ENDOMETRIOSIS ASSOCIATED OVARIAN CANCERS

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DISCLOSURES

Consulting/Advisory Boards:

GSK, MSD, Eisai, Abbvie, AstraZeneca

EPIDEMIOLOGY

- endometriosis is a chronic inflammatory disease
- affects 5-10% of fertile-age women

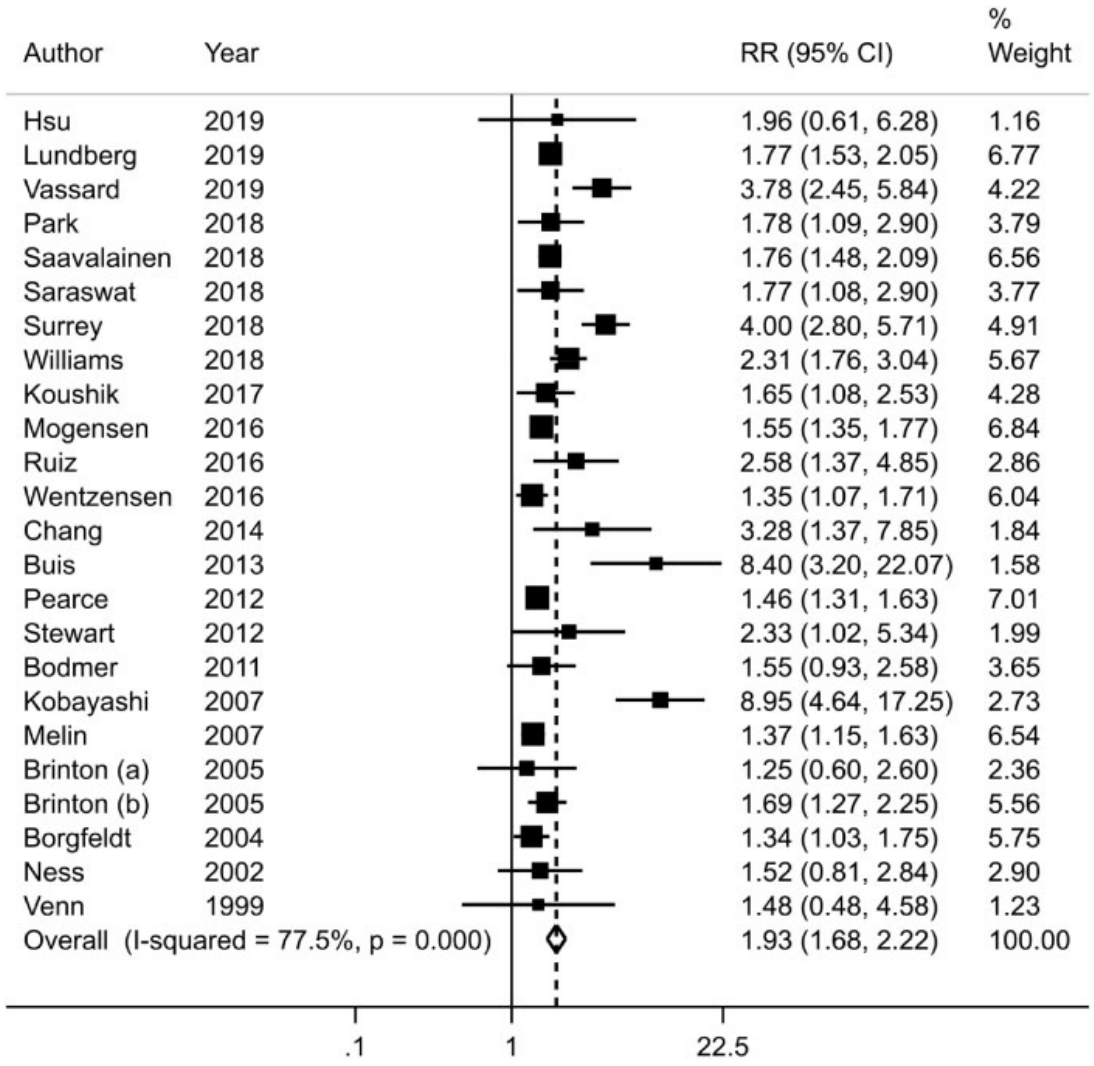
Kvaskoff et al 2021; Meta-analysis on 24 studies

- associates with increased risk of ovarian cancer:
  - RR 1.9
  - the risk is higher in registry based than by self-reported endometriosis dg (RR 2.07 vs 1.5)
- the association is strongest with:
  - clear cell RR 3.4
  - endometrioid RR 2.3
  - low grade serous RR 2.3

JOURNAL ARTICLE

Endometriosis and cancer: a systematic review and meta-analysis FREE

Marina Kvaskoff, Yahya Mahamat-Saleh, Leslie V Farland, Nina Shigesi, Kathryn L Terry, Holly R Harris, Horace Roman, Christian M Becker, Sawsan As-Sanie, Krina T Zondervan ...
Show more



