The Current Landscape of Gynecological Cancers

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Conflict of Interest Disclosure

- Participates in Advisory Boards of:

  Debiopharm, Immunomedics, Innate Pharma, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, WntResearch

- Lecturer fee from:

  Merck-Serono, BMS, MSD

Outline of Presentation

- Cervical cancer
  Management issues in early and advanced disease
  Targeted therapies and immunotherapy in recurrent CC
- Ovarian cancer
  The importance of complete CRS during initial surgery
  Milestones and controversies in systemic therapies
  PARP inhibitors a breakthrough
- Endometrial cancer
  Adjuvant therapy in high-risk endometrial cancer
  Targeted therapies and immunotherapy in recurrent EC

Management of Invasive Cervical Cancer

- Early stages (I – IIA): surgery (open or MIS) or radiotherapy
  postop CCRT in case of LN+

- Bulky stage I (IB2)
  Locally advanced (II-IVA)
  Any stage (except IVB) with LN+

  → Concurrent CRT standard
  → NACT → surgery*
  → CCRT → ACT*

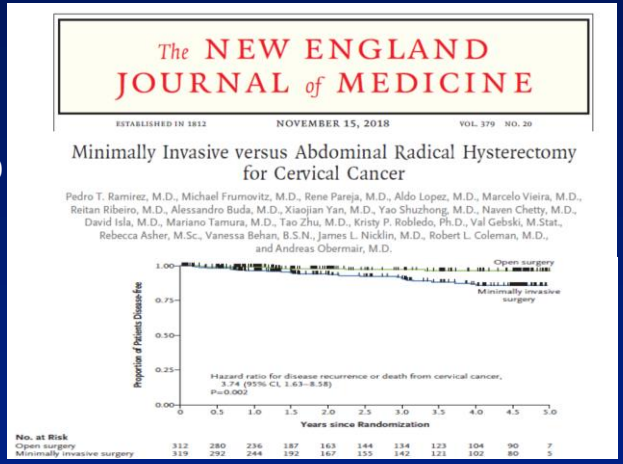
- Recurrent and/or
  metastatic cervical cancer

  → Surgery, RT, CT, TT, IT or BSC alone

*Movva S, Gold M, Grigsby P, Verschraegen C, ASCO 2009; Hacker NF, Jackson M, Vermorken JB. Cervical Cancer in Gynecologic Oncology (Berek J & Hacker NF, eds), 7th edition (2019, in press) *investigational*
CT=chemotherapy, TT=targeted therapy, IT=immunotherapy, NACT=neoadjuvant chemotherapy, ACT adjuvant chemother.

MIS in Early-Stage Cervical Cancer

- LACC prospective multi-institutional trial[1]
  Stages 1A1 +LVSI, 1A2 or IB1:MIS vs open (2008)
  Primary endpoint: DFS at 4.5 yrs, noninf. margin -7.2%
  740 patients planned, halted at 631 (2017)
  DFS 3-yr rate 91.2% vs 97.1% (MIS vs open)
  OS 3-yr rate 93.8% vs 99.0% (MIS vs open)
  Several limitations and criticisms


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

- Retrospective epidemiologic study[2]
  Stages 1A2 or 1B1: MIS vs open
  National Cancer Database: 2461 patients underwent RH (2010-2013):49.8% MIS
  79.8% of whom had robot assisted laparoscopy
  Median follow-up was 45 months
  Mortality at 4 yr 9.1% (MIS) vs 5.3% (open,p=0.002)

[1]Ramirez PT et al. N Engl J Med 2018; Melamed A et al. N Engl J Med 2018

CCRT in Advanced-Stage Cervical Cancer

Standard therapy: cisplatin 40 mg/m^2 x6 during RT

Ongoing trials aiming for improvement

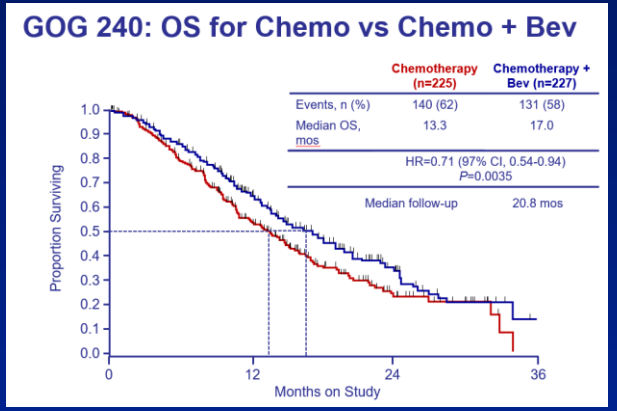
TACO trial	CCRT (40 mg/m^2 x6) vs CCRT (75 mg/m^2 x3)
Interlace trial	CCRT (40 mg/m^2 x5) vs NACT→CCRT
Outback trial	CCRT (40 mg/m^2 x5) vs CCRT→ACT
AIM2CERV trial	CCRT (40 mg/m^2 x4) →placebo IV up to 1 yr
	CCRT (40 mg/m^2 x4) →AXAL[&] (1x10^9 CFU) 1 yr

*[1]Morris et al, NEJM 1999; 340: 1137-43; [2]Rose et al, NEJM 1999; 340: 1144-53; [3]Keys et al, NEJM 1999; 340: 1154-61
[4]Whitney et al, JCO 1999; 17: 1339-48; [5]Peters et al, JCO 2000; 18; 1606-13
[&]ADXS11-001 (live attenuated *Listeria Monocytogenes* bioengineered molecule secreting a HPV-16-E7 fusion protein)

Management of R/M Cervical Cancer

- No gold standard for R/M disease: cisplatin alone and cisplatin plus paclitaxel ± bevacizumab are good options. Patients preferably should be treated in trials

- The addition of bevacizumab to cisplatin plus paclitaxel leads to a survival advantage of 3.7 mo at the cost of 3-8% more serious adverse events[1]



