Leiden University
Medical Center

Nieuwe ontwikkelingen “Immunotherapie bij gynaecologische maligniteiten”

Jan keizer Symposium
15 april 2026

Prof. dr. Judith Kroep MD PhD
Medical Oncology – Oncode Institute
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					

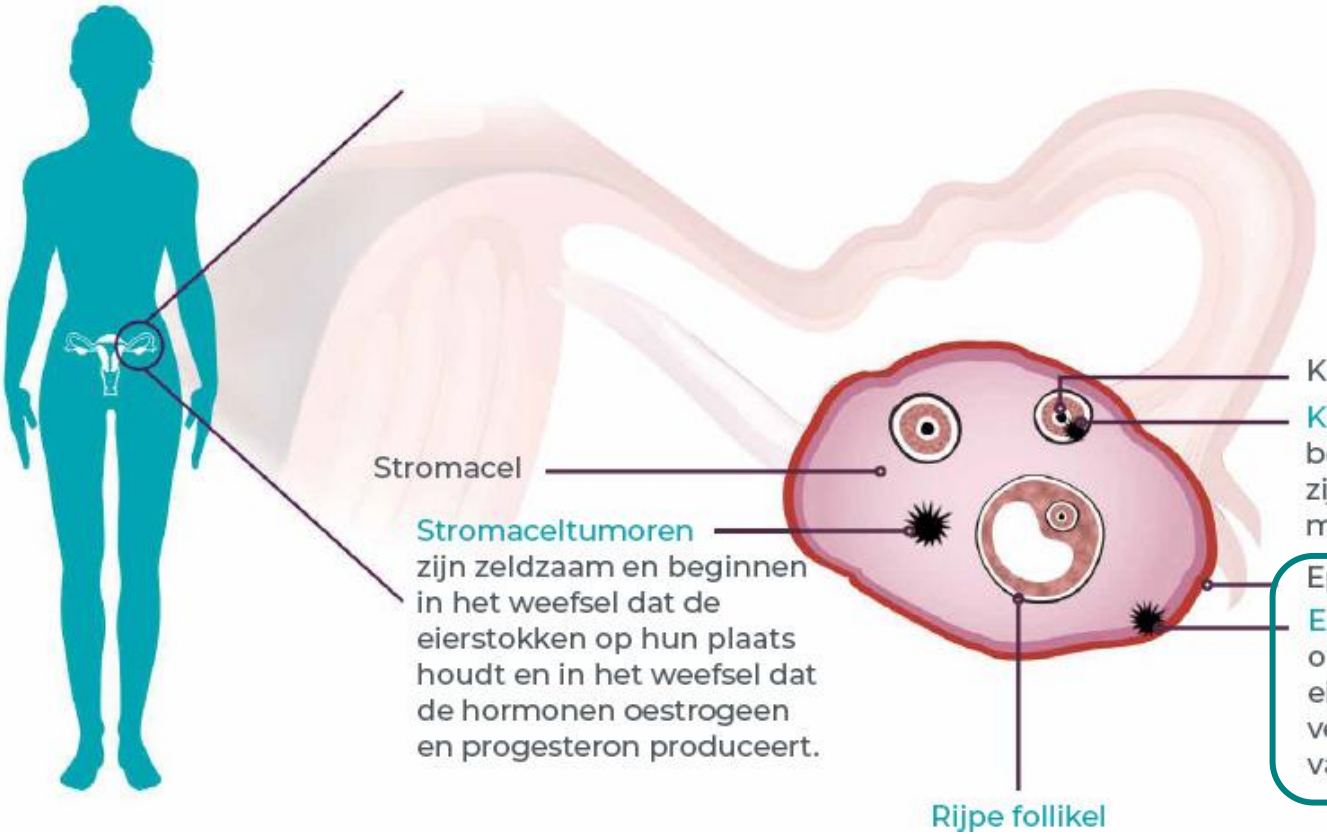
Introduction

- Epidemiology
- Ovarium cancer
- Endometrial cancer
  - Current therapy
  - New developments

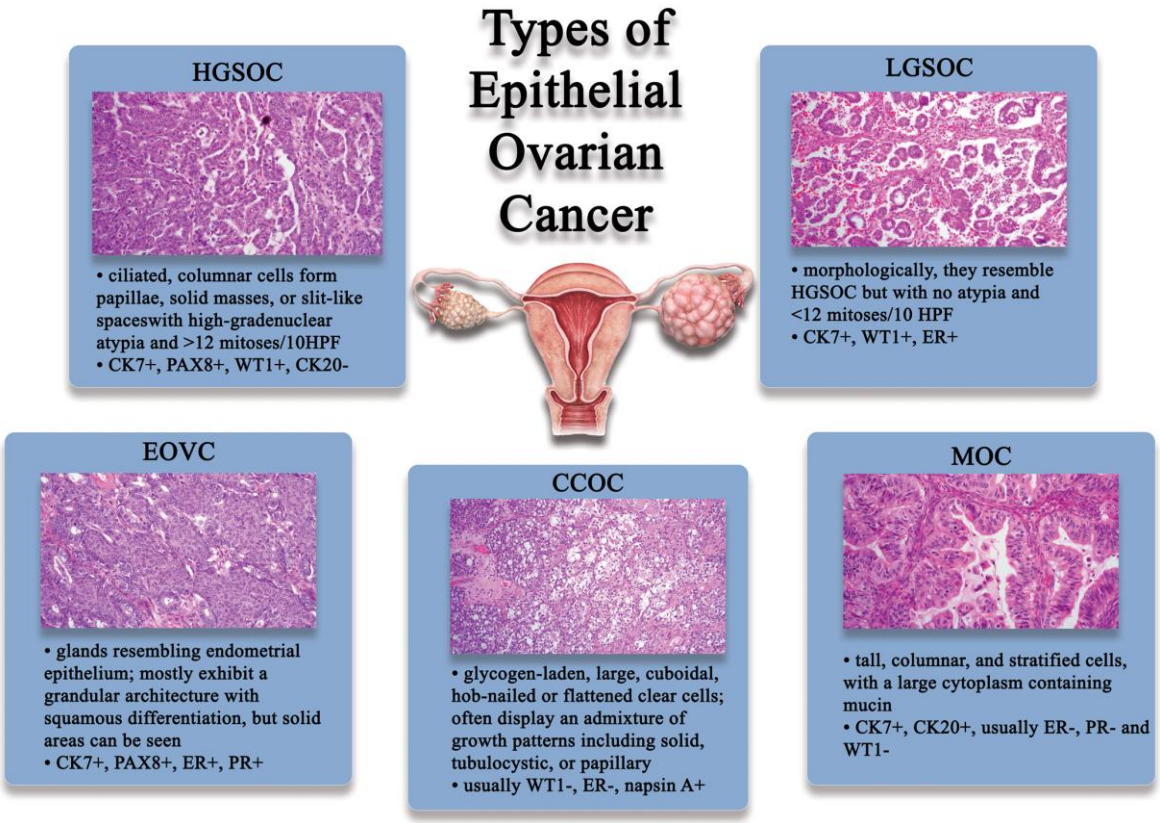
Epidemiology Ovarian Cancer

- 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

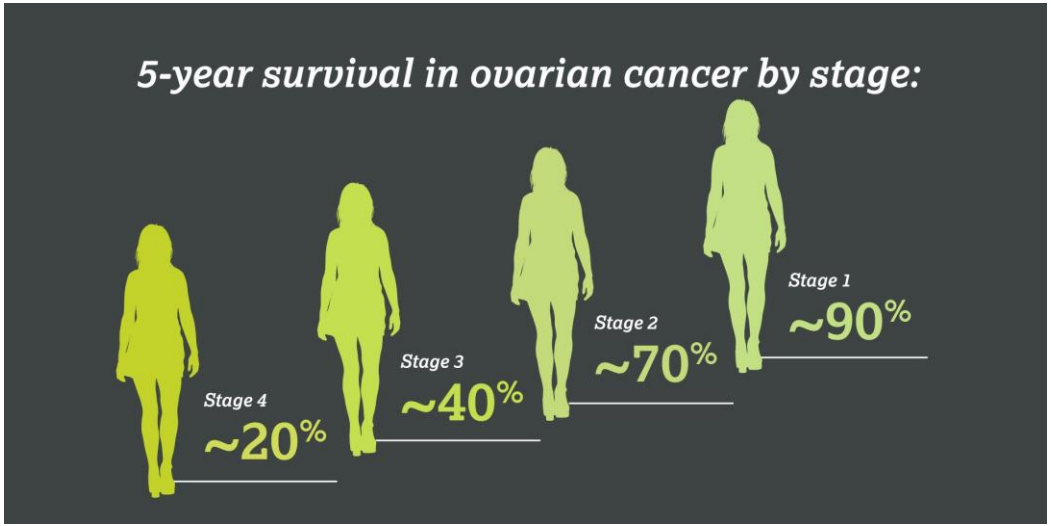


OC – ovarian cancer

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

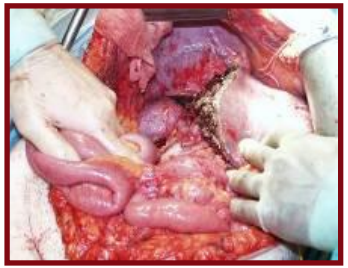
MOC – mucinous OC

5-year Overall Survival



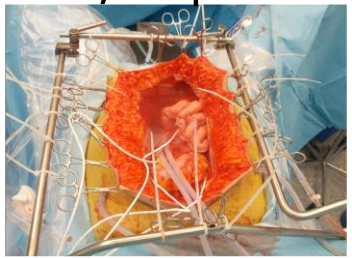
Filippova, Gyn Oncol 2021

Primary therapy (curative intent)



Surgery with maximum cytoreduction effort <1cm residual disease

+/- hipec

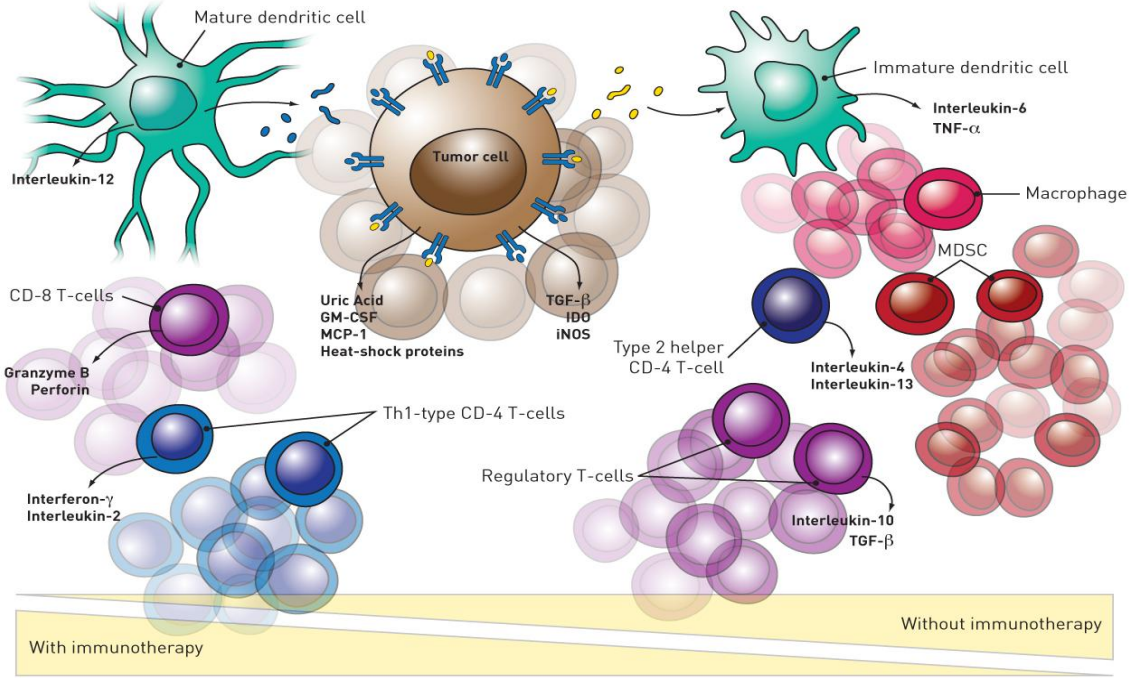


Chemotherapy +/- PARP inhibition
(Carboplatin + Paclitaxel)

