Over Kanserinde Yeni Tedavi Seçenekleri

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Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Sunum Planı

- Over Kanseri insidans ve mortalite
- Genetik risk faktörleri
- Evreleme
- Prognostik faktörler
- Adjuvan Tedavi
- İdame tedavi
- Platine duyarlı hastalarda tedavi
- Platine dirençli hastalarda tedavi
- Yeni tedaviler(PARP inhibitörleri, İmünoterapi)

Over Kanseri İnsidans ve Mortalite

Cancer Stat Facts: Ovarian Cancer

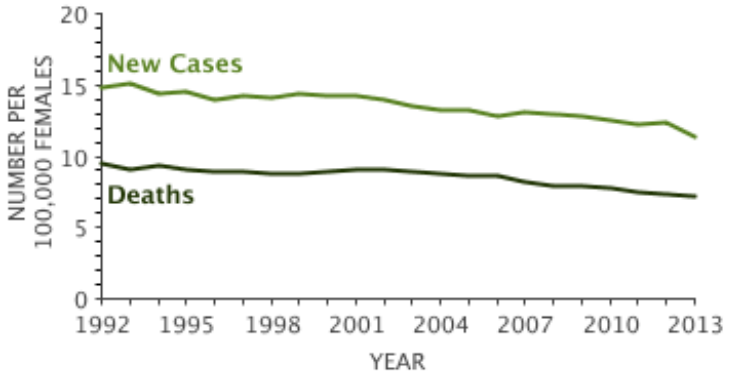
Expand All | Collapse All

Statistics at a Glance

Show Less –

At a Glance

Estimated New Cases in 2016	22,280
% of All New Cancer Cases	1.3%
Estimated Deaths in 2016	14,240
% of All Cancer Deaths	2.4%



Percent Surviving 5 Years

46.2%

2006–2012

Number of New Cases and Deaths per 100,000: The number of new cases of ovarian cancer was 11.9 per 100,000 women per year. The number of deaths was 7.5 per 100,000 women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

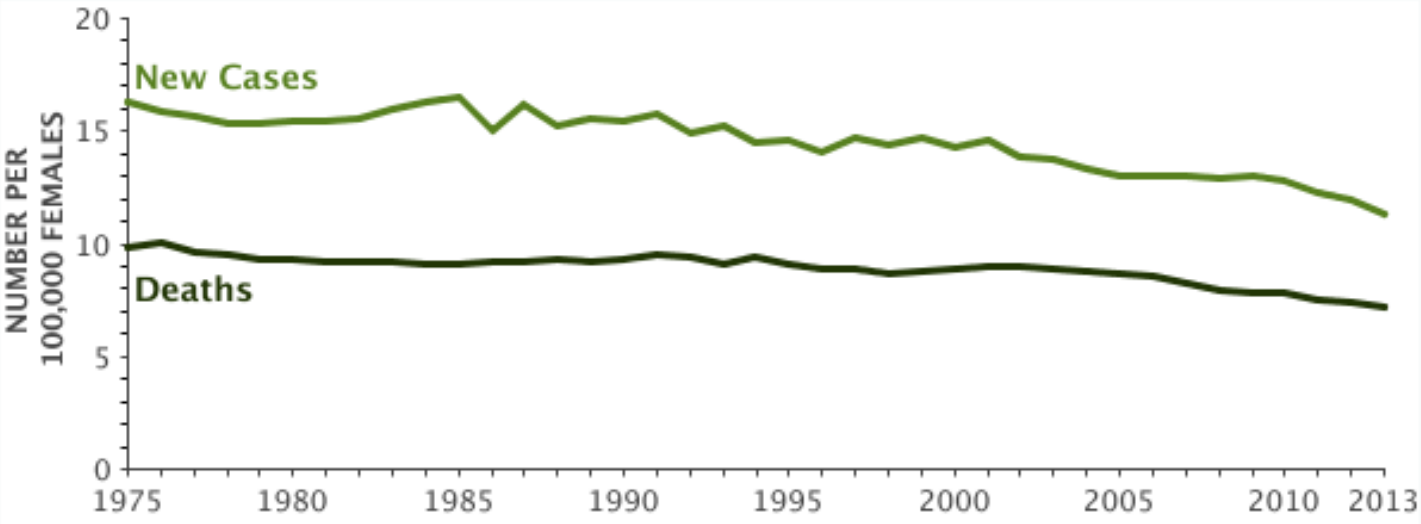
Lifetime Risk of Developing Cancer: Approximately 1.3 percent of women will be diagnosed with ovarian cancer at some point during their lifetime, based on 2011–2013 data.

Prevalence of This Cancer: In 2013, there were an estimated 195,767 women living with ovarian cancer in the United States.

Over Kanseri İnsidans ve Mortalite

New Cases, Deaths and 5-Year Relative Survival

View Data Table



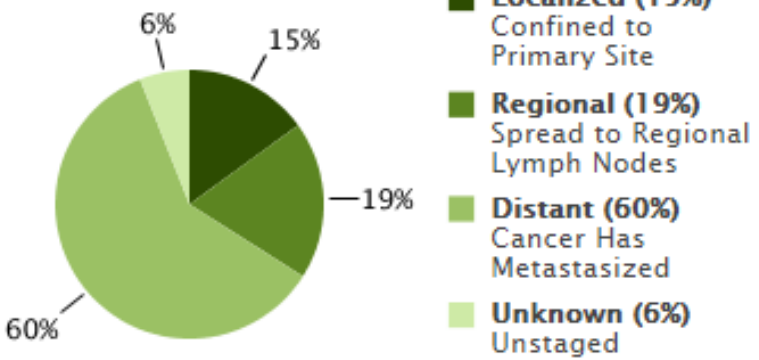
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	33.7%	38.2%	38.7%	40.4%	42.2%	43.0%	44.3%	46.2%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Females. Rates are Age-Adjusted.

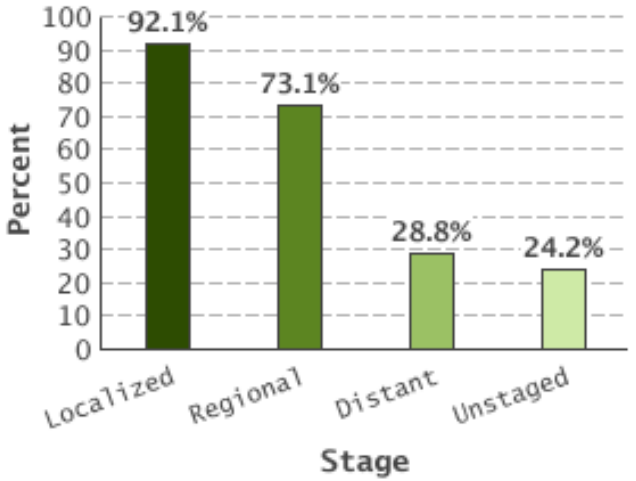
Over Kanseri İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Ovarian Cancer

Percent of Cases by Stage

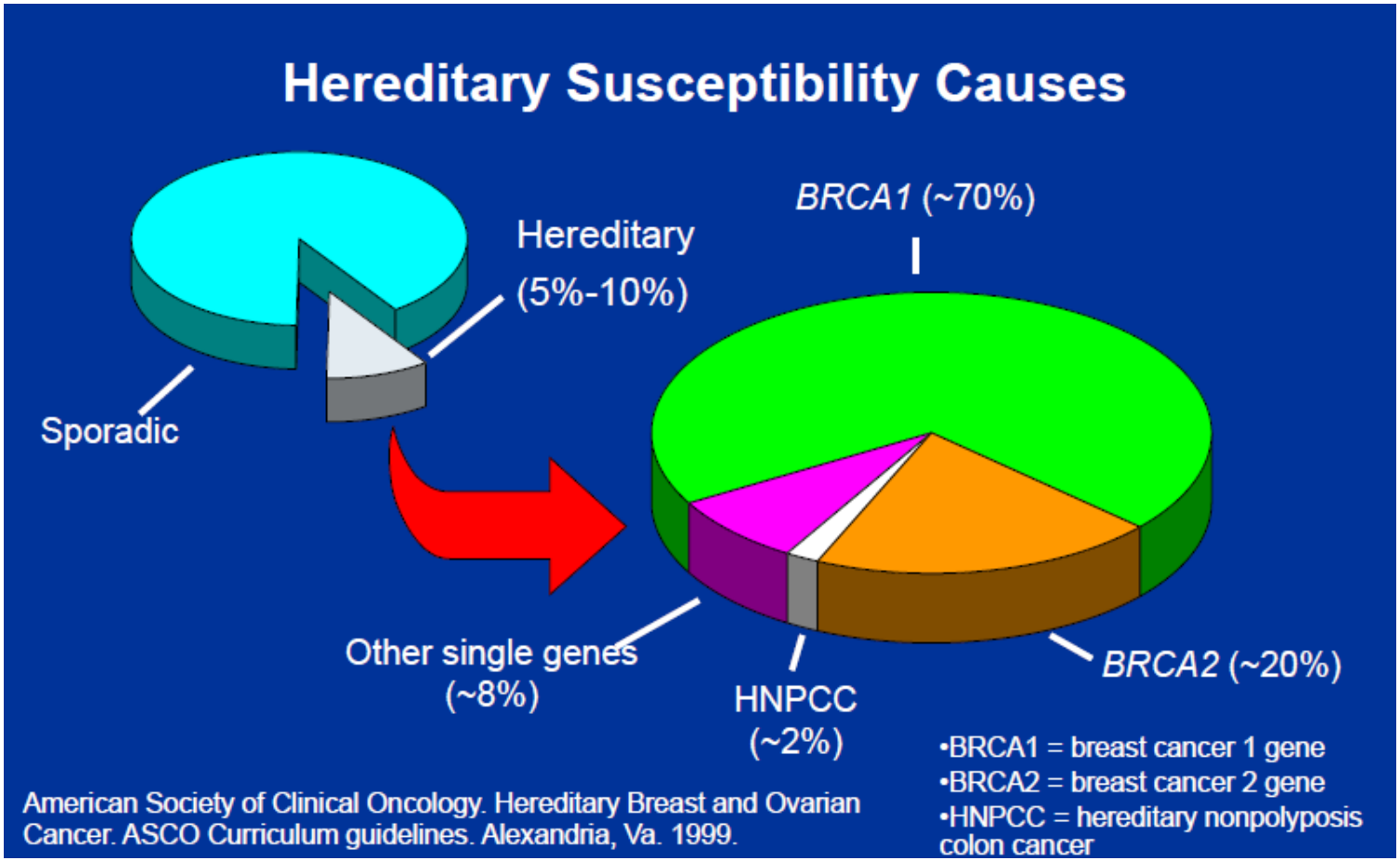


5-Year Relative Survival



SEER 18 2006-2012, All Races, Females by SEER Summary Stage 2000

Over Kanserinde Genetik Risk Faktörleri



Epitelyal Over Kanseri

Life Time Risks of Cancers Associated with Specific Genes

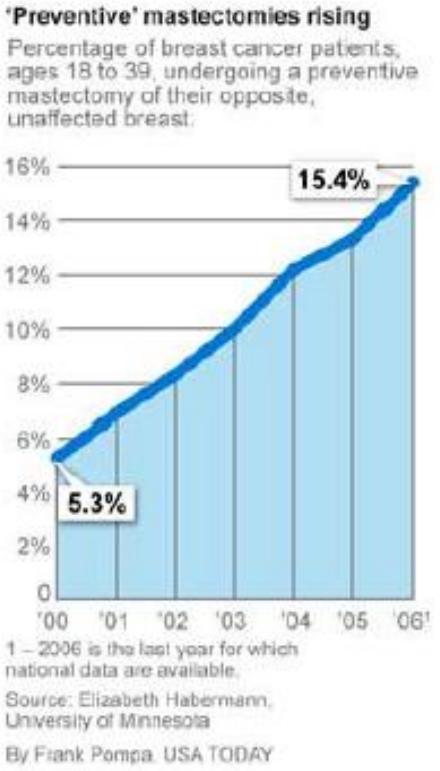
Cancer	*BRCA1*	*BRCA2*	*MMR*
Breast	35-60%	30-55%	No inc
Ovarian	30-40%	15-25%	6-20%
Endometrial	No inc	No inc	40-60%

1. Chen S, et al. *J Clin Oncol. 2007:25*(11):1329-1333.
2. Aarnio M, et al. *Int J Cancer.* 1999:81(2):214-218.

- BRCA1 = breast cancer 1 gene
- BRCA2 = breast cancer 2 gene
- HNPCC = hereditary nonpolyposis colorectal cancer
- MMR = mismatch repair

Onkolojide Jolie Etkisi

Jolie Revelation



NYT op/ed article
May 14th 2013

Over Kanserinde Risk Faktörleri

Risk Factors: Family History

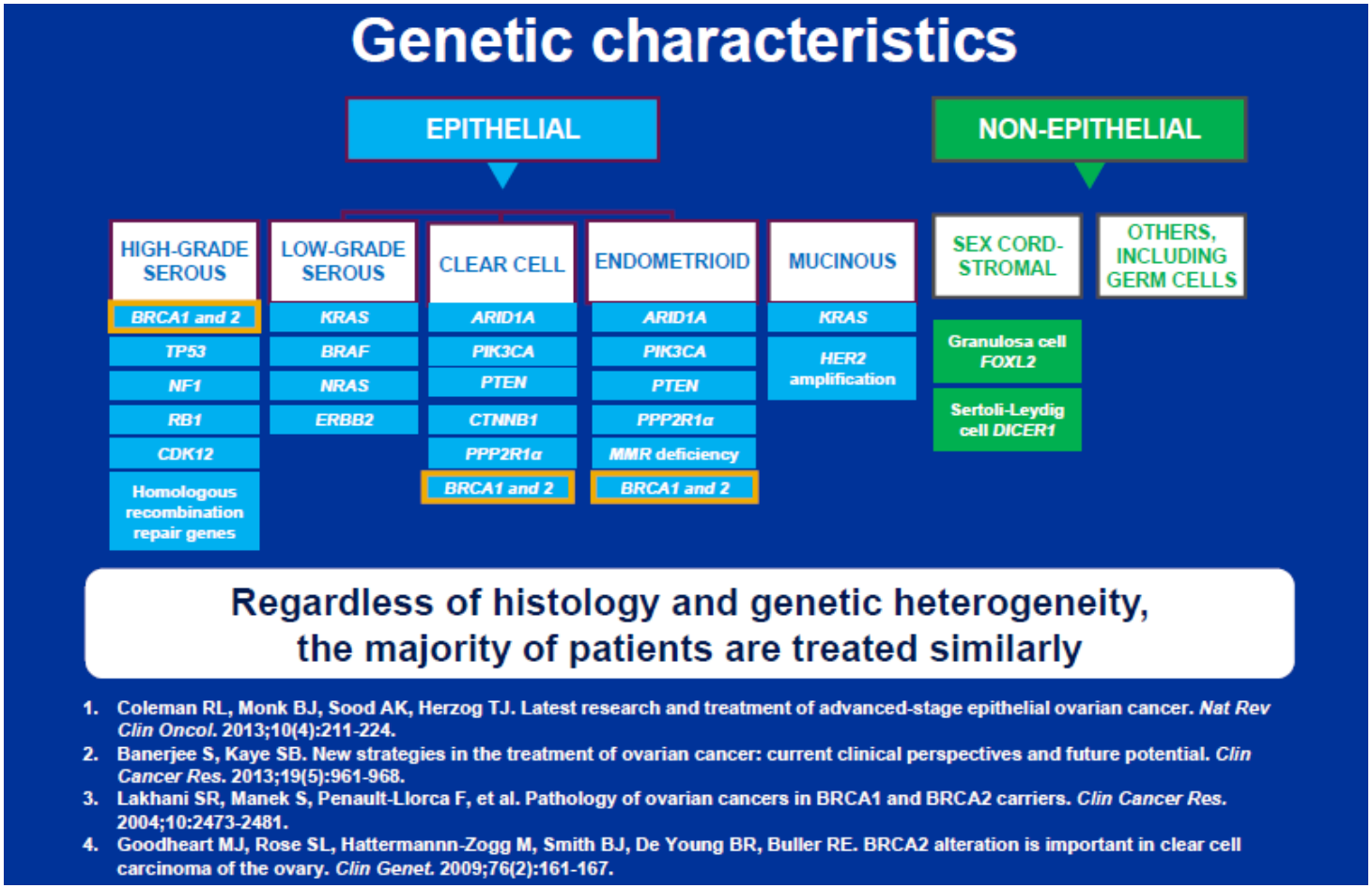
Family History of Ovarian Cancer	*Lifetime Risk*
General Population	1.4%
One Second-Degree Relative	3.0%
One First-Degree Relative	5.0%
Two First-Degree Relatives	11.0%

Over Kanseri Alt Gruplar

Pathology

Epithelial Carcinomas	90%
Germ Cell Neoplasms	2%
Stromal Tumors	7%
Miscellaneous	1%

Over Kanseri



1. Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol.* 2013;10(4):211-224.
2. Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res.* 2013;19(5):961-968.
3. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin Cancer Res.* 2004;10:2473-2481.
4. Goodheart MJ, Rose SL, Hattermannn-Zogg M, Smith BJ, De Young BR, Buller RE. BRCA2 alteration is important in clear cell carcinoma of the ovary. *Clin Genet.* 2009;76(2):161-167.

Epitelyal Over Kanseri

Serous	46%
Endometrioid	16%
Mucinous	13%
Clear Cell	7%
Undifferentiated	18%

Copeland L, in: DiSaia P and Creasman W, Clinical Gynecologic Oncology, Mosby Elsevier, 2007

Over Kanseri

Prognostic Factors

- Age
- Stage
- Volume of residual disease
- Histologic grade and type
- Performance status

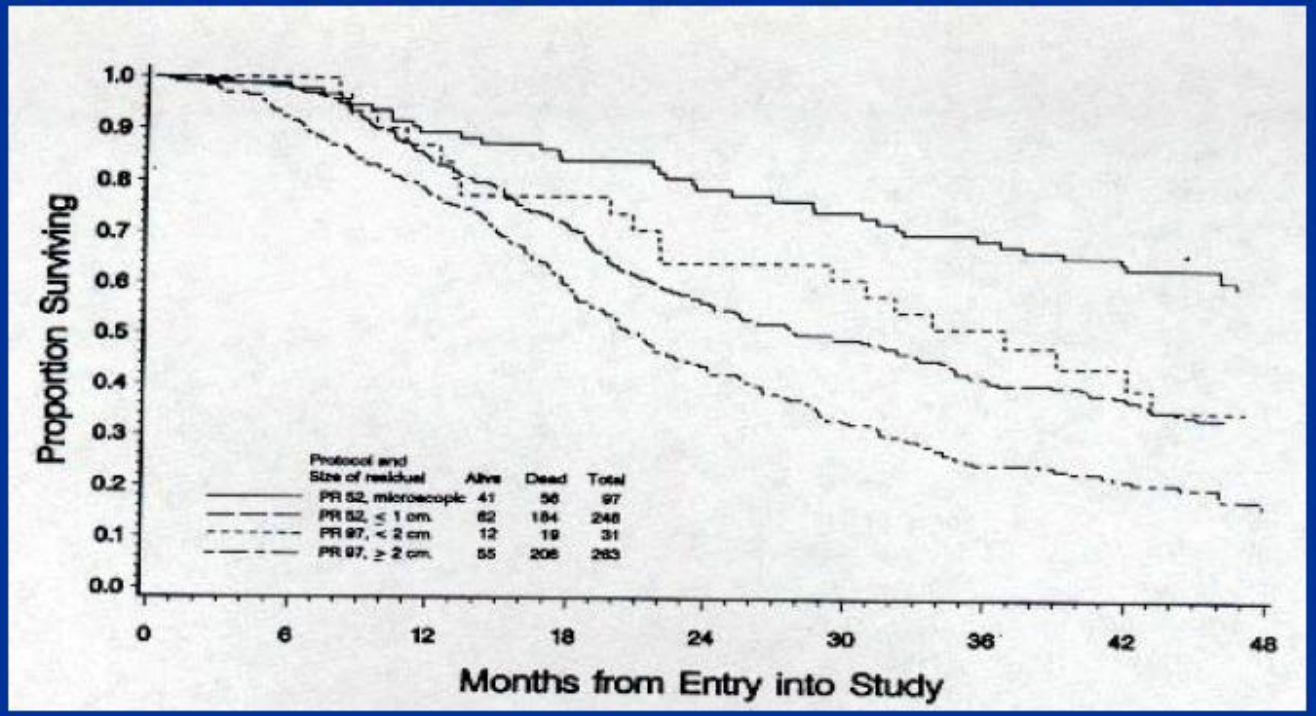
Over Kanseri Evreleme ve sağkalım Beklentisi

FIGO Stage

Stage	Description	Incidence	Survival
I	Confined to ovaries	20%	73%
II	Confined to pelvis	5%	45%
III	Spread IP or nodes	58%	21%
IV	Distant metastases	17%	<5%

Over Kanserinde Prognostik Faktörler

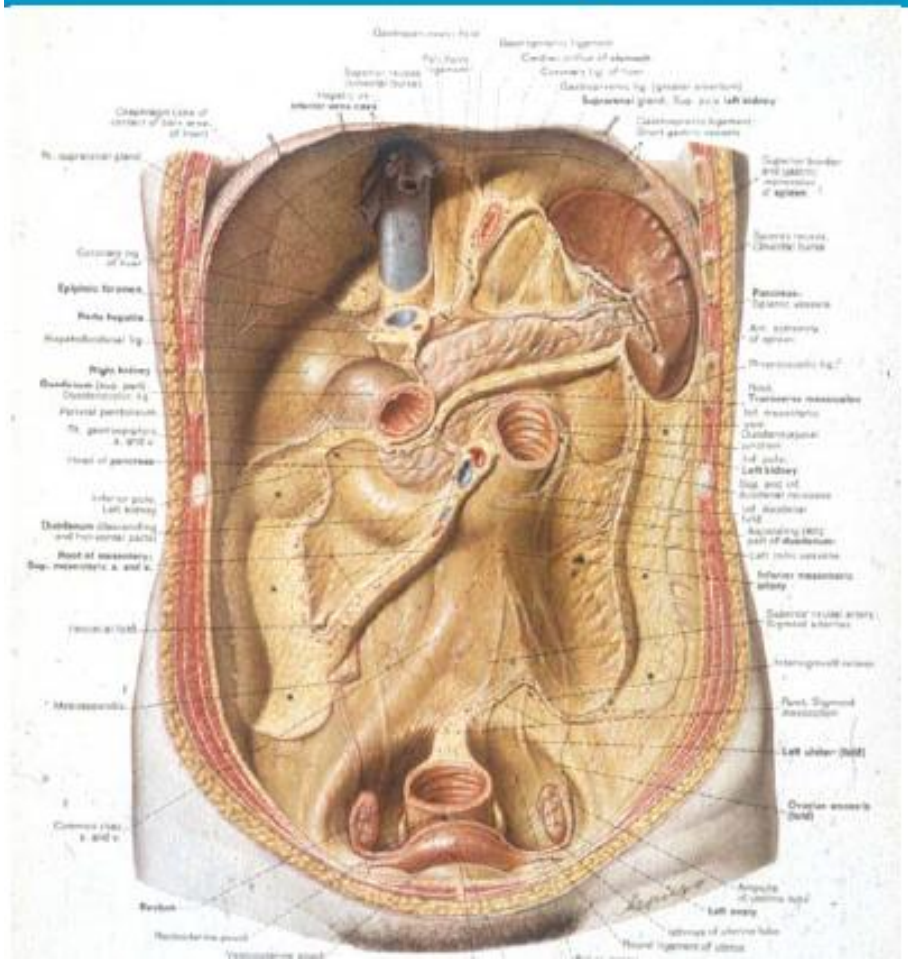
Impact of Residual Disease Volume on Survival



•Hoskins WJ, et al. *Am J Obstet Gynecol.* 1994;170:974-980.

