Low Grade Ovarian Cancer

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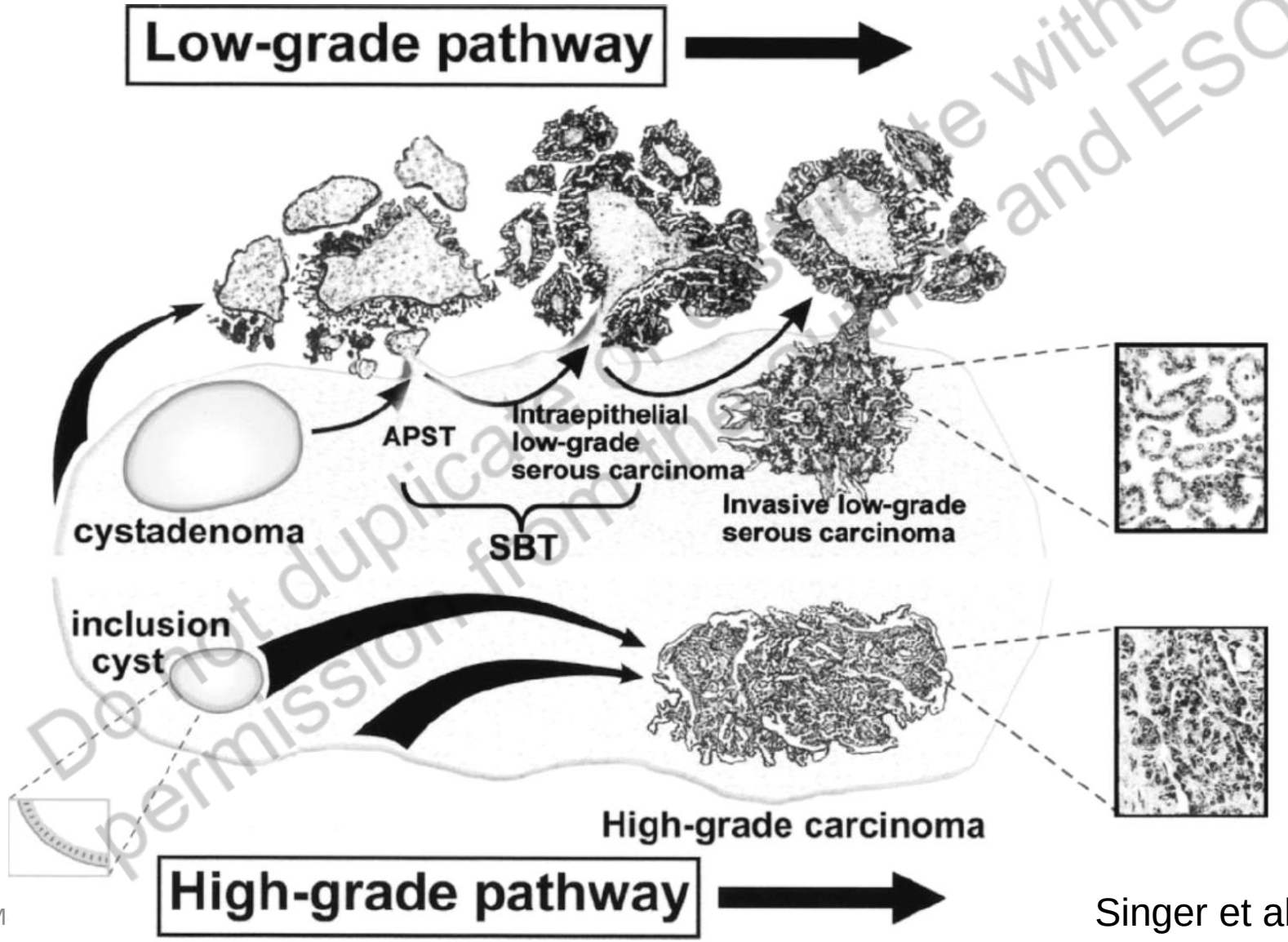
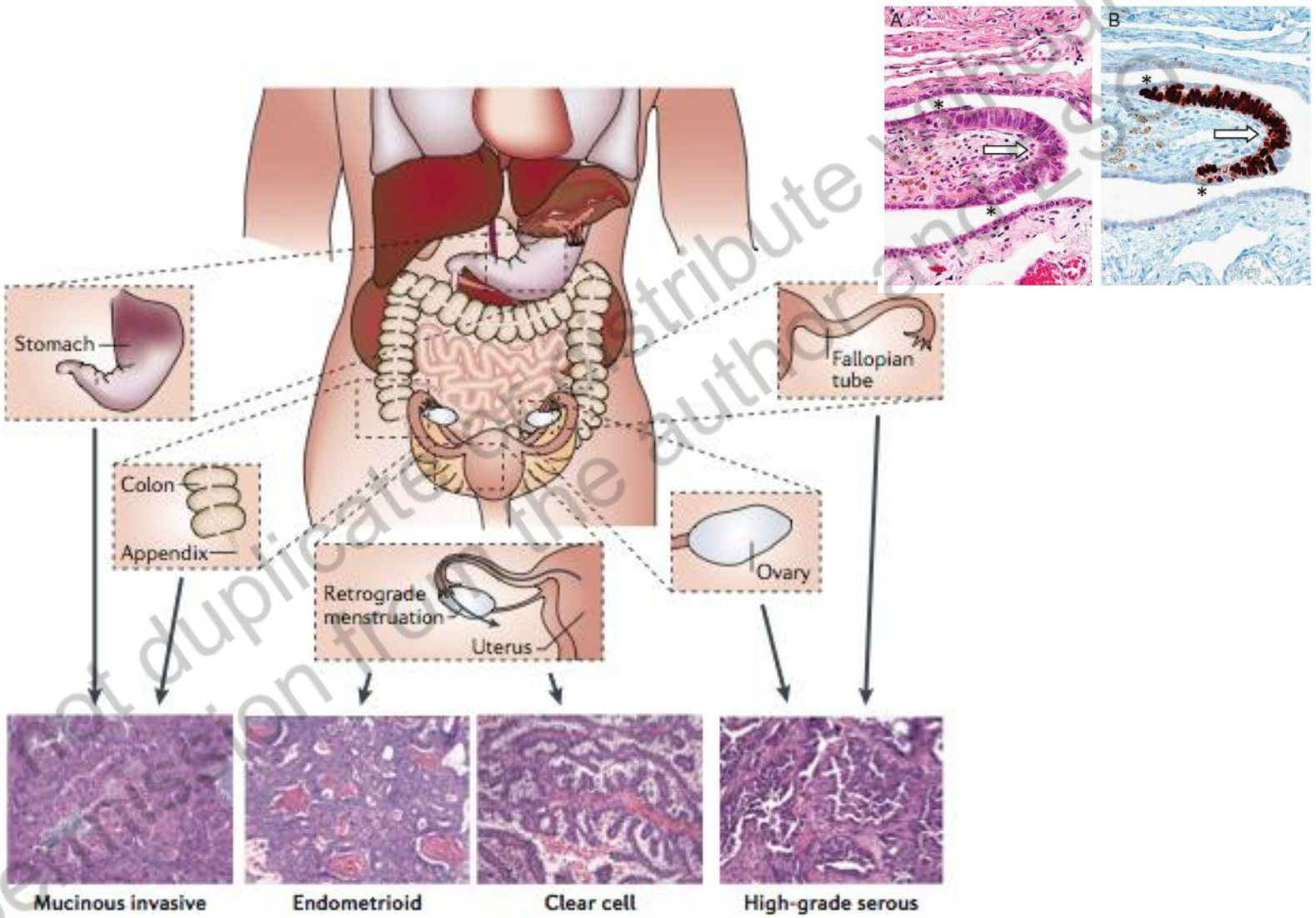
University of Berlin, Europe, one world!