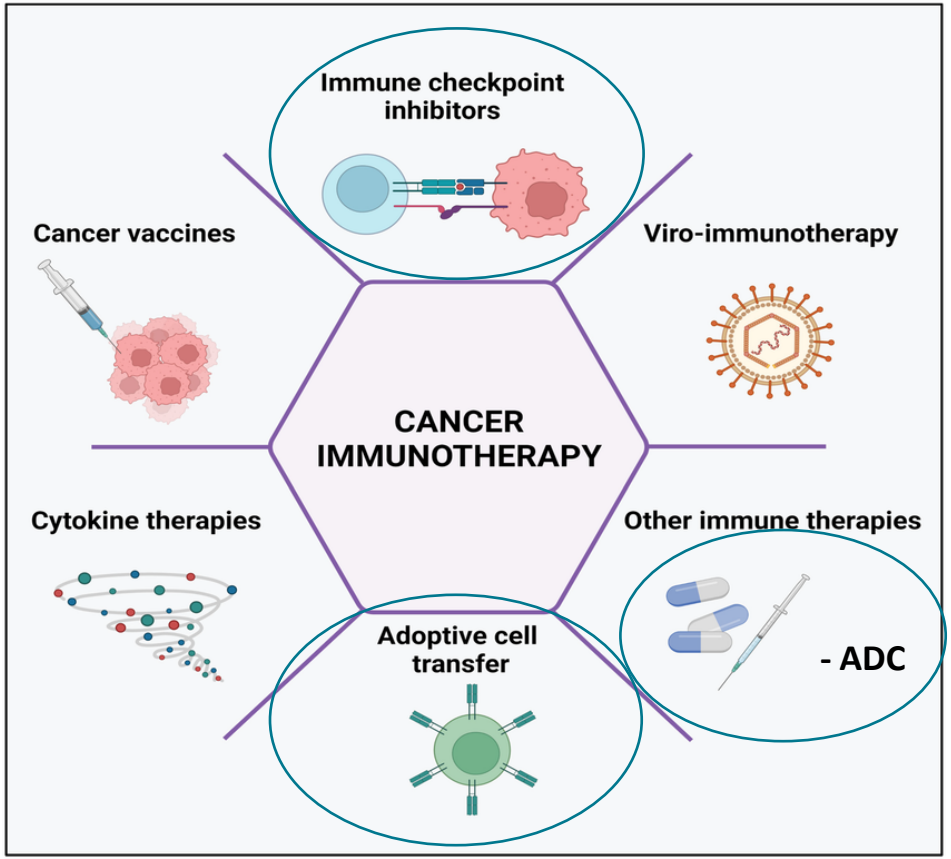
Immunotherapy Tumormicroenvironment

Immunostimulation

Immunosuppression



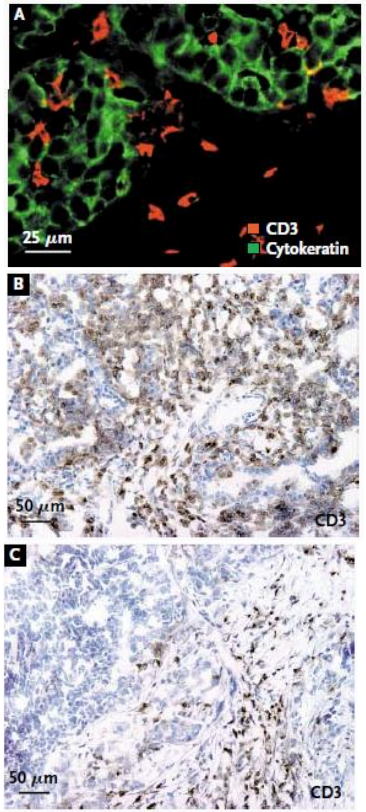
Cancer Immunotherapy Types

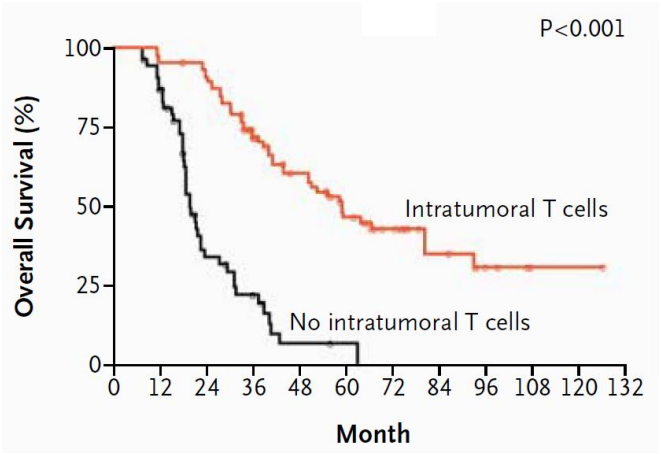


Checkpoint inhibition for primary Ovarian Cancer

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 + atezolizumab	18.4 19.5	negative
DUO-O	3	New EOC	CP/bev CP/bev/durva>bev/durvalumab 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 dostarlimab	19.2 20.6	negative
Keylynk001	3	New EOC	CP > olaparib CP+ pembro> olaparib/pembrolizumab	15.2 23.9	negative

Adoptive T cell therapy (ACT) in ovarian cancer



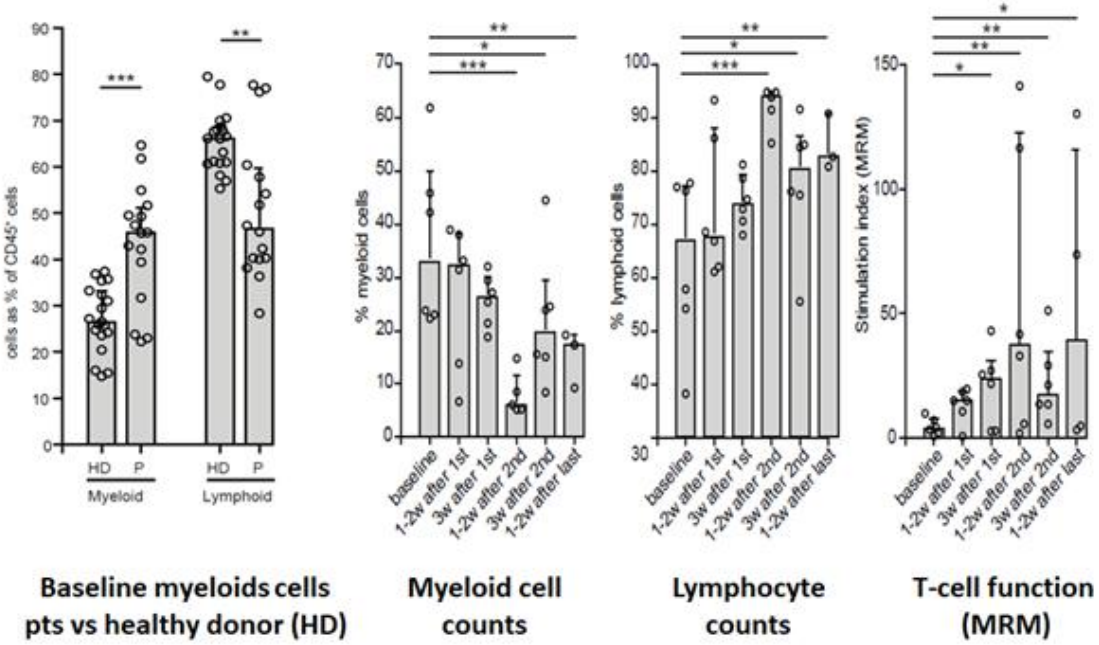


- The presence of tumor infiltrating lymphocytes (TIL) is associated with a longer overall survival in advanced stage EOC

Research

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

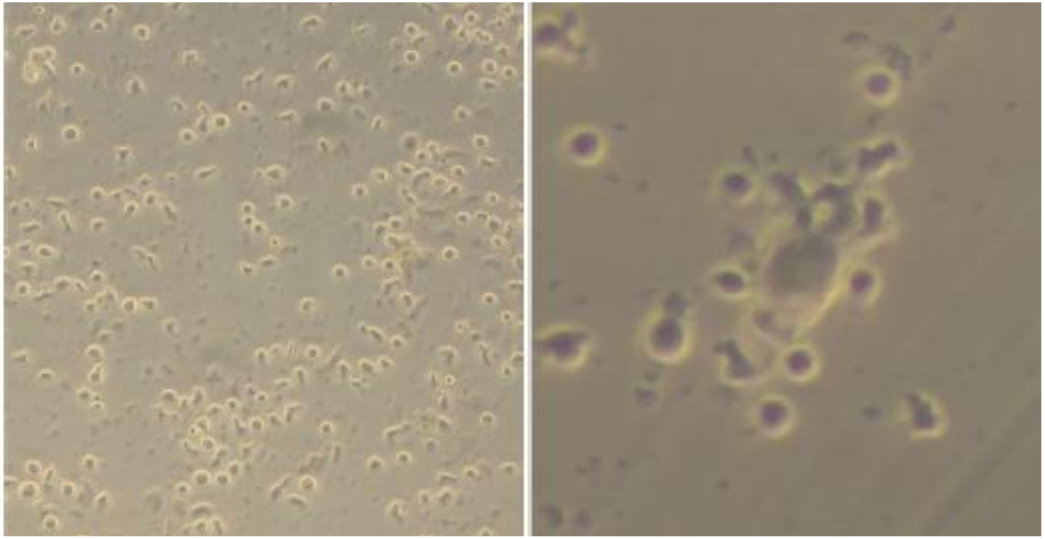
Lymphocyte counts

T-cell function (MRM)