Over Kanserinde Prognostik Faktörler

FIGO Stage	Suboptimal	Optimal	Complete
Bulge		1cm	



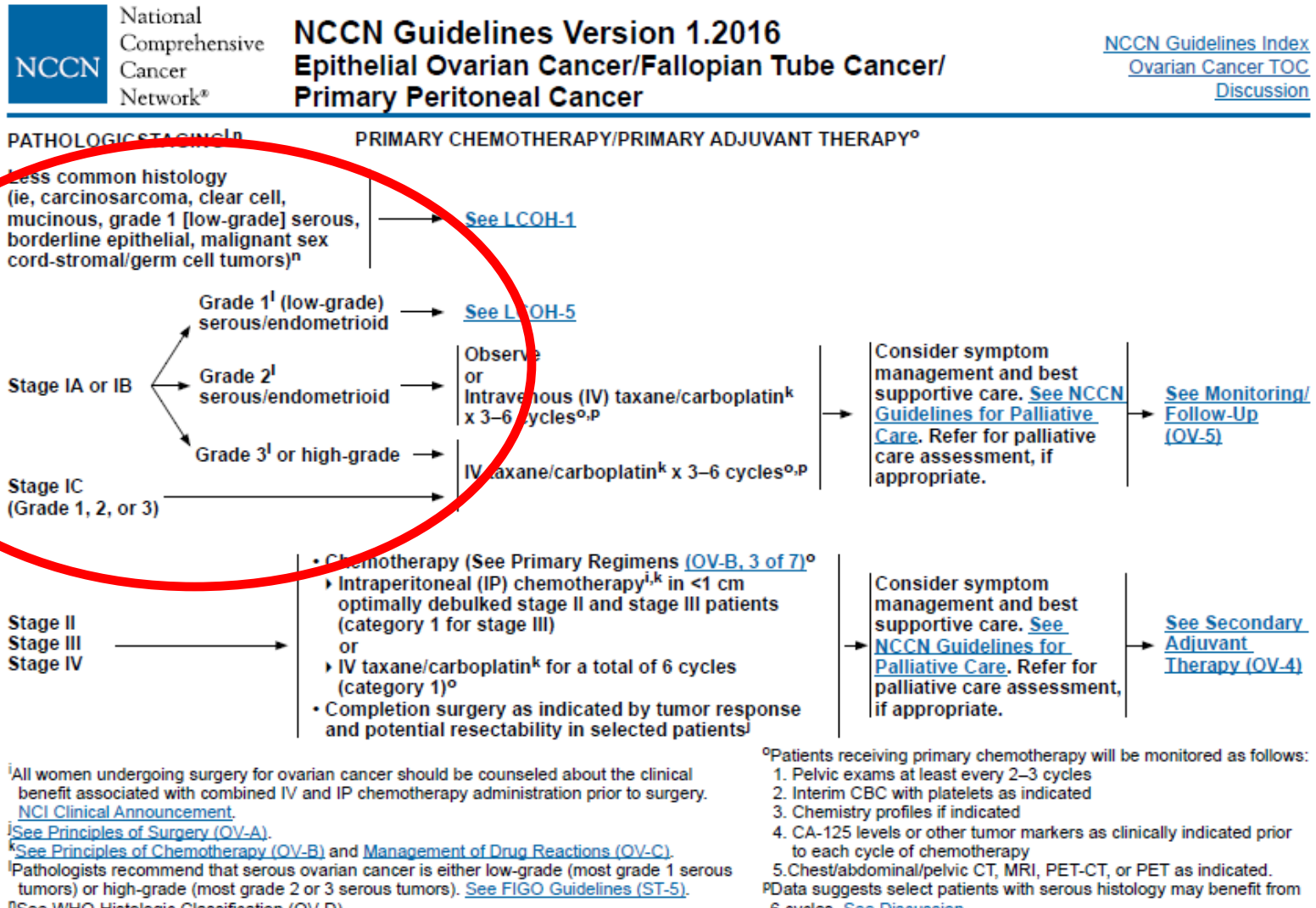
			Incidence	5yr OS
IV			5%	<5%
III	A	Micro	70%	21%
	B	≤2cm		
	C	>2cm/LN		
II	A	Ut/tubes	5%	45%
	B	Pelvic		
	C	Pelvic + IC		
I	A	Unilateral	20%	73%
	B	Bilateral		
	C	Ascites, +ve Washings, Surface, or Rupture		

Over Kanseri

Sık Kullanılan Terimler

- **Optimal opere-Yeterli cerrahi:** <1 cm tm yükü
- **Suboptimal opere-Yetersiz cerrahi:** ≥ 1 cm tm yükü
- **Primer debulking/cerrahi:** İlk cerrahi
- **İnterval debulking:** Neoadjuvan kemoterapi sonrası cerrahi (optimal/suboptimal)
- **Sekond Look:** Adjuvan kemoterapi sonrası batının patolojik açıdan değerlendirilmesi (araştırma amaçlı)
- **Sekonder debulking:** Tekrarlayan hastalıkta yapılan cerrahi (optimal/suboptimal)

Over Kanserinde Adjuvan Tedavi



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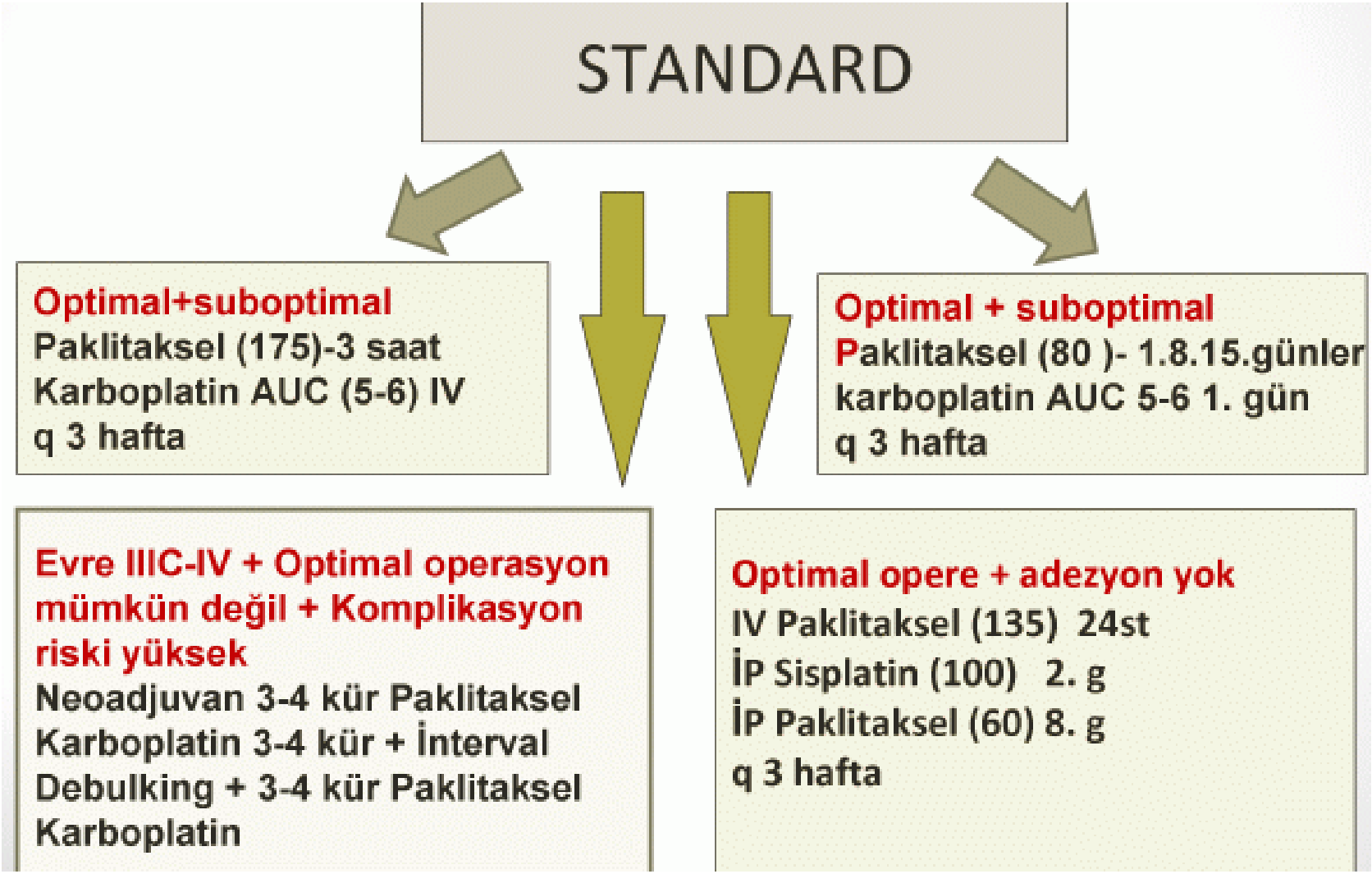

Over Kanserinde Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

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PRINCIPLES OF SYSTEMIC THERAPY (3 of 7)
Primary Chemotherapy/Primary Adjuvant Therapy Regimens[a]
Ovarian/Fallopian Tube/Primary Peritoneal/Carcinosarcoma/Clear Cell/Mucinous/Borderline Epithelial/Grade 1 (Low-Grade) Serous/Endometrioid

Stage II-IV

- **IP/IV Regimen**
  - Paclitaxel 135 mg/m² IV continuous infusion over 3 or 24 h[c] Day 1; cisplatin 75–100 mg/m² IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)
- **IV Regimens[b]**
  - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[d] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 followed by carboplatin[d] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes. Weekly for 18 weeks.[e] (category 1)
  - Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin[d] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Bevacizumab-containing regimens per ICON-7 and GOG-218:
    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[d] AUC 5–6 IV over 1 hour, and
    bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1. Repeat every 3 weeks x 5–6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 2B)
    or
    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[d] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles. (category 2B)

Additional options for the following less common histopathologies:

- **Carcinosarcoma (MMMT)**
  - Carboplatin/ifosfamide
  - Cisplatin/ifosfamide
  - Paclitaxel/ifosfamide (category 2B)
- **Mucinous tumors**
  - 5-FU/leucovorin/oxaliplatin
  - Capecitabine/oxaliplatin
- **Borderline epithelial carcinoma and grade 1 (low-grade) serous/endometrioid**
  - Hormone therapy (Aromatase inhibitors [ie, anastrozole, letrozole], leuprolide acetate, tamoxifen) (category 2B)

[a]See Discussion for references.
[b]IV regimens may be considered for neoadjuvant therapy for epithelial ovarian cancer.
[c]The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.
[d]Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement.
[e]This regimen may be considered for elderly patients or those with poor performance status.

Continued on OV-B (4 of 7)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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- Neoadjuvan? Adjuvan?
- IP kemoterapi?
- Doz dense ?
- Standart Kemoterapi
- Dosetaksel? Paklitaksel?
- Hangi hastalara Bevacizumab?

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Neoadjuvant

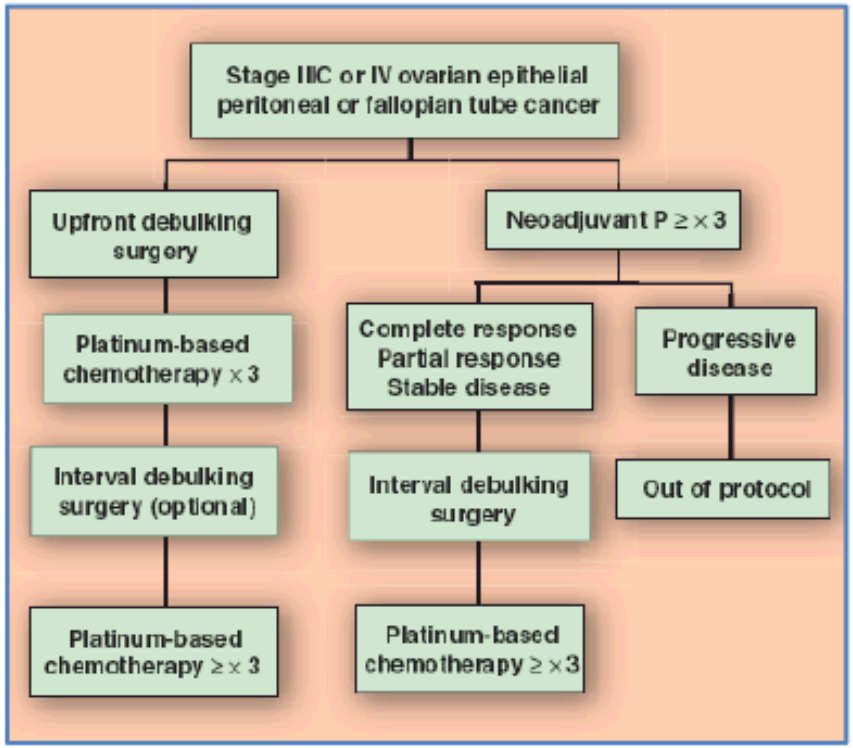

Figure 3: EORTC 55971 Trial Comparing Neoadjuvant Chemotherapy With Primary Debulking Surgery—Design of an ongoing study by the European Organization for Research and Treatment of Cancer (EORTC). P = platinum-based chemotherapy (carboplatin or cisplatin; other drugs allowed).

Vergote I, et al N Engl J Med 2010; 363:943

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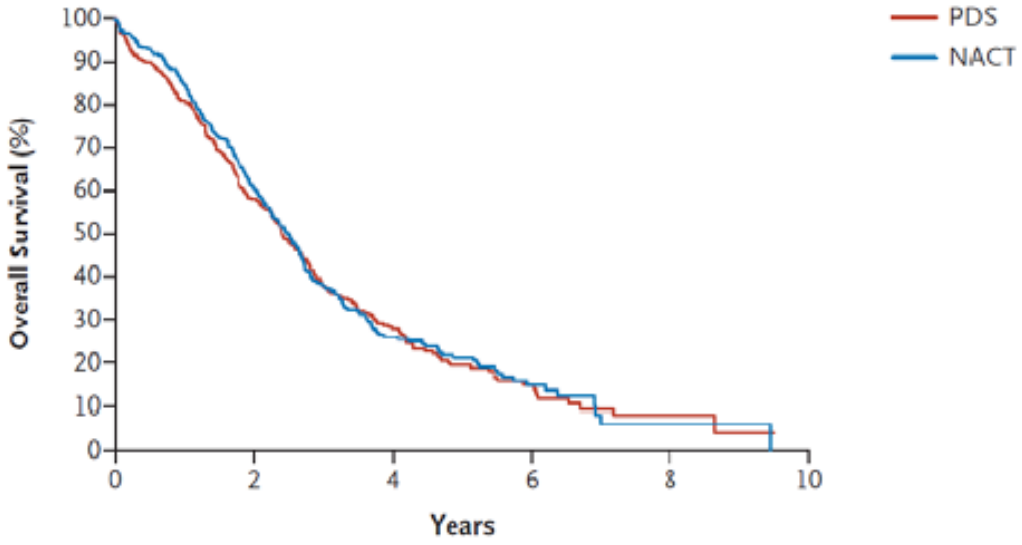
Neoadjuvant

A Intention-to-Treat Analysis



	No. of Events	No. of Patients at Risk				
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemo-therapy (NACT)	245	334	195	46	13	2

Vergote I, et al N Engl J Med 2010; 363:943

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Neoadjuvant

EORTC 55971 noninferior

CHORUS noninferior - postoperative mortality and serious (grade 3 or 4) postoperative adverse events were less common in patients enrolled in the NACT arm than in the PCS arm.

JCOG0602 trial - neoadjuvant arm experienced less blood loss and ascites during or after surgery and were less likely to experience grade 3 or 4 non-hematologic adverse events after surgery.

Critics:
1.Shorter median overall survival
2.More ≥65yos, poorer performance status, and had higher stage tumors.

Wright A, et al J Clin Oncol 2016;68:6907

Over Kanserinde IP Tedavi

GOG Protocol 172: Schema

Regimen I	**Paclitaxel 135 mg/m2/24h IV** **Cisplatin 75 mg/m2 IV** **Every 3 weeks for 6 cycles**
Regimen II	**Paclitaxel 135 mg/m2/24h IV d1** **Cisplatin 100 mg/m2 IP d2** **Paclitaxel 60 mg/m2 IP d8** **Every 3 weeks for 6 cycles**

*Stage III minimal residual <1.0 cm

Over Kanserinde IP Tedavi

GOG 172: Results

Parameter	IP	IV
PFS (median)	24 mos	18 mos
Survival (median)	66 mos	50 mos

*All differences highly statistically significant

Over Kanserinde Tedavi

Ovarian Carcinoma

GOG 172: Grade 3/4 Toxicities

Grade	Toxicities	IV, % (N = 210)	IP, % (N = 201)
G3/4	Leukopenia	64	76
G3/4	Thrombocytopenia	4	12
G3/4	GI	24	46
G3/4	Renal	2	7
G3/4	Neurologic	9	19
G3/4	Fatigue	4	18
G3/4	Infection	6	16
G3/4	Metabolic	7	27
G3/4	Pain	1	11

Armstrong DK, et al. *N Engl J Med.* 2006;354:34-43.

