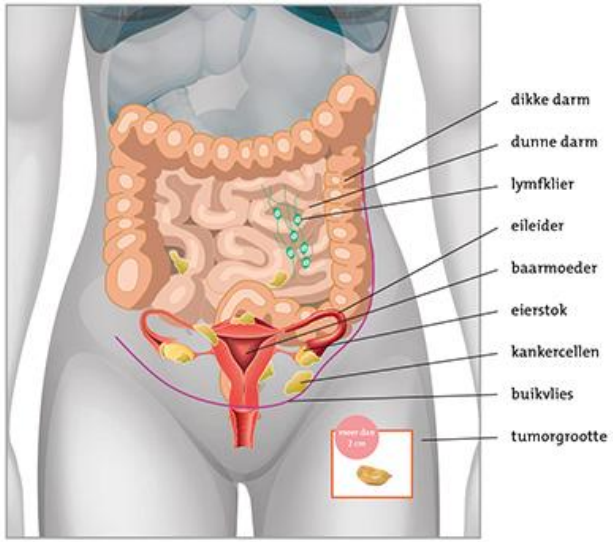


Overall survival



Van Driel, N Engl J Med. 2018

LOGISTIEK



1. Stadium III ovarium carcinoom
2. MDO: bepalen of er gestart wordt met neoadjuvant chemotherapie of primaire debulking
3. Beoordeling na 2 kuren: CT-scan, lab (ca125) en MDO
4. HIPEC screeningsdag:

- Gynaecoloog
- (stoma) Verpleegkundige
- Chirurg
- Oncoloog
- Lab via anesthesist

Consult Verpleegkundig specialist

Bespreken schriftelijke patiënten informatie

Aanvullende vragen naar aanleiding gesprek gynaecoloog

Chemobesmetting uitleg

Voeding/ beweging

Sociaal netwerk in kaart brengen (tijdelijk verblijf)

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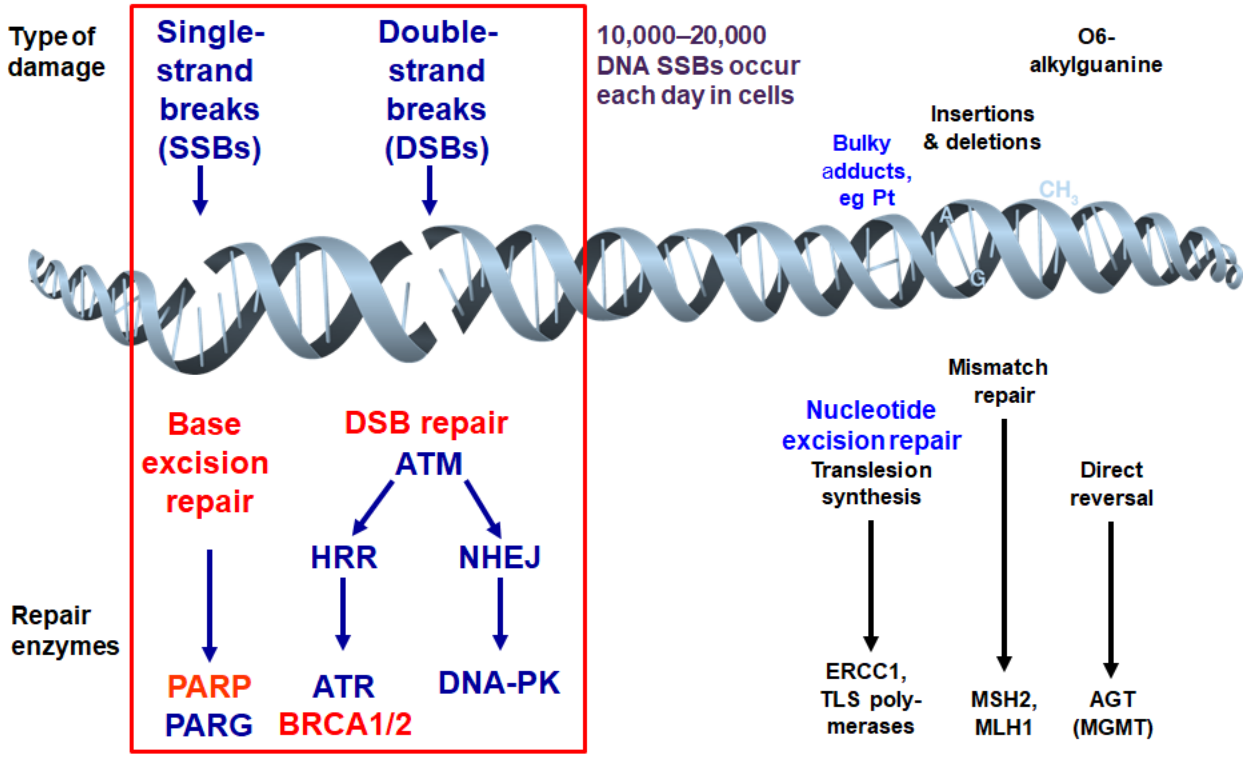
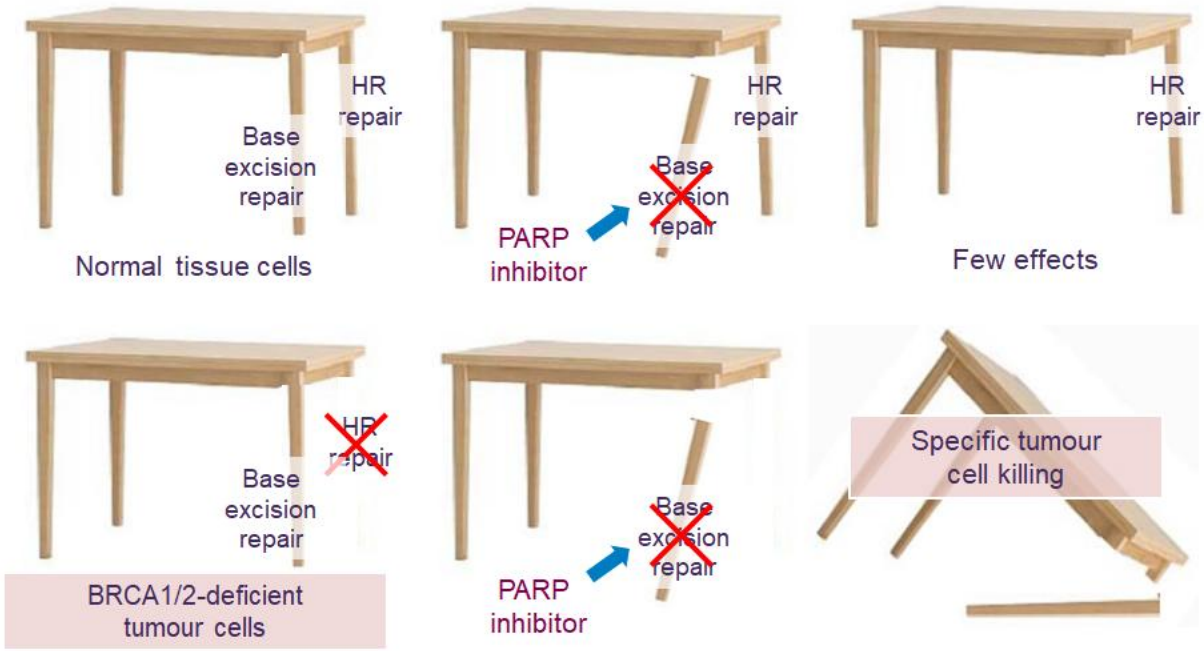
PARP inhibition