- Pazopanib, brivanib and sunitinib (RR 0-9%; mPFS ≤4.1 mo)*
  Gefitinib, erlotinib, lapatinib, cetuximab (RR 0-5%; mPFS ≤3.9 mo)*
  Temsirolimus (RR 3%, PFS 3.5 mo)*

[1]Tiwari KS et al. N Engl J Med 2014
**Hacker NF, Jackson M, Vermorken JB. Cervical Cancer: in Gynecologic Oncology (Berek J & Hacker NF, eds), 7th Edition, 2019*

Immunotherapy for Cervical Cancer

Study	Population	Agent	Results
Single agent ICI			
KEYNOTE 028[1]	PD-L1$^+$, recurrent	Pembro	ORR, 17.0%; DOR, 6 mo
KEYNOTE 158[2]	PD-L1$^+$, recurrent	Pembro	ORR, 14.3%, DOR, >11.7mo
Lheureux et al[3]	Recurrent	Ipilimumab	ORR, 2.9%
CheckMate 358[4]	Recurrent	Nivolumab	ORR, 5.0%
NRG-GY002[5]	Recurrent	Nivolumab	ORR, 4.0%
Adoptive T-cell therapy			
Stevanovic et al[6]	Recurrent	HPV TILS	ORR, 28.0% (5/18), 2CR
Vaccine therapy			
Huh et al[7]	Recurrent	Axalimogene filolisbac	12-month OS, 38.5%

[1]Frenel et al, JCO 2017; [2]Chung et al, JCO 2018; [3]Lheureux et al, JAMA Oncol 2018; [4]Hollebecque et al, JCO 2017; [5]Santin et al JCO 2018; [6]Stevanovic et al Science 2017; [7]Huh et al, JCO 2016

Modified from Levison et al. 2019 ASCO Educational Book

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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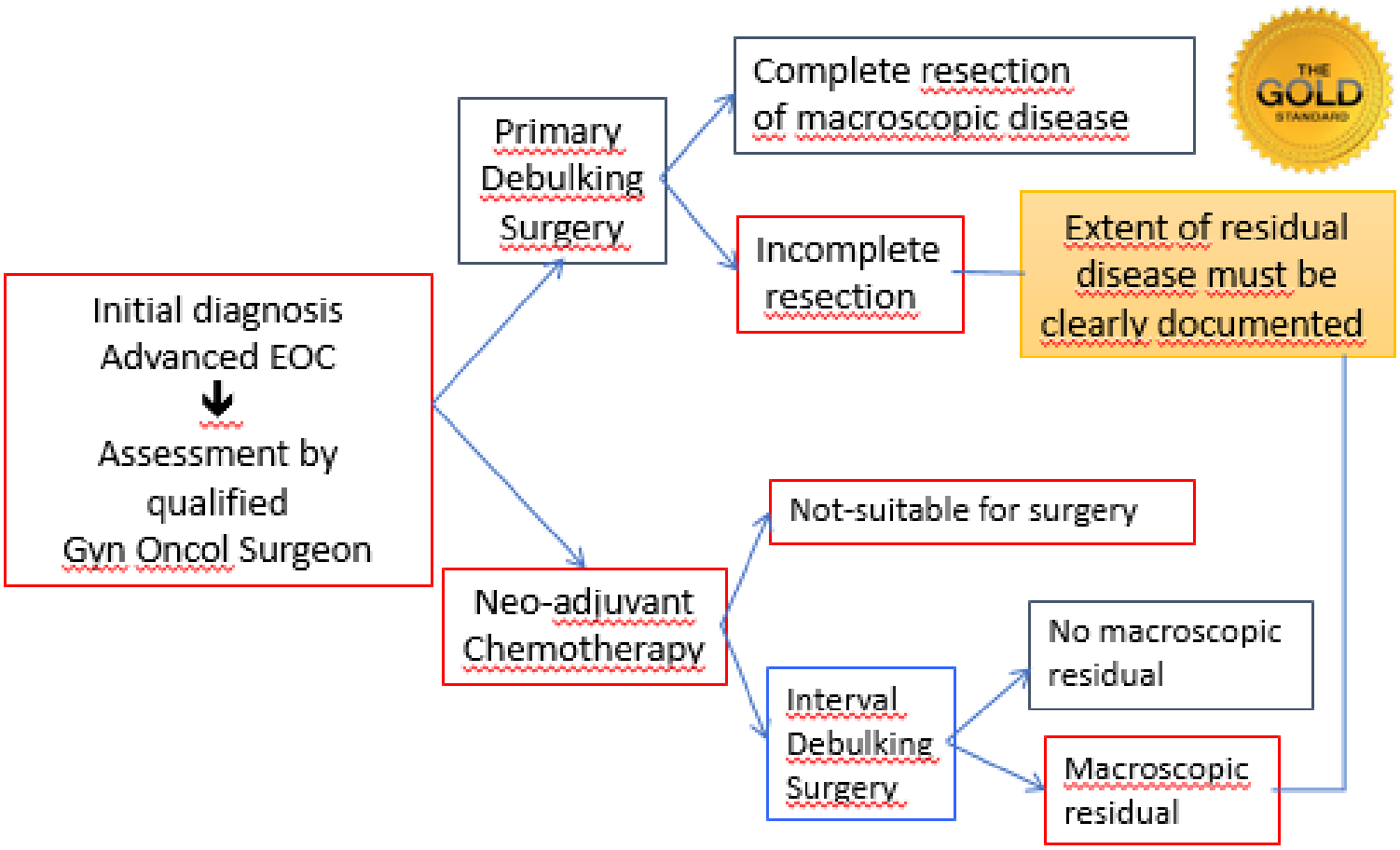
Published online 2 May 2019