Human Reprod Update 2021

VOL. 131, NO. 6, JUNE 2018 OBSTETRICS & GYNECOLOGY 1095

Gynecologic Oncology: *Original Research*

Risk of Gynecologic Cancer According to the Type of Endometriosis

Liisu Saavalainen, MD, Heini Lassus, MD, PhD, Anna But, MSc, Aila Tiitinen, MD, PhD, Päivi Härkki, MD, PhD, Mika Gissler, PhD, Eero Pukkala, PhD, and Oskari Heikinheimo, MD, PhD

Risk for ovarian cancer

- Overall SIR 1.8
- Endometrioid SIR 3.1
- Clear cell SIR 5.2
- Serous 1.4

- Finnish Hospital Discharge Register 1987-2012
- All first diagnosis of endometriosis
- Concomitantly with relevant surgical procedure
- n=49,933

- Cancers from Finnish Cancer Registry
- Reference: General population (SIR)

OVARIAN CANCER HISTOLOGY	TYPE OF ENDOMETRIOSIS		
	OVARIAN (n= 23 222)	PERITONEAL (n=20 197)	DEEP (n=2372)
ALL	**2.56 (1.98-3.27)**	1.32 (0.99-1.72)	1.41 (0.29-4.10)
Serous	1.62 (0.99-2.49)	1.21 (0.79-1.79)	2.05 (0.25-7.41)
Endometrioid	**4.72 (2.75-7.56)**	**2.03 (1.05-3.54)**	3.35 (0.08-18.7)
Clear Cell	**10.1 (5.50-16.9)**	2.76 (0.98-5.81)	0.00 (0.00-28.2)
Mucinous	1.29 (0.42-3.01)	0.80 (0.26-1.86)	2.05 (0.25-7.41)

Saavalainen et al. Obstet Gynecol 2018

Original Investigation

July 17, 2024

Endometriosis Typology and Ovarian Cancer Risk

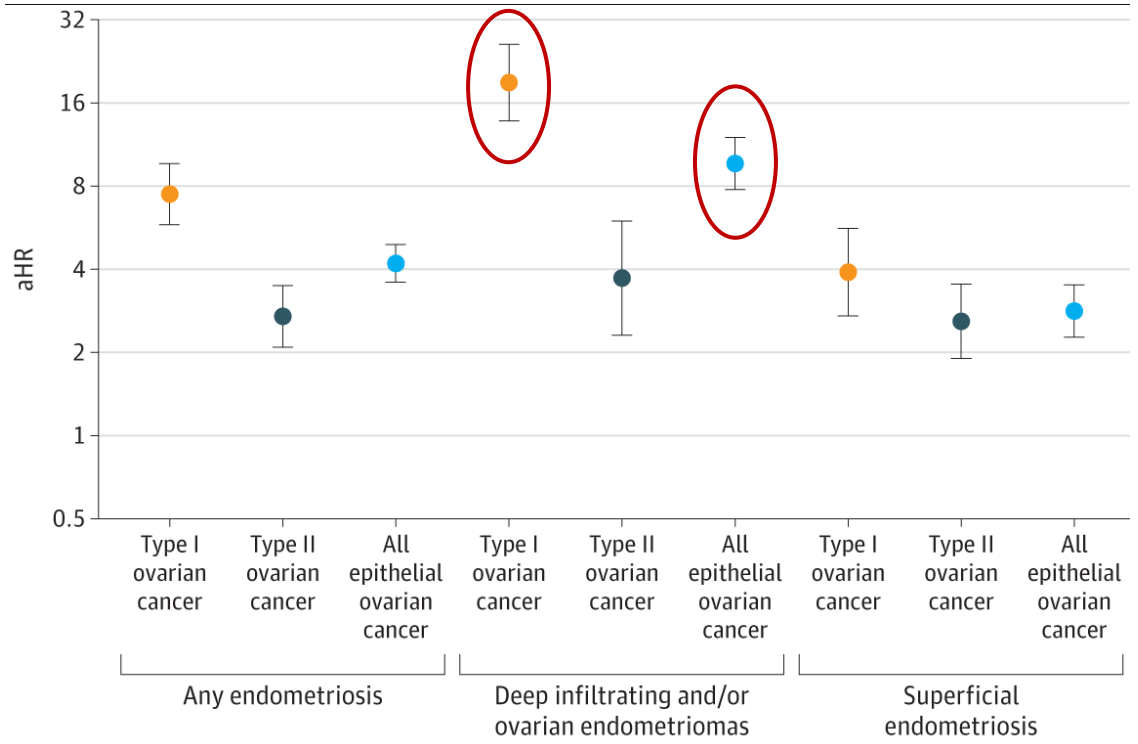
Mollie E. Barnard, ScD[1,2,3]; Leslie V. Farland, ScD[4]; Bin Yan, MSTAT[5]; et al

