



State of the Art – Gynaecological cancer Ovarian and Endometrial Cancer

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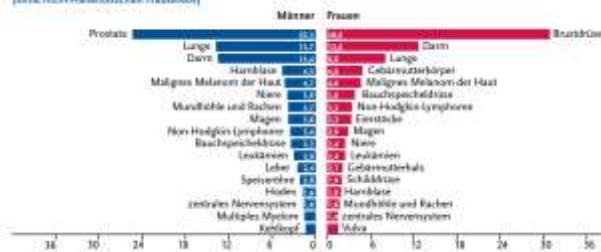
01 Ovarian Cancer



Ovarian cancer in Germany



Abbildung 3.0.1
Prozentualer Anteil der häufigsten Tumorkalzifikationen an allen Krebsneuerkrankungen in Deutschland 2012
[ohne nicht-neoplastischen Häufigkeiten]



9.000 newly diagnosed

Abbildung 3.0.2
Prozentualer Anteil der häufigsten Tumorkalzifikationen an allen Krebssterbefällen in Deutschland 2012



7.000 deaths

„RARE BUT DEADLY“

Ovarian cancer



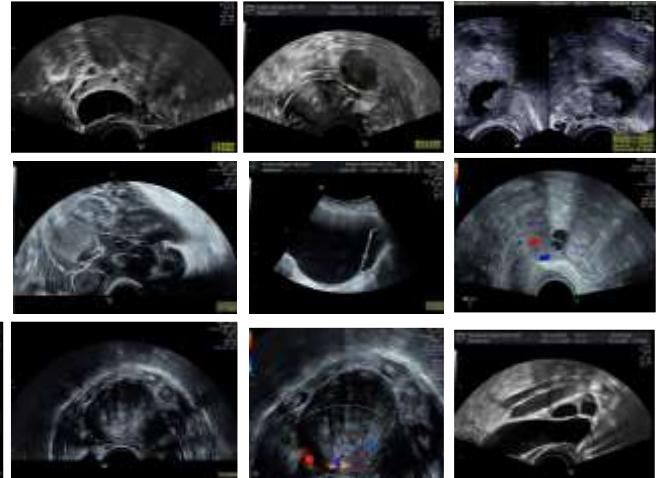
- › very limited symptoms
- › 70% diagnosed at STAGE III
- › no effective strategy for screening

Ovarian cancer and Screening



► Ovarian tumors are ...

- frequent
- easy to detect by US
- and benign.... with some rare exceptions



Ovarian cancer

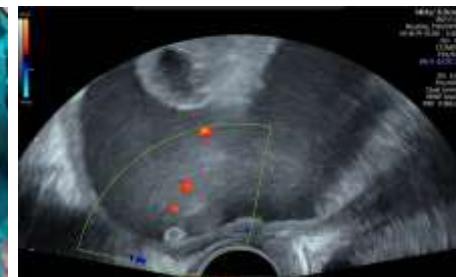


2 different situations at the time of primary diagnosis

Early stage (I-IIA)
~ 25-30%



Advanced stage (IIB-IV)
~ 70-75%



Ovarian cancer – open questions in early stage



Early stage (I-IIA)

~ 25-30%



- ▷ Radical surgical therapy?
- ▷ Relevance of the LND?
- ▷ Adjuvant therapy?

Optimal staging - early stage OC



- ▷ longitudinal laparotomy, inspection and palpation of the entire abdominal cavity
- ▷ peritoneal cytology
- ▷ peritoneal biopsies
- ▷ bilateral salpingoophorectomy
- ▷ hysterectomy
- ▷ omentectomy at least infracolic
- ▷ appendectomy (mucinous tumor type)
- ▷ lymphonodectomy pelvin and paraaortic

Optimal staging - early stage OC

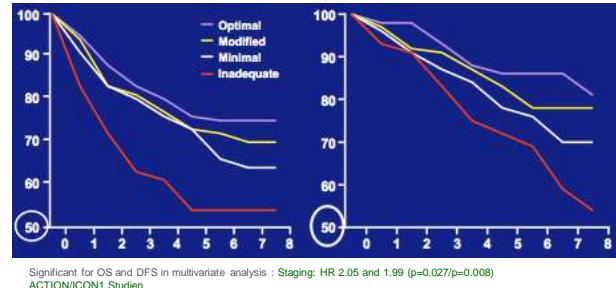


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- ▷ lymphonodectomy pelvin and paraaortic

Incidence of occult intra-abdominal metastases at "early stage": 20-30%

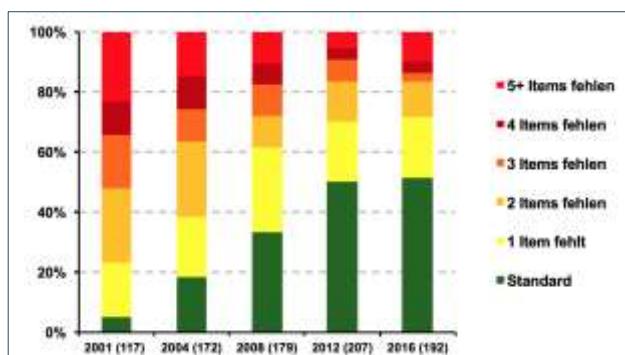
- Positive cytology 20 %
- Omentum majus 6 %
- Diaphragm 15 %
- Peritoneal biopsies 13 %
- Lymph nodes paraaortal 14 %
- Lymph nodes pelvin 8 %

JB Trimbos Int J Gynecol Cancer 2000



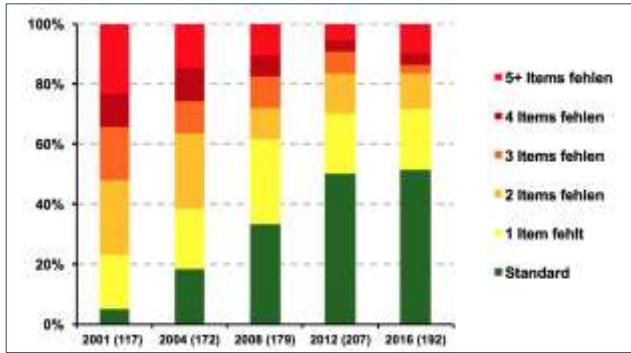
Optimal staging in early stage OC – real world data

Staging-OP in FIGO I-IIA
according to QS-OVAR (N=867)

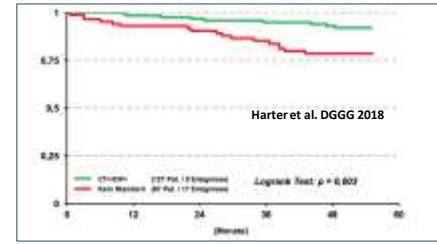


Optimal staging in early stage OC – real world data

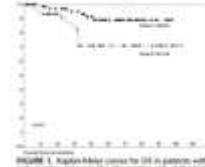
Staging-OP in FIGO I-IIA according to QS-OVAR (N=867)



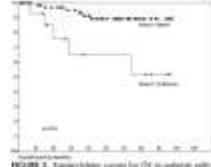
QS-OVAR Kohorte 2012: Treatment quality and survival (FIGO I IIA) (OP+: max. 1 missing)



Harter et al. DGGG 2018



Logrank Test: p = 0.003



Logrank Test: p = 0.003

Gimenez et al. Int J Gynecol Cancer 2018

Option for fertility sparing surgery?

- no randomized trials
- adequate staging required
- individual approach for unilateral tumor
- FIGO IA grade 1 (and possibly 2) serous, mucinous, endometrioid
- FIGO IC G1 ???

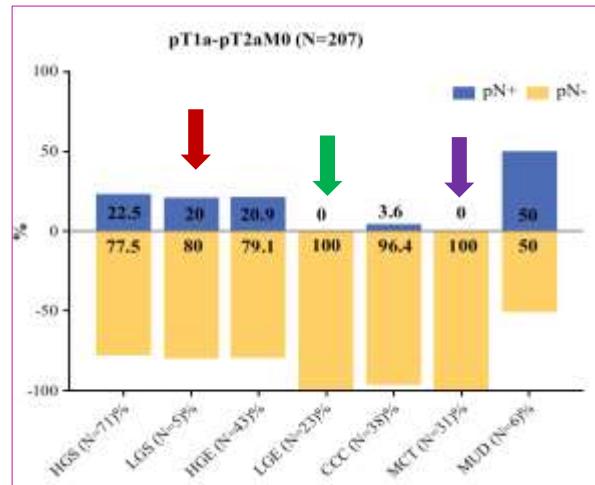
TABLE 2. Literature review of results of conservative management in EOC (7 series reported including >10 cases)¹

	Stage IA Grade 1	Stage IA Grade 2	Stage IA Grade 3	Stage IC Grade 1	Stage IC Grade 2	Stage IC Grade 3
Batian series	1 recurrence among 34 patients	3 recurrences among 8 patients	1 recurrence among 4 patients	No recurrence among 10 patients	1 recurrence among 6 patients	No recurrence among 3 patients
Zarara et al. ¹⁰	34 patients	8 patients	4 patients	10 patients	6 patients	3 patients
Ceballos et al. ¹¹						
Arriban series	2 recurrences among 33 patients	2 recurrences among 8 patients	No recurrence among 3 patients	No recurrence among 9 patients	1 recurrence among 3 patients	No recurrence among 2 patients
Schäfer et al. ¹²	33 patients	8 patients	3 patients	9 patients	3 patients	2 patients
Fried's series	1 recurrence among 13 patients	4 recurrences among 14 patients	1 recurrence among 3 patients	2 recurrences in 2 patients	No patient	1 recurrence in 1 patient
Morice et al. ¹³	13 patients	14 patients	3 patients	2 patients	No patient	1 patient
Bergfeldt et al. ¹⁴	No recurrence among 8 patients	No recurrence in 1 patient	No patient	No patient	No patient	1 recurrence in 1 patient
Park et al. ¹⁵	8 patients	1 patient	No patient	No patient	No patient	1 recurrence in 1 patient
Anchizat et al. ¹⁶	1 recurrence among 10 patients	No patient	1 recurrence in 1 patient	No recurrence in 3 patients	No recurrence in 1 patient	No recurrence in 1 patient
Shin et al. ¹⁷	1 recurrence among 95 patients	No recurrence in 12 patients	2 recurrences in 3 patients	5 recurrences among 81 patients	No recurrence in 7 patients	3 recurrences in 7 patients
Total:	11 (5%) recurrences among 287 patients	8 (20%) recurrences among 45 patients	8 (4%) recurrences among 10 patients	8 (8%) recurrences among 100 patients	4 (2%) recurrences among 14 patients	9 (33%) recurrences among 15 patients

Morice, Denschlag et al.
Int J Gynecol Cancer 2011

High rate of recurrence in potentially curative situation !