Research

Welters MJ, Sci Trans Med 2016

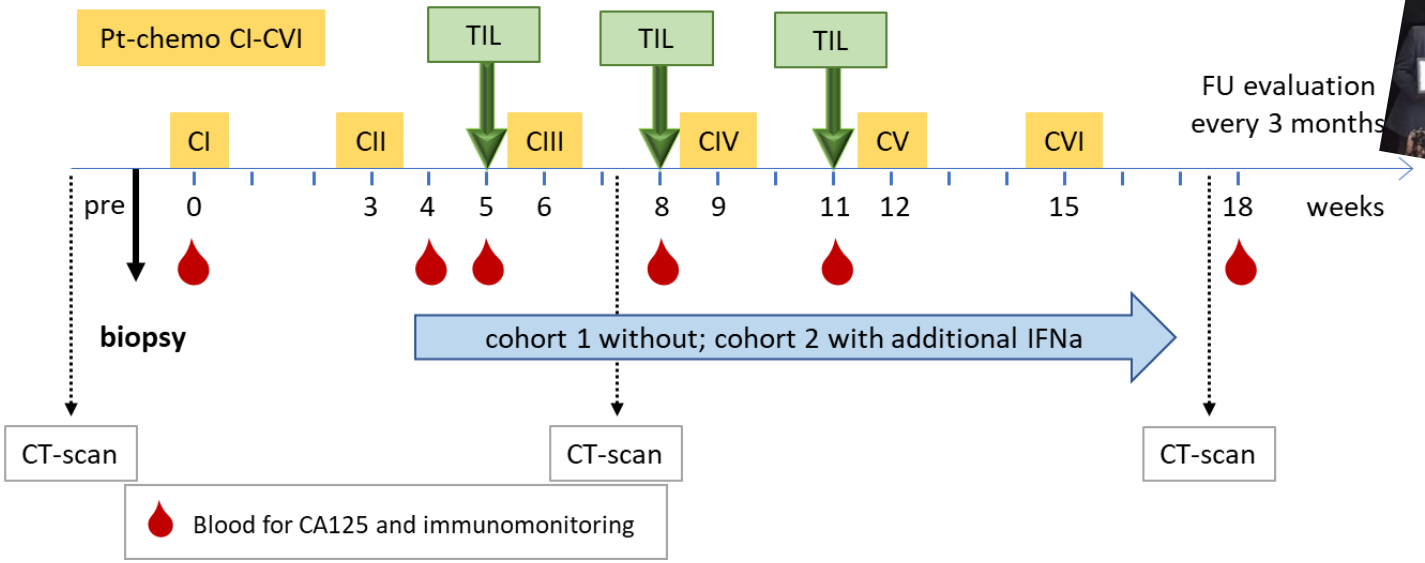
TIL production, culture and activity



https://www.youtube.com/shorts/fvRIGEpFrOI?t=10&feature=share/fvRIGEpFrOI?feature=share

Research

OVACUre: TIL during standard chemotherapy in ovarian cancer



Inclusion: Patients with recurrent platinum-sensitive EOC

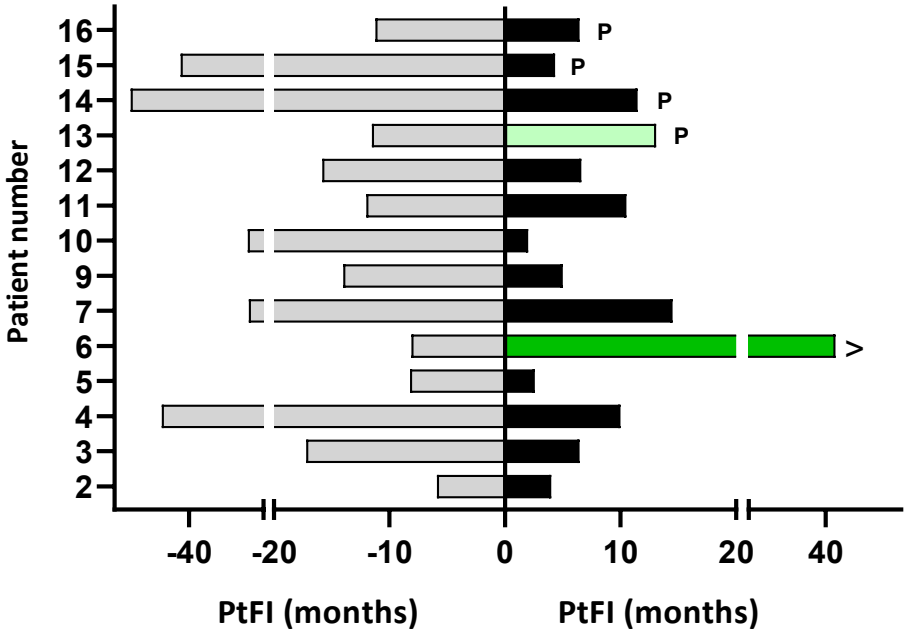
Primary objective: Safety and feasibilty *w/o IFNa*

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

Research

Verdegaal et al, J Immunotherapy Cancer 2023

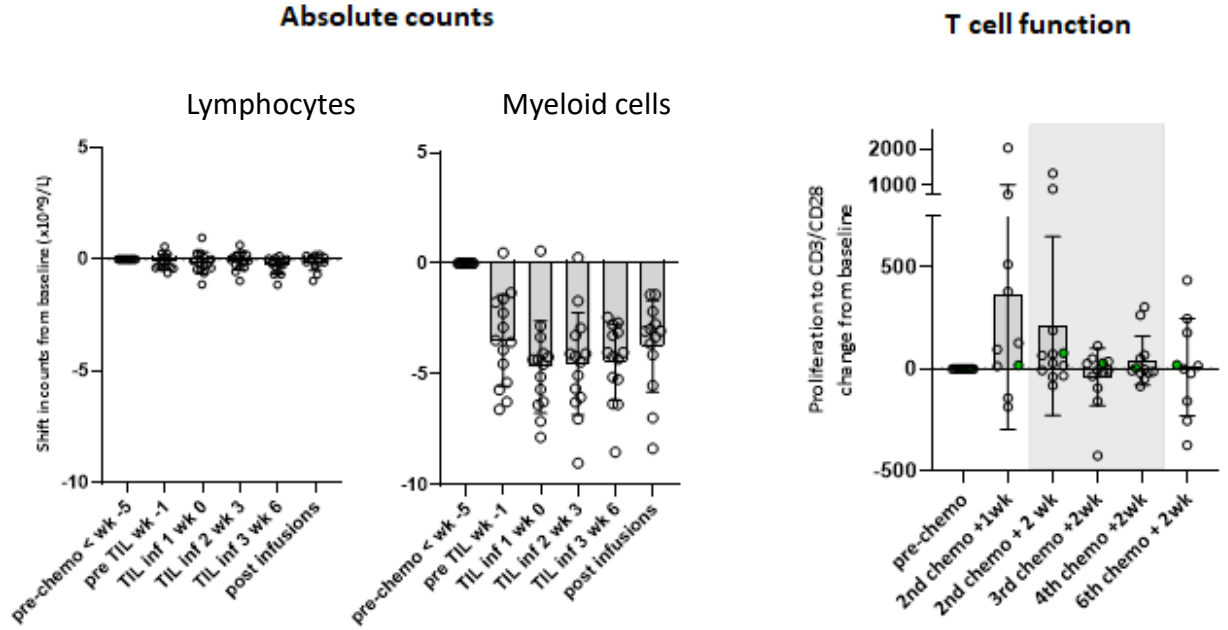
Promising tumor response



Research

Verdegaal et al, J Immunotherapy Cancer 2023

Changes in blood myeloid and lymphoid cell counts

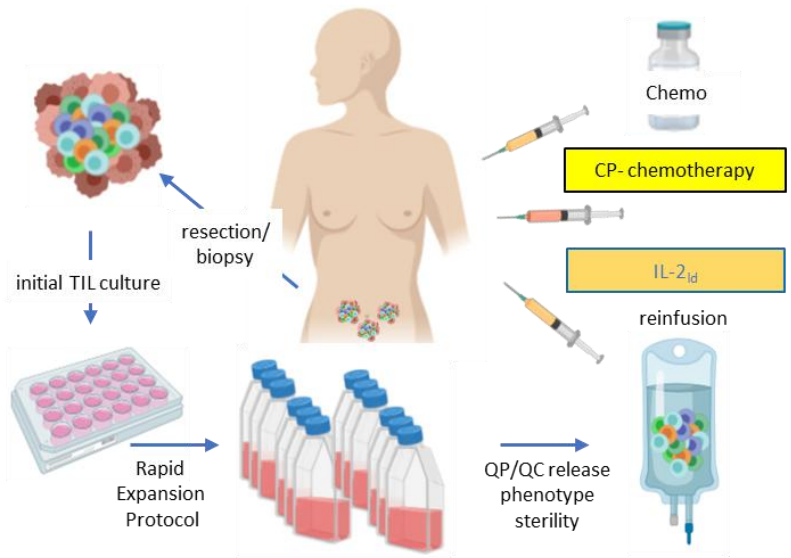


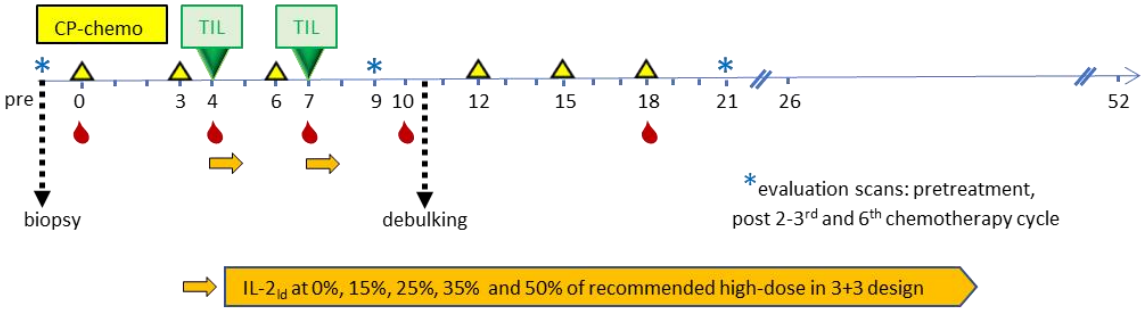
Myeloid cells are reduced by CP-chemotherapy while lymphoid cell frequencies and function are not affected

Research

Verdegaal et al, J Immunotherapy Cancer 2023

OVACURE-2 for primary stage IV ovarian cancer





Research

Checkpoint inhibition for Recurrent Ovarian Cancer

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	Positive for PFS & OS

Checkpoint inhibition for Recurrent Ovarian Cancer

Pembrolizumab plus weekly paclitaxel in platinum-resistant recurrent ovarian cancer (ENGOT-ov65/KEYNOTE-B96): a multicentre, randomised, double-blind, phase 3 study

Nicoletta Colombo, Emese Zsiros*, Gabriella Parma, Eliana Rulli, Alexandra Sebastianelli, Mariusz Bidzinski, Carlos Gallardo, Emad Matanes, Kosei Hasegawa, Fatih Kose, Manuel Magallanes-Maciel, Rebecca A Herbertson, Sumitra Ananda, Judith R Kroep, Andreia Cristina de Melo, Philip R Debruyne, Jae-Weon Kim, Jalid Sehouli, Marc-Edy Pierre, Sakari Hietanen, Claudio Zamagni, Xin Lu, Bradley J Monk, Robert L Coleman, Xuan Peng, Karin Yamada, Agata M Bogusz, Thibault De La Motte Rouge, Xiaohua Wu, on behalf of the ENGOT-ov65/KEYNOTE-B96 investigators†*

Summary

Background Epithelial ovarian cancer frequently recurs and becomes resistant to platinum chemotherapy. We investigated whether adding pembrolizumab to weekly paclitaxel, with or without bevacizumab, improves progression-free survival and overall survival compared with weekly paclitaxel, with or without bevacizumab, in participants with platinum-resistant recurrent ovarian cancer who had received one to two 2 previous systemic regimens.