» Author Affiliations | Article Information

JAMA. 2024;332(6):482-489. doi:10.1001/jama.2024.9210

JAMA

- Population-based cohort study from Utah population Database
- 78 893 women with endometriosis (dg 1992-2009)
- the risk ratios were higher than in previous works:
  - all ovarian cancers HR 4.20
  - type I cancer (cc, endometrioid, low grade serous, mucinous) HR 7.48
  - clear cell HR 11.1
  - endometrioid HR 7.96
  - type II cancer (hg serous) HR 2.7



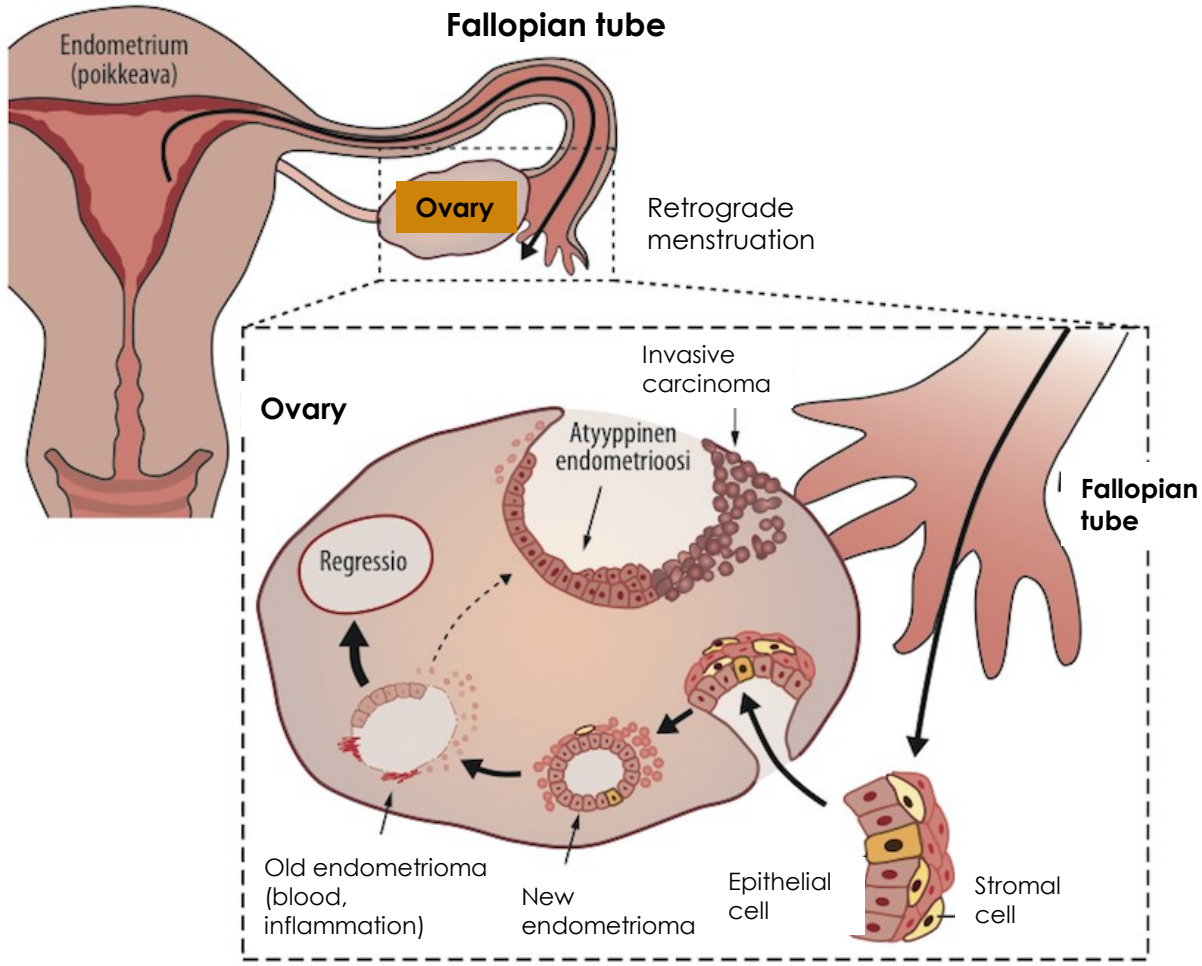
The risk was highest in deep infiltrating and ovarian endometriosis

Main differences compared to the Finnish registry study:

- Included also patients without surgery
- Tubal and peritoneal cancer diagnoses were included as well (C57 and C48)
- If the diagnosis of endometriosis and cancer were made in the same operation – the endometriosis index date was set 0.5 yrs before