Relevance of LND - early stage OC



Ann Surg Oncol (2016) 23:2053–2065
https://doi.org/10.1245/s10434-014-4412-5

Annals of SURGICAL ONCOLOGY
Volume 23 Number 12 December 2016

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Stage- and Histologic Subtype-Dependent Frequency of Lymph Node Metastases in Patients with Epithelial Ovarian Cancer Undergoing Systematic Pelvic and Para-aortic Lymphadenectomy

Bertram Holz^{1,2}, Philipp Bauer¹, MD, PhD^{1,2}, Bejhan Atesmen, MD, PhD^{1,2}, Sebastian Heilcke, MD, PhD¹, Stephanie Schuster, MD¹, Sonja Prader, MD¹, Maruska Bonner, MD¹, Anette-Florian-Eckhoff, MD, PhD¹, Alexander Tratz^{1,2}, and Andras da Bois, MD, PhD^{1,2}

- low grade endometrioid: no LN metastasis
- low grade mucinös: pT1-2a: no LN metastasis
- **CAVE: low grade serous: high rate of positive LN 20-73%**

LND may be omitted in certain histological subtypes

Adjuvant Tx - early stage OC



FIGO IA, G1 → no adjuvant chemo Tx

FIGO IA, G2, FIGO IB G1/2 → pt containing chemo Tx optional

all FIGO IC, FIGO IA/B G3 → pt containing chemo Tx

Limited data on certain subtypes → adjuvant chemo Tx to be discussed individually:

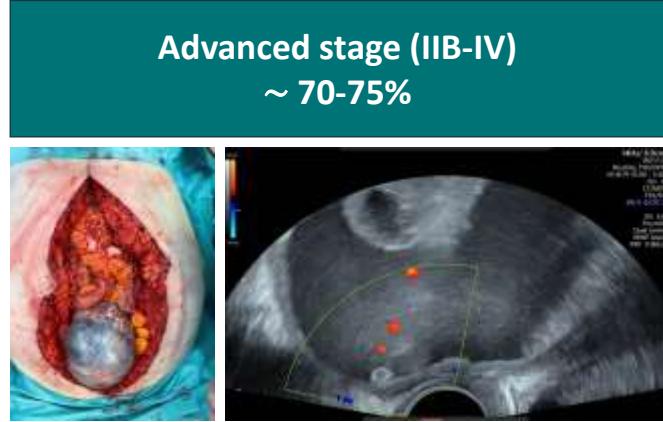
- clear cell carcinoma FIGO IA-IC1
- mucinous carcinoma FIGO IB/C G 1/2

Chemo Tx should contain pt, 6 cycles

Ovarian cancer - Standard of care in advanced stage



- ▷ Radical surgical therapy → intraabdominal complete resection
- ▷ First line med. Tx
- ▷ Maintenance Tx / BRCA / HRD diagnostic



Optimal surgery – advanced stage OC



FIGO IIB-IV

- ▷ longitudinal laparotomy, inspection and palpation of the entire abdominal cavity
- ▷ Complete resection → multivisceral surgery (BSO, hysterectomy, resection of bowel, spleen, liver, peritonectomy,)
- ▷ No LNE!



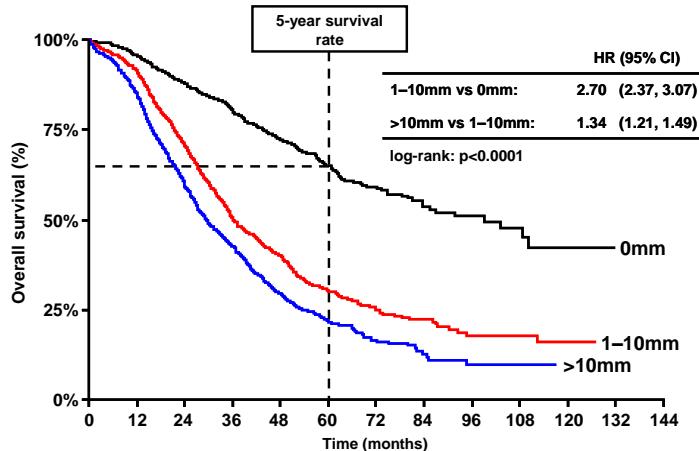
Complete resection rate in specialized centers in Germany: 60-70%

Residual Tumor at the end of surgery – the most important prognostic factor !



The impact of residual tumour on outcome in advanced ovarian cancer

Data from an individual patient meta-analysis of three randomised phase III trials with 3,126 patients



Complete debulking is important... because it saves the patients life !!!

10 % debulking improve OAS by approx 2,3 mths

du Bois A, et al. Cancer 2009;15:1234-44

How about LNE in advanced stage?



Abstr. 5500: LION – LYMPHADENECTOMY IN OVARIAN NEOPLASMS.
A prospective randomized AGO Study Group led Gynecologic Cancer Intergroup trial. AGO OVARIOPM/ENGOT-ov31.

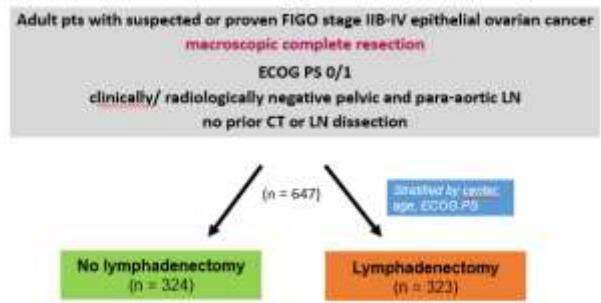
Philip Harter¹, J. Schutte², D. Lorusso³, A. Reuss⁴, I. Viegas⁵, C. Marth⁶, JW Kim⁷, F. Raspagliesi⁸, B. Lampert⁹, F. Landon¹⁰, W. Meier¹¹, D. Cibula¹², A. Mustea¹³, S. Maher¹⁴, I. Runnebaum¹⁵, B. Schmalzlaff¹⁶, A. Burges¹⁷, R. Kimmig¹⁷, U. Wagner¹⁸, A. du Bois¹⁹

¹AGO e.V., Germany, ²AGO e.V. Berlin, Germany, ³MITO e.Milano, Italy, ⁴KRK Heidelberg, Germany, ⁵OGCO Alzey, Germany, ⁶AGO-Aachen & Innsbruck, Austria, ⁷AGO & Bremen, Germany, ⁸MITO e.Milano, Italy, ⁹AGO & Duesseldorf, Germany, ¹⁰Mitglied e.Milano, Italy, ¹¹AGO & Düsseldorf, Germany, ¹²AGO & Prague, Czech Republic, ¹³AGO & Bucharest, Romania, ¹⁴AGO & Hamburg, Germany, ¹⁵AGO & Jena, Germany, ¹⁶AGO & Münster, Germany, ¹⁷AGO & Essen, Germany, ¹⁸AGO & Mainz, Germany, ¹⁹AGO St. Gallen, Switzerland

NC100712218

ASCO ANNUAL MEETING '17 - BASCO17

ENGOT
European Gynaecological Oncology Group
Gynecologic Oncology Intergroup
AGO St. Gallen



LION (AGO-OVAR OP.3)



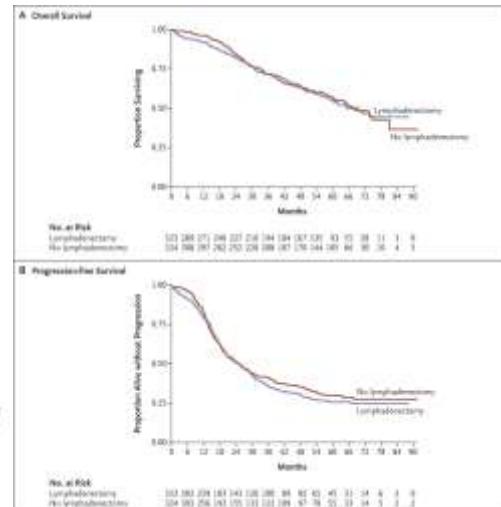
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms

P. Harter, J. Sehouli, D. Lenrousso, A. Reuss, I. Vergote, C. Marth, J.-W. Kim, F. Raspagliosi, B. Lampe, G. Aletti, W. Meier, D. Cibula, A. Mustea, S. Mahner, I.B. Runnebaum, B. Schmalzlfeild, A. Burges, R. Kimmig, G. Scambia, S. Gregg, F. Hilpert, A. Häslerburg, P. Hillemanns, G. Giorda, I. von Leffern, C. Schade-Brittinger, U. Wagner, and A. du Bois

In conclusion, in this trial involving patients with macroscopically complete resection of advanced ovarian cancer and clinically negative lymph nodes, systematic pelvic and paraaortic lymphadenectomy was not associated with better outcomes than no lymphadenectomy and was associated with a higher incidence of postoperative complications.