Over Kanserinde IP Tedavi

IP: Complications

- Low blood counts
- GI events
- Neurologic events
- Infection
- Metabolic events
- Pain
- Catheter complications

Only 42% completion rate

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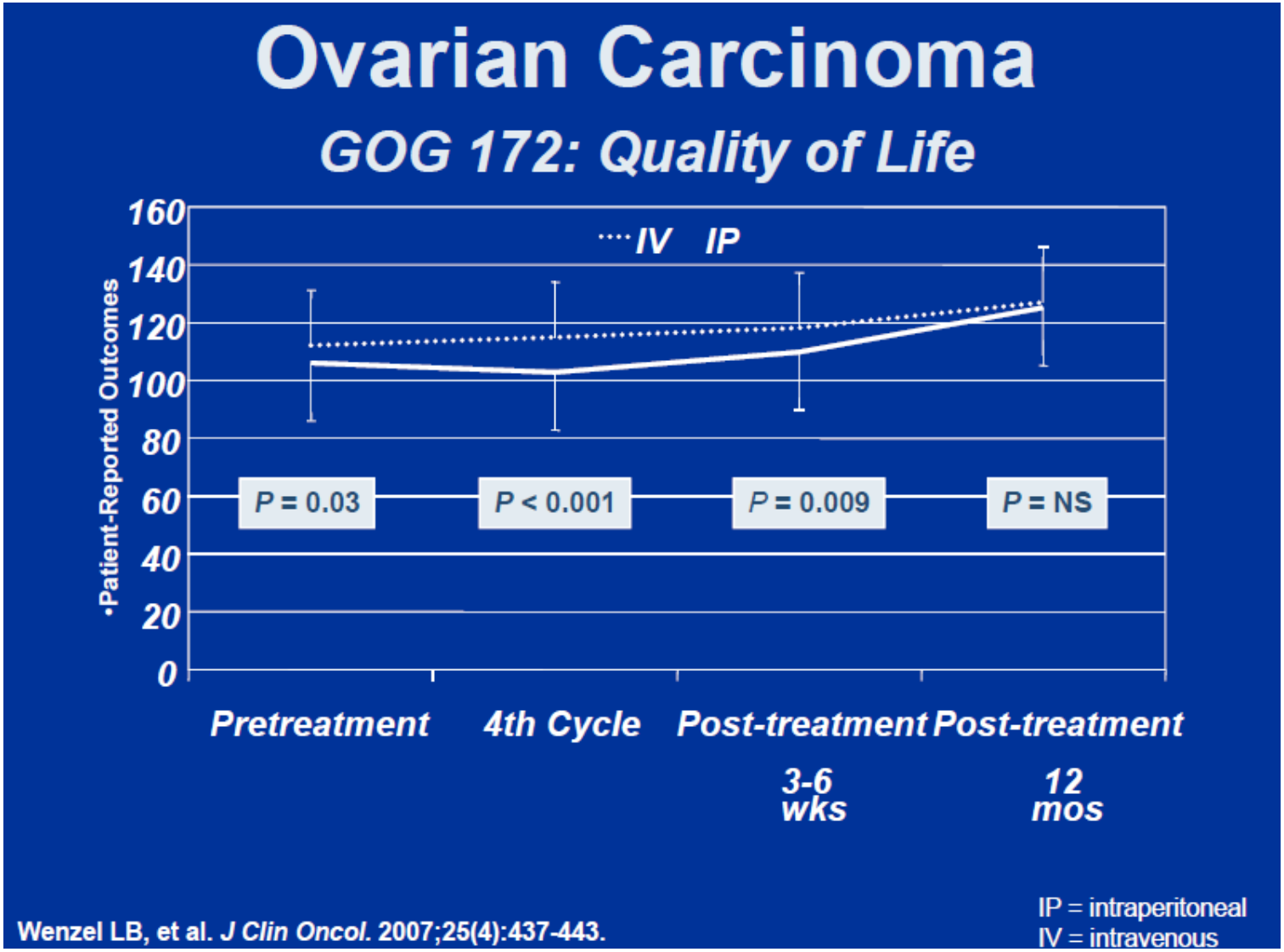

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IP: Key Studies

	GOG104 SWOG 8501 [1]	GOG114 [2]	GOG 172 [3]	GOG 252 [4]
Stage	Optimal III < 2 cm	Optimal III < 1cm	Optimal III < 1cm	Complete 57% II-III (IV 5%)
n=	546	462	415	1560
Rx Q21 #6 24hr Pac	IV Cis 100 IV Cyclo 600 vs. IP Cis 100 IV Cyclo 600	IV Cis 75 + Pac 135 vs. Carbo AUC9 #1-2 Q28 IP Cis 100 IV Pac 135	IV Cis 75 + Pac 135 vs. IV Pac 135 IP Cis 100 IP Pac 60 D8	IV Carbo AUC 6 IV weekly Pac 80 IV Bev 15 mg/kg.. vs. IP Carbo AUC 6 IP weekly Pac 80 vs. IV Pac 135 IP Cis 75 IP Pac 60 D8
PFS (mo)	NR	22 vs. 28	18 vs. 24	27 vs. 29 vs. 28 CT Q6mo
OS (mo)	41 vs. 49 P = 0.02	52 vs. 63 P = 0.05 (1-sided)	50 vs. 66 P = 0.03	PFS HR 0.95 1.01 P = 0.42 0.73

1. Alberts D, et al. NEJM 1996;335:1950; 2. Markman M, et al. J Clin Oncol. 2001;19:1001-7; 3. Armstrong D, et al. N Engl J Med. 2006;354:34-43; 4. Joan Walker SGO 2016

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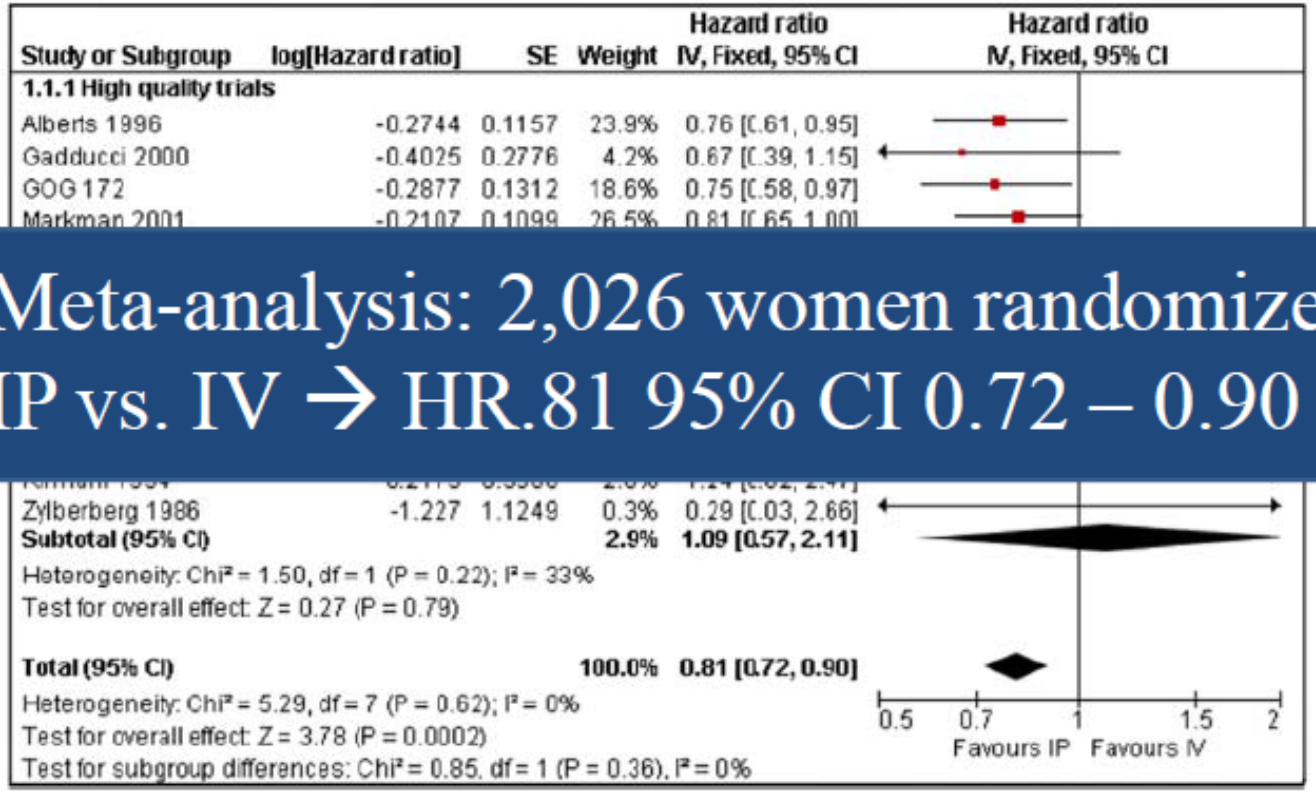
IP: Meta-analysis



Meta-analysis: 2,026 women randomized
IP vs. IV → HR.81 95% CI 0.72 – 0.90

Jaabeck K Cochrane Review 2011

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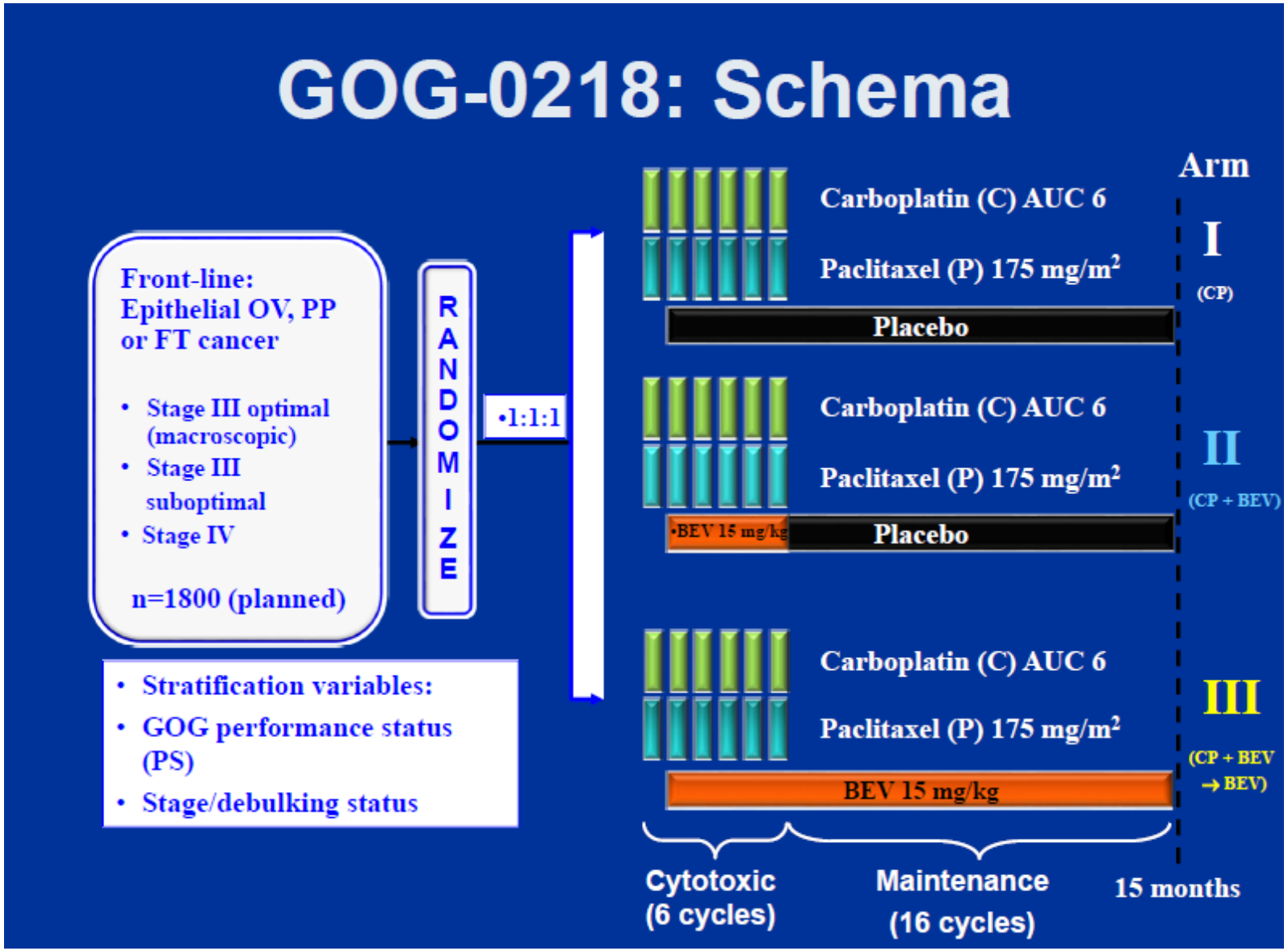

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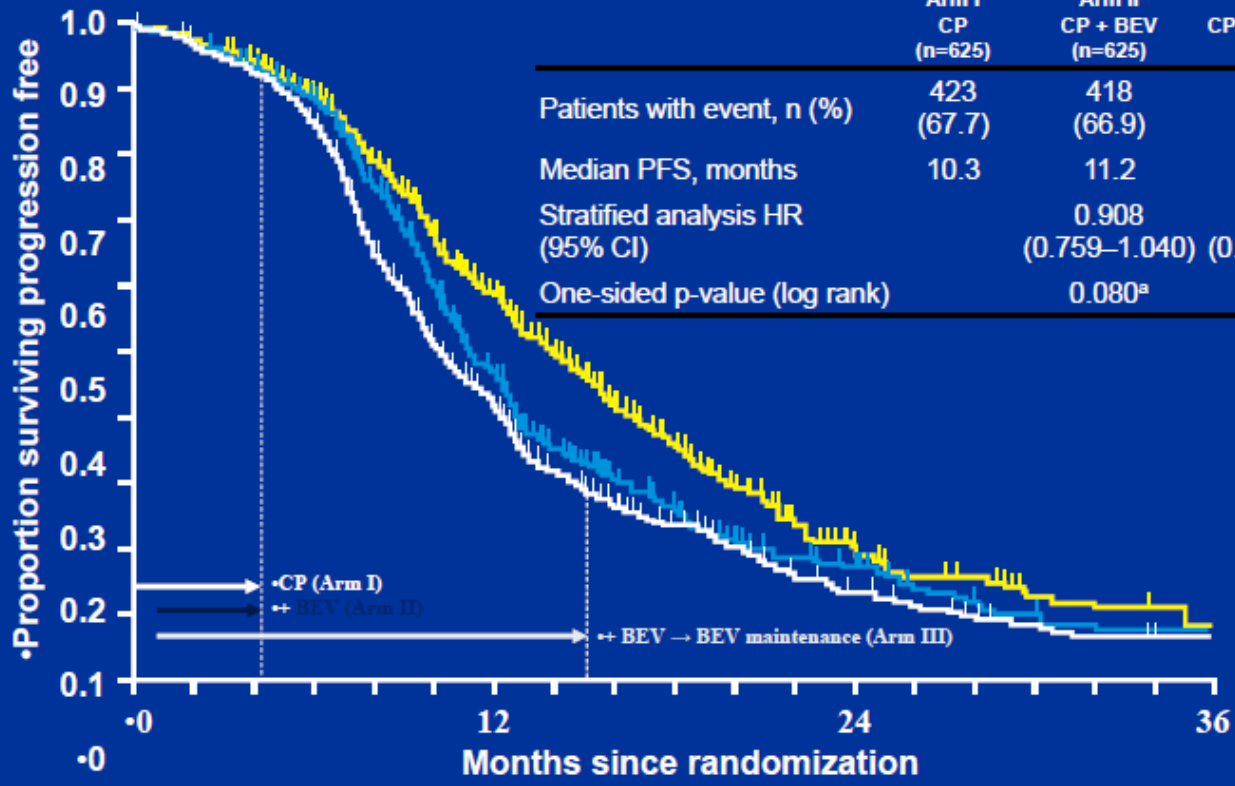
GOG-0218: PFS

	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]



•[a]p-value boundary = 0.0116

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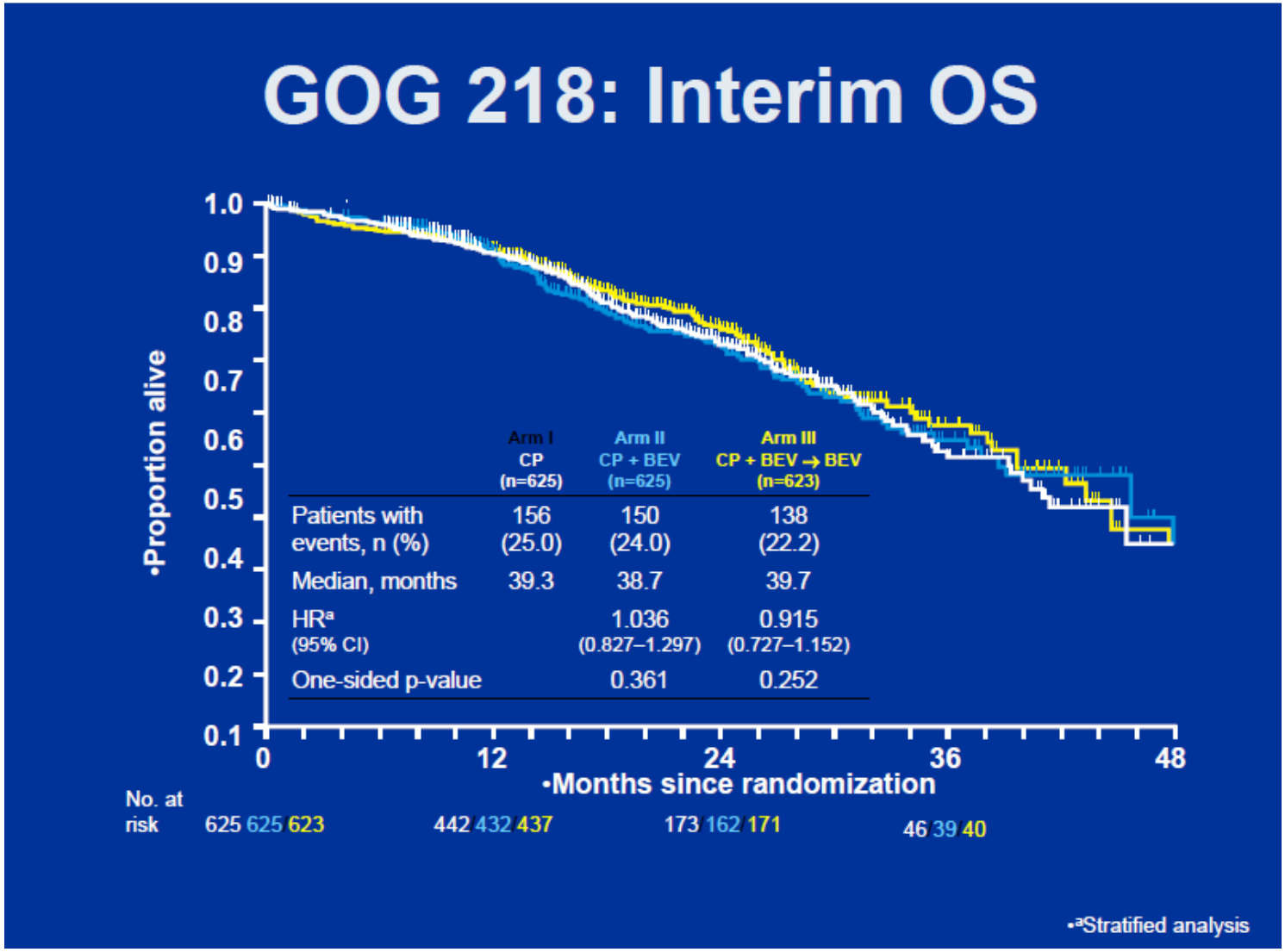

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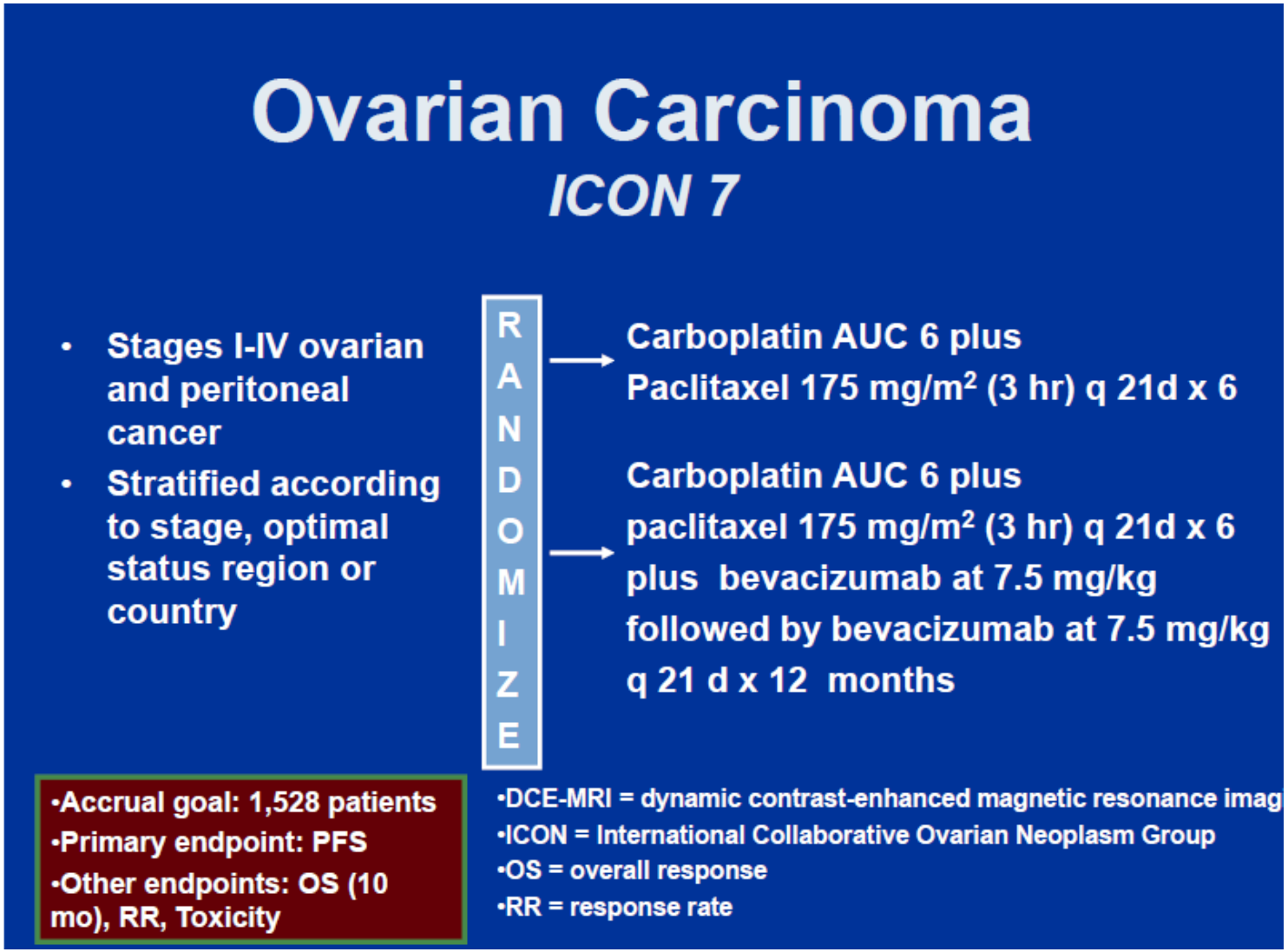