Published Online
April 10, 2026
https://doi.org/10.1016/S0140-6736(26)00602-1

FDA and EMA approval

Colombo et al, The Lancet 2026

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

R 1:1
N = 643

Pembrolizumab 400 mg
(Q6W, 18 cycles) +
Paclitaxel[a] 80 mg/m^2 Days 1, 8, 15
of each Q3W cycle
(± bevacizumab 10 mg/kg Q2W)

Placebo
(Q6W, 18 cycles) +
Paclitaxel[a] 80 mg/m^2 Days 1, 8, 15
of each Q3W cycle
(± bevacizumab 10 mg/kg Q2W)

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]

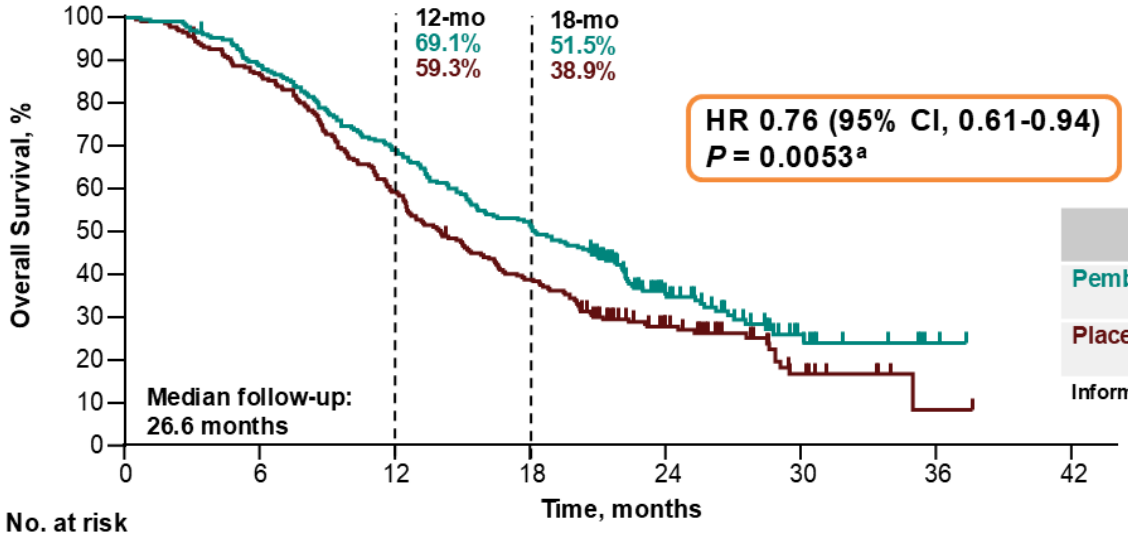
Primary Endpoint: PFS per RECIST v1.1 by investigator

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.

Colombo et al, The Lancet 2026

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%

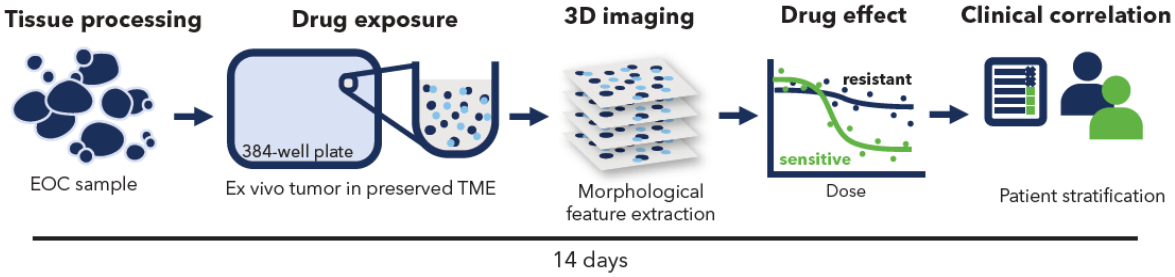
No. at risk

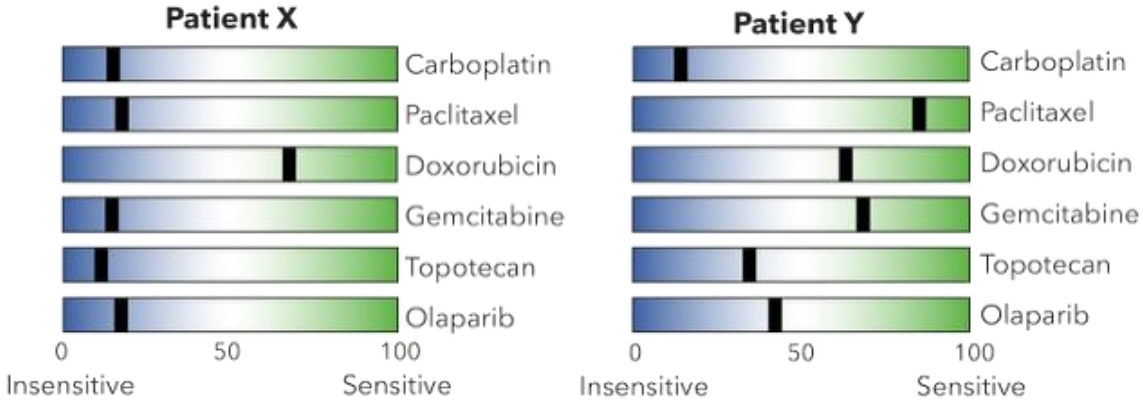
234	207	161	120	49	13	3	0
232	200	137	89	41	10	1	0

[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.