The dualistic model of ovarian cancer

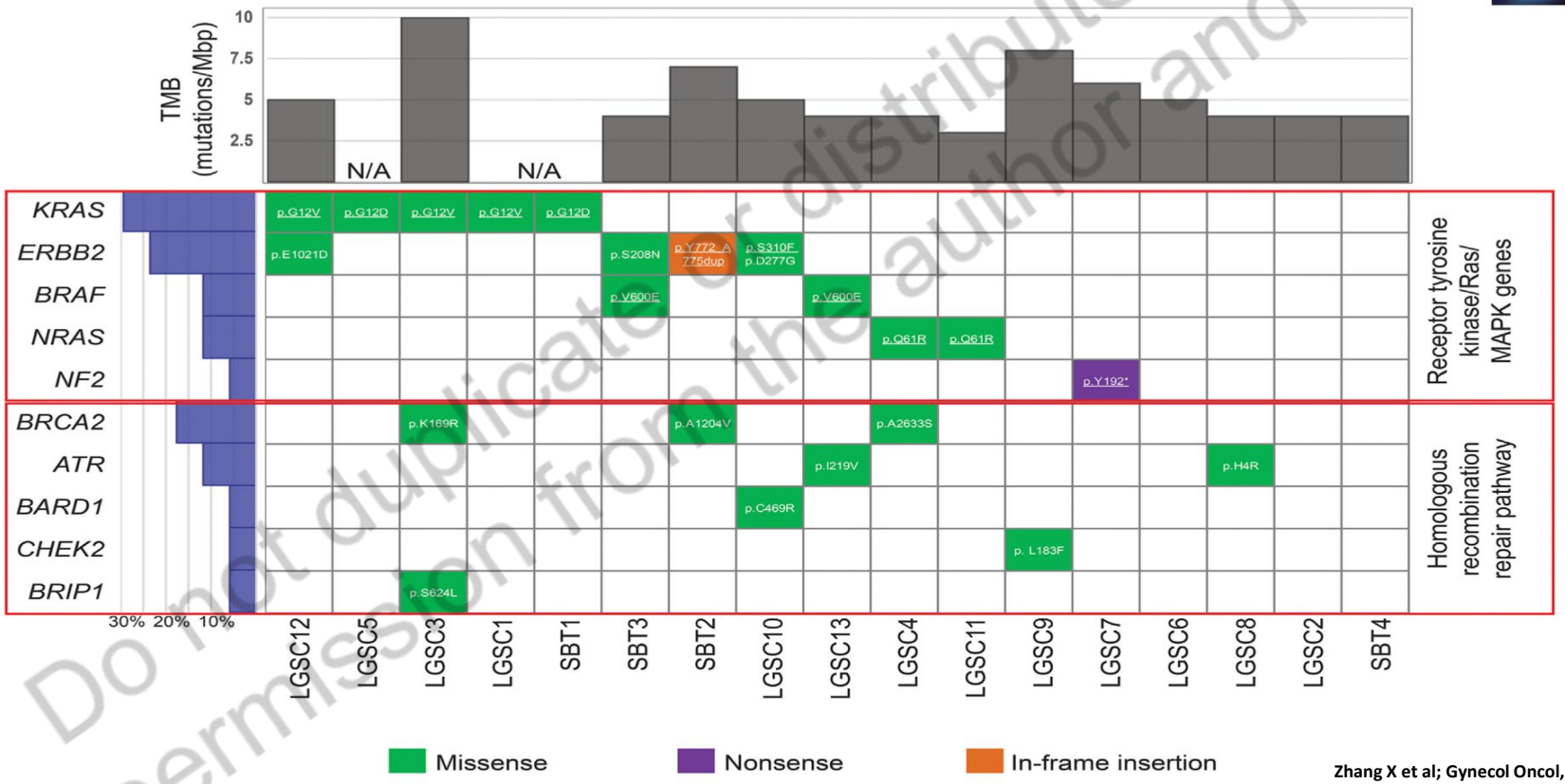


Singer et al. 2005



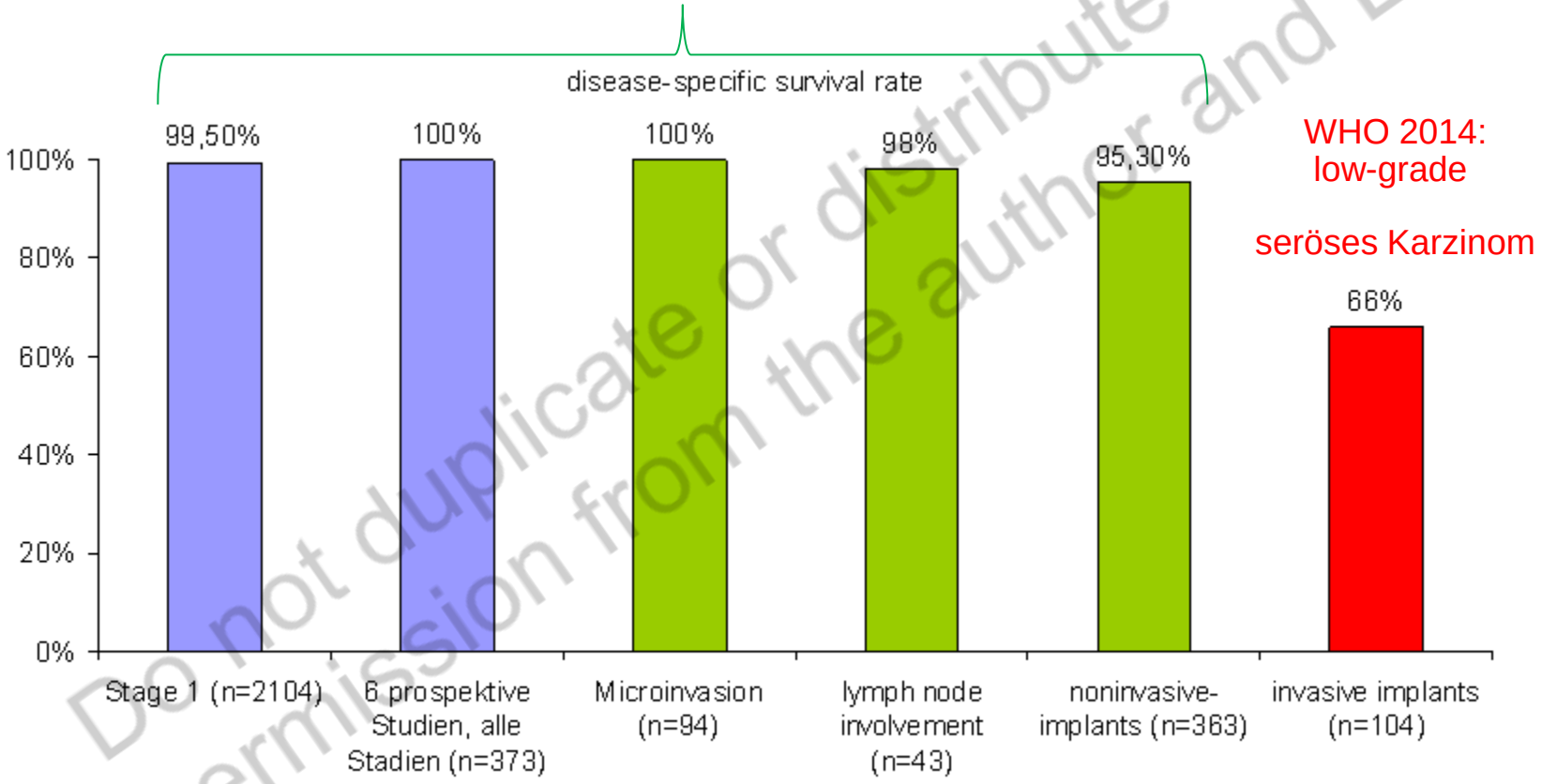
Sebastian Vaughan

What we didn't know…

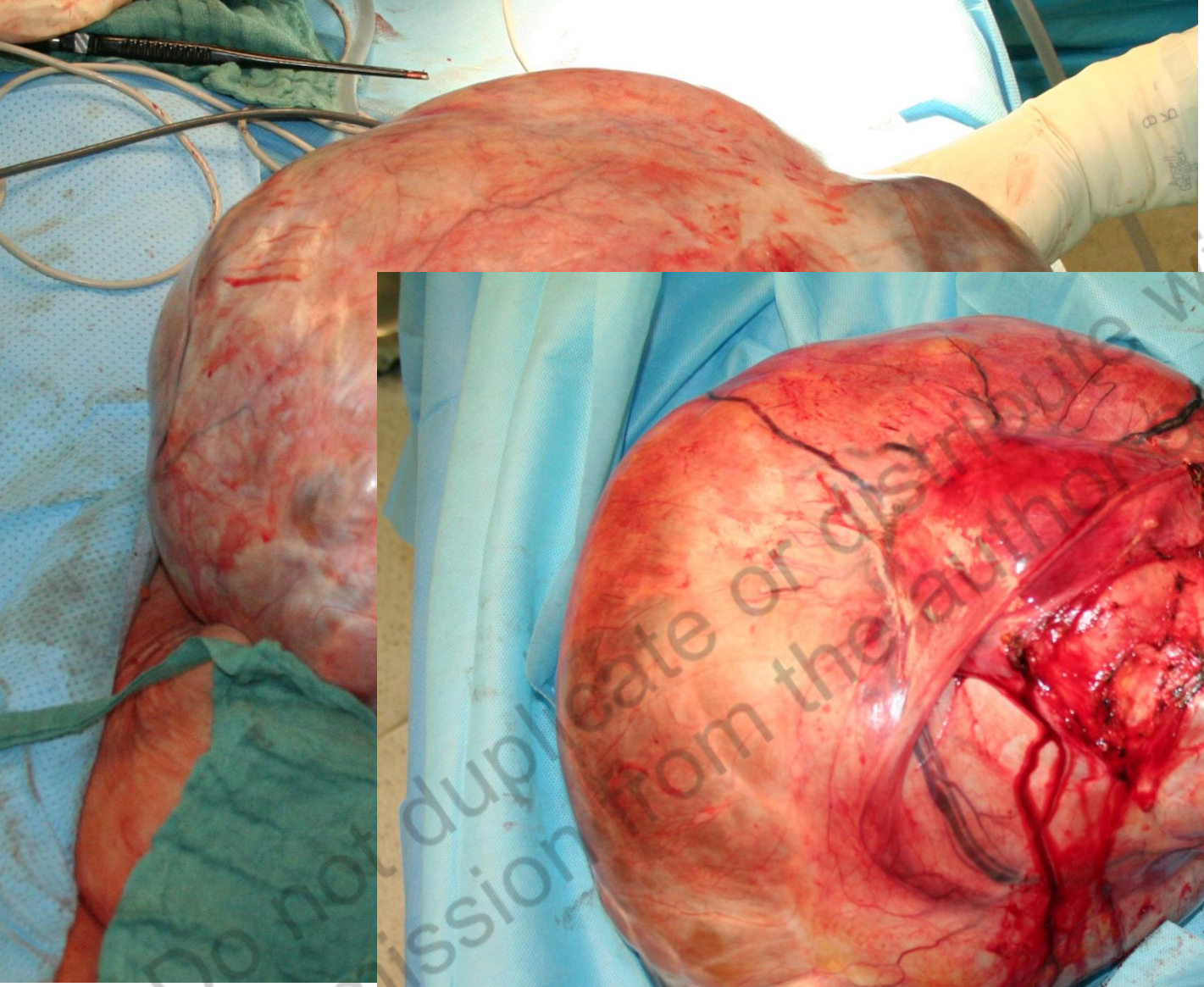


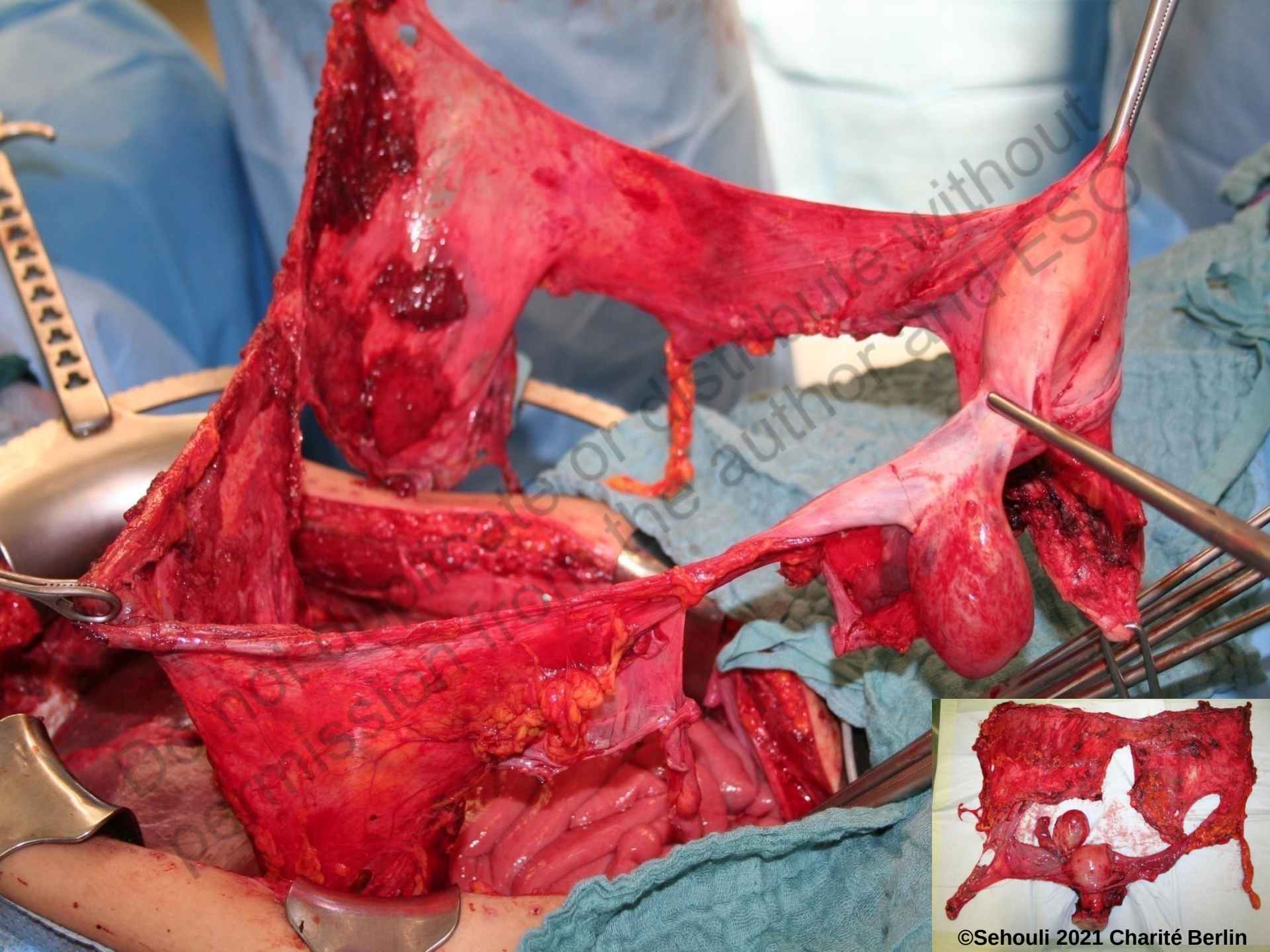
Zhang X et al; Gynecol Oncol, 2021

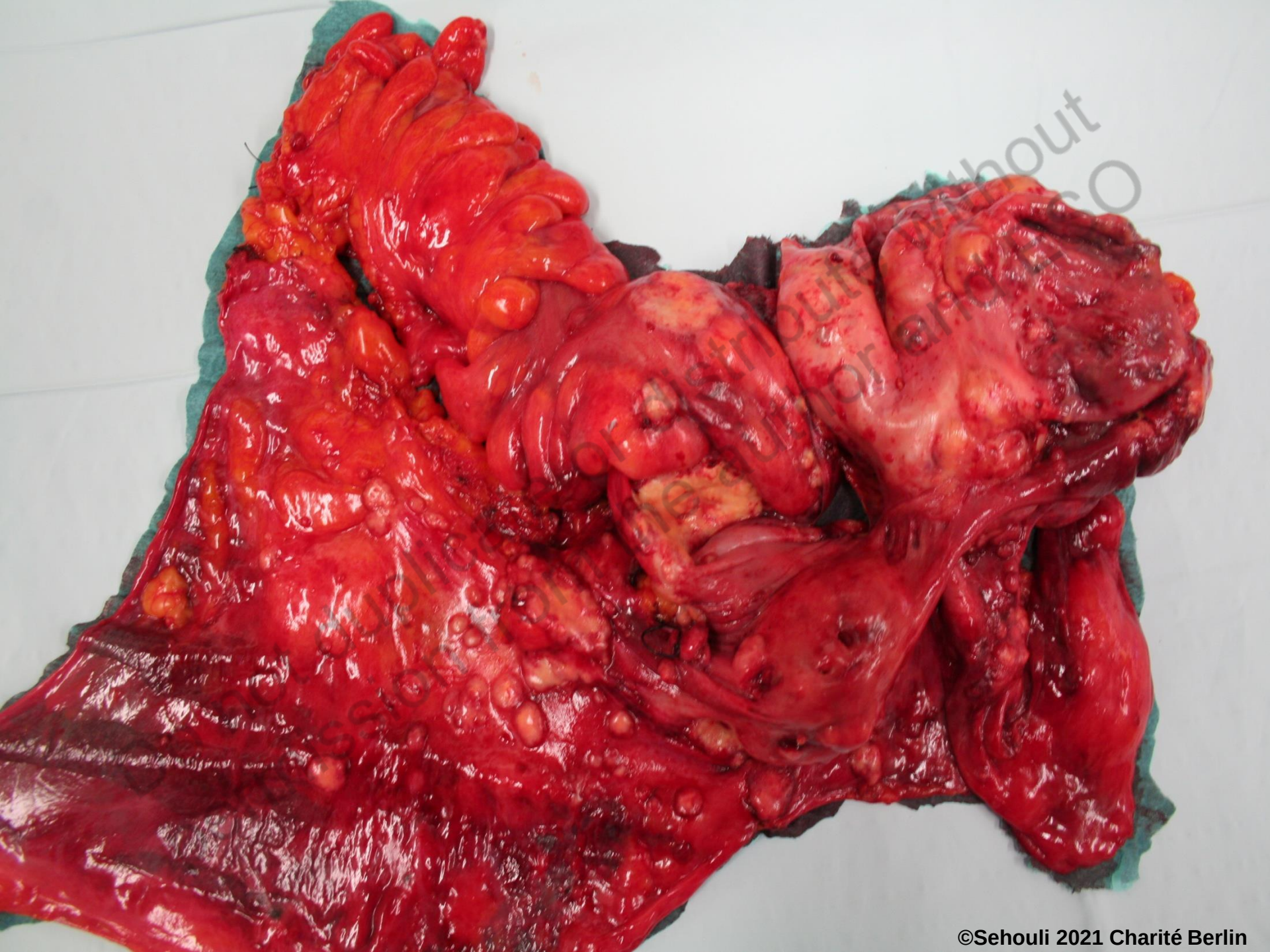
WHO 2014 - LGSC



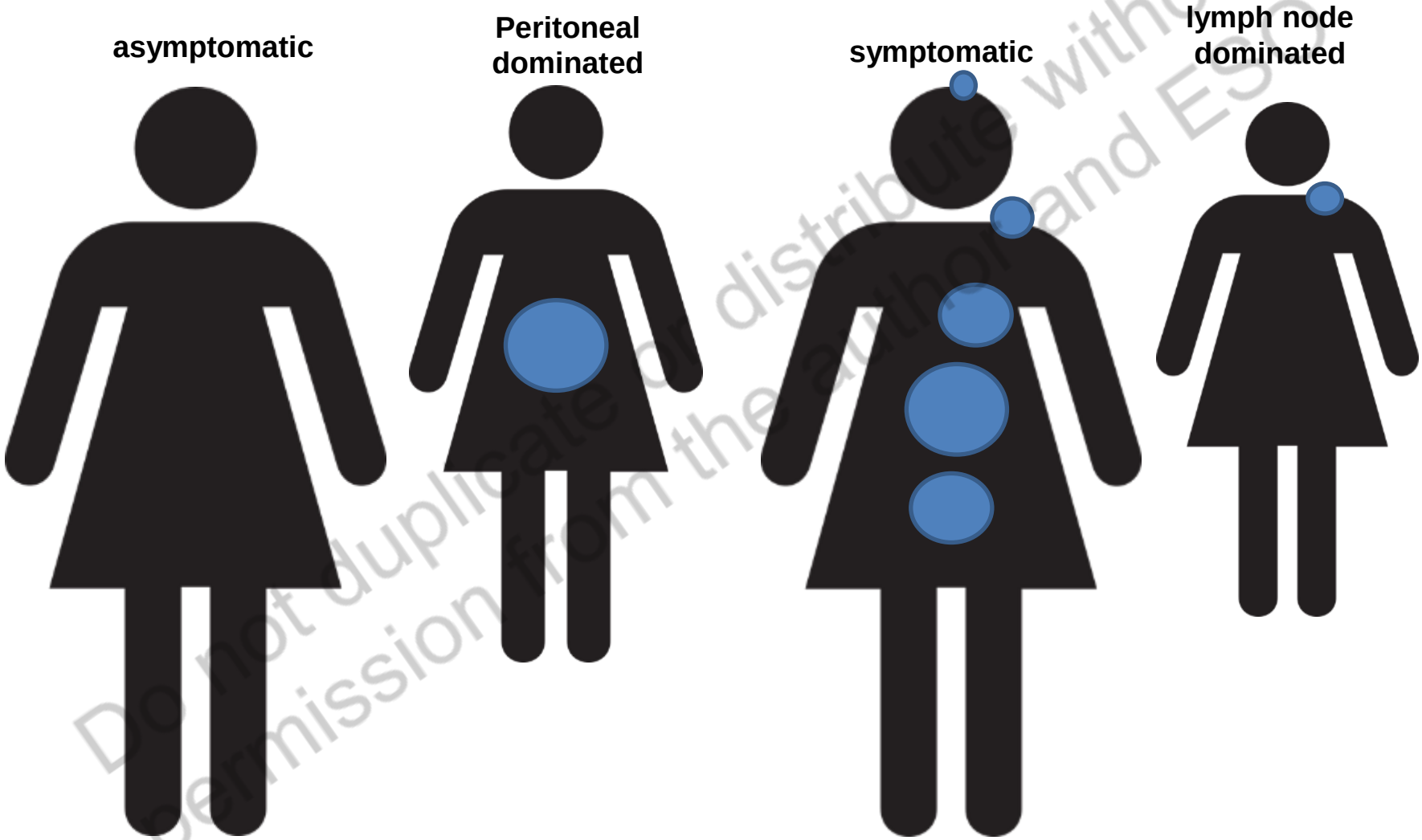
Seidman *Hum Pathol* 2000







Ovarian Cancer: more than one diesease!



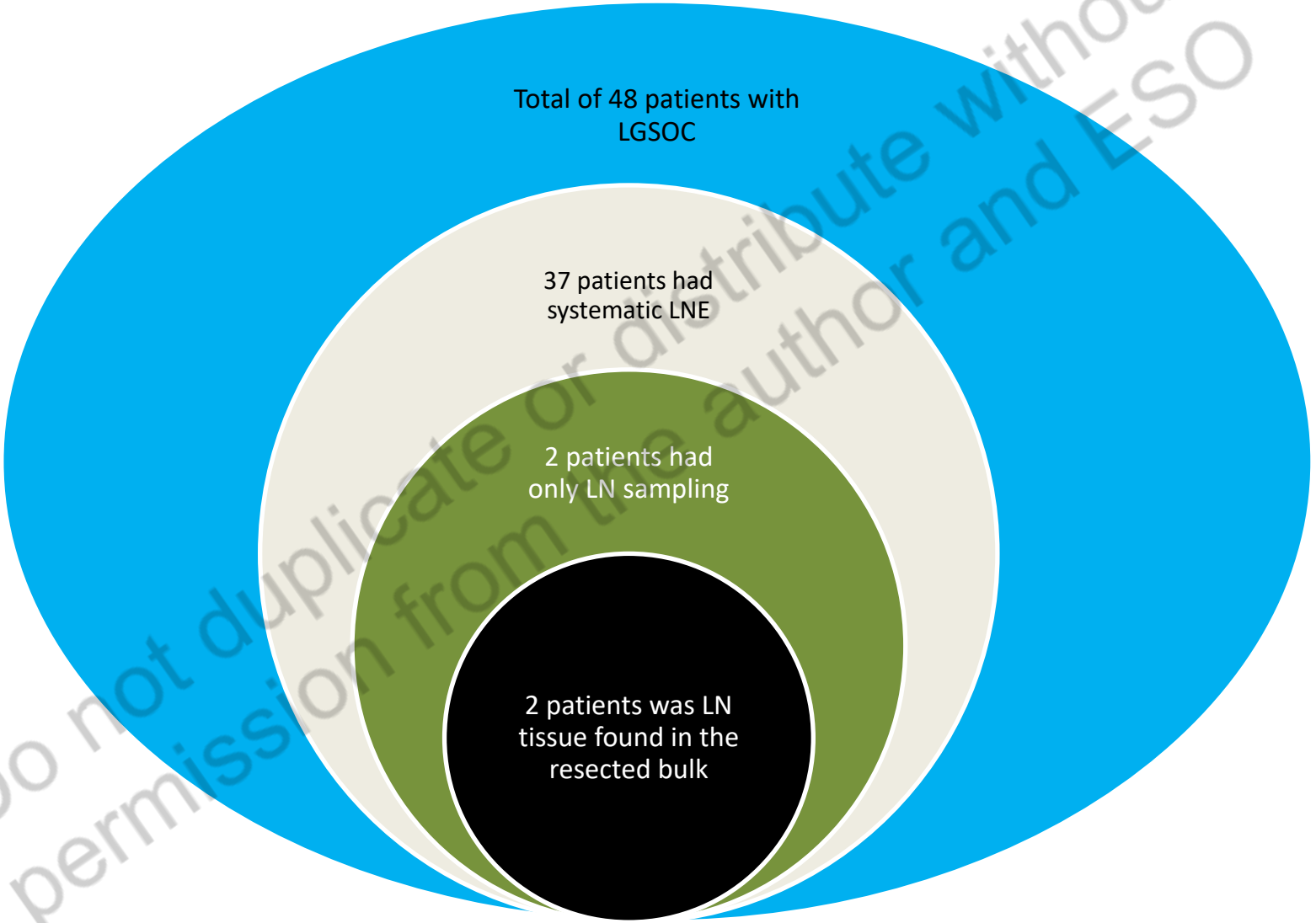
Tumorkonferenz Online

The Value of Serum CA125 in the Diagnosis of Borderline Tumors of the Ovary: A Subanalysis of the Prospective Multicenter ROBOT Study.