PARPi Mechanism of Action

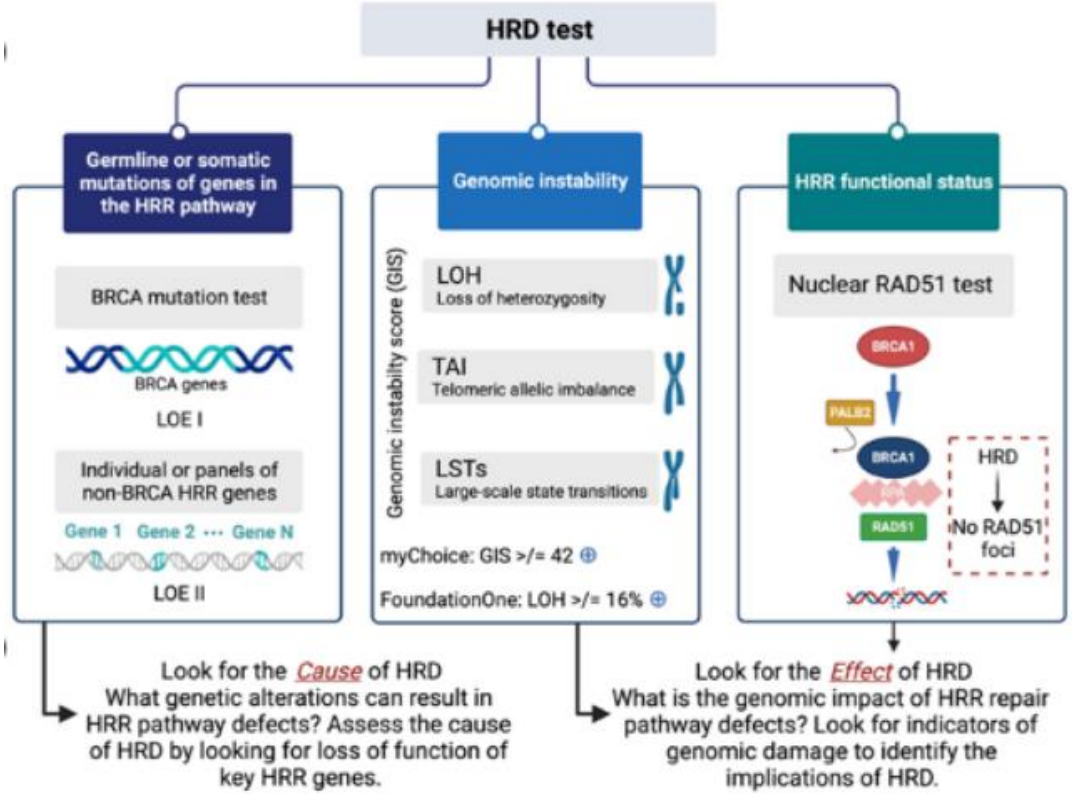


Jackson SP. Drug Discovery World, 2003

PARPi Mechanism of Action: tumor selective Synthetic Lethality



Homologous Recombination Deficiency



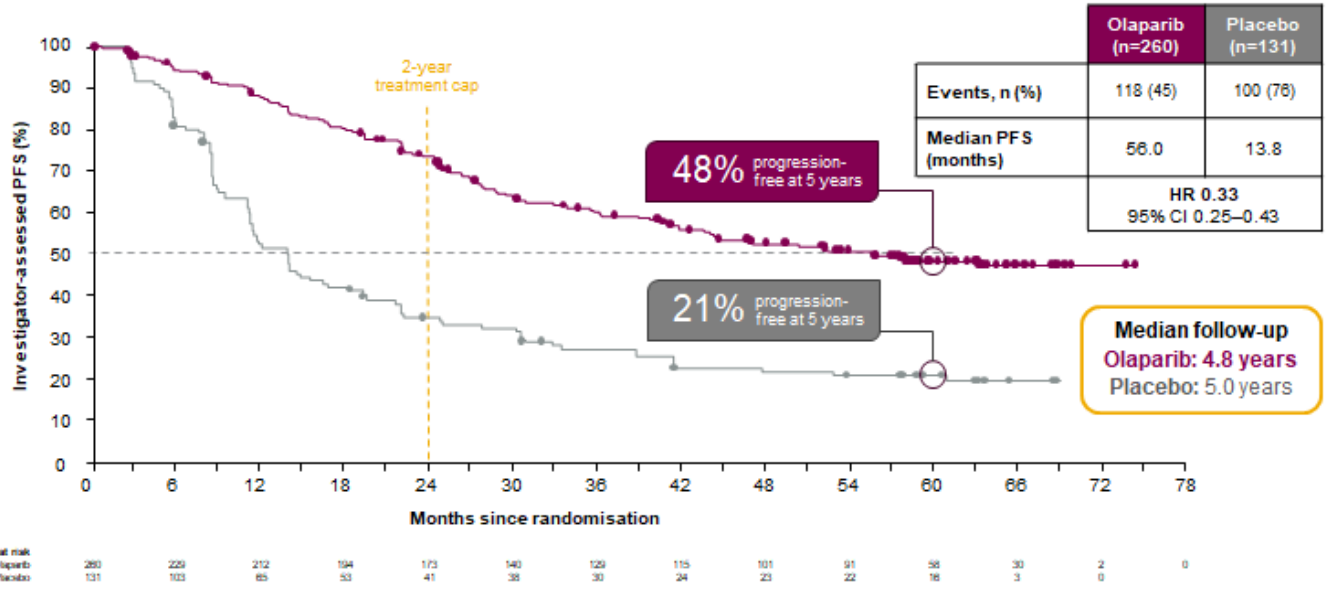
Mamgogna A J Pers Med 2023

1L PARPi Trials in EOC

Trial	Inclusion	PARPI
SOLO-1 (n=391)	BRCAm	Olaparib vs placebo
PAOLA1 (n=806)	BRCAmut HRD+	Olaparib-bevacizumab vs placebo-bevacizumab
PRIMA (n-733)	HRD+/HRD-	Niraparib vs placebo
Athena (n=1000)	HRD+/HRD-	Rucaparib vs placebo

1. Moore K NEJM 2018; 2. Ray-Coquard I NEJM 2019; 3. Gonzalez-Martin A NEJM 2019; 4. Burger RA NEJM 2011

SOLO-1: median progression free survival (PFS)



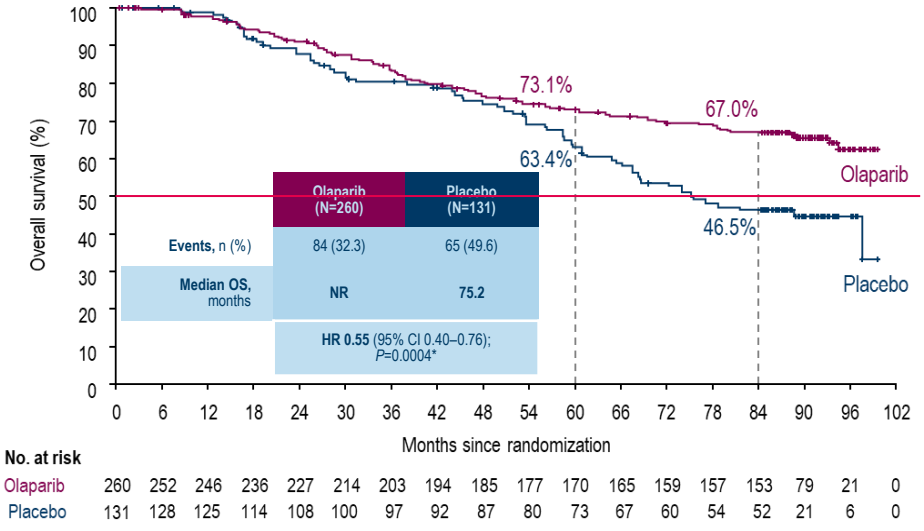
	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

Median follow-up
Olaparib: 4.8 years
Placebo: 5.0 years

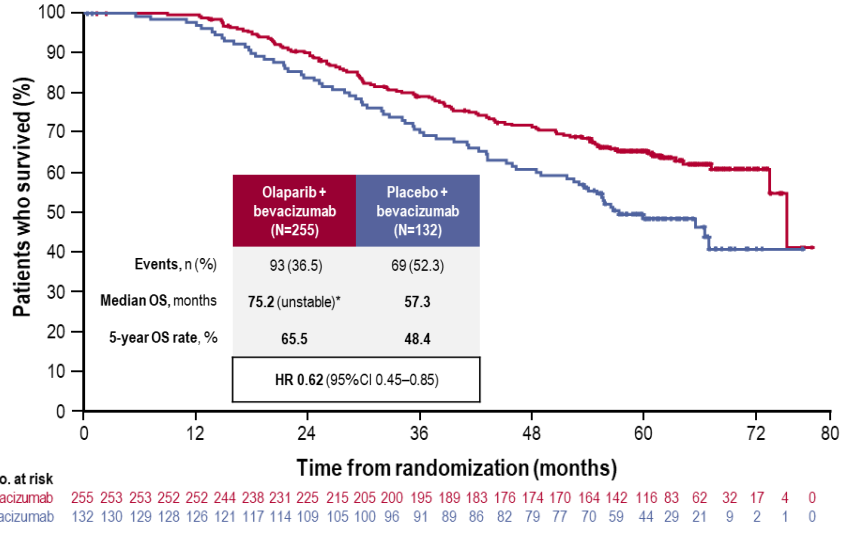
Banerjee S, et al. Presented at ESMO 2020. 19–21 September. Abstract

OS data SOLO-1 and PAOLA trials

BRCA+: SOLO-1 Overall Survival

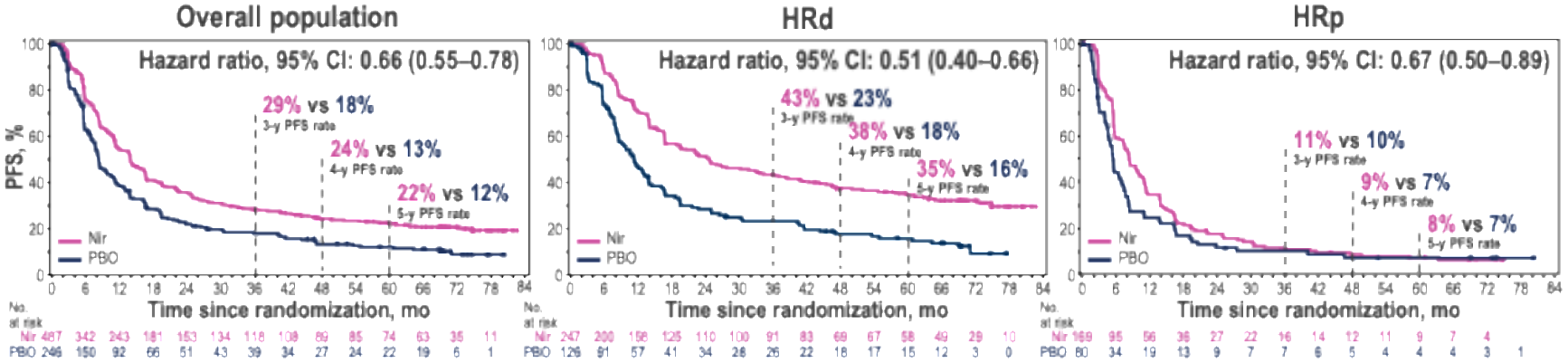


BRCA+/HRD+: PAOLA Overall Survival



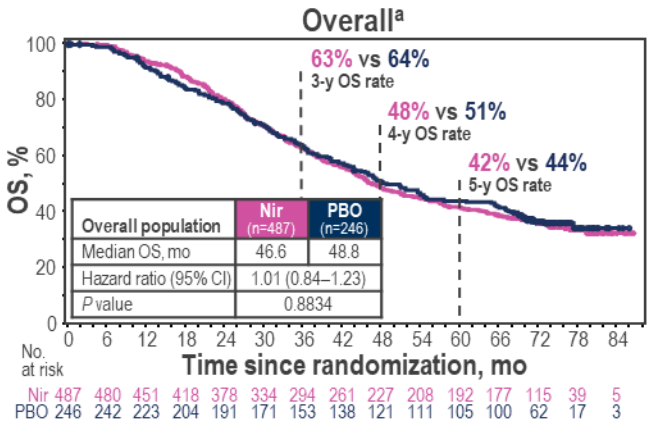
Di Silvestro P, et al. J Clin Oncol 2023
Ray-Coquard I, et al. Ann Oncol 2023

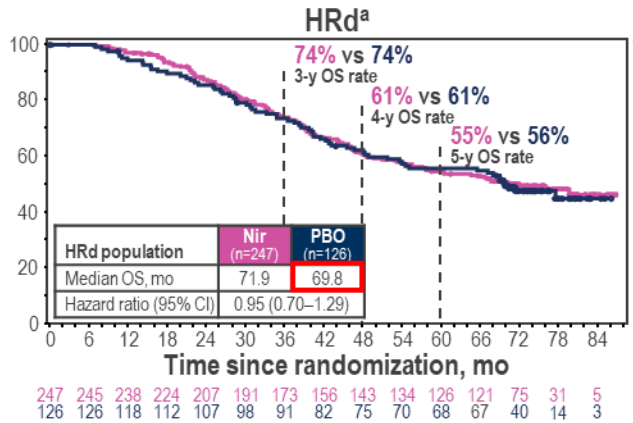
PRIMA trial: Niraparib Progression Free Survival (PFS)

