Leiden University
Medical Center

Nieuwe immunologische ontwikkelingen bij Gynaecologische Maligniteiten

Jan Keizer Symposium 2024

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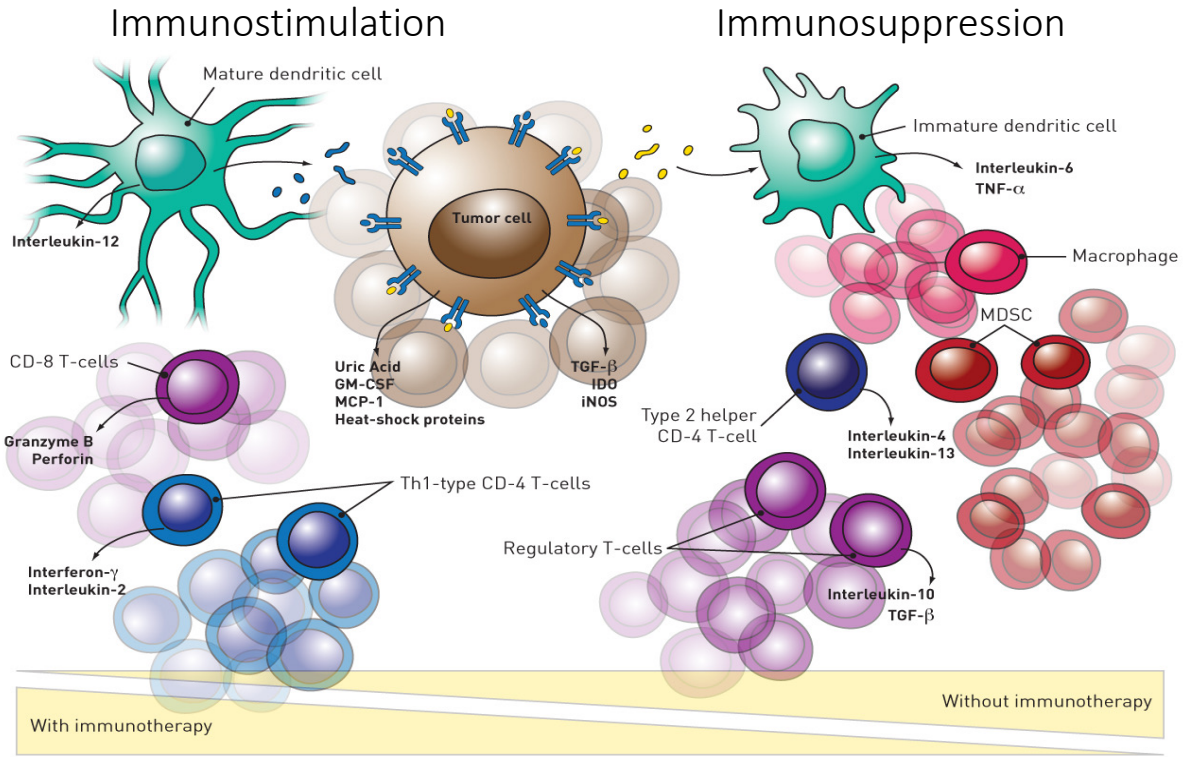
LEIDEN

Disclosure

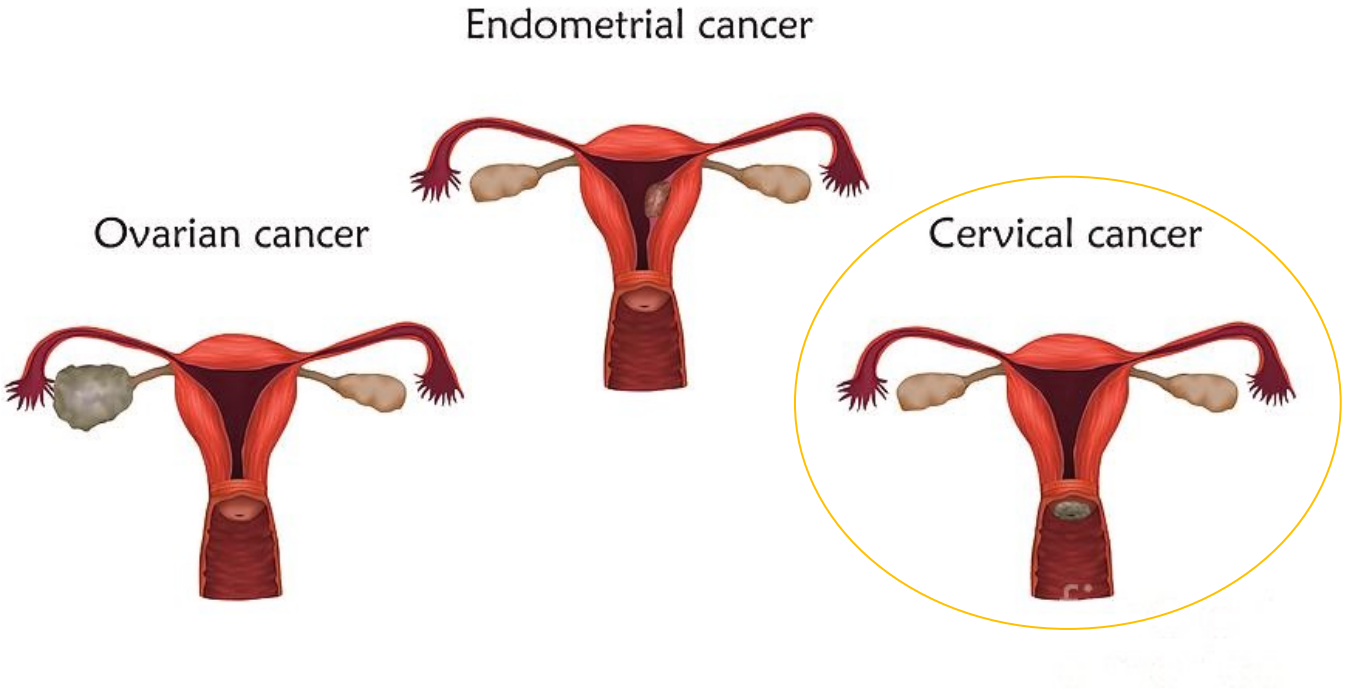
	No, nothing to disclose
x	Yes, please specify:

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

Immunotherapy (IO) TME

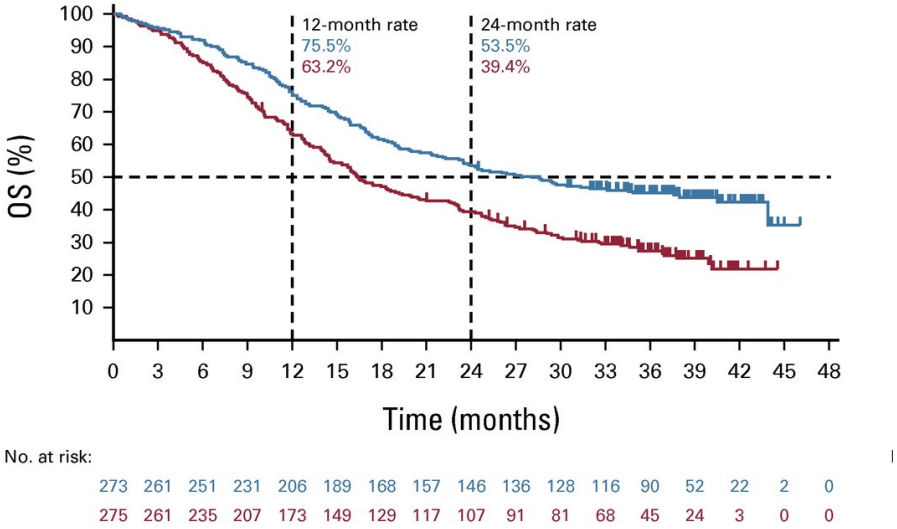


IO in Cervical Cancer



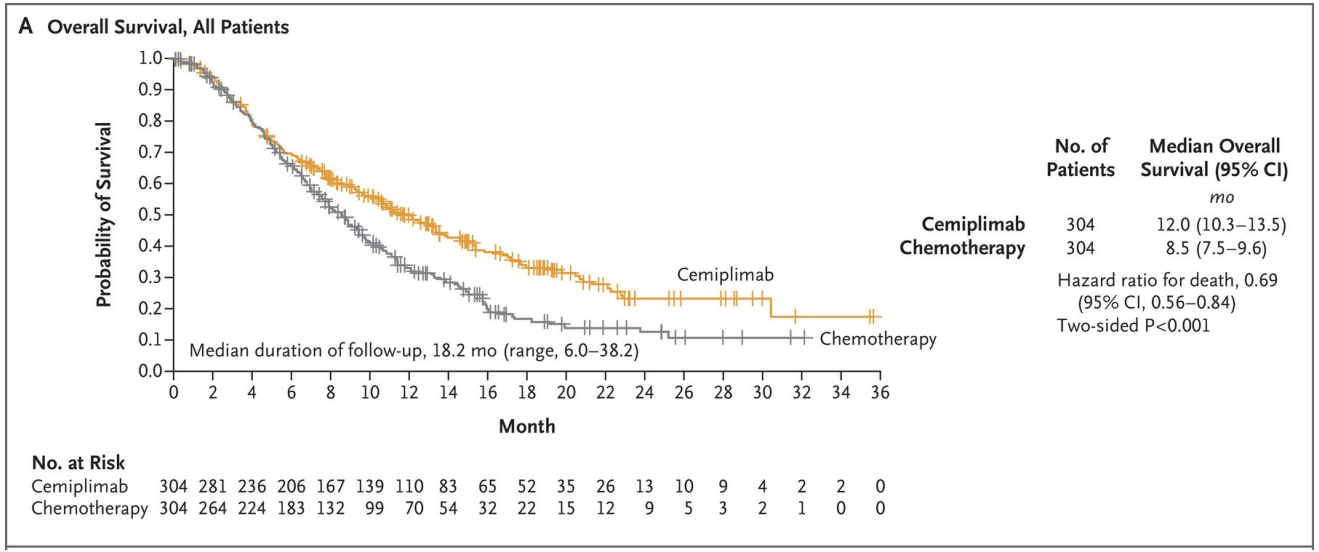
Addition of pembrolizumab to 1st line standard chemo-bevacizumab in advanced PD-L1+ cervical cancer (KEYNOTE 826)

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	153/273 (56.0)	28.6 (22.1 to 38.0)	0.60 (0.49 to 0.74)
Placebo + chemo ± bev	201/275 (73.1)	16.5 (14.5 to 20.0)	



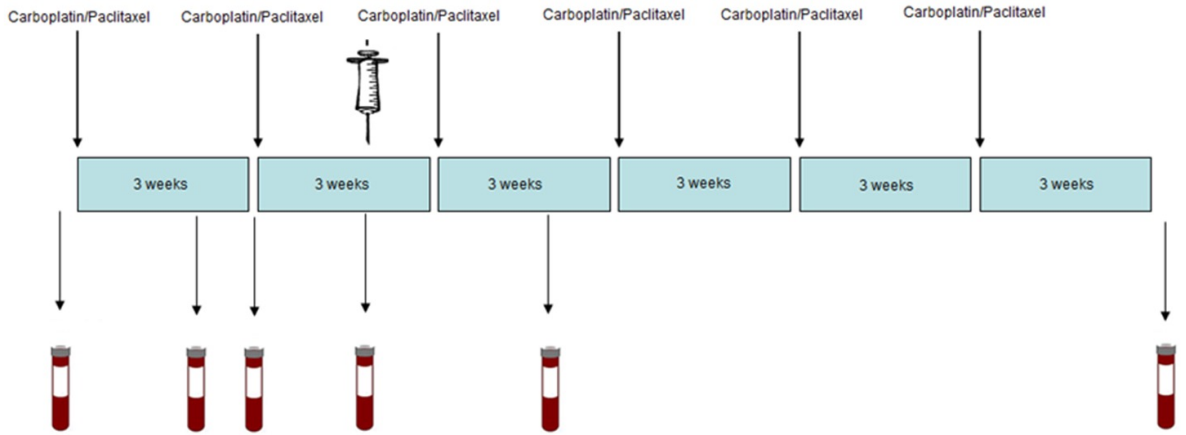
Colombo NEJM, 2021; Monk JCO 2023

Phase III cemiplimab vs investigator choice chemo 2nd line



Tewari KS, NEJM, 2022

HPV16 E6/E7 SLP vaccine in advanced Cervical Cancer

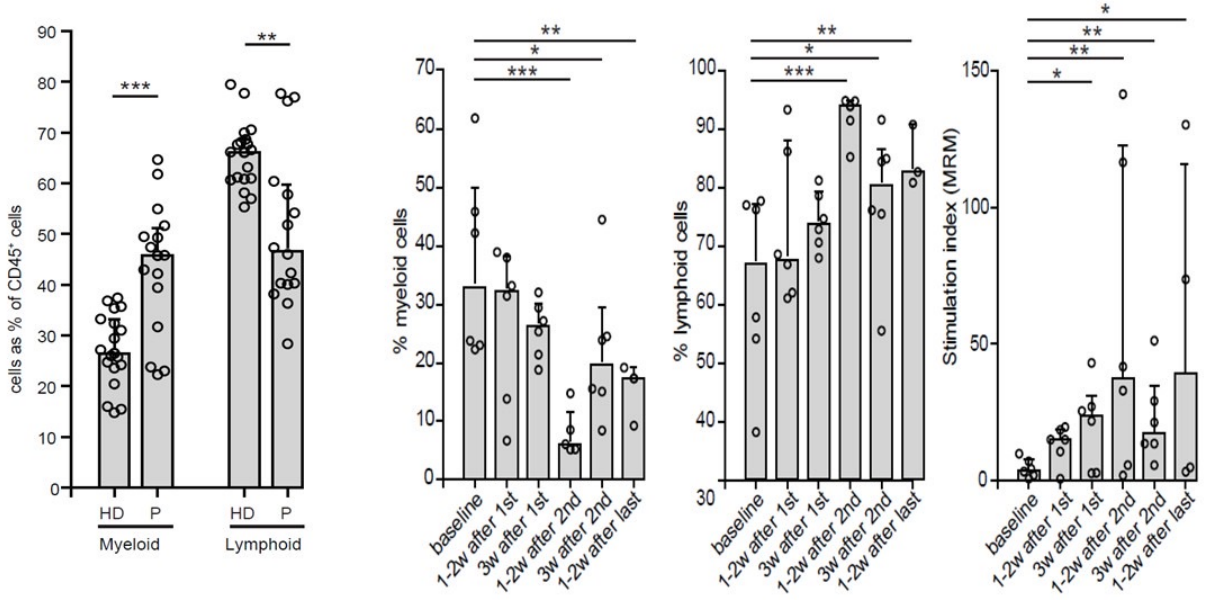


Aim: Study the effect of chemotherapy on (HPV specific) immunity and determine the optimal time-window to start immunotherapy.

Design: 2 cohorts: 6 pts carboplatin-paclitaxel, 12 pts also HPV-16 SLP vaccine

Welters, et al. Science Translational Medicine 2016

Carboplatin-paclitaxel normalizes myeloid cells, while maintaining lymphocytes and T-cell function



Baseline myeloids cells pts vs healthy donor (HD)

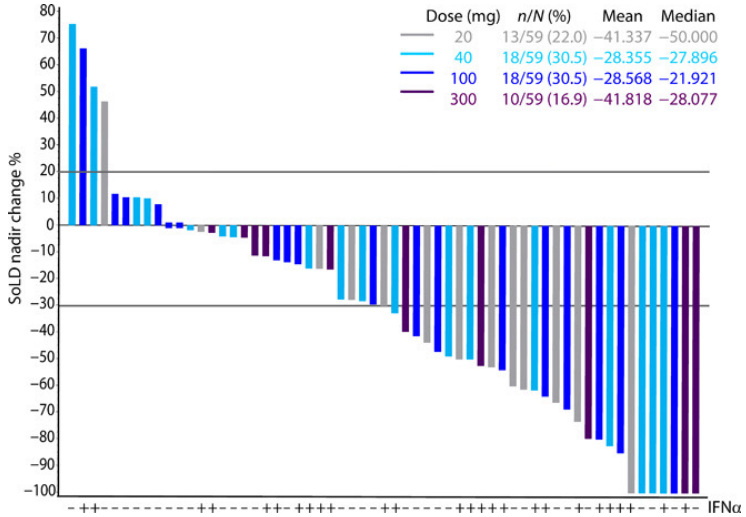
Myeloid cell counts

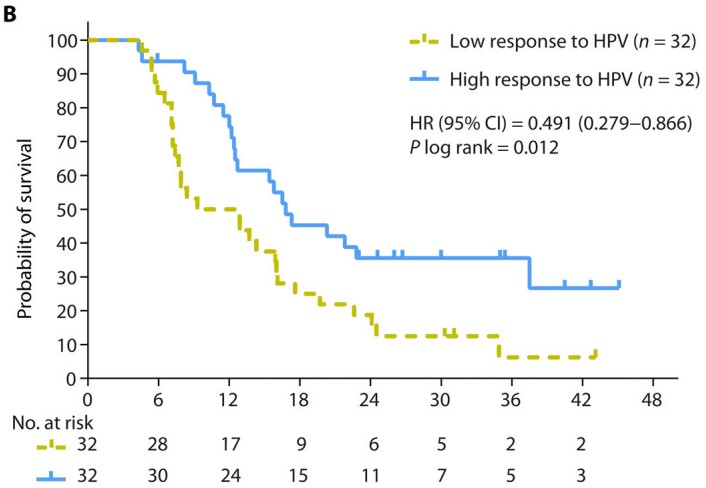
Lymphocyte counts

T-cell function (MRM)