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Ovarian Carcinoma

ICON 7: Results

Parameter	Protocol-Defined Analysis	Bulk Disease Analysis
PFS	HR=0.87, p=0.039	
CP (Arm I)	17.4 mos	
CP + BEV→BEV (Arm II)	19.8 mos	
OS	HR=0.84, p=0.099	HR=0.64, p=0.002
CP (Arm I)		28.8 mos
CP + BEV→BEV (Arm II)		36.6 mos

•Proc ASCO 2011: LBA 5006

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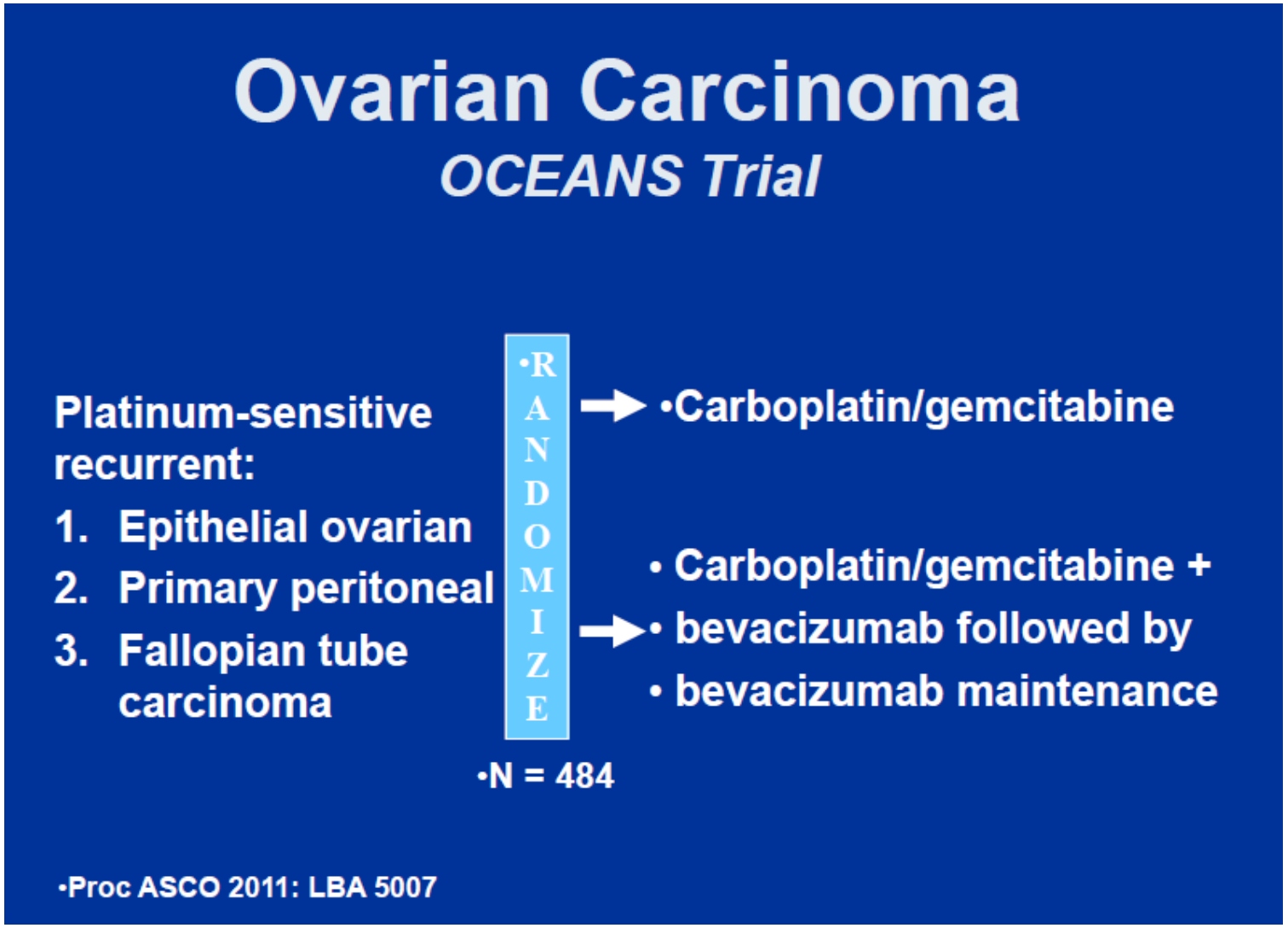

Over Kanserinde Tedavi

Ovarian Carcinoma

OCEANS: Results

Parameter	Gem/Carbo	Gem/Carbo Bev	
Patients	242	242	
Response Rate	57.4%	78.5%	P<0.0001
Median PFS	8.4 mos	12.4 mos	HR 0.484, p<0.001
Median OS	29.9 mos	35.5 mos	HR 0.751, p=0.094

•Proc ASCO 2011: LBA 5007

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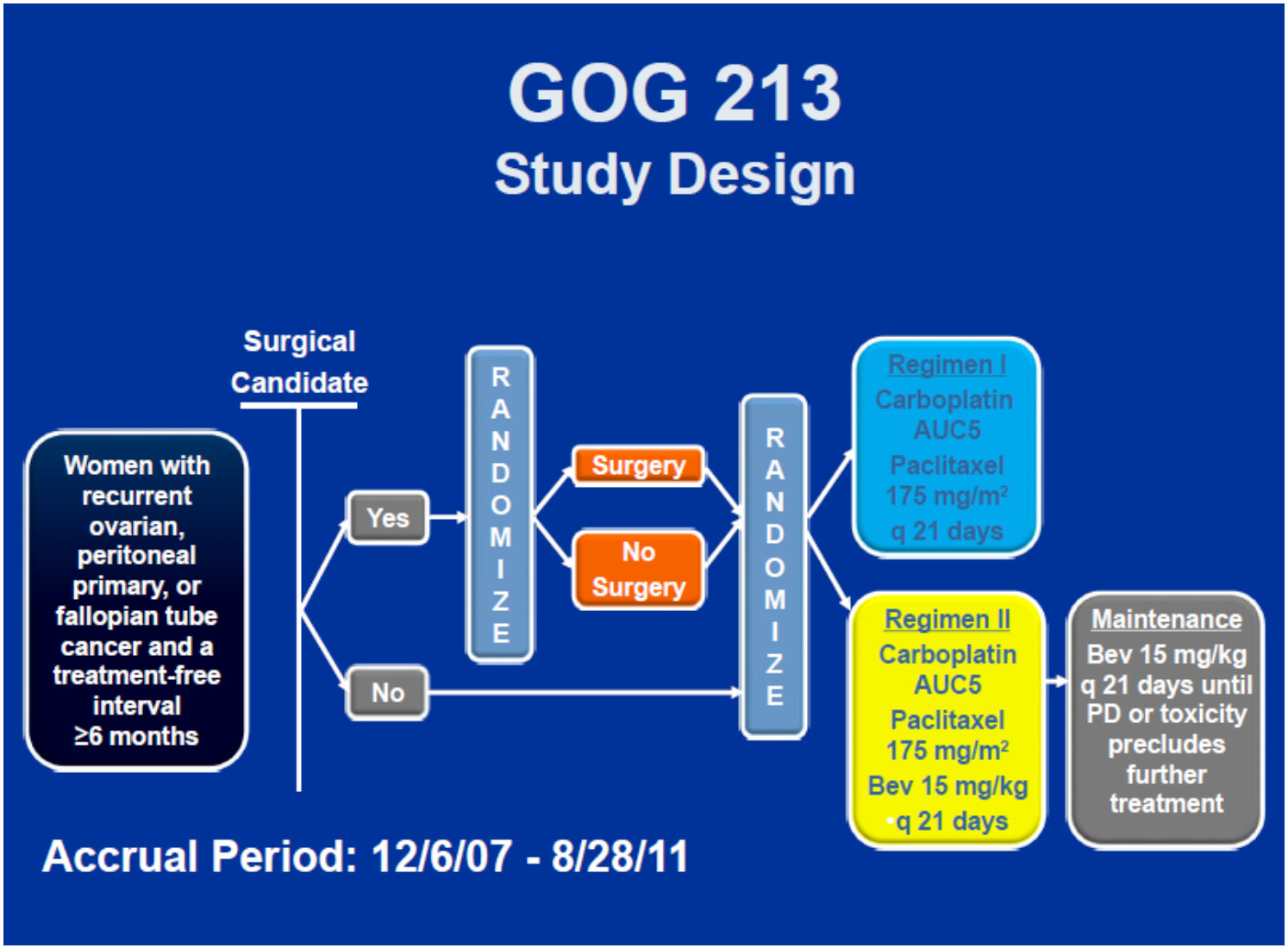

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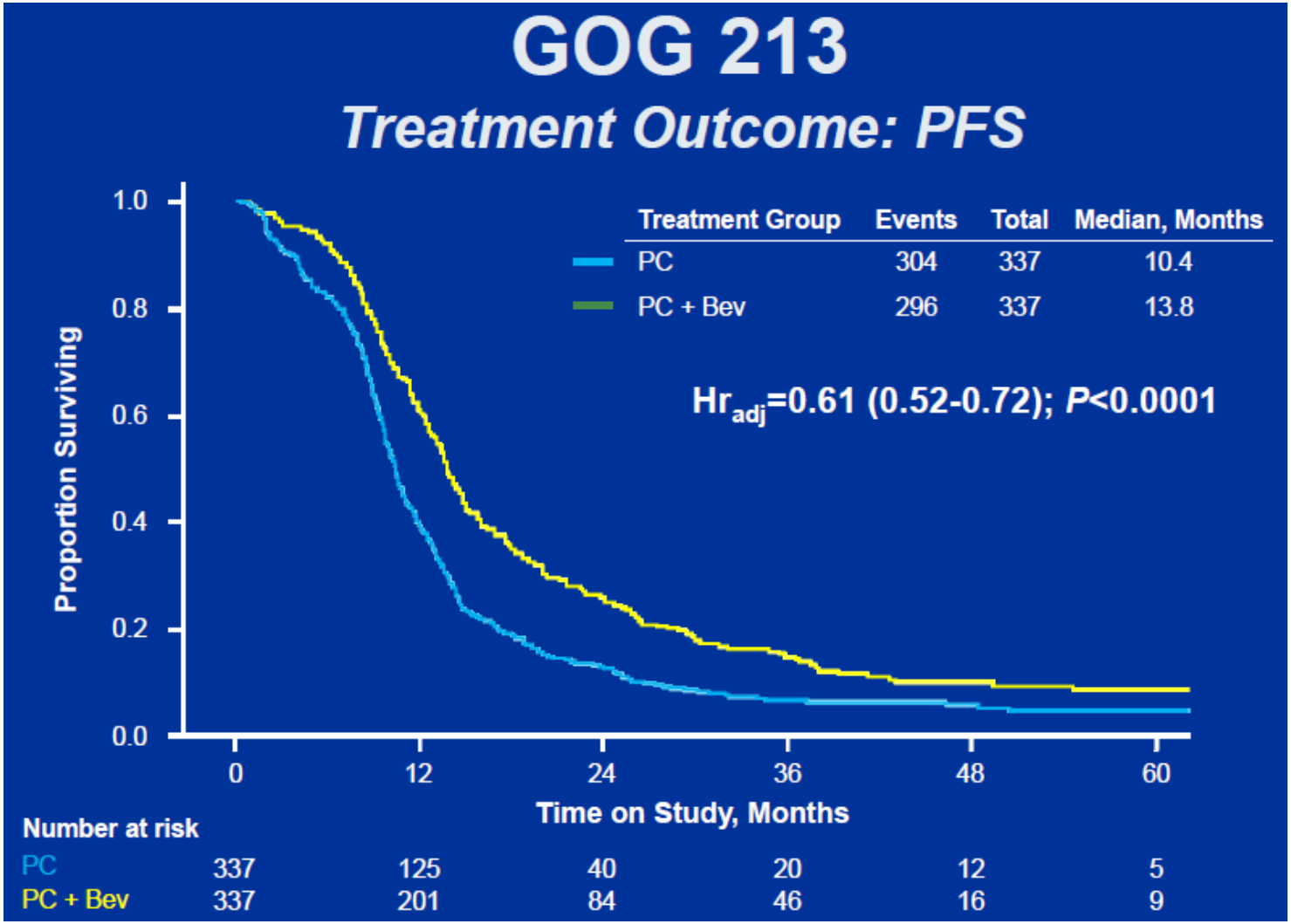

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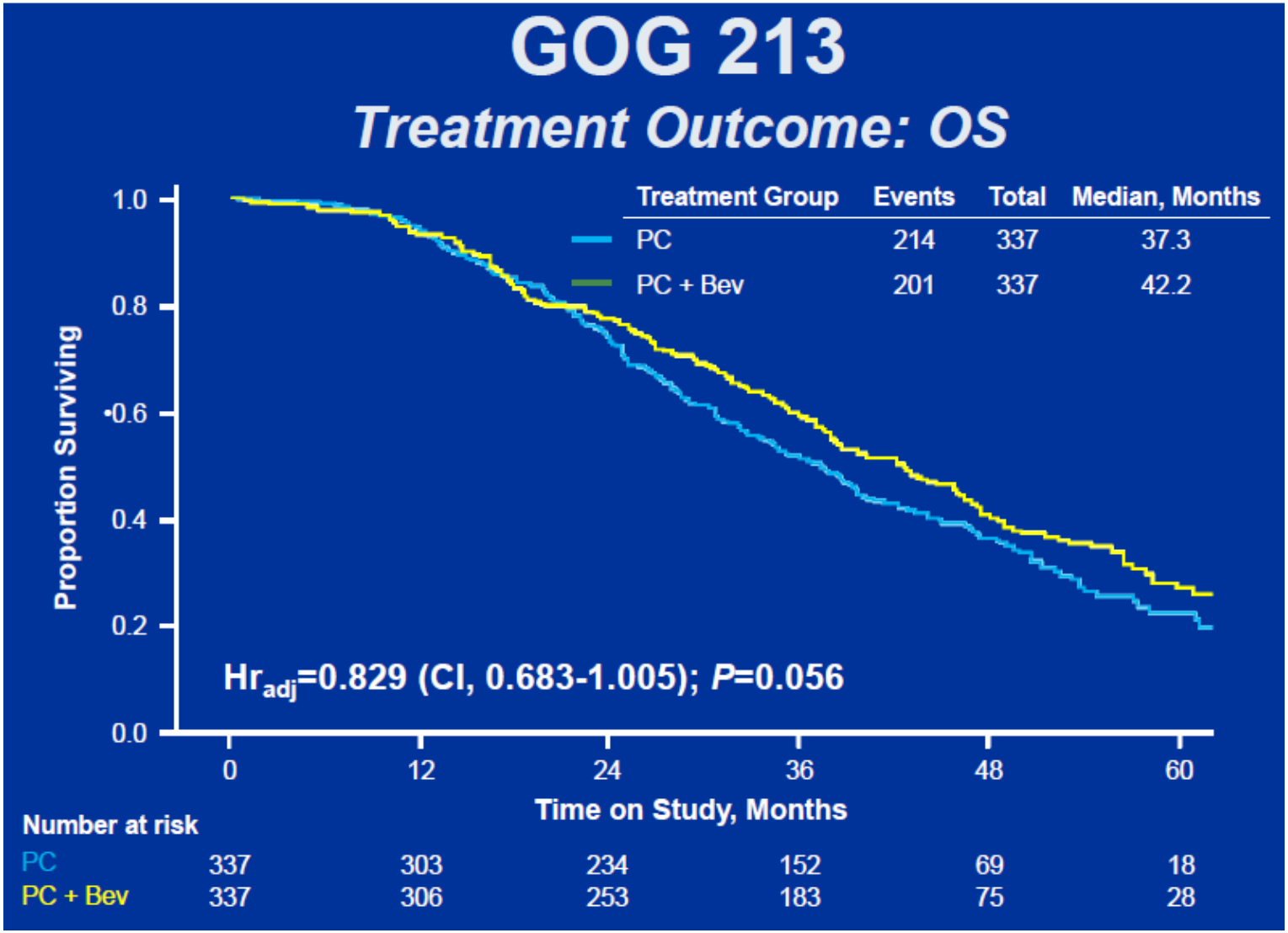

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  - Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 followed by carboplatin[d] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes. Weekly for 18 weeks.[e] (category 1)
  - Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin[d] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
  - Bevacizumab-containing regimens per ICON-7 and GOG-218:
    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[d] AUC 5–6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1. Repeat every 3 weeks x 5–6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 2B)

    or

    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[d] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles. (category 2B)

Additional options for the following less common histopathologies:

- **Carcinosarcoma (MMMT)**
  - Carboplatin/ifosfamide
  - Cisplatin/ifosfamide
  - Paclitaxel/ifosfamide (category 2B)
- **Mucinous tumors**
  - 5-FU/leucovorin/oxaliplatin
  - Capecitabine/oxaliplatin
- **Borderline epithelial carcinoma and grade 1 (low-grade) serous/endometrioid**
  - Hormone therapy (Aromatase inhibitors [ie, anastrozole, letrozole], leuprolide acetate, tamoxifen) (category 2B)

[a]See Discussion for references.
[b]IV regimens may be considered for neoadjuvant therapy for epithelial ovarian cancer.
[c]The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.
[d]Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement.
[e]This regimen may be considered for elderly patients or those with poor performance status.