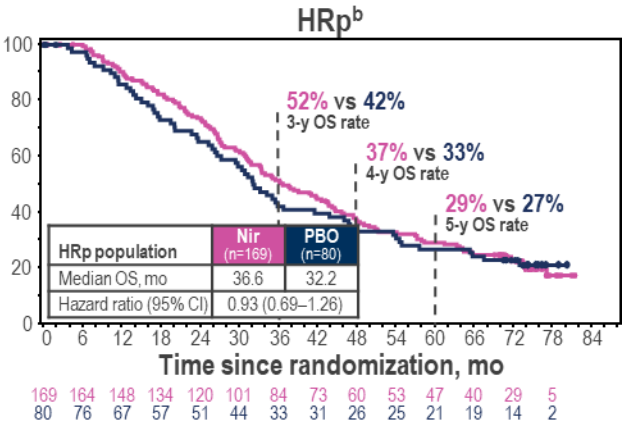


Gonzalez-Martin A, et al, NEJM 2019

PRIMA Overall Survival





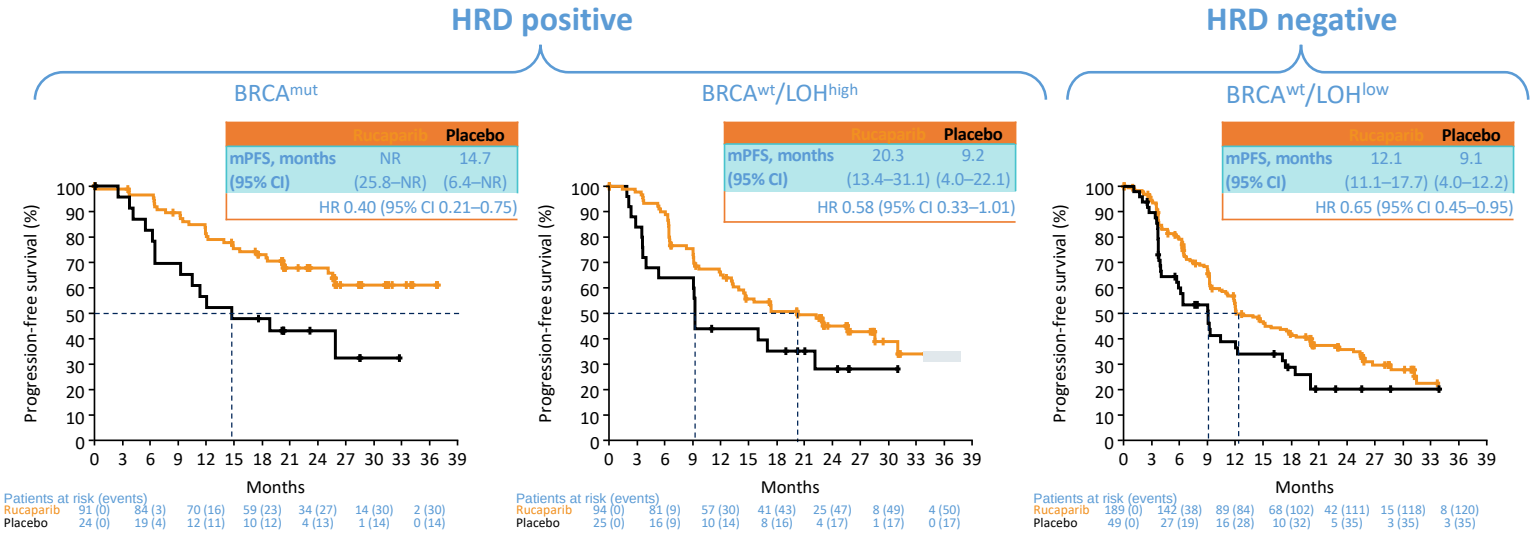


Monk, Ann Oncol 2024

Why have we not seen an OS benefit in PRIMA?

- Cross over (48% in de HRD population)
- The drug itself?
- Patient population – ethnicity?
- Study design
    - Risk profile?
    - Treatment duration?

Athena-mono: Rucaparib PFS

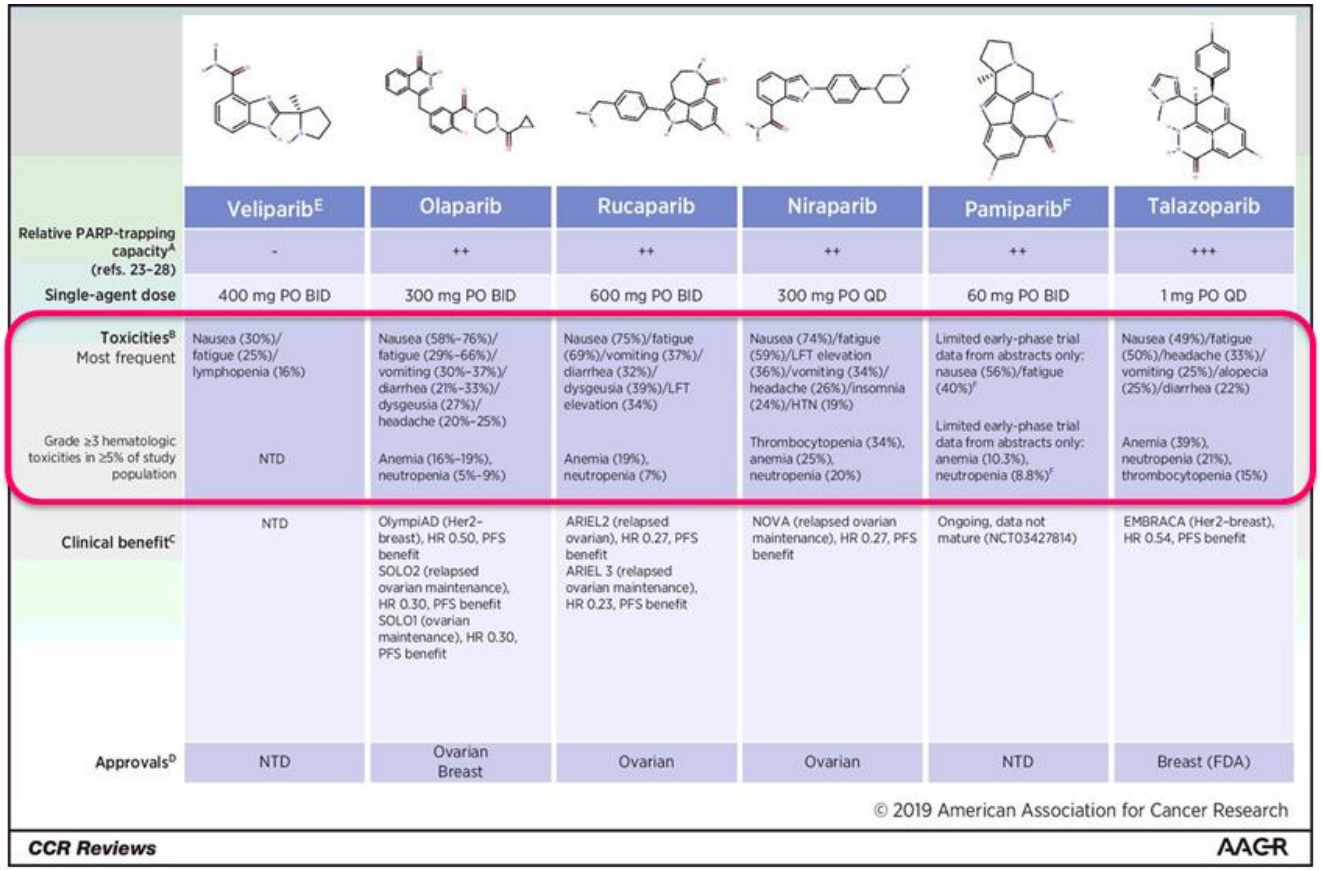


Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

Data cutoff date: March 23, 2022.

Monk BJ et al. J Clin Oncol. Published online June 6, 2022. doi.10.1200/JCO.22.01003e 2022

PARPi Toxicity



	Veliparib[E]	Olaparib	Rucaparib	Niraparib	Pamiparib[F]	Talazoparib
Relative PARP-trapping capacity[A] (refs. 23–28)	-	++	++	++	++	+++
Single-agent dose	400 mg PO BID	300 mg PO BID	600 mg PO BID	300 mg PO QD	60 mg PO BID	1 mg PO QD
Toxicities[B] Most frequent	Nausea (30%)/ fatigue (25%)/ lymphopenia (16%)	Nausea (58%–76%)/ fatigue (29%–66%)/ vomiting (30%–37%)/ diarrhea (21%–33%)/ dysgeusia (27%)/ headache (20%–25%)	Nausea (75%)/fatigue (69%)/vomiting (37%)/ diarrhea (32%)/ dysgeusia (39%)/LFT elevation (34%)	Nausea (74%)/fatigue (59%)/LFT elevation (36%)/vomiting (34%)/ headache (26%)/insomnia (24%)/HTN (19%)	Limited early-phase trial data from abstracts only: nausea (56%)/fatigue (40%)[F]	Nausea (49%)/fatigue (50%)/headache (33%)/ vomiting (25%)/alopecia (25%)/diarrhea (22%)
Grade ≥3 hematologic toxicities in ≥5% of study population	NTD	Anemia (16%–19%), neutropenia (5%–9%)	Anemia (19%), neutropenia (7%)	Thrombocytopenia (34%), anemia (25%), neutropenia (20%)	Limited early-phase trial data from abstracts only: anemia (10.3%), neutropenia (8.8%)[F]	Anemia (39%), neutropenia (21%), thrombocytopenia (15%)
Clinical benefit[C]	NTD	OlympiAD (Her2–breast), HR 0.50, PFS benefit SOLO2 (relapsed ovarian maintenance), HR 0.30, PFS benefit SOLO1 (ovarian maintenance), HR 0.30, PFS benefit	ARIEL2 (relapsed ovarian), HR 0.27, PFS benefit ARIEL 3 (relapsed ovarian maintenance), HR 0.23, PFS benefit	NOVA (relapsed ovarian maintenance), HR 0.27, PFS benefit	Ongoing, data not mature (NCT03427814)	EMBRACA (Her2–breast), HR 0.54, PFS benefit
Approvals[D]	NTD	Ovarian Breast	Ovarian	Ovarian	NTD	Breast (FDA)

CCR Reviews AACR

Pilie PG CCR 2019

PARPI indications NL for Ovarian Cancer

Curative setting

Maintenance therapy for FIGO III/IV **BRCA1/2mut** high grade EOC, in response following 1L platinum based chemotherapy (olaparib).

Palliative setting

Maintenance therapy for platinum sensitive relapsed high grade **BRCAmut** EOC, who are in response to platinum based chemotherapy. (olaparib/niraparib).

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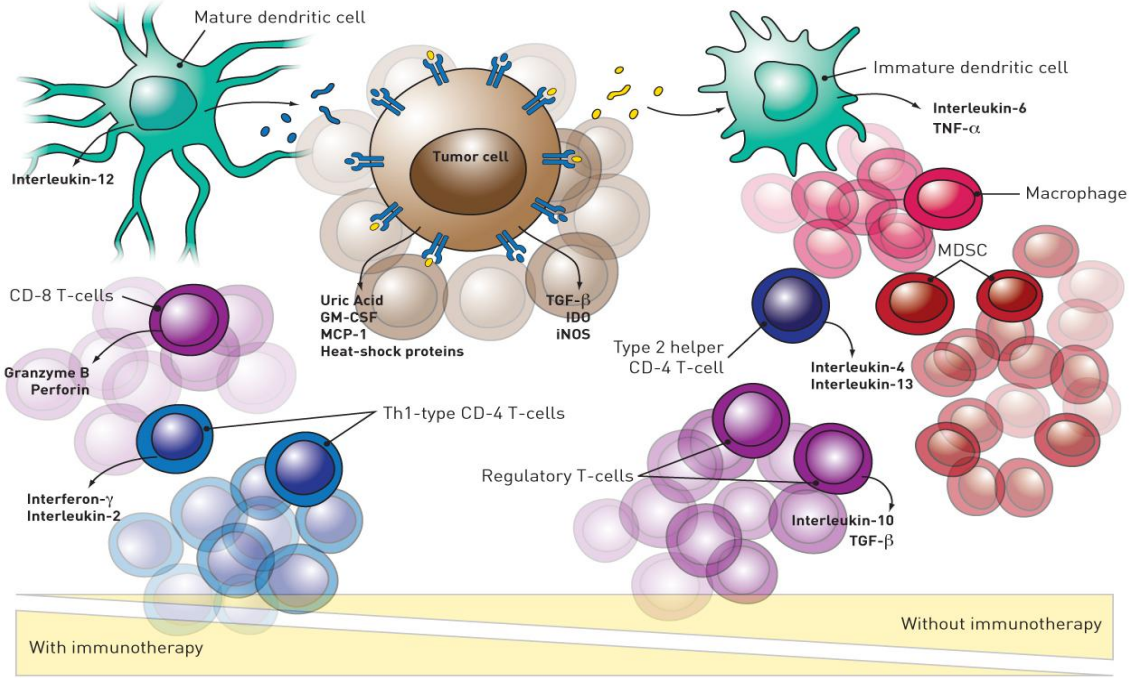
Immunotherapy