Welters, et al., Science Translational Medicine 2016; Dijkgraaf et al, Oncotarget 2015

Phase II HPV-16 vaccine + chemo/bevacizumab in advanced CxC

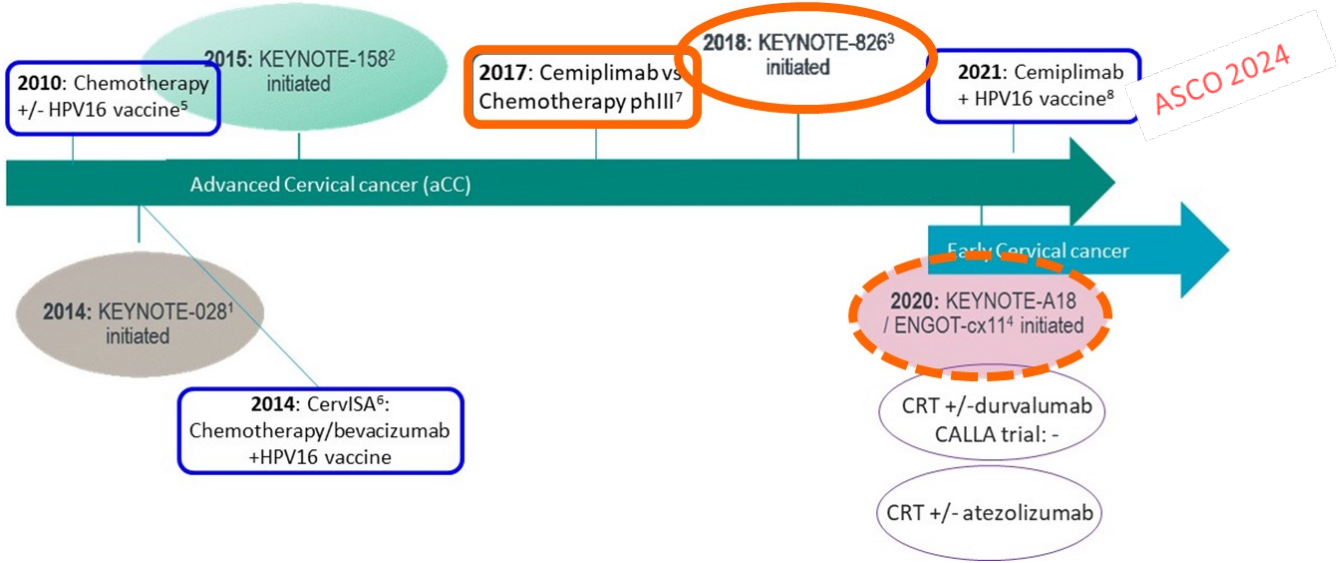




Melief JM et al., Sci Transl Med 2020

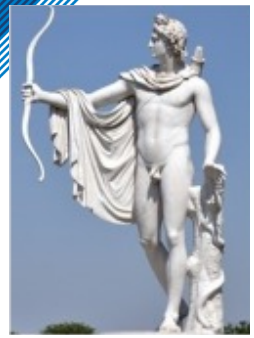
Summary IO in Cervical Cancer

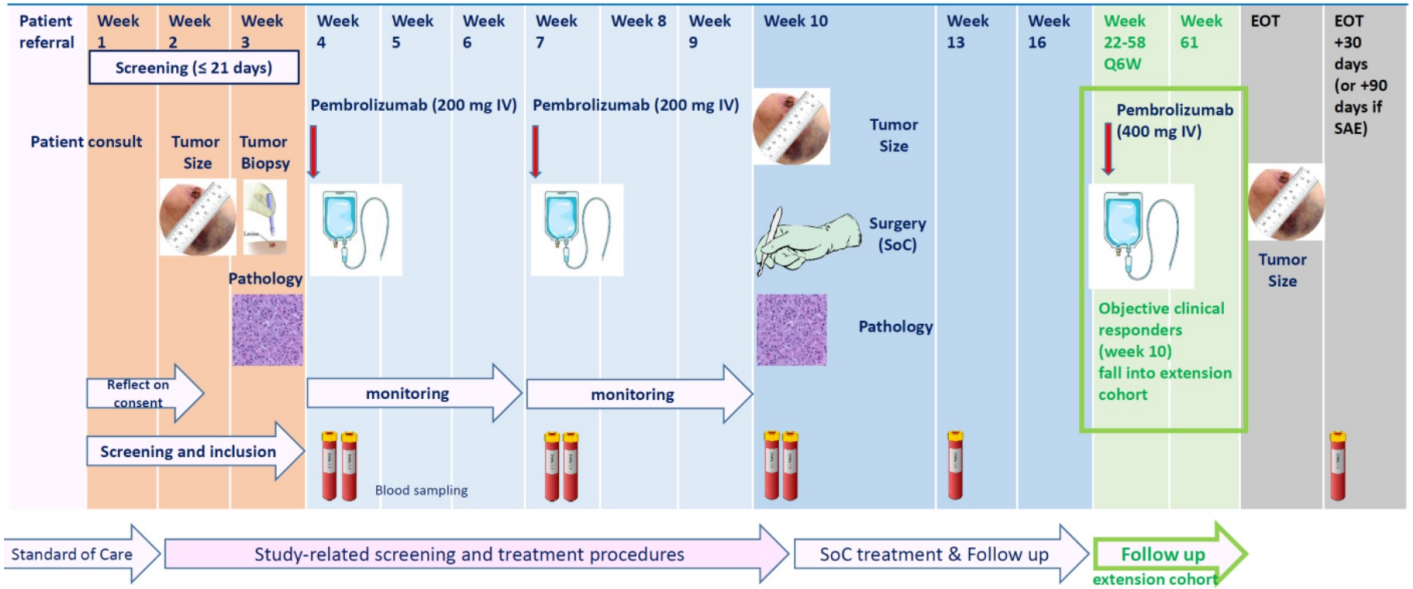
- Biomarkers: HPV and PD-L1
- 1st line: Pembrolizumab is added to 1st line therapy of advanced cervical cancer
- 2nd line: Cemiplimab
- Adjuvant setting: OS IO data follow



1.NCT02054806, 2.NCT02628067, 3.NCT03635567, 4.NCT04221945, 5. Welters Science Transl. med. 2016 6.NCT02128126, 7. NCT03257267, 8. NCT04646005

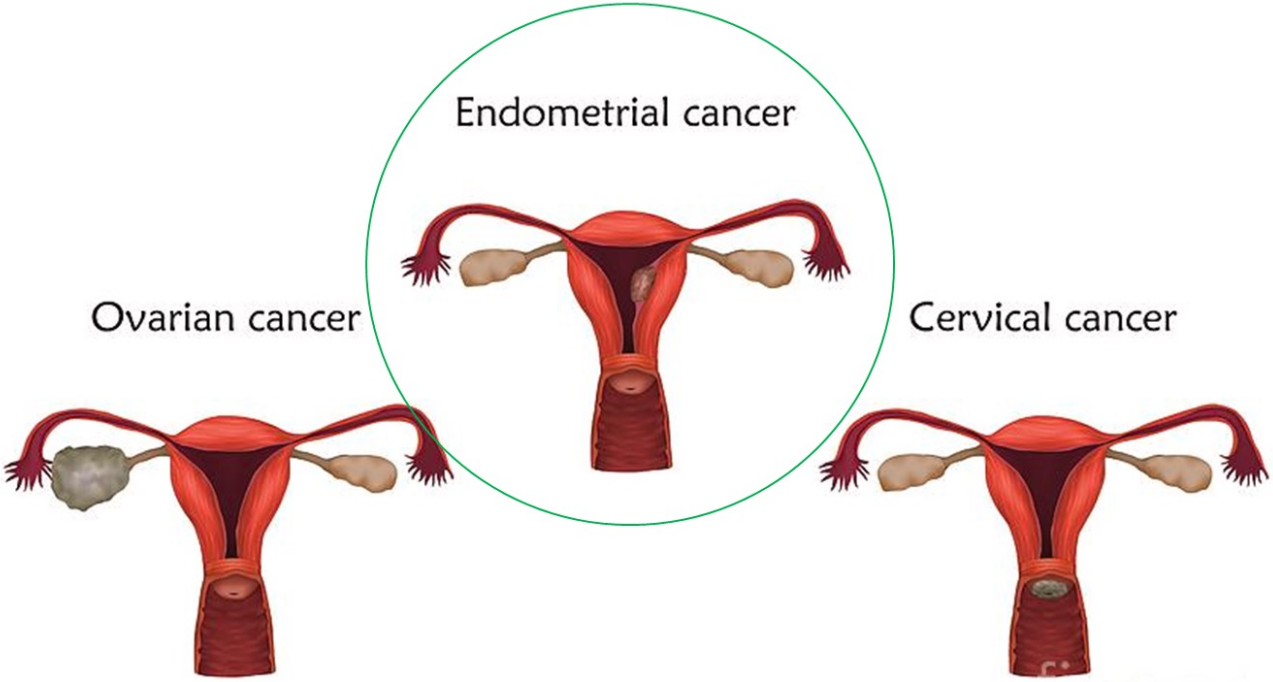
APOLLO neoadjuvant pembrolizumab in Vulvar SCC