Fotopoulou C[1], Sehouli J, Ewald-Riegler N, de Gregorio N, Reuss A, Richter R, Mahner S, Kommoss F, Schmalfeldt B, Fehm T, Hanker L, Wimberger P, Canzler U, Pfisterer J, Kommoss S, Hauptmann S, du Bois A; ROBOT investigators. Int J Gynecol Cancer. 2015 Sep;25(7):1248-52

- **METHODS:** CA125 data were extracted from the ROBOT multicenter study of patients with BOT treated between 1998 and 2008 in 24 German centers. While patients' data were retrieved retrospectively from hospital records and clinical tumor registries, follow-up and independent central pathology review were performed prospectively.
- **RESULTS:** We identified **127 patients** from the ROBOT database fulfilling the eligibility criterion of available CA125 at initial diagnosis. **Eighty-three (65.3%) patients had increased CA125 levels (>35 U/L).** Of the patients, 85.0% presented with serous and 13.4% with mucinous BOT histology, whereas 29.9% had stage I disease. Fifteen (11.8%) patients experienced a relapse. **Multivariate analysis identified raised CA125, young age, and serous histology as independent predictors of peritoneal implants of any type at initial presentation.** Raised CA125 at initial diagnosis was, however, not an independent predictor of future relapse.

Incidence and Pattern of Spread of Lymph Node Metastasis in Patients With Low-grade Serous Ovarian Cancer.
Wafa M, Braicu EI, Muallem MZ, Richter R, Taube E, Sehouli J, Grabowski JP. Anticancer Res. 2019



Limited efficacy of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors

Ines Vasconcelos, Jessica Olschewski, Ioana Braicu, Jalid Sehouli

- We identified 31 articles including 4965 patients.
- 592 patients presented non-invasive-, 244 invasive- and 77 unspecified implants.
- Nine studies included more than 90% stage I patients, while 11 included only advanced stage patients.
- Nineteen studies reported patients undergoing complete cytoreduction, ten reported response rates and eight compared survival outcomes.
- All studies provided information regarding either mortality or recurrence rates.
- A meta-analysis of the 13 studies providing separate mortality data for both treatment groups, including 2206 women, favored surgical treatment only (OR=7.44; 95% CI=3.39-16.32; p<0.0005)
- Regarding survival data, 4 studies reported no difference between groups.

At present, there is no evidence to support the use of adjuvant treatment in patients with BOT.

A meta-analysis on the impact of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors with invasive implants.

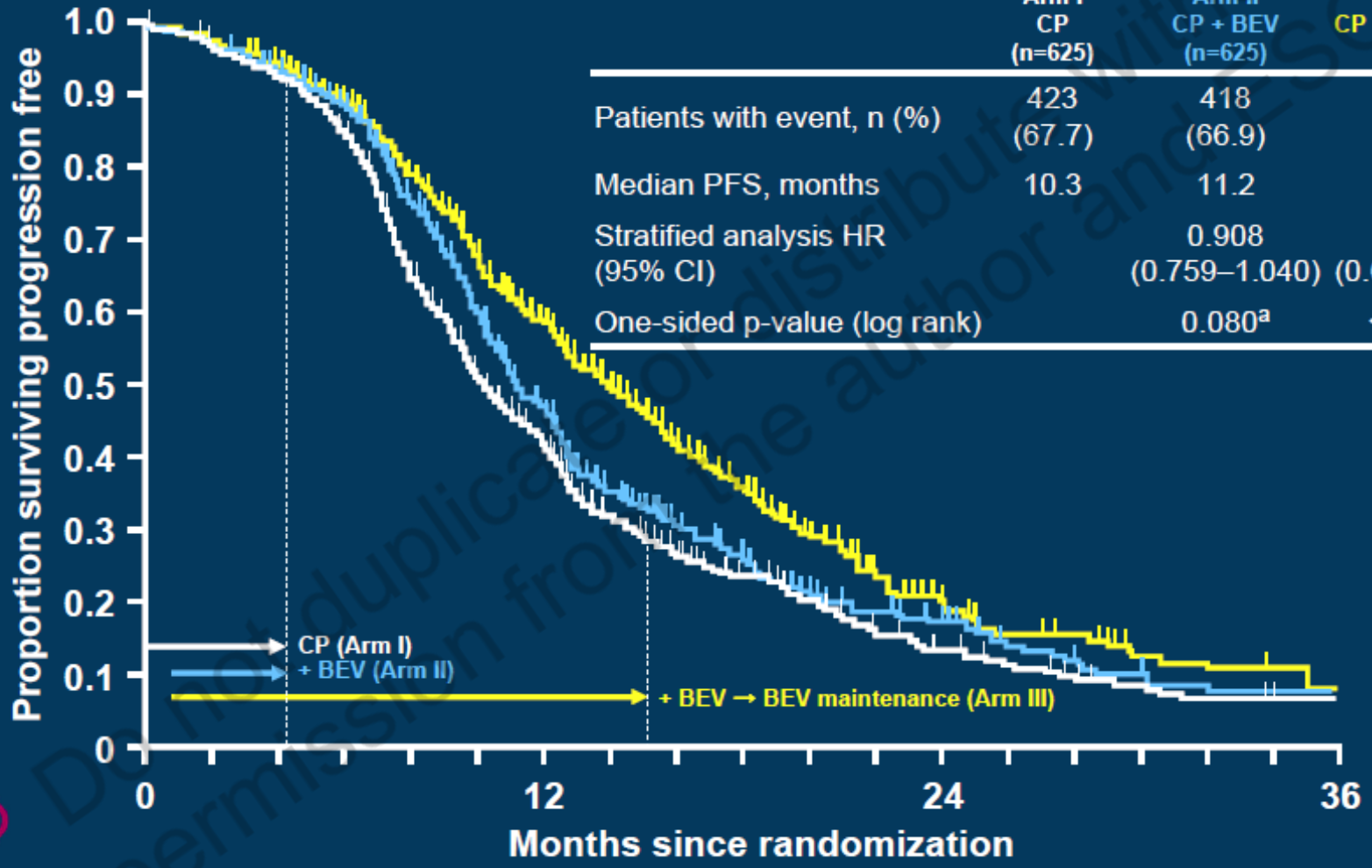
Vasconcelos I[1], Olschewski J[2], Braicu I[2], Sehouli J[2].

Oncologist. 2015 Feb;20(2):151-8. doi: 10.1634/theoncologist.2014-0144. Epub 2015 Jan 19.

- **METHODS:** The PubMed database was systematically searched for articles using the following terms: ((borderline) OR (low malignant potential) AND (ovarian)) AND ((tumor) OR (cancer)) AND (invasive implants) AND ((follow-up) OR (survival) OR (treatment) OR (chemotherapy) OR (adjuvant treatment) OR (surgery) OR (surgical treatment)).
- **RESULTS:** We identified 27 articles including 3,124 patients, 181 with invasive implants. All studies provided information regarding mortality or recurrence rates. Central pathological examination was performed in 19 studies. Eight studies included more than 75% stage I patients; 7 included only advanced-stage patients, and 14 included only serous BOT. The pooled recurrence estimates for both treatment groups (adjuvant treatment: 44.0%, upfront surgery: 21.3%) did not differ significantly ($p = .114$). A meta-analysis of the 6 studies providing separate mortality data for both treatment groups favored surgical treatment only, but this difference did not reach statistical significance ($.05 < p < .1$; odds ratio: 0.33; 95% confidence interval: 0.09-1.71; $p = .086$). We were unable to pool the results of the included studies because not all studies registered events in both treatment groups. Egger's regression indicated low asymmetry of the studies ($p = .39$), and no heterogeneity was found ($I(2) = 0\%$).
- **CONCLUSION:**
- **We did not find evidence supporting platinum-based adjuvant therapy for BOT with invasive implants.**

GOG-0218: Investigator-Assessed PFS

	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]



ASCO Annual '10 Meeting

[a]p-value boundary = 0.0116

ANTI - ANGIOGENIC AGENTS: BEVACIZUMAB

Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial

	Clear cell tumours*		Low-stage high-grade tumours		Low-grade serous tumours	
	Standard therapy (n=77)	Bevacizumab (n=82)	Standard therapy (n=75)	Bevacizumab (n=67)	Standard therapy (n=49)	Bevacizumab (n=31)
Follow-up duration (months)	52·5 (29·0–57·5)	50·7 (28·2–57·9)	55·3 (49·1–60·6)	55·4 (51·2–61·6)	50·5 (28·2–55·1)	55·3 (47·9–62·0)
Deaths	20 (26%)	24 (29%)	6 (8%)	9 (13%)	13 (27%)	7 (23%)
Log-rank test p value	p=0·74		p=0·44		p=0·60	
HR (95% CI)	1·09 (0·64–1·88)		1·49 (0·53–4·20)		0·78 (0·31–1·97)	
Non-proportionality p value†	p=0·58		p=0·002		p=0·07	
(Restricted) mean survival time (months; 95% CI)‡	48·0 (43·9–52·2)	47·6 (43·6–51·6)	56·2 (51·5–60·9)	57·5 (55·7–59·4)	50·4 (45·6–55·2)	50·5 (43·9–57·0)
Restricted mean survival time difference (95% CI)	−0·4 (−6·1 to 5·3)		1·3 (−3·7 to 6·4)		0·1 (−7·9 to 8·0)	

Data are median (IQR) or n (%), unless otherwise indicated. HRs, p values, and survival time differences are for differences between the standard therapy and bevacizumab groups. *The clear cell tumour group includes some patients with mixed histology. †Grambsch-Therneau test. ‡Restricted at 5 years.

Table 2: **Overall survival in predefined subgroups**

ANTI - ANGIOGENIC AGENTS: BEVACIZUMAB

Data about the activity of Bevacizumab in LGSC come from retrospective studies

Author	Type of study	Setting of disease	Patients	Outcomes
Grisham RN et al, 2014	Retrospective	Recurrent	17 patients Beva/chemo: 15 pts Beva alone: 2 pts	RR:55%
Schmeler KM et al, 2010	Retrospective	Recurrent	21 patients Beva/chemo: 20 pts Beva alone: 1 pt	RR: 41% CBR: 59%
Dalton HL et al, 2017	Retrospective	Recurrent	45 patients	RR: 47.5% CBR: 77.5% PFS: 10.2 months OS: 34.6 months

Clinical management of borderline tumours of the ovary: results of a multicentre survey of 323 clinics in Germany.

Coumbos A, Sehouli J, Chekerov R, Schaedel D, Oskay-Oezcelik G, Lichtenegger W, Kuehn W; North-Eastern German Society of Gynecological Oncology (NOGGO). Br J Cancer. 2009 Jun 2;100(11):1731-8. Epub 2009 May 12.

Clinical management of borderline tumours of the ovary
A Coumbos *et al*

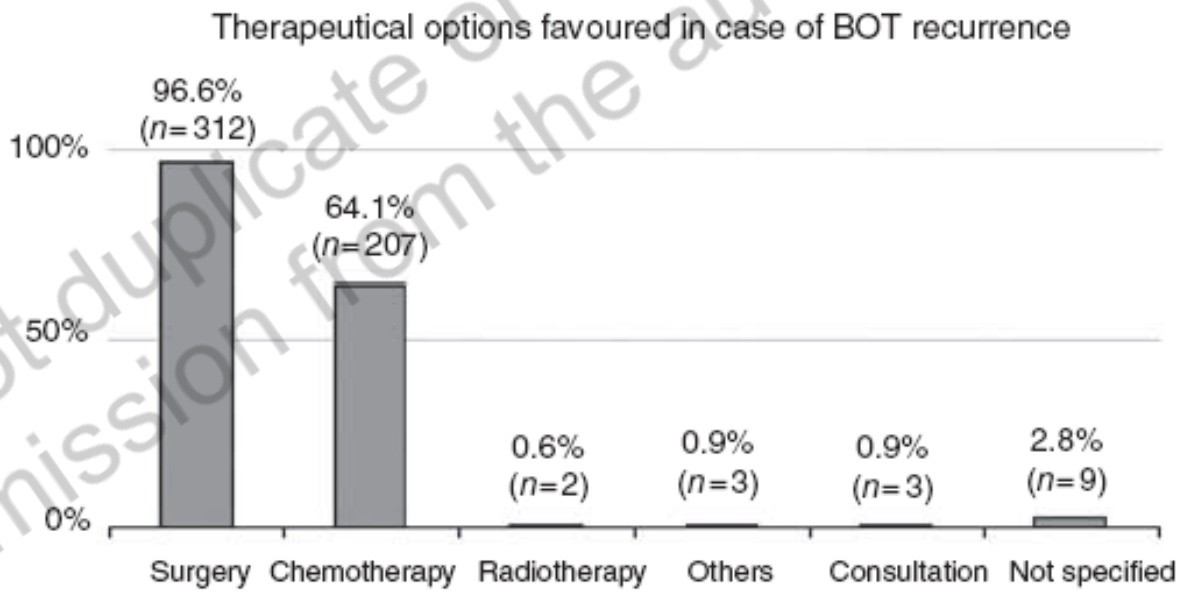
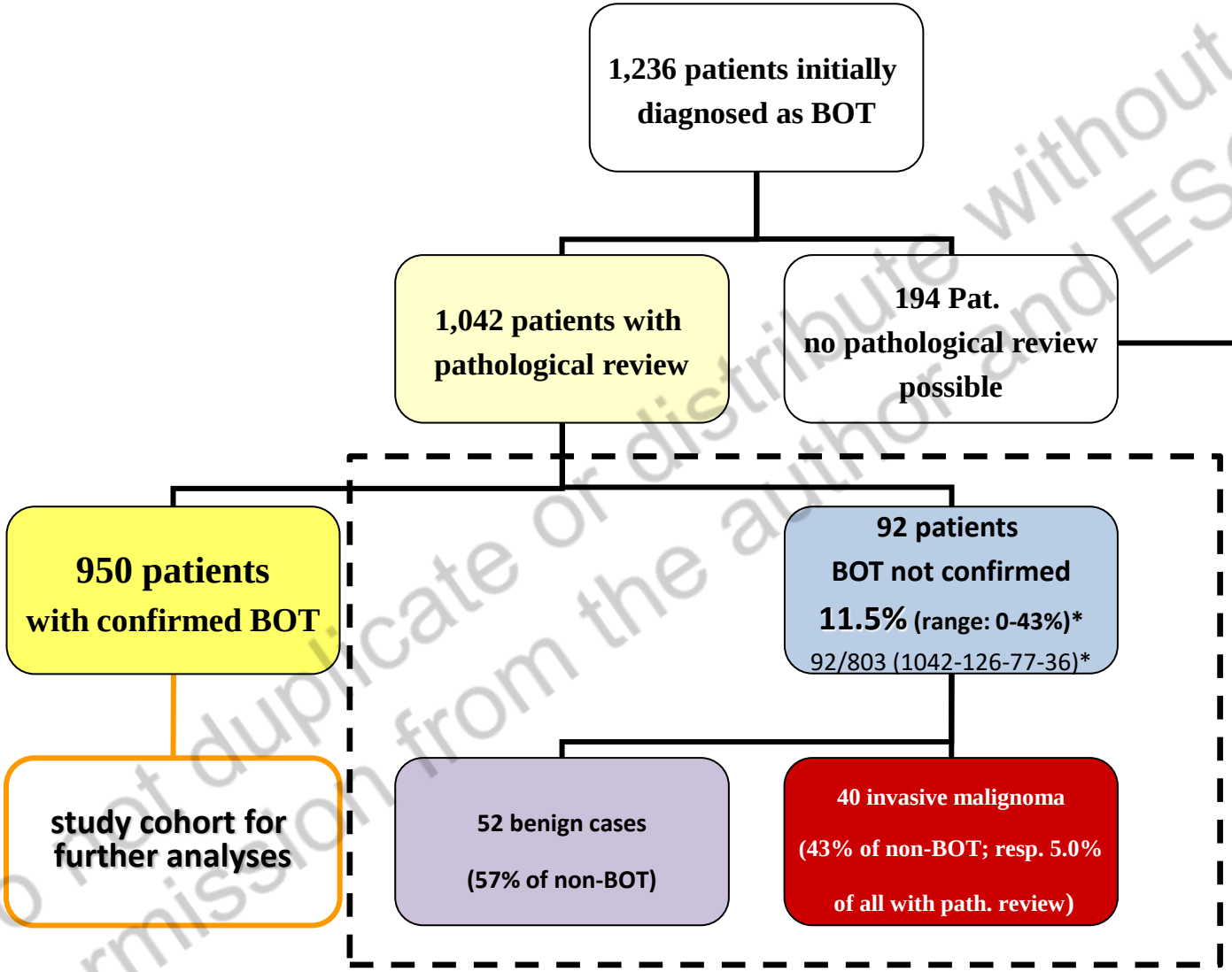


Figure 5 Management of the recurrence of BOT ($n = 323$, multiple answers are possible).