Colombo et al, The Lancet 2026

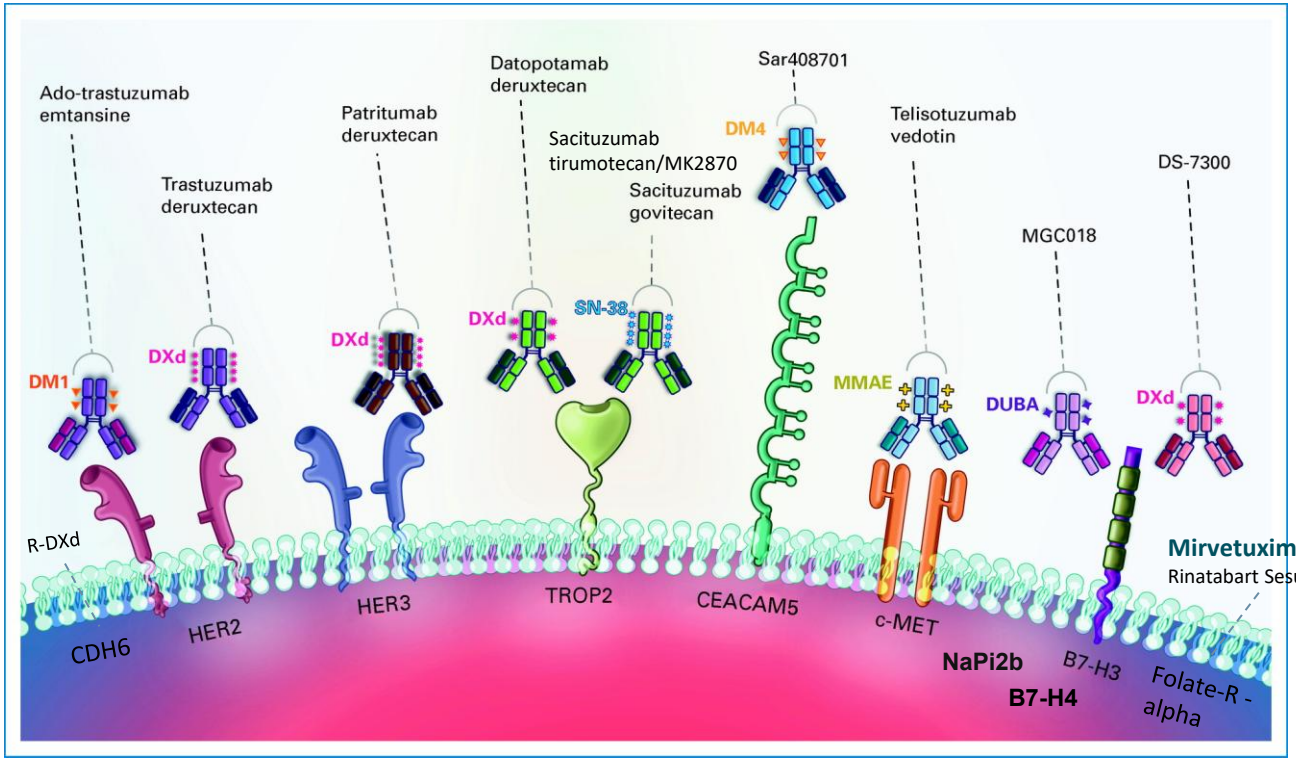
Drug sensitivity Score



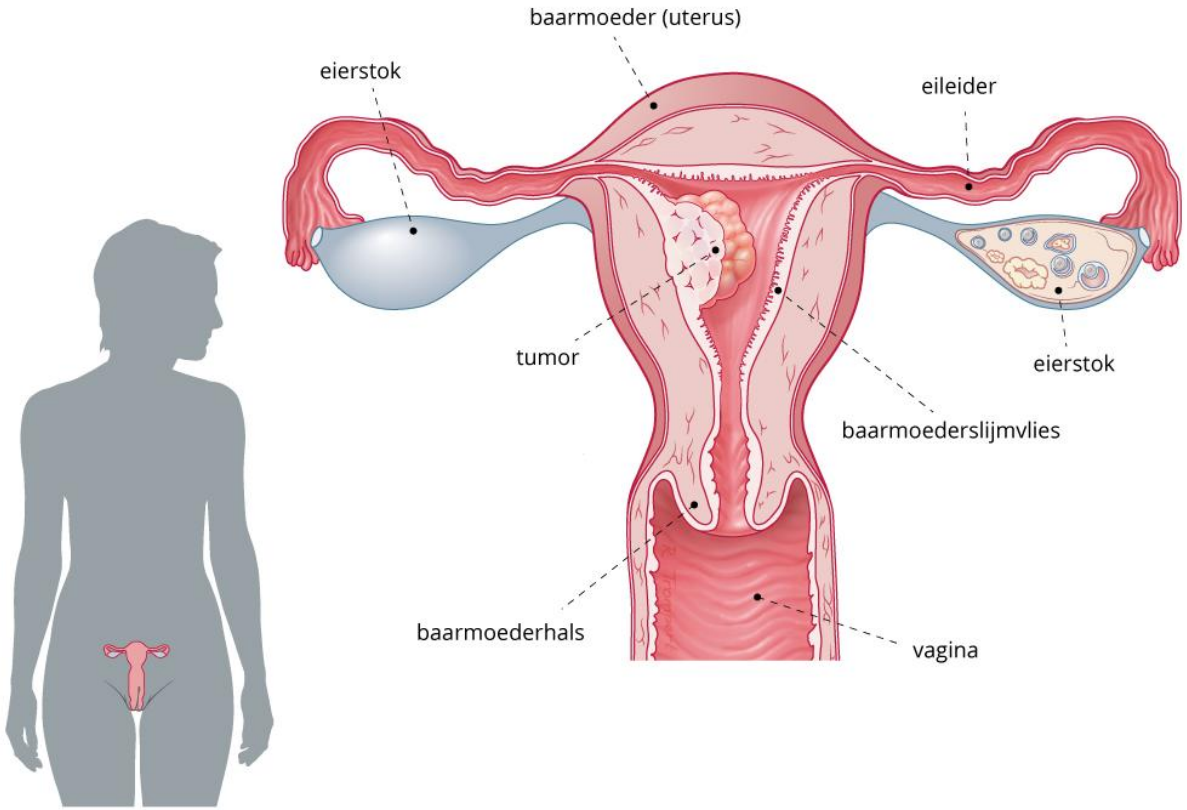


Koedoot E NPJ Precis Oncol. 2025

Antibody Drug Conjugates (ADC) are comming



Endometrial cancer

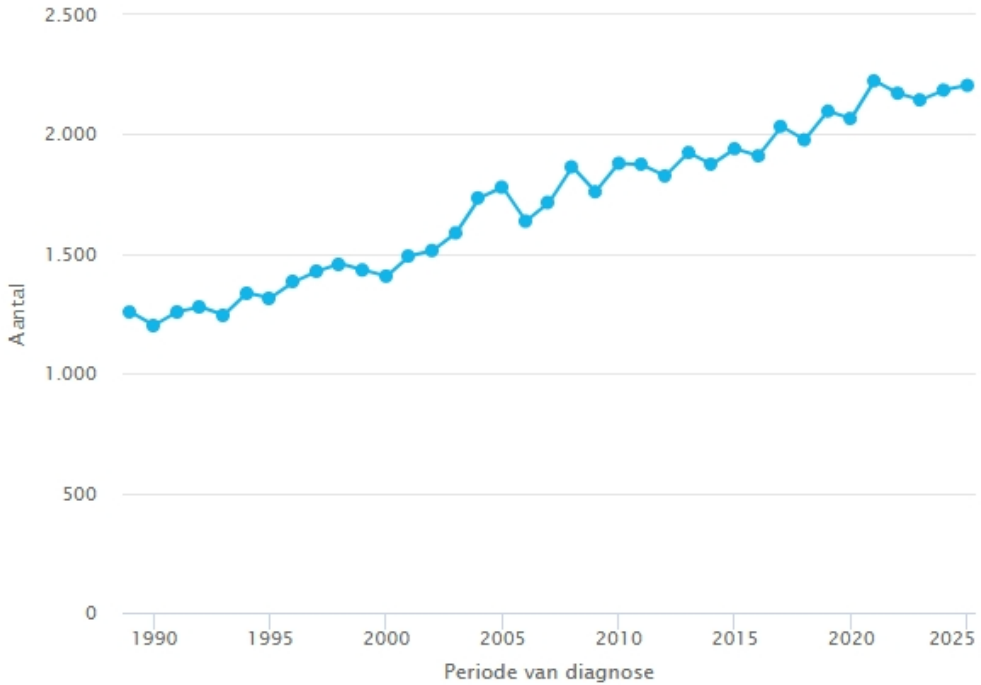


IKNL/NKR data Endometrium Carcinoom (EC)

Incidentie per jaar, Aantal

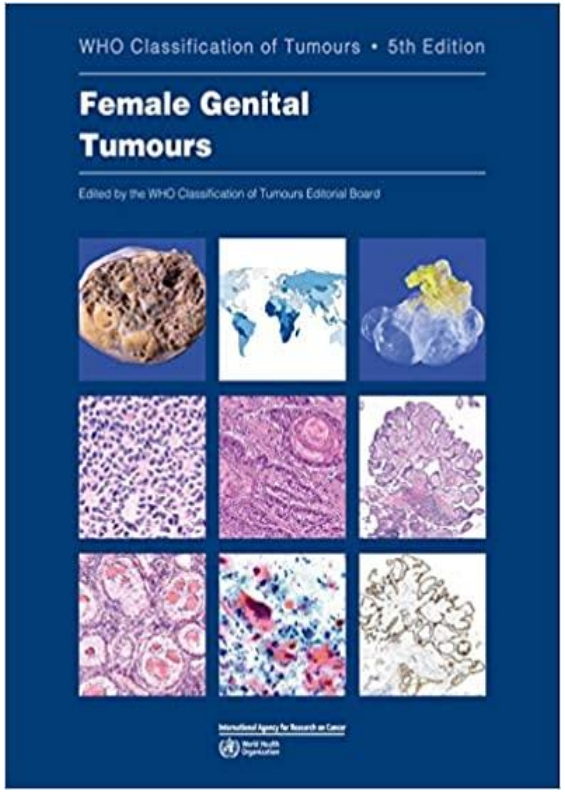
Baarmoederlichaamkanker

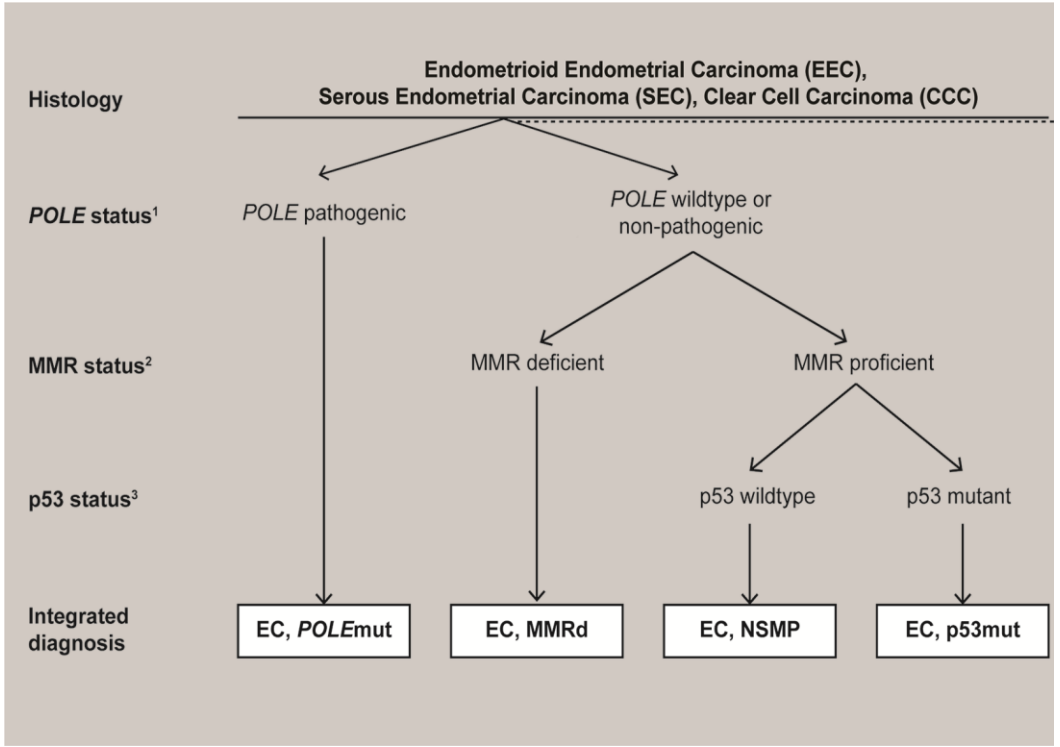
Geslacht: Vrouw | **Leeftijdsgroep:** Totaal | **Regio:** Nederland | **Stadium:** Totaal



2025, 2024: Deze cijfers betreffen voorlopige gegevens.

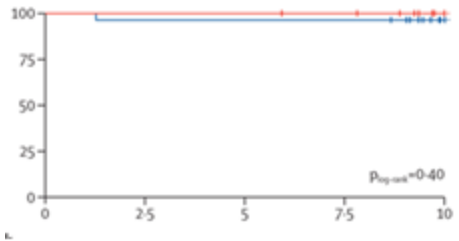
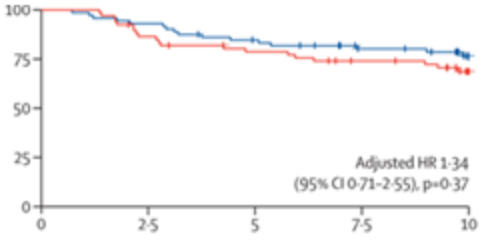
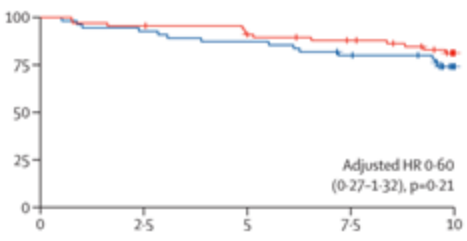
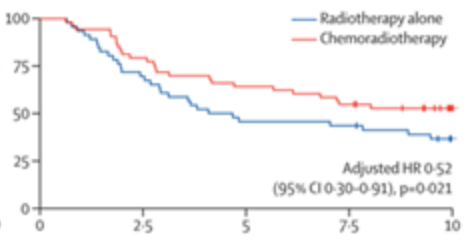
Diagnostic algorithm for the molecular classification of EC





Levine Nature 497, 67-73, 2013; Stelloo Clin Cancer Res 2016; Leon-Castillo J Clin Oncol 2020

Molecular classification is predictive - OS in PORTEC-3 cohort -

All stages *POLE*mut EC	All stages MMRd EC	All stages NSMP EC	All stages p53abn EC
			
Excellent RFS, regardless of treatment arm.	No benefit from CRT	Inconclusive benefit from CRT	Significant benefit from CRT