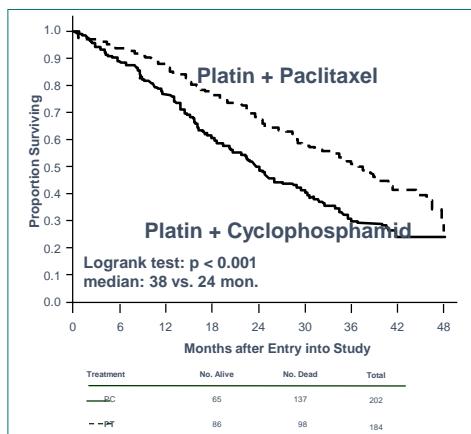
No LNE in advanced OC

N Engl J Med 2019; 380:822-832

Adjuvant CTx in OC

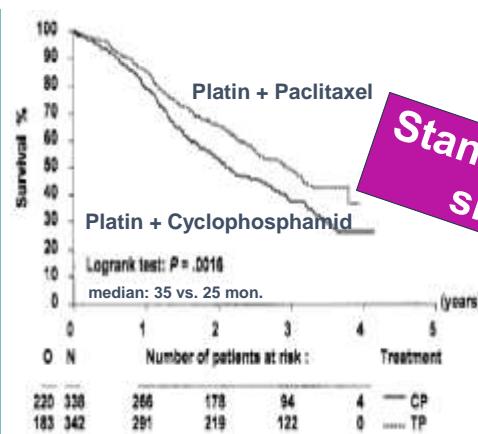


GOG 111: 410 Pat. FIGO III-IV TuR > 1cm



WP McGuire et al.; N Engl J Med 334 (1996)

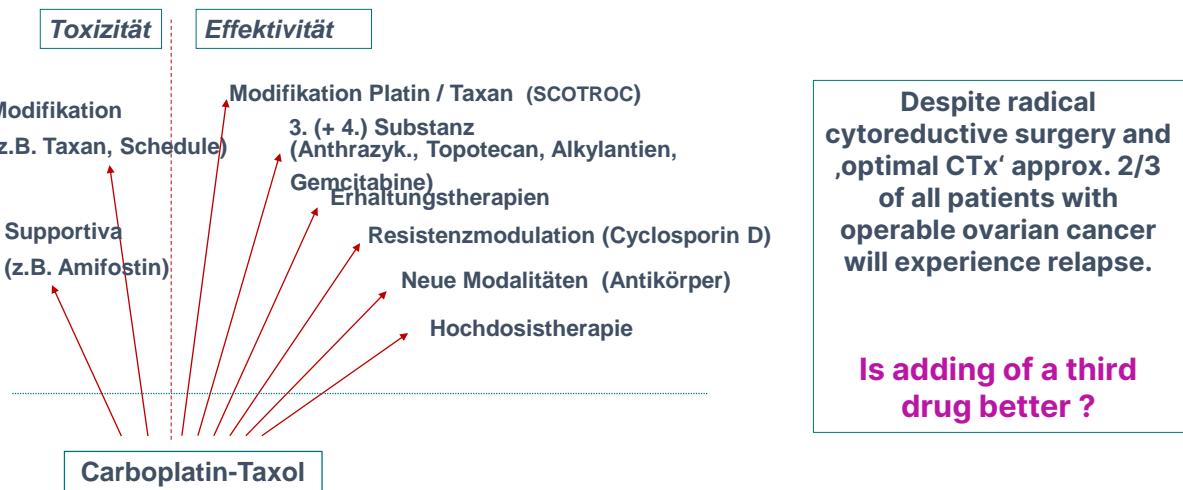
OV-10: 680 Pat. FIGO IIB-IV alle TuR



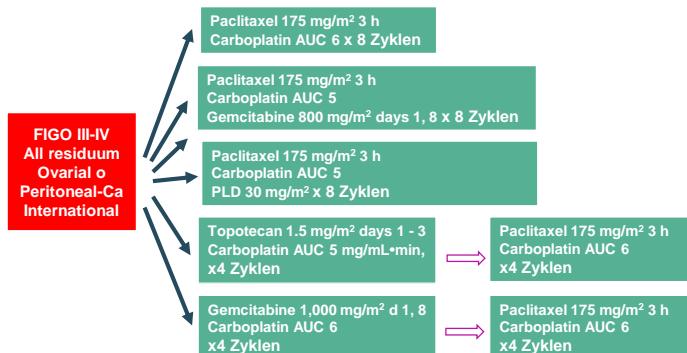
Standard of care
since '90

MJ Piccart et al.; J Natl Cancer Inst 92 (2000)

Standard Med Tx – Optimizing CTx



Is more better? - GOG 182



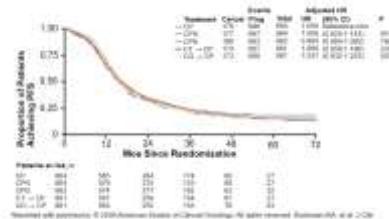
Interval cytoreduction allowed, no second-look surgery

Endpoints: PFI, survival, response

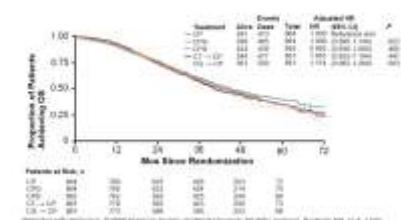
n > 4,000 patients

NO !

GOG0182-ICON5; PFS



GOG0182-ICON5; Overall Survival

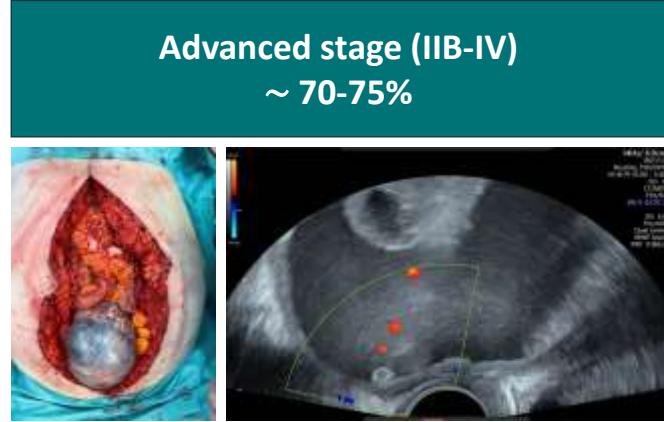


Bookman, ASCO 2006, #5002

Ovarian cancer - Standard of care in advanced stage



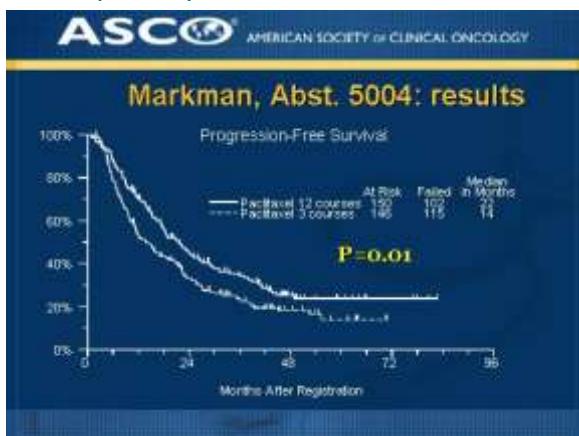
- Radical surgical therapy → intraabdominal complete resection
- First line med. Tx
- Maintenance Tx / BRCA / HRD diagnostic



Maintenance therapy – an old concept

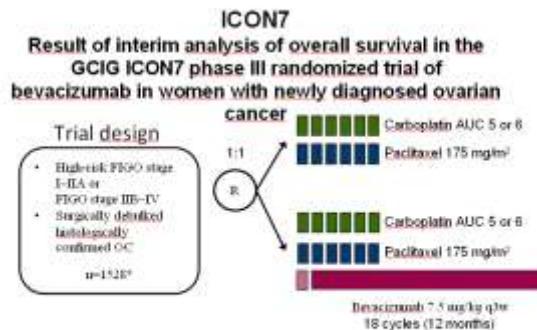


Will 12 months of paclitaxel prolong survival in patients with clinical complete remission after primary treatment ?



No positive evidence for CTx maintenance Tx in advanced OC

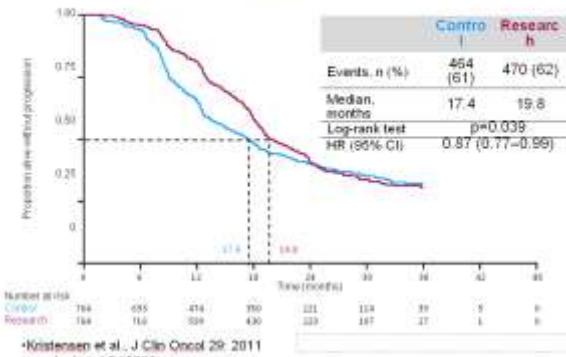
ICON 7 - Design



*Kristensen et al., J Clin Oncol 29; 2011 (suppl; abstr LBA5006).