SPECIAL ARTICLE

ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†

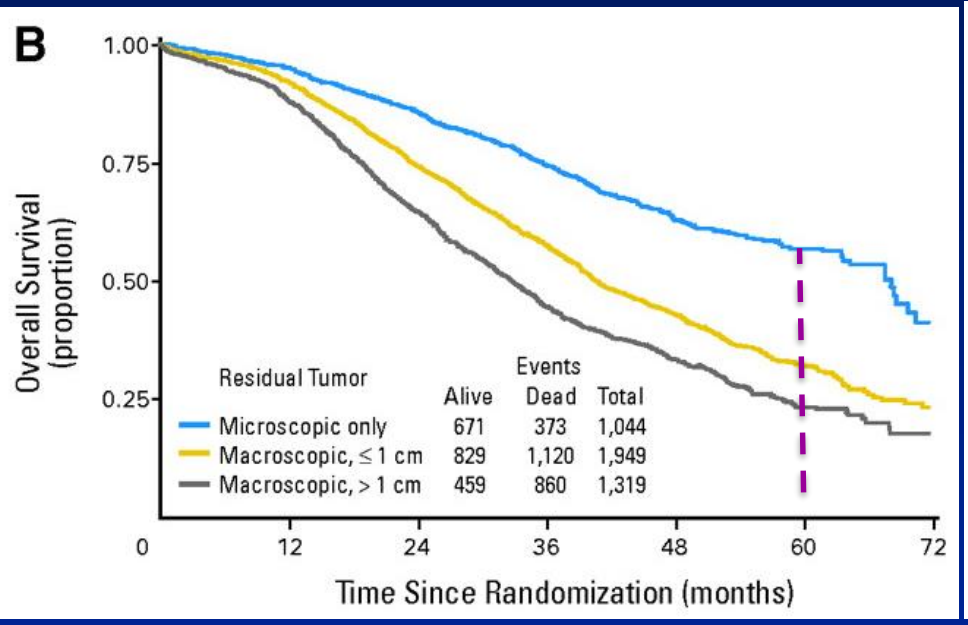
N. Colombo[1*], C. Sessa[2], A. du Bois[3], J. Ledermann[4], W. G. McCluggage[5], I. McNeish[6], P. Morice[7], S. Pignata[8], I. Ray-Coquard[9], I. Vergote[10,11], T. Baert[3], I. Belaroussi[7], A. Dashora[12], S. Olbrecht[10,11], F. Planchamp[13] & D. Querleu[14*], on behalf of the ESMO–ESGO Ovarian Cancer Consensus Conference Working Group[‡]

Management of Advanced Epithelial Ovarian Cancer

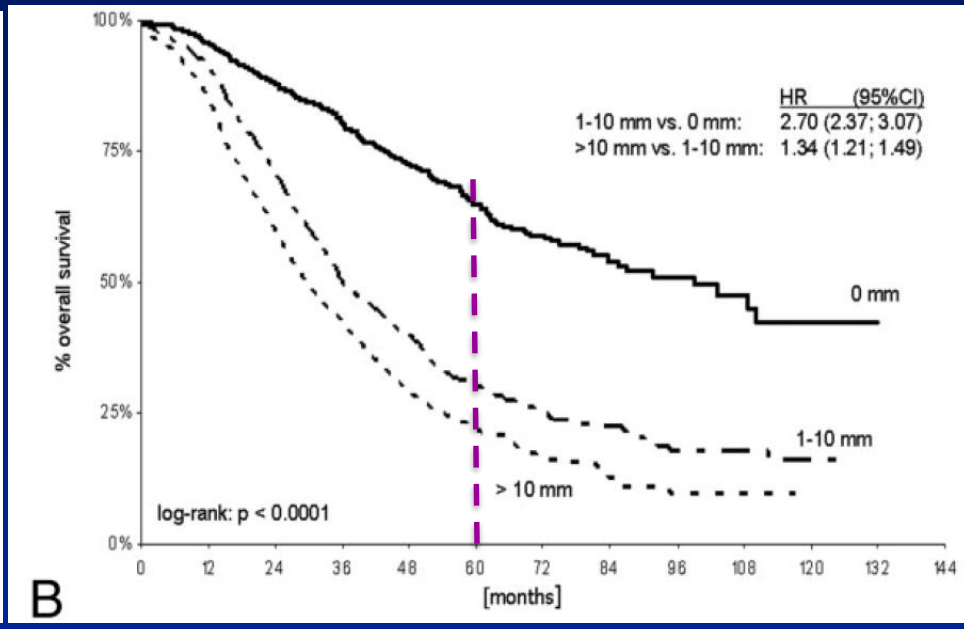


5th Ovarian Cancer Consensus Conference, Tokyo, Japan, November 2015
NCCN Guidelines Insight. Ovarian Cancer, version 1.2019, J Natl Compr Canc Netw 2019; 17: 896-909
(Courtesy of Antonio González Martin)