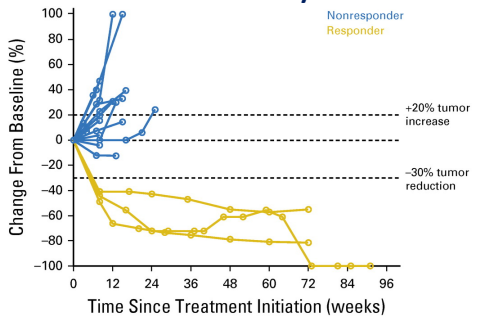
Jan dank voor coordinatie van oncologie uitjes

IO in Endometrial Cancer

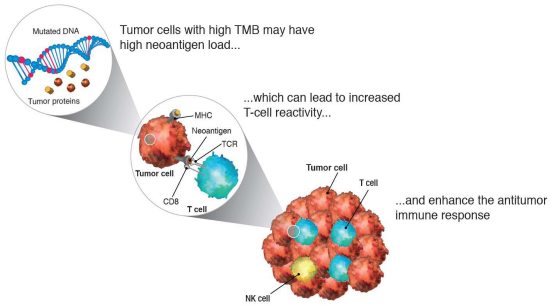


Biomarkers in Endometrial cancer (EC)

PD-L1+: Keynote 028: IO in PD-L1+ aEC
ORR only 13%



Tumor Mutational Burden



MMRd/MSI high
ORR about 45%

The NEW ENGLAND JOURNAL of MEDICINE

Perspective
OCTOBER 12, 2017

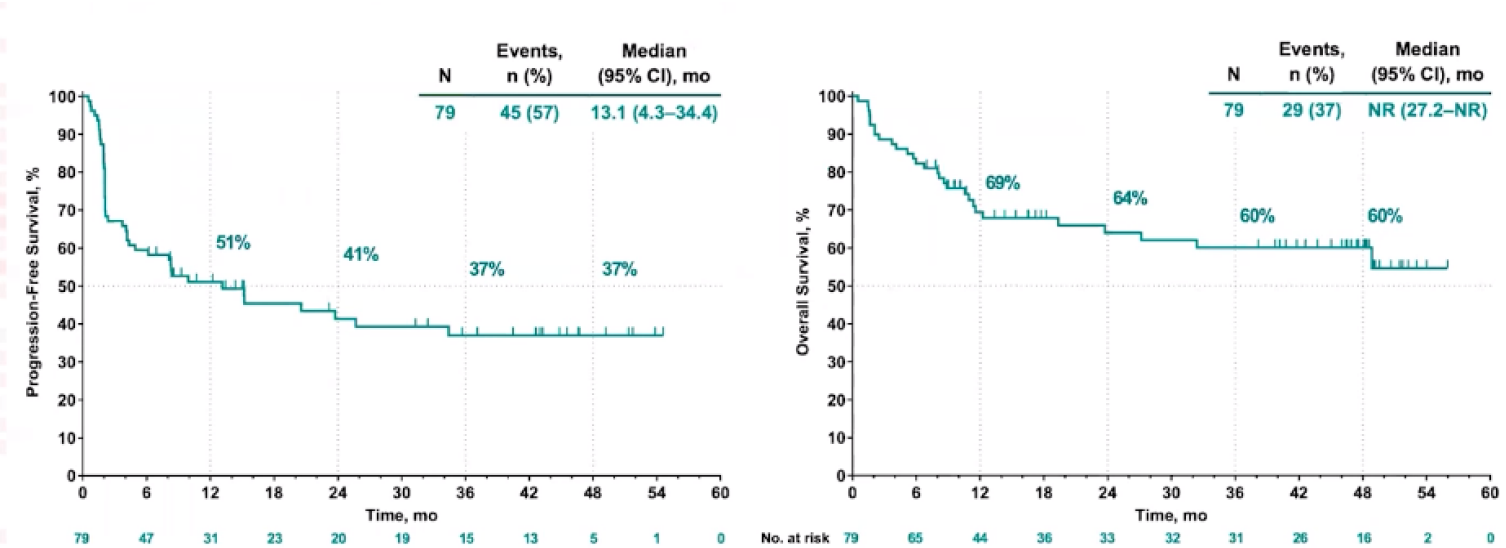
First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Tumor type*	MSI-high, %
Uterine corpus endometrial	**28.3**
Stomach adenocarcinoma	21.9
Colon adenocarcinoma	16.6
Rectal adenocarcinoma	9.2
Adrenal cortical	5.4
Esophageal	3.3
Ovarian	3.2
Hepatocellular	2.9
Cervical squamous	2.3

Ott PA J Clin Oncol 2017; McGrail DJ et al. Ann Oncol 2021; Cortes-Ciriano I et al. Nat Commun 2017;8:15180

IO in MMRd/MSI aEC durable response



O'Malley D, JCO, 2022

1st line trials Chemo plus IO in all-comers EC

	Dostarlimab RUBY-part1	Pembrolizumab NRG-GY018	Atezolizumab ATTEND	Durvalumab DUO-E
Treatment Chemotherapy + placebo vs	Plus dostarlimab	Plus pembrolizumab	Plus atezolizumab	Plus durvalumab Plus durva/olaparib
Duration IO	3 years	2 years	Until PD	Until PD
Patients	All comers	All comers	All comers	All comers
Prior (neo)Adj.	<6 mo	<12 mo	<6 mo	<12 mo
Prim. outcome	PFS, OS	PFS	PFS, OS	PFS
HR in MMRd subgroup	0.28	0.30	0.36	0.42
Registration	FDA/EMA			

Mirza MR NEJM 2023, Eskander R NEJM 2023 , Colombo N ESMO 2023, Westin S ESMO 2023

2nd line trials IO + antiangiogenesis inhibition

Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775

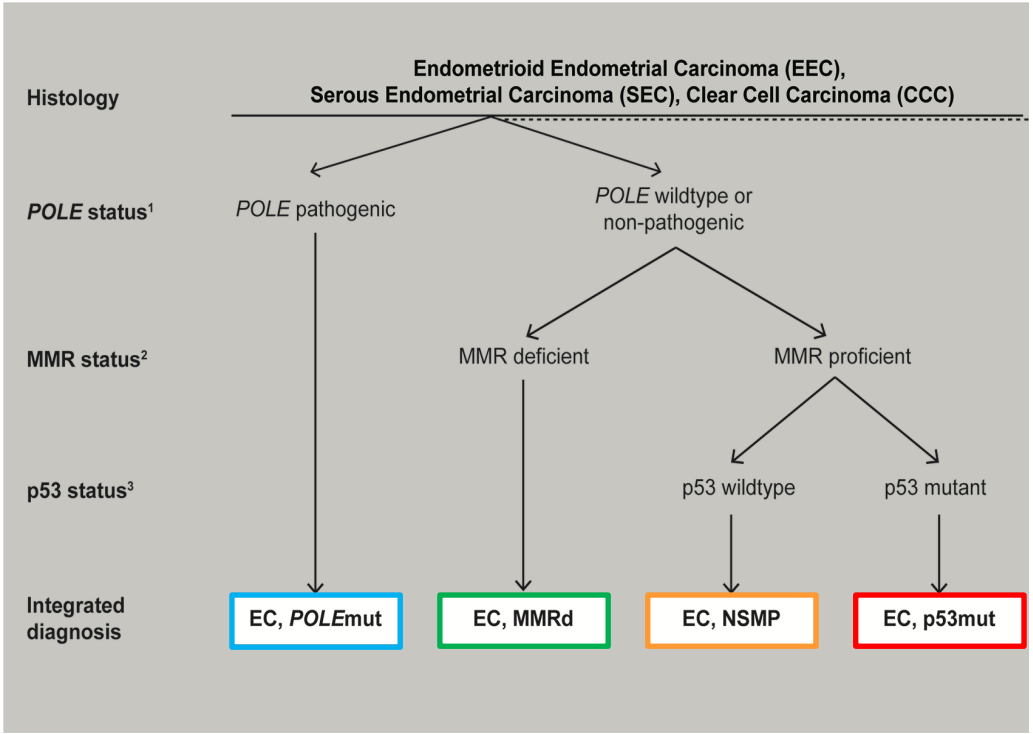
Vicky Makker, MD[1]; Nicoletta Colombo, MD[2]; Antonio Casado Herráez, MD[3]; Bradley J. Monk, MD[4]; Helen Mackay, MD[5]; Alessandro D. Santin, MD[6]; David S. Miller, MD[7]; Richard G. Moore, MD[8]; Sally Baron-Hay, MBBS[9]; Isabelle Ray-Coquard, MD[10]; Kimio Ushijima, MD[11]; Kan Yonemori, MD[12]; Yong Man Kim, MD[13]; Eva M. Guerra Alia, MD[14]; Ulus A. Sanli, MD[15]; Steven Bird, MS[16]; Robert Orlowski, MD[16]; Jodi McKenzie, PhD[17]; Chinyere Okpara, PhD[18]; Gianmaria Barresi, MD[19]; and Domenica Lorusso, MD[20]