• Dec 2006 to Feb 2009

ICON7 – Bevacizumab in ovarian cancer Updated PFS



BEV - Optimizing Duration of Tx

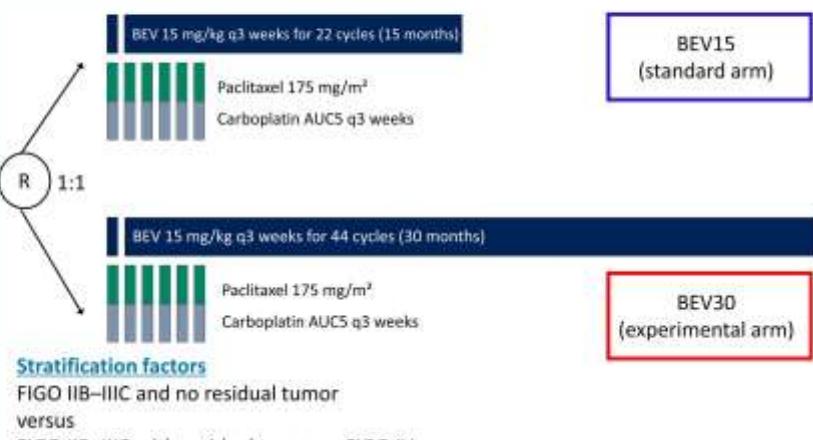


Trial design

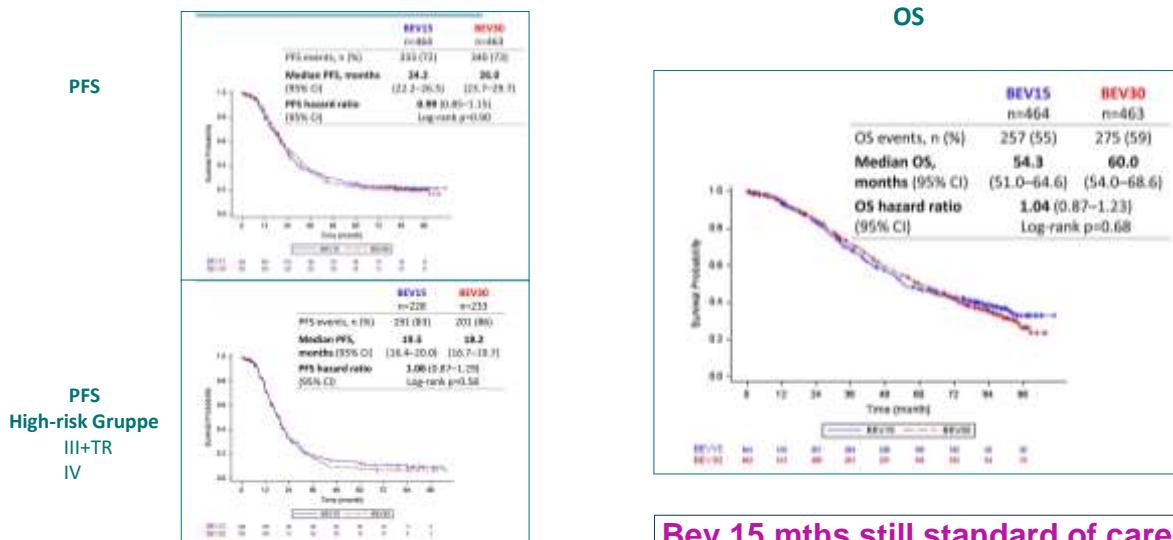
AGO-OVAR 17 BOOST / GINECO OV118 / ENGOT Ov-15



- Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (excluding non-epithelial and borderline tumors)
 - FIGO stage IIB-IV (any grade/histologic subtype)
 - Primary debulking surgery ≤8 weeks before treatment start, >4 weeks before first BEV dose
 - Adequate coagulation parameters, bone marrow, liver, and renal function
 - ECOG PS 0-2
 - Standard BEV exclusion criteria
- n = 927 Nov 2011 – Aug 2013



Medianes F-UP 85 mths

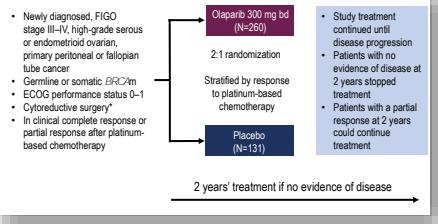


Jacobus Pfisterer et al. ASCO 2021, oral abstract S501

PARPi – first line Tx FIGO III/IV

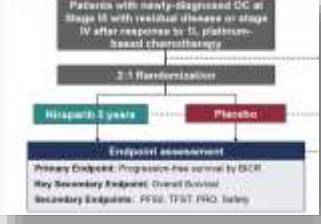


SOLO1



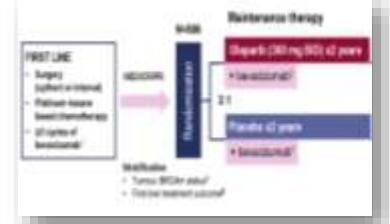
Moore et al. ESMO 2018

PRIMA



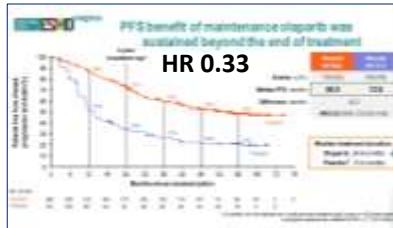
Gonzalez-Martin et al. ESMO 2019

PAOLA

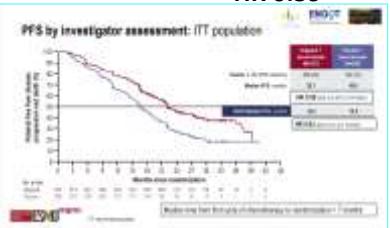
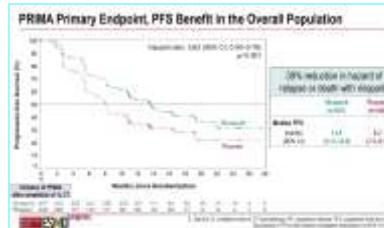


Ray-Coquard et al. ESMO 2019

HR 0.62



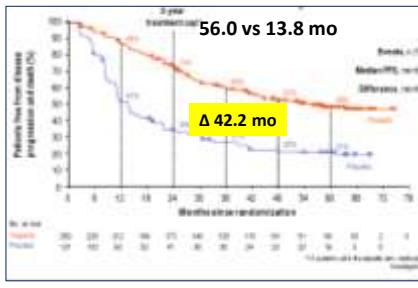
Moore et al. ESMO 2018 & Banerjee et al. ESMO 2020



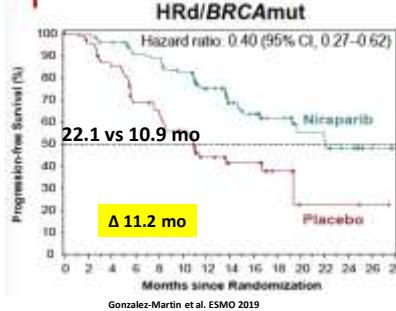
BRCA-Mutation



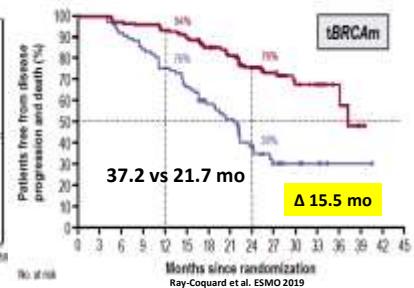
SOLO1



PRIMA



PAOLA



HR 0.33m(0.25-0.43)

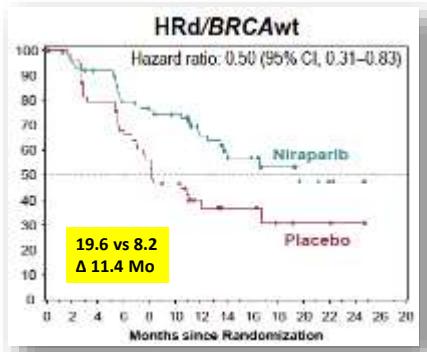
HR 0.40 (0.27-0.62)

HR 0.33 (0.25-0.45)

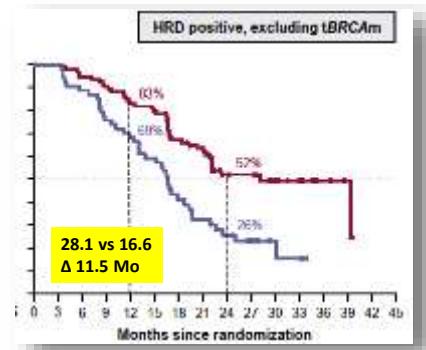
HRD-positiv- BRCAwt



PRIMA



PAOLA



HR 0.50 (0.31-0.83)

HR 0.43 (0.28-0.66)

	PRIMA	PAOLA
Medianes PFS –	HRd/BRCAwt: 19.6/ 8.2 mo	HRd/BRCAwt: 28.1/ 16.6 mo
HR	HRd/BRCAwt: 0.50 (s)	HRd/BRCAwt: 0.43 (s)

„Die Zulassung für Olaparib Filmtabletten in Kombination mit Bevacizumab in dieser Indikation ist auf Patienten mit positivem HRD Status beschränkt und erfolgte auf Basis einer präspezifizierten Subgruppenanalyse.“

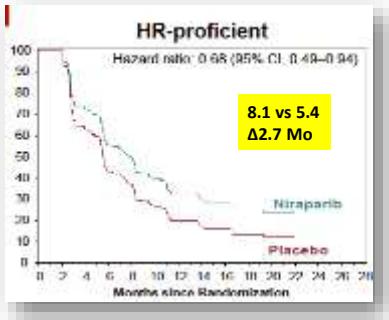
Gonzalez-Martin et al. ESMO 2019

Ray-Coquard et al. ESMO 2019

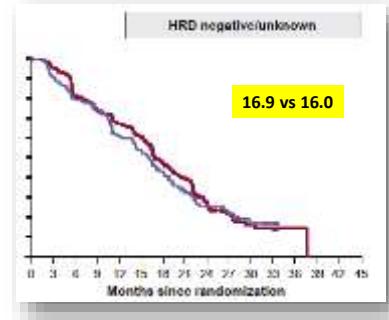
HRD-proficient/negative



PRIMA



PAOLA



HR 0.68 (0.49-0.94)