Optimal Cytoreduction after PDS the Most Important Prognostic Factor in ADOVCA

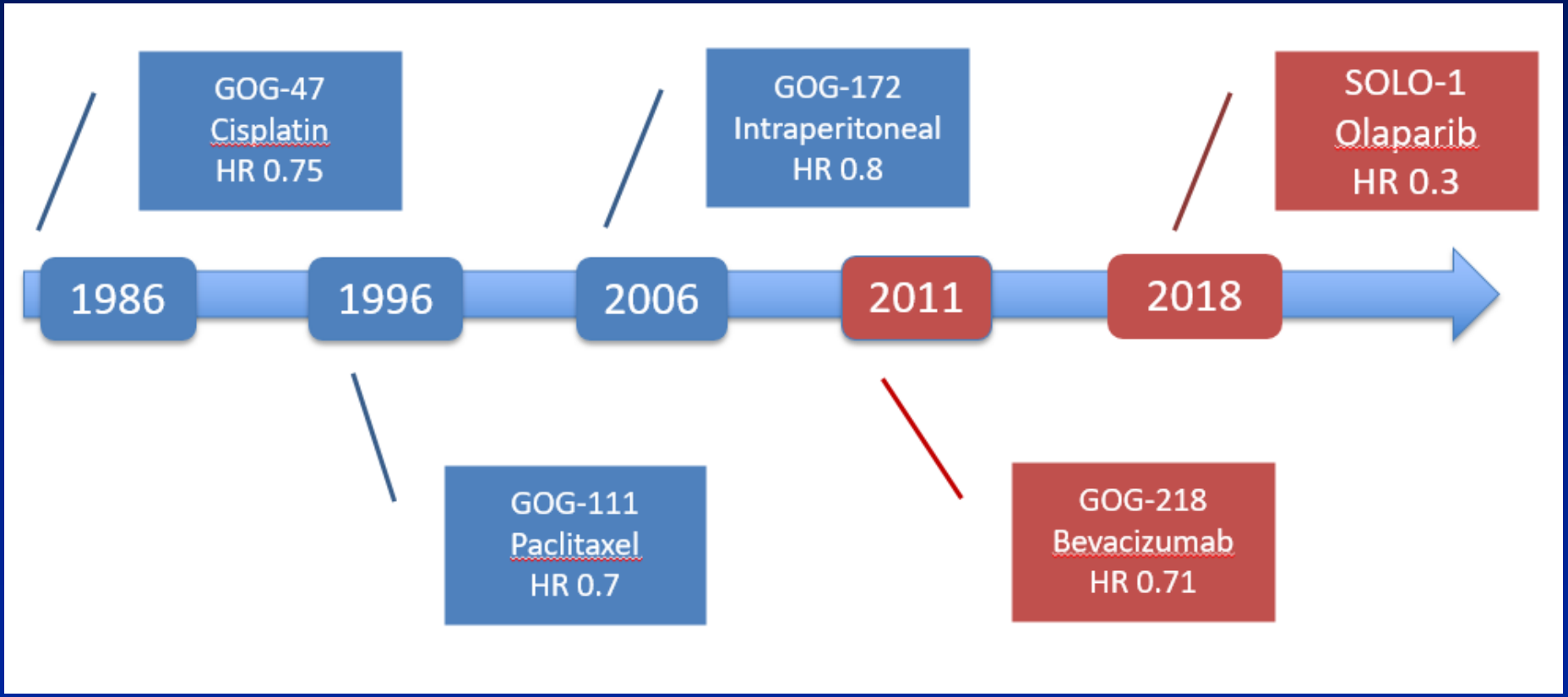


Bookman, M. A. et al. J Clin Oncol 2009



Du Bois et al. Cancer 2009

Milestones in PFS for Epithelial Ovarian Cancer in Front-line



Courtesy of Antonio González Martin

Systemic Therapy for Ovarian Cancer 2019
NCCN Guidelines: OC, version 1.2019

- Three-weekly carboplatin/paclitaxel (TC) standard chemotherapy for first-line therapy in ADOVCA (1998-2019)

- Acceptable alternative schedules a/o route of administration
  - Weekly IV paclitaxel plus 3-weekly IV carboplatin
  - Bevacizumab-containing regimens per ICON-7 or GOG-218
  - Intraperitoneal platinum-based chemotherapy (IPCT) in stage III patients after primary surgery with <1 cm residual disease*
  - HIPEC can be considered during IDS in stage III after NACT*

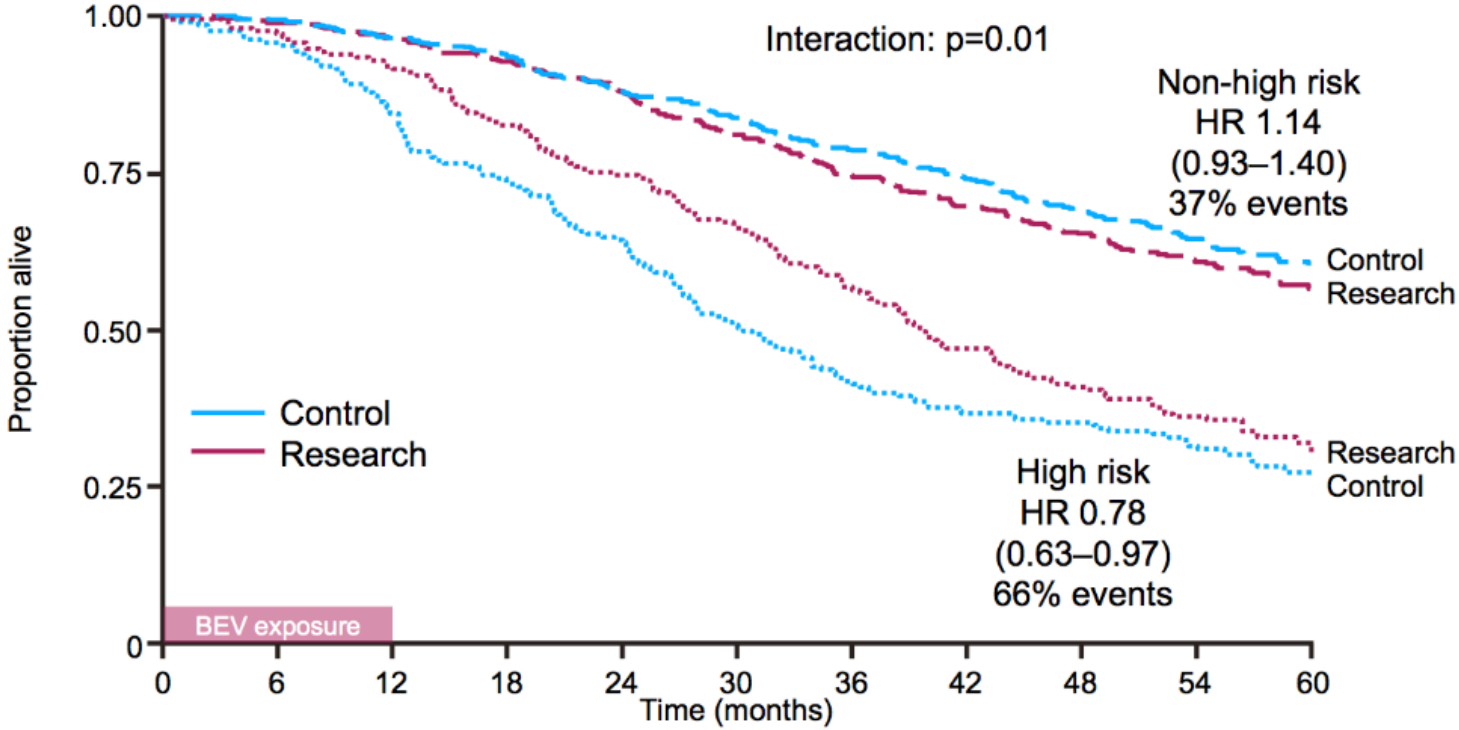
Fujiwara. Valencia meeting, 22.02.2019
**Not endorsed in the ESMO-ESGO conference (Milan 2018)*