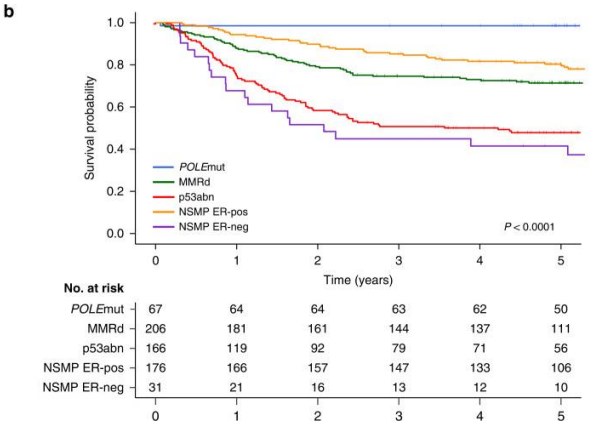
Post CCB, Lancet Oncol 2025

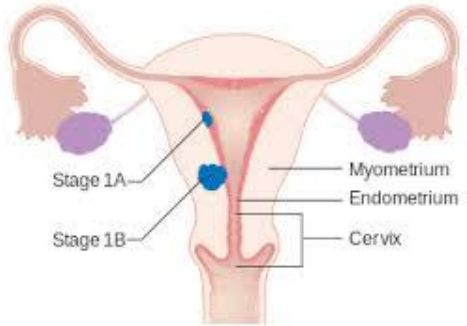
Molecular Classification helps which HR-EC needs adj Chemo

P53-abd: YES, regardless of stage (except stage IA without myometrial invasion)

Stage I/II POLE-mut, MMRd, NSMP ER+: NO

Unsure for NSMP ER-:





Vermij, BJC 2023

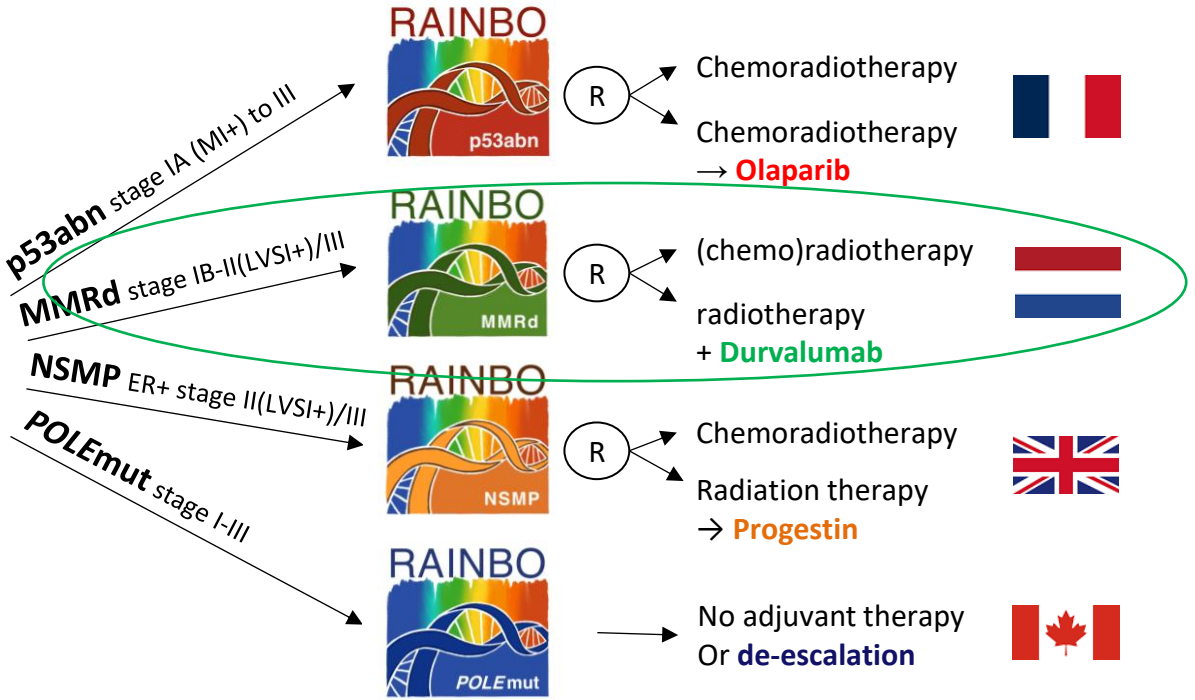
RAINBO program

RAINBO
TransPORTEC

Surgically resected EC

Eligible histotypes:
endometrioid, serous, clear cell, un/dedifferentiated, mixed and carcinosarcoma

⇨ Molecular Classification



RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

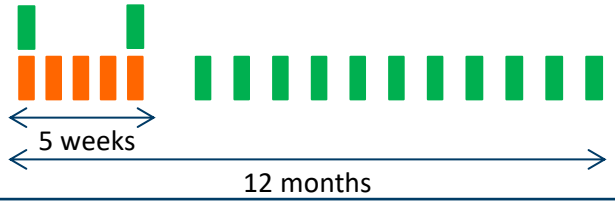
RAINBO Research Consortium, 2022

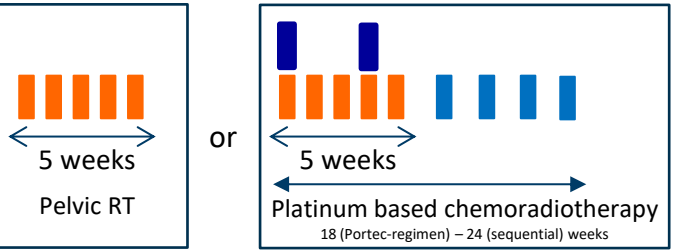
RAINBO MMRd-GREEN

Inclusion criteria:
- MMRd (*POLE* wildtype)
- FIGO 2009 Stage IB/II with LVSI or stage IIIA-C EC plus FIGO 2023 stage III
- WHO 0-1
- TLH-BSO/TAH-BSO regardless of lymph node staging
- No prior pelvic irradiation

1:1

Pelvic RT 45-48.6 Gy + 13x durvalumab 1500 mg **Q4W**





Primary objective:
- 3-yr RFS

Secondary objectives:
- OS, DSS
- Vaginal, pelvic, distant recurrences
- HRQoL
- Safety & tolerability
- Exploratory translational research

Sample size: 316 patients

Treatment initiated within max 10 weeks after surgery
Durvalumab initiated within the 1st week of adjuvant radiotherapy

MMRD-GREEN countries

RAINBO MMRd

Netherlands
Sponsor of MMRd-GREEN

Canada
Sponsor of *POLE*mut-BLUE

United Kindom
Sponsor of NSMP-ORANGE

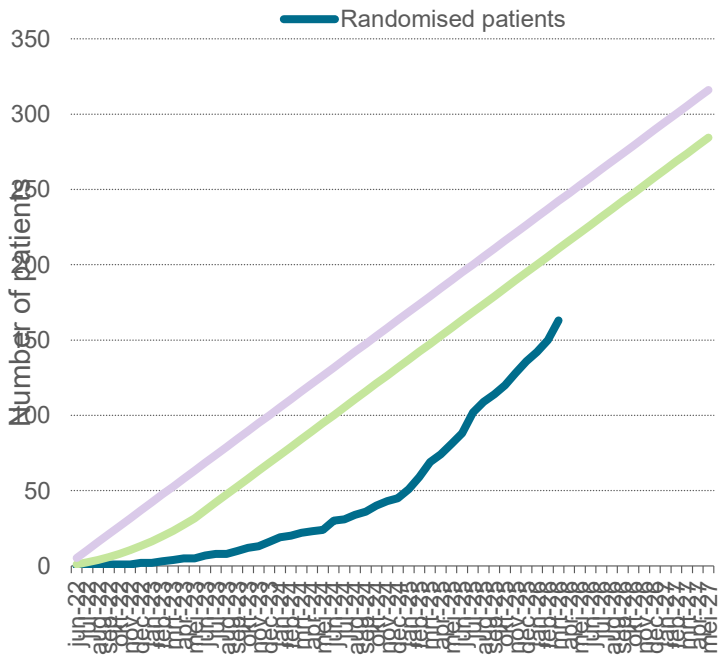
Belgium

Germany

France
Sponsor of p53abn-RED

Czech Republic

Italy



ENGOT-en14 MMRd-GREEN

RCT phase III adjuvant durvalumab (1 yr) plus radiotherapy vs (chemo)radiotherapy

Recruitment: 165/316 patients randomized

Primary Endpoint: 3-year RFS

Sponsor: LUMC/DGOG

Participating Country	status	Patient inclusion
Netherlands (DGOG)	Open 10 sites	46
France (GR/GINECO)	Open 10 sites	34
Germany (SH/AGO)	Open 7 sites	15
Belgium (BGOG)	Open 6 sites	6
Czech Republic (CEEGOG)	Open 4 sites	13
Italy (Gemelli/MITO)	Open 1 site	18
Canada (CCTG)	Open 8 sites	33
UK (NRCI)	Start up	

ENGOT-en14 *POLE*mut-BLUE

- ✓ CCTG central activation Dec 19, 2022
- ✓ 92/213 patients accrued (A1: 48/120; A2: 44/93)
- ✓ **Participating countries**:

Participating Country	status	Patient inclusion
Canada (CCTG)	Open 14 sites	56
Netherlands (DGOG)	Open 6 sites	18
France (GR)	Open 4 sites	0
Australia	Open 9 sites	1
New Zealand	Open 2 sites	1
United States (NRG)	Open 61 sites	12
Italy (MaNGO)	Open 3 sites	4
Norway	Open 1 site	0
UK (NRCI)	Start up	

Systemeem therapie recidief EC

Praktijk veranderende studies

1e lijn:

RUBY PART 1: C/T ± Dostarlimab → onderhoud dostarlimab

NRG-GY018: C/T ± Pembrolizumab → onderhoud pembrolizumab

DUO-E: C/T ± Durvalumab → onderhoud durvalumab ± olaparib

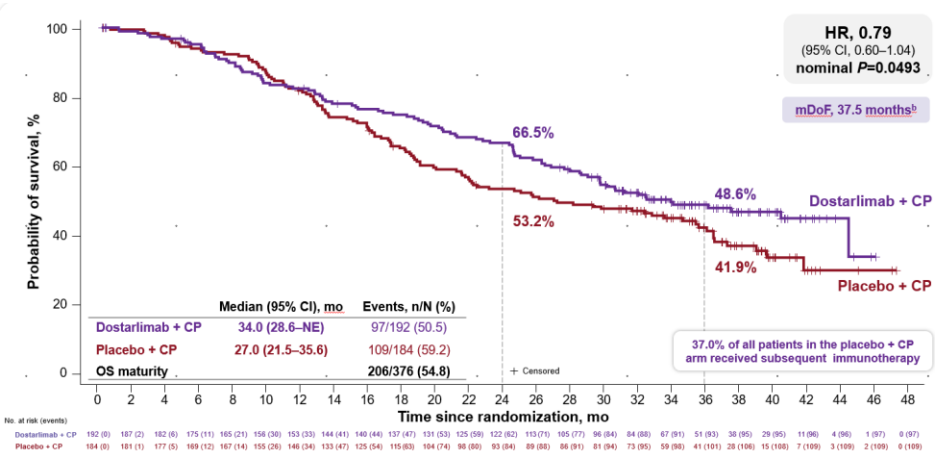
AtTEnd: C/T ± Atezolizumab + → onderhoud atezoluzimab

≥2e lijn:

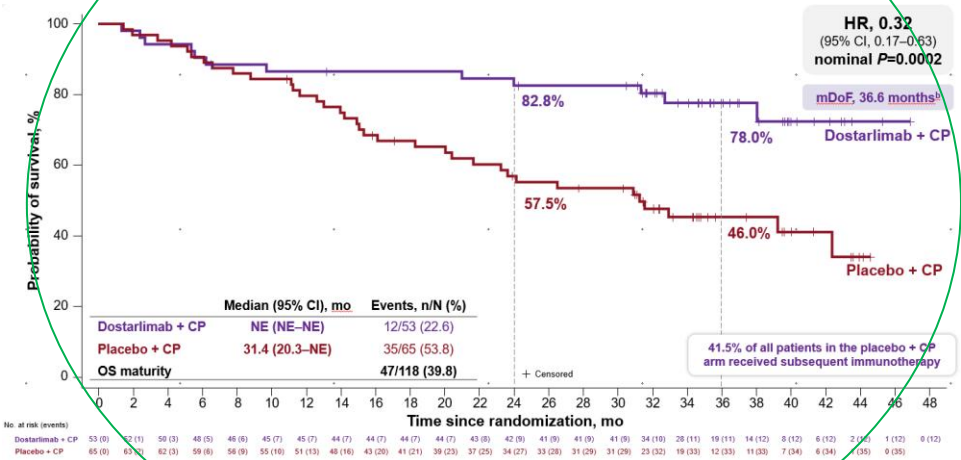
KEYNOTE-775: Pembrolizumab + lenvatinib

RUBY PART 1: dMMR vs pMMR

MMRp (exploratory)



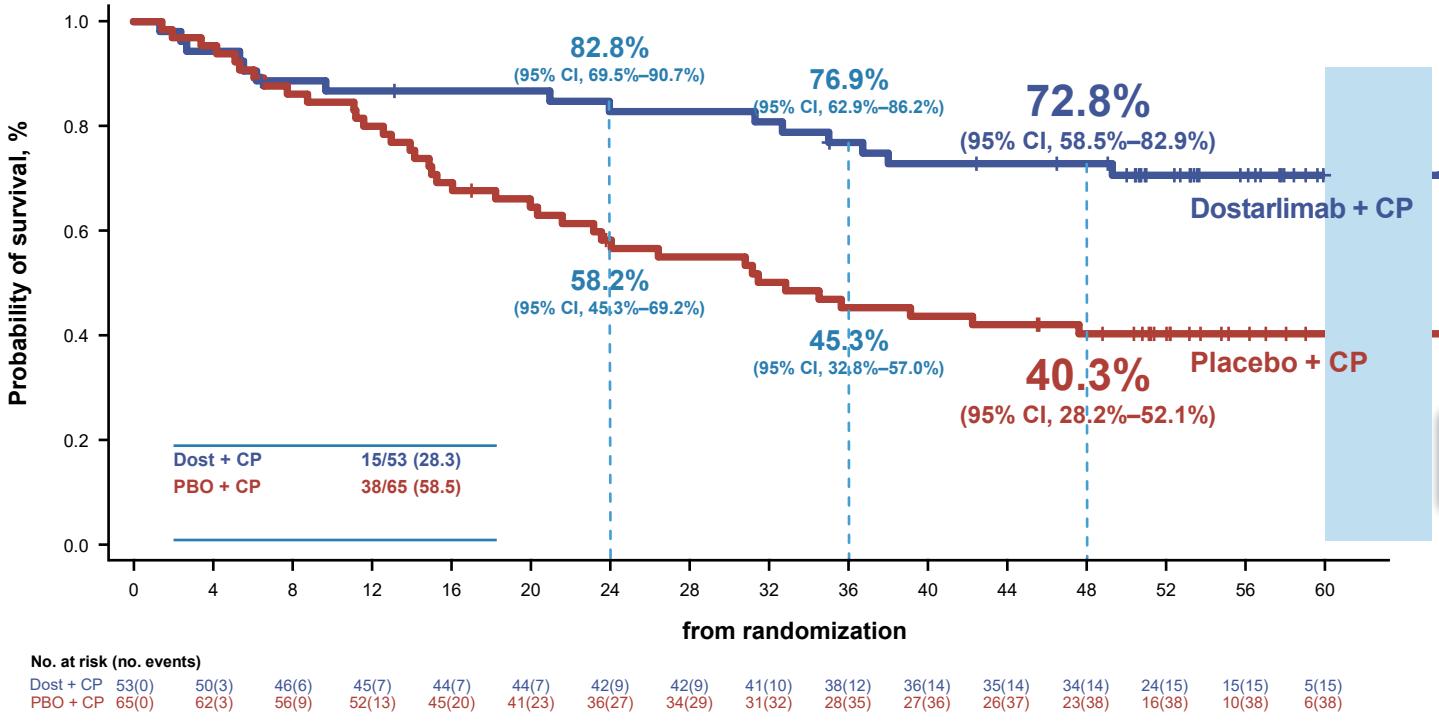
MMRd primary endpoint



Powel et al, ESMO GYN 2024

Robust OS benefit maintained at 4 years with dostarlimab + CP

Median OS not reached, 66% reduction in risk of death in the **MMRd** population



HR, 0.34
(95% CI, 0.19–0.63)

mOS, NE
(95% CI, NE–NE)

mOS, 32.8 mo
(95% CI, 21.6 mo to NE)

~71% of patients in the placebo arm that had FUACT received IO

Median duration of follow-up, 55.6 mo[a]

Click here to view exploratory subgroup analysis

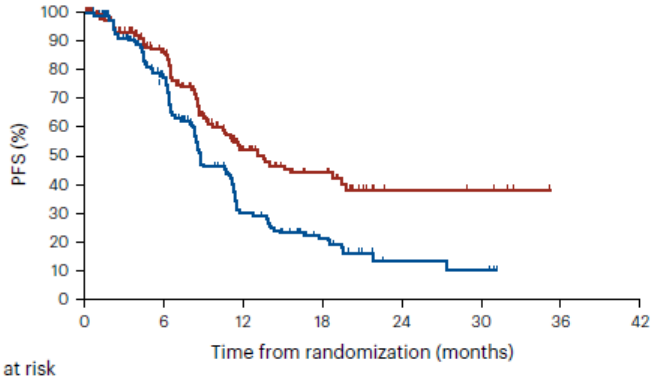
Powell MA, et al. SGO 2026; San Juan, Puerto Rico. Oral presentation.

NRG-GY018: C/P ± pembrolizumab PFS

MMRp

a

	Events, *n/N*	Median PFS (95% CI), months	HR (95% CI)[a], *P* value[b]
Pembrolizumab + CT	95/294	13.1 (10.6–19.5)	0.57 (0.44–0.74)
Placebo + CT	138/294	8.7 (8.4–11.0)	*P* < 0.0001

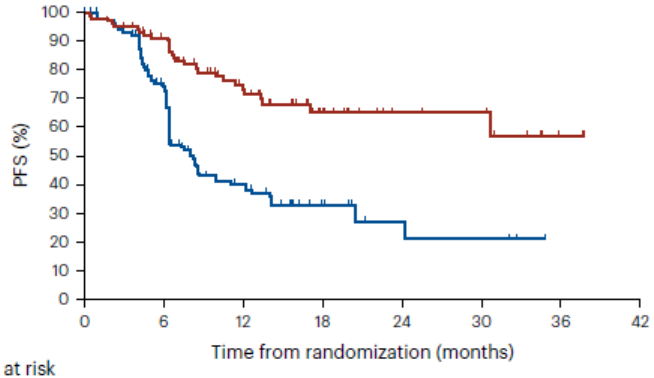


Number at risk								
Pembrolizumab + CT	294	162	57	29	7	6	0	0
Placebo + CT	294	144	36	15	4	3	0	0

MMRd

b

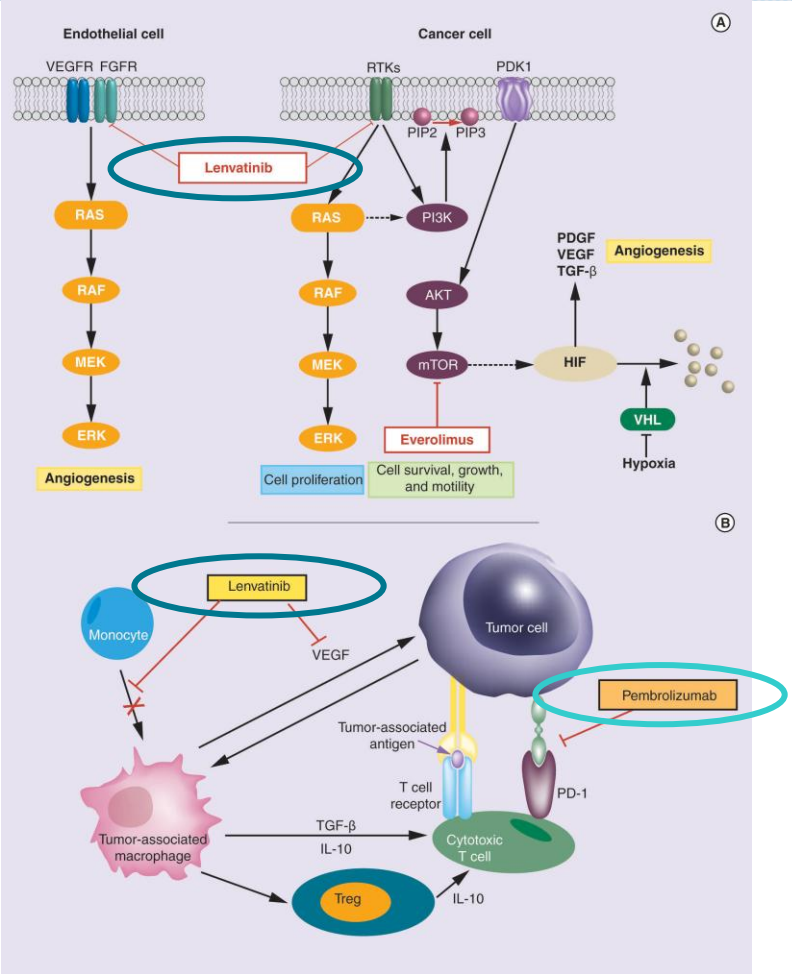
	Events, *n/N*	Median PFS (95% CI), months	HR (95% CI)[a], *P* value[b]
Pembrolizumab + CT	29/110	NR (30.7–NR)	0.34 (0.22–0.53)
Placebo + CT	60/112	8.3 (6.5–12.3)	*P* < 0.0001



Number at risk								
Pembrolizumab + CT	110	85	45	24	10	9	2	0
Placebo + CT	112	69	25	9	4	3	0	0