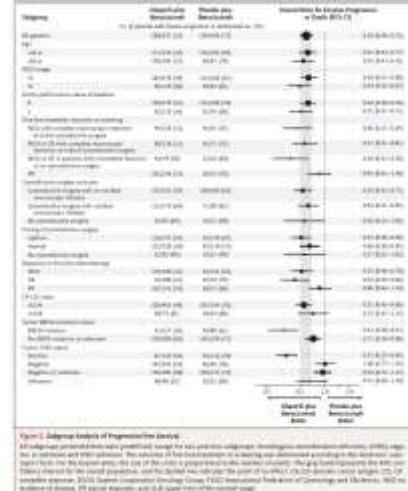
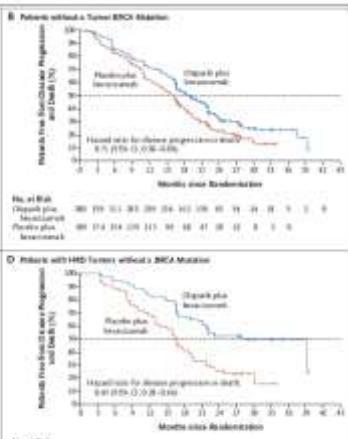
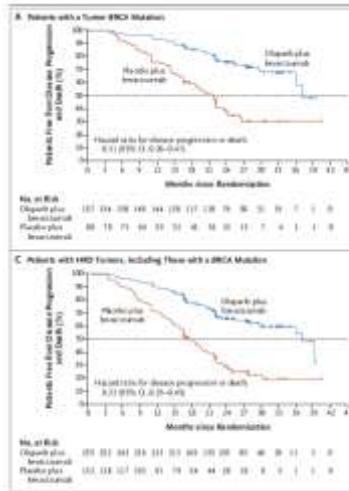
HR 0.92 (0.72-1.17)

	PRIMA	PAOLA
Medians PFS –	HRp: 8.1 / 5.4 mo	HRp: 16.9 / 16.0 mo
HR	HRp: 0.68 (s)	HRp: 0.92 (ns)

Gonzalez-Martin et al. ESMO 2019

Ray-Coquard et al. ESMO 2019

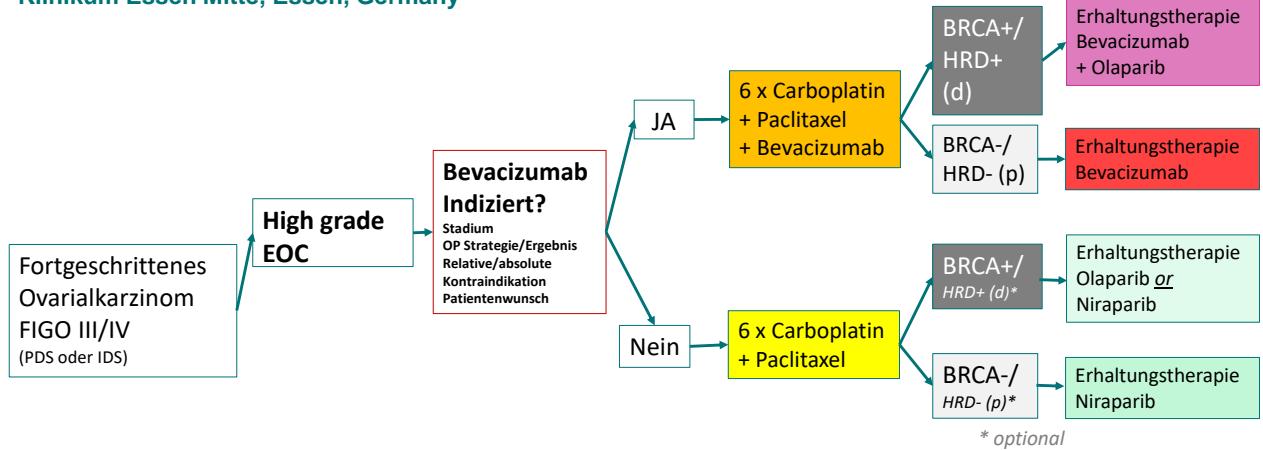
PARPi + Antiangiogenetic Tx?



PAOLA-1, NEJM 381; 25 (2019)

Option for an Algorithm: Maintenance Tx in advanced O

Klinikum Essen Mitte, Essen, Germany



And many more aspects - we did not talk about... 🩺

Newly diagnosed OC

- ▷ Early detection and Screening
- ▷ Genetics, genetic risk factors, prevention strategies
- ▷ NACT – an option for selected patients?
- ▷ Dose dense CTx
- ▷ Endoscopic surgery?
- ▷ Specific needs in comorbid patients?

Recurrent disease

- ▷ Is surgery still an option?
- ▷ What is the best medical strategy?
- ▷ pt again – mono CTx / combined CTx ?
- ▷ PARPi after PAPRi ?



02

Endometrial Cancer

riskscreening
lymphonodektomy
endometrialimmunoonkology
lymphonodektomyfactorstagingrobotic
laparatomyICGlaparoscopy
POLEpelvin MSI-high imaging
sentinel follow-upProfilinggeriatric
MSI-lowcancersurgery
molecularchemotherapy
paraaortal
rehabilitation
assessment

Endometrial cancer (EC)

Germany: Approx. 11.000 new cases / year, approx. 2.500 deaths / year

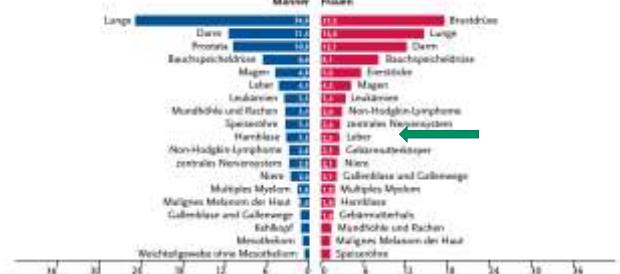
1/49 women will develop EC

Abbildung 3-0-0
Prozentualer Anteil der häufigsten Tumorklassifizierungen an allen Krebsneuerkrankungen in Deutschland 2012
(ohne nicht-melaninische Hautkrebs)



1/200 women will die because of EC

Abbildung 3-0-2
Prozentualer Anteil der häufigsten Tumorklassifizierungen an allen Krebssterbefällen in Deutschland 2012



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Endometrial cancer (EC)

Good prognosis because of early detection



Abbildung 3.17.4a
Absolute Überlebensraten bis 10 Jahre nach Erstdiagnose,
ICD-10 C54 – C55, Deutschland 2011–2012

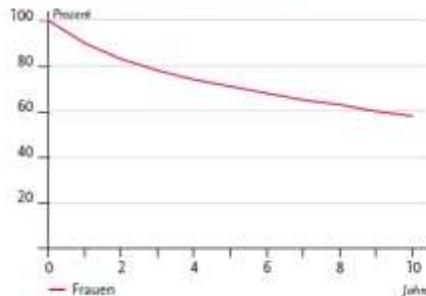
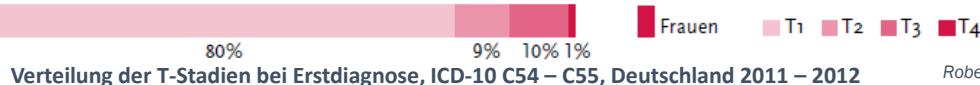
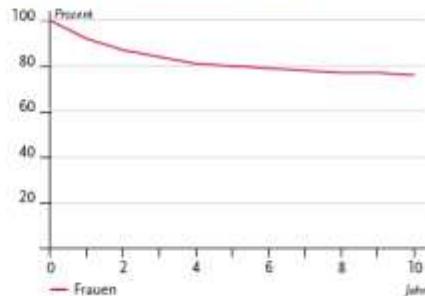


Abbildung 3.17.4b
Relative Überlebensraten bis 10 Jahre nach Erstdiagnose,
ICD-10 C54 – C55, Deutschland 2011–2012



Verteilung der T-Stadien bei Erstdiagnose, ICD-10 C54 – C55, Deutschland 2011 – 2012

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11. Regionale Qualitätskonferenz, Hamburg

Endometrial cancer (EC)

Good prognosis because of early detection



Abbildung 3.17.1a
Absolute Anzahl Erkrankungs- und Sterbefälle,
ICD-10 C54 – C55, Deutschland 1999 – 2010
je 100.000 [Erkrankungsstand]

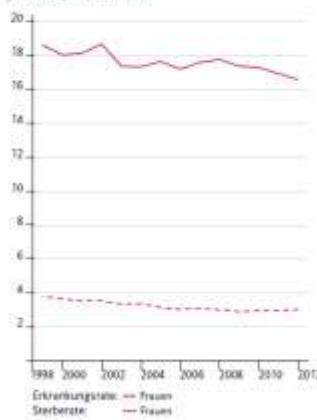
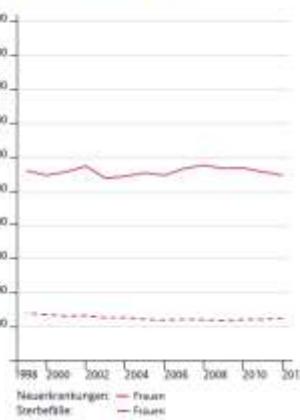


Abbildung 3.17.1b
Absolute Zahl der Neuerkrankungs- und Sterbefälle,
ICD-10 C54 – C55, Deutschland 1999 – 2012



Absolute Zahl der Neuerkrankungs- und Sterbefälle,
ICD-10 C54 – C55, Deutschland 1999 – 2012

But: high incidence – not improved since decades !!!

No improvement for outcome!!!