ICON 7 Trial

Final Outcome Results

Survival of ICON 7 by Risk Group

(High Risk: Residual disease >1 cm/ Stage IV)



Oza et al Lancet Oncol 2015

Trials of Anti-Angiogenic Therapy in ROC

Platinum-refractory/resistant

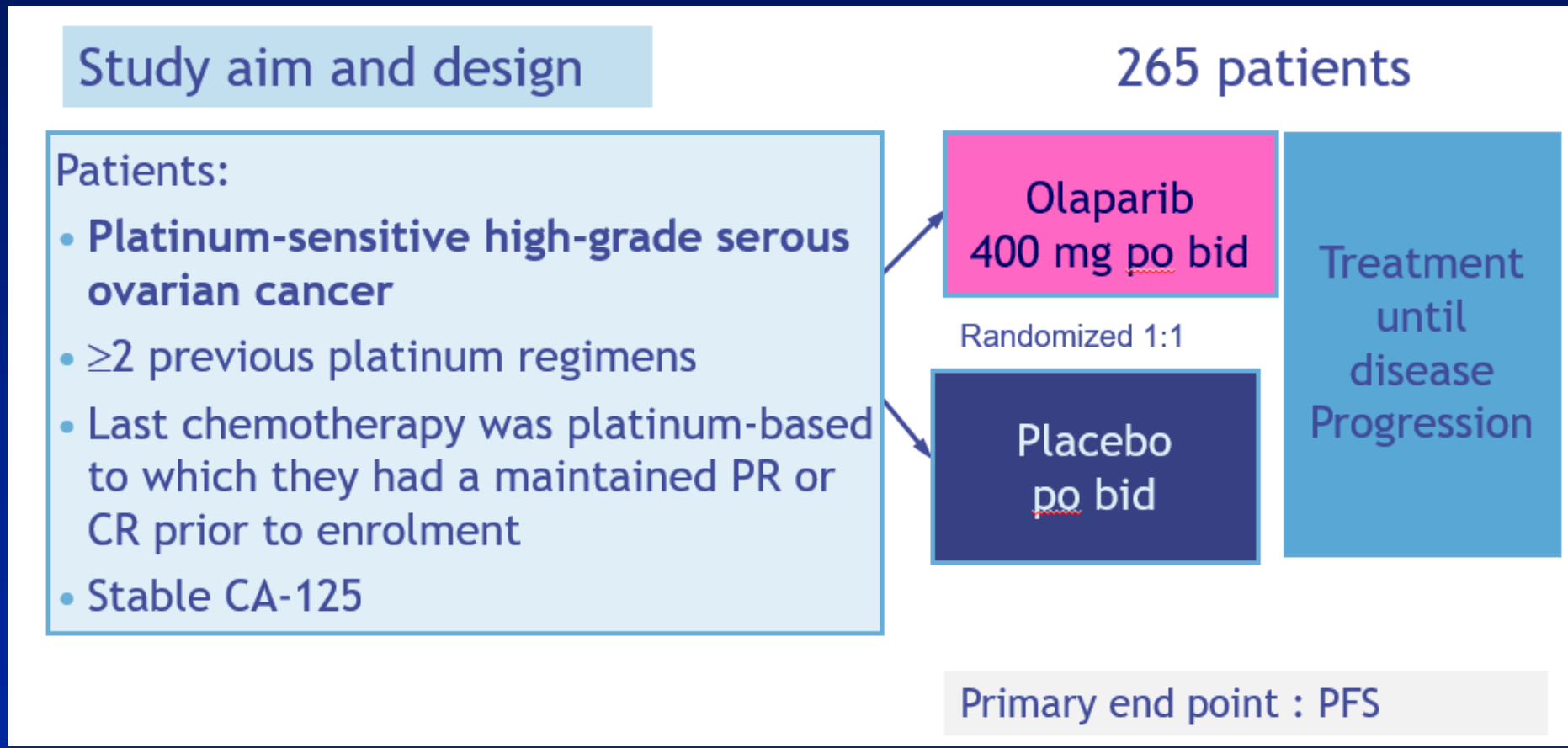
- **AURELIA trial***
  - Single agent non-Pt vs non-Pt+bev→PFS↑ with combo
- **MITO-11 trial****
  - Wkly paclitaxel vs same plus pazopanib→ PFS↑ with combo

Platinum-sensitive disease

- **OCEANS trial [+]**
  - GCx6 vs GC/bevx6 → bevacizumab maintenance→PFS↑
- **ICON 6 trial[++]**
  - Pt-based CTx6 vs Pt-based CTx6 plus cediranib vs Pt-based CTx6+cediranib→cediranib maintenance→PFS↑.