The German ROBOT-STUDY



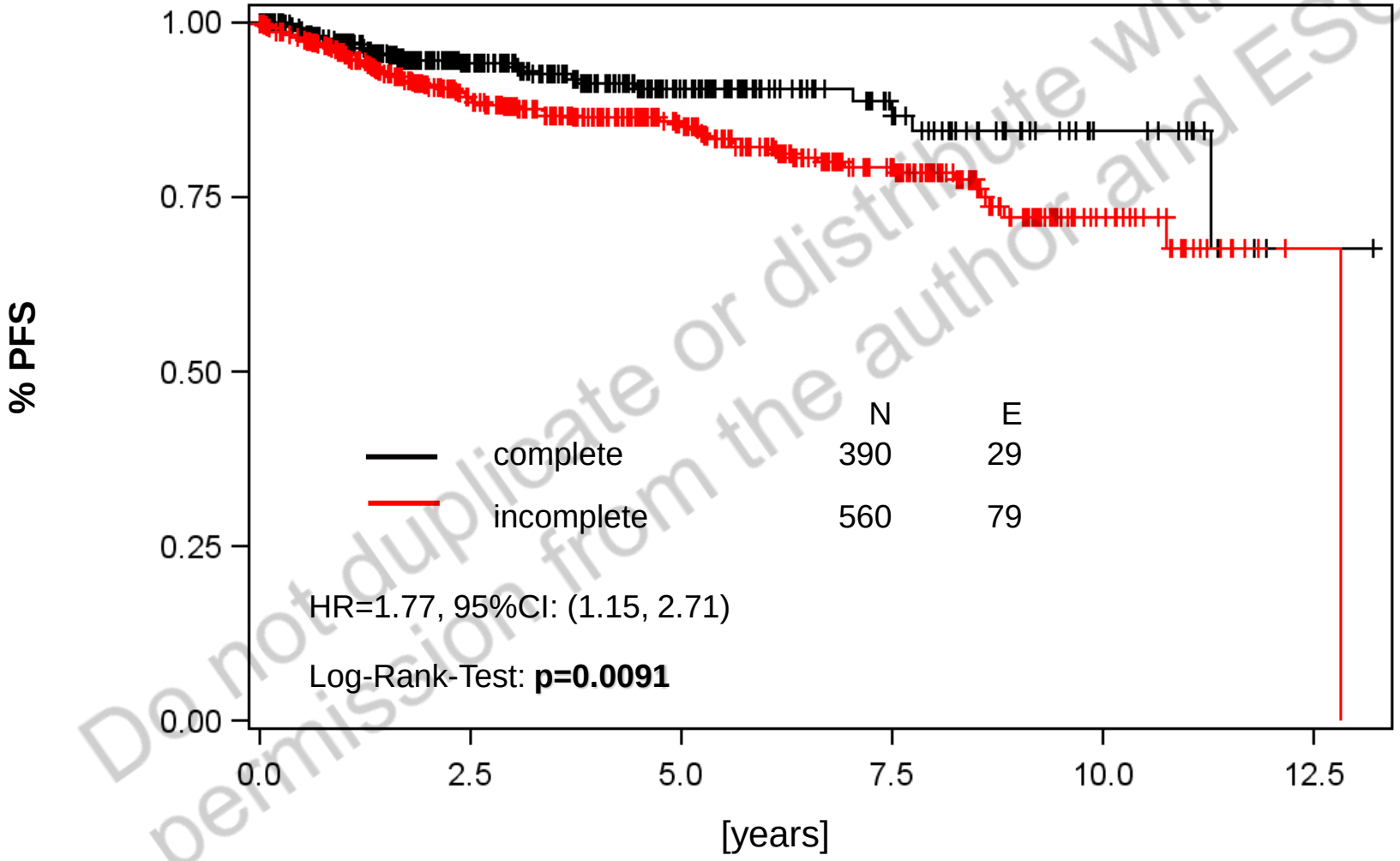
* 3 centers included patients only with confirmed BOT after pathological review.

Median observation period in this group was 41 months (interquartile 18–74).

Multivariate Cox model for PFS S-BOT

Factor	HR	95% CI	p
Post-OP Residual tumor	4.980	(2.131, 11.640)	0.0002
Implants present yes/no	2.743	(1.675; 4.494)	<0.0001
Organ preservation	2.363	(1.226; 4.554)	0.0102
Staging quality adequate vs. incomplete	2.188	(1.315; 3.683)	0.0026
Age [years]	0.838	(0.726; 0.968)	0.0166

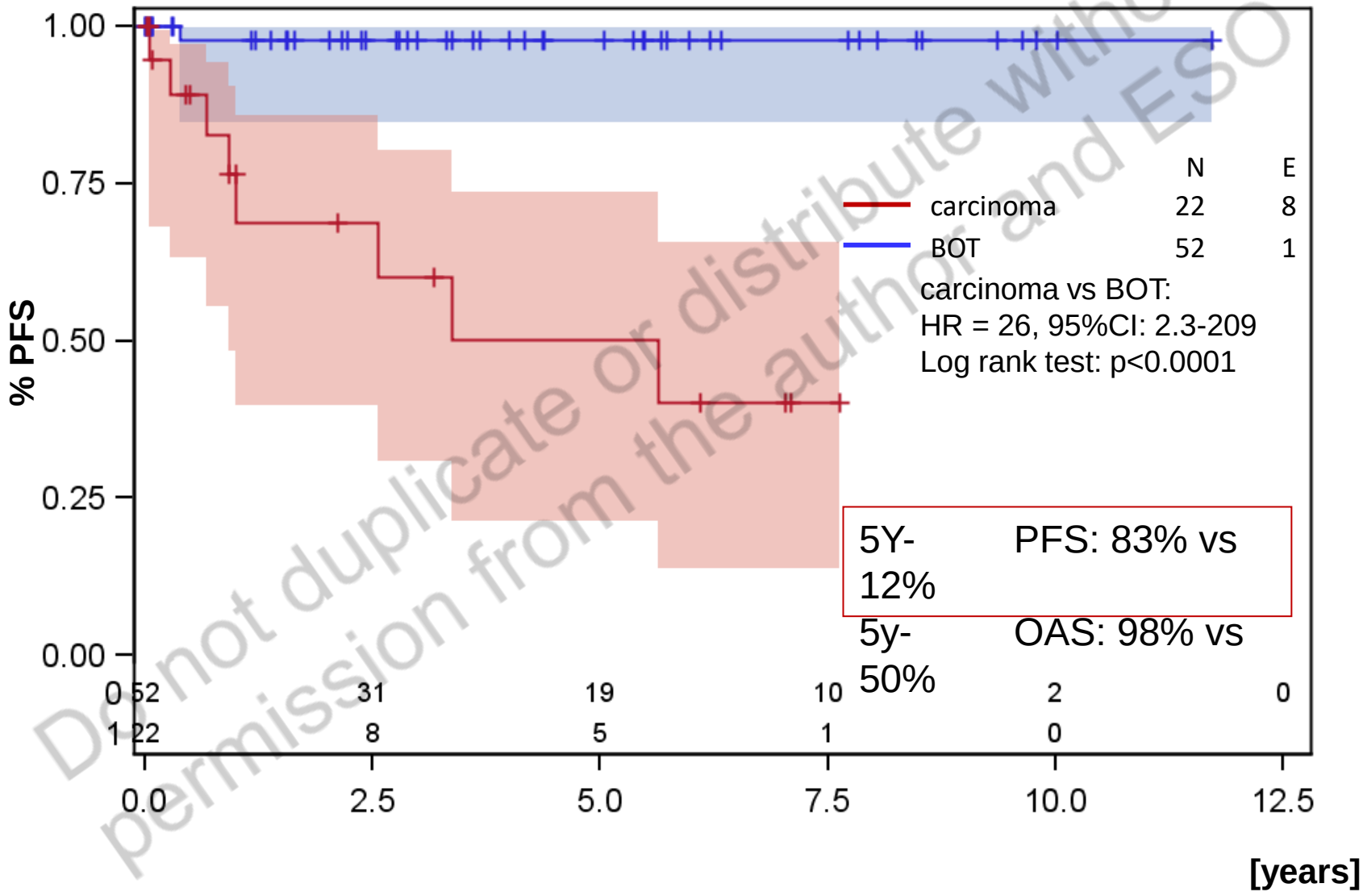
PFS staging complete vs. incomplete



Relapse

	N	%
Relapses	74	7.8
Relapse as BOT	52	70
Relapse as invasive carcinoma high grade	22 8 of 22	30 36

OAS after relapse – carcinoma vs. BOT at relapse



Low grade ovarian cancer and chemotherapy

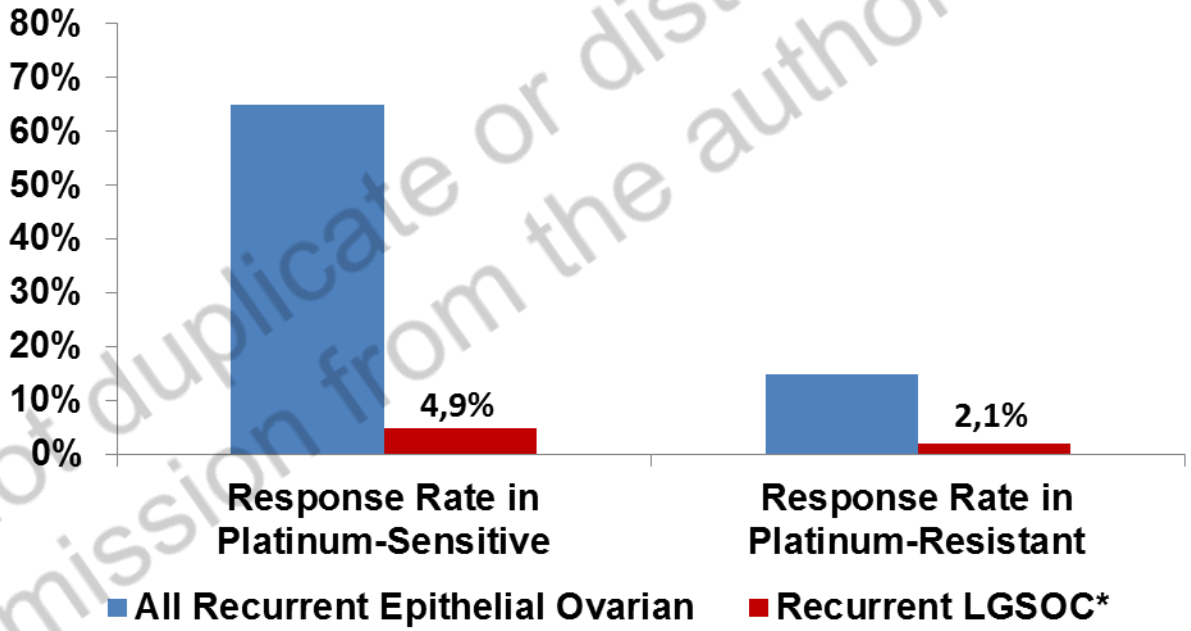
Low grade ovarian cancer has generally a low proliferation rate

…so how can response be an adequate endpoint of efficacy?

Low grade ovarian cancer has generally low symptoms

- *…so how can symptom controll be an adequate endpoint of efficacy?*
- *and low grade ovarian cancer are not homogenous*
- *and chemotherapy works not only cytotoxic and has several effects on the cancer cell and ist microenviroment*

Chemoresistence in LGSOC ?



*75% received 1-2 prior chemo regimens

Sources: Gonzalez-Martin et al. Ann Oncol 2005; Kushner et al. J Clin Oncol 2004; Mutch et al. J Clin Oncol 2007; Abushahin et al. J Clin Oncol 2006; Gershenson et al. Gynecol Oncol 2009

Gynecologic Oncology 140 (2016) 457–462

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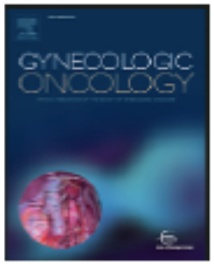


Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase

Jacek P. Grabowski [a,h,*], Philipp Harter [a], •, Florian Heitz [a], Eric Pujade-Lauraine [b], Alexander Reuss [c], Gunnar Kristensen [d], Isabelle Ray-Coquard [e], Julia Heitz [f], Alexander Traut [a], Jacobus Pfisterer [g], Andreas du Bois [a]

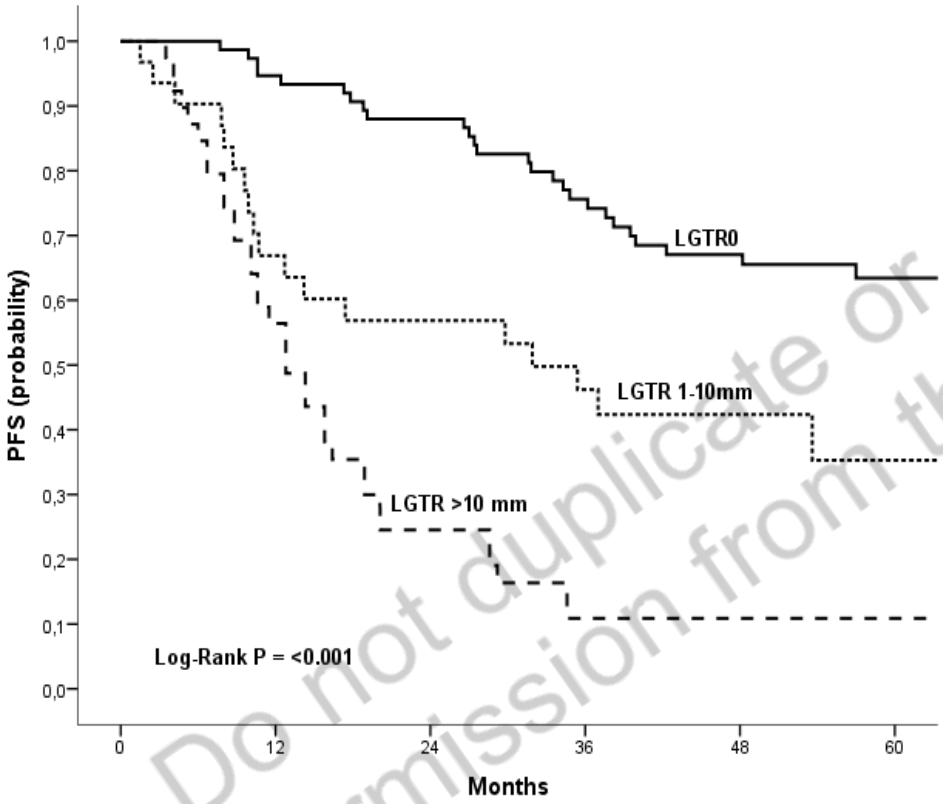
Responsiveness to chemotherapy

Table 3. The response rate in patients with LGSOC and HGSOC after incomplete primary cytoreduction with residual disease (TR) >1cm.

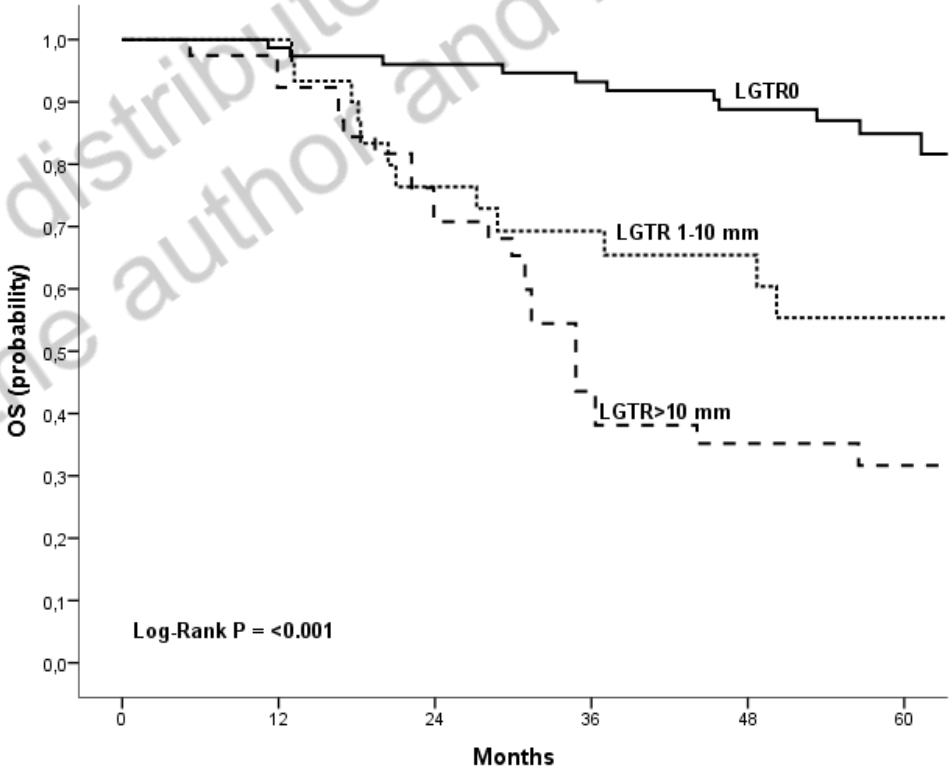
Variable	Number of Cycles	Response		No response		Relative risk (CI95%)	Odds-ratio (CI95%)	p-value
		CR	PR	SD	PD			
LGSOC	6 (3–10)	6 (15.4%)	3 (7.7%)	27 (69.2%)	3 (7.7%)	7.3 (3.9-13.8)	30.8 (10.9-97.5)	<0.001
HGSOC	6 (3–10)	67 (83.8%)	5 (6.3%)	6 (7.5%)	2 (2.5%)	0.24 (0.13-0.44)	1 (reference)	

Serous low-grade ovarian cancer (LGSOC)