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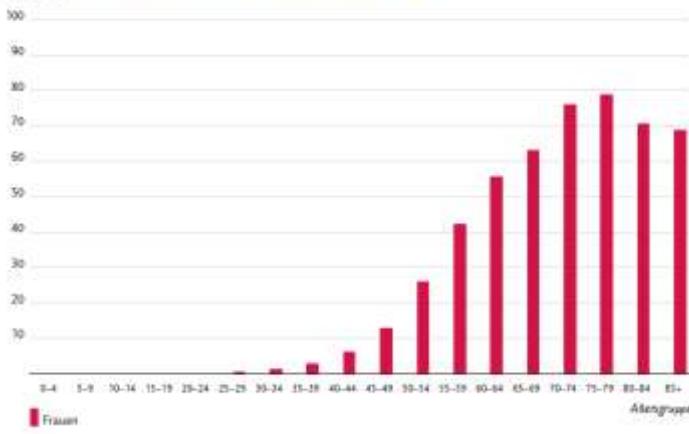
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Endometrial cancer (EC)

A disease of elderly and very old women



Abbildung 3-17-2
Altersspezifische Erkrankungspraten, ICD-10-Cx4-Cx5, Deutschland 2011–2012
je 100.000



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After more than 30 years - New aspects in EC



- ▷ New surgical strategies → Sentinel LNE, robotic surgery
- ▷ Molecular diagnostics → new classification of EC
- ▷ New options for medical treatment → immunooncological Tx and others



Standard of care EC since decades



- **Hysterectomy and BSO, radical hysterectomy only for selected cases, Lymphonodectomy in selected cases**
- Option for adj. Tx in according to stage (RTx, CTx)



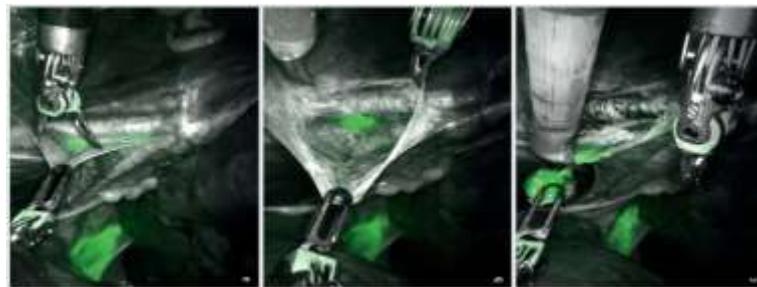
Complications and Adverse Events	Laparoscopy		Laparotomy		P
	No. of Patients	%	No. of Patients	%	
Haemorrhage complications	39	8	100	18	1.00
Wound	14	3	37	7	
Urinary	10	2	45	8	
Arterial	6	1	20	3	
Wound	7	1	21	1	
Urinary	6	1	18	1	
Others	10	2	29	5	
Postoperative adverse events episode n=21					
Wound	10	51	14	67	<.001
Urinary tract infection	5	27	10	45	
Pain	3	14	4	18	
Peritoneal adhesions	2	11	14	61	
Abdominal distension	1	5	11	50	
Arterial thromboembolism	1	5	14	67	
Pathology mistakes	1	5	20	100	
Bowel obstruction	1	5	14	67	
Haemorrhage	1	5	18	86	
Respiratory	1	5	12	55	
Urinary fistula	1	5	12	55	
Primary fistula	1	5	6	27	
Bladder fistula	1	5	6	27	
Urge incontinence	1	5	12	55	
Urinary tract infection	1	5	14	67	

Journal of Clinical Oncology, Volume 30, Issue 33, November 10, 2012

Supplemental Material: Adverse Events Associated With Laparoscopy Versus Laparotomy for Ovarian Carcinoma: Findings From the Southwest Oncology Group Gynecologic Oncology Adjuvant LAP Trial

Walker et al. JCO 2012
Walker et al. JCO 2009

New options for surgical Tx in EC



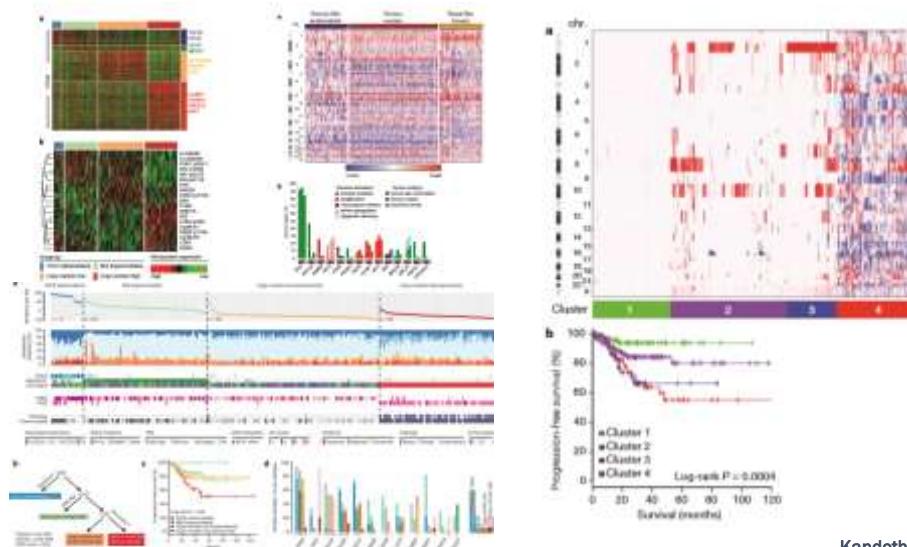
After more than 30 years - New aspects in EC



- New surgical strategies → Sentinel LNE, robotic surgery
- Molecular diagnostics → new classification of EC
- New options for medical treatment → immunooncological Tx and others



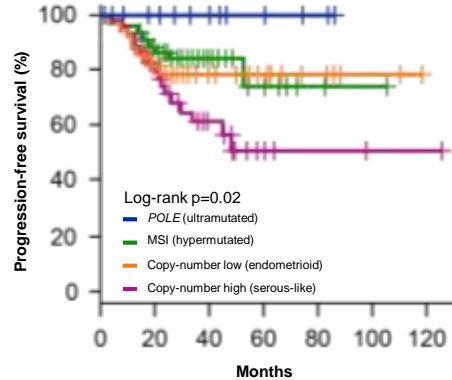
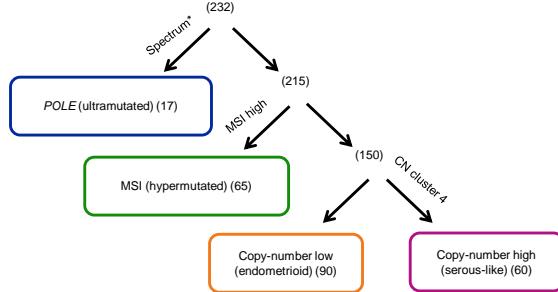
Ready for primetime - The Cancer Genome Atlas Research Network, Endometrial cancer



Kandoth et al., TCGA, Nature, 497: 67-73, 2013

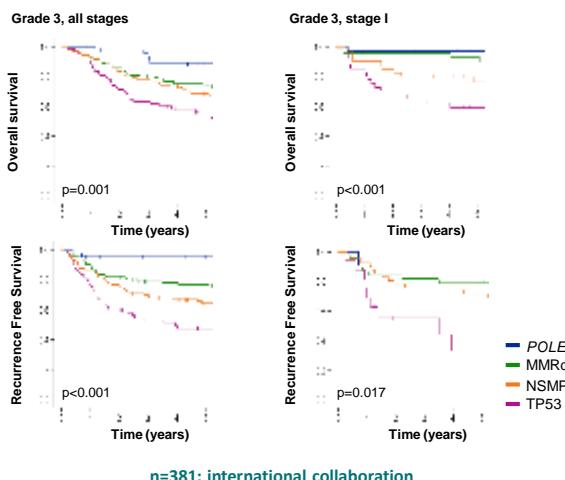
The Cancer Genome Atlas – Molecular subtypes

KANDOTH C ET AL. NATURE. 2013;497:67-73



45

Molecular classification of high grade endometrial cancer



Conclusions

- Grade 3 endometrial cancer is **not a homogeneous 'high risk' cohort**
- TGCA molecular groups have clear prognostic impact in high-grade EC
- Prognostic strength of molecular classification is independent of stage
- POLE almost zero events in grade 3 disease

→ Molecular subtyping should be performed prior to definite surgical therapy

Bosse et al, Am J Surg Pathol 2018



2020 ESGO / ESTRO / ESP

RISK GROUPS /GUIDELINES FOR MANAGEMENT OF PATIENTS WITH ENDOMETRIAL CANCER

Risk group	Molecular classification unknown	Molecular classification known†
Low	<ul style="list-style-type: none"> ► Stage IA endometrioid + low-grade + LVI negative or focal 	<ul style="list-style-type: none"> ► Stage I-II POLEmut endometrial carcinoma, no residual disease ► Stage IA MMRd/NSMP endometrioid carcinoma + low-grade + LVI negative or focal ► Stage IB MMRd/NSMP endometrioid carcinoma + low-grade + LVI negative or focal ► Stage IA MMRd/NSMP endometrioid carcinoma + high-grade + LVI negative or focal ► Stage IA p53abn and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion ► Stage I MMRd/NSMP endometrioid carcinoma + substantial LVI regardless of grade and depth of invasion ► Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVI status ► Stage II MMRd/NSMP endometrioid carcinoma
Intermediate	<ul style="list-style-type: none"> ► Stage IB endometrioid + low-grade + LVI negative or focal ► Stage IA endometrioid + high-grade + LVI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion 	<ul style="list-style-type: none"> ► Stage I-II MMRd/NSMP endometrioid carcinoma + substantial LVI regardless of grade and depth of invasion ► Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVI status ► Stage II MMRd/NSMP endometrioid carcinoma
High-intermediate	<ul style="list-style-type: none"> ► Stage I endometrioid + substantial LVI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade regardless of LVI status ► Stage II 	<ul style="list-style-type: none"> ► Stage III-IV MMRd/NSMP endometrioid carcinoma with no residual disease ► Stage I-IIA p53abn endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I-IIA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease ► Stage II-IVA with residual disease of any molecular type ► Stage IVB of any molecular type
High	<ul style="list-style-type: none"> ► Stage III-IV with no residual disease ► Stage I-IIA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease 	<ul style="list-style-type: none"> ► Stage III-IV MMRd/NSMP endometrioid carcinoma with no residual disease ► Stage I-IIA p53abn endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I-IIA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease ► Stage II-IVA with residual disease of any molecular type ► Stage IVB of any molecular type
Advanced metastatic	<ul style="list-style-type: none"> ► Stage III-IV with residual disease ► Stage IVB 	<ul style="list-style-type: none"> ► Stage III-IV with residual disease of any molecular type ► Stage IVB of any molecular type

Concin N, et al. *Int J Gynecol Cancer* 2020;0:12–39. doi:10.1136/ijgc-2020-002230



Molecular subtype stratified response to adjuvant therapy (learning from PORTEC-3): Canadian Cohorts (SGO 22) & Future directions

MMRd EC

No benefit from the addition of adjuvant chemotherapy to radiation in ESMO high risk and ESMO high, advanced and metastatic risk groups combined

NO CHEMO!!!

p53abn EC

Adjuvant chemotherapy resulted in a statistically significant improvement in OS and OS in ESMO high risk and ESMO high, advanced and metastatic risk groups combined compared to radiation only

45% UNDER treated
NEED Chemo
Some PARP?