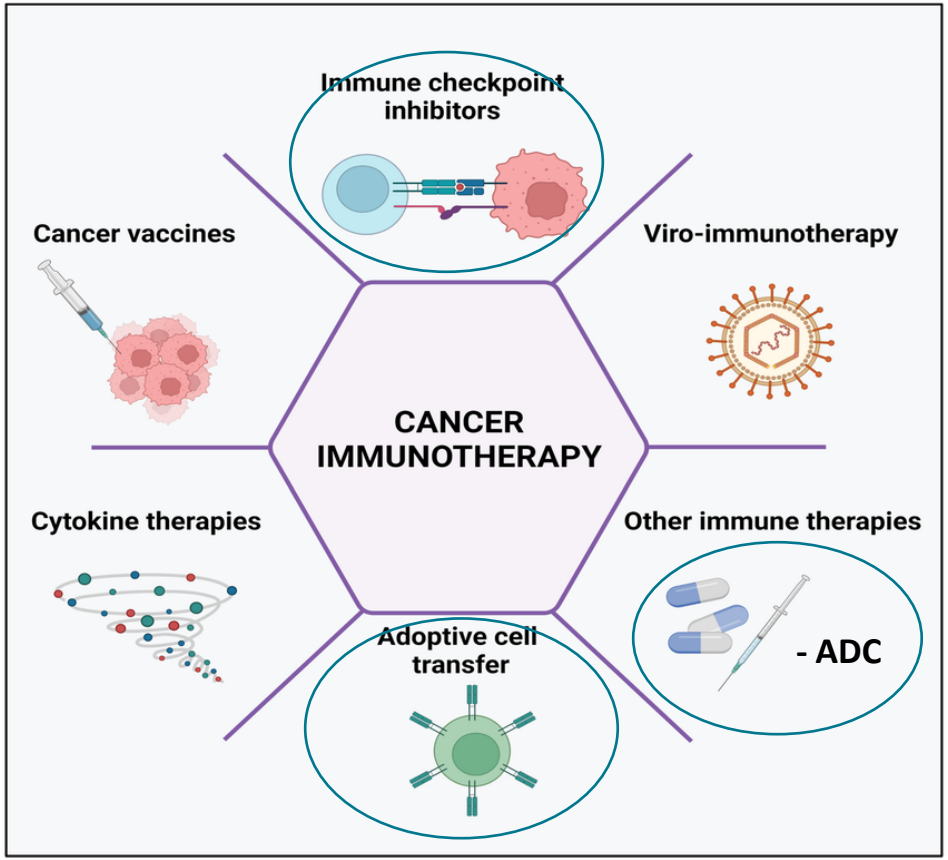
Immunotherapy Tumormicroenvironment

Immunostimulation

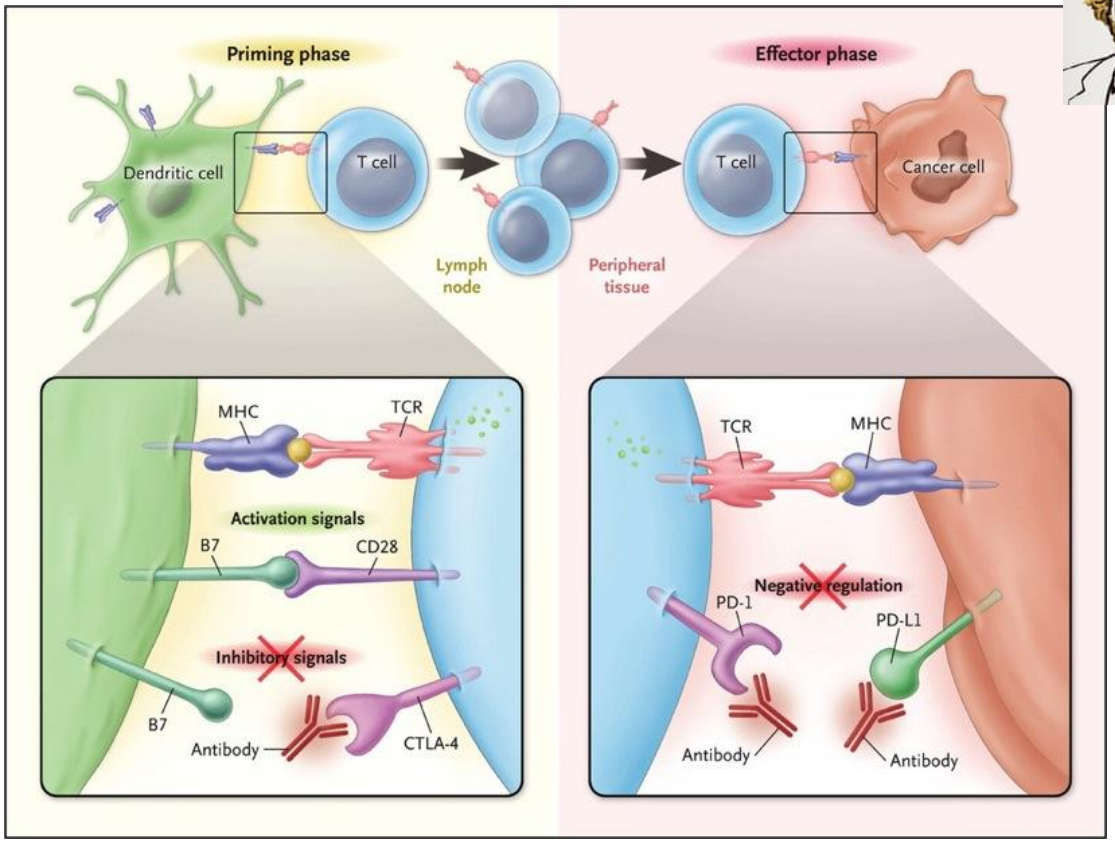
Immunosuppression



Cancer Immunotherapy Types



Checkpoint Inhibition: anti-CTLA4 and anti-PD1/PDL1



Antoni Ribas, NEJM epub June 2012

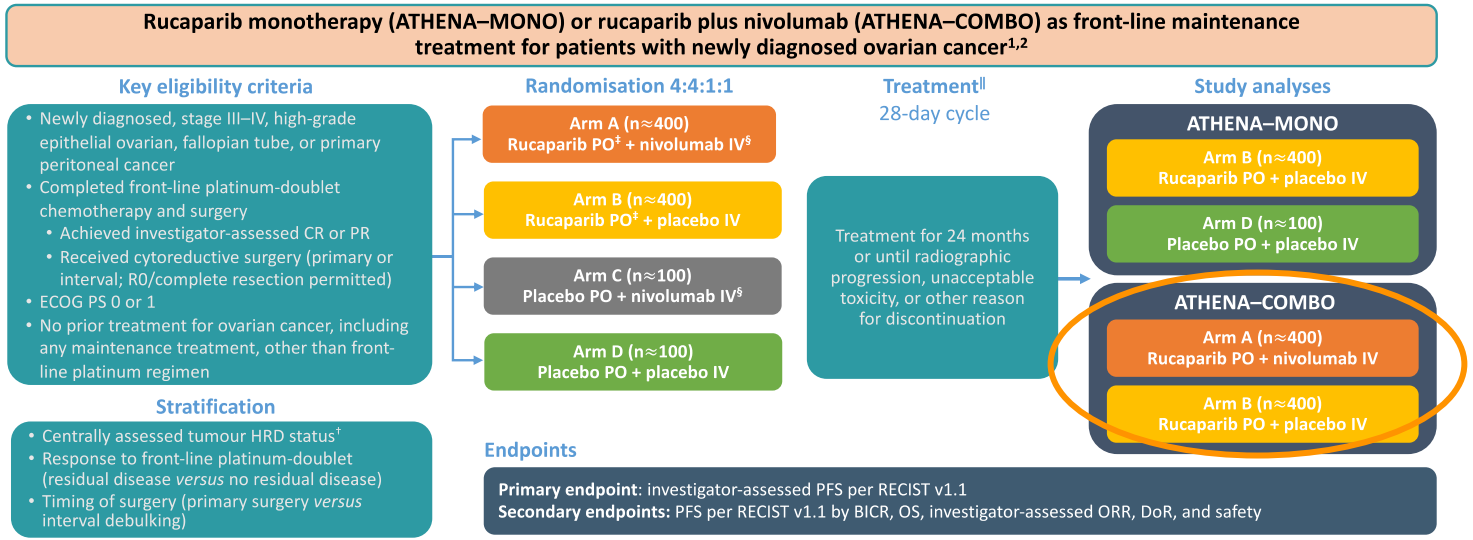
Track record of anti-PD-(L)1 on Ovarian Cancer Phase I /II

	Ipilimumab	Nivolumab	Pembrolizumab	Avelumab	Atezolizumab	Durvalumab
N	9	20	26/376	124	12	20
patients	Metastatic EOC	Platinum resistant EOC	After standard therapy, PD-L1+	Recurrent post Pt	Metastatic EOC	Metastatic EOC
Prior therapies	-	≥ 4: 55%	≥ 5: 38.5%	≥3 65.3% (excl adjuvant)	≥6: 58%	Median 4
PD-L1 prevalence	-	80%	100% CPS>10: 22%	77%	83%	>5%TC: 73%
ORR	**-**	**15%**	**11.5%**	**9.7%**	**25%**	**-**
mPFS	-	3.5	nr	2.6	2.9	-
mOS	-	20	nr	10.8	11.3 (IC2) 17.4 (IC3)	-

Track record of CPI on Ovarian Cancer (so far)

Trial	Phase	population	CPI	mPFS (mo)	OS (mo)
Javelin 100	3	New EOC	Carbo/Tax (CP) CP> avelumab CP+avelumab > avelumab	NR 16.8 18.1	negative
IMaGyn050	3	New EOC	CP/bev CP/bev + atezo	18.4 19.5	negative
DUO-O	3	New EOC	CP/bev CP/bev/durva>bev/durva CP/bev/durva>bev/durva/ola	19.3 20.6 24.2	negative *but no olaparib alone control arm
ATHENA-COMBO	3	New EOC	CP> rucaparib CP>rucaparib plus nivolumab	20.2 15.0	
FIRST	3	New EOC	CP>niraparib CP>niraparin plus dostarliman	19.2 20.6	negative
Keylynk001	3	New EOC	CP>olaparib CP+ pembro> olaparib/pembro	15.2 23.9	negative

Athena-mono: trial design



Approximately 1000 patients have been enrolled across 24 countries and randomised; the trial completed accrual in 2020