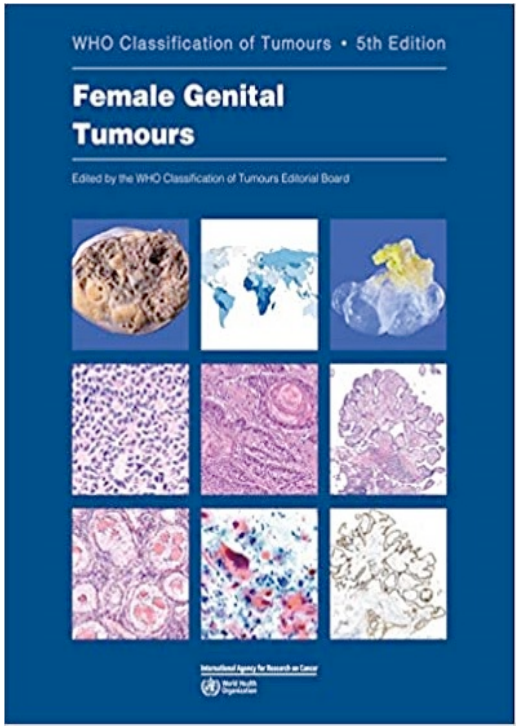
Lenvatinib plus pembrolizumab vs chemotherapy showed benefits in

- OS (pMMR HR, 0.70; **all-comer (HR:0.65) 11.9 => 18.7 mo**
- PFS (pMMR HR, 0.60; all-comer HR, 0.56), and
- ORR (pMMR patients, 32.4% v 15.1%; all-comers, 33.8% v 14.7%)

Makker V J Clin Oncol 2023

Molecular Classification EC

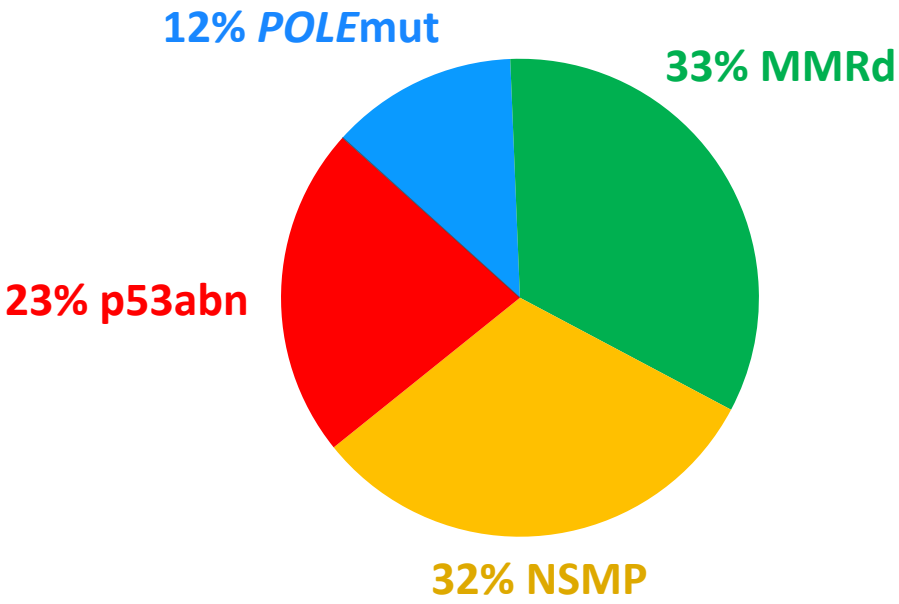


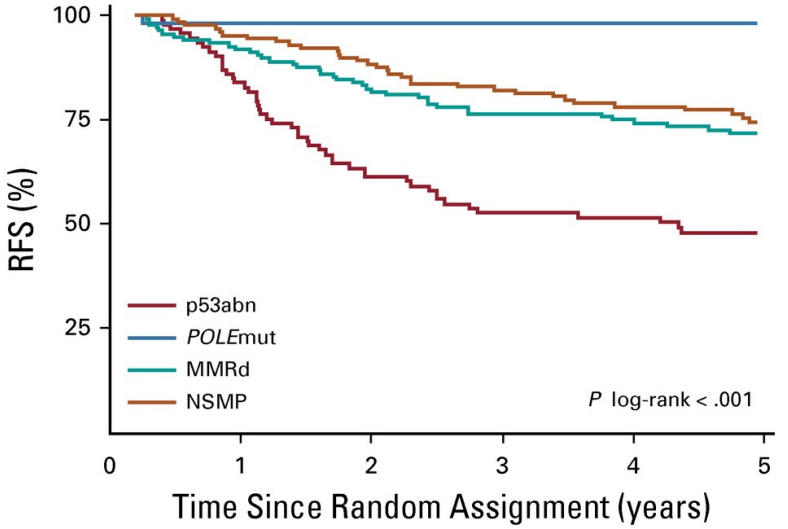


- Prognostically informative in low-, intermediate-, and high-risk EC

Vermij L Histopathology, 2020

Molecular EC classification in PORTEC-3 cohort



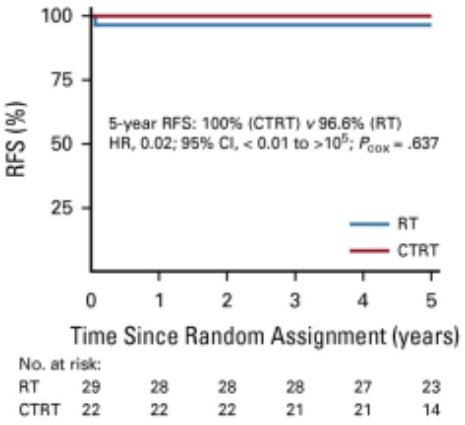


No. at risk:						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
MMRd	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