PATHOGENESIS

- **atypical endometriosis** - **precursor lesion of endometrioid and clear cell** ovarian carcinomas
- most of the endometriomas regress
- some progress to atypical endometriosis and cancer
  - chronic inflammation and oxidative stress due to iron load
- another precursor lesion - noncystic clear cell adenofibroma
- direct transition from atypical endometriosis to cancer seen in 15-35% of cases
- **similar molecular changes** in atypical endometriosis as in adjacent cancer: mutations of ARID1A, CTNNB1 and PIK3CA

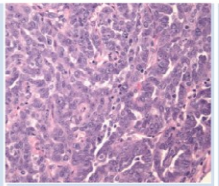
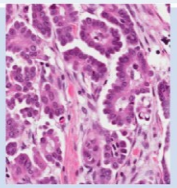
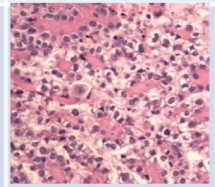
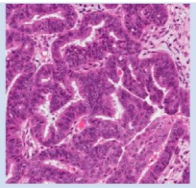
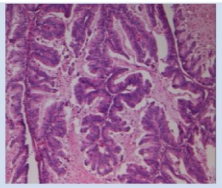


modified from Lassus et al. Duodecim 2015

Prat et al. Hum Pathol 2018; Wiegand et al. NEJM 2010; Matsumoto et al. Am J Clin Pathol 2015; Improta et al AIMM 2019; Marks et al Am J Clin Oncol 2020; Anglesio et al NEJM 2017

CLINICOPATHOLOGICAL CHARACTERISTICS

- Median age of dg 55-58 yrs
- WT1 negative (clear cell: Napsin, HNF1beta positive)
- Genetic predisposition: Lynch sdr (MMR mutations in germline)
- Hormone receptors
  - endometrioid ER >75% positive, PR >60% positive
  - clear cell ER 20% positive, PR <10% positive
- Overall prognosis is favorable in EAOCs
  - due to stage distribution: St I endometrioid 40% and clear cell 70%
- Poor prognosis in advanced disease

	75%	<5%	**10%**	**10%**	<5%
	HGSOC	**LGSOC**	**Clear Cell**	**Endometrioid**	**Mucinous**
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
Pathology					
Molecular features	CNA high *TP53* *BRCA1/2* HRD	CNA low MAPK act. *KRAS* *BRAF*	*ARID1A* PI3K/AKT act. RTK/Ras act. MMR	*PI3KCA* *ARID1A* *KRAS* Wnt/β-catenin act. *PTEN*	*KRAS* *HER2* amplif.

Lheureux et al, CA Cancer J Clin. 2019

Prat et al. Hum Pathol 2018; Hollis et al. Cancer Letters 2023;

MOLECULAR CHANGES

- Typical mutations

Endometrioid

CTNNB1 (30-50%)
PIK3CA (20-50%)
ARID1A (20-50%)
KRAS (15-40%)
PTEN (15-45%)

Clear cell

ARID1A (40-55%)
PIK3CA (40-55%)
PPP2R1A (10-20%)
KRAS (5-20%)
TERT (5-20%)

- MMR mutations
  - endometrioid 6-19%
  - cc 4-6%
- Mutations of *TP53* relatively infrequent in (as compared to HGSC):
  - endometrioid 10-25%
  - clear cell 5-20%
- Relatively low genomic complexity

Hollis et al. Cancer Letters 2023; Bolton et al. Clin Cancer Res 2022; Chen et al. Front Oncol 2021; Improta AIMM 2019