FoundationOne CDx) by Foundation Medicine

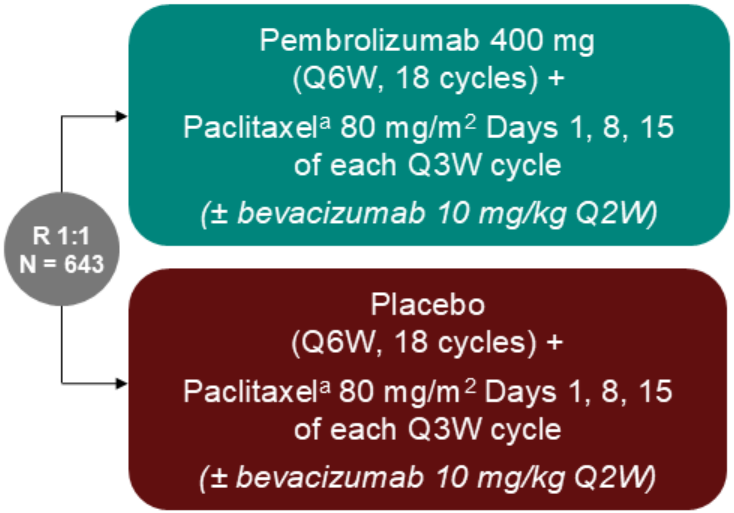
Track record of CPI on Ovarian Cancer (so far)

Trial	Phase	Population	CPI	mPFS (mo)
Ninja	3	PREOC	PLD or dFdC Nivolumab	3.8 2.0
Javelin 200	3	PREOC	PLD PDL + avelumab Avelumab	3.5 3.7 1.9
ATALANTE	3	PSEOC	CP/bev CP/bev+atezo	13.5 11.3
Keynote B96	3	PREOC	Weekly paclitaxel/bev Weekly paclitaxel/bev/ pembrolizumab	Recent ESMO data:

ENGOT-ov65/KEYNOTE-B96 Study Design (NCT05116189)

Key Eligibility Criteria

- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- 1 or 2 prior lines of therapy; at least 1 platinum-based chemotherapy
  - Prior anti-PD-1 or anti-PD-L1, PARPi and bevacizumab permitted
- Radiographic progression within 6 months after the last dose of platinum-based chemotherapy
- ECOG PS 0 or 1



Stratification Factors

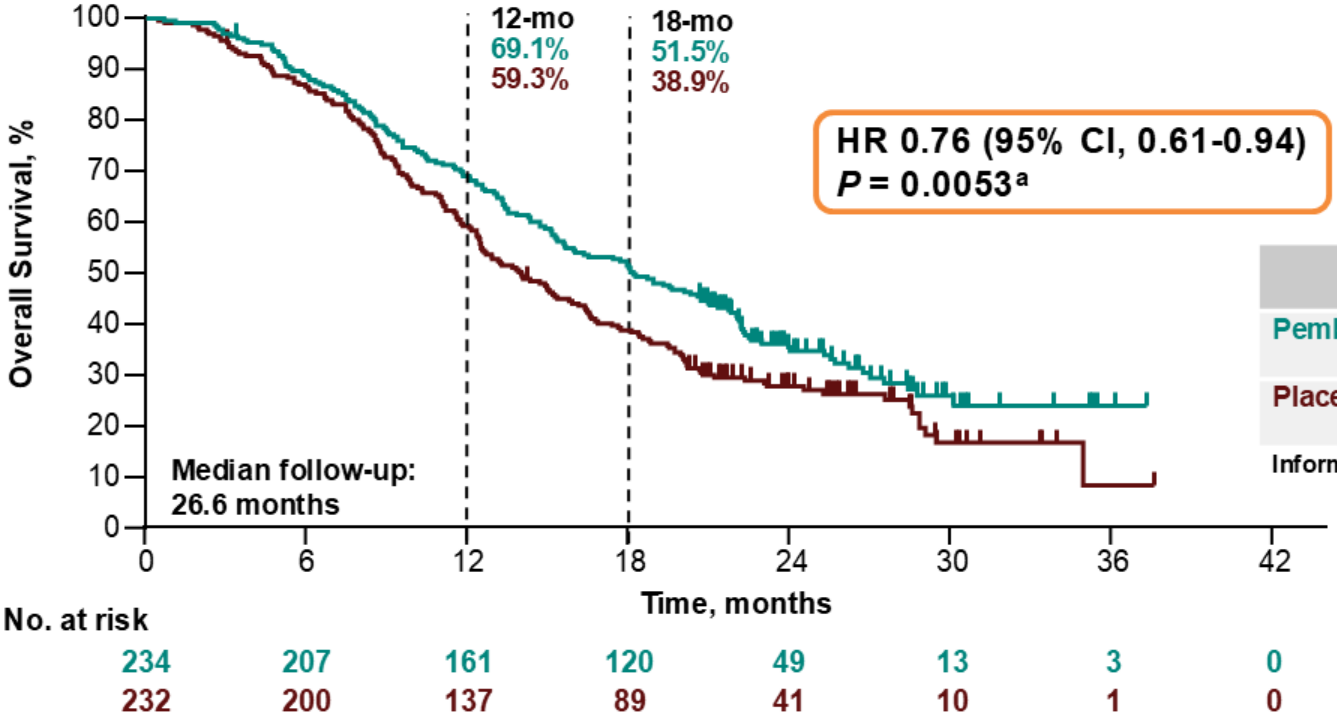
- Planned bevacizumab use (yes vs no)
- Region (US vs EU vs ROW)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)[b]

Primary Endpoint: PFS per RECIST v1.1 by investigator

Key Secondary: OS

[a]Docetaxel (75 mg/m^2 Q3W) may be considered in participants with severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel after consultation with the Sponsor. [b]The combined positive score (CPS) was assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and defined as the number of PD-L1 CPS ≥1 cells (tumor cells, lymphocytes, macrophages) divided by the total number of tumor cells × 100.

Key Secondary Endpoint: Overall Survival in the CPS ≥1 Population at IA2



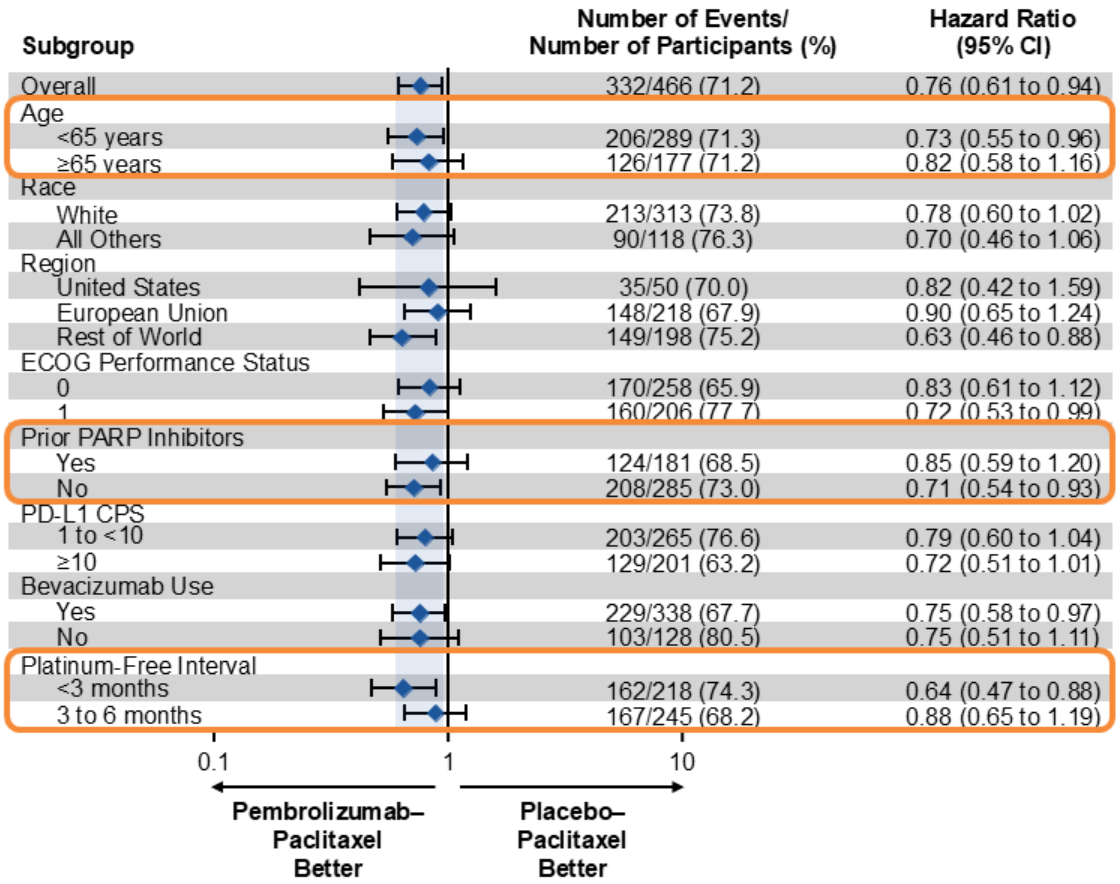
HR 0.76 (95% CI, 0.61-0.94)
***P* = 0.0053[a]**

	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	67.1%	18.2 (15.3-21.0)
Placebo Arm	75.4%	14.0 (12.5-16.1)

Information fraction: 90.0%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0083 at this planned second interim analysis. Data cutoff date: March 5, 2025.

Overall Survival in Subgroups in the CPS ≥1 Population at IA2



Data cutoff date: March 5, 2025.