Continued on OV-B (4 of 7)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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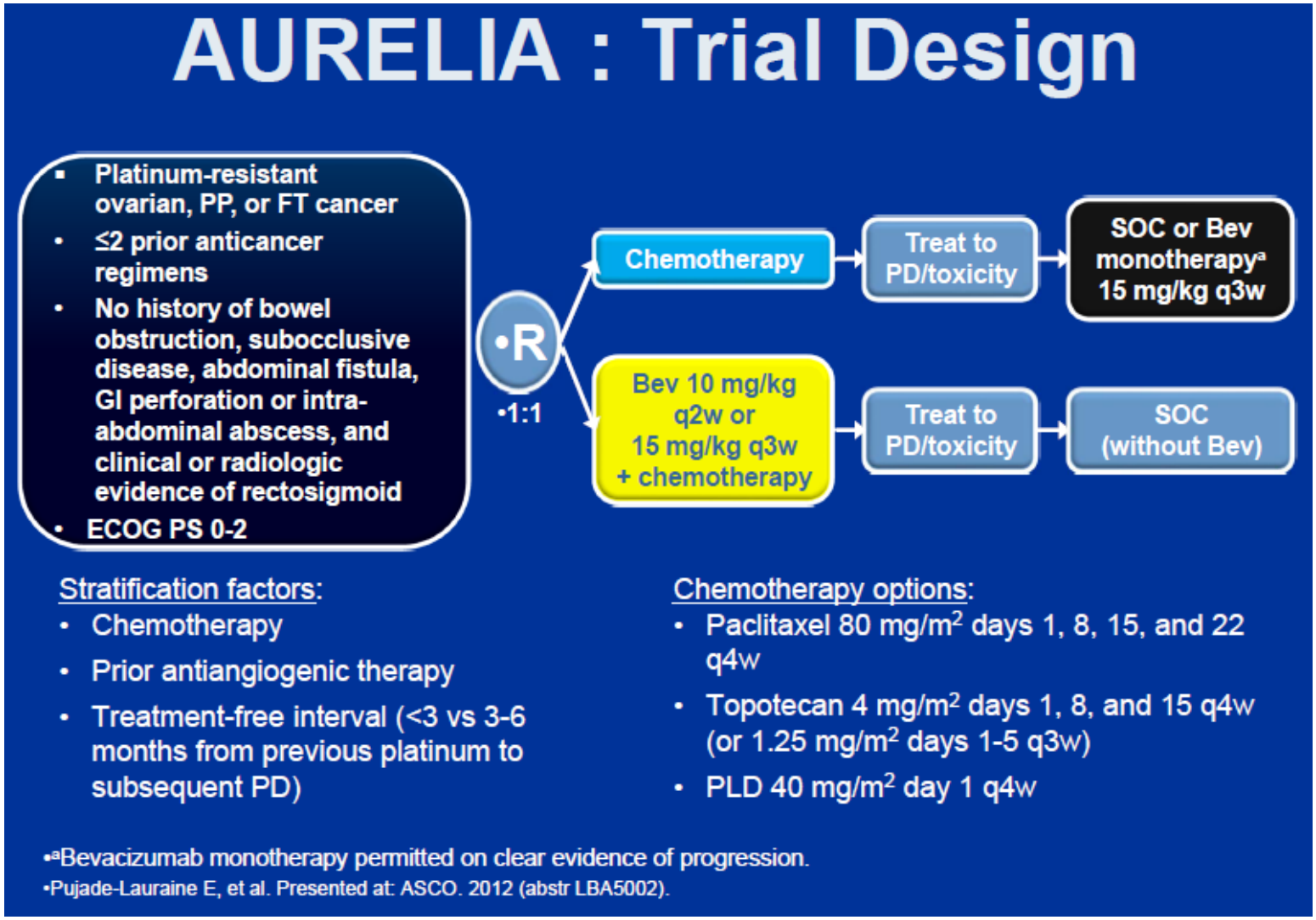

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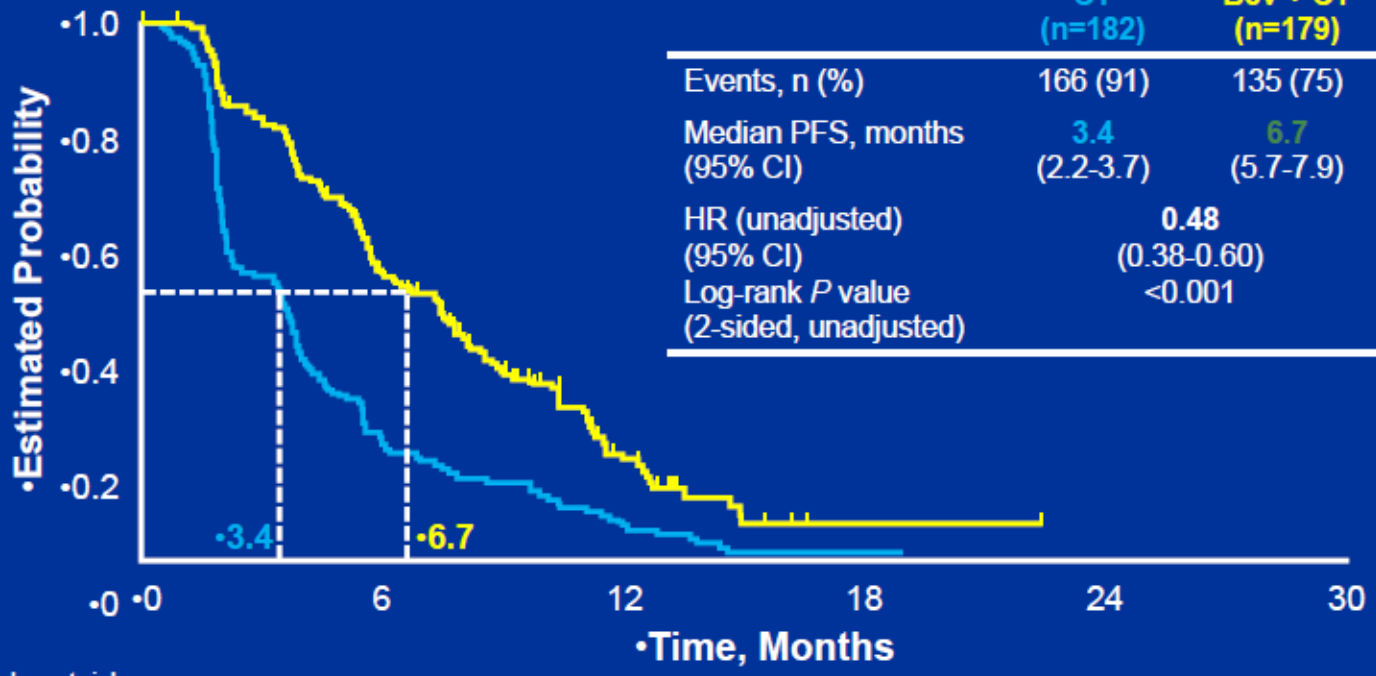
AURELIA : PFS



	CT (n=182)	Bev + CT (n=179)
Events, n (%)	166 (91)	135 (75)
Median PFS, months (95% CI)	3.4 (2.2-3.7)	6.7 (5.7-7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38-0.60)	
Log-rank *P* value (2-sided, unadjusted)	<0.001	

•Number at risk

•CT	•182	•93	•37	•20	•8	•1	•1	•0	•0
•Bev + CT	•179	•140	•88	•49	•18	•4	•1	•1	•0

•Pujade-Lauraine E, et al. Presented at: ASCO. 2012 (abstr LBA5002).

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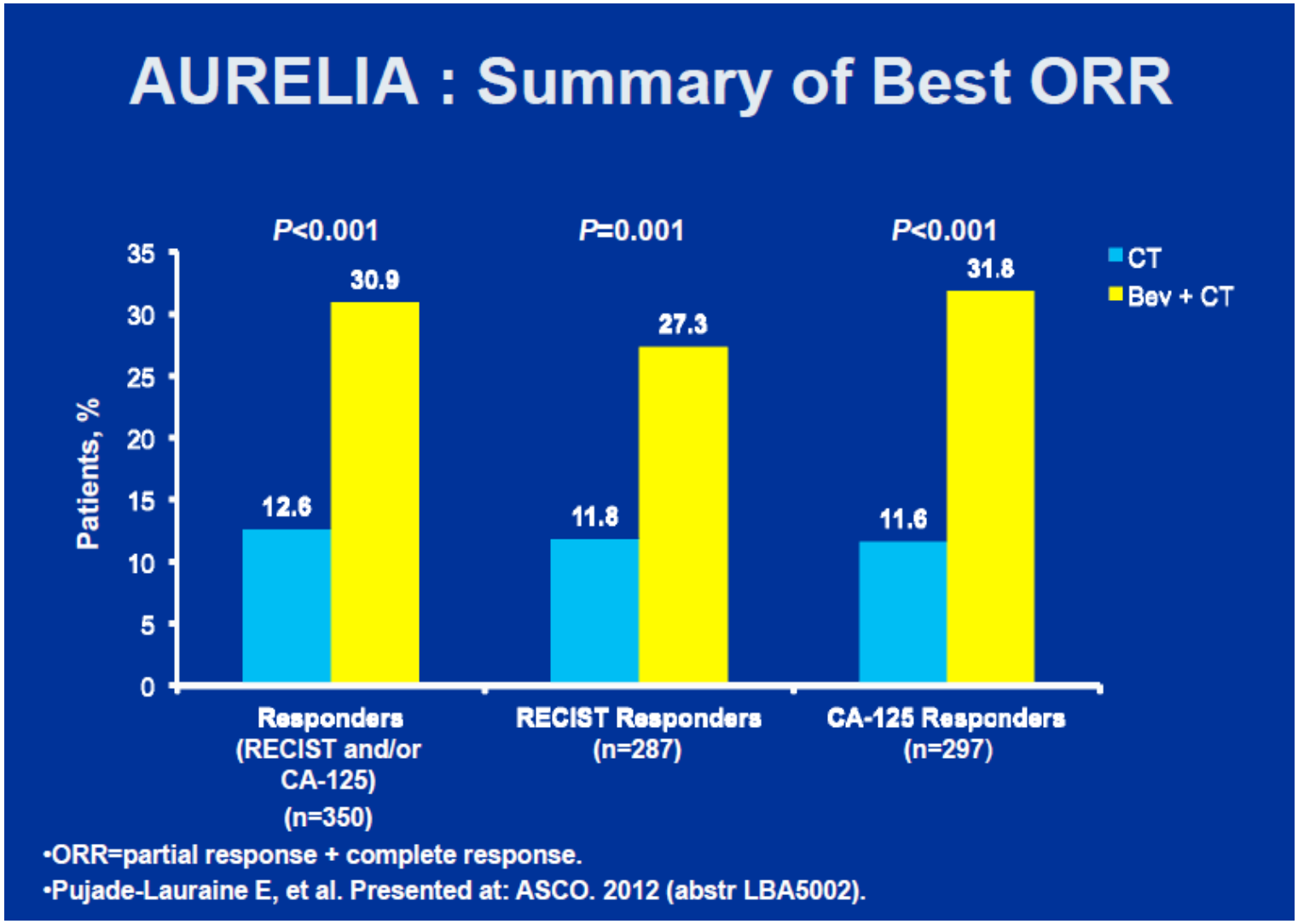

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AURELIA: Authors' Conclusions

- AURELIA is the first randomized phase III trial in platinum-resistant OC to demonstrate benefit with
  - Biologic therapy
  - A combination regimen vs monotherapy
- Bevacizumab plus chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer

•Pujade-Lauraine E, et al. Presented at: ASCO. 2012 (abstr LBA5002).

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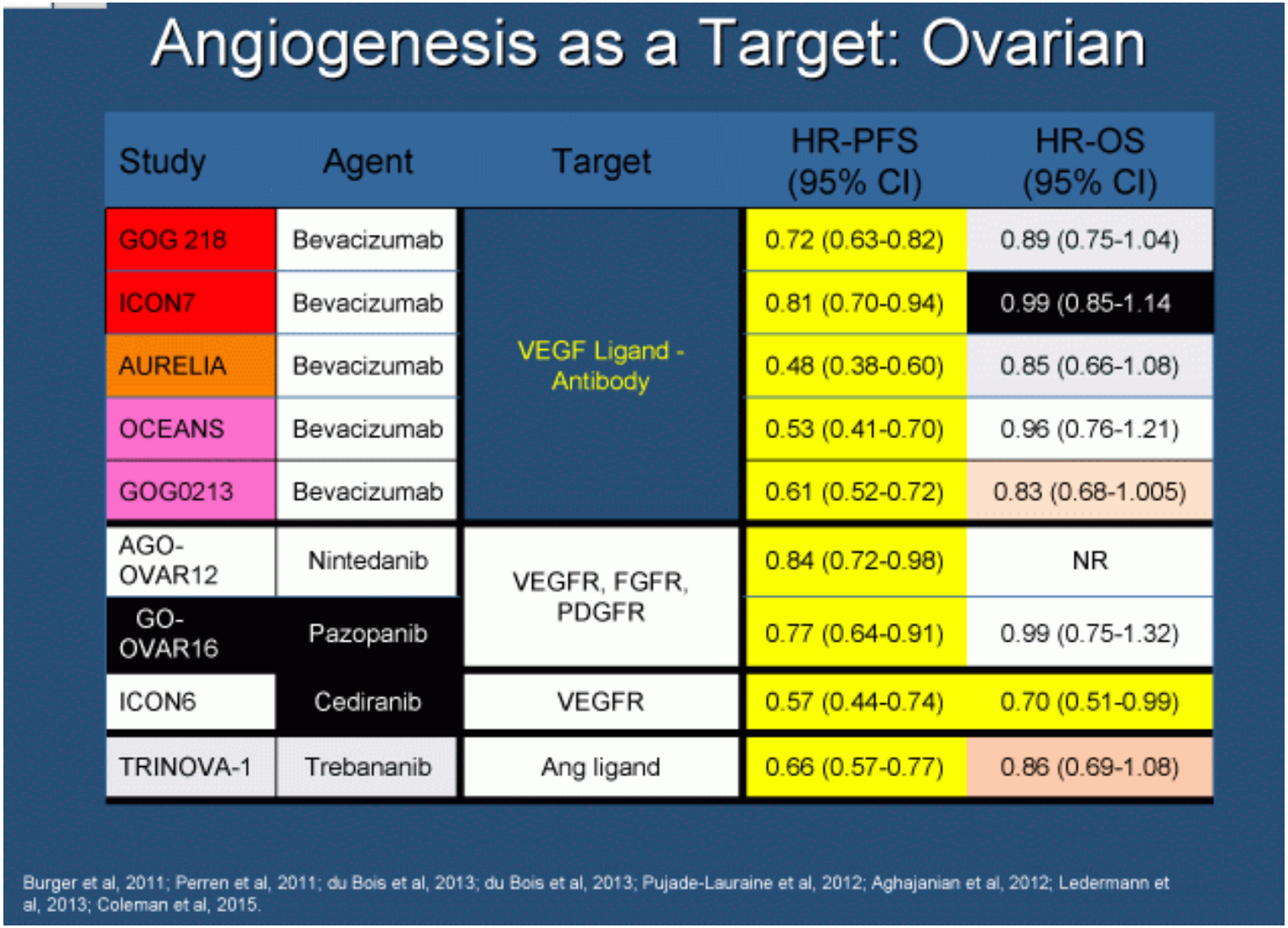

Angiogenesis as a Target: Ovarian

Study	Agent	Target	HR-PFS (95% CI)	HR-OS (95% CI)
GOG 218	Bevacizumab	VEGF Ligand - Antibody	0.72 (0.63-0.82)	0.89 (0.75-1.04)
ICON7	Bevacizumab		0.81 (0.70-0.94)	0.99 (0.85-1.14
AURELIA	Bevacizumab		0.48 (0.38-0.60)	0.85 (0.66-1.08)
OCEANS	Bevacizumab		0.53 (0.41-0.70)	0.96 (0.76-1.21)
GOG0213	Bevacizumab		0.61 (0.52-0.72)	0.83 (0.68-1.005)
AGO-OVAR12	Nintedanib	VEGFR, FGFR, PDGFR	0.84 (0.72-0.98)	NR
GO-OVAR16	Pazopanib		0.77 (0.64-0.91)	0.99 (0.75-1.32)
ICON6	Cediranib	VEGFR	0.57 (0.44-0.74)	0.70 (0.51-0.99)
TRINOVA-1	Trebananib	Ang ligand	0.66 (0.57-0.77)	0.86 (0.69-1.08)

Burger et al, 2011; Perren et al, 2011; du Bois et al, 2013; du Bois et al, 2013; Pujade-Lauraine et al, 2012; Aghajanian et al, 2012; Ledermann et al, 2013; Coleman et al, 2015.

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

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PRINCIPLES OF SYSTEMIC THERAPY (5 of 7)

Acceptable Recurrence Therapies for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer[g]

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	**Platinum-Sensitive Disease**[h,i] Carboplatin[1] Carboplatin/docetaxel[2,3] Carboplatin/gemcitabine[1] Carboplatin/gemcitabine/bevacizumab[j,k] (category 2B)[4] Carboplatin/liposomal doxorubicin[5] (category 1) Carboplatin/paclitaxel (category 1)[6] Carboplatin/paclitaxel (weekly)[7] Cisplatin[6] Cisplatin/gemcitabine[8]		**Single Agents** Bevacizumab[j,k,18,19] Olaparib[m,20,21]	
	Platinum-Resistant Disease Docetaxel[9] Etoposide, oral[10] Gemcitabine[11,12] Liposomal doxorubicin[11,12] Liposomal doxorubicin/bevacizumab[j,k,13] Paclitaxel (weekly)[14] ± pazopanib[15] Paclitaxel (weekly)/bevacizumab[j,k,13] Topotecan[16,17] Topotecan/bevacizumab[j,k,13]		**Single Agents** Bevacizumab[j,k,18,19] Olaparib[m,20,21]	
Other Potentially Active Agents	**Single Agents**[l,22] Altretamine, Capecitabine, Cyclophosphamide, Doxorubicin, Ifosfamide, Irinotecan, Melphalan, Oxaliplatin, Paclitaxel, Paclitaxel, albumin bound (nab-paclitaxel), Pemetrexed, Vinorelbine	Aromatase inhibitors Leuprolide acetate Megestrol acetate Tamoxifen	Pazopanib (category 2B)[23]	Palliative localized radiation therapy

[g]Patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and Fallopian tube. Int J Gyn Ca 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.

[h]In general, the panel would recommend combination regimens based on randomized trial data, especially in first relapses.

[i]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.

[j]In patients who have not previously received bevacizumab.

[k]Contraindicated for patients at increased risk of gastrointestinal perforation.

[l]Many of these agents have not been tested in patients who have been treated with modern chemotherapy regimens.

[m]For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with three or more lines of chemotherapy.[2]

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Ovarian Carcinoma

Japanese Trial: Schema

Regimen I	**Paclitaxel 180 mg/m2/3h** **Carboplatin AUC 6** **Repeat every three weeks**
Regimen II	**Paclitaxel 80 mg/m2/1h weekly** **Carboplatin AUC 6** **Repeat every 3 weeks**

*Stage II-IV disease

**n = 631

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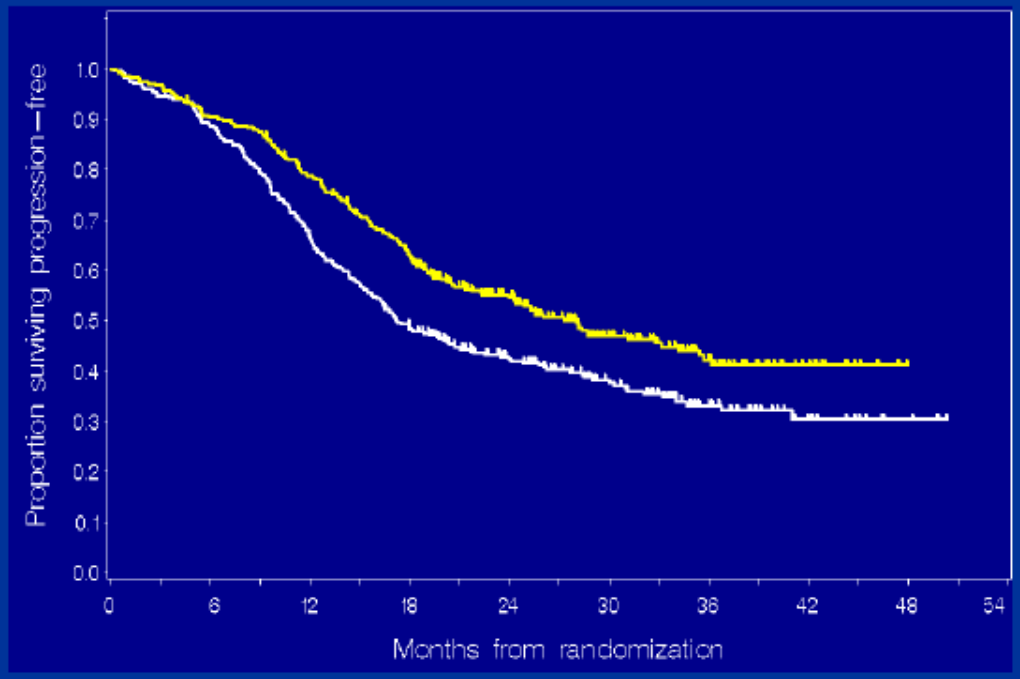
Japanese Trial: PFS



Treatment	n	Event	Median PFS	P value	HR	95%CI
c-TC	319	200	17.2 mos.			
dd-TC	312	160	28.0 mos.	0.0015	0.714	0.581-0.879