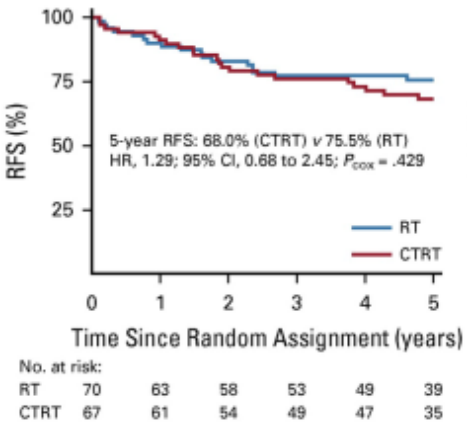
Léon-Castillo, JCO 2020

RFS per molecular subgroup in PORTEC-3 cohort

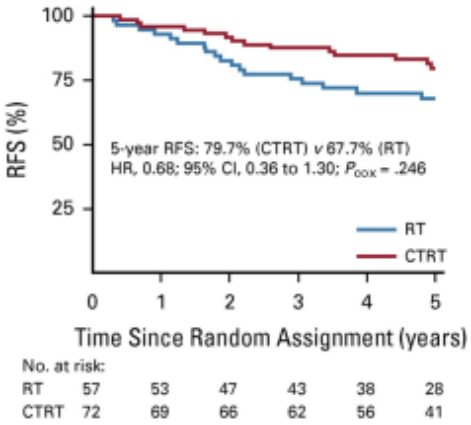
All stages *POLE*mut EC



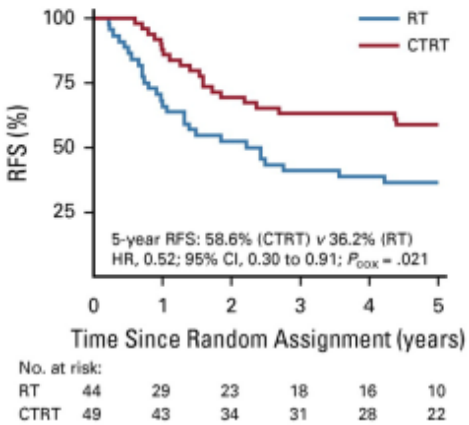
All stages MMRd EC



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

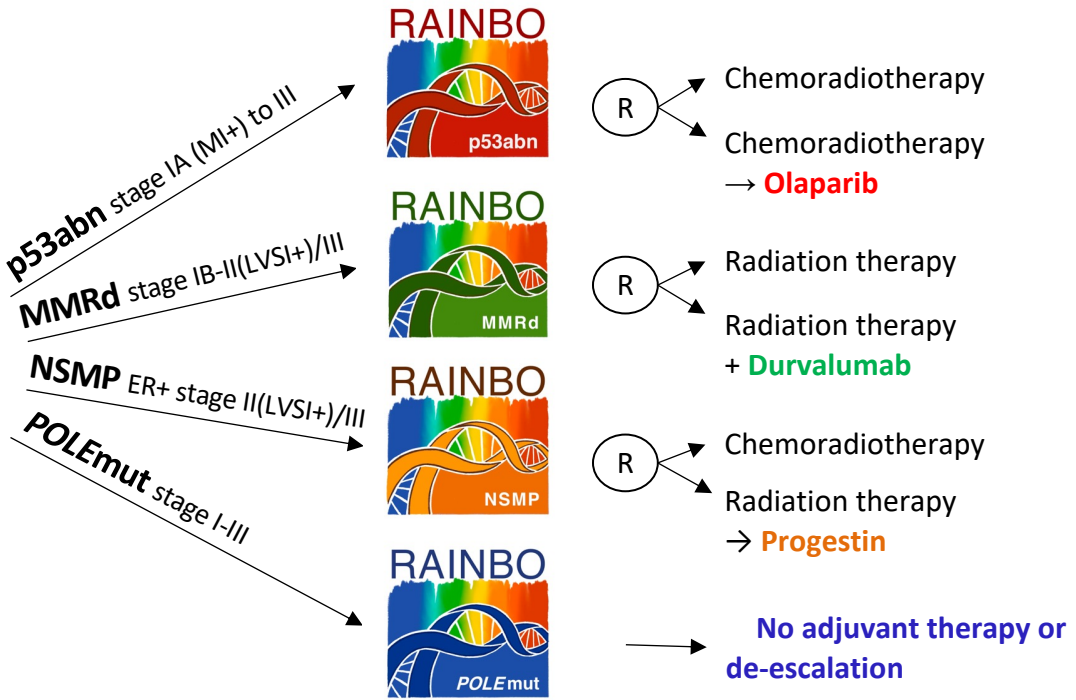
Léon-Castillo, JCO 2020

RAINBO program

Surgically resected EC

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

⇨ Molecular Classification

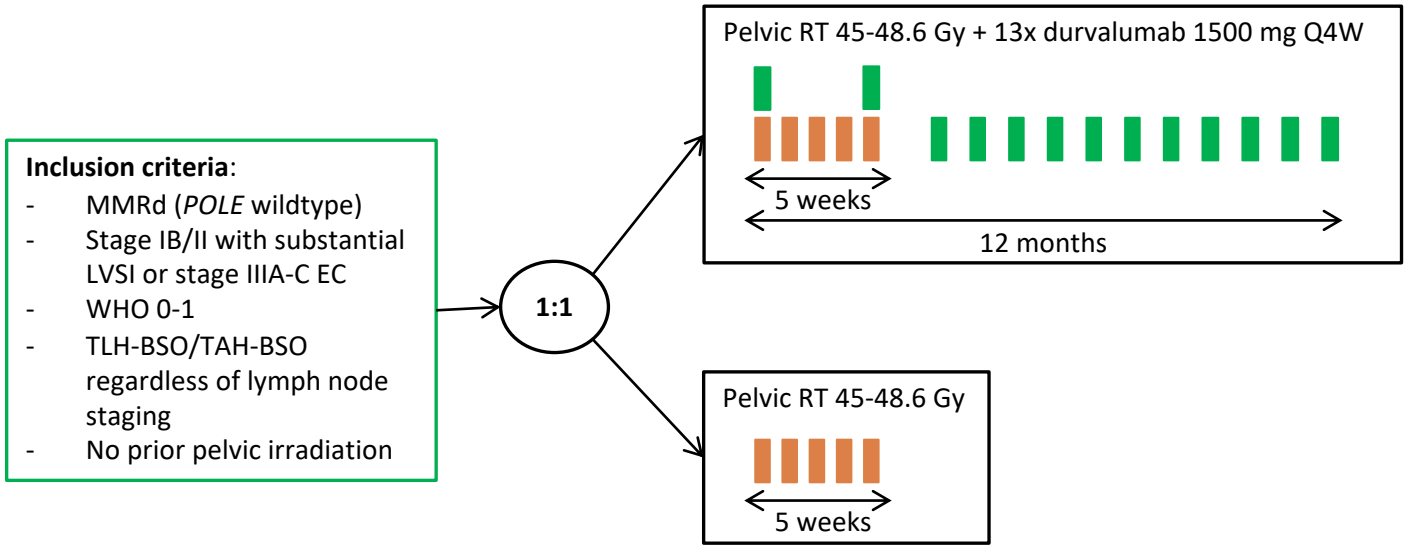


RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

RAINBO Research consortium Int J gyn cancer 2022

RAINBO MMRd-GREEN trial

TransPORTEC/GCIG/ENGOT-EN[1-4] - RAINBO



Primary objective:
- 3-yr RFS

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

Sample size: 316 patients

RAINBO Research consortium Int J gyn cancer 2022

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

India

Czech Republic

Italy

Brazil

- 9/10 centers in NL open
- MEC approvals of Netherlands, Canada, Belgium, France, Germany, Czech Republic and Italy
- India, UK and Brazil will follow

RAINBO Research consortium Int J gyn cancer 2022

Overarching and translational research project

	RAINBO p53abn	RAINBO MMRd	RAINBO NSMP	RAINBO *POLE*mut
Inclusion of:	Stage IA (MI+) - III	Stage Ib/II+LSVI - III	Stage II+LSVI - III	Stage I-III
Experimental Tx	CRT + PARP-i	EBRT + PDL1-i	EBRT + HT	De-escalated Tx
Control Tx	CRT	EBRT	CRT	Standard of care
Outcomes	RFS, OS, tox/QoL	RFS, OS, tox/QoL	RFS, OS, tox/QoL	RFS, OS, tox/QoL
Sample size	575	316	600	145

Uniform RAINBO Data Registration

Overarching RAINBO research project

Treatment efficacy, toxicity, quality of life and cost-utility

Translational research

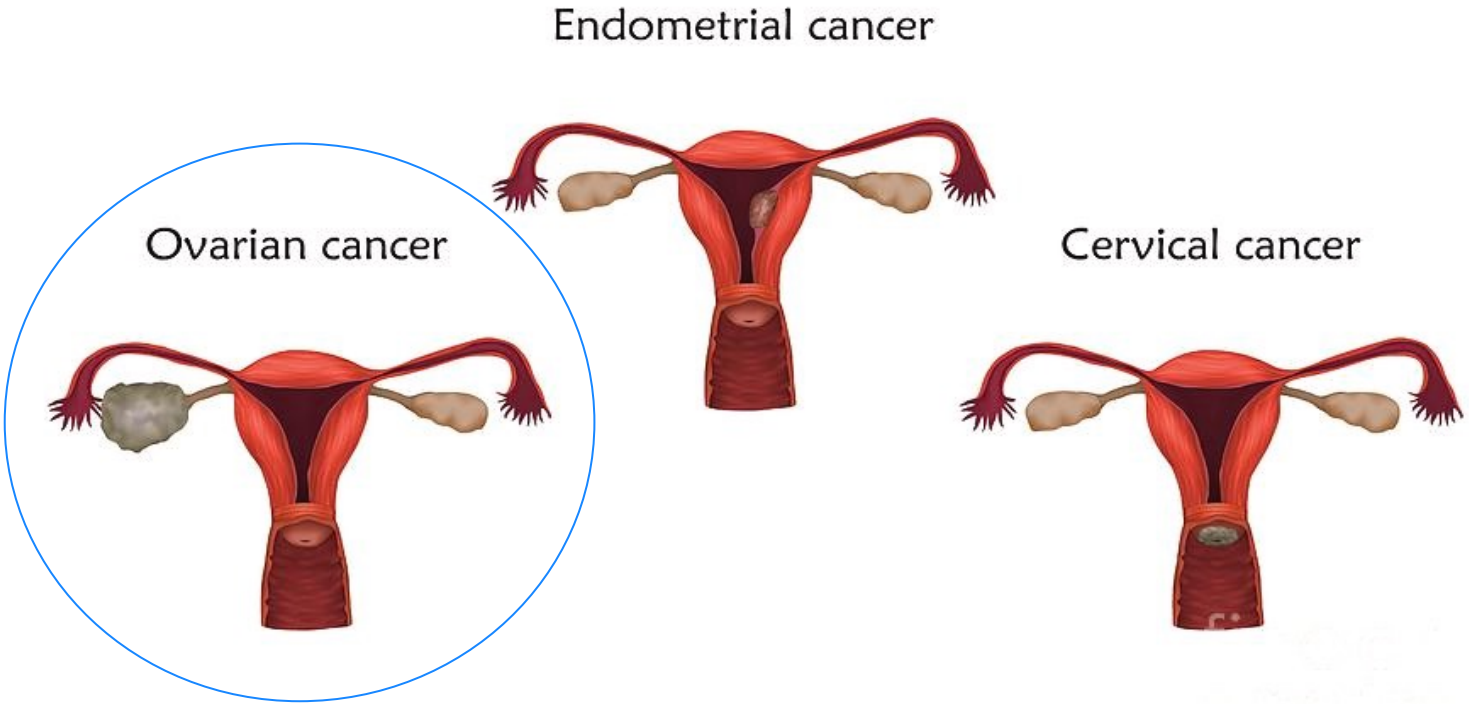
Tumor micro-environment, molecular features, tumor immunology, AI