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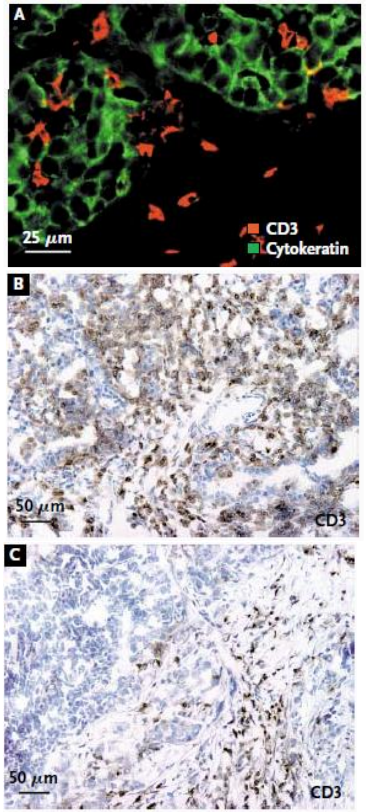
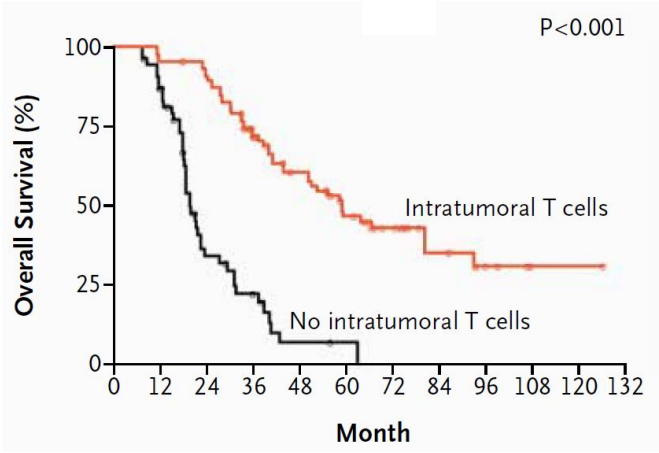
Future Perspectives

Who benefits most from IO? TIL, ADC, precision therapy

Adoptive T cell therapy (ACT) in ovarian cancer

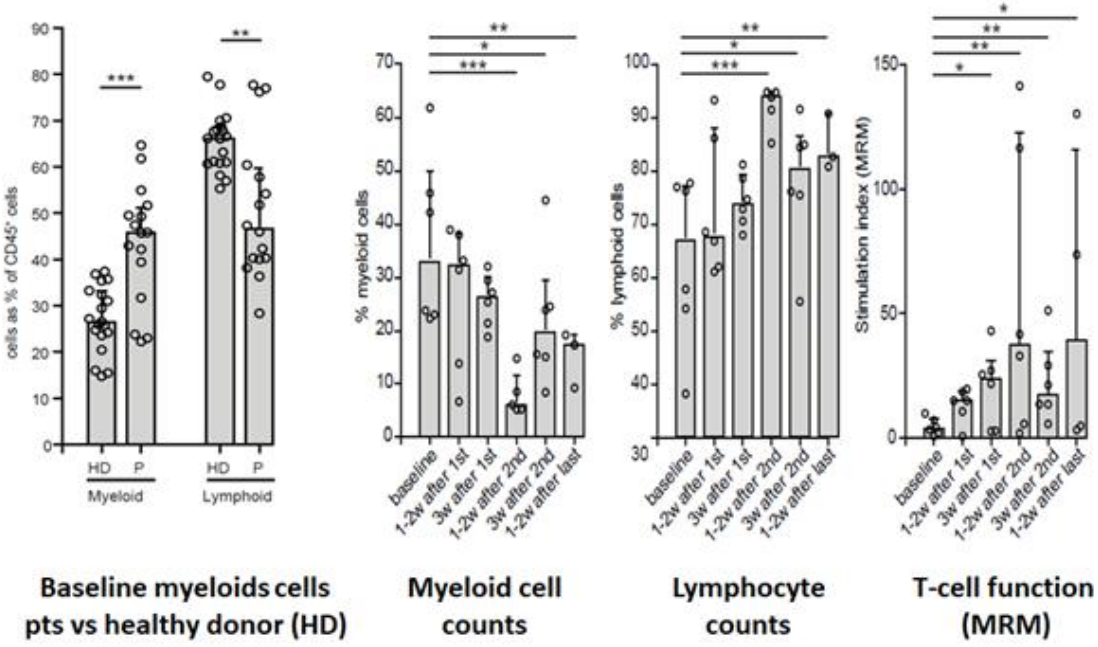




- The presence of tumor infiltrating lymphocytes (TIL) is associated with a longer overall survival in advanced stage EOC
- Despite evidence of a highly active immune tumor environment, immunotherapy has only limited success in ovarian cancer

Zhang et al NEJM 2003

Chemotherapy normalizes suppressive myeloid cells, while maintaining immune stimulating cells



Baseline myeloids cells pts vs healthy donor (HD)

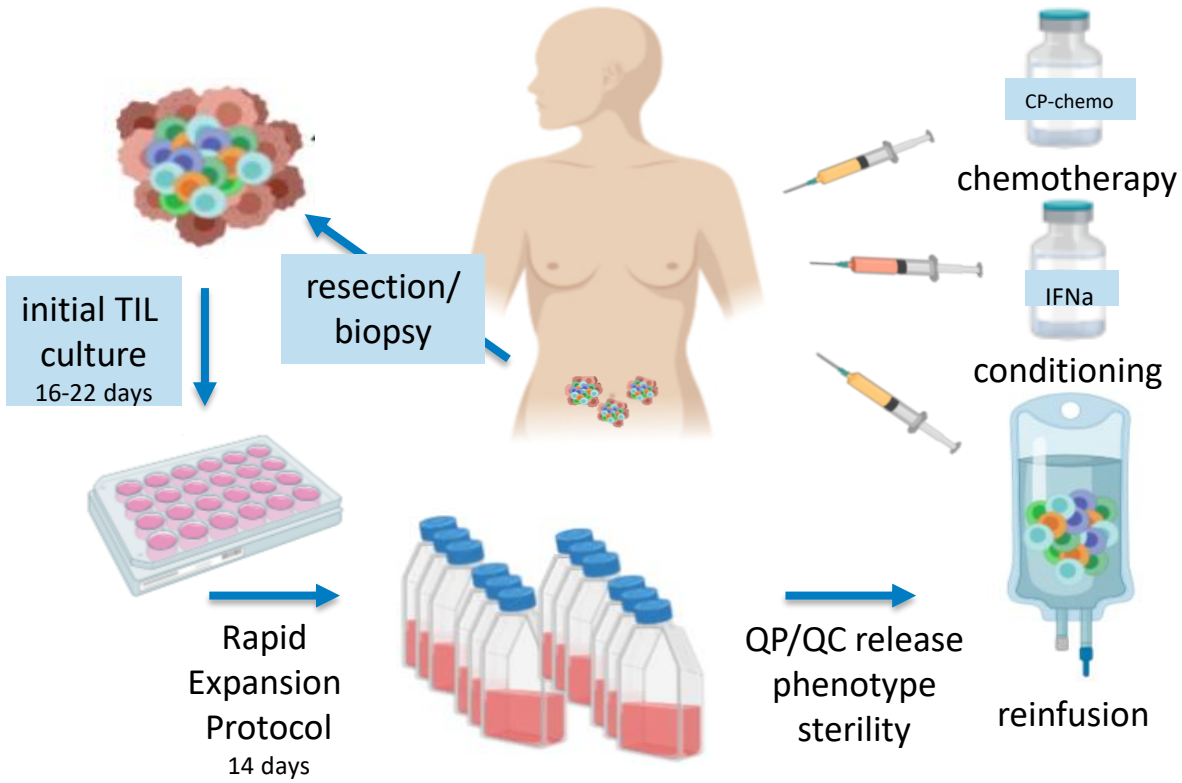
Myeloid cell counts

Lymphocyte counts

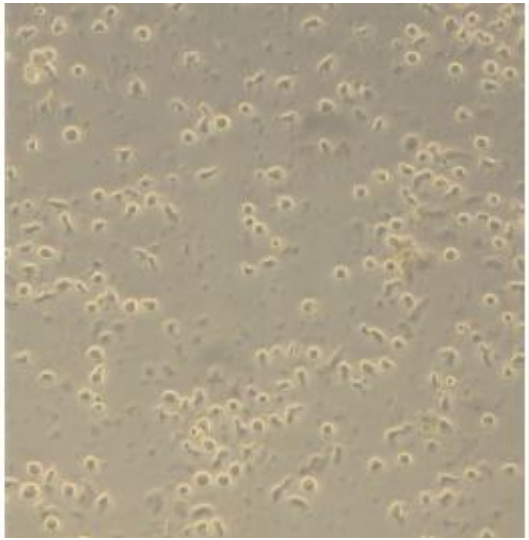
T-cell function (MRM)

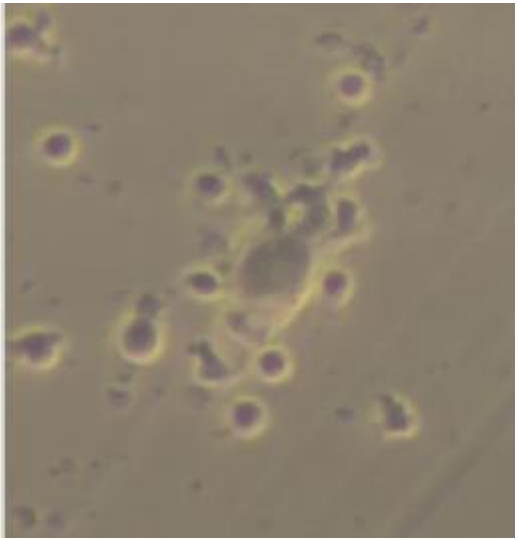
Welters MJ, Sci Trans Med 2016

Adoptive T-cell therapy using TIL

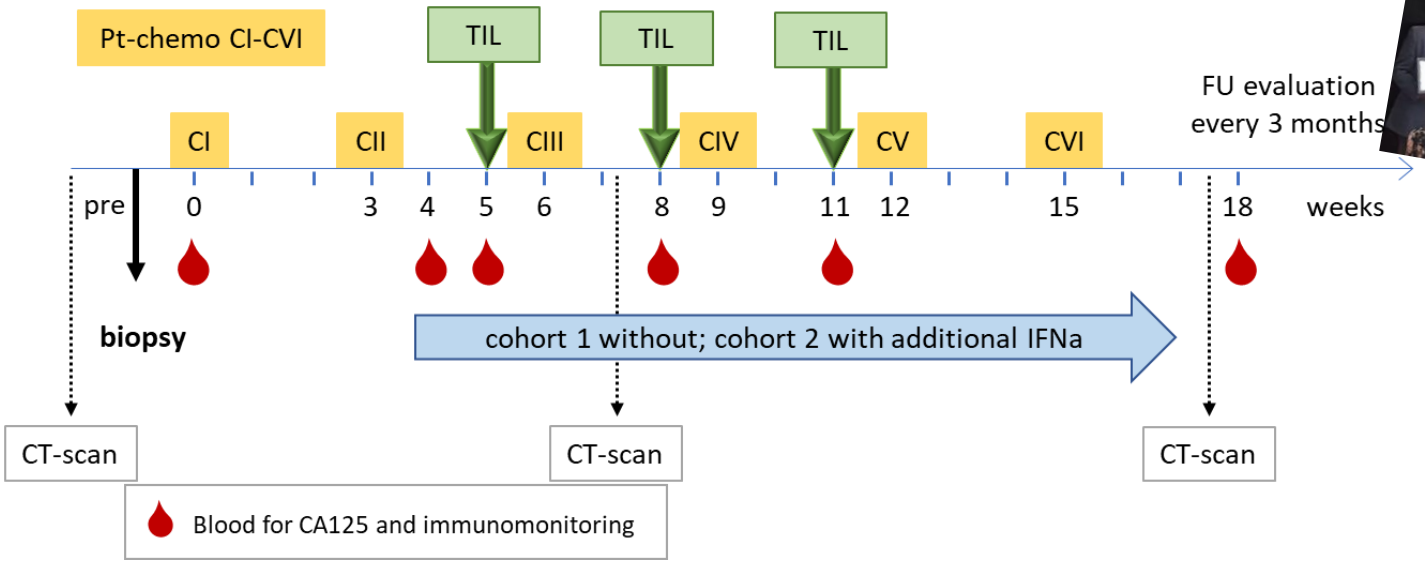


TIL production, culture and activity





OVACUre: TIL during standard chemotherapy in ovarian cancer



Inclusion: Patients with recurrent platinum-sensitive EOC

Primary objective: Safety and feasibilty *w/o IFNa*

Secondary objectives: best objective response, disease control rate, immunomodulation