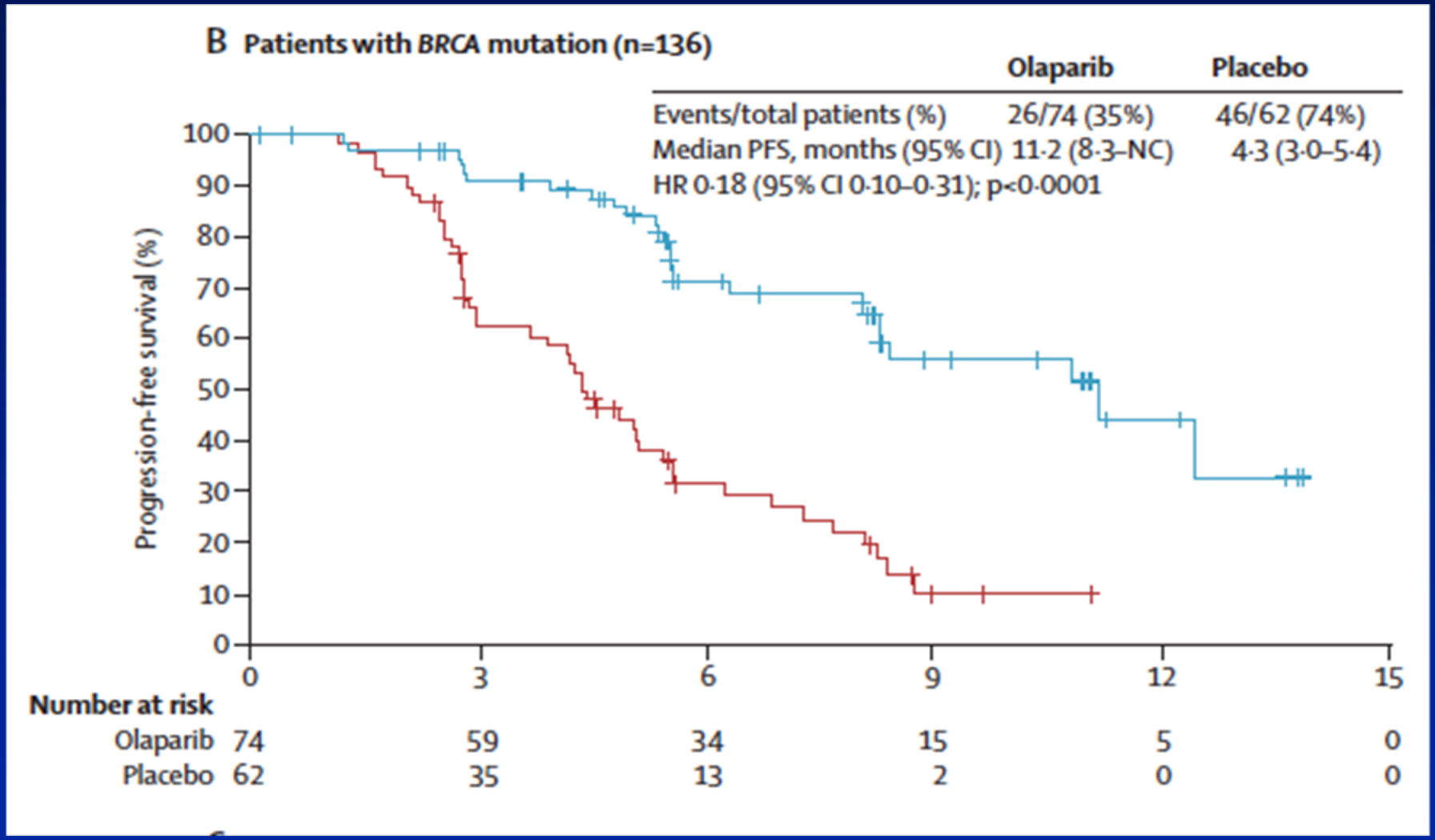
** JCO 2014; **Lancet Oncol 2015; [+]JCO 2012; [++]ECCO 2013; ASCO 2017*

Randomized Trial of Maintenance Olaparib in Platinum-sensitive High-Grade Serous Relapsed Ovarian Cancer



Ledermann J, et al. N Engl J Med 2012;366:1382–92

PFS in BRCA Mutated Patients



Ledermann et al. Lancet Oncol. 2014;15(8):852-861

Confirmatory Studies in Platinum-Sensitive ROC with Germline BRCA Mutation

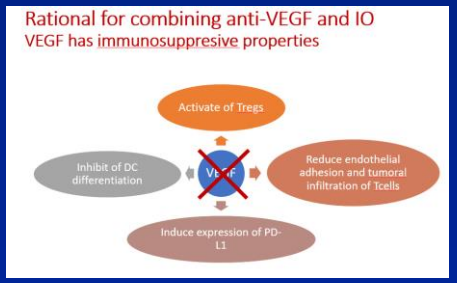
Study	Drug	formul.	Pts	Median PFS (HR)
• Ledermann	Olaparib	caps	136	11.2 vs 4.3 (0.18)
• Pujade	Olaparib	tabl	295	19.1 vs 5.5 (0.30)
• Coleman	Rucaparib	tabl	196	16.6 vs 5.4 (0.23)
• Mirza	Niraparib	caps	203	21.0 vs 5.5 (0.27)

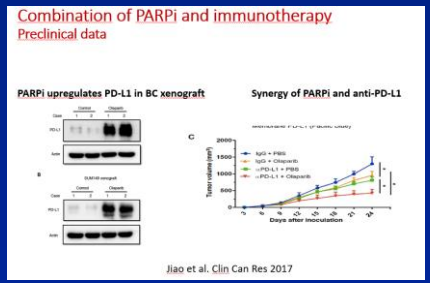
Ledermann Lancet Oncol 2014; Pujade Lancet Oncol 2017; Coleman Lancet Oncol 2017; Mirza NEJM 2016

Immunotherapy in Epithelial Ovarian cancer*

- Single agent CPI
  Response rates to CPIs are low, ranging from 6% to 22%
  Some impressive prolonged responses

- Multimodality immunotherapy (IT) strategies:
  - IT with chemotherapy
  - IT with other IT agents
  - IT with antiangiogenic therapy
  - IT with PARP inhibitors
  - IT + PARPi + antiangiogenic therapy