RAINBO Research consortium Int J gyn cancer 2022

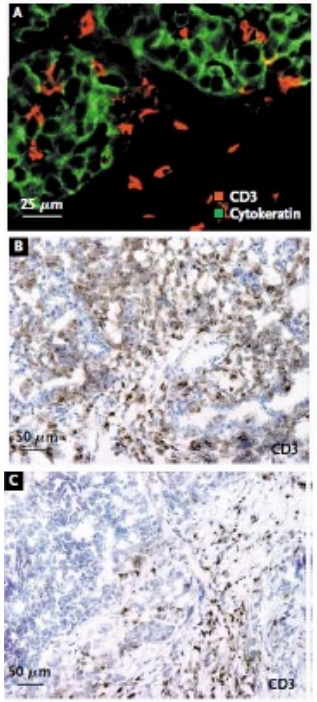
Dank voor de Research Coordinatie

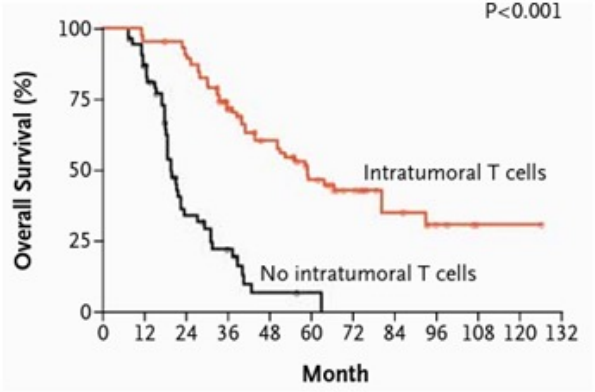
WSC
Med Onco
LUMC

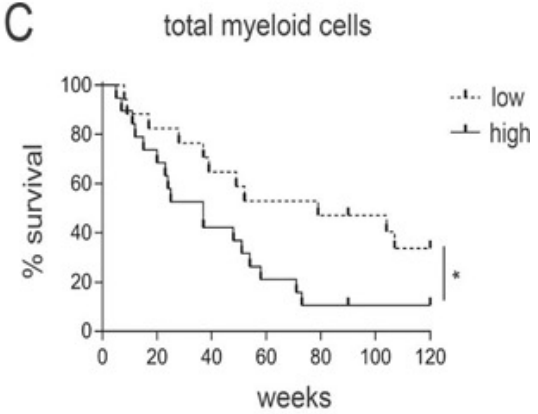
IO in Ovarian Cancer



TIL in Ovarian Cancer



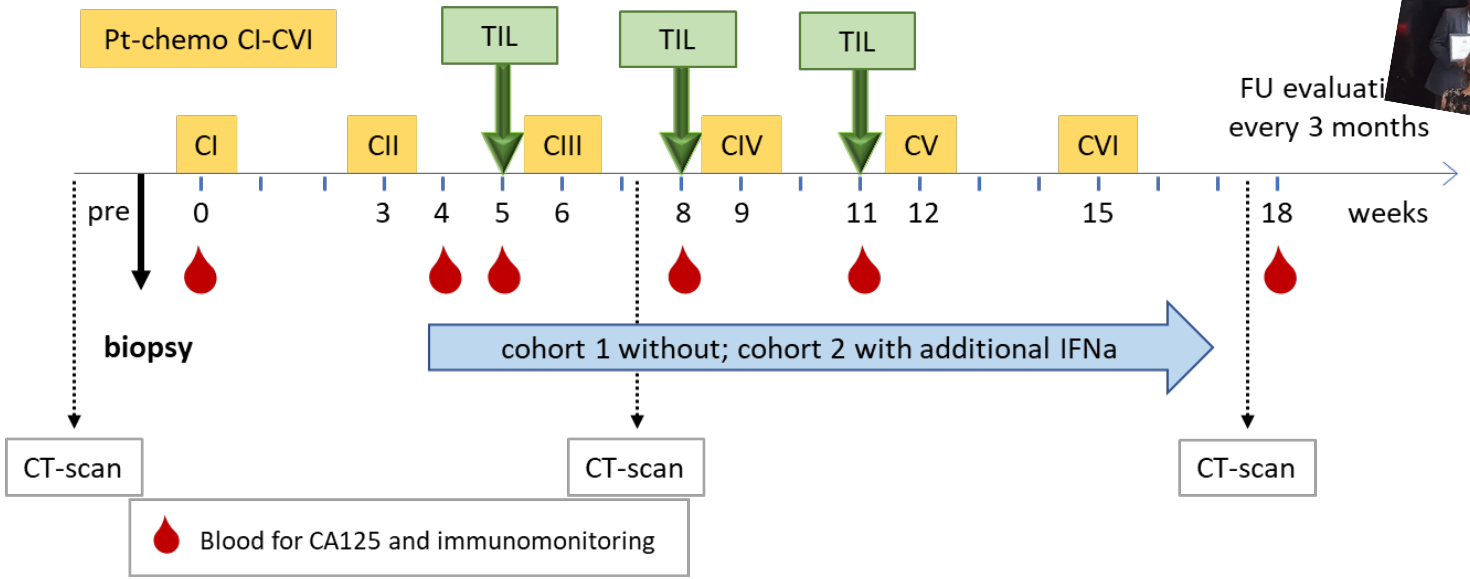




- The presence of tumor infiltrating lymphocytes (TIL) is associated with an improved OS in advanced stage EOC
- But tumor-specific T cell responses often hampered by local immunosuppressive cells

Zhang et al NEJM 2003; Santegoets Oncoimmunology 2018

OVACUre trial



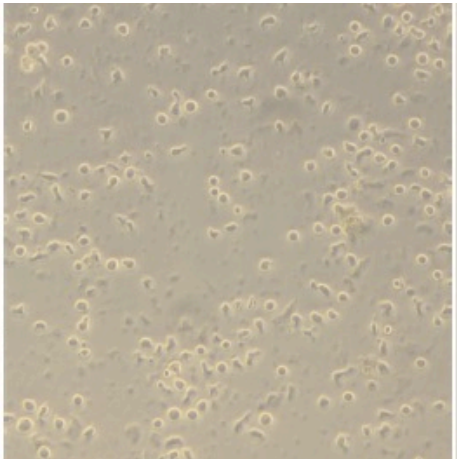
Inclusion: Patients with recurrent platinum-sensitive EOC

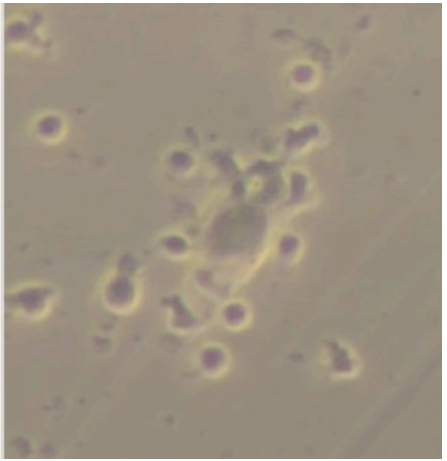
Primary objective: Safety and feasibilty *w/o IFNa*

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

Verdegaal EME, J Immunother. Cancer 2023

TIL production, culture and activity





Results primary endpoint

- It was feasible to obtain TIL for all patients

- TIL and/or IFNα related adverse events ≥ grade 3:

  TIL + Chemotherapy cohort (n=12)