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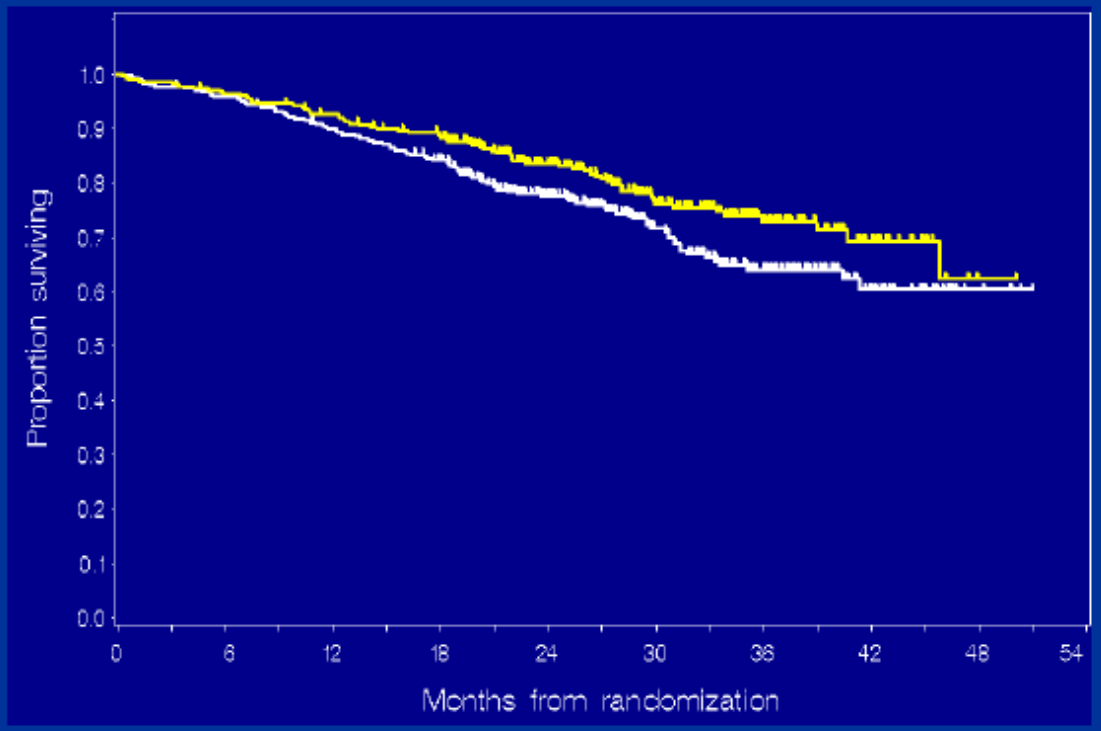
Japanese Trial: OS



Treatment	n	Event	2-yr survival	P value	HR	95%CI
c-TC	319	95	77.7%			
dd-TC	312	70	83.6%	0.0496	0.735	0.540-1.000

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GOG 262: Schema

Regimen I	Paclitaxel 175 mg/m2/3h Carboplatin AUC 6 Bevacizumab15 mg/kg Repeat q three weeks
Regimen II	Paclitaxel 80 mg/m2/1h weekly Carboplatin AUC 6 q 3 weeks Bevacizumab 15 mg/kg Repeat q 3 weeks

*Stage IIB-IV disease

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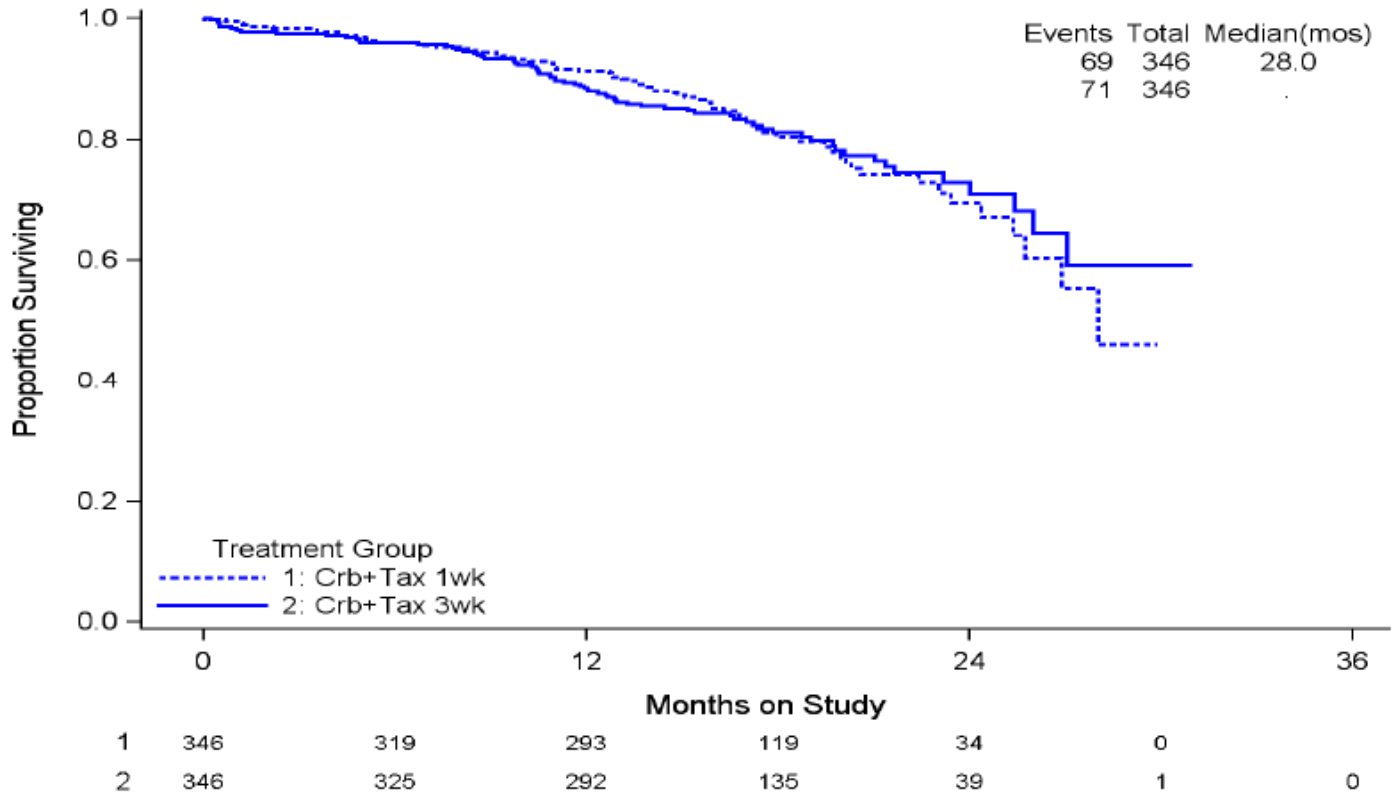
GOG 262: Overall Survival



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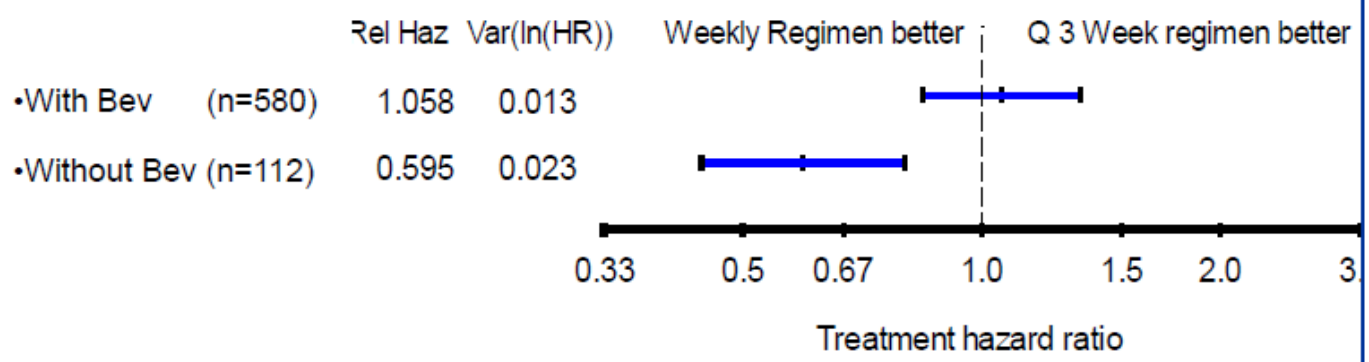
GOG-262: Subgroup Analyses of PFS



•p value for heterogeneity = 0.032

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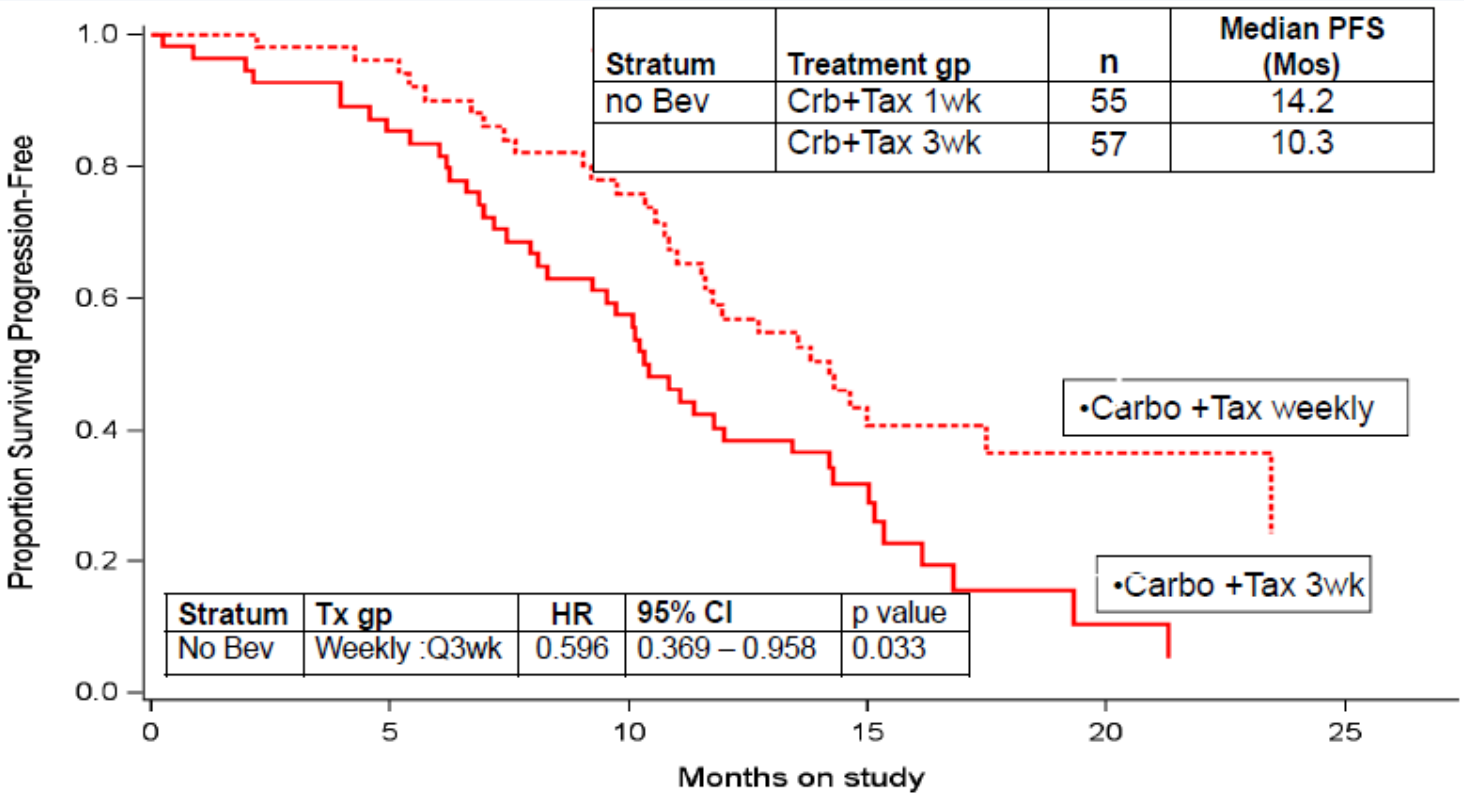
Ovarian Cancer

GOG 262: PFS for those choosing no bevacizumab (n=112)



Stratum	Treatment gp	n	Median PFS (Mos)
no Bev	Crb+Tax 1wk	55	14.2
	Crb+Tax 3wk	57	10.3

Stratum	Tx gp	HR	95% CI	p value
No Bev	Weekly :Q3wk	0.596	0.369 – 0.958	0.033

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Maintenance Therapy: Active Agents

- Paclitaxel
- Bevacizumab
- Pazopanib
- Olaparib

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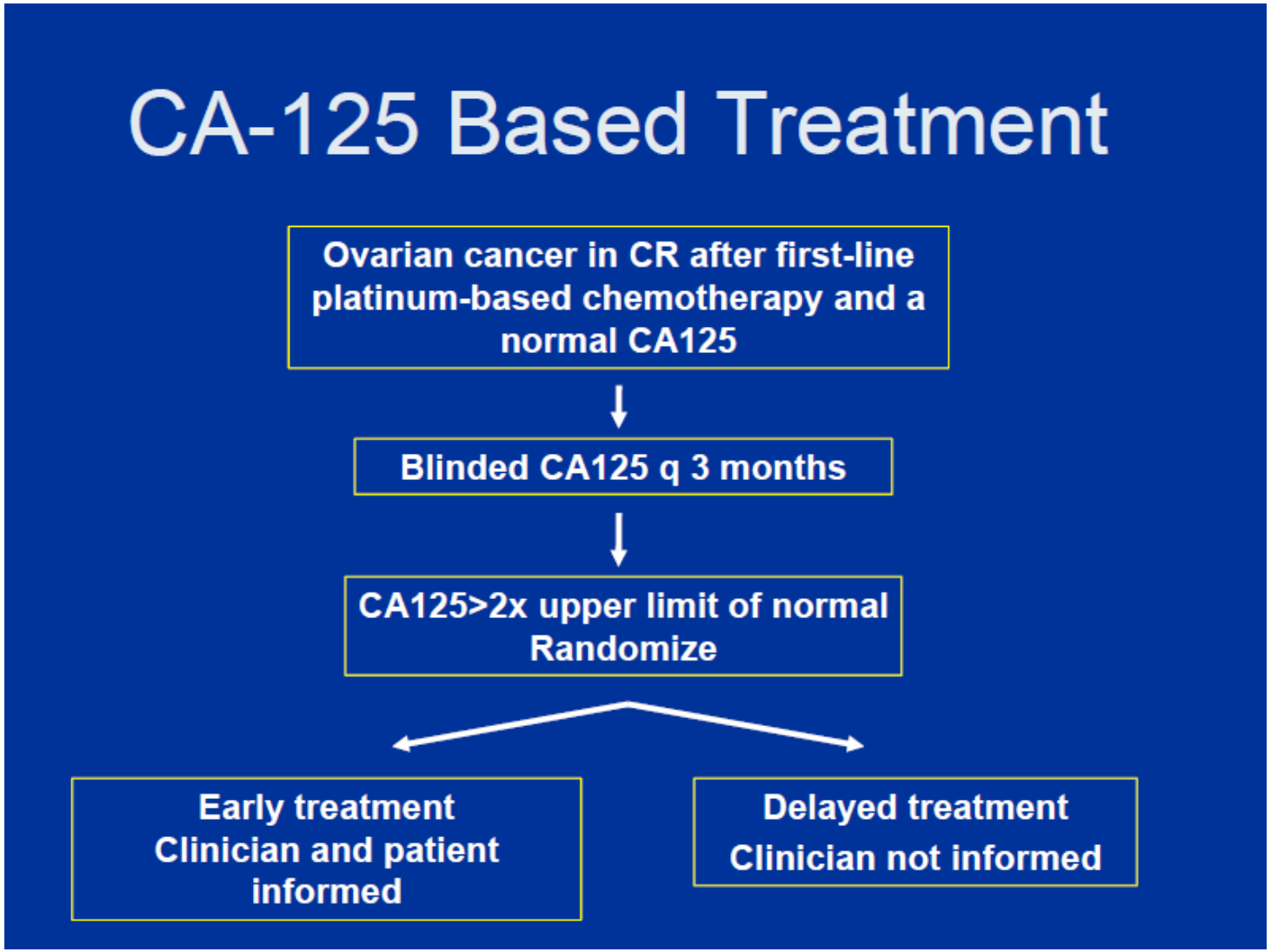

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CA-125 Based Treatment

Primary Endpoint

- Median survival of study population 70.8 months
- No difference in overall survival at 2 years
  - HR = 1.00
  - P = 0.98
  - Absolute difference 0.1%
- Time from randomization to deterioration of QoL
  - Early: 3.1 months
  - Delayed: 5.8 months
  - HR = 0.71, p = 0.001

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Post Recurrence/Progression Therapy

- Chemosensitive disease
  - Retreat with carboplatin-based doublet
  - Expected response 60+%, survival 30+ months
- Chemoresistant disease
  - Treat with alternative drug therapy
  - Expected response 12-32%, survival 8+ months

Nüks Over Kanserinde Tedavi

Chemosensitive Disease: Principles

- Retreat with same or similar regimen
- Carboplatin doublet regimen of choice
- Treatment to progression, unacceptable toxicity, or clinical complete remission
- Those with clinical CR and TFI >6 months should have repeat platinum doublet on further relapse

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PRINCIPLES OF SYSTEMIC THERAPY (5 of 7)
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Continued on OV-B (6 of 7)

Nüks Over Kanserinde Tedavi

Ovarian Carcinoma

Regimens for Platinum-Sensitive Disease

Regimen	Comparator	PFS	OS	Toxicity
Paclitaxel + Carboplatin	Carboplatin	HR = 0.76*	HR = 0.82*	>neuropathy <myelotoxicity
Gemcitabine + Carboplatin	Carboplatin	HR = 0.72*	HR = 0.96	>myelotoxicity
PLD + Carboplatin	Paclitaxel + Carboplatin	HR = 0.82*	HR = NS	Mucocutaneous vs neuropathy
Gemcitabine + Carboplatin + Bevacizumab	Gemcitabine + Carboplatin	HR = 0.48*	HR = 0.75	Hypertension Proteinuria

•Difference is statistically significant favoring the experimental regimen

Nüks Over Kanserinde Tedavi

Ovarian Carcinoma

Chemoresistant Disease: Cytotoxic Drugs

Drug	Regimen
PLD	40 mg/m2/dx1/4w
Topotecan	1.0-1.25 mg/m2/dx5/3w
Oral Etoposide	50 mg/m2/dx21d/4w
Gemcitabine	1000 mg/m2/wx3/4w
Weekly Paclitaxel	80 mg/m2/w
Docetaxel	75 mg/m2/3w

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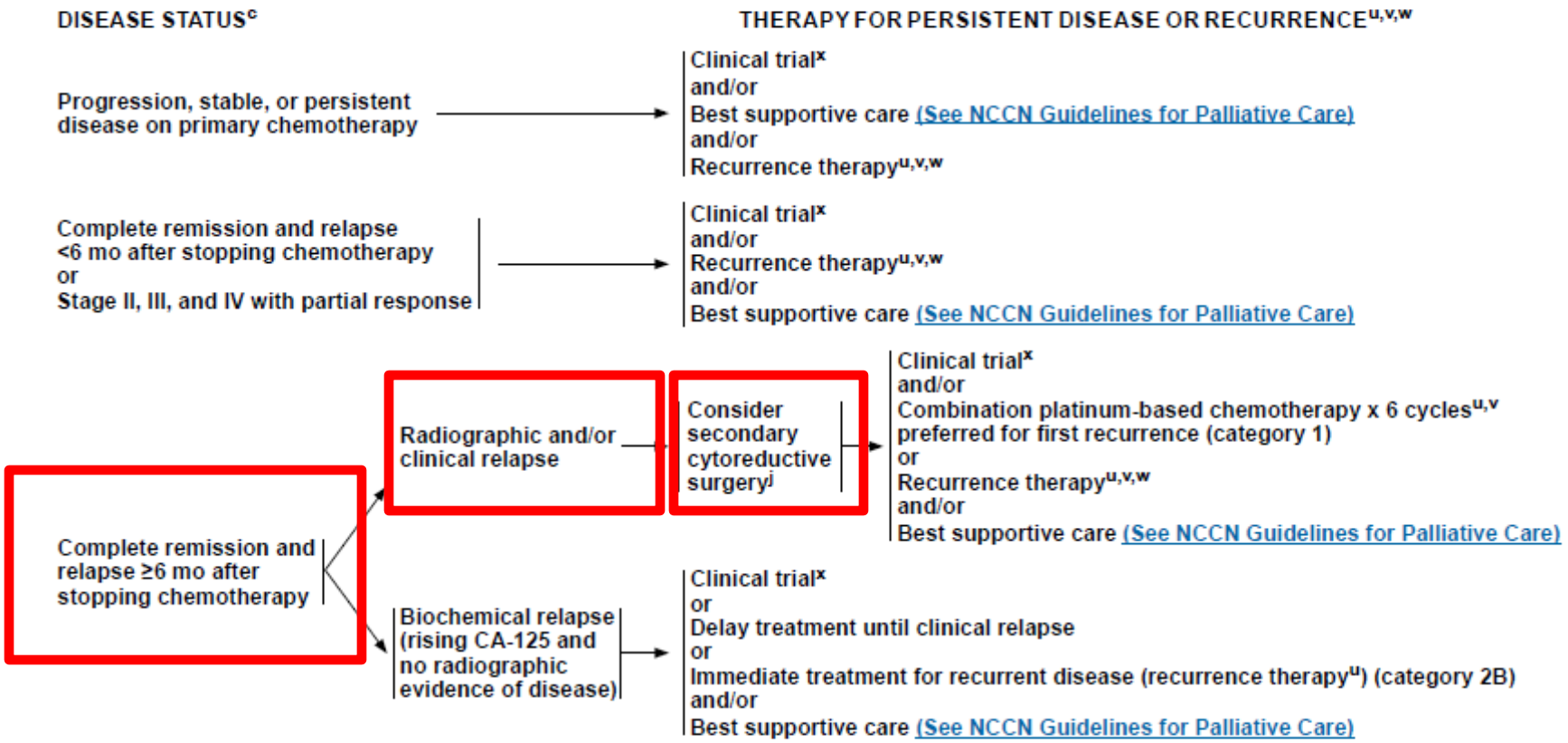


[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[j] See Principles of Surgery (OV-A).
[u] See Acceptable Recurrence Therapies (OV-B, 5 of 7).
[v] Patients who progress on 2 consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.
[w] See Ancillary Palliative Surgical Procedures in Principles of Surgery (OV-A 4 of 4).
[x] Clinical trials with newer agents should be strongly considered.