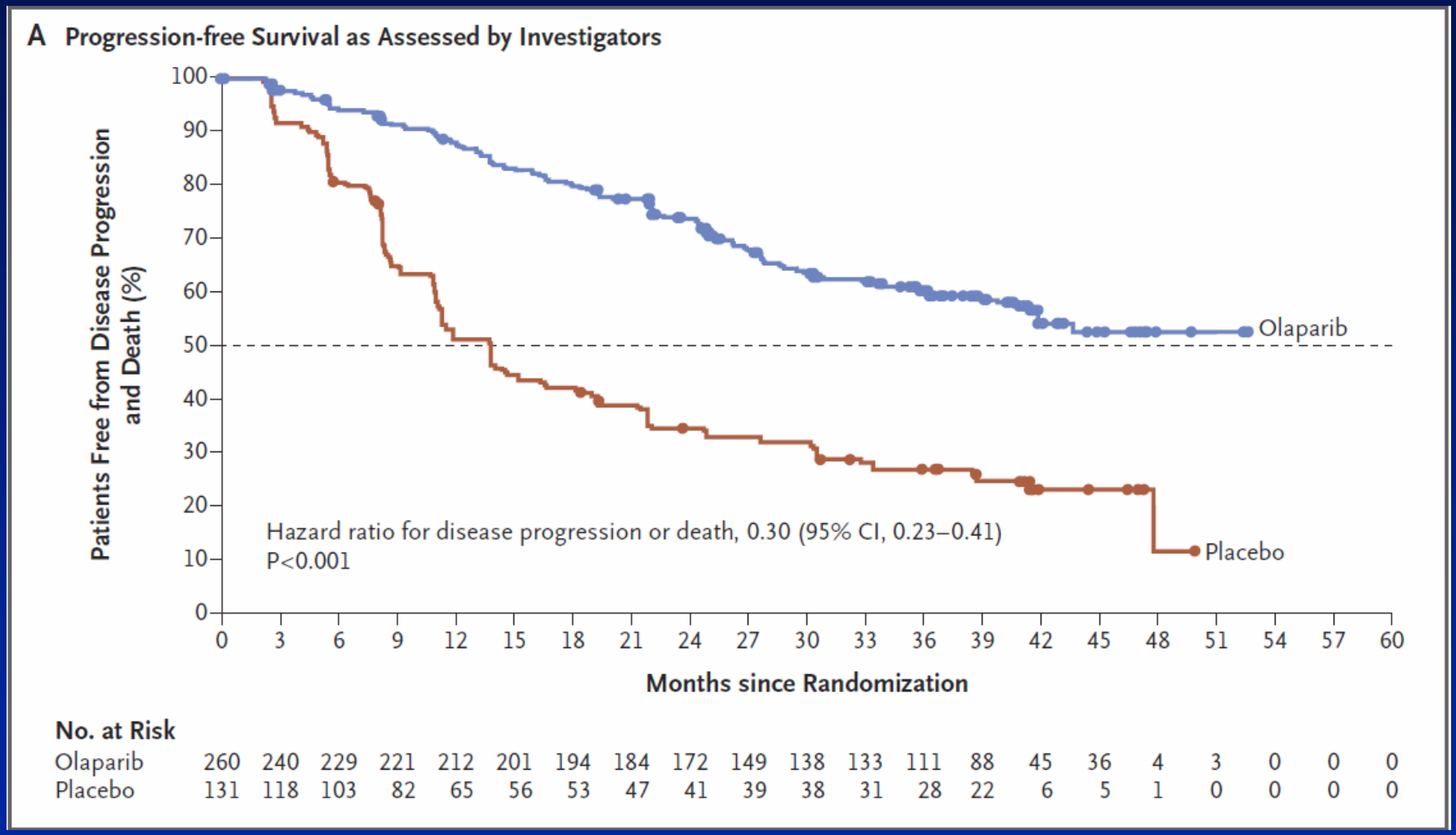
Levinson et al. 2019 ASCO Eductional Book

PARP-inhibitors Moving to First-Line*

Study	PARPi	Type of study
GOG3005 (Abbvie)	veliparib	TC+placebo→placebo vs TC+veliparib →placebo vs TC+veliparib→veliparib
PAOLA-1 (GINECO)	olaparib	TC+Bev→Bev+olaparib vs TC+Bev→Bev+ placebo
SOLO-1 (AZ)	olaparib	Olaparib vs placebo maintenance in BRCAm OC after Pt-based CT
PRIMA (tesaro)	niraparib	Niraparib vs placebo maintenance in BRCAm OC after Pt-based CT