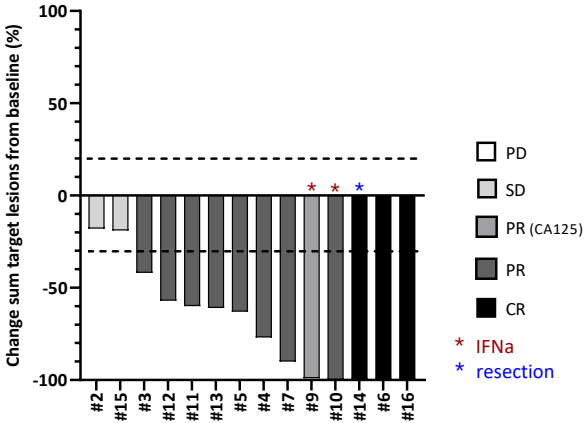
Verdegaal et al, J Immunotherapy Cancer 2023

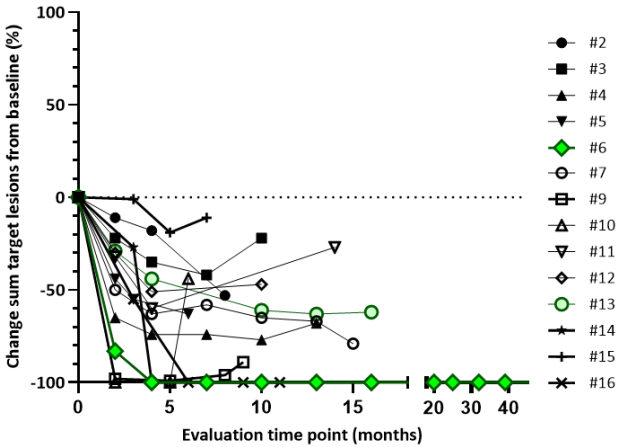
Feasibility and Safety assessment

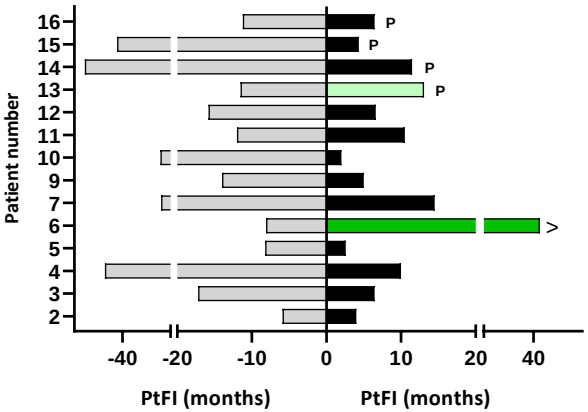
- ACT with TIL in ovarian cancer is feasible
- TIL during standard chemotherapy is safe
- IFNa ‘conditioning and support’ adds to chemotherapy-induced toxicity (thrombo- and neutropenia) → study low dose IL-2 support

Verdegaal et al, J Immunotherapy Cancer 2023

Promising tumor response





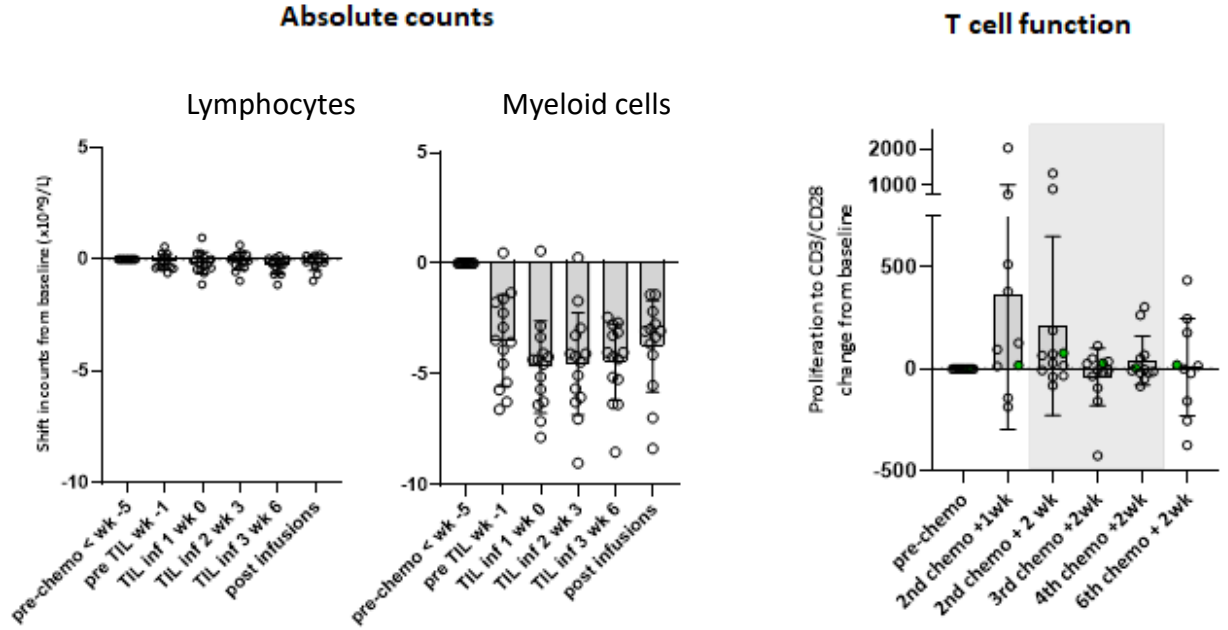


ORR 12/14 → 86%
DCR/CB; CR, PR and SD (>6 months) 13/14 → 93%

Generally, duration secondary responses shorter than prior responses to same regimen

Verdegaal et al, J Immunotherapy Cancer 2023

Changes in blood myeloid and lymphoid cell counts



Myeloid cells are reduced by CP-chemotherapy while lymphoid cell frequencies and function are not affected

Verdegaal et al, J Immunotherapy Cancer 2023

OVACUre trial Summary

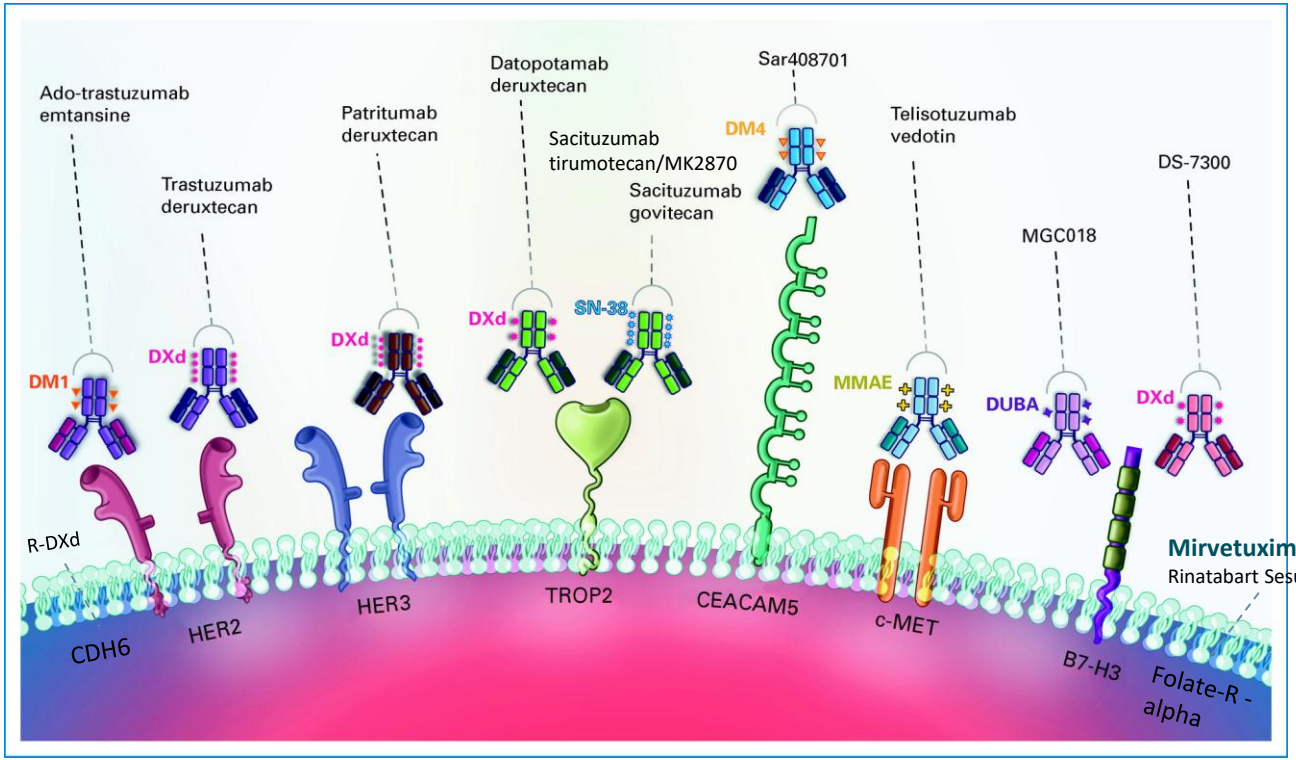
Tumor response

- Promising efficacy observed

Immune effects

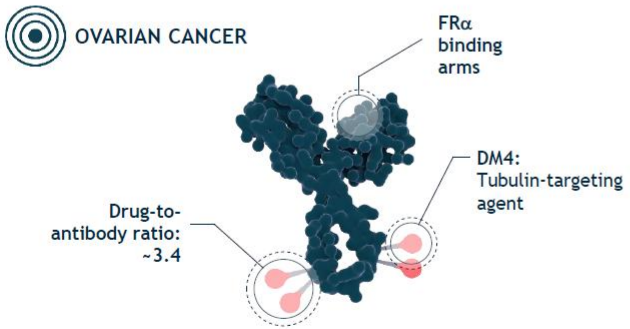
- Chemotherapy induced myeloid cell reduction and optimal myeloid/lymphocyte ratios obtained at 1-2 weeks after 2nd chemo; optimal timing TIL infusions
- CP-chemotherapy reduces serum level of IL-6; crucial factor for MDSC recruitment and differentiation in the TME
- Alternative less toxic IL-2 instead of IFNa may further improve outcome