Platine rezistan over kanseri tedavisinde PLD vs Gemsitabin

VOLUME 25 · NUMBER 19 · JULY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Gemcitabine Compared With Pegylated Liposomal Doxorubicin in Patients With Platinum-Resistant Ovarian Cancer

David G. Mutch, Mauro Orlando, Tiana Goss, Michael G. Teneriello, Alan N. Gordon, Scott D. McMeekin, Yanping Wang, Dennis R. Scribner Jr, Martin Marciniack, R. Wendel Naumann, and Angeles Alvarez Secord

From the Washington University School of Medicine, St. Louis, MO; Eli Lilly & Co, Indianapolis, IN; Texas Oncology Cancer Center, Austin; Sammons Cancer Center, Baylor University Medical Center, Dallas, TX; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Carilion GYN Oncology Associates, Roanoke, VA; Carolinas Medical Center, Charlotte; and the Duke University Medical Center, Durham, NC.

Submitted October 25, 2006; accepted April 4, 2007.

Supported by Eli Lilly & Co.

Presented in part at the 29th European Congress on Clinical Oncology, October 30-November 3, 2005, Paris, France; and at the 37th Annual Meeting of the Society of Gynecologic Oncologists, March 22-26, 2006, Palm Springs, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

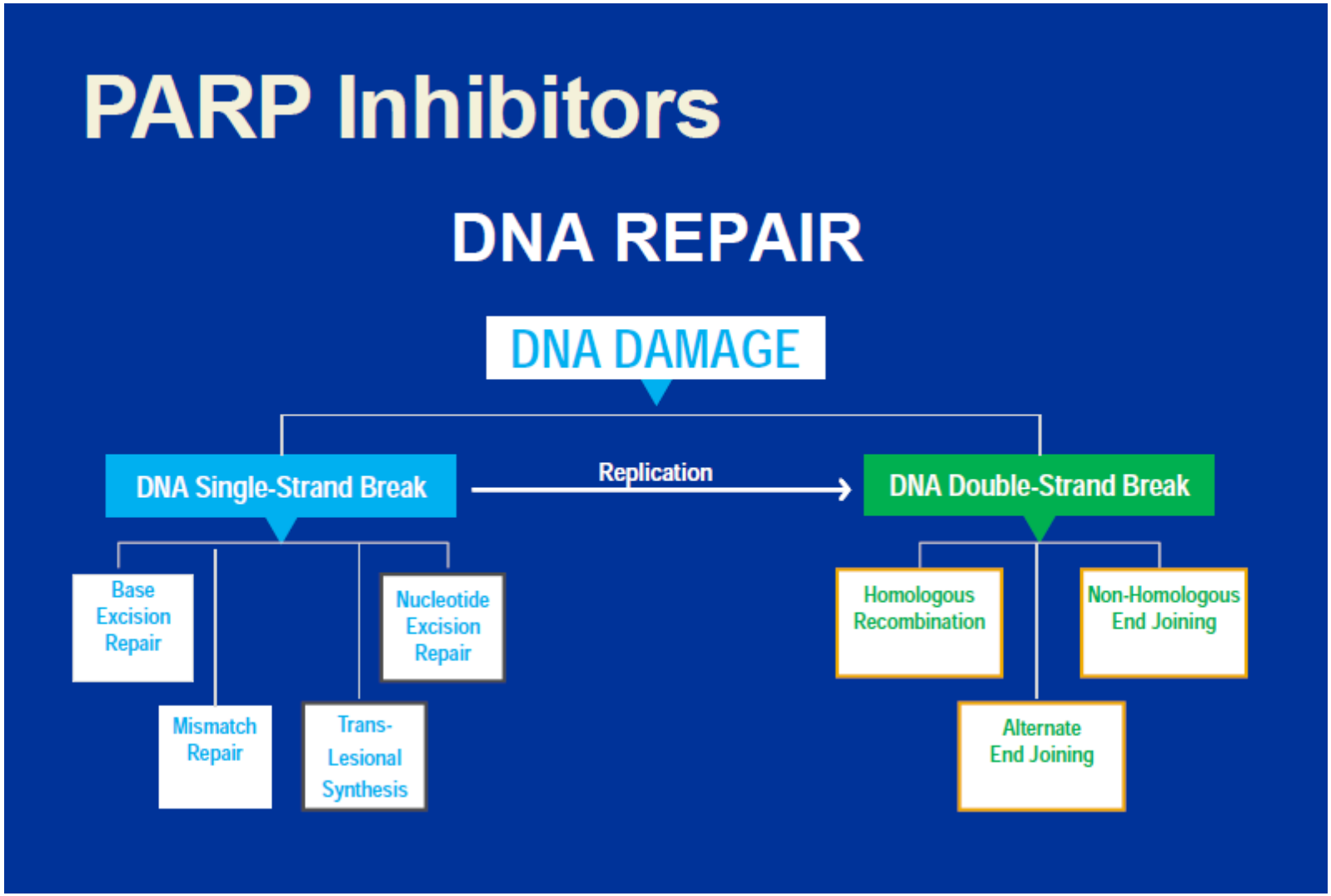
A B S T R A C T

Purpose
Ovarian cancer (OC) patients experiencing progressive disease (PD) within 6 months of platinum-based therapy in the primary setting are considered platinum resistant (Pt-R). Currently, pegylated liposomal doxorubicin (PLD) is a standard of care for treatment of recurrent Pt-R disease. On the basis of promising phase II results, gemcitabine was compared with PLD for efficacy and safety in taxane-pretreated Pt-R OC patients.

Patients and Methods
Patients (n = 195) with Pt-R OC were randomly assigned to either gemcitabine 1,000 mg/m^2 (days 1 and 8; every 21 days) or PLD 50 mg/m^2 (day 1; every 28 days) until PD or undue toxicity. Optional cross-over therapy was allowed at PD or at withdrawal because of toxicity. Primary end point was progression-free survival (PFS). Additional end points included tumor response, time to treatment failure, survival, and quality of life.

Results
In the gemcitabine and PLD groups, median PFS was 3.6 *v* 3.1 months; median overall survival was 12.7 *v* 13.5 months; overall response rate (ORR) was 6.1% *v* 8.3%; and in the subset of patients with measurable disease, ORR was 9.2% *v* 11.7%, respectively. None of the efficacy end points showed a statistically significant difference between treatment groups. The PLD group experienced significantly more hand-foot syndrome and mucositis; the gemcitabine group experienced significantly more constipation, nausea/vomiting, fatigue, and neutropenia but not febrile neutropenia.

Over Kanserinde Yeni Tedaviler



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BRCA MUTATIONS IN EPITHELIAL OVARIAN CANCER

In a population-based study of women with invasive, epithelial, nonmucinous ovarian cancer recruited without regard to family history, germline *BRCA1/2* mutations were found in 14% of cases overall

BRCA mutation status by subtype

		BRCA1/2 Mutation Positive (n=141)	
Histology	Number of Total Patients (N=1,001)	Number	%
Serous	709	118	16.6
High-grade serous	574	98	17.1
Clear cell	63	4	6.3
Endometrioid	119	10	8.4
Other	110	9	8.2
Any	1001	141	14.1

Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation–positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012;30(21):2654-2663.

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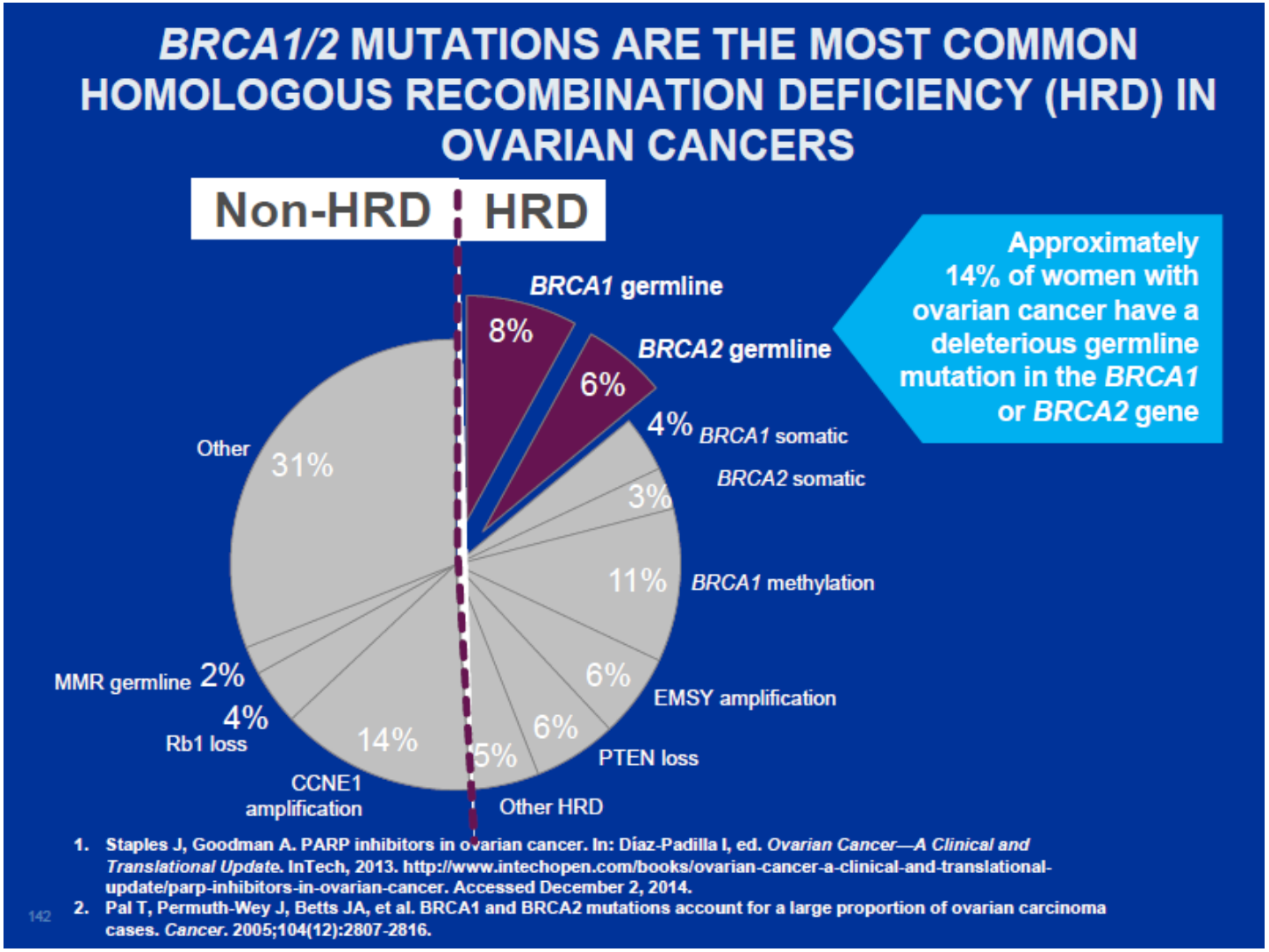

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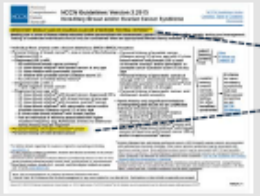
Genetic Testing: Guidelines



NCCN Guidelines Version 2.2015[a1]

Hereditary ovarian cancer testing criteria:

- Personal history of invasive ovarian* cancer

"[T]he NCCN Panel recommends testing for patients with a personal history of invasive epithelial ovarian cancer… diagnosed at any age" • — *Page MS-9*

* Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology.

ASCO Expert Statement[2]

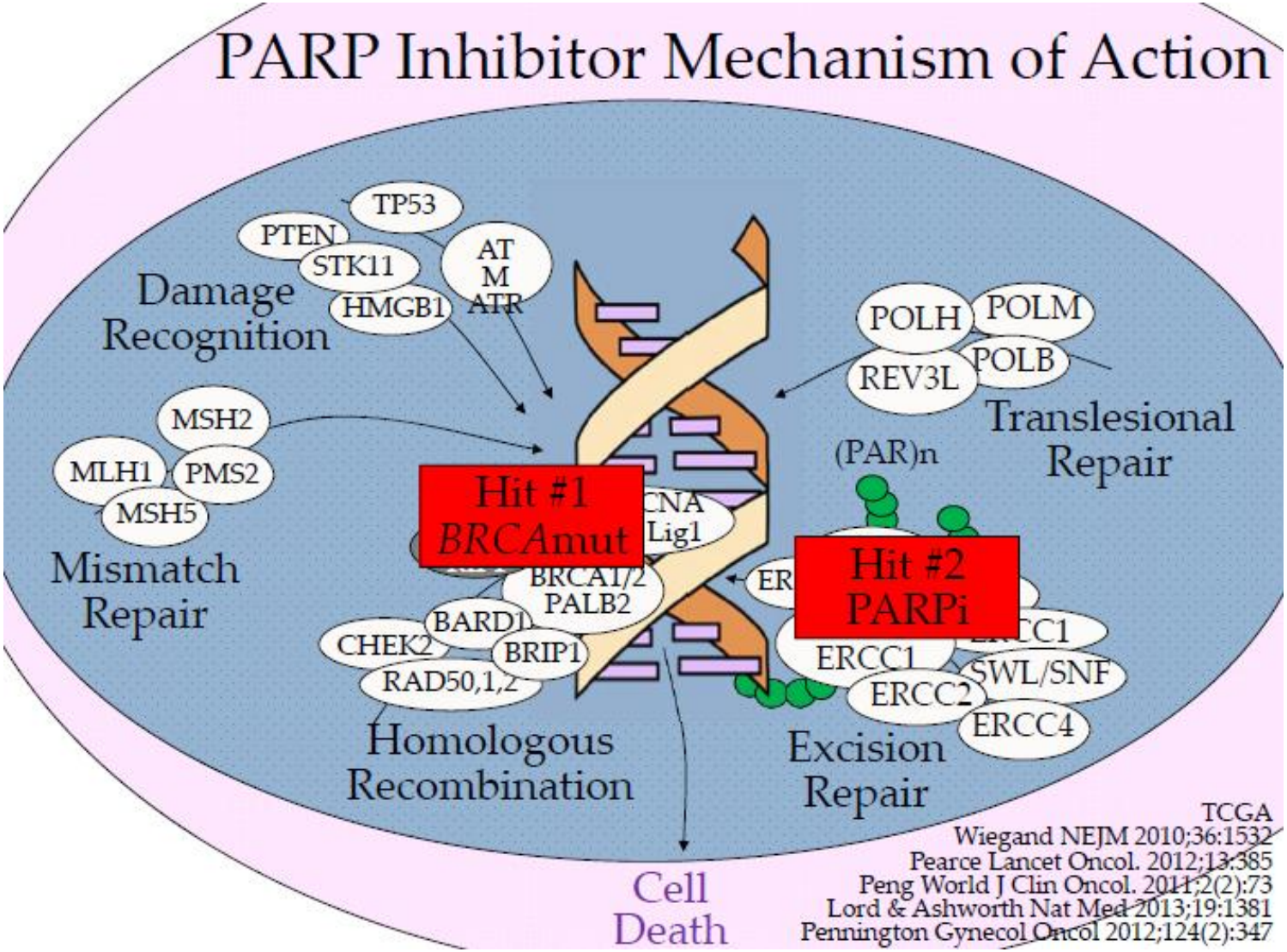
Cancers for which genetic counseling and testing should be considered, even in absence of family history:

- Epithelial ovarian, fallopian tube, or primary peritoneal cancer (most commonly, high-grade serous histology)

SGO Clinical Practice Statement October 2014[3]

The Society of Gynecologic Oncology (SGO) encourages the medical community to offer genetic counseling and testing to all women with ovarian, fallopian tube and peritoneal carcinoma.

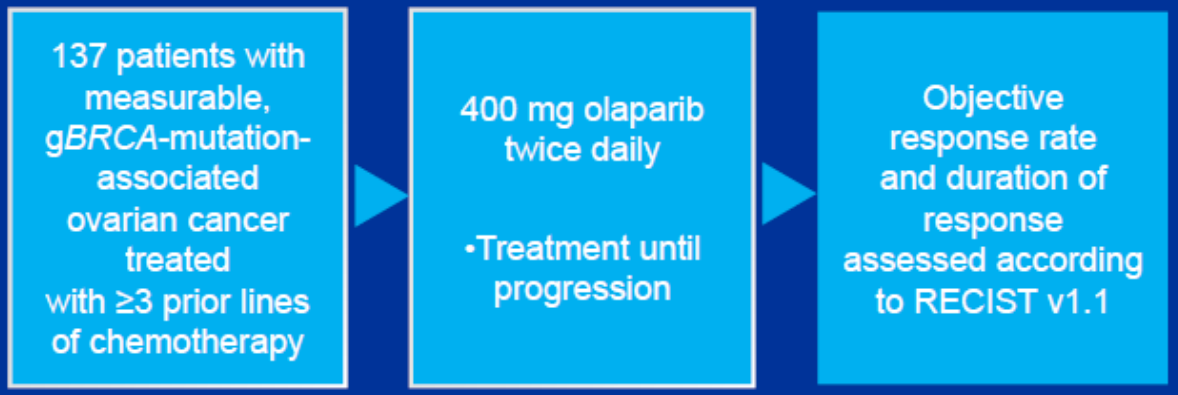
Over Kanserinde Yeni Tedaviler



Over Kanserinde Yeni Tedaviler

Olaparib: Study 1

PHASE 2, SINGLE-ARM, MULTICENTER TRIAL



Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33(3):244-250.

Over Kanserinde Yeni Tedaviler

Olaparib: Study 1

Efficacy Results

- Response Rate
  - Overall Response: 34%
  - Partial Response: 32%
  - Complete Response: 2%
- Response Duration
  - Median: 7.9 months
  - 95% CI: 5.6-9.6 months

Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33(3):244-250.

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Olaparib: Study 1

Response by platinum sensitivity (n=137)

PLATINUM SENSITIVITY	PATIENTS	RESPONDERS	RESPONSE RATE (95% CI)
Platinum sensitive	38	17	45% (29%, 62%)
Platinum resistant	77	22	29% (19%, 40%)
Platinum refractory	14	2	14% (2%, 43%)
Unknown	8	5	63% (24%, 91%)
TOTAL	137	46	34% (26%, 42%)

•Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.* 2015;33(3):244-250.