Moore, N Engl J Med, 2018; 379: 2495-2505
Ray-Coquard, ESMO 2019

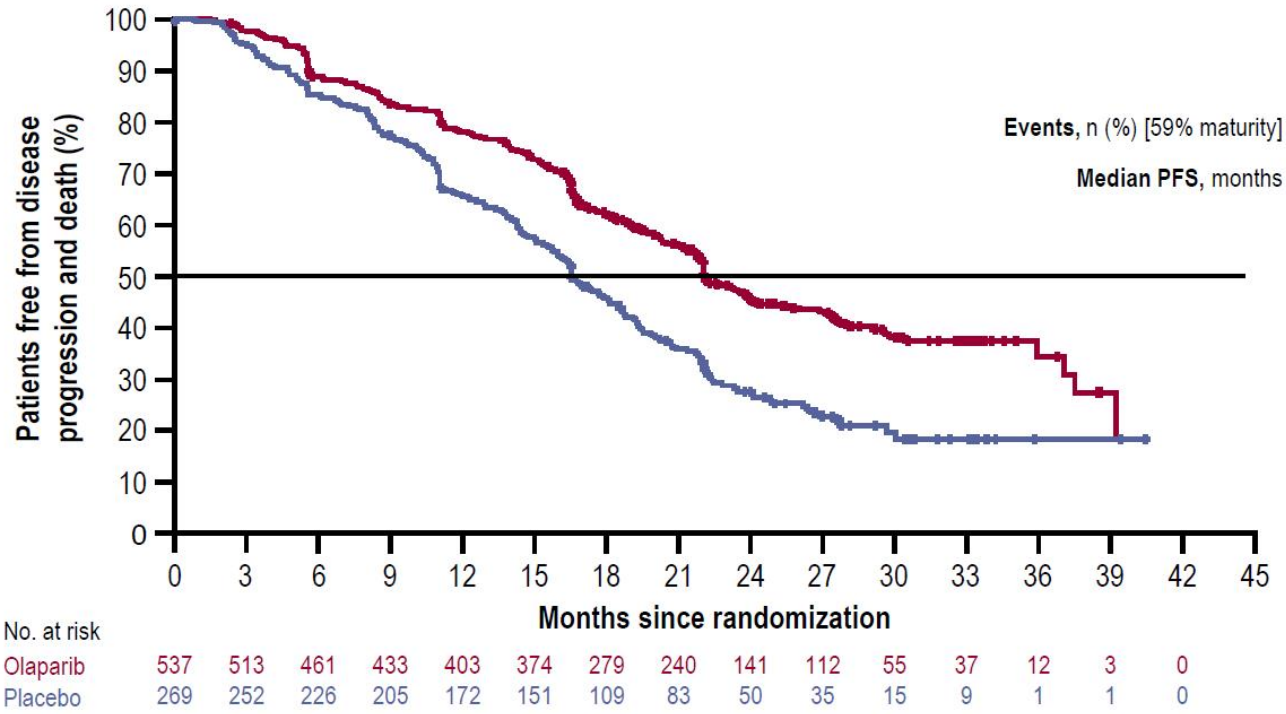
SOLO-1: Progression-free Survival



Moore, N Engl J Med, 2018; 379: 2495-2505

Paola-1 Study

PFS by investigator assessment: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	**22.1**	**16.6**

HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

Ray-Coquard I et al.

Annals of Oncology Advance Access published December 2, 2015

special article

Annals of Oncology 0: 1–26, 2015
doi:10.1093/annonc/mdv484

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

N. Colombo[1*], C. Creutzberg[2], F. Amant[3,4], T. Bosse[5], A. González-Martín[6,7], J. Ledermann[8], C. Marth[9], R. Nout[10], D. Querleu[11,12], M.R. Mirza[13] & C. Sessa[14] the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group[‡]

Surgical management of apparent stage I endometrial cancer

Surgery is the cornerstone in the treatment of endometrial cancer (MIS is recommended in the management of low-and intermediate risk EC and can be considered in patients with high-risk EC)

Indications for Adjuvant Radiotherapy in EC

- Risk factors LN invasion: stage, histotype, grade, MI, LVSI
- Two types of RT: EBRT for locoregional control
  VBT for vaginal vault control
- RT not indicated in low risk cases (gr 1-2 + <50% invasion)
- VBT (or EBRT*) indicated in intermediate risk (2 risk factors)
- EBRT and/or CT indicated in high-risk cases (3 risk factors, stages II and III)

** If PLND not performed*

Management Issues for Endometrial Cancer
Systemic therapy

- No routine adjuvant hormonal or chemotherapy. CRT not standard for high risk FIGO stages I and II, should be discussed in stage III (PORTEC-3)

- Hormonal therapy first choice for recurrence in HR-positive patients
  - Progestins: 200 mg/d MPA
  - SERMS (selective estrogen receptor modulators)

- Chemotherapy for hormone failures
  - Standard: paclitaxel/carboplatin (w/wo Bev)
  - Alternative: doxorubicin + cisplatin

- MisMatch-Repair deficient cancers are predicted to have a very large number of mutation-associated neoantigens that might be recognized by the immune system. In case of MSI positive endometrial carcinoma, CPI treatment should be considered

-

Endometrial cancer

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

Four genomic classes

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/*MLH1* methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232×10^{-6} mutations/Mb)	High (18×10^{-6} mutations/Mb)	Low ($2{\cdot}9\times10^{-6}$ mutations/Mb)	Low ($2{\cdot}3\times10^{-6}$ mutations/Mb)
Genes commonly mutated (prevalence)	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *PIK3R1* (65%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) *ARID5B* (47%)	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *PIK3R1* (40%) *ARID1A* (37%)	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *PIK3R1* (33%) *ARID1A* (42%)	*TP53* (92%) *PPP2R1A* (22%) *PIK3CA* (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumour grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grades 1 and 2	Grade 3
Progression-free survival	Good	Intermediate	Intermediate	Poor

Murali R, Lancet Oncol, 2014

Checkpoint Inhibitors in Endometrial Cancer

Study	Population	Agent	Results
Single agent CPI			
Le et al[1]	MMRd tumors (2 EC pts)	Pembro	ORR, 71%
KEYNOTE 028[2]	24 PD-L1$^+$ EC patients	Pembro	ORR, 13%
KEYNOTE 158,028,016[3]	MSI-H, 17 EC patients	Pembro	ORR, 37.7%
Fader et al[4]	MMRd tumors, recurrent	Pembro	ORR, 56%; DCR 89%
Santin et al[5]	2 pts (POLE & MSI-H)	Nivo	Resp.> 7 months
Hasegawa et al[6]	23 metastatic EC pts	Nivo	ORR, 23%;PFS 3.6 m
Fleming et al[7]	15 metastatic EC pts	Atezo	ORR, 13% (1 MSI-H)
GARNET[8]	MSI-H recurrent/adv.EC	TSR-042	ORR, 52%
Antiangiogenesis + CPI			
KEYNOTE 775[9]	Metastatic EC	Lenvat+pembro	ORR, 48%; DCR 96%

[1]Le et al, N Engl J Med 2015; [2]Ott et al, J Clin Oncol 2017; [3]KEYTRUDA 2019; [4]Fader et al, Gynecol Oncol 2016; [5]Santin et al, Clin Cancer Res 2016; [6]Hasegawa et al, J Clin Oncol 2018; [7]Fleming et al, J Clin Oncol 2017; [8]Oaknin et al, SGO meeting 2019; [9]Makker et al. J Clin Oncol 2017

Modified from Levinson et al. 2019 ASCO Educational Book

Thank you

Algorithm for selecting biological therapy in PS-ROC 2019