PFS



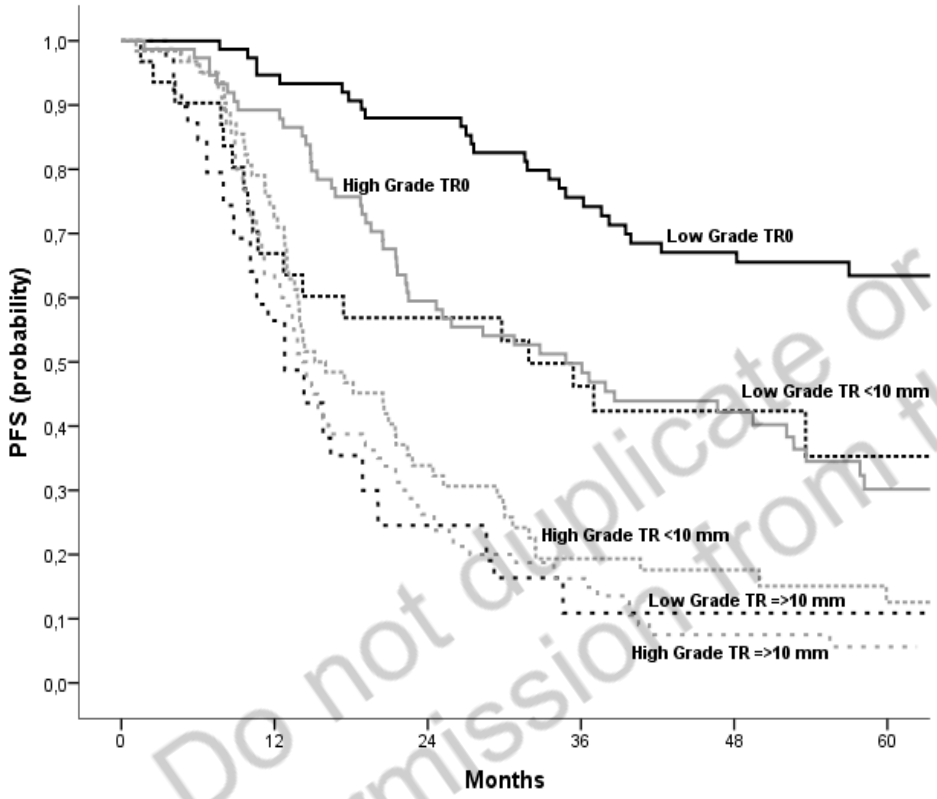
OS



Grabowski et al. 2016

Low-grade vs. High grade serös

PFS



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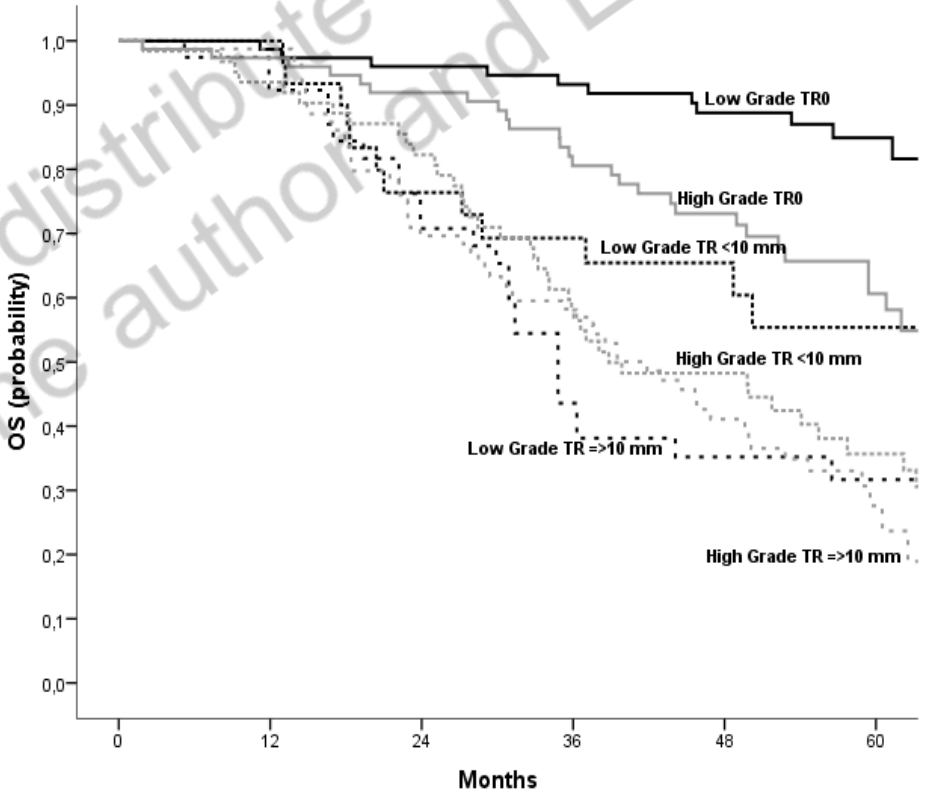
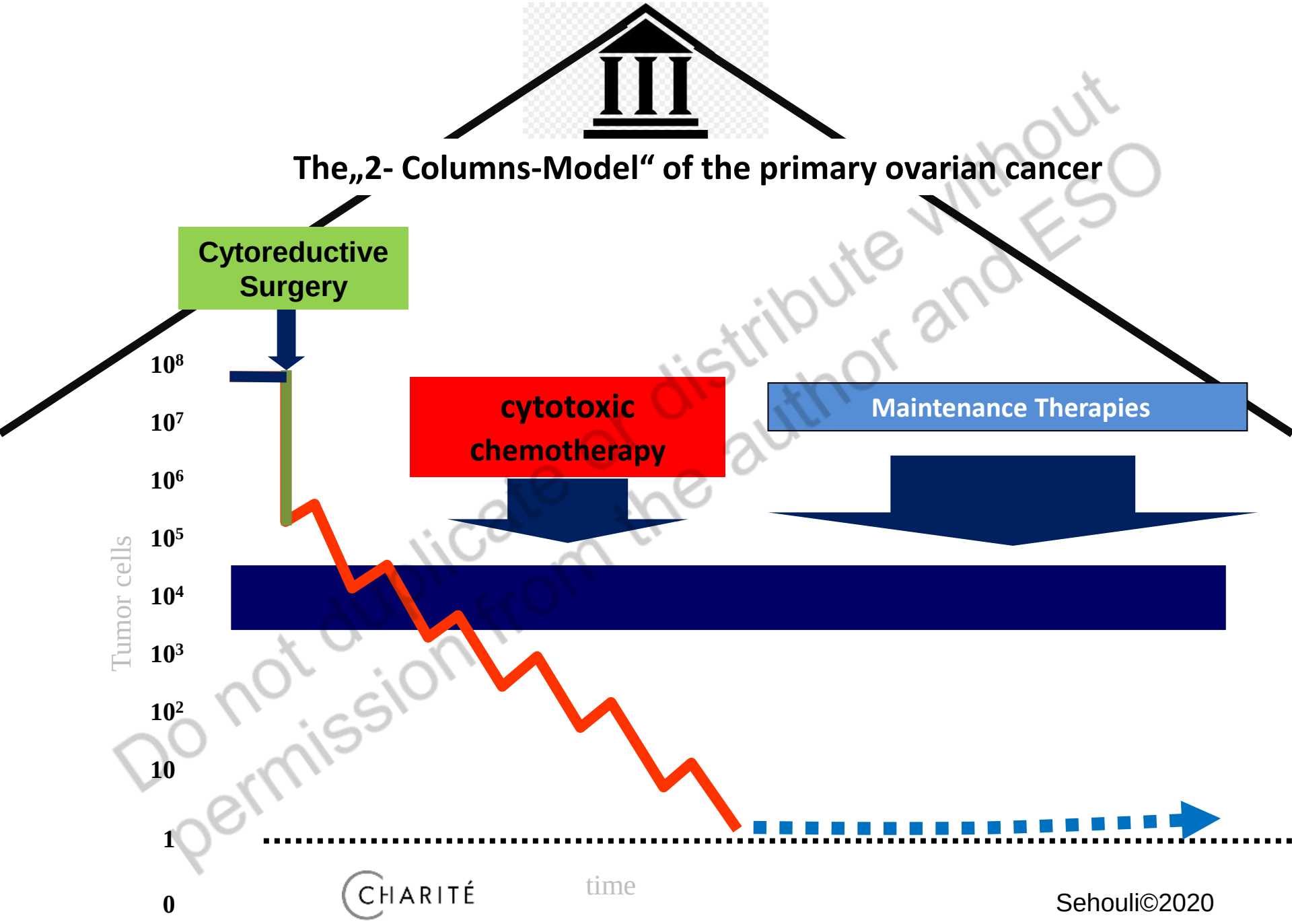


Grabowski et al. 2016

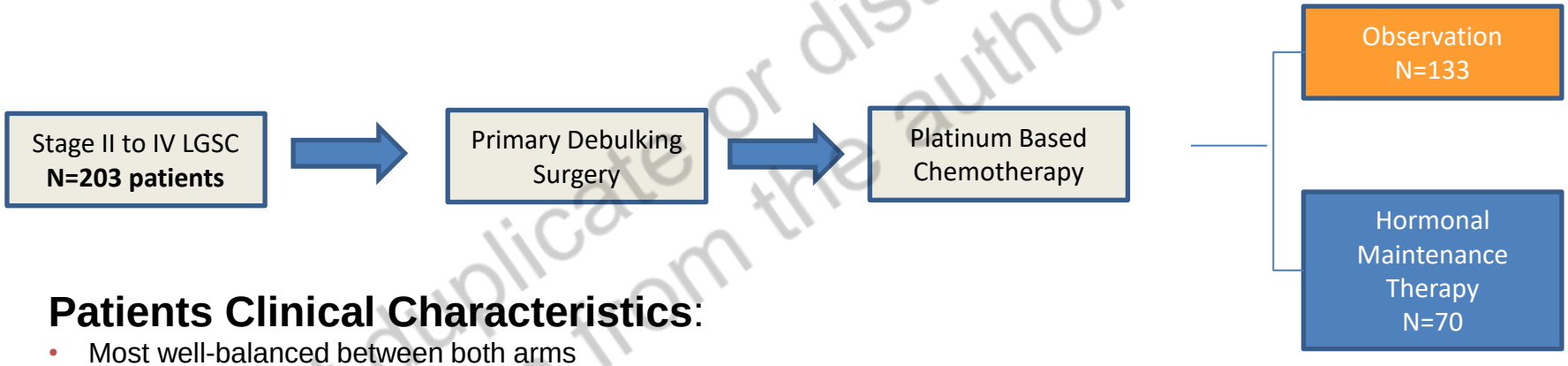
The„2- Columns-Model“ of the primary ovarian cancer



CHARITÉ

Journal of Clinical Oncology®

Hormonal Maintenance Therapy for Women With Low-Grade Serous Cancer of the Ovary or Peritoneum



Patients Clinical Characteristics:

- Most well-balanced between both arms
- Most patients Stage III disease
- **Significantly higher proportion of women in the HMT group had persistent tumor at completion of primary chemotherapy (60.0% v 8.3%).**

- Letrozole: 54.3%
- Tamoxifen: 28.6%
- Others: 17%

Gershenson DM, et al. J Clin Oncol.2017.

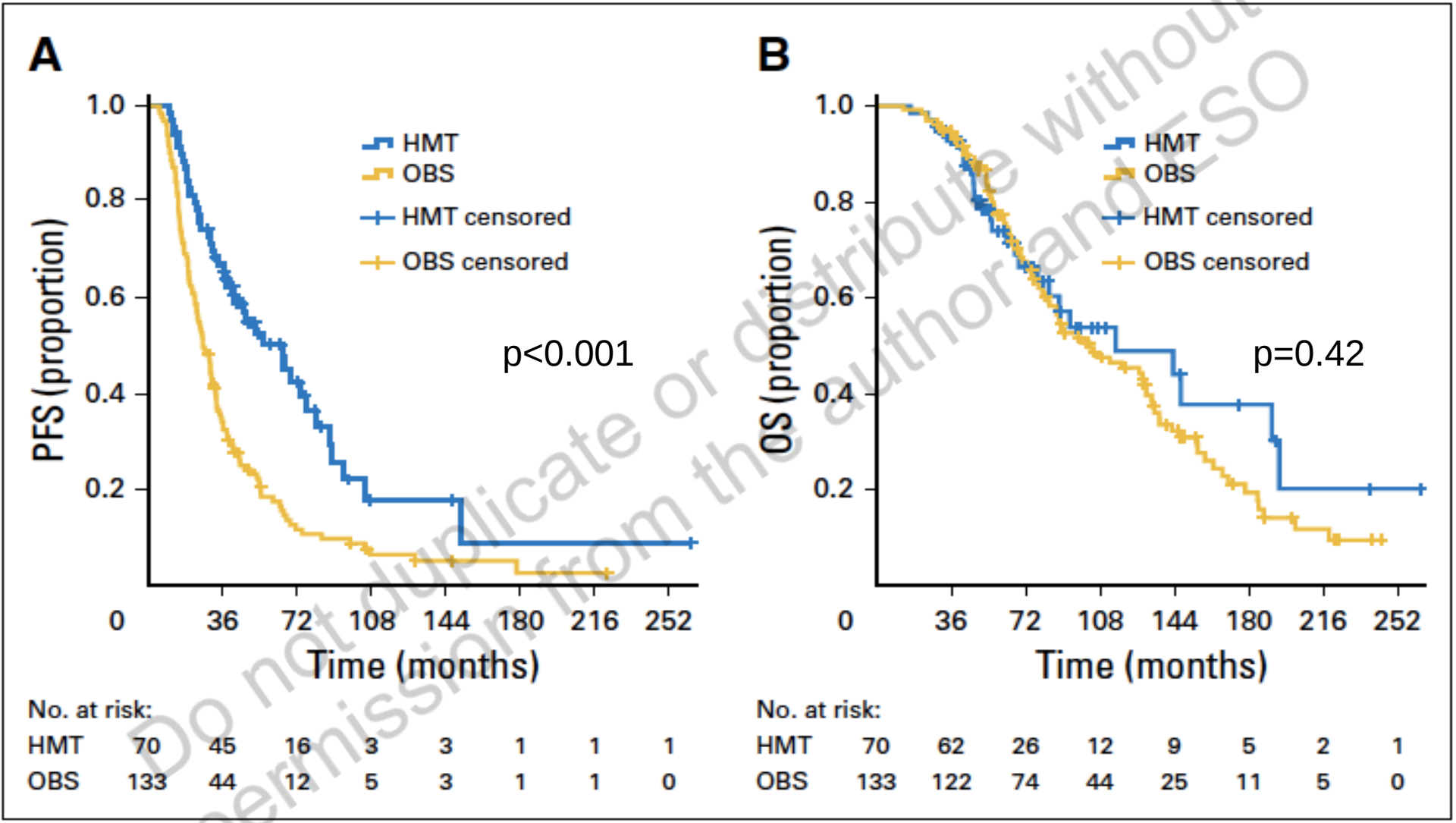
LGSOC and hormonal therapy

Table 1. Patient Demographic and Clinical Characteristics (N = 203)

Characteristic	HMT (n = 70), No. %	OBS (n = 133), No. %	
Primary site			.13
Ovary	48 (68.6)	104 (78.2)	
Peritoneum	22 (31.4)	29 (21.8)	
LGSC type			.01
De novo	58 (82.9)	125 (94.0)	
Recurrent LMP	12 (17.1)	8 (6.0)	
ER status‡			.67
Negative	1 (4.3)	2 (3.8)	
Positive	22 (95.7)	51 (96.2)	
PR status§			.39
Negative	6 (33.3)	23 (45.1)	
Positive	12 (66.7)	28 (54.9)	
FIGO stage			.04
II	1 (1.4)	8 (6.0)	
III	54 (77.1)	113 (85.0)	
IV	3 (4.3)	4 (3.0)	
Recurrent LMP	12 (17.1)	8 (6.0)	
Residual disease at end of primary surgery‖			.13
No gross disease	14 (22.2)	34 (33.3)	
Gross disease	49 (77.8)	68 (66.7)	
Platinum-based chemotherapy			.61
With taxane	57 (81.4)	112 (84.2)	
Without taxane	13 (18.6)	21 (15.8)	
Disease status at completion of chemotherapy¶			< .001
NED	28 (40.0)	121 (91.7)	
Persistent disease	42 (60.0)	11 (8.3)	