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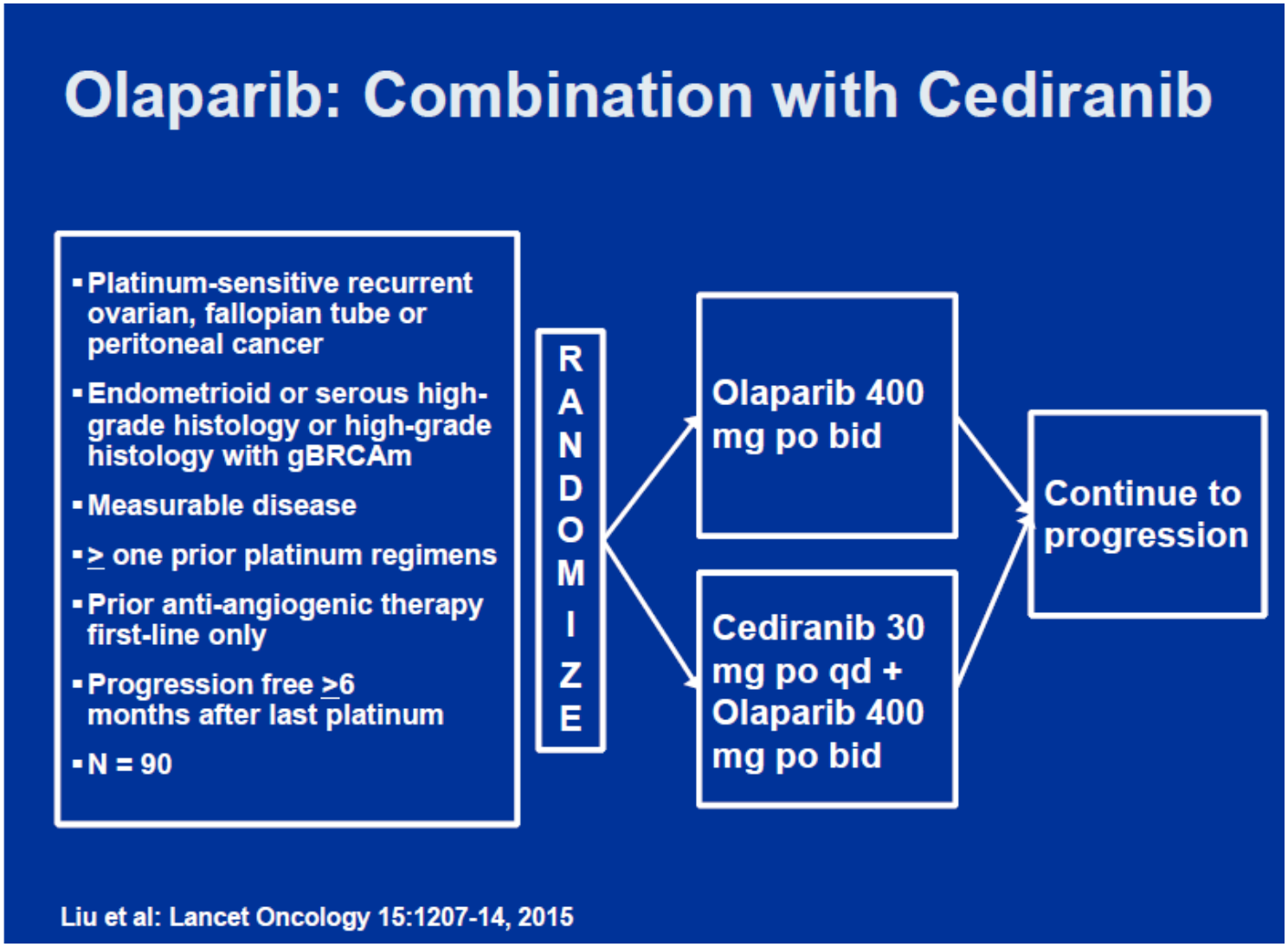

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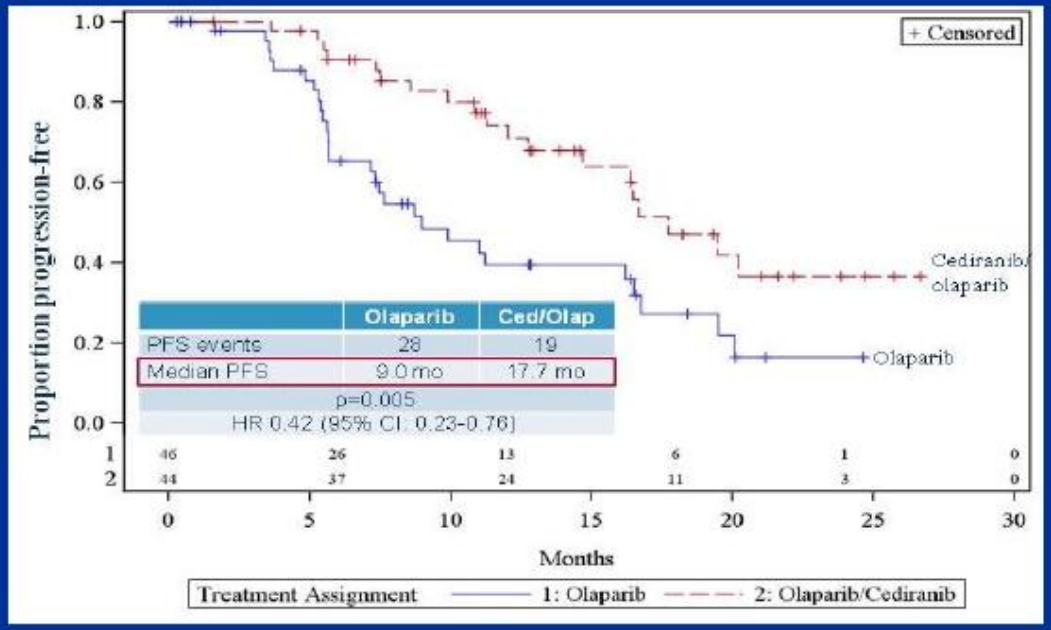
Olaparib: Combination with Cediranib

Primary Outcome: Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone



Liu et al: Lancet Oncology 15:1207-14, 2015

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Olaparib: Sumary of Endpoints in Randomized Phase II Trial of Olaparib +/- Cediranib in Platinum-Sensitive Serous Ovarian Carcinoma

	Olaparib n=46	Olaparib/Cediranib N=44
PFS, median mos	9.0 mos	17.7 mos
Hazard Ratio		0.42 (0.23-0.76) p=0.005
ORR (CR+PR), n (%)	22/46 (48%)	35/44 (80%)
Significance		p=0.002

Liu et al: Lancet Oncology 15:1207-14, 2015

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Randomized Phase II Trial of Olaparib +/- Cediranib in Platinum-Sensitive Serous Ovarian Carcinoma: Results by BRCA Mutation Status

	Olaparib n=46	Olaparib/Cediranib N=44
BRCA Mutation Positive		
PFS Events	13	10
PFS, median mos	16.5 mos	19.4 mos
Hazard Ratio		0.55 (0.24-1.27) p=0.16
BRCA Mutation Negative		
PFS Events	15	9
PFS, median mos	5.7 mos	16.5 mos
Hazard Ratio		0.32 (0.14-0.74) p=0.008

•Liu et al: Lancet Oncology 15:1207-14, 2015

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PARP Inhibitors: Phase II Efficacy Data in g/s*BRCA*mut Ovarian Cancer Patients

	Olaparib				Rucaparib	Niraparib	Veliparib	Talazoparib
Study	Audeh[1]	Kaye[2]	Gelmon[3]	Domchek[4]	ARIEL2 Part 1[5]/Study 010[6]	Matulonis[8]	Coleman[9]	Barclays Research
Phase	II	II	II	II	II	III	II	I
Dose	400 mg BID	400 mg BID	400 mg BID	400 mg BID	600 mg BID	300 mg QD	400 mg BID	1 mg QD
n =	33	32	17	137	23 - 204	360	50	14
Prior Lines	Median 3	3	3	≥3	≥3	≥2	1-3	NA
*BRCA*mut	Germline				gs*BRCA* & HGSOC	HGSOC	Germline	Germline
ORR % Plat Sens: Plat Res: Plat Ref:	34% 38% 30% X	31% X X X	X 60% 33% X	X 46% 30% 14%	X 50%[5] - 77%[6] X X gBRCA 80%[7] LOH^{high} 39%[7]		26% 35% 20% X	50% X X X
Med PFS	All: 9.5	All: 6.8	N/A	All: 7.9	12.8 g 7.2 s		All: 8.2	All: 8.0

1. Audeh MW, et al. *Lancet* 2010;376:245-251; 2. Kaye S, et al. *J Clin Oncol* 2012;30:372-379; 3. Gelmon KA, et al. *Lancet Oncol* 2011;12:852-861; 4. Domchek SM, et al. *ASCO* 2015 Abs 5529; 5. McNeish IA, et al. *ASCO* 2015 Abs 5508 & Kristeleit R, et al. *ECCO-ESMO* 2015 Abs 2700; 6. Shapira-Frommer R, et al. *ECC-ESMO* 2015 Abs P409; 7. Coleman R, et al. *ASCO* 2016 Abs 5540; 8. Matulonis UA, et al. *ASCO* 2016 Abs TPS5625; 9. Coleman RL, et al. *Gyn Onc* 2015;137:386-91

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PARP Inhibitors
Randomized Phase II Efficacy Data

	Olaparib			Veliparib	
Study	Study 12[1]	Study 19[2]	Study 41[5]	NCT01560104[6]	Metronomic[7]
Schema Doses	200 mg BID 400 mg BID PLD	Placebo vs. 400 mg BID	Placebo vs. 200 D1-10 (AUC 4) - 400 mg BID	Paclitaxel/carbo +/- 120 mg BID	Cyclophosphamide 50 mg QD +/- 60 mg velip QD
n =	97	256	173	158	74
Prior Lines	<12mo PFI	≥2	2-3	1-3	4 (1-9)
*BRCA*mut	Germline	HGSOC 54% g*BRCA*	HGSOC 38% n=107 g*BRCA*	Smokers	HGSOC and g*BRCA*mut
Response	25% vs. 31% vs. 18%				C VC RR 19% 11%
Med PFS months HR (P value)	6.5 vs. 8.8 vs. 7.1 NS (p=0.66)	8.4 vs. 4.8 (P<0.001) HR 0.18 g*BRCA*mut 11.2 vs 4.3 (p<0.001)[3]	12.2 vs. 9.6 HR 0.51 (p=0.0012)		2.3 vs. 2.1 (p=0.68)
OS HR		Initial OS p=0.75 3rd OS HR 0.73 p=0.02 NS[4]		OS 0.43 (0.26–0.70) 12.5 vs. 5.4 mm	

1. Kaye SB, et al. *J Clin Oncol* 2012;30:372-9; 2. Ledermann J, et al. *NEJM* 2012;366:1382-92; 3. Ledermann JA, et al. *Lancet Oncol.* 2014;15:852-61; 4. Ledermann JA, et al. *ASCO* 2016 A5501; 5. Oza AM, et al. *Lancet Oncol* 2015;16:87-97; 6. Ramalingham SS, et al. *ASCO* 2015 P8038; 7. Kummar S, et al *Clin Ca Res* 2015;21:1574-82

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PARP Inhibitors in Upfront Phase IIIs

	Olaparib SOLO	Rucaparib Talazoparib	Niraparib	Veliparib
Study	SOLO1		PRIMA	GOG 3005
Dose Schema	300 mg BID tabs vs. placebo 2:1		300 mg QD vs. placebo 2:1	Taxol carbo +/- 150 mg 3/400 mg BID
n =	344		305	734
Prior Lines	0		≥2	0
*BRCA*mut	Germline		HGSOC HRD-positive tumor	HGSOC
PFS HR Months P value	2018 Analysis			On Hold

clinicaltrials.gov

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

NCCN Guidelines Index
Ovarian Cancer TOC
Discussion

PRINCIPLES OF SYSTEMIC THERAPY (5 of 7)
Acceptable Recurrence Therapies for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer[g]

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	Platinum-Sensitive Disease[h,i] Carboplatin[1] Carboplatin/docetaxel[2,3] Carboplatin/gemcitabine[1] Carboplatin/gemcitabine/bevacizumab[j,k] (category 2B)[4] Carboplatin/liposomal doxorubicin[5] (category 1) Carboplatin/paclitaxel (category 1)[6] Carboplatin/paclitaxel (weekly)[7] Cisplatin[6] Cisplatin/gemcitabine[8]		Single Agents Bevacizumab[j,k,18,19] Olaparib[m,20,21]	
	Platinum-Resistant Disease Docetaxel[9] Etoposide, oral[10] Gemcitabine[11,12] Liposomal doxorubicin[11,12] Liposomal doxorubicin/bevacizumab[j,k,13] Paclitaxel (weekly)[14] ± pazopanib[15] Paclitaxel (weekly)/bevacizumab[j,k,13] Topotecan[16,17] Topotecan/bevacizumab[j,k,13]		Single Agents Bevacizumab[j,k,18,19] Olaparib[m,20,21]	
Other Potentially Active Agents	Single Agents[l,22] Altretamine, Capecitabine, Cyclophosphamide, Doxorubicin, Ifosfamide, Irinotecan, Melphalan, Oxaliplatin, Paclitaxel, Paclitaxel, albumin bound (nab-paclitaxel), Pemetrexed, Vinorelbine	Aromatase inhibitors Leuprolide acetate Megestrol acetate Tamoxifen	Pazopanib (category 2B)[23]	Palliative localized radiation therapy

[g]Patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and Fallopian tube. Int J Gyn Ca 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.

[h]In general, the panel would recommend combination regimens based on randomized trial data, especially in first relapses.

[i]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.

[j]In patients who have not previously received bevacizumab.

[k]Contraindicated for patients at increased risk of gastrointestinal perforation.

[l]Many of these agents have not been tested in patients who have been treated with modern chemotherapy regimens.

[m]For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with three or more lines of chemotherapy.[2]

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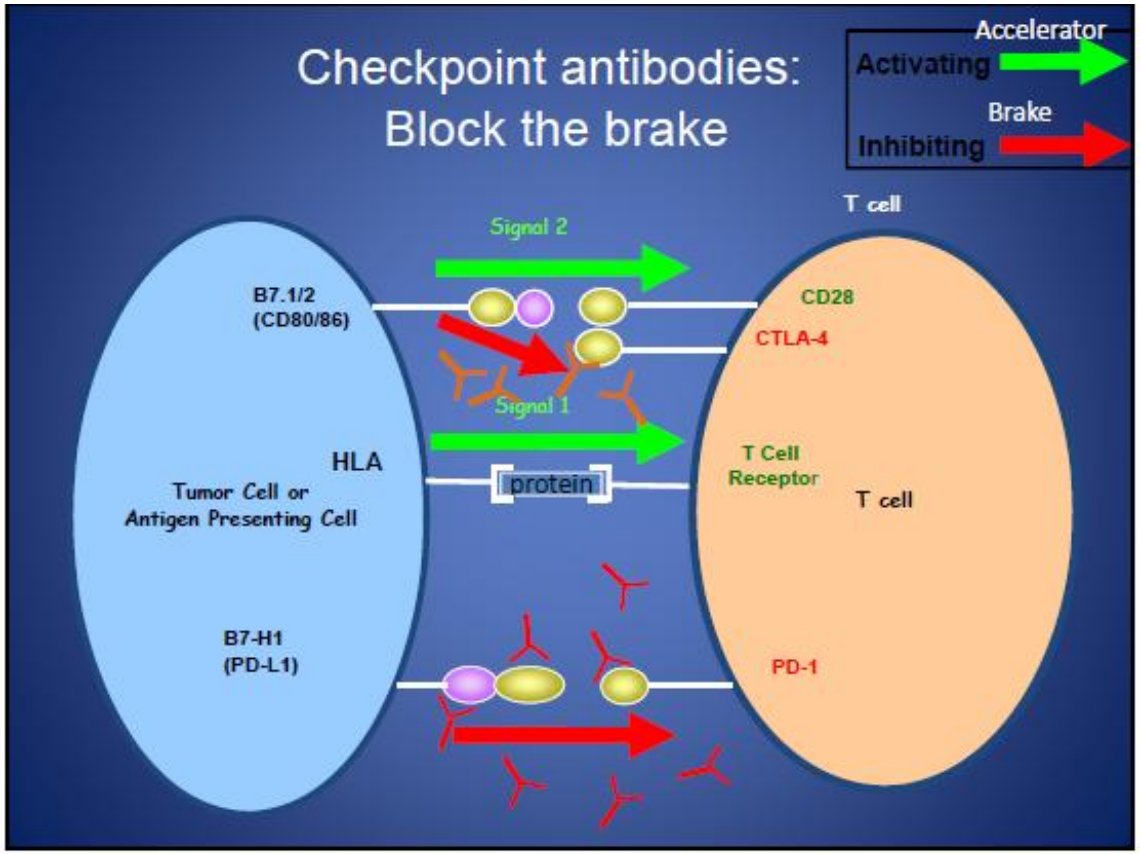

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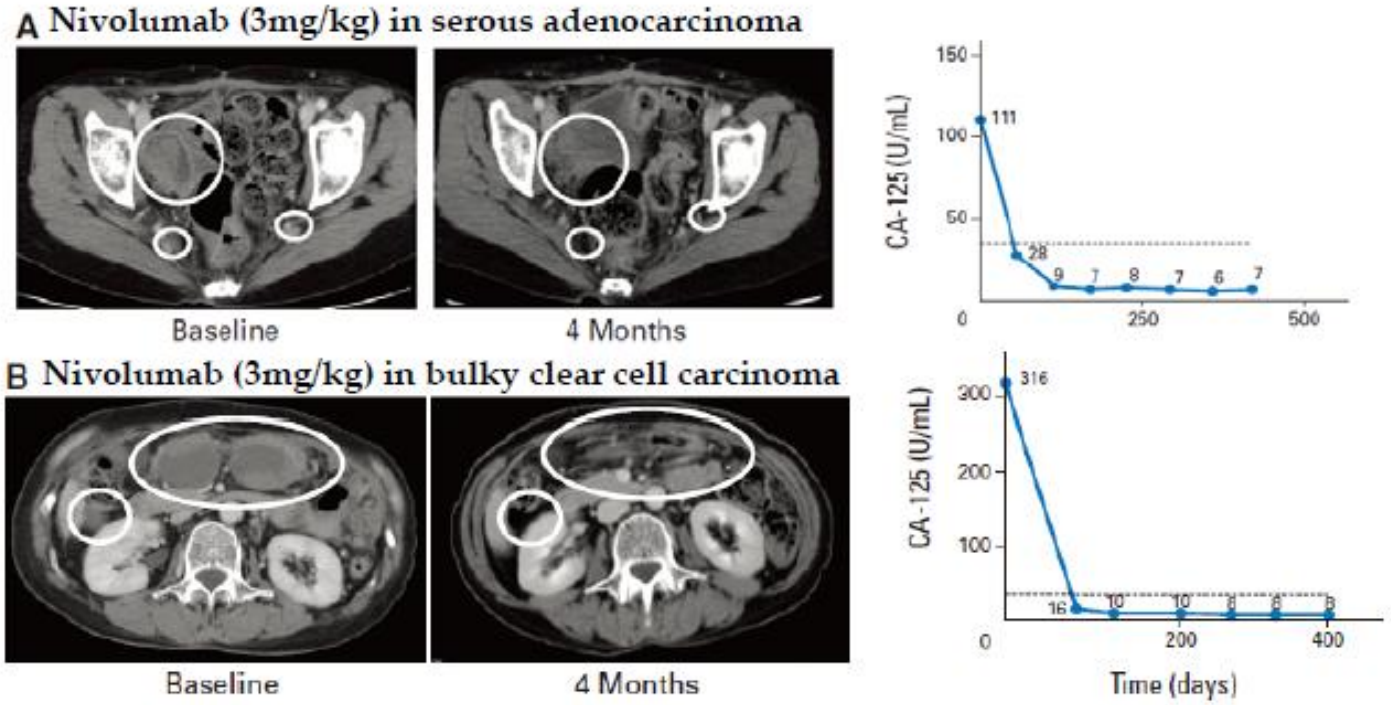
Immunotherapy in Ovarian Cancer

Nivolumab in Platinum-Resistant Ovarian Cancer



Hamanishi et al ASCO 2014 J Clin Oncol 2015;33:4015-4022

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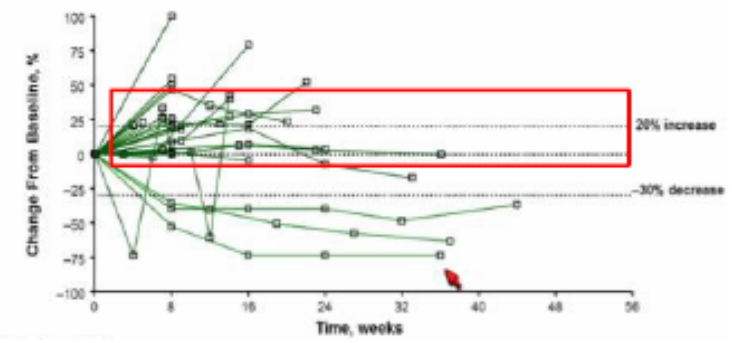
Immunotherapy in Ovarian Cancer

Advanced ovarian epithelial fallopian tube or primary peritoneal carcinoma
Exclusively on PD-L1 positive patients (n=26)

	N = 26		
Best Overall Response	n	%	95% CI
ORR	3	11.5	2.4–30.2
Complete response	1	3.8	0.1–19.6
Partial response	2	7.7	0.9–25.1
Stable disease	6	23.1	9.0–43.6
Progressive disease	17	65.4	44.3–82.8
Disease Control Rate	9	34.6	17.2–55.7



Antitumor activity and safety of pembrolizumab in patients with PD-L1 positive advanced ovarian cancer : interim results from phase 1b study
Presented by Andrea Varga et al 2015 ASCO annual meeting

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Immunotherapy in Ovarian Cancer

- Recurrent or refractory ovarian cancer (n=75)
- Phase Ib open-label expansion
- Activity
  - ORR of 10.7%
  - 2 of 2 clear cells responded
  - SD: 44% additional patients
  - DCR: 55%

Avelumab

Best overall response by RECIST 1.1, unconfirmed*	Ovarian (n=75) n (%)	95% CI
Complete response (CR)	0	
Partial response (PR)	8 (10.7)	
Stable disease (SD)	33 (44.0)	
Progressive disease (PD)	26 (34.7)	
Objective response rate (ORR)	**8 (10.7)**	**4.7, 19.9**
Disease control rate (DCR)†	41 (54.7)	

Disis ML et al ASCO 2015 Abs. 5509

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1st Line Immunotherapy Trials

Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100)
NCT02718417

Atezolizumab Front Line advanced Ovarian Cancer (FLOC)
ATALANTE: Atezolizumab vs Placebo Phase III Study in Late Relapse Ovarian Cancer Treated With Chemotherapy and Bevacizumab
NCT02891824