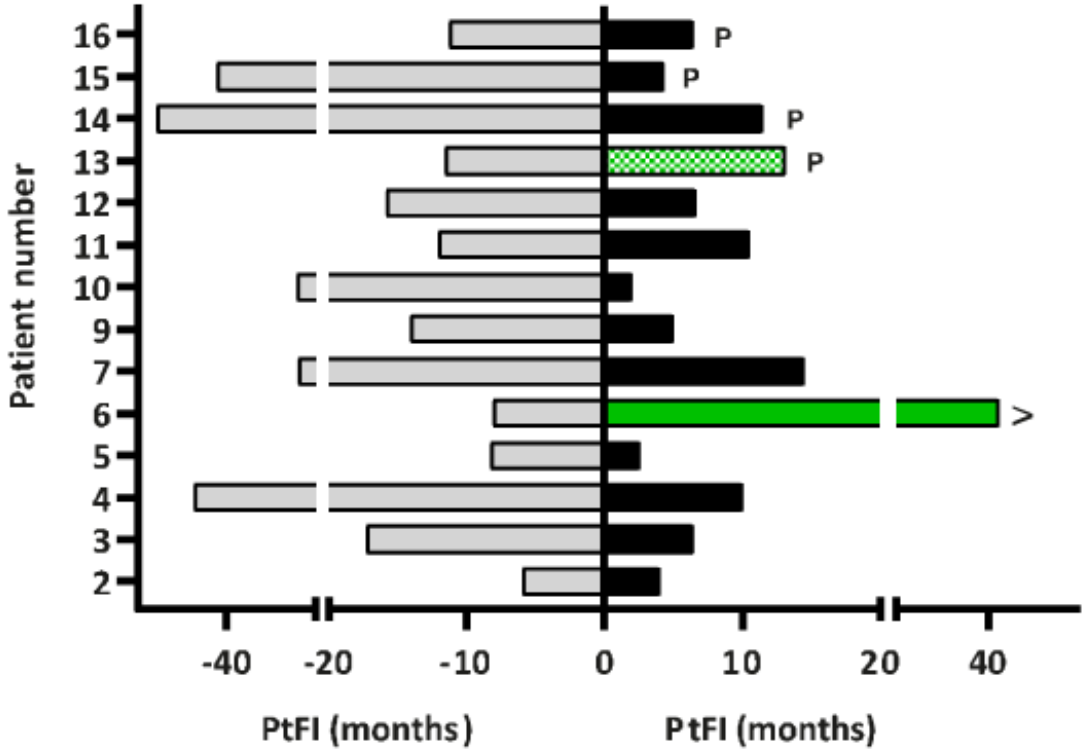
  - neutropenia grade 3: 1/12

  TIL + IFNα + Chemotherapy cohort (n=2)

  - Neutropenia grade 4: 2/2
  - Thrombocytopenia grade 3: 2/2

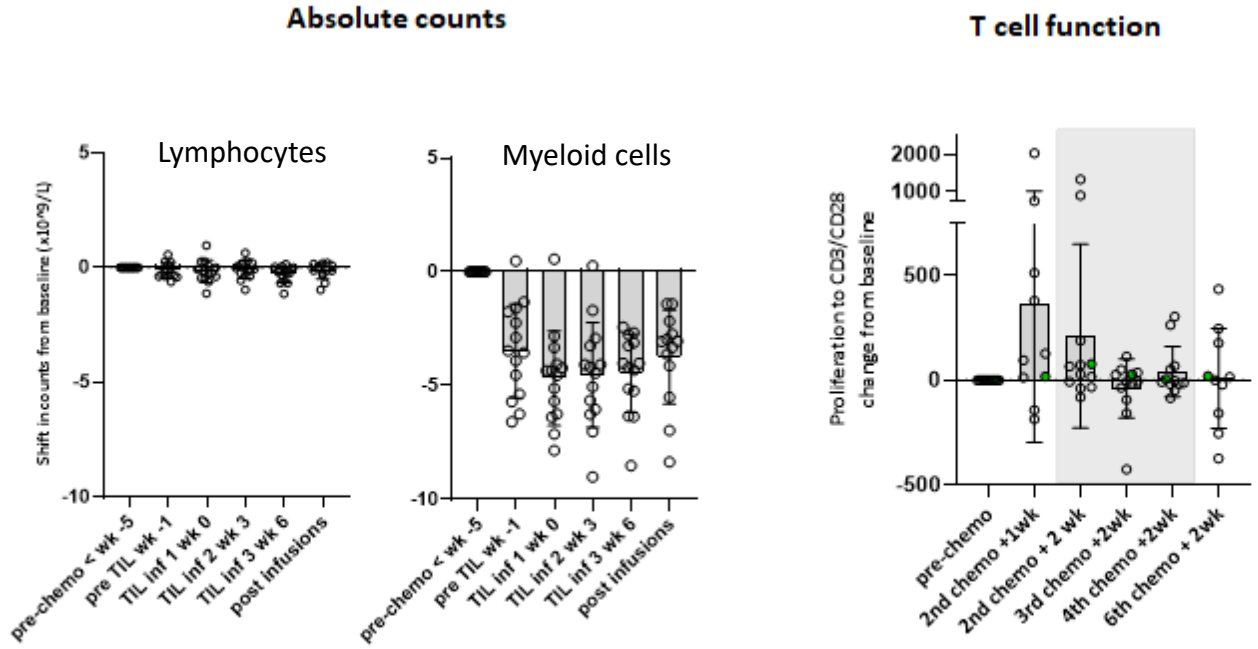
Verdegaal EME, J Immunother. Cancer 2023

Best overall response, platinum free interval



Verdegaal EME, J Immunother. Cancer 2023

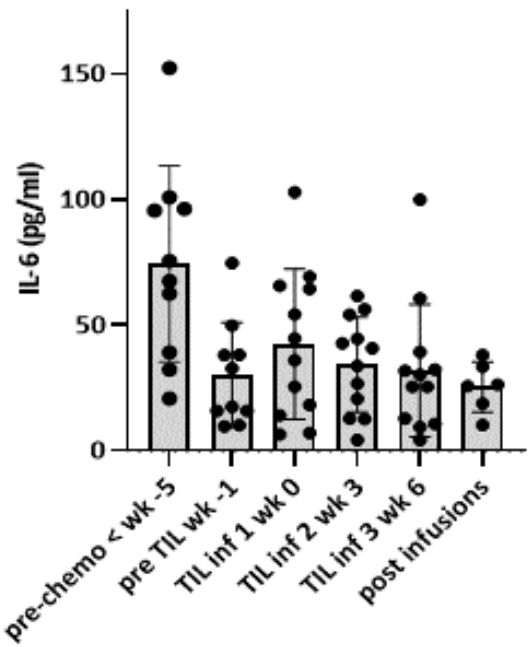
Changes in blood myeloid and lymphoid cell counts



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

Verdegaal EME, J Immunother. Cancer 2023

Change in systemic cytokine levels



- No changes in cytokines IL-7, IL-15 or IL-2
- Reduction of circulating IL-6, knowing that
  - increased serum IL-6 levels correlate with disease status and worse prognosis in EOC
  - Ovarian cancer-cell derived IL-6 can polarize monocyte differentiation into the suppressive M2 subtype

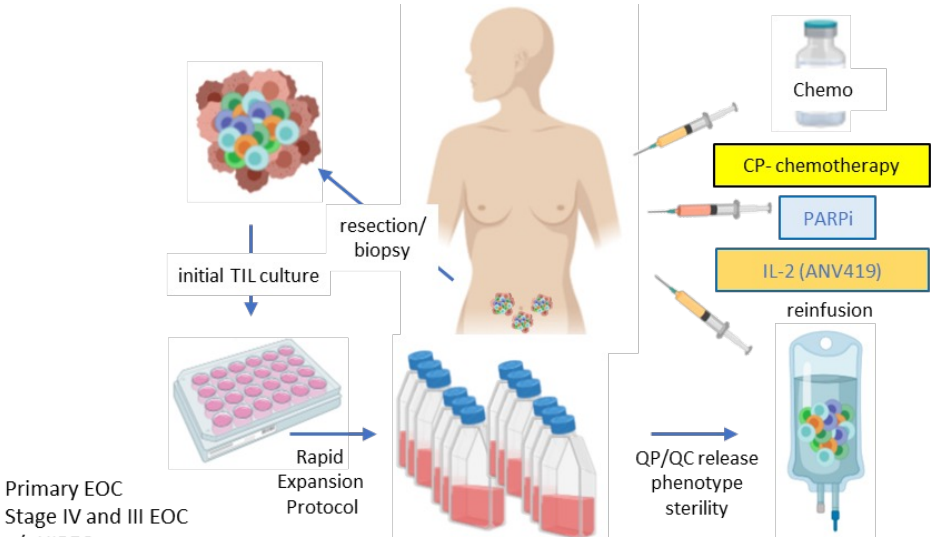
  => may change the TME in favor of anti-tumor immune response

Verdegaal EME, J Immunother. Cancer 2023

Summary: TIL +/- IFNα during chemotherapy – OVACUre -

- TIL during standard carboplatin-paclitaxel is safe and promising
- IFNα ‘conditioning’ was too toxic with chemotherapy
- Optimal normalization of myeloid cells 1-2 weeks after 2nd cycle
- IL-6 serum level reduction by therapy
- Promising early signs of efficacy were observed
- Phenotypic and functional testing of TIL and blood samples is ongoing

OVASTAR OVArian cancer STate-of-the-ARt TIL &ANV419 combination therapy



Willemijn Charity Golfdag

Summary Immunotherapy in GYN cancers

IO has a role

- in advanced Cervical Cancer (1st and 2nd line)
- In advanced Endometrial Cancer (1st and 2nd line)

IO expected

- (neo)adjuvant therapy in gynecologic cancers
- Vulva SCC: APOLLO study
- Endometrium Cancer: MMRd-GREEN trial in MMRd-EC
- Ovarian Cancer: more precision therapy and IO combination therapy is necessary ~ using TIL

Thank you, Questions?

Jan & Margret thank you so much !