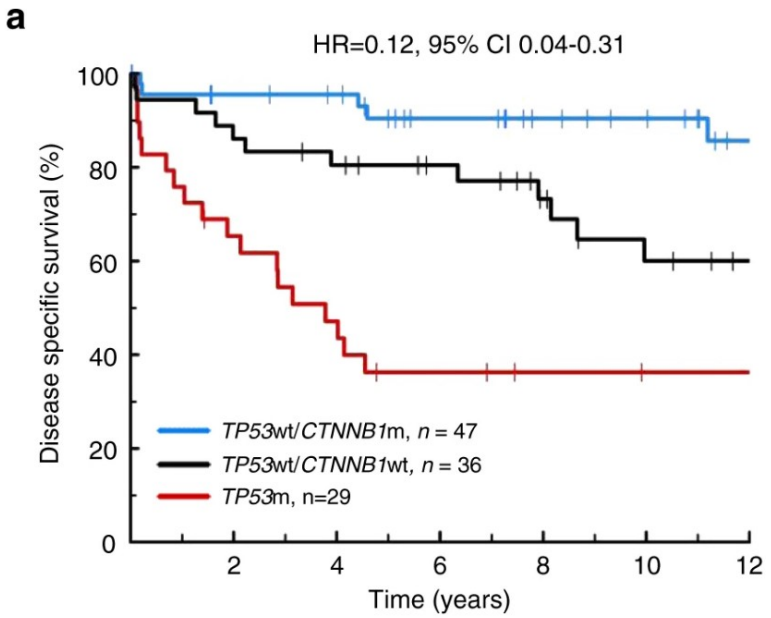
MOLECULAR SUBGROUPS – ENDOMETRIOID CA

Poor prognosis

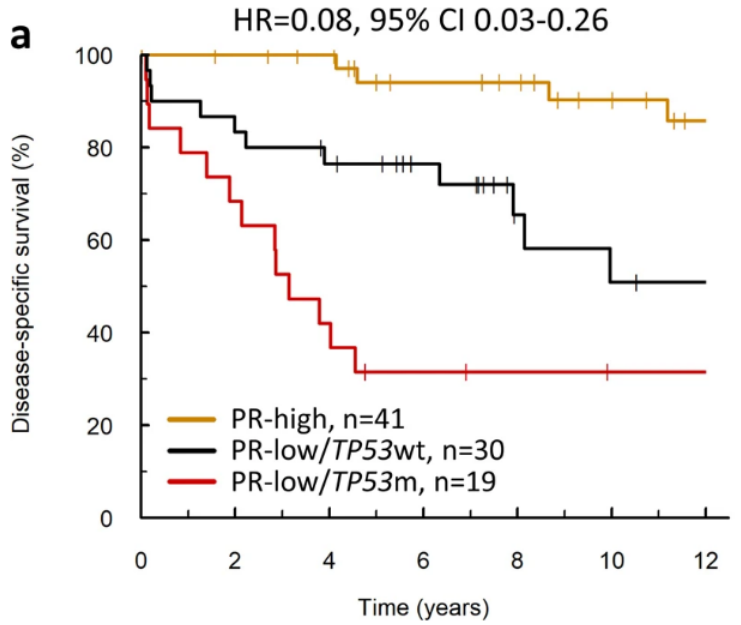
- ***TP53*** mutations/ **p53** aberrant expression

Favorable prognosis

- ***CTNNB1*** mutations
- **PR** expression



Hollis et al. Nature Comm 2020;
WES 112 EnOCs, UK Edinburgh



Hollis et al. npj Precision Oncol 2021;
IHC 90 EnOCs; UK Edinburgh

MOLECULAR SUBGROUPS – ENDOMETRIOID CA

- Similar findings by IHC (n=215; Helsinki University Hospital)

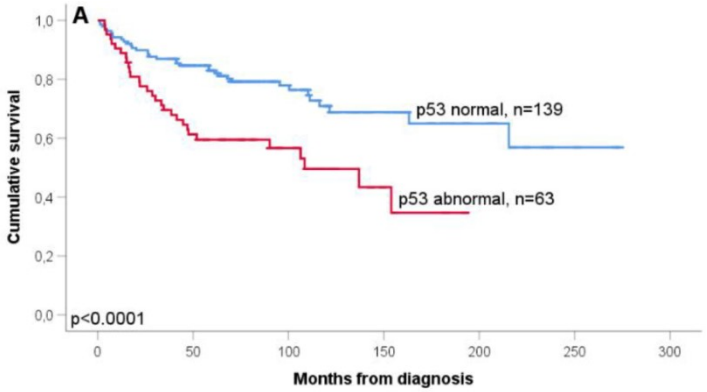
<u>Poor prognosis</u>

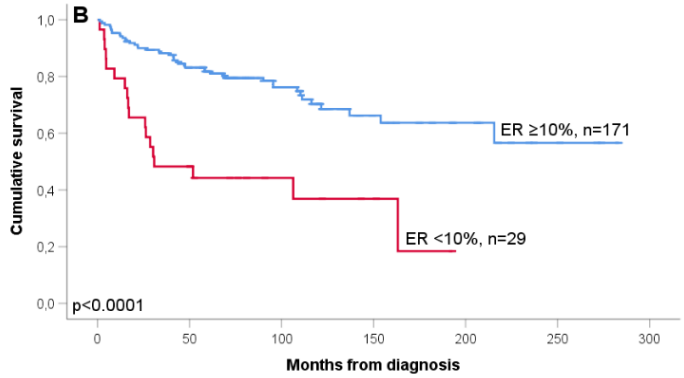
- **p53 aberrant** expression
- p16 positive expression
- **L1CAM** expression