NSMP EC

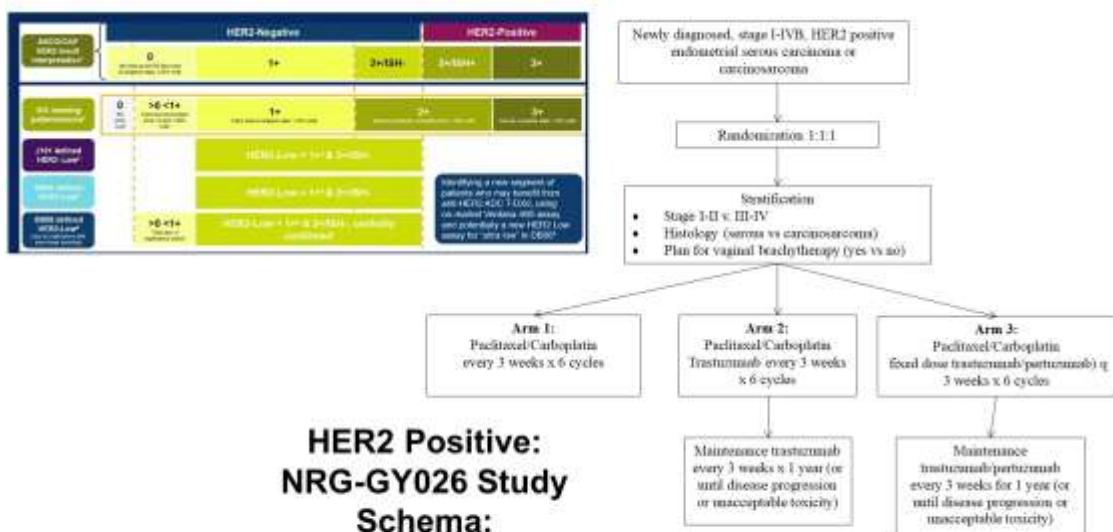
Patients who had radiation only appeared to have improved outcomes in ESMO high risk and ESMO high, advanced and metastatic risk groups combined compared to chemoradiation

RT better?
AI / progestin?

POLEmut EC

Small number of disease related events in this subtype, even in ESMO high risk group
Most deaths were non-cancer related

44% POLEmut EC were possibly overtreated



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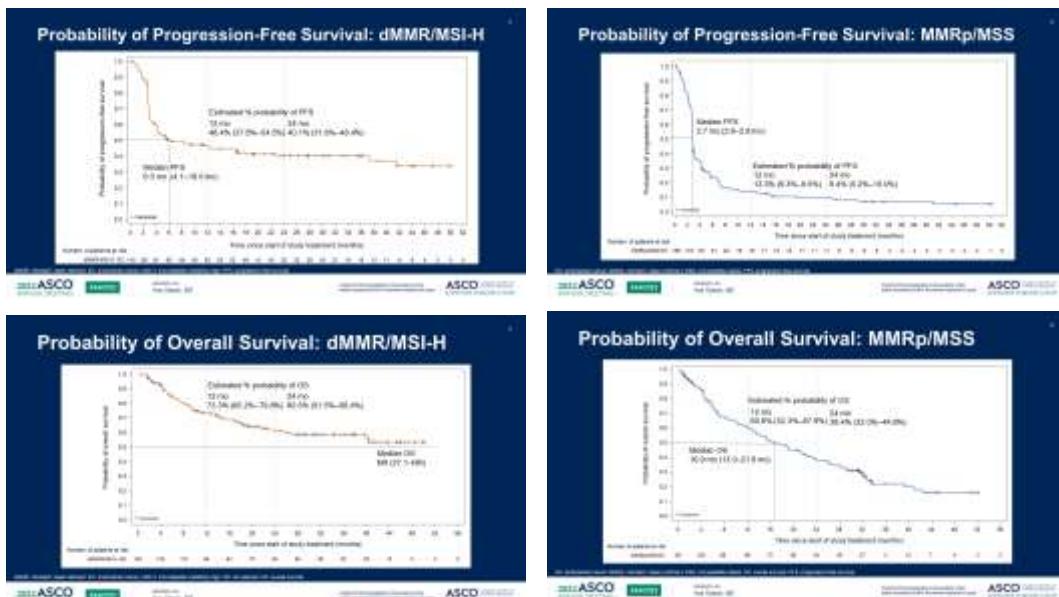
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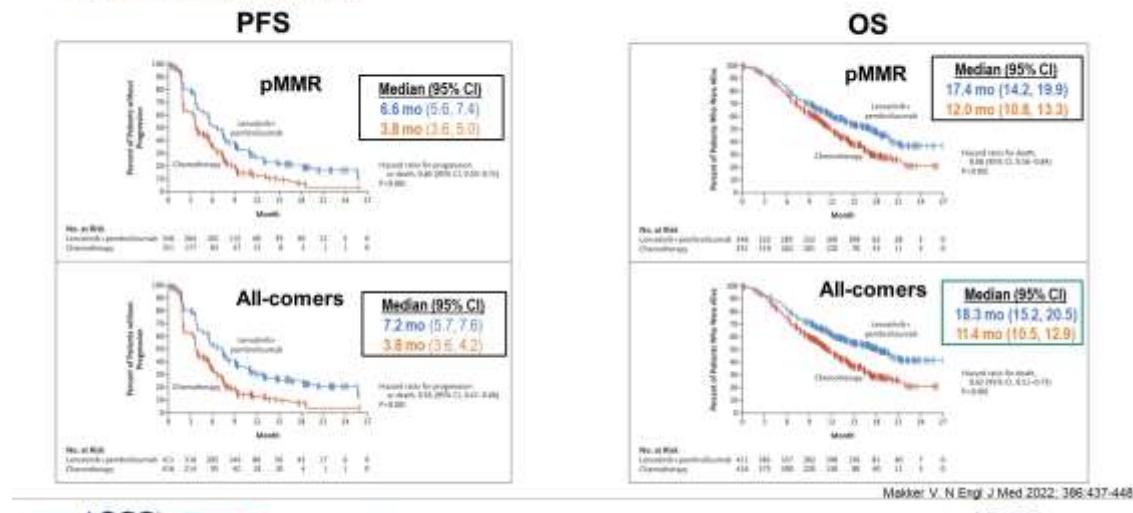
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Dostarlimab in recurrent EC – GARNET Trial



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Study 309/Keynote-775: Lenvatinib and Pembrolizumab vs. Physician's Choice Chemotherapy



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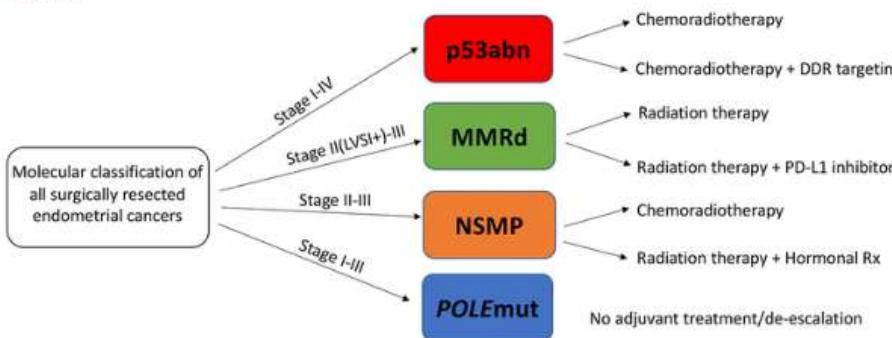
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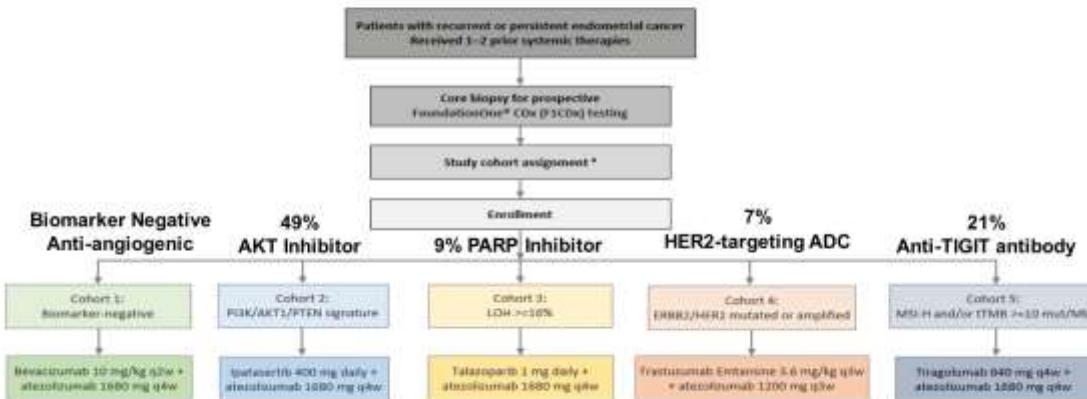
TransPORTEC RAINBO Umbrella Trial