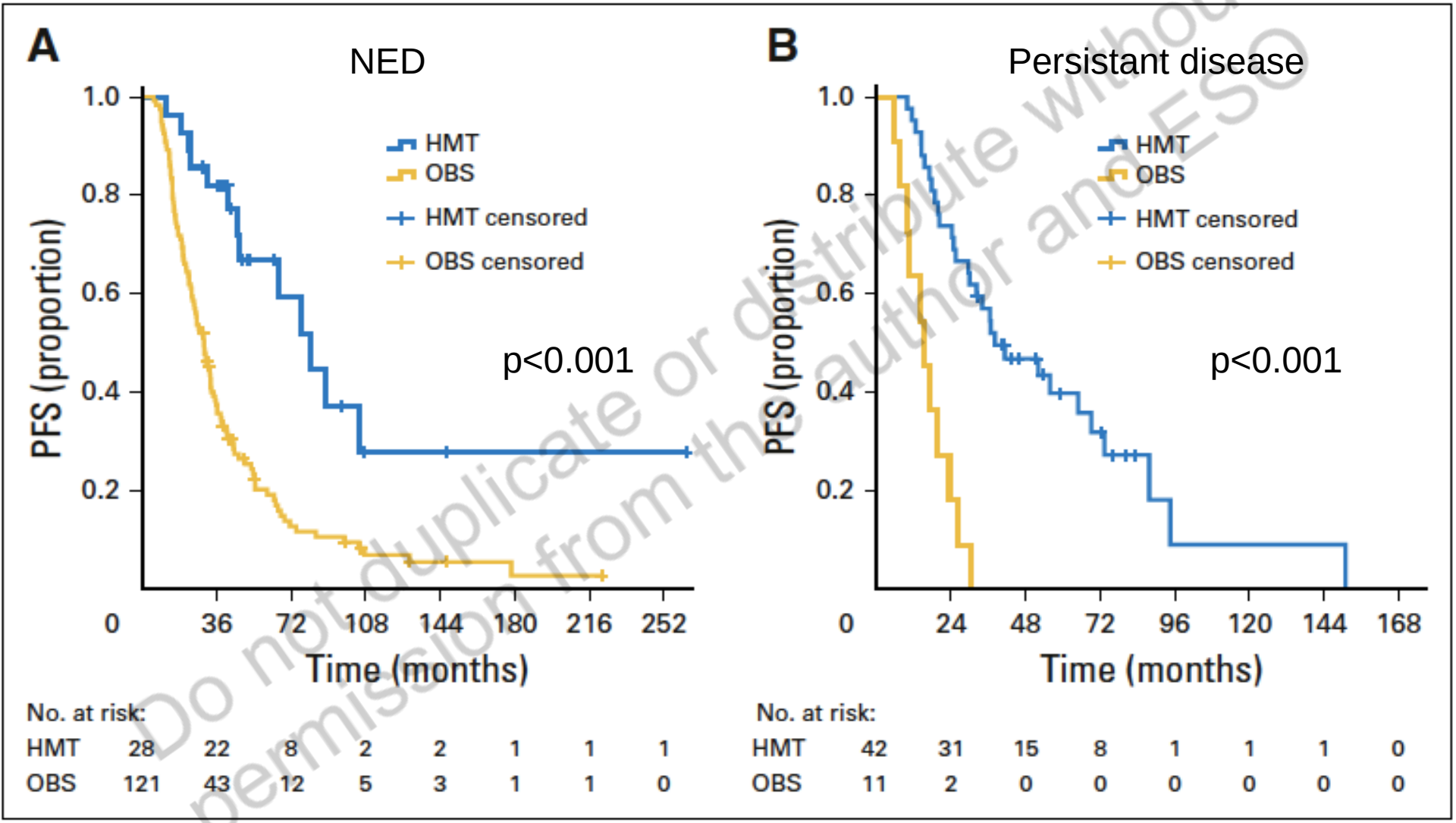
Gershenson et al. 2017

HMT and PFS/OS



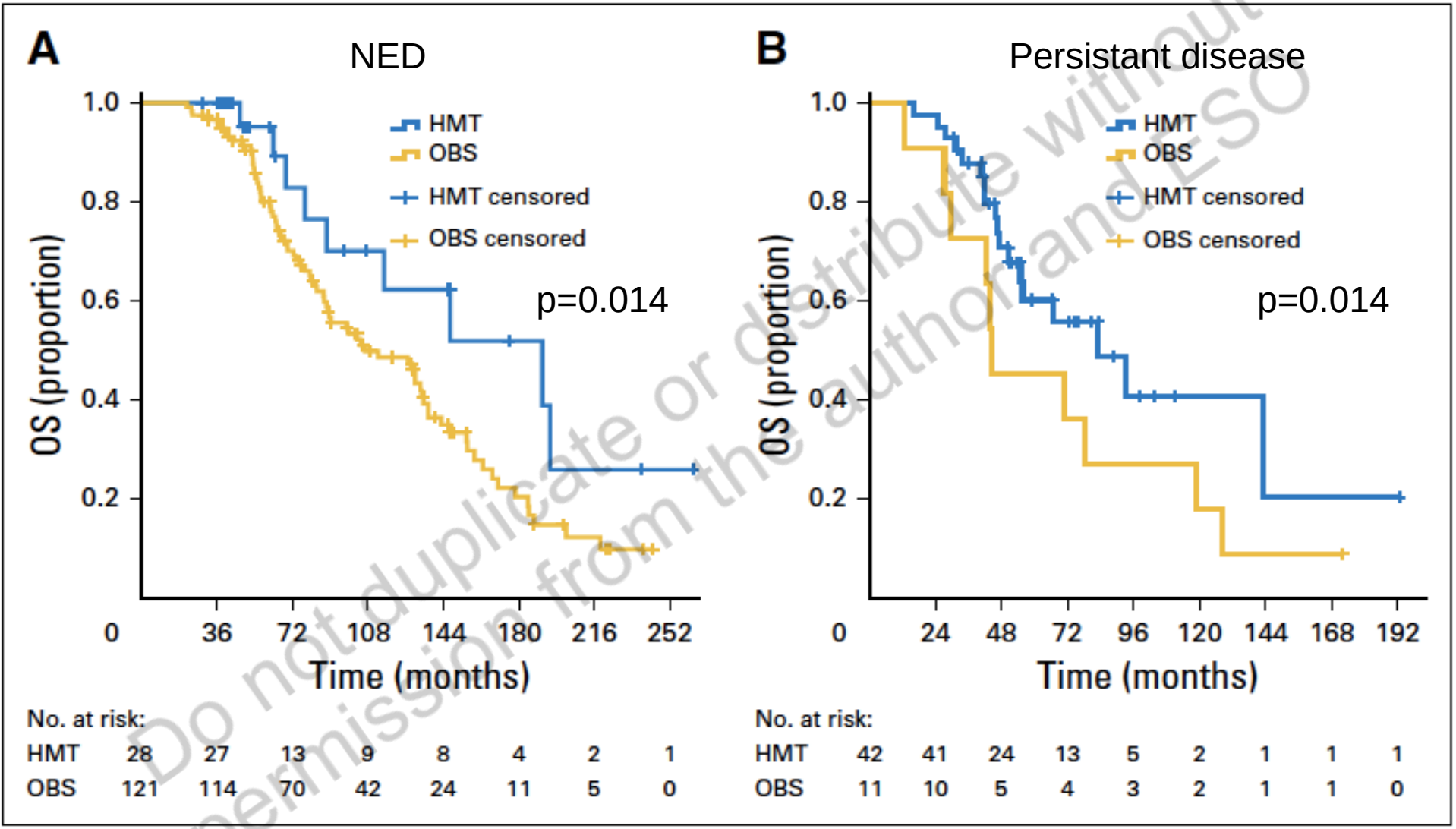
Gershenson et al. 2017

PFS and HMT according to disease



Gershenson et al. 2017

HMT and OS according to disease



Gershenson et al. 2017

Ki67 as a prognostic factor in low-grade serous ovarian cancer (LGSOC): a retrospective analysis of the Tumor Bank Ovarian Cancer /TOC)

Sehouli et al. 2017

PFS and OS according to Ki67 Expression

Ki67 Cut-Off: 7%

Fig.2 Progression-free-survival according to Ki67 value

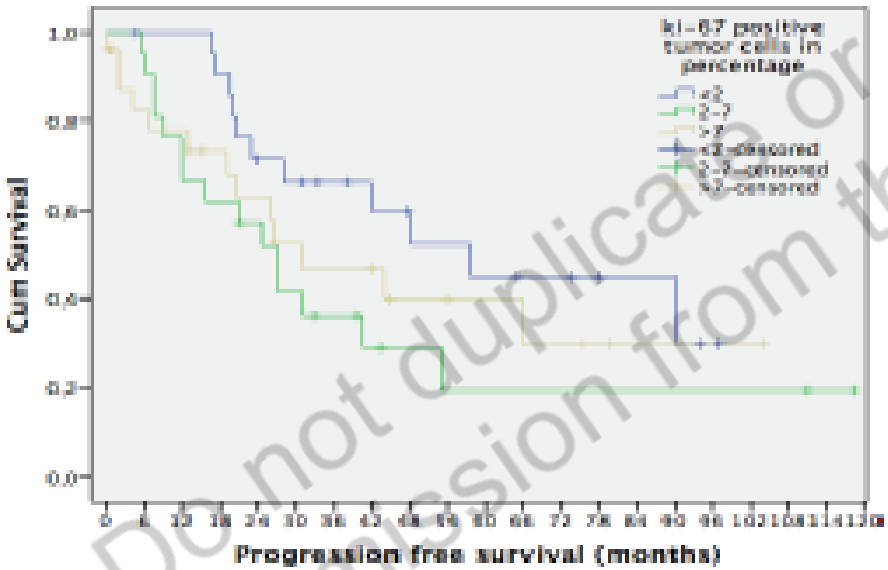
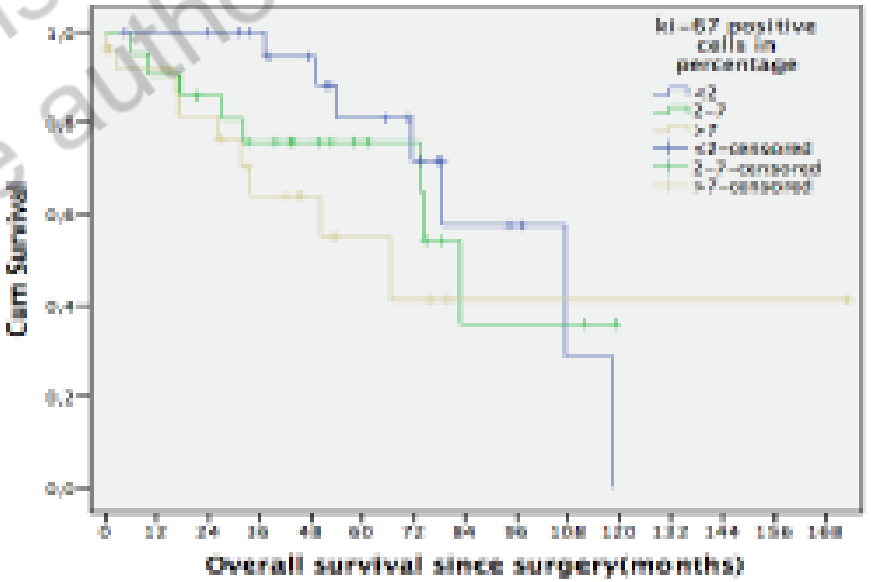


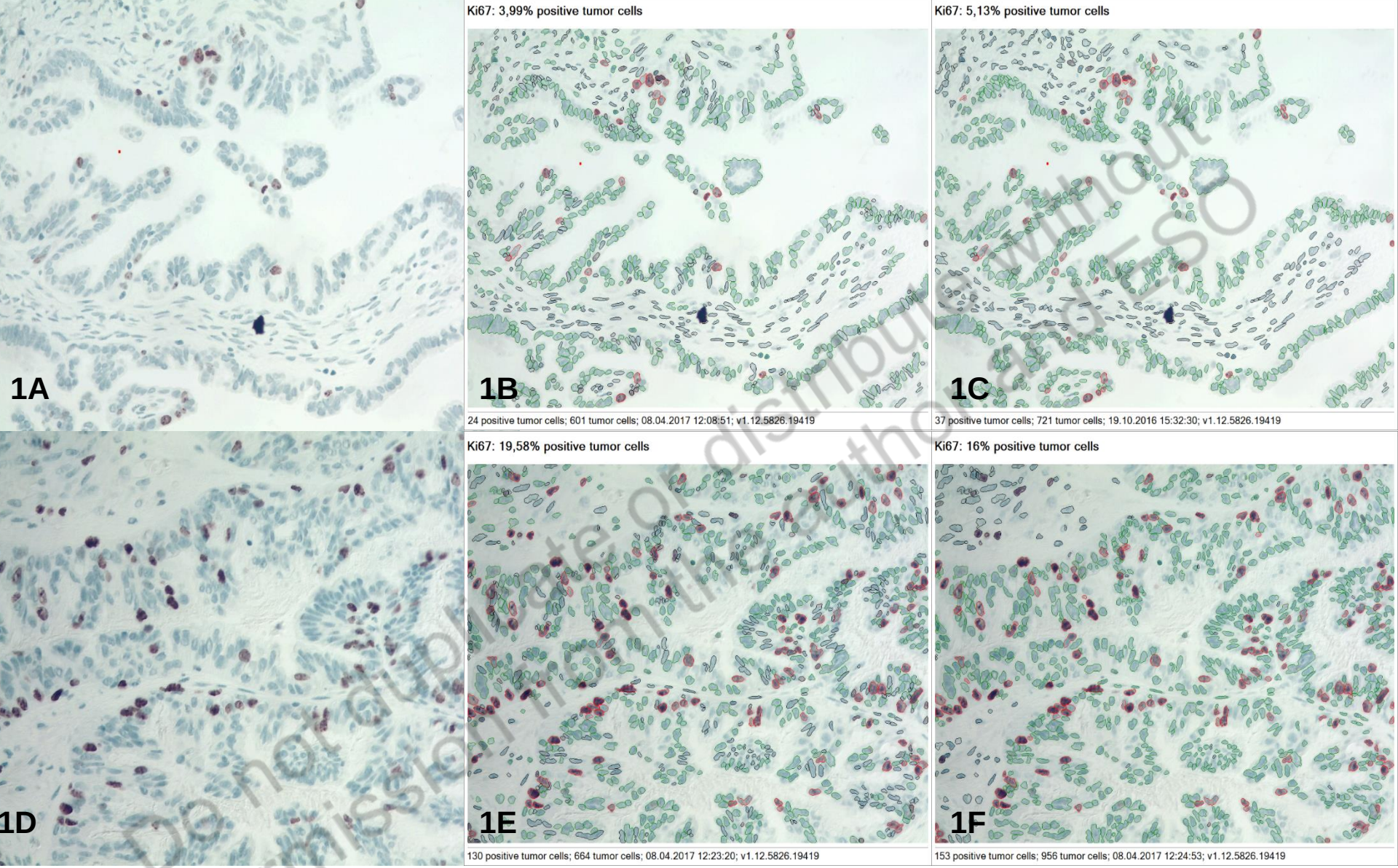
Fig. 3 Overall survival according to Ki67 value



Prognostic significance of Ki-67 levels and hormone receptor expression in low-grade serous ovarian carcinoma: an investigation of the Tumor Bank Ovarian Cancer Network.

Sehouli J, Braicu EI, Richter R, Denkert C, Jank P, Jurmeister PS, Kunze CA, Budczies J, Darb-Esfahani S, Schmitt WD, Traut A, Grabowski J, Taube ET, Plett H.

Hum Pathol. 2019



1A: Low-grade serous ovarian carcinoma IHC Ki67
1B: Initial Ki-67 evaluation by digital image analysis.
1C: Ki-67 evaluation after manual tumor/stroma separation Ki67
1D: Low-grade serous ovarian carcinoma IHC
1E: Initial Ki-67 evaluation by digital image analysis.
1F: Ki-67 evaluation after manual tumor/stroma separation

Parameters	Patients	Median	Range
Percentage of Ki67 positive cells in patients with no residual mass	53	3.59	0.28-26.07
Percentage of Ki67 positive cells in patients with residual mass **P=0.042**	16	8.01	0.43-83.51

PFS and OS according to Ki67 Expression

Fig.2 Progression-free-survival according to Ki67 value

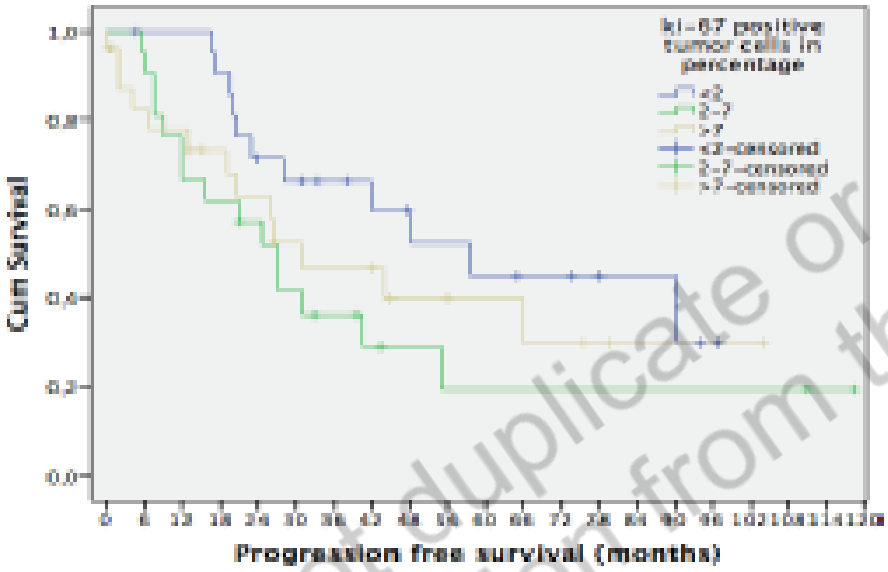
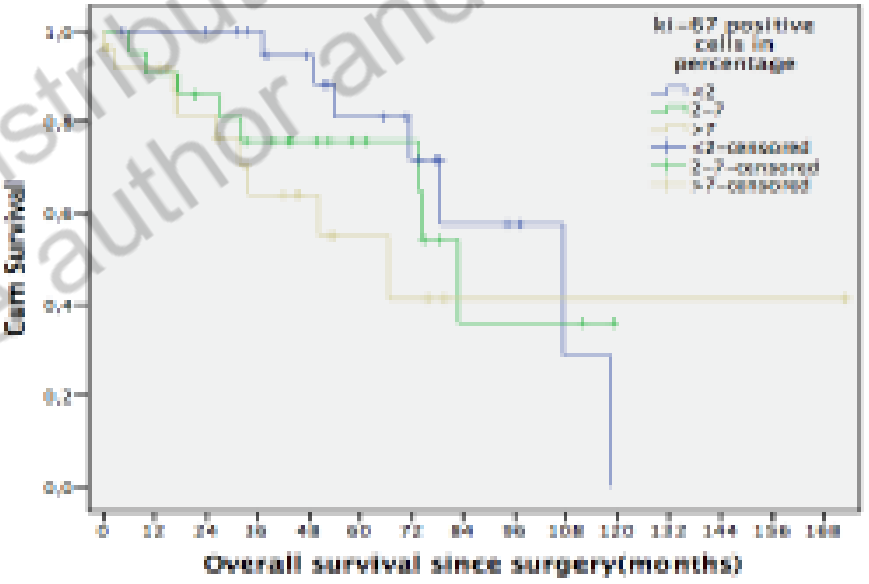