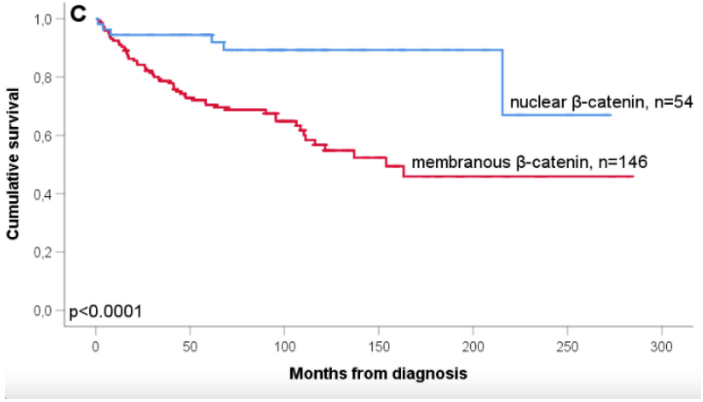
<u>Favorable prognosis</u>

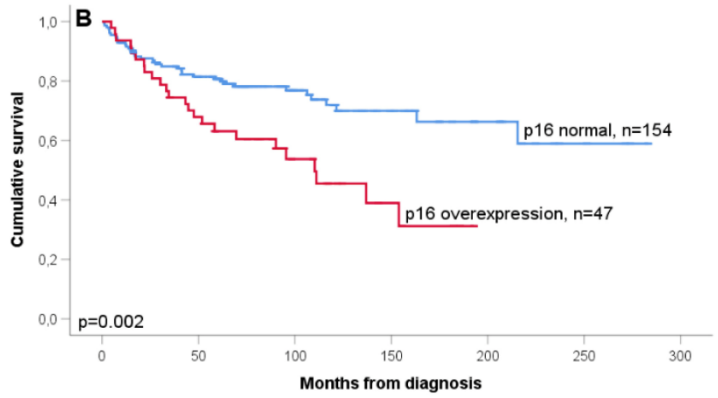
- nuclear **beta-catenin** expression
- **PR** expression
- **ER** expression

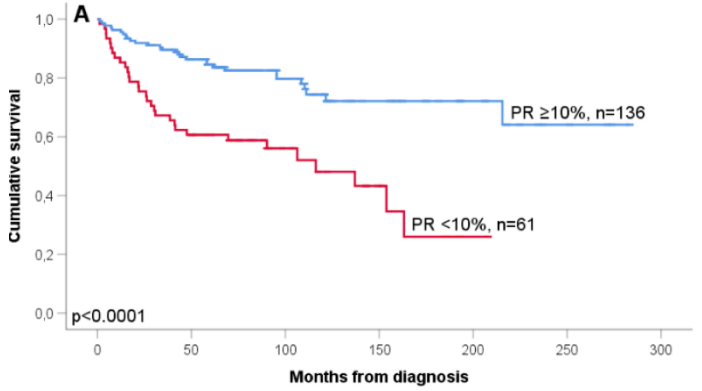
Soovares et al. Gynecol Oncol 2017 and Gynecol Oncol 2022