DDR- DNA damage response
PD-L1 inhibitor- immune checkpoint blockade therapy

A Phase IB/II Multi-Cohort Study of Targeted Agents with Atezolizumab for Patients with Recurrent or Persistent Endometrial Cancer

Alliance Foundation Trial EndoMAP NCT04486352

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Randomized Phase III Study of Maintenance Selinexor vs Placebo in Endometrial Cancer (ENGOT-EN5/GOG-3055/SIENDO): Impact of Subgroup Analysis and Molecular Classification

Vicky Makker¹, J Alejandro Pérez-Fidalgo², Alice Bergamini³, Daniel Spitz⁴, Toon Van Gorp⁵, Jalid Sehouli⁶, Jaroslav Klat⁷, Tamar Perr⁸, Amit Oza⁹, Estrid Heggdal¹⁰, Jason Konner¹¹, Eva M Guerra-Alia¹², Francesco Raspagliesi¹³, Stéphanie Henry¹⁴, Bradley J. Monk¹⁵, Jerónimo Martínez¹⁶, Brian Sklarowitz¹⁷, Sharon Shacham¹⁸, Marisol Raza Mirza¹⁹, Ignacio Vergote²⁰

¹Memorial Sloan Kettering Cancer Center, ²Hospital Clínico Universitario de Valencia, Valencia and GEICO, ³MITO and Department of Obstetrics and Gynecology, San Raffaele Scientific Institute, ⁴Hôpital Cancer Specialists, Sarah Cannon Research Institute, ⁵BOOG and Leuven Cancer Institute University Hospitals Leuven, Leuven, Belgium, ⁶NOCOGG and Department of Gynecology, European Competence Center for Ovarian Cancer, ⁷Charité Comprehensive Cancer Center, Charité-Berlin University of Medicine, ⁸CEOGOG and University Hospital Ostrava, ⁹GIGO and Sheba Medical Center, ¹⁰Princess Margaret Cancer Centre, University Health Network, ¹¹Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark, ¹²Memorial Sloan Kettering, Monmouth, ¹³Hospital Universitario Ramón y Cajal, Madrid and GEICO, ¹⁴MITO and Fondazione IRCCS Istituto Nazionale del Tumore- Milano, S.C. Ginecologia Oncologica, ¹⁵BOOG and Università Cattolica de L'Umanità, CHU UCL, Namur, Site Ste Elisabeth, Service d'onco-hématologie (SDRMN), Place Louise Godot 15 B-5000 Namur, ¹⁶GOG Foundation, University of Arizona, Creighton University, Phoenix, AZ USA, ¹⁷Hospital Virgen de la Arrixaca, Murcia and GEICO, ¹⁸Gynecologic Oncology, Mount Sinai Medical Center, ¹⁹Obstetrics and Gynecology, Florida International University, ²⁰Karyopharm Therapeutics, ²¹Hospitsyssel, Copenhagen, University Hospital, Denmark

Vicky Makker, M.D.

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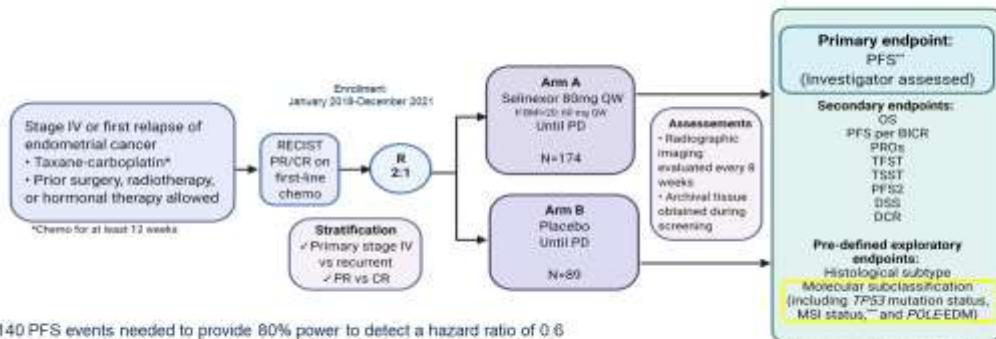
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Trial Design ENGO-EN5/GOG-3055/SIENDO



Stage IV or first relapse of endometrial cancer
endometrioid, serous, undifferentiated, or carcinosarcoma
(NCT03555422)



**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

BICR, blind independent central reviewer; BIM, body mass index; CR, complete response; DCR, disease control rate; DSB, disease-specific survival; EDM, exon deletion mutation; IHC, immunohistochemistry; MSI, microsatellite instability; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes; QW, once weekly; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TPST, time to first subsequent therapy; TSST, time to second subsequent treatment.

Previously presented at ESMO Virtual Plenary 2022 and GGO 2022

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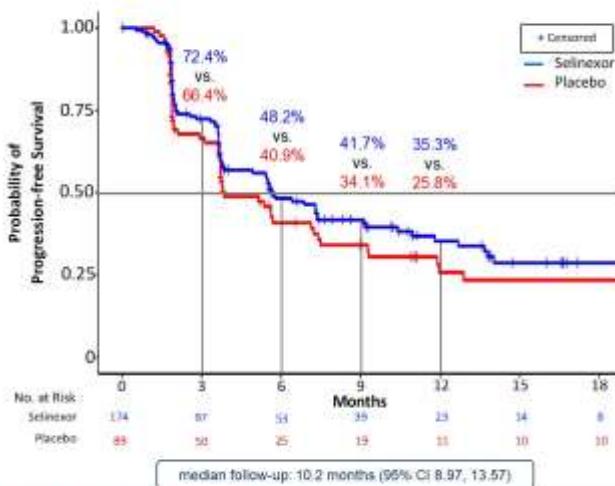
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Primary Endpoint: PFS in ITT Population



Median PFS

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGO statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

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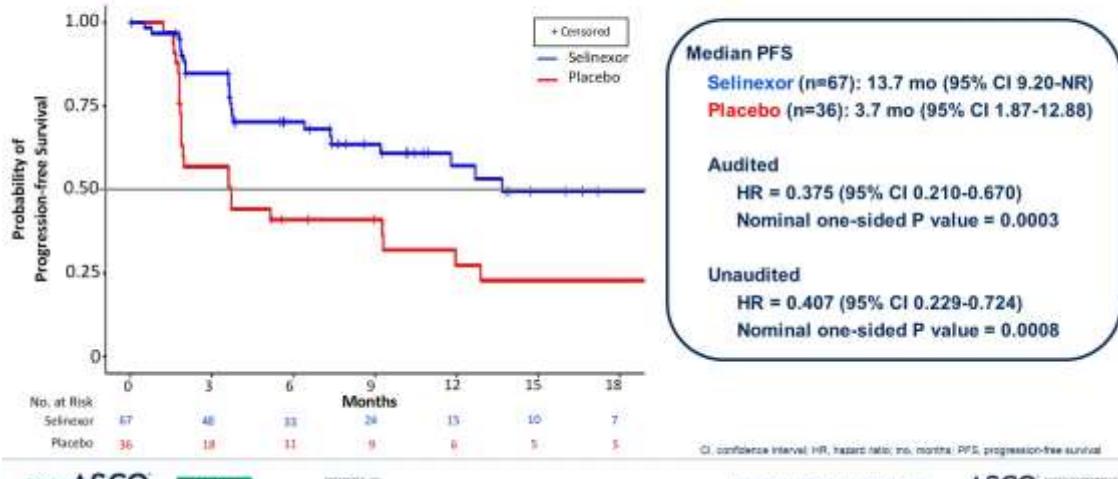


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Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC



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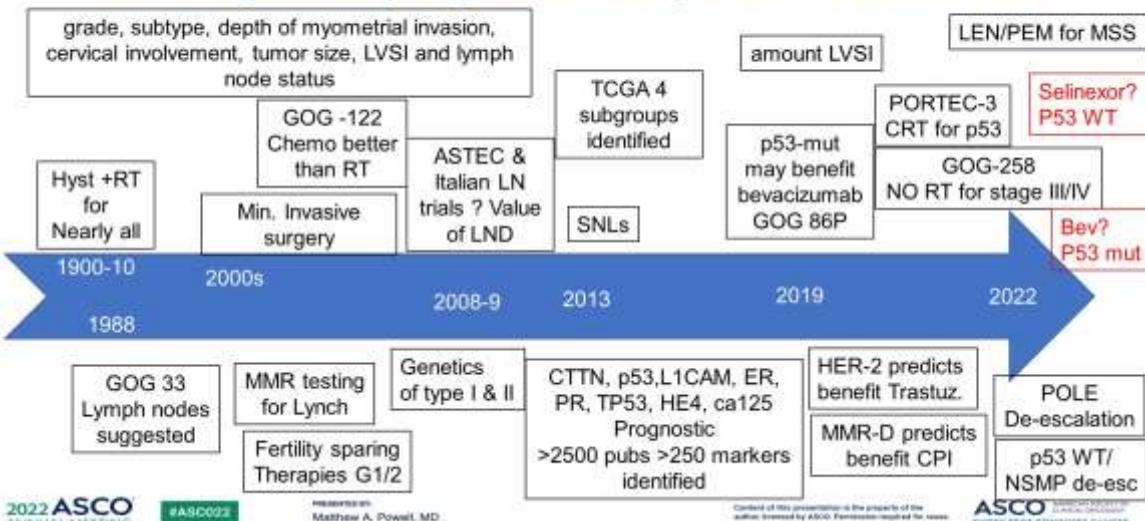
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History of management of Endometrial Cancer: Journey from prognostic to predictive markers



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*"Before I came here I was confused about this subject.
Having listened to your lecture I am still confused. But
on a higher level."*



Enrico Fermi
1901 - 1954



Prof. Dr. med. Gerhard Gebauer, MHM, MBA

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