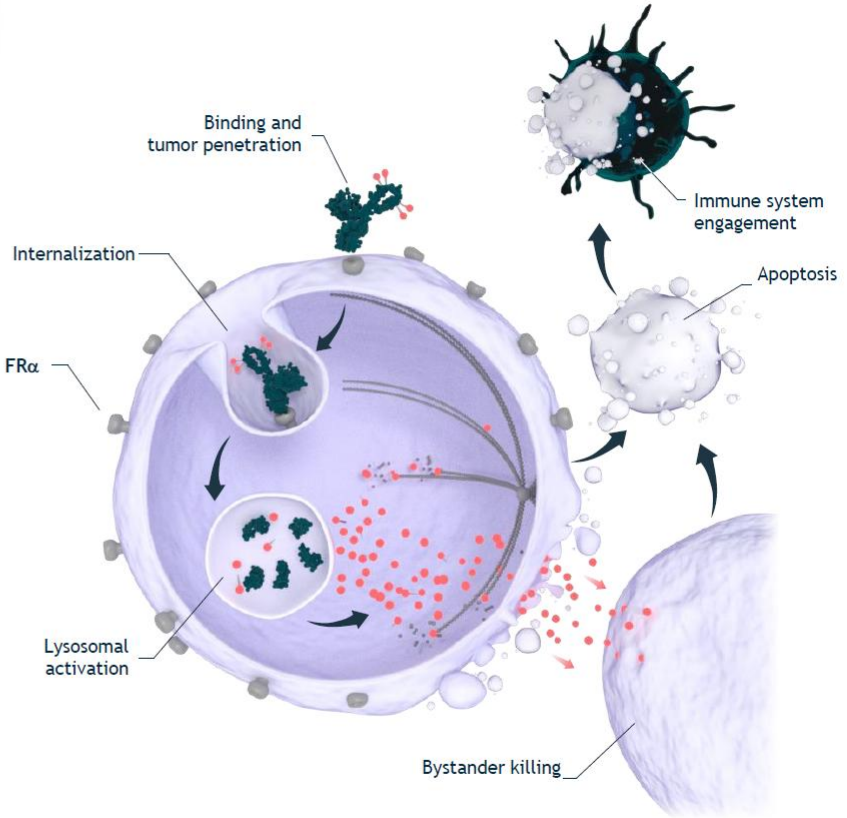
Antibody Drug Conjugates (ADC) are comming



Mirvetuximab Soravtansine Structure

ADC Structure and MOA[1-2]
Name: Mirvetuximab Soravtansine-gynx
Antibody target: FRα
Payload: DM4
Conjugation: Via lysine (random)
DAR: ~3.4
MOA: Microtubule disruption
Bystander targeting: Yes





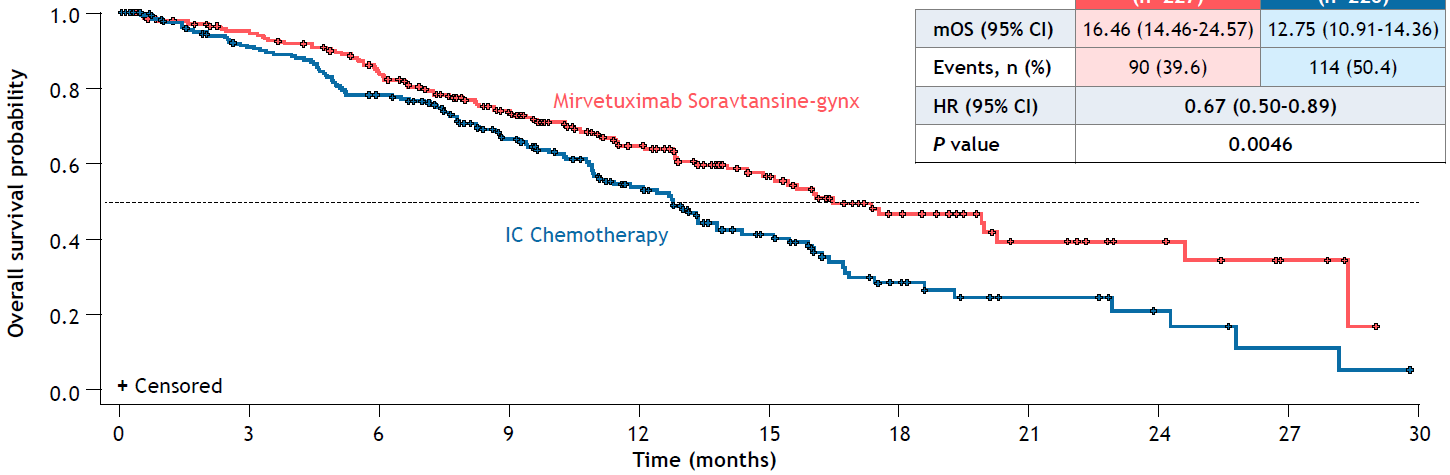
ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; FRα, folate receptor alpha; MOA, mechanism of action.
1. Moore K, et al. Poster presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103. 2. Ab O, et al. *Mol Cancer Ther*. 2015;14(7):1605-1613.

Mirvetuximab Soravtansine Overall Survival data

MIRASOL Trial

Overall Survival[a]

	MIRV (n=227)	IC Chemotherapy (n=226)
mOS (95% CI)	16.46 (14.46-24.57)	12.75 (10.91-14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50-0.89)	
P value	0.0046	



No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemotherapy	226	185	157	107	68	39	18	9	5	2	0

Adverse Events of Special Interest by Type of IC Chemotherapy[a]

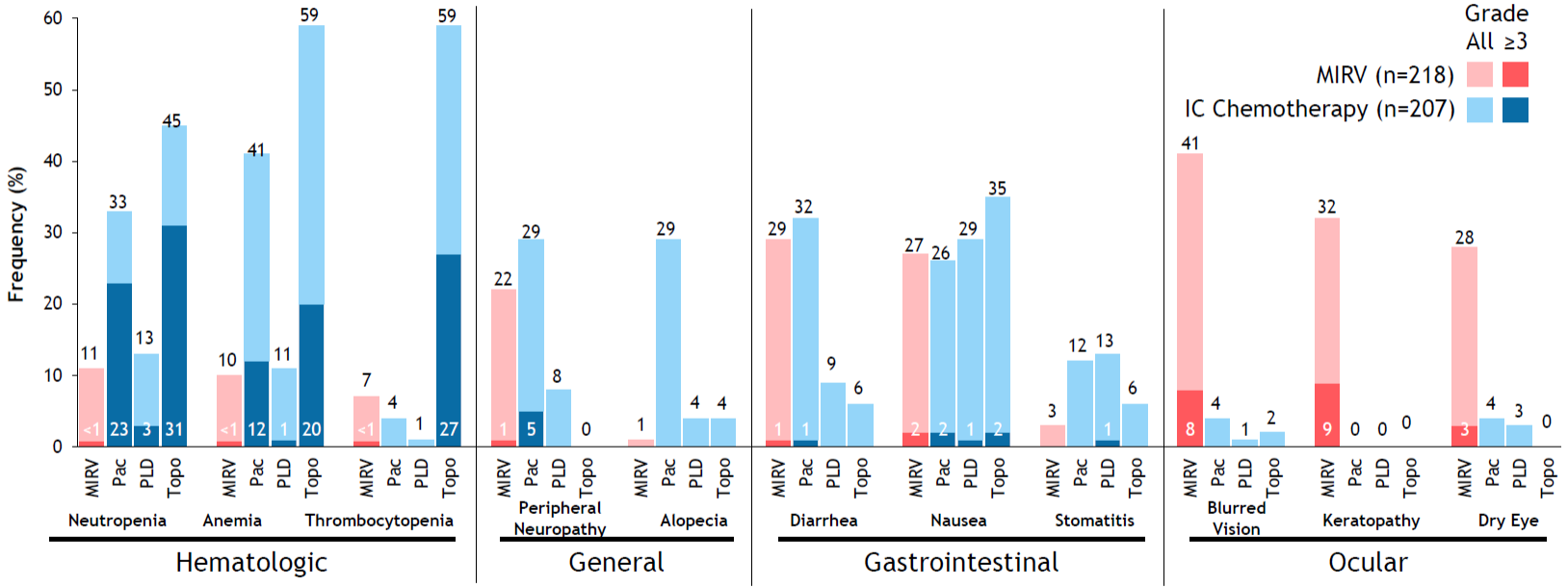
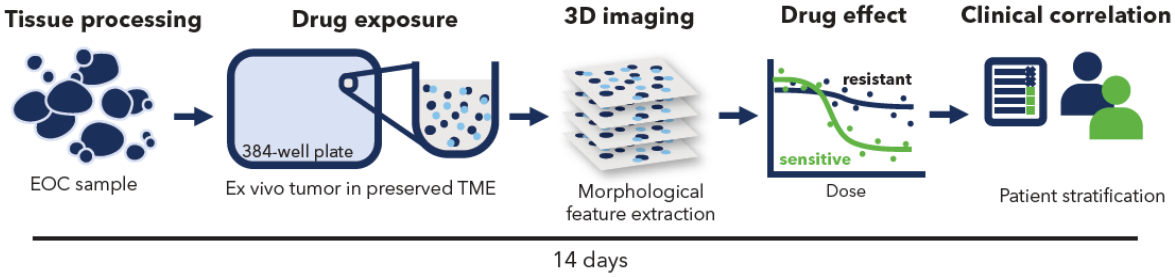


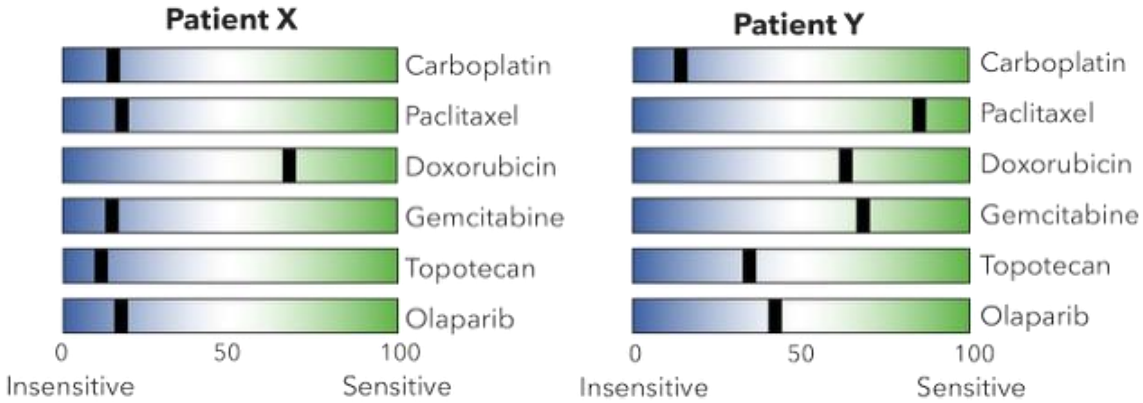
Figure adapted from Moore KN, et al.[1]
Data cutoff: March 6, 2023.
Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
IC, investigator's choice; MIRV, mirvetuximab soravtansine-gynx; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.
[a]Safety population.

1. Moore KN, et al. American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023. Presentation LBA5507. 2. Moore KN, et al. N Eng J Med. 2023;389:2162-2174, incl. supplementary appendix.

immunogen

Drug sensitivity Score (vitroscan)





Koedoot E NPJ Precis Oncol. 2025

Olijf

- Informatie over gynecologische kankers
- Ervaringsdeskundigen
- Lotgenoten
- Leven met/na kanker

Olijf
Patiëntenorganisatie gynaecologische kanker

https://olijf.nl/Gynaecologische kanker - algemeen | Olijf

Summary

- Ovarian cancer has poor prognosis and high unmet need
- Firstline therapy: chemotherapy plus/min HIPEC and plus/min PARPi
- Immunotherapy: checkpoint inhibition so far no standard therapy in Nl, TIL, Bispecific ab, ADC’s in trial
- Future perspectives: ADC’s, Cellular therapies
- OLIJF

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Thank you, Questions?