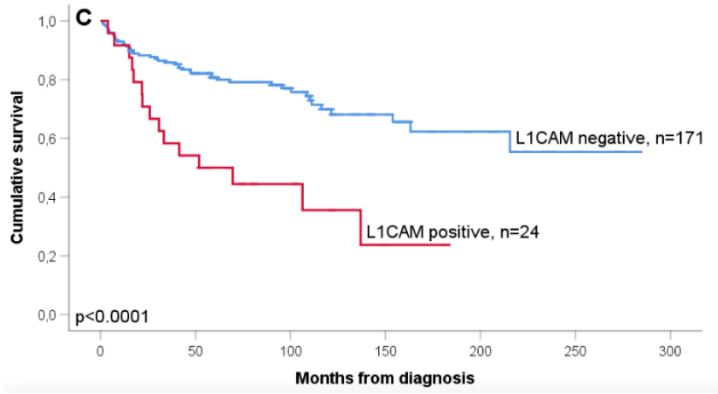










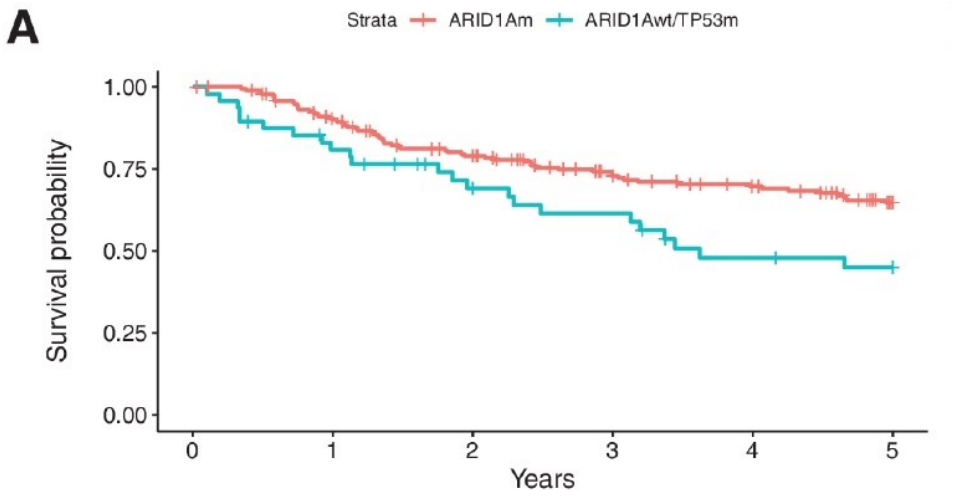


MOLECULAR SUBGROUPS – CLEAR CELL CA

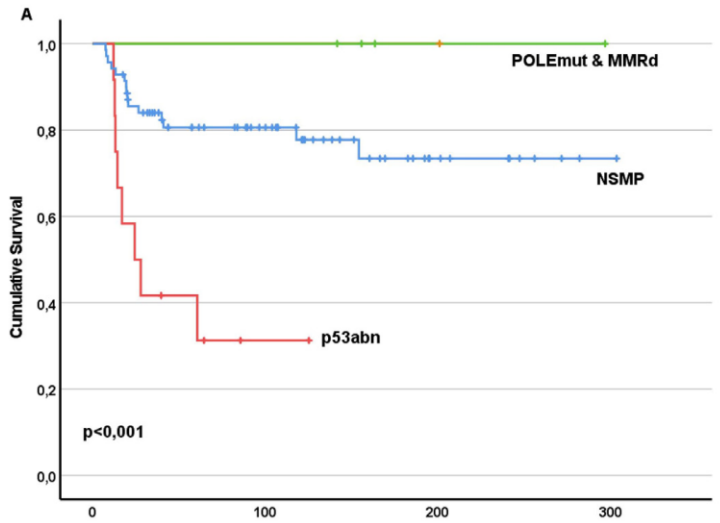
Whole genome/exome sequencing analysis projects identified subtypes of CCOC:

- ***ARID1A/PIK3CA*** mutations (canonical CCOC genes)
  - better prognosis
  - early stage disease
  - but resistance to chemotherapy
- **TP53** mutations
  - more advanced disease
  - poorer survival

Bolton et al. Clin Cancer Res 2022;
Nishijima et al. Scientific Rep 2024



Bolton et al. Clin Cancer Res 2022; n = 421



Similä-Maarala et al. Gynecol Oncol 2022

TCGA endometrial classification (n=115):

- **POLE ja MMRd** (4,5%)
  - excellent outcome
- **aberrant p53** (20%)
  - poor survival
- **NSMP** (76%)
  - intermediate prognosis

TARGETABLE PATHWAYS

Relatively low genomic complexity

- rational for targeting activated pathways
- several trials ongoing

PI3K-AKT-mTOR pathway

- phase II temsirolimus (mTOR inhibitor) + paclitaxel-carboplatin 1st line – no survival benefit (Farley Gyn Oncol 2022)
- phase II DICE TAK228 (mTOR inhibitor) + paclitaxel - closed, no results yet (NCT03648489)
- phase Ib inavolisib (PIK3CA inhibitor) +paclitaxel – recruiting (ISRCTN45319897)

PP2A

- dostarlimab and LB-100; (NCT06065462)

ARID1A

- ATARI – ceralasertib (ATR inhibitor) +/- olaparib and/or durvalumab; (NCT04065269); ongoing
- phase II Tazemetostat (EZH2 inhibitor) (NCT03348631); active, not recruiting

RAS-RAF-MAPK pathway

- MEK inhibitors

Hormonal treatment

- endometrioid ca
- aromatase inhibitors (Pan et al Curr Oncol 2010), MPA? (Hollis et al Gynecol Oncol 2019)

PARP inhibitors

- high grade endometrioid (HRD)

HER2

- no mut/amplif, expression in 20% of CCOCs
- HER2-targeted ADCs; other ADCs

IO-TRIALS

- IO-therapies have shown promise in clear cell ovarian carcinomas
- In contrast to high grade serous carcinomas where responses are rare
- Less is known about endometrioid carcinomas

(Zamarin et al. J Clin Oncol; Disis et al. Jama Oncol 2019; Matulonis et al. Ann Oncol 2019; Sia et al. Int J Gyn Cancer 2022)

- Several abstracts published in OCCC this year:

2024 ASCO ANNUAL MEETING

LEGORRETA CANCER CENTER BROWN UNIVERSITY

Lifespan

Final results of BrUOG 354:

A randomized phase II trial of nivolumab alone or in combination with ipilimumab for people with ovarian and other extra-renal clear cell carcinomas

Don S. Dizon, Cara Amanda Mathews, Shannon MacLaughlan David, Jason T Machan, Matthew James Hadfield, Eric I Marks, Rani Bansal, Christine McGinn, Faith Hassinger, Denise Luppe, Janine Grigelevich, Kelly A Mitchell, Adam Braga, Ashlee Sturtevant, Roxanne Wood, Ursula A. Matulonis, Alexi A. Wright, Susana M. Campos, Michael J. Birrer

Treatment	ORR (%)	Median PFS (range, months)	Median OS (range, months)
Nivolumab	14.3	2.2 (1.2-3.4)	17.3 (2.1-42.7)
Nivolumab/Ipilimumab	33.3	5.6 (1.6-29.1)	24.7 (5.7-NR)