Fig. 3 Overall survival according to Ki67 value



Relapse of Low Grade Ovarian Cancer (Charité-Algorythmus)

- Low grade Ovarian Cancer
- Reference Pathology? (allways if primary diagnosis before 2014 and in grade 2 classification)

- Study Option?
- Molecular Profiling/immunohistochemistry (Ki-67)

- No: PARP (HRD?)
- Bev: yes
- Antihormonal Therapy (Maintenance therapy?)
- Trametenib

2019 Sep;154(3):539-546.

Survival and prognostic factors in patients with recurrent low-grade epithelial ovarian cancer: An analysis of five prospective phase II/III trials of NOGGO metadata base

E Canaz[1], J P Grabowski[2], R Richter[2], E I Braicu[2], R Chekerov[2], J Sehouli[3]

- **Results.** Out of 1050 patients having the first recurrence, 42(4%) patients had low-grade and 1008(96%) patients had high-grade disease. In the subgroup of platinum-sensitive recurrences, progression-free survival (PFS) (*8.7m vs 9.7m, p=0.7*) and overall survival (OS) (23.9m vs 24.8m, *p=0.9*) did not differ between low-grade and high-grade diseases. In platinum-resistant recurrences, patients with low-grade ovarian cancer had significantly better PFS (7.6m vs 3.6m, *p=0.03*) and OS (41.9m vs 9.5m *p=0.002*) in comparison to those with high-grade cancer. At low-grade EOC, there were no significant PFS (*p=0.91*) and OS (*p=0.25*) differences between platinum-sensitive and –resistant recurrences. Patients with low-grade non-serous histology had lower PFS with compared to those with low-grade serous histology (*p=0.004*). At cox regression analysis presence of ascites and residual disease after secondary cytoreductive surgery were independently associated with poor PFS within low-grade recurrent EOC.
- **Conclusion.** Our study indicates, platinum sensitivity does not have any prognostic significance at recurrent low-grade EOC and non-serous histology is associated with poorer outcome at recurrence. Secondary surgical cytoreduction to no-gross residual disease and ascites are independently associated with disease progression.

Phase III Low Grade Serous Ovarian Cancer

Pat. mit rezidiverten oder persistierenden Low-grade serösen Karzinomen des Ovars, der Tuben oder des Peritoneums

nach vorheriger platin-haltiger CTX,
aber nicht mehr als 3 vorherige CTX,
unbegrenzt vorherige Hormontherapie

N = 300

Randomisation 2:1

Stratifikation
Platin-freies Interval:
≤6 Monate vs. > 6 Monate
systm. Vor-CTX:
1-2 vs. >2

MEK162
45mg BID

Paclitaxel 80 mg/m² d1,8, 15 q 4 wks, or
PLD 40 mg/m² q 4 wks, or
Topotecan 1,25 mg/m² d1-5 q 3 wks

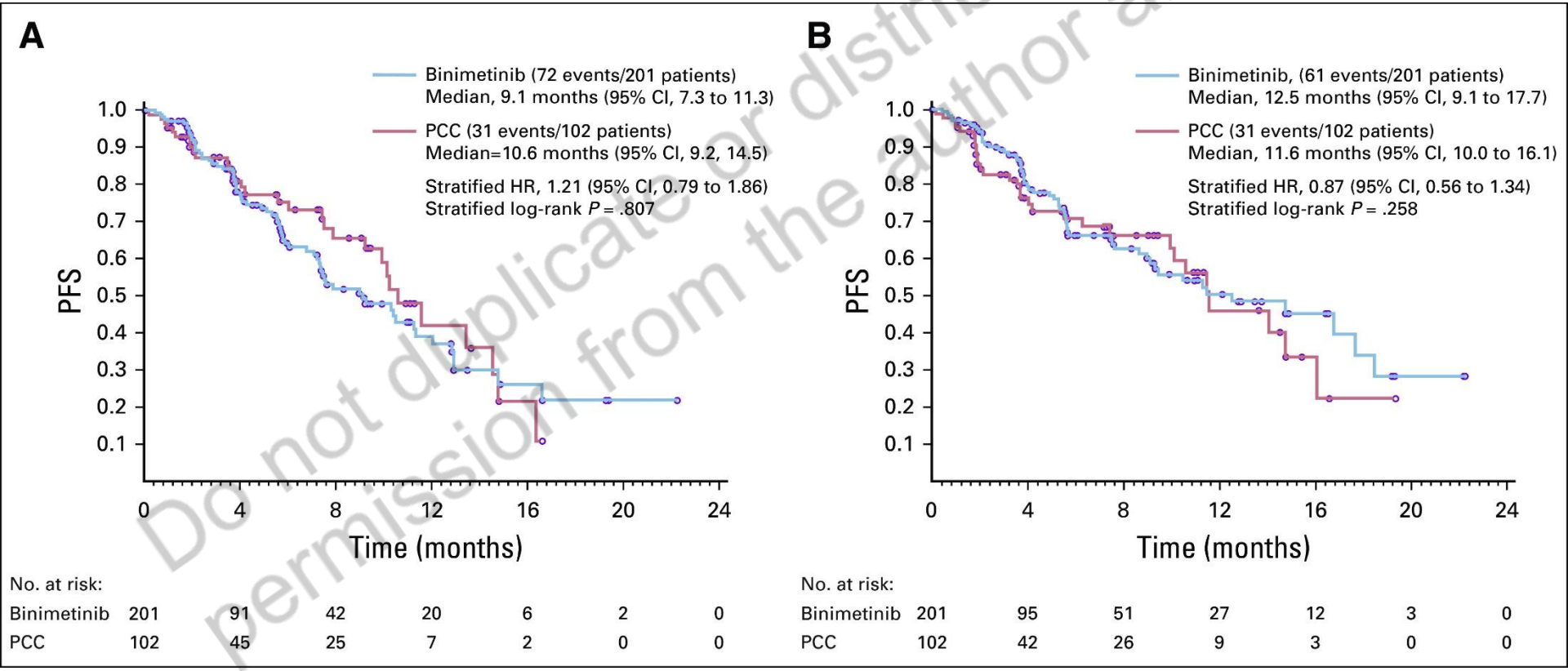
Primarer Endpunkt: PFS (HR = 0.60, 7 vs 11.67 Monate)
sekundärer Endpunkt: OS
Andere sekundäre Endpunkte: ORR, DOR, DCR, Safety, QOL, TR (Prädiktionsmarker)

ENGOT Model: C

J Clin Oncol. 2020 Nov 10; 38(32): 3753–3762.

MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum

Bradley J. Monk, MD,[1] Rachel N. Grisham, MD,[2] Susana Banerjee, PhD,[3] Elsa Kalbacher, MD,[4] Mansoor Raza Mirza, MD,[5] Ignacio Romero, MD,[6] Peter Vuylsteke, MD,[7,8] Robert L. Coleman, MD,[9] Felix Hilpert, MD,[10] Amit M. Oza, MD,[11] Anneke Westermann, MD, PhD,[12] Martin K. Oehler, MD, PhD,[13] Sandro Pignata, MD, PhD,[14] Carol Aghajanian, MD,[1] Nicoletta Colombo, MD,[15] Esther Drill, DrPH,[2] David Cibula, MD, PhD,[16] Kathleen N. Moore, MD,[17] Janna Christy-Bittel, MSN,[18] Josep M. del Campo, MD,[19] Regina Berger, PhD,[20] Christian Marth, MD, PhD,[21] Jalid Sehouli, MD,[22] David M. O'Malley, MD,[23] Cristina Churruca, MD,[24] Adam P. Boyd, PhD,[18] Gunnar Kristensen, MD, PhD,[25] Andrew Clamp, MD, PhD,[26] Isabelle Ray-Coquard, MD, PhD,[27] and Ignace Vergote, MD, PhD[28]

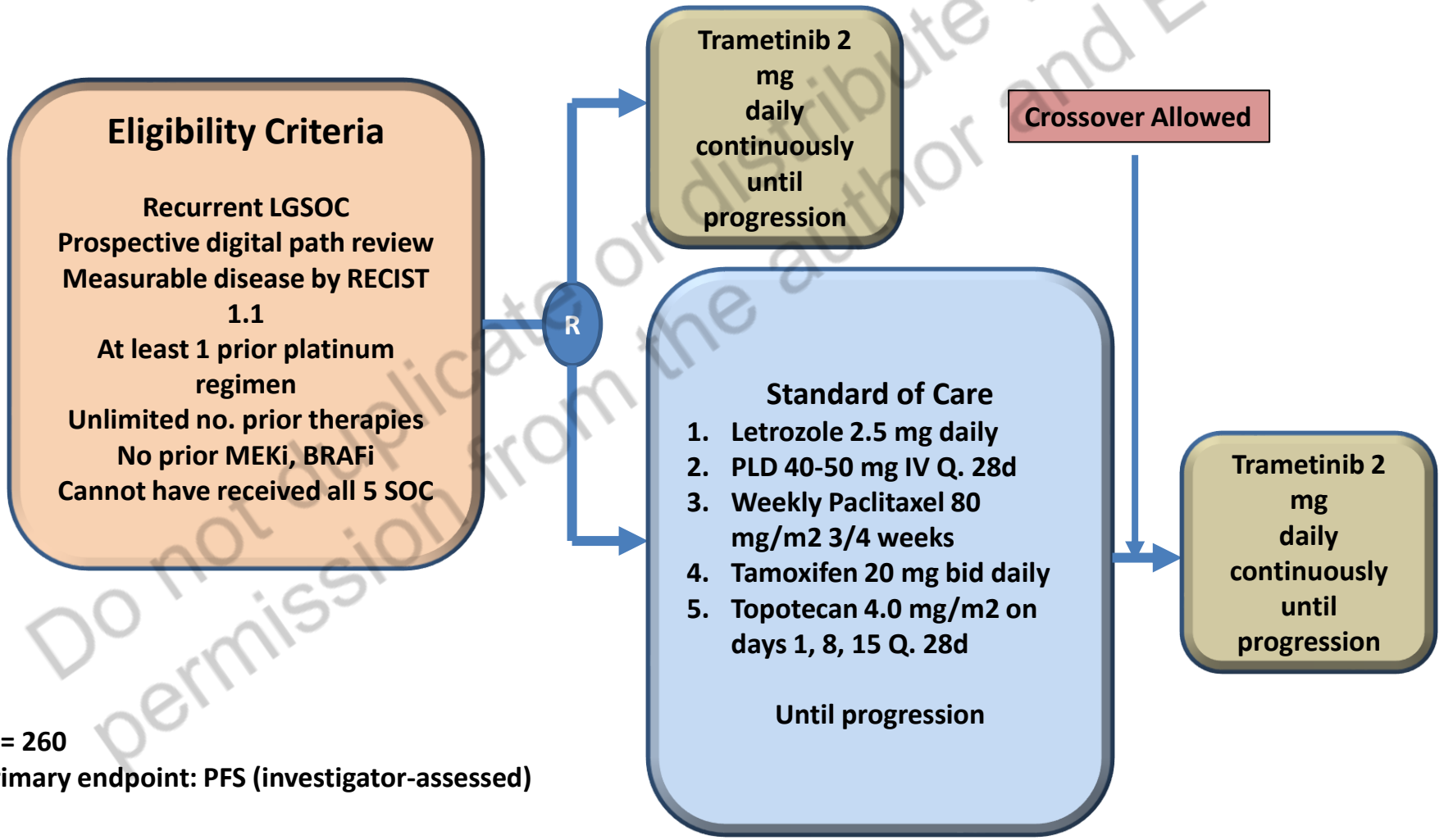


A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer

D M Gershenson, A Miller, W Brady, J Paul, K Carty, W Rodgers, D Millan, R L Coleman, K N Moore, S Banerjee, K Connolly, A A Secord, D M O'Malley, O Dorigo, S Gaillard, H Gabra, P Hanjani, H Huang, L Wenzel, C Gourley

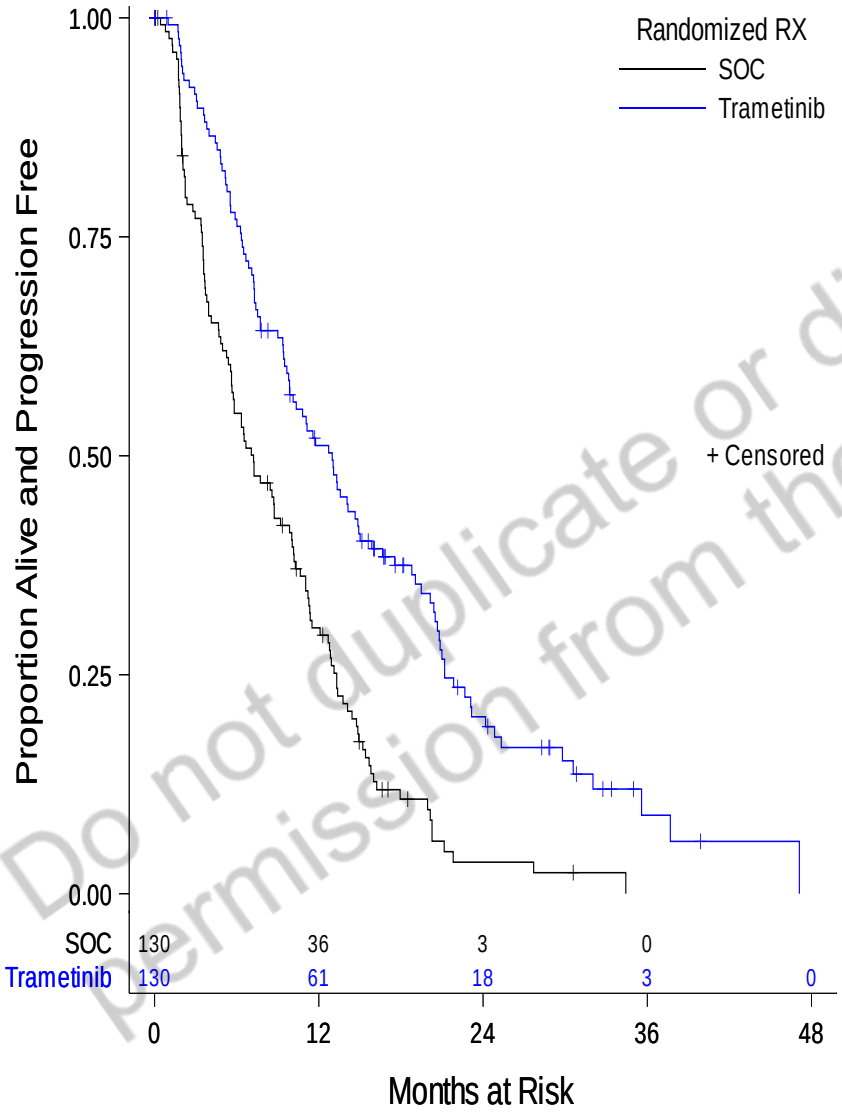
ClinicalTrials.gov Identifier: NCT02101788
This study was sponsored by NRG Oncology
CRADA Partner: Novartis

Study Design



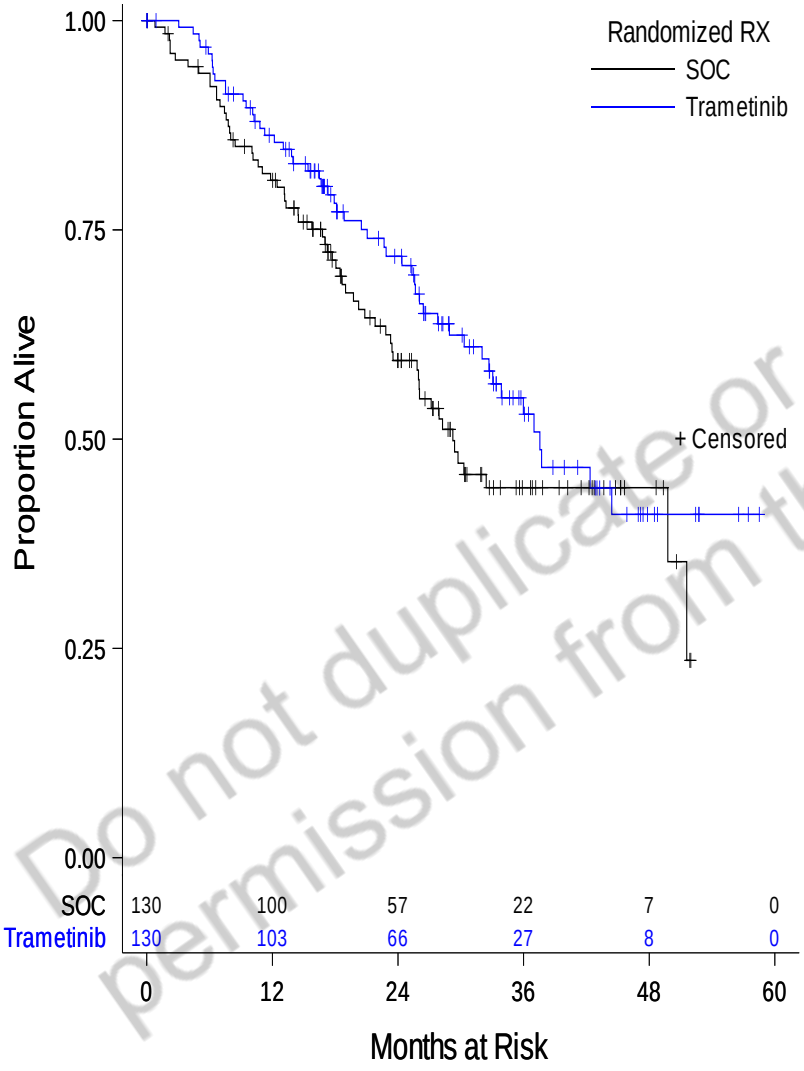
N = 260
Primary endpoint: PFS (investigator-assessed)