Eskander, Nature Medicine 2025

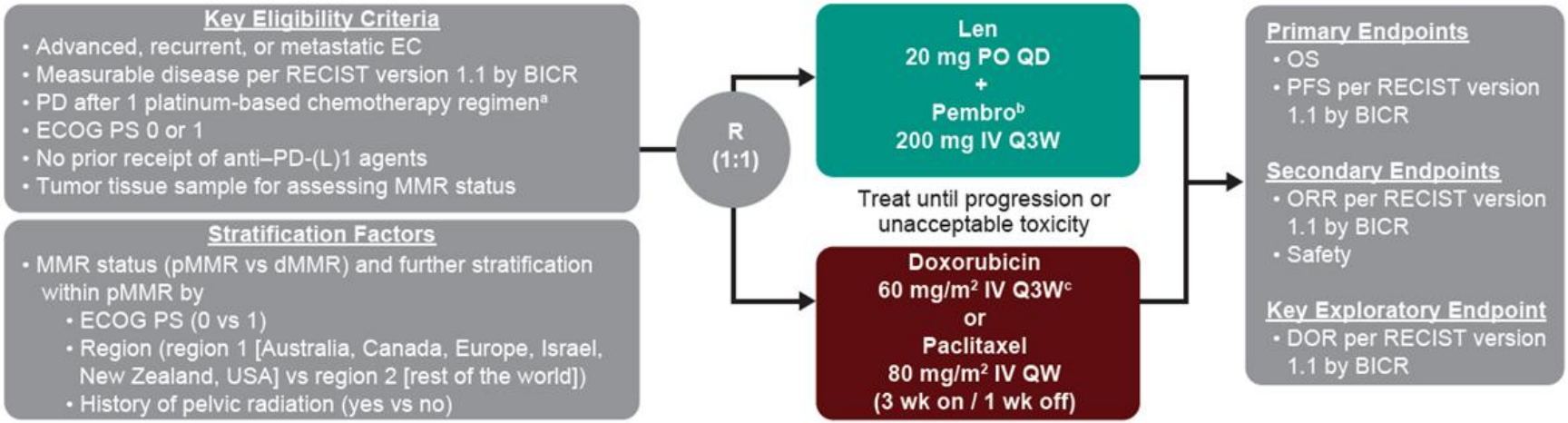
2e lijn Pembrolizumab en Lenvatinib mechanism



Lenvatinib a multitargeted receptor TKI,

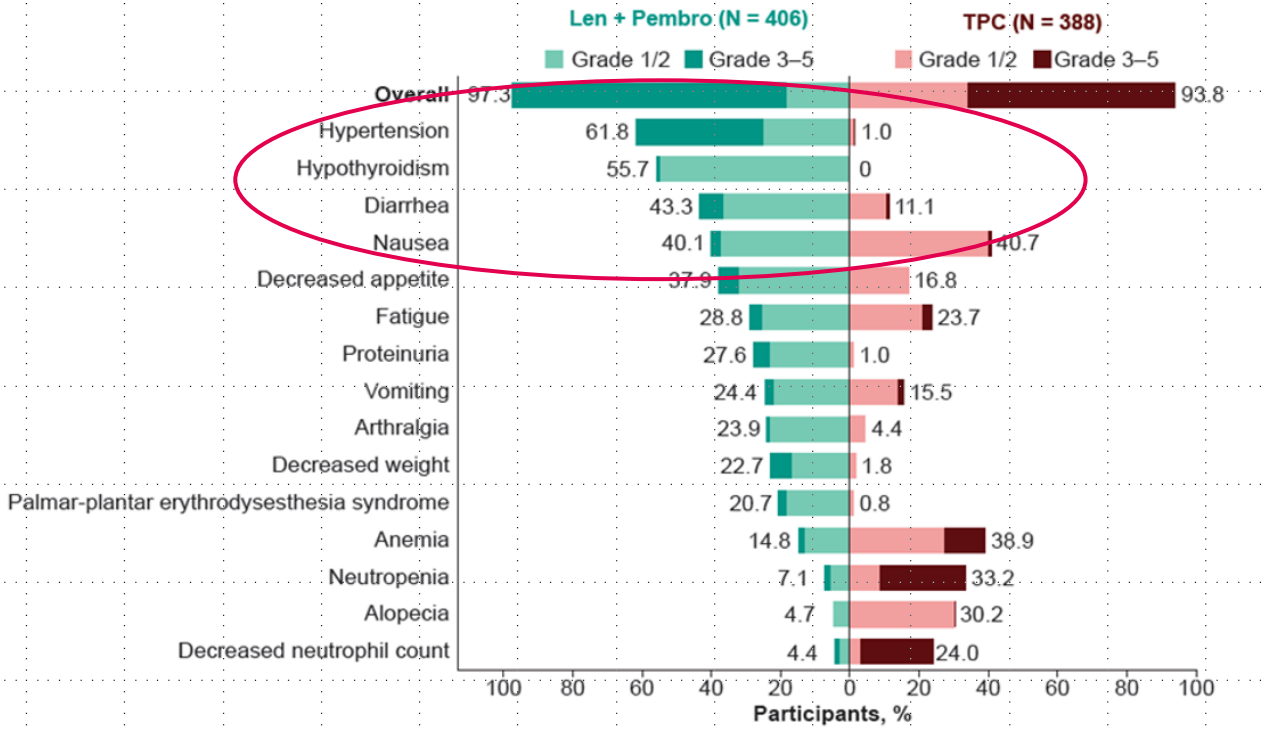
- Angiogenese remmer: remt VEGFR1, VEGFR2,VEGFR3
- oncogene pathway, incl. FGFR 1-4, PDGFRα, KIT, RET
- Immunomodulatie: preventie VEGF-gemedieerde immune suppressie
  - ↓tumor geassocieerde macrofagen (TAM
  - ↓TH2, ↑ TH1 => activatie memory T cellen

KN-775: >1L: lenvatinib/pembrolizumab (n=827)



Makker et al, ESMO 2025

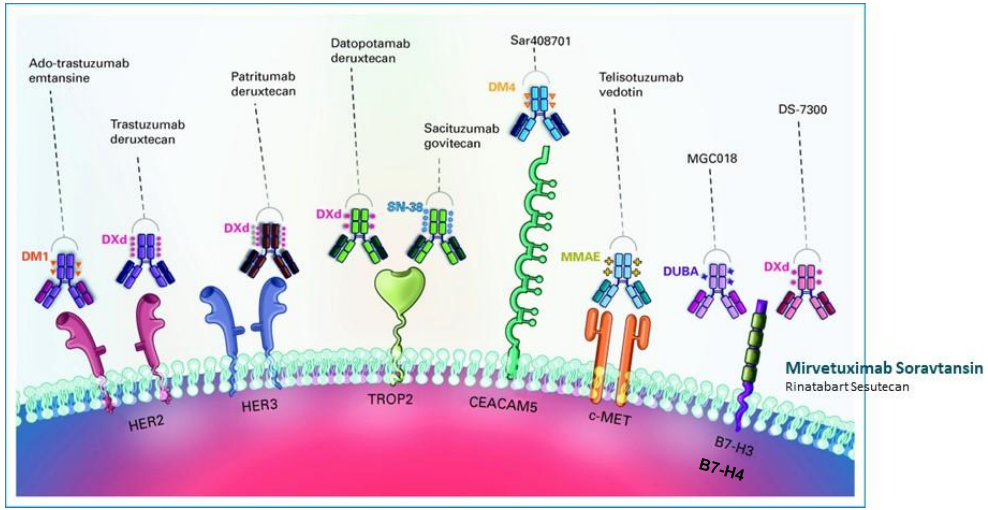
Toxiciteit Pembrolizumab en Lenvatinib



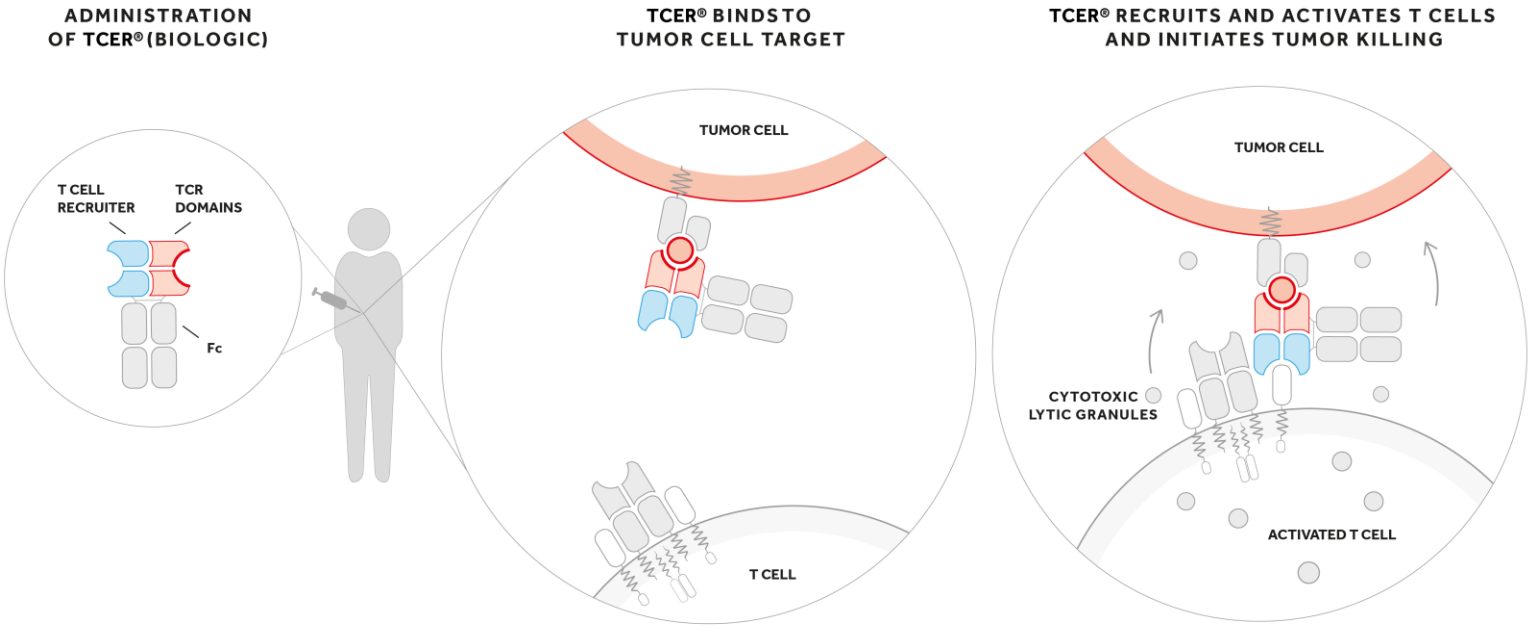
Colombo et al, The Oncologist, 2024; Makker et al, ESMO 2025

Future Developments

- Further refining therapy based on molecular markers
- Trials on ADC, bispecific antibodies and others



Bite: bispecific targeting CD3 op T-cel en prame op tumor cel in HLA-A2 EC



Summary Immunotherapy for EOC and EC

- **Ovarian cancer:** registration platinum resistant ovarian cancer pembro with paclitaxel +/- beva, so far no standard therapy in NL.
  - OVACURE2 for FIGO stage IV EOC
  - ADC for PSOC and PROC coming in trial
- **Endometrial cancer:**
  - Primary therapy in MMRd in RAINBO program (dostarlimab/pembro)
  - 2nd line with chemotherapy (pembro/lenvatinib)
  - 3rd line monotherapy (nivolumab) and ADC in trial
- **Future perspectives**: ADC's, BITE, TIL therapies, precision therapy

Olijf

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

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

Leiden University
Medical Center

Thank you, Questions?