Dizon et al. J Clin Oncol 2024; Abstr LBA5500 - NCT03355976

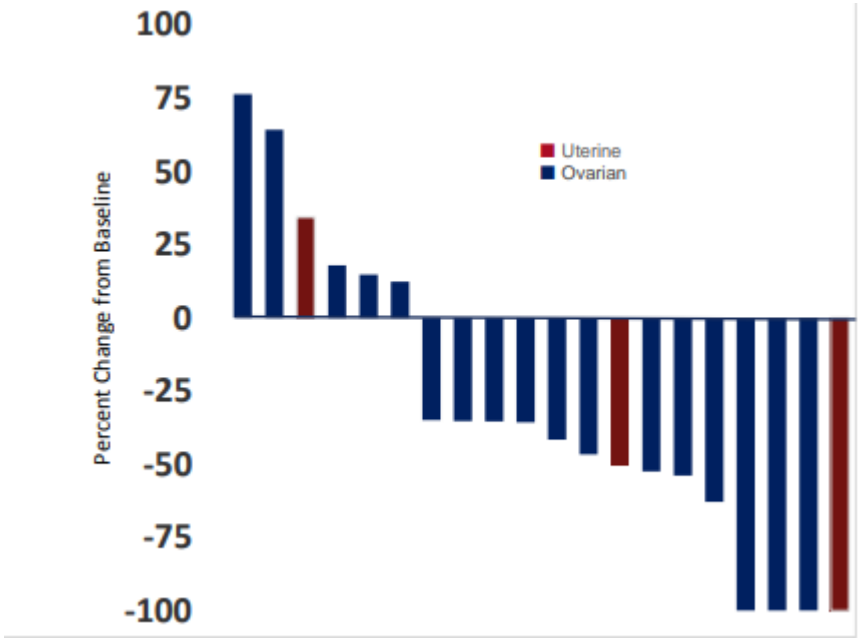
44 clear cell carcinomas:

- 44 ovarian
- 8 uterine
- 2 other

IO-TRIALS

BARCELONA 2024 ESMO congress

Nivolumab and Ipilimumab combination treatment in advanced gynaecological clear cell cancers: Results from the phase II MoST-CIRCUIT trial



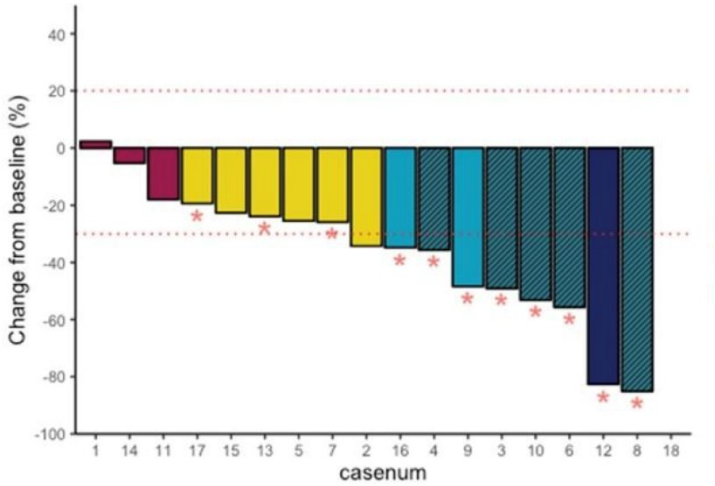
Combination of nivolumab and ipilimumab

26 clear cell carcinomas:

- 22 ovarian – ORR 50%
- 4 uterine – ORR 50%

Klein et al. Annals Oncol 2024; Abstr 713MO -

IGCS 2024 Annual Global Meeting DUBLIN OCTOBER16-18, 2024



A PHASE II TRIAL OF PEMBROLIZUMAB AND LENVATINIB IN RECURRENT OR PERSISTENT CLEAR CELL OVARIAN CARCINOMA (NCT05296512): STAGE 1 RESULTS

Combination of pembrolizumab and lenvatinib

18 clear cell ovarian carcinomas:

- 1 CR, 7 PR – ORR 44%
- Proceeds to stage 2 of the study

Lee et al. IGSC 2024 LB009/#1562 - NCT05296512

CONCLUSIONS

- **The risk of ovarian/pelvic cancer in patients with endometriosis may be higher than previously thought** (RR 1.9-4.2)
  - The risk is highest for **clear cell and endometrioid carcinomas**, and low grade serous carcinomas to lesser extent
- The **overall prognosis of EAOCs is good** due to **early stage** in the majority of cases, but **poor in advanced disease**
- **Atypical endometriosis** is the precursor of clear cell and endometrioid carcinomas
  - **Typical mutations (ARID1A, PIK3CA and CTNNB1)** already in atypical endometriosis
- **Combination IO-therapy** has shown promise in **clear cell** ovarian cancer
- **Understanding of the molecular subgroups of EAOCs** is needed for testing new therapies

We can see some signs, but not the whole picture yet…

Helsinki 22nd Nov 2024

Thank you!