Progression-Free Survival



	Trametinib	Control (SOC)
Median (Months) 95% CI	13.0 (9.9 – 15.0)	7.2 (5.6 - 9.9)
Hazard Ratio 95% CI	0.48 (0.36 – 0.64)	
One-sided p-value	< 0.0001	

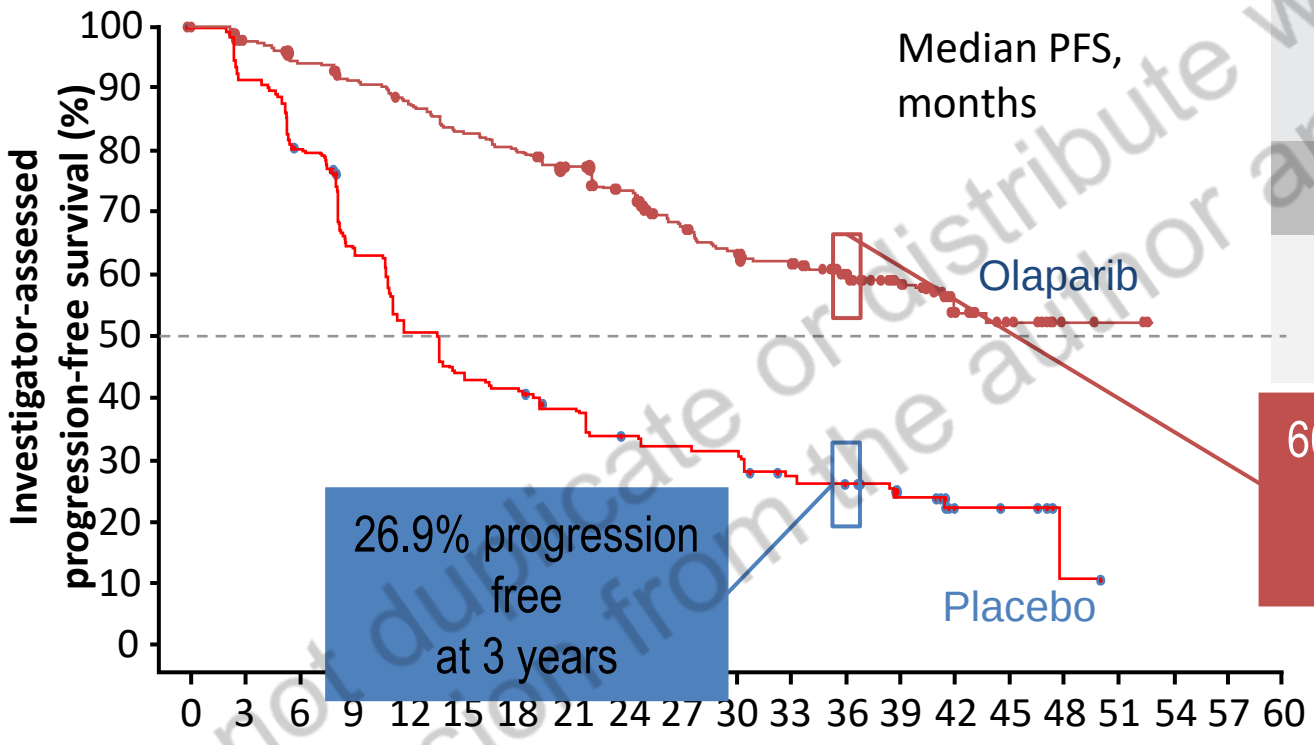
Overall Survival



	Trametinib	Control (SOC)
Median (Months) 95% CI	37.0 (30.3 to NE)	29.2 (23.5 to 51.6)
Hazard Ratio 95% CI	0.75 (0.51 – 1.11)	
One-sided p-value	0.054	

*The OS hazard in the SOC arm includes the effect of trametinib among crossover patients.

PFS by investigator assessment



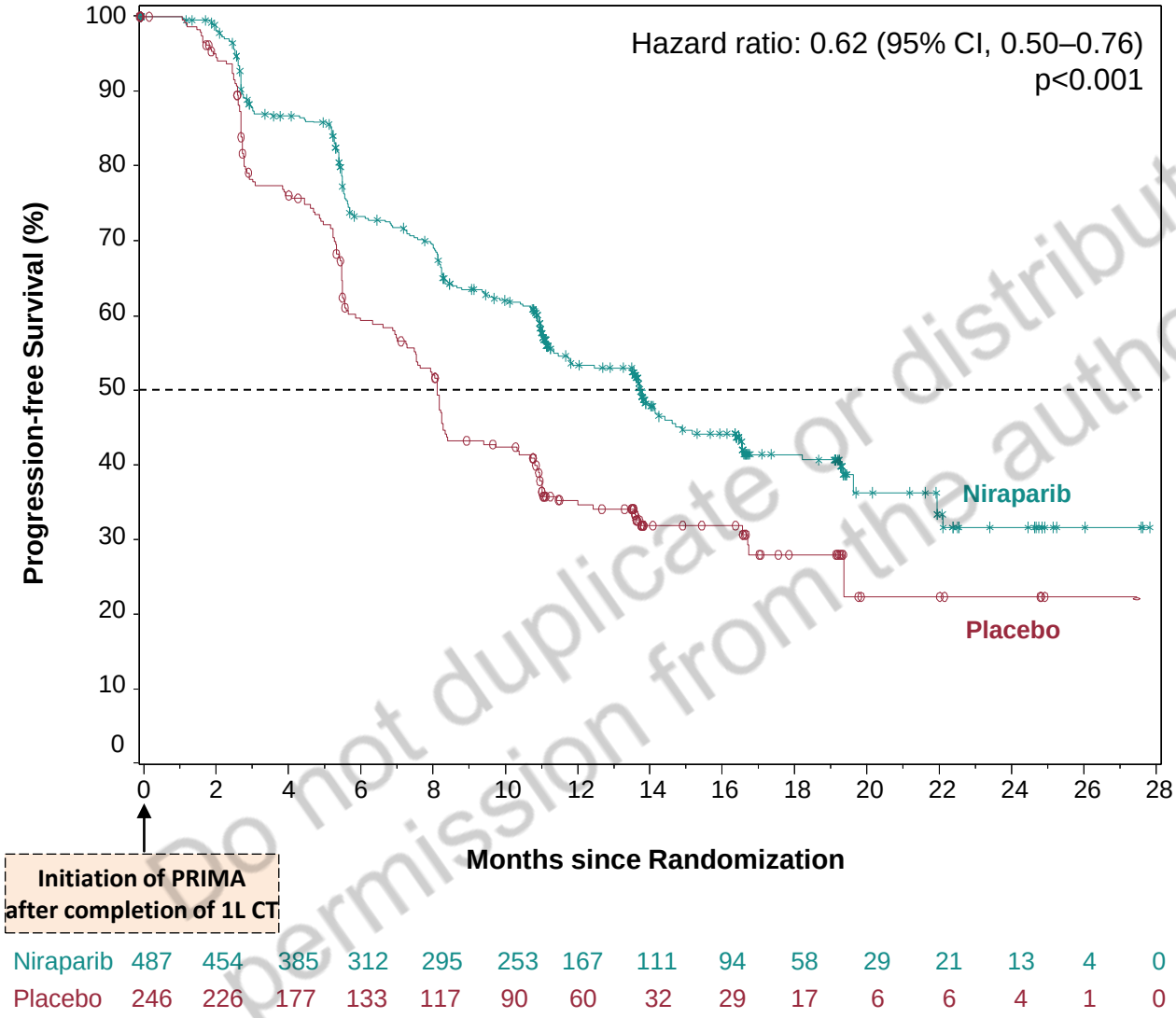
	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

No. at risk

Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

CI, confidence interval; NR, not reached

PRIMA Primary Endpoint, PFS Benefit in the Overall Population

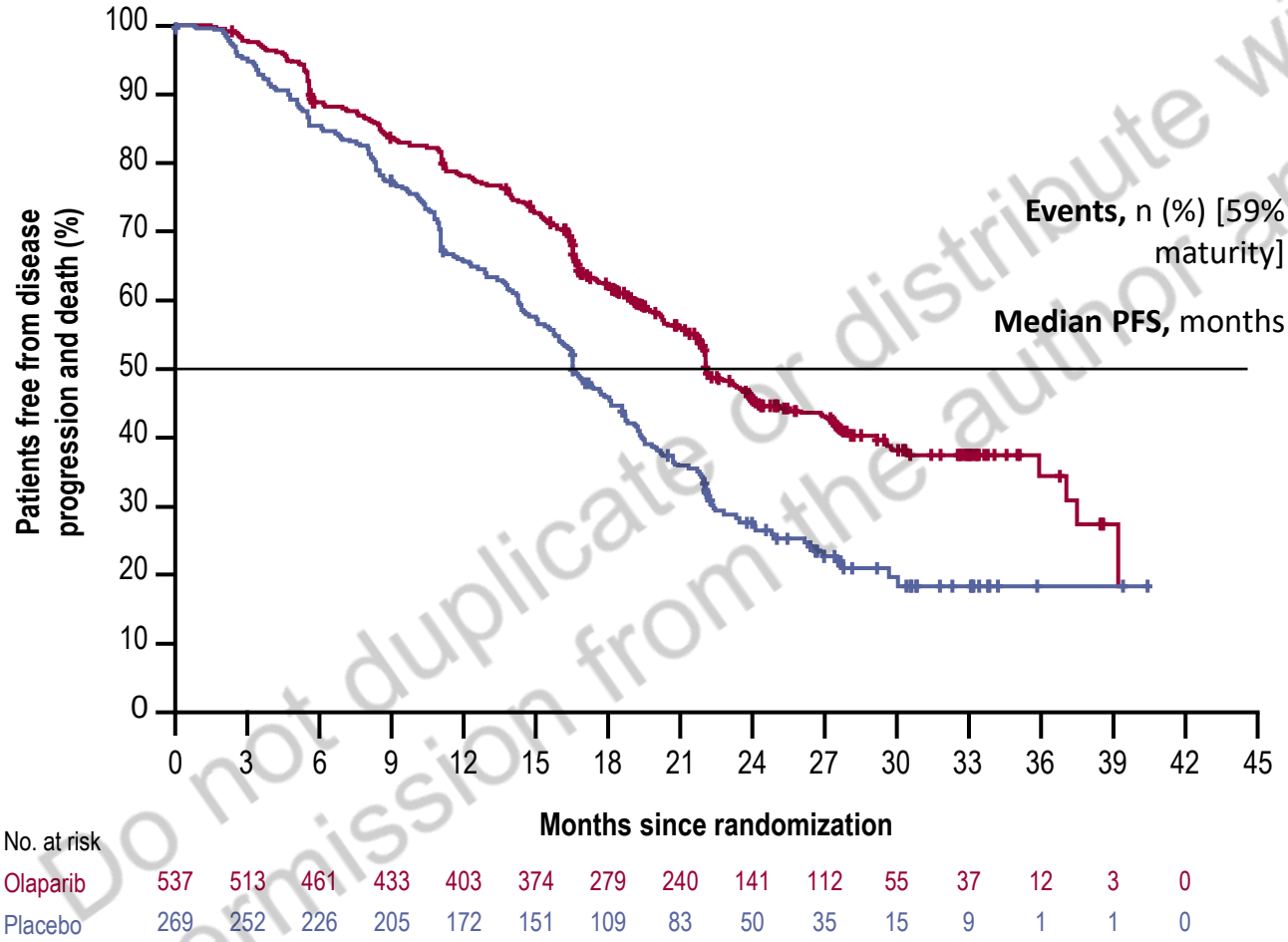


38% reduction in hazard of relapse or death with niraparib

	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months	13.8	8.2
(95% CI)	(11.5–14.9)	(7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

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

TREATMENT OPTION IN LOW GRADE OVARIAN CANCER

PRIMARY
SURGERY/
NO NEOADJUVANT APROACH!

PACLITAXEL/CARBOPLATIN

BEVACIZUMAB

AROMATASEINHIBITOR

RELAPSE

KI-67/MOLECULAR TUMOR BOARD

Peg. Lip. Dox/CARBOPLATIN

PACLITAXEL/CARBOPLATIN

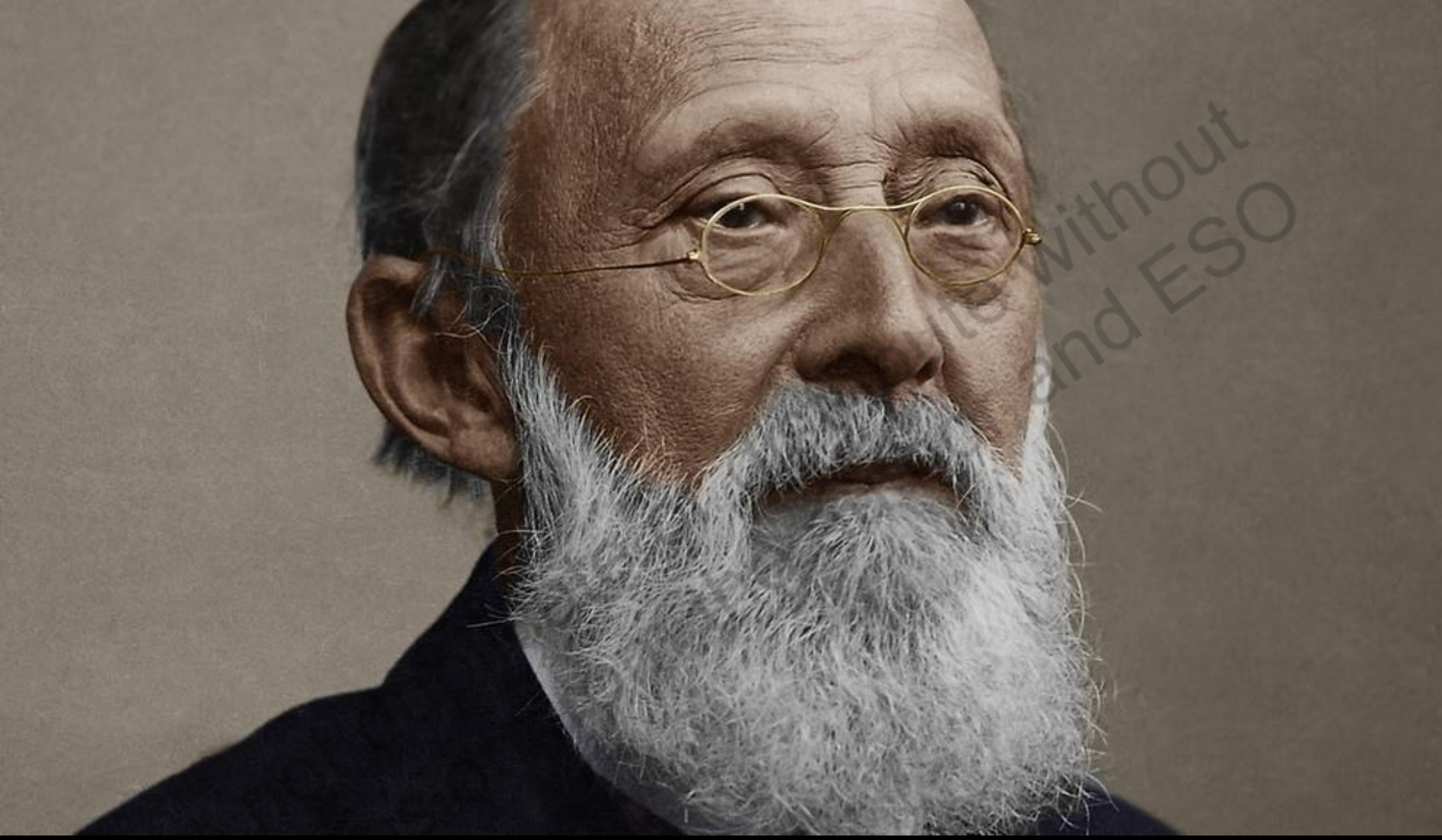
GEMCITABINEL/CARBOPLATIN

Peg.lip.Doc/Trabectidin

BEVACIZUMAB

TRAMETINIB

AROMATASEINHIBITOR



Rudolf Virchow (1821-1902)